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Case reports in gastrointestinal cancers 2022

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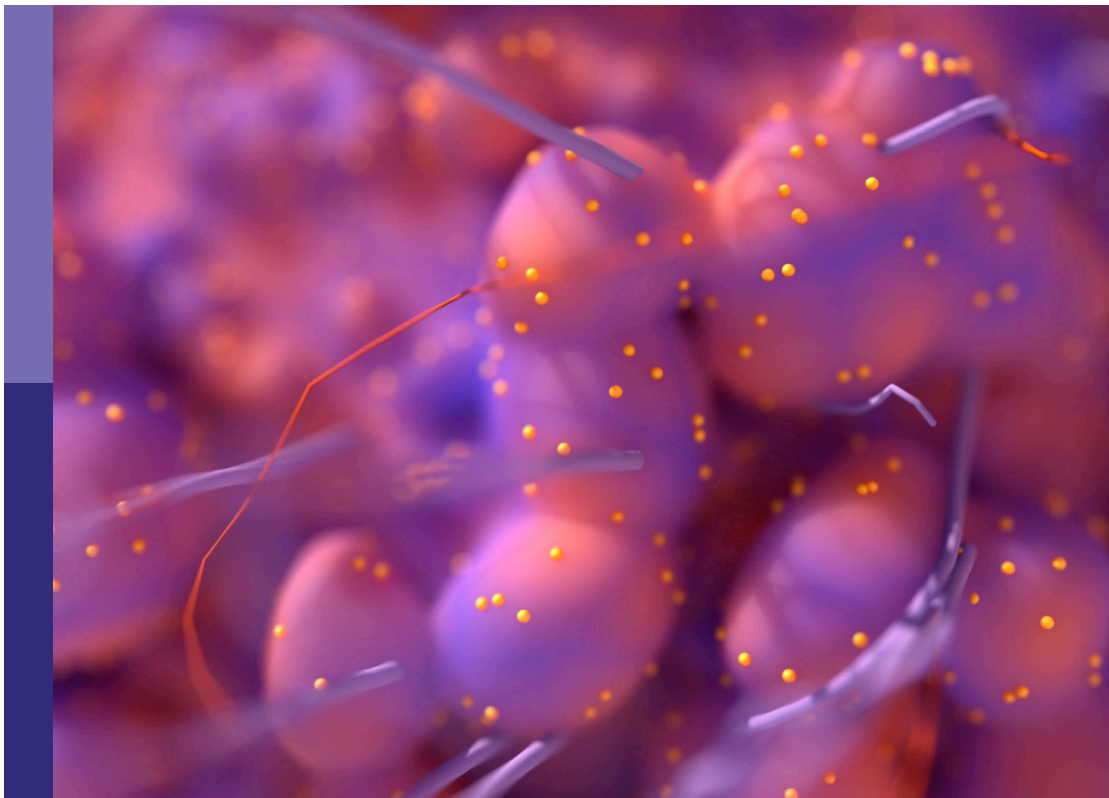

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Case reports in gastrointestinal cancers : 2022

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Editorial: Case reports in gastrointestinal cancers : 2022

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Editorial on the Research Topic
Case reports in gastrointestinal cancers : 2022

With the focus of journals and conferences on clinical trials and large registries, the value of unique individual cases cannot be underestimated. These individual case stories that tell compelling presentations and outcomes can be helpful.

The opportunity to oversee these submissions to the Research Topic within gastrointestinal cancers was of interest to me since it brings to focus a diverse array of case reports. Often, these are what the National Cancer Institute (NCI) calls the "exceptional responders" (1). It brings to light these patients with unique cancers and exceptional clinical outcomes. Figure 1 illustrates how each patient from diverse backgrounds and different cancers with their treatment journey typifies an individual story, and it needs to be viewed as such.

If we look at the spectrum of these individual reports, some are deep, brisk, durable, and sometimes curative outcomes to different kinds of novel therapies. Some are new or off-label usage of drugs for actionable markers in histologies or cancer types or settings for which they still are not approved by regulatory agencies or guidelines. Not all are about exceptional outcomes. Some of these reports highlight unexpected or not previously known side effects of drugs or point to mechanisms and/or ways to overcome and manage these issues. These can help inform the care of future patients. Not only that, from a practical standpoint, publications in peer-reviewed journals can help provide evidence supporting a strategy that biologically makes sense but needs clinical reports of similar stories. Insurance companies and guidelines committees seek more evidence before recommending or endorsing an approach for access to off-label therapies.

Advances are coming in subsets for patients with different types of cancers. We are also seeing agnostic approvals for markers like fusions that are rare events but very actionable. Real-world evidence and publications in this regard can be clinically meaningful. We have also found these helpful as initial proof-of-principle published evidence for investigator-initiated trials that can change practice.

FIGURE 1
Illustration showing how each patient from diverse backgrounds and different cancers with their treatment journey typifies an individual story.

Lastly, from an academic standpoint, these are also opportunities for students, clinical investigators, and multidisciplinary teams to have a place or home to highlight their work. I want to laud that the journal was open to case reports and hope readers, scientists, patients, caregivers, advocacy groups, and physicians who would benefit from this endeavor. Future directions are changes in clinical trial designs proposing n-of-1 trials as an opportunity to help expedite drug development (2).

Author contributions

PK: Writing – original draft, Writing – review & editing.

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Intrahepatic cholangiocarcinoma with gastric metastasis misdiagnosed as primary gastric cancer: A case report and literature review

Qingshun Zhu[1†], Shengyong Zhai[2†], Enkang Ge[1†], Lei Li[1†], Xuguang Jiao[2], Jinqiu Xiong[2], Guangxu Zhu[2], Yuanyuan Xu[2], Jianjun Qu[2*] and Zhengjiang Wang[2*]

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We describe a case of intrahepatic cholangiocarcinoma with gastric metastasis misdiagnosed as primary gastric cancer. In addition, combined with the literature, we summarized the clinical and imaging features of gastric metastasis of intrahepatic cholangiocarcinoma in order to improve the understanding of the preoperative diagnosis. Positron emission tomography/computed tomography (PET/CT) is accurate in evaluating the primary tumor, lymph node metastasis, and distant metastasis of patients. In addition, immunohistochemical staining can determine the primary site of metastatic adenocarcinoma. For patients who can not determine the location of the primary tumor, the rigorous preoperative examination is necessary, it can improve the accuracy of diagnosis and avoid excessive treatment of patients.

KEYWORDS

intrahepatic cholangiocarcinoma, metastasis, gastric, PET/CT, immunohistochemical staining

Introduction

Intrahepatic cholangiocarcinoma mainly metastases through direct invasion, often occurs through intrahepatic metastasis, advanced distant metastasis mainly occurs in the lung, bone, brain, and other organs, but intrahepatic cholangiocarcinoma gastric metastasis is very rare. Here, we report a patient who was misdiagnosed with primary gastric cancer with gastric metastasis of intrahepatic cholangiocarcinoma treated in our hospital. As far as we know, in the English literature that can be retrieved by PubMed, only 4 cases of gastric metastasis of intrahepatic bile duct adenocarcinoma have been

reported. This article combines a case of intrahepatic bile duct adenocarcinoma with gastric metastasis and reviews the related literature, hoping to attract more attention to this kind of disease in clinical practice.

Case presentation

A 57-year-old male patient presented to the local hospital in July 2017 for "epigastric pain and discomfort for one month". Gastroscopy showed a large ulcer in the gastric antrum, and biopsy pathology showed poorly differentiated carcinoma, tending to poorly differentiated adenocarcinoma. The patient was admitted to our hospital for surgical treatment. Physical examination showed that there was only mild tenderness in the upper abdomen without rebound pain, no palpable abdominal mass, no obvious jaundice in the skin and sclera, and no obvious enlargement of superficial lymph nodes. Serological examination showed that total bilirubin (TBILI) decreased (1.8umol/L, normal range 7.4-24.1umol/L), hemoglobin (HGB) decreased (93g/L, normal range 120-160g/L), carbohydrate antigen (CA) 724 increased slightly (7.66U/ml, normal range 0-6.9U/ml), carcinoembryonic antigen (CEA), CA19-9, CA125, alpha-fetoprotein (AFP) were all in the normal range. Thorax and abdomen plain scan and contrast-enhanced CT (Figures 1A–F) showed gastric cancer thickening in the gastric antrum, considering the tumor, and the tumor was not clearly demarcated from the left lobe of the liver; the size and shape of the liver were normal, the edge was smooth, and no abnormal density and enhancement lesions were found in the parenchyma. Small lymph nodes could be seen in the hepatogastric space, but no obvious enlarged lymph nodes were found in the retroperitoneum. We initially diagnosed it as gastric antrum malignant tumor. After multidisciplinary tumor consultation, we decided to carry out surgical treatment.

After excluding surgical taboos, the patient underwent surgery in August 2017. During the operation, the tumor was located in the gastric antrum, about 5 × 4cm in size, infiltrated into the serosa, the anterior wall adhered closely to the left lateral lobe of the liver, and the posterior wall adhered closely to the transverse colon. Enlarged lymph nodes could be seen around the tumor, but there were no obvious metastatic nodules in the liver, peritoneum, and transverse colon. The family members and trustees of the patients were informed of the intraoperative findings, the details of possible adverse prognoses, and the advantages and disadvantages of different surgical methods. After obtaining their consent and signing the informed consent form, we performed radical distal gastrectomy (Billroth II gastrointestinal reconstruction) and partial left lateral lobectomy of the liver (Figure 1G). The operation time was about 200min, the blood loss was about 200ml, no blood transfusion was performed. The postoperative pathology showed that the tumor was poorly differentiated adenocarcinoma. The tumor was closely related to the liver tissue, invading the entire layer of the gastric wall to the mucosa from outside to inside and accompanied by ulcer formation. Tumor cells could be seen in the lymphatic vessel, and the nerve was not invaded. 27 lymph nodes were dissected. None of these lymph nodes metastasized. Immunohistochemical staining showed that the tumor tissue expressed broad-spectrum cytokeratin (CKpan), CK-7, and CK-19, but not CK-20, S-100, CD-10, Heppar-1, CD-56, synaptophysin (Syn), chromogranin A (CgA), and Ki67 proliferative index was approximately 70% (Figures 2). After communicating with pathologists and considering the immunohistochemical results, we considered gastric metastasis from intrahepatic biliary adenocarcinoma.

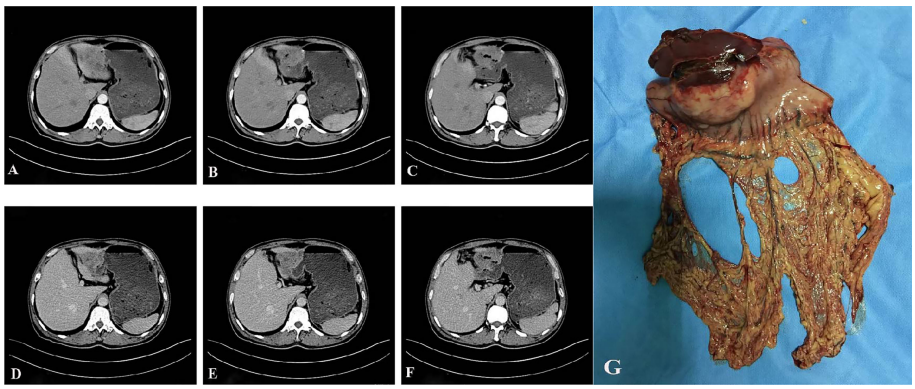

FIGURE 1
Preoperative auxiliary examination and postoperative specimen. **(A–F)**, abdominal enhanced CT showed gastric cancer thickening in the gastric antrum, and the tumor was not clearly demarcated from the left lobe of the liver; the size and shape of the liver were normal, the edge was smooth, and no abnormal density and enhancement foci were found in the parenchyma **(A–C)** shows the arterial phase; **(D–F)** shows portal venous phase). **(G)**, the distal stomach and part of the left lateral lobe of the liver after the operation.

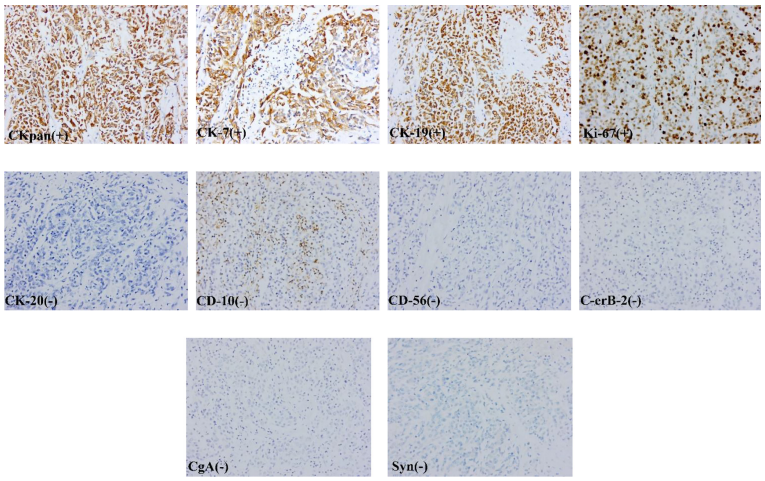

FIGURE 2
The tumor tissue expressed broad-spectrum cytokeratin (CKpan), CK-7, and CK-19, but not CK-20, C-erB-2, CD-10, CD-56, synaptophysin (Syn), chromogranin A (CgA).

The patient recovered smoothly without obvious postoperative complications and was discharged 11 days after the operation. We performed 8 cycles of chemotherapy with the gemcitabine + capecitabine regimen. The first chemotherapy begins one month after the operation, followed by the next cycle of chemotherapy at an interval of 21 days. The patients were reexamined every 3 months after the operation for 2 years and every 6 months after the operation for 3-5 years. No tumor recurrence or metastasis was found 5 years after the operation, and the patient is still alive.

Discussion

This patient was initially diagnosed as a malignant tumor of the gastric antrum, but according to the results of immunohistochemical staining, the diagnosis was modified to gastric metastasis of intrahepatic bile duct adenocarcinoma. Cholangiocarcinoma is a malignant tumor derived from bile duct epithelial cells, which can be divided into intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, and distal cholangiocarcinoma according to the location of the tumor (1). Intrahepatic cholangiocarcinoma is a malignant tumor originating from bile duct epithelial cells above the secondary bile duct. it is the second largest primary liver malignant tumor after hepatocellular carcinoma, accounting for 5% and 30% of primary liver cancer (2, 3). The early onset of intrahepatic cholangiocarcinoma often lacks typical clinical symptoms, most patients are often in the advanced stage and often accompanied by lymph node and surrounding organ metastasis. According to related literature reports, intrahepatic cholangiocarcinoma mainly metastases through direct invasion, often intrahepatic metastasis and advanced distant metastasis mainly occurs in the lung, bone, brain, breast, colon, skin, and blood system (4–6). Metastasis from intrahepatic cholangiocarcinoma to the stomach is very rare in clinical practice. As far as we know, in the English literature that can be retrieved by PubMed, only four cases of gastric metastasis of intrahepatic bile duct adenocarcinoma have been reported (Table 1). In this paper, we combined a patient with gastric metastasis of

TABLE 1 Summary of clinical data of gastric metastasis of intrahepatic cholangiocarcinoma.

Case	Sex	Age (years)	Clinical manifestation	Primary pathology	Treatment	Survival (months)	Reference
1	Female	67	Epigastric pain	Poorly	Resection	NA	Kim EM, et al. (7)
2	Male	58	Dysphagia	Poorly	Resection	Died (5 months)	Wang C, et al. (8)
3	Female	77	Epigastric pain	Poorly	Resection	Died (5 months)	Matsuo S, et al. (9)
4	Male	80	Jaundice	Poorly	Resection	Alive (12 months)	Imamura N, et al. (10)
5	Male	57	Epigastric pain	Poorly	Resection	Alive (5 years)	Present case

Follow-up since the operation; poorly, poorly differentiated adenocarcinoma; NA, no data available.

intrahepaticcholangiocarcinoma, and reviewed the related literature, hoping to attract more attention to this kind of disease in the clinic.

Ultrasonography (US) is a simple and widely used non-invasive method for the diagnosis of cholangiocarcinoma. Cholangiocarcinoma often shows hypoechoic or moderate echo mass, which can be distinguished from bile duct stones. The US can also judge the blood flow signal in the tumor and whether the tumor invades blood vessels. Endoscopic ultrasound has high resolution and is not disturbed by gas, so it can directly observe the lesions of the duodenal papilla and show the structure and focus of the bile duct wall more clearly. In addition, the help of ultrasound can also locate the tumor, combined with fine needle aspiration biopsy to determine the nature and source of the tumor. CT and magnetic resonance imaging (MRI) is the preferred imaging methods for the diagnosis of intrahepatic cholangiocarcinoma. On contrast-enhanced CT, intrahepatic cholangiocarcinoma can be distinguished from hepatocellular carcinoma. On abdominal contrast-enhanced CT, irregular masses around intrahepatic cholangiocarcinoma can be seen, accompanied by hepatic lobe atrophy and local intrahepatic bile duct dilatation. Because intrahepatic cholangiocarcinoma receives blood supply from the portal vein, and cholangiocarcinoma is mostly sclerotic, with more fibrous tissue, it shows venous phase or delayed phase enhancement on CT, while hepatocellular carcinoma gets blood supply from the hepatic artery and shows arterial phase enhancement on CT (11). Cholangiocarcinoma was characterized by low signal intensity on T1-weighted and high signal intensity on T2-weighted images. The dynamic contrast-enhanced scan showed enhancement around the delayed phase. MRI is of high value in preoperative staging, resectable evaluation, selection of surgical methods, and evaluation of prognosis of cholangiocarcinoma. Li reported that the combination of enhanced CT and MRI in the diagnosis of cholangiocarcinoma has high sensitivity and specificity, which can provide an imaging basis for clinical diagnosis and treatment (12). In addition, studies have reported the dense accumulation of the nucleotide tracer 18-fluorodeoxyglucose (^{18}F-FDG) in cholangiocarcinoma (13). PET scan combined with FDG accumulation can show cholangiocarcinoma as small as 1 cm of the bile duct, and it is considered that ^{18}F-FDG-PET and PET/CT are accurate in evaluating primary tumor, lymph node metastasis, and distant metastasis in patients with intrahepatic cholangiocarcinoma (14, 15).

Tumor markers are rarely expressed in normal tissues, but increased in tumor tissues and blood of tumor patients, which can reflect the occurrence and development of the tumor and the situation of recurrence and metastasis. CA19-9 and CEA are elevated in 40% and 85% of patients with cholangiocarcinoma, respectively, and these markers may indicate postoperative recurrence and metastasis (16). When CA19-9 and CEA were 176.3 IU/mL and 9.6 ng/mL respectively, CA19-9 and CEA could predict the prognosis of Overall Survival (OS) (17). However, there is no recommended reference value for tumor diagnosis in the world. Although the development of science and technology is getting faster and faster, it is still difficult to diagnose cholangiocarcinoma by hematology or imaging examination. cytological and pathological examination is the gold standard for the diagnosis of cholangiocarcinoma at present. however, it is difficult to distinguish the histological manifestations of intrahepatic bile duct adenocarcinoma from metastatic non-hepatic primary tumors. Based on cytology, combined with fluorescence *in situ* hybridization (FISH) cell analysis, the specificity of diagnosis was improved. The FISH analysis uses fluorescence-labeled DNA probes to detect specific chromosomal abnormalities. A large number of special chromosome abnormalities detected by FISH can complement the diagnosis of cholangiocarcinoma (18). However, in patients affected by primary sclerosing cholangitis and biliary stricture, biopsy samples are usually insufficient for molecular spectrum analysis. in addition, tissue sampling reports have high specificity but low sensitivity in the diagnosis of malignant biliary strictures. Finally, the high embryogenic property of BTC limits the accuracy of cytological and pathological methods. In this case, fluid biopsy has attracted more and more attention. Studies have shown that fluid biopsy has great potential in the early diagnosis of cancer, the identification of driver changes, the monitoring of treatment response and the detection of drug resistance mechanisms (19, 20). Therefore, it is necessary to do more research in the field of biomarkers and further identify the specific tumor markers of cholangiocarcinoma.

Compared with other organs, the stomach is a rare site of tumor metastasis. Secondary gastrointestinal tumors are defined as primary tumors that originate outside the gastrointestinal tract or are not continuous with primary tumors in other parts of the gastrointestinal tract. Through literature search, we summarized the rare primary sites of secondary gastric tumors (Table 2). We found that the survival time of patients with gastric secondary malignant tumor is often very short, unlike other cases, this patient still did not find tumor recurrence and metastasis 5 years after the operation. We think this report is special and worthy of study.

Intrahepatic cholangiocarcinoma often invades the adjacent bile duct and liver parenchyma through direct infiltration. Distant metastasis often occurs in the lung, bone, brain, and other organs, but intrahepatic cholangiocarcinoma gastric metastasis is very rare. This raises a question that needs to be considered: how intrahepatic cholangiocarcinoma metastases to the stomach. The answer to the question of direct invasion, lymph node metastasis, hematogenous metastasis, or multiple pathways remains to be discussed. We believe that the possibility of direct invasion is greater, because the primary tumor is located in the left lateral lobe of the liver, and the rear is in direct contact with the anterior wall of the stomach. When the tumor penetrates the visceral peritoneum, it is easy to cause metastasis of adjacent organs outside the liver. Secondly, in our

TABLE 2 Rare primary sites of secondary gastric tumors.

Case	Sex	Age (years)	Primary site	Histological type	Treatment	Outcome	IHC positive marker	Reference
1	Female	73	Breast	Invasive lobular carcinoma	Resection	Bone metastases (4 months)	Mammaglobin, ER	Gurzu S, et al. (21)
2	Female	67	Breast	Invasive ductal carcinoma	Resection	Died (5 months)	CK7, CDX2, E-cadherin, SLUG, CD44	Gurzu S, et al. (21)
3	Female	82	Skin	Malignant melanoma	Radiotherapy	Died (3 months)	Melan A, HMB45, SOX-10, S100	Yoshimoto T, et al. (22)
4	Male	55	Lung	Non-small cell lung cancer	Resection	Died (3 months)	NA	Shih-Chun C, et al. (23)
5	Female	51	Ovarian	Ovarian carcinoma	Resection	NA	PR, ER, (CK7), Wilms' tumor-1	Liu Q, et al. (24)
6	Female	70	Renal	Clear cell renal cell carcinoma	Resection	No recurrence (4 months)	CD10, CAIX	Koterazawa S, et al (25),
7	Male	71	Adrenal gland	Adrenocortical Carcinoma	Resection	Died (12 months)	Vimentin, Inhibin, Synaptophysin, NSE	Kovecsi A, et al. (26)

Follow up since the treatment; ER, estrogen receptor; PR, progesterone receptor; CK7, cytokeratin 7; NSE, neuron-specific enolase; NA, no data available.

case, cancer cells were found in the lymphatic vessels of the patient, which may not rule out the possibility of lymph node metastasis in addition to direct invasion.

At present, for the treatment of intrahepatic bile duct adenocarcinoma, radical surgery is still the only possible cure. The 7th edition of the American Cancer Federation (AJCC) staging manual recommends routine lymph node dissection for intrahepatic cholangiocarcinoma because it is helpful for accurate staging and prognosis evaluation (2, 27, 28). However, for most patients with cholangiocarcinoma, distant metastasis occurs at the time of the initial symptoms. For patients with advanced or unresectable diseases, local and systemic chemotherapy is the main treatment choice. their goal is to control local tumor growth, alleviate symptoms, improve and maintain quality of life. Among the local treatment methods, the best evidence and most promising results are transarterial radiation embolization (TARE), hepatic arterial infusion (HAI), transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). Among them, RFA is considered to be a good way to control the progression of local tumors, and the postoperative complications are low (29). In addition, comprehensive genome sequencing has determined the genetic pattern of each cholangiocarcinoma subtype. Therefore, promising molecular targets in precision medicine have been identified and are being evaluated in clinical trials, in which fibroblast growth factor receptor (FGFR) inhibitors have become a research hotspot in recent years, and futibatinib (TAS-120) has the potential to become a new treatment option for intrahepatic cholangiocarcinoma with abnormal FGFR2 (30, 31). With the use of drugs for PD-1/PD-L1 and CTLA-4, the treatment of immune checkpoint inhibitors (ICIS) has brought the treatment of cancer into a new field. Studies have shown that adjuvant therapy based on ICIS and chemotherapy has a certain guiding significance for the treatment of BTC (32, 33). At present, it is also possible to establish a preclinical model of CCA to clarify the causes and molecular mechanisms of carcinogenesis, tumor progression and metastasis; to find prognostic biomarkers and drug targets, and to test the efficacy of drugs and develop more effective treatments will also play a vital role in the development of cholangiocarcinoma treatment (34).

In our patients, we chose radical resection and postoperative adjuvant chemotherapy. At present, this treatment is beneficial to patients. However, surgical decisions should take into account the level of progress of the primary disease, and PET/CT is a very useful diagnostic tool for metastatic diseases (35). And immunohistochemical markers can determine the primary site of metastatic adenocarcinoma (36). Therefore, it is necessary to perform immunohistochemical staining on the biopsy tissue. If the location of the primary tumor cannot be determined, the removal of metastatic tumor tissue can help locate the primary tumor.

Conclusion

Gastric metastasis of intrahepatic cholangiocarcinoma is clinically rare, and we suspect that it is related to direct invasion, but the characteristic of this patient is that no obvious tumor in the liver was found by preoperative auxiliary examination. Therefore, a detailed preoperative examination is very necessary to improve the accuracy of diagnosis. PET/CT is accurate in evaluating patients' primary tumor, lymph node metastasis, and distant metastasis. in addition, immunohistochemical markers can determine the

primary site of metastatic adenocarcinoma. At present, radical resection and postoperative adjuvant chemotherapy may be beneficial to patients. In addition, targeted therapy and immunotherapy for intrahepatic cholangiocarcinoma have also become the focus of research. It is believed that the most beneficial treatment for patients with gastric metastasis of intrahepatic cholangiocarcinoma can be determined by further research in the future.

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

JQ and ZW: guarantees the integrity of the entire study and edited the manuscript. QZ, SZ, EG, and LL: prepared and edited the manuscript. XJ, JX, GZ, and YX: performed the literature research, data analysis, and text proofreading. All authors contributed to the article and approved the submitted version.

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Gallbladder cancer during pregnancy treated with surgery and adjuvant gemcitabine: A case report and review of the literature

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Background: Gallbladder cancer (GBC) represents the most common biliary tract cancer. Prognosis remains poor with 5-year overall survival rates less than 5% in advanced stages. GBCs are diagnosed more frequently in women, supposedly due to endocrine factors.

Case: A 35-year-old woman, diagnosed with a non-metastatic GBC in the 22nd week of gestation, underwent a complete surgical resection 5 weeks later. Adjuvant gemcitabine was administered without complications, temporarily discontinued in the 32nd week to allow childbirth. The patient was disease-free for more than 3 years with ongoing remission at the last visit in July 2022. During the follow-up period, the child had no developmental, cognitive, or other health issues.

Conclusion: Malignant tumors occur in about 0.1% of pregnant women, many are treated with chemotherapy. In oncology, the need to deliver optimal treatment in these patients represents a major concern. Both surgery and adjuvant chemotherapy of locally advanced GBC can be performed safely, with certain considerations, in the second trimester of pregnancy.

KEYWORDS

gallbladder cancer, chemotherapy, pregnancy, gemcitabin, biliary tract cancer

Introduction

Gallbladder cancer (GBC) is considered a highly fatal hepatobiliary malignancy due to its poor 5- year survival rate of 0-12% and median overall survival (OS) of less than 6 months in untreated patients (1). Worldwide, there is prominent geographic variability in GBC incidence (2), which can be illustrated by its distribution on the American continent, with high rates seen in South American countries (for example incidence ≥1.6 per 100,000 individuals in Chile) strongly contrasting with the US 0.56-0.82 low-incidence. While socio-economic factors explain these disparities (i.e. delayed access to cholecystectomy for gallstones (3)) the strong gender difference in the distribution of the disease does not. Even in low-incidence countries, women are affected 2-3 times more frequently than men (2). The association of GBC with the female gender has been hypothesized to be influenced by estrogens leading to an increase in the supersaturation of bile cholesterol, being therefore potentially involved in the pathogenesis of GBC mediated by gallstones (4). This over-representation of female gender, unfortunately, increases the risk for diagnoses during pregnancy. In the absence of metastasis, surgery and adjuvant chemotherapy are the cornerstones of treatment, but exposure during pregnancy to molecules described as deleterious to the fetus (5, 6) may lead to a decision to terminate the pregnancy or forego treatment leading to dramatic consequences (7). In order to provide data for this critical decision making, the case presented here is a pregnant patient diagnosed with GBC and treated by surgery and adjuvant gemcitabine chemotherapy during pregnancy with a follow-up of more than 3 years.

Case description

In February 2019, a 35-year-old African woman in the 22nd week of gestation presented with acute biliary pancreatitis due to gallbladder polyps. Two weeks later, the patient underwent a cholecystectomy by laparoscopy without maternal nor fetal complications. The histopathological examination revealed an incidental gallbladder carcinoma classified as pT2a pNx L0 V0 G2 R0 according to the American Joint Committee on Cancer staging system (8th edition). Additional examinations were therefore carried out, including a non-contrast magnetic resonance imaging (MRI) two weeks after the first surgery (Figure 1). Serum tumor markers including carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) were within normal limits (< 2 kU/L and 1.8 µg/L, respectively) and the expression of MMR proteins (MLH1, MSH2, MSH2 and PMS2) and HER-2 by immunohistochemistry in tumor tissue were normal. After a discussion with the patient, particular care was dedicated to maintain the pregnancy that the patient wished to preserve. Following multidisciplinary tumor board discussion, the patient underwent an open liver bi-segmentectomy of segments IVb and V showing two retro-portal lymph node metastases of GBC with one of them presenting capsular effraction. The tumor was classified pT2a pN1(2/8), grade 2, without lymphovascular invasion, stage IIIB. No postoperative complications were observed. Fetal growth, liquor volume, and end-diastolic flow on ultrasound at 26 weeks were normal.

After an explanation about the benefit-risk balance of adding chemotherapy treatment, the patient began adjuvant gemcitabin and the pregnancy was carried on until 32 weeks of gestation. Because of the risk of preterm delivery, the patient received corticosteroids for fetal lung maturation before hepatic surgery.

Between the 28th and 32nd week of pregnancy, the patient was treated with one cycle of gemcitabine chemotherapy (1000 mg/m2 on days 1 and 8 of a 21-day cycle) with no grade 2 or more adverse events. Chemotherapy was administered on an inpatient basis to facilitate fetal monitoring, and no adverse fetal effects were observed. The treatment was interrupted 2 weeks prior to the planned birth induction at 32 weeks. Because of breech position at admission, the patient underwent a cesarean section. The newborn girl had a birth weight of 1,570 g, a length of 41 cm, and a head circumference of 28.5 cm (all values in the normal range for gestational age). The Apgar score was 7/9/9 at 1, 5 and 10 minutes respectively.The placenta showed no signs of metastatic spread. A complete neonatal evaluation revealed no gross malformations, neurological or cardio-circulatory abnormalities, infection, or bone marrow suppression. Peripheral blood count was as follows: leukocytes 16.5x109/L, hemoglobin 17.3 g/dL, and platelets 417,000/µL). Supplemental enteral nutrition by nasogastric tube was required for the first 6 days. The infant developed indirect hyperbilirubinemia with jaundice and hemoglobin level of 13.2 g/dl on day 14, requiring iron infusion.

The infant was discharged from the hospital in very good general condition one month after the birth. Her weight was 2,380 g (below the third percentile), height 45 cm (below the third percentile), and head circumference 31 cm (below the third percentile). Pediatric follow-up at 8 and 18 months of corrected age confirmed normal physical and neurological development. At the latter visit, the infant's weight was 13 kg (above the 97th percentile), her height 87 cm (above the 97th percentile), and head circumference 48.5 cm (between the 75th and 90th percentile).

At 6 weeks postpartum, chemotherapy with gemcitabine was resumed using the same dosing schedule as during the pregnancy, in combination with capecitabine at 1500 mg orally twice a day for the first two weeks of every 3-week cycle and a total of 6 months were administered.

After finishing chemotherapy, the first follow-up imaging by abdominal MRI and thoraco- abdominal computed tomography (CT) was performed in October 2019, revealing no signs of local recurrence or distant metastases (Figures 1C–F). Further oncologic surveillance included clinical, laboratory (CEA, CA 19-9) and radiological monitoring. In this respect, the patient had a lung CT and abdominal MRI every three months in the first two years after the intervention, then the intervals were increased

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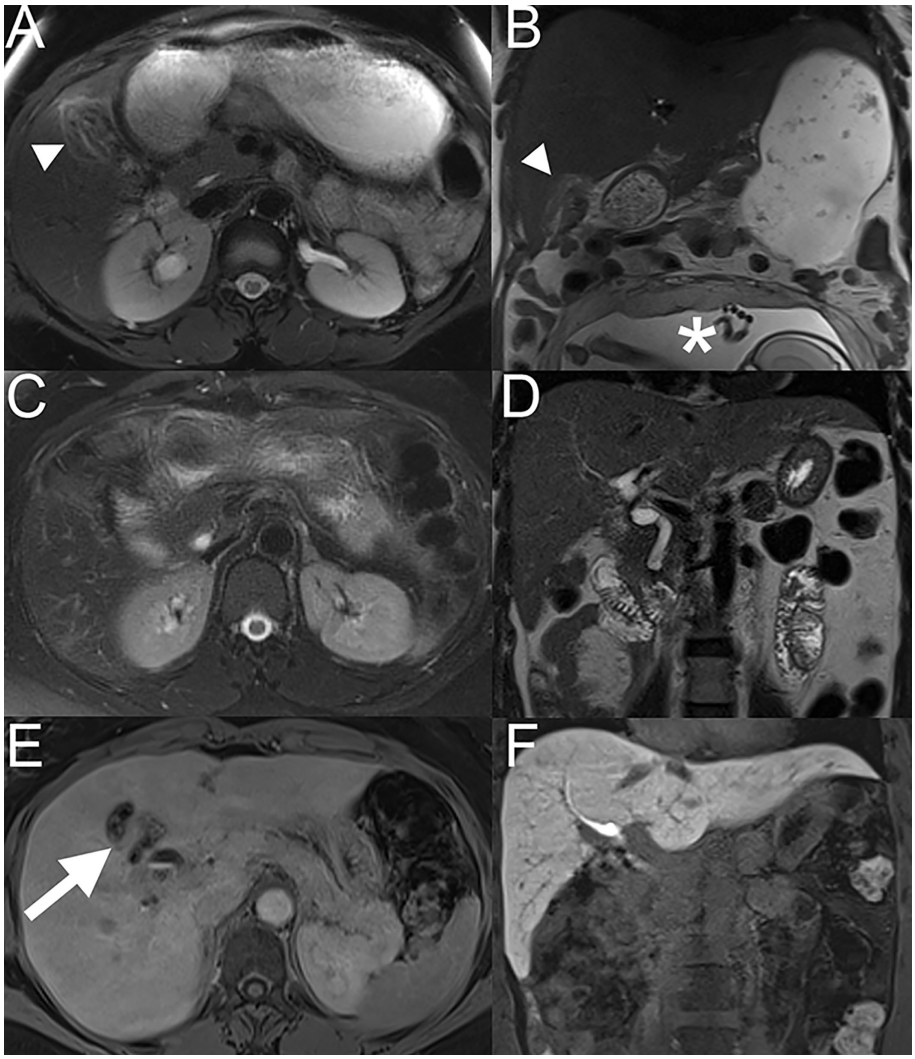

FIGURE 1
Liver MRI done 2 weeks after cholecystectomy. On axial fat-suppressed T2-weighted TSE **(A)** and coronal T2-weighted **(B)** images, mild hyperintense signal is seen at the edge of the surgical resection in segment IV and V. (*) Pregnant uterus at 26 weeks of amenorrhea. Liver MRI at 7 months follow-up, on axial fat-suppressed T2-weighted TSE **(C)** and coronal T2- weighted **(D)** images, the signal hyperintensity previously seen has disappeared. On the hepatobiliary phase (axial **(E)** and coronal **(F)** view), acquired at 20 minutes after injection of gadoxetic acid (Primovist), no metastases were seen. Some metal artefacts related to surgical clips post-cholecystectomy can been seen (arrow; **E**).

to every six months. This patient has been disease-free for more than 3 years with ongoing remission at the last visit in February 2022. Figure 2 summarizes the disease course in our patient.

Discussion

There is an increasing number of cancers discovered during pregnancies, as shown by several contemporary epidemiological studies (8). Concerning surgery, it can be safely carried out at any time during pregnancy. However, a higher risk of miscarriage has been reported in the first trimester. Also, the risk of small for gestational age fetuses has been reported when a pregnant patient undergoes a long abdominal procedure during pregnancy. Moreover, major abdominal and pelvic surgery is associated with increased morbidity and pregnancy complications, like premature delivery, throughout the whole gestation period. Therefore, watchful waiting policy can also be considered. Nevertheless, when the patient is at high risk for torsion (usually at gestational weeks 8-16), rupture infarction, or acute abdomen, surgical management is indicated (9).

If a choice is possible, the second trimester is preferable for surgery. Nevertheless, surgery should never be postponed if deemed to be crucial for patient care management (10).

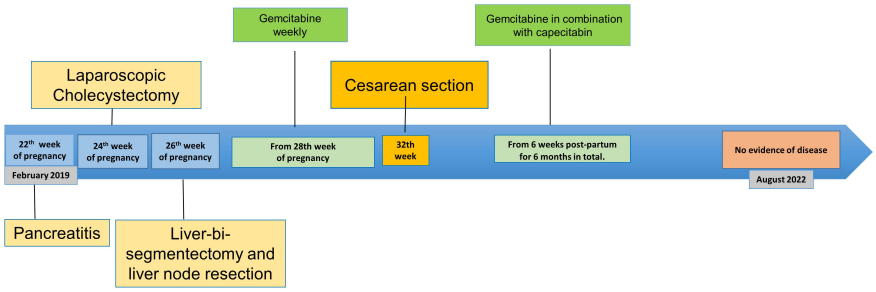

FIGURE 2
Timeline of disease course.

Given the propensity of GBC to spread to the regional lymph nodes and peritoneal surface, staging laparoscopy can help avoid unnecessary laparotomy in 38-62% of patients. Based on the aggressivity of the disease, staging laparoscopy is recommended in all cases of suspected or proven GBC. As a result, only 25% of patients will undergo potentially curative surgery and only 16% will survive more than 5 years (10). After curative surgery for biliary tract cancers, the ideal adjuvant chemotherapy has not been established but most centers used adjuvant capecitabine for 6 months based on the BILCAP phase III study. In this trial, although no significant difference in OS was observed, in an unadjusted intent-to-treat (ITT) analysis, a per-protocol analysis revealed significant results (median, 53 months in the chemotherapy arm *vs.* 36 months in the observation group; p=0.028). Furthermore, a pre-specified intent-to-treat analysis adjusted for nodal status, disease grade and sex also showed significant difference between the two groups. In the present case, due to the aggressivity of the disease, combination of gemcitabine/capecitabine was chosen.

Since capecitabine cross the placenta and have been shown to be teratogenic and embryolethal, it was decided to start with gemcitabine during pregnancy and add capecitabine after delivery. Furthermore, due to low-risk emetic risk induced by gemcitabine, no prophylactic anti-emetic therapy was prescribed in this case.

Providing the maximum benefit to the mother through early delivery and aggressive chemotherapy against aggressive form of cancers has clear drawbacks related to the induction of premature delivery and possible side effects of chemotherapy on the fetus, such as growth restriction, and anemia secondary to bone marrow suppression. Currently, it is widely accepted that chemotherapy can be safely administered during the second and third trimesters, always with close monitoring of the mother and fetus. The blood placenta barrier limits fetal exposure to cytotoxic drugs with a different transplacental capacity for various drugs (11). Furthermore, placental dissemination, as a rare manifestation of cancer in pregnancy, comprises in the first place a direct infiltration of placental tissue and less probably the presence of malignant cells in the intervillous space corresponding to invasion in the maternal vascular compartment. Owing to the anatomical and immune barrier of the placenta, fetal metastases are even less common (12).

To our knowledge, there are no studies describing whether the human placenta is an effective barrier to gemcitabine but only case reports (Table 1). The treatment was aligned with the assessment done by Briggs (18), considering: (a) gemcitabine molecular weight and negligible plasma protein binding (b) animal data (6) (c) trimester of pregnancy (avoiding first trimester which represents organogenesis) (d) very short plasma elimination half-life reducing the amount reaching the embryo–fetus allowing gemcitabine use from the second trimester of pregnancy.

Recently, a descriptive cohort study of 1,170 pregnant cancer patients (39% with breast cancer) aimed at analyzing changes over time in cancer, obstetric, and neonatal outcomes. The authors observed an increase in the use of chemotherapy during pregnancy, in parallel with an increase in live births, and a reduction in iatrogenic preterm deliveries, encouraging the management of these patients in high obstetric care units (19). Before starting any oncological treatment, a fetal examination with ultrasound should be performed after 8th week to exclude pre-existing abnormalities, because exposure to cytotoxic agents in the first trimester can interfere with fetal organogenesis, resulting in an increased risk of miscarriages and congenital malformations. If there is an urgent need to start chemotherapy during pregnancy, the option of preterm labor to avoid any delay in treatment initiation should be carefully discussed with the patient.

The present case represents the first description in the literature of gemcitabine administration in a pregnant woman with biliary tract cancer, successfully treated with surgery and adjuvant chemotherapy during gestation period, leading to a disease-free interval of more than 3 years. Table 1 summarize other case reports describing the results of gemcitabine-based chemotherapy during pregnancy. In addition, no acute or late side effects of chemotherapy were observed in the infant during 3-year follow-up.

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TABLE 1 Clinical experience with gemcitabine-based chemotherapy in pregnancy.

First author, year	Kim, 2008 (13)	Gurumurthy, 2009 (14)	Lubner, 2011 (15)	Wiesweg, 2014 (16)	Steinberg, 2020 (17)
Diagnosis	metastatic pulmonary adenocarcinoma + brain met	non-small-cell lung cancer	pancreatic adenocarcinoma	Metastatic cholangiocellular adenocarcinoma	Hodgkin lymphoma
Patient age [years]	35	38	37	38	29
Gestational age at treatment initiation [weeks]	9-22	25	24-31	18	Second trimester
Initial disease stage	stage IV with brain metastases	stage IV with bilateral lung metastases	Stage III		Relapse
Initial treatment intent	palliative	palliative	curative	palliative	Salvage therapy
Chemotherapy Doses et durées d'exposition	1st line: docetaxel and cisplatin (days 1 and 8) every 3 weeks) At 19 weeks, therapy was changed to gemcitabine and cisplatin (days 1 and 8) at 3- week intervals for two cycles 3rd line: gefitinib	gemcitabine (1000 mg/m2 on day 1 and 8) and carboplatin AUC 5 (day 1)	gemcitabine (1000 mg/m2) beginning her 24th week of pregnancy, until her 31st week.	Chimio semaine 18-29 cisplatin 50 mg/m2 on day 1 and gemcitabine 1,000 mg/m2 on days 1 and 8 of a 21-day cycle	gemcitabine, navelbine, doxorubicin liposome (3 cycles)
Response to gemcitabine-based treatment	progression	progression after 1 cycle		partial remission of the hepatic lesion. no signs of recurrent disease in the region of previous surgery. However, a slight progression of a previously very small pelvic metastasis was reported. Confirming our clinical impression during the previous weeks, bone metastases of the frontotemporal cranium, ribs, and ilium were revealed by bone scintigraphy and cranial CT. Abdominal MRI confirmed progressive disease in the liver and bone metastases with large soft tissue components.	progression
Outcome of the infant	About 2 months after the last dose, her pregnancy was diagnosed. A cesarean section was performed at 33 weeks to deliver a normal, 1490-g female infant (normal karyotype 46, XX) with Apgar scores of 8, 9, and 10 at 1, 5, and 10 minutes, respectively, and normal blood counts. An extensive examination of the infant failed to find any abnormalities. She was developing normally at 10 months of age	elective cesarean section at 28 4/7 weeks to a baby girl with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. The infant had multiple complications secondary to prematurity. The authors speculated that two unusual features, chronic lung disease and excessive secretions from her lungs, might have been related to either the chemotherapy or an effect of the malignancy itself. At 8 months of age, the infant had been weaned off of oxygen therapy and her neurodevelopment was age-appropriate	At 35 weeks, labor was induced to deliver a normal male infant with blood counts within normal limits. He was developing normally with a functionally intact immune system at nearly 2 years of age. The mother died 12 months after diagnosis (relapse was diagnosed 2 weeks after delivery, and 6 weeks off chemotherapy)	35 + 0, delivering a healthy female infant, APGAR 9/10/10, birth weight 1,840 g (20th percentile), length 41 cm (20th percentile), and head circumference 30 cm (30th percentile). The baby initially showed labored breathing with retractions but did not require supplemental oxygen, breathing spontaneously at all times. Examination revealed no evidence of gross malformations, neurological or cardiocirculatory abnormalities, and infection or bone marrow suppression (leukocytes 6.85/nL, hemoglobin 14.5 g/dL, and platelets 320/nL). Supplemental enteral feeding *via* nasogastric tube was necessary for 10 days. The baby was discharged from the hospital in very good general condition 1 month after her birth. Weight was 2,340 g (< third percentile), height 42 cm (< third percentile), and head circumference 31 cm (< third percentile).	healthy boy weighing 2.93 kg

(Continued)

TABLE 1 Continued

First author, year	Kim, 2008 (13)	Gurumurthy, 2009 (14)	Lubner, 2011 (15)	Wiesweg, 2014 (16)	Steinberg, 2020 (17)
Delivery time [weeks+days]	33	28+4		35	Third trimester
Follow-up patient	available during the first 10 months	the patient died 2 weeks postpartum		Although her head circumference was small, there were no neurological and behavioral defects and development was normal during 14 months of follow-up. A pediatric follow-up examination of the infant after a corrected age of 5 months confirmed normal physical and neurological development. In a second examination at a corrected age 12 months, development was found again appropriate for her age, with length at 1 cm below 3rd percentile and weight at the 10th percentile. The neuropediatric examination showed no abnormal findings. Chemotherapy with cisplatin and gemcitabine was resumed, palliative local radiotherapy administered to the sacrum, ilium, and femoral neck at a total dose of 20 Gy, and bisphosphonate therapy initiated. Only 2 weeks after the completion of the radiotherapy, disease progressed with new vertebral, mediastinal, and pulmonary metastases. Thus, second-line chemotherapy with 5-FU, folic acid, and oxaliplatin was initiated. Third-line therapy with paclitaxel was not tolerated due to severe polyneuropathy. Hence, weekly epirubicin was administered as fourth-line therapy. Fourteen months after the initial diagnosis massive progression of pulmonary, hepatic and bone metastases occurred. The patient died shortly afterward.	Post-delivery PET-CT showed progression of disease, and palpable nodes had begun to grow again.

Conclusion

A multidisciplinary approach involving surgeons, obstetricians, neonatologists and oncologists is required. In addition, shared decision-making with the patient and family members is indispensable in the management of cancer diagnosed during pregnancy. In addition, the maternal benefit of gemcitabine seems to outweigh the unknown fetal risk.

The present case report demonstrates that surgery of gallbladder cancer followed by adjuvant chemotherapy with gemcitabine can be carried out safely and effectively in the gestational period.

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

AD (11th author), ND, PS contributed to the conception and design of the study. AD (1st author) wrote the first draft of the manuscript. AM, PS, MG wrote sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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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.

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Case Report: A case of advanced duodenal adenocarcinoma in complete remission after chemotherapy combined with targeted therapy and radiotherapy

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Duodenal adenocarcinoma (DA) is an extremely rare and highly aggressive malignant tumor of the digestive system. Due to the lack of specific clinical characteristics, it is easy to misdiagnosis and miss diagnosis, and the lack of specific consensus and recommendation for treatment, so it often refers to stomach cancer and colorectal cancer. Now, we report a case of a patient with advanced DA who achieved complete remission (CR) after undergoing chemoradiotherapy combined with targeted therapy. The patient was pathologically diagnosed with DA after radical surgery in October 2020, and he failed to undergo adjuvant chemotherapy on time due to the COVID-19 outbreak. The patient found multiple lymph node liver and abdominal metastases 6 months after the operation. Considering the progression of the disease, XELOX regimen (oxaliplatin + capecitabine) chemotherapy was given for 1 cycle. After 1 cycle of treatment, the tumor markers remained elevated; the carcinoembryonic antigen (CEA) was 5.03 ng/ml (0–5 ng/ml), and the carbohydrate antigen 19-9 (CA19-9) was 747.30 U/ml (0–37 U/ml). The patient also developed intolerable capecitabine-related treatment-related adverse events (TRAEs), namely, hand–foot syndrome. For the above reasons, capecitabine was replaced as S-1 at cycle 2, and the chemotherapy regimen became SOX (oxaliplatin + S-1); bevacizumab injection was also added to the SOX regimen, and it was further treated regularly for 7 cycles with the regimen of SOX plus bevacizumab. Liver metastases showed a continuous narrowing trend throughout the treatment period; tumor markers also showed a downward trend. Finally, the patient achieved complete remission (CR) at cycle 7. After completion of chemotherapy, radiotherapy was administered to the resistant metastatic lymph nodes present in the patient's abdominal cavity for a total of 10 times. However, the patient developed severe bone marrow suppression and obstructive jaundice during the course of radiotherapy and finally failed to complete the radiotherapy plan. Currently, the patient continued maintenance therapy with bevacizumab and S-1 and showed no recurrence or metastasis after review. In this case of advanced DA,

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we referred to both CRC and gastric cancer in the treatment regimen of the patient. At the same time, targeted drugs and radiotherapy were also added to the basis of chemotherapy, which has no clear consensus recommendation or case for reference in the treatment of advanced DA. Thankfully, the patient's disease was controlled and remained stable after treatment with this regimen. Therefore, for patients with advanced DA who lack standardized treatment regimens and guidelines, the combination of chemotherapy with targeted therapy and radiotherapy may be one of the effective treatment modalities.

KEYWORDS

case report, duodenal adenocarcinoma, advanced stage, chemotherapy, radiotherapy, targeted therapy

Introduction

Duodenal adenocarcinomas (DA) represent 0.3%–1% of gastrointestinal malignancies, with an incidence rate of less than 0.5/100,000 (1). However, in terms of occurrence of small intestinal malignancies, DA represents a higher proportion, accounting for approximately 25%–35% (1, 2). Early diagnosis of DA is challenging, as it lacks specific clinical features, so it is prone to missed diagnosis or misdiagnosis as biliary and pancreatic disease and then misses the optimal treatment time and finally develops into advanced DA (3). As a result, the prognosis for the disease is often poor.

Hirashita et al. (4) found that patients with advanced DA had a significantly better prognosis after following the chemotherapy regimen for CRC than the patients who did not receive chemotherapy (P = 0.016). As a result, they believe that advanced DA, despite the poor prognosis, chemotherapy may allow them to achieve a degree of remission after the disease progresses. DA has low morbidity and high mortality rate, which leads to lack of standard diagnosis and treatment guidelines, while chemotherapy often refers to CRC or gastric cancer guidelines. Therefore, some individuals have shifted the strategy of advanced DA therapy to targeted therapy and more specific immunotherapy, but the current effective clinical evidence is still lacking. Here, we discuss the case of advanced DA patients who recover from disease progression after surgery and eventually achieve CR after treatment with chemotherapy plus targeted therapy and radiation.

Case report

A 53-year-old male patient with no family history or personal history of bowel cancer presented for "intermittent abdominal distention for more than 1 month". The patient did not experience nausea or vomiting, blood or black stools, abdominal pain or diarrhea, and fever or jaundice during the onset of the disease. Eating, defecation, and body position were not associated with bloating symptoms; urine color deepening was greater than before; and stool was normal.

The routine physical examination: the patient had better mental status, with stable vital signs and no yellowish skin and sclera, no enlarged superficial lymph nodes, and no liver and spleen enlargement affected; both lungs breathing sounds were normal; and no abnormal breathing sounds could be detected. There was no pain, rebound pain, and muscle tension, and bowel sounds can be heard in the whole abdomen, with an average of three to five times/minute. Weight loss was approximately 4–5 kg, and no remaining abnormalities were noted.

After admission, abdominal MRI scan was performed, and the results showed space occupying lesions in the hook region of the pancreatic head region; possibility of malignancy was high; the clinical stage of cT3N1Mx was concomitant, accompanied by bile duct system expansion; and multiple liver metastases may be present. The value of the tumor marker CA19-9 was 94.9 U/ml above the normal reference range (0–37 U/ml), and the CEA and lactate dehydrogenase (LDH) levels were in the normal range. Two ultrasound-guided liver biopsies were performed to clarify the patient's diagnosis, but these were negative. Finally, a PET/CT examination was performed, and the results showed the following: ampullary space-occupying lesions, possibly ampullary carcinoma; low-density nodules at liver S4 and S8; the tumor possibly showing metastasis; and the paralesional lymph nodes showing radioactive concentration, with high possibility of tumor metastasis. The patient also had low biliary obstruction. Second, we recommend the patient for endoscopic pathology by ultrasound, hoping to undergo surgical treatment after a clear pathologic diagnosis. However, because the patient had undergone two biopsies of liver puncture but had not obtained the pathological tissue, the patient and family members refused to perform endoscopic ultrasonography and hoped to undergo exploratory laparotomy as soon as possible to establish a clear

diagnosis. When the opinions of the patients and their families were integrated, the patient did not have obvious organic lesions in the heart, lung, kidney, and other organs, and both liver puncture tests did not show any positive findings in pathological tissue scan. In addition, the patient has developed low biliary obstruction with elevation of tumor landmarks. Consent was obtained after a multidisciplinary consultation to be transferred to surgical therapy.

Downward surgery under epidural composite general anesthesia occurred on 2 October 2020. The surgical name was "exploratory laparotomy + modified pancreaticoduodenectomy". Surgery was an R0 resection, starting with the resection of the pancreatic head, duodenum, proximal jejunum, distal stomach, common bile duct, and gallbladder, followed by the reconstruction of the three sites: the pancreas and transverse colon, common bile duct and jejunum, and stomach and jejunum. Surgical records showed the following: the surgical incision was located in the right upper quadrant, and the skin was cut about 24 cm through the rectus abdominis incision. Intraoperative exploration showed the following: no abdominal ascites, no implant nodules in the peritoneum, and the right liver surface adhered to the diaphragm, which was released. The imaging showed that the occupation of the liver and the surface of the whole liver were not touched, the volume of the gallbladder increased, and about 200 ml of dark-green bile was drained by decompression. The common bile duct was seen after dissection of the hepatic duodenal ligament, which had dilation, approximately 1.5 cm in diameter. A 1 cm * 1 cm mass was reached in the ampulla region of the inferior common bile duct with a hard texture. Enlargement of hilar lymph nodes, paraciliary choledochal lymph nodes, and common hepatic artery lymph nodes were found. The lesion was found to be resectable after free exploration, so the decision to perform pancreaticoduodenectomy was made. The gallbladder was removed, and a total of 12 parahepatic arteries and common bile duct lymph nodes were removed and submitted for examination. The common bile duct was cut above the gallbladder junction, draining all bile, cutting the common bile duct about 1.5 cm in diameter, and the distal bile duct was ligated. The broken end of the common bile duct was sent to the frozen pathological examination, and no tumor cells were found. The gastric tissue was severed between the gastric body and the antrum, and the pancreas was then exposed. The transverse mesentery was dissected until the inferior margin of the pancreas, revealing the pancreatic head and superior mesenteric arteries, cutting the jejunum at the 10-cm jejunum, distal suture, and proximal suture from the transverse colon mesoic pore pulled back to the right. The pancreatic tissue was cut open after ligating the severed blood vessels of the pancreas, and the posterior pancreatic hook process appeared and the posterior resection mesangium was ligated. Since then, the tissues of the pancreatic head, duodenum, proximal jejunum, distal stomach, and the common bile duct and gallbladder have been completely removed. Reconstruction was then performed. In pancreatic and jejunal anastomosis, after leaving free the distal jejunum, the transverse colon was mentioned above from the transverse colon posterior mesangial fissure, and the anastomosis was made at 5 cm from the jejunal fracture end and the pancreas. In common bile duct and jejunal anastomosis, a longitudinal incision equal to the aperture of the common bile duct was made in the lateral edge of the jejunum from the pancreas and jejunostomy, followed by common bile duct jejunoanastomosis. In gastric jejunum anastomosis, a transverse colonic anterior gastrojejunostomy was performed about 50 cm below the common hepatic jejunal anastomosis. An ampullary carcinoma was intraoperatively diagnosed. However, the postoperative pathology showed a poorly differentiated DA, tumor tissue invaded the base layer of the duodenal intestinal wall involving parenteral adipose tissue, and there is also nerve invasion, pancreatic resection (-), bile duct resection (-), gastric resection (-), duodenal resection (-), and lymph nodes 0/7 in each group. Therefore, this patient was eventually diagnosed with poorly differentiated DA.

After the operation, the patient failed to perform adjuvant chemotherapy on time due to the COVID-19 outbreak. Review at 6 months thereafter revealed an elevation of the tumor marker CA19-9 to 515.5 U/ml; the abdominal MRI found multiple nodules in the liver, low signal on the T1WI sequence, a slightly higher signal in T2WI, some lesions with T2WI, larger nodules located in S6, about 10 mm * 8 mm in size, and a high possibility of metastasis. Combined with the elevation of the patient's tumor markers, considering the patient's disease progression, admission to chemotherapy is recommended. The chemotherapy regimen for cycle 1 was the SOX regimen (oxaliplatin+S-1:oxaliplatin: 220 mg per dose, intravenous administration, administered once during a treatment cycle, 21 days is used for one treatment cycle, S-1: each time 60 mg, oral medication, twice daily for 14 consecutive days per treatment cycle). The SOX treatment regimen is guidelines for gastric cancer. Hematological indicators were checked before medication in cycle 2, and it was found that tumor markers continued to rise (CEA: 5.03 ng/ml, CA19-9: 747.30 U/ml). After 1 cycle of chemotherapy, the tumor markers still show a significant upward trend, perhaps indicating that chemotherapy alone cannot effectively control the progression of the disease; after a multidisciplinary consultation, it was agreed that targeted drugs might be added to try them out.

The patient's primary tumor was located in the duodenum, and postoperative immunohistochemistry was performed: HER-2(1+), VEGF(+), Topo-IIα(+2%), PDGER-α (-), Ki67 (+30%), KRAS (-), NRAS (-), BRAF (+), MLH1 (+50%), PMS2 (+40%), MSH2 (+60%), MSH6 (+40%). The patient developed capecitabine-related adverse drug reactions after 1 cycle of oral capecitabine. The main manifestation is hand–foot syndrome, reaching grade 4. Due to the above reasons, coupled with the patient being not too old and in good physical condition, after consulting with the family members and obtaining their

informed consent, capecitabine was replaced with S-1 during cycle 2 of chemotherapy. In addition, we added bevacizumab to conventional chemotherapeutic agents (the dose was 5 mg/kg, administered intravenously, administered once during a treatment cycle, and 21 days was used for one treatment cycle). Then, the patient regularly completed the following 7 cycles of treatment, and the patient tolerated the drug well throughout the treatment period and showed no serious drug-related adverse reactions again.

The patient was reviewed and evaluated on time throughout the treatment period. Evaluation criteria were according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1.1). The patient was rated as SD at cycle 3 (liver metastatic lesions decreased by 5% compared with before). At cycle 5, liver metastasis decreased by 30% and reached partial response (PR). The metastasis was visually invisible at cycle 7 and was assessed as complete remission (CR). During the entire treatment period from cycle 2 to the end of treatment, the liver metastases continued to decrease (ranging from 5% to 30%), and the tumor markers also decreased (CA19-9 decreased to normal levels from 949.0 U/ml and remained stable). When 8 cycles of treatment were completed, the patient's liver lesions were visually invisible from the initial 10 mm * 8 mm to the end of treatment.

After the end of chemotherapy, some lymph nodes in the hilar region and peritoneal cavity metastasis could not be significantly reduced compared with those before chemotherapy, which may be related to the tumor heterogeneity and drug tolerance. After a consultation in the radiotherapy department, they recommended abdominal radiotherapy. The original radiotherapy plan was 1.8 Gy each time, a total of 28 times, and a total radiation dose of 50.4 Gy. However, considering that the patient had experienced myelosuppression during chemotherapy and had a platelet decline after the second radiotherapy session (PLT: 70 * 10^9/l), combined with the patient's current physical state and disease condition, the radiotherapy schedule was changed to 20 times with a total radiation dose of 36 Gy. After radiotherapy, the abdominal metastatic lymph nodes showed a shrinkage trend, but the patient developed severe myelosuppression (PLT: 30 * 10^9/l) and jaundice after the 10th radiotherapy and finally failed to complete the radiotherapy plan. Bone marrow suppression seen during the radiotherapy process mainly showed decreased PLT, white blood cell (WBC), and neutrophil (NEU) count. The PLT value decreased to 30 * 10^9/l ((125–350 * 10^9/l), and the WBC value had a minimum drop to 1.5 * 10^9/l (3.5–9.5 * 10^9/l). The NEU value decreased to 0.8 * 10^9/l (1.8–6.3 * 10^9/l).

Up to the third degree according to the myelosuppression scores, the WBC levels were 1.29–1.0 * 10^9/l, NEU: 0.9–0.5 * 10^9/l, and PLT: 49–25 * 10^9/l. During radiotherapy, the patient's biochemical index was increased. Total bilirubin was 324.3 μmol/l (3.4–21 μmol/l), direct bilirubin was 180.80 μmol/l (0–3.4 μmol/l), indirect bilirubin was 143.50 μmol/l, and total bile acid was 13,000 U/l (5,300–11,300 U/l). The abnormalities of the above test indicators significantly fit with the jaundice symptoms of the patient. Subsequently, the patient underwent interventional therapy with "biliary drainage + biliary stenting", and the patient's jaundice symptoms significantly improved 3 days after surgery. However, the patient failed to continue the subsequent radiotherapy for factors such as myelosuppression and secondary infection. At present, the patient has been treated with bevacizumab plus S-1 for half a year, and no disease progression has occurred until June 2022 (Table 1).

Besides myelosuppression, drug-related adverse effects exist throughout patient treatment. For example, after the first cycle of capecitabine, the patient developed refractory hand–foot syndrome, mainly showing significant swelling and pain in the palm and foot with severe desquamation and ulcers, as well as local blisters and erythema. Such severe capecitabine-related adverse effects after 1 cycle are rare, as the drug-related adverse effects are usually proportional to the dose.

TABLE 1 The whole treatment process of the patient ,including date, treatment regimen, cycle and the changes of hematological indicators (CA19-9, CEA, LDH, WBC, NEU, HGB and PLT).

Date	regimen	Cycle	CA19-9	CEA	LDH	WBC	NEU	HGB	PLT
2020/10/2	operation	_	29.49	2.24	126	10.68	8.83	148	132
2021/4/11	XELOX	C1	516.5	4.78	141	5.49	3.52	145	108
2021/5/11	SOX+Bevacizumab	C2	748.3	5.03	210	6.08	3.57	136	103
2021/6/8	SOX+Bevacizumab	C3	180.1	4.21	200	5.01	3.15	127	99
2021/7/7	SOX+Bevacizumab	C4	105.9	3.81	186	4.55	2.2	135	101
2021/8/15	SOX+Bevacizumab	C5	42.1	2.18	150	3.21	1.93	130	98
2021/9/13	SOX+Bevacizumab	C6	21	2.07	188	2.21	1.8	133	89
2021/10/10	SOX+Bevacizumab	C7	15.5	1.87	197	2	1.97	131	78
2021/11/2	SOX+Bevacizumab	C8	10.9	1.8	125	2.2	2.01	139	82
2021/12/20	SOX+Bevacizumab+Radiotherapy	-	8.91	1.78	137	1.5	0.8	122	30
2021/12/31	Biliary stent implantation	-	12.31	2.21	165	2.3	2.12	138	55
2022/1/19-6/21	S-1+Bevacizumab	-	–	–	–	–	–	–	–

Fortunately, capecitabine was replaced with S-1 in cycle 2, after which the patient gradually resolved. Furthermore, the patient also inevitably developed oxaliplatin-related peripheral sensory neuropathy after 8 cycles of oxaliplatin treatment until the last cycle severity had reached stage 3. This is inevitable, but at this time the patient has successfully completed the treatment and the effect was good (Figures 1–8).

Discussion

The incidence of non-ampullary DA is extremely low, and it has been suggested that the low incidence of DA may be related to the existence of some protective mechanism. For example, the duodenal transport rhythm is fast, which can effectively reduce the exposure of carcinogens; in addition, the presence of intestinal secretions and fluids has a certain protective effect against the relatively sterile duodenum (5). Except for the lower morbidity rate, many DA patients do not show symptoms until the tumor growth is large enough or even develops into an advanced stage, often lacking in specific clinical manifestations, so the early diagnosis is extremely difficult; according to statistics, due to the above reasons, the average delayed diagnosis was about 2 to 15 months, and due to the complex tissue structure of the vicinity, patients are prone to misdiagnosis and missed diagnosis (6, 7).

If the patient can meet the conditions of surgical treatment, the pathological tissue examination after surgical resection can get a more accurate judgment. Although the intraoperative diagnosis is also more credible, many patients' lesions were located in the ampullary area, there are many surrounding tissues and organs, the structure is more complex, and the lesions are diverse; therefore, the pathological diagnosis is considered to be the most accurate. As reported in the article, the patient was diagnosed with an intraoperative ampullary carcinoma, while the postoperative pathology showed a non-ampullary DA. If the patient is found to have parenchymal organs, such as liver and lung metastases, once examined, the needle biopsy can also be considered for judgment, but it is often prone to negative or false positive results, which is often not accurate enough (7–9). As in the patient in this case, the liver metastasis puncture biopsy was performed twice, but the results were negative, and the intraoperative exploration did not touch the space-occupying lesion shown by the imaging of the whole liver surface. The imaging performance of the primary lesion of the patient in this case was not obvious, even with the possibility of missed diagnosis; in addition, the duodenum belongs to the small intestine, and the location was more special. Either gastroscopy or colonoscopy was difficult to cover, and the examination was mainly to the imaging, supplemented by the sponding hematological indicators.

Although DA is more malignant and progresses rapidly, surgery is still considered the best treatment for DA. A retrospective study was conducted by Juan Manuel Ramia et al. (10) found that the overall 5-year survival rate of all DA patients included in the study was 13% to 50%, and indeed there was some improvement in patients undergoing surgical resection compared with those without surgical treatment, from about 45% to 60%; patients were not surgically treated, the median survival was 7 months, and it was 0%–13% at 5 years (11). Studies have also found the survival status of the patient and the site of the disease. Without lymph node invasion, the survival rate of proximal duodenal tumors is 0% to 25% at 5 years after surgery, while the survival rate of distal tumors is as high as 62% (8, 9, 12, 13). The patient in our case also underwent radical surgical treatment, with surgical R0 resection, but the patient's disease still progressed rapidly, which may be related to the failure to perform adjuvant chemotherapy timely after

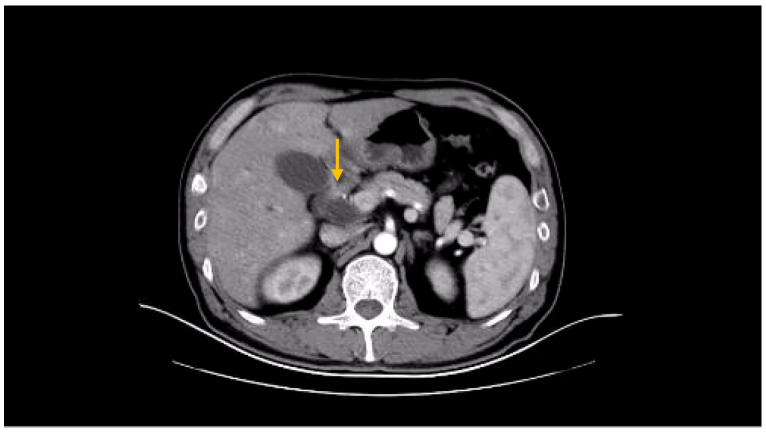

FIGURE 1
CT before operation (the tumor is located around the head of the pancreas).

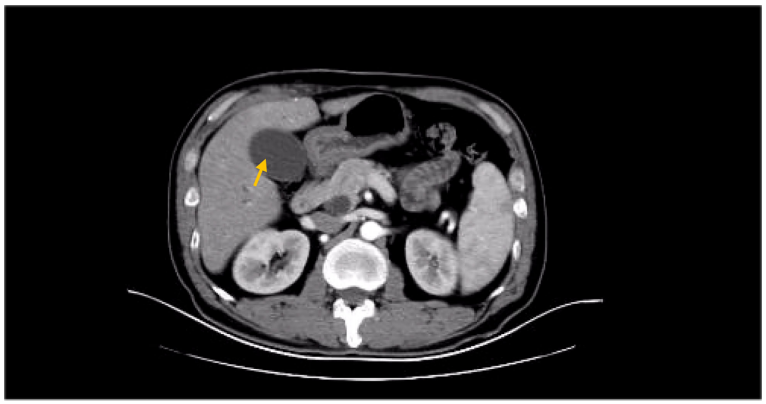

FIGURE 2
CT (enlargement of gallbladder due to biliary obstruction).

surgery. It can be seen that if radical resection can be supplemented with medication on time, it may be more beneficial to the control of the disease.

There is no clear indication and recommendation for the application of postoperative radiotherapy in DA treatment due to the lack of suitable prospective studies. Lim et al. (14) launched a retrospective study of the impact of postoperative adjuvant radiotherapy on survival outcomes in DA patients in 2017; the results found that the later the T stage, especially T4, the larger the tumor size and the higher the proportion of lymph node invasion; they also observed potential survival benefits in postoperative radiotherapy. Regarding the therapeutic effect of radiotherapy in DA, the toxicity of radiotherapy is also an important factor to consider, but due to the rarity of the tumor itself, the adverse effects after radiation are also mostly studies based on small data samples and have not been widely evaluated for (15). In the case we reported, the patient was also supplemented by abdominal radiotherapy after chemotherapy, and we observed a decrease in abdominal metastatic lymph nodes after radiotherapy (due to the COVID-19 outbreak, the patient's radiotherapy review was not performed in our hospital, so CT imaging images were not provided); however, because the patients later had obvious bone marrow suppression and obstructive jaundice, the radiotherapy plan was unfinished, but we can still think that patients did get some benefit from radiotherapy.

Due to the low incidence of DA, there are also very few prospective studies on the drug treatment of advanced DA, mostly in small and retrospective studies. Zaykowski et al. (16, 17) said in a study of palliative chemotherapy in patients with advanced DA showed that progression-free survival (PFS) in patients receiving advanced chemotherapy extended by 8 months compared with those who received no chemotherapy. In a phase II clinical study

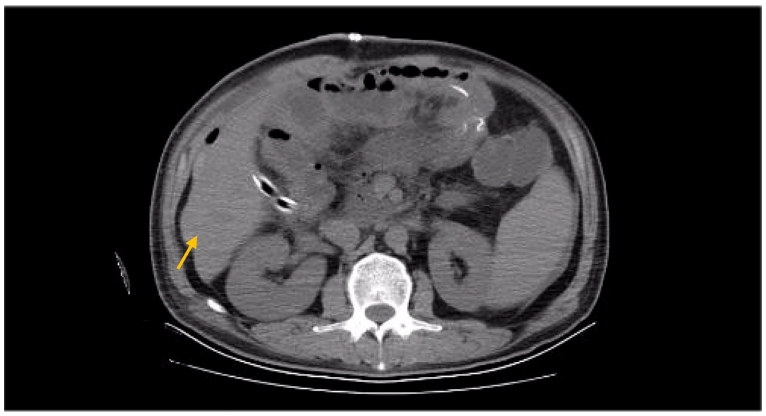

FIGURE 3
CT findings 1 month after surgery (no liver metastasis).

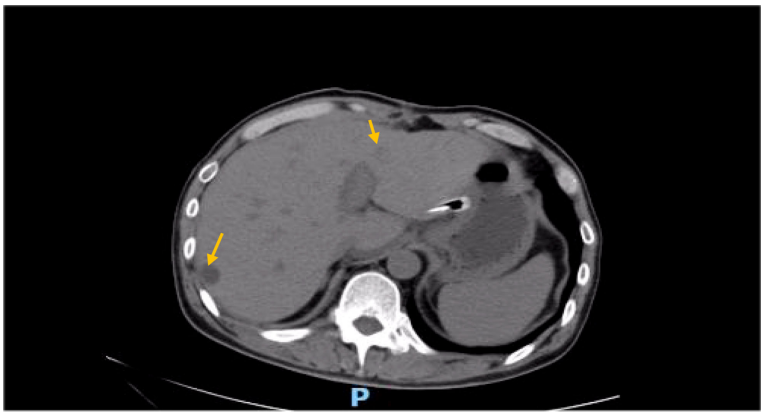

FIGURE 4
CT (liver metastasis) was performed.

of the XELOX regimen for advanced ampullary carcinoma and small bowel carcinoma, conducted by Overman et al. (16, 18), the results showed that the overall response rate (ORR) reached 50%, median time to progression (mTP) was 11.3 months, and median overall survival (mOS) was 20.4 months, indicating that chemotherapy in advanced DA could prolong survival. In addition, Wang et al. (16) once reported that in a patient with advanced DA who received 4 cycles of SOX treatment and 6 cycles of single-agent S-1 maintenance, the PFS reached 14 months, and the toxic effect of the drug administration was fully tolerated during the whole treatment. S-1 is a fluorouracil approved for advanced or metastatic gastric cancer; there is no report or recommendation about its use for DA treatment, but the above evidence shows that S-1 showed good efficacy and safety in patients with advanced DA and can be used as one of the treatment options of advanced DA patients, although further validation is still in clinical practice.

In this patient reported in our article, the first considered regimen was XELOX regimen, but the patient developed refractory capecitabine-related adverse reactions after 1 cycle of medication, so capecitabine was replaced with S-1 in the next cycle of treatment, and the regimen also became SOX. Although the patient was relieved with capecitabine-related adverse effects in the subsequent treatment and had no S-1-related adverse effects, the patient still had other drug-related adverse effects; he still had other drug-related adverse effects, such as oxaliplatin-

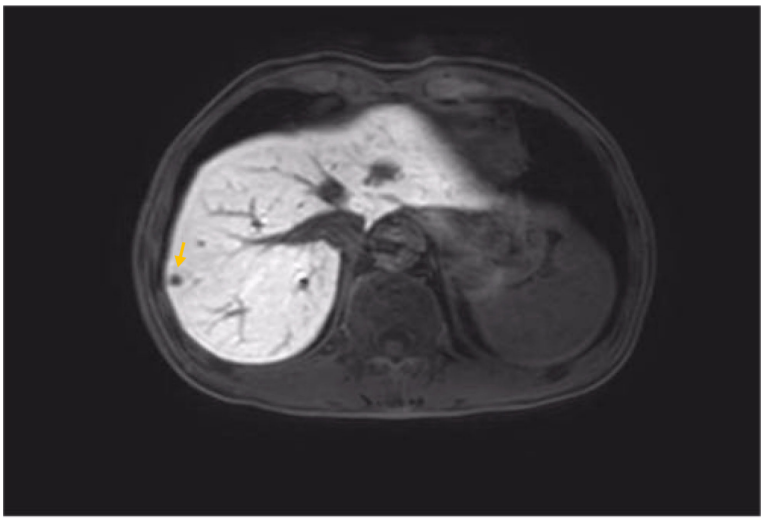

FIGURE 5
MRI findings 6 months after surgery (liver metastasis).

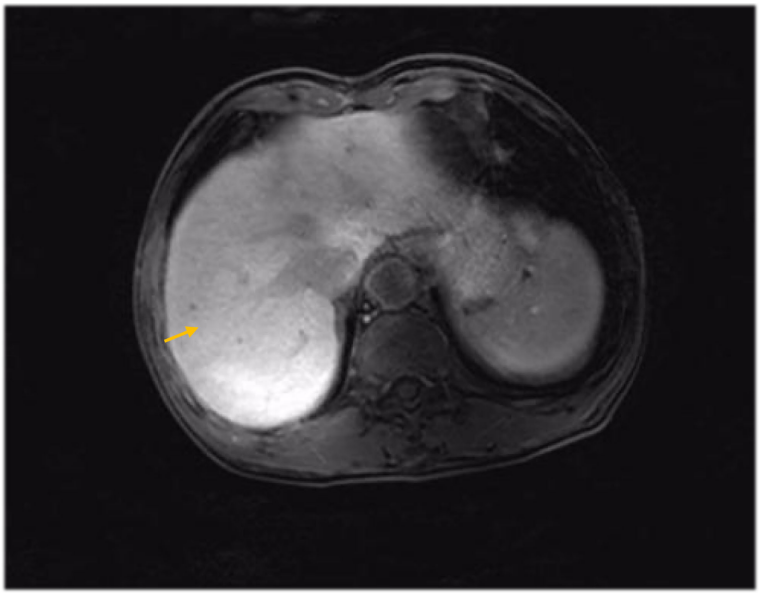

FIGURE 6
MRI findings during the patient's last chemotherapy session (liver metastases disappeared).

related peripheral neurotoxicity, even reaching 3° in cycle 8. Oxaliplatin-related or capecitabine-related adverse drug effects are associated with a cumulative dose effect, and in later cases, patients are in the same condition, perhaps to reduce oxaliplatin as appropriate, or try to change the 3-week regimen (oxaliplatin: 135 mg/m^2 for injection, administered once on 21 days) to a 2-week regimen (oxaliplatin for injection: 85 mg/m^2, administered once on 14 days). However, although such a treatment plan can reduce a single drug dose and reduce the degree of adverse reactions, the economic and time cost may become another problem. In the treatment of mCRC, the first-line scheme mainly includes oxaliplatin combined with fluorouracil and irinotecan combined with fluorouracil, and with the increase in OS, chemotherapy-related expected toxicity and exposure toxicity will increase, especially oxaliplatin dose-related peripheral neurotoxicity, although after withdrawal there will appear a certain degree of degradation; however, severity can lead to disability, seriously affecting the quality of life of patients (19, 20). Compared with oxaliplatin, irinotecan is generally well tolerated and its clinically relevant cumulative toxicity

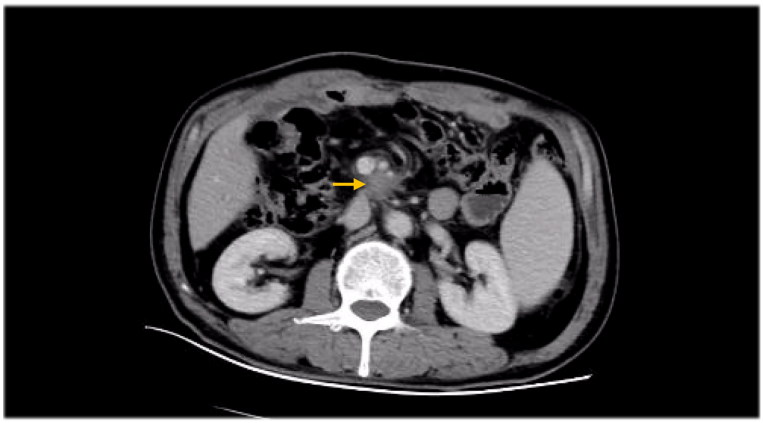

FIGURE 7
CT Before radiotherapy (abdominal metastatic lymph nodes).

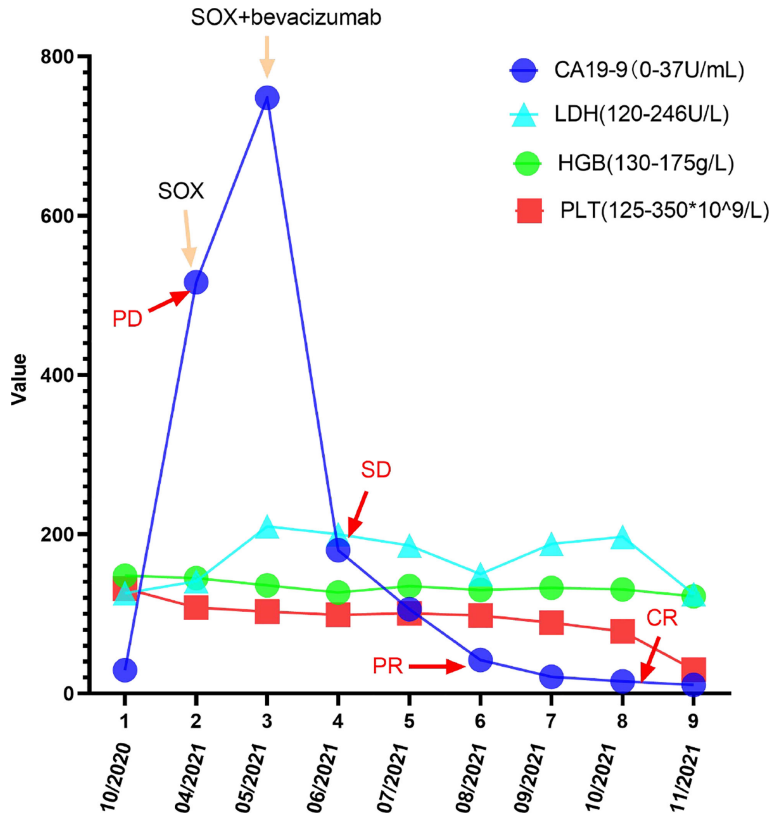

FIGURE 8
Changes in CA199, LDH, PLT, and HGB levels during the treatment and follow-up. The CA199 LDH, PLT, and HGB levels were measured in the patient's blood at periodic intervals throughout the clinical course and annotated with date, therapeutic approach, and treatment efficacy.

is less (19). Therefore, if patients develop disease progression again, they can consider irinotecan combined with fluorouracil to be considered as a treatment regimen, hoping to reduce the treatment toxicity of patients and increase the quality of life on the basis of prolonging the patient's survival.

Hirashita et al. (2) conducted a retrospective study of 25 patients with non-ampullary duodenal adenocarcinoma, mainly investigating the prognostic factors affecting patients with non-ampullary duodenal adenocarcinoma, and the benefit of chemotherapy in relapsed patients referring to the mCRC regimen; they found that the serum CA19-9 level, primary tumor size, depth of tumor invasion, lymph node metastasis, TNM stage, presence of lymphatic metastasis, vascular and nerve infiltration, and other factors were all important risk factors for recurrence; in addition, the relapsed patients receiving chemotherapy according to the mCRC regimen had a significantly better prognosis than those patients without chemotherapy (P = 0.016). The case we reported also had neurological invasion in this patient, which may also be related to the patient's disease progression.

The retrospective study conducted by Sakae et al. (21) also recommended high LDH and symptoms at diagnosis as new independent prognostic factors for OS. Unfortunately, the patients in our case showed no increase in LDH throughout the course; therefore, it is unknown whether LDH can be used as an independent influencing factor for DA prognosis. In addition, it has been reported that the survival rate of patients without lymph node metastasis was significantly higher than the rate in patients with lymph node metastasis (2, 22, 23). Therefore, it has been suggested to use lymph node metastasis as an important prognostic factor affecting the overall survival of DA patients, with a sensitivity of about 80% (2, 5, 24). We reported in this case that patients have reached R0 resection during surgery, but after the recurrence of liver metastasis they also had multiple abdominal lymph node metastasis, and the abdominal lymph nodes still failed to reach CR after chemotherapy. Abdominal metastasis of lymph nodes may affect the survival of patients; this is also the reason for the continued radiotherapy after the end of chemotherapy.

A case of advanced DA was reported by Kanehira et al. (25); the patient underwent chemotherapy after a laparoscopic gastrojejunostomy, using the chemotherapy regimen of S-1, plus cisplatin, then the abdominal CT after chemotherapy was reviewed; the results showed tumor shrinkage and that the

enlarged abdominal lymph nodes almost disappeared, after which the patient continued with S-1 maintenance chemotherapy for 1 year without recurrence. Although combination chemotherapy with S-1 and cisplatin is the standard treatment for advanced gastric cancer in Japan, there is no standard regimen for duodenal cancer (26). Wang et al. (16) once reported a case of a patient with advanced duodenal adenocarcinoma achieving CR after chemotherapy with the SOX regimen, which is very similar to the case in our text. Onkendi et al. (27) reported that patients were treated with leucovorin plus 5-FU plus irinotecan (FOLFIRI) or oxaliplatin (FOLFOX); disease remission rates in DA can be improved to some extent, but CR is still rare. In short, between the low incidence of duodenal cancer, large clinical research is difficult, and the standard treatment strategy is still a long way to go; however, reference to either gastric cancer or bowel cancer treatment is needed according to the patient-specific situation, to a certain extent, and the doctor's clinical experience and reference to typical successful cases are also needed.

For patients with advanced DA, the effect of chemotherapy on the long-term prognosis is relatively limited, so targeted therapy may be a potential direction to explore. After all, molecular targeted therapy has shown good results in multiple solid tumors. Human epidermal growth factor receptor-2 (Her-2), which is currently widely studied in adenocarcinoma, mainly promotes tumor invasion and metastasis by activating signaling pathways including Ras/MAPK and PI3K/Akt (28). At present, the overexpression of Her-2 and the amplification of the ERBB2 gene have been widely used in the treatment of breast cancer, gastric cancer, and colorectal cancer and have become a therapeutic target for prolonging patient survival, but its therapeutic potential in DA lacks clear evidence and sufficient data to support (28–30). Hamad et al. (31) added anti-Her-2 targeted drugs to the treatment of ERBB2 amplified patients with advanced DA, and combined with FOLFOX for neoadjuvant therapy, in the efficacy analysis, the patient showed significant tumor decline and no metastasis; moreover, no residual invasive adenocarcinoma was found in the postoperative pathological analysis, which was basically consistent with the previous neoadjuvant therapy response.

Gulhati et al. (32) conducted a single-center phase II clinical study of a bevacizumab combined with XELOX regimen in adenocarcinoma of advanced small bowel or an ampullary method to evaluate the benefit of combining bevacizumab with XELOX; there were 23 patients with small bowel adenocarcinoma, and the primary study endpoint was a 6-month PFS, with a 6-month PFS probability of 68% after combined bevacizumab, an ORR of 48.3%, an mPFS of 8.7 months, and a mOS of 12.9 months. Therefore, the XELOX regimen combined with bevacizumab is considered a feasible combination in the treatment of advanced DA, and this study is also the first prospective clinical study to evaluate the feasibility of targeted therapy in small bowel cancer.

In recent years, there have been several retrospective studies showing that patients with metastatic colon cancer with the primary tumor located on the right side (ileocecal to splenic area) have a significantly worse prognosis than on the left side (splenic to rectum). For patients with no mutations in the RAS gene, there was a clear relation between the efficacy of the anti-EGFR (cetuximab) and the tumor site and no significant association with site efficacy of anti-VEGFR (bevacizumab) (1). Moreover, a comparative chemotherapy combined with bevacizumab or cetuximab retrospective subgroup analysis shows the following: in the left CRC, cetuximab objective efficiency and overall survival better than bevacizumab, and in the right CRC, cetuximab but with some advantages in objective efficiency, although with overall survival than bevacizumab (19). Moreover, there is evidence that up to 96% of patients with small intestinal adenocarcinoma express VEGF-A, and the expression level of VEGF-A mRNA in ampullary duodenal carcinoma is significantly higher than that of adjacent normal intestinal mucosa (33, 34). This is one of the reasons why we chose bevacizumab as a targeted agent.

In this case report, the patient only underwent routine immunohistochemistry, without large-sample genetic testing, and more genetic mutations were unclear, but the addition of bevacizumab for vascular endothelial growth factor receptor (VEGFR) also showed good efficacy. Therefore, we can think that bevacizumab combined with chemotherapy can benefit patients with advanced DA to some extent. Moreover, some alterations in the target genes can indeed be the targets for the treatment of patients, especially for the tumors with a high malignant degree and some rare diseases, such as DA.

Except for targeted therapy, the rapid research progress of immunotherapy is also an aspect worthy of attention. After all, research on immune checkpoint inhibitors (ICIs) in recent years has indeed made relatively good achievements in many solid tumors, including esophageal cancer and CRC; for example, advanced esophageal squamous cell carcinoma has included ICIs in the first line. In DA patients, patients who also have microsatellite instability high (MSI-H) or deficiency of mismatch repair (dMMR) may also be the target population for ICI treatment. Studies have been found that 21% of patients in DA can have dMMR, which is significantly higher than 5% of CRC. Therefore, despite the low incidence of DA, the blockade against immune checkpoints is likely to be a significant opportunity for (35, 36). The patient reported in the case is currently relatively stable after chemoradiotherapy combined with targeted therapy. If the patient advances again in the later stage, then immunotherapy must also be a thing to be considered.

Early detection, early diagnosis, and early treatment must be the fundamental measures to improve the survival of DA patients. DA is often difficult due to its unique adjacent results and histological characteristics, so how to effectively screen people at high risk of DA is extremely urgent. Studies have shown that

familial polyposis, adenomatous disease, Crohn's disease, hereditary non-polyposis colorectal cancer, and Peutz–Jeghers syndrome (6, 8, 37). In addition, duodenal adenoma is also a recognized risk factor for the onset of DA, and its clinicopathological classification is called Spigelman classification, in which stage IV has the highest risk degree, and about 35% of patients with Spigelman stage IV develop (24, 38). Some research data also show that the duodenal polyp size and the emergence of high dysplasia are components of Spigelman stage IV, suggested as an important predictor of cancer risk; only the detailed reference criteria on this staging system or evaluation of treatment relevance has not yet been developed, which we need to continue to explore and study (4, 24).

In conclusion, due to the low incidence and extreme malignancy of DA, it is unrealistic to carry out large-scale clinical randomized controlled experiments, and research on the diagnosis and treatment of the disease is also greatly challenged. The patient we reported in this case, although already with advanced DA, was well controlled after treatment with SOX combined with bevacizumab. Therefore, in the diagnosis and treatment of DA, early detection is the best, but if unfortunately entering the advanced stage, actively receiving chemotherapy or using it in combination with targeted therapy, radiotherapy, and even immunotherapy may also greatly delay the progress of the disease. In summary, there is still a clear lack of guidelines and consensus for the diagnosis and treatment of advanced DA, and there is still a long way to go for the treatment of DA 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

The manuscript complies with the requirements of medical ethics and ethics, with the informed consent of the patient.

Author contributions

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

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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.

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Rare metastasis of gastric cancer to the axillary lymph node: A case report

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Lymph node metastasis of gastric cancer is more common, metastatic lymph nodes are often around the stomach, and metastasis is carried out in a certain order, but gastric cancer metastasis to axillary lymph nodes is very rare. Due to the small number of patients with this kind of metastasis, its clinical features and treatment are not very clear. We initially thought that the enlarged axillary lymph nodes were inflammatory lesions. Axillary lymph node biopsy was later diagnosed as gastric cancer metastases to axillary lymph nodes. The patient refused further treatment and died 11 months after the second operation because of multiple systemic metastases. We believe that metastasis of gastric cancer to axillary lymph nodes is rare and the prognosis is poor. In clinical work, the possibility of metastatic lymph nodes should be considered in patients with a history of gastric cancer with enlarged axillary lymph nodes.

KEYWORDS

gastric cancer, radical total gastrectomy, axillary lymph node metastasis, tumor markers, immunohistochemical staining

Introduction

Gastric cancer is a common malignant tumor of the digestive tract. Although morbidity and mortality have decreased in recent years, it is still the third largest cause of cancer death in the world (1). Advanced gastric cancer is often accompanied by lymph node metastasis and poor prognosis. Radical resection combined with standard lymph node dissection is still the main treatment for advanced gastric cancer (2). Lymph node metastasis of advanced gastric cancer often occurs in the lymph nodes around the stomach, and jump metastasis is rare, while axillary lymph node metastasis is rarer. According to the Japanese classification, axillary lymph node metastasis is considered to be distant metastasis of gastric cancer (3). Recently, we diagnosed and treated a patient

with gastric cancer with left axillary lymph node metastasis one month after radical total gastrectomy. The report is as follows.

Case presentation

A 67-year-old female patient was admitted to the local hospital because of epigastric pain and discomfort for one month. She was diagnosed as a malignant tumor of the gastric body by electronic gastroscopy and biopsy pathology. The abdominal enhanced CT shows multiple lymph nodes enlargement in the abdominal and retroperitoneum in the outpatient clinic of our hospital (Figures 1A, B). The patient received six cycles of chemotherapy in another hospital (SOX regimen for 1 cycle; S-1 and oxaliplatin. Paclitaxel, oxaliplatin, S-1, and Sintilimab for 5 cycles). After the end of chemotherapy, the effect of chmotherapy was evaluated as partial remission (PR). The patient asked for surgical treatment in our hospital. Physical examination showed that the abdomen was flat, the abdominal muscles were soft, the upper abdomen was mild deep tenderness, there was no rebound pain, and there was no obvious abdominal mass. Laboratory results showed that hemoglobin content decreased: 97g/L (normal range 110-150g/L). CA72-4:4.90U/mL (normal range 0-6.9U/mL), AFP: 1.30ng/mL (normal range 0-8.1ng/mL), CEA:1.13ng/mL (normal range 0-10ng/mL), CA199:17.71U/mL (normal range 0-37U/mL), CA125:2.85U/mL (normal range 0-30.2U/mL). There was no significant increase in serum tumor markers. After the end of neoadjuvant chemotherapy, we performed a PET-CT examination for the patient. ^{18}F-FDG PET-CT showed that the mass showed changes after chemotherapy, slight thickening of the lesser curvature of the stomach, the mass did not significantly absorb FDG, and it was found that the left axillary lymph node was enlarged, and the mass uptake of FDG increased slightly, but it was considered as an inflammatory lesion (Figures 1C). After multidisciplinary tumor consultation, we decided to perform the radical total gastrectomy on the patient, and regular examination of the enlarged lymph nodes in the left axilla. After obtaining the

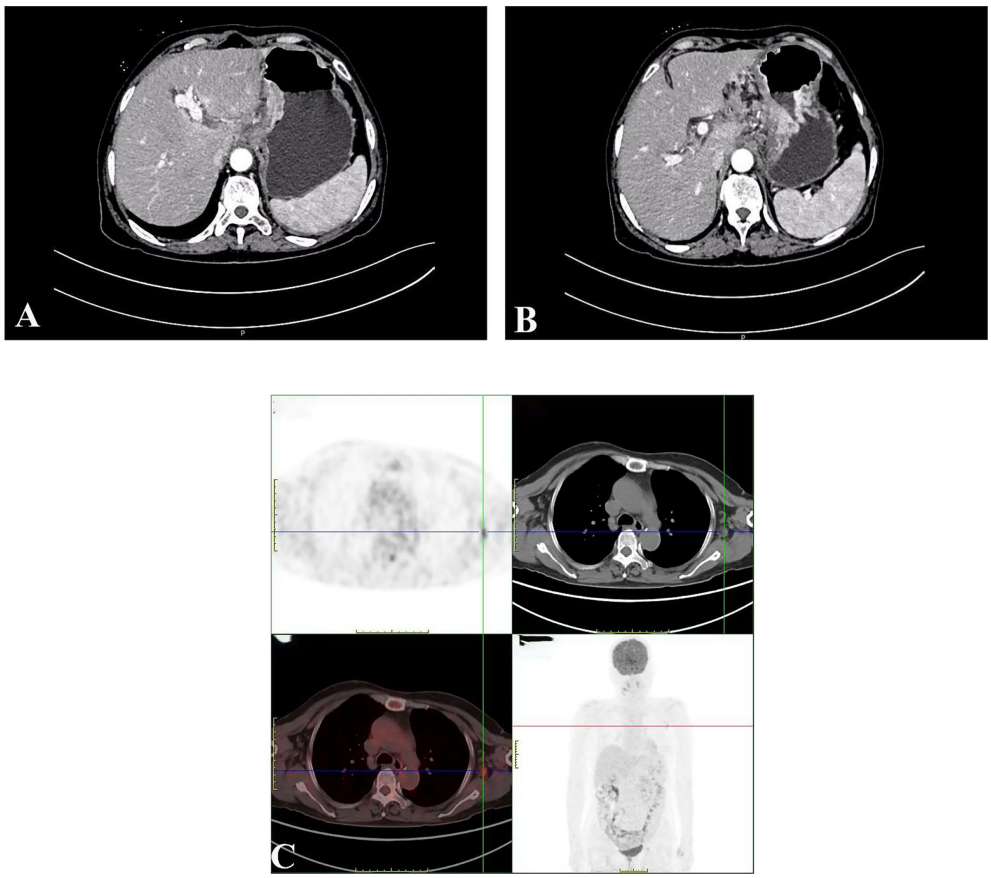

FIGURE 1
Abdominal enhancement CT showed obvious enhancement of the edge of the tumor in the arterial phase **(A)**; Abdominal enhanced CT showed enlarged retroperitoneal lymph nodes **(B)**; ^{18}F-FDG PET-CT showed that the left axillary lymph node was enlarged, and the mass uptake of FDG increased slightly, but it was considered as an inflammatory lesion **(C)**.

consent of the patient and her family, the patient underwent radical total gastrectomy (Roux-en-Y digestive tract reconstruction) in August 2021. Postoperative pathology showed that the area of ulcerative gastric cancer was about 4 × 3cm. The main tumor cells were poorly differentiated adenocarcinoma, local invasion of the deep muscular layer of the gastric wall, and tumor cells can be seen in the lymphatic vessels but no definite nerve invasion. Lauren's classification was the diffuse type (Figure 2A). Only one of the 21 lymph nodes had metastasis, which was located on the lesser curvature of the gastric wall, and no obvious tumor metastasis was found in the rest of the lymph nodes (ypT2N1M0 IIA). Immunohistochemical staining showed that tumor cells expressed CK8/18, individual cells expressed Syn, and did not express CgA, CD56, SALL4, Oct3/4, C-erb-B-2, and Ki-67 proliferative index was approximately 90%. The patient recovered smoothly without obvious postoperative complications and was discharged 13 days after radical total gastrectomy.

One month after radical total gastrectomy, the patient found that the left axillary mass grew faster than before and was accompanied by the limitation of left upper limb movement. Physical examination showed that the left axillary mass was about 4 × 2cm in size, hard, had an unclear boundary, and had a poor range of motion. Ultrasound examination of the bilateral breast and axilla showed that there was no obvious mass in the bilateral breast, and several hypoechoic lesions were found in the left axilla, the size of which was about 4.3 × 1.9cm, the boundary was clear, the cortex was thickened, the medulla was eccentric and the blood flow signal was abundant (Figure 3A). No obvious abnormality was found in mammary gland molybdenum target X-ray (Figures 3B, C), mediastinal and supraclavicular enlarged lymph nodes were not found in CT, and no obvious bone metastasis in whole-body bone scintigraphy (Figure 3D). The patient underwent the axillary lymph node biopsy in October 2021. During the operation, the enlarged lymph nodes were located next to the axillary vein, fused into clumps, hard texture, and closely combined with the surrounding tissues. Intraoperative frozen sections showed that there were 5 lymph nodes in the left axilla, and all of them had cancer metastasis. After that, we performed radical axillary lymph node dissection and 14 of the 18 lymph nodes had metastases. Pathology showed that the tumor cells were poorly differentiated adenocarcinoma. immunohistochemical staining showed that most of the tumor cells expressed Caudal-type homeobox 2 (CDX2), CK20, GATA binding protein 3 (GATA-3), and a small amount of sequence-binding protein (SATB) 2 and Mucin-5AC (MUC5AC), but no expression of CK7 and TTF-1 was found (Figures 2B–E). After communicating with pathologists, considering the immunohistochemical results and the history of gastric cancer, we considered that the left axillary lymph node tumor was metastasized by gastric cancer.

Outcome and follow-up

The patient received docetaxel and fluorouracil chemotherapy after radical axillary lymph node dissection, and a progressive increase in CEA, CA19-9, and CA72-4 was found (Figure 4). Three months after the second operation, the MR examination of cervical and thoracic vertebrae due to back pain

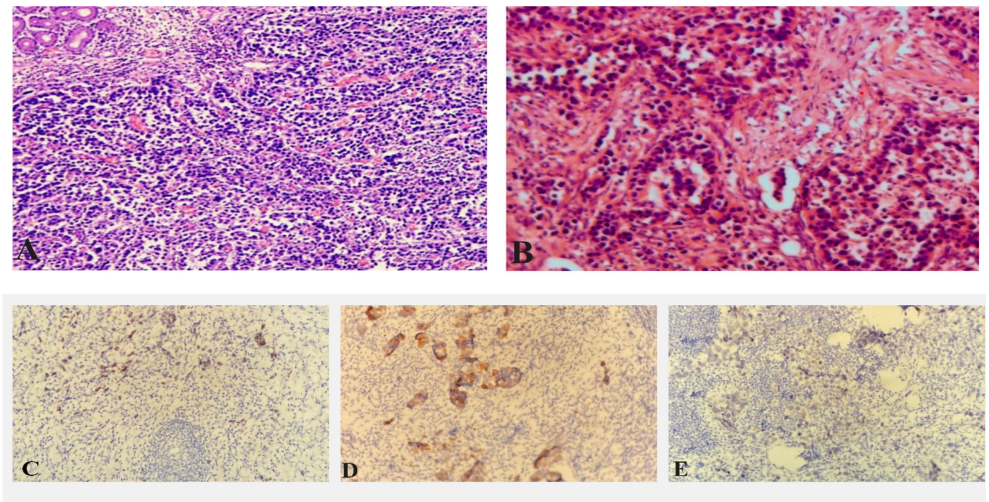

FIGURE 2
Pathological picture after radical total gastrectomy **(A)**; Pathological picture after radical axillary lymph nodes **(B)**; Immunohistochemical staining showed axillary lymph node tumor cells express CDX2 **(C)**; Immunohistochemical staining showed axillary lymph node tumor cells express CK20 **(D)**; Immunohistochemical staining showed some axillary lymph node tumor cells express SATB-2 **(E)**.

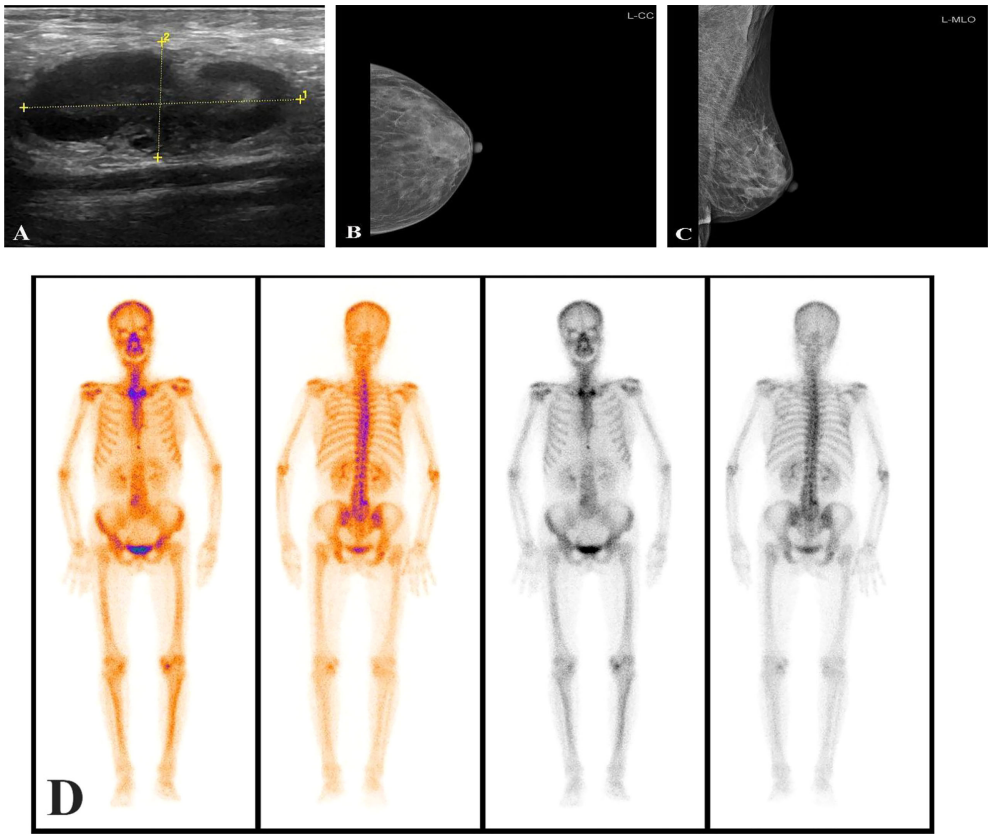

FIGURE 3
Axillary ultrasound showed enlarged axillary lymph nodes **(A)**; The mammary gland molybdenum target X-ray was not found obvious breast mass **(B, C)**; No obvious mass was found in whole-body bone scintigraphy **(D)**.

revealed secondary malignant tumors of the spine, but the patient refused to undergo whole-body bone imaging. CT of the chest and abdomen showed double clavicular and mediastinal enlarged lymph nodes, considering the malignant tumor. But the patient refused any treatment and died 11 months after the second operation.

Discussion

At present, although most patients with gastric cancer have received radical surgery and comprehensive treatment such as neoadjuvant chemotherapy, conversion therapy, or adjuvant chemotherapy, but some patients still have recurrence and metastasis of liver, lung, bone, or lymph nodes during postoperative follow-up (4). In patients with gastric cancer, axillary lymph node metastasis is very rare. Through literature search, we found 3 reports of axillary lymph node metastasis in gastric cancer (two of which do not have English abstracts). Kobayashi reported a case of left axillary solitary metastasis 21 months after radical distal gastrectomy and radical axillary lymph node dissection, and no tumor recurrence was found one year after the operation (5). In addition, cases of gastric malignant tumors due to the discovery of enlarged axillary lymph nodes were also reported, but the details were not reported in detail.

Postoperative axillary lymph node metastasis of gastric cancer should be differentiated from occult breast cancer (OBC). OBC refers to breast cancer with no primary breast lesion, but with axillary lymph node metastasis or other distant metastasis as the first symptom (6). Histopathological examination of axillary enlarged lymph nodes can make a definite diagnosis. Histopathological examination can not only reveal the pathological type of metastatic lesions but also further reveal the source of primary lesions by immunohistochemical staining (7). In this case, tumor cells expressed specific markers of digestive tract tumors (CDX2, CK20). Combined with the history of gastric malignant tumor, we considered that the left axillary lymph node tumor was metastasized by gastric cancer. Malignant tumors may increase tumor markers in the blood or body tissue. In addition, the increase of many specific tumor markers may indicate tumor recurrence and metastasis. Most tumor markers are effective prognostic tools that can be used to identify the risk of

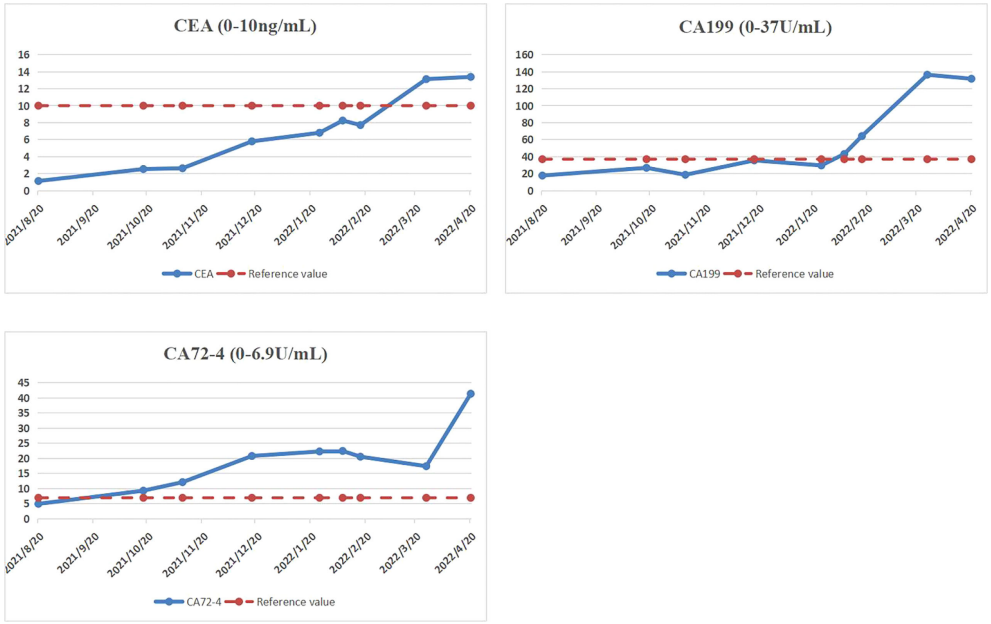

FIGURE 4
CEA, CA19-9, and CA72-4 increased gradually after radical axillary lymphadenectomy.

recurrence or metastasis (8). CA72-4 is a mucin-like glycoprotein that exists on the surface of many cancer cells. CA72-4 detection has good specificity for gastric cancer and can be used to determine the recurrence of GC and follow-up after treatment (9). CEA is the most widely used and most frequently used marker in digestive system tumors, the level of CEA is increased in some patients with advanced gastric cancer (10). Previous studies have found that the positive rate of CEA is 21.1%, the positive rate of CA19-9 is 27.8%, and the positive rate of CA72-4 is 30.0%. These three markers were significantly correlated with tumor stage and patient survival. Serum markers are not helpful for early cancer, but they are helpful in detecting recurrence and distant metastasis, predicting patient survival, and postoperative monitoring (8). In addition, the increased expression of Ki-67 was associated with the proportion of metastatic lymph nodes in the total number of lymph nodes and the advanced stage of the tumor (11). In this patient, before radical axillary lymph node dissection, the serological tumor markers were in the normal range and considering that it is very rare for gastric cancer to metastasize to axillary lymph nodes, we misjudged the patient's condition. It also suggests that we should consider the possibility of metastasis in patients with gastric cancer with enlarged axillary lymph nodes and biopsy of enlarged lymph nodes is a method to determine the primary tumor.

The lymph node metastasis of gastric cancer mainly occurs gradually along the lymph node drainage pathway, but the gastric malignant tumor shows cross-regional distant lymph node jump metastasis, which is difficult to explain by the conventional lymph node pathway. Kobayashi considered that the primary tumor may have invaded the lymphatic vessels of the chest wall because the lymphatic drainage of the axillary lymph nodes comes from the subcutaneous or intercostal lymphatic vessels of the chest wall (5). Parungo detected that the celiac lymph nodes can be drained directly to the chest wall lymph nodes by using a fluorescent tracer and then to the thoracic lymph nodes (12). We speculate that the axillary lymph node metastasis of gastric cancer may occur in the following ways: the first may be that the tumor cells invade the thoracic duct, then invade the blood circulation, and enter the left subclavian lymphatic vessel through the left subclavian vein. And to the axillary lymph node drainage direction countercurrent, resulting in axillary lymph node metastasis. The second possibility is that the tumor cells invade the lymphatic vessels of the abdominal wall or chest wall, resulting in axillary lymph node metastasis, because the superficial lymphatic vessels of the sub umbilical abdominal wall flow downward into the inguinal lymph nodes, and the supraumbilical lymphatic vessels flow upward into the axillary lymph nodes (13). The third possibility is that the tumor cells directly invade the blood circulation and when passing through the axilla, they are captured by the axillary lymph nodes and reproduce and grow in the axillary lymph nodes, resulting in axillary lymph node metastasis. In this case, we speculated that the tumor invaded the lymphatic vessels of the chest wall and then metastasized to the left axillary lymph nodes through the thoracic duct.

Lymph node metastasis of gastric cancer is an important index affecting the prognosis of gastric cancer. With the increase in the number of metastatic lymph nodes, the overall survival

rate of patients with gastric cancer decreased significantly (14). At the same time, the recurrence rate of patients with positive lymph nodes was significantly higher than that of patients with negative lymph nodes (15). Axillary lymph node metastasis of gastric cancer is considered to be a kind of distant metastasis, which is related to poor prognosis. Based on the relevant literature, it is not clear which treatment is more helpful to improve the prognosis of patients after surgical resection, adjuvant chemotherapy, or direct systemic chemotherapy. Pavlidis considered that metastatic adenocarcinoma, including solitary axillary lymph nodes, can be treated by surgery (16). Zhao reported that adequate lymph node dissection is essential for skip lymph node metastasis (17). Kobayashi reported that the left axillary lymph node metastasis occurred after the gastric cancer operation, there was no definite recurrence or metastasis within one year after radical lymphadenectomy (5). Nashimoto reported a case of gastric cancer who survived for more than 6 years after abdominal para-aortic lymph node dissection (18). Chieco reported a case of solitary metastasis of left axillary lymph nodes after operation of right colon cancer and there was no recurrence within 1 year after radical resection (19). Therefore, we speculate that postoperative axillary lymph node metastasis of gastric cancer can be considered as a local manifestation of systemic metastasis, and surgical resection of local recurrent lesions is a more effective treatment at present. However, unlike in other cases, axillary lymph node metastasis occurred one month after operation in this patient, so we speculate that the tumor cells have a high malignant potential. Therefore, we give adjuvant chemotherapy after the radical axillary lymphadenectomy.

Axillary lymph node metastasis is one of the sites of distant metastasis of gastric cancer. In the preoperative evaluation and postoperative reexamination of patients with gastric cancer, attention should be paid to axillary lymph node examination. The biopsy of enlarged lymph nodes is a good method to determine the primary tumor. For this patient, we underwent radical resection of metastatic lymph nodes, but the treatment of gastric cancer with axillary lymph node metastasis is still controversial. Further cases may be needed in the future to determine the appropriate surgical intervention and the duration of chemotherapy to determine which treatment is more beneficial to improve the prognosis of patients with postoperative axillary lymph node metastasis of gastric cancer.

Conclusion

Gastric cancer with axillary lymph node metastasis is very rare. Pathological examination of enlarged lymph nodes is a good method to identify primary tumors, which can improve the accuracy of diagnosis and avoid excessive treatment. At present, surgical resection of enlarged lymph nodes is a more effective treatment, but more studies are still needed to determine which treatment is more beneficial to improve the prognosis of patients with gastric cancer with axillary lymph node 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 human participants were reviewed and approved by the Weifang People's Hospital Ethics Committee. 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

JQ: guarantees the integrity of the entire study and edited the manuscript. QZ and LL: prepared and edited the manuscript. XJ, JX, SZ, GZ and PC: performed the literature research, data analysis, and text proofreading. All authors contributed to the article and approved the submitted version.

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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

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Case report: Rare isolated cystic hepatic metastasis of a patient with squamous cell lung carcinoma history and the prognosis

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Cystic hepatic metastasis of squamous cell carcinoma usually develops from necrosis due to insufficient blood supply, yet metastasis initially resembling simple liver cyst is rare. Here, we present a case of a patient with squamous cell lung carcinoma history who found an isolated cystic mass in the liver. Historical MR studies indicated that the mass did not exist 12 months ago and emerged as a small cystic lesion 7 months ago. Radiological findings and tumor markers level suggested metastasis, while 18F-Fluorodeoxyglucose (^{18}F-FDG) PET/CT showed moderate tracer uptakes in solid parts of the mass. Pathological study after surgery confirmed metastatic squamous cell carcinoma. Chemotherapy plus recombinant human endostatin and sintilimab therapy was employed after surgery; however, the patient developed remote metastasis of osteolytic lesions in the humerus bone and thoracic vertebra. Our case indicates that metastasis should be taken into consideration in emerging cystic hepatic lesion with malignant history.

KEYWORDS

cystic metastasis, squamous cell lung carcinoma, PET/CT, immunotherapy, 18F-FDG

Introduction

The diagnosis of hepatic cystic lesions ranges from benign to malignant situation, leading to different pathogenesis, clinical presentation, and radiological findings (1). Malignant cystic lesions of the liver usually develop from primary hepatobiliary tumor or metastases. The liver acts as a major organ of detoxication and receives blood from most of the digestive organs *via* the hepatic portal vein; thus, the primary source of a hepatic

metastasis varies greatly (2, 3), including colon cancer, gastrointestinal stromal tumor (GIST), pancreatic mucinous cystadenocarcinoma, pancreatic neuroendocrine tumor, ovarian cystadenocarcinoma, squamous cell lung cancer, sarcomas, and melanoma. Most of all hepatic metastases arise from the primary cancer of digestive organs. The cystic hepatic metastasis with the original source of squamous cell lung cancer is rare.

The internal cystic portion of hepatic cystic metastasis develops from central necrosis when the tumor outgrows its blood supply (4). The clinical history of primary malignance, epidemic area exposure, or infectious manifestation offers help for its differential diagnosis, which is commonly regarded as hepatobiliary tumor, parasitic disease, infectious abscess, or metastasis. Imaging examinations like contrast-enhanced computed tomography (CT), magnetic resonance (MR), and ultrasound (US) are indispensable methods to differentiate these diagnoses (5, 6). 18F-Fluorodeoxyglucose (^{18}F-FDG) PET/CT has been applied as a useful tool for malignance staging due to its whole-body scan and glucose-metabolic assessment for metastases (7). However, it is still necessary to perform aspiration biopsy for definitive pathological diagnosis of hepatic cystic lesion (8). The biopsy sample indicates not only its pathological type but also its gene mutation situation, which is an important referent condition for target therapy and immunotherapy. Target therapy has been realized as a promising strategy for cancer treatment while lots of new target medicine have been applied in clinical practice (9). However, target gene mutation is the prerequisite for its effective response. Immunotherapy has been an efficacious therapeutic approach for hemopoietic system cancer, but the curative response is still unsatisfactory for solid tumor (10).

Here, we present a case of a patient with squamous cell lung carcinoma history who found an emerging isolated cystic mass in the liver. Radiological findings, tumor markers level, and ^{18}F-FDG PET/CT suggested metastasis, which was confirmed by pathological study after surgery. Despite of the combined treatment of chemotherapy, anti-angiogenic approach, and programmed cell death protein 1 (PD-1) blockage, the patient developed remote metastasis. Our case indicates that metastasis should be taken into consideration in emerging cystic hepatic lesion with malignant history.

Case presentation

A 47-year-old man was admitted to the hospital because of a newly detected mass in the liver. The MR scan (Figures 1C, F) showed the mass as an isolated hepatic cystic lesion with solid component, with an approximate size of 9.6 cm × 10.7 cm × 9.2 cm. The solid part demonstrated heterogeneous intensity in T1-weighted imaging (T1WI) and T2-weighted imaging

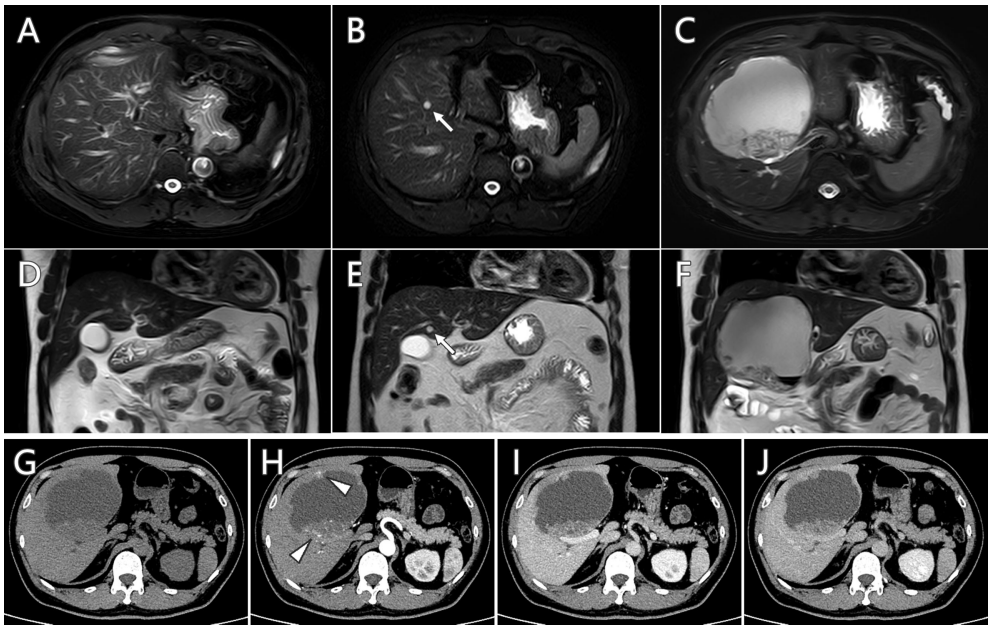

FIGURE 1
Serial follow-up MR imaging **(A–F)** and contrast-enhanced CT scan **(G–J)** of the hepatic cystic lesion. The newly detected lesion **(C, F)** did not exist 12 months ago **(A, D)** and emerged as a small cystic lesion 7 months ago (**B, E**, arrow). Mild enhancement at the solid parts (arrowhead) was observed in contrast-enhanced CT scan.

(T2WI). The MR scan showed hyperintensity in diffusion-weighted imaging (DWI) and hypointensity in apparent diffusion coefficient (ADC) map at the corresponding area. Historical MR studies indicated that the mass did not exist 12 months ago (Figures 1A, D) and emerged as a small cystic lesion 7 months ago (Figures 1B, E). Contrast-enhanced CT (Figures 1G–J) demonstrated mild enhancement at the solid parts of the mass. Serum tumor marker examination showed that the markers of CEA, CA724, CA199, and ProGRP ascended above normal level, while the markers of CA125, CA153, SCC-Ag, and NSE were at normal level. The liver enzyme of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase were elevated as well. In comprehensive consideration of radiological findings and tumor markers level, it suggested malignance.

The patient's medical history stated that he had tumorectomy in the left lung 4 years ago. The histopathological study of the lung tumor reported poorly differentiated squamous cell carcinoma. The immunohistochemical staining was positive for CK5/6, P63, P40, and CD56 and negative for TTF-1, CK7, NapsinA, ROS-1, C-MET, P53, Syn, and CgA. Ki–67 labeling index (Ki-67 LI) was about 80%. Epidermal growth factor receptor (EGFR) gene mutation examination result was negative. After surgery, he received six courses of chemotherapy (gemcitabine and nedaplatin) and 50 Gy of mediastinum radiotherapy, accompanied with two courses of recombinant human endostatin therapy. After that, serial follow-up examinations of CT, MR, and serum tumor markers showed no sign of recurrence in 4 years.

Considering the patient's malignance history, the hepatic mass suggested metastasis. ^{18}F-FDG PET/CT was performed for staging (Figure 2). Maximum intensity projection (MIP) image showed FDG-avid lesions in the liver, which were demonstrated as moderate tracer uptakes in solid parts of the mass, with SUVmax of 4.8–5.2. Since no other malignant lesions were detected in the PET/CT scan, the patient received tumor resection in November 2021 immediately. The pathological study (Figure 3) confirmed metastatic squamous cell carcinoma. The immunohistochemical staining reported positive for CK5/6, P40, P63, CK7, and CK19 and negative for CD56, Syn, CgA, hepatocyte, arginase-1, glypican-3, and CD10. Ki-67 LI was about 30%. Microsatellite instability examination reported stable results. No specific or clinically significant mutation was found for target therapy in lung cancer gene mutation examination, such as ALK, BRAF, EGFR, KRAS, MET, NTRK, PIK3CA, RET, and ROS1. The patient underwent chemotherapy (paclitaxel-albumin and nedaplatin) after surgery, accompanied with recombinant human endostatin therapy and sintilimab therapy. After surgery, the serum tumor markers level of CEA, CA724, and ProGRP declined immediately. However, the tumor marker of CA724 ascended again during chemotherapy (Supplementary Table S1), and the patient developed remote metastasis (Figure 4). Osteolytic metastatic lesions were found in the humerus bone and thoracic vertebra at the sixth course of chemotherapy. Despite of multiple anti-cancer strategy, it suggested disease progression and poor prognosis.

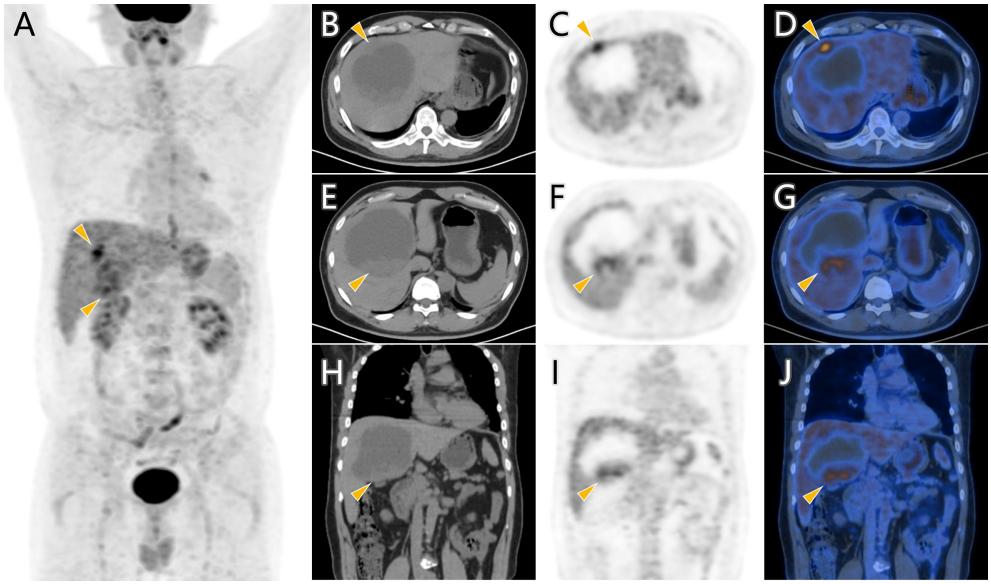

FIGURE 2
^{18}F-FDG PET/CT scan of the hepatic cystic mass. FDG-avid lesions (arrowhead) in MIP image **(A)** were demonstrated as moderate tracer uptakes in solid parts of the mass in axial images **(B–G)** and coronal images **(H–J)**.

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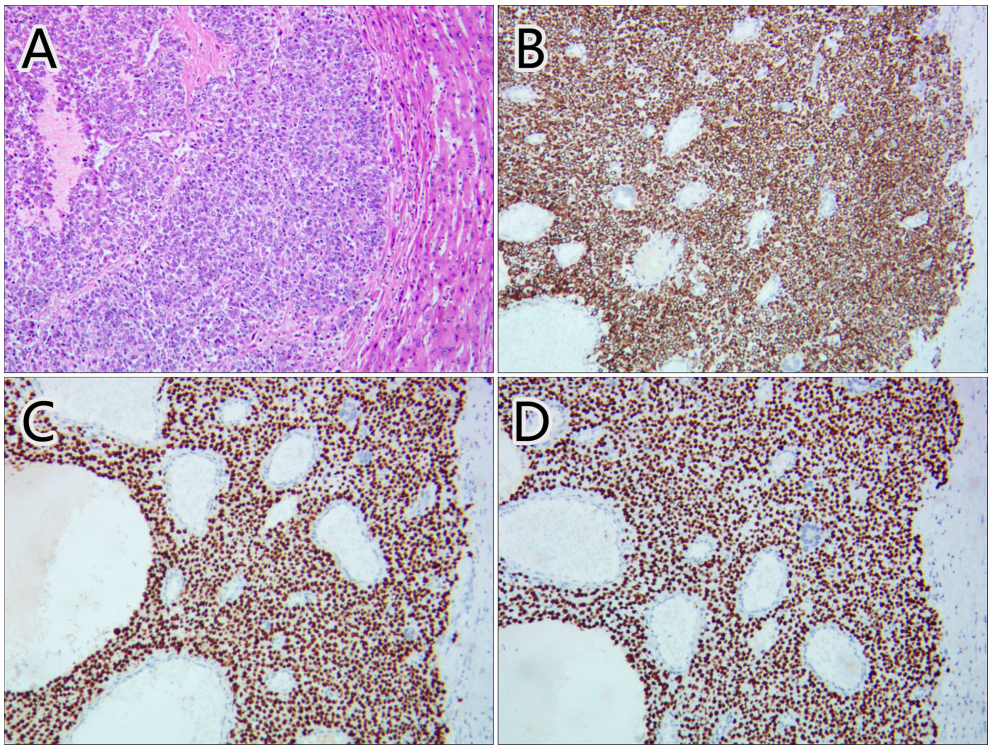

FIGURE 3
Pathological images of the hepatic mass. Hematoxylin–eosin staining **(A)** and immunohistochemical staining of CK5/6 **(B)**, P63 **(C)**, and P40 **(D)** confirmed the mass as metastatic squamous cell carcinoma.

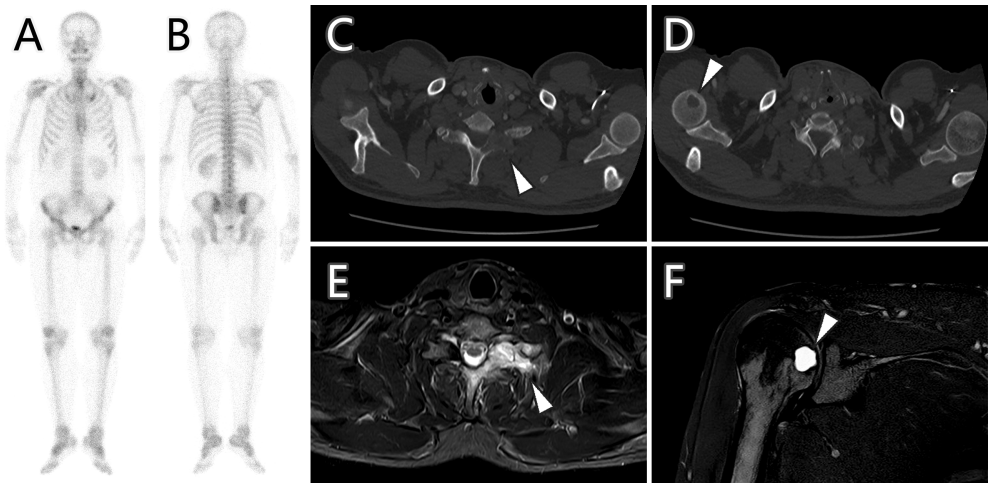

FIGURE 4
Bone scan, CT imaging, and MR imaging of bone metastases (arrowhead) after 6 months of treatment. Bone scan **(A, B)** showed no increased radioactive uptake, while CT imaging **(C, D)** demonstrated the metastases as osteolytic lesions with hyperintensity in MR spectral attenuated inversion recovery (SPAIR) sequence images **(E, F)**.

Discussion

The common primary sources for cystic hepatic metastasis are colon, kidney, prostate, ovary/testis, squamous cell carcinoma, gastrointestinal stromal tumor (GIST), and neuroendocrine tumor (1). The internal cystic portion may represent central necrosis as the tumor outgrows its blood supply, or mucinous component that is similar to the primary tumor, or secondary cystic degeneration such as GIST after imatinib treatment (2, 11, 12). Imaging examination is able to show the radiological characteristics of the hepatic cystic metastasis, such as size, border definitions, vessel displacement, and dynamic enhancement patterns. Hepatic metastases usually have hyperechoic component along with centrally hypoechoic lesions in US imaging. Cystic metastases are characterized as heterogeneous and ill-defined borders, irregular and incomplete septa, ragged inner surfaces with mural nodules, and enhanced rim in contrast-enhanced imaging examination in CT, MR, and US (13, 14). In our case, the MR and contrast-enhanced CT findings of the cystic metastasis were in accordance with the above-mentioned radiological characteristics. ^{18}F-FDG PET/CT has been applied as an effective examination in the field of benign and malignant diagnosis, prognosis evaluation, treatment efficacy evaluation, tumor recurrence detection, searching for an unknown primary with metastasis, biopsy guidance, and pre-surgical planning (15). The ^{18}F-FDG PET/CT scan in our case showed the malignance as a solitary mass with no other metastasis, which provided evidence for further surgical management.

The differential diagnoses of the hepatic cystic lesion can be divided into developmental, inflammatory, neoplastic, and trauma-related lesions (6, 16). Liver abscess is an important differential diagnosis for cystic hepatic metastases due to the complex symptoms or the indeterminate imaging features (17). In order to achieve more definitive diagnosis, it is necessary to integrate imaging examination with clinical and laboratory findings. Most of the hepatic cystic metastases share the same features with the primary tumor source. However, the metastasis in our case has its own characteristics. First, the metastasis was an isolated lesion, differing from multifocal lesions. Second, the cystic lesion initially resembled a simple liver cyst with fast growth and evolved into a cystic mass, which was different from solid metastasis developing necrosis due to insufficient blood supply (18). This atypical feature has also been illustrated in another case report of a nasopharyngeal carcinoma (NPC) patient who found liver cystic lesion after chemoradiotherapy, which initially resembled a simple liver cyst with fast growth and evolved into an abscess-like mass (14). Third, the moderate FDG uptake of the cystic lesion also differed from strong tracer uptake of regular primary squamous cell carcinoma in PET/CT scan. This case indicates that it may present dissimilar tumor behavior between original tumor and metastatic lesion. Moreover, the original tumor in this case is a poorly differentiated carcinoma, which may develop more variability and heterogeneity in metastasis than well-differentiated carcinoma (19). The spatial and temporal variability of biomarkers in solid tumors has been reported to explain the discrepancies between primary tumor and metastasis, suggesting the development of personalized medicine in oncology (20).

Despite of its rarity, cystic hepatic metastases of squamous cell carcinoma have been reported in other articles with various primary origins. Here, we present some cases that have exhibited representative characteristics. The first case noted that a large, well-defined, lobulated cystic lesion with poor contrast enhancement occupying both lobes of the liver was detected in a 52-year-old man who had NPC history 4 years ago (21). The biopsy of the hepatic cystic lesion reported poorly differentiated squamous cell carcinoma, and *in situ* hybridization for Epstein–Barr virus early RNAs confirmed the diagnosis of metastatic NPC. The second case was a 38-year-old female patient who had been diagnosed with cervical squamous cell carcinoma 10 months ago (22). The PET/CT scan found a cystic lesion in the liver after radiotherapy, which was diagnosed as squamous cell carcinoma metastasis by aspiration biopsy. The third case was a 69-year-old woman who had anal squamous cell carcinoma and underwent chemoradiotherapy and salvage abdominoperineal resection (23). She developed multifocal cystic lesions in the liver after surgery, and the lesions were revealed as metastatic squamous cell carcinoma by cytology of liver drainage and liver biopsy. All the above cases indicate that the hepatic metastasis of squamous cell carcinoma may have pseudocystic presentation; therefore, biopsy is necessary to manage definitive diagnosis.

Target therapy and immunotherapy have been realized as effective strategies for cancer management. These strategies use small pharmacological agent or monoclonal antibody in cancer lesions to prevent growth signal, stop angiogenesis signal, inhibit hormone supply, trigger cell death, or assist immune system recognition (24), which demonstrate dramatic therapeutic response. Our case showed no specific mutation in lung cancer gene mutation examination; thus, he could not benefit from specific target therapy against EGFR, ALK, BRAF, etc. Endostatin has the activity as modifiers of both angiogenesis and endothelial cell autophagy (25). A meta-analysis has investigated recombinant human endostatin combined with chemotherapy in patients with squamous cell lung cancer, which indicated better therapeutic effect by the combined treatment than chemotherapy alone, with no increased incidence of adverse reactions (26). In our case, the patient was tumor free for 44 months after the primary lung carcinoma treatment with endostatin and chemoradiotherapy. As an anti-PD-1 monoclonal antibody, sintilimab has been approved for squamous and non-squamous lung carcinoma in China, and the combination of sintilimab with other anti-cancer strategies have shown promising therapeutic efficacy (27). In a phase 3 clinical trial study of sintilimab plus platinum and gemcitabine as the first-line

treatment for advanced or metastatic squamous non-small cell lung cancer, the combined treatment revealed better progression-free survival than platinum and gemcitabine treatment (28). However, in our case, the endostatin and sintilimab treatment did not prevent remote metastasis after the secondary hepatic metastasis therapy, suggesting poor prognosis.

In conclusion, our case indicates that metastasis should be taken into consideration when emerging cystic lesion is observed in the liver, especially in a situation with malignant history.

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

CL contributed to data acquisition and analysis, literature review, and manuscript drafting and revision. XC and HS acquired examination image and interpreted data. LX collected the patient's necessary information (including the laboratory test results, the examination results, and the pathological reports). DL supervised the information collection and revised the manuscript. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.986603/full#supplementary-material

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Case report: Significant response to PD-L1 inhibitor after resistance to PD-1 inhibitor in an advanced alpha-fetoprotein-positive gastric cancer

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Alpha-fetoprotein-positive gastric cancer (AFPGC) is a type of gastric cancer with a high degree of malignancy. The disease is more common in the elderly, with a high prevalence in males and generally atypical clinical manifestations. For advanced patients, the current treatment options are limited and, to date, few cases of advanced AFPGC have been treated successfully with conventional chemotherapy. With the development of molecular biology and immunology, tumor immunotherapy offers more therapeutic options to patients with advanced gastric cancer. This study describes a case of advanced gastric cancer in a young woman with a high blood alpha-fetoprotein (AFP) level (>54,000 ng/mL). The patient showed initial promising results when programmed cell death-1 (PD-1) inhibitor treatment was combined with chemotherapy after systemic chemotherapy failed. When the disease progressed again after 129 days, adjustment of the treatment regimen to Atezolizumab in combination with Irinotecan and Surufatinib capsules achieved partial remission (PR). There were no immune-related pneumonia, myocarditis, or other adverse effects observed. The patient currently has an overall survival of more than 14 months. This case demonstrated that switching from PD-1 inhibitor to programmed cell death-Ligand 1 (PD-L1) inhibitor therapy may overcome potential resistance. It providing a reference for immunotherapy of patients with AFP-positive advanced gastric cancer.

KEYWORDS

positive alpha-fetoprotein, gastric cancer, PD-1, immunotherapy, chemotherapy

Introduction

Gastric cancer with elevated serum AFP levels confirmed histopathologically after excluding hepatitis, cirrhosis, hepatocellular carcinoma, germ-cell malignancy, and other illnesses that may cause AFP is referred to as AFPGC (1). AFPGC is considered to be one of the most aggressive tumor subtypes in gastric cancer. It has been reported that AFPGC accounts for 2.3%~7.1% of total gastric cancer in Asian countries and about 15% of total gastric cancer in western countries (2). It was reported that patient age, TNM stage and curable surgery were found to be associated with overall survival. The younger AFPGC patients are prone to have a more detrimental prognosis. A high level of AFP is an independent prognostic risk factor for gastric cancer because AFP is not only a product of the tumor but also plays a crucial role in proliferation, apoptosis, and angiogenesis of AFPGC cells (3). AFP has been reported to have a suppressive effect on lymphocyte transformation, to enhance tumor cell proliferation through the HGF and c-Met pathway (4), and to increase angiogenesis *via* Vascular Endothelial Growth Factor (VEGF) expression (5).

According to the World Health Organization (WHO) (2019) classification of gastric cancer, serum AFP may be elevated in several types of gastric adenocarcinoma, such as hepatoid adenocarcinoma and gastric adenocarcinoma with enteroblastic differentiation. Previous research has found that serum AFP levels are an independent risk factor impacting patient survival (6), and there is currently no effective treatment for AFPGC.

Here, we report the case of a 37-year-old woman suffering from gastric cancer with an extremely high expression of serum AFP level (>54,000 ng/mL). The patient showed initial promising results when PD-1 monoclonal antibody (mAb) treatment was combined with chemotherapy after systemic chemotherapy failed. When the disease progressed again after 129 days, adjustment of the treatment regimen achieved PR.

Case description

In January 2021, a 37-year-old woman complained of right upper abdomen discomfort and mild tenderness in a prone posture. She also had felt a palpable mass in the right upper abdomen. Physical examination revealed an enlarged liver with a bulge and palpable mass in the right abdomen. The lower margin of the enlarged liver was at the right midclavicular line about the level of the navel. The patient had tenderness in the liver area, and the Numeric Rating Scales (NRS) score was 2 points. The patient had no tumor-related family history and denied having a chronic liver illness (hepatitis, cirrhosis, and primary liver cancer) or combined reproductive system tumors. After hospitalization, an enhanced Computed Tomography (CT) examination was performed to further evaluate the patient's condition, which showed there were multiple nodular lesions in the liver with local gastric wall thickening (Figure 1A). Among the tumor markers, AFP levels were significantly elevated to more than 54,000 ng/ml (normal level: < 12 ng/ml), and the serum carcinoembryonic antigen (CEA) levels were 22.82 ng/ml (normal range: < 5 ng/ml) (Figures 2A, B). Gastroscopy revealed a giant crateriform ulcer within the stomach body (Figure 3A), and pathological examination showed a poorly differentiated adenocarcinoma. Immunohistochemical labeling revealed the presence of proficient mismatch repair (pMMR)/microsatellite stability (MSS) as well as deficiencies in Human Epidermal growth factor Receptor 2 (HER2) and EBV-encoded RNA (EBER) hybridization (Figures 3B–D). The patient was diagnosed with poorly differentiated gastric adenocarcinoma with liver metastases (HER2 negative). Meanwhile, the patient was a gastric cancer with elevated serum AFP levels. Hepatitis, liver cirrhosis and other diseases that may lead to elevated AFP were excluded. Therefore, this patient was an advanced AFPGC patient.

The patient received first-line chemotherapy in a two-drug combination regimen of paclitaxel liposome for injection and S-1 (tegafur/gimeracil/oteracil potassium). After two sessions of therapy, the disease status was stable, as determined by imaging. Then, in the third course, the S -1 dose was increased to 60 mg orally twice daily from day 1 to day 14 and continued to be combined with 210 mg paclitaxel liposome for injection. However, following the third session of chemotherapy, the patient reported that the upper abdominal distension was worse than before, and her AFP levels was consistently greater than 54,000 ng/ml. After communicating with the patient and completing the informed consent form for immunotherapy, the patient began to receive 200mg Tislelizumab injections in combination with 200mg Oxaliplatin treatment on April 17, 2021, every 21 days as a course. After two courses of treatment, the patient's abdominal distension was relieved. An abdominal CT scan indicated that the liver lesions were smaller than before, and gastric wall thickening was reduced. The imaging evaluation showed that the disease status was stable. The original regimen was continued for two courses, and imaging was performed after the fourth course to assess PR (Figure 1B). Regular reexamination showed a progressive decrease in AFP level to 7169 ng/ml and the CEA level dropped to within the normal range (Figures 2A, B). The patient's symptoms of pain in the liver area had been relieved and subsequently the analgesic drugs were stopped.

At 6 months post-diagnosis, the serum level of AFP had increased again to 21,520 ng/ml (Figure 2A). At the same time, CT revealed that the liver lesions had increased in size again (Figure 1C). The curative effect was evaluated as progressive disease (PD). Then, the patient was given third-line therapy of Tislelizumab combined with Apatinib 250 mg once a day for 3 cycles from August 23, 2021 to October 5, 2021. Unfortunately, the patient did not respond well to this treatment, and

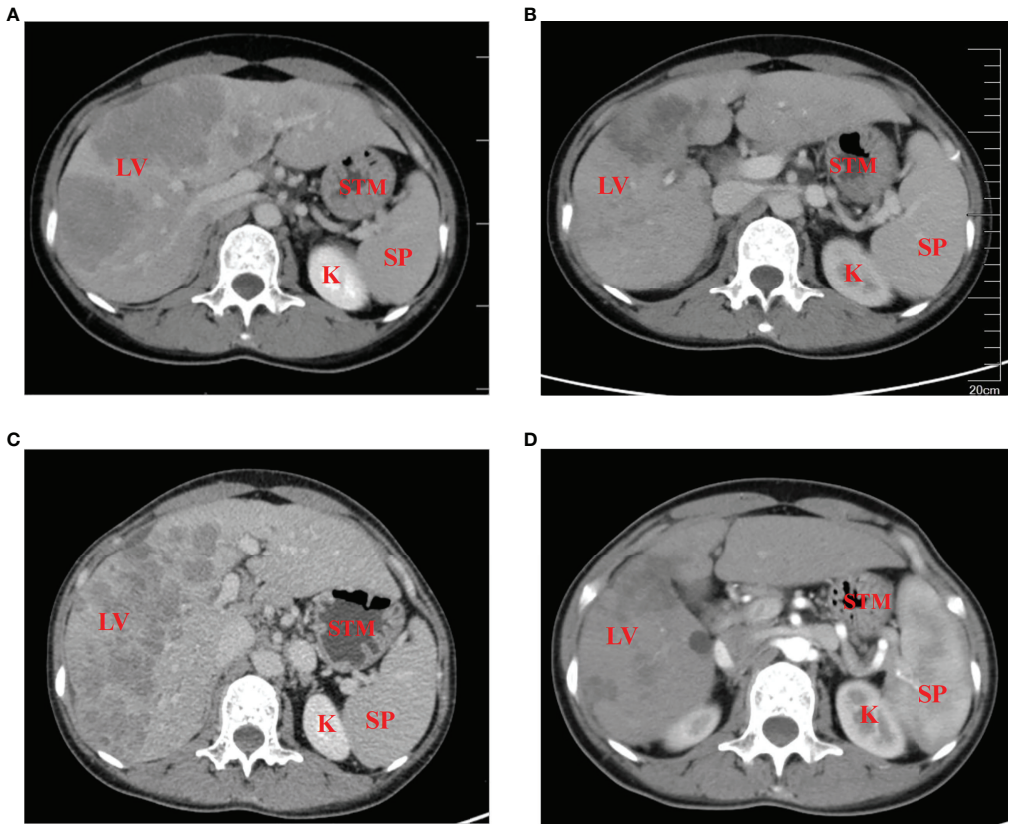

FIGURE 1
Contrast-enhanced CT scans of the patient **(A)** prior to, and **(B)** 5 months after the initiation of therapy. **(C)** At 6 months post-diagnosis, the curative effect was evaluated as progressive disease, with no effect of third-line therapy of Tislelizumab combined with Apatinib. **(D)** The disease returned to partial remission after treatment with the fourth-line treatment. LV, liver; STM, stomach; SP, spleen; K, kidney.

radiographic assessments continued to show progression of the disease. Therefore, a fourth-line treatment of Atezolizumab in combination with Irinotecan and Surufatinib capsules was considered from October 27, 2021. After 2 cycles of treatment, CT evaluation showed that the efficacy achieved PR again (Figure 1D), blood examination showed a progressive decrease in AFP level to 12,238 ng/ml (Figure 2A). Considering this positive response, another 5 cycles of Atezolizumab in combination with Irinotecan and Surufatinib therapy were conducted with the last treatment on March 23, 2022, and the efficacy was assessed as sustained PR.

The therapy was well tolerated by the patient during the whole treatment process, and the main adverse reactions were bone marrow suppression (leucopenia of 2 degrees) and digestive tract reactions (nausea and vomiting), which improved after treatment with Granulocyte-colony-Stimulating-Factor (G-CSF) and enhanced antiemetic therapy. There were no immune-related pneumonia, myocarditis, or other adverse effects observed. The patient currently has an overall survival of more than 14 months.

Discussion

AFPGC is a special and rare subtype of gastric carcinoma. The histological diagnosis of AFPGC is more common in poorly differentiated adenocarcinoma, which is strongly associated with larger tumor volume, deeper serous membrane infiltration, and higher levels of invasion, lymph node, and liver metastasis (7). AFPGC has a poorer prognosis than AFP-negative gastric cancer. The median survival of advanced AFPGC is about 9.3 months (8).

There is currently no standard treatment for this type of gastric cancer. However, early radical resection and active postoperative adjuvant chemotherapy have been shown to enhance the prognosis of AFPGC patients. For patients who have lost the chance of surgical treatment in the late stage, there is little literature on treatment. At present, the chemotherapy plan is mostly referred to as common gastric cancer, but the efficacy is worse than that of common gastric cancer. The median Overall Survival (OS) of patients is 9.3 months, and the 5-year survival rate is less than 20% (9). In 2018, Wang

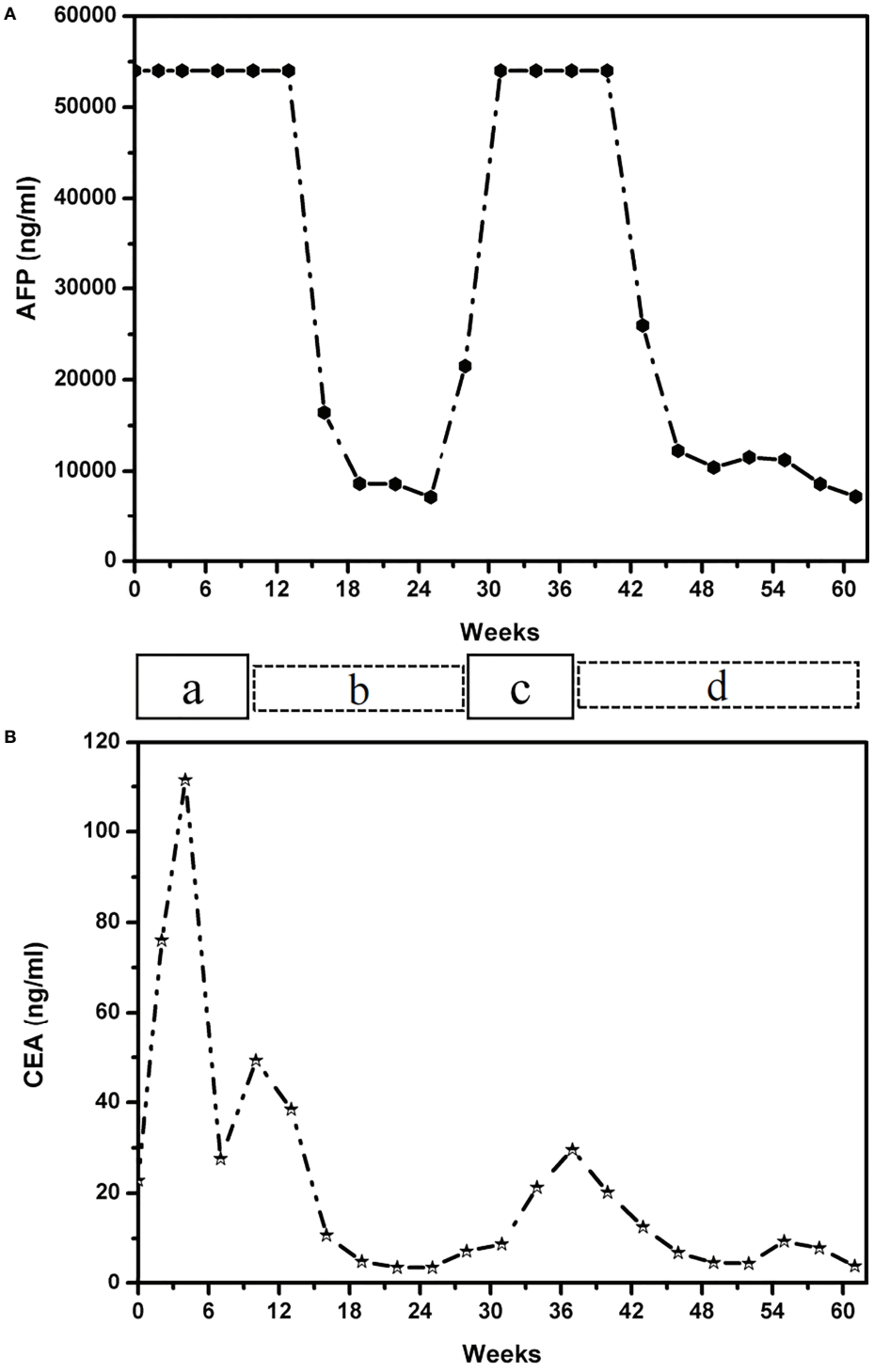

FIGURE 2
Graph depicting the patient's therapeutic course and serum tumor marker of AFP levels **(A)** and CEA level **(B)**. The patient received the following treatments: a, paclitaxel liposome plus S-1 (tegafur/gimeracil/oteracil potassium); b, Tislelizumab combined with Oxaliplatin; c, Tislelizumab combined with Apatinib; d, Atezolizumab in combination with Irinotecan and Surufatinib capsules. AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen.

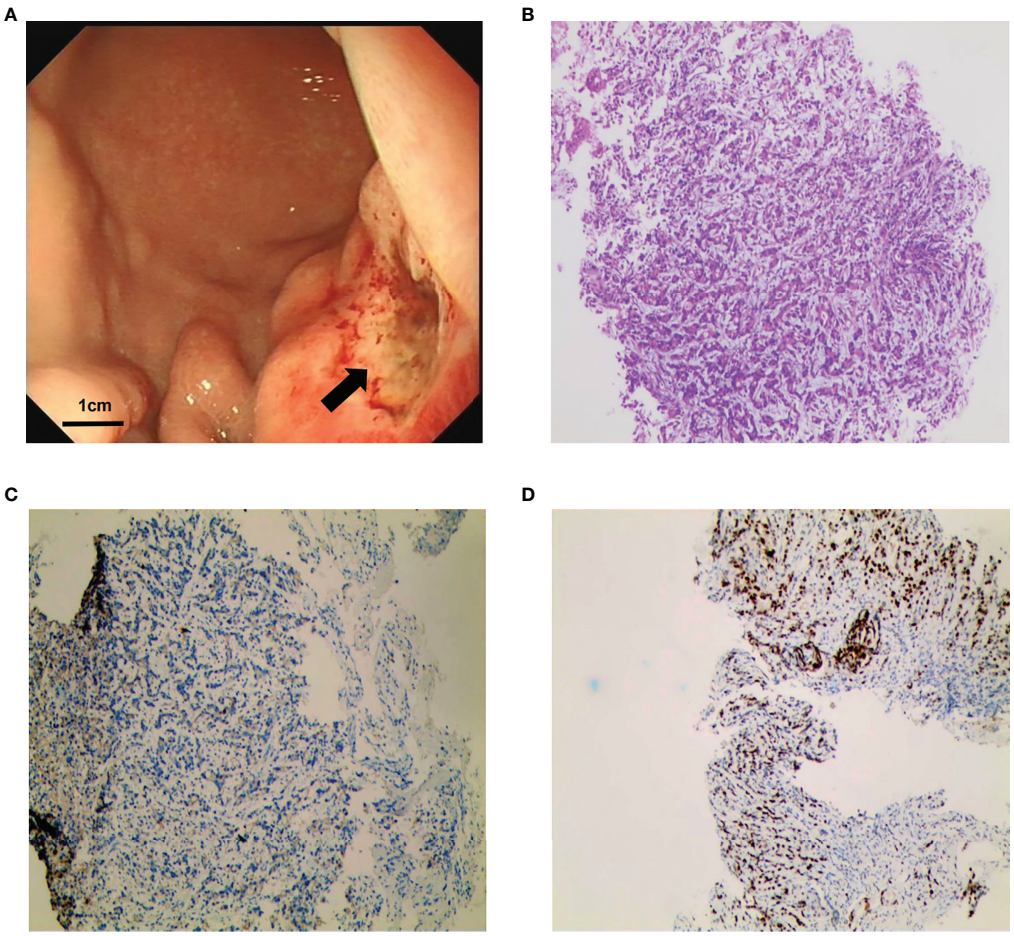

FIGURE 3
Gastroscopy and gastric biopsy pathology results. **(A)** Image of gastroscopy results, showing a tumor located at the body of the stomach (as indicated by the arrows). **(B)** Histopathological examination revealed poorly differentiated gastric adenocarcinoma (hematoxylin and eosin staining; magnification, ×100). **(C)** Negative staining for HER2 (magnification, ×100). **(D)** Positive staining for Mut L homolog 1 (MLH1) (magnification, ×100).

reported the efficacy of different chemotherapy regimens in 105 patients with advanced AFPGC, and the Overall Response Rate (ORR) of the platinum-based triple regimen was 56.1%, which was better than that of double-regimen (26.3%) (10). in 2021, Li reported that three patients received oral Apatinib 500 mg once a day combined with XELOX (Oxaliplatin/Capecitabine). One patient reached PR with progression-free survival(PFS) for more than 13 months in the first line treatment, and the other for 7 months, the third one had PFS for 3 months (11). Arakawa also reported that Ramucirumab targeting Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) had some efficacy in AFPGC patients with an OS of 16 months (12). In this case, the patient was confirmed to have multiple liver metastases at the time of diagnosis and lost the opportunity of surgical treatment. The patient failed to benefit from the first-line two-drug combined chemotherapy, and did not respond to Apatinib, which confirmed that the therapeutic effect was worse than that of ordinary gastric cancer, and the patient's treatment options were limited.

Immunotherapy has demonstrated some efficacy in the treatment of advanced gastric cancer in recent years. The checkmate-649 study (13) showed that the combination of Nivolumab and chemotherapy increased the duration of PFS and OS in patients with Combined Positive Score (CPS) ≥ 5 and CPS ≥ 1 compared with chemotherapy alone, and a statistical difference was seen in the entire population (13.8 months versus 11.6 months, HR = 0.80). The results of ATTRACTION-4 showed that the median PFS time (10.5 months: 8.3 months, HR=0.68) and ORR (57.5% vs 47.8%, P=0.0088) were significantly better than those of chemotherapy alone. Furthermore, this was population-wide research with no molecular marker selected (14). The results of the Checkmate-649 and ATTRACTION-4 studies confirm the role of immunochemotherapy in the first-line treatment of gastric

cancer. However, few studies have reported on the efficacy of advanced AFPGC immunotherapy. The patient described here, was a young female with MSS molecular typing and HER2 negative expression. The patient came with extensive liver metastasis and a significant tumor load. If the first therapy was ineffective, the patient might expect to live for only a short time. This patient did not benefit significantly from the three courses of first-line chemotherapy, and the AFP level was continuously above the critical value of 54,000 ng/ml. Due to the limited pathological tissue obtained by gastroscopy, the detection of PD-1 expression level could not be carried out. In the case of unknown PD-1 expression level, we chose Tiralizumab immunotherapy combined with oxaliplatin chemotherapy as the second line treatment. After 2 cycles of treatment, the AFP level decreased significantly and liver lesions shrank. PR was achieved after 4 cycles of treatment. The patient was relatively sensitive to PD-1 mAb combined with chemotherapy, but the remission period was short. Previous data suggest that Apatinib targeted anti-angiogenesis therapy was an effective way to overcome AFPGC. But unfortunately, this patient did not show efficacy in the treatment regimen of third-line. Sorafenib is one of the anti-VEGF drugs that has been reported to be effective (15, 16), but has not been reported in the treatment of AFPGC. In this case, the patient was changed to the PD-L1 ab therapy, when PD1 mAb resistance progressed. Surprisingly, it was found that the treatment effect was very good, and achieved immunotherapy re-challenge successfully. It demonstrated that switching from PD-1 inhibitor to PD-L1 inhibitor therapy may overcome potential resistance. The main mechanism is that PD-L1 mAb not only inhibit the PD1-PDL1 pathway, but also can activate DC cells and T cell functions by blocking the co-inhibition of B7.1 and PD-L1. At present, the disease is still in remission, there were no obvious adverse reactions during the whole treatment and it was well tolerated by the patient. The rise and fall in serum AFP levels during treatment were found to be positively correlated with the patient's condition, and elevation of serum AFP level may be detected prior to appearance of symptoms and imaging detection. Therefore, measuring the serum AFP levels as a follow-up marker is an important means that can be used to evaluate condition changes of a patient.

With the emergence of a new generation of gene sequencing technology, gastric cancer can be divided into different subtypes, based on gene mutations. In 2014, TCGA (The Cancer Genome Atlas) reported the results of genomic mapping of 295 cases of primary gastric Cancer and established four genomic subtypes (17), including microsatellite instability (MSI), Epstein-Barr virus infection (EBV+), and tumors with low aneuploidy (GS) genomic stability and high aneuploidy (CIN) chromosomal instability. According to Arora (18), loss of heterozygosity (LOH) is common in gastric cancer and can lead to chromosomal instability and the loss of tumor suppressor genes. The majority of tumors with increased AFP expression were categorized as chromosomal instability subtypes, with a 72% median index of allele loss. This was 50% higher than normal gastric adenocarcinoma. Patients with AFPGC may respond to immunotherapy due to their unique genetic characteristics. In addition, other studies demonstrated that CIN is a driver of metastatic progression, which may partially contribute to the aggressive phenotype of AFPGC. In all, the identification of these potential tumor drivers raises the potential for tumor-specific immunotherapy.

Previous research reported that several molecular factors such as Vascular Endothelial Growth Factor-C (VEGF-C), Signal Transducer and Activator of transcription 3 (STAT3), and Hepatocyte Growth Factor (HGF) seem to over-expressed more frequently in AFPGC than in stage-matched non-AFPGC (5, 19). Chen (20) found that ANGPTL6 is an important driver gene of angiogenesis in AFPGC development. ANGPTL6 promotes endothelial cell migration and tube formation through activation of ERK1/2 and AKT pathways. ANGPTL6 knockdown inhibits cancer cell apoptosis and invasiveness. These findings provide not only effective biomarkers for diagnosis but also attractive therapeutic targets for AFPGC patients.

In conclusion, AFPGC, as a special type of gastric cancer, has a low incidence but a high degree of malignancy. Improving the understanding of this type of gastric cancer can avoid misdiagnosing it as common gastric adenocarcinoma and underestimating its malignancy. At present, only a few cases have been reported on the conversion of PD-L1 mAb after the progress of PD-1 mAb therapy, and there is still a lack of large-scale prospective studies. However, there are still many open questions, for example, how to choose the treatment plan after the progress of PD-L1 mAb therapy? How to optimize the immune combination therapy model? Despite the need of further studies to tackle those questions, this case report represents an important exploration and potential breakthrough in the treatment of advanced gastric cancer with immunotherapy.

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 human participants were reviewed and approved by the ethics committee of Suzhou Municipal Hospital. 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

Conceptualization: FG, JS and TZ. Attending physicians for the patient: YF and LZ. Writing—original draft: LW. Editing draft: AH and BL. Supervision, FG, JS, and QZ. All authors contributed to the article and approved the submitted version.

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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.

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Esophageal low-grade intraepithelial neoplasia overlying multiple leiomyomas: A case report and review of the literature

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Background: Esophageal leiomyoma is the most common benign submucosal mesenchymal tumor. Esophageal intraepithelial neoplasia includes low-grade and high-grade intraepithelial neoplasia. The coexistence of epithelial lesions and the subepithelial lesion is rare. We recorded a case of esophageal low-grade intraepithelial neoplasia (LGIN) overlying multiple esophageal leiomyomas and followed with a review of the literature.

Case presentation: A 49-year-old female patient came for the treatment of esophageal lesions. The submucosal eminences were observed in the right posterior wall and the left anterior wall of the esophagus by Esophagogastroduodenoscopy (EGD). Additionally, we noticed the mucosa of the right wall with brown background color and the dilated, tortuous vessels by narrow-band imaging (NBI). Then we ensured that the submucosal lesions originated from the esophageal mucosal muscle by endoscopic ultrasonography (EUS) and enhanced CT. Subsequently, the submucosal eminence of the right posterior wall and the overlying mucosal lesion were removed together by endoscopic submucosal dissection (ESD). Postoperative pathological diagnosed esophageal submucosal leiomyoma with focal LGIN. Review EGD showed white scars on the right wall of the upper esophagus three months later, while pathological biopsy showed slight squamous epithelial hyperplasia in the left wall. We decided that the left submucosal lesion can be resected at a selective-time operation, and we continue to follow up as planned.

Conclusions: The case of intraepithelial neoplasia overlying the submucosal tumor is rare. Either missed diagnosis or overdiagnosis should be avoided through EGD and pathological biopsy.

KEYWORDS

esophageal low-grade intraepithelial neoplasia, multiple leiomyomas, overlying, case report, endoscape

Introduction

The coexistence of epithelial lesion and subepithelial tumor is rare. There were few case reports about the coexistence of esophageal leiomyoma and esophageal severe dysplasia (1–3) and early and advanced (4–7) esophageal squamous cell carcinoma (8–13) since 1987. Some of them were misdiagnosed as advanced esophageal cancer and received surgical operation, while other cases were only diagnosed as esophageal leiomyomas, which were found to be esophageal leiomyomas complicated with early or advanced esophageal cancer by pathological examination after endoscopic or surgical therapy. We recorded a case of esophageal low-grade intraepithelial neoplasia (LGIN) overlying multiple leiomyomas and followed with a review of the literature.

Case presentation

Symptoms and personal history

A 49-year-old female patient came to our hospital for the treatment of esophageal high-grade intraepithelial neoplasia overlying subepithelial tumor, which was confirmed at another hospital 4 months ago (Table 1). She complained of throat discomfort and mild dysphagia, which appeared after solid food, and without history of family malignancy and cigarette or alcohol use.

Physical and serological examination

Physical examination findings were typically normal. Serological examination showed no obvious abnormality.

Abbreviations: EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasonography; IEN, Intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia; RFA, radiofrequency ablation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NBI, narrow-band imaging.

Esophagogastroduodenoscopy

Esophagogastroduodenoscopy (EGD) demonstrated submucosal eminences in the right posterior wall and the left anterior wall of the esophagus, 18–25 cm away from the incisor teeth, with the widest diameter of about 1.5 cm. Multiple redness and shallow depressions were discovered on the right posterior wall surface additionally (Figure 1A). We noticed the mucosa of the right wall with brown background color by using narrow-band imaging (NBI) (Figure 1B). Meanwhile, the dilated and tortuous intrapapillary capillary loops with homogeneous distribution and increased density were displayed in the mucosa of the right wall under NBI-near focus (Figure 1C). There was no other special finding, such as hiatus hernia, reflux esophagitis, and gastric submucosal lesion on her esophagogastroscopy.

Endoscopic ultrasonography

We definite the origin and character of the lesion by endoscopic ultrasonography (EUS). We found that esophageal epithelial lesions are clearly stratified, while subepithelial lesion displayed as multiple uniform hypoechoic, irregularly shaped, and clear-boundary masses, which originated from the esophageal mucosal muscle layer and protruded to the cavity inside and outside. The largest one had an ultrasonic diameter of about 9.9×6.9 mm (Figure 1D).

Enhanced chest computed tomography

Enhanced chest CT showed that the wall of the upper and middle segments of the esophagus was slightly thickened and the lumen slightly narrowed (Figure 2).

Treatment and management

Endoscopic treatment

Subsequently, the submucosal eminence of the right wall (18–25 cm away from the incisor) and the overlying mucosal

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TABLE 1 Histopathological features.

Time of sampling	Method of sampling	Location of sampling	Type of staining	Results of pathology
23/07/2021 (another hospital)	Biopsy	Esophagus (20 cm away from the incisor)	HE	Chronic inflammation with focal squamous epithelium HGIN
16/08/2021	Specimen of ESD	Esophagus (the right posterior wall, 18–25c m away from the incisor)	HE	A submucosal spindle cell tumor of focal squamous epithelium with LGIN
		Submucosal tumor (SMT)	SMA	Positive
			Desmin	Positive
		Epithelial layer of mucous membrane	Ki-67	Positive (1%)
22/11/2021	Biopsy	Esophagus (the left wall, 18–21 cm away from the incisor)	HE	The squamous epithelium is mildly hyperplasia

HE, hematoxylin–eosin staining; HGIN, high-grade intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia; ESD, endoscopic submucosal dissection; SMA, smooth muscles actin.

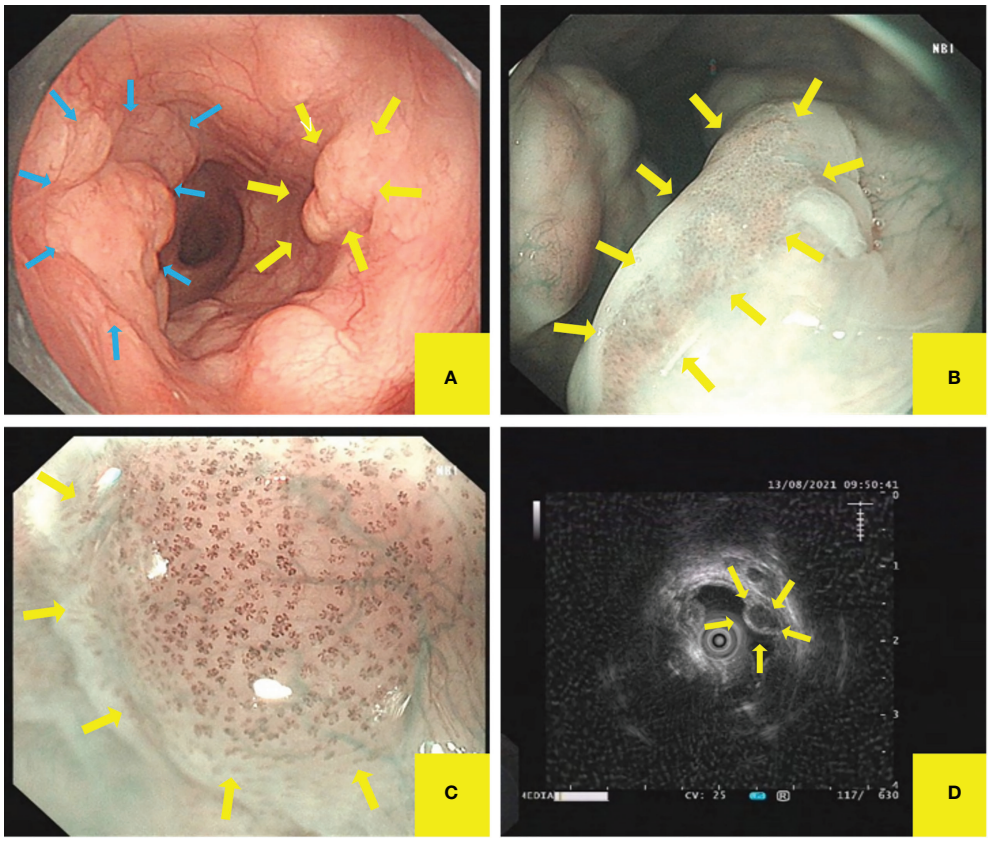

FIGURE 1
Esophagogastroduodenoscopy (EGD) and endoscopic ultrasonography (EUS) demonstrated esophageal mucosal and submucosal lesions. **(A)** The submucosal eminences were observed in the right posterior wall and the left anterior wall of esophagus. **(B, C)** Multiple shallow red depressions were observed on the right posterior wall surface. The mucosa background color was noticed by NBI, while the dilated and tortuous vessels on the top of the lesion were observed by NBI near focus. **(D)** EUS showed uniform hypoechoic inside, irregularly shaped, clear-boundary esophageal multiple hypoechoic mass, which originated from the mucosal muscle layer.

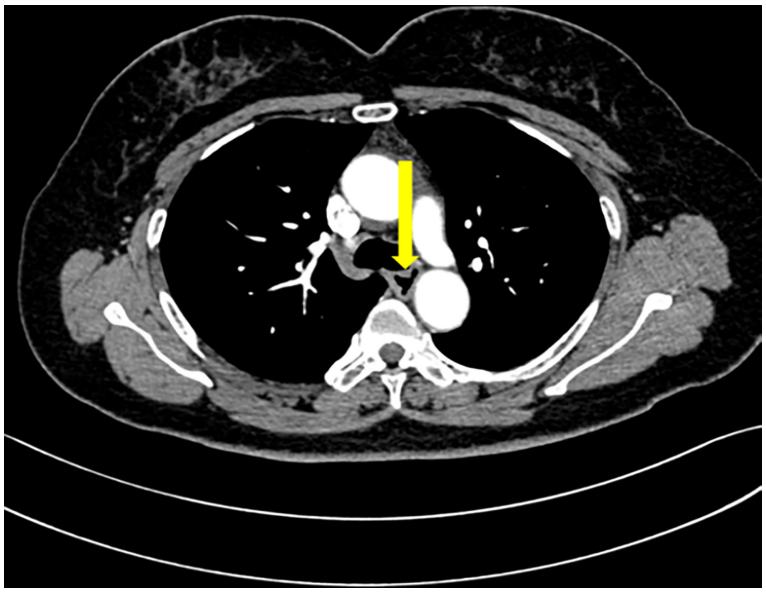

FIGURE 2
Enhanced chest CT. Enhanced chest CT showed that the wall of the upper and middle segments of the esophagus was slightly thickened and the lumen slightly narrowed.

lesion were removed together successfully by ESD without intraoperative complications such as bleeding and perforation, while the submucosal eminence of the left wall was not treated temporarily (Figure 3A).

Pathohistology

We observed the gross specimens after iodine staining and noticed unstained or lightly stained area located mainly at the top of the eminence (Figure 4A), which may be related to long-term friction and chronic inflammation. Pathological examination demonstrated submucosal spindle cell tumor with focal squamous epithelium LGIN in the esophagus through hematoxylin–eosin (HE), and finally diagnosed as submucosal leiomyoma with focal LGIN by immunohistochemistry staining (Table 1 and Figures 4B–G).

Management of follow-up

The patient was discharged 3 days later and arranged for follow-up 3 months after therapy. When she came back for follow-up, she represented that the symptoms of swallowing

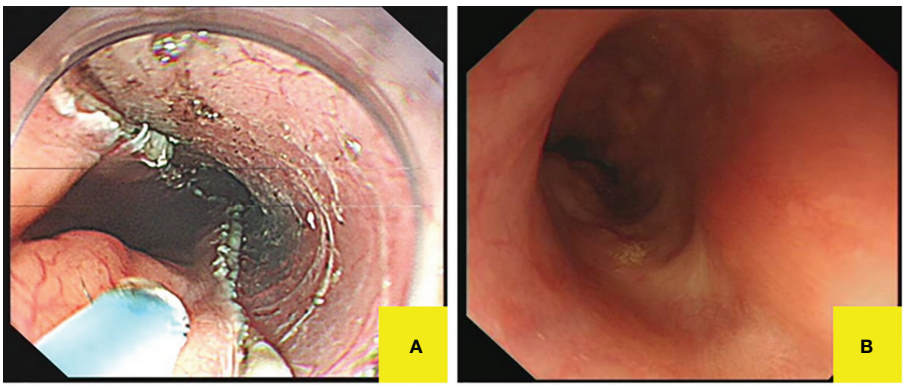

FIGURE 3
Postoperative endoscopic manifestations. **(A)** The right posterior wall lesion was completely resected without intraoperative complications. **(B)** Follow-up gastroscopy displayed white scars on the right lateral wall of the upper esophagus.

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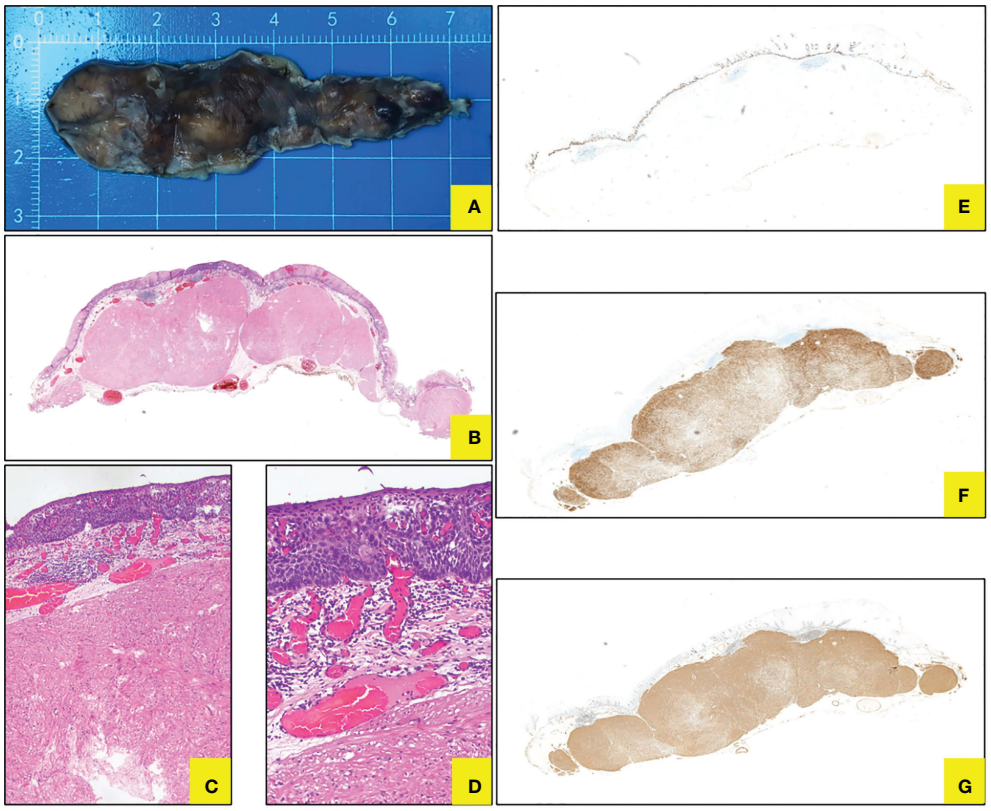

FIGURE 4
Histopathology for ESD specimen. **(A)** Gross specimen after ESD *in vitro*. **(B–D)** Coexistence of submucosal spindle cell neoplasm and focal squamous LGIN in HE staining (*10, 40, 100). **(E)** Ki76 showed LGIN. **(F)** Desmin staining displayed leiomyoma. **(G)** SMA staining displayed leiomyoma.

obstruction were relieved. Follow-up EGD noticed white scars on the right wall of the upper esophagus (Figure 3B), while there was a longitudinal submucosal eminence (18–21 cm away from the incisor) at the left wall, which showed a light brown color change without confirmed demarcation line under NBI. Then, we made the biopsy of the left mucosal lesion, and pathobiology showed slight squamous epithelial hyperplasia in the esophagus (Table 1). Then, we made a decision together that the left submucosal lesion can be resected on a selective-time operation, since the esophageal leiomyoma is a benign submucosal tumor and her symptoms have been relieved. We continue to follow up and arranged the next follow-up 1 year later.

Discussion and conclusions

The coexistence of esophageal leiomyoma and esophageal squamous cell carcinoma can be classified into two types: the overlying type and the separate type (3). The overlying type is rare, let alone multiple leiomyomas covered with esophageal LGIN. To our knowledge, there are no reports about esophageal LGIN overlying multiple leiomyomas before.

Esophageal leiomyoma, which stems from the smooth muscle or muscularis mucosa of the esophagus, is the most common benign submucosal mesenchymal tumor (14, 15). Esophageal leiomyoma can be asymptomatic and found accidentally (7, 9), and the incidence in autopsy series ranges from 0.005% to 5.1% (16, 17). It usually appears as a solitary tumor (97%) (11), and multiple leiomyomas are extremely rare. EGD and EUS can be used to diagnose leiomyoma. EUS can define the layer from which the SMT originates and determine an adequate endoscopic resection strategy (6), which has high diagnostic reliability (18). However, Sheng (19) reported that simple EGD and EUS may miss the diagnosis of leiomyoma combined with esophageal cancer or misdiagnose stromal tumor as leiomyoma. The endoscopic features of esophageal LGIN include mucous membrane turning to red or white, shallow depressions, and obscure or disappearing vessels. The typical pathological manifestations of LGIN are superficially located irregular nuclei, hyperchromatic, mildly enlarged, and nuclei that are oriented perpendicular to the basement membrane without observing the loss of nuclear polarity (20). In our case, the results of EGD, EUS, and biopsy pathological examinations suggested multiple tumors originating from the esophageal mucosal muscle layer and partly covered with LGIN.

Esophageal leiomyoma is considered to be a benign submucosal mesenchymal tumor with asymptomatic complaints unless the tumors are larger than 5 cm in diameter (21, 22). Esophageal leiomyoma has an extremely low possibility of converting into malignancy, and surgical treatment is recommended for tumors that are symptomatic or larger than 5 cm (23, 24). European Society of Gastrointestinal Endoscopy (ESGE) recommends against surveillance of gastrointestinal leiomyomas, provided that these lesions have typical ultrasonographic features (25). However, chronic irritation of the esophageal mucosa caused by intraluminal protrusion of the leiomyoma and esophageal stenosis may also induce or promote malignant transformation in the overlying epithelium (11).

The longest diameter of our patient's leiomyoma was larger than 5 cm, and the two lesions were located on the contralateral side of the esophagus, resulting in esophageal stenosis, which caused not only the symptoms of swallowing obstruction but also repeatedly friction and inflammatory stimulation of overlying mucosa of leiomyoma, which may be one of the causes of intraepithelial neoplasia.

In 2000, the World Health Organization (WHO) introduced the concept of intraepithelial neoplasia to diagnose precancerous lesions and early cancers of the gastrointestinal tract; LGIN is equivalent to mild and moderate dysplasia, and high-grade intraepithelial neoplasia (HGIN) is equivalent to severe dysplasia and carcinoma *in situ*. As a precancerous disease of esophageal cancer, cigarette and alcohol use are the main risk factors for LGIN (26), and Ki-67 can be used as a marker in histopathology. Our patient did not have the family malignancy history and the habit of cigarette or alcohol use. Her ESD specimen presented the squamous epithelium focal LGIN in HE and immunohistochemistry staining (including Ki-67) (27).

As to management and therapy, small asymptomatic esophageal leiomyomas could be followed up by surveillance (18). When the esophageal leiomyoma is large or symptomatic, and if it originates from the muscularis propria, it is recommended to choose endoscopic resection, which is a safe and effective procedure (6), while esophageal LGIN can also be treated by endoscopic resection or follow-up (28). Compared to surveillance, RFA led the reversion of dysplastic foci to normal epithelium and lower risk of progression to HGIN or carcinoma (29). However, even with careful endoscopic examinations, flat lesions that were considered eligible for RFA might harbor poor histological features, which increase the risk of lymph node metastasis (30). EMR and ESD are safe treatments, whereas ESD is easier than EMR to achieve *en bloc* resection and is appropriate for both epithelial and subepithelial lesions (31).

In our case, RFA is not applicable because of the swelling and uneven surface. Meanwhile, if we resect all of the lesions, there is a high probability of upper esophageal stenosis. Subsequently, we only performed ESD to remove the right lesions to achieve the effect of curing esophageal leiomyoma and LGIN simultaneously. By doing so, we can avoid the deterioration of intraepithelial neoplasia and esophageal stricture after circumferential resection.

In conclusion, the case of mucosal lesion overlying submucosal tumor is rare. Either overdiagnosis or missed diagnosis should be avoided through endoscopic examination and pathological biopsy. Additionally, treatment strategies should be formulated individually to maximize the benefit and minimize the risk for 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

The studies involving human participants were reviewed and approved by the Ethics Committee of The Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region. 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

WP, JW, CL, YH, JY conceived and designed the study, and were responsible for the final decision to submit for publication. All authors were involved in the development, review, and approval of the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Anlotinib combined with TAS-102 as the third-line treatment for a patient with metastatic colon cancer: A case report

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Chemotherapy combined with targeted therapy is a first-line and second-line treatment for metastatic colorectal cancer(mCRC), which has brought survival benefits to mCRC patients, however, disease progression is inevitable. More than 60% of patients still needed third-line treatment after the progress of second-line treatment. After the failure of second-line chemotherapy, treatment compliance and the physical tolerance of patients both decrease. Therefore, choosing an appropriate third-line treatment regimen is key to prolonging survival and improving quality of life. As a novel cytotoxic antitumor drug, trifluridine/tipiracil (TAS-102) is composed of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD can directly bind to the DNA of cancer cells to cause DNA dysfunction, thereby exerting antitumor effects. TPI can inhibit the degradation of FTD, thereby increasing its cytotoxicity. The few side effects of TAS-102 has become an important reason why clinicians present it as a treatment option to the patient for consideration, clinical trial data for progression free survival are lacking. The exploration of third-line treatment regimens with drug combinations has attracted much attention. This article reports a case of metastatic colon cancer (RAS/BRAF wild type, pMMR/Non-MSI-H), after failure of first-line and second-line therapies, the patient was eventually treated with anlotinib combined with TAS-102 as the third-line treatment. The treatment has shown good efficacy, with a long PFS benefit for more than 20 months and mild adverse reactions. This case reports demonstrates that anlotinib combined with TAS-102 is a promising third-line treatment regimen for refractory mCRC, and provides proof-of-concept for the clinical exploration of optimal third-line combination treatment regimens.

KEYWORDS

TAS-102, anlotinib, third-line, case report, metastatic colon cancer, mCRC

Introduction

According to GLOBOCAN data, in 2020, the global incidence of colorectal cancer (CRC) ranked third among all malignant tumours, and the mortality rate ranked second (1). In China, the incidence of CRC ranks third among malignant tumours, and the mortality rate ranks fifth among malignant tumours (2). Surgery and radiotherapy are the primary local treatments. However, due to the high recurrence rate and metastasis rate, systemic treatment is critical for prolonging patient survival. Immunotherapy can bring significant benefits to mCRC patients with microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR), but for patients with microsatellite stability (MSS)/microsatellite instability-low (MSI-L)/proficient mismatch repair (pMMR) who account for the majority of mCRC patients, chemotherapy-based therapy remains the mainstay of treatment. Although chemotherapy combined with targeted therapy provides survival benefits for patients with metastatic CRC (mCRC), disease progression is inevitable. An Italian retrospective study showed that among mCRC patients who progressed after second-line treatment, 63.3% still needed third-line treatment (3). Third-line treatment regimens are limited, resulting in a 5-year survival rate of only 11% (4). After the failure of second-line chemotherapy, treatment compliance and the physical tolerance of patients both decrease. Therefore, choosing an appropriate third-line treatment regimen is key to prolonging survival and improving quality of life. Currently, the third-line treatment drugs of mCRC recommended by guidelines include regorafenib, fruquintinib, and trifluridine/tipiracil (TAS-102). TAS-102 is a novel cytotoxic antineoplastic agent with few side effects which has emerged as an important reason for clinicians to consider it as a third-line treatment option for mCRC patients, but clinical trial data for progression free survival (PFS)are lacking. The exploration of third-line treatment regimens with drug combinations has attracted much attention. Anlotinib hydrochloride is a novel multitarget tyrosine kinase inhibitors (TKI). In China, Anlotinib has been approved for the standard treatment of several solid tumors, and also some small-sample clinical studies have shown its effectiveness in the third-line treatment of mCRC. This article reports a patient with mCRC who failed first-line and second-line chemotherapy combined with targeted therapy, and third-line treatment with anlotinib combined with TAS-102 achieved good efficacy, thus providing a reference for clinical work.

Case report

Clinical data and initial treatment

The patient, a 65-year-old male, presented to the hospital on 12 July 2018, without obvious causes of abdominal pain and distention. He had an ECOG score of 1, and no special past history or family history. Abdominal computed tomography (CT) on 13 July 2018 revealed tumours at the beginning of the caecum and ascending colon, slight dilation of the proximal small intestine, and multiple slightly larger lymph nodes in the surrounding area; the tumours were considered malignant. Colonoscopy (2018-07-15) revealed a caecal ulcer-type lesion in the ileocecal region, with a high possibility of malignancy. Regarding pathology, the ileocecal tissue biopsy showed inflammation with high-grade focal glandular intraepithelial neoplasia. On 20 July 2018, laparoscopic radical resection of right colon cancer was performed under general anaesthesia. Postoperative dissection of the specimen revealed a mass in the ileocecal region, approximately 5 cm in size, with complete obstruction of the intestinal lumen. Postoperative pathology indicated (ileocecal) ulcerative moderately differentiated tubular adenocarcinoma, with a size of 4*2.5 cm, penetrating the serosa, with no clear vascular and nerve invasion and no cancer involvement at the small intestinal resection margin, large intestine resection margin, and peripheral resection margin. There was no cancer in the appendix, indicating inflammatory changes. No metastatic cancer was found in the peri-intestinal lymph nodes (0/14). The immunohistochemistry results were as follows: epidermal growth factor receptor (EGFR) (partial +), Ki-67 (+ approximately 65%), MLH-1 (expression), MSH-2 (expression), MSH-6 (expression), PMS-2 (expression), and P53 (+90%). The postoperative diagnosis was postoperative stage II ileocaecal bowel cancer (pT4aN0M0), pMMR ECOG 1. Re-examination of chest CT during postoperative adjuvant chemotherapy (30 August 2018) (Figure 1A1) revealed a small nodule shadow in the left lower lung; the nodule had a cavity. Pulmonary nodules were followed up closely after surgery. Postoperative adjuvant treatment of bowel cancer was initiated on 31 August, 2018: XELOX chemotherapy for 1 cycle – oxaliplatin 200 mg d1 ivgtt; capecitabine 1500 mg bid d1-14 po q21d.

First-line treatment

On 3 September 2018, abdominal CT re-examination (Figure 1A2) due to abdominal pain revealed the following: 1. abdominal postoperative changes; 2. lower abdominal mass (metastasis was considered); and 3. a small amount of pelvic effusion. There was no definitive diagnosis. Positron emission tomography (PET)-CT examination on 4 September 2018 showed pelvic soft tissue nodules with increased 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) metabolism (metastatic tumour was considered) and small nodules in the lower lobe of the left lung with no increase in FDG metabolism; the small nodules were new compared to those initially observed on 26 October 2016. The following diagnoses were provided: 1. stage IV recurrence of ileocecal bowel cancer after surgery (rT0N0M1); 2. pelvic metastasis; 3. pulmonary nodular

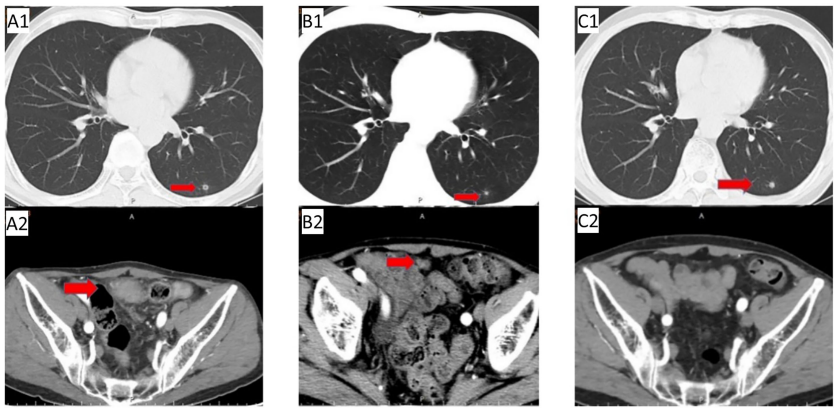

FIGURE 1
First-line treatment: **(A1/A2)** Baseline CT before first-line treatment; **(B1/B2)** CT after 2 cycles showed left lung nodules similar to before, pelvic metastases were significantly reduced; **(C1/C2)** follow-up CT on May 29, 2019 showed slightly enlarged left lung nodules, no pelvic metastases were observed.

metastasis?; and 4. ECOG 1. Gene detection was completed: KRAS (WT)/NRAS (WT)/BRAF (WT). On 26 September 2018, first-line treatment (cetuximab + capecitabine and oxaliplatin (XELOX)) for mCRC was initiated, and the efficacy was evaluated as PR after 2 cycles (Figure 1B1/B2). After 3 cycles of treatment, the patient refused oxaliplatin treatment due to thrombocytopenia and neurotoxicity (numbness in the hands and feet). After the 4th cycle, cetuximab + capecitabine chemotherapy was initiated. Abdominal CT re-examination (20 February 2019) revealed the following: 1. postoperative changes in the abdomen; 2. lower abdominal mass (metastasis was considered); and 3. small amount of pelvic effusion. Efficacy was evaluated as PR. Abdominal and chest CT were conducted regularly at follow up.

Second-line treatment

In May 2019, abdominal CT re-examination (Figure 1C2) showed no clear pelvic swelling, and chest CT (Figure 1C1) revealed small nodules in the left lower lung; the nodules were slightly larger than the nodules on previous imaging. The patient did not care about these changes. The patient felt that his physical condition was poor. He took Chinese medicine without consultation and was not admitted to the hospital. In June 2020, chest CT (Figures 2A1/A2)showed multiple nodules in both lungs, and metastasis was considered. On PET-CT, 1. the left lower lobe nodules were enlarged compared to the nodules on previous imaging, multiple new nodules developed in the remaining lungs, and FDG metabolism was increased in some lung regions. Metastatic tumours were considered. The pelvic nodules were significantly smaller than before, and the FDG metabolic activity was significantly lower than before; however, there was still residual tumour activity after treatment. Treatment with immune checkpoint inhibitors was recommended, but the patient refused the recommended treatment. Second-line chemotherapy with cetuximab + irinotecan for mCRC was initiated on 2 July 2020. After the first cycle, the patient refused to continue chemotherapy because of severe diarrhoea, and chest CT (Figures 2B1/B2) showed a reduction in the number of bilateral lung nodules.

Third-line treatment

Due to the serious side effects of previous chemotherapy, the patient rejected infusion chemotherapy and expected to choose oral drugs as much as possible. Therefore, TAS-102 was selected as the third-line treatment option for the patient. Considering that the benefits of third-line monotherapy of TAS-102 are limited, combined targeted therapy was suggested to improve treatment efficacy, which was accepted by the patient. Cetuximab + TAS-102 combined chemotherapy was initiated on 14 August 2020. After the first cycle, the patient had severe diarrhoea and grade IV granulocytopenia. Symptomatic treatment was administered to decrease diarrhoea and inflammation and elevate the WBC; cetuximab was discontinued after 2 weeks of application. Chest CT (24 November 2020) (Figure 2C1/C2) revealed that the number and size of pulmonary nodules increased. Considering that anlotinib is administered orally and some previous studies have shown that the adverse reactions caused by anlotinib in the treatment of mCRC are controllable, after informed consent of the patients, in December 2020, the third-line treatment regimen was adjusted to anlotinib + TAS-102 (TAS-102 40 mg d1-5, d8-12 bid po; q28d + anlotinib 10 mg d1-14 qd po; q21d).

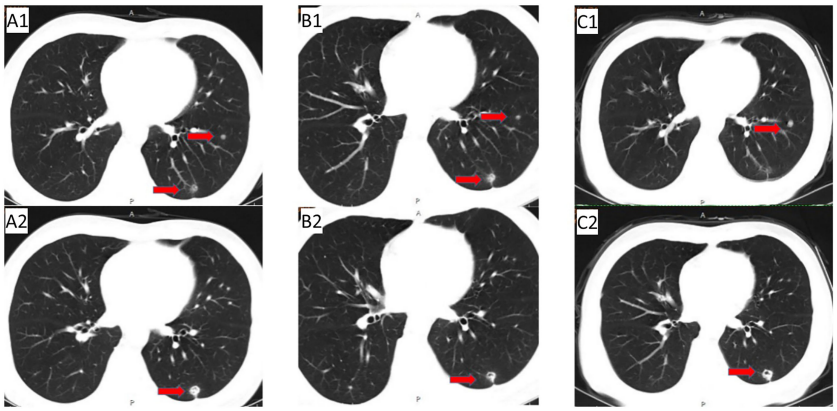

FIGURE 2
The period from the progression of lung metastasis to before the application of anlotinib + TAS-102 treatment: **(A1/A2)** Follow-up CT (2020.06.12): multiple nodules in bilateral lung; **(B1/B2)** CT (2020.08.12) after 1 cycle of second-line treatment; **(C1/C2)** initial application of cetuximab + TAS-102 in the third line, and discontinuation due to adverse reactions after only 2 cycles of cetuximab. On November 24, 2020, reexamination of CT showed that pulmonary nodules were increased and enlarged than before.

On 10 December 2020, the first cycle of anlotinib + TAS-102 treatment was initiated; the second cycle of anlotinib + TAS-102 treatment was initiated on 08 January 2021. Diarrhoea occasionally occurred; and granulocytopenia improved after treatment to elevate the WBC. The third cycle was not performed as scheduled due to the changes of precautionary measures over COVID-19 after the patient returned home, which prevented him from returning to the hospital. Abdominal CT re-examination (15 March 2021) showed no pelvic mass. On lung CT (15 March 2021) (Figures 3A1/A2), the bilateral lung nodules were larger than the nodule on previous imaging, and some cavities had formed. Anlotinib + TAS-102 treatment was continued on 17 March 2021, 28 April 2021, 9 June 2021, and 12 July 2021 for the 3rd through 6th cycles of treatment, respectively. Side effects of occasional diarrhoea and grade 1 granulocytopenia were observed. On 31 May 2021, abdominal CT showed no pelvic mass. Chest CT (Figures 3B1/B2) indicated that the pulmonary nodules were smaller than they were before and that some cavities had formed. SD was achieved by November 2021. In November 2021, the patient underwent multipoint radiotherapy for pulmonary lesions (GTV 4000 cGy, bilateral lung v5 40.13%, v20 10.34%). TAS-102 combined with anlotinib was continued after radiotherapy. The patient is still receiving treatment. The last re-examination (Figures 3C1/C2)

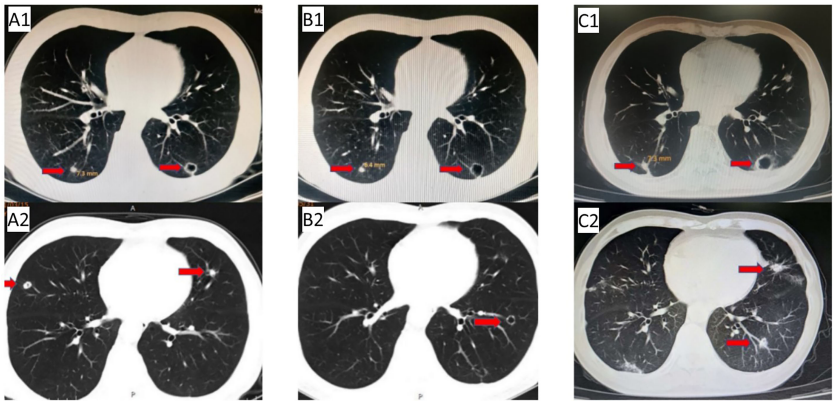

FIGURE 3
Anlotinib + TAS-102 treatment:**(A1/A2)** CT after 2 cycles (2021.03.15): the pulmonary nodules were larger than before (the right pulmonary nodules was 7.3 mm), and some cavities were formed; **(B1/B2)** reexamination CT (2021.05.31) showed that the right pulmonary nodules were smaller than before (6.4 mm); **(C1/C2)** last reexamination CT (2022.08.23): the right pulmonary nodules was 7.3 mm; multiple nodules in the left lung, and some cavities were formed.

was 23 August 2022. Efficacy was stable, and the PFS for Anlotinib + TAS-102 treatment was more than 20 months (Figure 4).

Discussion

The choice of drugs for the third-line treatment of mCRCis critical. The KNOTE-177 study demonstrated a significant benefit from immunotherapy in patients with MSI-H/dMMR mCRC, however, this group of patients accounted for only 5% of all mCRC patients (5). For patients with MSS/MSI-L/pMMR who account for the majority of mCRC patients, chemotherapy-based treatment remains the mainstay of treatment, regorafenib, fruquintinib, and TAS-102 in the standard treatment regimen each have their advantages. The CORRECT study included patients with mCRC after failure of standard therapy in 16 countries from North America, Europe, Asia, and Australia, and showed that the overall survival (OS) for patients who received regorafenib target treatment was 1.4 months longer than that for patients in the placebo group (6.4 vs. 5.0 months; P=0.0052) (6). The CONCUR study confirmed that the efficacy of regorafenib in patients with advanced CRC in the Asia-Pacific region was better than that in Western patients; the median PFS of the regorafenib and placebo groups was 3.2 months and 1.7 months (p<0.001) and the median OS was 8.8 and 6.3 months (p<0.001) (7). The FRESCO study of the third-line treatment of mCRC with fruquintinib included 416 patients. The results showed that OS (primary endpoint) of the fruquintinib group and the placebo group was 9.30 months (95% confidence interval (CI), 8.18-10.45) and 6.57 months (95% CI, 5.88-8.11), respectively; the PFS (secondary endpoint) was 3.71 months (95% CI, 3.65-4.63) and 1.84 months (95% CI, 1.81-1.84), respectively. Regarding other secondary endpoints, the objective response rates (ORRs) were 4.7% and 0% (p=0.01), and the disease control rates (DCRs) were 62.2% and 12.3% (p<0.001) (8). However, for patients with good physical performance, the premature use of fruquintinib or regorafenib targeted therapy is not clinically desirable. Some doctors still try third-line chemotherapy, demonstrating that chemotherapy is still the main cornerstone of treatment in the minds of physicians, especially for non-MSI-H patients.

As a novel cytotoxic antitumor drug, TAS-102 is composed of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD can directly bind to the DNA of cancer cells to cause DNA dysfunction, thereby exerting antitumor effects. TPI can inhibit the degradation of FTD, thereby increasing its cytotoxicity (9, 10). TAS-102 has been shown to provide clinical benefit to patients with mCRC in several studies and has therefore been approved for third-line treatment of mCRC in several countries. RECOUSE, a global Phase 3 study involving 406 patients with refractory advanced colorectal cancer in China, Korea, and Thailand, demonstrated that compared with placebo, TAS-102 prolonged OS by 1.8 months (7.1 months vs. 5.3 months, p<0.001) and mPFS by 0.3 months (2.0 months vs. 1.7 months, p<0.001) in patients with drug-resistant refractory mCRC after standard second-line treatment, regardless of geographic origin, or KRAS status (11). The TERRA study on TAS-102 that included Asian patients with refractory mCRC who were resistant or intolerant to standard chemotherapies showed that the OS of the treatment group and the placebo group were 7.8 months and 7.1 months, respectively (p=0.035), and that the mPFS were 2.0 months and 1.8 months, respectively (p <0.001) (12).

The results from the above studies suggest that the benefits of third-line monotherapy are limited and that it is imperative to explore potential drug combination regimens for the third-line treatment of mCRC. Due to the excellent safety of TAS-102 monotherapy, many studies evaluated the efficacy and safety of TAS-102 in combination with other drugs for the treatment of

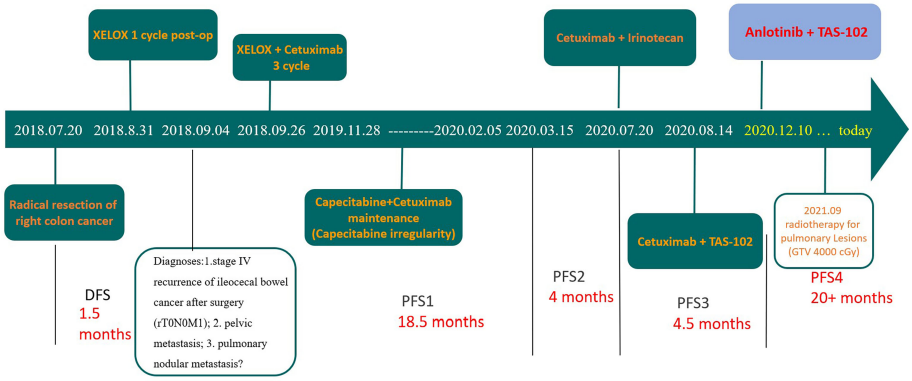

FIGURE 4
Diagnosis and treatment timeline.

refractory mCRC. The results of an open-label, single-arm, multicentre, phase 1/2 trial of TAS-102 plus bevacizumab initiated by Japanese investigators (C-TASK FORCE) showed that TAS-102 combined with bevacizumab for patients with mCRC who are resistant or intolerant to standard chemotherapy can achieve an mPFS of 5.6 months (95% CI, 3.4-7.6) (13). An open-label, randomized, phase 2 study in Denmark compared the efficacy of TAS-102 monotherapy and the combination of TAS-102 and bevacizumab in patients with refractory mCRC. The median OS obtained using the combination of TAS-102 and bevacizumab was 9.4 months (95% CI, 0.32-0.94), and the mPFS was 4.6 months (95% CI, 0.29-0.72). The mPFS of patients treated with TAS-102 monotherapy was 2.6 months (95% CI, 1.6–3.5) (14). The TAS-CC3 study is a prospective, nonrandomized, single-arm, multicentre, open-label phase II trial. In that study, for patients with mCRC, TAS-102 plus bevacizumab as a third-line treatment achieved a median PFS of 4.5 months (95% CI, 1.8-7.1) and median OS of 9.2 months (95% CI, 5.5-12.8) (15). In addition, in the APOLLON study, the median PFS and OS of patients with wild-type RAS mCRC treated with TAS plus panitumumab were 5.8 months (95% CI, 4.5-6.5) and 14.1 months (95% CI, 12.2-19.3), respectively (16). The results of these studies are encouraging, and thus, clinicians should further explore TAS-102 combination therapy for mCRC to extend time benefits for patients.

The patient in this case study had advanced colon cancer patient (wild-type Ras/BRAF gene; pMMR/Non-MSI-H). After second-line chemotherapy failed, the initial third-line chemotherapy regimen was cetuximab and TAS-102 because after indirectly comparing different drug regimens, the ORR/PFS/OS of cetuximab rechallenge therapy were all superior to those of other third-line therapy drugs, indicating that for RAS/BRAF WT mCRC patients, the application of cetuximab third-line rechallenge is also an optimized treatment strategy (17, 18). However, after treatment, the patient developed severe intolerable diarrhoea. As more and more evidence has proved the benefit of TAS-102 combined with bevacizumab in the third-line treatment of mCRC, and anlotinib also has some small-sample clinical studies in the third-line treatment of mCRC, and it is oral administration, anti-angiogenic therapy with anlotinib instead of bevacizumab seems to be more suitable for patients who are resistant to intravenous infusion. The regimen was adjusted to anlotinib in combination with TAS-102. Anlotinib hydrochloride is a novel multitarget tyrosine-kinase inhibitor (TKI) that can inhibit angiogenesis-related kinases, including VEGFR1/2/3, PDGFRα/β, FGFR1/2/3, c-Kit, Met, Ret, and Tie2. It can also inhibit tumour growth and metastasis by inhibiting a variety of tumour-associated kinase targets, such as EGFR, ALK, ABL, Aurora-A/B, DDR2, and EphB4 (19). Previous clinical studies have shown that anlotinib is effective for non-small-cell lung cancer (NSCLC), medullary thyroid carcinoma, and soft tissue sarcoma, with controllable adverse reactions (20). Anlotinib has been approved for the standard treatment of NSCLC, soft tissue sarcoma and small cell lung cancer in China. A multicentre, double-blind, placebo-controlled, randomized phase III trial (ALTER0703) enrolled 419 patients with refractory mCRC from 33 hospitals in China. In that study, the median PFS improved (4.1 months, 95% CI, 3.4 - 4.5). Subgroup analysis showed that in RAS/BRAF wild-type patients, anlotinib provided significant survival benefits. The authors of that study concluded that anlotinib significantly prolonged clinical benefits (PFS) for patients with refractory mCRC (21). In addition, a retrospective clinical study in China collected the clinical data of 105 mCRC patients from who failed at least two lines of chemotherapy, and the analysis showed that anlotinib was superior to chemotherapy as a third-line treatment of mCRC (PFS: 3.46 months vs 2.25 months,P< 0.001; OS: 9.22 months vs 6.95 months, P< 0.001), and similar to fuquinitinib or regorafenib (PFS: 3.46 months vs 3.33 months,P=0.347; OS: 9.22 months vs 9.38 months, P=0.499), and the related adverse reactions were tolerable (22).

From a number of completed clinical studies of TAS-102 or Anlotinib monotherapy in the treatment of mCRC, most of the adverse reactions of TAS-102 or anlotinib in the treatment of mCRC were tolerable and controllable. The most common adverse events associated with TAS-102 in RECOURSE were neutropenia (38%), leukopenia (21%) and neutropenic fever (4%) (11); in TERRA, the most common adverse events of grade 3 and above were neutropenia (33.2%), leukopenia (20.7%), and anaemia (17.7%). The adverse reactions can generally be controlled by reducing the dose, extending the interval between chemotherapy and administering relevant drugs for symptomatic management and are relatively manageable. The study also reported that TAS-102 was well tolerated in Asian patients with mCRC (12). The most common adverse reactions caused by anlotinib are fatigue, gastrointestinal toxicity, hypertension, proteinuria, rash, and hand-foot reactions. Most patients recover or improve after symptomatic treatment and drug dose reductions. The ALTER0703 study analysis concluded that for anlotinib in refractory mCRC, most common grade≥3 TRAEs were hypertension, increased γ-GT, and hand-foot skin reaction, the TRAEs were manageable,and the deterioration of QoL in anlotnib was as same as placebo for patients (21). For the patient in this case study, the side effects were only occasional diarrhoea and grade I granulocytopenia after adjusting the regimen to anlotinib + TAS-102.

To our knowledge, there are no reports on anlotinib combined with TAS-102 as a third-line treatment for patients with refractory mCRC. The treatment of the patient with advanced colon cancer in this study obtained the informed consent of the patient and family members. The patient was eventually treated with anlotinib combined with TAS-102 as the third-line treatment, rather than the standard third-line regimen of TAS-102 monotherapy, with informed consent. Medicine should be evidence-based and follow ethics, but individualized trials with patients' informed consent may lead to better efficacy.

The treatment has shown good efficacy, achieving a PFS benefit far beyond that of standard third-line therapy, with mild adverse reactions, and the patient is still receiving treatment. Radiation therapy has also been administered during treatment, resulting in stable disease control. This case reports demonstrates that anlotinib combined with TAS-102 is a promising third-line treatment regimen for refractory mCRC, and provides proof-of-concept for the clinical exploration of optimal third-line combination treatment regimens. As the previous TERRY study showed significant benefit of TAS-102 in Asian patients with mCRC, while subgroup analysis of ALTER0703 showed significant OS survival benefit of anlotinib in patients with RAS/BRAF wild-type, given that the patient reported in this case belonged to Asian non-MSI-H/pMMR and RAS/BRAF WT mCRC, whether this combination regimen of TAS-102+ anlotinib is more advantageous for this part of the population needs to be verified by further clinical studies.

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

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 individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QL and XZ provided equal contribution to this work. BZ and XC contributed to the conception and design and provided administrative support. CZ provided necessary information. XZ and QL took charge of the collection and assembly of data, conducted the disease analysis, provided the summary. All authors contributed to the article and approved the submitted version.

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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

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Case report: 10-year survival of a patient with a primary hepatic gastrointestinal stromal tumor

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Background: Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the gastrointestinal tract. Extra-gastrointestinal stromal tumors (EGISTs) predominantly arise outside the gastrointestinal tract, although primary hepatic GISTs are extremely rare. GISTs are highly aggressive; they often grow to a large size. Here, we report the 10-year survival of a patient with a primary hepatic GIST following sequential response therapy.

Case presentation: A 50-year-old Chinese man complained of fatigue and slight abdominal pain, and presented with a large lump in the liver, which was detected by computed tomography (CT). He was subsequently diagnosed with a primary hepatic GIST, based on CT-guided fine needle aspiration cytology and immunohistochemistry analyses. The presence of GIST or EGIST metastases was excluded using CT, esophagogastroduodenoscopy, colonoscopy, and ultrasound. Cytological examination showed that the tumor was composed of epithelioid and spindle cells. Immunohistochemistry analysis revealed positive staining for CD117 (KIT) and DOG1, and negative staining for CD34, S-100, and α-smooth muscle actin (SMA). Following tumor ablation with argon-helium cryosurgery, the patient received imatinib mesylate for 61 months. However, this treatment was discontinued because of disease progression, at which point interventional therapy was administered once. One month later, sunitinib malate was administered for 71 months. The patient achieved long-term survival for 135 months.

Conclusions: EGISTs can be easily misdiagnosed as other types of tumors because they have no specific characteristics to distinguish them during imaging examinations. However, our case study demonstrates that the long-term survival of patients with EGISTs can be achieved with molecular targeted therapy.

KEYWORDS

long-term survival, primary hepatic GIST, extra-gastrointestinal stromal tumors, imatinib, sunitinib, molecular-targeted therapeutic strategies

Introduction

Gastrointestinal stromal tumors (GISTs) are abdominal tumors of mesenchymal origin, which are located in the gastrointestinal tract. GISTs frequently contain mutations targeting genes encoding KIT (also known as CD117) or the platelet-derived growth factor receptor alpha (PDGFRA) (1, 2). KIT is a member of the type III receptor tyrosine kinase family, which also comprises PDGFRA and platelet-derived growth factor receptor beta (PDGFRB). Binding of KIT to its ligand, the stem cell factor (SCF), results in receptor homodimerization and kinase activation, which eventually leads to cell proliferation. The current diagnostic criteria for patients with GISTs are based on cytological, histological, and immunohistochemical findings, of which the most important is the expression of CD117 (3). GISTs typically occur in the gastrointestinal tract, including the stomach, small intestine, colorectum, and esophagus (4, 5). A minor subset of GISTs is found in other areas and are called extra-gastrointestinal stromal tumors (EGISTs). There are few cases of primary hepatic EGISTs reported in the literature, and only their complete surgical resection has been shown to achieve long-term survival (6, 7). Here, we report a case of a patient with a hepatic EGIST, diagnosed by computed tomography (CT)-guided fine needle aspiration cytology (FNAC), who achieved long-term survival through sequential response therapy without surgery.

Case description

A 50-year-old Chinese man complaining of fatigue and slight abdominal pain for 1 month was admitted to Harbin Medical University Cancer Hospital (Harbin, China) on 23 June 2009. He had a history of bronchiectasis, which had not required treatment, and no family history of cancer. His physical examination was unremarkable. His levels of tumor markers, such as carbohydrate antigen (CA) 199, CA125, carcinoembryonic antigen, and α-fetoprotein, were all normal. The patient's liver function was also normal. Dual-phase enhanced abdominal CT showed a 110 × 112 mm solid cystic lump in the right liver lobe, but no other abdominal mass (Figure 1A). The results of the patient's esophagogastroduodenoscopy (EGD) and colonoscopy were unremarkable. CT-FNAC analysis revealed that the tumor was composed of spindle and epithelioid cells with high mitotic activity. Immunohistochemical staining was positive for CD117 and DOG1 (Figure 2), but negative for CD34, S-100, and α-smooth muscle actin (SMA). GIST risk stratification is high according to the mass size, although there is no sufficient tumor area for accurate determination of mitotic rate since this is a small biopsy. The diagnosis was primary hepatic GIST.

The hepatic mass was treated by argon-helium cryosurgery in July 2009 (Figure 1B). One month later, treatment with imatinib mesylate (400 mg once daily) was initiated, and the patient tolerated its adverse effects (Figure 3A). By January 2011, the tumor mass in the right lobe of the liver had shrunk to 30 × 30 mm, as demonstrated in a routine CT examination (Figure 3B). However, by July 2012, the mass had increased to 55 × 78 mm (Figure 3C), reaching a size of 110 × 150 mm by September 2014 (Figure 3E), when pericardial effusion also became visible (Figure 3D). After 61 months of imatinib mesylate therapy, the patient was switched to an interventional therapy consisting of transcatheter embolization with iodized oil. After a month, the patient's tumor lesion shrank to 96 × 138 mm (Figure 3F). His treatment regimen was then changed to a daily dose of 50 mg of sunitinib malate; 4 weeks on, followed by 2 weeks off (a 4/2 schedule). The administration of sunitinib caused hypertension, and the patient received Plendil to lower his blood pressure.

Following treatment, the lesion became stable and only cystic changes were observed during the 30-month follow-up period (Figure 3G). No other lesions occurred before, during, or after treatment. The patient continued to receive sunitinib. However, by October 2019, the mass had again increased to 110 × 190 mm (Figure 3H). We conducted telephone follow-up appointments with the patient every 3 months, but learned that he had died on 20 September 2020. The final diagnosis was primary hepatic GIST with a total survival time of 135 months. Written informed consent was obtained from the patient for the publication of this study. The authors had access to information that could identify individual participants during or after data collection. The timeline of the patient's diagnosis, treatment, and response is shown in Figure 4.

Discussion

Preoperative diagnosis is challenging in most patients with EGISTs, especially in patients with primary hepatic GISTs. The GISTs often develop into large tumors. Thus, these patients are easily misdiagnosed as having other types of cancer, such as lymphoma, malignant fibrous histiocytoma, or neurogenic tumors (6). Patients with EGISTs often have a worse prognosis than those with GISTs (8). Previously, only the complete surgical resection of primary hepatic EGISTs was able to achieve long-term patient survival (9). The treatment method for EGISTs is the same as that for stromal tumors. However, EGISTs have a higher degree of malignancy and are associated with a poor prognosis. The long-term survival of patients with EGISTs is rare.

Abbreviations: GIST, gastrointestinal stromal tumor; EGIST, extra-gastrointestinal stromal tumor; CT, computed tomography; CT-FNAC, CT-guided fine needle aspiration cytology; PDGFRA, platelet-derived growth factor receptor alpha; PDGFRB, platelet-derived growth factor receptor beta; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; EGD, esophagogastroduodenoscopy.

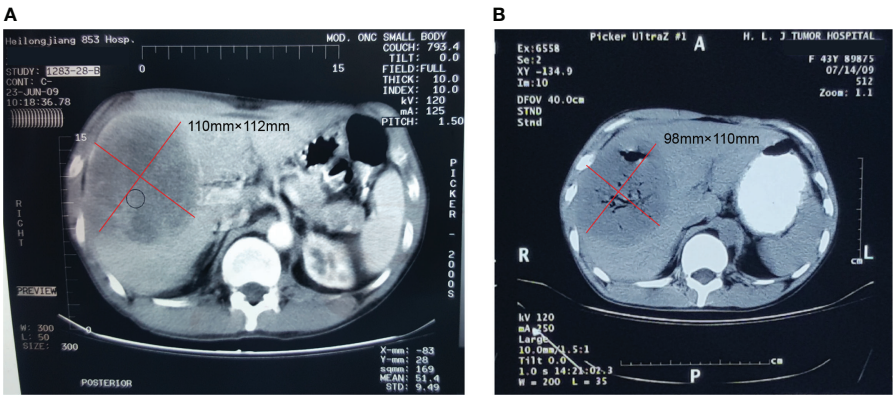

FIGURE 1
Contrast-enhanced computed tomography of the hepatic extra-gastrointestinal stromal tumor. **(A)** A 110 × 112 mm mass with solid and cystic components was observed in the right hepatic lobe, with an uneven enhancement in the arterial phase scan. **(B)** The hepatic mass was treated by argon-helium cryosurgery in July 2009, at which point the tumor was cystic and measured 98 × 110 mm.

In our case study, the patient had a large, solid, cystic mass in the right lobe of the liver. However, it was difficult to determine the nature of the tumor. Since the patient had a history of bronchiectasis and could not undergo hepatectomy, pathological diagnosis was obtained by CT-FNAC of the liver mass (10). Microscopic analysis revealed that the tumor was composed of spindle cells, some of which assumed a fence-like arrangement. In addition, there were signs of tumor hyperplasia. Biopsy specimens were small, and there was no evidence of nuclear fission across the whole field of vision. CD117 (KIT) is the most important immunohistochemical marker for the diagnosis of GIST; 94%–98% of GISTs stain positive for CD117, which is rarely expressed by other tumors. Additionally, 60%–80% of all GISTs stain positive for CD34 (11). To exclude neural tumors and smooth muscle tumors, S-100 and desmin staining, respectively, are usually recommended (3). Both the cell membrane and cytoplasm of our patient's tumor samples were highly CD117-positive. The final primary hepatic EGIST diagnosis was based on the fact that (1) no abnormal mass was identified in any other organs except for the liver and (2)

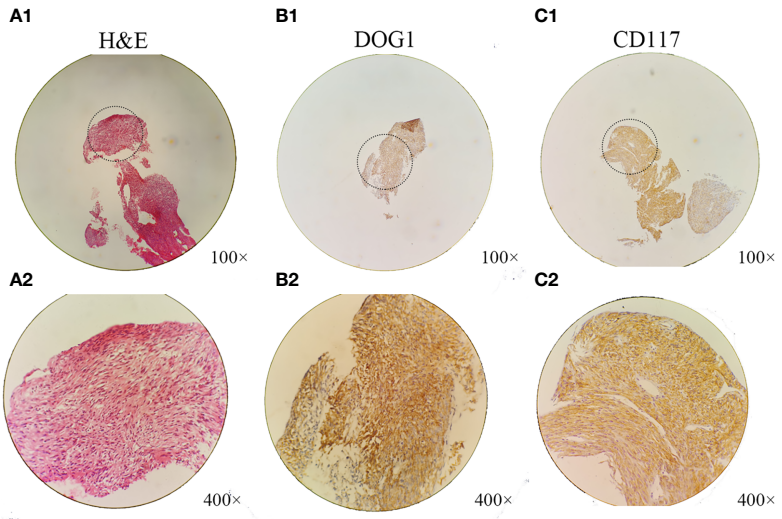

FIGURE 2
Histological and immunohistochemical analyses of the hepatic extra-gastrointestinal stromal tumor. **(A1, A2)** Microscopically, the tumor consisted of spindle cells with pleomorphic nuclei arranged into fascicles (hematoxylin–eosin stain; A1, ×100 magnification; A2, ×400 magnification). The patient's hepatic extra-gastrointestinal stromal tumor had the following immunohistochemical staining profile: **(B1, B2)** DOG1, **(C1, C2)** $CD117^{+}$ (**B1**, **C1**, ×100 magnification; **B2**, **C2**, ×400 magnification).

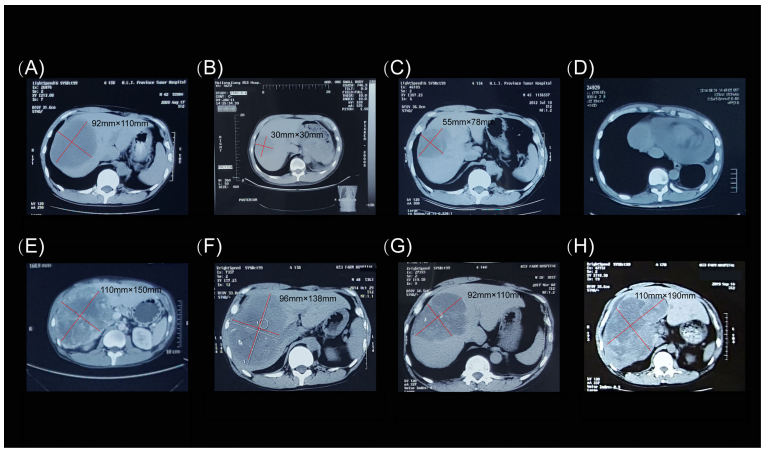

FIGURE 3
Computed tomography images of the hepatic extra-gastrointestinal stromal tumor. **(A)** In August 2009, prior to imatinib mesylate administration (400 mg once daily), the tumor mass measured 92 × 110 mm. **(B)** In January 2011, routine computed tomography examination showed that the lesion in the right hepatic lobe had shrunk to 30 × 30 mm. **(C)** In July 2012, the lesion grew to 55 × 78 mm. **(D)** Pericardial effusion was observed in August 2014. **(E)** In September 2014, the lesion measured 110 × 150 mm. **(F)** Before the patient was switched to sunitinib malate therapy (50 mg once daily on a 4/2 schedule), the tumor mass measured 96 × 138 mm. **(G)** In March 2017, the tumor was 92 × 110 mm in size. **(H)** The final computed tomography examination in October 2019 showed that the tumor mass measured 110 × 190 mm.

there was no evidence of other primary hepatic tumor or GIST metastases (12). Additionally, pre-, intra-, and post-operative assessment and imaging examinations, including EGD, colonoscopy, ultrasonography, and CT, revealed that the tumor was confined to the liver.

Complete surgical resection with a microscopic negative margin is the standard treatment for both GISTs and primary non-metastatic EGISTs. Peritoneal or hepatic metastases of GISTs can also be managed with localized methods such as radiofrequency ablation or chemoembolization (13). In the present case, the hepatic mass was treated with argon-helium cryosurgery in July 2009, because the patient had a history of bronchiectasis and could not undergo surgery.

Imatinib is a tyrosine kinase inhibitor (TKI) of KIT, prescribed for the treatment of GISTs and EGISTs. Imatinib can improve overall recurrence-free survival time, even in patients with advanced GISTs (14, 15). On diagnosis of an advanced GIST (unresectable, metastatic, or recurrent), therapy with imatinib mesylate should be immediately initiated, regardless of the patients' symptoms (16). One month after argon-helium cryosurgery, our patient was prescribed the standard dose of imatinib (400 mg once daily)

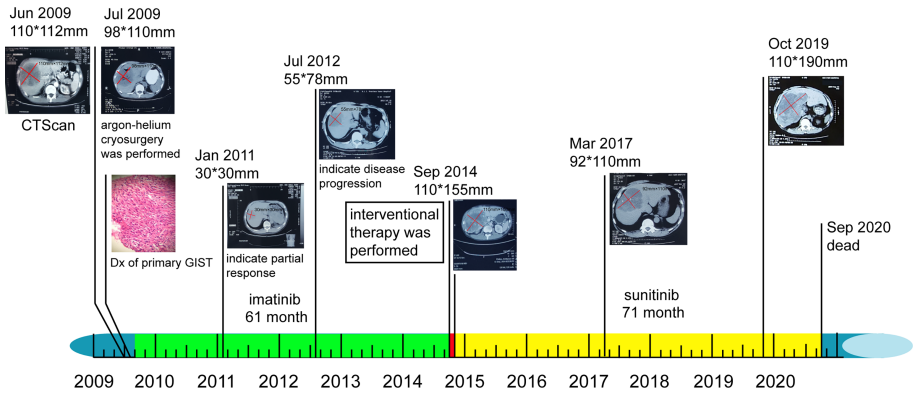

FIGURE 4
Timeline of patient's diagnosis, treatment, and response. Colored rectangles near the timeline represent individuals' sequential therapy durations: green, imatinib therapy; red, interventional therapy; and yellow, sunitinib therapy. Original magnification, ×400. Dx, diagnosis.

recommended for GIST treatment (17). The EGIST was sensitive to imatinib and gradually shrank over 18 months. However, imatinib is reported to have several side effects, such as pleural effusion (18); luckily, our patient tolerated these adverse effects.

Discontinuation of imatinib in patients demonstrating an initial favorable tumor response generally leads to rapid disease progression (19, 20). Therefore, continuous imatinib therapy is recommended, until the occurrence of intolerable adverse events or disease progression, or at the patient's refusal. In such cases, many patients respond to the re-continuous use of imatinib, but tumor shrinkage may be smaller than was achieved prior to treatment interruption (21). Indeed, the benefits of continuing treatment despite progressive disease have been reported, depending on the available treatment alternatives (22). For our patient, imatinib administration was discontinued after 61 months when the lesion had increased in size and pericardial effusion was evident. Hepatic arterial embolization and chemoembolization have been shown to induce a radiologic response or disease stabilization in cases of imatinib-resistant GIST (23). Thus, after developing resistance to imatinib therapy, our patient underwent transcatheter embolization with iodized oil, which caused his tumor mass to shrink within a month of this interventional treatment.

Sunitinib malate is an oral multitargeted receptor TKI with selectivity for KIT and PDGFRA. Sunitinib treatment recommendations are outlined in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) and by the European Society of Medical Oncology (24, 25). The objective response rate for sunitinib was reported to be nearly 10% in the treatment of patients with GISTs following imatinib failure, and the clinical benefit rate was ~65% (26). Additionally, the median progression-free survival of patients with GISTs receiving sunitinib was 6.8 months, which was four times longer than that of the placebo arm (26). According to a previously reported dosing schedule (27), a 50-mg daily dose of sunitinib was prescribed to our patient (on a 4/2 schedule) on completion of the interventional therapy. Recent reports confirmed that sunitinib is associated with cardiac toxicity and hypothyroidism (28, 29). Therefore, careful monitoring of hypertension, cardiac function, and thyroid hormone levels is necessary during sunitinib treatment. Our patient did develop hypertension but recovered well following felodipine therapy. The patient continued receiving sunitinib for a total of 71 months and survived for a total of 135 months from the time of diagnosis until his death. It is possible that the cause of death was hemorrhage as a result of tumor rupture.

In conclusion, we report a case of long-term survival of a patient with a primary hepatic EGIST, diagnosed by CT-FNAC. Primary hepatic EGISTs are extremely rare and are difficult to diagnose preoperatively. Thus, clinicians should consider administering imatinib and sunitinib, which are already used for the treatment of GISTs, to achieve long-term survival for patients with primary hepatic EGISTs.

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 Harbin medical university cancer hospital (KY2017-19). 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

HL and JL treated the patient. JL provided the first draft of the manuscript. HL drafted and revised the manuscript. MF performed the pathological tests. SZ reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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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

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Case report: A case of duodenal adenocarcinoma achieving significantly long survival treating with immune checkpoint inhibitors and chemotherapy without positive biomarkers

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Small bowel adenocarcinoma (SBA), particularly duodenal adenocarcinoma (DA), is a rare gastrointestinal cancer with a dismal prognosis. Data on SBA treatments are limited, and the therapeutic strategy remains uncertain. Currently, chemotherapy is the most used treatment; however, it has a poor median progression-free survival (mPFS) of no more than five months in the second-line setting. We report a case with DA that responded well to the immune checkpoint inhibitor (ICI) tislelizumab plus irinotecan in the second-line treatment. To our knowledge, this is the first report of administering ICIs plus chemotherapy to SBA. Despite the absence of microsatellite instability-high (MSI-H) and high tumor mutational burden (TMB), the patient with *TP53/KRAS* mutation achieved a significantly long PFS of 17 months, and the benefit is still ongoing. The mechanism of this remarkable efficacy might be associated with an increase in tumor immunogenicity after chemotherapy. The current study presents a promising effect of ICIs plus chemotherapy on SBA, affirming the need to investigate the clinical value of this combination in SBA and the underlying mechanism behind it.

KEYWORDS

small bowel adenocarcinoma, duodenal adenocarcinoma, ICIS, immunotherapy, chemotherapy

Introduction

Small bowel adenocarcinoma (SBA) is a rare gastrointestinal cancer with a poor prognosis, consisting of 50% duodenal, 30% jejunal, and 20% ileal adenocarcinoma (1). Although there were around 22.7 cases/million in 2004 (2), the incidence of SBA is increasing, with a prevalence in patients over the age of 50 and in men (3). The five-year life expectancy for SBA ranges from 14%–30% (4, 5), whereas the therapeutic options for advanced SBA remain inconclusive. Available data supported chemotherapy as first-line treatment, with a median progression-free survival (mPFS) of six to 11 months (6–8). The optimal mPFS for second-line chemotherapy was only five months (9, 10). Immunotherapy combined with chemotherapy appears to be the cornerstone of treatment for various cancer; however, the efficacy of this combination on SBA has yet to be investigated.

Here, we report the first case of previously treated duodenal adenocarcinoma (DA) with a significant response to second-line tislelizumab in combination with irinotecan. The patient with microsatellite stability (MSS) status, a low tumor mutation burden (TMB), and a *TP53/KRAS* mutation progressed after three months of first-line oxaliplatin-based chemotherapy (XELOX). However, the patient then responded effectively to the combination of immune checkpoint inhibitors (ICIs) and chemotherapy. Our study aims to present the therapeutic potential of ICIs plus chemotherapy in SBA and discuss this combination's underlying mechanism.

Current treatments for SBA

Chemotherapy

There is a dearth of evidence from phase III randomized controlled trials on the SBA treatment. The current therapeutic strategies are mainly derived from phase II studies or retrospective analyses. Oxaliplatin-based regimens (XELOX and FOLFOX) seem to be the most used and effective therapy in the first-line treatment, with an mPFS of six to 11 months and median overall survival (OS) of 15 to 22 months (6–8). In the single agent setting, a retrospective study demonstrated an mPFS of six months and an mOS of 11 months for gemcitabine (11). Triplet chemotherapy regimens, like FAM, CAPIRINOX, and FOLFIRINOX, were also evaluated with a dismal median OS ranging from 8 to 13 months (12, 13). For second-line therapy, an irinotecan-based regimen, FOLFIRI, was recommended with an mPFS of three to five months (9, 10). Taxane-based regimens are other options for second-line treatment, with an mPFS of 3.8 months (14).

Immunotherapy

The immunotherapy role in SBA is under evaluation. Pembrolizumab is an ideal choice for previously treated patients with MSI-H SBA. Marabelle A's study included 19 MSI-H patients, and the results showed that pembrolizumab had an ORR of 42.1% and an mPFS of 9.2 months (15). Similar results were observed in studies by Pedersen, K.S (16). and Cardin, D.B (17). However, the mPFS for patients with MSI-L/MSS was only 2.8 months. In Marabelle A's study (15), only one patient with MSS exhibited a confirmed partial response but correlated with high TMB. These findings suggested that predictive biomarkers may be important for administering immunotherapy in SBA.

Anti-vascular therapy

A phase II study reported that the mPFS of the XELOX regimen combined with bevacizumab was 8.7 months in first-line treatment (18). Despite the lack of statistical comparison, the mPFS of XELOX plus bevacizumab is comparable to that of XELOX alone, as reported by the same institution (6). However, another retrospective multicenter study reported an mPFS of 15 months in 10 metastatic duodenal and jejunal adenocarcinoma patients treated with bevacizumab plus platinum (19). Notably, among patients treated with bevacizumab-based regimens, the mPFS of six patients with high vascular endothelial growth factor-A (VEGF-A) expression was significantly higher than four patients with low VEGF-A expression, implying that VEGF-A expression might act as a predictor for bevacizumab efficacy.

Target therapy

It is known that the effect of the anti-epidermal growth factor receptor (EGFR) in colorectal cancer (CRC) depends on the *KRAS* mutation status. Theoretically, approximately 50% of SBA might be treated with anti-EGFR monoclonal antibodies. A case series demonstrated that anti-EGFR might play a role in SBA patients with wild-type *KRAS*. In the study, two *KRAS* wild-type patients had a partial response to cetuximab plus irinotecan, and one showed a complete response (20). In contrast, a phase II study reported unsatisfactory results. Among eight non-mutant *KRAS* SBA patients, panitumumab was administered; however, no clinical responses were observed (21). Moreover, 13 SBA patients with uncertain *KRAS* status were enrolled in a retrospective multicenter investigation. Cetuximab plus chemotherapy was administrated in first- or second-line treatment, and an ORR of 55% was observed (22). Nevertheless, the mPFS of these patients was only 5.5 months, whereas published data showed that SBA patients treated with XELOX or FOLFOX alone could achieve prolonged PFS. More research is required to identify anti-EGFR agents' efficacy in SBA.

Case presentation

The patient was a 50-year-old male. In November 2020, the patient was admitted to a local hospital with a stomachache and a tarry stool. Electronic gastroscopy found a huge ring-shaped mass

(Figure 1A) in the duodenal bulb, and a poorly differentiated adenocarcinoma was confirmed by biopsy. Subsequently, the patient came to our hospital seeking surgical treatment. Positron emission tomography/computed tomography (PET/CT) indicated a significant uneven thickening of the duodenal bulb's intestinal wall (47 × 40 mm) and multiple lymph node metastases (Figures 1B, C). The margins of the tumor were indistinguishable from surrounding organs (pancreatic head, gallbladder, and liver). The tumor stage was diagnosed as T4N2M0. The gastrointestinal surgeon assessed the tumor as unresectable and referred the patient to our department. We performed a Next-generation sequencing test of circulating tumor DNA to obtain the molecular profile because the patient refused to perform a biopsy again. Results of ctDNA suggested the presence of *TP53 p.S12F KRAS p.G12D* mutations, TMB 2.51 Mut/MB (low), and MSS (Supplementary ctDNA results).

According to published data for advanced SBA, oxaliplatin-based regimens were the most frequently used in first-line treatment with a mPFS of six to 11 months. Therefore, from December 22, 2020, to February 24, 2021, four cycles of the XELOX regimen (oxaliplatin 195 mg day 1, capecitabine 1.5 g bid day 1–14) were administered regularly. After two XELOX cycles, the tumor shrank slightly (35 × 28 mm, Supplementary Figures S1A, B), and the response evaluation criteria in solid tumors 1.1 (RECIST 1.1) indicated stable disease. However, at the end of March, the patient appeared with tarry stool again and was admitted to the gastroenterology department at a local hospital for symptomatic treatment. On April 6, 2021, a chest and abdominal contrast-enhanced CT suggested that the tumor progressed and fused with surrounding lymph nodes (65 × 63 mm, Figure 1D).

In second-line chemotherapy for SBA, available data suggested that the prognosis was poor regardless of the chemotherapy regimen. On the contrary, patients may benefit from immunotherapy and those sensitive to ICIs could achieve significantly longer survival. Therefore, immunotherapy was considered to be used in the second-line treatment, and chemotherapy was also administered due to the patient having no positive biomarkers associated with immunotherapy. On April 14, 2021, the patient was administered tislelizumab, an immune checkpoint inhibitor, in combination with irinotecan. The giant nodules in the intestinal wall and the lymph nodes shrunk significantly after two sessions of tislelizumab in combination with irinotecan (Supplementary Figures S1C, D). After 19 therapy sessions, the giant nodules in the intestinal wall disappeared, and the lymph nodes shrunk significantly (Figures 1E, F). Until September 14, 2022, the patient has

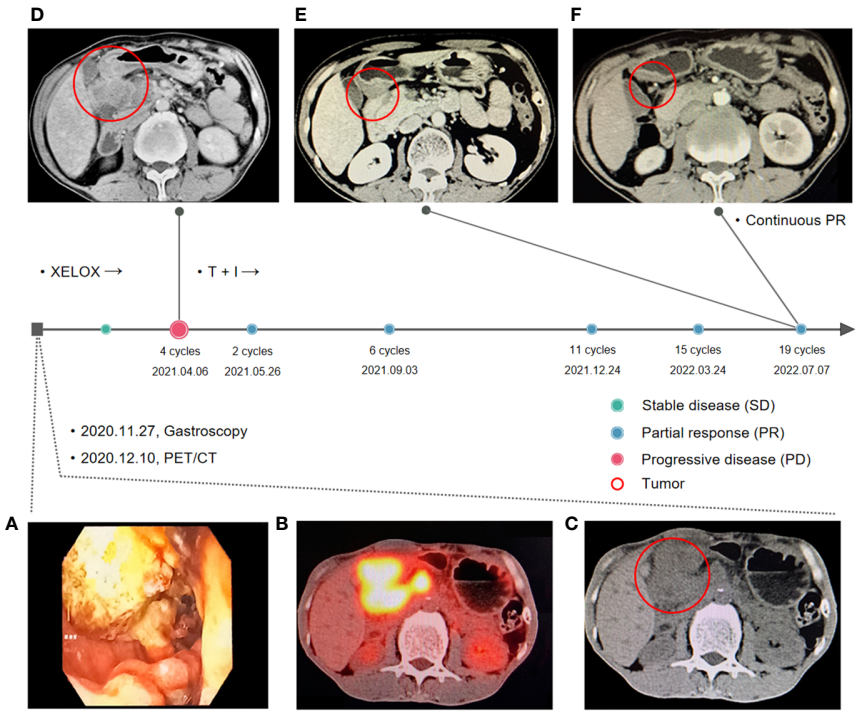

FIGURE 1
Treatment timeline. **(A)** Gastroscopy report at first visit: A large annular mass was observed in the duodenal bulb, extending to the upper part of the descending part. **(B, C)** Positron emission tomography/computed tomography (PET/CT) before the first-line treatment: a significant uneven thickening of the intestinal wall of duodenal bulb (47 × 40 mm) and multiple lymph node metastases. **(D)** Computed tomography after four sessions of XELOX treatment. The tumor progressed and fused with surrounding lymph nodes after four cycles of XELOX (65 × 63 mm). **(E, F)** Computed tomography after two and 19 sessions of tislelizumab in combination with irinotecan.

received 19 cycles of combination therapy of tislelizumab and irinotecan and three cycles of tislelizumab maintenance therapy.

Currently, there is no evidence about chemotherapy combined with ICIs for SBA. Despite the absence of MSS and low TMB, the patient responded well to immunotherapy combined with chemotherapy for 17 months, and the response is still ongoing. No serious adverse events occurred during the treatment. Compared to FOLFIRI regimens with an mPFS of five months in the second-line setting, this combination has achieved great success, which might be mainly attributed to the synergistic effect of immunotherapy and chemotherapy. However, the current study is only one case. The efficacy of the combination of chemotherapy and ICIs in SBA treatment should be further investigated.

The rationale for combining immunotherapy and chemotherapy in SBA

It was difficult to make a decision on the second-line therapy for the patient. First, the ORR of FOLFIRI in SBA was only 21% and the mPFS was 3.2 months (10), while FOLFIRI may be a better option compared with other regimens. Second, in the first-line therapy, the patient quickly developed resistance to fluorouracil and oxaliplatin, suggesting that it may be inappropriate to use fluorouracil in the second-line treatment. Third, SBA patients with positive biomarkers were sensitive to ICIs and likely to achieve significantly longer survival, but those with MSS/low TMB can hardly benefit from single ICIs (15). The effect of immunotherapy in combination with chemotherapy on SBA has not been reported, although this combination appears to be a cornerstone in the treatment of various cancers. It is well known that regardless of the status of MSS and TMB, ICIs combined with chemotherapy can significantly improve the prognosis of several gastrointestinal malignancies. Chemotherapy not only directly kills tumor cells but also produces a synergistic effect for ICIs by promoting immune recognition and countering immunosuppressive elements (23). On one side, tumor-specific antigens and damage-associated molecular patterns (DAMPs) released by chemotherapy-induced cell death can stimulate the maturation of the antigen-presentation cells and upregulate antigen presentation. In contrast, chemotherapy could modulate suppressive tumor immune microenvironment (TIME) by eliminating immune suppressor cells (regulatory T cells (24) and myeloid-derived suppressor cells (25, 26)) and repolarizing tumor-associated macrophage from M2-like to M1-like phenotype. Therefore, immunotherapy combined with chemotherapy was selected as the patient's second-line treatment.

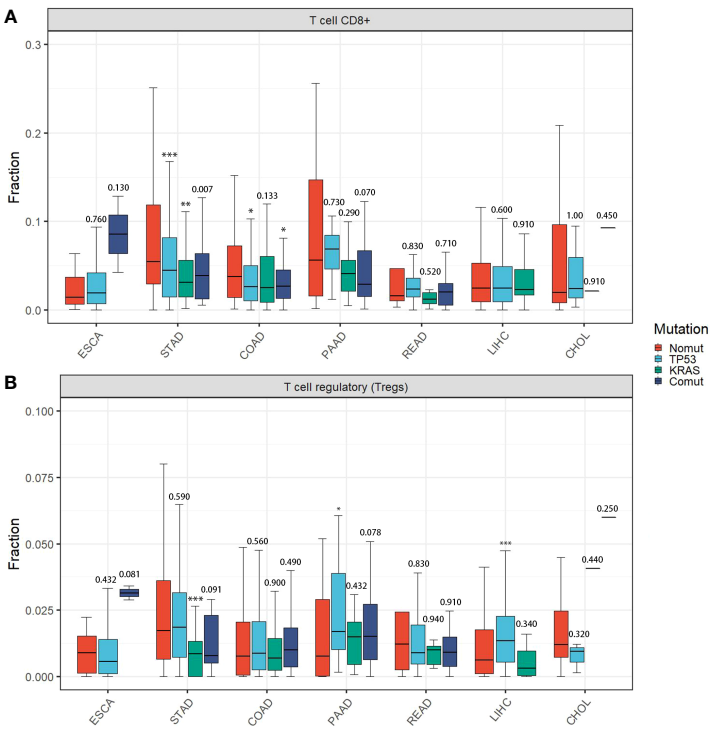

FIGURE 2
Immune cell infiltration among different TP53/KRAS mutation groups in gastrointestinal tumors. **(A)** T cell CD8+. **(B)** T cell regulatory (Tregs). P-values represented TP53/KRAS mutation groups compared to non-mutant group. (Wilcox test. *, P < 0.05; **, P < 0.01; ***, P < 0.001).

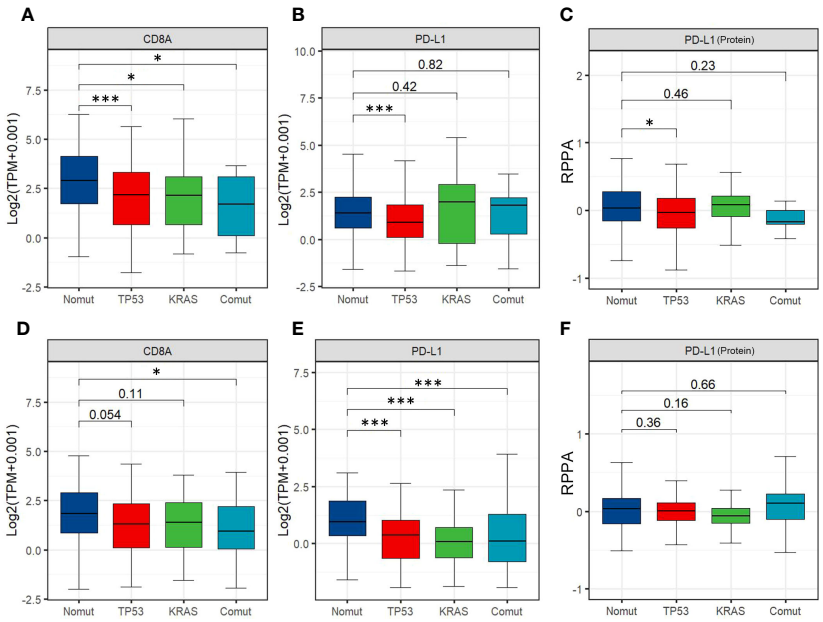

FIGURE 3
(A, B) Expression of CD8A and PD-L1 among STAD'sTP53/ KRAS mutation groups. **(C)** Expression of PD-L1 protein among different TP53/ KRAS mutation groups in STAD. **(D, E)** Expression of CD8A and PD-L1 among different TP53/ KRAS mutation groups in COAD. **(F)** Expression of PD-L1 protein among different TP53/ KRAS mutation groups in COAD. (Wilcox test. *, P<0.05; ***, P<0.001).

TP53/KRAS mutations: Potential immunotherapy biomarkers?

In our case, the patient without MSI-H and high TMB but with co-mutation of *TP53/KRAS* achieved great tumor regression after being treated with irinotecan plus tislelizumab. *TP53* and *KRAS* mutations have been found to exert remarkable effects on TIME in lung cancer, including increasing PD-L1 expression, facilitating T cell infiltration, and augmenting tumor immunogenicity (27). Retrospective analyses suggested *TP53/KRAS* co-mutation might serve as a predictive marker for ICI response in non-small cell lung cancer (27, 28). Thus, we investigated whether *TP53/KRAS* mutations play the same role in gastrointestinal tumors.

Therefore, we assessed the effects of *TP53/KRAS* mutations on TIME, transcriptome, and proteome in gastrointestinal tumors based on The Cancer Genome Atlas (TCGA) database. Seven types of tumors were evaluated, esophageal carcinoma (ESCA), stomach adenocarcinoma (STAD), liver hepatocellular carcinoma (LIHC), cholangiocarcinoma (CHOL), pancreatic adenocarcinoma (PAAD), colon adenocarcinoma (COAD), rectum adenocarcinoma (READ). We found that in STAD and COAD, *TP53/KRAS* mutation groups were associated with the "cold" tumor phenotype (a tumor that is unlikely to benefit from ICIs) (29). In the mutation group, immune cells (CD8+ T cell and regulatory T cell) were less infiltrated (Figures 2A, B), and the expression of *CD8A* and *PL-L1* was lower than in the wild-type *TP53/KRAS* group (Figure 3). Besides, reduced PD-L1 protein expression was also associated with *TP53* mutation in STAD. Although co-mutation appeared to be associated with a "hot" tumor phenotype in ESCA, the evidence was too weak due to insufficient sample size. Apart from this, no significant difference was detected. Unfortunately, these results did not support our hypothesis that *TP53* and *KRAS* mutations can serve as predictive biomarkers for ICI response in patients with gastrointestinal tumors. From a different perspective, however, this finding suggested that the patient's significant benefit was more likely to be associated with the combination of immunotherapy and chemotherapy.

Conclusion

The combination of ICI and chemotherapy should be considered for patients with advanced SBA, particularly duodenal adenocarcinoma.

Data availability statement

Accession numbers for bioinformatics analysis have been provided in Supplementary Table 1. The original contributions presented in the study are included in the article, 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 patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conception/Design: XC and H-BZ. Provision of study material or patients: XC and RZ. Collection and/or assembly of data: XC, XQ, and Y-CQ. Data analysis and interpretation: W-ZL, Y-SY and Y-JZ. Manuscript writing: XC and RZ. Final approval of manuscript: L-RL and YL. All authors have read and approved the submitted version of the manuscript.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.1046513/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Computed tomography after six **(A, B)**, 11 **(C, D)** and 15 **(E, F)** sessions of tislelizumab in combination with irinotecan.

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Endoscopic and pathohistologic features of early gastric signet ring cell carcinoma presented as elevated type: A case report

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Background: Almost all early gastric signet ring cell carcinomas (SRCCs) are the flat or depressed type, and the elevated type is rare. Here, we report the endoscopic and pathohistologic features of a rare case of SRCCs presented as the elevated type.

Case presentation: A 54-year-old man underwent esophagogastrodu odenoscopy in our hospital because of intermittent upper abdominal pain for 6 years. White light endoscopy revealed an elevated lesion that is smooth and reddish and covered with normal mucosa and looked like a polyp. Magnifying endoscopy with narrow-band imaging showed broadened intervening parts, an elongated pit, and a dense microvascular network with focal irregularity. The lesion was considered as early gastric cancer and completely resected with endoscopic submucosal dissection. Pathohistological examination confirmed that the lesion was pure early SRCC that was limited within the mucosal lamina propria (T1a).

Conclusion: Elevated pure gastric SRCC is rare. This is a report of early pure gastric SRCC presented as the elevated type and the description of its endoscopic and pathohistologic features, which will contribute to the early detection of gastric SRCC.

KEYWORDS

case report, early diagnosis, endoscopic feature, gastric cancer, signet ring cell carcinoma

Introduction

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death in the world (1). Gastric signet ring cell carcinoma (SRCC) is a histotype of gastric cancer, which is defined according to the WHO's classification as a poorly cohesive carcinoma composed mainly of tumor cells with a signet-ring morphology (2). Despite a decrease in the global overall incidence of gastric cancer in recent decades, the incidence of gastric SRCC is continually increasing (3). Previous studies showed that gastric SRCC portends a poor prognosis (4). However, with the advancement of diagnosis and treatment for early gastric cancer, the studies have demonstrated that the prognosis of SRCC at an early stage is better than other types of gastric cancer, while that of SRCC at an advanced stage is relatively poorer (5). The early detection of SRCC, therefore, is important for the improvement of a patient's prognosis. Early gastric cancer is mainly detected by endoscopy. Almost all gastric SRCCs are observed *via* endoscopy as flat or depressed lesions, and the elevated type is rare (6, 7). Here, we report a rare case of pure SRCC presented as an elevated lesion and evaluated the pathohistology of its elevated appearance.

Case presentation

A 54-year-old man underwent esophagogastroduodenoscopy (EGD) in our hospital because of intermittent upper abdominal pain for 6 years with a history of *Helicobacter pylori* infection and eradicating *H. pylori* treatment. The patient had no family history of gastric cancer. The C13 breath test was negative. EGD revealed an elevated lesion with the size of 7 mm at the great curvature of the gastric body, and no other abnormal lesion was detected in the stomach after a meticulous examination. White light endoscopy (WLE) showed that the elevated lesion was smooth and reddish, covered with normal mucosa, and looked like a polyp (Figure 1A). The endoscopic narrow-band image (NBI) showed that the elevated lesion presented as cyan change (Figure 1B). Indigo carmine dyeing showed a clear demarcation line and a slightly irregular surface pattern (Figure 1C). Magnifying endoscopy with NBI (ME-NBI) showed broadened intervening parts (intercrypt regions), an elongated pit, and a dense microvascular network with focal irregularity (Figures 1D, E). The widening of the crypt implies that there is some kind of tissue underneath the crypt, such as a tumor, lymphoma, and inflammatory growth that leads to the widening of the crypt. ME-NBI only displayed a dense microvascular network with focal irregularity that is not typical microvascular pattern of early gastric cancer. It is difficult to determine the nature of the lesion under endoscopy; therefore, we performed biopsy, and the examination of biopsy specimens revealed that the lesion was SRCC. We considered the lesion to be early intramucosal gastric cancer. Endoscopic therapy was performed. The lesion was completely resected with endoscopic submucosal dissection. The resected specimen was cut into slices, each at 2 mm width. The red lines represent lesion areas in each slice. Oral is the oral margin of the specimen. Anal is the anal margin of the specimen (Figure 2A). Pathohistology showed that the lesion was pure SRCC (pT1a, 0-IIa type, no venous or lymphatic invasions, and negative for horizontal and vertical margins). The basement of the lesion was occupied by dense fundus glands, and the cancer cells grew into the lumen and formed an elevated lesion (Figure 2B) with the characteristics of a gastric phenotype. There were positive Periodic acid-schiff (PAS) staining (Figure 2C), negative for mucin mucin 2 (MUC-2) (Figure 2D), diffusely positive for mucin (MUC)-5AC (Figure 2E), the Ki-67 level of 30% (Figure 2F), and positive P53 staining (Figure 2G). The further cadherin 1 (CDH1) germline mutation test for the patient was negative. Additional surgical resection is not needed, and no recurrence was observed in the 48-month follow-up.

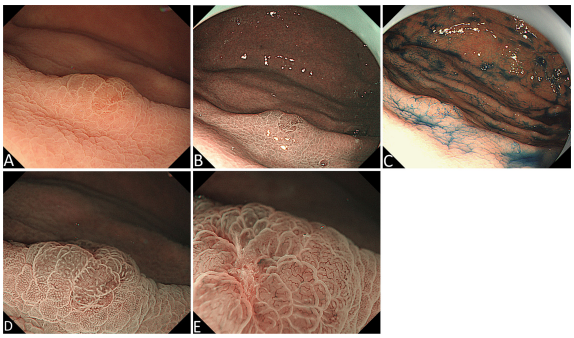

FIGURE 1
Endoscopic manifestation. **(A)** White light endoscopy (WLE) shows an elevated red and smooth lesion that is covered with normal mucosa and looks like a polyp. **(B)** Endoscopic narrow-band image (NBI) shows an elevated lesion with cyan change. **(C)** Indigo carmine dyeing shows a clear demarcation line and a slightly irregular shape. **(D)** and **(E)** Magnifying endoscopy with NBI shows broadened intervening parts (intercrypt regions), an elongated pit, and a dense microvascular network with focal irregularity.

Discussion

SRCC is a common histologic type of early gastric cancer, and, especially in the *H. pylori*–negative early gastric cancer, most are SRCCs (6, 8). Gastric SRCC usually shows lateral spread and destroys the structure of the stomach glands; therefore, the common endoscopic presentation of early gastric SRRC is a discolored, flat, or depressed lesion and elevated presentation is rare. The majority of elevated-type early gastric cancers is differentiated adenocarcinoma (9). In the previous literature, there were some occasional reports about SRCC presented as an elevated lesion. Most of the elevated gastric SRCC cases reported previously were not a single SRCC and usually composed of SRCC

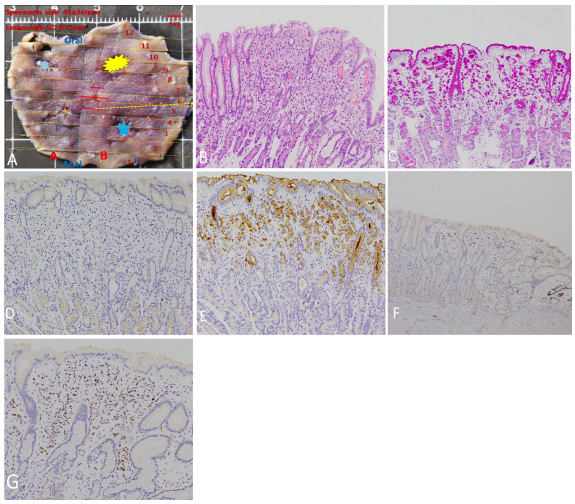

FIGURE 2
Pathohistologic manifestation. **(A)** The resected specimen. The stars represent the sites of four-quadrant biopsies. The red lines represent lesion areas in each slice. Oral is the oral margin of the specimen. Anal is the anal margin of the specimen. **(B)** Pathohistology shows pure signet ring cell carcinoma. The basement of the lesion is occupied by dense fundus glands, and signet ring cell carcinoma cells grow into the lumen to form an elevated lesion. **(C)** Positive PAS staining. **(D)** Negative MUC-2 staining. **(E)** Diffusely positive MUC-5AC staining. **(F)** Positive Ki-67 staining of 30%. The intense ki67 stain on a deep gland on the far right of the panel is just the proliferative end of the bottom of the crypt. **(G)** Positive P53 staining.

and moderately to poorly differentiated adenocarcinoma (10). The elevated formation was believed to be caused by obvious fibrogenesis or a combination of moderately to poorly differentiated adenocarcinoma, and SRCC produced the elevated lesion. In a case of elevated SRCC recently reported by Misumi et al. (11), there was also an obvious proliferation of fibromuscular tissue in the background mucosa surrounding the lesion that lifted both tumor and non-tumor tissue toward the luminal side to form an elevated appearance. In our case, it was pure SRCC and had no fibrogenesis in the mucosa surrounding the lesion and inside the lesion, which is different from previously reported gastric elevated SRCC. Considering the pathohistological finding in this case with dense fundus glands at the basement of the lesion and remnant glands within the lesion, it can be speculated that dense fundus glands prevent cancer cells from growing downward and remnant glands support cancer cells to grow into the lumen, which leads to the formation of an elevated lesion. Pure gastric SRCC presented as the elevated type is rare. When an elevated lesion was found in the stomach, endoscopists should first differentiate neoplastic from non-neoplastic lesions. It is also important to differentiate epithelial from non-epithelial tumors for a suspected tumor lesion. Endoscopists should not overlook the elevated type of SRCC, although it is rare. In addition, the surface of early gastric SRCC is often covered by a normal mucosal epithelium and it is sometimes difficult to differentiate the lesion from the other common elevated lesions based on only endoscopic findings. Therefore, a biopsy should be mandatory when a single elevated lesion is seen in the stomach. In addition, it is worth noting that this lesion displayed a dense microvascular network with focal irregularity that is not typical microvascular pattern of early gastric cancer and was not described in the previous literature. Whether the dense microvascular network with focal irregularity is also an abnormal microvascular pattern of early gastric cancer needs plenty of evidence and investigations.

In conclusion, elevated gastric SRCC is rare. We herein present the endoscopic and pathohistologic features of an early elevated pure gastric SRCC. To our knowledge, this is the first report of the elevated early pure gastric SRRC and the description of its endoscopic and pathohistologic features, which contributes to promote the early detection of gastric SRCC and improve patients' 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 author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Zunyi Medical University. 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

The study design was performed by BT and LD. The review of patient data and critical comments were performed by LD, XW, and BT. LD and XW reviewed and described the pathohistologic and endoscopic findings. The manuscript was written by LD and BT. All authors read and approved the final manuscript.

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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.

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Case Report: Endoscopic manifestations and clinical features of small intestinal lymphangioma—A report of two cases

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Objective: The aims of this study were to analyze the clinical characteristics, auxiliary examinations, and treatment measures of small intestinal lymphangioma and to improve the clinical diagnostic ability of clinicians.

Methods: This paper reports two cases of small intestinal lymphangioma in the Department of Gastroenterology, the First Affiliated Hospital of Soochow University, and makes a comprehensive analysis.

Results: A 31-year-old woman went to the hospital with complaints of dizziness, fatigue, and anemia. A 52-year-old woman complained of upper abdominal pain and went to the hospital with abdominal pain awaiting investigation. Both patients were subjected to three major routine examinations, tumor complete set, CT, capsule endoscopy, and deep enteroscopy, and both of them underwent complete resection of the affected intestinal segment. Pathology showed that both patients had small intestinal lymphangioma.

Conclusions: The clinical manifestations of small intestinal lymphangioma lack specificity. Capsule endoscopy and deep enteroscopy are helpful for clinical diagnosis, and pathological examination is still the gold standard. Surgical treatment can achieve better results.

KEYWORDS

case report, small intestinal lymphangioma, surgical treatment, clinical features, capsule endoscopy, enteroscopy

Introduction

Small intestinal lymphangioma is a rare disease of the digestive tract. It often presents as chronic gastrointestinal bleeding due to mucosal compression, bleeding, necrosis, or ulceration caused by enlarging the tumor. It accounts for 6% of small intestinal tumors in children and 1.4%–2.4% in adults (1). The clinical symptoms of small intestinal lymphangioma are insidious. It is not easy to detect at an early stage and is often found during physical examination. A study found that abdominal pain, gastrointestinal bleeding, and anemia are the most common clinical symptoms of small intestinal lymphangioma (2). In this paper, anemia and abdominal pain were the main reasons for the admission of two patients. Both patients underwent laparoscopic surgery and had favorable prognosis. Therefore, by reporting two cases in our hospital and reviewing domestic and foreign literature, it aims to provide some help for the diagnosis and treatment of small intestinal lymphangioma in clinical work.

Case reports

Patient A, a 31-year-old woman, went to the hospital on 1 June 2017 because of "fatigue and dizziness for 1 month and aggravation for 1 week". The patient developed dizziness and fatigue without obvious inducement 1 month ago, and her symptoms became worse in the past week. Then, she went to the emergency department of our hospital. Blood routine examination showed a hemoglobin (HGB) of 38 g/L, and esophagogastroduodenoscopy showed chronic superficial gastritis. Reexamination after blood replenishment treatment still showed severe anemia, and the symptoms of dizziness and fatigue did not improve significantly. Therefore, the patient was in the hospital due to "anemia of unknown origin". During hospitalization, the patient did not have nausea, vomiting, abdominal pain, abdominal distension, black stool, and bloody stool. Physical examination showed anemic appearance, soft abdomen, no tenderness, rebound pain, no obvious mass, and bowel sounds six times per minute. Admission diagnosis was as follows: anemia of unknown origin. Blood routine showed HGB 45 g/L; urine routine revealed 94 RBC/μl; stool occult blood test was positive; tumor full set showed erythropoietin >762.00 mIU/ml. Contrast-enhanced CT of chest, abdomen, and pelvis revealed a few fibrosis foci in the left lower lung, small hepatic cysts, and slightly reduced density of heart cavity, consistent with anemia. Capsule endoscopy showed that the mucosa at the proximal end of the jejunum is polypoid, with congestion, edema, erosion, white moss attachment, and active bleeding, as shown in Figure 1. Deep enteroscopy showed a granular hyperplasia of the mucosa 190–200 cm away from the ligament of Treitz. The surface was erosive, with white speckles attached, and the distal mucosa was normal, as shown in Figure 2. The initial diagnosis of the patient was jejunal lesion (nature unknown because of the patient's refusal of pathological examination). Under deep enteroscopy, the physician took three pieces of jejunal tissue 190–200 cm away from the ligament of Treitz with a total diameter of 0.2 cm. Pathology revealed chronic inflammation of jejunal mucosa and cystic dilatation of lymphatic vessels in the mucosa propria, as shown in Figure 3. The patient received surgical treatment on 14 June 2017. During the operation, the surgeon removed a section of intestine with a length of 17 cm and a diameter of 2–2.5 cm. There is a granular protrusion 5 cm away from the cutting end of one side, with a range of 7 cm × 5 cm × 1.5 cm. At the same time, the cut surface was bleeding, and milky white liquid flowed out from the peripheral adipose tissue. Pathology showed small intestinal angioma, and no lesions involved the resection end, as shown in Figure 3. The patient left the hospital after anti-inflammatory and nutritional support treatment.

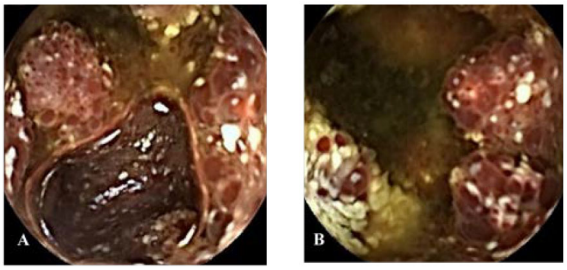

FIGURE 1
Capsule endoscopy **(A, B)** images of patient A. **(A, B)** Mucosa of the proximal jejunum showed polypoid elevation, surface hyperemia, edema, erosion, white moss attachment, and active bleeding.

Patient B, a 52-year-old woman, went to the hospital on 3 November 2020 because of "recurrent upper abdominal pain for more than 20 days". The patient had abdominal pain more than 20 days ago. The pain was mainly in the middle and upper abdomen, which was like a paroxysmal knife cutting and relieved after several seconds. There was no radiating pain in the waist and back, no abdominal distension, and no nausea and

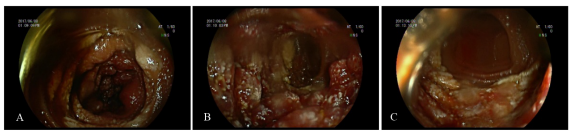

FIGURE 2
Deep enteroscopy **(A–C)** images of patient A. **(A–C)** Granular hyperplasia of the mucosa 190–200 cm away from the ligament of Treitz, and the surface was erosive, with white speckles attached.

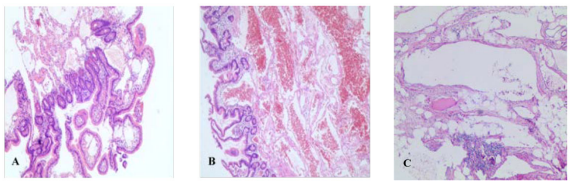

FIGURE 3
Pathological results (HE staining, ×100). **(A)** Pathology of patient A after deep enteroscopy. **(B)** Postoperative pathology of patient A. **(C)** Postoperative pathology of patient B.

vomiting. Physical examination showed tenderness in the middle and right upper abdomen without rebound pain and muscle tension. The abdomen is flat without gastrointestinal type or peristalsis wave, there was no obvious mass, and the bowel sounds are normal. Admission diagnosis revealed abdominal pain of unknown origin. There were no abnormalities in blood routine, CRP, biochemistry, AFP, CA19-9, and CEA. Abdominal enhanced CT showed local intestinal wall edema, structural disorder, and mesenteric edema, as shown in Figure 4. Esophagogastroduodenoscopy revealed bile retention fluid in the stomach. Capsule endoscopy showed ileal lesions, with multiple continuous nodular changes in the mucous membrane, and the surface was red and erosive, as shown in Figure 5. Contrast-enhanced CT of the small intestine showed segmental intestinal wall thickening in the terminal ileum with obvious edema of the

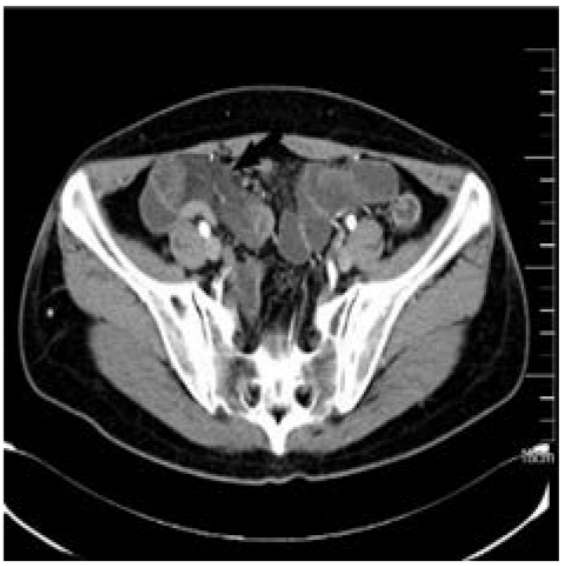

FIGURE 4
CT of patient B's abdomen. Pelvic local intestinal wall edema, disorder, and mesenteric edema.

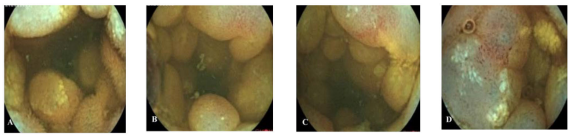

FIGURE 5
Capsule endoscopy of patient B. **(A–D)** The lesion mucosa showed continuous multiple nodular protrusions, with redness and erosion on the surface.

surrounding mesentery, which suggested the possibility of inflammatory bowel disease (IBD). CT three-dimensional reconstruction of small intestine showed segmental intestinal wall thickening in the distal ileum with obvious edema in the surrounding mesangium. After consultation with the imaging department, the patient was suspected to have Crohn's disease (CD) due to the ileal lesions. However, the clinical features and course of the patient did not conform to the typical manifestations of CD, so surgical treatment was important for diagnosis and treatment. The patient underwent surgical treatment on 1 December 2020. Intraoperative exploration revealed a 30-cm-long part of the small intestine with obvious edema and thickening 4.5 m away from the ligament of Treitz. The intestinal lumen was narrow and the mesangial surface was uneven, showing cystic jelly-like changes. During operation, the operator dissected a piece of intestine with a length of 38 cm and a diameter of 4–7 cm. There is an 11 cm × 7 cm mucous bulbous area 6.5 cm away from the cut end on one side and 15 cm from the cut end on the other side. The mesenteric surface was hard in texture, and the cut surface was spongy and gray yellow, as shown in Figure 6. Pathology indicated small intestinal lymphangioma, and no cancer involved both ends, as shown in Figure 3. After the operation, she left the hospital after receiving anti-inflammatory and nutritional support therapy.

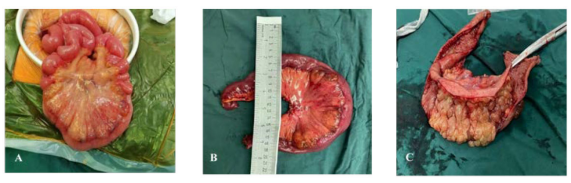

FIGURE 6
Surgical excision of gross specimen for patient B. **(A)** Diseased bowel piece; **(B)** cut a section of bowel intraoperatively, with a length of 38 cm and a diameter of 4–7 cm; **(C)** 6.5 cm from the end of one incision and 15 cm from the end of the other, a mucous vesicular uplift area of 11 cm × 7 cm can be seen. The mesentery surface is hard in texture, and the section is spongy and gray yellow.

Discussion

Lymphangioma is a benign tumor caused by congenital malformation of the lymphatic system (3). It usually occurs in the head, neck, and axilla of children. Lymphangioma occurring in the abdominal cavity is rare, especially in adults. The most common site of small intestinal lymphangioma was the mesentery, followed by omentum, retromesentery, and retroperitoneum (4). Mesenteric lymphoma is rare, accounting for less than 1% of all lymphangiomas (5, 6).

Through literature review, we found that there are no characteristic clinical manifestations in the early stage of small intestinal lymphangioma. With the enlargement of the tumor, it could cause various clinical symptoms. The common symptoms were abdominal pain caused by intestinal irritation, followed by gastrointestinal bleeding and anemia, intestinal obstruction, and hypoproteinemia. Some cases presented with non-specific gastrointestinal symptoms, such as nausea, vomiting, abdominal distension, diarrhea, and anorexia (7–9). In the process of clinical diagnosis and treatment, doctors rely solely on clinical manifestations, which could easily result in missed diagnosis and misdiagnosis. Extra examination can help to further clarify the diagnosis. Imaging examination has suggestive significance, among which CT examination has high sensitivity. It has more advantages among many imaging examination methods and is the first choice for patients with suspected small intestinal lymphangioma (2, 10). CT showed clear, non-enhanced cystic lesions (2). In gastrointestinal endoscopy, capsule endoscopy and deep enteroscopy play an important role in the diagnosis of small intestinal diseases. Capsule endoscopy can help locate small intestinal masses by directly viewing the whole small intestinal mucosa, which is one of the preferred methods for diagnosing small intestinal diseases (11). Microscopically, small intestinal lymphangioma showed multiple red grape-like nodules, vegetable patterns, or polypoid lesions on the intestinal wall, with erosion, ulceration, and bleeding on the surface. Deep enteroscopy can detect lesions and biopsy for pathological examination, which has a higher diagnostic value than other endoscopic methods (12). In recent years, capsule endoscopy and deep enteroscopy has improved the detection rate of small intestinal lymphangioma. However, since the lesion is located in the small intestine, endoscopic examinations often fail to detect the lesion site and thus miss the diagnosis. Therefore, for most patients, a diagnosis was made after surgical resection of the lesion and submission for pathology (13). Histopathological examination is still the gold standard for diagnosis. A large lymphatic cavity can be seen from the specimen under the microscope, with collagen and smooth muscle covered on the surface. Although small intestinal lymphangioma is a benign tumor, it can still show borderline changes and there is a risk of malignant transformation into lymphangiosarcoma. At the same time, we recommend patients to undergo radical surgical resection because the lesions may further grow and compress adjacent organs, resulting in volvulus, intestinal obstruction, secondary infection, rupture, bleeding, and other complications (14).

Small intestinal lymphangioma should be distinguished from intestinal endometriosis. Endometriosis refers to the growth of endometrial tissue outside the uterine cavity and myometrium. When ectopic endometrium invades the intestine, it is intestinal endometriosis. The disease has no specific clinical manifestations. When it invades the rectum and sigmoid colon, a series of intestinal symptoms such as abdominal pain, diarrhea, constipation, hematochezia, and even intestinal obstruction can occur. It is difficult to distinguish the two diseases based on clinical manifestations, and thus, it could easily result in misdiagnosis. The common diagnostic methods of this disease include ultrasound, CT, colonoscopy, and laparoscopy. Ultrasonography mainly showed thickening of the affected intestinal wall and hypoechoic changes (15, 16). Colonoscopy may show thickening of the intestinal wall at the lesion site, polypoid changes in the mucosa, and local eminence or intestinal lumen stenosis (17). Pathological examination is the best examination method. However, due to the lack of characteristic microscopic manifestations in the early stage of this disease and the lack of recognition of the characteristics of this disease by clinicians, the detection rate of endoscopic biopsy for pathological examination is low. Therefore, surgical treatment is the first choice for symptomatic patients with intestinal endometriosis, and pathological examination of the specimens removed during surgery can greatly improve the detection rate of the disease and achieve the purpose of treatment.

In this paper, two patients went to the hospital with anemia and abdominal pain as the main symptoms. CT examination of patient A showed no abnormality, while patient B showed intestinal wall edema and disorder; thus, a diagnosis could not be made. Capsule endoscopy and deep enteroscopy also failed to diagnose small intestinal lymphangioma. As patient B showed symptoms of IBD, other intestinal manifestations may cover up lymphangioma-related symptoms, leading to a missed diagnosis. The diagnosis is clear by pathological results, which further proved that pathological examination is still the gold standard for the diagnosis of small intestinal lymphangioma. According to the size and shape of the proliferative lymphatic vessels in the tumor, lymphangioma can be classified into three types: capillary lymphangioma, cavernous lymphangioma, and cystic lymphangioma (5). Sometimes, the three types of lymphatic vessels can coexist, which is difficult to classify. Surgical treatment is the gold standard treatment for small intestinal lymphangioma. In this study, both patients underwent laparoscopic exploratory laparotomy combined with partial small bowel resection to remove the diseased intestinal segment. Intraoperative pathology was performed on the diseased intestinal segment during the operation. Both patients

recovered well after anti-inflammatory and nutritional support treatment, and the disease has not recurred so far.

In conclusion, small intestinal lymphangioma is a rare tumor of the small intestine with a lack of clinical specificity. Imaging examination is of certain significance, and capsule endoscopy and deep enteroscopy are helpful for clinical diagnosis. The pathological results can make a definite diagnosis of small intestinal lymphangioma. Small intestinal lymphangioma is a benign tumor, but malignant transformation may exist. Surgical treatment is the first choice, with the advantages of quick recovery and good 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 author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Soochow University. 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

FL contributed to conception and design of the study. LW wrote the first draft of the manuscript. HF and BC wrote sections of the manuscript. All authors contributed to manuscript revision, read, 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.

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Post-operative ctDNA monitoring in stage I colon cancer: A case report

Stephanie L. Alden[1], Harmeet Dhani[2], Charuta C. Palsuledesai[2], Shifra Krinshpun[2], Adham Jurdi[2], Eric Christenson[3], Ilene Browner[3] and Samuel Rosner[3]*

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Circulating tumor DNA (ctDNA) level monitoring after surgery for colon cancer has been studied in stage II and III colon cancer to risk-stratify patients for adjuvant therapy. However, there is less data regarding the role of this diagnostic tool in the management of stage I disease, where current recommended surveillance is limited to screening colonoscopy at one year. In this report, we describe the case of a 57-year-old man with stage I colon cancer who underwent complete resection with adequate lymph node surgical sampling, normal preoperative CEA and no evidence of metastatic disease on initial imaging. The patient elected to undergo serial ctDNA monitoring after surgery. Rising ctDNA levels, five months after resection, prompted cross-sectional imaging which demonstrated metastatic disease to the liver. The patient subsequently received five cycles of leucovorin, 5-fluorouracil, oxaliplatin, and irinotecan with bevacizumab (FOLFOXIRI-Bev) and definitive microwave ablation to the liver metastases, with resulting undetectable ctDNA levels. The patient's imaging and colonoscopy one-year post-operatively showed no evidence of disease, with ctDNA levels remaining undetectable. This report highlights the value of ctDNA monitoring in patients with early-stage colon cancer and suggests that further, large-scale studies may be warranted to determine its appropriate clinical use.

KEYWORDS

circulating tumor (ctDNA), molecular residual disease, stage I, recurrence, case report, colon cancer

Introduction

While initial therapy for non-metastatic, resectable colon cancer is well-established, adjuvant chemotherapy is not recommended for those with stage I and low-risk stage II disease. Instead, surveillance of stage I disease after curative-intent resection solely involves colonoscopy one year after surgery (1). In stage II colon cancer, high risk factors such as

degree of differentiation, pathological stage, lymphovascular invasion, obstruction or perforation, and/or inadequate lymph node sampling have guided clinicians to offer adjuvant chemotherapy, however, recent studies suggest that these criteria may not optimally select for patients who benefit from treatment, which may account for the approximately 3-8% and 12-24% three-year recurrence rate seen in patients with stage I and II colorectal cancer, respectively (2–5). Current staging guidelines that dictate surveillance strategies for early-stage disease use tumor size and depth of invasion (T), lymph node involvement (N), and metastatic disease (M) (6). This current staging system does not incorporate genomic markers of risk, although they play a major role in characterizing underlying disease biology, as seen in many other malignancies, such as breast cancer and renal cell carcinoma (6–9).

More recent data suggest that circulating tumor DNA (ctDNA) level is a useful biomarker in colorectal cancer to identify patients at high risk of recurrence, as well as which patients may benefit from adjuvant therapy (10, 11). Studies have demonstrated that patients with stage I disease have lower pre-operative ctDNA levels as compared to patients with stage II and III disease, consistent with a lesser overall disease burden (12). While patients with stage I colon cancer are less likely to recur than those with stage II or stage III disease, those who do recur post-operatively have detectable ctDNA levels before recurrence is detected *via* imaging (12, 13). However, most studies of ctDNA in assessing recurrence risk are limited to patients with stage II and stage III colon cancer, with stage I patients only accounting for 4-16% of study populations (12–14). Currently no randomized clinical trials have explored the use of ctDNA for disease monitoring and treatment stratification in stage I disease (15, 16).

In this clinical vignette, we present a patient with stage I colon cancer whose clinical course changed dramatically as a result of incorporating post-operative ctDNA testing into recommended surveillance, leading to earlier detection of metastasis, modification in treatment plan, and an overall more favorable outcome. Thus, this case highlights the potential impact of this diagnostic tool's use in disease monitoring and perioperative management for early-stage colon cancer.

Case description

A 57-year-old male patient presented with new onset rectal bleeding. Evaluation with colonoscopy showed a mass in the hepatic flexure, with biopsy demonstrating moderately differentiated adenocarcinoma. Initial fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) demonstrated a small focus of FDG activity in the proximal transverse colon correlating with nodular soft tissue thickening on CT. No evidence of metastatic disease was present radiographically. An initial right hepatic lobe lesion noted on CT (Figure 1) and PET-scan was later confirmed to represent a benign hemangioma based on follow up magnetic resonance imaging (MRI). At the time of diagnosis, the patient had undetectable carcinoembryonic antigen (CEA) levels (Figure 2A).

The patient underwent a right hemicolectomy within one month of diagnosis. Histology showed a 2.1 cm lesion consistent with moderately differentiated adenocarcinoma with mucinous features invading the muscularis propria, with negative margins. Adequate lymph node sampling was performed, with 16 lymph nodes returning negative for adenocarcinoma. Final TNM staging was pT2N0M0, consistent with stage I colon cancer. Immunohistochemistry for mismatch repair (MMR) proteins demonstrated MMR-proficient tumor, with retained nuclear expression of MLH1, PMS2, MSH2, and MSH6. There was no lymphovascular invasion, perineural invasion, or macroscopic tumor perforation. Genomic analysis (Altera Tumor Genomic Profile, Natera, Inc.) showed that the tumor had low tumor mutational burden (TMB, 2 mutations/megabase), was microsatellite stable (MSS), and had genomic alterations including *APC* (D170 loss of function mutation), *APC* (E1397 stop gain mutation), *KRAS* (G12D), and PIK3R1 (K447_Y452 deletion).

Initially, the patient was offered surveillance with colonoscopy at one year after surgery, per National Comprehensive Cancer Network (NCCN) guidelines (1). However, after further discussion and shared decision-making, the patient pursued ctDNA testing using a personalized, tumor-informed platform (Signatera™ Molecular Residual Disease Test, Natera, Inc.). ctDNA was detected and quantified using a personalized, tumor-informed, multiplex PCR (mPCR) next-generation sequencing (NGS)-based assay (Signatera™, Natera, Inc.) as previously described (14). Briefly, a set of 16 high-ranked, patient-specific, somatic, clonal single nucleotide variants (SNVs) were selected for mPCR testing by whole-exome sequencing (WES) performed on formalin-fixed and paraffin-embedded (FFPE) tumor tissue and matched normal blood sample. The mPCR primers targeting the selected personalized SNVs were designed, synthesized, and used to track ctDNA in the patient's longitudinal plasma sample. Plasma samples with at least two out of 16 SNVs detected were considered ctDNA-positive. ctDNA concentration was reported as mean tumor molecules (MTM) per mL of plasma.

The patient's ctDNA level, measured using the assay described above, 25 days after surgery was 0.42 MTM/mL, with repeat ctDNA analysis six weeks after surgery indicating persistently low-level positive ctDNA at 0.55 MTM/mL (Figure 2A). Longitudinal ctDNA monitoring revealed an ongoing increase to 10.96 MTM/mL five months after surgery (Figures 2A, B). This rapid rise in ctDNA level prompted a CT scan of the chest, abdomen, and pelvis with contrast that detected a 2.4 x 1.8 cm ill-defined hypoattenuating lesion in

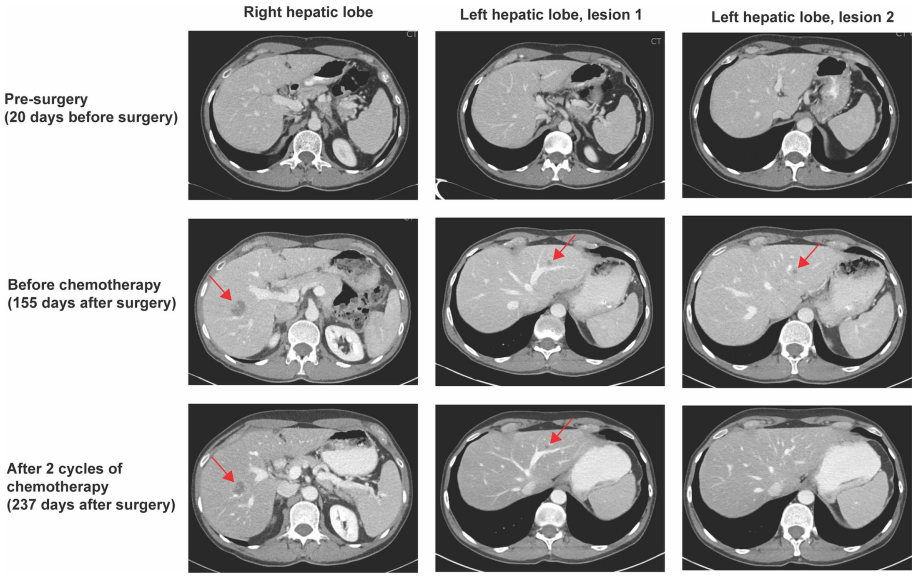

FIGURE 1
CT scan results. CT scan 20 days prior to right hemicolectomy did not show any evidence of metastatic disease (top panel). Rising ctDNA levels prompted a CT scan on post-operative day 155, which revealed a 2.4 x 1.8 cm ill-defined hypoattenuating lesion in the right hepatic lobe, as well as 0.8 cm and 0.4 cm nodules in the left hepatic lobe (red arrows, middle panel). An interval CT scan after two cycles of chemotherapy showed response of all hepatic lesions (red arrows, bottom panel).

the right hepatic lobe, as well as 0.8 cm and 0.4 cm nodules in the left hepatic lobe, concerning for oligometastatic disease (Figure 1). Given the patient's baseline molecular and histopathologic profile, standard multi-drug chemotherapy regimens were discussed for management of his now oligometastatic disease (1). Taking into account the patient's robust Eastern Cooperative Oncology Group (ECOG) performance status of 0, along with the goal of maximizing objective response to systemic therapy, a shared decision was made to initiate front-line fluorouracil, oxaliplatin, and irinotecan plus bevacizumab (FOLFOXIRI-Bev) to manage his oligometastatic colon cancer approximately five months after definitive surgery (1, 17).

Prolonged afebrile neutropenia requiring growth factor support complicated the patient's initial chemotherapy course and led to a delay in cycle two. A ctDNA level after the first cycle of FOLFOXIRI-Bev decreased to 0.04 MTM/mL (Figure 2A). Interval imaging after two cycles of chemotherapy showed a response of all hepatic lesions, with ctDNA level cleared to undetectable (0.00 MTM/mL) (Figure 1; Figure 2A). After completing three cycles of chemotherapy, in consultation with surgical oncology, the patient elected to have definitive microwave ablation of the three hepatic metastases. The patient's bevacizumab was held during the third cycle of chemotherapy, pre-operatively, but was resumed during his fourth cycle, post-ablation. The patient's ctDNA level remained undetectable (0.00 MTM/mL) (Figures 2A, B) throughout the remainder of his adjuvant treatment course. Considering the lack of detectable ctDNA and persistent side effects from chemotherapy experienced by the patient, a shared decision was made to defer the sixth cycle of chemotherapy and, overall, the patient completed five cycles of adjuvant chemotherapy. Colonoscopy one year after surgery was unremarkable, and no new metastatic lesions were noted on repeat CT scan after chemotherapy completion. Of note, the patient's CEA levels remained within normal limits (≤3.0 ng/mL per institutional assay) throughout his disease course, from diagnosis to recurrence to post-treatment monitoring (Figure 2A).

Discussion

Current surveillance for early-stage colon cancer after definitive resection entails measuring CEA levels, routine blood work, CT imaging, and colonoscopy (1). However, these diagnostic methods frequently fail to capture patients with micrometastatic disease who will recur without additional intervention. This notion is particularly true for patients with stage I disease, where current guidance forgoes radiographic monitoring, and little data exists regarding the risk for recurrence (1–5). In the clinical case presented above, serial ctDNA measurement prompted additional imaging, leading to earlier intervention, with aggressive systemic therapy as a bridge to definitive treatment.

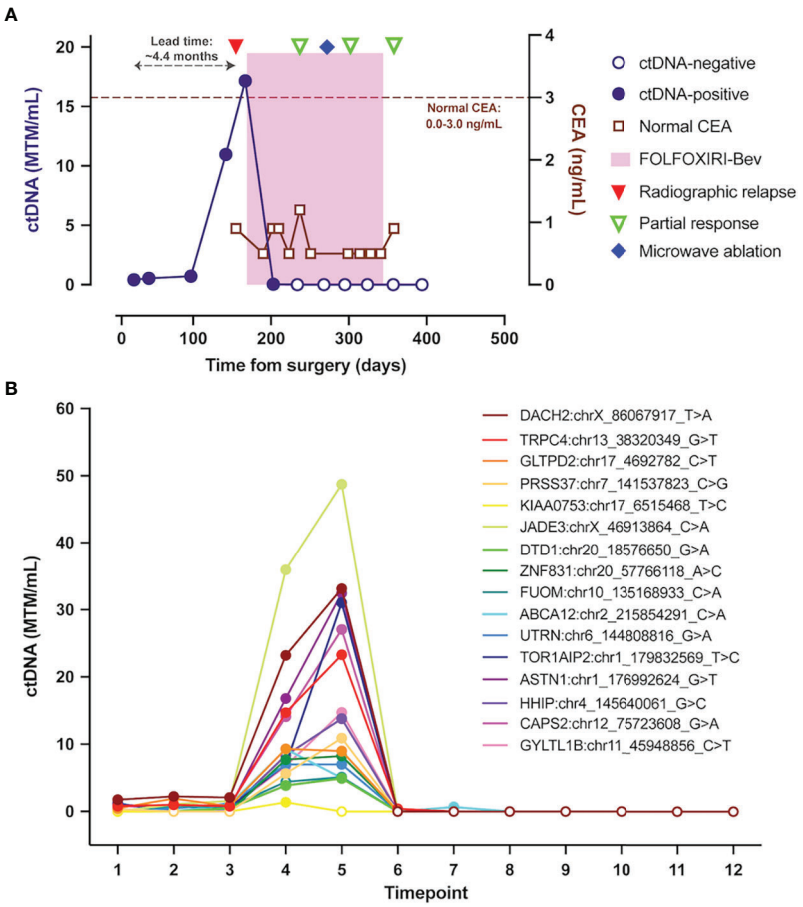

FIGURE 2
ctDNA dynamics throughout the clinical course. **(A)** Overview plot depicting composite ctDNA changes as measured in MTM/mL, along with radiographic imaging and therapeutic interventions. **(B)** Changes in levels of patient-specific variants identified and tracked using Signatera™ Molecular Residual Disease Test. ctDNA, circulating tumor DNA; MTM/mL, mean tumor molecules per milliliter of plasma.

Our patient's ctDNA levels after chemotherapy correlated with radiographic response after the first two cycles of chemotherapy. This combination of laboratory and radiologic improvement led the treatment team to pursue more definitive disease control with microwave ablation of his hepatic lesions. Consistent with findings in other studies, our patient's CEA level was negative despite radiologic evidence of recurrence and positive ctDNA (Figure 1; Figure 2A), suggesting that the use of multiple biomarkers to monitor for recurrence may enable earlier disease detection (12, 14–16, 18, 19).

ctDNA monitoring after definitive treatment of stage II and stage III colon cancer has shown promise in assessing recurrence risk, with the major focus being the use of ctDNA level to guide escalation and de-escalation of therapy in the adjuvant setting (10, 11, 15, 16). These encouraging findings have raised enthusiasm over the potential role ctDNA may ultimately play in personalizing peri-operative treatment strategies based on dynamics of molecular response (15, 16). As a result, almost a dozen clinical trials have been completed or are underway to determine if post-operative and post-adjuvant chemotherapy ctDNA monitoring can be used to tailor treatment based on detection of post-operative ctDNA levels (15, 16, 20). Such efforts may help better select patients in need of more aggressive treatment approaches, while simultaneously sparing those with undetectable ctDNA levels who may not benefit from further chemotherapy (10, 15, 16).

While studies evaluating the use of ctDNA to guide treatment have focused on the potential to refine patient selection for adjuvant chemotherapy in stage II colon cancer and potentially de-escalate therapy in patients with stage III colon cancer, few studies have focused on the use of ctDNA to determine when to escalate therapy in stage I colon cancer (10, 11, 15, 16, 20). Our case suggests that ctDNA could be a useful tool to select patients who should undergo closer monitoring to detect early recurrence, with the result being

curative treatment options. In those with stage I disease who do recur, ctDNA could also help guide duration and escalation of chemotherapy in the setting of recurrence. Anecdotally, in an interim analysis of the GALAXY trial, part of CIRCULATE Japan, the only patient with stage I colon cancer who was ctDNA positive after surgical resection eventually developed disease recurrence (21).

Given the anecdotal nature of a single report, findings and conclusions from this case may not be applicable to other clinical scenarios. Indeed, additional investigation into the accuracy and utility of ctDNA monitoring for early-stage disease is an ongoing area of research, albeit with significant clinical potential (22). The cost effectiveness of this intervention must also be taken into account, particularly given that patients with stage I disease are less likely to recur than those with stage II and III disease (16). Certainly, not all patients with lower risk stage I or II colon cancer require more intensive surveillance, however, non-invasive tools such as ctDNA monitoring may help further stratify patients to determine those who may benefit from additional monitoring and treatment. Looking forward, multi-modal approaches beyond the standard TNM staging classifications, with integration of genomic data, may better capture the risk of recurrence, as has been seen in other malignancies, such as lung adenocarcinoma (23). While still under investigation, such approaches may more accurately risk-stratify patients with early-stage disease.

Conclusion

Our clinical case highlights the potential benefits of ctDNA monitoring in stage I colon cancer. This diagnostic tool can help identify patients at increased risk for recurrence. In our case, early detection of low-volume metastatic disease after ctDNA monitoring prompted early and aggressive treatment strategies, ultimately leading to a favorable clinical outcome.

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. 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

All authors contributed to the article and approved the submitted version.

Conflict of interest

SA–No disclaimers to report. HD – Past employee of Natera, Inc., with stocks or option to own stocks. CP – Employee of Natera, Inc. with stocks or option to own stocks. SK – Employee of Natera, Inc. with stocks or option to own stocks. AJ – Employee of Natera, Inc. with stocks or option to own stocks. EC - Research Funding: Pfizer; Research Collaborations: Haystack Oncology, Natera; Consulting: Seres Therapeutics. IB – No disclaimers to report. SR– No disclaimers to report.

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Crystal-storing histiocytosis in the stomach: A case report and review of the literature

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Crystal-storing histiocytosis (CSH) is a rare disorder characterized by the accumulation of non-neoplastic histiocytes that contain intracytoplasmic crystallized immunoglobulins. Although CSH can occur in various organs, gastric CSH is very rare. Therefore, diagnosing gastric CSH remains a challenge. Here, we present the case of a 69-year-old man with localized gastric CSH who presented with positive fecal occult blood for 2 days. Gastroscopy showed that there was a piece of irregular whitish focus in the big bend of the gastric antrum, which was soft and elastic. Histologically, the biopsied gastric mucosa showed chronic inflammation, mild activity with erosion, and numerous eosinophilic mononuclear cells containing fibrillary crystalloid inclusions in the lamina propria. Immunohistochemically, these crystal-containing cells were positive for CD68/PGM1 and Igk, which revealed that the cells were histiocytes harboring kappa light chain-restricted immunoglobulin crystals. Electron microscopic examination showed numerous high-electron-density particles in the cytoplasm of cells, with crystal structures of different sizes and shapes. This case highlights how immunohistochemistry can help with differential diagnosis and classification.

KEYWORDS

crystal-storing histiocytosis, stomach, histopathology, immunoglobulin, electron microscopy

1 Introduction

Crystal-storing histiocytosis (CSH) is a rare lesion that results from the accumulation of immunoglobulins (Ig) in the form of crystals within tissue cells. CSH is descriptive and sounds innocuous; however, up to 90% of cases are associated with an underlying lymphoproliferative or plasma cell disease, such as multiple myeloma, lymphoplasmacytic

lymphoma, or monoclonal gammaglobulinemia of unknown significance (1–3). In other words, CSH is an under-recognized paraneoplastic phenomenon, and knowledge of CSH may help detect hidden malignancies. Subtle CSH can be overlooked, while extensive CSH can mask the accompanying lymphoma. Although CSH can involve various sites, such as the bone marrow, lungs, lymph nodes, liver, spleen, gastrointestinal tract, and kidney (1, 4), it is very rare in the stomach. Therefore, diagnosing gastric CSH remains a challenge. Here, we report a case of gastric CSH and review related literature.

2 Case presentation

A 69-year-old man was admitted with a chief complaint of positive stool occult blood for 2 days. The patient was emaciated and anemic. The laboratory test results were as follows: white blood cell count 6.3×10^9/L (normal: 4–10×10^9/L), neutrophil count 3.7×10^9/L (normal: 1.8–6.3×10^9/L), red blood cell count 3.38×10^{12}/L (normal: 4–5.5×10^{12}/L), C-reactive protein 26 mg/L (normal: 0–10 mg/L), hemoglobin 88g/L (normal: 120–160 g/L), average volume of red blood cells 79.9 fL (normal: 80–100 fL), and platelet count 299×10^9/L (normal: 100–300×10^9/L). Gastroscopy revealed a white irregular lesion in the gastric mucosa at the big bend of the gastric antrum, which was soft and elastic (Figure 1A). The patient underwent gastrointestinal endoscopy, the polyps found on colonoscopy were removed, folic acid supplementation was administered, and the symptoms of anemia improved. To date, he has had no disease progression, and no lymphoproliferative disease has been found.

Macroscopically, a piece of gastroscopy biopsy tissue was removed with a volume of 0.3 cm×0.3 cm×0.2 cm. Microscopic examination revealed that the biopsied gastric mucosa demonstrated chronic inflammation, mild activity with erosion, and numerous eosinophilic mononuclear cells containing fibrillary crystalloid inclusions in the lamina propria, which were composed of large polygonal and spindle histiocytes with abundant eosinophilic cytoplasm, round-to-ovoid eccentric nuclei, reticulate chromatin, and median nucleoli. Needle-shaped crystals were confined to the cytoplasm, and some were in parallel arrays (Figures 1B–D). Immunohistochemically, these crystal-containing cells were

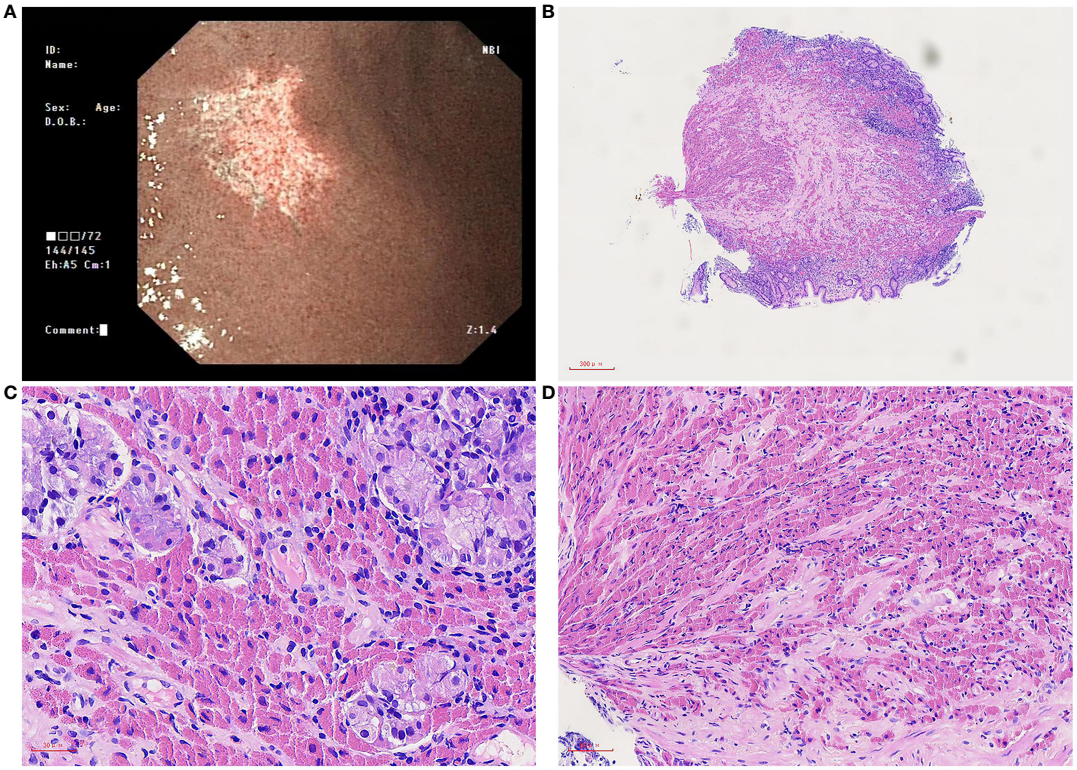

FIGURE 1
Microscopic of gastroscopy biopsy tissue. **(A)** Gastroscopy showed a piece of irregular whitish focus in the big bend of the gastric antrum. **(B)** On low power, the gastric mucosa is mildly chronic inflammation, mildly active with erosion, and a large amount of eosinophilic sub-stance deposits in the stroma, 40×. **(C)** On medium power, the inherent glands of the stomach were destroyed, a few remained glands, and a large number of tissue cells containing crystals in the stroma were infiltrated, 200×. **(D)** On high power, needle crystals in cells, 400×.

strongly positive for CD68/PGM1 (Figure 2A), but negative for CD20 (Figure 2B), CD138 (Figure 2C), CD79a (Figure 2D), CK (Supplementary Figure 1A), S-100 (Supplementary Figure 1B), desmin, smooth muscle actin (SMA), muscle-specific actin (MSA), and myosin. *Helicobacter pylori* (*H. pylori*, Supplementary Figure 1C) immunostaining was negative. Immunostaining of kappa light chain was strong and diffuse (Figure 2E). Immunostaining for the IgG heavy chain and λ light chain was negative. Congo red staining results were negative. Electron microscopic examination showed numerous high-electron-density particles in the cytoplasm of cells, with crystal structures with different sizes and shapes (Figure 2F). BIOMED-2 multiplex PCR analysis showed that immunoglobulin heavy chain (IgH-DH-JH) gene rearrangement and Igκ gene rearrangement were not detected.

3 Discussion

A PubMed search of the literature revealed that over 170 cases of CSH have been reported to date. However, only 17 gastric CSH (including the present case) have been described in English literature (3, 5–13). The detailed clinical and pathological findings of the patients are summarized in Table 1. Of these patients, 10 were men and seven were women. The mean age at diagnosis was 56 years (range, 35-86 years). There were two generalized (11.8%) and 15 localized (88.2%) types. Among them, nine patients (52.9%) were associated with or secondary to lymphoid/plasma cell neoplasm: four mucosa-associated lymphoid tissue (MALT) lymphoma with kappa restriction, one mantle cell lymphoma with lambda restriction, two diffuse large B cell lymphoma with kappa restriction, one multiple myeloma with lambda restriction, and one metachronous lymphoplasmacytic lymphoma involving the bone marrow and thymus. Five patients (31.2%) had no related diseases other than *H. Pylori* infection. During follow-up, four patients with *H. Pylori* infection had no other gastric lesions or symptoms (7–9). One patient died of an unrelated cause during the follow-up (7). Compared to other organs, gastric CSH is mainly localized, and approximately half of the cases are unrelated to clonal lymphoproliferative diseases. In contrast, they are often associated with *H. Pylori*-associated gastritis. However, in the process of reading the literature, there was one report that involved three cases (7), and their morphology was very similar to that of CSH. However, in one case the lesional cells were negative for CD68 while were positive for CD20 and CD79a. Moreover, all patients who were positive for *H. Pylori* only had anti-inflammatory treatment, and there were no other diseases during follow-up. Therefore, we only speculate that the exact diagnosis of this case may be Russell body gastritis (RBG); however, this requires further discussion.

Most importantly, gastric CSH needs to be differentiated from RBG, which can also show similar pathological changes. RBG is another rare entity characterized by abnormal immunoglobulin deposition in the stomach, closely related to

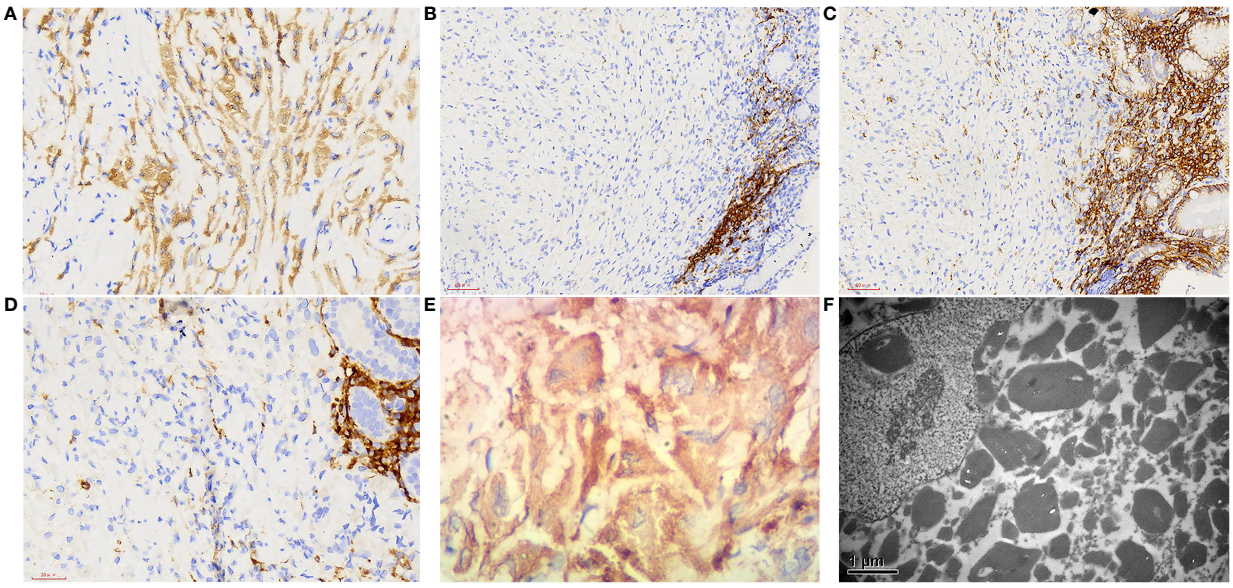

FIGURE 2
Immunophenotype and electron microscopic manifestations of gastroscopy biopsy tissue. **(A)** CD68, 400×; **(B)** CD20, 400×; **(C)** CD138, 400×; **(D)** CD79a, 400×; **(E)** kappa light chain, 400×; **(F)** Electron microscopic examination showed that a large number of high electron density particles were found in the cytoplasm of cells, with crystal structures with different sizes and shapes, 1000×.

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TABLE 1 Clinical and pathological findings of previously published cases of gastric crystal-storing histiocytosis in English literature.

Year	Study	Sex/Age (yr)	Endoscopic finding	*Helicobacter pylori* infection	Associated neoplasm	Ig light chain	Follow-up
1999	Jones et al. (5)	F/35	NS	NS	Thymic lymphoma	Polyclonal	Persist
2006	Stewart et al. (7)	M/82	Gastritis	Yes	No	Lambda	Died of an unrelated cause
2006	Stewart et al. (7)	M/81	Gastritis	Yes	No	Insufficient	No symptoms or lesions
2006	Stewart et al. (7)	F/52	Erosion	Yes	No	Lambda	No symptoms or lesions
2007	Joo et al. (8)	F/56	Polyps	Yes	No	Polyclonal	No residual lesion
2013	Yano et al. (9)	F/55	Discoloration with granularity	Yes	No	Polyclonal	Alive without disease
2014	Vaid et al. (10)	M/NS	Discolored patch	NS	No	Kappa	No
2016	Kanagal-Shamanna et al. (3)	M/43	Nodule	NS	MALT lymphoma	Kappa	Alive without disease
2016	Kanagal-Shamanna et al. (3)	M/51	NS	NS	Multiple myeloma	Lambda	No
2018	Arnold et al. (6)	NS†	Discoloration with granularity	Yes	MALT lymphoma	Kappa	Persist
2018	Arnold et al. (6)	NS†	Discoloration with granularity	Yes	MALT lymphoma	Kappa	Persist
2018	Arnold et al. (6)	NS†	Malignant-appearing mass	No	Mantle cell lymphoma	Lambda	Died of lymphoma
2018	Arnold et al. (6)	NS†	Malignant-appearing mass	No	DLBCL	Kappa	Died of lymphoma
2018	Fujita et al. (12)	72/F	diffuse granular mucosa	No	No	Kappa	Alive without disease
2020	Jooet al. (11)	M/79	Ulcer, flat nodularity	No	MALT lymphoma	Kappa	No
2021	Bansal et al. (13)	M/86	Forrest IIB gastric ulcer	Yes	DLBCL	Lambda	Persist
2022	Present case	M/69	irregular whitish focus	No	No	Kappa	No symptoms or lesion

F, female; NS, not stated; M, male; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B cell lymphoma.
†Including two females and two males with ages ranging from 56 to 82 years.

H. Pylori infection (67%) (14). RBG is composed of plasma cells with small concentrated spherical immunoglobulins surrounded by endoplasmic reticulum membrane (Mott cells) (15), which is different from CSH, which consists of predominantly of histiocytes with crystallized immunoglobulin in the lysosome. RBG cases also have similar characteristics, such as frequent kappa light-chain restriction of accumulated immunoglobulin (43%) (14). There were two cases of RBG associated with lymphoplasmacytic neoplasm: one with MALT lymphoma and the other with metachronous multiple myeloma 3 years after RBG diagnosis (16, 17). However, to date, RBG has been considered a unique inflammatory reaction rather than a paraneoplastic phenomenon. Therefore, gastric CSH seems to be more significant than RBG in terms of its association with lymphoproliferative diseases. In addition, the differential diagnosis of CSH may include various diseases characterized by the aggregation of large eosinophilic tumor cells (adult rhabdomyoma, granular cell tumor, and oncocytic neoplasms) or histiocytic aggregation (Langerhans cell histiocytosis, fibrous histiocytoma, xanthogranuloma, Gaucher's disease, and mycobacterial or fungal infection) (1–3, 6). CSH is rare and under-recognized thus may be easily misdiagnosed. In low-power image, CSH is characterized by polygonal or spindle-shaped tissue cells that contain abundant eosinophilic cytoplasm. In the high-power image, the refractile needle-like crystal substance filled the cytoplasm. Immunohistochemical analysis is helpful for differential diagnosis. In our case, immunohistochemical staining for CD68 confirmed that the

large pink cells were histiocytes. Electron microscopic examination showed that numerous high-electron-density particles were found in the cytoplasm of cells, with crystal structures with different sizes and shapes, such as needles, rectangles, polygons, and diamonds. S100 protein immunohistochemical staining ruled out the possibility of a granular cell tumor and Langerhans cell histiocytosis. Congo red was used to exclude amyloidosis, and desmin, MSA, and myogenin were used to exclude adult rhabdomyoma. CK was used to rule out the possibility of metastatic cancer. The definitive diagnosis was CSH.

At present, the pathogenesis of CSH is unclear and may involve many factors, including immunoglobulin overproduction, abnormal secretion, and impaired excretion. Immunoblotting, amino acid sequencing, mass spectrometry, and gene mutation study showed that the variable region of the Ig kappa light chain was replaced by abnormal amino acids, and the sequence change led to a change in the three-dimensional structure of immunoglobulin, which promoted the formation of protein crystals and resisted the degradation of lysosomes in tissue cells, resulting in crystal accumulation. Hereditary or acquired tissue cell processing defects (processing defects) and damage of enzyme degradation of tissue cells result in the formation of Ig crystals (3, 18, 19). Among the 17 gastric CSH cases, eight were Kappa Ig light chain cases (47.1%), five were lambda (29.4%), three were polyclonal (17.6%), and one case of unknown (5.9%).

The shape, size, and staining characteristics of the crystals were relatively constant in individual cases but varied widely between cases. They can be small (2-4 μm) or large (>40 μm long), rectangular, hexagonal, rhomboid, square, elliptical, curved, or semilunar, and resemble intact or broken needles, rods, spindles, prisms, pyramids, or double pyramids (20). Crystal formation may be related to the unique structure of the secreted immunoglobulin. The finding of cytoplasmic crystal structures on electron microscope can further support the diagnosis of CSH. In our case, numerous high-electron-density particles were observed by electron microscopy in the cytoplasm of cells, showing crystal structures with different sizes and shapes, such as needles, rectangles, polygons, and diamonds.

In conclusion, we report a case of gastric CSH and summarize the clinical and pathological features of gastric CSH reported in English literature in recent years. This case highlights how immunohistochemistry can help with differential diagnosis and classification. Pathologists should know the detailed histological features of CSH to avoid misdiagnosis, and at the same time, they should be highly suspicious of the existence of associated lymphoproliferative diseases. Once the pathological diagnosis of CSH is made, it is necessary to follow up the patients for potential lymphoproliferative diseases, including detailed clinical history, serum and urine protein examination, imaging examination, and bone marrow biopsy. The treatment and prognosis of patients with CSH vary significantly depending on the associated disease.

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 Beijing Chuiyangliu Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LK, XL, LW, and YJ participated in the collection of the clinical and pathological data. XZ and HX carried out HE and immunohistochemical staining. YZ, SW, and DZ carried out electron microscopy. LX carried out PCR analysis. LK, XL, and LX evaluated the pathology of this case. LK conducted a literature search and drafted this manuscript. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1024971/full#supplementary-material

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Case Report: Multiple colorectal cancers in a patient with Ulcerative colitis and Lynch syndrome: Is there a role for prophylactic colectomy? A short report and review of literature

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It is a known fact that Lynch syndrome (LS) and Ulcerative colitis (UC) are individually associated with increased risk of colorectal cancer. While there is no conclusive evidence to demonstrate a cumulative risk when these two conditions coexist, available data suggest early onset and synchronous cancers are synonymous to this group. We have reported an unusual case of multiple synchronous colorectal cancers in a young man with ulcerative colitis and Lynch syndrome also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC) gene mutation. We propose that conducting a detailed genetic mutation profile in LS patients may play a key role in guiding the intensity of endoscopic surveillance and that a concerted, pragmatic, patient guided approach should be adopted on the subject of prophylactic colectomy when UC and LS co-exist.

KEYWORDS

HNPCC: hereditary non-polyposis colorectal cancer, IBD - inflammatory bowel disease, colorectal cancer, Lynch syndrome, Ulcerative colitis (colitis ulcerosa)

Background

The development of colorectal cancer remains one of the most dreaded consequences of ulcerative colitis (UC) (1). Colonic lesions in these cases are frequently multiple and tend to occur in younger patients. Colorectal cancer (CRC) on a background of ulcerative colitis develops through a sequence of mucosal transformation from chronic inflammation to dysplasia and eventually to invasive adenocarcinoma (2). Therefore, colonoscopic surveillance is recommended with the aim of early detection of

precancerous or cancerous lesions in-order to reduce the risk of mortality from colorectal cancer in these patients. Ulcerative colitis is associated with a 1–2% risk for CRC after 10 years of disease, and this risk increases by 0.5–1% annually thereafter (3).The risk of developing colorectal cancer in Inflammatory bowel disease (IBD) is about 1.7 times greater than that of general population (4).

Lynch syndrome (LS) is known to carry the most common inherited colorectal cancer predisposition (5). The predisposition results from deficient mismatch repair gene that has compromised the ability to repair base-pair mismatches in Deoxyribonucleic acid (DNA). It is characterized by predominance of right sided colon cancer with a propensity for synchronous and metachronous lesions (5, 6). Although, CRC is the most common cancer associated with LS, cancers of the small bowel, endometrium, ureter, renal pelvis, hepatobiliary, ovary and stomach can also occur (5). LS accounts for about 3% of all new cases of colorectal cancer (5, 7). It is associated with a 6–77% lifetime risk for CRC that is determined in part by the particular mismatch repair (MMR) protein gene mutation. This reported lifetime CRC risk estimates range from 25 to 70% for MLH1 mutation carriers, 25 to 77% for MSH2 mutation carriers (8, 9), 6 to 22% for MSH6 mutation carriers (8, 10), and 8 to 34% for PMS2 mutation carriers (11). EPCAM mutation carriers have a risk comparable to MSH2 mutation carriers (12).

CRC has been shown to occur at a younger age in patients with concomitant LS and Inflammatory bowel disease (IBD) (4). Theoretically, this could suggest a cumulative risk in these patients, although there is not enough scientific evidence to demonstrate this. Limited literature (Table 1) on this group of patients makes the formulation of surveillance guidance or recommendation of prophylactic treatment options difficult. Detailed analysis of genetic molecular markers in these cases may help to individualize treatment and support use of advance endoscopy for surveillance and selection of patients who may benefit from prophylactic colectomy. This case report illustrates the role of genetically guided and individualized surgico-oncological treatment for patients with concurrent LS and UC. It further emphasizes the need for targeted and tailored colorectal surveillance program with anticipatory approach in managing colorectal cancer complexity and recurrence.

Case presentation

A 32 years-old male diagnosed with UC 7 years prior presented with non-bloody loose stool about 8-12 episodes per

TABLE 1 Literature review of CRC in patients with concurrent IBD and LS (Lynch syndrome).

Authors	Age	LS mutation	Cancer type	Stage	Location	Treatment
Matsuda et al., 1999 (13)	–	Amsterdam criteria diagnosed	Non-synchronous	–	Rectum	Resection of rectal stump
Minami et al., 2014 (14)	28	MSH2	Non-synchronous	–	Hepatic flexure	Total proctocolectomy
McNamara et al., 2015 (15)	46	MLH1	Non-synchronous	–	–	Colectomy
	33	PMS2	Non-synchronous	–	–	Colectomy
Derikx et al., 2016 (4)	34	MLH1	3 synchronous CRC	T2N1Mx (III)	Rectum	Excision of rectum and os coccyges amputation, neoadjuvant chemoradiation
	37	MLH1	3 synchronous CRC	T4aN2M1 (IV)	Sigmoid and appendix	Total colectomy, adjuvant chemotherapy, HIPEC
	34	MLH1	3 synchronous CRC	T2N0M0 (I)	Sigmoid	Subtotal colectomy
	38	PMS2	Non-synchronous	TxNxM1 (IV)	Hepatic flexure	–
	42	MSH6	Non-synchronous	T3N2M0 (III)	Splenic flexure	Left hemicolectomy, adjuvant chemotherapy
Barberio et al., 2022 (16)	66	MSH2	–	–	Sigmoid	Sigmoid resection
	28	MSH2	–	–	–	Ileal pouch-anal anastomosis
	49	MSH2	–	–	–	Ileostomy
	59	MSH2	–	–	–	Ileostomy
	47	MLH1	–	–	–	Ileostomy
	56	MLH1	–	–	Left colon	Left hemicolectomy
	35	MSH6	–	Stage IV	CRC with metastasis	–

day and anemia with no extra-intestinal manifestations. He was also known to have MSH2 mutation following genetic testing due to a strong family history of LS as depicted in the pedigree (Figure 1).

He had been managed conservatively using mesalazine and steroids until 2 years prior to presentation when he had an open right hemicolectomy for caecal low grade dysplastic tubulovillous adenoma found on surveillance colonoscopy. He had one surveillance colonoscopy performed a year after his initial procedure with findings of active colitis and single low-grade tubulovillous adenomas in the colon and rectosigmoid junction. Colonoscopy and biopsy done after index presentation revealed moderately active colitis, multiple rectal and sigmoid tubular adenomas with low grade dysplasia. An elective laparoscopic completion proctocolectomy and ileoanal pouch was proposed. However, intraoperative findings of left pelvic wall abscess with grossly thickened sigmoid colon mass coupled with extensive disease of rectum down to anorectal junction (Figure 2) necessitated an open completion proctocolectomy with terminal ileostomy.

Histology from the specimen revealed moderately differentiated adenocarcinoma arising from tubulovillous adenoma. The whole large bowel mucosa showed extensive adenomatous transformation with areas of low and high-grade dysplasia. Multiple foci (at least 21) of carcinomatous transformation were seen within these adenomas (pT3pN1bpMx, Dukes stage: C1, R0). We performed microsatellite instability (MSI) testing on sections from FFPE (formalin-fixed paraffin embedded) tumor blocks using the Idylla MSI Test. All four tumors tested were MSI-H. This is suggestive of an underlying mismatch repair defect (MMR), and

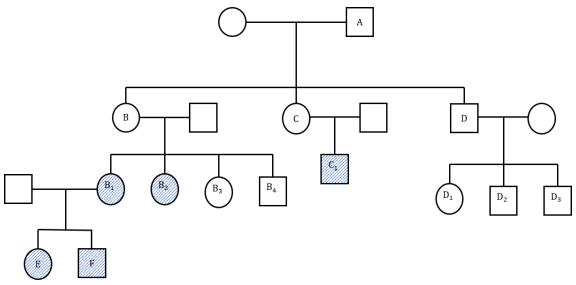

FIGURE 1
(Family pedigree). A: Bowel cancer at 54 years, not tested for lynch syndrome (LS) gene. B: Rectal cancer at 33 years, uterine cancer at 50 years, pancreatic cancer at 78 years, not tested. B1: hMSH2, colon cancer at 34 years. B2: MLH, PMS2, endometrial cancer and intraductal pancreatic neoplasia at 62 years. B3: LS gene negative. B4: LS gene negative. C: Renal cancer in 30s, not tested. C1: Bowel and kidney cancer at 30 years, LS gene positive. D: Bowel and liver cancer at 75 years. D1: LS gene negative. D2: LS gene negative. D3: LS gene negative. E: MSH2, Colon cancer at 32 years (Index patient). F: MSH2.

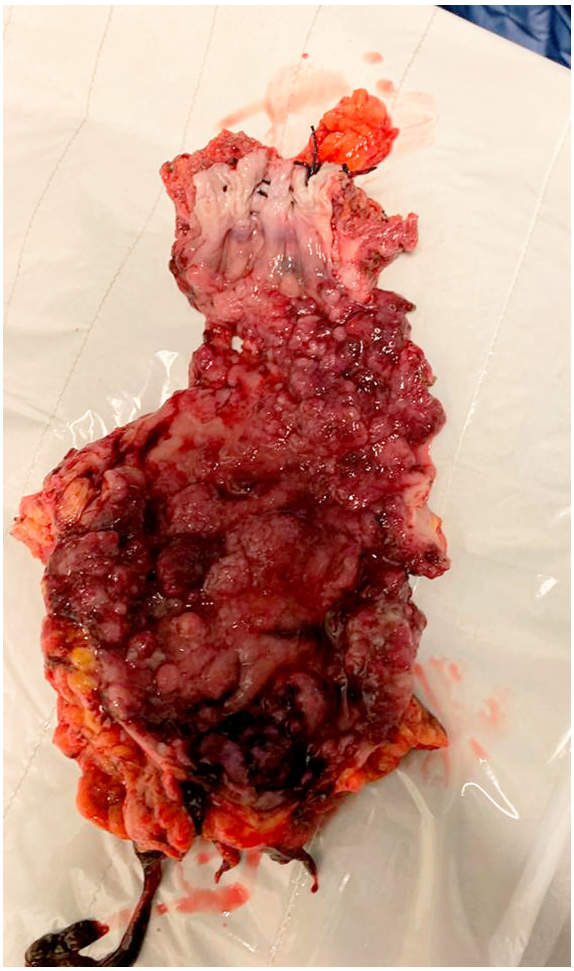

FIGURE 2
Gross specimen showing multiple foci of adenocarcinoma on background of tubulovillous adenoma with dysplasia in rectum.

further testing for MMR protein expression was performed using the VENTANA MMR antibodies. The adenomatous component showed preserved expression of MSH2 and MSH6, while the invasive component showed loss, consistent of Lynch syndrome. Next-generation sequencing (NGS) was performed using the pan cancer TruSight Tumor 170 kit on the NextSeq platform, KRAS and MSH2 gene mutation were detected from both the tubulovillious adenoma and the invasive carcinoma samples. A PIK3CA mutation was also detected in the invasive component. They were both negative for NTRK fusions. NRAS, BRAF, EGFR, APC and CTNNB1 mutation testing failed.

Following surgery, he had adjuvant chemotherapy with capecitabine and oxaliplatin (8 cycles) followed up by the standard colorectal surveillance program. During his second year of follow up, he developed some mucoid discharge from a perineal sinus. Further imaging computer tomography (CT)

scan then Positron emission Tomography (PET) Scan (Figure 3) revealed a pelvic cystic lesion, which was inconclusive on the PET scan.

Biopsy taken form the discharging sinus showed features of dysplastic glands in keeping with metastatic adenocarcinoma of colorectal origin. These findings were discussed at the complex colorectal cancer multidisciplinary team meeting and outcome was discussed with the patient which was either to commence palliative immunotherapy (Pembrolizumab) or to undergo extensive radical total pelvic exenteration. He opted for palliative immunotherapy which he has commenced.

Discussion

Our patient had endoscopically irresectable polypoid tubulovillious adenomas in the caecum for which he underwent right hemicolectomy with subsequent endoscopic surveillance. Two years later, he was found to have multiple low grade dysplastic polypoid lesions in the rectosigmoid area with background active ulcerative colitis. He underwent completion proctocolectomy due to the extensive nature of the polypoid lesion and encroachment of the anorectal junction but developed pelvic recurrence 18 months following adjuvant chemotherapy. We present the first case of multifocal (at least 21) synchronous adenocarcinoma of the sigmoid and rectum confirmed on histology in a patient with history of both LS and UC.

According to Bonadona et al, our patient's estimated cumulative risk of CRC (based on his LS genetic profile) by 70 years of age is 48% (95% CI, 30% - 70%) while Dowty et al. puts this estimate at 34% (8, 9). Thus, CRC risk varies in patients with MSH2 mutation. Although 17% of males with MSH2 mutations have estimated CRC risk of 0 – 10%, the risk of CRC is up to 100% in 18 percent of MSH positive men. As for UC, it is associated with up to 5% of all colorectal cancers. Several factors including male gender, young age at diagnosis and presence of extensive disease have been associated with the increase risk of CRC in UC patients (9). Therefore, presence of concomitant UC in LS could further increase his risk of CRC.

The chronic mucosal inflammation in UC induces a field change of cancer-associated molecular alterations resulting in epithelial dysplasia. CRC in UC is hypothesized to develop from dysplasia (4, 17). As a result of this mechanism, surveillance colonoscopy programs have been advised in order to reduce the CRC-associated morbidity and mortality in UC (18). According to the British, European and American endoscopy guidelines, surveillance endoscopy for dysplasia in IBD should begin between 6 to 10 years following diagnosis. Colonoscopy surveillance have shown promising result by reducing the risk of colonic cancer incidence and earlier detection stage of colonic cancer lesions as evidenced by Cochrane review of case controls and the St Mark's program (19).

The 2015 SCENIC consensus strongly recommends chromoendoscopy or high-definition white-light endoscopy for detection of dysplasia on surveillance in UC patients, in addition to colonoscopically targeted biopsies over random biopsies with aim of improving outcome. The British society of gastroenterology, European society of gastrointestinal endoscopy (ESGE) and American gastroenterological association have all recommended surveillance colonoscopy in patients with Lynch syndrome with the aim of identifying and removing premalignant lesions and reduction of cancer associated mortality by early detection of malignant lesions (17, 20). A recent (2020) well-designed, adequately powered randomized parallel trial in Lynch syndrome patients found that results from high-definition white-light endoscopy was comparable to pan-colonic chromoendoscopy if performed by experienced and dedicated endoscopist (21).

Despite these advances, CRC risk in LS is not completely eliminated by colonoscopic surveillance. In fact, the finding of mismatch repair deficient crypt foci in apparently normal colon, have led to the suggestion that there may be an "invisible pathway" to CRC without an endoscopically detectable polyp precursor and the lifetime risk of CRC in patients with high-risk genotypes (MLH1, MSH2) on colonoscopy surveillance have been found to be around 40 percent (22, 23). Caruso et al. offered a genetic hypothesis that proposed a suppressive effect of each condition on the other (24). Authors proposed that clinical IBD requires both susceptibility and development genes. They postulated that mutations causing LS suppress the IBD development genes such that LS patients develop only a subclinical asymptomatic form of IBD.

More recently, two large pathology reviews attempted to better characterize the pathogenesis of IBD-associated CRC by examining histomorphologic features of these cancers in

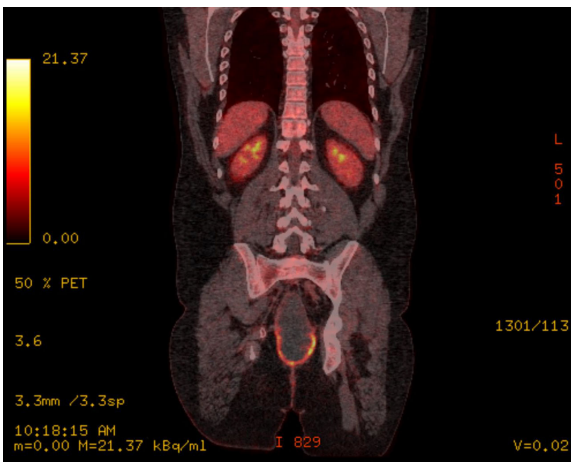

FIGURE 3
PET scan showing pelvic cystic lesion.

comparison with the histomorphology of microsatellite-stable (MSS) CRC, sporadic microsatellite instability-high (MSI-H) CRC, and LS-related CRC (22, 23, 25). Both groups demonstrate that IBD-associated CRC has morphologic similarities to both sporadic and hereditary MSI-H CRC compared to sporadic MSS CRC but also some unique features. Svrcek and colleagues further compared MSI-H and MSS IBD-associated CRC and show that MSI-H IBD-associated CRC even more closely resemble other MSI-H CRC. Taken together, the results suggest that IBD-associated CRC and LS-related CRC may share some common molecular events, but important differences in carcinogenesis generate the unique histomorphology of IBD-associated CRC. Furthermore, Svrcek et al. report a low frequency of MLH1 promoter methylation in IBD-associated CRC and suggest there are alternative mechanisms of MMR deficiency in these tumors. Later work by this same group proposes that dysregulation of inflammation-related micro-RNAs targeting MMR proteins may have a role in IBD-associated CRC development (26). The interrelation of CRC predisposition in LS and IBD may become clearer as more is understood about the pathogenesis of IBD and IBD-associated CRC, immune dysregulation in CRC, and the factors the modify cancer risk in LS patients.

Prophylactic colectomy is not considered a standard or necessary intervention for primary colorectal cancer risk reduction in patients with UC or LS. This may be because of the efficacy of colonoscopy surveillance in either group of patients. However, as available evidence suggests early onset of CRC in patients who have both LS and UC and the inherent propensity for synchronous CRC associated with this group. Total colectomy could serve both therapeutic and prophylactic purpose in patients who have developed CRC requiring segmental colectomy, although there is currently no proven survival benefit for more extensive surgery

Next generation sequencing based analysis has thoroughly characterized MSI positive cancers. MSI is a valuable diagnostic marker of LS and a potential predictive marker for response to immunotherapy and chemotherapy. This has made MSI and MSI- associated molecular changes in tumor of significant clinical importance with diagnostic and therapeutic implications (27).

Considering his background of both UC and LS, we propose that our index patient and other patients with similar background (concurrent IBD and LS) who develop CRC may benefit from panproctocolectomy in the first instance or a restorative proctocolecctomy rather than total colectomy or segmental resection. This decision could be better guided by the genetic mutation profile, lifetime risk of cancer using next generation sequencing. Furthermore, a more intense surveillance protocol that is personalized would perhaps help in detection of early recurrence in patient with MSI-High and deficient MMR, KRAS, NRAS and BRAF wild type. The use of monoclonal antibodies with specific targets has shown efficacy for advanced metastatic colorectal cancer, this principle has recently been explored in the treatment of colorectal cancer from lynch syndrome and ulcerative colitis with some promising results.

Conclusion

Patients with concurrent UC and LS have a greater CRC risk hence surgical management of such patients should be individualized. Available evidence suggests that these patients have a much higher risk of developing synchronous colorectal cancer at a younger age. In addition to the findings on colonoscopy surveillance, further genetic testing is required in making the decision for surgical-oncological treatment before intervention. We therefore propose that advanced colonoscopy is preferred to standard endoscopy for surveillance, with low threshold to offering panproctocolectomy as the first treatment option. Furthermore, we recommend a formal national registry that would capture the various management strategies which could be used to produce consensus for such rare conditions.

Data availability statement

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

Author contributions

AAA: Write up of manuscript and literature review. PW: Patient recruitment and contribution to patient management. ME: Molecular pathologist who performed and interpreted genetic mutations. SS: Histopathologist who provided the histopatholgy slides and annotation of the slides. RP: Operating surgeon who provided gross specimen images. AA: Study design, conceptualization of study and overall supervisor of study (Senior Author). 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.

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Undifferentiated hepatic carcinoma with osteoclast-like giant cells: A case report and literature review

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Osteoclast-like giant cell tumor (OGCT) is a common bone tumor, occasionally observed in some extraosseous organs, but rarely involving the digestive system, especially the liver. Previously reported osteoclast-like giant cell carcinoma of the liver often coexists with sarcomatoid or hepatocellular carcinoma. Undifferentiated liver tumors with osteoclast-like giant cells (OGCs) are extremely rare. Due to its rarity, there is no consensus for diagnosis and treatment of undifferentiated liver tumors with OGCs. Definitive diagnosis comes from surgery, so there is often a long delay in diagnosis following the occurrence of symptoms. This case describes an extremely rare case of an undifferentiated liver tumor with OGCs in detail. It also summarizes the previously published cases based on liver tumors with OGCs from August 1980 to June 2021, providing extensive evidence to improve preoperative diagnosis and management options.

KEYWORDS

osteoclast-like giant cell, undifferentiated hepatic carcinoma, diagnosis, treatment, prognosis

1 Introduction

Giant cell tumor of bone (GCTB) is a benign mesenchymal tumor, affecting mostly long bones. It usually develops in young adults (20–40 years old). Histologically, it is mainly composed of numerous osteoclast-like giant cells (OGCs) histologically (1). Notably this type of tumor, as reported, was also found at several extraskeletal sites (2). Among the digestive system organs, the pancreas was designated as the most vulnerable to developing this pathology (3). The occurrence of undifferentiated liver tumors manifesting as OGCs is an extremely rare event. According to the latest edition of the WHO classification of digestive system tumors, primary hepatic undifferentiated

carcinoma meets the diagnostic criteria for rare liver tumors (4). A total of 18 instances associated with hepatic tumors with cell components of OGCs have been described since the first case was reported in 1980 (5). However, less than three cases are undifferentiated liver tumors, with OGCs among these instances. Due to limited information, clinical manifestations and imaging features cannot be well understood and summarized. Misdiagnosis and delayed diagnosis might easily happen, leading to a poor prognosis. Here, we present a rare case of undifferentiated liver tumor with OGCs and review previously published cases of liver tumor with OGCs from August 1980 to June 2021. We discuss the epidemiology, clinical manifestations, imaging features, pathological features, differential diagnosis, treatments, and prognosis of OGCT in detail, which is to collect more information systematically for disease decision-making.

2 Case presentation

2.1 History and examination

A 68-year-old man presented with intermittent right upper quadrant (RUQ) abdominal pain for half a year. Additionally, a temperature of up to 38.3°C occurred more than a month ago with no apparent cause. Upon arrival, he admitted having diabetes for three years, treated with metformin and glimepiride. His vital signs were stable upon initial evaluation. There is no evidence of a family history of cancer. The patient had a long history of alcohol abuse (daily consumption of >250 g alcohol over the past 30 years). Physical examination revealed no noteworthy findings other than abdominal pain. Tumor markers revealed elevated alpha-fetoprotein (AFP) levels (7.03 ng/ml) and des-gamma-carboxy prothrombin (DCP) levels (33.0 mAU/ml). A complete hemogram showed elevated RDW-CV and AMC levels, and decreased RBC, HGB, HCT, and LY% levels. Liver function tests showed elevated ALT, AST, GGT, and glucose levels and decreased TP and albumin levels. Renal function tests showed elevated serum cystatin C levels. A complete hemogram, liver function, and renal function tests of the patient are presented in Table 1. Laboratory tests also showed positive E antibody and core antibody.

2.2 Abdominal imaging findings

A contrast-enhanced computed tomography (CT) scan of the upper abdomen displayed multiple slightly low-density masses and mixed-density nodules in the left lobe and the anterior segment of the right lobe. The largest mass was measured at 11.2 × 8.5 cm from an axial view. Lesions showed ring enhancement in the arterial phase and continuous enhancement in the portal phase. The sagittal part of the portal vein was infiltrated. Dilatation of the left intrahepatic bile duct combined with bile duct stones was observed. In addition, there were enlarged lymph nodes in the hepatic portal, portacaval space, and around the abdominal aorta (Figure 1).

TABLE 1 Blood tests.

Items	Result	Unit of measurement	Reference value	Mark
Red blood cell count, RBC	2.70	$\times10^{12}$/L	4.3–5.8	↓
Hemoglobin, HGB	78	g/L	130–175	↓
Hematocrit in blood, HCT	0.24	L/L	0.40–0.50	↓
Red blood cell distribution width coefficient of variation, RDW-CV	15	%	11.5–14.5	↑
Lymphocyte percentage, LY%	16.2	%	20–50	↓
Absolute monocyte Count, AMC	0.64	$\times10^{9}$/L	0.1–0.6	↑
Alanine aminotransferase, ALT	74	IU/L	<50	↑
Aspartate aminotransferase, AST	41	IU/L	<40	↑
Gamma-Glutamyl transpeptidase, GGT	72	IU/L	<60	↑
Total protein, TP	63.1	g/L	65.0–85.0	↓
Albumin	34.9	g/L	40–55	↓
Glucose	6.13	mmol/L	3.9–5.9	↑
Serum cystatin C	1.13	mg/L	0.51–1.09	↑

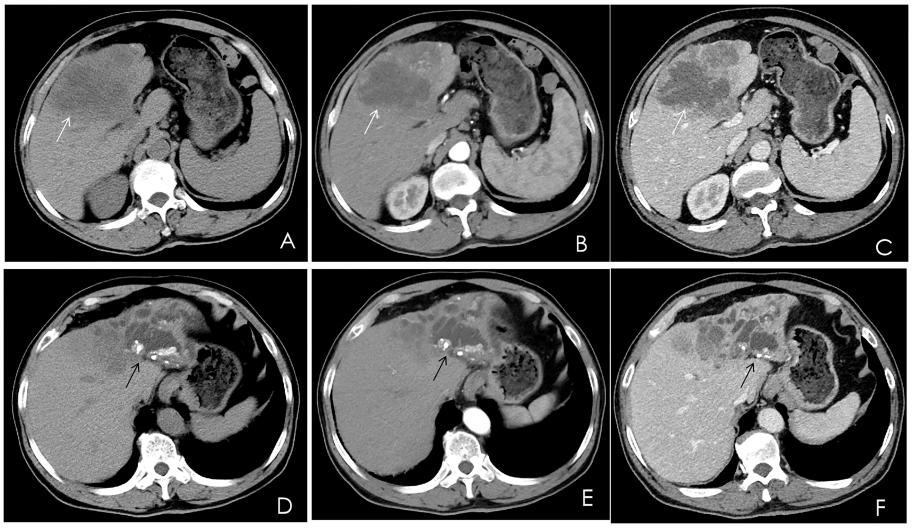

FIGURE 1
Multiphase contrast-enhanced CT of the upper abdomen, axial view. **(A)** A noncontrast CT showed multiple low-density masses and nodular mixed-density shadows in the left lobe and part of the anterior right lobe of the liver (white arrow). **(B)** The arterial phase showed heterogeneous ring enhancement (white arrow). **(C)** The venous phase showed continuous enhancement (white arrow). **(D–F)** The left branch of the intrahepatic bile duct and its branches were dilated, and high-density nodular shadows were seen in the liver (black arrow).

2.3 Surgery

A preoperative diagnosis of cholangiocarcinoma was made. Resection of the left lateral lobe, left medial lobe, right anterior lobe, and caudate lobe of the liver, hilar cholangioplasty, and cholecystectomy were performed to remove the whole mass after two days of admission, which appeared to have a complete tumor margin, a yellowish cross-section, and dilated partial bile ducts with stones inside. A lymphadenectomy was not performed. The operative time was 228 min. The blood loss was 500 cc, and a perioperative blood transfusion was not required. Surgical samples were taken and sent for pathological examination. There were no immediate postoperative complications.

2.4 Pathological findings

Histopathological analysis revealed that tumors were rich in osteoclast-like giant cells and neoplastic spindle-shaped cells (Figures 2A, B). Complete hepatic-lobule-like structures, edema of hepatocytes, intrahepatic cholestasis, lymphocyte, and plasma cell infiltration in the portal area were observed in the non-tumorous liver parenchyma of the resected specimen. Immunohistochemical staining showed that tumor cells were negative for EMA, Hepa, CK (Pan) (Figures 3A–C), desmin, CD34, S-100, SATB2, P63, P16, GS, GPC3, and CAM5.2, but positive for SMA, P53, Ki-67 (30%), ACT, CK8/18 (Figures 4A, B), and vimentin. PCR and Sanger sequencing: no H3F3A gene

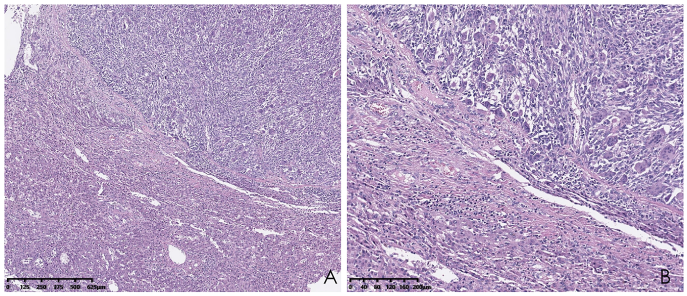

FIGURE 2
Hematoxylin and eosin (HE) staining of the liver biopsy sample shows osteoclast-like giant cells and neoplastic spindle-shaped cells. (**A**; hematoxylin and eosin, ×40); higher magnification of the destroyed liver structure lined by osteoclast-like giant cells and neoplastic spindle-shaped cells (**B**; hematoxylin and eosin, ×100).

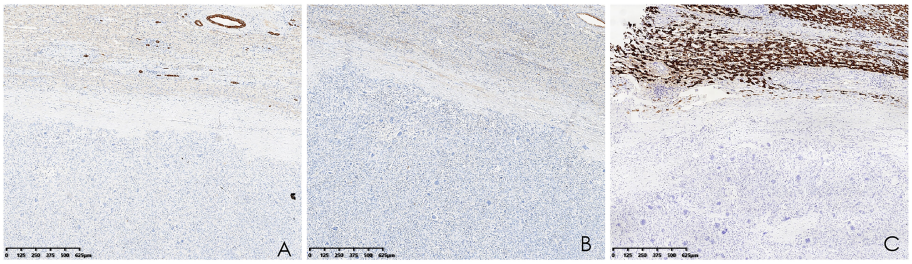

FIGURE 3
(A–C) Immunohistochemistry showed that CK (Pan), EMA, and Hepa were negative (hematoxylin and eosin, ×40).

mutation was detected. Combined with histopathology and immunohistochemistry, the diagnosis of undifferentiated carcinoma with osteoclast-like giant cells of the liver was considered. The possibility of metastatic tumors was excluded by a comprehensive clinical examination.

2.5 Postoperative course

The postoperative situation of the patient was stable, and he was discharged on the 12th day. At the first follow-up two months after hospital discharge, a chest CT showed that the lymph nodes in the mediastinum and right diaphragmatic corner were significantly increased. The patients and their families refused gene tests and agreed to perform GA chemotherapy was temporarily performed (gemcitabine 1.5 g d1; d8 + albumin paclitaxel 200 mg d1; d8). At the second follow-up five months after hospital discharge, metastases were found on CT scans of the head and chest. The patient and his family still refused the gene test and chose to undergo GP chemotherapy (gemcitabine 1,600 mg d1, 8 ivgtt + cisplatin 40 mg d1, 8; Q3w) and radiotherapy for the head. The current vital signs of the patient are stable. The patient is alive after 5-month follow-up.

3 Discussion

3.1 Epidemiology

Munoz et al. (5) first recorded an instance of OCGT of the liver, and some additional patients suffering from this rare tumor at the same site have been reported since then. These previously reported carcinomas were classified as tumors related to hepatocellular carcinomas, tumors related to cholangiocarcinomas or cystadenocarcinomas of the liver, tumors related to sarcomatous tumors, and undifferentiated tumors that were not related to conventional carcinomas, as presented in this case (6). Undifferentiated primary carcinoma of the liver itself is an uncommon type of cancer. The presence of osteoclast-like giant cells in undifferentiated carcinoma of the liver rarely occurs, classified as T3N0M0 and Stage III according to the third English edition of the Japanese classification of liver cancer. Only a few previous reports of liver tumors with giant cells resembling osteoclasts have been reported, so little is known about their biological behavior and clinical course.

It is well known that blood serum levels of PIVKA-II and AFP are useful indicators for the diagnosis of HCC. Suehiro et al. confirmed that a poorer prognosis is associated with a high level

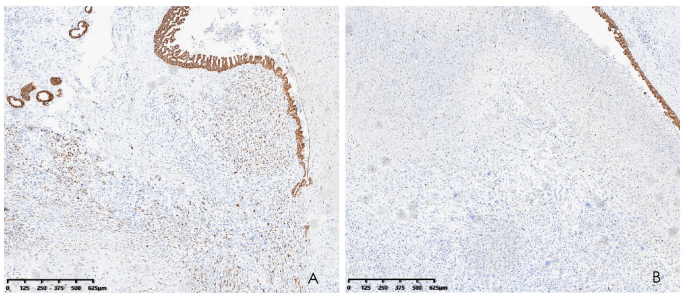

FIGURE 4
Immunohistochemistry demonstrated CK8/18 positivity in the tumor **(A)** and CK8/18 negativity for osteoclasts **(B)** (hematoxylin and eosin, ×40).

of serum PIVKA-II (7). In this case, the serum PIVKA-II level was elevated in this patient.

3.2 Clinical presentation

Case reports associated with hepatic tumors with OCGs, published from August 1980 to June 2021, were searched through the Biomedical Literature Database (PubMed). Clinical manifestations of hepatic tumors with OCGs are listed in Table 2. As evident from the 18 reported cases, the disease is more common in males (12, 66.7%), and its onset age ranges from 37 to 87 years old (average age: 63.7 years old), mostly affecting the left lobe of the liver. Several clinical symptoms have been reported at presentation, including abdominal pain, nausea, abdominal distension, fever, weight loss, and so on. Some cases were associated with cirrhosis (7, 38.9%) and hepatitis (6, 33.3%). AFP is a specific tumor marker for HCC, and the level of the tumor marker was elevated in four patients. As for previous history, most patients suffered from hypertension and diabetes (3, 5, 6, 8–22).

3.3 Radiologic characteristics

Hepatocellular carcinoma (HCC) accounts for most liver cancer, and classical HCC appears as arterial phase enhancement on CT followed by washout in the portal phase (23). Cholangiocarcinoma is prevalent in Asia and is divided into intrahepatic, hilar, and distal types. Intrahepatic cholangiocarcinomas show edge enhancement in the arterial phase and a progressive centripetal filling of the fibrous stroma in the delayed phase, with relative low density surrounding it. The imaging features of hilar cholangiocarcinoma are irregular thickening of the hilar bile duct wall, an eccentrically narrowed lumen, and dilation of the upper bile duct. Angiographic findings of distal cholangiocarcinoma included dilatation of the proximal bile duct, confluence of the bile ducts, and enlargement of the gallbladder with normal bile ducts below the stenotic segment. In our case, CT findings of undifferentiated carcinoma with osteoclast-like giant cells of the liver resembled cholangiocarcinoma. We suppose that large intrahepatic masses might contribute to obstruction of bile flow. These were risk factors for the development of cholestasis, bile duct dilatation, and bile duct stones. Lesions showed ring enhancement in the arterial phase and continuous enhancement in the portal phase. These enhancement characteristics suggested that tumors might be abundant in mesenchymal tissue. We summarized the imaging findings of 18 cases of HCC with OCGs reported so far (Table 3) (3, 5, 6, 8–22).

3.4 Pathological features

There are many controversies surrounding the origin and histogenesis of OCGT. A few studies have suggested that osteoclast-like giant cells were probably neoplastic and epithelial (24). Other studies held the opposite view, that tumors originated from mesenchymal tissue (25, 26). Munoz et al. first reported the case of an osteoclastoma-like giant cell tumor of the liver in 1980. They hypothesized that reticuloendothelial cells were involved in the origin of the tumor (5). Rosai proposed that multinucleated giant cells are always derived from non-epithelial cells with an osteoclastic phenotype and are essentially non-neoplastic, rather than determined by the location of the tumor and the presence of identifiable cancer components in the tumor (2). Based on immunohistochemistry, Sasaki et al. confirmed that the OGC expressed only histiocytic and mesenchymal markers (ACT, AAT, MUR, VIM, and CD68), and they remained negative for epithelial markers (EMA, CK 7, CK 8, and CK 19). Their findings support the view that OCG is non-tumor and non-epithelial (12). In this case, tumors were more likely to be of non-epithelial and mesenchymal origin based on the negative results of EMA and CK (Pan) and the positivity of Vim. The diagnosis of giant cell tumors of bone was unconsidered due to no H3F3A mutation. P53 expression tends to be associated with the differentiation degree of liver tumor cells, especially in poorly differentiated liver tumors, indicating a worse prognosis (27). Hepatic undifferentiated carcinoma is poorly defined from a clinicopathological and molecular perspective. After a full study of 14 cases of primary hepatic undifferentiated carcinoma, high mutation rates of the TERT and TP53 genes and high expression rates of PD-L1 were found, which may be useful biomarkers for potential immunotherapy strategies (28). However, despite a thorough explanation, the patient declined further genetic testing in our case.

3.5 Differential diagnosis

There are several subtypes of liver tumors that may be related to multinuclear giant cells and therefore require a differential diagnosis. Hepatocellular carcinoma with syncytial giant cells is a special variety of liver tumor. As the tumor exhibits positive cytokeratin 8 and Hep markers, hepatocellular carcinoma with syncytial giant cells is epithelial and probably arises from hepatocytes (29). Differently, the immunohistological results suggest a different origin of the giant cells, which is more likely to be mesenchymal for our type. As another type of liver tumor containing multinuclear giant cells, sarcomatoid HCC is featured by reactivity for CK 8, ALB, and fibrinogen, as well as for VIM (30). In addition, OCG-associated hepatocellular carcinoma contains two components, including a well-differentiated HCC characterized by

TABLE 2 Clinical manifestation of hepatic tumor with OCGTs.

Study	Year	Sex	Age	Clinical manifestation	Tumor location	Tumor size	Hepatic disease	Cirrhosis	Previous history	AFP
Phillip a. Munoz (5)	1980	man	87	lethargy, anorexia, and fluid retention	right lobe of the liver	11 cm in diameter	portal hypertension and chronic hepatic failure	macronodular cirrhosis of the liver	insulin-dependent diabetes; resection of Grade I1 papillary transitional cell carcinoma of the urinary bladder	normal
Hlroyukl Kuwano (8)	1984	man	54	general fatigue with slight fever, night sweating, weight loss	right lobe of the liver	6x5x12 cm	type b hepatilis	hepatic cirrhosis	negative	206.3 ng/ml
Salvatore Andreola (9)	1985	man	71	eneral fatigue and upper abdominal discomfort	right lobe of the liver	12 cm in diameter	hepatitisB	hepatic cirrhosis	chronic alcoholism	normal
Yutaka Hori (10)	1987	male	66	hematemesis, nausea, epigastric dullness, abdominal pain	inferior surface of the liver	unknown	negative	negative	negative	normal
Daniel L. Hood (11)	1989	woman	37	right upper quadrant abdominal pain and right shoulder pain	left hepatic lobe	1,761.25 ml	negative	negative	ovarian mucinous cystadenocarcinoma, total abdominal hysterectomy and bilateral salpingo-oophorectomy	normal
Atsushi Sasaki (12)	1997	Male	42	right abdominal pain and high-grade fever	posterior and medial segment	6.0 cm in diameter; 2.5 cm in diameter	hepatitis B	hepatic cirrhosis	negative	normal
Tohru Ikeda (13)	2003	Man	76	unremarkable	S4 and S7–8 regions of the liver	unknown	type C hepatitis	liver cirrhosis	negative	unknown
M. Ahaouche (14)	2005	man	57	abdominal pain	IVth hepatic segment	6 × 5.5 cm	negative	alcoholic cirrhosis	obesity, diabetes mellitus	12 ng/ml
Udo Rudloff (3)	2005	woman	61	abdominal pain	right lobe of the liver	7 × 7 × 10 cm	fatty liver; no hepatitis	negative	laparoscopic cholecystectomy; coronary artery disease; hypertension	normal
Juergen Bauditz (15)	2006	man	54	no clinical symptoms	segments II and III	7 cm	negative	negative	peripheral arterial disease, hypertension, esophageal reflux, hiatal hernia, and sleep apnea	normal
Chisato Tanahashi (16)	2009	woman	74	unremarkable	left lobe of the liver	10 × 5 cm	negative	negative	negative	unknown
Ryusuke Matsumoto (17)	2012	man	57	jaundice	left hepatic lobe	10 cm	negative	negative	negative	normal
Kyoung-Bun Lee (18)	2014	man	64	resection of a hepatic mass	segment 6	6.0 × 4.0 × 2.2 cm	hepatitis B	hepatic cirrhosis	liver cancer; transarterial embolization (TAE) three times for a 1.4-cm multinodular mass in segment 6 first and	36.1ng/mL

(Continued)

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TABLE 2 Continued

Study	Year	Sex	Age	Clinical manifestation	Tumor location	Tumor size	Hepatic disease	Cirrhosis	Previous history	AFP
									percutaneous ethanol injection (PEI) and TAE of a new lesion in segment 6 after 4 years.	
Lorenzo Dioscorid (19)	2015	woman	74	dull pain in the right upper quadrant associated with mild anemia	V–VI segments	10 × 7cm	negative	negative	negative	normal
Hans Helmut Dahm (6)	2015	man	68	a tumor of the right lobe of the liver based on ultrasonography that was performed during a routine examination	in segments 7 and 8 of the right liver lobe that adhered to the retroperitoneum.	6 cm in diameter	chronic periportal hepatitis	negative	Insulin dependent type 2 diabetes mellitus and hypertension	unknown
Bita Geramizadeh (20)	2017	woman	64	abdominal pain	right lobe of the liver	20 cm in the greatest diameter	negative	negative	negative	unknown
Meera Balakrishnn (21)	2021	woman	64	abdominal pain associated with nausea	fourth and fifth segments of the liver	11 × 7 cm^2	negative	negative	hypertension dyslipidemia	normal
Anke H. C. Gielen (22)]	2021	male	77	icterus, general fatigue	segment 8, parts of segments 4 and 5	8cm	negative	negative	hypertension, type 2 diabetes, and prostate cancer	215.5ng/ml

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TABLE 3 Imaging findings of hepatic tumors with OCGTs.

Study	Imaging findings
Phillip A. Munoz (5)	A liver scan with technetium sulfur colloid revealed diffuse hepatic parenchymal disease with a large focal lesion in the right lobe. A 67-gallium citrate scan suggested a primary liver tumor in addition to cirrhosis.
Hiroyuki Kuwano (8)	Celiac angiography showed a hypervascular tumor shadow, 7.5 × 6.5 cm, in the posterior area of the right lobe of the liver
Salvatore Andreola (9)	A liver echography showed a hypoechoic mass in the right lobe of the liver.
Yutaka Hori (10)	Serial CT scans showed a clustering tumor mass arising from the inferior surface of the liver with low attenuated areas in the mass
Daniel L. Hood (11)	n abdominal computed tomography (CT) scan showed a large hepatic mass
Atsushi Sasaki (12)	Two hepatic tumors were detected in the posterior segment (6.0 cm in diameter) and the medial segment (2.5 cm in diameter), respectively, by abdominal ultrasonography, computed tomography and abdominal angiography.
Tohru Ikeda (13)	unknown
M. Ahaouche (14)	ultrasound and CT scan identified a mass measuring 60 mm in maximum dimension located in the IVth hepatic segment. This nodule had extrahepatic extension and invaded the diaphragm. It was hypervascular and homogeneous.
Udo Rudloff (3)	Magnetic resonance imaging (MRI) of the abdomen confirmed an 8 × 8 × 10 cm mass within the right lobe of the liver involving segments V, VI, and VII. Endoscopic retrograde cholangiopancreatography (ERCP) showed common bile duct (CBD) dilation to 1.3 cm.
Juergen Bauditz (15)	CT demonstrated a 7 cm large inhomogeneous solid liver tumor involving segments II and III.B-mode sonography (HDI 5000, Philips) demonstrated a well-defined, inhomogeneous, cauliflower-like tumor with multiple small calcifications, causing retraction of the liver contour. Within the center of the tumor, a focal nodular hyperplasia (FNH)-like stellar scar was present. Contrast-enhanced sonography demonstrated an inhomogeneous perfused tumor with a large feeding artery heading towards the center of the tumor, radially branching to the periphery.
Chisato Tanahashi (16)	unknown
Ryusuke Matsumoto (17)	Abdominal computed tomography showed a 10-cm left hepatic lobe heterogeneous solid mass with low attenuated areas in the mass, multiple liver metastases and lung metastasis.
Kyoung-Bun Lee (18)	Magnetic resonance imaging showed a 5-cm lobulating soft tissue mass with an internal hemorrhagic component
Lorenzo Dioscorid (19)	the hepatic neoplasm was confirmed and shown to grow from a Riedel's segment towards the right iliac fossa with a close contiguity with ascending colon and caecum
Hans Helmut Dahm (6)	A computed tomography (CT) scan showed evidence of a malignant liver neoplasm.
Bita Geramizadeh (20)	CT scan showed an enlarged liver with a large mass in the right lobe of the liver with irregular borders and central necrosis, measuring 20 cm in the greatest diameter. A few smaller lesions were also present. Portal vein thrombosis was also identified.
Meera Balakrishnn (21)	Computed tomography (CT) scan showed a heterogeneous focal mass measuring 11x7cm2 occupying the fourth and fifth segments of the liver with areas of necrosis and prominent vessels passing through it. The mass infiltrated the gallbladder wall
Anke H. C. Gielen (22)	A computed tomography (CT) scan showed a liver neoplasm of 6.7 cm in segment 8

partial steatohepatitic morphology and abundant OCG forms mixed with hepatocellular cancer cells (22). The tumor in our case report showed coexistence of undifferentiated carcinoma of the liver and osteoclast-like giant cells, exhibiting negativity for hepatocellular and epithelial markers and positivity for cytokeratin 8/18 (CK8/18).

3.6 Treatment

Due to the rarity of the condition, there is not yet a standard therapy for it. It seems that surgery is still the main treatment for this ailment. Masatsugu et al. described radical surgery without any chemotherapy for an undifferentiated liver tumor that

TABLE 4 Prognosis of hepatic tumor with OCGTs.

Study	Diagnosis	Treatment	Postoperative treatment	Outcome
Phillip A. Munoz (5)	hepatic tumor with OCGTs	no	no	died 32 days later
Hiroyukl Kuwano (8)	HCC with OCGTs	A posterior segmentectomy of the right hepatic lobe with resection of the right diaphragm was performed.	no	metastasis; died four 42 days later
Salvatore Andreola (9)	hepatic tumor with OCGTs	cholecystectomy	no	metastasis; died 20 days later
Yutaka Hori (10)	hepatic tumor with OCGTs	TACE	TACE	died 42 days later
Daniel L Hood (11)	hepatic tumor with OCGTs	resection of the left hepatic lobe and part of the anterior abdominal wall	chemoradiotherapy	metastasis; died three months later
Atsushi Sasaki (12)	Sarcomatoid hepatocellular carcinoma with OCGT	atypical segmentectomy	transcatheteral arterial chemoembolization therapy (TACE)	metastasis, died 28 days later
Tohru Ikeda (13)	sarcomatoid tumor cells with OCGTs	trans-arterial embolization (TAE); Partial hepatectomy	Radiation therapy	metastasis; died one months later
M. Ahaouche (14)	hepatic tumor with osteoclast-like giant cells	lobectomy	no	died 3 months later
Udo Rudloff (3)	hepatic tumor with OCGTs	right hepatic lobectomy	no	metastasis; died three months later
Juergen Bauditz (15)	hepatic tumor with OCGTs	surgical resection of liver segments II and III	chemotherapy	metastasis; alive
Chisato Tanahashi (16)	HCC with OCGTs	left lobectomy	no	died of the disease at 110 days after operation.
Ryusuke Matsumoto (17)	hepatic tumor with OCGTs	no	no	died a few weeks later
Kyoung-Bun Lee (18)	Sarcomatoid hepatocellular carcinoma with OCGT	peripheral segmentectomy of segment 6	no	metastasis
Lorenzo Dioscorid (19)	HCC with OCGTs	hepatic resection of the V-VI segments	no	metastasis; died four months later
Hans Helmut Dahm (6)	HCC, sarcoma with OCGT	atypical segmentectomy	no	metastasis; tumor recurrence
Bita Geramizadeh (20)	hepatic tumor with OCGTs	atypical segmentectomy	no	died two months later
Meera Balakrishnn (21)	hepatic tumor with OCGTs	segmentectomy	chemotherapy	metastasis; died after 108 days
Anke H. C. Gielen (22)	HCC with OCGTs	resection of segment 8 and parts of segment 4 and 5 was performed.	no	alive in a good condition

achieved good results (31). According to Hood et al., a woman with recurrent OCGT of the liver was treated with 5-fluorouracil and adriamycin, external beam radiation, and radioimmune therapy (IgG, labeled with I-131) (11). The case reported by Kamitani et al. was treated with neoadjuvant chemotherapy before radical hepatectomy. After metastasis occurred two months after surgery, targeted treatment was adopted; however, the patient died five months later (32). In this case, the patient underwent surgery and postoperative adjuvant chemotherapy. The patient is alive after 5-month follow-up.

3.7 Prognosis

OCGTs with liver involvement tend to proliferate aggressively. It is apparent that nodal metastasis is the predominant mode of spreading, and the prognosis, even after resection, is usually dismal. Patients survive for weeks to months after surgery for OCGT of the liver. We summarized published cases associated with the prognosis of hepatic tumors with OCGTs from August 1980 to June 2021 on PubMed (Table 4) (3, 5, 6, 8–22). As evident from the 18 published cases, most patients died within 3 months of surgery, and only one patient was alive and in good condition.

4 Conclusion

Our study provided an in-depth look at imaging observations, treatment modalities, patterns of spread, and clinical outcomes to gain a more comprehensive understanding of this disease. Further studies on undifferentiated hepatic tumors with OGCs are recommended to analyze a suitable therapeutic strategy for this rare condition in the future.

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

YD, YW, YZ, and NY conducted the radiological analysis of CT images, XJ conducted the pathological analysis, and YD prepared the manuscript. BW revised the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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.

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Early hepatoid adenocarcinoma of the stomach with signet ring cell carcinoma: A case report and clinicopathological features

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Background: Hepatoid adenocarcinoma of the stomach (HAS) is a rare subtype of gastric cancer with poor prognosis, and its clinicopathological features are not well understood, so the pathology from the clinical biopsy is easily misdiagnosed, especially for special or atypical HAS. We present an extremely rare early HAS with signet ring cell carcinoma and evaluate its clinicopathological features.

Case presentation: A 51-year-old female patient of Chinese Han ethnicity with upper abdominal pain for 5 years and worsened abdominal pain for 1 month was admitted to our hospital. Esophagogastroduodenoscopy showed a submucosal tumor-like elevated lesion with central depression in the greater curvature of the junction between the antrum and body. Histopathological examination from the biopsy revealed medium–low-differentiation adenocarcinoma with signet ring cell carcinoma. Radical gastrectomy was performed, and the final diagnosis was early HAS with signet ring cell carcinoma.

Conclusions: HAS with signet ring cell carcinoma is a special type of HAS and extremely rare. It is first presented for this extremely rare type of HAS, which contributes to strengthen the understanding for the clinicopathological characteristics of HAS and especially promote early detection of HAS.

KEYWORDS

case report, clinicopathological feature, hepatoid adenocarcinoma, signet ring cell carcinoma, stomach

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Introduction

Hepatoid adenocarcinoma of the stomach (HAS) refers to a special type of gastric cancer with the characteristics of adenocarcinoma and hepatocarcinoid differentiation originating in the gastric mucosa with or without the increase of serum alpha fetoprotein (AFP). It is a rare form of gastric cancer, accounting for 0.3%–1% of all gastric cancers (1, 2). According to a literature search of PubMed/Medline, approximately 500 cases of HAS have been reported in the world, mainly in case reports and clinical or pathological analyses, but little is about the report of early HAS (3). HAS progresses rapidly, especially with high potential for liver and lymph node metastasis, and the prognosis is very poor (4, 5). The symptoms of patients with HAS are similar to those of common gastric cancer, and the diagnosis of HAS is mainly dependent on the endoscopy and pathological analysis. However, it is sometimes difficult to do pathological diagnosis by gastroscopic biopsy and is easily misdiagnosed. Thus, the challenge remains in the appropriate diagnosis of this rare entity, especially early diagnosis, to improve its unfavorable prognosis. We herein present an extremely rare early HAS with signet ring cell carcinoma and analyze its clinicopathological features that contribute to the improvement of the diagnosis of HAS.

Case presentation

A 51-year-old female patient of Chinese Han ethnicity was admitted to our hospital because of upper abdominal pain for 5 years and worsened abdominal pain for 1 month. There was no significant weight loss and special past medical history. Physical examination had no abnormal findings. Esophagogastroduodenoscopy (EGD) was performed. Under white light, the antrum and corpus presented as non-atrophic gastritis, without a sign of *Helicobacter pylori* infection. A 20-mm type 0–IIa+IIc lesion with submucosal tumor-like change in the greater curvature of the junction between the antrum and body was detected. The lesion has a sense of compactness and fullness with a central depression (Figures 1A, B). Narrow-band imaging (NBI) showed a brownish area with an indistinct boundary (Figure 1C). Magnified endoscopy with NBI (ME-NBI) at low and high magnification revealed that most parts of the lesion presented as a regular microvascular pattern and only small parts presented as an irregular microvascular pattern, and there was the presence of a demarcation line, widened intervening parts, and elongated pits (Figures 1D–F). It was considered as an undifferentiated cancer, lymphoepithelioid cancer, or other special type of tumor by endoscopy. The pathological examination from biopsy revealed that the lesion was medium–low-differentiation adenocarcinoma with signet ring cell carcinoma.

Abdominal computed tomography revealed a local inhomogeneous thickening of the gastric wall at the greater curvature of the gastric body, calcification of the right lobe of the liver, uterine fibroids, and right ovarian cyst. Serum tumor-associated antigen and tumor marker test showed that α-L-fucosidase, carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 153, carbohydrate antigen 125, ferritin,

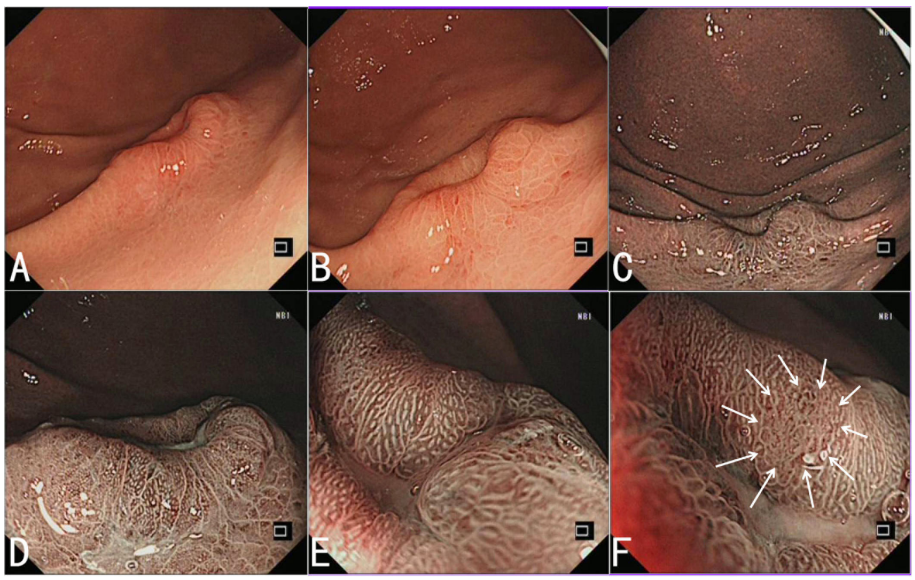

FIGURE 1
Endoscopic features of HAS. **(A, B)** White light endoscopy shows a 20-mm type 0–IIa+IIc lesion with submucosal tumor-like change in the greater curvature of the junction between the antrum and body. The lesion has a sense of compactness and fullness with a central depression. **(C)** NBI shows a brownish area with an indistinct boundary. **(D–F)** ME-NBI with low **(D)** and high **(E)** magnification shows that most parts of the lesion present as a regular microvascular pattern, and there is the presence of a demarcation line, some widened intervening parts, and elongated pits, and only small parts present as an irregular microvascular pattern (indicated by the arrow) **(F)**.

AFP, and human chorionic gonadotropin (hCG) were all normal.

Radical distal gastrectomy was performed for the patient. Surgery examination showed that the lesion was located in the greater curvature of the junction between the antrum and body, with a size of approximately 20 mm × 12 mm. The lesion did not break through the serous membrane and had no obvious adhesion with the surrounding tissues. A total of 20 lymph nodes in the greater curvature and nine in the lesser curvature of the stomach were palpated. There was no obvious metastasis in the liver, gallbladder, spleen, bilateral kidneys, transverse colon, mesentery, abdominal wall, and pelvic cavity.

Examination of the resected specimen revealed that there was a mucosal protuberant lesion with a central depression in the greater curvature of the junction between the antrum and body, and the size was 20 mm × 11 mm. The surrounding mucosa was smooth, with converging of the mucosal folds toward the lesion and fusion of the folds (Figure 2A). The crystal violet staining for the resected specimen more clearly revealed the morphology of the lesion (Figure 2B). The lesion and its surrounding tissues were taken every 2–3 mm for histopathological examination according to the cutting standard of early gastric cancer specimens (Figure 2C). The lymph nodes were also taken for histopathological examination.

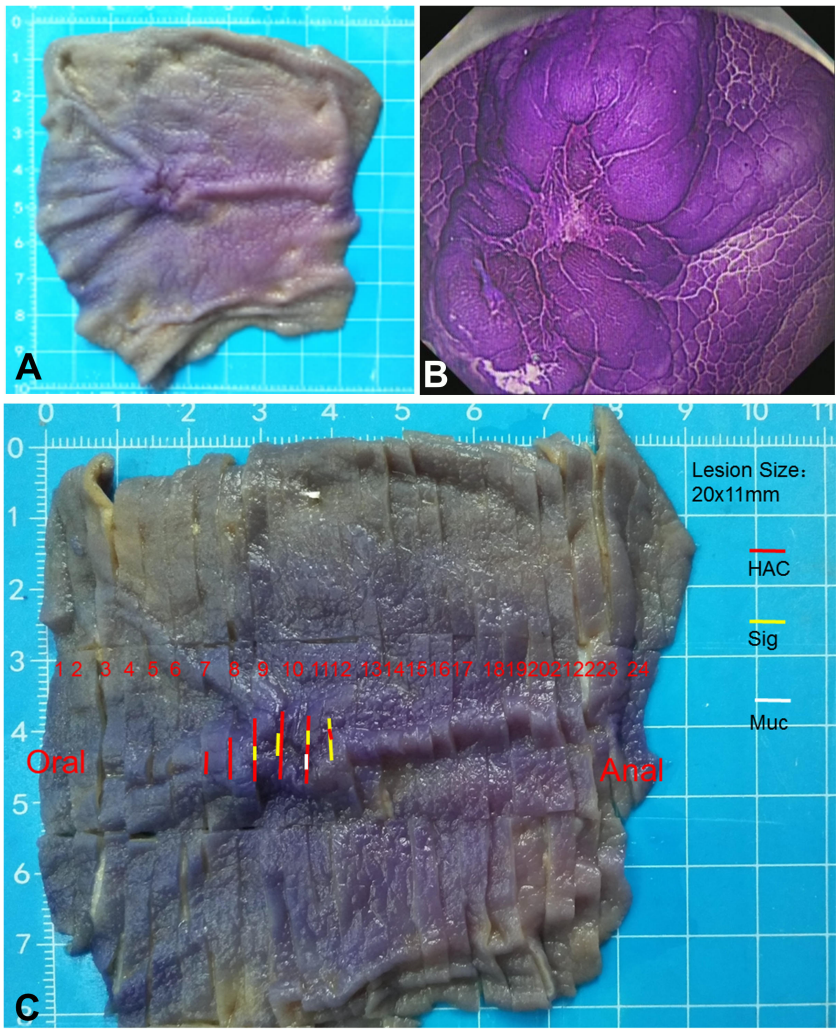

FIGURE 2
Macroscopic morphology of the resected specimen. **(A)** Macroscopic observation shows a protuberant lesion with a central depression. The surrounding mucosa is smooth, with the converging of the mucosal folds toward the lesion and the fusion of folds. **(B)** Crystal violet staining of the resected specimen more clearly shows the morphology of the lesion. **(C)** The lesion and its surrounding tissues are taken every 2–3 mm for histopathological examination according to the cutting standard of early gastric cancer specimens. HAC (red line), representing the areas with hepatoid adenocarcinoma of the stomach; Sig (yellow line), representing the areas with signet ring cell carcinoma; Muc (white line), representing the areas with the formation of mucin.

Microscopically, the infiltration of cancer tissue was limited to the mucosa and submucosa and reached the deep layer of the submucosa. The mucosal surface was almost covered by non-neoplastic epithelium (Figure 3A). The tumor cells exhibited a different pattern. Some cancer cells were arranged in the form of irregular nests, cords, or micro glandular tubes. The cells were large and cubic in size, rich and eosinophilic in the cytoplasm, and with round or oval nucleus, binucleate and small nucleoli, and hepatocyte-like appearance (Figure 3B). Some cancer cells displayed the form of signet ring and distributed diffusely (Figure 3C). There was mucus formation in the interstitium of some signet ring cells, and the signet ring cells floated in mucus (Figure 3D). The different forms of cancer cells were interlaced with each other (Figure 3E). In the submucosa, the stromal fibrous tissue of the cancer obviously proliferated to form a nodular shape with a clear boundary, and the lymphocyte focally infiltrated and formed lymphoid follicles (Figures 3A, F). The gastric mucosa around the cancer exhibited mild chronic non-atrophic gastritis. No cancer metastasis was found in the 20 lymph nodes of the greater curvature and nine lymph nodes of the lesser curvature of the stomach.

Immunohistochemical examination showed that the expressions of cytokeratin (CK) (Figure 4A), caudal-related homeobox transcription factor 2 (CDX2) (Figure 4B), and mucin 2 (Figure 4C) were positive; human epidermal growth factor receptor 2 (HER2), mucin 5AC, AFP (Figure 4D), and hCG were negative; and *in situ* hybridization showed that EBV-encoded RNA (EBER) was negative in the two forms of cancer cells. While the expressions of glypican-3 (Figure 4E), hepatocyte (Figure 4F), and spalt-like transcription factor 4 (SALL4) (Figure 4G) were positive in the hepatoid carcinoma cells. Periodic acid-Schiff (PAS) staining showed that the cytoplasms of signet ring cells were red (Figure 4H). No vascular invasion was found by CD31 and D2-40 examination.

According to histomorphology and immunohistochemical phenotypes, the final diagnosis was early HAS with signet ring cell carcinoma.

Discussion

HAS is a rare subtype of gastric cancer, originating from the gastric mucosa and exhibiting morphological features of gastric cancer and hepatoid adenocarcinoma, so it is considered to represent gastric carcinoma with hepatic differentiation and morphological similarity to hepatic cells. Since Ishikura et al. (6) first introduced HAS in 1985, HAS has been reported in individual cases in the world in the past time. The elevated serum AFP level is regarded as a significant feature of HAS (7). However, a proportion of HAS patients have not shown an increase in serum AFP level. In our case, serum AFP was normal and there was no expression of AFP in the tumor tissue either. The diagnosis of HAS is largely dependent on its histological characteristics and immunohistochemical analysis of tumor

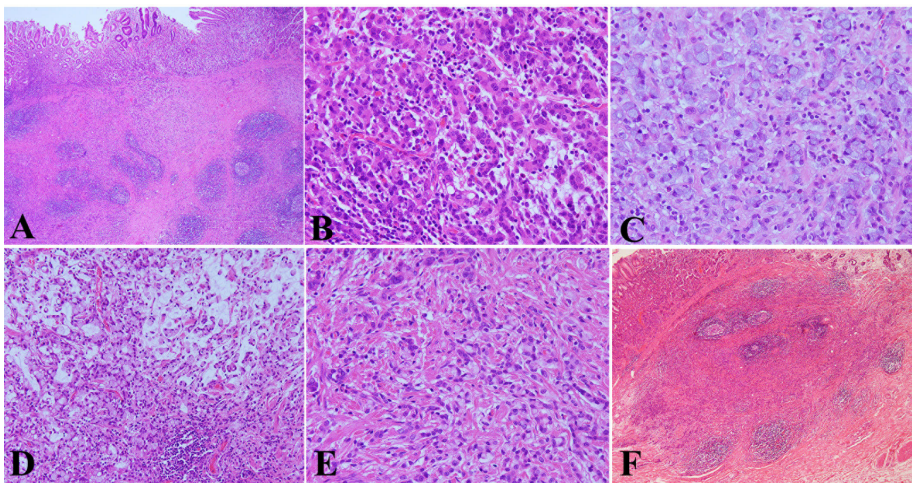

FIGURE 3
Pathological features of HAS by hematoxylin & eosin (HE) staining. **(A)** The infiltration of cancer tissue was limited to the mucosa and submucosa and reached the deep layer of the submucosa. The mucosal surface was almost covered by non-neoplastic epithelium (HE, ×40 magnification). **(B)** Some cancer cells were arranged in the form of irregular nests, cords, or micro glandular tubes. The cells were large and cubic in size, rich and eosinophilic in the cytoplasm, and with round or oval nucleus, binucleate and small nucleoli, and hepatocyte-like appearance (HE, ×400 magnification). **(C)** Some cancer cells displayed the form of a signet ring and distributed diffusely (HE, ×400 magnification). **(D)** There was mucus formation in the interstitium of some signet ring cells, the signet ring cells floated in mucus (HE, ×200 magnification). **(E)** The different forms of cancer cells were interlaced with each other (HE, ×400 magnification). **(F)** In the submucosa, the stromal fibrous tissue of the cancer obviously proliferated to form a nodular shape with a clear boundary, and the lymphocyte focally infiltrated and formed lymphoid follicles (HE, ×40 magnification).

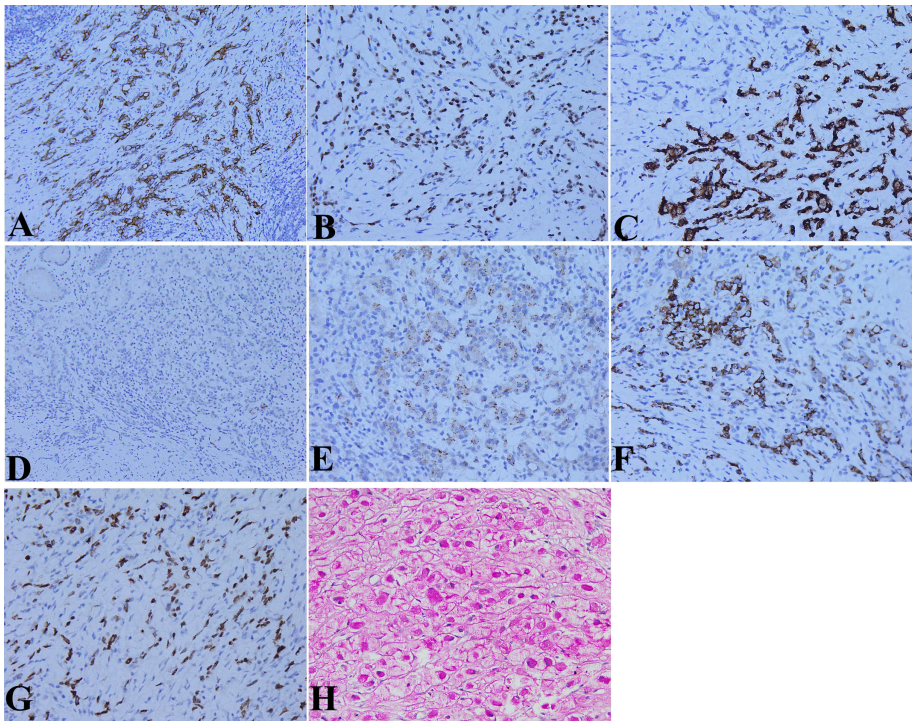

FIGURE 4
Molecular pathological features of HAS by immunohistochemical **(IHC)** staining and special staining. **(A)** Cytokeratin (CK) expression in the cytoplasm of two kinds of tumor cells (IHC staining, ×200 magnification). **(B)** Caudal-related homeobox transcription factor 2 (CDX2) expression in the nucleus of the two kinds of tumor cells (IHC staining, ×200 magnification). **(C)** Mucin 2 expression in the cytoplasm of the two kinds of tumor cells (IHC staining, ×400 magnification). **(D)** No alpha fetoprotein (AFP) expression in the cytoplasm of the two kinds of tumor cells (IHC staining, ×400 magnification). **(E)** Glypican-3 expression in the cytoplasm of hepatoid carcinoma cells (IHC staining, ×400 magnification). **(F)** Hepatocyte expression in the cytoplasm of hepatoid carcinoma cells (IHC staining, ×400 magnification). **(G)** Spalt-like transcription factor 4 (SALL4) expression in the nucleus of hepatoid carcinoma cells (IHC staining, ×400 magnification). **(H)** Red periodic acid-Schiff (PAS) staining in the cytoplasms of signet ring cells (IHC staining, ×400 magnification).

markers, regardless of its capacity to produce AFP. Similarity to AFP, glypican-3 and SALL4 are oncofetal proteins that are produced by the fetal liver (8, 9). Since there is no AFP expression in the cancer tissues of some HASs, whereas glypican-3 and SALL4 expressions are usually positive, glypican-3 and SALL4 are considered potentially more useful biomarkers of HAS than AFP (10). In our case, both glypican-3 and SALL4 were positive in the cancer tissue, there were remarkable histomorphologic features of hepatoid structure, and hepatocyte staining was positive in the cancer tissue; therefore, the diagnosis of HAS was determined. What is special in this case is that the tumor cells exhibited different patterns. In addition to features of hepatoid carcinoma and gastric adenocarcinoma, some cells displayed the form of a signet ring, with mucus formation in the interstitium of some areas, and PAS staining for the cytoplasm of the signet cell was positive. The different forms of tumor cells were intermingled with each other. In addition, the infiltration of cancer tissue was limited to the mucosa and submucosa, without vascular invasion and lymphatic metastasis. Therefore, the final diagnosis of early HAS with signet ring cell carcinoma was determined. This is an extremely rare type of HAS. To our knowledge, it is the first time that HAS with signet ring cell carcinoma is presented in the literature.

HAS is rare but has high malignancy and poor prognosis. Due to lack of specific endoscopic characteristics and finite pathological materials of the endoscopic biopsy, it is difficult to diagnose clinically and pathologically and easily misdiagnosed. In this case, EGD showed that the antrum and corpus exhibited non-atrophic gastritis without a sign of *H. pylori* infection, and there was a protuberant lesion with a central depression in the greater curvature of the junction between the antrum and body. There was an irregular microvascular pattern only in small parts of the lesion, some widened intervening parts, and elongated pits under ME-NBI. Therefore, we think that the endoscopist should pay special attention to abnormal alterations of the gastric mucosa, even in a state without a sign of atrophy and *H. pylori* infection. A previous study also showed that HAS is not related to known risk factors for developing a common gastric adenocarcinoma, *H. pylori* infection, or chronic atrophic gastritis (11). Histologically, the tumor was limited in the mucosa and submucosa, and the surface layer of the mucosa was almost covered by non-neoplastic epithelium. The

histopathology of the tumor was composed of hepatoid carcinoma, gastric adenocarcinoma, and signet ring cell carcinoma, and there was mucus formation in the interstitium of some areas. The hepatoid carcinoma, adenocarcinoma, and signet ring cell carcinoma were distributed in different regions and intermingled with each other. In the regions of adenocarcinoma and signet ring cell carcinoma, the component of adenocarcinoma was less, whereas signet ring cell carcinoma was relatively more. This histopathology was easily misdiagnosed as poorly differentiated adenocarcinoma with signet ring cell carcinoma, which should be paid more attention. Judging from the histopathological features of this case of HAS, we think that it may be more appropriate to call it gastric hepatoid signet ring cell carcinoma, but it needs the accumulation and study of more cases. It should be noted that the fibroid tissue in the submucosa was obviously proliferated, even nodular, and lymphocytes focally infiltrated and formed lymphoid follicles in the fibrous interstitium.

The molecular characteristics of HAS are not completely clear. Producing AFP is regarded as a significant feature of HAS, but a proportion of HAS has not shown an increase in serum AFP and the expression of AFP in HAS tissue. AFP production is believed to be related to HAS cell component percentage in a tumor (12). In this case, there was no increase in serum AFP and AFP expression of HAS tissue, which might be related to HAS cell component percentage in this tumor. SALL4 is a novel stem cell gene and highly expressed in both the murine and human fetal liver (13, 14). SALL4 expression has also been observed in the neofetal stomach, primitive germ cell tumors, enteroblastic adenocarcinomas, yolk sac tumors, and HAS (9). Analysis of molecular features of HAS indicated that SALL4 may play an essential role in HAS carcinogenesis (15). In this case, there was a high SALL4 expression in HAS tissue. In addition, we revealed that there were the expressions of CDX2 and mucin 2 in this HAS tissue, whereas mucin 5AC was negative, indicating that the tumor cells differentiated into intestinal epithelium.

In conclusion, HAS with signet ring cell carcinoma is a special type of HAS and extremely rare. This is the first report of endoscopic and histologic presentation of the case, which contributes to strengthen the understanding on its clinicopathological characteristics and especially promote early detection to improve the patient's outcome. Endoscopists and pathologists should pay attention to this disease to arrive at a correct diagnosis.

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 Zunyi Medical University. 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

The study design was performed by BT, XW, and LD. Review of patient data and critical comments were performed by XW, LD, CL, SZ, NT, JH, and BT. XW and LD reviewed and described the pathologic and endoscopic findings. The manuscript was written by XW, LD, and BT. All authors contributed to the article and approved the submitted version.

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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.

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Case Report: Perivascular epithelioid tumors of the gastrointestinal tract

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Background: Perivascular epithelioid cell tumor of the gastrointestinal tract (GI PEComa) is a rare mesenchymal neoplasm. GI PEComa is mostly observed in the colon and has a marked middle-aged female predominance. PEComa has no typical clinical or imaging manifestations or endoscopic characteristics. Therefore, the diagnosis of this disease mostly relies on pathological findings. HMB-45 is a sensitive immune marker of PEComa.

Case presentation: We reported a case of a middle-aged female with sigmoid colon PEComa. To exclude carcinogenesis, the large basal polyp in the sigmoid colon was removed by endoscopic mucosal resection (EMR). Immunohistochemistry analysis results showed that this lesion expressed HMB-45, which is a characteristic melanin marker of PEComa. Finally, the lesion was diagnosed as sigmoid colon PEComa. At the time of submission of this report, surgical resection was the primary treatment for PEComa. Though the characteristics of tumor biology and clinical behavior in PEComa are not clear, the boundary is clear, and the tumor can be completely removed. However, close follow-up is required after the surgery because of the lesion's undetermined benign and malignant nature.

Conclusion: The present case study emphasizes the importance of pathological diagnosis. Therefore, upon finding gastrointestinal polyps with a mucosal ulcer under endoscopy, the GI PEComa diagnosis should be considered. It is necessary to detect the characteristic melanin markers of PEComa. Due to the rarity of these cases, challenges are faced in diagnosing and treating PEComa.

KEYWORDS

perivascular epithelioid cell tumors, sigmoid colon, HMB-45, treatment, case report

Introduction

PEComa is a family of rare mesenchymal neoplasms with a marked female predominance. This disease's peak onset is observed in 40-49 years of age. In addition, a few cases occur in children or adolescents (1). In 1992, Bonetti et al. used "perivascular epithelioid cells (PEC)" to describe certain epithelioid cells with perivascular distribution and

expression of melanocyte markers (2). In 2002, the WHO defined PEComa as "a mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells" (3). The PEComa family mainly includes angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), clear-cell "sugar" tumor (CCST) of the lung, and malignant ligament clear cell tumor (CCMT) (4, 5). In addition, a rare group of PEComas called "PEComas–not otherwise specified" (PEComas-NOS), with similar morphology and immunophenotype, may arise in soft tissues (such as retroperitoneal, abdominopelvic, and cutaneous) and visceral sites (such as gastrointestinal, gynecologic, and genitourinary) (6, 7). In immunohistochemistry, virtually all PEComas express melanocytic markers, such as HMB-45 and Melan-A (5, 8, 9). PEComas exhibit neither characteristic clinical nor typical imaging and endoscopic manifestations. Therefore, PEComas are generally diagnosed using typical histological and immunohistochemical findings. PEComas-NOS manifests a broad biological behavior including benign, uncertain malignant potential, and malignant features. Folpe et al. proposed that "tumor size >5 cm, infiltrative growth pattern, high nuclear grade, necrosis, and mitotic activity >1/50 HPF" could predict malignant behavior of PEComas (10) Moreover, these features are the key to the prognostication of PEComa. Currently, wide-margin surgical resection is the best treatment method for PEComas. Additionally, some targeted molecular therapies are under the exploratory phase. Here, we present a case of PEComa of gastrointestinal tract located in the sigmoid colon of a female patient. The clinical and endoscopic findings and pathological features of this case are described to deepen our understanding of GI PEComa so as to improve its diagnostic accuracy and therapeutic effect (Figure 1).

Case presentation

A 47-year-old female was admitted to Binzhou Medical university hospital. The patient had no tumor-related family history or medical history of tuberous sclerosis complex (TSC), inflammatory bowel diseases, or malignant melanoma. Her physical examination results were within normal ranges. The blood and biochemical parameters, including the tumor markers such as the levels of serum CEA, CA19-9, AFP, CA15-3, and CA-125, were also within the normal ranges. The patient underwent a colonoscopy at the outpatient department of our hospital for constipation. The examination revealed a 1.5 cm × 2.0 cm polyp with surface erosion in the colon, 18 cm away from the anus. The polyp had a large basal lesion with an eroded surface. The patient was referred to our inpatient department for polyp resection.

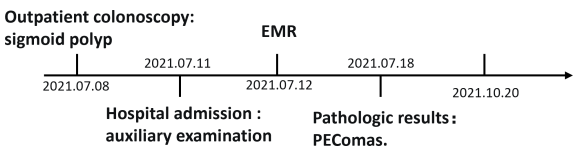

FIGURE 1
The case history.

Although we considered the possibility of neoplastic polyps, we did not consider the possibility of GI PEComa initially.

The well-circumscribed tumor was 2.0 cm in maximum diameter and had a wide base (Figures 2A–C). Because the tumor had a wide base, we used endoscopic mucosal resection (EMR) to remove the lesion (Figures 2D, E) and improve postoperative pathology.

Microscopically, the tumor is composed of nests of round, oval, or polygonal epithelioid cells with abundant clear eosinophilic granular cytoplasm. In our case, the nests were separated by thin fibrovascular septa (Figure 3A). The tumor cells had large nuclei with prominent nucleoli and the obvious local atypia of tumor cells (Figure 3B). The mitotic rate was >1/50HPF and about 20% of the cells expressed Ki67 (Figure 3E). In addition, the tumor showed invasive growth and foci of coagulation necrosis.

Immunohistochemically, the cells stained positive for HMB-45 (Figure 3C) and TFE-3 (Figure 3D). However, they were negative for Melan-A, desmin, smooth muscle actin (SMA), S-100, CD117, and CK (Figure 4). Therefore, depending on the endoscopy, histology, and immunohistochemistry results, we diagnosed the tumor as GI PEComa. Of note, we did not find any vascular invasion and base incision margin involvement in the postoperative pathology, which showed complete curative resection.

Given the tumor invasive growth, obvious local atypia, focal coagulation necrosis, mitotic rate >1/50HPF, and the high expression of Ki67, the possibility of malignancy was high. Therefore, we used chest X-ray, total abdominal CT, and gastroscopy to exclude metastasis.

We also conducted relevant laboratory and imaging examinations. The examinations did not show any signs of malignancy or metastasis. Combined with pathological findings, the case was diagnosed as GI PEComa with unclear benign and malignant origin. Therefore, a long-term follow-up was necessary to exclude tumor malignant transformation, recurrence, and metastasis. Three months after EMR, colonoscopy showed that the postoperative healing was good (Figure 2F). The laboratory examinations and abdominal and pelvic CT showed no signs of recurrence and metastasis.

Discussion

The gastrointestinal tract is the second most common location, after the uterus, of PEComa, accounting for 20-25% of the cases. The colon is the most common site of GI PEComa, followed by the small intestine, rectum, and stomach (11). Although PEComa shows a significant female predominance, the frequency of GI PEComa is similar in female and male patients (12). Based on previous case reports, the biological behavior of GI PEComa varies from benign to malignant. Most GI PEComas are benign or have uncertain malignant potential. However, a few cases show malignant behavior. Compared to other body parts, the malignancy rate of GI PEComa is relatively high (10–15).

Upon endoscopy examination, most GI PEComas exhibit clear edges, mostly polypoid lesions, necrosis, and mucosal ulcer. In previous reports, some GI PEComas were limited to the mucosa and submucosa, however, some extended to the muscular propria or even into the mesentery (12). Therefore, we could not diagnose GI PEComa only by the general manifestations observed during endoscopy. The final diagnosis depended on the pathological findings. Histologically,

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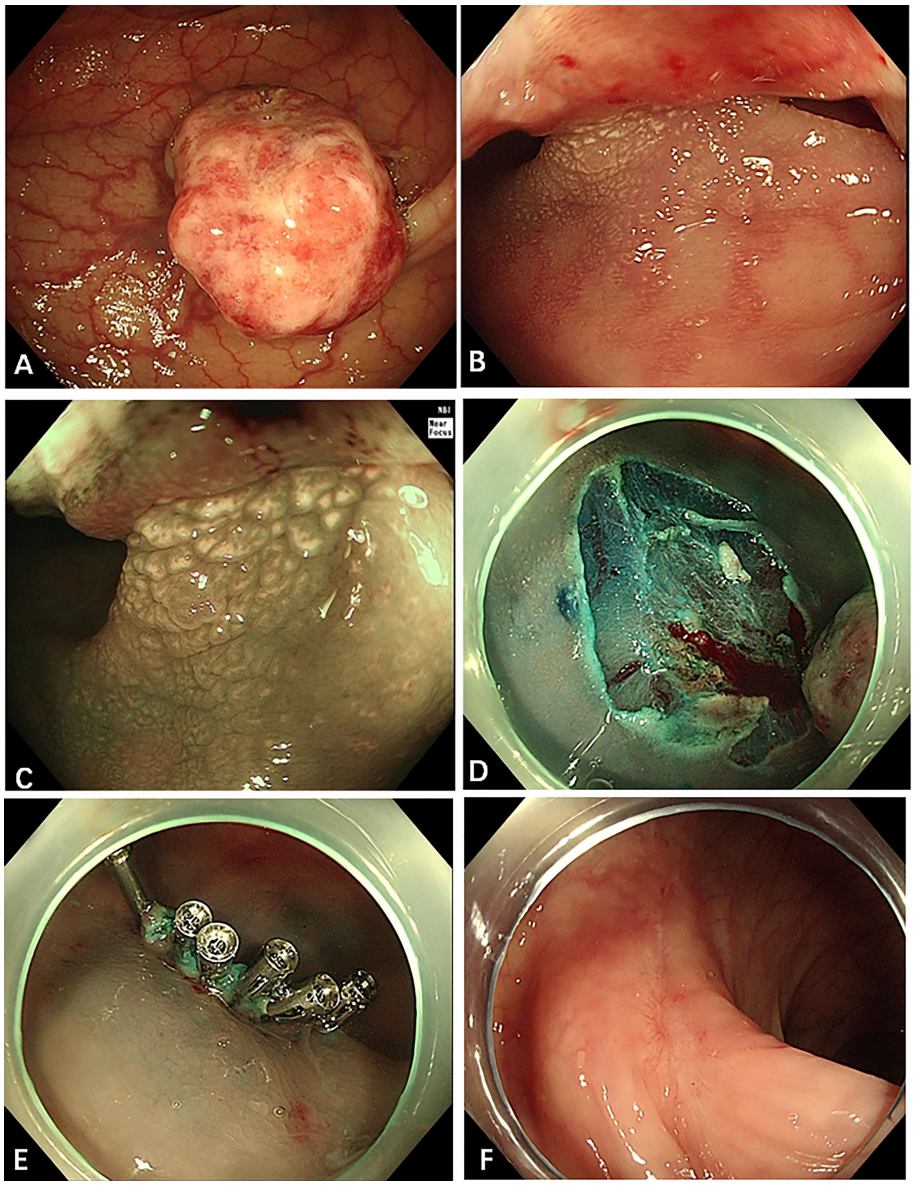

FIGURE 2
Endoscopic appearance of the sigmoid colon tumor. **(A–C)** There was a polypoid tumor in the sigmoid colon, 18 cm away from the anus, with a diameter of 1.5 cm × 2 cm and with a wide base. The surface of the polyp is eroded, and the gland tube and blood vessel under (Narrow Band Imaging, NBI) are not clearly observed. But the gland tube at the base is still regular. **(D, E)** A little blood oozed from the wound after EMR. We applied six endoscopic hemoclips to stop the bleeding. **(F)** Three months after the EMR, the wound was observed to be healed well.

PEComas are composed of nests of epithelioid cells, have abundant granular eosinophilic to clear cytoplasm, and are surrounded by a delicate capillary vasculature (16). In most cases, the tumor shows a nested, trabecular, or sheet-like architecture. In addition, the tumors often show prominent nuclear pleomorphism, including coarse chromatin, hyperchromasia, prominent nucleoli, and pleomorphism (12). Immunohistochemically, PEComas express both melanocyte and muscle markers (5). Of note, the most sensitive markers of melanocytes are HMB-45 and Melan-A (17). In our case, the tumor was described as a polyp or polypoid, was well-circumscribed, and had no specific diagnostic value. Initially, we did not consider the possibility of GI PEComa. However, sigmoid colon PEComa was diagnosed after the pathological biopsy due to its positive characteristic immunohistochemical features. PEComa may have TSC mutation and TFE3 gene fusion. However, no cytogenetic and genomic analyses of the tumor were performed.

Differential diagnosis with other gastrointestinal tumors is important. A benign submucosal tumor and gastrointestinal stromal tumor (GIST) have similar endoscopic and histological appearances as GI PEComa. However, the melanin (HBM45 and Melan-A) expression is typically negative in these tumors but always positive in PEComas. In addition, PEComas must be distinguished from melanoma, liomyoma, etc based on the results of the immunohistochemical analysis. Our case showed that the possibility of GI PEComa could not be ignored for polypoid lesions. Therefore, it was essential to perform histological and immunohistochemical examinations.

Most GI PEComas are benign or have uncertain malignant potential and do not metastasize. However, malignant PEComas

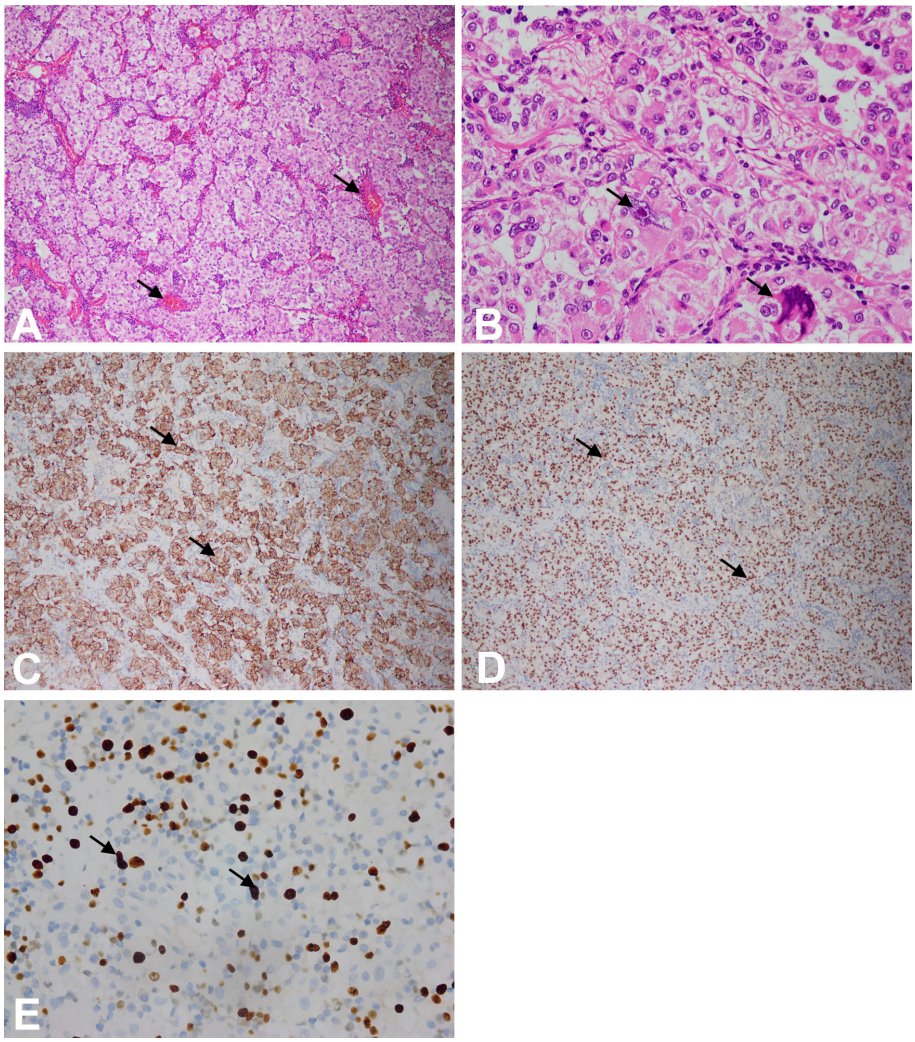

FIGURE 3
(A) Microscopic features of the tumor at 10× magnification using microscope. The tumor consisted of nests of epithelioid cells with clear-to-eosinophilic granular cytoplasm, as pointed by arrowheads. **(B)** Microscopic features of the tumor at 40× magnification using microscope. The tumor cells had large nuclei with prominent nucleoli, and the local atypia of tumor cells was obvious, as pointed by arrowheads. **(C)** The tumor cells were immunoreactive for HMB-45, and yellow was positive in the cytoplasm, as pointed by arrowheads (at 10× magnification using microscope). **(D)** The tumor cells were immunoreactive for TFE-3, and yellow was positive in the nucleus, as pointed by arrowheads (at 10x magnification using microscope). **(E)** Ki67 immunohistochemistry at 40× magnification using microscope.

demonstrate local invasion and/or metastatic spread. The optimal approach to treat PEComa is not yet clear (18). National Comprehensive Cancer Network (NCCN) guidelines indicate that surgical resection is the mainstay of treatment of GI PEComas, particularly for benign tumors (19). Moreover, in the current guidelines, no standardized regimen is provided to avoid its recurrence after surgery. In the current case report, malignant PEComa with metastasis was treated with adjuvant chemotherapy (20–23); however, a standard chemotherapeutic regimen is not established for advanced PEComa.

Presently, the knowledge about the molecular genetic alterations in PEComas is limited. In a previous report, two different molecular groups were identified, including the classic marker of TSC mutation and *TFE3* gene fusion. Further, molecular genetic studies revealed the deletion of 16p at the locus of the *TSC2* gene in PEComas. *TSC1* and *TSC2* genes negatively regulated the activation of mTOR (24). Therefore, for the palliative therapy of PEComas, mTOR inhibitors, such as sirolimus and everolimus, can be used in patients with TSC mutations (25). Also, targeting the VEGF/VEGFR signaling pathway may play an important role in the inhibition of tumorigenesis. Furthermore, it may be a viable treatment option for TFE3-related malignant PEComas. Studies have shown that VEGFR-2 inhibitor apatinib has therapeutic potential in PEComa patients with TFE3 rearrangement (26). Therefore, targeting the VEGF/VEGFR signaling pathway may be a novel therapeutic option for TFE3-associated malignant PEComas. However, the clinical cases are limited. Thus, combination-targeted therapy needs further exploration. Recently, Maren Schmiester found that the TSC1/2-mTOR pathway and TFE3 overexpression can promote tumorigenesis of PEComa (27).

We used endoscopic mucosal resection (EMR) to remove the tumor. EMR is a new endoscopic minimally invasive treatment with the advantages of lesser trauma, complete resection of lesion mucosa, and fewer complications. Although EMR has several advantages, such as fewer procedural complications, its use for PEComas is not the first

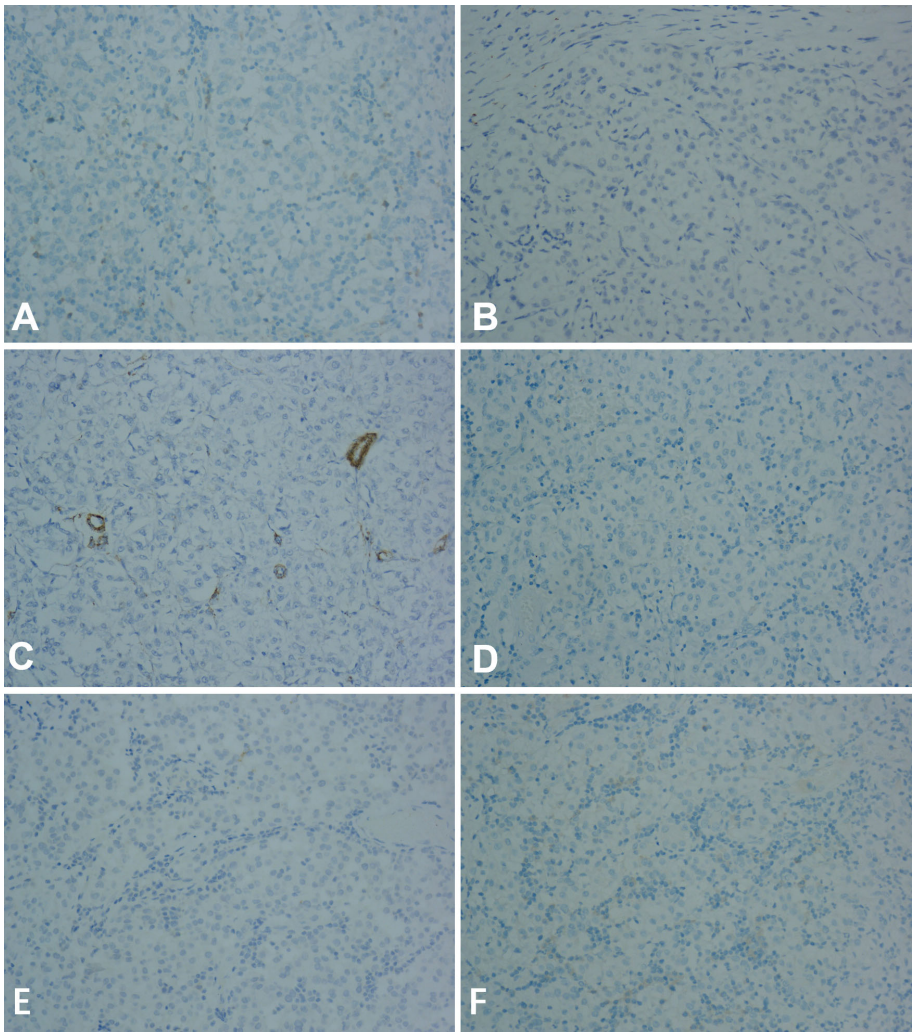

FIGURE 4
The tumor was negative for Melan-A, desmin, smooth muscle actin (SMA), S-100, CD117, and CK at 20x magnification using microscope. **(A)** Melan-A. **(B)** desmin. **(C)** smooth muscle actin (SMA). **(D)** S-100. **(E)** CK. **(F)** CD117.

treatment recommendation. Moreover, EMR for PEComa is not validated, and prospective data of PEComa patients are lacking. By differentiating between benign and malignant PEComas, EMR can potentially undertreat more aggressive diseases. Nonetheless, we did not find signs of malignancy and metastasis in our case; thus, no additional surgery or other adjuvant treatment was required.

Due to the rarity and the lack of standardized biological manifestation of PEComas, the diagnostic criteria of malignant PEComas are not fully agreed upon internationally. Therefore, the prognosis of PEComas, too, remains uncertain (28–30). However, the malignant behavior may be predicted by histological features, such as size more than 5 cm, invasive growth, high differentiation, mitotic rate ≥1/50HPF, necrosis, and vascular infiltration (13). Though the tumor size was less than 5 cm in the present case, coagulative necrosis was observed, showing that the PEComa had potential invasive growth with an uncertainty of being malignant. Therefore, a long-term follow-up with the patient is essential, throughout which endoscopy and imaging examinations will be performed regularly to exclude tumor recurrence and distant metastasis. So far, the patient has no specific symptoms of discomfort. No recurrence or distant metastases were observed during follow-up of 3 mo.

Conclusion

GI PEComas have no typical clinical and imaging manifestations or endoscopic characteristics. Thus, it is difficult to diagnose the tumor using these parameters and even ignore the possibility of PEComas. In the case of gastrointestinal polyps, especially mucosal ulcers, the possibility of GI PEComa should be considered. It is necessary to perform a pathological biopsy and immunohistochemical analysis of the excised tissues to assess the characteristic melanin markers of PEComas and confirm the benign or malignant nature of the lesion. Due to the rarity of GI PEComas and the limitation of clinical cases, we face challenges in diagnosing and treating them.

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

HY: Primary author (wrote most of the paper). YB and KL: Author of the manuscript, gastroenterologist involved in clinical management. GG and YL: Provided grammatical corrections to the manuscript. YZ was the pathologists responsible for the pathological diagnosis. CL: Provided reviews to the scientific content of the manuscript. NS: provided revisions to the scientific content of the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Ileal adenocarcinoma in a young pregnant woman: A rare case report

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Primary intestinal malignancies account for only 1%–3% of all malignant gastrointestinal tumors. Adenocarcinomas are uncommonly located in the ileum. Ileal adenocarcinoma (IA) is rare and difficult to diagnose because of its location. IA is common in older men and rare in young pregnant women. A 23-year-old pregnant woman was hospitalized several times for repeated vomiting and abdominal pain. Her symptoms were relieved after symptomatic treatment. She exhibited no typical manifestations of intestinal obstruction, such as abdominal distension, difficulty passing gas and defecation. Unfortunately, she was misdiagnosed with acute gastroenteritis. On the second day after delivery, the patient stopped passing gas and computed tomography (CT) revealed an intestinal obstruction. She was treated as paralytic ileus. However, in view of failed conservative management, she was decided for an exploratory laparotomy. A malignant ileal tumor 5cm from the ileocecal valve was found incidentally and was surgically excised accompanied with End-to-side anastomosis of ileal and transverse colon. The operation lasted 195 minutes. Pathological examination revealed an IA. Pregnant woman who experience symptoms of intestinal obstruction should be alert to the possibility of malignancy in the small intestine. IA is an insidious tumor in pregnant women. An "IA triad" can be defined as refractory vomiting, vague abdominal pain, and weight loss (or inadequate weight gain in pregnant women). Pregnant women with an IA triad should undergo investigation with endoscopy or, if necessary, magnetic resonance imaging (MRI).

KEYWORDS

abdominal pain, case report, ileal neoplasms, intestinal obstruction, pregnancy, vomiting

Introduction

Primary intestinal malignancies account for only 1%–3% of all malignant gastrointestinal tumors. By subtype, 30%–40% are adenocarcinomas, 35%–44% are neuroendocrine tumors, 10%–20% are lymphomas, and 12%–18% are gastrointestinal stromal tumors (1). Adenocarcinomas are usually located in the duodenum but rarely in the jejunum and

ileum (2). The diagnosis of intestinal carcinoma is usually delayed by more than 6 months because the clinical manifestations are nonspecific (3). Ileal adenocarcinoma (IA) is rare and difficult to diagnose because of its covert location. Takahashi et al. (4) reported 17 cases of early-stage IA during the period 1996–2016. The mean age of these patients was 66.1 years, the youngest being 55 years, and 15 of them were male. Thus, IA is more common in older men. However, ileum adenocarcinoma is rare in young patients, especially in young pregnant woman. Here we report the first case of IA in a young pregnant woman.

Case

A 23-year-old woman presented to our department at 33 and 3/7 gestational weeks (GWs) of her first pregnancy, complaining of vaginal bleeding for 2 days and vomiting and abdominal pain for 10 h.

She experienced nausea and severe vomiting (approximately 5–10 times a day) during the first trimester. The vomiting did not stop at the end of the first trimester but was less severe than before. Weight gain was approximately 5 kg since the beginning of her pregnancy. Routine screening during her pregnancy suggested that the patient was heterozygous for the alpha-thalassemia gene, and her hemoglobin value fluctuated between 85 and 105 g/L (normal value: 110 g/L). At 26 GWs, she was hospitalized because of vaginal bleeding and exacerbated vomiting. Her diagnosis was threatened premature labor and acute gastroenteritis. She was given symptomatic treatment (fluid rehydration and antiemetics). The vomiting abated and the vaginal bleeding stopped.

At 30 and 5/7 GWs, the patient was admitted to our department for abdominal pain and recurrent exacerbated vomiting. She was diagnosed with acute cholecystitis based on a gallbladder stone revealed by ultrasonography and abnormal neutrophil counting. Antibiotics and antiemetics were prescribed accordingly. Dexamethasone was also prescribed to promote fetal lung maturation. Her symptoms abated quickly. At 33 and 3/7 GWs (January 7, 2021), the patient experienced lower abdominal pain and vaginal bleeding after vomiting. The vomiting, abdominal pain, and vaginal bleeding became worse and she was again hospitalized.

Upon examination, the length of the gravid uterus was 26 cm, the abdominal circumference was 78 cm, and the cervix was dilated at 1 cm. The fetal heart rate was 130 beats per minute. No tenderness in the abdomen was obvious. Tests for polypeptides, antibodies against autoimmune hepatitis, and antibodies against hepatitis E, B, and C showed negative results. The amylase level was normal. The blood test results are listed in Table 1. Ultrasonography revealed a strong echogenic accumulation of 3.0 × 0.7 cm in the gallbladder cavity and a fetus whose size corresponded to the number of GW.

The patient denied any medical history of gastrointestinal symptoms such as emesis, melena, abdominal pain, or ileus before pregnancy. The patient and her family had no history of previous intestinal cancer. She was screened and was negative for hereditary non-polyposis colorectal cancer syndrome, Crohn's disease, Peutz-Jeghers syndrome, celiac disease, and cystic fibrosis. Her grandfather had died of hepatic carcinoma.

We prescribed glutathione to improve the patient's liver function, nifedipine to inhibit uterine contractions, and magnesium sulfate to protect the fetus's central nervous system. We also administered intramuscular dexamethasone sodium phosphate to promote fetal lung maturation.

During the treatment course, she suffered repeated vomiting that was accompanied by pain in the lower abdomen. Her appetite was thereby affected, and she ate only a little porridge at a time. She emptied her bowels every day, but only in small quantities.

We believed that her vomiting and pain would abate after delivery. She was treated symptomatically with mercoaluminum suspension to protect the gastric mucosa, metoclopramide to settle her stomach, and pethidine hydrochloride to relieve pain as necessary.

A live baby boy weighing 2120 g was delivered prematurely on January 20, 2021. The infant had Apgar scores of 9 in the first minute and 10 in the fifth minute.

Unfortunately, the patient still had postpartum nausea, vomiting, and abdominal distension and did not defecate for 2 days after delivery. On January 22, all bowel output stopped. Emergency CT

TABLE 1 Timeline of test results and the treatment process.

Test time	ALT (U/L)	AST (U/L)	TBA (umol/L)	TBIL (umol/L)	HGB (g/L)	WBC (10^9/L)	NEUT (%)	Treatments or Events
Jan. 9	152	128	1.7	9.7	105	5.66	85.3	Dexamethasone; Fluid infusion; Glutathione; Nifedipine
Jan. 12	247	157	2.3	9.1	99	4.77	71.2	Pethidine hydrochloride
Jan.14	224	142	1.9	8.7	97	3.97	60.9	Chinese traditional medicine
Jan. 17	243	161	2	10	NA	NA	NA	Ursodeoxycholic acid; Sucralfate suspension
Jan. 20	NA	NA	NA	NA	NA	NA	NA	Vaginal delivery of a healthy boy
Jan. 21	NA	NA	NA	NA	NA	NA	NA	Stops defecating
Jan. 22	229	162	10.3	8.8	NA	NA	NA	Polyene phosphatidyl choline; Exhaustion stops; Small intestine obstruction; Transferred
Jan. 25	NA	NA	NA	NA	NA	NA	NA	Laparotomy for unrelieved obstructive symptoms
Jan. 26	86	36	1.3	8.2	90	5.8	76.8	Parecoxib sodium; Glutathione
Feb. 2	19	19	0.7	8	85	4.01	56.1	Discharged without discomfort

Jan., January; Feb., February; NA, not applicable.

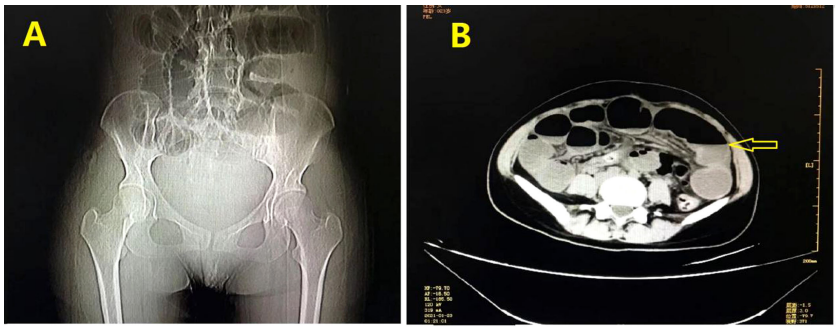

FIGURE 1
Imaging examination: **(A)** Digital radiology and CT scanning showed gas and fluid accumulation in the small intestine and indicated intestinal obstruction. **(B)** Liquid, air and high intestinal tension were visible (lesion was marked with yellow arrow).

indicated a small intestinal obstruction (Figure 1). Gastrointestinal decompression and enema treatment were administered.

There was still no anal discharge after non-surgical management for 2 days. Therefore, exploratory laparotomy with a vertical midline incision had to be performed for obvious abdominal distension. Approximately 200 mL of a yellow effusion was seen in the abdominal cavity. Intraoperatively, there was a hard constricting tumor measuring 2 cm × 2 cm located 5 cm from the ileocecal junction. The intestine was obstructed as evidenced by a dilated proximal bowel with blood, edematous fluid, and intestinal contents and collapsed distal bowel with many enlarged lymph nodes in the mesentery. (Figure 2). The specimens were removed from the middle section of the transverse colon about 10cm from the liver curvature of the colon and the terminal ileum about 15cm from the ileocecal valve.

A tumor of approximately 2 cm × 1.5 cm × 1.3 cm in size was removed from the ileum. It was an ulcerative high-grade tubular adenocarcinoma, which had invaded the whole ileal wall (Figure 3). Tumor emboli were visible in the blood vessel, but no perineural invasion was observed. Metastases were found in the lymph nodes around the colon and ileum, but no cancer involvement was apparent in the appendix, incisal edge of the ileum, and colon.

The patient was finally diagnosed with adenocarcinoma of the terminal ileum (pT4N2M0), abnormal liver function, gallstones, hypoproteinemia, preterm delivery (35 GWs), and alpha-thalassemia.

The patient was discharged on February 3, 2021. Adjuvant chemotherapy was strongly recommended, but she chose traditional Chinese medicine (TCM) instead. She came to our department as an outpatient for a checkup in April 2021. Enhanced CT scanning of her whole abdomen revealed multiple niduses in the liver, the largest being 2.6 cm, which indicated metastatic lesions (Figure 4). At the same time, she showed signs of cessation of menstruation, but an intrauterine gestational sac was found by color ultrasonography examination at the last follow-up on April 23 (Figure 5). This pregnancy was later spontaneously aborted.

She was hospitalized in the Traditional Chinese Medicine Hospital of Zigong for abdominal pain on July 7, 2021. *Brucea javanica* oil emulsion injection and other TCMs were used against the tumors. She underwent a chemotherapy regimen of oxaliplatin (100 mg) and bevacizumab (260 mg) administered on the first day of the cycle *via* intravenous infusion, plus oral capecitabine, 1 g twice a day for 14 days. This regimen was administered at 3-week intervals. The first, second, third, fourth, fifth, and sixth cycles of chemotherapy began on July 17, August 7, September 6, September 29, October 20, and November 15, 2021, respectively. CT revealed that the metastases in the liver were necrotic, but the metastases in the lymph nodes of the abdominal cavity had not changed. The patient's last treatment was pelvic tumor angiography and perfusion chemotherapy with irinotecan.

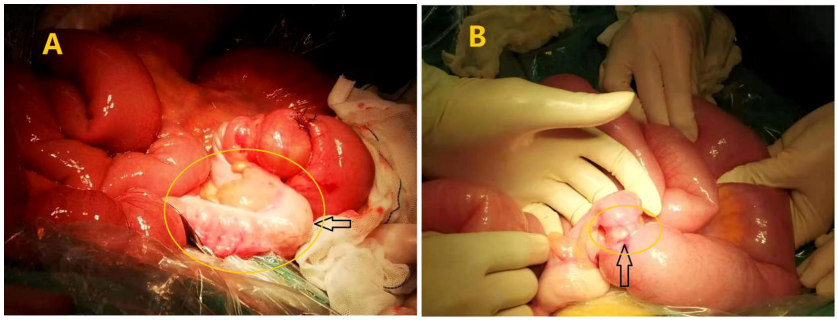

FIGURE 2
Surgical finding: **(A)** The cancer caused this part of the ileum to become ischemic and pale; **(B)** Annular stenosis in the ileum is indicated by the yellow circles.

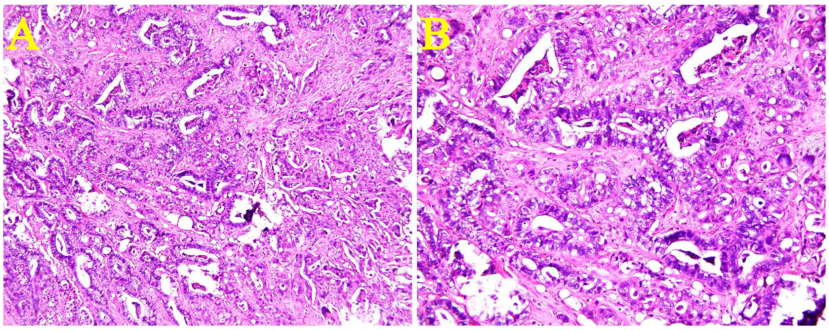

FIGURE 3
Microscopic view of the ileal adenocarcinoma. An ulcerative high-grade tubular adenocarcinoma had invaded the entire ileal wall. [Hematoxylin & eosin staining, **(A)**×100 and **(B)**×200].

She suffered constant abdominal pain, and her weight dropped to 35 kg because her appetite was poor. She died on February 26, 2022.

Discussion

Small bowel adenocarcinomas account for only 5% of all gastrointestinal malignancies (5). A retrospective analysis showed that the incidence of small intestinal tumors was 60.6% in the duodenum, 20.7% in the jejunum, and 18.7% in the ileum. The median age of patients was 63 years (range, 23–90 years) (6), which is consistent with the findings of Colina et al. (7).

The rising incidence of IA has been linked to age and alcohol consumption, a high-fat diet, high-sugar diet, smoked foods, and red meat. In contrast, a high intake of fish, coffee, fruits, and vegetables may reduce the risk (8–10). In most studies, the risk factors for IA are Lynch syndrome, inflammatory bowel disease, Crohn's disease, and familial adenomatous polyposis (6, 8). Our case had a negative history for these risk factors.

The most common clinical manifestations of IA are weight loss, vomiting, cramping abdominal pain, and occult gastrointestinal bleeding, but perforation is rare (8, 10–13). Vomiting and nausea may persist throughout a pregnancy in approximately 10% of affected women (14), so these symptoms are easily attributed to pregnancy. Our patient presented with vomiting (a typical symptom of pregnancy) and pain, which represented a threat of premature abortion. For pregnant women, inadequate weight gain is similar to weight loss in the general population.

Flexible enteroscopy performed with balloon-assisted or spiral techniques to explore the terminal ileum is a predominant and effective method for diagnosing IA, but it is less accurate than CT enteroclysis or video capsule endoscopy (VCE) (6, 10, 15). However, CT and contrast agents are contraindicated in pregnant women. VCE has the advantages of being simple, safe, reliable, and of short duration, and requires no anesthesia. Endoscopic indications during pregnancy are severe or refractory nausea and vomiting or abdominal pain according to the American Society for Gastrointestinal Endoscopy (16). The primary contraindications to VCE are known or suspected intestinal obstruction, strictures, fistulas, cardiac pacemakers, and swallowing disorders. Pregnancy is a relative contraindication according to the US Food and Drug Administration (16). Thus, pregnancy represents a dilemma for the diagnosis of IA. Under the surveillance of a multidisciplinary team, endoscopic examination could be performed safely. The advantage of magnetic resonance imaging (MRI) is that it does not expose the patient to radiation, and its use in this setting has been reported (17–

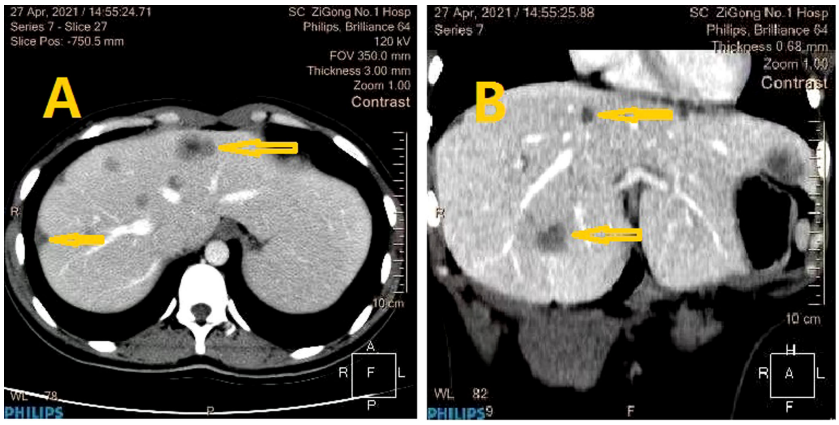

FIGURE 4
CT imaging: The metastatic liver lesion and low-density lesions in the liver was shown by CT (lesion was marked with yellow arrow) [**(A)**, **(B)** reflect different anatomical layers].

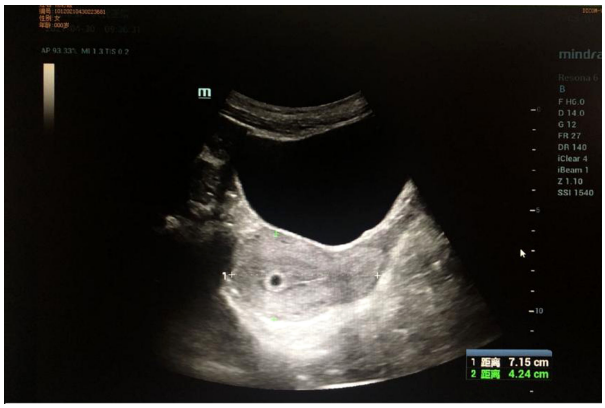

FIGURE 5
Ultrasound imaging: The gestational sac in the uterus was detected by ultrasound examination.

19). To date, unfortunately, almost all tumors in the jejunum and ileum have been detected during emergency surgery because of obstruction, perforation, or gastrointestinal bleeding, as in our patient. In retrospect, the indications in our case were sufficient for endoscopy or MRI evaluation. At least the upper digestive tract lesions can be ruled out by gastroscopy. After the upper digestive tract lesions are excluded, MRI can be considered to further explore the presence of lesions in the lower digestive tract. Such a procedure would keep safe for both the pregnant woman and the fetus, while also finding hidden lesions as much as possible.

Segmentectomy of the ileum and colon is the only cure for IA. Because lymph node metastasis strongly affects the prognosis, at least eight regional lymph nodes must be retrieved intraoperatively for evaluation (20). The combination of leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX) is the regimen most frequently used (6, 8). Cetuximab or panitumumab should not be used to treat small bowel adenocarcinoma (SBA) because it is clinically useless in RAS wild-type cases (6, 8). After systemic treatment, the patient should be closely monitored through physical examination and measurement of carcinoembryonic antigen or carbohydrate antigen 19-9 levels, or both. CT scanning of the chest, abdomen, and pelvis is necessary.

When malignancy is diagnosed during pregnancy, it is generally found at advanced stages (21). The lack of screening programs enhances the difficulty of detecting IA in particular. Huffman et al. reported that advanced age, advanced stage, and a lymphocyte-to-monocyte ratio of <1.56 were independent predictors of survival in cases of resectable SBA (22). The rate of recurrence of IA is as high as 77%, far higher than that of duodenal (54%) and jejunal adenocarcinomas (65%) (7). The prognosis is poor because IA is usually found at an advanced stage.

In our patient, IA caused only incomplete ileus, which was relieved after symptomatic treatment until the typical symptoms of ileus appeared after delivery. When the initial treatment of ileus failed, emergency surgery was needed, and only then was IA discovered unexpectedly. This is consistent with the report by Dabaja et al. that all cases of IA require emergency management (4).

We propose an "IA triad" definition of refractory vomiting, vague abdominal pain, and weight loss (or inadequate weight gain in pregnant women). We believe that this IA triad can alert medical professionals to the possibility of a malignant tumor in young pregnant patients. Timely detection of tumors may contribute to earlier staging, which strongly affects the prognosis. To avoid misdiagnosis in similar cases, attention should be paid to important symptoms, including refractory vomiting, vague abdominal pain, and weight loss (or inadequate weight gain in pregnant women). Perhaps in the near future, artificial intelligence modules in medical management systems can help us solve these problems (23).

Conclusion

Pregnant women who experience symptoms of intestinal obstruction should be alert to the possibility of small intestinal malignancy. IA is an insidious tumor in pregnant women. An IA triad can be defined as refractory vomiting, vague abdominal pain, and weight loss (or inadequate weight gain in pregnant women). Pregnant women with the IA triad should undergo investigation with endoscopy or, if necessary, magnetic resonance imaging.

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

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 for the publication of this case report.

Author contributions

CX was responsible for the conceptualization, data collection and original manuscript drafting. QC and CC reviewed the literature. CCand XX corrected the data and revised the manuscript. YZ collected pathological data and revised the manuscript. All authors have read and approved the final manuscript.

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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

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Primary hepatic angiosarcoma with noncirrhotic portal hypertension: A case report

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Background: Primary hepatic angiosarcoma (PHA) is a rare malignant tumor of mesothelial tissue origin in the liver. The diagnosis of PHA relies on pathology, and it is frequently misdiagnosed as multiple hepatic hemangioma. Noncirrhotic portal hypertension is a relatively rare pathological manifestation, and there are few reports of PHA as an uncommon cause of noncirrhotic portal hypertension.

Case summary: A 36-year-old male was admitted with abnormal liver function and suspected drug-induced liver injury (DILI), initially manifesting as multifocal hepatic hemangioma. The liver biopsy revealed features of noncirrhotic portal hypertension (NCPH), and the patient was eventually diagnosed with multifocal hepatic angiosarcoma.

Conclusion: Patients with PHA may present with NCPH in the liver due to injury to hepatic sinusoids; therefore, it is necessary to consider the possibility of unsampled vascular malignancy when hepatic masses are identified, and the histology is consistent with PHA.

KEYWORDS

primary hepatic angiosarcoma, noncirrhotic portal hypertension, diagnosis, treatment, pathology

Abbreviations: PHA, primary hepatic angiosarcoma; DILI, drug-induced liver injury; NCPH, noncirrhotic portal hypertension; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, glutamyl transferase; ALP, alkaline phosphatase; PET-CT, positron emission tomography – computed tomography; HVPG, hepatic venous pressure gradient; RUCAM, Roussel Uclaf Causality Assessment Method.

Introduction

Primary hepatic angiosarcoma (PHA), also known as hepatic vascular endothelial sarcoma, hepatic malignant angioendothelioma, or Kupffer cell sarcoma, is a rare malignant tumor of mesothelial tissue origin, accounting for 0.1–2% of primary liver malignancies (1, 2). It is the most common primary malignant mesothelial tumor in the liver and was first reported by Block in 1974 (3). PHA occurs mostly in adults, especially those aged 50 to 70 years old, with a male-to-female ratio of 4:1. Potential pathogenic factors include exposure to chemicals such as arsenic, vinyl chloride monomer, thorium dioxide, and radium (4). The clinical signs and symptoms of primary hepatic angiosarcoma are similar to those of chronic liver diseases, and patients often present with abdominal pain, weight loss, fatigue, and anorexia. Hepatosplenomegaly, abdominal effusion, and jaundice are also common in elderly male patients (5). PHA is fatal, with most patients dying within 6 months of liver failure or bleeding (2).

Non-cirrhotic portal hypertension (NCPH) is a heterogeneous group of liver diseases of vascular origin, usually manifesting as portal hypertension (PHT) but with preserved hepatic synthetic function and near-normal hepatic venous pressure gradient (HVPG) (6). PHA is a rare cause of NCPH; thus, case reports of PHA combined with NCPH are very rare.

Herein, we present the case of a young male patient with an abnormal liver function who was eventually diagnosed with hepatic angiosarcoma. The patient was hospitalized twice, initially misdiagnosed as drug-induced liver injury complicated by NCPH and hepatic hemangioma, and was finally diagnosed as liver angiosarcoma.

Case presentation

A 36-year-old man with a 20-year history of nephrotic syndrome with normal renal function and fluctuating urine protein levels had been treated with glucocorticoids and traditional Chinese medicine for more than 10 years. He was first hospitalized due to abnormal liver function. Routine laboratory tests revealed mild abnormal liver function [total bilirubin (TBIL) 41.9 μmol/L, direct bilirubin (DBIL) 22.7 μmol/L, alanine aminotransferase (ALT) 21.6 U/L, aspartate aminotransferase (AST) 81.1 U/L, gamma-glutamyl transferase (GGT) 517.5 U/L, alkaline phosphatase (ALP) 323 U/L]. Doppler ultrasound, CT scan, and contrast-enhanced MRI scan of the upper abdomen demonstrated multiple small masses in the liver, so hemangioma was considered. Also, the enlarged spleen and collateral vessels indicated the presence of portal hypertension. The patient underwent a percutaneous liver biopsy and soon after felt pain and discomfort in the right upper abdomen with transient blood pressure decline. The ultrasound confirmed bleeding and hemorrhagic shock due to the liver biopsy. The patient recovered after fluid rehydration, blood transfusion, and other supportive treatments. Pathological examination of the liver biopsy (Figure 1A) revealed congested hepatic sinusoids and peri-sinusoid fibrosis, as well as dilation of the interlobular veins and some extended into the surrounding hepatic sinus. These changes in liver histology were consistent with NCPH features that represent venous outflow stenosis with portal hypertension. There was no evidence of extra-hepatic portal vein obstruction, and the patient was diagnosed with a drug-induced liver injury [the Roussel Uclaf Causality Assessment Method (RUCAM) score 5] and secondary NCPH. Ursodeoxycholic acid was given, and regular outpatient follow-up was performed.

Three months after discharge, an outpatient contrast-enhanced MRI scan of the upper abdomen depicted enlarged hepatic masses. Considering the possibility of malignancy (Figure 1D), the patient was readmitted to the hospital. Routine laboratory tests revealed abnormal liver function [albumin (ALB) 21 g/L, TBIL 35.7 μmol/L, DBIL 14.0 μmol/L, ALT 67 U/L, AST 70 U/L, GGT 147 U/L, ALP 240 U/L]. Liver contrast-enhanced ultrasound and positron emission tomography-computed tomography (PET-CT) indicated the possibility of primary liver malignancy with intratumoral hemorrhage. Whole abdominal CTV demonstrated multiple masses in the liver and an enlarged spleen with a spleen-renal venous shunt (Figure 1E). The patient was transferred to the hepatobiliary surgery department and underwent laparoscopic resection of the liver lesions. Liver lesion biopsy pathology (Figures 1B, C) demonstrated that the tumor cells were slit and cable-like with a vascular network and growth along the liver sinusoids. Immunohistochemistry revealed high expression of CD34, CD31, and ERG (ETS transcription factor).

The patient was diagnosed with primary hepatic angiosarcoma and was treated with lenvatinib. In May 2020, he stopped taking lenvatinib due to progressively exacerbating liver function and died of severe intra-abdominal infection and acute kidney failure.

Discussion

PHA is a rare malignant tumor originating from the liver sinusoidal endothelial cells. Herein, we reported the case of a male patient who was admitted to hospital due to abnormal liver function. CT and MRI play an important role in diagnosing hepatic angiosarcoma, and there are four main types of PHA radiological presentation: multiple nodules, massive masses, massive masses with multiple nodules, and diffuse invasive micronodular tumors. Most lesions present hypodense on CT scans, but some are hyperdense due to spontaneous intraperitoneal or intratumoral hemorrhage (7). On contrast injection, most nodular lesions depict low-density enhancement, and some show irregular or annular enhancement. The MRI reflects the hemorrhagic, heterogeneous, and multivascular nature of the PHA lesions, typically areas of high signal intensity on T1-weighted images and distinct heterostructures on T2-weighted images, suggesting intratumoral hemorrhage and fibrous septa (8). Hepatic angiosarcoma can be distinguished from hepatic hemangiomas or other liver tumors by CT and MRI. Previous studies have reported that using non-enhanced, multiphase-enhanced, and late-delayed CT and MR imaging is an optimal imaging technique for accurately assessing PHA (7, 9). However, due to its rarity, PHA is easily misdiagnosed as multiple hepatic hemangioma.

The typical histology of hepatic angiosarcoma is tumor vascular-like cavities lined by spindle cells that project into the lumen to form papillary structures. The degree of differentiation of tumor cells varies greatly, with well-differentiated tumor cells resembling hemangioma and poorly differentiated tumor cells having obvious atypia. Tumor

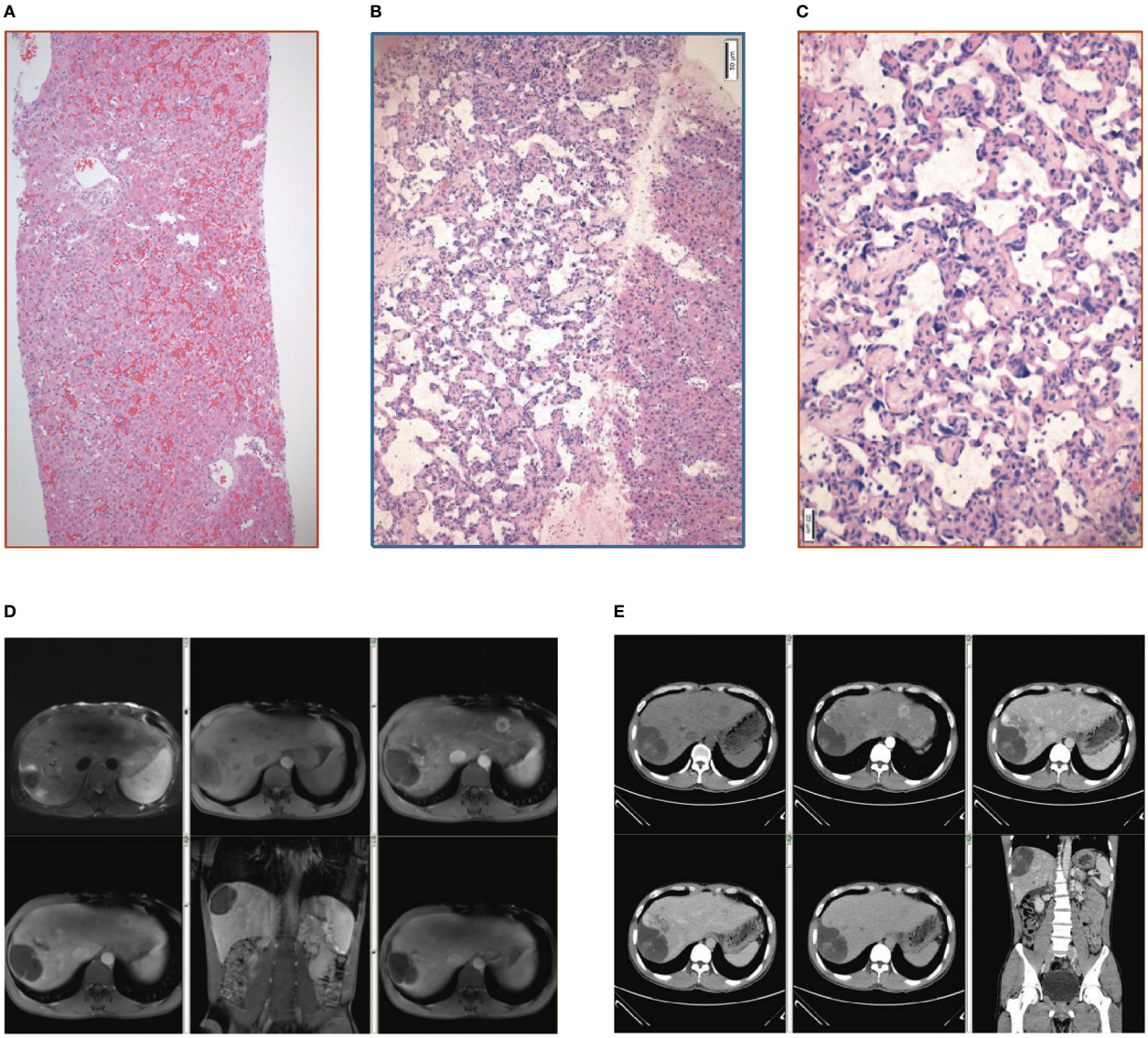

FIGURE 1
(A) Pathology of the liver tissue: HE staining (X10). **(B)** Pathology of the liver tissue: HE staining (X100). **(C)** Pathology of the liver tissue: HE staining (X200). **(D)** Contrast-enhanced MRI scan of the upper abdomen. **(E)** Whole abdominal CTV.

cells can look spongy with no obvious vascular space, giant cells, and pathological mitoses. They often spread along the sinus, terminal liver vein, and portal vein branches, and multilayer or prominent vascular lumen growth on the liver plate causes liver plate dissociation. Hepatocytes atrophy or disappear, the vascular cavity is enlarged, and the rapidly growing tumor tissue has visible residual hepatocytes, vascular lumen visible blood clots, and tumor cell debris (10). Immunohistochemically, liver sections are positive for CD31, CD34, D2-40, and factor VIII-associated antigens, with CD31 and factor VIII-associated antigens being the most specific markers (11).

Interestingly, this patient also presented with NCPH features. NCPH is a vascular liver disease of unknown etiology that presents clinically as portal hypertension (examples include thrombocytopenia secondary to hypersplenism and bleeding from esophagogastric varices or hypertensive gastropathy) with preserved hepatic synthetic function and near-normal hepatic venous pressure gradient (HVPG). It is characterized by increased pressure in the portal vein and its branches due to fibrosis of the intima and the absence of cirrhosis. The diagnosis of NCPH is mainly based on the following signs: a) hepatic hemodynamics and portal venography showing a high gradient of the portal sinus with fewer branches and increased portal caliber in the absence of thrombosis; b) liver biopsy showing thickening of portal vein fibers and no evidence of cirrhosis, necrosis, or inflammation (12). Although there is evidence that certain toxic substances (e.g., arsenic salts, thorium sulfate, vinyl chloride) may cause NCPH, the cause is often not identified. It has been suggested that some histological lesions of NCPH, such as hepatic sinusoidal cell hyperplasia, may lead to the development of angiosarcoma (4, 13, 14); however, there is no clear association between NCPH and hepatic angiosarcoma. In addition, a series of specific risk factors, such as arsenic, vinyl chloride, and androgenic steroids, which have a latency period of up to 20 years for their

carcinogenic effects, have been reported in 40% of patients with hepatic angiosarcoma (15, 16). As previously mentioned, these risk factors are also associated with NCPH development; therefore, NCPH and hepatic angiosarcoma may share the same triggering environmental factors. To our knowledge, there is a lack of literature describing the association between hepatic angiosarcoma and NCPH, with only eight published reports of NCPH and hepatic angiosarcoma-related cases, of which two patients had prior exposure to arsenic (17, 18), four patients with prior exposure to polyvinyl chloride (19), and two patients with unknown prior exposure history (19, 20). Furthermore, there have been reported cases of liver failure (21), which may be caused by portal fibrosis, destruction of the terminal portal nerve root in the liver, and liver parenchyma atrophy secondary to poor portal perfusion. In addition, PHA liver biopsies are extremely prone to bleeding, and as in this case, the liver biopsy caused transient hemorrhagic shock. Therefore, in patients with suspected PHA, non-surgical liver biopsy should be performed with extreme caution and careful evaluation before surgery is required.

Due to the rare incidence of PHA, there are no established treatment guidelines. Hepatectomy may be considered when the lesion is localized to one liver lobe. Patient survival may be prolonged with improved diagnostic techniques and liver transplantation, but the recurrence rate remains very high, and the prognosis is very poor (10). Also, PHA is considered an absolute contraindication to liver transplantation due to its dismal results. There are a few reports that chemotherapy is effective for PHA, and palliative care can be considered in cases of inoperable surgery. Local chemotherapy, such as transcatheter arterial chemoembolization (TACE) or systemic chemotherapy, can effectively prolong the life of patients, even equal to surgical outcomes (22, 23). PHA is a vascular-derived malignancy, so anti-angiogenic therapy may be a new potential strategy. There is a report of thalidomide combined with radiotherapy in a PHA patient with neck metastasis achieving a tumor-free state (23). Targeted therapies such as sorafenib and bevacizumab have limited efficacy in treating primary angiosarcoma of other organs; however, only one case of PHA was included in these studies (24, 25). An attempt to combine pazopanib, a PD-1 inhibitor, and RAK cells yielded effective results in an elderly PHA patient (26). These new approaches, alone or in combination with other therapeutic modalities, such as surgery and chemotherapy, need further investigation to assess their role in prolonging patient survival. Personalized therapeutic algorithms according to the genetics, molecular biology, histopathological features, and behavior of the tumors should be elaborated for the management of PHA 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

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

Author contributions: XW, XY, QG, BW, ZL collected and analyzed the data. XW, XY wrote the paper. YS and ZH critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Case report: First case of early adenoid cystic carcinoma and squamous cell carcinoma collision cancer treated by endoscopic submucosal dissection

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Background: Collision cancer, a rare tumor, rarely occurs in the esophagus. Most reported cases of esophageal collision cancers are advanced cancers that can only be treated with surgery or palliative chemoradiotherapy. Here, we report a rare case of collisional squamous cell carcinoma (SqCC) and adenoid cystic carcinoma (AdCC) that was detected in the early stages by endoscopy.

Case summary: A 66-year-old man presented with retrosternal pain after swallowing and underwent endoscopy. Pathological biopsy showed high-grade squamous intraepithelial neoplasia. The lesion was removed by endoscopic submucosal dissection (ESD) after magnification and endoscopic ultrasonography. Postoperative pathology proved that the lesion was collision cancer comprising SqCC and AdCC. After six months of postoperative follow-up, there was no recurrence of esophageal cancer.

Conclusions: We provided a case report related to the diagnosis and treatment of esophageal collision cancer, especially early collision cancer. More research is needed to provide insights into the management of collision cancers.

KEYWORDS

collision cancer, early esophageal cancer, esophageal squamous cell carcinoma, esophageal adenoid cystic carcinoma, endoscopic submucosal dissection

Abbreviations: AdCC, Adenoid cystic carcinoma; ASC, Adenosquamous carcinoma; ADC, adenocarcinoma; AVA, Avascular area; BLI-ME, Blue laser imaging magnifying endoscope; ESD, Endoscopic submucosal dissection; GIST, Gastrointestinal stromal tumor; NBI, Narrowband light imaging; SmCC, Small cell carcinoma; SMT, Submucosal tumor; SqCC, Squamous cell carcinoma.

Introduction

Collision cancer refers to a tumor that occurs at the same site but originates from two tissues that infiltrate each other but do not migrate to each other (1). Collision cancer has been reported in many sites of the human body, including the skin, crania, lung, bladder and uterus (2–4). In the digestive system, collision cancer mostly occurs in large digestive glands, such as the liver and pancreas (5, 6). Approximately 2.0% to 3.6% of collision cancers occur in the liver, and approximately 0.06% to 0.2% occur in the pancreas (7, 8). In contrast, this type of tumor is rarer in the digestive tract. A previous review reported 53 cases of collision cancers of the esophagus, stomach, small intestine and large intestine (9).

To date, 16 cases of esophageal collision cancer have been reported in the English literature (10–19). However, most previous reports on esophageal collision cancer described advanced cancer with tumor tissue invading the muscle layer, and all previously reported cases of esophageal collision cancer have been treated with radical surgical resection or palliative chemoradiotherapy. The collision of squamous cell carcinoma (SqCC) and small cell carcinoma (SmCC) was the most common combination.

Here, we report a rare case of a 66-year-old Chinese man with collisional cancer of SqCC and adenoid cystic carcinoma (AdCC), which was detected in the early stages by endoscopy. This is the first case of early esophageal collision cancer that was removed by endoscopic submucosal dissection (ESD) and had not recurred at 6 months of follow-up.

Case description

The patient was a 66-year-old man who was admitted to Beijing Friendship Hospital mainly because of retrosternal pain during swallowing for more than six months. The main symptom was a stabbing pain in the chest behind the breastbone when swallowing solid food, which was relieved after swallowing. He did not report dysphagia, acid regurgitation, heartburn, nausea, vomiting, or melena. There was no significant change in body weight in the past six months. In terms of past history, the patient had a smoking history of more than 30 years, approximately 30 cigarettes per day, and had quit smoking for 4 years. The patient had no other underlying diseases and no family history of cancer. Physical examination revealed no obvious abnormality.

The patient underwent electronic endoscopy in a local hospital on February 22, 2022. Flaky erosions were observed 29 cm away from the incisors, and they were approximately 0.8*1 cm in size with surfaces covered with white hair. A biopsy was taken from the erosion site, and the local hospital's pathology suggested high-grade squamous intraepithelial neoplasia.

After admission, the patient's routine blood, liver and kidney function, electrolytes, myocardial enzymes and other laboratory tests showed no abnormalities. Only the tumor marker prostate-specific antigen was increased. Enhanced chest computed tomography showed no esophageal space-occupying lesions or swollen lymph nodes around the esophagus.

The patient underwent endoscopy in our hospital on March 29, 2022. A type 0-IIa lesion, approximately 1*1 cm in size, was located in the middle of the esophagus and 28-29 cm from the incisors (Figure 1A). The lesion mucosa was red and rough, with good extension. The lesion boundary was clear under white light observation, and the lesion mucosa did not stain with 1.25% iodine staining. Blue laser imaging magnifying endoscopy (BLI-ME) revealed positive background staining (Figures 1B, C). The Japan esophageal society (JES) type was B1, and the avascular area (AVA) type was small AVA. Endoscopic ultrasonography suggested that the five-layer structure of the esophageal wall at the lesion

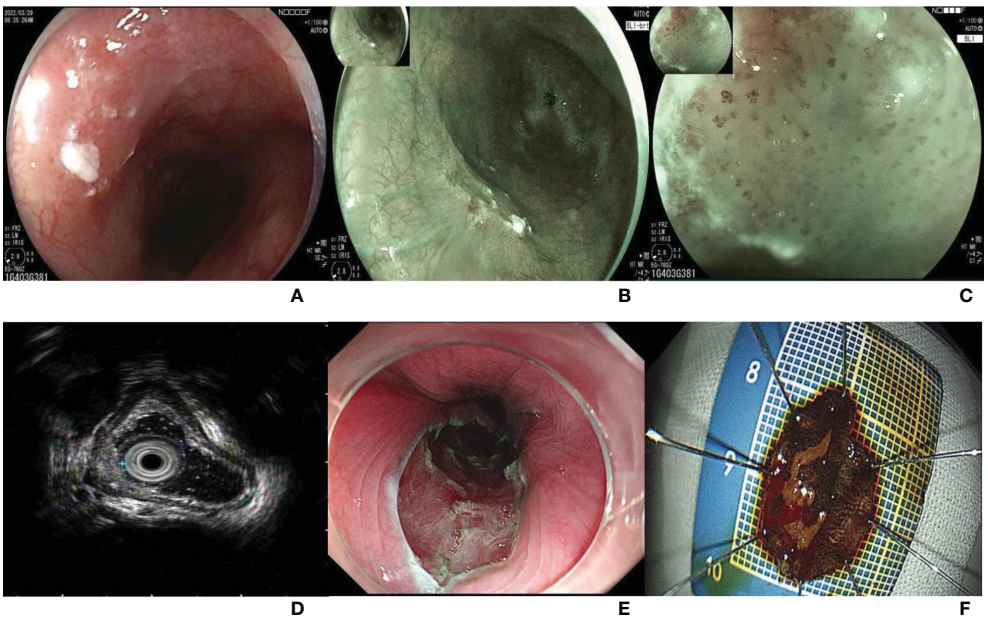

FIGURE 1
(A) A type 0-IIa lesion under white light endoscopy, approximately 1*1 cm in size, located in the middle of the esophagus and 28-29 cm from the incisors; **(B)** Esophageal lesion under blue laser endoscopy; **(C)** The background staining was positive under blue laser imaging magnifying endoscope. The JES type was B1, and the AVA type was small AVA. **(D)** Five-layer structure of the esophageal wall at the lesion was clear, and the mucosal layer was slightly thickened under ultrasound endoscope. **(E)** Esophageal wound after ESD. **(F)** An 18*14 mm esophageal mucosal tissue.

was clear, and the mucosal layer was slightly thickened (Figure 1D). ESD was performed to remove the diseased mucosa, and 18*14-mm esophageal mucosal tissue was obtained (Figures 1E, F). There were no short-term complications, such as bleeding, perforation or infection, after endoscopic surgery.

The postoperative pathological results showed that there were two malignant tumor components in the tissue submitted for examination (Figures 2, 3A). And microscopy revealed an abrupt transition between these two components that developed adjacently but never intermingled (Figure 3B). Combined with preoperative evaluation that failed to confirm any primary lesions that had metastasized to the esophagus, this patient was unequivocally diagnosed with an esophageal collision tumor. One of them was SqCC (approximately 4*2 cm in area) (Figure 3C). The cancer tissue infiltrated the lamina propria (pT1a-LPM). Another cancerous tissue was tubular and had cribriform structures with variably solid components (Figure 3D), which was located in the lamina propria and submucosa, with an infiltration depth of 60 μm into the submucosa (pT1b-SM1). Subsequent immunohistochemistry of this component yielded positive CD 117, S-100, p63, and CK8 staining (Figures 3E, F). Using the World Health Organization's classification of tumors of the digestive system 2019, we diagnosed this component as an AdCC (14*4 mm in area) (20). The horizontal resection margin was clean, and the tumor was approximately 20 microns away from the nearest vertical resection margin. This lesion was free of lymphovascular invasion.

Since the lesion had clean incisors and no vascular infiltration, additional surgery or chemoradiotherapy was not considered. After 6 months of follow-up, the patient did not complain of any discomfort. Three months after surgery, endoscopy revealed that there was a white scar approximately 28 to 29 cm away from the incisors in the middle esophagus, and esophageal stenosis and esophageal fistula were not observed. No abnormality was observed by narrowband light imaging (NBI), and no light staining was found after staining with 1.25% iodine solution.

Discussion

A collision tumor is a subtype of neoplasm consisting of two or more distinct cell populations, and some other types include composite tumors (no clear-cut interface or a transition zone between histological patterns) and carcinosarcomas (extensive intermingling between cell populations) (10). Furthermore, amphicrine neoplasms, one cell population exhibiting characteristics of both epithelial and sarcomatous cells, and cancer-to-cancer metastasis are also included in these rare neoplasms (21, 22). The diagnostic criteria of collision tumors proposed in the previous literature are as follows: a. two distinct topographically separate sites of origin for the two components must be present; b. there must be at least some separation of the two components so that, despite intimate mixing at points of juxtaposition, a dual origin can still be recognized; and c. at the areas of collision, in addition to intimate mixing of the two components, some transitional patterns may be seen (23). Combined with the results of immunohistochemistry, the pathological diagnosis of what we reported was that of an AdCC associated with an SqCC with features of a collision tumor.

According to the definition of collision cancer, the previous literature was strictly searched. As of August 31, 2022, a total of 16 cases (10–19) of esophageal collision cancer have been reported in the English literature (Table 1). Notably, most of the literature reports were from East Asia, and only 2 cases were from European and American countries. This may be related to the lower incidence of esophageal cancer in Western countries and the predominant pathological type of esophageal adenocarcinoma (24), while most esophageal collision tumors contain elements of squamous cell carcinoma. The incidence of esophageal collision cancer was higher in males than in females, with a male-to-female ratio of 13:3, mostly in the 60-70 years old age group. This distribution was similar to that of normal esophageal cancer.

The correct diagnosis of a collision tumor is difficult but crucial because individualized treatment and disease monitoring depend on the diagnosis. The medical history, clinical manifestations, and imaging findings of the collision tumor were not specific. The gold standard for routine tumor diagnosis (endoscopic pathological biopsy) yields the diagnosis of only one cancerous component in most cases; accordingly, our literature review yielded only 1 case (12) wherein a collision tumor was confirmed by endoscopic biopsy of the two components. Hence, it is important to examine multiple tumor biopsy sites to improve the efficacy of preoperative diagnosis. However, the difficulty of subsequent treatment due to fibrosis of the esophageal mucosa caused by multiple biopsies must be considered. Immunohistochemistry is a routine

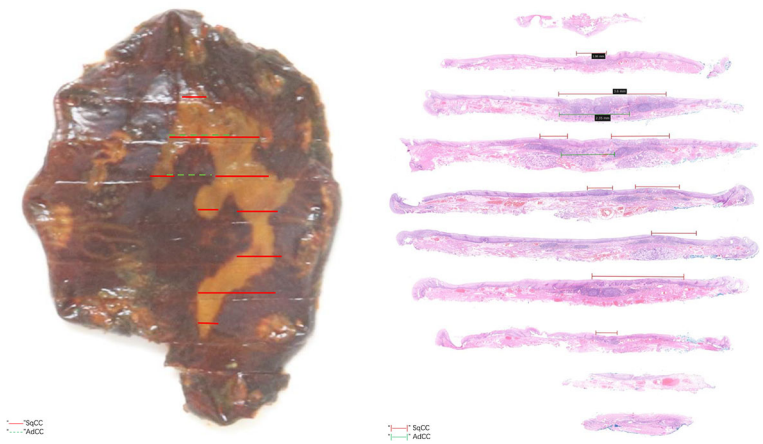

FIGURE 2
Translucent observation of the lesion and microscopic appearance of the lesion.

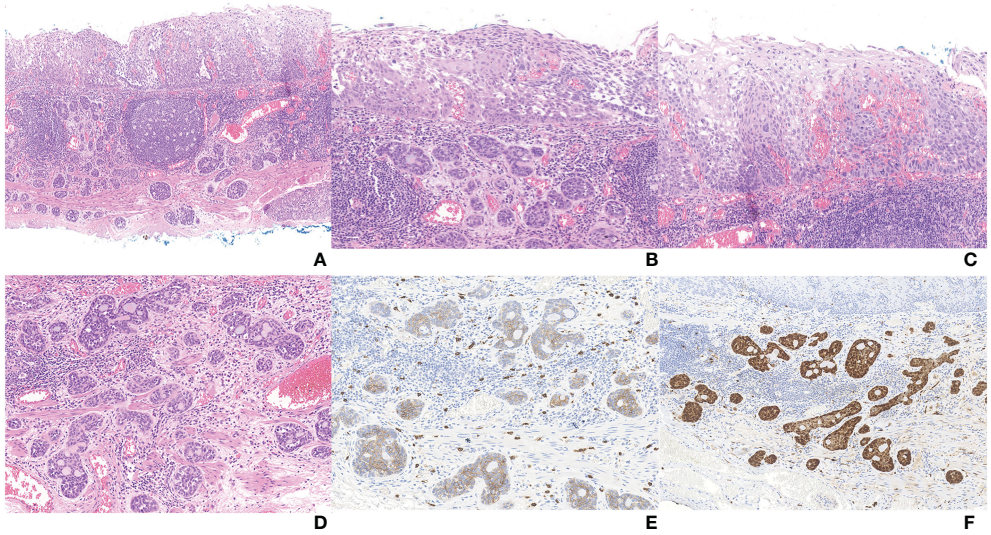

FIGURE 3
(A) Full view of collision carcinoma; **(B)** Area of collision between SqCC (up) and AdCC (down); **(C)** Area of SqCC; **(D)** Area of AdCC; **(E)** Immunohistochemical staining of AdCC (CD117); **(F)** Immunohistochemical staining of AdCC (S-100).

TABLE 1 Clinical Characteristics, Pathology, and Treatment Options of Esophageal Collision Tumors.

Author, year	Country	Age	Sex	Location	Gross type	Pathology of biopsy	Pathology of surgery	Pathologic stage	Surgical therapy	Overall survival
Schizas,2017	Greece	76	Male	Middle 1/3	Protuberant	ADC	SmCC+ADC +SRCC	pT3N1M0	+	6 months/ alive
Yao,2015	China	55	Male	Lower 1/3	NA	NA	SqCC+LMS	pT3N0M0	+	60 months/ alive
Choe,2020T	Korea	64	Male	Lower 1/3	Ulcerative	SqCC+SmCC	SqCC+SmCC	pT3N3M1	–	24 months/ died
Li,2013	China	66	Male	Lower 1/3	Ulcerative	SmCC	SqCC+SmCC	pT1bN1M0	+	18 months/ alive
Adachi,2014	Japan	62	Male	Middle 1/3	Medullary	ASC	SqCC+SmCC	pT1bN0M0	+	NA
Qian,2014	China	69	Male	Middle 1/3	Ulcerative	NA	SqCC+GIST	pT3N3M0	+	NA
Wilson,2000	America	51	Male	Lower 1/3	Protuberant	ADC	ADC+SmCC	NA	+	NA
Wang,2014	China	60	Male	Middle 1/3	Ulcerative	SqCC	SqCC+SmCC	pT3N2M0	+	17 months/ died
Wang,2014	China	66	Male	Lower 1/3	Protuberant	SmCC	SqCC+SmCC	pT1bN1M0	+	12 months/ alive
Wang,2014	China	57	Female	Middle 1/3	Protuberant	SqCC	SqCC+AdCC	pT1bN0M0	+	8 months/ alive
Kang,2020	Korea	70	Male	Middle 1/3	Ulcerative	SqCC	SqCC+SmCC	pT1bN0M0	+	NA
Zhang,2020	China	72	Male	Lower 1/3	Protuberant	ADC	SqCC+ADC	pT4N1M0	+	17 months/ died
Zhang,2020	China	75	Male	Lower 1/3	Medullary	SqCC	SqCC+ADC	pT4N1M1	+	49 months/ died
Zhang,2020	China	62	Male	Middle 1/3	Medullary	SqCC	SqCC+SmCC	pT4N2M0	+	13 months/ died
Zhang,2020	China	64	Female	Middle 1/3	Ulcerative	SmCC	SqCC+SmCC	pT2N0M0	+	78 months/ died
Zhang,2020	China	57	Female	Middle 1/3	Ulcerative	SqCC	SqCC+SmCC	pT1N0M0	+	48 months/ alive

SmCC, small cell carcinoma; SqCC, squamous cell carcinoma; ADC, adenocarcinoma; AdCC, adenoid cystic carcinoma; GIST, gastrointestinal stromal tumor; ASC, adenosquamous carcinoma; NA, not available.
"+", Undergone a surgical operation, "-", Did not undergo surgery.

method for pathological diagnosis. If immunohistochemistry remains inconclusive, molecular genetic analysis may be an important supplementary method for the diagnosis of collision tumors (25). Fukui et al. used gene sequencing to identify collision tumors and compound tumors (26).

To date, surgery remains the first-line treatment for patients with esophageal collision tumors, as is common for esophageal cancer. However, the presence of multiple components of collision tumors significantly alters treatment options, as it affects the adjuvant treatment options (10). No established guidelines are available. Some papers have argued that treatment should target the more aggressive component, while others consider that combined therapy targeting both tumor components can also be considered (27–29). More evidence is needed to determine the best individualized treatment for collisional tumors. The preoperative pathology of the case reported herein suggested high-grade intraepithelial neoplasia, which led us to use ESD. Postoperative pathological specimens were incidentally obtained as collision cancer. This contingency resulted in the current case being the only case of esophageal collision carcinoma that was removed endoscopically.

Notably, in this case, adenoid cystic carcinoma was one of the two cancerous components. This cancer is very rare in the esophagus, accounting for approximately 0.04%-0.16% of esophageal malignant tumors (30, 31). Due to the morphological similarity, the nomenclature of salivary tumors is adopted (32). AdCC is a type of submucosal tumor (SMT). The diagnosis of SMTs by endoscopic ultrasonography and the choice of ESD to remove submucosal lesions are controversial. He et al. (33) reported 224 upper gastrointestinal SMT patients detected with endoscopy who were further checked by EUS before receiving a series of ESD treatments; these patients also completed 3- and 12-month follow-up EUS detection. The accuracy rate of EUS in pathological diagnosis or the original layer was 82.6% (185/224) or 74.6% (167/224), respectively, and the ESD success rate was 92.9%. Residual tumors were detected with EUS in 3 patients (1.3%) at the 3-month follow-up, and no recurrence was observed during the 12-month follow-up period. Hence, endoscopic ultrasonography appears to be an effective routine follow-up for SMTs in the future, although the health and economic impacts of this measure remain unclear.

In summary, we described the clinical, histologic, and molecular features of a rare collision tumor comprising SqCC and AdCC, which was the first early esophageal collision tumor to be resected endoscopically. There was no recurrence after 6 months of follow-up. We provided more evidence for the diagnosis and treatment of esophageal collision cancer, especially early collision cancer.

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.

Author contributions

QZ, PL, and SZ treated the patient. ZL, YW, and RX wrote the paper. All authors contributed to the article and approved the submitted version.

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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

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Heterogeneous disease and intermittent treatment in metastatic colorectal cancer: A case report

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Background: Metastatic colorectal cancer is one of the most common causes of cancer death worldwide. RAS and BRAF mutational analyses are strongly recommended before beginning chemotherapy in the metastatic setting for their predictive role for the efficacy of anti-EGFR monoclonal antibodies. In most of cases, mutational status coincides between primary tumor and metastases. In RAS and BRAF wild-type patients treated with anti-EGFRs, after an induction treatment period, recent evidence supports the role of a maintenance treatment with fluoropyrimidines and anti-EGFRs. However, skin toxicity is the most described and limiting side-effect of maintenance. Moreover, it is described that the continuous administration of these monoclonal antibodies leads to an acquired resistance to anti-EGFRs, with subsequent treatment failure. Intermittent strategy with chemotherapy plus anti-EGFR may help maintain treatment efficacy, delaying resistance.

Case presentation: In this case report, we describe the case of a RAS-BRAF wild-type elderly patient undergoing first-line chemotherapy with FOLFOX + panitumumab, reporting response of disease on all metastatic sites except for a node. This node, surgically removed, revealed host BRAF V600 mutant clones. After surgery, patient continued chemotherapy with a stop-and-go strategy continuing to benefit from the same drugs after 4 years since diagnosis, and continuing to achieve response when on treatment, avoiding unacceptable anti-EGFR toxicity. This patient, still alive after 6 years since the diagnosis, represents the case of a good synergy between molecular profiling of disease, surgery, and intermittent treatment.

KEYWORDS

case report, anti-EGFR, resistance, intermittent strategy, RAS, BRAF, tumor heterogeneity, precision medicine

Introduction

Colorectal cancer (CRC) is the third most common tumor in men and the second in women, accounting for 10% of all tumor types worldwide. With more than 600,000 deaths estimated each year, CRC is the fourth most commonly diagnosed cancer globally (1–3).

During the last years, the deeper knowledge of tumor biology and molecular genetics has considerably influenced the treatment and survival of metastatic colorectal cancer (mCRC) patients with the introduction of molecularly targeted agents. In particular, EGFR has emerged as a key target for CRC, and anti-EGFR monoclonal antibodies (cetuximab and panitumumab) combined with cytotoxic chemotherapy are standard treatments for RAS wild-type mCRC patients because of their clinical efficacy and prolonged survival (4–6).

RAS and BRAF analyses are considered mandatory before planning a treatment: several studies reported that RAS mutant mCRC patients are unlikely to benefit from anti-EGFR antibodies and BRAF V600 mutations were shown to predict the lack of clinically meaningful efficacy of EGFR inhibitors (7); therefore, such therapies are not recommended for RAS/BRAF mutants (8). Moreover, following the recent evidence of clinical trials and updated guidelines, deficient mismatch repair (dMMR)/microsatellite instability (MSI) testing is recommended to select patients for immune checkpoint inhibition (ICI) in the first-line setting (9). After progression from first-line, identification of HER2 amplification is recommended in RAS wild-type patients to detect those who may benefit from HER2 blockade (10), although anti-HER2 inhibition is only recommended in second and further lines (11).

Giving a deeper insight, even in RAS and BRAF wild-type patients, the emergence of resistant tumor cell populations occurs almost inevitably, leading to treatment failure (12). The development of resistance and the evolutionary ability of cancer to adapt to treatment perturbations stem from spatial and temporal molecular heterogeneity of the tumor (13).

In mCRC patients, clinical data highlighted that the tumor genome evolves dynamically during treatment, showing the emergence of resistant mutated RAS clones during EGFR blockade, and their decline after the interruption of the anti-EGFR pressure (14). Moreover, in non-small cell lung and colorectal cancers, preclinical data suggested that alternative to the intrinsic existence of resistant clones, *de novo* resistant clones can develop during the course of prolonged EGFR blockade (15, 16). In this scenario, to limit the development of resistance and achieve long-term effectiveness in mCRC, the optimized use of anti-EGFRs through adaptive therapeutic strategies, such as the intermittent application like the stop and go approach, could be adopted to delay the onset of resistance.

Case presentation

We report the case of a 76-year-old woman (specific time points in Figure 1) diagnosed in December 2016 with stage IV RAS BRAF wild-type, poorly differentiated transverse colon adenocarcinoma with subcutaneous, pleural, left axillary, and abdominal lymph-node involvement (Figures 2A–D). A colonoscopy sample was used to perform RAS BRAF analysis, adopting the Oncomine Solid Tumour panel on Next Generation Sequencing (NGS) Ion Torrent platform, with a limit of detection of 5%.

In January 2017, the patient began chemotherapy with mFOLFOX-6 plus panitumumab. After six cycles, she reported a mixed response for a partial remission on metastatic sites but progressive disease on the axillary node (Figures 2E–H). During these first 3 months, the patient reported G1 skin rash, G1 peripheral neuropathy, and G2 neutropenia as side-effects, according to CTCAE 4.0.

This case was evaluated by a multidisciplinary team. Since disease progression only occurred at a single site, surgical excision of the left axillary node was scheduled (April 2017). Histopathological findings were compatible with metastasis from intestinal adenocarcinoma and the molecular assessment detected a BRAF V600E mutation that was probably the cause of resistance to panitumumab.

After surgery, the patient restarted chemotherapy with mFOLFOX-6 plus panitumumab for another six cycles and then continued with 5-FU/FA (De Gramont schedule) plus panitumumab as maintenance until March 2018. Afterwards, for persistent conjunctivitis (Grade 2, CTCAE 4.0) and considering the disease control, confirmed by a quarterly CT-scan, the patient began a treatment holiday period.

On June 2018, CT scan showed lung progression for evidence of two new lesions (Figures 3A, B). Therefore, the patient resumed 5-FU/FA + panitumumab until March 2019. During this period, disease stability and response on the new lung metastases were achieved (Figures 3C, D) and treatment was stopped temporarily for ocular toxicity (Grade 2, CTCAE 4.0) that was particularly bothersome for the patient.

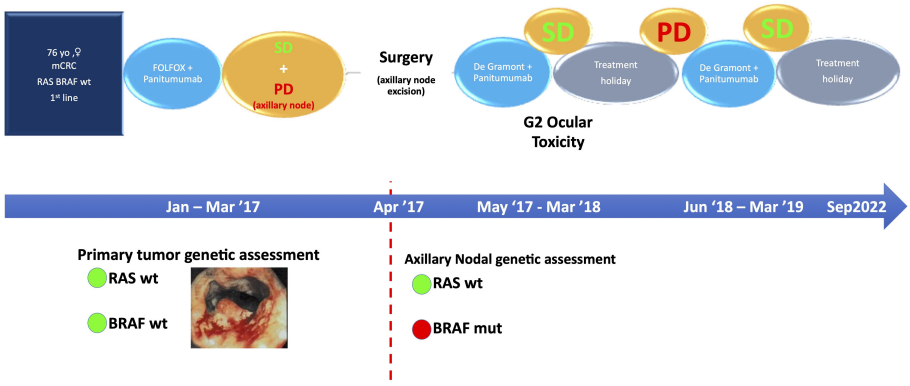

FIGURE 1
Specific time points corresponding to the diagnostic and therapeutic process. SD, stable disease; PD, progressive disease.

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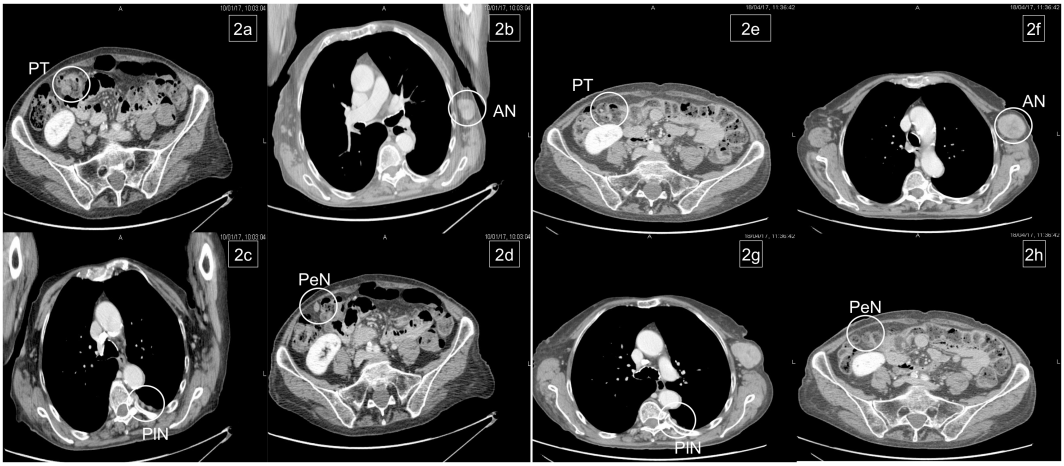

FIGURE 2
Basal metastatic sites at diagnosis: primary tumor (PT), left axillary node (AN), pleural nodes (PIN), and peritoneal node (PeN) **(A–D)**. Response to treatment after six courses: patient achieved response on primary tumor and all metastatic sites, except for the left axillary node **(E–H)**.

To date, with CT scan performed every two months, after 36 months since the last cycle and nearly 72 months since diagnosis, no evidence of disease progression has been observed and the patient's clinical condition was also preserved.

Discussion

Colorectal cancer is one of the most common malignancies in Western countries.

Molecular profiling of mCRC patients is mandatory before planning a treatment strategy as the initial choice will potentially influence survival. Mutational analysis of RAS and BRAF is on the basis of the molecular definition as the use of anti-EGFR antibodies in RAS-BRAF wild-type patients may help overcome a median survival time of 30 months.

Unfortunately, as formerly reported, tumor cells develop resistance towards anti-EGFRs, due to a selective pressure exerted by the continuous targeting of EGFR. One of the most stimulant challenges for oncologists is represented by understanding how to overcome this resistance or, at least, to mitigate and delay it.

In this report, an interesting aspect is represented by the spatial heterogeneity for the incomplete concordance between metastatic sites and primary tumor. KRAS mutations are generally believed to be early events in CRC carcinogenesis and thus high concordance between primary tumor and metastatic lesions is expected (17). A systematic review established a high concordance rate of KRAS mutational status between primary tumor and metastases (93%) (18).

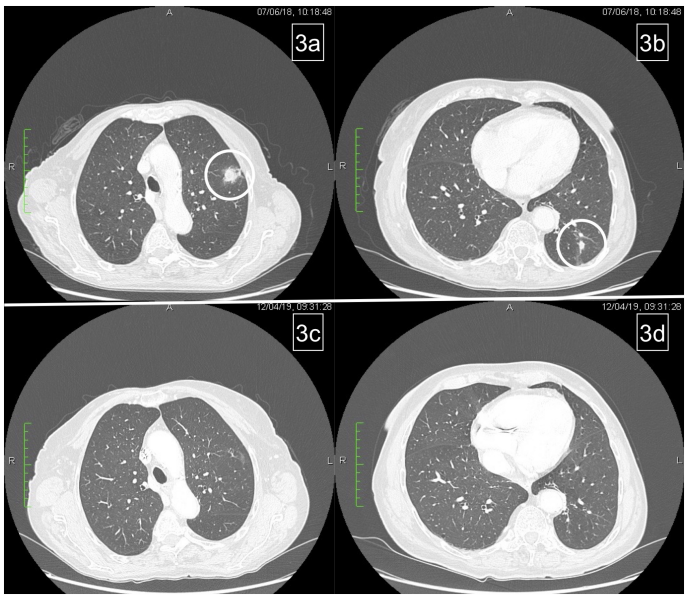

FIGURE 3
Pulmonary relapse **(A, B)**. Complete response of lung metastases after reintroduction of chemotherapy **(C, D)**.

As reported here, mutational status can be discordant among the primary tumor and nodes. As described in literature, nodal metastases in colon cancer are polyclonal (19–21).

These reports underline the need to consider spatial heterogeneity while treating a disease and as we report, recurring surgery is a strategy to overcome it. In fact, by removing the only metastatic site discordant with the mutational status of the tumor, the efficacy of panitumumab was preserved.

In mCRC patients receiving anti-EGFRs, the tumor genome evolves, dynamically promoting the spread of initially silent mutant subclones.

The selective pressure exerted by anti-EGFRs is considered one of the most consistent causes of resistance, as it could stimulate the increase of initially silent resistant clones that, however, decay in a time-dependent trend after discontinuation of anti-EGFR (22).

On the basis of such hypotheses, intermittent use of anti-EGFRs may represent a valid option to preserve efficacy and to prolong clinical benefit. Moreover, intermittent treatment may avoid the increase of typical toxicity such as skin rash and paronychia, encountering a better compliance of patients towards treatment. These were the reasons and rationale for which we adopted the intermittent therapeutic strategy for the treatment of our patient.

In this regard, a meta-analysis showed that intermittent strategies of administering first-line treatment to patients with unresectable mCRC do not result in a statistically significant reduction in overall survival (OS), and either improve or maintain quality of life (23). Moreover, the feasibility of intermittent use of chemotherapy was demonstrated in some clinical trials. The GISCAD study, which randomized 337 patients to receive intermittent or continuous treatment with FOLFIRI until disease progression, showed that the intermittent schedule was not inferior to continuous treatment for progression-free survival and OS (24).

While maintenance therapy with anti-VEGF agents is well coded until disease progression, no data are available on the optimal duration of anti-EGFRs. The VALENTINO trial (25) showed the superiority of the maintenance with panitumumab plus 5FU/FA compared with panitumumab alone after an induction treatment with FOLFOX plus panitumumab. Recently, an interesting *post hoc* analysis of this trial was performed on patients experiencing progressive disease not on treatment, undergoing a conventional second-line chemotherapy, or reinduction with anti-EGFR (all patients had an anti-EGFR free interval of at least 3 months). Patients receiving reinduction obtained a similar progression-free survival (PFS) but achieved a significant longer OS and higher response rate (RR) (26).

The recent results of PANAMA trial (27), where patients were randomized to maintenance treatment with 5FU/FA with or without panitumumab, showed an improved PFS and RR for subjects continuing anti-EGFR after induction chemotherapy. According to the design of this trial, patients progressing during maintenance treatment, received reinduction chemotherapy with FOLFOX plus panitumumab. PFS of reinduction therapy with FOLFOX plus panitumumab was 3.8 months (95% CI, 2.5–4.8) versus 6.3 months (95% CI, 4.7–8.2) in patients who had received FU/FA and panitumumab versus FU/FA alone as maintenance therapy (HR, 2.34; 95% CI, 1.54–3.56; p = 0.001). The temporary discontinuation of panitumumab during maintenance in the control arm of the PANAMA trial translated into an advantage in PFS when it was restarted.

As a contribution, our group recently presented the positive results of the IMPROVE study, a prospective, randomized, non-comparative, open-label, multicenter phase II study (28), with PFS on treatment (PFS_{OT}) as primary end-point. Unresectable, previously untreated RAS/BRAF wild-type mCRC patients were randomized to receive FOLFIRI plus panitumumab continuously until progression or eight cycles of the same regimen followed by a treatment free interval. This lasted until progressive disease, when another treatment period of eight cycles was restarted. This intermittent strategy was continued until progression occurred on treatment. Final results showed that the median PFS_{OT} was 12.6 months in the continuous arm and 17.6 months in the intermittent arm, with 1-year PFS_{OT} rates of 51.7% and 61.3%, respectively.

In conclusion, we would underline the importance of multidisciplinary choices as the acquisition of new intrinsic aspects, such as spatial and temporal heterogeneity, can translate into more effective treatment strategies.

In managing the case of our patient, as there was only one site of progression, excisional surgery helped us eradicate the only metastatic site not responding to the anti-EGFR antibody as the BRAF mutant and let us continue the same treatment with a great advantage for the patient, thanks to the intermittent strategy.

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

AA and AD provided ideas for this case. AD, AN, NZ, and AA drafted the manuscript. AP provided figures. AD, AN, MB, AB and AA acquired, analyzed, and interpreted the data. AC, LS, RC, CR, FF, CC, and PD diagnosed the disease and followed the patient during treatment and follow up. All authors revised the manuscript critically for important intellectual content and agreed to be accountable for all aspects of the work in 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 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

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Hemophagocytic lymphohistiocytosis in gastric cancer: A rare syndrome for the oncologist. Case report and brief review

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Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening condition characterized by uncontrolled activation of the immune system. HLH is a reactive mononuclear phagocytic response that occurs in association with a constellation of conditions such as malignancies and infections. The clinical diagnosis of HLH remains challenging because HLH can present with symptoms that significantly overlap with other causes of cytopenia, such as sepsis, autoimmune diseases, hematological cancers, and multiorgan failure. A 50-year-old man went to the emergency room (ER) for hyperchromic urine, melena, gingivorrhagia, and spontaneous abdominal wall hematomas. The first blood tests showed severe thrombocytopenia, alteration of the INR, and consumption of fibrinogen, and therefore, a diagnosis of disseminated intravascular coagulation (DIC) was made. A bone marrow aspirate showed numerous images of hemophagocytosis. With the suspicion of immune-mediated cytopenia, oral etoposide, intravenous immunoglobulin, and intravenous methylprednisolone were administered. Then, a diagnosis of gastric carcinoma was performed with a lymph node biopsy and gastroscopy. On the 30th day, the patient was transferred to the oncology ward of another hospital. On admission, he had serious piastrinopenia, anemia, hypertriglyceridemia, and hyperferritinemia. He was supported with a platelet transfusion and underwent a bone biopsy that showed a picture compatible with myelophthisis from diffuse medullary localization of a carcinoma of gastric origin. A diagnosis of HLH secondary to solid neoplasm was formulated. The patient started chemotherapy with oxaliplatin, calcium levofolinate, 5-fluorouracil bolus, 5-fluorouracil for 48 h (mFOLFOX6), and methylprednisolone. Six days after the third cycle of mFOLFOX6, the patient was discharged with the stabilization of his piastrinopenia condition. The patient continued chemotherapy with an improvement in his clinical conditions and normalization of hematological values. After 12 cycles of mFOLFOX, it was decided to start maintenance chemotherapy with capecitabine but, unfortunately, after only one cycle, HLH reappeared. The oncologist has to keep in mind the existence of HLH when there is an unusual clinical presentation of

cancer, such as cytopenia affecting ≥2 lineages and alterations of ferritin and triglycerides other than fibrinogen and coagulation. Increased attention and additional research as well as a close collaboration with hematologists are needed to benefit patients with solid tumors complicated by HLH.

KEYWORDS

hemophagocytic lymphohistiocytosis, gastric cancer, secondary hemophagocytic lymphohistiocytosis, disseminated intravascular coagulation, case report

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening condition characterized by uncontrolled activation of the immune system (1, 2).

HLH was first described in 1939 by Scott and Robb-Smith and again in 1952 when Farquhar and Claireaux reported a case of two infant siblings with progressive and fatal cytopenias, hepatosplenomegaly, and fever with the autopsy showing hemophagocytosis (3, 4). HLH has an estimated annual incidence of 1 per 800,000 people in Japan (5) and less than 10 per 1,000,000 children in Italy, Sweden, and the United States (6–8).

HLH can be classified into primary and secondary. Primary HLH is an inherited, autosomal recessive disorder associated with defects in perforin function. Perforin is a cytolytic protein found in the granules of cytotoxic T lymphocytes and natural killer cells. The degranulation of these leukocytes releases perforin, which inserts itself into the cell membrane of the target cell, creating a pore causing cell lysis and subsequently an inflammatory storm responsible for a constellation of signs, symptoms, and laboratory changes. Primary HLH typically presents in the first year of life with or without a positive family history. There is poor information regarding the relationship between HLH and the downregulation of the PI3K/AKT/mTOR signaling pathway. Mutation in the PIK3CD gene (NM_005026.3) is associated with activated PI3K delta syndrome, which is a primary immunodeficiency that could cause HLH (9). Secondary HLH is associated with infections, particularly Herpes viruses, malignancies, and autoimmune disorders. Secondary HLH can occur in children or adults. The exact mechanism of HLH secondary to a solid tumor has yet to be explained, but it is assumed that the hyperinflammation is triggered by the secretion of proinflammatory cytokines and persistent antigen stimulation by tumor cells. When HLH arises in association with rheumatologic disease, it is termed macrophage activation syndrome (MAS). MAS can be found with idiopathic arthritis and systemic lupus erythematosus, but it was also described in other rheumatological conditions (10–12). HLH associated with solid cancer is rare. In a study of 2,197 adults with HLH, only 1.46% (n = 32) of patients had HLH triggered by a solid tumor while it appeared in 981 patients who had hematologic malignancies (45%) (13).

To our knowledge, there are only two prior published studies of HLH triggered by gastric cancer in three patients. Our aim is to describe the fourth case in the world, and the first in Western countries, and make a brief review on HLH in gastric cancer precisely because HLH is a rare condition and is little known to oncologists.

Case presentation

A 50-year-old man went to the emergency room (ER) for hyperchromic urine, melena, and gingivorrhagia. A blood count showed Hb 14.1 g/dl (12–18), white blood cells 6.83×10^9/L, platelets 29×10^9/L (150–450), haptoglobin 0.4 g/L (0.3–2.0), fibrinogen 57 mg/dl (150–450), INR 1.68 (0.8–1.2), D dimer 35,000 µg/L (<500), reticlulocytes 1.97% (0.5–2.5), total bilirubin 0.73 mg/dl (0.2–1.3), PCR 7.53 mg/L (<3.5), creatinine 0.88 mg/dl (0.7–1.2), and AST 65 IU/L (8–47). The patient had no fever, and blood pressure and oxygenation parameters were normal; he complained of chest pain and had spontaneous abdominal wall hematomas. In his medical history, the patient reported arterial hypertension and myocardial infarction 3 years earlier with coronary stent placement. The cardiological assessment with an electrocardiogram showed outcomes of antero-septal necrosis and troponin was 0.034 mg/ml (<0.07). Faced with this laboratory picture, the 100-mg acetylsalicylic acid that he took daily was suspended. The patient was taking 3.75 mg of bisoprolol daily; 7.5 mg of zofenofril calcium, one tablet in the morning and one tablet in the evening; and 20 mg of atorvastatin daily. On the basis of the first tests, the hematologist diagnosed disseminated intravascular coagulation (DIC) with an ISTH score of 6 and a PLASMIC score of 3. A CT scan of the chest and abdomen with a contrast agent showed lymph nodes redundant in number and size in the mediastinum, in the celiac area, in the hepatic peduncle, and in the lumbar aortic retroperitoneum with a short axis of 12 mm. The bone window described some millimetric areoles of an osteorarefactive aspect in some dorsolumbar vertebrae and on the posterior arch of the fifth rib.

The bladder was normally distended with homogeneous content. A blood smear examination revealed rare schistocytes and some neutrophils with nucleus hypersegmentation. In the absence of fever, "cold" blood cultures were performed to rule out infection and subsequently yielded negative results. In the ER, the patient received a bag of platelets, and subsequently, in the Department of Medicine, he received 24 bags of fresh plasma in the first 2 days in addition to undergoing plasmapheresis. Prophylactic therapy started with meropenem 1 g three times a day. After 7 days of hospitalization, a PET-CT scan showed areas of pathological increase in glucose consumption on the lymph nodes of the mediastinum in the left

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paratracheal, subcarinal, and in the Barety lodge (SUV 8.3), in the celiac plexus and bilateral lumbar-aortic (SUV 8), and in the right lateral cervical (SUV 14.3), as well as multiple and disseminated areas of focal pathological accumulation in the medullary compartment of all skeletal segments (SUV 15.6). On the eighth day, a bone marrow aspirate was performed with subsequent evidence of numerous images of hemophagocytosis. A subsequent bone marrow aspiration demonstrated the absence of blast cells, karyotype abnormalities, and rearrangements of RAR and ABL1. The patient meanwhile received transfusions of fresh plasma daily and a bag of platelets almost every 2 days in the presence of severe thrombocytopenia. On the eighth day, a series of blood tests were performed: HIV 1 and 2 negative, IgM (negative) and IgG (positive) for Herpes simplex, IgM (negative) and IgG (positive) for Toxoplasma, and IgM (negative) and IgG (positive) for Epstein–Barr virus (EBV). Lupus anticoagulants (LAC) 1 and 2 were high with a LAC1/LAC2 ratio of 1.12 (<1.3), anticardiolipin antibodies (IgG and IgM) were negative, neutrophil anti-cytoplasmic antibodies (MPO and PR3) were negative, antibodies to B2 glycoprotein (IgM and IgG) were negative, the reuma test was <10 UI/ml (<15.0), complement C3 was 1.11 g/L (0.9–1.8) and C4 was 0.11 g/L (0.1–0.4), and a Widal–Wright test was negative.

On the ninth day of hospitalization, platelets had dropped to 15×10^9/L, Hb was 6.19 g/dl, and white blood cells were 7.57×10^9/L. With the suspicion of an immune-related cytopenia and DIC, the patient received oral etoposide 100 mg twice daily for 5 days, intravenous immunoglobulin 1 g/kg for 3 days, and intravenous methylprednisolone 1 g daily for 5 days. During hospitalization, the patient underwent transfusions of fresh plasma almost daily, a platelet transfusion was administered every 2 or 3 days, and a blood transfusion was administered a little less frequently.

On the 17th day, a supraclavicular lymph node was removed with a diagnosis of lymph node metastasis of adenocarcinoma compatible with gastric origin. By immunohistochemistry, neoplastic cells were positive for cytokeratin 7 and CDX2, and negative for CK20, TTF1, napsin A, PAX8, CD30, PLAP, and S100.

On the 23rd day, a fever of up to 38°C appeared, blood cultures were performed, and treatment was started with 400 mg of teicoplanin and 2 g of ceftazidime three times daily and 500 mg of metronidazole three times daily for 6 days. The blood cultures were negative and the fever disappeared within 7 days. On the 27th day, gastroscopy revealed, in the antrum, body, and fundus, a mucous membrane with a cobbled appearance. A biopsy was positive for infiltrating gastric carcinoma G 3 with signet ring cells.

On the 30th day, the patient was transferred, at his request, to our oncological institute—a referral center far from his residence. The entrance examinations showed plt 13×10^9/L, white blood cells 5.93×10^9/L, Hb 9.4 g/dl, fibrinogen 228 mg/dl, INR 1.5, total bilirubin 1.55 mg/dl, direct bilirubin 0.62 mg/dl, triglycerides 274 mg/dl (<150), and ferritin 15,026 µg/L (30–400). The physical examination was unremarkable except for diffuse cutaneous hematomas (Figure 1), and he had asthenia with a poor performance status. He was supported with a platelet transfusion, underwent a bone biopsy, and started a chemotherapy treatment with 85 mg/m^2 of oxaliplatin on day 1, 200 mg/m^2 of calcium levofolinate on day 1, 400 mg/m^2 of 5-fluorouracil bolus on day 1, 2,400 mg/m^2 of 5-fluorouracil on day 1 for 48 h (mFOLFOX6), and 16 mg of dexamethasone daily equal to 80 mg of methylprednisolone

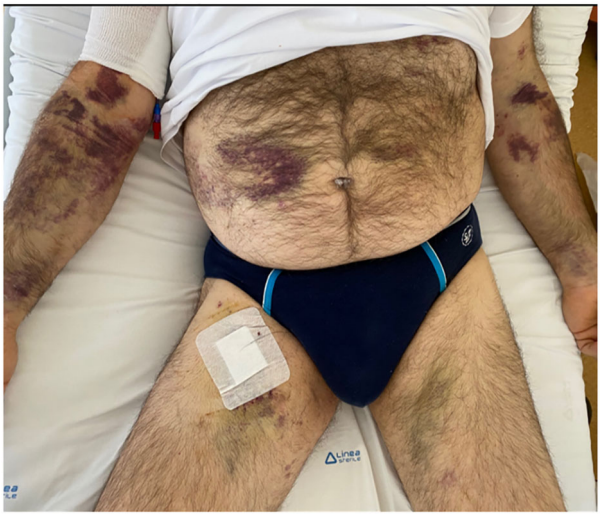

FIGURE 1
Cutaneous hematomas on oncology ward admission.

calculated on the basis of 1 mg/kg (for 39 days then tapering off by halving the dose every week until discontinued). The bone biopsy showed a picture compatible with myelophthisis from diffused medullary localization of a carcinoma of gastric origin. The biopsy was composed of extensive necrotic material without any viable neoplastic cells. Through immunohistochemistry, necrotic cells were found to be diffusely reactive for cytokeratin 7 (Supplementary Figure 1). A second cycle of mFOLFOX was repeated, by timing, after 2 weeks while the third cycle needed a few days' postponement due to neutropenia (0.7×10^9/L). During hospitalization in the oncology ward, the patient continued to have low platelet values with the need for a platelet transfusion almost every other day and a moderate need for a blood transfusion. Unlike hospitalization in the medicine ward where a plasma transfusion was preferred for low levels of fibrinogen, recombinant fibrinogen (Haemocomplettant®) 1 g e.v. was used in oncology if fibrinogen was <100 mg/dl. The patient received 12 bottles of Haemocomplettant during the 42 days of hospitalization in the oncology ward. Six days after the third cycle of mFOLFOX6, the patient was discharged with white blood cells 7.47×10^9/L, platelets 25×10^9/L, Hb 10.3 g/dl, fibrinogen 133 mg/dl, and INR 1.14. The patient continued the chemotherapy in Day Hospital with an improvement in his general condition. In August 2021, after four cycles of chemotherapy, a total body CT scan showed a stable disease, and the scan with bone window showed the appearance of widespread osteostructural inhomogeneity with a prevalent thickening character in all bone segments as per probable response to therapy.

After numerous cycles of FOLFOX chemotherapy, up to the 12th cycle, there was an improvement in platelet (101×10^9/L) and hemoglobin (10.5 g/dl) values. In December 2021, after 12 cycles of FOLFOX, a new total body CT scan showed slightly reduced lymphadenopathies both at the mediastinal level and at the intra- and retroperitoneal level. The scan with bone window showed an increase in osteostructural subversion with a prevalent thickening character in all bone segments due to an increase in sclerosis (Supplementary Figure 2). In light of the CT picture, because of the

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improved blood values, it was decided to start maintenance chemotherapy with capecitabine 1,250 mg/m^2 twice daily on days 1–14 of a 3-week cycle, but after only one course of therapy, the patient went to the local ER of his hospital with vomiting and hematomas at the level of the abdominal wall. A CT scan showed a small cerebral hemorrhage, platelets were 23×10^9/L, and Hb level was 9 g/dl. The patient was hospitalized and died a few days later. Figure 2 shows the trend of platelets, hemoglobin, and fibrinogen before and after treatment.

Discussion

Secondary HLH is a reactive mononuclear phagocytic response that occurs in association with a constellation of conditions such as malignancies and infections. The increased macrophage activation and macrophage proliferation produce upregulation of ferritin transport/secretion and inhibition of lipoprotein lipase and then an increase in serum ferritin and serum triglycerides, respectively. The increase in phagocytic activity provokes cytopenia too. Solid tumors associated with HLH are rare, and subsequently, an early diagnosis is more difficult. It is essential in this kind of syndrome to make an early diagnosis because without treatment, HLH is frequently fatal. In secondary HLH, 1-month mortality is estimated at 20% (14) and the median overall survival among patients with an underlying malignancy is 1.4 months (15), so prompt recognition is essential. Recently, we have had to consider another cause of HLH because immunotherapeutic strategies, used to treat several malignancies, may connect to this syndrome as well (16, 17).

Furthermore, we have to consider that HLH can occur not only during the development but also during the recurrence or relapse of malignancy (18). Various studies are trying to shed light on adult HLH.

In 2004, the Histiocyte Society proposed an updated set of criteria (HLH 2004 diagnostic criteria) to aid in the identification of patients with HLH for clinical trials (19). To make an HLH diagnosis, five of the following eight criteria must be met: fever, splenomegaly, cytopenias affecting ≥2 lineages (hemoglobin <9 g/dl, platelets <100×10^9/L, and neutrophils <1.0×10^9/L), hypertriglyceridemia (≥265 mg/dl) and/or hypofibrinogenemia (≤150 mg/dl), hemophagocytosis (in bone marrow, spleen, or lymph node), hyperferritinemia (≥500 μg/L), impaired NK cell function, and elevated soluble CD25 (sCD25) (i.e., sIL2R) (≥2,400 U/ml). sCD25 is not readily available at all institutions and can take time to return. It is important to note that these criteria were developed for the diagnosis of primary HLH. There is currently no universally accepted set of criteria for diagnosing HLH in the adult population.

In 2014, standardized criteria for the diagnosis of secondary HLH were published. Fardet et al. created and validated the HScore, which includes nine weighted variables (20). In our case, if we consider this scoring system available online (http://saintantoine.aphp.fr/score/), the probability for it to have been HLH is about 89% [maximal temperature strictly less 38.4°C, lower hemoglobin level less than or equal to 9.2 g/dl, higher ferritin level (ng/ml) strictly greater than 6,000, higher triglyceride level (mmol/L) between 1.5 and 4, lower fibrinogen level (g/L) less than or equal to 2.5, higher SGOT/ASAT level (UI/L) greater than or equal to 30, and hemophagocytosis features on bone marrow aspirate]. A web-based Delphi study proposed a similar list of criteria (21). These newly proposed criteria are a step towards improving the diagnosis of HLH in adults. The first obstacle or rather the first challenge for the clinician is, therefore, to try to understand an atypical clinical picture.

In our case, the first diagnosis was DIC, and then on the eighth day from admission to the ER, a diagnosis of HLH was hypothesized based on the low value of platelets, hemoglobin, and fibrinogen, and the description of numerous images of hemophagocytosis in the bone marrow aspirate; however, a fifth element was not looked for. The clinicians had no initial information about hypertriglyceridemia, low or absent natural killer cell activity, ferritin, increased soluble CD25 concentration, and splenomegaly while the fever appeared. It is interesting to note that DIC is reported in 40% of the cases in some series of HLH and is associated with high mortality rates, especially in patients with severe thrombocytopenia (13).

There is a lack of relevant trials to guide the treatment of cancer patients with HLH. The immunosuppressive agents used

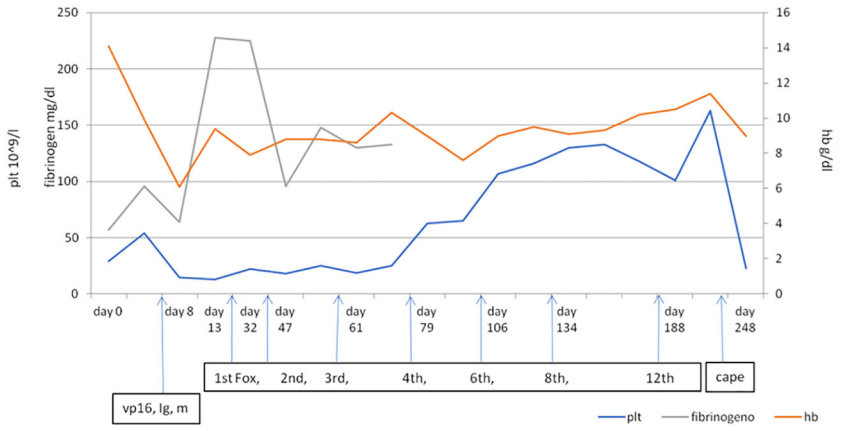

FIGURE 2
The trend of platelets, hemoglobin, and fibrinogen in relation to the treatments. Vp16, etoposide; Ig, immunoglobulin; m, methylprednisolone. First, 2nd, 3rd, 4th, 6th, 8th, and 12th cycles of Fox (Folfox); cape, capecitabine.

inthe treatment of HLH mainly include glucocorticoids, cyclophosphamide, cyclosporine, etoposide, and doxorubicin (19, 22).

Treatment in adults has been based on the HLH-94 study, a large prospective pediatric study conducted by the Histiocyte Society in 16-year-old patients with no history of immunosuppression or malignancy. This study investigated a treatment regimen that included an 8-week induction with dexamethasone and etoposide. If neurologic symptoms were present, they also received intrathecal methotrexate. If familial disease or relapsing disease was present, the patient received maintenance therapy with dexamethasone pulses, cyclosporine daily, and etoposide until the patient was able to undergo a stem cell transplant (23). This regimen resulted in improved outcomes but there were a significant number of early relapses (24).

As shown in Figure 2, it appears that the level of fibrinogen became more stable starting from mFOLFOX but probably also with the use of the Haemocomplettant rather than fresh plasma. In the same way, the trend of platelets and blood seems to become more stable with the reduction of dependence on blood transfusions and blood products. The calculation of the consumption of blood, platelets, and fresh plasma (Supplementary Figure 3) is based on three different time periods, and this could affect the value of this calculation and could be related to the management of different equipment.

To our knowledge, this is the fourth case of HLH in gastric cancer and the first case in a Western country. In 2021, Ramkumar, from India, reported a case of HLH in a 53-year-old man who underwent gastric endoscopic biopsy due to anorexia, persistent vomiting, and progressive mild pancytopenia (25). The patient underwent fine-needle aspiration cytology (FNAC) for supraclavicular lymphadenopathy, which showed lymph node histiocytosis and hemophagocytosis in the lymph node aspirate. The diagnosis was signet ring cell carcinoma of the stomach. A bone marrow aspiration biopsy revealed mild trilineage marrow hypoplasia with occasional hemophagocytic foci. The HLH preoperative diagnostic workup revealed hyperferritinemia (910 ng/ml), hypertriglyceridemia (490 mg/dl), and increased serum interleukin (IL-2) levels. The patient tested negative for EBV; hepatitis A, B, C, and E viruses; Widal; malarial parasite; and dengue. He underwent distal gastrectomy and a relative improvement of blood count was first observed on the first postoperative day (total count 3.9×10^9/L, platelet count 120×10^9/L, and Hb 10.5 mg/dl), but 2 weeks after surgery, gastrointestinal bleeding appeared and new tests were performed that confirmed HLH recurrence.

Again, in 2021, Zhou et al. from China (26), presented two cases of gastric cancer complicated with HLH. The patients received treatment including immunosuppressive agents immediately. After therapy, the two patients showed partial remission, but both died due to HLH relapse or progression of the primary tumor. The first was a 68-year-old man with intermittent fever and anorexia. He did a gastroscopy, and it revealed a tumor at the antrum of the stomach. Postoperative pathology confirmed gastric cancer, which was staged as pT1aN0M0 according to the 8th edition of the American Joint Committee on Cancer staging manual. After 1 week, the patient developed a fever but blood tests showed no evidence of hepatitis, human immunodeficiency virus (HIV), EBV, cytomegalovirus (CMV), syphilis, tuberculosis, bacterial infection, or other complications. A bone marrow biopsy indicated hemophagocytosis. After two cycles of the chemotherapy (20 mg of liposomal doxorubicin for 1 day, 100 mg of etoposide for 1 day, and 20 mg of methylprednisolone, twice daily for 3 days), the patient remained disease-free for 5 months but died from HLH relapse. The second patient was a 54-year-old woman with unresectable gastric adenocarcinoma diagnosed 5 months previously. After six cycles of chemotherapy, the patient was admitted to the hospital due to an unexplained fever lasting 10 days. She had hemorrhagic rashes all over her body and petechiae in her mouth. Blood tests indicated anemia, hypothrombinemia, and hypofibrinogenemia, as well as a significant increase in the levels of ferritin and sCD25. A bone marrow biopsy indicated hemophagocytosis. Secondary HLH was confirmed, and chemotherapy, based on etoposide (200 mg twice a week) together with dexamethasone (20 mg daily), was subsequently administered. She had an initial clinical benefit, rather than a laboratory benefit, and received three cycles of chemotherapy. Considering the pancytopenia, cyclosporine (75 mg twice daily) was continuously administered, but chemotherapy was stopped. The patient remained in a stable condition for 8 weeks, then intestinal bleeding appeared with subsequent renal failure and multiple organ failure.

In Table 1, we report a comparison of a diagnosis with three other cases of secondary HLH in gastric cancer patients. In the case

TABLE 1 Cases and hemophagocytic lymphohistiocytosis (HLH) 2004 diagnostic criteria.

HLH 2004	Case 1 Ramkumar	Case 2 Zhou	Case 3 Zhou	Case 4 Monti
Fever 38.5°C or higher		+	+	
Splenomegaly	+	+		
Cytopenia (affecting at least two of three cell lineages in peripheral blood)	+	+	+	+
Hypertriglyceridemia and/or hypofibrinogenemia	+		+	++
Hemophagocytosis in bone marrow or spleen or lymph nodes	+	+	+	+*
Low or absent NK cell activity		+		
Ferritin ≥500 μg/L	+	+	+	+
sCD25 ≥2,400 U/ml	+	+	+	

*Hemophagocytosis was present on the bone marrow aspirate.

reported by Ramkumar (25) and in our case, the diagnosis was for a signet ring cell cancer, while we have no clear information about the histology of gastric cancer in the other two cases by Zhou (26). Thus, we cannot speculate about the risks of HLH related to histology. In the case from Ramkumar (25) and in one case from Zhou (26), the HLH "exploded" in a clinical manner after a gastrectomy; if one does not know about HLH, it seems strange to learn of deaths after gastric cancer resection. In our case, the patient had the metastatic disease as in the case presented by Ramkumar (supraclavicular lymphadenopathy), while in one case presented by Zhou, the patient had unresectable gastric adenocarcinoma. HLH is likely to underlie the expression of an advanced gastric carcinoma. Gastric cancer most commonly spreads to the peritoneum, liver, or lungs while the incidence of bone metastasis is 2%–3% (27). Bone metastases diffusely invading the bone marrow from gastric cancer often manifest a rapid clinical course, and the prognosis is very poor due to hematologic disorders such as DIC and/or MAHA (microangiopathic hemolytic anemia). Etoh et al. (28) described that the median survival time in bone metastasis from gastric cancer was 2 and 11 months for the patients with or without hematologic (DIC and/or MAHA) disorders, respectively. Both disseminated DIC and thrombotic microangiopathy (TMA) cause microvascular thrombosis associated with thrombocytopenia, bleeding tendency, and organ failure (29). MAHA is required in TMA. DIC is often associated with TMA, and TMA is often associated with DIC, suggesting that a differential diagnosis between DIC and TMA may be difficult. In this report, clinicians tried to make a differential diagnosis using ISTH (score, 6), PLASMIC (score, 3), and HLH 2004 diagnostic criteria. The ISTH (score, 6) showed laboratory evidence consistent with DIC, and the PLASMIC score was used to stratify patients into low (0–4), intermediate (5), and high (6–7) risk of thrombotic thrombocytopenic purpura. The HLH 2004 diagnostic criteria evidenced five out of eight diagnostic criteria. Ultimately, in our case of HLH, there is also a DIC, but as we have tried to summarize above, there are hematological clinical pictures that can intersect and complicate the diagnosis. A limitation of our case report could be that hemophagocytosis was described from bone marrow aspirate while the bone biopsy did not show hemophagocytosis but infiltration by tumor cells; however, it is plausible that the initial therapy with etoposide, immunoglobulin, and steroid partially modified the HLH substrate. A second limitation is that we have no information about NK cell function, and sCD25. A third limitation is that we do not have clear data about the last admission of the patient to the ER at his local hospital, but his daughter informed us about her father's skin hematomas and small cerebral hemorrhage associated with piastrinopenia. An interesting aspect of our case is the good laboratory and clinical response obtained with FOLFOX chemotherapy and also the discrete survival of about 8 months. This survival, although limited, should be considered a good result for a patient with bone metastases from gastric cancer and, above all, with coagulation alteration if compared with literature data (28).

In this report, we showed a challenging case where secondary HLH is associated with gastric cancer. The oncologist has to keep in mind the existence of HLH when there is an unusual clinical presentation of cancer disease like cytopenias affecting ≥2 lineages and consider other pathophysiological possibilities besides myelophthisis and DIC.

Our experience points out the importance of finding and treating the cause of HLH as soon as possible, and low blood counts should not discourage the oncologist from treating the patient with chemotherapy in the same way as with hematological patients with bone marrow involvement.

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. 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

MM and GM designed the study; CG and VG did the literature search; LE, SA, DM, VG, and GF collected and analyzed the data. AA-S performed the pathological diagnosis of the bone marrow biopsy; MM wrote the manuscript; all authors contributed to the interpretation of the data; all authors read and approved the final version of the manuscript.

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Conflict of interest

GM worked as a consultant for Astellas and Servier; received honoraria and participated in the speaker bureau of Astellas, Menarini/Stemline, Pfizer, Servier, and Syros; and received research support from Abbvie, Astrazeneca, and Pfizer.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1010561/full#supplementary-material

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Unexpected curative effect of PD-1 inhibitor in gastric cancer with brain metastasis: A case report

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Background: Gastric cancer (GC) is the third most common cause of cancer-related death in the world. Several clinical trials have proven that the use of PD-1/PD-L1 inhibitors can improve the survival of late-stage GC patients and is suggested in NCCN and CSCO guidelines. However, the correlation between PD-L1 expression and the response to PD-1/PD-L1 inhibitors is still controversial. GC rarely develops brain metastasis (BrM) and currently there is no therapeutic protocol for GC BrMs.

Case presentation: We report a case of a 46-year-old male suffering from GC with PD-L1 negative BrMs 12 years after GC resection and 5 cycles of chemotherapy. We treated the patient with the immune checkpoint inhibitor (ICI) pembrolizumab and all metastatic tumors achieved a complete response (CR). A durable remission of the tumors is confirmed after 4 years of follow-up.

Conclusion: We shared a rare case with PD-L1 negative GC BrM responsive to PD-1/PD-L1 inhibitors, the mechanism of which is still unclear. The protocol of therapeutic choice for late-stage GC with BrM is urgently needed. And we are expecting biomarkers other than PD-L1 expressions to predict the efficacy of ICI treatment.

KEYWORDS

brain metastasis, gastric cancer, PD-1/PD-L1, PD-1 inhibitors, immunotherapy

1 Introduction

Brain metastasis (BrM) is one of the most common brain tumors in adults (1). An estimate of 20% of patients with cancer will suffer from BrMs (1). Lung cancer, breast cancer, and melanoma are the most frequent primary sites to develop BrMs. GC rarely develops BrMs and only accounts for 6% of all BrMs (2). However, in China, GC ranks the second

most frequently reported case among all malignant tumors, just behind lung cancer, and most of them are diagnosed in their late stage, which gives GC more opportunities to spread to distant organs (3). Traditionally, medical practices for BrMs include surgery combined with chemo- and radio-therapy. As for immunotherapy, high expression of PD-L1 is associated with poor prognosis in GC (4). Although the use of PD-1 inhibitor in GC has been included in 2022 NCCN guidelines and approved to be effective (5), the efficacy of PD-1 inhibitors against GC with BrM is not confirmed yet. In this case report, a GC patient with PD-L1 negative BrM was treated with pembrolizumab and later achieved an amazing recovery. Our results showed the possible efficacy of PD-1/PD-L1 inhibition for GC BrM patients, even in PD-L1 negative cases.

2 Case report

The patient is a 46-year-old male who received surgery and 5 cycles of chemotherapy for GC 12 years ago. In September 2018, the patient has suffered from severe headache with nausea and vomiting for one week and was admitted to our hospital. During the physical examination, the patient presented a positive Babinski sign and a grade IV muscle strength on the left side. Head computed tomography (CT) demonstrated a right temporal mass (Figure 1A). Positron-emission tomography-computed tomography (PET-CT) of the brain (Figure 2A) and chest (Figure 2B) showed evidence of multiple metastases.

In October 2018, the patient underwent his first cranial surgery (Figure 1B). Post-operative pathological test confirmed a metastatic adenoma (Figures 3A, B). One month later in November 2018, the patient underwent another surgery to remove the mediastinal metastasis in another hospital instead of administrating systemic chemotherapy. In December 2018, the patient was admitted to our emergency room once again with severe headache. Head MRI (Figure 1C) demonstrated a recurrent right temporal tumor (red arrow) *in situ* and a newly diagnosed right frontal tumor (yellow arrow) with apoplexy. A second emergency cranial surgery was performed. The right temporal tumor was resected, and the right frontal tumor was too risky to resect under the same bone window then left for chemo- and targeted therapy (Figure 1D). Unfortunately, one week after the second surgery, the patient suffered from severe headaches. CT showed an extradural hematoma in the surgical field (Figure 1E, red circle). However, the patient's relatives declined further surgical intervention. After systemic mannitol and intracranial pressure control, the hematoma remained stable.

Hematoxylin and eosin (HE)-stained (Figure 3C) specimens of the brain lesion revealed a poorly differentiated adenocarcinoma. Immunohistochemical (IHC) staining (Figure 3D) revealed the BrM was completely negative for B7H1 (PD-L1) in both immune cells and tumor cells, as the combined positive score (CPS) and tumor cell proportion score (TPS) of PD-L1 in this patient was rated below 1 and 1% respectively. However, we didn't know if PD-1 inhibitors would work in PD-L1 negative BrM patients. Therefore, in January 2019, pembrolizumab (200mg, iv. Day1) plus capecitabine (1.5g, bid, po. Day1-14) were still tried to treat the right frontal tumor (Figure 1F) based on the advice from a neuro-oncologist. To our surprise, the response was remarkable. Four weeks after the first cycle of administration, the MRI (Figure 1H) showed that the tumor shrank nearly 80% compared to 3 weeks earlier (Figure 1G). The patient then received 10 cycles of pembrolizumab plus capecitabine therapy since February 2019 and recovered quite well without any side effects. Eight weeks after the treatment began, the tumor site achieved a complete response (CR) (Figure 1I) according to the Response Evaluation Criteria in Solid Tumors (Recist, version 1.1). In March 2020, another PET-CT image confirmed a durable remission of the tumors in both head and chest (Figures 2C, D). During the last follow-up (May 2022), the MRI indicated no abnormal signal in the surgical field and right frontal lobe (Figure 1J). The overall clinical course is shown in Figure 1.

3 Discussion

Immunotherapy salvaged this late-stage GC patient, as the immune reaction against tumors was ignited by the PD-1 inhibitor. It has been reported that PD-L1 was highly expressed in GC and showed a negative correlation with survival (6). Given the encouraging results of immune checkpoint inhibitors (ICIs) in melanoma, non-small-cell lung cancer, renal cell cancer, and head and neck cancer, it seems reasonable to investigate the curative effect of these agents in GC.

Avelumab, a human anti-PD-L1 IgG1 antibody, has had its efficacy and safety validated in a phase Ib trial of advanced gastric or

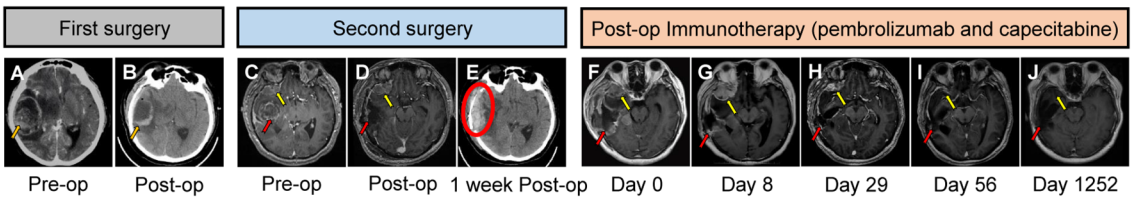

FIGURE 1
The timeline and brain imaging over course of treatment. Enhanced computed tomography (CT) image **(A)** showed a right temporal lesion (orange arrow) before the first cranial surgery. The lesion was resected as shown in figure **(B)** (orange arrow). Magnetic resonance imaging (MRI) (T1-weighted with gadolinium enhancement) **(C)** demonstrated a recurrent right temporal lesion (red arrow) *in situ* and a right frontal tumor (yellow arrow). MR T1 contrast **(D)** demonstrated the resected space of the right temporal tumor (red arrow) after the second cranial surgery. CT scanning **(E)** indicated an extradural hematoma (red circle) one week after the second cranial surgery. Figure **(F–J)** represent the MR T1 contrast images 1 day, 8 days, 29 days, 56 days and 1252 days after pembrolizumab administration.

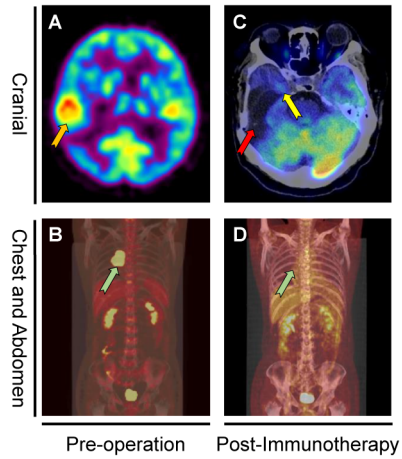

FIGURE 2
PET-CT before first cranial surgery and after immunotherapy. PET-CT showed a right temporal lesion (orange arrow) before the first cranial surgery **(A)**. Coronal PET-CT image **(B)** of the chest showed a right mediastinal metastasis (green arrow). Figure **(C)** showed the original tumor sites (red arrow and yellow arrow) remained stable without diseases recurrence. Coronal PET-CT image **(D)** of the chest indicated the tumor site (green arrow) remained stable without recurrence 16 months after mediastinal surgery.

gastroesophageal junction adenocarcinoma patients (7). The results showed the objective response rate (ORR) was 6.7% in both first-line switch-maintenance (1L-mn) and second-line (2L) subgroups and the median OS was 11.1 and 6.6 weeks in two arms (1L-mn and 2L

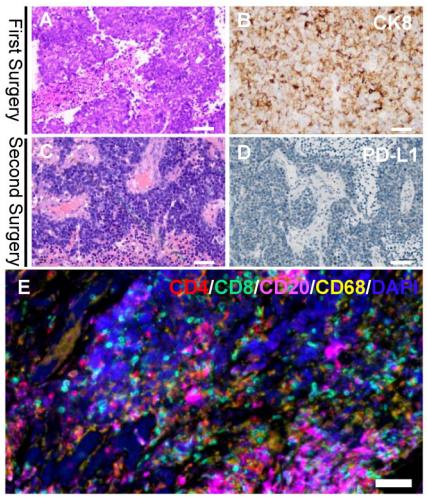

FIGURE 3
Histologic findings of the first and second cranial surgery. Hematoxylin and eosin (HE) staining **(A)** and positive cytokeratin 8 (CK8) immunohistochemistry staining **(B)** of the tumor tissue indicated a poorly differentiated adenocarcinoma (magnification, bar=50μm). HE staining **(C)** of the tumor tissue demonstrated a recurrent adenocarcinoma (magnification, bar=50μm). Immunohistochemistry of PD-L1 **(D)** was completely negative in both immune cells and tumor cells (magnification, bar=50μm). Multiplex immunohistochemistry/immunofluorescence (mIHC/IF) assay of the second brain metastasis specimens combining CD4, CD8, CD20 and CD68 markers **(E)** displayed a dense tumor-infiltrating CD8+ T lymphocytes surrounding the tumor cells (magnification, bar=50μm).

respectively), with a nonsignificant trend toward longer OS for PD-L1-positive patients in the 1L-mn subgroup (7). Durvalumab, another anti-PD-L1 antibody, showed clinical activity in GC with an ORR of 7% in a phase I study (8). Meanwhile, the phase I clinical trial of atezolizumab (anti-PD-L1 antibody), including 175 advanced incurable patients, confirmed complete and partial responses in 21% of non-small-cell lung cancer, 26% of melanoma, and 13% of other tumors including GC and colorectal cancer (9). And a statistical association between treatment response and PD-L1 expression in tumor-infiltrating immune cells was observed (9).

It is believed that the blood-brain barrier (BBB) is disrupted in BrM cases, resulting in a 'leakier' condition called blood-tumor barrier (BTB) (10), allowing ICIs to pass through and accumulate within the brain. Therefore, some BrMs could also benefit from ICI treatment. In a phase II trial of pembrolizumab in 18 melanoma and 18 non-small cell lung cancer (NSCLC) patients, the durable response rate of intracranial metastasis was 22% and 33%, respectively (11). In another cohort of 66 melanoma patients with BrMs treated with nivolumab or pembrolizumab, the intracranial ORR was 21% (12).

Traditionally, a low PD-L1 expression is believed to be associated with shorter progression free survival (PFS) and lower ORR (13, 14). Why is this PD-L1 negative GC BrM patient sensitive to anti-PD-1/PD-L1 immunotherapy? One reason might be that PD-L1 expression status alone is insufficient in determining which patients could benefit from PD-1/PD-L1 inhibitors (15). In addition, PD-L1 expression is heterogenous between primary tumor, metastatic lymph nodes and the BrM (16). Therefore, the drug responses would be determined by the integral PD-L1 expression status. As it is now impossible to know the PD-L1 expression rate in the primary tumor site of this patient, the validity of this explanation might be hard to prove. Besides, it is also reported that chemotherapy and immunotherapy together may reengineer tumor immunity and harness potential synergies (17, 18), which may happen in this case.

The BrM patients responsive to PD-1 inhibitor might get a dramatic clinical relief (11, 12). However, the response ratio remains quite low (9), making it essential to pick the right population. To delineate the mechanism behind this rare case, we performed a multiplex immunohistochemistry/immunofluorescence (mIHC/IF) assay combining CD4, CD8, CD20 and CD68 markers on the second cranial metastasis surgery specimens (Figure 3E) to show the pre-existing T cells, which are believed to be the prerequisite to the anti-PD-L1 response (19). The specimen displayed a dense tumor-infiltrating CD8+ T lymphocytes accompanied by CD68+ macrophages, which demonstrated an intense antitumor immune response within the tumor microenvironment and indicated a positive response to anti–PD-1/PD-L1 treatment.

In the context of immunotherapy, ICI treatment has been widely used in metastatic cancers other than GC BrM (9). Like primary solid tumors, abundant infiltrating T cells in the tumor microenvironment (TME) is the basis of a successful ICI treatment in disseminated cancers (20). Biomarkers associated with PD-1/PD-L1 treatment should be further explored to direct a more precise ICI treatment in metastatic cancers. In clinical scenario which needs rescue therapy like this case, ICI treatment is always in consideration regardless of PD-L1 expression unless a more convincible biomarker shows unfavorable result.

In summary, we have presented a case of PD-L1 negative GC BrM. After pembrolizumab treatment, all metastatic tumors achieved a surprisingly complete response. Our findings have proven that PD-L1 expression is not the only determinant of ICI responsiveness. Other biomarkers are urgently needed.

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

QW and ZS completed the main body of the manuscript. YM, WZ, WH, MG, XZ, JL and JX made decisions about the entire treatment process. YM and WH have critically revised the manuscript. ZS, QW and WH participated in the collection of patient data. All authors contributed to the article and approved the submitted version.

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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

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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

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Introduction: Gastric cancer (GC) complicated by bone marrow metastasis (BMM) and disseminated intravascular coagulation (DIC) represents poor prognosis and most of these patients would die in a few months. Active treatment strategies such as chemotherapy are effective in restoring coagulation function and prolonging patients' survival time. Immunotherapy including programmed death protein 1 (PD-1) or programmed death protein ligand 1 (PD-L1) inhibitors has emerged as a first-line treatment of gastric cancer. However, the efficacy of PD-1 inhibitor-based treatment strategies in these patients remains unknown.

Case description: Herein, we presented two cases of advanced gastric cancer (AGC) complicated by BMM and DIC, in which two patients received chemotherapy and PD-1 inhibitor as the first-line treatment. Both of them achieved a partial response after treatment, and the coagulation function was restored. The patient who discontinued the PD-1 inhibitor after 6 months experienced DIC relapse, whereas the other patient who maintained the PD-1 inhibitor treatment cycle remained responsive after 10 months.

Conclusions: We speculate that PD-1 inhibitor-based treatment strategies are effective and safe in prolonging survival against gastric cancer with BMM and DIC, and the coagulation function is well controlled by the treatment with a combination of immunotherapy and chemotherapy.

KEYWORDS

gastric cancer, bone metastasis, disseminated intravascular coagulation, programmed death protein 1 inhibitors, immunotherapy

Introduction

Gastric cancer (GC) is the fifth most common cancer and the fourth leading cause of cancer-related deaths worldwide, and remains a major health problem (1). In China, although the incidence and mortality of gastric cancer are decreasing annually, the numbers of new cases and deaths are still more than 390,000 and 280,000, respectively (1, 2).

Disseminated intravascular coagulation (DIC) is a severe syndrome, characterized by the pathological intravascular activation of coagulation of blood clotting factors, and usually results in organ dysfunction. Cancer-associated DIC is one of the complications of tumors, and it has been reported in several types of solid tumors, including gastric cancer (3, 4). Bone marrow metastasis (BMM) might be one reason for hematological abnormalities such as DIC and anemia, whereas less than 10% of patients with advanced gastric cancer (AGC) have bone metastasis (5, 6). The prognosis for patients with AGC complicated by DIC remains poor, with the median overall survival (OS) of patients without treatment being less than 3 months (4). Active treatment has been shown to benefit these patients in previous case reports (3, 4, 7–11). However, due to the limited studies of the treatment of AGC complicated by BMM and DIC, the best strategies remain unknown.

Recently, immune checkpoint inhibitors (ICIs), especially inhibitors of programmed death protein 1 (PD-1) and programmed death protein ligand 1 (PD-L1), have emerged as first-line treatment strategies in advanced gastric cancer (12). Many clinical trials have demonstrated that PD-1/PD-L1 inhibitors show impressive clinical efficacy (13–15). The safety profile of ICIs in patients with AGC has been acceptable, as previously reported. However, the efficacy and safety of PD-1 inhibitor-based treatment strategy in AGC complicated by BMM and DIC remain unknown.

As far as we know, the current study is the first to report the application of PD-1 inhibitors in AGC patients having BMM and DIC complications. Two patients were included, and both achieved partial response after the application of ICIs. However, the patient who discontinued the PD-1 inhibitor after 6 months experienced DIC relapse, whereas the other patient who maintained the PD-1 inhibitor treatment cycle remained responsive after 10 months. We observed that active antitumor treatment strategies contributed to restoring coagulation function, especially PD-1 inhibitor-based treatment strategies that are effective in prolonging survival time for cancer patients having DIC complications.

Case report

Case 1

A 65-year-old woman was admitted to our hospital on 16 March 2022, with epigastric pain for 2 months. Physical examination showed otherwise normal results, without bruise, bleeding, or other coagulation disorder symptoms. Gastric endoscopy showed hyperplasia, protuberance of cardia mucosa, and a diffuse thickened gastric wall, with a biopsy result that revealed a poorly differentiated gastric adenocarcinoma, classified into diffuse type according to Lauren's criteria. The results of immunohistochemical staining of gastric neoplasm specimens were negative for HER2, and the Combined Positive Score (CPS) of PD-L1 was 3. Abdominal computer tomography (CT) scanning showed a thickened gastric wall accompanied by multiple metastases including lung, bone, peritoneum, mesentery, and retroperitoneal lymph nodes. A marrow biopsy found that the malignant cell infiltrated the bone marrow. Additionally, results of next-generation sequencing (NGS) revealed microsatellite instability with a high tumor mutation burden (TMB-H) of 11.52 mutations per megabase (muts/Mb).

The blood count test showed platelet (PLT) counts of 72.0×10^9/L. Blood coagulation tests revealed prolonged prothrombin time [PT of 20.3 s; the international normalized ratio (INR) is 1.80], reduced fibrinogen level (Fbg of 0.66 g/L), elevated D-dimer level (39.07 μg/mL), and fibrin degradation product level (FDP of 105.7 μg/mL). Her DIC score was 7 points, according to the recommendation of the International Society on Thrombosis and Haemostasis (ISTH) committee (16). After excluding severe infectious diseases, trauma, or other reasons for DIC, the patient was finally diagnosed with advanced gastric adenocarcinoma accompanied by multiple metastases and DIC complications.

A regimen consisting of modified docetaxel combined with cisplatin, 5-fluorouracil (5-FU), and sintilimab (mDCF plus sintilimab) was initiated. The treatment strategy started on the third hospital day. Best supportive care was provided to the patient until the coagulation function was restored, including a transfusion of fresh frozen plasma, fibrinogen, and heparin. On the 12th day (27 March), the coagulation function was improved, with the platelet count of 274×10^9/L, PT of 11.4 s, INR of 0.99, D-dimer level of 13.96 μg/mL, and FDP level of 21.3 μg/mL. The patient was discharged on the 12th hospital day. The patient received chemotherapy and immunotherapy regularly at our hospital.

After three courses of treatment, the patient achieved partial response (Figure 1), according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) (17). A CT scan performed on 18 May revealed that the lesions in the stomach, peritoneum, and metastases of lymph nodes were reduced, whereas the lesion in the bone was stable. A significant decrease in tumor markers and improvement in coagulation tests indicated that gastric cancer was well controlled. However, due to the heavy economic burden, the patient decided to discontinue immunotherapy and received chemotherapy only on 29 June. After two courses of chemotherapy were given to the patient, laboratory tests showed a PLT count of 112×10^9/L, PT of 16.4 s, INR of 1.43, Fbg level of 0.36 g/L, D-dimer level of 23.42 μg/mL, and FDP of 33.1 μg/mL, suggesting that the DIC relapsed. The latest chemotherapy was given on 10 August, and the patient discontinued the treatment in our hospital. The progression-free survival was 6 months. No serious treatment-related adverse events were reported during the treatment.

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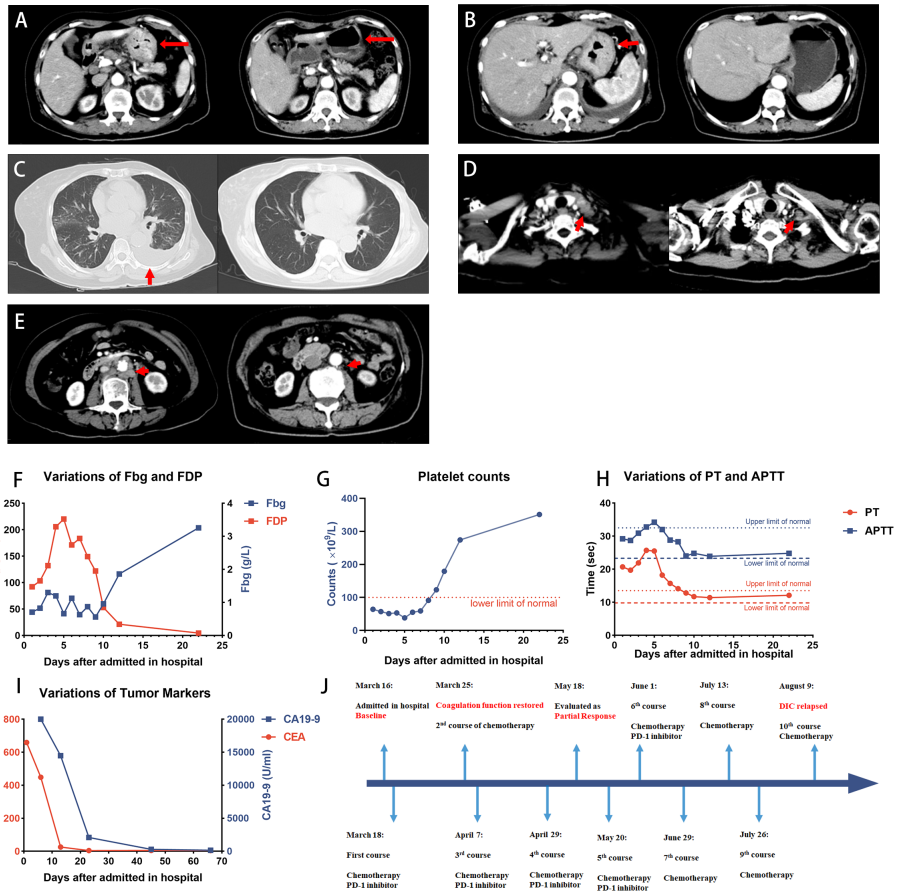

FIGURE 1
Case 1 patient achieved PR after the treatment. **(A–E)** CT images showing the patient's baseline disease (left panel) and response to treatment (right panel). **(A, B)** Diffuse thickened gastric wall significantly thinned after the treatment. **(C)** Pleural effusion indicated the left lung metastasis, and it was absorbed after the treatment. **(D)** Virchow's nodes were slightly reduced in size. **(E)** Retroperitoneal lymph nodes shrunk after the treatment. **(F–H)** Dynamic monitoring of Fbg level, FDP, platelet counts, PT, and APTT, suggested that the coagulation function was restored. **(I)** Dynamic monitoring of tumor markers during the treatment. **(J)** Timeline of the treatment. The patient discontinued PD-1 inhibitors on 29 June and received chemotherapy only, and DIC relapsed after 2 months. PR, partial response; Fbg, fibrinogen; FDP, fibrin degradation product; PT, prothrombin time; APTT, activated partial thromboplastin time.

Case 2

A 43-year-old man presented with epigastric pain and low back pain for 3 months and was admitted to our hospital on 28 January 2022. Endoscopy and biopsy identified a poorly differentiated gastric adenocarcinoma, classified into diffuse type. Immunohistochemical staining results were positive for HER2, the CPS of PD-L1 was 1, and microsatellite instability was detected. A CT scan revealed a thickened gastric wall, multiple metastases of lymph nodes, and multiple lesions in thoracic and lumbar vertebrae, suggesting that the patient had gastric cancer complicated by bone metastasis. Anemia was detected according to the blood count on 8 February, which showed a red blood cell (RBC) count of 2.92×10^{12}/L, hemoglobin (HGB) of 78.0 g/L, and a platelet count of 97.0×10^{9}/L. The coagulation test showed prolonged PT of 20.3 s, INR of 1.80, an elevated D-dimer level of 73.56 μg/mL, and an FDP level of 206.4 μg/mL). He was diagnosed with non-overt DIC because his score of 4 was less than the cutoff of 5 (16). On 17 February, another test revealed an RBC count of 2.54×10^{12}/L, HGB of 67.0 g/L, platelet count of 57.0×10^{9}/L, PT of 13.5 s, INR of 1.18, D-dimer level of 64.41 μg/mL, and FDP of 192.9 μg/mL.

After a diagnosis of advanced gastric carcinoma with multiple metastases, his therapy was initiated on 17 February, with a regimen of XELOX combined with trastuzumab and an immune checkpoint inhibitor, sintilimab. Supportive care of low molecular weight heparin (LMWH) was given to prevent venous thromboembolism (VTE) and DIC until the platelet counts and hemoglobin returned to the normal range. Zoledronic acid was also given because of bone metastases. After the first course of treatment, the patient's coagulation function was restored, and the hematologic profile improved.

The patient achieved partial response after 2 months (Figure 2). On 19 April, CT images revealed a significant reduction in thickened gastric wall and metastases of lymph nodes, whereas lesions in bone were kept stable. The level of tumor markers also decreased significantly. Now he has finished 13 courses of treatment and continues to receive treatment in our hospital, with

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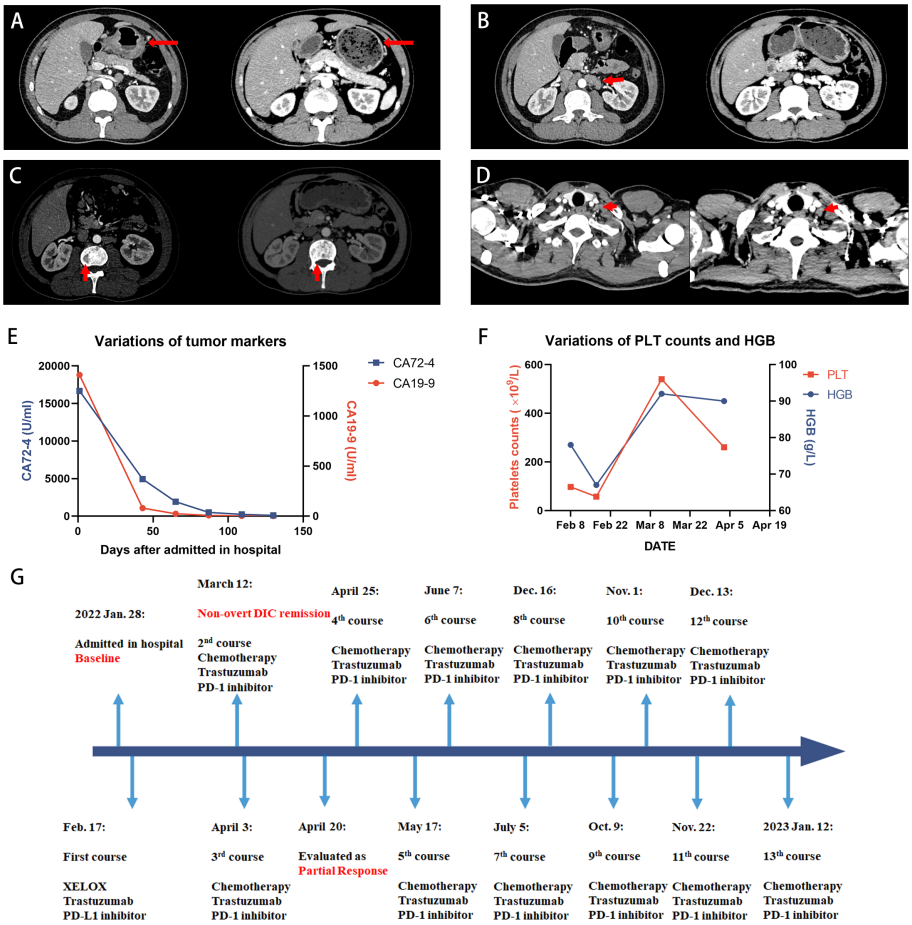

FIGURE 2
Case 2 patient achieved PR after the treatment. **(A–D)** The outcomes of CT scans at baseline (left panel) and 2 months after the treatment (right panel). **(A)** Thickened gastric wall thinned after the treatment. **(B)** Retroperitoneal lymph nodes significantly shrunk compared with the baseline. **(C)** The uneven density of the lumbar vertebrae was kept stable during the treatment. **(D)** Virchow's lymph nodes are slightly reduced in size. **(E)** The decline in the tumor marker level suggested that the treatment was effective. **(F)** Anemia remission and coagulation function were restored according to the dynamic monitoring of PLT counts and HGB level. PLT counts temporarily increased in the over-normal range on 8 March but finally returned to the normal range. **(G)** Timeline of the treatment. PLT, platelet; HGB, hemoglobin.

progression-free survival of 10 months. No serious treatment-related adverse events were reported during the treatment.

Discussion

We herein present two cases of PD-1 inhibitor-based treatment strategies in AGC with BMM and DIC. Although the patient of case 2 had not yet been diagnosed with DIC, he was classified into a subclinical type of cancer-related DIC because we believed that the tendency to progress to DIC is high (18). Both patients achieved a partial response after the treatment, and the coagulation function was restored.

Gastric cancers have a high probability of metastasizing to the liver and lung, but only less than 10% of the cancers metastasize to the bone (5). Malignant cells infiltrating the bone marrow space might result in anemia, thrombocytopenia, DIC, or other hematologic disorders. The prognosis for patients with AGC complicated by DIC remains poor, and the median OS of these patients without treatment was less than 3 months (4). Mainly reported in the form of case reports, the clinical characteristics of AGC with bone marrow metastasis and DIC remain unclear, and a standard treatment needs to be established.

DIC is an acquired syndrome originating from infectious or non-infectious diseases. One of the most frequent factors that promote DIC is sepsis. However, neither fever nor other symptoms of sepsis were presented in our two cases, suggesting that coagulation disorders were probably triggered by gastric cancer. Cancer-induced DIC is usually related to high expression of tissue factors, which can activate Factor XII and generate thrombin (19). DIC occurs due to the failure of controlling thrombin generation. Overexpression of fibrinolytic proteins may contribute to a hyperfibrinolytic condition (20). Cytokines may play a significant role in the pathogenesis of cancer-related DIC. Due to lack of data from high-quality research, the pathophysiology of cancer-related DIC remains unclear and needs to be further investigated. Treatment of primary diseases may relieve this severe syndrome.

Necrosis of malignant cells caused by chemotherapy may disrupt endothelial cells, aggravating the progression of DIC. Hematological abnormalities and poor performance status also raise the question on the tolerability and efficacy of chemotherapy. However, DIC management is promptly recognized, and appropriate management of the underlying disease is the main principle of treatment, according to the guidance of ISTH (16, 18). Previous retrospective studies have reported that chemotherapy for AGC with DIC has greater survival benefits than the best supportive care (9, 21). Chemotherapy regimens based on platinum, docetaxel, or fluoropyrimidine were most often used in the treatment (3, 4, 7–11). A study demonstrated that the chemotherapy regimen of 5-FU plus docetaxel was associated with prolonged survival after comparing different clinical treatments (4). However, the best treatment strategy remains under investigation.

Recently, immunotherapy has demonstrated impressive clinical efficacy and safety in the treatment of AGC. Immune checkpoint inhibitors (ICIs), such as PD-1/PD-L1 blockade, are the most commonly used agents in AGC. Nivolumab provided superior OS versus placebo in AGC patients regardless of the expression level of PD-L1, and nivolumab plus chemotherapy demonstrated significant improvement in OS versus chemotherapy, according to ATTRACTION-2 and CheckMate 649 studies (13, 15). Sintilimab plus XELOX performed better than placebo plus XELOX in the treatment of AGC, as reported by an ORIENT-16 study (14). The addition of trastuzumab, an antibody inhibitor of human epidermal growth factor receptor 2 (HER-2), to pembrolizumab and chemotherapy in the treatment of HER-2-positive gastric cancer also markedly reduced the tumor size and significantly improved the objective response rate (22). The safety profile of the addition of ICIs was consistent with the known safety profiles, suggesting that immunotherapy is safe (13–15, 22, 23). The main adverse events include dermatologic, gastrointestinal, and endocrine toxicities, whereas the hematological toxicity of ICIs is rare (24). The strategy of immunotherapy plus chemotherapy may thus have a potential for patients with cancers complicated by bone marrow metastasis and DIC.

We speculate that immunotherapy-based strategies would provide great efficacy in the treatment of gastric cancer-related DIC. After reviewing previous literature in PubMed and EMBASE, only two case reports were identified, which described the significant efficacy of atezolizumab and pembrolizumab in the treatment of urothelial carcinoma and bone marrow metastatic melanoma, respectively (25, 26). In our cases, two patients achieved partial response and their coagulation function was restored after treatment. However, the condition of the case 1 patient who discontinued immunotherapy on 29 June then received two courses of chemotherapy, worsened with DIC, and relapsed 2 months later, whereas case 2 patient is still receiving chemotherapy, targeted therapy, and immunotherapy in our hospital, with indicators of DIC still kept in the normal range. Different clinical outcomes of the case 1 patient with or without the PD-1 inhibitor may indicate that the combination of chemotherapy and immunotherapy would be better than chemotherapy alone. Unfortunately, few cases of the PD-1-based treatment strategy in cancer-related DIC are reported here and the findings need to be confirmed by larger cohorts of patients.

Our study is further constrained by the limitation of a case report. We did not set up a control group of AGC complicated by BMM and DIC which only received chemotherapy. Due to the limited number of these patients, it is difficult for us to set up such a control group. Therefore, it can hardly confirm the efficacy of PD-1 inhibitors alone in the treatment of these patients. Since cancer cells could express procoagulant molecules and cytokines, or cause microangiopathy to induce DIC, the treatment of primary cancer may be an effective strategy (19). We have a reason to speculate that immunotherapy would yield great efficacy in the treatment of cancer-related DIC. However, whether immunotherapy can be effective in AGC complicated by BMM and DIC or in minimizing adverse events still needs to be studied. Our conclusion still needs further validation in prospective clinical trials and basic experiments.

In summary, we presented two cases of PD-1 inhibitor-based treatment strategies in prolonging survival for patients with AGC with BMM and DIC whose prognosis is poor, and it could be considered as an initial treatment strategy for AGC with BMM and DIC.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Research Ethics Committee of Sun Yat-sen University Cancer Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

R-ZH, NC, and YH analyzed the patient data and drafted the manuscript. W-MH provided significant contributions to the analysis of pathological data. F-HW and D-LC designed the case report and revised the manuscript. 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.

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Sigmoido-vesical fistula secondary to sigmoid colon cancer presenting as urinary tract infection with *Lactococcus lactis*: A case report

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A colovesical fistula is a pathological communication between the colon and bladder. The symptoms include pneumaturia, fecaluria, and a lower urinary tract infection. The diagnosis is based on clinical symptoms, but the symptoms are not specific. Therefore, confirming the diagnosis is challenging. Urine cultures performed in patients with colovesical fistulas usually show growth of *Escherichia coli* or mixed growth of bowel organisms. Urinary tract infections caused by *Lactococcus lactis* are very rare, as it is rarely considered pathogenic in humans. We report the case of a 70-year-old woman who presented with symptoms of a recurrent urinary tract infection. Urine cultures were positive for *L. lactis*. Abdominopelvic computed tomography (CT) revealed focal thickening of the bladder wall and gas in the bladder. Cystoscopic examination and colonoscopy revealed sigmoid colon cancer and a sigmoido-vesical fistula. Laparoscopic surgical treatment was done. The patient recovered and was discharged 3 weeks later without chemoradiotherapy. On follow-up after 6 months, the patient was asymptomatic and stable. To our knowledge, this is the second reported case of *L. lactis* infection of the urinary tract and the first reported case in adults. *L. lactis* infection usually indicates the presence of serious underlying diseases such as malignancies, uncontrolled diabetes, and organ failure.

KEYWORDS

sigmoid colon cancer, sigmoido-vesical fistula, urinary tract infection, *Lactococcus lactis*, diabetes mellitus

Introduction

Colovesical fistula is a rare complication of various diseases, particularly diverticulitis and neoplasms of the colon and bladder. It is difficult to diagnose because of the atypical symptoms. *Lactococcus lactis* infection is very rare since it is considered nonpathogenic in humans. Here, we present the case of a 70-year-old woman with a recurrent urinary tract infection. Urine cultures revealed *L. lactis*. She was diagnosed with a sigmoido-vesical fistula secondary to sigmoid colon cancer, underwent surgical treatment, and recovered. To our knowledge, this is the first reported case of *L. lactis* infection of the urinary tract in adults.

Case presentation

A 70-year-old woman was admitted to our hospital due to urinary frequency, urgency, and hematuria of 1 month duration. She also complained of lower abdominal pain and 3 kg weight loss. She presented with a fever for 3 days during this period, with a peak body temperature of 38.3°C. Approximately 10 days prior to admission, she consulted the urology outpatient department and received anti-microbial treatment. Thereafter, only a slight resolution of symptoms was observed.

The patient had a history of type 2 diabetes mellitus for 10 years and was maintained with oral hypoglycemic drugs.

Upon physical evaluation, her vital signs were stable. Enlarged superficial lymph nodes were not palpable. Mild tenderness was observed in the lower abdominal region, without rebound tenderness. No costovertebral angle tenderness was noted.

Routine blood tests revealed a normal white blood cell count, hematocrit, and platelet count. Serum C-reactive protein level was increased to 78.38 mg/L (normal range: <10 mg/L). Routine urinalysis showed positive results for red cells (39/high power field), white cells (47/high power field), urine protein, and urine sugar. The fecal occult blood test results were positive. Serum tumor marker analysis revealed that carcinoembryonic antigen (CEA) was mildly elevated to 6.0 ng/ml (normal range: <5 ng/ml). Fasting plasma glucose was 13.6 mmol/L, and glycated hemoglobin A1c (HBA1C) was 8.9%. Urine culture was done thrice, which detected *L. lactis* in two readings. Ultrasound examination showed that the right bladder wall was thickened and revealed a 3.6 cm × 1.5 cm lesion, which was considered likely inflammatory tissue (Figure 1A).

On day 10 of admission, the temperature suddenly increased to 39.3°C with worsening lower urinary tract symptoms and lower abdominal pain. Also, foreign bodies were observed in the urine, described as similar to watermelon seeds and tea stems. Abdominopelvic computed tomography (CT) revealed focal thickening of the bladder wall and gas in the bladder (Figure 1B). The CT scan also showed thickening of the peritoneum in front of the bladder; however, no significant abnormalities were found in the small intestine or colon. Then computed tomography urography (CTU) was performed, which showed gas between the bladder dome and the adjacent sigmoid colon. These findings were consistent with a sigmoido-vesical fistula (Figure 1C). The urologic surgeon performed a cystoscopic examination, which showed turbid urine and a rough bladder wall (Figure 2A), but no fistula was found. Colonoscopy was then performed, which revealed sigmoid colon cancer that occupied nearly the entire colon (Figure 2B).

The patient was transferred to the general surgery department and underwent laparoscopic surgical treatment. The tumor was visualized to be in the sigmoid colon, where it was observed that the tumor had invaded the entire wall of the colon to the bladder. The colonic wall outside the tumor was adhered to the bladder wall. Enlarged lymph nodes were identified at the root of the mesenterium. No ascites or peritoneal neoplastic dissemination was found during intraoperative exploration.

A postoperative pathological examination (Figure 3) confirmed persistent, highly differentiated tubular adenocarcinoma (about 7.0 × 4.0 × 4.5 cm in size) accumulating almost the entire colonic wall. The tumor invaded through the muscularis propria into the subserosal adipose tissue. No metastasis was found in 15 peri-colonic lymph nodes. The pathological report also revealed fistulous tract formation between the sigmoid colon and the bladder with severe acute and chronic inflammation in the bladder wall. No tumor invasion was found in the bladder. The tumor was staged as T3N0M0 according to the TNM classification.

The patient recovered and was discharged 3 weeks later without chemo-radiotherapy. Six months after surgery, the patient exhibited normal eating and bowel habits and experienced a weight increase

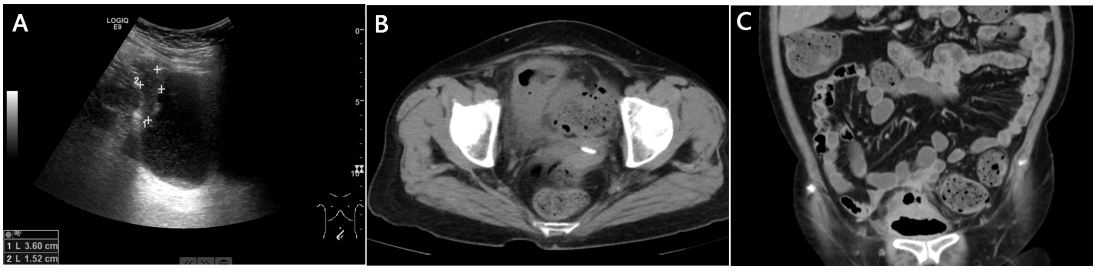

FIGURE 1
Imaging examinations. **(A)**: Ultrasound examination. The right bladder wall was thickened, and a 3.6 cm × 1.5 cm lesion was revealed; **(B)**: Abdominopelvic computed tomography (CT). Focal thickening of the bladder wall and gas in the bladder were noted; **(C)**: Computed tomography urography (CTU). Gas between the bladder dome and adjacent sigmoid colon, and a thickened bladder and sigmoid colon wall were revealed.

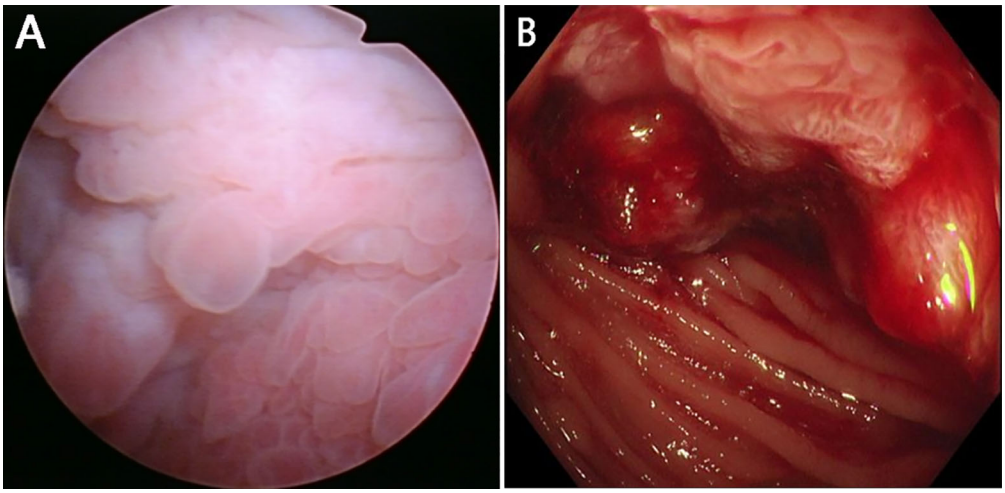

FIGURE 2
(A): Cystoscopic examination. Changes in the mucosa of the bladder were noted; **(B)**: Colonoscopy. Sigmoid colon cancer was revealed which occupied nearly the entire colon.

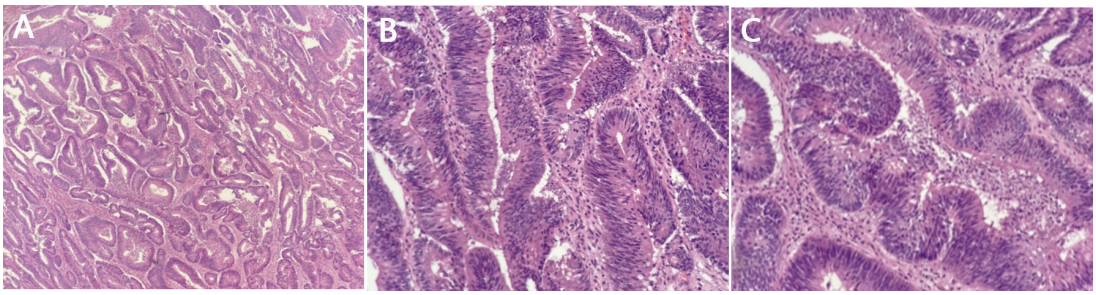

FIGURE 3
Postoperative pathological outcomes. Highly differentiated tubular adenocarcinoma. **(A)** ×40; **(B)** ×100; **(C)** ×200.

of 1 kg. The blood glucose level was normal and there were no symptoms of a urinary tract infection.

The case timeline is shown in Figure 4.

Discussion and conclusions

Colovesical fistulas are pathological communications between the colon and bladder (1). Among these, sigmoido-vesical fistulas are the most common (2). Etiological factors include inflammatory diseases, neoplasms of the colon and bladder, pelvic radiation therapy, and traumatic and iatrogenic injuries (3). Diverticulitis is the most common cause, accounting for approximately 65%–79% of cases. The second leading etiology is cancer, contributing 10%–20% of cases, with colonic adenocarcinoma being the most frequent type. Crohn's disease accounts for 5%–7% of cases (4).

Patients with colovesical fistulas usually present with pneumaturia (50%–85% of cases), fecaluria (51%–68% of cases),

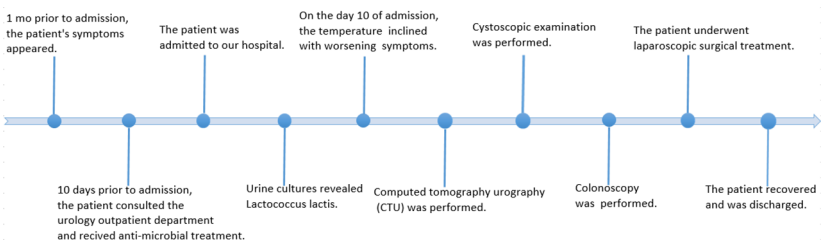

FIGURE 4
Case timeline.

and symptoms of lower urinary tract infection (57%–71%), which include frequency, urgency, suprapubic pain, and hematuria (1, 3–5). Our patient presented with urinary frequency, urgency, hematuria, lower abdominal pain, and weight loss.

The diagnosis is based on clinical symptoms; however, the symptoms and signs are not specific. It is challenging to confirm the diagnosis of a colovesical fistula, and it may take months before the condition is recognized. The patient in this case was monitored for almost a month before the diagnosis was confirmed. After admission, poor glycemic control was considered the probable cause of the urinary tract infection; however, the symptoms resolved partly after administration of insulin glargine and intravenous ceftazidime. Further work-up was performed when a sudden worsening of symptoms was observed despite ongoing treatment. A classical presentation of colovesical fistulas is Gouverneur syndrome, characterized by suprapubic pain, frequency, dysuria, and tenesmus (6), which were consistent with the patient. In this case, the fistula was caused by the tumor and repeated inflammatory reactions around it.

Another relevant concern is investigating the specific pathogen. Bacteria that commonly cause urinary tract infections include *Escherichia coli*, Klebsiella, and Enterobacter, which travel from the gastrointestinal tract and perineal area into the urinary tract. Previous studies reported that urine cultures performed in patients with colovesical fistulas showed growth of *E. coli* in approximately 33% of cases and mixed growth of bowel organisms or enterococci in approximately 65% of cases (1, 4). In this case, urine culture was performed three times, which revealed *L. lactis* twice.

Lactococcus is a genus of facultative anaerobic catalase-negative gram-positive intestinal cocci (7). This genus of bacteria is commonly used in manufacturing dairy products and has been investigated for use in the biotechnology industry as a delivery system for vaccines and other therapies (8). Urinary tract infections caused by *L. lactis* are very rare, as it is not considered pathogenic in humans. To our knowledge, this is the second reported case of *L. lactis* infection of the urinary tract and the first reported case in adults (7, 9). A preterm neonate was reported to experience a urinary tract infection caused by *L. lactis* from the gastrointestinal tract after ingestion of the mother's breast milk (9). *L. lactis* infection occurs more frequently in immunocompromised patients or those with significant underlying conditions such as malignancies, uncontrolled diabetes, and organ failure (10, 11). In our case, the patient had uncontrolled diabetes and sigmoid colon cancer; hence, she was more at risk for opportunistic infections.

CT showed free gas in the bladder, which was initially considered to be produced by bacteria. However, laboratory examinations showed mildly elevated CEA levels and a positive fecal occult blood test, which suggested a possible underlying lesion that should be further investigated. Hence, a clinical history and physical examination, supplemented by appropriate laboratory work-up and imaging, are required to prevent delay in diagnosis.

In conclusion, it is recommended to determine the specific etiology of recurrent urinary tract infections, and colovesical fistulas must be included as a differential diagnosis. If *L. lactis* infection is present, it is essential to identify the underlying diseases, such as malignancies, uncontrolled diabetes, and organ failure.

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 participant/patient(s) for the publication of this case report.

Author contributions

YA, QC, and YL were the physicians-in-charge of the patient, reviewed the literature, and contributed to manuscript drafting. LL, DW, and YY reviewed the literature and contributed to manuscript drafting. WK and DA were the patient's surgeons, analyzed and interpreted the imaging findings. DL performed the cystoscopy and was responsible for the interpretation of the findings. All authors contributed to the article and approved the submitted version.

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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.

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Squamous cell carcinoma of ascending colon with pMMR/MSS showed a partial response to PD-1 blockade combined with chemotherapy: A case report

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Primary colon squamous cell carcinoma (SCC) is extremely rare and associated with a poor prognosis. Moreover, there is no treatment guideline for this disease. Proficient mismatch repair/microsatellite-stable (pMMR/MSS) colorectal adenocarcinoma is refractory to immune monotherapy. Although the combination of immunotherapy with chemotherapy in pMMR/MSS colorectal cancer (CRC) is currently under investigation, the clinical activity of this approach in colorectal SCC remains unknown. In this article, we report the case of a pMMR/MSS CRC patient with ascending colon SCC who had high programmed cell death–ligand 1 (PD-L1) expression and the a missense mutation in codon 600 of the B-Raf proto-oncogene (BRAF ^{V600E}) mutation. The patient exhibited a significant response to the combination of immunotherapy and chemotherapy. After eight cycles of treatment with the combination of sintilimab and mFOLFOX6 (oxaliplatin, fluorouracil, and leucovorin), computed tomography–guided microwave ablation of the liver metastasis was performed. The patient achieved excellent durable response and continues to experience a good quality of life. The present case indicates that programmed cell death 1 blockade combined with chemotherapy may be an effective therapy for patients with pMMR/MSS colon SCC and high PD-L1 expression. Furthermore, PD-L1 expression may be a biomarker for immunotherapy in patients with colorectal SCC.

KEYWORDS

ascending colon, squamous cell carcinoma, immunotherapy, chemotherapy, pMMR/MSS, BRAF V600E, PD-L1

Introduction

Primary squamous cell carcinoma (SCC) of the colon is an extremely rare type of tumor; this disease accounts for 0.1%–2.5% of all colorectal malignancies (1). Owing to the rarity of the disease, a treatment guideline for colon SCC has not been established thus far. The current optimal treatment is surgical excision of the primary tumor, followed by

adjuvant chemoradiotherapy. The use of immunotherapy in colon SCC is infrequently reported. In this article, we report the case of a patient with proficient mismatch repair/microsatellite-stable (pMMR/MSS) colon SCC who had high programmed cell death-ligand 1 (PD-L1) expression and the $BRAF^{V600E}$ mutation. The patient showed significant response to the combination of programmed cell death 1 (PD-1) blockade and chemotherapy.

Case report

A 76-year-old female patient was admitted to hospital for lower abdominal intermittent pain and melena in November 2021. An obstructing mass in the ascending colon was detected through colonoscopy, and histopathology analysis confirmed the presence of poorly differentiated carcinoma. Abdomen–pelvis computed tomography (CT) revealed a large obstructing mass in the ascending colon invading the intestinal wall, accompanied by mesenteric lymphadenectasis in multiple lymph nodes and multiple liver metastases. Further examination through ^{18}F-fluorodeoxyglucose positron emission tomography/CT (PET/CT) showed hypermetabolism and segmental eccentric thickening of the ascending colon wall, which is consistent with colon cancer. The enlarged mesangial lymph nodes in the medial ascending colon, multiple intrahepatic nodules, and nodules in the right upper lobe with hypermetabolism were noted as metastases. The patient was diagnosed with primary colon SCC (cT4aN2aM1b, stage IV), accompanied by multiple liver and lung metastases.

The patient underwent a palliative right hemicolectomy and partial resection of the liver in November 2021. Histopathology demonstrated a poorly differentiated SCC of the ascending colon infiltrating the serosa. Metastatic lesions were found in lymph nodes (5/17). Poorly differentiated carcinoma was observed in the liver tissue; this finding is consistent with the liver metastasis of colon cancer. Immunohistochemistry (IHC) revealed the PD-L1 combined positive score (CPS) of 95, with pMMR/MSS status. Using the amplification refractory mutation system–polymerase chain reaction (ARMS-PCR), the $BRAF^{V600E}$ mutation was detected, while the analysis did not reveal mutations in the KRAS and NRAS genes. This kit can test the 12/13/61 codons of the Kirsten rat sarcoma viral oncogene homolog (KRAS) and Neuroblastoma RAS viral oncogene homolog (NRAS) genes, as well as detect the $BRAF^{V600E}$ mutation. After surgery, the patient refused to receive follow-up antitumor therapy due to poor physical condition.

New lesions were detected in the liver by CT 3 months after operation, and the patient was admitted to our hospital in February 2022. The biopsy of the hepatic lesions revealed metastatic SCC (Figure 1A). The PD-L1 CPS was 20 (Figure 1B). The immunohistochemical staining of the biopsy specimen revealed a positive expression of CK20 (Figure 1C), P40 (Figure 1D), P63, CK20, CK5/6, MLH1, MSH2, MSH6, and PMS2. The expression of PD-L1 protein was evaluated with an IHC method using a mouse monoclonal antihuman PD-L1 antibody (Clone 22C3; Dako).

Considering the poor physical condition of the patient and high expression of PD-L1, we administered immunotherapy with sintilimab (200 mg, once every 21 days (q21d)) plus chemotherapy with mFOLFOX6 (oxaliplatin, fluorouracil, and leucovorin). The mFOLFOX6 regimen consisted of oxaliplatin (120 mg intravenously guttae (ivgtt)), fluorouracil (600 mg iv, 3,625 mg civ 46 h), and leucovorin (600 mg ivgtt) and was administered every 14 days. After two cycles of combination therapy, CT showed that the liver lesion had shrunk from 28.7 to 18.46 mm (Figures 2A, B); hence, the patient had achieved a partial response. The liver lesion had shrunk to 6.39 mm after eight cycles of the combination therapy (Figure 2C). Significant tumor shrinkage was also observed in the lung lesion (Figures 2D–F). Importantly, there were no drug-related adverse events noted, except for grade 1 myelosuppression.

To improve the efficiency, the patient underwent CT-guided microwave ablation of liver metastases after eight cycles of the combined therapy. There were no residual lesions in the liver following the microwave ablation. Subsequently, monotherapy with sintilimab was administered once every 3 weeks. The patient continues to exhibit a stable response and experiences a good quality of life. In November 2022, the enlargement of retroperitoneal lymph nodes was discovered. Progression-free survival (PFS) was 8.5 months.

The patient provided informed consent for the publication of this case.

Discussion

Colorectal SCC typically occurs in the fifth decade of life, and the most common site is the right-sided colon. It is often diagnosed at an advanced stage with distant metastasis and has a worse prognosis compared with that of adenocarcinoma. Stage IV disease is linked to a mean survival period of 8.5 months (2). Considering the lack of treatment guidelines, therapeutic strategies for colorectal SCC are typically based on the management of adenocarcinoma. A 5-fluorouracil (FU)-based regimen is generally administered for the treatment of colorectal SCC. Copur et al. reported the case of a patient with SCC metastatic colorectal cancer (mCRC) who achieved an objective response after receiving cisplatin/etoposide/5-FU combination chemotherapy (3). Juturi et al. concluded that the combination of cisplatin, 5-FU, and leucovorin may be a treatment option for metastatic SCC of the colon (4). Considering the poor prognosis of colon SCC, the discovery of additional treatment strategies is urgently needed.

During the past decade, immunotherapy has rapidly developed and shown excellent antitumor efficacy against different types of cancer. The use of immune checkpoint inhibitors (ICIs) in the treatment of gastrointestinal tumors, particularly esophageal SCC, has resulted in great success. Nivolumab and pembrolizumab (anti-PD-1 monoclonal antibodies) were approved by the US Food and Drug Administration for the treatment of mCRC patients with microsatellite unstable–high (MSI-H) or deficient mismatch repair (dMMR) tumors. However, ICIs are mostly efficacious against dMMR/MSI-H CRC, while pMMR/MSS CRC is less susceptible

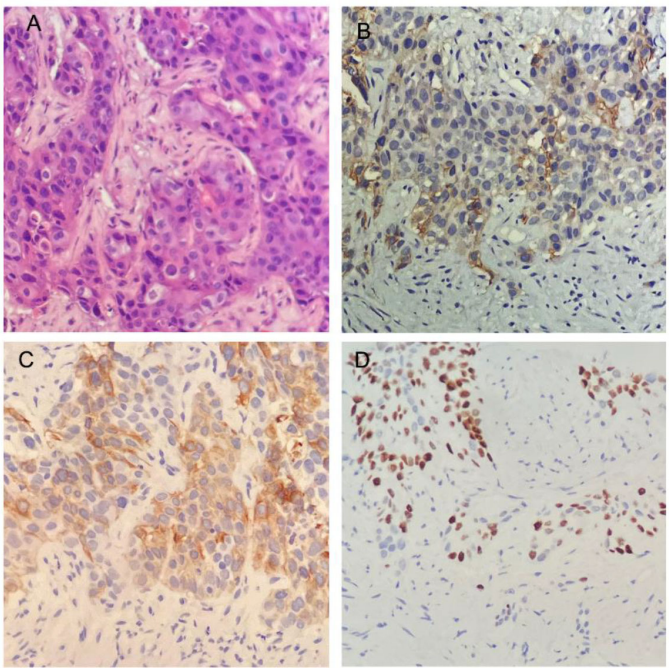

FIGURE 1
Histopathology and immunohistochemistry (IHC) of the biopsies from liver metastases. **(A)** Histological findings revealed squamous cell carcinoma (HE × 200). **(B)** IHC staining for the expression of programmed cell death–ligand 1 (×200). **(C, D)** IHC staining yielded positive results for CK20 **(C)** and P40 **(D)** (×200).

to these agents (5). Considering only 5% in stage IV CRC patients are detected as the dMMR/MSI-H phenotype, most CRC patients are not able to benefit from ICIs alone (6). ICI monotherapy exerted a limited antitumor effect in CRC patients with pMMR/MSS tumors. Therefore, novel strategies (including immunotherapy) are currently under evaluation to improve treatment outcomes and the quality of life. It has already been proven that oxaliplatin, fluorouracil, and leucovorin (FOLFOX) can activate PD-1+ CD8 T cells to induce tumor infiltration, which triggers tumor adaptive immune resistance, supporting the utilization of ICIs and chemotherapies like FOLFOX (7). Based on these findings, the combination of ICIs and chemotherapy has been extensively investigated to improve the clinical outcome of pMMR/MSS mCRC. The AtezoTRIBE trial revealed that the addition of

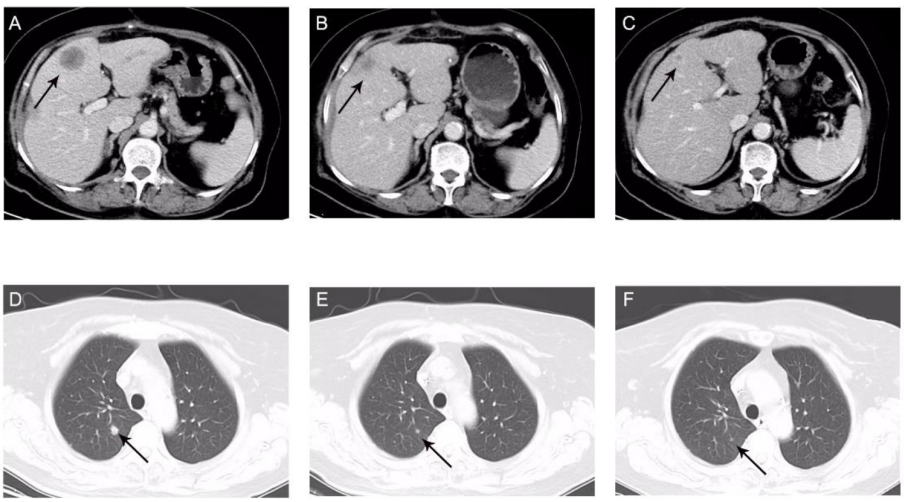

FIGURE 2
Computed tomography portal phase images. Maximum diameter of the liver **(A–C)** and lung **(D–F)** metastases. **(A)** 28.7 mm, before the combination therapy. **(B)** 18.46 mm, after two cycles of combination therapy. **(C)** 6.39 mm, after eight cycles of combination therapy. **(D)** Before combination therapy. **(E)** After two cycles of combination therapy. **(F)** After eight cycles of combination therapy.

atezolizumab to oxaliplatin, fluorouracil, leucovorin, and irinotecan plus bevacizumab prolonged the PFS of patients with mCRC in the pMMR/MSS subgroup (8).

However, due to the rarity of the disease, there are few reported cases involving the use of immunotherapy against colon SCC. In view of the overexpression of PD-L1, we selected sintilimab and mFOLFOX6 as the preferred treatment options for this case. The present patient received PD-1 blockade combined with chemotherapy for primary pMMR/MSS SCC of the ascending colon with high PD-L1 expression. This combination treatment demonstrated excellent antitumor efficacy.

The frequency of the expression of PD-L1 is observed at approximately 24% in colorectal adenocarcinoma (9), and related cases are rarely reported in colorectal SCC. In a previous case of adenosquamous carcinoma with PD-L1 overexpression, PD-L1 expression was restricted to the SCC component (10). Squamous cancer cells may express higher levels of PD-L1 than adenocarcinoma cells in colorectal adenosquamous carcinoma samples. High PD-L1 expression can predict the response of various types of cancer to anti-PD-1/PD-L1 therapy. Nevertheless, PD-L1 expression has not been approved as a predictive biomarker for immunotherapy in CRC. Although the use of immunotherapy for pMMR/MSS CRC adenocarcinoma was initially not recommended, the treatment of pMMR/MSS colon SCC patients with high PD-L1 expression using ICIs was associated with robust and durable clinical outcomes. He et al. reported a case of rectosigmoid-junction SCC with high PD-L1 expression and pMMR/MSS tumors. The patient achieved a significant clinical benefit after combination treatment with sintilimab and capecitabine (11). In the present case, we treated a patient with colon SCC, high expression levels of PD-L1, and the pMMR/MSS phenotype using PD-1 blockade combined with chemotherapy. The patient achieved an excellent durable response. Thus, it appears that PD-L1 expression is a potential prognostic biomarker for PD-1 blockade therapy in patients with colorectal SCC.

There were no effective and standard regimens for colorectal SCC. The present case shows that combined immunotherapy is effective for the treatment of patients with colorectal SCC and high PD-L1 expression. It might be a good treatment regimen for patients with colon SCC. Sintilimab with the mFOLFOX6 regimen is applied for the first time to treat the primary SCC of the ascending colon with a high expression of PD-L1, the pMMR/MSS status, and the $BRAF^{V600E}$ mutation. A significant antitumor efficacy was observed in the patient, suggesting that PD-1 blockade combined with chemotherapy may be an effective treatment for colorectal SCC patients. The level of PD-L1 expression may be a potential prognostic biomarker for the colorectal primary SCC.

Further randomized clinical trials with larger samples are warranted to validate the antitumor effect of PD-1 blockade combined with chemotherapy in patients with colorectal SCC, as well as to identify predictive biomarkers.

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 Weifang People's Hospital. 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

YL wrote the manuscript. JD, PZ, WM, HX gathered the patient's data. HX revised the manuscript. 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.

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Case report: Coexistence of sigmoid tumor with unusual pathological features and multiple colorectal neuroendocrine tumors with lymph node metastases

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The coexistence of adenocarcinoma and neuroendocrine neoplasm (NEN) in the same tumor is rare. What is rarer is that the neuroendocrine component is a well-differentiated neuroendocrine tumor (NET) Grade (G) 1. Most colorectal NETs are single, but multiple neuroendocrine tumors (M-NETs) are rare. Well-differentiated NETs rarely metastasize. Here, we present a unique case of a synchronous sigmoid tumor and multiple colorectal NETs with lymph node metastases. The sigmoid tumor consisted of adenocarcinoma and NET G1. The metastatic component was NET G1. A 64-year-old man underwent a colonoscopy for persistent changes in bowel habits and positive fecal occult blood for 1 year. An ulcerative lesion, which was diagnosed as colon cancer, was seen in the sigmoid colon. In addition, scattered lesions could be seen in the colon and rectum. Surgical resection was performed. Pathological findings suggested that the ulcerative lesion was composed of 80% adenocarcinoma and 20% neuroendocrine component (NET G1), while the remaining lesions were consistent with NET G1. At the same time, 11 lymph nodes around the resected intestinal segment were invaded by NET G1. The prognosis of the patient was good. After 13 months of follow-up, no recurrence and no metastasis were found. We hope to provide a reference and improve our understanding of the clinicopathological features and biological behavior of these unique tumors. We also aim to emphasize the importance of radical surgery and individualized treatment.

KEYWORDS

sigmoid neoplasm, multiple colorectal neuroendocrine tumors, lymph nodes metastases, neuroendocrine, adenocarcinoma, case report

1 Introduction

Colorectal cancer (CRC) is one of the major causes of cancer-related deaths. The most common histologic subtype of CRC is adenocarcinoma (1). According to the 2019 World Health Organization (WHO) classification, the neuroendocrine neoplasm (NEN) is subdivided into well-differentiated neuroendocrine tumor (NET; i.e., NET Grade (G) 1, NET G2, and NET G3) and poorly differentiated neuroendocrine carcinoma (NEC) (2). The coexistence of adenocarcinoma and NEN in one tumor is rare. Even rarer is the presence of a well-differentiated NET G1 component. Most colorectal NETs are single, and multiple neuroendocrine tumors (M-NETs) are rare (3). Lymph node metastasis of NETs is related to the degree of differentiation. Well-differentiated NETs rarely metastasize. This article reports an interesting case of synchronous sigmoid tumor consisting of 80% adenocarcinoma and 20% neuroendocrine component (NET G1) and multiple colorectal NETs with lymph node metastases. The sigmoid tumor presented with diffusely metastatic lymph nodes with NET G1 component, which is unique. Radical surgical resection and individualized treatment usually imply a good prognosis. We hope to provide a reference and improve our understanding of the clinicopathological features and biological behavior of these unique tumors.

2 Case presentation

A 64-year-old man presented to our hospital with persistent changes in bowel habits and positive fecal occult blood for 1 year in July 2021. His weight had dropped by approximately 10 kg since the disease onset. Personal and family history was not contributory. There was no previous history of intestinal inflammatory diseases or other related disease history. No obvious mass was found in the digital rectal examination, and no blood was found on the finger pad. Blood routine examination, biochemical examination, and tumor markers showed no obvious abnormalities. We did not check the levels of urinary 5-hydroxyindoleacetic acid or plasma serotonin because a NET was not suspected at that time. Colonoscopy was performed, and an ulcerative mass, approximately 3 * 3 cm in size, was seen in the sigmoid colon 15 cm proximal to the anal verge (Figure 1A), which was diagnosed as colon cancer. In addition, scattered lesions with a size of 0.4–1.0 cm could be seen in the colon and rectum (Figure 1B). A biopsy was performed, and histology revealed that the ulcerative mass was an adenocarcinoma and that the remaining lesions were NETs (G1). Abdominal and pelvic enhanced CT showed that the wall of the junction area between the rectum and sigmoid colon was thickened with abnormal enhancement, and multiple small lymph nodes were found in the mesorectum. Malignant tumors with lymph node metastasis might be considered. Based on the above findings, we considered that surgical resection was necessary.

The patient underwent total mesorectal excision (TME) and prophylactic ileostomy. Macroscopically, the ulcerative tumor was 4.0 * 3.0 * 1.0 cm in size. The cycle rate was 50% (30 mm/60 mm). The cut surface of the mass was gray-white, solid, and hard and was suspected to invade the deep muscularis propria. Histologically, the tumor was composed of a mixture of two components: moderately differentiated tubular adenocarcinoma (80%) and NET G1 (20%). The two coexisting, distinct tumor types were noted in separate areas, but other areas showed cross-growth (Figure 2). Adenocarcinoma invaded the muscularis propria, and the NET component invaded the submucosa in this mixed tumor. The immunohistochemical staining showed that the adenocarcinoma component was positive for CK, P53, and Ki-67. Desmin was positive in muscle tissue. Her-2 was 1+. The cell was also strongly positive for MSH2, MSH6, PMS2, and MLH1, suggesting mismatch repair proficient (pMMR). The other component was slightly positive for CK and Rb and was positive for CD56, Syn, and CgA (Figure 3), indicating that it was a neuroendocrine component. Ki-67 proliferation index was <2% (Figure 3), so it was diagnosed as NET G1. CD31, CD34, and D2-40 disclosed that NET G1 cells invaded blood vessels and lymphatic vessels, while adenocarcinoma components did not. We performed hematoxylin and eosin (H&E)

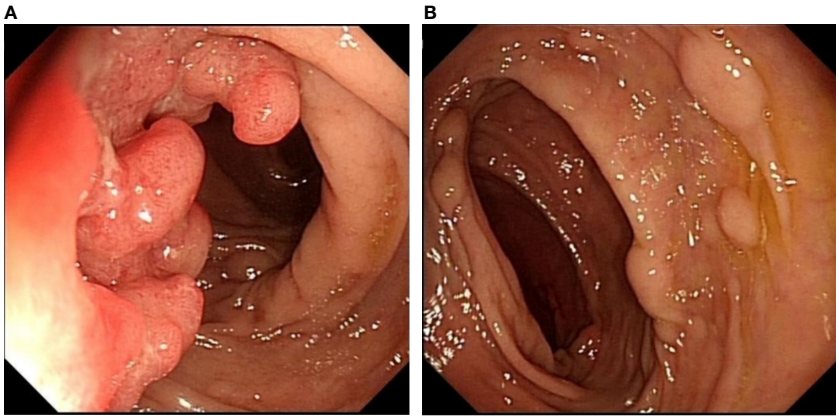

FIGURE 1
Colonoscopy showing an ulcerative mass, approximately 3 * 3 cm in size, located in the sigmoid colon 15 cm proximal to the anal verge **(A)**. Scattered raised lesions with a size of 0.4–1.0 cm located in the colon and rectum **(B)**.

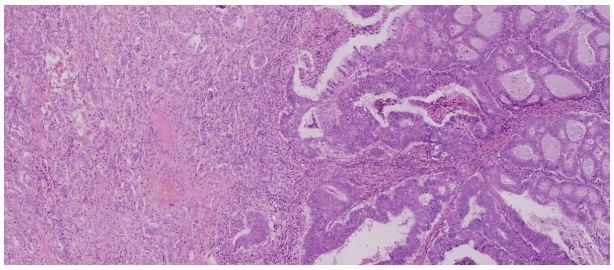

FIGURE 2
Adenocarcinoma and neuroendocrine tumor (NET) were noted in separate areas, but some areas showed cross-growth.

and Verhoeff's Van Gieson (EVG) staining to evaluate blood vessels. No abnormality was found. A raised lesion with a diameter of 0.7 cm was seen 2 cm away from the ulcerative tumor, and a nodule with a diameter of 0.5 cm was seen around the intestine. Pathological results confirmed that the raised lesion was a NET G1, invading the submucosa. There were 31 lymph nodes around the resected intestinal segment, of which 11 were invaded by NET G1 (Figure 4). No tumor was found in the biopsy of the proximal anastomosis, while a NET G1 was found in the distal anastomosis. In addition, considering that molecular detection of KRAS, NRAS, PIK3CA, and BRAF polygene mutations can predict the drug resistance of patients more accurately and guide clinical medication and scientific selection of treatment plan correctly, we performed KNBP gene mutation detection by amplification refractory mutation system (ARMS) fluorescence quantitative polymerase chain reaction, and no mutations in KRAS, NRAS, PIK3CA, and BRAF genes were detected. These pathological findings supported the diagnosis of adenocarcinoma with NET G1 (pT2N2bM0). The postoperative course was good. Since it was early-stage cancer and ^{99m}Tc-octreotide SPECT/CT showed no abnormalities, postoperative adjuvant therapy was not performed.

Five months later, the chest, abdominal, and pelvic enhanced CT showed no metastasis. Multiple red mucosal eminences were found around the anastomosis under the colonoscope. Biopsy was taken, and immunohistochemical staining showed the specimen was positive for Rb, CK, CD56, Syn, CgA, CgB, and SSTR2 and was negative for P53 and S-100. Ki-67 proliferation index was <2%. Therefore, it was consistent with NET G1. Considering that metastasis of NET G1 was found in the lymph nodes around the mixed tumor, we preferred to diagnose these NETs as metastatic tumors rather than independent tumors. Subsequently, the patient underwent ileostomy closure surgery and laparoscopic exploration. At the same time, transanal endoscopic microsurgery (TEM) was performed to remove the lesions found under colonoscopy before the operation. Combined with immunohistochemical staining, the postoperative pathological results showed that they were consistent with NET G1. The patient was followed up every 1–3 months after discharge and did not complain of related discomfort. Chest, abdominal, and pelvic enhanced CT, biochemical examination, blood routine examination, tumor markers, and colonoscopy showed no recurrence and metastasis 6 months after the second operation. Thirteen months after the operation, he is still alive and well.

3 Discussion

Due to their rarity, the diagnostic criteria, classification, mechanism, clinical behavior, and treatment options of tumors consisting of two types of components have been controversial. According to the definition, the neuroendocrine component and non-neuroendocrine component must account for more than 30% of the total tumor volume to be diagnosed as mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) (4). However, the 30% cutoff has been chosen arbitrarily and based on the assumption that a minor component generally does not affect the behavior (5). More

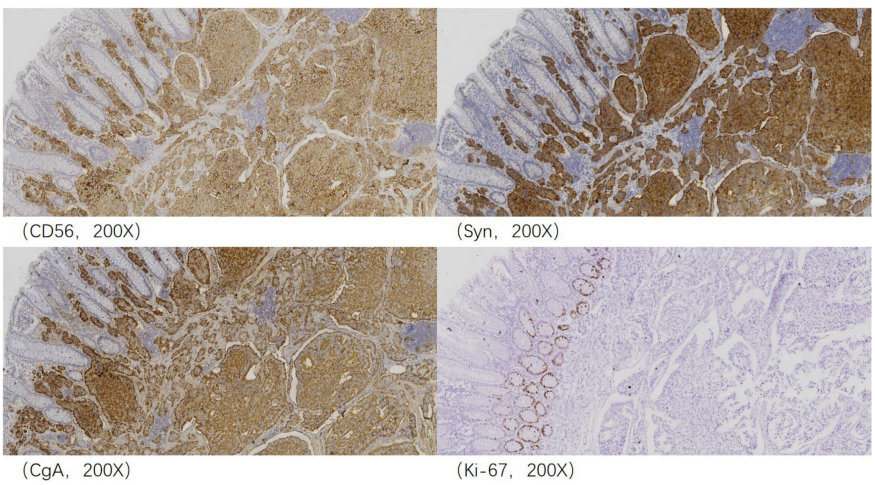

FIGURE 3
Immunohistochemical analysis revealed that the neuroendocrine component was positive for CD56, Syn, and CgA, and Ki-67 proliferation index was <2% and thus considered neuroendocrine tumor (NET) G1.

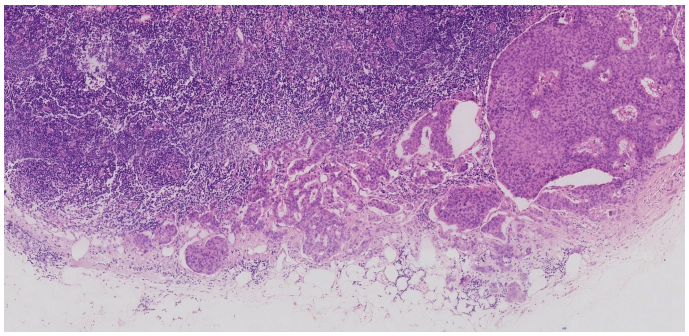

FIGURE 4
Some lymph nodes around the resected intestinal segment were invaded by neuroendocrine tumor (NET) G1.

and more clinical studies have shown that the 30% threshold may be too high. Previous studies have shown that the neuroendocrine and non-neuroendocrine components may both progress and metastasize independently (6). From this point of view, the natural behavior of this type of tumor is the sum of neuroendocrine and non-neuroendocrine components, not the mean (7). In our case, the proportion of neuroendocrine components in the mixed tumor was only 20%, which did not satisfy the criteria for MiNENs. We just diagnosed the mixed tumor as a sigmoid adenocarcinoma with a focal (20%) NET G1 component. However, it behaved aggressively with metastatic lymph nodes with NET G1 component, which affected the choice of treatment and prognosis to some extent. Fortunately, none of the lymph node metastases presented adenocarcinoma components.

When glandular and endocrine components are present in one tumor, their respective histological patterns are classified as composite tumors, collision tumors, and amphicrines (5). In a composite tumor, the distinct neuroendocrine and non-neuroendocrine components are intermingled. Collision applies when the two components are closely juxtaposed but never intermixed. When dual differentiation was present within the same cell, it can be defined as amphicrine. While the exact pathogenesis of these neoplasms is still a topic of open debate, the tumorigenesis of different types may be distinct (8–10). The first hypothesis about the mechanism of tumorigenesis is that the epithelial and endocrine components descend from different precursor cells independently and grow into the same space by chance. Another hypothesis is that the two components arise from a common multipotent progenitor stem cell with bidirectional differentiation. The third theory proposes that they occur contiguously. The microenvironment is altered by the first neoplasm, leading to the development of an adjacent second neoplasm, which is the result of the progressive accumulation of genetic alterations and aberrations. Finally, an amphicrine tumor is thought to be composed of a single cell type, in which each cell displays both neuroendocrine and non-neuroendocrine phenotypes (9, 10). In our case, the diagnosis of the sigmoid tumor was consistent with a composite tumor since the boundary of the two components was not clear.

Non-neuroendocrine components primarily originate from the mucosa, while neuroendocrine components usually occur in a deeper layer of the colon wall and are easily missed (11). As a result, misdiagnosis and underdiagnosis of the neuroendocrine component are likely to occur. Immunohistochemical study and gene detection play an important role in diagnosis. They are very useful in distinguishing a collision tumor from a composite tumor and in predicting which component contains the more aggressive histological profile. Most available molecular data have been obtained from colorectal mixed adenoneuroendocrine carcinoma (MANEC), in which the adenocarcinoma and NEC components share common driver genetic aberrations. The same results were also found in tumors consisting of adenocarcinomas and NETs (12). This also demonstrates that they originate from a common precursor cell, which undergoes dual differentiation after the first tumorigenic step (7, 13). However, the same conclusion was not confirmed in mixed adenoneuroendocrine tumors (MANETs), a combination of well-differentiated NETs and adenoma. Due to their inertia, those genetic mutations were not detected. Amplifications of KRAS, BRAF V600E, APC, MMR, and HER-2 occur in both components of MiNENs. One series of 44 cases found MMR deficiency in 38.6% of MiNENs. This conclusion increases the possibility of a potential response to programmed death 1 blockade (14). In addition, the molecular mechanisms involved in the occurrence and development of colorectal mixed tumors include some known changes related to the pathogenesis of colorectal adenocarcinoma (10). All these make the targeted therapies possible. In our patients, immunohistochemical study and gene detection played an important role in diagnosis and treatment. The sigmoid tumor was early-stage cancer, and ^{99m}Tc-octreotide SPECT/CT showed no abnormalities, so postoperative adjuvant therapy was not performed.

Tumors containing two types of histological components are often diagnosed with extensive lymph node and liver metastasis, which is the most important risk factor for poor prognosis. However, the mechanism driving the transfer remains unclear. A previous retrospective study (6) found that both regional lymph nodes and distant metastases were predominantly invaded by one component. However, distant metastases were mainly invaded by the neuroendocrine component. As the proportion of the neuroendocrine component in the primary tumor increased, the ratio of positive lymph nodes with pure neuroendocrine invasion also increased (6). Sakamoto et al. (15) reported the finding of extramural tumor deposits without lymph node structure (EX) in a patient with rectal NET G1, suggesting

that NETs can spread to form EX in a manner similar to colorectal carcinoma, even if it is well differentiated NET G1. Such conclusions indicate that the neuroendocrine component of these special tumors is most likely to be the primary cause of malignancy and should be considered when deciding the appropriate treatment. According to a recent large study (16), there is a significant survival difference among rectal neuroendocrine neoplasm patients with zero positive lymph node, one to four positive lymph nodes, and ≥5 positive lymph nodes. This conclusion should be taken into account when deciding the appropriate treatment of tumors containing neuroendocrine components. Lymph node metastasis of rectal NEN is mainly associated with the number of lesions, the differentiation degree, and the lymphovascular invasion. Multiple lesions can increase the risk of metastasis. A well-differentiated NET, especially the NET G1, rarely metastasizes. In our case, multiple lesions increased the metastasis risk to some extent. Moreover, combined with the hypothesis of the mechanism of a composite tumor, we speculate that the occurrence of lymph node metastasis of NET G1 may be related to the change in the surrounding environment caused by the coexisting adenocarcinoma component. More data are needed to confirm this possibility.

According to the report, in 169 patients with MiNENs or tumors with focal (non-)neuroendocrine component (<30%), only 16% were diagnosed by biopsy; the rest was confirmed through postoperative pathology (6). Thus, it is difficult to diagnose only with biopsy, and this also limits the choice of optimal treatment modalities. Treatment options for tumors containing two types of components are often complex due to their rarity, morphologic diversity, different primary origins, and a low diagnostic rate of preoperative biopsy. Individualized treatment strategies are required. If the neuroendocrine component is poorly differentiated, the tumor is usually treated according to the treatment standard corresponding to pure NEC. Alternatively, when the non-neuroendocrine component is the most represented one and presents more aggressively, the standard of care for epithelial tumors should be applied (8). MANETs have an excellent prognosis, thus not requiring large surgical resection (17). Laenkholm et al. (18) suggested that regardless of the tumor composition, patients should be evaluated for surgical treatment, as it is related to the best prognosis. Patients with disseminated mixed tumors have a very poor prognosis and usually need adjuvant chemotherapy. However, only a few studies on the effect of surgery exist. All of the studies are observational and hold a risk of selection bias, which may overestimate the beneficial effect of surgery (19). In our case, the sigmoid tumor was composed of adenocarcinoma and NET G1, which is a rare mix. Considering that the lesion in the sigmoid was mainly adenocarcinoma with lymph node invasion and the patient was also complicated with colorectal M-NETs, we performed intestinal segment resection on him. Although the main component of the tumor was adenocarcinoma, the component of lymph node metastasis was NET G1, so the prognosis may be better than that of adenocarcinoma metastasis. The patient is still alive and well 13 months after surgery, and further prognosis requires continuous follow-up. A good prognosis also depends on a timely operation. Nevertheless, radical surgery is currently the only hope for a cure and prolonged survival. Regular and adequate follow-up is essential to help rule out metastasis and assess prognosis.

4 Conclusion

Tumors composed of two histological components have distinct biological behavior. It is important to elucidate their mechanisms of tumorigenesis by immunohistochemical and gene detection investigations. Rectal M-NETs are associated with a high risk of lymph node metastasis, and treatment should be more radical. In mixed tumors, even well-differentiated NET G1 may metastasize, which may be due to the non-neuroendocrine component that alters the peritumoral environment. Radical surgery is the only hope for a cure currently, and individualized treatment strategies are required.

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 human participants were reviewed and approved by the ethics committees of Beijing Friendship Hospital, Capital Medical University. 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

SP and JGS researched the data and wrote the manuscript. KZ and JW reevaluated the pathological results and provided figures for this article. HYZ, YJW, and PL contributed to the discussion. YZ and YDW guided the writing ideas and reviewed the manuscript. All authors agree to be accountable for the content of the work. All authors contributed to the article and approved the submitted version.

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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.

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Case report: POLE (P286R) mutation in a case of recurrent intestinal leakage and its treatment

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In recent years, although new drugs and molecular markers have been used to treat metastatic colorectal cancer, there has been little progress in the immunotherapy of advanced colon cancer. The development of sequencing and multiomics technology helps us classify patients more accurately, and then find patients who may benefit from immunotherapy. The development of this advanced technology and immunotherapy based on new targets may herald a new era in the treatment of metastatic colorectal cancer. It is well known that colorectal cancer with dmmr/msi-h phenotype is sensitive to immunotherapy, yet the POLE mutation is the MSS phenotype in colorectal tumors but is also an effective target for immunotherapy. This paper describes a case of recurrent intestinal leakage that required multiple surgical procedures. A high-grade colon adenocarcinoma was identified on surgical histopathology after 18 months, and bevacizumab combined with oxaliplatin and capecitabine proved ineffective against this cancer. An analysis of gene expression indicated that POLE (P286R) mutation, TMB 119.333 mutation per 100 MB, and immune checkpoint inhibitor treatment had a significant impact. This case reminds us that the existence of malignant tumors should be considered for patients with repeated intestinal leakage, and emphasizes the importance of gene detection in the treatment of malignant tumors and the significance of POLE mutations in colorectal cancer.

KEYWORDS

POLE (P286R) mutation, recurrent intestinal leakage, molecular markers, metastatic colorectal cancer, immunotherapy

Background

Colorectal cancer (CRC) is a malignant tumor with a high mortality rate. Based on global cancer statistics in 2020, CRC was ranked third among cancers and the second leading cause of cancer-related deaths among men and women (1). Advanced CRC Patients remain virtually incurable despite advances in chemotherapy and targeted therapy. The use

of immunotherapy has made it possible to curtail disease and achieve long-term disease-free survival.

Intestinal leakage is a rare complication that is primarily associated with inflammatory bowel diseases, intestinal ulcers, intestinal tuberculosis, colorectal cancer, and abdominal surgery. The presence of a fistula in cancer patients indicates an advanced stage of the disease and increases mortality and incidence rates (2). In clinical practice, colorectal fistula is a common symptom of colon cancer. It is easy to misdiagnose early ascending colon tumors because they lack typical clinical manifestations, and the lumen of the ascending colon is large. In the literature, cecal or right colorectal cancer has been implicated as a cause of acute enteritis in 2%–15% of cases (3–5).

In the treatment of advanced cancer, cytotoxic inhibitors of lymphocytic death such as the programmed cell death 1 (PD-1) receptor inhibitor and anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) antibody have revealed impressive effectiveness. Studies have identified several positive predictive markers of immune checkpoint inhibitors ICI, including high-level microsatellite instability (MSI-high), overexpression of programmed cell death-ligand 1 (PD-L1), and elevated tumor mutation burden (TMB) (6). Genes encoding DNA polymerase epsilon (POLE) and delta 1 (POLD1) are crucial for proofreading and fidelity of DNA replication (7). Some case reports have demonstrated a correlation between POLE or POLD1 mutations and the clinical effectiveness of ICI (8, 9).

A POLE-mutated metastatic CRC refractory to both chemotherapy and targeted therapy was treated with a PD1 inhibitor (Terriprizumab) with complete clinical and pathological recovery without toxicity within a relatively short time frame. Advanced colorectal carcinomas are rarely present in this scenario.

Case report

A 34-year-old male presented with abdominal pain and distension with no previous history of colon cancer. His father died of colon cancer at the age of 50 years and received conservative treatment in the internal medicine department of a local hospital on 2 January, 2019. Due to the symptoms of peritonitis, an exploratory laparotomy was performed on 11 January, 2019, which revealed necrosis of the small intestine (90 cm) and a large amount of bloody fluid and intestinal contents in the abdominal cavity. The final procedure was an ileostomy along with abdominal drainage, which was considered an intestinal fistula. The patient was referred to our hospital's intestinal fistula specialist on 27 May, 2019. During the colonoscopy, there was widespread polypoid hyperplasia (>100), no neoplastic spaces were found, and the patient underwent two exploratory laparotomies and abdominal irrigations for repeated intestinal leakage in the following year. However, there was no evidence of malignancy in postoperative pathology; however, purulent fluid continuously oozed from the incision. During this period, the patient repeatedly had a high fever of 39°C, and his weight gradually decreased by 25 kg, but he did not vomit blood, show blood in his stool, or suffer jaundice.

On 20 May, 2020, a colonoscopy was performed again, and new growths were found around 3/4 of the circumference of the transverse colon wall approximately 60 cm from the anus, which was brittle, hard, and prone to bleeding. Additionally, more than 100 flat polyps with a size of about 0.2–0.5 cm were found in each segment of the colon. Serologically, carcinoembryonic antigen and carbohydrate antigen 19-9 were significantly elevated. The abdominal CT scan depicted an unclear boundary between the middle abdomen and ascending colon, local invasion of the head of the pancreas, and an enhanced scan displayed significant enhancement (Figure 1). On 5 June, 2020, the patient underwent a retroperitoneal tumor resection. During the operation, a 0.5×0.5 cm fistula was found at the colon anastomosis, and a 10×10 cm bossing could be touched in the ascending colon and invaded the head of the pancreas, making it difficult to move the fixation (Figure 2A). The postoperative pathology illustrated ulcerative moderately differentiated adenocarcinoma with a size of 6 *4.3*3 cm (Figures 2B, C). Cancer tissue infiltrated the intestinal wall and was located in the peripancreatic tissue, but no cancer tissue was found in lymph node 0/25.

On 16 June, 2020, PET/CT scans demonstrated a soft tissue mass (9.7*4.3 cm) in the middle abdomen, considered a malignant

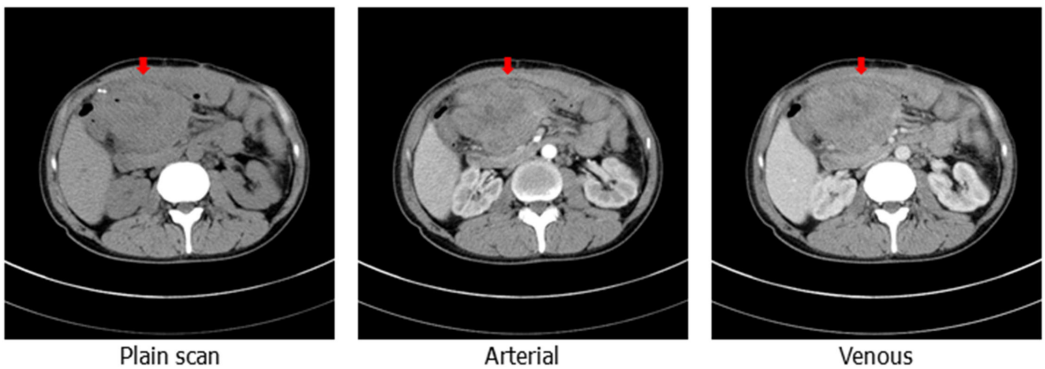

FIGURE 1
Computed tomography of the abdomen showing the upper abdominal mass with an unclear boundary with the surrounding intestinal canal, obvious enhancement can be observed on enhanced scanning (the red arrow shows the location of the package).

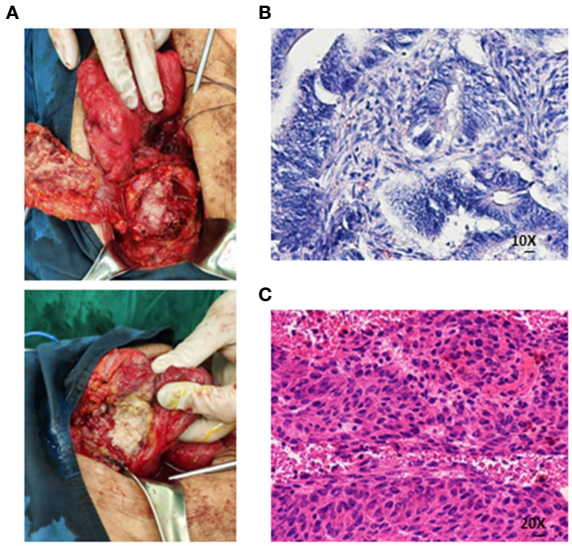

FIGURE 2
(A) The boundary between the mass and the surrounding intestine was unclear, and the central necrosis of the tumor was the flesh of fish-like.
(B, C) Medium-differentiated adenocarcinoma on histopathological assessment of the resected specimen (Both are hematoxylin-eosin staining).

tumor. Microsatellite instability (MSI) testing through immunohistochemistry demonstrated that the tumor was microsatellite stable (MSS). Next-generation sequencing (NGS) applying the Illnuina NovaSeq6000 (ACCB Biotech) using the patient's archival tumor tissue and blood showed RAS wild-type, POLE mutation, tumor mutation load 119.9 mutation/MB (Figure 3). A combination of oxaliplatin and fluorouracil chemotherapy was performed every two weeks for six cycles. According to the Response Evaluation Criteria In Solid Tumours (RECIST) criteria, the patient was deemed to have stable disease on CT at weeks 4/8, but the patient was assessed with progressive disease (PD) by CT at week 12. A genetic profile consistent with genetic instability (high tumor mutational burden, POLE mutation) and clear progression of FOLFOX led to the use of terriprizumab and bevacizumab on November 24, 2020. After one treatment cycle, the patient developed a soft abdominal mass protruding from the skin surface. A large amount of purulent fluid was extracted through the puncture and drainage, which healed with repeated

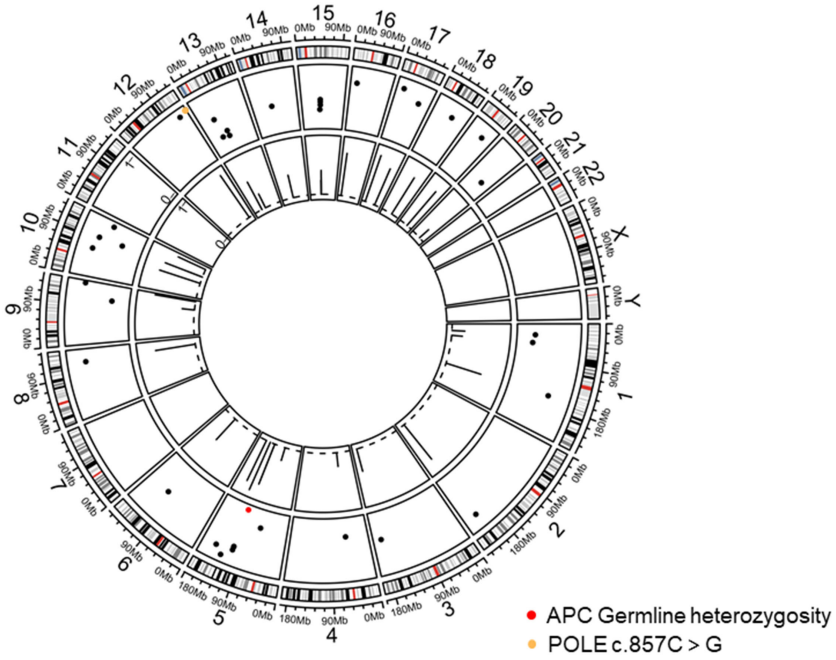

FIGURE 3
Tumor chromosome copy number map. The red dots display APC germline mutations on chromosome 5 and POLE mutation on chromosome 12.

irrigation and drainage. After two cycles of treatment, the patient's disease to was assessed partially responded (PR) by CT (Figure 4A), and the carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 50 levels returned to normal (Figure 4B). At the time of this report, the patient had a progression-free survival of 18 months, with ongoing clinical benefits and no immune-mediated toxicities. The case timeline is presented in Figure 5. Consent for publication was obtained from the patient for her case report.

Discussion

Complications of colon cancer can include obstruction, bleeding, and perforation. The clinical manifestation of the disease has been considered a prognostic factor for incidence and mortality (10). Early diagnosis and active surgical treatment may be the key to improving the prognosis of patients. Abscesses have been reported after colorectal cancer perforation. Shang Zhi Han (11) reported on three patients with abscess perforation caused by colon cancer and found that the tumor lesions were located in the right colon. The ascending colon has a large diameter, and the stool tends to be thin. Right colon cancer exhibits fewer symptoms of intestinal obstruction in the early stages than left colon cancer. Colon tumors can mimic abdominal diseases, with a broad spectrum of symptoms. The incidence of colorectal cancer perforation is 2.6%–7.8%, which is a rare case (12).

This case report describes a patient who developed a local abscess perforation. One and a half years after treatment for intestinal leakage, colon cancer was finally diagnosed, making this the most prolonged interval between onset and diagnosis reported in the literature. Additionally, other studies have shown that patients with colorectal tumor perforation have a higher survival rate due to better staging of the lymph nodes (13). This case report revealed a sizeable local mass but no metastases in the surrounding lymph nodes, consistent with the reported literature.

Before diagnosis, no tumors were found in two separate colonoscopy examinations, which is rare in clinical practice. According to studies on the value of colonoscopy, it may lead to interval cancers (ICs) before planned follow-up, accounting for 9% of all CRC diagnoses. The etiology of ICs can be divided into three categories: (1) missed diagnosis, (2) incomplete resection of advanced adenoma, and (3) faster tumor growth rate than that of sporadic colorectal cancer (14). Our case falls into the first category since it seemed premature, and new cancer had appeared, which confirms the experience (15). Willamson B (16) analyzed 39 ICs and found that a third of the 39 ICs had previously been reported to be significantly missed before the recent surgical report after the "difficult test". Similarly this patient did not continue the first

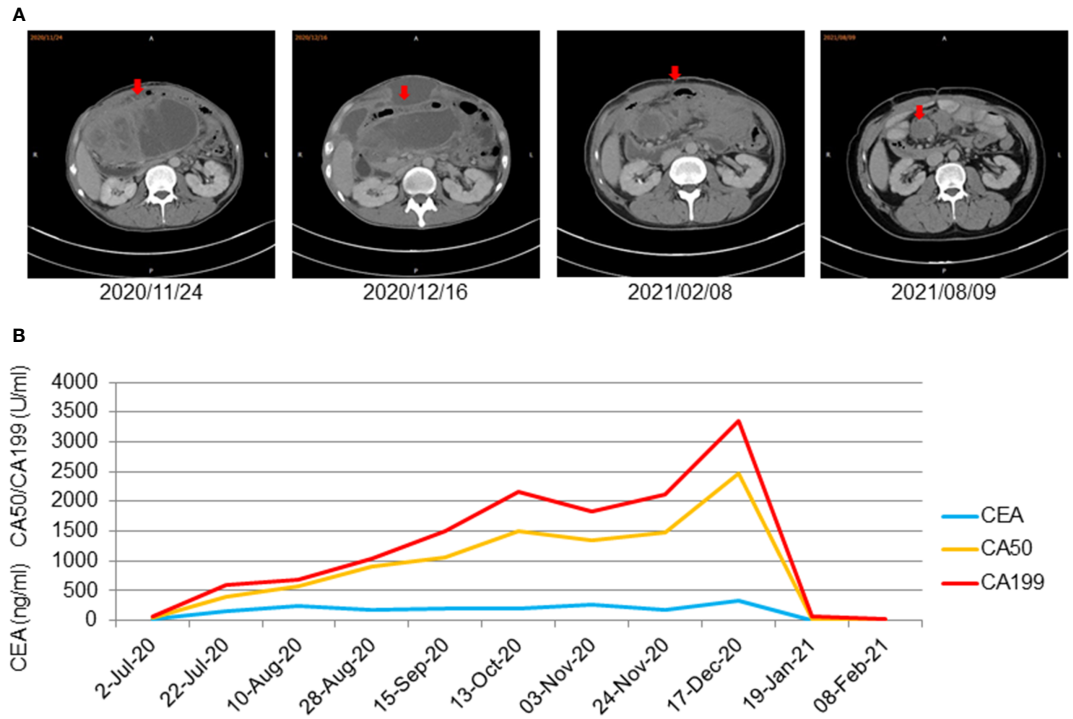

FIGURE 4
(A) CT showed that the abdominal mass decreased gradually after using treprizumab and remained stable for a long time (the red arrow displaysthe package's location). **(B)** Significant decrease of tumor markers of metastasized cancer under therapy with terriprizumab at 240 mg and bevacizumab at 500 mg every three weeks. Significant decrease of tumor markers of metastasized cancer under therapy with terriprizumab at 240 mg and bevacizumab at 500 mg every 3 weeks.

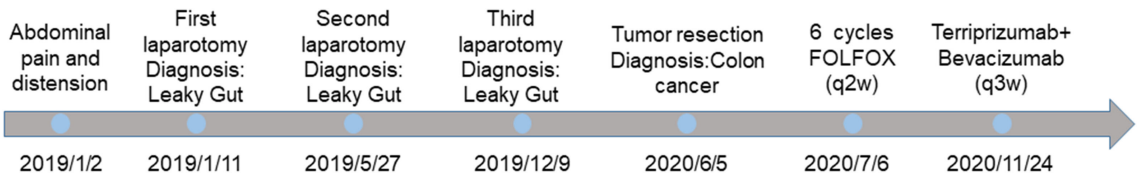

FIGURE 5
The case lifetime.

colonoscopy into the intestine due to the large angle at the point where the tube entered the enteric cavity at about 25 cm. This finding is consistent with those reported in the literature. An incomplete exam can lead to missed opportunities, which is also risky. Therefore, the monitoring interval was significantly shortened for those who worked hard and paid meticulous attention to the observation.

Over the past few years, molecular-targeted therapy has become increasingly important in treating advanced colorectal cancer. Keynote 177 trial results depict that pembrolizumab has been approved as a first-line treatment for metastatic colorectal cancer with MSI-high (17). A combination of ipilimumab and nivolumab has also been approved for metastatic colorectal cancer with high MSI or mismatch repair defects. Patients with a POLE gene mutation have been reported to benefit from immunotherapy, suggesting that the POLE gene may be a potential marker for CRC treatment (18, 19).B.J-C. Rousseau et al. (20) reported the first clinical trial to evaluate PD1 in MMR tumors with POLE mutation and found that nivolumab activity appeared in pathogenic mutations of the POLE, such as P286R, V4111L. The POLE mutation site in our case is P286R, which is consistent with the literature, indicating its sensitivity to immunotherapy. The mutation rates of somatic POLE-driving genes are reported to be 2.60% (Zhejiang University cohort), 1.50% (TCGA cohort), 1.00% (Japan cohort), and 1.00% (lancet cohort), respectively. The POLE driver gene mutation significantly increased mutation burden (average TMB of Zhejiang University: 217.98 mut/MB; 203.13 mut/MB in TCGA) (21). The mutation rates of the somatic POLE driver genes are reported to be 2.60% (Zhejiang University cohort), 1.50% (TCGA cohort), 1.00% (Japan cohort), and 1.00% (Lancet cohort). Extreme drive gene mutations significantly increased the mutation burden (average TMB of Zhejiang University: 217.98 mut/MB; 203.13 mut/MB in TCGA) (21). Wang et al. evaluated POLE/POLD1 nonsynonymous variants as biomarkers of immune checkpoint inhibitor treatment outcomes and concluded that they were independent factors for prolonged overall survival after adjustment for microsatellite stability and cancer type (22). It is still unclear why POLE mutations benefit from immune-targeted therapy. Most scholars agree that POLE mutations lead to a high TMB. Mutations in this gene, which contribute to proofreading and fidelity of DNA replication, can lead to a phenotype known as an ultramutator, with a high burden of single-nucleotide variants among human cancers. In many reports, the number of mutations (per Mb) in POLE category tumors is significantly higher than in common hypermutators (23, 24). This category is characterized by a staggering number of mutations and early-onset colorectal or uterine tumors compared to the common hypermutator. In our case, we also found high TMB, probably due to long-term immunotherapy.

The patient's father died of colon cancer and was diagnosed with multiple adenomatous polyps, no other person in the family has had a similar disease; however, genetic testing was unavailable. Patients with a typical familial adenomatous polyposis (FAP) phenotype have germline APC mutations. In the population without colectomy, 90% of individuals develop CRC during their lifetime. Children older than five years have a higher risk of developing duodenal cancer, pancreatic cancer, medulloblastoma, papillary thyroid cancer, and hepatoblastoma (25). Even though FAP is inherited by autosomal dominant inheritance, more than 30% of patients with APC germline mutations have no family genetic history, and it is speculated that those with index mutations have additional mutations (26). Germline pathogenic variants that affect exonuclease domains (POLE and POLD1) have a high risk of polymerase proofreading-associated polyposis (PPAP). In a national study in the UK which screened 2349 probands, the cumulative incidence of CRC was estimated to be approximately 90% in heterozygotes of the variant pol and 50% in POLD1 (27). NGS revealed the presence of an APC S996fs germline mutation. The mutation was an APC frameshift mutation, and the processing mechanism was evident. Accordingly, it is classified as a possible pathogenic mutation, according to American College of Medical Genetics and Genomics (ACMG). Germline mutations in APC lead to 95% of colorectal cancers (28, 29). Studies have demonstrated that somatic mutations in POLE and PTEN are the main trigger factors of tumorigenesis in tumors with defective POLE proofreading (23), which aligns with the patient's gene analysis. Patients' children should undergo next-generation sequencing tests, enteroscopy evaluations, and follow-ups; however, the patient refused because his children were too young.

Conclusions

In this case report, the clinical presentation and management were unique. The patient was diagnosed with colon cancer after a long time due to inadequate prediction of potential malignancies. Inaccurate diagnosis without recognizing the underlying malignancy can lead to incomplete treatment. Colorectal cancer is a clinically and molecularly heterogeneous disease that requires comprehensive genetic testing to detect rare genetic mutations, such as POLE mutations, to detect tumors harboring an ultramutator phenotype, especially in patients refractory to standard

chemotherapy. Further research is warranted to determine whether immuno-oncology therapy could be considered a first-line treatment for patients with cancer harboring POLE 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

Ethical review and approval was not required for the study on human participants 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

XC and YC provided the idea of the review. DX and GF wrote the manuscript. All authors read and approved the final manuscript.

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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

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Case Report: Intramural colonic signet ring cell carcinoma presenting as intestinal pseudo-obstruction: A case presentation and review of the literature

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Colorectal cancer (CRC) is the third most common cancer in the world. Other than adenocarcinomas, exceptional tumors of the colon and rectum represent a neglected clinical issue due to their rarity. Signet ring cell carcinoma (SRCC) is a rare subtype of CRC and has an extremely poor prognosis due to its advanced stage at diagnosis. Here we report a rare case of colorectal SRCC manifested as recurrent intestinal obstruction with a negative colonoscopy. Finally, he was diagnosed with signet ring cell carcinoma of the colon by postoperative pathology. It emphasized the special feature of intramural tumor growth without penetrating the mucosa in SRCC, which requires timely surgical intervention to avoid delay in diagnosis and treatment.

KEYWORDS

signet ring cell carcinoma, colorectal cancer, incomplete bowel obstruction, laparoscopic right hemicolon carcinoma radical resection, prognosis

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world and ranks as the second leading cause of cancer-specific death globally (1). Adenocarcinoma (AC) represents the most frequent form of CRC, accounting for about 98% of tumor histological types. However, other than adenocarcinomas, exceptional tumors of the colon and rectum represent a neglected clinical issue due to their rarity.

Primary signet-ring cell carcinoma (SRCC) is more likely to be seen in the stomach, which has been the fourth most common cause of cancer-related mortality worldwide (2). Colorectal signet ring cell carcinoma (SRCC) is rare and only accounts for about 1% of CRC subtypes with poor prognosis (3). It has the typical appearance of a "signet ring"

because the nuclei are pushed to the periphery of the cell by the intracytoplasmic mucinous component. Formally, a tumor is labeled SRCC when >50% of tumor cells show a "signet ring," whereas ACs with <50% signet ring cells are still classified as ACs with a signet ring cell component (4). Different from AC with morphology of intraluminal mass, colorectal SRCC often presents a markedly narrowed lumen due to diffuse circumferential thickening of the bowel wall and sometimes has an association with inflammatory bowel diseases (5, 6). Previous studies analyzed the primary symptoms of patients with colorectal SRCC at diagnosis and suggested its special features, like atypical and delayed clinical manifestations, a younger age at onset, and high false-negative rates of endoscopic biopsy, may result in frequently advanced stages and a poor prognosis in colorectal SRCC (7–9). In CRC, SRCC is generally considered to be associated with microsatellite instability-high (MSI-H), a well-established prognostic biomarker for better survival in patients with localized tumor stages (10). However, signet-ring cell carcinoma is associated with shorter survival in CRC patients, moreover, SRCC is associated with higher mortality even when the signet-ring cell component is less than 50% (10, 11). The therapy recommended for colorectal SRCC is typically palliative chemotherapy, which is identical to that recommended for AC (12).

In this case, we reported that a 54-year-old man who developed repeated bowel obstruction with a negative endoscopic biopsy was finally diagnosed with colorectal SRCC by postoperative histopathology. It emphasized the special feature of intramural tumor growth without penetrating the mucosa in SRCC, which required multiple examinations and timely surgery in case of a delay in diagnosis.

Case presentation

A 54-year-old man was admitted to the People's Hospital, Lahu-Wa-Bulang-Dai Autonomous County of Shuangjiang, Lincang, Yunnan, China, complaining of abdominal pain, diarrhea, nausea, and vomiting for more than 1 month. He had presented abdominal pain accompanied by yellow, watery diarrhea (two to three times a day) intermittently for the past month, and vomiting could relieve these symptoms at an early stage. However, his symptoms of abdominal pain and vomiting have been getting worse gradually over the last week. Thus, he was hospitalized at the People's Hospital of Shuangjiang on 12 August 2021.

He is nondrinking, nonsmoking, and has a history of renal insufficiency (serum creatinine level: 173.1 umol/L, n.v., 50–90 umol/L) due to renal calculus for 2 years. He has no family history of cancer or other gene-related diseases. On admission, a physical examination showed mild tenderness in the whole belly and a fading gurgling sound. Routine blood tests, coagulation function, hepatitis B, HIV, syphilis, liver function, myocardial enzymes, electrolytes, blood lipids, and glucose were all normal. Laboratory tests revealed slight increase in squamous cell carcinoma (SCC, 4.79 ng/ml; normal value (n.v.), <2.5 ng/ml), but carcinoembryonic antigen (CEA, 0.962 ng/ml; n.v., <5.093 ng/ml), carbohydrate antigen (CA)-199 (6.82 IU/ml, n.v., <37 IU/ml), CA-50 (2.24 IU/ml; n.v., <25 IU/ml), CA-242 (2.09 IU/ml; n.v., <20 IU/ml), CA-724 (1.77 IU/ml; n.v., <6 IU/ml), alpha-fetoprotein (AFP, 1.61 IU/ml; n.v., <6.05 IU/ml), neuron-specific enolase (NSE, 2.51 ng/mL; n.v., <6 ng/ml), abdominal computed tomography (CT) examination in emergency was performed to him and suggested intestinal obstruction (Figures 1A, B). As he presented no fever or chill and maintained diarrhea (three to four times a day), we provided conservative treatment after getting informed consent. Then he was given fasting, gastrointestinal decompression, empirical anti-infection therapy (ampicillin, 4 g, q12 h), and nutritional support for 5 days. When his obstructive symptoms were relieved, he underwent gastroscopy and colonoscopy during hospitalization. Gastroscopy showed no obvious abnormalities, and colonoscopy suggested ileocecal intraluminal stricture (Figures 2A–F), which made us unable to observe the end of the ileum. We recommended further CT enterography for this patient, but he refused this examination due to the potential risk of recurrent intestinal obstruction. No evidence of vasculitis, fungal elements, tuberculosis, or parasitic infection was found in further laboratory tests. Endoscopic biopsies of the ileocecal region revealed negative

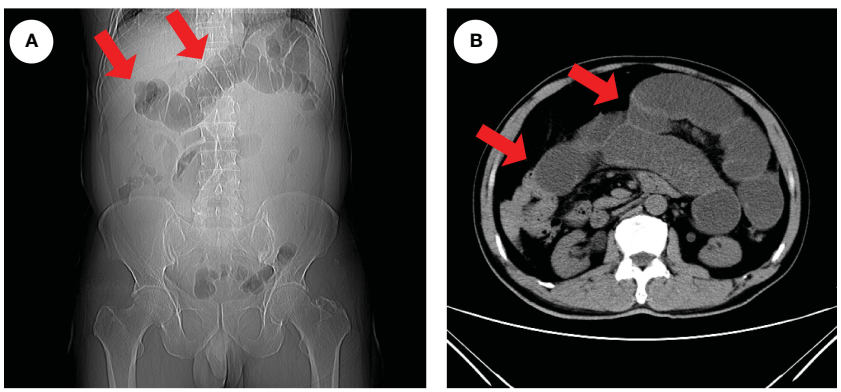

FIGURE 1
Radiologic findings of intestinal obstruction. An abdominal CT examination in an emergency was performed on the patient and revealed extensive dilatation of the transverse colon (red arrows), indicating proximal intestinal obstruction **(A, B)**.

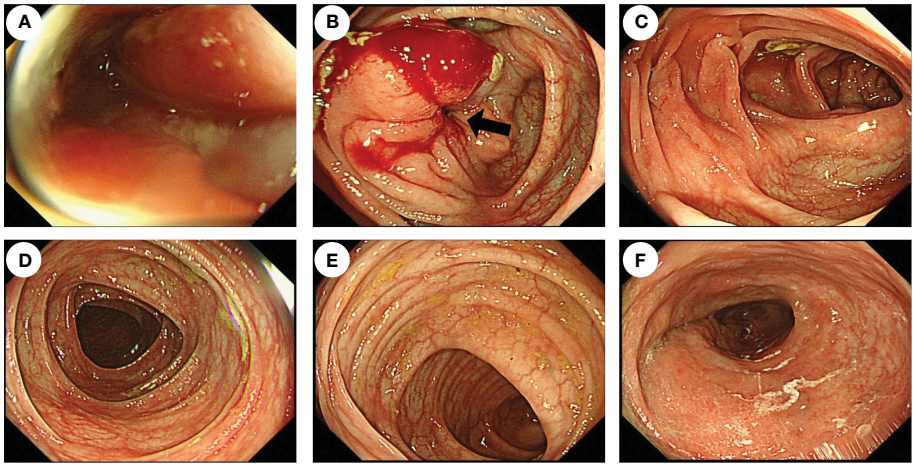

FIGURE 2
Endoscopic features of the patient before surgery. Colonoscopy showed that the cavity was obviously narrow in the ileocecal region (black arrow), which made the endoscope unable to pass through **(A, B)**, but there were no obvious abnormalities in the ascending colon **(C)**, transverse colon **(D)**, descending colon **(E)**, or rectum **(F)**.

histopathology. Thus, he was discharged from the hospital on 20 August 2021, and it was suggested that he have a liquid diet for at least two weeks and be followed up in an outpatient clinic every month. However, he presented with abdominal pain and diarrhea (six to eight times a day) again in 1 month, and it was even worse than before. Immediately, he was admitted to the Department of Emergency at the People's Hospital of Shuangjiang and received an abdominal CT examination on 24 September 2021. CT examination revealed a thicker intestinal wall than normal in the ileocecal region, indicating diverticulitis or tumor (Figures 3A–C). Radiographic examinations of the head, chest, and abdomen excluded distant metastases. Therefore, the patient received laparoscopic right hemicolon carcinoma radical resection in the Department of Surgery on 29 September 2021. Postoperative pathology revealed that it is a signet ring cell carcinoma with a size of 3 × 2.5 cm among moderately-to-poorly differentiated AC in the right colon (Figures 4A–C). SRCC occupies about 80% of the whole tumor with no heterogeneity (Figure 5A). The tumor invaded the whole layer of the colonic wall and partly nerves. Tumor thrombus can be found in vessels. No cancer invasion was found along the cutting edges of the surgical specimen. Immunohistochemistry staining showed E-Cadherin (+), MLH1 (+), MSH2 (+), MSH6 (+), and PMS2 (+), which indicates it is MSL-low (MSI-L) cancer (Figures 5B–F). Metastasis was found in the pericolonic lymph nodes (5/17). Afterwards, he was given regular chemotherapy with the FOLFOX strategy. He received a reexamination, including a colonoscopy and abdominal CT, on 8 February 2022, which revealed no obvious abnormalities. The patient was followed up in the Department of Gastroenterology at the People's Hospital of Shuangjiang until the completion of the article (July 2022) with a good prognosis.

Discussion

Colorectal SRCC is a histologically rare subtype of colorectal cancer (~1%) with atypical clinical manifestations, different pathological features, and indistinguishable biological behaviors compared to AC (13, 14). Unlike the intraluminal mass in AC, the patient with colorectal SRCC in this case appears to have thickening of

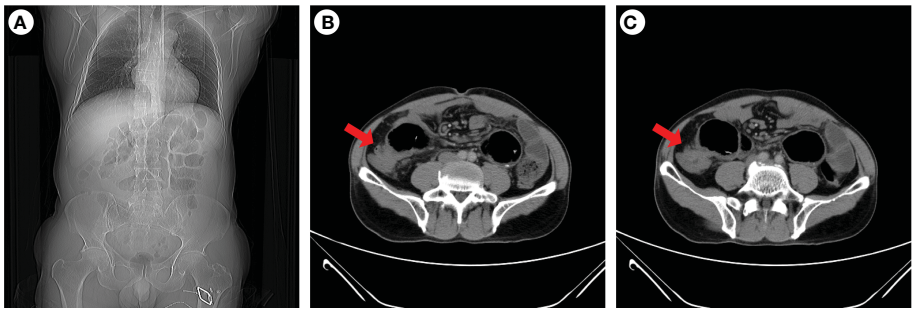

FIGURE 3
Abdominal CT examination of the patient when intestinal obstruction occurs again. Coronal images indicated gas and fluid accumulation in the intestine **(A)**, and transverse images revealed ileocecal intestinal wall thickening **(B, C)**. The red arrow indicaes the ileocecal junction.

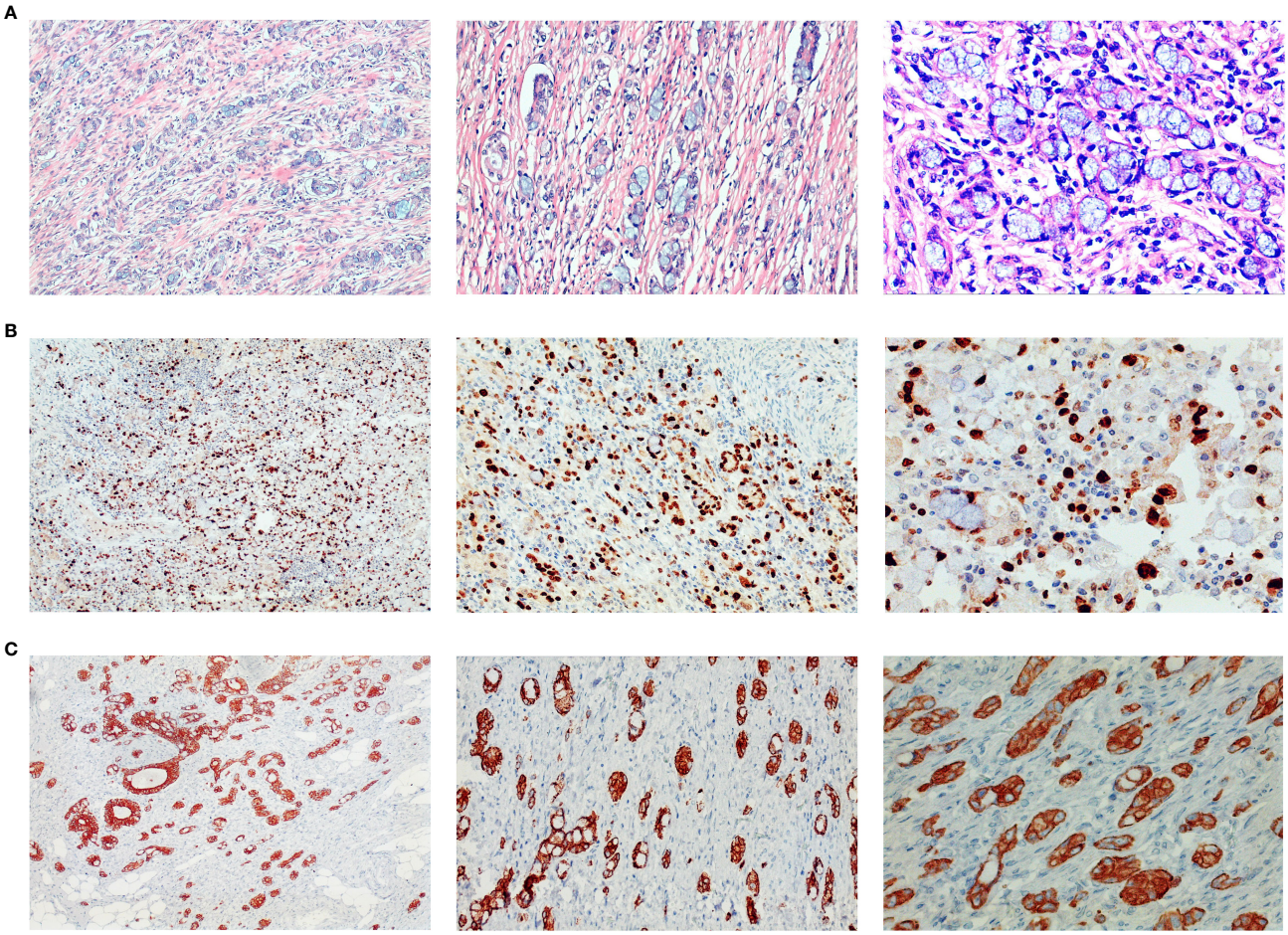

FIGURE 4
Histopathology of surgical specimens. Postoperative pathology showed signet ring cell carcinoma among moderately-to-poorly differentiated AC in the right colon. Hematoxylin and eosin staining showed signet-ring cell carcinoma **(A)**, and further immunohistochemistry staining showed ki-67 (>80% +) **(B)**, and CK8 (+) **(C)**. Pictures were magnified ×100 on the left, ×200 in the middle, and ×400 on the right.

the bowel wall in the right colon with a markedly narrowed lumen, which was suspected to be inflammatory bowel disease in the first place. As his symptoms of intestinal obstruction gradually worsened, he received an operation and was finally diagnosed with colorectal SRCC with AC according to postoperative pathology at the age of 54. Previous population-based studies revealed a mean age of about 65 years old at onset for colorectal SRCC, which is 3.5 years earlier than that of AC (3). However, the patient in this case was diagnosed much younger (54 years old) than the mean age (65 years old) for colorectal SRCC, which reminds clinical physicians to be on alert for colorectal SRCC with atypical features including a younger age at onset, clinical manifestations of incomplete intestinal obstruction, and negative results of endoscopy (6). Surgical treatment is necessary for patients with recurrent incomplete intestinal obstruction at a relatively young age.

The overall prognosis of colorectal SRCC is extremely poor, which may be due to the advanced stage at diagnosis (15, 16). SRCC was associated with worse 5-year survival significantly compared with AC in a population-based study including 1,972 colorectal SRCC cases. The survival difference was prominent at stage III (17). There were also various studies reporting that SRCC histology is an independent adverse prognostic factor after adjustment for covariates including tumor stage and location (10, 18). In CRC, MSI-H, or mismatch repair deficient (dMMR), is a well-established prognostic biomarker for better survival in SRCC patients with localized cancer stages, but SRCC is associated with shorter survival compared with other CRC patients (8, 10). It was reported that undefined postoperative adjuvant chemotherapy improved survival time in 936 stage II–III patients (19). The patient in this case underwent routine chemotherapy postoperatively according to a previous report that SRCC benefitted comparably from adjuvant fluorouracil-based chemotherapy compared with AC (17). He survived for 10 months until the time when this article finished with a good prognosis. We will continue to follow up in the future. It emphasized the special feature of intramural tumor growth without penetrating the mucosa in SRCC, which requires prompt operation in case of a delay in diagnosis. It gives us a good lesson that clinicians need to be highly alert to the occurrence of rare

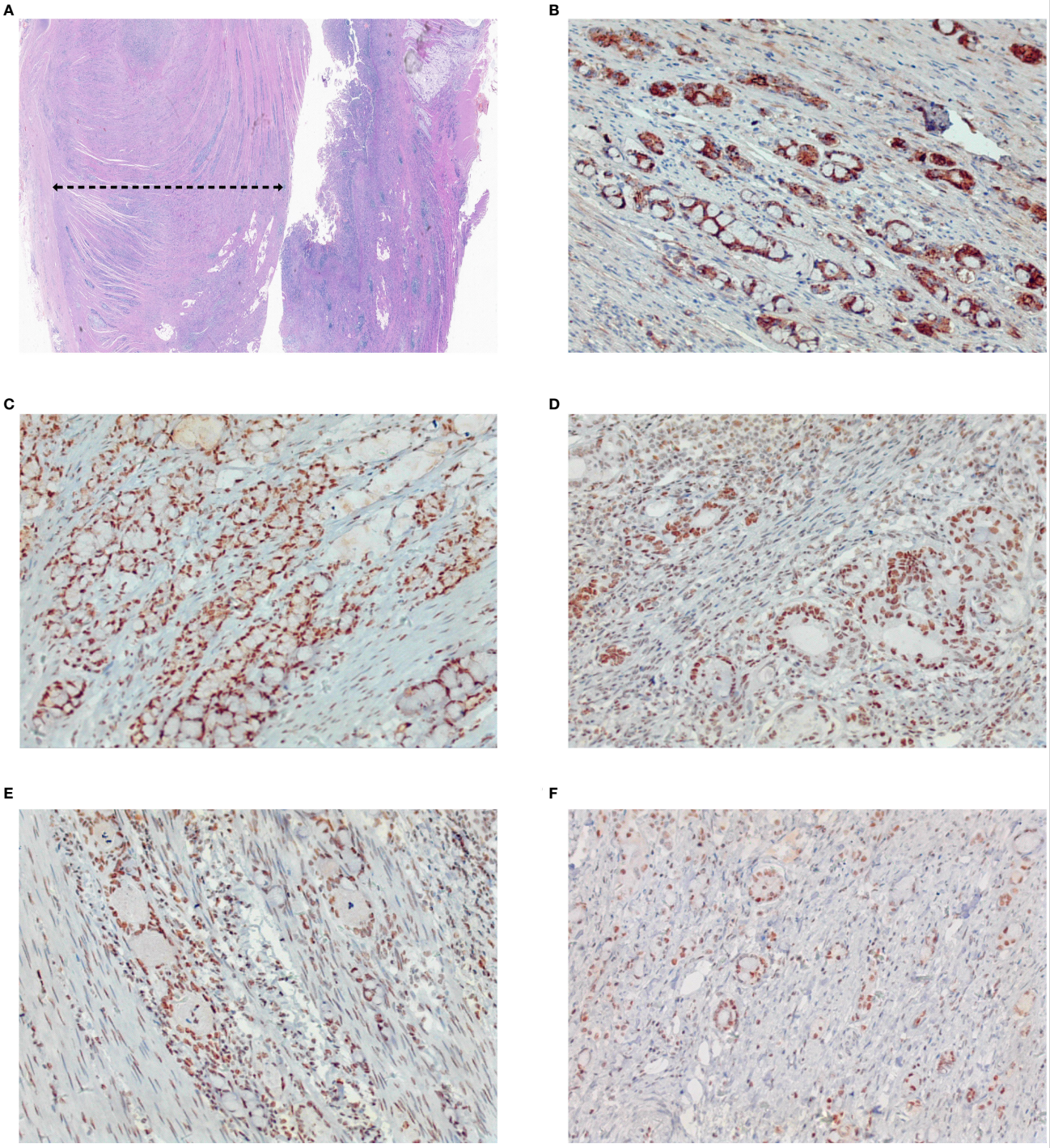

FIGURE 5
Pathological aggressiveness and microsatellite instability of the tumor. The tumor occupies about 80% of the whole tumor **(A)**. Immunohistochemistry staining showed E-Cadherin (+) **(B)**, MLH1 (+) **(C)**, MSH2 (+) **(D)**, MSH6 (+) **(E)**, and PMS2 (+) **(F)**, which indicates it is microsatellite instability-low (MSI-L) cancer. Original magnification ×4 for **(A)**, and magnification ×200 for **(B–F)**.

tumors in patients with recurrent episodes of intestinal obstruction with negative endoscopy. Meanwhile, it is necessary to consider surgical intervention in time and pay close attention to postoperative pathology.

In conclusion, this article reported a rare case of colorectal SRCC manifested as recurrent bowel obstruction and a negative result of an endoscopic biopsy. It emphasized the special feature of intramural tumor growth without penetrating the mucosa in SRCC, which requires timely surgical intervention to avoid delay in diagnosis and treatment. Postoperative treatment with fluorouracil-based chemotherapy may improve patients' survival time. The black dotted line refers to the tumor area.

Limitation

As a result of the patient's financial situation, there are no images of the gross specimen after surgery, nor are there positron emission tomography (PET)-CT results.

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

LF and GZ had the original idea for the article and guided treatment and management of the patient. GH and HD did endoscopy of this patient and agreed to be accountable for any questions about endoscopic work. YL, RZ, XL, and HL collected clinical laboratory data of the patient. YZ was responsible for all pathological work in this case and ensured that questions related to the accuracy or integrity of pathological staining were appropriately investigated and resolved. LF and YL wrote the article. All authors reviewed and approved the final draft of the article.

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Conflict of interest

Author YZ was employed by Kunming Jinyu Medical Laboratory 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.

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RET rearrangement-positive pancreatic cancer has remarkable response to pralsetinib: a case report

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Patients with metastatic pancreatic cancer have limited treatment options and a dismal prognosis. While *RET* fusion is rare (0.6%) in pancreatic cancer, the efficacy of RET-targeted treatment in patients with *TRIM33-RET* fusion has not been previously reported. Herein, we presented a case of a 68-year-old man with pancreatic cancer harboring *TRIM33-RET* fusion who responded remarkably to pralsetinib despite being intolerant to chemotherapy. To our knowledge, this is the first report on the clinical value of a single *TRIM33-RET* fusion in pancreatic cancer, which may benefit from the targeted therapy.

KEYWORDS

pancreatic cancer, RET fusion, pralsetinib, target therapy, RET inhibitors

1 Introduction

Pancreatic cancer has a high degree of malignancy and rapid progression. According to the latest statistics from the China National Cancer Center, the annual incidence of pancreatic cancer in China is approximately 4.29/100,000, a considerable increase from 15 years ago (1). For all stages combined, the 5-year survival rate was 5%–10% (2, 3). Chemotherapy remains the primary treatment for pancreatic cancer. However, the progression-free survival (PFS) for first-line chemotherapy in advanced pancreatic cancer patients is typically approximately 3–6 months (4). The advancement of targeted therapy has increased the number of potential benefits. Olaparib has been approved by the Food and Drug Administration (FDA) as a first-line maintenance treatment for metastatic pancreatic cancer patients with germline *BRCA1/2* mutations based on the improvement in progression-free survival demonstrated in a randomized phase III POLO trial (5). Larotrectinib and entrectinib have been approved as agnostic treatments for solid malignancies with *NTRK* fusion (6, 7). Patients harboring the *NRG1* gene fusion are sensitive to Zenocutuzumab (8). The activity of adagrasib and sotorasib in *KRAS G12C* pancreatic cancer also provides new hope for *KRAS*-mutant pancreatic cancer patients (9, 10). However, these drug-targeted genetic mutations only account for a low percentage of

pancreatic cancer cases. Therefore, it is essential to search for precision therapies based on genetic alterations for pancreatic cancer patients.

The proto-oncogene *RET* encodes a membrane receptor tyrosine kinase involved in many cellular processes, including the development of the central nervous system, peripheral nervous system, and kidney (11, 12). *RET* fusions are activated in a ligand-independent manner, promoting cancer cell proliferation and survival (13). As a result, RET fusion proteins have become an attractive target for precision medicine. RET inhibitors, such as selpercatinib and pralsetinib, have demonstrated efficacy in patients with *RET* fusion-positive tumors. The incidence of *RET* fusion in pancreatic cancer is 0.6% (14).

In this case, a *TRIM33-RET* fusion was detected through next-generation sequencing (NGS) in a patient with pancreatic ductal adenocarcinoma (PDAC) who responded well to pralsetinib.

2 Case presentation

A 68-year-old man was admitted to our hospital on 20 May 2021 due to persistent upper abdominal pain. The patient had no personal or family history of malignancy, pancreatitis, or liver disease. His serum CA 19-9 level was above 10,000 U/ml (Figure 1A), and his carcinoembryonic antigen (CEA) level was 68.7 U/ml. A CT scan revealed a 4.1 × 2.0-cm mass in the pancreatic uncinate process and a 3.8 × 2.4-cm mass in the liver (Figures 2A, B). Pathological evaluation of the tissue samples with liver biopsy indicated PDAC. Immunohistochemical (IHC) staining revealed that the cells were positive for CA19-9 and CK7 while negative for p53, CK20, AFP, and c-erbb-2. Ki-67 exhibited a 70% proliferative rate. To explore precision treatment options, a biopsy tissue sample from the patient was sent for NGS analysis using a 733-gene panel. The test was performed by a laboratory (3D Medicine Inc., Shanghai, China) certified by the College of American Pathologists (CAP), Clinical Laboratory Improvement Amendments (CLIA), and China National Accreditation Service for Conformity Assessment (CNAS). The tumor mutational burden (TMB) was 4.47 mutations/Mb, and the microsatellite status was stable. Meanwhile, a somatic *RET* fusion (*TRIM33-RET*) was detected (Figure 1B). Moreover, other pathogenic or likely to be pathogenic variations were detected, including somatic *TGFBR1* (*p.I66Yfs*9*, 23.94%) mutation, amplification of *BCORL1* (copy number = 6), and germline *RAD50* mutation (*RAD50*, *p.K722Nfs*6*). In addition, the patient was found to have wild-type variants in *HER2*, *BRCA1/2*, and *RAS/RAF*.

Based on the previous clinical research results (15–18), the patient's financial situation, genetic testing results, and guidelines, first-line chemotherapy (albumin-bound paclitaxel 200 mg/m^2, oxaliplatin 85 mg/m^2, and gemcitabine 1.4 g/m^2) was administered on 4 June 2021. However, the patient rapidly developed significant gastrointestinal toxicity and myelosuppression. Due to intolerance, the

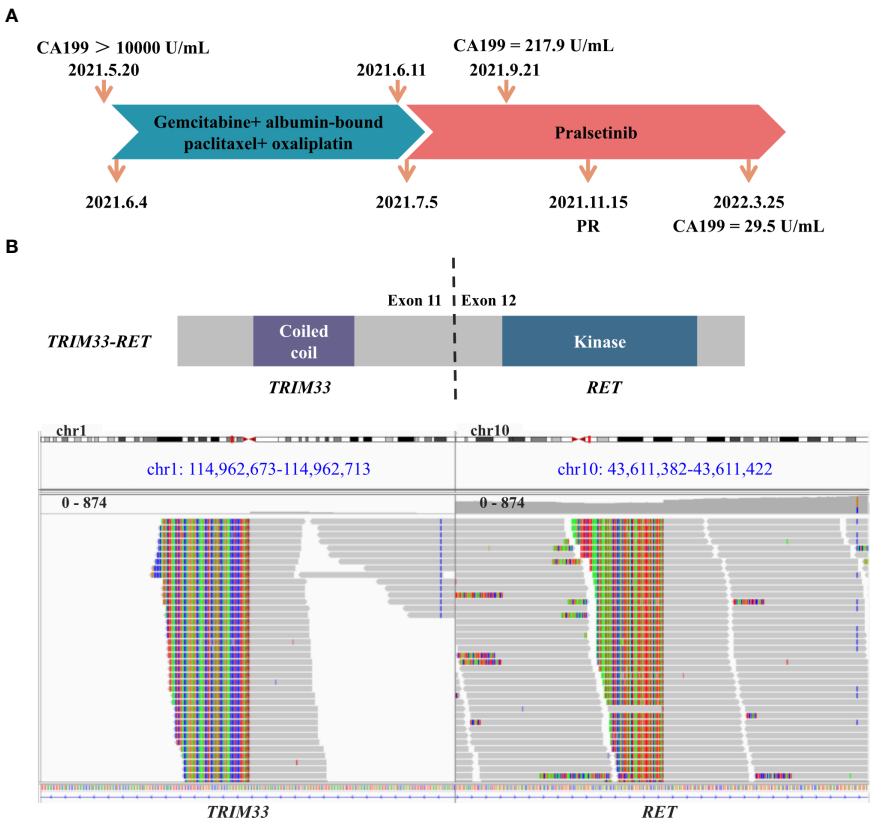

FIGURE 1
Schematic of treatment history and next-generation sequencing (NGS)-detected *RET* fusion. **(A)** The timeline of treatment and corresponding CA199 levels. **(B)** The schematic diagram and identification of the *TRIM33-RET* fusion. Sequencing reads of *TRIM33* and *RET* are visualized by the Integrative Genomics Viewer (IGV).

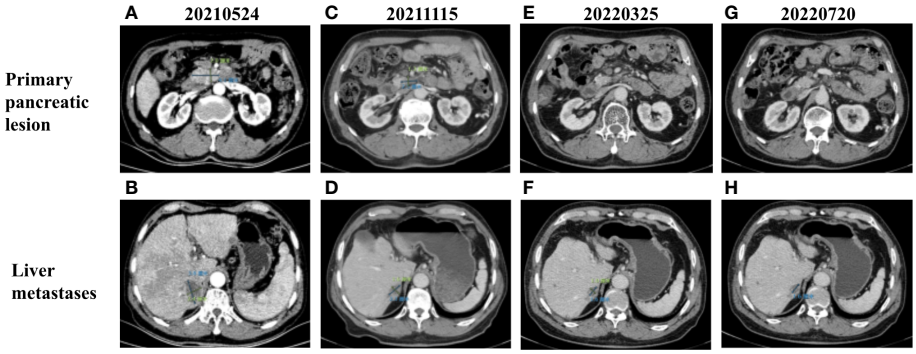

FIGURE 2
(A) CT images of primary pancreatic lesion with a size of 4.1 cm × 2 cm before treatment. **(B)** CT images of liver metastases with a size of 3.8 cm × 2.4 cm before treatment. Contrast-enhanced CT scan images completed in **(C, D)** November 2021, **(E, F)** March 2022, and **(G, H)** July 2022 demonstrating progressive decrease in the size of primary pancreatic and liver metastases.

patient only had one course of chemotherapy. Since 5 July 2021, the patient received 400 mg of pralsetinib daily. Four months later, the volume of the primary tumor decreased by approximately 39.0% (Figures 2A, C), and that of the metastases decreased by approximately 39.5% (Figures 2B, D) compared to that before treatment, and a partial response was confirmed. However, due to the adverse effect of anemia in the patient, the treatment dose was reduced accordingly. From 15 November 2021 to the present, the patient has been receiving 200 mg of pralsetinib daily for maintenance therapy. Also, the tumor biomarker cancer antigen CA199 dropped from a very high level (>10,000 U/ml) to 29.5 U/ml (Figure 1A). Currently, it was concluded that the patient reached a partial response. The patient's primary tumor and metastases were still shrinking (Figures 2E–H), and the progression-free survival was at least 12 months.

3 Discussion

The *TRIM33-RET* fusion protein contains a coiled-coil domain encoded by *TRIM33* exons 1–11 and a complete kinase domain encoded by *RET* exons 12–20, which may result in the activation of the RET tyrosine kinase. *RET* fusion is a rare genomic alteration in the PDAC. *TRIM33-RET* fusion has previously been reported in non-small cell lung cancer and oncocytic intraductal carcinoma of salivary glands (19, 20). We reported on a case of advanced PDAC that responded to pralsetinib as second-line systemic therapy. The PFS has been more than 12 months.

New targeted drugs for *RET* fusion are constantly emerging in succession (21). Recently, selpercatinib and pralsetinib were approved by the FDA for the treatment of lung and thyroid cancers with *RET* gene mutations or fusions (22), (23). Although no targeted drug for *RET* fusion-positive PDAC has been approved, ongoing clinical studies of target drugs for *RET* fusion in more cancer types are underway. The ARROW study is a multi-cohort, open-label, phase 1/2 study designed to investigate pralsetinib for the treatment of *RET*-altered solid tumors, including four patients with pancreatic cancer (24). The results confirmed that response occurred in 57% of 23 evaluable patients (24). The most common grade 3–4 treatment-related adverse events (TRAEs) in the pre-treated population were neutropenia, anemia, and hypertension (24). Notably, *JMJD1C-RET* fusion and *TRIM33-RET* fusion were detected in a pancreatic cancer patient who achieved an ongoing complete response at a treatment duration of 33.1 months (24). The LIBRETTO-001 study, a phase 1/2 study of selpercatinib in participants with advanced solid tumors, *RET* fusion-positive solid tumors, and medullary thyroid cancer, had been reported. Forty-five patients with *RET* fusion had been enrolled, including 12 patients with pancreatic cancer. The overall response rate (ORR) was 43.9% in 41 efficacy-evaluable patients confirmed by an independent review committee (25). Many novel selective RET inhibitors have shown good efficacy and low off-target toxicity in clinical trials (e.g., BLU-667 and LOXO-292), which encourages the development and research of more selective RET inhibitors (10). This is the first case report of a patient with only the *TRIM33-RET* fusion, a single fusion gene, detected who has an ongoing partial response to pralsetinib in PDAC.

4 Conclusion

In conclusion, this is the first case report in which a patient with only the *TRIM33-RET* fusion, a single fusion gene, detected in PDAC had a remarkable response to pralsetinib. This suggests the importance of NGS testing for patients with PDAC, especially those intolerant to chemotherapy.

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 The Local Ethics Review Committee. 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

CJ, TZ, and HW followed up the patient and collected patient data. SZ contributed to the writing of the original draft. ZC contributed to the collection of CT image data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author SZ was employed by 3D Medicines Inc.

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

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Case Report: Gastric cancer with chondromyxoid matrix similar matrix-producing metaplastic breast carcinoma: report of an undescribed entity

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Gastric cancer is a malignant epithelial neoplasm of the stomach, including adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, gastroblastoma and neuroendocrine neoplasms, without gastric metaplastic carcinoma. We describe a 69-year-old male patient with gastric cancer who presented with a novel, biphasic histologic morphology with one component consisting of poorly differentiated adenocarcinoma and the other component consisting of chondromyxoid matrix with adenocarcinoma transition to, between the two components without a spindle cell component. The histological morphology of this case is similar to matrix-producing metaplastic breast carcinoma. Therefore, we diagnose this case as gastric carcinoma with chondromyxoid matrix similar matrix-producing metaplastic breast carcinoma.

KEYWORDS

gastric cancer, chondromyxoid matrix, matrix-producing metaplastic carcinoma, adenocarcinoma, histologic morphology, case report

Introduction

Gastric carcinoma with chondromyxoid matrix similar matrix-producing metaplastic breast carcinoma is the first reported, which is a malignant epithelial tumor with heterologous mesenchymal differentiation. Our case is a carcinoma with a direct transition from adenocarcinoma to cartilaginous matrix lacking an intervening spindle cell component. This case is similar to metaplastic breast carcinoma with matrix-producing, which is characterized by a direct transition from invasive breast carcinoma no special type (IBC-NST) to cartilaginous/osseous matrix without an interspersed spindle cell component (1). We report this case because of its specific morphological features, which need to be described.

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Case presentation

A 69-year-old male patient presented with a gastric mass for one week. A gastric mass was found by gastric endoscopy in another hospital, and biopsy was performed. The pathological results showed chronic inflammation of the stomach, and no tumor cells were found. The patient's serum tumor marker CA72-4 was 433 IU/mL. For a clear diagnosis, abdominal CT and gastric endoscopy were performed again. A large mass was seen at the stomach fundus and cardia, with a central depression and erosion (Figures 1A, B). The rebiopsy results showed a malignant tumor of the stomach fundus and cardia, with a high possibility of adenocarcinoma. Furthermore, the patient had a history of hyperuricemia for many years and had taken colchicine orally for a long time. He also had grade 3 hypertension for more than 2 years and was treated with oral amlodipine besylate tablets. No smoking and no alcohol drinking.

Based on rebiopsy results, an open total gastrectomy was performed, which lasted approximately 4 hours with intraoperative bleeding of 100 ml. Gross examination showed a gray-white raised tumor with a size of approximately 10 cm×6.5 cm×4 cm at the stomach fundus and cardia (Figure 1C). The tumor section was relatively well circumscribed, gray-white and lightly hard. On microscopic examination, the tumor showed expansile infiltration with relatively well-circumscribed in low power (Figure 2A). Two distinct types of areas were seen within the tumor, including poorly differentiated adenocarcinoma area and area rich in chondromyxoid matrix, and the carcinoma transitions directly to chondromyxoid matrix (without spindle cell sarcomatoid component and osteoclast giant cell differentiation) (Figure 2B). The tumor cells in the adenocarcinoma area were arranged in a solid and cribriform pattern, with eosinophilic cytoplasm and large nuclei (Figure 2C). Eosinophilic nucleoli are obvious in high power, and pathological mitoses were easy to see (Figure 2D). The chondromyxoid matrix was widely distributed in a multinodular pattern, interspersed with poorly differentiated adenocarcinoma and directly migrating to it (Figure 2B). Tumor cells were trabecular, cord-like and single cells distributed in the chondromyxoid matrix (Figure 2E), with large nuclei, prominent eosinophilic nucleoli and obvious pathological mitoses (Figure 2F). The periphery of the nodules were more cellular with gradually diminishing cellularity toward the central area (Figure 2G). Hemorrhage and necrosis were present in the center of larger nodules (Figure 2H). Adenocarcinoma metastases were seen in 7 out of 21 lesser curvature lymph nodes.

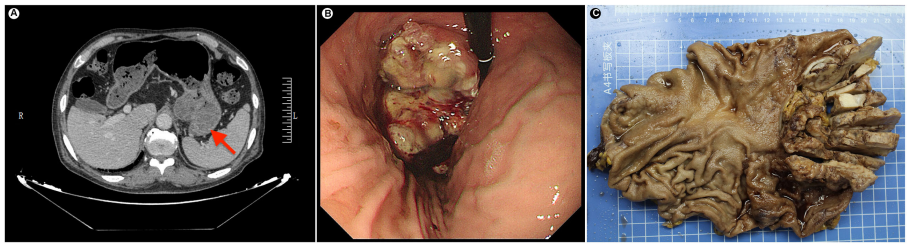

FIGURE 1
(A) Preoperative radiology image shows a large raised mass at the fundus-cardia (red arrow). **(B)** Gastric endoscopy shows a large raised mass at the fundus-cardia. **(C)** Gross photograph of the gastric specimen. The tumor section shows gray-white, slightly hard and relatively clear borders.

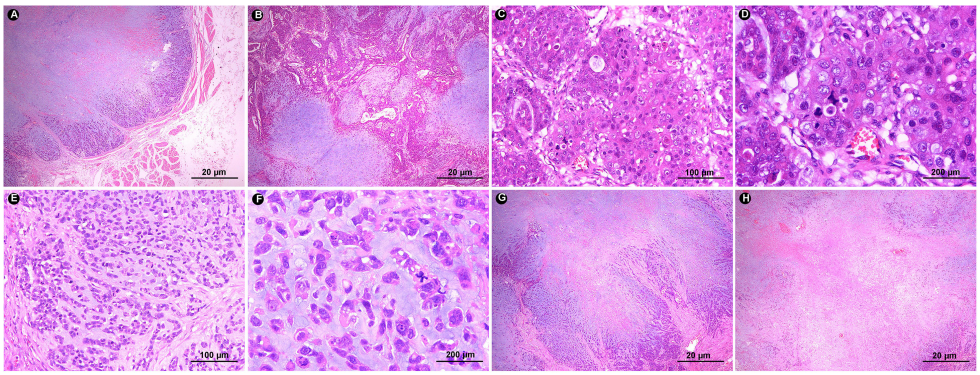

FIGURE 2
(A) In low power, the tumor border is relatively clear and shows expansile infiltration (HE ×20). **(B)** The tumor has two components: adenocarcinoma area and chondromyxoid matrix area. The chondromyxoid matrix exhibits multinodular growth with direct transition of adenocarcinoma components (HE ×20). **(C)** Tumor cells in the carcinomatous area exhibit solid and cribriform morphology (HE ×100). **(D)** Tumor cells show rich eosinophilic cytoplasm, obvious eosinophilic nucleoli and pathological mitosis (HE ×200). **(E)** In the chondromyxoid area, tumor cells are distributed in the form of beams, cords, and single cells within it (HE ×100). **(F)** Tumor cells are eosinophilic, with obvious nuclear atypia, prominent nucleoli, and easy-to-see pathological mitoses (HE ×200). **(G)** The chondromyxoid area is multinodular, with abundant tumor cells around the nodules and sparse tumor cells in the middle (HE ×20). **(H)** Hemorrhage and necrosis are seen in the larger nodules (HE ×20).

The adenocarcinoma cells expressed PCK, CK19, CK8/18, CK7, EMA and P53, showed focal positivity for S100, MUC5AC and MUC6, and were negative for AR. Tumor cells in the chondromyxoid matrix were positive for PCK, CK19, CK8/18, CK7 and S100 and negative for EMA, Calponin and P63. The Ki-67 index was approximately 50%. AB-PAS staining showed an abundant extracellular chondromyxoid matrix (Figure 3). In addition, the tumor cells were positive for MLH1, PMS2, MSH2 and MSH6 exhibiting microsatellite stability, and were negative for HER-2 and EBER.

The final diagnosis was poorly differentiated gastric carcinoma, partly poorly differentiated adenocarcinoma, and partly rich in chondromyxoid matrix, consistent with gastric carcinoma with chondromyxoid matrix similar matrix-producing metaplastic breast carcinoma. The tumor invaded the subserosa with vascular invasion and 7 out of 26 metastatic lymph nodes. After open total gastrectomy, no postoperative complications were found, and the patient was discharged after 2 weeks of hospitalization. Adjuvant chemotherapy was not accepted due to the patient's personal wishes. The patient developed multiple liver metastases within 5 months postoperatively and died of the disease 7 months later.

Discussion

In the 2019 WHO classification of digestive tumors, malignant epithelial tumors of the stomach are classified as adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, gastroblastoma and neuroendocrine neoplasms. This report describes a case of gastric carcinoma with chondromyxoid matrix in an elderly male who has a large tumor with a well-defined at the stomach fundus and cardia. Microscopically, poorly differentiated adenocarcinoma is located on the surface of the tumor and arranged in solid and cribriform patterns. The chondromyxoid matrix is located inside the tumor with multinodular distribution. The adenocarcinoma area directly transitioned to the chondromyxoid matrix area (no intervening spindle cell sarcoma component). The characteristics of gastric carcinoma with a chondromyxoid matrix are different from those of gastric adenocarcinoma, and are also different from gastric carcinosarcoma reported so far. Gastric carcinosarcoma includes carcinoma and sarcoma components, among which sarcoma components have been reported to include chondrosarcoma (2, 3), osteosarcoma (4, 5), leiomyosarcoma (4), rhabdomyosarcoma (5) and sarcoma undifferentiated. Morphologically, this case is similar to gastric cancer with a chondrosarcoma component that has been reported, while different for immunohistochemistry (2). The chondrosarcomatous component is negative for cytokeratins (CK8/18) in the literature. However, tumor cells in the chondromyxoid matrix area diffusely expressed a variety of cytokeratins (PCK, CK19 CK8/18 and CK7), similar to the expression of adenocarcinoma in our case. It is possible that this case is another form of gastric carcinosarcoma.

Interestingly, this case has similar features to matrix-producing metaplastic breast carcinoma, both morphologically and immunohistochemically (6). As Wargotz et al (7) described matrix-producing metaplastic breast carcinoma is divided into two types: diffuse and peripheral. In the peripheral type, tumor cells are concentrated around the nodule and gradually decrease from the outside to the inside, while the chondromyxoid matrix gradually increases, and hemorrhage and necrosis are seen in the center of the tumor. In this case, the chondromyxoid nodules accounted for 80% of the entire tumor. The tumor cells around the nodules are abundant, and hemorrhage and necrosis are also seen in the center of the large nodules, similar to the peripheral type. In addition, the diffuse positive expression of S-100 is a characteristic marker of matrix-producing metaplastic breast cancer. In this case, tumor cells in the chondromyxoid matrix area are diffusely positive for S-100, PCK, CK19, CK8/18 and CK7, and the chondromyxoid matrix shows blue by AB-PAS staining. Therefore, based on morphological features and immunohistochemistry, we prefer to classify this case as gastric

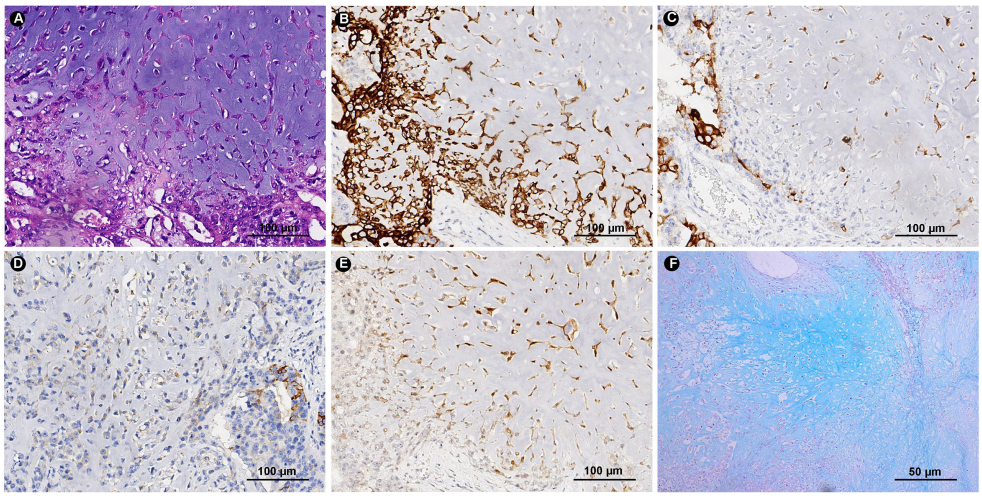

FIGURE 3
HE and Immunohistochemical. **(A)** The same site of HE section for immunohistochemical tissue sections (HE ×200). Tumor cells express CK7 **(B)**, EMA **(C)** MUC5AC **(D)** and S-100 **(E)** (IHC ×200). **(F)** Special histochemical staining of AB-PAS shows the abundant chondromyxoid matrix (Special stain ×100).

carcinoma with chondromyxoid matrix differentiation, which is not exactly equivalent to chondromyxoid sarcoma because the tumor cells in the chondromyxoid matrix area express a variety of keratins and may belong to a type of carcinosarcoma.

This case should be differentiated from gastric carcinosarcoma with chondrosarcoma, in which the chondrosarcoma component is focally expressed or negative for the epithelial markers CK and EMA, while the tumor cells in the chondromyxoid matrix area express a variety of keratins and EMA in this case. It should also be differentiated from metastatic matrix-producing metaplastic breast carcinoma, which has a history of breast cancer and the carcinoma component expresses GATA3, while this case does not.

In breast cancer, metaplastic breast cancer is more aggressive than the corresponding IBC-NST of the same age, stage and grade. Metaplastic carcinoma is characterized by a high stage, easy local recurrence and aggressive invasion, so the prognosis is poor. The prognosis of gastric adenocarcinoma is related to the degree of differentiation and the presence or absence of lymph node metastasis. In this case, the adenocarcinoma was moderately to poorly differentiated, and the chondromyxoid matrix component accounted for approximately 80%. Lymph node metastasis had already occurred at the time of diagnosis, and the metastatic component was adenocarcinoma. The patient developed multiple liver metastases 5 months postoperatively and died 7 months later. Although there was only one case, it also showed a poor prognosis, consistent with breast metaplastic carcinoma. In contrast to the treatment of gastric cancer, the treatment of breast cancer is mainly based on its molecular type, so it has no reference value. In this case, postoperative adjuvant chemotherapy is recommended, but the patient is unwilling to receive chemotherapy. He developed multiple liver metastases 5 months later and died of the disease 7 months after the operation, with a poor prognosis.

Conclusion

We report this case because the unique morphological features cannot be classified into existing histological subtypes of gastric cancer. Based on morphological features and immunohistochemistry and referring to the concept of matrix-producing metaplastic breast cancer, we prefer to classify this case as gastric carcinoma with chondromyxoid matrix differentiation, which may belong to a novel morphology of carcinosarcoma.

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 patients/participants for the publication of this case study.

Author contributions

XW, HH, and JY conceived the study. XW wrote the first draft of the manuscript. XW LZ, and ZZ acquired data. All authors contributed to the article and approved the submitted version.

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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

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