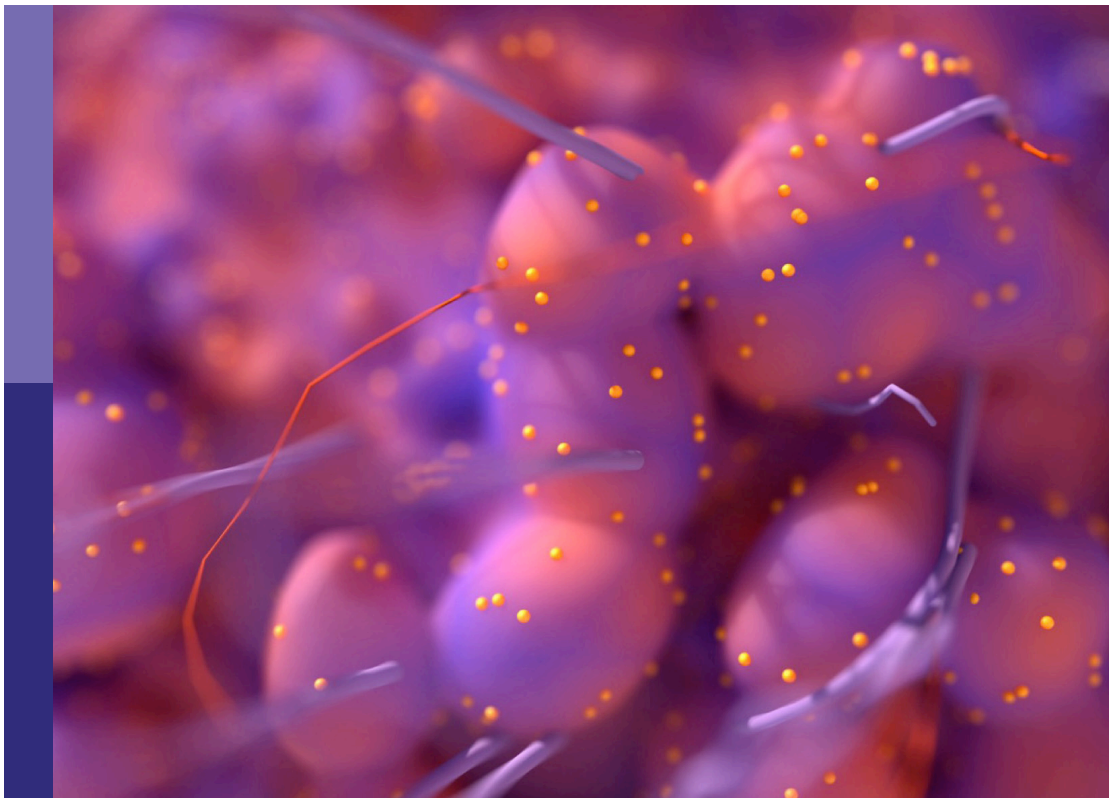
frontiers | Research Topics

Case reports in breast cancer 2023–2024

Edited by
Fengting Yan and Min Sun

Published in
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-8325-7162-0
DOI 10.3389/978-2-8325-7162-0

Generative AI statement
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Case reports in breast cancer 2023–2024

Topic editors

Fengting Yan — Swedish Cancer Institute, United States

Min Sun — University of Pittsburgh Medical Center, United States

Citation

Yan, F., Sun, M., eds. (2025). *Case reports in breast cancer 2023–2024*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-7162-0

Table of contents

frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 07 November 2025
DOI 10.3389/fonc.2025.1711001

OPEN ACCESS

EDITED AND REVIEWED BY
Kara Britt,
Peter MacCallum Cancer Centre, Australia

*CORRESPONDENCE
Fengting Yan
fengting.yan@swedish.org

RECEIVED 23 September 2025
ACCEPTED 27 October 2025
PUBLISHED 07 November 2025

CITATION
Yan F, Sun M and Kaplan H (2025) Editorial: Case reports in breast cancer 2023-2024. *Front. Oncol.* 15:1711001.
doi: 10.3389/fonc.2025.1711001

Editorial: Case reports in breast cancer 2023-2024

Fengting Yan[1]*, Min Sun[2] and Henry Kaplan[1]

[1]Swedish Cancer Institute, Seattle, WA, United States, [2]University of Pittsburgh Medical Center, Pittsburgh, PA, United States

KEYWORDS

breast cancer, case report, multi omics, DCIS, metastatic breast cancer

Editorial on the Research Topic
Case reports in breast cancer 2023–2024

Breast cancer remains one of the most prevalent malignancies worldwide, encompassing a wide spectrum of subtypes and therapeutic challenges. While studies utilizing large groups of patients are essential for understanding this disease and its treatment, individual reports of unusual or unrecognized cases can provide valuable insights (1, 2). These unique situations often lead to new research directions and therapies. As the use of multi-omic techniques and the availability of multi-omic data sets become more widespread in this era of precision medicine we will undoubtedly also see reports of important new and hopefully targetable biologic processes through the report of "n of 1" case studies (3, 4). The case reports noted in this compendium illustrate both the intricacies of managing early-stage and metastatic disease and the opportunities afforded by innovative therapies, unexpected clinical scenarios, and advances in personalized medicine. Collectively, these cases underscore the dynamic nature of breast cancer care and the importance of heightened clinical awareness as well as multidisciplinary collaboration.

A striking example involves bone marrow metastasis with necrosis presenting 11 years after an initial diagnosis of ductal carcinoma *in situ* (DCIS). This delayed recurrence underscores the importance of vigilant, long-term surveillance for patients with high-risk features, such as being under 40 years old, the size of the DCIS, nuclear grade, presence of necrosis, multifocality, surgical margins, and the mode of detection, even among those with seemingly early-stage disease.

Innovative approaches are also reshaping local treatment. One report describes intraoperative radiation therapy (IORT) as an alternative for patients who are unable to tolerate conventional external-beam regimens, particularly for those with difficulty staying still, or with vision impairment that prevent them from traveling to receive post-surgical radiation. This underscores the value of tailoring therapy to individual needs, thereby optimizing both compliance and comfort.

The management of triple-negative breast cancer (TNBC) is particularly challenging for patients who are survivors of B-cell acute lymphoblastic leukemia. Key challenges include cardiac toxicities from cumulative dose of doxorubicin and radiation, the use of immune checkpoint inhibitor after allogeneic stem cell transplantation (allo-SCT), and testing for hereditary cancer in patients with history of allo-SCT. These scenarios highlight the complexities involved managing patients with a secondary primary TNBC following successful treatment for acute leukemia and allo-SCT. They underscore the delicate balance

between aggressive treatment and the risk of adverse outcomes, reinforcing the importance of individualized strategies guided by multidisciplinary expertise.

Equally significant are the dynamic shifts in tumor biology. Hormone receptor conversion—cases transitioning from negative to positive status, or vice versa—reflects the evolving nature of metastatic disease and the need for periodic reassessment. Additionally, findings from the Plus-ENDO study support the use of ultrasound-based evaluations in advanced hormone receptor–positive disease for patients treated with CDK4/6 inhibitor-based therapy. Ultrasound demonstrated changes in lesions not only in size but also in echogenicity and the absence of vascularization. Ultrasound remains a practical and accessible tool for monitoring local response to medical treatments, particularly in unfit and elderly patients, allowing for a delay in more demanding and expensive exams. This approach has the potential to streamline monitoring and enhance treatment precision.

Rare and atypical presentations continue to challenge conventional diagnostic frameworks. Reports include metaplastic carcinoma, primary breast osteosarcoma, neuroendocrine breast carcinoma with a germline EGFR mutation, and incidental discoveries of invasive lobular carcinoma or anaplastic large cell lymphoma during surgery. Other unusual scenarios—such as ectopic breast cancer in males, renal pelvis metastasis following angiosarcoma surgery, fibroadenoma associated with atypical ductal hyperplasia, and infiltrating epitheliosis mimicking invasive carcinoma—demonstrate the wide range of clinical presentations. Breast cancer presenting as numb cheek syndrome without a discrete mass, as well as breast involvement from extramammary malignancies (including ovarian mucinous carcinoma, rectal carcinoma, papillary thyroid cancer, and endometrial clear cell carcinoma), highlights the need for thorough evaluation to avoid misdiagnosis. In addition, case reports provide valuable insights into the management of rare entities such as giant breast skin warts, malignant phyllodes tumors, and double mammary pseudangiomatous stromal hyperplasia, for which randomized data remain unavailable.

Complex histologies further complicate management. Multi-omic analysis of HER2-enriched, AR-positive breast carcinoma with apocrine differentiation and an oligometastatic course has provided important insights into the genomic and molecular landscape of this rare subtype, underscoring the need for personalized and comprehensive research approaches. Similarly, the report of concurrent breast myeloid sarcoma and a borderline phyllodes tumor illustrates how uncommon combinations can defy standard diagnostic categories, necessitating close multidisciplinary collaboration.

Targeted therapies continue to expand the treatment landscape. The use of Phesgo® (subcutaneous fixed-dose combination of trastuzumab and pertuzumab) in a patient undergoing hemodialysis illustrates the adaptability of HER2-targeted regimens in complex medical contexts. A case involving a young woman who achieved long-term complete remission with a third-line PARP inhibitor following immunotherapy highlights the potential for exceptional responses to targeted therapies. Likewise, novel agents such as fam-trastuzumab deruxtecan, ESG401 (a Trop-2 antibody–drug conjugate), and margetuximab offer new options for HER2-positive metastatic disease. Interestingly, even traditional chemotherapy, such as low-dose continuous 5-FU, has shown the capacity to induce remarkable responses in heavily pretreated TNBC with liver and bone marrow failure.

Emerging therapies, however, also bring new challenges. CDK4/6 inhibitors such as ribociclib, while effective, have been associated with rare toxicities including palinopsia, vitiligo-like reactions, and photosensitivity presenting as dyschromia. PIK3CA inhibitors such as alpelisib have similarly been linked to vitiligo-like toxicity, while urothelial injury has been reported as a rare complication of paclitaxel and trastuzumab. Case experience with ribociclib in a patient with acute hepatitis—an often excluded population—provides additional insight into managing complex comorbidities. These examples highlight the importance of balancing efficacy with safety, careful monitoring, and patient education.

Beyond oncologic control, psychosocial and functional considerations are equally critical. Rehabilitation strategies for lymphedema, for example, can significantly improve quality of life, reinforcing the importance of holistic care that addresses both physical and emotional well-being.

Taken together, these cases reflect the complexity of breast cancer management across the spectrum of disease. They reinforce the central role of personalized medicine, the necessity of integrating supportive care, and the value of sustained vigilance in follow-up. As new therapies expand possibilities and tumor biology continues to reveal its adaptive nature, clinicians must remain both innovative and flexible in their approach.

In conclusion, breast cancer care is defined by complexity, diversity, and continual evolution. The cases highlighted here demonstrate not only the challenges faced by patients and clinicians but also the opportunities created by advances in diagnostics, therapeutics, and multidisciplinary care. Moving forward, the integration of novel treatments with compassionate, individualized strategies will be essential to improving outcomes. With ongoing research and collaboration, we can continue to navigate this evolving landscape with both scientific rigor and human resilience.

Author contributions

FY: Writing – original draft, Writing – review & editing. MS: Conceptualization, Writing – review & editing. HK: Conceptualization, Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

1. Hong R, Xu B. Breast cancer: an up-to-date review and future perspectives.*Cancer Commun (Lond)*. (2022) 42:913–936. doi: 10.1002/cac2.12358

2. Pareja F, Bhargava R, Borges V F, Brogi E, Canas Marques R, Cardoso F, et al. Unraveling complexity and leveraging opportunities in uncommon breast cancer subtypes. *NPJ Breast Cancer*. (2025) 11:6. doi: 10.1038/s41523-025-00719-w

3. Gouda M A, Buschhorn L, Schneeweiss A, Wahida A, Subbiah V. N-of-1 Trials in Cancer Drug Development. *Cancer Discov*. (2023) 13:1301–19. doi: 10.1158/2159-8290.CD-22-1377

4. Kato S, Kim K H, Lim H J, Boichard A, Nikanjam M, Weihe E, et al . Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. *Nat Commun*. (2020) 11:4965. doi: 10.1038/s41467-020-18613-3

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 05 January 2023
DOI 10.3389/fonc.2022.1061679

OPEN ACCESS

EDITED BY
Mauro Giuseppe Mastropasqua,
University of Bari Medical School, Italy

REVIEWED BY
Prashanth Giridhar,
Tata memorial centre, India
Prasanth Penumadu,
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India

*CORRESPONDENCE
Krisha K. Mehta
Krisha.mehta@stonybrookmedicine.edu

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 04 October 2022
ACCEPTED 09 December 2022
PUBLISHED 05 January 2023

CITATION
Mehta KK, Nouvini R, Liu J, Wang Y and Stopeck A (2023) Case report: Metastatic metaplastic breast cancer with choriocarinomatous features: Targeting the choriocarcinoma component for cure.
Front. Oncol. 12:1061679.
doi: 10.3389/fonc.2022.1061679

Case report: Metastatic metaplastic breast cancer with choriocarinomatous features: Targeting the choriocarcinoma component for cure

Krisha K. Mehta[1]*, Rosa Nouvini[2], Jingxuan Liu[3], Yi Wang[3] and Alison Stopeck[4]

[1]Department of Medicine, Stony Brook University, Stony Brook, NY, United States, [2]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [3]Department of Pathology, Stony Brook University, Stony Brook, NY, United States, [4]Department of Medicine, Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, United States

Breast cancer with choriocarcinomatous features (BCCF) is a rare and aggressive breast cancer. BCCF carries a poor prognosis and there is unfortunately scant literature to guide treatment beyond surgical resection with most patients receiving standard regimens for breast cancer. In our case, we present a 42-year-old female with an initial hCG of 2,324 and two suspicious lesions of the right breast. On biopsy, each lesion had distinct histopathology with the larger lesion diagnosed as BCCF and the smaller lesion being an invasive ER/PR positive ductal carcinoma. The diagnosis of BCCF rather than metastatic choriocarcinoma was confirmed using DNA typing. Salvage chemotherapy targeting choriocarcinoma resulted in marked clinical and biomarker success including normalization of the hCG. After recurrent brain metastases were diagnosed, high dose chemotherapy with methotrexate was administered resulting in long term remission.

KEYWORDS

breast cancer with choriocarcinomatous features, choriocarcinoma, metaplastic breast cancer, chemotherapy, methrotrexate, long term remission

Background

Breast cancer with choriocarcinomatous features (BCCF) can be challenging to treat. In all cases, the diagnosis of choriocarcinoma should be excluded in the reproductive organs prior to attributing the breast findings to a metaplastic breast cancer. BCCF was first described in 1981 by Saigo and Rosen and since then there have been at least 18 cases reported in the literature (1). Histology and immunohistochemistry reveal human

chorionic gonadotropin (hCG) positive choriocarcinomatous cells (syncytiotrophoblasts and cytotrophoblasts) mostly in the background of DCIS or invasive carcinoma (2). The choriocarcinomatous area is usually surrounded by hemorrhage and necrosis. Serum hCG is variably expressed in BCCF. When hCG is elevated, it serves as an accurate marker for disease recurrence and response to treatment (3). BCCF carries a poor prognosis and there is unfortunately scant literature to guide treatment beyond surgical resection with most patients receiving standard regimens for breast cancer. In our case, we present a 42-year old female diagnosed with BCCF and recurrent brain metastases who is now disease free over 5 years from her last treatment after progressing through standard breast cancer regimens and responding to chemotherapy appropriate for choriocarcinoma.

Case presentation

A 42-year-old Gravida 3 Para 2 female presented post-op day #4 from a dilation and curettage (D+C) for a presumed missed abortion based on elevated hCG. Subsequent hCG increased from 2,324mIU/mL to 2,445 after D+C and she was sent to the hospital for evaluation of a suspected ectopic pregnancy. Endovaginal ultrasound revealed a complex subcentimeter cystic structure adjacent to the right ovary suspicious for an ectopic pregnancy. She received one dose of methotrexate (MTX) 0.5mg/kg with a second dose of MTX administered day 4 secondary to a rising hCG. Her hCG continued to rise and she underwent laparascopic surgery which revealed an edematous right fallopian tube which was excised, revealing benign pathology.

In the interim, the patient self-palpated a right breast mass and underwent mammography which revealed a high density mass in the right axillary tail. Bilateral breast magnetic resonance imaging (MRI) revealed an approximately 6.0cm mass in the 10 o'clock position abutting the pectoral muscle with two additional lesions measuring approximately 6mm that were 3mm and 1.2mm inferior to the main tumor mass highly suggestive of satellite lesions. Also found was a 6mm irregularly shaped enhancing lesion at 6 o'clock and an 8mm rounded right axillary lymph node suspicious for metastases. Core needle biopsy of the 6mm lesion at 6 o'clock revealed invasive ductal carcinoma, moderately differentiated, ER 80%, PR 80%, Ki-67 15%, and Her2 negative. GATA 3, cytokeratin 7, and mammoglobin were expressed, and the tumor cells did not express hCG as demonstrated in Figure 1. Core biopsy of the dominant 6cm mass at 10 o'clock revealed a very different picture with a poorly differentiated carcinoma with extensive hemorrhage and necrosis observed. Immunohistochemical stains found the tumor cells did not express estrogen, progesterone, or HER2 receptors (triple negative) with a markedly elevated proliferative marker, Ki-67, at 70%, with expression of cytokeratin 7, GATA3, and importantly, hCG as

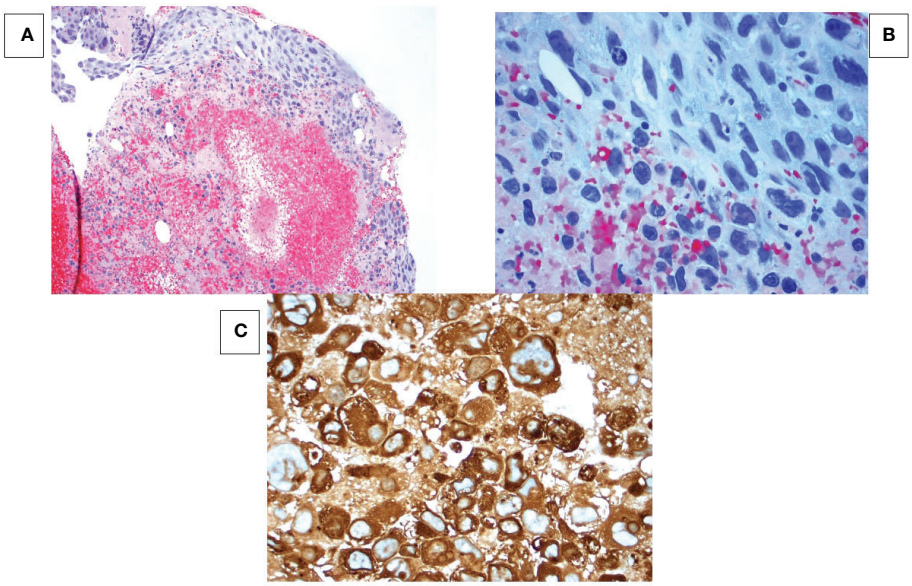


FIGURE 1
Breast mass at 10 o'clock position. **(A)** Hematoxylin-eosin (HE) stain at 100x magnification shows tumor cells in a hemorrhagic necrotic background. **(B)** HE stain at 400x magnification shows sheet-like formation of epithelial cells with pleomorphic hyperchromatic nuclei, multiple prominent nucleoli and abundant vacuolated cytoplasm. No syncytiotrophoblastic cells are seen. **(C)** Immunohistochemistry shows all cancer cells strongly express human chorionic gonadotropin (hCG).

demonstrated in Figure 2. She underwent staging with ^{18}F-FDG PET/CT (positron emission tomography with computed tomography) which revealed a large hypermetabolic (SUV 7.3) right breast mass measuring 4.5 x 3.0 cm with central necrosis, inflammatory skin changes, and several small mildly hypermetabolic right axillary lymph nodes concerning for early metastatic disease. No other sites of disease or abnormal uptake were noted. A brain MRI revealed no evidence of metastatic disease.

She initiated neoadjuvant treatment with dose dense AC [Adriamycin (60mg/m2) and Cyclophosphamide (600mg/m2)]. Clinically, there was no response to therapy and her hCG increased to 12,580mIU/mL after 2 cycles on treatment. Her therapy was then switched to a known salvage regimen for choriocarcinoma and she received alternating cycles of paclitaxel 135mg/m2 (day 1) and cisplatin 60mg/m2 (day 1) with paclitaxel 135mg/m2 (day 15) and etoposide 150mg/m2 (day 15) (TP/TE), for a total of 8 cycles (4 cycles of each treatment). Her hCG decreased markedly after her first cycle, as did her breast mass by physical exam. After completing 4 months of therapy, her hCG had normalized and her breast MRI revealed a partial response to treatment with no significant change in the smaller ER+ breast cancer at 6:00. She underwent a right modified radical mastectomy with a left risk reducing (prophylactic) mastectomy performed per patient wishes. Pathology of the BCCF cancer at 10:00 showed a 4.7cm necrotic mass without viable tumor cells. At the 6:00 position, two adjacent foci of invasive ductal carcinoma were seen, measuring 1.5cm and 2.3mm. The larger lesion was moderately differentiated, ER 29%, PR negative, HER2 negative, with a low Ki-67 at 3% and neither area expressed hCG by immunohistochemical analysis. Four of thirteen axillary lymph nodes contained metastatic disease with the largest metastatic focus at 2.5mm. Biomarkers on the involved lymph node revealed a high grade triple negative cancer with an elevated Ki-67 of 61%. Of note, hCG was not expressed in the lymph node by immunohistochemistry. DNA typing of the tumor was performed to confirm a primary breast cancer rather than metastatic choriocarcinoma. The tumor revealed only maternal DNA with no paternal DNA present confirming metaplastic breast cancer. Genetic testing of the patient did not reveal a deleterious BRCA mutation.

One week following her breast surgery and 3 weeks after completing neoadjuvant chemotherapy, she presented with a grand mal seizure and was found to have a hemorrhagic lesion measuring 2 cm in the left temporoparietal lobe associated with vasogenic edema. Her hCG level had increased from 2 to 48mIU/mL. She underwent left temporal craniotomy with tumor excision. Pathology revealed a high-grade metastatic carcinoma with hCG expression. She received a single stereotactic radiosurgery fraction of 15 Gy to the brain and comprehensive radiation treatment to the right chest wall and regional nodal areas (50 Gy in 25 fractions to the right chest wall, supraclavicular, axilla, and internal mammary nodes).

Two months after neurosurgery and stereotactic radiation, she was re-admitted to the hospital with recurrent neurologic findings. Her hCG had increased from 1 to 139mIU/mL. Repeat

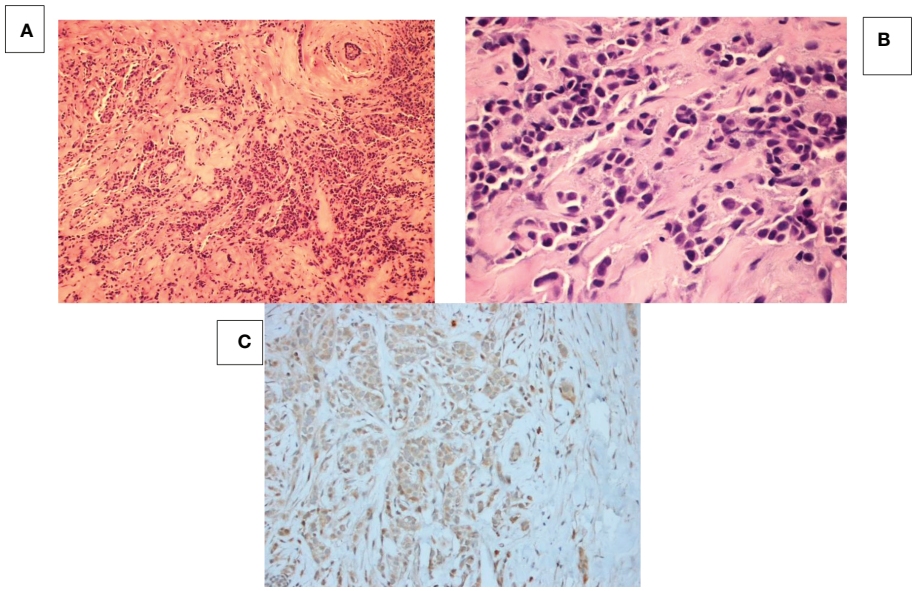


FIGURE 2
Breast mass at 6 o'clock position. **(A)** HE staining at 100x magnification shows tumor cells with sheets, tubular, cords or single cell formation infiltrating through desmoplastic stroma. **(B)** HE staining at 400x magnification shows moderately differentiated tumor cells with high nuclear: cytoplasmic ratio and pleomorphic hyperchromatic nuclei infiltrating through desmoplastic stroma. **(C)** hCG IHC shows that all the cancer cells are negative for beta-HCG.

MRI showed hemorrhage in the surgical bed. She underwent re-resection of the brain cavity and a small foci of residual/recurrent hCG expressing carcinoma was seen on pathology. She then went on to receive a total of five cycles of high dose MTX (3.5gm/m2 per cycle). Her hCG became undetectable after 3 cycles. Restaging PET/MRI prior to her final cycle of high dose methotrexate did not show any evidence of disease outside the brain. She was started on anastrazole one month after completion of high dose MTX. She is now over 5 years from completion of chemotherapy and 5 years from diagnosis and her hCG remains undetectable, her brain MRI shows only stable post-operative findings, and she is without evidence of active disease.

Discussion

BCCF, a rare, aggressive and unique entity, is a cancer characterized by cells including multinucleated synctiotrophoblast-like giant cells expressing hCG and one whose pathogenesis and optimal treatment remains undefined. Metaplastic changes associated with breast cancer include osseous, chondroid, matrix production, squamous, and spindle cells (4). It is thought that through a metaplastic process in carcinomatous breast cells, commonly infiltrating ductal carcinoma cells, choriocarcinomatous cells are formed. Metaplasia to choriocarcinoma has been seen in other adenocarcinomas as well including cancers of the esophagus, stomach and colon (5).

On gross examination, the tumor generally appears well circumscribed with hemorrhagic and necrotic components, similar to choriocarcinoma with breast metastasis. Typically, the choriocarcinomatous cells are associated with hemorrhage and necrosis in a background of either invasive ductal carcinoma or ductal carcinoma *in situ* (6). Choriocarcinomatous cells have been described as multinucleated, giant bizarre looking cells resembling syncytiotrophoblastic and cytotrophoblastic cells (7). Interestingly our case did not have the typical histologic pattern of BCCF as there was no component of invasive or *in situ* ductal carcinoma or multinucleated giant cells resembling syncytiotrophoblastic cells. However, some of the mononuclear tumor cells did resemble cytotrophoblastic cells. In addition, there was a second focus of typical invasive ductal breast cancer without hCG expression located in a different quadrant of the breast which may have been a second primary lesion versus potentially the precursor lesion for the BCCF. On immunohistochemistry, the choriocarcinomatous cells stain positive for hCG as in our case. It is important to note that 5 -21% of ductal carcinoma cells can also express hCG positivity on immunohistochemistry (4); and hCG expression alone does not confirm a BCCF diagnosis. Serum hCG is commonly elevated in BCCF. It can also be elevated in up to 12 – 33% of breast cancer patients who do not have evidence of choriocarcinoma or choriocarcinoma features in their tumor (1). ^{18}F-FDG PET/CT has also been used as a tool for detecting malignant tissue due to malignant cells accumulating FDG as a result of their high rates of glycolysis (8). Sung et al. used ^{18}F-FDG PET/CT to diagnose the tumor mass in one of their BCCF cases (8). Similarly, in our case ^{18}F-FDG PET/CT revealed a large hypermetabolic right breast mass measuring 4.5 x 3.0 cm and hypermetabolic right axillary lymph nodes consistent with her disease presentation.

BCCF must also be differentiated from metastatic choriocarcinoma to the breast. Patients with metastatic choriocarcinoma typically have a history of reproductive tumors and a primary breast tumor is not present (6). While uncommon, trophoblastic cancers can metastasize to the breast. DNA typing can be useful to exclude metastatic gestational trophoblastic disease and help differentiate choriocarcinoma versus BCCF. Choriocarcinoma, as a gestational cancer arising from hydatiform moles, carries both paternal and maternal genetic DNA. Thus, DNA genotyping is a definitive tool for distinguishing metastatic gestational trophoblastic cancer from other somatic cancers that mimic gestational tumors (9). As our patient's tumor consisted of only maternal DNA, we excluded a gestational origin to the cancer. To our knowledge, this is one of the first case reports that used DNA typing to differentiate between metastatic choriocarcinoma and BCCF.

As in most metaplastic breast cancers, immunohistochemistry is typically triple negative (minimal to no ER, PR, or HER2/neu expression) in BCCF. Siddiqui et al. did present a case in which there was immunohistochemical evidence of expression of both ER and PR in the background tumor with PR positivity and ER negativity in the giant cells. The lack of hormone receptor positivity adds to the complexity in treatment and disease-free survival. To add to the poor prognosis, patients with BCCF also present at a younger age (average age 48 years) and most present with palpable masses in the right breast (10). One theory to explain the aggressive clinical course characteristic of BCCF is that pregnancy associated proteins such as hCG suppress the immune system to protect materno-fetal immune reactivity and thereby permit cancer cells to evade host immunosurveillance (10).

The development of hemorrhagic brain metastases is another hallmark of choriocarcinoma, and our patient developed a symptomatic, hemorrhagic brain metastasis soon after stopping neoadjuvant chemotherapy. It is likely this metastasis was present at diagnosis, despite the normal brain MRI on staging, and suggests patients with BCCF often have a clinical course similar to patients with gestational trophoblastic.

Treatment of BCCF has not been well established. Unlike choriocarcinoma which has a favorable prognosis in the non-metastatic setting and responds well to chemotherapy, BCCF has a poor prognosis with variable survival rates depending on stage. Endocrine therapy, chemotherapy and surgery are the

10.3389/fonc.2022.1061679

TABLE 1 Previous case reports of BCCF with details of case, treatment and outcome.

Study (year)	Age (sex)	Pregnant (y/n)	Histology	Initial Serum bHCG	Stage	Treatment	PFS	OS
Saigo PE, 1981	55 (F)	N	IDC*, with co-existing anaplastic areas associated with necrosis & hemorrhage, choriocarcinomatous cells found in hemorrhagic area	N/A*****	IIA (T2N0M0)	Left radical mastectomy	N/A	7 months
Fowler CA, 1995	32 (F)	Y (mass felt during 3rd trimester & presented 6wks post partum)	Large mass w/ necrotic center, choriocarcinoma	9,920	IV (lung)	10 cycles Etoposide, MTX, Adriamycin, Vincristine, Cyclophosphamide	9 months	1 year
Murata T, 1999	38 (F)	N	Large-sized, oval-shaped tumor cells with occasional hemorrhagic necrosis. MGCs*** resembling syncytiotrophoblasts. DCIS**** background,	N/A	IIIA (T3N2M0)	Right MRM f/b radiation therapy and adjuvant 5FU derivative & anti-GnRH	2 months	7 months
Resetkova E, 2004	38 (F)	Y	Syncytial pattern of cells surrounded by rim of chronic lymphoplasmacytic infiltrate. Multiple atypical mitotic figures & focal tumor necrosis	<1	IB (T1bN0M0)	Excisional bx with clear margins, elective abortion, chemo (unknown)	1 year	N/A
Resetkova E, 2004	54 (F)	N	IDC with features of metaplastic ca. with a component of MGCs with a syncytiotrophoblast-like appearance. Adjacent necrosis & hemorrhage.	3.4	IIB (T3N0M0)	MRM, 2 cycles adjuvant chemo (unknown) + XRT R chest wall	6 months	N/A
Siddiqui NH, 2006	56 (F)	N	IDC & loosely cohesive giant cells with areas of hemorrhage. ER+/PR+ in background tumor cells and ER-/PR+ in the giant tumor	N/A	IIA (T2N0M0)	Right partial mastectomy f/b left breast radical mastectomy		7 months
Akbulut M, 2008	53 (F)	N	IDC with areas of necrosis & multinucleated syncytiotrophoblastic type giant cells and cytotrophoblast looking cells	N/A	Stage IIA (T2N0M0)	Left partial mastectomy with ALND		6 years
Akbulut M, 2008	50 (F)	N	IDC with numerous MGCs, tumor cells resembling syncytiotrophoblastic and cytotrophoblastic cells, extensive necrosis and hemorrhage	N/A	Stage IIA (T2N0M0)	Right radical mastectomy		4 years
Zhu Y, 2014	32 (F)	N	MGCs resembling syncytiotrophoblasts. Extensive hemorrhage, no infiltrating ductal ca or DCIS.	22,931	IV (lung, kidney)	**2 cy docetaxel + epirubicin →POD → 2cy docetaxel + cis → 1 cy docetaxel + Lobaplatin	37 months	N/A

(Continued)

TABLE 1 Continued

Study (year)	Age (sex)	Pregnant (y/n)	Histology	Initial Serum bHCG	Stage	Treatment	PFS	OS
						→toxicity → 3cy docetaxel + capecitabine → 9 cy capeceitabine		
Oguz A, 2014	69 (F)	N	IDC with most of tumor with choriocarcinomatous differentiation with perineural invasion	N/A	IA (T1N0M0)	Left MRM f/b 6 cy cyclophosphamide (500mg), doxorubicin (50mg), 5FU (500mg/m2)	23 months	N/A

*IDC, invasive ductal carcinoma; MTX, methotrexate; MRM, modified radical mastectomy; Cis, cisplatin,
** Doses of chemo used in this study were as follows: Q21day cycles, Docetaxel 75mg/m2 (1x/cycle), Epirubicin 75mg/m2 (1x/cycle), Cisplatin 75mg/m2 (1x/cycle), Lobaplatin 35mg/m2 (1x/cycle), Capecitabine 2g/m2 (2wk on, 1wk off)
***MGC, multinucleated giant cell
****DCIS, ductal carcinoma in situ
*****N/A – Not reported

commonly used treatment strategies for BCCF currently. Thus far, endocrine therapy such as tamoxifen or gonadotropin-releasing hormone analogues, has not shown significant effectiveness in the treatment of BCCF (10). Surgery has generally been proven to be effective in treating BCCF'; though there are many cases in which patient develop multiple metastases shortly after surgery (11). There are also other cases reported in which BCCF patients have a disease-free survival of 1 year or more after undergoing surgical resection (2, 12). Chemotherapy is often used as an adjuvant therapy to surgical resection with variable success. Standard breast cancer regimens seem to be relatively ineffective and regimens targeting the choriocarcinoma component (1), as in our case, may be more effective (see Table 1). Interestingly, capecitabine has also been described in at least one case report as an effective regimen in a case of refractory BCCF (10); and while not a standard regimen for choriocarcinoma it has been used as a salvage regimen in gestational trophoblastic neoplasia previously with success. In our case, we used salvage chemotherapy against choriocarcinoma (paclitaxel, cisplatin and etoposide) with marked clinical and biomarker success including normalization of the hCG after four months of treatment. After recurrent brain metastases were diagnosed, high dose chemotherapy with methotrexate was used as treatment and she currently has no evidence of disease over 5 years after receiving her final cycle of the chemotherapy. This is the first case to show the potential effectiveness of methotrexate in treating metastases to the brain from breast cancer with choriocarcinomatous features.

In summary, hCG when elevated, is a reliable tumor marker for disease monitoring in BCCF patients and DNA typing is a reliable confirmatory test for the diagnosis of BCCF versus metastatic choriocarcinoma. The successful treatment of our patient suggests therapies that target the metaplastic component of breast cancer, choriocarcinoma in our case, can be more effective than standard breast cancer regimens and should be considered early in the course of therapy in nonresponsive patients.

Data availability statement

The datasets presented in this article are not readily available because All PHI has been excluded in the article. Requests to access the datasets should be directed to KM, krisha.mehta@stonybrookmedicine.edu.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Saigo PE, Rosen PP. Mammary carcinoma with "choriocarcinomatous" features. *Am J Surg Pathol* (1981) 5(8):773–8. doi: 10.1097/00000478-198112000-00006

2. Erhan Y, Ozdemir N, Zekioglu O, Nart D, Ciris M. Breast carcinomas with choriocarcinomatous features: case reports and review of the literature. *Breast J* (2002) 8(4):244–8. doi: 10.1046/j.1524-4741.2002.08411.x

3. Resetkova E, Sahin A, Ayala AG, Sneige N. Breast carcinoma with choriocarcinomatous features. *Ann Diagn Pathol* (2004) 8:74–9. doi: 10.1053/j.anndiagpath.2004.01.003

4. Mohammadi A, Rosa M. Carcinoma of the breast with choriocarcinomatous features. *Arch Pathol Lab Med* (2011) 135(9):1097–100. doi: 10.5858/2010-0334-RSR1.1

5. Siddiqui NH, Cabay RJ, Salem F. Fine-needle aspiration biopsy of a case of breast carcinoma with choriocarcinomatous features. *Diagn Cytopathol* (2006) 34:694–7. doi: 10.1002/dc.20485

6. Oguz A, Dizdar O, Altundag O, Kucukoztas N, Rahatli S. Breast carcinoma with choriocarcinomatous differentiation: A rare case. *EJCRIM* (2014) 1. doi: 10.12890/2014_000017

7. Murata T, Ihara S, Nakayama T, Nakagawa SI, Higashiguchi T, Imai T, et al. Breast cancer with choriocarcinomatous features: A case report with cytopathologic details. *Pathol Int* (1999) 49:816–9. doi: 10.1046/j.1440-1827.1999.00940.x

8. Sung HJ, Maeng YI, Kim MK, Lee SJ, Kang SM, Bong JG, et al. Breast carcinoma with choriocarcinomatous features: a case report. *J Breast Cancer* (2013) 16(3):349–53. doi: 10.4048/jbc.2013.16.3.349

9. Buza N, Hui P. Genotyping diagnosis of gestational trophoblastic disease: Frontiers in precision medicine. *Mod Pathol* (2021) 34:1658–72. doi: 10.1038/s41379-021-00831-9

10. Zhu Y, Liu M, Li J, Jing F, Linghu R, Guo X, et al. Breast carcinoma with choriocarcinomatous features: A case report and review of the literature. *World J Surg Oncol* (2014) 12:239. doi: 10.1186/1477-7819-12-239

11. Fowler CA, Nicholson S, Lott M, Barley V. Choriocarcinoma presenting as a breast lump. *Eur J Surg Oncol* (1995) 21:576–8. doi: 10.1016/S0748-7983(95)97675-2

12. Akbulut M, Zekioglu O, Ozdemir N, Kapkac M. Fine needle aspiration cytology of mammary carcinoma with choriocarcinomatous features: a report of 2 cases. *Acta Cytol* (2008) 52:99–104. doi: 10.1159/000325443

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 23 January 2023
DOI 10.3389/fonc.2022.1013653

OPEN ACCESS

EDITED BY
Yusuf Tutar,
University of Health Sciences, Turkey

REVIEWED BY
Tanuja Shet,
Tata Memorial Hospital, India
Thomas Efferth,
Johannes Gutenberg University Mainz, Germany

*CORRESPONDENCE
Jiayi Wu
pinkscorpio@163.com
Xiaochun Fei
xcf0222@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 07 August 2022
ACCEPTED 12 December 2022
PUBLISHED 23 January 2023

CITATION
Zhu S, Wang H, Lin L, Fei X and Wu J (2023) Primary breast osteosarcoma in a patient previously treated for ipsilateral invasive ductal carcinoma: An unusual case report with clinical and genomic features.
Front. Oncol. 12:1013653.
doi: 10.3389/fonc.2022.1013653

Primary breast osteosarcoma in a patient previously treated for ipsilateral invasive ductal carcinoma: An unusual case report with clinical and genomic features

Siji Zhu[1†], Haoyu Wang[1†], Lin Lin[2], Xiaochun Fei[3*] and Jiayi Wu[1*]

[1]Department of General Surgery, Comprehensive Breast Health Center, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]Department of Clinical Laboratory, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3]Department of Pathology, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Primary breast osteosarcoma is a rare subtype of breast malignancy with limited clinical evidence, inadequate biological understanding, and unmet treatment consensus. Here, we report an unusual case of primary breast osteosarcoma developing in the same quadrant of the breast 2 years after initial dissection and radiation of invasive ductal carcinoma. Thorough evaluations of imaging and pathology were conducted while genomic alterations of both primary and secondary tumors, as well as peripheral blood samples, were explored through the next-generation sequencing technique. A comprehensive review of the current literature was also performed on this rare malignancy.

KEYWORDS

breast malignancy, extraskeletal osteosarcoma, primary breast osteosarcoma, genomic profile, molecular therapy

Introduction

Primary breast osteosarcoma (PBOS) is an extremely rare subtype of breast sarcoma, with published data being limited to case reports and small series (1). Given the rarity of this tumor and divergence concerning its histogenesis, diagnosis, treatment, and prognosis, there is no common consensus regarding the management of this specific kind of malignancy. Therefore, reporting each case and its challenges could be helpful to

expand the available knowledge base in the hopes of eventually improving patient care. Here, we report the case of a patient who developed a primary osteogenic sarcoma of the breast 2 years after being treated by surgery and radiation for invasive carcinoma of the ipsilateral breast. Genomic sequencing was conducted to further explore the molecular characteristics of this unusual malignancy.

Case description

Patient history and presentation

A 42-year-old woman presented with a 3-week history of a painless, mobile, firm, 2.5-cm lump in the lower outer quadrant of the left breast without axillary lymphadenopathy. No evidence of nipple retraction or discharge was observed. The physical exam of the contralateral breast was unremarkable.

She was already known, having been treated 2 years previously for a left invasive ductal carcinoma (lower outer quadrant, triple negative, grade 3, and Ki-67 70%) without nodal involvement (pT1bN0M0, stage IA). At that time, she underwent lumpectomy and sentinel lymph node biopsy followed by anthracycline/taxane-based adjuvant chemotherapy and radiotherapy (40 Gy in 15 fractions prescribed to ipsilateral whole breast with a 10-Gy boost in four fractions to the tumor bed).

At first, the new symptomatic swelling presenting in the same quadrant 2 years after primary treatment was highly suspicious of local recurrence. The mammography and ultrasonography revealed an irregular, bulky mass with a lobulated border in the lateral part of the left breast (Figures 1A–C). On MRI, there was a 3-cm mass in the lateral part of the left breast with a high signal intensity at the periphery of the tumor (Figure 1D). The diagnosis and treatment timeline are demonstrated in Supplementary Figure S1.

Pathological evaluation and diagnoses

The initial core needle biopsy suggested a spindle-cell malignant tumor with osteoid matrix and necrosis, and therefore, an excisional biopsy was then performed. On gross examination, the specimen was 50 mm × 40 mm × 30 mm and contained a medium-to-firm texture nodular lesion measuring 20 mm in maximum dimension and surrounded by fibro-fatty tissue.

Microscopically, the lesion was composed of abundant pleomorphic, spindle, and oval cells with infiltrative growth

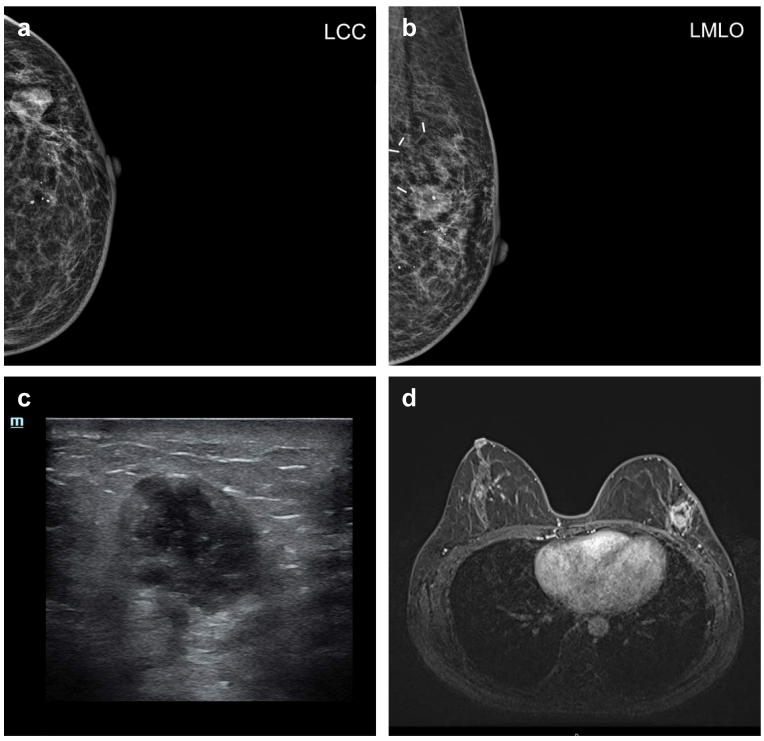


FIGURE 1
Radiology. **(A)** Left craniocaudal (LCC) view and **(B)** left mediolateral oblique (LMLO) view of mammography. **(C)** Representative ultrasound imaging of a breast lesion. **(D)** Representative MRI imaging of a breast lesion.

patterns. The tumor cells revealed eosinophilic cytoplasm, prominent nucleoli, and a high mitotic index. Osteoid matrix and necrosis were frequently seen at the periphery of the tumor (Figures 2A–C). No evidence of infiltrating ductal carcinoma or ductal carcinoma *in situ* was observed. The following immunohistochemistry (IHC) results were obtained: Cytokeratin AE1/AE3 (AE1/AE3) (−), cluster of differentiation 56 (CD56) (focal+), special AT-rich sequence-binding protein (SATB) (+), murine double minute2 (MDM2) (+), smooth muscle actin (SMA) (partial+), Ki-67 (80%), cytokeratin 7 (CK7) (−), estrogen receptor (ER) (−), progesterone receptor (PR) (−), human epidermal growth factor receptor 2 (Her2) (0), cluster of differentiation 34 (CD34) (−), and S-100 (−) (Figures 2D, E). The negativity of AE1/AE3, an epithelial marker, reconfirmed the lack of an epithelial component. On the other hand, SATB was proven to be involved in the process of osteoblastic differentiation, which also authenticated our pathological prognosis as PBOS (2).

Genomic panel

To validate the pathological diagnosis of PBOS and explore the molecular connections between the PBOS and the previous invasive ductal carcinoma (IDC), a commercially targeted NGS was performed on both primary and secondary tumor slices for somatic mutations and peripheral blood samples for germline gene variants. A total of 421 gene variants related to target therapy, immune therapy, chemotherapy response, and genetic predisposition among breast cancer patients were included in the genomic panel. No germline variations were found for this patient. Several copy number variant (CNV) events were identified in the PBOS sample, including CN gains of *FGFR1* and CN loss of *CDKN2A* and *TSC2*. Regarding somatic mutations, *PIK3CA* p.H1047R, *PTEN* p.V275G, *TP53* p.T81Nfs*64, and *TSC2* p.C728Lfs*34 were detected, with the highest variant allele frequency (VAF) of 59.22% happening in the *PIK3CA* mutation. Interestingly, somatic *PIK3CA* p.H1047R, *PTEN* p.V275G, and *TP53* p.T81Nfs*64 were repeatedly detected in both PBOS and IDC tumor samples. On the other hand, somatic *EGFR* p.E709K was uniquely found in the IDC sample.

A written and signed informed consent was obtained from the patients and presented as supplementary material.

Medical management

A CT of the chest, abdomen, and pelvis did not identify any metastases. An 18F-FDG PET/CT scanning was undertaken, and no evidence of a distant lesion or primary osteosarcoma arising from bone was detected, indicating that the breast lesion was primary osteosarcoma.

As per our institute routine, the patient was discussed in a multidisciplinary team (MDT), and a skin-sparing mastectomy followed by immediate breast reconstruction with a deep inferior epigastric perforator (DIEP) flap was achieved for her. According to the MDT's opinion, axillary lymph node sampling was not performed. No residual lesion was identified histologically. No adjuvant treatment was recommended. The patient is under regular follow-up right now. The latest follow-up was done on 25 November 2022, and the patient is still alive.

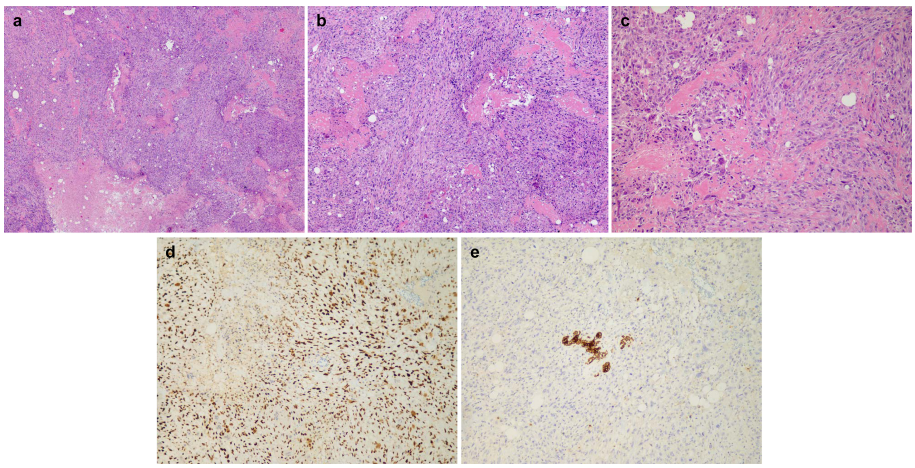


FIGURE 2
Histology: **(A)** ×25 magnification, **(B)** ×50 magnification, and **(C)** ×100 magnification of H&E staining for representative osteoid matrix and necrosis. **(D)** Immunohistochemistry (IHC) staining of SATB in representative tumor areas. **(E)** IHC staining of AE1/3 in representative tumor areas.

Discussion

Epidemiology

Primary breast sarcomas comprise only 0.0006%–1% of all breast malignancies, and PBOS is far less common, accounting for approximately 4%–12.5% of primary breast sarcomas (1, 3). To our knowledge, only approximately 150 cases have been published in the literature (4). Additionally, a study from Nottingham University showed that the vast majority of reported PBOS were actually some variants of metaplastic breast carcinoma due to the lack of a comprehensive histological and IHC evaluation (5).

Clinical presentation

There is a wide range of onset ages of PBOS in the literature, ranging from range from 16 to 96 years old (6, 7). Meanwhile, in contrast to skeletal osteosarcomas, which tend to present at a younger age, three relatively large series published in the 1990s from MD Anderson, Mayo Clinic, and Armed Forces Institute of Pathology in Washington, DC, reported the same major age span of 40–60 years (1, 3, 8).

PBOS typically presents as a hard, painless, palpable mass with no attendant evidence of nipple discharge or retraction, nor axillary lymphadenopathy (1, 9). Similar to malignant phyllodes tumors, PBOS exhibits rapid growth, which may account for the large average size (4.6 cm) at presentation (10).

Predisposing factors

A prior history of burns, trauma, or even a foreign body has been reported in some cases of PBOS (1, 6). In addition, some cases presented with a history of epithelial breast cancer on the same side or contralateral side (11, 12). Of note, some patients have been reported to have developed PBOS after undergoing radiotherapy (13, 14). It has been reported in previous literatures that the interval of developing radiotherapy-induced sarcoma (RIS) was more than 10 years (15, 16). In this case, the patient developed PBOS after having surgery and radiotherapy for breast cancer, with a relatively shorter latency period of only 2 years. On the other hand, chemotherapy may also contribute to the newly developed sarcoma. In a retrospective cohort study from the SEER database, it was found that alkylating agents were associated with a higher risk of developing sarcomas with a RR of 7.7 (17). Additionally, another cohort study found that chemotherapy shortened the median interval of RIS development from 14 to 8 years compared with chemotherapy-free patients. Strikingly, alkylating agents and anthracyclines, which generate DNA double-strand breaks, have been reported to significantly shorten the latency of radiotherapy-induced sarcomas (18). The history of ipsilateral breast cancer, the trauma of previous surgery, radiation exposure, and chemotherapy agents may all be the risk factors for developing PBOS. However, there was no conclusive evidence of the driving carcinogenesis factors. Hence, the tumor could be described as "postradiation" rather than "radiation-associated."

Imaging and pathological diagnostic workup

The workup of the diagnosis for PBOS included imaging evaluation and pathological diagnosis. For a breast lump, mammography and ultrasound were most commonly used. However, the mammographic and ultrasonic findings of PBOS would present similarly to benign lesions such as fibroadenoma, which may lead to misdiagnosis (19). Furthermore, before labeling them as a PBOS, other neighbors' origins such as underlying ribs, sternum, and even the pectoralis muscle, as well as metastatic osteosarcoma from the bone, must be ruled out. Hence, in the case of evidence for PBOS on a core needle biopsy, in addition to the routine workup for breast cancer, some other evaluations, such as CT, MRI, skeletal scintigraphy, or PET/CT, may be included. Dynamic contrast-enhanced MRI could be used for additional evaluation and information (20). CT and PET/CT can be useful to identify distant metastases while also playing important roles in ruling out primary skeletal osteosarcomas together with skeletal scintigraphy (9, 21).

Concerning pathological diagnosis, the utility of core needle biopsy in the preoperative workup of patients with PBOS has been described in some literatures (22–24). However, as a case reported in 2019 described, a core needle biopsy from a calcified breast lesion was initially misdiagnosed as benign metaplastic ossification, and only after lumpectomy was the breast osteosarcoma identified, demonstrating the importance of excision sampling (25). Numerous tumors of the breast-producing cartilage, osteoid, and bone, such as metaplastic carcinoma and malignant phyllodes tumors with osteosarcomatous differentiation, should be taken into consideration in differential diagnoses (5, 6, 24). In this case, given the history of ipsilateral breast cancer, it was essential to identify whether it was an ipsilateral carcinoma recurrence. The absence of epithelial cells on extensive immunohistochemistry could rule out the diagnosis of metaplastic carcinoma and, logically, the local recurrence of previous breast cancer. Therefore, given the complexity of PBOS, confirmation of a consistent morphologic pattern required sampling of the whole lesion and extensive sectioning.

Treatment

Due to the rarity of breast osteosarcomas, there is no general and comprehensive consensus on the management of PBOS. As

the literatures reported, PBOS tends to be similar to sarcomas arising at other locations, presenting local aggression with blood spread rather than lymphatic spread (1, 23). Achieving a negative margin either with wide local excision or a simple mastectomy without axillary assessment is likely to be the most judicious option for the majority of patients (4, 10, 26, 27). Of note, the pathological diagnosis before definite surgery was quite important to guide axillary management.

Aside from surgical principles, the benefits of chemotherapy and radiation for PBOS have also been discussed in many literatures (8, 19, 28–30). Based on limited published works, the role of chemotherapy is uncertain with differing regimens and outcomes, and radiotherapy does not appear to improve outcomes. However, due to the unfavorable prognosis reported, chemotherapy and chest wall irradiation have been suggested by some authors to reduce the risk of recurrence, particularly for patients with a tumor size of more than 5 cm (28, 29, 31).

In our opinion, an appropriate approach, including surgery and administration of chemotherapy or radiotherapy, must be balanced against the consequences of these treatments on a case-by-case basis. In this case, taking the relatively young age (42 years old), small tumor size (2 cm), history of breast cancer with chemo/radiotherapy, and patient's opinion into consideration, the multidisciplinary team finally suggested the radical surgery as mastectomy followed by immediate breast reconstruction, without axillary assessment or adjuvant therapy.

Genomic information and histogenesis exploration

Despite a comprehensive understanding of the genomic landscapes of both breast cancer and osteosarcoma (32), little is known about the genomic features and histological origins of PBOS due to its extremely rare morbidity. According to previous literatures, extraskeletal osteosarcoma (ESOSA) generally shared similarities in pathological and molecular characteristics with conventional adolescent osteosarcoma (33). In our case, a frameshift mutation of *TP53* (p.T81Nfs*64) indicated a total loss of function; a missense mutation of another tumor suppressor, *PTEN*, was also detected. Both of these mutations were typical genomic alteration events in conventional osteosarcoma, accounting for 80% and 44% of the cases, respectively (34). Moreover, CNV events including *FGFR1* gain and *CDKN2A* loss were commonly identified in osteosarcoma, as previously reported, proving the pathological diagnosis of PBOS from a molecular aspect. Nevertheless, despite considerable alterations in phosphatidylinositol 3-kinase/mammalian target of the rapamycin (PI3K/mTOR) pathway (35), variants including *PIK3CA* mutation, *TSC2* mutation, and *TSC2* loss were extremely rare in conventional osteosarcoma (34). For example, the *PIK3CA* mutation was found in approximately 3% of sarcomas according to TCGA database (36) and was barely been reported until its first discovery in 2012 (35, 37). Interestingly, it has been reported that ESOSA may display unique genomic alterations compared with conventional osteosarcomas, especially with more mutations in *PIK3CA* and PI3K/mTOR pathways (33). Moreover, a patient-derived cell line of PBOS was recently established and validated by NGS genomic testing. A somatic mutation of *PIK3CA* p.H1047R was also detected, indicating that ESOSA, especially PBOS, may harbor actionable genomic alterations in *PIK3CA* and PI3K/mTOR pathways (38).

To investigate the potential histogenesis and evolution of our case, the genomic profiles were also compared between the PBOS and initial IDC samples. Notably, despite distinctive histopathological features, somatic *PIK3CA* p.H1047R, *PTEN* p.V275G, and *TP53* p.T81Nfs*64 were repeatedly detected in both PBOS and IDC tumor samples. The high genomic similarity made us wonder whether these two chronological malignancies had the same origins in tumorigenesis. Shared mutations may indicate a predominant clone, which could be identified as a common ancestor, or cancer stem cells (CSCs), during early tumor formation. Multipotent CSCs could then differentiate into multiple cell lineages and passively accumulate branch mutations under external pressures such as radiation and trauma (39). Several studies have delivered evidence or opinions supportive of our hypothesis (5, 40, 41). It has been reported through an animal experiment that canine mammary osteosarcomas could originate from a pluripotent mammary stem cell (40). Literature reviews and case reports also offered evidence that PBOS may be epithelial in origin and underwent an ossifying evolution process (5, 41). Still, current evidence is not valid enough to elucidate the histogenesis of PBOS.

On the other hand, could the newly diagnosed PBOS be a metaplastic recurrence of primary Triple-negative breast cancer (TNBC)? To explore this question, the genomic documents of PBOS were compared to those of metastatic TNBC in previous literatures. Although breast cancer could develop new genomic alterations during metastatic progression, several studies have found that recurrent TNBC shared similar genomic profiles compared with matched primary TNBC (42, 43). *TP53* mutation was mostly detected (~80%) in both primary and metastatic TNBC, while *PTEN* mutation occurred in 8% of advanced TNBC, which were both detected in our case. Thus, it is really hard to differentiate PBOS from a TNBC recurrence. Nevertheless, when we look at the intrinsic subtype of TNBC defined by Lehmann et al., it is shown that *PIK3CA*, *PTEN*, and PI3K/mTOR pathways are mostly altered in the mesenchymal-like subtype. TNBC with mesenchymal-like features had genomic similarity with metaplastic breast cancers, which harbored lineage plasticity, including cartilaginous differentiation (44). Taken together, the genomic profile of paired tumors may indicate that the PBOS originated from the primary IDC and progressed from metaplastic components; however, more solid evidence is required.

Finally, genomic alterations may provide additional clues for treatment options. Although several databases (45) and scales (46) based on molecular targets have recently been released to guide target therapies for malignancies, evidence for rare tumors is lacking due to the rarity of morbidity. Still, case reports have shown that for rare tumors with actionable molecular alterations, targeted treatment would deliver clinical benefits (47, 48). Back to this case, both *PTEN* p.V275G and *TP53* p.T81Nfs*64 were classified as having uncertain clinical relevance according to previous literatures, and there are currently no approved drugs targeting *PTEN* or *TP53* mutations, with only preclinical attempts. *TSC2* mutation, which could contribute to the activation of the PI3K pathway, may be targeted by mTOR inhibitor everolimus in noncancerous diseases such as tuberous sclerosis (49, 50). On the other hand, somatic *PIK3CA* p.H1047R has become a targetable alteration for advanced breast cancer patients since the successful clinical trial of SOLAR-1 and the final approval of alpelisib (51). Thus, the *PIK3CA* mutation detected in our patient may indicate potential sensitivity to alpelisib. Nevertheless, it has also been reported that fulvestrant failed to deliver antiproliferative effects on a patient-derived PBOS cell line harboring a *PIK3CA* mutation (38). Furthermore, a patient-derive xenograft (PDX) model of PBOS has lately been reported, which offered an *in vivo* platform for the investigation of genome-informed treatment strategies (52). Hence, to further confirm the efficacy of anti-*PIK3CA* antigens for PBOS, preclinical models may provide more information.

Conclusion

Primary breast osteosarcoma is a rare malignant tumor with divergence regarding its histogenesis, diagnosis, and management. In addition, as our case presented, a history of ipsilateral breast carcinoma could make the dilemma even worse. A thorough imaging review and meticulous pathological evaluation would be helpful to find the best plan of treatment. Moreover, complementary genomic approaches would also help us better understand its intrinsic features, even giving the opportunity for genome-informed targeted therapy for PBOS. Given the limited available data to guide management, further clinical and translational research is needed to optimize the treatment of this aggressive disease. Meanwhile, reporting each case and publishing them would be beneficial in gathering more information and offering collective efforts for finally managing this rare malignancy.

Data availability statement

Data presented in this paper are available upon request.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SZ and JW were responsible for case management. SZ, JW, and HW contributed to the case review. XF conducted the pathological review. LL performed the targeted gene panel test. HW was responsible for the genomic evaluation. SZ and HW were the principal writers of the manuscript. JW and XF reviewed and provided valuable insight in the preparation of the paper. All authors contributed to the article and approved the submitted version.

Funding

SZ was funded by a scientific research project of the Shanghai Municipal Health Commission (20194Y0419).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1013653/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Timeline. Diagnosis and treatment timeline of this case.

References

1. Silver SA, Tavassoli FA. Primary osteogenic sarcoma of the breast: A clinicopathologic analysis of 50 cases. *Am J Surg Pathol* (1998) 22(8):925–33. doi: 10.1097/00000478-199808000-00002

2. Bartlett H, Elghobashy M, Deshmukh N, Rao R, Shaaban AM. Radiation-associated primary osteosarcoma of the breast. *Pathobiology* (2020) 87(5):322–6. doi: 10.1159/000509580

3. Adem C, Reynolds C, Ingle JN, Nascimento AG. Primary breast sarcoma: Clinicopathologic series from the Mayo clinic and review of the literature. *Br J Cancer* (2004) 91(2):237–41. doi: 10.1038/sj.bjc.6601920

4. Yoon CS, Kang SS. Primary osteosarcoma of the breast: A case report. *Ann Surg Treat Res* (2017) 93(1):57–60. doi: 10.4174/astr.2017.93.1.57

5. Rakha EA, Tan PH, Shaaban A, Tse GM, Esteller FC, van Deurzen CHM, et al. Do primary mammary osteosarcoma and chondrosarcoma exist? a review of a large multi-institutional series of malignant matrix-producing breast tumours. *Breast* (2013) 22(1):13–8. doi: 10.1016/j.breast.2012.09.010

6. Bahrami A, Resetkova E, Ro JY, Ibañez JD, Ayala AG. Primary osteosarcoma of the breast: Report of 2 cases. *Arch Pathol Lab Med* (2007) 131(5):792–5. doi: 10.5858/2007-131-792-POOTBR

7. Yahaya JJ, Odida M. Primary osteosarcoma of the breast with extensive chondroid matrix in a teenager female patient: The paradoxical diagnosis in breast mastopathy. *Int Med Case Rep J* (2020) 13:11–7. doi: 10.2147/IMCRJ.S233674

8. Barrow BJ, Janjan NA, Gutman H, Benjamin RS, Allen P, Romsdahl MM, et al. Role of radiotherapy in sarcoma of the breast–a retrospective review of the M.D. *Anderson experience Radiother Oncol* (1999) 52(2):173–8. doi: 10.1016/S0167-8140(99)00070-5

9. Mujtaba B, Nassar SM, Aslam R, Garg N, Madewell JE, Taher A, et al. Primary osteosarcoma of the breast: Pathophysiology and imaging review. *Curr Probl Diagn Radiol* (2020) 49(2):116–23. doi: 10.1067/j.cpradiol.2019.01.001

10. Murakami S, Isozaki H, Shou T, Sakai K, Yamamoto Y, Oomori M, et al. Primary osteosarcoma of the breast. *Pathol Int* (2009) 59(2):111–5. doi: 10.1111/j.1440-1827.2008.02338.x

11. Milne DM, Sookar N, Umakanthan S, Rampersad F, Olivier L, Ali J. Primary osteosarcoma of the breast in a patient treated previously for invasive ductal carcinoma: An unusual presentation of a very rare primary breast malignancy. *Case Rep Surg* (2020) 2020:1594127. doi: 10.1155/2020/1594127

12. Yadav BS, Bansal A, Sharma SC, Javid SH, Anderson BO, Vaklavas C, et al. A 62-year-old woman with osteogenic sarcoma in the contralateral breast 15 years after treatment for breast cancer. *Semin Oncol* (2013) 40(2):135–44. doi: 10.1053/j.seminoncol.2013.01.010

13. Meunier B, Levêque J, Le Prisé E, Kerbrat P, Grall JY. Three cases of sarcoma occurring after radiation therapy of breast cancers. *Eur J Obstet Gynecol Reprod Biol* (1994) 57(1):33–6. doi: 10.1016/0028-2243(94)90107-4

14. Alpert LI, Abaci IF, Werthamer S. Radiation-induced extraskeletal osteosarcoma. *Cancer* (1973) 31(6):1359–63. doi: 10.1002/1097-0142(197306)31:6<1359::AID-CNCR2820310609>3.0.CO;2-F

15. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CDM, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: An analysis of 26,758 cases. *Int J Cancer* (2006) 119(12):2922–30. doi: 10.1002/ijc.22239

16. Rouhani P, Fletcher CDM, Devesa SS, Toro JR. Cutaneous soft tissue sarcoma incidence patterns in the U.S. : an analysis of 12,114 cases. *Cancer* (2008) 113(3):616–27. doi: 10.1002/cncr.23571

17. Veiga LHS, Vo JB, Curtis RE, Mille MM, Lee C, Ramin C, et al. Treatment-related thoracic soft tissue sarcomas in US breast cancer survivors: A retrospective cohort study. *Lancet Oncol* (2022) 23(11):1451–64. doi: 10.1016/S1470-2045(22)00561-7

18. Zhang AY, Judson I, Benson C, Wunder JS, Ray-Coquard I, Grimer RJ, et al. Chemotherapy with radiotherapy influences time-to-development of radiation-induced sarcomas: A multicenter study. *Br J Cancer* (2017) 117(3):326–31. doi: 10.1038/bjc.2017.198

19. Bennett DL, Merenda G, Schnepp S, Lowdermilk MC. Primary breast osteosarcoma mimicking calcified fibroadenoma on screening digital breast tomosynthesis mammogram. *Radiol Case Rep* (2017) 12(4):648–52. doi: 10.1016/j.radcr.2017.06.008

20. Ho JS, Rahmat K, Alli K, Wong KT, Yip CH. Primary breast osteosarcoma: Dynamic contrast-enhanced magnetic resonance imaging, proton spectroscopy and diffusion weighted imaging findings. *Ann Acad Med Singap* (2012) 41(10):473–5. doi: 10.47102/annals-acadmedsg.V41N10p473

21. Yang J-G, Li C-L, Hao R-R, Zou L-F. Primary osteogenic sarcoma of breast detected on Tc-99m MIBI scintigraphy and Tc-99m MDP skeletal scintigraphy. *Ann Nucl Med* (2008) 22(1):79–82. doi: 10.1007/s12149-007-0074-3

22. Trihia H, Valavanis C, Markidou S, Condylis D, Poulianou E, Arapantoni-Dadioti P. Primary osteogenic sarcoma of the breast: cytomorphologic study of 3 cases with histologic correlation. *Acta Cytol* (2007) 51(3):443–50. doi: 10.1159/000325764

23. Ogundiran TO, Ademola SA, Oluwatosin OM, Akang EE, Adebamowo CA. Primary osteogenic sarcoma of the breast. *World J Surg Oncol* (2006) 4:90. doi: 10.1186/1477-7819-4-90

24. Roll GR, Lee AY, Royaie K, Visser B, Hanks DK, Knudson MM, et al. Acquired a amyloidosis from injection drug use presenting with atraumatic splenic rupture in a hospitalized patient: A case report. *J Med Case Rep* (2011) 5:29. doi: 10.1186/1752-1947-5-29

25. Dekkers IA, Cleven A, Lamb HJ, Kroon HM. Primary osteosarcoma of the breast. *Radiographics* (2019) 39(3):626–9. doi: 10.1148/rg.2019180181

26. Tsubochi H, Sato N, Kaimori M, Imai T. Osteosarcomatous differentiation in lung metastases from a malignant phyllodes tumour of the breast. *J Clin Pathol* (2004) 57(4):432–4. doi: 10.1136/jcp.2003.012336

27. Dragoumis D, Bimpa K, Assimaki A, Tsiftsoglou A. Primary osteogenic sarcoma of the breast. *Singapore Med J* (2008) 49(11):e315–e7. Available at: https://pubmed.ncbi.nlm.nih.gov/19037539/.

28. Kallianpur AA, Gupta R, Muduly DK, Kapali A, Subbarao KC. Osteosarcoma of breast: A rare case of extraskeletal osteosarcoma. *J Cancer Res Ther* (2013) 9(2):292–4. doi: 10.4103/0973-1482.113392

29. Conde DM, Morais LC, Pacheco CF, Ferreira RB, Sousa-e-Silva ÉPd, Nunes AR, et al. Primary osteosarcoma of the breast: Pathological and imaging findings. *Rev Assoc Med Bras (1992)* (2015) 61(6):497–9. doi: 10.1590/1806-9282.61.06.497

30. Szajewski M, Kruszewski WJ, Ciesielski M, Smiałek-Kusowska U, Czerepko M, Szefel J. Primary osteosarcoma of the breast: A case report. *Oncol Lett* (2014) 7(6):1962–4. doi: 10.3892/ol.2014.1981

31. Marinova L, Hadjieva T, Kanchev E, Vicheva S. Synchronous primary mammary osteosarcoma and invasive breast cancer. a case report - pathohistological and immunohistochemical analysis. *Rep Pract Oncol Radiother* (2015) 20(1):72–6. doi: 10.1016/j.rpor.2014.04.003

32. Eugenie S, Kleinerman RG eds. *Current advances in the science of osterosarcoma*. Springer (2020) 1–33.

33. Jour G, Wang L, Middha S, Zehir A, Chen W, Sadowska J, et al. The molecular landscape of extraskeletal osteosarcoma: A clinicopathological and molecular biomarker study. *J Pathol Clin Res* (2016) 2(1):9–20. doi: 10.1002/cjp2.29

34. Kansara M, Teng MW, Smyth MJ, Thomas DM. Translational biology of osteosarcoma. *Nat Rev Cancer* (2014) 14(11):722–35. doi: 10.1038/nrc3838

35. Perry JA, Kiezun A, Tonzi P, Van Allen EM, Carter SL, Baca SC, et al. Complementary genomic approaches highlight the PI3K/mTOR pathway as a common vulnerability in osteosarcoma. *Proc Natl Acad Sci U S A* (2014) 111(51):E5564–E73. doi: 10.1073/pnas.1419260111

36. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. *Cancer Discovery* (2012) 2(5):401–4. doi: 10.1158/2159-8290.CD-12-0095

37. Choy E, Hornicek F, MacConaill L, Harmon D, Tariq Z, Garraway L, et al. High-throughput genotyping in osteosarcoma identifies multiple mutations in phosphoinositide-3-kinase and other oncogenes. *Cancer* (2012) 118(11):2905–14. doi: 10.1002/cncr.26617

38. Kito F, Oyama R, Noguchi R, Hattori E, Sakumoto M, Endo M, et al. Establishment and characterization of novel patient-derived extraskeletal osteosarcoma cell line NCC-ESOS1-C1. *Hum Cell* (2020) 33(1):283–90. doi: 10.1007/s13577-019-00291-z

39. Nassar D, Blanpain C. Cancer stem cells: Basic concepts and therapeutic implications. *Annu Rev Pathol* (2016) 11:47–76. doi: 10.1146/annurev-pathol-012615-044438

40. Hellmén E, Moller M, Blankenstein MA, Andersson L, Westermark B. Expression of different phenotypes in cell lines from canine mammary spindle-cell tumours and osteosarcomas indicating a pluripotent mammary stem cell origin. *Breast Cancer Res Treat* (2000) 61(3):197–210. doi: 10.1023/A:1006410020384

41. Guo W, Cao Y, Teng G, Liu J, Su J. Evolution and prognosis of breast osteosarcoma: A case report. *Oncol Lett* (2016) 11(1):789–91. doi: 10.3892/ol.2015.3921

42. Bertucci F, Ng CKY, Patsouris A, Droin N, Piscuoglio S, Carbuccia N, et al. Genomic characterization of metastatic breast cancers. *Nature* (2019) 569(7757):560–4. doi: 10.1038/s41586-019-1056-z

43. Aftimos P, Oliveira M, Irrthum A, Fumagalli D, Sotiriou C, Gal-Yam EN, et al. Genomic and transcriptomic analyses of breast cancer primaries and matched metastases in AURORA, the breast international group (BIG) molecular screening initiative. *Cancer Discovery* (2021) 11(11):2796–811. doi: 10.1158/2159-8290.CD-20-1647

44. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest* (2011) 121(7):2750–67. doi: 10.1172/JCI45014

45. Chakravarty D, Gao J, Phillips SM, Kundra R, Zhang H, Wang J, et al. OncoKB: A precision oncology knowledge base. *JCO Precis Oncol* (2017) 2017 (1):1–16. doi: 10.1200/PO.17.00011

46. Mosele F, Remon J, Mateo J, Westphalen CB, Barlesi F, Lolkema MP, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: A report from the ESMO precision medicine working group. *Ann Oncol* (2020) 31(11):1491–505. doi: 10.1016/j.annonc.2020.07.014

47. Gupta M, Sherrow C, Krone ME, Blais EM, Pishvaian MJ, Petricoin EF, et al. Targeting the NTRK fusion gene in pancreatic acinar cell carcinoma: A case report and review of the literature. *J Natl Compr Canc Netw* (2021) 19(1):10–5. doi: 10.6004/jnccn.2020.7641

48. Alwaqfi RR, Samuelson MI, Guseva NN, Ouyang M, Bossler AD, Ma D. PTCH1-GLI1 fusion-positive ovarian tumor: Report of a unique case with response to tyrosine kinase inhibitor pazopanib. *J Natl Compr Canc Netw* (2021) 19(9):998–1004. doi: 10.6004/jnccn.2021.7058

49. MacKeigan JP, Krueger DA. Differentiating the mTOR inhibitors everolimus and sirolimus in the treatment of tuberous sclerosis complex. *Neuro Oncol* (2015) 17(12):1550–9. doi: 10.1093/neuonc/nov152

50. Henske EP, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. *Nat Rev Dis Primers* (2016) 2:16035. doi: 10.1038/nrdp.2016.35

51. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for -mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med* (2019) 380(20):1929–40. doi: 10.1056/NEJMoa1813904

52. Wu NF, Wu J, Yamamoto J, Aoki Y, Hozumi C, Bouvet M, et al. The first mouse model of primary osteosarcoma of the breast. *In Vivo* (2021) 35(4):1979–83. doi: 10.21873/invivo.12466

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 25 January 2023
DOI 10.3389/fonc.2022.1070744

OPEN ACCESS

EDITED BY
Louis W.C. Chow,
Organisation for Oncology and Translational Research (OOTR)
Hong Kong SAR, China

REVIEWED BY
Stephanie M. McGregor,
University of Wisconsin-Madison, United States
Fan Chai,
Chongqing General Hospital, China

*CORRESPONDENCE
Amadora Li En Choo
amadora.choo@mohh.com.sg

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 15 October 2022
ACCEPTED 23 December 2022
PUBLISHED 25 January 2023

CITATION
Choo ALE, Sim LS-j, Sittampalam K, Tan WC, Tay AZE, Nadarajah R, Tan VKM and Sim Y (2023) Breast metastasis from endometrial clear cell carcinoma: A case report and review of the literature.
Front. Oncol. 12:1070744.
doi: 10.3389/fonc.2022.1070744

Breast metastasis from endometrial clear cell carcinoma: A case report and review of the literature

Amadora Li En Choo[1*], Llewellyn Shao-jen Sim[2], Kesavan Sittampalam[3], Wei Chong Tan[4], Amos Zhi En Tay[3], Ravichandran Nadarajah[5], Veronique Kiak Mien Tan[6,7,8] and Yirong Sim[6,7,8]

[1]Department of General Surgery, Singapore General Hospital, Singapore, Singapore, [2]Department of Diagnostic Radiology, Singapore General Hospital, Singapore, Singapore, [3]Department of Anatomical Pathology, Singapore General Hospital, Singapore, Singapore, [4]Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore, [5]Department of Obstetrics and Gynaecology, Singapore General Hospital, Singapore, Singapore, [6]Department of Breast Surgery, Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, Singapore, Singapore, [7]Department of Breast Surgery, Division of Surgery and Surgical Oncology, Singapore General Hospital, Singapore, Singapore, [8]SingHealth Duke-NUS Breast Centre, Singapore, Singapore

Metastasis to the breast from extra-mammary malignancies are rare, accounting for less than 1% of all breast cancers. Endometrial cancer, a common gynecological malignancy, often spreads to the pelvis, abdominal lymph nodes, peritoneum or the lungs. Endometrial metastasis to the breast is extremely rare, and while there have been isolated case reports of endometrial serous carcinoma with breast metastasis, it has not been reported in the case of clear cell carcinoma. We present a rare case of a 70 year old Chinese lady who had a metastatic endometrial clear cell carcinoma with metastasis to the breast, mimicking an inflammatory breast cancer clinically. We reviewed the current literature and describe the challenges in differentiating primary from metastatic breast lesions, as well as clinical, radiological and histopathological features that may help to differentiate the two. Tumour metastasis to the breast *via* lymphatic or hematogenous route can affect their radiological features: the former mimicking inflammatory breast cancer and the latter with features similar to benign breast lesions. Regardless, histological features with immunohistochemical staining is still the gold standard in diagnosing metastatic breast lesions and determining their tissue of origin. Breast metastases from extra-mammary malignancies are uncommon and it is even rarer for endometrial clear cell carcinoma to spread to the breast. Nonetheless, this case highlights the importance of keeping an open mind and engaging a multidisciplinary team for the care of complex patients.

KEYWORDS

breast cancer, endometrial cancer, endometrial clear cell carcinoma, metastasis, secondary breast cancer

Introduction

Metastasis to the breast from extra-mammary malignancies are rare, accounting for less than 1% of all breast cancers (1). The more common cancers that spread to the breast include melanomas and hematological malignancies such as leukemias and lymphomas (2). Others such as lung, ovarian, and gastric cancers have been reported (3–5) but are rare.

We present to you a rare case of metastatic spread of clear cell endometrial carcinoma to the breast. Endometrial cancer, most commonly affecting postmenopausal women in their sixth or seventh decade, may spread *via* direct local invasion or lymphatic or hematological route. Typical sites of metastasis include local pelvic recurrence, abdominal lymph nodes, peritoneum, or the lungs (6). Endometrial metastasis to the breast is extremely rare. It has been reported in the case of serous histology; however, to the best of our knowledge, endometrial clear cell carcinoma with breast metastasis has not been reported before.

Case report

A 70-year-old Chinese woman presented with postmenopausal bleeding and a left breast lump for a month. Examination revealed a 6-cm left retro-areolar mass with nipple retraction and skin erythema that resembles inflammatory breast cancer. An ultrasound pelvis showed a 7.0 × 4.9 × 5.4-cm ill-defined hypoechoic mass in the anterior wall of the uterus, and the endometrium was thickened at 8.7 mm.

Mammogram (Figure 1) found a vague asymmetric density in the left upper outer quadrant, corresponding to the palpable lump. The overlying skin was thickened with slight retraction of the left nipple. No spiculated mass, suspicious clustered microcalcifications, or architectural distortion was identified. An 8 × 8 mm partially circumscribed nodule was seen in the right axillary tail, corresponding to the intramammary lymph node seen on subsequent ultrasound. Abnormal lymph nodes were seen in both axillae, denser on the right.

Breast ultrasound revealed multiple vague and ill-defined heterogeneously hypoechoic lesions extending from the 11 to 3 o'clock positions of the left breast (Figures 2A–D). These hypoechoic lesions had irregular margins and were tubular in shape, suggesting an intraductal origin. The whole extent of these lesions measured approximately 61 × 15 × 53 mm (transverse and longitudinal planes) and 42 × 9 × 53 mm (radial and anti-radial planes). The breast stroma surrounding these lesions (and extending to the retroareolar region) appeared echogenic and stiff on elastography, suggesting desmoplasia. This probably accounted for the asymmetric density seen on

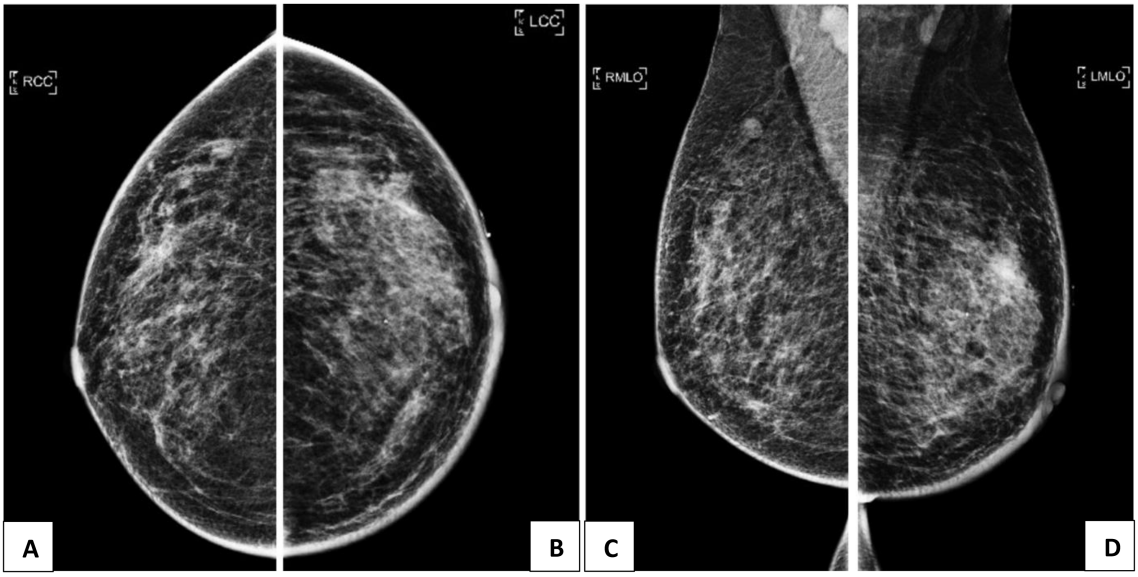


FIGURE 1
(A, C): Mammogram of the right breast showing an 8 x 8mm partly circumscribed nodule in the right axillary tail, corresponding to the intramammary lymph mode on ultrasound. Abnormal lymph nodes are also seen in bilateral axillae, denser on the right. **(B, D)**: Mammogram of the left breast showing a vague asymmetric density in the upper outer quadrant, corresponding to the palpable lump. The overlying skin is thickened with slight retraction of the nipple.

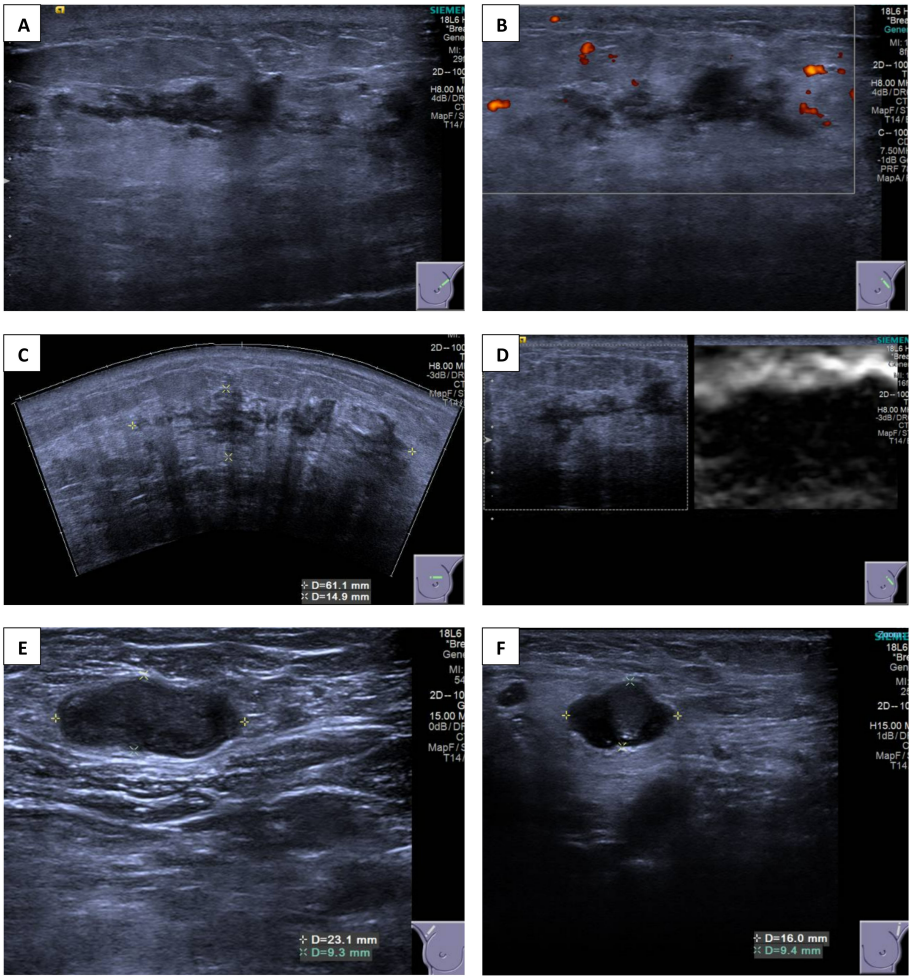


FIGURE 2
(A–D) Ultrasound images of the left breast showing multiple ill-defined heterogeneously hypoechoic lesions extending from the 11 o'clock to 3 o'clock position. **(E, F)** Ultrasound images of bilateral axilla showing abnormal axillary lymphadenopathy.

mammogram. Parenchymal edema and skin thickening were seen in the left breast. In addition, abnormal intramammary lymph nodes were present in the right breast upper outer quadrant, and there were also multiple abnormal lymph nodes in both axillae, compatible with metastasis (Figures 2E, F).

The patient underwent concurrent biopsies for both endometrial and breast lesions. She underwent a hysteroscopy, dilatation, and curettage, where the endometrium was found to be irregular and polypoidal with a large tumor that extended to the endocervix. As such, cervical biopsies were also performed to look for cervical involvement or synchronous cervical cancer. Histology from the endometrial curettage revealed high-grade carcinoma with clear cell features, and cervical biopsy revealed endometrial carcinoma.

As for the breast, she underwent ultrasound-guided core needle biopsies of the most prominent ill-defined lesion at the left breast 2 o'clock position and the largest abnormal right axillary lymph node. Interestingly, both the breast and endometrial lesions had significant morphologic resemblance on histology (Figure 3). Immunohistochemical staining of the left breast tumor and right axillary lymph node (Figures 4, 5) showed negative results for breast markers GATA-3 and mammaglobin but showed diffusely positive results for PAX8, which is frequently expressed in endometrial carcinoma. We therefore concluded that the left breast lesion and right axillary lymph node were metastasis from the endometrial carcinoma, rather than a breast primary. A positive expression of napsin A supported the diagnosis of a clear cell subtype (7), although it

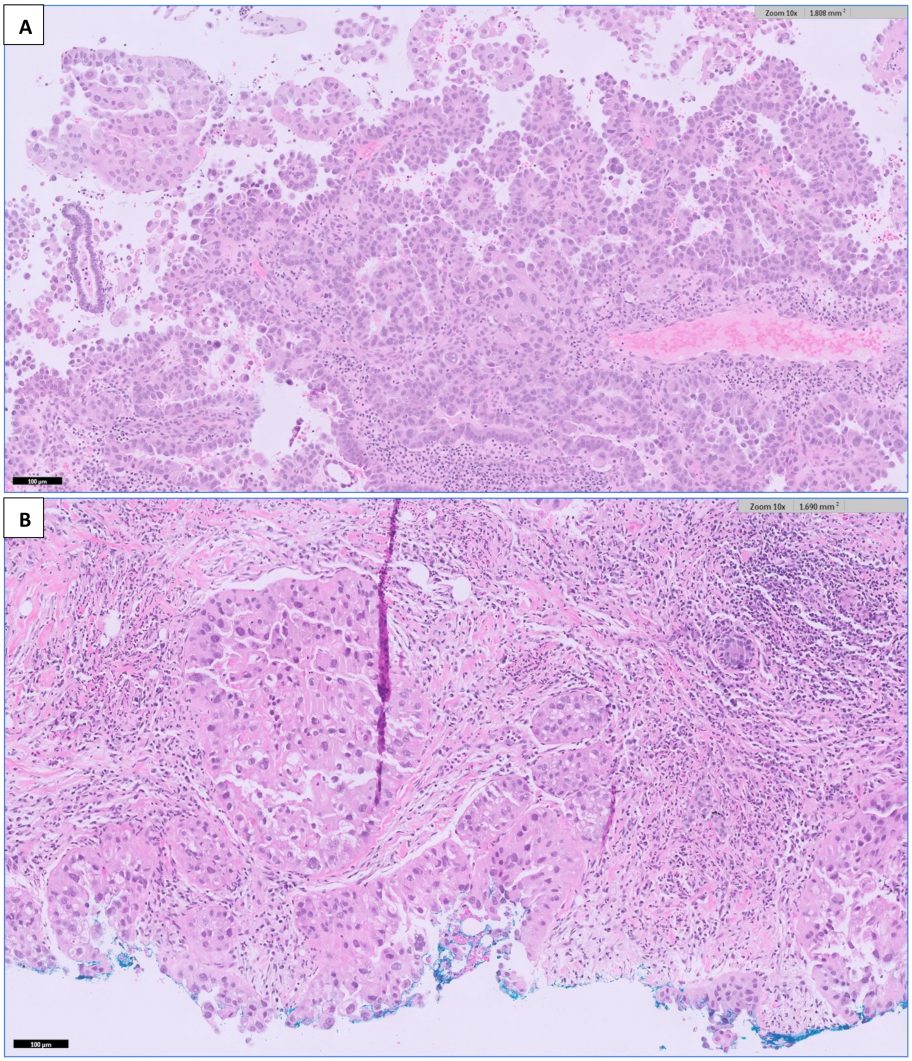


FIGURE 3
H&E-stained sections at 100× magnification of **(A)** the endometrial curettage specimen, showing high-grade endometrial carcinoma with clear cell features. Fragments of tumor tissue are seen with tubulo-papillary and glandular architecture with a hobnailed appearance. The cells contain nuclear atypia, pleomorphism, and prominent nucleoli with areas of clear cytoplasm. **(B)** The breast tumor shows similar morphology to the endometrial tumor in Figure 3.

was slightly anomalous in this case that the tumor stained positive for estrogen receptor (ER), which is usually negative or focal in clear cell carcinoma (8). HER2 expression showed a negative result.

A computed tomography scan of the thorax, abdomen, and pelvis showed ascites with omental nodularity concerning for peritoneal metastasis, as well as extensive lymphadenopathy involving the retroperitoneal, pelvic, periportal, bilateral axillary, and mediastinal lymph nodes. Overall findings were suggestive of metastatic endometrial clear cell carcinoma, and the patient was started on palliative chemotherapy with paclitaxel and carboplatin. She was also initiated on letrozole given that her tumor was estrogen receptor (ER)-positive.

Discussion

Metastatic disease to the breast is rare compared with primary breast cancers. A new lesion in the breast or axilla is far more likely to represent a new primary breast tumor, even in a patient with a history of extramammary malignancy (9).

10.3389/fonc.2022.1070744

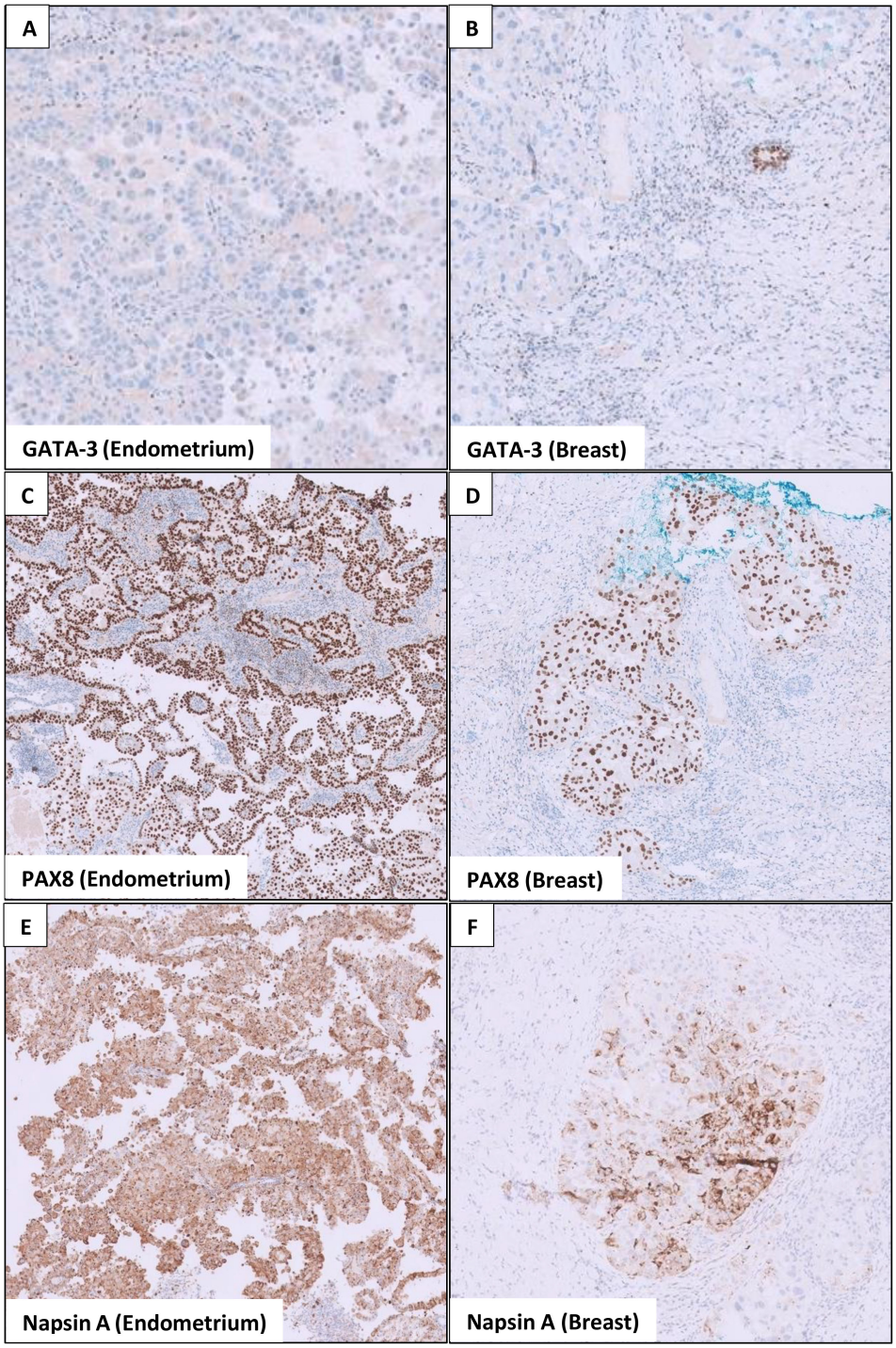


FIGURE 4
Immunohistochemical stains show similarities in the endometrial and breast tumor. **(A)** The endometrial tumor stains negative for GATA-3 (a breast marker). **(B)** Similarly, the breast tumor also stains negative for GATA-3, although the adjacent breast ducts are positive. **(C, E)** show that the endometrial tumor stains positive for PAX8 (marker for Müllerian tumors) and napsin A (marker for clear cell carcinoma). In **(D, F)** the breast tumor similarly stains positive for PAX8 and napsin A, whereas the adjacent breast tissues are negative.

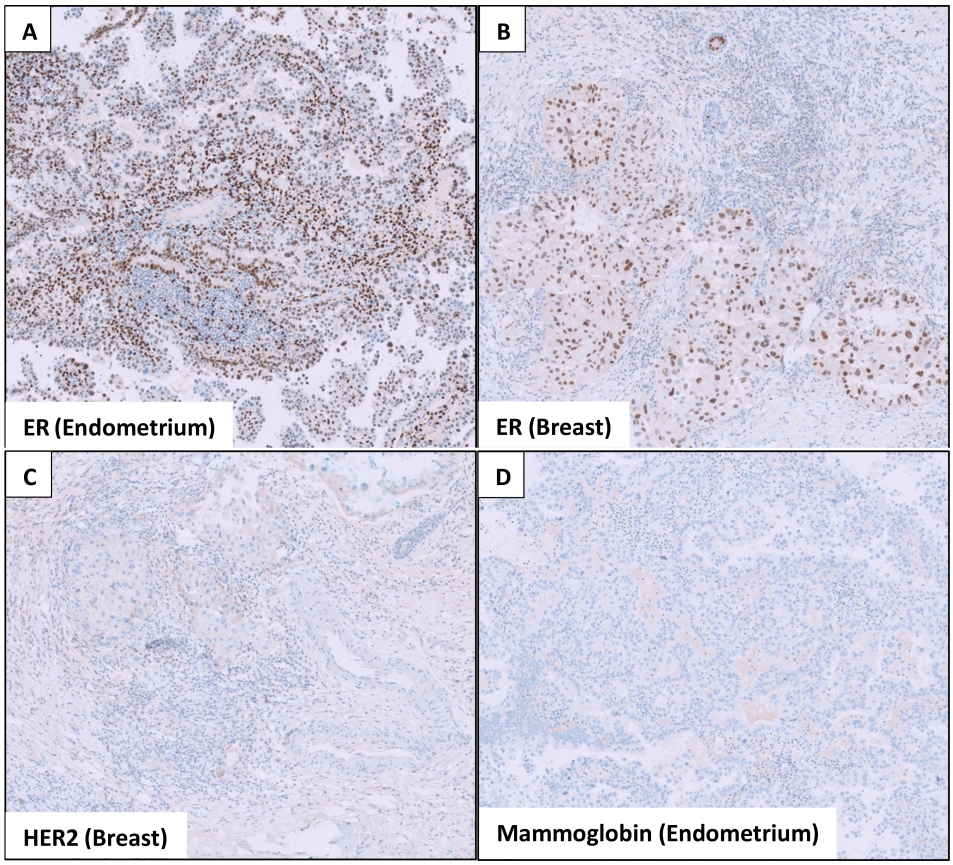


FIGURE 5
Immunohistochemical stains show that both the **(A)** endometrial and **(B)** breast tumors stain positive for estrogen receptor (ER). **(C)** The breast tumor is negative for HER2 expression, and **(D)** the endometrial tumor does not express mammaglobin, a breast marker.

Nonetheless, distinguishing the two is key as treatment and prognosis differ greatly.

Clinically, breast metastasis and primary breast tumors present similarly with a palpable, non-tender lump. However, unlike primary breast cancer, up to a third of patients with extramammary breast metastasis have multiple lesions as opposed to a single solitary tumour (7). Skin changes such as peau d'orange, nipple retraction, and nipple discharge are also uncommon. Notably, metastatic breast masses tend to grow rapidly and close to the skin, possibly due to lymphatic involvement, which may induce skin edema or erythema that may be mistaken for inflammatory breast cancer (10, 11), as was the case for our patient.

Imaging may help to differentiate primary from secondary breast tumors. Features common to primary breast cancer such as spiculations, calcifications, parenchymal distortion, posterior acoustic shadowing, desmoplastic reaction, secondary skin, and nipple changes are typically not seen in breast metastasis (12). Conversely, metastatic lesions tend to be well-circumscribed with clearly defined borders and lack surrounding inflammatory changes, occasionally mimicking benign breast lesions (13, 14). Interestingly, radiological characteristics differ depending on whether the tumor spreads to the breast *via* the lymphatic or hematogenous route. Hematogenous metastasis tends to feature as single or multiple oval, well-circumscribed, and hypoechoic masses affecting the upper outer quadrant, the most richly vascularized area within the breast (13). Axillary lymph node involvement is also less common (14). In contrast, lymphatic spread is often associated with axillary and internal mammary lymphadenopathy. The sonographic appearance of lymphatic metastasis may also mimic inflammatory primary breast cancer by demonstrating heterogenous echogenicity, coarse trabecular pattern, skin thickening, and lymphoedema, due to obstruction of the draining lymphatics (12).

Histopathological examination and immunohistochemistry are key to the diagnosis of breast metastases. The presence of carcinoma *in situ* along with invasive ductal components almost always confirms the diagnosis of primary breast cancer (13). A positive expression of mammaglobin, GATA binding protein 3 (GATA-3), and gross cystic disease fluid protein 15 (GCDFP-15) supports primary breast cancer (15). Triple-negative breast cancers, however, may not express

GCDFP-15, GATA 3, or mammaglobin, and in such cases, SOX-10 may be helpful (16). On the other hand, PAX8 expression is a sensitive marker for endometrial carcinoma (17) and napsin A supports the clear cell subtype (18). Nonetheless, it must be recognized that some overlap exists between the immunohistochemical markers seen in breast and endometrial cancers. For example, estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor may be positive or negative in both breast and endometrial cancers (19) and are less useful in distinguishing the two.

In this case, the clinical context, histopathological morphology, and napsin A expression favored the diagnosis of a clear cell subtype of high-grade endometrial carcinoma in the breast. Nonetheless, we acknowledge the diagnostic overlap between serous and clear cell subtypes of high-grade endometrial cancers, compounded by the lack of a definite biomarker to differentiate them. Therefore, it is important to be mindful of the range of high-grade endometrial cancers that may appear in the breast and to consider all differentials. As breast metastases from extramammary malignancies can be challenging to diagnose and manage, a multidisciplinary team involving a breast surgeon, radiologist, pathologist, and medical oncologist is often helpful.

To the best of our knowledge, there have been seven cases of endometrial serous carcinoma with breast metastasis reported in the current literature (9, 12, 20, 21); however, this is the first case report of clear cell endometrial carcinoma with breast metastasis. This is likely because clear cell carcinoma is a rare subtype accounting for less than 5% of endometrial carcinomas. Yet, they are associated with an aggressive clinical behavior and unfavorable prognosis (22). They have an increased propensity for lymphovascular invasion and approximately 45% of patients having extrauterine metastasis at time of diagnosis (23). Microscopically, they are characterized by clear hobnail cells and majority are positive for napsin A, as was the case for our patient.

Conclusion

Breast metastases from extramammary malignancies are rare. Endometrial clear cell carcinoma metastasizing to the breast is even more unique, with this being the first known case report in the current literature. In general, the prognosis of patients with metastasis to the breast is poor, with a reported median survival of only 10–15 months from the time of diagnosis and over 70% having widespread metastatic disease (13). As such, an early and accurate diagnosis of extramammary breast metastasis is important, so that appropriate treatment can be instituted for these patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

AC and YS conceptualized the manuscript. AC wrote the original draft of the manuscript. LS contributed to the radiology images and assisted with revisions of the manuscript. KS and AT contributed to the histology slides. All authors were involved in the care of the patient and have read and approved the final paper.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Georgiannos SN, Chin Aleong J, Goode AW, Sheaff M. Secondary neoplasms of the breast. *Cancer* (2001) 92(9):2259–66. doi: 10.1002/1097-0142(20011101)92:9<2259::AID-CNCR1571>3.0.CO;2-O

2. Akçay MN. Metastatic disease in the breast. *Breast* (2002) 11(6):526–8. doi: 10.1054/brst.2002.0467

3. Vizcaíno I, Torregrosa A, Higueras V, Morote V, Cremades A, Torres V, et al. Metastasis to the breast from extramammary malignancies: A report of four cases and a review of literature. *Eur Radiol* (2001) 11(9):1659–65. doi: 10.1007/s003300000807

4. Lee SH, Park JM, Kook SH, Han BK, Moon WK. Metastatic tumors to the breast: mammographic and ultrasonographic findings. *J Ultrasound Med* (2000) 19(4):257–62. doi: 10.7863/jum.2000.19.4.257

5. Ali RH, Taraboanta C, Mohammad T, Hayes MM, Ionescu DN. Metastatic non-small cell lung carcinoma a mimic of primary breast carcinoma–case series and literature review. *Virchows Archiv* (2018) 472(5):771–7. doi: 10.1007/s00428-017-2262-4

6. Kurra V, Krajewski KM, Jagannathan J, Giardino A, Berlin S, Ramaiya N. Typical and atypical metastatic sites of recurrent endometrial carcinoma. *Cancer Imaging* (2013) 13(1):113–22. doi: 10.1102/1470-7330.2013.0011

7. Iwamoto M, Nakatani Y, Fugo K, Kishimoto T, Kiyokawa T. Napsin a is frequently expressed in clear cell carcinoma of the ovary and endometrium. *Hum Pathol* (2015) 46(7):957–62. doi: 10.1016/j.humpath.2015.03.008

8. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: More than two types. *Lancet Oncol* (2014) 15(7):e268–78 doi: 10.1016/S1470-2045 (13)70591-6

9. McEachron J, Mendoza R, Lee YC, Kanis MJ. Breast metastases: A rare manifestation of advanced uterine serous carcinoma. *Gynecol Oncol Rep* (2019) 30:100500. doi: 10.1016/j.gore.2019.100500

10. Noguera J, Martínez-Miravete P, Idoate F, Diaz L, Pina L, Zornoza G, et al. Metastases to the breast: A review of 33 cases. *Australas Radiol* (2007) 51(2):133–8. doi: 10.1111/j.1440-1673.2007.01681.x

11. Feder JM, de Paredes ES, Hogge JP, Wilken JJ. Unusual breast lesions: Radiologic-pathologic correlation. *RadioGraphics* (1999) 19(suppl_1):S11–26. doi: 10.1148/radiographics.19.suppl_1.g99oc07s11

12. Lin T, Lin D, Zhang Z, Shah BA. Metastatic endometrial serous carcinoma to the breast. *Appl Radiol* (2017) 46(11):42–5.

13. Williams SA, Ehlers RA, Hunt KK, Yi M, Kuerer HM, Singletary SE, et al. Metastases to the breast from nonbreast solid neoplasms. *Cancer* (2007) 110 (4):731–7. doi: 10.1002/cncr.22835

14. Mun SH, Ko EY, Han BK, Shin JH, Kim SJ, Cho EY. Breast metastases from extramammary malignancies: Typical and atypical ultrasound features. *Korean J Radiol* (2014) 15(1):20. doi: 10.3348/kjr.2014.15.1.20

15. Bonacho T, Rodrigues F, Liberal J. Immunohistochemistry for diagnosis and prognosis of breast cancer: a review. *Biotech Histochem* (2020) 95(2):71–91. doi: 10.1080/10520295.2019.1651901

16. Kriegsmann K, Flechtenmacher C, Heil J, Kriegsmann J, Mechtersheimer G, Aulmann S, et al. Immunohistological expression of SOX-10 in triple-negative breast cancer: A descriptive analysis of 113 samples. *Int J Mol Sci* (2020) 21 (17):6407. doi: 10.3390/ijms21176407

17. Yemelyanova A, Gown AM, Wu LSF, Holmes BJ, Ronnett BM, Vang R. PAX8 expression in uterine adenocarcinomas and mesonephric proliferations. *Int J Gynecol Pathol* (2014) 33(5):492–9. doi: 10.1097/PGP.0b013e3182a54afa

18. Nili F, Tavakoli M, Izadi-Mood N, Saffar H, Sarmadi S. Napsin-a expression, a reliable immunohistochemical marker for diagnosis of ovarian and endometrial clear cell carcinomas. *Iran J Pathol* (2020) 15(2):81–5. doi: 10.30699/ijp.2020.106598.2222

19. Wang C, Tran DA, Fu MZ, Chen W, Fu SW, Li X. Estrogen receptor, progesterone receptor, and HER2 receptor markers in endometrial cancer. *J Cancer* (2020) 11(7):1693–701. doi: 10.7150/jca.41943

20. DeLair DF, Corben AD, Catalano JP, Vallejo CE, Brogi E, Tan LK. Non-mammary metastases to the breast and axilla: a study of 85 cases. *Modern Pathol* (2013) 26(3):343–9. doi: 10.1038/modpathol.2012.191

21. Fulciniti F, Losito S, Botti G, Mattia DD, Mura AL, Pisano C, et al. Metastases to the breast: role of fine needle cytology samples. *Our Exp nine cases 2 years Ann Oncol* (2008) 19(4):682–7. doi: 10.1093/annonc/mdm546

22. Abdulfatah E, Sakr S, Thomas S, Al-Wahab Z, Mutch DG, Downdy S, et al. Clear cell carcinoma of the endometrium. *Int J Gynecol Cancer* (2017) 27(8):1714–21. doi: 10.1097/IGC.0000000000001050

23. Silwal S, Yadav SK, Amalraj B, Mandeel M, Krishnamoorthy G. Clear cell carcinoma of the endometrium in a patient presenting with postmenopausal bleeding but negative endometrial biopsy. *Case Rep Oncol* (2021) 14(3):1768–72. doi: 10.1159/000520878

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 14 February 2023
DOI 10.3389/fonc.2023.1023787

OPEN ACCESS

EDITED BY
Margarita Ivanova,
Lysosomal and Rare Disorders Research and Treatment Center, United States

REVIEWED BY
Benoit Paquette,
University of Sherbrooke, Canada
Meriem Messaoudene,
University of Montreal Hospital Centre (CRCHUM), Canada

*CORRESPONDENCE
Lingshuang Liu
liuls107@163.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 25 August 2022
ACCEPTED 01 February 2023
PUBLISHED 14 February 2023

CITATION
Qin R, Qian J, Shan M, Ruan G, Yang X, Wang Y and Liu L (2023) Case report: Response to endocrine therapy in triple-negative breast cancer metastases with altered hormone receptors.
Front. Oncol. 13:1023787.
doi: 10.3389/fonc.2023.1023787

Case report: Response to endocrine therapy in triple-negative breast cancer metastases with altered hormone receptors

Ruoyan Qin[1†], Jie Qian[2†], Mengjun Shan[1], Guangxin Ruan[1], Xiaofeng Yang[1], Yanwen Wang[3] and Lingshuang Liu[1*]

[1]Department of Oncology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [2]Department of Emergency Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3]Department of Pathology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Triple-negative breast cancer refers to breast cancer patients with negative estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2). Metastatic triple-negative breast cancer is predominantly treated with chemotherapy, but later-line treatment remains challenging. Breast cancer is highly heterogeneous, and the expression of hormone receptors is often inconsistent between primary and metastatic lesions. Here, we report a case of triple-negative breast cancer 17 years after surgery with lung metastases for 5 years that progressed to pleural metastases after multiple lines of chemotherapy. The pleural pathology suggested ER (+) and PR (+) and transformation to luminal A breast cancer. This patient received fifth-line letrozole endocrine therapy and achieved partial response (PR). The patient's cough and chest tightness improved after treatment, associated tumor markers decreased, and progression-free survival (PFS) exceeded 10 months. Our results may be of clinical relevance for patients with hormone receptor alterations in advanced triple-negative breast cancer and suggest that individualized regimens should be developed for breast cancer based on the molecular expression of tumor tissue at the primary and metastatic sites.

KEYWORDS

triple-negative breast cancer, metastases, altered hormone receptors, later-line treatment, endocrine therapy

Highlights

- Triple-negative breast cancer may exhibit postoperative metastatic hormone receptor alteration
- Individualized treatment based on re-evaluated primary tumor and metastatic hormone receptors may have survival benefit for patients with triple-negative breast cancer

Introduction

Breast cancer is the most common malignancy in women in terms of incidence and has the second highest mortality (1). The treatment strategy is based on molecular typing, with the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) being the most important. These receptors define four different subtypes of breast cancer: luminal A (ER/PR positive, Her2 negative), luminal B (ER and/or PR positive, HER2 positive), HER2 overexpressing (HER2 positive only) and triple negative (2), each with a different treatment strategy and prognosis. Triple-negative breast cancer accounts for 15%-20% of all breast cancers (3) and is characterized by a higher risk of recurrence and poorer prognosis (4). Later-line treatment options are limited and poorly tolerated. In the treatment of advanced breast cancer, biological marker inconsistencies between the primary and metastatic breast cancer sites are often identified, which may impact the treatment strategy and prognosis of metastatic breast cancer, leading to altered treatment outcomes and results. Loss of hormone receptors may lead to a poorer prognosis. Patients with positive ER and PR transitions may benefit from endocrine therapy, and HER2-positive patients may choose to receive targeted therapy.

Here, we present a patient with triple-negative breast cancer who exhibited postoperative metastatic hormone receptor changes. The patient benefited from endocrine therapy, suggesting that a re-biopsy should be performed for recurrent metastatic lesions to reassess the molecular status (5).

Case presentation

A 67-year-old Chinese woman was admitted to Longhua Hospital of Shanghai University of Traditional Chinese Medicine on September 27, 2021, complaining of cough and chest tightness for 1 week. The patient had a history of postoperative right breast cancer of 17 years with metastasis in both lungs for more than 5 years. She underwent right breast lump resection and modified radical right mastectomy on June 4, 2004. The resected lump was 3*3*2.8 cm^3 in size, and pathology showed grade III invasive ductal carcinoma (right breast). Fifteen ipsilateral axillary lymph nodes were identified during the operation and showed no sign of malignancy on pathological examination. Immunohistochemistry revealed ER (-), PR (-), SMA(-), EMA(+), S-100(-),P53(-),C-erbB-2(-),bcl-2(-),nm23(+),Ki-67(-), AE1/AE3(+),Vimentin(+), GFAP (-). At that point, the stage was p-T2N0M0 IIA. The patient was treated with a CMF regimen (CTX600mg+MTX30mg+5-Fu500mg ivgtt q3w). Adjuvant chemotherapy was given 6 times after surgery, followed by a regular follow-up review. The patient underwent PET-CT (Positron Emission Computed Tomography) on December 6, 2016, showing mild FDG metabolism in small nodules in the posterior segment of the upper right lung lobe, possibly indicating malignancy (1.1 cm, SUVmax1.9). Multiple small nodules were also identified in the basal segment of the lower right lobe and in the subpleural area of the lower left lobe and upper left lobe (7mm, SUVmax2.2). In addition, multiple enlarged lymph nodes with increased FDG metabolism were observed in the mediastinum and right hilar region (1.6*1.3 cm, SUVmax19.5) (Figure 1A). The patient refused to undergo diagnostic puncture and was re-staged r-T0N0M1 stage IV (lung, mediastinum, hilar lymph nodes) according to imaging. She received first-line DO chemotherapy (docetaxel 60mg d1d8+oxaliplatin 100mg d1d8 ivgtt q3w), achieving stable disease (SD). The first-line treatment resulted in 16 months of progression-free survival (PFS) (Figures 1B, C). The patient's second-line treatment was based on the first-line treatment plus bevacizumab (docetaxel 60mg d1d8 + oxaliplatin 100mg d1d8 + bevacizumab 300mg d1 ivgtt q3w), which also achieved SD and led to 9 months of PFS (Figures 1D, E). The third-line therapy was capecitabine (capecitabine 1.5g BID PO d1-d14 q3w), which also achieved SD. In April 2021, computed tomography (CT) scans revealed increased exudate in the lower lobe of the right lung, and new right pleural effusion, indicating progressive disease (PD). Following the third-line treatment, the patient demonstrated a PFS of 28 months (Figures 1F, G). She was then treated with fourth-line vincristine soft gels (vincristine 100mg qw PO q3w). On the night of the same day, she developed increased hoarseness, fever, nausea, and diarrhea 7-8 times. Therefore, vincristine was stopped, and her condition improved with symptomatic treatment.

In September 2021, the patient attended the hospital due to aggravation of coughing and chest tightness for 1 week and underwent right-sided thoracentesis and drainage. Physical examination revealed low breathing sound in right lung. The patient received symptomatic support treatment including cough relieving and considerate nursing. 510 ml of bloody pleural fluid was drained, and the pathology of pleural fluid (pleural cell mass) suggested metastatic adenocarcinoma. Combined with the immunostaining results, cell morphology and clinical history, the findings were consistent with breast cancer metastasis. Immunohistochemistry showed ER(+,90% strong positive), PR (+,80% strong positive), HER-2.(1+), Ki-67(10%+), CK20(-), GATA3(+), SOX10(-), CK7(+), TTF-1(-), EMA(+), calretinin (mesothelial+), WT-1(mesothelial+) (Figures 2A–F). PET-CT revealed a soft tissue mass in the right hilar lung (26.7*38.4mm, SUVmax 20.05), focal high-density nodules in the right anterior chest wall (14*8mm, SUVmax 3.67), multiple nodules in both lungs, multiple lymph nodes in the bilateral clavicular region, bilateral hila and mediastinum (12mm, SUVmax17.06), and multiple lesions in the right pleura with abnormally high FDG metabolism (SUVmax 13.52) which were considered to be caused by multiple tumor metastases (Figures 1H1, H2). The patient was started on fifth-line letrozole endocrine therapy since October 2021. In February 2022, CT scans revealed decreasing right upper lung hilar soft tissue shadow, right

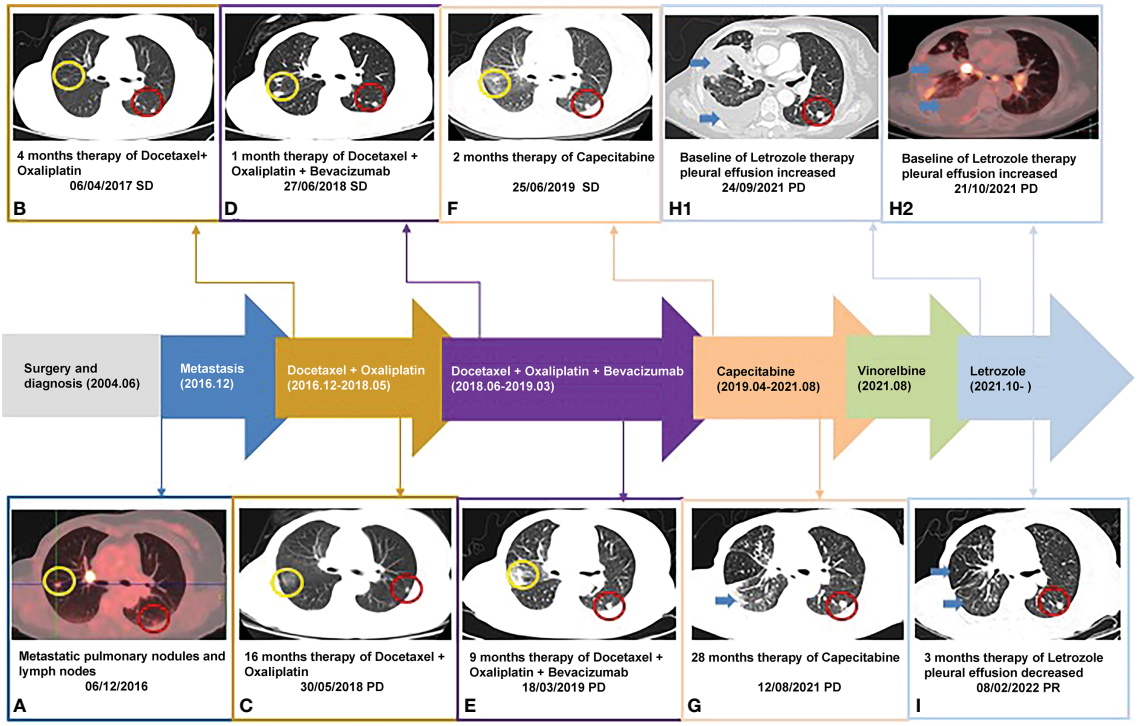


FIGURE 1
Timeline of the patient: **(B-G, H1, I)** were taken with Chest CT scanner and **(A, H2)** were taken with PET-CT scanner; yellow circle: right pulmonary nodule; red circle: right pulmonary nodule; blue arrow: pleural effusion.

pleural fluid and mediastinal right hilar lymph nodes (Figure 1I). Treatment efficacy was categorized as partial response (PR). The patient's cough and chest tightness were significantly relieved. Physical examination showed clear breath sounds in both lungs. The related tumor markers CA153 and CA125 showed a decreasing trend (Figure 3). Currently, the PFS reached 10 months, and the patient is still under follow-up.

Discussion

Triple-negative breast cancer is characterized by a lack of estrogen, progesterone and HER2 receptor expression, resulting in ineffective endocrine and HER2-targeted therapies. Chemotherapy remains the most common basic treatment for triple-negative breast

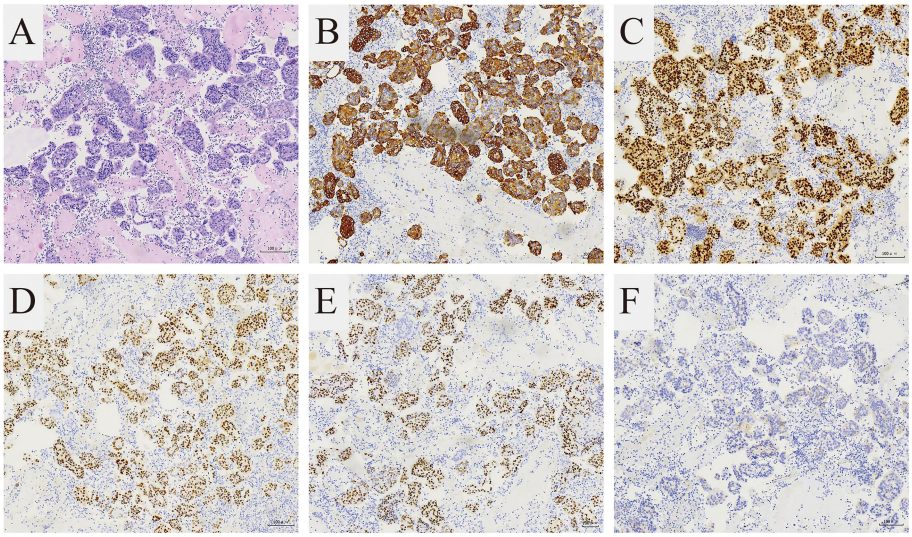


FIGURE 2
Pathological features of the cell blocks of the pleural fluid. **(A)** The H and E stain showed that the tumor is composed of small round cells (magnification 100×). The immunohistochemical stain showed **(B)** CK7 (+) and **(C)** GATA3 (+) supporting breast cancer metastasis (magnification 100×). The immunohistochemical stain showed **(D)** ER (+), **(E)** PR (+), **(F)** HER-2(1+) representing Luminal A subtype (magnification 100×).

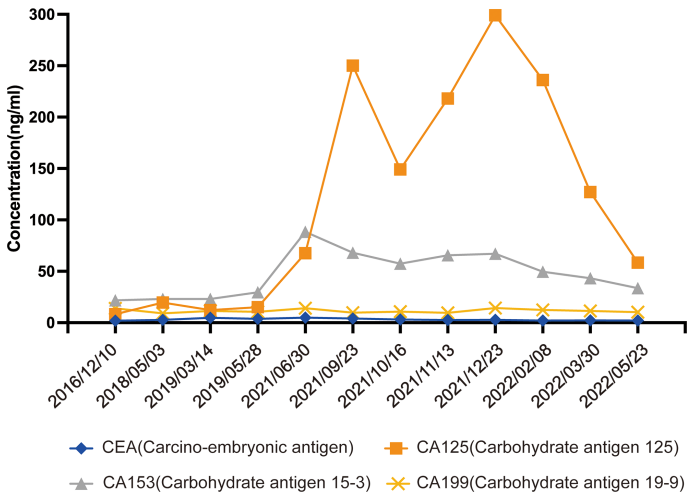


FIGURE 3
Serum tumor biomarker during treatment.

cancer, including single agent and combination chemotherapy based on paclitaxel, capecitabine, and vincristine, which can be combined with bevacizumab anti-angiogenesis. However, drug resistance inevitably occurs, with limited later-line treatment options and poor survival prognosis. During the course of breast cancer, hormone receptor expression in metastases may differ from the primary lesion. Given this inconsistency, the ASCO expert group, Chinese Consensus Guidelines for Advanced Breast Cancer, recommends re-biopsy of metastases to determine treatment based on the ER and PR status of the metastases. However, there are still many barriers to biopsy of recurrent tumor metastases (6), such as the risk of major complications, patient refusal, differences in puncture detection techniques, and low representativeness of tissue specimens. In this case, the patient experienced a 17-year tumor course with postoperative bilateral lung metastases from triple-negative breast cancer. Following multiple lines of chemotherapy resistance and intolerance, the tumor metastasized to the pleura, with pleural fluid pathology immunohistochemistry revealing CK7 (+) and GATA3 (+), supporting breast cancer metastasis. However, the results ER (+) and PR (+) supported a transformation to luminal A breast cancer, which was treated according to hormone receptor alterations to benefit from letrozole endocrine therapy.

The inherent heterogeneity of breast cancer and the changes that occur during its evolution result in distinct biological features between primary and metastatic foci. The hormone receptors ER and PR are important prognostic factors and predictors of endocrine therapy efficacy in breast cancer, suggesting the importance of detecting the expression of hormone receptors. We analyzed 15 relevant studies from 2010 to 2020 and showed that the receptor expression in recurrent metastatic breast cancer lesions varied to different degrees compared to the primary lesions (Table 1) (7–21). Relatively high inconsistency was observed for hormone receptors, especially PR, and relatively low inconsistency for HER2; hormone receptor loss was more common than hormone receptors turning positive. Yeung reviewed (22) 47 studies of paired primary and metastatic sites (3384 cases) and came to similar conclusions: the rates of inconsistency were 14%, 21%, and 10% for ER, PR, and HER2, respectively, and the rates of decrease and increase in receptor expression were 9.17% and 4.51%, respectively. The results also demonstrated that the rates of receptor inconsistency differed between metastatic sites, suggesting that inconsistency is a real biological phenomenon. The inconsistency of hormone receptors may affect the treatment and management of patients, highlighting the possibility of potential therapeutic agents (17). Consistent with previous literature, it is rare for this patient to change from triple negative breast cancer to hormone receptor positive.

The variation in metastatic receptor expression may result from several factors, including differences in sampling and detection, tumor heterogeneity, and antitumor therapy. In terms of sampling and detection, differences in sampling methods of tissue specimens, representativeness of sampling, immunohistochemical staining, and accuracy of detection methods are inevitable. Tumor heterogeneity refers to changes in tumors during continuous proliferation and differentiation and changes in molecular biological characteristics or genetic level. Tumor heterogeneity can be divided into spatial heterogeneity (different regions of the same tumor) and temporal heterogeneity (discrepancy between primary tumors and secondary tumors). The underlying mechanisms are mainly believed to involve the clonal evolutionary theory and the stem cell theory, in which the tumor microenvironment and the tumor treatment process play major roles. The above theories explain the inconsistency between the receptors of metastatic and primary foci of breast cancer. Curtit (13) reported that previous chemotherapy, especially anthracycline-based chemotherapy, was significantly associated with alterations in ER receptors. Our patient presented with a long postoperative metastatic course and had received CMF adjuvant chemotherapy, docetaxel-based chemotherapy and capecitabine chemotherapy. Therefore, the changes in metastatic receptors might be associated with tumor heterogeneity and chemotherapy history.

Previous studies have reported the impact of inconsistent receptor expression on subsequent treatment and prognosis. Considering that the presence of ER, PR or HER2 expression in metastases suggests an opportunity for patients to receive endocrine therapy or targeted therapy, treatment resistance may occur when receptor status is lost.

TABLE 1 Literature review of ER, PR and HER2 discordance between primary tumors and corresponding metastatic sites.

Reference	Cases	Metastatic sites	Type of analysis	ER (Gain/Loss) (%)	PR (Gain/Loss) (%)	HER2 (Gain/Loss) (%)	Change in Therapy (%)
Thompson 2010 (7)	137	LR/DM	Biomarkers reassessment	10.2 (2.2/8.0)	24.8 (8.8/16.0)	2.9 (2.2/0.7)	17.5
Amir 2011 (8)	231	LR/DM	Reports review	12.6 (3.0/9.6)	31.2 (7.0/24.2)	5.5 (4.1/1.4)	14.2
Amir 2011 (9)	94	LR/DM	Biomarkers reassessment	16.0 (4.3/11.7)	40.4 (4.2/36.2)	9.6 (7.2/2.4)	14
Bogina 2011 (10)	140	LR/DM	Biomarkers reassessment	6.4 (0.7/5.7)	21.4 (3.6/17.8)	0.7 (0.7/0)	7.3
Dieci 2012 (11)	119	LR/DM	Biomarkers reassessment	13.4 (2.5/10.9)	39.0 (8.5/30.5)	11.8 (8.4/3.4)	10.9
Hoefnagel 2012 (12)	233	DM	Biomarkers reassessment	10.3 (-/-)	30.0 (-/-)	-(-/-)	–
Curtit 2013 (13)	235	LR/DM	Biomarkers reassessment	17.0 (4.7/12.3)	29.3 (7.2/22.1)	4 (1.0/3.0)	–
Duenas 2014 (14)	184	LR/DM	Biomarkers reassessment	21.3 (12.5/8.8)	34.6 (12.8/21.8)	16.4 (10.0/6.4)	31
Shiino 2016 (15)	153	LR/DM	Biomarkers reassessment	18.3 (3.9/14.4)	26.1 (6.5/19.6)	6.5 (3.9/2.6)	–
Erdem 2016 (16)	393	LR/DM	Biomarkers reassessment	27.2 (12.2/15.0)	38.6 (10.2/28.4)	14.4 (10.1/4.3)	–
McAnena 2018 (17)	132	LR/DM	Biomarkers reassessment	20.4 (4.5/15.9)	37.7 (4.5/33.2)	3 (1.5/1.5)	6.8
Woo 2019 (18)	152	LR/DM	Biomarkers reassessment	6 (0.7/5.3)	26.3 (2.0/24.3)	7.9 (2.0/5.9)	–
Nguyen 2019 (19)	67	LR/DM	Biomarkers reassessment	26.9 (14.9/12.0)	38.8 (13.4/25.4)	22.4 (14.9/7.5)	–
Jud 2020 (20)	142	LR	Biomarkers reassessment	14.9 (-/-)	22.7 (-/-)	18.3 (-/-)	–
Blancas 2020 (21)	45	LR/DM	Biomarkers reassessment	20 (8.9/11.1)	20 (4.4/15.6)	15.4 (5.1/10.3)	–

LR, local recurrences; DM, distant metastases; ER, estrogen receptor; PR, progesterone receptor.

In 6.8-31% of patients, the treatment strategy is switched due to changes in molecular markers (7–11, 14, 17). In terms of prognosis, Bogina (10) showed that among patients with local recurrence and primary ER, patients whose recurrence foci turned negative for PR had a significantly shorter median distant metastasis-free survival (MFS) than those who remained PR positive (p= 0.005). Dieci (11) showed that patients with hormone receptor ER/PR and HER2 loss had shorter overall survival (OS) (P = 0.06 and P = 0.0002) and post-recurrence survival (PRS) after relapse (P=0.01 and P=0.008) than those without hormone receptor loss. McAnena (17) also came to similar conclusions, reporting that luminal A breast cancer patients who converted to triple-negative breast cancer had significantly worse survival after recurrence than those with persistent luminal A breast cancer (P < 0.05). Furthermore, the difference in overall survival was close to statistical significance (P=0.064). Hoefnagel (12) showed that patients who changed ER/PR receptor status to negative or to positive had a similar prognosis to patients with persistent negative receptor expression but shorter overall survival compared to patients with persistently positive receptor expression. Positive primary hormone receptors ER and PR indicate a good prognosis, while negative status indicates a poor prognosis. Loss of receptors in recurrent metastases also appears to be associated with poor prognosis. There are fewer data related to the prognostic impact of receptor acquisition.

In conclusion, this case report highlights a partial response to endocrine therapy in a patient with triple-negative breast cancer metastases with altered hormone receptors.

Our research suggests that re-evaluation of the diagnosis based on primary tumor and metastatic hormone receptors is the key to implementing individualized treatment of tumor heterogeneity, especially for triple-negative breast cancer. This subject is worthy of further clinical research and discussion.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RQ, JQ and LL: Conceptualization, methodology, and review. RQ, XY, and YW: Data collection and analysis, writing, and editing. GR and MS: Literature research. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Shanghai Municipal Health Commission (20214Y0375) and Shanghai Science and Technology Commission (19401971200), and the Shanghai Hospital Development Center (SHDC12018124).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA: Cancer J Clin* (2022) 72(1):7–33. doi: 10.3322/caac.21708

2. Prat A. Comprehensive molecular portraits of human breast tumours. *Nat (London)* (2012) 490(7418):61–70. doi: 10.1038/nature11412

3. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *New Engl J Med* (2010) 363(20):1938–48. doi: 10.1056/NEJMra1001389

4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* (2018) 68(6):394–424. doi: 10.3322/caac.21492

5. Van Poznak C, Harris LN, Somerfield MR. Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American society of clinical oncology clinical practice guideline. *J Clin Oncol* (2015) 33(24):2695–704. doi: 10.1200/JOP.2015.005215

6. Gupta SM, Wallace MJ, Cardella JF, Kundu S, Miller DL, Rose SC. Quality improvement guidelines for percutaneous needle biopsy. *J Vasc interv Radiol* (2010) 21 (7):969–75. doi: 10.1016/j.jvir.2010.01.011

7. Thompson AM, Jordan LB, Quinlan P, Anderson E, Skene A, Dewar JA, et al. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: The breast recurrence in tissues study (BRITS). *Breast Cancer Res: BCR* (2010) 12(6):R92. doi: 10.1186/bcr2771

8. Amir E, Clemons M, Purdie CA, Miller N, Quinlan P, Geddie W, et al. Tissue confirmation of disease recurrence in breast cancer patients: Pooled analysis of multi-centre, multi-disciplinary prospective studies. *Cancer Treat Rev* (2011) 38(6):708–14. doi: 10.1016/j.ctrv.2011.11.006

9. Amir E, Miller N, Tannock IF, Freedman O, Kassam F, Simmons C, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. *J Clin Oncol* (2012) 30(6):587–92. doi: 10.1200/JCO.2010.33.5232

10. Bogina G, Bortesi L, Marconi M, Venturini M, Lunardi G, Coati F, et al. Comparison of hormonal receptor and HER-2 status between breast primary tumours and relapsing tumours: Clinical implications of progesterone receptor loss. *Virchows Archiv* (2011) 459(1):1–10. doi: 10.1007/s00428-011-1097-7

11. Dieci MV, Barbieri E, Piacentini F, Ficarra G, Betteli S, Dominici M, et al. Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: A single-institution analysis. *Ann Oncol* (2013) 24(1):101–8. doi: 10.1093/annonc/mds248

12. Hoefnagel LD, Moelans CB, Meijer SL, van Slooten HJ, Wesseling P, Wesseling J, et al. Prognostic value of estrogen receptor alpha and progesterone receptor conversion in distant breast cancer metastases. *Cancer* (2012) 118(20):4929–35. doi: 10.1002/cncr.27518

13. Curtit E, Nerich V, Mansi L, Chaigneau L, Cals L, Villanueva C, et al. Discordances in estrogen receptor status, progesterone receptor status, and HER2 status between primary breast cancer and metastasis. *Oncol (Dayton Ohio)* (2013) 18(6):667–74. doi: 10.1634/theoncologist.2012-0350

14. de Dueñas EM, Hernández AL, Zotano ÁG, Carrión RM, López-Muñiz JI, Novoa SA, et al. Prospective evaluation of the conversion rate in the receptor status between primary breast cancer and metastasis: Results from the GEICAM 2009-03 ConvertHER study. *Breast Cancer Res Treat* (2014) 143(3):507–15. doi: 10.1007/s10549-013-2825-2

15. Shiino S, Kinoshita T, Yoshida M, Jimbo K, Asaga S, Takayama S, et al. Prognostic impact of discordance in hormone receptor status between primary and recurrent sites in patients with recurrent breast cancer. *Clin Breast Cancer* (2016) 16(4):e133~e140. doi: 10.1016/j.clbc.2016.05.014

16. Erdem GU, Altundag K, Ozdemir NY, Sahin S, Demirci NS, Karatas F, et al. Comparative study of receptor discordance between primary and corresponding metastatic lesions in breast cancer. *J BUON* (2017) 22(2):365–76.

17. Mcanena PF, Mcguire A, Ramli A, Curran C, Malone C, McLaughlin R, et al. Breast cancer subtype discordance: Impact on post-recurrence survival and potential treatment options. *BMC Cancer* (2018) 18(1):203. doi: 10.1186/s12885-018-4101-7

18. Woo JW, Chung YR, Ahn S, Kang E, Kim EK, Kim SH, et al. Changes in biomarker status in metastatic breast cancer and their prognostic value. *J Breast Cancer* (2019) 22(3):439–52. doi: 10.4048/jbc.2019.22.e38

19. Nguyen TH, Nguyen VH, Nguyen TL, Nguyen TL, Qiuyin C, Phung TH, et al. Evaluations of biomarker status changes between primary and recurrent tumor tissue samples in breast cancer patients. *BioMed Res Int* (2019), 7391237. doi: 10.1155/2019/7391237

20. Jud SM, Hatko R, Emons J, Lauterbach B, Hack CC, Preuß C, et al. Discordance between primary breast cancer and ipsilateral breast cancer tumor recurrence as a function of distance. *J Clin Med* (2020) 9(12):4033. doi: 10.3390/JCM9124033

21. Blancas I, Muñoz-Serrano AJ, Legerén M, Ruiz-Ávila I, Jurado JM, Delgado MT, et al. Immunophenotypic conversion between primary and relapse breast cancer and its effects on survival. *Gynecol Obstet Invest* (2020) 85(3):259–66. doi: 10.1159/000505591

22. Yeung C, Hilton J, Clemons M, Mazzarello S, Hutton B, Haggar F, et al. Estrogen, progesterone, and HER2/neu receptor discordance between primary and metastatic breast tumours–a review. *Cancer Metastasis Rev* (2016) 35(3):427–37. doi: 10.1007/s10555-016-9631-3

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 09 March 2023
DOI 10.3389/fonc.2023.1067264

OPEN ACCESS

EDITED BY
Luigi Cavanna,
Ospedaliera di Piacenza, Italy

REVIEWED BY
Cristina M. Failla,
Institute of Immaculate Dermatology (IRCCS), Italy
Youwen Zhu,
Xiangya Hospital, Central South University, China

*CORRESPONDENCE
Armando Orlandi
Armando.orlandi@policlinicogemelli.it

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 11 October 2022
ACCEPTED 17 February 2023
PUBLISHED 09 March 2023

CITATION
Pasqualoni M, Orlandi A, Palazzo A, Garufi G, Cannizzaro MC, Pontolillo L, Pannunzio S, Cutigni C, Sollena P, Federico F, Bria E and Tortora G (2023) Case report: Vitiligo-like toxicity due to ribociclib during first-line treatment of metastatic breast cancer: two cases of premature interruption of therapy and exceptional response.
Front. Oncol. 13:1067264.
doi: 10.3389/fonc.2023.1067264

Case report: Vitiligo-like toxicity due to ribociclib during first-line treatment of metastatic breast cancer: two cases of premature interruption of therapy and exceptional response

Mariangela Pasqualoni[1,2], Armando Orlandi[1]*, Antonella Palazzo[1], Giovanna Garufi[1,2], Maria Chiara Cannizzaro[1,2], Letizia Pontolillo[1,2], Sergio Pannunzio[1,2], Claudia Cutigni[1,2], Pietro Sollena[3], Francesco Federico[4], Emilio Bria[1,2] and Giampaolo Tortora[1,2]

[1]Comprehensive Cancer Center, Medical Oncology Unit, Fondazione Policlinico Universitario 'A. Gemelli' – IRCCS, Rome, Italy, [2]Catholic University of Sacred Heart, Rome, Italy, [3]Department of Dermatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [4]Department of Pathology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Cancer treatment-related adverse events (AEs) are sometimes associated with outcomes for cancer patients, especially with the newest therapies such as target therapy and immunotherapy. A few years ago, the first-line therapy for hormone-receptor-positive metastatic breast cancer (mBC) patients has been deeply changed by the introduction of cyclin-dependent kinase (CDK) 4/6 inhibitors, and now, we are improving our knowledge about their AEs and significance in clinical practice. Here, we report our experience with two cases of vitiligo-like lesions that occur early during treatment with ribociclib. We tried to change the CDK4/6 inhibitor for one patient, but the skin reaction persisted. Both patients retained only the endocrine therapy alone and had an unexpected durable progression-free survival (PFS). Some data on skin toxicities, including vitiligo-like lesions by CDK4/6 inhibitors, have recently been reported in the literature, but for the first time, we highlight a possible correlation with improved survival outcomes of patients. Uncovering the etiology of this toxicity, verifying the involvement of the immune system, and demonstrating a possible positive impact in survival represent an intriguing research objective for the near future.

KEYWORDS

breast cancer, CDK4/6 inhibitor, skin adverse event, vitiligo, lymphocytic infiltration

Introduction

Breast cancer (BC) is the first leading cause of death for cancer in women. Approximately 20% of BCs spread outside the mammary gland, becoming a metastatic disease, and 70%–80% of these have a Hormone receptor-positive/HER2-negative (HR+/HER2−) immunophenotype (1).

Cyclin-dependent kinases 4 and 6 (CDK4/6) regulate cell-cycle progression, and their overexpression is frequent in luminal BCs; consequently, the inhibition of the pathway consisting of cyclin D, CDK4/6, and retinoblastoma protein is an effective therapeutic strategy for these BC subtypes (2). Therefore, nowadays, the first-line standard of care (SOC) despite age, comorbidities, and the number or sites of metastatic disease is the association of the endocrine therapy with CDK4/6 inhibitors such as ribociclib, palbociclib, and abemaciclib. Thanks to this treatment, the progression-free survival (PFS) of patients with metastatic breast cancer (mBC) is approximately a little more than 2 years with a consistent improvement also for overall survival (OS) (3–5). However, we do not know any predictive biomarkers of response to this treatment yet.

In the literature, there is a known association between treatment toxicity and clinical outcomes for several types of cancer drugs (6). For example, it is well-known how immunologically related adverse events (AEs) predict a good response to immunotherapy (7) or, for BC patients, how post-menopausal symptoms predict improved outcomes among women taking adjuvant endocrine therapy (8).

Pivotal studies of CDK4/6i have shown that the most common cutaneous side effects are mild, with grade 3 rashes only occurring in 0.9% of patients, and at the same time, no evidence of impact on prognosis was shown for skin rash incidence or grade of toxicity (3–5).

Vitiligo is an autoimmune skin disorder that originates from the loss of functional melanocytes of the epidermis, resulting in the appearance of hypopigmented skin areas. In patients affected by malignant melanoma, vitiligo-like lesions occur spontaneously or during anticancer treatments with an incidence that is 10-fold higher than that in the general population (9). Moreover, several studies suggest that the appearance of depigmented patches could be a clinically visible immuno-related event associated with clinical benefit in the context of immunotherapy for melanoma cancer patients (10). In patients with or treated for non-melanoma malignancies, vitiligo-like disorders are absolutely rare.

We discuss two cases of metastatic HR+/HER2− mBC patients treated with the association therapy of CD4/6 inhibitors plus endocrine therapy with a remarkable and durable response after severe skin toxicity and persistent residual diffuse areas of vitiligo-like lesions.

Case 1

In 2008, a 46-year-old woman was diagnosed with estrogen receptor-positive (80%), progesterone receptor-negative (0%), human epidermal growth factor receptor-2 (HER2)-negative, low-grade (G1) invasive cancer of the right breast (pT2N2, M0; Ki-67 index 2%). Primary treatment was right quadrantectomy and excision of sentinel lymph node, adjuvant chemotherapy (docetaxel and cyclophosphamide for six cycles), irradiation of the affected breast and supra- and infraclavicular nodes, and adjuvant endocrine therapy with tamoxifen for 5 years (until 2013).

Thereafter, the patient remained relapse-free for 13 years, until an MRI was performed due to an accidental trauma and revealed metastases in the whole column. The next contrast-enhanced total-body CT scan confirmed numerous osteolytic lesions in all vertebral metamers and showed metastases also in the sternum and pelvis lymph nodes of 2.7 cm [target lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 criteria]. The patient's Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0, and she did not have any comorbidities.

In consideration of the recurrence sites, it was decided not to perform a biopsy, and according to the history of the patient, in July 2017, she started a systemic therapy with a CDK4/6 inhibitor, ribociclib 600 mg/day (three 200-mg tablets daily for 3 weeks every 4 weeks), plus endocrine therapy with letrozole (2.5 mg/day) as the SOC for HR+/HER2− metastatic BC patients (3–5). After 3 months of therapy, the patient developed itchiness followed by a diffuse erythematous-vesicular cutaneous rash in certain areas that evolved into leukodermic lesions (on the trunk, legs, and both arms) (Figure 1A). Thus, we primarily performed a dose reduction of ribociclib (400 mg/day, two 200-mg tablets daily for 3 weeks every 4 weeks) in association with oral (dexamethasone) and topical (clobetasol) steroids. Despite our change in therapy, the cutaneous toxicity did not resolve; thus, after another cycle of therapy with dose-reduced ribociclib (400 mg/day), the use of systemic antineoplastic drugs was stopped, retaining only the endocrine therapy. After 3 months without a cyclin-CD4/6 inhibitor, the cutaneous rash and itchiness disappeared, but depigmentation areas remained (Figure 1B).

A histopathologic examination of a skin biopsy specimen was performed and showed a mild lymphocytic infiltrate (CD8+) along the basement membrane layer (Figure 2A). The Fontana Masson staining test was negative with no single melanocytes and few melanophages in the dermis (Figure 2B). Also, P53 expression was determined using immunohistochemical analysis with evidence of strong immunostaining in basal and supra-basal layers in depigmented skin (Figures 2C, D).

During the treatment, the patient underwent contrast-enhanced total-body CT scans every 3–4 months, and the best response documented was a stable disease per RECIST v1.1. Furthermore, all osteolytic bone metastases became blastic bone metastases.

Accordingly, owing to the good response of cancer to the association therapy despite the toxicity, we tried to give the patient another CDK4/6 inhibitor, palbociclib (125 mg/day, one 125-mg tablet daily for 3 weeks every 4 weeks), with letrozole. After a few days of the first cycle, the patient again developed an erythematosus cutaneous rash; thus, we immediately stopped the therapy. The patient underwent treatment with antihistamine

10.3389/fonc.2023.1067264

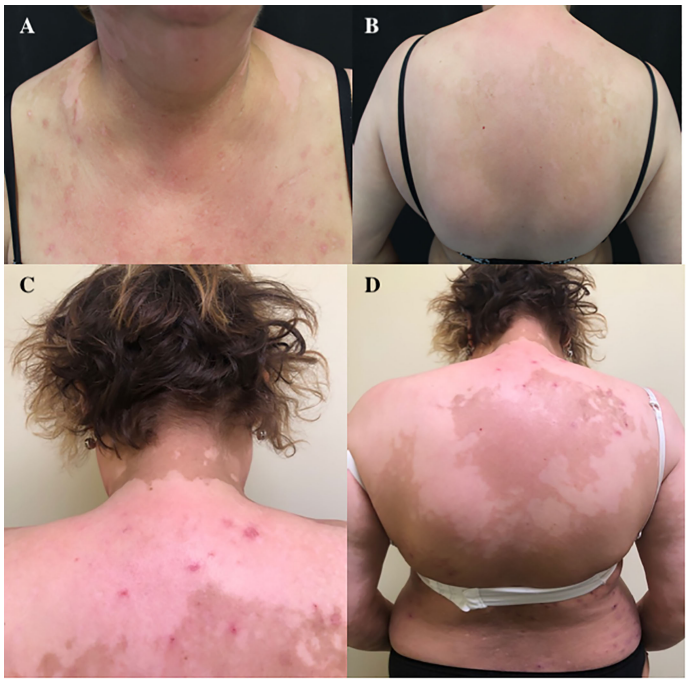


FIGURE 1
(A) Erythematous-vesicular cutaneous rash after 3 months of therapy with ribociclib. **(B–D)** Residual depigmented areas of the back.

(ebastine) and topical steroid (clobetasol) therapy, thus controlling the cutaneous rash.

Currently, the patient is still taking endocrine therapy alone with letrozole (ongoing at the time of writing), and she has persistent and extensive vitiligo-like lesions (Figures 1C, D), but she remains in good clinical condition. She will be followed up with a regular CT scan every 3–4 months.

The last radiological evaluation was performed in November 2021, and it confirmed a persistent response to our treatment, with a PFS of more than 4 years (50 months) despite taking the CDK4/6

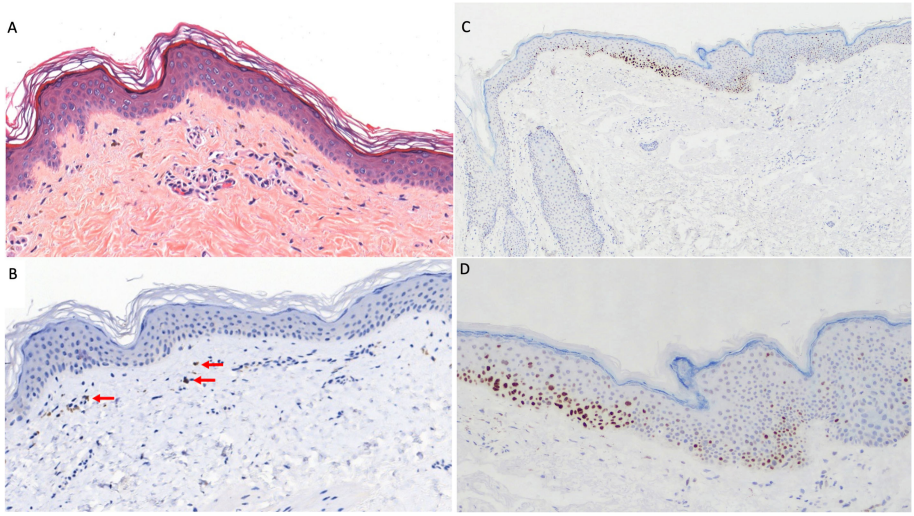


FIGURE 2
Skin histopathologic and immunohistochemical examination. **(A)** Mild perivascular lymphocytic infiltrate in the superficial dermis extended along the basal layer (hematoxylin–eosin, original magnification ×100). **(B)** Focally detected melanin (red arrows) in few dermal melanophages (melan-A monoclonal antibody, A103, Invitrogen; original magnification ×100). **(C, D)** Strong P53 expression (mouse monoclonal anti-P53 antibody MS–738-R7-LabVision/Neomarkers, USA) in basal and supra-basal layers in depigmented skin at original magnification ×50 **(C)** and ×100 **(D)**.

inhibitor for a few months, which compares favorably with the median PFS of 25.3 months with the combination therapy in the Phase 3 MONALEESA-2 study (5).

Case 2

An 80-year-old woman has a history of early BC ER/PR-positive, HER2-negative diagnosed in 1995 (pT2, pN0, M0) for which she underwent a right quadrantectomy and homolateral axillary lymphadenectomy followed by adjuvant radiotherapy and then endocrine therapy with tamoxifen for 5 years according to her premenopausal state. Ten years after surgery, the patient has had a local recurrence of the disease in the upper external right quadrant for which a right upper quadrantectomy was performed in 2005 (ductal invasive BC ER/PR-positive, HER2-negative, grade 1; pT1c). After that, hormonal therapy with anastrozole (1 mg/day) was started according to her post-menopausal state for 5 years, until 2010.

In 2017, because of the high values of tumor markers CEA and CA15.3, the patient underwent a CT scan that documented multiple lung and liver metastases and mediastinal lymph nodes confirmed by the next PET/CT with 18-FDG. The ECOG PS was 0 and she did not have any comorbidities. Therefore, according to her oncological history, in October 2017, she started a first-line endocrine therapy with letrozole (2.5 mg/day) plus CDK4/6i ribociclib (400 mg/day, two 200-mg tablets daily for 3 weeks every 4 weeks).

After 12 months of treatment, the patient developed itchiness and then a diffuse erythematous-vesicular cutaneous rash similar to our first case; this was followed by some areas evolving into permanent depigmented lesions. Thus, the use of systemic antineoplastic drugs was stopped, retaining only letrozole. After 1 month without ribociclib, the cutaneous rash and itchiness disappeared, but several extensive depigmentation areas remained (Figures 3A, B). Despite the attempt to resume treatment with a reduced dose of ribociclib (at both 400 and 200 mg/day), the rash with widespread itching recurred, and therefore, it was decided to permanently discontinue ribociclib and to continue letrozole alone.

During the treatment, the patient underwent CT scans every 3–4 months, and the best response documented was stable disease. In October 2021, the patient underwent a PET/CT-18FDG that documented a persistent complete metabolic response to the treatment with a median PFS of 39 months despite the discontinuation of combination therapy.

Discussion

HR+/HER2− is the subtype of mBC with a better survival outcome thanks to the first-line use of CDK4/6 inhibitors with endocrine therapy (3–5). We reported two cases of HR+/HER2− mBC patients who achieved long-term stabilization of the disease with endocrine therapy alone after approximately only a few months with the SOC in the first-line setting, which is endocrine therapy with ribociclib.

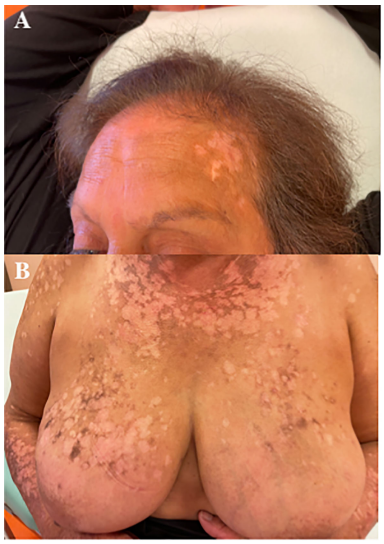


FIGURE 3
(A, B) Extensive depigmentation cutaneous areas after 1 month of stopping the therapy with ribociclib.

Usually, CDK4/6 inhibitors are well tolerated and AEs are typically easily managed with dose modification and supportive care measures. Without a comparative study between the different possible combinations of palbociclib, ribociclib, and abemaciclib in first- and second-line therapy, the choice of physicians is currently mainly driven by the different toxicity profiles of these drugs. The most common AE reported with palbociclib and ribociclib is neutropenia, while the most common AE reported with abemaciclib is diarrhea. Treatment discontinuation was significantly higher with abemaciclib than with palbociclib, but similar between ribociclib and palbociclib. Nowadays, cutaneous AEs are not taken into consideration when choosing what CD4/6 inhibitor to give to the patient. Nevertheless, real-world data have shown that skin toxicity could reduce the tolerability of the therapy for our BC patients, leading to a 25% discontinuation rate (11). Alopecia is the most frequent dermatological AE (7%–33%) of all CD4/6 inhibitors, and it has occurred after approximately 3–4 months of treatment. Other frequent dermatological AEs are maculopapular rash and pruritus, which are commonly mild in severity and more frequent with ribociclib than with palbociclib and abemaciclib. Palbociclib was more associated with dry skin and onychoclasis (11).

We know that cutaneous toxicities diminish the quality of life (QoL) of patients, which impacts their treatment adherence and can affect their personal, social, and workplace relationships, jeopardizing the treatment's success and patient survival (12). Notably, their frequency and severity may be associated with clinical benefit from anticancer therapies; thus, mitigating these events is of importance to maintaining dose intensity and QoL.

The patients in our case reports have had pruritus and an extensive cutaneous rash, the first one after 2 months of therapy and the second one after 1 year. Due to this event, both patients stopped the treatment with CDK4/6 inhibitors, but in both cases, they developed persistent skin-depigmented vitiligo-like areas.

Cancer patients treated with anti-PD1/PD-L1 therapies as well as with tyrosine kinase inhibitors (imatinib, cabozantinib, and pazopanib) experience common skin immune-related AEs such as vitiligo-like lesions, rash, and pruritus (13–15). Moreover, vitiligo occurs in approximately 20% of melanoma patients, which is higher than that of the general population (0.5%–1%), which could be associated with better clinical response and survival (15). It probably occurs due to the immune activation against melanoma-associated antigens expressed by normal melanocytes (MART-1 and gp-100) as a result of cross-reaction from melanoma cells that share the same antigens (16).

Our patients have had very good outcomes despite their skin AEs, with a median PFS that is more similar to the typical value of the combination therapy than that of the endocrine therapy alone. We can speculate about the early onset and/or the severity of the skin AEs in our patients and their eventual prognostic role as well as the correlation between our patients' persistent response to the therapy.

In 2020, Sollena et al. reported an international retrospective study including patients with advanced BC who developed vitiligo-like lesions during treatment with CDK4/6i. Of the 16 patients included in this study, 3 have undergone a cutaneous biopsy of the hypopigmented areas, resulting in the detection of a mild lymphocytic infiltrate along the basement membrane layer with few melanophages in the dermis and a negative Fontana staining (17). These results are similar to what we have found in our patient. In one case, we tried to change the treatment by switching from ribociclib to palbociclib without success. It is possible that the mechanism behind this skin AE is class related.

One possible mechanism to explain this rare skin reaction to CDK4/6 inhibitors is hypothesized by Sollena et al.: that alterations in keratinocyte precursor proliferation and the apoptosis induced by CDK4/6i may lead to a loss of survival stimuli and passive melanocyte premature death, with the consequent onset of hypopigmented lesions (17). This hypothesis is consistent with the results of the histological examination of the skin in the first patient reported in this case series. In fact, we observed evidence of signs of apoptosis in basal and supra-basal layers (P53+), a lymphocytic infiltrate CD8+, and hypopigmentation with few melanophages in the dermis (Fontana staining negative).

At the same time, an intriguing immune-mediated mechanism may justify a correlation between the irreversible vitiligo-like skin toxicity and the exceptional response with limited exposure to CDK4/6 inhibitors. Skin toxicity of CDK4/6 inhibitors, in addition to inducing a passive death of melanocytes, could determine an activation against BC-associated antigens expressed by normal melanocytes. As a result of cross-reaction from melanocytes that could share some antigens also expressed by BC (18), an immune reaction could occur that feeds and makes vitiligo-like toxicity irreversible and, at the same time, helps control the metastatic disease. This hypothesis is also supported by the presence of lymphocyte infiltrates in the skin biopsy performed in the first case report, but other *in vitro* and *in vivo* studies are needed to verify this theory and better understand this peculiar toxicity of these new drugs.

In conclusion, these two case reports documented response to endocrine therapy alone after a premature interruption of CDK4/6i due to a severe cutaneous AE with a vitiligo-like irreversible outcome in two patients with metastatic HR+/HER2− BC that, at the time of last follow-up, both have a PFS of approximately 40 months. Nowadays, the prognostic value of AEs and especially vitiligo-like toxicity in patients treated with CDK4/6i remains unknown and warrants further investigation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not provided for this study on human participants because the approval of the ethics committee is not required for the collection of clinical cases in Italy. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AP, GG, LP, MC, SP and CC were involved in the care of the patients. MP and AO wrote the final version of the manuscript. PS and FF made the histological images and their descriptions. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast cancer statistics, 2022. *CA Cancer J Clin* (2022) 72(6):524–41. doi: 10.3322/caac.21754

2. Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. *Breast Cancer Res* (2016) 18(1):17. doi: 10.1186/s13058-015-0661-5

3. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* (2017) 35(32):3638–46. doi: 10.1200/JCO.2017.75.6155

4. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* (2016) 375(20):1925–36. doi: 10.1056/NEJMoa1607303

5. Hortobagyi, Gabriel N, Salomon M, Stemmer, Howard A, Burris, et al. «Ribociclib as first-line therapy for HR-positive, advanced breast cancer». *New Engl J Med* (2016) 375(18):1738–48. doi: 10.1056/NEJMoa1609709

6. Abola MV, Prasad V, Jena AB. Association between treatment toxicity and outcomes in oncology clinical trials. *Ann Oncol* (2014) 25(11):2284–9. doi: 10.1093/annonc/mdu444

7. Fiala O, Sorejs O, Sustr J, Kucera R, Topolcan O, Finek J. Immune-related adverse effects and outcome of patients with cancer treated with immune checkpoint inhibitors. *Anticancer Res* (2020) 40(3):1219–27. doi: 10.21873/anticanres

8. Fontein DB, Seynaeve C, Hadji P, Hille ET, van de Water W, Putter H, et al. Specific adverse events predict survival benefit in patients treated with tamoxifen or aromatase inhibitors: an international tamoxifen exemestane adjuvant multinational trial analysis. *J Clin Oncol* (2013) 31(18):2257–64. doi: 10.1200/JCO.2012.45.3068

9. Failla CM, Carbone ML, Fortes C, Pagnanelli G, D'Atri S. Melanoma and vitiligo: In good company. *Int J Mol Sci* (2019) 20(22):5731. doi: 10.3390/ijms20225731

10. Nakamura Y, Tanaka R, Asami Y, Teramoto Y, Imamura T, Sato S, et al. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolumab: A multi-institutional retrospective study. *J Dermatol* (2017) 44(2):117–22. doi: 10.1111/1346-8138.13520

11. Raschi E, Fusaroli M, La Placa M, Ardizzoni A, Zamagni C, Poluzzi E, et al. Skin toxicities with cyclin-dependent kinase 4/6 inhibitors in breast cancer: Signals from disproportionality analysis of the FDA adverse event reporting system. *Am J Clin Dermatol* (2022) 23(2):247–55. doi: 10.1007/s40257-021-00645-0

12. Suh Oh HJ, Flórez Menéndez Á, Sacristán Santos V, Fernández Ribeiro F, Vilanova-Trillo L, Constenla Figueiras M, et al. Cutaneous adverse events and quality of life in outpatients receiving anticancer agents: Results from an observational, cross-sectional study. *Drugs Context*. (2020) 9:2020–6-6. doi: 10.7573/dic.2020-6-6

13. Zarogoulidis P, Huang H, Tsiouda T, Sardeli C, Trakada G, Veletza L, et al. Immunotherapy "Shock" with vitiligo due to nivolumab administration as third line therapy in lung adenocarcinoma. *Respir Med Case Rep* (2017) 26(22):283–6. doi: 10.1016/j.rmcr.2017.10.006

14. Dai J, Belum VR, Wu S, Sibaud V, Lacouture ME. Pigmentary changes in patients treated with targeted anticancer agents: A systematic review and meta-analysis. *J Am Acad Dermatol;* (2017) 77(5):902–910.e2. doi: 10.1016/j.jaad.2017.06.044

15. Lommerts JE, Bekkenk MW, Luiten RM. Vitiligo induced by immune checkpoint inhibitors in melanoma patients: an expert opinion. *Expert Opin Drug Saf.* (2021) 20(8):883–8. doi: 10.1080/14740338.2021.1915279

16. Mandelcorn-Monson RL, Shear NH, Yau E, Sambhara S, Barber BH, Spaner D, et al. Cytotoxic T lymphocyte reactivity to gp100, MelanA/MART-1, and tyrosinase, in HLA-A2-positive vitiligo patients. *J Invest Dermatol* (2003) 121(3):550–6. doi: 10.1046/j.1523-1747.2003.12413.x

17. Sollena P, Nikolaou V, Soupos N, Kotteas E, Voudouri D, Stratigos AJ, et al. European Network for cutaneous ADverse event of oncologic drugs (ENCADO) group. vitiligo-like lesions in patients with advanced breast cancer treated with cycline-dependent kinases 4 and 6 inhibitors. *Breast Cancer Res Treat* (2021) 185(1):247–53. doi: 10.1007/s10549-020-05914-w

18. Sellappan S, Grijalva R, Zhou X, Yang W, Eli MB, Mills GB, et al. Lineage infidelity of MDA-MB-435 cells: Expression of melanocyte proteins in a breast cancer cell line. *Cancer Res* (2004) 64(10):3479–85. doi: 10.1158/0008-5472.CAN-3299-2

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 17 May 2023
DOI 10.3389/fonc.2023.1176868

OPEN ACCESS

EDITED BY
Charles Theillet,
Institut du Cancer de Montpellier (ICM), France

REVIEWED BY
Irene Konstantopoulou,
National Centre of Scientific Research Demokritos, Greece
Moom Rahman Roosan,
Chapman University, United States

*CORRESPONDENCE
M. Hammad Rashid
Mohammad.Rashid@utoledo.edu

RECEIVED 01 March 2023
ACCEPTED 02 May 2023
PUBLISHED 17 May 2023

CITATION
Sagan OA, Rothstein A, Jambunathan B, Hadziahmetovic M, Antoniolli A and Rashid MH (2023) Case report: Neuroendocrine breast carcinoma with a germline EGFR T790M mutation. *Front. Oncol.* 13:1176868. doi: 10.3389/fonc.2023.1176868

Case report: Neuroendocrine breast carcinoma with a germline EGFR T790M mutation

Olivia A. Sagan[1], Anna Rothstein[1], Bhaghyasree Jambunathan[1], Mersiha Hadziahmetovic[1], Anita Antoniolli[2] and M. Hammad Rashid[3]*

[1]The University of Toledo College of Medicine and Life Sciences, Toledo, OH, United States, [2]Promedica Physicians, Sylvania, OH, United States, [3]University of Toledo Medical Center – Dana Cancer Center, Toledo, OH, United States

Background: The epidermal growth factor receptor (EGFR) p.Thr790Met (T790M) mutation was discovered as a resistance mechanism in patients with lung cancer treated with first- and second-generation tyrosine kinase inhibitors. Further studies revealed the EGFR T790M mutation in treatment-naive non-small cell lung carcinoma (NSCLC) and as a rare germline mutation strongly associated with NSCLC. Somatic EGFR T790M mutations have been reported in a limited population of patients with triple-negative breast cancer. There are no previous reports of a germline EGFR T790M mutation found in a patient with breast cancer.

Case presentation: We present a rare case of a 42-year-old woman with a rapidly progressing 8 cm mass in the right lateral breast. An additional right breast mass with multiple lymph nodes characteristic or suspicious of metastasis was found. Ultrasound-guided biopsy showed high-grade, poorly differentiated invasive neuroendocrine carcinoma of the right breast and metastatic carcinoma of a right axillary lymph node. Genetic testing revealed a germline EGFR T790M mutation. The patient underwent neoadjuvant chemotherapy, right mastectomy with lymph node dissection, adjuvant radiation to the right chest wall and axilla, and adjuvant chemotherapy.

Conclusion: This is the first reported case of a patient with high-grade neuroendocrine carcinoma, triple-negative breast cancer and a germline EGFR T790M mutation. Further investigation is needed to find a possible correlation between the cancer in this patient and her mutation. Since there are no current guidelines, further research is also needed to define screening protocols for patients with germline EGFR T790M mutations. Additional treatment options and cancer risk could also be found with further research, which would benefit all patients with a germline EGFR T790M mutation.

KEYWORDS

neuroendocrine breast cancer, germline EGFR T790M mutation, triple-negative breast cancer (TNBC), EGFR mutation, chemotherapy

Abbreviations: EGFR/EGF receptor, epidermal growth factor receptor; NSCLC, non-small cell lung carcinoma; TKI, tyrosine kinase inhibitor; T790M, p.Thr790Met; BC, breast cancer; TNBC, triple-negative breast cancer; LN, lymph node; FISH, fluorescence *in situ* hybridization.

Background

As our understanding of molecular genetics in health care expands, specific gene mutations have been characterized and targeted for various cancer treatments. One of these genes is the epidermal growth factor receptor (EGF-receptor or EGFR) gene. The EGF receptor actuates several downstream pathways that regulate a variety of different cellular processes, including DNA synthesis and cell proliferation, which makes it crucial for cancer development (1, 2). In 2004, the presence of activating somatic mutations in the EGF receptor tyrosine kinase domain was identified in non-small cell lung carcinoma (NSCLC) after seeing an increased response in patients treated with wild-type EGFR tyrosine kinase inhibitors (TKI) compared to standard platinum-based chemotherapy (3–7). These mutations are found on exon 19 (deletion), exon 20 (insertion), and exon 21 (L858R point mutation) (8–15). These developments led to first- and second-generation TKIs becoming the standard of care for patients with EGFR-mutated NSCLC (6, 7, 16–18).

However, a specific subset of patients with NSCLC was found to progress while on first- or second-generation TKI. In more than 50% of these patients, the point mutation of EGFR p.Thr790Met (T790M) on Exon 20 was acquired after exposure to TKI, making the first- and second-generation TKI ineffective (19–21). Osimertinib was approved in 2018 as a third-generation TKI for any patient with EGFR-mutated NSCLC who had progressed to first- or second-generation TKI, regardless of the EGFR T790M mutation status (22). Although most patients develop the EGFR T790M mutation after treatment with TKIs, there have been documented cases of patients with treatment-naive EGFR T790M positive NSCLC. The prevalence of the EGFR T790M mutation has been reported between less than 5% and 40% in treatment-naive NSCLC (11, 23–27). The prevalence can vary greatly depending on the study and the technique used (28). Even with this variation, it is clear that the EGFR T790M mutation is not simply a post-TKI treatment resistance mechanism. Although these reports are rare, cases of germline EGFR T790M mutations have also been documented (29, 30). These cases have been of isolated individuals and families, and up to 90% of these patients have been diagnosed with lung adenocarcinoma (30–39).

The EGFR gene also plays an important role in breast cancer (BC). When the EGFR gene is abnormally expressed in BC, it is usually overexpressed or amplified. Although there have been isolated cases of activation of EGFR mutations in BC, this is very rare (3, 40–50). To investigate the role of TKIs in BC, the prevalence of EGFR T790M mutations has been researched. Few patients were found to have this somatic mutation, mainly in patients with triple-negative BC (TNBC) (50, 51). There have not been previously documented cases of patients with a germline EGFR T790M mutation and BC. The importance of the EGFR gene in BC has been clearly defined, but the extent and prevalence of the EGFR T790M mutation in BC have not yet been fully determined.

We present a rare and interesting case of a young woman who developed high-grade neuroendocrine carcinoma, TNBC and was found to have a germline EGFR T790M mutation.

Case presentation

Our patient is a 42-year-old woman who initially presented with a small palpable mass on her right breast with accompanying burning pain. She stated that it had been growing rapidly over 6 to 8 weeks. She also reported night sweats, back pain, headaches, depression, anxiety, and memory loss. In particular, her respiratory review of the systems was negative and she had no smoking history. The patient has a history of hypertension, depression, intramural uterine leiomyoma, and a left breast fibroadenoma removed 20 years ago. In particular, her family history of cancer includes her daughter (leukemia) and her maternal aunt (colon cancer). Her father's medical history is unknown. An initial physical exam showed swelling of the right breast. Palpation demonstrated an 8 cm mass in the right upper outer and lower outer quadrants and a walnut-sized mass in the right axillary tail. No tenderness, skin d'orange appearance, nipple discharge, or supraclavicular lymphadenopathy were documented.

The further imaging was promptly completed. A diagnostic mammogram with ultrasound of the right breast showed an irregular hypoechoic mass of 2.9 x 2.1 x 1.9 cm in the position of 10:00 of the right breast, which was highly suggestive of malignancy. An ultrasound of the right axilla showed an abnormally enlarged lymph node (LN) measuring 2.8 x 1.9 x 1.5 cm with an abnormal cortical thickness of 1 cm. This was noted to be highly concerning for a metastatic LN. An ultrasound-guided biopsy of the right breast mass and the right axillary LN was performed. The specimen of the right breast mass showed invasive high-grade neuroendocrine carcinoma of the breast with extensive necrosis. The LN was positive for metastatic carcinoma. By immunohistochemistry, breast markers were ER negative, PR negative and HER2neu equivocal and not amplified by fluorescence *in situ* hybridization (FISH). It is noteworthy that BRCA1 and BRCA2 were wild-type. Testing for germline mutations in 83 genes associated with genetic disorders was performed. Only one likely pathogenic variant was identified in the EGFR gene: c.2369 C>T {p. Thr790Met}. This mutation was heterozygous. Somatic alterations were checked using an assay that interrogates 324 genes and introns of 36 genes involved in rearrangements. Somatic alterations frequently observed in malignancies and variants of unknown significance were discovered (see Table 1). The tumor was Microsatellite stable, and Mutational Burden was 3 Muts/Mb. Tumor-infiltrating Immune Cell score was 10%, and Tumor Cell score was 0%. Tumor characteristics included that it was GATA-3 negative, CK7 patchy positivity with many cells showing a "dot-pattern" of staining, GCDFP-15 negative, Mammaglobin patchy moderately strong positivity in malignant cells with majority of cells negative, Synaptophysin positive, Chromogranin rare strong positivity in malignant infiltrate with "dot-pattern", TTF-1 scattered positive cells, and CK20 negative. The patient declined testing of family members, primarily due to a history of Acute Lymphoblastic Leukemia in her child and fear of stigmatization.

Magnetic resonance imaging further characterized the previously biopsied right 10:00 breast lesion as irregular and lobulated with central areas of necrosis and heterogeneous

TABLE 1 Results of somatic alterations and variants of unknown significance found in patient.

Gene	Alteration	Gene	Variant of Unknown Significance
EGFR	T790M	BRAF	E26D
PTEN	splice site 209 + 5G>A	IGF1R	N747S
RB1	loss	PTCH1	E48_N49insE
TP53	P58fs*65	SDHA	amplification
		CDKN2A/B	amplification
		IRS2	N28_H29insN
		RAF1	Q255P
		EPHA3	T406N
		NF1	S665F
		RB1	rearrangement
		FGF10	amplification
		PARK2	R191W
		RICTOR	amplification

enhancement predominantly in the periphery. The mass was measured 3 x 2.8 x 2.6 cm without skin invasion. Another mass was observed at 9:00 in the right breast, measuring 6 mm in greatest dimension and 2.7 cm away from the mass at 10:00. The previously biopsied right axillary LN was measured as 3.7 x 2.7 x 2.7 cm. There was also an 11 mm round LN with a near complete loss of normal fatty hilum superficial to the biopsy-proven metastatic LN in the axillary tail. At least six additional level I right axillary LNs were highly suspicious of metastatic LNs. Also, there was an abnormally enlarged level II LN, measuring 1.6 cm, that was suspicious for a metastatic LN. Three adjacent level II LNs were not enlarged, but did look suspicious relative to their left-sided counterparts. No internal mammary or level III lymphadenopathy was observed. A PET-CT showed abnormally increased FDG activity within the lateral aspect of the right breast and right axilla, but no other sites.

The patient's diagnosis was high-grade neuroendocrine carcinoma of the right breast (cT3 cN1-2 M0), clinical prognostic stage IIIC. Neoadjuvant chemotherapy consisting of four cycles of doxorubicin and cyclophosphamide followed by 12 cycles of paclitaxel and carboplatin was started. Carboplatin was discontinued after ten cycles due to neuropathy, which is managed with gabapentin. Once the chemotherapy regimen was completed, the patient's breast mass was significantly decreased in size. The patient then underwent a right mastectomy with dissection of the right LNs, which showed residual ypT1aN1a. She developed lymphedema after surgery, but received treatment in the lymphedema clinic. A postoperative CTA-Chest showed multiple sub-centimeter indeterminate pulmonary nodules. She completed 25 adjuvant radiation fractions to the right chest wall and LN and developed grade 2 radiation dermatitis, which improved with treatment. The metastatic study completed after radiation showed no change in previously known sub-centimeter lung nodules. The patient then completed 8 cycles of adjuvant oral capecitabine. CT of chest/abdomen/pelvis done immediately after adjuvant chemotherapy revealed no change in lung nodules and no evidence of metastatic disease. CT of chest/abdomen/pelvis, brain MRI, and bone scan 7 months after adjuvant chemotherapy revealed no evidence of metastatic disease and stable appearance of chest (see Figure 1). The patient remains clinically disease free as of the last follow-up.

Discussion

The EGFR gene is important in many different types of cancer. Most commonly found at exon 19, 20 or 21 of the EGFR gene, activating somatic mutations are important targets in the treatment of NSCLC with TKI and monoclonal antibody (3–14, 52). Additionally, the EGFR T790M mutation, located in exon 20 of the EGFR gene, was first discovered as a somatic resistance

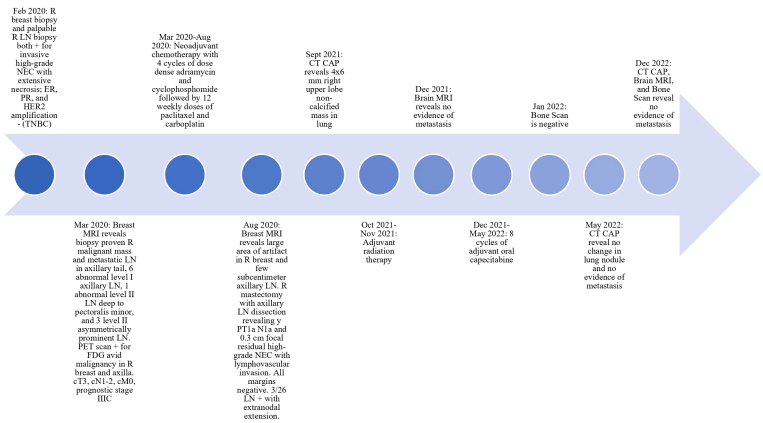


FIGURE 1
Timeline of Patient Diagnosis and Treatment. LN, lymph node; CT CAP, CT of chest/abdomen/pelvis; TNBC, triple negative breast cancer; NEC, neuroendocrine carcinoma.

mechanism in patients with NSCLC who underwent treatment with first- or second-generation TKIs. A third-generation TKI, osimertinib, was approved in 2018 for patients with EGFR-mutated NSCLC, regardless of the status of the EGFR T790M mutation (22). Unfortunately, some patients also developed resistance to osimertinib through additional resistance mechanisms, including HER2 amplification and histologic transformation from NSCLC to high-grade, poorly differentiated, neuroendocrine lung cancer (18, 53–55).

Germline EGFR T790M mutations have been implicated in the development of lung cancer by acting as weak oncogenes (37, 38). Most patients with NSCLC and a germline EGFR T790M mutation also have a concurrent activating somatic EGFR mutation (35, 36). Only a minority of patients have a T790M mutation as their only EGFR mutation (33). Germline EGFR T790M mutations are estimated to occur in 1% of patients with NSCLC and between 0.15 and 0.54% of all cancer patients (29, 30, 38, 56). Germline mutations have been reported primarily in white patients, with few reported in those with East Indian or Asian ancestry (29, 36). This mutation is typically associated with a young age at the time of cancer diagnosis. It has been suggested that patients exhibit anticipation, with the youngest recorded patient diagnosed with this mutation and NSCLC at 29 years old (36). This highlights the importance of the EGFR T790M mutation in NSCLC as a resistance mechanism to treatment and also increases the risk of lung cancer without a significant predisposition to other types of cancer.

Although the EGFR T790M mutation has been associated with NSCLC, there are only rare cases of the EGFR T790M mutation associated with BC. Teng et al. (50) reported EGFR mutations in 11.8% of 70 TNBC cases studied. The two most common mutations found were exon 19 deletions and exon 21 substitutions. In particular, no EGFR mutations were found at exon 20, which is the location of the EGFR T790M mutation (50) (see Figure 2). In a review of 131 BC patients, three patients were reported to have infiltrating ductal carcinoma with lone EGFR T790M mutations. While two of these patients had TNBC, all three mutations were somatic (51). Another interesting case is of a non-smoking woman with a history of BC who developed mutated lung adenocarcinoma; however, this mutation was not present in the breast connective tissue and was determined to be somatic (33).

The case we have presented is the first reported case of a germline EGFR T790M mutation in a patient with high-grade neuroendocrine TNBC. Since this is the first reported case, no association between the germline EGFR T790M mutation and TNBC can be made at this time. However, with the increasing amount of genetic testing performed on cancer patients and the ever-expanding testing options, there could be more cases in the future that would allow us to conclude germline EGFR T790M mutations and BC. Additional research on the EGFR T790M mutation may provide more treatment options for patients with any cancer mutated by EGFR T790M. This patient was not treated with a TKI, as no specific treatment guidelines are defined for breast neuroendocrine carcinomas (57). Still, third-generation TKIs may be a possible treatment option for them in the future based on their mutation. This case also highlights the importance of understanding the resistance mechanisms of the EGFR T790M mutation to third-generation TKI. Since one of the resistance mechanisms of EGFR T790M-mutated NSCLC is to histologically transform into high-grade, poorly differentiated, small cell lung cancer after treatment with osimertinib, studying this resistance

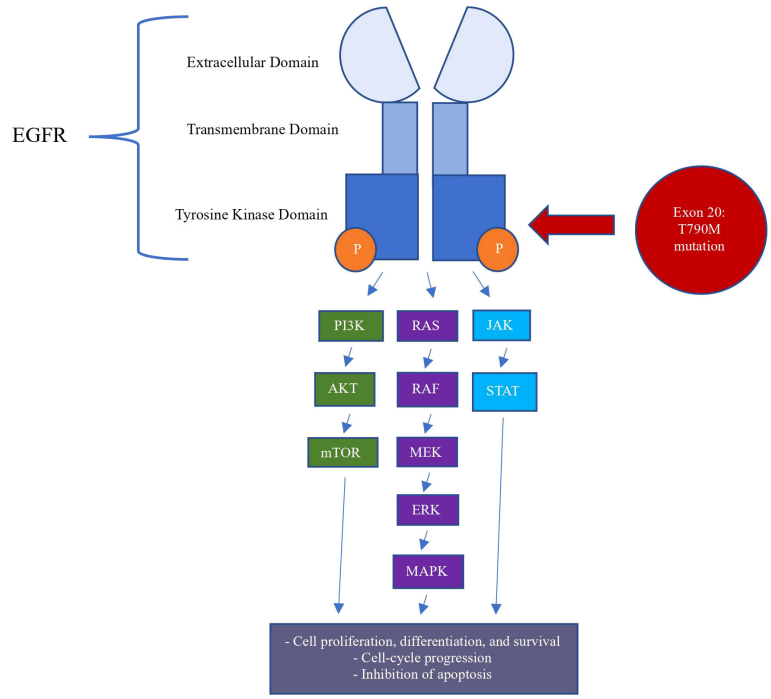


FIGURE 2
Intracellular Pathways of EGFR T790M Mutation in Pathogenesis of Breast Cancer.

mechanism may lead to a connection between the patient's EGFR T790M mutation and neuroendocrine TNBC. Caution, however, will need to be exercised for such correlations as BC is a prevalent disease, and this is currently an incidental discovery.

There is a lack of high-quality data regarding therapeutic options in patients with disease progression of neuroendocrine carcinoma of the breast (58). Neuroendocrine carcinoma follows a more aggressive course than ductal carcinoma (57, 59). Options for treatment include chemotherapy according to neuroendocrine malignancy guidelines (60). There are case reports of response with immunotherapy (61, 62); however, there is no well-described correlation with conventional predictors of response to immunotherapy such as PD-L1 expression, high tumor mutational burden, and microsatellite instability. There are reports of response with peptide receptor radionuclide therapy in patients with metastatic neuroendocrine breast carcinoma and overexpression of somatostatin receptors as evidenced by nuclear scintigraphy (63, 64). The somatic PTEN mutation in this patient also provides the theoretical option of using mTOR inhibition for clinical benefit (65). TROP-2 protein expression has been observed in some patients with neuroendocrine breast carcinoma, suggesting a role for targeted therapy with sacituzumab govitecan (66, 67). Similarly, predictive expression of FOLR1 and H3K36Me3 has been observed in subsets of neuroendocrine BC, which may pave the way for future usage of newer drugs such as farletuzumab and mirvetuximab soravtansine (FOLR1) and histone deacetylase inhibitors (H3K36Me3) (66).

This case also highlights the complicated nature of genetic testing. While specific mutations have provided patients with life-changing treatments, there are many other times when a mutation is found with no particular significance at the time of the test or when the mutations found lead to more questions than answers. In the case of our patient, these new questions revolve around what other cancer screening must be done beyond screening and surveillance of her known disease. There are no standard guidelines for cancer screening in patients with identified EGFR T790M mutations. Patients who have germline EGFR T790M mutations require further studies to assess the presence of lung cancer. Our patient is no different due to her germline mutation and the multiple sub-centimeter indeterminate pulmonary nodules found on her postoperative CTA chest. Although these could be benign, serial imaging should be done to properly characterize these nodules. However, this patient does not have any other EGFR mutations, which is a rarity in germline EGFR T790M-mutated NSCLC patients (33). While no significance can be tied to this currently, this can affect her risk of developing lung cancer. A detailed family history is essential, as this germline mutation is most commonly associated with lung adenocarcinoma. The unknown paternal health history of this patient could provide more information about her case. Furthermore, patients with germline EGFR T790M mutations should seek genetic counseling for themselves and their first-degree relatives. Oxnard et al. (35) also recommend following those with germline EGFR T790M to determine optimal screening and counseling strategies. As more is learned about the EGFR T790M mutation, screening protocols for patients with germline EGFR T790M mutations should be clearly defined to increase the chance of survival of these patients and possibly their families.

Conclusion

This case is unique due to the patient's presentation and her mutation status. At this time, no association can be made between BC and EGFR T790M mutation. Further investigation of the EGFR T790M mutation could elucidate an increased risk of breast or other types of cancer beyond NSCLC. Additional uses for TKIs could also be found along with defined cancer screening protocols to benefit patients who have a germline EGFR T790M mutation. Continued research on the EGFR T790M mutation will help this patient and many others today and in the future with their cancer prevention and treatment.

Patient perspective

The patient had struggled emotionally throughout the process. She had developed grade 1 neuropathy while receiving adjuvant chemotherapy and palmar-plantar erythrodysesthesia while receiving capecitabine.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The authors have obtained written informed consent from the patient for the publication of this case history and applicable data.

Author contributions

OS contributed to the review of the literature and the writing and editing of the case report. AR contributed to the review of the literature and the writing and editing of the case report. BJ contributed to the editing of the case report. MH contributed to reviewing the case history. AA contributed to reviewing the case history. MR was critical to the direction, editing, and submission of the case report. All authors contributed to the article and approved the submitted version.

Funding

The University of Toledo, College of Medicine and Life Sciences, Department of Medicine provided funding.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Russo A, Franchina T, Ricciardi GRR, Picone A, Ferraro G, Zanghì M, et al. A decade of EGFR inhibition in EGFR-mutated non small cell lung cancer (NSCLC): old successes and future perspectives. *Oncotarget.* (2015) 6(29):26814–25. doi: 10.18632/oncotarget.4254

2. Zhang Z, Stiegler AL, Boggon TJ, Kobayashi S, Halmos B. EGFR-mutated lung cancer: a paradigm of molecular oncology. *Oncotarget.* (2010) 1(7):497–514. doi: 10.18632/oncotarget.186

3. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* (2004) 350 (21):2129–39. doi: 10.1056/NEJMoa040938

4. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science.* (2004) 304(5676):1497–500. doi: 10.1126/science.1099314

5. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A.* (2004) 101(36):13306–11. doi: 10.1073/pnas.0405220101

6. Cross DAE, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discovery* (2014) 4(9):1046–61. doi: 10.1158/2159-8290.CD-14-0337

7. Recondo G, Facchinetti F, Olaussen KA, Besse B, Friboulet L. Making the first move in EGFR-driven or ALK-driven NSCLC: first-generation or next-generation TKI? *Nat Rev Clin Oncol* (2018) 15(11):694–708. doi: 10.1038/s41571-018-0081-4

8. Ramlau R, Cufer T, Berzinec P, Dziadziuszko R, Olszewski W, Popper H, et al. Epidermal growth factor receptor mutation-positive non-Small-Cell lung cancer in the real-world setting in central Europe: the INSIGHT study. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* (2015) 10(9):1370–4. doi: 10.1097/JTO.0000000000000621

9. Shi Y, Li J, Zhang S, Wang M, Yang S, Li N, et al. Molecular epidemiology of EGFR mutations in Asian patients with advanced non-Small-Cell lung cancer of adenocarcinoma histology - mainland China subset analysis of the PIONEER study. *PloS One* (2015) 10(11):e0143515. doi: 10.1371/journal.pone.0143515

10. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget.* (2016) 7(48):78985–93. doi: 10.18632/oncotarget.12587

11. Rosell R, Molina MA, Costa C, Simonetti S, Gimenez-Capitan A, Bertran-Alamillo J, et al. Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations. *Clin Cancer Res Off J Am Assoc Cancer Res* (2011) 17(5):1160–8. doi: 10.1158/1078-0432.CCR-10-2158

12. Chou TY, Chiu CH, Li LH, Hsiao CY, Tzen CY, Chang KT, et al. Mutation in the tyrosine kinase domain of epidermal growth factor receptor is a predictive and prognostic factor for gefitinib treatment in patients with non-small cell lung cancer. *Clin Cancer Res Off J Am Assoc Cancer Res* (2005) 11(10):3750–7. doi: 10.1158/1078-0432.CCR-04-1981

13. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* (2005) 97(5):339–46. doi: 10.1093/jnci/dji055

14. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res* (2004) 64(24):8919–23. doi: 10.1158/0008-5472.CAN-04-2818

15. Friedlaender A, Subbiah V, Russo A, Banna GL, Malapelle U, Rolfo C, et al. EGFR and HER2 exon 20 insertions in solid tumours: from biology to treatment. *Nat Rev Clin Oncol* (2022) 19(1):51–69. doi: 10.1038/s41571-021-00558-1

16. Barker AJ, Gibson KH, Grundy W, Godfrey AA, Barlow JJ, Healy MP, et al. Studies leading to the identification of ZD1839 (IRESSA): an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer. *Bioorg Med Chem Lett* (2001) 11(14):1911–4. doi: 10.1016/S0960-894X(01)00344-4

17. Moyer JD, Barbacci EG, Iwata KK, Arnold L, Boman B, Cunningham A, et al. Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res* (1997) 57(21):4838–48. Available at: https://aacrjournals.org/cancerres

18. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer.* (2019) 121(9):725–37. doi: 10.1038/s41416-019-0573-8

19. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res Off J Am Assoc Cancer Res* (2013) 19(8):2240–7. doi: 10.1158/1078-0432.CCR-12-2246

20. Oxnard GR, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res Off J Am Assoc Cancer Res* (2011) 17(6):1616–22. doi: 10.1158/1078-0432.CCR-10-2692

21. Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PloS Med* (2005) 2(3):e73. doi: 10.1371/journal.pmed.0020073

22. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-Small-Cell lung cancer. *N Engl J Med* (2018) 378(2):113–25. doi: 10.1056/NEJMoa1713137

23. Sequist LV, Martins RG, Spigel D, Grunberg SM, Spira A, Jänne PA, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. *J Clin Oncol Off J Am Soc Clin Oncol* (2008) 26(15):2442–9. doi: 10.1200/JCO.2007.14.8494

24. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* (2009) 361 (10):947–57. doi: 10.1056/NEJMoa0810699

25. Inukai M, Toyooka S, Ito S, Asano H, Ichihara S, Soh J, et al. Presence of epidermal growth factor receptor gene T790M mutation as a minor clone in non-small cell lung cancer. *Cancer Res* (2006) 66(16):7854–8. doi: 10.1158/0008-5472.CAN-06-1951

26. Su KY, Chen HY, Li KC, Kuo ML, Yang JCH, Chan WK, et al. Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter EGFR tyrosine kinase inhibitor response duration in patients with non-small-cell lung cancer. *J Clin Oncol Off J Am Soc Clin Oncol* (2012) 30(4):433–40. doi: 10.1200/JCO.2011.38.3224

27. Maheswaran S, Sequist LV, Nagrath S, Ulkus L, Brannigan B, Collura CV, et al. Detection of mutations in EGFR in circulating lung-cancer cells. *N Engl J Med* (2008) 359(4):366–77. doi: 10.1056/NEJMoa0800668

28. Ye X, Zhu ZZ, Zhong L, Lu Y, Sun Y, Yin X, et al. High T790M detection rate in TKI-naive NSCLC with EGFR sensitive mutation: truth or artifact? *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* (2013) 8(9):1118–20. doi: 10.1097/JTO.0b013e31829f691f

29. Girard N, Lou E, Azzoli CG, Reddy R, Robson M, Harlan M, et al. Analysis of genetic variants in never-smokers with lung cancer facilitated by an Internet-based blood collection protocol: a preliminary report. *Clin Cancer Res Off J Am Assoc Cancer Res* (2010) 16(2):755–63. doi: 10.1158/1078-0432.CCR-09-2437

30. Hu Y, Alden RS, Odegaard JI, Fairclough SR, Chen R, Heng J, et al. Discrimination of germline EGFR T790M mutations in plasma cell-free DNA allows study of prevalence across 31,414 cancer patients. *Clin Cancer Res Off J Am Assoc Cancer Res* (2017) 23(23):7351–9. doi: 10.1158/1078-0432.CCR-17-1745

31. Shukuya T, Takahashi K. Germline mutations in lung cancer. *Respir Investig* (2019) 57(3):201–6. doi: 10.1016/j.resinv.2018.12.005

32. Bell DW, Gore I, Okimoto RA, Godin-Heymann N, Sordella R, Mulloy R, et al. Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR. *Nat Genet* (2005) 37(12):1315–6. doi: 10.1038/ng1671

33. Prudkin L, Tang X, Wistuba II. Germ-line and somatic presentations of the EGFR T790M mutation in lung cancer. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* (2009) 4(1):139–41. doi: 10.1097/JTO.0b013e3181915f92

34. Thomas A, Xi L, Carter CA, Rajan A, Khozin S, Szabo E, et al. Concurrent molecular alterations in tumors with germ line epidermal growth factor receptor T790M mutations. *Clin Lung Cancer.* (2013) 14(4):452–6. doi: 10.1016/j.cllc.2013.01.005

35. Oxnard GR, Miller VA, Robson ME, Azzoli CG, Pao W, Ladanyi M, et al. Screening for germline EGFR T790M mutations through lung cancer genotyping. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* (2012) 7(6):1049–52. doi: 10.1097/JTO.0b013e318250ed9d

36. Lou Y, Pecot CV, Tran HT, DeVito VJ, Tang XM, Heymach JV, et al. Germline mutation of T790M and Dual/Multiple EGFR mutations in patients with lung adenocarcinoma. *Clin Lung Cancer.* (2016) 17(2):e5–11. doi: 10.1016/j.cllc.2015.11.003

37. Yu HA, Arcila ME, Harlan Fleischut M, Stadler Z, Ladanyi M, Berger MF, et al. Germline EGFR T790M mutation found in multiple members of a familial cohort. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* (2014) 9(4):554–8. doi: 10.1097/JTO.0000000000000052

38. Gazdar A, Robinson L, Oliver D, Xing C, Travis WD, Soh J, et al. Hereditary lung cancer syndrome targets never smokers with germline EGFR gene T790M mutations. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* (2014) 9(4):456–63. doi: 10.1097/JTO.0000000000000130

39. Tibaldi C, Giovannetti E, Vasile E, Boldrini L, Gallegos-Ruiz MI, Bernardini I, et al. Inherited germline T790M mutation and somatic epidermal growth factor receptor mutations in non-small cell lung cancer patients. *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* (2011) 6(2):395–6. doi: 10.1097/JTO.0b013e3182059a6f

40. Lv N, Xie X, Ge Q, Lin S, Wang X, Kong Y, et al. Epidermal growth factor receptor in breast carcinoma: association between gene copy number and mutations. *Diagn Pathol* (2011) 6:118. doi: 10.1186/1746-1596-6-118

41. Gumuskaya B, Alper M, Hucumenoglu S, Altundag K, Uner A, Guler G. EGFR expression and gene copy number in triple-negative breast carcinoma. *Cancer Genet Cytogenet.* (2010) 203(2):222–9. doi: 10.1016/j.cancergencyto.2010.07.118

42. Park HS, Jang MH, Kim EJ, Kim HJ, Lee HJ, Kim YJ, et al. High EGFR gene copy number predicts poor outcome in triple-negative breast cancer. *Mod Pathol Off J U S Can Acad Pathol Inc.* (2014) 27(9):1212–22. doi: 10.1038/modpathol.2013.251

43. Uramoto H, Shimokawa H, Nagata Y, Ono K, Hanagiri T. EGFR-activating mutations are not present in breast tumors of Japanese patients. *Anticancer Res* (2010) 30(10):4219–22. Available at: https://ar.iiarjournals.org/

44. Tilch E, Seidens T, Cocciardi S, Reid LE, Byrne D, Simpson PT, et al. Mutations in EGFR, BRAF and RAS are rare in triple-negative and basal-like breast cancers from Caucasian women. *Breast Cancer Res Treat* (2014) 143(2):385–92. doi: 10.1007/s10549-013-2798-1

45. Nakajima H, Ishikawa Y, Furuya M, Sano T, Ohno Y, Horiguchi J, et al. Protein expression, gene amplification, and mutational analysis of EGFR in triple-negative breast cancer. *Breast Cancer Tokyo Jpn* (2014) 21(1):66–74. doi: 10.1007/s12282-012-0354-1

46. Bhargava R, Gerald WL, Li AR, Pan Q, Lal P, Ladanyi M, et al. EGFR gene amplification in breast cancer: correlation with epidermal growth factor receptor mRNA and protein expression and HER-2 status and absence of EGFR-activating mutations. *Mod Pathol Off J U S Can Acad Pathol Inc.* (2005) 18(8):1027–33. doi: 10.1038/modpathol.3800438

47. Reis-Filho JS, Pinheiro C, Lambros MBK, Milanezi F, Carvalho S, Savage K, et al. EGFR amplification and lack of activating mutations in metaplastic breast carcinomas. *J Pathol* (2006) 209(4):445–53. doi: 10.1002/path.2004

48. Generali D, Leek R, Fox SB, Moore JW, Taylor C, Chambers P, et al. EGFR mutations in exons 18-21 in sporadic breast cancer. *Ann Oncol Off J Eur Soc Med Oncol* (2007) 18(1):203–5. doi: 10.1093/annonc/mdl322

49. Secq V, Villeret J, Fina F, Carmassi M, Carcopino X, Garcia S, et al. Triple negative breast carcinoma EGFR amplification is not associated with EGFR, kras or ALK mutations. *Br J Cancer.* (2014) 110(4):1045–52. doi: 10.1038/bjc.2013.794

50. Teng YHF, Tan WJ, Thike AA, Cheok PY, Tse GMK, Wong NS, et al. Mutations in the epidermal growth factor receptor (EGFR) gene in triple negative breast cancer: possible implications for targeted therapy. *Breast Cancer Res BCR* (2011) 13(2):R35. doi: 10.1186/bcr2857

51. Bemanian V, Sauer T, Touma J, Lindstedt BA, Chen Y, Ødegård HP, et al. The epidermal growth factor receptor (EGFR / HER-1) gatekeeper mutation T790M is present in European patients with early breast cancer. *PloS One* (2015) 10(8):e0134398. doi: 10.1371/journal.pone.0134398

52. Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N, et al. Amivantamab in EGFR exon 20 insertion–mutated non–Small-Cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase I study. *J Clin Oncol* (2021) 39(30):3391–402. doi: 10.1200/JCO.21.00662

53. Takezawa K, Okamoto I, Tanizaki J, Kuwata K, Yamaguchi H, Fukuoka M, et al. Enhanced anticancer effect of the combination of BIBW2992 and thymidylate synthase-targeted agents in non-small cell lung cancer with the T790M mutation of epidermal growth factor receptor. *Mol Cancer Ther* (2010) 9(6):1647–56. doi: 10.1158/1535-7163.MCT-09-1009

54. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* (2011) 3(75):75ra26. doi: 10.1126/scitranslmed.3002003

55. Jänne PA, Yang JCH, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* (2015) 372(18):1689–99. doi: 10.1056/NEJMoa1411817

56. Wu JY, Yu CJ, Chang YC, Yang CH, Shih JY, Yang PC. Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer. *Clin Cancer Res Off J Am Assoc Cancer Res* (2011) 17(11):3812–21. doi: 10.1158/1078-0432.CCR-10-3408

57. Wei B, Ding T, Xing Y, Wei W, Tian Z, Tang F, et al. Invasive neuroendocrine carcinoma of the breast: a distinctive subtype of aggressive mammary carcinoma. *Cancer.* (2010) 116(19):4463–73. doi: 10.1002/cncr.25352

58. Sun H, Dai S, Xu J, Liu L, Yu J, Sun T. Primary neuroendocrine tumor of the breast: current understanding and future perspectives. *Front Oncol* (2022) 12:848485. doi: 10.3389/fonc.2022.848485

59. Martinez EO, Jorns JM, Kong AL, Kijak J, Lee WY, Huang CC, et al. Primary breast neuroendocrine tumors: an analysis of the national cancer database. *Ann Surg Oncol* (2022) 29(10):6339–46. doi: 10.1245/s10434-022-12123-w

60. Özdirik B, Kayser A, Ullrich A, Savic LJ, Reiss M, Tacke F, et al. Primary neuroendocrine neoplasms of the breast: case series and literature review. *Cancers.* (2020) 12(3):733. doi: 10.3390/cancers12030733

61. Stimes N, Stanbery L, Albrethsen M, Trivedi C, Hamouda D, Dworkin L, et al. Small-cell breast carcinoma with response to atezolizumab: a case report. *Immunotherapy.* (2022) 14(9):669–74. doi: 10.2217/imt-2021-0100

62. Symeonidis D, Papageorgiou G, Liatsos A, Trihia H, Lianos E, Kosmas C. High grade neuroendocrine carcinoma of the breast, first line and maintenance immunotherapy. *Anti-Cancer Drugs* (2022) 33(1):91. doi: 10.1097/CAD.0000000000001126

63. Savelli G, Zaniboni A, Bertagna F, Bosio G, Nisa L, Rodella C, et al. Peptide receptor radionuclide therapy (PRRT) in a patient affected by metastatic breast cancer with neuroendocrine differentiation. *Breast Care* (2012) 7(5):408–10. doi: 10.1159/000343612

64. Liu Q, Zhang J, Kulkarni HR, Baum RP. 177Lu-DOTATOC peptide receptor radionuclide therapy in a patient with neuroendocrine breast carcinoma and breast invasive ductal carcinoma. *Clin Nucl Med* (2020) 45(5):e232. doi: 10.1097/RLU.0000000000003005

65. Weeber F, Cirkel GA, Hoogstraat M, Bins S, Gadellaa-van Hooijdonk CGM, Ooft S, et al. Predicting clinical benefit from everolimus in patients with advanced solid tumors, the CPCT-03 study. *Oncotarget.* (2017) 8(33):55582–92. doi: 10.18632/oncotarget.16029

66. Vranic S, Palazzo J, Sanati S, Florento E, Contreras E, Xiu J, et al. Potential novel therapy targets in neuroendocrine carcinomas of the breast. *Clin Breast Cancer.* (2019) 19(2):131–6. doi: 10.1016/j.clbc.2018.09.001

67. Bardia A, Mayer IA, Diamond JR, Moroose RL, Isakoff SJ, Starodub AN, et al. Efficacy and safety of anti-Trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. *J Clin Oncol* (2017) 35(19):2141–8. doi: 10.1200/JCO.2016.70.8297

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 08 June 2023
DOI 10.3389/fonc.2023.1184952

OPEN ACCESS

EDITED BY
Vittorio Gebbia,
University of Palermo, Italy

REVIEWED BY
Debora Basile,
San Giovanni Di Dio Hospital, Italy
Antonio Di Meglio,
Institut Gustave Roussy, France

*CORRESPONDENCE
Grazia Arpino
grazia.arpino@unina.it

RECEIVED 12 March 2023
ACCEPTED 19 May 2023
PUBLISHED 08 June 2023

CITATION
Di Costanzo F, Carrano S, Iengo G, Cefaliello A, Cossiga V, Morisco F, Giuliano M, De Angelis C and Arpino G (2023) Ribociclib in newly diagnosed hepatitis B infection: A case report. *Front. Oncol.* 13:1184952. doi: 10.3389/fonc.2023.1184952

Ribociclib in newly diagnosed hepatitis B infection: A case report

Fabrizio Di Costanzo[1], Simone Carrano[1], Gennaro Iengo[1], Amedeo Cefaliello[1], Valentina Cossiga[2], Filomena Morisco[2], Mario Giuliano[1], Carmine De Angelis[1] and Grazia Arpino[1]*

[1]Division of Medical Oncology, Department of Clinical Medicine, University of Naples Federico II, Naples, Italy, [2]Department of Clinical Medicine and Surgery, Diseases of the Liver and Biliary System Unit, University of Naples "Federico II", Naples, Italy

Breast cancer is the most frequently diagnosed cancer in women worldwide. Actually CDK4/6 inhibitor Ribociclib is approved for the treatment of metastatic hormone-positive and human epidermal growth factor receptor 2 (HER 2)-negative breast cancer, but comorbidities like infectious or cardiovascular diseases may limit its use.

Case report: A 45-year-old woman was diagnosed with metastatic breast cancer in September 2021; also, her hepatitis screening resulted positive for hepatitis B infection. Patient assumed eradicative therapy for hepatitis and bit after started oncological therapy with Ribociclib.

Outcome: Frequent check of hepatological function was observed since start of eradicative therapy; liver transaminases and bilirubin kept to not rise despite start of oncological treatment with Ribociclib. Patient's Performance Status was also not compromised and revaluation at 4, 9 and 13 months showed partial response and then stable disease.

Discussion: hepatotoxicity of Ribociclib is reported as a possible side effect, and often positivity for hepatitis is cause of exclusion from therapy; in our case, no hepatotoxicity was noted and patient obtained response in terms of control of both infectious and oncological diseases.

KEYWORDS

Ribociclib, hepatitis B, luminal breast cancer, CDK4/6 inhibitors, tenofovir disoproxil fumarate

Introduction

Female breast cancer is the most commonly diagnosed cancer worldwide; in Europe more than 400.000 women are affected every year (1), and more than 130.000 deaths due to metastatic breast cancer were reported in 2018 (2).

Prognosis and mortality are tightly linked to patient-dependent factors and to the molecular biology of the tumor itself; assessing the estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (Erbb2, formerly HER2) expression profile is the first step to classifying the patient's disease into prognostic and histological subtypes. The majority of patients - approximately 70% - are HR-positive and HER2-negative, with an incidence of triple positive, triple negative and HER2-enriched disease of 11%, 12% and 4% respectively (3).

The present first-line treatment involves association of CDK4/6 inhibitors and endocrine therapy as the standard of care for ER and PgR positive, HER2 negative MBC (2). Improvements in efficacy endpoints shown by these drugs were also accompanied by favorable toxicity and safety profiles, especially when compared to traditional chemotherapy (4–10); most recent data shows that, after a 53.5 median follow up, Cdk4/6 inhibitor Ribociclib is associated to significant improvements in Overall survival and Progression-free survival when administered with goserelin plus nonsteroidal aromatase inhibitor (NSAI) or tamoxifen (median OS 58.7 months with ribociclib versus 48.0 months with placebo; mPFS 27.5 months with Ribociclib versus 13.8 months, MONALEESA-7 trial (11)); Abemaciclib plus fulvestrant also prolonged Progression free survival versus placebo/fulvestrant (mPFS, 16.4 vs 9.3 months); and overall survival (OS, 46.7 vs 37.3 months; MONARCH-2 trial (12);) or when associated with NSAI (OS 67.1 months with abemaciclib plus NSAI versus 54.5 months with placebo and a NSAI; mPFS 28.2 vs 14.8 months, MONARCH-3 trial (13);). Last updates from PALOMA trial series, studying Palbociclib, seem to not show a clear advantage of the cdk4/6 inhibitor plus fulvestrant in overall survival, and the observed difference in this case was not statistically significant.

No less important, secondary publications reported that Health-related Quality of life assessment was satisfactory in patients receiving ribociclib, abemaciclib or palbociclib + ET versus placebo + ET (14–16).

Although their action and structure mechanisms are similar, differences in their toxicity profiles were nevertheless reported; Abemaciclib showed a minor rate of hematopoietic toxicity compared to Ribociclib and Palbociclib, but a major rate of diarrhea and fatigue (17, 18).

Among them, Ribociclib can induce QT prolongation and requires a periodic check of cardiac electrophysiology.

Moreover, MONALEESA series trials reported a significant rate of liver toxicity in patients treated with Ribociclib vs placebo, evidence confirmed by real life experiences; liver injury included grade 3/4 hypertransaminasemia (affecting up to 8% of patients and often enduring for many weeks despite discontinuation of therapy) (19, 20) to fulminant hepatitis (21).

This data led to their approval in combination with AI or fulvestrant in therapy for metastatic luminal breast cancer as first-line treatment or after failure of previous ET, while a first-line chemotherapy is usually reserved for patients unable to assume oral therapies or at risk of imminent organ failure (2) - though recent evidence shows relevant efficacy of cdk4/6 inhibitors even in these cases (22).

Among other patient-related prognostic factors in the treatment of MBC, infectious diseases are comorbidities that often affect treatment effectiveness and intensity; of these, one of the most common infective agents is infection with hepatitis B virus (HBV), still an important endemic infection with significant morbidity and mortality (23).

Despite vaccination programs, the spread of HBV infection and related disease is sustained by migrants and refugees with high HBsAg prevalence rates, that favor the diffusion in low endemic countries in Europe (like Italy, Germany, United Kingdom etc.) (24, 25).

In clinical practice, the presence of a preexistent unknown HBV infection or an infection not under surveillance in patients with newly diagnosed cancer is a real possibility. A recent work reports that on above 3000 newly diagnosed oncological patients screened for HBV, the observed rate for previous infection was 6.5%, and for chronic HBV 0.6% (26); an HBV screening is clearly necessary, but it can also represent cause of delay in starting oncological therapy.

In fact the prophylactic or therapeutic use of antivirals agents is able to prevent HBV replication or reactivation in the different serological categories related to HBV status during immunosuppressive or chemotherapy treatment. At moment very few data are available for patients with actively replicating HBV infection and oncological treatment; in many trial series involving cdk4/6 inhibitors their inclusion was demanded on clinician judgement (27, 28), or excluded at all (29); hence, the need to assess safety of these drugs in particular cohorts of patient, like the HBV-infected ones, whose clinical management is underreported.

Case presentation

A 45-year-old, no smoker Caucasian woman was diagnosed with metastatic breast cancer in September 2021. In August 2021, she had undergone a right breast core biopsy, and histological examination diagnosed invasive ductal breast cancer: hormonal receptor status (ER and PgR) was positive, HER2 was not overexpressed, Ki-67 was 60%.

In September 2021, staging with 18FDG PET/CT detected breast disease, axillary and mediastinal lymph node metastases, humerus, iliac and ischium bone metastases; contrast-enhanced breast MRI and bone scintigraphy both confirmed metastatic disease.

Combination therapy with Ribociclib 600mg/die for 21 days with 28-days cycle plus Letrozole 2.5mg/day plus Triptorelin 3.75mg every four weeks was adopted as first-line treatment for this pre-menopausal, hormone receptor-positive and HER2-negative MBC. Patient had no other comorbidities and did not assume drugs before starting therapy.

Before proceeding with treatment, we evaluated infectious markers, and found hepatitis B serology positive for infection as reported below:

T0 –September 2021.

- HBsAg positive
- HBV DNA 4383 IU/mL
- HBsAb Negative
- HBcAb IgG Positive
- HBcAb IgM Negative
- HBeAg Negative
- Normal transaminases and liver function tests; no HDV coinfection.

The assessment of hepatic fibrosis by a transient elastography (fibroscan), reported a value of hepatic stiffness of 3.3 kPa and of CAP (Controlled Attenuation Parameter) of 199dB/m, indicative of absence of fibrosis and steatosis.

Following the hepatologist's recommendations, the patient started treatment with Tenofovir disoproxil fumarate 245 mg/day for her diagnosis of hepatitis B HBeAb positive with the recommendation to check hepatitis B status (quantitative HBV-DNA) and liver function weekly, especially during the first month of treatment with Ribociclib.

As such, during the first cycle of treatment with Ribociclib in September 2021, we carried out weekly evaluations of HBV DNA levels, which significantly decreased (28 UI/ml) and subsequently negativized (<10 UI/ml) (Figure 1).

After three cycles of treatment with Ribociclib, in January 2022, 18FDG PET plus contrast-enhanced CT and breast MRI were repeated (Figure 2). The patient achieved a complete metabolic response and a partial response of disease (PR), according to Response Evaluation Criteria for Solid Tumors [RECIST1.1 (30)].

Compared to September 2021, there were no areas of uptake at the 18FDG PET and there was a significant reduction of the breast site, lymph node and bone metastases in the contrast-enhanced CT and breast MRI; revaluations were performed in May 2022, when 18FDG PET, contrast-enhanced CT and breast MRI confirmed disease stability (Figure 3), and in September 2022 (stable disease).

Both times, HBV DNA levels continued to be undetectable.

Most importantly, treatment was well tolerated - with hematological toxicity not more than grade 2 according to CTCAE criteria and no need for dose reduction. No febrile neutropenia or QTc prolongation were reported; no liver toxicity emerged and the patient did not experience episodes of fatigue. Moreover, despite undergoing such an intense treatment, patient's mood was constantly good; she did not ask or manifest need of psychological support and, to the date, patient shows a positive thinking and feelings of gratitude (Figure 4).

Discussion

Female breast cancer is the leading diagnosed tumor worldwide; prognosis and treatments are related to tumor stage at time of diagnosis, and for women with non-metastatic disease (almost 65% (31, 32), therapeutic goals are tumor eradication and preventing recurrence.

Metastatic breast cancer is still an incurable disease; nevertheless, outcomes are constantly improving and new drugs are challenging this statement.

In the choice of treatment, patient status and comorbidities play a key role; infectious diseases like hepatitis often lead to the discontinuation of treatment for patients undergoing cytotoxic therapy, and many chemotherapy regimens - like anthracycline-based therapy - have been proven to cause HBV reactivation in patients with solid organ malignancies (33–35).

In our case, the first choice we had was which cdk4/6 inhibitor pick for the patient; even if a direct head-to-head comparison is not available, no clear differences in terms of efficacy between the three molecules emerge from clinical practice and clinician's choice is

	15.9.2021	29.9.2021	13.10.2021	15.10.2021	17.11.2021	12.01.2022	23.02.2022
HBV DNA	4383 UI/mL	Start of therapy with TENOFOVIR	28 UI/mL	First cycle of RIBOCICLIB	<10 UI/mL	-	-
AST	12 UI/L		15 UI/L		13 UI/L	18 UI/L	18 UI/L
ALT	11 UI/L		12 UI/L		15 UI/L	21 UI/L	20 UI/L
ALP	94 UI/L		101 UI/L		113 UI/L	120 UI/L	118 UI/L

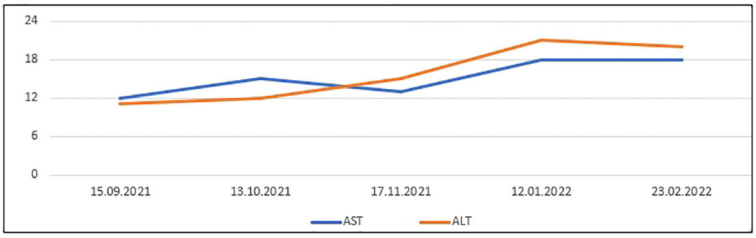


FIGURE 1
Five month-follow up of HBV DNA and liver function parameters: while HBV DNA decreased after Tenofovir, no signs of toxicity occurred after combination of Ribociclib + ET + Tenofovir.

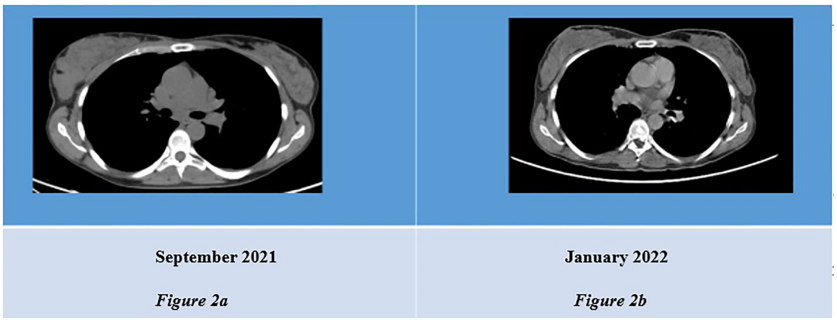


FIGURE 2
(A) CT scan showing thickened right mammal gland. **(B)** Revaluation CT scan showing reduced mass in infero-external right breast.

usually based on patient's age and comorbidities and on the slightly different specter of toxicities, however the switch among inhibitors is allowed if the patient develops severe side effects from one of those (20).

In our case, possible interactions with antivirals agents were a major factor to evaluate.

In order to avoid drug-induced excessive toxicities and further liver injury in the context of HBV infection, a discussion with hepatologist was hold and pharmacokinetics of all three cdk4/6 inhibitors were considered, as no clear contraindication emerged from a first analysis of literature.

Ribociclib is well known as a strong CYP3A4/5 time-dependent inhibitor, especially when administered at a 600 mg dose, and the FDA leaflet recommends to avoid the concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, protease inhibitor for HIV and HCV, itraconazole, ketoconazole, posaconazole, voriconazole, ritonavir, saquinavir) because of the increase in the recorded CDKis plasma exposure that may lead to increased toxicity (36). Clinical decision about choosing Ribociclib for our patient was based on efficacy data showed by MONALEESA-7 trial, the only available study enrolling premenopausal MBC patient exclusively, and on the favorable manageability profile reported in patients with impairment of hepatic or renal function (37, 38).

As our hepatologist did not find any contraindication for use of Ribociclib in this patient and considered Tenofovir disoproxil fumarate a valid option to further protect from HBV reactivation during

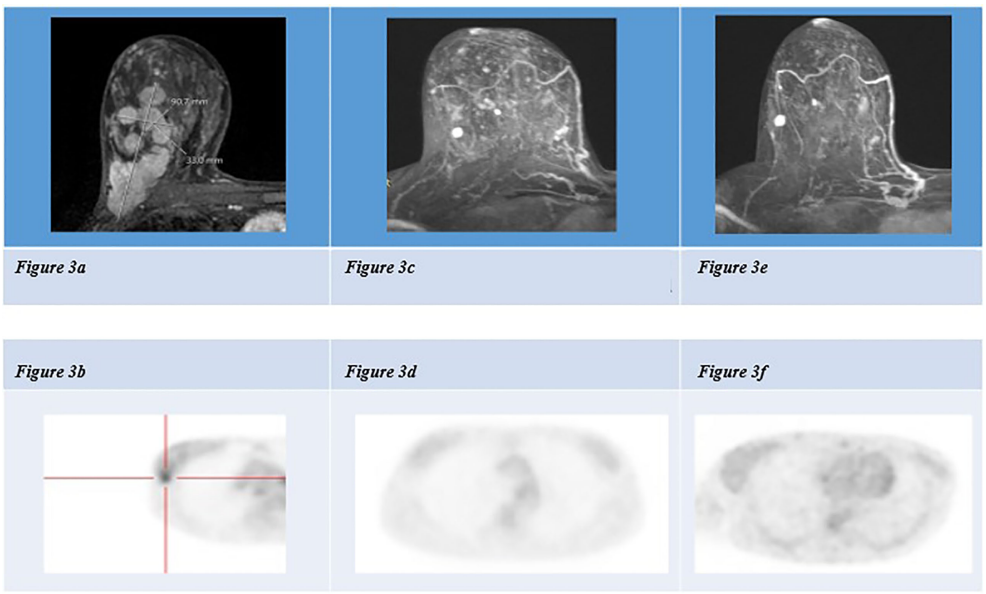


FIGURE 3
(A) Breast MRI of September 2021: multiple lesions occupying an area of 90x33x60mm in the right breast, below, 18-FDG PET scan of September 2021 showing contrast enhancement in right breast **(B). (C)** Breast MRI of January 2022: subcutaneous nodules at infero-external and infero-internal right quadrants, with no 18- FDG uptake (see below, **D**). **(E)** Breast MRI of May 2022: subcutaneous nodules at infero- external and infero-internal right quadrants, with no 18-FDG uptake (see below, **F**).

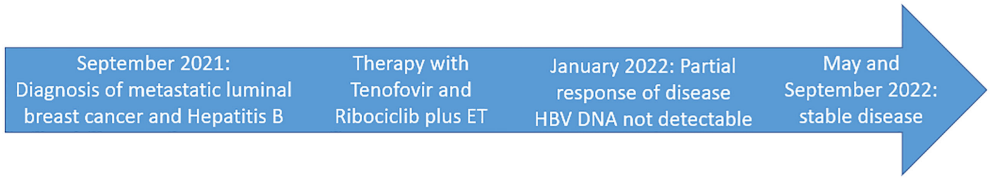


FIGURE 4
Timeline with most relevant case episodes.

oncological treatment, we assessed this association as a reasonably low risk therapy for both oncological and infective diseases.

To the best of our knowledge, no case of concomitant Cdk 4/6 inhibitor + ET and anti HBV infection therapy were previously reported; the decision to treat this patient is supported by the good safety profile showed by Ribociclib both in the MONALEESA trial series and in the clinical practice and noticing the patient's good Performance Status.

Conclusions

We observed that it is possible to treat Hepatitis B-infection and Luminal metastatic breast cancer with both eradicative and oncological therapies; the result obtained in terms of any grade toxicity, the liver functionality remaining unaffected, the maintained response and the control over HBV infection are an encouraging outcome for treatment of patients with luminal breast cancer and hepatitis B infection.

Clearly, a risk-benefit assessment is always necessary for every patient; Authors' proposition is that the report can be useful to clinicians when treating patients with important comorbidities like hepatitis B infection.

We also believe that this case strengthens the importance of a multidisciplinary approach. After discussion with hepatologist we were able to choose adequate therapy and, importantly, our young patient was supported from a dedicated nutritionist and, if needed, psycho-oncologist in order to fully address any potential need; this kind of integrated management allow to assess patient-tailored therapies that generally grant a prompt support and care of adverse events.

However we recognize that this integrated approach is not always feasible in all institutions and, eventually, collaboration among smaller and larger institutions should be implemented in order to deliver the same standard of care to all patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant for the publication of this case report.

Author contributions

All authors contributed equally to this work.

Conflict of interest

MG reports consulting fees for Consulting or advisory Role: Lilly, Novartis, Pfizer, AstraZeneca; Speaker's Bureau: Lilly, Novartis, Pfizer, Eisai, Roche, AstraZeneca, Daichii Sankyo, MSD; Travel, accommodation, expenses: Novartis, Pfizer, Roche. CD reports personal fees from Roche, AstraZeneca, Lilly, GSK, Novartis, Seagen and Pfizer, Advisory Board for Roche, AstraZeneca, Lilly, GSK, Novartis, Seagen and Pfizer, support for attending meetings and/or travel Roche, AstraZeneca, Lilly, GSK, Novartis, Celgene and Pfizer, grants from Novartis. GA reports personal fees from Novartis; personal fees from Lilly, grants and personal fees from Roche, grants, personal fees and non-financial support from Pfizer, grants, personal fees and non-financial support from AstraZeneca, personal fees from Daichi, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Dafni U, Tsourti Z, Alatsathianos I. Breast cancer statistics in the European union: incidence and survival across European countries. *Breast Care (Basel).* (2019) 14 (6):344–53. doi: 10.1159/000503219

2. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* (2021) 32(12):1475-–95. doi: 10.1016/j.annonc.2021.09.019

3. *American Cancer society. breast cancer facts & figures 2019-2020.* Atlanta: American Cancer Society, Inc (2019).

4. Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med* (2018) 379:1926–36. doi: 10.1056/NEJMoa1810527

5. Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med* (2019) 381 (4):307–16. doi: 10.1056/NEJMoa1903765

6. Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol* (2018) 19(7):904–15. doi: 10.1016/S1470-2045(18)30292-4

7. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer – PALOMA 2 clinical trial. *N Engl J Med* (2016) 375 (20):1925–36. doi: 10.1056/NEJMoa1607303

8. Zhang QY, Sun T, Yin YM, Li HP, Yan M, Tong ZS, et al. MONARCH plus: abemaciclib plus endocrine therapy in women with HR+/HER2- advanced breast cancer: the multinational randomized phase III study. *Ther Adv Med Oncol* (2020) 12:1758835920963925. doi: 10.1177/1758835920963925

9. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Hart L, et al. LBA17_PRd; overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer (ABC) treated with endocrine therapy (ET) + ribociclib (RIB). *Ann Oncol* (2021) 32 (suppl 5):S1283–346. doi: 10.1016/j.annonc.2021.08.2090

10. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal b breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* (2020) 21(1):33–43. doi: 10.1016/S1470-2045(19)30786-7

11. Lu YS, Im SA, Colleoni M, Franke F, Bardia A, Cardoso F, et al. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR+/HER2- advanced breast cancer in MONALEESA-7: a phase III randomized clinical trial. *Clin Cancer Res* (2022) 28(5):851–9. doi: 10.1158/1078-0432.CCR-21-3032

12. Sledge GWJr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* (2017) 35(25):2875–84. doi: 10.1200/JCO.2017.73.7585

13. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. A. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* (2017) 35(32):3638–46. doi: 10.1200/JCO.2017.75.6155

14. Harbeck N, Franke F, Villanueva-Vazquez R, Lu YS, Tripathy D, Chow L, et al. Health-related quality of life in premenopausal women with hormone-receptor-positive, HER2-negative advanced breast cancer treated with ribociclib plus endocrine therapy: results from a phase III randomized clinical trial (MONALEESA-7). *Ther Adv Med Oncol* (2020) 12:1758835920943065. doi: 10.1177/1758835920943065

15. Goetz MP, Martin M, Tokunaga E, Park IH, Huober J, Toi M, et al. Health-related quality of life in MONARCH 3: abemaciclib plus an aromatase inhibitor as initial therapy in HR+, HER2- advanced breast cancer. *Oncologist* (2020) 25(9):e1346–54. doi: 10.1634/theoncologist.2020-0084

16. Rugo HS, Diéras V, Gelmon KA, Finn RS, Slamon DJ, Martin M, et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. *Ann Oncol* (2018) 29(4):888–94. doi: 10.1093/annonc/mdy012

17. Onesti CE, Jerusalem G. CDK4/6 inhibitors in breast cancer: differences in toxicity profiles and impact on agent choice. *A systematic Rev meta-analysis. Expert Rev Anticancer Ther* (2021) 21(3):283–98. doi: 10.1080/14737140.2021.1852934

18. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med* (2018) 382:514–24. doi: 10.1056/NEJMoa1911149

19. Fuentes-Antrás J, de Luna A, López de Sá A, Ocaña A, García-Sáenz JÁ, Moreno F. Safety and efficacy of cyclin-dependent kinase inhibitor rechallenge following ribociclib-induced limiting hypertransaminasemia. *Breast* (2020) 54:160–3. doi: 10.1016/j.breast.2020.10.007

20. Meynard L, Grellety T. CDK 4/6 inhibitor successful rechallenge after limiting hepatic toxicity. *Breast J* (2020) 26(2):255–7. doi: 10.1111/tbj.13532

21. Topcu A, Yasin AI, Shbair AT, Besiroglu M, Simsek M, Sucuoglu Z, et al. A case report of fulminant hepatitis due to ribociclib with confirmed by liver biopsy in breast cancer. *J Oncol Pharm Pract* (2022) 28(1):242–6. doi: 10.1177/10781552211027931

22. Lu Y-S, Mahidin EIBM, Azim H, Eralp Y, Yap YS, Seock-Ah I, et al. Primary results from the randomized phase II RIGHT choice trial of premenopausal patients with aggressive HR+/HER2– advanced breast cancer treated with ribociclib + endocrine therapy vs physician's choice combination chemotherapy. *Presented at SABCS* (2022) 6-10:2022. doi: 10.1158/1538-7445

23. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis b virus infection: a systematic review of data published between 1965 and 2013. *Lancet* (2015) 386:1546–55. doi: 10.1016/S0140-6736(15)61412-X

24. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet* (2012) 380:2095–128. doi: 10.1016/S0140-6736(12)61728-0

25. European Association for the Study of the LiverEASL 2017 clinical practice guidelines on the management of hepatitis b virus infection. *Lancet Oncol* (2020) 21 (1):33–43. doi: 10.1016/j.jhep.2017.03.021

26. Ramsey SD, Unger JM, Baker LH, Little RF, Loomba R, Hwang JP, et al. Prevalence of hepatitis b virus, hepatitis c virus, and HIV infection among patients with newly diagnosed cancer from academic and community oncology practices. *JAMA Oncol* (2019) 5(4):497–505. doi: 10.1001/jamaoncol.2018.6437

27. Available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1903765/suppl_file/nejmoa1903765_protocol.pdf.

28. Available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1607303/suppl_file/nejmoa1607303_protocol.pdf.

29. Available at: https://ascopubs.org/doi/suppl/10.1200/JCO.2017.75.6155/suppl_file/protocol_2017.756155.pdf.

30. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).". *Eur J Cancer* (2009) 45(2):228–47. doi: 10.1016/j.ejca.2008.10.026

31. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nat* (2012) 490(7418):61–70. doi: 10.1038/nature11412

32. Centers for Disease Control and Prevention. *Incidence and relative survival by stage at diagnosis for common cancers. USCS data brief, no. 25.* (2021) Atlanta, GA: Centers for Disease Control and Prevention.

33. Perrillo RP, Martin P, Lok AS. Preventing hepatitis b reactivation due to immunosuppressive drug treatments. *JAMA* (2015) 313:1617. doi: 10.1001/jama.2015.2571

34. Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US food and drug administration warnings on hepatitis b reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology* (2015) 61:703–11. doi: 10.1002/hep.27609

35. Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with hepatitis b virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* (2004) 90:1306–11. doi: 10.1038/sj.bjc.6601699

36. Roncato R, Angelini J, Pani A, Cecchin E, Sartore-Bianchi A, Siena S, et al. CDK4/6 inhibitors in breast cancer treatment: potential interactions with drug, gene, and pathophysiological conditions. *Int J Mol Sci* (2020) 21:6350. doi: 10.3390/ijms21176350

37. Samant S, Yang S, Miller M, Ji Y. Pharmacokinetics of ribociclib in subjects with hepatic impairment;. *J Clin Pharmacol* (2021) 61(8):1001–9. doi: 10.1002/jcph.182

38. Price GL, Sudharshan L, Ryan P, Rajkumar J, Sheffield KM, Nash Smyth E, et al. Real world incidence and management of adverse events in patients with HR+, HER2- metastatic breast cancer receiving CDK4 and 6 inhibitors in a united states community setting. *Curr Med Res Opin* (2022) 13:1–13. doi: 10.1080/03007995.2022.2073122

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 16 June 2023
DOI 10.3389/fonc.2023.1046003

OPEN ACCESS

EDITED BY
Areerat Suputtitada,
Chulalongkorn University, Thailand

REVIEWED BY
Tevfiktolga Sahin,
İnönü University, Türkiye
Nguyen Hai Nam,
Cho Ray Hospital, Vietnam

*CORRESPONDENCE
Zhen-Hua Song
songzhenhuaszh9@126.com
Bu-He Tang
tangbuhe2008@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
RECEIVED 16 September 2022
ACCEPTED 23 May 2023
PUBLISHED 16 June 2023

CITATION
Sui Y-F, Tong L-Q, Lin X-F, Wu H-X, Shi J-Q, Wang S-S, Tang B-H and Song Z-H (2023) Revitalizing quality of life: a case report on the beneficial impact of comprehensive rehabilitation therapy in treating upper-limb lymphedema following breast cancer surgery. *Front. Oncol.* 13:1046003. doi: 10.3389/fonc.2023.1046003

Revitalizing quality of life: a case report on the beneficial impact of comprehensive rehabilitation therapy in treating upper-limb lymphedema following breast cancer surgery

Yan-Fang Sui[1†], Lang-Qian Tong[2†], Xia-Fei Lin[1], Hai-Xia Wu[1], Jing-Qin Shi[1], Shan-Shan Wang[1], Bu-He Tang[3*] and Zhen-Hua Song[1*]

[1]Department of Rehabilitation Medicine, Affiliated Haikou Hospital of Xiangya Medical College, Central South University, Haikou, China, [2]Department of Nuclear Medicine, Affiliated Haikou Hospital of Xiangya Medical College, Central South University, Haikou, China, [3]Department of Rehabilitation Medicine, Hainan Sino-german orthopaedic Hospital, Haikou, China

Objective: To underscore the paramount significance of incorporating comprehensive rehabilitation therapy as a crucial aspect of managing lymphedema caused by breast cancer surgery, and to illuminate our first-hand experience and insights gained in utilizing this approach.

Methods: We present a case report of a breast cancer survivor who had been suffering from persistent left upper-limb edema for over 15 years, who was effectively treated with a combination of conventional rehabilitation (seven-step decongestion therapy) and a comprehensive rehabilitation program (seven-step decongestion therapy, along with core and respiratory function training, as well as functional brace wearing). The efficacy of the rehabilitation therapy was evaluated through a comprehensive assessment

Results: Although the patient underwent the conventional rehabilitation program for one month, only limited improvement was observed. However, after an additional month of comprehensive rehabilitation treatment, the patient exhibited significant improvement in both lymphedema and the overall function of the left upper limb. The patient's progress was quantified by measuring the reduction in arm circumference, which demonstrated a notable decrease. Furthermore, improvements in joint range of motion were observed, with forward flexion of the shoulder enhancing by 10°, forward flexion improving by 15°, and elbow flexion increasing by 10°. In addition, manual muscular strength tests revealed an increase in strength from Grade 4 to Grade 5. The patient's quality of life was also significantly improved, as evidenced by the increase in the Activities of Daily Living score from 95 to 100 points, the increase in the the Functional Assessment of Cancer Therapy: Breast score from 53 to 79 points, and the decrease in the Kessler Psychological Distress Scale score from 24 to 17 points.

Conclusion: While seven-step decongestion therapy has been shown to be effective in reducing upper-limb lymphedema caused by breast cancer surgery, it has limitations in treating more chronic cases of the condition. However, when combined with core and respiratory function training and functional brace wearing, seven-step decongestion therapy has been shown to be even more effective in reducing lymphedema and improving limb function, ultimately leading to significant improvements in quality of life.

KEYWORDS

breast cancer, comprehensive rehabilitation, functional brace, lymphedema, seven-step decongestion therapy

Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide and continues to be a major global health concern (1). Breast cancer incidence rates have been rapidly increasing in China, making it one of the countries with the fastest-growing rates of breast cancer globally (2–4). The primary components of breast cancer surgery typically involve lumpectomy and/or axillary lymph node dissection (2). Lymphedema can result from a variety of causes including surgery, chemotherapy, radiotherapy, trauma, infection, obesity, and other personal factors (4, 5).

Breast cancer-related lymphedema (BCRL) affects about 25% of women following breast cancer surgery (1, 6). This condition can have a significant impact on a patient's quality of life and physical function (5–7).The typical treatments for breast cancer-related lymphedema (BCRL) involve lymphatic drainage, elastic bandaging, exercise therapy, and other rehabilitation therapies. However, there is limited research on comprehensive rehabilitation therapy for this condition (8–13).Therefore, a case is presented to underscore the significance of comprehensive rehabilitation and share the practical knowledge gained from it. The presented case involves a patient who experienced left upper-limb swelling for over 15 years following breast cancer surgery. Although conventional therapy yielded limited improvements, the patient's lymphedema and function markedly improved after undergoing one month of comprehensive rehabilitation.

Case presentation

A 51-year-old female patient who had undergone modified radical resection of her left breast and had been experiencing left upper limb swelling and limited mobility for 15 years was admitted to the Affiliated Haikou Hospital of Xiangya Medical College. The patient underwent modified radical resection of the left breast on April 19, 2006, following preoperative chemotherapy, due to a mass found on the left breast. The specific details regarding the intraoperative lymph node dissection are unknown. However, intraoperative pathology confirmed the mass as Grade 3 invasive ductal cancer, and the patient received postoperative concurrent chemotherapy and radiation. The patient experienced redness, swelling, pain, and increased skin temperature in the left upper limb six months after the surgery. This was diagnosed as cellulitis of the left upper limb caused by *Staphylococcus aureus* infection. The patient received appropriate treatments that provided some relief from the pain, but these treatments were irregular. Nonetheless, the left upper limb remained swollen. As the patient was left-handed, the swelling of her left hand had a serious impact on the quality of life. Consequently, she sought rehabilitation treatment at our hospital.

During the post-admission examination, it was noted that the left upper limb and left hand were significantly swollen in comparison with the contralateral side. However, there was no elevation in the skin temperature and palpation revealed that the skin was rigid, tensed, and had reduced elasticity. The left upper extremity displayed hypoesthesia and was found to have positive pitting and Stemmer indications. (Figure 1) Ultrasound examination of the axilla indicated that neither the deep nor superficial veins of the left upper limb were thrombosed. Figure 2 illustrates the specific measurement method used. Initially, the patient underwent a conventional rehabilitation program with seven-step decongestion therapy (14) for a duration of one month, and Table 1 showed an improvement in patient's left upper lymphedema. But the rehabilitation progress was sluggish and unsatisfactory. To enhance the progress of rehabilitation and identify any additional factors that might be hindering the recovery, a comprehensive rehabilitation therapy was adopted, including the conventional seven-step decongestion therapy, the posture and respiratory assessment combined with their corresponding training and bracing wearing (details can be seen in the Supplement). According to the assessment, the patient exhibited abnormal posture, weakened strength in the respiratory and core muscles, and was incapable of sustaining a functional position of the left upper limb for prolonged periods. The substantial edema in the patient's left upper limb caused an imbalance in the strength between the left and right sides of the body, leading to an unnatural posture. Based on the reassessment findings, there was implementation of core and respiratory function training as well as utilization of a functional brace (i.e., upper arm-waist fixing brace)

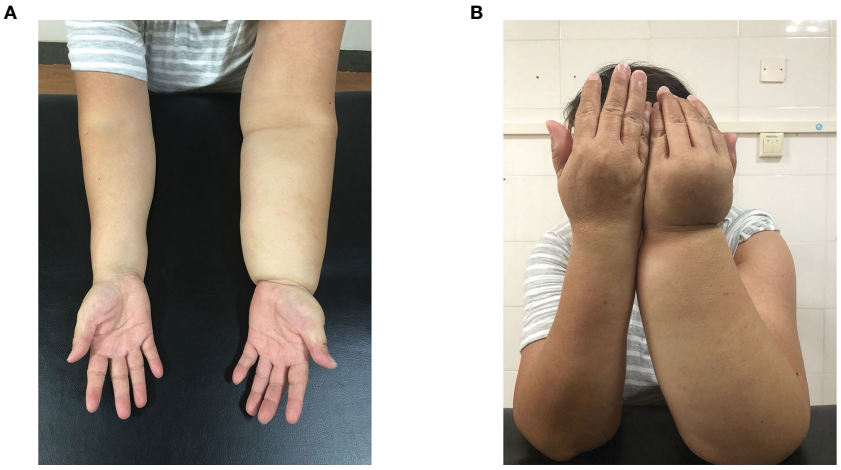


FIGURE 1
Left Upper Limb Lymphedema. (**A**: Palmar Side of Forearm, **B**: Dorsal Side of Forearm).

(Figure 3). A brace was designed and utilized to stabilize the lumbar spine, prevent lateral trunk flexion, and support upper arm abduction during upper-limb activities. The brace also reduced weight bearing of the edematous upper limb and allowed for extended functional activity time. A low-temp. thermoplastic sheet brace was selected due to its good shaping properties, and lightweight, breathability, high strength, and waterproof nature. Appropriate sheets were chosen and limb part sizes were measured. Low-temp. thermoplastic sheets of 3 different specifications and models were selected based on hardness and breathability needed for different fixations. Sheets were put in 65-70°C water and heated for 1-3 min. Softened materials were removed, dried, and shaped. Hook-and-loop fasteners and screws were used to fix, with padding for protection. Elastic sleeves should be worn on affected limb before wearing. To wear, first fix trunk part and Velcro, then upper arm part and Velcro, and adjust to prevent skin compression. Release Velcro every 2 hrs to relieve local pressure. Tables 2, 3 shows the changes before and after the comprehensive rehabilitation therapy. Figure 4 shows the edema of the patient's left upper limb after treatment. The treatment flow chart outlined the whole intervention process (Figure 5).

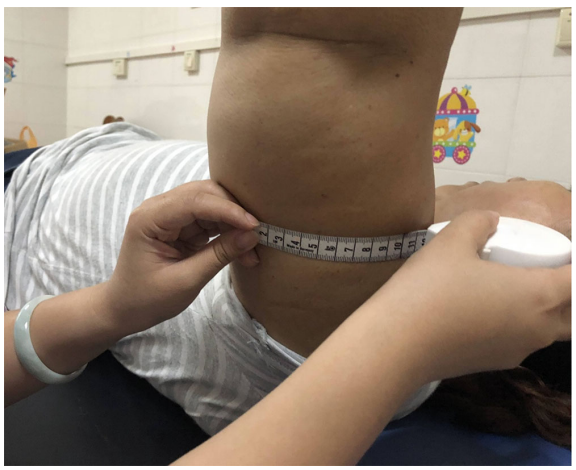


FIGURE 2
Measurement Method for Left Upper Limb Lymphedema.

The Ethics Committee of the Affiliated Haikou Hospital of Xiangya Medical College has approved this case report, and the informed consent of the patient has been obtained.

Discussion

The prevailing view in most studies is that lymphatic obstruction is the underlying cause of upper-limb lymphedema following breast cancer surgery, although the exact mechanism remains unclear (7–10). Treatments such as surgery, radiotherapy, chemotherapy, and others can obstruct or disrupt the lymphatic return pathway in the upper limb. This can result in the retention of lymphatic fluid containing protein in the interstitial spaces, which in turn increases colloid osmotic pressure, and reduces the difference between inside and outside the blood vessels. Consequently, a large amount of fluid from capillaries can enter these spaces. Proteins present in the lymphatic fluid can stimulate the multiplication and release of collagen by fibroblasts. This can lead to fibrosis of subcutaneous tissue and inhibit lymphatic return. As a result of lymphatic vessel dilation and edema, the walls of the vessels thicken and harden and fibrinogen emboli may appear in the lumen. This obstructs lymphatic return and sets off a vicious cycle (1).

According to Stanton et al. (15) long-term work overload can lead to lymphatic pump failure and decompensation, which can eventually cause lymphedema. Bates (16) proposed the concept of interstitial space pressure dysregulation as the potential mechanics for this process. In addition, postoperative radiation can lead to fibrosis and further damage to lymphatic vessels regions such as the proximal limb, axillary, thoracic, and cervical regions where lymphatic fluid stagnation already exist. This can negatively impact, lymphatic return and worsen limb edema.

10.3389/fonc.2023.1046003

TABLE 1 The changes of arm circumference within the first month.

Days	Measured from the ulnar styloid process to the shoulder with 10 cm intervals				
	0	10 cm	20 cm	30 cm	40 cm
1	22	33	38	38	45
2	21.5	32	37.5	37	44
3	21	32	38	36.5	43.5
4	21	32	38	36	43
5	20.5	31.7	37.8	37	43.7
6	20.5	31.7	37	37	43
7	21.9	32.5	38	37	42.5
8	20.4	32.3	37.5	37	43
9	20	32.3	37.6	37	43
10	20.5	32.3	37.5	37.2	43.5
11	20.5	32	37	36.8	43.5
12	20	32	37	36.9	43.5
13	20	32	37	36.8	43.5
14	20	32	36.5	36.5	43.5
15	19.5	32	36.5	36.6	43.5
16	20	31.9	36.6	36.4	43.5
17	19.5	31.9	36.4	36.5	43.5
18	19.5	31.8	36.2	36.3	43.5
19	20	31.9	36	36.3	43.5
20	19.5	31.8	36.1	36.2	43.5
21	19.5	31.8	35.8	36.2	43.5
22	19.5	31.8	35.7	36.3	43.5
23	19.5	31.8	35.5	36.2	43.5
24	19	31.7	35.4	36	43.5
25	19	31.7	35	36	43.5
26	19	31.7	35	36	43.5
27	19	31.7	35	36	43.5
28	19	31.7	35	36	43.5
29	19	31.7	35	36	43.5
30	19	31.7	35	36	43.5

The standard treatment for lymphedema is complex decongestion therapy (CDT) (17). This therapy typically includes skin care, lymphatic drainage, elastic bandage compression, and functional exercise of the affected limb as part of the international CDT protocol (18). Seven-step CDT is a technique that aims to open the lymphatic route, soothe scar tissue, and utilize CDT-based pressure wave therapy. Shockwave therapy has shown potential benefits on BCRL according to previous research. One possible mechanism is that stretching the skin creates tension on the anchoring filaments, which pulls the Lymphatic Endothelial Cell (LEC) and allows junctions between LEC to open. This leads to fluid accumulation entering the lymphatic lumen and being collected. Additionally, it has been found to reduce skin fibrosis and impact the molecular aspects of lymphangiogenesis. However, there are limitations to its use, including mode (focused or radial), treatment area, treatment frequency, and dosage. When used in combination with CDT, it can significantly improve the volume of lymphedema, skin thickness, and shoulder ROM compared to CDT used alone.

10.3389/fonc.2023.1046003

FIGURE 3
Functional Brace Wearing.

However, the current evidence for these benefits is of low methodological quality (19). Previous studies have demonstrated that seven-step CDT following breast cancer surgery can be effective in improving upper-limb lymphedema (14). Liposuction is also a potential treatment option for reducing lymphedema volume, but in this case, the patient declined this treatment option.

In the present study, one month after undergoing seven-step decongestion therapy, the patient's left upper-limb lymphedema was alleviated. However, further reduction in the lymphedema was not observed after reaching a certain extent, possibly due to subcutaneous tissue fibrosis from prolonged lymphedema after breast cancer surgery (1). It may also have been caused by CDT limitations (1, 18, 19). Thereafter, through the combination of respiratory and core muscle training and the correction of abnormal posture, the patient's left upper-limb lymphedema was significantly reduced.

Lymphatic fluid circulation relies on various factors such as lymphatic vessel pumping, arterial pulsation, muscle contraction, and thoracic negative pressure. The radical mastectomy of breast cancer destroyed lymph nodes, lymphatic pumping, and surrounding muscle tissue, reducing lymphatic return. In the present study, the patient's strength, endurance, and coordination of respiratory muscles were improved, abnormal posture was adjusted, thoracic mobility was improved, thoracic breathing ability was strengthened, and thoracic negative pressure was increased, which boosted lymphatic return (20). Additionally, active rehabilitation has been shown to promote lymphatic vessel regeneration and restore vessel continuity by establishing extensive connections between normal tissues containing lymph nodes and those with lymphatic obstruction, thereby draining excessive lymphatic fluid from edematous areas (11).

We studied the effects of comprehensive rehabilitation therapy on lymphedema following breast cancer surgery. The patient in this case had persistent lymphedema and subcutaneous tissue fibrosis as a result of the surgery, and the efficacy of seven-step CDT alone was

TABLE 2 The changes of arm circumference.

Comparisons	Measured from the ulnar styloid process to the shoulder with 10 cm intervals				
	0	10 cm	20 cm	30 cm	40 cm
The left arm circumference (cm)					
Before the comprehensive treatment	22	33	38	38	45
After the comprehensive treatment	18	27	33.8	33	39
The difference (D) between the two arms about the circumference (cm)					
Before the comprehensive treatment	14	11.5	9	14	9
After the comprehensive treatment	10	5.5	4.8	9	3

10.3389/fonc.2023.1046003

TABLE 3 Changes before and after the comprehensive treatment.

	Before the comprehensive treatment	After the comprehensive treatment
Range of forward flexion	0-150°	0-160°
Range of shoulder abduction	0-140°	0-155°
Range of elbow flextion	0-110°	0-120°
Range of wrist dorsiflex	0-30°	0-30°
Muscle strength Grade of the left upper arm	The deltoid and extensor carpi muscles are Grade 4, with a grip strength of 10 kg; another muscles are Grade 5.	All the left upper arm muscles are Grade 5.
The Barthel Index of Activities of Daily Living (ADL), (points)	95	100
The Functional Assessment of Cancer Therapy: Breast (FACT-B), (points)	53	79
Physical well-being	10	13
Social/family well-being	15	20
Emotional well-being	3	15
Functional well-being	15	18
Additional concerns	10	13
Kessler Psychological Distress Scale, (points)	24	17

FIGURE 4
Left Upper Limb Lymphedema After Treatment.

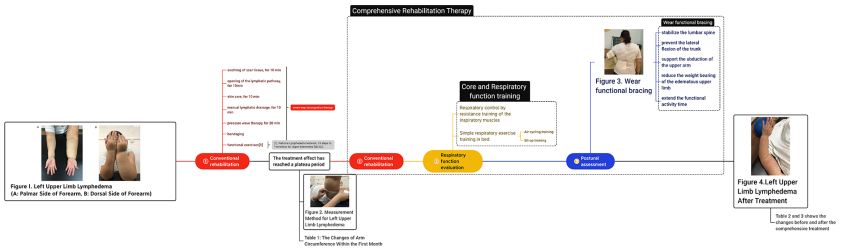


FIGURE 5
The flow chart of treatment.

limited in the sequelae stage of breast cancer surgery. Moreover, by conducting a targeted assessment of the patient's dysfunction, we were able to identify the underlying cause and provide specific training. Additionally, a custom auxiliary brace was used to correct the malfunction.

Conclusions

Seven-step decongestion therapy is a useful treatment option for managing upper-limb lymphedema in the aftermath of breast cancer surgery. However, this therapy may have limitations for patients with chronic and prolonged conditions. To address these challenges, a comprehensive rehabilitation approach can be employed, which combines seven-step decongestion therapy with core and respiratory function training, and functional brace wearing. This combined approach has been shown to significantly improve lymphedema symptoms, enhance limb function, and ultimately lead to an improved quality of life for patients with long-standing lymphedema.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Affiliated Haikou Hospital of Xiangya Medical College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design of the research: Y-FS, JQ-S. Acquisition of data: S-SW Analysis and interpretation of the data: X-FL, H-XW. Statistical analysis: L-QT. Obtaining financing: Z-HS. Writing of the manuscript: Y-FS, L-QT. Critical revision of the manuscript for intellectual content: Z-HS, B-HT. All authors contributed to the article and approved the submitted version.

Funding

Project supported by Hainan Province Clinical Medical Center, NO:0202067. Supported by Hainan Provincial Natural Science Foundation of China, NO:822QN497.

Acknowledgments

We would like to acknowledge the hard and dedicated work of all the staff that implemented the intervention and evaluation components of the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1046003/full#supplementary-material

References

1. Martin ML, Hernandez MA, Avendano C, Rodriguez F, Martinez H. Manual lymphatic drainage therapy in patients with breast cancer related lymphoedema. *BMC Cancer* (2011) 11:94. doi: 10.1186/1471-2407-11-94

2. Zhou Y, Zhang S. Research progress on postoperative rehabilitation of patients with breast cancer. *Chin Gen Pract* (2014) 18):2051–5. doi: 10.3969/j.issn.1007-9572.2014.18.001

3. Chen WQ, Zheng RS, Zhang SW, Li N, Zhao P, Li GL, et al. Report of incidence and mortality in china cancer registries, 2008. *Chin J Cancer Res* (2012) 24(3):171–80. doi: 10.1007/s11670-012-0171-2

4. Yesil H, Eyigor S, Inbat M, Bulut F. The effects of complex decongestive therapy on kinesthetic sense of hands, upper extremity function, and quality of life in patients with breast cancer-related lymphedema. *Turk J Phys Med Rehabil* (2021) 67(2):211–7. doi: 10.5606/tftrd.2021.5191

5. He L, Qu H, Wu Q, et al. Lymphedema in survivors of breast cancer. *Oncol Lett* (2020) 19(3):2085–96. doi: 10.3892/ol.2020.11307

6. Jia J. To standardize the diagnosis and treatment process of upper limb lymphedema after breast cancer surgery. *Chin J Rehabil Med* (2018) 33(04):375–8. doi: 10.3969/j.issn.1001-1242.2018.04.001

7. McLaughlin SA, Brunelle CL, Taghian A. Breast cancer-related lymphedema: risk factors, screening, management, and the impact of locoregional treatment. *J Clin Oncol* (2020) 38(20):2341–50. doi: 10.1200/JCO.19.02896

8. Gillespie TC, Sayegh HE, Brunelle CL, Daniell KM, Taghian AG. Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. *Gland Surg* (2018) 7(4):379–403. doi: 10.21037/gs.2017.11.04

9. Nguyen TT, Hoskin TL, Habermann EB, Cheville AL, Boughey JC. Breast cancer-related lymphedema risk is related to multidisciplinary treatment and not surgery alone: results from a Large cohort study. *Ann Surg Oncol* (2017) 24(10):2972–80. doi: 10.1245/s10434-017-5960-x

10. Paskett ED, Dean JA, Oliveri JM, Harrop JP. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. *J Clin Oncol* (2012) 30(30):3726–33. doi: 10.1200/JCO.2012.41.8574

11. Panchik D, Masco S, Zinnikas P, Hillriegel B, Lauder T, Suttmann E, et al. Effect of exercise on breast cancer-related lymphedema: what the lymphatic surgeon needs to know. *J Reconstr Microsurg* (2019) 35(1):37–45. doi: 10.1055/s-0038-1660832

12. Gutierrez-Espinoza H, Araya-Quintanilla F, Olguin-Huerta C, Valenzuela-Fuenzalida J, Gutierrez-Monclus R, Moncada-Ramirez V. Effectiveness of manual therapy in patients with distal radius fracture: a systematic review and meta-analysis. *J Man Manip Ther* (2022) 30(1):33–45. doi: 10.1080/10669817.2021.1992090

13. Huang TW, Tseng SH, Lin CC, Bai CH, Chen CS, Hung CS, et al. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. *World J Surg Oncol* (2013) 11:15. doi: 10.1186/1477-7819-11-15

14. Zhang H, Zhong Q, Zhang H, Liu L, Liu L, Zhang L, et al. Effects of seven-step complex decongestion therapy on upper limb lymphedema after operation for breast cancer. *Chin J Rehabil Theory Pract* (2017) 23(9):1015–20. doi: 10.3969/j.issn.1006-9771.2017.09.006

15. Stanton AW, Modi S, Bennett BT, Purushotham AD, Peters AM, Levick JR, et al. Lymphatic drainage in the muscle and subcutis of the arm after breast cancer treatment. *Breast Cancer Res Treat* (2009) 117(3):549–57. doi: 10.1007/s10549-008-0259-z

16. Bates DO. An interstitical by pothesis for breast cancer related lymphedema. *Pathophysiology* (2010) 17(4):289–94. doi: 10.1016/j.pathophys.2009.10.006

17. Leal NF, Carrara HH, Vieira KF, Ferreira CH. Physiotherapy treatments for breast cancer-related lymphedema: a literature review. *Rev Lat Am Enfermagem* (2009) 17(5):730–6. doi: 10.1590/S0104-11692009000500021

18. Koo JH, Song SH, Oh HS, Oh SH. Comparison of the short-term effects of hyperbaric oxygen therapy and complex decongestive therapy on breast cancer-related lymphedema: a pilot study. *Med (Baltimore)* (2020) 99(11):19564. doi: 10.1097/MD.0000000000019564

19. Tsai YL, TJ I, Chuang YC, Cheng YY, Lee YC. Extracorporeal shock wave therapy combined with complex decongestive therapy in patients with breast cancer-related lymphedema: a systemic review and meta-analysis. *J Clin Med* (2021) 10 (24):5970. doi: 10.3390/jcm10245970

20. Su J, Pan C, Cao T, Miao P. Effect of resistance breathing training on breast cancer related lymphedema. *Chin J Rehabil Theory Pract* (2016) 22(11):1318–21. doi: 10.3969/j.issn.1006-9771.2016.11.017

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 26 June 2023
DOI 10.3389/fonc.2023.1211645

OPEN ACCESS

EDITED BY
Jitendra Singh Nigam,
All India Institute of Medical Sciences, Bibinagar, India

REVIEWED BY
Maroun Bou Zerdan,
SUNY Upstate Medical University, United States
Biswajit Dey,
North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, India
Tarun Kumar,
All India Institute of Medical Sciences (Patna), India

*CORRESPONDENCE
Tenghua Yu
yutenghua0107@sina.cn
Wen Chen
156149619@qq.com
Zhengkui Sun
sunzhengkui@sohu.com
Meng Zhou
573915293@qq.com

RECEIVED 25 April 2023
ACCEPTED 12 June 2023
PUBLISHED 26 June 2023

CITATION
Xu J, Liu C, Yu C, Yu T, Fan F, Zhang X, Huang C, Chen W, Sun Z and Zhou M (2023) Breast mass as the first sign of metastasis from rectal carcinoma: a case report and review of the literature. *Front. Oncol.* 13:1211645. doi: 10.3389/fonc.2023.1211645

Breast mass as the first sign of metastasis from rectal carcinoma: a case report and review of the literature

Jiawei Xu[1,2], Chao Liu[1], Chengdong Yu[1], Tenghua Yu[1*], Fan Fan[1], Xiaofang Zhang[2], Chuansheng Huang[2], Wen Chen[1*], Zhengkui Sun[1*] and Meng Zhou[1*]

[1]Department of Breast Surgery, Jiangxi Cancer Hospital, The Second Affiliated Hospital of Nanchang Medical College, Jiangxi Clinical Research Center for Cancer, Affiliated Cancer Hospital of Nanchang University, Nanchang, Jiangxi, China, [2]Department of Pathology, Jiangxi Cancer Hospital, The Second Affiliated Hospital of Nanchang Medical College, Jiangxi Clinical Research Center for Cancer, Affiliated Cancer Hospital of Nanchang University, Nanchang, Jiangxi, China

We present a case report of a 41-year-old woman who developed a left breast mass 18 months after undergoing Dixon rectal cancer surgery. The purpose of this case report is to highlight the possibility of breast metastases in patients with colorectal cancer and emphasize the importance of careful evaluation and follow-up as well as timely and accurate diagnosis and management of the metastatic disease. During the physical examination in 2021, we noted that the lower border of the mass was 9 cm from the anal verge and that it occupied approximately one-third of the intestinal lumen. A pathological biopsy revealed the mass in the patient's intestinal lumen was a rectal adenocarcinoma. The patient underwent Dixon surgery for rectal cancer and received subsequent chemotherapy. The patient had no prior history of breast-related medical conditions or a family history of breast cancer. During the current physical examination, we discovered multiple lymphadenopathies in the patient's left neck, bilateral axillae, and left inguinal region, but none elsewhere. We observed a large erythema of about 15x10 cm on the patient's left breast, with scattered hard nodes of varying sizes. Palpation of the area beyond the upper left breast revealed a mass measuring 3x3 cm. We conducted further examinations of the patient, which revealed the breast mass and lymphadenopathy on imaging. However, we did not find any other imaging that had significant diagnostic value. Based on the patient's conventional pathology and immunohistochemical findings, combined with the patient's past medical history, we strongly suspected that the patient's breast mass was of rectal origin. This was confirmed by the abdominal CT performed afterward. The patient was treated with a chemotherapy regimen consisting of irinotecan 260 mg, fluorouracil 2.25 g, and cetuximab 700 mg IV drip, which resulted in a favorable clinical response. This case illustrates that colorectal cancer can metastasize to unusual sites and underscores the importance of thorough evaluation and follow-up, particularly when symptoms are atypical. It also highlights the importance of timely and accurate diagnosis and management of metastatic disease to improve the patient's prognosis.

KEYWORDS

rectal neoplasms, breast tumor, neoplasm metastases, recurrent, case report

Case

Without any previous history of breast-related illness or family history of breast cancer, a 41-year-old female patient presented at our hospital with a lump in her left breast that had been present for 2 months. In 2021, the patient underwent a physical examination, during which it was noted that the lower border of the mass was 9 cm from the anal verge and occupied approximately one-third of the intestinal lumen. The patient's initial treatment for rectal cancer was completed at Wannian County People's Hospital. A pathological biopsy confirmed the presence of rectal low-differentiated adenocarcinoma, which was graded as rectal adenocarcinoma stage III (T3N2M0) (Figure 1). The immunostaining results showed CDX-2(+), CK8/18(+), CgA(-), Syn(-), Her-2(1+), CD34(suggestive of vascular tumor embolus), D2-40(+), S-100(suggestive of nerve invasion), CK20(+), and Ki-67 about 90% (+). After undergoing Dixon surgery for rectal cancer, the patient received subsequent chemotherapy without prior neoadjuvant therapy. The exact regimen and doses of the patient's chemotherapy consisted of 5 courses of bevacizumab 400 mg along with oxaliplatin 200 mg IV drip after surgery, and oral capecitab 1.5 g twice daily for 14 consecutive days. Every 21 days is a cycle. The patient with rectal cancer did not receive radiotherapy. The reason for not proceeding with radiotherapy was that the patient strongly rejected this treatment option. However, patient's initial treatment for rectal cancer was considered successful until she presented with a lump in her left breast 18 months later.

Physical examination revealed multiple enlarged lymph nodes in the left neck, bilateral armpits, and left groin area. A large red swollen area of approximately 15 x 10 cm was observed in the left breast with hard nodules of various sizes scattered around it (Figure 2). Palpation of the left breast also revealed a 3 x 3 cm lump outside the upper part. The patient's other physical examinations were negative, and the tumor markers (CEA, CA 19-9, CA 15-3) were all in the normal range.

A breast color doppler ultrasound revealed edema and thickening of the subcutaneous soft tissue in the patient's left breast, along with multiple irregular low echo images in the thickened area. The largest image measures 21 x 10 mm in extent. The patient's chest CT confirmed an enlargement in the volume of the left breast, irregular thickening of the skin, and the presence of soft tissue shadows with unclear boundaries. Furthermore, the multiple swollen lymph nodes previously detected in the breast color ultrasound were also confirmed by chest CT. Fortunately, the patient's head CT, abdominal ultrasound, and gynecological ultrasound did not reveal any abnormal changes,

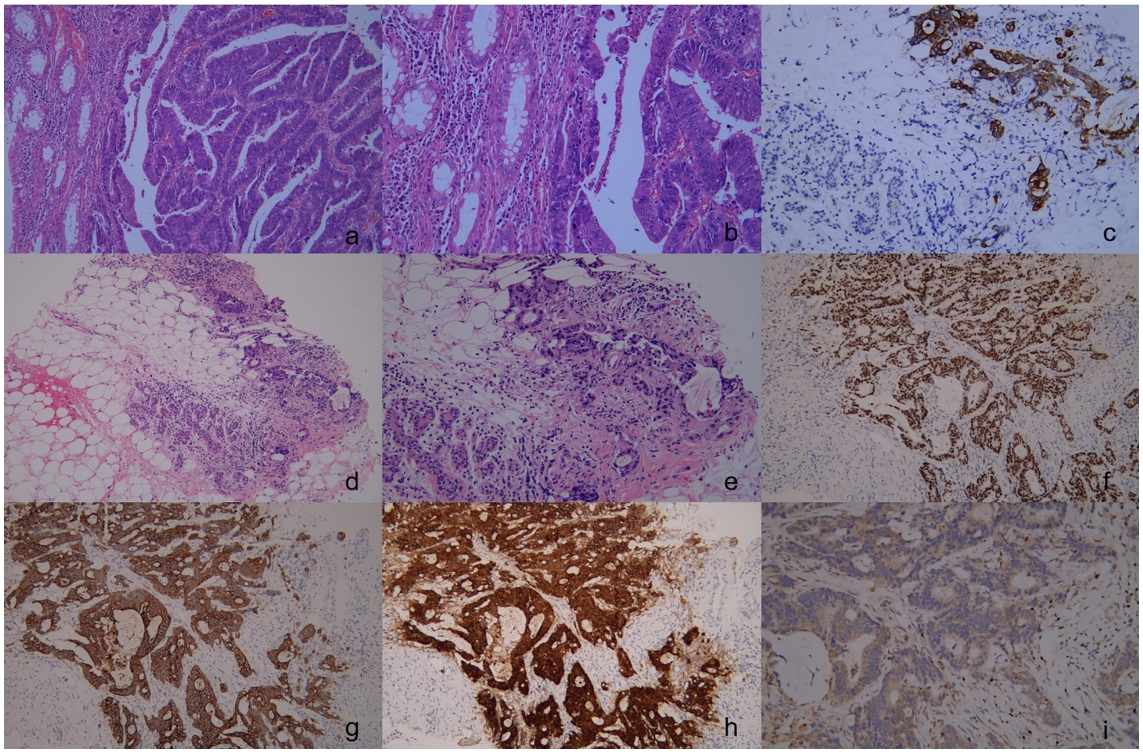


FIGURE 1
The pathology and immunohistochemical staining of rectal cancer specimens in the first operation. Show an irregular glandular growth pattern with intraglandular necrotic debris, with a large nucleus, hyperchromatic nuclei, obvious nuclear atypia, cytoplasmic depletion, red staining, and invasive growth. ((**A**), H&E stain, ×100), ((**B**), H&E stain, ×200), Immunohistochemical staining revealed that the rectal cancer cells were positive for CK20 ((**C**) ×100). Upon pathological examination of the breast tumor specimen, malignant cells were observed along with normal breast tissue. The glandular epithelium was found to proliferate into papillary and tubular structures, with large nuclei, with hyperchromatic nuclei, obvious nuclear -atypia, and cytoplasmic depletion. The cells exhibited invasive growth, with no carcinoma in situ component detected. (**D**, H&E stain, ×100), (**E**, H&E stain, ×200), Immunohistochemical staining revealed that the breast tumor cells were positive for CK20 (**F** ×100), CDX-2 (**G** ×100), Villin (**H** ×100), and were negative for GATA-3 (**I** ×100).

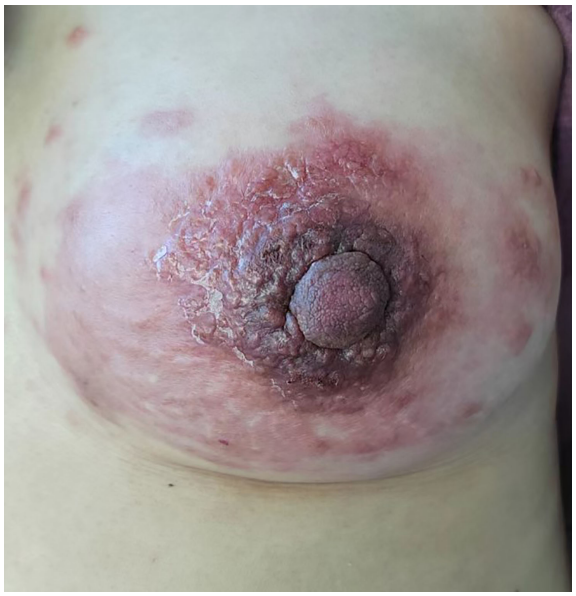


FIGURE 2
Large redness and swelling visible in the left breast at the time of presentation.

but the patient strongly refused to undergo the mammogram examination due to her complaint of being unable to tolerate the pain associated with it (Figure 3).

To determine the nature of the patient's breast lump, we performed a rough needle puncture. Routine pathological showed that the lump we took showed an adeno-tubular arrangement with large nuclei and heteromorphism, which was considered to be an invasive carcinoma, while immunohistochemistry suggested ER(-), PR(-), HER-2(0), GATA-3(-), CDX-2(+), CK20(+), Villin(+), Ki-67 (+,70%) (Figure 1).

Based on the patient's medical history and positive rectal cancer marker on immunohistochemistry, we suspected that the breast mass was of rectal origin. To investigate further, we performed an abdominal CT examination which revealed bowel wall thickening at the anastomotic orifice, nodules in the adjacent peri-intestinal space, and multiple enlarged lymph nodes in the left inguinal region, parietal iliac vessels, and retroperitoneum. Due to these findings, we strongly recommended that the patient undergo an enteroscopy and biopsy to confirm the diagnosis. However, the patient declined the procedure due to economic constraints and concerns about discomfort.

Although we did not obtain the results of the enteroscope, our multidisciplinary team (MDT) team, evaluated the patient's medical history and physical examination, combined with the patient's imaging examination and pathological findings, and eventually diagnosed the patient as having recurrent rectal cancer with a breast mass as the initial symptom. Given the suspected origin of the breast mass from the alimentary canal, the patient was transferred to the Department of Gastrointestinal Oncology for treatment. As our department specializes in breast surgery, we deemed it appropriate to transfer the patient to a department that could provide more specialized care for her condition. The patient was treated with a chemotherapy regimen of irinotecan 260 mg and fluorouracil 2.25 g combined with cetuximab 700 mg intravenous drip. The patient was last evaluated on February 21, 2023, the patient underwent an abdominal CT scan which showed that several small nodules with a short diameter of less than 1 cm in the adjacent peri-intestinal space were smaller than before, and the enlarged lymph nodes in the left inguinal region, adjacent to the

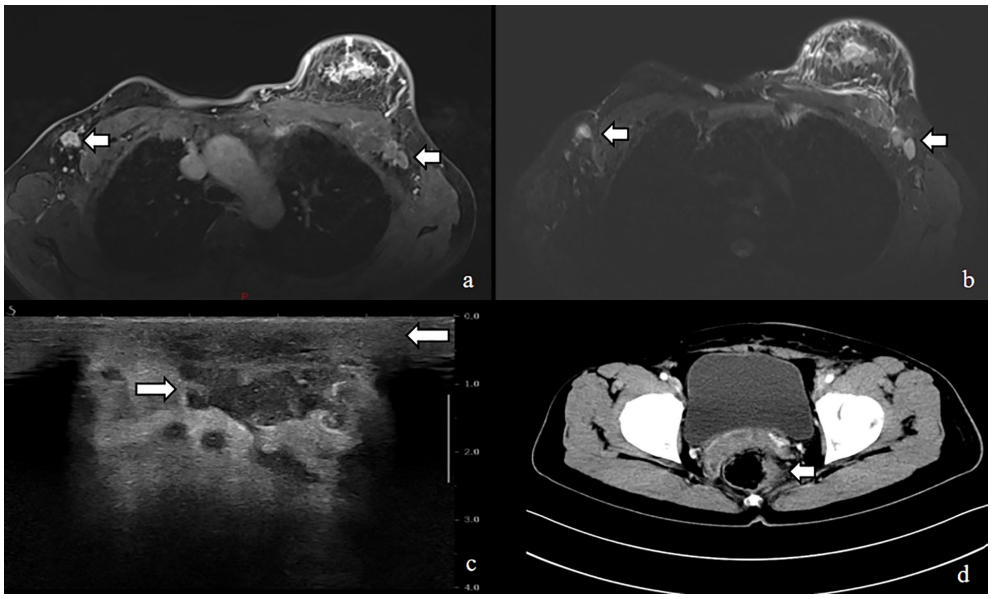


FIGURE 3
MRI image shows **(A, B)** enlarged left breast with multiple foci of scattered abnormal enhancement and enlarged lymph nodes in the left axilla, Ultrasound shows **(C)** thickened subcutaneous soft tissue in the left breast and multiple irregular hypoechoic areas, CT shows **(D)** uneven thickening and enhancement of the rectal anastomosis wall with small nodules in the adjacent peri-intestinal space.

iliac vessels and the retroperitoneum were slightly reduced (Figure 4). These findings suggest a positive response to the chemotherapy treatment.

Discussion

Breast tumors of non-breast origin are rare, accounting for only a small proportion of all breast tumors (approximately 0.4%-5.1%). While metastases to the breast are known to occur in a variety of primary cancers, including lymphoma, lung cancer, and melanoma, rectal cancer as the origin of a breast mass is an extremely rare occurrence (1–4). Rectal cancer is the third most common cancer worldwide, with approximately 20% of patients presenting with distant metastases at the time of initial diagnosis, but such metastases are typically found in the lymph nodes, liver, or lungs (5, 6). Because of the differences in the follow-up and management of the two diseases, a definite diagnosis of these extremely rare cases is the key to the whole process.

Patients with breast metastases from rectal cancer present a diagnostic challenge for clinicians as there is no specific non-invasive method to confirm the diagnosis. Clinical manifestations are non-specific and usually include palpable breast lumps and axillary fossa lymphadenopathy. Skin changes such as redness and swelling may also be present, but these can also be seen in advanced breast cancer. Diagnosis based on clinical manifestations alone is difficult (7–9). Unfortunately, patients with breast metastases from rectal cancer do not show any specific imaging characteristics, and previous literature reports have shown that a significant number of patients are misdiagnosed with primary breast cancer or benign breast diseases based on imaging alone (10, 11).

When evaluating breast masses on ultrasound, it is important to distinguish those that originate from non-breast tissues from breast cancer. On ultrasound images, breast masses that originate from non-breast tissues tend to appear as well-defined, round, or oval, hypoechoic masses. They can be single or multiple and may occasionally appear minimally micro-lobulated. In contrast, breast cancer on ultrasound images is typically observed as a solid mass with irregular borders, microlobulations, or a spiculated appearance. Additionally, calcifications may appear as bright white spots in breast cancer cases. Breast masses that arise from non-breast tissues can appear as non-specific occupying lesions on mammography. These lesions may be solitary or multiple and usually lack calcifications. Additionally, diffuse opaque structural deformities may be observed in one or both breasts. In contrast, breast cancer typically appears as masses or clusters of microcalcifications on molybdenum target images. These small mineral deposits in breast tissue may be accompanied by irregular borders, microlobulations, or a spiculated appearance (10, 12–18).

Diagnosing breast metastases from rectal cancer is an uncommon and challenging task that typically requires routine pathology and immunohistochemistry. It is crucial to provide the pathologist with the patient's complete medical history at the time of presentation. In a retrospective study of 85 non-breast-derived breast tumors, some cases of misdiagnosis occurred due to the pathologist's inadequate knowledge of the patient's past medical history. Therefore, emphasizing the importance of proper documentation and communication of past medical history is vital for accurate diagnosis and treatment (11).

Rectal cancer metastasizing to the breast is a rare occurrence, and there is limited understanding of its pathogenic mechanism. The presence of such metastasis indicates widespread dissemination and is associated with an unfavorable prognosis. Due to the scarcity of reported cases, it is challenging to determine the exact incidence of this metastatic pattern. To address this, we conducted a comprehensive analysis of existing literature, including 20 previously reported cases along with our own case.

Among the reported cases, a total of 20 patients had rectal cancer metastasizing to the breasts. The average age of these patients was 43.15 years, with the majority being females (Table 1). Only three male patients were reported. In 40% of the cases, metastasis was observed exclusively in the breast. In 45% of the cases, metastasis was observed in the left breast, consistent with our

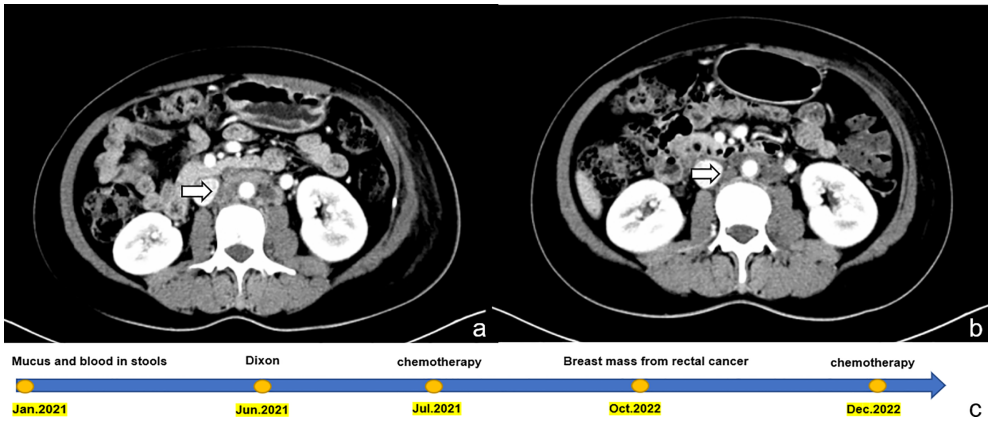


FIGURE 4
Shows a comparison of abdominal CT images before and after chemotherapy in the patient, and a timeline of the patient's treatment process. **(A)** displays the image prior to chemotherapy, with enlarged lymph nodes indicated by the arrow. **(B)** displays the image after three courses of chemotherapy, with the same lymph nodes indicated by the arrow now visibly reduced in size. This visual representation highlights the effectiveness of chemotherapy in reducing the size of the lymph nodes. **(C)** timeline of the patient's treatment process.

TABLE 1 Reported cases of rectal cancer metastasis to breast.

Study	Age	Sex	Metastasis	Time of detection of breast metastases	Location
Our study	41	Female	Breast	18months	Left
Alexander, H.R (19).	28	Female	Breast/Lung	11months	Right
Lal, R (20).	69	Female	Breast/Skin/Lung/Brain	1year	Left
Mihai, R (21).	53	Female	Breast/Skin	5years	Left
Hisham, R.B (22).	32	Female	Breast/Spine/Left eye/Orbit.	10months	Left
Wakeham, N (23).	45	Female	Breast/Liver/Lung	2 years	Bilateral
Li, H.C (24).	54	female	Breast/Lung/Skull base/Neck soft tissue	>2months	Right
Singh, T (1).	42	Female	Breast/Liver/Brain	11months	Right
Wang, T (7).	38	Male	Breast/Liver	7 years	Right
Sanchez, L.D (25).	36	Female	Breast	4months	Left
Makhdoomi, R (9).	28	Female	Breast	9months	Bilateral
Ahmad, A (26).	28	Female	Breast/Liver	0	Right
Aribas, B (27).	21	Female	Breast/Skin	10months	Bilateral
Shah, M (28).	49	Female	Breast	4months	Left
Hejazi, S.Y (29).	47	Female	Breast	3 years	Left
Hsieh, T.-C (30).	44	Female	Breast/Liver	7months	Right
Cheng, X (31).	57	Male	Breast	5months	Right
Wang, D.-D (32).	59	Female	Breast	16months	Left
Gur, E.O (33).	47	Male	Breast	2 years	Bilateral
Dai, Y (34).	45	Female	Breast/Lung	3 years	Left

case, while in 15% of the cases, both breasts were affected. The onset of metastasis varied, with reports ranging from as early as 2 months to as late as 7 years. In our case, metastasis was diagnosed within 18 months from the initial diagnosis of rectal primary.

In pathology, breast metastasis diagnosis relies on several histological features, such as well-defined margins, the absence of ductal carcinoma in situ, and no calcifications. However, even with the patient's medical history, making a definitive diagnosis through conventional pathology can be challenging due to the similar growth patterns between metastatic carcinoma and breast cancer. Additionally, rare primary breast tumors, such as primary signet-ring cell carcinoma (SRCC), can be easily confused with metastatic signet-ring cell carcinoma, further complicating the diagnosis (2, 35). Distinguishing between rectal SRCC and other types of cancer based solely on pathological staining can be challenging. However, the good news is that colorectal SRCC can be distinguished using immunohistochemical markers such as negative Hep Par 1, homogeneous CDX2 nuclear positivity, and diffuse cytoplasmic positivity for MUC2 and MUC5AC in colorectal SRCC (36, 37).

Immunohistochemistry plays a critical role in diagnosing breast metastases from colorectal cancer by using specific markers to differentiate them from primary breast cancer. Two commonly used markers in gastrointestinal cancer diagnosis are cytokeratin proteins 20 (CK20) and cytokeratin proteins 7 (CK7). Typically, gastrointestinal cancer will show positive staining for CK20 and negative staining for CK7 (38). while primary breast tumors show the opposite staining pattern (39, 40). The literature suggests that CK20 expression in breast metastatic tumors is less than 6%, whereas the expression of CK7 in gastric metastasis of breast cancer can be as high as 83.34% (41). While CDX2 is useful in determining alimentary-derived tumors, it's important to note that while most colorectal carcinomas are CDX2 positive, many gastric carcinomas are not. Furthermore, CDX2 can also be expressed in carcinomas originating from other sites, such as ovarian, endometrial, and lung cancers. Contrary to beliefs, studies have reported some expression of CDX2 in breast cancer, although at lower levels compared to gastrointestinal tumors. Nonetheless, CDX2 can still be a useful marker in distinguishing alimentary-derived tumors, including metastases from colorectal cancer, from primary breast cancer (40, 42, 43).

Although SATB2 expression is generally higher in breast, colon, and rectal cancer patients compared to their normal counterparts, it is utilized as a diagnostic marker for colorectal cancer in clinical settings (44–46). This is because SATB2 has been found to exhibit high sensitivity and specificity in colorectal adenocarcinoma, making it a valuable tool for diagnosing the disease. Studies have also suggested that a three-marker panel comprising SATB2, CK20, and CDX2 can improve the detection of metastatic colorectal cancer in liver biopsy tissues (47, 48).

As relatively specific markers for breast-derived tumors, GATA binding protein 3 (GATA3), mammaglobin, and gross cystic disease

fluid protein 15 (GCDFP-15) are useful in determining the origin of the tumor (49). The expression level of GATA3 in breast cancer tissues is significantly higher than that of GCDFP-15 and mammaglobin, making GATA3 a particularly useful marker in identifying the origin of a tumor (50, 51). Moreover, GATA3 has higher sensitivity in identifying primary and metastatic breast cancers, and its expression rate in metastatic breast cancer is even as high as 96% (52). In addition, the combination of Villin and CDX2 markers can be used to infer the primary site of metastatic cancer. When both markers show positive staining, the tumor can be considered alimentary tract origin (53). The immunohistochemical results of this case were GATA-3 (-), CDX-2 (+), CK20 (+), and Villin (+). Based on these findings, the patient was eventually diagnosed with rectal cancer breast metastasis by our Multidisciplinary Team (MDT).

Systemic therapy is typically the preferred treatment for rectal cancer breast metastasis, while surgery is not usually recommended. However, metastasectomies are increasingly used for colorectal liver and lung metastases and have shown the potential to prolong survival in patients with well-controlled primary disease (24). Studies have also demonstrated that, when combined with effective systemic chemotherapy, metastasectomy can be an effective means of extending the survival of these patients (3, 25). Due to the rarity of this condition, there is no consensus on the best chemotherapy regimen to obtain definitive results. Considering the patient's individual circumstances, a chemotherapy regimen consisting of 260 mg of irinotecan and 2.25 g of fluorouracil, in addition to a 700 mg intravenous drip of cetuximab, was administered. In addition, targeted therapy has emerged as a promising option for the treatment of metastatic colorectal cancer. Studies have shown that the use of targeted therapies can significantly improve the median overall survival in these patients, with a reported median survival of approximately 30 months (54).

The prognosis for patients with rectal cancer breast metastasis is poor, with a mean survival period of 14.9 months (30). Obviously, diagnosis is the most critical part of the entire process, which means that patients can receive early targeted treatment and improve their prognosis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

This case report has been approved by the Ethics Committee of Jiangxi Cancer Hospital. Written informed consent was obtained from the participant for the publication of this case report.

Author contributions

JX, CY, and CL contributed to the writing of the manuscript text, reviewed the manuscript, and TY, FF, XZ, and CH contributed to the data collection process. WC, ZS, and MZ made a significant contribution to the manuscript by creating and formatting the figures, as well as reviewing the manuscript overall. All authors contributed to the article and approved the submitted version.

Funding

This work was financially supported by the National Natural Science Foundation of China (82160565), the Youths Program of the Natural Science Foundation of Jiangxi Province (20212BAB216063), the Distinguished Young Scholars Fund of Jiangxi Cancer Hospital (2021DYS04). Jiangxi Provincial Health Commission General Science and Technology Plan Project (202210055. 20221100) Jiangxi Postgraduate Innovation Fund (YC2022-s206).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Singh T, Premalatha C, Satheesh C, Lakshmaiah K, Suresh T, Babu KG, et al. Rectal carcinoma metastasizing to the breast: a case report and review of literature. *J Cancer Res Ther* (2009) 5(4):321. doi: 10.4103/0973-1482.59904

2. Madan AK, Ternovits C, Huber SA, Pei LA, Jaffe BM. Gastrointestinal metastasis to the breast. *Surgery* (2002) 132(5):889–93. doi: 10.1067/msy.2002.126013

3. Ahmad SS, Khalilullah K, McGowan K, Dillon K. Unexpected destination! rectal carcinoma metastasis to breast. *J Surg Case Rep* (2019) 2019(3):rjz036. doi: 10.1093/jscr/rjz036

4. Markani LK, Markani FK, Kadivar M, Hossinaei N, Safari E. Breast metastasis from gastric carcinoma: a case report. *Caspian J Internal Med* (2022) 13(1):132.

5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

6. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* (2022) 72(1):7–33. doi: 10.3322/caac.21708

7. Wang T, Lv Y-G, Yan Q-G, Yuan S-F, Ling R, Chen J-H, et al. Rectal carcinoma metastatic to the male breast after 7 years: case report. *Oncol Res Treat* (2011) 34 (10):544–6. doi: 10.1159/000332225

8. Jia L, Yu F, Ang L, Fei L. Breast metastases from rectal carcinoma. *Chin Med J* (2011) 124(8):1267–9.

9. Makhdoomi R, Mustafa F, Ahmad R, Malik S, Sheikh S, Baba KM. Bilateral breast metastasis from mucinous adenocarcinoma of the rectum: a case report and review of the literature. *Turk Patoloji Derg* (2013) 29(3):231–4. doi: 10.5146/tjpath.2013.01178

10. Vergier B, Trojani M, De Mascarel I, Coindre JM, Le Treut A. Metastases to the breast: differential diagnosis from primary breast carcinoma. *J Surg Oncol* (1991) 48 (2):112–6. doi: 10.1002/jso.2930480208

11. DeLair DF, Corben AD, Catalano JP, Vallejo CE, Brogi E, Tan LK. Non-mammary metastases to the breast and axilla: a study of 85 cases. *Modern Pathol* (2013) 26(3):343–9. doi: 10.1038/modpathol.2012.191

12. Yeh C-N, Cheng-Hung L, Chen M-F. Clinical and ultrasonographic characteristics of breast metastases from extramammary malignancies. *Am Surgeon* (2004) 70(4):287. doi: 10.1177/000313480407000402

13. Mun SH, Ko EY, Han B-K, Shin JH, Kim SJ, Cho EY. Breast metastases from extramammary malignancies: typical and atypical ultrasound features. *Korean J Radiol* (2014) 15(1):20–8. doi: 10.3348/kjr.2014.15.1.20

14. Bartella L, Kaye J, Perry N, Malhotra A, Evans D, Ryan D, et al. Metastases to the breast revisited: radiological–histopathological correlation. *Clin Radiol* (2003) 58 (7):524–31. doi: 10.1016/S0009-9260(03)00068-0

15. AlSharif S, Alshamrani KM, Scaranelo A, Khoumais N, Subahi A, Mesurolle B. Unusual Male breast lesions. *J Clin Imaging Sci* (2021) 11. doi: 10.25259/JCIS_43_2021

16. Lattin GEJr., Jesinger RA, Mattu R, Glassman LM. From the radiologic pathology archives: diseases of the male breast: radiologic-pathologic correlation. *Radiographics* (2013) 33(2):461–89. doi: 10.1148/rg.332125208

17. Surov A, Fiedler E, Holzhausen H-J, Ruschke K, Schmoll H-J, Spielmann R-P. Metastases to the breast from non-mammary malignancies: primary tumors, prevalence, clinical signs, and radiological features. *Acad Radiol* (2011) 18(5):565–74. doi: 10.1016/j.acra.2010.12.009

18. Guo R, Lu G, Qin B, Fei B. Ultrasound imaging technologies for breast cancer detection and management: a review. *Ultrasound Med Biol* (2018) 44(1):37–70. doi: 10.1016/j.ultrasmedbio.2017.09.012

19. Alexander HR, Turnbull AD, Rosen PP. Isolated breast metastases from gastrointestinal carcinomas: report of two cases. *J Surg Oncol* (1989) 42(4):264–6. doi: 10.1002/jso.2930420412

20. Lal R, Joffe J. Rectal carcinoma metastatic to the breast. *Clin Oncol* (1999) 11 (6):422–3. doi: 10.1053/clon.1999.9098

21. Mihai R, Christie-Brown J, Bristol J. Breast metastases from colorectal carcinoma. *Breast* (2004) 13(2):155–8. doi: 10.1016/S0960-9776(03)00125-5

22. Hisham RB, Thuaibah H, Gul YA. Mucinous adenocarcinoma of the rectum with breast and ocular metastases. *Asian J Surg* (2006) 29(2):95–7. doi: 10.1016/S1015-9584(09)60115-9

23. Wakeham N, Satchithananda K, Svensson W, Barrett N, Comitis S, Zaman N, Ralleigh G, et al. Colorectal breast metastases presenting with atypical imaging features. *Br J Radiol* (2008) 81(965):e149–53. doi: 10.1259/bjr/62391254

24. Li HC, Patel P, Kapur P, Huerta S. Metastatic rectal cancer to the breast. *Rare Tumors* (2009) 1. doi: 10.4081/rt.2009.e22

25. Singh T, Premalatha C, Satheesh C, Lakshmaiah K, Suresh T, Babu KG, et al. Rare case of breast tumor secondary to rectal adenocarcinoma. *South Med J* (2008) 101 (10):1062–4. doi: 10.1097/SMJ.0b013e318183d071

26. Ahmad A, Baiden-Amissah K, Oyegade A, Absar M, Swainson K, Titi S. Primary sigmoid adenocarcinoma metastasis to the breast in a 28-year-old female: a case study and a review of literature. *Korean J Pathol* (2014) 48(1):58. doi: 10.4132/KoreanJPathol.2014.48.1.58

27. Aribas B, Onursever A, Kiziltepe T, Aydin H, Cosar S, Uzun H. Breast metastasis from rectal adenocarcinoma: a case report with US and CT findings. *Imaging Med* (2016) 8:89–92.

28. Shah M, et al. Isolated breast metastasis mimicking as second primary cancer–a case report. *J Cancer Metastasis Treat* (2016) 2:391–5. doi: 10.20517/2394-4722.2016.22

29. Hejazi SY, Alghamdi FA, Zaidi NH. Rectal cancer metastasizing to breast: a case report and review of literature. *Case Rep Clin Med* (2016) 5(2):43–9. doi: 10.4236/crcm.2016.52008

30. Hsieh T-C, Hsu C-W. Breast metastasis from colorectal cancer treated by multimodal therapy: case report and literature review. *Medicine* (2019) 98(51). doi: 10.1097/MD.0000000000018016

31. Cheng X, et al. Rare case of a male breast tumour secondary to poorly differentiated rectal adenocarcinoma. *Trans Cancer Res* (2020) 9(12):7676. doi: 10.21037/tcr-20-1936

32. Wang D-D, Yang S-J, Chen W-X. Breast metastasis from rectal carcinoma: a case report and review of the literature. *Malawi Med J* (2021) 33(3):226–8. doi: 10.4314/mmj.v33i3.11

33. Gur EO, Onak C, Bayar EE, Yazıcı A, Kokulu İ, Hacıyanlı S, et al. Rectum mucinous adenocarcinoma metastasis to bilateral breast in a male patient: a case report. *Breast J* (2020) 26(3):517–9. doi: 10.1111/tbj.13580

34. Dai Y, Jin Y, Lan A, Ding N, Jiang L, Liu S. Breast metastasis from rectal signet-ring cell carcinoma: a case report and review of literature. *Front Oncol* (2022) 12. doi: 10.3389/fonc.2022.873354

35. Principe DR, Raicu A, Cataneo J, Beverley HR, Hyser M. Perforating duodenal ulcer with umbilical herniation as a metastatic complication of primary signet ring cell carcinoma of the breast. *J Surg Case Rep* (2021) 2021(3):rjab034. doi: 10.1093/jscr/rjab034

36. Seog WJ, et al. An extremely rare case of rectal signet ring cell carcinoma. *Gastroenterol Res* (2022) 15(2):106. doi: 10.14740/gr1516

37. Chu PG, Weiss LM. Immunohistochemical characterization of signet-ring cell carcinomas of the stomach, breast, and colon. *Am J Clin Pathol* (2004) 121(6):884–92. doi: 10.1309/A09ERYMFR64NERDW

38. Fleming M, et al. Colorectal carcinoma: pathologic aspects. *J gastrointestinal Oncol* (2012) 3(3):153.

39. Park JH, Kim JH. Pathologic differential diagnosis of metastatic carcinoma in the liver. *Clin Mol Hepatol* (2019) 25(1):12. doi: 10.3350/cmh.2018.0067

40. Lin Y, Wong SI, Wang Y, Lam C, Peng X. Periampullary metastases from breast cancer: a case report and literature review. *Case Rep oncological Med* (2019) 2019. doi: 10.1155/2019/3479568

41. Rodrigues MVR, Tercioti-Junior V, Lopes LR, Coelho-Neto JdS , Andreollo NA. Breast cancer metastasis in the stomach: when the gastrectomy is indicated? *ABCD. Arquivos Brasileiros Cirurgia Digestiva (São Paulo)* (2016) 29:86–9. doi: 10.1590/0102-6720201600020005

42. Moskaluk CA, et al. Cdx2 protein expression in normal and malignant human tissues: an immunohistochemical survey using tissue microarrays. *Modern Pathol* (2003) 16(9):913–9. doi: 10.1097/01.MP.0000086073.92773.55

43. Dabir PD, Svanholm H, Christiansen JJ. SATB 2 is a supplementary immunohistochemical marker to CDX 2 in the diagnosis of colorectal carcinoma metastasis in an unknown primary. *Apmis* (2018) 126(6):494–500. doi: 10.1111/apm.12854

44. Roy SK, Shrivastava A, Srivastav S, Shankar S, Srivastava RK. SATB2 is a novel biomarker and therapeutic target for cancer. *J Cell Mol Med* (2020) 24(19):11064–9. doi: 10.1111/jcmm.15755

45. Yu W, Ma Y, Ochoa AC, Shankar S, Srivastava RK. Cellular transformation of human mammary epithelial cells by SATB2. *Stem Cell Res* (2017) 19:139–47. doi: 10.1016/j.scr.2017.01.011

46. Yu W, Ma Y, Shankar S, Srivastava RK. SATB2/β-catenin/TCF-LEF pathway induces cellular transformation by generating cancer stem cells in colorectal cancer. *Sci Rep* (2017) 7(1):1–13. doi: 10.1038/s41598-017-05458-y

47. Zhao L-H, Chen C, Mao C-Y, Xiao H, Fu P, Xiao H-L, et al. Value of SATB2, ISL1, and TTF1 to differentiate rectal from other gastrointestinal and lung well-differentiated neuroendocrine tumors. *Pathology-Res Pract* (2019) 215(7):152448. doi: 10.1016/j.prp.2019.152448

48. Zhang Y-J, et al. SATB2 is a promising biomarker for identifying a colorectal origin for liver metastatic adenocarcinomas. *EBioMedicine* (2018) 28:62–9. doi: 10.1016/j.ebiom.2018.01.001

49. Gown AM, Fulton RS, Kandalaft PL. Markers of metastatic carcinoma of breast origin. *Histopathology* (2016) 68(1):86–95. doi: 10.1111/his.12877

50. Sangoi AR, Shrestha B, Yang G, Mego O, Beck AH. The novel marker GATA3 is significantly more sensitive than traditional markers mammaglobin and GCDFP15 for identifying breast cancer in surgical and cytology specimens of metastatic and matched primary tumors. *Appl immunohistochem Mol morphol: AIMM* (2016) 24(4):229. doi: 10.1097/PAI.0000000000000186

51. Ni Y-B, Tsang J, Shao M-M, Chan S-K, Cheung S-Y, Tong J, To K-F, et al. GATA-3 is superior to GCDFP-15 and mammaglobin to identify primary and metastatic breast cancer. *Breast Cancer Res Treat* (2018) 169(1):25–32. doi: 10.1007/s10549-017-4645-2

52. Miettinen M, Cue PAM, Sarlomo-Rikala M, Rys J, Czapiewski P, Wazny K, et al. GATA 3–a multispecific but potentially useful marker in surgical pathology–a systematic analysis of 2500 epithelial and non-epithelial tumors. *Am J Surg Pathol* (2014) 38(1):13.

53. Dum D, Lennartz M, Menz A, Kluth M, Hube-Magg C, Weidemann S, et al. Villin expression in human tumors: a tissue microarray study on 14,398 tumors. *Expert Rev Mol Diagnostics* (2022) 22(6):665–75. doi: 10.1080/14737159.2022.2104122

54. Martinelli E, et al. Implementing anti-epidermal growth factor receptor (EGFR) therapy in metastatic colorectal cancer: challenges and future perspectives. *Ann Oncol* (2020) 31(1):30–40. doi: 10.1016/j.annonc.2019.10.007

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 31 July 2023
DOI 10.3389/fonc.2023.1240865

OPEN ACCESS

EDITED BY
Nicola Fusco,
University of Milan, Italy

REVIEWED BY
Carlo Pescia,
University of Milan, Italy
Mariia Ivanova,
European Institute of Oncology IRCCS, Italy

*CORRESPONDENCE
Andrea Cavalli
andrea.cavalli@iit.it
Alessandro Coppe
alessandro.coppe@iit.it

†These authors share last authorship

RECEIVED 15 June 2023
ACCEPTED 05 July 2023
PUBLISHED 31 July 2023

CITATION
Poggiali B, Ponzetti A, Malerba M, Landuzzi F, Furia F, Charrance D, Trova S, Perseghin V, Falcone PA, Alliod V, Malossi A, Carassai P, Familiari U, Vecchi M, Gustincich S, Schena M, Cavalli A and Coppe A (2023) Multiomic analysis of HER2-enriched and AR-positive breast carcinoma with apocrine differentiation and an oligometastatic course: a case report.
Front. Oncol. 13:1240865.
doi: 10.3389/fonc.2023.1240865

Multiomic analysis of HER2-enriched and AR-positive breast carcinoma with apocrine differentiation and an oligometastatic course: a case report

Brando Poggiali[1], Agostino Ponzetti[2], Marica Malerba[1], Fabio Landuzzi[1], Federica Furia[1], Debora Charrance[1], Sara Trova[3], Vittoria Perseghin[1], Patrizia A. Falcone[4], Valentina Alliod[2], Alessandra Malossi[2], Pierpaolo Carassai[5], Ubaldo Familiari[5], Manuela Vecchi[3], Stefano Gustincich[3], Marina Schena[2], Andrea Cavalli[1,6*†] and Alessandro Coppe[1*†]

[1]CComputational and Chemical Biology, Italian Institute of Technology (IIT), CMP³VdA, Aosta, Italy, [2]Oncologia e Ematologia oncologica, Ospedale Umberto Parini, Aosta, Italy, [3]Non-Coding RNAs and RNA-Based Therapeutics, Italian Institute of Technology (IIT), CMP³VdA, Aosta, Italy, [4]Biologia Molecolare Oncologica e Virologica, Analisi Cliniche, Ospedale Umberto Parini, Aosta, Italy, [5]Anatomia Patologica, Ospedale Umberto Parini, Aosta, Italy, [6]Centre Européen de Calcul Atomique et Moléculaire (CECAM), Ecole Polytechnique Fé dérale de Lausanne, Lausanne, Switzerland

Breast carcinoma is the most prevalent cancer among women globally. It has variable clinical courses depending on the stage and clinical-biological features. This case report describes a 56-year-old female with invasive breast cancer without estrogen or progesterone receptor expression, with apocrine differentiation, and with no germline variants in the BRCA1 and BRCA2 genes. Throughout the clinical course, the patient exhibited discordant results for HER2 in immunohistochemistry and *in situ* hybridization. During the second relapse, the disease displayed apocrine microscopic features. The tumor underwent analysis for the androgen receptor, GCDFP-15, RNA-seq, and whole-genome sequencing (WGS) to identify the breast cancer subtype and to characterize the cancer genome. Our bioinformatic analysis revealed 20,323 somatic SNV/Indels, including five mutations in cancer-related genes that are believed to be responsible for the tumor's development. Two of these mutations were found in the *PIK3CA* and *TP53* genes. Furthermore, the tumor tissue exhibited large copy number alterations to the chromosomes, which could impact gene expression through complex mechanisms and contribute to the tumor phenotype. Clustering algorithms applied on RNA-sequencing data categorized this cancer as a HER2+ subtype. The second-line capecitabine chemotherapy treatment is ongoing, and the patient is responding well. Bioinformatic results support the current treatment decision and open the way to further treatments.

KEYWORDS

breast cancer, personalized medicine, NGS, bioinformatic analysis, apocrine carcinoma, case report, WGS, nanopore

Introduction

Breast cancer is the most common cancer in women, with over 2.2 million new cases and 684,996 deaths reported in 2020 (1). While early-stage (non-metastatic) breast cancer is considered curable, advanced or metastatic breast cancer remains incurable, with a 5-year survival rate of only 38% (2). However, therapeutic strategies are available. Their main goal is prolonging survival and maintaining quality of life, and even better results can be obtained in the oligometastatic setting (3, 4).

The tumor's histological and molecular characteristics influence breast cancer treatment decisions. Indeed, breast cancer is a molecularly heterogeneous disease, and several classifications have been developed to group tumors based on their molecular features. Sørlie et al. classified breast cancers based on their gene expression profile (5) into five intrinsic subtypes: Luminal A, Luminal B, HER2-enriched, Basal-like, and Normal breast-like. Each category has well-defined classical immunochemistry markers, such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 (6). Invasive apocrine carcinoma is a rare subtype of non-luminal breast cancer. Invasive apocrine carcinoma is HER2-positive in ~30% of cases and displays significant biological aggressiveness, potentially related to the activation of the androgen receptor (AR) pathway (7, 8). Identifying the correct molecular subtype is crucial for treatment decisions because each subtype has specific therapeutic targets and different prognoses (9). Furthermore, germline mutation in *BRCA1/2* and somatic mutations, such as copy number alterations (CNAs) and single nucleotide variants (SNV) in driver genes (e.g. *TP53*, *PIK3CA*), have prognostic relevance for the therapy outcome and survival (10–13), including in subtypes like apocrine carcinoma (14). The complexity of breast cancer and its variability in responding to different treatments underscores the need for personalized medicine.

In this paper, we present a case report of a patient with an ER/PR-negative invasive breast cancer, which, from a clinical-molecular perspective, exhibited a discordant HER2 status and expression of the AR. At the second relapse, the tumor displayed partial apocrine features and a pathogenetic *PIK3CA* mutation. The clinical course could be defined as oligometastatic, and the response was obtained with both first-line paclitaxel and second-line capecitabine combined with radiotherapy.

At the second relapse, we performed both whole-genome and transcriptome sequencing analyses to fully characterize the tumor's genomic variations and gene expression. Our findings provide insight into the molecular characteristics of this unique breast cancer subtype and may contribute to the development of more effective personalized treatment strategies.

Case presentation

We present the case of a 56-year-old female with no significant medical history or family history of cancer. During routine screening in November 2015, she was diagnosed with localized left breast cancer. The patient underwent a breast-wide excision with sentinel lymph node biopsy, revealing a breast carcinoma not otherwise specified (NOS), grade 2 according to Elston-Ellis classification, without expression of ER or PR, and with a HER2 score of 2+ (Figure 1) but without amplification at fluorescence *in situ* hybridization (FISH). The Ki-67 labeling index was 40%, and the disease was classified as pT1c-pN1(sn). Post-operative computed tomography scan and bone scintigraphy showed no signs of distant metastasis. From February to August 2016, the patient received adjuvant chemo-radiotherapy with epirubicin, cyclophosphamide, and paclitaxel. This was followed by 45 Gy in 20 fractions on the left breast plus 5 Gy boost on the surgical bed. *BRCA1* and *BRCA2* analysis showed no mutations.

During follow-up, in December 2020, a left supraclavicular lymph node appeared and an 18-fluorodeoxyglucose (18-FDG) positron emission tomography-computed tomography (PET-CT) scan confirmed the disease relapse in five non-bulky supraclavicular and retropectoral lymph nodes. A lymph-nodal ultrasound-guided core biopsy revealed malignant cells from breast carcinoma that were ER-negative and PR-negative with a HER2-score of 3+ (Figure 1) but without gene amplification at chromogenic *in situ* hybridization (CISH). PD-L1 staining with Ventana SP142 clone was negative on tumor-infiltrating lymphocytes with an IC score of less than 1%.

After discussing the risks and benefits of a single-agent chemotherapy with the patient and her relatives, she received first-line chemotherapy with Paclitaxel from February 2021 to January 2022. This produced a partial response to the disease; however, the chemotherapy caused persistent maximum grade (maxG) 2 peripheral neuropathy.

In February 2022, ultrasonography and PET-CT confirmed the clinical suspicion of oligoprogression in a new supraclavicular lymph node at a site anterior to the previous site, and in two internal mammary nodes.

After a multidisciplinary discussion, supraclavicular lymph node surgical excision was performed, and histopathological analysis showed a gross cystic disease fluid protein 15 (GCDFP-15) positive breast carcinoma with partial apocrine differentiation and expression of the AR in 95% of cells. The carcinoma was ER-negative, PR-negative, and HER2 3+, but without amplification at CISH and FISH. A revision was performed in a referral center in Turin, Italy, and the HER2 IIC was downstaged to 2+ disease. The histopathological samples from breast disease (2015) and the first lymph nodal relapse were re-assessed and showed positivity for the AR and GCDFP-15.

Next-generation sequencing (NGS) analysis was performed on the metastatic supraclavicular lymph node using *Myriapod NGS Cancer Panel DNA*. This showed a *PIK3CA* p.His1047Arg mutation with an allelic frequency of 26.39%. After excluding a dihydropyrimidine dehydrogenase (DPYD) polymorphism, the patient began receiving second-line capecitabine in April 2022. From June to July 2022, consolidation radiotherapy was performed on the left infra-supraclavicular region and a local boost of 9 Gy with maxG2 fatigue, maxG1 hand-foot syndrome grade, and maxG2 radiodermatitis.

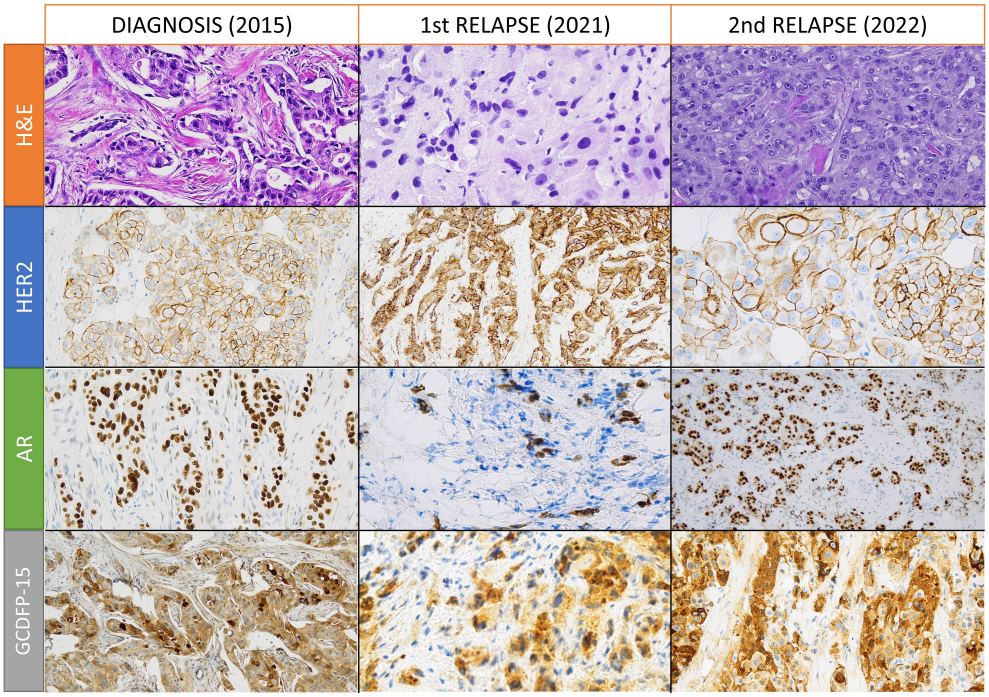


FIGURE 1
Hematoxylin and eosin (H&E) and immunohistochemical stainings for human epidermal growth factor receptor 2 (HER2), androgen receptor (AR), and gross cystic disease fluid protein 15 (GCDFP-15) in samples from diagnosis, first relapse, and second relapse. All images are obtained with 200X magnification, except for HER2 and AR stainings of the second relapse (obtained with 400X and 100X magnification, respectively).

In November 2022, after the sixth cycle of capecitabine, a PET-CT scan with 18-FDG showed a metabolic response at all disease sites, without any pathological FDG-capitation.

The second-line chemotherapy is ongoing.

Genomic profiling of the tumor

Genomic DNA was extracted from peripheral blood (control) and the metastatic supraclavicular lymph node, obtained from the second relapse. Whole-genome sequencing (WGS) was performed on the two samples using a PCR-free library approach and the Novaseq 6000 System with target coverages of 60X and 120X for the blood and tumor samples, respectively. The NVIDIA Clara Parabricks pipelines were used to identify germline and somatic variants, which were annotated and filtered using an in-house pipeline (see Supplementary Materials).

No pathogenic or likely pathogenic germline variants were found in breast cancer predisposition genes including *BRCA1* and *BRCA2* (15). After subtracting the germline variants from the metastatic tumor sample, we detected 20,323 somatic mutations (16,544 SNVs and 3,779 Indels). In particular, we identified five mutations in five cancer-related genes (see Table 1) that could be responsible for the tumor's development. Two of these mutations were classified as pathogenic according to CLINVAR (16): a *PIK3CA* mutation with a variant allele frequency of 34.17%, and a *TP53* mutation with a variant allele frequency of 55.71%. CLINVAR did not classify the mutations in *NFB2*, *ATM*, or *BTK* as clinically significant. CANCERVAR software classified the mutation in *NFKB2* as having uncertain significance (tier III) based on three types of evidence. It classified the mutation in *ATM* as potentially clinically significant (tier II) based on 8 types of evidence. Lastly, the mutation in *BTK* was classified as having uncertain significance based on seven types of evidence.

To investigate the type of somatic mutations and the processes that generated them, we performed a mutational signatures analysis using R (www.r-project.org) and the MutationalPatterns (17) R/Bioconductor package. We analyzed 16,544 SNVs for mutational changes and sequence context, and generated a plot that represents the abundance of somatic SNVs in trinucleotide contexts, which is also defined as a 96-mutational profile (see Figure 2A). The most abundant nucleotide change was T>G, and the most enriched mutational trinucleotide contexts were ATT and TTT sequences. We decomposed the 96-mutational profile into different mutational signatures stored in COSMIC (18). Their relative contributions are shown in Figure 2B. We detected seven substitution mutational signatures (SBSs) in the tumor sample: SBS1, SBS9, SBS17b, SBS28, SBS37, SBS40, and SBS89. SBS40 contributed the most to the 96-mutational profile. The number of mutations attributed to SBS40 correlates with patient age in different types of human cancer (18), although the etiology is unknown. SBS1 is attributed to the deamination of 5-methylcytosine and is a clock-like signature, with the number of mutations correlating with age in normal cells and cancer cells (19). SBS9 seems to be due to the activity of polymerase η (18). The etiology of SBS17b, SBS28, SBS89, and SBS37 is unknown. However, SBS17b is associated with fluorouracil (5FU) chemotherapy treatment and damage inflicted by reactive oxygen species (ROS) (20).

TABLE 1 Somatic variants obtained from the WGS bioinformatic analysis.

GENE	CHR	POSITION	REF	ALT	HGVS.c	HGVS.p	COVERAGE	ALLELE COVERAGE	FREQUENCY	CLINVAR	CLINVAR STATUS	CANCERVAR	gnomAD	CADD
PIK3CA	chr3	179234297	A	G	c.3140A>G	p.His1047Arg	120	79,41	34.17 %	Pathogenic	3	Tier_II_potential [10]	.	22.5
TP53	chr17	7675088	C	T	c.524G>A	p.Arg175His	70	31,39	55.71 %	Pathogenic	2	Tier_I_strong [11]	1.548e-05	23.4
NFKB2	chr10	102400117	G	CLI	c.1507G>C	p.Val503Leu	68	35,33	48.53 %	.	-1	Tier_III_Uncertain [3]	.	23.7
ATM	chr11	108312478	G	C	c.5986G>C	p.Glu1996Gln	106	58,48	45.28 %	.	-1	Tier_II_potential [8]	.	24.1

We used CNVkit software (21) to analyze copy number variations (CNVs) in the genome. The copy number profiles for all autosomal chromosomes in the blood and tumor samples are shown in Figures 2C, D, respectively. Each colored dot represents the *log2* ratio in a sequence range of 750 bp, while the red line is the average *log2* ratio on a broader region. The red line of blood chromosomes lies exactly on the *log2* ratio value of zero, which means that they do not have any CNAs. In contrast, the tumor shows large CNVs in the chromosomes. Our focus was on cancer-associated genes located in chromosomal regions detected with CNV analysis. We identified 2,414 genes in duplicated regions, with 1294 of these coding for proteins, and 1528 genes in deleted regions, with 768 of these coding for proteins (Table S1). To identify potential tumor-specific genes, we filtered these genes using a list of 723 cancer-associated genes from the Cancer Gene Census website (https://cancer.sanger.ac.uk/census), resulting in 45 duplicated and 90 deleted genes (Table S2). We decided to perform CNV analysis in the tumor sample using data from third-generation sequencing technology. This was to reduce problems related to the short-read sequencing methodology in the CNV analyses, such as secondary alignments due to highly repetitive regions and technical duplicates. The tumor sample was sequenced, and we obtained a genome coverage of 27.54X, an N50 length of 45,147 bp, and a mean length of 17,518.9 bp. The CNV analysis was performed by setting a bin of 10,000 bp to reduce the high variance of the *log2* ratio in each bin probability due to the lack of a reference and the lower coverage relative to the Illumina experiment. Nevertheless, the CNV analysis obtained with PromethION 24 (Oxford Nanopore Technologies) showed large chromosome alterations to the tumor genome (Figure 2E), which strongly correspond to the alteration detected using Illumina sequencing data (Figure 2D).

Finally, tumor mutational burden (4.65 muts/Mb) and microsatellite instability (0.04% of mutated microsatellites) analyses did not show any relevant results (see Supplementary Materials).

Gene expression analysis of the tumor sample

To gain insight into the gene expression profile of the metastatic tumor sample, we conducted a comprehensive analysis using RNA sequencing (RNA-Seq) with the NovaSeq 6000 System (Illumina) and an in-house pipeline (Supplementary Materials). To supplement our analysis, we incorporated publicly available datasets, including a total of 28 healthy breast tissue samples (including 15 adjacent noncancerous tissues) downloaded from NCBI SRA (project accession numbers: PRJNA292118, PRJNA855324, PRJNA839244). We also used RNA-sequencing data from 1085 breast cancer patients obtained from the TCGA datasets (see Supplementary Materials).

Next, we compared the expression levels of the tumor-specific genes located in CNVs in our tumor sample to those of 10 healthy breast tissue samples from the PRJNA855324 and PRJNA839244 projects. In the set of 47 duplicated genes, we detected 24 genes in our tumor sample with higher expression levels than healthy breast tissues (Table S3), while 2 genes had lower expression levels. For

10.3389/fonc.2023.1240865

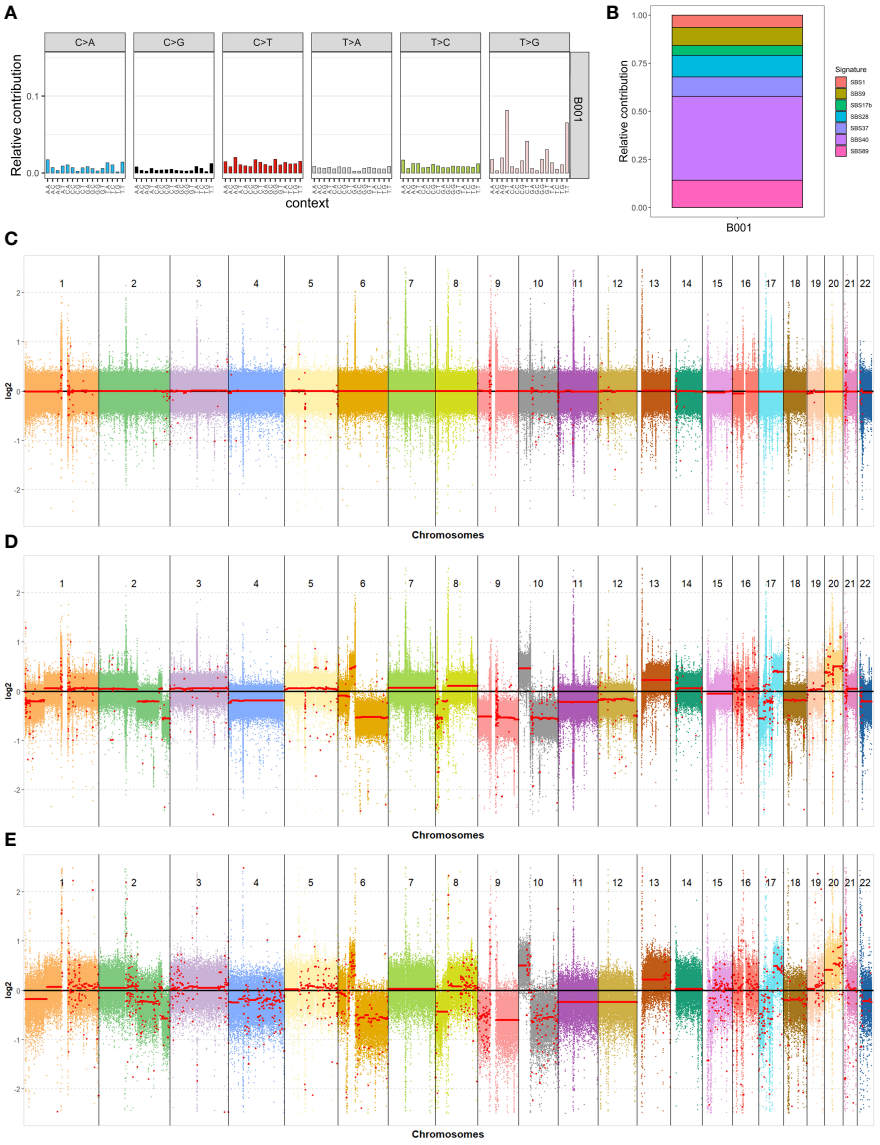


FIGURE 2
Genomic analysis of the blood and tumor samples. **(A)** 96-mutational profile; **(B)** Relative contribution of the different mutational signatures identified after the decomposition of the 96-mutational profile; **(C–E)** Results of the copy number variations analysis for all autosomal chromosomes: blood and tumor samples using short reads data **(C, D)** and tumor sample using long reads data **(E)**, respectively.

the deleted genes, 25 had a lower expression, and 4 had a higher expression (Table S4).

We also examined the expression levels in the tumor sample of critical genes involved in breast cancer, including *Progesterone Receptor* (*PGR*), *Estrogen Receptor 1* (*ESR1*), *Human Epidermal growth factor Receptor 2* (*HER2*, also known as *ERBB2*), *Marker Of Proliferation Ki-67* (*MKI67*), and *AR*. Subsequently, we compared these levels with those observed in 28 samples of healthy breast tissue. The resulting heatmap (Figure 3A) showed that the tumor sample had low expression levels for *PGR* and *ESR1*, medium expression levels for *MKI67*, and high expression levels for *HER2* and *AR*.

To further understand the molecular subtype of our tumor sample, we performed cluster analysis of 1085 breast cancer patients from TCGA datasets using different sets of genes. Figure 3B reports a heatmap built with the four genes used to classify the breast cancer subtypes: *PGR*, *ESR1*, *HER2*, and *MKI67*. These four genes capture a structure in the data: there is a light green cluster containing Basal-like patients, a pink cluster with HER2+ patients, and on the right branch of the dendrogram there are Luminal A and Luminal B samples, which are not separated. Our sample is in the pink cluster close to the HER2+ patients. Figure 3C shows a t-distributed stochastic neighbor embedding (t-SNE) plot built using PAM50 genes. In this case, we see: i) a well-defined cluster related to Basal-like and HER2+ patients; ii) Luminal A and Luminal B clusters that partially overlap; and iii) Normal-like patients with no well-defined location in the plot. Our sample is in the HER2-enriched cluster. To gain a complete picture of the tumor's gene expression profile, we analyzed 18,987 coding genes in the human genome using the t-SNE statistical method. While the resulting clusters were not well-defined for all subtypes, we were still able to identify a cluster of

10.3389/fonc.2023.1240865

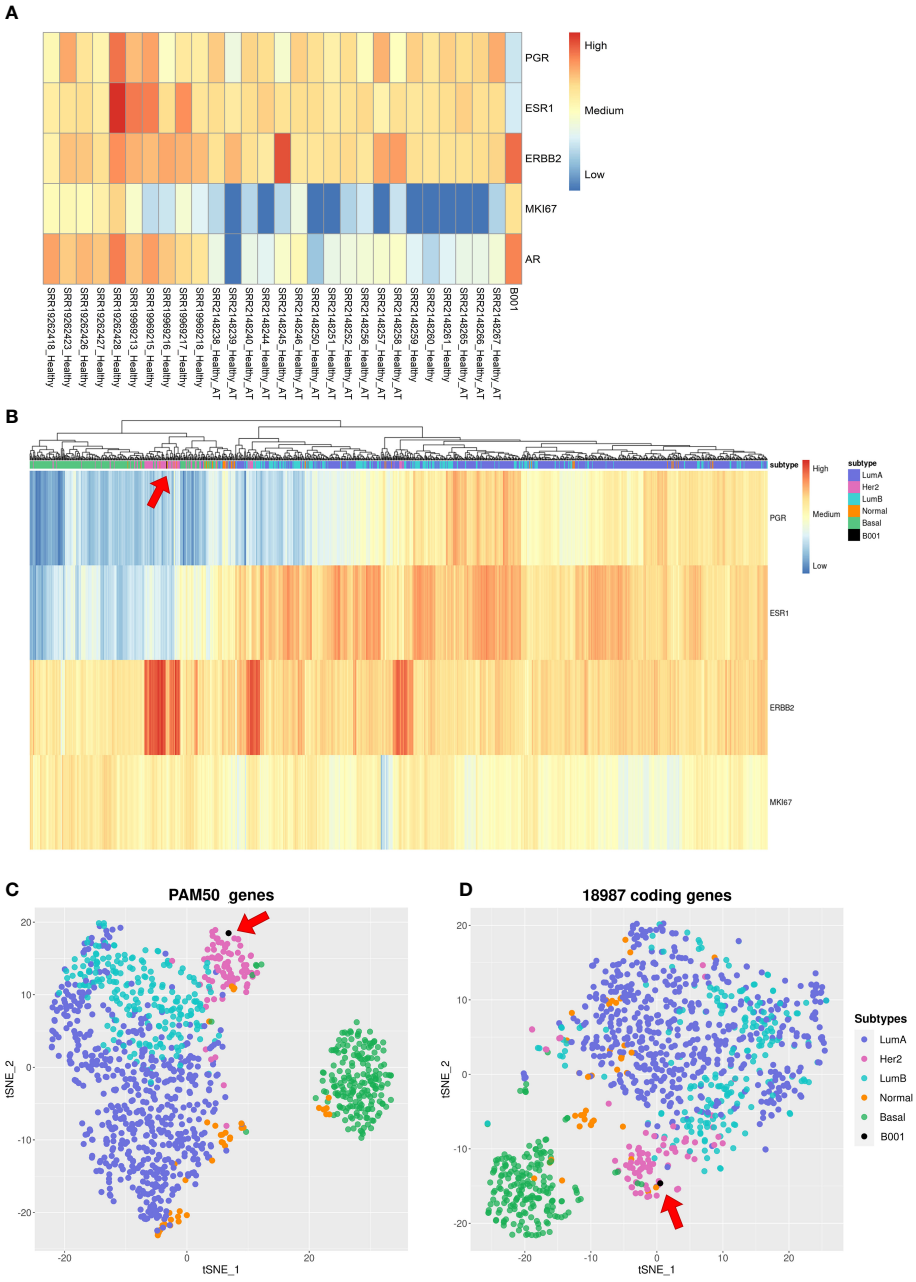


FIGURE 3
Gene expression analysis of the tumor sample. **(A)** Hierarchical clustering heatmap with gene expression levels of *PGR*, *ESR1*, *HER2*, *MKI67*, and *AR* in breast cancer tissue from 28 healthy patients and from our tumor sample; **(B)** Hierarchical clustering heatmap showing gene expression levels of *PGR*, *ESR1*, *HER2*, and *MKI67* of 1085 breast cancer patients in the TCGA dataset and our tumor sample; **(C, D)** T-SNE algorithm with 1085 breast cancer patients in the TCGA dataset and our tumor sample using PAM50 genes and 18987 coding genes, respectively.

patients with Basal-like subtypes and a blurry cluster of HER2+ individuals, which contained our sample (Figure 3D).

Discussion

Adapting the clinical and molecular classification of breast cancer to a single patient's disease is one of the most difficult tasks for medical and molecular oncologists.

In this study, we investigated the deep molecular issues of a patient with a metastatic ER-negative and PR-negative breast cancer with partial apocrine differentiation, in agreement with GCDFP-15 expression, and an oligometastatic clinical course. Since the diagnosis, the disease exhibited a moderate (2+) or strong (3+) expression of the HER2 protein, but CISH or FISH analyses were negative, thus indicating a HER2-low disease (22). After more than 20 years of clinical use of anti-HER2, emerging data and improved analytical methods mean that the dichotomous classification of a

positive or negative HER2 clinical category is evolving towards a continuum (23, 24). Here, our patient did not receive any anti-HER2 antibodies associated with conventional chemotherapy. At diagnosis, this choice was based on the HER2 2+/FISH-negative result. At relapse, despite the HER2 3+ result, CISH was performed (FISH was not available at our center at that time) because of the slow and oligometastatic behavior. Single-agent paclitaxel was then administered with a progression-free interval of nearly one year. At the second oligometastatic relapse, the case was revised in a referral center. Both CISH and FISH for *HER2* were performed, again with negative results. Thus, systemic treatment with single-agent capecitabine was chosen because of the possibility of concurrent radiotherapy, obtaining a complete metabolic response.

The tumor genome revealed a complex picture, with 20,323 somatic mutations (16,544 SNVs and 3,779 Indels). We found an enrichment of T>G nucleotide change in the SNVs, and mutational signature analysis associated some of the somatic mutations with the patient's age. Additionally, we detected SBS17b, associated with fluorouracil chemotherapy treatment and damage inflicted by ROS, which could be due to the patient's drug treatments. However, most SBSs do not yet have a known etiology. Further studies are needed to identify the etiology of these SBSs and increase the value of mutational signature analysis for personalized medicine. After filtering the variants, we identified five SNVs potentially associated with the development of cancer in our patient: *PIK3CA*, *TP53*, *NFKB2*, *ATM*, and *BTK*. Pathogenic mutations in *PIK3CA* and *TP53* were hypothesized to be drivers of the cancer. Because the sample's tumor purity was higher than 80%, the mutation in *TP53* seemed to be present in all the cancer cells (allele frequency 55.71%), while the mutation in *PIK3CA* was present in a large percentage of them (allele frequency 34.17%). We also observed large chromosomal duplications and deletions in several chromosomes, highlighting the genomic instability of the tumor sample. These alterations presented a *log2* between -1 and 1, except in rare cases, which indicated their presence in one or more tumor cell subpopulations but not in the entire population of tumor cells. Given the large size of these alterations, we hypothesize that several genes and regulatory elements are involved and contribute to the cancer phenotype. To the best of our knowledge, this report is the first scientific paper showing chromosome alterations in apocrine breast cancer using short-read and long-read sequencing approaches.

Our RNA-seq analysis characterized the tumor sample's gene expression profile. The results supported the immunohistochemical analysis in classifying the breast cancer subtype. Three different clustering approaches were used to achieve the goal: 1) Hierarchical clustering using Euclidean distance and complete-linkage method with *PGR*, *ESR1*, *HER2*, and *MKI67* genes, 2) *t-SNE* with PAM50 genes, 3) *t-SNE* with 18987 coding genes. All three methods clustered our sample with the HER2+ samples. This result, combined with the immunohistochemical analysis, led us to categorize this breast cancer sample as a HER2-positive subtype, although no *HER2* amplification at FISH was found. These promising results with clustering approaches highlight the need for a machine learning model running on gene expression data to improve the classification of breast cancer subtypes.

The results from the NGS and genomic/transcriptomic analysis confirmed our previous treatment choice but also opened the way for further treatments. Given the evidence of a strong intracellular driver (i.e. *PIK3CA*) combined with an inactivating *TP53* mutation, conventional chemotherapy is a more suitable candidate than anti-androgen or anti-HER2 therapy to stop neoplastic progression. However, if there is further progression, then the positivity of RNA for HER2 and AR pathways will support the use of anti-HER2 drug conjugates (25) or anti-androgenic treatments, possibly combined with off-label use of anti-PIK3CA treatment (26).

Although WGS and RNA-seq demand sophisticated infrastructure and expertise, they provide a comprehensive molecular characterization of the tumor. Our report and bioinformatics analysis offer an innovative personalized omics approach that could complement standard clinical practices and serve as a foundation for further fundamental research.

Conclusion

This case study presents a complex picture of a 56-year-old woman patient with oligometastatic breast cancer with an intermediate phenotype between HER2-positive and triple-negative. The slow clinical course allowed the use of a sequential rather than all-in approach.

The genomic-bioinformatic analysis revealed five SNVs potentially associated with the development of cancer in the patient, as well as large chromosomal duplications and deletions. Somatic SNV mutations were associated with the patient's age and chemotherapy treatment. RNA-seq analysis supported immunohistochemical analysis in classifying the breast cancer subtype as HER2-positive, although the disease was clinically defined as HER2-low. Overall, the study provides valuable insights into the complex genomic and molecular landscape of breast cancer with partial apocrine differentiation, and emphasizes the need for personalized and comprehensive approaches in cancer research and treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The research was conducted in accordance with the principles embodied in the Declaration of Helsinki, in accordance with the Guidelines ICH-GCP and the applicable regulations. The study was approved by the Ethical Committee of the Regional Hospital "U. Parini". The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

ACa, BP, ACo, MS, AP, MV, SG conceptualized and designed the research. MV, MM, ST, VP, UF performed sample collection and sequencing. ACo, BP, FL, DC, FF carried out bioinformatic data analysis and tables/figures creation. ACo, BP, AP conducted manuscript drafting. ACa, MS, AP, MV, ST, UF, ACo, BP, PF, VA, AM, PC reviewed the written manuscript and participated in the modification. All authors contributed to the article and approved the submitted version.

Funding

The research center CMP^{3}VdA and the Project 5000genomi@VdA are co-founded by "Fondo Europeo di Sviluppo Regionale (FESR) Programma Investimenti per la crescita e l'occupazione 2014/20" (European Social Fund, ESF, and European Regional Development Fund, ERDF), the Autonomous Region of the Aosta Valley, and the Italian Ministry of Labour and Social Policy (CUPB68H19005520007). BP, MM, FF, VP, DC have carried out this work supported by a grant of the EU-ESF, the Autonomous Region of the Aosta Valley, and the Italian Ministry of Labour and Social Policy.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1240865/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Case report timeline. Presented according to CARE guidelines. The dotted line is for ongoing treatments.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

2. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* (2021) 32(12):1475–95. doi: 10.1016/j.annonc.2021.09.019

3. Dorn PL, Corbin KS, Al-Hallaq H, Hasan Y, Chmura SJ. Feasibility and acute toxicity of hypofractionated radiation in large-breasted patients. *Int J Radiat Oncol Biol Phys* (2012) 83(1):79–83. doi: 10.1016/j.ijrobp.2011.05.074

4. Kent CL, McDuff SGR, Salama JK. Oligometastatic breast cancer: where are we now and where are we headed?-a narrative review. *Ann Palliat Med* (2021) 10(5):5954–68. doi: 10.21037/apm-20-1128

5. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA* (2001) 98(19):10869–74. doi: 10.1073/pnas.191367098

6. Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J, et al. Breast cancer intrinsic subtype classification, clinical use and future trends. *Am J Cancer Res* (2015) 5(10):2929–43.

7. Dellapasqua S, Maisonneuve P, Viale G, Pruneri G, Mazzarol G, Ghisini R, et al. Immunohistochemically defined subtypes and outcome of apocrine breast cancer. *Clin Breast Cancer*. (2013) 13(2):95–102. doi: 10.1016/j.clbc.2012.11.004

8. Vranic S, Feldman R, Gatalica Z. Apocrine carcinoma of the breast: A brief update on the molecular features and targetable biomarkers. *Bosn J Basic Med Sci* (2017) 17(1):9–11. doi: 10.17305/bjbms.2016.1811

9. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. *Nat Rev Dis Primers* (2019) 5(1):67. doi: 10.1038/s41572-019-0122-z

10. Hurvitz SA, Gonçalves A, Rugo HS, Lee KH, Fehrenbacher L, Mina LA, et al. Talazoparib in patients with a germline BRCA-mutated advanced breast cancer: detailed safety analyses from the phase III EMBRACA trial. *Oncologist* (2020) 25(3):e439–50. doi: 10.1634/theoncologist.2019-0493

11. Varna M, Bousquet G, Plassa LF, Bertheau P, Janin A. TP53 status and response to treatment in breast cancers. *J Biomedicine Biotechnol* (2011) 2011:1–9. doi: 10.1155/2011/284584

12. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for -mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med* (2019) 380(20):1929–40. doi: 10.1056/NEJMoa1813904

13. Hu W, Li M, Zhang Q, Liu C, Wang X, Li J, et al. Establishment of a novel CNV-related prognostic signature predicting prognosis in patients with breast cancer. *J Ovarian Res* (2021) 14(1):103. doi: 10.1186/s13048-021-00823-y

14. Sun X, Zuo K, Yao Q, Zhou S, Shui R, Xu X, et al. Invasive apocrine carcinoma of the breast: clinicopathologic features and comprehensive genomic profiling of 18 pure triple-negative apocrine carcinomas. *Mod Pathol* (2020) 33(12):2473–82. doi: 10.1038/s41379-020-0589-x

15. Lázaro C, Lerner-Ellis J, Spurdle A. *Clinical DNA Variant Interpretation: Theory and Practice*. Academic Press (2021). p. 436.

16. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res* (2018) 46:D1062–7. doi: 10.1093/nar/gkx1153

17. Manders F, Brandsma AM, de Kanter J, Verheul M, Oka R, van Roosmalen MJ, et al. MutationalPatterns: the one stop shop for the analysis of mutational processes. *BMC Genomics* (2022) 23(1):134. doi: 10.1186/s12864-022-08357-3

18. Bamford S, Dawson E, Forbes S, Clements J, Pettett R, Dogan A, et al. The COSMIC (Catalogue of Somatic Mutations in Cancer) database and website. *Br J Cancer* (2004) 91(2):355–8. doi: 10.1038/sj.bjc.6601894

19. Alexandrov LB, Kim J, Haradhvala NJ, Huang MN, Ng AWT, Wu Y, et al. *The Repertoire of Mutational Signatures in Human Cancer* (2020) doi: 10.1101/322859.

20. Koh G, Degasperi A, Zou X, Momen S, Nik-Zainal S. Mutational signatures: emerging concepts, caveats and clinical applications. *Nat Rev Cancer* (2021) 21(10):619–37. doi: 10.1038/s41568-021-00377-7

21. Talevich E, Shain AH, Botton T, Bastian BC. CNVkit: genome-wide copy number detection and visualization from targeted DNA sequencing. *PloS Comput Biol* (2016) 12(4):e1004873. doi: 10.1371/journal.pcbi.1004873

22. Tarantino P, Hamilton E, Tolaney SM, Cortes J, Morganti S, Ferraro E, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol* (2020) 38 (17):1951–62. doi: 10.1200/JCO.19.02488

23. Marchiò C, Annaratone L, Marques A, Casorzo L, Berrino E, Sapino A. Evolving concepts in HER2 evaluation in breast cancer: Heterogeneity, HER2-low carcinomas and beyond. *Semin Cancer Biol* (2021) 72:123–35. doi: 10.1016/j.semcancer.2020.02.016

24. Sajjadi E, Venetis K, Ivanova M, Fusco N. Improving HER2 testing reproducibility in HER2-low breast cancer. *Cancer Drug Resist* (2022) 5(4):882–8. doi: 10.20517/cdr.2022.29

25. Lang Y, Wu B, Liu X. Economic evaluation of trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer in the United States. *Breast Cancer*. (2022) 14:453–63. doi: 10.2147/BCTT.S389696

26. Mir MA. *Combinational Therapy in Triple Negative Breast Cancer*. Academic Press (2022). 260 p.

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 04 August 2023
DOI 10.3389/fonc.2023.1214660

OPEN ACCESS

EDITED BY
Huiming Lu,
University of Texas Southwestern Medical Center, United States

REVIEWED BY
Gitana Maria Aceto,
University of Studies G. d'Annunzio Chieti and Pescara, Italy
Julio Morales,
University of Oklahoma, United States

*CORRESPONDENCE
Roberta Caputo
r.caputo@breastunit.org

RECEIVED 30 April 2023
ACCEPTED 20 July 2023
PUBLISHED 04 August 2023

CITATION
Caputo R, Pagliuca M, Pensabene M, Parola S and De Laurentiis M (2023) Long-term complete response with third-line PARP inhibitor after immunotherapy in a patient with triple-negative breast cancer: a case report.
Front. Oncol. 13:1214660.
doi: 10.3389/fonc.2023.1214660

Long-term complete response with third-line PARP inhibitor after immunotherapy in a patient with triple-negative breast cancer: a case report

Roberta Caputo[1*], Martina Pagliuca[2,3], Matilde Pensabene[1], Sara Parola[4] and Michelino De Laurentiis[1]

[1]Division of Breast Oncology, Istituto Nazionale Tumori - IRCCS - Fondazione G. Pascale, Naples, Italy, [2]Clinical and Translational Oncology, Scuola Superiore Meridionale (SSM), Naples, Italy, [3]U981 Molecular Predictors and New Targets in Oncology, Gustave Roussy, Villejuif, France, [4]Unità Operativa Oncologia del PO di San Felice a Cancello, Caserta, Italy

While standard treatment has shown efficacy in patients with breast cancer gene (*BRCA*) mutations, recurrence rates are high and additional effective therapies are needed. Olaparib, a poly adenosine diphosphate–ribose polymerase (PARP) inhibitor, approved for the treatment of metastatic germline *BRCA1*/*BRCA2* breast cancer (BC), has demonstrated evidence of a progression-free survival (PFS) benefit, good safety profile, and improved quality of life compared with standard chemotherapy. We here describe the case of a patient with *BRCA1* mutated advanced BC and a long history of response to chemotherapy and immunotherapy who received systemic treatment with olaparib. First diagnosed in March 2011 at the age of 38 years with early-stage BC of the right breast, she underwent quadrantectomy plus ipsilateral axillary lymphadenectomy and adjuvant treatments with chemotherapy regimen containing 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by radiotherapy. Five years later, following a contralateral nodule detection leading to left breast quadrantectomy, she received adjuvant systemic treatment with docetaxel plus cyclophosphamide and radiotherapy. Gene testing showed a germline *BRCA1* deleterious variant, and she underwent bilateral prophylactic mastectomy and oophorectomy. One year later, skin metastasis and bone infiltrations were detected, and she was started on first-line systemic treatment. The patient was enrolled in the IMpassion131 trial (investigating atezolizumab addition to paclitaxel) but unblinding showed that she was randomized in the placebo arm. She received second-line systemic therapy with LAG525 plus carboplatin (CLAG525B2101 trial) resulting in a PFS of 14 months. At disease progression, she was eligible for systemic third-line therapy with olaparib (300 mg twice daily) and had a complete response after 6 months of therapy and a PFS of 40 months at the time of writing. To the best of our knowledge, this is the first report of a complete response following treatment with third-line systemic olaparib in a long-responding patient and relatively good tolerability and quality of life, pre-treated with both chemotherapy and immunotherapy.

KEYWORDS

advanced breast cancer, *BRCA* mutation, triple negative breast cancer, PARP inhibitor, immunotherapy

1 Introduction

Despite advances in treatments and increasingly early detection through screening programs, breast cancer (BC) remains the world's most prevalent cancer with 2.3 million women diagnosed with BC in 2020 and 685,000 deaths (1). BC affects a staggering 1 in 8 women over their lifetime, with an incidence of 109.2 per 100,000 in women aged under 40 (2). The *BRCA1* and *BRCA2* pathogenic variants, identified over 30 years ago, still constitute the most clinically relevant predisposition genes. Although quoted risks vary according to different evidence, data from prospective cohort studies show that the risk for BC is 72% (at age 80) for *BRCA1* mutation (hereafter used as a synonym for pathogenic variant) carriers, and 69% for *BRCA2* mutation carriers (3). Patients diagnosed with BC associated with *BRCA* pathogenic variants frequently suffer from aggressive, high-risk disease since recurrence rates are high, despite standard-of-care treatments including surgery, radiation, and chemotherapy/immunotherapy. There remains a large unmet need for additional novel targeted therapies that produce improved and long-lasting outcomes in this patient population.

BRCA1 and *BRCA2* are tumor-suppressor genes that encode proteins involved in the repair of DNA double-strand breaks through the homologous recombination repair (HRR) pathway. BCs associated with *BRCA* mutations are more prone to double-strand DNA breaks that cannot be repaired because of a defective HRR pathway. Poly adenosine diphosphate–ribose polymerase (PARP) enzymes are fundamental to repair DNA single-strand breaks, and cells that lack functional *BRCA1*/*BRCA2* are sensitive to PARP inhibition. PARP inhibitors target cancers with defects in HRR leading to synthetic lethality and cancer cell apoptosis (4). Olaparib, an orally administered PARP inhibitor, was approved for metastatic BC by the United States Food and Drug Administration (FDA) (January 2018) and for locally advanced/metastatic BC by the European Medicines Agency (EMA) (April 2019), based on the positive results of the randomized, controlled, open-label, multicenter, international, phase 3 OlympiAD trial (5, 6). The study enrolled patients with a germline *BRCA* (g*BRCA*) mutation and human epidermal growth factor receptor type 2 (HER2)-negative metastatic BC who received no more than two previous chemotherapy regimens for metastatic disease (7). Results showed that monotherapy with olaparib (205 patients assigned to olaparib arm 300 mg twice daily) provided a significant benefit over standard therapy of the physician's choice (TPC; capecitabine, eribulin, or vinorelbine in 21-day cycles, 97 patients). Median PFS was 2.8 months longer (7.0 vs. 4.2 months) and the risk of disease progression or death was 42% lower with olaparib monotherapy than with TPC. Importantly, quality of life (QoL) consistently improved with olaparib vs. TPC, with a higher proportion of olaparib-treated patients rating their best overall response as "improvement" (33.7% vs. 13.4%). Most adverse events (AEs) in the intervention arm were grade 1/2, and the proportion of patients reporting grade 3 or higher AEs was lower with olaparib (38.0%) than with TPC (49.5%). Olaparib dose interruptions did not significantly affect treatment duration, and few patients discontinued olaparib therapy because of AEs (<5%). In the present manuscript, we report the case of a patient with *BRCA1* mutated (*BRCA1*m) advanced BC who received systemic treatment with olaparib after a long history of response to chemotherapy and immunotherapy.

This case report follows the CARE Guidelines (8).

2 Case report

Our patient is a Caucasian woman without relevant personal medical history, except for a mild bronchial asthma seldom treated with low-dose corticosteroids. In March 2011, at the age of 38 years, she was first diagnosed with early-stage BC of the right breast (Figure 1). Breast and axillary lymph node ultrasound scan showed a nodule with irregular margins (23 mm diameter) in the upper-outer quadrant of the right breast. Bilateral mammography demonstrated radiopacity in the right breast and fine-needle aspiration biopsy retrieved malignant cells (C5) (Figure 2). Subsequently, core needle biopsy showed an infiltrating ductal carcinoma (ER: 0%, PgR: 0%, Ki-67: 30%, HER2-neu: 0), and tumor markers were as follows: CA-15.3 20.7 U/ml, CEA 2.1 ng/ml. No distant metastases were detected. Thus, she underwent right breast-conserving surgery and ipsilateral axillary lymphadenectomy. Postoperative TNM classification was pT2 (28mm) G3 pN1a (1+/20). She received adjuvant treatment (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2, three cycles, every 21 days, and subsequent docetaxel 100 mg/m^2, three cycles, every 21 days) and radiotherapy to the right breast.

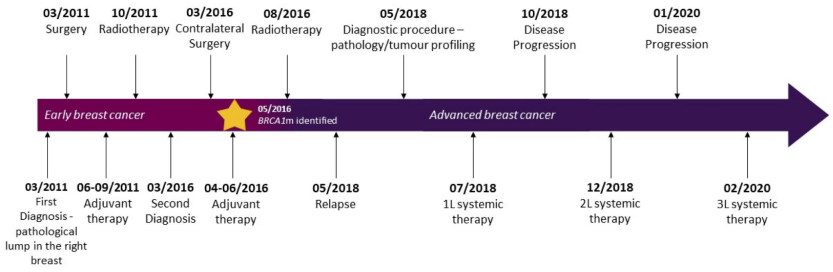


FIGURE 1
Case report timeline. 1L, first line; 2L, second line; 3L, third line.

10.3389/fonc.2023.1214660

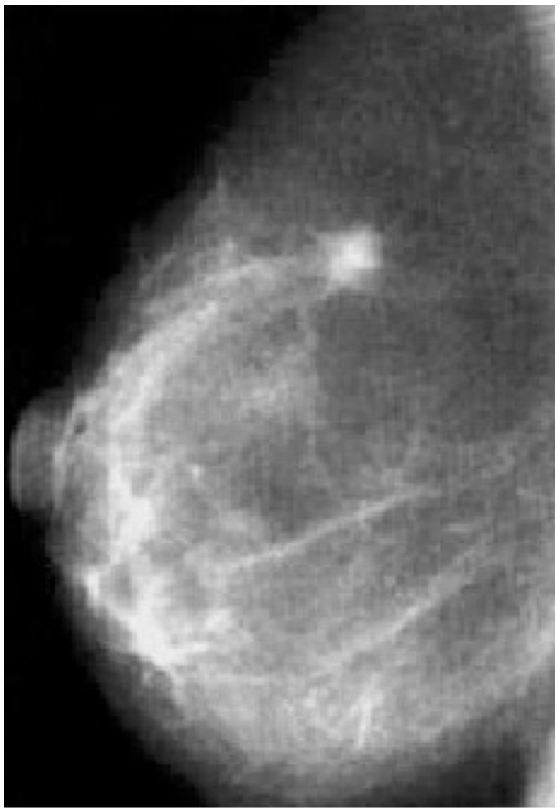


FIGURE 2
Baseline mammography showing pathological lump in the right breast.

Follow-up was negative until March 2016 when a second contralateral nodule (15 mm) was identified. Again, there was no evidence of distant metastases. Breast-conserving surgery (left breast quadrantectomy) and ipsilateral axillary sampling were performed [postoperative pT1c 18 mm, pN0 (0/10), ER: 0%, PgR: 0%, Ki-67: 75%, HER2-neu: 0], followed by treatment with docetaxel 600 mg/m^2 plus cyclophosphamide 75 mg/m^2 for four cycles every 21 days and subsequent radiotherapy.

She was referred to the Hereditary Cancer Genetics Clinic at the University Federico II in Naples, Italy, due to the early-onset metachronous BC and the family history including breast and ovarian cancer (grandmother). In May 2016, the result of germline *BRCA* gene testing showed the deleterious variant c.3514G>T p.Glu1172* in the *BRCA1* gene. She underwent bilateral prophylactic mastectomy and oophorectomy in June and July 2017, respectively. She was disease-free for 1 year; then, in May 2018, the PET-CT scan showed involvement of skin of the left breast, increased uptake in multiple lymph nodes of the left axilla and left internal mammary, and bone infiltrations (fourth and sixth left ribs) (Figure 3). Pathological examination showed skin metastasis from breast carcinoma (ER: 0%, PgR: 0%, Ki-67: 80%, HER2-neu: 0). Tumor serum markers were within the normal values: CA-15.3 13.9 U/ml, CEA 2.1 ng/ml.

In July 2018, she was enrolled in the phase III IMpassion131 trial investigating treatment with chemotherapy and immunotherapy [atezolizumab 840 mg or placebo by intravenous infusion on Days 1 and 15 (± 3 days) every 28 days along with paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days until disease progression or unacceptable toxicity]. She received four cycles of therapy. Trial unblinding at disease progression showed that the patient was in the placebo arm.

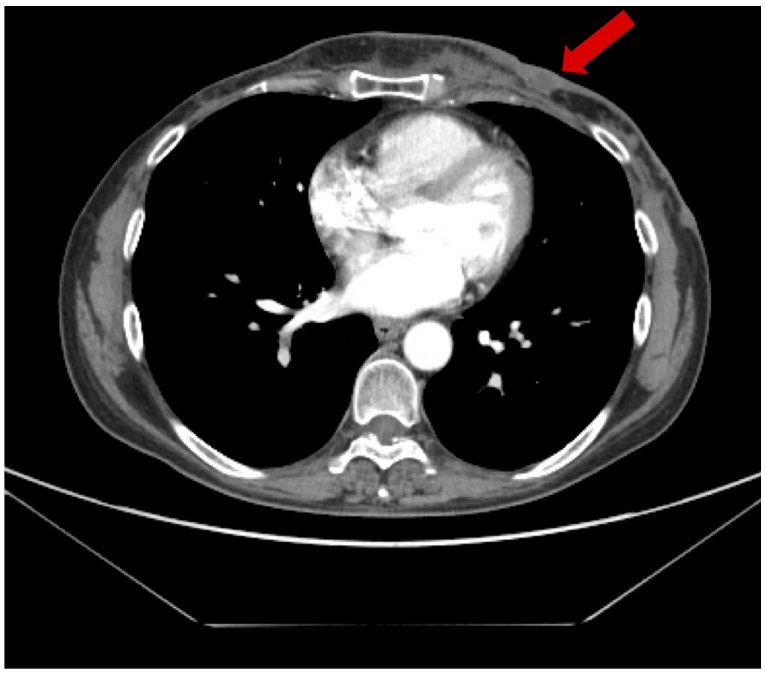


FIGURE 3
First evidence of metastatic disease on baseline PET-CT scan.

In December 2018, she developed mild cough and dyspnea, and chest CT showed the left chest wall disease progression. Thus, she discontinued the ongoing treatment for metastatic BC and was enrolled in the CLAG525B2101 trial investigating LAG525 in combination with spartalizumab, or with spartalizumab and carboplatin, or with carboplatin (Figure 4A). LAG525 is a humanized IgG4 monoclonal antibody, acting as a checkpoint inhibitor that binds the Lymphocyte-activation gene 3 (LAG-3) protein and prevents its interaction with class II major histocompatibility complex (MHC-II) molecules. While spartalizumab is a monoclonal antibody directed against the human programmed death-1 (PD-1) receptor, it also inhibits immune checkpoint. The patient received LAG525 (400 mg every 21 days) in combination with carboplatin (AUC 6 every 21 days), both intravenously (iv) for a total of 17 cycles until disease progressed. The PFS was 14 months. AEs included thrombocytopenia grade 3 (G3), diarrhea G1, vomiting G1, and hypothyroidism G2; carboplatin was discontinued after 10 cycles due to infusion-related hypersensitivity reaction.

In February 2020, as a patient with a germline *BRCA* mutation who had received no more than two previous chemotherapy regimens for metastatic disease, she was eligible for olaparib (300 mg twice daily) therapy (Figure 4B). Treatment was well tolerated apart from G2 anemia, which imposed a dose reduction—the olaparib dose after 7 months was 100 mg plus 150-mg tablets twice daily. Other reported AEs were nausea, vomiting, and diarrhea (all G1). There was no evidence of increased uptake on PET/CT scan (Figure 4C). Treatment with olaparib produced a complete response after 6 months, and at the time of writing, the patient had a PFS of 40 months. It should be, moreover, emphasized how grateful the patient was to be able to receive an effective therapy that did not negatively affect her QoL. Indeed, she had been aware of the advanced stage of disease since she was 45, and that the PFS with the first line of treatment was only 5 months. The complete disease response achieved with a long-lasting and overall well-tolerated oral treatment also increases adherence to the therapy itself, enhancing its efficacy.

3 Discussion and conclusion

The diagnostic and therapeutic landscape of BC has changed dramatically in recent years, leading to the introduction of systemic targeted therapies that improve response rates and prolong survival, while maintaining QoL. Our patient was first diagnosed with early BC at the age of 38 years. First-line therapy as part of the IMpassion131 trial was weekly paclitaxel plus placebo (without atezolizumab) and PFS was 5 months. The IMpassion131/130 trials investigated the benefit of adding the immune stimulating agent atezolizumab to a taxane backbone chemotherapy in the first-line treatment of metastatic triple-negative BC (TNBC) (9, 10). Results from the IMpassion130 study indicated improved PFS and clinically meaningful overall survival (OS) benefit with atezolizumab plus nab-paclitaxel in patients with programmed death-ligand 1 (PD-L1)-positive disease and that atezolizumab plus nab-paclitaxel may constitute an important therapeutic option in this disease with high unmet need. However, these results were not replicated in the follow-up IMpassion131 study—atezolizumab plus paclitaxel did not improve PFS or OS in the intention-to-treat (ITT) population or the PD-L1-positive group vs. paclitaxel alone. Second-line therapy was immunotherapy with LAG525, which inhibits LAG-3 (an inhibitory immunoreceptor linked to reduced T-cell proliferation and cytokine production), plus carboplatin (11). Overall, 17 cycles were administered (carboplatin was discontinued after 10 cycles due to AEs) and PFS was 14 months. Olaparib was administered as a third-line therapy based on the results of the landmark OlympiAD trial that showed it to improve PFS and, in addition, to reduce hospitalization (advantage of oral therapy vs. iv) as well as ameliorate QoL, compared with chemotherapy (7, 12). Since then, the OlympiA study demonstrated "practice-changing results"—the first to report the benefits of an adjuvant PARP inhibitor for early stage of germline *BRCA1/2*-mutation-associated BC. This phase III, double-blind, randomized trial enrolled patients with HER2-negative early BC with *BRCA1* or *BRCA2* germline pathogenic or likely pathogenic variants and high-risk clinicopathological factors, who had received local treatment and neoadjuvant/adjuvant chemotherapy. Patients who received olaparib after a median follow-up of 3.5 years experienced a 37% reduction in invasive disease-free survival, including local and metastatic recurrence of BC, other new cancers, and death due to any cause. Among patients with high-risk, HER2-negative early BC with germline *BRCA1/BRCA2* deleterious variants, adjuvant olaparib, after completion of local treatment and neoadjuvant/adjuvant chemotherapy, was associated with significantly longer survival free of invasive or distant disease than placebo. More importantly, a benefit in OS rate was reported with the use of olaparib in this population in an adjuvant setting (4-year OS Δ 3.4%, 95% CI 0.1% to 6.8%). The principal investigator of the study concluded that "patients who received olaparib after surgery and chemotherapy were more likely to be alive without cancer, [as well as] avoid metastasis, than the patients who received placebo—after 10 years of evaluation of PARP inhibitors in BC, a therapy that could likely save many lives is finally at hand" (13, 14). It should be acknowledged that, to date, we have some evidence of the efficacy of PARP inhibitors in the treatment of non-germline *BRCA*m advanced BC. The randomized controlled phase II S1416 trial reported the addition of veliparib to platinum chemotherapy to be effective in metastatic germline *BRCA*-wildtype TNBC with a BRCA-like phenotype, namely, with homologous recombination deficiency (HRD) leading to genomic instability (15). Olaparib monotherapy was further evaluated in the phase II TBCRC 048 trial in a population of patients with advanced BC with germline (other than *BRCA*) or somatic (including *BRCA*) pathogenic variants in DNA damage response pathway genes. Objective responses to the PARP inhibitor were reported in patients with somatic *BRCA1/2* or germline partner and localizer of BRCA2 gene (*PALB2*) mutations (16). In conclusion, our case report shows that in a patient with metastatic BC, third-line therapy with olaparib can lead to a rapid and durable response with clinical complete remission with a relatively good quality of life.

10.3389/fonc.2023.1214660

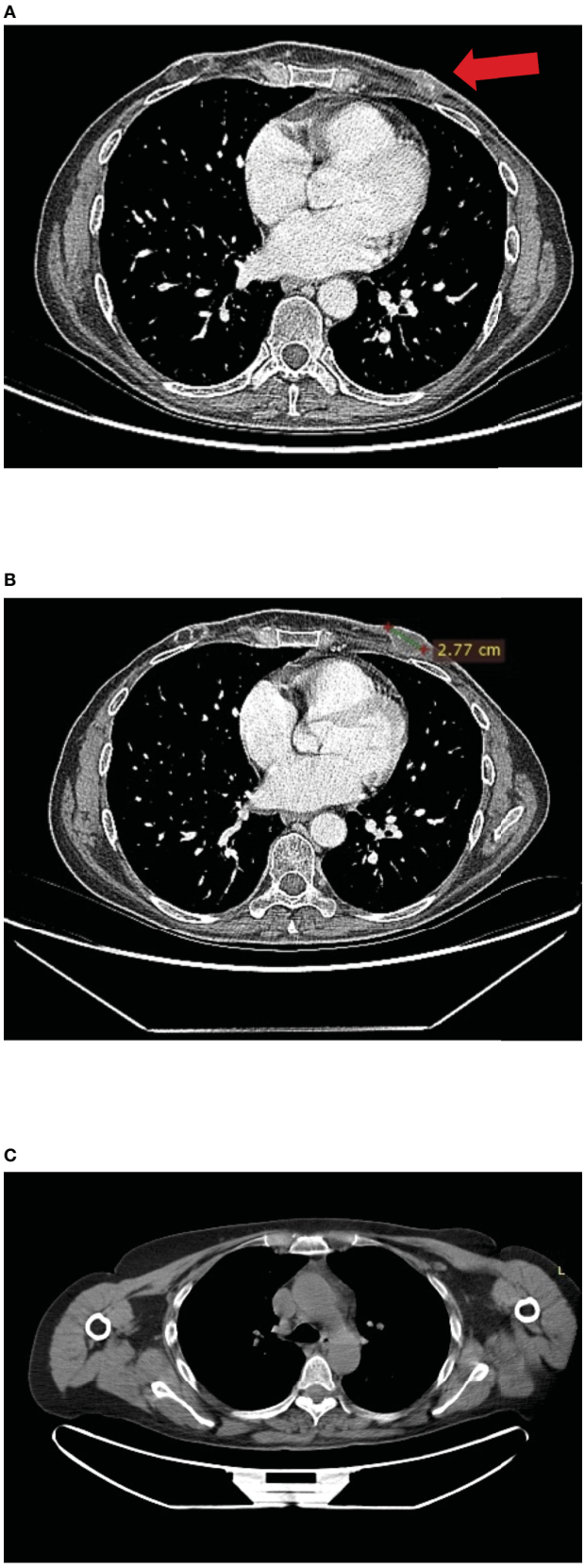


FIGURE 4
(A) CT scan images of left chest wall disease progression at enrolment in the IMpassion131 trial. **(B)** CT scan images at enrolment in CLAG525B2101 trials. **(C)** Complete response after 6 months of treatment with olaparib; no contrast enhancement at PET-CT scan.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this manuscript.

Author contributions

RC and MPe conceptualized the manuscript. RC, MPa, and SP wrote the original draft of the manuscript. ML contributed to the radiology images and reviewed the manuscript. All authors substantially contributed to the conception, data acquisition, and interpretation of the report. All authors agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

Conflict of interest

RC reports advisory role from Roche, Novartis, Pfizer, Lilly, Amgen, Pierre Fabre, Astra Zeneca, MSD, Seagen, Gilead, Takeda, Ipsen, and Sanofi; MPa reports travel grants from Pfizer and Gilead; ML reports honoraria and advisory role from Roche, Novartis, Pfizer, Lilly, Amgen, Pierre Fabre, Astra Zeneca, MSD, Seagen, Gilead, Takeda, Ipsen, and Sanofi Genzyme.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. World Health Organization. *Breast Cancer Fact Sheet WHO* . Available at: https://www.who.int/news-room/fact-sheets/detail/breast-cancer (Accessed Jan 2022).

2. Cancer Research UK. *Cancer Incidence by Age* (2020). Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Two (Accessed Jan 2022).

3. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips K-A, Mooij TM, Roos-Blom M-J, et al. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. *JAMA* (2017) 317(23):2402. doi: 10.1001/jama.2017.7112

4. Cortesi L, Rugo HS, Jackisch C. An overview of PARP inhibitors for the treatment of breast cancer. *Target Oncol* (2021) 16(3):255–82. doi: 10.1007/s11523-021-00796-4

5. U.S. Food and Drug Administration. *FDA approves olaparib for germline BRCA-mutated metastatic breast cancer* (2018). Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-germline-brca-mutated-metastaticbreast-cancer (Accessed Jan 2022).

6. *AstraZeneca. Lynparza approved in EU for the treatment of germline BRCA-mutated HER2-negative advanced breast cancer* (2019). Available at: https://www.astrazeneca.com/media centre/press-releases/2019/lynparza-approved-in-eu-for-the-treatment-of-germline-brca-mutat ed-her2-negative-advanced-breastcancer-10042019 (Accessed Jan 2022).

7. Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. *New Engl J Med* (2017) 377(6):523–33. doi: 10.1056/NEJMoa1706450

8. Riley DS, Barber MS, Kienle GS, Aronson JK, von Schoen-Angerer T, Tugwell P, et al. CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol* (2017) 89:218–35. doi: 10.1016/j.jclinepi.2017.04.026

9. Miles D, Gligorov J, André F, Cameron D, Schneeweiss A, Barrios C, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. *Ann Oncol* (2021) 32(8):994–1004. doi: 10.1016/j.annonc.2021.05.801

10. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* (2020) 21(1):44–59. doi: 10.1016/S1470-2045(19)30689-8

11. Lin C-C, Garralda E, Schöffski P, Hong D, Siu L, Martin M, et al. 387 A Phase II, multicenter study of the safety and efficacy of LAG525 in combination with spartalizumab in patients with advanced malignancies. *J Immunother Cancer* (2020) 8(Suppl 3):A412. doi: 10.1136/jitc-2020-SITC2020.0387

12. Sanchez AM, Orlandi A, Franceschini G, De Lauretis F, Terribile D, Franco A, et al. OlympiAD trial: moving to a next level of treatment for patients with BRCA mutation and her2-negative metastatic breast cancer. *Ann Palliat Med* (2020) 9(2):510–1. doi: 10.21037/apm.2020.01.14

13. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med* (2021) 384:2394–405. doi: 10.1056/NEJMoa2105215

14. Geyer CE Jr, Garber JE, Gelber RD, Yothers G, Taboada M, Ross L, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol* (2022) 33(12):1250–68. doi: 10.1016/j.annonc.2022.09.159

15. Rodler E, Sharma P, Barlow WE, Gralow JR, Puhalla SL, Anders CK, et al. Cisplatin with veliparib or placebo in metastatic triple-negative breast cancer and BRCA mutation-associated breast cancer (S1416): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* (2023) 24(2):162–74. doi: 10.1016/S1470-2045(22)00739-2

16. Tung NM, Robson ME, Ventz S, Santa-Maria CA, Nanda R, Marcom PK, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol* (2020) 38(36):4274–82. doi: 10.1200/JCO.20.02151

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 24 August 2023
DOI 10.3389/fonc.2023.1184738

OPEN ACCESS

EDITED BY
Parvez Khan,
University of Nebraska Medical Center,
United States

REVIEWED BY
Asad Ur Rehman,
University of Nebraska Medical Center,
United States
Aatiya Ahmad,
University of Nebraska Medical Center,
United States

*CORRESPONDENCE
Chung-Hsing Chang
miriamchangch@gmail.com

RECEIVED 12 March 2023
ACCEPTED 03 August 2023
PUBLISHED 24 August 2023

CITATION
Jhan J-Y, Wang W-E, Chu S-C, Cheng C-H and Chang C-H (2023) Case Report: Ribociclib-induced phototoxicity presented as dyschromia with subsequent bullae formation. *Front. Oncol.* 13:1184738. doi: 10.3389/fonc.2023.1184738

Case Report: Ribociclib-induced phototoxicity presented as dyschromia with subsequent bullae formation

Jyun-Yan Jhan[1], Wei-En Wang[1], Sung-Chao Chu[2], Chiu-Hsuan Cheng[3] and Chung-Hsing Chang[1,4,5]*

[1]Skin Institute, Department of Dermatology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, [2]Department of Hematology-Oncology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan, [3]Department of Pathology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan, [4]Doctoral Degree Program in Translational Medicine, Tzu Chi University and Academia Sinica, Taipei, Taiwan, [5]Institute of Medical Sciences, College of Medicine, Tzu Chi University, Hualien, Taiwan

Ribociclib, a cyclin-dependent kinase 4/6 inhibitor, is a novel targeted therapy for advanced-stage breast cancer. Although ribociclib-induced cutaneous side effects have been previously noted, they have not been well documented. Herein, we present a case of ribociclib-induced phototoxicity, which manifested as dyschromia over sun-exposed forearms and neck initially and as bullae formation subsequently. A 71-year-old woman with metastatic breast cancer developed dyschromia after daily treatment with ribociclib (600 mg) for 7 months. Skin biopsy of the pigmented lesion revealed interface dermatitis with melanin incontinence and dyskeratotic cells and ballooning keratinocytes with loss of melanocytes in the basal layer. Further, clefting at the basal layer of epidermis was noted in a more hyperpigmented field. Fontana–Masson staining revealed melanophages in the dermis. Human Melanoma Black-45 staining revealed decreased melanocyte numbers in the epidermis above the cleft. Immunohistochemical analyses revealed activated CD1a+ epidermal Langerhans cells and infiltrating CD4+ and CD8+ T cells in the epidermis and dermis, thereby indicating type IV hypersensitivity that was associated with damage to keratinocytes and melanocytes. To prevent progression of bullous dermatitis, we advised the patient to discontinue ribociclib and prescribed oral and topical prednisolone. Due to the risk of phototoxicity, we educated the patient on sun-protection strategies. The patient's skin lesions subsided during the 2 months of treatment. Phototoxicity with dyschromia is a rare but significant ribociclib-induced cutaneous side effect. Early diagnosis, rapid ribociclib withdrawal, protection from sunlight, and prompt treatment are critical for preventing subsequent severe bullous dermatosis.

KEYWORDS

breast cancer, cyclin-dependent kinases 4/6 inhibitor, ribociclib, drug allergy, dyschromia, phototoxicity, bullae, case report

Abbreviations: CDK: cyclin-dependent kinase, HER2−: human epidermal growth factor receptor 2 negative, HMB: Human Melanoma Black, HR+: hormone receptor-positive.

1 Introduction

Breast cancer is one of the leading causes of death among patients with malignant tumors. In 2020, breast cancer was responsible for 680,000 deaths worldwide (1). Recently, the anti-breast cancer therapeutic plan was established based on staging and hormone receptors (HRs). Previously, patients with advanced-stage breast cancer of an HR-positive (HR+) and a human epidermal growth factor receptor 2-negative (HER2−) status were usually treated with single-agent endocrine therapy; however, these treatments did not achieve long-lasting effects due to drug resistance (2, 3).

In recent years, several classes of targeted therapies have been developed for the treatment of breast cancer. These include cyclin-dependent kinase (CDK) 4/6 inhibitors, including palbociclib, ribociclib, and abemaciclib. These drug therapies have been approved by the Food and Drug Administration for the treatment of metastatic breast cancer with (HR+)/(HER2−) expression (4, 5).

CDKs are a group of kinases that regulate the cell cycle, and CDK4/6 modulates G1/S phase transition during DNA synthesis; this cell cycle control system is usually disrupted in cancers. The estrogen receptor–cyclin D1-CDK4/6-retinoblastoma pathway plays an important role in estrogen receptor-positive breast cancer development. Therefore, CDK4/6 inhibitors exert an anti-cancer effect through the inhibition of this pathway (6).

Previous studies have revealed the common adverse effects of ribociclib; these include neutropenia, anemia, fatigue, diarrhea, a prolonged QTc, and an elevated liver function (7, 8). However, the important, severe dermatological side effects of this drug have not been sufficiently documented. Herein, we present a case of ribociclib-induced phototoxicity and bullae formation.

2 Case presentation

A 71-year-old woman presented with hypertension, hypertriglyceridemia, and diabetes mellitus. A mass in the right breast of the patient was initially observed at least 2 years ago, and the patient had visited the general surgery outpatient department because of a fungating lesion that had persisted for 3 months. A follow-up tumor biopsy had revealed infiltrating lobular carcinoma luminal B1 (estrogen receptor: 70%, progesterone receptor: 30%; HER2−). Positron emission tomography revealed pleural seeding and, liver and bone metastasis. Hence, the patient was newly diagnosed with a right inflammatory breast-infiltrating lobular carcinoma with multiple metastases (cT4N3cM1, stage IV). Subsequently, the patient received a daily combination therapy of letrozole (an aromatase inhibitor) and ribociclib (600 mg) along with a monthly injection of denosumab.

Seven months later, the patient developed grayish pigmentation on the four limbs and trunk; these were especially prominent on the sunlight-exposed forearms (Figure 1). The patient reported progressive pigmentation and pruritus of the lesion. Laboratory data revealed no neutropenia. Thereafter, the department of hematology referred the patient to the dermatology outpatient clinic for further evaluation. A skin biopsy examination of the pigmented lesion was performed; pathological examination revealed interface dermatitis with melanin incontinence. Notably, dyskeratotic cells and clefting at the basal layer of epidermis were identified (Figures 2A, B). Fontana–Masson staining for melanin revealed that the melanophages was distributed unevenly and generally present in the upper dermis (Figures 2C, D). Human Melanoma Black-45 (HMB-45) staining revealed decreased melanocyte numbers in both normal and clefting skin lesions (Figures 2E, F). Therefore, the hyperpigmented skin lesion was speculated to have been caused by altered melanin distribution and melanocyte numbers.

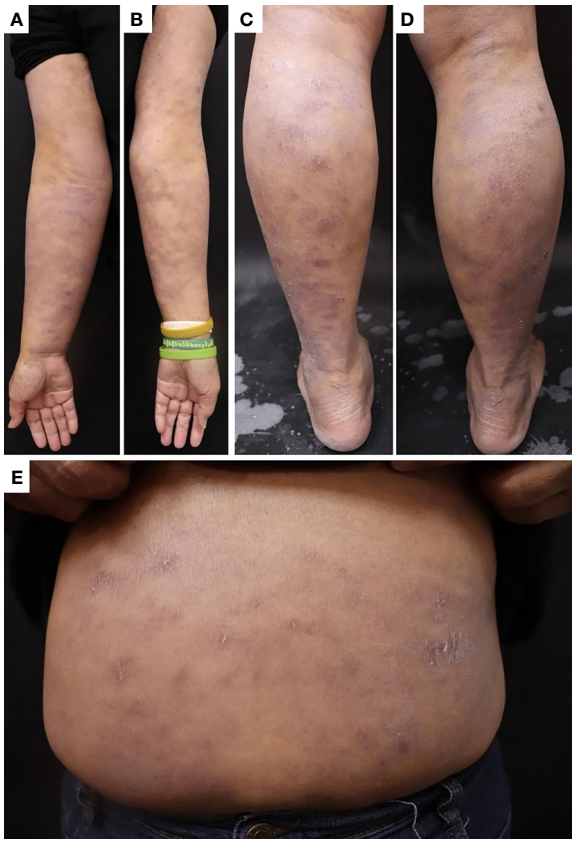


FIGURE 1
Skin pigmentation in the **(A)** right forearm, **(B)** left forearm, **(C)** left lower leg, **(D)** right lower leg, and **(E)** trunk.

Further, immunohistochemical staining revealed activated epidermal Langerhans cells presenting with CD1a as well as CD3+, CD4+, and CD8+ T cells infiltrating into the epidermis and dermis; these findings indicated type IV hypersensitivity (Figures 3A–H). Thus, a clinicopathological diagnosis of ribociclib-induced phototoxicity, manifesting initially as dyschromia and subsequently as bullous dermatosis, was made.

Owing to the severe dermatological side effects, we advised the hematologist to withdraw ribociclib and prescribe oral (20 mg/day) and topical prednisolone instead; however, treatment with letrozole was continued. Additionally, the patient was educated on appropriate sun protection. The patient's skin lesions subsided during the 2-month treatment. The oncologist switched the treatment from ribociclib to palbociclib, and no dermatological adverse effects were subsequently noted.

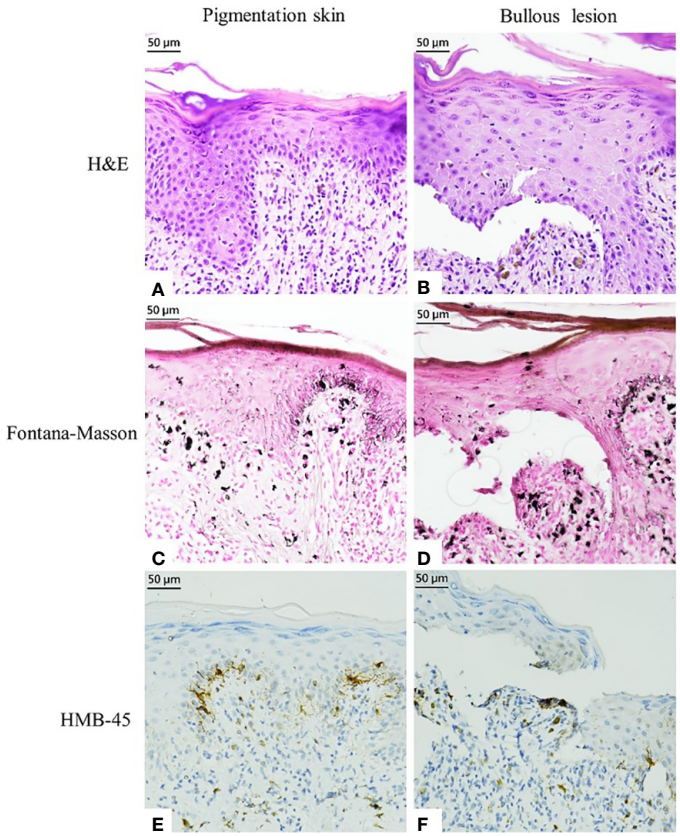


FIGURE 2
Histopathological examination and immunostaining finding of pigmented markers in the pigmented skin and bullous lesion. **(A, B)** Hematoxylin and eosin staining. **(C, D)** Fontana–Masson Staining. **(E, F)** HMB-45 staining.

3 Discussion

As reported by Yang L et al., CDK4/6 inhibitors are associated with adverse events, such as neutropenia, leukopenia, thrombocytopenia, anemia, fatigue, diarrhea, febrile neutropenia, nausea, and elevated alanine aminotransferase levels (9). Ribociclib, a CDK4/6 inhibitor, also has a similar side effect profile, especially in relation to hematological problems. In addition, severe dermatological side effects, such as skin rash, vitiligo, and alopecia, have been reported in recent years (7, 10); however, these have been relatively less documented. To date, few cases of severe ribociclib-induced dermal toxicity, such as those of the Stevens–Johnson syndrome, toxic epidermal necrolysis, and erythema dyschromicum perstans-like pigmentation, have been reported in the literature (11–13).

Several cases of ribociclib-induced dyschromia, such as those of vitiligo (14–16), have been reported; however, the detailed mechanisms involved, including pathological examination and immunohistochemistry findings, are not well understood. Hence, we examined the results of Fontana–Masson staining and HMB-45 staining in the present case. Both staining methods revealed a reduced melanocyte number and the presence of melanin in the dermis. Besides, another report revealed the effect of ribociclib-induced pyknosis in keratinocytes (17); we also found dyskeratotic cells in the epidermis in our case. Therefore, we speculated that ribociclib-related dyschromia resulted from the uneven distribution of melanin and a decreased number of melanocytes, which are caused by impaired keratinocytes and melanocytes in the basal layer zone. The toxicity of ribociclib to these cells may originate from its inhibition of CDKs. However, further research is needed to validate this.

In the present case, the patient developed pigmented patches on the trunk and extremities, particularly over the forearms, 7 months after receiving ribociclib. Skin biopsy revealed interface dermatitis with melanin incontinence and clefting at the epidermal–dermal junction, similar to that observed in subepidermal bullous disease. The patient was diagnosed with phototoxicity with type IV hypersensitivity and subepidermal bullous dermatosis based on positive immunohistochemical staining for CD1a, CD3, CD4, and CD8.

To overcome the dermatological side effects of ribociclib, we first ceased ribociclib administration. To ensure continuation of anti-cancer therapy, we experimentally replaced ribociclib with palbociclib after obtaining the patient's consent. Thereafter, we closely monitored the patient and educated them about sun protection; the dyschromia with bullae formation eventually subsided. The beneficial influence of this change may be attributed to immunotolerance or basic differences in the effects of CD4/6 inhibitors (such as subtle differences in the kinase selectivity between the two drugs); however, further studies are required to confirm this.

Drug-induced photosensitivity has attracted growing interest in recent years (18). Photosensitivity is categorized as either

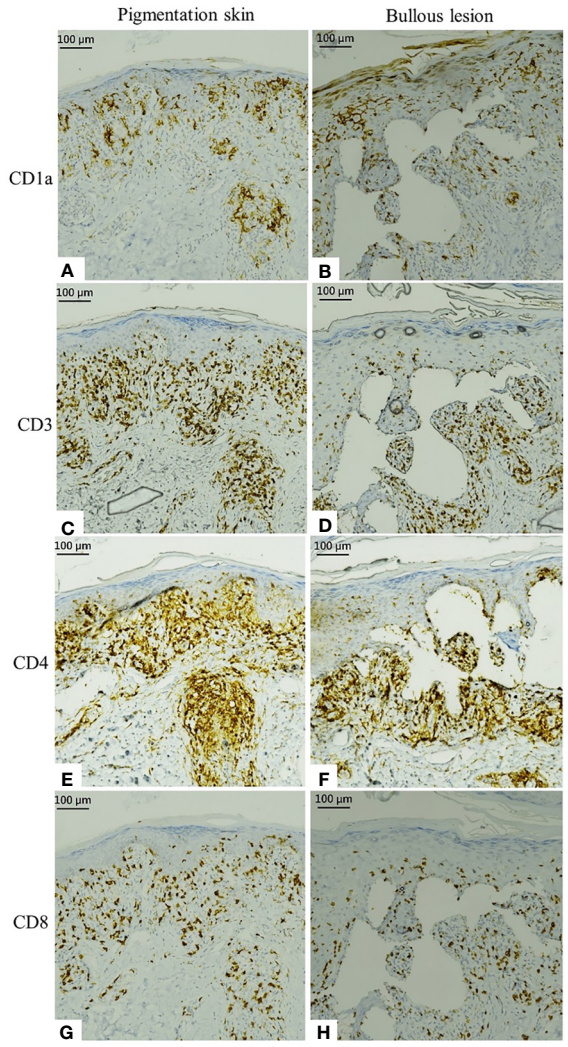


FIGURE 3
Immunostaining of specimens from the pigmented skin and bullous lesion. **(A, B)** Activated epidermal Langerhans cells present with CD1a. **(C, D)** Immunohistochemical staining of CD3. **(E, F)** Infiltrating CD4. **(G, H)** Infiltrating CD8.

phototoxic or photoallergic. It occurs due to photosensitizing agents and subsequent exposure to ultraviolet or visible light. A previous study revealed that the photosensitive effect of CDK inhibitors was through the inhibition of ATP-binding cassette G2 (19). One case report also revealed ribociclib-induced photosensitive skin lesions in a patient with metastatic breast cancer (20). To our knowledge, the present case is the first on ribociclib-induced phototoxicity.

CDK inhibitors represent a novel class of targeted therapies for cancer treatment. However, they are associated with severe adverse effects that should be monitored for meticulously. In the present report, we revealed an association between ribociclib and phototoxicity with subepidermal bullous dermatosis and hyperpigmentation; this is a rare expression of drug allergy. Therefore, it is important for clinicians to closely monitor for cutaneous side effects and impart education on sun protection during clinical treatment with CDK4/6 inhibitors.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

J-YJ and W-EW wrote this manuscript. C-HCha diagnosed and treated the patient as well as reviewed and edited the manuscript. S-CC provided the case and clinical explanation. C-HChe assisted with pathological slide preparation and immunohistochemistry. All authors contributed to the manuscript and approved the submitted version.

Acknowledgments

We would like to thank the patient for their cooperation and permission to publish this case.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1184738/full#supplementary-material

References

1. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: global statistics for 2020 and 2040. *Breast* (2022) 66:15–23. doi: 10.1016/j.breast.2022.08.010

2. Hanker AB, Sudhan DR, Arteaga CL. Overcoming endocrine resistance in breast cancer. *Cancer Cell* (2020) 37:496–513. doi: 10.1016/j.ccell.2020.03.009

3. Saatci O, Huynh-Dam KT, Sahin O. Endocrine resistance in breast cancer: from molecular mechanisms to therapeutic strategies. *J Mol Med (Berl)* (2021) 99:1691–710. doi: 10.1007/s00109-021-02136-5

4. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* (2016) 375:1738–48. doi: 10.1056/NEJMoa1609709

5. Eggersmann TK, Degenhardt T, Gluz O, Wuerstlein R, Harbeck N. CDK4/6 Inhibitors expand the therapeutic options in breast cancer: palbociclib, ribociclib and abemaciclib. *BioDrugs* (2019) 33:125–35. doi: 10.1007/s40259-019-00337-6

6. Petrossian K, Kanaya N, Lo C, Hsu PY, Nguyen D, Yang L, et al. ERα-mediated cell cycle progression is an important requisite for CDK4/6 inhibitor response in HR+ breast cancer. *Oncotarget* (2018) 9:27736–51. doi: 10.18632/oncotarget.25552

7. Silvestri M, Cristaudo A, Morrone A, Messina C, Bennardo L, Nisticò SP, et al. Emerging skin toxicities in patients with breast cancer treated with new cyclin-dependent kinase 4/6 inhibitors: a systematic review. *Drug Saf* (2021) 44:725–32. doi: 10.1007/s40264-021-01071-1

8. Braal CL, Jongbloed EM, Wilting SM, Mathijssen RHJ, Koolen SLW, Jager A. Inhibiting CDK4/6 in breast cancer with palbociclib, ribociclib, and abemaciclib: similarities and differences. *Drugs* (2021) 81:317–31. doi: 10.1007/s40265-020-01461-2

9. Yang L, Xue J, Yang Z, Wang M, Yang P, Dong Y, et al. Side effects of CDK4/6 inhibitors in the treatment of HR+/HER2- advanced breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Ann Palliat Med* (2021) 10:5590–9. doi: 10.21037/apm-21-1096

10. Anjaneyan G, Keechilat P, Duraisamy P, Eapen M. Ribociclib-induced extensive vitiligo-like lesions: possible pathomechanisms with clinical, dermoscopic and histological correlation. *BMJ Case Rep* (2022) 15:e248782. doi: 10.1136/bcr-2022-248782

11. Bozkaya Y, Ay B. Toxic epidermal necrolysis associated with ribociclib in a patient with metastatic breast cancer. *Breast J* (2020) 26:773–4. doi: 10.1111/tbj.13570

12. López-Gómez V, Yarza R, Muñoz-González H, Revilla E, Enrech S, González-Valle O, et al. Ribociclib-related Stevens-Johnson syndrome: oncologic awareness, case report, and literature review. *J Breast Cancer* (2019) 22:661–6. doi: 10.4048/jbc.2019.22.e44

13. Mariano M, Donati P, Cameli N, Pigliacelli F, Morrone A, Cristaudo A. Ribociclib-induced erythema dyschromicum perstans (ashy dermatosis)-like pigmentation in a metastatic breast cancer patient. *J Breast Cancer* (2021) 24:117–21. doi: 10.4048/jbc.2021.24.e1

14. Sharaf B, AlMasri R, Abdel-Razeq N, Salama O, Hamad I, Abunasser M, et al. Vitiligo-like lesions in a patient with metastatic breast cancer treated with cyclin-dependent kinase (CDK) 4/6 inhibitor: a case report and literature review. *Clin Cosmet Investig Dermatol* (2022) 15:5–10. doi: 10.2147/CCID.S344867

15. Silvestre Torner N, Aguilar Martínez A, Echarri González MJ, Tabbara Carrascosa S, Román Sainz J, Gruber Velasco F. Ribociclib-induced vitiligo: a case report. *Dermatol Pract Concept* (2022) 12:e2022045. doi: 10.5826/dpc.1202a45

16. Chan OB, Su JC, Yazdabadi A, Chan A. Drug induced vitiligo-like depigmentation from a CDK 4/6 inhibitor. *Asia Pac J Clin Oncol* (2022) 18:e154–6. doi: 10.1111/ajco.13585

17. Akbaş N, Akbaş EM, Süleyman Z, Çiçek B, Ağgül AG, Mokhtare B, et al. Effect of adenosine triphosphate on ribociclib-induced skin toxicity in rats. *Cutan Ocul Toxicol* (2023) 42:32–7. doi: 10.1080/15569527.2023.2166524

18. Hofmann GA, Weber B. Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences. *J Dtsch Dermatol Ges* (2021) 19:19–29. doi: 10.1111/ddg.14314

19. An R, Hagiya Y, Tamura A, Li S, Saito H, Tokushima D, et al. Cellular phototoxicity evoked through the inhibition of human ABC transporter ABCG2 by cyclin-dependent kinase inhibitors *in vitro*. *Pharm Res* (2009) 26:449–58. doi: 10.1007/s11095-008-9738-5

20. Verma V, Bhari N. Ribociclib induced photosensitive skin lesions. *Indian Dermatol Online J* (2022) 14:105–6. doi: 10.4103/idoj.idoj_99_22

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 27 September 2023
DOI 10.3389/fonc.2023.1233208

OPEN ACCESS

EDITED BY
Armando Pérez Torres,
National Autonomous University of Mexico, Mexico

REVIEWED BY
Oscar Diaz,
National Autonomous University of Mexico, Mexico
Megan Kalambo,
University of Texas MD Anderson Cancer Center, United States

*CORRESPONDENCE
Yidong Zhou
zhouyd@pumch.cn
Qiang Sun
sunqiangpumc@sina.com

†These authors share first authorship

RECEIVED 01 June 2023
ACCEPTED 01 September 2023
PUBLISHED 27 September 2023

CITATION
Lian J, Gao L, Yao R, Zhou Y and Sun Q (2023) Case Report: A 13-year-old adolescent diagnosed as malignant phyllodes tumor combined with rhabdomyosarcoma differentiation. *Front. Oncol.* 13:1233208. doi: 10.3389/fonc.2023.1233208

Case Report: A 13-year-old adolescent diagnosed as malignant phyllodes tumor combined with rhabdomyosarcoma differentiation

Jie Lian†, Lu Gao†, Ru Yao, Yidong Zhou* and Qiang Sun*

Department of Breast Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Phyllodes tumor (PT) is an infrequent type of breast neoplasm, constituting a mere 0.5%–1.5% of the entirety of breast tumors. The malignant phyllodes tumor (MPT) comprises only 15% of all phyllodes tumors, and its transformation into rhabdomyosarcoma (RMS) is exceedingly rare in clinical practice. Given its insensitivity to chemotherapy and radiotherapy, treatment options for MPT patients are limited, leaving complete surgical resection as the only option. Therefore, it is imperative to investigate the effective utilization of the heterogeneous differentiation characteristics of MPT to expand treatment alternatives for these patients. In this case report, we represent a 13-year-old adolescent diagnosed with giant breast MPT with RMS differentiation and pulmonary metastasis. The initial step in the treatment process involved radical surgical resection, followed by the administration of four cycles of VDC/IC chemotherapy, which is widely recognized as the standard chemotherapy for RMS. Regrettably, the delay in initiating chemotherapy resulted in minimal observable changes in the size of the pulmonary metastatic nodule. Additionally, a comprehensive literature review on the characterization of MPT with heterogeneous differentiation was conducted to enhance comprehension of the diagnosis and treatment of this uncommon disease in clinical practice. Meanwhile, this case also reminds the doctors that when we diagnose a patient as MPT, it is crucial to consider its heterogenous nature and promptly initiate adjuvant treatment. By targeting the differentiation element of MPT, it becomes feasible to overcome the previously perceived limitation of surgical intervention as the sole treatment option.

KEYWORDS

phyllodes tumor, rhabdomyosarcoma, treatment strategy, heterogeneous differentiation, pediatric sarcoma

Introduction

Phyllodes tumor (PT), classified as the fibroepithelial tumor of breast composing of epithelial and stromal elements, is a rare kind of pathological subtype in the clinical practice (1). The World Health Organization (WHO) has recently revised the classification of phyllodes tumors based on their histopathological characteristics. The PT can be divided into benign PT, borderline PT, and malignant PT (MPT), where MPT accounts for 15% in all PT (2). (MPT) is characterized by histopathological features such as stromal hypercellularity, atypia, increased mitoses of ≥10/10 high-power fields (HPFs), permeative tumor borders, and stromal overgrowth (3, 4). The stromal components of MPT exhibit heterogeneity and have the potential to transform into rhabdomyosarcoma (RMS), liposarcoma, and osteosarcoma (5). The absence of effective therapeutic interventions, coupled with the propensity for early distant metastasis and frequent recurrence, presents a formidable challenge in clinical practice. The average age of diagnosis for PT is 40–45 years, which is comparatively younger than the typical age range (2, 6). Previously, there have been reports of adolescent patients diagnosed with PT. However, there is a scarcity of reports on adolescent patients diagnosed with MPT with RMS differentiation. In this study, we present a case of a 13-year-old adolescent diagnosed with the rare giant MPT of the breast combined with RMS differentiation. Additionally, we provide a comprehensive summary of the clinical characteristics of such patients, aiming to serve as a valuable resource for the diagnosis and treatment of similar cases.

Case presentation

A 13-year-old female patient was initially referred to our hospital due to the presence of a large mass in her left breast, accompanied by nipple inversion (Figure 1A). She reported that the mass had been in existence for a duration of 3 years; however, initially, the only symptom observed was asymmetry in the size of her bilateral mammary glands, which did not receive significant attention. In March of this year, the mass began to exhibit progressive growth, with an accelerated rate of growth observed since July. A breast ultrasound examination was carried out at a separate medical institution, which identified a substantial mass measuring 13.6 cm ×10.9 cm ×7.0 cm with an irregular contour, completely occupying and substituting the tissue of the left breast. The mass exhibited progressive growth starting in March of this year, with an accelerated rate of growth observed since July. Subsequently, a core biopsy was conducted to assess the pathological characteristics of the mass. The findings from the core biopsy revealed that the mass was a fibroepithelial tumor exhibiting atypia and necrosis, with the possibility of being classified as a borderline type.

After being referred to our hospital, a repeat breast ultrasound evaluation was performed. The results indicated the presence of a 13.1 cm ×11.8 cm ×8.6 cm mixed-echo mass in the left breast, accompanied by a dot strip blood flow signal. Additionally, the normal mammary gland was significantly compressed. The mammographic diagnosis confirmed that the mass occupied the entire left breast.

The physical examination indicated that the mass exhibited characteristics of both cystic and solid nature, displaying limited activity. No pertinent family history pertaining to the breast tumor was reported. Given the suspicion surrounding the pathological attributes of the mass, coupled with the patient's young age, a comprehensive excision of the mass was performed (Figures 1B, C). Subsequently, the excised mass was sent to the pathology department for identification of its pathological subtype. Following the surgery, the patient experienced a smooth recovery and was

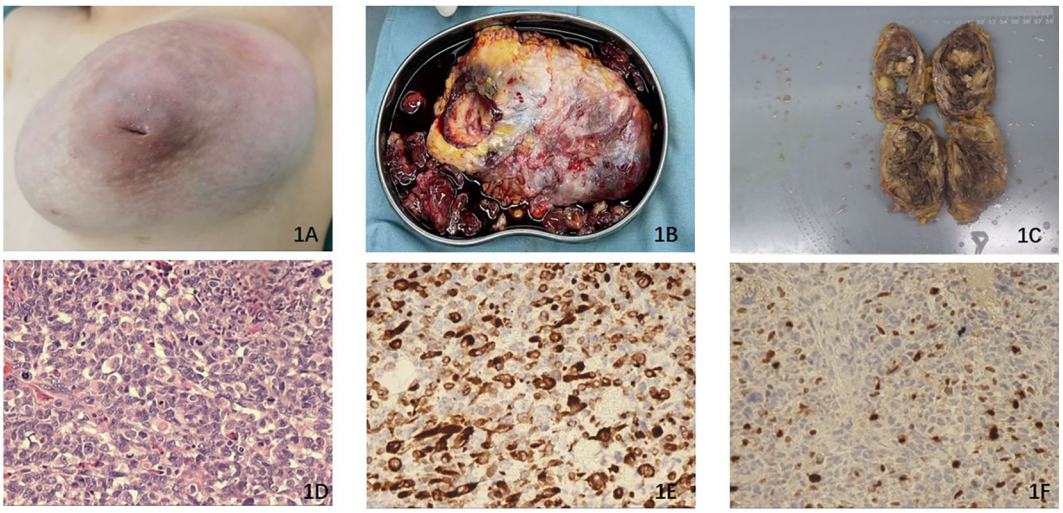


FIGURE 1
(A) The left breast exhibited nipple inversion and is filled with a large combined mass. **(B)** The broken surgical piece of the mass. **(C)** The surgically removed mass is longitudinally incised and measures 13.0 cm ×10.0 cm × 9.0 cm in diameter. **(D)** The histopathological section (hematoxylin and eosin staining) of the tissue from the surgical piece. **(E)** Immunohistochemistry results revealed the expression of Desmin, which is considered a characteristic feature of RMS. **(F)** Immunohistochemistry results demonstrated the expression of Myogenin.

discharged to her residence after 3 days. The pathological findings ultimately confirmed that the mass was a combination of MPT with heterogenous differentiation, specifically rhabdomyosarcoma, as depicted in Figure 1D. Immunohistochemistry results revealed weakly positive staining for AE1/AE3, positive staining for Desmin (Figure 1E), and positive staining for Myogenin (Figure 1F). Additionally, the Ki67 index was determined to be 75%. Desmin and myogenin were identified as useful markers for differential diagnosis (7).

Regrettably, local recurrence occurred rapidly, with the reappearance of the mass in the left breast resembling a ping pong ball and exhibiting aggressive growth on 3 October (Figure 2A). Consequently, the patient was re-referred to our hospital for further evaluation. A repeat breast ultrasound was conducted to assess the size and characteristics of the lesion, revealing a 5.7 cm×5.5 cm ×4.5 cm mixed-echo composition with strip blood flow signal. Based on these findings, it was postulated that the possibility of a malignant phyllodes tumor (MPT) was considerable. Additionally, MPTs with a high expression level of Ki-67 (>50%) are more likely to exhibit distant metastasis (8, 9). Considering the rapid recurrence following the previous operation and the high level of Ki-67 expression of the mass, the mastectomy procedure was conducted with the objective of ensuring a maximally negative margin, while the operation area was subjected to warm distilled water immersion to induce hypotonic lysis and subsequent death of tumor cells. The patient exhibited satisfactory recovery and was discharged from the hospital.

Subsequent pathological examination revealed the presence of a heterogenous differential component, specifically rhabdomyosarcoma combined with slice necrosis, consistent with previous findings. Immunohistochemical analysis demonstrated weakly positive expression of SMA and AE1/AE3, positive expression of Desmin and CD34, and an elevated Ki67 index of 85% Figure 2B. It indirectly demonstrated that the stroma of the mass had the prominent role in the development of the MPT progression in our patient.

Then, she went to another hospital for further treatment. Unfortunately, about weeks ago, pulmonary nodules were found by the computer tomography (CT) and positron emission tomography/computed tomography (PET/CT) (Figures 3A, B), which were suspected to be the lung metastasis. Chemotherapy should be promptly initiated to impede the further progression of the tumor. Consequently, the patient underwent four cycles of chemotherapy, with cycles 1 and 3 consisting of vincristine 2 mg/m^2, doxorubicin 30 mg/m^2, and cyclophosphamide 500 mg/m^2, and cycles 2 and 4 comprising ifosfamide 100 mg/m^2 and etoposide 1.8 g/m^2. Every cycle was separated by 1 month. However, following two cycles of chemotherapy, the size of the suspected lung metastasis decreased from 2 cm to 1.7 cm, indicating a partial response, although the overall efficacy of the chemotherapy was not satisfactory. Following the subsequent evaluation, the patient had resection of the lung nodule and undergo the subsequent cycles of chemotherapy.

Discussion

PT is a rare form of breast neoplasm, comprising 0.5%–1.5% of all cases, while MPT accounts for only 10%–15% of all PTs (8, 10). It constitutes complex mammary fibroepithelial lesions and can be graded as begin, broadline, and malignant. Although benign tumors are the most common, some PTs have the potential to locally recur and progress to sarcoma, as exemplified in the case we present. Notably, the incidence and recurrence rates of PT are higher among Asian patients compared to those in Western countries (11). The feature in our case is that the patient is diagnosed with MPT combined with RMS differentiation. It is worth mentioning that MPT can be mistakenly identified as primary breast sarcoma due to the presence of heterologous sarcomatous differentiation in the stromal tissue. A key distinction between MPT with sarcomatous differentiation and primary sarcoma is the absence of an epithelial component in the latter. In order to provide a comprehensive understanding, we have conducted a review of the clinical characteristics of PT with heterogeneous elements, which are presented in Table 1 (12–19). In our reported case, the predominant recurrence element is rhabdomyosarcoma, while the

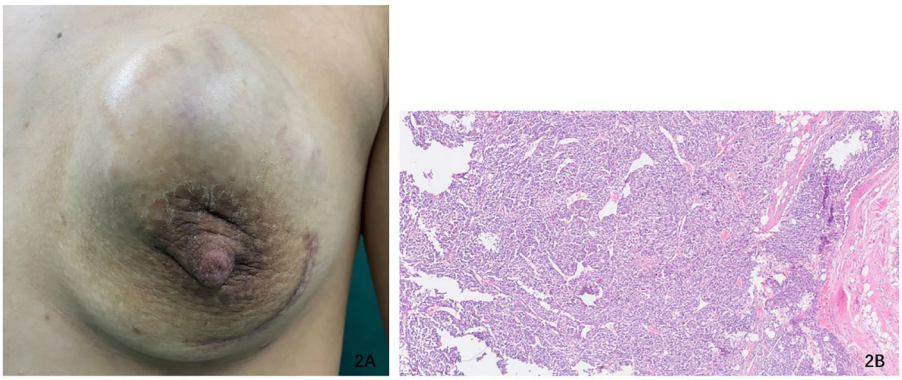


FIGURE 2
(A) The recurrent mass presented a diameter of 5.7 cm × 5.5 cm ×4.5 cm in the left breast within 2 months. **(B)** PT × 40—the histopathological section (hematoxylin and eosin staining) of the tissue from the second surgical piece.

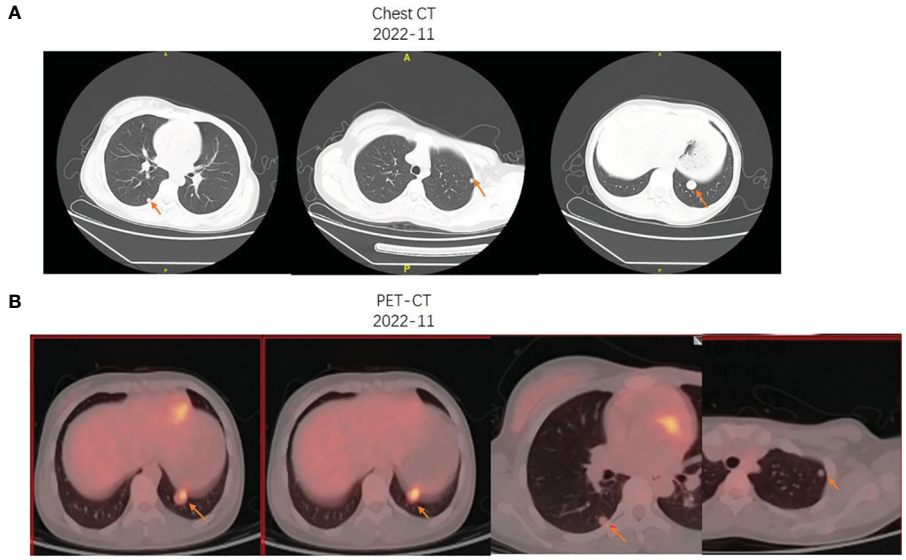


FIGURE 3
(A) The chest CT imaging presented the multiple pulmonary nodules in the right and left lung, with the biggest metastasis measuring nearly 2 cm. **(B)** The 18F-FDG PET/CT showed an increased FDG uptake of the largest left pulmonary nodule (inferior lobe; SUVmax, 3.9) and mild FDG uptake of the multiple pulmonary nodules.

presence of epithelium in MPT is scarcely observed. This observation aligns with the characteristic of MPT, which involves uncontrolled growth of the stroma and epithelial outgrowth. Previous studies speculated that the overexpression of IGF-II and c-myc would drive the invasive stromal proliferation and sarcomatous differentiation, while c-kit expression was associated with poor prognosis and could be designed as a therapeutic target (20). Recently, Ahmed et al. demonstrated that the expression level of cancer stem markers in the stroma of MPT were negatively correlated with the overall survival of MPT patients, and the dysregulation of epithelial–mesenchymal transition may fuel the aggressive behavior of the stroma in MPT (4).

Previous studies revealed that if the RMS was the major component in the MPT, the difference in clinical presentation and therapeutic strategies may not be so obvious between the MPT with RMS differentiation and the primary RMS. Therefore, it is imperative to comprehensively consider the clinical features of both MPT and rhabdomyosarcoma in order to develop appropriate management strategies for our reported patient (21). RMS is an infrequent non-epithelial tumor in clinical practice, primarily affecting children and comprising approximately 50% of soft tissue tumors. However, its occurrence in breast malignant tumors is exceedingly rare, accounting for <1% of total RMS cases (22, 23).

The clinical presentations of MPT and RMS are similar. Both of them may represent with the rapidly increased painless mass (24), potentially accompanied by symptoms resulting from the mass' impact on neighboring organs and neurovascular structures (25). In reality, the majority of patients may initially disregard the mass until it undergoes rapid growth within a brief timeframe, similar to the patient that we present, who initially only observed the asymmetry of their bilateral mammary glands. Additionally, the infrequent symptom of hypoglycemia resulting from the elevated expression level of IGF-2 in the tumor tissue has been previously documented (26). The physical examination findings in our patient encompass nipple inversion, a mass exhibiting both cystic and solid components with limited activity. Other symptoms, such as skin ulceration, invasion of the chest wall, and bloody nipple discharge, have also been sporadically reported (6). The occurrence of quick local recurrence (LR) is an additional characteristic observed in our case. In comparison to begin PT, the frequency of LR was higher in MPT (8% vs. 18%) (27). Multicenter investigations have indicated that positive margin serves as an independent risk factor for LR, while other risk factors encompass breast-conserving surgery, negative margins measuring <1 cm, tumor size ≥5 cm, mitoses, infiltrating tumor border, moderate/severe stromal cellularity, severe stromal atypia, severe stromal overgrowth, and tumor necrosis (27–29). Unfortunately, the patient that we report in this case had several risk factors for recurrence including the omission of the chemotherapy after the first surgery, acceptance of breast-conserving surgery, tumor size ≥ 5 cm, and combination of tumor necrosis. Therefore, the recurrence happened just 2 months after the surgery. The phenomenon that the recurrence component is mainly the RMS demonstrated that the aggressive behavior of MPT may be caused by the stroma. Furthermore, hematogenous metastasis happens more frequently than lymph node metastasis for MPT, and previously reported metastatic sites for MPT included lung, liver, adrenal, brain, bone, duodenum, heart, orbit, and ovarian (2, 8, 30). Meanwhile, the lung is also the common metastatic site for RMS, thus considering the lung nodule in our patient as the metastatic MPT and initiating the adjuvant chemotherapy immediately were reasonable (31).

The gold standard for the diagnosis of MPT with heterogenous differentiation still relies on pathology. Core needle biopsy is a

TABLE 1 The clinical characteristics of PT with heterogeneous elements previously reported.

No.	Reference	Sex/ Age	Size	Malignant/ Begin/ Broadline	Heterogenous element	IHC	Metastatic interval	Metastatic site	Therapeutic strategy	Prognosis until reported
1	Barnes, L. et al. 1978 (12)	F/45	10~12 cm	Malignant	rhabdomyosarcoma	NA	2 years	lung, brain	1.radical mastectomy for the breast mass 2.the entire left resection for the lung metastasis 3. irradiation for the brain metastasis	died 2.5 years after the first breast mass radical mastectomy
2	Guerrero, M.A et al. 2003 (13)	F/96	17 x 17 x 8 cm	Malignant	liposarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma	NA	NA	NA	wide excision	died 10 months after the surgery
3	Tsubochi, Sato et al. 2004 (14)	F/54	9 x 7 x 6 cm	Malignant	osteosarcoma	vimentin (+), cytokeratin (+), S-100(+), CD34(+), and HER2(+), P53(-)	1 year	lung	subcutaneous mastectomy	NA
4	Vergine, Guy et al. 2015 (15)	F/71	2.5 cm	Malignant	Melanoma	Melan A (+), pan-melanoma (+), S100(+), HMB45(+), CD34 (+), SMA (+), AE1/3(-), P53(-), MIB1(+)	NA	NA	completion mastectomy	without relapse or distant metastasis
5	Narla, Stephen et al. 2018 (16)	F/28	14 x 14 x 8 cm	Malignant	liposarcoma	NA	NA	NA	completion mastectomy	lost to follow-up
6	Jin, Bi et al. 2021 (17)	F/59	5.5 x 4.0 x 3.5 cm	Malignant	osteosarcoma	SMA (+), SATB2(+), Ki67(40%), Ckpan (-)	NA	NA	wide local excision	without relapse or distant metastasis
7	Tu He Ta Mi Shi, Wang et al. 2021 (18)	F/52	8 x 6 x 5.5 cm	Malignant	mixed liposarcoma (myxoid liposarcoma and pleomorphic liposarcoma	AE1/3(+), vimentin (+), S-100 (-), Ki67(90%), E-cadherin (-), p63(-)	NA	NA	radical mastectomy	without relapse or distant metastasis
8	Han, Liu et al. 2022 (19)	F/69	4.3 x 4.1 x 3.3cm	Malignant	rhabdomyosarcoma	MyoD1(+), myogenin(+), desmin(+), α-SMA(+), Ki67 (63%)	NA	NA	radical mastectomy, VAC therapy (vincristine, actinomycin D, cyclophosphamide)	without relapse or distant metastasis

NA, not mentioned in the reported article.

10.3389/fonc.2023.1233208

valuable diagnostic tool, and the pathology should include stromal hypercellularity, atypia, increased mitoses of ≥10/10 HPFs, permeative tumor borders, and stromal overgrowth (3). In addition, the existence of heterologous sarcomatous differentiation, such as RMS differentiation in our cases, will make PTs classified as MPT regardless of other pathological features (32). Rhabdomyoblasts cells with atypia such as ribbon, tadpole-like, oval shape, or undifferentiated rhabdomyoblasts with scant cytoplasm are crucial for the diagnosis of RMS (33). Furthermore, RMS cells also represent skeletal muscle gene products such as myosin, desmin, myoglobin, and MYOD1 immunohistochemically (25). However, confined by the limitation of the tissue size obtained from the core needle biopsy, the diagnosis may not be accurate regardless of MPT or RMS, while sometimes, histopathological examination after complete removal of the tumor was indispensable just as in the case we reported. For example, delayed diagnosis for RMS happens frequently, as fibroadenoma and mastopathy may take up the majority of the mass and interfere the judgement of the pathologist (34). As for non-invasive examination, in our case, the difference between ultrasound outcomes before the first surgery and after the recurrence was not significant. In fact, as for MPT with RMS differentiation, imaging examination can facilitate in locating the mass, evaluating the invasion of the border, assessing the distant metastasis, and stratifying the risk level, but may be not conductive to distinguish different breast tumors. However, we still recommended that the patient in our case receives the ultrasound examination monthly after the second surgery to detect the recurrence as early as possible.

As we mentioned before, the therapeutic strategies should take both the MPT and RMS into consideration, especially for RMS, as the main recurrence component identified in our patient. For MPT, no systemic standard therapy strategies have been established, and the National Comprehensive Cancer Network (NCCN) guidelines recommend the complete surgical resection with at least 1-cm margins without sentinel lymph node biopsy for the treatment of MPT. Surgeons may more likely perform breast-conservation operation instead of mastectomy for pediatric MPT patients considering their quality of life in the future (35, 36). However, as previously stated, breast conservation is a risk factor for the LR, and the patient receiving only lumpectomy combined with other risk factors that we report in this case recurred within 2 months after the surgery. The use of adjuvant therapy for MPT has also been explored, but standard pathological data and prospective, multicentric chemotherapy, or radiotherapy studies are needed to improve the overall MPT survival (37). Alkylating-agent-based chemotherapy or the combination of nab-paclitaxel, cisplatin, and liposomal doxorubicin chemotherapy with radiotherapy have been reported to be an effective option for metastatic MPT (38, 39). Adjuvant radiation could reduce the LR for MPT patients receiving extensive local resection but not benefit the MPT patients accepting mastectomy (40).

Different from the dilemma of MPT, which mainly relied on the surgery, it has long been demonstrated that the treatment for RMS is multimodality. Surgery still takes the dominant role in the whole therapeutic strategy. Apart from surgery, RMS is sensitive to cytotoxic chemotherapy and radiotherapy (25). Vincristine, dactinomycin, and alkylating agents are mainstream drugs for the treatment of the RMS, with an expectation of at least 40% improvement of the survival rate compared with the surgery alone (41, 42). However, chemotherapy should be cautious to be applied for adolescent patients, as alkylating agent chemotherapy will cause the ovarian failure and result in infertility (43). Therefore, Mance et al. harvested and frozon the ova of a 17-year-old patient diagnosed as primary breast RMS before the initiation of adjuvant chemotherapy (44). In addition, cisplatin chemotherapy-related hearing loss was also reported and should be paid attention to in the clinical practice (45). More robust evidence has demonstrated that the use of radiotherapy can improve the long-term prognosis for RMS patients. Radiotherapy is recommended to initiate after 12 weeks of chemotherapy (four cycles), and the overall assessment is necessary. The dose of radiotherapy depends on several factors including the stage, the risk group, the site of RMS, the histology group, the degree of surgery, and the addition of the chemotherapy (46–48). Delay or omission of radiotherapy may increase the risk of recurrence (42). Europe RMS 2005 study revealed that in combination of radiotherapy, the improvement of approximately 10% in 3-year event-free survival (EFS) was observed for high-risk RMS patients, while the 3-year EFS could be improved from 39% to 56% for very high-risk RMS patients (49). The RMS is sensitive to the ionizing radiation, but the adverse effect brought by radiotherapy is still controversial. Radiotherapy-related adverse events include the secondary malignancy, joint stiffness, facial growth retardation, neuroendocrine dysfunction, and cognitive sequelae (25, 45). To reduce the adverse events brought by traditional radiotherapy, researchers are focusing on the proton radiotherapy. Ladra et al. designed a phase II multicenter clinical research and revealed that proton therapy can reduce the irradiation dose, which decreased the acute toxicity but with the same rate of local disease control (47).A multicenter clinical research in Japan treating children with 36–60 GyE (median, 50.4 GyE) irradiation dose also demonstrated that the proton radiotherapy could achieve the same short-term effect with fewer adverse events compared to photon radiotherapy (48).

For metastatic RMS patients, radiotherapy is still disputed, as the authoritative classification of patient subgroups that can benefit more from the radiotherapy than others are absent and myelosuppression caused by radiotherapy may restrict the effect of chemotherapy (49). However, for patients with one or more lung metastases, whole lung radiotherapy is recommended (50). Compared with other metastatic sites, pulmonary metastatic nodules are more likely to benefit from the radiotherapy. A retrospective review revealed that the pulmonary local control could be improved from 10% to 56% by applying the radiotherapy, and the 5-year-progression-free survival (PFS) for lung metastasis was 29% compared with other types of metastases, which was 7% (51).

The chemotherapy strategy for our patient was the four cycles of vincristine–doxorubicin–cyclophosphamide/ifosfamide–etoposide (VDC/IE) chemotherapy, which is the main chemotherapy strategy for the treatment of Ewing sarcoma family of tumors (52). Furthermore, VDC/IE can be used for intermediate-risk RMS, and GOC ARST0431 revealed that compressing the dosing

interval to allow the patients to receive the maximum amount of effective agents at a short period of time in combination with radiotherapy sensitizers can improve 3-year EFS of 69% for metastatic RMS compared with previous RMS therapeutic research. This improvement was achieved without a concomitant rise in the incidence of adverse reactions, thereby surpassing the outcomes of prior therapeutic investigations in RMS (53).

Conclusion

In this study, we present a case of an adolescent patient who was diagnosed with MPT with RMS differentiation, contributing novel perspectives on treatment approaches for these uncommon diseases. Pathology remains crucial in the diagnosis of MPT, and the integration of imaging examinations can aid in assessing the severity and monitoring the occurrence of relapse and distant metastases. The heterogeneous nature of MPT is of utmost importance in clinical practice, as it can significantly influence disease progression and guide therapeutic decision-making. As in the patient that we report in this case, both the biological feature of MPT and RMS should be taken into consideration for the clinical decision-making. Surgery with negative margin is critical to reduce the recurrence or metastasis and improve the overall survival for both the MPT and RMS patient. Adjuvant chemotherapy and radiotherapy are controversial for pure PT patients, but robust evidence has revealed that RMS patients will benefit a lot from such treatments. It is regrettable that the patient did not promptly receive adjuvant chemotherapy upon initial diagnosis of MPT with RMS differentiation. This serves as a reminder to medical professionals that MPT patients with RMS differentiation can also benefit from the multimodal treatment typically administered to primary RMS patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the study involving human samples in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the participant's legal guardian for the publication of this case report and any identifiable material contained.

Author contributions

YZ designed the idea of the article. JL, YZ, and RY collected the patient's clinical and pathological data. JL is the major contributor in writing the first draft of the manuscript. YZ and LG revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was sponsored by National High Level Hospital Clinical Research Funding (2022-PUMCH-B-039). The funders did not participate in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We would like to thank Department of Pathology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Department of Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences for providing the patient's clinical information.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Khan SA, Badve S. Phyllodes tumors of the breast. *Curr Treat Options Oncol* (2001) 2(2):139–47. doi: 10.1007/s11864-001-0056-y

2. Strode M, Khoury T, Mangieri C, Takabe K. Update on the diagnosis and management of Malignant phyllodes tumors of the breast. *Breast* (2017) 33:91–6. doi: 10.1016/j.breast.2017.03.001

3. Yom CK. Malignant phyllodes of breast. *Adv Exp Med Biol* (2021) 1187:601–12. doi: 10.1007/978-981-32-9620-6_32

4. Ahmed SS, Lim JCT, Thike AA, Iqbal J, Tan PH. Epithelial-mesenchymal transition and cancer stem cell interactions in breast phyllodes tumours: immunohistochemical evaluation of EZH2, EZR, HMGA2, CD24 and CD44 in

correlation with outcome analysis. *J Clin Pathol* (2022) 75(5):316–23. doi: 10.1136/jclinpath-2020-207068

5. Hemalatha AL, Sindhuram VS, Asha U. MFH mimic in breast: A high-grade Malignant phyllodes tumor. *Case Rep Pathol* (2012) 2012:835687. doi: 10.1155/2012/835687

6. Telli ML, Horst KC, Guardino AE, Dirbas FM, Carlson RW. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. *J Natl Compr Canc Netw* (2007) 5 (3):324–30. doi: 10.6004/jnccn.2007.0027

7. Li DL, Zhou RJ, Yang WT, Wang J, Yao XH, Cheng YF, et al. Rhabdomyosarcoma of the breast: a clinicopathologic study and review of the literature. *Chin Med J (Engl)* (2012) 125(14):2618–22.

8. Vempuluru VS, Mishra DK, Kaliki S. Malignant phyllodes tumor of the breast with metastasis to the orbit: A rare case report. *Ophthalmic Plast Reconstr Surg* (2021) 37(1):e5–7. doi: 10.1097/IOP.0000000000001693

9. Suárez Roa Mde L, Ruiz Godoy Rivera LM, Vela Chávez T, Pérez Sánchez M, Meneses García A. Breast Malignant phyllodes tumour metastasising to soft tissues of oral cavity. *Clin Transl Oncol* (2007) 9(4):258–61. doi: 10.1007/s12094-007-0049-9

10. Ruiz-Flores L, Ebuoma LO, Benveniste MF, Nagi C, OrtizPerez T, Benveniste AP. Case report: metastatic phyllodes tumor. *Semin Ultrasound CT MR* (2018) 39 (1):122–6. doi: 10.1053/j.sult.2017.05.011

11. Grinlinton ME, McGuinness MJ, Christie M, Oldfield R, Ramsaroop R, Moss D. Ethnic disparities in Phyllodes Tumour in Aotearoa New Zealand: a retrospective review. *ANZ J Surg* (2022) 92(3):431–6. doi: 10.1111/ans.17453

12. Barnes L, Pietruszka M. Rhabdomyosarcoma arising within a cystosarcoma phyllodes. Case report and review of the literature. *Am J Surg Pathol* (1978) 2(4):423–9. doi: 10.1097/00000478-197812000-00009

13. Guerrero MA, Ballard BR, Grau AM. Malignant phyllodes tumor of the breast: review of the literature and case report of stromal overgrowth. *Surg Oncol* (2003) 12 (1):27–37. doi: 10.1016/S0960-7404(03)00005-7

14. Tsubochi H, Sato N, Kaimori M, Imai T. Osteosarcomatous differentiation in lung metastases from a Malignant phyllodes tumour of the breast. *J Clin Pathol* (2004) 57(4):432–4. doi: 10.1136/jcp.2003.012336

15. Vergine M, Guy C, Taylor MR. Phyllodes tumor of the breast with Malignant melanoma component: A case report. *Int J Surg Pathol* (2015) 23(6):483–8. doi: 10.1177/1066896915592018

16. Narla SL, Stephen P, Kurian A, Annapurneswari S. Well-differentiated liposarcoma of the breast arising in a background of Malignant phyllodes tumor in a pregnant woman: A rare case report and review of literature. *Indian J Pathol Microbiol* (2018) 61(4):577–9. doi: 10.4103/IJPM.IJPM_238_17

17. Jin Y, Bi L, Yang R, Yang R, Zhang X, Li S, et al. Breast osteosarcoma originating from a Malignant phyllodes tumor: A case report of a rare neoplasm. *Med (Baltimore)* (2021) 100(47):e27908. doi: 10.1097/MD.0000000000027908

18. Tu He Ta Mi Shi ME, Wang N, Yao Q, Dong SS, Feng X, Zhao J, et al. A case of phyllodes tumor of the breast with mixed liposarcoma: case report and literature review. *Onco Targets Ther* (2021) 14:3003–11. doi: 10.2147/OTT.S298379

19. Han J, Liu S, Shioya A, Kumagai M, Morioka E, Noguchi M, et al. Recurrent Malignant phyllodes tumor of the breast: An extremely rare case of recurrence with only rhabdomyosarcoma components. *SAGE Open Med Case Rep* (2022) 10:2050313x221116667. doi: 10.1177/2050313X221116667

20. Sawyer EJ, Poulsom R, Hunt FT, Jeffery R, Elia G, Ellis IO, et al. Malignant phyllodes tumours show stromal overexpression of c-myc and c-kit. *J Pathol* (2003) 200 (1):59–64. doi: 10.1002/path.1318

21. Pietruszka M, Barnes L. Cystosarcoma phyllodes: a clinicopathologic analysis of 42 cases. *Cancer* (1978) 41(5):1974–83. doi: 10.1002/1097-0142(197805)41:5<1974::AID-CNCR2820410543>3.0.CO;2-C

22. Stuart A, Radhakrishnan J. Rhabdomyosarcoma. *Indian J Pediatr* (2004) 71 (4):331–7. doi: 10.1007/BF02724100

23. Pollard SG, Marks PV, Temple LN, Thompson HH. Breast sarcoma. A clinicopathologic review of 25 cases. *Cancer* (1990) 66(5):941–4. doi: 10.1002/1097-0142(19900901)66:5%3C9

24. Reinfuss M, Mituś J, Duda K, Stelmach A, Ryś J, Smolak K. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. *Cancer* (1996) 77(5):910–6. doi: 10.1002/(SICI)1097-0142(19960301)77:5<910::AID-CNCR16>3.0.CO;2-6

25. Skapek SX, Ferrari A, Gupta AA, Lupo PJ, Butler E, Shipley J, et al. Rhabdomyosarcoma. *Nat Rev Dis Primers* (2019) 5(1):1. doi: 10.1038/s41572-018-0051-2

26. Liu Y, Zhang M, Yang X, Zhang M, Fan Z, Li Y, et al. Severe hypoglycemia caused by a giant borderline phyllodes tumor of the breast: A case report and literature review. *Front Endocrinol (Lausanne)* (2022) 13:871998. doi: 10.3389/fendo.2022.871998

27. Lu Y, Chen Y, Zhu L, Cartwright P, Song E, Jacobs L, et al. Local recurrence of benign, borderline, and Malignant phyllodes tumors of the breast: A systematic review and meta-analysis. *Ann Surg Oncol* (2019) 26(5):1263–75. doi: 10.1245/s10434-018-07134-5

28. Choi N, Kim K, Shin KH, Kim Y, Moon HG, Park W, et al. Malignant and borderline phyllodes tumors of the breast: a multicenter study of 362 patients (KROG 16-08). *Breast Cancer Res Treat* (2018) 171(2):335–44. doi: 10.1007/s10549-018-4838-3

29. Choi N, Kim K, Shin KH, Kim Y, Moon HG, Park W, et al. The characteristics of local recurrence after breast-conserving surgery alone for Malignant and borderline phyllodes tumors of the breast (KROG 16-08). *Clin Breast Cancer* (2019) 19(5):345–353.e2. doi: 10.1016/j.clbc.2019.04.003

30. Tada Y, Yasunaga M, Tomonobe H, Yamada Y, Hori E, Okugawa K, et al. A case of Malignant phyllodes tumor of the breast metastasizing to the ovary. *Int J Surg Pathol* (2022) 30(4):427–31. doi: 10.1177/10668969211056912

31. Oberlin O, Rey A, Lyden E, Bisogno G, Stevens MC, Meyer WH, et al. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. *J Clin Oncol* (2008) 26(14):2384–9. doi: 10.1200/JCO.2007.14.7207

32. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology* (2016) 68(1):5–21. doi: 10.1111/his.12876

33. Dziuba I, Kurzawa P, Dopierała M, Larque AB, Januszkiewicz-Lewandowska D. Rhabdomyosarcoma in children - current pathologic and molecular classification. *Pol J Pathol* (2018) 69(1):20–32. doi: 10.5114/pjp.2018.75333

34. Yuan Y, Hou J, Pan Y. Rhabdomyosarcoma of the breast: Report of a rare Malignancy. *Cancer Biol Ther* (2017) 18(9):676–80. doi: 10.1080/15384047.2017.1360440

35. Xiao Y, Jiang Y, Xiong Y, Ruan S, Huang T. Pediatric Malignant phyllodes tumors of the breast: characteristics and outcomes based on the surveillance epidemiology and end results database. *J Surg Res* (2020) 249:205–15. doi: 10.1016/j.jss.2019.12.031

36. Lawrence AE, Saito J, Onwuka A, Port E, Bowder A, Courtney C, et al. Management of pediatric breast masses: A multi-institutional retrospective cohort study. *J Surg Res* (2021) 264:309–15. doi: 10.1016/j.jss.2021.01.041

37. Confavreux C, Lurkin A, Mitton N, Blondet R, Saba C, Ranchère D, et al. Sarcomas and Malignant phyllodes tumours of the breast–a retrospective study. *Eur J Cancer* (2006) 42(16):2715–21. doi: 10.1016/j.ejca.2006.05.040

38. Neron M, Sajous C, Thezenas S, Piperno-Neumann S, Reyal F, Laé M, et al. Impact of metastasis surgery and alkylating-agent-based chemotherapy on outcomes of metastatic Malignant phyllodes tumors: A multicenter retrospective study. *Ann Surg Oncol* (2020) 27(5):1693–9. doi: 10.1245/s10434-019-08097-x

39. Koukourakis IM, Zygogianni A, Kouloulias V, Koukourakis MI. Successful treatment of a locally recurrent and metastatic Malignant phyllodes tumor with accelerated radiotherapy and Nab-Paclitaxel, Cisplatin, and Liposomal Doxorubicin chemotherapy. *Chemotherapy* (2021) 66(3):82–6. doi: 10.1159/000517246

40. Boutrus RR, Khair S, Abdelazim Y, Nasr S, Ibraheem MH, Farahat A, et al. Phyllodes tumors of the breast: Adjuvant radiation therapy revisited. *Breast* (2021) 58:1–5. doi: 10.1016/j.breast.2021.03.013

41. Gallego S, Bernabeu D, Garrido-Pontnou M, Guillen G, Hindi N, Juan-Ribelles A, et al. GEIS-SEHOP clinical practice guidelines for the treatment of rhabdomyosarcoma. *Clin Transl Oncol* (2021) 23(12):2460–73. doi: 10.1007/s12094-021-02654-1

42. Yechieli RL, Mandeville HC, Hiniker SM, Bernier-Chastagner V, McGovern S, Scarzello G, et al. Rhabdomyosarcoma. *Pediatr Blood Cancer* (2021) 68 Suppl 2:e28254. doi: 10.1002/pbc.28254

43. Cui W, Stern C, Hickey M, Goldblatt F, Anazodo A, Stevenson WS, et al. Preventing ovarian failure associated with chemotherapy. *Med J Aust* (2018) 209 (9):412–6. doi: 10.5694/mja18.00190

44. Mance M, Smuđ-Orehovec S, Vrbanović-Mijatović V, Mijatović D. Primary alveolar rhabdomyosarcoma of the breast in a 17-year-old girl. *JCO Oncol Pract* (2020) 16(2):93–5. doi: 10.1200/JOP.19.00476

45. Paulino AC, Simon JH, Zhen W, Wen BC. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys* (2000) 48(5):1489–95. doi: 10.1016/S0360-3016(00)00799-9

46. Terezakis SA, Wharam MD. Radiotherapy for rhabdomyosarcoma: indications and outcome. *Clin Oncol (R Coll Radiol)* (2013) 25(1):27–35. doi: 10.1016/j.clon.2012.07.009

47. Ladra MM, Szymonifka JD, Mahajan A, Friedmann AM, Yong Yeap B, Goebel CP, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. *J Clin Oncol* (2014) 32(33):3762–70. doi: 10.1200/JCO.2014.56.1548

48. Mizumoto M, Murayama S, Akimoto T, Demizu Y, Fukushima T, Ishida Y, et al. Preliminary results of proton radiotherapy for pediatric rhabdomyosarcoma: a multi-institutional study in Japan. *Cancer Med* (2018) 7(5):1870–4. doi: 10.1002/cam4.1464

49. Mandeville HC. Radiotherapy in the management of childhood rhabdomyosarcoma. *Clin Oncol (R Coll Radiol)* (2019) 31(7):462–70. doi: 10.1016/j.clon.2019.03.047

50. Schoot RA, Chisholm JC, Casanova M, Minard-Colin V, Geoerger B, Cameron AL, et al. Metastatic rhabdomyosarcoma: results of the european paediatric soft tissue sarcoma study group MTS 2008 study and pooled analysis with the concurrent BERNIE study. *J Clin Oncol* (2022) 40(32):3730–40. doi: 10.1200/JCO.21.02981

51. Mohan AC, Venkatramani R, Okcu MF, Nuchtern JG, Vasudevan SA, Mahajan A, et al. Local therapy to distant metastatic sites in stage IV rhabdomyosarcoma. *Pediatr Blood Cancer* (2018) 65(2). doi: 10.1002/pbc.26859

52. Granowetter L, Womer R, Devidas M, Krailo M, Wang C, Bernstein M, et al. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. *J Clin Oncol* (2009) 27(15):2536–41. doi: 10.1200/JCO.2008.19.1478

53. Weigel BJ, Lyden E, Anderson JR, Meyer WH, Parham DM, Rodeberg DA, et al. Intensive multiagent therapy, including dose-compressed cycles of ifosfamide/etoposide and vincristine/doxorubicin/cyclophosphamide, irinotecan, and radiation, in patients with high-risk rhabdomyosarcoma: A report from the children's oncology group. *J Clin Oncol* (2016) 34(2):117–22. doi: 10.1200/JCO.2015.63.4048

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 30 October 2023
DOI 10.3389/fonc.2023.1255832

OPEN ACCESS

EDITED BY
Xiaowei Qi,
Army Medical University, China

REVIEWED BY
Luigi Pio Guerrera,
University of Campania Luigi Vanvitelli, Italy
Mayank Kumar,
Columbia University, United States

*CORRESPONDENCE
Adham Hijab
adhamhij@gmail.com

RECEIVED 09 July 2023
ACCEPTED 16 October 2023
PUBLISHED 30 October 2023

CITATION
Hinich MG and Hijab A (2023) Acrofacial vitiligo secondary to PI3KCA inhibitor, alpelisib: case report.
Front. Oncol. 13:1255832.
doi: 10.3389/fonc.2023.1255832

Acrofacial vitiligo secondary to PI3KCA inhibitor, alpelisib: case report

Maayan Geller Hinich[1] and Adham Hijab[1,2]*

[1]Oncology Division, Ziv Medical Centre, Safed, Israel, [2]Radiotherapy Unit, Ziv Medical Centre, Safed, Israel

Alpelisib plus fulvestrant is a valid second or advanced line of treatment for patients with metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who harbor an activating PIK3CA mutation. The well-known side effects of alpelisib are hyperglycemia, rash, and diarrhea. Herein, we report a case of a woman who developed diffuse depigmented macules on the face, arms and legs, three months after initiating alpelisib. Both clinical and histopathological findings were consistent with new-onset vitiligo. To our knowledge, this is the first case described in literature which suggests a causal relationship between alpelisib and irreversible dermatological adverse effect.

KEYWORDS

vitiligo, alpelisib, breast cancer, PIK3CA, skin adverse effects

Introduction

Around 40% of patients with hormone receptor (HR)- positive, HER2 negative breast cancer have an underlying activating mutation in PIK3CA gene which encodes the catalytic p110α subunit of the phosphatidylinositol 3-kinase (PI3K) class I enzyme (1). Alpelisib is an α-selective PI3K (PIK3CA) inhibitor which is taken orally. The pivotal SOLAR-1 trial, demonstrated a clinical benefit of alpelisib plus fulvestrant in patients with HR-positive, HER2-negative, advanced breast cancer with PIK3CA mutation, who progressed on previous hormonal therapy (2). Indeed, based on these results, alpelisib plus fulvestrant has gained FDA approval and is an established second or subsequent line of treatment for patients with advanced hormonal-positive, HER2-negative breast cancer with a PIK3CA mutation. The most frequently encountered adverse events that are associated with alpelisib are hyperglycemia, gastrointestinal symptoms (diarrhea, nausea), and rash.

Vitiligo, is an irreversible depigmentation disorder, that is occasionally observed as a consequence of treatment with checkpoint inhibitors. Various tyrosine kinase inhibitors could also induce pigmentary changes including hypopigmentation and hyperpigmentation. To date, there are no reports of vitiligo secondary to PIK3CA inhibitor, alpelisib. We present a case of a woman who developed vitiligo few months after starting this novel targeted agent.

Patient information

A 46 years old, otherwise healthy, premenopausal woman was diagnosed in 2016 with regionally advanced infiltrating ductal carcinoma (stage IIIA T3N1M0) of right breast. The tumor was positive for hormone receptors' expression (ER and PR positive), without HER2 amplification (HER2 + 1 by immunohistochemistry), and with a Ki67 between 5% to 10%. She went on to receive neoadjuvant chemotherapy (with a documented minimal response), followed by mastectomy with axillary node dissection, and adjuvant radiotherapy. Residual tumor was still evident in the right breast (scattered foci of grade 3 invasive ductal carcinoma, same hormonal and HER2 profile) with 7 out of 12 dissected axillary lymph nodes involved by carcinoma. Adjuvant hormonal therapy with tamoxifen was initiated along with ovarian suppression.

In 2021, patient developed recurrence (biopsy-proven) with a disseminated disease in liver, mediastinum, and lungs. Hormonal and HER2 profile was consistent with the initial tumor diagnosed in 2016. Treatment with CDK4/6 inhibitor (Ribociclib) plus fulvestrant was commenced. In June 2022, a disease progression in liver and bones was documented. Molecular profiling revealed PIK3CA mutation and treatment with alpelisib plus fulvestrant was started in August 2022. Shortly after, patient developed hyperglycemia which required dose reduction of alpelisib (dose reduced from 300 mg to 250 mg daily).

Clinical findings

Three months after the initiation of alpelisib, patient developed skin discoloration in arms, legs, and face that was very suggestive of vitiligo (Figure 1). She was referred to a comprehensive dermatologic

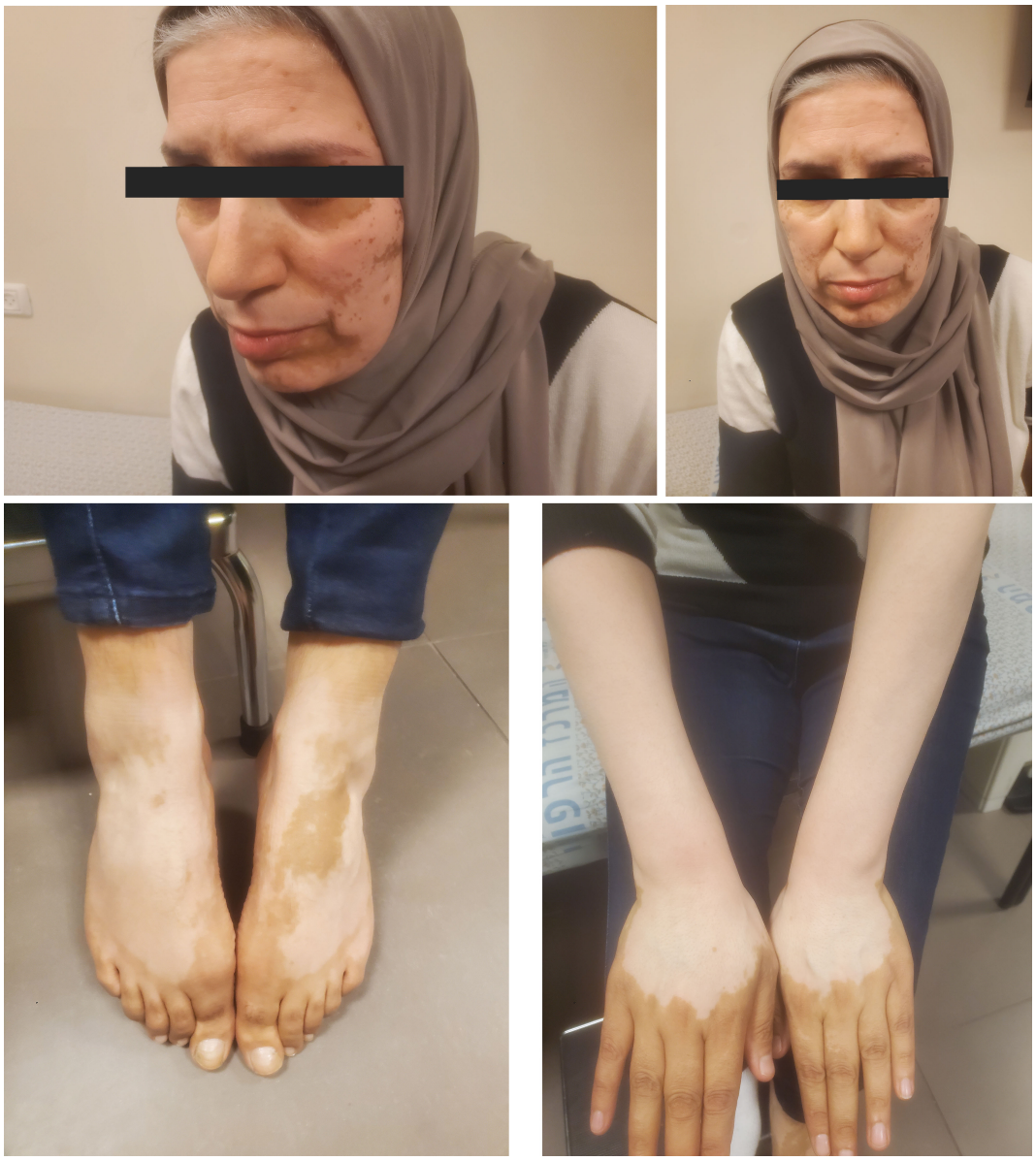


FIGURE 1
Diffuse areas of depigmented skin apparent in the areas of face, arms, and lower legs.

assessment. A skin biopsy was obtained, which was remarkable for atrophic epidermis with scattered melanophages in the upper dermis. Notably, the patient did not have neither personal or familial history of dermatological disorders nor did not start any new concomitant medications. Soon after this, the patient experienced a substantial disease progression in the form of visceral crisis due to significant deranged liver function tests, she went on to receive doublet chemotherapy comprised of carboplatin and gemcitabine.

Discussion

Although not life-threatening, vitiligo could profoundly impact quality of life as a result of a significant change in appearance. In the medical oncology field, vitiligo is commonly known to be associated with immunotherapy. In this regard, sometimes patients find comfort in the fact that it could be a positive predictive biomarker for treatment response (3). An autoimmune mechanism is one of the main hypothesis behind the development of vitiligo, therefore the association between checkpoint inhibitors and vitiligo is tangible. However, melanocytes destruction caused by oxidative stress secondary to radical oxygen species (ROS), is another plausible mechanism of vitiligo (4). The Nuclear factor erythroid 2-related factor2 (Nrf2) is a downstream component of the PI3K/Akt pathway and is a major transcription factor of ROS scavengers (5, 6). In addition, the expression of anti-apoptotic proteins such as BCL-2 is upregulated, while pro-apoptotic molecules such as caspase 3 and 9 is attenuated by the activation of PI3K/Akt pathway (7), thus preventing apoptotic death in melanocytes which could be secondary to oxidative stress. Therefore, inhibition of PI3KCA by alpelisib could hamper melanocytes' ability to manage oxidative stress leading to melanocytes' destruction and eventually to vitiligo.

Despite its rarity, both clinicians and patients alike should be aware of the chances of developing this sequela as it is generally irreversible and could be quite disfiguring, leading to psychological distress and anxiety.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AH: Writing – original draft, Writing – review & editing. MH: Writing – original draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Koboldt DC, Fulton RS, McLellan MD, Schmidt H, Kalicki-Veizer J, McMichael JF, et al. Comprehensive molecular portraits of human breast tumours. *Nature.* (2012) 490(7418):61–70. doi: 10.1038/nature11412

2. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. *New Engl J Med* (2019) 380(20):1929–40. doi: 10.1056/NEJMoa1813904

3. Byrne KT, Turk MJ. New perspectives on the role of vitiligo in immune responses to melanoma. *Oncotarget.* (2011) 2(9):684–94.

4. Denat L, Kadekaro AL, Marrot L, Leachman SA, Abdel-Malek ZA. Melanocytes as instigators and victims of oxidative stress. *J Invest Dermatol* (2014) 134(6):1512–8. doi: 10.1038/jid.2014.65

5. *PI3K/Akt-Nrf2 and anti-inflammation effect of macrolides in chronic obstructive pulmonary disease* . Available at: https://pubmed.ncbi.nlm.nih.gov/30827233/ (Accessed June 27, 2023).

6. Zhuang Y, Wu H, Wang X, He J, He S, Yin Y. Resveratrol attenuates oxidative stress-induced intestinal barrier injury through PI3K/Akt-mediated Nrf2 signaling pathway. *Oxid Med Cell Longev* (2019) 2019:7591840. doi: 10.1155/2019/7591840

7. Shi Q, Zhang W, Guo S, Jian Z, Li S, Li K, et al. Oxidative stress-induced overexpression of miR-25: the mechanism underlying the degeneration of melanocytes in vitiligo. *Cell Death Differ* (2016) 23(3):496–508. doi: 10.1038/cdd.2015.117

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 15 January 2024
DOI 10.3389/fonc.2023.1305584

OPEN ACCESS

EDITED BY
Massimo Broggini,
Mario Negri Institute for Pharmacological Research (IRCCS), Italy

REVIEWED BY
Antonio Giordano,
Temple University, United States
Karl Reinhard Aigner,
MEDIAS Burghausen Clinic, Germany

*CORRESPONDENCE
Yuan Yuan
yuan.yuan@cshs.org

RECEIVED 02 October 2023
ACCEPTED 19 December 2023
PUBLISHED 15 January 2024

CITATION
Chan B, Lee JS and Yuan Y (2024) Case report: An exceptional responder of low-dose continuous 5-FU in a patient with *de-novo* stage IV triple-negative breast cancer with liver and bone marrow failure.
Front. Oncol. 13:1305584.
doi: 10.3389/fonc.2023.1305584

Case report: An exceptional responder of low-dose continuous 5-FU in a patient with *de-novo* stage IV triple-negative breast cancer with liver and bone marrow failure

Bryan Chan[1], Jin Sun Lee[2] and Yuan Yuan[2]*

[1]Internal Medicine Department, Huntington Hospital, Pasadena, CA, United States, [2]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, United States

Continuous low-dose 5-FU was popularized as a therapy for pretreated metastatic breast cancer for the past few decades, spurred by the advent of the electronic infusion pump. Capecitabine, otherwise known by its trade name Xeloda, is a prodrug of 5-fluorouracil (5-FU), which is administered orally in many chemotherapy regimens, and plays a role in metastatic breast cancer treatment refractory to traditional anthracyclines and taxane therapy. In this case presentation, we describe a unique case of refractory *de-novo* stage IV triple-negative breast cancer presented with right breast primary invasive ductal carcinoma, extensive lymphadenopathy, with biopsy proven bone marrow infiltration, diffuse hepatomegaly, splenomegaly, significant hyperbilirubinemia, and bone marrow failure treated with continuous 5-FU infusion and subsequently oral capecitabine after initial treatment failure with nab-paclitaxel and sacituzimab govitecan. With this case presentation, the authors aim to showcase the versatility of 5-FU and its prodrug in treatment of metastatic triple-negative breast cancer with severe bone marrow and liver involvement while highlighting key physiologic and pharmacologic mechanisms.

KEYWORDS

5-FU, stage IV breast cancer, triple negative, bone marrow failure, exceptional responder, liver failure

1 Introduction

Triple-negative breast cancer (TNBC) accounts for about 15% of all newly diagnosed breast cancers worldwide and is among the most aggressive histologic subtype, with fewer treatment options and a poorer prognosis overall compared to other forms of invasive breast cancers. Demographically, TNBC tends to be more common in women younger than

40 years of age, have a BRCA mutation, or are ethnically Black. Around 6% of metastatic breast cancers arise *de novo* although, ironically, this statistic is likely lower in TNBC compared to those with HER2-positive disease (1).

As few as 20% of breast cancer patients and 40% of metastatic breast cancer patients will develop hepatic metastases at some time during their disease course. Metastatic spread to the liver often presents clearly as a well-defined mass easily diagnosed on radiographic imaging. The clinical course of these patients, particularly in those with cancer infiltration to the hepatic sinusoids, are often complicated by significant elevations in bilirubin and hypoalbuminemia and can even lead to ascites, encephalopathy, and fulminant hepatic failure. One recent case study features a patient with stage IV ER-positive breast cancer with biopsy-proven diffuse intrasinusoidal hepatic metastasis that presented with right upper quadrant abdominal pain and bilateral lower extremity swelling—weekly treatment with low-dose Adriamycin resulted in prompt reversal of her liver function testing to baseline (2).

Meanwhile, symptomatic bone marrow carcinomatosis (characterized by diffuse infiltrative growth of tumor cells in the bone marrow) is an extremely rare occurrence in patients with breast cancer, representing as few as 0.17% of cases (3). Primary clinical signs of bone marrow carcinomatosis are anemia and thrombocytopenia, often so severe as to require supplemental transfusions and bone marrow stimulants. Thus, in the event of multiorgan disease, treatment can be conceivably complex and multifaceted and may require interdisciplinary collaboration between oncologists, other sub-specialists, and hospitalist teams.

Continuous low dose 5-FU was popularized as a therapy for pretreated metastatic breast cancer for the past few decades, spurred by the advent of the medtronic infusion pump. However, there has been a dearth of recent data regarding its application among metastatic TNBC patients. In this case presentation, the authors aim to showcase the versatility of continuous 5-FU in treatment of metastatic triple negative breast cancer with severe bone marrow and liver involvement.

2 Case presentation

Patient is a 35 year-old Asian, otherwise healthy female without significant family history of cancer, who was originally diagnosed with *de-novo* stage IV triple-negative invasive ductal carcinoma via ultrasound fine needle aspiration of the right breast mass on 13/12/2022. The initial breast biopsy performed at outside clinic showed grade 3, ER negative, PR negative, HER2 IHC 2+, and negative by FISH. Subsequent fine needle aspiration of the right axillary lymph node was consistent with metastatic carcinoma of the breast on 17/12/2022. Patient was noted to have significantly decreased platelet count to 25K on 17/01/2023. A PET/CT dated 31/01/2023 showed a right hypermetabolic breast mass of 2.5 cm × 1.9 cm with extensive adenopathy in the neck, chest, pelvic, and upper abdomen (Figure 1). The patient was initially admitted on 20/02/2023 for evaluation of persisting vaginal bleeding and thrombocytopenia, status post-uterine artery ablation. Inpatient workup included a bone marrow biopsy, which showed metastatic breast cancer in at least 50% of the bone marrow. There were not enough biopsied tissues for PD-L1 expression test. While awaiting further tests, including PD-L1 expression, from the second biopsy, the patient started cycle 1 day 1 of weekly nab-paclitaxel and received a total of three doses dated 25/02/23, 04/03/2023, and 11/03/2023 with noted significant reduction of right breast mass but resulting pancytopenia responding to romiplostim, epoetin, and filgrastim as well as intermittent red blood cell transfusion and daily platelet transfusion. A repeat axillary lymph node biopsy confirmed high-grade metastatic carcinoma, ER 15%, PR 0%, HER2 IHC 0, Ki-67 85%. Tissue NGS did not show any targetable alteration. Genetic testing via Ambry Genetics was positive for VUS in TSC2 but otherwise negative for any other pathogenic variant. Patient

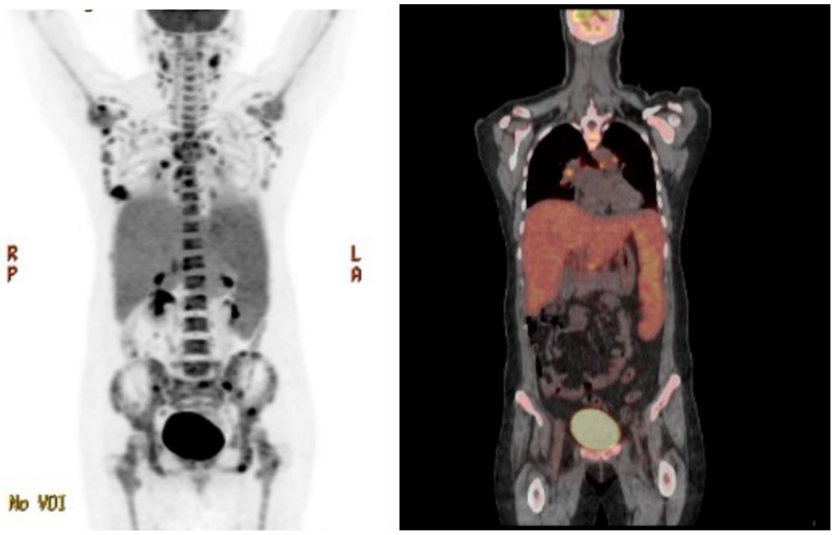


FIGURE 1
PET-CT highlighting metastatic TNBC with spread to the neck, sternum, thoracic spine, upper abdomen, and pelvis.

finished cycle 1 of nab-paclitaxel with excellent clinical response, and the right breast mass was decreased in size to approximately 3 cm × 2 cm on palpation; the plan was to continue therapy.

However, patient was re-admitted for hyperbilirubinemia on 27/03/2023 with a total bilirubin of 5.4 mg/dl with elevated liver function tests (AST 197 U/L/ALT 79 U/L). Patient's vitals were collected in the ER, which showed that she was afebrile and hemodynamically stable with normal respirations and heart rate. Notable findings on exam included scleral icterus, diffuse jaundice, and a 3-cm nodular, tender breast lesion in the lateral 9 o'clock region. There was no asterixis, changes in mental status or other notable findings on the physical exam. CT scan showed diffuse hepatomegaly measuring 21.8 cm and diffuse splenomegaly, measuring 24 cm (Figure 2) without discrete lesions, which caused abdominal pain and bloating. Further workup failed to identify biliary ductal obstruction. Patient was subsequently started on salvage chemotherapy with weekly sacituzimab govitecan (SG) dated 29/03/2023 and 04/04/2023. Liver function testing initially improved, but subsequently worsened, with total bilirubin at a maximum of 20.7 mg/dl dated 06/04/2023. Patient was started on third-line therapy with continuous 5-FU planned for 10 total days from 10/04/2023 to 20/04/2023. The patient experienced remarkable clinical response, with total bilirubin dropping steadily and liver function testing improving daily (Figure 3). The patient also intermittently received inpatient radiation therapy to the liver (which resulted in transient elevations in liver function tests), requiring momentary stopping of continuous 5-FU. She was then transitioned from 5-FU to oral capecitabine after dated 21/04/2023 at a dose of 1000 mg/m^2, 14 days on and 7 days off. Upon discharge, the patient remained on a regimen of oral capecitabine, and total bilirubin had dropped remarkably to 2.9 mg/dl. Upon follow-up at 5 months, the patient remains on capecitabine with sustained clinical response with no significant adverse side effects. 27/05/2023 restaging CT chest/abdomen/pelvis showed improve hepatomegaly at 18.4 cm, splenomegaly at 17.5 cm and stable bone metastasis. Patient was continued on capecitabine, restaging CT 11/08/2023 showed stable hepatomegaly and splenomegaly and stable bone metastasis. Clinically patient is doing well with ECOG PS of 0, lab work showed platelet count of 128k/UL, total bilirubin 1.2 mg/dl, AST 62 U/L, ALT 69 U/L without additional growth factor support (Figure 4).

3 Discussion

Here, we described a unique case of refractory *de-novo* stage IV triple-negative breast cancer presented with right breast primary invasive ductal carcinoma, extensive lymphadenopathy, with biopsy proven bone marrow infiltration, diffuse hepatomegaly, splenomegaly, significant hyperbilirubinemia, and bone marrow failure treated with continuous 5-FU infusion and subsequently oral capecitabine after initial treatment failure with nab-paclitaxel, and SG.

Bone marrow failure is a rare event in breast cancer, with symptomatic bone marrow carcinomatosis being a difficult condition to treat given the limited literature (3). The patient's pancytopenia was of concern during the aforementioned initial hospitalization, and the patient ultimately required growth factors support with romiplostim, epoetin, and filgrastim as well as intermittent red blood cell transfusion and daily platelet transfusion. The patient's initial treatment of a cytotoxic agent (nab-paclitaxel) likely exacerbated the patient's precarious hematologic state, although cytopenia was present even prior to chemotherapy initiation and likely secondary to infiltration of the neoplasm to the bone marrow (resulting in bone marrow failure). In terms of histology, invasive lobular carcinomas are more likely than invasive ductal carcinomas to present with symptomatic bone marrow infiltration (4).

In addition to bone marrow carcinomatosis, the patient's breast cancer also presented with metastatic spread to the liver with marked hepatosplenomegaly, likely a reflection of diffuse, massive intrasinusoidal infiltration of the hepatic system. Although the patient did show signs of hepatocellular damage with significant

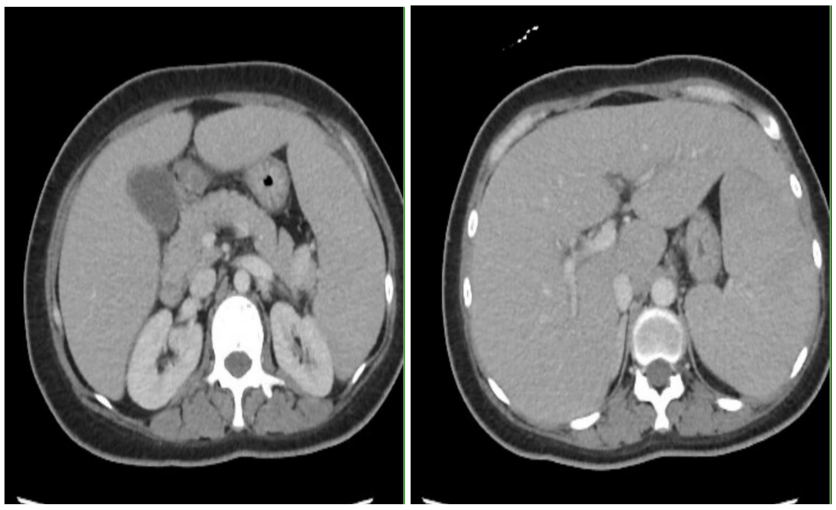


FIGURE 2
CT scan with contrast showing marked hepatosplenomegaly.

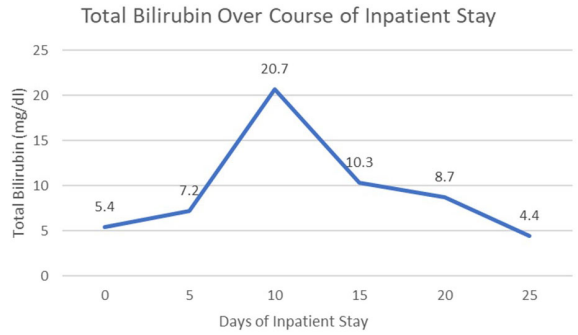


FIGURE 3
Total bilirubin over course of inpatient stay.

clinical markers such as significant hyperbilirubinemia, transaminitis and elevated alkaline phosphatase, the patient did not technically meet the definition of acute fulminant hepatic failure, given an INR generally below 1.5, and absence of hepatic encephalopathy on exam. Regardless, the patient's trend of bilirubin was a useful clinical marker of treatment response in this rare presentation, given a difference of nearly 18 mg/dl before and after finishing inpatient treatment with continuous 5-FU.

It is extremely unusual that the patient had remarkable response to 5-FU and capecitabine after initial failure of salvage SG showed in this case. For patients with stage IV triple-negative right breast cancer (TNBC) without PD-L1 expression, typical first-line therapy typically consists of chemotherapy rather than chemoimmunotherapy, and both platinum and taxanes are considered appropriate options with similar outcomes (5). Second-line treatment is less standardized, but SG has emerged as a primary contender after treatment failure after first-line or second-line therapy with phase III ASCENT trial showed both progression free survival (PFS) and overall survival (OS) benefit, which led to FDA approval of the first antibody-drug conjugate in metastatic TNBC (6, 7).

Metronomic chemotherapy regimens involve continuous administration of low-dose chemotherapy agent with no or short-regular treatment-free intervals has known to offer important advantages including continuous drug exposure and significantly reduced toxicity (8, 9). The pharmacokinetic characteristics and low-toxicity profile make low-dose 5FU or capecitabine an ideal drug for metronomic administration.

Meanwhile, while continuous 5-FU has been utilized in the past for meaningful palliative results of pretreated, resistant metastatic breast cancer that failed standard first-line therapy, response rates were typically modest (10). In this case, continuous 5-FU was able to successfully "unpack" the bone marrow without increasing episodes of bleeding or an increased need for inpatient transfusions, demonstrating excellent clinical response. The mechanism of action of 5-FU is that of a thymidylate synthase (TS) inhibitor, interrupting DNA replication and thus causing oxidative stress, with rapidly dividing cells (such as cancer cells or newer cells in the bone marrow) undergoing cell death via "thymineless death" (11). This concept has also been highlighted by Banys-Paluchowski et al. in a recent review, which showed that metronomic chemotherapy may be an effective alternative to conventional chemotherapy by using low doses of continuous chemotherapy, reducing the risk of cancer cell resistance and possible disease progression (12).

Capecitabine acts as an antimetabolite that gets broken down to fluorouracil, also known as 5-FU, which ultimately interferes with the production of DNA by blocking the action of thymidylate synthase. Capecitabine has been widely adopted as an adjuvant treatment of TNBC with residual disease after neoadjuvant chemotherapy after the CREATE-X trial demonstrated disease free survival and overall survival benefits (13). The routine use of adjuvant capecitabine in early stage TNBC may have changed the potential utility of its use in metastatic or refractory setting. In addition, toxicity may often affect gastrointestinal, hematologic, and integumentary systems, and patients may require either dose-reduction or treatment discontinuation for symptom resolution; hand is a rather common adverse reaction, often involving focal irritation, erythema and peeling of the hands or feet, and is also present as an adverse reaction to various other forms of chemotherapy. The patient in this case was able to tolerate capecitabine and 5-FU without significant adverse effects such as hand–foot syndrome; biology may play a role, with patients with certain ethnic background being able to tolerate the medications better than others (14).

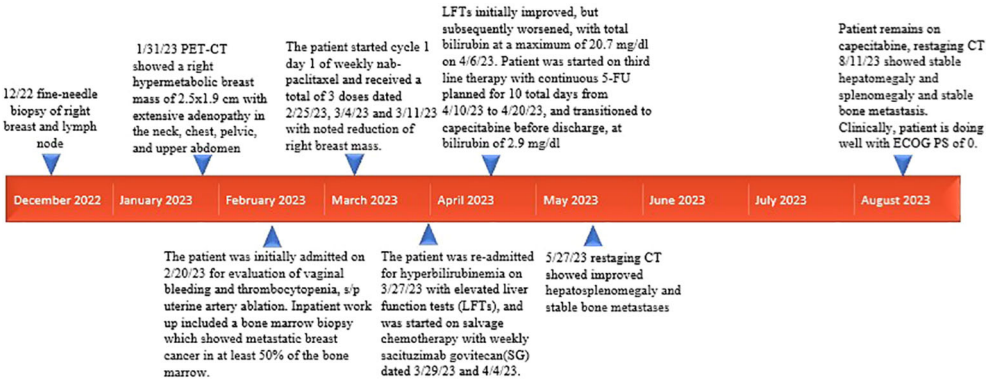


FIGURE 4
Timeline of relevant clinical events (2022–2023).

4 Conclusion

In this case presentation, we present a unique case of refractory *de-novo* stage IV TNBC with bone marrow carcinomatosis, severe thrombocytopenia, profound hyperbilirubinemia (total bilirubin over 20 mg/dl), and liver and spleen infiltration. Patient had a remarkable response to continuous metronomic dose of daily 5-FU infusion and subsequently oral capecitabine after refractory response to nab-paclitaxel and subsequent SG. Through highlighting the remarkable clinical response of the patient despite worsening metastatic disease with multiorgan sequelae, the authors hope to showcase not only the complex physiology of late stage TNBC but also better highlight the utility of metronomic 5-FU infusion and capecitabine for those with refractory disease (15). More research is needed to further understand the mechanism of action for the metronomic dosed chemotherapy agent and how to define the optimal biological dose of such an agent to market its utility in the era of immunotherapy and antibody drug conjugates.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BC: Conceptualization, Validation, Writing – original draft, Writing – review & editing. JL: Writing – review & editing. YY: Conceptualization, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Müller V, Hein A, Hartkopf AD, Fasching PA, Kolberg H-C, Hadji P, et al. Occurrence and characteristics of patients with *de novo* advanced breast cancer according to patient and tumor characteristics - A retrospective analysis of a real world registry. *Eur J Cancer* (2022) 172:13–21. doi: 10.1016/j.ejca.2022.05.015

2. Afiat T-PN, Hembree TN, Dean EA, Araujo C, Pena LR, Rosa M, et al. Diffuse intrasinusoidal hepatic metastasis from breast cancer presenting as liver failure: effective and rapid treatment with weekly low-dose adriamycin. *Am J Case Rep* (2020) 21:e924141. doi: 10.12659/AJCR.924141

3. Yang R, Jia L, Lu G, Lv Z, Cui J. Symptomatic bone marrow metastases in breast cancer: A retrospective cohort study. *Front Oncol* (2022) 12:1042773. doi: 10.3389/fonc.2022.1042773

4. Demir L, Akyol M, Bener S, Payzin KB, Erten C, Somali I, et al. Prognostic evaluation of breast cancer patients with evident bone marrow metastasis. *Breast J* (2014) 20(3):279–87. doi: 10.1111/tbj.12264

5. Tutt A, Ellis P, Kilburn L, Gilett C, Pinder S, Abraham J, et al. The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). *Cancer Res* (2015) 75:1–3. doi: 10.1158/1538-7445.SABCS14-S3-01

6. Bardia A, Mayer IA, Diamond JR, Moroose RL, Isakoff SJ, Starodub AN, et al. Efficacy and safety of anti-trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. *J Clin oncology: Off J Am Soc Clin Oncol* (2017) 35(19):2141–8. doi: 10.1200/JCO.2016.70.8297

7. Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med* (2019) 380(8):741–51. doi: 10.1056/NEJMoa1814213

8. Emmenegger U, Kerbel RS. Five years of clinical experience with metronomic chemotherapy: achievements and perspectives. *Onkologie.* (2007) 30(12):606–8. doi: 10.1159/000111479

9. Cazzaniga ME, Capici S, Cordani N, Cogliati V, Pepe FF, Riva F, et al. Metronomic chemotherapy for metastatic breast cancer treatment: Clinical and preclinical data between lights and shadows. *J Clin Med* (2022) 11(16):4710. doi: 10.3390/jcm11164710

10. Regazzoni S, Pesce G, Marini G, Cavalli F, Goldhirsch A. Low-dose continuous intravenous infusion of 5-fluorouracil for metastatic breast cancer. *Ann Oncol* (1996) 7 (8):807–13. doi: 10.1093/oxfordjournals.annonc.a010759

11. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. *Nat Rev cancer* (2003) 3(5):330–8. doi: 10.1038/nrc1074

12. Banys-Paluchowski M, Schütz F, Ruckhäberle E, Krawczyk N, Fehm T. Metronomic chemotherapy for metastatic breast cancer–a systematic review of the literature. *Senologie-Zeitschrift für Mammadiagnostik und-therapie* (2016) 13(04):180–8. doi: 10.1055/s-0042-105871

13. Masuda N, Lee S-J, Ohtani S, Im Y-H, Lee E-S, Yokota I, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *New Engl J Med* (2017) 376(22):2147–59. doi: 10.1056/NEJMoa1612645

14. Saif MW. Capecitabine and hand–foot syndrome. *Expert Opin Drug safety* (2011) 10(2):159–69. doi: 10.1517/14740338.2011.546342

15. Derakhshan F, Reis-Filho JS. Pathogenesis of triple-negative breast cancer. *Annu Rev Pathol* (2022) 17:181–204. doi: 10.1146/annurev-pathol-042420-093238

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 18 January 2024
DOI 10.3389/fonc.2023.1258474

OPEN ACCESS

EDITED BY
Siqi Chen,
Washington University in St. Louis,
United States

REVIEWED BY
Heng Sun,
University of Macau, China
Yaping Sun,
Yale University, United States
Wenqing Zhang,
The Ohio State University, United States

*CORRESPONDENCE
Yan Li
liyan1101@suda.edu.cn

RECEIVED 14 July 2023
ACCEPTED 28 December 2023
PUBLISHED 18 January 2024

CITATION
Cao T, Duan Z, Zhu J, Wu J, Chen J, Jiang M, Lu X and Li Y (2024) Case report: Urothelial injury in a female with breast cancer: a rare adverse event after the combination of paclitaxel and trastuzumab.
Front. Oncol. 13:1258474.
doi: 10.3389/fonc.2023.1258474

Case report: Urothelial injury in a female with breast cancer: a rare adverse event after the combination of paclitaxel and trastuzumab

Tinghua Cao[1], Zhipei Duan[1], Jing Zhu[1], Jing Wu[1], Jun Chen[1], Mingjun Jiang[2], Xialiang Lu[3] and Yan Li[1]*

[1]Department of Oncology, Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, Suzhou, China, [2]Department of Urinary Surgery, Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, Suzhou, China, [3]Department of Pathology, Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, Suzhou, China

Several breast cancer (BC) patients showed urinary tract infection after adjuvant trastuzumab plus paclitaxel, but no case of urothelial injury has been reported. In this case, we report a 47-year-old female patient with stage I invasive ductal carcinoma in the left breast presenting with urothelial injury after the combination of trastuzumab and paclitaxel. Initially, the patient was highly suspected of having urinary tract infection as she showed abdominal and low back pain, as well as urinary irritation symptoms and hematuria. Unfortunately, the conditions were not attenuated after anti-infection therapy. Contrast-enhanced CT showed extensive exudation and edema in the bilateral renal pelvis, ureter, and bladder, together with dilatation and effusion in the renal pelvis and ureter. Cystoscopy showed extensive congestion, edema, and erosion in the bladder epithelium. Pathological analysis demonstrated slight thinning or even loss in the uroepithelial cell layer and interstitial congestion. In addition, there was growth arrest in the epithelial cells. Immunohistochemistry indicated HER2 expression in the urothelial cells. Finally, the patient was diagnosed with urothelial injury after combination of paclitaxel and trastuzumab. The symptoms were spontaneously cured with no administration of any antibiotics in the 3-month follow-up.

KEYWORDS

trastuzumab, paclitaxel, urothelial injury, adverse events, urinary tract infection, case report

Introduction

The adjuvant paclitaxel and trastuzumab has been commonly utilized for treating breast cancer (BC), which has greatly reduced the risk of recurrence and improved the patient's survival (1, 2). Inevitably, many patients experience mild or even severe adverse events (AEs). Several BC patients show symptoms of urinary tract infection after trastuzumab and paclitaxel (3), but few or even no cases showed urothelial injury sharing similar symptoms with urinary tract infection (4). We hypothesized that the possibility that urothelial injury was misdiagnosed as urinary tract infection may help explain this. In this study, we reported a case of a 47-year-old female BC patient presenting with urothelial injury after paclitaxel and trastuzumab combination, which was initially misdiagnosed as urinary tract infection. This case report may contribute to our understanding of the AEs involving the urinary tract.

Case presentation

A 47-year-old lady with BC presented to our hospital for treatment. Before presenting to our department, she received modified radical resection in a hospital in Shanghai. Postoperative pathological results showed invasive ductal carcinoma (stage IA, pT1cN0M0), with no lymph node involvement. Immunohistochemistry (IHC) test results were estrogen receptor (ER) negative and progesterone receptor (PR) negative but HER2 positive. After excluding the contraindications of chemotherapy, the patient was given adjuvant therapy using paclitaxel and trastuzumab (5). On day 3, the patient showed abdominal and low back pain, as well as urinary irritation symptoms (e.g., frequent and urgent urination, dysuria) and hematuria. Routine blood test indicated neutropenia. On this basis, the patient was highly suspected of having urinary tract infection. She received ceftazidime and levofloxacin for 3 days. As the conditions showed no attenuation, she was switched to Tylenol anti-infective therapy. The results for urine bacterial and fungal cultures and smear microscopy in tuberculosis were negative. Urinary ultrasound showed hydronephrosis. Unfortunately, the conditions were not attenuated after 1-week anti-infection therapy. Antibiotics were then terminated and replaced with dexamethasone. Cystoscopy was completed, and a biopsy was done 6 days later with pathologic testing. Contrast-enhanced CT indicated extensive exudation and edema in the bilateral renal pelvis, ureter, and bladder, together with dilatation and effusion in the renal pelvis and ureter (Figures 1–3). Cystoscopy showed extensive congestion, edema, and erosion in the bladder epithelium. Urinary tract pathology indicated slight thinning or even loss in the epithelial cell layer of the urinary tract, together with interstitial congestion. In addition, there was growth arrest in the epithelial cells, with a high possibility of cellular exfoliation. IHC indicated HER2 positivity in the urinary tract (Figure 4). Finally, the patient was diagnosed with urothelial injury rather than urinary tract infection after combination of paclitaxel and trastuzumab. In the 3-month follow-up, the symptoms were spontaneously cured with no administration of any antibiotics. This study was performed according to the convention of the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University. Written informed consent was obtained from the patient.

Discussion

Urinary tract infection has been commonly reported in patients who underwent combined trastuzumab and paclitaxel. Nevertheless, no studies have reported cases with urothelial injury after such a regimen. In this study, our patient was initially misdiagnosed with urinary tract infection as she showed symptoms of urinary irritation. For a typical lower urinary tract infection, a 3-day anti-infection therapy regime is generally sufficient. Conversely, complex cases involving the upper urinary tract often require a prolonged antibiotic course, usually spanning 7 days to 14 days. The efficacy of treatments for urinary tract infections is commonly discernible

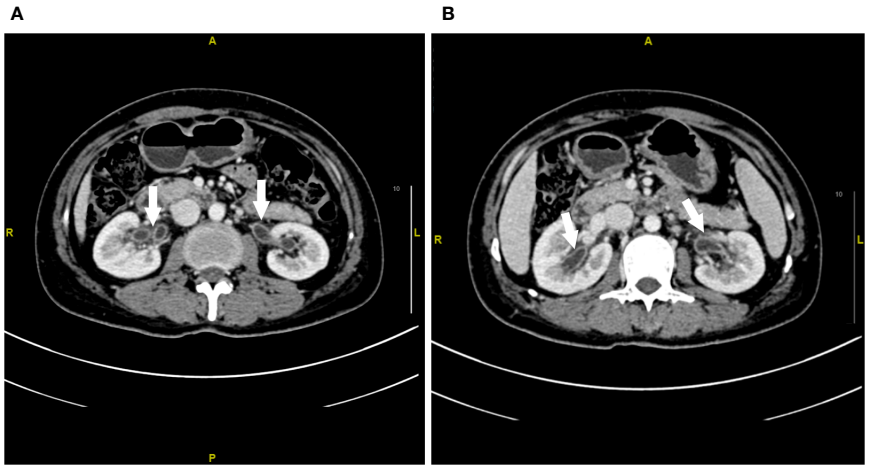


FIGURE 1
Contrast-enhanced CT imaging of the renal pelvis at week 1 after urinary tract irritation. **(A, B)** Extensive exudation and edema in the bilateral renal pelvis. The white arrow represents the edema of the renal pelvis.

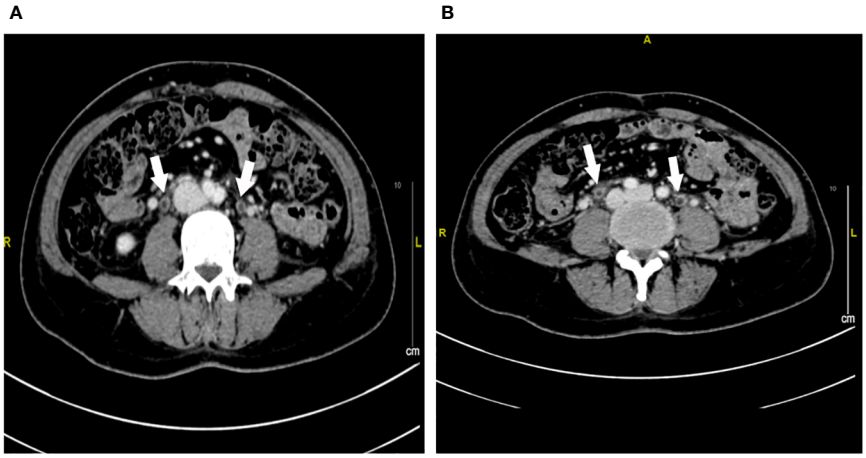


FIGURE 2
Contrast-enhanced CT imaging of the ureter at week 1 after urinary tract irritation. **(A, B)** Extensive exudation and edema in the bilateral ureter. The white arrow represents the edema of the ureter.

within an approximate timeframe of 3 days. In cases of poor response to 3- or 7-day antibiotic therapy, subsequent evaluations (including repeated routine urinalyses, midstream urine cultures, and enhanced CT scans when necessary) successfully excluded the possibility of urinary tract infection. Bladder biopsy, together with the spontaneous cure, confirmed the possibility of urothelial injury induced by trastuzumab or paclitaxel. This case report may enhance our understanding of the AEs involving the urinary tract after trastuzumab or paclitaxel.

To investigate whether the urothelial injury was induced by trastuzumab and/or paclitaxel, we investigated the metabolism of these two drugs based on the previous literature. The total prototype drug in urine after paclitaxel administration was 1.5%–9% of the administered dose; the majority was eliminated by the organs except kidney (6), with a half-life of merely 6–13 h (7). Therefore, complete elimination was achieved after a period that was about 5.0-fold of the half-life. In contrast, the half-life for trastuzumab was 28–38 days, with a subsequent clearance period of up to 27 weeks (8). Meanwhile, the urothelial injury was completely cured at month 4, which could be explained by the pharmacokinetics of trastuzumab rather than paclitaxel. Moreover, the patient showed expression of HER2 on the uroepithelial cells, together with decreased proliferation, thinning, or even loss of bladder epithelial cells. These validated that the urothelial injury was induced by trastuzumab.

The exact mechanism of trastuzumab-induced AEs in urinary tract is still unclear due to the rarity of studies. HER2 expression has been frequently detected in the organs or tissues involved by trastuzumab-induced AEs. According to The Human Protein Atlas website on HER2 expression in partial normal tissues (9), *HER2* RNA and protein were detected in human skin, pulmonary tissues, digestive tract, and cardiac tissues, respectively. Indeed, trastuzumab has been well acknowledged to induce AEs in these

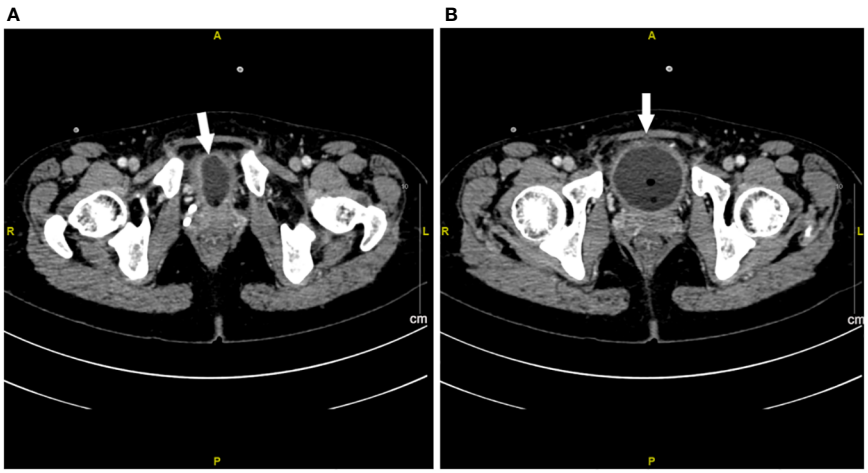


FIGURE 3
Contrast-enhanced CT imaging of bladder at week 1 after urinary tract irritation. **(A, B)** Extensive exudation and edema in bladder. The white arrow represents the edema of the bladder.

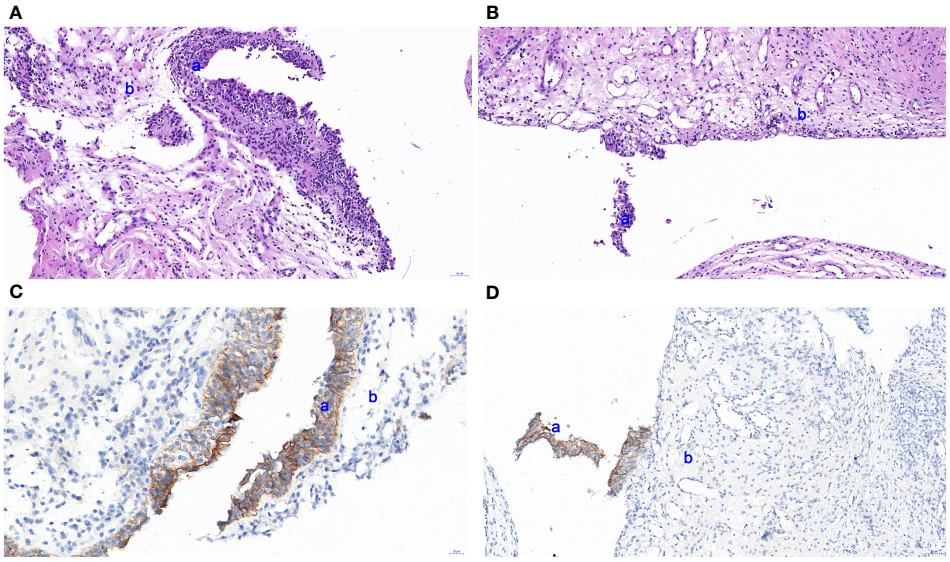


FIGURE 4
HE staining based on a urothelial biopsy specimen and IHC for HER2 expression in the urinary tract. **(A, B)** Slight thinning or even loss in the epithelial cell layer of the urinary tract. **(C, D)** IHC indicated slight thinning or loss of epithelial cells detected by pathological EnVision method staining. a and b represent the transitional cell and inherent layer of connective tissue, respectively. The images were observed under a magnification of ×100.

sites. HER2-targeted therapies (e.g., trastuzumab, lapatinib, pertuzumab) have been reported to carry risks of cardiopulmonary, hematologic, gastrointestinal, and other AEs (2). HER2 plays crucial roles in several biological processes in normal tissues, such as cellular differentiation, necrosis, and proliferation (10). Trastuzumab-induced AEs may be associated with its interaction with HER2 in these cells. For instance, trastuzumab-induced cardiotoxicities may be associated with the interaction between trastuzumab and HER2 expressed in cardiomyocytes that is necessary for the maintenance of cardiac structure and function (11). In addition, as HER2 is involved in the maintenance of membrane integrity in normal gastrointestinal tissues; the inhibition of HER2 expression induced by trastuzumab may lead to a range of gastrointestinal AEs in HER2-overexpressing BC patients (10). HER2 is also expressed in normal urothelial cells. In this case, the patient showed high HER2 expression, and trastuzumab may interact with HER2 expressed in normal cells, resulting in the occurrence of urothelial injury.

Trastuzumab has been well acknowledged as an anti-HER2 drug, and there are ample evidence-based and real-world data on safety. Individual differences and co-administration often lead to unrecognized AEs, which can affect the correct diagnosis and treatment adjustment. The case reported herein suggests that trastuzumab can directly cause urothelial injury, the severity of which may be related to the level of HER2 expression within the individual and the dose of the drug used. This AE has not been reported before, and this case report can provide a basis for clinical recognition and management of this AE in a timely manner. Additionally, this helps promote further research on the mechanisms related to the AEs of targeted therapeutic agents, which can better contribute to the safety of clinical treatment.

Conclusion

In this case report, we report a rare case showing urothelial injury after combined therapy based on trastuzumab and paclitaxel. It was induced by trastuzumab based on the drug metabolism analysis, together with the expression of HER2 on the urinary epithelial cells, decreased proliferation, thinning, or even loss of bladder epithelial cells. Meanwhile, we hope to raise attention on differential diagnosis between urothelial injury and infection after the combination of trastuzumab and paclitaxel.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TC: Formal analysis, Visualization, Writing – original draft. ZD: Formal analysis, Writing – review & editing. JZ: Formal analysis, Writing – review & editing. JW: Formal analysis, Writing – review & editing. JC: Investigation, Writing – review & editing. MJ: Investigation, Writing – review & editing. XL: Investigation, Writing – review & editing. YL: Conceptualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* (2011) 365:1273–83. doi: 10.1056/NEJMoa0910383

2. Perez EA, Dang C, Lee C, Singh J, Wang K, Layton JB, et al. Incidence of adverse events with therapies targeting HER2-positive metastatic breast cancer: a literature review. *Breast Cancer Res Treat* (2022) 194:1–11. doi: 10.1007/s10549-021-06469-0

3. de Langen AJ, Jebbink M, Hashemi SMS, Kuiper JL, de Bruin-Visser J, Monkhorst K, et al. Trastuzumab and paclitaxel in patients with EGFR mutated NSCLC that express HER2 after progression on EGFR TKI treatment. *Br J Cancer* (2018) 119:558–64. doi: 10.1038/s41416-018-0194-7

4. FDA. (2008). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/103792s5175lbl.pdf.

5. Tolaney SM, Guo H, Pernas S, Barry WT, Dillon DA, Ritterhouse L, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* (2019) 37:1868–75. doi: 10.1200/jco.19.00066

6. Royer I, Alvinerie P, Wright M, Monsarrat B, Ho LK, Armand JP. Paclitaxel metabolites in human plasma and urine: Identification of 6α-hydroxytaxol, 7-epitaxol and taxol hydrolysis products using liquid chromatography/atmospheric-pressure chemical ionization mass spectrometry. *Rapid Commun Mass Spectrometry* (1995) 9:495–502. doi: 10.1002/rcm.1290090605

7. Aronson JK ed. Paclitaxel. In: *Meyler's Side Effects of Drugs*, *Sixteenth Edition*. Oxford: Elsevier. p. 445–52.

8. Maximiano S, Magalhaes P, Guerreiro MP, Morgado M. Trastuzumab in the treatment of breast cancer. *BioDrugs* (2016) 30:75–86. doi: 10.1007/s40259-016-0162-9

9. *The Human Protein Atlas website on HER2 expression*. Available at: https://www.proteinatlas.org/ENSG00000141736-ERBB2.

10. Al-Dasooqi N, Bowen JM, Gibson RJ, Sullivan T, Lees J, Keefe DM. Trastuzumab induces gastrointestinal side effects in HER2-overexpressing breast cancer patients. *Invest New Drugs* (2009) 27:173–8. doi: 10.1007/s10637-008-9152-1

11. Moilanen T, Jokimaki A, Tenhunen O, Koivunen JP. Trastuzumab-induced cardiotoxicity and its risk factors in real-world setting of breast cancer patients. *J Cancer Res Clin Oncol* (2018) 144:1613–21. doi: 10.1007/s00432-018-2682-9

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 19 January 2024
DOI 10.3389/fonc.2023.1268617

OPEN ACCESS

EDITED BY
Xiaowei Qi,
Army Medical University, China

REVIEWED BY
Bilgin Kadri Aribas,
Bülent Ecevit University, Türkiye
Armando Pérez Torres,
National Autonomous University of Mexico, Mexico

*CORRESPONDENCE
Li Chun
1306839492@qq.com

RECEIVED 28 July 2023
ACCEPTED 28 December 2023
PUBLISHED 19 January 2024

CITATION
Chun L, Zeng Z, Guo Q and He Y (2024) Case report: The first case of concurrent breast myeloid sarcoma and borderline phyllodes tumor with malignant features.
Front. Oncol. 13:1268617.
doi: 10.3389/fonc.2023.1268617

Case report: The first case of concurrent breast myeloid sarcoma and borderline phyllodes tumor with malignant features

Li Chun[1*], Zhen Zeng[2], Qianyu Guo[3,4] and Yangjun He[5]

[1]Department of Integrative Oncology (Rehabilitation Technology), Sichuan Nursing Vocational College, Chengdu, China, [2]Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, China, [3]Department of Urology, Feinberg School of Medicine, Northwestern University, Chicago, IL, United States, [4]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, United States, [5]Department of Breast Surgery, Chengdu Seventh People's Hospital, Chengdu, China

Background: Myeloid sarcoma (MS) is a rare hematological malignancy characterized by the formation of a solid mass of myeloblasts outside the bone marrow, such as in the lymph nodes, skin, or bone. MS may arise *de novo* or concurrently with acute myeloid leukemia (AML), myeloproliferative neoplasm (MPN), or myelodysplastic syndrome (MDS). MS accounts for less than 1% of extramedullary acute myeloid leukemia cases. Phyllodes tumors (PTs) are a rare fibroepithelial breast tumor that can be benign, malignant, or borderline, and account for less than 1% of all breast cancers.

Case presentation: We present a unique case of a 50-year-old woman with both breast MS and borderline PT with malignant features, which presented a diagnostic challenge. The patient initially presented with a mass in her right breast, and the initial fine-needle biopsy revealed the presence of immature myeloperoxidase $(MPO)^+$ myeloid cells consistent with MS. Subsequent pathological analysis of tumor tissues after neoadjuvant radiotherapy and chemotherapy showed a borderline PT with malignant features. Following excision of the tumor, the patient experienced a local recurrence, which was also surgically removed. At 8 months post-surgery, the patient remains free of recurrence under close follow-up.

Conclusion: This case highlights the importance of considering the possibility of concurrent malignancies in the differential diagnosis of complex breast masses and underscores the challenges involved in diagnosing and managing such cases. Additionally, we also emphasize the value of neoadjuvant radiotherapy and chemotherapy in MS.

KEYWORDS

breast cancer, myeloid sarcoma (MS), borderline phyllodes tumor with malignant features, neoadjuvant radiotherapy, neoadjuvant chemotherapy

1 Introduction

Myeloid sarcoma (MS) is a rare and distinct form of hematological malignancy that is characterized by the extramedullary accumulation of myeloblasts. Also known as chloroma, granulocytic sarcoma, or extramedullary myeloid tumor, MS can manifest in various organs, including the skin, lymph nodes, soft tissues, liver, spleen, and bones. There are three types of MS based on the type of cell and degree of differentiation involved: granulocytic sarcoma (GS) type, primitive mononuclear cell sarcoma type, and triple hematopoietic cell myeloid sarcoma type. MS may arise *de novo* or concurrently with AML, myeloproliferative neoplasm (MPN), or myelodysplastic syndrome (MDS), and can even be the initial presentation of AML or a manifestation of AML recurrence (1). The diagnosis of MS can be clinically challenging. Breast phyllodes tumors are a rare type of breast tumor, comprising only 0.3-1.0% of all breast tumors (2), and are classified into benign, borderline, and malignant subtypes. In this case report, we present a unique case of a female patient diagnosed with concurrent breast MS and borderline phyllodes tumor (borderline PT) with malignant features, which, to our knowledge, has not been previously reported.

2 Case presentation

A 50-year-old woman presented to the 7th People's Hospital of Chengdu with an erythematous breast mass that was painful and had central necrosis in the upper outer quadrant of her right breast (Figures 1A–D). Physical examination revealed an immobile mass in the upper outer quadrant of her right breast, with an orange-peel appearance, but no signs of nipple retraction were noted. The patient had a medical history of well-controlled hypertension, which was being treated with felodipine and enalapril. She denied any history of smoking, alcohol or substance abuse, and had no family history of cancer. Her physical examination, aside from the breast mass, was unremarkable.

Breast ultrasound revealed an 8.8cm mass with mixed solid echogenic and cystic anechoic components. (Figure 1E). The contrast-enhanced CT scan showed an 11.7×8.9cm mass occupying a substantial portion of the right breast, accompanied by right axillary lymphadenopathy (Figure 1F). An ultrasound-guided fine needle biopsy revealed the presence of immature myeloid cells (Figures 1G–I). Immunohistochemistry (IHC) analysis demonstrated strong expression of CD68KP1 (Figure 2A), CD45 (Figure 2B), CD33, Cyclin D1 and CD4, with weak positivity for myeloperoxidase (MPO), and a high level of Ki67 expression (80%). The cells were negative for CD34 (Figure 2C), CD3 (Figure 2D), CD20 (Figure 2E), CD79a (Figure 2F), CD14, CD117, and terminal deoxynucleotidyl transferase (TdT). A bone marrow biopsy was performed, and there was no evidence of systemic hematological malignancies such as AML, MPD, or MDS. Therefore, the patient was diagnosed with isolated myeloid sarcoma (MS).

The patient underwent neoadjuvant radiotherapy and chemotherapy, which included cytarabine and daunorubicin. After undergoing two cycles of chemotherapy, which included cytarabine at a dose of 100 mg/m2 administered over days 1-7, and daunorubicin at a dose of 60 mg/m2 over days 1-3, a follow-up CT scan revealed a significant reduction in the size of the breast mass (4cm×3cm) and a ground-glass appearance in the upper lobes of both lungs (Figures 3A–D). The patient presented with newly onset of dry cough and dyspnea. Empirical treatment with cefoperazone-tazobactam was initiated, but did not result in significant improvement of the patient's condition. A fungal infection was suspected, and she was switched to voriconazole, which resolved her respiratory symptoms within 2 weeks. However, the patient declined subsequent cycles of chemotherapy due to adverse effects. Three months after completing chemotherapy, the patient underwent a right mastectomy. Histological analysis of the surgical specimen revealed the presence of both epithelial and mesenchymal components. Benign epithelial components are illustrated in Figure 3E. The spindle-shaped hyperproliferative fibroblasts, representative of the malignant components, are shown in Figure 3F. The cartilage region is considered to be heterogenous mesenchyme, which is associated with tumor invasion. (Figure 3G). Notably, these malignant interstitial cells are characterized by the permeative border (Figure 3H), heteromorphism and abundant mitosis, with a visible nuclear division rate of 11/10HPF (Figures 3I, J). In summary, the pathological analysis aligns with a diagnosis of borderline phyllodes tumor with malignant features. The IHC analysis demonstrated strong expression of ER (Figure 4A), PR, SMA and SATB2, with a moderate level of Ki67 expression (25-30%) (Figure 4B) and weak positivity for CD117 (Figure 4C) and Blc2 (Figure 4D). The tissues were negative for P63 (Figure 4E), CD34 (Figure 4F). CD10 (Figure 4G), desmin, cytokeratin-5/6 (Figure 4H).

The patient developed a local recurrence at the site of the surgical incision 4 months after the initial mastectomy and underwent another surgical excision to remove the new lesion. The subsequent pathological analysis confirmed the presence of borderline PT with malignant features. The patient has been closely monitored every 2 months since the second surgery and has remained disease-free for the past 8 months.

3 Discussion

MSs are rare tumors of immature myeloid cells that can occur outside the bone marrow, including the skin, lymph nodes, testes, intestines, bones, and central nervous system (3–7). Although MSs often develop concurrently with or after the diagnosis of myeloid malignancies (1, 8–10), cases of primary MS without any blood or bone marrow involvement (11–13), like our case, have also been reported. The rarity of MS can make diagnosing it challenging, leading to a higher incidence of misdiagnosis. Differential diagnoses of MS include various hematological malignancies such as

Abbreviations: MS, Myeloid Sarcoma; AML, Acute myeloid leukemia; MPN, Myeloproliferative neoplasm; MDS, Myelodysplastic syndrome; PTs, Phyllodes tumors; IHC, Immunohistochemistry.

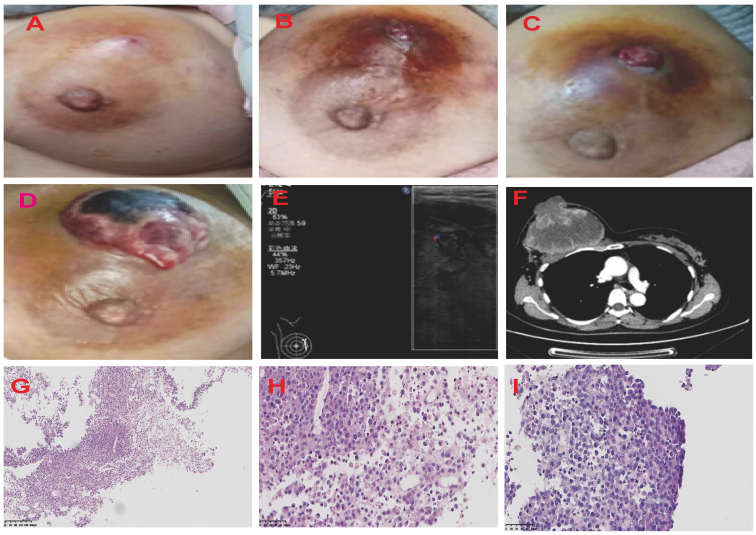


FIGURE 1
Graphic Representation of Breast Lesion Progression Over Time. The series of four images chronicle the evolution of the right breast lesion from March to April 2021. **(A)** The image of the breast lesion on [5/3/2021]. The patient initially presented with marked breast swelling and tenderness. **(B)** The image of the breast lesion on [5/4/2021]. **(C)** The image of the breast lesion on [23/4/2021]. **(D)** The image of the breast lesion on [25/4/2021]. The breast lesion has evolved into a mass with profound erythema and sinus tract. The ultrasound and CT images of the patient's right breast **(E, F)**. The H&E staining of MS. **(G)** The description of myeloblasts and lymphoid H&Ex100. **(H)** The description of myeloblasts and lymphoid H&Ex400. **(I)** The description of tumor cells H&Ex400. H&E, hematoxylin and eosin.

anaplastic large-cell lymphoma and diffuse large B-cell lymphoma, as well as solid tumors such as breast carcinoma and melanoma (5, 13). Thus, a precise diagnosis of MS requires extensive immunophenotyping to confirm the myeloid origin of the malignancy. In our case, we observed the typical profile of myeloid malignant cells in the initial biopsy, which showed immunoreactivity to markers such as MPO (5) and CD33. Due to the rarity of myeloid sarcoma, there is currently no established consensus on the optimal treatment approach. Some previous studies have suggested that a combination of radiotherapy and chemotherapy may be beneficial for MS patients (14, 15), which is similar to our case. However, there is conflicting evidence, as another study reported no survival benefit in patients with isolated MS who were treated with radiation and chemotherapy (4).

PTs are considered an uncommon fibroepithelial neoplasms of the breast (16), which are classified into three subtypes: benign, borderline and malignant. The benign PTs are more common, An article analyzing 170 cases found that benign, borderline and malignant PTs incidence are 54.1%, 11.2% and 34.7% respectively (17). PTs pose diagnostic challenges, as they can be difficult to distinguish from fibroadenoma (18, 19). Histologically, PTs are characterized by a leaflike architecture resulting from an enhanced intracanalicular growth pattern, cleft-like spaces lined by epithelium, and hypercellular stroma. Malignant PT is

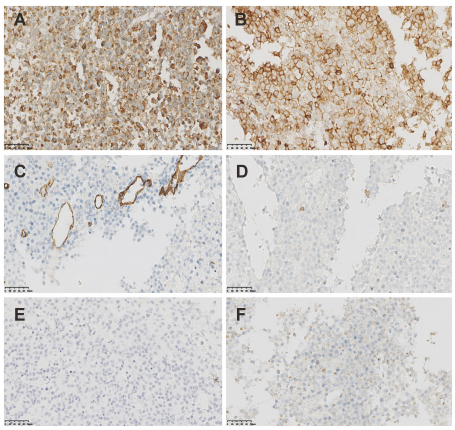


FIGURE 2
The IHC staining of MS. **(A)** Strong positivity of CD68KP1 (×200). **(B)** Strong positivity of CD45(×200). **(C)** Negative staining of CD34(×200). **(D)** Negative staining of CD3(×200). **(E)** Negative staining of CD20(×200). **(F)** Negative staining of CD79a(×200).

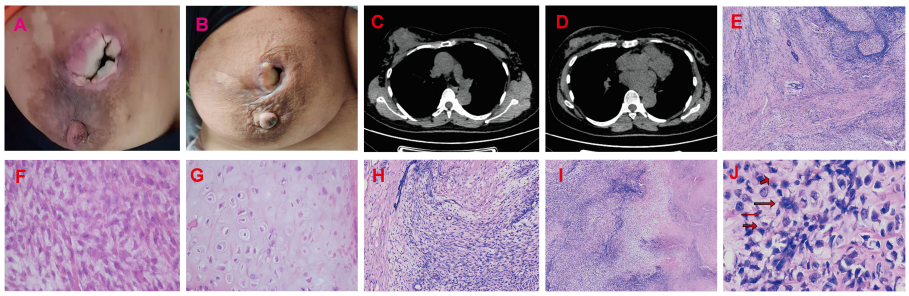


FIGURE 3
Radiotherapy and chemotherapy significantly reduced the size of the breast mass. **(A, B)** Graphic representation of breast lesion after radiotherapy and chemotherapy. **(C, D)** The CT images of the patient's right breast after radiotherapy and chemotherapy. The H&E staining of Borderline Phyllodes Tumor with malignant features. **(E)** The benign epithelial components H&E×4. **(F)** The staining depicting of the spindle cell region H&E×400. **(G)** The staining illustrating the cartilage region H&E×400. **(H)** The permeative border of the borderline PT with malignant features H&E×100. **(I)** The interstitial overgrowth of borderline PT with malignant features H&E×40. **(J)** The nuclear division and pathological nuclear division H&E×400. H&E = hematoxylin and eosin.

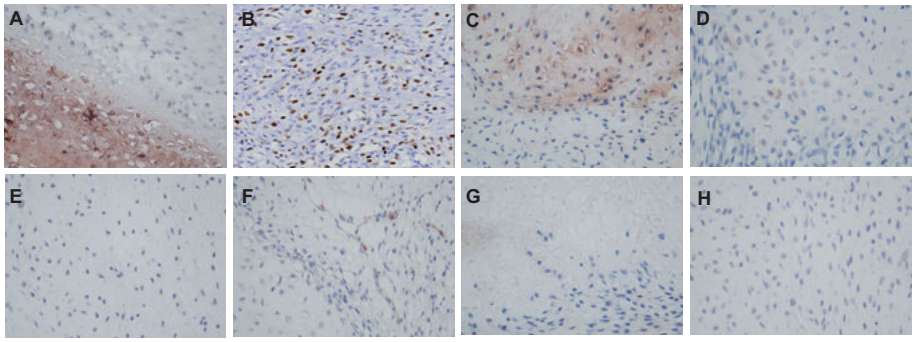


FIGURE 4
The IHC staining of Borderline Phyllodes Tumor with malignant features. **(A)** Strong positivity of ER×400. **(B)** A moderate level of Ki67 expression×200. **(C)** Weakly positivity of CD117 ×400. **(D)** Weakly positivity of P63 ×400. **(E)** Weakly positivity of Bcl2×400. **(F)** Negative staining of CD34×400. **(G)** Negative staining of CD10×400. **(H)** Negative staining of CK5/6 ×400. IHC, Immunohistochemistry.

characterized by marked stromal cellularity and nuclear pleomorphism, stromal overgrowth, and more than 10 mitoses per 10 HPF. The presence of heterologous sarcomatous elements (liposarcoma, chondrosarcoma, and osteosarcoma) alone qualifies a PT as malignant (20). In our case, the histological analysis revealed spindle cell and cartilage regions, with notable heteromorphism and mitosis in the spindle cell area. Additionally, there are reports indicating that the stromal cells of phyllodes tumors can express p63, cytokeratins and CD117 (21–23). Notably, CD117 expression in the stroma has been linked to predicting disease recurrence. In our patient, there were observed expressions of ER, PR, CD117, SMA, and SATB2, aligning with the previously documented trend as she experienced local recurrence.

To our knowledge, this is the first reported case of co-existing breast PT and MS. The co-occurrence posed further diagnostic challenges but also provides insights into the management of isolated MS. There is no definitive consensus regarding the optimal treatment and follow-up of primary extramedullary MS. Our patient benefited from neoadjuvant radiotherapy and chemotherapy, which led to a significant reduction in the breast mass and subsequent surgical excision with a clean margin. To our surprise, the repeated analysis of the surgical specimen revealed borderline PT with malignant features, without evidence of co-existing metastatic disease. We believe that the neoadjuvant therapies led to MS remission. This case highlights the importance of a comprehensive diagnostic approach and individualized treatment plan for patients with rare co-existing malignancies, such as PT and MS.

4 Conclusion

To our knowledge, this marks the inaugural report of a simultaneous occurrence of MS and PT in the breast. A prior study unveiled the coexistence of PT with anaplastic ependymoma (19), emphasizing the intricate nature of PT diagnosis when intertwined with other malignancies. Our case emphasizes the significance of adopting a comprehensive diagnostic approach to ensure precision, particularly in complex cases. The effective management of our patient's condition with neoadjuvant radiotherapy and chemotherapy additionally underscores the potential advantages of this treatment strategy for individuals with myeloid sarcoma.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LC: Resources, Writing – original draft. ZZ: Writing – review & editing, Methodology. QG: Writing – review & editing, Methodology. YH: Data curation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors would like to express their sincere gratitude to the patient and their family for their invaluable support, cooperation, and willingness to participate in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* (2016) 127(20):2391–405. doi: 10.1182/blood-2016-03-643544

2. Guerrero MA, Ballard BR, Grau AM. Malignant phyllodes tumor of the breast: review of the literature and case report of stromal overgrowth. *Surg Oncol* (2003) 12 (1):27–37. doi: 10.1016/s0960-7404(03)00005-7

3. Goyal G, Bartley AC, Patnaik MM, Litzow MR, Al-Kali A, Go RS. Clinical features and outcomes of extramedullary myeloid sarcoma in the United States: analysis using a national data set. *Blood Cancer J* (2017) 7(8):e592. doi: 10.1038/bcj.2017.79

4. Lontos K, Yabes JG, Farah RJ, Boyiadzis M. Impact of upfront chemotherapy on overall survival in isolated myeloid sarcoma. *Leukemia* (2021) 35(4):1193–6. doi: 10.1038/s41375-020-01017-z

5. Pileri SA, Ascani S, Cox MC, Campidelli C, Bacci F, Piccioli M, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia* (2007) 21(2):340–50. doi: 10.1038/sj.leu.2404491

6. Valbuen JR, Joan H, Admirand M, Gabriela Gualco ML, Jeffrey Medeiros M. Myeloid sarcoma involving the breast. *Arch Pathol Lab Med* (2005) 129:32–8. doi: 10.5858/2005-129-32-MSITB

7. Zhao H, Dong Z, Wan D, Cao W, Xing H, Liu Z, et al. Clinical characteristics, treatment, and prognosis of 118 cases of myeloid sarcoma. *Sci Rep* (2022) 12(1):6752. doi: 10.1038/s41598-022-10831-7

8. Miyazato H, Sono H, Naiki Y, Miyatake J, Nozaki Y, Yamaguchi T, et al. Detection of myeloperoxidase gene expression by in *situ* hybridization in a case of granulocytic sarcoma associated with AML-M0. *Leukemia* (2001) 15(11):1797–9. doi: 10.1038/sj.leu.2402270

9. Marra A, Martino G. Placental myeloid sarcoma. *Blood* (2020) 135(16):1410. doi: 10.1182/blood.2020004975

10. Wilson CS, Medeiros LJ. Extramedullary manifestations of myeloid neoplasms. *Am J Clin Pathol* (2015) 144(2):219–39. doi: 10.1309/AJCPO58YWIBUBESX

11. Qian X, Gigantelli JW, Abromowitch M, Morgan LA, Suh DW. Myeloid sarcoma in the orbit. *J Pediatr Ophthalmol Strabismus* (2016) 53:e64–8. doi: 10.3928/01913913-20161102-01

12. Artinyan A, Guzman E, Maghami E, Al-Sayed M, D'Apuzzo M, Wagman L, et al. Metastatic parathyroid carcinoma to the liver treated with radiofrequency ablation and transcatheter arterial embolization. *J Clin Oncol* (2008) 26(24):4039–41. doi: 10.1200/JCO.2007.15.9038

13. Menasce LP, Banerjee SS, Beckett E, Harris M. Extra-medullary myeloid tumor (granulocytic sarcoma) is often misdiagnosed: a study of 26 cases. *Histopathology* (1999) 34(5):391–8. doi: 10.1038/sj.leu.2404491

14. Zuo X, Wang Y, Zhou Y, Luo L, Liu M. Primary granulocytic sarcoma of cervix (PGSC): review and analysis of 13 cases. *Blood* (2014) 124(21):5271–1. doi: 10.1182/blood.V124.21.5271.5271

15. Frietsch JJ, Hunstig F, Wittke C, Junghanss C, Franiel T, Scholl S, et al. Extra-medullary recurrence of myeloid leukemia as myeloid sarcoma after allogeneic stem cell transplantation: impact of conditioning intensity. *Bone Marrow Transplant* (2021) 56 (1):101–9. doi: 10.1038/s41409-020-0984-4

16. Rayzah M. Phyllodes tumors of the breast: A literature review. *Cureus* (2020) 12 (9):e10288. doi: 10.7759/cureus.10288

17. Reinfuss M, Mitus J, Duda K, Stelmach A, Rys J, Smolak K. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. *Cancer* (1996) 77(5):910–6. doi: 10.1002/(sici)1097-0142(19960301)77:5<910::aid-cncr16>3.0.co;2-6

18. Kazakov DV, Spagnolo DV, Stewart CJ, Thompson J, Agaimy A, Magro G, et al. Fibroadenoma and phyllodes tumors of anogenital mammary-like glands: A series of 13 neoplasms in 12 cases, including mammary-type juvenile fibroadenoma, fibroadenoma with lactation changes, and neurofibromatosis-associated pseudoangiomatous stromal hyperplasia with multinucleated giant cells. *Am J Surg Pathol* (2010) 34:95–103. doi: 10.1097/PAS.0b013e3181c6e5c5

19. Aribas BK, Sahin G, Uluoglu O, Bozgul M, Barit G, Torun E. Subcutaneous sacrococcygeal anaplastic ependymoma with Malignant cystosarcoma phylloides of the breast. *J Neurological Sci (Turkish)* (2012) 29:402–9.

20. Zhang Y, Kleer CG. Phyllodes tumor of the breast: histopathologic features, differential diagnosis, and molecular/genetic updates. *Arch Pathol Lab Med* (2016) 140 (7):665–71. doi: 10.5858/arpa.2016-0042-RA

21. Cimino-Mathews A, Sharma R, Illei PB, Vang R, Argani P. A subset of Malignant phyllodes tumors express p63 and p40: a diagnostic pitfall in breast core needle biopsies. *Am J Surg Pathol* (2014) 38(12):1689–96. doi: 10.1097/PAS.0000000000000301

22. Chia Y, Thike AA, Cheok PY, Yong-Zheng Chong L, Man-Kit Tse G, Tan PH. Stromal keratin expression in phyllodes tumours of the breast: a comparison with other spindle cell breast lesions. *J Clin Pathol* (2012) 65(4):339–47. doi: 10.1136/jclinpath-2011-200377

23. Tan PH, Jayabaskar T, Yip G, Tan Y, Hilmy M, Selvarajan S, et al. p53 and c-kit (CD117) protein expression as prognostic indicators in breast phyllodes tumors: a tissue microarray study. *Mod Pathol* (2005) 18(12):1527–34. doi: 10.1038/modpathol.3800488

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 08 March 2024
DOI 10.3389/fonc.2024.1354152

OPEN ACCESS

EDITED BY
Abhishek Mahajan,
The Clatterbridge Cancer Centre,
United Kingdom

REVIEWED BY
Fenglin Dong,
The First Affiliated Hospital of Soochow University, China
Mamatha Chivukula,
Sutter Health, United States

*CORRESPONDENCE
Rong Ge
gerong123@sina.com

RECEIVED 12 December 2023
ACCEPTED 19 February 2024
PUBLISHED 08 March 2024

CITATION
Wang L, Zhao W, Zhou J and Ge R (2024) Case report: Fibroadenomas associated with atypical ductal hyperplasia and infiltrating epitheliosis mimicking invasive carcinoma. *Front. Oncol.* 14:1354152. doi: 10.3389/fonc.2024.1354152

Case report: Fibroadenomas associated with atypical ductal hyperplasia and infiltrating epitheliosis mimicking invasive carcinoma

Li Wang, Wei Zhao, Jue Zhou and Rong Ge*

Department of Pathology, Ningbo Clinical Pathology Diagnosis Center, Ningbo, China

Infiltrating epitheliosis (IE) is an uncommon type of complex sclerosing lesion in the breast. This condition is characterized by the infiltration of ducts into a scleroelastotic stroma, along with the presence of cells that display architectural and cytological patterns similar to those observed in usual ductal hyperplasia. We herein report a case of a 24-year-old woman who presented with bilateral breast nodules, which were initially identified as multiple fibroadenomas based on ultrasound findings. The patient underwent Mammotome system and regional mastectomy procedures, and subsequent pathological analysis confirmed the presence of multiple fibroadenomas with atypical ductal hyperplasia and infiltrating epitheliosis. This case discusses the challenges faced in diagnosing malignancy in a patient with multiple fibroadenomas accompanied by atypical ductal hyperplasia and infiltrating epitheliosis.

KEYWORDS

breast, infiltrating epitheliosis, fibroadenoma, carcinoma, MEC

1 Introduction

Fibroadenoma is a biphasic tumor composed of epithelial and stromal components, and it is the most common type of benign breast tumor that often presents in young women. However, in approximately half of the cases, fibroadenoma exhibits proliferative changes such as sclerosing adenosis, papillary apocrine metaplasia, and epithelial calcifications, which classify it as a complex fibroadenoma and a long-term risk factor for breast cancer (1).

Infiltrating epitheliosis (IE) is a rare complex sclerosing lesion of the breast, characterized by infiltrating ducts immersed in a scleroelastotic stroma and filled with cells exhibiting architectural and cytological patterns reminiscent of usual ductal hyperplasia (2). Due to limited experience with this phenomenon, we present an

unusual case of fibroadenomas with atypical ductal hyperplasia and IE and analyze the challenges in diagnosis to minimize misdiagnosis and mistreatment.

2 Case presentation

A 24-year-old woman presented with complaints of bilateral mammary gland nodules that had been present for 1 month. She had no family history of breast cancer or ovarian lesions. Conventional laboratory investigations, including complete blood cell count, biochemical analysis, and serum levels of carcinoembryonic antigen, did not reveal any abnormalities.

Ultrasound (US) examination revealed multiple hypoechoic masses with clear borders and smooth margins (as shown in Figure 1). The masses measured 1.1cm×0.5cm, 1.6cm×0.5cm, 1.3cm×0.6cm, 1.9cm×0.8cm, 1.8cm×0.8cm, 1.7cm×1.2cm, 2.2cm×1.3cm, and 2.2cm×0.8cm in the left breast at the positions of 2 o'clock, 6 o'clock, 9 o'clock, and 10 o'clock, and 1.4cm×0.7cm, 1.2cm×0.5cm, 2.7cm×1.3cm, 1.6cm×0.8cm, and 2.1cm×0.9cm in the right breast at the positions of 12 o'clock, 3 o'clock, 4 o'clock, 6 o'clock, and 11 o'clock. Color Doppler flow imaging (CDFI) did not show any obvious blood flow signals. Additionally, there were no palpable bilateral axillary lymph nodes.

This patient is preparing for pregnancy and requests surgical removal of the breast mass in preparation for breastfeeding after childbirth. She underwent an excisional biopsy, and the frozen section analysis revealed characteristics consistent with fibroadenoma. The breast regional mastectomy was performed using the Mammotome system and regional mastectomy procedures. Routine sections of the tissue samples showed that almost all of the nodules were conventional fibroadenomas, except for one nodule in the right breast that exhibited atypical ductal hyperplasia (as shown in Figure 2A).

In the surrounding stroma, there were several scattered tubules that were partially absent in the myoepithelium (as shown in Figure 2B). Immunohistochemical staining for P63, SMA, CK5/6, and CK14 (as shown in Figure 3A) and Calponin (as shown in Figure 3B) confirmed this finding. The estrogen receptor (ER) was 2+ (80% positive), progesterone receptor (PR) was 3+ (90% positive), and human epidermal receptor-2 (HER-2) showed a membranous reaction of 0+. S100 protein staining was negative (as shown in Figure 3C). The Ki-67 index, which indicates the proliferative activity of cells, was <5%. Collagen IV evidenced a continuous layer of basal lamina surrounding the glands (as shown in Figure 3D). Therefore, the final diagnosis is multiple fibroadenomas with atypical ductal hyperplasia and IE.

3 Discussion

IE is a non-malignant breast lesion characterized by an infiltrative growth pattern and focal absence of myoepithelial cells (MECs) (3). It was initially described by John Azzopardi (4) in 1979 and referred to as "sclerosing adenosis with pseudo-infiltration" (5) or "sclerosing papillary proliferation" (6). Although its classification

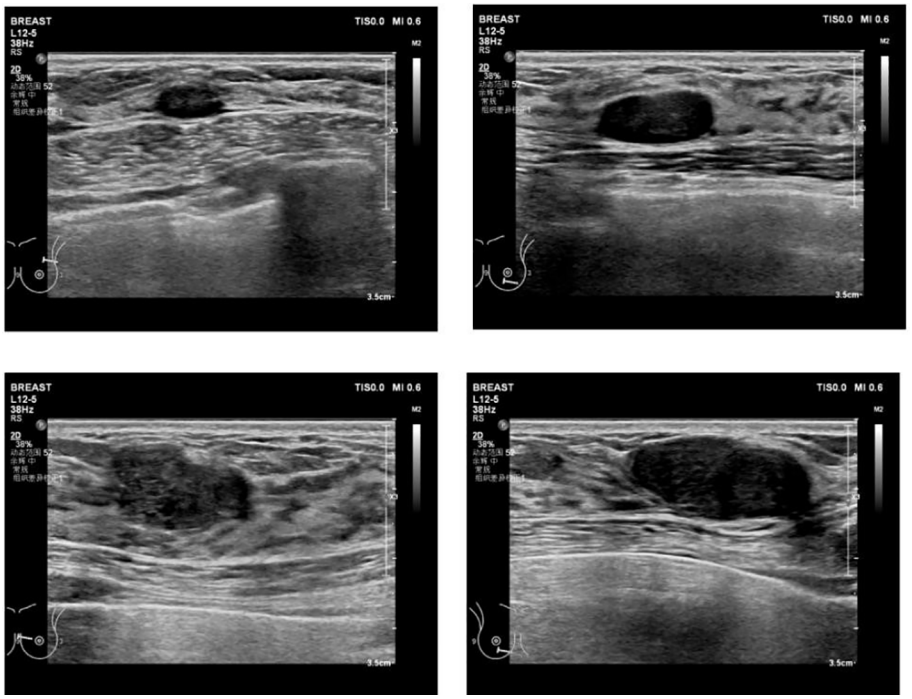


FIGURE 1
Ultrasound(US): bilateral mammary glands were irregular and flaky, local tissues were thickening, and there is structural disorder. There are several regular-shaped and well-circumscribed hypoechoic masses with envelope in her both breasts. CDFI: there was no obvious blood flow signal. Bilateral axillary lymph nodes were not palpable.

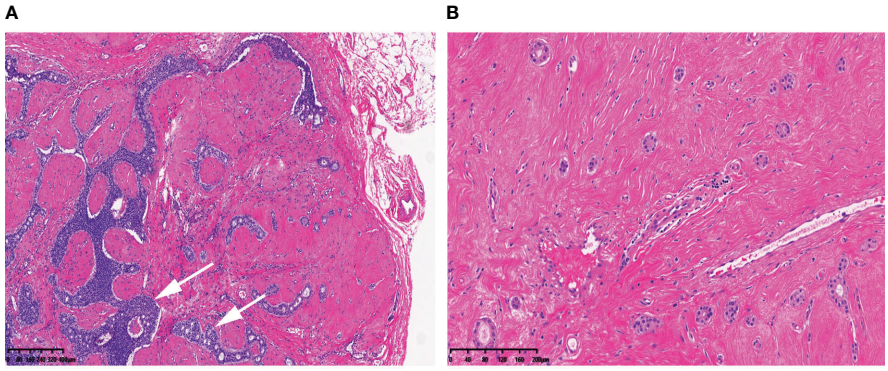


FIGURE 2
Morphological features: **(A)** one of the fibroadenomas in the right breast with intra-ductal epithelial hyperplasia, partly monoclonal sieve-like hyperplasia (arrows). **(B)** Several scattered tubules are observed in the surrounding stroma. Scale bars: **(A)** 80 μm; **(B)** 40 μm.

remains controversial, most pathologists currently classify IE within the spectrum of radial scar or complex sclerosing lesion (RS/CSL) (2).

Recent studies have suggested that IE may be neoplastic rather than hyperplastic and that the PI3K pathway is involved in its pathogenesis (2). The PI3K pathway plays crucial roles in cell survival, proliferation, and migration, and alterations in this pathway have been observed in 25%–50% of breast carcinomas (7), particularly low-grade and estrogen-receptor-positive carcinomas (8). Katie et al. reported that the frequency of PIK3CA mutations in RS was notably higher than the 25%–30% mutation frequency of invasive breast cancer (9). It has been indicated by Carey et al. that IE lesions may serve as a substrate from which ductal carcinoma *in situ* and low-grade adenosquamous carcinoma can originate. Furthermore, a subset of these lesions may have the potential to progress to invasive cancer (2).

In this case, the ultrasound images of fibroadenoma with IE cannot be distinguished from the other common fibroadenomas because all the nodules of preoperative ultrasound imaging presented with regular-shaped and well-circumscribed hypoechoic masses. Regrettably, the surgically removed nodules are not marked accordingly so that the differences of ultrasound imaging between it and other nodules could not be retrospectively analyzed based on pathological diagnosis.

Pathologically, IE can be easily mistaken for invasive carcinoma due to its infiltrative growth pattern with focal absence of

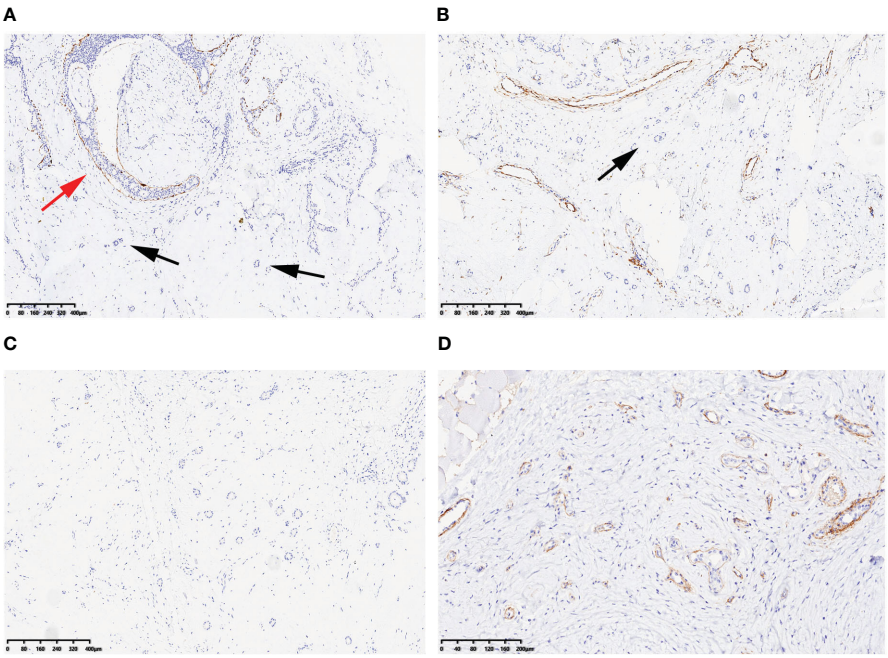


FIGURE 3
Immunohistochemical findings: CK14 **(A)** and Calponin **(B)** were preservative at the periphery of atypical ductal hyperplasia (red arrow), but were partly absent at scattered tubules in the surrounding stroma (black arrows). S100 protein was negative **(C)**. Collagen IV evidenced a continuous layer of basal lamina surrounding the glands **(D)**. Scale bars: **(A–C)** 80 μm; **(D)** 40 μm.

myoepithelial cells (MECs). The histological characteristics of IE, as described by Eusebi and Millis (10), include the following: (a) the bulk of the lesion is composed of florid epitheliosis, often with a focal squamoid appearance; (b) scleroelastotic stromal changes are seen throughout the lesion, adjacent to epithelial foci, rather than confined to a central scleroelastotic nidus as observed in radial scars or complex sclerosing lesions; and (c) the frequent presence of a desmoplastic stromal reaction and keloid-like fibrous bands. Additionally, the involved ducts often exhibit irregular or jagged edges, and the proliferating epithelium often appears to "flow out" into the adjacent stroma (3, 11). Failure to recognize these exceptions such as IE and microglandular adenosis (MGA) can potentially result in incorrect classification as an invasive carcinoma, particularly tubular carcinoma (10–12) (Table 1).

Invasion is typically defined by the absence or breach of the basement membrane (BM) barrier between malignant epithelial cells and the surrounding stroma (3). However, these benign lesions that lack myoepithelial cells (MECs) exhibit infiltrating single-layer glands surrounded by a well-developed layer of BM (3). Due to the simplicity of immunohistochemical identification of the MEC layer, it is often used as a surrogate marker for invasion through the BM. It is important to note that MECs are predominantly lost at the periphery of IE, with frequent preservation at the epithelial–stroma interface in the center (3). In other words, MECs may be present in the proximal part of a duct but absent in the distal part.

On the other hand, MGA glands are lined by a single layer of cuboidal epithelial cells surrounded by a basal lamina, without any evidence of interposed MECs (13, 14). However, the lumens of this lesion often contain an amorphous eosinophilic material (11). Cells of MGA typically exhibit positive staining for low-weight keratins and S100 protein, but they are negative for estrogen receptor, progesterone receptor, and HER-2 (15). Therefore, the absence of MECs is not used as a criterion for diagnosing invasion because it can be observed in both benign and malignant lesions.

The management of infiltrative epitheliosis (IE) should follow the same approach as that of other complex sclerosing lesions so far (2).

TABLE 1 Differences and similarities of differential diagnosis.

	IE	MGA	TC
Glandular distribution	Irregular	Random	Wild
Shape of glands	Jagged edges	Round	Irregular to angulated
Stroma	Desmoplastic	Hyline/fibrofatty	Desmoplastic
Luminal secretion	Absent	Amorphous eosinophilic material	Absent
1 cell layer	Yes	Yes	Variable
MEC IHC	Absent	Absent	Absent
BL (Coll IV, Laminin)	Present	Present	Absent
S100	Absent	Present	Absent

IE, infiltrative epitheliosis; MGA, microglandular adenosis; TC, tubular carcinoma; MEC, myoepithelial cell; IHC, immunohistochemistry; BL, basal lamina; Coll IV, collagen IV.

Additionally, careful monitoring is essential due to the risk of malignant transformation. Given the rarity of IE and the limited available data, further studies are necessary to understand its clinical behavior and to define the most appropriate surgical treatment.

In conclusion, infiltrative epitheliosis (IE) with an infiltrative growth pattern is a rare complex sclerosing lesion of the breast that can be mistaken for invasive carcinoma due to the absence of myoepithelial cells. Although IE is not routinely recognized in breast pathology practice at present, it does exist within the spectrum of breast lesions. Recognition of this rare lesion is important not only as an academic exercise but also for advancing our clinical understanding of IE, which may provide an ideal platform for studying the molecular mechanisms involved. Further studies are needed to better understand the clinical behavior of IE and to define appropriate management strategies for this rare breast lesion.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ningbo Clinical Pathology Diagnosis Center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LW: Writing – original draft. WZ: Data curation, Writing – review & editing. JZ: Writing – review & editing. RG: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Project of NINGBO Leading Medical & Health Discipline, Project Number: 2022-F30.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Mannello F, Tonti GAM. Benign breast diseases: classification, diagnosis, and management. *Oncologist.* (2006) 11:1132–4. doi: 10.1634/theoncologist.11-10-1132

2. Eberle CA, Piscuoglio S, Rakha EA, Ng CKY, Geyer FC, Edelweiss M, et al. Infiltrating epitheliosis of the breast: characterization of histological features, immunophenotype and genomic profile. *Histopathology*. (2016) 68:1030–9. doi: 10.1111/his.12897

3. Rakha EA, Miligy IM, Gorringe KL, Toss MS, Green AR, Fox SB, et al. Invasion in breast lesions: the role of the epithelial–stroma barrier. *Histopathology*. (2018) 72:1075–83. doi: 10.1111/his.13446

4. Azzopardi JG. *Overdiagnosis of Malignancy*. London, UK: W.B. Saunders Company, Ltd (1979).

5. McDivitt RW, Stewart RE, Berg JW. *Tumors of the breast*. Washington, DC: Armed Forces Institute of Pathology (1968).

6. Fenoglio C, Lattes R. Sclerosing papillary proliferations in the female breast. *A benign lesion often mistaken carcinoma. Cancer.* (1974) 33:691–700. doi: 10.1002/(ISSN)1097-0142

7. Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. *J Clin Oncol.* (2010) 28:1075–83. doi: 10.1200/JCO.2009.25.3641

8. Troxell ML, Levine J, Beadling C, Warrick A, Dunlap J, Presnell A, et al. High prevalence of PIK3CA/AKT pathway mutations in papillary neoplasms of the breast. *Modern Pathology.* (2010) 23:27–37. doi: 10.1038/modpathol.2009.142

9. Katie L, Wolters DA, Warrick A, Beadling C, Corless CL, Troxell ML. Frequent PIK3CA mutations in radial scars. *Diagn Mol Pathol.* (2013) 22:210–4. doi: 10.1097/PDM.0b013e318288b346

10. Eusebi V, Millis RR. Epitheliosis, infiltrating epitheliosis, and radial scar. *Semin Diagn Pathology.* (2010) 27:5–12. doi: 10.1053/j.semdp.2009.12.008

11. Foschini MP, Eusebi V. Microglandular adenosis of the breast: a deceptive and still mysterious benign lesion. *Hum Pathology.* (2018) 82:1–9. doi: 10.1016/j.humpath.2018.06.025

12. Yong Hannah Wen BW, Reis-Filho JS. Microglandular adenosis: a non-obligate precursor of triple-negative breast cancer? *Histol Histopathol.* (2013) 28:1099–108. doi: 10.14670/HH-28.1099

13. Chen W, Wang C, Zhang ZH, Zhang WM, Xu Y, Song GX. [Clinicopathologic features of mammary microglandular adenosis with carcinoma: a study of 5 cases]. *Zhonghua Bing Li Xue Za Zhi.* (2017) 46:530–5. doi: 10.3760/cma.j.issn.0529-5807.2017.08.003

14. Sandra J Shin PTS, Da Silva L, Jayanthan J, Reid L, Lakhani SR, Rosen PP. Molecular evidence for progression of microglandular adenosis (MGA) to invasive carcinoma. *Am J Surg Pathol.* (2009) 33:496–504. doi: 10.1097/PAS.0b013e31818af361

15. Kravtsov O, Jorns JM. Microglandular adenosis and associated invasive carcinoma. *Arch Pathol Lab Med.* (2019) 144:42–6. doi: 10.5858/arpa.2019-0049-RA

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 11 March 2024
DOI 10.3389/fonc.2024.1349073

OPEN ACCESS

EDITED BY
Nan Wang,
First Affiliated Hospital of Zhengzhou University, China

REVIEWED BY
Omar Hamdy,
Mansoura University, Egypt
Amit Sehrawat,
Rishikesh, India

*CORRESPONDENCE
Zhibin Tan
zhibint@gmail.com

RECEIVED 04 December 2023
ACCEPTED 16 February 2024
PUBLISHED 11 March 2024

CITATION
Tan Z and Tan SY (2024) Numb cheek syndrome in breast cancer: a case report. *Front. Oncol.* 14:1349073. doi: 10.3389/fonc.2024.1349073

Numb cheek syndrome in breast cancer: a case report

Zhibin Tan[1,2]* and Si Ying Tan[3,4,5]

[1]Department of Neurology, National Neuroscience Institute, Singapore, Singapore, [2]Neuroscience Academic Clinical Programme, Duke-NUS Medical School, Singapore, Singapore, [3]SingHealth Duke-NUS Breast Centre, SingHealth, Singapore, Singapore, [4]Department of Breast Surgery, Division of Surgery and Surgical Oncology, Singapore General Hospital, Singapore, Singapore, [5]Department of Breast Surgery, Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, Singapore, Singapore

Background: Numb cheek syndrome, a rare corollary of numb chin syndrome, is due to infra-orbital neuropathy. It can occur in association with an underlying malignancy, which can cause neuropathy by direct malignant nerve infiltration or via a paraneoplastic mechanism. Although numb cheek syndrome has been reported in association with a variety of cancers, it has previously not been reported in association with breast cancer. We report a case of left breast cancer presenting with left numb cheek syndrome.

Case presentation: A 65-year-old woman presented to the Neurology clinic with a 7-month history of left cheek numbness and occasional cheek tenderness. Examination revealed slightly diminished pin-prick sensation in the left cheek and a vaguely palpable left breast lump. A magnetic resonance imaging scan of the brain showed abnormal enhancement of the left maxillary nerve at the foramen rotundum, but cerebrospinal fluid analysis was normal. Mammography, ultrasound scans, and core biopsy of the left breast confirmed the diagnosis of invasive left breast carcinoma (estrogen and progesterone receptor negative, c-erb-B2 equivocal, fluorescence *in-situ* hybridization negative). There was no evidence of distant metastases on computed tomography and bone scintigraphy scans. The patient underwent neoadjuvant chemotherapy (4 cycles of doxorubicin and cyclophosphamide, followed by 4 cycles of paclitaxel and carboplatin), and left breast wide excision and sentinel lymph node biopsy, and a repeat magnetic resonance imaging scan performed 2 months after surgical resection showed resolution of the left maxillary nerve enhancement. The patient's left numb cheek symptoms improved over a course of 5 months after cancer resection but did not completely resolve.

Conclusions: Our case represents the first reported left numb cheek syndrome in association with breast cancer, due to maxillary neuropathy without any discrete mass or compressive cause. To avoid delays in diagnosing malignancy, physicians and surgeons should be aware that numb cheek syndrome can occur in association with an underlying malignancy, and that breast cancer should be counted amongst the possibilities.

KEYWORDS

breast cancer, malignancy, numb cheek, maxillary, trigeminal, neuropathy

1 Introduction

Numb chin syndrome, a manifestation of mental neuropathy, can be associated with a variety of benign causes, but it can also uncommonly be a presentation of malignant disease (1). Numb cheek syndrome is an even rarer corollary phenomenon, caused by infra-orbital or maxillary neuropathy, which can also be associated with malignancy (2). While numb chin syndrome has been well described in association with breast cancer (3), numb cheek syndrome has not.

Herein, we present a case of left breast cancer presenting with left numb cheek syndrome.

2 Case presentation

A 65-year-old woman with a past medical history of hyperlipidemia and benign hyperplastic colonic polyps presented to the Neurology specialist outpatient clinic for a 7-month history of left cheek numbness, having been referred by her General Practitioner. Her numbness was a negative sensory symptom, which she described as a sensation of cheek swelling even though it appeared normal in the mirror, accompanied by diminished sensation to touch. There was also occasional tenderness on palpation of her left cheek. There were otherwise no symptoms over her left forehead, left mandible, or any part of the right face. The patient denied having any constitutional symptoms, but she had a family history of breast cancer, with her sister having been diagnosed with left breast invasive ductal carcinoma (estrogen and progesterone receptor positive, c-erb-B2 negative) at the age of 44-years-old. The patient was not taking any medications prior to presentation.

On examination, pin-prick sensation was 20% diminished over the left cheek compared to the right cheek. The area of numbness spanned the skin over the left maxilla, left lower eyelid, and left philtrum. The rest of the neurological examination, including examination of the other cranial nerves and of the long tracts, was normal. No asymmetry of motor power in trigeminal nerve-innervated muscles (pterygoids and masseter) was detected. Attention was paid to the skin and buccal mucosa overlying the area of numbness, but no lesions were seen.

As the symptoms were mild and non-disabling, no medications were prescribed at first presentation. A magnetic resonance imaging (MRI) scan of the brain and cranial nerves was performed approximately 1 year from onset of symptoms (5 months from presentation), revealing a non-compressive, T2-hyperintense, T1 isotense, gadolinium-enhancing lesion of the left maxillary nerve in the foramen rotundum (Figure 1). The rest of the brain parenchyma was unremarkable.

Blood tests, including a panel of onconeural antibodies, were unremarkable (Table 1). A lumbar puncture was performed 13 months from onset, showing a normal opening pressure of 16.5cmH_2O. Cerebrospinal fluid (CSF) analysis showed normal CSF cell counts (CSF red blood cell count 0/μL, CSF white blood cell count 1/μL), normal CSF protein level (0.29g/L), and a normal CSF-to-serum glucose ratio of 0.6 (CSF glucose 3.5mmol/L, paired serum glucose 5.6mmol/L). A panel of CSF microbiological and cytometric tests were unyielding (Table 1). CSF cytology did not find any malignant cells. CSF onconeural antibodies were not tested, due to institutional limitations on test availability.

A computed tomography (CT) scan of the chest, abdomen, and pelvis did not find any evidence of malignancy or metastasis. Mammography and ultrasound scans of the breasts, performed 14 months after the onset of left numb cheek, showed a 6 × 10 × 6mm area of left breast upper outer quadrant hypoechoic tissue, suspicious for malignancy (Figure 2). With knowledge of the scan findings, a vague left breast nodule was palpable on examination. Core biopsy provided histological confirmation of left breast triple-negative ductal carcinoma with apocrine change (estrogen and progesterone receptor negative, c-erb-B2 equivocal, fluorescence *in-situ* hybridization negative). A technetium bone scintigraphy scan did not show any evidence of bony metastases.

Following recommendations made at a multi-disciplinary tumor board meeting, the patient underwent neoadjuvant

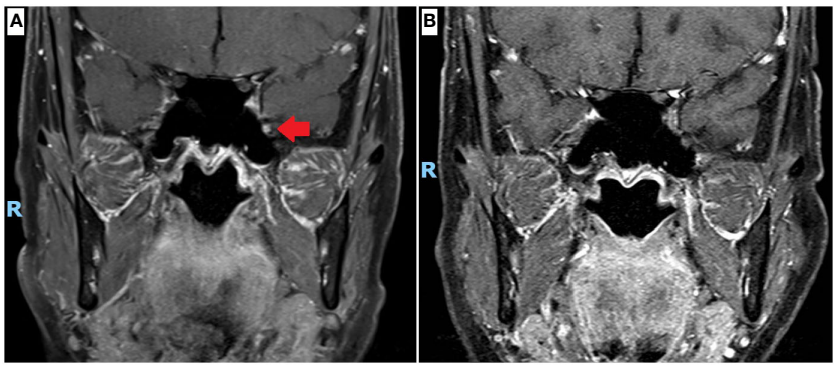


FIGURE 1
Magnetic resonance imaging (MRI) scan of the cranial nerves. **(A)** Coronal projection, T1 with gadolinium contrast at 12 months since onset of left numb cheek, showing left maxillary nerve enhancement at the foramen rotundum (red arrow). **(B)** Coronal projection, T1 with gadolinium contrast at 26 months since onset, performed after completion of neoadjuvant chemotherapy and surgical resection of breast cancer, showing resolution of left maxillary nerve enhancement.

TABLE 1 Summary of blood and cerebrospinal fluid investigations.

Tests on serum/blood	
Infectious/ Para-infectious	*Hepatitis B* surface antigen *Hepatitis C* antibody
Inflammatory/ autoimmune	CRP, ESR Anti-nuclear antibody Anti-double stranded DNA antibody ANCA, anti-MPO antibody, anti-PR3 antibody Extractable nuclear antigen profile (anti-Smith, anti-ribonucleoprotein, anti-Ro, anti-La, anti-Scl 70, anti-Jo 1 antibodies)
Malignancy	Onconeural antibodies (Hu, Yo, Ri, CRMP5, amphiphysin, PNMA2/Ta, recoverin, SOX1, titin, zic4, GAD65, Tr)
Tests on CSF	
Infectious/ Para-infectious	Gram stain, culture Acid fast bacilli smear and culture *Mycobacterium tuberculosis* complex DNA amplification Fungal microscopy and culture VDRL PCR tests (*Escherichia coli, Hemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae*, CMV, *Enterovirus*, HSV1, HSV2, HHV6, *Human parechovirus*, VZV, *Toxoplasma, Cryptococcus*)
Malignancy	Flow cytometry Cytology

All negative or normal. ANCA, anti-neutrophil cytoplasmic antibody; CRMP5, collapsin response mediator protein 5; CRP, c-reactive protein; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; GAD65, glutamic acid decarboxylase 65-kilodalton isoform; HHV6, human herpes virus 6; HSV, herpes simplex virus; LGI1, leucine-rich glioma inactivated 1; MPO, myeloperoxidase; PCR, polymerase chain reaction; PNMA2, paraneoplastic antigen Ma2; PR3, proteinase 3; SOX1, Sry-like high mobility group box 1; VDRL, venereal disease research laboratory; VZV, varicella zoster virus.

chemotherapy (4 cycles of doxorubicin and cyclophosphamide, followed by 4 cycles of paclitaxel and carboplatin) over the course of 7 months (17 to 23 months since left numb cheek onset). She then underwent left breast wide excision and sentinel lymph node biopsy 24 months after onset, with histology showing residual ductal carcinoma *in-situ* 1mm away from the closest resection margin. Two sentinel lymph nodes were negative for malignancy.

Prior to the commencement of chemotherapy, the patient underwent a repeat MRI scan of the brain and cranial nerves (16 months after onset). There were no changes from the original MRI scan (12 months after onset); with persistent enhancement of the left trigeminal nerve at the foramen rotundum noted. After completion of neoadjuvant chemotherapy and surgical resection, a repeat MRI scan (26 months after onset) showed resolution of the left trigeminal nerve enhancement (Figure 1).

Clinically, the patient's symptom of left numb cheek with occasional tenderness remained persistent throughout the course of neoadjuvant chemotherapy. Only after surgical resection did she report a gradual improvement in cheek numbness and pain. At follow-up 5 months after surgical resection, the patient reported only minimal numbness over the left philtrum. Mammography at 4 months (scheduled as part of national cancer screening that the patient was subsequently enrolled in) after surgical resection did not show any evidence of malignancy.

3 Discussion

Breast cancer is the most commonly diagnosed cancer worldwide, with approximately 2.3 million new cases and 685,000 deaths per year (4). Early diagnosis is imperative in the management of breast cancer, given that those with more advanced disease at diagnosis have worse prognoses, with 5-year survival rate declining from 97% for those with stage 1 disease to 48% for those with stage 4 disease (5). Despite the high prevalence and urgency of diagnosis, breast cancer can be easily missed in a patient with the unusual and seemingly benign presentation of numb cheek syndrome. This is illustrated by our case, in which the first MRI scan of the brain was arranged with low priority, and performed 5 months after initial presentation, leading to a significant delay in detection of the maxillary nerve abnormality which turned out to be the sole extra-mammary site of disease. We therefore wish to raise awareness amongst physicians and surgeons that a presentation with unilateral numb cheek can be associated with not only malignancy in general, but also specifically breast cancer.

Prior reports of malignant numb cheek syndrome have been in association with extra-mammary cancers, such as recurrent basal cell epithelioma, newly diagnosed squamous cell carcinoma of the face, metastatic prostate adenocarcinoma, and anaplastic small cell carcinoma of the lung with anti-Hu antibody (2, 6, 7). Trigeminal neuropathy, when reported in association with breast cancer, has been secondary to mechanical compression or radiologically visible tumor infiltration by an adjacent metastatic mass. The sites of involvement reported have been more proximal segments of the trigeminal nerve, from its pontine origin to the Gasserian ganglion, resulting in wider areas of hemifacial dysesthesia or pain (i.e., trigeminal neuralgia) (8–10). To our knowledge, our case represents the first case of a true numb cheek syndrome associated with breast cancer, with symptoms and signs confined to the territory of the second division of the trigeminal nerve (i.e., maxillary nerve), with no discrete mass or compressive cause found. Numb cheek syndrome is traditionally localized to an infra-orbital neuropathy, but our patient with maxillary neuropathy at the foramen rotundum presented with numb cheek syndrome because the cutaneous distribution of the infra-orbital nerve is coterminous with the field of the maxillary nerve (2).

In our patient, the unyielding CSF tests and lack of explanation for the abnormal maxillary nerve signal on MRI led to our search for distant tumors. We favored a CT scan of her thorax, abdomen, and pelvis because it was more readily available, but a Positron Emission Tomography (PET) scan was also being considered. Ultimately, a PET scan was not performed for our patient because application of our national age-appropriate cancer-screening guidelines (recommending mammography and ultrasound breast scans) had already identified a plausible cause of her maxillary nerve abnormality.

Interestingly, our patient's CT scan report did not detect the presence of any underlying breast tumor, even on retrospective review. While existing guidelines do not recommend the use of CT

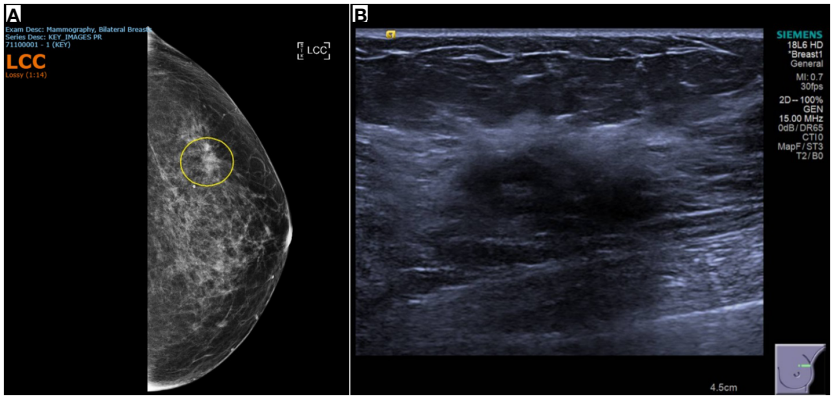


FIGURE 2
Breast imaging showing tissue that was subsequently proven to be triple-negative ductal carcinoma with apocrine change. **(A)** Mammography of the left breast showing heterogeneously dense breast stroma, with an area of distortion in the left breast upper outer quadrant, and a density, persisting on cone compression. **(B)** 28 x 12 x 21mm left breast 1 o'clock vague area of ill-defined hypoechoic tissue, associated with mild distortion and posterior shadowing.

scans for breast cancer screening due to scant evidence of benefit and higher radiation exposure, there is some evidence that CT scans with cuts as fine as 1.25mm may be comparable to mammography in sensitivity (11, 12). For our patient, breast cancer may have gone undetected on CT scan because the slice thickness was 3mm, possibly causing a 6 × 10 × 6mm lesion to appear small and non-specific.

This was also an opportune revisitation of the pathophysiology of numb cheek syndrome. Left maxillary neuropathy in our patient may have been the result of hematogenous spread, leading to leptomeningeal metastasis and/or direct nerve infiltration. This possibility is supported by previous reports of breast cancer with metastatic involvement of other nerves (13). Furthermore, triple-negative breast cancer, like that of our patient, has also been reported to have a preponderance for early nervous system metastases, with approximately one-third of cases eventually developing brain metastases (14, 15). The lack of malignant cells in our patient's CSF cytology does not rule out leptomeningeal metastasis or direct parenchymal infiltration, because CSF cytology has suboptimal sensitivity for both kinds of metastases (16, 17). However, when combined with the normal CSF protein concentration and lack of CSF pleocytosis in our patient, leptomeningeal metastasis becomes less likely, given that the majority of patients with leptomeningeal metastasis will have abnormalities in both CSF cell counts and protein concentrations (18).

A paraneoplastic mechanism also remains a viable explanation. Paraneoplastic neuropathy is thought to be the result of onconeural antibodies targeting cross-reacting intracellular antigens of neuronal and tumoral tissues, with T-cell cytotoxicity likely playing a role in neuronal injury (19). Although our patient's onconeural antibody tests returned negative, existing panels are unlikely to be exhaustive. Given that paraneoplastic neuropathy can lead to long-term deficits with or without anti-tumor treatment and even immunotherapy, our patient's improved but persistent symptoms after neoadjuvant chemotherapy and surgical tumor resection do not rule out a paraneoplastic mechanism (20).

Other pathologic mechanisms, such as mechanical nerve compression and adjacent osseous involvement, have been suggested for numb cheek or chin syndrome (1), but these were not observed in our patient, given the absence of adjacent masses or bony metastases on her scans.

4 Conclusions

We presented a case of numb cheek syndrome in association with breast cancer, hoping to raise awareness that numb cheek syndrome can occur in association with malignancy, where we postulate that it can be due metastasis or paraneoplastic neuropathy involving the infra-orbital or maxillary nerve, even without a discrete adjacent mass causing nerve compression. Although not previously reported until now, breast cancer should be included in the list of malignancies that can be associated with numb cheek syndrome.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for this case report involving one human subject in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. ST: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Burt RK, Sharfman WH, Karp BI, Wilson WH. Mental neuropathy (numb chin syndrome). A harbinger of tumor progression or relapse. *Cancer*. (1992) 70:877–81. doi: 10.1002/1097-0142(19920815)70:4<877:aid-cncr2820700425>3.0.co;2-g

2. Campbell WW Jr. The numb cheek syndrome: a sign of infraorbital neuropathy. *Neurology*. (1986) 36:421–3. doi: 10.1212/wnl.36.3.421

3. Horton J, Means ED, Cunningham TJ, Olson KB. The numb chin in breast cancer. *J Neurol Neurosurg Psychiatry*. (1973) 36:211–6. doi: 10.1136/jnnp.36.2.211

4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71:209–49. doi: 10.3322/caac.21660

5. Elobaid Y, Aamir M, Grivna M, Suliman A, Attoub S, Mousa H, et al. Breast cancer survival and its prognostic factors in the United Arab Emirates: A retrospective study. *PLoS One*. (2021) 16:e0251118. doi: 10.1371/journal.pone.0251118

6. Rabadi MH. Progressive lip numbness due to numb chin and cheek syndrome in a patient with prostate cancer. *Radiol Case Rep*. (2020) 15:1996–8. doi: 10.1016/j.radcr.2020.07.085

7. Raaphorst J, Vanneste J. Numb cheek syndrome as the first manifestation of anti-Hu paraneoplastic neuronopathy. *J Neurol*. (2006) 253:664–5. doi: 10.1007/s00415-005-0047-1

8. Madabhavi I, Sarkar M, Sandeep KS, Modi M. Isolated trigeminal neuralgia: An early weird presentation of carcinoma breast. *J Cancer Res Ther*. (2022) 18:1820–2. doi: 10.4103/jcrt.JCRT_712_20

9. Hirota N, Fujimoto T, Takahashi M, Fukushima Y. Isolated trigeminal nerve metastases from breast cancer: an unusual cause of trigeminal mononeuropathy. *Surg Neurol*. (1998) 49:558–61. doi: 10.1016/S0090-3019(97)00181-X

10. Viviano M, Donati D, Lorenzini G. Metastatic carcinoma presenting as neuralgia involving the trigeminal nerve. *J Can Dent Assoc*. (2012) 77:c32.

11. Ren W, Chen M, Qiao Y, Zhao F. Global guidelines for breast cancer screening: A systematic review. *Breast*. (2022) 64:85–99. doi: 10.1016/j.breast.2022.04.003

12. Desperito E, Schwartz L, Capaccione KM, Collins BT, Jamabawalikar S, Peng B, et al. Chest CT for breast cancer diagnosis. *Life (Basel)*. (2022) 12:1699. doi: 10.3390/life12111699

13. Zhang J, Yang YN, Liu C, Dong YP, Zhang YL. Multiple nerve root metastasis of breast carcinoma: a report of two cases. *Gland Surg*. (2021) 10:1542–6. doi: 10.21037/gs-20-708

14. Jin J, Gao Y, Zhang J, Wang L, Wang B, Cao J, et al. Incidence, pattern and prognosis of brain metastases in patients with metastatic triple negative breast cancer. *BMC Cancer*. (2018) 18:446. doi: 10.1186/s12885-018-4371-0

15. Kuksis M, Gao Y, Tran W, Hoey C, Kiss A, Komorowski AS, et al. The incidence of brain metastases among patients with metastatic breast cancer: a systematic review and meta-analysis. *Neuro Oncol*. (2021) 23:894–904. doi: 10.1093/neuonc/noaa285

16. Nakasu Y, Deguchi S, Nakasu S, Yamazaki M, Notsu A, Mitsuya K, et al. Diagnostic accuracy of cerebrospinal fluid liquid biopsy and MRI for leptomeningeal metastases in solid cancers: A systematic review and meta-analysis. *Neurooncol Adv*. (2023) 5:vdad002. doi: 10.1093/noajnl/vdad002

17. Bae YS, Cheong JW, Chang WS, Kim S, Oh EJ, Kim SH. Diagnostic accuracy of cerebrospinal fluid (CSF) cytology in metastatic tumors: an analysis of consecutive CSF samples. *Korean J Pathol*. (2013) 47:563–8. doi: 10.4132/KoreanJPathol.2013.47.6.563

18. Bönig L, Möhn N, Ahlbrecht J, Wurster U, Raab P, Puppe W, et al. Leptomeningeal metastasis: the role of cerebrospinal fluid diagnostics. *Front Neurol*. (2019) 10:839. doi: 10.3389/fneur.2019.00839

19. Zoccarato M, Grisold W, Grisold A, Poretto V, Boso F, Giometto B. Paraneoplastic Neuropathies: What's New Since the 2004 Recommended Diagnostic Criteria. *Front Neurol*. (2021) 12:706169. doi: 10.3389/fneur.2021.706169

20. Berzero G, Karantoni E, Dehais C, Ducray F, Thomas L, Picard G, et al. Early intravenous immunoglobulin treatment in paraneoplastic neurological syndromes with onconeural antibodies. *J Neurol Neurosurg Psychiatry*. (2018) 89:789–92. doi: 10.1136/jnnp-2017-316904

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 18 March 2024
DOI 10.3389/fonc.2024.1364011

OPEN ACCESS

EDITED BY
Tommaso Susini,
University of Florence, Italy

REVIEWED BY
Anandraj Vaithy,
Mahatma Gandhi Medical College and Research Institute, India
Behnaz Jahanbin,
Tehran University of Medical Sciences, Iran

*CORRESPONDENCE
Puay Hoon Tan
tanpuayhoon28@gmail.com

RECEIVED 01 January 2024
ACCEPTED 01 March 2024
PUBLISHED 18 March 2024

CITATION
Laokulrath N, Lim SK, Lim HY, Gudi M and Tan PH (2024) Case report: Metastatic ovarian mucinous carcinoma to the breast: diagnostic challenges and pitfalls.
Front. Oncol. 14:1364011.
doi: 10.3389/fonc.2024.1364011

Case report: Metastatic ovarian mucinous carcinoma to the breast: diagnostic challenges and pitfalls

Natthawadee Laokulrath[1,2], Siew Kuan Lim[3], Hwee Yong Lim[4], Mihir Gudi[2] and Puay Hoon Tan[2,5,6]*

[1]Department of Pathology, Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Department of Pathology and Laboratory Medicine, Kandang Kerbau (KK) Women's and Children's Hospital, Singapore, Singapore, [3]Solis Breast Care and Surgery Centre, Singapore, Singapore, [4]Novena Cancer Centre, Singapore, Singapore, [5]Luma Medical Centre, Singapore, Singapore, [6]Parkway Laboratory Services Ltd, Singapore, Singapore

Metastases to the breast from extramammary sources are extremely rare, with the ovary, primarily high-grade serous carcinoma, being the most common origin. We report a case of breast metastases from advanced stage ovarian mucinous carcinoma in a 48-year-old female— a case hitherto unreported in the literature. The case is noteworthy for its atypical presentation marked by an areolar rash, clinically suggestive of Paget disease of the nipple. This unique clinical scenario, coupled with histopathological examination revealing *in-situ*-like carcinoma component, posed a diagnostic challenge in discerning the tumour origin. We emphasize the need for heightened awareness among pathologists to avoid misdiagnosing metastatic carcinomas as primary breast tumours, a potential pitfall with significant clinical implications.

KEYWORDS

metastatic to the breast, *in-situ*-like structures, basement membrane, nipple metastasis, ovarian mucinous carcinoma

1 Introduction

Non-mammary metastatic carcinoma to the breast and axilla constitutes a rare subset, accounting for only 0.2-1.1% of all breast malignancies (1, 2), with haematologic metastases excluded. The gynaecologic tract is the most prevalent primary extramammary site, notably the ovary (3). High-grade ovarian serous carcinoma is the predominant type, followed by the much less common metastatic ovarian clear cell carcinoma (3).

Remarkably unusual, metastatic ovarian mucinous carcinoma to the breast has been scarcely documented, with only two related cases in the literature. One case involved seromucinous carcinoma (4), a subtype of endometrioid carcinoma according to the latest WHO classification of female genital tumours (5). Another patient had a mixed mucinous

and mesonephric cystadenocarcinoma (6), where the breast biopsy exhibited a solely mesonephric appearance.

Herein, we present a distinct case of breast metastasis originating from advanced ovarian pure mucinous carcinoma, a scenario not previously documented. In this report, we delineate the intriguing histologic findings and discuss the diagnostic challenges inherent in such rare occurrences.

2 Case report

A 48-year-old Chinese female with a previous diagnosis of mucinous ovarian cancer, initially identified in January 2022, experienced recurrence shortly after completing chemotherapy. The patient re-presented with extensive peritoneal disease, which showed a short duration response to second-line chemotherapy. Her disease progression was marked by rapid growth of two right breast masses, measuring 50 mm and 10 mm at 9 o'clock and 10 o'clock, respectively. Radiological assessments revealed interval detection of an FDG avid irregular lesion in the retro-areolar region of the right breast (size of 3.6cm x 2.3cm) (Figure 1A), with several new small mildly FDG avid satellite lesions seen in the rest of the right breast.

In addition to the breast masses, clinical examination detected a right areolar rash (Figure 1C). Core biopsies without prior fine needle aspiration cytology were performed on both masses, along with a nipple incisional biopsy.

Histological examination of the core biopsies from both masses revealed an invasive carcinoma characterized by dispersed nests, trabeculae, and tubules, comprising 10-75% of the tumour, infiltrating amidst benign and variably inflamed breast lobules and oedematous stroma. Predominantly, the tumour cells exhibited high-grade nuclei with abundant eosinophilic and foamy cytoplasm. Some regions displayed atypical glandular structures, partially lined by nuclei of relatively lower grade, featuring abundant basophilic apical mucin seamlessly transitioning into highly pleomorphic epithelial cells. Notably, no extracellular mucin, cystic-papillary structures, conspicuous goblet cell, or signet ring morphologies were observed. There were dense collagenous bands encircling a few glands, resembling intact basement membranes. Adjacent to these bands were inconspicuous, stretched-out, and compressed cells, akin to myoepithelial cells. Lymphovascular invasion was evident in three foci within one section of the breast core obtained from the 9 o'clock mass, while its presence in the 10 o'clock mass was equivocal. Additionally, the 9 o'clock lesion exhibited a fibroadenoma with carcinoma involvement. Non-neoplastic breast tissue revealed adenosis accompanied by chronic inflammation.

Immunohistochemistry (IHC) analysis showed diffuse positive reactivity for PAX 8 in the nuclei of the malignant cells, while GATA3, GCDFP15, and WT1 exhibited negative staining. Positive CA125 reactivity was observed in the malignant glands. Smooth muscle myosin heavy chain (SMMHC) revealed general negativity around malignant glands and tumour nests, with scattered peripheral positivity around some malignant groups. CK5 highlighted scattered malignant cells, with some tumour nests showing apparent peripheral positive decoration. p63 was negative around tumour nests and malignant glands. Mammaglobin displayed patchy faint to weak cytoplasmic blush in occasional malignant cells. ER and PR were negative, evidenced by no staining, with optimally stained normal breast epithelium. Equivocal HER2 IHC staining (score 2+) was noted in 30% and 40% of tumour cells in the 9 o'clock and 10 o'clock lesions, respectively, displaying weak-to-moderate intensity. VENTANA HER2 Dual ISH DNA Probe cocktail showed positive results (group 1) for *HER2* gene amplification; the average HER2: CEP17 ratios were 2.7 and 3.2 in the 9'clock and 10 o'clock tumours,

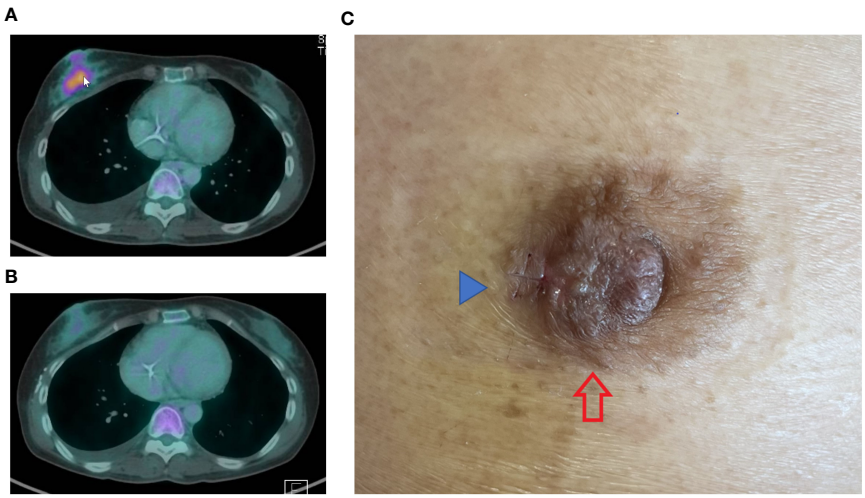


FIGURE 1
PET CT images dated 16/10/2023 **(A)** depict a highly metabolic right breast lesion. The cancer exhibited significant response following only 3 cycles of combination chemotherapy incorporating Trastuzumab (TCH regimen), as evidenced by the image from 18/12/2023 **(B)**. The nipple **(C)** showed a rash at the lateral aspect of the right nipple areolar complex (red arrow), clinically mimicking Paget disease. A small surgical scar (blue arrow) is observed at the lateral edge of the rash, attributed to a recent incisional skin biopsy.

respectively. A detailed representation of the histology and immunohistochemical studies of the core biopsies of the breast masses is provided in Figure 2.

The nipple biopsy section demonstrated malignant glands and nests with identical histomorphology to the carcinomas described above. The infiltrating carcinoma involved the epidermis, dermis, and deeper parts of the nipple stroma and areolar muscle. Focal epidermal erosion was identified, though the epidermis was devoid of abnormal intraepidermal epithelial clusters. Several malignant cells exhibited cytoplasmic mucinous vacuoles, and dermal lymphovascular invasion was present (Figure 3).

The histology of the primary ovarian tumour was unavailable for review. Subsequent biopsies, displaying identical appearances, revealed multiple metastases to the omentum - the largest tumour deposit being 5 cm, pelvic peritoneum, bilateral sides of the diaphragm, liver capsule and gallbladder bed, including to the serosa, muscularis propria and mucosa of the sigmoid colon. The basement membrane-like matrix with occasional basal stretched-out cells were also noted in the section of metastatic carcinoma to the omentum and pelvic peritoneum (Figure 3B).

Upon identification of a positive (HER2) Dual *In Situ* Hybridization (DISH) result in both the breast and peritoneal specimens, the clinical chemotherapeutic regimen was revised to a more manageable and well-tolerated combination with an anti-HER2 drug. The tumour exhibited a remarkable and positive response to the modified chemotherapeutic regimen (Figure 1B).

3 Discussion

We present an unusual case of metastatic ovarian mucinous carcinoma, clinically presenting as breast masses and a nipple rash mimicking Paget disease of the nipple. Histologically, the carcinoma exhibited infiltration into periductal and perilobular areas, sparing terminal duct-lobular structures, and involving a fibroadenoma. Notably, the carcinoma displayed mucinous features with high-grade cytomorphology, lacking extracellular mucin and the characteristic appearance of mucinous cystadenocarcinoma of the breast, specifically the absence of cystic areas with papillary epithelial proliferation.

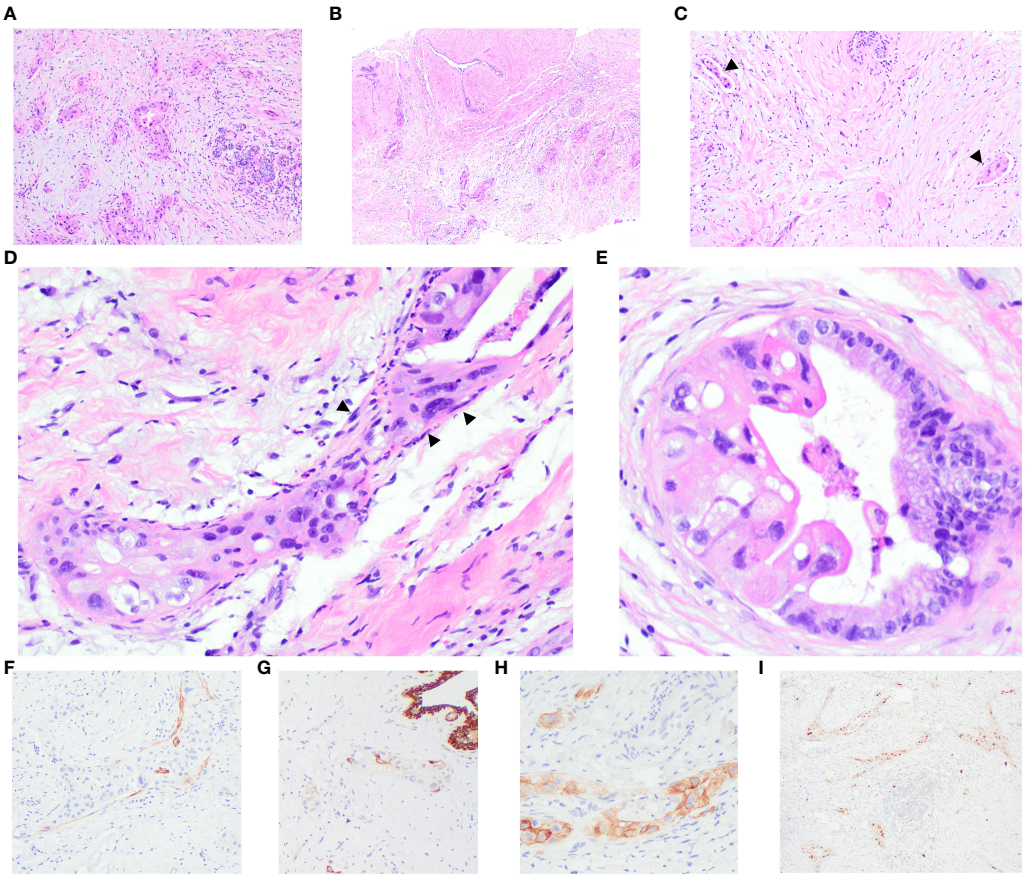


FIGURE 2
Breast core biopsies illustrate the invasive carcinoma, showing perilobular infiltration **(A)** and involvement of a fibroadenoma **(B)**. Multiple foci of lymphovascular invasion are evident (arrowheads) **(C)**. Distinctive features include dense collagenous bands encircling some glands, resembling a basement membrane with stretched-out and compressed cells (arrowheads), akin to myoepithelial cells **(D)**. A few glands are partially lined by columnar cells with lower-grade nuclei and abundant basophilic apical mucin, transitioning seamlessly into highly pleomorphic epithelial cells **(E)**. IHC results demonstrate scattered positivity for smooth muscle myosin heavy chain (SMMHC) **(F)** and cytokeratin 5 (CK5) **(G)** around the tumour nests. Carcinoma cells display positive staining for CA125 **(H)** and PAX8 **(I)**.

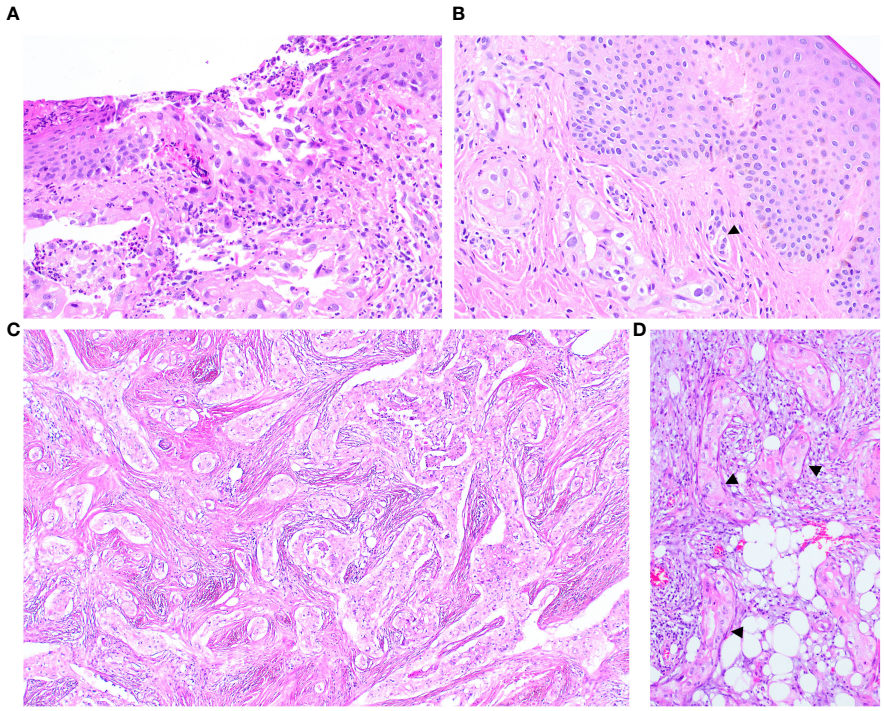


FIGURE 3
The nipple biopsy reveals infiltrating carcinoma involving the epidermis with focal epidermal erosion **(A)**, extending into the dermis with dermal lymphovascular invasion (arrow) **(B)**. The metastatic carcinoma in the omentum shows a comparable morphology to the tumour present in the breast **(C)** an *in-situ*-like structure (arrow) is also identified **(D)**.

Distinctive features included a subset of glands partially lined by tall columnar cells exhibiting relatively lower grade nuclei and abundant basophilic intracytoplasmic mucin, reminiscent of Mullerian mucinous epithelium. These features deviate from the typical morphology of invasive mammary carcinoma. Considering the patient's history of ovarian mucinous carcinoma (which was not initially available), the diagnosis of metastatic carcinoma was favoured. However, the mucinous differentiation was only focally present and it is acknowledged that the tumour appearance may be influenced by chemotherapy, and the biopsy samples may not fully capture the heterogeneous morphology of the tumour. Consequently, the possibility of a primary breast carcinoma could not be definitively ruled out.

The presence of a basement membrane-like matrix encircling tumour nests and glands, coupled with occasional juxtaposition of stretched-out, flat to oval darker-stained nuclei, prompted consideration of *in-situ* carcinoma and a primary tumour. However, immunohistochemical staining for myoepithelial cells revealed mostly equivocal positivity though some accentuation of peripheral staining could be potentially interpreted as reflecting attenuated myoepithelial cells. Interestingly, upon comparing the histology with that of biopsies from other metastatic sites in subsequent specimens, the *in situ*-like pattern was also observed in the pelvic peritoneal sections, refuting the notion of a genuine *in-situ* process for this appearance.

Immunohistochemically, the carcinoma cells exhibited diffuse positivity for PAX8 and CA125, while testing negative for breast immunomarkers such as GATA3 and GCDFP15. The combined histologic findings and immunoprofile supported a metastatic ovarian origin.

Literature reviews underscore the rarity of metastatic extramammary carcinomas to the breast, with only a small proportion (11%) (3) presenting with breast or axillary lesions as the initial manifestation, while the majority (77%) (3) already have disseminated disease upon breast metastasis detection. Clinical history proves pivotal for accurate diagnosis, but in instances where information is lacking or inaccessible, non-mammary metastases can be challenging to identify and may be misdiagnosed as primary breast cancer.

The patients' age ranges from 15 to 83 years, with a median age of 54 years (3). Tumour sizes exhibit a median of 1.68 cm, ranging from 0.5 to 18 cm (3). Radiologically, metastatic tumours often lack specific features but are typically unilateral, singular masses, and frequently located in the upper outer quadrant, accounting for 50-60% of cases (7, 8). These findings may mimic benign and malignant breast tumours, adding complexity to the diagnostic process.

Histologically, metastatic tumours in the breast can disclose various patterns (7, 9, 10), including a circumscribed tumour, which is the most prevalent, featuring a well-defined mass surrounded by normal breast tissue. In some cases, the tumours form nodules distributed around ducts and lobules. Another pattern involves lymphangitis carcinomatosis, where multiple dispersed tumour clusters are present within dilated lymphatic spaces. In addition, a

diffuse involvement of breast parenchyma may occur, indicating a more widespread infiltration of tumour cells throughout the breast tissue.

Microscopic findings identified in prior studies indicative of metastasis include features that are unusual for breast carcinoma (1, 3, 11, 12), the absence of *in-situ* carcinoma (1, 3, 11, 12), a well-circumscribed or pushing tumour border enveloped by a fibrous pseudocapsule (3, 11), the lack of elastosis (1, 11, 12), and the presence of multiple satellite foci (11). While lymphatic emboli are recognized as suggestive of metastatic disease (1, 12), it is noteworthy that lymphovascular invasion was found to be absent in 87% of cases in one study (3).

The presence of an intraductal component of carcinoma is consistently noted in the literature as supportive evidence for primary breast cancer (1, 3). However, we highlight the potential diagnostic pitfall of relying solely on *in-situ* appearances to support the diagnosis of primary breast carcinoma. *In situ*-like metastatic foci that mimic *in-situ* mammary carcinoma have been occasionally reported in the literature, offering two plausible explanations for this phenomenon. The first scenario involves the spread of metastatic ovarian cancer cells into existing mammary ducts, as illustrated by Maeshima Y. et al. (4), where the *in situ*-appearing architecture exhibited neoplastic cells having the same morphology as metastatic seromucinous carcinoma, surrounded by confirmed myoepithelium. A similar finding is described in metastatic colonic adenocarcinoma to the biliary tract, where intraepithelial growth mimics primary intrabiliary carcinoma (13). The second scenario is lymphovascular invasion mimicking *in situ* disease, proposed by Gupta D et al. (14), involving metastatic renal cell carcinoma and metastatic ovarian papillary serous adenocarcinoma. These cases showed multiple tumour emboli floating within and plugging lymphatic spaces. In some foci, metastatic carcinoma cells adhered to the endothelium and expanded the lymphatic spaces, mimicking ductal carcinoma *in situ*. Conclusive evidence was provided by immunohistochemically highlighting the endothelium with CD31, CD34, and Ulex europaeus, observing adjacent vascular structures with accompanying extensive lymphovascular invasion. Also noted in the study was desmoplastic and inflammatory response around dilated lymphatic spaces and necrosis within the tumour clusters in lymphatic spaces mimicking periductal stromal change and comedonecrosis seen in ductal carcinoma *in situ*, respectively (14).

To differentiate DCIS from tumour emboli, myoepithelial and endothelial immunomarkers should be considered. Caution is warranted in the evaluation of myoepithelial immunohistochemical (IHC) markers, as 84.2% (15) of ductal carcinoma *in situ* (DCIS) cases have demonstrated diminished IHC expression in myoepithelial cells, particularly in high-grade DCIS. Of note, smooth muscle myosin heavy chain (SMMHC) exhibits significantly reduced reactivity in these cases. In this context, SMA, p75, p63, and calponin may offer greater sensitivity and may be preferable for assessing myoepithelial cells (15). Additionally, the expression of D2-40, commonly employed for detecting lymphovascular invasion, has been observed in varying degrees in myoepithelial cells in mammary carcinoma *in situ* (16).

The encircling collagenous band around epithelial nests may resemble a native basement membrane. Such basal-membrane-like structures have also been documented in breast carcinoma metastasis to the lymph nodes (17) and many types of malignant tumours, for example, basaloid squamous carcinoma of the gastrointestinal tract (18) and pancreas (19), and invasive basal cell carcinoma of the skin (20). In the context of breast carcinoma, the presence of *in-situ*-like structures in metastatic sites supports their being reactive stroma rather than an *in-situ* process (21).

In our case, immunohistochemical stains for myoepithelial cells (SMMHC, CK5 and p63) produced equivocal results with some suggestion of focal positive rimming of occasional malignant nests. The existence of multiple foci of lymphovascular invasion and the proximity of small vessels adjacent to the *in-situ*-like foci raise the possibility of tumour emboli mimicking carcinoma *in situ*. Additionally, the basement membrane-like structures were identified in extramammary tumours (pelvic peritoneum), supporting metastatic disease.

Therefore, reviewing the histology of the prior malignancy and other synchronous tumours might assist in the diagnosis, as exemplified in our case. The likelihood of a diagnosis of metastatic carcinoma is strengthened if there is similar morphology to the prior carcinoma.

Immunohistochemical stains can be valuable in identifying the primary site of the tumour; however, they can also introduce complexity into the diagnosis, particularly in cases of mucinous-type ovarian carcinoma. This subtype tends to exhibit a divergent immunohistochemical profile from the typical pattern (CK7+/CK20-/PAX8+) observed in other epithelial-type ovarian tumours. CK7 and CK20 show varied positivity in ovarian mucinous tumours, with the majority displaying positivity for CK7 (22). The staining variability observed poses a challenge in differentiating ovarian mucinous tumours from primary breast carcinoma. The immunoprofile of CK7 positivity and CK20 negativity is akin to that of breast carcinoma, while addition of PAX8 positivity aligns more with an ovarian origin.

However, PAX8, a Mullerian immunomarker, is negative in 80-90% of ovarian mucinous carcinomas (23, 24). Similarly, SOX17, identified as a novel and promising biomarker with high specificity for gynaecologic tumours, produced positive results in only 23% of ovarian mucinous carcinomas (25). It is noteworthy that PAX8 positivity with variable staining intensity and tumour percentage is also observed in 6.02% of invasive mammary carcinoma, mostly high-grade with triple-negativity (26).

WT1 is not contributory in distinguishing between ovarian mucinous and breast carcinoma, as both can be negative (23). This observation is supported by Nonaka D et al. (23), in their study, where they found that WT1 expression was observed in 64% of pure and 33% of mixed mucinous breast carcinomas. The expression of WT1 was usually weak and focal in most of the positively staining breast tumours (3).

CA125 proves to be helpful in this context, as 90% of ovarian carcinomas are positive for CA125, exhibiting strong and diffuse staining, while the majority of breast carcinomas are negative for CA125 (27). Only 16% of primary and 12% of metastatic breast

carcinomas showed weak and focal positivity (27). Mucinous cystadenocarcinoma of the breast has also been reported to be negative for CA125, although data on this entity are limited due to its rarity (28).

Breast immunomarkers prove highly valuable in this situation, as the majority of ovarian carcinomas were negative for these markers (29–31). It is important to note that a subset of ovarian mucinous carcinomas (2 out of 20 cases in one study (29)) can be positive for GATA3 (29), and 4% of ovarian tumours can express GCDFP-15 as well (2). TRPS1 appears to have higher sensitivity and specificity than GATA3 (31). Therefore, using TRPS1 immunohistochemistry as an adjunct with traditional breast and other markers may confirm or exclude a breast origin. However, 8% of ovarian non-serous carcinoma showed variable positivity for TRPS1 (31).

In our case, positivity for PAX8 and CA125 and negativity of markers associated with a breast origin supported ovarian metastasis. The metastatic carcinoma also exhibited HER2 amplification. HER2 overexpression has been documented in 25-40% of ovarian mucinous carcinomas (32, 33). Therefore, pathologists should exercise caution and not be misled by a positive HER2 result as supportive evidence for primary breast origin.

Nipple involvement by metastatic carcinoma is an exceedingly uncommon occurrence. Our case represents, to our knowledge, the first reported instance of nipple involvement by metastatic ovarian carcinoma, clinically manifesting as an areolar rash and mimicking Paget disease of the nipple. Histological examination revealed epidermal erosion with tumour involvement, albeit without the presence of intraepidermal tumour nests. While the literature review identified a limited number of cases depicting metastatic ovarian high-grade serous carcinoma and clear cell carcinoma to the breast, simulating inflammatory breast carcinoma, and an ovarian serous carcinoma metastases to an intramammary lymph node mimicking a primary breast carcinoma (34–38), such a clinical presentation was not evident in our cases. Furthermore, the antecedent case reports did not report nipple involvement.

The identification of a metastatic tumour within the breast commonly heralds an unfavourable prognosis, as a substantial proportion of patients already manifest widespread disease. According to a case series (3), mortality was observed in 96% of patients with available follow-up data, culminating in a median survival period of 15 months subsequent to the diagnosis of the breast or axillary lesion.

In summary, we highlight the crucial importance of accurate diagnosis when dealing with these tumours to avoid unnecessary surgical procedures or treatments. The case presented emphasizes a diagnostic strategy that focuses on identifying morphology favouring metastatic carcinoma, particularly considering the patient's history of extramammary malignancy and the unusual histology that does not align with primary breast cancer. The identification of carcinoma *in-situ*-like foci, while conventionally indicative of a breast primary, introduces a potential diagnostic pitfall. Awareness of mimics, such as a basement membrane-like matrix or *in-situ*-like structures signifying the dissemination of metastatic cancer cells into pre-existing mammary ducts and lymphatic emboli, is crucial. Consequently, the *in-situ* appearance should not be construed as conclusive pathognomonic evidence of primary disease unless complemented by additional histologic and immunohistochemical support. Comparing tumour histology with specimens from primary and metastatic sites refines diagnosis. Tailoring immunohistochemical stains based on the patient's non-breast malignancy history and carcinoma morphology is crucial. A broad immunohistochemical panel, including multiple organ-specific markers for potential origins, is imperative to avoid pitfalls in interpretation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the studies involving humans because this is a case report and it does not require an ethics committee review. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NL: Writing – original draft, Writing – review & editing. SL: Resources, Writing – review & editing. HL: Resources, Writing – review & editing. MG: Writing – original draft, Writing – review & editing. PT: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. We acknowledge the support of the Singapore Breast Surgery Centre in the publication of this article.

Acknowledgments

We thank Ms. Nur Diyana for administrative assistance with the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. WHO classification of Tumours Editorial Board. *Breast tumours, WHO classification of tumours series. 5th ed*. Lyon, France: International Agency for Research on Cancer (2019).

2. Bombonati A, Lerwill MF. Metastases to and from the breast. *Surg Pathol Clin*. (2012) 5:719–47. doi: 10.1016/j.path.2012.06.004

3. DeLair DF, Corben AD, Catalano JP, Vallejo CE, Brogi E, Tan LK. Non-mammary metastases to the breast and axilla: a study of 85 cases. *Mod Pathol*. (2013) 26:343–9. doi: 10.1038/modpathol.2012.191

4. Maeshima Y, Osako T, Morizono H, Yunokawa M, Miyagi Y, Kikuchi M, et al. Metastatic ovarian cancer spreading into mammary ducts mimicking an *in situ* component of primary breast cancer: a case report. *J Med Case Rep*. (2021) 15:78. doi: 10.1186/s13256-020-02653-w

5. WHO classification of Tumours Editorial Board. *Female Genital tumours, WHO classification of tumours series. 5th ed*. Lyon, France: International Agency for Research on Cancer (2020).

6. Ibach JRJr. Carcinoma of the ovary metastatic to breast. A case report and review of the literature. *Arch Surg*. (1964) 88:410–4. doi: 10.1001/archsurg.1964.01310210084013

7. Hajdu SI, Urban JA. Cancers metastatic to the breast. *Cancer*. (1972) 29:1691–6. doi: 10.1002/1097-0142(197206)29:6<1691::aid-cncr2820290637>3.0.co;2-4

8. Li J, Wahab R, Brown AL, Guarnieri B, Lewis K, Mahoney MC, et al. Extramammary metastases to the breast. *Radiographics*. (2023) 43:e230036. doi: 10.1148/rg.230036

9. Nielsen M, Andersen JA, Henriksen FW, Kristensen PB, Lorentzen M, Ravn V, et al. Metastases to the breast from extramammary carcinomas. *Acta Pathol Microbiol Scand A*. (1981) 89:251–6. doi: 10.1111/j.1699-0463.1981.tb00218.x

10. McIntosh IH, Hooper AA, Millis RR, Greening WP. Metastatic carcinoma within the breast. *Clin Oncol*. (1976) 2(4):393–401.

11. Judson K, Argani P. Intraductal spread by metastatic islet cell tumor (well-differentiated pancreatic endocrine neoplasm) involving the breast of a child, mimicking a primary mammary carcinoma. *Am J Surg Pathol*. (2006) 30:912–8. doi: 10.1097/01.pas.0000206220.08232.2d

12. Lee SK, Kim WW, Kim SH, Hur SM, Kim S, Choi JH, et al. Characteristics of metastasis in the breast from extramammary Malignancies. *J Surg Oncol*. (2010) 101:137–40. doi: 10.1002/jso.21453

13. Riopel MA, Klimstra DS, Godellas CV, Blumgart LH, Westra WH. Intrabiliary growth of metastatic colonic adenocarcinoma: a pattern of intrahepatic spread easily confused with primary neoplasia of the biliary tract. *Am J Surg Pathol*. (1997) 21:1030–6. doi: 10.1097/00000478-199709000-00007

14. Gupta D, Merino MI, Farhood A, Middleton LP. Metastases to breast simulating ductal carcinoma *in situ*: report of two cases and review of the literature. *Ann Diagn Pathol*. (2001) 5:15–20. doi: 10.1053/adpa.2001.21476

15. Hilson JB, Schnitt SJ, Collins LC. Phenotypic alterations in ductal carcinoma *in situ*-associated myoepithelial cells: biologic and diagnostic implications. *Am J Surg Pathol*. (2009) 33:227–32. doi: 10.1097/PAS.0b013e318180431d

16. Rabban JT, Chen YY. D2-40 expression by breast myoepithelium: potential pitfalls in distinguishing intralymphatic carcinoma from *in situ* carcinoma. *Hum Pathol*. (2008) 39:175–83. doi: 10.1016/j.humpath.2007.06.018

17. Kordek R. Ductal carcinoma *in situ*-like structures in metastatic breast carcinoma. *Pathol Res Pract*. (2005) 200:831–4. doi: 10.1016/j.prp.2004.08.006

18. Takubo K, Mafune K, Tanaka Y, Miyama T, Fujita K. Basaloid-squamous carcinoma of the esophagus with marked deposition of basement membrane substance. *Acta Pathol Jpn*. (1991) 41:59–64. doi: 10.1111/j.1440-1827.1991.tb03273.x

19. Marucci G, Betts CM, Liguori L, Eusebi V. Basaloid carcinoma of the pancreas. *Virchows Arch*. (2005) 446:322–4. doi: 10.1007/s00428-004-1181-3

20. El-Shabrawi L, LeBoit PE. Basal cell carcinoma with thickened basement membrane: a variant that resembles some benign adnexal neoplasms. *Am J Dermatopathol*. (1997) 19:568–74. doi: 10.1097/00000372-199712000-00003

21. Rakha EA, Miligy IM, Gorringe KL, Toss MS, Green AR, Fox SB, et al. Invasion in breast lesions: the role of the epithelial-stroma barrier. *Histopathology*. (2018) 72:1075–83. doi: 10.1111/his.13446

22. Vang R, Gown AM, Barry TS, Wheeler DT, Yemelyanova A, Seidman JD, et al. Cytokeratins 7 and 20 in primary and secondary mucinous tumors of the ovary: analysis of coordinate immunohistochemical expression profiles and staining distribution in 179 cases. *Am J Surg Pathol*. (2006) 30:1130–9. doi: 10.1097/01.pas.0000213281.43036.bb

23. Nonaka D, Chiriboga L, Soslow RA. Expression of pax8 as a useful marker in distinguishing ovarian carcinomas from mammary carcinomas. *Am J Surg Pathol*. (2008) 32:1566–71. doi: 10.1097/PAS.0b013e31816d71ad

24. Tabrizi AD, Kalloger SE, Köbel M, Cipollone J, Roskelley CD, Mehl E, et al. Primary ovarian mucinous carcinoma of intestinal type: significance of pattern of invasion and immunohistochemical expression profile in a series of 31 cases. . *Int J Gynecol Pathol*. (2010) 29:99–107. doi: 10.1097/PGP.0b013e3181bbbcc1

25. Zhang X, Yao J, Niu N, Li X, Liu Y, Huo L, et al. SOX17: A highly sensitive and specific immunomarker for ovarian and endometrial carcinomas. *Mod Pathol*. (2023) 36:100001. doi: 10.1016/j.modpat.2022.100001

26. Lu S, Yakirevich E, Hart J, Wang L, Wang Y. PAX8 expression in breast cancer. *Appl Immunohistochem Mol Morphol*. (2021) 29:293–8. doi: 10.1097/PAI.0000000000000883

27. Tornos C, Soslow R, Chen S, Akram M, Hummer AJ, Abu-Rustum N, et al. Expression of WT1, CA 125, and GCDFP-15 as useful markers in the differential diagnosis of primary ovarian carcinomas versus metastatic breast cancer to the ovary. *Am J Surg Pathol*. (2005) 29:1482–9. doi: 10.1097/01.pas.0000176429.88702.36

28. Wang X, Li Y, Zhao P, Jia H, Dong X, Zhang L, et al. Primary mucinous cystadenocarcinoma of the breast: a clinicopathologic analysis of one case and review of the literature. *Int J Clin Exp Pathol*. (2020) 13(10):2562–8.

29. Terzic T, Mills AM, Zadeh S, Atkins KA, Hanley KZ. GATA3 expression in common gynecologic carcinomas: A potential pitfall. *Int J Gynecol Pathol*. (2019) 38:485–92. doi: 10.1097/PGP.0000000000000541

30. Lagendijk JH, Mullink H, van Diest PJ, Meijer GA, Meijer CJ. Immunohistochemical differentiation between primary adenocarcinomas of the ovary and ovarian metastases of colonic and breast origin. Comparison between a statistical and an intuitive approach. *J Clin Pathol*. (1999) 52:283–90. doi: 10.1136/jcp.52.4.283

31. Ai D, Yao J, Yang F, Huo L, Chen H, Lu W, et al. TRPS1: a highly sensitive and specific marker for breast carcinoma, especially for triple-negative breast cancer. *Mod Pathol*. (2021) 34:710–9. doi: 10.1038/s41379-020-00692-8

32. Smithgall MC, Yemelyanova A, Mathew S, Gogineni S, He B, Zhang T, et al. HER2/ERBB2 immunohistochemical expression and copy number status in ovarian mucinous tumors. *Int J Gynecol Pathol*. (2023) 43. doi: 10.1097/PGP.0000000000000966

33. Kim SK, Cho NH. HER2-positive mucinous adenocarcinomas of the ovary have an expansile invasive pattern associated with a favorable prognosis. *Int J Clin Exp Pathol*. (2014) 7(7):4222–30.

34. Pipal VR, Singh P, Pipal DK, Elhence P. Skin metastases in ovarian Malignancy: A case report with literature review. *J Midlife Health*. (2023) 14:49–52. doi: 10.4103/jmh.jmh_137_22

35. Achariyapota V, Chuangsuwanich T, Benjapibal M. Inflammatory breast cancer from metastatic ovarian cancer. *Case Rep Obstet Gynecol*. (2016) 2016:3476143. doi: 10.1155/2016/3476143

36. Klein RL, Brown AR, Gomez-Castro CM, Chambers SK, Cragun JM, Grasso-Lebeau L, et al. Ovarian cancer metastatic to the breast presenting as inflammatory breast cancer: a case report and literature review. *J Cancer*. (2010) 1:27–31. doi: 10.7150/jca.1.27

37. Musa A, Joiner M, Dzul S, Miller SR. Metastatic spread of serous ovarian carcinoma to the bilateral breasts: a rare presentation. *BMJ Case Rep*. (2022) 15: e251721. doi: 10.1136/bcr-2022-251721

38. Susini T, Olivieri S, Molino C, Castiglione F, Tavella K, Viligiardi R. Ovarian cancer initially presenting as intramammary metastases and mimicking a primary breast carcinoma: a case report and literature review. *J Womens Health (Larchmt)*. (2010) 19:169–74. doi: 10.1089/jwh.2009.1465

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 21 March 2024
DOI 10.3389/fonc.2024.1296328

OPEN ACCESS

EDITED BY
Nosheen Masood,
Fatima Jinnah Women University, Pakistan

REVIEWED BY
Anam Nayab,
University of Science and Technology of China, China
Sidra Abbas,
Fatima Jinnah Women University, Pakistan

*CORRESPONDENCE
Yangang Zhang
urozyg@163.com

†These authors have contributed equally to this work

RECEIVED 18 September 2023
ACCEPTED 12 March 2024
PUBLISHED 21 March 2024

CITATION
Guo F, Sun S, Niu X, Wang Y, Yao W, Yue P, Deng X, Shang J and Zhang Y (2024) Renal pelvis metastasis following surgery for breast angiosarcoma: a case report and literature review. *Front. Oncol.* 14:1296328. doi: 10.3389/fonc.2024.1296328

Renal pelvis metastasis following surgery for breast angiosarcoma: a case report and literature review

Fuyu Guo[1†], Shiwei Sun[1,2†], Xiangnan Niu[3,4†], Yue Wang[1], Wei Yao[1], Peng Yue[1], Xiaoqian Deng[1], Jiwen Shang[1,3,4] and Yangang Zhang[1,3,4*]

[1]Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Taiyuan, China, [2]Department of Urology, Taiyuan Central Hospital of Shanxi Medical University, Taiyuan, China, [3]Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China, [4]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Renal metastasis of breast angiosarcoma is rare. This article reports the medical records of a patient diagnosed with breast angiosarcoma who underwent radical mastectomy and was found to have multiple lung metastases 3 years after surgery and renal pelvic metastasis 4 years after surgery. The patient underwent robot-assisted laparoscopic radical nephroureterectomy and sleeve resection of the intramural segment of the ureter, and postoperative pathology and immunohistochemical staining confirmed the diagnosis of renal pelvic metastasis of breast angiosarcoma. The patient received anlotinib for lung metastases following surgery and was followed up for 4 months after surgery. Currently, the patient has symptoms of coughing and hemoptysis but no other discomfort. The diagnosis and treatment of this rare malignant tumor remain challenging.

KEYWORDS

breast angiosarcoma, renal pelvis cancer, tumor metastasis, diagnosis, treatment, robot-assisted laparoscopic surgery

1 Introduction

Breast angiosarcoma (BA) is a highly invasive malignant tumor that originates from the endothelial cells of the breast blood vessels. It is most common in women aged 20-40 years and accounts for less than 1% of all breast cancers. The 5-year overall survival rate is only around 30% (1, 2). BA can metastasize hematogenously to the contralateral breast, lungs, bones, liver, ovaries, skin, and subcutaneous tissues, whereas metastasis to the orbital tissues and lymph nodes is rare (3, 4). Primary breast angiosarcoma (PBA) often presents as a rapidly enlarged round-like mass located in the depths of the breast in a short period of

time, which can show traumatic purplish-red changes when the tumor is superficial or invades the skin (1, 5). However, there is currently no literature on PBA that has metastasized to the kidney or renal pelvis. Here, we describe the diagnosis and treatment of PBA in a 33-year-old female.

2 Case description

The patient is a 33-year-old female, with no family history of breast tumor. In October 2019, she underwent needle biopsy of a right breast mass and was diagnosed with PBA (Figure 1). Immunohistochemical staining showed AE1/AE3 (- [Indicates a negative result]), CK7 (-), GATA3 (-), Vimentin (+ [Indicates a positive result]), CD34 (+), CD31 (+), SMA (-), calponin (-), ER (-), PR (-), CerbB-2 (0), β-catenin (cytoplasmic +), CD10 (-), and Ki67 (approximately 70% +) (Figure 2). The patient received radical mastectomy and paclitaxel for 10 cycles. In January 2022, due to coughing and bloody sputum, she underwent computed tomography (CT) of the lungs and needle biopsy; she was subsequently diagnosed with multiple lung metastases. The patient received targeted therapy and showed a poor response to apatinib but achieved good control after switching to anlotinib.

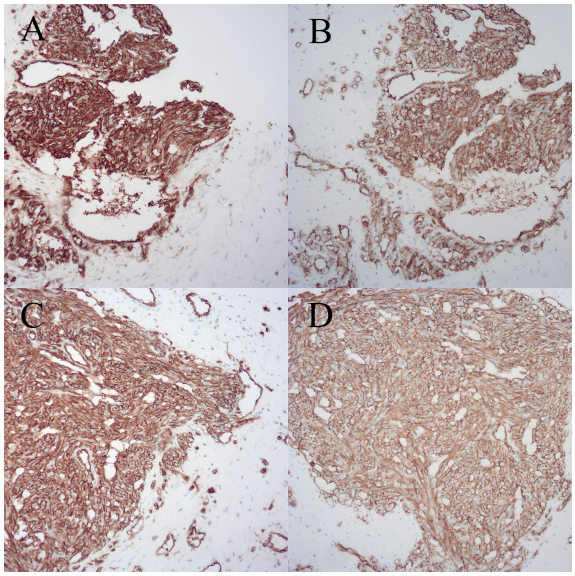


FIGURE 2
Breast biopsy specimen with immunohistochemical staining. **(A)** Specimen 1, CD31. **(B)** Specimen 1, CD34. **(C)** Specimen 2, CD31. **(D)** Specimen 2, CD34.

3 Diagnostic assessment

On November 15, 2022, the patient was admitted to the hospital due to gross hematuria for 10 h, accompanied by dizziness and fatigue. The blood cell analysis revealed hemoglobin (Hb) at 76 g/L and a red blood cell (RBC) count of 2.45×10^{12}/L. Urinalysis showed an entire field of RBCs. The chest CT scan showed multiple solid nodules in both lungs, with the larger one located in the apicoposterior segment of the upper lobe of the left lung, measuring approximately 1.79 × 1.39 cm. The edge of the nodule was lobulated and uniformly enhanced on a contrast-enhanced scan. Abdominal CT suggested destruction of the structure of the right renal pelvis and calyces, with a lump-like and slightly high-density shadow in the renal sinus area, with the largest cross-sectional size approximately 4.46 × 4.81 cm. Contrast-enhanced scanning revealed multiple irregularly enhanced areas inside the mass in the arterial phase with multiple small blood vessels visible. The adjacent renal parenchyma exhibited decreased enhancement. CT revealed a malignant tumor in the right renal pelvis that had metastasized from other origins, or a bleeding pseudoaneurysm (Supplementary Figures 1, 2). Cystoscopy revealed no ureteral bleeding, and a biopsy of the bladder tissue revealed chronic inflammation of the mucosa. Urine cytology results were grade II and urine fluorescence *in situ* hybridization (FISH) was negative. Owing to the patient's wishes, no further treatment was administered.

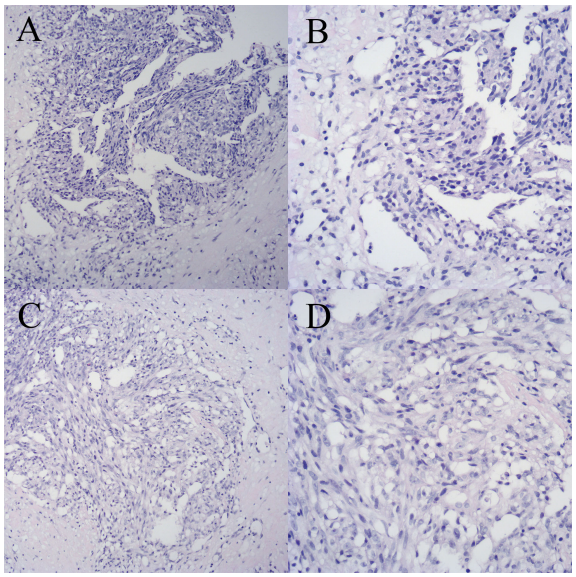


FIGURE 1
Breast biopsy specimen with hematoxylin and eosin (HE) staining. **(A)** Specimen 1 (×100). **(B)** Specimen 1 (×200). **(C)** Specimen 2 (×100). **(D)** Specimen 2 (×200).

After 3 months, CT showed an increase in the number and size of the lung lesions, and the tumor in the right renal pelvis was slightly larger, with the largest cross-sectional size of approximately 6.60 × 8.10 cm (Figure 3). Renal angiographic ultrasound showed that the tumor began to enhance at 17 s and then rapidly increased as a whole, with no enhancement visible inside the tumor throughout, reaching a peak at 20 s with high enhancement, and subsiding slightly earlier than the surrounding renal parenchyma (Supplementary Figure 3). The patient underwent robot-assisted laparoscopic right nephroureterectomy and transurethral cystoscopy for bladder clot removal (Supplementary Figure 4). Bleeding was observed at the right ureteral orifice during surgery. Postoperative pathology showed a tumor measuring 7.00 × 5.50 × 3.70 cm in the right renal pelvis, with cancerous tissue penetrating

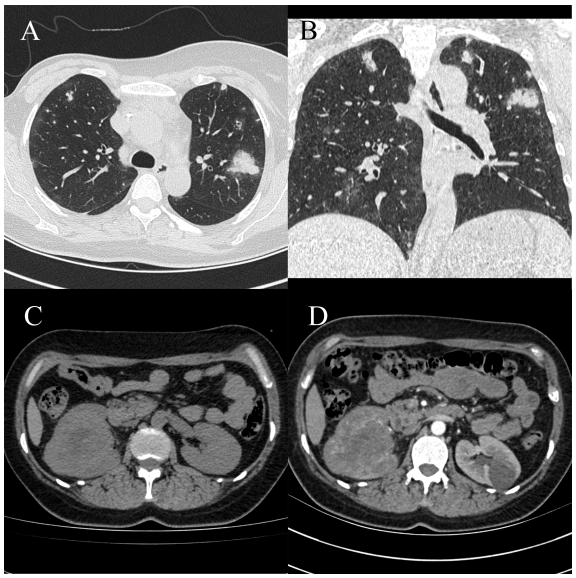


FIGURE 3
Computed tomography (CT) scan showing an increase in the number and size of lung lesions compared to previous results, with a slight increase in the right renal sinus mass. **(A)** Chest CT scan, horizontal position. **(B)** Chest CT scan, coronal position. **(C)** Abdominal CT scan, horizontal position. **(D)** Abdominal CT scan, arterial phase, horizontal position.

the perirenal fat and visible cancerous tissue in the blood vessels. Immunohistochemical staining showed CK20 (-), 34βE12 (-), β-catenin (membrane and cytoplasmic +), p63 (-), GATA-3 (focally weak +), S100P (-), Uroplakin II (-), CK7 (-), Ki67 (approximately 70% +), AE1/AE3 (-), EMA (-), Vimentin (+), CD31 (partial +), CD34 (+), SMA (-), Desmin (-), PAX-8 (-), INI-1 (expression), OCT3/4 (-), ALK D5F3 (-), CyclinD1 (partial +), HMB45 (-), Melan-A (partial +), S100 (-), Myogenin (-), Fli-1 (+), TLEl (+), and CD99 (partial cytoplasmic +) (Supplementary Figures 5, 6). The pathological diagnosis was consistent with angiosarcoma, partially presenting with an epithelial-like morphology. Follow-up at 4 months postoperatively showed symptoms of coughing and hemoptysis, with no other discomfort. CT revealed no abnormalities in the surgical area of the right kidney, but showed aggravation of lung metastasis (Supplementary Figure 7).

4 Discussion

BA is a rare malignant tumor. There are only a few retrospective studies and case reports but no large randomized controlled trials. Therefore, there are still no clear guidelines and evidence to guide the treatment of this disease. Surgery is still the main treatment at present (1). Due to the aggressive and multifocal nature of angiosarcoma, the prognosis is poor when the margins are positive (6). Currently, breast angiosarcoma is mainly treated with mastectomy to achieve as negative a margin as possible, and the recurrence rate after breast-conserving surgery is high (7, 8). There is still no definite evidence that adjuvant chemotherapy and radiotherapy can improve patient survival.

Angiosarcoma may present local recurrence and distant metastasis in the early stage, and the prognosis is significantly worse than that of other breast tumors. Studies have shown that DFS and OS of low - and medium-grade breast tumors are significantly longer than those of high-grade tumors (7, 9). PBA is prone to metastasize to the contralateral breast, lungs, bones, liver, ovaries, skin, and subcutaneous tissues hematogenously. However, there is currently no record of metastasis to the kidneys or renal pelvis. This disease can be differentiated from the following conditions.

Primary carcinoma of the renal pelvis: This is a subtype of urothelial carcinoma. Ureteroscopy and histopathological examinations are the gold standard for this form of carcinoma. Urine cytology and urine FISH examination are economical and convenient non-invasive methods with good sensitivity and specificity (10). Immunohistochemical (IHC) Staining is an application of immunostaining. It is based on antigen-antibody reaction, where it uses antibodies to determine the tissue distribution of an antigen of interest, such as tumor antigens. IHC is an important tool in diagnostic and research. The most important markers for malignant urothelial carcinoma are GATA3, CK7, CK20, and p63 (11), whereas for angiosarcoma, CD31 is the most specific marker for endothelial cell differentiation, and CD34 is more sensitive. Ki-67 reflects the mitotic rate of cells and is higher in sarcomas with invasive characteristics (12). The transcription factors ETS-related gene (ERG) and friend leukemia integration 1 (FLI-1) are new antibodies with high sensitivity and specificity compared with CD34 and CD31 (13).

Renal pelvic hematoma, otherwise known as renal pseudoaneurysm, is a renal pseudotumor caused by the rupture and bleeding of small renal parenchymal arteries. CT scans showed a slightly high-density mass with a clear boundary from the renal parenchyma, which could cause compression of the renal pelvis and calyces without signs of destruction. In the acute or subacute phase, the density of the mass may increase slightly owing to the entry of contrast agents into the lesion through the ruptured blood vessels.

Renal artery aneurysm: On CT, it appears as a uniform, slightly high-density mass with clear edges and calcifications on the wall. The tumor body was clearly enhanced. The difference is that the degree of aneurysm enhancement is the same as that of the abdominal aorta and renal artery at any time, and renal artery angiography remains the gold standard for diagnosis and treatment (14).

Nephroureterectomy is the gold standard treatment for upper urinary tract tumors, including total resection of the affected kidney and ureter to the ureteral orifice. Due to the long learning time for laparoscopic techniques, high surgical difficulty, and high tension in bladder incision suture reconstruction, its further promotion and application are limited. Robot-assisted laparoscopy has many advantages over traditional laparoscopy, including a three-dimensional high-definition surgical view, simulated arms with seven degrees of freedom, and the ability to automatically filter hand tremors (15). Currently, there are few reports of single-position robot-assisted laparoscopic nephroureterectomy for renal pelvic carcinoma in China. In this case, the patient had a minor

intraoperative injury, good postoperative recovery, and no adverse complications.

This study is the first reported case of renal metastasis from a PBA to date. The diagnosis and treatment of this rare malignant tumor remain challenging.

5 Patient perspective

The patient is satisfied with the treatment effect. The personal information related to the patient has been hidden from this manuscript. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

FG: Conceptualization, Data curation, Project administration, Writing – original draft. SS: Conceptualization, Data curation, Writing – original draft. XN: Conceptualization, Data curation, Writing – original draft. YW: Data curation, Writing – original draft. WY: Data curation, Writing – original draft. PY: Data curation, Writing – original draft. XD: Data curation, Writing – original draft. JS: Supervision, Writing – review & editing. YZ: Conceptualization, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to thank Editage (www.editage.cn) for English language editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1296328/full#supplementary-material

References

1. Abdou Y, Elkhanany A, Attwood K, Ji W, Takabe K, Opyrchal M. Primary and secondary breast angiosarcoma: single center report and a meta-analysis. *Breast Cancer Res Treat*. (2019) 178:523–33. doi: 10.1007/s10549-019-05432-4

2. Hodgson NC, Bowen-Wells C, Moffat F, Franceschi D, Avisar E. Angiosarcomas of the breast. *Am J Clin Oncol*. (2007) 30:570–3. doi: 10.1097/COC.0b013e3181131d62

3. Ooe Y, Terakawa H, Kawashima H, Ikeda H, Inaki N. Bilateral primary angiosarcoma of the breast: A case report. *J Med Case Rep*. (2023) 17:1–6. doi: 10.1186/s13256-023-03791-7

4. Champeaux-Orange E, Bonneau C, Raharimanana B, Favre A, Ibrahim M, Breteau N. Angiosarcome mammaire primitif: à Propos de deux cas. *Cancer/Radiothérapie*. (2009) 13:209–12. doi: 10.1016/j.canrad.2009.02.004

5. Fraga-Guedes C, André S, Mastropasqua MG, Botteri E, Toesca A, Rocha RM, et al. Angiosarcoma and atypical vascular lesions of the breast: diagnostic and prognostic role of myc gene amplification and protein expression. *Breast Cancer Res Treat*. (2015) 151:131–40. doi: 10.1007/s10549-015-3379-2

6. Gervais MK, Burtenshaw SM, Maxwell J, Dickson Bc, Catton CN, Blackstein M, et al. Clinical outcomes in breast angiosarcoma patients: A rare tumor with unique challenges. *J Surg Oncol*. (2017) 116:1056–61. doi: 10.1002/jso.24780

7. Taffurelli M, Pellegrini A, Meattini I, Orzalesi L, Tinterri C, Roncella M, et al. Secondary breast angiosarcoma: A multicentre retrospective survey by the national Italian association of breast surgeons (Anisc). *Breast*. (2019) 45:56–60. doi: 10.1016/j.breast.2019.02.011

8. Li GZ, Fairweather M, Wang J, Orgill DP, Bertagnolli MM, Raut CP. Cutaneous radiation-associated breast angiosarcoma. *Ann Surg*. (2017) 265:814–20. doi: 10.1097/sla.0000000000001753

9. McClelland S, Hatfield J, Degnin C, Chen Y, Mitin T. Extent of resection and role of adjuvant treatment in resected localized breast angiosarcoma. *Breast Cancer Res Treat*. (2019) 175:409–18. doi: 10.1007/s10549-019-05172-5

10. Liu J, Peng X, Ning X, Li T, Peng S, Wang J, et al. Clinical value of fluorescence in situ hybridization positive of exfoliated urothelial cells in urothelial carcinoma. *J*

PEKING Univ (HEALTH SCIENCES). (2017) 49:585–9. doi: 10.3969/j.issn.1671-167X.2017.04.006

11. Vlajnic T, Bubendorf L. Diagnostische und prädiktive marker in der harntraktzytologie. *Der Pathologe*. (2022) 43:99–104. doi: 10.1007/s00292-022-01053-9

12. Nahed AS, Shaimaa MY. Ki-67 as a prognostic marker according to breast cancer molecular subtype. *Cancer Biol Med*. (2016) 13:496–504. doi: 10.20892/j.issn.2095-3941.2016.0066

13. Varghese B, Deshpande P, Dixit S, Koppiker C, Jalnapurkar N. Primary angiosarcoma of the breast: A case report. *J Radiol Case Rep*. (2019) 13:15–25. doi: 10.3941/jrcr.v13i2.3449

14. LI S, Xiao J. Renal pseudotumors: ct diagnosis and differential diagnosis. *J Med Postgrad*. (2006) 19:788–92. doi: 10.16571/j.cnki.1008-8199.2006.09.008

15. Wei H, Miao J, Zhang Q, Qian L, Li E, Xu X, et al. Clinical observation of single-docking robot-assisted laparoscopic radical nephroureterectomy for renal pelvic carcinoma. *Chin J Gen Pract*. (2022) 20:39–42 + 71. doi: 10.16766/j.cnki.issn.1674-4152.002271

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 27 March 2024
DOI 10.3389/fonc.2024.1359886

OPEN ACCESS

EDITED BY
Daniel P. Bezerra,
Oswaldo Cruz Foudantion (FIOCRUZ), Brazil

REVIEWED BY
Mario Murguia-Perez,
Mexican Social Security Institute, Mexico
Manoj Gopal Madakshira,
Eastern Command Hospital, India

*CORRESPONDENCE
Xiuming Miao
xiumingmiao@163.com

RECEIVED 22 December 2023
ACCEPTED 12 March 2024
PUBLISHED 27 March 2024

CITATION
Yu M, Shi G, Gao Z, Wu K, Wei C, Li X and Miao X (2024) A case report and a literature review of double mammary pseudoangiomatous stromal hyperplasia associated with galactoma during pregnancy. *Front. Oncol.* 14:1359886. doi: 10.3389/fonc.2024.1359886

A case report and a literature review of double mammary pseudoangiomatous stromal hyperplasia associated with galactoma during pregnancy

Minmin Yu[1], Guangxi Shi[2], Zong Gao[3], Kai Wu[1], Cuilei Wei[1], Xiaohong Li[4] and Xiuming Miao[1]*

[1]Pathology Department, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China, [2]Breast and Thyroid Surgery Department, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China, [3]Neurosurgery Department, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China, [4]First Clinical School of Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China

Pseudoangiomatous stromal hyperplasia (PASH) is a benign interstitial hyperplasia of the breast that usually occurs in premenopausal or perimenopausal women. It is usually characterized by localized lesions or clear boundary masses, and diffuse double breast enlargement is rare. PASH is considered a hormone-dependent disease that is commonly progesterone related. There are no imaging characteristics, and both benign and suspicious malignant signs can be seen. The definitive diagnosis of PASH depends on a pathological diagnosis, and it is necessary to be vigilant in distinguishing between benign and malignant tumors with similar breast histopathology. Here, we report the case of a 23-year-old multipara patient with bilateral diffuse pseudoangiomatous stromal hyperplasia of the breast during pregnancy who presented with macromastia and reviewed the literature to further understand the clinical features, pathological diagnosis, differential diagnosis, treatment and prognosis of pseudoangiomatous stromal hyperplasia of the breast.

KEYWORDS

mammary gland, pseudoangiomatous stromal hyperplasia, pregnancy period, tumor, breast

Background

Pseudoangiomatous stromal hyperplasia (PASH) can exist independently and is mainly or entirely composed of stromal cells (1). It is a rare benign lesion of the breast that was first described by Vuitch et al. (1986). The age of onset ranges from 12 to 86 years (2), and it is most common in premenopausal women and less common in perimenopausal women and

men. It has also been reported in preadolescent women, patients with immune deficiency and patients taking immunosuppressants (3, 4). The etiology and pathogenesis of PASH are still unclear, and most scholars believe that its pathogenesis is related to hormone dependence. Most clinical cases involve palpable masses, very few of which can grow diffusely to form giant mammary disease. The clinical manifestations and imaging features are nonspecific (4, 5) and are often ignored or missed. A definitive diagnosis of PASH depends on a pathological diagnosis, and clinicians should be vigilant in distinguishing between benign and malignant tumors with histopathology similar to that of other breast tumors. We report a 23-year-old patient with bilateral diffuse pseudoangiomatous stromal hyperplasia of the breast during pregnancy who presented with galactoma. We also reviewed the literature to further understand the clinical features, pathological diagnosis, differential diagnosis, treatment and prognosis of patients with pseudoangiomatous stromal hyperplasia of the breast.

Clinical data

A 23-year-old female patient who conceived normally for the first time in January 2018 underwent a cesarean section in November and gave birth to a healthy baby girl. During pregnancy, bilateral mammary glands slightly increased in size symmetrically, and there was normal postpartum lactation. Multiple forms of galactostasis occurred during lactation, and after self-mammary physical therapy, lactation resumed, continuing for half a year. The patient became pregnant again in April 2019. At 12 weeks of pregnancy, asymmetry of the bilateral mammary glands increased, bumps were palpated, and occasional pain was felt. No treatment was administered, and the fetus was found to be normal during pregnancy. In February 2020, a healthy baby girl was delivered by cesarean section again. One week after delivery, bilateral breast gland enlargement was obvious, with a small amount of milk secretion, which continued to increase within three months, accompanied by back pain, local skin thickening and pruritus, and no milk secretion. She took the traditional Chinese medicines Rupixiao and Dianshi pills and then remained in stable condition. She came to our hospital on July 21, 2022, and a color ultrasound examination revealed changes in diffuse edema in both breasts (BI-RADS category 3). Breast MRI revealed multiple nodules and masses in both breasts, which were considered inflammatory granulomas. Pathologic results of tumor resection of the breast mass under local anesthesia revealed pseudohemangiomatoid stromal hyperplasia. One month after the operation, both breasts enlarged rapidly and affected the patient's life. On August 29 of the same year, double breast mass resection under general anesthesia plus bilateral breast reduction and lift was performed at another hospital, and the pathological results were the same as before. Six months after the operation, the patient developed a new breast mass, which grew rapidly, and the breast volume of the patient returned to its initial size, accompanied by thickening, hardening, and redness of the skin under the areola. This preoperative serological examination of female hormones revealed an increase in estradiol of 3834.49 pmol/ml, and the estradiol level reached a normal value after the operation. After full communication between the surgeon and the patient, bilateral subcutaneous gland resection, inverted mastectomy and skin biopsy were performed on July 4, 2023. Postoperative pathology revealed breast pseudohemangiomatoid stromal hyperplasia, epidermal hyperplasia with hyperkeratosis, granulosa thickening and chronic inflammatory cell infiltration in the dermis. No recurrence was found at the 5-month follow-up after the operation.

Imaging examination

Mammography revealed that both mammary glands appeared as lumps of varying size that were elliptic, with borders or partial borders, calcification, or structural distortion (Figures 1A, B).

Color ultrasound revealed that the double mammary gland was not clear, the structure was more disordered, the internal echo was not uniform, there were thick spots and light spots, and a patchy irregular sparse area could be seen. CDFI: No important abnormal blood flow in either mammary gland. There were many low-echo and no-echo zones in both breasts. The largest diameter of the no-echo zone was approximately 15.9 mm, and the diameter of the low-echo zone was approximately 19.6-53.9 mm. The shape was regular, the boundary was clear, and the echo was uniform (Figures 1C, D).

Routine pathological examination

General manifestations

The left and right mastectomy specimens weighed 5 kg and 5.5 kg, respectively. The sections were multinodular, 0.5-2.5 cm in diameter. The sections were gray and grayish brown, the internodules showed edema or mucous changes, and multiple sac-like structures of different sizes could be seen without bleeding or necrosis (Figure 2). The skin tissue of the breast was rough, thickened and pigmented.

Pathologic features

The histopathological features under the double mastoscope were similar, as shown by typical PASH images; PASH was diffusely distributed in the interlobular and intralobular tissues of the breast, similar to fibrous scar tissue; irregular fissured spaces of varying sizes were visible; the spaces were lined with mild fusiform cells; and no red blood cells were found in the lacunae. At the same time, there was common ductal epithelial hyperplasia, apocrine metaplasia, columnar cell hyperplasia and cystic changes, and flocculent secretions in the cystic cavity. Luteal phase changes were observed in normal breast lobular units, including lobular-specific interstitial edema, myoepithelial cell vacuolation, and high columnar ductal epithelium with apical plasma secretion. Epidermal hyperplasia of breast skin with hyperkeratosis, granulosa thickening with

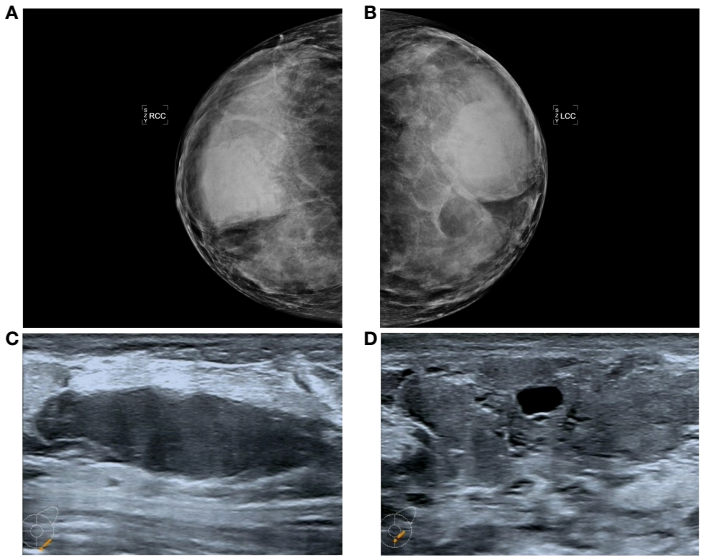


FIGURE 1
Manifestations **(A, B)** in the PASH image showed changes in the double milk molybdenum target, which showed an oval isondense mass. **(C, D)** show ultrasound changes in both breasts, manifested as hypoechoic nodules with clear boundaries and cystic changes.

acanthosis, superficial dermis and perivascular lymphocyte infiltration were observed (Figures 3A–F). Immunohistochemical results showed that the fusiform cells of the lacunar lining had positive expression of CD34+, SMA+, CD99+ and BCL-2+, while the vascular and lymphatic endothelial cells labeled with CD31 and D2-40 were negative and Ki-67 was <1%. The duct epithelium had positive expression of ER and PR, and the ER showed a heterogeneous expression pattern with varying intensity. The expression of PR was greater than that of ER, and most of the cells were strongly positive. The fusiform cells of the lacunar lining were negative (Figures 3G–I).

Discussion

PASH is a benign mesenchymal disease of the breast. It is most common in premenopausal or perimenopausal women, and the histopathological features are excessive proliferation of breast interstitial myofibroblasts and the production of rich collagen, which is localized, nodular or diffuse. The clinical manifestations of PASH are localized lesions, which are usually found by chance along with benign and malignant breast diseases. A study by Ibrahim et al. (6) showed that PASH could be found by chance in up to 23% of continuous breast specimens. In addition, 25% of male breast development cases have been reported (7, 8). In contrast, nodular and diffuse PASH, as independent lesions, are rare in clinical practice and typically present as a unilateral, clearly defined mass similar to breast fibroadenoma or lobe tumor, which is more common on one side without nipple or skin changes. A very small number of patients showed diffuse and rapidly enlarging masses on both mammary glands, and only two cases of PASH-related macrosomia in both breasts during pregnancy, accompanied by redness, swelling and orange peel changes, were reported (9, 10). Two previously reported cases of

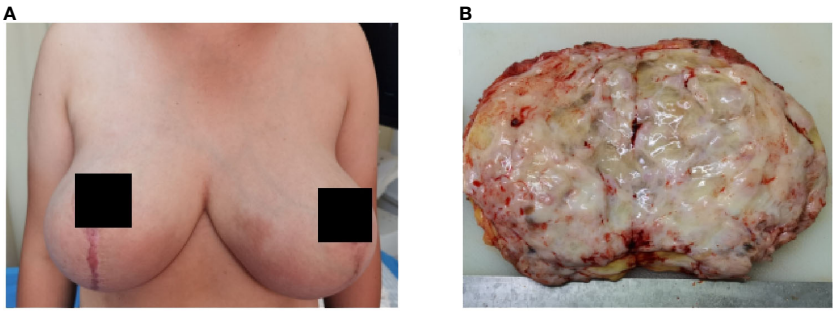


FIGURE 2
Bilateral mammary gland enlargement in patient **(A)** before surgery; **(B)** gross manifestations of tumor resection.

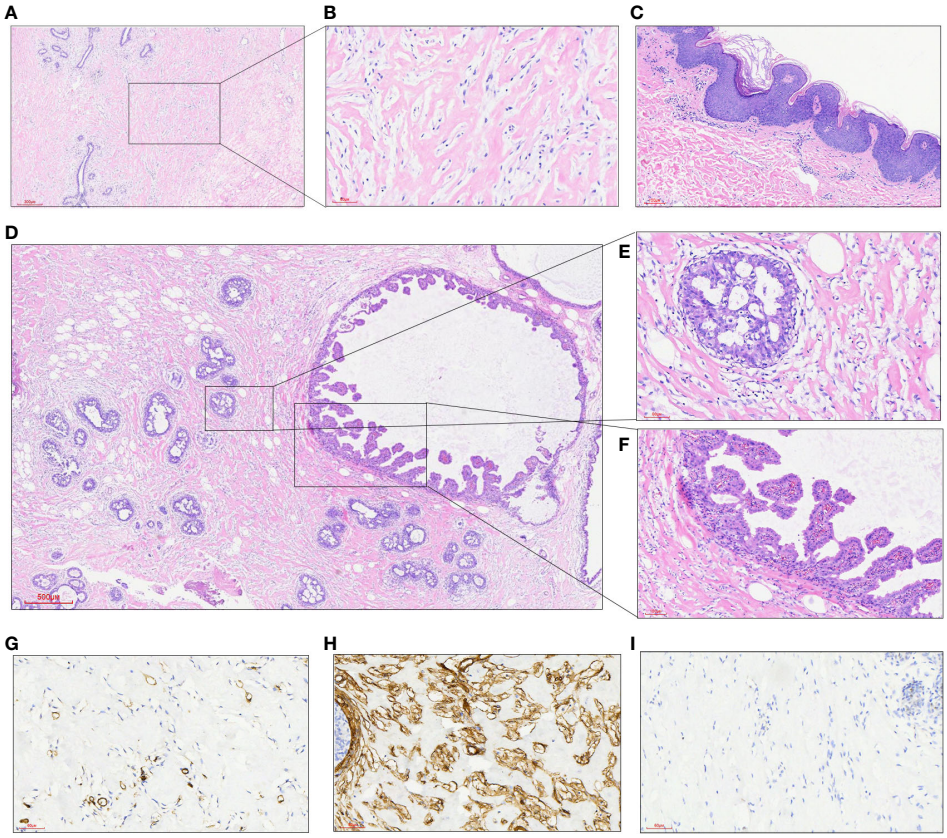


FIGURE 3
(A) At low power, a dense collagen matrix around and within the lobules was observed, with slit-like spaces (HE, 40X); **(B)** there were many fissure-like spaces in the dense collagenous breast interstitium, in which benign spindle cells were arranged without cytological atypia (HE, 200X); **(C)** epidermal hyperplasia of breast skin with hyperkeratosis, granulosa thickening and acanthosis edema; **(D)** focal points showed multiple intraductal common type (UDH) and papillary hyperplasia areas (HE, 40X); **(E)** a local enlarged UDH of the breast (HE, 200X); **(F)** ductal epithelial papillary hyperplasia of the breast (HE, 200X); **(G)** fusiform cells between fissures did not express the vasogenic marker CD31 (200X); **(H)** the expression of CD34 in fusiform cells between fissures was diffusively strong (200X); **(I)** PR was not expressed in fusiform cells of the interface (200X).

bilateral diffuse mammary pseudoangiomatous stromal hyperplasia during pregnancy presented with macromastia (Table 1). The first patient was a 33-year-old dichorionic diamniotic twin at 14 weeks of gestation who presented bilateral breast enlargement in early gestation, accompanied by back pain, limited movement, respiratory disorders and skin damage. The presence of PASH was confirmed by histopathology. Bilateral skin-sparing mastectomy was performed at 16 weeks gestation, and immediate reconstruction was performed. The fetuses were normal throughout the pregnancy, and healthy twins were delivered by cesarean section at 38 weeks gestation. Another 43-year-old primiparous woman presented at week 22 3/7 with bilateral breast enlargement, accompanied by back pain, limited mobility, respiratory disturbance, and skin damage. The patient had a history of a right breast mass on PASH 4 years prior. The patient had attempted to conceive with clomiphene and intrauterine insemination for 3 months and subsequently exhibited significant growth of the right mammary gland, which was pathologically confirmed as PASH. Bilateral mastectomy was performed at 6.5 months of gestation, and the patient delivered naturally to term with a healthy fetus and no other complications. In our case, a 23-year-old female presented with asymmetric enlargement of the bilateral mammary glands at the third month of gestation, with bumps and occasional pain. After delivery, bilateral mammary glands continued to substantially increase in size, without milk secretion, accompanied by local skin thickening and pruritus, and inflammatory granuloma was considered at first diagnosis. Pathology of the tissue from resection under local anesthesia revealed pseudohemangiomatoid stromal hyperplasia of the breast; this development recurred twice within 12 months after local resection, and the patient finally underwent total glandular resection of both breasts. No recurrence was observed in five months of follow-up.

PASH imaging often shows no specific changes, and both benign and suspicious malignant signs can be observed. It has been reported that nearly 53% of patients with PASH syndrome show abnormalities on screening mammograms (7), and the most common manifestation of PASH syndrome on X-rays is a lump of varying size, usually round or oval, with a border on the edge or a partial border (11). The most common feature of PASH in breast B-

10.3389/fonc.2024.1359886

TABLE 1 Overview of the two cases of bilateral breast PASH during pregnancy reported in the literature and this case.

Case	Age	Childbearing	Medical history	Course	Disease time	Clinical feature	Skin changes	Histopathology	Time and method of operation	Follow-up	References
1	33 yr	primigravida	bronchial asthma	initial	at 14 weeks of dichorionic diamniotic twin pregnancy presented	bilateral breast; breast tenderness, back pain with movement limitation and respiratory impairment.	multiple skin ulcerations	typical PASH	bilateral skin-sparing mastectomy at 16 weeks of the pregnancy	no recurrence; healthy twins were delivered by cesarean section at 38 weeks of gestation	(9)
2	43 yr	primigravida	tamoxifen for 3 month; infertility; *in vitro* fertilization (IVF)	recurrence	at 22 3/7 weeks of gestation	bilateral breast; edema throughout her bilateral breasts, bra strap grooving and tenderness with palpation	darkening, moderate erythema and edema	typical PASH	bilateral mastectomy at second trimester of gestation	no recurrence; delivering at term via spontaneous vaginal delivery	(10)
3	23 yr	multipara	multiple galactostasis during first lactation	recurrence	at 12 weeks of gestation	bilateral breast gland enlargement;	thickening and pruritus	typical PASH	bilateral subcutaneous gland resection, inverted mastectomy on July 4, 2023	no recurrence	this case

ultrasonography is a well-defined low-echo or equal-echo oval mass enhanced by transmission, while the presence of fibrocystic changes can lead to a heterogeneous appearance, generally without calcification (12). Mammography examination mostly revealed round or oval isodense masses with clear boundaries. Polger et al. (13) performed a mammography examination of 7 PASH patients and found isodense masses with a diameter of 1.1-11 cm and no calcification. Breast magnetic resonance imaging (MRI) shows mass or nonmass enhancement and benign dynamic changes (8, 12). In this case, the imaging examination also revealed many low-echo and no echo areas, clear boundaries and uniform echoes.

The histopathological characteristics of PASH can be divided into classic and fascicular types according to the microscopic manifestations. Fissure-like communication branches can be observed in typical PASH, and the inner wall of the fracture is composed of proliferated spindle cells without obvious nuclear atypia or nuclear division. There were no red blood cells in the fissure, and the interwoven collagen fibers exhibited hyaline degeneration. The lesions usually surround the breast lobules, widen the space between the lobules, or extend into the lobules but do not destroy the normal structure of the lobules (2, 14). PASH may be mistaken for low-grade angiosarcoma, which has a true vascular space, on pathological examination (12, 15). Fascicular PASH has more abundant cells, and the fusiform cells in the lesion are arranged in bundles and lack a fissure structure, which is often observed in conjunction with myofibroblastoma (12, 15). In our case, the areas of interlobular and netted interlobular mesenchyme in both breasts were replaced by typical PASH, the lobular units were enlarged or irregular, but no lobular structure was destroyed, and the ductal epithelium was accompanied by exuberant hyperplasia. Common hyperplasia, papillary hyperplasia, columnar cell transformation, cystic dilatation, and flocculent protein secretion can be observed in the cystic dilatation gland lumen, as can nontypical hyperplasia and carcinoma *in situ*. Relatively normal uninvolved lobular units showed luteal phase changes, lobular-specific interstitial edema, myoepithelial cell vacuolation, high columnar ductal epithelium with apical plasma secretion, and no lactation.

The etiology and pathogenesis of PASH remain unclear. Some researchers have combined the histopathological characteristics of PASH and the clinical characteristics of recurrent, multiple and accompanied neoplastic breast lesions, and most scholars believe that its pathogenesis may involve excessive and abnormal responses of breast myofibroblasts to progesterone stimulation (2, 14, 16). Studies have shown that progesterone receptors are highly expressed in PASH stromal cells but not in normal breast stromal cells. Since progesterone is produced by the metabolism of cytochrome P450, drugs metabolized by cytochrome P450, such as clonazepam, sodium valproate and risperidone, increase the level of progesterone and thus stimulate the growth of PASH (16, 17). In this case, the patient presented with galactoma during pregnancy and experienced two recurrences. Histopathology revealed that diffuse PASH in both breasts presented changes in the extent of galactoma changes without structural damage to lobular units, accompanied by vigorous breast ductal epithelium; relatively normal lobular units presented luteal phase changes, lobular

specialized interstitial edema, and myoepithelial vacuolation; and the ductal epithelium presented a highly columnar shape with apical plasma secretion. However, no lactation was observed, so the patient could not breastfeed normally after delivery. Combined with the pathogenesis and histopathological findings of the patients, we agree with most scholars that the occurrence of breast PASH is closely related to the increase in progesterone. The occurrence of PASH during pregnancy is due to progesterone secreted by the placenta, which stimulates hyperplasia of mammary stromal myofibroblasts. However, the hypothesis that PASH is associated with elevated hormone levels is controversial. A study by Erin Bowman et al. conducted a retrospective data analysis of 24 patients with PASH and revealed that 95% of the samples were positive for ER or PR, which supported its developmental hormonal basis (12). Interestingly, both the ER and PR were not expressed in the spindle cells of the interstitium in this patient, while both were expressed in the ductal epithelium, with the PR being considerably more highly expressed than the ER. In addition, patients have transient prolactin increases during onset, and whether there is a correlation between them needs to be further confirmed. The pathogenesis of this disease remains to be studied.

Breast PASH needs to be differentiated from low-grade hemangiosarcoma, phyllodes tumor, metaplastic carcinoma with spindle cell differentiation, and hamartoma. Primary hemangiosarcoma of the breast is relatively rare. The tumor is invasive and often has unclear boundaries with surrounding tissues. The histological manifestations are anastomotic branched blood vessels lined with atypical endothelial cells, which express factor VIII, CD31, CD34 and other markers (18). Phyllodes tumors of the breast are biphasic tumors with hyperplasia of the stroma and epithelium of the breast. Hyperplasia of the stroma stimulates the disordered growth of glands, resulting in irregular branching of ducts and distorted lobules and disordered distribution of stroma and glands, forming a blade-like structure, which can be focally combined with PASH. The foliar structure is lined with the ductal epithelium of the breast. The duodenal epithelium expresses glandular epithelial markers (19). Metaplastic carcinoma accompanied by spindle cell differentiation refers to infiltrating adenocarcinoma rich in spindle cells. Spindle cells are heteromorphic and can be nests, sheets or braided, and the cells exhibit certain heteromorphism accompanied by varying amounts of nuclear division; interstitial cells may exhibit varying degrees of collagenization and express the epithelial-labeled spindle cells AE1/AE3, CK7, CK8/18, etc. Breast hamartomas contain varying amounts of fat, fibrous tissue and smooth muscle tissue, and disorganized ducts and lobules can also be observed, possibly accompanied by PASH. The clinical manifestations and imaging findings of PASH in pregnancy overlap with those of granulomatous lobular mastitis (GLM) in the mass stage, which is easily misdiagnosed as GLM and needs to be confirmed by pathological examination.

There are currently no standards for the treatment of PASH. Different treatment options are often selected according to different clinical manifestations. For local lesions, clinicians often choose observation, follow-up, and regular monitoring. Among the principles for the management of benign breast diseases announced at the 19th Annual Meeting of the American College of Breast Surgeons in 2018, the first is that the breast PASH region of asymptomatic patients is removed by irregular surgery (20). Those with nodular lesions > 2 cm need complete resection, and for those with small volumes, follow-up is recommended (12, 21, 22). When nodular PASH presents as macromastia, which affects its appearance, or when the tumor increases rapidly in a short period and it is difficult to determine whether it is benign or malignant, surgical resection is often the first choice of treatment. Ryu et al. (23) reported that patients with galactoma could be treated with breast reduction surgery, and total resection was generally not considered. The patient only underwent local resection of the breast mass at the first visit, and the patient relapsed twice within 11 months after local resection; finally, she underwent total glandular resection of both breasts. The patient recovered well after surgery, and no recurrence was observed at the 4-month follow-up. The recurrence rate of PASH after resection can reach 28.5%, and follow-up is still needed after resection (24). Regarding the timing of surgery for PASH during pregnancy, Jennifer Wang et al. suggested that the best time for surgical intervention is in the early second trimester, after fetal organogenesis has been completed, when the uterine floor is located below the sacral point. It is likely that pregnant women who undergo mastectomy due to PASH-induced mastectomy in the second trimester will recover quickly from an obstetrical point of view, and the risk to the fetus is low. We believe that surgical total mastectomy to prevent the recurrence of PASH-related giant mastectomy is a better treatment. Several researchers have reported a possible role for antihormone therapy in the treatment of breast PASH, but there are insufficient data to demonstrate the effectiveness of such medical management (10, 25, 26).

The prognosis of PASH is good, and no cases of Pash-related death have been reported (3, 16, 26). Drinka et al. (27) confirmed that PASH can accompany invasive breast cancer, but there is no evidence that PASH can promote the occurrence or progression of breast cancer. Degnim (28) reviewed the biopsies of 9065 women who had benign mastectomy biopsies between 1967 and 1991 and estimated the relative risk of subsequent breast cancer with PASH using the standardized incidence ratio (SIR), finding that the presence of PASH did not imply an increased risk of subsequent breast cancer compared with the general population (27).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MY: Writing – original draft, Writing – review & editing. GS: Writing – original draft, Writing – review & editing. ZG: Writing – original draft, Writing – review & editing. KW: Writing – original draft, Writing – review & editing. CW: Writing – original draft, Writing – review & editing. XL: Writing – original draft, Writing – review & editing. XM: Writing – original draft, Writing – review & editing.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Rowe JJ, D'Alfonso TM, Pauwels P, Vai-Bernal JF. Pseudoangiomatous stromal hyperplasia. In: *WHO Classification of Tumors Editorial Board. Breast tumors, 5th ed*, vol. 2. Lyon (France): International Agency for Research on Cancer. (2019). Available at: https://publications.iarc.fr/581.

2. Estes A, Cao L, Miller ME. "Pseudoangiomatous stromal hyperplasia: overview and clinical management.". *J Bridge Breast Surg*. (2020). doi: 10.21037/abs-20-86

3. Alikhassi A, Skarpathiotakis M, Lu FL, Curpen B. Pseudoangiomatous stromal hyperplasia of the breast, imaging and clinical perspective: A review. *Breast Dis*. (2023) 42:147–53. doi: 10.3233/BD-220072

4. Yigit B, Citgez B, Celayir MF, Yetkin S, Tanik C, Mihmanli M. Pseudoangiomatous stromal hyperplasia causing severe breast enlargement in a 15-year-old girl: A case report. *J Pak Med Assoc*. (2020) 70:1263–5. doi: 10.5455/JPMA.27271

5. Vashistha A, Rundla M, Khan F, Om P. Idiopathic gigantomastia with Pseudoangiomatous stromal hyperplasia: A case report. *Int J Surg Case Rep*. (2020) 77:915–9. doi: 10.1016/j.ijscr.2020.09.151

6. Ibrahim RE, Sciotto CG, Weidner N. Pseudoangiomatous hyperplasia of mammary stroma. Some observations regarding its clinicopathologic spectrum. *Cancer*. (1989) 63:1154–60. doi: 10.1002/1097-0142(19890315)63:6<1154::aid-cncr2820630619>3.0.co;2-q

7. Raj SD, Sahani VG, Adrada BE, Scoggins ME, Albarracin CT, Woodtichartpreecha P, et al. Pseudoangiomatous stromal hyperplasia of the breast: multimodality review with pathologic correlation. *Curr Probl Diagn Radiol*. (2017) 46 (2):130–5. doi: 10.1067/j.cpradiol.2016.01.005

8. Speer ME, Yoon EC, Berg WA, Chang Sen LQ. Pseudoangiomatous stromal hyperplasia: radiologic-pathologic correlation. *J Breast Imaging*. (2022) 5:67–72. doi: 10.1093/jbi/wbac051

9. Krawczyk N, Fehm T, Ruckhäberle E, Mohrmann S, Riemer J, Braunstein S, et al. Bilateral diffuse pseudoangiomatous stromal hyperplasia (PASH) causing gigantomastia in a 33-year-old pregnant woman: case report. *Breast Care (Basel)*. (2016) 11:356–8. doi: 10.1159/000450867

10. Wang SJ, Maheswaran S, Reiss R, Portnow LH, Brock J, Novak L, et al. Gestational pseudoangiomatous stromal hyperplasia presenting as gigantomastia: A case report of a rare breast entity with clinical recommendations by a multidisciplinary team. *Case Rep Surg*. (2023) 2023:9279934. doi: 10.1155/2023/9279934

11. Parameswaran PR, Renganathan R, Subramaniam P, Thakur V. Radiological spectrum of pseudoangiomatous stromal hyperplasia of breast-A case series. *Indian J Radiol Imaging*. (2022) 32:582–90. doi: 10.1055/s-0042-1750174

12. Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, et al. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J*. (2012) 18:242–7. doi: 10.1111/j.1524-4741.2012.01230.x

13. Polger MR, Denison CM, Lester S, Meyer JE. Pseudoangiomatous stromal hyperplasia: mammographic and sonographic appearances. *AJR Am J Roentgenol*. (1996) 166:349–52. doi: 10.2214/ajr.166.2.8553945

14. Kelten Talu C, Boyaci C, Leblebici C, Hacihasanoglu E, Bozkurt ER. Pseudoangiomatous stromal hyperplasia in core needle biopsies of breast specimens. *Int J Surg Pathol*. (2017) 25:26–30. doi: 10.1177/1066896916660763

15. Woo SH, Kang H, Choi WJ, Kim EK. Pseudoangiomatous stromal hyperplasia of the breast in a female adolescent presenting as bilateral gigantomastia. *J Breast Cancer*. (2023) 26:391–6. doi: 10.4048/jbc.2023.26.e21

16. Choi YJ, Ko EY, Kook S. Diagnosis of pseudoangiomatous stromal hyperplasia of the breast: ultrasonography findings and different biopsy methods. *Yonsei Med J*. (2008) 49:757–64. doi: 10.3349/ymj.2008.49.5.757

17. Virk RK, Khan A. Pseudoangiomatous stromal hyperplasia: an overview. *Arch Pathol Lab Med*. (2010) 134:1070–4. doi: 10.5858/2008-0686-RS.1

18. Wang XY, Jakowski J, Tawfik OW, Thomas PA, Fan F. Angiosarcoma of the breast: a clinicopathologic analysis of cases from the last 10 years. *Ann Diagn Pathol*. (2009) 13:147–50. doi: 10.1016/j.anndiagpath.2009.02.001

19. Bi J, Tang H, Lin X, Yu X, Liang Y, Zhang L, et al. Morphological features of 52 cases of breast phyllodes tumours with local recurrence. *Virchows Arch*. (2022) 481 (4):519–31. doi: 10.1007/s00428-022-03383-8

20. Rao R, Ludwig K, Bailey L, Berry TS, Buras R, Degnim A, et al. Select choices in benign breast disease: an initiative of the american society of breast surgeons for the american board of internal medicine choosing wisely® Campaign. *Ann Surg Oncol*. (2018) 25(10):2795–800. doi: 10.1245/s10434-018-6584-5

21. Malik D, Basher RK, Mittal BR, Jain TK, Bal A, Singh SK. 68Ga-PSMA expression in pseudoangiomatous stromal hyperplasia of the breast. *Clin Nucl Med*. (2017) 42:58–60. doi: 10.1097/RLU.0000000000001445

22. Vyas S, Greenwood HI, Jankowski T, Freimanis RI, Kallianos KG, Henry TS, et al. A case of acute onset gigantomastia in a 20-year-old woman. *Clin Imaging*. (2020) 68:57–60. doi: 10.1016/j.clinimag.2020.06.020

23. Ryu EM, Whang IY, Chang ED. Rapidly growing bilateral pseudoangiomatous stromal hyperplasia of the breast. *Korean J Radiol*. (2010) 11:355–8. doi: 10.3348/kjr.2010.11.3.355

24. Kurt E, Turanlı S, Markoç F, Berberoğlu U. How to manage pseudoangiomatous stromal hyperplasia: our clinical experience. *Turk J Med Sci*. (2017) 47:1410–5. doi: 10.3906/sag-1702-140

25. Seltzer MH, Kintiroglou M. Pseudoangiomatous hyperplasia and response to tamoxifen therapy. *Breast J*. (2003) 9:344. doi: 10.1046/j.1524-4741.2003.09426.x

26. Gresik CM, Godellas C, Aranha GV, Rajan P, Shoup M. Pseudoangiomatous stromal hyperplasia of the breast: a contemporary approach to its clinical and radiologic features and ideal management. *Surgery*. (2010) 148:752–8. doi: 10.1016/j.surg.2010.07.020

27. Drinka EK, Bargaje A, Erşahin ÇH, Patel P, Salhadar A, Sinacore J, et al. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a clinicopathological study of 79 cases. *Int J Surg Pathol*. (2012) 20:54–8. doi: 10.1177/1066896911418643

28. Degnim AC, Frost MH, Radisky DC, Anderson SS, Vierkant RA, Boughey JC, et al. Pseudoangiomatous stromal hyperplasia and breast cancer risk. *Ann Surg Oncol*. (2010) 17:3269–77. doi: 10.1245/s10434-010-1170-5

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 16 April 2024
DOI 10.3389/fonc.2024.1295772

OPEN ACCESS

EDITED BY
Dirk Geerts,
University of Amsterdam, Netherlands

REVIEWED BY
Anca Maria Cimpean,
Victor Babes University of Medicine and Pharmacy, Romania
Sarbjeet Makkar,
Washington University in St. Louis, United States

*CORRESPONDENCE
Liliana Montella
liliana.montella@aslnapoli2nord.it

†These authors share senior authorship

RECEIVED 17 September 2023
ACCEPTED 11 March 2024
PUBLISHED 16 April 2024

CITATION
Montella L, Di Marino L, Marino MA, Riccio V, Del Gaudio N, Altucci L, Berretta M and Facchini G (2024) Case report: An ultrasound-based approach as an easy tool to evaluate hormone receptor-positive HER-2-negative breast cancer in advanced/metastatic settings: preliminary data of the Plus-ENDO study. *Front. Oncol.* 14:1295772. doi: 10.3389/fonc.2024.1295772

Case report: An ultrasound-based approach as an easy tool to evaluate hormone receptor-positive HER-2-negative breast cancer in advanced/metastatic settings: preliminary data of the Plus-ENDO study

Liliana Montella[1*], Luigi Di Marino[2], Maria Adele Marino[3], Vittorio Riccio[4], Nunzio Del Gaudio[5], Lucia Altucci[5,6†], Massimiliano Berretta[7†] and Gaetano Facchini[1†]

[1]Oncology Operative Unit, "Santa Maria delle Grazie" Hospital, ASL Napoli 2 NORD, Pozzuoli, Italy, [2]Breast Unit, Clinica Pineta Grande, Castel Volturno, Italy, [3]Oncology Operative Unit, "S.Maria della Pietà" Hospital, Casoria, Italy, [4]Ospedale S.Maria della Pietà, Casoria, Italy, [5]Department of Precision Medicine, "Luigi Vanvitelli" University of Campania, Napoli, Italy, [6]Molecular Biology and Genetics Research Institute, Biogem, Ariano Irpino, Italy, [7]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Background: Hormone receptor-positive tumors are unlikely to exhibit a complete pathological tumor response. The association of CDK 4/6 inhibitor plus hormone therapy has changed this perspective.

Case presentation: In this study, we retrospectively reviewed the charts of patients with a diagnosis of luminal A/B advanced/metastatic tumors treated with a CDK 4/6 inhibitor-based therapy. In this part of the study, we present clinical and ultrasound evaluation. Eight female patients were considered eligible for the study aims. Three complete and five partial responses were reported, including a clinical tumor response of 50% or more in five out of nine assessed lesions (55%). All patients showed a response on ultrasound. The mean lesion size measured by ultrasound was 27.1 ± 15.02 mm (range, 6–47 mm) at the baseline; 16.08 ± 14.6 mm (range, 0–40 mm) after 4 months (T1); and 11.7 ± 12.9 mm (range, 0–30 mm) at the 6 months follow-up (T2). Two patients underwent surgery. The radiological complete response found confirmation in a pathological complete response, while the partial response matched a moderate residual disease.

Conclusion: The evaluation of breast cancer by ultrasound is basically informative of response and may be an easy and practical tool to monitor advanced tumors, especially in advanced/unfit patients who are reluctant to invasive exams.

KEYWORDS

breast cancer, hormone-responsive, radiology, ultrasound, CDK4/6 inhibitors

1 Introduction

Advanced breast cancer includes, according to the 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5) (1), both inoperable locally advanced breast cancer (LABC) and metastatic breast cancer (MBC). LABC is often considered a candidate for therapies with the aim of tumor shrinkage before the surgery, decreasing the rate of mastectomy in favor of less demolition surgery, testing the *in vivo* drug sensitivity, and tailoring treatment according to the pathological response obtained.

The indication for neoadjuvant chemotherapy in hormone receptor-positive (HR+)/HER2-negative tumors is not straightforward (2). While recent trials reach 60% of pathological response rate (pCR) in HER2-positive and triple-negative tumors and are rapidly changing therapeutic algorithms (3, 4), standard chemotherapy produces an inadequate pCR (0%–18%) (1) and breast-conserving surgery (5) approximately 60% in advanced HR + tumors with a low Ki-67 proliferation rate. A large study starting from 134,574 HR+ breast cancer patients extracted data on 29,250 patients undergoing neoadjuvant chemotherapy and reported approximately 8% of pCR (6). As in the HER-2 and TN tumors, pCR correlates with improved survival (7).

In 2013, the St. Gallen International Expert Consensus defined luminal A and luminal B tumors as ER-positive, HER2-negative tumors having respectively Ki-67 low and PR high, or Ki-67 high or PR (8). Almost uniformly, a Ki-67 <14% is associated with a luminal A profile, while above 14% corresponds to a luminal B tumor (9). Given the fluctuating Ki-67 value across the different studies, the definition of luminal A- or B-like is often adopted. The St. Gallen International Consensus Guidelines for the treatment of early breast cancer 2021 (10), acknowledging the conclusions from another working group (9), identified the groups of tumors with Ki-67 <5% and with Ki-67 >30% and recommended chemotherapy only in the latter group. The definition of the best treatment for the in-between band remains a controversial matter. Molecular characterization of the different histological subtypes has increasingly contributed to defining precision oncology-guided therapeutic algorithms (10). Some features such as luminal B subtype, high proliferation, and lack of progesterone receptor (2) may be predictive of increased pCR rates; however, information on efficacy outcomes is scarce, while surrogate endpoints such as Ki67 reduction are often adopted in clinical trials (11).

Alternative strategies have been explored including, very recently, the combination of chemo- and immunotherapy, which lead to an increased rate of pCR in luminal-B like BC defined as HR-positive/HER2-negative, Ki-67 ≥ 20%, and/or histological grade 3 (12). In other instances, a genomic-based approach was used to differentiate high- to low-risk luminal A BC patients and address the first to neoadjuvant chemotherapy and the others to endocrine therapy (13).

The interest in endocrine preoperative strategies for HR+ positive tumors has been progressively growing. Different CDKs have been investigated in BC. They have a prognostic role and are a pharmacological target for therapeutic intervention (14).

Seven studies have investigated CDK4/6 inhibitors in neoadjuvant HR+ positive, HER-2 negative BC (Supplementary Table S1). Most of the studies previously reported focused on the antiproliferative effect detected *in vivo* and showed moderate clinical activity. The need for periodical biopsies to assess tumor changes for study purposes has raised some ethical issues.

To date, many studies focus on pCR as a primary objective, which is quite disappointing (15), while there is a relative lack of information coming from radiological tools used during follow-up, which could be preliminary informative and maybe predictive of treatment response. The imaging of the breast is essential in the diagnosis, staging, and monitoring of breast cancer. In clinical practice, the response is mostly evaluated by ultrasound (US) or magnetic resonance imaging (MRI), the second one showing high sensitivity in the detection of a residual tumor. Additionally, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) provides functional information at baseline and after treatment and was shown to correlate with pCR (16, 17). Compared to MRI, US can be considered easier to perform, does not require the injection of exogenous contrast agents, and is less expensive. It is classically considered operator dependent, which is a limit that may be overcome by the selection of a unique and skilled operator. US is accurate in size evaluation, but less comprehensive than mammography in providing an overall view. This technique can simply be used to monitor treatment response. However, the US is not used for RECIST due to operator dependency.

We argue that an integrative approach including clinical and radiological information should best define the therapeutic algorithms of HR+, HER-negative breast cancer patients undergoing medical treatments. Therefore, we evaluate a series of advanced/metastatic HR+ patients treated with CDK 4/6 I+AI in a real-world setting, making the radiological assessment the cornerstone in comparison with clinical outcomes and pathological findings.

2 Case description

We retrospectively evaluated our archive of advanced and metastatic pre-and post-menopausal breast cancer patients with a pathologically confirmed ER+ and HER2− (0 or 1+ by IHC or FISH negative) invasive breast cancer treated with a combination of CDK 4/6 I+AI as per clinical practice. In detail, CDK 4/6 inhibitors used in this study were palbociclib and ribociclib. Palbociclib was used at a dose of 125 mg taken by mouth with food on 21 days and 7 days off schedule (on days 1–21 of each 28-day cycle). Ribociclib was administered at 600 mg/day: 3 weeks ON and 1 week OFF. Letrozole was the first-line endocrine treatment for all patients. Letrozole was administered every day of each 28-day cycle at a dose of 2.5 mg. Goserelin was administered to pre-menopausal subjects as a subcutaneous injection every 28 days at a dose of 3.6 mg.

No limit was formally defined for Ki-67. At baseline, an advanced stage was required related to the tumor (≥ T3 or surgically unresectable) or lymph nodes (≥ N2, upper arm edema due to breast and lymphnodes involvement). Metastatic patients at presentation with evaluable primary tumors were also considered eligible. Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0–2, adequate organ, and marrow function. Exclusion criteria included previous treatment with CDK4/6 inhibitors, organ failure, and treatment intolerance.

The study was approved by our Institutional Review Board (Campania Centro Ethical Committee approval n.391, N.Reg 22/2022) and followed the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was required before study entry.

The primary study aim was the evaluation of clinical and US tumor response.

Tumor and lymph nodes were clinically evaluated after 1 month of treatment and thereafter every 2 months/3 months with clinical and US examination. RX mammography, breast MRI, and PET/CT with FDG were performed after 4 months/6 months and in case of suspected progression. Computed tomography was performed as a staging procedure at study entry, after 4 months/6 months, and as clinically required.

Clinical response rate (cRR) was evaluated clinically using bi-dimensional clinical measurements and radiologically using the US before the start of treatment and every 4 months subsequently.

A single lesion, even in the case of multifocal, was chosen and evaluated at time 0, at time 1 (T1) after 4 months/6 months of therapy, and at time 2 (T2) after 8 months/12 months. B-mode US was performed in a supine and lateral position, with both upper limbs facing upwards. To study the breast lesion, a conventional B-mode US and Color-Doppler US were performed with a 4–14-MHz linear array transducer. In compliance with the 5th edition of the BI-RADS classification (18), the imaging characteristics have been recorded on a spreadsheet Excel database: size, position, shape, orientation to the skin, margins, echogenicity pattern, posterior characteristics, and vascularization. The secondary aims were the rate of response by MRI and PET, the rate of conservative surgery, the pCR obtained, changes in Ki-67, and immunohistochemistry from baseline in response to therapy and safety. The pathology exam of the resected specimen at the time of surgery was evaluated and assessed by a well-qualified pathologist. pCR was defined as the absence of invasive disease in the breast and sampled axillary lymph nodes (ypT0 ypN0). Residual tumor was defined according to the Residual Cancer Burden Index (19).

Clinically responder patients remained on treatment until disease progression if metastatic and without a fixed end-of-treatment point in case of locally advanced disease. A complete metabolic response was considered mandatory for surgical referral. If a surgical intervention was considered appropriate by the Multidisciplinary Teams, CDK 4/6 inhibitor was stopped at least 2 weeks before surgery, whereas letrozole was continued till the day of surgery.

The patients were regularly monitored with complete blood count and blood chemistry. All toxicities encountered during the study were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events, v3.0. Dosage reductions were performed according to the manufacturer's datasheet.

From a screening of 24 patients treated with CDK 4/6 I+IA, we selected eight patients with *in situ* primary breast tumors and advanced or metastatic disease having complete clinical and radiological records. All but two patients were postmenopausal (age range, 48–84 years; mean, 64 years). Two patients had a bilateral BC, three patients had advanced BC, and five had metastatic BC at study entry. The comprehensive characteristics of the patients are reported in Table 1.

Two patients underwent surgery. The surgical intervention was in both cases radical mastectomy with axillary lymph node dissection.

The median number of CDK4/6 I + AI cycles before surgery was 8 (range, 6–10). The interval between the start-up of treatment and surgical procedure was 1 year and 6 months, respectively.

Before the treatment, the patients had clinically and radiologically large tumors [four out of 10 tumors were staged T2 (40%), three tumors were T3 (30%), and three were T4 (30%)]. All patients but two had clinical/radiological suspected nodal metastases.

Nine lesions having complete data were evaluated. Mean lesion size was 27.1 ± 15.02 mm [range, 6–47 mm) at the baseline; 16.08 ± 14.6 mm (range, 0–40 mm) after 4 months (T1), and 11.7 ± 12.9 mm (range, 0–30 mm) at 6 months follow-up (T2). In Table 2, the lesions' size for each patient is listed. Imaging features were noted according to the Breast Imaging Report and Data System (BI-RADS) lexicon. Imaging features were noted according to the Breast Imaging Report and Data System (BI-RADS) lexicon as reported in Table 3. From baseline to T1, two out of seven (28%) lesions changed their shape from irregular to oval.

10.3389/fonc.2024.1295772

TABLE 1 Patients' characteristics.

Patient	Advanced/metastatic disease	Carcinoma type	Luminal	Stage	US response	Surgery	RCB
1	M	D	B	IIIC	PR	Y	3
2	A	NOS	A	II		Y	0
					CR		
3	A	L	B	IIIA	PR	N	–
4	M	D+D	A+B	IV	CR	N	–
5	M	L+L	B+B	IV	PR	N	–
6	M	D	A	IV	PR	N	–
7	M	D	B	IV	PR	N	–
8	A	L	A	IIIB	CR	N	–

*A, advanced; M, metastatic; D, ductal; L, lobular; NOS, not otherwise specified; RCB, residual cancer burden; Y, yes; N, no; CR, complete response; PR, partial response.

None of the lesions changed their orientation with reference to the skin or margins. The only lesion described as complex at T1 had a combined posterior pattern at baseline. Furthermore, compared to the baseline, two lesions showed a better-defined duct infiltration after the first cycle of treatment. All lesions at T1 demonstrated absent vascularization. At T2, four lesions completely disappeared. Of the five visible lesions in the US, only 2/5 (40%) kept an irregular shape. Furthermore, all the lesions visible were hypoechoic with associated posterior shadowing. Five out of nine assessed lesions (55%) showed a clinical tumor response of 50% or more, including 4/5 (80%) complete responses and 1/5 (20%) partial responses. Changes in tumor sizes and shapes can be seen in Figure 1. Analysis of the area of cancer on bi-dimensional measurement before and after treatment showed that the mean values were 27.1 ± 15.02 mm at baseline, 16.08 ± 14.6 mm at T1, and 11.7 ± 12.9 mm at T2, respectively. All patients (100%%) showed a response in the US. In four cases, the lesion size halved as compared with basal.

The two patients that underwent surgery were selected because of a metabolic complete response by PET/CT. In detail, one of them had a complete radiological response, the other reported a partial response. The radiological complete response found confirmation in a pCR, while the partial response matched an RCB-II (moderate residual disease). In this latter case, Ki-67 lowered from 40% to 6%.

Treatment with the CDK 4/6 inhibitors was generally well tolerated. In detail, only two patients aged more than 65 required a lower dose, and only one patient aged 84 years needed both dose reduction and prolonged drug rest to allow hematological recovery.

3 Discussion and conclusion

Approximately 80% of patients with breast cancer are diagnosed at an age >50, and luminal A BC is most diagnosed in over 70 years population (20). This epidemiological landscape requires customized management in real-world practice that regards the frequent old age of our patients' population and acceptance of treatment/diagnostic procedures.

HR+ breast cancer larger than 2 cm, with involved lymph nodes and high Ki-67 index, have been considered candidates for preoperative treatments. Assessment of breast cancer treatment

TABLE 2 Lesion distribution and T0, T1, and T2 size by patient.

Patient	No. of lesions	Size (mm) T0	Size (mm) T1	Size (mm) T2
1	1	18	10	10
2	2	11.5	0	0
3	3	44	40	30
4	4	14	10	0
5	5	36.5	30.5	23
6	6	47	33	30
7	7	31	11	14
8	8	36	10	0
	9	6	0	0

10.3389/fonc.2024.1295772

TABLE 3 BI-RADS descriptors at T0, T1, and T2 evaluation.

BI-RADS descriptors		T0	T1	T2
Shape	Irregular	7/9 (78%)	3/7 (43%)	2/5 (40%)
	Oval	1/9 (11%)	3/7 43%)	2/5 (40%)
	Round	1/9 (11%)	1/7 (14%)	1/5 (20%)
Orientation	Parallel	4/9 (44%)	3/7 (43%)	3/5(60%)
	Not-parallel	5/9 (56%)	4/7 (57%)	2/5 (40%)
Margins	Circumscribed	–	–	–
	Not-circumscribed	9/9 (100%)	7/7 (100%)	5/5 (100%)
Echo pattern	Hypoechoic	5/9 (56%)	6/7 (86%)	5/5 (100%)
	Complex cystic and solid	3/9 (33%)	1/7 (14%)	–
	Heterogeneous	1/9 (11%)	–	–
Posterior features	None	–	–	–
	Enhancing	–	–	–
	Shadowing	5/9 (56%)	6/7 (86%)	5/5 (100%)
	Combined pattern	4/9 (44%)	1/7 (14%)	–
Associated features	Skin changes	7/9 (78%)	2/7 (28%)	2/5 (40%)
	Edema	1/9 (11%)	3/7 (43%)	1/5 (20%)
	Duct infiltration	1/9 (11%)	2/7 (28%)	2/5 (40%)
Vascularization	Absent	2/9 (22%)	7/7 (100%)	5/5 (100%)
	Vessels in rim	1/9 (11%)	–	–
	Internal	6/9 (67%)	–	–
No lesion			2/9 (22%)	5/9 (56%)

response is challenging, with the potential of underestimation or overestimation of residual cancer for the available different imaging techniques. Both morphological and functional imaging methods can be used to assess the response to treatments. Morphological techniques, such as full-field digital mammography (FFDM), digital breast tomosynthesis (DBT), and the US, and advanced techniques, such as breast MRI, contrast-enhanced spectral mammography (CESM), 18F-FDG PET/CT, and MRI, are nowadays pivotal in breast cancer. The selection of the imaging methods depends on the availability and should always be established in the multidisciplinary tumor board (21–25).

Ultrasound may be useful to predict the molecular subtype before pathological diagnosis (26) as reported by Zhu et al., having evaluated ultrasound features concerning more than 80 patients. This report emphasizes the value of the US in breast cancer that should not be neglected within the array of more complex radiological techniques.

In our series, the number of each histotype (Table 1) limited an extensive description of US reports correlated to histology.

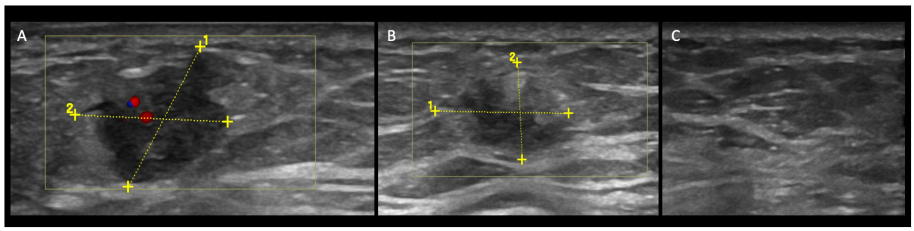


FIGURE 1
Case patient no. 4. **(A)** Color-Doppler US demonstrates a hypoechoic mass with an irregular shape and not-circumscribed margin, vertical orientation posterior, and internal vascularization at baseline. **(B)** At T1, the lesion changed the size (14 mm to 11 mm), and the vascularization at Color Doppler is now absent. The echo pattern remained hypoechoic. At T2 **(C)**, the lesion is not visible anymore.

US is superior to FFDM, DBT, and clinical breast examination in monitoring the response to NAC and is overall well tolerated by the patients. Sonographic evaluation of the residual tumor includes not only the size but also changes in tumor echogenicity and a decreased mass stiffness, and both could be considered good predictors of a pCR (27, 28). US is not used for RECIST due to operator dependency. However, US is easily accepted by patients and may be routinary and repeatedly performed. Moreover, the percentage of US diameter reduction after three cycles of treatment showed acceptable sensitivity and specificity response in a study on 64 patients (27).

In our cases, US demonstrated how the lesions changed not only in size but also in echogenicity and, by using the BI-RADS lexicon, the associated features described at the baseline. The most salient changes were the absence of vascularization after the first cycle of treatment and the changes in echogenicity after the second cycle of treatment.

Several factors may influence US breast evaluation. Body fat-driven obesity and breast fat density and their changes according to menopausal status are known factors influencing radiological assessment (29).

Efforts have been devoted to unraveling the impact of body mass index (BMI) on the therapeutic response among breast cancer patients, yet controversy persists. A recent meta-analysis disclosed that overweight/obese patients exhibited a lower pCR rate compared to under/normal weight counterparts (30).

In detail, also the assessment of the axilla may change with varying patient BMI, thus possibly conditioning the selection of a given radiological technique (31).

Defining a precise sensitivity for ultrasound alone proves challenging, with variations strongly dependent on lesion size, breast tissue type, and, as with all methods, patient selection.

While breast density stands as an independent risk factor for breast cancer, the widely acknowledged association between overweight/obesity and breast cancer development, particularly impacting the prognosis of HR-positive postmenopausal breast cancer, prompts further exploration. Various studies suggest that factors such as the chronic inflammatory state, circulating adipokines, insulin, insulin-like growth factor (IGF), and sex hormones may play pivotal roles in mediating the link between overweight/obesity and breast cancer (32).

The histological BC subtypes notoriously correlate with a different response to medical treatment. A different sensitivity in detecting pCR after NAC was found to be related to parameters such as estrogen receptor expression, on the one hand and HER-2 overexpression, luminal B, or Ki-67 proliferation >14%, on the other hand, respectively favoring MRI and PET-CT (33). Therefore, the need for radiological studies set by subtypes is progressively acknowledged (34).

While luminal A tumors are poorly chemoresponsive and better candidates for the association of CDK4/6 and aromatase inhibitors (CDK 4/6 I+AI), luminal B tumors represent an area of investigation. The NCT04137640 (35) is investigating the efficacy of the CDK 4/6 inhibitor palbociclib plus letrozole in comparison to chemotherapy in locally advanced breast cancer with ≤30% Ki-67 with group allocation according to Ki-67. The PREDIX LumB (NCT02603679) (35) is a phase II study that enrolled luminal B tumors and compares two sequences of treatments: weekly paclitaxel versus the combination of the CDK 4/6 inhibitor palbociclib and standard endocrine treatment for an initial phase of 12 weeks with following cross-over for further 12 weeks of treatment (neoadjuvant phase: 24 weeks) and adjuvant chemotherapy for both groups.

RIBOLARIS (NCT05296746) (35) used ribociclib as neoadjuvant treatment for clinically high-risk ER+ and HER2− breast cancer with a choice of CDK 4/6 inhibitor prosecution or alternately treatment with chemotherapy in the adjuvant phase according to the pathological and biological response assessed by Prosigna.

CDK 4/6 I+AI combination shows distinctive features as compared to other therapies. First, from a biological point of view, the inhibition of growth arrest may be reversible. CDK4/6 inhibition induces cytostatic effect in cell cultures and solid tumor models with potential regression associated with the intrinsic tumor cell turnover (36). Variably, according to the studied models, growth arrest may be irreversible or not (36). This aspect translates into Ki-67 changes during and at treatment, stopping with a rapid rise while off-therapy. From a clinical point of view, further consequences are hypothetical prolonged treatments to achieve the best response and redefinition of the best time for surgical intervention, which, in clinical studies, canonically falls 16–20 weeks after the start of treatment. This window may be functional for chemo- but not for CDK 4/6 inhibitor-based treatment. In line with this concept, NEOLETRIB trial (NCT05163106) (35), RIBOLARIS, and FELINE pre-specified a study treatment of 24 weeks or at least 6 months.

Ki-67 determination at 2–4 weeks of treatment has been considered the most accurate surrogate endpoint in neoadjuvant endocrine treatments. However, the recognized limits are represented by heterogeneous Ki-67 within the tumor, which required more than one biopsy to best collect comprehensive information and the invasive nature of repeated biopsies (37). From a biological approach, we then moved to a radiological-centered approach. This pattern has been typically described by MRI but is also detected by US and results to be predictive of worse outcomes compared to concentric shrinkage (38).

Similar to MRI, US is a technique that does not expose the woman to radiation and its related risks. However, opposite to MRI, there are no contraindications to the breast US. Furthermore, breast US is a valid tool that is widely available, and it is not prone to time slots and shortage of equipment as much as MRI. Furthermore, breast US is cheap, its cost being comparable to that of mammography and much lower than that of breast MRI REF. In Italy, the cost of a single breast MRI (250€) is up to seven times higher than that of one breast US (35.89 €). Yet, these ways are less expensive compared to the costs of a breast MRI in the US (>500 $).

Therefore, the US preserves its role as an easy and practical tool to monitor local response to medical treatments, especially in unfit and elderly patients, reserving a delayed time for more demanding and expansive exams. Further prospective studies including a larger number of patients should define the value of each tool and best guide diagnostic guidelines drafting in NAC. At present, we highlight the role of a basic breast US in the follow-up of advanced/metastatic BC with *in situ* tumors. In a time of limited

economic resources, the appropriate use of each radiological technique should be encouraged.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the Campania Centro Ethical Committee. The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

LM: Writing – review & editing, Writing – original draft. LDM: Writing – review & editing, Resources, Investigation, Conceptualization. MM: Writing – review & editing, Writing – original draft, Supervision, Project administration, Formal analysis, Data curation. VR: Writing – review & editing, Visualization, Supervision. NG: Writing – review & editing, Validation, Supervision. LA: Writing – review & editing, Visualization, Validation, Supervision. MB: Writing – review & editing, Visualization, Validation, Supervision. GF: Writing – review & editing, Visualization, Validation, Supervision.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to thank the following: Campania Regional Government Lotta alle Patologie Oncolog-iche iCURE (CUP B21C17000030007); MIUR Proof of Concept (POC01_00043); and MISE2020: Nabucco 1682; VALERE: Vanvitelli per la Ricerca Program: EPInhibitDRUGre (CUP B66J20000680005); and Bando giovani ricercatori D.R. n.834 del 30/09/2022 Università Vanvitelli: IDEA (CUP: B63C22001470005) for supporting NG and LA team.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1295772/full#supplementary-material.

References

1. Cardoso F, Paluch–Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol.* (2020) 31:1623–49. doi: 10.1016/j.annonc.2020.09.010

2. Torrisi R, Marrazzo E, Agostinetto E, De Sanctis R, Losurdo A, Masci G, et al. Neoadjuvant chemotherapy in hormone receptor–positive/HER2–negative early breast cancer: When, why, and what. *Crit Rev Oncol Hematol.* (2021) 160:103280. doi: 10.1016/j.critrevonc.2021.103280

3. van der Voort A, Liefaard MC, van Ramshorst MS, van Werkhoven E, Sanders J, Wesseling J, et al. Efficacy of neoadjuvant treatment with or without pertuzumab in patients with stage II and III HER2–positive breast cancer: a nationwide cohort analysis of pathologic response and 5–year survival. *Breast.* (2022) 65:110–5. doi: 10.1016/j.breast.2022.07.005

4. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. KEYNOTE–522 investigators. Pembrolizumab for early triple–negative breast cancer. *N Engl J Med.* (2020) 382:810–21. doi: 10.1056/NEJMoa1910549

5. Gu J, Groot G, Holtslander L, Engler–Stringer R. Understanding women's choice of mastectomy versus breast conserving therapy in early–stage breast cancer. *Clin Med Insights Oncol.* (2017) 11:1179554917691266. doi: 10.1177/1179554917691266

6. Zeidman M, Alberty–Oller J, Ru M, Pisapati KV, Moshier E, Soojin Ahn S, et al. Use of neoadjuvant versus adjuvant chemotherapy for hormone receptor–positive breast cancer: a National Cancer Database (NCDB) study. *Breast Cancer Res Treat.* (2020) 184:203–12. doi: 10.1007/s10549-020-05809-w

7. Haque W, Verma V, Hatch S, Klimberg VS, Butler EB, Teh BS. Response rates and pathologic complete response by breast cancer molecular subtype following neoadjuvant chemotherapy. *Breast Cancer Res Treat.* (2018) 170:559–67. doi: 10.1007/s10549–018–4801–3

8. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart–Gebhart M, Thürlimann B, et al. Panel members Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol.* (2013) 24:2206–23. doi: 10.1093/annonc/mdt303

9. Feeley LP, Mulligan AM, Pinnaduwage D, Bull SB, Andrulis IL. Distinguishing luminal breast cancer subtypes by Ki67, progesterone receptor or TP53 status provides prognostic information. *Mod Pathol.* (2014) 27:554–61. doi: 10.1038/modpathol.2013.153

10. Burstein HJ, Curigliano G, Thürlimann B, Weber WP, Poortmans P, Regan MM, et al. Panelists of the St Gallen Consensus Conference. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus

Guidelines for treatment of early breast cancer 2021. *Ann Oncol*. (2021) 32:1216–35. doi: 10.1016/j.annonc.2021.06.023

11. Cabrera–Galeana P, Muñoz–Montaño W, Lara–Medina F, Alvarado–Miranda A, Pérez–Sánchez V, Villarreal–Garza C, et al. Ki67 changes identify worse outcomes in residual breast cancer tumors after neoadjuvant chemotherapy. *Oncologist*. (2018) 23:670–8. doi: 10.1634/theoncologist.2017–0396

12. Dieci MV, Guarneri V, Tosi A, Bisagni G, Musolino A, Spazzapan S, et al. Neoadjuvant chemotherapy and immunotherapy in luminal B–like breast cancer: results of the phase II GIADA trial. *Clin Cancer Res*. (2022) 28:308–17. doi: 10.1158/1078–0432.CCR–21–2260

13. Han W. Personalized neoadjuvant strategy in luminal A breast cancer to increase BCS rate (PLATO study). *J Clin Oncol*. (2020) 38:vi17. doi: 10.1093/annonc/mdy318.030

14. Bao X.–J, Wenli L, Sun T, Wang J–W, Liu X–F, Li M–X, et al. Clinical data analysis of CDKs expression and prognosis in breast cancer. *WCRJ*. (2023) 10:e2475. doi: 10.32113/wcrj_20231_2475

15. Hong K, Yao L, Sheng X, Ye D, Guo Y. Neoadjuvant therapy of cyclin–dependent kinase 4/6 inhibitors combined with endocrine therapy in HR+/HER2– breast cancer: A systematic review and meta–analysis. *Oncol Res Treat*. (2021) 44:557–67. doi: 10.1159/000518573

16. Groheux D. Predicting pathological complete response in breast cancer early. *Lancet Oncol*. (2014) 15:1415–6. doi: 10.1016/S1470–2045(14)71020–4

17. Li P, Wang X, Xu C, Liu C, Zheng C, Fulham MJ, et al. 18F–FDG PET/CT radiomic predictors of pathologic complete response (pCR) to neoadjuvant chemotherapy in breast cancer patients. *Eur J Nucl Med Mol Imaging*. (2020) 47:116–1126. doi: 10.1007/s00259–020–04684–3

18. American College of Radiology. *ACR BI–RADS atlas: breast imaging reporting and data system. 5th ed*. Virginia, Reston: American College of Radiology (2013).

19. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol*. (2007) 25:4414–22. doi: 10.1200/JCO.2007.10.6823

20. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—Epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—An updated review. *Cancers (Basel)*. (2021) 13:4287. doi: 10.3390/cancers13174287

21. Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. NCCN guidelines® Insights: breast cancer, version 4.2021. *J Natl Compr Cancer Netw*. (2021) 19. doi: 10.6004/jnccn.2021.0023

22. Park J, Chae EY, Cha JH, Shin HJ, Choi WJ, Choi Y–W, et al. Comparison of mammography, digital breast tomosynthesis, automated breast ultrasound, magnetic resonance imaging in evaluation of residual tumor after neoadjuvant chemotherapy. *Eur J Radiol*. (2018) 108:261–8. doi: 10.1016/j.ejrad.2018.09.032

23. Vinnicombe SJ, MacVicar AD, Guy RL, Sloane JP, Powles TJ, Knee G, et al. Primary breast cancer: mammographic changes after neoadjuvant chemotherapy, with pathologic correlation. *Radiology*. (1996) 198:333–40. doi: 10.1148/radiology.198.2.8596827

24. Goldberg H, Zandbank J, Kent V, Leonov–Polak M, Livoff A, Chernihovsky A, et al. Chemotherapy may eradicate ductal carcinoma in *situ* (DCIS) but not the associated microcalcifications. *Eur J Surg Oncol*. (2017) 43:1415–20. doi: 10.1016/j.ejso.2017.04.011

25. Mun HS, Kim HH, Shin HJ, Cha JH, Ruppel PL, Oh HY, et al. Assessment of extent of breast cancer: comparison between digital breast tomosynthesis and full–field digital mammography. *Clin Radiol*. (2013) 68:1254–9. doi: 10.1016/j.crad.2013.07.006

26. Zhu J–Y, He H–L, Jiang X–C, Bao H–W, Chen F. Multimodal ultrasound features of breast cancers: correlation with molecular subtypes. *BMC Med Imaging*. (2023) 23:57. doi: 10.1186/s12880–023–00999–3

27. Evans A, Whelehan P, Thompson A, Purdie C, Jordan L, Macaskill J, et al. Prediction of pathological complete response to neoadjuvant chemotherapy for primary breast cancer comparing interim ultrasound, shear wave elastography and MRI. *Ultraschall Med*. (2018) 39:422–31. doi: 10.1055/s–0043–111589

28. Dobruch–Sobczak K, Piotrzkowska–Wróblewska H, Klimonda Z, Roszkowska–Purska K, Litniewski J. Ultrasound echogenicity reveals the response of breast cancer to chemotherapy. *Clin Imaging*. (2019) 55:41–6. doi: 10.1016/j.clinimag.2019.01.021

29. Chu A, Sung P, Lee J, Cheun J–H, Hwang K–T, Lee K, et al. Association of body composition fat parameters and breast density in mammography by menopausal status. *Sci Rep*. (2022) 12:22224. doi: 10.1038/s41598-022-26839-y

30. Wang H, Zhang S, Yee D, Basu S, Beckwith H, Potter D, et al. Impact of body mass index on pathological complete response following neoadjuvant chemotherapy in operable breast cancer: a meta–analysis. *Breast Cancer*. (2021) 28:618–29. doi: 10.1007/s12282-020-01194-w

31. Macaione I, Galvano A, Graceffa G, Lupo S, Latteri M, Russo A, et al. Impact of BMI on preoperative axillary ultrasound assessment in patients with early breast cancer. *Anticancer Res*. (2020) 40:7083–8. doi: 10.21873/anticanres.14736

32. Zhao C, Hu W, Xu Y, Wang D, Wang Y, Lv W, et al. Current landscape: the mechanism and therapeutic impact of obesity for breast cancer. *Front Oncol*. (2021) 11:704893. doi: 10.3389/fonc.2021.704893

33. Baysal H, Serdaroglu AY, Ozemir IA, Baysal B, Gungor S, Erol CI, et al. Comparison of magnetic resonance imaging with positron emission tomography/computed tomography in the evaluation of response to neoadjuvant therapy of breast cancer. *J Surg Res*. (2022) 78:223–32. doi: 10.1016/j.jss.2022.04.063

34. Jones EF, Hathi DK, Freimanis R, Mukhtar RA, Chien AJ, Esserman LJ, et al. Current landscape of breast cancer imaging and potential quantitative imaging markers of response in ER–positive breast cancers treated with neoadjuvant therapy. *Cancers (Basel)*. (2020) 12:1511. doi: 10.3390/cancers12061511

35. *clinicaltrials.gov* (Accessed 24rd April 2023).

36. Knudsen ES, Witkiewicz AK. The strange case of CDK4/6 inhibitors: mechanisms, resistance, and combination strategies. *Trends Cancer*. (2017) 3:39–55. doi: 10.1016/j.trecan.2016.11.006

37. Barchiesi G, Mazzotta M, Krasniqi E, Pizzuti L, Marinelli D, Capomolla E, et al. Neoadjuvant endocrine therapy in breast cancer: current knowledge and future perspectives. *Int J Mol Sci*. (2020) 21:3528. doi: 10.3390/ijms21103528

38. Fukada I, Araki K, Kobayashi K, Shibayama T, Takahashi S, Gomi N, et al. Pattern of tumor shrinkage during neoadjuvant chemotherapy is associated with prognosis in low–grade luminal early breast cancer. *Radiology*. (2018) 286:49–57. doi: 10.1148/radiol.2017161548

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 19 April 2024
DOI 10.3389/fonc.2024.1372710

OPEN ACCESS

EDITED BY
Dirk Geerts,
University of Amsterdam, Netherlands

REVIEWED BY
Eunice Van Den Berg,
University of the Witwatersrand, South Africa
Hanen Bouaziz,
Salah Azaiez Institute, Tunisia

*CORRESPONDENCE
Qin Ou
ouqin1980@163.com

RECEIVED 18 January 2024
ACCEPTED 03 April 2024
PUBLISHED 19 April 2024

CITATION
Li W, Ou Q, Li Y and Yuan LY (2024) Malignant phyllodes tumor of the breast with predominant osteosarcoma and chondrosarcomatous differentiation: a rare case report and review of literature. *Front. Oncol.* 14:1372710. doi: 10.3389/fonc.2024.1372710

Malignant phyllodes tumor of the breast with predominant osteosarcoma and chondrosarcomatous differentiation: a rare case report and review of literature

Wenfang Li[1], Qin Ou[2]*, Yingdong Li[3] and Linlin Yuan Yuan[3]

[1]Taihe Hospital, Hubei University of Medicine, Shiyan, China, [2]Department of Pathology, School of Basic Medical Sciences, Hubei University of Medicine, Shiyan, Hebei, China, [3]Department of General Surgery, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China

Background: Phyllodes tumors (PTs), which account for less than 1% of mammary gland tumors, composed of both epithelial and stromal components. If a malignant heterologous component is encountered, PT is considered malignant. Malignant phyllodes tumors (MPTs) only account for 8% to 20% of PTs. We report a case of MPT with osteosarcoma and chondrosarcoma differentiation and review the literature to discuss the differential diagnosis and therapy.

Case presentation: A 59-year-old Chinese woman come to our hospital because of a palpable mass she had had for 1 months in the left breast. Preoperative core needle biopsy (CNB) was performed on the left breast mass on January 11, 2023. Pathological diagnosis was malignant tumor, the specific type was not clear. Mastectomy and sentinel lymph node biopsy of the left breast was performed. No metastasis was found in 3 sentinel lymph nodes identified by carbon nanoparticles and methylene blue double staining. Heterologous osteosarcoma and chondrosarcomatous differentiation of phyllodes tumor were observed. Immunohistochemistry: spindle tumor cells ER(-), PR(-), HER-2 (-), CK-pan(-), CK7(-), CK8(-), SOX10(-), S100(-), and MDM2(-), CK5/6(-), P63(-), P40(-) were all negative. CD34:(+), SATB2(+), P53(90% strong), CD68 (+), Ki-67 (LI: about 60%). No ductal carcinoma *in situ* was found in the breast. Fluorescence *in situ* hybridization (FISH) indicated USP6 was negatively expressed on formalin-fixed, paraffin-embedded (FFPE) tissue sections.

Conclusion: MPTs are rare, and heterologous differentiation in MPTs is exceedingly rare. It could be diagnosed by pathology when metaplastic carcinoma, primary osteosarcoma, or myositis ossificans were excluded. This case could help clinicians to improve the prognosis and treatment of this disease.

KEYWORDS

malignant phyllodes tumors, breast tumor, osteosarcoma, chondrosarcoma, thoracic oncology

1 Introduction

Phyllodes tumors (PTs), which account for less than 1% of mammary gland tumors, composed of both epithelial and stromal components (1). Malignant phyllodes tumors (MPTs) only account for 8% to 20% of PTs (2). The World Health Organization has subcategorized PTs into benign, borderline, and malignant categories on the basis of 5 histological parameters: stromal cellularity, stromal atypia, tumor margins, mitotic activity, and stromal overgrowth (3). MPTs are characterized by marked stromal cellularity, stromal growth, nuclear atypia, increased mitotic activity (≥10 per 10 high power fields), and infiltrative tumor margins (4). Moreover, the presence of heterologous sarcomatous elements such as osteosarcoma, chondrosarcoma, or liposarcoma within the tumor were frequently observed (5). Due to the limitation of rare incidence, it is difficult to proceed randomized trials and prospective cohort studies for MPTs with heterologous sarcomatous elements (6).

This study describes a case/patient with osteosarcomatous and chondrosarcomatous heterologous elements within a MPT based on detailed imaging and histopathologic records, and we review the literature to describe the characteristics and therapy of MPT with osteosarcoma and chondrosarcomatous differentiation.

2 Clinical data

Patient, ×××, female, 59 years old, due to "presented with a mass in the left breast for more than 1 month". On January 7, 2023, she was admitted to the breast surgery Department of Taihe Hospital, Hubei University of Medicine. In the past 1 month, she felt a mass in the left breast, and the nipple was not bleeding or leaking. The patient had a history of hypertension for 30 years and cerebral hemorrhage for more than 1 year. In 2013, she underwent "left breast mass resection" in our hospital, and the pathological report was cystic hyperplasia (left breast). Clinical physical examination: a hard mass of about 3.0×2.0cm in size could be detected at 4cm from the nipple in the upper outer quadrant of the left breast, with no obvious tenderness, non-smooth surface, unclear boundary, and limited motion. No obvious abnormalities in the contralateral breast were found. There is no obvious mass in the bilateral axilla. The color ultrasound of the breast showed that there was a low-echo mass located at the edge of the mammary gland at 2 points in the left upper quadrant, with a size of 23×25×19mm, the boundary was not clear, and the shape was irregular, and no strong punctate echo was observed (Figure 1A). The combination of contrax-enhanced ultrasound suggested hypoechoic mass in the left breast, uneven enhancement in the arterial phase, unsmooth boundary, slow regression in the venous phase, and obvious enlargement in the lesion area identified as BI-RADS Category V. Reactive hyperplasia of bilateral axillary lymph nodes.

Preoperative core needle biopsy (CNB) was performed on the left breast mass on January 11, 2023. Pathological diagnosis was malignant tumor, the specific type was not clear, and further diagnosis was to be made after surgery. The patient given up breast conserve surgery. Mastectomy and sentinel lymph node biopsy of the left breast was performed. No metastasis was found in 3 sentinel lymph nodes identified by carbon nanoparticles and methylene blue double staining. Pathological examination results: the size of the left breast was 23×18×3.0cm, and the fusiform skin was attached, the size of which was 19.5×7.0cm (Figure 1B). The size of the tumor was 3.0cm×2.5cm×2.2cm. The section was grayish-white and slightly hard in nature, and the boundary was poorly defined or poorly circumscribed. The tumor was 2.2cm away from the skin and 0.5cm away from the deep margin. TNM stage given was pT2N0M0.

The tumor is composed of two components: (1) The normal breast lobular structure is disordered or disappeared. The tumor has a lobulated mass (Figure 1C), which is composed of epithelial and stromal components. The epithelial cells are columnar or cuboidal without obviously atypia. Stromal cells are fusiform, the cytological atypia was obvious (Figure 1D), with 10 mitotic images/10HPF. And the epithelioid stromal cells are interspersed with short fusiform plump cells and mononuclear/multinucleoma giant cells. Local stromal cells form pseudoadenoid or clumps or nests. Mesenchymal myxoid changes in some areas of the tumor, the mesenchymal cells are sparse, epithelioid or spindle, and scattered tumor giant cells are also seen. About 1/5 of the tumor interstitial tissues showed fibrosis or hyalinoid degeneration. (2) Heterogenic components of tumor mesenchyma were observed: cartilage and bone tissue. The cartilage tissue presented cartilaginous islands of different sizes. The stroma showed a tumor osteoid rimmed by tumor cells along with osteoclastic giant cells, osteosarcoma differentiation. Tumor cells surrounded trabeculae, and the cell atypia was significant, showing mitotic images (Figure 1E). Chondrocytes of different density were observed with obvious cell atypia, and mitotic images (Figure 1F). ③ Immunohistochemistry: Spindle tumor cells ER(-), PR(-), HER-2(-), CK-pan(-), CK7(-), CK8(-), SOX10(-), S100(-), and MDM2(-), CK5/6(-), P63(-), P40(-) were all negative. CD34:(+), SATB2(+), P53(90% strong), CD68 (+), Ki-67(LI: about 60%) (Figure 2). ④ No ductal carcinoma *in situ* was found in the breast, and no metastasis were found in axillary lymph nodes. Pathological consultation advice of Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology: Malignant (breast) phyllodes tumor with osteosarcoma and chondrosarcoma differentiation was considered.

2.1 Fluorescence *in situ* hybridization

Two-color separation probe kit was purchased from Lbp Medicine Science & Technology (Guangzhou, China) which was adopted to detect USP6 on formalin-fixed, paraffin-embedded (FFPE) tissue sections. The probe is located on chromosome 17p13.2, the proximal (proximal centromere) probe marks red fluorescence, and the distal (proximal telomere) probe marks green fluorescence. Fluorescence *in situ* hybridization (FISH) testing procedure was in strict accordance with the standardized steps: The 3-5μm thick tissue was sliced, incubated for 2 h at (65 ± 5)°C, dewaxed and hydrated, deionized boiled at (100 ± 5)°C for 20 min, digested by pepsin for 15 min, dripped with a probe, denatured at 85°C for 5 min, and hybridized at 37°C for 10-18 h. Nuclear restaining of 4 ‘, 6-diamidino-2 ‘phenylindole (DAPI) under fluorescence microscope.

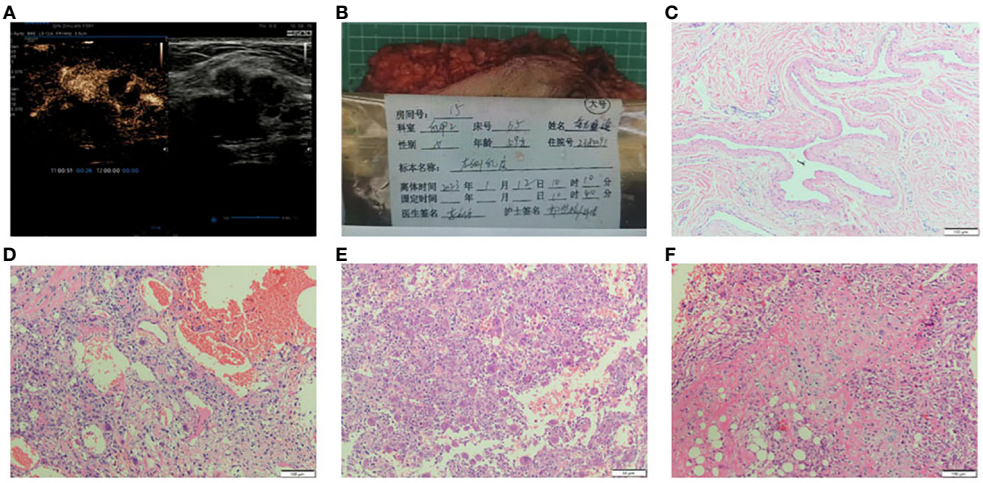


FIGURE 1
(A) Breast US images revealed a hypoechoic irregular mass in the breast left upper quadrant, with a size of about 23×25×19mm, the boundary was not uneven and no strong punctate echo was observed. The combination of contrax-enhanced ultrasound suggested the mass uneven enhancement in the arterial phase, unsmooth boundary, slow regression in the venous phase, and obvious enlargement in the lesion area. **(B)** The whole excised tissue of the left breast. **(C)** The resected specimen showed leaf-like (phyllodes) epithelial pattern (HE×100). **(D)** Stromal overgrowth, tumor giant cells and many abnormal mitosis are noted (HE×100). **(E)** The stroma showed a tumor osteoid rimmed by tumor cells along with osteoclastic giant cells, osteosarcoma differentiation (HE×100). **(F)** The section showed tumor cells with chondrosarcomatous differentiation, the chondrocyte density is different, the cell atypia is obvious, the nuclear mitosis and cartilage islands can be observed (HE×100).

Results Interpretation: The FISH results were interpreted independently by two experienced pathologists: 200 neoplastic cells in a blind fashion using an Olympus BX53 fluorescence microscope (Japan) were counted, the distance between red signal and green signal was > 2 signal points as positive cells, and the proportion of positive cells was > 10% as positive for separation and rearrangement (7). FISH showed USP6 positively rate was 2% which indicated negative expression on sections (Figure 3).

After radical resection of the left breast, anthracycline and ifosfamide chemotharapy were adopted for four cycles, and the patient still survived without any recurrence after eight months of follow up.

3 Discussion

MPTs are identified when the tumor exhibits marked stromal nuclear pleomorphism, stromal overgrowth, with infiltrating borders, markedly increased stromal cellularity, stromal overgrowth with severe nuclear atypia (8). Higher malignancy

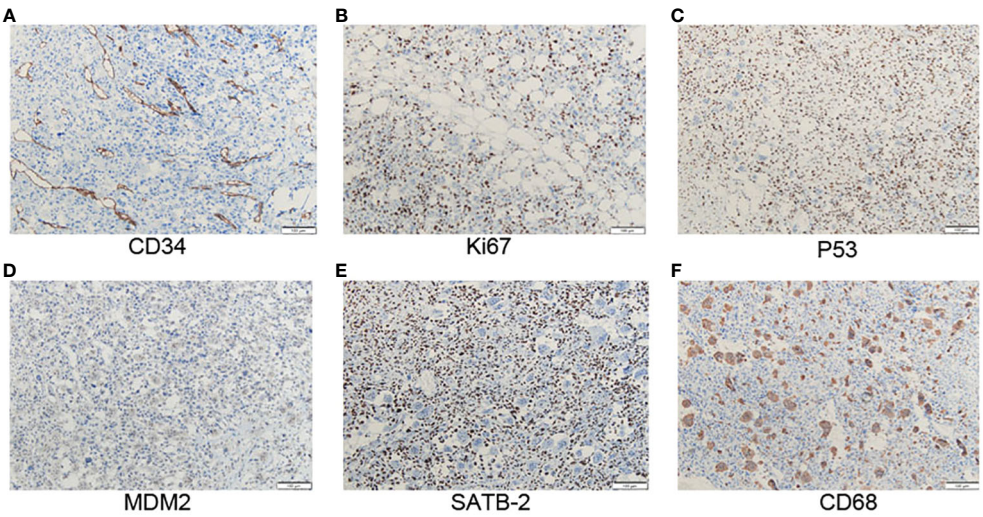


FIGURE 2
(A) Positive staining with CD34 in atypical stromal cells (x100). **(B)** The positive staining with Ki-67 in atypical stromal cells is about 60% (x100). **(C)** The positive staining with p53 in atypical stromal cells is about 90% (x100). **(D)** MDM2 is negative expressed in stromal cells (x100). **(E)** SATB2 is positively stained in atypical stromal cells (x100). **(F)** CD68 is expressed in osteoclastic giant cells (x100).

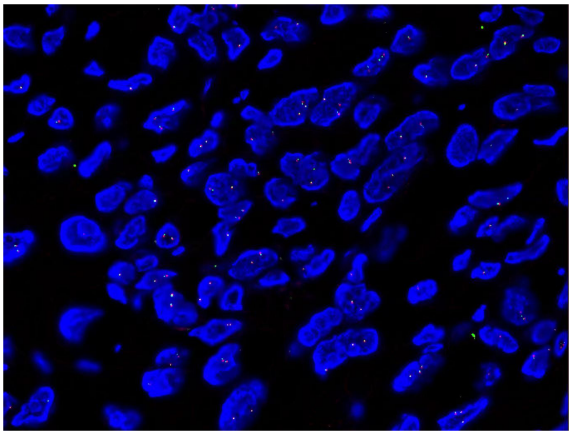


FIGURE 3
FISH showed USP6 positively rate was 2% which indicated negative expression on sections (x1000).

grade, presence of heterologous elements, younger age, larger tumor size, and recent rapid tumor growth are poor prognostic factors for MPTs of the breast (9). Heterologous differentiation in MPTs is exceedingly rare, but there are MPTs with chondrosacomatous or osteosarcomatous differentiation reported (10). MPTs with the histological osteosarcomatous subtype increase mortality by 33% (11). MPTs accompanied by osteosarcoma only accounts for 1.3% of phyllodes tumors in the breast (12). According to Silver et al, MPTs with osteosarcomatous components are potentially more aggressive and could spread to the lung, bone, brain, contralateral breast. In our patient, we describe a MPT with osteosarcoma and chondrosarcomatous differentiation.

Stromal and epithelial cells of the breast tissues are the mainly components to develop malignancy. According to the different malignancy of both cells, it could been diagnosed as benign or malignant diseases (13). In the present case, most of the stromal cells were fibrosarcoma-like interlacing fascicles of spindle cells with stromal overgrowth. Multinucleated stromal giant cells have been rerorted in phyllodestumors. Focal areas of osteosarcoma and/or chondrosarcomatous differentiation were hemothera. MPT is also diagnosed when malignant heter-elements such as osteosarcoma, chondrosarcoma, and rhabdomyo-sarcoma are present even if the other features are absent. Chondrosarcomatous component even constituted over 80% of the tumor volume which is indeed rare (14).

In breast tumor, it is found that osteosarcoma or chondrosarcoma might occur in 3 different diseases: primary osteosarcoma of the breast as with a pure osteosarcoma or chondrosarcoma, as the stromal component of a histologically MPT, or as osteosarcomatous or chondrosarcomatous differentiation in a metaplastic carcinoma (15). Primary osteosarcoma of the breast is also a rare primary breast tumor which accounts for only 1% of breast tumors and < 5% of all osteosarcomas (16). The possibility of metastasis of osteosarcoma from other sites should be ruled out first, and it has the following two characteristics in histology: neoplastic osteogenesis or osteoid matrix; No epithelial component. The immunophenotype of primary osteosarcoma was strongly positive for vimentin, strongly positive for CD68 in osteoclastic multinucleated giant cells, and negative for ER, PR, Her-2 and epithelial markers (17). Some evidence suggests that MPTs with osteosarcomatous hemotherapy on are more aggressive, but compared with primary osteosarcomas in general, they have a much lower risk of metastasis (18).

Metaplastic carcinoma of the breast also have sarcoma like elements, including spindle cell sarcoma, chondrosarcoma, osteosarcoma, rhab-domyosarcoma, or a mixture of them (19). However, high molecular weight cytokeratin and p63 usually were positive in metaplastic carcinoma. These could be helpful in hemotherapyio these two tumors (20). It is also reported that p63 could also been diffusely and focally expressed in MPT (21). In this patient, we could also observe sporadic p63 expression, but lack of CK expression, these molecular markers help to eliminate metaplastic carcinoma or primary osteosarcoma. Special AT-rich sequence-binding protein 2 (SATB2) induces local chromatin loops to facilitate transcription. SATB2 immunostaining is commonly used as a marker for colorectal adenocarcinoma and osteosarcoma (22). In our patient, SATB2 expression was strong positive, which indicated osteosarcoma tissues. CD34 is also observed in MPT (23), this is in line with our case, that CD34 is positively expressed.

Another differential diagnosis of MPT is breast myositis ossificans. Myositis ossificans is defined as a self-limiting pseudotumor composed of reactive hypercellular fibrous tissue and bone. USP6 rearrangements have been identified as a consistent genetic driving event in aneurysmal bone cyst and nodular fasciitis (24). It is therefore an integral part of the diagnostic workup when dealing with (myo)fibroblastic lesions of soft tissue and bone. USP6 rearrangement provided evidence of a relationship with nodular fasciitis and aneurysmal bone cyst (25). In our patient, the USP-6 is negative and supplies another strong proof to eliminate the diagnosis of myositis ossificans.

Recent next generation sequencing analyses had revealed novel genetic alterations in PT but lacked a further hemotherapyion of their relationship to different PT features and outcome (26). Malignant progression is associated with heterocytogenetic abnormalities, including MYC amplification, p53 mutation, increases in chromosomes 1q, 5p, 7 and 8, and loss of 6q, 9p, 10p, 13q, 16q and 19 (27). MED12 mutations are associated with alterations in related genes in the Wnt, TGFB, and THRA pathways (28, 29). Lin et al. demonstrated that ALDH1 and/or GD2 markers could be used for cancer stem cell research in patients with MPT (30).

The epithelial-mesenchymal transition (EMT) increased with the progression of MPTs tumor grade. Nuclear expression of the EMT proteins TWIST and Foxc2 is associated with increased tumor grade and deterioration of histological features (31, 32). Additional mutations or copy number alterations in known cancer driver genes NF1, RB1, TP53, PIK3CA, ERBB4, and EGFR have been identified in borderline and malignant MPTs through next-generation sequencing (33, 34). These molecules provide an important biological basis for the occurrence and development of MPTs, and provide a theoretical basis for molecular diagnosis and therapeutic targets in clinical practice.

Metastatectomy has been correlated with increased overall survival (of 25.9 versus 9.9 months; P = .01) in MPT (35). The

definitive treatment for phyllodes tumor is wide surgical excision with at least 1-2 cm of negative margins, or mastectomy, depending on the size of the tumor and the patient's breast size (36). Histological size ≥45 mm and dense stromal cellularity were demonstrated as histological risk factors of local recurrence of PT (37). Radiotherapy has often been associated with palliation and pain control in metastatic, malignant neoplasia. Anthracycline containing chemotherapy regimens has been associated with improved overall survival (22.4 months versus 13.2 months; $P = .040$). Anthracycline and alkylating agent-based combination regimens were most frequently administered (38). In the present case, metastatectomy was performed, anthracycline and ifosfamide hemotherapy were adopted, and the patient still survived without any recurrence.

Our case report illustrates that breast osteosarcoma and chondrosarcoma differentiation originating from an MPT is remarkably difficult to diagnose and manage. The standard treatment comprises complete excision of the tumor with wide margins or total mastectomy. A multiple oncology gene mutations happen and promote the malignant progression. The adjuvant therapy is still controversial due to the lack of multi-center large patients records and suitable clinical trials. Further research must be conducted to elucidate accurate diagnosis and clarify the best treatment for these tumors.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of Shiyan Taihe Hospital (NO.2023KS55). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

WL: Writing – review & editing, Writing – original draft, Resources, Funding acquisition. QO: Writing – original draft, Project administration, Methodology, Investigation, Data curation. YL: Writing – original draft, Methodology, Data curation. LY: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Shiyan City Scientific Research and Development Project (22Y32).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Bogach J, Sriskandarajah A, Wright FC, Look Hong NCanadian Phyllodes Tumor Consensus Panel. Phyllodes tumors of the breast: Canadian national consensus document using modified delphi methodology. *Ann Surg Oncol.* (2023) 30:6386–6397. doi: 10.1245/s10434-023-13912-7

2. Chen K, Xu J, Wang W, Jiang R, Zhang H, Wang X, et al. Clinical outcomes and biomarkers of phyllodes tumors of the breast: a single-center retrospective study. *Cancer Med.* (2023) 12:11363–74. doi: 10.1002/cam4.5849

3. Tan BY, Fox SB, Lakhani SR, Tan PH. Survey of recur rent diagnostic challenges in breast phyllodes tumours. *Histopathology.* (2023) 82:95–105. doi: 10.1111/his.14730

4. Sars C, Sackey H, Frisell J, Dickman PW, Karlsson F, Kindts I, et al. Current clinical practice in the management of phyllodes tumors of the breast: an international cross-sectional study among surgeons and oncologists. *Breast Cancer Res Treat.* (2023) 199:293–304. doi: 10.1007/s10549-023-06896-1

5. Louie AD, Rosenberger LH. Phyllodes tumors of the breast: addressing the gaps in consensus recommendations for clinical management. *Ann Surg Oncol.* (2023) 30:6296–8. doi: 10.1245/s10434-023-14147-2

6. Md Nasir ND, Koh VCY, Cree IA, Ruiz B, Águila JD, Armon S. Phyllodes tumour evidence gaps mapped from the 5th edition of the WHO classification of tumours of the breast. *Histopathology.* (2023) 82:704–12. doi: 10.1111/his.14856

7. Zhang Y, Qiu Y, Zhang X, He X, Chen C, Chen M, et al. USP6-associated soft tissue tumors with bone metaplasia: clinicopathologic and genetic analysis and the identification of novel USP6 fusion partners. *Front Oncol.* (2023) 12:1065071. doi: 10.3389/fonc.2022.1065071

8. Wei Y, Dai Y, Guan Q, Min N, Geng R, Hu H, et al. Predicting the recurrence-free survival of phyllodes tumor of the breast: a nomogram based on clinicopathology features, treatment, and surgical margin. *Gland Surg.* (2023) 12:152–64. doi: 10.21037/gs-22-542

9. Liu J, Li F, Liu X, Lang R, Liang R, Lu H. Malignant phyllodes tumors of the breast: the Malignancy grading and associations with prognosis. *Breast Cancer Res Treat.* (2023) 199:435–44. doi: 10.1007/s10549-023-06933-z

10. Ko SY. Malignant phyllodes tumor of the breast with heterologous osteosarcoma and chondrosarcomatous differentiation: a rare case report with imaging findings. *Radiol Case Rep.* (2023) 18:1982–8. doi: 10.1016/j.radcr.2023.02.039

11. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. (2016) 68:5–21. doi: 10.1111/his.12876

12. Silver SA, Tavassoli FA. Osteosarcomatous differentiation in phyllodes tumors. *Am J Surg Pathol*. (1999) 23:81 5–21. doi: 10.1097/00000478-199907000-00010

13. Ni Y, Tse GM. Spindle cell lesions of the breast: a diagnostic algorithm. *Arch Pathol Lab Med*. (2023) 147:30–7. doi: 10.5858/arpa.2022-0048-RA

14. Vera-Sempere F, García-Martínez A. Malignant phyllodes tumor of the breast with predominant chondrosarcomatous differentiation. *Pathol Res Pract*. (2003) 199:841–5. doi: 10.1078/0344-0338-00505

15. Hall RR, Schammel CM, Devane AM, Scopteuolo A, Schammel DP. High grade phyllodes tumor with osteosarcomatous differentiation: case report and review of the literature. *Radiol Case Rep*. (2023) 18:3127–34. doi: 10.1016/j.radcr.2023.05.074

16. Hu QC, Mei X, Feng Y, Ma JL, Zhao ZY, Shao ZM, et al. Early local recurrence presents adverse effect on outcomes of primary breast sarcoma[J]. *Medicine(Baltimore)*. (2016) 95:e2422. doi: 10.1097/MD.0000000000002422

17. Gutnik L, Ren Y, Thomas SM, Plichta JK, Greenup RA, Fayanju OM, et al. Malignant phyllodes tumor and primary breast sarcoma; distinct rare tumors of the breast. *J Surg Oncol*. (2022) 125:947–57. doi: 10.1002/jso.26820

18. Laforga JB. Malignant giant phyllodes tumor with heterologous osteosarcomatous differentiation and aneurysmatic bone cyst-like features. *Breast J*. (2020) 26:1387–8. doi: 10.1111/tbj.13788

19. Chaudhary D, Balhara K, Mandal S, Mallya V, Tomar R, Khurana N, et al. Metaplastic breast carcinoma: analysis of clinical and pathologic features, a five-year study. *J Cancer Res Ther*. (2023) 19:1226–30. doi: 10.4103/jcrt.jcrt_1229_21

20. Yang X, Chen L, Shen Y. Breast metaplastic carcinoma with osteosarcomatous differentiation: a case report and literature review. *Clin Pathol*. (2022) 15. doi: 10.1177/2632010X221118056

21. Chu X, Wu M, Yang J, Fu Y, Wang X, Wang H, et al. Organoid models derived from patients with Malignant phyllodes tumor of the breast. *Breast Cancer Res Treat*. (2023) 200:193–201. doi: 10.1007/s10549-023-06973-5

22. Dum D, Kromm D, Lennartz M, De Wispelaere N, Büscheck F, Luebke AM, et al. SATB2 expression in human tumors: a tissue microarray study on more than 15 000 tumors. *Arch Pathol Lab Med*. (2023) 147:451–64. doi: 10.5858/arpa.2021-0317-OA

23. Chu X, Wu M, Yang J, Fu Y, Wang X, Wang H, et al. Organoid models derived from patients with Malignant phyllodes tumor of the breast. *Breast Cancer Res Treat*. (2023) 200:193–201. doi: 10.1007/s10549-023-06973-5

24. Wang JC, Li WS, Kao YC, Lee JC, Lee PH, Huang SC, et al. Clinicopathological and molecular characterisation of USP6-rearranged soft tissue neoplasms: the evidence of genetic relatedness indicates an expanding family with variable bone-forming capacity. *Histopathology*. (2021) 78:676–89. doi: 10.1111/his.14268

25. Bekers EM, Eijkelenboom A, Grünberg K, Roverts RC, de Rooy JWJ, van der Geest ICM, et al. Myositis ossificans - another condition with USP6 rearrangement, providing evidence of a relationship with nodular fasciitis and aneurysmal bone cyst. *Ann Diagn Pathol*. (2018) 34:56–9. doi: 10.1016/j.anndiagpath.2018.01.006

26. Tsang JY, Shao Y, Poon IK, Ni Y-B, Kwan JS, Chow C, et al. Analysis of recurrent molecular alterations in phyllodes tumour of breast: insights into prognosis and pathogenesis. *Pathology*. (2022) 54:678–85. doi: 10.1016/j.pathol.2022.03.008

27. Kuijper A, Snijders M, Berns J, Kuenen-Boumeester V, Wall E, Albertson DG, et al. Genomio profiling by arary comparative genomic hybridization reveals novel DNA copy number changes in breast phyllodes tumours. *Cell Oncol*. (2009) 31:31–9. doi: 10.1155/2009/410672

28. Chang HY, Koh VCY, Md Nasir ND, Ng CCY, Guan P, Thike AA, et al. MED12, TERT and RARA in fibroepithelial tumours of the breast. *J Clin Pathol*. (2020) 73:51–6. doi: 10.1136/jclinpath-2019-206208

29. Piscuoglio S, Ng CK, Murray M, Burke KA, Edelweiss M, Geyer FC, et al. Massively parallel sequencing of phyllodes tumours of the breast reveals actionable mutations, and TERT promoter hotspot mutations and TERT gene amplification as likely drivers of progression. *J Pathol*. (2016) 238:508–18. doi: 10.1002/path.4672

30. Lin JJ, Huang CS, Yu J, Liao GS, Lien HC, Hung JT. Malignant phyllodes tumors display mesenchymal stem cell features and aldehyde dehydrogenase/disialoganglioside identify their tumor stem cells. *Breast Cancer Res*. (2014) 16:R29. doi: 10.1186/bcr3631

31. Wang J, Wang WL, Sun H, Huo L, Wu Y, Chen H, et al. Expression of TRPS1 in phyllodes tumor and sarcoma of the breast. *Hum Pathol*. (2022) 121:73–80. doi: 10.1016/j.humpath.2022.01.002

32. Chen K, Xu J, Wang W, Jiang R, Zhang H, Wang X, et al. Clinical outcomes and biomarkers of phyllodes tumors of the breast: a single-center retrospe ctive study. *Cancer Med*. (2023) 12:11363–74. doi: 10.1002/cam4.5849

33. Muller KE, Tafe LJ, de Abreu FB, Peterson JD, Wells WA, Barth RJ, et al. Benign phyllodes tumor of the breast recurring as a Malignant phyllodes tumor and spindle cell metaplastic carcinoma. *Hum Pathol*. (2015) 46:327–33. doi: 10.1016/j.humpath.2014.10.014

34. Tan J, Ong CK, Lim WK, Ng CCY, Thike AA, Ng LM, et al. Genomic landscapes of breast fibroepithelial tumors. *Nat Genet*. (2015) 47:1341–5. doi: 10.1038/ng.3409

35. Goodwin B, Oyinlola AF, Palhang M, Lehman D, Platoff R, Atabek U, et al. Metastatic and Malignant phyllodes tumors of the breast: an update for current management. *Am Surg*. (2023) 89(12):6190–6. doi: 10.1177/00031348231198114

36. Zervoudis S, Xepapadakis G, Psarros N, Bothou A, Tsikouras P, Galazios G, et al. Management of Malignant and borderline phyllodes tumors of the breast: our experience. *J Buon*. (2019) 24:1521–5.

37. Mimoun C, Legay L, Lorphelin H, Leveau-Vallier AS, Cornelis F, Miquel C, et al. Histological risk factors for local recurrence of phyllodes tumors of the breast. *Anticancer Res*. (2023) 43:143–7. doi: 10.21873/anticanres.16143

38. Samii E, Hurni Y, Huber D. Management and outcomes of metastatic and recurrent Malignant phyllodes tumors of the breast: a systematic literature review. *Eur J Breast Health*. (2023) 19:191–200. doi: 10.4274/ejbh.galenos.2023.2023-3-2

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 26 April 2024
DOI 10.3389/fonc.2024.1381541

OPEN ACCESS

EDITED BY
Dirk Geerts,
University of Amsterdam, Netherlands

REVIEWED BY
Carlos Martinez-Perez,
University of Edinburgh, United Kingdom
Mariia Ivanova,
European Institute of Oncology IRCCS, Italy

*CORRESPONDENCE
Jianghua Ding
doctor0922@126.com

†These authors have contributed equally to this work

RECEIVED 03 February 2024
ACCEPTED 15 April 2024
PUBLISHED 26 April 2024

CITATION
Huang J, Liu L and Ding J (2024) Case report: From negative to positive: a remarkable journey of ER, PR and HER2 status in a patient with metastatic breast cancer. *Front. Oncol.* 14:1381541. doi: 10.3389/fonc.2024.1381541

Case report: From negative to positive: a remarkable journey of ER, PR and HER2 status in a patient with metastatic breast cancer

Jiaqi Huang[1†], Lan Liu[2†] and Jianghua Ding[1*]

[1]Department of Oncology, Jiujiang University Affiliated Hospital, Jiujiang, Jiangxi, China, [2]Department of Ultrasonic Diagnosis, Jiujiang University Affiliated Hospital, Jiujiang, Jiangxi, China

Breast cancer is the most common malignant tumor in women, posing a serious threat to women's health. HER2 has been identified as a key oncogene and prognostic factor in breast cancer. Recent studies have reported inconsistencies in ER, PR, and/or HER2 expression between primary breast tumors and metastatic lesions. Rarely is it reported that all three biomarkers experience conversion. In this report, we present the case of a female patient with relapsed and metastatic breast cancer, whose histology transformed from initially triple-negative to Luminal-B type (HER2 positive) (i.e., ER, PR, and HER2 positive). She underwent systematic chemotherapy, targeted therapy, and cranial radiotherapy, which was followed by maintenance treatment with targeted and endocrine therapy. Currently, she has been in nearly complete remission (nCR) for more than 12 months. For recurrent and metastatic breast cancer, it is necessary to perform the second biopsy for metastases, which would contribute to precision treatment and prognosis improvement.

KEYWORDS

breast cancer, ER, PR, HER2, transformation, negative, positive

Introduction

According to the latest National Cancer Report, breast cancer is the most common malignant tumor and the second leading cause of cancer mortality in Chinese females (1). The therapeutic strategies for newly-diagnosed breast cancer include surgery, chemotherapy, radiotherapy, targeted therapy, and endocrine therapy. The choice of treatment depends on the stage of TNM, pathology, molecular types, and physical conditions (2). For relapsed and metastatic breast cancer, the treatment strategy is primarily based on the original pathological and molecular types of the cancer (2). Recently, several retrospective studies have reported inconsistent biomarkers, i.e. estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor

receptor-2 (HER2), between the primary lesions and metastases of breast cancer (3–6). The majority of the discordance occurred only one or two of ER, PR and HER2 status. It is rarely reported that all three biomarkers simultaneously changed between primary lesion and recurrent & metastases. In this report, we present a case of a female patient with stage IIIA breast cancer who experienced a transition from initial triple-negative to Luminal-B type (HER2 positive) after recurrence and metastasis. As a result, she received anti-HER2 therapy plus chemotherapy and achieved nearly complete remission (nCR).

Case report

On March 2, 2018, a 31-year-old woman complained of a palpable mass in the left breast for more than 2 months. The serum levels of CEA and CA153 were 22.5ng/ml and 46.8U/ml, respectively. Then she was diagnosed with left breast cancer and underwent a modified radical resection at Jiujiang University Affiliated Hospital. Postoperative pathology revealed invasive ductal carcinoma of the left breast, non-specific type, with left axillary lymph nodes metastasis (5/23). Immunohistochemical examinations showed ER (-), PR (-), HER2 (-), and Ki-67 (80% +), indicating triple-negative type breast cancer (Figure 1). Because the patient possessed a certain degree of medical knowledge, she required further examination of HER2 by fluorescence *in situ* hybridization (FISH). The negative status of HER2 was typically confirmed by FISH.

The stage of TNM was pT2N2aM0, stage IIIA. Due to the high risk of relapse (≥4 axillary lymph node positive), the patient received adjuvant chemotherapy since April 4, 2018. Specifically, the combined regimen consisted of epriubicin and cyclophosphamide (EC) for 4 cycles with 1 cycle every 3 weeks. Then, she was treated with albumin-bound paclitaxel (T) for 4 cycles per 3 weeks cycle. On Oct. 10, adjuvant radiotherapy was administered to the chest wall and regional lymph node drainage field, with 25 daily doses (fractions) of 2.0 Gy to a total dose of 50Gy over 5 weeks. The patient was followed up regularly and examined every 3 months during the first 2 years after surgery, including tumor markers, breast ultrasound, chest and abdominal CT, and brain MRI examinations. Sine the third year after operation, she received regular evaluation every 6 months. The patient was in good condition and no signs of tumor recurrence were found.

In December 2022, the patient complained of right upper abdominal discomfort, loss of appetite and occasional nausea. The patient was examined at our Hospital on December 22, 2022. The CEA level was 32.86ng/ml. The CA153 level was greater than 342.5ng/ml. Abdominal CT indicated multiple metastatic tumors of the liver (Figure 2). On January 4, 2023, the brain magnetic resonance imaging (MRI) was performed. It found an abnormal signal in the right frontal nodule, suggesting metastasis. Cervical lymph node ultrasonography showed abnormal structural lymph nodes in the bilateral neck region II and left neck region V. The maximum diameter of lymph nodes was only 1.4 cm. Also, the physical examination showed no significantly palpable superficial lymph nodes. Thus, the patient received percutaneous color ultrasound-guided needle biopsy of liver biopsies on January 4, 2023. Pathological findings supported that the liver metastases were consistent with breast cancer. Immunohistochemistry results showed ER (70% +), PR (40% +), Ki-67 (40% +), as well as the positive expression of HER2 (2+). Furthermore, the positive status of HER2 was confirmed by FISH detection (Figure 1). Finally, the patient was diagnosed with Luminal B type (HER2 positive), i.e. ER, PR, and HER2 positive. The patient received stereotactic radiotherapy (SRT) with DT50Gy/10F for the solid brain metastasis on January 8, 2023. Concurrently, the patient received the combined treatment of docetaxel(D), trastuzumab (H), and pertuzumab(P) (D-HP) for 6 cycles, with each cycle lasting 3 weeks, starting from January 11, 2023. The clinical efficacy was evaluated based on the Response Evaluation Criteria for Solid Tumors (RECIST1.1), including complete response (CR) and partial

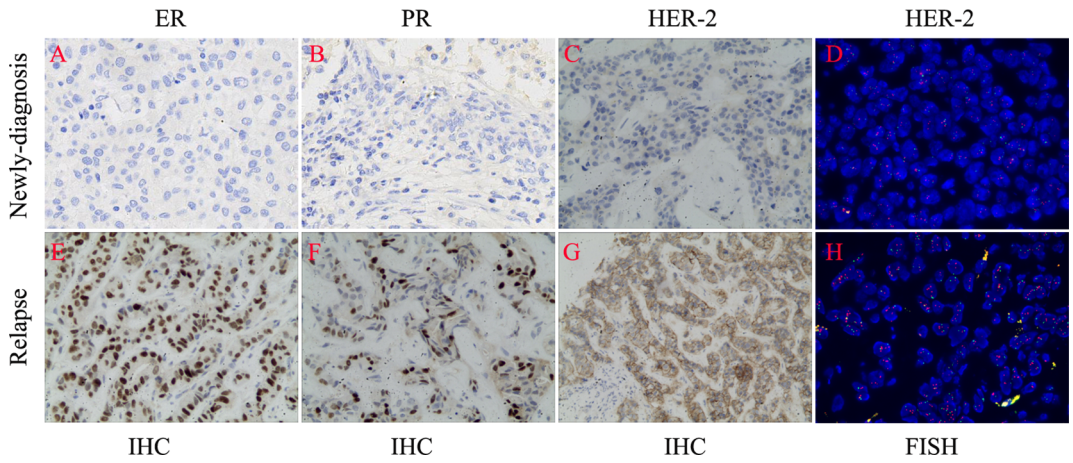


FIGURE 1
The changes of biomarkers between newly-diagnosed and relapsed biopsies. **(A–D)** Negative expression of ER, PR, and HER-2. **(E–H)** Positive expression of ER, PR, and HER-2.

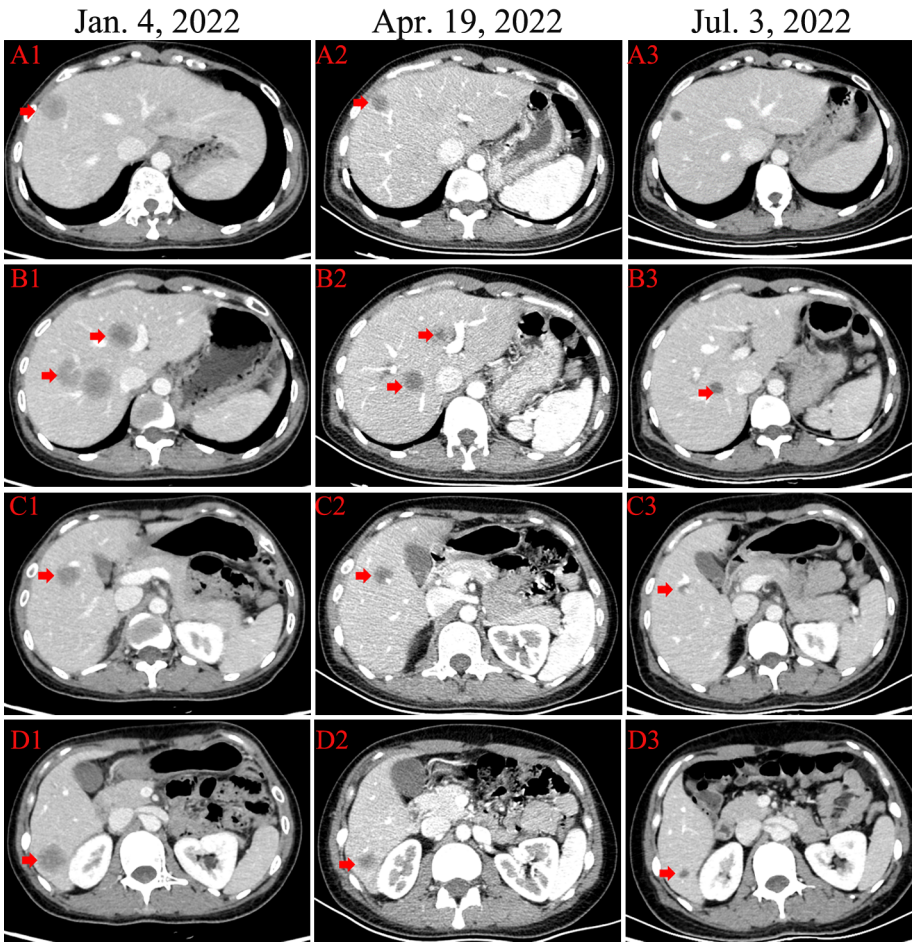


FIGURE 2
The CT changes of different metastatic lesions from liver **(A–D)**.

remission (PR). CR indicates that all lesions disappear completely, and all pathological lymph nodes reduce to normal size (short diameter < 1cm), lasting for more than 1 month. PR means that the total maximum diameter of all measurable lesions reduces by over 30%, lasting for more than 1 month. Nearly CR (nCR) refers to that the majority of all measurable lesions disappear, but only a few tiny residual foci remain.

After 3 cycles of treatment, the clinical efficacy showed partial remission (PR). After 6 cycles of treatments, the patient achieved complete remission (CR) of cervical metastatic lymph nodes and brain metastasis (Figure 3). For liver metastases, the clinical efficacy showed partial remission (PR). Since May 21, 2023, the patient began to receive maintenance therapy, which included trastuzumab, leuprorelin, letrozole, and Abemaciclib (an inhibitor of CDK4/6). Currently, the patient is receiving regular maintenance therapy without any clear discomfort. In December 2023, the latest efficacy was evaluated, and the hepatic metastatic lesions almost disappeared, indicating nCR (Figure 2). She has achieved progression-free survival (PFS) of over 12 months and the overall survival of 69 months up to now (Figure 4). The patient still undergoes close follow-up and receives regular examination every 6 months.

Discussion

Previously, it was believed that breast cancer was a static disease in terms of pathology. However, in-depth molecular studies have found that breast cancer should be considered as a spatially and temporally dynamic disease, i.e. that the heterogeneities exist in different sites between primary tumors and metastases, and different phases between initial diagnosis and recurrence (7). The phenomenon of heterogeneity between primary and metastatic lesions has attracted increasing attention from clinicians in the field of breast cancer. Timmer M et al. compared the status of ER, PR, and HER2 in primary tumors with brain metastases in 24 patients with breast cancer. They found that 25-37.5% of patients exhibited discordant receptor status between the primary tumor and brain lesions (4). Nishimura R et al. reported the changes in ER, PR, Ki-67, and HER2 status between primary and recurrent lesions in 97 patients with breast cancer. Following relapse, ER and PR decreased while Ki-67 increased. Subtype changes occurred in 24.7% of the patients (5). Lin M et al. compared the changes in HER2 status between primary tumors and paired recurrent/metastatic lesions in 1299 patients with breast cancer. The incidence of discordance was 28.5% (370/1299), indicating the

10.3389/fonc.2024.1381541

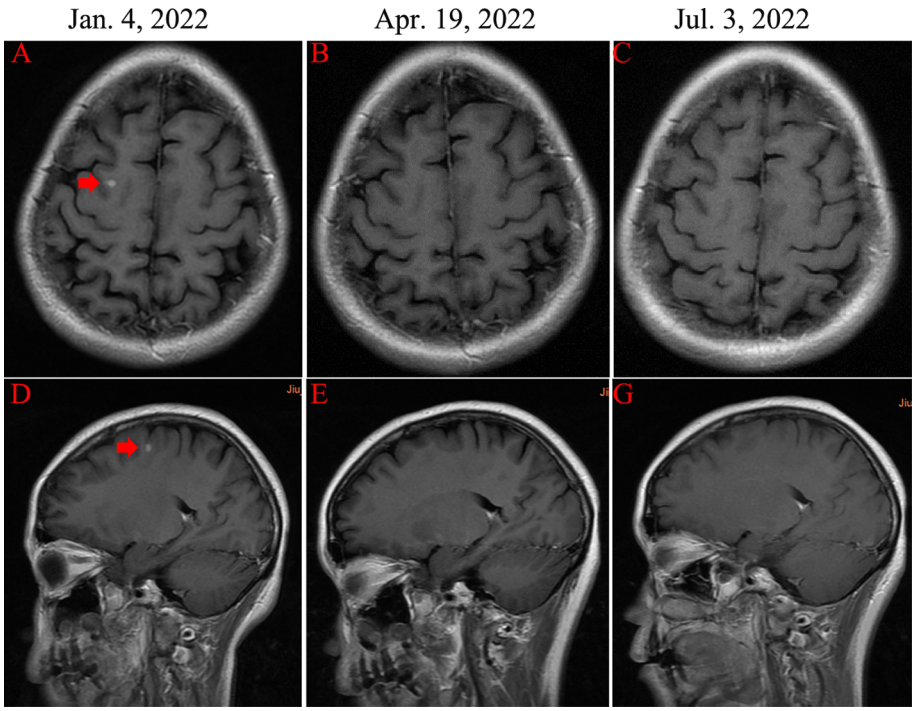


FIGURE 3
Magnetic resonance imaging (MRI) examinations of right frontal lobe metastasis (red arrow). **(A, D)** The presence of solid brain metastasis (diameter of 1 cm). **(B, E)** and **(C, G)** The disappearance of brain metastasis.

conversion of primary-to-metastatic HER2 status (3). The results indicated that the heterogeneity between primary and metastatic lesions is an important clinical issue that cannot be ignored.

The underlying mechanisms have been partly ascribed to clonal evolutions, which contribute to genetic heterogeneity during malignant progression. Sprouffske K et al. faithfully mimicked the clonal evolution of metastasis process in the patient-derived tumor xenografts (PDX) from breast cancer. During the process of clonal selection, some subclones remain stable, some expand, and others vanish over time. Furthermore, clonal evolution leads to genetic heterogeneity and different clinical outcomes (8). A prospective analysis of circulating tumor DNA (ctDNA) was performed by next-generation sequencing (NGS) in 37 patients with HR-positive, HER2-negative breast cancer who were classified as secondary resistance. The occurrences of new mutations were 0% (0/9) for the chemotherapy group, 42.1% (8/19) for the CDK4/6 inhibitors plus endocrine treatment (CE group), and 36.3% (4/11) for the chemotherapy followed by CE group (p=0.024). The results strongly indicated that chemotherapy or CDK4/6 inhibitors may influence the change of clonal evolution among breast cancer patients (9). Liquid biopsy by Kujala J et al. detected 56.2 ± 7.2% of somatic variants present both in the matched primary tumor and metastatic sites from breast cancer patients. Apparently, liquid biopsy may identify novel driver variants and therapeutic targets absent from the tumor tissue DNA (10). In the clinical setting, ctDNA may be an ideal surrogate for longitudinal monitoring of genetic heterogeneity from breast cancer patients who can't obtain tissue specimen (7). Another potential explanation may be attributed to that a second

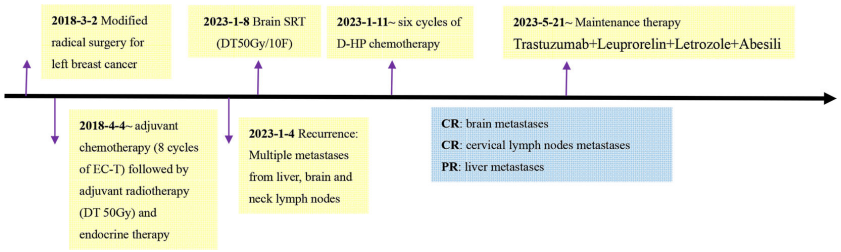


FIGURE 4
Detailed time course of the patient's clinical course and therapeutic regimens.

local lesion (*in situ* or invasive) could have developed concomitantly with the primary DCIS or in the period between the primary tumor and recurrence, which could be a plausible explanation for the luminal metastases. Thus, it is necessary and important to follow-up the patients with breast cancer.

According to the studies, all the insistences occurred in only one or two of three receptors (ER, PR, and HER2 receptors) in breast cancer patients at the stages of initial diagnosis and recurrence & metastasis (3–5). However, the transition from triple-negative to ER, PR, and HER2 positive status was rarely observed. In our report, we present a case of a female patient newly diagnosed with triple-negative breast cancer, who experienced multiple metastases to the liver, brain, and cervical lymph nodes 57 months after the operation. A re-biopsy of the liver metastases revealed a conversion into ER, PR, and HER2 positive status. In this case, the liver was the optimal site available for re-biopsy. As a result, the patient received accurate detection and precision medicine. Encouragingly, the patient achieved nCR for all the metastases after systematic treatments. This re-confirmed the correct diagnosis after disease relapse and metastasis. In contrast, re-biopsy from brain metastasis is not easily available for breast cancer patients. In this clinical setting, liquid biopsy of ctDNA [including cerebrospinal fluid (CSF)] may be an alternative option for these types of patients (11).

Conclusions

The discrepancy in the biomarkers of ER, PR, and HER2 status presents a significant clinical challenge in patients with breast cancer, particularly between primary tumors and metastatic lesions. Simultaneous conversion of all three biomarkers is a rare occurrence during the disease progression of breast cancer. This study presents a case of a female patient with initial triple-negative breast cancer who transformed to ER, PR, and HER2-positive status after recurrence and metastasis. Consequently, she underwent systematic treatment, including chemotherapy, targeted therapy, cranial radiotherapy, and maintenance treatment. The patient achieved a promising complete response (nCR) for over 12 months up to now. The final results of CLEOPATRA study reported that mOS and 8-year OS rates were significantly higher in the D-HP group than that in was D-H (docetaxel-trastuzumab) group (*mOS*: 57.1 *vs.* 40.8 months; *8-year OS rates*: 37% *vs.* 23%) (12). Therefore, we have reasons to believe that the patient is likely to have an excellent outcome. This report highlights the necessity and importance of secondary biopsy in patients with breast cancer, which could significantly facilitate precise diagnosis and treatment.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethic Committee of Jiujiang University Affiliated Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JH: Investigation, Methodology, Writing – original draft. LL: Data curation, Formal analysis, Methodology, Writing – original draft. JD: Conceptualization, Software, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Tao X, Li T, Gandomkar Z, Brennan PC, Reed WM. Incidence, mortality, survival, and disease burden of breast cancer in China compared to other developed countries. *Asia Pac J Clin Oncol.* (2023) 19:645–54. doi: 10.1111/ajco.13958

2. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. *Lancet.* (2021) 397:1750–69. doi: 10.1016/S0140-6736(20)32381-3

3. Lin M, Luo T, Jin Y, Zhong X, Zheng D, Zeng C, et al. Her2-low heterogeneity between primary and paired recurrent/metastatic breast cancer: implications in treatment and prognosis. *Cancer.* (2023) 130:851–62. doi: 10.1002/cncr.35101

4. Timmer M, Werner JM, Rohn G, Ortmann M, Blau T, Cramer C, et al. Discordance and conversion rates of progesterone-, estrogen-, and her2/neu-receptor

status in primary breast cancer and brain metastasis mainly triggered by hormone therapy. *Anticancer Res*. (2017) 37:4859–65. doi: 10.21873/anticanres.11894

5. Nishimura R, Osako T, Okumura Y, Tashima R, Toyozumi Y, Arima N. Changes in the er, pgr, her2, p53 and ki-67 biological markers between primary and recurrent breast cancer: discordance rates and prognosis. *World J Surg Oncol*. (2011) 9:131. doi: 10.1186/1477-7819-9-131

6. Pellas U, Bauer A, Baros IV, Fattorini C, Tot T. Her2-low metastases of her2-negative primary tumors: a single institution analysis of intertumoral and internodal heterogeneity in node-positive breast cancer. *Front Oncol*. (2023) 13:1167567. doi: 10.3389/fonc.2023.1167567

7. Kavan S, Kruse TA, Vogsen M, Hildebrandt MG, Thomassen M. Heterogeneity and tumor evolution reflected in liquid biopsy in metastatic breast cancer patients: a review. *Cancer Metastasis Rev*. (2022) 41:433–46. doi: 10.1007/s10555-022-10023-9

8. Sprouffske K, Kerr G, Li C, Prahallad A, Rebmann R, Waehle V, et al. Genetic heterogeneity and clonal evolution during metastasis in breast cancer patient-derived tumor xenograft models. *Comput Struct Biotechnol J*. (2020) 18:323–31. doi: 10.1016/j.csbj.2020.01.008

9. Decker T, Bichler M, Birtel A, Fischer G, Geiger K, Gaenger S, et al. Clonal evolution in patients with hormone receptor positive, her-2 negative breast cancer treated with chemotherapy or cdk4/6 inhibitors. *Oncol Res Treat*. (2022) 45:248–53. doi: 10.1159/000523758

10. Kujala J, Hartikainen JM, Tengstrom M, Sironen R, Auvinen P, Kosma VM, et al. Circulating cell-free dna reflects the clonal evolution of breast cancer tumors. *Cancers (Basel)*. (2022) 14:1332. doi: 10.3390/cancers14051332

11. Fitzpatrick A, Iravani M, Mills A, Vicente D, Alaguthurai T, Roxanis I, et al. Genomic profiling and pre-clinical modelling of breast cancer leptomeningeal metastasis reveals acquisition of a lobular-like phenotype. *Nat Commun*. (2023) 14:7408. doi: 10.1038/s41467-023-43242-x

12. Swain S, Miles D, Kim S, Im Y, Im S, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. (2020) 21:519–30. doi: 10.1016/S1470-2045(19)30863-0

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 30 April 2024
DOI 10.3389/fonc.2024.1382985

OPEN ACCESS

EDITED BY
Eriko Katsuta,
Yokohama City University Graduate School of Medicine, Japan

REVIEWED BY
Roxana Pintican,
University of Medicine and Pharmacy Iuliu Hatieganu, Romania
Nektarios Koufopoulos,
University General Hospital Attikon, Greece

*CORRESPONDENCE
Tiantian Liang
tiantianliang2021@163.com
Yu Jing
linxiwhale@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 06 February 2024
ACCEPTED 17 April 2024
PUBLISHED 30 April 2024

CITATION
Tong Y, Liu S, Zhao L, Zhang Z, Hu H, Jing Y and Liang T (2024) The treatment process of a giant phyllodes tumor of the breast: a case report and review of the literature. *Front. Oncol.* 14:1382985. doi: 10.3389/fonc.2024.1382985

The treatment process of a giant phyllodes tumor of the breast: a case report and review of the literature

Yujun Tong[1†], Siyu Liu[1†], Lijuan Zhao[1], Zhen Zhang[1], Haiyan Hu[1], Yu Jing[2*] and Tiantian Liang[3*]

[1]Department of Breast Center, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, China, [2]Department of Neurology, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, China, [3]Department of Pharmacy, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, China

Giant phyllodes tumors are rare fibroepithelial tumors that are usually larger than 10 cm in diameter, have rapid tumor growth, and are easily recurrent. They are frequently accompanied by skin necrosis and infection, particularly in malignant phyllodes tumors. This case report presents a 50-year-old woman who presented to the hospital with a huge left breast mass that was ruptured and infected. The patient received anti-infective treatment and underwent mastectomy and skin grafting, which indicated a malignant phyllodes tumor. The tumor was completely excised after a local recurrence in the chest wall 6 months post-surgery. Unfortunately, one year later, the patient pass away due to multiple organ failure. Giant phyllodes tumor management presents challenges to the surgeon. This case is being presented to enhance understanding and treatment of phyllodes tumors, specifically giant malignant phyllodes tumors, with the aim of improving patients' quality of life.

KEYWORDS

giant phyllodes tumor, recurrence, diagnosis, treatment, surgery

1 Introduction

Phyllodes tumors are an uncommon occurrence, comprising less than 1% of all breast tumors (1). They are biphasic fibroepithelial tumors that encompass both stromal and epithelial components. Typically, these tumors manifest as painless nodules with a propensity for rapid growth within a short duration. The World Health Organization (WHO) has classified phyllodes tumors into three distinct histotypes based on clinicopathological characteristics: benign, borderline, and malignant. These histotypes are observed in approximately 60%-75%, 15%-20%, and 10%-20% of cases, respectively (2). Most phyllodes tumors are around 4 cm in size, but less than 10% grow larger than 10 cm

and are called giant tumors (3). Giant malignant phyllodes tumors are rare and hard to treat. Surgery remains the primary treatment option, with very few surgical studies on giant phyllodes tumors. This case involved a very aggressive giant malignant phyllodes tumor that recurred, spread, and died within a short period of time despite undergoing mastectomy.

2 Case report

In June 2019, the patient identified a small lump in her left breast without associated discomfort or identifiable etiology, yet she refrained from seeking medical attention or undergoing evaluation. By September 2020, the lump exhibited rapid growth prompting her to present at a clinic where she received a misdiagnosis of mastitis, leading to an incision and drainage procedure. Subsequently, the wound failed to heal, and the tumor extended along the incision site. In November 2020, she was admitted to the Department of Breast Surgery at Mianyang Central Hospital, affiliated with the University of Electronic Science and Technology of China in Mianyang, China. We created a timeline of key points in the patient's diagnosis and treatment (Table 1). Her vital signs were as follows. Physical examination revealed a large, irregular mass in the left breast measuring 17 cm x 15 cm x 10 cm with unclear borders and rupture (Figure 1). The skin over the mass became necrotic, with a foul odor and oozing fluids. This caused slight pain. The patient did not have a fever. No enlarged lymph nodes were found in the axilla or clavicle. The patient had no other medical history. Her father died from liver and pancreatic cancer. Lab results revealed an abnormal complete blood count, indicating a high white blood cell count of 10,610/μl and a high platelet count of 468,000/μl. The bacterial culture of exudate was positive for Pseudomonas aeruginosa and Enterococcus faecalith. Liver and kidney function, tumor markers, and other tests were normal. The mass had ruptured upon admission, so mammography and ultrasonography were not possible. Contrast-enhanced magnetic resonance imaging (MRI) showed a large mass in the left breast with an unclear border (Figure 2). The imaging studies, including computed tomography scan of the thorax, abdominal ultrasound, and bone scan, did not show any signs of distant metastasis. The results of the core needle biopsy supported the diagnosis of a phyllodes tumor in the breast. The patient received a four-day course of intravenous antibiotics and wound care. The white blood

TABLE 1 A timeline of key points in the patient's diagnosis and treatment.

Date	Symptom	Diagnosis	Treatment
June 2019	A painless mass on the left breast was found without any pain or discomfort	No	No treatment was given
September 2020	Rapid growth of the left breast mass	Misdiagnosis of mastitis at a clinic	Incision and drainage procedure performed.
November 2020	Left breast mass measured 17 cm x 15 cm x 10 cm with ill-defined and ruptured borders, skin exhibited necrosis, foul odor, and oozing fluid	Giant malignant phyllodes tumor with infection	Four-day course of intravenous antibiotics, wound care, mastectomy, and skin graft
May 2021	Subcutaneous nodule on the anterior part of the sternal body measuring approximately 3.0 cm x 2.5 cm.	Local recurrence of the malignant phyllodes tumor	Localized expended resection of the mass and displacement of the medial right breast gland to the anterior thoracic region
June 2022	Multiple metastases in the liver, lung, and brain	Patient succumbed to multiple organ failure	–

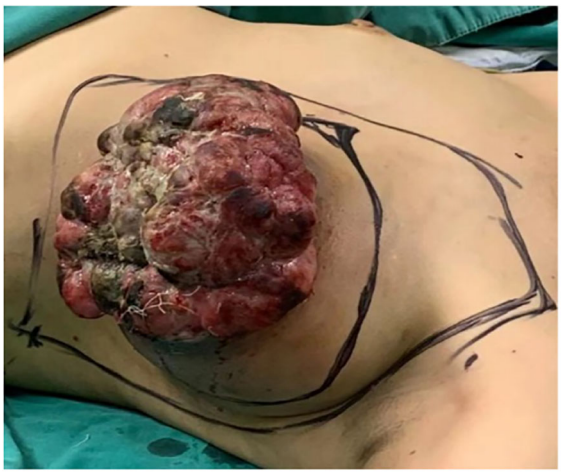


FIGURE 1
The preoperative measurement of the left breast mass was 17 cm x 15 cm x 10 cm.

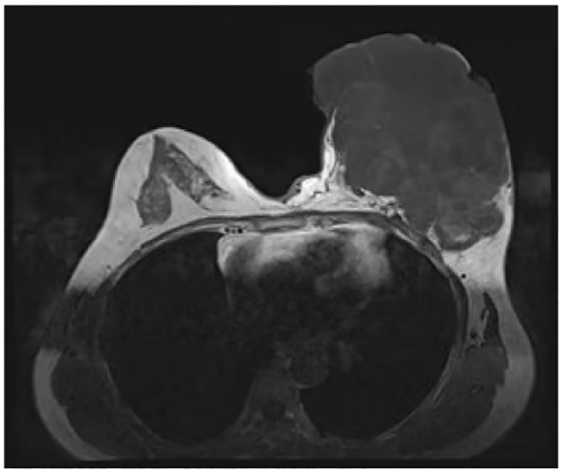


FIGURE 2
Contrast-enhanced magnetic resonance imaging findings. The boundary between the mass and the pectoralis major muscle was indistinct, with persistent signs of infection observed.

cell count of 7880/μl indicated successful management of the infection before undergoing mastectomy.

Following standard disinfection and draping procedures, the entirety of the mass was meticulously wrapped and secured using sterile gauze to prevent potential contamination. During the surgery, surgeons noted significant vascularity of the tumor and minor adhesion to the base of the pectoralis major fascia. Subsequently, a horizontal oval incision was made to excise the entire breast, encompassing the nipple, areola, and pectoralis major fascia, while preserving the pectoralis major and pectoralis minor muscles. After excision, the wound underwent meticulous irrigation with warm sterile water to remove any debris or blood. Subsequently, hemostasis was achieved. To facilitate wound healing and chest reconstruction, skin from the abdomen was harvested and transplanted onto the chest. The patient was diagnosed with a malignant phyllodes tumor. Follow-up evaluation confirmed successful removal of breast tissue measuring 20 cm × 17 cm, with no tumor spread to the pectoralis major fascia. The histopathological examination demonstrated typical morphological features of malignant phyllodes tumors, marked stromal cellularity, marked stromal cell anisotropy with a few ductal epithelial component visible in the middle, characteristic leaf-like fronds protruding into cystically dilated fissures, mitotic rate of ≥ 10/10 high power fields, stromal overgrowth, and infiltrative tumor borders (Figure 3). The patient experienced no wound-related complications during hospitalization and was discharged on the 13th day after surgery.

Although postoperative radiotherapy was recommended due to uncertainty about achieving sufficient negative margins for the ruptured giant tumor, the patient declined. In May 2021, the patient presented to Mianyang Central Hospital with a subcutaneous nodule anterior to the sternal body measuring approximately 3.0 cm x 2.5 cm (Figure 4). Subsequently, the patient underwent a localized expended resection of the mass, resulting in a significant defect necessitating an incision in the right inframammary fold to displace the medial right breast gland to the anterior thoracic region, with negative surgical margins. The final histological diagnosis revealed a recurrent malignant phyllodes tumor. Subsequently, the patient declined postoperative radiotherapy despite medical advice. After one year of monitoring, the patient developed liver, lung, and brain metastases, leading to multiple organ failure and death. The reporting of this study follows CARE guidelines (4).

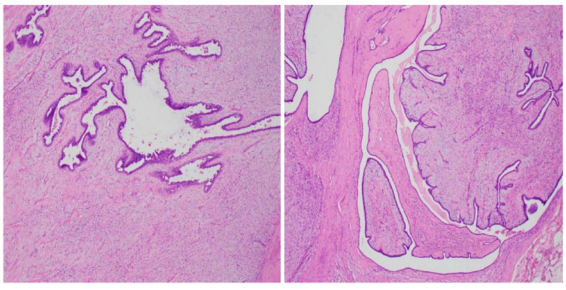


FIGURE 3
Histological analysis of the surgical specimen demonstrated heightened cellularity surrounding the glandular structures, along with cellular atypia, elevated mitotic activity, as well as hemorrhage and necrosis (HE staining; magnification 100x).

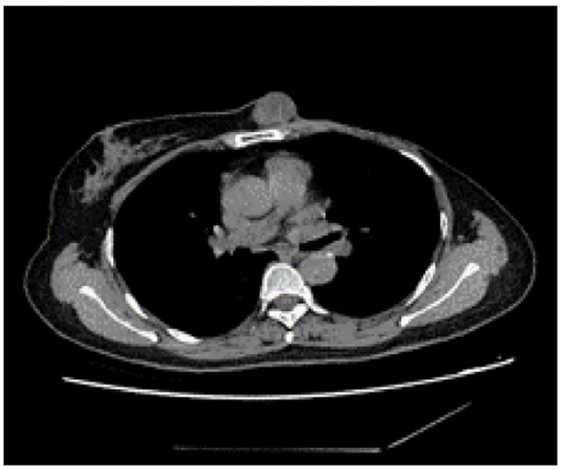


FIGURE 4
Computed tomography of the thorax identified a subcutaneous mass anterior to the sternum, measuring approximately 3.0 cm x 2.5 cm, characterized by smooth margins and regular morphology.

3 Discussion

According to the WHO classification, phyllodes tumors are fibroepithelial neoplasms characterized by distinct intracanalicular architectural patterns and leaf-like stromal fronds. These features are accompanied by luminal epithelial and myoepithelial layers and stromal hypercellularity. Phyllodes tumors are stratified into three subgroups (benign, borderline, and malignant) based on criteria including stromal cellularity, stromal atypia, stromal overgrowth, mitotic activity, and tumor margins (as shown in Table 2) (2, 5). Immunohistochemical analysis has shown positive expression of vascular endothelial growth factor receptor (VEGFR), P53, CD117, P16, and epidermal growth factor receptor (EGFR) in malignant phyllodes tumors. Studies have demonstrated that malignant phyllodes tumors exhibit lower expression of CD34, with CD34 expression showing an inverse correlation with unfavorable histological characteristics (6–8). The primary objective is to differentiate malignant phyllodes tumors from spindle cell metaplastic breast carcinomas and primary breast sarcomas.

Spindle cell metaplastic breast carcinomas may contain varying amounts of malignant epithelial components, with some cases lacking epithelial components entirely or showing heterologous mesenchymal differentiation. The identification of diffuse broad-spectrum cytokeratin or p63 expression in malignant spindle cells may indicate the presence of metaplastic carcinoma, as these proteins are typically not expressed in malignant phyllodes tumors (9, 10). Breast sarcomas are a rare subset of malignant

TABLE 2 Histopathological features of benign, borderline and malignant phyllodes tumors of the breast.

Subgroups	Stromal cellularity	Stromal atypia	Stromal overgrowth	Mitosis (/mm^2 HPFs)	Tumor margin
Benign	Mild	Mild	Absent	< 2.5	Well defined
Borderline	Moderate	Moderate	Absent or focal	2.5 - 5.0	Well defined and focally infiltrative
Malignant	Marked	Marked	Present	> 5.0	Infiltrative

HPE, high-powered field.

tumors that arise from the mesenchymal tissue of the breast, characterized by a lack of distinctive histological features. In contrast to malignant phyllodes tumors, which typically exhibit a sarcomatous pattern in the stromal tissue and a benign epithelial component, breast sarcomas do not display benign epithelial components or leaf-like stromal fronds (11). Studies have suggested a potential association between genetic predispositions, such as Li-Fraumeni syndrome, and an elevated risk of developing breast sarcomas through TP53 mutations (12, 13).

Diagnosis of breast phyllodes tumors prior to surgical intervention remains challenging. Ultrasound and mammography lack specificity in imaging phyllodes tumors. Prior studies have not established the efficacy of MRI in the detection of breast phyllodes tumors (14). Histopathological assessment remains the gold standard for diagnosing these tumors. Ultrasound-guided core needle biopsy (CNB) has emerged as the preferred method for obtaining tissue samples from suspicious breast lesions for histopathological examination due to its safety, speed, and convenience. Nonetheless, the heterogeneous nature of phyllodes tumors poses a challenge in distinguishing them from epithelial neoplasms or fibroadenomas during biopsy procedures, potentially leading to missed diagnoses. Research indicates that CNB has an approximate 50% accuracy rate in diagnosing phyllodes tumors, with larger tumor size correlating significantly with discordant biopsy results (15).

Surgical intervention is the mainstay of treatment for phyllodes tumors. Benign phyllodes tumors exhibit no heightened risk of local recurrence following any type of resection. Conversely, mastectomy for borderline and malignant phyllodes tumors has been shown to improve local recurrence rates and disease-free survival (16–18). The majority of studies have demonstrated a lack of statistically significant disparity in overall or cancer-specific survival rates among patients with phyllodes tumors who underwent wide excision compared to mastectomy. Margins are still a matter of debate. While systematic reviews have not found a consistent correlation between positive margins and local recurrence in benign and borderline phyllodes tumors (14), a negative margin has been consistently associated with decreased recurrence risk in malignant phyllode tumors (19). Moo et al. discovered that patients with benign phyllodes tumors who underwent re-excision due to positive or close margins did not experience lower rates of local recurrence (20). The National Comprehensive Cancer Network (NCCN) recommends a negative margin of more than 1cm for malignant phyllodes tumors. However, Thind et al. found no significant difference in local recurrence or survival rates between borderline and malignant phyllodes tumors with margins of 1 cm versus >1cm (21). Failure to accurately measure tumor margins during surgery, particularly in cases of giant and ruptured tumors with unclear borders, may contribute to early recurrence of phyllodes tumors. It is increasingly acknowledged that the appropriate surgical margin width should be tailored to the specific subtype of the phyllodes tumor. Mastectomy is primarily employed for larger and recurrent tumors, particularly those of a malignant nature. Giant phyllodes tumors typically encompass the entire breast and present challenges in achieving adequate resection margins. It is important to recognize that in cases where phyllodes tumors reach significant size, complete removal of breast tissue and the tumor-infiltrated soft tissues can decrease the likelihood of local tumor recurrence. Patients with positive surgical margins for benign phyllodes tumors could be follow-up closely, while borderline and malignant phyllodes tumors with margins of more than 1cm should be a localized expanded resection. Khosravi-Shahi, P et al. demonstrated that over 90% of malignant phyllodes tumor cases did not exhibit axillary lymph node metastasis, thus supporting the recommendation to avoid axillary surgery (22).

Certain researchers argue that breast reconstruction may pose a potential risk for phyllodes tumors, which are known for their high recurrence rate. While certain studies suggest that recurrence is not directly linked to breast reconstruction, the possibility of local recurrence could lead to reconstruction failure, necessitating multiple surgeries and imposing additional physical, psychological, and financial strain on patients (23, 24). Therefore, timely surgical intervention is recommended for giant borderline or malignant phyllodes tumors to prevent complications such as tumor compression of the chest wall and invasion of the thoracic cavity. Preoperative assessment of tumor compression or invasion of the chest wall is essential (25). Surgical procedures should be performed cautiously to ensure complete excision of the tumor and to prevent residual disease or compromise of the tumor's integrity, which may result in short-term recurrence (26). Careful handling of the tumor envelope during surgery is crucial, requiring blunt separation to maintain its integrity. In cases where the envelope is compromised, meticulous identification and dissection of the tumor, along with demarcation of normal tissue, are imperative. Preservation of normal skin and muscle is a priority to adequately cover the wound during complete tumor dissection and attainment

of negative margins. For cases where the tumor was ulcerated prior to surgery, it is recommended to meticulously cover and isolate the ulcerated area with gauze during the procedure to prevent contamination of the operative site. Management of large skin defects may necessitate plastic restoration techniques such as skin grafts or rotation flaps.

Adjuvant radiotherapy has been shown to decrease local recurrence rates in borderline and malignant phyllodes tumors, especially following breast-conserving surgery, and is particularly beneficial for individuals under 45 years of age and those with tumors larger than 5cm (27, 28). Nevertheless, there is currently no evidence supporting the efficacy of postoperative adjuvant radiotherapy in improving overall survival for primary phyllodes tumors, as indicated by the NCCN guidelines. The efficacy of adjuvant chemotherapy, endocrine therapy, and targeted therapy for phyllodes tumors remains unproven.

Phyllodes tumors predominantly metastasize hematogenously, with distant metastases occurring in 9% of malignant cases, most commonly in the lungs and bones. Recurrence rates of 10-17%, 14-25%, and 23-30% have been reported in the literature for benign, borderline, and malignant phyllodes tumors, respectively (29). Additionally, the pathology of recurrent tumors often presents a more severe condition. Patients afflicted with malignant phyllode tumors who experience distant metastases face a grim prognosis, with an average survival time of 4 to 17 months (30). Research has not identified a disparity in overall survival rates between mastectomy and locally extended resection following recurrence. Therefore, in accordance with NCCN guidelines, wide margin re-excision and postoperative radiotherapy may be deemed appropriate for cases of local recurrence subsequent to the resection of malignant phyllode tumors.

This particular case study serves to enhance the knowledge of diagnosing and treating malignant phyllodes tumors, as well as examining the surgical techniques used for managing large malignant phyllodes tumors. The preservation of the mammoplasty approach may be considered as a viable option when sufficient margins are achieved. Mastectomy may be considered as a treatment option for giant phyllodes tumors in cases where oncoplastic excision fails to yield satisfactory reconstructive outcomes. Limited research exists on the efficacy of combining mastectomy with breast reconstruction in such cases. The complexity of tumor localization poses challenges for reconstruction, necessitating careful preoperative planning to ensure safe and satisfactory oncoplastic outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The studies involving humans were approved by Ethics Committee of Mianyang Central Hospital (S20230213-01). The studies were conducted in accordance with the local legislation and institutional requirements. The patient's personal information has been deidentified. Prior to the study, patient consent to treatment was obtained. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YT: Conceptualization, Writing – original draft. SL: Conceptualization, Writing – original draft. LZ: Writing – review & editing. ZZ: Writing – review & editing. HH: Conceptualization, Writing – review & editing. YJ: Data curation, Formal analysis, Writing – review & editing. TL: Data curation, Formal analysis, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by Wu Jieping Medical Foundation (Grant No.320.6750.2023-18-102).

Acknowledgments

We appreciate all the reviewers who participated in the review.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Mishra SP, Tiwary SK, Mishra M, Khanna AK. Phyllodes tumor of breast: a review article. *ISRN Surg*. (2013) 2013:361469. doi: 10.1155/2013/361469

2. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, et al. The 2019 World Health Organization classification of tumours of the breast. *Histopathology*. (2020) 77:181–5. doi:10.1111/his.14091

3. Lissidini G, Papa G, Ashoor AA, Girardi A, Crown A, Toesca A, et al. Giant Malignant phyllodes tumor of the breast: insights into optimal management and reconstructive options for a rare and challenging entity. *Breast J*. (2020) 26:2400–2. doi: 10.1111/tbj.14095

4. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D. The CARE guidelines: consensus-based clinical case reporting guideline development. *Glob Adv Health Med*. (2013) 2:38–43. doi: 10.7453/gahmj.2013.008

5. Tan PH, Ellis IO. Myoepithelial and epithelial-myoepithelial, mesenchymal and fibroepithelial breast lesions: updates from the WHO Classification of Tumours of the Breast 2012. *J Clin Pathol*. (2013) 66:465–70. doi: 10.1136/jclinpath-2012-201078

6. Vilela MH, de Almeida FM, de Paula GM, Ribeiro NB, Cirqueira MB, Silva AL, et al. Utility of Ki-67, CD10, CD34, p53, CD117, and mast cell content in the differential diagnosis of cellular fibroadenomas and in the classification of phyllodes tumors of the breast. *Int J Surg Pathol*. (2014) 22:485–91. doi: 10.1177/1066896914521290

7. Tse GM, Lui PC, Vong JS, Lau KM, Putti TC, Karim R, et al. Increased epidermal growth factor receptor (EGFR) expression in Malignant mammary phyllodes tumors. *Breast Cancer Res Treat*. (2009) 114:441–8. doi: 10.1007/s10549-008-0030-5

8. Niezabitowski A, Lackowska B, Rys J, Kruczak A, Kowalska T, Mitus J, et al. Prognostic evaluation of proliferative activity and DNA content in the phyllodes tumor of the breast: immunohistochemical and flow cytometric study of 118 cases. *Breast Cancer Res Treat*. (2001) 65:77–85. doi: 10.1023/a:1006457304526

9. Tse GM, Tan PH, Chaiwun B, Putti TC, Lui PC, Tsang AK, et al. p63 is useful in the diagnosis of mammary metaplastic carcinomas. *Pathology*. (2006) 38:16–20. doi: 10.1080/00313020500444625

10. Zhang Y, Kleer CG. Phyllodes tumor of the breast: histopathologic features, differential diagnosis, and molecular/genetic updates. *Arch Pathol Lab Med*. (2016) 140:665–71. doi: 10.5858/arpa.2016-0042-RA

11. Lim SZ, Ng CCY, Rajasegaran V, Guan P, Selvarajan S, Thike AA, et al. Genomic profile of breast sarcomas: a comparison with Malignant phyllodes tumours. *Breast Cancer Res Treat*. (2019) 174:365–373g. doi: 10.1007/s10549-018-5067-5

12. Malkin D, Li FP, Strong LC, Fraumeni JFJR, Nelson CE, Kim DH, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science*. (1990) 250:1233–8. doi: 10.1126/science.1978757

13. Lahat G, Lazar A, Lev D. Sarcoma epidemiology and etiology: potential environmental and genetic factors. *Surg Clin North Am*. (2008) 250:451–81. doi: 10.1016/j.suc.2008.03.006

14. Bogach J, Shakeel S, Wright FC, Hong NJL. Phyllodes tumors: A scoping review of the literature. *Ann Surg Oncol*. (2022) 29:446–59. doi: 10.1245/s10434-021-10468-2

15. Zhou ZR, Wang CC, Yang ZZ, Yu XL, Guo XM. Phyllodes tumors of the breast: diagnosis, treatment and prognostic factors related to recurrence. *J Thorac Dis*. (2016) 8:3361–8. doi: 10.21037/jtd.2016.11.03

16. Ben Hassouna J, Damak T, Gamoudi A, Chargui R, Khomsi F, Mahjoub S, et al. Phyllodes tumors of the breast: a case series of 106 patients. *Am J Surg*. (2006) 192:141–7. doi: 10.1016/j.amjsurg.2006.04.007

17. Kim S, Kim JY, Kim DH, Jung WH, Koo JS. Analysis of phyllodes tumor recurrence according to the histologic grade. *Breast Cancer Res Treat*. (2013) 141:353–63. doi: 10.1007/s10549-013-2684-x

18. Lim RS, Cordeiro E, Lau J, Lim A, Roberts A, Seely J. Phyllodes tumors-the predictors and detection of recurrence. *Can Assoc Radiol J*. (2021) 72:251–7. doi: 10.1177/0846537119899553

19. Spitaleri G, Toesca A, Botteri E, Bottiglieri L, Rotmensz N, Boselli S, et al. Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. *Crit Rev Oncol Hematol*. (2013) 88:427–36. doi: 10.1016/j.critrevonc.2013.06.005

20. Moo TA, Alabdulkareem H, Tam A, Fontanet C, Lu Y, Landers A, et al. Association between recurrence and re-excision for close and positive margins versus observation in patients with benign phyllodes tumors. *Ann Surg Oncol*. (2017) 24:3088–92. doi: 10.1245/s10434-017-5955-7

21. Thind A, Patel B, Thind K, Isherwood J, Phillips B, Dhaliwal K, et al. Surgical margins for borderline and Malignant phyllodes tumours. *Ann R Coll Surg Engl*. (2020) 102:165–73. doi: 10.1308/rcsann.2019.0140

22. Khosravi-Shahi P. Management of non metastatic phyllodes tumors of the breast: review of the literature. *Surg Oncol*. (2011) 20:e143–8. doi: 10.1016/j.suronc.2011.04.007

23. Pimiento JM, Gadgil PV, Santillan AA, Lee MC, Esposito NN, Kiluk JV, et al. Phyllodes tumors: race-related differences. *J Am Coll Surg*. (2011) 213:537–42. doi: 10.1016/j.jamcollsurg.2011.07.012

24. Guillot E, Couturaud B, Reyal F, Curnier A, Ravinet J, Laé M, et al. Management of phyllodes breast tumors. *Breast J*. (2011) 17:129–37. doi: 10.1111/tbj.2011.17.issue-2

25. Kudela E, Kajo K, Kozubik E, Rokos T, Pribulova T, Danko J, et al. Recurrent giant Malignant phyllodes tumor of the breast. *Case Rep Obstet Gynecol*. (2021) 2021:2476691. doi: 10.1155/2021/2476691

26. Tremblay-LeMay R, Hogue JC, Provencher L, Poirier B, Poirier É, Laberge S, et al. How wide should margins be for phyllodes tumors of the breast? *Breast J*. (2017) 23:315–22. doi: 10.1111/tbj.12727

27. Barth RJ Jr., Wells WA, Mitchell SE, Cole BF. A prospective, multi-institutional study of adjuvant radiotherapy after resection of Malignant phyllodes tumors. *Ann Surg Oncol*. (2009) 16:2288–94. doi: 10.1245/s10434-009-0489-2

28. Zeng S, Zhang X, Yang D, Wang X, Ren G. Effects of adjuvant radiotherapy on borderline and Malignant phyllodes tumors: A systematic review and meta-analysis. *Mol Clin Oncol*. (2015) 3:663–71. doi: 10.3892/mco.2015.503

29. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. (2016) 68:5–21. doi: 10.1111/his.12876

30. Wei Y, Yu Y, Ji Y, Zhong Y, Min N, Hu H, et al. Surgical management in phyllodes tumors of the breast: a systematic review and meta-analysis. *Gland Surg*. (2022) 11:513–23. doi: 10.21037/gs-21-789

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 07 May 2024
DOI 10.3389/fonc.2024.1348343

OPEN ACCESS

EDITED BY
Simona Ruxandra Volovat,
Grigore T. Popa University of Medicine and Pharmacy, Romania

REVIEWED BY
Petra Tesarova,
Charles University, Czechia
Jerzy Chudek,
Medical University of Silesia, Poland

*CORRESPONDENCE
Catarina Pulido
pulido.catarina@gmail.com

RECEIVED 02 December 2023
ACCEPTED 29 March 2024
PUBLISHED 07 May 2024

CITATION
Pulido C, Albuquerque J, Correia J and Passos-Coelho JL (2024) Case report: Treatment with Phesgo® in a patient receiving hemodialysis.
Front. Oncol. 14:1348343.
doi: 10.3389/fonc.2024.1348343

Case report: Treatment with Phesgo® in a patient receiving hemodialysis

Catarina Pulido*, Joana Albuquerque, Jorge Correia and José Luís Passos-Coelho

Oncology Department, Hospital da Luz Lisboa, Lisbon, Portugal

Introduction: Patients with metastatic HER2-positive breast cancer have multiple therapeutic options. However, most are not studied in the renal replacement therapy (RRT) setting.

Case report: We report the use of Phesgo® (subcutaneous fixed-dose combination of trastuzumab and pertuzumab) combined with exemestane as a first-line treatment of metastatic HER2-positive breast cancer in a hemodialysis patient with multiple comorbidities. Partial response was attained, with disease progression after 8 months without evidence of significant toxicity.

Discussions: This case report is, to our knowledge, the first published case documenting the use of Phesgo® in a hemodialysis patient. No new safety signs were seen, and activity was documented, adding support to the use of this drug combination in such a patient population.

KEYWORDS

case report, Phesgo, hemodialysis, advanced breast cancer, HER2-positive

1 Introduction

Breast cancer is the most frequent malignancy worldwide, responsible for a great burden of disease among women with multiple chronic conditions, including end-stage renal disease (ESRD). The improvement in survival of patients treated with renal replacement therapy (RRT) increases the chance of cancer development, with a higher incidence of breast cancer being reported in this population (1, 2).

Chronic kidney disease (CKD) does not limit surgical treatment or radiotherapy but affects the pharmacokinetics (PK) of drugs used as systemic treatment, increasing the risk of toxicity and making efficacy less predictable. These patients are usually excluded from clinical trials, and the available evidence on treatment efficacy and tolerance comes from case reports. Regarding the use of trastuzumab, no significant changes in PK were found in the RRT setting, with similar outcomes independent of drug formulation (intravenous or subcutaneous) (3–5). However, for pertuzumab, a different anti-HER2 monoclonal antibody, there are limited data on PK, and consequently, there is no recommendation for administering this drug to patients on RRT. To

our knowledge, the only case report of a patient on hemodialysis treated with trastuzumab and pertuzumab used the intravenous formulation and documented the known and manageable toxicity profile without new efficacy concerns (6).

Herein, we report a further case of a patient on RRT treated with trastuzumab and pertuzumab, adding the first published report of the use of Phesgo® (a subcutaneous fixed-dose combination of pertuzumab and trastuzumab) in this population. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

2 Case report

2.1 Patient information

We report the case of a 52-year-old woman, autonomous and professionally active, without family or social support, with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 1. She noted a lump in her right breast and was diagnosed with breast cancer in 2019: invasive carcinoma of the breast, of no special type, G2, estrogen receptor (ER)-positive (90%), progesterone receptor-negative, HER2 3+, Ki67 60%, staged as cT3(m)N3M0—prognostic stage group IIIB.

Her medical family history included maternal breast cancer at 68 years old and paternal CKD. The patient had multiple comorbidities, namely, CKD. When she was 9 years old, she was diagnosed with Fanconi syndrome. She has been on hemodialysis three times a week (medium 3.7 hours per session) since 1998. From 1982 to 1990, the patient was on hemodialysis as well, having received a transplant in 1990 that failed in 1998. At the time of the first oncology consultation, the patient presented a left arm aneurysm of the arteriovenous fistula, secondary hyperparathyroidism, secondary hypertension, severe pulmonary hypertension, uremic neuropathy, malnutrition, chronic hepatitis C virus infection genotype 2, prior acute colonic diverticulitis complicated with abscess with surgical management and colostomy, major depression, and status post-thyroidectomy and right neck dissection (May 2017) for papillary thyroid carcinoma.

2.2 Clinical findings

The patient was asthenic, and her physical exam denoted malnutrition, a right breast lesion measuring 10 × 7 cm, right axilla and right supra- and infraclavicular lymphadenopathies, and right arm lymphedema. The remaining physical exam found no evidence of breast cancer metastatic disease (cM0).

2.3 Timeline

Given the diagnosis of locally advanced HER2-positive, ER-positive breast cancer, along with the patient's comorbidities and preferences (prioritizing tolerability and flatly refusing chemotherapy), neoadjuvant therapy with subcutaneous trastuzumab and oral tamoxifen was started in January 2020. The best response was a partial response with good tolerance and no cardiac toxicity. After 6 months of therapy, and repeatedly thereafter, curative surgery was proposed, which the patient refused, maintaining trastuzumab and hormonal therapy up until July 2022, when after 30 months of therapy, locoregional, skin, pleural, peritoneal, and lymph node progression was confirmed (Figure 1A). During this period (until July 2022), the case was rediscussed in the tumor board, and alternatives such as radiotherapy were discussed and dismissed considering it would not be curative by itself nor effective palliating the lymphedema—the only local symptom the patient presented at that point.

2.4 Diagnostic assessment

At the tumor board and considering the advice of the patient's nephrologist, first-line treatment with paclitaxel, trastuzumab, and pertuzumab was recommended.

2.5 Therapeutic interventions

The patient refused chemotherapy, so she was started on Phesgo® combined with exemestane in August 2022 (by then, the patient was postmenopausal). Phesgo® was administered every 21 days, 24 hours after the last hemodialysis session and 24 hours before the next.

2.6 Follow-up and outcomes

Three weeks after starting Phesgo® and exemestane, a reduction in the dimensions of the breast and skin lesions was already noted (Figure 2).

In the first response evaluation by positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG), a partial metabolic response was documented with a clear decrease in the uptake in the breast lesion, the lymph nodes, and the pleural nodules, in addition to a decrease in the pleural effusion volume (Figure 1B). In January 2023, all the skin lesions had disappeared.

No adverse events were noted, and the left ventricle ejection fraction and strain remained within the normal range (Table 1).

The patient completed 10 cycles of Phesgo® until April 2023, when some of the skin lesions reappeared, the breast lesion increased in size, and new left axillary lymph nodes were identified (Figure 2). FDG-PET in April 2023 documented disease progression in the breast, pleura, peritoneum, and lymph nodes (Figure 1C). The patient maintained an ECOG-PS of 1 and started a second-line anti-HER2 therapy recommended by the tumor board.

2.7 Discussion

Our report is, to our best knowledge, the first published case report of Phesgo® treatment in a patient on hemodialysis. The choice of Phesgo®, a subcutaneous fixed-dose formulation of pertuzumab and trastuzumab, instead of the intravenous formulation was justified by the right arm lymphedema, the left arm aneurysm of the arteriovenous fistula, and the limited

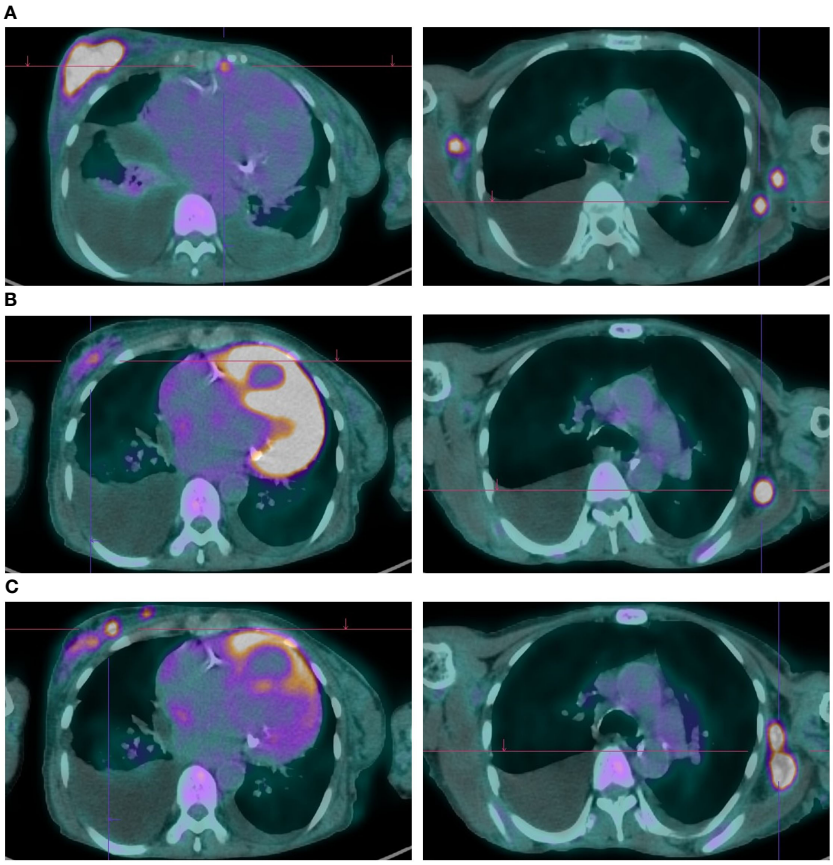


FIGURE 1
Metabolic and radiologic evaluation on FDG-PET of cancer lesions throughout Phesgo® treatment. **(A)** Obtained on July 22, 2022; showed disease progression with an increased atypical lesion in the right breast and bilateral lymphadenopathies. **(B)** Captured on January 10, 2023; demonstrated a favorable response to Phesgo® treatment with reduced breast lesion size and improved lymphadenopathies. **(C)** Obtained on April 20, 2023; indicated disease progression with new hypermetabolic foci, pleural effusion, ascites, and lytic lesions.

vascular access options. Also, according to PHranceSCa trial results, most patients prefer the subcutaneous formulation, with the most common reasons being "less time in the clinic" and "more comfortable during administration", which were very important to this professionally active patient, already spending much time in the hemodialysis center (7). In the absence of dose and schedule recommendations, we chose to administer Phesgo® on a different day from dialysis, which was conducted at another institution. Due to pertuzumab's high molecular weight (148 kDa), removal of Phesgo® by hemodialysis was not expected (8). Despite prior reports suggesting that a lower glomerular filtration rate could be associated with an increased risk of cardiotoxicity for both trastuzumab and pertuzumab, our patient did not experience cardiac toxicity. Considering the limited safety and dosage data for aromatase inhibitors (AI) in patients with a glomerular filtration rate under 30 mL/min, we chose exemestane due to its minimal renal elimination (<1%) compared to other options (anastrozole 11%, letrozole 90%, and fulvestrant 8%) (9). In the case presented, Phesgo progression-free survival (PFS) was 8 months, lower than reported in the phase II PERTAIN trial, which compared the

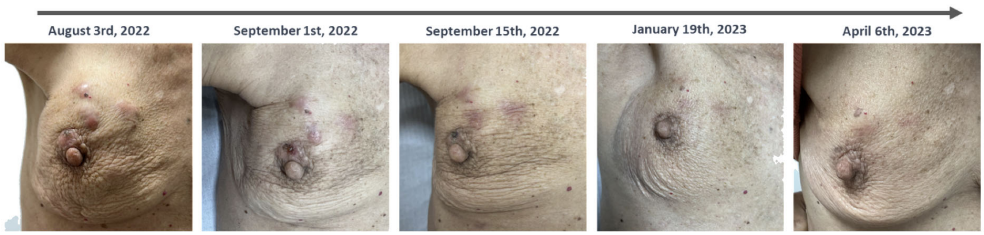


FIGURE 2
Temporal evolution of clinical breast and skin lesions. A favorable clinical response was evident following the initiation of Phesgo in August 2022, with complete resolution of skin lesions observed by January 2023. However, upon completing 10 cycles of Phesgo by April 2023, there was a recurrence of skin lesions, concurrent with an increase in the size of the breast lesion and the identification of new left axillary lymphadenopathies.

TABLE 1 Temporal evolution of left ventricular ejection fraction and strain.

Date	GLS	LVEF
May 2022	−15.8%	53%
September 2022	−15.7%	50%
January 2023	–	50%
April 2023	−16.3%	53%

The table illustrates the temporal evolution of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) documenting normal values for both parameters throughout the recorded period.

combination of trastuzumab plus pertuzumab plus an AI with trastuzumab plus an AI, with a median PFS of 20.6 *vs.* 15.8 months [hazard ratio (HR) 0.67, p = 0.006]. While these results are encouraging for a chemotherapy-free regimen, it must be noted that one-half of patients received induction chemotherapy with a taxane prior to switching to maintenance exemestane. Furthermore, patients with CKD or other comorbidities and patients with disease progression on prior trastuzumab were excluded from the trial, which may explain the lower PFS observed in this case (10–12). One limitation of this report is the absence of pharmacokinetic data, which were not collected considering that they would not lead to therapy modification (in the absence of guidance for that) but would add morbidity and costs to the patient's care.

To conclude, our report demonstrates the safe and effective use of the association of trastuzumab plus pertuzumab in a patient with end-stage renal disease undergoing RRT and raises no red flags to the administration of the subcutaneous fixed-dose formulation in this setting. More studies are needed to assess the PK of anticancer drugs in patients on RRT and its efficacy and security in a real-world population. Meanwhile, some important lessons can be taken from this case, such as the importance of a multidisciplinary approach including medical subspecialties, in this case, nephrology. This was key to allowing the patient access to innovative oncological treatment despite her comorbidities and in accordance with her preferences. Raising awareness and special recommendations are needed for this patient's subgroup not only to guide drug use and dosing but also to preclude undertreatment, especially in the curative setting.

3 Patient perspective

The treatment was well tolerated and administered in a comfortable schedule, permitting the maintenance of hemodialysis and most of the planned daily activities. The response in the breast was significant, with regression of the main lesions. This treatment is a valid option for disease control in patients with advanced disease (unresectable locally advanced or metastatic) and multiple comorbidities who cannot tolerate and/or refuse chemotherapy after being duly informed. In oncology and especially in the palliative setting, patient preferences are important and should be considered in shared decision-making. Information on disease course and treatment recommendations must be tailored to the individual patient and account for his/her preferences since some treatments may impact an outcome such as survival at the cost of a decrease in quality of life or patient independence.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

CP: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. JA: Conceptualization, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. JC: Conceptualization, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. JP-C: Conceptualization, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. F. Hoffman-La Roche provided financial support for the publication of this article.

Acknowledgments

We acknowledge the patient for allowing this publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Lin MY, Kuo MC, Hung CC, Wu WJ, Chen LT, Yu ML, et al. Association of dialysis with the risks of cancers. *PloS One*. (2015) 10:e0122856. doi: 10.1371/journal.pone.0122856

2. Butler AM, Olshan AF, Kshirsagar AV, Edwards JK, Nielsen ME, Wheeler SB, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996-2009. *Am J Kidney Dis*. (2015) 65:763–72. doi: 10.1053/j.ajkd.2014.12.013

3. Micallef RA, Barrett-Lee PJ, Donovan K, Ashraf M, Williams L. Trastuzumab in patients on haemodialysis for renal failure. *Clin Oncol (R Coll Radiol)*. (2007) 19:559. doi: 10.1016/j.clon.2007.04.008

4. Gori S, Foglietta J, Lunardi G, Inno A, Cardinali B, Millo E, et al. Pharmacokinetics of trastuzumab in haemodialysis. *Breast J*. (2015) 21:329–31. doi: 10.1111/tbj.12407

5. Kokkali S, Ternant D, Kemmel V, Levêque D, Wendling F, Barthelemy P, et al. Intravenous and subcutaneous administration of trastuzumab in a patient on peritoneal dialysis. *Br J Clin Pharmacol*. (2021) 87:3372–4. doi: 10.1111/bcp.14731

6. Gaertner KM, Poornima IG, Hilton C. Trastuzumab and pertuzumab in hemodialysis: A case report. *J Oncol Pharm Pract*. (2021) 27:1799–801. doi: 10.1177/10781552211003641

7. O'Shaughnessy J, Sousa S, Cruz J, Fallowfield L, Auvinen P, Pulido C, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): A randomised, open-label phase II study. *Eur J Cancer*. (2021) 152:223–32. doi: 10.1016/j.ejca.2021.03.047

8. Department of clinical pharmacology and pharmacoepidemiology, University Medical Center Heidelberg. Available online at: https://dosing.de/popup_niere.php?monoid=883 (Accessed 5th July 2023).

9. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, Poole C, De Placido S, Osborne CK, et al. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-positive metastatic or locally advanced breast cancer (PERTAIN): A randomized, open-label phase II trial. *J Clin Oncol*. (2018) 36:2826–35. doi: 10.1200/JCO.2017.76.7863

10. Bednarek A, Mykała-Cieśla J, Pogoda K, Jagiełło-Gruszfeld A, Kunkiel M, Winder M, et al. Limitations of systemic oncological therapy in breast cancer patients with chronic kidney disease. *J Oncol*. (2020) 2020:7267083. doi: 10.1155/2020/7267083

11. Arpino G, de la Haba-Rodriguez J, Ferrero JM, De Placido S, Osborne CK, Klingbiel D, et al. Abstract PD3-02: Final analysis of PERTAIN: A randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of first-line pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in patients with HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer. *Cancer Res*. (2021) 81:PD3–02. doi: 10.1158/1538-7445.SABCS20-PD3-02

12. Arpino G, de la Haba Rodríguez J, Ferrero JM, De Placido S, Osborne CK, Klingbiel D, et al. Pertuzumab, trastuzumab, and an aromatase inhibitor for HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer: PERTAIN final analysis. *Clin Cancer Res*. (2023) 29:1468–76. doi: 10.1158/1078-0432.CCR-22-1092

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 16 May 2024
DOI 10.3389/fonc.2024.1404706

OPEN ACCESS

EDITED BY
Robert Wesolowski,
The Ohio State University, United States

REVIEWED BY
Zouina Sarfraz,
Fatima Jinnah Medical University, Pakistan
Fabiana Gregucci,
Ospedale Generale Regionale Francesco Miulli, Italy

*CORRESPONDENCE
Boštjan Šeruga
bseruga@onko-i.si

RECEIVED 21 March 2024
ACCEPTED 30 April 2024
PUBLISHED 16 May 2024

CITATION
Pavlin T, Blatnik A and Šeruga B (2024) Challenges in the management of operable triple-negative breast cancer in a survivor of the B-cell acute lymphoblastic leukemia: a case report.
Front. Oncol. 14:1404706.
doi: 10.3389/fonc.2024.1404706

Challenges in the management of operable triple-negative breast cancer in a survivor of the B-cell acute lymphoblastic leukemia: a case report

Tina Pavlin[1,2], Ana Blatnik[2,3] and Boštjan Šeruga[1,2]*

[1]Division of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia, [2]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, [3]Department of Clinical Cancer Genetics, Institute of Oncology Ljubljana, Ljubljana, Slovenia

Background: Operable triple-negative breast cancer (TNBC) is an unfavorable subtype of breast cancer, which usually requires an aggressive perioperative systemic treatment. When TNBC presents as a second primary cancer after cured acute leukemia, its management might be challenging.

Case presentation: We present a case report of a young postmenopausal woman with an operable TNBC who had a history of the B-cell acute lymphoblastic leukemia (B-ALL) and graft versus host disease (GVHD) after allogeneic stem cell transplantation (allo-SCT). A history of previous treatment with anthracyclines and radiotherapy and GVHD limited the use of doxorubicin for treatment of her TNBC. Due to the history of GVHD, perioperative treatment with pembrolizumab was omitted. Genetic testing was challenging due to the possible contamination of her tissues with the donor's cells after allo-SCT. In samples of our patient's buccal swab, peripheral blood, and tumor tissue, a pathogenic variant in the partner and localizer of *BRCA2* (*PALB2*) gene was found. With neoadjuvant chemotherapy which included carboplatin, a pathologic complete response was achieved. Although our patient has a low risk for recurrence of TNBC, her risk for the development of new primary cancers remains substantial.

Conclusion: This case highlights challenges in the systemic treatment, genetic testing, and follow-up of patients with operable TNBC and other solid cancers who have a history of acute leukemia.

KEYWORDS

triple negative breast cancer, acute lymphoblastic leukaemia, second primary cancer, genetic testing, follow-up, case report

Background

Triple-negative breast cancer (TNBC) accounts for approximately 15% of all breast cancers and is clinically defined as lacking expression of the estrogen receptor (ER) and progesterone receptor (PR) and overexpression of the human epidermal growth factor receptor (HER) 2. Historically, TNBC has been characterized by an aggressive natural history and worse disease-specific outcomes as compared with other breast cancer subtypes (1). A modern systemic therapy of the operable TNBC includes perioperative chemotherapy (ChT) (i.e., anthracyclines, taxanes with or without carboplatin and capecitabine in patients with residual disease after surgery), an immune checkpoint inhibitor (ICI) pembrolizumab, and an inhibitor of the poly (ADP-ribose) polymerase (PARP) olaparib in patients with breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*) pathogenic germline variants (2). When TNBC presents as a second primary cancer after cured acute leukemia, its management might be challenging.

Second primary breast cancers are among the most common second non-skin cancers in survivors of childhood cancers (3). For pediatric patients with an acute lymphoblastic leukemia (ALL), a reported cumulative risk of second primary cancers ranges from 1.2% to 3.3% after 10 to 15 years of follow-up (3–6). More than 80% of ALL results from the clonal proliferation of abnormal B-cell progenitors (B-ALL). ChT for B-ALL consists of induction, consolidation, and long-term maintenance, with central nervous system (CNS) prophylaxis given at intervals throughout therapy. Allogeneic stem cell transplantation (allo-SCT) is a treatment of choice for patients with ALL after first relapse and is also recommended for high-risk patients in the first complete remission (7). Graft versus host disease (GVHD) is a serious and potentially deadly complication of the allo-SCT, which occurs by the donor's immune effector cells recognizing and destroying the recipient's tissues and organs, often in the first 3 months after the allo-SCT. After the allo-SCT, 20%–80% of patients develop acute GVHD and 6% to 80% chronic GVHD (8–10). While ALL in children is a highly curable disease, a long-term survival rate in adults with ALL is 30%–45% (7, 11, 12).

Here, we present a case which highlights challenges in the systemic treatment, genetic testing, and follow-up of a patient with an operable TNBC and a history of B-ALL.

Case report

A timeline of the patient's diagnosis and treatment process is presented in Figure 1. A 40-year-old postmenopausal woman presented with a palpable lump in her right breast in 2022. Mammography showed a suspicious tumor mass of 18 × 20 mm in the upper inner quadrant. She underwent a core needle biopsy, and the breast pathologist reported invasive ductal carcinoma, G3, ER 0%, PR 0%, HER 2 negative, and Ki-67 70%–80%. Computed tomography scan of the thorax and abdomen and bone scan did not show distant metastases. Magnetic resonance imaging (MRI) of the right breast showed a mass sized 21 × 14 mm without involvement of the axillary lymph nodes (cT2 N0 M0, stage IIA). Her family history revealed that her maternal grandmother had an abdominal cancer at the age of 81, one maternal cousin had a tonsil cancer at the age of 57, another maternal cousin had a buccal mucosa cancer at the age of 56, her maternal aunt had a lung cancer at the age of 77, and her paternal uncle had a rectosigmoid cancer at the age of 65. She had a menarche at the age of 14 and went into an iatrogenic menopause after treatment of her B-ALL at the age of 26. She was gravity and parity 0 and never took any hormonal therapy. She had no history of smoking and drinking alcohol but a known allergy to vancomycin. Her history was significant for hyperthyroidism, which was treated with radioiodine and for B-ALL.

In 2007, at the age of 25, our patient was diagnosed with B-ALL, common type, Philadelphia chromosome negative. She was treated

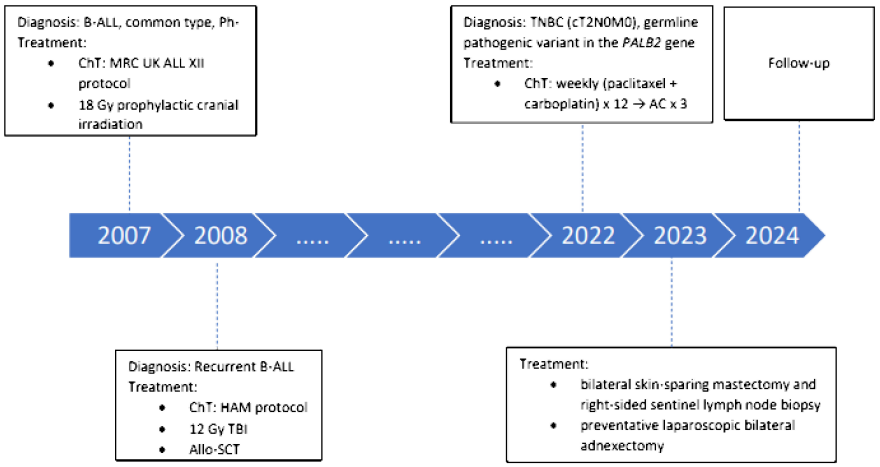


FIGURE 1
Timeline of the patient's diagnosis and treatment process. AC, adriamycin, cyclophosphamide; B-ALL, B-cell acute lymphoblastic leukemia; ChT, chemotherapy; HAM, high-dose cytosine arabinoside and mitoxantrone; MRC UK, Medical Research Council United Kingdom; PALB2, partner and localizer of *BRCA2*; Ph-, Philadelphia chromosome-negative; TBI, total body irradiation; TNBC, triple- negative breast cancer.

with ChT according to the Medical Research Council United Kingdom ALL XII ChT protocol which also included daunorubicin. She also received 18-Gy prophylactic cranial irradiation. At that time, our patient rejected treatment with an allo-SCT after induction treatment. In 2008, her B-ALL relapsed and she received ChT according to the high-dose cytosine arabinoside and mitoxantrone (HAM) protocol and myeloablative 12-Gy total body irradiation (TBI) followed by the allo-SCT. The donor was her mother who was blood type compatible but HLA incompatible. In 2009, she was diagnosed with acute and chronic intestinal, hepatic, and skin GVHD, and for a while she was on and off corticosteroids. At the time of diagnosis of her breast cancer, her B-ALL was in complete remission and she did not have any symptoms of the GVHD. During treatment of the B-ALL, she received a cumulative dose of 120 mg/m^2 of daunorubicin and 30 mg/m^2 of mitoxantrone, which is altogether equivalent to 220 mg/m^2 of doxorubicin.

A multidisciplinary breast cancer tumor board recommended neoadjuvant systemic treatment followed by mastectomy with or without adjuvant systemic treatment. Her baseline echocardiogram was normal. The plan was to treat her with neoadjuvant ChT, consisting of 12 weekly applications of paclitaxel (80 mg/m^2) and carboplatin (area under the curve [AUC] 1.5), followed by three instead of four cycles of the dose-dense doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) to not to exceed the overall cumulative dose of doxorubicin of 400 mg/m^2. A consulting hematologist did not advise against the coadministration of the granulocyte-colony stimulating factor (G-CSF) during ChT and treatment with pembrolizumab. After only 4 weeks of neoadjuvant ChT with paclitaxel and carboplatin, primary tumor was not palpable anymore and 7 weeks later, MRI showed a complete radiologic response. Due to the excellent response of primary tumor to ChT and a history of GVHD, treatment with pembrolizumab was omitted. At this point, a multidisciplinary tumor board recommended a continuation of the planned treatment with dose-dense doxorubicin and cyclophosphamide and G-CSF followed by surgery. The last dose of ChT was reduced due to the symptomatic anemia. Otherwise, our patient tolerated treatment with ChT very well. Because of the young age and TNBC pathology, she was referred to a geneticist. Genetic testing for a hereditary breast cancer using a multigene panel was performed using a buccal swab and peripheral blood. Both samples were positive for a heterozygous pathogenic variant in the partner and localizer of the *BRCA2* (*PALB2)* gene [c.1451T>A p. (Leu484*)]. Since she was after allo-SCT and there was a risk for contamination with the donor's cells, a genetic analysis of the primary breast tumor was performed, which confirmed a pathogenic variant in the *PALB2* gene with a variant allele frequency of 68%. A germline pathogenic variant in the *PALB2* gene was suspected, and therefore she underwent a bilateral skin-sparing mastectomy and right-sided sentinel lymph node biopsy with immediate reconstruction with implants. As our patient was already postmenopausal, she also opted for the immediate preventative laparoscopic bilateral adnexectomy. The postoperative period was uneventful. With neoadjuvant ChT, a pathologic complete response (pCR) was achieved. More than 1 year after surgery, our patient is well and free of cancer.

Discussion

Patients with operable TNBC usually require multidisciplinary treatment with neo/adjuvant systemic therapy, surgery, and adjuvant radiotherapy to decrease a risk of recurrence and death due to the breast cancer (12, 13). There may be some additional challenges in the management of patients with early TNBC who were previously treated for B-ALL.

Firstly, a risk for the development of cardiac toxicity after treatment of TNBC may be substantially increased in patients who were previously treated for B-ALL. Based on the literature, a recommended maximum lifetime cumulative dose of doxorubicin is 550 mg/m^2, or, in patients who had received previous mediastinal radiation, 450 mg/m^2 (14). The probability of developing congestive heart failure (CHF) is estimated to be around 1% to 2% at a cumulative dose of 300 mg/m^2, and thereafter, a risk for the development of CHF increases steeply (3% to 5% at 400 mg/m^2; 5% to 8% at 450 mg/m^2, and 6% to 20% at 500 mg/m^2) (15, 16). Furthermore, radiotherapy is another known substantial risk factor for the development of cardiovascular (CV) disease (17, 18). Additionally, patients who receive allo-SCT have a 2.3-fold higher risk of the premature CV death (19). As compared with autologous recipients, recipients of the allo-SCT have a higher incidence of long-term CV events (20). Treatment of GVHD includes the use of immunosuppressants, including corticosteroids, leading to a higher prevalence of risk factors for CV disease such as dyslipidemia, hypertension, and insulin resistance (21, 22). In the allo-SCT survivors, chest radiation prior to transplantation is associated with a 9.5-fold increase in the development of coronary artery disease (21, 22). Altogether, our patient received an equivalent of 220 mg/m^2 of doxorubicin and 12-Gy TBI before the allo-SCT and was later also treated for GVHD. To minimize a risk for the development of heart disease, our plan was not to exceed a cumulative dose of 400 mg/m^2 of doxorubicin. Instead of the full dose of 240 mg/m^2 (4 × 60 mg/m^2), our patient received 162 mg/m^2 of doxorubicin for her TNBC. However, an anthracycline-free ChT regimen containing carboplatin and paclitaxel/docetaxel might also be a valid treatment option in our patient (23, 24). The G-CSF usage allows administration of higher cumulative doses of ChT and better survival rates, which may both be associated with a higher occurrence rate of second cancers (25). According to the results of systematic review, G-CSF increases a risk for the development of acute myeloid leukemia and myelodysplastic syndrome but not for the ALL (25). Evidence also suggests that G-CSF does not increase a risk for the development of GVHD (26). We conclude that administration of G-CSF is safe in patients with a history of B-ALL.

Secondly, use of ICIs after allo-SCT may increase a risk for the development of GVHD. A contemporary systemic treatment of patients with an operable TNBC now beside ChT also includes an ICI pembrolizumab. In the KEYNOTE 522 phase III study, an addition of pembrolizumab to the neoadjuvant ChT with paclitaxel, carboplatin, doxorubicin, and cyclophosphamide resulted in a higher pCR rate (64.8% vs. 51.2%) and improvement in the event-free but not overall survival (27). However, studies showed that in patients with various relapsed hematologic malignancies

who were previously treated with allo-SCT, treatment with ICIs was highly efficacious but also increased a risk for the development of GVHD (14% acute, 9% chronic), including GVHD-related deaths (28). A history of GVHD and a short time interval between the allo-SCT and treatment with an ICI are both associated with a higher risk for the development of GVHD. A risk for the development of GVHD remains increased for several months after treatment with an ICI and is higher when combinations of ICIs are used (29–31). A time interval between the allo-SCT and the diagnosis of TNBC in our patients was long (i.e., 14 years), but data on the safety of ICIs in such cases are still lacking. Due to the history of GVHD and the excellent response to ChT, treatment with pembrolizumab was omitted in our patient. Oncologists should be aware that treatment with an ICI can lead to devastating complications related to GVHD in patients who previously received allo-SCT for hematologic malignancy.

Thirdly, testing for hereditary cancer may be challenging in patients with a history of allo-SCT. When dealing with a young patient with TNBC, genetic testing is of great importance, due to the fact that up to 40% of the early-onset and/or familial TNBC have germline pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, and some other genes (32). Accordingly, our patient was referred to a geneticist, but since she was an allo-SCT recipient, and her mother was a donor, choosing the most appropriate and reliable biological sample for genetic testing proved difficult (33, 34). After the allo-SCT, not only blood cells but also other cell subtypes may be replaced by cells of donors' origin during a process called adult stem cell plasticity phenomenon (33). Bone marrow and peripheral blood stem cells have a potential to transdifferentiate or dedifferentiate into neural, bone, muscular, cartilage, liver, gut, alveolar, buccal, epidermal, or endothelial cells, and these exogenous cells can represent between 0.1% and 10% of tissue-specific cells after allo-SCT. However, it has been shown that hair follicle cells lack adult stem cell plasticity and they remain of the recipient's origin for more than 20 years after the allo-SCT (33). The best biological sample for genetic testing is still being debated, but the National Comprehensive Cancer Network guidelines recommend that DNA of allo-SCT recipients should be extracted from the skin fibroblasts, hair follicles, or other non-hematopoietic origin tissue of the allo-SCT recipients. When this is not possible, buccal swab can be considered as an appropriate alternative source of DNA even though buccal epithelial cells can be replaced by donor-derived cells (33–35). In our case, patient's buccal swab, peripheral blood and tumor tissue were tested, and all samples were positive for a pathogenic variant in the *PALB2* gene (c.1451T>A p.(Leu484*)). The variant allele frequency in tumor tissue was high, suggesting that our patient's TNBC developed predominantly due to the *PALB2* variant; however, previous management of her B-ALL could also have contributed to the development of TNBC. Considering that the patient's blood sample presumably consisted of donor cells, genetic testing might have incidentally identified her mother as a carrier of the *PALB2* pathogenic variant. As her mother has not undergone genetic testing due to her advanced age, her carrier status cannot be verified. As testing for *PALB2* variants can be important for cancer risk assessment and screening as well as pregnancy planning, our patient's maternal relatives were offered genetic counselling, but they have not responded to the invitation so far. This case highlights a possibility that genetic testing performed after allo-SCT might reveal pathogenic variants of donor's origin, which might have clinical implications for the donor (36). A *PALB2*-variant breast cancer is usually associated with an aggressive clinicopathological features and is often of triple-negative phenotype (37). PALB2 protein participates in a process of the homologous recombination, and there is evidence that rapid and durable responses could be achieved with a platinum-based chemotherapy in *PALB2*-associated breast cancers (37). In our patient, a combination of carboplatin and paclitaxel resulted in a rapid complete clinical response of the primary tumor, which is in line with previous reports.

Finally, in children and young adults who are treated for various hematologic malignancies, it is important to consider a risk for new primary cancers later in life. Our case also indicates that among patients who develop a second primary solid cancer after hematologic malignancy, there is a subset of patients who have a hereditary cancer. It is well known that biallelic pathogenic variants in the *PALB2* gene result in a subtype of Fanconi anemia, whereas the monoallelic pathogenic variant in *PALB2* predisposes carriers to different cancers such as breast, pancreatic, and ovarian cancers (38). In carriers of the pathogenic variant in the *PALB2* gene, a lifetime risk for the development of breast cancer is 40%–60%, for ovarian cancer 3%–5%, and for pancreatic cancer 2%–3%. Guidelines of the European Society of Medical Oncology recommend that women with pathogenic variants in the *PALB2* should have clinical breast examination every 6–12 months at age 20–25 years, annual MRI at age 20–29 years, and annual breast MRI and/or mammogram at age 30–75 years; they should also consider a risk-reducing mastectomy and adnexectomy. Screening for pancreatic cancer with an annual MRI and/or endoscopic ultrasound from the age of 50 (or 5–10 years younger than the affected relative) can also be considered, when at least one first- or second-degree, presumably *PALB2*-positive relative develops exocrine pancreatic cancer (39). Due to pathogenic variant in *PALB2* our patient underwent bilateral skin-sparing mastectomy and preventative bilateral adnexectomy and is now in the follow-up program in our cancer center. After mastectomy, there was no need for adjuvant irradiation, which could increase a risk for the development of new primary breast cancer in the case of breast-conserving surgery. Fortunately, our patient achieved a pCR and has a very low risk for the recurrence of TNBC. However, after intensive treatment with ChT and radiotherapy, which she received for her B-ALL and TNBC and a known pathogenic variant in the *PALB2* gene, her risk for the development of new primary cancers other than breast and ovarian cancers, particularly pancreatic cancer, may be substantial. Pancreatic cancer surveillance is a contentious subject, with controversies regarding the identification of high-risk individuals, imaging methods, screening intervals, and patient outcomes. In the future, patients such as ours will hopefully benefit from personalized risk assessment and additional blood-based as well as radiomic biomarkers, including the use of artificial intelligence (40). An annual whole-body MRI might also prove useful for this patient, considering her risk of other new primary cancers.

Conclusions

To our knowledge, this is a first published report which comprehensively highlights the complexity of management of a patient with a second primary TNBC after cured acute leukemia, which was also treated with an allo-SCT. A potential benefit of systemic anticancer therapy should be carefully balanced against its possible harms in patients with a second primary TNBC. Additionally, in patients with a history of allo-SCT, genetic testing for a hereditary cancer may be challenging. Patients with a second primary solid cancer and a history of hematologic malignancy, especially those with a known hereditary cancer, have a substantial risk for new primary cancers. Future research should focus on the development of optimal personalized follow-up programs in this population of patients. Furthermore, development of effective new systemic therapies (e.g., next-generation immunotherapy and targeted agents) which in contrast to ChT do not substantially increase a risk for new primary cancers would be of great importance especially for young patients with TNBC and other solid cancers, which have a complicated treatment history.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TP: Conceptualization, Investigation, Resources, Writing – original draft. AB: Conceptualization, Investigation, Writing – review & editing. BŠ: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was supported by the Slovenian Research and Innovation Agency (ARIS), grant P3–0321.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Liu Y, Yu T. Clinicopathological characteristics and prognosis of triple-negative breast cancer invasive ductal carcinoma with ductal carcinoma in *situ*. *J Cancer Res Clin Oncol*. (2023) 149:11181–91. doi: 10.1007/s00432–023-04895–9

2. Bianchini G, De Angelis C, Licata L, Gianni L. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. *Nat Rev Clin Oncol*. (2022) 19:91–113. doi: 10.1038/s41571–021-00565–2

3. Morton LM, Onel K, Curtis RE, Hungate EA, Armstrong GT. The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. *Am Soc Clin Oncol Educ Book*. (2014), e57–67. doi: 10.14694/EdBook_AM.2014.34.e57

4. Hijiya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm FG, et al. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. *JAMA*. (2007) 297:1207–15. doi: 10.1001/jama.297.11.1207

5. Demoor-Goldschmidt C, de Vathaire F. Review of risk factors of secondary cancers among cancer survivors. *Br J Radiol*. (2019) 92:20180390. doi: 10.1259/bjr.20180390

6. Liang F, Zhang S, Xue H, Chen Q. Risk of second primary cancers in cancer patients treated with cisplatin: a systematic review and meta-analysis of randomized studies. *BMC Cancer*. (2017) 17:871. doi: 10.1186/s12885–017-3902–4

7. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J*. (2017) 7:e577. doi: 10.1038/bcj.2017.53

8. Zhang L, Yu J, Wei W. Advance in targeted immunotherapy for graft-Versus-Host disease. *Front Immunol*. (2018) 9:1087. doi: 10.3389/fimmu.2018.01087

9. Braun LM, Zeiser R. Immunomodulatory therapies for the treatment of graft-versus-host disease. *HemaSphere*. (2021) 5:e581. doi: 10.1097/HS9.0000000000000581

10. Bouchlaka MN, Redelman D, Murphy WJ. Immunotherapy following hematopoietic stem cell transplantation: potential for synergistic effects. *Immunotherapy*. (2010) 2:399–418. doi: 10.2217/imt.10.20

11. Loghavi S, Kutok JL, Jorgensen JL. B-acute lymphoblastic leukemia/lymphoblastic lymphoma. *Am J Clin Pathol*. (2015) 144:393–410. doi: 10.1309/AJCPAN7BH5DNYWZB

12. Baranova A, Krasnoselskyi M, Starikov V, Kartashov S, Zhulkevych I, VlasenkoV, et al. Triple-negative breast cancer: current treatment strategies and factors of negative prognosis. *J Med Life*. (2022) 15:153–61. doi: 10.25122/jml-2021–0108

13. Curigliano G, Burstein HJ, Gnant M, Loibl S, Cameron D, Regan MM, et al. Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023. *Ann Oncol*. (2024) 34:970–86. doi: 10.1016/j.annonc.2023.08.01

14. Venkatesh P, Kasi A. *Anthracyclines*. Treasure Island (FL: StatPearls Publishing (2023)

15. Rahman AM, Yusuf SW, Ewer MS. Anthracycline-induced cardiotoxicity and the cardiac-sparing effect of liposomal formulation. *Int J Nanomed*. (2007) 2:567–83.

16. Accord Healthcare Inc. *Doxorubicin injection® product monograph*. Kirkl Quebec: Acord Healthcare Inc. (2018).

17. Siaravas KC, Katsouras CS, Sioka C. Radiation treatment mechanisms of cardiotoxicity: A systematic review. *Int J Mol Sci*. (2023) 24:6272. doi: 10.3390/ijms24076272

18. Belzile-Dugas E, Eisenberg MJ. Radiation-induced cardiovascular disease: review of the unrecognized pathology. *J Amm Heart Assoc*. (2021) 10(18):e021686. doi: 10.1161/JAHA.121.021686

19. Auberle C, Lenihan D, Gao F, Cashen A. Late cardiac events after allogeneic stem cell transplant: incidence, risk factors, and impact on overall survival. *Cardiooncology*. (2023) 9:1–8. doi: 10.1186/s40959–022-00150–1

20. Vasbinder A, Hoeger CW, Catalan T, Anderson E, Chu C, Kotzin M, et al. Cardiovascular events after hematopoietic stem cell transplant: incidence and risk factors. *JACC Cardiooncol*. (2023) 5:821–32. doi: 10.1016/j.jaccao.2023.07.007

21. Tuzovic M, Mead M, Young PA, Schiller G, Yang EH. Cardiac complications in the adult bone marrow transplant patient. *Curr Oncol Rep*. (2019) 21:28. doi: 10.1007/s11912–019-0774–6

22. Blaes A, Konety S, Hurley P. Cardiovascular complications of hematopoietic stem cell transplantation. *Curr Treat Opt Cardiovasc Med*. (2016) 18:15. doi: 10.1007/s11936–016-0447–9

23. Yu KD, Ye FG, He M, Fan L, Ma D, Mo M, et al. Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer: A phase 3 randomized clinical trial. *JAMA Oncol*. (2020) 6:1390–6. doi: 10.1001/jamaoncol.2020.2965

24. Sharma P, López-Tarruella S, García-Saenz JA, Ward C, Connor CS, GómezHL, et al. Efficacy of neoadjuvant carboplatin plus docetaxel in triple-negative breast cancer: combined analysis of two cohorts. *Clin Cancer Res*. (2017) 23:649–57. doi: 10.1158/1078–0432.CCR-16–0162

25. Lyman GH, Yau L, Nakov R, Krendyukov A. Overall survival and risk of second Malignancies with cancer chemotherapy and G-CSF support. *Ann Oncol*. (2018) 29:1903–10. doi: 10.1093/annonc/mdy311

26. Gupta AK, Meena JP, Haldar P, Tanwar P, Seth R. Impact of G-CSF administration post-allogeneic hematopoietic stem-cell transplantation on outcomes: a systematic review and meta-analysis. *Am J Blood Res*. (2021>) 11:544–63.

27. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Berg J, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. (2020) 382:810–21. doi: 10.1056/NEJMoa1910549

28. Ijaz A, Khan AY, Malik SU, Faridi W, Fraz MA, Usman M, et al. Significant Risk of Graft-versus-Host Disease with Exposure to Checkpoint Inhibitors before and after Allogeneic Transplantation. *Biol Blood Marrow Transplant*. (2019) 25:94–9. doi: 10.1016/j.bbmt.2018.08.028

29. Köhler N, Ruess DA, Kesselring R, Zeiser R. The role of immune checkpoint molecules for relapse after allogeneic hematopoietic cell transplantation. *Front Immunol*. (2021) 12:634435. doi: 10.3389/fimmu.2021.634435

30. Sterling C, Webster J. Harnessing the immune system after allogeneic stem cell transplant in acute myeloid leukemia. *Am J Hematol*. (2020) 95:529–47. doi: 10.1002/ajh.25750

31. Roshandel E, Tavakoli F, Parkhideh S, Akhlaghi SS, Ardakani MT, Soleimani M, et al. Post-hematopoietic stem cell transplantation relapse: Role of checkpoint inhibitors. *Health Sci Rep*. (2022) 5:e536. doi: 10.1002/hsr2.536

32. Hahnen E, Hauke J, Engel C, Neidhardt G, Rhiem K, Schmutzler RK, et al. Germline mutations in triple-negative breast cancer. *Breast Care*. (2017) 12:15–9. doi: 10.1159/000455999

33. Škerl P, Krajc M, Blatnik A, Novaković S. Genetic testing and counseling of a recipient after bone marrow transplant from a sibling harboring a germline BRCA1 pathogenic mutation. *Oncol Rep*. (2017) 38:279–82. doi: 10.3892/or.2017.5703

34. Themeli M, Waterhouse M, Finke J, Spyridonidis A. DNA chimerism and its consequences after allogeneic hematopoietic cell transplantation. *Chimerism*. (2011) 2:25–8. doi: 10.4161/chim.2.1.1527

35. Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. National Comprehensive Cancer Network (2024). Available online at: https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1503

36. Pryce A, Van Eerden E, Cody M, Oakes J, DeSalvo A, Bannon S, et al. Genetic findings of potential donor origin following hematopoietic cell transplantation: recommendations on donor disclosure and genetic testing from the world marrow donor association. *Transplant Cell Ther*. (2024) 30:143–54. doi: 10.1016/j.jtct.2023.11.019

37. Toss A, Ponzoni O, Riccò B, Piombino C, Moscetti L, Combi F, et al. Management of PALB2-associated breast cancer: A literature review and case report. *Clin Case Rep*. (2023) 11:e7747. doi: 10.1002/ccr3.7747

38. Wu S, Zhou J, Zhang K, Chen H, Luo M, Yuexin L, et al. Molecular mechanisms of PALB2 function and its role in breast cancer management. *Front Oncol*. (2020) 10:301. doi: 10.3389/fonc.2020.00301

39. Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. *Ann Oncol*. (2023) 34:33–47. doi: 10.1016/j.annonc.2022.10.004

40. Bogdanski AM, van Hooft JE, Boekestijn B, Bonsing BA, Wasser MNJM, Klatte DCF, et al. Aspects and outcomes of surveillance for individuals at high-risk of pancreatic cancer. *Fam Cancer*. (2024). doi: 10.1007/s10689–024-00368–1

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 17 June 2024
DOI 10.3389/fonc.2024.1338661

OPEN ACCESS

EDITED BY
Zheng Wang,
Shanghai Jiao Tong University, China

REVIEWED BY
Zhi Ling Teo,
Peter MacCallum Cancer Centre, Australia
Rong Mu,
CSL Parkville, Australia

*CORRESPONDENCE
Juanjuan Li
juanjuan.li@whu.edu.cn
Xiangpan Li
rm001227@whu.edu.cn

†These authors share first authorship

RECEIVED 16 February 2024
ACCEPTED 27 May 2024
PUBLISHED 17 June 2024

CITATION
Lan Y, Zhao J, Zhao F, Li J and Li X (2024) Partial response to trastuzumab deruxtecan (DS8201) following progression in HER2-amplified breast cancer with pulmonary metastases managed with disitamab vedotin (RC48): a comprehensive case report and literature review.
Front. Oncol. 14:1338661.
doi: 10.3389/fonc.2024.1338661

Partial response to trastuzumab deruxtecan (DS8201) following progression in HER2-amplified breast cancer with pulmonary metastases managed with disitamab vedotin (RC48): a comprehensive case report and literature review

Yanfang Lan[1†], Jiahui Zhao[1†], Fangrui Zhao[1], Juanjuan Li[2*†] and Xiangpan Li[1*†]

[1]Department of Oncology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China, [2]Department of Breast and Thyroid Surgery, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

Breast cancer remains one of the predominant malignancies worldwide. In the context of inoperable advanced or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer, systemic management primarily relies on HER2-targeting monoclonal antibodies. With the successful development of anti-HER2 antibody-drug conjugates (ADCs), these agents have been increasingly integrated into therapeutic regimens for metastatic breast cancer. Here, we present the case of a 42-year-old female patient with HER2-positive pulmonary metastatic breast cancer who underwent an extensive treatment protocol. This protocol included chemotherapy, radiation therapy, hormonal therapy, surgical intervention on the breast, and anti-HER2 therapies. The anti-HER2 therapies involved both singular and dual targeting strategies using trastuzumab and the ADC disitamab vedotin (RC48) over an 8-year period. After experiencing disease progression following HER2-targeted therapy with RC48, the patient achieved noticeable partial remission through a therapeutic regimen that combined trastuzumab deruxtecan (DS8201) and tislelizumab. The data suggest a promising role for DS8201 in managing advanced stages of HER2-amplified metastatic breast cancer, especially in cases that demonstrate progression after initial HER2-directed therapies using ADCs. Furthermore, its combination with anti-PD-1 agents enhances therapeutic efficacy by augmenting the anti-tumoral immune response.

KEYWORDS

antibody-drug conjugate, trastuzumab deruxtecan, disitamab vedotin, tislelizumab, Her2-amplified breast cancer

Introduction

Breast cancer remains a predominant malignancy worldwide. Incorporating both sexes, it accounts for 11.6% of all cancer cases, second only to lung cancer. Notably, among women, it is the most frequently diagnosed cancer (1). Human epidermal growth factor receptor 2 (HER2)-positive breast cancers make up 25–30% of all breast cancer cases, often indicating a worse prognosis compared to luminal subtype (2–4). Due to tumor heterogeneous, HER2 positive breast cancer present various treatment sensitivities and different survival outcomes. A correlation exists between the development of distant metastases and increased mortality rates in breast cancer patients (5). Common metastatic sites include the bone, liver, lung, and brain across all breast cancer subtypes. Advanced systemic therapy for inoperable or metastatic HER2-positive breast cancer primarily relies on HER2-targeting monoclonal antibodies. Currently, the standard of care in initial and second-line settings involves pertuzumab and trastuzumab in conjunction with chemotherapy, preferably a taxane, trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (DS8201) (6). Subsequent lines of therapy may consider alternative HER2-targeted combinations, including options such as or tyrosine kinase inhibitors (TKIs) like tucatinib and neratinib (7).

Antibody-drug conjugates (ADCs) consist of tumor antigen-specific monoclonal antibodies bound to potent cytotoxic agents via stable, cleavable, or non-cleavable chemical linkers. Due to successful advancements in ADC pharmaceuticals, these agents have been progressively incorporated into treatment protocols for various diseases. Disitamab vedotin (RC48) is an example of an anti-HER2 ADC; it combines hertuzumab (a novel anti-HER2 mAB) with monomethyl auristatin E (MMAE) through a cleavable linker (8). A consolidated analysis of a phase I dose-escalation study (NCT02881138) and a parallel open-label phase Ib trial (NCT03052634) showed that HER2-positive breast cancer patients achieved an objective response rate (ORR) of 31.4%, along with a median progression-free survival (PFS) of 5.8 months (9, 10). DS-8201 is another ADC, featuring an anti-HER2 antibody linked to a cytotoxic topoisomerase I inhibitor through a cleavable tetrapeptide-based linker. As highlighted in the global phase 2 study DESTINY-Breast01, DS-8201 exhibited significant clinical efficacy in HER2-positive metastatic breast cancer patients who had received extensive prior therapies, including treatment with pertuzumab or T-DM1 (11). Despite the encouraging prospects of both RC48 and DS8201 in breast cancer management, existing literature lacks reports on the effectiveness of DS8201 following a failed RC48 regimen.

In this report, we describe a patient with HER2-positive breast cancer, characterized by pulmonary metastases, who exhibited resistance to RC48 treatment after undergoing a range of therapeutic interventions. These interventions included chemotherapy, radiation therapy, targeted therapies, and surgical intervention on the breast. Remarkably, the patient responded positively to a treatment regimen that included DS8201 and tislelizumab (Figure 1).

Case presentation

In April 2015, a 42-year-old woman who has no family history of breast, ovarian or other cancers noticed bilateral breast asymmetry, minor enlargement of the left breast, and palpable enlargement of lymph nodes in the medial left breast. Subsequent pathological examination of a left breast aspirate revealed ER (+20%), PR (-), HER2 (3+), Ki-67 (+80%). The clinical diagnosis was grade III invasive ductal carcinoma of the left breast with axillary lymph node metastasis [TNM stage: T3N2acM0 (i+)] (Figures 2A, B). Following the diagnosis, the patient began a treatment regimen consisting of 4 cycles of EC regimen (epirubicin 100 mg/m^2, Q21d and cyclophosphamide 600 mg/m^2, Q21d), followed by 4 cycles of TH regimen (docetaxel 100 mg/m^2, Q21d and trastuzumab, 8mg/kg on day1, then 6mg/kg Q21d), along with one year of trastuzumab-targeted therapy (6 mg/kg, Q21d). In June 2016, after declining a recommendation for radical mastectomy, she received radiation therapy targeting the left supraclavicular lymphatic drainage area and axillary lymph nodes (CTV: 25F/50Gy), as well as the left breast (CTV: 25F/50Gy). She

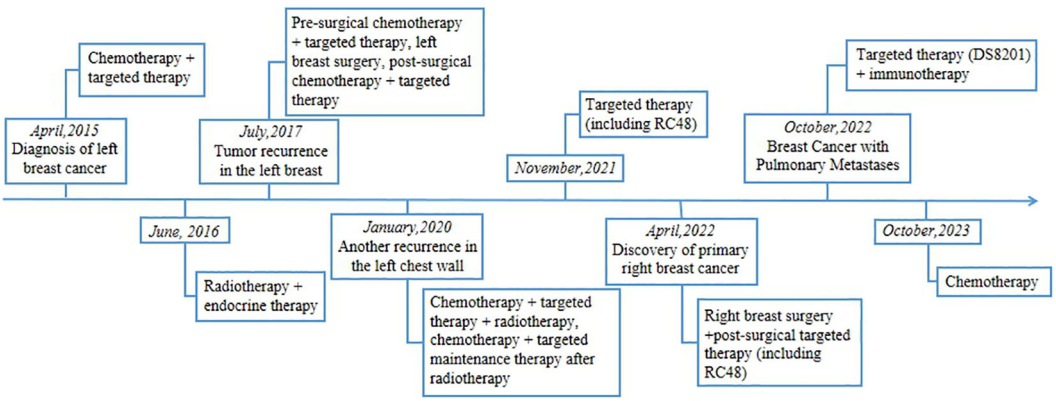


FIGURE 1
Patient's Treatment Timeline.

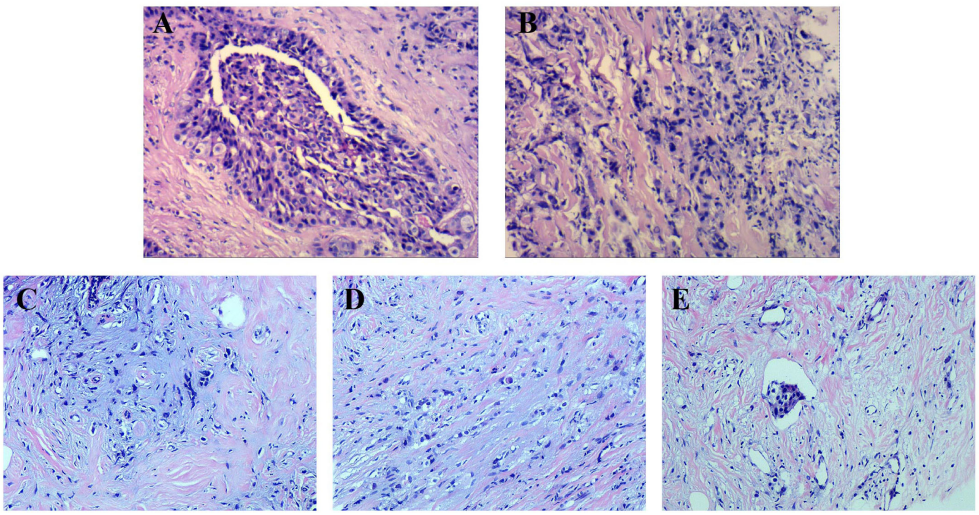


FIGURE 2
Histopathologic Examinations of the Primary Tumor Focus in the Left Breast and the Right Breast Before Operation. **(A, B)** HE-stained images of the primary tumor focus (100×). **(C–E)** HE-stained images of the tumor focus on the right breast (40×).

also initiated endocrine therapy with a combination of goserelin (Zoladex 3.6mg, Q28d), a luteinizing hormone-releasing hormone analog, and anastrozole (1mg, QD), an aromatase inhibitor.

In July 2017, the patient experienced tumor recurrence in the left breast, leading to the initiation of 6 cycles of TH regimen (docetaxel 100 mg/m^2, Q21d and trastuzumab 8mg/kg on day1, then 6mg/kg Q21d), along with another year of trastuzumab-targeted therapy (6 mg/kg, Q21d). In November 2017, she underwent a total left mastectomy with axillary lymph node dissection at Renmin Hospital of Wuhan University. Postoperative assessments, which included immunohistochemistry, revealed the following markers: E-Cad (+), ER (-), HER2 (3+), Ki-67 (+10%), P120 (+), P63 (-), and PR (-). After the surgery, she stopped the endocrine therapy and received a chemotherapy regimen combined with targeted therapy (capecitabine 1000 mg/m^2, Bid, two consecutive weeks followed by a one-week break and pyrotinib 400mg, QD).

The onset of 2020 brought another recurrence in the left chest wall. Consequently, her treatment strategy was revised to include chemotherapy combined with targeted therapy, specifically albumin paclitaxel (260 mg/m^2, Q21d), along with trastuzumab (8mg/kg on day1, then 6mg/kg Q21d) and pertuzumab (840mg on day1, then 420mg Q21d), for a total of six cycles. She then underwent radiation therapy targeting the left chest wall (CTV: 2Gy/33F/66Gy) and continued maintenance treatment with capecitabine (1000 mg/m^2, Bid, two consecutive weeks followed by a one-week break) and pyrotinib (400mg, QD) post-radiotherapy.

In November 2021, the patient switched to an RC48 regimen (2.5mg/kg, Q14d) following a right breast aspiration biopsy that revealed tumor cells (Figures 2C–E). After six cycles, her treatment regimen was modified to RC48 (2.5mg/kg, Q14d) and apatinib (850mg, QD), which is a tyrosine kinase inhibitor that selectively inhibits the vascular endothelial growth factor receptor-2. On April 1, 2022, she underwent a mastectomy along with axillary lymph node dissection for right breast cancer. Histopathology revealed primary right breast cancer with axillary lymph node involvement (11/34), and immunohistochemistry showed the following markers: invasive carcinoma AR (+70%), CK5/6 (-), E-Cadherin (+), ER (-), HER2 (3+), Ki-67 (+60%), P120 (membrane+), P63 (-), PR (-). After the surgery, she began a treatment regimen comprising RC48 (2.5mg/kg, Q14d) and pertuzumab (420mg, Q21d).

Concurrent with her earlier treatments, the patient began experiencing coughing symptoms in December 2021. Despite receiving anti-infective treatment, the cough persisted. In September 2022, her respiratory symptoms worsened, leading to resting dyspnea. A subsequent ciliary bronchoscopy at our facility confirmed the presence of cancer cells (Figures 3A–C). A bronchial specimen biopsy was then conducted, and pathological results showed metastatic invasive carcinoma of the breast, thus clinically indicating breast cancer metastasis (Figures 3D, E). Immunohistochemistry results showed negative expression for programmed cell death ligand 1 (PD-L1), with a Combined Positive Score (CPS) of 0 (Figures 3F, G). CA125 level measured on October 10, 2022, was 96.2 U/ml. A chest CT scan from the same date showed carcinomatous lymphangitis in a lung lesion. Consequently, the treatment swith to the combination of DS8201 (200mg, q21d) and anti-PD-1 immunotherapy (tislelizumab 200mg, q21d).

After two cycles of that treatment, a significant alleviation of the symptoms of resting dyspnea was observed. After five cycles, a comparative analysis with pre-treatment CT scans revealed a notable reduction in the size of multiple lung nodules and nodular foci and improved carcinomatous lymphangitis (Figure 4). On February 24, 2023, the level of CA125 was 32.9 U/ml, indicating a decrease compared to the previous measurement. The treatment efficacy was evaluated as a partial response (PR). The following adverse effects were observed during treatment and markedly relieved by symptomatic treatments: nausea, fatigue, vomiting, alopecia, constipation, and decreased appetite. No

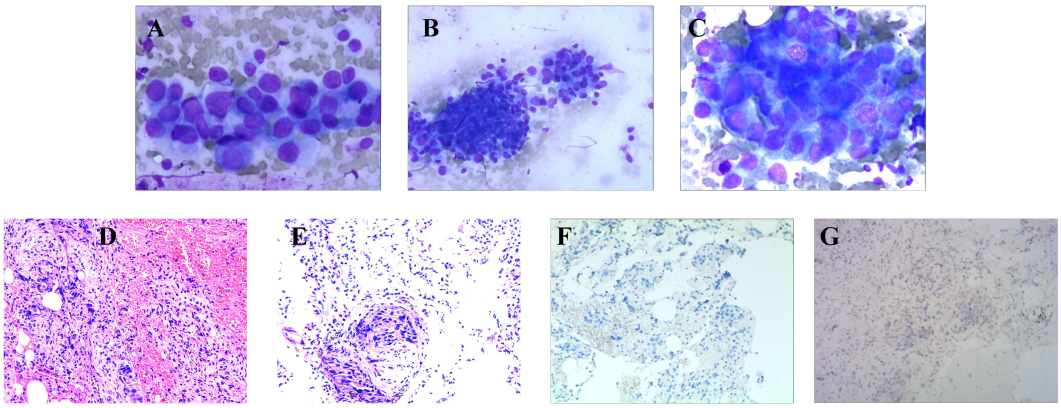


FIGURE 3
Brush Cytology, Histopathologic, and Immunohistochemical Examinations of Biopsy Tissue from Pulmonary Metastasis. **(A–C)** Light microscope images of brush cytology; cancer cells are visible (**A, C**: 200×; **B**:100). **(D, E)** HE-stained images of biopsy tissue from the pulmonary metastasis focus (40×). **(F, G)** PD-L1: Negative (**F**: 40×; **G**: 100×).

severe or life-threatening adverse events were reported. Unfortunately, after 12 cycles, the response was evaluated as PD. In October 2023, she began a chemotherapy regimen of gemcitabine (1000mg/m^2, days 1 and 8 of a 21-day cycle) plus nedaplatin (80mg/m^2, Q21d) and underwent genetic testing, which revealed the detection of two somatic mutations associated with targeted drugs, HER2 (amplification) and PIK3CA (exon 21, c.3140A > G, with alteration of protein p.H1047R), but no BRCA1 or BRCA 2 mutations. However, a deterioration in physical status and a severe lung infection were noted after 3 cycles. Regrettably, the patient passed away in late January 2024.

Discussion

This report outlines the case of a young patient battling advanced pulmonary metastases stemming from HER2-amplified breast cancer. She has undergone a myriad of treatments for recurrent conditions throughout her illness, including chemotherapy, radiotherapy, targeted therapy, and surgery. Notably, she demonstrated a significant response to a treatment regimen that included DS8201 and tislelizumab, despite disease progression under RC48 and other therapies. To our knowledge, this represents a unique and unprecedented case in the literature on breast cancer.

Prior studies have revealed that the prognosis of breast cancer correlates with the expression levels of estrogen receptor (ER) and progesterone receptor (PR) (12). And just as several earlier studies have reported differences in ER and PR expression between primary tumors and recurrent or metastatic tumors, we noticed the loss of ER expression after recurrence in the left breast in this case (13, 14). Possible reasons for this phenomenon include technical problems with poor reproducibility of immunohistochemistry, tumor heterogeneity (15, 16). In addition, the patient had a PI3KCA

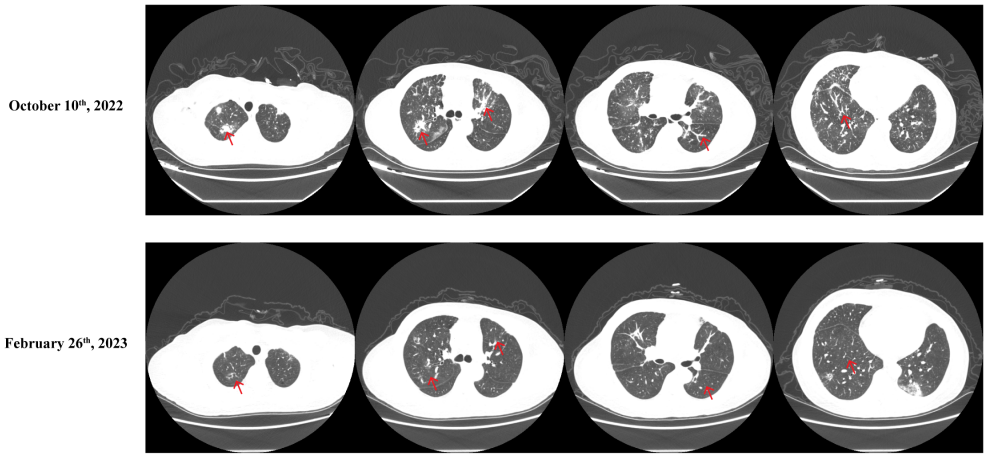


FIGURE 4
Comparative Chest CT Scans Conducted Before and After the Fifth DS8201 and Tislelizumab Treatment Regimen Cycle. Before: October 10, 2022, After: February 26, 2023.

mutation. Previous studies have indicated that the PI3K/AKT/mTOR pathway is associated with the maintenance of endocrine resistance (17). The loss of ER expression along side the PIK3CA mutation were likely significant factors that could have contributed to endocrine treatment resistance. And the data from a retrospective study demonstrated that in patients with early-stage breast cancer, after adjusting treatment according to receptor expression in recurrent/metastatic lesions, the majority of patients were maintained progression-free during the follow-up period (18).

HER2-positive tumors are intrinsically linked to poorer survival outcomes compared to cases characterized by estrogen receptor (ER)-positive, HER2-negative breast cancer. However, the past three decades have seen relentless research and development of anti-HER2 agents, leading to significantly improved prognoses for patients diagnosed with both early and advanced stages of HER2-positive breast cancer. Alternative therapeutic agents for HER2-positive breast cancer range from HER2-targeted monoclonal antibodies (such as trastuzumab and pertuzumab), HER2-targeted ADCs (like T-DM1 and DS8201), and small molecule tyrosine kinase inhibitors (including lapatinib, neratinib, pyrotinib and tucatinib). Regrettably, the primary guidelines, which recommend dual blockade with trastuzumab and pertuzumab as a first-line treatment followed by T-DM1 as a second-line treatment, have remained unchanged since 2012. Nevertheless, the landscape underwent a significant transformation after 2019, marked by an influx of clinical trials and subsequent approval of three novel agents: DS-8201, tucatinib, and neratinib. This development signals a promising shift in the therapeutic landscape (19). DS-8201, classified as an ADC, is particularly noteworthy.

ADCs constitute a complex fusion of monoclonal antibodies specific to tumor antigens, combined with stable chemical linkers—either cleavable or non-cleavable—and highly potent cytotoxic agents. The ADC-antigen complex is internalized upon binding to the target, primarily through clathrin-mediated endocytosis (20). This triggers a cascade of intracellular events, starting with forming an early endosome, which matures into a late endosome before undergoing lysosomal fusion. The fate of the ADC depends on the type of linker it possesses: cleavable linkers are subject to mechanisms such as hydrolysis, enzymatic cleavage by proteases, or reductive cleavage of disulfide bonds, primarily within the cytoplasm, thereby bypassing lysosomal transport. Conversely, ADCs with non-cleavable linkers require complete proteolytic degradation within the lysosome.

After its intracellular release, the cytotoxic component induces cell death through mechanisms like DNA intercalation or inhibition of microtubule polymerization. This triggers a series of events within the cellular environment, potentially including the bystander killing of adjacent tumor cells and stromal tissue, which may have absorbed the drug through diffusion, depending on the hydrophobic properties of the cytotoxic payload (21). Moreover, ADCs play a crucial role in activating complement systems and facilitating the influx of immune effector cells at the tumor site, using various strategies like complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), or antibody-dependent cellular phagocytosis (ADCP) (22). For example, T-DM1 has shown efficacy in increasing the population of tumor-infiltrating lymphocytes within primary human breast cancers and promoting effector T-cell infiltration in murine breast tumors (23).

As of March 2023, the FDA has globally approved 15 ADC medications. Notably, T-DM1 and DS8201 have received FDA approval for managing HER2-positive breast cancer, as supported by the results of the EMILIA, KATHERINE, and DESTINY-Breast01 clinical trials (11, 24, 25). Specifically, T-DM1 is approved for treating previously treated HER2-positive metastatic breast cancer. At the same time, DS8201 received expedited FDA approval for patients with unresectable or metastatic HER2-positive breast cancer who have undergone at least two anti-HER2-based treatment regimens in a metastatic setting, aligning closely with the current case under discussion. Additionally, DS8201 is approved for treating adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction cancer (GC/GEJC), provided they have received prior trastuzumab-based therapy. The striking response of a patient with metastatic HER2-amplified and L755S-mutated breast cancer to T-DM1 and DS8201, after showing resistance to other HER2-targeted drugs, exemplifies the specific anticancer potential of anti-HER2 ADCs (26).

Numerous clinical studies have demonstrated the efficacy of RC48 in treating patients with either locally advanced or metastatic HER2-overexpressing gastric cancer, including adenocarcinoma of the gastroesophageal junction, following a minimum of two systemic chemotherapy courses (27–29). It is also effective for those with advanced or metastatic uroepithelial cancer who have previously received platinum-containing chemotherapy and have shown HER2 overexpression of either 2+ or 3+ on immunohistochemistry (29, 30). In June 2021, China's Center for Drug Evaluation designated RC48 as a breakthrough therapy for HER2-positive individuals with metastatic breast cancer (MBC) with advanced liver metastases who had undergone treatment with trastuzumab and paclitaxel. Subgroup analyses from two studies published by the American Society of Clinical Oncology outline the benefits of RC48 treatment, regardless of the presence of HER2 gene mutations or fusions (31). In one specific case, a patient with stage IV (cT4N3M1) hormone receptor (HR)-positive and HER2-positive invasive ductal carcinoma, who presented with systemic metastases including the brain, underwent 26 cycles of initial anti-HER2 targeted therapy along with chemotherapy. After experiencing disease progression, the patient received four cycles of second-line therapy (trastuzumab + piritinib + capecitabine), which unfortunately led to further disease progression. The patient then received 12 cycles of RC48 as the third-line therapy, which resulted in significant benefit without severe adverse effects and extended overall survival beyond three years (32). Therefore, advanced breast cancer patients stand to benefit from RC48 therapy. Ongoing clinical trials are further investigating the role of RC48 in the therapeutic landscape of breast cancer. As a result, it appears reasonable to hypothesize that RC48 could play a significant role in achieving remission in patients with HER2-positive breast cancer, even though its current indication does not include breast cancer.

The mechanisms underlying resistance to anti-HER2 ADCs are diverse, as elucidated through studies focusing on T-DM1 and

DS8201. Firstly, resistance may arise from reduced HER2 levels or structural changes in the receptor (33, 34). Secondly, altered HER2 internalization processes can also contribute to resistance. Specifically, the endomorphin A2 protein aids in internalizing complexes formed post-HER2 binding by anti-HER2 ADCs, ultimately leading to endosome formation. Notably, silencing this protein in HER2-positive cells has inhibited HER2 internalization, reducing responsiveness to agents like trastuzumab and T-DM1 (35). Additionally, the ubiquitination and subsequent transport of HER2 to lysosomes could be modified due to its relationship with the chaperone protein HSP90. The combined action of 17-AAG-mediated HSP90 inhibition and trastuzumab enhances HER2 endocytosis into lysosomes, promoting further degradation within these organelles (36). Moreover, an increased recycling rate of endosomes containing HER2 back to the plasma membrane could limit the delivery of T-DM1 to the lysosome, thus restricting its intracellular release. This could be attributed to the rapid recycling rate of HER2 observed following trastuzumab binding (37). Thirdly, resistance might occur due to changes in lysosomal functions (38). The efficient transport of anti-HER2 ADCs to lysosomes and their subsequent processing by lysosomal enzymes are crucial for liberating the attached payloads. Lysosomes are intrinsically acidic and contain proteolytic capabilities regulated by the vacuolar proton pump H+-ATPase (V-ATPase), crucial in maintaining lysosomal pH. Fourthly, resistance could emerge from increased expression and functionality of plasma membrane drug efflux pumps, a mechanism widely studied in the realm of chemotherapy resistance. Regarding T-DM1, it has been found that specific ABC family pumps can eject the compound Lys-MCC-DM1 into the extracellular environment, thereby preventing its interaction with tubulin (39). Furthermore, attention should be given to protein modifications integral to signaling pathways. Variations in the expression of cyclin B1, polo-like kinase 1 (PLK1), and PTEN, among others, have been suggested to induce drug resistance to T-DM1 (40–42). Concurrently, SLX4 loss-of-function mutations have been implicated in resistance to DS8201 (43).

In this case, the patient resisted RC48 but responded positively to DS8201 with a tislelizumab regimen. Approximately 60% of HER2-negative metastatic breast cancers display low levels of HER2, as indicated by an immunohistochemical (IHC) score of either 1+ or 2+, along with negative *in situ* hybridization (ISH) results (44, 45). Unfortunately, current HER2-targeted therapies have not improved clinical outcomes for patients with this subtype, leaving them with limited targeted therapy options following the progression of primary treatment and mainly relegating them to single-agent palliative chemotherapy (46).

First-generation ADCs like T-DM1 use non-cleavable linkers to attach the cytotoxic payload to the antibody, thereby preventing its release into the extracellular space. This approach is highly effective against cells with elevated HER2 expression but has limited efficacy against those with low to moderate HER2 levels. Conversely, second-generation ADCs, including DS8201 and RC48, employ cleavable linkers, allowing for partial payload release into the extracellular space and thereby affecting cells that do not overexpress HER2 (47). Clinical trials support this notion; the DESTINY-Breast04 and Daisy studies showed favorable outcomes using DS8201 in treating patients with low HER2-expressing breast cancer and even in those with HER2–0 breast cancer (47, 48). However, T-DM1's efficacy is constrained in these low-HER2 cases (33, 49).

A distinct advantage of RC48-ADC is its elevated cytotoxicity at low concentrations. The valine-citrulline (VC) linker used in RC48 is stable and undergoes cleavage by histone proteases only upon endocytosis into lysosomes, subsequently liberating the payload to destroy target cancer cells (50). Additionally, the HER2 antibodies in T-DM1 and DS8201 are derivatives of trastuzumab, whereas RC48 employs hertuzumab. Optimized for screening, hertuzumab shows a higher affinity for HER2 targets than trastuzumab, potentially making it more effective against cancers with low or fluctuating HER2 expression levels. In comparison to other HER2-ADC medications, RC-48 demonstrates superior endocytosis, irrespective of V-ATPase activity, and lacks lysosomal resistance (8).

In light of the available evidence, we hypothesize that the patient's observed resistance to RC-48 primarily stems from increased expression and activity of plasma membrane drug efflux pumps and changes in other genetic and protein components. However, we cannot entirely rule out other potential mechanisms of resistance.

In a similar case, a 67-year-old male with HER2-positive metastatic parotid gland carcinoma was documented. The patient experienced disease progression following a parotidectomy, complemented by adjuvant cisplatin-based chemoradiation, neratinib, and T-DM1. Upon progression on this last HER2-targeted therapy, he showed a complete response to DS8201, which has been sustained for the past seven months (51). Regardless of prior treatment with either RC48 or T-DM1, patients in both cases responded favorably to DS8201. This is consistent with findings from the DESTINY-Breast01 clinical trial, where DS8201 exhibited durable anti-tumor activity in patients with HER2-positive metastatic breast cancer who were previously treated with ADCs. Therefore, considering DS8201 as a subsequent line of therapy for such individuals may be highly beneficial.

A recent case report reported that combined therapy with the RC48 and zibelizumab (a PD-1 inhibitor) achieved successful control of recurrent HER2-positive breast cancer resistant to trastuzumab (52). Moreover, according to the results of former studies, regardless of the PD-L1 expression status, the application of PD-1 monotherapy or the combination of PD-1/PD-L1 inhibitors with chemotherapy can benefit the patients (53, 54). Alongside DS8201, our patient underwent empirical treatment with tislelizumab, a humanized IgG4 anti-PD-1 monoclonal antibody, despite PD-L1 negativity in bronchial specimen biopsy results. Current research highlights that ADCs can enhance anti-tumor immune responses, thus improving the effectiveness of combination therapies. For example, Iwata et al. demonstrated that the combined use of DS8201 and anti-PD-1 antibodies exceeded the efficacy of either treatment alone, possibly due to enhanced T-cell activity and upregulated PD-L1 expression facilitated by DS8201 (55). Similarly, Müller et al. noted the superior efficacy of combining T-DM1 with

anti-CTLA-4/anti-PD-1 therapy over monotherapies, attributing this to the potentiation of both innate and adaptive immune responses (56). Studies have also shown that U3–1402, an ADC targeting HER3, amplifies functionalities and infiltration of innate and adaptive immune cells, thereby sensitizing tumors to immunotherapies. Furthermore, preclinical mouse model studies indicated that ADCs could upregulate PD-1 in CD8 T cells and PD-L1 in tumor cells/tumor-associated macrophages, along with increasing tumor-infiltrating lymphocytes, compared to drug controls (23). Therefore, combining ADCs with immunotherapy may inhibit upregulated immunosuppressive pathways, further enhancing tumor control.

In this case, the patient was switched to another ADC drug DS8201 treatment after RC48 resistance, and the two were connected with different cytotoxic agents to avoid cross-resistance. In addition, combined with tislelizumab immunotherapy increased the anti-tumor efficacy to the patient. However, we need to consider that patients may have a decrease in drug effectiveness and an increase in toxic side effects after multiline drug administration. Further studies should be conducted to explore the efficacy and safety of treatment with an alternative ADC drug after ADC drug resistance.

Conclusion

In conclusion, this case highlights a remarkable response to a DS8201 and tislelizumab regimen in the context of advanced HER2-positive lung metastasis originating from breast cancer previously treated with RC48. The findings offer preliminary evidence underscoring the potential role of DS8201 in managing advanced HER2-amplified lung metastases from breast cancer, particularly in cases that have progressed after initial HER2-targeted therapies. Moreover, combining DS8201 with anti-PD-1 agents could further boost the tumor immune response, enhancing therapeutic efficacy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Institutional Ethics Committee of the Faculty of Medicine at Renmin Hospital of Wuhan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YL: Writing – original draft. JZ: Writing – original draft. FZ: Writing – original draft. JL: Writing – review & editing. XL: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This investigation was financially supported by the Natural Science Foundation of Hubei Province under grant numbers 2019CFB721; the Health and Family Planning Commission of Hubei Province under grant numbers WJ2017M027; the Cisco hausen Cancer Research Foundation under grant number Y-HS202101-0079; the Interdisciplinary Innovative Talents Foundation from Renmin Hospital of Wuhan University under grant number JCRCWL-2022-003; the Research Foundation on Cutting-edge Cancer Supportive Care under grant number cphcf-2022-146; the Key Research and Development Project of Hubei Province's Technical Innovation Plan under grant number 2023BCB020.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2018) 68:394–424. doi: 10.3322/caac.21492

2. Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. *Biol Res*. (2017) 50:33. doi: 10.1186/s40659-017-0140-9

3. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist*. (2009) 14:320–68. doi: 10.1634/theoncologist.2008-0230

4. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. (1987) 235:177–82. doi: 10.1126/science.3798106

5. Chavez-MacGregor M, Mittendorf EA, Clarke CA, Lichtensztajn DY, Hunt KK, Giordano SH. Incorporating tumor characteristics to the american joint committee on cancer breast cancer staging system. *Oncologist*. (2017) 22:1292–300. doi: 10.1634/theoncologist.2017-0116

6. Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet*. (2023) 401:105–17. doi: 10.1016/S0140-6736(22)02420-5

7. Pernas S, Tolaney SM. Clinical trial data and emerging strategies: HER2-positive breast cancer. *Breast Cancer Res Treat*. (2022) 193:281–91. doi: 10.1007/s10549-022-06575-7

8. Shi F, Liu Y, Zhou X, Shen P, Xue R, Zhang M. Disitamab vedotin: a novel antibody-drug conjugates for cancer therapy. *Drug Deliv*. (2022) 29:1335–44. doi: 10.1080/10717544.2022.2069883

9. Cullinane C, Fleming C, O'Leary DP, Hassan F, Kelly L, O'Sullivan MJ, et al. Association of circulating tumor DNA with disease-free survival in breast cancer: A systematic review and meta-analysis. *JAMA Netw Open*. (2020) 3:e2026921. doi: 10.1001/jamanetworkopen.2020.26921

10. Modi ND, Sorich MJ, Rowland A, McKinnon RA, Koczwara B, Wiese MD, et al. Predicting thrombocytopenia in patients with breast cancer treated with ado-trastuzumab emtansine. *Clin Breast Cancer*. (2020) 20:e220–e8. doi: 10.1016/j.clbc.2019.10.001

11. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. (2020) 382:610–21. doi: 10.1056/NEJMoa1914510

12. Kutomi G, Mizuguchi T, Satomi F, Maeda H, Shima H, Kimura Y, et al. Current status of the prognostic molecular biomarkers in breast cancer: A systematic review. *Oncol Lett*. (2017) 13:1491–8. doi: 10.3892/ol.2017.5609

13. Berghuis AMS, van Deurzen CHM, Koffijberg H, Terstappen L, Sleijfer S, MJ IJ. Real-world data on discordance between estrogen, progesterone, and HER2 receptor expression on diagnostic tumor biopsy versus tumor resection material. *Breast Cancer Res Treat*. (2019) 175:451–8. doi: 10.1007/s10549-019-05141-y

14. Matsumoto A, Jinno H, Murata T, Seki T, Takahashi M, Hayashida T, et al. Prognostic implications of receptor discordance between primary and recurrent breast cancer. *Int J Clin Oncol*. (2015) 20:701–8. doi: 10.1007/s10147-014-0759-2

15. Aurilio G, Disalvatore D, Pruneri G, Bagnardi V, Viale G, Curigliano G, et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. *Eur J Cancer*. (2014) 50:277–89. doi: 10.1016/j.ejca.2013.10.004

16. Turner KM, Yeo SK, Holm TM, Shaughnessy E, Guan JL. Heterogeneity within molecular subtypes of breast cancer. *Am J Physiol Cell Physiol*. (2021) 321:C343–c54. doi: 10.1152/ajpcell.00109.2021

17. Nunnery SE, Mayer IA. Targeting the PI3K/AKT/mTOR pathway in hormone-positive breast cancer. *Drugs*. (2020) 80:1685–97. doi: 10.1007/s40265-020-01394-w

18. Peng L, Zhang Z, Zhao D, Zhao J, Mao F, Sun Q. Discordance in ER, PR, HER2, and ki-67 expression between primary and recurrent/metastatic lesions in patients with primary early stage breast cancer and the clinical significance: retrospective analysis of 75 cases. *Pathol Oncol Res*. (2021) 27:599894. doi: 10.3389/pore.2021.599894

19. Cesca MG, Vian L, Cristóvão-Ferreira S, Pondé N, de Azambuja E. HER2-positive advanced breast cancer treatment in 2020. *Cancer Treat Rev*. (2020) 88:102033. doi: 10.1016/j.ctrv.2020.102033

20. Kalim M, Chen J, Wang S, Lin C, Ullah S, Liang K, et al. Intracellular trafficking of new anticancer therapeutics: antibody-drug conjugates. *Drug Des Devel Ther*. (2017) 11:2265–76. doi: 10.2147/DDDT

21. Li F, Emmerton KK, Jonas M, Zhang X, Miyamoto JB, Setter JR, et al. Intracellular released payload influences potency and bystander-killing effects of antibody-drug conjugates in preclinical models. *Cancer Res*. (2016) 76:2710–9. doi: 10.1158/0008-5472.CAN-15-1795

22. Khera E, Thurber GM. Pharmacokinetic and immunological considerations for expanding the therapeutic window of next-generation antibody-drug conjugates. *BioDrugs*. (2018) 32:465–80. doi: 10.1007/s40259-018-0302-5

23. Müller P, Kreuzaler M, Khan T, Thommen DS, Martin K, Glatz K, et al. Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade. *Sci Transl Med*. (2015) 7:315ra188. doi: 10.1126/scitranslmed.aac4925

24. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. (2012) 367:1783–91. doi: 10.1056/NEJMoa1209124

25. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. (2019) 380:617–28. doi: 10.1056/NEJMoa1814017

26. Mukohara T, Hosono A, Mimaki S, Nakayama A, Kusuhara S, Funasaka C, et al. Effects of ado-trastuzumab emtansine and fam-trastuzumab deruxtecan on metastatic breast cancer harboring HER2 amplification and the L755S mutation. *Oncologist*. (2021) 26:635–9. doi: 10.1002/onco.13715

27. Wang Y, Gong J, Wang A, Wei J, Peng Z, Wang X, et al. Disitamab vedotin (RC48) plus toripalimab for HER2-expressing advanced gastric or gastroesophageal junction and other solid tumours: a multicentre, open label, dose escalation and expansion phase 1 trial. *EClinicalMedicine*. (2024) 68:102415. doi: 10.1016/j.eclinm.2023.102415

28. Nie C, Xu W, Guo Y, Gao X, Lv H, Chen B, et al. Immune checkpoint inhibitors enhanced the antitumor efficacy of disitamab vedotin for patients with HER2-positive or HER2-low advanced or metastatic gastric cancer: a multicenter real-world study. *BMC Cancer*. (2023) 23:1239. doi: 10.1186/s12885-023-11735-z

29. Peng Z, Liu T, Wei J, Wang A, He Y, Yang L, et al. Efficacy and safety of a novel anti-HER2 therapeutic antibody RC48 in patients with HER2-overexpressing, locally advanced or metastatic gastric or gastroesophageal junction cancer: a single-arm phase II study. *Cancer Commun (Lond)*. (2021) 41:1173–82. doi: 10.1002/cac2.12214

30. Sheng X, Yan X, Wang L, Shi Y, Yao X, Luo H, et al. Open-label, multicenter, phase II study of RC48-ADC, a HER2-targeting antibody-drug conjugate, in patients with locally advanced or metastatic urothelial carcinoma. *Clin Cancer Res*. (2021) 27:43–51. doi: 10.1158/1078-0432.CCR-20-2488

31. Wang J, Liu Y, Zhang Q, Feng J, Fang J, Chen X, et al. RC48-ADC, a HER2-targeting antibody-drug conjugate, in patients with HER2-positive and HER2-low expressing advanced or metastatic breast cancer: a pooled analysis of two studies. *Wolters Kluwer Health*. (2021) 39:1022–1022. doi: 10.1200/JCO.2021.39.15_suppl.1022

32. Wu Q, He L, Luo J, Jin W, Xu Y, Wang C. Long-term remission under Disitamab Vedotin (RC48) in HR-positive/HER2-positive metastatic breast cancer with brain meningeal, and bone marrow involvement: A case report. *Oncol Lett*. (2022) 24:339. doi: 10.3892/ol

33. Burris HA 3rd, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol*. (2011) 29:398–405. doi: 10.1200/JCO.2010.29.5865

34. LoRusso PM, Weiss D, Guardino E, Girish S, Sliwkowski MX. Trastuzumab emtansine: a unique antibody-drug conjugate in development for human epidermal growth factor receptor 2-positive cancer. *Clin Cancer Res*. (2011) 17:6437–47. doi: 10.1158/1078-0432.CCR-11-0762

35. Baldassarre T, Truesdell P, Craig AW. Endophilin A2 promotes HER2 internalization and sensitivity to trastuzumab-based therapy in HER2-positive breast cancers. *Breast Cancer Res*. (2017) 19:110. doi: 10.1186/s13058-017-0900-z

36. Raja SM, Clubb RJ, Bhattacharyya M, Dimri M, Cheng H, Pan W, et al. A combination of Trastuzumab and 17-AAG induces enhanced ubiquitinylation and lysosomal pathway-dependent ErbB2 degradation and cytotoxicity in ErbB2-overexpressing breast cancer cells. *Cancer Biol Ther*. (2008) 7:1630–40. doi: 10.4161/cbt.7.10.6585

37. Austin CD, De Mazière AM, Pisacane PI, van Dijk SM, Eigenbrot C, Sliwkowski MX, et al. Endocytosis and sorting of ErbB2 and the site of action of cancer therapeutics trastuzumab and geldanamycin. *Mol Biol Cell*. (2004) 15:5268–82. doi: 10.1091/mbc.e04-07-0591

38. Ríos-Luci C, García-Alonso S, Díaz-Rodríguez E, Nadal-Serrano M, Arribas J, Ocaña A, et al. Resistance to the antibody-drug conjugate T-DM1 is based in a reduction in lysosomal proteolytic activity. *Cancer Res*. (2017) 77:4639–51. doi: 10.1158/0008-5472.Can-16-3127

39. Robey RW, Pluchino KM, Hall MD, Fojo AT, Bates SE, Gottesman MM. Revisiting the role of ABC transporters in multidrug-resistant cancer. *Nat Rev Cancer*. (2018) 18:452–64. doi: 10.1038/s41568-018-0005-8

40. Sabbaghi M, Gil-Gómez G, Guardia C, Servitja S, Arpí O, García-Alonso S, et al. Defective cyclin B1 induction in trastuzumab-emtansine (T-DM1) acquired resistance in HER2-positive breast cancer. *Clin Cancer Res*. (2017) 23:7006–19. doi: 10.1158/1078-0432.CCR-17-0696

41. Saatci Ö, Borgoni S, Akbulut Ö, Durmuş S, Raza U, Eyüpoğlu E, et al. Targeting PLK1 overcomes T-DM1 resistance *via* CDK1-dependent phosphorylation and inactivation of Bcl-2/xL in HER2-positive breast cancer. *Oncogene*. (2018) 37:2251–69. doi: 10.1038/s41388-017-0108-9

42. Aghazadeh S, Yazdanparast R. Activation of STAT3/HIF-1α/Hes-1 axis promotes trastuzumab resistance in HER2-overexpressing breast cancer cells *via* down-regulation of PTEN. *Biochim Biophys Acta Gen Subj*. (2017) 1861:1970–80. doi: 10.1016/j.bbagen.2017.05.009

43. Mosele M, Lusque A, Dieras V, Deluche E, Ducoulombier A, Pistilli B, et al. LBA1 Unraveling the mechanism of action and resistance to trastuzumab deruxtecan (T-DXd): Biomarker analyses from patients from DAISY trial. *Ann Oncol*. (2022) 33:S123. doi: 10.1016/j.annonc.2022.03.277

44. Schettini F, Chic N, Brasó-Maristany F, Paré L, Pascual T, Conte B, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer*. (2021) 7:1. doi: 10.1038/s41523-020-00208-2

45. Tarantino P, Hamilton E, Tolaney SM, Cortes J, Morganti S, Ferraro E, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol*. (2020) 38:1951–62. doi: 10.1200/JCO.19.02488

46. Fehrenbacher L, Cecchini RS, Geyer CE Jr., Rastogi P, Costantino JP, Atkins JN, et al. NSABP B-47/NRG oncology phase III randomized trial comparing adjuvant chemotherapy with or without trastuzumab in high-risk invasive breast cancer negative for HER2 by FISH and with IHC 1+ or 2. *J Clin Oncol*. (2020) 38:444–53. doi: 10.1200/JCO.19.01455

47. García-Alonso S, Ocaña A, Pandiella A. Resistance to antibody-drug conjugates. *Cancer Res*. (2018) 78:2159–65. doi: 10.1158/0008-5472.Can-17-3671

48. Diéras V, Deluche E, Lusque A, Pistilli B, Bachelot T, Pierga J, et al. *Trastuzumab deruxtecan (T-DXd) for advanced breast cancer patients (ABC), regardless HER2 status: A phase II study with biomarkers analysis (DAISY)*. San Antonio, Texas, USA: San Antonio Breast Cancer Symposium (2021).

49. Krop I, LoRusso P, Miller K, Modi S, Yardley D, Rodriguez G, et al. *A phase 2 study of the HER2 antibody-drug conjugate trastuzumab-DM1 (T-DM1) in patients (pts) with HER2-positive metastatic breast cancer (MBC) previously treated with trastuzumab, lapatinib, and chemotherapy*. GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND: Oxford Univ Press (2010).

50. Bargh JD, Isidro-Llobet A, Parker JS, Spring DR. Cleavable linkers in antibody-drug conjugates. *Chem Soc Rev*. (2019) 48:4361–74. doi: 10.1039/C8CS00676H

51. Shukla ND, Chiang RS, Colevas AD. Metastatic parotid gland carcinoma with ERBB2 amplification with complete response to fam-trastuzumab deruxtecan. *J Natl Compr Canc Netw*. (2022) 20:102–4. doi: 10.6004/jnccn.2021.7089

52. Fan S, He L, Sang D. Combination therapy with antibody-drug conjugate RC48 (disitamab vedotin) and zimberelimab (PD-1 inhibitor) successfully controlled recurrent HER2-positive breast cancer resistant to trastuzumab emtansine: A case report. *Oncol Lett*. (2023) 26:1–6. doi: 10.3892/ol

53. Gadgeel SM, Rodríguez-Abreu D, Halmos B, Garassino MC, Kurata T, Cheng Y, et al. Pembrolizumab plus chemotherapy for metastatic non-small-cell lung cancer with programmed cell death ligand 1 tumor proportion score less than 1%: pooled analysis of outcomes after 5 years of follow-up. *J Thorac Oncol*. (2024). doi: 10.1016/j.jtho.2024.04.011

54. Brahmer JR, Lee JS, Ciuleanu TE, Bernabe Caro R, Nishio M, Urban L, et al. Five-year survival outcomes with nivolumab plus ipilimumab versus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer in checkMate 227. *J Clin Oncol*. (2023) 41:1200–12. doi: 10.1200/JCO.22.01503

55. Iwata TN, Ishii C, Ishida S, Ogitani Y, Wada T, Agatsuma T. A HER2-targeting antibody-drug conjugate, trastuzumab deruxtecan (DS-8201a), enhances antitumor immunity in a mouse model. . *Mol Cancer Ther*. (2018) 17:1494–503. doi: 10.1158/1535-7163.MCT-17-0749

56. Haratani K, Yonesaka K, Takamura S, Maenishi O, Kato R, Takegawa N, et al. U3–1402 sensitizes HER3-expressing tumors to PD-1 blockade by immune activation. *J Clin Invest*. (2020) 130:374–88. doi: 10.1172/jci126598

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 16 August 2024
DOI 10.3389/fonc.2024.1419246

OPEN ACCESS

EDITED BY
Dirk Geerts,
University of Amsterdam, Netherlands

REVIEWED BY
Dharmendra Kumar Yadav,
Gachon University, Republic of Korea
Desh Deepak Singh,
Amity University Jaipur, India

*CORRESPONDENCE
Reshma Mahtani
reshma.mahtani@baptisthealth.net

RECEIVED 17 April 2024
ACCEPTED 24 July 2024
PUBLISHED 16 August 2024

CITATION
Mahtani R, Harpalani N, Yan F, Phiel K and Kovalenko I (2024) Expanding treatment options for patients with HER2+ metastatic breast cancer with margetuximab plus chemotherapy: a case report series. *Front. Oncol.* 14:1419246. doi: 10.3389/fonc.2024.1419246

Expanding treatment options for patients with HER2+ metastatic breast cancer with margetuximab plus chemotherapy: a case report series

Reshma Mahtani[1,2,3]*, Natasha Harpalani[2], Fengting Yan[4,5], Kristen Phiel[6] and Iuliia Kovalenko[7]

[1]Miami Cancer Institute – Medical Oncology, Baptist Health South Florida, Miami, FL, United States, [2]Miami Cancer Institute, Baptist Hospital of Miami, Miami, FL, United States, [3]Memorial Sloan Kettering Cancer Alliance, Miami Cancer Institute, Miami, FL, United States, [4]Breast Medical Oncology, Swedish Cancer Institute, Seattle, WA, United States, [5]First Hill - True Family Women's Cancer Center, Swedish Health Services, Seattle, WA, United States, [6]Eversana, Amherst, MA, United States, [7]Internal Medicine, University of Pittsburgh Medical Center (UPMC) Harrisburg, Harrisburg, PA, United States

Background: Human epidermal growth factor receptor 2 protein (HER2)-positive (+) metastatic breast cancer (MBC) is an aggressive disease and patients often undergo multiple lines of therapy following HER2 targeted therapies. The most recent National Comprehensive Cancer Network (NCCN) guidelines recommend margetuximab plus chemotherapy as fourth-line or later therapy for HER2+/hormone receptor (HR) + or negative (–) MBC. The aim of this case series is to provide information regarding margetuximab utilization in clinical practice as later-line therapy in women with HER2+ MBC.

Case summaries: Margetuximab plus chemotherapy was used as fourth- or later-line treatment in patients who had received multiple HER2-targeted agents, including trastuzumab, pertuzumab, ado-trastuzumab emtansine, trastuzumab deruxtecan, tucatinib, and neratinib. Patients responded to margetuximab plus chemotherapy with real-world progression-free survival (PFS) of 3, 4, and 7 months.

Conclusion: Clinical outcomes from three heavily pretreated patients with metastatic HER2+/HR+ MBC demonstrated that margetuximab plus chemotherapy resulted in real-world PFS comparable to that reported in the controlled pivotal clinical trial and support use of this targeted therapy option in appropriately identified patients.

KEYWORDS

margetuximab, HER2+, metastatic breast cancer, later-line treatment, case report

Introduction

Human epidermal growth factor receptor 2 (HER2)-positive (+) breast cancer (BC) is a subtype of breast cancer where amplification of the *HER2* gene results in HER2 receptor overexpression, which is a major driver of tumor development and progression (1). HER2+ BC accounts for approximately 14% of total BC cases in the United States; it is highly aggressive and has a high associated risk for mortality (2–4). Overall, patients with HER2+ BC have a poor prognosis. The 5-year survivals in patients with HER2+/hormone receptor (HR) + and HER2+/HR negative (–) metastatic (M) BC are 45.6% and 39.5%, respectively (2). Management of patients with HER2+ BC was revolutionized by the advent of trastuzumab, a monoclonal antibody (mAb) targeting HER2 (5). Chemotherapy in combination with trastuzumab (+/- pertuzumab) is routinely utilized in the (neo)adjuvant setting for patients with early-stage HER2+ BC. Dual HER2 blockade with trastuzumab and pertuzumab has become part of the standard of care for women with stage II and III HER2+ BC (6–8). Nevertheless, approximately 30% of patients still experience recurrence or metastasis despite receiving treatment in the early-stage setting (9). The combination of trastuzumab plus pertuzumab and chemotherapy is a preferred first-line treatment for HER2+ MBC (10–12), but ultimately most patients experience progression of disease on this therapy (13). In fact, patients with HER2+ MBC generally go on to receive multiple lines of therapy and, with rare exceptions, HER2+ MBC remains incurable, highlighting the need for additional treatment options (14, 15).

The high rate of disease progression despite HER2-targeted therapy with trastuzumab has prompted continued development of biologics and small molecules targeting HER2 (16, 17). Fragment crystallizable (Fc)-engineering strategies have been used to customize mAbs, enhancing their cytotoxic and antitumor potencies; margetuximab was developed using this technology (18). Results from the phase 3 SOPHIA trial showed that the combination of margetuximab with chemotherapy in patients with HER2+ unresectable or MBC previously treated with HER2-directed therapies was significantly superior to trastuzumab plus chemotherapy for extending progression-free survival (PFS) (19). Median overall survival (OS) was similar to trastuzumab (20). Results from this trial supported the indication for margetuximab in combination with chemotherapy for the treatment of adult patients with HER2+ MBC who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease (21).

Additionally, pharmacogenomic targeting in HER2+ MBC may improve outcomes for patients carrying the CD16A-F allele for the Fc-gamma receptor due to the increased affinity of margetuximab for this allele over trastuzumab. In a preplanned, exploratory analysis of SOPHIA, the margetuximab-based regimen was superior to trastuzumab plus chemotherapy in prolonging overall survival (OS) in patients with the CD16A-158FF genotype (21). The MARGOT trial (NCT04425018) is currently evaluating the role of personalized treatment of stage II-III HER2+ BC in patients with the FF or FV CD16A genotype with paclitaxel plus margetuximab and pertuzumab vs paclitaxel plus trastuzumab and pertuzumab (22).

Despite the demonstrated improvement in PFS, a favorable risk-benefit profile (20, 21, 23), and the inclusion in the NCCN guidelines for use as fourth-line or later therapy for HER2+/HR+ or – MBC (12), margetuximab plus chemotherapy may remain underutilized in clinical practice (23). This may be due to the increasing number of later-line options for the treatment of HER2+ MBC (12) and uncertainty regarding best use of margetuximab in clinical practice. The aim of the three cases presented here is to describe margetuximab use as later-line therapy for HER2+ MBC in real-world clinical practice. All patient cases have been deidentified to protect patients' and their families' privacy.

Case 1: 72-year-old woman, sixth-line margetuximab plus chemotherapy, 3 months PFS

Presentation and diagnosis

The patient was a 72-year-old woman with no evidence of a germline *BRCA* mutation, who was originally diagnosed with BC in 2010 (at age 59 years), when she underwent right lumpectomy sentinel node biopsy (Figure 1). Final pathology confirmed a 2 mm invasive ductal carcinoma, estrogen receptor (ER) + (95%) and progesterone receptor (PR) + (80%); HER2 status could not be determined due to insufficient tissue for testing. The decision was made to not offer adjuvant chemotherapy and trastuzumab given the overall small amount of invasive disease (pT1aN0M0). She underwent adjuvant radiation and took tamoxifen for a couple months but discontinued due to intolerance. She was followed and did well until 2017 when she reported discomfort in her low back, which led to imaging that revealed widespread bone metastases. A biopsy of the left sacrum confirmed invasive ductal carcinoma (IDC), ER+, PR–, and HER2+ (3+ by immunohistochemistry [IHC]).

Clinical course

As first-line treatment, the patient received paclitaxel, trastuzumab, and pertuzumab which resulted in disease control for approximately 2 years. She then developed progressive bone metastases. Treatment was changed to ado-trastuzumab emtansine (T-DM1), providing disease control for approximately 12 months, at which point further progression was noted in bone and she had developed neuropathy. Treatment with fulvestrant in combination with abemaciclib and trastuzumab was given for approximately 6 months, at which point she developed symptomatic progression of disease in the bone, multiple nodal sites, and in the lung. She was then treated with trastuzumab deruxtecan. Although imaging confirmed a response to trastuzumab deruxtecan, she developed grade 2 pneumonitis that required discontinuation (24, 25). The patient then received tucatinib plus capecitabine and trastuzumab (26) but

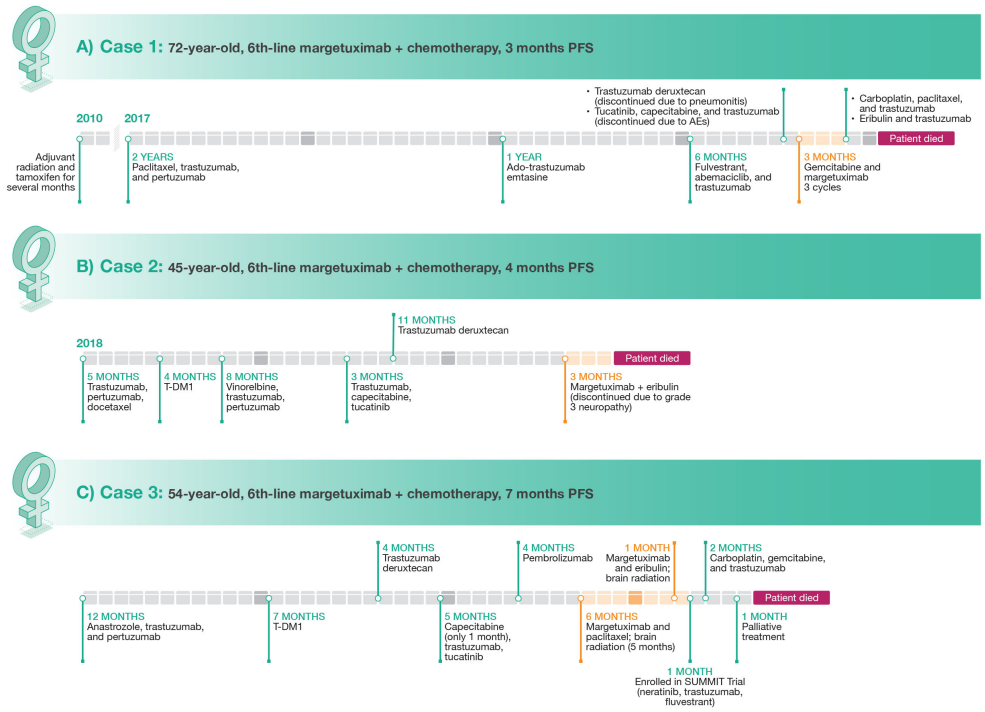


FIGURE 1
Clinical course of therapy and treatment lengths for Case 1 **(A)**, Case 2 **(B)**, and Case 3 **(C)**.

developed elevations in liver function tests that responded to dose reductions, but due to lack of appetite and intermittent diarrhea, the patient elected to discontinue treatment (27). Imaging performed in July 2022 after discontinuation of therapy demonstrated further progression of disease, with new lytic bone lesions and new metastases identified in the liver. In July 2022, the patient started treatment with gemcitabine and margetuximab. After 3 cycles, a repeat PET scan showed definitive improvement in hepatic lesions and mild improvement in bony lesions. However, this combination was stopped after the patient was hospitalized at the end of October 2022 (3 months) with suspected progression of disease and development of ascites. Treatment was then changed to carboplatin, with re-challenge of paclitaxel, in combination with trastuzumab, with no response noted on imaging. Ultimately, therapy with eribulin and trastuzumab was also not effective and unfortunately the patient succumbed to her disease.

Case 2: 45-year-old woman, sixth-line margetuximab plus chemotherapy, 4 months PFS

Presentation and diagnosis

The patient was a 45-year-old woman with no significant medical history who presented with a self-palpated mass in the right breast for 4 months in 2018 (Figure 1). A right breast biopsy indicated grade 3 ductal invasive carcinoma that was ER– and PR– with equivocal results for HER2 by IHC but positive results with fluorescent *in situ* hybridization (FISH). A staging computed tomography (CT) scan at diagnosis demonstrated a large number of liver lesions. Laboratory results indicated elevations in both alanine aminotransferase and aspartate aminotransferase. The diagnosis for this patient was *de novo* HER2+/HR– MBC (HER2 low) with liver metastases.

Clinical course

First-line treatment was trastuzumab plus pertuzumab and docetaxel (THP) as recommended by NCCN (12) and supported by results of the CLEOPATRA trial (10). Monitoring during treatment consisted of laboratory assessment every 3 weeks, periodic cardiac function evaluation, and a CT scan. After 5 months, the patient progressed on THP and was switched to T-DM1 (28) and remained on this antibody-drug conjugate for 4 months until progression. Vinorelbine plus trastuzumab and pertuzumab was used in third line for 8 months (29), trastuzumab plus capecitabine and tucatinib in fourth line for 3 months (26), and trastuzumab deruxtecan in fifth line for 11 months (30). After disease progression, the patient was switched to margetuximab plus eribulin (19). She responded to this treatment and was stable on the regimen for 4 months. She then developed grade 3 neuropathy and treatment was discontinued.

Case 3: 54-year-old woman, sixth-line margetuximab plus chemotherapy, 7 months PFS

Presentation and diagnosis

A 54-year-old woman with no significant family or social history potentially related to BC was initially diagnosed with clinical stage IV (cT2cN1(f)M1) IDC of the right breast that was ER+/PR+ (90%/75%) and HER2+ (>30%) as well as high-grade ductal carcinoma *in situ* of the right breast (Figure 1). Whole-body PET/CT scan also revealed multiple osseous metastatic lesions. Lumbar lesion biopsy confirmed ER+/PR+ (90%/80%) HER+ (30%) MBC.

Clinical course

The patient refused neoadjuvant chemotherapy and completed a 12-month course of anastrozole plus trastuzumab and pertuzumab (31). She then underwent palliative mastectomy of the right breast, prophylactic mastectomy of the left breast, and right axillary node excision. Pathology revealed multifocal grade 3 IDC with skin, skeletal muscle, and lymphovascular invasion. Following initial treatment, the patient underwent a 7-month course of therapy with T-DM1. Repeat PET/CT showed disease progression with hypermetabolic lesions in the neck and right axillary and mediastinal lymph nodes as well as in the right pectoralis muscle and new skeletal lesions. The patient was then switched to trastuzumab deruxtecan (32), which was discontinued 4 months later due to disease progression indicated by a PET/CT scan that revealed F-fluorodeoxyglucose (FDG)-avid supraclavicular and mediastinal lymph nodes as well as multiple soft tissue nodules along the right chest wall. The patient was then started on a combination therapy with capecitabine, trastuzumab, and tucatinib (27). Capecitabine was withheld one month later during palliative chest wall radiation therapy. A CT bone scan 5 months later showed progressive adenopathy including new lesions in the right paratracheal and right hilar lymph nodes. Foundation one genetic testing was performed and revealed microsatellite (MS)-stability, tumor mutational burden of 10 mutations per megabase, amplification in *AKT3*, *IKBKE*, *MDM4*, *PIK3C2B*, and *RAD21*; mutations in *CDC73* (W43) and *PIK3CA* (E453del, C420R); and *EED* (NM_003797) rearrangement in exon 9. Molecular profiling testing revealed that tumor tissue was ER+ (90%), amplified for ERBB2 (HER2/neu), PR+, programmed death ligand 1-positive (IHC; Sp142), MS, *NTRK* fusion negative, *AR* mutation positive, *BRCA1* and *BRCA2* negative, *PIK3CA* mutated, and *PTEN* mutation positive. The patient was started on pembrolizumab and refused chemotherapy at that time. She developed disease progression after 4 months.

At this point, it was decided to start the patient on margetuximab in combination with paclitaxel as her sixth line of therapy. Her only adverse event on this regimen was a grade 1 elevation in liver enzymes. She underwent brain magnetic resonance imaging (MRI) one month later, which revealed 5 to 6 subtentorial enhancing masses. She then underwent brain radiation therapy along with right femoral neck therapy. One month later, the patient had a positive treatment response with left cervical lymphadenopathy size reduction. Her only side effect was fatigue. Follow-up PET/CT scan revealed resolution of multiple FDG-avid uptake areas, including the parotid gland, neck, supraclavicular fossa, axilla, hilar areas, and mediastinum as well as the right adrenal gland and retroperitoneal nodules. Unfortunately, brain MRI one month later revealed multiple new enhancing lesions. Her PET/CT scan after an additional 4 months showed disease progression with new hypermetabolic lymph nodes in the neck, axilla, mediastinum, and right hilum along with new hypermetabolic foci in the skeleton and chest skin. The patient was offered alternative treatments but preferred to remain on margetuximab. Paclitaxel was discontinued and the patient was started on a combination of margetuximab with eribulin. She also underwent repeat brain radiation therapy. Unfortunately, with the addition of eribulin, the patient developed nausea, vomiting and fatigue prompting emergency department (ED) visits. CT of the abdomen performed in the ED showed worsening metastatic disease. The patient also reported recurrence of right chest wall nodules. Eribulin was discontinued one month later and margetuximab was discontinued after a total of 7 months due to disease progression. The patient then was enrolled in the SUMMIT trial and was treated with neratinib plus trastuzumab and fulvestrant (33) for one month, which was changed to a combination of carboplatin, gemcitabine, and trastuzumab one month later due to disease progression. Brain MRI 2 months later showed disease progression. Due to poor overall prognosis, the patient elected to proceed with palliative treatment. The patient died one month later.

Discussion

Results from the patients included in these case reports indicate that patients with HER2+ MBC are likely to receive many lines of treatment. This is consistent with large scale reviews. Assessment of 59 patients with HER2+ MBC treated at a single academic center indicated that 40% of patients received at least 5 lines of treatment that included chemotherapy and >10% received at least 10 lines (34). A more recent larger study of 1390 patients with HER2+ MBC indicated 39.6% of patients received at least 4 lines of treatment (35).

The results for these cases also underscore the difficulties involved in sequencing later lines of treatment for HER2+ MBC. It is recognized that optimal sequencing of anti-HER2 agents in patients with advanced HER2+ BC is essential for maximizing the benefit of each line of treatment and slowing the progression of metastases (36). However, there are several NCCN-recommended therapies for HER2+ advanced/MBC (12), each possessing different mechanisms of action and safety profiles. Deciding on the best treatment sequencing for an individual patient is a significant challenge (36). Importantly, evidence-based recommendations to guide sequencing in later lines of therapy are lacking (12). This is

reflected by the treatment sequencing for the three patients described in this paper. First-line treatment for all three patients included chemotherapy in combination with trastuzumab and pertuzumab, consistent with NCCN recommendations based on the results from the landmark CLEOPATRA trial (10, 11). Second-line treatment for each patient included T-DM1 which was the standard at the time these patients were treated (based on the EMILIA trial), but has recently been replaced by trastuzumab deruxtecan based on results from DESTINY-Breast03 (12, 28, 37). Treatment after progression on T-DM1 varied.

The combination of margetuximab and chemotherapy was used as sixth-line therapy in these cases; it provided results consistent with those from the phase 3 SOPHIA trial supporting its approval by the US Food and Drug Administration. This study included 536 patients with HER2+ BC (metastatic in ~98% of patients). Similar to the patients described in these case studies, all patients enrolled in SOPHIA had received trastuzumab, all but one had received prior pertuzumab, and 91.2% had received prior T-DM1. One-third of the patients in the trial had received ≥2 prior lines of treatment (19). The median PFS for margetuximab plus chemotherapy in SOPHIA was 5.8 months (19); real-world PFS for the 3 patients described in this report was 3, 4, and 7 months.

Similar results were seen with earlier use. Results from a recently published case study of a patient initially diagnosed with HER2+/HR– IDC that metastasized to the liver after one cycle of chemotherapy who received margetuximab plus capecitabine as fourth-line treatment indicated PFS of 7 months with this regimen (38). Another case study reported a patient with HER2+ histological grade III MBC and IDC who developed bone and liver metastases who experienced a complete response that was sustained for at least 6 months (the last evaluation reported) after receiving third-line treatment with margetuximab (39).

In the presented cases, two of the patients treated with margetuximab plus eribulin had clinically important adverse events, neuropathy in one and nausea, vomiting, and fatigue with severity that prompted ED visits in another. The extent to which margetuximab or eribulin contributed to these events is not clear. Results from a phase 1 study in which margetuximab was delivered as monotherapy to patients with advanced HER2+ solid tumors indicated no occurrences of neuropathy. Fatigue, nausea, and vomiting were reported in 24%, 29%, and 24% of patients, respectively, but none of these events were grade ≥3 in severity (40). Review of safety data for eribulin in patients with BC indicated that peripheral neuropathy occurred in 28.5% of patients (grade 3/4 in 1.5%) (41). Fatigue was reported for 23.7% of patients and nausea in 35.7% (41).

Gaining information regarding the clinical benefits and risks of margetuximab in the real world is important for several reasons. First, there is no clear choice for systemic therapy after progression on third-line treatment in patients with recurrent unresectable or metastatic HER2+ MBC. Additionally, it has been reported that results achieved with cancer therapy in the real world often fall short of those reported in controlled clinical trials (42) [compare results from Verma et al. (28) with those from Nakayama et al. (43)]. The results demonstrated in this small series of patients treated with margetuximab and chemotherapy are therefore reassuring. The case studies described here and in other recent publications (38, 39) suggest that the efficacy and safety of margetuximab in routine clinical practice are comparable to those reported in controlled clinical trials (19). This supports the view that margetuximab plus chemotherapy is a viable choice for fourth- or later-line therapy even though new additional single agents and combinations now may be used prior. This conclusion is consistent with the place in therapy for margetuximab as recommended in the NCCN treatment guidelines (12).

The results presented and reviewed underscore the importance of real-world evidence as a complement to data from controlled clinical trials. The importance of real-world experience is well established, as these observations often involve patients with disease characteristics, comorbidities, and complications that would result in their exclusion from clinical trials (44). While results from real-world clinical experience may not match that from controlled clinical trials (45), understanding the efficacy and safety of a therapy across the range of patients in which it might be used is one of multiple factors that should be considered in optimizing treatment selection. Others include patient goals and preferences, their prioritization of efficacy vs risk for adverse events, favored route of administration, and impact on quality of life (46).

While real-world results including those from case studies can complement those from randomized controlled trials, uncontrolled observations do have important limitations including that they are inherently prone to bias in selection of therapy for specific patients and confounded by factors typically controlled for in clinical trials (47). Further, the ability to generalize results from very small patients samples to larger populations is limited (48).

Going forward, selection of margetuximab for treatment may be based on genomic testing, as ongoing trials seek to clarify the role for upfront allelic variation testing. Results from the SOPHIA trial suggests the importance of determining the CD16A genotype in candidates for margetuximab treatment (21), and the use of genotyping is being evaluated prospectively in the ongoing MARGOT study (22).

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the studies involving humans because a written informed consent was obtained from each participant for the publication of data included in this article. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RM: Conceptualization, Writing – original draft, Writing – review & editing. NH: Writing – original draft, Writing – review & editing. FY: Writing – original draft, Writing – review & editing, Conceptualization. KP: Writing – original draft, Writing – review & editing. IK: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by MacroGenics.

Acknowledgments

The authors thank Bob Rhoades, PhD for manuscript preparation and editorial assistance.

Conflict of interest

RM has the following disclosures to report: Agendia, Amgen, Astra Zeneca, Daiichi Sankyo, Eisai, Genentech, Gilead, Hologic, Eli Lilly, Merck, Novartis, Pfizer, Puma, Sanofi, SeaGen, Stemline, Sermonix. Author KP was employed by Eversana.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Krishnamurti U, Silverman JF. HER2 in breast cancer: a review and update. *Adv Anat Pathol*. (2014) 21:100–7. doi: 10.1097/PAP.0000000000000015

2. National Cancer Institute. Cancer Stat Facts: Female Breast Cancer Subtypes (2022). Available online at: https://seer.cancer.gov/statfacts/html/breast-subtypes.html (Accessed June 26, 2023).

3. Haque R, Ahmed SA, Inzhakova G, Shi J, Avila C, Polikoff J, et al. Impact of breast cancer subtypes and treatment on survival: an analysis spanning two decades. *Cancer Epidemiol Biomarkers Prev*. (2012) 21:1848–55. doi: 10.1158/1055-9965.EPI-12-0474

4. Callahan R, Hurvitz S. Human epidermal growth factor receptor-2-positive breast cancer: current management of early, advanced, and recurrent disease. *Curr Opin Obstet Gynecol*. (2011) 23:37–43. doi: 10.1097/GCO.0b013e3283414e87

5. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. *Ann Oncol*. (2007) 18:977–84. doi: 10.1093/annonc/mdl475

6. Burstein HJ. Adjuvant systemic therapy for HER2-positive breast cancer (2023). Available online at: https://www.uptodate.com/contents/adjuvant-systemic-therapy-for-her2-positive-breast-cancer/print (Accessed June 26, 2023).

7. Martínez-Sáez O, Waks AG. Individualizing curative-intent therapy in HER2-positive early-stage breast cancer. *Curr Treat Options Oncol*. (2023) 24:479–95. doi: 10.1007/s11864-023-01070-7

8. Tan AR, Im SA, Mattar A, Colomer R, Stroyakovskii D, Nowecki Z, et al. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study. *Lancet Oncol*. (2021) 22:85–97. doi: 10.1016/S1470-2045(20)30536-2

9. Yang J, Ju J, Guo L, Binbin J, Shi S, Yang Z, et al. Prediction of HER2-positive breast cancer recurrence and metastasis risk from histopathological images and clinical information via multimodal deep learning. *Comput Struct Biotechnol J*. (2021) 20:333–42. doi: 10.1016/j.csbj.2021.12.028

10. Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. (2013) 14:461–71. doi: 10.1016/S1470-2045(13)70130-X

11. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. (2015) 372:724–34. doi: 10.1056/NEJMoa1413513

12. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 4.2023 Breast Cancer (2023). Available online at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (Accessed June 26, 2023).

13. Thill M, Wimberger P, Grafe A, Klare P, Luedtke-Heckenkamp K, Reichert D, et al. Dual HER2 blockade with pertuzumab (P) and trastuzumab (T) in patients with HER2-positive metastatic breast cancer (mBC) relapsing after adjuvant treatment with T: results from a German non-interventional study (NIS) HELENA (NCT01777958). *Breast Cancer Res Treat*. (2022) 196:311–21. doi: 10.1007/s10549-022-06710-4

14. Palumbo R, Sottotetti F, Riccardi A, Teragni C, Pozzi E, Quaquarini E, et al. Which patients with metastatic breast cancer benefit from subsequent lines of treatment? An update for clinicians. *Ther Adv Med Oncol*. (2013) 5:334–50. doi: 10.1177/1758834013508197

15. Gion M, Trapani D, Cortés A, Valenza C, Lin N, Cortés J, et al. Systemic therapy for HER2-positive metastatic breast cancer: moving into a new era. *Am Soc Clin Oncol Educ Book*. (2022) 42:1–11. doi: 10.1200/EDBK_351222

16. Mercogliano MF, Bruni S, Mauro FL, Schillaci R. Emerging targeted therapies for HER2-positive breast cancer. *Cancers (Basel)*. (2023) 15:1987. doi: 10.3390/cancers15071987

17. Essadi I, Benbrahim Z, Kaakoua M, Reverdy T, Corbaux P, Freyer G. HER2-positive metastatic breast cancer: available treatments and current developments. *Cancers (Basel)*. (2023) 15:1738. doi: 10.3390/cancers15061738

18. Alasmari MM. A review of margetuximab-based therapies in patients with HER2-positive metastatic breast cancer. *Cancers (Basel)*. (2022) 15:38. doi: 10.3390/cancers15010038

19. Rugo HS, Im SA, Cardoso F, Cortés J, Curigliano G, Musolino A, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. (2021) 7:573–84. doi: 10.1001/jamaoncol.2020.7932

20. Rugo HS, Im SA, Cardoso F, Curigliano G, Musolino A, Pegram MD, et al. Margetuximab versus trastuzumab in patients with previously treated HER2-positive advanced breast cancer (SOPHIA): final overall survival results from a randomized phase 3 trial. *J Clin Oncol*. (2023) 41:198–205. doi: 10.1200/JCO.21.02937

21. Margetuximab. Prescribing information (2023). MacroGenics, Inc. Available online at: https://www.margenza.com/pdf/prescribing-information.pdf (Accessed June 26, 2023).

22. Clinical Trials.gov. MARGetuximab Or Trastuzumab (MARGOT) (2023). Available online at: https://clinicaltrials.gov/ct2/show/NCT04425018 (Accessed June 26, 2023).

23. Royce M, Osgood CL, Amatya AK, Fiero MH, Chang CJG, Ricks TK, et al. FDA approval summary: margetuximab plus chemotherapy for advanced or metastatic HER2-positive breast cancer. *Clin Cancer Res*. (2022) 28:1487–92. doi: 10.1158/1078-0432.CCR-21-3247

24. Guo Z, Ding Y, Wang M, Liu J, Zhai Q, Du Q. Safety of trastuzumab deruxtecan: a meta-analysis and pharmacovigilance study. *J Clin Pharm Ther*. (2022) 47:1837–44. doi: 10.1111/jcpt.13777

25. Rugo HS, Bianchini G, Cortes J, Henning JW, Untch M. Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer. *ESMO Open*. (2022) 7:100553. doi: 10.1016/j.esmoop.2022.100553

26. Lin NU, Borges V, Anders C, Murtha RK, Paplomata E, Hamilton E, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. (2020) 38:2610–9. doi: 10.1200/JCO.20.00775

27. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. (2020) 382:597–609. doi: 10.1056/NEJMoa1914609

28. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. (2012) 367:1783–91. doi: 10.1056/NEJMoa1209124

29. Perez EA, López-Vega JM, Petit T, Zamagni C, Easton V, Kamber J, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET cohort 1 final results. *Breast Cancer Res*. (2016) 18:126. doi: 10.1186/s13058-016-0773-6

30. Narayan P, Osgood CL, Singh H, Chiu H-J, Ricks TK, Chow ECY, et al. FDA approval summary: fam-trastuzumab deruxtecan-nxki for the treatment of unresectable or metastatic HER2-positive breast cancer. *Clin Cancer Res*. (2021) 27:4478–85. doi: 10.1158/1078-0432.CCR-20-4557

31. Arpino G, de la Haba Rodríguez J, Ferrero JM, De Placido S, Osborne CK, Klingbiel D, et al. Pertuzumab, trastuzumab, and an aromatase inhibitor for HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer: PERTAIN final analysis. *Clin Cancer Res*. (2023) 29:1468–76. doi: 10.1158/1078-0432.CCR-22-1092

32. Tamura K, Tsurutani J, Takahashi S, Iwata H, Krop IE, Redfern C, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol*. (2019) 20:816–26. doi: 10.1016/S1470-2045(19)30097-X

33. Jhaveri KL, Goldman JW, Hurvitz SA, Guerrero-Zotano A, Unni N, Brufsky A, et al. Neratinib plus fulvestrant plus trastzuzumab (N+F+T) for hormone receptor-positive (HR+), HER2-negative, HER2-mutant metastatic breast cancer (MBC): outcomes and biomarker analysis from the SUMMIT trial. *J Clin Oncol*. (2022) 40:1028. doi: 10.1200/JCO.2022.40.16_suppl.1028

34. Seah DSE, Luis IV, Macrae E, Sohl J, Litsas, Winer EP, et al. Use and duration of chemotherapy in patients with metastatic breast cancer according to tumor subtype and line of therapy. *J Natl Compr Cancer Netw*. (2014) 12:71–80. doi: 10.6004/jnccn.2014.0008

35. Collins J, Nordstrom B, Kwong J, Murphy B, Pavilack M. A real-world evidence study of treatment patterns among patients with HER2-positive metastatic breast cancer. *Cancer Res*. (2021) 81:PS7–82. doi: 10.1158/1538-7445.SABCS20-PS7-82

36. Tesch ME, Gelmon KA. Targeting HER2 in breast cancer: latest developments on treatment sequencing and the introduction of biosimilars. *Drugs*. (2020) 80:1811–30. doi: 10.1007/s40265-020-01411-y

37. Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med*. (2022) 386:1143–54. doi: 10.1056/NEJMoa2115022

38. Li J, Lu Q, Zhou H, Xu F, Huang J, Hong R, et al. Significant response to margetuximab in Chinese HER2-positive metastatic breast cancer patient who progressed after second-line targeted therapy. *Anticancer Drugs*. (2022) 34:892–95. doi: 10.1097/CAD.0000000000001471

39. Chang H, Hu T, Hu J, Ding T, Wang Q, Cheng J. Complete response in patient with liver metastasis of HER2-positive breast cancer following therapy with margetuximab: a case report. *Anticancer Drugs*. (2022) 34:883–7. doi: 10.1097/CAD.0000000000001466

40. Bang YJ, Giaccone G, Im SA, Oh DY, Bauer TM, Nordstrom JL, et al. First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors. *Ann Oncol*. (2017) 28:855–61. doi: 10.1093/annonc/mdx002

41. Perez-Garcia JM, Cortes J. The safety of eribulin for the treatment of metastatic breast cancer. *Expert Opin Drug Saf*. (2019) 18:347–55. doi: 10.1080/14740338.2019.1608946

42. Mailankody S, Prasad V. Overall survival in cancer drug trials as a new surrogate end point for overall survival in the real world. *JAMA Oncol*. (2017) 3:889–90. doi: 10.1001/jamaoncol.2016.5296

43. Nakayama T, Yoshinami T, Yasojima H, Kittaka N, Takahashi M, Ohtani S, et al. Real-world effectiveness of post-trastuzumab emtansine treatment in patients with HER2-positive, unresectable and/or metastatic breast cancer: a retrospective observational study (KBCSG-TR 1917). *BMC Cancer*. (2021) 21:795. doi: 10.1186/s12885-021-08504-1

44. Huang Bartlett C, Mardekian J, Cotter MJ, Huang X, Zhang Z, Parrinello CM, et al. Concordance of real-world versus conventional progression-free survival from a phase 3 trial of endocrine therapy as first-line treatment for metastatic breast cancer. *PloS One*. (2020) 15:e0227256. doi: 10.1371/journal.pone.0227256

45. Gidwani R, Franks JA, Enogela EM, Caston NE, Williams CP, Aswani MS, et al. Survival in the real world: A national analysis of patients treated for early-stage breast cancer. *JCO Oncol Pract*. (2022) 18:e235–49. doi: 10.1200/OP.21.00274

46. Bland KA, Mustafa R, McTaggart-Cowan H. Patient preferences in metastatic breast cancer care: A scoping review. *Cancers (Basel)*. (2023) 15:4331. doi: 10.3390/cancers15174331

47. Azoulay L. Rationale, strengths, and limitations of real-world evidence in oncology: A Canadian review and perspective. *Oncologist*. (2022) 27:e731–8. doi: 10.1093/oncolo/oyac114

48. Walker SG, Carr JE. Generality of findings from single-case designs: It's not all about the "*N. Behav Anal Pract*. (2021) 14:991–5. doi: 10.1007/s40617-020-00547-3

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 20 August 2024
DOI 10.3389/fonc.2024.1422800

OPEN ACCESS

EDITED BY
James Cheng-Chung Wei,
Chung Shan Medical University Hospital, Taiwan

REVIEWED BY
Suzana Ljubojevic Hadzavdic,
University Hospital Centre Zagreb, Croatia
Angelo Guttadauro,
University of Milano-Bicocca, Italy

*CORRESPONDENCE
Zhenhua Sun
bjxh100@163.com

†These authors have contributed equally to this work

RECEIVED 30 April 2024
ACCEPTED 30 July 2024
PUBLISHED 20 August 2024

CITATION
Wang C, Zhao Y, Sun Z and Li M (2024) Case report: A case of giant breast skin warts caused by HPV infection. *Front. Oncol.* 14:1422800. doi: 10.3389/fonc.2024.1422800

Case report: A case of giant breast skin warts caused by HPV infection

Chaohui Wang†, Yuyang Zhao†, Zhenhua Sun* and Mingjun Li

Department of Thyroid and Breast Surgery, Affiliated Hospital of Jiangsu University, Zhenjiang, China

GCA, also known as Buschke-Lowenstein tumor, is a rare sexually transmitted disease associated with HPV types 6 and 111. These warts are considered histologically benign, but there is a risk of localized invasion and development of malignancy. This malignant transformation occurs most often in the perianal and vulvar areas, and involvement of other sites is relatively rare2. In this case, we report a rare case of a giant wart originating from breast skin infected with HPV and progressing to cutaneous squamous cell carcinoma.

KEYWORDS

human papillomavirus (HPV), condyloma acuminatum (CA), Buschke-Lowenstein tumor, squamous cell carcinoma (SCC), skin tumor

Introduction

Giant condyloma acuminatum (GCA), also known as Buschke–Lowenstein tumor, is a rare sexually transmitted disease associated with HPV types 6 and 11 (1). These warts are considered histologically benign, but there is a risk of localized invasion and development of malignancy. This malignant transformation occurs most often in the perianal and vulvar areas, and involvement of other sites is relatively rare (2). In this case, we report a rare case of a giant wart originating from breast skin infected with HPV and progressing to cutaneous squamous cell carcinoma.

Case report

A 64-year-old male patient presented with a right breast lump that was first noticed 10 years ago and was not taken seriously by the patient at that time. The lump gradually increased, significantly accelerating growth over the past year. The patient denied other breast lumps and skin changes. The patient had no history of significant medical or surgical disease and denied history of unhealthy sexual activity, but had history of poor personal hygiene as a public bathroom worker and had no family history of similar disease.

During breast examination in the supine position, a large, hard, non-pressure mass was found in the patient's right breast, measuring about 72 mm × 80 mm × 48 mm, with a cauliflower-like appearance and localized ulceration accompanied by purulent secretion.

Bilateral breast ultrasonography and computed tomography (CT) of the chest and abdomen were performed. Ultrasonography showed an inhomogeneous hypoechoic mass in the right breast, accompanied by abundant blood flow signals (Figure 1). Chest CT examination showed a soft tissue mass of about 72 mm × 80 mm × 47 mm in size in the right breast area, with irregular morphology and cauliflower-like changes, which was connected with the nipple and showed noticeable uneven enhancement. The tissue behind the nipple was also thickened and strengthened (Figure 2). The remaining CT examinations of the abdomen and pelvis were negative. Tumor-associated antigen examination showed elevated carcinoembryonic antigen 11.78 ng/mL (standard reference value

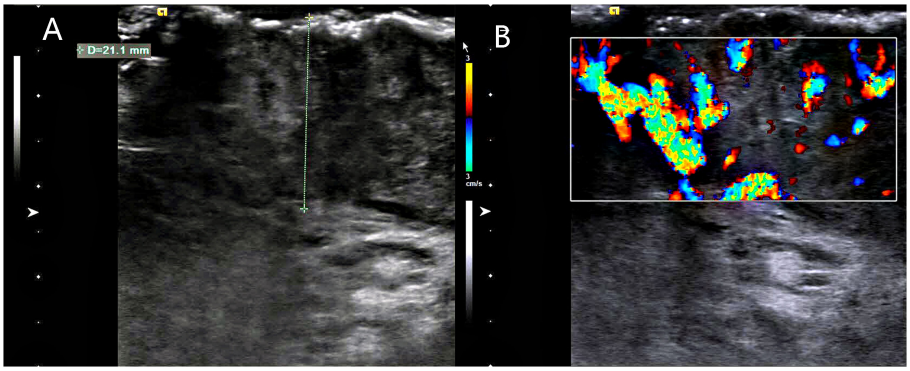


FIGURE 1
Breast ultrasonography. **(A)** A large mass was seen on the surface of the right chest wall, the thickest part of which was about 21.1mm, and the inner part of the mass was uneven and hypoechoic. **(B)** color Doppler flow imaging(CDFI): abundant blood flow signal is seen inside the mass.

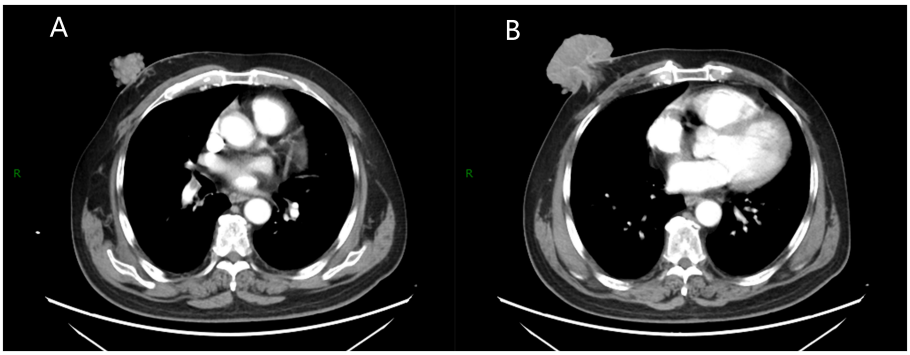


FIGURE 2
Chest enhanced scan. **(A)** A soft tissue mass with irregular shape and cauliflower-like changes was seen in the right breast area, which was connected with the nipple and showed obvious uneven enhancement. **(B)** The tissue behind the nipple shows thickening and strengthening.

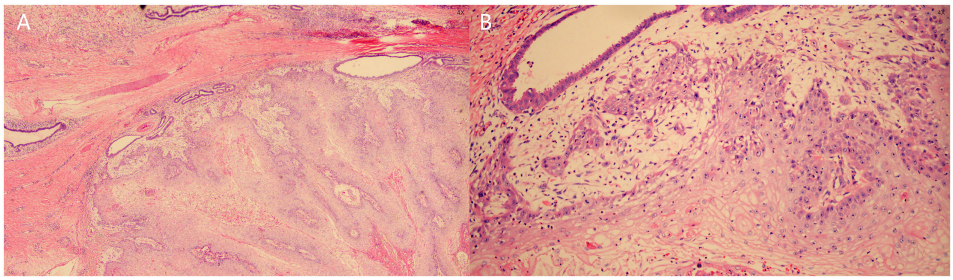


FIGURE 3
Histopathologic examination. **(A)** Papillary and pestle-and-ball heterogeneous hyperplasia of squamous epithelium with koilocyte formation, chronic suppurative inflammation in some areas, and hyperplasia and dilatation of mammary ducts. **(B)** Squamous epithelial verrucous and papillomatous hyperplasia with some areas of carcinoma, carcinoma areas of highly differentiated squamous cell carcinoma with superficial mesenchymal infiltration of skin and soft tissues.

<5 ng/mL) and squamous cell-associated antigen 6.79 ng/mL (standard reference value <2.5 ng/mL). The patient underwent a lumpectomy under general anesthesia. Intraoperative rapid cytopathological analysis showed abnormal squamous epithelial hyperplasia with scooped cell formation, chronic suppurative inflammation in some areas, and hyperplasia and dilatation of the mammary ducts. We decided that shuttle incision for the right breast be performed to enlarge the resection. Postoperative pathological analysis showed that the lesion tissue was consistent with squamous epithelial warts with squamous cell carcinoma (Figure 3). HPV DNA 11 positive was found in the wart specimen. The patient did not receive additional adjuvant therapy after the operation. At regular return visits for 2 years, the patient recovered well and did not see any tumor recurrence.

Discussion

Condyloma acuminatum (CA) is the most common of the sexually transmitted infections and is caused primarily by HPV infection. A small number of CA show papillary chronic hyperplasia and form giant warts known as Buschke–Lowenstein tumors. Despite the benign appearance of the tumor and the minimal degree of cellular proliferation, the tendency for highly differentiated carcinomas may result in downward compression and displacement of the tumor into deeper tissues rather than direct infiltration or metastasis (3). In 56% of patients with GCA, malignant changes may occur (2). This malignant change may be associated with persistent disease, prolonged chronic inflammatory stimulation, and repeated physical and pharmacologic treatments. In the case we report, it is unclear why this patient developed a large wart on his breast skin. We only know that as a public bathroom worker, this patient is at high risk for HPV infection. Why did the HPV infection lead to the development of a large wart rather than a condyloma acuminatum in the breast skin, and under what factors did the wart progress to SCC of the skin? In this process, host immunity, infected HPV types or variants may be involved in tumor formation and progression (4).

The diagnosis of GCA is mainly based on physical signs and pathological examination. It is necessary to differentiate tumors in the breast area from malignant tumors, and examining blood tumor antigens can help distinguish malignant tumors. CT and ultrasonography are also necessary to determine the involvement of organs and lymph nodes (5), and GCA treatment aims to remove the tumor, not to cure HPV. Although there are no standardized treatment guidelines for GCA, and there is insufficient evidence to show the effectiveness of medical treatments, such as interferon, radiotherapy, and chemotherapy (6), the treatment is based on localized surgical excision, which is ineffective in the treatment of extensive lesions and deep lesions combined with carcinoma and is very difficult to treat (7). The chances of efficacious treatment are limited and could be very tricky. In the case of affecting the whole breast, the psychological impact on the patient has to be considered. Still, the initial imaging suggests that the tumor has invaded the post-nipple tissue. We carefully chose to excise the tumor together with the mammary glands. The postoperative pathological results showed that the tumor did not invade the mammary tissue, and the surgical margins were all negative. For patients who develop SCC malignancy and metastasis, it is essential not to forget subsequent adjuvant therapy.

Conclusion

We reported GCA originating from the breast skin, demonstrating that breast GCA requiring surgical excision may harbor occult SCC. Pathologic examination is necessary to determine whether malignancy has occurred and whether it has invaded the breast. Follow-up with adjuvant therapy is important for patients who develop malignancy and metastasis of SCC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CW: Writing – original draft, Writing – review & editing. YZ: Writing – original draft, Writing – review & editing. ZS: Writing – review & editing. ML: Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Dorota P-B, Roman N, Herms F, Jean-Laurent C, Fouéré S, Vivien B. The pathogenesis of giant condyloma acuminatum (Buschke-lowenstein tumor): An overview. *Int J Mol Sci*. (2022). doi: 10.3390/ijms23094547

2. Mustafa A, Sami A, Adem T, Emrah S, Ertugrul K, Kemal Baris S. Squamous cell carcinoma arising from perianal buschke-lowenstein tumor (Giant condyloma acuminatum): Comprehensive literature review. *J Gastrointestinal Cancer*. (2021). doi: 10.1007/s12029-021-00713-y

3. Sheela K, Yogindher S, Manjiri P. Buschke–Lowenstein tumor: An intermediate between condyloma acuminata and verrucous carcinoma. *Indian J Sex Transm Dis AIDS*. (2022). doi: 10.4103/ijstd.ijstd_72_22

4. Abigail W, Chrysalyne DS. Cutaneous squamous cell carcinoma. *Hematol-Oncol Clin North Am*. (2019). doi: 10.1016/j.hoc.2018.08.001

5. Sheral SP, Esraa A-J, Brent K, Peeyush B. CT imaging of condyloma acuminata. *Radiol Case Rep*. (2023). doi: 10.1016/j.radcr.2023.05.076

6. Joško Z, Davor P, Samer E-S, Maja B, Hulina D, Zlatko H. A surgical approach to giant condyloma (Buschke-Löwenstein tumour) with underlying superficial vulvar carcinoma: A case report. *Oncol Lett*. (2012). doi: 10.3892/ol.2012.1027

7. Fawaz B, Vieira C, Decker A, Lawrence N. Surgical treatment of verrucous carcinoma: a review. *J Dermatolog Treat*. (2022) 33:1811–5. doi: 10.1080/09546634.2021.1914312

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 24 September 2024
DOI 10.3389/fonc.2024.1429326

OPEN ACCESS

EDITED BY
Elena Sperk,
University of Heidelberg, Germany

REVIEWED BY
Jayant Sharad Vaidya,
University College London, United Kingdom
Lixue Xuan,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

*CORRESPONDENCE
Sheldon Feldman
sfeldman@montefiore.org

RECEIVED 07 May 2024
ACCEPTED 02 September 2024
PUBLISHED 24 September 2024

CITATION
Bhimani F, McEvoy M, Chen Y, Gupta A, Pastoriza J, Fruchter S, Bitan ZC, Tomé WA, Mehta K, Fox J and Feldman S (2024) Case report: IORT as an alternative treatment option for breast cancer patients with difficulty staying still. *Front. Oncol.* 14:1429326. doi: 10.3389/fonc.2024.1429326

Case report: IORT as an alternative treatment option for breast cancer patients with difficulty staying still

Fardeen Bhimani[1], Maureen McEvoy[1], Yu Chen[1], Anjuli Gupta[1], Jessica Pastoriza[1], Shani Fruchter[1], Zachary C. Bitan[1], Wolfgang A. Tomé[2], Keyur Mehta[2], Jana Fox[2] and Sheldon Feldman[1]*

[1]Breast Surgery Division, Department of Surgery, Montefiore Medical Center, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY, United States, [2]Department of Radiation Oncology, Montefiore Medical Center, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY, United States

Background: Administering radiation therapy to individuals with intellectual disabilities (ID) and psychiatric patients taking antipsychotics poses challenges, especially with whole breast irradiation (WBI) due to difficulty staying still (DSS). In such scenarios, intraoperative radiotherapy (TARGIT-IORT) provides an alternative. Although prior studies have shown its applicability in special cases where WBI may be contraindicated, there is a paucity of literature emphasizing its role in patients with ID and psychiatric conditions who have DSS. Therefore, our case series aims to highlight the applicability of administering TARGIT-IORT in such patients.

Case reports: Four breast cancer patients underwent lumpectomy and TARGIT-IORT. Among them, two patients had ID, with one experiencing a decreased range of motion. The other two had psychiatric disorders, including schizophrenia and bipolar disorder, both manifesting involuntary movements and DSS. Three patients had invasive ductal carcinoma (IDC), and one had invasive lobular carcinoma (ILC). All patients undergoing TARGIT-IORT tolerated the procedure well. Notably, none of the patients exhibited evidence of disease on follow-up.

Conclusion: Our study underscores the potential use of TARGIT-IORT as a viable treatment option for breast cancer patients with intellectual and psychiatric disabilities. Unlike traditional EBRT, TARGIT-IORT offers a single radiation dose, addressing challenges associated with compliance or DSS. Our findings demonstrate positive outcomes and tolerance, especially in patients where standard oncologic procedures are difficult to achieve. TARGIT-IORT could also benefit breast cancer patients with concurrent movement disorders like Parkinson's disease and other movement disorders. Nonetheless, future studies are needed to reinforce its applicability for patients with DSS.

KEYWORDS

breast cancer, intraoperative radiotherapy, TARGIT, IORT, intellectual disability, schizophrenia, bipolar disorder, psychiatric disorders

Introduction

Breast cancer is the most common newly diagnosed malignancy among women across the United States (1). Of all the cancers diagnosed in women, breast cancer accounts for about 30% of the cases (2). It was estimated that approximately 310,720 women will be diagnosed with breast cancer in 2024 (3). Historically, mastectomy was considered the sole treatment option, even for early-stage breast cancer. However, numerous studies have indicated that adopting a more conservative surgical approach together with adjuvant radiation for small breast cancers can yield comparable long-term outcomes in locoregional recurrence and survival. This shift has led to a transition from mastectomy to breast-conserving surgery (BCS) involving quadrantectomy and, eventually, lumpectomy for early breast cancer (4–6). Similarly, a change in preference has also been seen in selected patients undergoing radiation therapy, with patients receiving partial breast irradiation (PBI) delivered over 1-3 weeks instead of the traditional whole-breast irradiation (WBI). Another option is intraoperative radiotherapy (TARGIT-IORT), which allows for a single dose to be given at the time of lumpectomy. The appeal of TARGIT-IORT lies in its intrinsic advantages of tissue preservation, as well as convenience, making it a popular choice among patients (7–10).

The administration of daily external beam radiation requires patients to lie flat and still, and to abduct the ipsilateral arm above the level of the shoulder. This can be a significant challenge for patients with intellectual disability (ID) and psychiatric disorders (11, 12). Individuals with ID often find it difficult to remain still, and psychiatric patients on antipsychotics may experience bradykinesia, akathisia, and tardive dyskinesia (13). This can make radiation treatments potentially unsafe or even impossible, and thus poses a potential contraindication for radiation in patients with difficulty staying still (DSS). While the occurrence of breast cancer among women with ID is comparable to that in the general population (14–16), studies have revealed a significantly increased risk of overall and breast cancer-specific mortality in this group (17, 18). Similarly, psychiatric patients have a similar incidence of breast cancer as the general population but face higher mortality rates (19). The rising incidence of breast cancer, coupled with a growing population of individuals diagnosed with ID (14, 20–22) as well as those with psychiatric disorders who frequently experience delayed diagnoses of breast cancer (23, 24), may present a potential threat to overall breast cancer survival rates. In such scenarios for patients with DSS, TARGIT-IORT presents itself as an attractive radiation alternative that allows for a single dose to be administered at the time of BCS. Prior studies have documented that TARGIT-IORT can be highly advantageous in specific scenarios, such as for patients with prior breast cancer seeking a second chance at breast conservation, those with movement disorders like Huntington's or Parkinson's, multiple sclerosis, wheelchair-bound, autism, or other patients with DSS, those struggling with radiation cycle compliance, or individuals who have previously received mantle radiation (25–29). In our study, we defined DSS as any patient with neurological, psychiatric, and/or developmental problems resulting in movement disorder, thereby impeding their capacity to undergo external beam radiation (EBRT). Although prior studies have shown TARGIT-IORT's applicability in special clinical cases selected as per the ASTRO criteria where WBI might be contraindicated (30–33), there is a paucity of literature examining the role of TARGIT-IORT in patients with ID and psychiatric illness with DSS. Thus, our case series aims to highlight the applicability of administering TARGIT-IORT in such patients.

Case reports

Patient 1

A 66-year-old woman with severe developmental delay and behavioral disorder, who is non-verbal and unable to perform range of motion due to cognitive limitations, underwent a routine bilateral screening mammogram and ultrasound in 2014, which revealed a 1.3 cm mass in the 2:00 axis in the left breast and a 0.3 cm simple cyst in the right 7:00 axis. A follow-up mammogram revealed a 2 cm mass in the left lateral breast, and the ultrasound showed a 1.7 x 1.3 x 1.5 cm mass at the left 1:00, 4 cm from the nipple. From 2014 to 2018, successive annual ultrasounds documented a reduction in the size of the left breast mass, progressively diminishing from 1.8 cm to 1.2 cm to 0.7 cm to 0.4 cm, eventually disappearing completely. However, a follow-up ultrasound in 2019 detected a new 0.8 cm mass in the right breast at the 1:00 axis. The patient was unable to cooperate with an ultrasound-guided biopsy for a suspicious lesion in the right breast. Given her condition, she was deemed unfit for surgery and advised to undergo regular follow-up ultrasounds. A targeted ultrasound performed 9 months later demonstrated the right breast mass increased to approximately 1.1 to 1.5 cm from its previous size. Left breast ultrasound showed no mass, which was previously present. A biopsy of the right breast was eventually performed in the clinic, and it revealed grade 3 poorly differentiated invasive ductal carcinoma (IDC). The tumor was diagnosed as clinical stage IA T1 N0 M0, and tumor markers were ER-positive, PR-positive, and Her-2 positive by FISH (signal ratio of 2.11 and a copy number of 7.0.) The patient's case was discussed in the Multidisciplinary Tumor Board (MTB), and it was collectively decided to offer neoadjuvant treatment. Following this, she started a combination of subcutaneous pertuzumab/trastuzumab/hyaluronidase. Upon completion of this course, she was started on exemestane. The patient's case was again discussed in MTB, and it was collectively decided to treat her with curative intent and offer her lumpectomy with sentinel lymph node biopsy and TARGIT-IORT.

Wide local excision was performed, and the Intrabeam 600 system (Zeiss, Oberkochen, Germany) (Figure 1) delivered IORT sequentially. A 35-mm spherical applicator delivered 20 Gy to the surgical margin for 17 minutes. Intraoperative ultrasound determined that the applicator's closest margin to the skin was approximately 1.3 cm, and the absorbed dose from TARGIT-IORT radiation on the skin's surface was 1.96 Gy.

TARGIT-IORT and surgery were uneventful. The histology of the right breast revealed pathological stage IIA T2 N0 grade 3 IDC spanning 4.5cm x 3cm. The tumor was fully removed with clear

FIGURE 1
Dressed Intrabeam 600 miniaturized 50 KV X-Ray linear accelerator with 40 mm applicator mounted (Zeiss, Oberkochen, Germany).

margins. The tumor was ER/PR-positive but Her-2 negative. Adjuvant treatment with T-DM1 and radiation therapy would have been ideal, but due to the patient's severe developmental delay, she couldn't undergo infusions or daily radiation treatments. Therefore, it was determined that the aromatase inhibitor (A.I.), along with subcutaneous pertuzumab/trastuzumab/hyaluronidase, would be used for her adjuvant treatment. This treatment regimen has been ongoing for 10 months, and she is currently showing no evidence of disease during follow-up assessments (Table 1).

Patient 2

A 47-year-old female with intellectual disability presented after a diagnostic mammogram. She was unable to provide any history. However, her proxy mentioned that her mother had also been diagnosed with intellectual disability. Her ultrasound finding demonstrated left 11:00-12:00 o'clock 6 cm from the nipple a hypoechoic mass with irregular margins measuring 1.8 x 1.6 x 2.1 cm. Her right breast subareolar region showed a large, predominantly hypoechoic mass with mild lobulations measuring over 6 cm. An ultrasound-guided biopsy of the left breast revealed grade 2 moderately differentiated IDC. The tumor was diagnosed as clinical stage IA T1 N0 M0, and tumor markers were ER +, PR +, and Her-2 negative. Right breast biopsy revealed a fragmented fibroepithelial lesion, but the size of the lesion made phyllodes a differential. Her case was discussed at the MTB, and it was collectively decided to offer her a bilateral lumpectomy with left SLNB and left-sided TARGIT-IORT.

Wide local excision was performed on each breast, and TARGIT-IORT was delivered to the left breast using a 35-mm diameter spherical applicator, delivering a dose of 20 Gy for 20 minutes. The measured absorbed dose from the Intrabeam TARGIT-IORT system radiation on the skin surface was 1.01 Gy for the left breast.

The surgery and TARGIT-IORT were both uneventful. Histology of the left breast confirmed the presence of IDC measuring 2.5 cm with DCIS grade 3, ER/PR+, Her 2-, stage IIA T2 N0 M0. The tumor was fully removed with clear margins. The right breast was diagnosed as a benign phyllodes tumor spanning 7.4 cm with focal atypical lobular hyperplasia. The patient is 4 months postoperative and shows no signs of disease on follow-up; she is receiving tamoxifen as adjuvant therapy.

Patient 3

A 70-year-old female with a history of schizophrenia managed with antipsychotic medication and subsequent tardive dyskinesia presented with a 7-month history of breast pain and a mass in her left breast. Subsequent mammography and ultrasound revealed a 2.2 x 1.1 x 1.5 cm mass at the left 8:00 axis, 3 cm from the nipple. Ultrasound-guided biopsy confirmed clinical stage IIA T2 N0 M0 left IDC, moderately differentiated, ER+, PR+, and Her-2 positive at the 8:00 axis. Surgical options were discussed, and she expressed a preference for lumpectomy. However, her tardive dyskinesia made her ineligible for external beam radiation.

The case was reviewed at the MTB, and it was decided collectively to offer her neoadjuvant treatment with Paclitaxel/Herceptin/Pertuzumab followed by lumpectomy and SLNB along with TARGIT-IORT.

Subsequently, wide local excision was performed, and TARGIT-IORT was delivered using a 35-mm diameter spherical applicator, delivering a dose of 20 Gy for 20 minutes. Intraoperative ultrasound determined that the closest margin of the applicator to the skin was approximately 11.2 mm, and the dose absorbed from TARGIT-IORT radiation on the skin surface was 2.67 Gy.

The surgery and TARGIT-IORT were uneventful. Histology of the left breast demonstrated a few foci of grade-3 DCIS with no residual invasive carcinoma following neoadjuvant chemotherapy. The span of DCIS could not be determined since there were only a few scattered foci. The tumor was stage 0 Tis N0 M0 with clear margins. Adjuvant treatment with Trastuzumab and an A.I. was initiated, and the patient showed no signs of disease on their 3-month postoperative follow-up.

TABLE 1 Summary of patient data.

Patient	Age (Years)	Final Pathology	Pathological Size (mm)	Size of the Tumor Resected (cm)	Applicator Size (mm)	Laterality	Complications	Adjuvant Therapy
1	66	IDC	45	3.1 x 5.2 x 4.5	30	Right	Development Delay + Behavioral Disorder	Aromatase Inhibitor + Pertuzumab/ Trastuzumab/ Hyaluronidase
2	47	IDC + DCIS	25	5 x 5 x 2.4	35	Left	Intellectual Disability	Tamoxifen
3	70	DCIS	NA*	1.5 x 5 x 5.5	35	Left	Tardive dyskinesia	Aromatase Inhibitor + Trastuzumab
4	59	ILC	15	3.3 x 3 x 0.7	40	Right	Traumatic Brain Injury (TBI)	Aromatase Inhibitor

*No residual invasive carcinoma. Span could not be determined due to a few scattered foci.

Patient 4

A 59-year-old female, an active smoker with a PMHx of traumatic brain injury (TBI), bipolar disease, depression, anxiety, COPD, and asthma, presented after an abnormal screening mammogram of the right breast. A subsequent diagnostic mammogram demonstrated a questioned mass in the right breast with indistinct margins, and due to the patient's inability to tolerate further mammographic imaging, a targeted ultrasound was performed, identifying a mixed echotexture mass located at the11:00 o'clock axis 10 cm from the nipple. The biopsy of the right breast revealed invasive lobular carcinoma (ILC) ER+, PR negative, and Her-2 negative with clinical stage IA T1 N0 M0. Her PMHx of TBI resulted from a possible stroke that occurred 15 years ago secondary to a drug overdose, which resulted in involuntary movements and muscle stiffness along with a broad-based gait and increased lower extremity movements.

The case was reviewed at the MTB, and it was decided collectively to offer her lumpectomy with TARGIT-IORT. Wide local excision with right-sided TARGIT-IORT and SLNB was performed. A 40-mm applicator delivered 20 Gy in 25 minutes. Both surgery and TARGIT-IORT were uneventful. Intraoperative ultrasound determined that the closest margin of the applicator to the skin was approximately 8.5 mm, and the absorbed dose from TARGIT-IORT radiation on the skin's surface was 4.28 Gy (Table 2). Histology of the right breast revealed grade 2 ILC forming a 1.5 cm mass. The tumor was stage IA T1 N0 M0, ER+, PR negative, and Her-2 negative and had clear margins. Adjuvant treatment with an A.I. was initiated, and she currently has no evidence of disease on her 6-month follow-up.

TABLE 2 Dose reported is for the closest skin bridge measurement (applicator to skin distance) as determined using ultrasound measurements localization measuring the 4 cardinal positions of superior, medial, inferior, lateral and has been determined using the validated model presented in Brodin et al. (82) The 95% confidence interval is shown in parentheses.

Patient	Treatment Time (min:sec)	Right Breast Closest Skin bridge distance (mm)	Dose to Skin Breast (Gy)
Patient 1	16:40	13.2	1.96 (1.73-2.24)
Patient 2	19:40	19.4	1.01 (0.93-1.12)
Patient 3	19:56	11.2	2.67 (2.36-3.03)
Patient 4	24:41	8.5	4.28 (3.85-4.77)

Discussion

An intellectual disability is characterized by restrictions in intellectual functioning and adaptive behavior, encompassing practical, social, and conceptual skills. It typically manifests before the age of 22 years (34) with an Intelligence Quotient or IQ of at least 2 standard deviations below the mean (35). While the occurrence of breast cancer among women with ID is comparable to that in the general population (14–16), studies have revealed a significantly increased risk of overall and breast cancer-specific mortality in this group (17, 18). Furthermore, there is growing evidence suggesting that women with ID are more prone to a higher prevalence of risk factors associated with breast cancer, which places them at an increased risk of developing breast cancer when compared to their counterparts in the general population (36–38). These risk factors include nulliparity, inadequate physical activity, and elevated rates of obesity (36, 37, 39–42). Additionally, women with an ID exhibit limited knowledge regarding breast awareness and breast cancer (15), consequently resulting in late-stage presentation and poorer clinical outcomes. Similarly, psychiatric patients have breast cancer incidence that mirrors the general population but face higher mortality rates (19). Some of the contributing factors for higher mortality are that psychiatric patients have fewer breast cancer surgeries, receive less radiation therapy, and have more metastases at presentation than the general population (19). Additionally, psychiatric patients are impacted by nulliparity, obesity, and exposure to antipsychotics, which further elevates their risk of developing breast cancer (43–45). Multiple studies have shown that individuals with pre-existing disabilities are

more likely to receive a mastectomy and less likely to receive chemotherapy and radiation therapy (46–49).

Amongst patients with ID and psychiatric illnesses, EBRT may not be feasible due difficulty staying still (DSS) during treatment. This could potentially result in either inadequate treatment or necessitate a more aggressive approach such as mastectomy. A major challenge in administering EBRT are patients who have DSS. Prior literature has demonstrated that performing EBRT can be challenging when patients can't lie flat or appropriately abduct the arm (11, 12). In our study, each of the four patients faced obstacles that would have hindered their capacity to endure EBRT, stemming from physical discomfort or movement disorders that compromised their ability to remain still. In our case series, Patient 1 experienced challenges with arm abduction due to limited range of motion and could not even tolerate her biopsy procedure. Although Patient 2 was responsive to simple commands, there was uncertainty about her capacity to withstand EBRT. Conversely, Patients 3 and 4 exhibited movement disorders that rendered them unsuitable candidates for EBRT. Additionally, performing EBRT might have precluded the safe and/or consistent administration of radiation therapy in these patients. A study conducted by Sreeraman et al. (50) found that patients with pre-existing psychiatric conditions who were treated with radiation for head and neck cancer had a higher rate of treatment breaks than patients with no psychiatric history. Apart from this, healthcare providers may lean towards recommending radical surgical interventions for psychiatric patients due to issues related to patient cooperation (49). A study conducted by Abdullah et al. (51) found that patients with schizophrenia exhibited verbal or physical aggression toward their healthcare providers before radiation therapy was offered. Additionally, the overall financial burden in patients with pre-existing psychiatric illnesses undergoing EBRT is higher compared to non-psychiatric patients. Waddle et al. (52) conducted a study to assess the expenses associated with acute and follow-up care in psychiatric patients receiving radiation treatment. Their findings revealed that acute costs were significantly higher in the psychiatric group, with a difference of $3389 (95% confidence interval [CI] for difference, –$1993 to $8771; $45,293 vs $41,904; P = .039) (52). Moreover, follow-up costs were notably elevated in the psychiatric group, demonstrating a difference of $9653 (95% CI for difference, $1,642-$17,664; $28,084 vs $18,431; P = .003) (52).

To bridge some of these concerns, TARGIT-IORT can be a prudent option for patients where EBRT may not be feasible. TARGIT-IORT is a type of accelerated partial breast irradiation (APBI) that enables the delivery of a single high dose of radiation directly to the surgical margins shortly after tumor removal. It utilizes low-energy 50kVp photons to minimize scatter and radiation exposure to neighboring critical organs due to the steep dose fall-off past the applicator surface. For example, using a 30-mm applicator, the dose decreases by 49% at a distance of 5 mm from the applicator surface and by 28% at a distance of 10 mm (8, 53, 54). The advantage of utilizing TARGIT-IORT is that it allows for a single dose to be administered at the time of lumpectomy, which can be extremely beneficial for patients who can't tolerate EBRT and/or have DSS. Patients who struggle with compliance and fail to complete their radiation treatment may otherwise be better suited for mastectomy (55). TARGIT-IORT offers these patients an alternative to mastectomy, thereby mitigating the increased morbidity and potential complications associated with this larger surgery. Furthermore, a major concern with administering EBRT is patients with DSS. A study by Kim et al. (26) highlighted the use of adjuvant radiation therapy in a patient with Huntington disease with choreiform movements. Their challenge was to control these choreiform movements sufficiently enough to provide EBRT, which they achieved with olanzapine; however, this led to treatment delay. Conversely, TARGIT-IORT, performed under anesthesia, circumvents issues related to involuntary movements, making it a preferable option and avoiding the additional steps and risks associated with the management of movement disorder during EBRT and further treatment delays.

In addition to these special considerations, the utilization of TARGIT-IORT provides further benefits compared to EBRT. The use of WBI has been associated with various adverse effects, notably increased non-breast cancer-related mortality (56). WBI also increases the risk of secondary cancers and heart disease (57–59). In a study involving 134 breast cancer patients, 90 of whom underwent WBI, the rate ratio for lung cancer incidence over ≥ 10 years was 2.10 (95% CI, 1.48 to 2.98; P = 0.001) (57). Additionally, WBI has been linked to various heart diseases, including ischemic heart disease, myocardial infarction, valvular disease, coronary stenosis, pericarditis, and other cardiac abnormalities (57–59). WBI can also exacerbate cosmetic outcomes due to skin toxicity and fibrosis, especially when boosting the tumor bed (60). In contrast, TARGIT-IORT significantly reduces the non-breast cancer-related mortality rate (45 vs. 74 events for TARGIT-IORT and EBRT, respectively; hazard ratio 0.59; 95% CI, 0.40 to 0.86; P=0.005), including cardiovascular causes (56). Additionally, a randomized trial involving 2,298 patients conducted by the TARGIT group found that IORT was non-inferior to EBRT, with local recurrence rates of 2.11% for IORT compared to 0.95% for EBRT (56). Moreover, the same group analyzed long-term outcomes in these patients, assessing tumor size, grade, receptor status, and lymph node status that affected local recurrence-free survival, as well as the impact of local recurrence on distant relapse and mortality (61). They observed no difference in 5-year local recurrence-free survival between TARGIT-IORT and EBRT across all tumor subgroups. An additional benefit of TARGIT-IORT is that it may reduce the risk of secondary lung cancers, which are commonly associated with smokers undergoing EBRT (62). Notably, neither Patient 3 nor Patient 4 in our study, whether former or active smokers, experienced complications during their respective follow-up periods. The TARGIT-A trial randomized 3451 patients to WBI (1730) or TARGIT-IORT (1721) to analyze toxicities and complications. Wound-related complications were similar between the two groups, but TARGIT-IORT had significantly fewer grade 3 or 4 toxicities and better cosmesis than WBI (63, 64). TARGIT-IORT has also been

shown to yield better breast-related quality of life and overall quality of life (65, 66). Moreover, because of its shorter treatment duration and fewer visits, TARGIT-IORT may result in higher patient compliance, potentially improving the overall patient experience (67). This is of particular significance for individuals with ID residing in nursing homes, who may otherwise require frequent visits to complete their radiation cycles, as well as for psychiatric patients who may be prone to noncompliance with their radiation treatments. Thus, TARGIT-IORT becomes a more feasible alternative for these patients.

When administering radiation therapy, another crucial factor to consider is pain, particularly in patients with ID. There is a paucity of research on pain in individuals with ID, possibly because they are routinely excluded from pain studies. This exclusion could be attributed to the numerous functional limitations and underlying neurological conditions, which often complicate pain presentation and measurement (68). Additionally, long-standing beliefs about pain insensitivity or indifference in ID patients may further contribute to this gap in research (69). However, emerging evidence suggests that individuals with ID may be more sensitive to painful stimuli under certain circumstances, contrary to previous beliefs (70, 71). They may exhibit greater pain-evoked potentials (72–74) and are more likely to experience chronic pain compared to typically developing peers (75). Estimates indicate that chronic pain prevalence in ID averages around 70%, considerably higher than the general population (76, 77). Upon comparing TARGIT-IORT vs. EBRT in terms of pain, Andersen et al. (78) conducted a study revealing that persistent pain in the breast area, side of the chest, axilla, or arm after EBRT was reported in 33.9% of cases, compared to 24.6% in the TARGIT-IORT group (P = 0.11). Similarly, Corcia et al. and Welzel et al. found that EBRT patients experienced moderately higher levels of breast and arm pain compared to TARGIT-IORT. This finding is particularly relevant for Patients 1 and 2 in our study, who both had ID and were non-verbal. Receiving EBRT may have resulted in higher levels of persistent pain for them, which they would been unable to express. Additionally, elderly patients, including Patients 1 and 3 in our study, might have potentially benefited from surgery and endocrine therapy alone, avoiding radiation treatment altogether (79). However, the decision to administer radiotherapy to these patients was influenced by the findings of the Cancer and Leukemia Group B (CALGB) 9343 trial, which demonstrated that combining radiation therapy with endocrine therapy improved locoregional recurrence prevention in women aged 70 and above (80). Moreover, the PRIME II study, a randomized trial involving 1,326 patients with non-metastatic hormone receptor-positive breast cancer, all aged 65 and older, who underwent breast-conserving surgery and were receiving adjuvant hormone therapy, found a significantly higher rate of local recurrence after 10 years in patients who did not receive radiation therapy compared to those who did (9.8% vs. 0.9%) (81), thereby supporting our decision to include radiotherapy in our patient's treatment plan. Furthermore, it is noteworthy that none of the 4 patients experienced any acute or chronic toxicities following breast-conserving surgery and TARGIT-IORT. In addition, all of the patients in our study tolerated the TARGIT-IORT well and developed no local recurrence on follow-up. Notably, all four individuals received outpatient treatment, avoiding potential complications associated with hospitalization. As the number of breast cancer cases increases, there may be a higher probability of encountering patients with DSS; thus, future studies are required to further evaluate the utility of TARGIT-IORT vs. WBI for patients with DSS in order to establish new guidelines.

Our study has several limitations. First, our study has a small sample size. Second, the retrospective nature of the study introduces inherent limitations. Third, our study had a short follow-up period. Finally, our study lacked measurement of pain scale, a cosmesis scale, and patient-reported outcomes, which could have provided a more comprehensive understanding of the treatment effects in this specific group of patients.

Conclusion

Our study underscores the potential use of TARGIT-IORT as a viable treatment option for breast cancer patients with intellectual and psychiatric disabilities. Unlike traditional EBRT, TARGIT-IORT offers a single radiation dose, addressing challenges associated with compliance or DSS. Our findings demonstrate positive outcomes and tolerance, especially in patients where standard oncologic procedures are difficult to achieve. TARGIT-IORT could also benefit breast cancer patients with concurrent movement disorders like Parkinson's disease and other movement disorders. Nonetheless, future studies are needed to reinforce its applicability for patients with DSS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The requirement of ethical approval was waived by Albert Einstein College of Medicine/Montefiore Einstein Comprehensive Cancer Center - Office of Human Research Affairs for the studies involving humans. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. MM: Conceptualization, Investigation, Supervision, Visualization, Writing – original draft, Writing – review & editing. YC: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. AG: Conceptualization, Supervision, Visualization, Writing – original draft, Writing – review & editing. JP: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. SNF: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. ZB: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. WT: Data curation, Investigation, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. KM: Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. JF: Conceptualization, Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. SDF: Conceptualization, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. American Cancer Society. *Cancer Facts & Figures 2021*. Atlanta: American Cancer Society (2021). Available at: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2021.html.

2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. (2022) 72:7–33. doi: 10.3322/caac.21708

3. American Cancer Society. Cancer facts and figures 2024 (2024). Available online at: https://www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html#:~:text=The%20American%20Cancer%20Society's%20estimates,will%20die%20from%20breast%20cancer.

4. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. (2002) 347:1233–41. doi: 10.1056/NEJMoa022152

5. Christiansen P, Carstensen SL, Ejlertsen B, Kroman N, Offersen B, Bodilsen A, et al. Breast conserving surgery versus mastectomy: overall and relative survival-a population based study by the Danish Breast Cancer Cooperative Group (DBCG). *Acta Oncol*. (2018) 57:19–25. doi: 10.1080/0284186X.2017.1403042

6. Blichert-Toft M, Nielsen M, Düring M, Møller S, Rank F, Overgaard M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol*. (2008) 47:672–81. doi: 10.1080/02841860801971439

7. Skandarajah AR, Lynch AC, Mackay JR, Ngan S, Heriot AG. The role of intraoperative radiotherapy in solid tumors. *Ann Surg Oncol*. (2009) 16:735–44. doi: 10.1245/s10434-008-0287-2

8. Vaidya JS, Tobias JS, Baum M, Keshtgar M, Joseph D, Wenz F, et al. Intraoperative radiotherapy for breast cancer. *Lancet Oncol*. (2004) 5:165–73. doi: 10.1016/S1470-2045(04)01412-3

9. Alvarado MD, Conolly J, Park C, Sakata T, Mohan AJ, Harrison BL, et al. Patient preferences regarding intraoperative versus external beam radiotherapy following breast-conserving surgery. *Breast Cancer Res Treat*. (2014) 143:135–40. doi: 10.1007/s10549-013-2782-9

10. Tang A, Cohan CM, Beattie G, Cureton EL, Svahn JD, Lyon LL, et al. Patients older 65 years with early breast cancer prefer intraoperative radiation as a locoregional treatment choice. *Ann Surg Oncol*. (2021) 28:5158–63. doi: 10.1245/s10434-021-09618-3

11. Breast radiotherapy after breast-conserving surgery. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Canadian Association of Radiation Oncologists. *CMAJ*. (1998) 158 Suppl 3:S35–42.

12. Levitt SH, Khan FM, Potish RA. Levitt and Tapley's technological basis of radiation therapy: practical clinical applications. (No Title). (1992).

13. Mathews M, Gratz S, Adetunji B, George V, Basil B. Antipsychotic-induced movement disorders: evaluation and treatment. *Psychiatry (Edgmont)*. (2005) 2:36–41.

14. Reidy M, Denieffe S, Foran S. Cancer screening in women with intellectual disabilities: an Irish perspective. *J Intellectual Disabilities*. (2014) 18:51–60. doi: 10.1177/1744629514521067

15. Truesdale-Kennedy M, Taggart L, McIlfatrick S. Breast cancer knowledge among women with intellectual disabilities and their experiences of receiving breast mammography. *J Adv Nurs*. (2011) 67:1294–304. doi: 10.1111/j.1365-2648.2010.05595.x

16. Wilkinson JE, Cerreto MC. Primary care for women with intellectual disabilities. *J Am Board Fam Med*. (2008) 21:215–22. doi: 10.3122/jabfm.2008.03.070197

17. Cuypers M, Schalk BWM, Boonman AJN, Naaldenberg J, Leusink GL. Cancer-related mortality among people with intellectual disabilities: A nationwide population-based cohort study. *Cancer*. (2022) 128:1267–74. doi: 10.1002/cncr.v128.6

18. Hirvikoski T, Boman M, Tideman M, Lichtenstein P, Butwicka A. Association of intellectual disability with all-cause and cause-specific mortality in Sweden. *JAMA Netw Open*. (2021) 4:e2113014. doi: 10.1001/jamanetworkopen.2021.13014

19. Kisely S, Crowe E, Lawrence D. Cancer-related mortality in people with mental illness. *JAMA Psychiatry*. (2013) 70:209–17. doi: 10.1001/jamapsychiatry.2013.278

20. Collins K, McClimens A, Mekonnen S, Wyld L. Breast cancer information and support needs for women with intellectual disabilities: a scoping study. *Psychooncology*. (2014) 23:892–7. doi: 10.1002/pon.v23.8

21. Hanna LM, Taggart L, Cousins W. Cancer prevention and health promotion for people with intellectual disabilities: an exploratory study of staff knowledge. *J Intellect Disabil Res*. (2011) 55:281–91. doi: 10.1111/j.1365-2788.2010.01357.x

22. Satgé D, Sauleau EA, Jacot W, Raffi F, Azéma B, Bouyat JC, et al. Age and stage at diagnosis: a hospital series of 11 women with intellectual disability and breast carcinoma. *BMC Cancer*. (2014) 14:150. doi: 10.1186/1471-2407-14-150

23. Desai MM, Bruce ML, Kasl SV. The effects of major depression and phobia on stage at diagnosis of breast cancer. *Int J Psychiatry Med*. (1999) 29:29–45. doi: 10.2190/0C63-U15V-5NUR-TVXE

24. Bhattacharya M, Parsons H, Call K, Blaes A, McAlpine D. Impact of a pre-existing diagnosis of mental illness on stage of breast cancer diagnosis among older women. *Breast Cancer Res Treat*. (2023) 197:201–10. doi: 10.1007/s10549-022-06793-z

25. Thangarajah F, Heilmann J, Malter W, Kunze S, Marnitz S, Mallmann P, et al. Breast conserving surgery in combination with intraoperative radiotherapy after previous external beam therapy: an option to avoid mastectomy. *Breast Cancer Res Treat*. (2018) 168:739–44. doi: 10.1007/s10549-017-4657-y

26. Kim JN, Meyer J, Kwon Y, Yung R, Lin Y, Flanagan M. Breast cancer therapy and huntington disease: A case report. *Adv Radiat Oncol*. (2022) 7:101025. doi: 10.1016/j.adro.2022.101025

27. Silverstein MJ, Kim B, Lloyd S, Chen P, Lin K. ASO author reflections: intraoperative radiation therapy (IORT): will it survive in the USA? *Ann Surg Oncol*. (2023) 30:6090–2. doi: 10.1245/s10434-023-13982-7

28. Keshtgar M, Tobias JS, Vaidya JS, Williams N, Stacey C, Metaxas M, et al. Breast cancer patients treated with intra-operative radiotherapy [IORT] alone when conventional external beam radiation therapy [EBRT] was not possible. *J Clin Oncol*. (2008) 26:11517–. doi: 10.1200/jco.2008.26.15_suppl.11517

29. Boehm KM, Chen J, Trichter S, Abdallah H, Zhuo R, Nowak EJ, et al. Characterization of recurrences following second breast-conserving surgery with intraoperative radiotherapy. *Ann Surg Oncol*. (2020) 27:1638–44. doi: 10.1245/s10434-019-07908-5

30. Keshtgar MR, Vaidya JS, Tobias JS, Wenz F, Joseph D, Stacey C, et al. Targeted intraoperative radiotherapy for breast cancer in patients in whom external beam radiation is not possible. *Int J Radiat Oncol Biol Phys*. (2011) 80:31–8. doi: 10.1016/j.ijrobp.2010.01.045

31. Keshtgar MR, Eaton DJ, Reynolds C, Pigott K, Davidson T, Gauter-Fleckenstein B, et al. Pacemaker and radiotherapy in breast cancer: is targeted intraoperative radiotherapy the answer in this setting? *Radiat Oncol*. (2012) 7:128. doi: 10.1186/1748-717X-7-128

32. Bhimani F, Johnson K, Brodin NP, Tomé WA, Fox J, Mehta K, et al. Case report: can targeted intraoperative radiotherapy in patients with breast cancer and pacemakers be the new standard of care? *Front Oncol*. (2022) 12:927174. doi: 10.3389/fonc.2022.927174

33. Bhimani F, McEvoy M, Gupta A, Pastoriza J, Shihabi A, Basavatia A, et al. Case Report: Bilateral targeted intraoperative radiotherapy: a safe and effective alternative for synchronous bilateral breast cancer. *Front Oncol*. (2023) 13:1276766. doi: 10.3389/fonc.2023.1276766

34. American Association of Intellectual and Developmental Disabilities. Defining criteria for intellectual disability 2023 . Available online at: https://www.aaidd.org/intellectual-disability/definition.

35. Luckasson R, Borthwick-Duffy S, Buntinx WH, Coulter DL, Craig EMP, Reeve A, et al. *Mental retardation: Definition, classification, and systems of supports*. Washington, DC: American Association on Mental Retardation (2002).

36. Lalor A, Redmond R. Breast screening for post-menopausal women. *Learn Disability Practice*. (2009) 12: 28-33. doi: 10.7748/ldp2009.11.12.9.28.c7380

37. Parish SL, Rose RA, Luken K, Swaine JG, O'Hare L. Cancer screening knowledge changes: results from a randomized control trial of women with developmental disabilities. *Res Soc Work Practice*. (2012) 22:43–53. doi: 10.1177/1049731511415550

38. Taggart L, Truesdale-Kennedy M, McIlfatrick S. The role of community nurses and residential staff in supporting women with intellectual disability to access breast screening services. *J Intellect Disabil Res*. (2011) 55:41–52. doi: 10.1111/j.1365-2788.2010.01345.x

39. Hsieh K, Rimmer JH, Heller T. Obesity and associated factors in adults with intellectual disability. *J Intellect Disabil Res*. (2014) 58:851–63. doi: 10.1111/jir.2014.58.issue-9

40. Hilgenkamp TI, Reis D, van Wijck R, Evenhuis HM. Physical activity levels in older adults with intellectual disabilities are extremely low. *Res Dev Disabil*. (2012) 33:477–83. doi: 10.1016/j.ridd.2011.10.011

41. McCarron M. Growing older with an intellectual disability in Ireland 2011. In: *First results from the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA)*. School of Nursing and Midwifery, Trinity College Dublin (2011).

42. McCarron M, McCallion P, Carroll R, Burke E, Cleary E, McCausland D, et al. Advancing years, Different challenges. In: *Wave 2 IDS-TILDA: findings on the ageing of people with an intellectual disability: an intellectual disability supplement to the Irish Longitudinal Study on Ageing* (2014). The university of Dublin Trinity College: Dublin Ireland. Available at: https://www.tcd.ie/tcaid/assets/pdf/Wave_2_Report_October_2014.pdf

43. Tran E, Rouillon F, Loze JY, Casadebaig F, Philippe A, Vitry F, et al. Cancer mortality in patients with schizophrenia: an 11-year prospective cohort study. *Cancer*. (2009) 115:3555–62. doi: 10.1002/cncr.v115:15

44. Catts VS, Catts SV, O'Toole BI, Frost AD. Cancer incidence in patients with schizophrenia and their first-degree relatives - a meta-analysis. *Acta Psychiatr Scand*. (2008) 117:323–36. doi: 10.1111/j.1600-0447.2008.01163.x

45. Hippisley-Cox J, Vinogradova Y, Coupland C, Parker C. Risk of Malignancy in patients with schizophrenia or bipolar disorder: nested case-control study. *Arch Gen Psychiatry*. (2007) 64:1368–76. doi: 10.1001/archpsyc.64.12.1368

46. Groß SE, Pfaff H, Swora M, Ansmann L, Albert US, Groß-Kunkel A. Health disparities among breast cancer patients with/without disabilities in Germany. *Disabil Health J*. (2020) 13:100873. doi: 10.1016/j.dhjo.2019.100873

47. Kwon J, Kim SY, Yeob KE, Han HS, Lee KH, Shin DW, et al. The effect of disability on the diagnosis and treatment of multiple myeloma in korea: A national cohort study. *Cancer Res Treat*. (2020) 52:1–9. doi: 10.4143/crt.2018.702

48. Shinden Y, Kijima Y, Hirata M, Nakajo A, Tanoue K, Arigami T, et al. Clinical characteristics of breast cancer patients with mental disorders. *Breast*. (2017) 36:39–43. doi: 10.1016/j.breast.2017.08.010

49. Hwang M, Farasatpour M, Williams CD, Margenthaler JA, Virgo KS, Johnson FE. Adjuvant chemotherapy for breast cancer in patients with schizophrenia. *Oncol Lett*. (2012) 3:845–50. doi: 10.3892/ol.2012.560

50. Sreeraman R, Vijayakumar S, Chen AM. Correlation of radiation treatment interruptions with psychiatric disease and performance status in head and neck cancer patients. *Support Care Cancer*. (2013) 21:3301–6. doi: 10.1007/s00520-013-1907-3

51. Abdullah KN, Janardhan R, Hwang M, Williams CD, Farasatpour M, Margenthaler JA, et al. Adjuvant radiation therapy for breast cancer in patients with schizophrenia. *Am J Surg*. (2015) 209:378–84. doi: 10.1016/j.amjsurg.2014.07.004

52. Waddle MR, Niazi S, Aljabri D, White L, Kaleem T, Naessens J, et al. Cost of acute and follow-up care in patients with pre-existing psychiatric diagnoses undergoing radiation therapy. *Int J Radiat Oncol Biol Phys*. (2019) 104:748–55. doi: 10.1016/j.ijrobp.2019.03.021

53. Rollins KE, Lobo DN. Intraoperative goal-directed fluid therapy in elective major abdominal surgery: A meta-analysis of randomized controlled trials. *Ann Surg*. (2016) 263:465–76. doi: 10.1097/SLA.0000000000001366

54. Chen Y, Goenka A, Sharma A, Wang L, Cao Y, Jamshidi A. SU-F-T-654: pacemaker dose estimate using optically stimulated luminescent dosimeter for left breast intraoperative radiation therapy. *Med Phys*. (2016) 43:3614–. doi: 10.1118/1.4956839

55. Farasatpour M, Janardhan R, Williams CD, Margenthaler JA, Virgo KS, Johnson FE. Breast cancer in patients with schizophrenia. *Am J Surg*. (2013) 206:798–804. doi: 10.1016/j.amjsurg.2012.06.013

56. Vaidya JS, Bulsara M, Baum M, Wenz F, Massarut S, Pigorsch S, et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. *BMJ*. (2020) 370:m2836. doi: 10.1136/bmj.m2836

57. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol*. (2017) 35:1641–9. doi: 10.1200/JCO.2016.72.0722

58. Wennstig AK, Garmo H, Wadsten L, Lagerqvist B, Fredriksson I, Holmberg L, et al. Risk of coronary stenosis after adjuvant radiotherapy for breast cancer. *Strahlenther Onkol*. (2022) 198(7):630-8. doi: 10.1007/s00066-022-01927-0

59. McGale P, Darby SC, Hall P, Adolfsson J, Bengtsson NO, Bennet AM, et al. Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol*. (2011) 100:167–75. doi: 10.1016/j.radonc.2011.06.016

60. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol*. (2015) 16:47–56. doi: 10.1016/S1470-2045(14)71156-8

61. Vaidya JS, Bulsara M, Baum M, Wenz F, Massarut S, Pigorsch S, et al. New clinical and biological insights from the international TARGIT-A randomised trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer. *Br J Cancer*. (2021) 125:380–9. doi: 10.1038/s41416-021-01440-8

62. Vaidya JS, Bulsara M, Wenz F, Sperk E, Massarut S, Alvarado M, et al. The TARGIT-A randomized trial: TARGIT-IORT versus whole breast radiation therapy: long-term local control and survival. *Int J Radiat Oncol Biol Phys*. (2023) 115:77–82. doi: 10.1016/j.ijrobp.2022.08.029

63. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. (2014) 383:603–13. doi: 10.1016/S0140-6736(13)61950-9

64. Corica T, Nowak AK, Saunders CM, Bulsara MK, Taylor M, Williams NR, et al. Cosmetic outcome as rated by patients, doctors, nurses and BCCT.core software assessed over 5 years in a subset of patients in the TARGIT-A Trial. *Radiat Oncol*. (2018) 13:68. doi: 10.1186/s13014-018-0998-x

65. Corica T, Nowak AK, Saunders CM, Bulsara M, Taylor M, Vaidya JS, et al. Cosmesis and breast-related quality of life outcomes after intraoperative radiation therapy for early breast cancer: A substudy of the TARGIT-A trial. *Int J Radiat Oncol Biol Phys*. (2016) 96:55–64. doi: 10.1016/j.ijrobp.2016.04.024

66. Welzel G, Boch A, Sperk E, Hofmann F, Kraus-Tiefenbacher U, Gerhardt A, et al. Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A. *Radiat Oncol*. (2013) 8:9. doi: 10.1186/1748-717X-8-9

67. Coombs NJ, Coombs JM, Vaidya UJ, Singer J, Bulsara M, Tobias JS, et al. Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. *BMJ Open*. (2016) 6:e010703. doi: 10.1136/bmjopen-2015-010703

68. Barney CC, Andersen RD, Defrin R, Genik LM, McGuire BE, Symons FJ. Challenges in pain assessment and management among individuals with intellectual and developmental disabilities. *Pain Rep*. (2020) 5:e821. doi: 10.1097/PR9.0000000000000822

69. Bottos S, Chambers C, Oberlander T, Symons F. *Pain in Children and Adults with Developmental Disabilities*. (2006). Brookes Publishing Co.: Baltimore, MD.

70. LaChapelle DL, Hadjistavropoulos T, Craig KD. Pain measurement in persons with intellectual disabilities. *Clin J Pain*. (1999) 15:13–23. doi: 10.1097/00002508-199903000-00004

71. Nader R, Oberlander TF, Chambers CT, Craig KD. Expression of pain in children with autism. *Clin J Pain*. (2004) 20:88–97. doi: 10.1097/00002508-200403000-00005

72. Benromano T, Pick CG, Granovsky Y, Defrin R. Increased evoked potentials and behavioral indices in response to pain among individuals with intellectual disability. *Pain Med*. (2017) 18:1715–30. doi: 10.1093/pm/pnw349

73. Defrin R, Pick CG, Peretz C, Carmeli E. A quantitative somatosensory testing of pain threshold in individuals with mental retardation. *Pain*. (2004) 108:58–66. doi: 10.1016/j.pain.2003.12.003

74. Riquelme I, Montoya P. Developmental changes in somatosensory processing in cerebral palsy and healthy individuals. *Clin Neurophysiol*. (2010) 121:1314–20. doi: 10.1016/j.clinph.2010.03.010

75. Ramstad K, Jahnsen R, Skjeldal OH, Diseth TH. Characteristics of recurrent musculoskeletal pain in children with cerebral palsy aged 8 to 18 years. *Dev Med Child Neurol*. (2011) 53:1013–8. doi: 10.1111/j.1469-8749.2011.04070.x

76. van der Slot WMA, Benner JL, Brunton L, Engel JM, Gallien P, Hilberink SR, et al. Pain in adults with cerebral palsy: A systematic review and meta-analysis of individual participant data. *Ann Phys Rehabil Med*. (2021) 64:101359. doi: 10.1016/j.rehab.2019.12.011

77. Committee IPRC. *National pain strategy: a comprehensive population health-level strategy for pain* Vol. 36. . Washington, DC: US Department of Health and Human Services, National Institutes of Health (2016).

78. Andersen KG, Gärtner R, Kroman N, Flyger H, Kehlet H. Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: a randomized trial. *Breast*. (2012) 21:46–9. doi: 10.1016/j.breast.2011.07.011

79. Kirwan CC, Coles CE, Bliss J, Group PPW. It's PRIMETIME. Postoperative avoidance of radiotherapy: biomarker selection of women at very low risk of local recurrence. *Clin Oncol (R Coll Radiol)*. (2016) 28:594–6. doi: 10.1016/j.clon.2016.06.007

80. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol*. (2013) 31:2382–7. doi: 10.1200/JCO.2012.45.2615

81. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, investigators PI. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. (2015) 16:266–73. doi: 10.1016/S1470-2045(14)71221-5

82. Brodin NP, Mehta KJ, Basavatia A, Goddard LC, Fox JL, Feldman SM, et al. A skin dose prediction model based on in *vivo* dosimetry and ultrasound skin bridge measurements during intraoperative breast radiation therapy. *Brachytherapy*. (2019) 18:720–6. doi: 10.1016/j.brachy.2019.05.012

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 04 November 2024
DOI 10.3389/fonc.2024.1470560

OPEN ACCESS

EDITED BY
Meghana V. Trivedi,
University of Houston, United States

REVIEWED BY
Erika Nicole Brown,
Houston Methodist Willowbrook Hospital, United States
Rodney Hunter,
Texas Southern University, United States

*CORRESPONDENCE
Ingrid Karmane Sumou
ingridsumou@gmail.com

RECEIVED 25 July 2024
ACCEPTED 09 October 2024
PUBLISHED 04 November 2024

CITATION
Sumou IK and Hui CV (2024) Case report: Efficacy of later-line fam-trastuzumab deruxtecan in a patient with triple-positive breast cancer with brain metastases.
Front. Oncol. 14:1470560.
doi: 10.3389/fonc.2024.1470560

Case report: Efficacy of later-line fam-trastuzumab deruxtecan in a patient with triple-positive breast cancer with brain metastases

Ingrid Karmane Sumou* and Cheng Vai Hui

Department of Oncology, Centro Hospitalar Conde de São Januário, Macao, Macao SAR, China

Fam-trastuzumab deruxtecan (T-DXd) has demonstrated substantial antitumor activity and durable responses in patients with human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer. We report here the treatment outcomes of T-DXd in a patient with HER2+ breast cancer with brain metastases that repeatedly recurred and progressed after two lines of salvage therapy. In 2016, a 23-year-old G0P0 female with risk factors including menarche at age 9 years, Li-Fraumeni syndrome, and a strong family history of cancer was diagnosed with bilateral, triple-positive breast cancer. She received chemotherapy, HER2-targeted therapies, total mastectomy, and locoregional radiotherapy, but a brain metastasis in the left parieto-occipital lobe was detected in 2020. After receiving capecitabine, lapatinib, gonadotropin-releasing hormone (GnRH) agonist, and tamoxifen, multiple new lesions appeared in the brain after 14 months. The patient then received capecitabine, neratinib, GnRH agonist, and letrozole; however, her brain metastases still progressed after 7 months. In 2022, she started T-DXd treatment. Good response to treatment was observed 4 months later, including a continuous decrease in the cancer antigen 15-3 level, a reduction in the size of the major brain tumor, and the absence of new lesions. Now aged 30, the patient is continuing to receive T-DXd treatment to prevent recurrence. We conclude that T-DXd was effective for the treatment of brain metastases in this young patient with triple-positive metastatic breast cancer who had multiple risk factors and had received several anti-HER2 therapies prior to T-DXd.

KEYWORDS

antibody-drug conjugate, triple-positive breast cancer, human epidermal growth factor receptor 2 (HER2), brain metastasis, fam-trastuzumab deruxtecan

1 Introduction

Breast cancer (BC) is the most common cancer worldwide (1), and BC tumors that overexpress human epidermal growth factor receptor 2 (HER2) comprised about 14% of all new cases in the USA from 2016–2020 (2). Although HER2+ tumors tend to be more aggressive than other BCs, the prognosis varies depending on the co-expression of hormone receptors (HRs), namely estrogen receptor (ER) and progesterone receptor (PR), and patients with triple-positive BC tumors tend to be younger (≤ 49 years) (3). Among patients with advanced BC, approximately 25% developed brain metastasis, with the number climbing to 30–40% in those with HER2-positive tumors (4). Treatments targeted at HER2, which include monoclonal antibodies, antibody-drug conjugates (ADCs), and small-molecule tyrosine kinase inhibitors (TKIs), have led to greatly improved survival in patients with HER2+ tumors (4).

The current standard of care for patients in the metastatic setting is first-line dual-HER2 monoclonal antibody therapy with pertuzumab and trastuzumab, plus a taxane (5, 6). Globally, patients with unresectable or metastatic HER2+ BC that progressed on ≥ 2 prior therapies also now have the option of the antibody-drug conjugate fam-trastuzumab deruxtecan (T-DXd) (7). T-DXd consists of a HER2-targeted antibody and a cleavable, membrane-permeable topoisomerase I inhibitor that is preferentially released inside of cancer cells (8). In the DESTINY-Breast01 trial of heavily pretreated patients with unresectable or metastatic HER2+ BC, T-DXd provided an objective response rate (ORR) of 62%, an 18.2-month (95% confidence interval [CI], 15.0 months to not evaluable) duration of response, and a small (1.6%) rate of further disease progression (7). A subgroup analysis (9) showed that the efficacy of T-DXd was also durable in those with brain metastases (N = 24), with a confirmed ORR of 58.3% (95% CI, 36.6–77.9) and a median progression-free survival (PFS) of 18.1 months (95% CI, 6.7–18.1). In a subsequent trial (DESTINY-Breast02) of a similar patient population, T-DXd was compared with treatment of physician's choice (capecitabine plus either trastuzumab or lapatinib) (10). This trial confirmed the positive benefit–risk profile of T-DXd, which showed a median PFS of 17.8 months (vs. 6.9 months in the other group; hazard ratio [HR], 0.36; 95% CI, 0.28–0.45; $P < 0.0001$) over a median follow-up of 21.5 months. Furthermore, in the prospective phase 2 TUXEDO-1 trial of 15 patients with HER2+ BC and active brain metastases, treatment with T-DXd led to a high intracranial response rate (73.3%; 95% CI, 48.1–89.1) (11). In the retrospective ROSET-BM study (12), T-DXd was also shown to have promising efficacy in HER2+ BC patients with active brain metastases as well as leptomeningeal carcinomatosis, which are associated with poor prognosis and remain difficult to treat (4, 13).

In this report, we detail the case of a 30-year-old woman with triple-positive BC who developed brain metastases that was successfully treated with third-line T-DXd. The reporting of this case conforms to the CARE guidelines (14). Written informed consent was obtained from the patient to publish this paper.

2 Case description

2.1 Diagnosis of triple-positive breast cancer with multiple risk factors

Our patient, a G0P0 female, was diagnosed with bilateral, triple-positive invasive ductal carcinoma (Ki-67 index range: 45–80%) at the age of 23 in January 2016. Pre-treatment positron emission tomography (PET) and magnetic resonance imaging (MRI) detected a multicentric lesion (4.0 cm × 4.5 cm) at the 2H position of the left breast, with left axillary lymph node metastases (level I–III), and two lesions (2.8 cm × 2.1 cm at 8H and 2.4 cm × 1.8 cm at 10H) in the right breast (Table 1). The tumor in the left breast was clinically staged as IIIA cT2N2M0, and those in the right breast were staged as IIA cT2(m)N0M0. Genetic analysis identified a *TP53* mutation (possibly germline), suggesting the possibility of Li-Fraumeni syndrome. Individuals with this syndrome have a significantly increased risk of developing breast cancer and are recommended to undergo frequent oncological monitoring (15). Our patient tested negative for pathogenic variants of *BRCA1*, *BRCA2* and *PTEN*, but reported a strong family history of cancers that included nasopharyngeal, liver, and colon cancers among the maternal and paternal grandparents. She also experienced early menarche (age, 9 years), which is a well-established risk factor for breast cancer (16).

2.2 Treatment of breast primary

In February 2016, the patient was treated with weekly paclitaxel, HER2-targeted monoclonal antibody therapies (trastuzumab + pertuzumab), and gonadotropin-releasing hormone (GnRH) agonist for 16 weeks. All of the masses became non-palpable after treatment. A post-neoadjuvant chemotherapy PET scan showed metabolic quiescence in both breasts and axilla. In August 2016, she underwent a bilateral nipple-sparing total mastectomy, left axillary dissection, right sentinel node biopsy, and implant insertion. Pathology revealed the following: no residual tumors in the left tumor bed at 2H (ypT0N1M0) and the right tumor bed at 8H; residual invasive ductal carcinoma grade II (0.2 cm with 3 foci), with no lymphovascular invasion, a posterior margin of 1 cm, and associated ductal carcinoma *in situ* in the right tumor bed at 10H, scored as ypT1N0(sn)(i-)M0, with triple positivity (ER Allred score of 8, PR Allred score of 6, and HER2 immunohistochemistry [IHC] score 3+) and a Ki-67 index of 7%; and involvement of 3/20 left axillary nodes (largest: 0.8 cm with 0.3 cm extracapsular extension), but no involvement among 4 sentinel nodes in the right axilla. The patient received adjuvant locoregional radiotherapy (RT; 40 Gy in 15 fractions) of the left supraclavicular fossa and the left chest in November 2016. She was maintained for up to 1 year on anti-HER2 therapy with trastuzumab and pertuzumab, with a GnRH agonist and letrozole.

TABLE 1 Timeline and course of treatment for the patient.

Diagnosis	Treatment	Date
Primary bilateral invasive ductal carcinoma with lymph node involvement	Neoadjuvant paclitaxel 80 mg/m^2 IV weekly for 16 weeks; trastuzumab 8 mg/kg (loading) IV for first cycle, followed by 6 mg/kg Q3W; pertuzumab 840 mg (loading) IV for first cycle, followed by 420 mg Q3W; leuprolide 11.25 mg IM Q3M	Feb 2016
	Bilateral nipple-sparing total mastectomy, left axillary dissection, right sentinel node biopsy, implant insertion	Aug 2016
	Locoregional RT; trastuzumab 6 mg/kg Q3W + pertuzumab 420 mg Q3W for up to 1 year; leuprolide 11.25 mg IM Q3M; letrozole 2.5 mg orally daily	Nov 2016
Second primary RT-induced sarcoma of chest wall	Wide local excision with clear margins	Oct 2018
Metastatic brain lesions from breast primary	Tumor resection (7 x 5 cm dura-based lesion in left parieto-occipital lobe); local and whole-brain RT; capecitabine 1000 mg b.i.d. for day 1–14 Q3W (2 weeks on, 1 week off); lapatinib 750 mg daily for first week, followed by 1250 mg daily thereafter; leuprolide 11.25 mg IM Q3M; tamoxifen 10 mg b.i.d.	Jun 2020
Metastatic bone and recurrent brain lesions	Corpectomy; capecitabine 1000 mg b.i.d. for day 1–14 Q3W (2 weeks on, 1 week off); neratinib 120 mg daily for 2 weeks, then 160 mg daily for 1 week, followed by 240 mg daily thereafter; leuprolide 11.25 mg IM Q3M; letrozole 2.5 mg orally daily; denosumab 120 mg SC Q4W	Nov 2021; Mar 2022; Apr 2022
Progression of brain metastases	T-DXd 5.4 mg/kg Q3W; antiemetics and corticosteroids as needed	Nov 2022–Ongoing

2.3 Brain metastasis from breast primary and second primary malignancy

In October 2018, she was diagnosed with a second primary malignancy: a RT-induced undifferentiated pleomorphic sarcoma (1.1 cm) of the left chest wall, which was treated with wide local excision with clear margins. Eighteen months later, she presented with headache and diplopia, and received an MRI scan that showed a firm, dural-based tumor (7.0 cm × 5.0 cm) with hypervascularity in the left parieto-occipital lobe (Figure 1A). Tumor resection revealed pathology consistent with metastatic BC. She completed RT (40 Gy in 10 fractions) for the brain tumor bed and whole-brain RT (30 Gy in 10 fractions). In August 2020, she was given capecitabine, lapatinib, a GnRH agonist, and tamoxifen as first-line treatment for the metastatic BC.

Follow-up computed tomography (CT) and MRI scans conducted between October 2020 and March 2021 showed no evidence of tumor recurrence. Considering the risk of colorectal cancer associated with Li-Fraumeni syndrome, two colonoscopies were conducted (April 2019 and April 2021), neither of which showed any significant findings.

2.4 Management of recurrences of brain metastases

In November 2021, an MRI showed multiple bone metastases at the L1, L3, L5, and S1 vertebrae. The patient was given denosumab 120 mg subcutaneously every 4 weeks (upon the drug approval from the hospital committee since April 2022). The L3 segment had spinal canal invasion, with pathological fracture and spinal stenosis, which was treated with a corpectomy. The pathological results indicated metastatic BC remained to be triple positive (ER 5, PR 0, HER2 IHC score 3+, and a Ki67 index of 25%). A brain MRI scan in the following month showed recurrence, with multiple lesions in the left parieto-occipital region (largest: 3.4 cm × 2.9 cm × 4.1 cm) (Figure 1B). In March 2022, the patient received second-line treatment comprising capecitabine plus targeted therapy with neratinib, a GnRH agonist, and letrozole (her menses stopped in October 2021). A follow-up brain MRI scan 1 month later showed a partial response, and a CT scan in October 2022 showed stable disease. However, after 7 months of neratinib treatment, MRI showed disease progression of the left parieto-occipital brain lesion (Figure 1C). We initiated third-line treatment with T-DXd (5.4 mg/kg once every 3 weeks) in November 2022. T-DXd has proven its superiority over chemotherapy in late lines, and for closer observation of adverse effects, hormonal therapy was saved sequentially after the chemo-containing ADC.

A chest CT scan 4 months later showed that there had been no progression in the T2 vertebra, in which remained a round osteoblastic lesion (1.5 cm × 1.5 cm; Figure 2). This CT scan also showed some fibrous stripes in the upper lobe of the left lung, but no other abnormalities were observed. Furthermore, monitoring of the cancer antigen 15-3 (CA15-3) level showed a continuous decrease from 48.5 U/mL to 11.2 U/mL between December 2022 and April 2023. Brain MRI showed that the size of the major mass in the left parieto-occipital lobe had decreased from 3.7 cm × 3.0 in November 2022 to 2.0 cm × 1.7 cm in April 2023 (Figure 3). Several cysts and small lesions remained in the left parieto-occipital region; however, no new lesions or midline shifts were found, and the ventricles and basal cisterns appeared normal. We concluded that the brain metastases responded well to treatment with T-DXd, and the patient has since been asymptomatic. Follow up chest and abdomen CT scans in July 2023 and October 2023 consistently

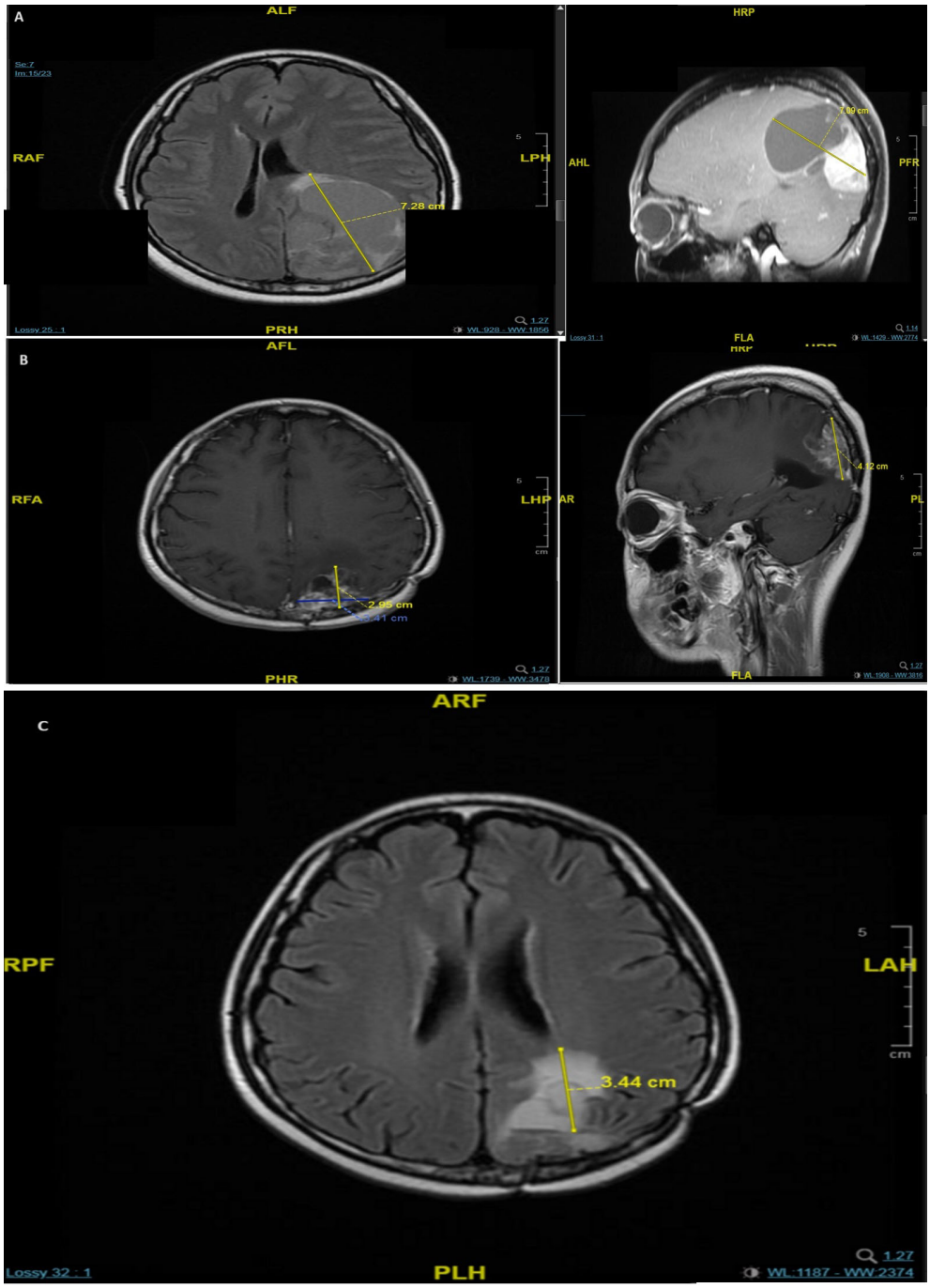


FIGURE 1
MRI scans of brain metastases in the patient showing a 7 × 5 cm dural-based tumor in the left parieto-occipital lobe in May 2020 **(A)**, recurrence with multiple lesions in the left parieto-occipital region in December 2021 **(B)**, and progression of the major lesion in the left parieto-occipital region in November 2022 **(C)**.

showed post-surgical change of the lumbar spine in stable status with no new visceral or bony lesions.

The patient remains on T-DXd at the time of this writing in November 2023. To manage the potential side effects of T-DXd, supportive measures including antiemetics and corticosteroids were provided. The patient also received nursing and health education related to the new systemic therapy, as well as exercise and diet counseling. During follow-up visits while on therapy, the patient reported that she was able to maintain her professional and personal activities, including continuing her teaching career and volunteering at a cancer patient group to help other patients. From the perspective of quality of life, the treatment not only helps the patient achieve intact everyday functioning, but also enables her to actively participate in the community.

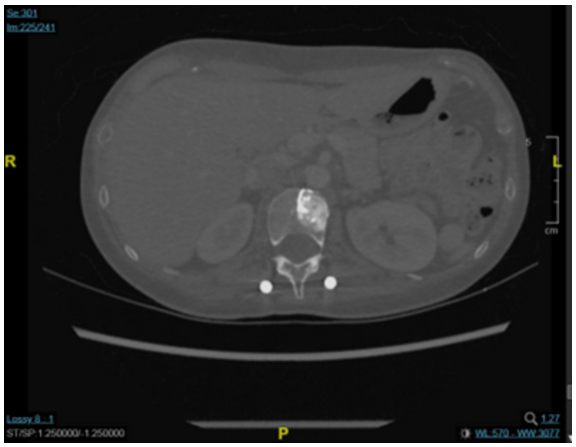


FIGURE 2
Chest CT scan of the T2 vertebral metastasis in March 2023.

3 Patient perspective

T-DXd was accessible and effective for the treatment of brain metastases with triple-positive metastatic BC who had multiple risk factors and received multiple anti-HER2 therapies.

4 Discussion

For what used to be a tumor subtype with an aggressive phenotype bearing high recurrence rates and very poor outcomes, HER2+ advanced BC now beholds more treatment options. The introduction of HER2-directed therapies, most notably, trastuzumab, pertuzumab, ADCs such as trastuzumab emtansine (T-DM1) and T-DXd, and TKIs such as lapatinib, neratinib, pyrotinib, and tucatinib, has shown improvements in the prognosis of patients with HER2+ metastatic BC.

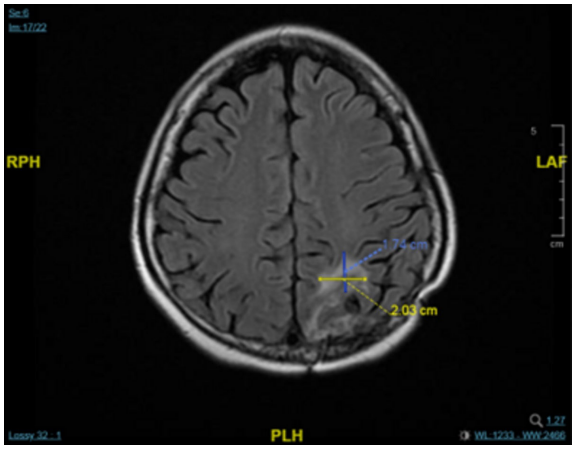


FIGURE 3
MRI scan showing a decrease in the mass in left parieto-occipital lobe after treatment with T-DXd in April 2023.

T-DXd has shown magnificent activity in patients pretreated with T-DM1. In the DESTINY-Breast01 trial of 184 heavily pretreated patients with a median of 6 prior lines of therapy, T-DXd provided a median PFS of 16.4 months. Responses were observed in 112 patients (60.9%; 95% CI, 53.4–68.0); the disease control rate was 97.3% (95% CI, 93.8–99.1) (17). These groundbreaking data resulted in the U.S. Food and Drug Administration (FDA) granting accelerated approval to T-DXd for patients with HER2+ cancer who have received 2 or more prior anti-HER2-targeted therapies in the metastatic setting (18).

Tucatinib is another agent with proven efficacy when given as third-line treatment for HER2+ advanced BC. Based on results from the phase 2 HER2CLIMB trial (19), the FDA approved tucatinib for use with trastuzumab and capecitabine in patients with unresectable or metastatic HER2+ BC, including those with brain metastases, who have been pretreated with at least 1 prior HER2-directed regimen in the metastatic setting (20). According to the trial, patients benefited with a statistically significant improvement in ORR (40.6% [95% CI, 35.3–46.0] vs. 22.8% [95% CI, 16.7–29.8]; $P < 0.001$), median PFS (7.8 vs. 5.6 months; HR, 0.54; 95% CI, 0.42–0.71; $P < 0.001$) and median overall survival (OS; 21.9 vs. 17.4 months; HR, 0.66; 95% CI, 0.50–0.88; $P = 0.005$) (19). Patients with brain metastases also experienced an improvement in intracranial PFS (9.9 vs. 4.2 months; HR, 0.32; 95% CI, 0.22–0.48; $P < 0.0001$), intracranial ORR (47.3% [95% CI, 33.7–61.2] vs. 20.0% [95% CI, 5.7–43.7]; $P = 0.03$), and OS (18.1 vs. 12.0 months; HR, 0.58; 95% CI, 0.40–0.85; $P = 0.005$) (21). Nevertheless, in real world setting it all comes down to accessibility and socio-economics, with disparity in drug approvals and reimbursement strategies across different countries.

Neratinib in combination with capecitabine was approved for HER2+ advanced or metastatic BC following 2 or more anti-HER2-based regimens. In the phase 3 NALA trial, 621 eligible patients were randomized to receive either neratinib plus capecitabine or lapatinib plus capecitabine. The 12-month PFS rate was higher with use of the neratinib combination (28.8%; 95% CI, 23.1–34.8) than with the lapatinib combination (14.8%; 95% CI, 10.3–20.1), but there was no significant improvement in the 12-month OS rate (HR, 0.881; 95% CI, 0.72–1.07; $P = 0.2086$), with almost twice as common Grade 3 diarrhea (24.4% vs. 12.5%) (22). The limited clinical benefits plus the high toxicity make this agent less appealing when compared with other existing options approved by the FDA.

Margetuximab, an anti-HER2 monoclonal antibody, was approved for use with chemotherapy in patients with metastatic HER2+ BC following 2 or more HER2-directed therapies, with at least 1 being for metastatic disease. In the phase 3 SOPHIA trial, 536 eligible patients were randomized to receive margetuximab or trastuzumab. Margetuximab, designed to elicit an antibody-drug-mediated cellular cytotoxicity response, reached a statistically significant yet clinically modest improvement in median PFS (5.7 vs. 4.4 months; HR, 0.71; 95% CI, 0.58–0.86; $P < 0.001$), with improved ORR (22% vs. 16%; $P = 0.06$) (23). However, it appears only to work in patients who have a particular genotype that puts them at a higher risk of not being able to generate that response. This agent was locally inaccessible, plus we do not have a way to test for that genotype.

In view of the relatively large molecular size, ADCs were considered unlikely to penetrate the blood-brain barrier (BBB) and thus inefficacious for the treatment of brain metastases (24). However, prior RT to the brain tumor bed and whole-brain RT might induce leakage of the BBB at the site of metastases through apoptosis and senescence in cells of the

neurovascular unit (25). Additionally, RT might lead to vascular leakage and further permeabilize the BBB by reducing astrocytes, pericytes, and tight junction proteins in paracellular channels (25), allowing T-DXd to penetrate the brain parenchyma and act on the tumors.

In the phase 2 TUXEDO-1 trial, T-DXd provided a high intracranial response rate (73.3%; 95% CI, 48.1–89.1) among patients with active brain metastases from HER2+ BC (11). Our patient also demonstrated the efficacy and safety of T-DXd for the treatment of brain metastases. After development and progression of brain lesions, our patient was started on T-DXd as third-line treatment and had a rapid reduction in the size of the major brain mass, with a significant decline in CA15-3 within the first 4 months. She found T-DXd well-tolerated and reported no serious adverse events.

T-DXd can be given as a second-line treatment in patients with metastatic HER2+ BC. In the phase 3 DESTINY-Breast03 trial (26), T-DXd significantly improved PFS (28.8 vs. 6.8 months; HR, 0.33; 95% CI, 0.26–0.43; P < 0.0001) and OS both not reached [NR] (HR, 0.64; 95% CI, 0.47–0.87; P = 0.0037) compared with T-DM1 in the second-line setting. The benefit of T-DXd over T-DM1 (PFS, 15.0 vs. 3.0 months; HR, 0.25; 95% CI, 0.13–0.45; ORR, 67.4% vs. 20.5%) was consistently demonstrated in the subgroup of patients with brain metastases (27). The European Society for Medical Oncology has recommended T-DXd as a second-line treatment option for patients with HER2+ BC (28).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

IS: Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing, Formal analysis. CH: Data curation, Investigation, Supervision, Writing – original draft, Writing – review & editing, Formal analysis, Validation.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

Supported academically by AstraZeneca (Hong Kong) Limited and Daiichi Sankyo (Hong Kong) Limited.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71:209–49. doi: 10.3322/caac.21660

2. SEER Research Data. *Cancer Stat Facts: Female Breast Cancer Subtypes*. Available online at: https://seer.cancer.gov/statfacts/html/breast-subtypes.html (accessed August, 2023).

3. Fan Y, Wang Y, He L, Imani S, Wen Q. Clinical features of patients with HER2-positive breast cancer and development of a nomogram for predicting survival. *ESMO Open*. (2021) 6:100232. doi: 10.1016/j.esmoop.2021.100232

4. Courtinard C, Barbet V, Schiappa R, Pilleul F, Michiels S, Dabakuyo S, et al. Real-world effectiveness of post-trastuzumab emtansine treatment for human epidermal growth factor receptor 2-positive metastatic breast cancer: a multicenter, matched cohort analysis from the Epidemiology Strategy and Medical Economics database (2008-2018). *ESMO Real World Data Digital Oncol*. (2024) 4:1–9. doi: 10.1016/j.esmorw.2024.100043

5. Kunte S, Abraham J, Montero AJ. Novel HER2-targeted therapies for HER2-positive metastatic breast cancer. *Cancer*. (2020) 126:4278–88. doi: 10.1002/cncr.33102

6. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. (2020) 21:519–30. doi: 10.1016/s1470-2045(19)30863-0

7. Rugo HS, Bianchini G, Cortes J, Henning JW, Untch M. Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer. *ESMO Open*. (2022) 7:100553. doi: 10.1016/j.esmoop.2022.100553

8. Doi T, Shitara K, Naito Y, Shimomura A, Fujiwara Y, Yonemori K, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. *Lancet Oncol*. (2017) 18:1512–22. doi: 10.1016/s1470-2045(17)30604-6

9. Jerusalem G, Park YH, Yamashita T, Hurvitz SA, Modi S, Andre F, et al. Trastuzumab deruxtecan in HER2-positive metastatic breast cancer patients with brain metastases: A DESTINY-breast01 subgroup analysis. *Cancer Discov*. (2022) 12:2754–62. doi: 10.1158/2159-8290.Cd-22-0837

10. André F, Hee Park Y, Kim SB, Takano T, Im SA, Borges G, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive

metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. (2023) 401:1773–85. doi: 10.1016/s0140-6736(23)00725-0

11. Bartsch R, Berghoff AS, Furtner J, Marhold M, Bergen ES, Roider-Schur S, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. *Nat Med*. (2022) 28:1840–7. doi: 10.1038/s41591-022-01935-8

12. Yamanaka T, Niikura N, Nomura H, Kusama H, Yamamoto M, Matsuura K, et al. Abstract PD7-01: Trastuzumab deruxtecan for the treatment of patients with HER2-positive breast cancer with brain and/or leptomeningeal metastases: A multicenter retrospective study (ROSET-BM study). *Cancer Res*. (2023) 83:PD7–01. doi: 10.1158/1538-7445.SABCS22-PD7-01

13. Mollica L, Leli C, Puglisi S, Sardi S, Sottotetti F. Leptomeningeal carcinomatosis and breast cancer: a systematic review of current evidence on diagnosis, treatment and prognosis. *Drugs Context*. (2021) 10. doi: 10.7573/dic.2021-6-6

14. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D. The CARE guidelines: consensus-based clinical case reporting guideline development. *Glob Adv Health Med*. (2013) 2:38–43. doi: 10.7453/gahmj.2013.008

15. Kratz CP, Achatz MI, Brugières L, Frebourg T, Garber JE, Greer MC, et al. Cancer screening recommendations for individuals with li-fraumeni syndrome. *Clin Cancer Res*. (2017) 23:e38–45. doi: 10.1158/1078-0432.Ccr-17-0408

16. Yang PJ, Hou MF, Ou-Yang F, Tsai EM, Wang TN. Association of early-onset breast cancer with body mass index, menarche, and menopause in Taiwan. *BMC Cancer*. (2022) 22:259. doi: 10.1186/s12885-022-09361-2

17. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. (2020) 382:610–21. doi: 10.1056/NEJMoa1914510

18. U.S. Food & Drug Administration. *FDA approves fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive breast cancer*. Available online at: https://fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2-positive-breast-cancer (accessed October, 2023).

19. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. (2020) 382:597–609. doi: 10.1056/NEJMoa1914609

20. U.S. Food & Drug Administration. *FDA approves tucatinib for patients with HER2-positive metastatic breast cancer*. Available online at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tucatinib-patients-her2-positive-metastatic-breast-cancer (accessed November, 2023).

21. Lin NU, Borges V, Anders C, Murthy RK, Paplomata E, Hamilton E, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol*. (2020) 38:2610–9. doi: 10.1200/jco.20.00775

22. Saura C, Oliveira M, Feng YH, Dai MS, Chen SW, Hurvitz SA, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol*. (2020) 38:3138–49. doi: 10.1200/jco.20.00147

23. Rugo HS, Im SA, Cardoso F, Cortés J, Curigliano G, Musolino A, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: A phase 3 randomized clinical trial. *JAMA Oncol*. (2021) 7:573–84. doi: 10.1001/jamaoncol.2020.7932

24. Li H, Li H. A narrative review of the current landscape and future perspectives of HER2-targeting antibody drug conjugates for advanced breast cancer. *Transl Breast Cancer Res*. (2021) 2:29. doi: 10.21037/tbcr-21-22

25. Allen BD, Limoli CL. Breaking barriers: Neurodegenerative repercussions of radiotherapy induced damage on the blood-brain and blood-tumor barrier. *Free Radic Biol Med*. (2022) 178:189–201. doi: 10.1016/j.freeradbiomed.2021.12.002

26. Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet*. (2023) 401:105–17. doi: 10.1016/s0140-6736(22)02420-5

27. Jacobson A. Trastuzumab deruxtecan improves progression-free survival and intracranial response in patients with HER2-positive metastatic breast cancer and brain metastases. *Oncologist*. (2022) 27:S3–4. doi: 10.1093/oncolo/oyac009

28. ESMO. *ESMO Metastatic Breast Cancer Living Guidelines, HER2-positive Breast Cancer, v1.1 May 2023*. Available online at: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/her2-positive-breast-cancer/her2-positive-breast-cancer (accessed August, 2023).

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 04 November 2024
DOI 10.3389/fonc.2024.1422817

OPEN ACCESS

EDITED BY
Wei Yao,
Tongji Hospital, Wuhan, China

REVIEWED BY
Kai Chen,
Sun Yat-sen Memorial Hospital, China
Hong Hu,
Shenzhen People's Hospital, China
Liang Xu,
Third Hospital of Nanchang, China

*CORRESPONDENCE
Jian Chen
chenjian2003@aliyun.com
Hongmei Zheng
2022ZL0002@hust.edu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 24 April 2024
ACCEPTED 09 October 2024
PUBLISHED 04 November 2024

CITATION
Huang W, Yang Y, Zhan P, Jiang L, Chen J and Zheng H (2024) Case report: A rare case of breast and multiorgan metastases secondary to papillary thyroid carcinoma. *Front. Oncol.* 14:1422817. doi: 10.3389/fonc.2024.1422817

Case report: A rare case of breast and multiorgan metastases secondary to papillary thyroid carcinoma

Wenqin Huang[1†], Yalong Yang[1†], Peng Zhan[1†], Liang Jiang[2], Jian Chen[2*] and Hongmei Zheng[1*]

[1]Department of Breast Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, National Key Clinical Specialty Construction Discipline, Hubei Provincial Clinical Research Center for Breast Cancer, Wuhan Clinical Research Center for Breast Cancer, Wuhan, Hubei, China, [2]Department of Head and Neck Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Papillary thyroid carcinoma (PTC) is generally considered a highly indolent endocrine malignancy, often accompanied by cervical lymph node metastasis and rarely involving distant metastases. We present a rare case of a 37-year-old woman with PTC, who exhibited regional lymph node metastasis, right breast metastasis, and probable right psoas major and multiple bone metastases. Initial symptoms included hoarseness, and subsequent examination revealed a secondary malignant tumor in the right breast, originating from the thyroid gland. This case highlights an unusual pattern of multiple systemic metastasis in PTC, particularly the rare occurrence of breast metastasis.

KEYWORDS

Papillary thyroid carcinoma, breast secondary malignant tumor, *BRAF* gene, *RET* gene, case report

Introduction

Monitoring and epidemiological data show that thyroid cancer is the most common endocrine malignant tumor, and the incidence in female patients is almost three times than that in male patients (1, 2). Among various histological types, papillary thyroid carcinoma (PTC) is the most common type, accounting for 70%–80% of all cases (3). PTC is usually known as an inert tumor, with a 10-year survival rate of approximately 93% (3, 4). The cancer-related deaths attributed to encapsulated non-invasive follicular PTC variants have not been reported, and the estimated risk of recurrence is less than 1% (1). Conversely, specific gene mutation-harboring PTC subtypes exhibit heightened aggressiveness, correlating with advanced tumor stages and lymph node metastases at initial diagnosis (1). Despite garnering heightened research interest and an expanding case repository for these aggressive variants, the occurrence of multiple metastases in PTC, particularly breast

metastasis, remains an exceedingly unusual clinical phenomenon. Here, we present a case study of a 37-year-old female patient who developed breast and multiorgan metastases as a sequel to PTC.

Case description

Informed consent was obtained from the patient, who signed a consent form.

A 37-year-old female patient was diagnosed with PTC after initially presenting with hoarseness. In the preoperative routine examination, the physical examination revealed a hard, movable mass with a diameter of approximately 1.0 cm in contact with the left thyroid gland. This mass moved up and down with swallowing and was not tender. Upon physical examination, palpable multiple masses were observed within the right thyroid gland, with the largest measuring approximately 2.0 cm × 3.0 cm. Additionally, multiple enlarged lymph nodes were palpable on both sides of the neck, of which the larger one on the left side was approximately 3.0 cm in diameter, and the larger one on the right side was approximately 2.0 cm in diameter. Thyroid ultrasound revealed multiple punctate calcifications in both lobes, along with the presence of multiple nodules classified as TI-RADS 4c in both lobes and a follicular cyst in the left lobe categorized as TI-RADS 2. Furthermore, it indicated enlarged lymph nodes in bilateral II, III, IV, and VI zones of the neck, suggestive of metastatic lymph nodes (Figure 1A). Neck CT scanning demonstrated scattered nodules and masses bilaterally within the thyroid gland, prompting consideration of thyroid cancer. The scan also revealed extensive lymph node metastasis in bilateral Ib–V regions and the anterior–superior mediastinum, as well as multiple instances of bone destruction in the lower cervical spine, indicative of metastasis (Figure 1B). Breast color Doppler ultrasound examination identified a solid mass in the right breast, classified as BI-RADS 4b, prompting an ultrasound-guided biopsy for pathological assessment (Figure 1C). Histopathological analysis confirmed the presence of adenocarcinoma in the right breast mass, which, upon correlation with HE morphology and immunophenotyping, was consistent with a thyroid origin. Immunohistochemistry results showed TTF-1 (+), PAX-8 (+), TG (+), GATA-3 (−), TRPS1 (weak +), P53 (weak +, wild type expression), Ki67 (ClONE: SP6) (Li:2%), and *BRAF* (V600E) (−). CCDC6-*RET* (Exon 1–Exon 12) gene fusion was positive (Figure 2).

Combined with the above suggested metastasis, in order to investigate whether there is metastasis in other distant organs of the patient, we advocate the utilization of positron emission tomography–computed tomography (PET-CT) imaging. The findings indicate the presence of multiple, slightly hypoechoic nodules within the bilateral lobes of the thyroid gland, prompting the consideration of thyroid cancer. Furthermore, the possibility of lymph node metastasis is entertained in the bilateral neck, supraclavicular region, and mediastinum, based on observed abnormalities. In the outer lower quadrant of the right breast, soft tissue density nodules were discernible, raising the suspicion of metastatic lesions, thereby not excluding breast cancer as a differential diagnosis. Additionally, an abnormal nodular radioactive concentration shadow in the right psoas major muscle suggests the likelihood of metastatic involvement. Bone destruction was also observed in the second rib and the seventh cervical vertebra on the right side, and bone metastasis was considered (Figure 3).

The patient underwent a comprehensive surgical procedure encompassing bilateral thyroidectomy coupled with dissection of bilateral central and cervical lymph nodes. Postoperative pathological examination revealed a papillary carcinoma of the common type, exhibiting intraglandular dissemination, with a little hobnail-like subtype (<1%). This subtype was further characterized by invasion into the thyroid capsule and extracapsular adipose tissue. Metastatic carcinoma was identified in 26 out of 57 lymph nodes examined. Immunohistochemical analysis indicated a negative *BRAF* (V600E) status in the thyroid cancer cells.

For breast metastatic lesions, without the excisional biopsy, the possibility of an independent tumor solely originating in the breast cannot be excluded. In such cases, we performed the local excision for biopsy, which can not only confirm its origin but also specify its nature (5). Therefore, the patient also underwent resection of the right breast mass under local anesthesia. Pathological examination suggested that (right breast) adenocarcinoma, combined with medical history and HE morphology, was consistent with the source of thyroid cancer. So far, the postoperative pathological examination results confirmed that the patient's breast malignant tumor originated from a thyroid malignant tumor.

According to the current treatment principles for metastatic tumors (6), for breast metastatic lesions, only a local tumor resection is performed, without radiation therapy and chemotherapy related to metastatic breast cancer. After the tumor resection, it is clear that the metastatic breast cancer originates from thyroid cancer. According to the diagnosis and treatment suggestions for differentiated thyroid cancer (DTC), the patient is recommended to receive subsequent iodine-131 treatment.

Subsequently, the patient received iodine-131 treatment, and the condition was well controlled. Follow-up to August 2024, the patient lived in other provinces and did not receive any examination and treatment. The patient reported that the general condition was good, but the hoarseness was not improved.

Discussion

Distant metastases in PTC are infrequent, manifesting in less than 10% of individuals diagnosed with DTC. Notably, half of these metastases are already present at the time of initial tumor detection, whereas the remaining instances may remain undetected until several decades after treatment (1). The incidence of thyroid cancer metastasis is heightened in patients harboring invasive histological subtypes, including the high cell, columnar, hobnail, and solid variants. The lung and bone are the most frequently implicated sites of metastasis, accounting for 49% and 25% of all cases, respectively. Concurrent involvement of both sites occurs in 15% of cases, while metastases to the brain, liver, and skin are comparatively rare (1). In clinical practice, metastatic dissemination to atypical organs, such as the breast, skin, eyes, pancreas, and skeletal muscle, is infrequently reported. The diagnosis of distant

10.3389/fonc.2024.1422817

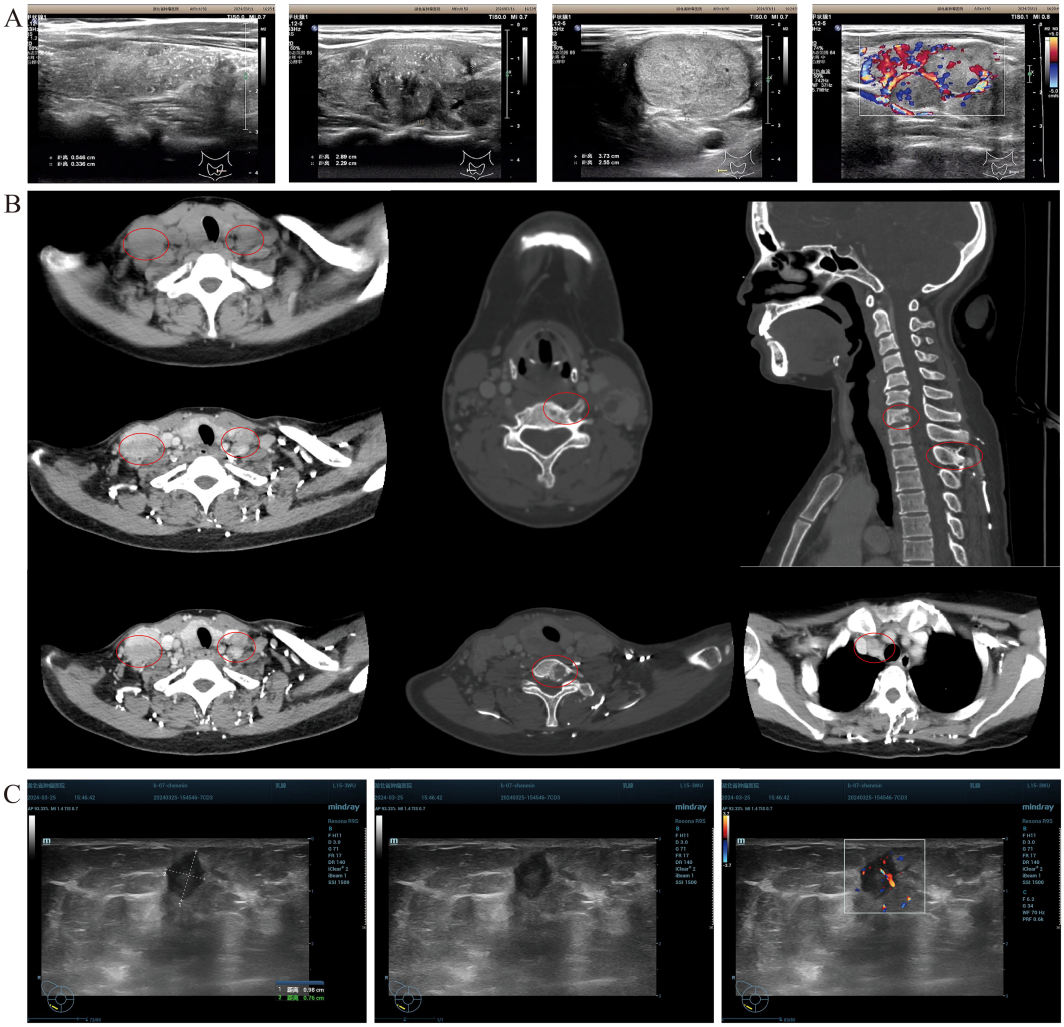


FIGURE 1
Patient imaging evaluation. **(A)** Thyroid color Doppler ultrasound revealed the presence of multiple punctate strong echoes within the bilateral lobes of the thyroid gland. These findings were accompanied by multiple hypoechoic and isoechoic masses, exhibiting indistinct boundaries and irregular contours. The internal echogenicity was heterogeneous, with evidence of multiple small calcifications. CDFI demonstrated discernible blood flow signals within these masses. Additionally, multiple lymph node echoes with well-defined boundaries but irregular shapes were identified in the bilateral cervical regions (zones II, III, IV, and VI). Some of these lymph nodes exhibited fusion, and the structure of the cortex and medulla was not clear. A subset of these lymph nodes displayed intense punctate echoes, and CDFI confirmed the presence of blood flow signals. **(B)** CT scan of the neck showed multiple lymph node metastasis in the anterior–superior mediastinum and multiple bone destruction in the lower cervical spine. **(C)** Breast color Doppler ultrasound examination of the right breast detected a 0.95 × 0.77 × 0.84 cm low-echoic mass, characterized by a clear boundary and an irregular shape. Certain sections of this mass exhibited angular features, with an aspect ratio > 1. CDFI analysis further revealed abundant blood flow signals within the mass.

metastasis is typically predicated on the presentation of clinical symptoms or the detection of suspicious imaging findings. The overall mortality rates at 5 and 10 years subsequent to the diagnosis of distant metastasis are 65% and 75%, respectively (1).

In the case reported by Dris Kharroubi et al., there was a 19-year-old woman with multifocal typical PTC without local lymph node infiltration. After receiving surgical treatment and radioactive iodine treatment, breast metastases were found after a radioactive iodine scan (7). Compared with the case reported by Kharroubi et al., the local infiltration of the primary tumor in our case was more serious and there were more distant metastases. In the case reported by Dan Zhang et al., there was a middle-aged female patient with papillary thyroid oncocytoma with distant metastasis of the breast and cervical spine. In the case of multiple recurrences, she only received surgical treatment of the primary tumor and eventually died of cancer cachexia (8). The case we reported is similar to the case reported by Dan Zhang et al., which is also a middle-aged female patient with cervical lymph node infiltration and distant metastasis of breast and cervical spine. However, the primary tumor subtypes of the two are different, and the compliance is also different.

BARF and *RET* genes are associated with distant metastasis of PTC. *BRAF* V600E mutations are frequently observed in subsets of PTC, exhibiting more aggressive clinicopathological profiles, as

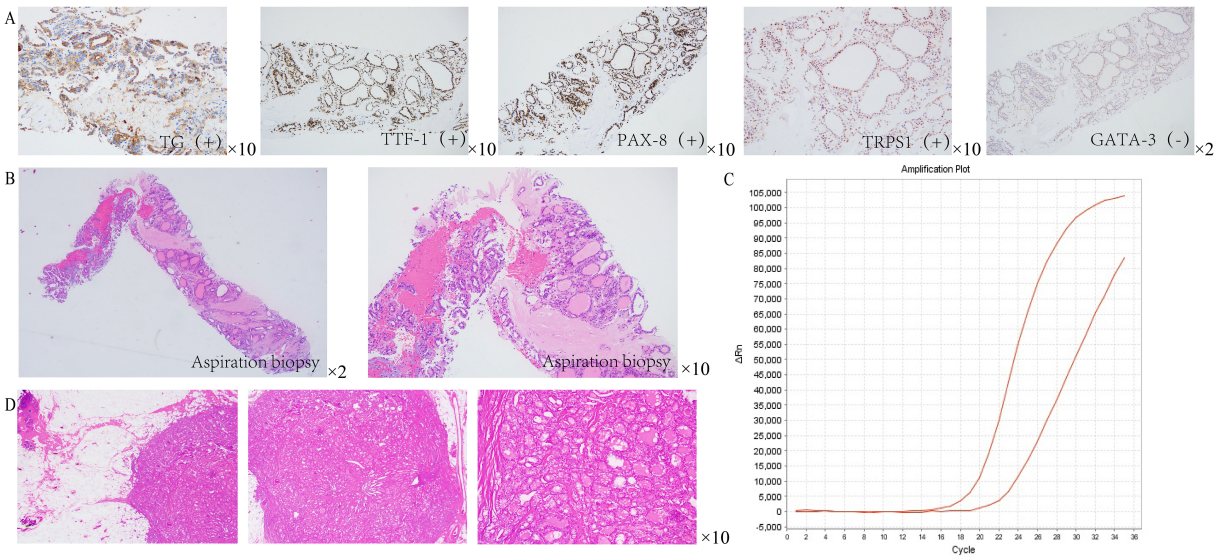


FIGURE 2
Pathological results of breast tissue in patients. **(A)** Immunohistochemical analysis revealed positive staining for thyroglobulin (Tg), thyroid transcription factor-1 (TTF-1), and PAX-8. Notably, TRPS1 staining was observed to be weakly positive, whereas GATA-3 staining was definitively negative. **(B)** HE staining showed that the right breast mass was consistent with adenocarcinoma. **(C)** PCR results indicated a positive fusion of the CCDC6-*RET* gene (Exon 1 to Exon 12). **(D)** HE staining of the resected specimen from the right breast mass confirmed the presence of (right breast) adenocarcinoma.

reported in the literature (9). In the case of this patient, a positive CCDC6-*RET* (Exon 1–Exon 12) gene fusion was detected. *RET* kinase fusion occurs in a minority of PTC patients, ranging from 10% to 20% (10), and it exhibits a mutually exclusive pattern with other driver mutations, including *BRAF* and *RAS* mutations, as well as alternative receptor tyrosine kinase (*RTK*) fusions, indicating *RET* fusion as a pivotal oncogenic event in the pathogenesis of PTC (10).

At present, studies have shown that mutations, including fusions, involving the *BRAF* and *RET* genes are associated with a higher likelihood of a clinical diagnosis of thyroid cancer (11). Simultaneously, several studies have emphasized that the incidence of lymph node and distant metastasis in thyroid cancer exhibiting *BRAF* gene mutations is notably low, suggestive of a potential protective mechanism (12). Conversely, individuals harboring *RET* gene fusion mutations demonstrate a heightened predisposition towards lymph node, nerve, vascular, and distant metastases (13). Additionally, the current investigation of relevant gene mutations of DTC primarily focuses on the prediction of the metastasis to lymph node or bone. As for organ metastasis, particularly specific to the breast, whether it possesses certain characteristics of gene mutations remains uncertain due to the lack of large-scale validation. As a result, a definitive correlation and a theoretical conclusion cannot be drawn at this time. We will try to do some exploration on this aspect. We anticipate that there will be more research in this area in the future.

In accordance with established guidelines (1), all patients diagnosed with DTC ought to undergo neck ultrasonography and serum thyroglobulin (Tg) and thyroglobulin antibody (TgAb) detection within 6 to 18 months after initial therapeutic intervention. For high-risk PTC patients, as exemplified in this case report, if the therapeutic response is favorable, a more rigorous assessment of serum Tg and TgAb levels is paramount to accurately gauge the treatment efficacy pertaining to distant metastases.

We conducted multidisciplinary team consultations with thyroid surgeons and oncologists, and concluded that the patient's thyroid cancer is currently well-differentiated PTC, and postoperative adjuvant therapy is still based on iodine-131 radiotherapy to treat metastases. However, in view of the large number of metastases and the large range of lesions in patients, we would also recommend that patients undergo external radiotherapy at the relevant site. At the same time, in view of the patient's pathological type suggesting *BRAF V600E* mutation and *RET* gene mutation, we may suggest that the patient should be treated with vemurafenib, trimetinib, and dabrafenib mesylate to treat *BRAF V600E* mutant tumors. If the above treatment methods fail to achieve satisfactory results, pratinib can be used to treat *RET* fusion thyroid cancer, and sorafenib and other small-molecule multikinase inhibitors targeted the inhibition of Raf kinase.

In summary, despite the generally favorable prognosis of PTC, the potential for distant or even multiple organ metastases underscores the importance of meticulous attention to PTC classification, specific gene expression profiling, postoperative adjuvant therapies (encompassing endocrine therapy, biological therapy, radiotherapy, and others), and rigorous follow-up protocols. Such comprehensive management strategies are vital

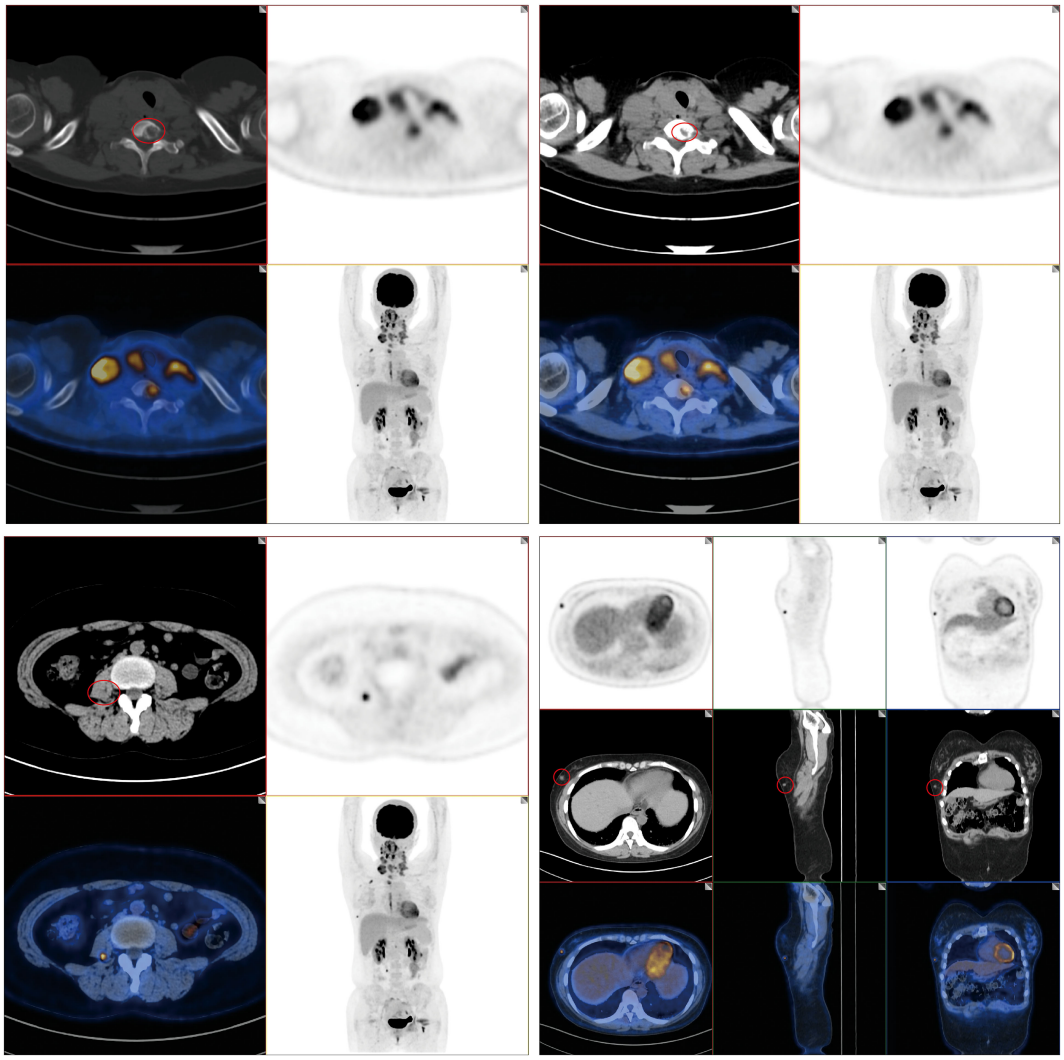


FIGURE 3
PET-CT results of patients. PET-CT imaging revealed multiple, slightly hypoechoic nodules within the bilateral thyroid lobes, suggesting the possibility of lymph node metastasis in the bilateral neck, supraclavicular region, and mediastinum. Furthermore, soft tissue density nodules were discernible in the outer lower quadrant of the right breast. Additionally, a nodular abnormal radioactive concentration shadow was observed in the right psoas major muscle; bone destruction was evident in the right second rib and seventh cervical vertebra.

for ameliorating poor prognostic outcomes associated with this disease.

Conclusion

Despite thyroid cancer being an endocrine malignancy characterized by high indolence and generally favorable prognosis, it necessitates vigilant attention. In clinical practice, heightened emphasis should be placed on the detection and assessment of multiple genetic markers in patients with PTC. Furthermore, for patients harboring high-risk factors for metastasis, surveillance must encompass not only lymph node and bone metastases but also potential dissemination to other bodily tissues, including the breast. Additionally, we aspire to gain deeper insights into the correlations and underlying mechanisms linking clinical manifestations such as the onset, progression, and metastasis of thyroid cancer with multiple genetic mutations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

WH: Writing – original draft, Resources. YY: Writing – original draft, Methodology. PZ: Writing – original draft. LJ: Funding acquisition, Writing – original draft. JC: Conceptualization, Supervision, Writing – review & editing. HZ: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Hubei Province Medical Youth Top Talent Project (EWT (2023)65, Oncology), the Hubei Provincial Natural Science Foundation Innovation and Development Joint Fund Project (2024AFD454), the Chen Xiao-Ping Foundation for the Development of Science and Technology of Hubei Province (CXPJJH123001-2320), and the Hubei Cancer Hospital Biomedical Center Research Project (grant number 2022SWZX03,2022SWZX09).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor WY declared shared parent affiliation with the authors at the time of review.

Publisher's note

References

1. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. (2019) 30:1856–83. doi: 10.1093/annonc/mdz400

2. Liu Y, Wang J, Hu X, Pan Z, Xu T, Xu J, et al. Radioiodine therapy in advanced differentiated thyroid cancer: Resistance and overcoming strategy. *Drug Resist Updat*. (2023) 68:100939. doi: 10.1016/j.drup.2023.100939

3. Erdem H, Gündogdu C, Sipal S. Correlation of E-cadherin, VEGF, COX-2 expression to prognostic parameters in papillary thyroid carcinoma. *Exp Mol Pathol*. (2011) 90:312–7. doi: 10.1016/j.yexmp.2011.01.008

4. Londero SC, Krogdahl A, Bastholt L, Overgaard J, Pedersen HB, Hahn CH, et al. Papillary thyroid carcinoma in Denmark, 1996-2008: outcome and evaluation of established prognostic scoring systems in a prospective national cohort. *Thyroid*. (2015) 25:78–84. doi: 10.1089/thy.2014.0294

5. Bonichon F, Buy X, Godbert Y, Pointillart V, Henriques de Figueiredo B, Gangi A, et al. Local treatment of metastases from differentiated thyroid cancer. *Ann Endocrinol (Paris)*. (2015) 76:1S40–6. doi: 10.1016/S0003-4266(16)30013-0

6. Elsamna ST, Suri P, Mir GS, Roden DF, Paskhover B. The benefit of primary tumor surgical resection in distant metastatic carcinomas of the thyroid. *Laryngoscope*. (2021) 131:1026–34. doi: 10.1002/lary.29053

7. Kharroubi D, Richa C, Saie C, Chami L, Lussey-Lepoutre C. Solitary breast metastasis from thyroid papillary carcinoma revealed on whole-body radioactive 131I scan. *Clin Nucl Med*. (2020) 45:687–8. doi: 10.1097/RLU.0000000000003115

8. Zhang D, Zhu XL, Jiang J. Papillary thyroid carcinoma with breast and bone metastasis. *Ear Nose Throat J*. (2023) 102:259–62. doi: 10.1177/01455613221145273

9. Liu R, Xing M. TERT promoter mutations in thyroid cancer. *Endocr Relat Cancer*. (2016) 23:R143–55. doi: 10.1530/ERC-15-0533

10. Salvatore D, Santoro M, Schlumberger M. The importance of the RET gene in thyroid cancer and therapeutic implications. *Nat Rev Endocrinol*. (2021) 17:296–306. doi: 10.1038/s41574-021-00470-9

11. Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. *Nat Rev Endocrinol*. (2011) 7:569–80. doi: 10.1038/nrendo.2011.142

12. Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. *Endocr Rev*. (2007) 28:742–62. doi: 10.1210/er.2007-0007

13. Wang Z, Tang P, Hua S, Gao J, Zhang B, Wan H, et al. Genetic and clinicopathologic characteristics of papillary thyroid carcinoma in the Chinese population: high BRAF mutation allele frequency, multiple driver gene mutations, and RET fusion may indicate more advanced TN stage. *Onco Targets Ther*. (2022) 15:147–57. doi: 10.2147/OTT.S339114

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 14 November 2024
DOI 10.3389/fonc.2024.1440126

OPEN ACCESS

EDITED BY
Monica Cantile,
G. Pascale National Cancer Institute Foundation (IRCCS), Italy

REVIEWED BY
Marco Lucioni,
University of Pavia, Italy
Fengbo Huang,
Zhejiang University, China

*CORRESPONDENCE
Euitae Kim
ket799@naver.com

RECEIVED 29 May 2024
ACCEPTED 16 October 2024
PUBLISHED 14 November 2024

CITATION
Kim E (2024) Incidental discovery of invasive lobular carcinoma and anaplastic large cell lymphoma during sentinel lymph node biopsy: a case report.
Front. Oncol. 14:1440126.
doi: 10.3389/fonc.2024.1440126

Incidental discovery of invasive lobular carcinoma and anaplastic large cell lymphoma during sentinel lymph node biopsy: a case report

Euitae Kim*

Department of Surgery, Dankook University College of Medicine, Cheonan, Republic of Korea

This study reports a rare case of concurrent invasive lobular carcinoma (ILC) of the breast and ALK-negative anaplastic large cell lymphoma (ALCL) detected during sentinel lymph node biopsy (SLNB). A 55-year-old female underwent breast cancer surgery following abnormal breast screening results, revealing ILC histologically. Unexpectedly, SLNB identified ALCL, later confirmed on pathology. The patient received no ALCL-specific treatment due to lack of additional lesions and remained recurrence-free post-surgery. The paper discusses diagnostic challenges, emphasizing comprehensive evaluation and multidisciplinary collaboration. It highlights the rarity of simultaneous ALCL and breast cancer without prior radiation, stressing the importance of clinical vigilance. Despite challenges in differentiation and treatment optimization, individualized patient care is crucial. Further research into concurrent ALCL and breast cancer is essential for improved management strategies. This case underscores complexities in managing rare malignancies and emphasizes the need for tailored approaches for optimal patient outcomes.

KEYWORDS

lymphoma, large-cell, anaplastic, sentinel lymph node biopsy, case report, invasive lobular carcinoma

Introduction

Breast cancer is the most common malignant condition in women globally as of 2020, with almost 2.26 million women newly diagnosed in that year. It ranks fifth among the most common causes of cancer-related death worldwide, yet it remains the leading cause of cancer death in less developed countries (1). Studies conducted by Gilchrist (2) and Zeidman and Buss (3) in the 1940s demonstrated that metastatic cells spread through

regional lymphatics in an organized and reproducible manner, laying the groundwork for the evolution of Sentinel lymph node biopsy (SLNB). As a result, SLNB has become an integral part of contemporary breast cancer treatment, serving both as a staging and therapeutic tool, with axillary surgery traditionally considered essential (4). Anaplastic large cell lymphoma (ALCL) is a subtype of T-cell lymphoma (TCL) characterized by the presence of large cells and a strong, diffuse expression of the activation marker CD30. It is further classified into ALK-positive (ALK+) and ALK-negative (ALK-) subtypes based on the expression or absence of anaplastic lymphoma kinase (ALK) (5). Additionally, ALK-negative ALCL is currently categorized into systemic, primary cutaneous, and breast implant-associated ALCL (6). However, the simultaneous occurrence of ILC and ALK-negative ALCL is exceedingly rare and, to our knowledge, has not been previously reported. We aim to report on a case of ALCL incidentally detected during SLNB performed during breast cancer surgery in a patient who did not undergo breast augmentation with implants.

Case description

A 55-year-old female patient visited the outpatient clinic after being recommended to undergo a tissue biopsy due to abnormal findings identified during regular breast screening mammograph (MMG) and breast ultrasound (US). The patient had previously undergone regular breast screening with MMG every two years, and no significant findings were observed during that period. She had no previous diagnosed conditions and was not taking any medications. The patient mentioned a family history of her father passing away from pancreatic cancer and her sister undergoing treatment for breast cancer. She started menarche at the age of 15 and is currently not in menopause. After the outpatient visit, an US was performed, revealing an indistinct margin hypoechoic mass measuring 1.5 cm, located 4 cm from the nipple at the 9 o'clock direction of the patient's right breast (Figure 1). A core needle biopsy was performed on the detected mass, and the histological examination confirmed invasive lobular carcinoma (ILC). The immunohistochemistry staining results were estrogen receptor (ER) positive with an Allred score of 8, progesterone receptor (PR) positive with an Allred score of 8, human epidermal growth factor receptor-2 (HER2) score of 2, indicating equivocal result, and no amplification of HER2 was detected according to fluorescent *in situ* hybridization (FISH). To assess the staging of the patient before surgery, a breast magnetic resonance imaging (MRI), chest computed tomography (CT), abdominopelvic CT (A-P CT), and a bone scan were performed. The results of the examinations did not reveal any distant metastasis. The breast MRI showed a 2.1 cm x 1.1 cm x 2.2 cm lesion that was confirmed ILC (Figure 2A), and a suspicious lymph node measuring 1.7 cm was identified at axillary level I (Figure 2B). Additionally, a 0.5 cm low echoic lesion was observed in the 1 o'clock position of the right breast on breast US, and it was decided to remove it concurrently during the breast cancer surgery. Three weeks after the outpatient visit, the patient underwent a right breast lumpectomy and a SLNB. During the surgery, two lymph nodes were harvested for SLNB and they were examined using frozen section biopsy, which confirmed metastasis. As a result, an axillary lymph node dissection was performed for levels I and II of the axillary lymph nodes. The final pathologic report revealed that the breast cancer measured 3cm x 3cm in size ILC. The nuclear grade and histologic grade were both grade 1, indicating a well-differentiated tumor. Lobular carcinoma *in situ* was extensively present. Lympho-vascular invasion was not identified, and there was no lymph node metastasis among the 15 axillary lymph nodes examined, including the 2 sentinel lymph nodes. The hormone receptor status showed that the ER and PR were positive with an Allred score of 8. However, the HER-2 score was 1, indicating a negative result. The p53 protein was negative, suggesting no abnormalities, and the Ki-67 proliferation index was 10%, indicating a low level of cell proliferation. Interestingly, the final histological examination results differed from the intraoperative frozen section analysis as no evidence of breast cancer metastasis was found in the axillary lymph nodes. Enlarged sentinel lymph nodes were examined for pathologist's intraoperative consultation. At that time large atypical cells were noted in the sinuses of the sentinel lymph nodes and it was difficult to distinguish metastatic lobular carcinoma from malignant lymphoma. Thus, the final decision for the sentinel lymph nodes was deferred to permanent sections. The lumpectomy specimen of the breast revealed typical microscopic features of invasive lobular carcinoma with associated extensive lobular carcinoma *in situ* (Figure 3A). Immunohistochemically the tumor cells revealed lack of E-cadherin expression (Figure 3B) and diffuse strong positivity for ER and PR. Therefore, the breast lesion was diagnosed as invasive lobular carcinoma. But the microscopic features of sentinel lymph nodes revealed proliferation of atypical large cells within sinuses (Figure 4A). Immunohistochemically the atypical cells were negative for cytokeratin (Figure 4B) and ER. Thus, the possibility of metastatic carcinoma was excluded. The atypical large cells in the sentinel lymph nodes were positive for CD45, CD30 (Figure 4C), and MUM1, and negative for ALK, CK-multi (AE1/AE3), ER, CD10, EBV (*in situ* hybridization), CD15, EMA,

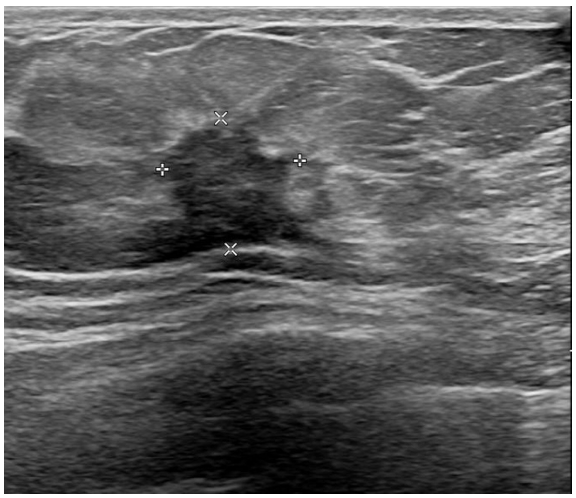


FIGURE 1
Ultrasound image of a breast lesion.

FIGURE 2
Breast MRI image of **(A)** breast and **(B)** axillary area.

granzyme B, TIA-1, p53, PAX-5, and CD20 (L26). The Ki-67 labeling index was high, and focal positivity was noted for CD3, CD2, CD4, CD5, CD8, CD45RO (UCHL1), and CD43. CD68 positivity was observed in sinusoidal histiocytes, while PR, CK5/6, E-Cadherin, p63, and bcl-2 were non-contributory. These findings led to the final diagnosis of ALK-negative ALCL in the sentinel lymph nodes.

Based on these final pathological results, the patient was diagnosed with both breast cancer and ALCL. The patient was referred to the hemato-oncology department for further testing and

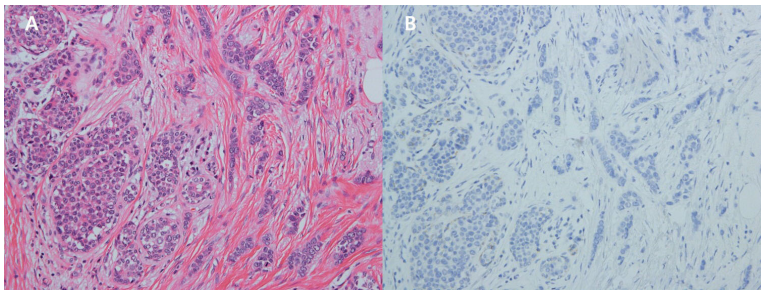


FIGURE 3
(A) x200 HE The breast tumor shows characteristic morphologies of invasive pleomorphic lobular carcinoma (right) and lobular carcinoma *in situ* (left). **(B)** x200 Immunohistochemistry Breast tumor cells are negative for E-cadherin.

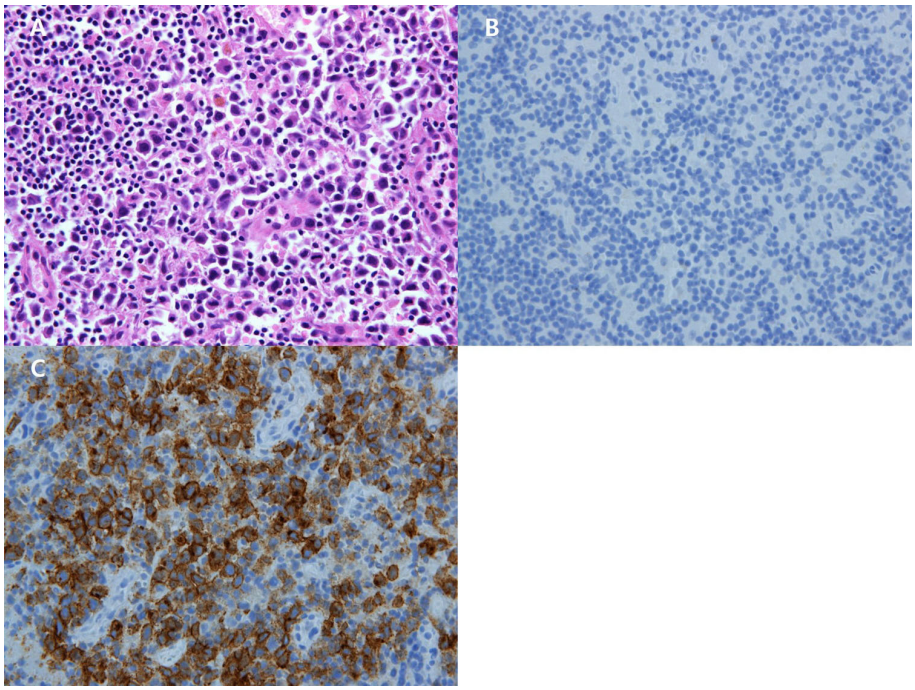


FIGURE 4
(A) x200 Immunohistochemistry Atypical large cells are positive for CD30. **(B)** x200HE The sentinel lymph node shows proliferation of large atypical lymphocytes within sinuses. **(C)** x200 Immunohistochemistry Large atypical cells are negative for cytokeratin.

confirmation of ALCL. No additional lesions of ALCL were found in the chest CT and A-P CT performed as part of the preoperative evaluation. As adjuvant radiation therapy was planned to include the surgical site in the right axillary area, it was decided to observe the patient's progress without additional treatment for ALCL. Six months after completing radiation therapy, follow-up examinations —including breast MRI, chest CT, and A-P CT—did not reveal any evidence of breast cancer or ALCL recurrence. Consequently, the decision was made to continue observation at six-month intervals while the patient received ovarian function suppression injections and tamoxifen as adjuvant treatment for breast cancer. Over the subsequent four years, no specific findings of recurrence or progression were observed, and the patient remains under ongoing surveillance.

Discussion

Axillary nodal involvement has been firmly established as a prognostic indicator, with a decrease in 5-year survival ranging from approximately 28% to 40% in affected patients (7) Therefore, axillary surgery serves not only as a staging tool but also contributes to locoregional control, potentially leading to improved survival outcomes. The role of axillary surgery in clinically node-negative (cN0) axilla was initially investigated in trials conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-04) and the Cancer Research Campaign Working Party (King's/Cambridge) (8, 9). These trials demonstrated that treatment of cN0 axilla with either surgery or radiotherapy did not confer a survival benefit compared to observation and treatment at the time of recurrence. As a result, SLNB has emerged as a guiding tool for determining disease staging and the need for axillary lymph node dissection.

It is already known that the incidence of breast cancer in young female patients increases after treatment of lymphoma due to chest radiotherapy performed for the treatment of Hodgkin lymphoma (HL) (10, 11). However, it is very rare that invasive breast cancer and axillary lymphoma are simultaneously identified in patients with no previous history of radiation therapy. In a previous literature report, there have been several reports of focal lymphoma in sentinel lymph node biopsy or axillary lymphoma *in situ* performed during surgery in patients with invasive breast cancer or ductal carcinoma *in situ*, but no reports of ALCL been identified as in this case (12–14).

The co-occurrence of breast cancer and lymphoma is a rare clinical scenario, one that remains poorly understood by oncologists, hematologists, and pathologists alike. In this case, the patient presented with ILC of the breast and ALK– ALCL, an uncommon combination. ILC itself is a less frequent subtype of breast cancer, often associated with a diffuse, infiltrative growth pattern and later-stage diagnosis (1, 2). ALK– ALCL, on the other hand, is a rare and aggressive form of lymphoma that typically affects older adults, with a median age of diagnosis in the sixth decade of life (5, 16). The patient in this case fits within

the expected age range for both diseases, which may point to an age-related vulnerability or a potential shared mechanism, such as immune dysregulation, leading to the development of both malignancies.

ALCL is a type of TCL characterized by large cells and strong CD30 expression. It is divided into ALK+ and ALK- groups, with each comprising about 50% of cases. ALK+ ALCL is more common in children and has a better prognosis, while ALK- ALCL is more common in adults and has a more aggressive behavior (15). Diagnosis of ALK- ALCL can be challenging due to its morphological similarity to other large TCL with CD30 expression. Recent molecular studies have identified diverse genetic alterations in ALK- ALCL, leading to potential further subtyping based on genetic abnormalities (1, 15).

Differentiating between ALK- ALCL and carcinomas can be challenging due to potential morphological overlap, particularly in poorly differentiated cases. Carcinomas lack "hallmark" cells and exhibit glandular or squamous differentiation, distinguishing them from ALCL. ALK- ALCL is negative for cytokeratins and germ cell markers OCT3/4 and SALL4. Poorly differentiated carcinomas are cytokeratin-positive and lack CD30 and T-cell markers, with variable expression of organ-specific transcription factors. Careful interpretation of epithelial membrane antigen (EMA) is warranted, as it may be positive in ALK- ALCL (5). As a result, it is deemed that reaching a definitive conclusion from intraoperative frozen section pathology results would have been difficult.

Differentiating ALCL from other CD30+ lymphomas, such as HL, PTCL, and Mycosis Fungoides (MF), is critical due to differences in treatment approaches and prognosis. ALCL, characterized by large anaplastic cells expressing CD30, can be divided into ALK+ and ALK- subtypes, with distinct clinical and pathological features (5). HL, another CD30+ lymphoma, typically presents with Reed-Sternberg cells in a mixed inflammatory background. While CD30 expression is a common feature, ALCL differs by the presence of hallmark cells and the potential for ALK expression, which is absent in HL. Additionally, ALCL usually exhibits a more aggressive clinical course than HL, necessitating a different therapeutic strategy (6). PTCL is a heterogeneous group of T-cell malignancies, some of which can express CD30. However, unlike ALCL, PTCL lacks the characteristic large anaplastic cells with horseshoe-shaped nuclei. Immunophenotypic differences, such as the lack of ALK expression and distinct genetic aberrations, further aid in differentiating PTCL from ALCL (15). MF, primarily a cutaneous T-cell lymphoma, can exhibit CD30 positivity, particularly in transformed cases or in Sézary syndrome. However, MF typically presents with skin lesions and follows an indolent course, contrasting with the often systemic and aggressive nature of ALCL. The histopathological examination in MF shows epidermotropism and smaller, cerebriform lymphocytes, which are distinct from the large anaplastic cells of ALCL (16). In summary, while CD30 expression is a shared feature among these lymphomas, the diagnosis of ALCL is supported by its unique cellular morphology, the potential presence of ALK expression, and its distinct clinical presentation. Accurate differential diagnosis is essential for guiding appropriate therapeutic decisions and improving patient outcomes.

The management of ALK- ALCL poses challenges similar to those encountered in ALK+ ALCL. Despite higher relapse rates, current frontline therapies, primarily CHOP regimen (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone), yield unsatisfactory results with 5-year progression-free survival rates ranging from 30% to 55% (16). In most cases of follicular lymphoma that was concurrently diagnosed with breast cancer, adjuvant chemo therapy was administered (12). However, in the patient reported by Cox et al., who had low-grade follicular lymphoma, observation without adjuvant chemo therapy was also pursued (17). In our case, apart from ALCL identified solely in the axillary lymph nodes, no other suspicious lesions were found, and the patient did not exhibit any specific symptoms, so additional treatment for ALCL was not administered.

Recent advancements in molecular diagnostics, such as testing for DUSP22 and TP63 rearrangements, could offer valuable insights into ALK-negative ALCL prognosis and aid in distinguishing it from peripheral T-cell lymphoma (PTCL) NOS (5, 15). Although these tests were not performed in this case due to the lack of systemic lymphadenopathy and the stable condition of the patient, they might be considered in future cases to refine diagnosis and treatment plans.

Conclusion

In conclusion, our report highlights a rare case of concurrent ILC of the breast and ALK- ALCL detected incidentally during SLNB. This underscores the necessity of thorough diagnostic evaluation and multidisciplinary collaboration in managing complex malignancies. The concurrent presence of ALCL and breast cancer without prior radiation therapy underscores the need for heightened clinical suspicion and comprehensive pathological assessment to ensure accurate diagnosis and appropriate treatment planning. The rarity of simultaneous ALCL and breast cancer without prior radiation therapy underscores the importance of heightened clinical suspicion and comprehensive pathological assessment to ensure accurate diagnosis and appropriate treatment planning. Challenges persist in differentiating ALCL from other large TCL and optimizing treatment strategies for ALK- ALCL. While our case contributes to existing literature, further research into the molecular characteristics and prognostic implications of concurrent ALCL and breast cancer is warranted to guide future management decisions. This case exemplifies the complexities inherent in managing rare malignancies and emphasizes the importance of individualized patient care and a multidisciplinary approach to optimize outcomes. Further research into the molecular characteristics and prognostic implications of concurrent ALCL and breast cancer is warranted to guide future management decisions.

Data availability statement

The datasets presented in this article are not readily available because nothing to restrict. Requests to access the datasets should be directed to EK, ket799@naver.com.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EK: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The present research was supported by the research fund of Dankook University in 2024.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71:209–49. doi: 10.3322/caac.21660

2. Gilchrist RK. Fundamental factors governing lymphatic spread of carcinoma. *Ann Surg*. (1940) 111:630–9. doi: 10.1097/00000658-194004000-00014

3. Zeidman I, Buss JM. Experimental studies on the spread of cancer in the lymphatic system. I. Effectiveness of the lymph node as a barrier to the passage of embolic tumor cells. *Cancer Res*. (1954) 14:403–5.

4. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a meta-analysis. *Cancer*. (2006) 106:4–16. doi: 10.1002/cncr.v106:1

5. Pina-Oviedo S, Ortiz-Hidalgo C, Carballo-Zarate AA, Zarate-Osorno A. ALK-negative anaplastic large cell lymphoma: current concepts and molecular pathogenesis of a heterogeneous group of large T-cell lymphomas. *Cancers (Basel)*. (2021) 13. doi: 10.3390/cancers13184667

6. Schwab U, Stein H, Gerdes J, Lemke J, Kirchner H, Schaadt M, et al. Production of a monoclonal antibody specific for Hodgkin and Sternberg-Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. *Nature*. (1982) 299:65–7. doi: 10.1038/299065a0

7. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer*. (1989) 63:181–7. doi: 10.1002/1097-0142(19890101)63:1<181::AID-CNCR2820630129>3.0.CO;2-H

8. Fisher B, Montague E, Redmond C, Barton B, Borland D, Fisher ER, et al. Comparison of radical mastectomy with alternative treatments for primary breast cancer. A first report of results from a prospective randomized clinical trial. *Cancer*. (1977) 39:2827–39. doi: 10.1002/1097-0142(197706)39:6<2827::AID-CNCR2820390671>3.0.CO;2-I

9. Michael B, John L, David A, Diana M, Christopher W, Austin G, et al. Cancer research campaign (King's/Cambridge) trial for early breast cancer. A detailed update at the tenth year. Cancer Research Campaign Working Party. *Lancet*. (1980) 2:55–60.

10. Moskowitz CS, Chou JF, Wolden SL, Bernstein JL, Malhotra J, Friedman DN, et al. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol*. (2014) 32:2217–23. doi: 10.1200/JCO.2013.54.4601

11. Schaapveld M, Aleman BMP, Eggermond AM, Janus CPM, Krol ADG, Maazen RWM, et al. Second cancer risk up to 40 years after treatment for hodgkin's lymphoma. *N Engl J Med*. (2015) 373:2499–511. doi: 10.1056/NEJMoa1505949

12. Tamaoki M, Nio Y, Tsuboi K, Nio M, Tamaoki M, Maruyama R, et al. A rare case of non-invasive ductal carcinoma of the breast coexisting with follicular lymphoma: A case report with a review of the literature. *Oncol Lett*. (2014) 7:1001–6. doi: 10.3892/ol.2014.1885

13. Laudenschlager MD, Tyler KL, Geis MC, Koch MED, Graham DB. A rare case of synchronous invasive ductal carcinoma of the breast and follicular lymphoma. *S D Med*. (2010) 63:123–5.

14. Mirkheshti N, Mohebtash M. A rare case of bilateral breast lobular carcinoma coexisting with primary breast follicular lymphoma. *J Community Hosp Intern Med Perspect*. (2019) 9:155–8. doi: 10.1080/20009666.2019.1579611

15. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Barreto de Oliveira Araujo I, Berti E, et al. The 5th edition of the world health organization classification of hematolymphoid tumors: lymphoid neoplasms. *Leukemia*. (2022) 36:1720–48. doi: 10.1038/s41375-022-01620-2

16. Adams SV, Newcomb PA, Shustov AR. Racial patterns of peripheral T-cell lymphoma incidence and survival in the United States. *J Clin Oncol*. (2016) 34:963–71. doi: 10.1200/JCO.2015.63.5540

17. Cox J, Lunt L, Webb L. Synchronous presentation of breast carcinoma and lymphoma in the axillary nodes. *Breast*. (2006) 15:246–52. doi: 10.1016/j.breast.2005.06.009

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 27 November 2024
DOI 10.3389/fonc.2024.1444431

OPEN ACCESS

EDITED BY
Dharmendra Kumar Yadav,
Gachon University, Republic of Korea

REVIEWED BY
Yuanzhi Chen,
Xiamen University, Xiamen, China
Arianna Dri,
Aviano Oncology Reference Center (IRCCS), Italy

*CORRESPONDENCE
Fuming Qiu
qiufuming@zju.edu.cn
Jian Huang
drhuangjian@zju.edu.cn

RECEIVED 05 June 2024
ACCEPTED 12 November 2024
PUBLISHED 27 November 2024

CITATION
Zhao J, Huang F, Xu X, Zhang Y, Xing X, Huang J and Qiu F (2024) Case report: Prolonged benefit of ESG401, a Trop2 antibody-drug conjugate, in endocrine-refractory hormone receptor-positive, HER-2 negative metastatic breast cancer. *Front. Oncol.* 14:1444431. doi: 10.3389/fonc.2024.1444431

Case report: Prolonged benefit of ESG401, a Trop2 antibody-drug conjugate, in endocrine-refractory hormone receptor-positive, HER-2 negative metastatic breast cancer

Jing Zhao[1,2,3], Fengbo Huang[3,4], Xia Xu[5], Yan Zhang[1,3], Xiaoyan Xing[6], Jian Huang[2,3,7,8]* and Fuming Qiu[1,2,3,7]*

[1]Department of Medical Oncology, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China, [2]Key Laboratory of Tumor Microenvironment and Immune Therapy of Zhejiang Province, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China, [3]Cancer Institute, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China, [4]Department of Pathology, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China, [5]Department of Pathology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang, China, [6]Shanghai Escugen Biotechnology Co., Ltd, Shanghai, China, [7]Cancer Center, Zhejiang University, Hangzhou, Zhejiang, China, [8]Department of Breast Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

Breast cancer (BC) remains a leading cause of cancer-related mortality in women, with hormone receptor-positive (HR+) tumors accounting for a significant proportion of cases. Despite advancements in endocrine therapy (ET), resistance remains a challenge in metastatic settings. The use of cyclin-dependent kinases 4/6 (CDK4/6) inhibitors in combination with endocrine therapy has notably improved survival. In China, when patients develop resistance to CDK4/6 inhibitors (CDK4/6i) or face financial constraints that prevent their use, chemotherapy becomes the standard treatment approach. This highlights an urgent need for effective treatments following CDK4/6i therapy. ESG401 is a novel trophoblast cell-surface antigen 2 (Trop2) directed antibody-drug conjugate (ADC) with promising preclinical and early clinical efficacy and safety data. We report a case of a 61-year-old female with HR +HER2- metastatic breast cancer (MBC) who developed resistance to fulvestrant and subsequent chemotherapy but achieved a durable partial response (PR) lasting more than 22.5 months following ESG401 treatment. This case underscores the potential role of Trop2-directed ADCs, such as ESG401, in overcoming endocrine resistance and providing meaningful clinical benefit in heavily pretreated patients with HR+/HER2- MBC. Furthermore, the patient's

exceptionally long clinical benefit distinguishes her from other patients receiving ESG401 treatment. Further exploration of the use of ESG401 in HR+HER2- MBC patients, as well as a deeper understanding of the characteristics of patients that may impact sustained efficacy, in expanded clinical trials is warranted.

KEYWORDS

hormone receptor-positive, metastatic breast cancer, endocrine resistance, Trop2 antibody-drug conjugate, case report

1 Introduction

Breast cancer (BC) remains the most frequently diagnosed cancer, accounting for approximately 24.5% of all new cancer cases in 2020, and is the primary cause of cancer-related mortality in women (1). Hormone receptor-positive (HR+) tumors constitute 70-80% of all breast cancers (2). Due to the strong dependency of breast tumor development on the estrogen-estrogen receptor (ER) axis, estrogen suppression therapy and ER antagonists are the main treatments for hormone receptor-positive HER2-negative (HR+HER2-) metastatic breast cancer (MBC) (3). However, not all patients exhibit a favorable response to endocrine therapy (ET). Primary and acquired resistance to ET remains a challenge.

Several studies have revealed that endocrine therapy combined with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) has the potential to overcome resistance to ET and significantly improve survival rates (4–6). Additionally, alternative options such as PIK3CA inhibitors (7), mTOR inhibitors (8), AKT inhibitors (9), and emerging oral selective estrogen receptor degraders (SERDs) are gaining attention as later-line treatments (10). However, the accessibility of some of these treatments is limited in China. For patients who have exhausted endocrine therapy-based options, single-agent chemotherapy remains the standard of care. However, later-line chemotherapy is associated with limited effectiveness, reduced quality of life, and significant toxicity, highlighting the pressing unmet medical needs of these individuals.

ESG401 is a novel antibody-drug conjugate (ADC) comprising a humanized IgG1 monoclonal antibody targeting trophoblast cell-surface antigen 2 (Trop-2) linked to the topoisomerase I inhibitor SN-38 via a proprietary stable-cleavable linker with a drug-to-antibody ratio (DAR) of 8. The preliminary results of a phase I/II study in locally advanced/metastatic solid tumors revealed that ESG401 is safe and well tolerated with promising efficacy in heavily pretreated patients (11). Here, we report a patient with HR+/HER2- MBC who exhibited primary resistance to fulvestrant and had received multiple prior chemotherapy treatments but demonstrated a durable response lasting more than 22 months after treatment with ESG401. At the time of writing, the patient has maintained this response and is still receiving treatment, demonstrating excellent effectiveness and tolerability to ESG401. This case highlights the prolonged clinical benefit achieved by this patient following ESG401 treatment.

2 Case description

In October 2019, a 61-year-old female patient presented to our hospital for the detection of multiple lung nodules by computed tomography (CT). She was diagnosed with lobular breast cancer (luminal B subtype) and underwent a modified radical mastectomy 5 years prior. She underwent adjuvant chemotherapy (epirubicin and cyclophosphamide followed by docetaxel) and received letrozole as adjuvant endocrine therapy until admission. She had a history of asthma, which was well controlled. There were no clinical symptoms or positive signs on physical examination. The chest CT revealed numerous pulmonary nodules, thickening of the bilateral pleural nodules, and enlarged lymph nodes in the mediastinum (Figures 1A, B). Endobronchial ultrasound-guided transbronchial needle aspiration of the mediastinum lymph node confirmed the recurrence of ER-positive, PR-negative, and HER2 2+/fluorescence *in situ* hybridization-negative breast cancer (Figures 1C–G). Metastases were not found in the brain, bones, or abdomen. She was diagnosed with metastatic lobular BC (lung, lymph node and pleural). The patient was advised to undergo CDK4/6 inhibitor-based endocrine therapy but was unable to afford it and declined the treatment at that time. Fulvestrant, a selective estrogen receptor down regulator, was administered. However, a CT scan performed 3 months later revealed significant growth in the lung nodules and a new mass in the liver (Figure 2), indicating primary resistance to endocrine therapy. Then, the patient underwent nine cycles of albumin-bound paclitaxel (200 mg, administered intravenously on Days 1 and 8 every 21 days) as second-line therapy, achieving a partial response (PR), followed by maintenance therapy with capecitabine. The progression-free survival (PFS) time was 13.6 months. Eribulin (2 mg, administered intravenously on Day 1 and Day 8, every 21 days) was then initiated as third-line therapy, resulting in another PR. Maintenance treatment with eribulin was continued for 14.7 months.

10.3389/fonc.2024.1444431

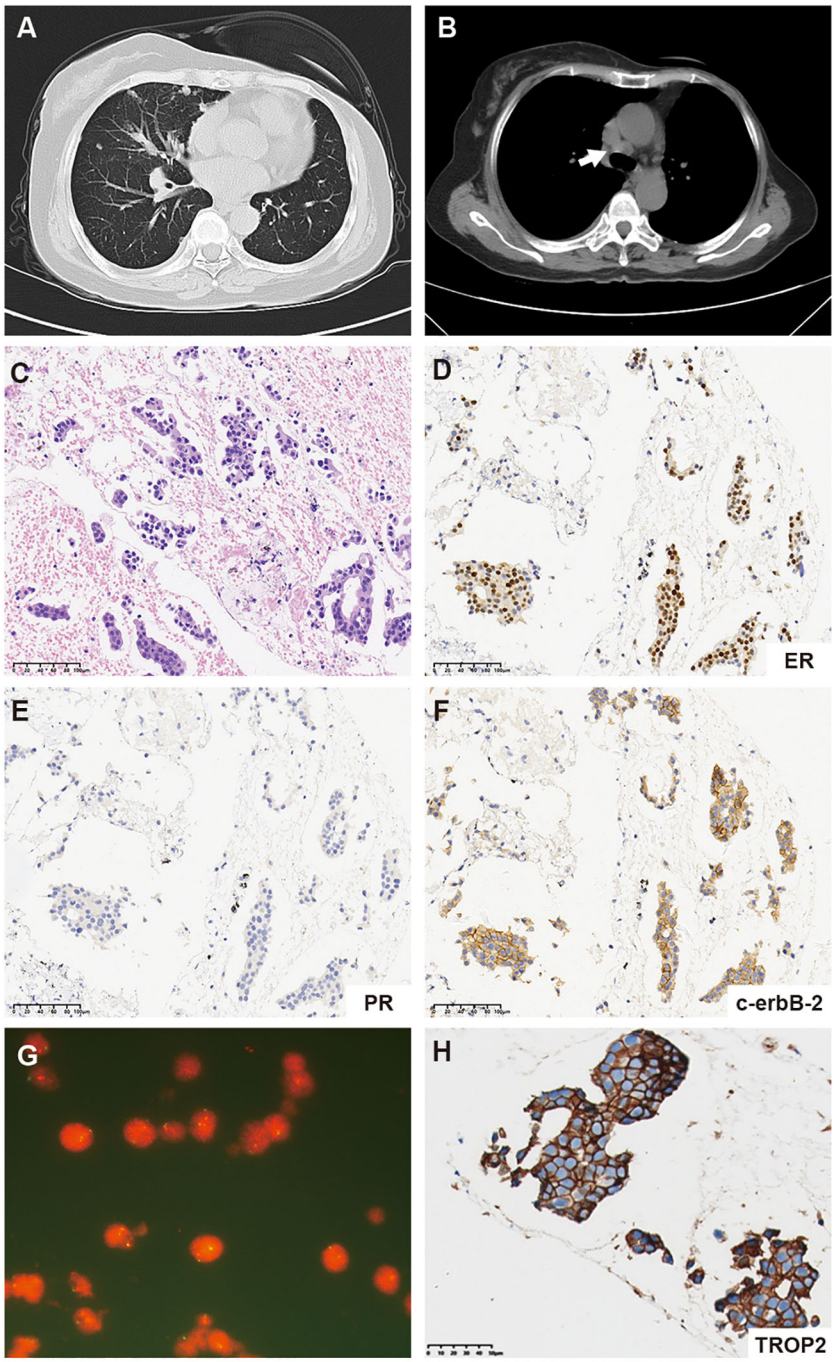


FIGURE 1
(A) Representative computed tomography (CT) scan images of the lung. **(B)** CT scan images of mediastinum lymph node metastases (white arrow). **(C)** Hematoxylin and eosin-stained (HE) section of a metastatic mediastinal lymph node (20×). **(D–F)** Immunohistochemistry (IHC) staining for ER, PR, and c-erbB-2 (HER2) expression in the metastatic mediastinal lymph node. **(G)** Fluorescence *in situ* hybridization (FISH) of the metastatic mediastinum lymph node revealed negative HER2 amplification. **(H)** Immunohistochemistry (IHC) staining for TROP2 expression in the metastatic mediastinal lymph node.

In May 2022, progression of the liver metastatic lesion was observed (Figure 2). The patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 and was subsequently recommended to participate in a phase I/II clinical trial designed to evaluate the safety and antitumor effects of ESG401 (Shanghai Escugen Biotechnology Co., Ltd. Shanghai, China) in solid tumors (NCT04892342). ESG401 is a novel ADC with a humanized IgG1 antibody against the Trop2 antigen and the small molecule SN-38, which is a topoisomerase I inhibitor. An innovative stable and cleavable linker was used to combine the antibody to the payload with a DAR of 8. After providing informed consent, the patient received ESG401 treatment (12 mg/kg intravenously on Day 1, Day 8, and Day 15 every 28 days) on May 25, 2022. Trop2 status was assessed via IHC, revealing an H-

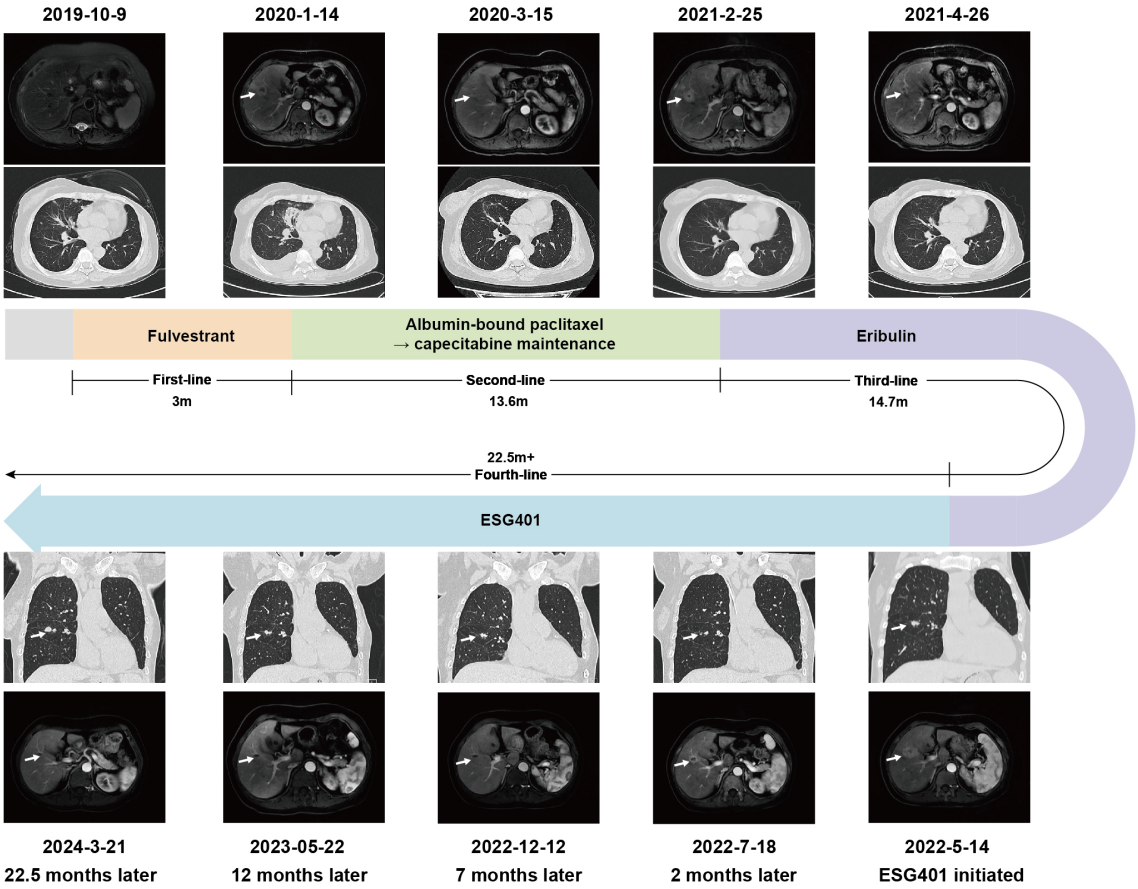


FIGURE 2
Imaging evolution of the patient treatment timeline and image efficacy evaluation.

score of 250, which was considered to be a high expression of Trop2 (Figure 1H). After two treatment cycles, the CT scan showed a significant reduction in the size of the liver metastases, from 33 mm to 17 mm (a reduction of 48.5%), the overall efficacy of the patient was determined as PR according to RECIST 1.1. Four weeks later, the PR was confirmed. Subsequently, the patient's lesions further decreased, with a total reduction in the sum of the longest diameters of the target lesions of 52.6%. At the time of writing (May 2024), the patient had sustained a beneficial response for 23.6 months. The latest CT scan from March 21, 2024, revealed a sustained PR for the liver mass. Although a lung nodule has gradually gotten larger, the overall assessment of efficacy is still a PR. The pharmacokinetic profile of this patient indicates that, irrespective of whether they received a single or multiple dose of ESG401, the concentrations of both the total antibody and the intact ADC remained similar. However, the concentration of SN-38 was significantly lower compared to the total antibody and ESG401, with a maximum concentration (Cmax) of 6.5 ng/ml and an area under the curve (AUC) of 136 ng·h/ml. The pharmacokinetics (PK) profiles of total antibody and ADC drug are very similar, indicating that ESG401 is very stable in circulation (Figure 3). The patient has experienced very mild and easily manageable adverse reactions, including grade 2 neutropenia, grade 1 diarrhea, and anemia, during ESG401 treatment. The patient maintains an excellent performance status and has a high quality of life.

3 Discussion

Endocrine resistance, which refers to resistance to estrogen or ER suppression, remains a significant hurdle for patients with HR +/HER2- BC. For MBC, primary endocrine resistance is defined as disease progression during the first 6 months of first-line ET (12). The mechanism is intricate and potentially linked to modifications in the estrogen receptor pathway (e.g., ESR1 mutations) or upstream signaling pathways of growth factors (e.g., the PI3K/Akt/mTOR pathway) (13). In the last two decades, there have been notable advancements in the discovery and approval of novel medications targeting the ER and upstream signaling pathways. Among the drugs available in China, CDK4/6i combined with fulvestrant is the standard treatment for patients who have progressed on aromatase inhibitors (AIs) (14). In our specific case, the patient opted against receiving CDK4/6i treatment due to financial limitations and subsequently experienced rapid

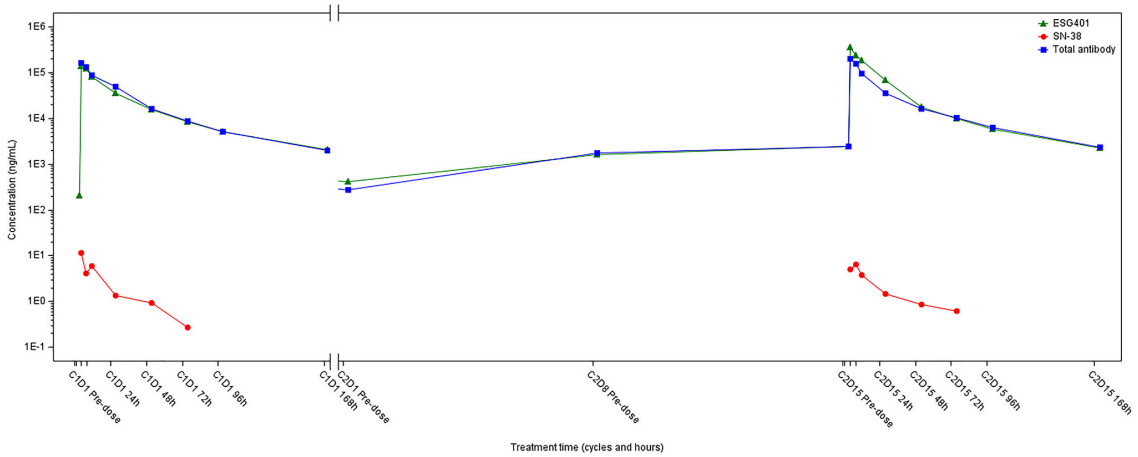


FIGURE 3
The plasma drug concentration-time curve of ESG-401, total antibody and SN-38 of the patient.

progression while on fulvestrant monotherapy. In addition to chemotherapy, the mTOR inhibitor everolimus in combination with exemestane is a favorable option, potentially prolonging PFS in patients who are refractory to nonsteroidal AIs (8). Nevertheless, the relatively high toxicity profile of everolimus limits its utilization. Although currently unavailable in China, PI3K and AKT inhibitors have shown potential to improve prognosis in HR+/HER2- BC patients with activation of the PI3K/AKT/mTOR pathway, providing an alternative strategy to overcome endocrine resistance (7, 9, 15).

ADCs are a class of targeted therapies that consist of monoclonal antibodies conjugated with cytotoxic drugs. The monoclonal antibody component enables specific recognition and binding to cancer cell surface antigens, while the cytotoxic drug payload delivers a potent anticancer effect directly to tumor cells. Trastuzumab emtansine (T-DM1) is the first approved ADC that targets HER2 (16). Compared with T-DM1, trastuzumab deruxtecan (T-DXd), another ADC that targets HER2, has been shown to improve survival outcomes in patients with HER2-positive MBC (17); it also improves survival outcomes in patients with MBC with low HER2 expression compared to those receiving standard chemotherapy (18). Trop-2 is another target of interest in breast cancer. It was initially identified in 1981 as a protein prominently present on the surface of trophoblast cells (19). However, subsequent studies revealed its intricate involvement in cancer cell processes, including growth, proliferation, migration, invasion, and survival (20). In breast cancer, expression of the TROP-2 gene has been identified across all subtypes, with particularly elevated levels observed in HR+ HER2-negative and triple-negative breast cancer (TNBC) compared to HER2-positive disease (21). Elevated TROP-2 expression was correlated with poorer survival outcomes (22).

Sacituzumab govitecan (SG) is the first ADC directed against Trop-2 and was recently approved in China for patients with metastatic triple-negative breast cancer (mTNBC) who have undergone two or more lines of chemotherapy. SG consists of a humanized anti-Trop-2 monoclonal antibody linked to SN-38 via a hydrolysable CL2A linker (23). Datopotamab deruxtecan (Dato-DXd) is another Trop2-targeted ADC that combines a humanized anti-TROP-2 IgG1 monoclonal antibody with a topoisomerase I inhibitor through a cleavable tetrapeptide linker, achieving a DAR of 4. Although these three drugs are all Trop2-targeting ADCs, there are certain differences in their molecular composition. A comparison of these three drugs can be found in Table 1.

In HR+HER2- MBC patients resistant to endocrine therapy, sacituzumab govitecan significantly increased the median progression-free survival (mPFS) (5.5 months vs. 4.0 months) and median overall survival (mOS) (14.4 months vs. 11.2 months) compared to that with conventional chemotherapy (24). However, safety analysis revealed a greater incidence of adverse events (AEs) in the SG group, with notable neutropenia, diarrhea, nausea, vomiting, alopecia, and fatigue. The hydrolysable CL2A linker, which is designed for extracellular hydrolysis, leads to an earlier release of free SN-38 into the circulation, leading to a higher peak cytotoxin concentration, a higher exposure and potentially contributing to an increase in AEs (25).Compared to investigator's choice of chemotherapy, datopotamab deruxtecan (Dato-DXd) led to significant improvement in PFS (6.9 months vs. 4.9 months) and presented a favorable safety profile in a phase III trial for HR+/HER2- MBC (26). These studies demonstrate that Trop2-directed

TABLE 1 Comparison of molecular composition of Three Trop2 Directed Antibody-Drug Conjugates (ADCs).

Product	ESG401	Trodelvy	DS-1062
Antibody	Sacituzumab	Sacituzumab	Datopotamab
Payload	SN-38	SN-38	DXd
Linker	MC-VC-PAB	CL2A	GGFG
Type of Linker	Enzyme dependent	pH-dependent	Enzyme dependent
DAR	8	7.6	4

ADCs offer substantial promise as a novel therapeutic approach for HR+/HER2- MBC.

An optimal linker for an ADC should possess adequate stability to transport the payload to the desired site while also exhibiting sufficient lability to release an effective quantity of payload either within the tumor or in the tumor microenvironment (TME) (27). ESG401 is a novel ADC directed toward Trop2 that utilizes an innovative stable cleavable linker designed to conjugate SN38 to a humanized monoclonal antibody targeting Trop2 with a DAR of 8. In the design of ESG401, it is expected that, due to the increased stability of the linker, the intact ADC molecule will be less likely to dissociate in systemic circulation, resulting in lower systemic exposure of the free payload. It showed that the longer half-life of intact ADC in the patient than SG (49.0 vs.23.4 hours), with lower exposure of SN38, reflected in the ratio of SN38 to ADC (0.002% vs. 0.07%) (28). Furthermore, the pharmacokinetic evaluation of the patient, the same as other patients from the trial, exhibited notably reduced maximum concentration (Cmax) levels (6.5 vs. 98.0 ng/ml) and area under the curve (AUC) values (136 vs. 3696 ng·h/ml) for SN-38 when contrasted with the published pharmacokinetic profile of SG (28). These PK characteristics suggest that ESG401 is more stable in circulation. This may mechanistically explain the patient's milder off-target toxicities, such as neutropenia, nausea, and diarrhea. The toxicity profile of ESG401 was moderate, as reported, the most frequent treatment-related adverse events (TRAEs) of Grade 3 or higher were leukopenia (29%) and neutropenia (31%) (11). There were no Grade 3 or higher events of thrombocytopenia, diarrhea, skin rash, or oral mucositis. The clinical trial protocol for participating patients also provides detailed guidelines on the management of potential adverse events (AEs), including intervention thresholds and any necessary dose modifications due to toxicity (Supplementary Table 1).

This profile is attributed to the stability of the ADC molecule conferred by the proprietary linker of ESG401 and the reduced release of free payload in the system, thereby minimizing off-target toxicity. The cleavable linker and membrane-permeable payload SN-38 enable it to exert a "bystander effect" (29). In tumor-bearing mouse models, compared with tumors treated with SG, tumors treated with ESG401 had higher levels of and longer exposure to both free SN38 and total SN38 within tumor tissues. The combination of decreased serum release and increased exposure of SN-38 within tumor tissues indicated the reliable efficacy and exceptional safety of ESG401 in an animal model. Initial findings from a phase I/II clinical trial assessing the safety, tolerability, pharmacokinetics, and antitumor effects of ESG401 in patients with locally advanced or metastatic solid tumors have been reported (11). Thirty-five heavily treated patients (with a median of 4 (2-10) prior lines of treatment) were enrolled. Among 33 patients assessed for efficacy, the ORR and DCR across various dosage regimens were 36.4% (12/33) and 63.6% (21/33), respectively. Specifically, in a subgroup of 13 patients receiving therapeutically relevant doses of HR+/HER2- MBC, the ORR and DCR were 62% (8/13) and 77% (10/13), respectively. These promising efficacy signals suggest a favorable treatment effect of ESG401 for HR+/HER2- MBC, which is consistent with the case of this patient with exceptionally long clinical benefit that we have reported. In addition, an open-label, randomized, active-controlled, multicenter, Phase III study (NCT06383767) of ESG401 versus Investigator's Choice Chemotherapy (ICC) is currently underway. This trial involves patients with HR+/HER2- locally advanced or metastatic breast cancer who have progressed during endocrine therapy, are unsuitable for endocrine treatment, and have received at least one prior line of systemic chemotherapy. The study also aims to validate the findings from this case study in a larger patient cohort. In our case, the patient who rapidly progressed on fulvestrant and subsequently received two additional lines of chemotherapy achieved a significant PR following treatment with ESG401. This favorable response lasted for more than 22.5 months with excellent tolerance and good quality of life, exceeding the duration achieved with previous chemotherapy; this response period was also much longer than the published mPFS from studies using SG (5.5 months) and Dato-Dxd (6.8 months) in the same indication population. This prolonged response may be attributed to the unique mechanism of action of ADCs with cytotoxic payloads, which may unaffected by resistance mechanisms typically associated with endocrine therapy. Additional contributing factors include high Trop2 expression (H-score: 250). In the ASCENT trial, a more favorable overall survival (OS) trend was observed in patients with higher Trop2 expression (30). Furthermore, low tumor burden, good performance status, and the demonstrated efficacy of ESG401 also likely contributed to the therapeutic benefit. Some possible underlying unveiled reasons may have an impact as well. Further exploration of these factors that may contribute to the patient's prolonged duration response will help to further elucidate the mechanism of drug action and provide meaningful guidance for the treatment of such patients. Moreover, diverse reactions to ESG401 were observed in hepatic and pulmonary lesions, emphasizing the heterogeneous nature of tumors. Variability in TROP2 expression across distinct metastatic loci in breast cancer has been documented (31). Re-evaluation through lung metastasis re-biopsy at the onset of progressive disease (PD) could offer valuable insights into the resistance mechanisms of ESG401, thus guiding subsequent therapeutic strategies. Furthermore, the patient's HER2 status is 2+. Trastuzumab-deruxtecan (T-DXd), an ADC targeted to HER2, could be an alternative treatment strategy. In DESTINY-Breast04 trial, T-DXd demonstrated improved PFS and OS benefit in advanced HER2-low breast cancer compared to chemotherapy of physician's choice (18).

The limitations of this case study include the absence of CDK4/6 inhibitor therapy, which has become a cornerstone in treating luminal-like metastatic breast cancer. This patient did not receive CDK4/6 inhibitors due to financial constraints and personal choice. In the clinical trial (NCT04892342) she participated in, 78% of the 65 HR+/HER2- patients had prior exposure to CDK4/6 inhibitors. Among the 58 efficacy evaluable patients, the ORR was 27.7% for those with prior CDK4/6 inhibitor treatment and 54.5% for those without (unpublished internal data). These results were derived from a retrospective analysis, which may be influenced by baseline imbalances and the small sample size, making it unclear whether prior CDK4/6 inhibitor use affects the efficacy of ESG401. Additionally, the patient did not undergo molecular testing, so her suitability for targeted therapies, such as PIK3CA/AKT/mTOR inhibitors, remains unknown. Further studies are needed to explore

the potential interaction between gene-targeted therapies and TROP2 ADCs in a larger cohort. Another important point is that, although the patient experienced only mild and easily manageable adverse reactions, including grade 2 neutropenia, grade 1 diarrhea, and anemia, during over 22.5 months of ESG401 treatment, this Phase I study did not include standardized quality-of-life assessments or patient-reported outcome measures. Therefore, any improvement in the patient's quality of life has not been objectively demonstrated. In the planned Phase III study, quality-of-life assessments will be included as one of the secondary endpoints.

In conclusion, for patients with endocrine-refractory HR +/HER2- MBC, Trop2-directed ADCs represent an optimal choice for later lines of therapy. Enhanced ADC engineering holds significant promise for maximizing both the efficacy and safety of these agents. ESG401 has demonstrated favorable tolerability with promising signs of efficacy in heavily pretreated patients. Further investigations through expanded clinical trials in HR+/HER2- MBC, as well as a deeper understanding of the characteristics of patients that may impact sustained efficacy, are warranted.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JZ: Writing – original draft. FH: Data curation, Writing – review & editing. XXu: Data curation, Writing – review & editing. YZ: Formal analysis, Writing – review & editing. XXi: Writing – original draft. JH: Writing – review & editing. FQ: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

XXi was employed by Shanghai Escugen Biotechnology Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1444431/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71:209–49. doi: 10.3322/caac.21660

2. Masood S. Estrogen and progesterone receptors in cytology: A comprehensive review. *Diagn Cytopathol*. (1992) 8:475–91. doi: 10.1002/dc.2840080508

3. NCCN. *Nccn clinical practice guidelines in breast cancer*. USA: National Comprehensive Cancer Network (2024). Available online at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

4. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, her2-negative metastatic breast cancer that progressed on previous endocrine therapy (paloma-3): Final analysis of the multicenter, double-blind, phase 3 randomized controlled trial. *Lancet Oncol*. (2016) 17:425–39. doi: 10.1016/S1470-2045(15)00613-0

5. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. (2020) 382:514–24. doi: 10.1056/NEJMoa1911149

6. Sledge GW Jr., Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, erbb2-negative breast cancer that progressed on endocrine therapy-monarch 2: A randomized clinical trial. *JAMA Oncol*. (2020) 6:116–24. doi: 10.1001/jamaoncol.2019.4782

7. Rugo HS, Lerebours F, Ciruelos E, Drullinsky P, Ruiz-Borrego M, Neven P, et al. Alpelisib plus fulvestrant in pik3ca-mutated, hormone receptor-positive advanced breast cancer after a cdk4/6 inhibitor (bylieve): One cohort of a phase 2, multicenter, open-label, non-comparative study. *Lancet Oncol*. (2021) 22:489–98. doi: 10.1016/S1470-2045(21)00034-6

8. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. (2012) 366:520–9. doi: 10.1056/NEJMoa1109653

9. Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, et al. Capivasertib in hormone receptor-positive advanced breast cancer. *N Engl J Med*. (2023) 388:2058–70. doi: 10.1056/NEJMoa2214131

10. Bidard FC, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase iii emerald trial. *J Clin Oncol*. (2022) 40:3246–56. doi: 10.1200/JCO.22.00338

11. Ma F, Qiu F, Tong Z, Wang J, Tan Y, Bai R, et al. Preliminary results from a first-in-human study of esg401, a trophoblast cell-surface antigen 2 (trop2) antibody drug conjugate (adc), in patients with locally advanced/ metastatic solid tumors. *J Clin Oncol*. (2023) 41:1100. doi: 10.1200/JCO.2023.41.16_suppl.1100

12. Hanker AB, Sudhan DR, Arteaga CL. Overcoming endocrine resistance in breast cancer. *Cancer Cell*. (2020) 37:496–513. doi: 10.1016/j.ccell.2020.03.009

13. Hart CD, Migliaccio I, Malorni L, Guarducci C, Biganzoli L, Di Leo A. Challenges in the management of advanced, er-positive, her2-negative breast cancer. *Nat Rev Clin Oncol*. (2015) 12:541–52. doi: 10.1038/nrclinonc.2015.99

14. CSCO. *Guidelines of Chinese society of clinical oncology (csco)for breast cancer*. China: Chinese Society of Clinical Oncology (2024). Available at: https://meeting.csco.org.cn/pdf/web/viewer.html?file=/Upload/Periodical/20240813104807.pdf.

15. Andre F, Ciruelos EM, Juric D, Loibl S, Campone M, Mayer IA, et al. Alpelisib plus fulvestrant for pik3ca-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Final overall survival results from solar-1. *Ann Oncol*. (2021) 32:208–17. doi: 10.1016/j.annonc.2020.11.011

16. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for her2-positive advanced breast cancer. *N Engl J Med*. (2012) 367:1783–91. doi: 10.1056/NEJMoa1209124

17. Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with her2-positive metastatic breast cancer: Updated results from destiny-breast03, a randomized, open-label, phase 3 trial. *Lancet*. (2023) 401:105–17. doi: 10.1016/S0140-6736(22)02420-5

18. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab deruxtecan in previously treated her2-low advanced breast cancer. *N Engl J Med*. (2022) 387:9–20. doi: 10.1056/NEJMoa2203690

19. Lipinski M, Parks DR, Rouse RV, Herzenberg LA. Human trophoblast cell-surface antigens defined by monoclonal antibodies. *Proc Natl Acad Sci U S A*. (1981) 78:5147–50. doi: 10.1073/pnas.78.8.5147

20. Zaman S, Jadid H, Denson AC, Gray JE. Targeting trop-2 in solid tumors: Future prospects. *Onco Targets Ther*. (2019) 12:1781–90. doi: 10.2147/OTT.S162447

21. Vidula N, Yau C, Rugo H. Trophoblast cell surface antigen 2 gene (tacstd2) expression in primary breast cancer. *Breast Cancer Res Treat*. (2022) 194:569–75. doi: 10.1007/s10549-022-06660-x

22. Ambrogi F, Fornili M, Boracchi P, Trerotola M, Relli V, Simeone P, et al. Trop-2 is a determinant of breast cancer survival. *PloS One*. (2014) 9:e96993. doi: 10.1371/journal.pone.0096993

23. Bardia A. A closer look at sacituzumab govitecan-hziy. *Clin Adv Hematol Oncol*. (2020) 18:715–7.

24. Rugo HS, Bardia A, Marme F, Cortes J, Schmid P, Loirat D, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. (2022) 40:3365–76. doi: 10.1200/JCO.22.01002

25. Tarcsa E, Guffroy MR, Falahatpisheh H, Phipps C, Kalvass JC. Antibody-drug conjugates as targeted therapies: Are we there yet? A critical review of the current clinical landscape. *Drug Discovery Today Technol*. (2020) 37:13–22. doi: 10.1016/j.ddtec.2020.07.002

26. Bardia A, Kalinsky K, Tsurutani J, Hamilton EP, Johnston S, Sohn J, et al. Datopotamab deruxtecan (dato-dxd), a trop2 antibody-drug conjugate, vs investigators' choice of chemotherapy (icc) in previously-treated, inoperable or metastatic hormone-receptor (hr) positive, her2-negative (hr+/her2-) breast cancer: Tropion-breast01. *Ann Oncol*. (2022) 33:S663–S. doi: 10.1016/j.annonc.2022.07.1858

27. Tarantino P, Ricciuti B, Pradhan SM, Tolaney SM. Optimizing the safety of antibody-drug conjugates for patients with solid tumors. *Nat Rev Clin Oncol*. (2023) 20:558–76. doi: 10.1038/s41571-023-00783-w

28. Ocean AJ, Starodub AN, Bardia A, Vahdat LT, Isakoff SJ, Guarino M, et al. Sacituzumab govitecan (immu-132), an anti-trop-2-sn-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: Safety and pharmacokinetics. *Cancer*. (2017) 123:3843–54. doi: 10.1002/cncr.v123.19

29. Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of sn-38, a metabolite of the camptothecin derivative cpt-11, in the antitumor effect of cpt-11. *Cancer Res*. (1991) 51:4187–91.

30. Bardia A, Rugo HS, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Final results from the randomized phase iii ascent clinical trial in metastatic triple-negative breast cancer and association of outcomes by human epidermal growth factor receptor 2 and trophoblast cell surface antigen 2 expression. *J Clin Oncol*. (2024) 42:1738–44. doi: 10.1200/JCO.23.01409

31. Kojima. Abstract po3-15-12: Expression and co-expression patterns of trop2 and her2 in breast cancer: Implications for bispecific antibody-drug conjugate therapy. *Cancer Res*. (2024) 84:Abstract PO3–15–2. doi: 10.1158/1538-7445

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 05 December 2024
DOI 10.3389/fonc.2024.1473881

OPEN ACCESS

EDITED BY
Robert Wesolowski,
The Ohio State University, United States

REVIEWED BY
Tito Brambullo,
University of Padua, Italy
Arya Mariam Roy,
University at Buffalo, United States

*CORRESPONDENCE
Shuzhen Liu
18265617159@163.com

RECEIVED 31 July 2024
ACCEPTED 19 November 2024
PUBLISHED 05 December 2024

CITATION
Nie Y, Song C, Wang J, Wu K, Yu M, Shen X, Bian Y and Liu S (2024) Triple-negative ectopic breast cancer of the male scrotum: a case report.
Front. Oncol. 14:1473881.
doi: 10.3389/fonc.2024.1473881

Triple-negative ectopic breast cancer of the male scrotum: a case report

Yuhui Nie[1,2], Chen Song[1], Jingru Wang[3], Kun Wu[1], Mingxin Yu[1], Xin Shen[1], Yandong Bian[1] and Shuzhen Liu[2*]

[1]School of Clinical Medicine, Shandong Second Medical University, Weifang, Shandong, China, [2]Weifang People's Hospital, Shandong Second Medical University, Weifang, Shandong, China, [3]Center for Precision Pathological Diagnosis, Weifang People's Hospital, Shandong Second Medical University, Weifang, Shandong, China

Male breast cancer represents only 1% of all breast malignancies, with ectopic breast cancer in men being even rarer and highly prone to diagnostic challenges. Extramammary Paget's disease (EMPD), a rare cutaneous tumor with non-specific clinical symptoms, is susceptible to misdiagnosis. This report discusses the case of an older male patient who presented with a scrotal mass, later identified as ectopic breast invasive adenocarcinoma upon pathological examination post-lesion excision. Immunohistochemistry confirmed a triple-negative profile and EMPD diagnosis, with no malignancies detected in either breast. Despite multiple treatment regimens and recurrence following adjuvant chemotherapy, the disease progressed with associated chemotherapy-related side effects, resulting in a 25.5-month survival period. The scarcity of literature on male ectopic breast cancer complicates the understanding of its incidence and optimal treatment strategies, increasing the risk of misdiagnosis. This study highlights the diagnostic and therapeutic challenges of this rare case, emphasizing the need for early recognition of atypical manifestations. The manuscript aims to assist clinicians by sharing case-specific insights and reviewing pertinent literature to enhance comprehension and management of similarly rare cases.

KEYWORDS

scrotal mass, ectopic breast cancer, triple negative, Paget's disease, treatments

Introduction

Embryonic mammary development begins around the fourth week of gestation, forming a ventral mammary ridge extending from the axilla to the inner thigh. Incomplete resorption of this tissue can lead to residual ectopic mammary glands (1). Although ectopic breast tissue undergoes similar pathophysiological changes as normal breast tissue, only an insignificant fraction (approximately 1%) develops cancer in these sites (2). Ectopic mammary glands are most commonly identified in the axillae of women,

with cases in men, particularly in the scrotal region, being significantly rare and cancer in these sites even rarer. Paget's disease (PD), initially described by James Paget in the breast in 1874, was later identified in the male genital region by Crocker in 1889. This condition primarily involves intraepidermal adenocarcinoma, characterized by malignant growth of non-keratinizing epithelial cells known as Paget cells. Scrotal involvement in extramammary PD (EMPD) is uncommon, accounting for only 14% of cases, compared to the vulvar type (65%) and perianal type (20%) (3). This study details a rare case of breast cancer originating in ectopic mammary tissue within the scrotum of a male patient, accompanied by EMPD of the scrotal skin, highlighting the diagnostic and therapeutic challenges posed by this uncommon condition.

Case report

In June 2020, a 63-year-old male patient with no family history of malignancies presented to our hospital's surgical department with a 5-month history of a scrotal skin lesion near the base of the penis, accompanied by occasional pain, no discharge, and ineffective self-medication attempts. The patient reported no discomfort in the axilla or breast, and physical examination revealed no palpable masses. Ultrasound imaging showed subcutaneous hypoechoic tissue at the base of the penis, measuring 1.3 cm × 0.7 cm × 1.7 cm, with regular morphology, indistinct borders, and a significant blood flow signal. Moreover, imaging of the kidneys, ureter, and bladder (including the prostate) showed no abnormalities. Due to limited awareness of the condition, a multidisciplinary surgical strategy discussion was not conducted, and a simple excision of the scrotal mass was performed. Postoperative pathological examination confirmed the scrotal mass as an invasive adenocarcinoma. (Figure 1A), with EMPD of the scrotal skin (Figure 1B), as well as evidence of nerve invasion and cancerous embolism in the chorioallantoic duct. The immunohistochemical analysis revealed cytokeratin 7 (CK7) positivity, CK20 negativity, GATA3 positivity, gross cystic disease fluid protein 15 (GCDFP-15) negativity, and raised androgen receptor (AR) (3+, 60%) (Figures 1C–G), with estrogen receptor (ER) and progesterone receptor (PR) negativity, and a human epidermal growth factor receptor 2 (C-erB-2) score of 2+ (Figures 1H–J). Further Fluorescence *In Situ* Hybridization (FISH) testing yielded negative results. Based on these pathological and immunohistochemical results, a diagnosis of triple-negative invasive carcinoma of ectopic breast origin was made. Following the surgical procedure, the patient consulted the Thyroid and Breast Surgery Department for further breast examination. A positron emission tomography (PET)-computed tomography (CT) scan detected multiple lymph node metastases in the left inguinal region (Figure 2), leading to an inguinal lymph node dissection. Postoperative pathology confirmed metastasis from the scrotal invasive adenocarcinoma. Two months later, pelvic CT and magnetic resonance imaging (MRI) identified a space-occupying lesion in the left inguinal region (Figures 3A–D), raising suspicion for inguinal lymph node metastasis. Systemic chemotherapy and regular monitoring were recommended.

Based on the PET-CT findings and prior inguinal lymph node dissection, an aspiration biopsy was not performed for the suspected lymph node metastasis noted on pelvic imaging. The patient subsequently received four cycles of adjuvant chemotherapy with paclitaxel liposomal (175 mg/m^2) and nedaplatin (75 mg/m^2) from August to October 2020, resulting in disease stability upon follow-up. In August 2021, the patient presented again with a scrotal mass, which was excised and confirmed to be an invasive adenocarcinoma of ectopic mammary origin. During postoperative re-examination, an ultrasound of the inguinal lymph nodes once more indicated metastasis, prompting the patient to return to our department for further treatment. Further investigations revealed metastatic spread to the liver (Figures 3E–H), bilateral pubic bones, and the left acetabular bone (Figure 4). A liver mass biopsy confirmed metastatic invasive adenocarcinoma with immunohistochemistry consistent with triple-negative status. Programmed death-ligand 1 (PD-L1) testing indicated a combined positive score (CPS) of less than 1, assessed on the Dako platform with the 22C3 antibody clone using the CPS standard (Figure 1K), suggesting ineligibility for immune checkpoint inhibitor therapy. The patient experienced rapid disease progression, with multiple pathological examinations indicating ectopic breast origin. A physical and ultrasound examination of the breast and axilla revealed no significant abnormalities. Given the patient and their family's urgent desire for treatment, chemotherapy with the TE regimen (albumin-bound paclitaxel 250 mg/m^2 and epirubicin 70 mg/m^2) was initiated following a multidisciplinary consultation. Although denosumab has demonstrated better efficacy and safety over zoledronic acid for bone metastasis management, due to constraints related to national insurance coverage and personal financial limitations, the patient opted for zoledronic acid, administered every three weeks, to manage bone metastasis while minimizing financial burden. During this period, the treatment achieved partial remission (PR). However, after seven cycles, treatment was discontinued due to secondary neurotoxic effects, including head and facial paresthesia, and extremity numbness. The patient was subsequently transitioned to maintenance chemotherapy with capecitabine (1250 mg/m^2). After two cycles, intrahepatic metastases progressed, promoting a repeat biopsy and confirming triple-negative status via immunohistochemistry. Subsequently, the patient received a single cycle of gemcitabine (1 g/m^2), carboplatin (area under the curve [AUC] = 5), and bevacizumab (7.5 mg/kg). However, side effects, including grade 4 thrombocytopenia and grade 3 leukopenia, necessitated platelet transfusions, administration of recombinant human thrombopoietin, and support to restore leukocytes and platelets. Consequently, gemcitabine was not administered on day 8 of this cycle.

Upon discharge, the patient was referred to a higher-level hospital for further pathological evaluation. The findings revealed metastatic adenocarcinoma in the left inguinal lymph nodes (2/4), consistent with scrotal invasive adenocarcinoma, and a liver puncture showed metastatic adenocarcinoma. Given these results,

10.3389/fonc.2024.1473881

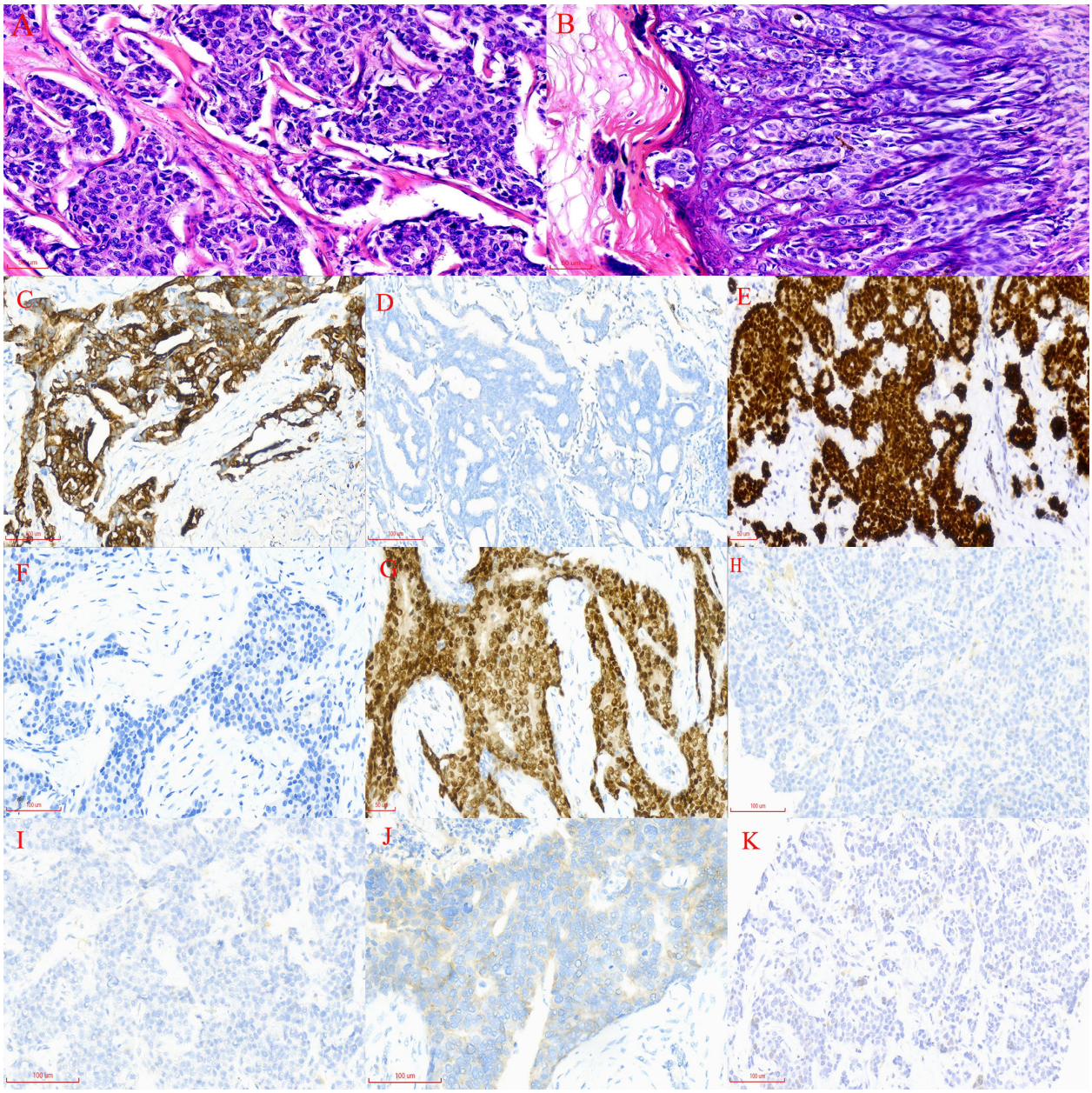


FIGURE 1
(A) Widespread infiltration of cancer cells in the scrotal subcutaneous tissue, with indistinct cellular borders, increased nuclear-cytoplasmic ratio, acidophilic cytoplasm, deviated nuclei, basophilic staining, enlarged nuclear volume, pronounced heterogeneity, and pathological nuclear division (magnification, x200). **(B)** Irregularly arranged epidermal cells with varying sizes, red-stained cytoplasm, and blue-stained nuclei, identified as Paget's cells. These cells exhibit large nuclei with loose chromatin, prominent nucleoli, and irregular edges; they are distributed in a band-like pattern along the epidermis (magnification, x200). **(C)** CK-7 immunohistochemical staining of the subcutaneous scrotal mass: brownish-yellow staining indicates CK-7 positive cells, while hematoxylin-stained nuclei appear blue (x200). **(D)** CK-20 immunohistochemical staining of the subcutaneous scrotal mass: absence of brown staining indicates no CK-20 expression in the sample (x200). **(E)** GATA-3 immunohistochemical staining of the subcutaneous scrotal mass: brown staining highlights GATA-3 positive cells (x200). **(F)** GCDFP-15 immunohistochemical staining of the subcutaneous scrotal mass: lack of brown staining indicates no GCDFP-15 expression in the sample (x200). **(G)** AR immunohistochemical staining of the subcutaneous scrotal mass: brown staining denotes AR-positive cells, with approximately 60% of cells showing positivity (x200). **(H)** Immunohistochemical ER nuclear staining in scrotal dermal cells displaying a light blue color (magnification, x200). **(I)** Immunohistochemical PR nuclear staining in scrotal dermal cells displaying a light blue color (magnification, x200). **(J)** Immunohistochemical Human Epidermal Growth Factor Receptor 2 nuclear staining in scrotal dermal cells appearing pale blue (magnification, x200). **(K)** PD-L1 testing in liver metastatic tissue using the CPS, calculated by dividing the number of PD-L1 positive cells (including tumor cells, lymphocytes, and macrophages) by the total number of viable cells, then multiplying by 100. A CPS of <1 indicates low PD-L1 expression (magnification, x200).

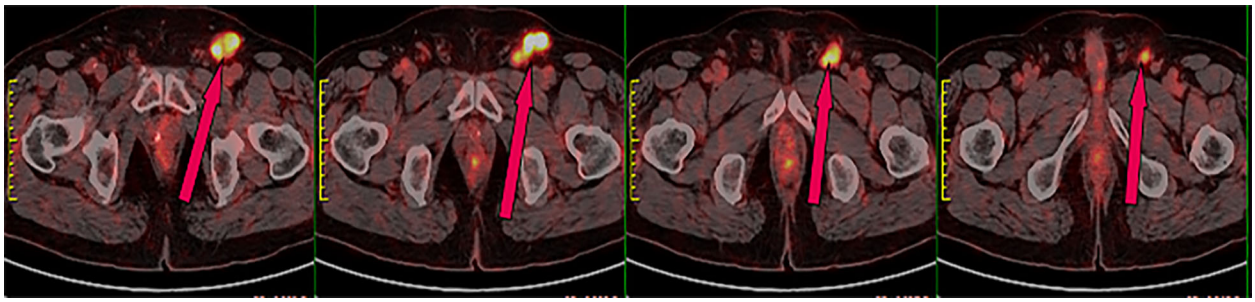


FIGURE 2
PET-CT scan showing radioactive uptake in the left inguinal lymph nodes, indicative of malignant metastasis.

scrotal ectopic breast origin was considered. Subsequently, the patient received vedolizumab (120 mg) at the same hospital. During hospitalization, the patient developed a high fever reaching 39.7°C, initially treated with piperacillin-tazobactam followed by meropenem; however, the infection persisted with limited improvement. Despite intensive treatment efforts from the medical team and the patient' family, therapeutic options were limited due to specific molecular profiles and expression levels of relevant markers.

A comprehensive timeline chart was developed to visually represent the patient's treatment history and key clinical events (Table 1). This table systematically documents the patient's journey from initial symptom recognition to final treatment, highlighting significant interventions such as operation, imaging, and chemotherapy. By providing a clear overview of the treatment process and its influence on disease progression, this timeline is a valuable reference to inform clinical decision-making.

Discussion

Breast cancer is one of the most prevalent malignancies worldwide, predominantly affecting women and typically arising in the breast tissue. Ectopic breast cancer, a rare variant, develops along the embryonic milk line, which extends from the axilla to the groin, with the axilla being the most common site for ectopic breast cancer. To date, only three cases of male ectopic breast cancer outside the axilla have been documented in the English literature, with sites including the abdominal wall, perineum, and suprapubic region (4). In this report, a case of ectopic breast cancer is reported in the scrotum, situated within the perineal area. Furthermore, the patient was diagnosed with Paget's disease, which added complexity to both the diagnostic and treatment approach (5).

Ectopic breast tissue is more susceptible to malignant transformation than normal breast tissue, primarily due to ductal stagnation. However, ectopic breast cancer remains uncommon, given the low incidence of ectopic breast tissue (6). The incidence of male breast cancer accounts for less than 1% of all breast cancers, and ectopic breast cancer represents approximately 0.3% to 0.6% of these cases (7, 8). The average age of diagnosis for ectopic breast cancer is approximately 54 years, roughly 6 years younger than the average age of diagnosis for conventional breast cancer (4). Ectopic breast cancer lacks distinct symptoms; common manifestations include palpable masses with or without tenderness, and skin changes such as erythema, ulcers, and other lesions (8, 9). However, due to the low incidence and its higher prevalence among women, there is limited diagnostic and treatment experience for male ectopic breast cancer, frequently resulting in delayed diagnosis. In the perineal region, EMPD can present with skin manifestations similar to those of ectopic breast cancer. Extramammary Paget's disease is an adenocarcinoma originating in the skin or appendages, primarily affecting apocrine gland regions. Its main sites of occurrence are the vulva, followed by the perianal area, scrotum, penis, and axilla, predominantly affecting older individuals aged 60 to 70 years (10, 11). In a study of 246 Asian male patients with EMPD, the average age of onset was found to be 64 years (12). Research by Yin et al. indicates that the crude incidence rate of EMPD in mainland China is approximately 0.4 per million population (13). Besides being rare, EMPD presents with non-specific symptoms; initial manifestations commonly include itching, erythema, and dryness, which can progress to eczematous lesions, crusting, ulcers, or papillomatous changes. Therefore, patients may undergo prolonged treatments before a definitive diagnosis is made. Topical steroids or antifungal medications can further alter skin manifestations, complicating diagnostic processes (14).

Ectopic breast cancer and EMPD in the perineal region share similar clinical features, and the patient's age of onset (63 years) aligns with the typical age range for EMPD, which can add to diagnostic challenges. Extramammary Paget's disease is classified into primary and secondary types, with primary EMPD being CK7 positive and CK20 negative. Conversely, secondary EMPD is usually associated with an underlying malignancy and shows CK7 and CK20 positivity (15). In this case, the scrotal Paget's disease is classified as primary EMPD, unrelated to ectopic breast cancer, with the scrotal lesions representing EMPD manifestations. The final diagnosis was ectopic breast cancer in the scrotum with coexisting EMPD.

Male ectopic breast cancer is sporadic, making the prognosis uncertain, and there is currently no established expert consensus on its management (16, 17). Treatment for male ectopic breast cancer generally follows protocols similar to those for primary breast cancer, primarily involving surgical excision, supported by chemotherapy, radiotherapy, endocrine therapy, targeted therapy,

10.3389/fonc.2024.1473881

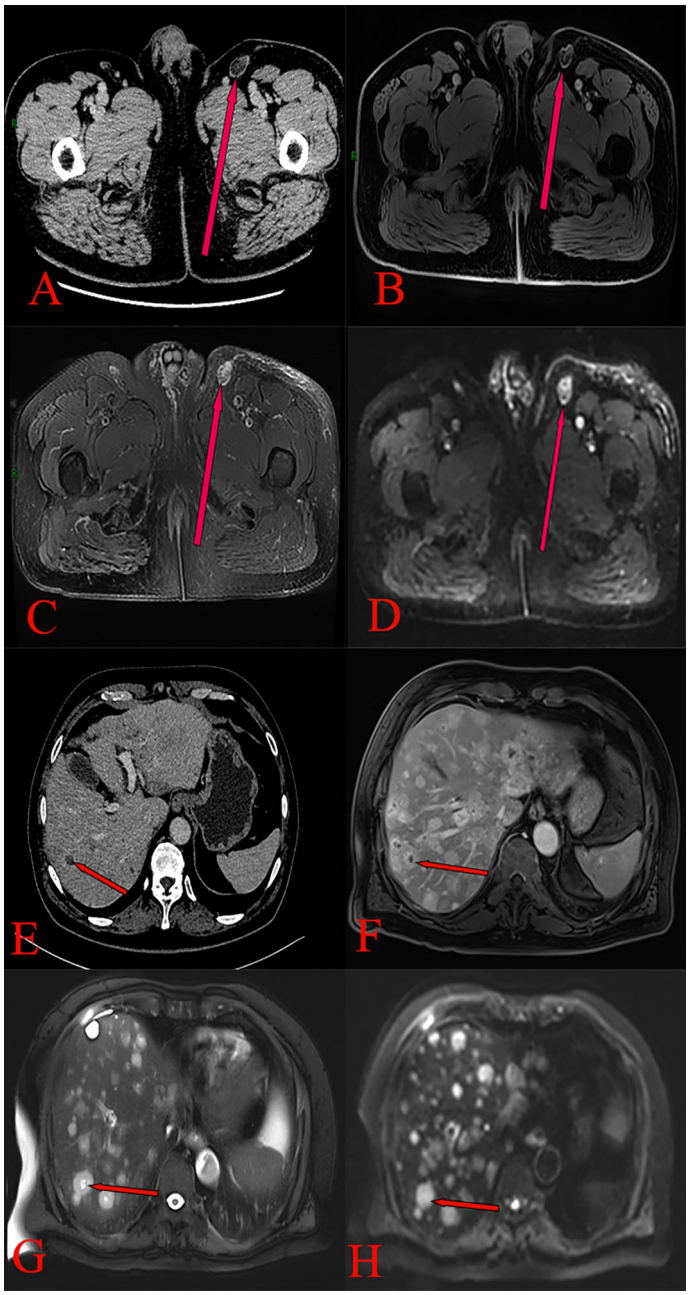


FIGURE 3
(A) Pelvic CT scan showing an irregular soft tissue density mass in the left inguinal region, with blurred borders and mild enhancement. **(B)** Pelvic MRI T1 phase pelvic image showing a low-signal nodular shadow in the left inguinal region. **(C)** Pelvic MRI T2 phase showing high-signal nodular shadows in the left inguinal region, with fat suppression resulting in a high signal. **(D)** Pelvic MRI DWI phase demonstrating restricted diffusion in a left inguinal nodule. **(E)** Enhanced CT scan of the upper abdomen showing multiple rounded hypodense liver lesions, exhibiting no enhancement. **(F)** Upper abdominal MRI T1 phase revealing multiple round, long T1 signal shadows in the liver. **(G)** Upper abdominal MRI T2 phase revealing multiple round, long T2 signal shadows in the liver, with substantial enhancement on the contrast-enhanced scan. **(H)** Upper abdominal MRI DWI phase revealing multiple intrahepatic round signal shadows with limited diffusion.

and the recently emerging immunotherapy. It is noteworthy that ectopic breast cancer exhibits greater aggressiveness than typical breast cancer, primarily in two aspects: first, the rate of lymph node positivity is higher than in breast cancer (18). Patients with vulvar ectopic breast cancer who underwent local wide excision and inguinal lymph node dissection showed pathological results indicating lymph node involvement in all cases (19). Second, ectopic breast cancer has a higher propensity for recurrence and metastasis, particularly to the bones and brain, following simple excision (20). Despite the increased likelihood of lymph node involvement, sentinel lymph node biopsy is not recommended for patients with ectopic breast cancer due to the reduced sensitivity of

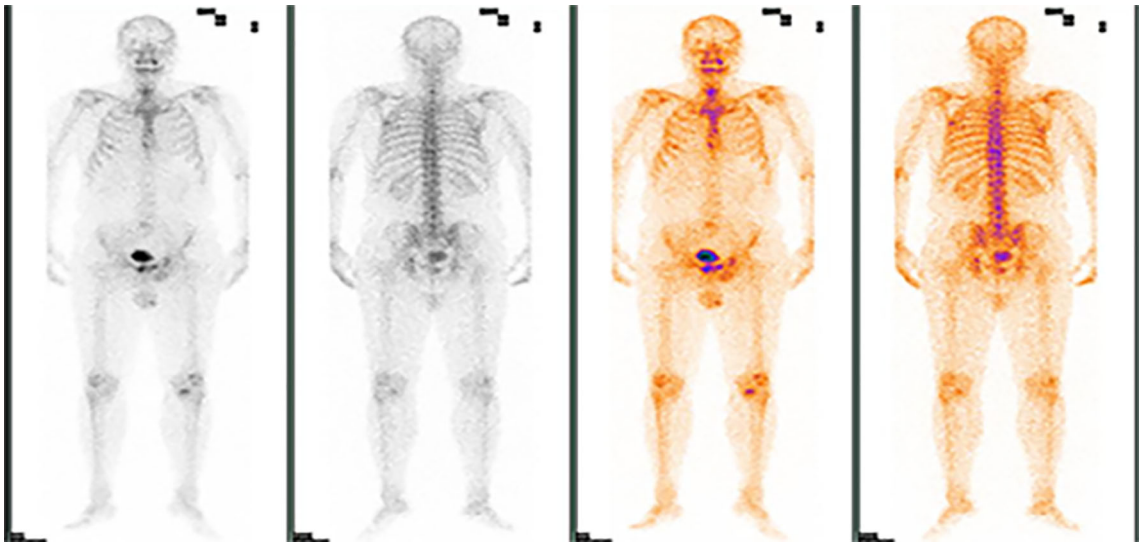


FIGURE 4
ECT demonstrating foci of abnormal radiological distribution with varying morphologies and sizes in the bilateral suprapubic branches, left acetabulum, and other regions.

inguinal lymph nodes in dye uptake (21). To mitigate the risk of distant metastasis, postoperative local radiotherapy is recommended. Apart from traditional prognostic factors such as anatomical tumor-node-metastasis (TNM) staging, molecular subtype, histological grade, and Ki-67 index (22), genetic factors should be incorporated into traditional prognostic models, which could enhance prediction accuracy for male ectopic breast cancer. Currently, tests such as Oncotype DX (Exact Sciences Corporation,

TABLE 1 Comprehensive treatment timeline of the patient.

Date	Event	Category
January 2020	Patient discovered a scrotal mass near the base of the penis, red with occasional pain.	Initial Observation
June 6, 2020	Presented to Urology Department.	Initial Diagnosis
June 8, 2020	Scrotal lesion excision surgery performed under spinal anesthesia.	Surgery
June 12, 2020	Postoperative pathology showed invasive adenocarcinoma with Extramammary Paget's disease of the scrotal skin.	Pathology
June 28, 2020	PET/CT showed multiple hypermetabolic lymph nodes in the left inguinal region, indicating metastasis.	Imaging
July 8, 2020	Underwent inguinal lymph node dissection; multiple enlarged lymph nodes fused into a mass.	Surgery
August 6, 2020	Chest-abdominal-pelvic CT showed left inguinal mass.	Imaging
August 13 - October 25, 2020	Completed four cycles of chemotherapy with paclitaxel liposome and nedaplatin.	Chemotherapy
August 28, 2021	Follow-up revealed a recurrent scrotal mass.	Follow-up
September 6, 2021	Second scrotal lesion excision surgery performed.	Surgery
October 14, 2021 - March 6, 2022	Seven cycles of TE regimen chemotherapy completed.	Chemotherapy
April 20, 2022	Started capecitabine maintenance therapy.	Maintenance Therapy
May 11, 2022	Enhanced CT showed multiple liver metastases, indicating disease progression.	Imaging
May 13, 2022	Started treatment with gemcitabine, carboplatin, and bevacizumab; developed thrombocytopenia.	Chemotherapy
June 13, 2022	Received disitamab vedotin treatment; developed fever during hospitalization.	Treatment
July 2022	Patient passed away.	Outcome

PET/CT, Positron Emission Tomography/Computed Tomography; CT, Computed Tomography; TE, Nab-Paclitaxel + Epirubicin; EMPD, Extramammary Paget's disease.

Madison, Wisconsin, USA) and MammaPrint (Agendia N.V., Amsterdam, The Netherlands) have shown utility in assessing the likelihood of distant metastasis (23, 24).

However, EMPD is relatively less invasive, with slow disease progression (17, 20). Surgical treatment remains the primary approach for EMPD, supplemented by options including laser ablation, radiotherapy, chemotherapy, and topical treatment comprising 5% imiquimod cream or cytotoxic agents combined with 1% fluorouracil cream (25, 26).

The patient's prognosis was poor, with an overall survival of only 25.5 months. Critical contributing factors include the tumor's triple-negative molecular subtype, which has limited treatment options; poor responsiveness to treatment, with rapid recurrence and metastasis following chemotherapy despite multiple treatment lines; and the rarity of the disease, which led to delayed diagnosis, limited understanding of its characteristics, and an initial treatment plan that was not optimally tailored to the patient's specific needs.

Scrotal ectopic breast cancer and EMPD present with atypical symptoms and lack specific imaging findings, highlighting the importance of preoperative multidisciplinary consultation. Such consultation is essential for defining the surgical strategy, postoperative adjuvant treatment plan, and follow-up protocol. In this case, the patient did not undergo multidisciplinary evaluation, and only a simple lesion excision was performed, resulting in a non-standardized treatment course that led to recurrence and distant metastasis. Based on our experience, to minimize the risk of local recurrence, metastasis, or the malignant transformation of residual ectopic breast tissue, all cases of ectopic breast cancer are recommended to undergo evaluation by a multidisciplinary team (including surgeons, oncologists, radiation oncologists, radiologists, and pathologists) to address critical questions:

1. What should the surgical strategy be? Should a local excision or extensive resection be performed? Is sentinel lymph node biopsy necessary, or should lymph node dissection be considered?
2. What is the optimal adjuvant treatment? Given the rarity of ectopic breast cancer, treatment plans should be personalized, taking into account the patient's risk factors, tumor characteristics, and overall health.
3. What is the best follow-up plan? What should be the frequency of follow-up visits? Which diagnostic tests should be included in the follow-up regimen?

Conclusion

Scrotal ectopic breast cancer and scrotal Paget's disease are exceedingly uncommon conditions characterized by non-specific early symptoms and the lack of distinctive findings on imaging. Diagnosis relies entirely on histopathological examination. Therefore, when conventional treatments for skin lesions prove ineffective, a high index of suspicion should be maintained, and a biopsy should be performed. Once a diagnosis is confirmed, a multidisciplinary expert consultation is essential to create a personalized treatment plan tailored to the patient's unique case.

Limitations

This study has several limitations. First, it is based on a single case, which limits the generalizability and extrapolation of the results. Second, the PD-L1 testing used the 22C3 diagnostic reagent. However, current research suggests that in triple-negative breast cancer, 22C3 and SP142 cannot be used interchangeably. Due to the limitations of the hospital platform, only 22C3 was available. Both reagents should ideally be tested simultaneously to ensure patients are not excluded from immunotherapy. Finally, after bone metastasis developed, zoledronic acid was chosen for treatment due to national insurance coverage and the patient's financial constraints. Without significant economic pressure, denosumab, which is more effective with fewer side effects, should be the preferred treatment for bone metastasis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethical Review Committee of Weifang People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SL: Funding acquisition, Writing – original draft. YN: Writing – original draft. CS: Writing – review & editing. KW: Writing – review & editing. MY: Writing – review & editing. XS: Writing – review & editing. YB: Writing – review & editing. JW: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sghaier S, GHalleb M, Marghli I, Bouida A, Ben Hassouna J, Chargui R, et al. Primary ectopic axillary breast cancer: a case series. *J Med Case Rep*. (2021) 15:412. doi: 10.1186/s13256-021-02998-w

2. Grossl N. Supernumerary breast tissue: historical perspectives and clinical features. *South Med J*. (2000) 93:29–32. doi: 10.1097/00007611-200093010-00005

3. Dauendorffer JN, Herms F, Baroudjian B, Basset-Seguin N, Cavelier-Balloy B, Fouéré S, et al. Penoscrotal paget's disease. *Ann Dermatol Venereol*. (2021) 148:71–6. doi: 10.1016/j.annder.2020.08.051

4. Famá F, Cicciú M, Sindoni A, Scarfó P, Pollicino A, Giacobbe G, et al. Prevalence of ectopic breast tissue and tumor: A 20-year single center experience. *Clin Breast Cancer*. (2016) 16:e107–12. doi: 10.1016/j.clbc.2016.03.004

5. Byon JH, An AR, Shin JY, Choi EJ. Ectopic male breast cancer in suprapubic area that relapsed with hematogenous metastasis. *J Breast Cancer*. (2021) 24:344–8. doi: 10.4048/jbc.2021.24.e21

6. Cooper JC, Hew KE, Audlin KM, Im DD, Matsuo K. Synchronous of breast and vulvar Paget's disease: a case report. *Eur J Gynaecol Oncol*. (2012) 33:534–6. doi: 10.12892/ejgo201205534

7. Eom HJ, Ko BS, Song IH, Gong G, Kim HH. Ectopic male breast cancer in the perineum: A case report. *J Breast Cancer*. (2017) 20:404–7. doi: 10.4048/jbc.2017.20.4.404

8. Zhong GB, Ye XQ, Liu JL, Xiao SZ, Huang QH, Wei W. Male accessory breast cancer on the abdominal wall: a case report and literature review. *Onco Targets Ther*. (2018) 11:6625–31. doi: 10.2147/OTT.S184185

9. Nihon-Yanagi Y, Ueda T, Kameda N, Okazumi S. A case of ectopic breast cancer with a literature review. *Surg Oncol*. (2011) 20:35–42. doi: 10.1016/j.suronc.2009.09.005

10. St Claire K, Hoover A, Ashack K, Khachemoune A. Extramammary paget disease. *Dermatol Online J*. (2019) 25:13030/qt7qg8g292. doi: 10.5070/D3254043591

11. Reddy VS, Gaba S, Tewari M, Prakash G, Mittal S. Extramammary paget's disease of the penis and scrotum. *Indian J Surg Oncol*. (2024) 15:149–52. doi: 10.1007/s13193-023-01870-1

12. Kang Z, Zhang Q, Zhang Q, Li X, Hu T, Xu X, et al. Clinical and pathological characteristics of extramammary Paget's disease: report of 246 Chinese male patients. *Int J Clin Exp Pathol*. (2015) 8:13233–40.

13. Nabavizadeh R, Vashi KB, Nabavizadeh B, Narayan VM, Master VA. Extramammary Paget's disease: Updates in the workup and management. *Asian J Urol*. (2022) 9:451–9. doi: 10.1016/j.ajur.2022.08.001

14. Zhang N, Gong K, Zhang X, Yang Y, Na Y. Extramammary Paget's disease of scrotum–report of 25 cases and literature review. *Urol Oncol*. (2010) 28:28–33. doi: 10.1016/j.urolonc.2008.07.002

15. Kuan SF, Montag AG, Hart J, Krausz T, Recant W. Differential expression of mucin genes in mammary and extramammary Paget's disease. *Am J Surg Pathol*. (2001) 25:1469–77. doi: 10.1097/00000478-200112000-00001

16. Cheng Y, Li N, Eapen A, Parajuli R, Mehta R. Somatic BRCA2 mutation-positive concurrent accessory male breast cancer (BC) and non-small cell lung cancer (NSCLC): excellent efficacy of palbociclib, fulvestrant and leuprolide in platinum-exposed and endocrine-refractory BC associated with cyclin D1 and FGFR1 amplification and of carboplatin, paclitaxel and radiation in NSCLC. *Case Rep Oncol*. (2019) 12:494–9. doi: 10.1159/000501304

17. Wang CX, Guo SL, Han LN. Successful treatment of accessory breast cancer with endocrine therapy. *J Zhejiang Univ Sci B*. (2017) 18:70–5. doi: 10.1631/jzus.B1600220

18. Routiot T, Marchal C, Verhaeghe JL, Depardieu C, Netter E, Weber B, et al. Breast carcinoma located in ectopic breast tissue: a case report and review of the literature. *Oncol Rep*. (1998) 5:413–7. doi: 10.3892/or.5.2.413

19. Trambaiolo Antonelli C, Portelli F. . Extramammary paget disease. In: van Krieken J, editor. *Encyclopedia of Pathology*. Springer, Cham (2019). p. 4868–72.

20. Bansal VY, Bansal VV, Shah SV, Bellige AR. Primary ectopic breast carcinoma arising in the inguinal region in a male patient. *J Cancer Res Ther*. (2022) 18:837–9. doi: 10.4103/jcrt.JCRT_777_20

21. Cheng P, Kong M. A case of vulvar ectopic breast tissue. *Chin Clin J Obstetrics Gynecology*. (2019) 20:77. doi: 10.13390/j.issn.1672-1861.2019.01.030

22. Visconti G, Eltahir Y, Van Ginkel RJ, Bart J, Werker PM. Approach and management of primary ectopic breast carcinoma in the axilla: where are we? A comprehensive historical literature review. *J Plast Reconstr Aesthet Surg*. (2011) 64:e1–11. doi: 10.1016/j.bjps.2010.08.015

23. Vinay DS, Kwon BS. Harnessing immune checkpoints for cancer therapy. *Immunotherapy*. (2018) 10:1265–84. doi: 10.2217/imt-2017-0168

24. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science*. (2018) 359:1350–5. doi: 10.1126/science.aar4060

25. Brown RS, Lankester KJ, McCormack M, Power DA, Spittle MF. Radiotherapy for perianal Paget's disease. *Clin Oncol (R Coll Radiol)*. (2002) 14:272–84. doi: 10.1053/clon.2002.0092

26. Berman B, Spencer J, Villa A, Poochareon V, Elgart G. Successful treatment of extramammary Paget's disease of the scrotum with imiquimod 5% cream. *Clin Exp Dermatol*. (2003) 28 Suppl 1:36–8. doi: 10.1046/j.1365-2230.28.s1.12.x

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 19 December 2024
DOI 10.3389/fonc.2024.1470986

OPEN ACCESS

EDITED BY
Pranab Dey,
Post Graduate Institute of Medical Education and Research (PGIMER), India

REVIEWED BY
Gargi Kapatia,
All India Institute of Medical Sciences, Bathinda (AIIMS Bathinda), India
Shruti Gupta,
All India Institute of Medical Sciences, Raebareli, India

*CORRESPONDENCE
Fengjiang Qu
qufengjiang@jlu.edu.cn
Di Wu
Di_Wu@jlu.edu.cn

RECEIVED 26 July 2024
ACCEPTED 11 November 2024
PUBLISHED 19 December 2024

CITATION
Liu H, Zhao G, Fan Z, Wu D and Qu F (2024) Metaplastic carcinoma of the breast containing three histological components: a case report. *Front. Oncol.* 14:1470986. doi: 10.3389/fonc.2024.1470986

Metaplastic carcinoma of the breast containing three histological components: a case report

Huan Liu[1], Gang Zhao[1], Zhimin Fan[1], Di Wu[1]* and Fengjiang Qu[2]*

[1]Breast Surgery Department, General Surgery Center, The First Hospital of Jilin University, Changchun, China, [2]Emergency Surgery Department, The First Hospital of Jilin University, Changchun, China

Malignant breast tumors mainly arise from the ductal and lobular epithelium, whereas sarcomas, which originate from the stromal tissues of the breast, account for less than 5% of cases. Mostly, these tumors consist of a single tissue type, rendering malignant breast tumors with three distinct tissue types exceedingly rare. We report a unique case of a malignant breast tumor comprising three tissue types: squamous cell carcinoma (approximately 25%), invasive ductal carcinoma (approximately 5%), and fibrosarcoma (approximately 70%). Given the case's rarity, pre-operative imaging and tumor biopsy failed to yield definitive diagnostic information, we detail the patient's clinical and therapeutic process, providing insights for physicians on clinical diagnosis and treatment.

KEYWORDS

breast malignant tumor, squamous cell carcinoma, invasive ductal carcinoma, fibrosarcoma, carcinoma mixed type

1 Introduction

Malignant breast tumors are the most common type of cancer in women and are the leading cause of cancer-related deaths among females (1). Based on tissue origin, breast malignancies are classified into epithelial-origin breast carcinomas and mesenchymal-origin breast sarcomas. Breast carcinoma has become the second most prevalent malignant tumor globally, following lung cancer in incidence (2), whereas breast sarcoma is rare (1, 3).

The vast majority of malignant breast tumors have a single histopathological component, and cases where both tissue components coexist are exceedingly rare. Here, we report a case of a malignant breast tumor that contains three histological components: squamous cell carcinoma, invasive ductal carcinoma, and high-grade fibrosarcoma.

2 Case description

In July 2018, a 68-year-old woman presented to the Breast Surgery Outpatient Clinic at the First Hospital of Jilin University, finding a mass in her left breast discovered five years earlier. Five years earlier, she incidentally found a 1.0cm×1.0cm lump in her left breast, causing occasional pain but it was never formally diagnosed or treated; Two years ago, the lump abruptly grew to 5.0cm×3.0cm, yet it remained untreated; Last month, the skin covering the lump turned red and swollen. She has an 8-year history of hypertension, with no other tumor history or familial predispositions. Physical examination showed redness and swelling in the left breast's upper outer quadrant, alongside a hard, palpable 6.0cm×6.0cm mass with an irregular surface, unclear boundaries, and limited mobility. Breast ultrasound and mammography identified an irregular, slightly dense mass in the left breast's upper outer quadrant, measuring 58.2mm×26.1mm and 5.0cm×5.0cm, respectively, both classified as BI-RADS category 3 (see Figure 1). Extensive imaging and lab tests, including bone emission computed tomography (ECT) scan, abdominal and Chest computed tomography (CT), neck lymph node, and cardiac ultrasounds, along with complete blood count and liver and kidney function tests, found no significant abnormalities. Upon admission, a biopsy of the left breast mass indicated a complex, fragile tissue composition with atypical cells, suggesting further investigation. Pending exclusion of metaplastic breast carcinoma or fibroepithelial tumor. Immunohistochemical tests show Ki-67(+30%), and P53(+40%), P63(focal+), cytokeratin (CK) 5/6(+), cytokeratin (CK) 7(+), ER (-), pan-cytokeratin (CK-pan) (+), CD68(+), calponin (-), E-cadherin (+), vimentin (+), CD34(-), indicating active cellular proliferation and mutation. Examination of pus and blood cells revealed atypical squamous epithelial cells and numerous lobulated nucleated granulocytes. The final diagnosis was left breast cancer (cT3N0M0) and hypertension.

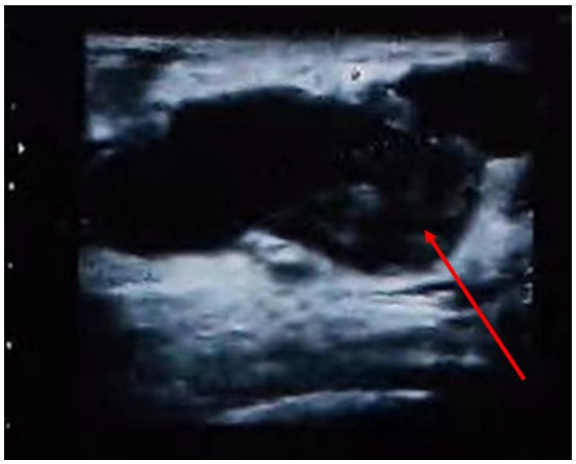


FIGURE 1
Breast color Doppler ultrasound of the patient at the first admission. The red arrow shows the tumor.

On August 9, 2018, following preoperative examinations that showed no significant contraindications, the patient underwent a simple mastectomy of the left breast and sentinel lymph node biopsy under general anesthesia. The postoperative pathology report indicated that the tumor was 50% cystic and 50% solid, with the solid portion being slightly papillary, grayish-white, and firm. The total volume of the tumor was approximately 5.0cm×4.0cm×3.0cm. Histologically, it was identified as metaplastic carcinoma/sarcomatoid carcinoma, comprising squamous cell carcinoma (~25%), invasive ductal carcinoma (~5%), and high-grade fibrosarcoma (~70%) (refer to Figures 2A–C). The tumor was graded MBNG 3, with no metastasis observed in the sentinel lymph nodes (0/2). Immunohistochemical testing confirmed a mix of squamous cell carcinoma, invasive ductal carcinoma, and sarcoma, showing Ki-67(+30%), ER (-), PR (-), HER2 (invasive ductal carcinoma 2+), E-cadherin(invasive ductal carcinoma +), cytokeratin (CK) 5/6(squamous carcinoma+), P40(squamous carcinoma+), cytokeratin (CK) 7(invasive ductal carcinoma+), pan-cytokeratin (CK-pan) (carcinoma+), vimentin(sarcoma+), smooth muscle actin (SMA) (sarcoma focal+). The patient, with a height of 160cm, weight of 68kg, and body surface area of 1.75m^2, recovered well postoperatively, and based on the condition and pathology results, was given 5 cycles of AC regimen adjuvant chemotherapy (doxorubicin 70mg per cycle, ifosfamide 4000mg per cycle, every 21 days). No radiotherapy was administered. After chemotherapy, the patient was lost to follow-up, and attempts to contact her or her relatives were unsuccessful.

3 Discussion

We report a case of carcinosarcoma, a malignant breast tumor comprising squamous cell carcinoma, invasive ductal carcinoma, and high-grade fibrosarcoma components. Carcinosarcoma, an aggressive form of metaplastic breast cancer (MpBC), represents less than 1% of all breast cancers (4). This cancer mainly affects postmenopausal women aged 49-61 years (5, 6). The tumor typically manifests as a rapidly growing mass, averaging 2.0cm to 5.5cm in diameter. Despite their large size, these tumors rarely involve axillary lymph nodes (6–8). Instead, early blood-borne metastasis to organs like the liver and lungs is more prevalent (9). Previous studies have shown that MpBC often presents benign imaging characteristics on mammography and ultrasound. Mammographic findings typically reveal a high- or iso-dense oval or irregular mass with narrow, indistinct, or ill-defined margins. On ultrasound, it frequently appears as a simple hypoechoic mass with similarly narrow or poorly defined borders (6). The patient first identified a lesion in her left breast at 63, and 5 years had passed by the time of her initial consultation. The presence of multiple tumor

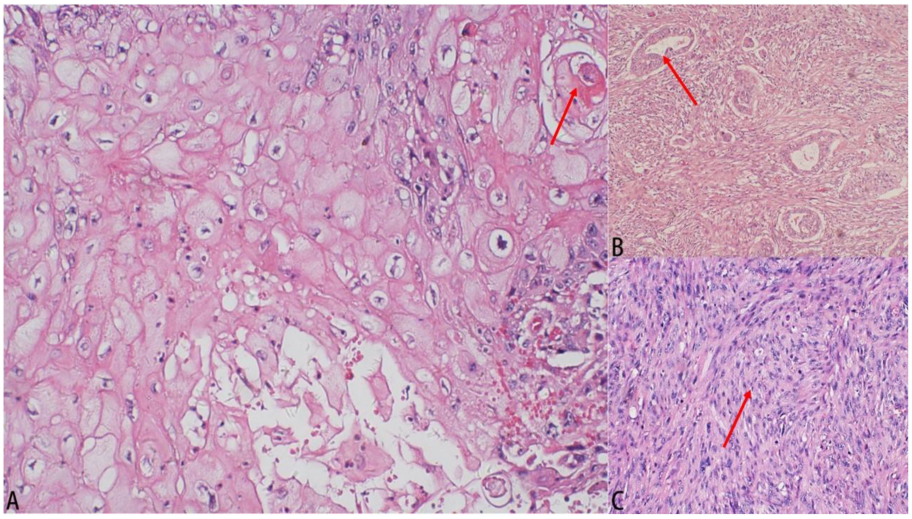


FIGURE 2
Results of pathological examination. **(A)** Histological image (hematoxylin–eosin staining, 100×): squamous cell carcinoma. **(B)** Histological image (hematoxylin–eosin staining, 100×): invasive ductal carcinoma. **(C)** Histological image (hematoxylin-eosin staining, 100×): High-grade fibrosarcoma.

components resulted in a unique growth pattern, with the tumor rapidly expanding to nearly half the breast's volume within two years before consultation. Imaging revealed the tumor's expansive growth without evidence of axillary lymph node involvement. Ultrasound and mammography suggested a benign tumor, while pulmonary and abdominal CT scans found no metastatic lesions, rendering the imaging results nonspecific (5, 6, 8, 10). Consistent with previous study findings (6). This factor has impeded clinicians' capacity for accurate carcinosarcoma diagnosis. Despite preoperative core needle biopsy, the lesion's high heterogeneity (11) rendered the small sample insufficient for pathological diagnosis, complicating accurate preoperative assessment (9).

Regarding immunohistochemistry, previous studies have relatively consistently concluded that most tumors exhibit a triple-negative phenotype, with a minority being ER/PR-positive or HER2-positive (12–15). The study found no statistically significant association between hormone receptor status and survival outcomes (12, 16). Differences in HER2 status are also unlikely to contribute to variations in survival (15). However, one study involving 13 patients with MpBC found an association between hormone receptor expression and lymph node metastasis, as well as a correlation between HER2 expression and tumor histologic grade, tumor size, and lymph node metastasis (14). Given the rarity of MpBC—and the even lower prevalence of hormone receptor-positive or HER2-positive cases—it remains uncertain whether hormone receptor status and HER2 expression significantly impact prognosis. Larger clinical studies are needed in the future to validate these findings.

The absence of extensive clinical trials on MpBC means there are no definitive treatment guidelines (9). Thus, treatment decisions rely on clinical staging and the patient's immunohistochemical phenotype at consultation. MpBC 's hallmark is the transformation of tumor

TABLE 1 Comparison of clinical manifestations, imaging findings, treatment, and prognosis between the two cases.

Feature	Chao Li et al. (26)	This Case
Admission Year	2018	2018
Gender	Female	Female
Age	77	68
Tumor Size	10.0cm×10.0cm	6.0cm × 6.0cm
Breast Affected	Right	Left
Location in Breast	Outer quadrant	Upper outer quadrant
Mammography Findings	Not performed	Slightly dense mass, no calcifications
Histological Type	Squamous cell carcinoma, invasive ductal carcinoma, and high-grade sarcoma	Squamous cell carcinoma (about 25%) + invasive ductal carcinoma (about 5%) + high-grade fibrosarcoma (about 70%)
Metastasis	Axillary lymph node, bone, lung	None observed
Surgery	Palliative mastectomy	Simple mastectomy and sentinel lymph node biopsy
Chemotherapy	Doxorubicin + Cyclophosphamide, Paclitaxel, Capecitabine	Doxorubicin + Ifosfamide
Radiotherapy	Not performed	Not performed
Prognosis	Lung metastasis reappeared 7 months post-surgery, treated with albumin-bound paclitaxel and carboplatin, alive at 11-month follow-up	Lost to follow-up

epithelium into squamous and/or mesenchymal components. Treatment recommendations generally follow those for invasive breast cancer (8, 9). Most patients are triple-negative (7, 17), yet they respond less effectively to neoadjuvant chemotherapy than typical triple-negative cancers, showing a complete response rate of around 10% (6, 9, 18). Consequently, surgery plus adjuvant therapy is the preferred treatment (6). In this case, the Her-2 receptor was scored as 2+, but the patient declined further clarification of Her-2 gene status via FISH testing. Despite the undetermined Her-2 gene status, the postoperative treatment plan leans towards managing a triple-negative phenotype.

Due to the tumor's large size, which disqualified the patient for breast-conserving surgery, the primary treatment option was mastectomy with axillary sentinel lymph node biopsy or dissection (9). Research indicates that MpBC patients undergoing postoperative adjuvant radiotherapy have a 30% lower mortality rate compared to those who do not receive radiation, highlighting the potential benefits of radiation therapy (6, 19). The selection of postoperative adjuvant chemotherapy regimens is guided by the status of estrogen and progesterone receptors, HER2 expression, and TNM staging. Studies suggest that squamous epithelial component cases benefit from platinum-based chemotherapy, while sarcomatous component cases respond well to anthracycline and cyclophosphamide-based regimens (5). Moreover, the presence of BRCA gene mutations in some patients indicates potential benefits from poly (ADP-ribose) polymerase inhibitor therapy (5).

The World Health Organization (WHO) classifies MpBC into six subtypes based on the mesenchymal and epithelial components of the tumor: (1) low-grade adenosquamous carcinoma, (2) fibromatosis-like metaplastic carcinoma, (3) squamous cell carcinoma, (4) spindle cell carcinoma, (5) metaplastic carcinoma with heterologous mesenchymal differentiation, and (6) mixed metaplastic carcinoma (6, 20). This case falls under the mixed metaplastic carcinoma subtype. Previous studies have found that fibromatosis-like metaplastic carcinoma and low-grade adenosquamous carcinoma are relatively sluggish. In contrast, other metaplastic variants tend to be aggressive, chemotherapy-resistant, and highly prone to metastasis (21, 22). Two large studies reported better survival rates for patients with metaplastic carcinoma exhibiting heterologous mesenchymal differentiation (23, 24). Regarding which subtype has the poorest survival rate, a series study involving 132 patients identified a lower survival rate in patients with metaplastic squamous cell carcinoma (23). Another study with 364 patients reported poorer clinical outcomes in those with spindle cell carcinoma (24). Additionally, some research suggests that patients with mixed metaplastic carcinoma may have lower survival rates than those with other subtypes (12, 20, 25). Due to the rarity of MpBC, large-scale clinical data are still needed to determine whether statistically significant prognostic differences exist between subtypes.

Our PubMed search for literature on metaplastic breast cancers with more than two histological types yielded only a single report meeting our criteria. We compared the characteristics of our case with the one found in the literature, as detailed in Table 1.

Literature indicates MpBC generally has a poor long-term prognosis (9–11), identifying surgical treatment and TNM staging as independent predictors of overall survival. Higher TNM stages correlate with lower overall survival rates, while surgical intervention improves these rates (18). Due to the loss of follow-up, the precise prognosis for our reported patient remains unknown; Chao Li et al. (26) described a malignant breast tumor case with three histological types and existing bone and lung metastases at diagnosis. The patient underwent a palliative mastectomy and survived for at least 11 months postoperatively. Our case, also featuring a tumor with three histological types, was diagnosed with the lesion confined to the breast, with no local lymph node or distant metastasis. Given the postoperative systemic treatment and lack of metastasis at diagnosis, we speculate our patient's prognosis surpasses that in Chao Li et al.'s report. Despite the loss to follow-up, we surmise survival exceeded 11 months post-surgery.

We present a rare case of MpBC featuring three distinct tissue types, characterized by a large tumor with a propensity for skin invasion. Imaging studies provided nonspecific results, and accurate diagnosis depended on a comprehensive pathological examination of the tumor. Surgery is the primary treatment, and although prognosis is generally poor, early detection and treatment, alongside advancements in immunotherapy, can enhance both cure and survival rates.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of the First Hospital of Jilin University. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by-product of routine care or industry. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

HL: Conceptualization, Data curation, Investigation, Software, Writing – original draft. GZ: Data curation, Software, Writing – review & editing. ZF: Methodology, Project administration,

Supervision, Writing – review & editing. DW: Formal analysis, Project administration, Supervision, Validation, Writing – review & editing. FQ: Funding acquisition, Project administration, Resources, Visualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The author states that the study, authorship, and/or publication of this article was obtained by Doctor of excellence program (DEP) The First Hospital of Jilin University. Number: JDYY-DEP-2023019 financial support.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Makki J. Diversity of breast carcinoma: histological subtypes and clinical relevance. *Clin Med Insights Pathol.* (2015) 8:23–31. doi: 10.4137/CPath.S31563

2. Bray F, Laversanne M, Sung HYA, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca-a Cancer J Clin.* (2024) 74:229–63. doi: 10.3322/caac.21834

3. Voutsadakis IA, Zaman K, Leyvraz S. Breast sarcomas: Current and future perspectives. *Breast.* (2011) 20:199–204. doi: 10.1016/j.breast.2011.02.016

4. Jenkins S, Kachur ME, Rechache K, Wells JM, Lipkowitz S. Rare breast cancer subtypes. *Curr Oncol Rep.* (2021) 23:54. doi: 10.1007/s11912-021-01048-4

5. Tray N, Taff J, Adams S. Therapeutic landscape of metaplastic breast cancer. *Cancer Treat Rev.* (2019) 79:101888. doi: 10.1016/j.ctrv.2019.08.004

6. Thomas HR, Hu B, Boyraz B, Johnson A, Bossuyt VI, Spring L, et al. Metaplastic breast cancer: A review. *Crit Rev Oncol Hematol.* (2023) 182:103924. doi: 10.1016/j.critrevonc.2023.103924

7. Thomas A, Douglas E, Reis JS, Gurcan MN, Wen HY. Metaplastic breast cancer: current understanding and future directions. *Clin Breast Cancer.* (2023) 23:775–83. doi: 10.1016/j.clbc.2023.04.004

8. McKinnon E, Xiao P. Metaplastic carcinoma of the breast. *Arch Pathol Lab Med.* (2015) 139:819–22. doi: 10.5858/arpa.2013-0358-RS

9. Papatheodoridi A, Papamattheou E, Marinopoulos S, Ntanasis-Stathopoulos I, Dimitrakakis C, Giannos, et al. metaplastic carcinoma of the breast: case series of a single institute and review of the literature. *Med Sci (Basel Switzerland).* (2023) 11:35. doi: 10.3390/medsci11020035

10. Bian TT, Lin Q, Wu Z, Cui C, Qi C, Li L, et al. Metaplastic carcinoma of the breast: Imaging and pathological features. *Oncol Lett.* (2016) 12:3975–80. doi: 10.3892/ol.2016.5177

11. Narayan P, Kostrzewa CE, Zhang ZG, O'Brien DAR, Mueller BA, Cuaron JJ, et al. Metaplastic carcinoma of the breast: matched cohort analysis of recurrence and survival. *Breast Cancer Res Treat.* (2023) 199:355–61. doi: 10.1007/s10549-023-06923-1

12. Cimino-Mathews A, Verma S, Figueroa-Magalhaes MC, Jeter SC, Zhang Z, Argani P, et al. A clinicopathologic analysis of 45 patients with metaplastic breast carcinoma. *Am J Clin Pathol.* (2016) 145:365–72. doi: 10.1093/ajcp/aqv097

13. El Zein D, Hughes M, Kumar S, Peng X, Oyasiji T, Jabbour H, et al. Metaplastic carcinoma of the breast is more aggressive than triple-negative breast cancer: A study from a single institution and review of literature. *Clin Breast Cancer.* (2017) 17:382–91. doi: 10.1016/j.clbc.2017.04.009

14. Budzik MP, Patera J, Sobol M, Czerw AI, Deptala A, Badowska-Kozakiewicz AM. Clinicopathological characteristics of metaplastic breast cancer - analysis of the basic immunohistochemical profile and comparison with other invasive breast cancer types. *Breast.* (2019) 43:135–41. doi: 10.1016/j.breast.2018.12.004

15. Nelson RA, Guye ML, Luu T, Lai LL. Survival outcomes of metaplastic breast cancer patients: results from a US population-based analysis. *Ann Surg Oncol.* (2015) 22:24–31. doi: 10.1245/s10434-014-3890-4

16. Abada E, Kim S, Dozier K, Fehmi O, Jang H, Fehmi Z, et al. Estrogen receptor status has no prognostic relevance in metaplastic breast carcinoma. *Cancer Treat Res Commun.* (2022) 33:100630. doi: 10.1016/j.ctarc.2022.100630

17. Weigelt B, Kreike B, Reis JS. Metaplastic breast carcinomas are basal-like breast cancers: a genomic profiling analysis. *Breast Cancer Res Treat.* (2009) 117:273–80. doi: 10.1007/s10549-008-0197-9

18. Schwartz TL, Mogal H, Papageorgiou C, Veerapong J, Hsueh EC. Metaplastic breast cancer: histologic characteristics, prognostic factors, and systemic treatment strategies. *Exp Hematol Oncol.* (2013) 2:31. doi: 10.1186/2162-3619-2-31

19. Moreno AC, Lin YH, Bedrosian I, Shen Y, Babiera GV, Shaitelman SF. Outcomes after treatment of metaplastic versus other breast cancer subtypes. *J Cancer.* (2020) 11:1341–50. doi: 10.7150/jca.40817

20. McCart Reed AE, Kalaw E, Nones K, Bettington M, Lim M, Bennett J, et al. Phenotypic and molecular dissection of metaplastic breast cancer and the prognostic implications. *J Pathol.* (2019) 247:214–27. doi: 10.1002/path.2019.247.issue-2

21. McMullen ER, Zoumberos NA, Kleer CG. Metaplastic breast carcinoma update on histopathology and molecular alterations. *Arch Pathol Lab Med.* (2019) 143:1492–6. doi: 10.5858/arpa.2019-0396-RA

22. Reddy TP, Rosato RR, Li X, Moulder S, Piwnica-Worms H, Chang JC. A comprehensive overview of metaplastic breast cancer: clinical features and molecular aberrations. *Breast Cancer Res.* (2020) 22:121. doi: 10.1186/s13058-020-01353-z

23. Tadros AB, Sevilimedu V, Giri DD, Zabor E, Morrow M, Plitas G. Survival outcomes for metaplastic breast cancer differ by histologic subtype. *Ann Surg Oncol.* (2021) 28:4245–53. doi: 10.1245/s10434-020-09430-5

24. Rakha EA, Tan PH, Varga Z, Tse GM, Shaaban AM, Climent F, et al. Prognostic factors in metaplastic carcinoma of the breast: a multi-institutional study. *Br J Cancer.* (2015) 112:283–9. doi: 10.1038/bjc.2014.592

25. Han M, Salamat A, Zhu L, Zhang HA, Clark BZ, Dabbs DJ, et al. Metaplastic breast carcinoma: a clinical-pathologic study of 97 cases with subset analysis of response to neoadjuvant chemotherapy. *Modern Pathol.* (2019) 32:807–16. doi: 10.1038/s41379-019-0208-x

26. Li C, Fang HF, Lu HF. Case report of a breast mass with three types of Malignant tumors-squamous cell carcinoma, invasive ductal carcinoma, and breast sarcoma. *Oncotargets Ther.* (2021) 14:3193–7. doi: 10.2147/OTT.S304145

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 19 December 2024
DOI 10.3389/fonc.2024.1430341

OPEN ACCESS

EDITED BY
Zheng Wang,
Shanghai Jiao Tong University, China

REVIEWED BY
Francesco Schettini,
August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Spain
Olesya A. Kharenko,
Syantra Inc, Canada

*CORRESPONDENCE
Tamara Martos
tamaramartos@gmail.com

RECEIVED 09 May 2024
ACCEPTED 31 October 2024
PUBLISHED 19 December 2024

CITATION
Martos T, Saint-Gerons M, Masfarre L, Castro-Henriques M, Martinez-Garcia M, Servitja S and Albanell J (2024) Palinopsia associated with the CDK4/6 inhibitor ribociclib during the first-line treatment of metastatic breast cancer: two case reports. *Front. Oncol.* 14:1430341. doi: 10.3389/fonc.2024.1430341

Palinopsia associated with the CDK4/6 inhibitor ribociclib during the first-line treatment of metastatic breast cancer: two case reports

Tamara Martos*, Marta Saint-Gerons, Laura Masfarre, Maria Castro-Henriques, Maria Martinez-Garcia, Sonia Servitja and Joan Albanell

Hospital del Mar, Parc de Salut Mar, Barcelona, Spain

The most frequently used standard treatment for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer patients consists of a CDK4/6 inhibitor (abemaciclib, ribociclib, or palbociclib) combined with endocrine therapy. Despite CDK4/6 inhibitors being part of routine care in the last few years, new adverse events continue to be reported. Here, we report two cases of palinopsia, a rare neurological visual disturbance that refers to the persistence or recurrence of a visual image after the removal of visual stimuli in patients treated with ribociclib and letrozole. Neuro-ophthalmological assessments and brain MRIs did not find any organic cause. However, palinopsia was related in a time- and dose-dependent manner to the intake of ribociclib. Following a one-level dose reduction of ribociclib, palinopsia was mild and well tolerated. Both patients continued the treatment with ribociclib, with one of them for almost 2 years. Based on the identification of two cases in our hospital in a short period of time, it is tempting to suggest that ribociclib-related palinopsias may not be uncommon. We propose that physicians should be aware of this ribociclib-associated adverse event. Patients presenting this symptom should undergo a routine workup (neuro-ophthalmological assessment and brain MRI) and, if negative, be reassured of its relation with ribociclib as well as the safety of continuing on this drug.

KEYWORDS

palinopsias, ribociclib, breast cancer, adverse events, ophthalmologic toxicity

Highlights

- For the first time, palinopsias had been described to be related to ribociclib as a rare adverse event in patients with metastatic breast cancer.

Introduction

Breast cancer accounts for approximately 30% of female cancers and has a mortality-to-incidence ratio of 15%. Approximately 20% of the patients suffer a metastatic relapse after the treatment for early breast cancer, and approximately 5% have *de novo* stage IV metastatic disease. Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative disease is the most common subtype of breast cancer. Abemaciclib, palbociclib, and ribociclib are the three CDK4/6 inhibitors approved for HR+, HER2-negative advanced breast cancer in combination with endocrine therapy (1–3). The combination of endocrine therapy with ribociclib, abemaciclib, and ribociclib has become the first-line standard of care (SOC) for locally advanced inoperable or metastatic HR+, HER2− breast cancer patients due to its benefits in progression-free survival and overall survival. The overall adverse event (AE) profile of the different CDK4/6 inhibitors is well known. However, each CDK4/6 inhibitor (CDK4/6i) has distinct AEs, mainly due to their different degrees of specificity and potency in terms of inhibition of CDK4 and CDK6. With the widespread use of these agents, rare toxicities of CDK4/6 inhibitors are being reported. To our knowledge, neurological AEs, including palinopsia, due to CDK4/6 inhibitors have not been reported to date. Here, we report two cases of women who described palinopsias during ribociclib therapy in a time- and dose-dependent manner.

Case 1

In 2002, a 46-year-old woman with a history of Raynaud's syndrome and hypothyroidism was diagnosed with HR-positive [estrogen receptor (ER) 95%, progesterone receptor (PR) 95%] HER2-negative low-grade invasive cancer (NOS) of the right breast cancer (pT1cpN1aM0). The primary treatment was a right radical mastectomy. The patient received adjuvant chemotherapy (docetaxel, cyclophosphamide, and doxorubicin for six cycles), irradiation of the affected breast and supra- and infraclavicular nodes, and adjuvant endocrine therapy with tamoxifen for 7 years.

The patient remained free of relapse until August 2021. At this point, the patient consulted a general practitioner for hip pain. A bone scintigraphy and a CT scan were performed, which identified a left iliac lesion suspicious of bone metastases and unspecific lung nodes. A bone biopsy revealed invasive breast cancer (NOS, ER+ 100%, PR+ 100%, HER2-negative). In September 2021, she was started on ribociclib 600 mg/day (three 200-mg tablets daily for 3 weeks every 4 weeks) plus letrozole (2.5 mg/day continuous).

In November 2021, the patient came to our hospital. We performed a PET/TC scan that did not reveal additional metabolic foci of disease, other than the known left iliac lesions. We continued ribociclib and letrozole and planned radiation therapy [stereotactic body radiation therapy (SBRT)] to the bone lesion (January 2022). Ribociclib was discontinued for three consecutive weeks to avoid an overlap with radiation therapy. In March 2022, the patient referred persistence of small motion visual images in dim conditions after the removal of visual stimuli, i.e., palinopsia. Retrospectively, the patient acknowledged that palinopsia started in cycle 1 of ribociclib, from day 1 to day 21, and disappeared in the week off ribociclib (Figure 1) It was moderately disturbing, and the pattern was the same for each cycle. As palinopsia was absent in the 3-week period while off ribociclib (but not letrozole) when she had the radiation therapy, the patient suspected a drug-related cause and discussed it with us. A

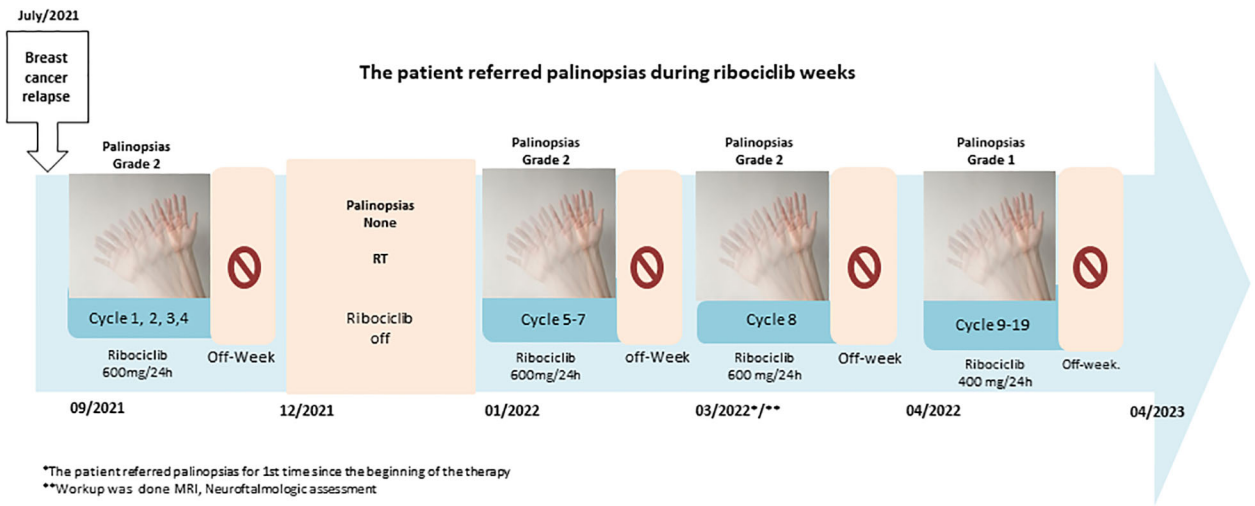


FIGURE 1
Cronologic symptoms in case 1 during the intake of Riboclib. *The patient referred palinopsias for 1st time since the beginning of the therapy. **Workup was done MRI, Neuroftalmologic assessment.

workup was performed, including a neurological examination and a neuro-ophthalmological assessment. Her best-corrected visual acuity was 20/20 in both eyes (OU). She had equal and reactive pupils with no relative afferent pupillary defect. Slit-lamp biomicroscopy, intraocular pressure, and funduscopy revealed normal OU. Optical coherence tomography showed a normal peripapillary retinal nerve fiber layer, macular, and ganglion cell layer analysis of OU. Automated visual fields revealed a normal field of OU, as did a laboratory blood test and a brain MRI. None of them revealed any organic cause of palinopsia. The chronology of symptoms and ribociclib intake and the absence of alterations in complementary tests guide the etiology of palinopsia as a rare adverse event related to ribociclib. In April 2022, after careful discussion with the patient, the ribociclib dose was lowered to 400 mg/day. Following dose reduction, palinopsia disappeared until July 2022. The palinopsia reappeared at a very light degree and low frequency. Since then, the patient has been on ribociclib therapy at 400 mg and has very mild, non-daily palinopsias and no evidence of disease progression (October 2024).

Case 2

In December 2022, a 28-year-old premenopausal woman with a history of lymphoma, treated with polychemotherapy (scheme REPOCH), radiotherapy, and surgery of residual mass in 2018, was diagnosed with breast cancer. She had a metastatic invasive high grade with HR-positive (ER 99%, PR 0%) and HER2-negative [immunohistochemistry (IHC) 0+] breast cancer. She had cT3cN1M1 disease. Distant metastasis was located in the brain (parietal lobe and both left and right cerebellar hemispheres) and peritoneum. A biopsy of the peritoneal node confirmed metastases from breast cancer. Brain metastasis was not amenable to surgical resection and did not require immediate radiation therapy In January 2023, the patient started first-line systemic therapy with luteinizing hormone-releasing hormone (LHRH) analogs (goserelin 3.6 mg sc q28days), letrozole (2.5 mg q24h), and ribociclib (three 200-mg tablets daily for 3 weeks followed by 1 week off, every 4 weeks). The patient reported that on the third day of ribociclib the appearance of mild abnormal visual symptoms related to motion when the visual field was no longer there (palinopsia). These images were present every day during bright light conditions or at night. Palinopsia disappeared the first day of the week off ribociclib, and no neurological additional disturbances were reported by the patient. A neuro-ophthalmologist conducted a visual exam: the patient's best-corrected visual acuity was 20/20 in both eyes. She had equal and reactive pupils with no relative afferent pupillary defect. Slit-lamp biomicroscopy, intraocular pressure, and funduscopy were normal OU. Optical coherence tomography showed a normal peripapillary retinal nerve fiber layer, macular, and ganglion cell layer analysis of OU. Automated visual fields revealed a normal field of OU. Brain metastases were not considered as a cause of the patient's palinopsia. According to the clear temporal relationship of palinopsia with ribociclib intake and our experience with case 1, we considered this an AE of ribociclib. The patient continued the treatment with ribociclib and endocrine therapy. Palinopsia persisted at the same mild intensity during the on-ribociclib weeks, without any impact on her routine activities.

Discussion

Since the approval of CDK4/6i for HR+, HER2-negative metastatic breast cancer (mBC), these drugs have become the first line of therapy in combination with aromatase inhibitor or fulvestrant. Usually, CDK4/6is are well tolerated, and AEs are generally manageable with dose modification and supportive care measures. The most common AE reported of palbociclib and ribociclib is neutropenia, while the most common AE reported of abemaciclib is diarrhea. No neurological visual adverse events had been described related to CDK4/6i (2, 4).

Palinopsia is a rare neurological visual disturbance that refers to the persistence or recurrence of a visual image after the removal of visual stimuli. Although the exact physiopathology of this phenomenon remains unknown, pathophysiological causes include dysfunction of the coordinate systems of the parietal lobes (5) and the pathways involving processing and feedback of light and motion with alteration of serotonergic activity (6). It is classified into two subgroups: hallucinatory and illusionary. Hallucinatory palinopsia indicates a central nervous system (CNS) alteration, and the causes include neoplasms, seizures, arteriovenous malformation, stroke, or infection. However, illusory palinopsia is strikingly dependent on external light or the motion of an object and is characterized by prolonged indistinct or unformed perseverated images or light (longer than physiological afterimages). The causes include drugs, migraines, menstrual cycle, hallucinogen persisting perception disorder, head injuries, or metabolic diseases (7–11).

Case reports had been published of palinopsias related to prescription drugs: trazodone, nefazodone, mirtazapine, topiramate, clomiphene, oral contraceptives, and risperidone (12–14). Palinopsia usually occurs after introducing the aforementioned drugs or increasing their dose, and it resolves after discontinuation. The pathophysiology of drug-induced palinopsia is based on alterations in neurotransmitters and their receptors, such as the serotonergic system or disruption in GABAergic transmission, which is facilitated by the 5HT2a receptor (15, 16). Estrogens interact with neurotransmitters, including the brain's cholinergic and serotonergic systems, and hormonal therapies could interfere with the normal CNS process involved concerning the visual field. However, CDK4/6is are not cell-specific, so these agents can interfere not only with the cell cycle of cancer cells but also with the cell cycle of healthy cells in brain tissue. Nevertheless, further investigation is still required to understand the exact mechanisms as well as potential risk factors.

Patients with palinopsias may present to general practitioners, neurologists, or ophthalmologists with visual symptoms, which may be misdiagnosed. Palinopsias need proper ophthalmological and neurological physical exams. Visual acuity, pupil, tonometry, extraocular movement, and external exams are needed, although physical exam and workup are almost always non-contributory, and diagnosis is largely based on information from the clinical history (14).

The two patients described above experienced visual abnormalities early during the ribociclib therapy. The differential diagnoses included CNS spread or toxicity related to aromatase inhibitors. A neurological exhaustive physical exam by a specialized

oncologist disregarded other neurological symptoms, and an MRI was performed without evidence of metastases in CNS in the first case and absence of deterioration in the second case. A neuro-ophthalmologist performed a visual exam and did not find ocular pathology. The close temporal relationship between the therapeutic regimen with ribociclib and the reversibility after the ribociclib withdrawal in our patients suggests the direct involvement of palinopsias and CDK4/6i. The woman described in the second case has CNS metastases, but she had not experienced such episodes until the beginning of CDK4/6i therapy. Her abnormal visual alterations started while on ribociclib therapy and disappeared when the therapy was discontinued. In this case, the patient had brain M1; however, the chronology and the clinical course of these symptoms guided our clinical suspicion that palinopsias could be related to ribociclib.

Palinopsia should be distinguished from physiological afterimages or toxicity related to aromatase inhibitors (AIs). Physiological afterimages are a common and benign phenomenon that appears after viewing a bright stimulus and shifting visual focus is thought to derive mainly from photobleaching of the retina, although newer evidence indicates a contribution from cerebral processes (17–19).

The incidence of ocular toxicity related to AI is quite variable. It had been described previously as dry eyes, Sjögren's syndrome, and ocular surface abnormalities in AI-treated breast cancer patients. Several clinical studies evidenced that hormonal therapy with AI impacts the ocular surface and Meibomian glands. Retinopathy and maculopathy were reported, which could present as blurred vision or ocular pain. These symptoms are accompanied by alterations in ocular coherence tomography in the foveal and parafoveal areas (20).

Ribociclib combined with AI is the first-line therapy in HR-positive, HER2-negative advanced breast cancer since the data published in MONALEESA-2 and MONALEESA-7 trials show substantial benefit in progression-free survival (PFS) and overall survival (OS) compared with hormonal therapy alone. In the pivotal trials, no visual alterations were reported related to CDK4/6i therapy. However, since the approval by Health Authorities worldwide, ribociclib has been used widely, which allows clinicians to identify new, rare adverse events like cutaneous toxicity (21, 22); but to our knowledge, no case of ribociclib-related palinopsia has been described.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TM: Writing – original draft, Writing – review & editing. MS-G: Writing – review & editing. LM: Writing – review & editing. MC-H: Writing – review & editing. MM-G: Writing – review & editing. SS: Writing – review & editing. JA: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hortobagyi GN, Stemmer SM, Burris HA, Yap Y-S, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. (2016) 375:1738–48. doi: 10.1056/NEJMoa1609709

2. Hortobagyi GN, Stemmer SM, Burris HA, Yap Y-S, Sonke GS, Hart L, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med*. (2022) 386:942–50. doi: 10.1056/NEJMoa2114663

3. Im S-A, Lu Y-S, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. (2019) 381:307–16. doi: 10.1056/NEJMoa1903765

4. Jhonson S, Martin M, Di Leo A, Im S-A, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NJP Breast Cancer*. (2019) 5:5. doi: 10.1038/s41523-018-0097-z

5. Dubois J, Vanrullen R. Visrual trails: do the doors of perception open periodically. *PloS Biol*. (2011) 9(5):e1001056. doi: 10.1371/journal.pbio.1001056

6. Sierra-Hidalgo F. Palinopsia induced by topiramate and zonsamide in a patient with migraine. *Clin Neuropharm*. (2013) 6(2):63–4. doi: 10.1097/WNF.0b013e3182849208

7. Yilmaz H, Erkin EF, Mavioğlu H, Sungurtekin U. Changes in pattern reversal evoked potentials during menstrual cycle. *Int Ophthalmol*. (1998) 22:27–30. doi: 10.1023/a:1006165126702

8. Canonico PL, Giammona G, Condorelli DF, Scapagnini U. Comparative effects of estrogens and prolactin on nigral and striatal GAD activity. *Brain Res*. (1982) 232:238–41. doi: 10.1016/0006-8993(82)90633-3

9. Johnson SF, Loge RV. Palinopsia due to nonketotic hyperglycemia. *West J Med*. (1988) 148(3):331–2.

10. Lauterbach E, Abdelhamid A, Annandale JB. Posthallucinogen-like visual illusions (palinopsia) with risperidone in a patient without previous hallucinogen exposure: possible relation to serotonin 5HT2a receptor blockade. *Pharmacopsychiatry*. (2000) 33:38–41. doi: 10.1055/s-2000-8452

11. Venkatesth R, Yadv NK, Sinha S. Illusory palinopsias induced by in *vitro* fertilization treatment: a case report. *J Clin Med Rep*. (2019) 13(1):164. doi: 10.1186/s13256-019-2115-7

12. Ihde-Scholl T, Jefferson JW. Mitrazapine-associated palinopsia. *J Clin Psiquiatry*. (2001) 62(5):373. doi: 10.4088/JCP.v62n0512a

13. Kraus RP. Visual "trails" with nefazodone treatment. *Am J Psyquiatry*. (1997) 153:1365–6. doi: 10.1176/ajp.153.10.1365b

14. Gersztenkorn D, Lee AG. Palinopsia revamped: A systematic review of the literature. *Survey ophtalmol*. (2015) 60(1):1–35. doi: 10.1016/j.survophthal.2014.06.003

15. Le Grand SM, Supornsilpchai W, Saengjaroentham C, Anan Srikiatkhachorn A. Serotonin depletion leads to cortical hyper excitability and trigeminal nociceptive facilitation via the nitro oxide pathway. *Headache*. (2011) 51:1152–60. doi: 10.1111/j.1526-4610.2011.01931.x

16. Shen RY, Andrade R. 5-Hydroxytryptamine2 receptor facilitates GABAergic neurotransmission in rat hippocampus. *J Pharm Exp There*. (1998) pp. 285:825–12.

17. Brindley GS. Two near properties of foveal after-images and a photochemical hypothesis to explain them. *J Physiol*. (1962) 164:168–79. doi: 10.1113/jphysiol.1962.sp007011

18. Shimojo S, Kamitani Y, Nishida S. Afterimage of perceptually filled-in surface. *Science*. (2001) 293:1677–80. doi: 10.1126/science.1060161

19. Virsu V. Retinal mechanisms of visual adaptation and afterimages. *Med Biol*. (1978) 56(2):84–96.

20. Servan D, Costea DO, Zgura A, Tudosie MS, Dascalu AM, Gangura GA, et al. Ocular side effects of aromatase inhibitor endocrine therapy in breast cancer – A review. *In Vivo*. (2022) 36:40–8. doi: 10.21873/invivo.12674

21. Pasqualoni M, Orlandi A, Palazzo A, Garufi G, Cannizzaro MC, Pontolillo L, et al. Case report: Vitiligo-like toxicity due to ribociclib during first-line treatment of metastatic breast cancer: two cases of premature interruption of therapy and exceptional response. *Front Oncol*. (2023) 13:1067264. doi: 10.3389/fonc.2023.1067264

22. Vrana E, Mylona S, Bobos M, Kontovinis L, Papazisis K. Ribociclib and palbociclib-induced erythema multiforme: a case report. *Oxf Med Case Rep*. (2022) 2022(11):omac116. doi: 10.1093/omcr/omac116

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 23 December 2024
DOI 10.3389/fonc.2024.1473896

OPEN ACCESS

EDITED BY
Frederick Dirbas,
Stanford University, United States

REVIEWED BY
Hirotaka Suto,
Hyogo Cancer Center, Japan
Wenxuan Zhang,
Stony Brook Medicine, United States

*CORRESPONDENCE
Zhonghai Du
13573603087@163.com

RECEIVED 31 July 2024
ACCEPTED 09 December 2024
PUBLISHED 23 December 2024

CITATION
Zhang S, Du Z, Wu J, Zhang X and Dong W (2024) Case report: Bone marrow metastasis and bone marrow necrosis occurring 11 years after ductal carcinoma *in situ* of the breast. *Front. Oncol.* 14:1473896. doi: 10.3389/fonc.2024.1473896

Case report: Bone marrow metastasis and bone marrow necrosis occurring 11 years after ductal carcinoma *in situ* of the breast

Shuting Zhang[1,2], Zhonghai Du[2]*, Jun Wu[2], Xiaoli Zhang[2] and Wei Dong[3]

[1]Graduate Institute, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China, [2]Department of Oncology, Weifang Hospital of Traditional Chinese Medicine, Weifang, Shandong, China, [3]Department of Pathology,Weifang Hospital of Traditional Chinese Medicine, Weifang, Shandong, China

Ductal carcinoma *in situ* (DCIS), a noninvasive breast cancer, rarely metastasises to distant locations. When the initial lesion is stable, bone marrow metastasis (BMM) and bone marrow necrosis (BMN) are even less common. Here, we report the case of a 47-year-old female patient who underwent localized surgery and radiotherapy for right-sided DCIS. The patient also had a mutation in the breast cancer susceptibility gene 1 (*BRCA1*, OMIM: 113705) and tested positive for the progesterone and estrogen receptors. After 11 years of disease-free survival, the patient developed severe thrombocytopenia, anemia, fever, malaise, generalized multifocal pain, and irregular vaginal bleeding. A nodule was later found in the right axilla, and a postoperative biopsy revealed tumor cells from the breast. After three bone marrow biopsies, ^{18}F-fluorodeoxyglucose, positron emission tomography, computed tomography (^{18}F-FDG PET/CT) scans, and other examinations, she was finally diagnosed with breast cancer BMM and BMN (stable primary lesion without bone metastasis). Despite symptomatic supportive treatment, the patient ultimately died rapidly as her condition deteriorated. In this case, we explored the possible mechanisms of BMM in this patient with DCIS by reviewing the literature related to this case and discussing the heterogeneous clinical presentation and pathologic phenotype. The diagnostic and therapeutic course of this case was extremely challenging. This suggests to clinicians that regular checkups and monitoring are necessary, even if the rate of distant metastasis from DCIS is low.

KEYWORDS

ductal carcinoma in situ, bone marrow metastasis, bone marrow necrosis, bone marrow biopsy, ^{18}F-FDG PET/CT, BRCA1, triple-negative breast cancer

1 Introduction

Breast ductal carcinoma *in situ* (DCIS) is characterized by abnormal epithelial cells restricted within the mammary ducts, surrounded by intact myoepithelial cells and basement membrane (1). It accounts for about 25% of new breast cancer diagnoses and is considered non-invasive as long as it remains within the ducts (2–4). However, low-grade DCIS has the potential to progress into invasive cancer, with rare occurrences of distant metastasis reported at only 0.14% (5, 6). The most common sites of distant metastasis in breast cancer are the lungs, bones, liver, and brain (7–9). Symptomatic bone marrow metastasis (BMM) is an exceptionally rare complication in DCIS, with most cases arising in the context of invasive breast cancer (10). In addition, asymptomatic bone marrow metastases are reported in 20-30% of patients with early-stage breast cancer and are usually caused by disseminated tumor cells (DTCs) that are clinically insignificant (10, 11). Under specific conditions (e.g., changes in the tumor microenvironment caused by systemic inflammation), these dormant cells may be reactivated. When circulating tumor cells (CTCs) invade the bone marrow, replacing normal tissue and causing symptoms like anemia, thrombocytopenia, and coagulation abnormalities, it's called symptomatic bone marrow involvement (10, 12). Bone marrow necrosis (BMN) is a rare clinicopathologic condition, often overlooked in living patients, characterized by extensive necrosis of hematopoietic tissues and stroma, with symptoms including bone pain, fever, and hematologic abnormalities such as anemia and thrombocytopenia (13, 14). Common symptoms of bone pain are due to inflammation and increased pressure within the bone caused by the metastasis or necrosis of bone marrow, which activates the peripheral sensory nerve endings within the bone marrow by releasing inflammatory mediators and mechanical compression or deformation (15). Malignant tumors are the main cause of BMN, accounting for approximately 90% of BMN cases, with malignant diseases of the hematopoietic system accounting for 60%, and extensive BMN secondary to solid tumors are rare and are usually an end-stage manifestation of symptomatic BMM (14). This report describes a rare case of a female patient who developed symptomatic BMM and eventually BMN 11 years after breast-conserving surgery and radiotherapy. By reviewing the relevant literature, we attempted to analyze the pathological mechanism, clinical characteristics, and treatment options to provide a reference for diagnosing and managing similar cases.

2 Case description

A 47-year-old woman presented to our hospital on February 24, 2024, with fatigue and neck, shoulder, and back pain for the past month. She had been admitted to the hospital in January 2013 for "bloody right nipple discharge for two months." At that time, she underwent a segmental excision of the right breast lesion and a biopsy of the anterior lymph nodes. The lesion was completely excised with negative margins. Pathologic findings showed non-invasive right breast ductal carcinoma *in situ* (Figures 1A–C). Immunohistochemistry detected carcinoma *in situ* estrogen receptor (ER) (+90%), progesterone receptor (PgR) (+80%), human epidermal growth factor receptor 2 (HER2) (+), E-cad (+), 34βE12 (+), P120 (membrane +), Ki-67 (<10%), P53 (+<10%), and SMA (+) (Figure 2A). The breast cancer was graded as pTisN0M0. Genetic testing showed a positive result for the S1 locus of the *BRCA1* gene. The patient refused further right mastectomy. Eight weeks after surgery, the patient underwent conformal radiotherapy to the right breast at a dose of DT: 4800cGy/25f, with enhanced DT to the right breast surgical area: 800cGy/4f. The patient was discharged with a good recovery. Despite being advised to take tamoxifen (20 mg daily) due to her hormone receptor-positive (HR+) breast cancer, the patient stopped the medication a few days after discharge and did not attend regular follow-up examinations.

On this admission, the patient reported heavy and prolonged menstrual flow for the last two months. There was a history of Coronavirus disease 2019 (COVID-19) infection in previous months. The patient denied any family history of genetic disorders or malignant tumors. The breast examination was unremarkable, showing no changes in the right breast or the scar area from the right axillary surgery. Routine blood tests showed platelets (16×10^9/L) and hemoglobin 51 g/L. Tumor markers showed CA153 at 45 U/L, while CEA and CA125 were within normal ranges. On March 2, the patient developed a fever accompanied by vaginal bleeding of about 40 ml, and platelets continued to fall (12×10^9/L). Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Nucleic Acid Test Returns Positive. Two days later, her plasma D-dimer increased to 55.29 mg/L. By March 7, her alkaline phosphatase had abnormally increased to 2398 U/L. Computed tomography (CT) scans of the craniocerebral, thoracic, abdominal, and pelvic regions, along with breast MRI, did not reveal any recurrence or other metastatic foci of breast cancer. Subsequent ^{18}F-FDG PET/CT examination showed no abnormal metabolism in the area of the right breast surgery or elsewhere in the body (Figures 3A, B), diffuse hyperdensity in the bone marrow cavity, mainly located in the medial skeleton, suggestive of BMM, and no destruction of the bone cortex. (Figures 3C, D). Serum immunofixation electrophoresis revealed normal serum immunoglobulin G, A, and M levels, reducing the likelihood of multiple myeloma.

Upon the patient's admission to the hospital, we performed the first bone marrow aspiration biopsy. The biopsy results indicated metastatic cancer in the marrow. Immunohistochemistry results showed ER (-), PgR (-), and HER2 (-). We conducted another bone marrow aspiration biopsy two weeks later to clarify the diagnosis. We examined two pieces of bone marrow tissue obtained from different puncture sites in the patient's iliac bone, and both results confirmed BMN (Figures 1D–F). The immunohistochemistry results of bone marrow samples showed ER (-), PgR (-), HER2 (-), GATA3 (-), and GCDFP (-) (Figure 2B). We transfused red blood cells, platelets, and plasma and provided antiviral therapy, symptomatic hemostasis, analgesia, and herbal adjuvant therapy until the definitive diagnosis was achieved.

Surprisingly, a mass was found near the patient's right axilla during a physical examination one month later. The mass measured approximately 1.5 cm × 2 cm with no redness, ulceration, or

tenderness. A puncture biopsy revealed tumor cells. Subsequently, the patient underwent tumor resection, and the pathology showed invasive adenocarcinoma (Figures 1G–I). Immunohistochemistry showed ER (-), PgR (+5%), c-erbB-2 (1+), E-cad (+), GATA-3 (±), GCDFP-15 (-), Ki67 (+ 50%), and p120 (membrane +) (Figure 4). Based on all examinations and laboratory results, we diagnosed the patient with invasive ductal carcinoma of the breast with bone marrow metastasis and axillary metastasis. The patient had an Eastern Cooperative Oncology Group (ECOG) physical status score 4. After assessing the patient's physical condition, we decided on conservative supportive treatment. On April 19, the patient presented with a gradual worsening of pain in the right upper extremity. One week later, the patient once more presented with heavy vaginal bleeding, malaise, fever, and dyspnea following exertion. The treatment was terminated based on the patient's expressed wishes. She subsequently succumbed to her illness the following day.

3 Discussion

DCIS is usually not considered metastatic. However, our patient developed BMM and BMN 11 years after the diagnosis of DCIS, a rare occurrence (16). Clinicopathologic parameters associated with aggressive recurrence and distant metastasis include patient age (<40 years), DCIS size, nuclear grade, presence or absence of consolidated necrosis, histologic type, Ki-67 staining, multifocality, surgical margins, and mode of detection (asymptomatic versus screening test) (17, 18). The patient was 35 at diagnosis, prompted by bloody nipple discharge. No other regular risk factors for distant metastasis were present. Because distant metastases after DCIS are rare and mostly reported as case studies, none of these risk factors were statistically significant. Generally, the mechanisms of recurrence and metastasis in early-stage breast cancer are linked to the completeness of initial treatment, the dormancy and activation of tumor cells, genetic factors, and changes in the tumor microenvironment (19, 20).

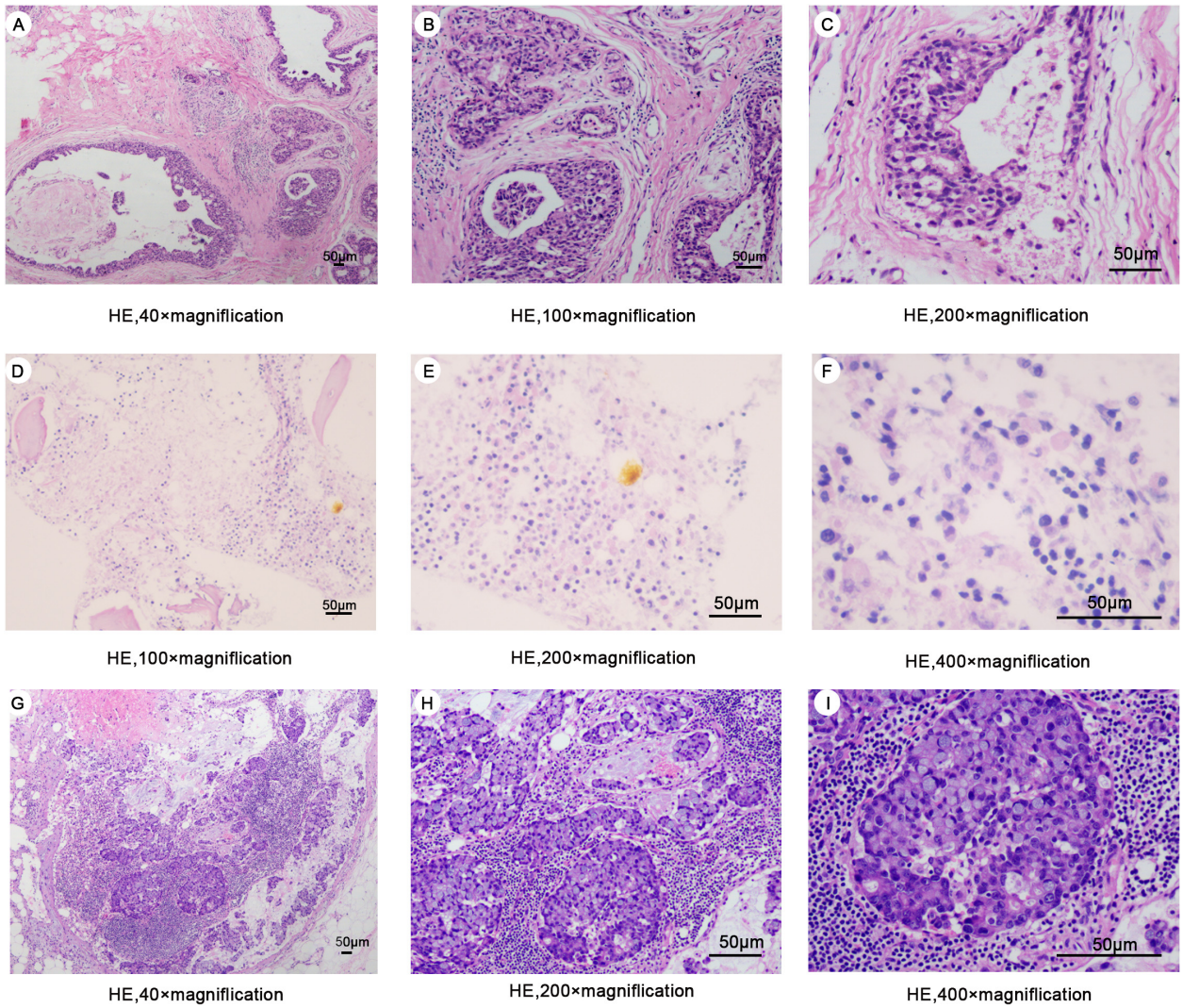


FIGURE 1
(A–C) Hematoxylin-eosin staining of surgical excision specimens of the right breast in 2013 **(D–F)** Hematoxylin-eosin staining of bone marrow biopsy specimens in 2024. **(G–I)** Hematoxylin-eosin staining of a specimen of the right axillary mass in 2024.

Standard treatment for DCIS includes radiotherapy (RT) following breast-conserving surgery (BCS) (21). The NSABP protocol B-17 showed a 12-year local recurrence rate of 32% for DCIS patients treated with resection only and 16% for resection plus radiotherapy (22). Tamoxifen is a selective estrogen receptor modulator (SERM) that is widely used to treat early-stage breast cancer that is hormone receptor-positive (ER+/PgR+) and can significantly reduce the risk of breast cancer recurrence and death (23). Studies have shown that adding tamoxifen to local excision and radiation therapy in ER-positive DCIS patients can reduce the 10-year risk of recurrence (24). However, noncompliance with tamoxifen therapy, especially early discontinuation, may lead to increased recurrence and mortality in breast cancer patients (20, 25). Patients did not take tamoxifen regularly, potentially expanding the recurrence risk.

The tumor microenvironment (TME) plays a crucial role in BMM, promoting tumor cells' survival, dormancy, and eventual reactivation. Breast cancer cells can reprogram the bone marrow microenvironment, which promotes tumor cell adhesion, angiogenesis, and remodeling of the bone marrow stroma (26). Dormant tumor cells typically survive the successful treatment of the primary tumor and enter a clinically asymptomatic state (27). In the bone marrow, immune cells help form pre-metastatic niches, creating an environment favorable for the survival of DTCs (28, 29). These immune cells secrete pro-inflammatory cytokines that enhance breast cancer tumor cell migration and colonization and mediate the reactivation of dormant DTCs, leading to significant metastasis after long-term dormancy (30). Emerging evidence suggests that COVID-19 can reactivate dormant tumor cells in response to microenvironmental cues, such as inflammatory or immune-mediated signals, leading to tumor progression and metastasis, systemic inflammation, widespread coagulation dysfunction, and multi-organ dysfunction (31). Upon admission, this patient was infected with COVID-19 but was not systematically treated. After this admission, the patient was re-infected with COVID-19, accompanied by fever, elevated D-dimer, and falling platelets. The patient tested positive for the novel coronavirus and had a fever, which conformed to the typical presentation of COVID-19 (32). Subsequently, the patient's condition deteriorated dramatically. We speculate that the patient's BMM after 11 years of asymptomatic survival and the rapid development of BMN may be due to immune activation by COVID-19, resulting in a transformation from asymptomatic BMM to symptomatic BMM.

Distant metastasis of breast DCIS in the absence of local lesion recurrence is rare. Previous studies have reported two cases of DCIS where patients developed metastases to the liver, lung, bone, and colon after breast-conserving surgery and endocrine therapy despite the stability of the primary lesion (33, 34). Unlike them, the patient in this case had hardly received any endocrine treatment, and the site of distant metastasis was the bone marrow, which is much more aggressive, has a worse prognosis, and is much rarer. Notably, this patient initially experienced abnormal symptoms, including irregular vaginal bleeding, heavy and prolonged menstrual

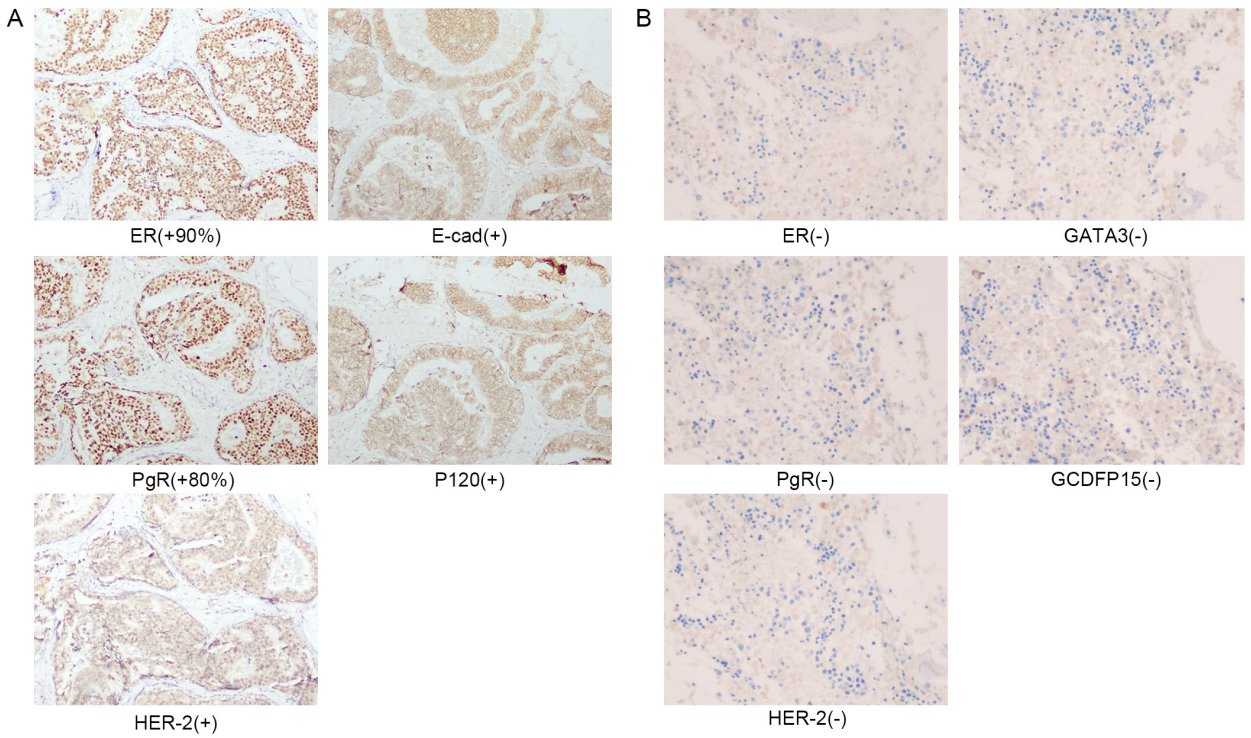


FIGURE 2
(A) Immunohistochemical staining of right breast surgical excision specimen in 2013. **(B)** Immunohistochemical staining of the second bone marrow biopsy in March 2024.

periods, and later bone pain. As the condition progressed, severe pain (NRS score 8) developed in multiple areas. An increase in vaginal bleeding accompanied each worsening of clinical symptoms. The patient's fever gradually returned to normal after antiviral treatment, which complicated the diagnosis. Laboratory findings associated with BMN typically reveal anemia, thrombocytopenia, elevated alkaline phosphatase levels, decreased blood calcium, and increased plasma D-dimer. However, these manifestations do not necessarily occur simultaneously (35). Upon admission, the patient presented with anemia and low platelet counts. Subsequent laboratory tests revealed a progressive increase in plasma D-dimer, elevated alkaline phosphatase, decreased blood calcium, and abnormal liver function. Nonetheless, these indicators lack specificity.

Symptomatic bone marrow metastasis (BMM) with a stable primary lesion is rare and prone to misdiagnosis. The patient was admitted to the hospital, and peripheral blood tests showed anemia and a persistent drop in platelets. The initial chest CT examination showed no recurrence or metastasis in the breast, while the PET-CT examination showed diffuse high density in the bone marrow cavity and no metabolic abnormalities in the right breast, armpit, or other areas. These findings made the diagnosis more difficult. In this case, the first step was to rule out hematologic disorders. Bone marrow examination is a high-yield test for identifying BMM from solid tumors (36, 37). In some cases where the primary tumor is occult, immunohistochemical results of bone marrow aspiration and bone marrow biopsy can help identify an unknown primary tumor (36). The first bone marrow biopsy confirmed metastatic cancer of undetermined origin, while further tests ruled out blood disorders. Although BMM is generally straightforward to detect, pinpointing the exact primary site can be challenging. Mammary BMM is commonly associated with bone metastases, and its occurrence without bone metastasis is extremely rare (34). Whole-body CT scans showed no bone metastases, and no cortical bone destruction was observed in the results of the PET-CT. A bone marrow biopsy confirmed metastatic cancer in the bone marrow, yet systemic examination findings remained inconclusive, making the diagnostic process more challenging. The eventual identification of a painless right axillary mass, absent on earlier imaging, was pivotal for diagnosis. By integrating findings from three bone marrow biopsies, PET-CT scans, and the axillary mass, it was concluded that the patient exhibited invasive carcinoma of the breast with BMM and BMN, accompanied by axillary metastasis. Extensive BMN is rare in solid tumors and is highly susceptible to underdiagnosis and misdiagnosis. A retrospective analysis showed that out of 16,651 bone marrow biopsy specimens, only 2 cases of BMN were associated with breast cancer (38). In this case, with an insidious primary disease and nonspecific symptoms, an aggressive multisite bone marrow

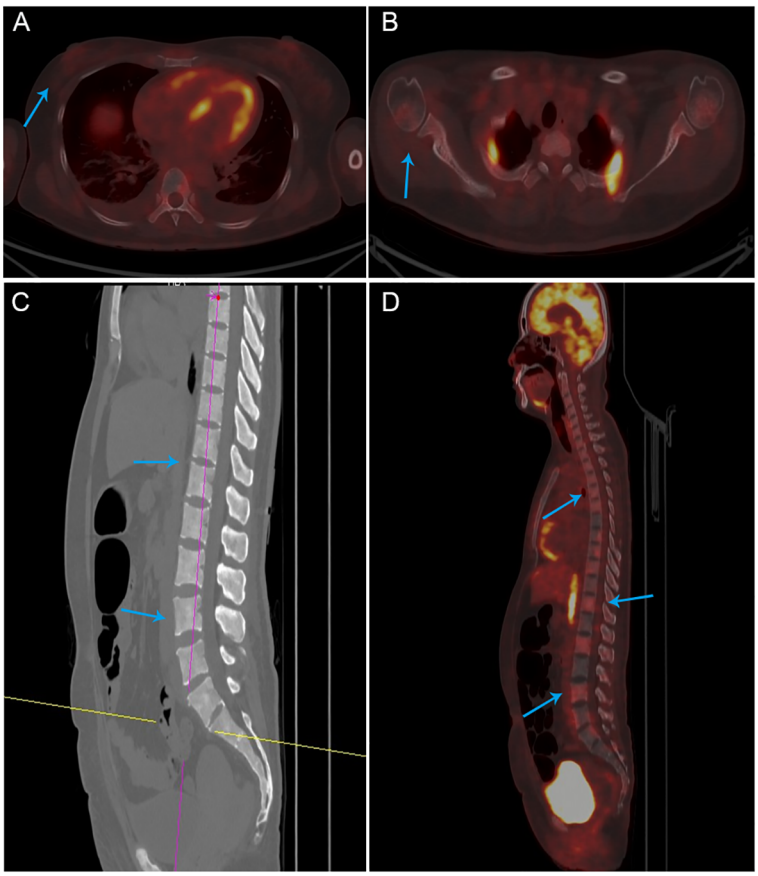


FIGURE 3
PET-CT images **(A, B)** There was no abnormal metabolism in the area of the right breast surgery or the axilla. **(C, D)** Diffuse hyperdensity in the medullary cavity of the bone, no destruction of the bone cortex.

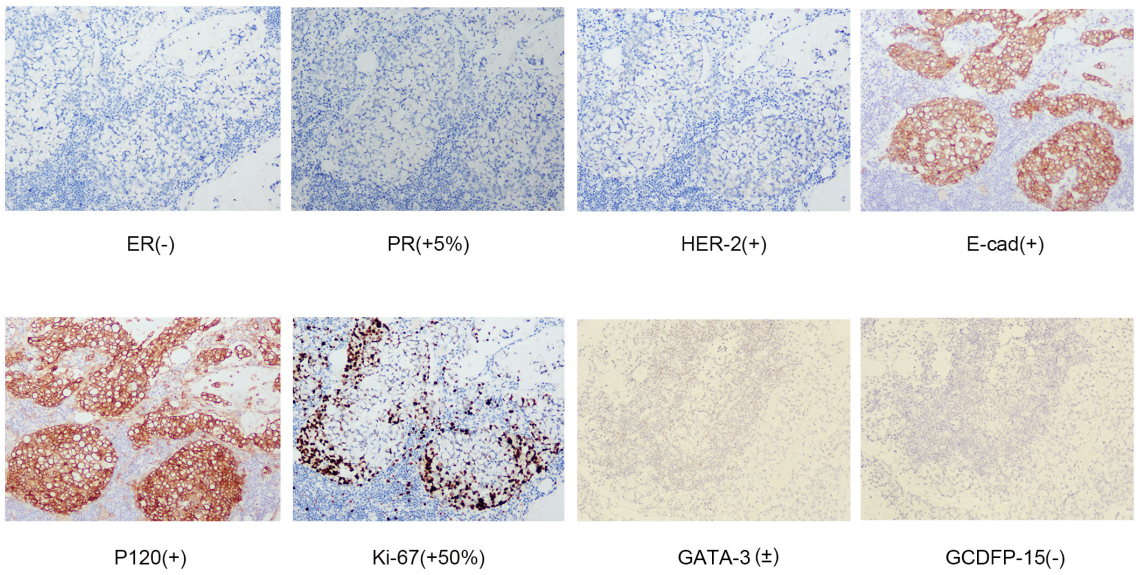


FIGURE 4
Immunohistochemical staining of a specimen of the right axillary mass in 2024.

aspiration biopsy and PET-CT were performed, which provided the prerequisites for the final definitive diagnosis.

Management of bone marrow metastasis remains a clinical challenge due to the lack of established guidelines (39). Due to the rarity of bone marrow metastases from breast cancer, there is a lack of systematic treatment guidelines, and the published literature consists mainly of case reports and studies with small sample sizes. Personalized treatment plans based on the molecular profile of the tumor and the patient's clinical condition are essential for optimizing outcomes. Chemotherapy is the mainstay of treatment, and weekly paclitaxel therapy is stable and much less toxic. However, bone marrow toxicity of cytotoxic drugs remains an unavoidable problem. Fluorouracil analogs have shown promising efficacy in clinical application and have been reported to be effective for bone marrow metastasis and DIC in gastric cancer (40). Interestingly, Chan, B. reported a case of bone marrow metastasis from triple-negative breast cancer in which the patient developed liver failure after first-line application of albumin-bound paclitaxel, which was then stabilized and controlled by continuous application of 5-FU infusion, followed by oral capecitabine (41). For HER-positive breast cancer bone marrow metastases, adding antibody-drug couplings targeting HER2 prolongs patient survival (42). By searching the literature, we have seen that immunotherapy has shown promising efficacy in bone marrow metastasis of other types of tumors (43). Still, for triple-negative breast cancer, the application has only been reported for metastasis to other sites (44, 45). No studies are related to the application of immune checkpoint inhibitors for BMM. Further studies are expected to address this issue. It has been found that BMM patients' OS strongly correlates with platelet levels and ECOG scores (34, 46). In this case, the patient was ultimately diagnosed with BMN and had significant suppression of bone marrow hematopoiesis, with symptoms such as grade IV thrombocytopenia (12 × 109/L) and vaginal bleeding. Moreover, the patient was fragile (ECOG 4), and chemotherapy could not be applied in this case. The patient and family agreed to conservative supportive care. Although the patient's condition improved slightly with plasma transfusion, platelet transfusion, analgesics, anti-infection measures, and herbal medicine, the lack of effective interventions for BMN and the patient's critical condition led to a deterioration in her condition, and she died the day after being discharged from the hospital. This case highlights the urgent need for further research into effective treatment strategies for BMN associated with breast cancer, especially for patients with severe comorbidities and impaired bone marrow function.

Breast cancer is a remarkably heterogeneous malignant tumor, and its temporal heterogeneity (dynamic changes in molecular characteristics between primary and recurrent foci) and spatial heterogeneity (differences between different metastatic sites) pose significant diagnostic and therapeutic challenges (44, 45). In this case, the patient's breast cancer progressed from ductal carcinoma *in situ* (ER+/PgR+/HER2+) to invasive ductal carcinoma (ER-/PgR-/HER2-) and showed further molecular phenotypic changes in bone marrow metastasis and axillary metastasis. The first bone marrow biopsy showed metastatic carcinoma and subsequent bone marrow biopsies showed bone marrow necrosis, suggesting a dynamic change in molecular phenotype, culminating in a triple-negative phenotype. The evolution of breast cancer from ductal carcinoma *in situ* to invasive ductal carcinoma is characterized by changes in hormone receptor and HER2 status reflecting the heterogeneity of its molecular phenotype, and mutations in the *BRCA1* gene in the genetic background may play an important role in this process. Elevated expression of the *BRCA1* gene, an essential

gene involved in DNA damage repair, cell cycle regulation, and genome stability, is closely associated with an increased risk of early distant metastasis in ER+ breast cancer patients (19, 47). *BRCA1* gene mutations are strongly associated with genomic instability, epithelial mesenchymal transition (EMT), and immune microenvironmental interactions, leading to significant inter- and intratumoral heterogeneity, which affects clinical outcomes and drug resistance (48). Our patient carries a *BRCA1* mutation, and she declined the recommendation for prophylactic mastectomy. The exact time point of the molecular typing change remains uncertain due to the lack of adequate follow-up review in this case, which constitutes a significant limitation.

4 Conclusion

We describe a rare case of a female patient who developed symptomatic bone marrow metastasis (BMM) and bone marrow necrosis (BMN) 11 years after the diagnosis of DCIS. DCIS may develop into a tumor that is highly aggressive under certain circumstances. Regular follow-up examinations after systemic therapy are necessary. In breast cancer patients presenting with unexplained anemia, fatigue, fever, bone pain, or abnormal vaginal bleeding while the primary lesion remains stable, the possibility of bone marrow metastasis or bone marrow necrosis should be considered. A bone marrow biopsy should be performed actively, and a PET-CT examination should be performed if necessary to confirm the diagnosis as soon as possible. Early treatment can benefit patient survival.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SZ: Investigation, Writing – original draft, Writing – review & editing. ZD: Investigation, Supervision, Writing – review & editing. JW: Writing – review & editing, Supervision. XZ: Writing – review & editing, Supervision. WD: Writing – review & editing, Supervision.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Allred DC. Ductal carcinoma in situ: terminology, classification, and natural history. *J Natl Cancer Inst Monogr*. (2010) 2010:134–8. doi: 10.1093/jncimonographs/lgq035

2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2024) 74:229–63. doi: 10.3322/caac.21834

3. Coleman WB. Breast ductal carcinoma in situ: precursor to invasive breast cancer. *Am J Pathol*. (2019) 189:942–5. doi: 10.1016/j.ajpath.2019.03.002

4. Ward EM, DeSantis CE, Lin CC, Kramer JL, Jemal A, Kohler B, et al. Cancer statistics: Breast cancer in situ. *CA Cancer J Clin*. (2015) 65:481–95. doi: 10.3322/caac.21321

5. Koh VCY, Lim JCT, Thike AA, Cheok PY, Thu MMM, Li H, et al. Behaviour and characteristics of low-grade ductal carcinoma in *situ* of the breast: literature review and single-centre retrospective series. *Histopathology*. (2019) 74:970–87. doi: 10.1111/his.2019.74.issue-7

6. Roses RE, Arun BK, Lari SA, Mittendorf EA, Lucci A, Hunt KK, et al. Ductal carcinoma-*in-situ* of the breast with subsequent distant metastasis and death. *Ann Surg Oncol*. (2011) 18:2873–8. doi: 10.1245/s10434-011-1707-2

7. Chen W, Hoffmann AD, Liu H, Liu X. Organotropism: new insights into molecular mechanisms of breast cancer metastasis. *NPJ Precis Oncol*. (2018) 2:4. doi: 10.1038/s41698-018-0047-0

8. Yates LR, Knappskog S, Wedge D, Farmery JHR, Gonzalez S, Martincorena I, et al. Genomic evolution of breast cancer metastasis and relapse. *Cancer Cell*. (2017) 32:169–84.e7. doi: 10.1016/j.ccell.2017.07.005

9. Largillier R, Ferrero JM, Doyen J, Barriere J, Namer M, Mari V, et al. Prognostic factors in 1,038 women with metastatic breast cancer. *Ann Oncol*. (2008) 19:2012–9. doi: 10.1093/annonc/mdn424

10. Hartkopf AD, Brucker SY, Taran F-A, Harbeck N, von Au A, Naume B, et al. Disseminated tumour cells from the bone marrow of early breast cancer patients: Results from an international pooled analysis. *Eur J Cancer*. (2021) 154:128–37. doi: 10.1016/j.ejca.2021.06.028

11. Braun S, Vogl FD, Naume B, Janni W, Osborne MP, Coombes RC, et al. A pooled analysis of bone marrow micrometastasis in breast cancer. *N Engl J Med*. (2005) 353:793–802. doi: 10.1056/NEJMoa050434

12. Yang R, Jia L, Cui J. Mechanism and clinical progression of solid tumors bone marrow metastasis. *Front Pharmacol*. (2024) 15:1390361. doi: 10.3389/fphar.2024.1390361

13. Janssens AM, Offner FC, Van Hove WZ. Bone marrow necrosis. *Cancer: Interdiscip Int J Am Cancer Society*. (2000) 88:1769–80. doi: 10.1002/(SICI)1097-0142(20000415)88:8<1769::AID-CNCR3>3.0.CO;2-H

14. Paydas S, Ergin M, Baslamisli F, Yavuz S, Zorludemir S, Sahin B, et al. Bone marrow necrosis: clinicopathologic analysis of 20 cases and review of the literature. *Am J Hematol*. (2002) 70:300–5. doi: 10.1002/ajh.10114

15. Ivanusic JJ. Molecular mechanisms that contribute to bone marrow pain. *Front Neurol*. (2017) 8:458. doi: 10.3389/fneur.2017.00458

16. Udayasiri RI, Luo T, Gorringe KL, Fox SB. Identifying recurrences and metastasis after ductal carcinoma in *situ* (DCIS) of the breast. *Histopathology*. (2023) 82:106–18. doi: 10.1111/his.14804

17. Bannani S, Rouquette S, Bendavid-Athias C, Tas P, Levêque J. The locoregional recurrence post-mastectomy for ductal carcinoma in situ: Incidence and risk factors. *Breast*. (2015) 24(5):608–12. doi: 10.1016/j.breast.2015.06.005

18. Ekatah GE, Turnbull AK, Arthur LM, Thomas J, Dodds C, Dixon JM. Margin width and local recurrence after breast conserving surgery for ductal carcinoma in situ. *Eur J Surg Oncol*. (2017) 43:2029–35. doi: 10.1016/j.ejso.2017.08.003

19. Chang HJ, Yang UC, Lai MY, Chen CH, Fann YC. High BRCA1 gene expression increases the risk of early distant metastasis in ER(+) breast cancers. *Sci Rep*. (2022) 12:77. doi: 10.1038/s41598-021-03471-w

20. Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat*. (2011) 126:529–37. doi: 10.1007/s10549-010-1132-4

21. Sagara Y, Freedman RA, Vaz-Luis I, Mallory MA, Wong SM, Aydogan F, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: A population-based longitudinal cohort study. *J Clin Oncol*. (2016) 34:1190–6. doi: 10.1200/JCO.2015.65.1869

22. Wehner P, Lagios MD, Silverstein MJ. DCIS treated with excision alone using the National Comprehensive Cancer Network (NCCN) guidelines. *Ann Surg Oncol*. (2013) 20:3175–9. doi: 10.1245/s10434-013-3176-2

23. Bryce CJ. Tamoxifen in early breast cancer. *Lancet*. (1998) 352:403. doi: 10.1016/S0140-6736(05)60500-4

24. Allred DC, Anderson SJ, Paik S, Wickerham DL, Nagtegaal ID, Swain SM, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. *J Clin Oncol*. (2012) 30:1268–73. doi: 10.1200/JCO.2010.34.0141

25. Barron TI, Connolly R, Bennett K, Feely J, Kennedy MJ. Early discontinuation of tamoxifen: a lesson for oncologists. *Cancer*. (2007) 109:832–9. doi: 10.1002/cncr.v109:5

26. Yip RKH, Rimes JS, Capaldo BD, Vaillant F, Mouchemore KA, Pal B, et al. Mammary tumour cells remodel the bone marrow vascular microenvironment to support metastasis. *Nat Commun*. (2021) 12:6920. doi: 10.1038/s41467-021-26556-6

27. Gomis RR, Gawrzak S. Tumor cell dormancy. *Mol Oncol*. (2017) 11:62–78. doi: 10.1016/j.molonc.2016.09.009

28. Ridge SM, Sullivan FJ, Glynn SA. Mesenchymal stem cells: key players in cancer progression. *Mol Cancer*. (2017) 16:31. doi: 10.1186/s12943-017-0597-8

29. Pittet MJ, Michielin O, Migliorini D. Clinical relevance of tumour-associated macrophages. *Nat Rev Clin Oncol*. (2022) 19:402–21. doi: 10.1038/s41571-022-00620-6

30. Baram T, Rubinstein-Achiasaf L, Ben-Yaakov H, Ben-Baruch A. Inflammation-driven breast tumor cell plasticity: stemness/EMT, therapy resistance and dormancy. *Front Oncol*. (2020) 10:614468. doi: 10.3389/fonc.2020.614468

31. Francescangeli F, De Angelis ML, Zeuner A. COVID-19: a potential driver of immune-mediated breast cancer recurrence? *Breast Cancer Res*. (2020) 22:117. doi: 10.1186/s13058-020-01360-0

32. Abobaker A, Raba AA, Alzwi A. Extrapulmonary and atypical clinical presentations of COVID-19. *J Med Virol*. (2020) 92:2458–64. doi: 10.1002/jmv.v92.11

33. Wang Z, Zhang X, Ren H, Zhang L, Chen B. Multiple metastases of the liver and lung after breast-conserving surgery for ductal carcinoma *in situ* without microinvasion of the breast: A case report and literature review. *Front Oncol*. (2022) 12:855899. doi: 10.3389/fonc.2022.855899

34. Yang R, Jia L, Lu G, Lv Z, Cui J. Symptomatic bone marrow metastases in breast cancer: A retrospective cohort study. *Front Oncol*. (2022) 12:1042773. doi: 10.3389/fonc.2022.1042773

35. Chen R, Wu J, Yang J, Wei C, Liang D, Du J, et al. Analysis and clinical characteristics of 23 cases of bone marrow necrosis. *Clin Lymphoma Myeloma Leukemia*. (2021) 21:e356–e64. doi: 10.1016/j.clml.2020.12.001

36. Khan S, Awan SA, Jahangir S, Kamran S, Ahmad IN. Bone marrow metastasis in clear cell renal cell carcinoma: A case study. *Cureus*. (2019) 11:e4181. doi: 10.7759/cureus.4181

37. Rani HS, Hui M, Manasa PL, Uppin SG, Uppin MS, Paul TR, et al. Bone marrow metastasis of solid tumors: A study of 174 cases over 2 decades from a single institution in India. *Indian J Hematol Blood Transfus*. (2022) 38:8–14. doi: 10.1007/s12288-021-01418-9

38. Wool GD, Deucher A. Bone marrow necrosis: ten-year retrospective review of bone marrow biopsy specimens. *Am J Clin Pathol*. (2015) 143:201–13. doi: 10.1309/AJCP0TN1MCMOLMPK

39. Akagi H, Shimada A, Chin K, Domoto H. Successful stabilization of symptomatic bone marrow metastasis two times in a breast cancer patient. *Anticancer Res*. (2021) 41:3139–44. doi: 10.21873/anticanres.15099

40. Suto H, Inui Y, Okamura A. Long-term survival of a patient with gastric cancer with bone marrow metastasis receiving S-1 plus oxaliplatin beyond three years: a case report and literature review. *Front Oncol*. (2024) 14:1449212. doi: 10.3389/fonc.2024.1449212

41. Chan B, Lee JS, Yuan Y. Case report: An exceptional responder of low-dose continuous 5-FU in a patient with *de-novo* stage IV triple-negative breast cancer with liver and bone marrow failure. *Front Oncol*. (2023) 13:1305584. doi: 10.3389/fonc.2023.1305584

42. Wu Q, He L, Luo J, Jin W, Xu Y, Wang C. Long-term remission under Disitamab Vedotin (RC48) in HR-positive/HER2-positive metastatic breast cancer with brain meningeal, and bone marrow involvement: A case report. *Oncol Lett*. (2022) 24:339. doi: 10.3892/ol.2022.13459

43. Huang RZ, Chen N, Hu Y, Hu WM, Wang FH, Chen DL. Case report: PD-1 inhibitor-based treatment strategies in gastric cancer complicated by bone marrow metastasis and disseminated intravascular coagulation: A report of two cases. *Front Oncol*. (2023) 13:1019702. doi: 10.3389/fonc.2023.1019702

44. Andrade de Oliveira K, Sengupta S, Yadav AK, Clarke R. The complex nature of heterogeneity and its roles in breast cancer biology and therapeutic responsiveness. *Front Endocrinol (Lausanne)*. (2023) 14:1083048. doi: 10.3389/fendo.2023.1083048

45. Zardavas D, Irrthum A, Swanton C, Piccart M. Clinical management of breast cancer heterogeneity. *Nat Rev Clin Oncol*. (2015) 12:381–94. doi: 10.1038/nrclinonc.2015.73

46. Niu L, Lv H, Zhang M, Zeng H, Fu S, Cui S, et al. Clinicopathological features and prognosis of breast cancer combined with symptomatic bone marrow metastases: A 10-year, single-center, real-world study of 67 cases. *Cancer Med*. (2023) 12:10672–83. doi: 10.1002/cam4.v12.9

47. Fu X, Tan W, Song Q, Pei H, Li J. BRCA1 and breast cancer: molecular mechanisms and therapeutic strategies. *Front Cell Dev Biol*. (2022) 10:813457. doi: 10.3389/fcell.2022.813457

48. Sun H, Zeng J, Miao Z, Lei KC, Huang C, Hu L, et al. Dissecting the heterogeneity and tumorigenesis of BRCA1 deficient mammary tumors via single cell RNA sequencing. *Theranostics*. (2021) 11:9967–87. doi: 10.7150/thno.63995

Frontiers in Oncology

Advances knowledge of carcinogenesis and tumor progression for better treatment and management

The third most-cited oncology journal, which highlights research in carcinogenesis and tumor progression, bridging the gap between basic research and applications to imrpove diagnosis, therapeutics and management strategies.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact