frontiers | Research Topics

Case reports in thrombosis 2024

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Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-8325-6349-6
DOI 10.3389/978-2-8325-6349-6

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Case reports in thrombosis: 2024

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Citation

Spiezia, L., Kipshidze, N., eds. (2025). *Case reports in thrombosis: 2024*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6349-6

Table of contents

frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 01 May 2025
DOI 10.3389/fcvm.2025.1614440

OPEN ACCESS

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RECEIVED 18 April 2025
ACCEPTED 22 April 2025
PUBLISHED 01 May 2025

CITATION
Spiezia L (2025) Editorial: Case reports in thrombosis: 2024.
Front. Cardiovasc. Med. 12:1614440.
doi: 10.3389/fcvm.2025.1614440

Editorial: Case reports in thrombosis: 2024

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KEYWORDS

venous thromboembolism, anticoagulants, case report, risk factors, thrombophilia

Editorial on the Research Topic
Case reports in thrombosis: 2024

This editorial presents a collection of articles published in Frontiers in Cardiovascular Medicine: Case Reports in Thrombosis: 2024. The manuscripts collected in this Research Topic are characterized by a wide variety of topics from genetic risk factors of venous thromboembolism to the management of rare and potentially fatal comorbidities. We hope that the reader will obtain vital insights for daily clinical practice. We would like to thank all the reviewers and the Editorial Office staff for their invaluable contribution. The following are the articles in the Frontiers in Cardiovascular Medicine: Case Reports in Thrombosis: 2024.

Pulmonary artery in situ thrombosis due to patent ductus arteriosus: a case report, by Wang et al.

Pulmonary artery *in situ* thrombosis (PAIST) is a rare condition and it refers to a thrombus originating in the pulmonary arterial tree, independently of peripheral thrombosis (1). Clinicians often misdiagnose PAIST as pulmonary embolism (PE) as both conditions manifest as low-density filling defects on computer tomography angiography. This case describes a healthy 59-year-old male hospitalized due to sudden onset of dyspnea with no fever or chest pain, suggesting PE. The patient received anticoagulation and antibiotics for a staphylococcus infection. A reevaluation of imaging revealed the pulmonary obstruction was in proximity to a patent ductus arteriosus (PDA), thus confirming the diagnosis of PAIST. The patient underwent open-heart surgery for PDA ligation and resection of the thrombus; he recovered well and was discharged with a prescription of digoxin and oral rivaroxaban. The authors underscore the importance of considering differential diagnoses for PE—and PAIST in particular—in patients with a single pulmonary lesion and no evidence of peripheral thrombosis.

Case report: Madelung disease with postoperative priapism and multiple venous thromboses, by Guo et al.

Madelung disease is a rare, benign metabolic disease of unknown pathogenesis characterized by symmetrical subcutaneous fat deposits throughout the body (2). Treatment consists mainly of lipectomy or liposuction. This case describes a 49-year-old male affected by type II Madelung disease with bilateral fat deposits in thighs, who developed unexplained priapism and multiple venous thromboses following each of four liposuction, and subsequent skin and fasciocutaneous flap surgeries. Continuously adjusted anticoagulation improved the patient's coagulation profile. Postoperative hypercoagulability is rare in Madelung disease, nevertheless, the authors highlight the

importance of a thorough preoperative assessment of the thrombotic risk and constant postoperative monitoring to improve prognosis and outcomes.

A case of Rapamycin-eluting stent for the treatment of refractory stenosis of arteriovenous fistula stenosis, by Xiong et al.

An autologous arteriovenous fistula (AVF) is the preferred vascular access for patients who require hemodialysis. The most recurrent complication of AVF is stenosis and restenosis following recanalization via percutaneous transluminal angioplasty (PTA) or bare metal stent placement. The authors describe a 51-year-old female with end stage chronic kidney disease undergoing hemodialysis since 2014 via autologous AVF. The patient was repeatedly hospitalized for stenosis of the autologous AVF which was treated by PTA. Ultimately, another PTA was performed and an ultrasound-guided rapamycin-eluted stent placed; the vascular access did not develop another stenosis or thrombosis for a record 14 months, until the stent collapsed. Rapamycin inhibits smooth muscle cell proliferation and obstructive arteriopathy. The authors offer a potentially lifesaving therapeutic measure to preserve vascular accesses in patients undergoing dialysis prone to refractory stenosis.

Case Report: Ectopic pulmonary embolism as a complication of bronchial artery embolization, by Liu et al.

Bronchial artery embolization (BAE) is the first-line treatment in patients with massive hemoptysis (3). The present case describes a 59-year-old male with multiple congenital bronchial artery-pulmonary artery fistulas who was admitted due to acute hemoptysis. Treatment with hemocoagulase and vitamin K1 was unsuccessful, and an emergency BAE was performed due to sudden massive hemoptysis. The patient was readmitted two weeks later due to recurrent hemoptysis. Computed tomography pulmonary angiography showed pulmonary embolism treated with therapeutic low-molecular-weight heparin and percutaneous catheter-directed embolectomy. Hemoptysis resolved within 24 h and dyspnea improved significantly; he was discharged with a 3-month prescription of oral rivaroxaban. Histological analysis revealed that embolization particles entered the pulmonary circulation via an occult fistula masked by multiple bronchial artery branches. The 12-month follow-up showed no recurrences of dyspnea or hemoptysis. It is vital to thoroughly identify all abnormal communications — atypical fistulas, anastomoses — between the pulmonary and bronchial circulations and select appropriate embolization material during BAE.

Case Report: IVC-agenesis and FVL mutation; successful DVT/PE treatment with direct oral anticoagulation (Factor Xa inhibitor), by Siddiqui et al.

Inferior vena cava (IVC) agenesis is a rare congenital malformation wherein collateral veins develop to maintain adequate blood flow to the heart from the lower extremity. This compensatory mechanism increases significantly the risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). Heterozygous factor V Leiden is an inherited thrombophilia that carries a six- to eightfold increased risk of VTE (4). This case describes a 28-year-old obese male presenting with right lower extremity swelling and pain. Laboratory analyses and imaging revealed FVL and IVC agenesis, and the patient was diagnosed with extensive right extremity DVT by Doppler ultrasound. He received intravenous heparin and later switched to oral apixaban upon discharge. Indefinite anticoagulation with a well-tolerated oral anticoagulant remains the most effective strategy to mitigate the risk of recurrent thrombosis.

Case Report: PROS1 (c.76 + 2_76 + 3del) pathogenic mutation causes pulmonary embolism, by Ding et al.

Venous thromboembolism is a life-threatening condition that can be caused by several genetic disorders (5). Protein S is an essential natural anticoagulant whose deficiency results in hypercoagulability (6). This study reports the case of a 28-year-old male who presented with hemoptysis and right chest pain, who was diagnosed with acute pulmonary embolism and pneumonia. After receiving oxygen therapy and anticoagulation therapy, the patient underwent thrombus aspiration and thrombolysis. Genetic testing revealed a heterozygous mutation of protein S. Albeit extremely rare, inherited thrombophilia linked to PROS1 mutations may cause pulmonary embolism in subjects in apparent good health and with no obvious risk factors. Thrombolytic therapy and anticoagulation were effective in this patient.

Perioperative management of caesarean section for a pregnant woman with Sjögren's syndrome and pulmonary embolism: A case report, by Liu et al.

Sjögren's syndrome (SjS) is a chronic inflammatory autoimmune disease that affects predominantly women, whose complexity and complications increase significantly during pregnancy (7). This study describes a 37-week pregnant woman with SjS who presented with chest tightness and suffocation. She was hospitalized and scheduled for an emergency caesarean section due to low oxygen saturation and fetal distress. Sjögren's syndrome renders perioperative anesthesia management quite challenging. Furthermore, SjS can promote a hypercoagulable state. After a safe delivery, the patient was diagnosed with pulmonary embolism and lower extremity deep vein thrombosis. The authors highlight that pregnant women with SjS should receive critical care focused on maintaining fluid balance, continuous oxygen therapy and anticoagulation.

Rare and life-threatening iliac vein stent infection following radiotherapy, by Liao et al.

Radiotherapy (RT) may cause major tissue damage and other severe complications. This case describes a 43-year-old female who received multiple sessions of RT following cervical cancer surgery, and developed severe complications from improper iliac vein stent placement. Two months after completing RT, the patient presented with right lower extremity edema and pain. She was diagnosed with a compression of the right common iliac vein, thus prompting a stent placement. Over a month later, the patient was rehospitalized with high fever, recurrent right lower extremity swelling and severe pain. An exploratory laparotomy revealed a large abscess in the right iliac fossa, a colonic fistula with fecal leakage, and occluded iliofemoral stents. The stents were promptly removed, the veins ligated and the fistula repaired with a colostomy. Clinicians should thoroughly investigate common post-RT symptoms which may obscure underlying

conditions. Preoperative evaluations for stent placement should include CT scans, especially in cancer patients, to accurately assess pelvic and abdominal anatomy.

Successful management of coagulation dysfunction in a patient with fulminant myocarditis: A case report, by Dong et al.

Fulminant myocarditis (FM) is a life-threatening condition predominately caused by viral infections and characterized by abrupt onset, diffuse myocardial inflammation and rapid clinical deterioration (8). Direct virus- and immune-mediated damage to myocardial cells may result in extensive myocardial dysfunction and impaired contractility, culminating in cardiogenic shock. This case report describes the case of a 51-year-old male hospitalized for intermittent abdominal distension, breathlessness and fatigue. Laboratory analyses showed antibodies to Coxsackievirus B3 and echovirus. The clinical management of the patient focused on three main areas: improvement of organ function, correction of coagulation disorders, and control of inflammation and infection. This case highlights the difficulty of managing a patient with FM complicated by cardiogenic shock, respiratory failure, severe liver injury and coagulopathy. It is essential to identify the underlying etiology of FM and implement a comprehensive therapeutic approach to improve outcomes.

Case Report: Maintaining a balance between vascular access patency and stable dissection status in a hemodialysis patient with unrepaired type A aortic dissection, by Lai et al.

Type A aortic dissection is a lethal condition wherein a tear develops within the vascular wall, treated surgically. This peculiar case describes a 72-year-old male undergoing hemodialysis since 2019 and diagnosed in 2017 with unrepaired extensive type A aortic dissection. The patient was admitted in 2022 due to a first episode of dialysis catheter occlusion which was resolved by urokinase thrombolysis. In the following eight months, the patient experienced four additional episodes: 2 resolved by urokinase thrombolysis and 2 treated by catheter replacement. The patient ultimately requested LMWH during hemodialysis, which presented a challenge for the clinicians due to the absence of standardized guidelines for the use of heparin in patients with unrepaired type A aortic dissection. Clinicians administered a lower dose of 1,000 U of intravenous LWMH which was gradually increased till a maximum of 2,000 U, combined with constant imaging surveillance of the dissection. This allowed the patient to safely undergo about four hours of hemodialysis each time for 25 consecutive months without experiencing further catheter occlusion and the dissection remained stable. The authors underscore the rarity of a patient living a normal life for over seven years with an unrepaired extensive aortic dissection. They hypothesized that it may due to the patient's extremely well-controlled blood pressure—hemodialysis-related dehydration and antihypertensive medication—and a spontaneous thrombosis occluding the dissection.

Author contributions

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

Conflict of interest

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

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.

Generative AI statement

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

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 27 August 2024
DOI 10.3389/fcvm.2024.1449989

OPEN ACCESS

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RECEIVED 25 June 2024
ACCEPTED 05 August 2024
PUBLISHED 27 August 2024

CITATION
Xiong Y, Tu B, Zhang M, Chen B, Lai Q, Chen J, Chen L and Wan Z (2024) Case Report: A case of rapamycin-eluting stent for the treatment of refractory stenosis of arteriovenous fistula stenosis.
Front. Cardiovasc. Med. 11:1449989.
doi: 10.3389/fcvm.2024.1449989

Case Report: A case of rapamycin-eluting stent for the treatment of refractory stenosis of arteriovenous fistula stenosis

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For patients with repeated stenosis of autologous arteriovenous fistula, percutaneous transluminal angioplasty (PTA) or bare metal stent placement had limited efficacy. Rapamycin was reported to inhibit neointimal hyperplasia and keep blood vessels patent. In this study, we reported a case with refractory stenosis, i.e., a short duration of patency maintenance after each repeated PTA, which was treated with a rapamycin-eluting stent (RES). The RES extended the patency duration from 4 to 5 months on average to 14 months. The stent was used to maintain dialysis for over 30 months. RES may be an effective way to treat refractory stenosis and salvage limited vascular resources.

KEYWORDS

arteriovenous fistula, refractory stenosis, rapamycin-eluting stent, percutaneous transluminal angioplasty, end-stage renal disease

Introduction

Autologous arteriovenous fistula (AVF) is the preferred vascular access for patients with end-stage renal disease (ESRD), accounting for 80.5% of all vascular access (1), and is also known as the "lifeline" of dialysis patients. However, AVF is prone to restenosis due to various reasons, and neointimal hyperplasia is the most common one (2). It was reported that the 2-year patency rate of AVF is only 38%–56% (3). Percutaneous transluminal angioplasty (PTA) is an effective way to deal with AVF restenosis (4). However, a few patients may experience repeated stenosis in the short term. For these patients, repeated PTA or bare metal stent placement had limited efficacy.

Drug-eluting stents (DESs) can effectively reduce the risk of vascular restenosis through coated antiproliferative drugs, such as rapamycin or paclitaxel, which can be slowly released into the surrounding tissues to inhibit neointimal hyperplasia and keep blood vessels patent. In addition, the stent itself can provide long-term vascular support for maintaining patency. DESs have been proven to be effective in the treatment of restenosis in patients with percutaneous coronary intervention (5). However, the literature on DESs for treating repeated stenosis of AVF in ESRD patients is limited, especially for rapamycin-eluting stents (RESs). Here, we reported a case of using an RES to treat refractory stenosis of AVF, which resulted in a long-term patency duration.

Case presentation

A 51-year-old female patient was diagnosed with chronic kidney disease (stage 5) which was caused by polycystic kidney disease. This patient had a history of hypertension and no other complications, such as diabetes or coronary heart disease. Furthermore, she had no history of smoking or drinking wine. Her body mass index was 18.47. This patient had received hemodialysis since 2014. On 10 November 2015, an autologous AVF in the right wrist was created in our hospital which was occluded 1 month later. Then, we reconstructed an AVF in the right forearm during open surgery on 30 December 2015. This AVF was used for hemodialysis for approximately half a year and was occluded again. An ultrasound-guided PTA was performed to clear the occlusion on 29 June 2016, with a balloon of 5 mm × 40 mm. Shortly thereafter, this patient underwent replete angioplasty because of repleted stenosis in right forearm AVF on 11 October 2016, and 7 February 2017, with a balloon of 6 mm × 40 mm.

On 23 May 2017, this patient was hospitalized again because of decreased flow volume in the right forearm AVF. Preoperative ultrasonoscopy indicated a significant juxta anastomotic stenosis, with a diameter of 1.0 mm and a length of 1.5 cm (Figure 1A). No thrombosis or calcification was found. Because of the short duration of patency maintenance after each repeated PTA, after a discussion, the team decided to perform another PTA with RES placement in the right forearm AVF. Informed consent was obtained before the procedure.

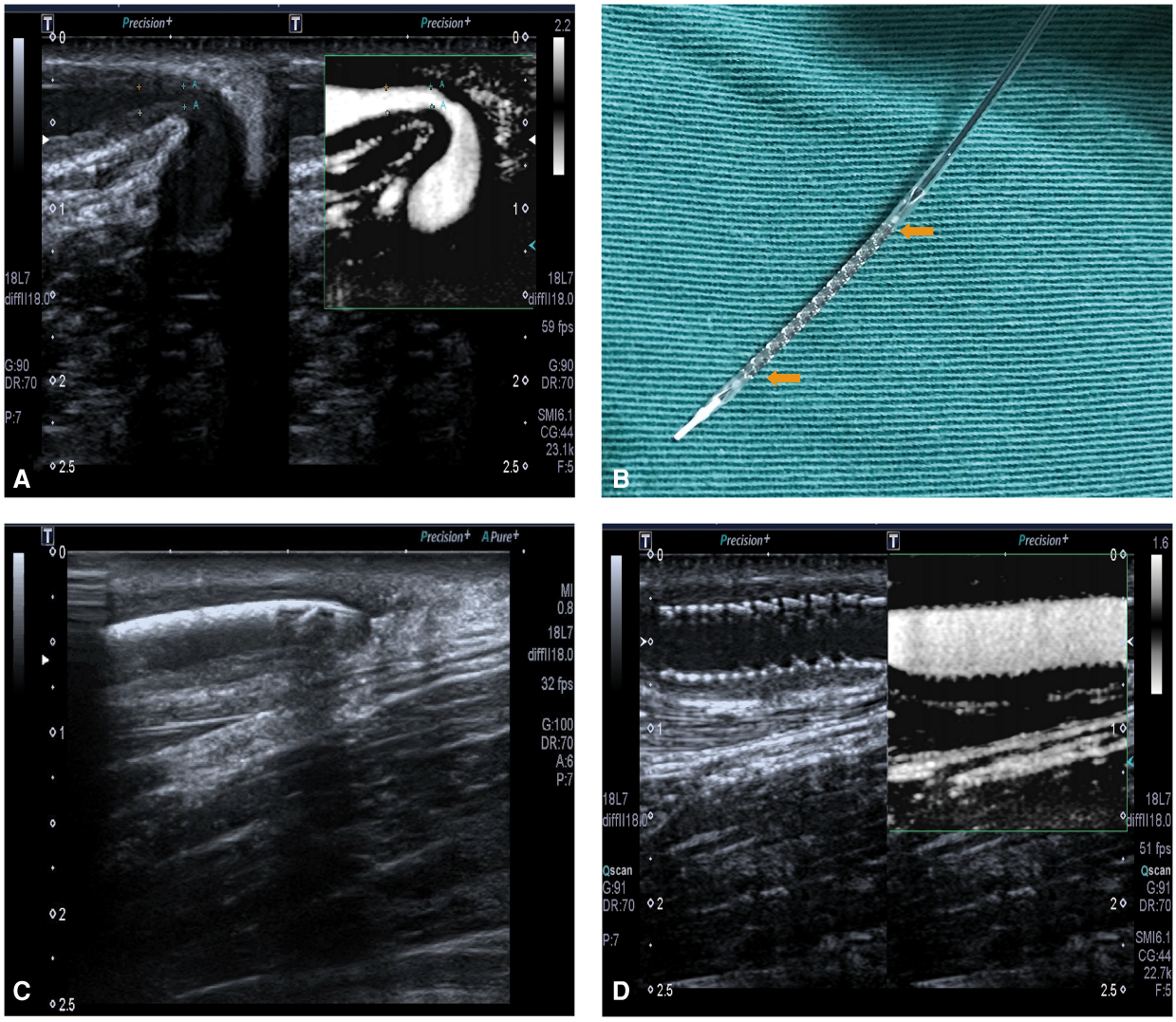

FIGURE 1
(A) The restenosis of right forearm autologous AVF on 23 May 2017. **(B)** RES. The yellow arrows show the main body of the stent, with a balloon inside it. **(C)** The ultrasound localization of RES which shows the RES was placed at the site of stenotic lesion. **(D)** The fully expanded RES, with a patent blood flow.

Procedure

After the brachial plexus block, a 5F-R vascular sheath (Terumo, Tokyo, Japan) was inserted into the cephalic vein. A guide wire (Abbott Vascular, Santa Clara, California, USA) of 0.014 in. was advanced along the vein slightly across the stenotic lesion. A balloon of 5 mm × 20 mm was advanced along the guide wire and across the stenotic lesion to the anastomotic site, followed by balloon angioplasty of the stenotic lesion, the outflow vein, and the anastomotic site using 20–24 atm, repeated three times. The balloon was subsequently removed. Then the RES (NOYA, Beijing, China), a balloon-expandable stent with a diameter of 4.5 mm and length of 22 mm, was placed in the stenotic lesion with the guidance of ultrasonography (Figures 1B,C). The RES was fully expanded by a balloon angioplasty using 16 atm.

After PTA and RES placement, the ultrasound images showed that the diameter of the brachial artery was 5.9 mm, with a flow volume of 521 ml/min. In the segment of the cephalic vein near an anastomosis, a 22 cm stent was observed. The stent was closely fitted to the vascular wall, and a color Doppler ultrasound showed filled blood flow through the stent, with a peak velocity of 210 cm/s (Figure 1D). The diameter of the middle segment of the forearm cephalic vein was 3.8 mm, with an intimal medial thickness of 1.4 mm and a peak velocity of 256 cm/s.

The right forearm AVF was patent for hemodialysis until the stent collapsed on 27 July 2018, with a primary patent duration of 14 months. No other postoperative complications occurred before the stent collapsed, such as thrombosis, heart failure, pseudoaneurysm, infection, or hemodialysis access-induced distal ischemia syndrome. Though the flow volume was acceptable, we still decided to expand the stent using PTA (Figure 2). On 30 July 2019, another restenosis occurred in the proximal part of the outflow vein of the right forearm AVF and was treated using ultrasound-guided PTA. On 26 December 2019, a thrombosis

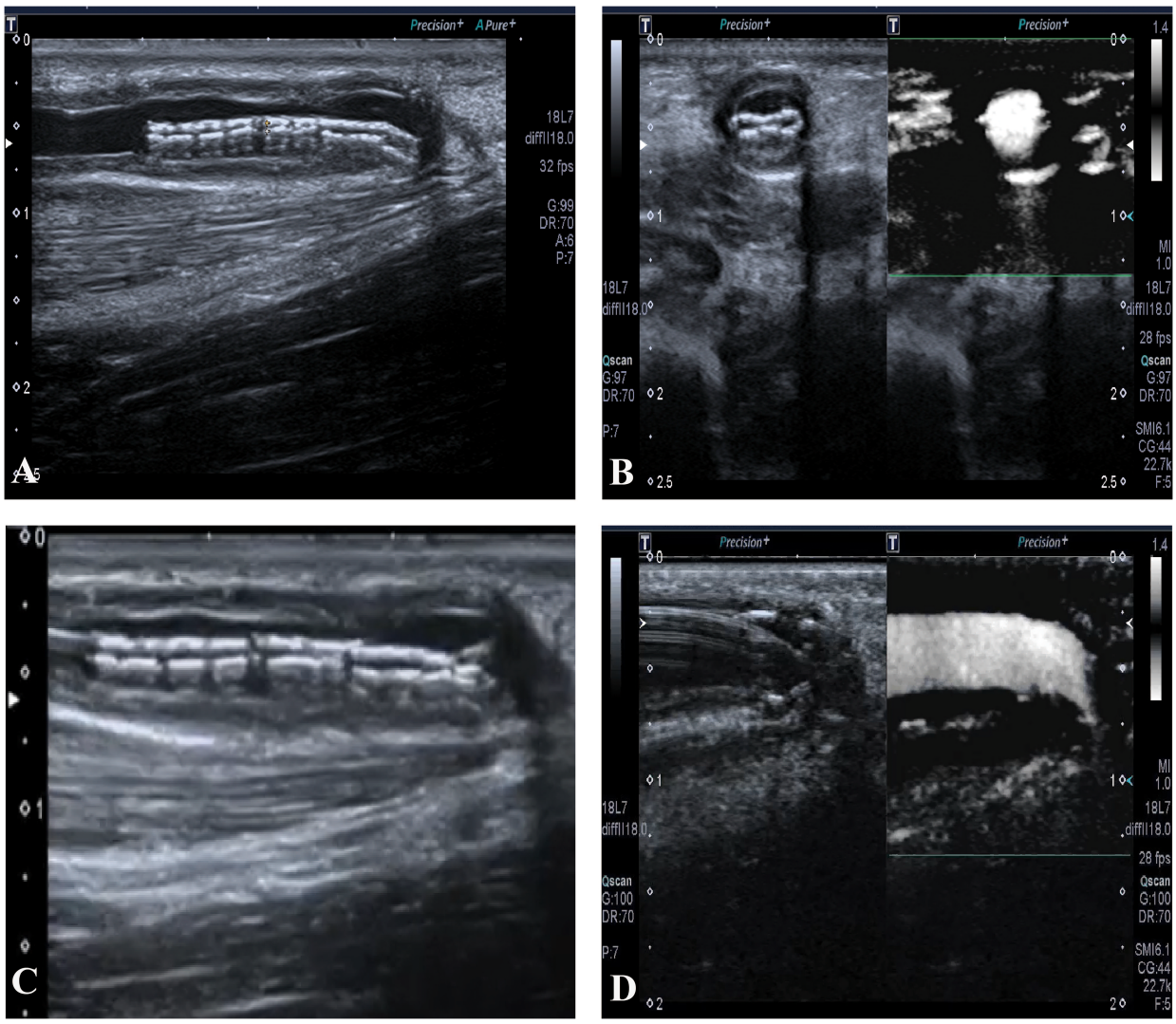

FIGURE 2
(A) The collapsed stent in long-axis view. (B) The collapsed stent in short-axis view, with acceptable blood flow. (C) The guide wire advances through the collapsed stent. (D) The expansion of the collapsed stent using percutaneous transluminal angioplasty.

related to the restenosis in the proximal part was found by ultrasonography. Hence, the right forearm AVF was discarded. Instead, an arteriovenous graft (AVG) in the left forearm was constructed for maintenance hemodialysis since then, with one PTA procedure annually on average up to now.

Discussion

Though DESs and drug-eluting balloons have been proven to be effective in treating restenosis in patients with acute cardiovascular events (6), the evidence for using DESs to treat refractory stenosis in AVF patients is lacking. A pilot study reported the efficacy of a paclitaxel-eluting stent (PES) for treating AVF dysfunction. With a mean follow-up of 202 days, seven out of nine patients had patent AVFs (7). A case report reported that the PES significantly extended the interval time of repeated balloon angioplasty from 3.1 to 5 months (8). A study demonstrated that among 14 patients who received a PES, the primary patency rates at 6 and 12 months were 64% and 29%, respectively, which were more pronounced than that of their last conventional balloon angioplasty (29% and 7%, respectively) (9). All these studies demonstrated effective improvement when using a PES to treat frequent restenosis.

To the best of our knowledge, no study has reported the use of an RES for treating frequent restenosis in AVF patients. In this study, the RES extended the patency duration from 4 to 5 months on average to 14 months. The stent was used to maintain dialysis for over 30 months. Furthermore, the stent collapsed only once and another restenosis occurred in the meantime.

Rapamycin, also known as sirolimus, is a macrolide antibiotic class immunosuppressant. It inhibits the degradation of the cyclin-dependent kinase inhibitor (p27), thereby suppressing the G1 phase of the cell cycle and preventing cells from entering the next cycle (10). This mechanism explains its anti-smooth muscle cell proliferation properties and ability to inhibit thrombosis formation on stents. In addition, rapamycin can block the synthesis of proteins required for cell division, and its binding to FKBP12 weakens mTOR activity, further suppressing the cell cycle (11).

Another strength of this case is the guidance by ultrasonography, which helped monitor the position of the stent in real-time, and clearly showed the shape of the stent and its adhesion to the blood vessel wall. In addition, ultrasonography had the advantage of allowing us to evaluate the hemodynamics after stent placement and subsequently monitor the long-term patency.

A study reported that a balloon-expandable stent is vulnerable to external compression and this can result in collapse. This may be the main reason for the collapse of our case as the RES was placed in a cephalic vein, a superficial anatomy (12). In addition, rough operation may also lead to a collapse, which suggests experience and gentle handling are needed (13).

In conclusion, ultrasound-guided rapamycin-eluting stent placement is effective for treating refractory stenosis of AVF, with acceptable adverse events and long-term patency. This may be an effective way to salvage limited vascular resources.

Data availability statement

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

Ethics statement

Ethical approval was not required for the study involving 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 participant/patient(s) for the publication of this case report.

Author contributions

YX: Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. BT: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. MZ: Formal Analysis, Investigation, Software, Validation, Visualization, Writing – original draft. BC: Data curation, Formal Analysis, Software, Validation, Visualization, Writing – original draft. QL: Data curation, Formal Analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft. JC: Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing – original draft. LC: Formal Analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft. ZW: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article.

This study was supported by the Appropriate Technology Promotion Project of Chongqing Health Commission (grant number: 2022jstg009).

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 27 August 2024
DOI 10.3389/fcvm.2024.1449556

OPEN ACCESS

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RECEIVED 20 June 2024
ACCEPTED 13 August 2024
PUBLISHED 27 August 2024

CITATION
Guo L, Li W, Xu X and Xiao H (2024) Madelung disease with postoperative priapism and multiple venous thromboses: case report and literature review.
Front. Cardiovasc. Med. 11:1449556.
doi: 10.3389/fcvm.2024.1449556

Madelung disease with postoperative priapism and multiple venous thromboses: case report and literature review

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Madelung disease is an uncommon metabolic disorder of uncertain pathogenesis, distinguished by the symmetric accumulation of nonencapsulated adipose tissue within the subcutaneous layer of the neck, abdomen, thighs, and other anatomical regions. This condition has been tightly connected with comorbidities including diabetes, dyslipidemia, hyperuricemia, hypothyroidism, and adrenal dysfunction, as well as sensory, motor, and autonomic polyneuropathy. The prevalence of Madelung disease is conspicuously higher in Mediterranean and Eastern European, with a distinct scarcity within the Asian population. Surgical interventions involving lipectomy and liposuction represent the foremost and most efficacious treatment approach. Herein, we present a case encompassing type II Madelung disease featuring bilateral thighs adipose tissue accumulation. The patient exhibited unexplained priapism alongside multiple venous thrombosis during four surgical interventions. The infrequent manifestation of postoperative hypercoagulability in patients of Madelung disease merits broad attention, owing to the potentiality for extensive venous thrombosis and consequential severe outcomes such as pulmonary embolism or cerebral infarction arising from thrombus dislodgment. Building upon this clinical scenario, we systematically documented the clinical manifestations and disease progression in this patient, meticulously analyzed the causes of complications, and proposed targeted preventive measures. Additionally, we conducted a comprehensive review of the relevant literature to summarize the clinical and epidemiological features of Madelung disease and to elucidate its mechanisms. This study will provide a valuable reference for future clinical treatments and mitigate perioperative complications of Madelung disease.

KEYWORDS

Madelung disease, benign symmetric lipomatosis, liposuction, priapism, thrombosis

1 Introduction

Madelung disease (MD), also recognized as benign symmetric lipomatosis (BSL), multiple symmetric lipomatosis (MSL), and Launois-Bensaude syndrome, is a sporadic and uncommon metabolic disorder (1). It was initially described by Brodie in 1846 and systematically defined by Madelung in 1888 (2). The hallmark of MD is the symmetric accumulation of nonencapsulated adipose tissue within the subcutaneous layer of anatomical regions such as the head, neck, shoulders, and other sites, resulting in distinctive physical features termed "hamster cheeks", "horse collar" or "buffalo hump" (3, 4). The widely accepted classification proposed by Enzi delineates two anatomically based types of MD. Type I is the most common

form, and predominantly involves symmetric deposition in the neck, shoulders, supraclavicular triangle, and proximal upper limbs, whereas type Ⅱ is characterized by deposits in the abdomen and thighs, occasionally resembling normal obesity (5). Notably, gender influences the occurrence of MD, with men often manifesting type I and women more exhibiting type Ⅱ. 2161. In the 1990s, a four-fold classification introduced by Donhauser included neck distribution, pseudo-athletic appearance, gynoid presentation, and abdominal type (6). In addition, rare occurrences of adipose tissue deposits in unusual sites like breasts (7), tongue (8), and scrotum (9) have been documented. These clinical manifestations generally progress slowly, remain painless, and rarely exhibit malignancy (10). However, progressive neck adipose tissue accumulation may lead to serious complications such as neck stiffness, dysphagia, dysphonia, breathing difficulties, headache, and even sleep apnea syndrome (11). While MD can manifest across various ethnic groups, a preponderance of reported cases is notably observed within Mediterranean and Eastern European populations, particularly prevalent in regions such as Portugal and Italy (12). Relatively speaking, this condition demonstrates rarity within the Asian population (13). The exact prevalence and incidence of MD remain elusive, but estimates are available for certain countries. For example, the incidence of Italy males is approximately 1 in 25,000. It affects males more often with a male-to-female ratio of approximately 15:1–30:1, and 30–60 years appear to be the highest risk age of affection (14). The pathogenesis of MD remains incompletely understood. Current hypotheses suggest that mutations in mitochondrial DNA and a reduction in adrenergic-mediated lipolysis are primary contributing factors to the development of MD (15). The diagnosis of MD primarily relies on medical history, clinical features, and imaging modalities, particularly computed tomography (CT) or magnetic resonance imaging (MRI), to ascertain adipose tissue deposition (16). Differential diagnosis should encompass conditions such as morbid obesity, other types of lipomatosis, goiter, salivary gland disease, Cushing's disease, and neoplastic transformations (17). Given the absence of standardized guidelines, the management of MD varies under different conditions, encompassing health intervention, medication, lipolytic injection, and surgical procedures such as liposuction and lipectomy. Among these options, surgical interventions are considered as the foremost and most efficacious treatment modalities (18, 19). Herein, we present a case encompassing type II MD featuring bilateral thighs adipose tissue accumulation. Notably, the patient exhibited unexplained priapism alongside multiple venous thrombosis throughout the body during four surgical interventions. Building upon this clinical scenario, we systematically documented the clinical manifestations and disease progression in this patient, meticulously analyzed the causes of complications, and proposed targeted preventive measures. Additionally, we conducted a comprehensive review of the relevant literature to summarize the clinical and epidemiological features of MD and to elucidate its mechanisms. This study will provide a valuable reference for future clinical treatments and mitigate perioperative complications of MD.

2 Case presentation and data extraction

A 49-year-old Chinese male presented with excessive thigh thickening, which first appeared 4 years ago and had significantly worsened over the past year (Figures 1A,B). The diffuse symmetric thickening spanned from the hip to the knee level, with a maximum diameter of 30 cm. The MRI suggested a significant thickening of the subcutaneous fat layer and adipose tissue filling within the muscle interstices, leading to a diagnosis of MD (Figures 1C,D). Administering 1.0 g of intravenous cefazolin sodium daily for three consecutive days perioperatively as preoperative prophylactic antibiotic treatment. Considering the substantial wound, the first liposuction surgery, as well as fascial and skin flap plasty, was limited to the patient's left thigh, popliteal fossa, knee, and hip. Approximately 4,000 ml of adipose tissue were successfully extracted. The risk of venous thromboembolism (VTE) was evaluated preoperatively and postoperatively using the Caprini assessment scale (20). The patient was assessed at intermediate risk postoperatively due to three risk factors, age 41–60 years, a body mass index greater than 25 kg/m^2, and undergoing major surgery lasting over 45 min. Following the guidelines for VTE prophylaxis, the patient was administered 40 mg of enoxaparin sodium subcutaneously for two consecutive days. The histopathological assessment of the excised tissue revealed an adipogenic lesion without murine double minute 2 gene amplification, supporting the diagnosis of MD (Figures 1E,F).

After the liposuction surgery, the patient exhibited dark red coloration in the left thigh skin flap, along with epidermal detachment and scab formation. Concurrently, priapism and scrotal swelling were observed. Then left thigh debridement was conducted, and the patient experienced occasional exacerbation of priapism. Each instance of penile cavernous body suction and lavage provided slight relief. Penile and vascular ultrasound examinations showed no abnormalities, and the patient declined the penile head-cavernous body shunt operation. However, on the fourth day after the left thigh debridement, the patient's priapism symptoms dramatically worsened, accompanied by intolerable pain and significant hematuria. Laboratory blood tests revealed many indicator values surpassing the established reference compared with the results during hospitalization (Table 1). Alterations in indicators such as C-reactive protein and Interleukin-6, substantiated the progression of infection. Especially, the coagulation indicator tests revealed the D-dimer and fibrin and fibrinogen degradation products (FDP) levels surged to 38.00 mg/L FEU and 80.0 mg/L respectively (Figure 2). Lower abdominal computed tomography angiography (CTA) indicated right internal iliac vein embolism, while urological ultrasound demonstrated right hydronephrosis and ureteral dilatation. Subsequent bladder

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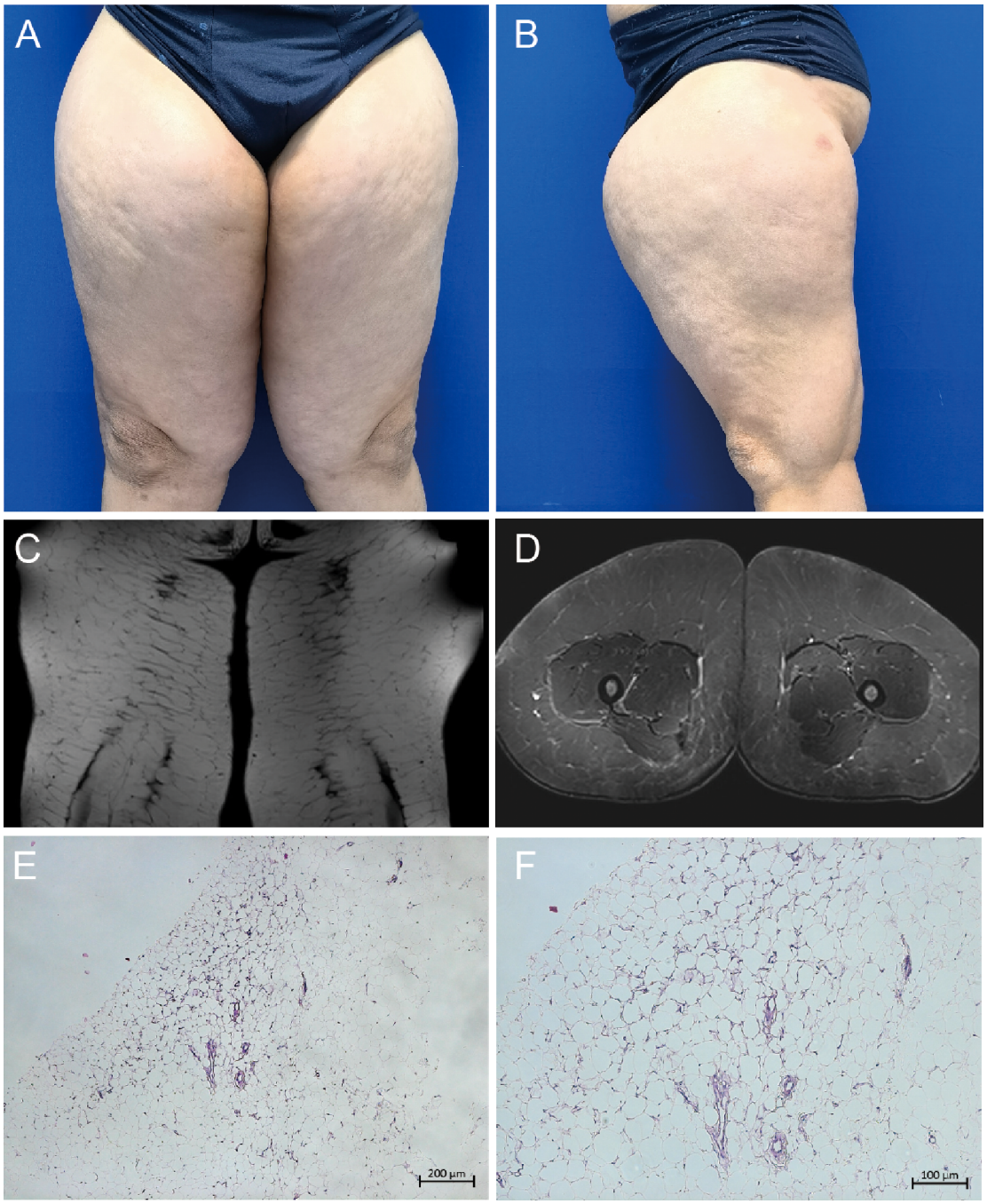

FIGURE 1
Phenotypic manifestations of Madelung disease. **(A, B)** Frontal and lateral view of bilateral thighs; **(C, D)** magnetic resonance imaging showing coronal and cross section of bilateral thighs; **(E, F)** histopathological assessment of the excised tissue revealing an adipogenic lesion.

irrigation and anticoagulant treatment led to partial improvement in the patient's condition. The anticoagulant treatment strategy was continuously adjusted based on Caprini assessment results, blood coagulation indicators, and imaging findings. Initially, 60 mg of enoxaparin sodium was administered for four consecutive days, followed by 60 mg of nadroparin calcium for 16 consecutive days. After stabilization, 60 mg of edoxaban tosilate tablets were administered orally daily for 2 months. Additionally, wound area secretion culture suggested successive infections with Escherichia coli, Acinetobacter baumannii, and Klebsiella pneumoniae. Intravenous administration of ceftriaxone sodium, tigecycline, imipenem-cilastatin sodium, and colistin sulfate, along with the topical application of silver sulfadiazine, constituted the spectrum of antibiotics employed in practice. During anticoagulation therapy, the extremity venous ultrasound suggested the development of bilateral cephalic vein thrombosis (Figures 3A,B), along with left

10.3389/fcvm.2024.1449556

TABLE 1 Results of blood tests during hospitalization and at the exacerbation of abnormal priapism.

Variable	At admission		At the exacerbation		Reference range	
	Value	Trend	Value	Trend	Value	Unit
Infection indicators						
C-reactive protein	—	—	118	↑	<5.00	mg/L
Interleukin-6	—	—	164	↑	0.00–7.00	pg/ml
Procalcitonin	—	—	1.56	↑	<0.046	ng/ml
Hemocyte analysis						
Erythrocyte count	4.43	→	3.17	↓	4.3–5.8	$\times10^{12}$/L
Hemoglobin	133	→	95	↓	130–175	g/L
Hematocrit	0.40	→	0.30	↓	0.40–0.50	L/L
Platelet count	166	→	262	→	100–300	$\times10^{9}$/L
Leukocyte count	5.43	→	24.56	↑	3.5–9.5	$\times10^{9}$/L
Neutrophilic segmented granulocyte,%	62.5	→	88.6	↑	40–75	%
lymphocyte,%	27.8	→	3.9	↓	20–50	%
Monocyte,%	7.4	→	7.2	→	3–10	%
Eosinophil,%	1.7	→	0.1	↓	0.4–8.0	%
Basophil,%	0.6	→	0.2	→	0.0–1.0	%
Neutrophilic segmented granulocyte	3.39	→	21.76	↑	1.8–6.3	$\times10^{9}$/L
Lymphocyte	1.51	→	0.96	↓	1.1–3.2	$\times10^{9}$L
Monocyte	0.40	→	1.77	↑	0.1–0.6	$\times10^{9}$/L
Eosinophil	0.09	→	0.02	→	0.02–0.52	$\times10^{9}$/L
Basophil	0.03	→	0.05	→	0.00–0.06	$\times10^{9}$/L
Biochemical indicators						
Total bilirubin	8.7	→	20.3	→	5.0–28.0	umol/L
Direct bilirubin	2.4	→	13.2	↑	<8.8	umol/L
Indirect bilirubin	6.3	→	7.1	→	<20	umol/L
Total bile acid	5.0	→	8.1	→	<15	umol/L
Alanine aminotransferase, ALT	14	→	141	↑	<50	IU/L
Aspartate aminotransferase, AST	14	→	86	↑	<40	IU/L
AST/ALT ratio	1.00		0.61			
Alkaline phosphatase	70	→	443	↑	51–160	IU/L
Glutamyl transpeptidase	20	→	443	↑	<60	IU/L
Total protein	65.3	→	56.4	↓	65.0–85.0	gL
Albumin, ALB	43.4	→	33.5	↓	40.0–55.0	g/L
Globulin, GLOB	21.9	→	22.9	→	20.0–40.0	g/L
ALB/GLOB ratio	1.98	→	1.46	→	1.24–2.40	
Glucose	4.71	→	9.10	↑	3.90–5.90	mmol/L
Urea	5.3	→	5.2	→	3.1–8.0	mmol/L
Creatinine	71	→	87.00	→	68–108	umol/L
Estimated glomerular filtration rate	104.73		89.70			ml/min/1.7
Cystatin-C	1.06	→	1.44	↑	0.51–1.09	mg/L
Uric acid	344	→	176	↓	240–290	umol/L
Triglyceride	0.76	→	0.93	→	0.29–1.83	mmol/L
Total cholesterol	4.70	→	3.63	→	2.80–5.70	mmol/L
High density lipoprotein cholesterol	1.52	→	0.80	↓	>0.90	mmol/L
Low density lipoprotein cholesterol	2.86	→	2.48	→	<4.0	mmol/L
Non-high density lipoprotein cholesterol	3.18		2.83			mmol/L
Creatine kinase	42	→	27	→	19–226	IU/L
Lactic dehydrogenase	131	→	288	↑	120–150	IU/L
Hydroxybutyrate dehydrogenase	101	→	211	↑	72–182	IU/L
Sodium	140.8	→	125.4	↓	137.0–147.0	mmol/L
Potassium	3.89	→	4.22	→	3.50–5.30	mmol/L
Chlorine	106.3	→	89.1	↓	99.0–110.0	mmol/L
Calcium	2.25	→	2.01	↓	2.11–2.52	mmol/L
Magnesium	0.89	→	0.72	↓	0.75–1.02	mmol/L
Inorganic phosphorus	1.03	→	0.96	→	0.85–1.51	mmol/L

The symbols employed for indicating blood test outcomes are as follows: "—" signifies the non-availability of the corresponding laboratory measurement; "→" signifies the test value falls within the predefined reference range; "↑" signifies the test value exceeds the predefined reference range; and "↓" signifies the test value is below the predefined reference range.

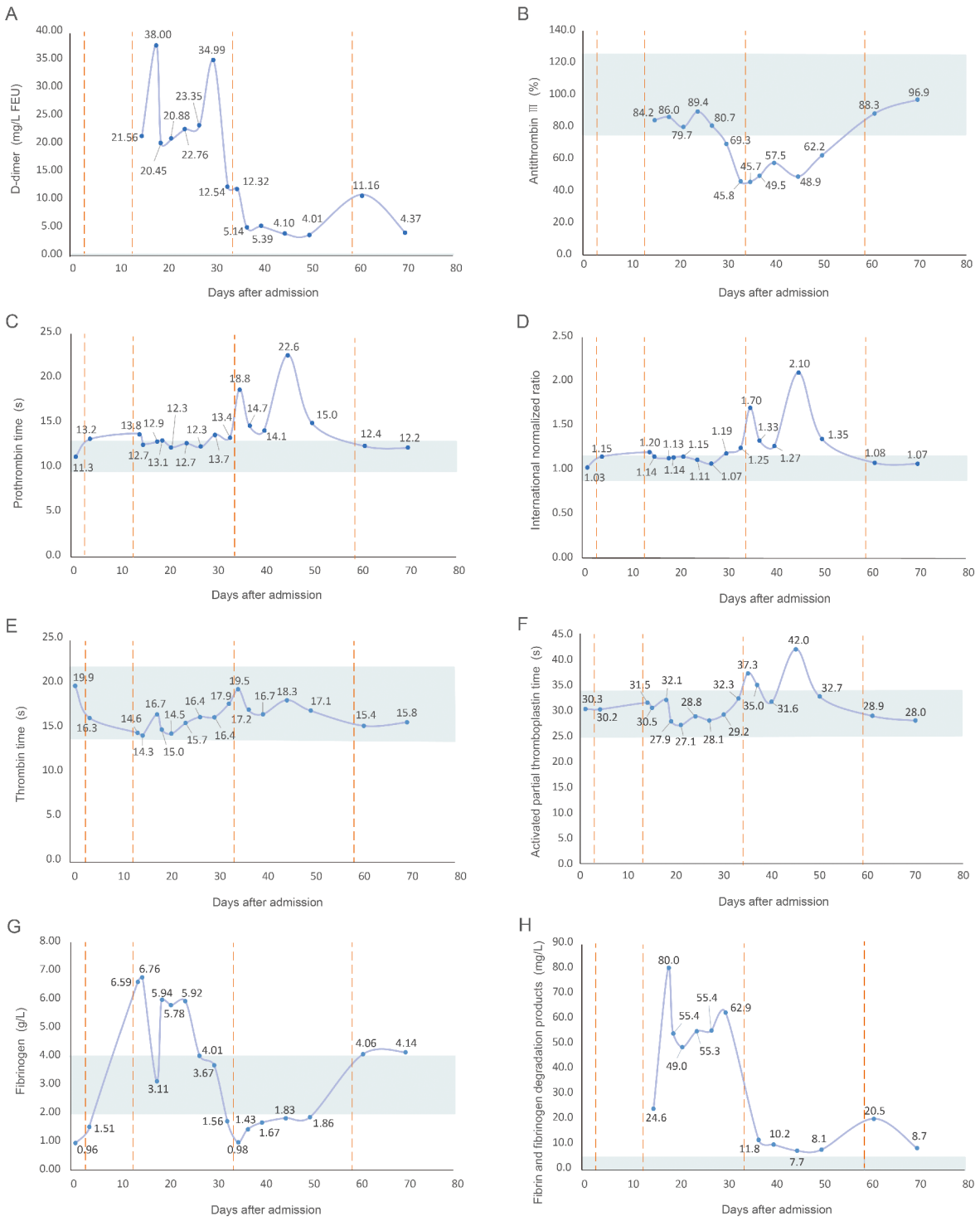

FIGURE 2
Line graph of alterations in coagulation indicators after the patient's admission. **(A)** D-dimer, with a reference range of <0.55 mg/L FEU; **(B)** antithrombin III, with a reference range of 75.0%–125.0%; **(C)** prothrombin time, with a reference range of 9.6–12.8 s; **(D)** international normalized ratio, with a reference range of 0.88–1.15; **(E)** thrombin time, with a reference range of 14.0–22.0 s; **(F)** activated partial thromboplastin time, with a reference range of 24.8–33.8 s; **(G)** fibrinogen, with a reference range of 2.00–4.00 g/L; **(H)** fibrin and fibrinogen degradation products, with a reference range of <5.0 mg/L. The shaded region denotes the reference range of coagulation indicators, the solid line illustrates value fluctuations in the coagulation indicators, and the dashed line represents the time of the patient's four surgeries after admission.

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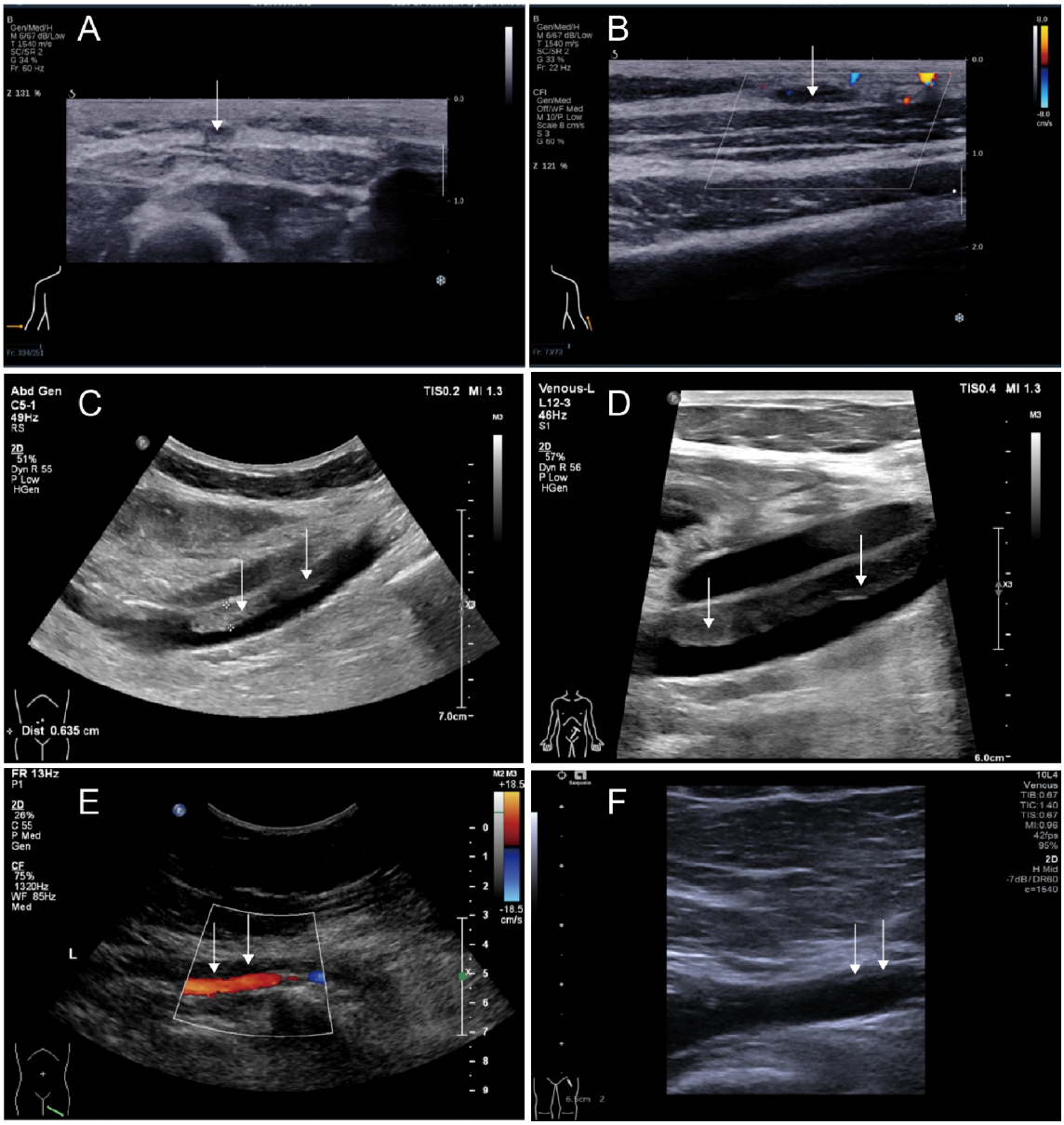

FIGURE 3
Ultrasonographic findings of multiple venous thromboses. **(A)** Right cephalic vein; **(B)** left cephalic vein; **(C)** right external iliac vein; **(D)** left external iliac vein; **(E)** left popliteal vein, **(F)** left common femoral vein.

common femoral vein reflux and bilateral calf soft tissue swelling. Abdominal venous ultrasound revealed bilateral external iliac venous mural thrombus (Figures 3C,D). Subsequently, the patient underwent skin grafting for the traumatized area of the left thigh, with the donor areas being successively the right thigh and scalp. Follow-up extremity venous ultrasound revealed left popliteal vein thrombosis and left common femoral vein thrombosis (Figures 3E,F). When the patient was discharged from the hospital 10 days after the fourth surgery, most of the skin graft pieces exhibited good viability and the peritraumatic flap demonstrated an appropriate fit. Additionally, an improvement in priapism and swelling was observed. The patient was advised to continue oral anticoagulant therapy, with regular monitoring of coagulation function and venous ultrasound reviews.

3 Discussion

The underlying mechanisms driving the pathogenesis of MD remain unclear. A prominent hypothesis posits that MD's initiation is underpinned by the tumor-like proliferation of brown adipose tissue, a phenomenon closely tied to the diminished lipolysis stemming from reductions in β-adrenergic receptor numbers or activity (15). Additionally, perturbations in

the mitochondrial function of adipose tissues constitute an integral facet, encompassing compromised respiratory chain integrity and attenuated cytochrome C oxidase activity (21, 22). In MD patients associated with lipodystrophic syndrome, the MNF2 gene is mutated and exhibits an autosomal recessive form, with the causative variant p.Arg707Trp in the homozygous or composite heterozygous state (23). This gene encodes mitofusin-2, which is involved in mitochondrial fusion and endoplasmic reticulum-mitochondrial interactions (24). Defects in MNF2 result in uncoupling protein 1-negative unilocular adipocytes with enlarged and disorganized mitochondria, reduced mitochondrial DNA levels, increased expression of mitochondrial oxidative stress-related genes, and a marked decrease in leptin and lipocalin expression (25). Moreover, in a family presenting with myopathy and lipodystrophic syndrome, a phenotype resembling MD in non-dystrophic regions was linked to the mutation of the homozygous Lipase E gene, which encodes hormone-sensitive lipase, a key enzyme in triglyceride metabolism (26). Beyond these Mendelian forms, studies suggest that MD shows detectable mitochondrial DNA pathogenic variants, such as MT-TK, pos.8344A > G, and m.8357T > C (27, 28). These identified genes could represent potential therapeutic targets. While the definitive mechanism is elusive, alcoholism emerges as a discernible catalyst for MD advancement (29). Patients with a chronic history of alcohol consumption comprise 60%–90% of cases and frequently suffer from secondary liver dysfunction and cirrhosis (30, 31). In addition, MD has also been tightly connected with the presence of several metabolic disorders, encompassing diabetes, dyslipidemia, hyperuricemia, gynecomastia, hypothyroidism, and adrenal dysfunction (3, 30, 32). Besides, sensory, motor, and autonomic polyneuropathy are concurrently identified in approximately 85% of individuals afflicted with MD (33). In accordance with Enzi's classification system (5), the presented case corresponds to type II. The feature of local adipose tissue accumulation of bilateral thighs renders differentiation from alternative forms of obesity or neoplastic conditions more straightforward. This patient's long-term history of alcohol abuse, along with risk factors such as gender, age, and obesity, likely played a significant role in the progression of MD. Especially, the patient's familial background is noteworthy, given that both parents are close relatives and his sister exhibited comparable clinical manifestations. This familial aggregation potentially furnishes an avenue for understanding the pathogenesis of MD.

Therapeutic approaches for MD encompass nonsurgical and surgical modalities. Nonsurgical interventions offer a limited therapeutic impact. While alcohol cessation and weight reduction may decelerate adipose mass enlargement and restore metabolic equilibrium to a relative extent, their ability to halt disease progression and effectuate reversal remains uncertain (34). Furthermore, effective and definitive pharmacotherapy for MD has yet to be established. In select reports, intralipotherapy involving the injection of phosphatidylcholine or deoxycholate has been proposed as a noninvasive intervention. Likewise, although this method effectively restrains adipose mass growth, its capacity to reduce volume is less corroborated (35). Besides, while studies have advocated the use of β2-agonist salbutamol for lipolysis induction through adrenergic stimulation, the clinical efficacy of such conservative approaches remains contentious (7, 33, 36). Surgical management aims to address cosmetic deformities, alleviate compressive symptoms, and safeguard crucial vascular and neural structures. Empirical evidence indicates surgical intervention as the foremost and most efficacious treatment modality, including lipectomy, liposuction, or their combination (19). Lipectomy predominates among reported cases, facilitating thorough exposure and meticulous excision with decreased inadvertent damage to contiguous structures. However, complete lipectomy presents technical challenges due to the absence of a discernible capsule demarcating the lipomatous tissue (37). Liposuction's rising popularity stems from its low complication morbidity, simplicity, lesser invasiveness, and enhanced cosmetic outcomes (19). Nevertheless, liposuction is considered as an adjunct therapy in numerous instances, due to the formidable density and fibrous composition of the adipose mass (38). Moreover, achieving comprehensive removal, whether through lipectomy or liposuction, proves intricate given the nonencapsulated nature, multidirectional expansion, and potential to involve diverse structures, rendering recurrence nearly inevitable (39). In conclusion, both lipectomy and liposuction offer merits and limitations. Surgeons should judiciously select the optimal therapies based on disease localization and extent, patient expectations, and the surgeon's proficiency. In consideration of the extensive adipose tissue infiltration, and relatively diminished vascular and neural structures around the thighs, left thigh liposuction was undertaken, aiming to minimize procedural trauma and postoperative complications. Regrettably, postoperative priapism and thrombosis emerged. Therefore, deferral of right thigh liposuction was deemed prudent.

The patient's hospitalization spanned a total of 72 days, during which he exhibited abnormal priapism and discernible swelling of the scrotal region for more than 2 months. In addition, the patient had previously encountered urinary difficulties devoid of evident causation. A possible explanation was that the patient had related pathological conditions like abnormal neurological function or hormone secretion, and surgical stress, trauma, and urinary tract infection triggered intractable priapism. In addition to the priapism, the patient experienced postoperative multiple venous thromboses distributed throughout the body which indicated a heightened propensity for an *in vivo* hypercoagulable state at this juncture. This perilous state then gradually waned around the third operation in response to appropriate and continuously adjusted anticoagulant therapy. Therefore, the patient did not develop symptoms, such as dyspnea or chest pain, nor the corresponding imaging manifestations of pulmonary embolism. The mechanism underlying multiple venous thromboses across various anatomical regions can be delineated as follows. First, the preoperative coagulation status was not sufficiently evaluated, and the postoperative venous ultrasound of the abdomen and limbs was not promptly addressed. Second, the liposuction surgery was characterized by prolonged duration, wide-range lesion involvement, and substantial surgical trauma. In response to the

postoperative epidermal detachment, the patient underwent a second debridement surgery. Thus, anticoagulation was carefully managed during both surgeries to prevent postoperative bleeding. Third, the patient's adipose accumulation was primarily concentrated in both thighs, exerting prolonged compression on the blood vessels. It may have impacted the morphology and function of the lower extremity veins, with the defect becoming fully apparent post-surgery. Fourth, the patient's prolonged bedridden state after the surgery decelerated venous flow rates. Fifth, despite prompt support therapy of fluid replacement, the imbalance between exudation and relatively insufficient intake could potentially lead to blood concentration. Last, infection contributed to thrombosis by inducing the increased production of procoagulant compounds such as thrombin. Similarly, trauma, including major surgery, stimulated the release of proinflammatory cytokines and disrupted the regulation of tissue factor and thrombin, leading to a prothrombotic state (40). Evidence suggested that patients hospitalized in septic states faced a higher risk of VET (41). Consequently, the surgical trauma, along with the postoperative infectious state and septic predisposition, promoted the development of VET.

According to the International Society of Aesthetic Plastic Surgery Global Survey Result, liposuction was the most common surgical procedure in 2023 as in 2022, with more than 2.2 million (https://www.isaps.org/discover/about-isaps/global-statistics/reports-and-press-releases/global-survey-2023-full-report-and-press-releases/, accessed on July 29, 2024). A systematic review investigating the safety of large-volume liposuction revealed that the incidence of pulmonary embolism ranks second only to blood loss requiring transfusion among major surgical complications (42). Moreover, pulmonary thromboembolism is the most frequent major complication that can lead to death in patients undergoing liposuction (43). Therefore, it is imperative for plastic surgeons to thoroughly assess each MD patient's risk factors for deep vein thrombosis and formulate a comprehensive preventive strategy before performing liposuction. Instances of postoperative hypercoagulability leading to thromboses in patients with MD are relatively infrequent. A recent study documented a MD patient displayed thromboses in the local intermuscular veins of the bilateral calf and the left posterior tibial vein, along with multiple thromboembolisms in pulmonary arteries following the second cervical surgery (44). In another case, a patient manifested painful pressure-induced swelling and stasis dermatitis in the left calf initially presumed to signify deep vein thrombosis. However, substantial fatty infiltrative anomalies were discerned in his left calf and bilateral thighs through CTA. Consequently, this patient was finally diagnosed with MD, along with adipose tissue accumulation leading to deep venous compression (45). Hence, vigilance is essential to discern thrombosis or embolism symptom following MD surgery, with CT or MRI serving as pivotal tools for differential diagnosis. Preventive measures in accordance with anticoagulation standards must be diligently adhered to. First, the preoperative evaluation should comprehensively assess coagulation status and thrombotic risk, wherein coagulation indicators like D-dimer and imaging modalities like lower extremity venous ultrasonography should be promptly addressed. Second, vigilant monitoring of vital signs, localized status of lower limbs, pulmonary indications, as well as fluid balance variations is imperative. Third, patients should be educated to minimize bedridden periods, engage in timely mobilization, and consider the use of elastic stockings. Last, establishing a multidisciplinary collaborative approach involving hematology, interventional medicine, and other pertinent departments, and adjusting anticoagulation strategies tailored to the individual patient's evolving condition is suggested.

4 Conclusion

In this study, we present a case of type II MD featuring bilateral thighs adipose tissue accumulation. The patient exhibited unexplained priapism alongside multiple venous thromboses after the liposuction surgery. The infrequent manifestation of postoperative hypercoagulability in MD patients merits broad attention, owing to the potentiality for extensive venous thromboses and subsequent pulmonary embolism or cerebral infarction. Comprehensive assessment of coagulation risk assumes paramount significance in enhancing the prognosis of MD patients, with coagulation indicator surveillance and recurrent venous ultrasonography serving as pivotal tools for risk appraisal. Vigilant postoperative monitoring of vital signs, localized status of lower limbs, pulmonary indications, and fluid balance alterations, as well as proactive guidance to encourage early mobilization and the utilization of elastic stockings, holds substantial preventive value. Finally, the direct correlation between MD and the observed priapism or hypercoagulability necessitates further observation. Future studies describing relevant clinical cases for expanded comprehension are necessary.

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 on Biomedical Research, West China Hospital of Sichuan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LG: Data curation, Investigation, Writing – original draft. WL: Conceptualization, Methodology, Writing – original draft. XX: Writing – review & editing. HX: Data curation, Funding acquisition, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by the Science and Technology Support Program of Sichuan Province (Grant No. 2022YFS0131).

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 02 September 2024
DOI 10.3389/fcvm.2024.1456360

OPEN ACCESS

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RECEIVED 28 June 2024
ACCEPTED 13 August 2024
PUBLISHED 02 September 2024

CITATION
Liu M, Liu J, Chen S, Gao X, Zhong J, Sun L, Li F and Li C (2024) Case Report: Ectopic pulmonary embolism as a complication of bronchial artery embolization.
Front. Cardiovasc. Med. 11:1456360.
doi: 10.3389/fcvm.2024.1456360

Case Report: Ectopic pulmonary embolism as a complication of bronchial artery embolization

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Bronchial artery embolization (BAE) is currently the first-line treatment for massive hemoptysis. Previous studies have proven its safety and efficacy, with mild, transient, and reversible complications. This case described a patient with congenital multiple bronchopulmonary fistulas who underwent BAE due to massive hemoptysis. However, due to an overlooked and misdiagnosed atypical fistula, the patient experienced an ectopic pulmonary embolism and subsequently secondary pulmonary infarction. He eventually exhibited a full postoperative recovery following percutaneous catheter-directed embolectomy. This case revealed a type of occult fistula masked by multiple bronchial artery branches, which may be a potential risk factor for an ectopic pulmonary embolism during BAE. We propose that it is crucial to identify abnormal anastomosis, especially atypical fistula, and select appropriate embolization materials during BAE.

KEYWORDS

case report, hemoptysis, bronchial artery embolization, atypical bronchopulmonary fistula, ectopic pulmonary embolization

Introduction

Bronchial artery embolization (BAE) is the primary treatment for recurrent hemoptysis unresponsive to drug therapy, particularly in patients with progressive hemoptysis (1, 2). Despite its safety and efficacy, BAE carries an inherent risk of complications. For example, ectopic embolism is one of the rare and serious complications that arise as a result of vascular malformations of the pulmonary and bronchial arteries, such as fistulas. These include bronchial artery-pulmonary artery fistula, bronchial artery-pulmonary venous fistula, pulmonary arterio-venous fistula, and other abnormal communications between systematic artery and pulmonary vessels, which can be further divided into congenital and acquired fistula (3–6).

Herein, we report a patient with multiple congenital bronchopulmonary artery fistulas complicated by an ectopic pulmonary embolism during BAE. In this case, a type of occult fistula masked by multiple bronchial artery branches was described. It confirmed that materials injected into the bronchial circulation could indeed reach the pulmonary circulation during BAE.

Case presentation

A 59-year-old man was admitted due to acute hemoptysis, with an estimated blood loss of 100–200 ml/day. The patient had a history of hypertension for more than 5 years and was treated with amlodipine (5 mg once daily). He had no prior chronic lung disease and was a non-smoker, without alcohol consumption, illicit drug use, and any home or occupational exposures. On admission, a physical examination revealed a body temperature of 36.4°C, blood pressure of 135/80 mmHg, heart rate of 80 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 93% on room air. A chest CT scan showed scattered ground-glass opacities in the right middle lobe. His coagulation profile, renal function, and liver function were within normal limits. Initial treatment with Hemocoagulase Bothrops Atrox (2U intravenously twice daily) and vitamin K1 (10 mg intravenous drip once daily) was administered without yielding satisfactory effects. Subsequently, emergency BAE was performed due to sudden massive hemoptysis.

Bronchial angiography identified multiple anastomoses between the hypertrophic bronchial arteries and the right subsegmental pulmonary artery (Figure 1), without filling defects in the pulmonary artery, as confirmed by pulmonary angiography (Figure 2A). Two typical fistulas, originating from the right bronchial artery (Figure 1A) and the subclavian artery (Figure 1B), were identified and successfully embolized with coils (Figures 1D,E). Another atypical fistula, arising from the aortic arch, between the right bronchial artery and the pulmonary artery was initially misdiagnosed due to tortuosity, dilation, and hyperplasia at the vessel end (Figure 1C). Therefore, 500–700 μm polyvinyl alcohol (PVA) particles were used to embolize the terminal branches of the aberrant bronchial artery. However, during the procedure, it was noted that some embolic particles seemed to disappear, resulting in an ineffective embolization of the target vessels. Coils were subsequently used to embolize the culprit bronchial arteries (Figure 1F). Considering the possibility of an ectopic embolism due to particle translocation, selective pulmonary angiography confirmed filling defects in the right lower lobe (Figure 2B). Given the non-thrombotic embolism and the potential risk for recurrence of hemoptysis, anticoagulation and antiplatelet therapies were not prescribed. In addition, the patient had no special discomfort and declined attempts to remove the particles via endovascular intervention. He was discharged with alleviated hemoptysis 3 days later.

However, 2 weeks later, the patient was readmitted to the emergency department due to recurrent hemoptysis. Ultrasonography demonstrated no deep vein thrombosis. Computed tomography pulmonary angiography revealed a pulmonary embolism accompanied by secondary pulmonary infarction. He was administered therapeutic low-molecular-weight heparin and subsequently underwent a percutaneous catheter-directed embolectomy. Postoperative pulmonary angiography

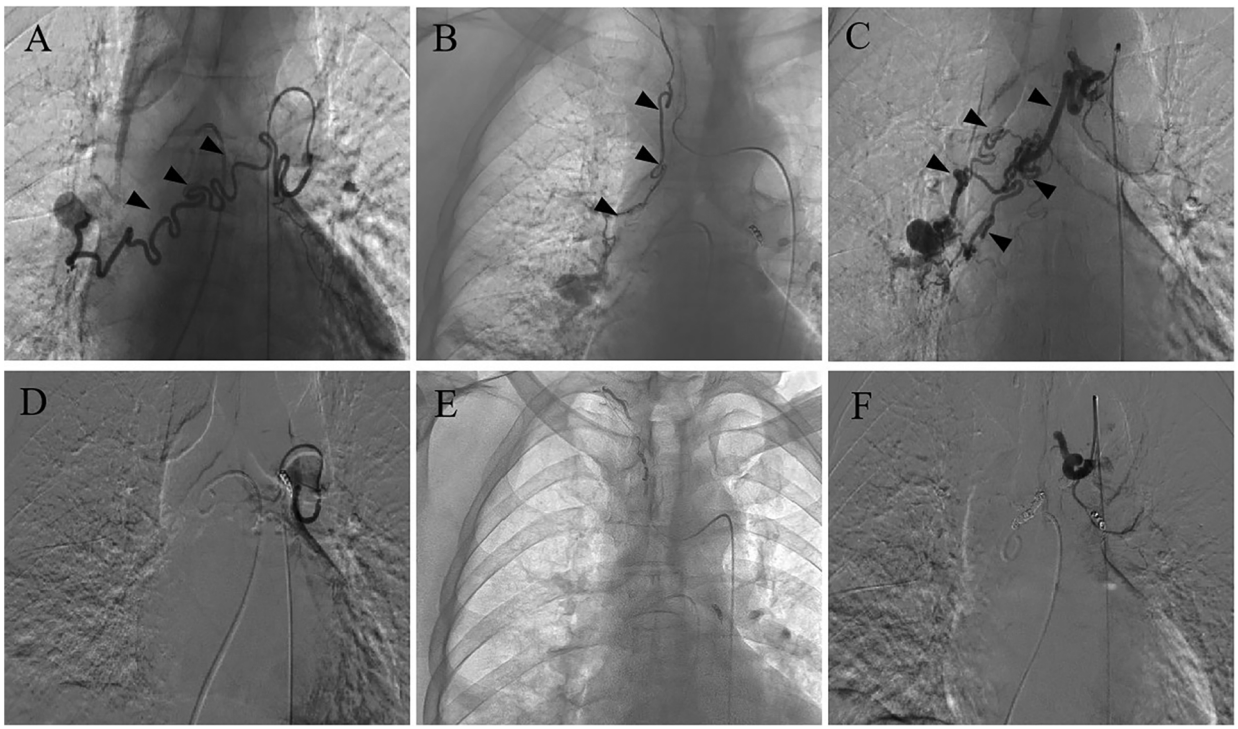

FIGURE 1
Bronchial arteriography before and after BAE. **(A)** A fistula between the right bronchial artery and pulmonary artery. **(B)** A fistula between the subclavian artery and pulmonary artery. **(C)** An atypical fistula, originating from the arcus aortae, between the right bronchial artery and pulmonary artery, featuring multiple tortuous and dilated branches with distal vascular beds. **(D–F)** The coil successfully embolized the target vessel and the bronchial artery-pulmonary artery fistula was occluded after BAE.

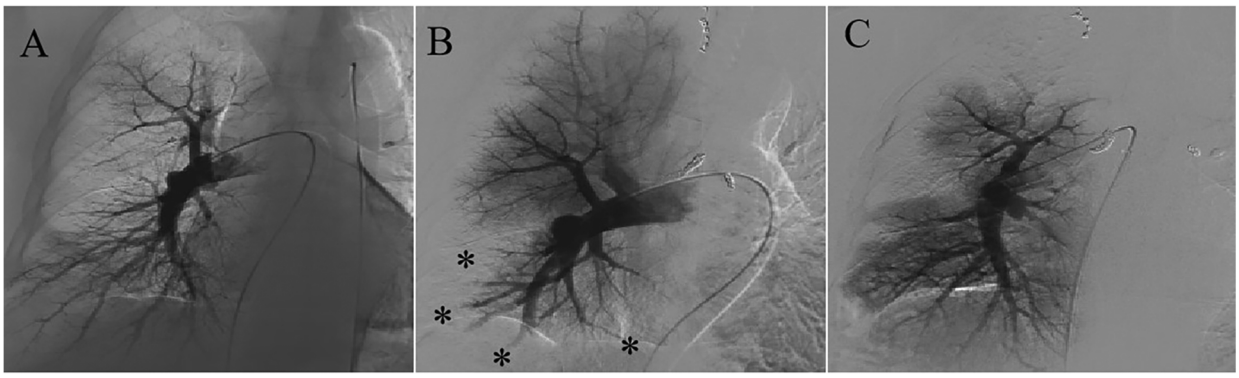

FIGURE 2
Pulmonary angiography before and after BAE. **(A)** There was no filling defect in the pulmonary artery before BAE. **(B)** Filling defects in the right subsegmental pulmonary artery after BAE were confirmed. **(C)** Restoration of pulmonary perfusion after percutaneous catheter-directed embolectomy.

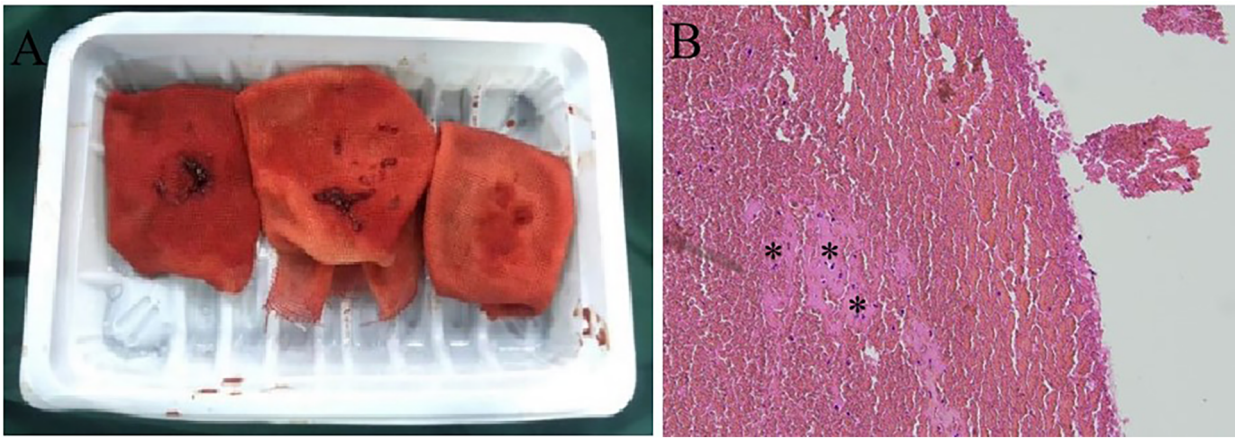

FIGURE 3
Percutaneous catheter-directed embolectomy. **(A)** The granular beaded material and thrombus mixture was aspirated in surgery. **(B)** Histological examination confirmed the presence of a mixed thrombus with scattered refractive, round-like, or patchy particles.

demonstrated restoration of pulmonary perfusion (Figure 2C). The granular beaded material and thrombus mixture was removed (Figure 3A). Histological examination confirmed a mixed thrombus with scattered refractive, round-like, or patchy particles (Figure 3B). It was thought to be *in situ* thrombosis in the pulmonary artery secondary to translocated particles during the interventional procedure. The following day, hemoptysis was stopped with remarkable relief of his dyspnea. He was discharged and switched to oral rivaroxaban for 3 months without thrombotic recurrence. There were no recurrences of episodic dyspnea or hemoptysis during the 12-month follow-up.

Discussion

We report a case of ectopic pulmonary embolism following BAE. To the best of our knowledge, this is the first report that a particulate embolic agent caused an ectopic pulmonary embolism and secondary pulmonary infarction during the procedure. According to the literature, the overall complication rate of BAE is 13.4%, including 0.2% with major complications (7). Improper technique has resulted in complications such as hematoma at the puncture site, pseudoaneurysm, stress hypertension, bronchial artery, or aortic dissection (8). Post-embolization syndrome includes fever, chest tightness, chest pain, cough, dysphagia, and hiccups (9). Rare complications encompass tracheal fistula, broncho-esophageal fistula, diaphragmatic paralysis, myocardial infarction, micro-infarctions in renal and splenic tissues, ischemic bowel disease, systemic infarctions, and localized skin necrosis (10–15). Notably, neurological complications are one of the most severe complications of BAE (16, 17). These complications manifest as transient dysfunctions or irreversible impairments (18, 19).

Post-embolization syndrome is one of the most common complications. This may stem from local irritation due to the

embolic material and ischemic tissue injury from the embolization of the target vessel. One of the most severe complications of BAE is an ectopic embolism due to non-targeted embolization. Inadequate hyperselective embolization, challenges in super-selection, or suboptimal angiography can result in misembolization. Backflow of embolic material and plaque shedding from the vascular wall may also lead to an ectopic embolism. In addition, anastomosis, especially fistula between the bronchial arteries and other vessels, is the most common cause of ectopic embolization. Embolic agents could pass through anastomotic branches into the pulmonary or systemic circulation, resulting in a pulmonary embolism or even multiple organ micro-infarctions (20, 21). In our case, we revealed two typical bronchopulmonary artery fistulas and successfully embolized these with coils. Another atypical fistula, featuring multiple tortuous and dilated branches, was overlooked and misdiagnosed. An ectopic pulmonary embolism still occurred despite PVA particles with a diameter of 500–700 μm being used. As there were no prior pulmonary diseases, this case is considered a congenital bronchopulmonary artery fistula. Compared to the secondary compensatory collateral circulation, this fistula had a wider diameter, facilitating the passage of embolic particles. This case indicates that it is crucial to identify pulmonary vessel fistulas during BAE. An occult fistula masked by multiple tortuous and dilated bronchial arterial branches may be a potential risk factor for an ectopic pulmonary embolism during BAE. Physicians should be alert to the formation of fistulas during the operation. Digital subtraction angiography (DSA) is the gold standard for the diagnosis of fistulas. In suspected cases, targeted multi-angle angiography is necessary to identify these occult atypical fistulas.

Normal communication exists between the systemic and pulmonary circulations. Over 70 years ago, studies reported that substances injected into the bronchial circulation could reach the pulmonary circulation in lobectomy specimens from patients with bronchiectasis (22). Robbins et al. described a patient with chronic thromboembolic pulmonary disease who underwent BAE for hemoptysis (20). Eventually, a large amount of material composed of a thrombus and eosinophilic microspheres was found in the tissues dissected by endarterectomy. As no anastomoses between the bronchial arteries and other vessels were observed during surgery, almost all the mechanisms of ectopic embolism after BAE were suspected. In this instance, particles were found to have been translocated into the pulmonary artery via a congenital bronchopulmonary artery fistula, causing *in situ* thrombosis and pulmonary infarction, through imaging and pathological examination. This case corroborates previous studies, demonstrating that materials injected into the bronchial circulation could indeed reach the pulmonary circulation.

Currently, there are no evidence-based guidelines for treating complications following BAE. Most symptoms are transient and reversible, resolving themselves with symptomatic treatment. Although this patient experienced no immediate notable discomfort, he eventually required percutaneous pulmonary thrombectomy due to the ectopic pulmonary embolism resulting in secondary pulmonary infarction. Given the limited experience of this complication, the optimal treatment strategy remains unclear. This case demonstrates that vascular intervention may be necessary for patients with a severe ectopic pulmonary embolism. Further research is essential to develop strategies for preventing and managing this potentially severe complication.

In conclusion, embolization materials injected into the bronchial circulation were vulnerable to translocating into the pulmonary artery. It is crucial to identify abnormal communications, particularly occult atypical fistulas, between the bronchial and pulmonary circulations to prevent ectopic pulmonary embolization during BAE. Although most postoperative complications of BAE are minor, vigilance is still essential due to the potential risk of serious complications.

Data availability statement

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

Ethics statement

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

ML: Data curation, Writing – original draft, Writing – review & editing. JL: Data curation, Investigation, Supervision, Writing – original draft, Writing – review & editing. SC: Data curation, Formal Analysis, Writing – review & editing. XG: Data curation, Funding acquisition, Writing – original draft. JZ: Data curation, Formal Analysis, Writing – original draft. LS: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. FL: Formal Analysis, Project administration, Supervision, Validation, Visualization, Writing – review & editing. CL: Conceptualization, Formal Analysis, Project administration, Supervision, Visualization, Writing – review & editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Wuhan Medical Research Project (WX20D85) and China Postdoctoral Science Foundation (2023TQ0383).

Conflict of interest

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

Publisher's note

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TYPE Case Report
PUBLISHED 10 September 2024
DOI 10.3389/fcvm.2024.1433847

OPEN ACCESS

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RECEIVED 16 May 2024
ACCEPTED 19 August 2024
PUBLISHED 10 September 2024

CITATION
Wang Y, Rong C, Lu M and Zhang W (2024) Pulmonary artery *in situ* thrombosis due to patent ductus arteriosus: a case report. Front. Cardiovasc. Med. 11:1433847. doi: 10.3389/fcvm.2024.1433847

Pulmonary artery *in situ* thrombosis due to patent ductus arteriosus: a case report

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Background: Pulmonary Artery *in situ* Thrombosis (PAIST) refers to a thrombus forming within the pulmonary arterial system, distinct from an embolus originating from elsewhere in the body (e.g., the deep veins of the lower extremities) and traveling to the lungs where it lodges and forms.
Case presentation: We present a case of PAIST caused by the arterial ductus arteriosus. The patient primarily presented with dyspnea, and the chest pain dichotomy Computed Tomography Angiography(CTA) suggested that a nodular low-density filling defect was seen in the lumen of the left pulmonary artery trunk. Initially, pulmonary embolism (PE) was suspected. However, upon reevaluation of the imaging, it became apparent that the patient's pulmonary artery obstruction was closely associated with the ductus arteriosus. After admission, the patient was treated with sodium ampicillin (2.0 g Q12H) for infection, heparin sodium (5,000 IU Q12H) for anticoagulation, and metoprolol succinate extended-release tablets (23.75 mg QD) to correct cardiac remodeling, among other treatments. Subsequently, the patient underwent a cardiac surgery involving the ligation of the arterial duct, resection of pulmonary artery lesions, and open-heart surgery with extracorporeal circulation support. Postoperative examination of the pulmonary artery mass indicated coagulation tissue. The final diagnosis was "PAIST".
Conclusion: Both PAIST and PE manifest as low-density filling defects in the pulmonary arteries. However, due to the relative unfamiliarity with PAIST, such findings are often initially attributed to PE.

KEYWORDS

pulmonary artery *in situ* thrombosis, congenital heart disease, patent ductus arteriosus (PDA), pulmonary embolism, PAIST

1 Background

PAIST typically arises amidst pathophysiologic lung changes, featuring thrombosis within the pulmonary arterial system. This condition often presents with thrombus propagation from the peripheral to the central pulmonary arteries, inducing hemodynamic alterations within the lungs. Consequently, patients may experience symptoms like dyspnea and chest pain, albeit right heart insufficiency is a rare occurrence (1, 2). Various factors, including structural lung changes, infections, trauma, and sickle cell disease, can precipitate focal inflammation and dysfunction of the pulmonary vascular endothelium, thereby fostering the development of PAIST. The precise mechanism underlying its formation remains elusive and may entail pulmonary artery endothelial cell damage, heightened blood viscosity, augmented blood flow, and inflammation (1, 2). A study on a clinical translational model of blunt chest trauma first demonstrated the occurrence of *de novo* pulmonary thrombosis, further supporting the formation of *in situ* pulmonary artery thrombi following severe trauma (3).

Literature reports suggest that PAIST seems more likely to occur in patients with acute chest syndrome (ACS) who have elevated platelet counts and lower hemolysis rates (4). PAIST is relatively rare, and the exact incidence is unknown, However, there is growing evidence in the literature suggesting that the incidence of PAIST may have been underestimated, particularly in recent years, as seen in case review studies of COVID-19 patients with concurrent PE, Literature reports indicate that pulmonary artery thrombosis in COVID-19 is an immune-mediated inflammatory thrombosis, with an incidence of pulmonary artery thrombosis/embolism of 36% among COVID-19 patients (5–8). Knudson et al. recently reviewed injury data from 888,652 trauma patients in the National Trauma Data Bank (NTDB) and reported a significant increase in the incidence of PE, while the incidence of deep vein thrombosis (DVT) did not increase (9). Currently, there is no diagnostic gold standard for PAIST, and the absence of specific imaging or pathological manifestations to determine the etiology of thrombosis makes it primarily a diagnosis of exclusion. Imaging tests, however, can be relied upon to aid in the diagnosis (1), such as Computed tomography pulmonary angiography right (CTPA) or Magnetic resonance imaging (MRI).PAIST has a better prognosis and is treated similarly to PE with therapeutic measures such as anticoagulation, thrombolysis, and surgery (1, 2). A retrospective study involving 23 patients with PAT indicated that thrombolysis of *in situ* pulmonary artery thrombi occurs more slowly compared to pulmonary embolism (10). In this paper, we report a case of PAIST suspected to be PE and review the relevant literature.

2 Case presentation

The patient, a 59-year-old male, was admitted to the hospital due to "sudden dyspnea persisting for more than half a day". He experienced a sudden onset of dyspnea without accompanying chest pain, cough, fever, or other discomforts. He had (6–8) previously been in good health. Physical examination on admission revealed the body temperature was 36.5°C, the pulse rate was 99 beats per minute, the breathing rate was 20 beats per minute, blood pressure was 151/100 mmHg (1 mmHg = 0.133 kPa), his spirit was clear and the speech is clear, there was no cyanosis of the lips or mouth, and there was no filling of the jugular veins. Breath sounds were coarse in both lungs, and no dry or wet rales were heard. The apical beat was located between the 5th intercostal space and 0.5 cm outside the left midclavicular line, the cardiac border was enlarged, and a continuous mechanical murmur could be heard in the second intercostal space at the left edge of the sternum, but no murmur was heard in the rest of the heart.

Auxiliary tests: blood gas analysis: pH: 7.41, pCO2: 28 mmHg, pO2: 112 mmHg, SO2 98%, D-dimer: 1,640.39 ng/ml, N-terminal cerebral natriuretic peptide precursor: 361.31 pg/ml; leukocytes: 16.02 × 10^9/L, neutrophil percentage 94%, ultrasensitive C-reactive protein 29.22 mg/L, calcitonin 1.31 ng/ml, creatinine: 208.0 umol/L; Electrocardiogram (ECG): sinus rhythm Abnormal EKG I, avl, V1\R\V6 leads T-wave is low and inverted. Cardiac ultrasound (Figure 1): EF 59%, the patient's arterial duct is not fully closed and there is a left-to-right blood shunt with a maximum velocity of the shunt of approximately 440 cm/s. There is a 21 × 14 mm bulge in the left pulmonary artery. Enlarged left atrium (39 mm anteroposterior diameter), hypodiastolic left ventricle. The right atrium and right ventricle had no abnormalities and mild mitral regurgitation. CTA of chest pain diathesis (Figure 2): nodular low-density filling defects are seen in the lumen of the left pulmonary arterial trunk in close relation to the ductus arteriosus. The left pulmonary artery trunk is altered, and PE is considered a high possibility. Lower extremity venous ultrasound: right calf intermuscular vein thrombosis (acute phase.)

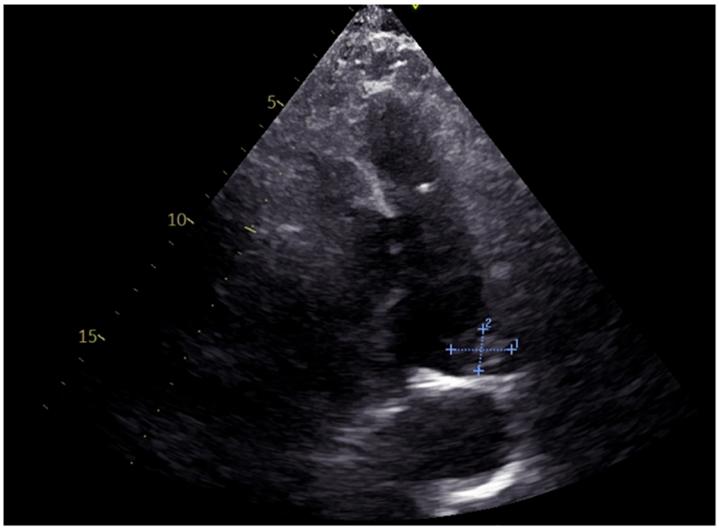

FIGURE 1
ECG: abnormal echoes of the left pulmonary artery, to be excluded superfluous (21 × 14 mm)?

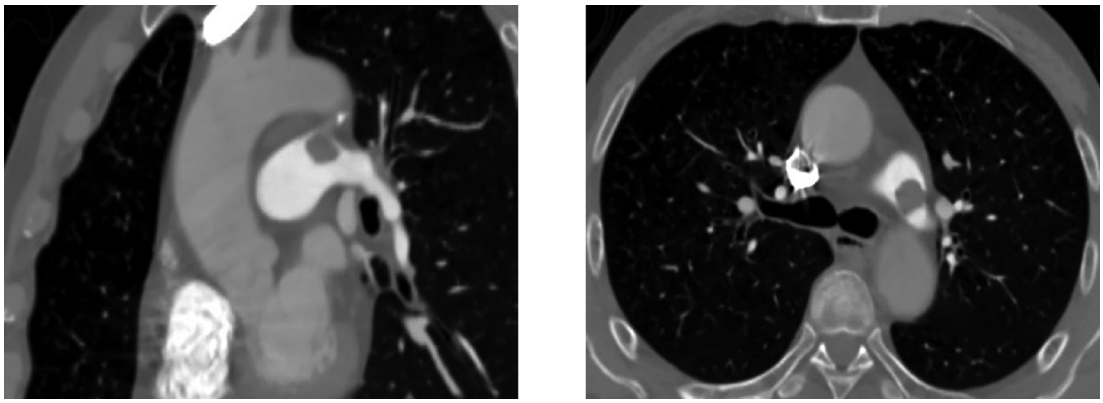

FIGURE 2
CTA of chest pain diathesis: nodular low-density filling defect in the left pulmonary artery trunk in relation to the ductus arteriosus.

PET-CT (Figure 3) suggests: no abnormal hypermetabolic foci in the pulmonary artery tract. Blood culture (anaerobic and aerobic): human staphylococcus. Admission diagnosis: pulmonary artery occupational lesion to be investigated. After admission, the patient was treated with sodium ampicillin (2.0 g Q12H) for infection, heparin sodium (5,000 IU Q12H) for anticoagulation, and metoprolol succinate extended-release tablets (23.75 mg QD) to correct cardiac remodeling, among other treatments, and his condition was relieved. Later, to further clarify the diagnosis, on the 9th day after admission, the patient underwent cardiac surgery with pulmonary artery ligation and pulmonary artery resection and extracorporeal circulation-assisted open cardiac surgery, and the pulmonary artery organisms were sent to the pathology after the surgery, which suggested normal blood clots. After 16 days of hospitalization, the patient was discharged from the hospital after his condition improved. Upon discharge, the patient was prescribed rivaroxaban 10 mg daily and digoxin 0.25 mg daily. During telephone follow-ups one week and two weeks after discharge, the patient reported a significant relief of dyspnea. Twenty days later, during an outpatient follow-up, a cardiac ultrasound: EF 65%, after arterial catheter ligation, after resection of pulmonary valve redundancy, with mild tricuspid regurgitation. Regular follow-up of patients in outpatient clinics. Reviewing the patient's medical history again, the patient did not have chest pain, fever and other discomforts, cardiac ultrasound suggested arterial duct failure, chest pain dichotomy CTA showed that the nodular low-density filling defect in the trunk of the left pulmonary artery was closely related to the ductus arteriosus, and PET-CT did not show show significant hypermetabolism of the pulmonary arteries. The pulmonary artery occupying lesion was considered to be a PAIST formation due to arterial ductus arteriosus, endothelial injury due to sustained high flow and pressure at the main pulmonary artery junction, and increased vascular shear.

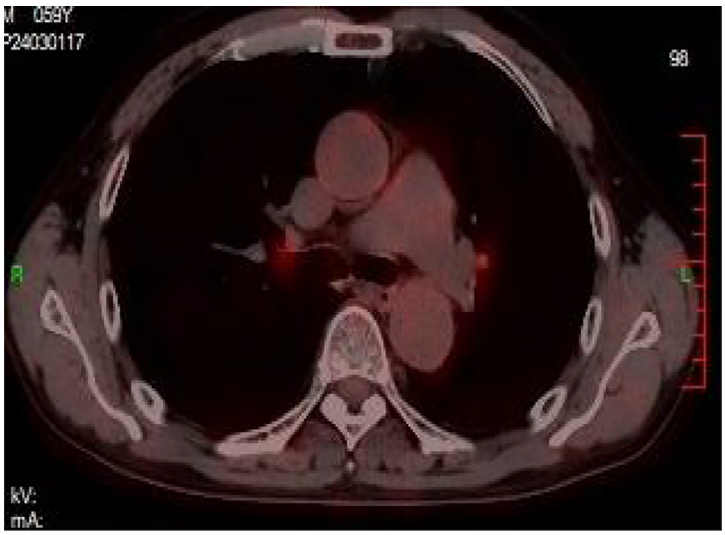

FIGURE 3
PET-CT: No abnormal hypermetabolic foci were seen in the pulmonary artery tract.

3 Discussion

PAIST refers to pulmonary arterial system *ab initio* thrombosis, meaning pulmonary artery (PA) occlusion occurs independently of peripheral thrombosis (1, 2, 11, 12). Hence, a case of isolated PE without deep vein thrombosis (DVT) is likely indicative of PAIST (1). However, the presence of peripheral thrombus does not rule out PAIST, as demonstrated in this case of PAIST with acute thrombosis of the deep veins in the right lower extremity.The specific etiology and pathogenesis of PAIST formation is unknown (2), and it has been reported that lung injury, infection, trauma, congenital heart disease, pulmonary hypertension(PH), radiotherapy, white stuffing syndrome, platelet activation, cytokine-mediated immunopathological response, and intravascular hemolysis can lead to the formation of PAIST (1, 2, 11–15), meanwhile, the thrombotic potential of Covid-19 has been recognized (8, 14, 15). PAIST originates in a hypoxic and inflammatory environment, leading to pulmonary vascular endothelial cell dysfunction in response to various factors such as disease, injury, and medications. This dysfunction results in an imbalance between thrombosis and fibrinolysis (1, 2). Endothelial dysfunction and platelet activation are key mechanisms involved in *in situ* thrombosis (13), along with age-dependent factors and neutrophil involvement (12, 16). In this case, the patient was a middle-aged male with a history of congenital heart disease in which arterial ductus arteriosus caused sustained high flow and pressure at the main pulmonary artery junction, and finally pulmonary artery endothelial cell damage, which impaired the antithrombotic function of the arterial wall by down-regulating the endothelial nitric oxide synthase (eNOS) or stimulating the expression of the adhesion receptor (8, 13), and, thus, formation of an *in situ* thrombus at the junction out of the main pulmonary artery.

The clinical manifestations of PAIST are nonspecific and similar to those of PE (Table 1), which may manifest as dyspnea, chest tightness, chest pain, palpitations, fever, hemoptysis, and other symptoms, and are less likely to cause right heart dysfunction, whereas PE often has right atrial and right ventricular changes, but it remains difficult to differentiate between the two in terms of symptoms (1–3). In this case, the patient presented with dyspnea, but without any right atrial or right ventricular changes or pulmonary hypertension (PH), which provides little support for the diagnosis of PAIST.

PAIST is a rare condition that lacks specific diagnostic criteria and imaging manifestations, often leading to misdiagnosis as PE (1). However, understanding its pathophysiological features and utilizing appropriate imaging techniques can aid in accurate diagnosis (1). In PE, the distribution of emboli is typically multiple rather than single, and they are commonly found in the lower lobes of the lungs rather than the upper lobes. In contrast, PAIST tends to manifest as a single lesion, frequently occurring at the site of an anomaly or lesion in the pulmonary artery (5, 10). The imaging manifestations of PAIST typically present in peripheral arteries as non-occlusive and eccentric lesions, often at an obtuse angle to the vessel wall and without vasodilation. In contrast, pulmonary embolism (PE) commonly exhibits centrally located emboli (proximal to segmental branches), frequently occlusive, with vasodilation, and at an acute angle to the vessel wall (4, 11, 17, 18). Solated pulmonary embolism: imaging often shows pulmonary artery obstruction. PAIST: may not have obvious features of acute obstruction, imaging may show that the thrombus *in situ* is more tightly bound to the wall of the pulmonary artery, and the morphology and density features may vary. Thrombosed pulmonary arteries are often located in lung tissue with underlying pathology, such as inflammation or tumour, and tend to be located in the distal branches, usually not involving the main trunk of the pulmonary artery. Alternatively, as in this case, the thrombus may form near the pulmonary artery connected to the ductus arteriosus (1, 10–13). In this case, the patient's imaging revealed a single filling defect in the left pulmonary artery trunk, located near the arterial conduit, with an unobstructed distal artery. Additionally, the lung parenchymal lesion was adjacent to the artery. Consequently, despite the presence of lower-extremity venous thrombosis, we attributed the low-density filling defect in the pulmonary artery to PAIST formation.

PAIST has received limited study, and its treatment parallels that of PE, including therapeutic options like anticoagulation, thrombolysis, and surgery. Hemoptysis is one of the most frequent complications associated with PAIST (1, 2, 11). It has also been reported that the treatment of *in situ* PAT may depend on the location of thrombosis in the pulmonary arterial tree and aspects of the specific clinical situation (1, 13). Inhibition of platelet activity through antiplatelet agents decreases the likelihood of recurrent PA thrombotic events following discontinuation of anticoagulation

TABLE 1 Differential diagnosis of PAIST and PE.

	PAIST	PE
Symptomatic	Symptoms such as dyspnea, chest tightness, chest pain, palpitations, fever, hemoptysis, etc., less likely to cause right heart dysfunction	Dyspnea, chest tightness, chest pain, palpitations, fever, hemoptysis and other symptoms, often causing right heart dysfunction
Etiology	Lung injury, infection, trauma, congenital heart disease, etc.	peripheral thrombosis
Pathogenesis	Pulmonary artery endothelial cell damage, increased blood viscosity, increased blood flow velocity, inflammation and so on	Abnormal blood flow, vascular endothelial damage, or hypercoagulability of blood
Embolism characteristics	Mostly solitary lesions, often occurring at sites of pulmonary artery anomalies or lesions	Multiple more than single, located in the lower lobes of the lungs more than the upper lobes
Site of occurrence	Common in peripheral arteries, nonocclusive and eccentric, obtuse angle to vessel wall, no vasodilation	Often centrally located (i.e., proximal to segmental branches), mostly occlusive, with vasodilatation and at an acute angle to the vessel wall
Curing	Anticoagulation, thrombolysis and surgical, anti-inflammatory, anti-platelet aggregation	Anticoagulation, thrombolysis and surgery
Prognosis	Good prognosis, may progress to chronic thromboembolic pulmonary hypertension	Low-risk and low-intermediate-risk have a better prognosis, intermediate-high-risk and high-risk have a worse prognosis and can progress to chronic thromboembolic pulmonary hypertension

therapy (13). Inflammation is recognized as one of the causative mechanisms of *in situ* thrombosis, suggesting potential benefits for patients with *in situ* thrombosis from anti-inflammatory therapy (1). We should decide whether to go for anticoagulation only after considering the patient's symptoms, bleeding risk, and comorbidities (1, 11).

Our patient was previously in good health and had a low risk of bleeding, and was admitted to the hospital and treated with anti-infection and anticoagulation, and then underwent cardiac surgical operation of vein catheter ligation and resection of pulmonary artery lesion and extracorporeal circulation-assisted open heart surgery. Since the rate of thrombus regression in patients with PAIST is slower than that in patients with pulmonary embolism (10). The patient was then advised to continue taking oral anticoagulant rivaroxaban upon discharge from the hospital, with the decision for anticoagulation guided by the findings of outpatient follow-up visits. PAIST generally carries a favorable prognosis, but delayed diagnosis and treatment may lead to progression to chronic thromboembolic pulmonary hypertension (CTEPH) (13).

4 Conclusion

The clinical manifestations of PAIST lack specificity, and there is no definitive diagnostic gold standard. The incidence is often underestimated, and it is prone to misdiagnosis as PE (1, 2, 11–13). Hence, when encountering a solitary lesion within the pulmonary artery in clinical practice, differentiation from *in situ* thrombosis is necessary. In particular, the presence of underlying lesions of the pulmonary arteries, in this case thrombosis in the vicinity of the pulmonary artery connected to the ductus arteriosus, aided the diagnosis. Further research on PAIST is warranted to better understand its imaging characteristics, natural progression, and its significance in different disease contexts, ultimately informing treatment strategies and improving patient outcomes.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee of the First Hospital of Jilin University. The studies were conducted in accordance with the local legislation and institutional requirements. The 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: Validation, Writing – original draft, Writing – review & editing. CR: Data curation, Software, Writing – review & editing. ML: Conceptualization, Data curation, Writing – review & editing. WZ: Funding acquisition, Resources, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. Clinical Research Program of Jilin Province (2022LC092).

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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TYPE Case Report
PUBLISHED 11 October 2024
DOI 10.3389/fcvm.2024.1459579

OPEN ACCESS

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RECEIVED 04 July 2024
ACCEPTED 23 September 2024
PUBLISHED 11 October 2024

CITATION
Ding P, Zhou Y, Yang M, Li S, Zhang S and Zhi L (2024) Case Report: PROS1 (c.76+2_76+3del) pathogenic mutation causes pulmonary embolism.
Front. Cardiovasc. Med. 11:1459579.
doi: 10.3389/fcvm.2024.1459579

Case Report: PROS1 (c.76+2_76+3del) pathogenic mutation causes pulmonary embolism

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Background: Genetic variation plays an extremely important pathogenic role in the development of venous thromboembolism (VTE). Genetic protein S (PS) deficiency caused by PROS1 gene mutation is an important risk factor for hereditary thrombophilia.
Case introduction: In this case, we report a 28-year-old male patient who developed a severe pulmonary embolism during his visit. The patient had experienced one month of chest pains, coughing and hemoptysis symptoms. CTPA confirmed an acute pulmonary embolism with multiple filling defects in both pulmonary arteries. Ultrasound showed no thrombosis in the veins of both lower limbs. The patient's father and grandfather have a history of lower limb venous thrombosis. The patient was diagnosed with acute pulmonary embolism and pneumonia. The serum PS level significantly decreased (detection result: 10%, normal range: 77–143). Gene sequencing revealed a heterozygous missense mutation in PROS1 c.76+2_76+3del (base deletion), and further testing revealed that the genetic variation originated from his father. The patient was treated with heparin anticoagulant therapy, catheter thrombus aspiration, and catheter thrombolysis. After treatment, the patient's chest pain symptoms were relieved, and there were no symptoms such as difficulty breathing. On the 7th day of admission, the patient was transferred to a general hospital for further treatment.
Conclusion: Hereditary thrombophilia caused by mutations in the PROS1 (c.76+2_76+3del) gene is extremely rare. In clinical practice, heparin and rivaroxaban treatment are beneficial.

KEYWORDS

pulmonary embolism, PROS1, pathogenic mutation, protein S deficiency, case report

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of unexpected death in patients and poses a serious threat to patient safety. PE is a common and potentially life-threatening cardiovascular condition. Its detection is often challenging due to the non-specificity of the patient's symptoms and signs (1). Although the 30-day mortality rate following pulmonary embolism has decreased, approximately 20% of patients still die before or shortly after diagnosis, particularly those with hemodynamic instability (2). The risk factors for PE can be categorized into hereditary and acquired. Acquired factors include long-term immobilization, major surgery, trauma, and certain medications. Genetic risk factors include deficiencies in protein S (PS), protein C (PC), antithrombin III

deficiency, prothrombin gene mutations, and Leiden factor V (3). Hereditary PS deficiency is a rare autosomal dominant disorder caused by mutations in the PROS1 gene on chromosome 3, primarily presenting as venous thrombosis. Mutations in the PROS1 gene lead to alterations in the synthesis or function of PS. Based on differences in PS antigen levels and cofactor activity, PS deficiency can be classified into types I, II, and III. Studies have shown that individuals from families with mixed type I/III PS deficiency experience increased risks of hypercoagulable states and thrombosis in both type I and type III deficiencies. This indicates that both types (I and III) of PS deficiency impair anticoagulant function, thereby heightening the risk of venous thrombosis (4). Here we present a case of a young man hospitalized due to dyspnea and hypoxemia. Computerized Tomography Pulmonary Angiogram (CTPA) confirmed acute PE, and genetic sequencing identified a PROS1 missense mutation (c.76+2_76+3del).

Case presentation

A 28-year-old male patient, previously in good health, was admitted to the hospital due to a cough and chest pains. In August 2023, the patient developed a cough without any obvious cause, with bloody sputum. On September 8, 2023, he was admitted to a local hospital with a cough and right-sided chest pain. Blood tests revealed elevated D-dimer (5.79 mg/L, ↑) and whole blood C-reactive protein (48.28 mg/L, ↑). CTPA confirmed acute pulmonary embolism with multiple filling defects in both pulmonary arteries (Figure 1). He was subsequently diagnosed with acute pulmonary embolism and pneumonia after receiving alteplase (100 mg), morphine (10 mg), and cefmetazole (2 g every 8 h). Due to severe chest pain, breathing difficulties, and hypoxemia (SPO_2 around 85% at rest), the patient was referred to our intensive care unit (ICU) on September 14, 2023. The patient's father and grandfather have a family history of lower limb venous thrombosis. He is neither obese nor sedentary, and he has no history of smoking or alcohol consumption.

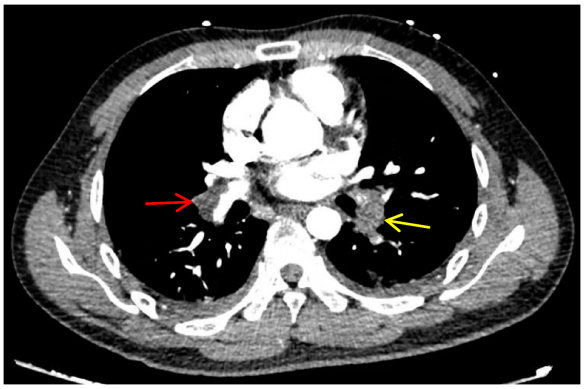

FIGURE 1
CTPA shows multiple pulmonary artery-filling defects in both lungs. The red arrow represents the main trunk of the right pulmonary artery, and the yellow arrow represents the lower left pulmonary artery.

After being transferred to the ICU, the patient received non-invasive ventilator-assisted breathing, using continuous positive airway pressure ventilation (pressure support: 10 cmH_2O, oxygen concentration: 30%–60%, positive end expiratory pressure: 5 cmH_2O), and intermittent high-flow oxygen inhalation (oxygen concentration: 30%–60%, airflow rate: 30–50 L/min). For anticoagulation heparin sodium was continuously infused at 750–1,250 units per hour, maintaining the activated partial thromboplastin time (APTT) at 60–80 s (normal range: 34–43). On September 15, 2023, the patient underwent pulmonary artery thrombus aspiration and thrombolytic therapy in the intervention room.

The surgical procedure was as follows. Following local anesthesia, the operator punctured the femoral vein and successfully inserted an 8 F sheath. A 0.035 mm diameter guidewire was used to introduce a 10 F long sheath into the pulmonary artery trunk. Angiography revealed filling defects in the right pulmonary artery trunk at the middle and lower lobe openings and in the distal branches. To address this, the operator repeatedly performed thrombus aspiration using a 10F thrombus aspiration catheter, whilst administering 100,000 units of urokinase as an adjunctive treatment. Follow-up angiography showed marked improvement in the filling defects of the right pulmonary artery trunk, with minimal residual defects and clear visualization of the distal branches. The procedure was completed successfully, and followed by sheath removal and effective compression for hemostasis.

After surgery, the patient continued to receive heparin sodium anticoagulant therapy, with regular monitoring of APTT, fibrinogen, and D-dimer levels (Figure 2). Testing for thrombotic disorders revealed a protein S level of 10% (normal range: 77–143 for males), while plasminogen (PLG), antithrombin III (AT-III), and protein C tests were negative.

Follow-up

By the 7th day of admission, the patient's condition had improved and he was transferred to a local hospital for further treatment. The patient was treated with rivaroxaban (20 mg orally, once daily). After 6 months, his condition remained stable, with no recurrence of bleeding or thrombosis.

Mutation site gene detection results and pathogenicity analysis

Whole exome sequencing was used to analyze the gene coding regions in this case. The average sequencing depth was above 90X, with 98% of sequences exceeding 20X coverage. Genetic testing showed a heterozygous mutation (c.76+2_76+3del) in the 76th intron of the PROS1 gene on chromosome 3. Further analysis confirmed that the genetic variant was inherited from the patient's father (Table 1 and Figure 3). No abnormalities were detected in other thrombosis-related genes, including Jak-2

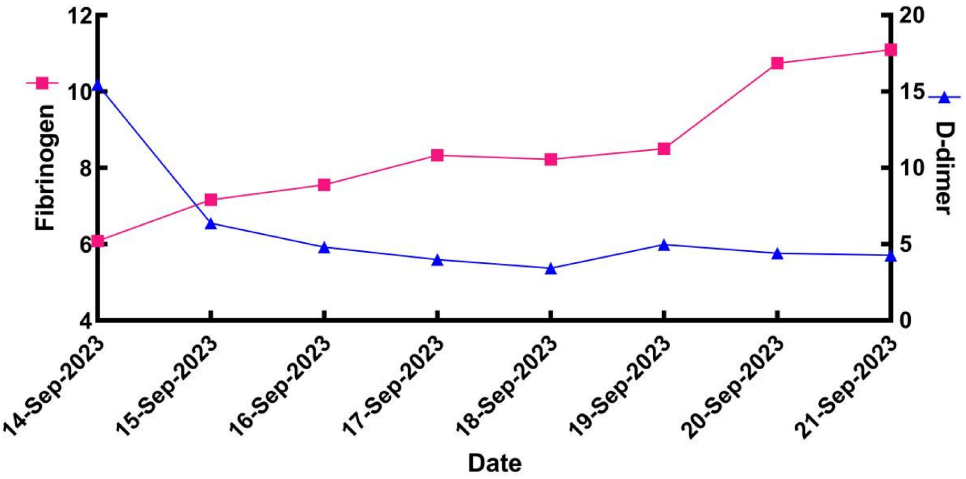

FIGURE 2
Fibrinogen and D-dimer levels of patients during ICU treatment.

TABLE 1 Results of sanger verification.

Verify the site information	Relation	Sample test number	Verification result
PROS1 chr3:93692515_93692516	Patient	NP25F15780	Loss of heterozygosity
Intron:1/14	Father	VP25D10449	Loss of heterozygosity
NM_000313.4: c.76+2_76 +3del	Mother	VP25D10448	Wild type

(myeloproliferative neoplasms), F2 (prothrombin G20210A), F5 (Factor V Leiden mutation), SERPINC1 (antithrombin III), and PROC (protein C). We used SpliceAI and Pangolin scores software (5) for pathogenicity prediction analysis, with a Donor Loss score of 0.98, indicating that the gene mutation is highly likely to cause it to lose its normal splicing function.

Discussion and literature review

This section discusses a case of PROS1 (c.76+2_76+3del) gene mutation causing PS deficiency, which led to pulmonary embolism. The patient was treated with catheter thrombolysis, heparin, and rivaroxaban, resulting in an improvement to the patient's condition.

The PROS1 gene encodes PS, a protein that plays a crucial role in the human coagulation system. Mutations or deletions in this gene can cause functional abnormalities in PS, increasing the risk of thrombosis and other coagulation disorders. A large cohort study involving 140,214 participants from the UK Biobank investigated the impact of pathogenic variants related to genetic hemostatic disorders. It found that mutations in SERPINC1, PROC, and PROS1 significantly increased the risk of deep vein thrombosis and pulmonary embolism (6). Mutations in the PROS1 gene can occur in either coding exons or non-coding introns. Xu Fei et al. (7) reported heterozygous mutations occurring in the exon region, including c.458_458delA (p.Lys153Serfs*6), c.1687C>T (p.Gln563stop), and c.200A>C (p.Glu67Ala). Earlier studies have shown that intronic mutations often lead to abnormal RNA splicing, which was a common cause of PS deficiency in the UK thrombophilia cohort (8). In addition, multiple studies have found that intronic mutations, such as c.346+5G>C, c.602-2delA, and c.260-1G>A, lead to abnormal PS levels (9–11). In a previous study, we reported a PROS1 gene exon mutation (12). In this case, a deletion mutation occurred at the second and third base pairs of intron 76 in the PROS1 gene, resulting in impaired PS synthesis and subsequent pulmonary embolism.

Protein S is a multifunctional protein involved in various physiological processes, such as hemostasis, inflammation, and other cellular mechanisms. During the hemostasis process, PS acts as a cofactor for activated protein C (APC)-mediated protein hydrolysis by binding to APC, which is essential for effective APC-dependent coagulation regulation. Additionally, PS functions as a cofactor in the tissue factor pathway inhibitor (TFPI) pathway, regulating the extrinsic coagulation pathways (13). PS deficiency is closely associated with deep vein thrombosis. Hereditary PS deficiency is a rare but significant autosomal dominant genetic disorder, with deep vein thrombosis and pulmonary embolism being the main clinical manifestations in heterozygous patients (14). In clinical practice, thrombophilia testing is recommended for patients with a family history of venous thromboembolism and/or thrombophilia, in addition to for those with unexplained recurrent deep vein thrombosis (15). One of the key diagnostic steps is assessing plasma PS levels and activity. Patients diagnosed with hereditary PS deficiency usually require long-term anticoagulation therapy to prevent clot formation.

Pulmonary embolism is the third leading cause of cardiovascular death worldwide, following a stroke or heart attack. Severe pulmonary embolism cases often require advanced life support in the ICU. ICU interventions focus on oxygen

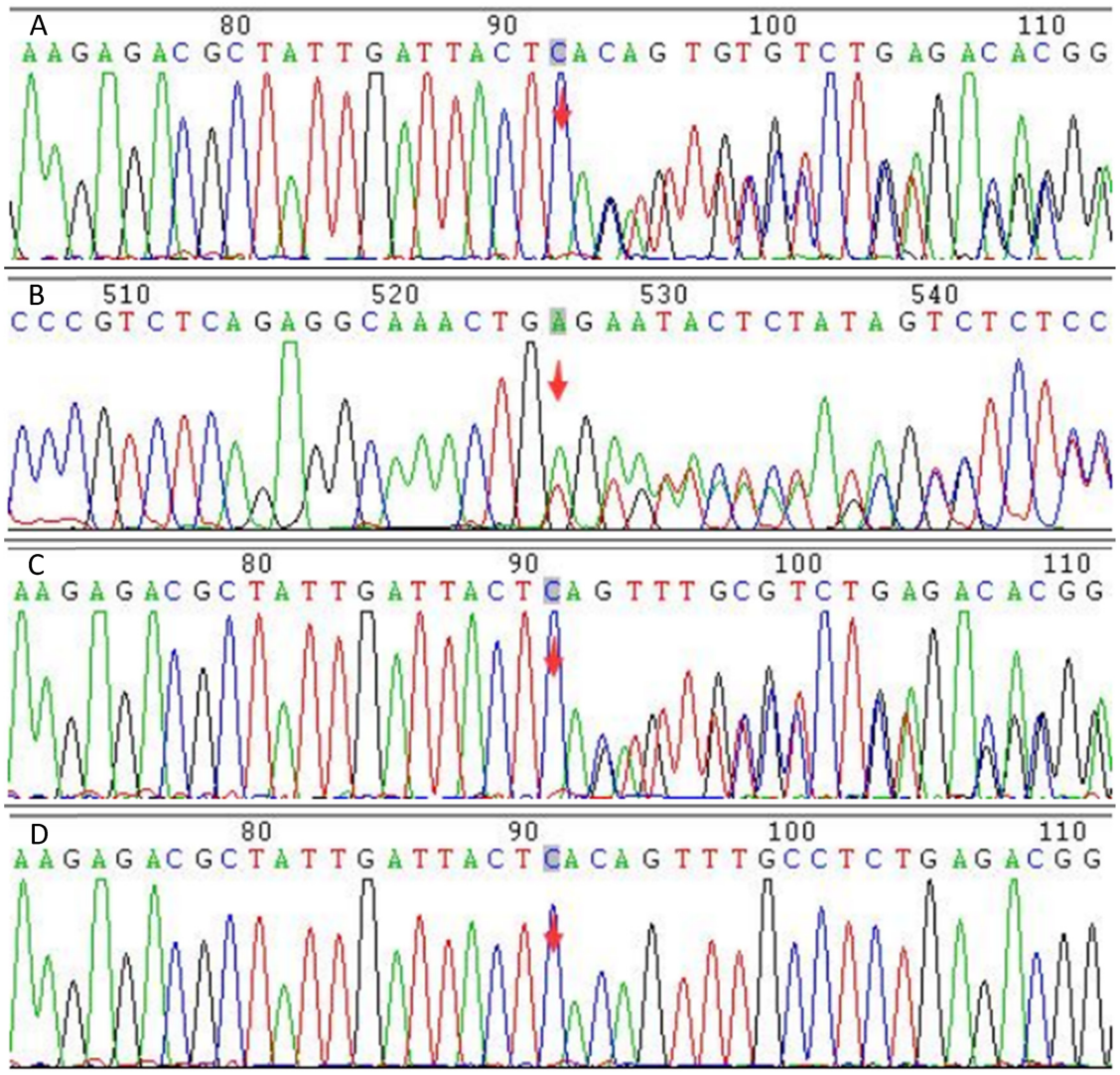

FIGURE 3
Figure 3 shows the Sanger sequencing results for the patient and their parents. (A) shows the forward sequencing of the patient's gene, (B) the reverse sequencing, (C) the forward sequencing of the father's gene, and (D) the forward sequencing of the mother's gene. The red arrow marks the mutation site. The sequence diagrams to the right of the arrow show a bimodal pattern in both the patient and the father, while the mother's sequence is unimodal. This indicates that the c.76+2_76+3del mutation, present in both the patient and the father, is a base deletion in the splicing donor region of the PROS1 gene. This mutation is predicted to cause mRNA splicing abnormalities.

delivery, fluid management, and catecholamine administration until pulmonary circulation is restored and right ventricular (RV) unloading is achieved (16). Anticoagulant and fibrinolytic therapies are crucial in managing thrombosis. Catheter-directed thrombolysis (CDT) has gained attention as an emerging technology. Studies have shown that CDT significantly reduces the right ventricular/left ventricular diameter ratio and lowers the incidence of adverse events or major bleeding in patients with moderate to high-risk acute PE (17). Compared with systemic fibrinolysis, CDT offers the potential advantage of enhancing thrombolysis through a synergistic effect of higher local fibrinolytic drug concentrations and mechanical thrombus disruption while minimizing the risk of major bleeding, especially intracranial hemorrhage (18). Following thrombolytic therapy, anticoagulation, and CDT, the patient's condition improved without any risk of bleeding.

Conclusion

Protein S deficiency caused by mutations in the PROS1 gene is the genetic basis for this patient's pulmonary embolism. Thrombolytic therapy rapidly restores blood flow by promoting clot dissolution, while anticoagulant therapy maintains patency by preventing the formation of new clots. As an emerging treatment, catheter-directed thrombolysis is particularly suitable for patients requiring thrombolysis who are at an increased risk of bleeding.

Data availability statement

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

Ethics statement

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

Author contributions

PD: Conceptualization, Writing – original draft. YZ: Data curation, Writing – original draft. MY: Data curation, Investigation, Writing – original draft. SL: Visualization, Writing – original draft. SZ: Writing – review & editing. LZ: Writing – review & editing.

Funding

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

Conflict of interest

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

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 13 January 2025
DOI 10.3389/fcvm.2024.1538728

OPEN ACCESS

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RECEIVED 03 December 2024
ACCEPTED 30 December 2024
PUBLISHED 13 January 2025

CITATION
Dong S, Peng Q, Lu K, Wei Q and Yang J (2025) Successful management of coagulation dysfunction in a patient with fulminant myocarditis: a case report.
Front. Cardiovasc. Med. 11:1538728.
doi: 10.3389/fcvm.2024.1538728

Successful management of coagulation dysfunction in a patient with fulminant myocarditis: a case report

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Fulminant myocarditis (FM) is an acute, diffuse inflammatory myocardial disease characterized by abrupt onset and extremely rapid progression. Patients typically exhibit haemodynamic abnormalities that may lead to respiratory failure, liver and renal failure, and subsequent coagulopathy. Collectively, these complications significantly increase the risk of early mortality. Currently, there is limited research on coagulation dysfunction associated with FM; therefore, achieving a rebalancing of the coagulation system is a challenge for successful treatment. We report a case of coagulation disorder secondary to FM, in which the patient recovered successfully and was discharged following comprehensive treatment and correction of coagulation function. By analyzing the etiology of this condition and emphasizing strategies for correcting coagulation disorders, we aim to provide valuable references for clinical diagnosis and management.

KEYWORDS

fulminant myocarditis, cardiogenic shock, acute liver injury, coagulation dysfunction, anticoagulation, case report

Introduction

Fulminant myocarditis (FM) is a specific form of inflammatory myocardial disease characterized by a complex pathogenesis involving the overactivation of cardiac innate immunity and the subsequent development of an inflammatory storm (1). The etiological factors contributing to this condition can be categorized into infectious and non-infectious agents, with viral infections identified as the predominant cause. Common viruses associated with myocarditis include enteroviruses, particularly coxsackievirus group B, as well as adenovirus, parvovirus B19, human herpesvirus 6, and COVID-19 (2, 3). Currently, the most extensively studied mechanism pertains to myocarditis induced by coxsackievirus B3 infection. The primary pathogenic mechanisms involve both direct viral damage to myocardial cells and immune-mediated damage, which ultimately lead to myocardial cell dysfunction and impaired contractility (4). As the disease progresses to FM, patients may experience severe hemodynamic instability, arrhythmias, respiratory failure, and other critical complications. Therefore, it is imperative that the patient's symptoms and clinical signs are meticulously evaluated and treated promptly. Notably, if the critical phase is successfully navigated, the long-term prognosis tends to improve. The cornerstone of managing FM includes the application of mechanical circulatory support devices to maintain hemodynamic stability and ensure adequate organ perfusion (1). Additionally, combined immune

support therapy, which involves administering appropriate doses of glucocorticoids and immunoglobulins, is essential for effectively modulating immune responses (5).

Clinically, viral myocarditis may present as acute heart failure, ventricular arrhythmias, or cardiogenic shock, and it is associated with significant morbidity and mortality (6). The hypoperfusion and venous congestion resulting from cardiogenic shock can lead to damage and dysfunction in multiple target organs, including the heart, lungs, kidneys, liver, intestines, and brain (7). Among these, liver dysfunction is a critical contributor to coagulation dysfunction, as the liver is responsible for synthesizing most coagulation factors. Impaired liver function disrupts the synthesis of these factors, resulting in an imbalance between procoagulant and anticoagulant mechanisms, which can precipitate either bleeding or thrombotic events (8). Moreover, severe liver dysfunction often results in thrombocytopenia, which can occur due to several mechanisms, including increased platelet destruction from hypersplenism, diminished hepatic synthesis of thrombopoietin, and an inadequate response from the bone marrow (9). This thrombocytopenia further increases the risk of bleeding complications.

Consequently, maintaining coagulation balance through appropriate anticoagulation and blood product supplementation poses a significant challenge and is a critical aspect of managing these patients. In this report, we present a case of cardiogenic shock and acute liver injury secondary to FM, which resulted in coagulation dysfunction. The patient was effectively treated following a comprehensive therapeutic approach.

Case presentation

A 51-year-old male patient presented to a local hospital for treatment after experiencing intermittent abdominal distension for over 10 days, accompanied by breathlessness and fatigue for the preceding 5 days. Upon hospitalization, the clinician diagnosed him with cholecystitis and initiated a course of anti-inflammatory and anti-infective therapy, which was administered for 5 days. Despite this intervention, the patient's symptoms worsened, manifesting as chest tightness, cough, dyspnea, lower limb edema, and orthopnea. As a result, the clinician expanded the diagnosis to include dilated cardiomyopathy, cardiogenic shock, atrial flutter, pleural effusion, peritoneal effusion, and abnormal liver and renal function. The treatment regimen was subsequently modified to incorporate intermittent non-invasive ventilator-assisted ventilation and symptomatic support aimed at increasing blood pressure, improving cardiac function, controlling the ventricular rate, and maintaining homeostasis; however, the patient's symptoms did not exhibit significant improvement. Consequently, he was transferred to our hospital, a tertiary cardiac specialty facility, on February 25, 2023, where he was diagnosed with heart failure, cardiomyopathy, and cardiogenic shock. Upon taking the patient's medical history, he denied any history of hypertension, diabetes, stroke, hepatitis, typhoid fever, or schistosomiasis, and he reported no known drug or food allergies. Regarding his family history, the patient's father is deceased, with the cause of death unknown, while his mother is alive and has no known cardiovascular disease.

Upon admission, the patient was conscious and exhibited mild scleral jaundice, diminished breath sounds bilaterally, and wet rales in the lower lung fields. Auscultation revealed no murmurs at any of the heart valves. Laboratory results indicated elevated cardiac biomarkers, specifically high-sensitivity cardiac troponin I (hscTnI) at 0.694 ng/ml, myoglobin at 219 ng/ml, and N-terminal pro B-type natriuretic peptide (NT-proBNP) at 5,682 pg/ml. Additionally, liver and renal function tests demonstrated impairment, with albumin at 33 g/L, alanine aminotransferase (ALT) at 5,358.2 U/L, aspartate aminotransferase (AST) at 16,734.6 U/L, lactate dehydrogenase (LDH) at 13,134 U/L, total bilirubin (TBIL) at 54.9 μmol/L, direct bilirubin (DBIL) at 21.2 μmol/L, and creatinine at 193 μmol/L. Inflammatory markers were significantly elevated, with a white blood cell count of 14.2×10^9 /L, procalcitonin at 0.27 ng/ml, interleukin-6 at 33.2 pg/ml, interleukin-8 at 238 pg/ml, and high-sensitivity C-reactive protein at 14.4 mg/L. Furthermore, coagulation-related markers indicated dysfunction, with prothrombin time (PT) at 60.7 s, activated partial thromboplastin time (APTT) at 35.6 s, fibrinogen at 1.0 g/L, D-dimer at 104.5 μg/ml, thrombin-antithrombin complex at 116.5 ng/ml, antithrombin III at 43.0%, and platelet count (PLT) at 52×10^9 /L.

The electrocardiogram indicated sinus rhythm with frequent premature ventricular contractions, poor precordial R-wave elevation, T-wave abnormalities, and a prolonged QT interval. Echocardiographic findings revealed a left ventricular ejection fraction (LVEF) of 20%. Both the left atrium (4.0 cm) and left ventricle (6.0 cm) were enlarged, and there was a general reduction in septal and left ventricular wall motion. The findings also indicated mild aortic regurgitation, severe mitral regurgitation, moderate tricuspid regurgitation, and markedly reduced left ventricular systolic function. Additionally, a small amount of fluid was noted in the pericardial cavity, along with a significant accumulation of fluid in the right pleural cavity. Based on the clinical signs and symptoms, electrocardiographic changes, elevated markers of myocardial injury, and echocardiographic evidence of myocardial damage observed after admission, the patient was comprehensively assessed and diagnosed with FM. Given the patient's history of antecedent infection, further testing for antibodies to myocarditis-associated viruses was conducted. The results were positive for IgM antibodies to coxsackievirus B3 and echovirus. Therefore, the patient's FM was attributed to a viral infection, which subsequently led to cardiogenic shock and severe coagulopathy.

Clinical management in this case focuses on three primary areas, the first of which is the improvement of organ function. Cardiac volume overload was addressed through negative volume balance, maintaining a deficit of 2,000 ml per day for the first four days. Cardiogenic shock was managed with norepinephrine at a dose of 0.15 μg/kg/min and dopamine at 5 μg/kg/min. An intra-aortic balloon pump (IABP) was implanted on day four of admission to enhance cardiac output and improve organ perfusion; it was withdrawn after four days of support. Amiodarone hydrochloride was administered at a rate of 30 mg/h

to control arrhythmias and manage atrial flutter. Additional treatments included liver protection with reduced glutathione (1.8 g/day), diuresis, and supportive therapy such as oxygen therapy. The second area of focus was the correction of coagulation disorders. Based on laboratory findings, an International Society on Thrombosis and Haemostasis (ISTH) dominant disseminated intravascular coagulation (DIC) score of 7 (threshold >5) was obtained, suggesting a suspicion of DIC. However, the addition of a factor VIII (FVIII) activity of 176.5% and an APTT of 35.6 s did not support the diagnosis of DIC. Consequently, we initiated anticoagulation with unfractionated heparin, starting at a dose of 400 U/h, which was subsequently adjusted to 300 U/h for one week, along with continuous monitoring of D-dimer levels. Anticoagulation was accompanied by replacement therapy, including the infusion of fresh frozen plasma (FFP), with 200 ml administered on day two and another 200 ml on day five. Supplemental fibrinogen was infused, totaling 12 units of cryoprecipitate and 0.5 g of fibrinogen, to maintain fibrinogen levels above 1.2 g/L and prevent bleeding. For platelet replacement, 1 unit of platelets was infused when the platelet count dropped to 18×10^9 /L, with continuous monitoring. The third area of focus was the control of inflammation and infection. Management included intravenous human immunoglobulin (PH4) at a dose of 10 g/day for five days to provide immunosupportive therapy, alongside low-dose methylprednisolone at 40 mg for five days as an anti-inflammatory treatment.

TABLE 1 Monitoring of organ functions.

Parameters	Day 1	Day 3	Day 7	Day 13
Echocardiogram				
LVEF (%)	20	38	42	43
LVID (cm)	6.2	6.0	4.3	3.7
Biochemical indicators				
hscTnI (ng/ml)	0.69	0.34	0.15	/
NT-proBNP (pg/ml)	5,682.0	814.8	292.5	29.4
ALT (IU/L)	5,358.2	4,240.3	961.4	189.5
AST (IU/L)	16,734.6	5,477.2	111.0	67.0
TBIL (μmol/L)	54.9	85.2	78.9	33.0

LVEF, left ventricular ejection fraction; LVID, left ventricularend-systolic dimension; hscTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.

After comprehensive treatment, the patient's organ function gradually improved, as evidenced by significantly better examination indices (Table 1). Echocardiography revealed a LVEF of 43%, with normal left atrial and left ventricular dimensions. Additionally, there was a reduced amplitude of septal motion, while the amplitude of left ventricular wall motion remained normal. Coagulation monitoring indicated that coagulation parameters had been corrected (Figure 1), with

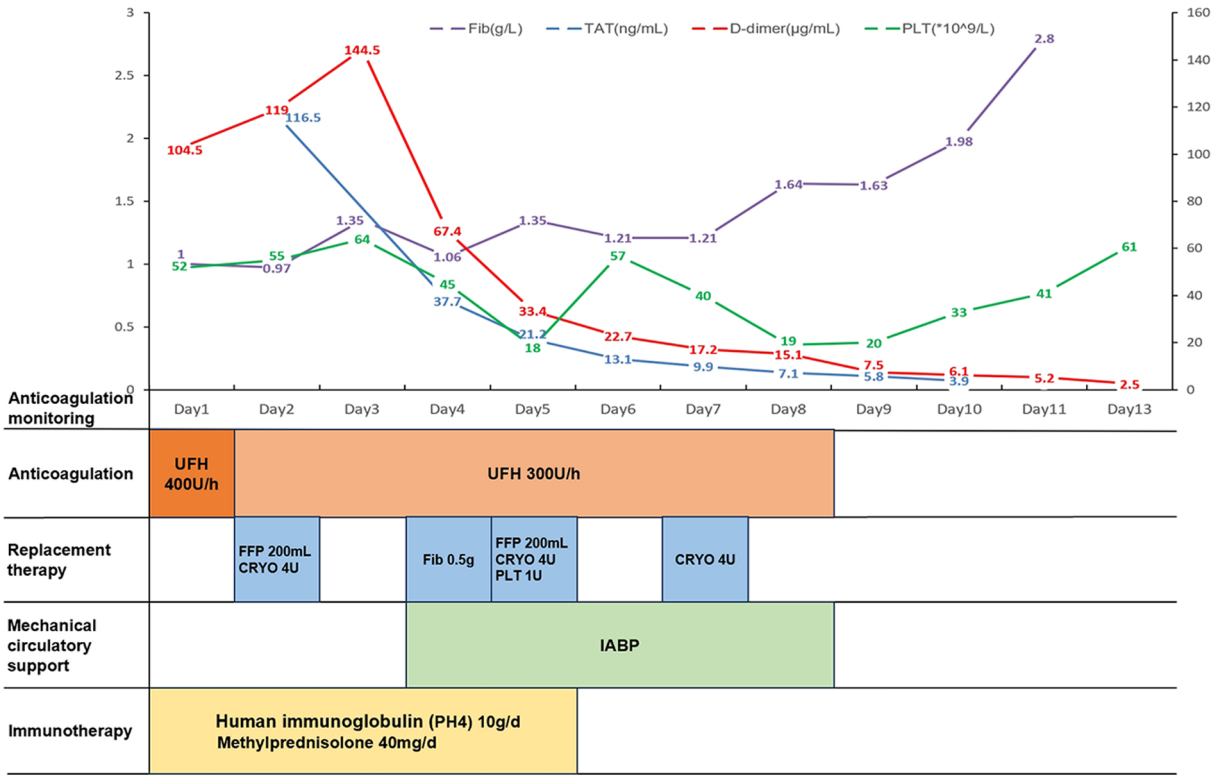

FIGURE 1
Chronological framework for anticoagulation therapy and monitoring. Fib, fibrinogen; TAT, thrombin-antithrombin complex; PLT, platelet count; UFH, unfractionated heparin; FFP, fresh frozen plasma; CRYO, cryoprecipitate; IABP, intra-aortic balloon pump.

results showing fibrinogen at 2.8 g/L, D-dimer at 2.5 μg/ml, PLT at 61×10^9 /L, PT at 12 s, and APTT at 27.9 s. The patient's condition stabilized, allowing for discharge on March 11, 2023, following evaluation by the attending physician. The patient returned for follow-up visits in the first and fourth months post-discharge, during which liver function, markers of myocardial damage, and platelet counts were found to have returned to normal levels. These findings suggest a favorable prognosis for the patient.

Discussion

We report the case of a patient with rapidly progressive disease characterized by severe hemodynamic disturbances and multi-organ damage, specifically affecting the liver and kidneys. These manifestations, in conjunction with prodromal symptoms and evidence of myocardial injury, are consistent with a clinical diagnosis of FM. Upon admission, the patient underwent testing for antibodies to myocarditis-associated viruses. While positive viral serology does not confirm myocardial infection, it may indicate an interaction between the peripheral immune system and the source of the infection. Previous studies have suggested that viral serology has a limited role in diagnosing viral myocarditis due to the high prevalence of circulating IgG antibodies to cardiophilic viruses in the general population, even in the absence of viral heart disease (10). However, our patient tested positive for IgM antibodies to coxsackievirus B3 and echovirus, which may indicate a recent infection with these viruses, thereby supporting the diagnosis of viral myocarditis. The confirmation of viral myocarditis typically relies on endomyocardial biopsy (EMB) (4). However, in this case, EMB was not performed due to the patient's severe coagulopathy and the associated high risk of bleeding from invasive procedures. Furthermore, it is essential to rule out coronary artery disease and other cardiovascular conditions, such as hypertension and acute myocardial infarction, as well as extracardiac non-inflammatory disorders that could account for the clinical manifestations of FM (11). This is particularly important because these conditions may present with similar symptoms, including chest pain, and elevated levels of circulating biomarkers of myocardial injury, such as troponin and B-type natriuretic peptide (12).

In terms of aetiological treatment, there are currently no approved pathogen-directed or antiviral therapies for patients with viral myocarditis. Given the limited evidence supporting the efficacy of intravenous immunoglobulin therapy in this context, the International Society of Cardiology has refrained from making specific recommendations regarding its use. The pathogenesis of myocardial dysfunction in myocarditis is primarily attributed to a maladaptive hyperimmune response triggered by viral infection; thus, therapies aimed at modulating the immune response are considered potentially beneficial (13). In the case of our patient, and in the absence of a specific antiviral agent targeting coxsackievirus and echovirus, human immunoglobulin (PH4) was selected as an immunosupportive therapy. This choice is predicated on its content of neutralizing enterovirus antibodies, which may confer effectiveness against the implicated viral pathogens. Additionally, the patient received hormonal anti-inflammatory treatment to further support the management of the immune response. However, multicentre, placebo-controlled trials of intravenous immunoglobulin therapy in adult patients are necessary to establish its efficacy in individuals with biopsy-proven myocarditis.

Notably, the patient was admitted with cardiogenic shock and severe liver injury, which were believed to result from inadequate perfusion and venous congestion associated with the cardiogenic shock. This condition led to liver injury and failure, subsequently causing coagulopathy. The incidence of liver dysfunction in patients with acute heart failure has been reported to range from 20% to 30% (14). The coagulation indices indicated the presence of coagulation disorders, consistent with liver dysfunction, which included deficiencies in coagulation factors (such as fibrinogen and vitamin K-dependent factors), thrombocytopenia, and hyperfibrinolysis. The patient's coagulation parameters were characterized by decreased fibrinogen, decreased PLT, prolonged PT, and significantly elevated D-dimer levels, leading to a calculated score indicative of overt DIC. The question arises: is this patient's coagulation disorder due to liver failure or DIC? Notably, FVIII activity was measured at 176.5%, with an APTT of 35.6 s—neither of which supports a diagnosis of DIC. When liver function tests are markedly abnormal, it can be challenging to ascertain whether laboratory changes stem from liver disease, DIC, or a combination of both. The level of FVIII activity serves as a critical differentiating factor; FVIII is synthesized not only in the liver but also by extrahepatic endothelial cells. In patients with liver disease, increased levels of extrahepatic synthesis often result in normal or elevated FVIII activity. In contrast, patients with DIC typically exhibit significantly reduced levels of FVIII and other coagulation factors due to depletion resulting from coagulation overactivation (15, 16).

In patients with both abnormal liver function and coagulopathy, the question arises: do they require anticoagulation? Liver insufficiency is a recognized risk factor for venous thrombosis, and anticoagulation is indicated in patients with acute liver injury, even in the presence of prolonged PT and thrombocytopenia (17). Unfractionated heparin is often considered the optimal choice for anticoagulation due to its short half-life, reversibility, non-renal clearance, and ease of monitoring (18). Consequently, we administered a low dose of unfractionated heparin (300 U/h) for anticoagulant therapy and observed a sustained decrease in D-dimer levels. In patients with FM, managing coagulation disorders presents a significant challenge that necessitates careful consideration of treatment strategies. Anticoagulation is often emphasized in patients with liver dysfunction; however, those with acute liver injury face an increased risk of bleeding due to impaired synthesis of coagulation factors and platelet dysfunction. This risk can be exacerbated by anticoagulation therapy (19). To mitigate this,

supplementation with FFP and specific clotting factors may help restore hemostatic balance in patients suffering from severe liver dysfunction secondary to FM. The use of FFP in patients with liver disease remains controversial due to its potential to exacerbate portal hypertension. Nevertheless, in non-cirrhotic patients, fibrinogen levels below 1 g/L are associated with an increased risk of bleeding, and maintaining levels above 1.2 g/L is recommended for those experiencing active bleeding (20). Our treatment protocol includes intermittent supplementation of FFP in small doses, alongside cryoprecipitate infusion, to maintain fibrinogen levels above 1.2 g/L and achieve a balance between anticoagulation and hemostasis. Clinically, we have observed that the combined use of FFP and cryoprecipitate is effective in addressing coagulopathy in patients with FM. This strategy not only reduces bleeding risks but also supports overall recovery by stabilizing hemostatic function. Additionally, attention must be given to platelet levels, which are crucial for hemostasis. The use of IABP support led to a mechanical destruction of platelets, resulting in a count of 18×10^9 /L. Given that the IABP could not be temporarily withdrawn at that time, we evaluated the situation and decided to transfuse 1 unit of platelets. However, the platelet count subsequently decreased again, from 57×10^9 /L to 19×10^9 /L. After careful assessment, we opted to withdraw IABP support, and considering the low risk of bleeding, we did not proceed with additional platelet transfusions. As the patient's liver function gradually improved, we observed a corresponding rebound in platelet counts. Our treatment strategy, which involved simultaneous supplementation and anticoagulation, effectively corrected the patient's coagulation function, leading to a favorable prognosis.

Conclusions

This case underscores the complexity of managing a patient with FM complicated by cardiogenic shock, severe liver injury, and coagulopathy. The therapeutic challenges in such critically ill patients necessitate an active search for the underlying etiology. It is essential to maintain a delicate balance within the coagulation system while implementing a combination of therapeutic regimens. This includes developing an optimal anticoagulation strategy and determining appropriate timing for interventions. Furthermore, alternative therapies must be considered, balancing the associated risks of bleeding and thrombosis. Such comprehensive management is crucial for improving patient outcomes in this intricate clinical scenario.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Medical Ethics Committee of the Wuhan Asia Heart Hospital (approval no. 2024-B083). 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

SD: Conceptualization, Writing – original draft, Writing – review & editing. QP: Data curation, Writing – original draft. KL: Methodology, Writing – original draft. QW: Conceptualization, Writing – review & editing. JY: Supervision, Writing – review & editing.

Funding

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

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 Cardiovascular Medicine

TYPE Case Report
PUBLISHED 24 March 2025
DOI 10.3389/fcvm.2025.1561645

OPEN ACCESS

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RECEIVED 16 January 2025
ACCEPTED 10 March 2025
PUBLISHED 24 March 2025

CITATION
Lai Q, Chen L, Gao X, Tie H and Wan Z (2025) Case Report: Maintaining a balance between vascular access patency and stable dissection status in a hemodialysis patient with unrepaired type A aortic dissection. Front. Cardiovasc. Med. 12:1561645. doi: 10.3389/fcvm.2025.1561645

Case Report: Maintaining a balance between vascular access patency and stable dissection status in a hemodialysis patient with unrepaired type A aortic dissection

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Introduction: Type A aortic dissection (AD) is a lethal situation with high mortality within short time after onset. We present here a rare hemodialysis patient whose condition was comorbid with unrepaired type A AD. The challenge we face is whether low-molecular-weight heparin (LMWH) should be used during dialysis.

Case presentation: A 72-year-old man with a history of hemodialysis for 2 years and 7 months sought medical attention due to thrombosis of the dialysis catheter. He had been diagnosed with an unrepaired type A aortic dissection (involving the aortic root, the ascending aorta, the aortic arch, the descending aorta, the abdominal aorta, the left common iliac artery, and the femoral artery) for more than 5 years. LMWH was not given during the previous dialysis process because of concerns about the rupture of the dissection. The lesion was salvaged via urokinase thrombolysis. However, the anticoagulant-free dialysis pattern occasionally caused dialyzer clotting and further increased the risk of catheter dysfunction. The patient repeatedly experienced dysfunction of the catheter in the following 8 months, with 2 episodes resolved via thrombolysis and 2 episodes replaced with new catheters. Finally, LMWH was used for each dialysis session to prevent thrombosis, with the dosage gradually increasing from 1,000 units to 2,000 units. The dosage of 2,000 units could support sufficient 4-hour dialysis for each session. Twenty-five months have passed since then, the patient has not experienced any further occlusion of the catheter, and the aortic dissection has not shown obvious changes (neither obvious expansion nor rupture).

Conclusion: Reducing the dosage of LMWH during hemodialysis is a feasible solution to maintain a balance between hemodialysis access patency and stable dissection status in this particular patient.

KEYWORDS

type A aortic dissection, hemodialysis, heparin, access patency, case report

10.3389/fcvm.2025.1561645

Introduction

Type A aortic dissection (AD) is a lethal situation with high mortality within short time after onset. Although the 30-day or in-hospital mortality of type A AD after surgical repair has decreased to less than 20%, only a scarce group of patients enter the chronic phase without intervention (1–4). With the widespread use of frozen elephant trunk repair technique, the in-hospital mortality rate of type A AD has decreased to below 10% in recent years (5). We present here a rare hemodialysis patient whose condition was comorbid with unrepaired type A AD. As a procedure involving extracorporeal circulation, anticoagulant use is a standard practice during hemodialysis. However, anticoagulants may disrupt the stability of the dissection. There is a lack of literature on how to make decisions in this situation. The challenge we face is whether anticoagulants should be used during dialysis.

Case report

A 72-year-old man was admitted on 20 April 2022 due to the first episode of dialysis catheter dysfunction. The patient was diagnosed with stage 3 chronic kidney disease in 2012 and developed stage 5 disease in 2019. Because the patient had reached the indications for hemodialysis and the vascular conditions in the upper limbs were too poor to create an arteriovenous fistula or graft, a long-term central venous catheter was placed in the right internal jugular vein in September 2019. Afterwards, the patient underwent regular hemodialysis (3 times per week).

The patient had a long and complex history of illness (Table 1). The patient had been diagnosed with type A aortic dissection for more than 5 years. Computed tomography (CT) revealed extensive dissection involving the aortic root, the ascending aorta, the aortic arch, the descending aorta, the abdominal aorta, the left common iliac artery, and the femoral artery (Figures 1, 2). The diameter of the ascending aorta remained at 83–89 mm after 2019. Because CT angiography failed to detect the site of the intimal tear and because of the lack of technical capabilities, the patient had not received any repair surgery. When the patient started hemodialysis therapy, low-molecular-weight heparin (LMWH) was not administered because of the concerns about inducing dissection rupture. The anticoagulant-free dialysis pattern frequently caused dialyzer clotting, but could still maintain the patient's normal physiological state.

When dialysis catheter dysfunction occurs, thrombosis (usually located at the opening of the catheter) is the first possible cause. The routine procedure involves first performing urokinase thrombolysis and then aspirating with a syringe. If catheter dysfunction is solely caused by a thrombus, this operation can extract the thrombus and restore blood flow. If urokinase thrombolysis does not work, a fibrin sheath is likely to have formed, and the catheter must be replaced. This episode of catheter dysfunction was salvaged via urokinase thrombolysis, and the patient was discharged. However, the patient experienced an additional 4 episodes of catheter dysfunction in the following 8 months. Two episodes were solved with urokinase thrombolysis (August and October 2022), and the other two episodes were treated with catheter replacement (May and November 2022). The patient was bothered by repeated catheter dysfunction and requested heparin usage during hemodialysis. Given that there is currently no reference on the use of LMWH in this situation, doctors have decided to start with low-dose LMWH in combination with surveillance imaging of the aortic dissection. Typically, 4,000 units of LMWH are administered per hemodialysis session. Starting in January 2023, 1,000 units of LMWH were administered intravenously during each hemodialysis session. The problem of dialyzer clotting improved but still occurred occasionally. The dosage gradually increased to 1,500 units in June 2023 and 2,000 units in July 2023, which enabled the patient to complete 4 h of adequate hemodialysis almost each session. The last follow-up was in December 2024. The patient did not experience new catheter dysfunction after the catheter was changed in November 2022, and the aortic dissection did not significantly change (neither obvious expansion nor rupture).

TABLE 1 Medical history of the patient.

Year	Medical situation	Treatment
2002	The patient was diagnosed with hypertension with a reading of 160/94 mmHg.	Valsartan was administered.
2006	Fasting blood glucose level rose to 7.8 mmol/L.	Not treated.
2007	Discovery of aortic insufficiency during physical examination.	The patient was not treated because there were no obvious symptoms.
2012	The patient was diagnosed with stage 3 chronic kidney disease with a serum creatinine level of 144 μmol/L.	1. Insulin therapy for diabetes started in April and fasting blood glucose was controlled at 6–7 mmol/L. 2. Traditional Chinese medicine was administered for the treatment of chronic kidney disease.
2016	The patient was diagnosed with rheumatic heart disease, aortic valve stenosis with aortic insufficiency, dilatation of the ascending aorta, and coronary atherosclerotic heart disease. The main symptoms included mental fatigue and shortness of breath after the activity, blackouts, chest pain, dizziness, paleness, and dyspnea.	Ascending aortic replacement and aortic valve replacement were performed on April 11th. Postoperative ultrasound revealed normal valve opening and closing with good circulation. The patient was discharged on April 21st.
2017	Postoperative follow-up examination revealed a type A aortic dissection on January 19th. The blood pressure had been controlled at 100–130/70–80 mmHg in the last five years.	No repair surgery was performed because computed tomography did not reveal any intimal tears, and the visiting hospital lacked technical capabilities because of the extensive lesion range.
2019	The obvious symptoms of uremia appeared: glomerular filtration rate <15 ml/min, serum creatinine level >400 μmol/L, edema of both lower limbs, fatigue, shortness of breath after activity, and poor appetite.	A long-term central venous catheter was placed in the right neck in September. Afterwards, the patient underwent regular hemodialysis (3 times per week). Moreover, antihypertensive medication was discontinued due to dialysis-induced hypotension and decrease in blood pressure during non-dialysis period. Systolic blood pressure was maintained at 100–100 mmHg.
2022	The patient experienced repeated fainting and was diagnosed with bradycardia in January.	Implantation of a pacemaker for the treatment of bradycardia.

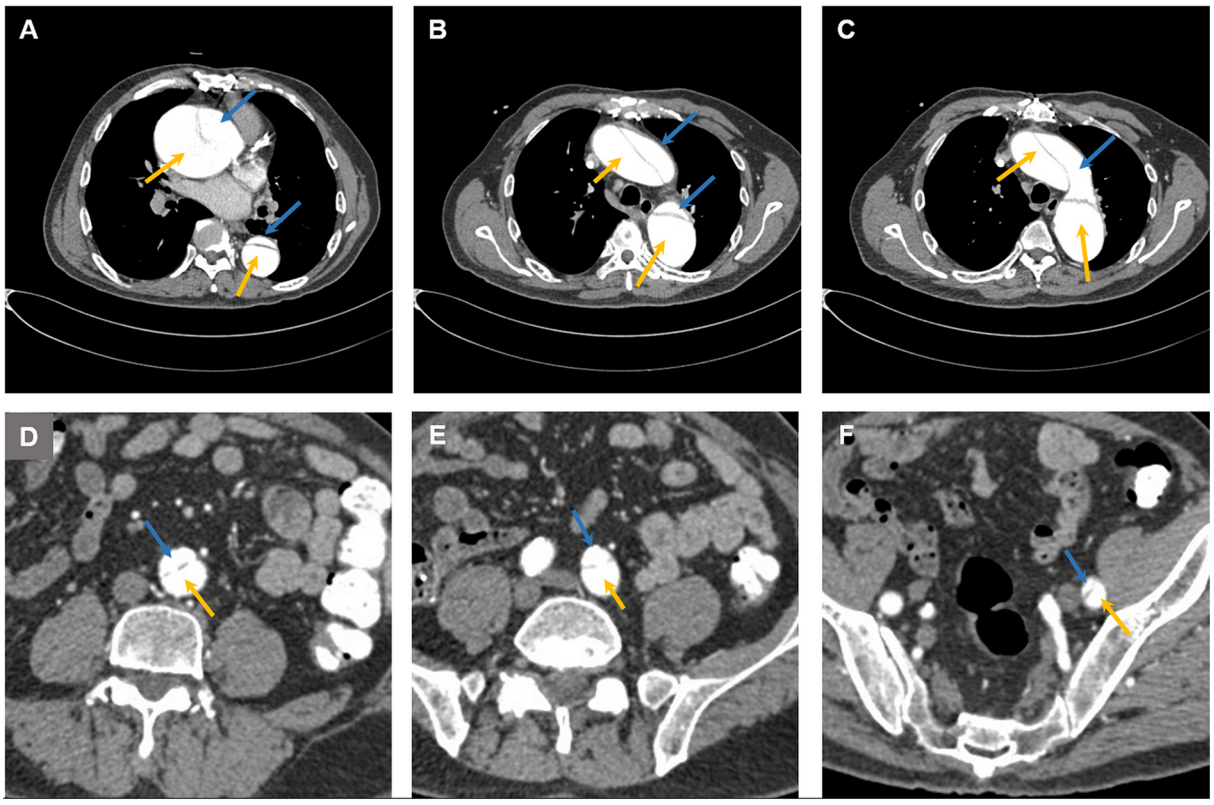

FIGURE 1
Computed tomography images showing aortic dissection at **(A)** the aortic root, **(B)** the ascending aorta, the descending aorta, **(C)** the aortic arch, **(D)** the abdominal aorta, **(E)** the left common iliac artery, and **(F)** the femoral artery. The blue arrow indicates the false lumen, and the yellow arrow indicates the true lumen.

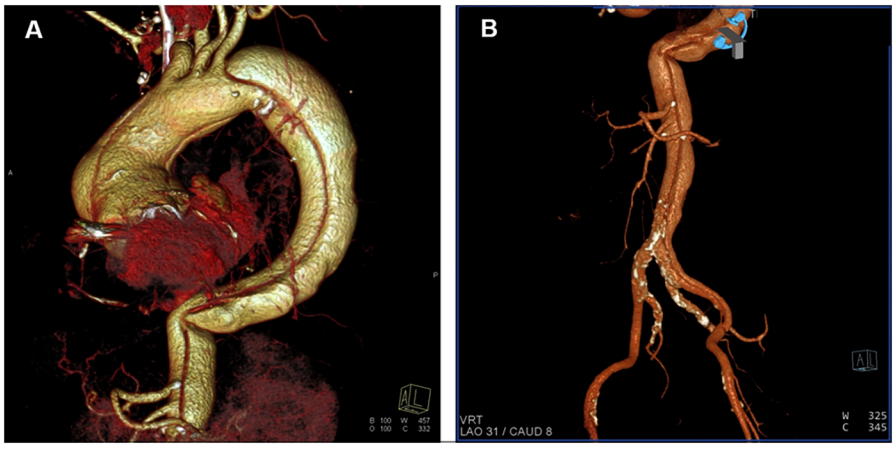

FIGURE 2
Three-dimensional (3D) reconstruction images from computed tomography angiography. **(A)** Thoracic reconstruction showing dissection of the ascending aorta, the aortic arch, and the descending aorta. **(B)** Abdominal reconstruction showing dissection of the abdominal aorta, the left common iliac artery and the femoral artery.

Discussion

One notable feature of this case is that the patient has survived stably for over 7 years with unrepaired extensive type A aortic dissection. WK Kim et al. reported that in patients with unrepaired type A AD, the cumulative adverse aortic event rate in those with an aortic diameter ≥55 mm was 27.8% ± 9.1% (6). The diameter of the ascending aorta in this case was 83–89 mmm. The length of

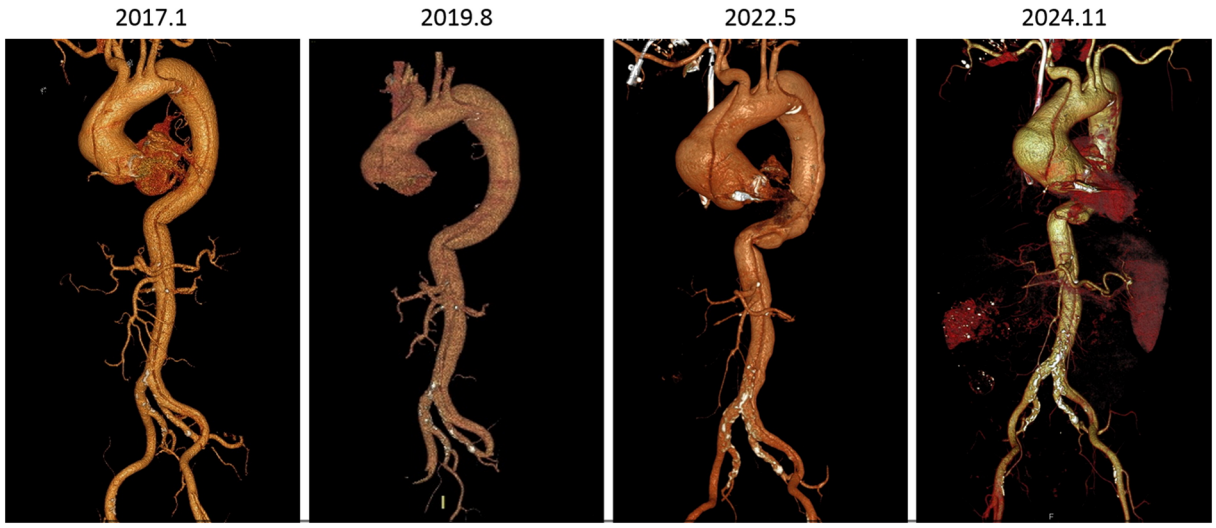

FIGURE 3
Computed tomography angiography images of different time points.

stable survival in this case is quite spectacular considering the patient's lesion range, age, aortic diameter, and complex comorbidities. DM Nemtut et al. reported a patient who experienced ascending aortic dissection, descending aortic dissection, and abdominal aortic dissection within a couple of years and eventually died of periaortic hematoma and severe anemia after surgical treatment (7). We have several speculations about the possible mechanism of the patient's long-term survival. First, the patient's blood pressure was well controlled. Second, spontaneous thrombosis probably occurred and blocked the arterial tear because the dissection has not obviously changed since 2019 (Figure 3). Additionally, the aortic dissection may worsen renal function because the renal artery was also affected and dilated, although the direct etiology of renal failure is highly likely to be chronic nephritis.

Uncontrolled hypertension is the most common risk factor for aortic dissection (8). However, the patient's blood pressure had been within the normal range for the last five years before dissection was found. The cause of dissection is highly suspected to be related to the valve replacement surgery. CT angiography did not detect any intimal tear. It is suspected that blood flowed into the intima and media from the site of valve replacement and gradually tore to the femoral artery under gravity. However, this suspicion cannot be confirmed. The CT results of the patient were normal at discharge (10 days post-surgery), and the patient did not experience any severe chest pain before the discovery of the dissection (7 months later). It is even impossible to determine the onset of dissection. The patient's stable state also benefits from controlled blood pressure. After the discovery of the aortic dissection, blood pressure control was strengthened. After hemodialysis was initiated, dehydration during the dialysis process had a synergistic effect on lowering blood pressure. As a result, the patient not only experienced dialysis-related hypotension but also gradually recovered to normal blood pressure during the non-dialysis period and ceased antihypertensive medication. The prevalence of chronic dialysis hypotension was reported to be 8% in long-term dialysis patients (9). However, a literature search did not reveal similar cases of spontaneous recovery of blood pressure in hemodialysis patients. We have no clue about the underlying mechanism.

Naturally occurring thrombus formation in the false lumen may halt the disease progression in AD, but the impact of anticoagulants on the status of AD is unclear (10, 11). On the basis of conservative considerations, LMWH was not used in the current case when initiating hemodialysis. However, the anticoagulant-free dialysis pattern results in frequent dialyzer clotting and further leads to dialysis inadequacy (12). Frequent catheter blockages in our patient were likely also related to the heparin-free dialysis pattern. Small blood clots may flow back into the patient's body, and unfortunately, the catheter is more prone to thrombus deposition than autogenous blood vessels are (13). Thrombosis inside catheters further increases the formation of fibrin sheaths, which is a major cause of catheter malfunction (14, 15). Adopting a compromise heparin dosage (half of the normal dosage) seems to be a relatively appropriate solution, as it can solve the problem of repeated catheter occlusion. Regarding the potential benefits of heparin-free dialysis, a study of 12 thousand patients in the United States revealed that it was associated with neither decreased risk of mortality or bleeding nor increased risk of atherothrombosis or venous thromboembolism (16). Therefore, current attention to the dissection state is focused on maintaining reasonable blood pressure and surveillance imaging, and heparin use does not seem to be a particularly high-risk factor.

In summary, reducing the dosage of heparin during hemodialysis is a feasible solution for balancing aortic dissection status and dialysis patency in this particular patient. Since no

similar case has been reported before, our experience can provide a reference for colleagues.

Data availability statement

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

Ethics statement

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

Author contributions

QL: Data curation, Investigation, Resources, Writing – review & editing. LC: Data curation, Investigation, Resources, Writing – review & editing. XG: Investigation, Resources, Writing – review & editing. HT: Software, Visualization, Writing – review & editing. ZW: Data curation, Investigation, Resources, Supervision, Writing – original draft, Writing – review & editing.

Funding

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

Conflict of interest

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

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 26 March 2025
DOI 10.3389/fcvm.2025.1458064

OPEN ACCESS

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RECEIVED 01 July 2024
ACCEPTED 07 March 2025
PUBLISHED 26 March 2025

CITATION
Siddiqui A, Hatfield T, Nguyen Q and Waris W (2025) Case Report: IVC-agenesis and FVL mutation; successful DVT/PE treatment with direct oral anticoagulation (factor Xa inhibitor). Front. Cardiovasc. Med. 12:1458064. doi: 10.3389/fcvm.2025.1458064

Case Report: IVC-agenesis and FVL mutation; successful DVT/PE treatment with direct oral anticoagulation (factor Xa inhibitor)

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Inferior vena cava (IVC) agenesis is a rare congenital anomaly that has been implicated in up to 5% of unprovoked deep vein thrombosis (DVT) cases in young men under 30 years old. We present the case of a 28-year-old obese Caucasian male who arrived at our hospital with significant pain and swelling in his right lower extremity. The patient had no prior medical history or family history of DVT or cardiovascular conditions. A venous Doppler ultrasound revealed an extensive right lower extremity DVT. Further imaging with a computed tomography (CT) pulmonary embolism (PE) protocol scan of the chest and abdomen identified IVC agenesis along with pulmonary emboli in the left central pulmonary arteries. A hypercoagulability workup was positive for a heterozygous Factor V Leiden (FVL) mutation, an additional thrombophilic risk factor. The patient was initially managed with an intravenous heparin drip and was later transitioned to long-term direct Factor Xa inhibitor therapy. To our knowledge, this is the first reported case of extensive venous thromboembolism (VTE) due to concurrent IVC agenesis and FVL mutation successfully treated with direct Factor Xa inhibition. This case highlights the complexity of managing patients with multiple thrombogenic risk factors and raises a discussion on the rationale for lifelong anticoagulation in such individuals.

KEYWORDS

inferior vena cava agenesis, factor V Leiden, deep vein thrombosis, pulmonary embolism, direct oral anticoagulant

Introduction

Inferior vena cava (IVC) agenesis is a rare congenital anomaly with its prevalence ranging between 0.0005% and 1% (1). Though rare, it is still a cause for concern since literature has shown as much as 5% of young men under the age of 30 who suffer from unprovoked DVTs are affected by IVC agenesis (2). This condition results from embryonal dysgenesis during the prenatal stage (3). The absence of an IVC leads to the development of extensive collateral veins to maintain adequate blood flow to the heart. This compensatory mechanism, however, increases the risk of venous thromboembolisms (VTE), including deep vein thrombosis (DVT) and pulmonary embolisms (PE). VTEs are critical conditions that can result in severe complications, including stroke, PE, and sudden death.

Inherited thrombophilias such as the heterozygous factor V Leiden (FVL), further amplify VTE risk by production of a factor V protein that is resistant to inhibition by Protein C. Research suggests that individuals with a heterozygous FVL mutation have a 6–8-fold increased risk of developing VTE, while those with a homozygous mutation face an 80-fold increase (4). The coexistence of IVC agenesis alongside inherited thrombophilia complicates the clinical management of affected VTE patients, and underscores the importance of effective treatment strategies to mitigate the risk of life- threatening complications.

Case description

A 28 year old male arrived at our hospital with a one day history of right lower extremity swelling and pain. Patient stated it was painful to move his right calf muscle, and that he had a general feeling of tightness around it. He denied any inciting incidents that could have caused the symptoms and stated that walking on the leg worsened it. He denied chest pain, shortness of breath, and any personal or family medical history of cardiovascular related diseases, including DVTs. He also stated he was not currently taking any medications, though his past medical history included depression, anxiety, and seizures. His past surgical history included a right shoulder surgery and vagal nerve stimulator implant. He denied any history of tobacco, alcohol, illicit drug use.

Upon physical examination, we found that our patient had swelling of his right lower extremity with a purple discoloration of his overlying skin of the affected region. The swelling extended from his right ankle up to the lower aspect of his right knee. He exhibited no deficits to motor strength and sensation across his extremities. Auscultation of his heart and lungs was unremarkable. Strong dorsalis pedis pulses bilaterally and brisk capillary refill times were appreciated. His abdomen was soft, and non-tender with normal bowel sounds. Overall neuropsychiatric status was unremarkable with normal affect, judgment/insight.

His vital signs were relatively stable; pulse oximetry measured 99% O2 saturation, with a blood pressure of 127 systolic over 66 diastolic. His pulse was 82 beats per minute, and his respiratory rate was at 17 per minute. His temperature was 98.2 degrees Fahrenheit.

Initial diagnostic workup included a venous doppler ultrasound of the right lower extremity, which yielded findings of thrombus extending from the common femoral vein distally into the popliteal and greater saphenous veins (Figure 1C).

Comprehensive metabolic panel demonstrated normal kidney function and electrolyte levels, with slightly elevated ALT reading of 67 units/L (Tables 1–3). Blood analysis demonstrated elevated mean platelet volume and monocyte percentage, alongside low lymphocyte percentage of his total white blood cell composition (Tables 1–3).

Hematologic workup yielded a heterozygous FVL mutation (c. 1601G>A, p.Arg534Gln). Patient tested negative for IgA, IgG, and IgM antibodies against Beta-2 glycoproteins, and cardiolipin. He also tested negative for abnormal levels of homocysteine in his serum.

Patient consented to further investigation involving contrast-enhanced CT scans of his chest which yielded filling defects within the central pulmonary arteries on the left consistent with pulmonary emboli (Figure 1B). Abdominal CT scan showed agenesis of the inferior vena cava with extensive collateralization (Figure 1A), and enlargement of the right common iliac and femoral veins consistent with DVT found on ultrasound (Figure 1C).

After DVT was confirmed via doppler ultrasound, patient was immediately started on a standard Heparin weight-based IV drip. Once further work-up and labs were completed, a decision was made to transition patient from IV Heparin to oral anti-coagulation utilizing Apixaban 5 mg twice-daily upon discharge.

Since his discharge with the new diagnosis, our patient has remained symptom-free for 13 months, with no recurrence or worsening of his DVT or PE. The patient's right lower extremity swelling has completely resolved, and he has not reported any new episodes of shortness of breath, chest pain, or other complications associated with his pulmonary embolism. He has successfully resumed his daily activities, including the physical demands of his nursing studies, with significantly reduced pain and swelling. His ability to walk, stand for prolonged periods, and participate in clinical rotations has markedly improved, allowing him to progress in his training without significant limitations.

Given the congenital nature of his IVC agenesis and the associated risk of recurrent thromboembolic events, our multidisciplinary team—including specialists from interventional radiology, vascular surgery, and hematology—agreed that long-term anticoagulation therapy remains the most appropriate management strategy. Due to the complexity of his vascular anatomy, thrombectomy was deemed unsuitable, and no viable surgical interventions are currently available. Therefore, the decision was made to continue anticoagulation therapy indefinitely with Apixaban 5 mg twice daily to minimize the risk of further thrombotic events.

We continue to monitor the patient closely through outpatient follow-ups every three months, assessing for potential complications such as recurrent DVTs, post-thrombotic syndrome, or anticoagulation-related adverse effects. As newer mechanical interventions become available, we will reassess treatment options in collaboration with our multidisciplinary team to determine if a more definitive approach to managing his IVC agenesis emerges.

Discussion

In managing a patient with a heterozygous FVL mutation without prior VTE history, education and routine care are typically sufficient. Management of an acute VTE in the setting of an inherited thrombophilia involves anticoagulation for at least three to six months. Indefinite anticoagulation is a decision that is subject to the physician's clinical judgment, based on various risk factors on a case by case basis including multiple thrombophilic mutations, strong family history of VTE,

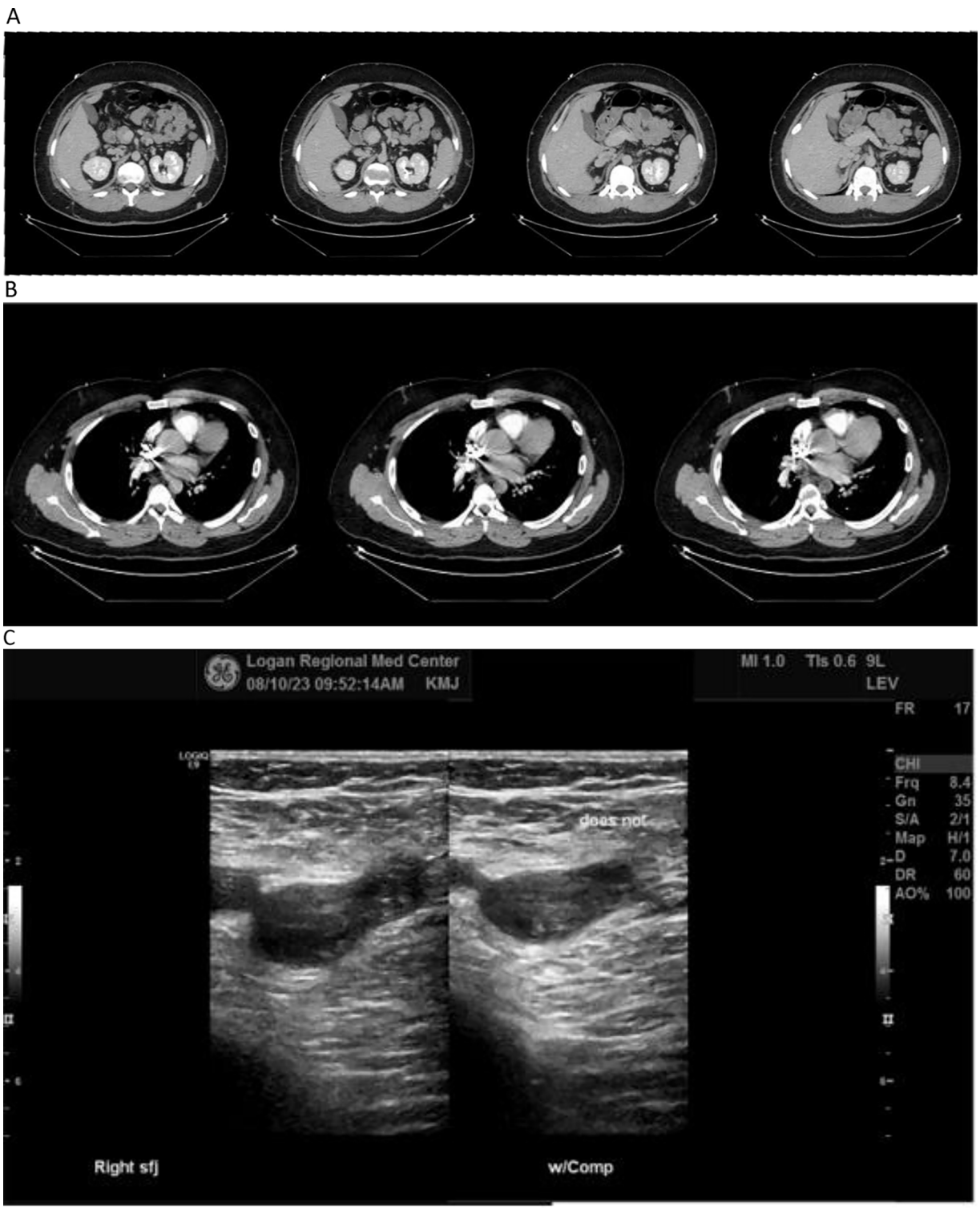

FIGURE 1
(A–C) diagnostic imaging. **(A)** CT of abdomen with contrast. **(B)** CT of chest with contrast. **(C)** Venous doppler ultrasound of right leg. Contrast-enhanced CT scans of patient's abdomen **(A)** and chest **(B)** showing evidence of pulmonary emboli in left central pulmonary arteries, and agenesis of the inferior vena cava with extensive collateralization. Venous Doppler ultrasound of the right lower extremity **(C)** showing thrombus present from the common femoral vein distally into the popliteal vein extending into the greater saphenous vein.

TABLE 1 Complete blood count (CBC) with differential.

Test	Result	Reference ranges
WBC	9.1 thousand/mm^3	4.8–10.8 thousand/mm^3
RBC	4.61 million/mm^3	4.2–5.4 million/mm^3
Hemoglobin	14.1 g/dl	14–18 g/dl
HCT	42.4%	42.0%–52.0%
MCV	92.0 fL	78–98 fL
MCH	30.6 pg	27–31 pg
RDW	12.5%	10.7%–14.0%
Platelet count	198 k/mm^3	130–400 k/mm^3
MPV	9.4 fL	6.6–9.3 fL
Gran %	72.4%	42.2%–75.2%
Lymphocyte %	15.6%	20.5%–51.1%
Monocyte %	10.6%	1.7%–9.3%
Eosinophil %	0.8%	0.0%–10.0%
Basophil %	0.3%	0.0%–0.8%

TABLE 2 Comprehensive metabolic profile.

Test	Result	Reference ranges
Glucose	92 mg/dl	70–110 mg/dl
BUN	13 mg/dl	7–18 mg/dl
Creatinine	0.8 mg/dl	0.6–1.3 mg/dl
eGFR	123.63	

TABLE 3 Electrolyte panel, and liver enzyme measurements.

Test	Result	Reference ranges
Sodium	138 mmol/L	135–145 mmol/L
Potassium	4.2 mmol/L	3.5–5.1 mmol/L
Chloride	104 mmol/L	98–107 mmol/L
CO2	26.6 mmol/L	21–32 mmol/L
Calcium	9.1 mg/dl	8.5–10.1 mg/dl
Total protein	7.6 gm/dl	6.4–8.2 gm/dl
Albumin	4.0 gm/dl	3.4–5.0 gm/dl
Bilirubin, total	0.6 mg/dl	0.0–1.0 mg/dl
SGOT/AST	24 Units/L	15–37 Units/L
SGPT/ALT	67 Units/L	30–65 Units/L
Alkaline phosphatase	68 Units/L	50–136 Units/L

anatomically extensive DVT, and life- threatening PE. In our patient's case, he has both a heterozygous Factor V Leiden deficiency and IVC agenesis. He also had an extensive DVT on his right side extending from his great saphenous vein to femoral vein, and PE. Current guidelines are lacking for this complex situation.

Current literature demonstrates that two groups encountered similar challenges in managing IVC agenesis in their patients. In 2014, Lamparello et al. managed a patient with DVT, IVC agenesis, and FVL mutation with indefinite vitamin K antagonist therapy (3). In 2019, Estevez Cruz et al. described treating a patient with DVT and IVC agenesis using a direct Factor Xa inhibitor indefinitely, reporting no new DVT events over four years of follow-up (5). Though the two groups (Estevez Cruz, and Lamparello) ultimately discharged their patients with different treatment regimens, both reported no established guidelines in medical literature of what anticoagulant to utilize.

The decision to discharge our patient on direct Factor Xa (Apixaban) was largely due to the difficulty in managing Vitamin K antagonist (VKA) treatment. Experts recommend patients spend at least 65% of their VKA treatment in the appropriate therapeutic range (calculated as TTR), but a review in 2016 by Schein et al., found patients on average spent ~54%–65% in the TTR appropriate range (6). Maintaining the target therapeutic range for VKA treatment, like Warfarin, is challenging due to factors like missed appointments, doses, and drug interactions. Deviations from the ideal INR range (2, 3) can lead to thrombotic events or severe bleeding, including gastrointestinal and intracranial hemorrhages.

Our decision to select Apixaban over other direct oral anticoagulant (DOAC) drugs, and VKAs was attributed to its low-risk comprehensive safety profile. In a review by Ballestri et al. published in 2023, it was cited that one study found DOAC drugs reduced the risk of intracranial hemorrhage by over 40% compared to VKAs (specifically, Apixaban reduced the risk by 57%, while Rivaroxaban did by 41%) (7, 8). The review also cites Apixaban as having the best safety profile for GI bleeds compared to VKAs and other DOACs (7).

A recent study by Bravo-Perez et al. published in 2024 analyzed 122 patients with IVC agenesis and venous thrombosis, identifying 18 patients (16%) with an FVL mutation, underscoring a potential link between congenital vascular anomalies and inherited thrombophilia (9). Most patients (89%) were initially treated with vitamin K antagonists (VKAs), while a smaller subset received direct oral anticoagulants (DOACs) as frontline therapy (7 patients) or were switched from VKAs to DOACs after initial treatment (16 patients). Another 7 patients remained on low-molecular-weight heparin (LMWH) without transitioning to oral therapy. The study reported a 40% recurrence rate of venous thrombosis, with recurrence significantly higher (51%) in those who discontinued anticoagulation compared to those on indefinite therapy (35%). Recurrence was defined as radiologically confirmed new thrombotic events at a different site from the initial clot, accompanied by clinical symptoms. Among patients with both IVC agenesis and FVL mutation, inherited thrombophilia was significantly associated with a higher risk of recurrent thrombosis (aOR 3.19, 95% CI 1.09–9.32, $p = 0.034$). Overall, although IVC-agenesis serves as a congenital anomaly that may appear as a primary driver of thrombosis, we still believe based on the statistics published in this study that it further stresses the importance of evaluating genetic and image-based thrombophilia testing in all young patients with unprovoked DVTs. The study commented on how often simple and easy steps undertaking abdominal imaging can help discover previously unknown congenital anomalies like IVC-agenesis that can make a life-changing difference in a first time unprovoked DVT patient. We also believe that this landmark study evaluating an otherwise difficult to find dataset of 122 patients supports the importance of having IVC-agenesis patients remain on life-long anticoagulation to help reduce the risk of recurrent thrombosis.

Indefinite anticoagulation remains the most effective strategy for reducing recurrent thrombotic events in patients with IVC

agenesis, particularly those with additional risk factors such as FVL mutation. Given the high recurrence risk in this population, lifelong anticoagulation with a well-tolerated DOAC like Apixaban offers the best balance between efficacy and safety. However, as endovascular and surgical interventions evolve, future studies are needed to explore alternative treatment options that may provide a more definitive solution for patients with congenital vascular anomalies like IVC agenesis.

Conclusion

The coexistence of IVC-agenesis and heterozygous FVL mutation in a young patient can lead to unprovoked DVT, and PE development. This case underscores the rarity and complexity of treating patients with multiple predisposing factors for VTE. The successful use of direct oral Factor Xa oral anticoagulation (Apixaban) in this scenario highlights its potential as a viable long-term treatment option, opening new discussions for managing similar complex cases in the future.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Logan Regional Medical Center ethics committee/institutional review board. 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

AS: Conceptualization, Writing – original draft, Writing – review & editing. TH: Conceptualization, Investigation, Writing – review & editing. QN: Conceptualization, Investigation, Writing – review & editing. WW: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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.

Publisher's note

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TYPE Case Report
PUBLISHED 11 April 2025
DOI 10.3389/fcvm.2025.1467309

OPEN ACCESS

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RECEIVED 19 July 2024
ACCEPTED 27 March 2025
PUBLISHED 11 April 2025

CITATION
Liu F, Wang X, Yuan S, Xu L, Shan K, Wang L, Huang J and Zheng Q (2025) Perioperative management of caesarean section for a pregnant woman with Sjögren's disease and pulmonary embolism: a case report. Front. Cardiovasc. Med. 12:1467309. doi: 10.3389/fcvm.2025.1467309

Perioperative management of caesarean section for a pregnant woman with Sjögren's disease and pulmonary embolism: a case report

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Background: Sjögren's disease (SjD) is a chronic inflammatory autoimmune disease with significant female predominance, characterised by lymphocyte proliferation and progressive damage to exocrine glands. The complexity of the condition of women with SjD and the incidence of complications substantially increase during pregnancy, which undoubtedly has consequences on both maternal health and neonatal outcomes. Pulmonary embolism (PE) is associated with increased perinatal mortality. However, PE has rarely been reported in pregnant women with SjD.
Case presentation: A 40-year-old pregnant woman was diagnosed as having SjD. During admission, she experienced chest tightness and suffocation and was scheduled for caesarean section under combined spinal-epidural anaesthesia because of sustained low oxygen saturation and foetal distress. Postoperative pulmonary artery computed tomography angiography confirmed that the patient had developed a pulmonary embolism during the perioperative period. After multidisciplinary consultation, the patient underwent inferior vena cava filter implantation, anticoagulation, oxygen therapy, and anti-infection therapy; both the mother and neonate recovered and were discharged.
Conclusion: Early identification and comprehensive perioperative monitoring during the prenatal period are vital in patients with SjD complicated by PE.

KEYWORDS

Sjögren's disease, autoimmune diseases, pulmonary embolism, venous thromboembolism, pregnancy, female, cesarean section, case report

Introduction

Sjögren's disease (SjD) is a complex chronic inflammatory autoimmune disease characterised by reduced secretion of exocrine glands, which predominantly damages the salivary and lacrimal glands, nose, upper respiratory tract, and oropharynx; the vagina may also be affected. The pathogenesis of SjD is multifaceted and involves both genetic predispositions and environmental triggers (1). It is characterised by a chronic inflammatory process within the exocrine glands, driven by an abnormal immune response to autoantigens, such as Ro/SSA and La/SSB, mediated by both B and T cells. This immune dysregulation results in the infiltration of lymphocytes into exocrine glands, causing damage to their physiological structure and function (2).

The reported incidence and prevalence of SjD differ according to the classification criteria applied. A comprehensive systematic review of relevant studies estimated the incidence at approximately 6.9 cases per 100,000 person-years and prevalence of approximately 60.8 cases per 100,000 individuals (3). SjD predominantly affects females, with a female-to-male ratio of 9:1–28:1 (4). The prevalence of secondary SjD, which occurs in conjunction with other autoimmune diseases, fluctuates according to the specific associated conditions.

SjD is a slowly progressive condition with a wide range of clinical manifestations. Patients often present with sicca symptoms, including dry eyes and dry mouth, but may also experience extraglandular involvement, such as arthritis, neuropathy, pulmonary disease, and renal complications (5, 6). This disease has various clinical characteristics and induces multiple systemic complications that cause difficulties and challenges in perioperative anaesthesia management. Research has shown that SjD can promote the development of a hypercoagulable state of blood, thereby increasing the risk of venous thromboembolism (VTE) and pulmonary embolism (PE). This hypercoagulability is thought to be related to the chronic inflammatory state and immune dysregulation characteristic of SjD (7). In addition, the risk of adverse pregnancy outcomes increases in women with SjD, underscoring the need for specialised care during pregnancy and the perinatal period (8).

We report the case of a 40-year-old female patient with SjD who underwent caesarean section and developed PE during the perioperative period. Here, we discuss our management strategies for this case, emphasising the need for vigilant monitoring, appropriate thromboprophylaxis, and careful consideration of the unique challenges posed by SjD in the perioperative setting.

Case presentation

A 40-year-old woman at 37 weeks of pregnancy complained of chest tightness and suffocation and visited our hospital for treatment on 4 April 2024. This patient was previously diagnosed with SjD at another hospital, after which she received treatment with oral hydroxychloroquine sulphate (0.2 g twice a day) for 5 weeks until admission. Symptoms on admission included limb fatigue, palpitations, dry mouth, dry eyes, and Raynaud phenomenon. The patient's vital signs were recorded upon admission. The patient's non-invasive blood pressure was 120/75 mmHg, heart rate fluctuated between 110 and 130 beats per minute, and respiratory rate and body temperature were 15 beats per minute and 36.5°C, respectively. Analyses of the results of the autoantibody and routine examinations were as follows: the anti-SSA antibody concentration was 67.62 RU/ml, the antinuclear antibody (ANA) was positive, the anti Ro52 antibody concentration was greater than 400 RU/ml; complete blood count revealed that the white blood cell count was 9.03×10^9/L, haemoglobin concentration was 136 g/L, and platelet count was 214×10^9/L; plasma D-dimer concentration was 15.97 μg/ml, B-type natriuretic peptide concentration was 200 pg/ml; sensitive troponin I concentration was 0.624 ng/ml; and creatine kinase isoenzyme concentration was 7.51 ng/ml. No apparent abnormalities were found in the other laboratory test results (immunological test results are shown in Table 1). However, foetal heart monitoring revealed that although it manifested as regular uterine contractions, there were frequent deceleration phenomena, and the lowest foetal heart rate could be reduced to 86 beats/minute. Based on the patient's symptoms and results of clinical examinations, as well as consultation opinions from relevant departments, surgeons considered foetal distress and suggested emergency caesarean section to deliver the pregnancy.

The patient was urgently transferred to the operating room 2 h after admission, and a routinely established vein circuit was used to monitor the non-invasive arterial pressure, heart rate, electrocardiography, and pulse oxygen saturation. The patient's blood oxygen saturation was 90%–91% without oxygen inhalation and increased to 97%–98% after mask oxygen inhalation. Arterial blood gas analysis was performed immediately; the lactate value was 1.9 mmol/L, end-tidal carbon dioxide ($ETCO_2$) pressure was 25 mmHg, and other parameters were generally normal. Considering the abovementioned symptoms and laboratory results, PE was considered. The possibility of acute aortic dissection, coronary syndrome, and left heart failure pulmonary oedema persisted. Subsequently, the patient was manoeuvred into the appropriate position, and the intervertebral lacunae were selected between L3 and L4 as puncture points to implement combined spinal-epidural anaesthesia with 0.5% ropivacaine 2.5 ml. When the sensory block reached T6, the surgeon commenced the surgery. A 3.15 kg female infant was delivered using a transverse incision in the lower abdomen, with an Apgar score of 10 points at 1 and 5 min after delivery. Subsequently, 4 ml of 1.5% lidocaine was administered via the epidural catheter, and 20 mg of furosemide was administered via intravenous injection to reduce the volume load. The course of anaesthesia and surgery was uneventful, and the patient received 500 ml of physiological saline. The urine

TABLE 1 Preoperative rheumatoid immune-related test results.

Project Name	Test Results	Concentration Unit	Reference Range
Anti-nRNP/Sm antibody	<2.00	RU/ml	0–20
Anti-Sm antibody	3.14	RU/ml	0–20
Anti-SSA antibody	438.52	RU/ml	0–20
Anti-SS-B antibody	<2.00	RU/ml	0–20
Anti-Scl-70 antibody	<2.00	RU/ml	0–20
Anti-Jo-1 antibody	<2.00	RU/ml	0–20
Anti-AMA-M_2 antibody	3.37	RU/ml	0–20
Anti-GBM antibody	<2.00	RU/ml	0–20
Anti-PR3 antibody	<2.00	RU/ml	0–20
Anti-MPO antibody	<2.00	RU/ml	0–20
Anti-dsDNA antibody	<2.00	IU/ml	0–30
Anti-ACA antibody lgG/lgA/lgM	3.48	RU/ml	0–20
Anti-ANA antibody	Positive		Negative
Main karyotype	Homogeneous		
Main karyotype titres	1:640		
Secondary karyotype	Granular		
ASO	<51.90	IU/ml	0–200
RF	14.30	IU/ml	0–20

volume and blood loss were 150 and 300 ml, respectively, during the entire surgery. The patient returned to the ward after the removal of the epidural catheter and connection of patient-controlled intravenous analgesia (PCIA) with sufentanyl and dexmedetomidine at the end of the operation.

One day after the operation, although the patient did not complain of discomfort such as chest tightness and breathlessness, the oxygen saturation remained at 95%–96% without oxygen inhalation. The patient received two subcutaneous injections of 60 mg enoxaparin to prevent lower limb thrombosis. The plasma D-dimer concentration increased to 88.68 μg/ml, and echocardiography revealed that the general pulmonary artery was obviously widened, with an estimated pulmonary artery systolic pressure of approximately 37 mmHg and moderate echogenicity in the right pulmonary artery. Pulmonary artery computed tomography angiography (CTA) revealed multiple columnar filling defects in the lumen of the pulmonary artery trunk and its branches (Figure 1). The analysis of the above results supports the clinical diagnosis of multiple PE and right ventricular dysfunction. Multidisciplinary consultations recommend adopting critical care, providing continuous oxygen therapy, maintaining fluid balance, and actively engaging in anticoagulant therapy. In addition, ultrasonography of both lower limbs suggested left popliteal vein thrombosis; thus, the patient was treated with implantation of a lower-limb venous filter. She was transferred to the intensive care unit (ICU) after the operation and received symptomatic treatments such as high-flow oxygen therapy, moxifloxacin for anti-infection, enoxaparin for anticoagulation (enoxaparin 7,500 units subcutaneously every 12 h), gastric protection, and improvement of microcirculation. The patient's symptoms and clinical examination results improved after the above series of therapies in the ICU, and she was transferred to the respiratory department for subsequent treatment 5 days later. Re-examination of lower limb venous ultrasound showed that the venous lumen decreased, blood flow resumed smoothly, plasma D-dimer concentration decreased to 1.69 μm/ml, and there were no obvious abnormalities in others. During this period, the infant was in excellent health and fed milk powder. Both the patient and infant were permitted to leave the hospital safely on the tenth day of hospitalisation. The patient was requested to continue taking oral medication for anticoagulation (rivaroxaban orally, 15 mg twice daily for 2 weeks, then increasing the dosage to 20 mg per dose) and protection of the liver after discharge. The patient was admitted on 9 May 2024 for the removal of the inferior vena cava filter. Her condition was stable, and subsequent treatment included continuing oral rivaroxaban for anticoagulation for 2 months, with regular follow-up appointments (Figure 2).

Discussion

Epidemiological studies have revealed that the prevalence of SjD, one of the most frequent systemic autoimmune diseases (SAD), is significantly higher in females (up to approximately 95%) than in men (9). There is no evidence suggesting that SjD affects female fertility. Nevertheless, women with SAD are more likely to experience complications during pregnancy than those without corresponding diseases. As one of the target organs during pregnancy, the placentas of patients with SjD may be damaged, causing functional impairment. Maternal antibodies, such as anti-SSA and anti-SSB antinuclear antibodies, can also enter the foetus through the placental barrier and affect intrauterine development, resulting in a high incidence of adverse foetal outcomes (10–12). Pregnancy itself can also affect SjD progression by significantly increasing the production and expression of autoantibodies under the influence of elevated hormone and prolactin levels. Approximately 30% of patients with SjD experience disease progression during pregnancy (13). Fortunately, with the further recognition of SAD and the development of perinatal management, an increasing number of pregnant women with SjD can safely undergo gestation. Notably, manifestations of SjD vary and involve multiple systems. Lung involvement is a common and serious complication, including interstitial lung disease, airway disease, and lymphoproliferative disorders with varying degrees of severity (14).

In contrast, several studies have indicated that patients with SjD, especially those with concomitant interstitial lung disease and anti-SSA antibody positivity, have a higher risk of VTE and PE, which may be related to reduced blood flow velocity and endothelial

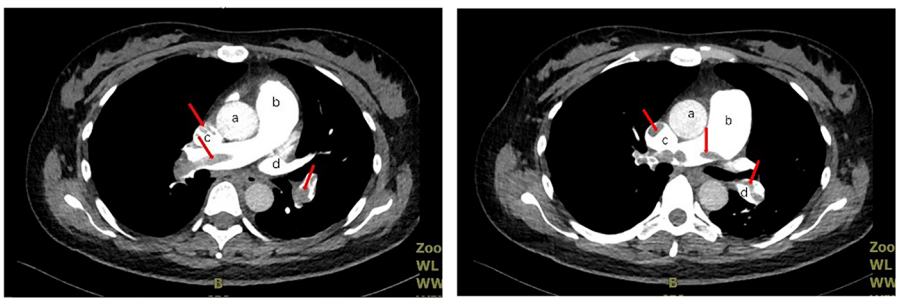

FIGURE 1
Pulmonary artery CTA image, a, aorta; b, pulmonary artery trunk; c, right pulmonary artery; d, left pulmonary artery (the red arrow indicates multiple embolisms in the left and right pulmonary arteries and pulmonary artery trunks).

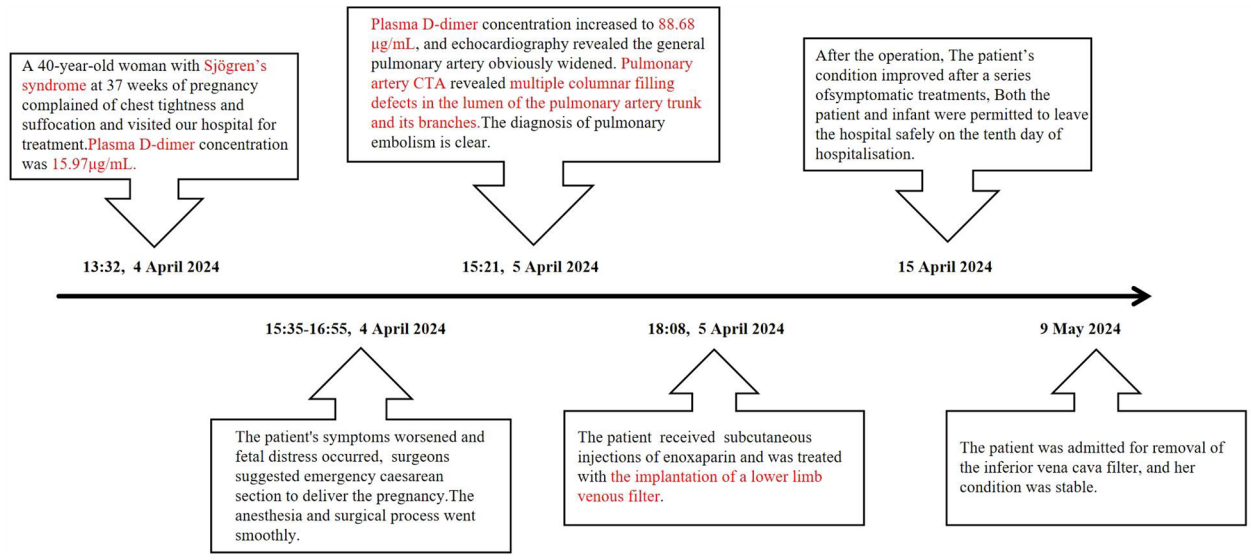

FIGURE 2
Case timeline.

damage (15, 16). The onset of SjD is accompanied by a significant inflammatory process that produces various cytokines and inflammatory mediators that damage vascular endothelial cells, leading to immune vasculitis and the formation of an inflammatory microenvironment that is conducive to thrombosis (17–19). PE is a clinical and pathophysiological syndrome caused by endogenous or exogenous emboli that block the main trunk or branches of the pulmonary artery, leading to pulmonary circulation disorders. Approximately 75%–90% of PE cases originate from deep vein thrombosis in the lower extremities, and peripartum PE is one of the chief causes of sudden maternal death (20). Pregnant women exhibit an increase in coagulation factors and a decrease in anticoagulant factors, with the fibrinolysis process inhibited. This results in a hypercoagulable state during pregnancy, which may persist for 6–8 weeks postpartum. The vein has a wider diameter and a slower flow velocity during gestation. Physiological compression of the left common iliac vein makes it more prone to thrombosis; thus, researchers agree that peripartum PE mainly originates from thrombosis of the left lower limb. Moreover, caesarean section can cause damage to pelvic tissue and blood vessels, coupled with the stress response of surgery, which can easily activate the body's coagulation system (21).

SjD has diverse clinical manifestations accompanied by multiple organ injuries, and pregnancy can increase the complexity of the illness. Therefore, perioperative anaesthetic management of SjD combined with pregnancy remains a challenge. In this case, the patient had been diagnosed with SjD in the previous prenatal examination, mainly due to respiratory and circulatory symptoms, including chest tightness, shortness of breath, and palpitation, which in turn required an emergency caesarean section to deliver the pregnancy. First, adequate preoperative assessment of patients according to their general condition is crucial, focusing on symptoms and simultaneously discriminating against other fatal complications at the same time. The detection of anti-SSA, ANA, and anti-Ro52 antibodies on admission, combined with typical related symptoms (dry mouth, dry eyes, and Raynaud phenomenon), confirmed the diagnosis of SjD (9). The available literature has identified that the cardiovascular system is a target of SjD and that all parts of the heart can be affected, mainly characterised by pulmonary arterial hypertension, pericarditis, and cardiac arrhythmias (22). With this in mind, B-type natriuretic peptide, sensitive troponin I, creatine kinase isoenzymes, and electrocardiograms were detected and observed, and no apparent abnormalities were found. The patient's preoperative plasma D-dimer levels increased abnormally. D-dimer is a soluble fibrin degradation biomarker that can be measured in whole blood or plasma. The fibrinolytic system produces it through the orderly decomposition of thrombi and has been extensively investigated for the diagnosis of VTE or PE. In terms of the outcome, the increase in D-dimer levels in this case indicated the subsequent occurrence of PE. However, there are some limitations to D-dimer testing for the diagnosis of the above diseases: the specificity of detection decreases with pregnancy, cancer, recent surgery, or trauma, and D-dimer levels increase with gestational age and complicated pregnancies; therefore, combining the results of imaging examinations may increase the diagnostic accuracy (23).

It is more likely that deep vein thrombosis (DVT) and PE were present before surgery, and we chose combined spinal-epidural anaesthesia after eliminating the relative taboos. Compared to general anaesthesia, intraspinal anaesthesia inhibits the sympathetic nervous system, dilates blood vessels below the blocking plane, and accelerates blood flow in the lower limb blood vessels (24). Intraspinal anaesthesia also has a positive effect on blood rheological properties, significantly reducing red blood cell viscosity and effectively inhibiting blood clots (25). Local anaesthetics, including ropivacaine, can inhibit coagulation

by preventing platelet aggregation and particle release (26). Although the arterial blood gas analysis before anaesthesia was normal, we found that the blood oozing out during intraspinal anaesthesia was dark black, adding to the situation that she had sustained low oxygen saturation and $ETCO_2$ pressure with symptoms of cyanosis of the lips, chest tightness, and suffocation. There are reasons to doubt that the patient may have experienced PE during surgery. Fortunately, continuous intraoperative oxygen therapy and accurate fluid management are crucial to ensure a smooth operative finish, and both the mother and baby were doing well after the operation.

The D-dimer concentration continued to rise after the caesarean section for some time, and an accurate clinical diagnosis of PE and DVT was made, ultimately relying on pulmonary artery CTA and ultrasound. Subsequently, the patient underwent all interventions in sequence, including lower-limb venous filter implantation, anticoagulation, oxygen therapy, and other symptomatic treatment measures, and was finally discharged from the hospital on the tenth day of hospitalisation.

The outcomes of this case were satisfactory. Several aspects of the perioperative period are worth discussing and further improving. First, when faced with a high degree of suspected PE with anoxic signs, pectoralgia, or other conditions, related examinations, including bedside cardiac and lower limb ultrasonography and pulmonary artery CTA, should be performed to immediately clarify the diagnosis before surgery, which is available for subsequent haemodynamic and respiratory support therapy. Simultaneously, anticoagulants or thrombolytic therapy should be administered as early as possible. Heparin is a commonly used anticoagulant in clinical practice, and the injection of heparin after caesarean section is mainly used to prevent DVT in the lower limbs. Guidelines recommend administering anticoagulant drugs 6–12 h after caesarean section to reduce the risk of perinatal bleeding in patients with PE (27). Thrombolytic drugs can directly or indirectly convert fibrinogen into fibrinolytic enzymes, rapidly degrade fibrin, and dissolve blood clots. Thrombolytic therapy with urokinase or recombinant tissue-type plasminogen activator combined with anticoagulant therapy has a positive effect on patients with acute PE. In a study of 28 cases of thrombolysis during pregnancy, Leonhardt et al. found that the effective rate was 90%, the foetal mortality rate after thrombolysis treatment was 23% (including three cases of induced abortion), and no significant sequelae were found in surviving newborns after delivery (28). Therefore, systemic or catheter-directed thrombolysis may have been a good treatment option for this patient. Second, in addition to routine monitoring such as electrocardiography, non-invasive blood pressure, pulse oximetry, and body temperature, invasive measurement of continuous arterial pressure should be established to monitor circulatory systemic situations in real time and obtain blood samples for arterial blood gas analysis. General anaesthesia may be a better option for PE patients with a confirmed diagnosis and unstable haemodynamics or for those who have already received anticoagulant treatment. Finally, the epidural catheter was removed immediately after surgery; however, considering that the patient would soon receive anticoagulant or thrombolytic therapy, it may be more favourable to postpone catheter removal contingent on different medication regimens.

Conclusion

Patients with SjD are at a high risk of developing PE and VTE during pregnancy. The key to dealing with such cases is to quickly identify the early onset of signs, definitively diagnose them, and provide direct treatment with the help of imaging examinations. Therefore, high-quality perioperative anaesthesia management, as typified by appropriate oxygen therapy and volume management, is helpful for improving patient prognosis.

Data availability statement

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

Ethics statement

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

Author contributions

FL: Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Funding acquisition, Conceptualization, Investigation, Methodology, Supervision. XW: Data curation, Funding acquisition, Investigation, Supervision, Writing – review & editing. SY: Data curation, Investigation, Writing – review & editing. LX: Data curation, Writing – review & editing. KS: Formal analysis, Methodology, Writing – review & editing. LW: Methodology, Supervision, Writing – review & editing. JH: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. QZ: Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. Support was provided by the Qingdao Key Health Discipline Development Fund (QDZDZK2022094).

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 28 April 2025
DOI 10.3389/fcvm.2025.1532300

OPEN ACCESS

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RECEIVED 21 November 2024
ACCEPTED 16 April 2025
PUBLISHED 28 April 2025

CITATION
Liao J, Ma Y, Wu Z, Wang X and Zhao J (2025) Rare and life-threatening iliac vein stent infection following radiotherapy: a case report emphasizing clinical urgency and preoperative stent evaluation.
Front. Cardiovasc. Med. 12:1532300.
doi: 10.3389/fcvm.2025.1532300

Rare and life-threatening iliac vein stent infection following radiotherapy: a case report emphasizing clinical urgency and preoperative stent evaluation

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This case report discussed a 43-year-old female who underwent multiple radiotherapy sessions after cervical cancer surgery and experienced serious complications due to simultaneous iliac vein stent placement immediately after thrombus aspiration without adequate evaluation of the indication for stent placement. Two months after radiotherapy, the patient developed right lower limb edema and pain, which led to the discovery of an iliac vein thrombosis. Subsequent stent placement without thorough evaluation resulted in severe complications, including infection and sepsis. Despite initial symptom relief, the patient was readmitted with high fever and severe pain, and imaging revealed gas around the stent, indicating infection. An exploratory laparotomy uncovered a large abscess and a colonic fistula. The stents were removed, and the patient underwent aggressive anti-infection treatment involving meropenem and vancomycin, along with surgical repair of the fistula. This case highlights the importance of accurate diagnosis and careful consideration of stent placement in preventing severe outcomes, including the rare but serious risk of venous stent infections requiring surgical intervention.

KEYWORDS

iliac vein stent, venous stent infection, radiotherapy complications, cervical cancer, colonic fistula

Introduction

Post-radiotherapy complications in cervical cancer patients can be complex and challenging to diagnose. Radiotherapy, while effective in treating malignancies, can cause significant damage to surrounding tissues, leading to complications such as fibrosis, abscess formation, and vascular compression, although these complications are very rare (1). Patients often present with non-specific symptoms such as nausea, vomiting, and abdominal pain, which can obscure more serious underlying conditions (2). Accurate diagnosis and comprehensive preoperative assessments, including advanced imaging techniques like CT scans, are crucial to identify these complications early and plan appropriate interventions.

Additionally, patients with gynecologic malignancies often enter a hypercoagulable state following surgery, rendering them particularly susceptible to deep vein thrombosis (DVT) (3). The use of chemotherapy agents can further exacerbate this risk by contributing to endothelial damage and dysregulation of coagulation pathways (3).

Consequently, when such patients develop DVT alongside the rare complications discussed above (e.g., fibrosis or abscess formation after radiotherapy)—the latter of which can compress the iliac vein and further exacerbate DVT—the clinical scenario becomes markedly more complex (4). Determining whether to recanalize the deep venous system and proceed with iliac vein stent placement can pose significant challenges, and inadequate evaluation may lead to severe consequences. This complexity underscores the importance of meticulous preoperative planning and individualized treatment strategies, as illustrated by the case presented in this report.

Case presentation

A 43-year-old female patient previously treated with a total hysterectomy and bilateral adnexectomy for cervical cancer underwent three chemotherapy cycles and 28 radiation therapy sessions. Throughout the radiation therapy, she frequently reported nausea, vomiting, and abdominal pain, in addition to unexplained fevers peaking at 39°C. Two months following the completion of radiation, she developed right lower limb edema with pain. Ultrasound imaging performed at a local hospital suggested right external iliac vein thrombosis. An intervention under local anesthesia included catheter-directed thrombolysis which revealed "compression of the right iliac vein," leading to a series of procedures: inferior vena cava angiography, filter placement, deep venous aspiration thrombectomy, right iliofemoral vein balloon dilation, and iliofemoral venous stent placement. Although the procedures initially alleviated her symptoms, the patient discontinued rivaroxaban one month later due to gastrointestinal bleeding. She was subsequently admitted to our hospital with recurrent right lower limb swelling and severe pain, alongside a fever of 42°C.

Laboratory tests revealed a normal white blood cell count (WBC) of 6.7×10^9/L despite markedly elevated infection markers, including C-reactive protein (CRP) at 74.2 mg/L, interleukin-6 (IL-6) at 79.3 pg/ml, and procalcitonin (PCT) at 73.8 ng/ml, suggestive of a severe systemic inflammatory response. Meanwhile, pancytopenia was observed, with hemoglobin (Hb) at 51 g/L and platelet count (PLT) at 44×10^9/L. Physical examination identified moderate pitting edema in the right lower limb and the foot below the left ankle. Blood cultures indicated dual infection with Escherichia coli and Enterococcus faecalis. Venous ultrasound suggested thrombosis in the right femoral and superficial femoral veins. An abdominal CT showed gas accumulation around the stent in the right external iliac and femoral veins with surrounding soft tissue swelling (Figure 1). We suspected an iliac vein stent infection leading to sepsis and planned an exploratory laparotomy to identify and manage the source of infection. Importantly, we decided against removing the filter during this hospital stay, planning its removal after assessing the risk of pulmonary embolism.

Intraoperatively, a large abscess was discovered in the right iliac fossa, containing pus-soaked iliofemoral vein stents with thrombosis inside the stent and the adjacent vein (Figure 2). A 2 cm fistula was identified in the right wall of the rectosigmoid junction, leaking feces. We removed the iliofemoral vein stents, ligated the common iliac and femoral veins, repaired the colonic fistula, and created a colostomy. Postoperative management in the ICU involved aggressive anti-infection treatment initially with meropenem (1 g every 8 h) and vancomycin (1 g every 12 h), later stepped down to piperacillin-tazobactam (4.5 g every 8 h) after improvement of infection markers. Anticoagulation therapy began with fondaparinux sodium 2.5 mg daily starting on postoperative day 7 and gradually transitioned to rivaroxaban 20 mg daily at one month postoperatively, with dynamic monitoring and dose adjustment based on coagulation risk assessment. At a three-month follow-up, she was afebrile with no new DVT detected (Table 1).

Discussion

This case highlights the complexities of diagnosing and managing post-radiotherapy complications in cervical cancer patients, particularly when common post-treatment symptoms such as abdominal pain might obscure underlying developments like pelvic abscesses. These complications necessitate a high degree of vigilance. The abdominal pain in this case may have initially been linked to a pelvic abscess, which may have already formed during radiotherapy, subsequently leading to vein compression (5). This oversight emphasizes the need for careful consideration of radiotherapy-related complications. In this instance, it precipitated significant damage to colonic tissue, leading to a complex pelvic infection and the formation of a colonic fistula. And the hypercoagulable state in postoperative cervical cancer patients inherently presents a high risk for deep vein thrombosis (DVT), further obscuring the investigation into the underlying causes of DVT (6). These diagnostic oversights resulted in an incorrect assessment and the inappropriate placement of a venous stent, which subsequently caused severe complications, underscoring the critical need for accurate diagnosis and intervention planning.

Moreover, the involvement of the iliac vein and the subsequent infection of its stent draws attention to the differential diagnosis of iliac vein compression, including May-Thurner Syndrome (also known as Iliac Vein Compression Syndrome, IVCS). Traditionally associated with left-sided iliac vein compression, IVCS is increasingly recognized as affecting the right side and contributing to clinical symptoms (7). Additionally, it is important to note that while venography can diagnose iliac vein compression and is considered the gold standard for diagnosing pelvic congestion syndrome, its diagnostic accuracy and specificity are still lower compared to vascular ultrasound examinations. It often cannot clearly identify the extrinsic compression on the venous lumen (8). In this case, although guidelines mention that venous stents can extend across the inguinal ligament when the lesion is long and involves the deep femoral vein, there was no clear evidence indicating that the lesion length necessitated such an extended stent placement (9). However, the local operation records confirmed that the initial placement of the stent was appropriate; however, we believe that subsequent infection led to bacterial adhesion and gas formation,

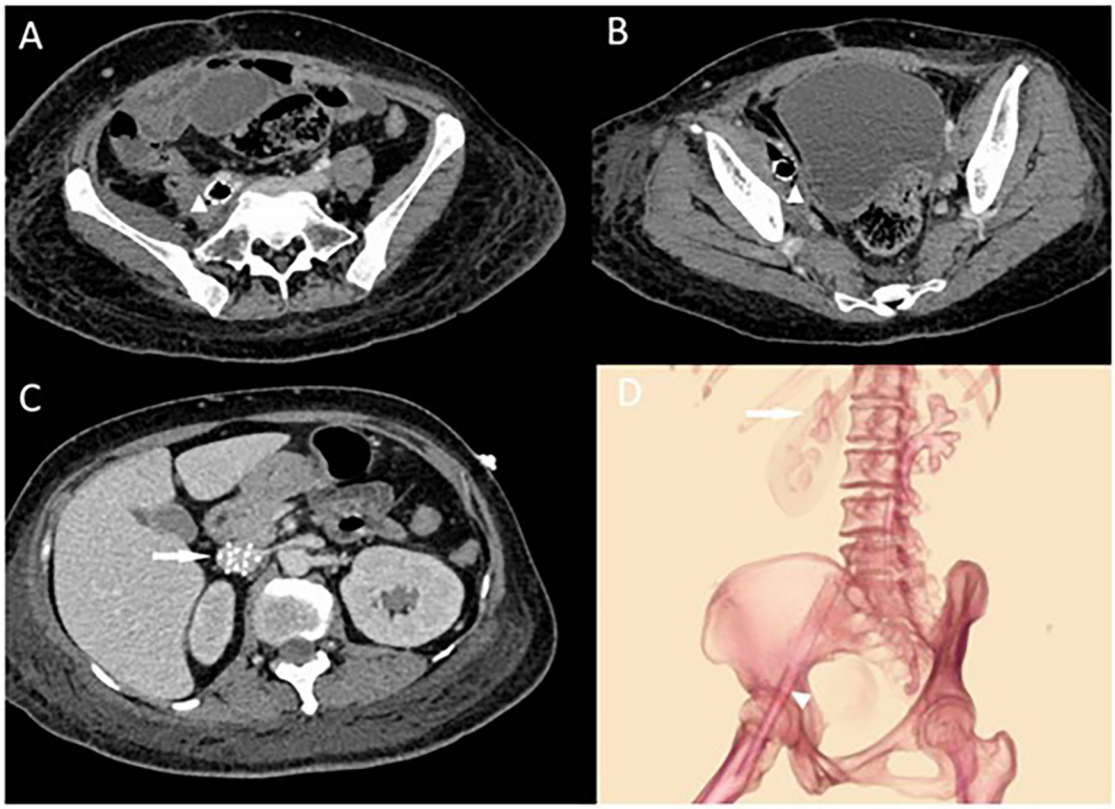

FIGURE 1
(A,B) Abdominal CT showing right external iliac vein and femoral vein stent with pneumatization and surrounding soft tissue swelling with pneumatization. The triangular markers indicate the abscess and the changes in the surrounding soft tissues around the stents. In **(C)**, the arrow points to the locally placed inferior vena cava (IVC) filter situated within the IVC. **(D)** Illustrates the positions of the IVC filter and the two stents, showing their course crossing over the inguinal ligament.

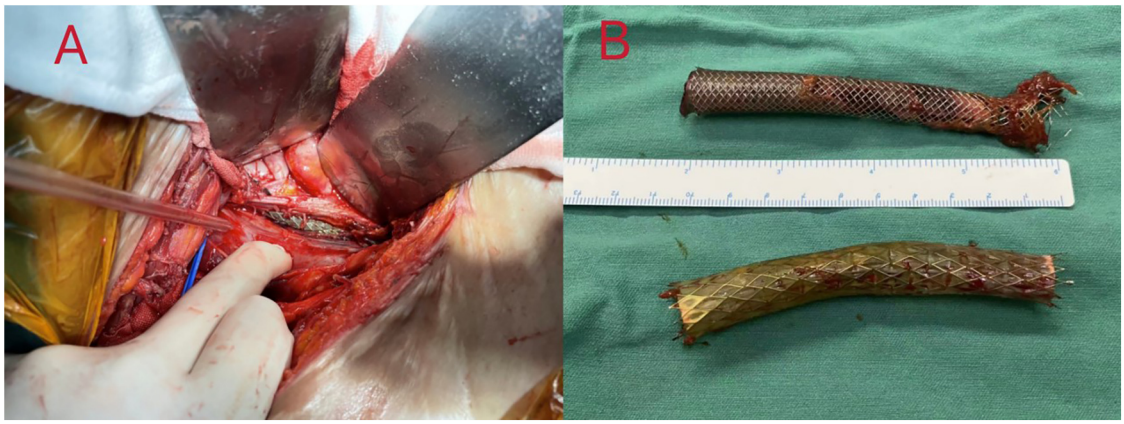

FIGURE 2
(A) after aspiration of the pus by dissection, an incision of the iliac vein was seen to expose the venous stent. **(B)** Complete removal of two different types of venous stents, which were seen to be covered with a large amount of pus moss. The covered stent is a GORE® VIABAHN® 10 mm × 60 mm, and the bare stent is a Wallstent® 12 mm × 60 mm.

causing stent retraction and displacement to an "unreasonable" position across the inguinal ligament. For patients with an existing stent infection, the literature indicates that surgical removal of the stent is typically necessary. Although venous stent infections are rare, when they do occur, they are serious and often resistant to antibiotic treatment (10, 11). In this case, as in the few other reported cases of iliac vein stent infection primarily caused by Staphylococcus epidermidis from the skin, aggressive

TABLE 1 Timeline of the patient's clinical course and key interventions.

Timepoint	Event
7 months before admission	Underwent hysterectomy and bilateral salpingo-oophorectomy, followed by 3 cycles of chemotherapy and 28 sessions of radiotherapy.
5 months before admission	Developed persistent high fever (>39 °C) without an apparent cause.
3 months before admission	Presented with lower extremity swelling and underwent venography, resulting in the placement of a vena cava filter and iliac vein stent.
Day 2 after admission	Emergency surgery was performed, and the patient was transferred to the intensive care unit (ICU).
Postoperative Day 1	Successfully extubated and resumed spontaneous breathing; body temperature normalized.
Postoperative Day 6	Transferred back to the general ward.
Postoperative Day 20	Discharged and referred to a local hospital for continued care.
Three-month follow-up	Afebrile with no new deep vein thrombosis detected.

antibiotic treatment was not effective (12). Thus, the stent was surgically removed. Unlike arterial stents, which are more prone to hematogenous infections, venous stent infections are exceedingly rare. However, when they do occur, they similarly require removal to effectively manage the infection.

In this patient's case, the hysterectomy and bilateral adnexectomy indirectly resulted in a higher dose of postoperative radiotherapy to the rectum and colon, rendering that region more vulnerable to bacterial overgrowth. After more than 20 radiotherapy sessions, the bowel segment sustained sufficient damage to develop radiation enteritis and, eventually, a chronic fistula, which likely explains the patient's recurrent high fevers without a clear trigger prior to DVT onset. Moreover, the associated pelvic abscess caused by the fistula may have further compressed the iliac vein, thereby exacerbating the DVT. Although subsequent stent placement in the iliac vein briefly alleviated her symptoms, its proximity to the fistula introduced a foreign body into an already compromised region, facilitating bacterial colonization and precipitating severe sepsis. The intestinal origin of this infection was confirmed by blood cultures revealing Escherichia coli and Enterococcus faecalis, consistent with a gastrointestinal source. Consequently, opting for one-stage iliac vein stent placement in this setting was not appropriate.

Conclusion

When dealing with patients with high fever and signs of infection after venous stent surgery, we should consider the possibility of a rare venous stent infection. Analyzing the cause of the infection is necessary. Identifying the primary site of infection and route of transmission is crucial for subsequent infection eradication, and prompt removal of the stent to eliminate the infection source is an effective and feasible approach. For cancer patients, stent placement should be approached with extreme caution. Comprehensive pre-operative assessments, such as CT scans to accurately define pelvic and abdominal anatomy, are essential (2). Relying solely on venography to suggest iliac vein compression as a basis for stent placement can lead to tragic outcomes, causing significant patient harm. Ensuring thorough and accurate diagnostic workup is imperative to prevent such severe complications and ensure better patient outcomes.

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 Human Research Review Committee at West China Hospital, Sichuan University (Chengdu, China). 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

JL: Writing – original draft, Writing – review & editing, Formal analysis, Methodology, Software. YM: Formal analysis, Writing – review & editing. ZW: Resources, Writing – review & editing. XW: Data curation, Writing – review & editing. JZ: Supervision, Writing – review & editing.

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.

Generative AI statement

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

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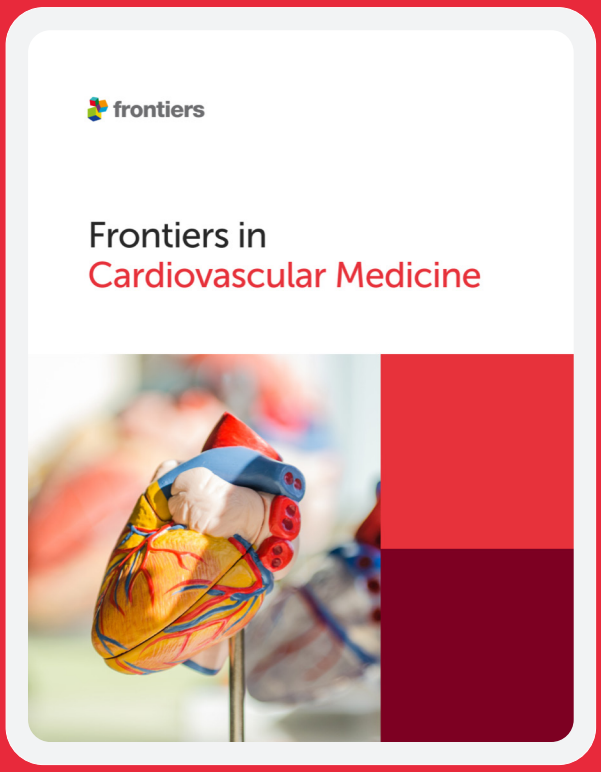

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