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Case reports in intensive care medicine 2025

Edited by
Cheng Zhu, Zhongheng Zhang and Yuetian Yu

Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-7291-7
DOI 10.3389/978-2-8325-7291-7

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Case reports in intensive care medicine 2025

Topic editors

Cheng Zhu — Shanghai Jiao Tong University, China

Zhongheng Zhang — Department of Emergency Medicine, Sir Run Run Shaw Hospital, China

Yuetian Yu — Shanghai Jiao Tong University, China

Citation

Zhu, C., Zhang, Z., Yu, Y., eds. (2026). *Case reports in intensive care medicine 2025*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-7291-7

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frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 04 December 2025
DOI 10.3389/fmed.2025.1747490

OPEN ACCESS

EDITED AND REVIEWED BY
Devesh U. Kapoor,
Gujarat Technological University, India

*CORRESPONDENCE
Yuetian Yu
✉ fishyyt@sina.com
Zhongheng Zhang
✉ zh_zhang1984@zju.edu.cn

†These authors have contributed equally to this work

RECEIVED 16 November 2025
ACCEPTED 24 November 2025
PUBLISHED 04 December 2025

CITATION
Zhu C, Lin B, Zhang Z and Yu Y (2025) Editorial: Case reports in intensive care medicine 2025. *Front. Med.* 12:1747490. doi: 10.3389/fmed.2025.1747490

Editorial: Case reports in intensive care medicine 2025

Cheng Zhu[1†], Bin Lin[2,3†], Zhongheng Zhang[4,5*] and Yuetian Yu[2,6*]

[1]Department of Disease Prevention and Control, Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China, [2]Key Laboratory of Intelligent Pharmacy and Individualized Therapy of Huzhou, Huzhou, China, [3]Department of Pharmacy, Changxing People's Hospital, Changxing Branch, Second Affiliated Hospital of Zhejiang University School of Medicine, Huzhou, China, [4]Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China, [5]Provincial Key Laboratory of Precise Diagnosis and Treatment of Abdominal Infection, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China, [6]Department of Critical Care Medicine, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

KEYWORDS

intensive care medicine, case reports, personalized medicine, heterogeneity, clinical phenotypes, artificial intelligence

Editorial on the Research Topic
Case reports in intensive care medicine 2025

The landscape of Intensive Care Medicine (ICM) is one of constant tension between the urgent need for standardized, evidence-based protocols and the profound biological and clinical heterogeneity of the patients we treat. The presentations of critically ill patients are a complex tapestry woven from unique genetic backgrounds, diverse comorbidities, varying sites and types of infection, and vastly different host immune responses. This inherent variability is the fundamental challenge that confronts every intensivist at the bedside (1). While large-scale randomized controlled trials (RCTs) and meta-analyses provide the essential scaffolding for our practice, they often obscure the individual patient narrative, generating population-level evidence that may not fit the unique circumstances of a specific case. It is within this gap between the generalizable knowledge of RCTs and the nuanced reality of individual patient care that the humble case report finds its powerful and enduring voice.

This Frontiers in Medicine Research Topic, "*Case reports in intensive care medicine 2025*," was conceived with this very principle in mind. Our goal was to curate a collection of clinical narratives that not only inform and educate but also illuminate the path toward a more personalized, precise future for critical care. The 11 manuscripts accepted for this Research Topic serve as compelling testaments to the diversity of critical illness. They chronicle diagnostic dilemmas, innovative therapeutic maneuvers, unexpected complications, and hard-won clinical victories. More importantly, they argue persuasively for an evolution in our approach from a model of "one-size-fits-all" to one of "right treatment, for the right patient, at the right time."

The unyielding challenge of heterogeneity in the ICU

The quest for standardization in ICM is understandable. Protocols for sepsis management, ventilator liberation, and nutrition delivery bring order to chaos and have undoubtedly improved overall outcomes. However, the limitations of this approach

become starkly apparent when faced with the biological reality of critical illness (2). Two patients with identical Sequential Organ Failure Assessment (SOFA) scores may have arrived at that point through entirely different pathophysiological pathways and may possess dramatically different capacities for recovery (3).

This heterogeneity is most vividly exemplified in sepsis, a core focus of modern ICM. Once considered a monolithic entity, sepsis is now recognized as a syndrome encompassing multiple distinct endotypes and subphenotypes (4). Through unsupervised machine learning analyses of large clinical and transcriptomic datasets, researchers have consistently identified categories such as the "hyperinflammatory" subphenotype (characterized by high vasopressor demand, metabolic acidosis, and inflammatory markers) and the "immunosuppressive" subphenotype (marked by lymphocyte exhaustion and a high risk of secondary infection). These subphenotypes demonstrate markedly different responses to therapy; for instance, the hyperinflammatory group may derive harm from liberal fluid resuscitation, while the immunosuppressive group might benefit from immunostimulatory agents (5).

The cases in this Research Topic reflect this heterogeneity beyond sepsis. We encounter patients with rare autoimmune etiologies of respiratory failure, unusual presentations of toxicological emergencies, and complex post-operative courses defying standard management algorithms. One case details the challenge of managing a patient with a rare genetic disorder who develops acute respiratory distress syndrome (ARDS), where conventional ventilator strategies prove insufficient or even detrimental. Another describes a cryptic source of infection in an immunocompromised host, where the usual microbiological suspects are absent, demanding a broader, more imaginative diagnostic approach (6). These narratives force us to acknowledge that our protocols are starting points, not destinations. They are maps that require constant interpretation and deviation based on the unique terrain of each patient.

Case reports as the bedrock of experiential learning and incremental progress

In an era dominated by the hierarchy of evidence, case reports are sometimes unfairly relegated to a lower tier. This perspective overlooks their multifaceted and critical role in the advancement of ICM. They are not merely "anecdotes" but are, in fact, the fundamental units of clinical experience, serving several indispensable functions:

1. Catalysts for Discovery and Hypothesis Generation: Many groundbreaking advances in medicine began with a single, astute observation. A case report documenting an unexpected drug effect, a novel complication of a device, or a successful application of a therapy in a new context can generate hypotheses that fuel subsequent rigorous research. The report in this Research Topic on the use of a specific antidote for an uncommon poisoning, for instance, provides a template for management that may not be covered in any guideline but could be life-saving for a future patient.
2. Enhancing Diagnostic Acumen: Critically ill patients often present with constellations of symptoms that are diagnostically ambiguous. Case reports that detail rare mimics of common conditions, such as a non-infectious condition masquerading as septic shock, or an unusual metabolic disorder presenting as unexplained lactic acidosis, and they serve as vital educational tools. They broaden the differential diagnosis for clinicians worldwide, fostering a culture of intellectual curiosity and diagnostic rigor at the bedside.
3. Illustrating Therapeutic Innovation and Nuance: While RCTs tell us whether a treatment works on average, case reports often show us how it can be applied, adapted, and tailored in complex, real-world scenarios. A case in this topic detailing the meticulous, PK/PD-guided dosing of antibiotics in a patient with augmented renal clearance and septic shock provides a masterclass in personalized antimicrobial therapy. It moves beyond the trial protocol of fixed-dosing and demonstrates the art and science of optimizing drug exposure for an individual, which is a cornerstone of antimicrobial stewardship (7, 8).
4. Documenting Pitfalls and Fostering Safety: Not all cases end in success. Reporting on unexpected treatment failures, diagnostic errors, or rare adverse events is a courageous and essential form of collective learning. By analyzing what went wrong, we build systems and cognitive checks to prevent future occurrences. A case describing a complication related to a specific mode of extracorporeal membrane oxygenation (ECMO), for example, alerts other centers to a potential risk, enhancing safety for patients globally (9).

The 11 cases in this Research Topic collectively form a rich repository of this type of practical, frontline knowledge. They are a testament to the clinical wisdom that is accumulated not only through large datasets but also through the deep, reflective engagement with individual human stories.

The compass for the future: navigating toward truly individualized care

The narratives presented here are more than just historical accounts, they are signposts pointing toward the future of ICM. The journey toward personalized critical care will be propelled by the integration of several key technological and philosophical shifts, many of which are prefigured in the cases of this Research Topic.

1. From Syndromes to Subphenotypes: The future lies in moving from classifying patients by broad syndromes to rapidly identifying their specific biological subphenotype. This will involve point-of-care technologies such as rapid transcriptomic profiling, metabolomic analysis, and focused genetic testing. Imagine a future where within hours of ICU admission, we can determine not just that a patient has sepsis, but that they have an immunosuppressive endotype with specific monocyte dysfunction, guiding us toward targeted immunostimulation rather than blanket, and potentially harmful, immunosuppression.
2. The Rise of the Digital Guardian: The vast, continuous streams of data generated in the ICU from vital signs and ventilator waveforms to laboratory results and nursing notes are

beyond the integrative capacity of the human brain. Artificial intelligence (AI) and machine learning (ML) algorithms are poised to become indispensable partners. They can analyze this data in real-time to predict clinical deterioration earlier than current scoring systems, identify subtle subphenotypes, and even recommend personalized interventions. An AI system could, for example, analyze a patient's hemodynamic profile, inflammatory markers, and medication history to suggest the optimal vasopressor, its dose, and the ideal timing for antibiotic redosing based on real-time PK modeling (10).

3. Pharmacogenomics and Advanced Therapeutic Drug Monitoring (TDM): The paradigm of "one dose fits all" is particularly dangerous in the critically ill, whose pharmacokinetics are wildly altered by capillary leak, organ dysfunction, and extracorporeal circuits. The future entails routine TDM for a much wider array of drugs, particularly antibiotics, coupled with pharmacogenomic data (11, 12). Knowing a patient's genetic predisposition for metabolizing sedatives or responding to vasoactive agents will allow for truly bespoke pharmacotherapy from the outset.
4. Dynamic, Biomarker-Driven Treatment Courses: The rigid, calendar-based duration of antibiotic therapy or ventilator support is increasingly recognized as obsolete. The future is dynamic, guided by serial biomarkers. The use of procalcitonin to guide antibiotic discontinuation is an early example. Future strategies will incorporate a panel of biomarkers to answer the pivotal question daily: "Does this patient still need this specific intervention?" This aligns perfectly with the principles of antimicrobial de-escalation and ventilator liberation, ensuring therapies are applied only as long as they are beneficial (13, 14).

The cases in this Research Topic, in their detailed documentation of individual patient trajectories, underscore the necessity of this evolution. They show us clinicians thinking on their feet, adapting to new information, and crafting bespoke management plans. They are, in essence, early, human-powered examples of the personalized medicine we aim to systematize with technology.

Conclusion

The case reports compiled in "*Case reports in intensive care medicine 2025*" are far more than isolated clinical curiosities. They are vital threads in the rich fabric of our specialty's knowledge. They remind us that the art of healing in the ICU lies in balancing the robust, population-derived evidence of our guidelines with the deep, empathetic, and nuanced understanding of the individual before us.

As Guest Editors, we extend our deepest gratitude to the authors who have generously shared their experiences, challenges, and insights. It is our sincere hope that this Research Topic will not only serve as a valuable educational resource but also inspire a renewed appreciation for the narrative in medicine. The path to precision critical care is a long and complex one, but each carefully observed and documented case report brings us a step closer. By listening to the stories of our patients, we learn not only how to be better doctors but also how to build a more intelligent, responsive, and ultimately more human, system of care for the most vulnerable among us.

Author contributions

CZ: Writing – review & editing, Writing – original draft. BL: Writing – review & editing, Writing – original draft. ZZ: Writing – review & editing, Writing – original draft. YY: Writing – original draft.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the Project of the Key Laboratory of Multiple Organ Failure, Ministry of Education (2023KF07 and 2024KF03), the Key Laboratory of Intelligent Pharmacy and Individualized Treatment in Huzhou City (HZKF-20240101), and Medical and Health Technology Project of Zhejiang Province (2025KY1575).

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The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 26 May 2025
DOI 10.3389/fmed.2025.1598248

OPEN ACCESS

EDITED BY
Zhongheng Zhang,
Sir Run Run Shaw Hospital, China

REVIEWED BY
Rosanna Carmela De Rosa,
Colli Monaldi Hospital, Italy
Özlem Öner,
Dokuz Eylul University, Türkiye
Necati Gokmen,
Dokuz Eylul University, Türkiye

*CORRESPONDENCE
Jialin Liu
✉ ljl11243@rjh.com.cn
Hongping Qu
✉ qhp10516@rjh.com.cn

†These authors have contributed equally to this work

RECEIVED 22 March 2025
ACCEPTED 28 April 2025
PUBLISHED 26 May 2025

CITATION
Xu J, Zhong M, Liu D, Guan J, Qi X, Tan R, Li P, Zhao Z, Qu H and Liu J (2025) A modified CO-related EIT parameter was used to evaluate pulmonary ventilation-perfusion ratio during prone position and inhaled nitric oxide therapy: a case report.
Front. Med. 12:1598248.
doi: 10.3389/fmed.2025.1598248

A modified CO-related EIT parameter was used to evaluate pulmonary ventilation-perfusion ratio during prone position and inhaled nitric oxide therapy: a case report

Jing Xu[1†], Ming Zhong[2†], Di Liu[2], Jiayi Guan[2], Xiaoling Qi[1], Ruoming Tan[2], Pengcheng Li[3], Zhanqi Zhao[4], Hongping Qu[2*] and Jialin Liu[1*]

[1]Department of Geriatrics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [3]Department of Industrial Engineering, Tsinghua University, Beijing, China, [4]School of Biomedical Engineering, Guangzhou Medical University, Guangzhou, China

Introduction: Assessment of the V/Q ratio is crucial for understanding the pathophysiology of iNO therapy and prone position in ARDS patients. Recently, the concept of the absolute V/Q ratio measured by EIT has emerged. In this study, we first describe a case where a modified EIT parameter was employed to clinically monitor the absolute V/Q ratio in an ARDS patient during both prone positioning and iNO therapy.

Case presentation: This report describes the case of a 69-year-old ARDS patient with refractory hypoxemia who underwent prone position and iNO therapy. The patient exhibited a positive response to the treatment, showing improved oxygenation and absolute V/Q. A modified EIT-derived parameter, the cardiac output (CO)-related V/Q match index, was utilized to evaluate the absolute V/Q ratio, demonstrating improved consistency with the oxygenation index compared to conventional indicators.

Conclusion: This case elucidates the significance of the EIT-derived parameter—CO-related V/Q match index, revealing its benefits in evaluating the V/Q ratio under the various treatment strategies when compared to traditional ones.

KEYWORDS

acute respiratory distress syndrome, electrical impedance tomography, inhaled nitric oxide therapy, V/Q ratio, case report

Introduction

The ventilation/perfusion (V/Q) ratio plays a crucial role in assessing acute respiratory distress syndrome (ARDS) severity and guiding treatment decisions (1). While electrical impedance tomography (EIT) offers a non-invasive way to monitor lung ventilation and perfusion at the bedside (2), accurately evaluating the absolute V/Q ratio for the entire lung

remains challenging. This difficulty arises because conventional EIT-based assessments of V/Q matching do not account for the impact of cardiac output (3), a key determinant in the matching of blood flow to ventilated lung areas. A recent study sought to overcome this shortcoming by incorporating cardiac output metrics, thereby facilitating the computation of absolute V/Q ratios in different lung regions (3). Despite these advances, the study did not succeed in delineating a definitive parameter that encapsulates the comprehensive lung V/Q match. Consequently, we devised an innovative parameter derived from EIT, termed the cardiac output (CO)-related V/Q match index. This parameter was derived by aggregating the variance in the absolute V/Q ratio at each pixel, as detected by EIT, in relation to the optimal V/Q value.

In this report, we present the case of a 69-year-old patient with ARDS who underwent thoracoscopic radical surgery. Postoperatively, the patient encountered severe hypoxemia, and EIT assessment indicated a significantly impaired V/Q ratio. To enhance oxygenation, the patient was treated with prone positioning and inhaled nitric oxide (iNO) therapy. Throughout the treatment, the conventional V/Q ratio assessed via EIT did not reliably indicate the trend of changes in the patient's oxygenation status. In contrast, CO-related V/Q match index showed a robust correlation with the patient's oxygenation fluctuations. The modified index provided a nuanced understanding that partially elucidates the physiological mechanisms at play in the efficacy of prone positioning and inhaled nitric oxide (iNO) therapy for the management of ARDS. The deployment of this modified parameter has yielded encouraging outcomes, delivering valuable insights that can inform and guide clinical treatment strategies for ARDS patients.

Case presentation

Patient history

A 69-year-old male patient who underwent thoracoscopic radical surgery for esophageal cancer developed acute respiratory distress syndrome (ARDS). Pulmonary *Klebsiella pneumoniae* infection was identified based on the sputum culture results. Due to worsening oxygenation and infection progression, he was transferred to the intensive care unit (ICU). Tracheostomy were initiated two days before the admission. Past medical history includes hypertension, pulmonary tuberculosis, and a smoking history of approximately 1 pack per day.

Upon admission, the patient exhibited tachypnea (RR 35–40/min) and significant ventilator-patient asynchrony. The heart rate was 140 bpm, with a blood pressure of 98/56 mmHg. Bilateral lung auscultation disclosed moist rales, and the patient had cold, clammy skin. Mechanical ventilation were administrated utilizing a pressure control mode with pressure control (PC) set at 19 cmH_2O, positive end-expiratory pressure (PEEP) at 6 cmH_2O, and Fraction of inspired oxygen (FiO_2) of 1. Blood gas analysis revealed a pH of 7.376, Partial pressure of carbon dioxide ($PaCO_2$) of 51 mmHg, partial pressure of oxygen (PaO_2) of 68.2 mmHg. Laboratory findings showed a white blood cell count of 21.4 × 10^9/L, C-reactive protein level of 300 mmol/L, procalcitonin level of 13.47 (ng/mL). Patient diagnosis includes: 1. Acute respiratory distress syndrome (ARDS); 2. Septic shock (due to pneumonia and bloodstream infection); 3. Hospital-acquired pneumonia; 4. Hypernatremia; 5. Acute kidney injury (stage III); 6. Esophageal malignancy (post-thoracoscopic esophagectomy for esophageal cancer); 7. Cerebral infarction; Neuromuscular blocking drugs were administered to interrupt the patient's spontaneous respiratory efforts. Fluid resuscitation and vasopressor support (Norepinephrine, 0.37 μg/kg/min, and Vasopressin at 3 ml/h) were administered to maintain a blood pressure at 130/70 mmHg. The patient received a stable antibiotic regimen based on antimicrobial susceptibility testing, including ceftazidime-avibactam for Klebsiella pneumoniae and sulbactam for Acinetobacter baumannii, with colistin nebulization. After 5 days, improvements in CRP and PCT levels led to discontinuation of intravenous antibiotics by day 7 and nebulization by day 10. Fluid management focused on maintaining blood pressure with a negative balance, except for the initial shock day, and remained relatively stable during NO treatment. A pulse index continuous cardiac output (PICCO) catheter was inserted for hemodynamic monitoring.

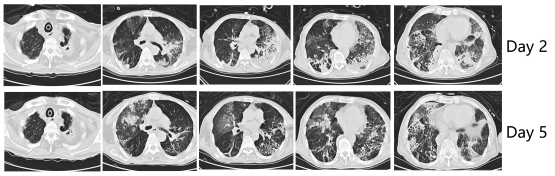

FIGURE 1
CT images of the lung. Upper of the picture presents CT images of patients at Day 2 and Lower reflects Day 5.

On Day 2, a CT scan revealed diffuse bilateral lung infiltration with significant consolidation, particularly in gravity-dependent areas, notably the left lung (Figure 1). Despite stabilizing blood pressure (110/60 mmHg), severe hypoxemia persisted (PaO_2/FiO_2 = 77 mm Hg). Therefore, prone positioning for 16 h per day was initiated on Day 3, along with iNO therapy at 15 parts per million (ppm) to enhance oxygenation (Figure 2). At the time of our treatment, no universal guidelines specified a particular iNO dose for ARDS patients. Initial doses typically range from 5–10 ppm, with adjustments based on patient response (4). The maximum iNO dose can reach up to 80 ppm, with no significant toxicity reported (5). In our protocol, we initiated iNO therapy at 10 ppm and increased the dose by 5 ppm every 10 min to monitor SpO_2 changes. This allowed us to determine the lowest effective dose to maintain SpO_2 without significant drops (> 10%), ultimately identifying 15 ppm as the optimal dose. To better evaluate lung ventilation and perfusion, EIT examination was employed in real-time during therapy, facilitating the optimization of PEEP titration and determination of treatment timing. Unlike traditional V/Q ratio assessment methods, we introduced cardiac output and minute ventilation to calculate the absolute value of V/Q, and developed a modified index to comprehensively assess the overall pulmonary V/Q situation.

Within 24 h of prone positioning and iNO therapy initiation, the patient's oxygen index increased from 77 mmHg to 112 mmHg. By Day 5, significant improvement in oxygenation was noted, with the patient maintaining an oxygen index consistently above 200 mmHg during supine positioning. CT scan indicated absorption of bilateral lower lung consolidations. At that time,

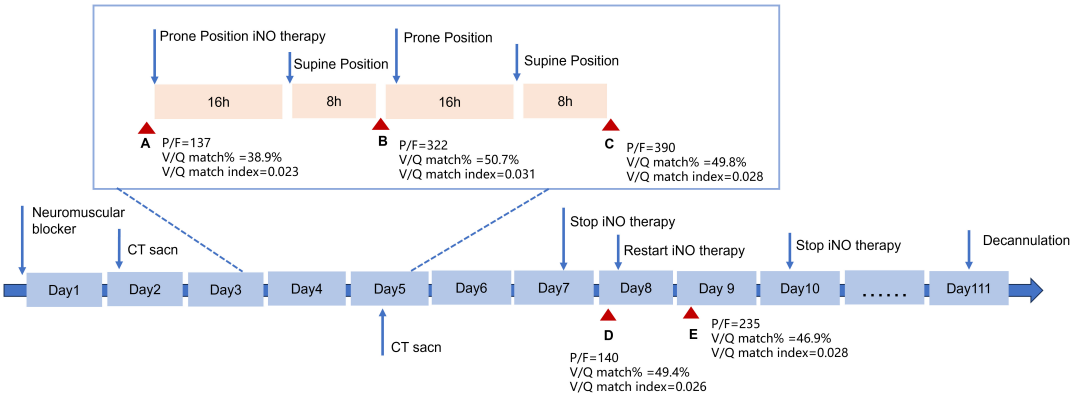

FIGURE 2
Time line depicting the treatment course of the patients. Red triangle indicates the time detecting ventilation and perfusion by EIT.

the patient had evident facial pressure ulcers accompanied by skin bleeding. The patient started to exhibit agitation and intolerance to the prone position despite receiving the standard dosage of sedative medication. Weighing the pros and cons, it was decided to discontinue prone position. On Day 7, iNO therapy was ceased, resulting in a gradual decline in oxygenation index to below 150 mmHg and showed a continuing downward trend. After evaluating the patient's lung perfusion using EIT, we opted to reintroduce NO inhalation therapy. Consequently, the patient's oxygenation showed gradual improvement. On Day 10, we ceased the NO inhalation treatment, and the patient maintained satisfactory oxygenation levels. Following anti-infective treatment, sputum clearance, and pulmonary rehabilitation therapies, the patient's reliance on mechanical ventilation gradually decreased. On the 111th day post-admission, successful extubation was achieved, leading to the patient's transfer to a convalescent facility for continued care.

EIT methods and analysis

The EIT belt was placed at the fifth intercostal space around the patient's chest wall and connected to the EIT monitor (PulmoVista.500; Dräger Medical GmbH, Lübeck, Germany). The patient was deeply sedated and mechanically ventilated on pressure control mode. EIT assessment was conducted with the patient in the supine position before initiating iNO therapy (A), at 24 h after initiation iNO therapy in the prone position (B), at 48 h after initiating iNO therapy in the prone position (C), 24 h after discontinuing iNO therapy (D) and 24 h after restarting iNO therapy (E). To acquire perfusion data, a 10 ml bolus of 10% NaCl solution was injected through the central venous catheter during an 8-s end-expiratory breath hold. Cardiac output was measured using a pulse index continuous cardiac output (PICCO) catheter, and minute ventilation was recorded from the mechanical ventilator simultaneously with EIT measurements. The EIT data were digitally filtered using a low-pass filter with a cut-off frequency of 0.67 Hz to eliminate periodic cardiac-related impedance changes. Offline analysis of the EIT data was performed using software provided by Dräger (Drager EIT Analysis Tool 6.3, 2016), along with algorithms developed by our research team.

Ventilation pixel values were calculated as the impedance change between expiration and inspiration, resulting in the generation of a ventilation map. Pixel values lower than 10% of the maximum value were excluded. Perfusion values of pixels were determined by measuring the slope of the time-impedance curve during the descending phase, providing a relative perfusion image. Pixel values lower than 10% of the maximum value were excluded. To interpret the V/Q ratio obtained through EIT, the following parameters were calculated:

- The Non-CO related parameters: Only perfused fraction is defined as the fraction of perfused pixels relative to the total number of pixels. Only ventilated fraction is defined as the fraction of ventilated pixels relative to the total number of pixels. V/Q match fraction is defined as the both perfused and ventilated pixels divided by the total number of pixels.
- CO-related parameters: The V/Q ratio of each pixel was calculated by dividing absolute ventilation by absolute perfusion, as previously reported (3): $V/Q = (V\%i \times MV \times 0.7)/(Q\%i \times CO)$. Shunt, low V/Q, normal V/Q, high V/Q and dead space pixels were defined as V/Q ratio ≤ 0.1, $0.1 < V/Q \leq 0.8$, $0.8 < V/Q \leq 1.25$, $1.25 < V/Q \leq 10$ and $V/Q \geq 10$, respectively.
  Unlike traditional methods of assessing the V/Q ratio, we incorporated cardiac output and minute ventilation into our calculations to determine the absolute value of V/Q. Additionally, we have developed a modified index that allows for a comprehensive assessment of the overall pulmonary V/Q status.
- CO-related V/Q match index, corresponding to the reciprocal of the variance of the ventilation-perfusion ratio for all pixels relative to 1. For details, CO-related V/Q match index = Var(V/Q)1. Where: Var(V/Q) represents the variance of the ventilation-perfusion ratio (V/Q) for all pixels. V denotes ventilation. Q denotes perfusion. Var indicates variance. The V/Q ratio aligns with the algorithm detailed in the preceding section regarding "CO-related parameters."

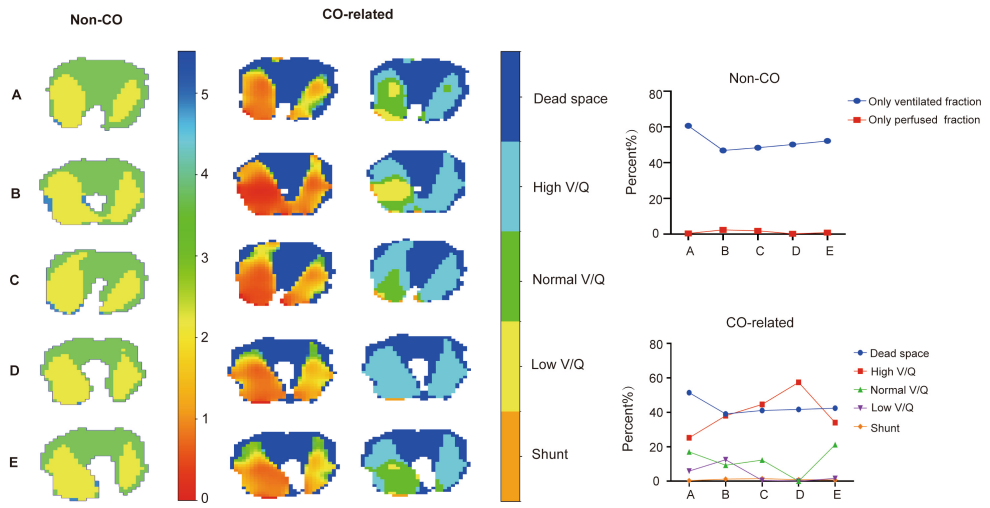

FIGURE 3
EIT maps of lung V/Q ratio with or without introduction of CO and MV at different time points. The left column shows the overlap of ventilation and perfusion maps using conventional methods. The middle column displays the absolute V/Q ratio heatmap incorporating cardiac output and mechanical ventilation into the analysis. The color gradient ranging from red to blue in the diagram represents the V/Q ratio, which ranges from 0 to 10. The right column exhibits the V/Q ratio map divided into dead space (dark blue), shunt (orange), low V/Q (yellow), normal V/Q (green) and high V/Q (light blue) regions. The line graph shows the change of the specific data of the EIT maps.

EIT results

In the conventional V/Q map, there was a significant decrease (60.7% vs. 46.9%) in the only perfused regions of the patient after 24 h of iNO therapy, while the only ventilated regions showed minimal changes. In the CO-related V/Q map, the dead space (shunt) regions changed similarly to the only perfused (only ventilated) regions in Non CO-related V/Q maps, with a notable increase in the low V/Q region (5.9% vs. 12.5%) (Figure 3; Table 1). The normal V/Q region of the patient exhibited a downward trend after prone positioning and iNO therapy, experienced a significant decrease after stopping iNO therapy (12.3% vs. 0%) (Table 1), and quickly rebounded upon resumption of iNO therapy (0% vs. 21.2%) (Table 1), while the change trend of the high V/Q region was the opposite (Figure 3).

After 24 h of iNO inhalation therapy, V/Q matching regions significantly increased (50.7% vs. 38.9%) (Figure 4; Table 1), and then gradually declined. The CO-related V/Q match index also increased after the initial 24 h (0.031 vs. 0.028) (Table 1) and decreased after iNO therapy cessation (0.026 vs. 0.028) (Table 1), but rebounded after resuming iNO therapy (0.028 vs. 0.026) (Table 1), aligning with the trend in the patient's oxygenation index (Figure 4).

Discussion

This case presents a biologic model to explore the capability of a modified EIT-derived parameter, CO-related V/Q match index, in assessing V/Q ratio in patients undergoing prone position and iNO therapy. It also revealed, for the first time, the noticeable increase in the absolute V/Q ratio, as indicated by the CO-related V/Q match index, resulting from the implementation of iNO.

Since 1993, iNO has been extensively studied as a rescue therapy for patients with ARDS (4). However, the overall mortality of ARDS patients did not show significant differences after iNO therapy (6). One possible explanation is the challenge in identifying which patients may benefit the most from iNO therapy (4). iNO works by selectively dilating pulmonary blood vessels, improving V/Q matching by increasing perfusion in well-ventilated areas of the lung (7). In this case, the patient had a high proportion of dead space, suggesting a potential benefit from iNO compared to those with a high proportion of shunt. While it may have been difficult to attribute the improvement in oxygenation solely to iNO, especially in the presence of prone positioning during early treatment, the subsequent decline in oxygenation and decrease in the V/Q ratio upon discontinuing iNO, followed by improvement after resuming iNO therapy, suggests the beneficial impact of iNO in the patient's treatment. Besides, during the NO inhalation period, the patient's antibiotic regimen, fluid management, and mechanical ventilation settings remained relatively stable, which allows us to partially exclude these factors as significant confounders.

EIT has emerged as a powerful tool for monitoring ventilation-perfusion (V/Q) matching in ARDS, offering real-time insights that are crucial for guiding therapeutic interventions such as PEEP optimization (8), prone positioning, and inhaled nitric oxide (iNO) therapy (9, 10). In traditional V/Q assessment, the V/Q match fraction was calculated by combining ventilation and perfusion maps to determine the proportion of lung areas that were both ventilated and perfused (11). However, this approach lacked explicit numerical values for the V/Q ratio, which omitted important information about lung V/Q match. Recent studies have highlighted the critical role of incorporating cardiac output (CO) in EIT-based V/Q assessments, demonstrating that neglecting CO can introduce significant bias, particularly in patients with an alveolar ventilation to cardiac output (VA/QC) ratio greater than 1 (3). This finding emphasizes the need for accurate calibration methods to ensure reliable V/Q assessments. Our study introduces a novel CO-related V/Q match index, which builds on these insights by providing a more precise measure of V/Q matching. In this

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TABLE 1 The EIT derived parameters of patients in different time points.

	A	B	C	D	E
Time point	Before iNO therapy and prone position	24 h after iNO	48 h after iNO	After stopping iNO	24 h after restarting iNO therapy
Dead space (%)	60.7	46.9	48.4	50.2	52.2
Shunt (%)	0.4	2.4	1.9	0.23	0.88
VQ match (%)	38.9	50.7	49.8	49.4	46.9
Dead space (%)	51.4	39.1	41.1	41.7	42.4
High V/Q (%)	25.2	38.0	44.6	57.4	34.0
Normal V/Q (%)	17.0	9.3	12.3	0	21.2
Low V/Q (%)	5.9	12.5	0.5	0	1.6
Shunt (%)	0.34	1.2	1.5	0.89	0.72
V/Q match index	0.023	0.031	0.028	0.026	0.028
Artery blood gas					
P/F (mmHg)	77	112	390	140	235
$PaCO_2$ (mmHg)	37.7	43.8	54.7	56.9	53.3
Ventilator parameters					
PC (cmH_2O)	21	21	20	20	19
PEEP (cmH_2O)	8	8	6	6	6
P_{peak}	30	30	27	26	25
Pplat	19	19	16	16	15
FiO_2 (%)	70	50	50	70	60
Vt (mL)	348	373	430	406	371
MV (L/min)	10.6	11	13	12.8	10.9
Cardiac output (L/min)	5	5.1	4.3	3.1	5

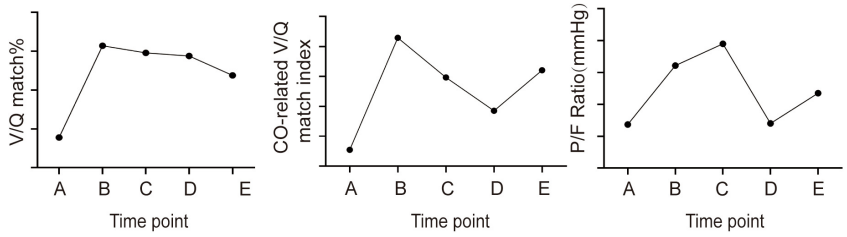

FIGURE 4
The change trend of V/Q match fraction, CO-related V/Q match index, and patient oxygenation index at different time points.

particular case, the patient experienced three fluctuations during treatment, but the V/Q match fraction only showed a significant increase during the first fluctuation (Figure 4). The failure of the V/Q match fraction to reflect changes in the patient's condition during the second and third fluctuations can be attributed to the fact that these changes were primarily driven by alterations in ventilation and perfusion proportions, rather than the fraction of areas with both ventilation and perfusion. This assumption is supported by the use of absolute V/Q ratio measurements. During the second fluctuation, the patient's MV remained relatively stable (12.8 L vs. 13 L) while the CO significantly decreased (3.1 L vs. 4.3 L) (Table 1). As a result, the overall absolute V/Q ratio increased, leading to a reduction in areas with a normal V/Q ratio and an increase in areas with a high V/Q ratio (Figure 3). However, the different classifications of V/Q regions only show changes in their respective proportions. A single value change cannot represent the overall V/Q match of the lung, and therefore, none of these parameters correlates well with the patient's oxygenation index. Our parameter combines the advantages of the above two methods while addressing their limitations. It calculates the absolute value of V/Q for each pixel of lung using CO and MV, thereby maximizing the information content and accuracy. It reflects the V/Q match of the whole lung region in the way of variance, providing a simple and intuitive quantitative index for the overall match of lung ventilation and perfusion.

Currently, CO can be measured using both invasive and non-invasive methods. Invasive techniques provide accurate but require arterial catheterization and carry potential risks. Non-invasive methods, such as transthoracic echocardiography (TTE) and the Ultrasound Cardiac Output Monitor (USCOM) (12), offer comparable accuracy to invasive techniques and are more feasible for use in the ICU setting. Electrical impedance tomography (EIT) offers a non-invasive alternative for CO monitoring by analyzing thoracic electrical bioimpedance (13). Recent studies have shown that EIT can be calibrated to provide CO measurements, even without invasive monitoring, by using the pulsatility signal in the EIT data (14). This approach has been validated in ARDS patients, demonstrating good agreement with invasive methods. EIT-derived CO can also be used to assess absolute V/Q, which enhances the clinical utility of EIT in monitoring and guiding treatments for ARDS (14). This advancement allows for the application of these methods in calculating our novel V/Q parameter, thereby broadening its applicability.

The limitations of this case include the restricted number of EIT assessment time points, which hindered a robust validation of the modified parameter's efficacy. Additionally, while the optimal V/Q ratio can span a range from 0.8 to 1.0, our analysis exclusively selected 1.0 as the ideal value for calculating the modified index relative to this benchmark. This approach may have partially influenced the outcomes, particularly for patients whose predominant V/Q ratio was 0.8. Despite the relative stability of our treatment protocols during the NO inhalation period, our case did not explore the relationship between other therapies and the P/F ratio, such as antibiotic therapy or fluid balance. Additionally, integrating the CO-related V/Q match index into routine clinical practice faces challenges, including the lack of standardization in lung perfusion assessment using EIT and the complexity added by the invasive nature of the PiCCO method for measuring cardiac output. The generalizability of our findings is limited due to the single-case nature of the study, and further validation in larger, diverse cohorts is needed.

Conclusion

In conclusion, this case elucidates the significance of the modified EIT-derived parameter——CO-related V/Q match index, revealing its benefits in evaluating the V/Q ratio under the various treatment strategies when compared to traditional ones.

Data availability statement

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

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the 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

JX: Investigation, Data curation, Software, Writing – original draft, Conceptualization, Methodology, Writing – review and editing, Formal Analysis. MZ: Investigation, Writing – review and editing, Methodology, Writing – original draft, Visualization, Data curation, Formal Analysis, Conceptualization. DL: Writing – review and editing, Investigation, Data curation. JG: Methodology, Software, Writing – original draft. XQ: Investigation, Writing – review and editing. RT: Resources, Funding acquisition, Writing – review and editing. PL: Methodology, Software, Investigation, Writing – review and editing. ZZ: Validation, Methodology, Writing – review and editing, Software. HQ: Methodology, Project administration, Validation, Conceptualization, Supervision, Funding acquisition, Resources, Writing – review and editing. JL: Validation, Supervision, Conceptualization, Methodology, Project administration, Investigation, Funding acquisition, Writing – review and editing, Formal Analysis.

Funding

The authors declare that financial support was received for the research and/or publication of this article. This study was supported by the Scientific Research Project Plan of Shanghai Municipal Health Commission (20224Y0029) and National Natural Science Foundation of China (82202405) awarded to JX. Shanghai Science and Technology Commission Project (23Y11900100) awarded to RT.

Acknowledgments

We would like to thank the patient and his guardians for their participation in the study.

Conflict of interest

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

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Case Report
PUBLISHED 18 July 2025
DOI 10.3389/fphar.2025.1572578

OPEN ACCESS

EDITED BY
Yuetian Yu,
Shanghai Jiao Tong University, China

REVIEWED BY
Deniz Gezer,
Mersin City Hospital, Türkiye
Darpanarayan Hazra,
Sultan Qaboos University, Oman

*CORRESPONDENCE
Xiangdong Jian,
jianxiangdongvip@vip.163.com

RECEIVED 07 February 2025
ACCEPTED 10 July 2025
PUBLISHED 18 July 2025

CITATION
Tian Q, Shang R, Liu Y, Liu H, Zheng Y and Jian X (2025) Case Report: Third-degree atrioventricular block and respiratory failure caused by clozapine poisoning.
Front. Pharmacol. 16:1572578.
doi: 10.3389/fphar.2025.1572578

Case Report: Third-degree atrioventricular block and respiratory failure caused by clozapine poisoning

Qiaoxin Tian[1,2], Ruikai Shang[1,2], Yuru Liu[2,3], Hongyu Liu[2], Yingying Zheng[2] and Xiangdong Jian[1,2]*

[1]Department of Occupational and Environmental Health, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China, [2]Department of Poisoning and Occupational Diseases, Emergency Medicine, Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China, [3]School of Nursing and Rehabilitation, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

Background: This case report details the management of a patient who presented with third-degree atrioventricular block and rhabdomyolysis secondary to clozapine intoxication.

Case summary: The patient was a 55-year-old man who took 100 tablets of clozapine and was transferred to our hospital from a lower-level hospital for treatment. Upon arrival at our hospital, he was in a coma and was assisted with mechanical ventilation. Upon admission, based on the results of toxicological tests and laboratory examination; computed tomography, magnetic resonance imaging, and echocardiography findings, and the patient's clinical manifestations, the diagnosis of third-degree atrioventricular block and rhabdomyolysis due to excessive intake of clozapine was confirmed. The patient received comprehensive treatment, including blood purification, organ protection, nutritional support, and cardiac rate enhancement. The patient was clinically cured and discharged. Clozapine-induced central nervous system inhibition can be dose-dependent, thus leading to coma and organ damage at high doses. Considering that no specific antidotes are available, cases involving clozapine toxicity require careful management. In this instance, beyond the central nervous system and respiratory depression, the patient also exhibited third-degree atrioventricular block and rhabdomyolysis, which warrant significant attention.

Conclusion: Many patients with clozapine poisoning have been admitted to our department. Clozapine poisoning mostly causes symptoms such as accelerated heart rate, but in our patient's case, third-degree atrioventricular block and rhabdomyolysis symptoms occurred unusually. For clozapine poisoning, timely and appropriate management is crucial for the recovery of patients.

KEYWORDS

clozapine, poisoning, atrioventricular block, rhabdomyolysis, respiratory failure

1 Introduction

Clozapine, with the molecular formula $C_{18}H_{19}ClN_4$, was the first atypical antipsychotic drug, initially synthesized in 1959 (Khokhar et al., 2018). It exerts complex pharmacological effects by potently blocking 5-hydroxytryptamine receptors and dopamine receptors in the brain (Khokhar et al., 2018). Additionally, it possesses anticholinergic, antihistaminergic, and anti-α-adrenergic properties and modulates glutamatergic and γ-aminobutyric acid systems (Olney et al., 1999; Wenthur and Lindsley, 2013). Despite being withdrawn from the market in 1970 due to cases of agranulocytosis, clozapine was reapproved by the United States Food and Drug Administration in 1990 (Hippius, 1999). To this day, the precise mechanism by which clozapine is highly effective in treating refractory schizophrenia has not been fully clarified. Clozapine has a weak affinity for D2 receptors, but it can bind more closely to 5-hydroxytryptaminergic, α -adrenergic, metabolic glutaminergic, and muscarinic receptors. In addition, it has neuroprotective, anti-proliferative, and anti-inflammatory actions. The metabolite of clozapine, *N*-desmethylclozapine, can act as a positive allosteric modulator of the muscarinic M1 receptor and an agonist of the M4 receptor. This mechanism of action is likely to contribute to the unique therapeutic effect of clozapine. Although its use is associated with adverse reactions affecting the respiratory, digestive, and circulatory systems, clozapine remains widely prescribed because clozapine has significant advantages over other dopamine receptor blocker antipsychotic drugs in managing refractory schizophrenia: it is more effective in reducing positive symptoms; reducing the risk of recurrence/hospitalization, suicidal behavior, substance abuse, and aggressive behavior; enhancing social functions including employment; and reducing the risk of death (Correll, 2025). Therefore, its clinical use has been re-approved in China and abroad, with a utilization rate of 39.0% in China (Jingping and Shenxun, 2015). Cases of acute clozapine poisoning, often due to overdose or accidental ingestion, occur frequently. This report details a case of acute clozapine poisoning confirmed through toxicological testing, where the patient developed third-degree atrioventricular block and respiratory failure.

2 Case description

Ethical approval was obtained from the Ethics Committee of Qilu Hospital of Shandong University, and informed consent was obtained from the patient.

A 55-year-old man with schizophrenia, who had been taking oral clozapine, was transferred from a low-level hospital to our hospital with a ventilator on 13 February 2024, for "altered consciousness for 2 days" On admission, physical examination showed a temperature of 36.9°C, heart rate of 49 beats/min, respiratory rate of 15 breaths/min, blood pressure of 132/61 mmHg, and SpO_2 of 99%. He was in a sedated and analgesic state (Glasgow Coma Scale, 1-1–3, 5) and was on mechanical ventilation. His pupils were approximately 2.0 mm in diameter, with sluggish light reflexes. Lung examination revealed coarse breath sounds without wet rales. No pathological murmur was detected in the heart. The abdomen was soft, and the liver and spleen were not palpable. No spinal or limb deformities were noted, and physiological reflexes were present without pathological signs.

3 Diagnostic assessment

Initial diagnoses included altered consciousness, respiratory failure, and suspected drug poisoning. After admission, various examinations were performed promptly. Toxicology test results revealed a clozapine concentration of 1800.00 ng/mL. An electrocardiogram indicated third-degree atrioventricular block (Figure 1), and laboratory test results indicated creatine kinase levels of 9255 U/L, creatine kinase-myocardial band (CK-MB) levels of 29.20 ng/mL, myoglobin levels of 368.00 ng/mL, and cardiac troponin levels of 237.72 ng/L. The patient was diagnosed with acute clozapine poisoning, respiratory failure, third-degree atrioventricular block, and rhabdomyolysis.

4 Intervention

After admission, continuous ventilator-assisted ventilation was provided. Considering that the patient's inflammatory indicators such as PCT (0.159 ng/mL), NEU% (78.6%), and LYM% (13.20%) were abnormal; presence of apoptosis and inflammation in both lungs; and excessive concentration of clozapine, hemoperfusion and continuous renal replacement therapy were required. Therefore, we used flucloxacillin for anti-infection. Meanwhile, we used diuretics to promote excretion and intravenous injection of fat emulsion for detoxification and nutritional support. We invited cardiology experts for consultation who recommended the use of a temporary pacemaker. The patient was in a coma. After repeated communication, the patient's family insisted on conservative treatment and signed a document refusing the installation of a pacemaker (Liang et al., 2011). By the third day of admission, his heart rate had decreased to 32 beats/min. A temporary cardiac pacemaker was recommended, but the patient's family declined. On the sixth day, sedation was reduced, and he was weaned off the ventilator. On the seventh day, the tracheal tube was removed, and furosemide and flucloxacillin were discontinued. The creatine kinase level decreased to 122 U/L, and the CK-MB decreased to 4.5 ng/mL. After the patient regained consciousness, we inquired about the medical history. Before the patient fell into a coma, 100 tablets of clozapine were taken orally, and no other drugs were used simultaneously. This information was consistent with the results of the toxicological tests. On the eighth day, his spontaneous heart rate increased, allowing a gradual reduction in isoproterenol. By the ninth day, head magnetic resonance imaging showed a few ischemic and degenerative foci in the brain (Figure 2), and chest computed tomography images showed a few areas of pneumonia in both lungs (Figure 3). An echocardiogram indicated left ventricular dilation, with a posterior diameter of 57 mm (normal value: 38.7–54.7 mm) (Figure 4). On the 12th day, after discontinuing isoproterenol, his spontaneous heart rate stabilized at 55 beats/min, with no symptoms such as blackouts, dizziness, or syncope. The patient was discharged on the 14th day.

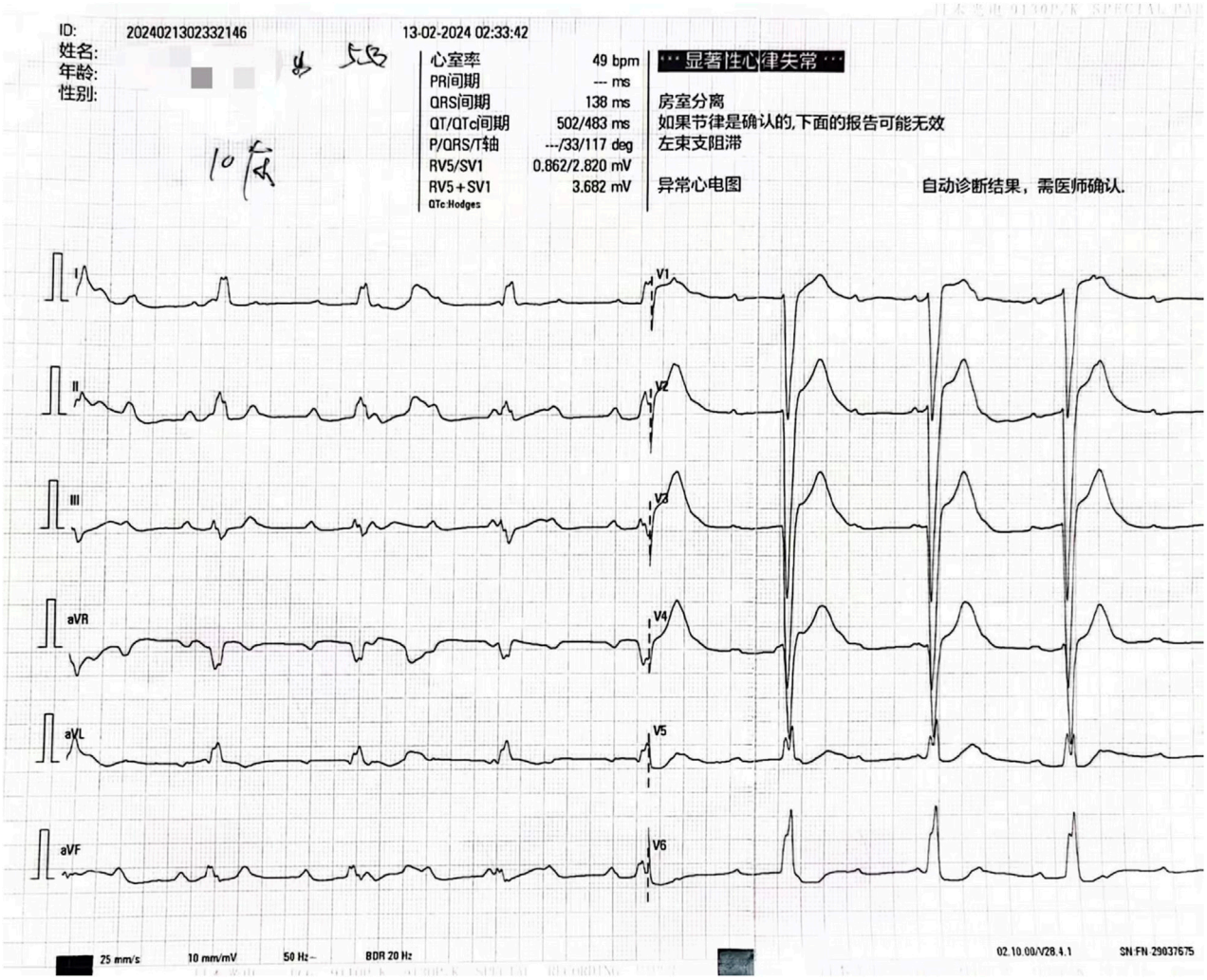


FIGURE 1
Electrocardiogram showed third-degree atrioventricular block.

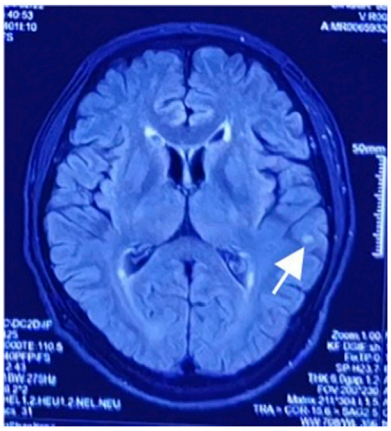


FIGURE 2
Magnetic resonance imaging examination revealed a few ischemic lesions in the brain.

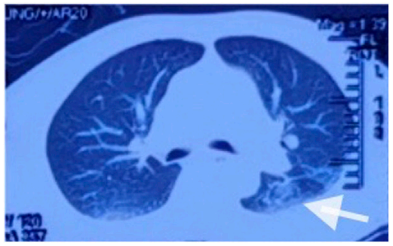
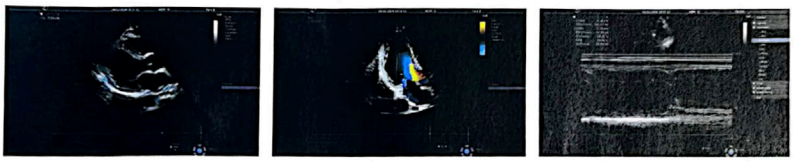


FIGURE 3
Chest computed tomography scan revealed slight pneumonia in both lungs.

5 Follow-up

Follow-up phone calls confirmed that he remained self-sufficient in daily life and had no significant abnormal manifestations.



超声所见：
一、各心腔和大血管超声扫查和相关测量以及室壁运动分析：
升主动脉：32mm(21.2～35.6mm)，左房前后径：38mm(23.5～39.5mm)，左室前后径：57mm(38.7～54.7mm)↑，室间隔：11mm(6.6～11.9mm)，左室后壁：9mm(6.1～11.3mm)，右室前后径：26mm(14.7～31.1mm)，右房长径：53mm(35.3～54.9mm)，右房横径：43mm(25～45mm)，主肺动脉：25mm(15～27.5mm)。
心房正位，心室右袢，房、室及大血管连接关系正常；房、室间隔未见明显回声中断；左室壁运动欠协调，左室壁动度尚可；各组瓣膜结构未见明显异常。

二、心功能测定常用参数：
LVEF：0.56（M超）　　EDV：140ml　　SV：79ml

三、彩色和频谱多普勒：
1、收缩期左房内可见分布局限的二尖瓣反流束；
2、收缩期右房内可见分布局限的三尖瓣反流束，CW测最大反流压差约26mmHg，估测肺动脉收缩压约31mmHg；
3、舒张期左室流出道可见分布少量的主动脉瓣反流束；
4、PW测二尖瓣前向血流频谱E峰>A峰。

超声提示：
左室扩大
二尖瓣反流（轻度）
三尖瓣反流（轻度）

FIGURE 4
Echocardiographic report.

6 Discussion

Clozapine is recommended for use at a blood concentration of 300–420 ng/mL. When its blood concentration exceeds 600 ng/mL, patients may experience adverse reactions (Rajkumar et al., 2013), while toxic symptoms typically develop at concentrations above 1,000 ng/mL (Haack et al., 2003). Clozapine poisoning primarily manifests as central nervous system depression, respiratory depression, and cardiovascular dysfunction (Krämer et al., 2010). At high doses, the dose-dependent central nervous system inhibition often leads to coma. Severe clozapine poisoning may cause respiratory depression, characterized by changes in breathing rhythm, cyanosis of the lips, and apnea. Aspiration pneumonia caused by toxic coma is a leading cause of death in clozapine-related cases (Krämer et al., 2010). Therefore, clinicians must closely monitor comatose patients for respiratory complications. Acute clozapine poisoning commonly affects the cardiovascular system, manifesting as hypertension, tachycardia, and prolonged QTc interval (Krämer et al., 2010). The symptoms of acute clozapine poisoning include dysarthria, myoclonus, bradykinesia, tremors, nausea, vomiting, dry mouth, excessive salivation, and fever (Krämer et al., 2010). Studies have shown that psychotropic drugs may cause an increase in troponin, which was also observed in this case (Wan et al., 2025). The diagnosis relies primarily on medical history, physical examination, and blood concentration testing. A low blood concentration of clozapine does not rule out acute clozapine poisoning, as there have been reports of poisoning occurring within the therapeutic window. In this case, the patient presented with third-degree atrioventricular block and rhabdomyolysis in addition to central nervous system and respiratory depression. Complete atrioventricular block induced by clozapine is rare, with only two cases reported in the literature (Gabeler and van Miltenburg, 2011; Türe et al., 2019). This condition may result from clozapine-mediated inhibition of sinus node depolarization and reduced adrenergic sensitivity (Krobert et al., 2006). Clozapine is cardiotoxic and has been linked to myocarditis and cardiomyopathy (Siskind et al., 2020). Clozapine-induced reduction of selenium, an important antioxidant involved in myocardial recovery, impairs the repair of the damaged conduction system and causes a conduction block (Vaddadi et al., 2003). In this case, myocardial damage was evident from an elevated serum high-sensitivity troponin level of 237.72 ng/L at admission (normal value <17.5 ng/L) and left ventricular dilation observed on echocardiography. When third-degree atrioventricular block occurs, it is essential to promptly identify the cause, manage infections, and correct electrolyte disorders. Cardiac pacing therapy should be administered when hemodynamic instability is caused by a slow ventricular rate. However, the patient's family refused temporary cardiac pacing in this case.

Rhabdomyolysis occurs when damage to muscle cells results in the release of cellular contents into the bloodstream. Rhabdomyolysis is usually defined as creatine kinase >1000 IU/L or CK > 5 times the normal upper limit (Stahl et al., 2020). Early intervention is critical for preventing life-threatening complications, such as acute kidney injury. In this case, the peak creatine kinase level was 9255 IU/L; therefore, the diagnosis of rhabdomyolysis was confirmed. The mechanism by which clozapine causes rhabdomyolysis is also unclear, but all muscle injuries follow a common pathway: the muscle cell membrane is directly destroyed or muscle cell energy is depleted (Bosch et al., 2009), and free calcium enters the cell and activates the protease and apoptosis pathways (Giannoglou et al., 2007). The production of reactive oxygen species leads to mitochondrial dysfunction and, ultimately, cell death (Giannoglou et al., 2007). Previously, we reported a case of rhabdomyolysis caused by olanzapine poisoning, which may have been related to the muscular toxicity of the drug and long-term muscle compression caused by coma (Yu et al., 2021).

Currently, no specific antidote for clozapine poisoning exists. Symptomatic supportive treatment remains the mainstay, and maintaining the stability of respiration and circulation is important (Levine and Ruha, 2012). When patients consume large amounts of oral medicine and have serious complications, toxic symptoms can be alleviated by blood purification (Kirilochev et al., 2024). In cases of unexplained bradycardia encountered in clinical practice, the possibility of cardiac dysfunction due to high-dose or long-term oral administration should be considered.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Shandong University Qilu Hospital Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QT: Writing – original draft, Writing – review and editing. RS: Data curation, Investigation, Writing – review and editing. YL: Data curation, Investigation, Writing – review and editing. HL: Data curation, Investigation, Writing – review and editing. YZ: Data curation, Investigation, Writing – review and editing. XJ: Data curation, Investigation, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We thank the staff of the Department of Toxicology and Occupational Disease, Emergency Department, Qilu Hospital, Shandong University, for their support with the sample and clinical data collection.

Conflict of interest

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

Generative AI statement

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

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 21 July 2025
DOI 10.3389/fmed.2025.1613583

OPEN ACCESS

EDITED BY
Yuetian Yu,
Shanghai Jiao Tong University, China

REVIEWED BY
Rubino Nunziata,
Centro Sanitario Locale Napoli 1 Centro, Italy
Mohan Chandu Uppalapati,
Chalapathi Institute of Pharmaceutical Sciences, India
Owais Aljafri,
Ministry of Health, Saudi Arabia

*CORRESPONDENCE
Linhao Ma
macro118@139.com

RECEIVED 17 April 2025
ACCEPTED 01 July 2025
PUBLISHED 21 July 2025

CITATION
Wu X, Duan L and Ma L (2025) Oral high-dose sertraline-induced acute pancreatitis: a case report and literature review.
Front. Med. 12:1613583.
doi: 10.3389/fmed.2025.1613583

Oral high-dose sertraline-induced acute pancreatitis: a case report and literature review

Xiaoying Wu[1], Liwei Duan[1] and Linhao Ma[1,2]*

[1]Department of Emergency Medicine, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, Shanghai, China, [2]Department of Medical Affairs, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, Shanghai, China

Acute pancreatitis (AP) is characterized by acute inflammation and pancreatic injury, with gallstones and chronic alcohol use representing the most common etiologies. Although drug-induced pancreatitis (DIP) accounts for fewer than 3% of AP cases, its recognition as a significant contributor to AP is growing. Sertraline, a widely prescribed selective serotonin reuptake inhibitor (SSRI), is associated with diverse adverse effects, even at therapeutic doses. We present a case of a 27-year-old female with a history of depression who developed mild acute pancreatitis following a sertraline overdose. Diagnostic evaluation, including computed tomography (CT) and serological analysis, revealed pancreatic parenchymal swelling and elevated serum amylase levels, confirming AP. Other potential causes were systematically excluded. The patient's condition resolved following drug discontinuation and standard supportive therapy. This case underscores the need for heightened clinical awareness of SSRI-associated pancreatitis, particularly in the context of overdose.

KEYWORDS

sertraline, acute pancreatitis, drug-induced pancreatitis, overdose, SSRIs

Introduction

Drug-induced pancreatitis (DIP) is a well-defined but underrecognized etiology of acute pancreatitis (AP), triggered by direct toxicity or metabolic effects of medications (1). Diagnosis requires fulfillment of established AP criteria (e.g., revised Atlanta classification), exclusion of alternative causes (e.g., gallstones, alcohol), and symptom resolution upon drug cessation. Despite its inclusion in clinical guidelines, DIP remains underdiagnosed due to nonspecific presentation, the absence of definitive biomarkers, and limited clinician familiarity with drug-related pancreatic injury—particularly for medications not classically associated with pancreatic toxicity (e.g., antidepressants, immunosuppressants) (2). More than 264 different drugs from various classes were found associated with AP, but as a result of the general lack of formal epidemiological studies, the magnitude of the risk of most of these medications remained unknown. Several studies have been published that have analysed how many cases of AP can be associated with the use of drugs (3). These studies have established the prevalence of drug-induced AP cases at 0.03% in Canada, 0.05% in Korea, 0.2% in France and 0.3% in Switzerland (4). However, mechanistic understanding remains incomplete, and epidemiological data are scarce due to underreporting and diagnostic challenges. This case report highlights sertraline, a selective serotonin reuptake inhibitor (SSRI), as a potential culprit in DIP—a association infrequently documented in the literature. We present a confirmed case of sertraline-induced AP following overdose, emphasizing the importance of pharmacovigilance and systematic exclusion of DIP in atypical AP presentations.

Case description

A 27-year-old female presented to the emergency department 3 h after ingesting 1,000 mg of sertraline (20*50 mg tablets). She had been prescribed sertraline 75 mg daily for depression diagnosed 1 month prior. The patient denied alcohol use, binge eating, biliary disease, or prior pancreatic/surgical interventions (e.g., endoscopic retrograde cholangiopancreatography). On examination, she was ambulatory, afebrile (37.2°C), with stable vital signs (pulse 92 bpm, respiratory rate 20/min, BP 118/83 mmHg). Abdominal examination revealed no tenderness, rebound, or guarding. Cardiac and pulmonary auscultation was unremarkable. Laboratory findings at admission included: Serum amylase: 228 U/L (reference: 30–110 U/L); Leukocytosis: 13.23 × 10 < sup > 9</sup>/L; Total bilirubin: 24.4 μmol/L; Arterial blood gas: pH 7.43, actual bicarbonate 19 mmol/L, carbon dioxide partial pressure 3.9 KPa, lactate 3.2 mmol/L. Other parameters (liver enzymes, electrolytes) were within normal limits. Admission CT: No pancreatic or biliary abnormalities (Figure 1A). Twelve hours post-admission, serum amylase rose to 684 U/L, while repeat CT demonstrated pancreatic edema without biliary obstruction or gallstones (Figure 1B). Urinary amylase remained negative (inconsistent with serum trends; assay-specific limitations noted), aligning with atypical DIP presentations where urinary markers may lag behind serum elevations.

The patient met diagnostic criteria for AP per Chinese Guidelines (2021) (5) and Atlanta classification: (1) Serum amylase >3*upper limit; (2) Characteristic CT findings. Her BISAP score of 0 predicted mild disease. Management included: Gastric lavage (for overdose); fluid resuscitation (lactated Ringer's: 250 mL/h), antibiotics (ceftriaxone), acid suppression and gastric mucosa protection (pantoprazole 40 mg IV BID); Supportive care (fasting). Monitoring: Serial amylase (down-trending to 241 U/L at 24 h) and repeat CT (normalization, Figure 1C). Sertraline was discontinued, and AP resolved without complications. On the third day of hospitalization (72 h), the patient had no complaints and requested discharge. Rechallenge with 50 mg sertraline during follow-up did not recur symptoms, suggesting dose-dependent toxicity. Combining the medical history and medication use, Per the China National Center for Adverse Drug Reaction Monitoring criteria (6), this case was graded as "probable" due to: Temporal association (onset ≤12 h post-overdose); Exclusion of alternative causes (biliary, alcohol, metabolic); Biochemical/histologic plausibility (SSRI-induced sphincter of Oddi dysfunction). Notably, rechallenge with sertraline 50 mg during follow-up did not recur, suggesting dose-dependent toxicity (Figures 2, 3).

Discussion

Drug-induced pancreatitis (DIP) accounts for 0.1–3.4% of acute pancreatitis (AP) cases, with a rising incidence reported in recent years, primarily documented through case reports and retrospective studies. Due to ethical constraints, prospective studies or rechallenge trials are rarely feasible, leaving retrospective analyses and case series as the primary sources of evidence. Diagnosing DIP remains challenging, as definitive confirmation often requires drug rechallenge, which is seldom performed in clinical practice. Instead, most cases rely on presumptive diagnosis, based on temporal drug exposure and the exclusion of other etiologies. The lack of specific biomarkers or imaging features further complicates differentiation from other causes of AP. Currently, no universally accepted diagnostic criteria exist, and DIP remains largely a diagnosis of exclusion (7). A 2023 multicenter analysis of 1,060 DIP cases established antitumor agents (16.89%), antibiotics (12.08%), anticonvulsants (9.72%), and antipsychotics (3.77%) as the predominant causative agents, with severity stratification showing mild (68.77%), moderate (11.13%), and severe

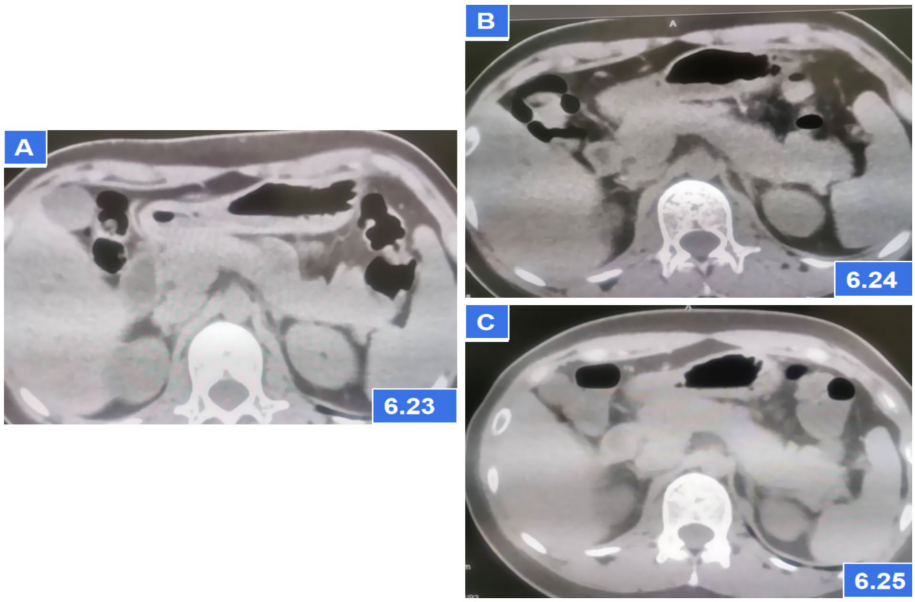

FIGURE 1
Abdominal CT showing pancreatic parenchymal swelling; **(A)** CT scans on the first day after admission; **(B)** CT scans at 6 h later after admission; **(C)** CT scans after AP diagnosis and treatment for 2 days.

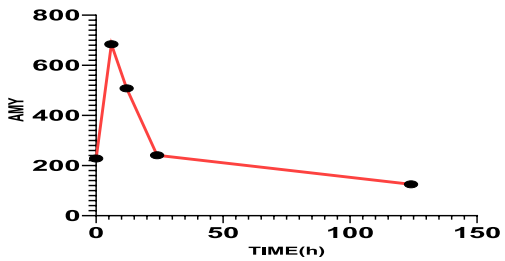

FIGURE 2
The serum amylase value on the first day after admission was 228 U/L, 6 h later was 684 U/L, 12 h later was 508 U/L, 24 h later was 241 U/L, and 120 h later was 125 U/L.

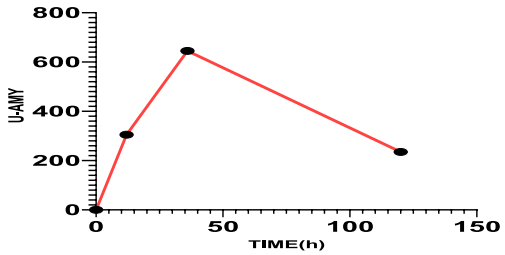

FIGURE 3
The value of urinary amylase was 305 U/L after 12 h, 645 U/L after 30 h, and 235 U/L after 120 h.

AP (20.09%) (8). Mechanistic studies demonstrate three validated pathways for DIP: (i) direct acinar cell toxicity via intracellular metabolite accumulation, (ii) sphincter of Oddi dyskinesia observed in cholescintigraphy studies, and (iii) delayed-type hypersensitivity reactions confirmed through lymphocyte transformation testing (9). While SSRIs account for <1% of DIP cases in pharmacovigilance databases, the temporal association in this case meets the Karch-Lasagna criteria for adverse drug reaction causality: (1) Chronological plausibility: Pancreatitis onset occurred 30 days after sertraline initiation, consistent with the 7–21 day latency period reported in confirmed SSRI-induced AP cases. (2) Dechallenge response: Serum lipase normalized (from 684 U/L to 125 U/L) within120 hours of discontinuation, mirroring the 72-h resolution window documented in prior cases. (3) Exclusion of confounders: Comprehensive workup ruled out gallstones (abdominal CT), hypertriglyceridemia (Due to the limited emergency conditions, blood lipid was not checked. However, after communication with the laboratory department, no lipemia was found in serum specimens, so hyperlipidemia was excluded) and alcohol use (4) Rechallenge data: The patient denied the history of pancreatitis, cholecystitis, gallstones and other drug history. He had an annual physical examination and no obvious gallbladder or pancreatic disease was found, suggesting a sertraline-specific effect. It has been found that after an overdose of sertraline or other selective serotonin reuptake inhibitors (SSRIs), some patients show no clinical symptoms, while others may present with somnolence, tremors, nausea, vomiting, dilated pupils, tachycardia, electrocardiogram changes, etc. (10). However, This case suggests that it may cause AP, providing partial support for sertraline-related AP. Combining the patient's medication history, the temporal rationality of AP occurrence, the potential risk of sertraline-induced AP, improvement after discontinuation of the drug and symptomatic treatment, and other factors that may induce AP, a comprehensive analysis and judgment suggest that this may be DIP caused by sertraline. This biochemical and temporal profile aligns with the 2024 AGA guidelines for DIP diagnosis, while the rapid clinical improvement is consistent with a meta-analysis of a case–control study on the risk of acute pancreatitis and SSRI use (11). The Naranjo Adverse Drug Reaction Probability Scale score of 6 ("probable") further supports this association.

The relationship between SSRIs and DIP remains controversial. A population-based case–control study including 4,631 AP patients found a possible association between SSRIs and AP (12). Another meta-analysis involving 17,548 AP patients from four studies showed that the combined odds ratio (OR) for AP risk with SSRIs was 1.26 (95% CI: 1.13–1.40). Subgroup analysis indicated that the first 2 weeks of SSRI use were a high-risk period for AP, with the risk 1.48 times higher than after 2 weeks. This meta-analysis provided evidence of a significant positive correlation between SSRI use and AP risk, with a higher risk within the first 2 weeks of use, which should be taken seriously (13).

Sertraline is one of the most widely used SSRIs and a classic antidepressant. However, due to inconsistent latency periods and the absence of rechallenge data—often precluded for ethical reasons—the causal relationship remains uncertain, sertraline is classified as Category IV according to the Badalov classification criteria. There are very few reports of sertraline causing DIP. We searched and collected published data on sertraline-induced DIP in PubMed and found only four cases to date. However, due to the lack of a consistent latency period and absence of drug rechallenge, the evidence is weak, and the classification has been updated to Category III (14). Recent studies emphasize the need for further pharmacovigilance to clarify this potential association, particularly as SSRIs continue to be extensively prescribed worldwide.

In this case, the patient exhibited no significant clinical symptoms 3 h after an acute sertraline overdose. Diagnosis of acute pancreatitis (AP) was confirmed biochemically (amylase elevation >3*the upper limit of normal) and radiologically (characteristic CT findings). Other etiologies were ruled out, as the patient denied alcohol use, comorbidities, or concurrent medications. Notably, the rapid onset following overdose and resolution upon drug discontinuation support sertraline as the likely culprit. Unlike prior reports implicating polypharmacy or alcohol, this case had minimal confounders. The patient had tolerated a therapeutic dose (50 mg/day) for 1 month without incident, suggesting dose-dependent toxicity, as AP occurred only after overdose and did not recur upon resuming the standard dose. While rechallenge was ethically unfeasible, the temporal association aligns with recent evidence linking SSRIs to drug-induced pancreatitis (DIP). This underscores the need for vigilance regarding AP in intentional overdoses, particularly with psychotropic agents.

Conclusion

Drug-induced pancreatitis (DIP) is a rare etiology of acute pancreatitis (AP), associated with hundreds of medications. Familiarity with published case reports and research on implicated drugs is essential for clinicians to promptly recognize DIP and incorporate this possibility into therapeutic decision-making. This case report contributes clinical evidence supporting the association between sertraline and AP. Given the expanding use of antidepressants

across diverse age groups, clinicians should maintain a high index of suspicion for SSRI-related acute pancreatitis, including sertraline, particularly in cases of intentional overdose. These findings underscore the importance of heightened clinical awareness and implement appropriate monitoring protocols for potential sertraline-induced acute pancreatitis. Especially in patients presenting after suicide attempts involving drug overdose.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Department of Emergency Medicine, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, Shanghai. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant(s)/patient(s) for the publication of this case report.

Author contributions

XW: Data curation, Formal analysis, Supervision, Writing – original draft, Conceptualization, Investigation, Methodology, Project administration, Validation. LD: Data curation, Formal analysis, Supervision, Investigation, Writing – review & editing. LM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Supervision, Writing – review & editing, Methodology, Project administration, Resources, Validation.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

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

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The authors declare that no Gen AI was used in the creation of this manuscript.

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TYPE Case Report
PUBLISHED 13 August 2025
DOI 10.3389/fmed.2025.1626194

OPEN ACCESS

EDITED BY
Cheng Zhu,
Shanghai Jiao Tong University, China

REVIEWED BY
István Fekete,
University of Debrecen, Hungary
Dimash Davletov,
Kazakh National Medical University, Kazakhstan

*CORRESPONDENCE
Bing-Hu Li
libinghu1982@163.com

RECEIVED 10 May 2025
ACCEPTED 31 July 2025
PUBLISHED 13 August 2025

CITATION
Yang S, Wang J-H, Huang B, Guo F-Q and Li B-H (2025) Emergent carotid artery stenting with tirofiban in a patient with traumatic intracranial hemorrhage and carotid artery dissection: a case report.
Front. Med. 12:1626194.
doi: 10.3389/fmed.2025.1626194

Emergent carotid artery stenting with tirofiban in a patient with traumatic intracranial hemorrhage and carotid artery dissection: a case report

Shu Yang, Jian-Hong Wang, Bin Huang, Fu-Qiang Guo and Bing-Hu Li*

Department of Neurology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, China

Endovascular therapy (EVT) is an effective treatment for large vessel occlusion, including carotid artery dissection (CAD). However, when large vessel occlusion (LVO) occurs in acute ischemic stroke (AIS) patients with concomitant intracranial hemorrhage (ICH), it can be difficult for clinicians to make a treatment decision. We report the case of a patient in their 60s who was admitted due to sudden right limb weakness. Emergency computed tomography (CT)/CTA showed a hematoma in the right parietal lobe and a possible dissection of the left internal carotid artery. The patient underwent emergent carotid artery stenting (eCAS) followed by postoperative tirofiban administration. At six-month follow-up, there was no evidence of new bleeding, clinical function had recovered, and no re-stenosis was observed. For patients with AIS due to CAD complicated by ICH, eCAS combined with tirofiban may offer clinical benefits. However, further research is still needed to confirm our findings.

KEYWORDS

acute cerebral infarction, carotid artery dissection, case report, endovascular therapy, emergent carotid artery stenting, traumatic intracranial hemorrhage

Introduction

Endovascular therapy (EVT) is an effective treatment for patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO) (1). In clinical practice, patients with acute ischemic stroke (AIS) who develop concurrent intracranial hemorrhage (ICH) may be excluded from EVT. However, a meta-analysis indicated that EVT is feasible in AIS patients with concurrent intracranial hemorrhage (ICH), although it is associated with poor functional outcomes and high mortality rates (2). It still needs to be determined which patients are suitable for EVT. Regarding the etiology of LVO, carotid artery dissection (CAD) is one of the common causes (3). The primary treatments for CAD are antithrombotic therapies using either anticoagulants or antiplatelet drugs (4). EVT is only required in cases of symptomatic cervical artery stenosis or occlusion. A recent study revealed that EVT may improve functional outcomes in patients with LVO due to CAD and an admission National Institutes of Health Stroke Scale (NIHSS) score ≥6 but not in those with an NIHSS score <6 (5). However, it is still unclear whether EVT or the best medical treatment is more suitable for patients with AIS and CAD. Clinically, when patients have AIS and concurrent CAD with ICH, it is difficult for clinicians to make decisions. Here, we present the case of a patient in their 60s with traumatic ICH who developed AIS due to CAD.

Case presentation

A patient in their 60s was admitted due to the sudden onset of right-sided limb weakness and speech difficulties lasting for 5 h. Physical examination revealed drowsiness, left eye deviation, aphasia, muscle strength of grade 2 in the right limbs and left lower limb, and a left upper limb fracture. The NIHSS score was 22.

The medical history was unremarkable. Furthermore, five days before, the patient was involved in a car accident, resulting in a fracture of the left upper limb (a distal linear fracture of the left radial bone and a fracture of the left ulnar styloid process, both without significant displacement) and an intracranial hemorrhage in the right parietal lobe. A non-contrast head computed tomography (CT) scan revealed a hematoma measuring 23 mm × 23 mm. The patient subsequently developed left-sided limb weakness, with muscle strength of grade 2. The patient received external fixation for the left arm fracture and no specific treatment for the cerebral hemorrhage, aside from blood pressure control, with blood pressure maintained below 140 mmHg. The patient denied a history of hypertension, diabetes, or smoking. There was no family history of genetic disorders.

Emergency non-contrast computed tomography (CT) showed a subacute hematoma in the right parietal lobe (23 mm*23 mm*12 mm) (Figure 1A). Head CT perfusion (CTP) showed a low perfusion area of 298 mL and a mismatch ratio of 49.7 (Figure 1B). Head and neck CTA indicated severe stenosis at the C1 segment of the left internal carotid artery (Figure 1C). Further digital subtraction angiography (DSA) showed an intimal flap on the middle section of the C1 segment of the left internal carotid artery. Considering the patient's history of trauma and the findings from head and neck CTA, there was a high possibility of carotid artery dissection (CAD) caused by trauma (Figure 1D).

Given the medical history, imaging findings, and clinical manifestations, a multidisciplinary team—including neurology, neurosurgery, and critical care medicine—suggested that the patient's new neurological symptoms were caused by AIS due to left internal CAD. The patient was at high risk for cerebral ischemia, cerebral edema, and even cerebral herniation. Internal carotid artery recanalization is currently considered the best treatment option for this patient. The patient had a 5-day history of traumatic cerebral hemorrhage, with no evidence of hematoma enlargement on CT re-examination, and a low risk of bleeding assessed by the HAS-BLED score (1 point). The final treatment plan included emergent carotid artery stenting (eCAS) followed by antiplatelet drugs (6). Given the advantages of a shorter plasma half-life and rapid recovery of platelet function after discontinuation, tirofiban was selected as the antiplatelet drug.

After obtaining informed consent from the patient's family members, eCAS was performed using a Wallstent 9*50 mm carotid stent (Figure 1E) and tirofiban was administered. The dose of tirofiban was calculated at 0.1 μg/Kg/min. For a patient weighing 50 kg, the dose of tirofiban should be 6 mL/H. However, due to concerns about hematoma enlargement, a relatively lower dose of 4 mL/H was administered continuously.

On the 9th day post-stenting, the patient showed improvement in right limb muscle strength to grade 4 while receiving continuous tirofiban infusion at 4 mL/H. A head CT scan was performed, which showed absorption of the hematoma (Figure 1F). Given the absorption of the hematoma and the absence of new bleeding, as well as the better prevention of stent thrombosis, the antithrombotic treatment was planned to transition to oral dual antiplatelet therapy. Considering clopidogrel resistance, tirofiban was replaced with dual antiplatelet therapy with aspirin (100 mg/day) plus ticagrelor (90 mg/Bid) (7). The use of tirofiban was discontinued 4 h after the oral administration of aspirin and ticagrelor. Aspirin plus ticagrelor was planned to be switched to aspirin monotherapy after 6 months (8).

On the 45th day post-stenting, the patient showed progressive improvement in neurological symptoms but still had mild dysarthria at the time of discharge. The patient was fully conscious, with slightly slurred speech, right limb muscle strength of grade 5, left upper limb weakness, left lower limb muscle strength of grade 2, an NIHSS score of 5, and a modified Rankin Scale (mRS) score of 3.

At six-month follow-up, right limb muscle strength had fully recovered to grade 5. Head CT/CTA (Figures 1G,H) showed that the hematoma had mostly resolved, with no signs of narrowing in the stent.

Discussion

Although EVT is an effective treatment for patients with AIS due to LVO, there are no recommendations for AIS patients with concurrent ICH. A meta-analysis (2) including six studies and 49 patients demonstrated that the overall incidence rate of successful revascularization was 85.3% and functional independence was achieved in 20% of patients. This meta-analysis suggests that EVT is feasible in AIS patients with concurrent ICH; however, it is associated with poor functional outcomes and high mortality rates. In the original studies included in this meta-analysis, no LVO was due to CAD and no emergent carotid artery stenting (eCAS) was performed. In our case of traumatic ICH complicated by CAD, the decision between performing EVT—with its risk of hemorrhage progression—and opting for conservative treatment—with its risk of poor clinical outcomes—posed a significant dilemma.

CAD is a common cause of stroke, accounting for up to 25% of cases in adults under 50 years of age (7). eCAS for CAD remains controversial. Cervical artery dissection is a relatively uncommon complication following trauma. For patients without hypoperfusion, eCAS may be unsuitable (7). However, previous studies have demonstrated that eCAS may improve distal perfusion in patients with neurological deficits due to hypoperfusion (9). Therefore, for this case, eCAS was considered reasonable. However, another issue that needs to be considered regarding this case is the periprocedural antithrombotic regimen.

For eCAS, appropriate antithrombotic treatment is indispensable, as early in-stent thrombosis may occur in 5–20% (10), but the optimal antithrombotic regimen still needs to be determined. A retrospective single-center study investigating the efficacy and safety of tirofiban compared to aspirin in patients with AIS undergoing eCAS showed that periprocedural antithrombotic therapy with tirofiban was associated with a lower risk of in-stent thrombosis and sICH within 24 h after eCAS compared to aspirin (11). Another meta-analysis including 34 studies involving 1,658 patients suggested that good functional outcomes are comparable across different antithrombotic treatment regimens, with trends favoring glycoprotein IIb/IIIa

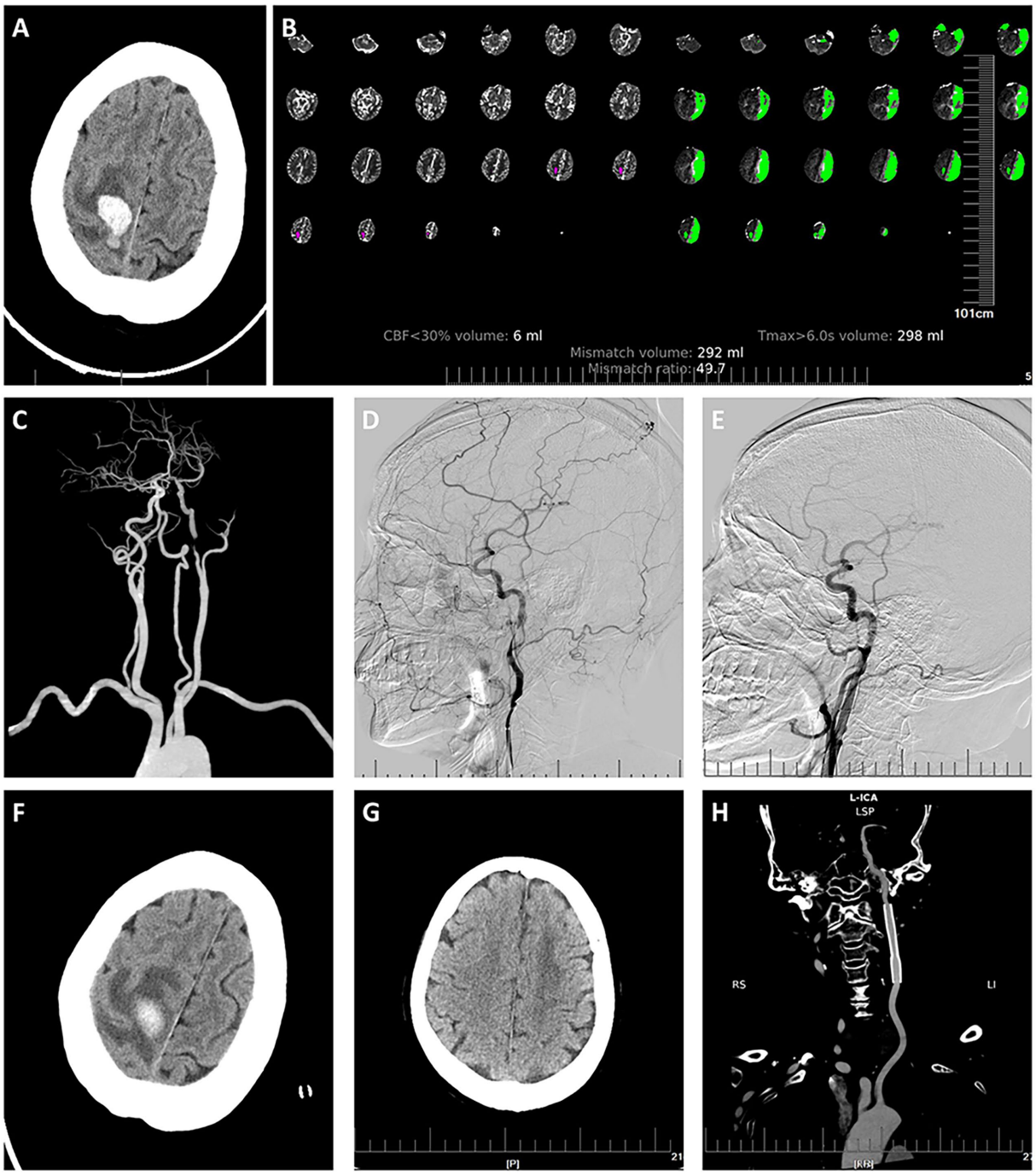

FIGURE 1
Brain images of the patient. **(A)** Emergency head CT showed a subacute right parietal lobe hematoma measuring 23 mm*23 mm*12 mm. **(B,C)** Emergency head and neck CTA and CTP. CTA indicated severe stenosis at the C1 segment of the left internal carotid artery. CTP showed a low perfusion area of 298 mL and a mismatch of 49.7. **(D)** Emergency angiography on admission showed an intimal flap in the middle section of the C1 segment of the left internal carotid artery. **(E)** Immediate angiography post-stenting. **(F)** Head CT 9 days after stenting. G: Head CT 6 months after stenting showed absorption of the hematoma. **(H)** Head and neck CTA 6 months after stenting showed no signs of narrowing in the stent.

inhibitors over dual or single antiplatelet therapy in terms of good functional outcomes (12). This further supports the efficacy and safety of tirofiban. Therefore, the patient in this case was administered tirofiban immediately after eCAS. Follow-up brain CT showed no new bleeding and no enlargement of the previous hematoma.

A limitation of this report is that it is based on a single case, so the findings cannot be generalized. In particular, the safety of tirofiban in patients with acute ICH has not been established, and the risk of hemorrhagic complications is considered unacceptably high in this context.

In conclusion, for patients with AIS due to CAD complicated by ICH, eCAS with tirofiban may offer clinical benefits. This case provides a reference for clinicians to make decisions when faced with similar cases. Although previous studies suggest that EVT is feasible in AIS patients with concurrent ICH, it is associated with poor functional outcomes and high mortality rates. Therefore, our results require further research for confirmation.

Data availability statement

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

Ethics statement

The study was approved by the Ethics Committee of Sichuan Provincial People's Hospital (2025-343). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SY: Data curation, Writing – original draft. J-HW: Writing – original draft, Data curation, Methodology. BH: Writing – original draft. F-QG: Writing – review & editing, Conceptualization. B-HL: Supervision, Writing – review & editing, Data curation, Visualization, Conceptualization.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We are grateful to the patient and her family for their willingness to participate in this case report. Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 20 August 2025
DOI 10.3389/fmed.2025.1634047

OPEN ACCESS

EDITED BY
Somchai Amornyotin,
Mahidol University, Thailand

REVIEWED BY
Eric Teichner,
Sidney Kimmel Medical College (SKMC), United States
Ersin Kuloglu,
Giresun University, Türkiye
Adarsh Kumar,
Vardhman Mahavir Medical College & Safdarjung Hospital, India
Felipe Arturo Valenzo Hernandez,
IMSS-BIENESTAR, Mexico
Nicholas Schoenmann,
Augusta University, United States

*CORRESPONDENCE
Zhongheng Zhang
✉ zh_zhang1984@zju.edu.cn

RECEIVED 23 May 2025
ACCEPTED 27 July 2025
PUBLISHED 20 August 2025

CITATION
Zhou P, Hong Y, Cai H, Zhou X, He S, Zhou H, Yang J, Chen P, Xia B, Lei X, Yang S and Zhang Z (2025) Red yeast rice-induced severe rhabdomyolysis complicated by acute kidney injury and respiratory failure: a case report. *Front. Med.* 12:1634047. doi: 10.3389/fmed.2025.1634047

Red yeast rice-induced severe rhabdomyolysis complicated by acute kidney injury and respiratory failure: a case report

Pengmin Zhou, Yucai Hong, Huabo Cai, Xiaoyu Zhou, Shunpeng He, Haotian Zhou, Jie Yang, Pengpeng Chen, Boming Xia, Xiong Lei, Suibi Yang and Zhongheng Zhang*

Department of Emergency Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China

Red yeast rice (RYR), a commonly used supplement with statin-like properties, is generally considered safe but may cause severe adverse effects such as rhabdomyolysis. We report a rare case of severe RYR-induced rhabdomyolysis complicated by acute kidney injury (AKI) and respiratory failure, with diaphragmatic dysfunction as a key contributing factor. A 78-year-old woman developed progressive proximal muscle weakness, dyspnea, and tea-colored urine after taking RYR (2 g/day) for 1 month. She rapidly progressed to respiratory failure requiring intubation and mechanical ventilation. Laboratory tests showed a peak creatine kinase (CK) of 112,985 U/L, serum myoglobin (>3,000 μg/L), and AKI. Bedside ultrasound demonstrated diaphragmatic dysfunction, while electromyography (EMG) revealed preserved nerve conduction. Myositis-specific and paraneoplastic antibody panels were negative. She received continuous renal replacement therapy (CRRT), plasma exchange (PE), hemoperfusion (HP), and supportive care. During hospitalization, she developed deep vein thrombosis (DVT), pneumonia, and ileus, all of which resolved with treatment. At discharge, she had been weaned from mechanical ventilation and had partially recovered renal and muscle function. At follow-up, she was stable, ambulating, and performing daily functions without symptom recurrence. Although her initial presentation mimicked immune-mediated necrotizing myopathy (IMNM), the absence of myositis-specific antibodies and clinical improvement without immunosuppressive therapy supported a diagnosis of toxic rhabdomyolysis. This case highlights the importance of recognizing supplement-related toxicity and initiating timely organ-targeted supportive care. This appears to be the first reported case of RYR-induced rhabdomyolysis complicated by both AKI and respiratory failure from diaphragmatic dysfunction.

KEYWORDS

red yeast rice, rhabdomyolysis, acute kidney injury, respiratory failure, statin-associated myopathy

Introduction

Red yeast rice (RYR) is a traditional Chinese nutraceutical obtained by fermenting white rice with the mold *Monascus purpureus*. It has gained global popularity as a dietary supplement for cholesterol reduction, primarily due to its content of monacolin K—a naturally occurring statin analog chemically identical to lovastatin (1). Although.

commonly marketed as a "natural" and safer alternative to prescription statins, RYR shares similar pharmacodynamic properties and, consequently, a comparable profile of adverse effects (1, 2)

Among these effects, rhabdomyolysis is a serious and potentially life-threatening complication, characterized by the breakdown of skeletal muscle and the subsequent release of intracellular contents—including creatine kinase (CK) and myoglobin—into the bloodstream (1, 3). While statin-induced rhabdomyolysis has been extensively described, reports of RYR-associated cases remain limited, and severe presentations involving multiorgan dysfunction are exceedingly rare (1).

Here, we present a rare and severe case of RYR-induced rhabdomyolysis in an elderly woman, uniquely complicated by acute kidney injury (AKI) and ventilatory failure secondary to diaphragmatic dysfunction. The clinical presentation mimicked statin-induced immune-mediated necrotizing myopathy (IMNM) in its early clinical course; however, the absence of myositis-specific antibodies and the patient's marked clinical improvement without immunosuppressive therapy supported a diagnosis of toxic rhabdomyolysis.

This appears to be the first documented case of RYR-induced rhabdomyolysis complicated by both AKI and ventilatory failure. This report highlights the potential systemic risks of over-the-counter supplements like RYR and emphasizes the need for clinical awareness.

Case presentation

History of present illness

A 78-year-old woman presented with a 9-day history of low back pain and progressive lower limb weakness, accompanied by worsening dyspnea over the past 3 days. The patient's symptoms began with acute-onset low back pain and leg fatigue, and she rapidly became unable to walk or sit unassisted. She subsequently developed slurred speech, chewing difficulty, and profuse sweating. At the referring hospital, 1 day before transfer to our ICU, she became somnolent due to carbon dioxide retention and required endotracheal intubation and mechanical ventilation. Arterial blood gas analysis performed at the referring hospital revealed a $PaCO_2$ of 80 mmHg at the time of intubation.

Past medical history

The patient had a longstanding history of hypertension for over 10 years, managed with oral amlodipine, and type 2 diabetes mellitus for ~6 months, which was managed with diet control alone. Her home supplements included Coenzyme Q10, Omega-3, and *Ganoderma lucidum* spore powder. Six months prior to the current admission, she was hospitalized for hyperglycemia management, during which routine tumor marker screening revealed elevated carcinoembryonic antigen (19.72 ng/ml) and carbohydrate antigen 72-4 (300 U/ml). However, subsequent abdominal imaging and endoscopic evaluations did not reveal any evidence of malignancy. Two months before admission, she underwent elective surgical resection of an ovarian cyst. Histopathological analysis confirmed the lesion to be benign. Notably, she began taking RYR (2 g daily) 1 month before symptom onset. She denied the use of any prescription statins during this period.

Physical examination

Upon admission to the Intensive Care Unit (ICU), the patient was intubated and sedated, with stable vital signs. After cessation of sedation, she was fully alert and able to follow commands, although full orientation could not be assessed due to intubation. Neurological examination revealed symmetric proximal muscle weakness, graded as 2/5 in the upper limbs and 1/5 in the lower limbs according to the Medical Research Council (MRC) scale, while distal muscle strength was preserved at 4/5. Deep tendon reflexes were absent, and Babinski signs were negative bilaterally. Pupils were equal in size and reactive to light. Cardiopulmonary examinations were unremarkable. Abdominal examination revealed a soft, non-tender abdomen with normal bowel sounds. Tea-colored urine was noted through the indwelling Foley catheter.

Laboratory and imaging examinations

On admission, laboratory tests revealed markedly elevated CK (30,454 U/L), serum myoglobin (>3,000 μg/L) and creatinine (167 μmol/L), consistent with severe rhabdomyolysis and acute kidney injury. Additional findings included significantly increased levels of lactate dehydrogenase (2,096 IU/L), alanine aminotransferase (ALT, 641 U/L), and aspartate aminotransferase (AST, 749 U/L). Her complete blood count on admission showed leukocytosis (white blood cell count, 17.1×10^9/L), with a hemoglobin level of 134 g/L and a platelet count of 239×10^9/L. Acute phase reactants were mildly elevated, with a C-reactive protein level of 11.0 mg/L and a procalcitonin level of 0.08 ng/ml. Urinalysis revealed both hematuria and proteinuria.

A comprehensive neuromuscular workup was performed to exclude other etiologies. Head computed tomography (CT) scans were normal. Lumbar puncture revealed clear cerebrospinal fluid (CSF) with no albuminocytologic dissociation. Electromyography (EMG) demonstrated mildly prolonged F-M latencies and reduced F-wave persistence, but motor and sensory nerve conduction studies were otherwise unremarkable, arguing against a primary neurogenic process.

To investigate for an autoimmune cause, comprehensive myositis-specific and paraneoplastic autoantibody panels were tested and found to be negative. These included myositis-specific antibodies (e.g., anti-HMGCR, anti-SRP, anti-Mi-2) and neuronal antibodies (e.g., anti-Hu, anti-Yo, anti-Ri). Further diagnostic investigations, such as muscle MRI or biopsy, were also deferred at this stage, given that MRI was unfeasible on a ventilated patient and biopsy results would not be timely enough to guide acute management.

TABLE 1 Clinical timeline of the patient.

Hospital day	Event
D-9	Back pain and leg weakness onset
D-3	Worsening dyspnea
D-1	Somnolence due to hypercapnia; intubated
D0	ICU admission; CRRT started
D1	Plasma exchange ×1
D2	Hemoperfusion ×1; lower limb DVT
D3	Plasma Exchange ×1
D4	CK decreased; rehab initiated
D5	Plasma Exchange ×1
D8	VAP with fever; treated with antibiotics
D11	CRRT discontinued
D12	Hemodialysis started; paralytic ileus noted
D16	Tracheostomy; G3 dysphagia on Kubota test
D19	Ventilator weaned
D20	Afebrile; infection improved
D22	Paralytic ileus resolved
D28	Tracheostomy capped
D35	Renal recovery; dialysis stopped
D42	Swallowing adequate; oral intake resumed
D44	Stable discharge

CRRT, continuous renal replacement therapy; DVT, deep vein thrombosis; CK, creatine kinase; VAP, ventilator-associated pneumonia; G3, grade 3 dysphagia based on the Kubota water swallow test. D0 indicates the day of ICU admission; D–x represents days prior to ICU admission.

To identify the cause of respiratory failure, a chest CT scan was performed and was normal. Subsequently, bedside diaphragm ultrasound performed during tidal breathing with pressure support of 5 cmH_2O, focused on the right hemidiaphragm for optimal acoustic window and data quality, showing an excursion of 0.91 cm, end-expiratory thickness of 0.14 cm, end-inspiratory thickness of 0.18 cm, and a thickening fraction (TFdi) of 28.5%—findings consistent with right diaphragmatic dysfunction. A comprehensive assessment of global diaphragmatic function and other accessory respiratory muscles was not performed due to technical limitations.

Diagnosis

The patient was diagnosed with severe rhabdomyolysis complicated by AKI and respiratory failure, likely induced by RYR intake. A detailed differential diagnosis is discussed below.

Treatment and clinical course

The initial step in management was the immediate discontinuation of RYR. On D0 (counted from ICU admission; see Table 1), aggressive intravenous hydration and urine alkalinization were initiated to support renal protection. However, due to persistent oliguria, worsening metabolic acidosis, and rising creatinine levels, continuous renal replacement therapy (CRRT) was promptly started. Given the limited efficacy of CRRT in clearing myoglobin, and in light of the early diagnostic ambiguity between toxic and immune-mediated processes, three sessions of therapeutic plasma exchange (PE) were performed for potential immunomodulation and enhanced myoglobin clearance. Additionally, one session of hemoperfusion (HP) was undertaken to further assist in myoglobin removal, although its role remains investigational. As shown in Figure 1, the patient's CK level peaked at 112,985 U/L on D3. With a sustained decline in CK levels and gradual clinical improvement, CRRT was subsequently transitioned to intermittent hemodialysis (IHD) on D12, administered three times per week. Trends in serum CK and creatinine levels throughout the hospitalization, along with the corresponding therapeutic interventions, are presented in Figure 1.

In parallel with ongoing renal support, early rehabilitation training was initiated on D4 to maintain muscle strength and support respiratory function. Due to persistent difficulty in weaning from mechanical ventilation, likely related to diaphragmatic dysfunction, a tracheostomy was performed on D16. Following tracheostomy, swallowing evaluation was performed for the first time, as reliable assessment had not been feasible during intubation. The Kubota water swallow test revealed grade 3 dysphagia. Accordingly, nasogastric feeding, which had been initiated during intubation, was continued following the tracheostomy.

As respiratory function continued to improve, the patient was successfully weaned from mechanical ventilation on D19. After further clinical stabilization, she was transferred to the rehabilitation unit on D25, where she participated in a comprehensive multidisciplinary program comprising physical therapy, occupational therapy, acupuncture, and physiotherapy, aimed at enhancing cardiopulmonary endurance and restoring both upper and lower limb muscle strength. On D35, serum creatinine levels had returned to near baseline, and hemodialysis was discontinued. The patient maintained adequate urine output and stable renal function thereafter. On D42, a videofluoroscopic swallowing study confirmed adequate swallowing function, and oral intake was safely resumed. The patient was discharged in stable condition on D44.

Her clinical course was also complicated by deep vein thrombosis (DVT), ventilator-associated pneumonia, and paralytic ileus, all of which resolved with targeted therapies and did not significantly delay her overall recovery. A timeline of key clinical events during the patient's hospital stay is summarized in Table 1.

Outcome

After 45 days of hospitalization, the patient was discharged in a clinically stable condition, with spontaneous respiration, intact cognition, and hemodynamic stability. The tracheostomy tube was capped. Swallowing function improved (Kubota grade 2), and oral intake was resumed.

Muscle tone was normal [Modified Ashworth Scale (MAS) score 0]. Muscle strength was graded as 4+ proximally in the upper limbs, 3/5 in the lower limbs, and 5/5 distally, according to the MRC scale. The Modified Barthel Index was 30, reflecting a high level

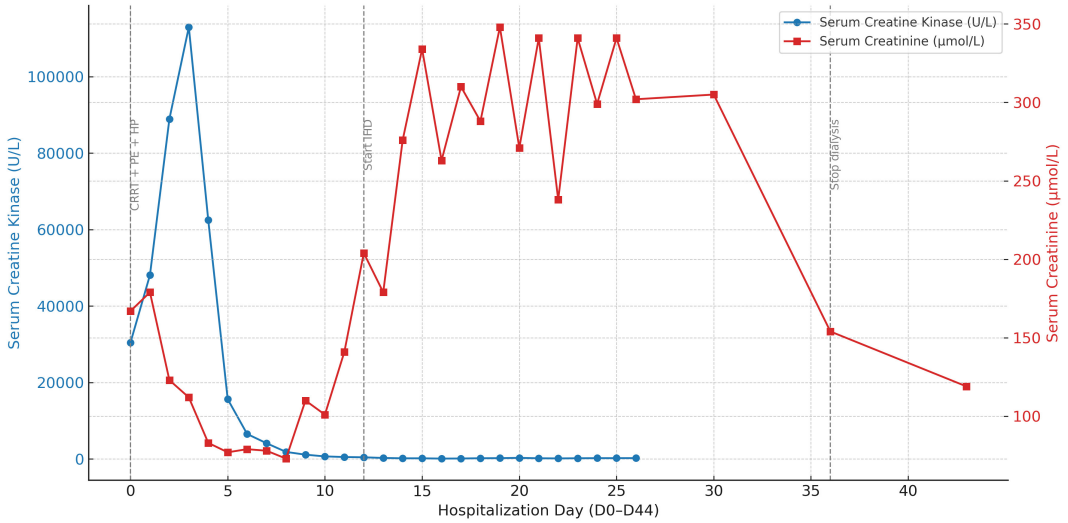

FIGURE 1
Temporal trends of serum creatine kinase and creatinine during hospitalization. This figure depicts the 45-day trajectory of serum creatine kinase (CK) and serum creatinine (Cr) levels in a patient with red yeast rice (RYR)-induced rhabdomyolysis, complicated by acute kidney injury and respiratory failure. CK (blue solid line with circular markers, left *Y*-axis) and Cr (red solid line with square markers, right *Y*-axis) are plotted to reflect muscle injury and renal function, respectively. Gray vertical dashed lines denote three major therapeutic stages: (1) early intensive therapy, including continuous renal replacement therapy (CRRT, D0–11), plasma exchange (PE, D1, 3, and 5), and hemoperfusion (HP, D2); (2) initiation of intermittent hemodialysis (IHD) on D12; and (3) termination of dialysis on D35. The dual *Y*-axis design facilitates simultaneous visualization of muscular and renal biomarker dynamics in relation to therapeutic interventions. Clinically, these trends illustrate that the resolution of severe rhabdomyolysis (indicated by the early decline in CK) preceded the delayed recovery of consequent acute kidney injury, which required a prolonged period of dialysis before renal function improved (indicated by the decline in Cr after D35). CK, creatine kinase; Cr, creatinine; CRRT, continuous renal replacement therapy; PE, plasma exchange; HP, hemoperfusion; IHD, intermittent hemodialysis.

TABLE 2 Functional and neurological assessment.

Parameter	D0	D4	D10	D24	D28	D44
Upper limbs—proximal	2/5 (MRC)	2+/5	3/5	4/5	4+/5	4+/5
Upper limbs—distal	4/5	4/5	4/5	4+/5	4+/5	5/5
Lower limbs—proximal	1/5	2/5	2+/5	2+/5	2+/5	3/5
Lower limbs—distal	4/5	4/5	4/5	4/5	4/5	5/5
Deep tendon reflexes	Absent	NA	NA	NA	++	++
Muscle tone (MAS)	G0	G0	G0	G0	G0	G0
Kubota swallow test	NA	NA	NA	G3	G3	G2
Sitting/Standing balance	NA	NA	NA	NA	0/0	2/0
ADL (MBI)	NA	NA	NA	NA	10	30
6-min walk test	NA	NA	NA	NA	NC	NC
MMSE	NA	NA	NA	NA	28	30

MRC, Medical Research Council scale (used for muscle strength assessment, range 0–5); MAS, Modified Ashworth Scale; G, grade; G0, grade 0; G2, grade 2; G3, grade 3; NA, not assessed; NC, not completed; ADL, activities of daily living; MBI, Modified Barthel Index; MMSE, Mini-Mental State Examination; Absent, deep tendon reflexes not elicited; ++, normal deep tendon reflexes.
Muscle strength (rows 1–4) is graded using the MRC scale.
Sitting/Standing balance is presented as X/Y, where X = sitting balance score and Y = standing balance score.

of functional dependency. She could not complete the 6-min walk test due to limited endurance. Cognitive function was intact, with a Mini-Mental State Examination score of 30. Serial assessments of muscle strength, swallowing ability, activities of daily living, and cognitive function are summarized in Table 2.

Urine output was adequate, with stable creatinine and CK levels. Hemodialysis was discontinued. The patient was transferred to a local hospital for continued rehabilitation. Her recovery trajectory underscores the effectiveness of early organ-targeted supportive care and multidisciplinary rehabilitation in the management of severe toxic rhabdomyolysis.

Follow-up

At ~3 months after symptom onset, a telephone follow-up was conducted. The patient had successfully undergone decannulation of the tracheostomy tube and was able to walk and engage in light outdoor activities such as strolling. She resumed basic daily activities independently. Renal function remained stable without recurrence of AKI, and serum creatinine levels continued to be within normal limits. No relapse of muscle weakness or respiratory symptoms was reported.

Discussion

RYR, a fermented product rich in monacolin K—a compound chemically identical to lovastatin—is widely used as a lipid-lowering supplement. Though perceived as a "natural" alternative to prescription statins, RYR carries comparable pharmacological effects and potential for adverse reactions, including hepatotoxicity, myopathy, and in rare cases, severe rhabdomyolysis (1).

In the present case, the patient developed severe systemic manifestations ~1 month after initiating RYR supplementation, raising important diagnostic and therapeutic considerations. We herein discuss three key aspects of this case: differential diagnosis, systemic complications, and therapeutic challenges.

Differential diagnosis: distinguishing myopathic from neurogenic weakness and excluding IMNM

The patient presented with acute symmetrical proximal muscle weakness and respiratory failure, prompting a systematic neuromuscular evaluation. Given the recent intake of RYR, a statin-like toxic effect was initially suspected. Nevertheless, because such presentations may arise from a broad spectrum of neuromuscular disorders, distinguishing between myopathic and neurogenic causes was essential.

Unlike the classic ascending, distal-to-proximal pattern of weakness in Guillain–Barré syndrome (GBS), our patient exhibited symmetrical proximal muscle weakness, a hallmark of myopathies (4). Moreover, while areflexia is common in GBS, it is not pathognomonic; critically ill patients may transiently lose reflexes due to severe myopathy or sedation. Lumbar puncture revealed normal CSF parameters without albuminocytologic dissociation, further lowering the likelihood of GBS (5). EMG demonstrated normal nerve conduction velocities and amplitudes, which were also inconsistent with a neurogenic process (4).

Laboratory findings strongly supported a myopathic process. While markedly elevated serum CK (peaked at 112,985 U/L) and myoglobin (>3,000 μg/L) were pathognomonic for severe myonecrosis, the transaminase profile was more complex. Initially, it followed a pattern suggestive of muscle injury, with a predominant rise in AST and preserved hepatic synthetic and excretory functions (6). However, the co-existing marked elevation of ALT pointed to a composite etiology, likely involving both direct release from myonecrosis and a concurrent hypoxic liver injury (6, 7). Collectively, the clinical presentation, electrophysiological studies, and laboratory data pointed toward a primary myopathic etiology.

Following exclusion of neurogenic causes, attention shifted to primary myopathies. Given the patient's RYR supplementation, which contains statin-like compounds, and the presence of respiratory involvement, IMNM was considered (8). IMNM typically presents with subacute proximal muscle weakness, sustained CK elevation, and positivity for anti-HMGCR or anti-SRP antibodies (9). Respiratory failure, a known complication of severe IMNM, is rarely seen in toxic rhabdomyolysis, making the clinical presentation particularly concerning. Although myositis-specific antibodies were negative, further evaluation with muscle biopsy or MRI is generally recommended in antibody-negative cases to confirm the diagnosis (10–12). However, MRI was not feasible due to mechanical ventilation, and muscle biopsy was expected to take more than 4 weeks for processing. Therefore, a stepwise approach was adopted: we prioritized clinical observation and supportive treatment, with the intent to reassess the need for further testing based on therapeutic response. The patient exhibited progressive clinical improvement and a steady decline in CK levels without immunosuppressive therapy. This favorable recovery trajectory was inconsistent with IMNM and instead supported a diagnosis of toxic rhabdomyolysis.

Other potential etiologies such as viral myositis or inherited metabolic myopathies were also considered, but deemed less likely due to the absence of a viral prodrome and the patient's advanced age of first presentation, respectively.

Thus, we clinically diagnosed RYR-induced toxic rhabdomyolysis based on the temporal association with supplement use, muscle involvement pattern, negative autoantibodies, and favorable response to supportive care. Consequently, further investigations such as muscle biopsy and MRI were deemed unnecessary.

Systemic complications of RYR-induced rhabdomyolysis: AKI and respiratory failure

Rhabdomyolysis is characterized by extensive skeletal muscle breakdown, resulting in the release of intracellular components—such as myoglobin, CK, and electrolytes—into the circulation (13). In severe cases, this process may lead to systemic complications, including AKI, electrolyte imbalances, and, more rarely, respiratory failure (14–16).

In this case, two major complications developed.

First, AKI manifested early, with oliguria and a progressive rise in creatinine, necessitating CRRT, followed by IHD. This course was consistent with myoglobin-induced acute tubular injury (17).

Second, ventilatory pump failure, primarily driven by diaphragmatic dysfunction, manifested as severe hypercapnic (Type II) respiratory failure necessitating intubation. This conclusion was supported by objective data: the absence of pulmonary or cardiac causes on a normal chest CT scan and preserved cardiac function ruled out primary lung parenchymal diseases and cardiogenic pulmonary edema. Additionally, massive pulmonary embolism was considered unlikely given the patient's stable hemodynamics and the predominantly hypercapnic (Type II), rather than hypoxemic (Type I), nature of the respiratory failure. Primary neurological causes for ventilatory failure were also systematically excluded. A central nervous system origin was inconsistent with the patient's alertness and ability to follow commands when not sedated, a finding supported by a normal head CT scan. Peripheral neuropathies, such as Guillain–Barré Syndrome, were ruled out by the myopathic pattern of weakness, normal cerebrospinal fluid analysis, and normal nerve conduction studies (4, 5). Furthermore, bedside ultrasound of the right hemidiaphragm, a reliable indicator of overall diaphragmatic function in systemic myopathy, revealed significantly reduced excursion (0.91 cm; normal >1.34 cm) and thickening fraction (TFdi 28.5%; normal 30%−36%), findings consistent with diaphragmatic dysfunction (18). The patient's profound, symmetrical proximal limb weakness (MRC 1-2/5) provided clear clinical evidence of global myopathy, suggesting that accessory respiratory muscles (e.g., intercostals, scalenes), being skeletal muscles, were also likely affected by the same myotoxic process. The progression to overt respiratory failure

TABLE 3 Comparison of rhabdomyolysis cases with respiratory failure.

Feature	Present case (This Study)	Gindre et al. (19)	Gentili et al. (20)	Devalaraju et al. (21)
Study type	Case Report	Case Report	Case Report	NIS Database Study
Etiology	RYR toxicity	CMV infection	CPT II deficiency (triggered by fever and fasting)	Concurrent pancreatitis
Patient profile	78-year-old woman	32-year-old woman	4-year-old boy	5,421 patients
Peak CK (U/L)	112,985	177,000	320,000	Not reported
Key complications	Respiratory failure and AKI	Respiratory failure (no AKI)	Respiratory failure and AKI	Respiratory failure is a predictor of mortality
Mechanism of respiratory failure	Confirmed diaphragmatic dysfunction	Generalized muscle weakness	Severe muscle injury; diaphragmatic dysfunction not confirmed	Hypothesized to be respiratory muscle damage
Outcome	Partial recovery with residual weakness	Full recovery	Full recovery	High mortality in those with multi-organ failure; individual recovery not reported

RYR, red yeast rice; CMV, cytomegalovirus; CPT II, carnitine palmitoyltransferase II; AKI, acute kidney injury; NIS, nationwide inpatient sample.

demonstrated the decompensation of the entire respiratory muscle apparatus, as the weakened accessory muscles could not sustainably compensate for the failing diaphragm. The temporal correlation between massive CK elevation and respiratory failure, followed by respiratory recovery as CK levels declined, supports diaphragmatic dysfunction secondary to toxic rhabdomyolysis.

Our case shares key similarities and differences with other rare reports of severe rhabdomyolysis complicated by respiratory failure.

For instance, Gindre et al. described a case of cytomegalovirus (CMV)-associated rhabdomyolysis in an immunocompetent adult, complicated by respiratory failure due to generalized muscle weakness, with no pulmonary or cardiac pathology identified (19).

Additionally, Gentili et al. reported a pediatric case of carnitine palmitoyltransferase II (CPT II) deficiency in which acute respiratory failure was the first manifestation of rhabdomyolysis. The authors attributed this to severe muscle injury and hypoventilation, although specific diaphragmatic dysfunction was not confirmed (20).

In a population-based study, Devalaraju et al. (21) found that respiratory failure was a significant predictor of in-hospital mortality in patients with concurrent pancreatitis and rhabdomyolysis. While respiratory muscle function was not directly assessed, they hypothesized that damage to respiratory musculature might partly explain the increased mortality (21). A detailed comparison of these cases is presented in Table 3.

However, none of these prior cases involved RYR as the precipitating factor. The 2025 EFSA safety assessment acknowledged severe adverse effects of RYR but did not document respiratory failure cases (1). Such severe systemic involvement following RYR use has, to our knowledge, not been previously reported.

Thus, this case expands the known spectrum of RYR toxicity, demonstrating that it may involve respiratory skeletal muscles and cause life-threatening ventilatory failure. Ongoing vigilance for multiorgan dysfunction is essential in patients with supplement-induced severe myopathies.

Therapeutic challenge: myoglobin clearance and renal protection

Management of severe RYR-induced rhabdomyolysis presents significant therapeutic challenges, particularly in achieving effective myoglobin clearance and renal protection. Prompt discontinuation of the offending agent, aggressive intravenous hydration, and renal support remain the cornerstone of treatment (1).

In our patient, a multimodal approach was employed, including CRRT, plasma exchange, and hemoperfusion. CRRT was essential for maintaining fluid, electrolyte, and acid-base balance; however, its efficacy in eliminating myoglobin is limited by the molecule's intermediate size and protein-binding characteristics (22). Plasma exchange was initiated early due to diagnostic uncertainty, as IMNM and GBS had not been excluded at admission. It was considered for its potential immunomodulatory effects and possible myoglobin clearance, although supporting evidence remains limited (23). Hemoperfusion, used adjunctively in this case, is a promising yet investigational approach for enhancing myoglobin removal in severe rhabdomyolysis (22).

Despite these interventions, there is no standardized or highly effective method for targeted myoglobin clearance. The patient's recovery with supportive care highlights the effectiveness of early, organ-targeted management, even without specific myoglobin removal techniques. Nonetheless, the protracted renal recovery and dialysis dependence during hospitalization underscore the limitations of current therapies.

Future advances may focus on novel hemoadsorption devices, such as CytoSorb® cartridges, which have shown potential for improving myoglobin clearance when initiated early (22). Furthermore, early biomarkers predicting severe AKI risk and individualized thresholds for initiating extracorporeal therapies could refine treatment algorithms. Prospective studies are urgently needed to establish evidence-based protocols for optimizing myoglobin clearance and improving renal outcomes in severe rhabdomyolysis.

Limitations

Our assessment of respiratory muscle function, while indicative of diaphragmatic dysfunction, had certain limitations. First, the sonographic evaluation of the diaphragm, a primary muscle of respiration, was confined to the right hemidiaphragm. While this approach is justified by its technical feasibility and improved data quality compared to left-sided assessment, it precludes a complete evaluation of global diaphragmatic function and does not account for potential asymmetric involvement. Second, a specific sonographic assessment of the accessory inspiratory muscles (e.g., parasternal intercostals) was not performed. Such an evaluation could have provided additional quantitative data regarding the patient's respiratory workload and the degree of compensatory recruitment from these secondary muscle groups. Nevertheless, the systemic nature of rhabdomyolysis strongly implies global respiratory muscle involvement, consistent with the observed ventilatory pump failure.

Patient perspective

During her prolonged and arduous hospitalization, the patient expressed significant regret over her use of the supplement, attributing her severe illness to its consumption. Her recovery was slow, which was a source of considerable anxiety, and she frequently voiced concerns about the extent of her long-term recovery and whether she would regain her independence. However, her determination throughout rehabilitation, culminating in the functional improvements documented at follow-up, ultimately tells a story of resilience in the face of a life-threatening, supplement-induced critical illness.

Conclusion

We report a rare and severe case of RYR-induced toxic rhabdomyolysis complicated by AKI and respiratory failure secondary to diaphragmatic dysfunction, which, to our knowledge, is the first documented case of RYR-induced rhabdomyolysis complicated by both AKI and respiratory failure. The diagnostic challenge with IMNM was clarified by negative serology and rapid clinical improvement without immunosuppressive therapy. The patient recovered following early withdrawal of RYR and organ-targeted supportive care.

This case highlights the critical importance of early recognition of supplement-induced toxic myopathies, timely differentiation from autoimmune neuromuscular disorders, and prompt initiation of multidisciplinary supportive therapies.

Clinicians should remain highly vigilant for serious complications, even with seemingly "natural" over-the-counter products such as RYR, particularly in older adults with comorbidities.

Further research is needed to better delineate the clinical spectrum of RYR toxicity and to develop evidence-based strategies for myoglobin clearance and organ protection in rhabdomyolysis-associated AKI.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PZ: Writing – original draft, Visualization, Conceptualization, Writing – review & editing. YH: Supervision, Writing – review & editing. HC: Supervision, Writing – review & editing. XZ: Investigation, Writing – review & editing. SH: Writing – review & editing, Investigation. HZ: Investigation, Writing – review & editing. JY: Investigation, Writing – review & editing. PC: Formal analysis, Writing – review & editing, Data curation. BX: Formal analysis, Data curation, Writing – review & editing. XL: Formal analysis, Writing – review & editing, Data curation. SY: Writing – review & editing, Data curation, Formal analysis. ZZ: Funding acquisition, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. Z.Z. received funding from the National Natural Science Foundation of China (Nos. 82472243 and 82272180), the China National Key Research and Development Program (No. 2023YFC3603104), the Huadong Medicine Joint Funds of the Zhejiang Provincial Natural Science Foundation of China (No. LHDMD24H150001), the China National Key Research and Development Program (No. 2022YFC2504500), a collaborative scientific project co-established by the Science and Technology Department of the National Administration of Traditional Chinese Medicine and the Zhejiang Provincial Administration of Traditional Chinese Medicine (No. GZY-ZJ-KJ-24082), the General Health Science and Technology Program of Zhejiang Province (No. 2024KY1099), the Project of Zhejiang University Longquan Innovation Center (No. ZJDXLQCXZCJBGS2024016), and Wu Jieping Medical Foundation Special Research Grant (320.6750.2024-23-07).

Acknowledgments

The authors thank the ICU team for their support in patient care and data collection. During the preparation of

this work, the authors used ChatGPT 4.0 (OpenAI) for the limited purpose of language editing and polishing to enhance the manuscript's readability and clarity. The AI tool was not used for generating scientific content, interpreting data, or drawing conclusions. All intellectual content is the original work of the authors.

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The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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The author(s) declare that Gen AI was used in the creation of this manuscript. Generative AI (ChatGPT, OpenAI) was used under human supervision to assist in improving the clarity, language expression, and structure of the manuscript. All content was critically reviewed and edited by the author(s), who take full responsibility for the final version.

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 29 August 2025
DOI 10.3389/fmed.2025.1627241

OPEN ACCESS

EDITED BY
Zhongheng Zhang,
Sir Run Run Shaw Hospital, China

REVIEWED BY
Matilde Ruiz Garcia,
National Institute of Pediatrics, Mexico
Dewu Bi,
The Fourth People's Hospital of Nanning, China

*CORRESPONDENCE
Katharina Feil
katharina.feil@uni-tuebingen.de

RECEIVED 12 May 2025
ACCEPTED 18 August 2025
PUBLISHED 29 August 2025

CITATION
Feil K, Ruf B, Behling F, Kozak G, Gohla G, Riessen R, Haap M, Poli S, Hennersdorf F, Ziemann U and Mengel A (2025) Case Report: severe *Mycoplasma pneumoniae*-associated acute disseminated encephalomyelitis in an adult: challenges in diagnosis and management.
Front. Med. 12:1627241.
doi: 10.3389/fmed.2025.1627241

Case Report: severe *Mycoplasma pneumoniae*-associated acute disseminated encephalomyelitis in an adult: challenges in diagnosis and management

Katharina Feil [1]*, Benjamin Ruf[2,3,4,5], Felix Behling[6,7], Gabor Kozak[1,7], Georg Gohla[8], Reimer Riessen[5], Michael Haap[5], Sven Poli[1,7], Florian Hennersdorf[8], Ulf Ziemann[1,7] and Annerose Mengel[1,7]

[1]Department of Neurology and Stroke, University of Tübingen, Tübingen, Germany, [2]Department of Internal Medicine I, University Hospital Tübingen, University of Tübingen, Tübingen, Germany, [3]M3 Research Center for Microbiome, Metabolome and Malignome, Faculty of Medicine, University of Tübingen, Tübingen, Germany, [4]Cluster of Excellence iFIT (EXC 2180) "Image Guided and Functionally Instructed Tumor Therapies," University of Tübingen, Tübingen, Germany, [5]Department of Medicine, Medical Intensive Care Unit, University Hospital Tübingen, Tübingen, Germany, [6]Department of Neurosurgery, University of Tübingen, Tübingen, Germany, [7]Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany, [8]Department of Diagnostic and Interventional Neuroradiology, University of Tübingen, Tübingen, Germany

We report a rare case of severe *Mycoplasma (M.) pneumoniae*-associated acute disseminated encephalomyelitis (ADEM) in a previously healthy 26-year-old woman. The patient presented with delayed-onset encephalopathy following a mild respiratory infection. Rapid neurological deterioration, signs of transtentorial herniation, and refractory intracranial hypertension necessitated emergency decompressive hemicraniectomy. Diagnostic workup revealed elevated *M. pneumoniae* IgM and borderline PCR positivity. The patient was successfully treated with corticosteroids, intravenous immunoglobulin, and targeted azithromycin. Complete clinical and radiological recovery was achieved. This case emphasizes the need for awareness of severe *M. pneumoniae*-associated CNS manifestations and highlights the challenges in diagnosis and management.

KEYWORDS

acute disseminated encephalomyelitis (ADEM), *Mycoplasma pneumoniae*, neurointensive care, decompressive hemicraniectomy, intracranial hypertension

Introduction

Acute disseminated encephalomyelitis (ADEM) is a monophasic, immune-mediated demyelinating disease of the central nervous system (CNS), primarily affecting children (1). Adult cases are rare and often more severe. *Mycoplasma (M.) pneumoniae*, a common respiratory pathogen, is a recognized but infrequent trigger of ADEM, with CNS involvement in <0.1% of cases (2). *M. pneumoniae* shows seasonal circulation with winter peaks but can occur year-round (3). We describe a rare and severe adult case

requiring neurointensive care and neurossurgical intervention, emphasizing diagnostic and therapeutic challenges, particularly in the context of the 2024 *M. pneumoniae* outbreak.

Case description

In late August 2024, the 26-year-old patient, who was otherwise healthy and on no regular medication, presented with subjective right leg heaviness following a recent upper respiratory tract infection marked by subfebrile fever, cough, and malaise. Neurological examination and duplex sonography to rule out deep vein thrombosis were unremarkable. Her symptoms were initially managed symptomatically with ibuprofen and were clinically attributed to post-viral myalgia. Approximately 3 weeks into the illness, she received a first course of antibiotic therapy with amoxicillin (500 mg three times daily), which was switched to oral azithromycin (500 mg once daily) 2 days prior to hospital admission. Four weeks after symptom onset, her condition acutely deteriorated and she experienced acute consciousness deterioration with meningism and a Glasgow Coma Scale (GCS) of 10. On admission to our neurological intensive care unit (NICU), she displayed global aphasia, severe right-sided hemiparesis, a positive Babinski sign on the right, multimodal neglect, and upbeat nystagmus as well as a spontaneous nystagmus to the left (National Institutes of Health Stroke Scale (NIHSS)

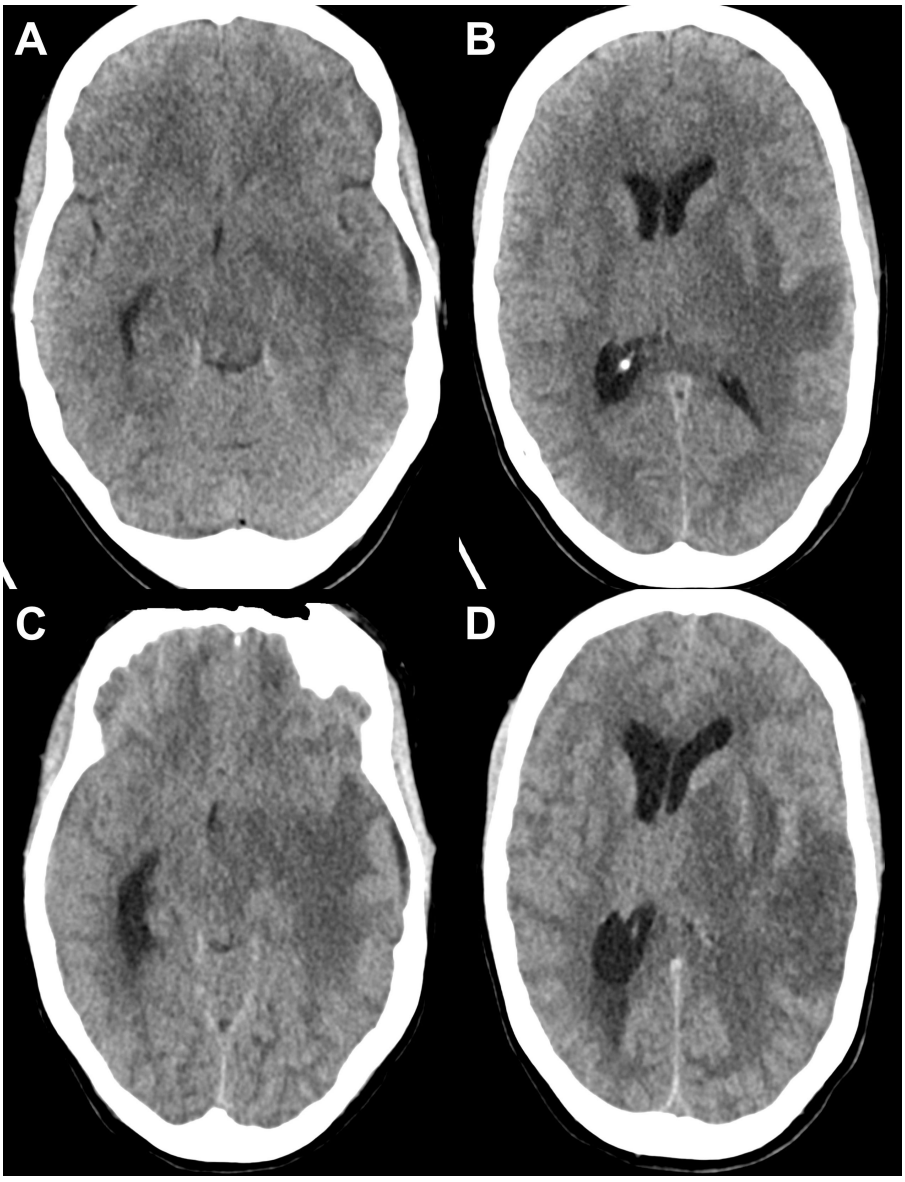

FIGURE 1
The first row displays two axial slices from the initial CT scan obtained in the emergency setting at the level of the brainstem **(A)** and the thalamus **(B).** Imaging revealed an ill-defined hypodensity in the left temporal region involving both the white matter and the cortical/juxtacortical areas, accompanied by extensive edema, resulting in a rightward midline shift and compression of the left lateral ventricle. No hemorrhage was detected. The second row (**C,D**) shows the follow-up CT scan obtained 2 days later, demonstrating the progression of the lesion, worsening edema, and an increasing mass effect.

22). Initial non-contrast cranial computed tomography (CT) revealed extensive cortical and subcortical hypodensities and swelling of the left temporal lobe and the left internal as well external capsule and consecutive mass effect and midline shift of 6 mm, but no hemorrhage, ischemia, or vascular abnormalities. Findings were initially interpreted as consistent with herpes encephalitis (Figures 1A, B). Cerebrospinal fluid analysis (CSF) showed pleocytosis (522 cells/µl, 86% mononuclear cells, 14% polymorphonuclear cells), elevated lactate (3.7 mmol/L), and normal glucose (45 mg/dl). Initial treatment included empiric aciclovir, ceftriaxone, and ampicillin. Ampicillin was discontinued on day 3 following negative results for *Listeria*. Polymerase chain reaction (PCR) testing for herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and *cytomegalovirus* (*CMV*), Human herpesvirus 6 (HHV-6) was negative. Tick-borne encephalitis serum IgG was positive consistent with complete prior vaccination, the last one three years earlier. Comprehensive microbiological testing ruled out bacterial, fungal, and mycobacterial infections. Multiple bacterial cultures from CSF and blood showed no growth after 48 h and remained negative throughout the 5-day incubation period. PCR testing for *Neisseria meningitidis, Streptococcus pneumoniae, Streptococcus agalactiae, Haemophilus influenzae, Escherichia coli K1*, *Listeria monocytogenes, and Mycobacterium tuberculosis* PCR (TB-PCR) was negative. Mycobacterial cultures, incubated for 7 weeks, showed no growth. Further testing for *M. pneumoniae* and *Chlamydia pneumoniae* in CSF was negative, though the *Chlamydia pneumoniae* test was performed outside of accredited diagnostic standards, and sensitivity/specificity data were unavailable. Fungal screening, including *Cryptococcus neoformans*, was negative. Serological testing ruled out syphilis (*Treponema pallidum). I*n addition, testing for Aquaporin-4 (AQP4) and Myelin Oligodendrocyte Glycoprotein (MOG) antibodies was negative. Additional CSF analysis showed a slightly elevated liquor/serum index, consistent with non-specific intrathecal B-cell activation. There was no evidence for neuroborreliosis. In addition, a comprehensive autoimmune antibody panel was performed in serum and CSF, including antibodies for autoimmune and limbic encephalitis (NMDA-R, AMPA-R, GABA-B-R, LGI1, CASPR2, DPPX), and paraneoplastic antibodies (Hu, Yo, Ri, CV2/CRMP5, Ma2/Ta, amphiphysin), all of which were negative. Tracheal secretion PCR showed borderline-positive *M. pneumoniae* (Cq 41.6), corroborated by elevated IgM and IgG titers.

The patient's condition deteriorated over the next 24 h, initially to GCS 6-7, and subsequently to GCS 3. Neurological examination revealed central oculomotor disturbances with skew deviation, characterized by left hypertropia greater than right, incomplete right oculomotor nerve palsy, anisocoria (left > right). Cushing's triad (bradycardia, hypertension, and deep respiration), suggesting impending transtentorial herniation. Skew deviation was assumed to be of central origin, although secondary ocular misalignment due to the right oculomotor nerve palsy could not be definitively excluded. The clinical signs were consistent with transtentorial herniation, although direct brainstem involvement due to extensive edema could not be entirely ruled out. Repeat CT imaging revealed progressive cerebral edema, brainstem compression, increased midline shift, and signs of herniation (Figures 1C, D). The patient was intubated, and an intracranial pressure (ICP) probe was placed, revealing elevated pressures at around 30 mmHg. Conservative ICP management was initiated including deep sedation, osmotherapy, and head elevation under close monitoring of ICP and Neurological Pupillary Index (NPI). Subsequent contrast-enhanced MRI demonstrated a lesion in the left temporal hemisphere involving the cortical ribbon, characterized by circularly arranged T2-hypointense, linear-to-punctate, and partially bead-like organized structures with centrally predominant hyperintense areas. There was no evidence of hemosiderin deposition or definitive diffusion restriction. The edema extended to the basal ganglia, thalamus, and midbrain, maintaining continuity with a lesion in the left cerebellum. The cerebellar lesion exhibited mixed signal behavior on T2-weighted sequences and appeared hypercellular with corresponding signal reduction on the ADC map. Post-contrast imaging showed no enhancement of the infratentorial lesion, whereas the supratentorial temporal lesion demonstrated faint, irregular, marginal contrast enhancement resembling an open-ring pattern, with the opening directed laterally. The intracranial CSF spaces remained collapsed, with persistent midline shift to the right and signs of CSF obstruction. Infratentorial findings included effacement of the perimesencephalic cisterns and herniation of the cerebellar tonsils through the foramen magnum, consistent with secondary cerebellar tonsillar descent due to elevated intracranial pressure. The imaging findings continued to demonstrate evidence of supra- and infratentorial elevated ICP and CSF obstruction. The rapidly progressive cerebral pathology displayed features that were not characteristic of a single defined entity. Differential diagnoses included encephalitic, inflammatory, or infectious processes, as well as a possible demyelinating condition (Figures 2A–D and Table 1).

With the failure of maximal conservative measures to control the elevated ICP exceeding 20 mmHg and the need for further diagnostic clarification via brain biopsy, an emergency decompressive hemicraniectomy was performed. Intraoperatively, multiple biopsies were obtained from the left temporal lobe. Histopathology revealed reactive astrocytosis in gray matter without evidence of neoplasia or infection. The absence of white matter in the probe limited confirmation of demyelination.

Taking all together, the clinical findings and clinical course, neuroimaging and other diagnostic studies, were strongly suggestive of *M. pneumoniae*-associated ADEM. The patient was then further treated with high-dose methylprednisolone (1 g/day for 5 days) and intravenous immunoglobulin (2 g/kg over 4 days) to address the presumed autoimmune component of ADEM. Given the serological confirmation of *M. pneumoniae*, azithromycin was introduced on day 5 of admission at a dose of 500 mg intravenously once daily and continued for 10 days as targeted antimicrobial therapy.

Serial MRI evaluations demonstrated progressive improvement in the extensive T2 hyperintense FLAIR abnormalities in the left hemisphere, initially involving the basal ganglia, mesencephalon, pons, and left cerebellum indicating a favorable radiological response to therapy. By mid-October, she was extubated, in the further course alert, and orientated, though with persistent right-sided motor deficits. The patient had no observed epileptic seizures. During the episode of decreased consciousness, antiseizure treatment was initiated under the differential diagnosis of focal status epilepticus but was discontinued within a few days. After sedation weaning, continuous EEG monitoring

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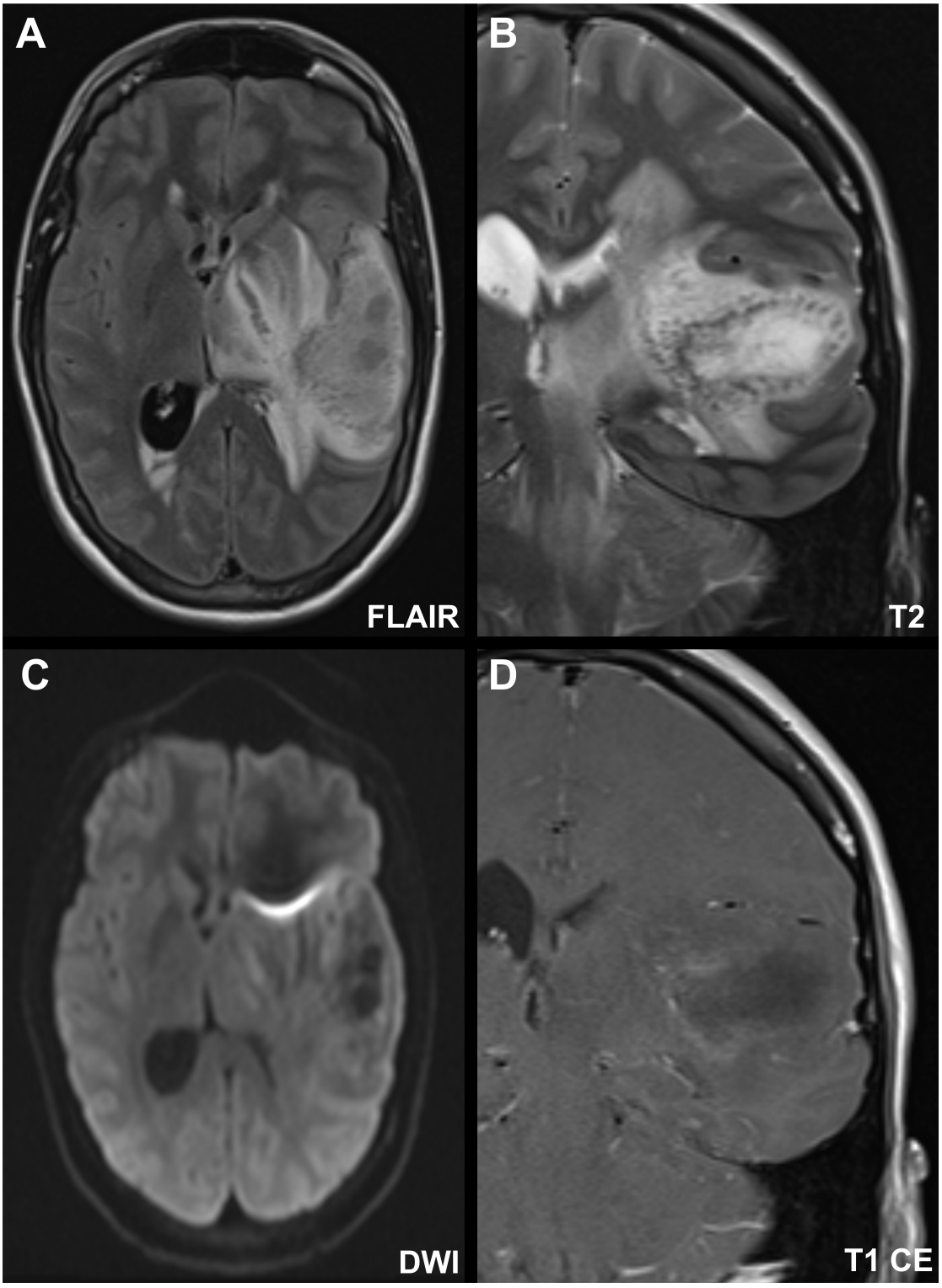

FIGURE 2
Illustrated are fluid attenuated inversion recovery (FLAIR, A), T2-weighted (B), diffusion weighted imaging (DWI, C), and contrast-enhanced (CE) T1-weighted images from an MRI scan obtained immediately after the progression detected on the CT scan. The images showed a left temporal lesion **(A)** extending **(B)** to the left thalamus, the left cerebral peduncle to the midbrain and the left cerebellar hemisphere. The temporal area is characterized by circularly arranged T2-hypointense, linear-to-punctate, and partially bead-like structures with centrally predominant hyperintense areas. Due to the mass effect, the images demonstrated signs of increased intracranial pressure with hydrocephalus, midline shift, narrowed perimesencephalic cisterns and slight low-lying cerebellar tonsils. There was no evidence of true diffusion restriction, although some regions within the lesion exhibited features suggestive of hypercellularity **(C)**. Following contrast administration, the lesion displayed faint, irregular marginal enhancement resembling an open-ring pattern **(D)**.

TABLE 1 Timeline of clinical course, diagnostics, and treatment.

Time (days from onset)	Clinical event	Diagnostics	Treatment
Day 0	Upper respiratory tract infection	—	Symptomatic
Day 21	Amoxicillin begun	—	—
Day 26–27	Azithromycin added	—	—
Day 28 (Thursday)	NICU admission (NIHSS 22, GCS 10)	CT, CSF	Acyclovir, ceftriaxone
Day 29–31	Neurological deterioration (GCS 3, herniation signs)	MRI, ICP monitoring	Conservative ICP management
Day 32 (Monday)	Refractory ICP → Hemicraniectomy	—	Surgery, biopsies
Day 33	Diagnosis: *M. pneumoniae*-associated ADEM	IgM↑, PCR borderline, CSF−	Methylprednisolone, IVIG
Day 34–38	Clinical stabilization	—	Azithromycin (10 days)
Month 2	Clinical recovery, weaning, mobilization	MRI: improving lesions	—
December 2024	Cranioplasty performed	—	—
May 2025 (month 8)	Full neurological recovery (NIHSS 0)	MRI: near-complete resolution	

showed no epileptiform activity. Cranioplasty was successfully performed in December 2024 with an uneventful postoperative course. No formal neuropsychological assessment was performed during the acute hospital stay. During subsequent inpatient neurorehabilitation, neuropsychological testing revealed transient short-term memory deficits according to the patient's own account. At the latest follow-up approximately 8 months after the acute event, MRI showed complete resolution of the previous signs of herniation. Clinically, the patient demonstrated full neurological recovery (NIHSS 0, mRS 0). No further immunomodulatory treatment was required. The patient has since returned to her previous employment after a gradual reintegration period.

Discussion

This case highlights rare but severe neurological complications of *M. pneumoniae* infection in adults. While *M. pneumoniae* is a common cause of atypical pneumonia, central nervous system (CNS) manifestations such as ADEM are exceedingly rare, occurring in less than 0.1% of cases (1). Surveillance data indicate that *M. pneumoniae* activity has resumed typical seasonal circulation following the COVID-19 pandemic. Population-level monitoring from British Columbia, Canada, showed that detection rates increased after implementation of a syndromic nucleic acid amplification test panel - a multiplex PCR assay detecting multiple respiratory pathogens in a single run - while overall incidence remained within expected seasonal levels (3). *M. pneumoniae* is a recognized trigger for autoimmune diseases via molecular mimicry, immune modulation, and inflammatory responses (2). ADEM has an incidence of approximately 8 per 1.000.000 people per year. Most cases occur in children, with an average age of 5–8 years (4–6). As ADEM is an uncommon illness in adults, the precise incidence in adults is unknown (7). Seasonal variation has been observed, with higher incidence during winter and spring, coinciding with peaks in infections (4). Although the precise pathogenesis is not completely understood, ADEM is an autoimmune demyelinating disease of the CNS caused by an inflammatory reaction in the brain and spinal cord. The onset is typically acute and often rapidly progressive, with multifocal neurological deficits (8). ADEM is usually triggered by environmental stimuli in genetically susceptible individuals. One proposed mechanism involves molecular mimicry, where myelin autoantigens such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein share antigenic determinants with an infecting pathogen. Antiviral antibodies or cell-mediated responses cross-react with these antigens, resulting in widespread CNS demyelination (9). Its expanding clinical phenotype increasingly overlaps with MOG antibody-associated disorders. A population-based study from Minnesota reported the prevalence of ADEM without MOG antibodies at 3.3 per 100.000 and MOG-associated demyelination prevalence at 1.9 per 100.000 (10).

Clinical, radiographic, and pathological features of ADEM can mimic multiple sclerosis (MS) and experimental autoimmune encephalomyelitis in animal models (1, 10). Although ADEM is typically monophasic, recurrent demyelinating episodes in children or adults may lead to a diagnosis of MS (1, 11). ADEM is part of a continuum of CNS demyelinating disorders, including MS, acute hemorrhagic leukoencephalitis, transverse myelitis, and optic neuritis. ADEM has been associated with several viral infections - such as measles, mumps, rubella, VZV, *EBV*, CMV, and HSV - as well as bacterial infections, including *M. pneumoniae*.(1) Pathophysiologically, *M. pneumoniae*-associated ADEM likely involves a combination of direct microbial invasion and immune-mediated mechanisms, including molecular mimicry and bystander activation. These processes lead to widespread demyelination, primarily in the CNS white matter (12).

Diagnosing ADEM remains challenging due to the absence of specific biomarkers (6, 8). The diagnosis is supported by the rapid progression of encephalopathy, multifocal neurological deficits, characteristic MRI findings, and the exclusion of alternative diagnoses (6, 8). Brain MRI typically reveals large, poorly demarcated, hyperintense lesions on T2/FLAIR sequences, predominantly affecting white matter, deep gray matter, brainstem, and cerebellum. Black hole lesions on T1-weighted MRI, indicative of chronic inflammation in MS, are not typical in ADEM.(11) In

our patient, imaging revealed multifocal supra- and infratentorial lesions of varying sizes, ranging from punctate to large flocculent lesions, with areas of open-ring or absent contrast enhancement. The lesions involved the deep white matter as well as the juxtacortical white matter–gray matter interface. A preceding infection and abnormal CSF findings, such as mild lymphocytic pleocytosis and elevated protein, support the diagnosis but are not required. Diagnostic certainty is often delayed due to the time required for serological and CSF analyses, including tests for MOG and aquaporin-4 antibodies, as well as CSF oligoclonal bands. In our case, the patient exhibited a remarkably elevated CSF cell count, which is atypical for "normal" autoimmune disorders such as ADEM, where pleocytosis is usually mild to moderate. This finding raises important questions regarding the underlying pathophysiology. A high CSF cell count may indicate an additional infectious or inflammatory component, while no specific pathogen was identified in the CSF. Further, the delayed onset of neurological symptoms highlights the complexity of identifying *M. pneumoniae*-associated ADEM. It raises questions about whether *M. pneumoniae* was the primary trigger or a secondary infection following an earlier viral illness. However, the presence of elevated *M. pneumoniae* IgM strongly supports a direct association. Despite these uncertainties, the clinical, radiological, and serological findings collectively supported ADEM as the primary diagnosis.

Immunosuppression is the cornerstone of ADEM management. High-dose corticosteroids, such as methylprednisolone or dexamethasone, remain first-line treatment, followed by a 3–6 week taper of oral prednisolone (11, 13, 14). Evidence suggests that methylprednisolone is superior to dexamethasone in achieving favorable outcomes (13). Rapid tapering (<3 weeks) is associated with higher relapse rates and poorer outcomes, (6) for cases unresponsive to corticosteroids, alternative therapies such as intravenous immunoglobulin (IVIG, 0.4 g/kg intravenously daily for 5 days) and/or plasmapheresis, have shown efficacy. Some evidence suggests that a combination of corticosteroids and IVIG may be beneficial, especially in patients with an initial poor response to corticosteroids (15). In our case, the aggressive disease course necessitated early immunomodulatory therapy with a combination of corticosteroid pulse therapy and IVIGs, and surgical intervention with decompressive craniectomy alleviated life-threatening ICP crises. Antimicrobial treatment with azithromycin targeted the underlying *M. pneumoniae* infection, further contributing to neurological recovery, and achieving an excellent outcome.

Compared to pediatric ADEM, where full recovery occurs in 50%–76% of cases (11), adult cases often follow a more severe clinical course, with complete recovery in only 10%–46% (5, 6, 11). Mortality rates in fulminant ICU-treated patients range from 8%–25% (16). Recovery from ADEM occurs typically within 1–6 months, though residual deficits are more common in adults (11).

Conclusion

This case highlights the importance of recognizing *M. pneumoniae* as a potential cause of severe neurological manifestations in adult patients. The unusually high prevalence of *M. pneumoniae* infections in 2024 further emphasizes the need for increased clinical vigilance, as outbreaks may lead to a rise in associated complications such as ADEM. Prompt diagnosis, aggressive immunotherapy, and NICU treatment including surgical intervention in cases of refractory ICP elevation are essential for optimizing outcomes. Future research should focus on elucidating the pathophysiology and improving therapeutic strategies for *M. pneumoniae*-associated ADEM.

Patient perspective

The patient reported being unaware of the potential severity of respiratory infections. After a prolonged ICU and rehabilitation stay, she made a full neurological recovery and has since resumed her normal life and employment. She expressed deep gratitude for the intensive care and neurorehabilitation provided.

Data availability statement

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

Ethics statement

Ethical approval was not required for the studies involving humans because Individual case report; written informed consent of patient and relatives was given. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KF: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. BR: Data curation, Resources, Writing – review & editing. FB: Data curation, Resources, Writing – review & editing. GK: Data curation, Resources, Writing – review & editing. GG: Data curation, Formal Analysis, Resources, Writing – review & editing. RR: Writing – review & editing. MH: Writing – review & editing. SP: Data curation, Resources, Writing – review & editing. FH: Data curation, Writing – review & editing. UZ: Supervision, Writing –

review & editing. AM: Data curation, Project administration, Resources, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We acknowledge support from the Open Access Publication Fund of the University of Tübingen.

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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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 29 September 2025
DOI 10.3389/fmed.2025.1687102

OPEN ACCESS

EDITED BY
Yuetian Yu,
Shanghai Jiao Tong University, China

REVIEWED BY
Khalil Ayadi,
University of Sfax, Tunisia
Cesar Adolfo Nieves Perez,
Hospital Ángeles Pedregal, Mexico

*CORRESPONDENCE
Mohammad Nizam Mokhtar
✉ drnizam@ukm.edu.my

RECEIVED 16 August 2025
ACCEPTED 19 September 2025
PUBLISHED 29 September 2025

CITATION
Azaharuddin I, Mokhtar MN, Ding CH, Azmi MI, Abdullah FH, Su YP and Zainudin A (2025) *Nocardia* infection: a rare case report of a cerebellar mass. *Front. Med.* 12:1687102. doi: 10.3389/fmed.2025.1687102

Nocardia infection: a rare case report of a cerebellar mass

Izzuddin Azaharuddin[1], Mohammad Nizam Mokhtar[1]*, Chuan Hun Ding[2], Mohd Imree Azmi[3], Farah Hanim Abdullah[1], Yik Peng Su[1] and Affiza Zainudin[2]

[1]Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Univerisiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [2]Department of Medical Microbiology and Immunology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [3]Department of Radiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Introduction: Central nervous system (CNS) nocardiosis is a rare but lethal opportunistic infection, presenting a formidable diagnostic and therapeutic challenge, especially in immunocompromised populations. The most common presentation is a cerebral abscess.

Case presentation: We report the case of a 53-year-old male with a history of relapsed and refractory multiple myeloma who presented with an acute change in mental status and ataxia. Initial clinical suspicion centered on a posterior circulation ischemic event. However, magnetic resonance imaging (MRI) revealed a large, rim-enhancing cerebellar mass with associated obstructive hydrocephalus. The patient underwent surgical excision of the lesion, and subsequent microbiological culture confirmed an abscess caused by a *Nocardia* species. He was treated with a prolonged course of targeted antimicrobial therapy, including intravenous imipenem, followed by oral linezolid and trimethoprim-sulfamethoxazole. At the 3-month outpatient follow-up after discharge, the patient was found to have thrombocytopenia, attributed to the side effects of oral trimethoprim-sulfamethoxazole. Treatment was subsequently maintained with oral linezolid 600 mg for 1 year. Despite improvement of the abscesses, the patient ultimately succumbed to the progression of his long-standing multiple myeloma.

Conclusion: This case underscores the importance of including uncommon opportunistic pathogens like *Nocardia* in the differential diagnosis of CNS lesions in immunocompromised patients. A definitive diagnosis via microbiological analysis of tissue specimens is imperative to guide appropriate antimicrobial therapy and achieve a favourable clinical outcome.

KEYWORDS

***Nocardia*, infection, central nervous system, cerebellar mass, intensive care unit**

Introduction

The genus *Nocardia* comprises a diverse group of aerobic, gram-positive, weakly acid-fast bacilli that form characteristic branching filaments (1). These organisms are ubiquitous in the environment but are an infrequent cause of human disease. The taxonomy of the genus is complex and continuously evolving, with numerous species now recognized as clinically significant, which complicates identification efforts (2, 3). When nocardiosis occurs, it can manifest as a severe localized or disseminated process. The primary route of acquisition is typically via inhalation, leading to pulmonary disease with potential for subsequent hematogenous dissemination to other organ systems (4, 5). The central nervous system CNS

is the most common site of extrapulmonary disease, affecting a significant proportion of patients with systemic nocardiosis (6, 7).

The diagnosis of CNS nocardiosis is often challenging due to its nonspecific clinical and radiological features, which can mimic other pathologies such as infectious etiologies, or more notably, metastatic brain tumors (6, 8). Immunocompromised individuals represent the highest-risk population, with corticosteroid use being a common predisposing factor (7, 9). This highlights the need for a high index of suspicion in this vulnerable patient group.

We present a compelling case of a patient with a history of multiple myeloma who developed a *Nocardia* cerebellar abscess. This case highlights the diagnostic difficulties of such a presentation and emphasizes the necessity of considering rare opportunistic pathogens in patients with a compromised immune system.

Case presentation

A 53-year-old male with a five-year history of relapsed and refractory immunoglobulin A kappa (IgAκ) multiple myeloma presented with an acute change in mental status and profound instability, specifically altered consciousness and ataxia with no other cerebellar signs. The patient was also noted to be semi-dependent in his activities of daily living. His medical history was notable for multiple lines of therapy for the kappa (IgAκ) multiple myeloma, including proteasome inhibitors, immunomodulatory drugs, and an autologous stem cell transplant. His course had been complicated by numerous sequelae, including pathological fractures, hypercalcemia-induced delirium, acute kidney injury, and neutropenic sepsis. At the time of presentation, he was receiving a salvage regimen of daratumumab, pomalidomide, and dexamethasone.

The initial symptoms of altered consciousness and ataxia were attributed to a presumed posterior circulation ischemic event. A magnetic resonance imaging (MRI) revealed a large, 3.4 × 3.5 × 3.2 cm mass in the left cerebellum (Figures 1A–C), which exhibited restricted diffusion and rim enhancement. The mass was exerting a significant effect on the fourth ventricle, resulting in obstructive hydrocephalus. The leading differential diagnoses at this juncture were CNS lymphoma and a cerebellar abscess. Diffusion-weighted imaging (DWI) was also performed (Figures 1A,B) and showed findings that were most suggestive of an abscess.

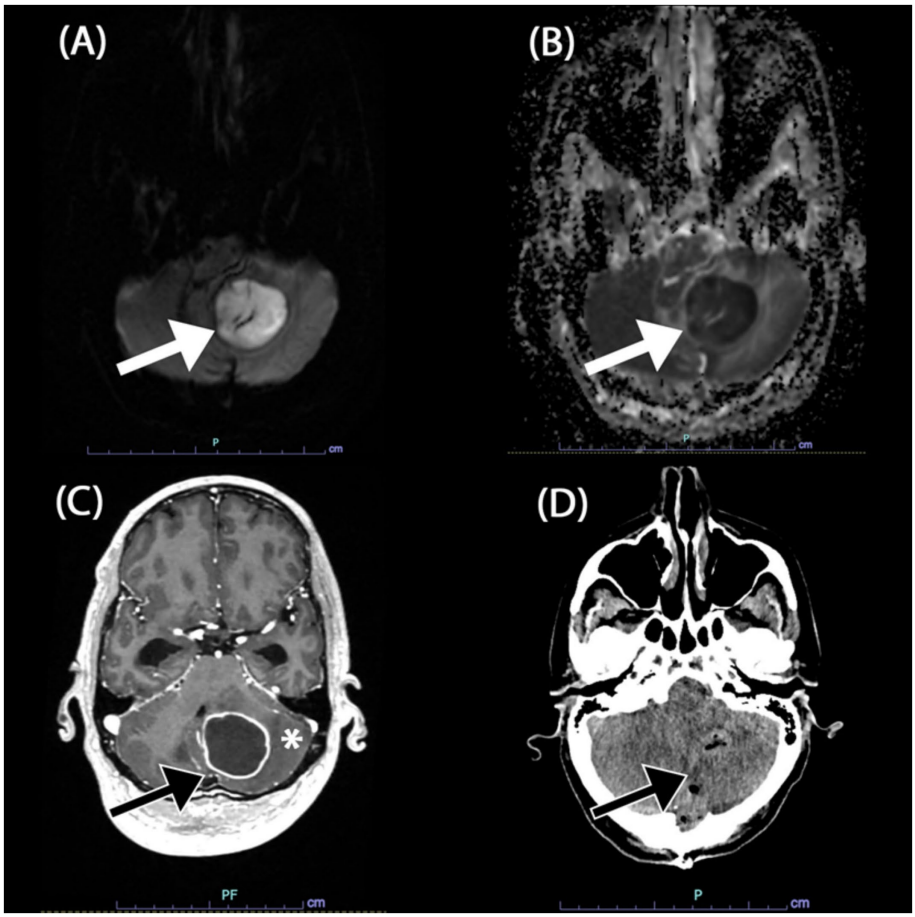

FIGURE 1
Magnetic resonant imaging (MRI) of the brain in axial views. **(A,B)** DWI b1000 and ADC showed restricted diffusion of the mass in the left cerebellum (white arrow). **(C)** Post-gadolinium contrast T1-weigted image revealed rim enhancing component of the mass (black arrow) associated with surrounding oedema (*). Note the compression onto the fourth ventricle causing obstructive hydrocephalus (not shown). **(D)** Post-operative non-contrasted computed tomography (CT) of the brain in axial view revealed the post operative air locules (black arrow) in the left cerebellum without bleed and resolution of fourth ventricle compression.

A right-sided external ventricular drain (EVD) was placed to treat the obstructive hydrocephalus. Cerebrospinal fluid (CSF) analysis revealed a high opening pressure but was otherwise unremarkable, with low protein (<68 mg/L), elevated glucose (5.04 mmol/L), and negative cultures. Forty-eight hours after EVD placement, the patient underwent surgical excision of the cerebellar lesion. Intraoperatively, the mass was noted to be encapsulated and rubbery, containing a yellowish, caseous material. A definitive diagnosis was established by the microbiology laboratory, where cultures of the abscess material yielded *Nocardia* species (Figures 2, 3). The isolate demonstrated sensitivity to imipenem and trimethoprim-sulfamethoxazole (cotrimoxazole).

The patient's postoperative course was managed in the intensive care unit (ICU). An extensive evaluation for other concurrent infections, including serial blood cultures and a comprehensive panel of serologies, was negative. A non-contrasted CT brain did not show any significant bleed and resolved obstructive hydrocephalus (Figure 1D). A CT scan of the chest, abdomen, and pelvis revealed findings consistent with ventilator-associated pneumonia but no definitive primary focus of nocardiosis.

His antimicrobial regimen was initiated with intravenous imipenem 500 mg four times daily for 28 days and intravenous trimethoprim-sulfamethoxazole for 13 days. He was subsequently transitioned to a long-term oral regimen of oral linezolid 600 mg twice daily and oral trimethoprim-sulfamethoxazole two tablets a day twice weekly for a total duration of 1 year.

Over the ensuing weeks, the patient exhibited a steady and significant neurological recovery. His level of consciousness, coordination, and speech gradually returned to his functional baseline. A follow-up CECT brain one-month post-surgery demonstrated a marked reduction in the size of the cerebellar lesion at $1.5 \times 2.4 \times 2.4$ cm (previously $3.4 \times 3.5 \times 3.2$ cm) with a lesser degree of mass effect. He was ultimately discharged in a stable condition to complete his extended course of antibiotic therapy as an outpatient.

During the outpatient clinic visits after 3 month being discharged, patient was found to have thrombocytopenia and was attributed to a side effect of oral trimethoprim-sulfamethoxazole and the treatment was only maintained with oral linezolid 600 mg for one-year duration. Patient condition of consciousness, coordination, and speech has significant improvement. Six months after the procedure, patient developed recurrence of multiple myeloma but opted for palliative care and refused reinduction of chemotherapy. Despite improvement of the abscesses, the patient succumbed due to progression of his long-standing multiple myeloma. The clinical timeline of the patient progression in shown in Figure 4.

Discussion

This case provides a compelling illustration of a rare but critical opportunistic infection in an immunocompromised patient. The patient's underlying multiple myeloma and extensive treatment history created a state of profound T-cell-mediated immune deficiency, which is the quintessential risk profile for invasive nocardiosis, particularly with the use of newer agents (10, 11). The pathogenesis of nocardial dissemination to the CNS is facilitated by specific virulence factors, which allow the organism to evade phagocytic killing and promote hematogenous seeding of the brain (4).

The diagnostic journey in this case highlights several classic challenges of CNS nocardiosis. The initial misdiagnosis of a stroke is

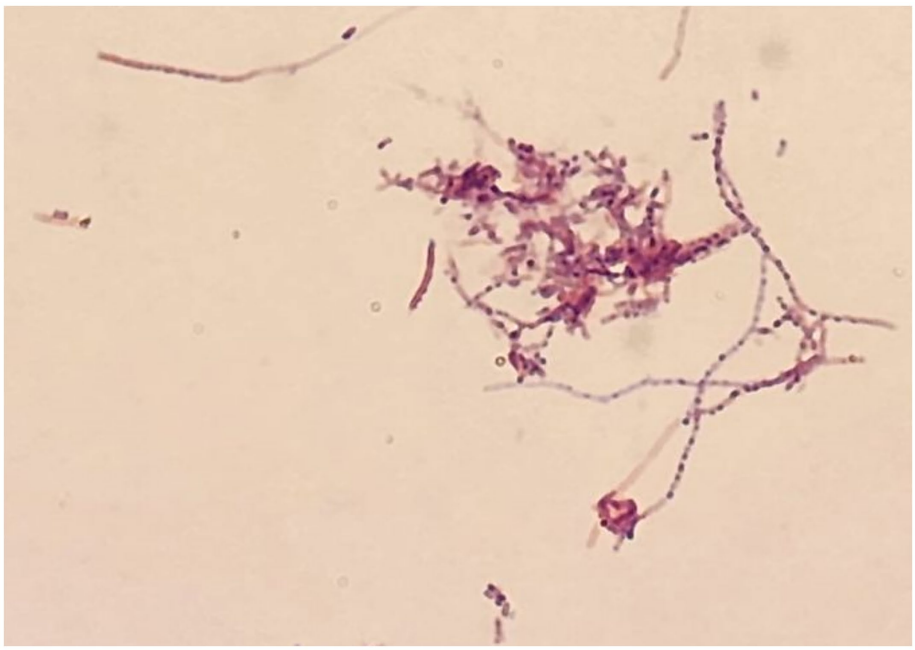

FIGURE 2
Microscopic examination of the excised cerebellar lesion showing branching, filamentous Gram-positive bacteria consistent with *Nocardia* species (Gram stain, 1,000× magnification).

FIGURE 3
Culture of the excised lesion on blood agar demonstrating the characteristic dry, chalky, white-tan colonies of *Nocardia* species.

a common pitfall, driven by the nonspecific and often insidious onset of neurological symptoms, which can lead to critical delays in appropriate treatment (7). Furthermore, the neuroimaging finding of a ring-enhancing lesion, while suggestive of an abscess, is not pathognomonic and shares features with high-grade neoplasms and other infections, making a definitive radiological diagnosis challenging (6, 8). The patient's clinical presentation, combined with the presence of multiple myeloma, placed CNS lymphoma high on the list of differential diagnoses. The definitive diagnosis was only established through surgical excision of the lesion, which confirmed the presence of a pyogenic abscess and, importantly, yielded cultures positive for *Nocardia* sp.

A crucial diagnostic principle underscored by this case is the low utility of CSF analysis for encapsulated brain abscesses. The negative CSF cultures are consistent with the literature, where the diagnostic yield of CSF is reported to be low in the absence of concomitant meningitis (7, 12, 13). This emphasizes that for a patient with a suspected nocardial abscess, a lumbar puncture is an insufficient diagnostic step, and clinical efforts must be aggressively directed toward obtaining a tissue specimen. Direct aspiration or excision of the lesion remains the gold standard for diagnosis, as it provides the highest yield for both histopathology and, critically, culture for antimicrobial susceptibility testing (7, 14). The extended time required for culture results creates a diagnostic-therapeutic gap where empirical therapy must be initiated without definitive susceptibility data.

The successful outcome in this patient was predicated on a multimodal therapeutic strategy that combined aggressive neurosurgical intervention with prolonged, targeted antimicrobial therapy (7, 14, 15). This combined approach is consistently associated with the best survival rates in CNS nocardiosis. Surgical intervention was vital not only for establishing the diagnosis but also for source control, reducing the intracranial mass effect, and decompressing the obstructed ventricular system.

The antimicrobial regimen was designed based on established principles for treating severe nocardiosis. The initial use of combination intravenous therapy with imipenem and trimethoprim-sulfamethoxazole is a standard approach, though more recent data suggest a trend toward using combinations with better CNS penetration (4, 7, 16). In this case, the regimen was complicated by the patient's reaction to trimethoprim-sulfamethoxazole leading to thrombocytopenia, which necessitated a switch to oral Linezolid-based regimen only. This highlights the practical challenges of managing long-term antimicrobial therapy in a critically ill and immunocompromised patient. The transition to a long-term oral regimen containing linezolid is also consistent with current evidence. Linezolid offers excellent oral bioavailability and CNS penetration and has near-universal *in vitro* activity against *Nocardia* species, making it a cornerstone of modern therapy, particularly when prolonged treatment is required (4, 17, 18). The planned one-year duration of therapy is appropriate for CNS disease in an immunocompromised host, as shorter courses are associated with a higher risk of relapse (7). This extended duration, however, necessitates vigilant monitoring for potential toxicities, particularly the myelosuppression and neuropathy associated with long-term linezolid use (19, 20).

Although the abscess resulting from nocardiasis was managed successfully with the antibiotic regimen, the progression of his multiple myeloma prevented us from completing the planned one-year course of treatment.

Conclusion

CNS nocardiosis remains a significant diagnostic and therapeutic challenge that requires a high index of suspicion, particularly in patients with profound immunosuppression. This case highlights the classic pitfalls in diagnosis, including non-specific clinical and radiological

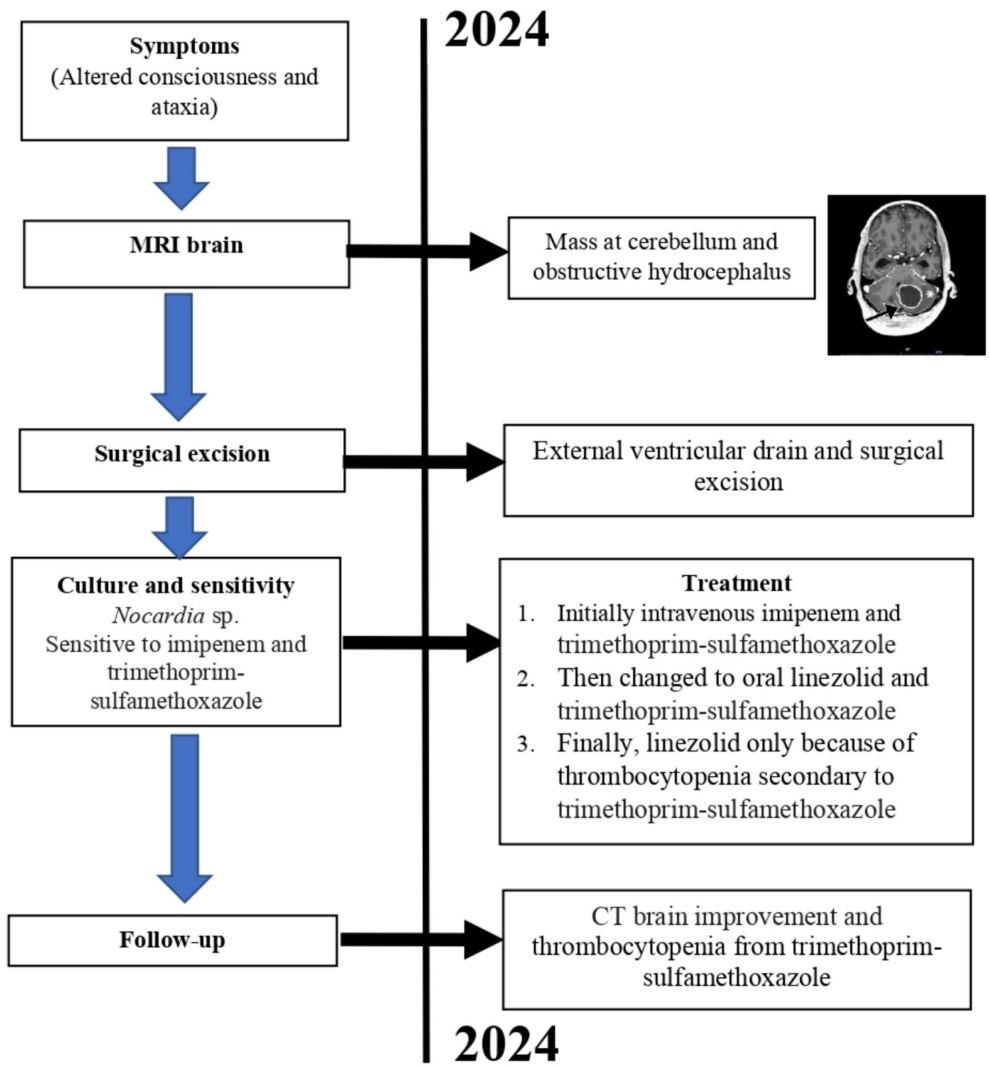

FIGURE 4
Case report timeline. Presented according to CARE guidelines.

presentations, and reinforces the principle that a definitive diagnosis requires direct tissue sampling. An optimal outcome is contingent upon an aggressive, multidisciplinary approach that combines prompt neurosurgical intervention for source control with a prolonged course of targeted, multi-drug antimicrobial therapy guided by susceptibility testing and any adverse reaction related to the treatment.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Research Ethics Committee National University of Malaysia. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

IA: Writing – review & editing, Writing – original draft. MM: Writing – original draft, Writing – review & editing. CD: Conceptualization, Writing – original draft. MA: Writing – review & editing, Investigation. FA: Formal analysis, Writing – original draft, Supervision. YS: Project administration, Methodology, Writing – review & editing. AZ: Validation, Writing – review & editing, Visualization, Resources.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

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

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 02 October 2025
DOI 10.3389/fmed.2025.1670782

OPEN ACCESS

EDITED BY
Yuetian Yu,
Shanghai Jiao Tong University, China

REVIEWED BY
Yanwen Chen,
University of Pittsburgh, United States
Wenjian Mao,
Nanjing University, China

*CORRESPONDENCE
Fangyu Yu
✉ yufangyu0574@zcmu.edu.cn

†These authors have contributed equally to this work

RECEIVED 22 July 2025
ACCEPTED 22 September 2025
PUBLISHED 02 October 2025

CITATION
Li P, Wu Y, Ge D, Xu R, Zhang Q, Li Y, Zhang L and Yu F (2025) Case Report: Non-Catheter-Related arterial hemorrhage as a complication of hemoperfusion in hypertriglyceridemic pancreatitis: mechanistic hypotheses and multidisciplinary strategies. *Front. Med.* 12:1670782. doi: 10.3389/fmed.2025.1670782

Case Report: Non-Catheter-Related arterial hemorrhage as a complication of hemoperfusion in hypertriglyceridemic pancreatitis: mechanistic hypotheses and multidisciplinary strategies

Pochen Li [1†], Yang Wu[2†], Danxia Ge[1], Ruyi Xu[1], Qianping Zhang[1], Yujiao Li[1], Lingyao Zhang[1] and Fangyu Yu[1*]

[1]Intensive Care Unit, Ningbo Municipal Hospital of Traditional Chinese Medicine (TCM), Affiliated Hospital of Zhejiang Chinese Medical University, Ningbo, China, [2]Department of Respiratory, Ningbo Municipal Hospital of Traditional Chinese Medicine (TCM), Affiliated Hospital of Zhejiang Chinese Medical University, Ningbo, China

Hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is a rapidly progressive and increasingly prevalent subtype of acute pancreatitis. Hemoperfusion (HP) is commonly employed as a prompt and effective method to lower serum triglyceride (TG) levels. However, in the context of anticoagulant administration and underlying coagulopathy, this approach may precipitate severe hemorrhagic complications. We report a case involving a female patient with HTG-AP who underwent HP for markedly elevated TG levels. Upon admission, the patient exhibited mildly prolonged thrombin time. Following the second session of HP, she developed hemorrhagic shock. Imaging revealed massive hemoperitoneum initially suspected to result from venous catheterization. Subsequent digital subtraction angiography (DSA) confirmed active arterial bleeding from a branch of the right internal iliac artery, which was successfully managed by embolization. Post-procedural evaluation suggested that the arterial rupture was likely due to increased vascular fragility caused by systemic inflammation from acute pancreatitis, further aggravated by anticoagulant exposure during HP. This case underscores the critical importance of pre-treatment bleeding risk assessment, especially in patients with pre-existing coagulation abnormalities. In cases of acute hemorrhage, clinicians must remain alert to non-iatrogenic bleeding sources associated with the underlying pathology and therapeutic interventions. Individualized anticoagulation strategies and vigilant hemodynamic and coagulation monitoring are essential to mitigate the risk of treatment-associated hemorrhagic events.

KEYWORDS

hypertriglyceridemia-induced acute pancreatitis, hemoperfusion, spontaneous hemorrhage, anticoagulation strategy, endovascular intervention

1 Introduction

Hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is a distinct subtype of acute pancreatitis, increasingly observed in specific populations (1). It is characterized by rapid progression and a high risk of multi-organ dysfunction, posing significant clinical challenges. Studies have demonstrated that when serum triglyceride (TG) levels exceed 11.3 mmol/L, intensified pancreatic lipolysis leads to excessive free fatty acid (FFA) release (2). These FFAs exert direct cytotoxic effects on pancreatic parenchyma and capillary endothelium, triggering local injury and systemic inflammatory response syndrome (SIRS). To rapidly clear circulating lipids and arrest disease progression, blood purification techniques–particularly hemoperfusion (HP) –have been widely adopted (3, 4).

While extracorporeal blood purification offers effective early intervention, it introduces a non-negligible risk of bleeding, primarily due to anticoagulation (5). Furthermore, acute pancreatitis itself may predispose patients to spontaneous hemorrhage. Recent reports have highlighted cases of deep arterial bleeding during HP unrelated to vascular access injury (6, 7).

We present a rare case of massive abdominopelvic hemorrhage in a patient with HTG-AP undergoing routine HP. The bleeding originated from a branch of the internal iliac artery remote from the catheterization site. Through this case, we aim to enhance clinical awareness of spontaneous arterial bleeding associated with HP, especially in the context of underlying coagulopathy.

2 Case presentation

A 30-year-old woman was admitted via the emergency department on April 2, 2025, with abdominal pain lasting 10 h. On presentation, her temperature was 37.3 °C; blood pressure, 130/97 mmHg; heart rate, 66 bpm; and respiratory rate, 14 breaths/min. Physical examination revealed clear consciousness, normal skin and mucosa, and marked tenderness in the left upper abdominal quadrant. The patient denied any history of bleeding disorders, anticoagulant or antiplatelet use, and was not menstruating at presentation.

Initial laboratory tests revealed a markedly elevated TG level of 35.91 mmol/L, serum amylase at 204 U/L, and urinary amylase at 1016 U/L. Non-contrast abdominal CT demonstrated pancreatic tail swelling with hypodense areas and mild peripancreatic exudation, consistent with HTG-AP. Coagulation studies showed prolonged thrombin time (TT) at 29.1 s and mildly elevated fibrinogen. Additional labs included Alanine Aminotransferase (ALT) 19 U/L, Aspartate Aminotransferase (AST) 18 U/L, creatinine 35 μmol/L, Blood Urea Nitrogen (BUN) 3.47 mmol/L, potassium 4.06 mmol/L, sodium 130.6 mmol/L, and total calcium 2.22 mmol/L. Blood routine showed White Blood Cell count (WBC) 16.5 × 10^9/L, Red Blood Cell count (RBC) 4.67 × 10^{12}/L, Platelet count (PLT) 228 × 10^9/L, Hemoglobin (HGB) 163 g/L, and C-Reactive Protein (CRP) 6.2 mg/L.

The patient received intravenous esomeprazole 40 mg q12h, somatostatin 3 mg q12h, and phloroglucinol 100 mg BID, along with fluid resuscitation, insulin, and 10% glucose. HP was initiated to lower TG levels. A right femoral venous catheter was placed under ultrasound guidance using a standardized protocol, with correct positioning confirmed. HP was conducted using the MG330 cartridge, with each session lasting 2 h. A total of 3 sessions were scheduled. Anticoagulation consisted of sodium heparin with a loading dose of 3000 U followed by continuous infusion at 1500 U/h.

Approximately 6 h after the second session, the patient developed sudden tachycardia (>120 bpm), hypotension (nadir SBP 80 mmHg), and abdominal distension. Physical examination revealed positive shifting dullness. HGB dropped acutely from 129 g/L to 78 g/L–a 51 g/L decline–suggesting concealed intra-abdominal hemorrhage. Hematocrit also declined significantly. β-hCG was negative (Figure 1).

During this period, dynamic laboratory monitoring demonstrated a progressive decline in PLT counts (228 × 10^9/L at admission, 267 × 10^9/L on April 3 at 06:53, 238 × 10^9/L at 14:51, 137 × 10^9/L at 18:22, and 114 × 10^9/L on April 4 at 09:39). Meanwhile, D-dimer increased from 0.39 mg/L at admission to 1.23 mg/L, 2.01 mg/L, and 3.31 mg/L, while fibrin degradation products (FDP) rose to 10.0 and 9.6 mg/L during the acute hemorrhagic phase. In parallel, TG decreased markedly following HP: from 35.91 mmol/L at admission to 18.32 mmol/L after the first treatment, and further down to 2.58 mmol/L and 1.77 mmol/L after subsequent sessions (Figure 2).

Resuscitation included fluid replacement, transfusion of leukocyte-depleted red cells and fresh frozen plasma, and norepinephrine infusion. Bedside ultrasound showed intra-abdominal fluid and a hypoechoic pelvic mass. Abdominal CT confirmed hemoperitoneum with loculated fluid collections up to 106 × 77 mm. Emergency digital subtraction angiography (DSA) was performed (Figure 3).

DSA revealed no extravasation along the venous access or iliac vein trajectory. The right femoral, common iliac, and external iliac arteries appeared intact. However, active contrast extravasation was identified in a branch of the right internal iliac artery. Endovascular embolization was performed, yielding immediate hemodynamic improvement (Figure 4). Post-procedure HGB levels stabilized between 72–77 g/L at 1, 4, and 10 h postoperatively, and the patient's condition gradually improved.

Following embolization and supportive care, the patient's condition stabilized and she was successfully transferred out of the ICU. She was discharged on April 26. At outpatient follow-up on May 13, her clinical status remained stable, with HGB 117 g/L, RBC count 4.41 × 10^{12}/L, TG 2.39 mmol/L, and serum amylase 48 U/L. No recurrent hemorrhage or relapse of pancreatitis was observed during the follow-up period.

3 Discussion

Acute pancreatitis (AP) is a common abdominal emergency that may lead to local necrosis, abscess formation, and systemic complications (8). Although HTG-AP often has a favorable prognosis when promptly treated, spontaneous hemorrhagic events–including intra-abdominal and retroperitoneal bleeding–may occur in severe cases, posing considerable risk (9). Literature reports indicate that potential hemorrhagic vascular complications are associated with a mortality rate of 34%–52% in cases of AP (6). Arterial bleeding, though rare, is more abrupt and

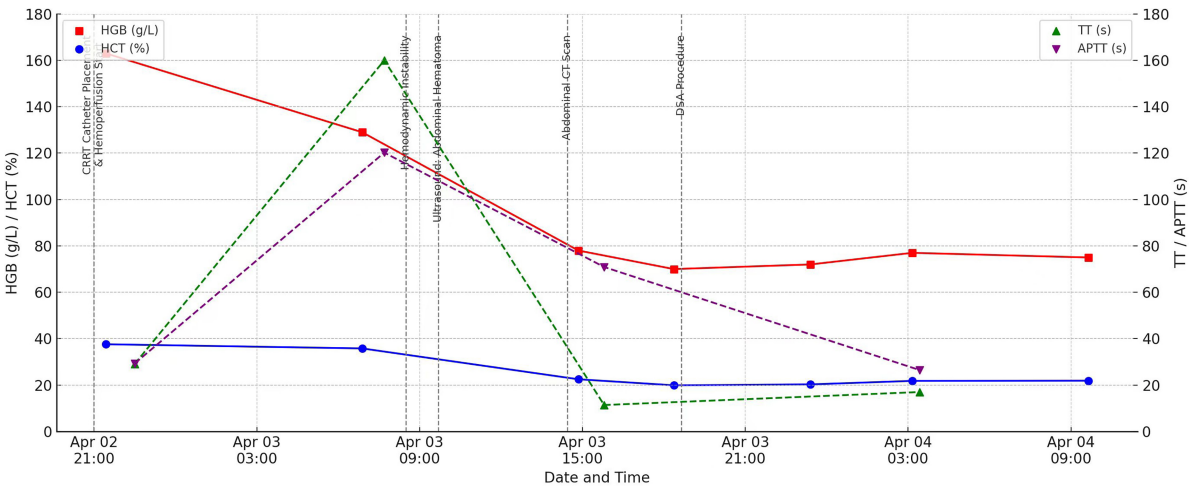

FIGURE 1
Trends in Hemoglobin (HGB), Hematocrit (HCT), Activated Partial Thromboplastin Time (APTT), and Thrombin Time (TT), annotated with key clinical events.

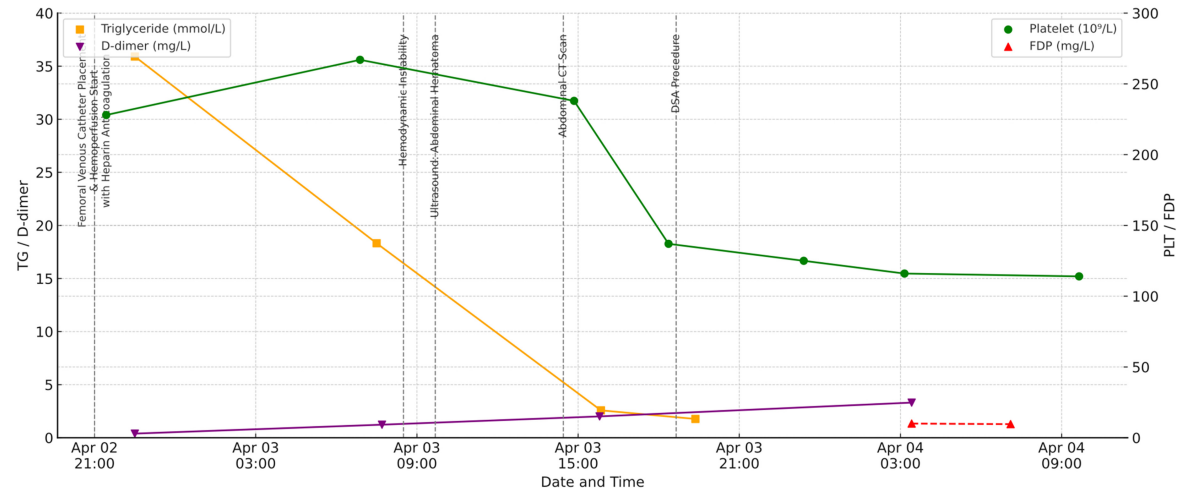

FIGURE 2
Trends in platelet count (PLT), D-dimer, fibrin degradation products (FDP), and triglycerides (TG), annotated with key events.

life-threatening. For example, in 2023, Yamazaki M et al. (10) described a case of acute pancreatitis complicated by rupture of a gastroduodenal artery pseudoaneurysm, which was successfully treated via surgical intervention. A 2022 case report in Frontiers in Surgery documented a retroperitoneal hemorrhage secondary to pancreatitis-associated pancreatic pseudocyst rupture (11).

In this case, hemorrhagic shock occurred after the second HP. DSA confirmed that the hemorrhage originated from a remote internal iliac artery branch, unrelated to catheterization, prompting further investigation into the underlying mechanism. Based on interdisciplinary discussion, we propose a multifactorial mechanism:

(1) Disease-related vascular fragility: In HTG-AP, pancreatic lipase–mediated hydrolysis of triglycerides leads to the release of FFAs, which exert direct cytotoxic effects on both pancreatic acinar and vascular endothelial cells. This FFA-mediated injury induces acinar necrosis and disrupts endothelial barrier integrity through oxidative stress, nitric oxide inhibition, and activation of TLR4/NF-κB–dependent inflammatory pathways. The resultant inflammatory cascade, characterized by neutrophil infiltration and cytokine release, increases microvascular permeability and compromises vessel wall stability. Consequently, this cascade may predispose patients to spontaneous hemorrhage under physiological stress, even in the absence of visible pseudoaneurysms (12, 13).

(2) Hemoperfusion-induced coagulation disturbances: Adsorption cartridges may non-selectively remove coagulation proteins such as fibrinogen, prothrombin, and antithrombin III (14). This patient's prolonged TT upon admission suggested a baseline coagulation deficit. Combined with systemic anticoagulation, this likely exacerbated bleeding risk, particularly in patients with abnormal APTT or TT.

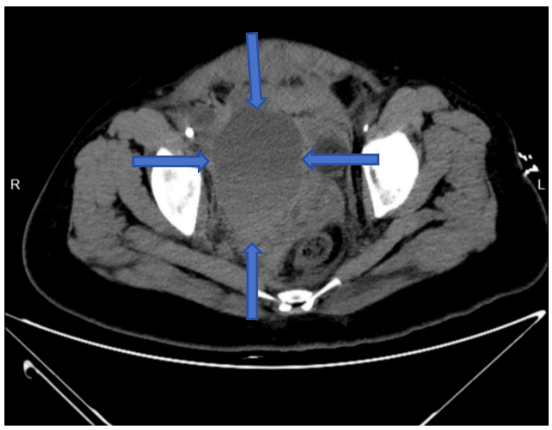

FIGURE 3
Axial abdominal CT scan showing a hematoma (indicated by arrow).

(3) Exclusion of autoimmune coagulopathy (15): Post-stabilization, autoimmune screening (ANA, anti-dsDNA, ACL, anti-β2GPI, anti-Sm, anti-SSA, LAC) was negative. Although hereditary or acquired coagulopathy could not be fully excluded due to patient's financial constraints, no specific factor deficiency was documented.

Although angiography excluded catheter-related vascular injury and demonstrated focal bleeding from a distal branch of the internal iliac artery, the precise etiology of this hemorrhage could not be determined with certainty. While disease-related vascular fragility and systemic anticoagulation were considered the most likely contributors, we acknowledge that iatrogenic factors cannot be entirely excluded. This limitation underscores the importance of maintaining vigilance for both spontaneous and procedure-related causes of bleeding when managing patients with HTG-AP undergoing HP.

It is noteworthy that in patients with acute pancreatitis complicated by hemorrhage, the possibility of disseminated intravascular coagulation (DIC) must always be considered. In this case, dynamic laboratory monitoring showed a progressive decline in platelet counts, together with rising D-dimer levels and elevated FDP, findings consistent with consumptive coagulopathy and raising concern for DIC. However, the absence of systemic microthrombi, the lack of overt ecchymoses or generalized bleeding tendency, and the focal arterial rupture demonstrated by angiography collectively argued against overt DIC. The patient's stabilization and favorable recovery following targeted embolization further supported this interpretation.

Furthermore, the necessity of HP in HTG-AP remains controversial. Although HP achieves rapid TG reduction, recent evidence has questioned its impact on long-term prognosis, with some studies suggesting no significant improvement in outcomes and a potential association with increased ICU utilization (16). In this case, HP was selected to achieve prompt biochemical control; however, whether HP should be routinely performed in HTG-AP requires further validation through high-quality clinical studies. Therefore, the decision to initiate HP should be made cautiously, balancing the biochemical benefit against the uncertain effect on patient-centered outcomes and the potential risk of additional harm.

Collectively, these mechanisms highlight a multifactorial hemorrhagic risk profile involving disease pathology, procedural anticoagulation, and potential undiagnosed coagulopathy.

4 Clinical Implications

This case illustrates that although rare, spontaneous arterial hemorrhage during HP in HTG-AP can be catastrophic. Vigilant risk assessment and timely intervention are essential. In conjunction with the relevant consensus (17), we propose the following recommendations:

(1) Pre-treatment assessment: Evaluate TT, APTT, FIB, D-dimer, liver and renal function, and–where feasible–platelet function and coagulation factor levels. High-risk patients may benefit from alternative anticoagulation (e.g., regional citrate, heparin-free regimens, or low-dose protocols).

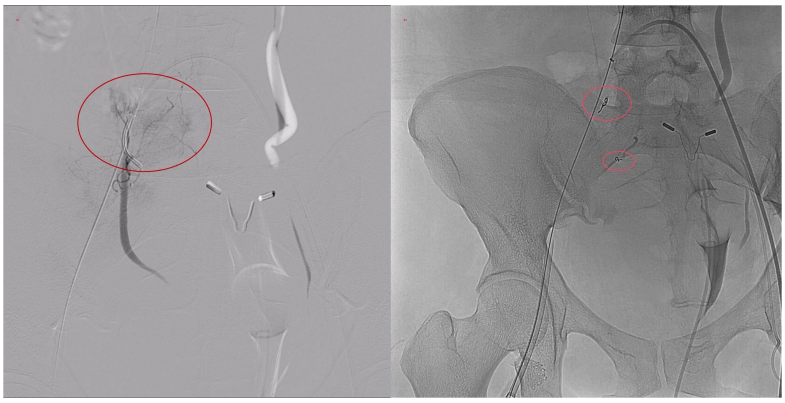

FIGURE 4
Digital subtraction angiography (DSA) images. **(a)** Active contrast extravasation from a distal branch of the internal iliac artery. **(b)** Post-embolization angiogram demonstrating successful occlusion of the bleeding site with metallic coils.

(2) Enhanced intra- and post-procedural monitoring: Monitor vital signs, urine output, and HGB dynamically during and 6–12 h post-treatment. Early signs (distension, dullness, hypotension) warrant prompt imaging. Do not rely solely on access site inspection–deep arterial sources must be considered.
(3) Early imaging and interventional strategy: Rapid access to ultrasound, CT, and DSA is critical. Interventional radiology should be integrated into the acute care algorithm for suspected internal hemorrhage.
(4) Patient communication and multidisciplinary care: Informed consent must include discussion of non-access-related hemorrhage. When bleeding occurs, management by a multidisciplinary team–including intensivists, interventional radiologists, and hepatobiliary surgeons–is essential.
(5) Future research: Large-scale, prospective studies are needed to identify predictors of HP-associated bleeding and optimize anticoagulation protocols. Innovations in cartridge design may further enhance safety.

Data availability statement

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

Ethics statement

The publication of this case report was conducted in accordance with the principles of the Declaration of Helsinki. The studies involving humans were approved by Institutional Review Board of Ningbo Municipal Hospital of Traditional Chinese Medicine ((LW-2005-027). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent for publication of clinical data and accompanying images was obtained from the patient or their legally authorized representative.

Author contributions

PL: Data curation, Formal analysis, Investigation, Methodology, Writing–original draft, Writing–review & editing. YW: Data curation, Investigation, Methodology, Writing–original draft, Writing–review & editing. DG: Data curation, Writing–original draft, Writing–review & editing. RX: Formal analysis, Writing–review & editing. QZ: Formal analysis, Writing–review & editing. YL: Formal analysis, Writing–review & editing. LZ: Formal analysis, Writing–review & editing. FY: Data curation, Methodology, Writing–review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was funded by the Critical Care Medicine Laboratory Project of Ningbo Municipal Hospital of Traditional Chinese Medicine.

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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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 02 October 2025
DOI 10.3389/fmed.2025.1650313

OPEN ACCESS

EDITED BY
Yuetian Yu,
Shanghai Jiao Tong University, China

REVIEWED BY
Chandrashekar Janakiram,
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University of Pennsylvania, United States
Fatma Mohammed,
Najran University, Saudi Arabia

*CORRESPONDENCE
Huaixiang Zhai
✉ 840843121@qq.com

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

RECEIVED 19 June 2025
ACCEPTED 22 September 2025
PUBLISHED 02 October 2025

CITATION
Shi M, Li L and Zhai H (2025) Oral frailty and its influencing factors among ICU patients with oral endotracheal intubation: a cross-sectional study.
Front. Med. 12:1650313.
doi: 10.3389/fmed.2025.1650313

Oral frailty and its influencing factors among ICU patients with oral endotracheal intubation: a cross-sectional study

Min Shi[1†], Lei Li[2†] and Huaixiang Zhai[1*]

[1]Critical Care Medicine, The First People's Hospital of Lianyungang, Lianyungang, China, [2]Lianyungang Disease Prevention Control Center, Lianyungang, China

Objective: To investigate the level and factors associated with oral frailty among ICU patients with oral endotracheal intubation, and to provide references for the construction of targeted nursing intervention programs in the future.
Methods: In this single-centre, cross-sectional study, a total of 226 patients with oral endotracheal intubation in ICU were selected by convenience sampling method. General data questionnaire, the Oral Frailty Index-8, the Oral Health Assessment Tool, the Nutritional Risk Screening 2002 and the Frail Scale were used for the study.
Results: The scores of oral frailty in ICU patients with oral endotracheal intubation were 3.00 (2.00, 4.00), of which 36.73% (83/226) were high risk. Age, marital status, duration of oral endotracheal intubation and oral health level were the influencing factors of oral frailty in ICU patients with oral endotracheal intubation (all $p < 0.05$).
Conclusion: The risk of oral frailty among ICU patients with oral endotracheal intubation is prevalent. In addition to airway management, medical staff should pay attention to the level of oral frailty according to the patient's specific situation, and do a good job of prevention and control management to reduce the risk of oral frailty.

KEYWORDS

ICU, oral endotracheal intubation, oral frailty, influencing factor, cross-sectional study

1 Introduction

Oral endotracheal intubation (1) is an important means of life support in the ICU. It can maintain the patency of the patient's respiratory tract and improve oxygenation status. However, at the same time, it affects the oral environment. In severe cases, it may damage oral functions and increase the physical and mental burden of patients (2). Study (3) shows that poor oral health is one of the common problems among patients with invasive mechanical ventilation in the ICU. The establishment of artificial tracheas interferes with the normal oral functions of patients. Patients have limited chewing function, reduced oral saliva, decreased self-cleaning ability, accumulation of airway secretions, and even cause swallowing dysfunction (4). Relevant studies (5) showed that patients with tracheal intubation are prone to complications such as respiratory tract infections due to misaspiration. Studies (6, 7) have reported that patients with long-term tracheal intubation connected to a ventilator for assisted breathing showed functional impairment such as choking when drinking water or drooling 4 h after extubation. Poor oral health of patients is prone to increase their risk of frailty (8). It may even cause physical, psychological and social impairments, thereby leading to a decline

in the quality of life related to oral health in patients (9). Therefore, the current situation of the quality of life related to oral health in patients should be given more attention (10). Effective oral care management is regarded as one of the important measures to prevent related complications in patients with mechanical ventilation (11). Relevant studies (12) show that the oral health care practice programs in our country are still in the development stage.

Studies show that the incidence of oral frailty in China is higher than that in developed countries such as Japan (13). This might be due to differences in healthcare, culture, etc., or perhaps because of variations in research methodologies (14). Oral frailty has a significant impact on the health, possibly increasing the risk of physical frailty, disability and death, and is closely related to muscle loss, cognitive decline and deterioration of quality of life (15–17). By assessing the oral frailty of patients, it can help us identify the risk of their death at an early stage (18). Studying the occurrence of oral frailty and intervention measures is of great significance for improving the oral health of patients, enhancing their quality of life and delaying aging. At present, China pays more attention to the physical, psychological and cognitive frailty of patients, but the research on oral frailty is relatively insufficient. Dibello et al. (19) pointed out that decreased chewing ability, difficulty in swallowing and tooth loss are the main characteristics of oral frailty. These problems can significantly affect the daily living ability of patients and increase the risk of physical frailty. Another study also found that poor oral health is significantly associated with frailty, with tooth loss and chewing difficulties being key risk factors (20). Research (21) shows that the oral environment and function affect the recovery of the body and are even related to the daily activities of patients after discharge. Therefore, paying attention to oral conditions can not only effectively prevent complications such as ventilator-associated pneumonia (22), but also be conducive to promoting the recovery of patients.

Foreign scholars have paid attention to oral frailty earlier and have carried out related research, while the attention to oral frailty in China is also gradually increasing (23). Currently, the main focus is on the incidence and influencing factors of oral frailty, etc. Studies (24–28) show that the incidence of oral frailty in China ranges from 25.19 to 64.3%. Research (29) shows that oral frailty is age-related. With the increase of age, the occlusal function, chewing function and swallowing function of the elderly all decline to varying degrees. Meanwhile, living habits can also affect the degree of oral frailty. People who live alone or often eat alone have a higher risk of developing oral frailty (30). Different research subjects have different levels of oral frailty, and the focus of attention also varies. For instance, among elderly patients with long-term T2DM duration of more than 10 years, particular attention should be paid to fewer functional natural teeth, suboptimal dental restoration status, elevated FBG levels, and coexisting cognitive impairment (31). There are numerous risk factors for oral frailty in patients. It is very necessary to discover and warn of the risk factors of oral frailty in patients in a timely manner. Relevant research suggests incorporating oral health into physical health assessment, which is of great significance for preventing the overall progression of individual frailty (32). Therefore, formulating effective intervention measures for oral frailty in the future to prevent oral frailty in patients is of great significance for healthy.

Therefore, from the perspective of patients with oral endotracheal intubation in the ICU, this study explores the level of oral frailty and its influencing factors, with the aim of enhancing the attention of medical staff to the oral health level of patients with oral endotracheal intubation in the ICU in clinical work. At the same time, it also provides a reference for formulating intervention measures to improve oral frailty in the future.

2 Materials and methods

2.1 Study design and participants

Convenience sampling method was used to select patients with oral endotracheal intubation in the ICU of a tertiary general hospital in Lianyungang City, Jiangsu Province, China, from August 2024 to January 2025 as the study subjects. All patients provided a signed written informed consent form for the use of their data. The study complied with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital (KY-20250514001-01).

Inclusion criteria included: (1) age ≥18 years old; (2) When awake /RASS score was 0, the duration of oral endotracheal intubation was ≥48 h; and (3) The patient's condition is stable and they can communicate through verbal or non-verbal means (such as writing), and independently complete the result responses throughout the process. Exclusion criteria included: (1) presence of cognitive impairments or mental disorders; (2) comorbidity with acute or severe diseases.

According to the requirements of statistical variable analysis, the required sample size should be 5–10 times the number of variables (33), calculation formula: Number of variables × (5 to 10) + Number of variables × (5 to 10) × inefficiency. In this study, there are 19 variable factors, and Considering the inefficiency of 10% questionnaire, the required sample size is at least 105 cases, and a total of 226 patients were investigated in the end.

2.2 Research tools

2.2.1 General information questionnaire

The researcher developed a general information questionnaire to investigate the general sociological information and related situations of the research participants through literature reading and data searching. The content included gender, age, marital status, smoking history, drinking history, education level, average monthly income, occupation, Body Mass Index (BMI), number of chronic co-morbidities, length of stay in ICU, duration of oral endotracheal intubation, whether surgical treatment was performed, whether sedative medication was used, whether dry mouth was present, and whether denture was present.

2.2.2 Oral Frailty Index-8

This scale was developed by Tanaka et al. (34). There are a total of 8 items, mainly covering five aspects: chewing ability, swallowing function, presence of dentures, oral health care behaviors, and social activities, which were scored by "yes" and "no." Entries 1–3 "yes" were scored as 2 points and "no" as 0 points, entries 4 ~ 5 "Yes" scored 1 point, "No" scored 0 points, and entries 6–8 "Yes" was scored as 0 points and "No" was scored as 1 point, and the total score ranges from 0 to 11 points. The higher the score, the worse the condition of oral

debility (35), where 0–2 is low risk, 3 is medium risk, and ≥4 is high risk (24). The Cronbach's α coefficient for the scale in this study was 0.699. The items of this scale are concise, the data is easy to collect, and it has good predictability (36). Even without the direct participation of oral professionals, medical staff can accurately assess it (37).

2.2.3 Oral Health Assessment Tool

The Oral Health Assessment Tool (OHAT) was Chineseized by Wang Jieqiong (38) and others on the basis of the revised scale by Chalmers (39) and others, and includes 8 entries for lips, tongue, gingival tissues, saliva, natural teeth, denture, oral cleanliness, and dental pain. Adopt Likert 3-level scoring method, from "healthy" to "unhealthy" score 0 ~ 2., with a total score of 0 to 16, with higher scores indicating poorer oral health. The Cronbach's α coefficient for this scale was 0.871 in this study.

2.2.4 Nutritional Risk Screening 2002

This scale was developed by Kondrup et al. (40). It was used to assess the risk of malnutrition in the study population, including three aspects: disease severity (0–3 points), nutritional impairment (BMI, recent weight changes and changes in eating, 0–3 points), age (≥70 years: "yes" scores 1, "no" scores 0), and a total score of 0–7 points, with a score of ≥3 indicating the presence of malnutrition (41).

2.2.5 Frail Scale

The scale is localized by Wei Yin (42) and others based on the frail screening tool proposed by the a European, Canadian and American Geriatric Advisory Panel (43), including five aspects, such as fatigue, resistance movement, walking difficulty, multi-disease coexistence and weight change, each item "yes" counts 1 point, "no" counts 0 points, and the total number is 0 to 5 points. 0 is classified as low risk, 1–2 as medium risk, and ≥3 as high risk. The Cronbach's α coefficient of the scale in this study was 0.891.

2.3 Data collection

The on-site survey was conducted by uniformly trained researchers, and one-on-one investigation is conducted with unified and colloquial instructions to explain the purpose and significance of this survey. The questionnaires were filled out on the spot and collected on the spot, and the completeness of the data was checked in time to ensure the authenticity and validity of the questionnaires. This study investigated the oral frailty level of patients 0 to 12 h after tracheal intubation removal, lasting for 10 to 30 min. Selecting this time point for the measurement of outcome indicators can not only avoid the impact of intubation on the patient's condition and expression, but also maintain the timeliness of the effect of oral tracheal intubation on the patient's oral frailty. Throughout the process, the patients were covered with bed curtains to protect their privacy. For research subjects with lower educational attainment or Poor audio-visual quality, assistance will be provided in the form of questions and answers.

2.4 Statistical analysis

The statistical analysis of this study was conducted using SPSS 26.0. The quantitative data were analyzed using frequencies and percentages. The measurement data conforming to normal distribution were expressed as mean ± standard deviation, and the two independent samples t-test was used for inter-group comparison. Those that did not conform to normal distribution were represented by median and quartile. Mann–Whitney U test was used for comparison between the two groups of data, Kruskal-Wallis H test was used for comparison between multiple groups of data, and Spearman correlation analysis was used for correlation. The variables with statistical significance were taken as independent variables by single factor analysis, and multivariate linear regression analysis was used for multivariate analysis. $p < 0.05$ was considered statistically significant.

3 Results

3.1 Characteristics of participants

A total of 226 patients were recruited for this study, including 108 males (47.8%) and 118 females (52.2%). Additional demographic details are shown in Table 1.

3.2 Univariate analysis of ICU patients with oral endotracheal intubation with different characteristics

As shown in Table 1, items with statistically significant differences in marital status, education level, occupation, whether surgical treatment was performed, nutritional risk, frailty risk.

3.3 Oral frailty score of ICU patients with oral endotracheal intubation, and correlation analysis with age, length of stay in ICU, duration of oral endotracheal intubation and oral health level

The results of the analysis showed that the oral frailty score of ICU patients with oral endotracheal intubation was 3.00 (2.00, 4.00) points, with 28.32% (64 patients) at low risk, 34.96% (79 patients) at medium risk, and 36.72% (83 patients) at high risk. Spearman correlation analysis showed that the correlation coefficients of oral frailty score with age, length of stay in ICU, duration of oral endotracheal intubation and oral health level were $r = 0.654$, 0.515, 0.560 and 0.505, respectively, all $p < 0.001$. Detailed results are provided in Table 2.

3.4 Influencing factors of oral frailty among ICU patients with oral endotracheal intubation

The oral frailty score was used as the dependent variable and the variables with statistically significant differences in the univariate analysis were used as independent variables for multiple linear regression analysis. Age, length of stay in the ICU, duration of oral tracheal intubation and oral health level were brought in as original values. The assignment of values for marital status, educational level, occupation, whether surgical treatment was performed, nutritional

TABLE 1 Comparison of oral frailty levels in ICU patients with oral tracheal intubation of different characteristics.

Characteristics	*N* (Percentage/%)	Z/H	*P*
Gender		−1.166	0.244
Male	108 (47.8%)		
Female	118 (52.2%)		
Marital status		9.511	0.009
Married	207 (91.6%)		
Unmarried	2 (0.9%)		
Divorced/widowed	17 (7.5%)		
Smoking history		−1.863	0.062
Yes	63 (27.9%)		
No	163 (72.1%)		
Drinking history		−0.342	0.732
Yes	82 (36.3%)		
No	144 (63.7%)		
Education level		10.071	0.018
Primary school and below	57 (25.2%)		
Junior high school	84 (37.2%)		
High school/technical secondary school	66 (29.2%)		
College/university degree or above	19 (8.4%)		
Average monthly income (yuan)		3.251	0.197
<1,000	59 (26.1%)		
1,000 ~ 5,000	79 (35.0%)		
>5,000	88 (38.9%)		
Occupation		49.927	<0.001
Employed	43 (19.0%)		
Retirement	151 (66.8%)		
Unemployed/Freelancer/self-employed	32 (14.2%)		
Body Mass Index (kg/m^2)		0.065	0.968
<18.5	61 (27.0%)		
18.5 ~ 23.9	120 (53.1%)		
≥24	45 (19.9%)		
Number of chronic co-morbidities		5.281	0.071
0	25 (11.1%)		
1	81 (35.8%)		
≥2	120 (53.1%)		
Whether surgical treatment was performed		−2.556	0.011
Yes	59 (26.1%)		
No	167 (73.9%)		
Whether sedative medication was used		−1.825	0.068
Yes	119 (52.7%)		
No	107 (47.3%)		
Whether dry mouth was present		−0.858	0.391
Yes	120 (53.1%)		
No	106 (46.9%)		
Whether denture was present		−0.819	0.413

(Continued)

TABLE 1 (Continued)

Characteristics	*N* (Percentage/%)	Z/H	*P*
Yes	90 (39.8%)		
No	136 (60.2%)		
Nutritional risk		−3.827	<0.001
Yes	86 (38.0%)		
No	140 (62.0%)		
Frailty risk		29.234	<0.001
Low	8 (3.5%)		
Medium	107 (47.4%)		
High	111 (49.1%)		

TABLE 2 The correlation between oral frailty score and age, length of stay in ICU, duration of oral tracheal intubation, and oral health level score (*r* value).

Item	Age	Length of stay in ICU	Duration of oral tracheal intubation	Oral health level
Oral frailty	0.654	0.515	0.560	0.505

All $P < 0.001$.

risk and frailty risk is as follows (marital status:1 = Married, 2 = Unmarried, 3 = Divorced/widowed; educational level:1 = Primary school and below, 2 = Junior high school, 3 = High school/technical secondary school, 4 = College/university degree or above; occupation:1 = Employed, 2 = Retirement, 3 = Unemployed/Freelancer/self-employed; whether surgical treatment was performed:1 = Yes, 2 = No; nutritional risk:1 = Yes, 2 = No; frailty risk:1 = Low, 2 = Medium, 3 = High). Multiple linear regression showed that age, marital status, duration of tracheal intubation and oral health were the influencing factors of oral frailty in ICU patients with oral endotracheal intubation. Table 3 presents the multiple linear regression analysis results.

4 Discussion

The present study utilized a cross-sectional design to investigate the degree of oral frailty and its influencing factors among ICU patients with oral endotracheal intubation. The study's findings revealed that ICU patients with oral endotracheal intubation exhibited oral frailty scores of 3.00 (2.00, 4.00) points, with 28.32% (64 patients) at low risk, 34.96% (79 patients) at medium risk, and 36.72% (83 patients) at high risk. The proportion of high-risk patients was lower than that of the survey results of the elderly in the community by Wang Lin et al. (26) (59.2%), which may be due to differences in research objects; ICU nurses use oral care solution every day to provide oral care for patients by wiping, rinsing and other reasonable ways to help patients clean their mouths and improve their comfort; Healthcare professionals provide patients with targeted treatment and care measures and 24 h care to facilitate their early recovery stage. However, the results of this study are higher than those of Irie et al. (44) (28.1%), which may be attributed to regional differences in the study subjects and differences in the study base. The study (45) shows that the elderly in Japan have a high awareness of oral health and visit dental clinics regularly. However, patients with oral catheterization in ICU are affected by many factors. Endotracheal catheterization and dental pads in the mouth lead to limited chewing function, stranded swallowing function, inability to eat orally, weakened oral self-purification ability, which is not conducive to the operation of oral care, and easy to induce oral infection and even ventilator-associated pneumonia (46). In addition, due to the critical condition of patients with oral endotracheal intubation in ICU, patients and their families pay more attention to the patient's condition and treatment effect, and then ignore oral problems. This suggests that healthcare professionals should promptly identify the risk of oral frailty among ICU patients with oral endotracheal intubation, carry out oral frailty risk screening when the patient's condition permits, and provide relevant professional knowledge and nursing care measures for patients in a targeted manner. For patients who have already experienced oral frailty, effective interventions, such as attempting to integrate appropriate nursing techniques of Chinese medicine, can help patients slow down the decline of oral function, reduce the risk of oral frailty among ICU patients with oral endotracheal intubation, improve the oral status and the quality of life, and promote the recovery of the patients.

The results of this study show that age is an influencing factor for oral frailty in ICU patients with oral endotracheal intubation, and the older the patients are, the higher the level of oral frailty is, which is consistent with the results of Tu Hangjia et al. (25). This may be due to the deterioration of body function with the increasing age of patients, and the worse oral environment due to oral catheterization, which leads to the decline of oral function. Oral weakness occurs, and decreased oral function is prone to malnutrition and muscle loss (47). Studies (48) have shown that oral function exercise as well as increased protein intake are beneficial in improving oral function. Therefore, medical staff should pay attention to the oral function of patients with oral tube intubation, especially older patients, and should follow the doctor's advice to remove the tracheal intubation as soon as possible if the condition permits, which can not only reduce the risk of infection, but also help improve the oral status of patients. The patient was instructed to eat reasonably after extubation and gradually increase protein intake to improve the patient's nutritional status and then reduce the risk of oral weakness.

The analysis results found that marital status was significantly associated with a higher risk of oral frailty in ICU patients with oral endotracheal intubation. Compared with patients with spouses, patients without spouses had a higher risk of oral frailty, which was similar to the results of previous studies (30), and single eaters were more likely to suffer from oral frailty (49). Nagayoshi et al. (50) showed

TABLE 3 Multivariate analysis of oral frailty in patients with oral tracheal intubation in the ICU.

Independent variable	β	SE	β'	t	95%CI	P
Constant	−2.93	0.764	–	−3.837	(−4.436 ~ −1.425)	<0.001
Age	0.068	0.011	0.444	6.133	(0.046 ~ 0.090)	<0.001
Marital status	0.458	0.172	0.113	2.663	(0.119 ~ 0.797)	0.008
Education level	0.037	0.103	0.016	0.354	(−0.167 ~ 0.240)	0.723
Occupation	−0.081	0.162	−0.022	−0.497	(−0.401 ~ 0.239)	0.620
Length of stay in ICU	−0.021	0.025	−0.104	−0.844	(−0.071 ~ 0.028)	0.400
Duration of oral endotracheal intubation	0.142	0.029	0.595	4.842	(0.084 ~ 0.200)	<0.001
Whether surgical treatment was performed	0.143	0.208	0.029	0.685	(−0.268 ~ 0.553)	0.494
Oral health	0.067	0.029	0.145	2.286	(0.009 ~ 0.125)	0.023
Nutritional risk	−0.097	0.197	−0.022	−0.494	(−0.485 ~ 0.291)	0.622
Frailty risk	−0.102	0.196	−0.027	−0.519	(−0.487 ~ 0.284)	0.604

that marital status correlates with oral debility, in which men with a partner have better oral function, probably because the companionship of their spouses enriches their daily life and improves their tongue and lip movement during communication (51). Related studies (52) have shown that oral debility is detrimental to an individual's physical and mental health as well as social development, and the patients in this study received love and support from their partners or spouses during regular visits, which was important for their physical and mental recovery. While our data suggest an association, the underlying mechanisms remain unexplored. Future studies incorporating measures of social support, psychological stress, and health behaviors are warranted to elucidate the potential pathways linking marital status and oral health outcomes. In the future, it is recommended that medical staff guide patients to carry out oral function rehabilitation exercises in a planned way (53), and encourage family members to participate in them, which is conducive to reducing the risk of oral weakness.

The results of this study show that the duration of oral endotracheal intubation is an influencing factor for oral frailty in ICU patients with oral tracheal intubation, which is similar to the results of previous studies (12). The duration of oral tracheal intubation is correlated with oral frailty. However, as this study was a cross-sectional design, this result only indicates an association between the two. It cannot be inferred that the longer the time of oral tracheal intubation, the more likely oral frailty will occur, nor can the influence of reverse causality or potential confounding factors be ruled out. The duration of oral tracheal intubation is associated with the risk of complications, such as pressure injury, ventilator-associated pneumonia, etc. (54). In addition, patients with critical illness and decreased oral immunity are prone to various oral diseases, aggravating oral weakness and not conducive to recovery of the disease. Studies (55) have shown that oral health affects body function, and poor oral health may lead to malnutrition, muscle atrophy, etc., and may even trigger death (56). As ICU medical staff focus on patient recovery and treatment and nursing effects, and pay little attention to oral health care (12), it is suggested to strengthen the training of oral expertise and skills in the future, and encourage dental specialists to join the treatment and nursing of ICU patients with severe illness, so as to develop a multidisciplinary collaborative medical work mode. Especially for patients with oral tube intubation in ICU, medical staff should assess the patient's condition in real time, conduct off-line training if the condition permits, and pull out the tracheal intubation as soon as possible (57), so as to avoid oral weakness to the greatest extent.

In this study, it was found that oral health level was an influential factor for oral frailty in ICU patients with oral endotracheal intubation, and the poorer the oral health status, the higher the oral frailty level, which was consistent with the results of Li Yi et al. (27). Oral health conditions mainly include lips, tongue, gum tissue, saliva, natural teeth, dentures, oral cleanliness, and toothache. Oral catheterization may affect the patient's oral environment, such as compression of oral tissue and interference with oral saliva secretion, and tooth loss may also occur, leading to decreased patient comfort and limited oral function (58). At the same time, patients cannot clean their mouths by themselves during the process of oral tube intubation, and mainly rely on oral care provided by medical staff. Once oral cleaning is incomplete, it is easy to cause patients' oral flora imbalance, which will lead to oral problems and accelerate oral weakness. Studies (59) have shown that effective oral management can improve the oral environment of patients with oral tube intubation, while different oral care methods have different effects on the oral environment of patients with oral tube intubation in ICU (60, 61). Therefore, healthcare professionals should take a reasonable approach to assess the oral condition of patients with tracheal intubation (2), construct a personalized oral care plan for them (62), provide perfect and comprehensive nursing measures, improve the oral environment, and enhance the quality of life. In addition, based on the actual situation of oral care for patients with oral catheterization in ICU in China and combined with oral nursing practice experience at home and abroad, oral nurses in intensive care can be developed to provide professional and perfect oral health care services for patients, thus reducing the occurrence of oral weakness in patients with oral catheterization.

There are several limitations to this cross-sectional study. First, we adopted a convenient sampling method, which might affect the external validity of the research results and introduce selection bias. Specifically, our sample size is relatively small, and all the samples are from a tertiary hospital, which may not fully represent the broader

group of ICU patients with oral tracheal intubation. Moreover, patients with different severity of the disease have different perceptions of oral frailty, which may lead to differences between the sample and the overall population. Second, the study has several limitations inherent to cross-sectional research, such as subjective bias, which may not fully reflect the actual situation. There may be recall bias in patients' self-reports, thus leading to overestimation. Although this assessment tool mainly relies on self-reported outcomes by patients, the scale includes elements of oral professional examination, which can accurately assess even without the direct participation of oral professionals, such as "Are there dentures/prosthetics?" Third, the scope of this study was limited to a certain moment, and no longitudinal tracking of outcome indicators was conducted. It failed to dynamically reflect the changes in oral vulnerability of ICU patients who received oral tracheal intubation, nor could it identify subgroups with different needs. Finally, no other factors that might affect ICU patients with oral tracheal intubation, such as baseline comorbidities and duration of sedation, were examined. Although we adjusted for multiple potential confounding factors, due to data availability issues, we were unable to adjust for baseline comorbidities and sedation duration, which may affect the accuracy of the results. Future research should prioritize the collection of these key clinical data for more thorough analysis. Despite these limitations, this study revealed the oral frailty among ICU patients with oral endotracheal intubation and its influencing factors, which has several implications for future research and practice. In the future, the research team will strive to overcome limitations, adopt more rigorous sampling methods, add objective outcome indicators, and collect longitudinal data, etc., to verify our findings. And this study illustrates the need for interventions to improve the oral frailty among ICU patients with oral endotracheal intubation. Future research should further expand the sample size and conduct multi-center investigations. At the same time, a more in-depth factor analysis of this scale should be carried out, and methods such as test–retest reliability should be considered to comprehensively evaluate its reliability. Therefore, in the future, the research team hopes to be able to find more effective and economical intervention strategies based on the existing research foundation and around the research hotspots of this topic (63–66).

5 Conclusion

The results of this study showed that the risk of oral frailty was common in patients with oral endotracheal intubation in ICU. Older age, no spouse, longer intubation time, and poor oral health are associated with an increased incidence of oral frailty in patients with oral tracheal intubation in the ICU. However, before clarifying the causal relationship, clinical decisions still need to be made with caution. It is suggested that ICU medical staff should pay attention to the assessment of oral frailty risk in patients with oral catheterization, pay special attention to key groups, formulate personalized intervention plans for patients with different characteristics, improve the oral health of patients with oral catheterization in ICU, reduce the risk of oral frailty, and promote early recovery. This study was a cross-sectional study and could not dynamically assess the changes in patients with oral frailty. In the future, multi-center, large-sample longitudinal studies can be carried out to further explore the level of oral frailty in critically ill 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

The studies involving humans were approved by Ethics Committee of the First People's Hospital of Lianyungang. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MS: Project administration, Visualization, Investigation, Formal analysis, Writing – review & editing, Validation, Data curation, Funding acquisition, Resources, Supervision, Conceptualization, Methodology, Software, Writing – original draft. LL: Conceptualization, Methodology, Data curation, Visualization, Validation, Software, Writing – review & editing, Project administration, Supervision, Funding acquisition, Resources, Writing – original draft, Formal analysis. HZ: Software, Writing – review & editing, Writing – original draft, Data curation, Formal analysis, Conceptualization, Validation.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We are grateful to all patients included in our study, investigators, site staff who put their efforts into research.

Conflict of interest

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

Generative AI statement

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 15 October 2025
DOI 10.3389/fmed.2025.1645839

OPEN ACCESS

EDITED BY
Zhongheng Zhang,
Sir Run Run Shaw Hospital, China

REVIEWED BY
Basim Dubaybo,
Wayne State University, United States
Rafal Adam Januszek,
Andrzej Frycz Modrzewski Krakow University, Poland
Giuseppe Fiorentino,
Colli Hospital, Italy

*CORRESPONDENCE
Huihui Lu
13413519777@139.com

RECEIVED 12 June 2025
ACCEPTED 29 September 2025
PUBLISHED 15 October 2025

CITATION
Wang Y, Deng Q, Tang S, Yu F, Lv Y, Liu Z, Lin L and Lu H (2025) A patient with acute pulmonary embolism caused by hyaluronic acid injection underwent nursing care of extracorporeal membrane oxygenation support therapy: a case report. *Front. Med.* 12:1645839. doi: 10.3389/fmed.2025.1645839

A patient with acute pulmonary embolism caused by hyaluronic acid injection underwent nursing care of extracorporeal membrane oxygenation support therapy: a case report

Yan Wang[1], Qidan Deng[2], Shili Tang[1], Fenhao Yu[1], Yunhao Lv[1], Zhi Liu[1], Lizhen Lin[3] and Huihui Lu[2]*

[1]Department of Intensive Care Unit, Affiliated Qingyuan Hospital, Guangzhou Medical University, Qingyuan People's Hospital, Qingyuan, China, [2]Department of Nursing, Affiliated Qingyuan Hospital, Guangzhou Medical University, Qingyuan People's Hospital, Qingyuan, China, [3]Department of Cardiovascular Medicine, Affiliated Qingyuan Hospital, Guangzhou Medical University, Qingyuan People's Hospital, Qingyuan, China

This article summarizes the nursing management of a patient who developed acute pulmonary embolism with concomitant cardiopulmonary arrest following intravaginal hyaluronic acid injection, requiring extracorporeal membrane oxygenation (ECMO) support. The main measures are rapid activation of the treatment plan to improve the efficiency of treatment; teamwork and safe transfer; early implementation of target temperature management to promote neurological prognosis; implementation of individualized anticoagulation strategies and infection control strategies; and autologous blood transfusion techniques to reduce blood loss during ECMO withdrawal. After 9 days of active treatment and refined care, the patient's condition was stable, and she was transferred to the general ward to continue treatment for 2 days and was discharged after recovery. At 1-month follow-up after discharge, the patient's consciousness was clear, her speech was clear, and the muscle strength of the limbs was back to normal. The cooperation of a mature ECMO team was important in the rescue and treatment of this patient, which could shorten the response time in all aspects of the rescue and improve the success rate of rescue and treatment. The application of individualized therapeutic measures and high-quality nursing care is the key to promote the recovery of this patient.

KEYWORDS

acute pulmonary embolism, extracorporeal membrane oxygenation, cardiac arrest, thrombolysis, nursing care

1 Introduction

Acute pulmonary thromboembolism (PTE) refers to a constellation of clinical and pathophysiological phenomena resulting from impaired respiratory and pulmonary circulatory functions. This condition arises due to the obstruction of pulmonary arterial branches or trunks caused by embolization of thrombi that originate predominantly in the deep veins of the lower extremities—a condition known as deep vein thrombosis (DVT)—and subsequently migrate to the pulmonary arteries (1, 2). In patients with acute pulmonary embolism, obstruction of the pulmonary arteries, reduction or even interruption of blood flow can trigger right ventricular failure, all of which are key contributors to the patient's death (3). Among

PTE patients, those who develop severe circulatory collapse within 30 days have a mortality rate of between 16 and 25%. In patients who develop complications of cardiac and respiratory arrest, the mortality rate is between 52 and 65%, and approximately 10% of patients die within the first hour of the onset of the disease (4, 5). Acute massive pulmonary thromboembolism (PTE) is a critical condition that can precipitate obstructive shock and cardiac arrest. It is distinguished by its rapid progression and high mortality rate if not promptly diagnosed and managed. The early use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can significantly reduce the working pressure of the right ventricle and enhance the function of the right ventricle, thus ensuring hemodynamic stabilization and tissue oxygenation recovery (6). With the development of the medical cosmetic industry, complications after hyaluronic acid injection have gradually attracted attention, and pulmonary embolism, as one of the serious complications, poses a great threat to patients' lives. The ICU plays a critical role in the management of such critically ill patients. Recently, the ICU of our hospital successfully employed VA-ECMO technology in the treatment of a patient who experienced cardiac arrest following a pulmonary thromboembolism (PTE) induced by an intravaginal hyaluronic acid injection. The following are some of our experiences and reports on emergency and nursing care.

2 Case presentation

We report the case of a 40-year-old Chinese female patient, was admitted to the hospital for "dizziness, chest tightness, and profuse sweating for more than 5 h." The patient was admitted to our hospital at 20:30 on November 07, 2024, after an intravaginal injection of hyaluronic acid in a beauty institute, and the emergency personnel found that her blood pressure could not be measured at the scene, and she was admitted to our hospital after initial resuscitation. Emergency examination revealed significant enlargement of the right heart, suggesting shock secondary to right heart failure. Despite the administration of high-dose vasoactive agents, the patient's blood pressure remained unstable, prompting the immediate initiation of ECMO rescue therapy. The emergency bedside ECMO procedure was performed at 00:35 on November 8. At 00:55, the patient's heart rate decreased to 30 beats per minute, accompanied by loss of consciousness and absence of major arterial pulses. Resuscitative measures, including external chest compressions, endotracheal intubation for mechanical ventilation, and intravenous administration of epinephrine, were immediately instituted. Spontaneous heartbeat returned at 00:58, and ECMO major circulation was successfully established by 01:00.

When the patient was transferred to ICU, she had a temperature of 36.6 °C, heart rate of 113 beats/min, respirations of 12 beats/min (invasive ventilator-assisted ventilation), and a blood pressure of 85/74 mmHg (VA-ECMO maintenance circulation); she was in a state of psychiatric drug sedation and analgesia, with an acute facies, and cold and wet body. During the course of VA-ECMO, the patient was provided with a variety of therapies including target temperature management, sedation and analgesia, and anti-infection. Considering the patient's sudden chest tightness, dizziness, and sweating, the patient performed vaginal hyaluronic acid injection and filling treatment in a beauty institution before the onset of the disease, and the injected material was crosslinked sodium hyaluronate gel, with an injection volume of 27 pcs (27 mL), which was combined with the emergency cardiac ultrasound of the right cardiac system significantly enlarged, pulmonary arterial hypertension, and the electrocardiogram suggesting the manifestation of SIQIIITIII, and although the lung CTA did not show any obvious changes, it still could not exclude that hyaluronic acid mistakenly enters into the vessels to cause particulate obstruction of the small branches of the pulmonary artery is possible, and the possibility of acute non-thrombotic pulmonary embolism and obstructive shock is currently considered to be high. Given the indeterminate etiology, a multidisciplinary consultation involving pulmonology, cardiology, pharmacy, aesthetic medicine, and other relevant specialties was convened to guide diagnosis and management. On the second day, the patient demonstrated improved neurological responsiveness, evidenced by the ability to withdraw the stimulated limb, prompting discontinuation of therapeutic hypothermia and initiation of controlled rewarming. Combined with the multidisciplinary joint consultation opinion agreed with the diagnosis of non-thrombotic pulmonary embolism, but due to the hyaluronic acid residue spread to the terminal branch vessels of the pulmonary artery, which was difficult to be dissolved by drugs, it was recommended to continue the VA-ECMO adjuvant therapy. Treatment was continued with anti-infection, maintenance of stable internal environment, nutritional support and other treatments, waiting for the recovery of cardiac function. On the fifth day, the patient's consciousness was clear, the tidal volume was OK, and she could cooperate with the treatment, and she was given oxygen in the endotracheal tube, the patient's spontaneous respiration was smooth, the depth of respiration was OK, respiratory rate was 17–20 times/min, cough reflex was good, and there was a small amount of white sputum in the endotracheal tube. The patient's peripheral oxygen saturation was 99%, the respiratory sounds of both lungs were coarse, and a small amount of wet rales were detected in both lower lungs. Arterial blood gas analysis revealed the following: pH 7.47, whole blood base excess −0.9 mmol/L, extracellular fluid base excess −1.1 mmol/L, lactate 0.8 mmol/L, sodium 139 mmol/L, potassium 4.2 mmol/L, partial pressure of oxygen (PaO_2) 168 mmHg, partial pressure of carbon dioxide ($PaCO_2$) 31 mmHg. Considering that the patient's consciousness was clear, cooperated with the treatment, and had good spontaneous respiration, she was given suction to clean the secretions in the oral cavity and tracheal tube, and the tracheal tube was extubated. On the sixth day, the patient's heart rate increased to 135–140 beats/min during the VA-ECMO flow reduction test, and bedside ultrasound monitoring showed that the right heart was expanding and the left heart was contracting normally, considering that there was still the possibility of obstruction, and continued to give VA-ECMO assisted treatment. On the eighth day, the patient entered the programmed withdrawal, gradually down-regulated ECMO assisted flow, observed the heart rate, blood pressure to maintain stability, heart rate 80 beats/min, blood pressure about 125/55 mmHg, review of cardiac ultrasound patient's cardiac contraction is better than before, aortic phase VTI more than 10 cm/s, then clamp the tube back to the 400 mL of blood clamped off the end of the arterial perfusion and the end of the venous blood diversion, respectively, to pull out the ECMO line, the puncture port localized deep purse-string suture, the ECMO line. On the ninth day, the patient's condition was stable and she was transferred to the

general ward for further treatment. On the eleventh day, the patient recovered well and was discharged.

3 Discussion

3.1 Rapid activation of ECMO treatment plan to improve treatment efficiency

Teamwork in extracorporeal cardiopulmonary resuscitation (ECPR) has been reported to not change the duration, hospitalization days, and mortality of ECMO, but it does improve the resuscitation outcome of ECPR (7). In 2015, an ECPR team was established in our hospital led by ICU 1, and more than 400 cases of ECMO have been performed so far. Emergency medical team doctors quickly judged that the patient met the indications for ECMO treatment, and immediately started the ECMO rapid response system, the ECMO team received the emergency call at 00:10, and the ECMO team of four health care workers arrived at the emergency resuscitation room at 00:30, doctor 1 talked to the family and signed the informed consent; doctor 2 prepared the skin, disinfection and other preparations; at the same time, nurse 1 inspected the operating environment, the meanwhile, nurse 1 inspected the operation environment, arranged the pre-filling position of the ECMO machine reasonably, connected the power supply, oxygen source and gas source, and prepared the pre-filling line; nurse 2 participated in the cooperation of tube placement, and passed the items in an orderly manner according to the operation procedure.

November 8, 00:35 Initiation of operation; Chen et al. (8) demonstrated that during cardiopulmonary resuscitation, circulatory perfusion decreases significantly over time, which leads to a lower success rate of vascular puncture, whereas percutaneous ultrasound guidance significantly improves the success rate of puncture. Expert consensus points out that the classic pathway for establishing VA-ECMO is the femoral vein (drainage cannula)—common femoral artery (perfusion cannula). The insertion site for the perfusion cannula can also be the subclavian artery or axillary artery. This pathway is used as an alternative when the femoral artery access is not feasible, but it may lead to arm swelling and excessive cerebral perfusion due to over-perfusion of the upper limbs. The carotid artery, when used as a perfusion cannula, is commonly chosen as the last option in adults due to the potential increased risk of acute brain injury and is not recommended (9). Therefore, after systemic heparinization of the patient, the team used ultrasound to assist in locating the puncture site and inserted a 21 Fr Maikewei ECMO venous drainage cannula along the guidewire, with a length of approximately 44 cm. Ultrasound confirmed that the tip of the drainage cannula was located at the opening of the right atrium. The procedure was continued with the same method for the right femoral artery puncture to place the arterial return cannula, inserting a 17 Fr Maikewei ECMO arterial return cannula along the guidewire to a depth of 15 cm. Wang et al. (10) found that the absence of distal perfusion catheters is an independent risk factor for acute limb ischemia. Preventive placement of distal perfusion catheters can reduce the occurrence of acute limb ischemia. To avoid distal limb ischemia in the right lower limb, selective right femoral artery puncture and catheter infusion were performed using the same method. A single-lumen 8 Fr venous catheter was inserted for distal perfusion of the right lower limb, approximately 15 cm in depth. Ultrasound confirmed that the catheter was located in the femoral artery. At 00:55 during ECMO cannulation, the patient experienced loss of consciousness and loss of aortic pulsation, ECPR was initiated rapidly, chest compressions, endotracheal intubation, ventilator-assisted ventilation, and epinephrine injection were performed immediately, and the patient's heartbeat recovered at about 00:58, and the VA-ECMO was successfully switched to ECMO at 01:00. The whole operation process was 25 min.

3.2 Teamwork for safe transit

According to the guidelines and the "5P transfer system," safe and rapid transfer was realized (11, 12). (1) Specialized ECMO personnel assess the condition and transfer route; during the transfer process, they are responsible for observing and adjusting the machine parameters and giving relevant medical advice; after the transfer, they work with specialized nurses to determine the machine position and sort out the ECMO tubing; (2) Prior to transport, the ECMO specialist nurse will meticulously inspect the function of all ECMO components, monitor the oxygen tank pressure, and organize and secure the ECMO circuits. Subsequently, they will collaborate with the attending physician to assess the patient's condition and evaluate the efficacy of the nursing interventions; observe the ECMO tubing during the transfer process to prevent pulling and pulling; check the transfer items and medicines, comb the ventilator tubing and vascular access and fix them appropriately; and ensure the safety of the ventilator tubing and venous access during the transfer process; (3) The emergency department physician, based on the specialist's assessment, explains the transport risks to the family, coordinates with the receiving unit, confirms the required diagnostic items, and issues corresponding medical orders prior to patient transfer. Under multidisciplinary collaboration, the medical and nursing team worked together to smoothly transfer the patient into ICU ward 1. The whole transfer process ensured that the patient's vital signs were stable, the analgesic and sedative measures were appropriate, and the family highly recognized the efficiency of the transfer.

3.3 Early target temperature management favorable neurological prognosis

The American Heart Association (AHA) and the European Resuscitation Council (ERC) in their guidelines both recommend subcooling for cardiac arrest patients, taking various measures to lower the core body temperature of patients to achieve Targeted Temperature Management (TTM) to reduce the cerebral metabolic rate and reduce the degree of brain damage after cardiac arrest, and to improve survival and neurological prognosis (13, 14). The clinical value of TTM as a key intervention to improve the neurological prognosis of patients with cardiac arrest has been confirmed by several randomized controlled studies (15). After this patient underwent ECMO transfer, the temperature of the variable temperature water tank was rapidly adjusted to 35 °C, which rapidly brought the body temperature down to 35 °C and maintained it in this process for 24 h. After the end of the

maintenance period, the patient entered the rewarming phase, which strictly followed the principle of stepwise warming, with a gradual recovery in the temperature range of 0.1–0.2 °C/h until the body temperature reached 36.5 °C, which was done in order to prevent rapid rewarming from leading to increased neurological damage. During the course of TIM treatment, the patient did not experience adverse symptoms such as chills or diarrhea. In this case, the patient underwent TTM therapy supported by extracorporeal membrane oxygenation (ECMO), which exemplifies the synergistic application of multimodal life support techniques in modern critical care medicine. The patient was followed up in the first month after discharge and was found to be still lucid, with a cerebral performance category (CPC) of 1 and a good neurological prognosis.

3.4 Anticoagulation management during ECMO operation

Systemic heparinized anticoagulation is critical to ensure that ECMO works properly (16, 17). Patients with ECMO frequently develop multiple complications, of which gastrointestinal bleeding and intracranial hemorrhage are two of the most serious, and IV thrombolysis, particularly when combined with the systemic anticoagulation required for ECMO support and especially in patients who have undergone recent CPR or surgical procedures, will inevitably increase the risk of major bleeding (18–20). The patient has a BMI of 17.1 and underwent prosthetic implantation in multiple sites, including the breast and hip, 3 years ago, with specific details unclear. The patient has no history of VTE. Upon admission, the initial ACT was 295 s, APTT was 69.4 s, and the platelet count was 252×10^9/L. Therefore, a meticulous anticoagulation management plan was designed for the patient during the ECMO operation: During the operation phase of ECMO, we used sodium heparin at a dose of 5–40 IU/(kg/h) for continuous intravenous pumping and monitored the activated partial thromboplastin time (q4h) to ensure that the APTT was maintained in the range of 40–60 s and the ACT was maintained in the range of 180–220 s. At the same time, platelets, fibrinogen, and other indexes were dynamically rechecked (21). During the period of assistance, the patients' APTT was up to 103 s, and ACT was maintained at 140–295 s. No obvious active bleeding was observed, and no complications such as thromboembolism occurred. Coagulation function was closely monitored during ECMO support, and specific values are shown in Figure 1. A moderate decrease in platelet count was noted post-ECMO initiation. Although heparin-induced thrombocytopenia (HIT) was a consideration, the clinical probability based on the 4 T's score was low. The platelet count recovered without switching to an alternative anticoagulant like fondaparinux, suggesting a non-HIT etiology. Bedside ultrasound technology was used to monitor the patient's cardiopulmonary function and the presence of pleural and abdominal fluid in real time to rule out thoracic and abdominal hemorrhage. On day 8, when the cardiac ultrasound examination confirmed that the patient's cardiac function had improved, the patient's heart rate and blood pressure performed well in the programmed withdrawal trial, and the ECMO was withdrawn in a timely manner.

3.5 Infection control strategies

Prevention and control of nosocomial infection during extracorporeal membrane oxygenation (ECMO) support is a critical aspect that affects patient prognosis. Evidence-based medical studies have shown that the incidence of nosocomial infections in ECMO patients fluctuates from 9 to 65%, which is significantly higher than that in the general population of critically ill patients, which is closely related to immunosuppression caused by extracorporeal circulation, multiple invasive operations, and prolonged exposure to the intensive care environment (22). In accordance with institutional protocol for all ECMO procedures, broad-spectrum antibiotic prophylaxis was administered following cannulation to mitigate the risk of nosocomial infections. In our center, we constructed an infection prevention and control system based on the multidisciplinary team (MDT) model, which consists of a core team of experts in critical care medicine, infection control, clinical pharmacy, microbiology and nursing, and we established a risk assessment matrix through the Delphi method, focusing on catheter-related bloodstream infection, CRBSI, and other infections. bloodstream infection (CRBSI), ventilator-associated pneumonia (VAP) and catheter-associated urinary tract infection (CAUTI). Precision prevention and control were implemented with the following specific intervention strategies:

3.5.1 Catheter-related bloodstream infection prevention and control

In accordance with the guidelines of the American Society of Infectious Diseases, the "zero tolerance" vascular access management standard was established: chlorhexidine gluconate (2%) ethanol (70%) compound disinfectant was used to disinfect the vascular access three times in a spiral pattern (clockwise → counterclockwise → clockwise), the diameter of disinfection was >15 cm, and the drying time was strictly >2 min; "3-2-1" medication change mechanism was established: the first dressing change was performed 3 days after the puncture, and the dressing was changed every 2 days thereafter. The "3-2-1" dressing change mechanism: the first dressing change was performed 3 days after puncture, and the dressing was changed every 2 days thereafter, and blood/seepage >1 cm^2 was found to be changed immediately, and the process of changing the dressing was strictly in accordance with the WHO five-moment principle of hand hygiene. Vascular ultrasound Doppler was applied to assess the catheter position and thrombosis risk weekly, and the anticoagulation regimen was adjusted in conjunction with the coagulation results.

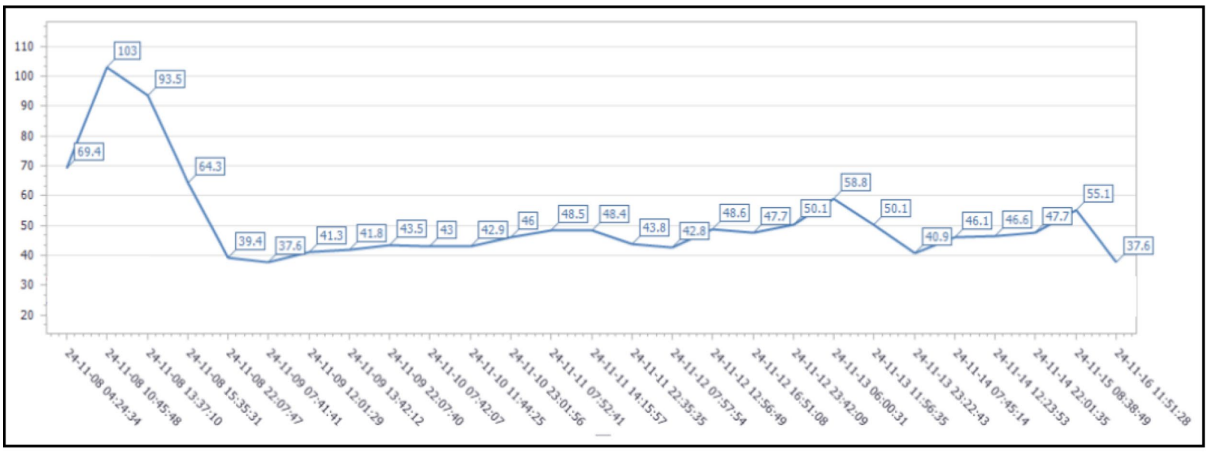
3.5.2 Prevention and control of ventilator-associated pneumonia

A modified version of the VAP intensive care strategy (Ventilator Bundle 2.0) was implemented: subglottic suction was performed using an intelligent negative pressure control system (−20 to −30 cmH_2O), and pulsatile rinsing (5 mL of saline) combined with continuous low-negative-pressure suction (−5 cmH_2O) was performed every 4 h. Oral care was performed by applying 0.12% chlorhexidine cotton balls for six-sided wiping method (buccal surface of teeth → tongue → occlusal

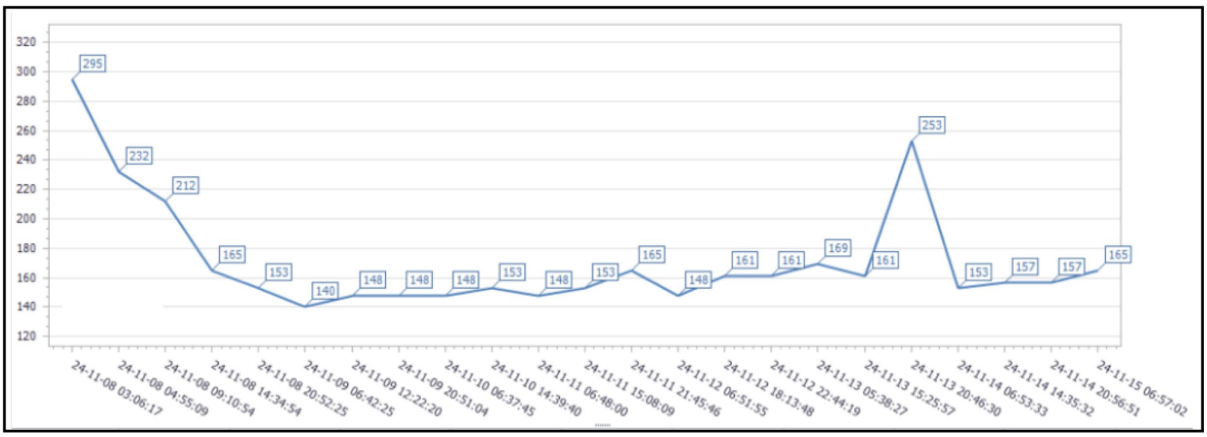
surface → hard palate → buccal mucosa → sublingual), together with the electric toothbrush to mechanically remove the biofilm three times a day. The bed was maintained with the head of the bed elevated at 35 ± 5°, with real-time monitoring of angular excursions by means of a built-in accelerometer. The ventilator humidification tank used an active heating guide wire system to maintain the airway outlet gas temperature of 37 ± 0.5 °C and relative humidity of 100%, and the amount of condensate dumping was monitored every shift (>200 mL/day suggesting excessive humidification).

3.5.3 Catheter-associated urinary tract infection prevention and control

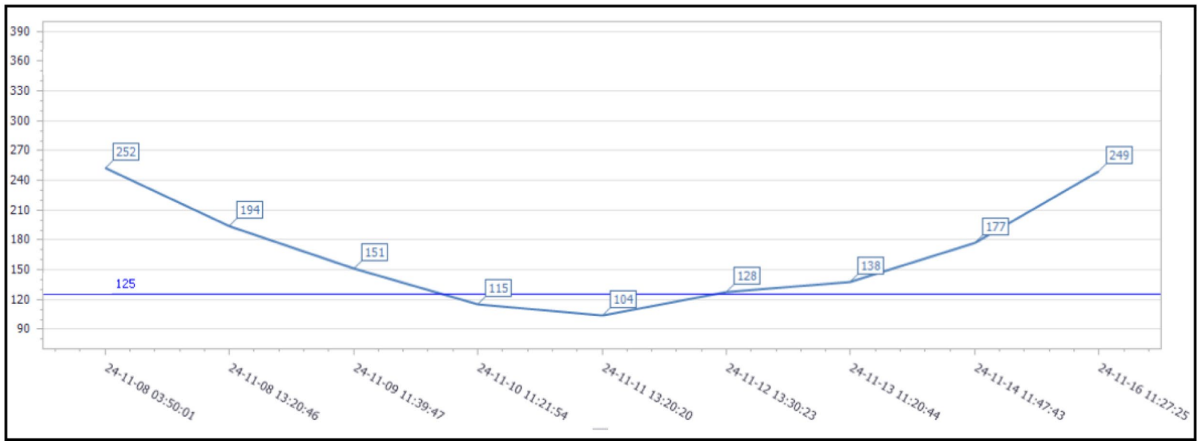
Proper immobilization, keeping the urinary catheter airtight, drainage below the level of the bladder, timely dumping of urine, and



APTT



ACT



platelet count

FIGURE 1 (Continued)

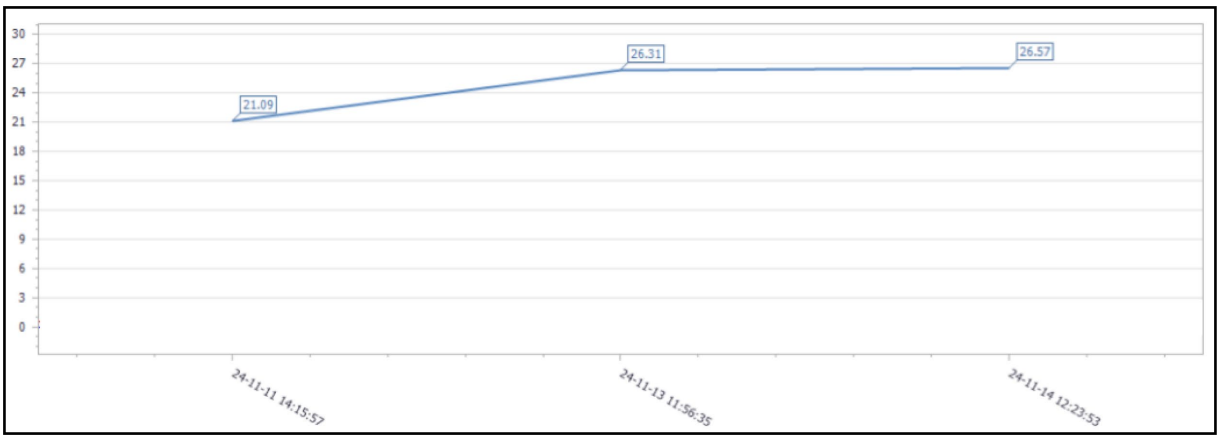


FIGURE 1
Dynamic changes in APTT, ACT, platelet count, and D-dimer during the patient's hospitalization.

perineal wiping twice a day. Perineal care was performed using a two-step method: first, the urethral opening to the perineum was scrubbed with 0.05% povidone-iodine cotton balls (unidirectional cleansing), and then rinsed and dried with saline.

3.5.4 Protective isolation

Single room isolation, specialized care, no family visits, video visits. Pay attention to infection indicators such as white blood cells, C-reactive protein and calcitoninogen, as well as changes in body temperature.

With these interventions, no nosocomial infections occurred in this ECMO patient.

3.6 Autologous blood transfusion to reduce blood loss during ECMO withdrawal

Extracorporeal membrane pulmonary oxygenation (ECMO) support is often accompanied by significant blood component destruction and the need for allogeneic transfusion, and autologous blood reinfusion (ABR), an evidence-based hemoprotective strategy, has been demonstrated to reduce allogeneic red blood cell transfusion by up to 30 to 50%, as well as to reduce the risk of complications such as transfusion-related acute lung injury (TRALI) and the risk of complications such as transfusion-related circulatory overload (TACO) (23). Based on the International Extracorporeal Life Support Organization (ELSO) guidelines and the consensus on blood management, this study systematically describes the standardized operational procedures for autologous blood recovery during the withdrawal phase of ECMO.

Our center uses a modified closed blood recovery system to implement goal-oriented autologous blood recovery before ECMO withdrawal. The operation follows a "three-phase control method":

Pre-flush phase: 0.9% saline (500 mL) was connected to the tee in front of the centrifugal pump, and the whole blood storage bag (500 mL) was connected to the side hole tee at the return end of the ECMO, the ECMO line was pre-flushed with 0.9% saline, and the centrifugal pump was connected to the centrifugal pump through the tee valve (with the rotational speed set to 2,500 ± 50 rpm) to maintain a pressure gradient in the line of less than 50 mmHg.

Blood collection stage: Clamp the blood-drawing end (venous side) and blood-returning end (arterial side) of the ECMO, open the three-way channel of the centrifugal pump and the channel of the blood-collection bag, introduce 0.9% NS into the ECMO line in negative-pressure suction mode (−100 to −150 mmHg), and the blood is injected into the blood-collection bag through the side hole of the arterial end, and the bag is gently shaken to make the blood and the preservative fluid mix well.

Blood retrieval phase: Within 30 min after withdrawal of the machine, blood was transfused at a rate of 2–4 mL/kg/h using a transfusion device treated with a transfusion warming device (37 ± 1 °C), with simultaneous monitoring of central venous pressure and mixed venous oxygen saturation to maintain hemodynamic stability. About 400 mL of autologous blood was eventually recovered, and the recovered blood was delivered to the patient according to the transfusion procedure after withdrawal of the machine.

4 Conclusion

Hyaluronic acid microparticles, often introduced into the systemic circulation through procedures such as cosmetic injections, may reach the lungs via blood flow if inadvertently entering vascular structures. Generally, larger microparticles (e.g., >100 μm) are more likely to occlude larger branches of the pulmonary arteries, while smaller particles (e.g., 10–100 μm) may travel into finer vasculature. When these microparticles lodge in pulmonary arteries or their branches-due to size compatibility with vascular diameters-they cause mechanical obstruction. As foreign entities, they trigger immune responses by attracting inflammatory cells. These cells release mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), inducing local inflammation, damaging vascular endothelial cells, and exacerbating tissue hypoxia and functional impairment. Concurrently, hyaluronic acid microparticles can disrupt the

normal vasomotor function of pulmonary vessels, leading to increased pulmonary vascular resistance and exacerbating pulmonary hypertension. This impairs pulmonary gas exchange and, in severe cases, may result in critical outcomes such as respiratory failure. When hyaluronic acid is erroneously injected into vaginal blood vessels, it enters the circulatory system. As the lungs are a primary filtration organ, the circulating acid can form emboli that occlude the pulmonary arteries or their branches, causing pulmonary embolism. Furthermore, the injection procedure may induce local vascular injury and disrupt coagulation homeostasis, elevating the risk of thrombosis. These thrombi can subsequently dislodge and migrate to the pulmonary vasculature, causing embolic events. This case represents our institution's first ECMO-treated patient with acute pulmonary embolism resulting from intravaginal hyaluronic acid injection, with no similar rescue experiences reported domestically or internationally. Multidisciplinary consultation agreed with the diagnosis of non-thrombotic pulmonary embolism, but due to the spread of hyaluronic acid residue to the terminal branches of the pulmonary artery, it was difficult to be dissolved by drugs, and there was no indication for interventional thrombolysis, so it was recommended to continue VA-ECMO-assisted treatment, and the patient was discharged from the hospital after active resuscitation and nursing care. The professional ECMO team can quickly start the ECMO treatment plan, early management of target body temperature can promote the prognosis of neurological function, personalized anticoagulation method and autologous blood transfusion technology to prevent bleeding in patients with high bleeding risk and improve the efficiency of treatment. This case provides a novel therapeutic direction and offers valuable insights for the management of acute pulmonary embolism resulting from intravaginal hyaluronic acid injections.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Affiliated Qingyuan Hospital, Guangzhou Medical University, Qingyuan People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

YW: Writing – original draft, Writing – review & editing. QD: Writing – original draft, Writing – review & editing. ST: Data curation, Formal analysis, Writing – review & editing. FY: Data curation, Formal analysis, Writing – review & editing. YL: Project administration, Supervision, Writing – review & editing. ZL: Methodology, Project administration, Supervision, Writing – review & editing. LL: Data curation, Formal analysis, Writing – review & editing. HL: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This research was supported by the Guangdong Medical Science and Technology Research Fund Program (A2024691 and B2025700).

Acknowledgments

The authors thank the patient and her family for consenting to publish this case report.

Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 16 October 2025
DOI 10.3389/fmed.2025.1604360

OPEN ACCESS

EDITED BY
Yuetian Yu,
Shanghai Jiao Tong University, China

REVIEWED BY
Pawel Swietach,
University of Oxford, United Kingdom
Suresh Kari,
University of British Columbia, Canada

*CORRESPONDENCE
Said Kortli
✉ kortlisaid@outlook.com

RECEIVED 01 April 2025
ACCEPTED 29 September 2025
PUBLISHED 16 October 2025

CITATION
Kortli S, Amathieu R and Ghalayini M (2025) Dancing with death at pH 6.8 and lactate of 29 mmol/L: extreme survival in severe metformin-associated lactic acidosis - a case report.
Front. Med. 12:1604360.
doi: 10.3389/fmed.2025.1604360

Dancing with death at pH 6.8 and lactate of 29 mmol/L: extreme survival in severe metformin-associated lactic acidosis - a case report

Said Kortli[1]*, Roland Amathieu[1,2] and Mohamed Ghalayini[1]

[1]Intensive Care Unit, Gonesse General Hospital, Paris, France, [2]UFR SMBH (Santé, Médecine, Biologie Humaine), Université Sorbonne Paris Nord, Bobigny, France

Lactic acidosis is a serious metabolic disorder characterized by an accumulation of lactate in the body, which can lead to a severe acid-base imbalance. Metformin-associated lactic acidosis is a rare but life-threatening complication of metformin therapy, particularly in the setting of acute kidney injury or other conditions that impair lactate clearance. In this case report, we present the remarkable survival of a patient who experienced severe metformin-associated lactic acidosis with a blood pH of 6.8 and a lactate level of 29 mmol/L, which are typically considered incompatible with life.

KEYWORDS

lactic acidosis, acute kidney injury, metformin-intoxication, hemodialysis (HD), extreme survival

1 Introduction

Metformin is a first-line pharmacological treatment for type 2 diabetes mellitus (T2DM) due to its efficacy in improving glycemic control, weight neutrality, and low risk of hypoglycemia (1). It works primarily by inhibiting hepatic gluconeogenesis and improving insulin sensitivity, with most patients tolerating the drug well. However, in rare cases, metformin can lead to a life-threatening condition known as metformin-associated lactic acidosis (MALA). MALA is characterized by severe lactic acidosis, often defined by hyperlactatemia (lactate $>$ 5 mmol/L), profound acidemia (pH $<$ 7.35), and an elevated anion gap (2). Though rare, MALA carries a high mortality rate, with estimates ranging from 30 to 50% in reported cases (3).

The pathophysiology of MALA is multifaceted and involves the accumulation of metformin in the setting of impaired renal clearance, leading to mitochondrial dysfunction and increased lactate production (4). Unlike other forms of lactic acidosis, the primary driver in MALA is not tissue hypoxia but rather the inhibition of mitochondrial oxidative phosphorylation and gluconeogenesis, leading to reduced lactate utilization by the liver (5). This makes MALA distinct from other causes of lactic acidosis, such as sepsis or ischemia, where hypoperfusion and anaerobic metabolism dominate.

Certain risk factors predispose patients to MALA. Acute kidney injury (AKI) or chronic kidney disease (CKD) is one of the most significant risk factors, as metformin is predominantly eliminated renally through glomerular filtration and tubular secretion (6). Other contributing factors include conditions that increase lactate production or impair its clearance, such as sepsis, hypoxia, heart failure, or hepatic dysfunction (7). While lactic

acidosis is a known complication of critical illness, the presence of metformin exacerbates the metabolic derangements due to its direct effects on mitochondrial function.

Although severe lactic acidosis with pH < 7.0 and lactate > 20 mmol/L is often deemed incompatible with life, there are rare reports of survival with aggressive supportive care (8).

In this report, we detail the extraordinary survival of a patient with MALA who presented with extreme acidemia (pH 6.8) and hyperlactatemia (lactate 29 mmol/L)—values rarely associated with recovery. This case emphasizes the importance of early recognition, a thorough understanding of MALA's unique pathophysiology, and the need for timely multimodal therapeutic strategies, including renal replacement therapy and hemodynamic stabilization.

2 Case presentation

A 52-year-old woman with a history of poorly controlled type 2 diabetes mellitus (HbA1c 17%) and hypertension was admitted to the emergency department with complaints of progressive fatigue and generalized weakness over the preceding 48 h. Her medical history included long-term metformin therapy (2 g/day) for diabetes and antihypertensive treatment with amlodipine. She reported poor adherence to diabetes management and dietary recommendations. On further questioning, she denied recent gastrointestinal symptoms, chest pain, or significant alcohol intake but noted reduced oral intake over the previous days due to malaise.

2.1 Initial assessment

On admission, the patient appeared lethargic and drowsy. Vital signs revealed hypotension (blood pressure 85/55 mmHg), tachycardia (heart rate 110 beats per minute), tachypnea (respiratory rate 28 breaths per minute), and hypothermia (core body temperature 34 °C).

Capillary blood glucose testing revealed hypoglycemia (3.2 mmol/L), and clinical examination was notable for cold extremities, delayed capillary refill, and dry mucous membranes, consistent with dehydration and circulatory shock. No focal signs of infection were evident upon physical examination, although a urine dipstick test showed leukocyturia and nitrituria.

2.2 Laboratory investigations revealed severe metabolic derangements

Arterial Blood Gas (ABG): pH 6.78, pCO_2 19 mmHg, bicarbonate 8.5 mmol/L, base excess −24 mmol/L.

The Davenport diagram (Figure 1), which illustrates the patient's arterial acid–base values (pH 6.78, HCO_3^- 8.5 mmol/L, PCO_2 19 mmHg), shows that her data point lies outside the expected isocurves. This deviation may reflect a potential measurement error in the reported CO_2 and/or pH values (from which HCO_3^- is calculated), rather than a limitation of the standard bicarbonate-CO_2 buffering model. Additionally, any unmeasured anion gap would manifest as a corresponding reduction in HCO_3^-.

Serum Lactate: 29 mmol/L (reference range: 0.5–2.0 mmol/L).

Electrolytes: Sodium 133 mmol/L, potassium 5.9 mmol/L, chloride 102 mmol/L.

Renal Function: Serum creatinine 3.2 mg/dL (baseline 0.9 mg/dL), blood urea nitrogen (BUN) 58 mg/dL, consistent with acute kidney injury (AKI).

Liver Function Tests: Within normal limits.

Complete Blood Count: Leukocytosis (14,000/μL) with neutrophil predominance, hemoglobin

12.5 g/dL, platelets 210,000/μ L.

Other Tests: Normal troponin levels, negative blood cultures initially.

Urine Analysis: Pyuria and bacteriuria, later confirmed as *Klebsiella pneumoniae* on culture.

The clinical presentation was characterized by severe metabolic acidosis (pH 6.78), profound hyperlactatemia (29 mmol/L), and AKI in the context of metformin use, strongly indicative of metformin-associated lactic acidosis (MALA). This diagnosis was confirmed by a markedly elevated serum metformin concentration of 100 μg/mL (normal < 10 μ g/mL).

Table 1 summarizes the progression of key laboratory parameters from admission (Day 0) to post-recovery (Day 10). By Day 10, all values, including lactate, serum bicarbonate, and creatinine, had normalized or approached baseline, reflecting resolution of metabolic derangements and restoration of renal function. Liver function tests remained normal throughout the clinical course, and serial troponin measurements were consistently unremarkable. Initial blood cultures showed no growth, while urinalysis demonstrated pyuria and bacteriuria, with subsequent culture identifying *Klebsiella pneumoniae*.

The patient's clinical course highlights the hallmark features of MALA, including severe metabolic acidosis, hyperlactatemia, and AKI, which resolved with prompt intervention. By Day 10, the patient achieved full clinical recovery, with normalization of inflammatory markers and laboratory parameters.

2.3 Clinical course and management

The patient was admitted to the intensive care unit (ICU) for further management. Given the severity of her presentation, a multimodal therapeutic approach was initiated:

2.3.1 Hemodynamic stabilization

Aggressive fluid resuscitation with isotonic crystalloids was initiated to correct hypovolemia and improve tissue perfusion.

Aggressive fluid resuscitation was initiated with isotonic crystalloids (normal saline), with an initial bolus of 2 liters administered in the first 6 h. Norepinephrine infusion was commenced at 2 h post-admission, starting at 0.1 μg/kg/min and titrated to a maximum dose of 5.64 μg/kg/min to maintain mean arterial pressure above 65 mmHg. The high vasopressor requirements reflected the profound distributive shock characteristic of severe MALA, where acidemia-induced myocardial depression and vasodilation compromise hemodynamic stability.

Norepinephrine titration followed a protocolized approach based on hemodynamic response and lactate clearance. Peak

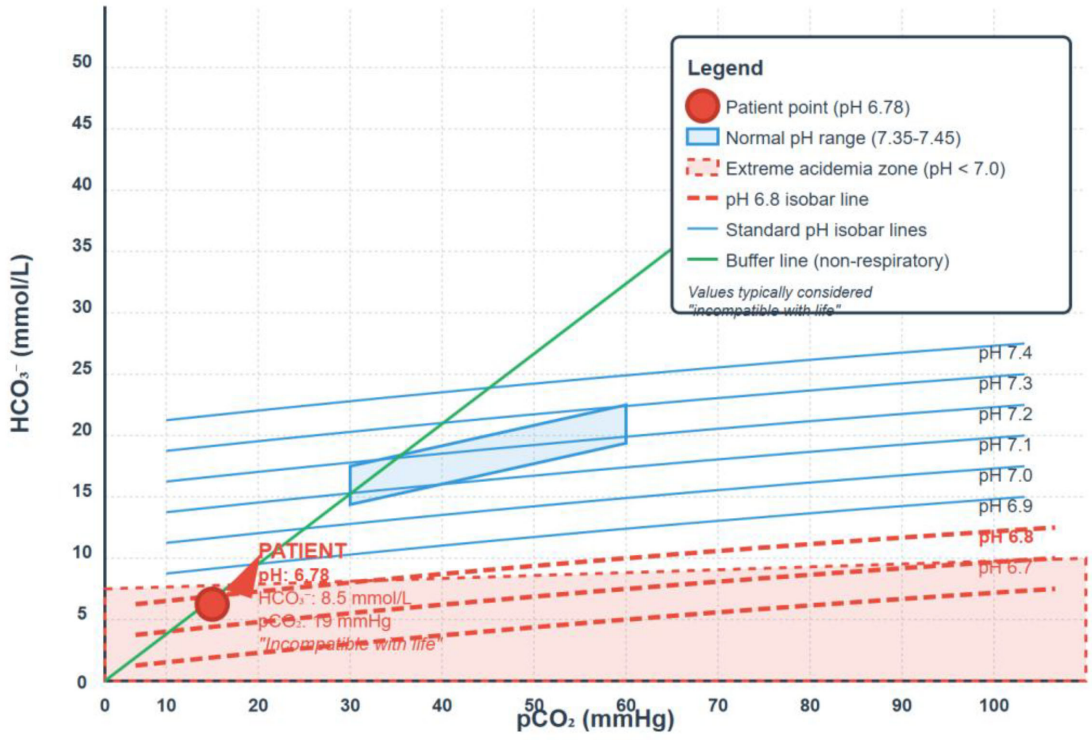

FIGURE 1
The Davenport diagram illustrating the patient's arterial acid–base values.

TABLE 1 Comparison of key laboratory parameters on admission (Day 0) and after clinical recovery (Day 10), with corresponding normal reference ranges.

Parameters	On admission (Day 0)	After recovery (Day 10)	Normal range
pH	6.78	7.40	7.35 – 7.45
Lactate (mmol/L)	29	1.2	0.5 – 2.0
Bicarbonate (mmol/L)	29	24.0	22 – 28
Creatinine (mg/dL)	1.66	0.95	0.6 – 1.2
BUN (mg/dL)	21	13.2	7 – 20
K+ (mmol/L)	5.9	4.2	3.5 – 5.0
Na+ (mmol/L)	133	139	135 – 145
WBC (/μL)	14,000	7,200	4,000 – 11,000

BUN, blood urea nitrogen; WBC, white blood cell count.

vasopressor requirements occurred within the first 24 h, after which progressive down-titration was possible as metabolic acidosis corrected and cardiac contractility improved. By 72 h, vasopressor support was completely discontinued, reflecting restoration of cardiovascular function and resolution of distributive shock.

2.3.2 Renal replacement therapy (RRT)

Early and prolonged intermittent hemodialysis was initiated within 6 h of ICU admission, with a total duration of 20 h. This therapy aimed to remove accumulated metformin, correct acidemia, and improve lactate clearance. Dialysis fluid was bicarbonate-buffered to help restore metabolic balance.

Our patient received 20 h of intermittent hemodialysis using bicarbonate-buffered dialyzate (bicarbonate concentration 35 mmol/L) to optimize acid-base correction. The choice of intermittent hemodialysis over continuous renal replacement therapy (CRRT) was based on its superior metformin clearance capacity and rapid correction of severe acidemia. Studies demonstrate that intermittent hemodialysis achieves metformin clearance rates of 200–500 mL/minute compared to 50 mL/minute with CRRT (9).

2.3.3 Empirical antibiotic therapy

Empirical broad-spectrum antibiotics (piperacillin-tazobactam 4 g IV every 6 h and amikacin 30 mg/kg daily) were initiated at 12 h to address the confirmed *Klebsiella pneumoniae* urinary tract infection. This intervention was crucial as sepsis represents a common precipitating factor for MALA and contributes to ongoing lactate production through tissue hypoperfusion.

2.3.4 Metabolic monitoring and RRT adjustment

Continuous monitoring of arterial blood gases every 4 h during the first 24 h guided RRT intensity and duration. The bicarbonate-buffered dialyzate concentration was maintained at 35 mmol/L throughout treatment to optimize acid-base correction without precipitating metabolic alkalosis. Lactate clearance served as the primary endpoint for RRT efficacy, with treatment continued until lactate normalized to <2 mmol/L.

2.3.5 Pharmacological transitions

Metformin therapy was permanently discontinued upon diagnosis confirmation. The patient was transitioned to insulin therapy using a continuous infusion protocol (starting at 0.1 units/kg/hour) to maintain glucose control during the acute phase, with subsequent conversion to subcutaneous insulin before discharge. This transition acknowledges the absolute contraindication to metformin rechallenge following MALA.

2.3.6 Additional supportive measures

Hypoglycemia was managed with continuous dextrose infusion until stabilization of blood glucose levels.

Electrolyte imbalances were closely monitored and corrected (including hyperkalemia).

2.3.7 Renal function recovery

Serial monitoring of serum creatinine demonstrated progressive improvement from the peak of 3.2 mg/dL to baseline values within 10 days. The rapid renal recovery likely reflects the reversible nature of acute tubular necrosis secondary to hypoperfusion rather than metformin-induced nephrotoxicity, as metformin itself does not cause direct kidney injury.

These comprehensive interventions, implemented in a coordinated, time-sensitive manner, demonstrate the importance of multimodal therapy in MALA management. The successful outcome despite extreme metabolic derangements underscores the potential for recovery when evidence-based protocols are rigorously applied in this life-threatening condition.

2.3.8 Outcome and follow-up

Despite the severity of her metabolic derangements (pH 6.78 and lactate 29 mmol/L), the patient showed remarkable improvement within 48 h. Key milestones in her recovery included:

- Progressive hemodynamic stabilization with down-titration of norepinephrine.
- Arterial pH demonstrated progressive recovery from the initial value of 6.78, with marked improvement following initiation of renal replacement therapy at 6 h post-admission (Figure 2).
- By day 3, vasopressor support was discontinued, and renal function began to recover.
- Metformin was permanently discontinued due to the risk of lactic acidosis associated with acute renal impairment, and a basal-bolus insulin regimen was initiated. This regimen included glargine (0.2 IU/kg at bedtime) and aspart (0.05 IU/kg before meals), with the goal of achieving fasting blood glucose levels of 6–8 mmol/L and postprandial levels below 10 mmol/L. Prior to discharge on Day 17, the patient received comprehensive education on insulin injection techniques, self-monitoring of blood glucose (4–6 capillary measurements daily), and individualized dietary and lifestyle counseling. Figures illustrating the biological progression mirrored the clinical improvement:

The patient was successfully weaned off mechanical support and discharged from the intensive care unit (ICU) on Day 5. Intermittent hemodialysis was initiated 6 h after admission and continued for a total of 20 h, resulting in significant improvement in metabolic and renal parameters (Figure 3). Plasma lactate levels, which were critically elevated at admission (30 mmol/L), decreased rapidly to 1.0 mmol/L by Hour 86. Concurrently, serum bicarbonate levels rose from 8.5 mmol/L to 24.7 mmol/L, reflecting correction of severe metabolic acidosis. Serum creatinine peaked at 164 μmol/L (1.92 mg/dL) at Hour 76 but gradually declined to 99 μmol/L (1.12 mg/dL) by Hour 173. Acid–base balance normalized by Day 4, and hemodynamic stability was achieved, allowing for vasopressor support to be discontinued by Day 3.

The comprehensive clinical timeline, including presentation, key findings, therapeutic interventions, and recovery milestones over the first 120 h, is illustrated in Figure 4. By Day 10, all key laboratory values, including pH, lactate, bicarbonate, and

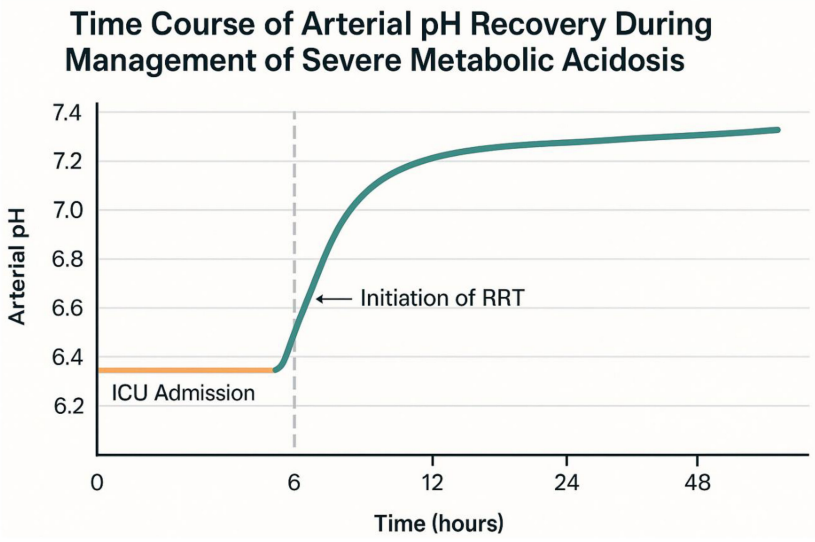

FIGURE 2
Time course of arterial pH recovery during management of severe acidemia.

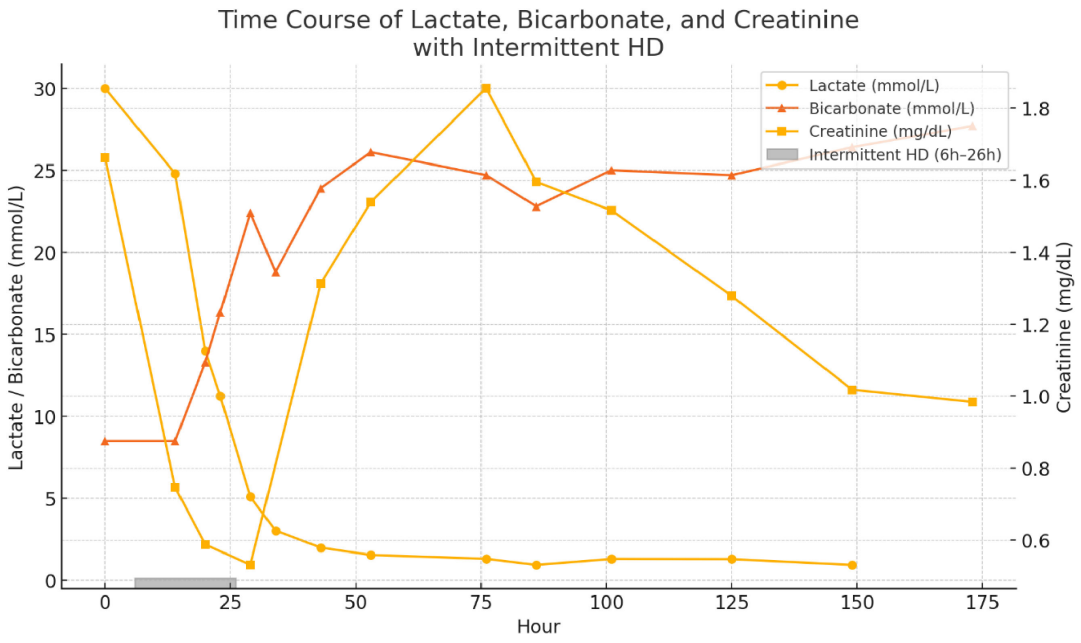

FIGURE 3
Time course of plasma lactate (circles), serum bicarbonate (triangles) and serum creatinine (squares) from admission (Hour 0) through Hour 173. The shaded bar just above the x axis denotes the 20-h intermittent hemodialysis session initiated at Hour 6.

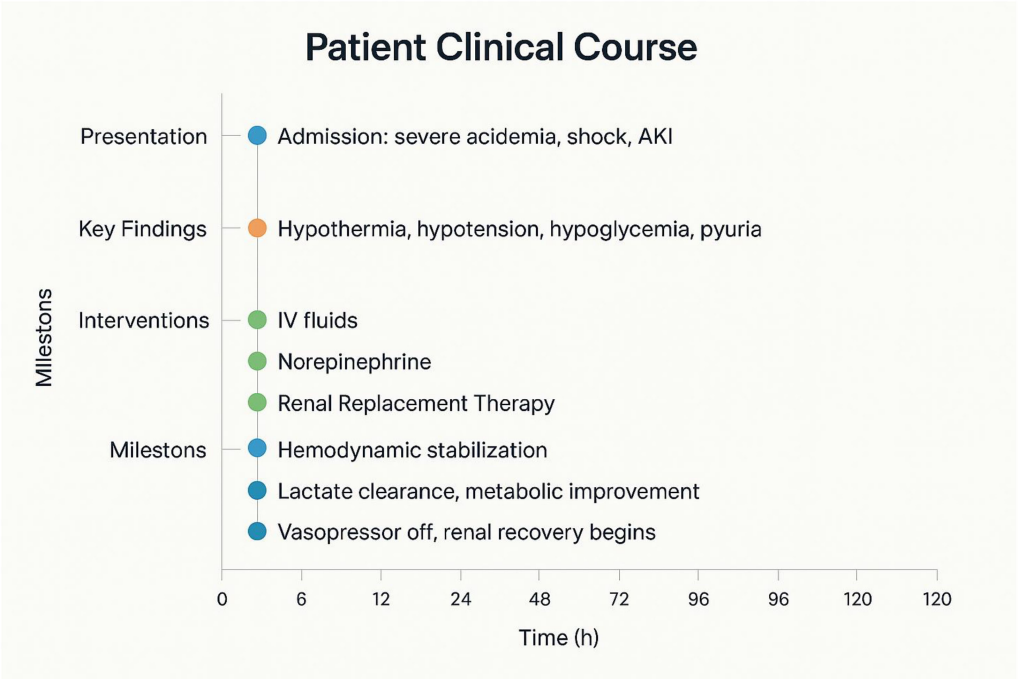

FIGURE 4
Timeline chart summarizing the patient's clinical presentation, key findings, therapeutic interventions, and recovery milestones over 120 h.

creatinine, had returned to or near normal ranges (Table 1), permitting the cessation of renal replacement therapy. Metformin therapy was permanently discontinued, and the patient was transitioned to an insulin-based regimen. She was counseled on the importance of strict glycemic control, adherence to treatment protocols, and the necessity of regular follow-up care. The patient's recovery trajectory highlights the effectiveness of timely hemodialysis and supportive care in resolving metabolic derangements and achieving clinical stability.

This case highlights the potential for survival in MALA, even in the presence of extreme acidemia and hyperlactatemia, when aggressive and timely interventions are implemented.

3 Discussion: pathophysiology of metformin-associated lactic acidosis (MALA)

Metformin-associated lactic acidosis (MALA) is a rare but severe complication of metformin therapy, characterized by the accumulation of lactate and profound acidemia. Its pathophysiology involves a complex interplay of mitochondrial dysfunction, impaired lactate clearance, and predisposing clinical conditions.

3.1 Mitochondrial dysfunction induced by metformin

Metformin primarily acts by inhibiting hepatic gluconeogenesis through suppression of mitochondrial respiratory chain complex I. This inhibition reduces ATP production and shifts cellular metabolism toward anaerobic glycolysis, resulting in increased production of lactate (10). Under normal circumstances, lactate is utilized by the liver for gluconeogenesis. However, metformin's suppression of gluconeogenesis leads to reduced lactate consumption, further contributing to its accumulation.

Additionally, at high plasma concentrations, metformin directly impairs mitochondrial oxidative phosphorylation, exacerbating lactate production and reducing the cell's ability to buffer acidemia. This mechanism is particularly pronounced in the liver and skeletal muscle, where mitochondrial energy demands are high (1).

3.2 The role of renal dysfunction

Metformin is predominantly cleared by the kidneys through glomerular filtration and active tubular secretion. In the setting of acute kidney injury (AKI) or chronic kidney disease, reduced clearance of metformin leads to its accumulation, amplifying its inhibitory effects on mitochondrial respiration (2).

Furthermore, renal dysfunction impairs lactate clearance, as the kidneys contribute up to 30% of lactate metabolism under normal conditions (3). This dual impairment—metformin accumulation and reduced lactate metabolism—creates a vicious cycle that accelerates the development of severe lactic acidosis.

3.3 Acidosis and the impact on cellular function

The profound acidemia observed in MALA (pH < 7.0) has significant physiological effects:

- **Hemodynamic instability:** Acidosis impairs myocardial contractility and systemic vascular tone, contributing to distributive and cardiogenic shock (4). This exacerbates tissue hypoperfusion and further promotes anaerobic metabolism and lactate production.
- Intracellular dysfunction: A low intracellular pH disrupts enzymatic activity and ion gradients, compounding mitochondrial dysfunction and impairing cellular recovery mechanisms.

3.4 Triggers and predisposing factors

While metformin alone rarely causes lactic acidosis, precipitating factors such as AKI, sepsis, or hypoxia are almost always involved. In this case, the urinary tract infection with *Klebsiella pneumoniae* likely contributed to systemic inflammation and sepsis-related hypoperfusion, further increasing lactate production. The patient's poorly controlled type 2 diabetes (HbA1c 17%) may have also predisposed her to metabolic stress and reduced lactate clearance.

3.5 Reframing the lactate threshold in MALA

Although lactate levels > 20 mmol/L and pH < 6.8 are traditionally considered incompatible with life, MALA appears to have a unique pathophysiology compared to other forms of lactic acidosis, such as those seen in sepsis or ischemia. In MALA, the predominant mechanism is impaired lactate clearance and mitochondrial dysfunction, rather than overwhelming lactate production secondary to tissue hypoxia. This distinction may partly explain the potential for survival in extreme cases, provided aggressive supportive therapy is initiated promptly (5).

3.6 Role of renal replacement therapy

Renal replacement therapy (RRT) plays a dual role in the management of MALA:

- **Metformin elimination:** Hemodialysis effectively removes metformin due to its low molecular weight and lack of protein binding.
- **Lactate and acid-base correction:** RRT helps to normalize lactate levels and correct acidemia by buffering the extracellular environment. While lactate itself is not directly removed by hemodialysis, the improvement in metabolic homeostasis and hemodynamics indirectly reduces lactate production.

3.7 Strengths of the current case

3.7.1 Extreme survival at record-breaking parameters

This case represents one of the most severe documented survivals of MALA, with a blood pH of 6.78 and lactate of 29 mmol/L—values that approach the physiological limits of life. While Kajbaf and Lalau demonstrated survival is possible with pH as low as 6.5 and lactate up to 35 mmol/L, such extreme cases remain exceptionally rare in literature.

Most reported MALA cases involve less severe acidemia, such as the case reported by Mahmood et al. (pH 6.57, lactate 16.3 mmol/L) or the case by Rodríguez-Villar et al. (pH 7.042, lactate 20.0 mmol/L).

3.7.2 Multidisciplinary care excellence

The case exemplifies the critical importance of coordinated time-sensitive interventions in MALA management. The successful outcome was achieved through seamless integration of emergency medicine, intensive care, nephrology, and pharmacy expertise. Early recognition within 6 h of admission, immediate initiation of renal replacement therapy, and aggressive hemodynamic support demonstrate the potential for survival when evidence-based protocols are rigorously implemented.

3.7.3 Novel insights into MALA pathophysiology

This case provides valuable insights into the unique pathophysiology of MALA compared to other forms of lactic acidosis. Unlike sepsis-related acidosis where tissue hypoxia predominates, this patient's survival despite extreme acidemia supports the concept that MALA involves primarily impaired lactate clearance rather than overwhelming lactate production. The patient's-maintained consciousness despite pH 6.78 contrasts sharply with typical expectations, where altered mental status typically occurs at pH < 6.9.

3.8 Limitations and methodological considerations

3.8.1 Single case report limitations

As an isolated case report, this study has inherent limitations in generalizability and statistical power. The exceptional nature of survival at these extreme parameters may represent an outlier rather than a reproducible outcome, limiting the ability to extrapolate management strategies to other patients with severe MALA.

3.8.2 Absence of long-term follow-up data

While the patient achieved complete renal recovery within 10 days and was discharged on day 5, the manuscript lacks extended follow-up data beyond immediate hospitalization. Long-term neurological outcomes, cardiovascular sequelae, and diabetes management strategies are not addressed. Studies suggest that MALA survivors generally have good long-term outcomes, but individual variation exists.

3.8.3 Missing pharmacokinetic data

The case lacks detailed pharmacokinetic analysis of metformin clearance during dialysis, which would provide valuable insights for optimizing RRT protocols. While the serum metformin level was elevated at 100 μg/mL, serial measurements during dialysis would have enhanced understanding of clearance kinetics and treatment adequacy.

3.8.4 Limitation of the bicarbonate-CO_2 buffering model

One limitation of this case is that the reported values for pH, CO_2, and HCO_3^- do not meet the expected equilibrium conditions for the carbonic acid-bicarbonate buffer system. Given the low magnitude of fluxes in physiological systems, the likelihood of this buffer system being out of equilibrium is minimal. Therefore, these deviations may be attributed to either measurement error or calculation discrepancies. While this does not undermine the overall clinical findings, it highlights the need for cautious interpretation of extreme values in acid-base disturbances.

3.8.5 Limited mechanistic investigation

The manuscript does not explore potential genetic or metabolic factors that might have contributed to this patient's remarkable survival. Individual variation in mitochondrial function, lactate metabolism, or acid-base buffering capacity could explain exceptional outcomes but were not investigated.

4 Literature context and comparative analysis

4.1 Treatment modality comparisons

This case utilized 20 h of intermittent hemodialysis, contrasting with other successful approaches in the literature. Keller et al. reported success with continuous renal replacement therapy (CRRT) in six patients with severe MALA (mean pH 6.92, lactate 14.4 mmol/L), achieving survival through high-volume hemofiltration (6). Gatti et al. demonstrated improved mortality rates (21.4%) using sustained low-efficiency dialysis (SLED) in 28 patients, suggesting multiple effective dialytic approaches (7).

The choice between intermittent hemodialysis and CRRT remains debated. While this case achieved success with intermittent hemodialysis, other reports suggest CRRT may be superior for hemodynamically unstable patients (8). The key appears to be early initiation rather than specific modality selection.

4.2 Mortality rate context

The survival in this case is particularly remarkable given historical mortality rates in severe MALA. Early case series reported mortality rates of 30%–50%, while more recent series with aggressive management show improved outcomes. Gatti et al. achieved 21.4% mortality in their SLED series, with all deaths occurring within 24 h (7). This temporal pattern suggests that patients surviving the initial critical period have excellent prognosis, as demonstrated in our case.

4.3 Precipitating factor analysis

Unlike many MALA cases precipitated by acute dehydration (86.4% in Gatti's series) or sepsis, this patient's primary trigger was urinary tract infection with *Klebsiella pneumoniae* (7). The combination of poor glycemic control (HbA1c 17%) and medication non-adherence likely contributed to her susceptibility, highlighting the importance of patient education and regular monitoring.

4.4 Clinical presentation variability

The patient's preserved consciousness despite extreme acidemia contrasts with typical expectations. Most literature describes progressive mental status changes with severe acidosis, yet remarkable cases exist of patients maintaining alertness at extremely low pH values (11). This highlights the unpredictable nature of MALA presentation and the importance of not using clinical appearance alone to guide treatment intensity.

4.4.1 Clinical implications and lessons

This case demonstrates the critical interplay between mitochondrial dysfunction, renal impairment, and acid-base imbalance in MALA. Early recognition and aggressive intervention are paramount to interrupt the pathological cascade. The patient's recovery highlights the importance of:

- Early initiation of renal replacement therapy to address metformin accumulation and acidemia.
- Hemodynamic stabilization with vasopressors to restore tissue perfusion and mitigate anaerobic metabolism.
- Identification and treatment of precipitating factors, such as infections, to prevent further lactate accumulation.

5 Conclusion

Metformin-associated lactic acidosis (MALA) is a rare but life-threatening condition with a complex pathophysiology involving mitochondrial dysfunction, impaired lactate clearance, and contributing factors such as renal impairment or sepsis. This case demonstrates that survival is possible even in the presence of extreme acidemia (pH 6.8) and hyperlactatemia (lactate 29 mmol/L)—values traditionally considered incompatible with life—when aggressive and timely multimodal interventions are implemented. Early recognition of MALA, combined with targeted therapeutic strategies such as renal replacement therapy, hemodynamic stabilization, and correction of precipitating factors, is critical for improving patient outcomes. This case underscores the importance of understanding the unique mechanisms of MALA to guide effective management and highlights the resilience of physiological systems when supported by prompt, comprehensive care.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee of the Gonesse General Hospital approved this study. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

SK: Writing – original draft, Writing – review & editing. RA: Validation, Writing – review & editing. MG: Formal analysis, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We are grateful to the patient who kindly consented to the presentation of this case in this 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.

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