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Case reports in atherosclerosis and vascular medicine: 2022

Topic editor

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Table of contents

04 Concurrent Takayasu Arteritis and Vascular Ehlers–Danlos Syndrome: A Case Report
Kyota Hashimoto, Ryota Sakai, Akiko Shibata, Yusuke Okada, Syoichi Yoshinaga, Takahiko Kurasawa, Tsuneo Kondo and Koichi Amano

10 Spontaneous coronary artery dissection and atherosclerosis in a young man with systemic lupus erythematosus: A case report and literature review
Hongbo Huang, Xiaojuan Ma, Linjie Xu, Xin Wang, Dazhuo Shi, Fuhai Zhao and Ying Zhang

18 Case report: Traumatic carotid artery dissection after 7D High-Intensity Macro- and Micro-Focused Ultrasound treatment for skin laxity of the neck
Fenghe Du, Jiang Shao, Zhichao Lai, Kang Li, Chaonan Wang and Bao Liu

24 Giant left coronary artery diagonal branch left ventricular fistula: A case report and review of literature
Jingyue Wang, Huicong Zhang, Qian Tong and Quanwei Wang

32 Case report: Ultrasound-Assisted endovascular therapy for carotid artery floating thrombus
Peng Wang, Zhenzhen Wang, Jie Pan, Kefeng Lu, Litao Sun and Yu Geng

38 Case report: Cement entrapped in the inferior vena cava filter after pedicle screw augmentation
Xinqiang Han, Yongzhen Zhang, Zhu Wang and Mengpeng Zhao

45 Case report: Unusual persistent hypotension and acute occlusion after peripheral paclitaxel balloon angioplasty
Lin Yang, Jianlin Liu and Chao Liu

51 Degos disease with multiple intestinal perforations: A missed-opportunity case report and literature review
Wen Ai, Zhihua Liang, Feng Li and Haihua Yu

57 Compression syndromes of the popliteal artery due to intramuscular ganglion cyst of the biceps femoris: A case report and literature review
Kai Zheng, Wentao Yang, Hualiang Ren, Shengxing Wang, Mingsheng Sun, Wangde Zhang and Chunmin Li

63 Case report: Multiple arterial stenoses induced by autosomal-recessive hypophosphatemic rickets type 2 associated with mutation of ENPP1: a case study
Jie Liu, Xitao Song, Daming Zhang, Yan Jiang, Mingsheng Ma, Zhengqing Qiu, Weibo Xia and Yuexin Chen

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CASE REPORT
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Concurrent Takayasu Arteritis and Vascular Ehlers–Danlos Syndrome: A Case Report

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Takayasu arteritis (TAK) is a rare primary systemic inflammatory vasculopathy. It is classified as a large-vessel vasculitis and is known to cause inflammatory aneurysms and vascular stenosis. Vascular Ehlers–Danlos syndrome (vEDS) is an autosomal dominant condition known to cause multiple aneurysms and arterial dissection at a young age owing to a mutation in the gene for type III collagen, *COL3A1*. Here, we present a case of TAK associated with vEDS with the development of multi-organ infarction of the brain, kidney, and spleen owing to multiple arterial aneurysms and stenosis of the internal carotid artery. The patient was successfully treated using anti-inflammatory agents, glucocorticoids, and tocilizumab with the addition of interventional radiology. In our case, a high inflammatory response led to vasculitis being the main cause of the disease with concurrent vEDS. When patients develop multiple aneurysms, stenosis, and dissections leading to multiple organ infarctions, a systemic differential diagnosis to consider concurrent vasculitis syndrome and non-inflammatory vasculopathy, including hereditary disorders, is important even with time constraints.

Keywords: Takayasu arteritis, vascular Ehlers-Danlos syndrome, neutrophil, tocilizumab, interventional radiology

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INTRODUCTION

Takayasu arteritis (TAK) is a rare primary systemic inflammatory vasculopathy of unknown etiology. It is classified as a large-vessel vasculitis (LVV), predominantly affecting the aorta and/or its major branches; however, arteries of any size may be affected (1). Inflammatory aneurysms and stenosis depending on the vascular wall thickening are common features of this disease. There are no specific laboratory diagnostic markers; however, a high inflammatory response, such as a high C-reactive protein (CRP) level and specific radiographic findings, are helpful for the diagnosis. Recently, tocilizumab (TCZ), a humanized anti-interleukin (IL)-6 receptor (IL-6R) monoclonal antibody, is a promising agent for TAK when administered in combination with glucocorticoids (GCs) for the remission-induction therapy (2). Ehlers–Danlos syndrome (EDS) is a hereditary disorder that affects connective tissues, such as the skin, joints, and blood vessel walls. The International Consortium on Ehlers–Danlos syndrome and related disorders proposed an updated EDS classification in 2017, which presently recognizes 13 subtypes (3). One of these subtypes, vascular Ehlers–Danlos syndrome (vEDS), is known to cause multiple aneurysms and arterial dissection at a young age. This is inherited in an autosomal dominant manner and is due to a mutation in the gene for type III collagen, *COL3A1*. Midsize arteries are the most commonly

involved, and arterial rupture is the most common cause of sudden death. Genetic sequencing is the gold standard for diagnosing vEDS; however, obtaining genetic results is time-consuming, which adds to the ethical consideration. In urgent situations, clinicians are required to diagnose and treat diseases based on limited information. Herein, we report a case of TAK associated with vEDS with the development of multi-organ infarction of the brain, kidney, and spleen due to multiple aneurysms and stenosis of the internal carotid artery. The patient was successfully treated by anti-inflammatory agents, GCs, TCZ, and interventional radiology (IVR).

CASE REPORT

A 28-year-old Japanese man was admitted to our hospital with hypovolemic shock secondary to abdominal hemorrhage and hemiplegia due to a left cerebral infarct. Thirteen days prior to his admission, he developed a right lower abdominal and back pain that worsened in the prone position. Seven days before admission, he had a fever of 38°C and had visited another hospital where his serum CRP level was 13.8 mg/dL (normal range, 0–0.15 mg/dL). Since contrast-enhanced computed tomography (CT) showed a splenic and right renal infarction with multiple aneurysms of the hepatic, right renal, left common iliac, and right internal iliac arteries, and no intra-abdominal bleeding was observed, he was started on anticoagulant therapy, heparin, on admission at that hospital for a week. On the morning of his admission, he experienced undifferentiated dizziness and aggravated abdominal pain. His systolic blood pressure was noted to be in the 60s, and intra-abdominal bleeding from multiple aneurysms was observed on abdominal CT. He was rushed to our emergency room for hypovolemic shock due to bleeding from that hospital.

His medical history included bronchial asthma in childhood, ventricular septal defect, osteoma ossificans, and herpes zoster. Additionally, his family history included a grandmother with spinocerebellar degeneration, a grandfather with hypertension, a father with rheumatoid arthritis and dyslipidemia, and a mother with diabetes mellitus. Further, there was no family history of EDS, other genetic diseases, or sudden cardiovascular death in relatives. The patient showed no difference in blood pressure in the upper extremities. The neurological findings included a complete paralysis of the right upper and lower limbs and dysarthria. No other findings were observed in the remaining physical examinations. Blood tests revealed a markedly elevated inflammatory response with a white blood cell count of 38,000/μL (neutrophil: 99%, lymphocyte: 1%) and CRP of 5.02 mg/dL. All autoantibodies and blood culture test results were negative. A transthoracic cardiac ultrasound revealed no vegetation. Contrast-enhanced CT and angiography showed multiple aneurysms of the hepatic, splenic, right renal, left common iliac, and right internal iliac arteries, as well as infarction of the spleen and right kidney with intra-abdominal bleeding (**Figures 1A–C**). The hepatic aneurysm was enlarged compared to those taken at another hospital 1 week prior (from 13.6 × 7.8 to 16.5 × 13.0 mm). No vascular occlusion was observed on the contrast-enhanced CT scan. Contrast-enhanced magnetic resonance imaging (MRI) of the head and neck showed infarction of the left middle cerebral artery region (**Figure 1D**) and left internal carotid artery aneurysm, stenosis, and dissection (**Figure 2A**). Contrast enhancement was observed around the stenotic area; however, a positron emission tomography (PET) scan of the entire body 1 week after starting the treatment revealed no abnormalities. In other words, rupture of the aneurysm leading to intra-abdominal bleeding and stroke-induced progression of vascular stenosis were observed in a short period. IVR was performed shortly after admission. Embolization was performed to treat the hepatic and splenic artery aneurysms, and the bleeding stopped. Although vEDS was a differential diagnosis, the patient had a severe inflammatory response, probably due to vasculitis.

We administered intravenous methylprednisolone (mPSL) [1,000 mg/day] for 3 days, followed by prednisolone (PSL) at a dose of 70 mg/day (1.2 mg/kg), with the dose reduced every 1–2 weeks (**Figure 3**). Human leukocyte antigen testing (HLA) showed B52, which is common in patients with TAK. Following the administration of GCs, 162 mg of tocilizumab was subcutaneously administered weekly. The inflammatory response and paralytic symptoms improved gradually. No relapse after discharge from our hospital was observed on administering low dose GCs and weekly TCZ. When a neck MRI was performed again in the outpatient clinic after 6 months of remission-induction therapy, there was a decrease in the contrast effect and an improvement in the internal carotid artery stenosis (**Figure 2B**). Although there were no physical findings and family history consistent with vEDS, a follow-up CT scan revealed a dissection of the celiac trunk and the right femoral artery, which was associated with IVR. Finally, the patient was tested for *COL3A1* gene mutation, and a positive result was obtained.

DISCUSSION

To the best of our knowledge, this is the first case report demonstrating TAK associated with vEDS with a combination of inflammatory and non-inflammatory underlying causes and the subsequent development of multi-organ infarcts of the brain, kidney, and spleen due to multiple arterial aneurysms and stenosis of the internal carotid artery. Despite the urgency and the critical situation, we could arrive at a conclusive diagnosis by adequately performing physical examinations, imaging radiography, and blood tests. In addition, there have been no reports of catheter-based aneurysm embolization in the acute stage of TAK and vEDS, as observed in this case. Causes of non-atherosclerotic peripheral arterial stenosis and aneurysm, such as polyarteritis nodosa and Behçet's disease (BD), were considered differential diagnoses for systemic vasculitis. In contrast, segmental arterial mediolysis (SAM), infectious aneurysms, and hereditary elastic fibrous disorders, such as EDS, Loeys–Dietz syndrome, and Marfan syndrome, were considered differential diagnoses for non-inflammatory vasculopathy (4). The key to diagnosis in such cases includes performing an adequate physical examination, the presence of significantly

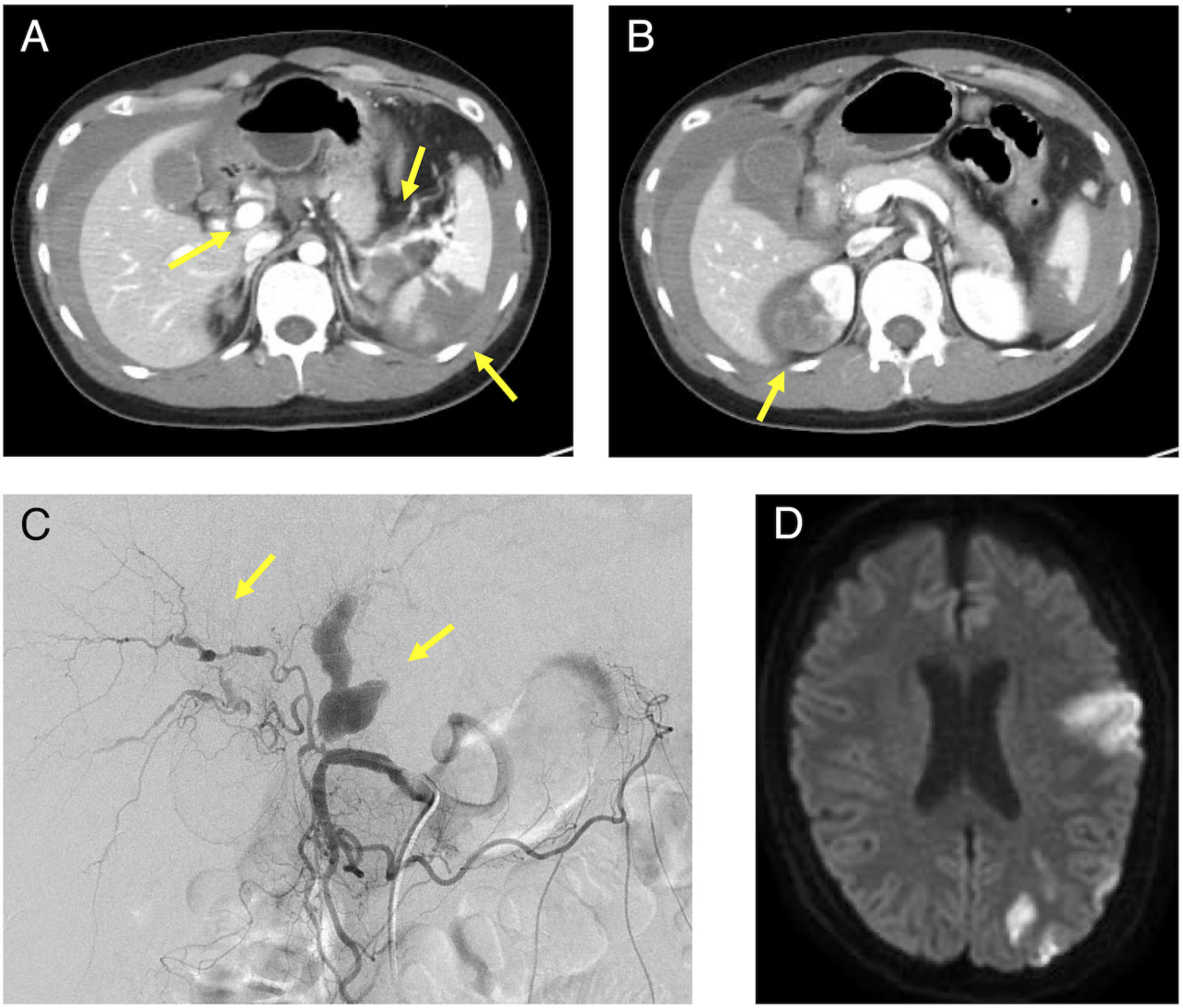

FIGURE 1 | Contrast-enhanced CT, angiography, and head MRI of the patient. **(A)**: Intra-abdominal hemorrhage, splenic infarction, and hepatic and splenic artery aneurysm were observed in the area indicated by the arrow and **(B)**: Right renal infarction was observed in the area indicated by the arrow on the contrast-enhanced abdominal CT. **(C)**: A proper hepatic artery aneurysm was observed in the area indicated by the arrow on angiography. **(D)**: A cerebral infarction was observed in the left middle cerebral artery territory on the plain MRI of the brain. MRI, magnetic resonance imaging; CT, computed tomography.

elevated inflammatory response markers in blood tests, and specific radiographic findings. Consequently, we diagnosed TAK based on the high inflammatory response, positive HLA-B52, perivascular inflammation and stenosis, and multiple arterial aneurysms. Previous research has uncovered the genetic components involved in the pathogenesis of TAK, and HLA-B52:01 is the only definite genetic factor globally (5–8). One reason for observing no abnormalities on the PET scan, in this case, was because it was taken 1 week after treatment initiation; the inflammation could have disappeared. Second, due to poor resolution on PET scan, most of the affected vessels were medium-sized in this case and could, thus, not be detected by PET scan. Although we cannot deny the possibility that the patient developed an inflammatory response due to bleeding or infarction, it does not explain the inflammatory findings around the left internal carotid artery observed on contrast-enhanced MRI. In addition, there was no rupture or enlargement of the abdominal aneurysm after the immunosuppressive therapy for ∼1 year.

In addition, the concurrent diagnosis of vEDS was established based on the genetic results of the *COL3A1* gene mutation. An analysis of a previous study in Japanese patients with vEDS revealed a low frequency of young patients presenting with serious clinical findings, such as arterial rupture/dissection/aneurysm and perforation or rupture of the gastrointestinal tract (5). However, our patient developed

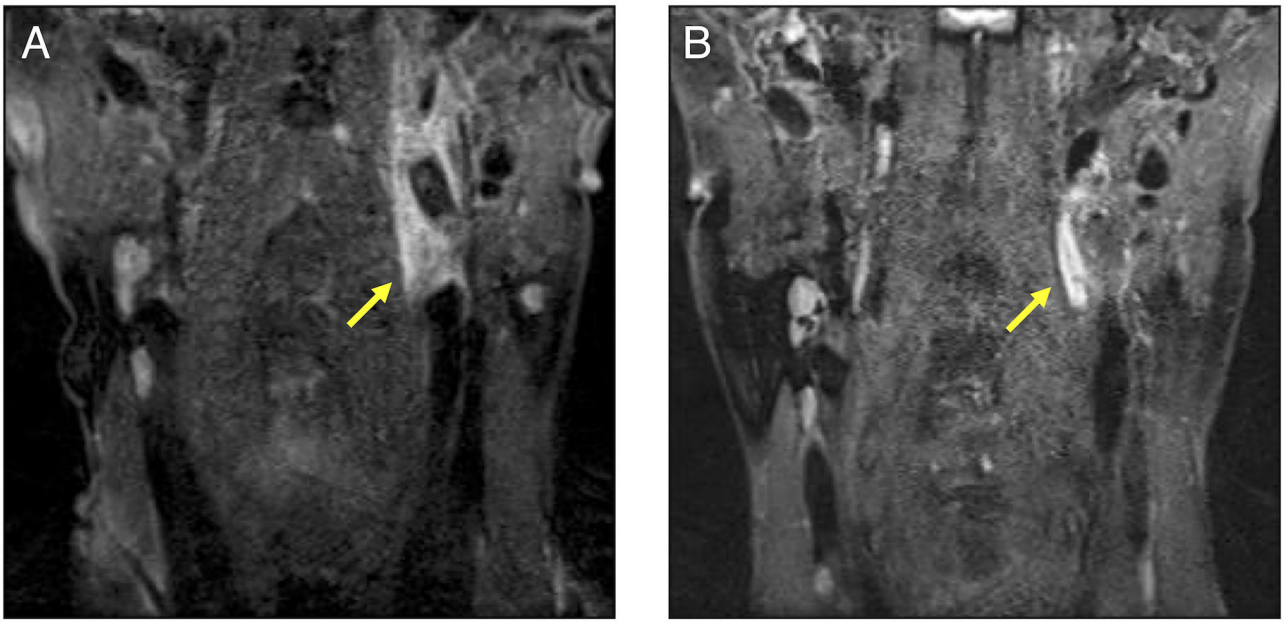

FIGURE 2 | A cervical contrast-enhanced MRI comparison before and after the treatment in our patient. **(A)**: This MRI was performed before treatment. Aneurysm, stenosis, and dissections were observed in the left internal carotid artery indicated by the arrow. A contrast effect was also observed around the lesion. **(B)**: The participant underwent MRI as an outpatient after treatment. The contrast effect around the left internal carotid artery had decreased. MRI, magnetic resonance imaging.

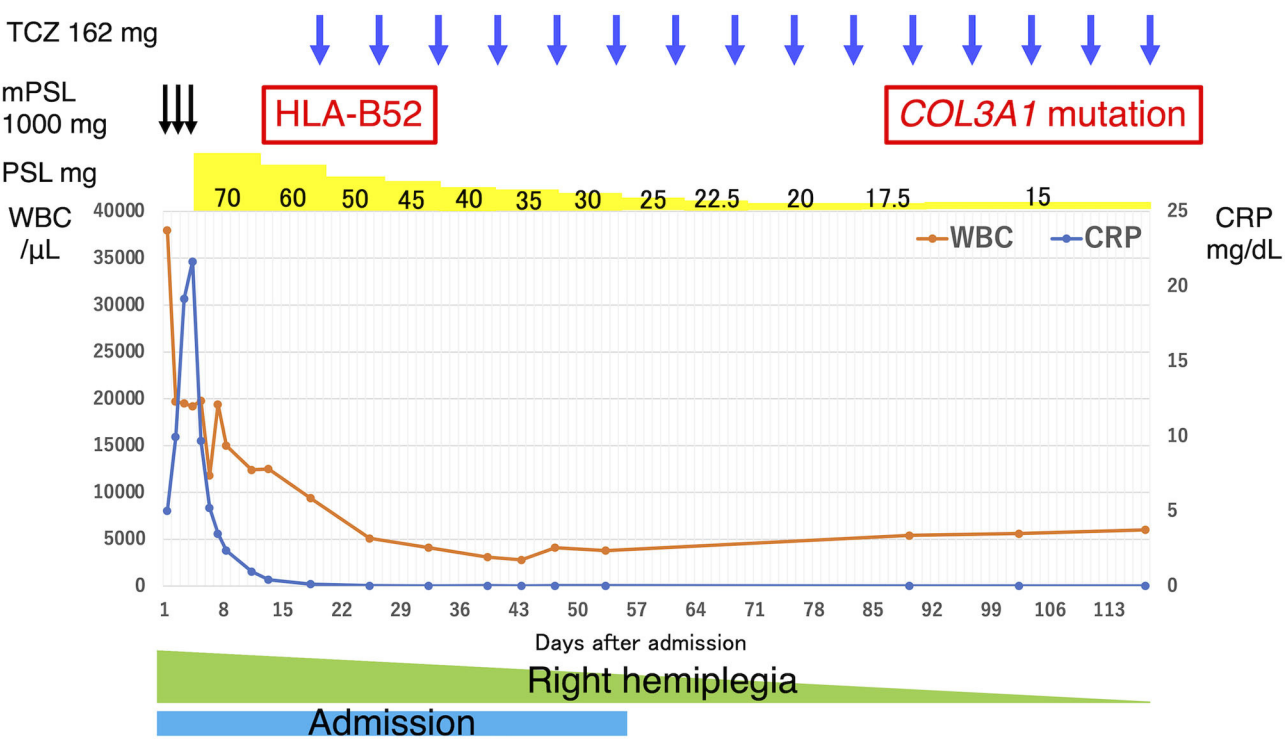

FIGURE 3 | Clinical course of our patient. The vertical axis of the graph represents the WBC count and CRP levels, and the horizontal axis represents the number of days since admission. The drug content, dosage, dosing interval, and results of the generic tests are noted above the graph. The duration of admission and hemiplegia are shown in the graph. CRP, C-reactive protein; TCZ, tocilizumab; mPSL, methylprednisolone; PSL, prednisolone; WBC, white blood cell.

a severe intra-abdominal hemorrhage and organ infarction, possibly due to vasculitis complications. Although the presence of vEDS does not change the treatment, the complication of vEDS could lead to rapid progression of rupture or stenosis, as in this case, and late therapeutic intervention could have resulted in a fatal outcome. Moreover, aneurysms were observed in the medium-sized vessels; therefore, polyarteritis nodosa was also a high priority in the differential diagnosis in this case. Although mutations in the adenosine deaminase 2 gene are known to cause polyarteritis nodosa in young people (9), genetic analysis performed in our patient yielded negative results. A notable feature of this case was the marked increase in neutrophils at the onset of vasculitis. Neutrophils and neutrophil extracellular traps (NETs) contribute to the pathogenesis of systemic vasculitis, including small and medium-sized vasculitis and LVV (10). Therefore, the elevation of neutrophils may be consistent with vasculitis due to TAK in this case. In addition, BD, which is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, central nervous system inflammatory, and/or vascular lesions (1), was also one of the important differential diagnoses in this case. However, all these characteristics are not necessarily present, as apparent in our case. Vascular BD is characterized by blood vessels with a neutrophil-dominating infiltration around the vasa vasorum, compared with inflammatory aneurysms and TAK (11). Therefore, neutrophils may have induced rupture or dissections of aneurysms in this case. In contrast, SAM, a non-inflammatory vascular disorder, was excluded since a systematic review concluded that the median age of onset for this disease is 57 years (range, 0–91 years). Furthermore, catheterization alone often improves the disease status because of its non-inflammatory nature (12), which is inconsistent with our case. In addition, results that might be consistent with a diagnosis of an infected inflammatory aneurysm were not observed.

EDS is a group of 13 hereditary connective tissue diseases characterized by decreased joint mobility, hyperextension of the skin, and tissue fragility. Additionally, vEDS is a type of EDS, causing aneurysms and arterial dissection in juveniles. Shalhub et al. emphasized the importance of confirming *COL3A1* mutations for the diagnosis of vEDS (13). Although there was no family history of vEDS in this patient, it has been reported that only 48.8% of the 86 patients who tested positive for *COL3A1* had a positive family history, suggesting that vEDS cannot be excluded based on family history alone (14). Specifically designed small interfering RNAs (siRNAs) can effectively silence the pathogenic variant allele of *COL3A1*. To enhance normal allelic expression, intracellularly expressed lysyl oxidase can regulate the transcription of the *COL3A1* promoter (15). Hence, genetic mutations cannot necessarily regulate gene expression, which can change the phenotype. In addition, a study that analyzed genetic mutations and clinical manifestations of vEDS suggested that specific *COL3A1* mutations may not be associated with the complications of this disease phenotype (16, 17). However, it has similarly been suggested that the probability of severe complications, such as ruptured aneurysms, increases with age, emphasizing the importance of a follow-up (17).

A recent study reported a case of EDS-hypermobility type combined with TAK; however, there is no information on TAK associated with vEDS (18). In another study, Caudrelier et al. reported a case of a young woman with vEDS and polyarteritis nodosa (19). The patient had multiple arterial aneurysms, mainly in medium-sized vessels, and was treated with steroids, cyclophosphamide, and azathioprine. This report suggests that vEDS and vasculitis may coexist and can be treated by anti-inflammatory agents, such as GCs, and immunosuppressive agents. In our case, genetic results for vEDS were delayed and were received after treatment with remission-induction therapy. The delay in diagnosis and treatment could have led to catastrophic results; however, the patient was successfully treated with anti-inflammatory agents, GCs, TCZ, and IVR. Therefore, cases of multiple arterial aneurysms and dissections with an inflammatory response should be considered for treatment with anti-inflammatory drugs to reduce the progression of inflammation.

CONCLUSION

It is pivotal to perform a systemic differential diagnosis to consider concurrent vasculitis syndrome and non-inflammatory vasculopathy, including hereditary disorders, even within time constraints in patients with multiple aneurysms, stenosis, and dissections, as this could lead to multiple organ infarctions of undetermined cause.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the relevant individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

KH: wrote the draft of the manuscript and described the figures. RS: conceived, designed, wrote the manuscript, and treated the patient as a primary attending physician. AS, YO, SY, TKu, TKo, and KA: contributed to the patient's clinical care, writing the manuscript, and providing fruitful advice. All authors have read and approved the final version of the manuscript.

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Spontaneous coronary artery dissection and atherosclerosis in a young man with systemic lupus erythematosus: A case report and literature review

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Background: Spontaneous coronary artery dissection (SCAD) is a rare coronary artery disease that frequently occurs in young, female patients without risk factors, and conservative treatment is often recommended for its management. The patient reported here is a male patient with systemic lupus erythematosus (SLE).

Case summary: We described a 28-year-old man with SLE who presented with acute ST-segment elevation myocardial infarction (STEMI), and was diagnosed with SCAD through a long dissection of the left anterior descending branch (LAD) by coronary angiography. The patient was treated with percutaneous coronary intervention (PCI) with stent implantation. Ten years later, he developed in-stent stenosis and other coronary atherosclerosis and was retreated with PCIs. Based on this case and according to the literature review, the existing treatment and prognosis of SLE with spontaneous coronary artery dissection and atherosclerosis are discussed.

Conclusion: Cardiovascular complications should be considered in patients with systemic lupus erythematosus, although they may not initially be atherosclerotic diseases. Attention should be paid to distinguish spontaneous coronary dissection in order to minimize missed or delayed diagnoses and take appropriate managements, as well as the development of atherosclerosis in SLE patients, and timely intervention has a better prognosis.

KEYWORDS

systemic lupus erythematosus, spontaneous coronary artery dissection, atherosclerosis, percutaneous coronary intervention, case report

Introduction

Spontaneous coronary artery dissection (SCAD) is defined as the formation of vascular false lumens due to a noninvasive and nonmedical separation of the coronary artery wall (1), with an incidence of 0.28 to 1.1% (2). Patients with SCAD usually present with acute coronary syndrome (ACS), and are misdiagnosed as atherosclerotic coronary artery disease whose management is different from SCAD (3). Therefore, current diagnosis and treatment are important. Its etiologies mainly include fibromuscular dysplasia (FMD), estrogen fluctuation periods such as pregnancy, connective tissue disease, and autoimmune diseases (4), such as systemic lupus erythematosus, which was the case in our patient here. SLE is an independent risk factor for cardiovascular disease (5), and cardiovascular disease has become the most common cause of death in SLE patients at late stage, especially atherosclerosis (6).

In our case, the young SLE patient presented with chest pain and was found a long dissection in the LAD by coronary angiography, so he was diagnosed with SCAD and underwent PCI. He survived well for years after PCI but still inevitably developed in-stent stenosis and other coronary atherosclerosis, and he received PCIs again.

Case presentation

A young man was treated with prednisone in 2007 after a diagnosis of SLE due to the presence of malar rash and positive SLE-related antibodies, including antinuclear antibodies (ANA) (but negative anticardiolipin antibodies); however, the steroids were discontinued after the patient's symptoms had resolved. Since then, the patient has been hospitalized several times due to acute pericarditis, acute pleurisy, myocarditis, coronary arteritis, and lupus nephritis (LN), as well as repeated chest tightness and suffocation symptoms. In August 2011, at the age of 28 years, the patient developed persistent chest tightness and retrosternal pressure without obvious inducement, accompanied by profuse sweating, which could not be relieved spontaneously after rest, so he visited the emergency department of Xiyuan Hospital. An electrocardiogram showed ST-segment elevation in I, II, III, AVF, and V2–V6 (Figure 1), and cardiac enzyme levels were increased, so he was considered as STEMI. An emergency coronary angiography showed a long dissection and thrombus shadow since the diagonal branch in the left anterior descending branch (LAD) (Figure 2A), while the left main artery (LM), left circumflex branch (LCX), and right coronary artery (RCA) showed no abnormalities, and SCAD was diagnosed. To prevent further development of the coronary dissection in the anterior descending artery to the aorta, which could lead to disease aggravation, a stent (Lepu Medical Technology Co., Ltd. Beijing, China, LOT:201103001) was implanted at the LAD lesion (Figure 2B).

The patient had a long history of SLE, and newly discovered dyslipidemia and supraventricular tachycardia, with no history of smoking or alcohol consumption. After the PCI stent implantation, the patient had a multidisciplinary consultation and was given medical treatment, including aspirin 100 mg and clopidogrel 75 mg every day for antiplatelet therapy, atorvastatin 20 mg a day for lipid-lowering, metoprolol 12.5 mg twice daily for rate control, and methylprednisolone 50 mg per day for reducing the myocardial oxygen consumption. After discharge, the patient had taken dual antiplatelets for 1 year and clopidogrel for another year, but he had spontaneously stopped the glucocorticoid and statin due to concern of adverse reactions.

Years later (July 2021), the patient was readmitted to the hospital because he relapsed of chest tightness and suffocation which was worse than before. These symptoms occured during exercise and lasted for approximately 3–5 min and could be relieved after rest. Electrocardiogram returned to normal (Figure 3), and computed tomography angiography (CTA) that was performed on this admission suggested: (1) Severe stenosis at the proximal end of the LAD stent and moderate stenosis at the distal end of the stent. (2) Moderate stenosis at the proximal segment of the RCA; severe stenosis at the middle segment; and moderate stenosis at the distal segment. The patient was admitted for coronary arteriography, which showed there was 100% occlusion of the LAD from the stent and the collateral circulation was provided by the acute marginal artery (AM) (Figure 4A); there was 40% stenosis of the middle LCX; there was 80% localized stenosis in the middle RCA1 segment and 90% localized stenosis at RCA2 segment (Figure 4B). To open the occluded lesion of the LAD and the lesions of the RCA, PCI was performed. During PCI, because the guide wire could not correspond to the collateral circulation emitted by AM, the distal LAD was not successfully dredged. Therefore, the LAD operation was abandoned, the RCA lesions were treated first, and a drug-eluting stent (Essen Technology Co.,Ltd. Beijing, China, LOT:10200243) and a drug-coated balloon (Henan Qingzhou Medical Instrument Co., Ltd. Henan, China, LOT:06200611A1) were placed at the RCA, thus promoting the establishment of collateral circulation (Figure 4D). Three months later, the LAD lesion had retreated, and three drug-coated balloons (Henan Qingzhou Medical Instrument Co., Ltd. Henan, China, LOT:06210817A1, 06210621A1, 06210626A1) were placed (Figure 4C). The patient's chest tightness was relieved after the two PCIs, and the patient was given treatment for the secondary prevention of coronary heart diseases, with the main drug treatments being prednisone 15 mg a day, hydroxychloroquine 0.2 g twice daily and aspirin 100 mg per day, clopidogrel 75 mg per day, isosorbide mononitrate 20 mg every day, and rosuvastatin 10 mg once daily. Six months after discharge, the patient had no episodes of chest pain, and rheumatologists advised him to reduce the dose of prednisone and add azathioprine 125 mg per day for SLE. The main events of the patient showed in Table 1.

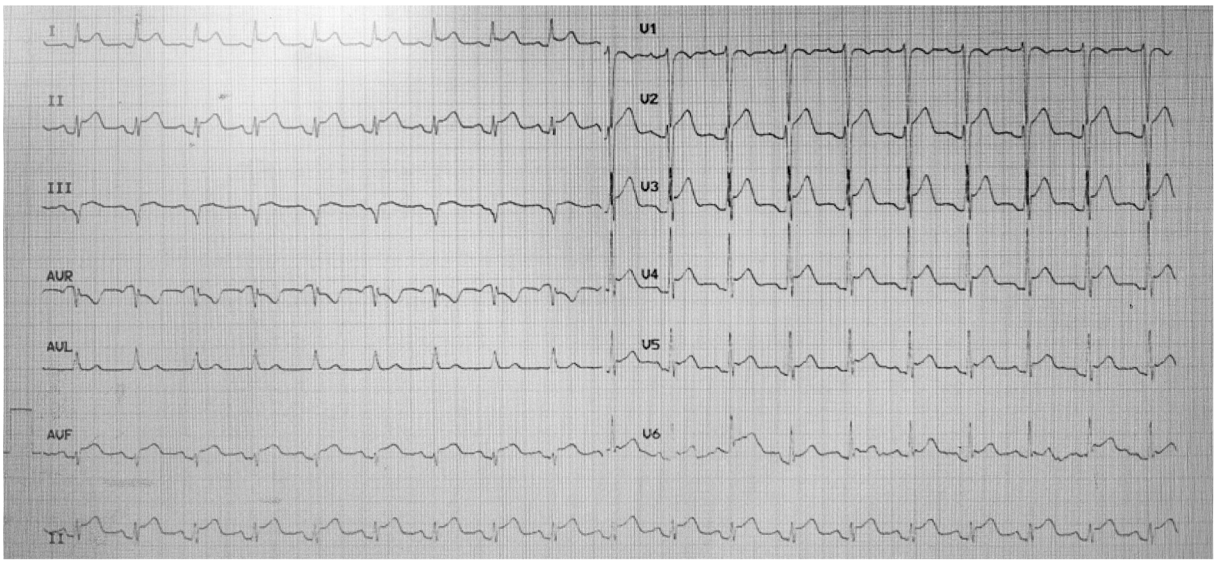

FIGURE 1
Emergency electrocardiogram in August 2011.

Discussion

Spontaneous coronary artery dissection

SCAD is an uncommon cause of myocardial infarction and sudden cardiac death, and it frequently occurs in young, female patients without cardiovascular disease risk factors (4). SCAD is a nonatherosclerotic disease (7). There are two mechanisms regarding the pathogenesis of SCAD. One is that the coronary intima is torn, which can occur due to various reasons, leading to bleeding in the media and the false lumen, which compresses the true lumen. The other is spontaneous rupture and bleeding of nutrient vessels of the arterial wall to form a hematoma, which compresses and causes stenosis (7). Patients with SCAD usually present with ACS, and studies have estimated that the incidence of SCAD is as high as 4% of patients with ACS (3), with chest pain being the most common symptom and the LAD being the most commonly involved vessel (8). SCAD in women occurs mainly in the postpartum period, while the main trigger in men is extreme physical activity (7).

With the development of medical imaging, the diagnosis of SCAD has increased than before. Despite some limitations, coronary angiography is still the first diagnostic tool for SCAD (9). Lesions are easily misdiagnosed as atherosclerotic plaques or coronary spasms when the imaging only shows luminal stenosis due to hematomas during SCAD. Familiarization with the angiographic variants of SCAD is the key to minimizing missed or delayed diagnoses (3). The other diagnostic techniques include intracoronary ultrasound, optical coherence tomography (OCT), and computed tomography coronary angiography (CTCA) to complement coronary angiography and confirm the diagnosis (3, 9).

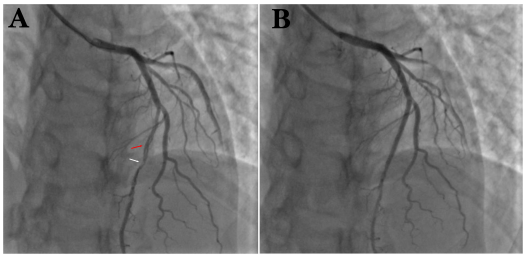

FIGURE 2
(A) Coronary angiography suggests spontaneous coronary artery entrapment (red arrow) and thrombotic shadow (white arrow) in LAD. **(B)** After implantation of 1 stent at the entrapment.

The goal of treatment is to reduce the patient's symptoms and prevent recurrence (4). Conservative treatment is the mainstay of SCAD and most patients can heal completely over time (3). Pharmacological treatments, such as antiplatelet agents, β-blockers, angiotensin-converting enzyme inhibitors, and statins, are preferred when the patient's symptoms do not progress and hemodynamics are stable (3, 9). β-blockers have been shown advantages in reducing recurrent SCAD, but evidence is still lacking (4). Thrombolysis is contraindicated for SCAD because it may be effective to dissolve the thrombus in the false lumen (3). The dissolution of intraluminal thrombi may aggravate bleeding and worsen the dissection. Clinical

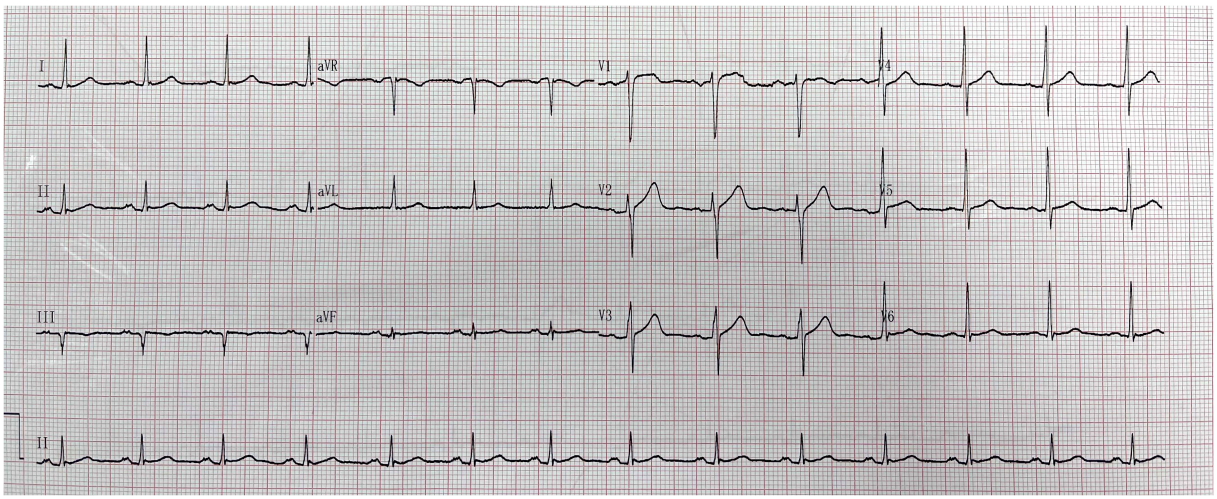

FIGURE 3
Emergency electrocardiogram in July 2021.

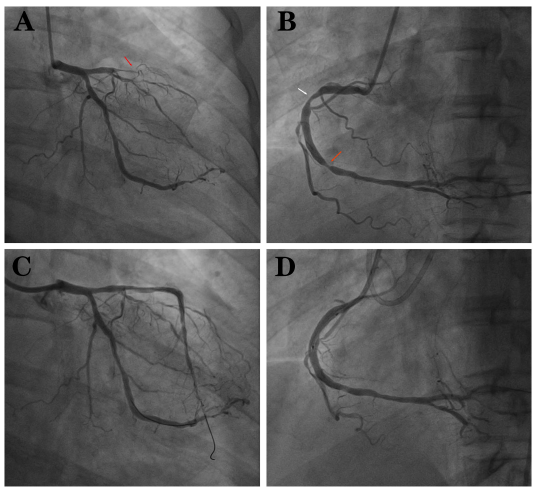

FIGURE 4
(A) LAD 100% occlusion (red arrow). **(B)** RCA with two stenoses (red and white arrows). **(C)** LAD after implantation of 3 drug balloons. **(D)** RCA after implantation of 1 stent and 1 drug balloon.

TABLE 1 Timeline of events.

Timeline	Events
11 August 2011	Persistent chest tightness and retrosternal pressure without obvious inducement, accompanied by profuse sweating. ECG showed ST-segment elevation in I, II, III, AVF, and V2–V6. Cardiac enzyme levels were increased. Emergency coronary angiography showed long dissection in left anterior descending branch (LAD). PCI was performed with one stent.
24 July 2021	chest tightness and suffocation, lasted for approximately 3–5 min and could be relieved after rest. ECG showed normal.
26 July 2021	CTA showed severe stenoses at the LAD stent and RCA.
27 July 2021	Coronary arteriography defined the locations of stenoses and a drug-eluting stent and a drug balloon were placed at the RCA.
19 October 2021	Three drug balloons were placed at LAD.

deterioration after thrombolytic therapy in patient with SCAD has been described (10). PCI is selected when there is persistent ischemia, hemodynamic instability, and only single vessel dissection (2). However, PCI would fail due to the difficulty of technical operation or the development of intravascular hematoma displacement because of the stent placement, which even further leads to the spread of the hematoma (3, 9). Moreover, there is an increased risk of subsequent in-stent stenosis and thrombosis, and no studies have shown the duration of antiplatelet therapy in SCAD patients with PCI. In our case, the patient had received dual antiplatelet therapy after SCAD-PCI for 12 months and prolonged monotherapy. Previous studies have shown more options for CABG following failed PCI (11). Coronary artery bypass grafting (CABG) is used for left main and multivessel dissections (2), but graft occlusion is found to be more common in the postoperative follow-up (3). In addition, the use of statins seems to result in SCAD relapses (7). However, the use of statins in SLE patients and patients with dyslipidemia will still be considered, as shown later.

In retrospective studies, recurrent SCAD was found to mainly occur in female, myofiber dysplasia patients (7).

The shifting in sex hormones in women during pregnancy, postpartum, perinatal and other periods may lead to connective tissue, hemodynamics and intravascular structural changes that weaken the vascular wall, resulting in intimal rupture or intramural hematoma formation and SCAD (12). Fibromuscular dysplasia (FMD) has been shown to affect the coronary arteries. The incidence of FMD in SCAD patients ranges from 31 to 72%, and this is important for the diagnosis and treatment of SCAD in a clinical screening of FMD (4). Angiography can show a peripheral arterial "beaded" pattern (13), and the possibility of SCAD should not be ignored when patients with FMD present with symptoms of chest pain. The patient in this case was male and had no FMD, but he used steroids because of SLE. In SLE patients, there appears to be an increased susceptibility to spontaneous dissection due to the chronic inflammation of the vessels (14). There was reported that steroid-induced SCAD (15), and steroid using was present in 0.66% of SCAD in a cohort study (16).

SLE and atherosclerosis

For SLE patients, the development of glucocorticoid and immunosuppressive therapies targeting disease activity has led to a significant reduction in early mortality due to active lupus and infection, but the risk of death caused by cardiovascular disease among SLE paients has remained essentially unchanged (17). Meanwhile, SLE accelerates the development of cardiovascular diseases, especially atherosclerosis (6). The mechanism of atherosclerosis in SLE patients is complex and may interact under the conditions of traditional risk factors, lupus-associated factors, immune-inflammatory factors, and therapeutic factors (18).

Traditional cardiovascular risk factors

SLE patients have a high prevalence of traditional cardiovascular risk factors, such as dyslipidemia, hypertension, hyperglycemia, hyperhomocysteinemia, insulin resistance and other metabolic syndromes (19), and smoking, obesity, and sedentary lifestyle also accelerate the formation of atherosclerosis. Even after correcting for traditional cardiovascular risk factors, the prevalence of CVD in SLE patients has increased (20). The main risk factor is dyslipidemia in our patient, and he was hypertriglyceridemia that characterized by mild increases in triglycerides (TG) and decreases in high density lipoprotein-cholesterol (HDL-C), while low density lipoprotein-cholesterol (LDL-C) was borderline high. He did not belong to familial hyperlipidaemia. The combination of high TG and low HDL-C levels (together with the presence of small, dense LDL particles), referred to as atherogenic dyslipidaemia, is a common lipid disorder associated with increased cardiovascular disease risk (21). It has been shown that 48.1% of SLE patients treated with lipid-lowering drugs did not achieve the targeted lipid level (22). Dyslipidemia increases the risk of cardiovascular events in SLE patients, and dyslipidemia in SLE patients is also exacerbated by the disease activity (23). The mechanism of the interaction between them is complex and has not been fully elucidated. Normally, HDL has an antiatherosclerotic effect, mainly by allowing excess cholesterol to be excreted from the body. This cholesterol reversal mechanism allows the body to have cholesterol efflux capacity (CEC); however, CEC is impaired in lupus patients (24). In the inflammatory environment created by SLE, especially in the acute phase, HDL can be converted from inflammatory molecules to proinflammatory molecules that promote LDL oxidation, and Ox-LDL is further phagocytosed by macrophages to further form foam cells, which become the basis of atherosclerotic plaques (25). There is evidence that the systemic inflammatory burden in SLE patients disrupts cholesterol homeostasis (26), which contributes to dyslipidemia and exacerbates the formation of atherosclerosis in SLE patients.

Lupus-associated factors

In SLE, in addition to the direct vascular damage caused by inflammatory phenomena, immune complexes formed by auto-antibodies can also mediate endothelial cell damage (27), such as antinuclear antibodies (ANA), antiphospholipid antibodies (aPLs) and antidouble stranded DNA (anti-dsDNA) antibodies, among which anti-dsDNA antibodies are associated with abnormal activation of innate immune cells, leading to endothelial dysfunction and promoting atherosclerosis. Moreover, patients who are positive for anti-dsDNA antibodies are more likely to develop neutrophil extracellular traps (NETs) than negative patients (28). NETs are prominent fibrous networks of activated neutrophil membranes that themselves act as barriers to limit and eliminate pathogens at sites of inflammation; however, NETs degradation is blocked and prolonged in the autoimmune disease setting (29). NETs enhance immune stimulation, which damages the endothelium and accelerates the formation of atherosclerosis (30). Some cytokines that will be overexpressed in SLE, such as IFN-α (31), INF-γ (32) and TNF-α(33) lead to inflammatory cell recruitment, stimulate macrophage activation, induce matrix metalloproteinase secretion, and upregulate adhesion molecule expression to promote atherosclerosis.

Treatment-related factors

As the disease progresses, the therapy of SLE can also lead to the development of atherosclerosis (34). Glucocorticoids, as basic drugs, play an irreplaceable role in the treatment of acute SLE and vital organ damage and have been instrumental in reducing mortality in the active phase of SLE in recent years (35). However, the long-term use of steroids

will cause continuous high levels of glucocorticoids in the body, which increases the risk of concurrent cardiovascular events in SLE patients (36). The increased prevalence of traditional cardiovascular risk factors may also be related to the development of hyperlipidemia, hypertension and obesity induced by glucocorticoids (37). During long-term maintenance therapy, the use of glucocorticoids should be minimized and discontinued if possible (34). Ruiz-Arruza et al. (38) showed that reducing the dose of oral prednisone, combined with other treatments such as immunosuppressive or biologic drugs, can reduce glucocorticoid-related damage, thereby improving cardiovascular outcomes. In a cohort study in China, the use of hydroxychloroquine and azathioprine in SLE patients increased the probability of survival (39). Hydroxychloroquine (HCQ), as an antimalarial drug, not only has a good effect on SLE disease activity and prevention of injury but also has a significant effect on lowering traditional cardiovascular risk factors such as dyslipidemia and diabetes. In fact, antimalarial therapy has been regarded as a potential atheroprotective agent (40). HCQ may play a role in lowering cholesterol levels by upregulating LDL receptors, potentially counteracting the negative effects of prednisolone on blood lipids and slowing the development of atherosclerosis (41, 42). In addition, HCQ can also always reduce the risk of thrombosis by inhibiting platelet aggregation (43). Therefore, all SLE patients should be treated with HCQ, as long as there are no contraindications (44). However, attention should be given to the development of hydroxychloroquine maculopathy, and the patients should have regular eye screenings (44). Immunosuppressive drugs such as methotrexate (MTX) and azathioprine (AZA) should be used when GC in combination with HCQ has poor efficacy (5). Biological therapy is mainly used in the clinical situation in which SLE patients remain resistant to conventional immunosuppressive agents, but for all disease manifestations, it is difficult to solve all of the problems with only one biological therapy (17, 34).

For the risk of cardiovascular complications in SLE patients, the commonly used Framingham risk score (FRS) underestimates the cardiovascular risk of SLE patients. A retrospective study found that the modified FRS using 2.0 multiplier has increased the sensitivity of this indicator from 0.13 to 0.31 (45). Although the 2019 European League Against Rheumatism (EULAR) guidelines recommend the application of SCORE to assess the risk of cardiovascular disease in patients for 10 years, the risk in SLE patients is still underrated (5). At present, there is no direct comparison of the performance of most commonly used general risk assessment tools in SLE. Therefore, it is recommended to conduct a comprehensive assessment of traditional and disease-related risk factors, and to provide individualized prevention and treatment according to the patient's situation (46).

Clinical strategies for SLE with atherosclerosis

In the prevention and treatment of atherosclerosis in SLE patients, the first is the control of risk factors, including but not limited to smoking cessation, maintaining an ideal weight, avoiding a sedentary lifestyle, and controlling blood pressure, blood glucose, blood lipids, and homocysteine (20). Dyslipidemia should be treated aggressively. Statins in SLE patients are still controversial, and long-term use of statins may be associated with drug-induced lupus (47, 48). However, it has also been shown that statins reduce the premature mortality of patients with autoimmune rheumatic diseases (49). Watanabe et al. (50) showed that starting statins within 3 months of the onset of SLE reduced the risk of thrombosis. Statins should still be considered based on the patient's lipid levels and the presence of other risk factors (39). In SLE patients, their blood pressure should be more strictly controlled compared to the general population. Thiazide diuretics should be used with caution in SLE (51). Folic acid can reduce homocysteine serum concentrations and reduce its toxicity to the endothelium and can be used as a preventive treatment (21). Vitamin D reduces endothelial damage by reducing NETosis activity and may also be a targeted therapy for SLE (29).

In SLE patients with preexisting atherosclerosis, cardiovascular drugs are necessary. Auto-antibodies have procoagulant activity, and low-dose aspirin can reduce the risk of vascular thrombosis prophylactically (52). Patients with SLE may be more prone to adverse cardiac outcomes after coronary revascularization by PCI or CABG, so the risk reduction after revascularization should be aggressive (53). Cohort studies in Taiwan have also demonstrated that SLE patients require repeat PCI within 1 year compared with non-SLE patients (54).

Conclusion

In summary, we reported a case of systemic lupus erythematosus with spontaneous coronary dissection and coronary atherosclerosis in a young man. When dealing with patients with SLE, attention should be given to cardiovascular complications, although it may not start out as atherosclerotic disease. Although SCAD is rare, it has a high risk level as an attack, so clinicians should take note of the young patients with chest pain without cardiovascular diseases previously and respond proportionally. At the same time, attention should also be paid to the development of atherosclerosis in SLE patients.Traditional cardiovascular risk factors and a combination of medications are used to reduce the damage caused by glucocorticoids, to prolong the survival time of SLE patients and improve the quality of life.

Data availability statement

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

Ethics statement

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

Author contributions

HH, XM, LX, and XW organized data and figures, performed the literature research and wrote the manuscript. FZ performed PCIs and provided figures. YZ and DS provided study concept and critical revision of the manuscript for intellectual content. All authors contributed to the manuscript production and the final revision.

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Conflict of interest

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

The reviewer JC has shared affiliation with some of the authors, HH and LX, to the handling editor at time of review.

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Case report: Traumatic carotid artery dissection after 7D High-Intensity Macro- and Micro-Focused Ultrasound treatment for skin laxity of the neck

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Background: Trauma is a relatively uncommon etiology of carotid artery dissection. Trauma is both penetrative and trivial, which can lead to carotid artery dissection. In the current study, we present an unusual case in which carotid artery dissection was potentially triggered by the damaging thermal effect of 7D High-Intensity Macro- and Micro-Focused Ultrasound (7D HIFU), which has been proposed as a safe and effective non-surgical modality for skin rejuvenation.

Case summary: A 41-year-old woman developed headache and clinical manifestations of cerebral infarction after 7D HIFU, aimed at removing neckline. Head and neck magnetic resonance angiography (MRA) and computed tomography angiogram (CTA) revealed severe stenosis and dissection of the left internal carotid artery. Neither the patient's history nor the physical examination showed any special indicators. After resection of the left carotid artery dissection, autologous great saphenous vein interposition grafting, and simple mastoidectomy, the patient underwent head and neck MRA, which revealed recanalization of the left internal carotid artery.

Conclusion: Although mild or moderate complications of 7D HIFU, such as erythema, edema, transient dysesthesia, and motor nerve paresis, have been previously reported, a few previous literature studies documented severe complications of the cosmetic procedure. However, many recent studies pointed out the possibility of 7D HIFU damaging adjacent non-target tissues due to inadequate focal depth of HIFU treatment. Our case is the first to indicate that 7D HIFU could cause carotid artery dissection. We propose that better visualization systems and more rigorous operator training are needed

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to reduce the risk of the potential off-target damaging effect of 7D HIFU by reporting the case in which the damaging heat effect of 7D HIFU precipitated the carotid artery dissection HIFU.

KEYWORDS

traumatic carotid artery dissection, 7D High-Intensity Macro- and Micro-Focused Ultrasound, peripheral vascular disease, surgery, case report

Introduction

Carotid artery dissection, a prominent contributor to ischemic stroke in young and middle-aged patients, is caused by tearing of the arterial lining, resulting in intramural hematoma and stroke (1). Carotid artery dissection is most commonly spontaneous. The annual incidence of spontaneous carotid artery dissection is 2.5–3 per 100,000 people (1). Trauma, however, is an uncommon etiology of carotid artery dissection (2). High-Intensity Macro- and Micro-Focused Ultrasound (HIFU) has been known to be a safe and effective non-surgical treatment for skin laxity (3, 4). We present an unusual case in which the damaging heat effect of 7D HIFU was the potential trigger of carotid artery dissection in a non-elderly woman.

Case report

A 41-year-old woman with no risk factors for cardiovascular disease and carotid artery dissection presented with speech difficulties and hemiplegic gait 2 weeks after the 7D HIFU cosmetic procedure for removing necklines. After 7D HIFU treatment, the patient had a constant, throbbing headache (NRS 2–9 points), which gradually spread from the occipital to the temporal area and was slightly alleviated by overextension of the neck. Headache was accompanied by dizziness, amaurosis, nausea, and drowsiness but was not associated with vomiting or tinnitus. Headache was not alleviated by analgesics and gradually aggravated over the past 2 weeks. MRI of the patient's head showed an ischemic stroke in the left parietal lobe, the left temporal lobe, and the left insular lobe. In addition, head and neck magnetic resonance angiography (MRA) and computed tomography angiogram (CTA) revealed dissection and severe stenosis in the left internal carotid artery (Figures 1, 2). Physical examination revealed no specific findings. We consider the damaging heat effect of the 7D HIFU to be the primary trigger of the left internal carotid artery dissection and the severe carotid artery stenosis through overall consideration of the present history, past history, physical examination, and imaging examination of the patient.

The patient was diagnosed with severe left internal carotid artery stenosis, left internal carotid artery dissection, and cerebral infarction. The patient was presented with symptomatic cerebral infarction after the 7D HIFU cosmetic procedure on the neck. Both CTA and MRA revealed carotid artery dissection accompanied by severe carotid artery stenosis. The severe stenosis of the carotid artery, most likely a complication of 7D HIFU, was the cause of cerebral infarction in this patient. The symptoms of cerebral infarction occurred within 6 months when severe carotid artery stenosis was initially detected. Therefore, carotid stenosis in this patient should be defined as symptomatic (5). According to the ESC guideline for the treatment of extracranial carotid artery disease, surgery is recommended for patients with symptomatic severe carotid artery stenosis (5). Therefore, the patient underwent resection of the left carotid artery dissection under general anesthesia.

After successful anesthesia, the patient was in the supine position with the head tilted to the right and the shoulders elevated. The surgical field was routinely disinfected and draped. A 5-cm oblique incision was made at the anterior edge of the left sternocleidomastoid muscle. Severe adhesion was observed in the subcutaneous fat layer. After the layer-by-layer incision, the left external and common carotid arteries were exposed, and vessel loops were placed as controls (Figure 3A). In addition to the carotid artery, the ansa cervicalis and the vagus nerve were carefully dissociated and protected (Figure 3B). Blue-purple changes of about 3 cm in length were observed on the surface of the initial segment of the left internal carotid artery, with the weak pulsation of the left internal carotid artery (Figure 3A). Since the upper pole of the pathological lesion on the internal carotid artery could not be seen, a part of the mastoid was removed. After exposing the internal carotid artery at the distal end of the styloid process, the boundary between the normal blood vessel and the diseased internal carotid artery could be identified (Figure 3B). The normal internal carotid artery was about 2 mm in diameter. While simple mastoidectomy was performed, a 5-cm longitudinal incision was made in the left groin, and the main trunk of the great saphenous vein of about 5 cm was taken. The great saphenous vein graft was fully expanded by heparin saline and placed at the internal carotid end of the bypass tube. After systemic heparinization with 5,000 units of heparin, the left common carotid artery, the external carotid artery, and the distal end of the internal carotid artery were blocked to establish bypass

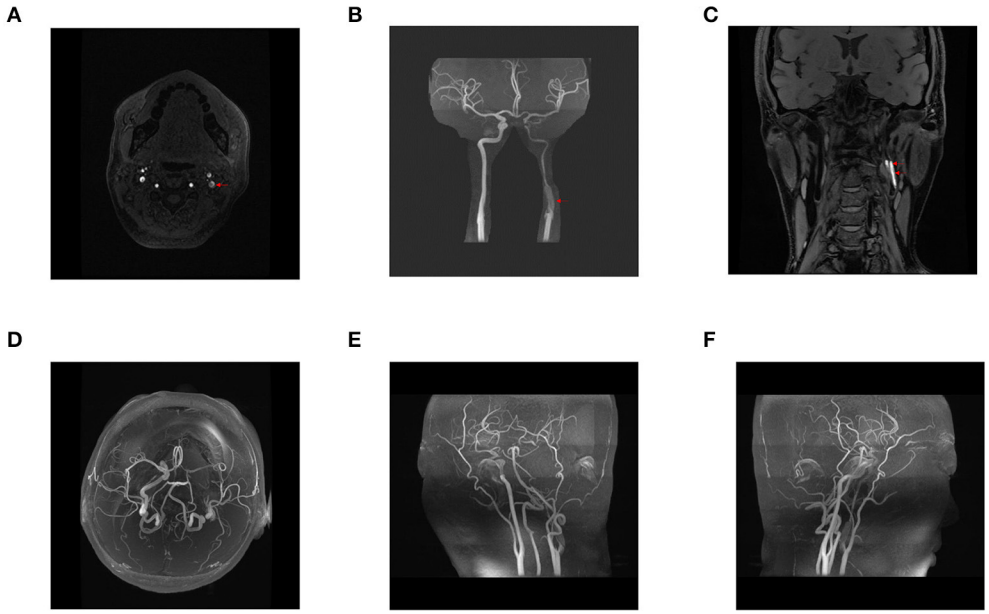

FIGURE 1
Preoperative head and neck magnetic resonance angiography (MRA), three-dimensional reconstruction of head and neck MRA, and blood flow assessment. A dissection at the origin of the left internal carotid artery was observed, and the left internal carotid artery was severely stenosed **(A–C)**. Stenosis at the origin of the left internal carotid artery was associated with an intermural hematoma **(C)**. The right internal carotid, bilateral middle, and anterior cerebral arteries showed no apparent thickening, stenosis, or signal loss **(D–F)**. The bilateral vertebral, basilar, posterior cerebral arteries and their branches were clearly displayed, with no obvious thickening and stenosis **(E,F)**. The bilateral posterior communicating arteries were found opened **(D)**. Blood flow assessment: arterial spin labeling (ASL) revealed a basic symmetry of cerebral blood flow in both cerebral hemispheres.

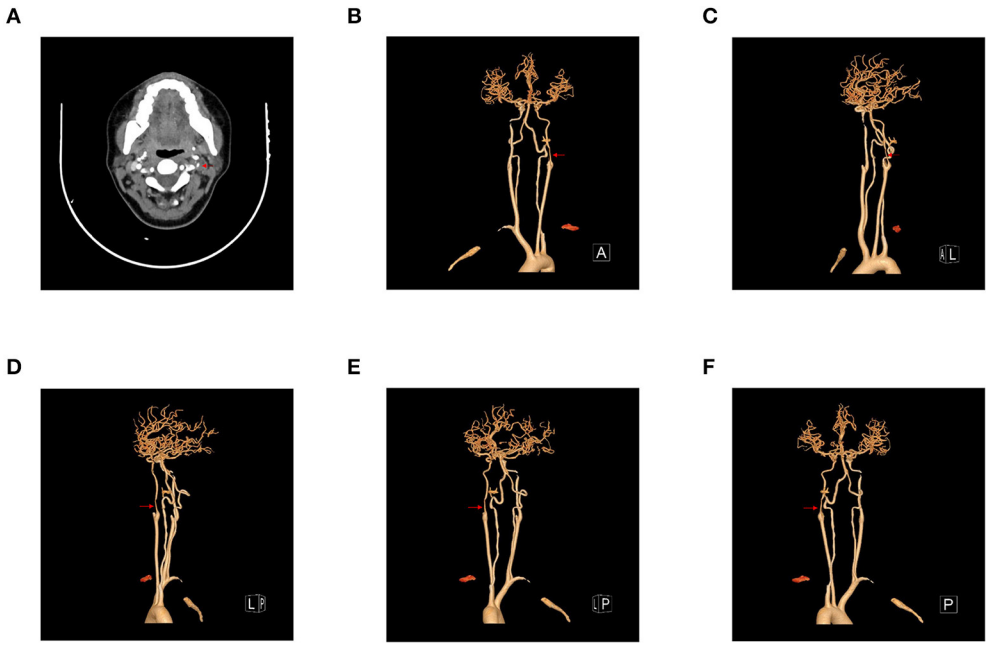

FIGURE 2
(A–F) Preoperative head and neck computed tomography angiogram (CTA) and three-dimensional reconstruction of head and neck CTA. Head and neck CTA showed dissection and severe stenosis at the origin of the left internal carotid artery.

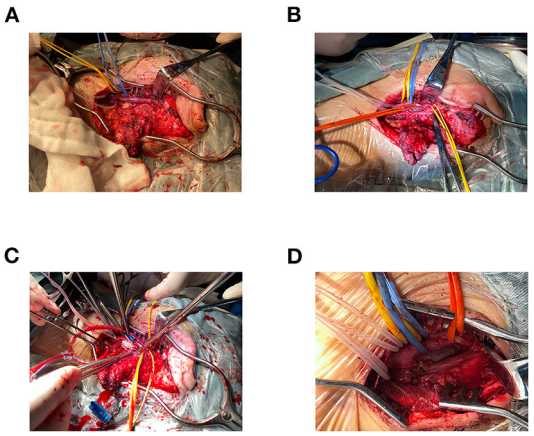

FIGURE 3
(A–D) Surgical procedure. The surgical procedure consisted of left carotid artery dissection resection, autologous great saphenous vein interposition grafting, and simple mastoidectomy.

(Figure 3C). After performing longitudinal dissection of the lesion segment of the internal carotid artery, we observed arterial dissection, thrombus in the false lumen, complete occlusion of a part of the true lumen, and unclear intimal structure (Figure 3C). CV-6 sutures were used to perform an end-to-end anastomosis between the internal carotid artery and the great saphenous vein. After the anastomosis was successful, the diverter tube was withdrawn and exhausted, and no apparent active bleeding or oozing at the anastomotic stoma could be detected. After withdrawing the bypass tube, the left common carotid artery and internal carotid artery were blocked, and the common carotid artery-great saphenous vein anastomosis was performed using a CV-6 suture (Figure 3D). No ongoing bleeding or oozing was detected, and pulsation of the distal end of the internal carotid artery was satisfactory. The left sternocleidomastoid muscle was severed, and the surface of the mastoid was embedded. The patient returned to the ICU ward after the operation. Postoperative head and neck MRA of the patient showed recanalization of the left internal carotid artery (Figure 4).

Discussion

The patient was a young woman who developed headache and later presented with manifestations of cerebral infarction after 7D HIFU for neckline removal. Head and neck MRA and CTA examination of the patient revealed severe stenosis and dissection of the left internal carotid artery. The patient had nothing special in terms of past history. Physical examination revealed no specific findings.

Carotid artery dissection can be spontaneous or traumatic. Spontaneous carotid artery dissection, which accounts for a significant majority of carotid dissection cases, is most commonly idiopathic, and patients often have a family history of arterial dissection and are associated with atherosclerosis, hypertension, and connective tissue disorders, including Ehlers–Danlos syndrome, Marfan syndrome, and fibromuscular dysplasia (6). However, this patient had no relevant family or past history.

Severe trauma accounts for only about 4% of carotid artery dissections (2). Traumatic dissections occur primarily in young patients and are difficult to diagnose due to the lack of symptoms in some patients or distraction from severe life-threatening injuries (7, 8). Both penetrative and blunt trauma have been reported to be the etiology of carotid artery dissection (6). Trivial trauma, including violent coughing, tooth brushing, and chiropractic manipulations, may also be a potential etiology of carotid artery dissection (6).

7D High-Intensity Macro- and Micro-Focused Ultrasound is a non-invasive treatment of skin laxity with few reported adverse effects (9). The 7D HIFU device generates high-energy-focused ultrasound that quickly penetrates the epidermis and the subcutaneous fat layer, stimulating the contraction of the membrane of the superficial musculoaponeurotic system (SMAS) layer and instantly raising the tissue temperature to 65°C. The transient increase in temperature stimulates the collagen and elastic fibers in the SMAS layer to shrink and tighten by the thermal coagulation effect, removing the wrinkles on the skin (3). Previously, mild complications of 7D HIFU, such as erythema, purpura, postinflammatory hyperpigmentation, geometrical wheals or striations, subcutaneous nodules, and edema, have been reported. Moderate complications of 7D HIFU documented in a few previous studies include transient dysesthesia and motor nerve paresis. However, severe or prolonged complications of HIFU have not yet been reported (3).

Previous animal studies demonstrated structural alterations of the whole vascular wall after HIFU treatment (10, 11). Following a session of HIFU treatment, endothelial desquamation, subendothelial edema, and leukocyte infiltration were detected in the vascular intima (10). Histological examination of the vascular media and adventitia revealed collagen shrinkage, separation, and disruption (10). The thermal coagulation effect caused by tissue absorption of HIFU mediates hyalinization and stiffening of the collagen fiber in the vascular media, making the vessel fragile and prone to rupture (12). Apart from the thermocoagulation effect, inertial cavitation, which originates from the rarefaction of HIFU, has been proposed as another critical mechanism underlying the vascular damaging effect of HIFU, as evidenced by the positive association between the severity of vascular endothelial damage and the amplitude of acoustic pressure (13). Therefore, when applied directly to the artery, HIFU could theoretically trigger arterial dissection by

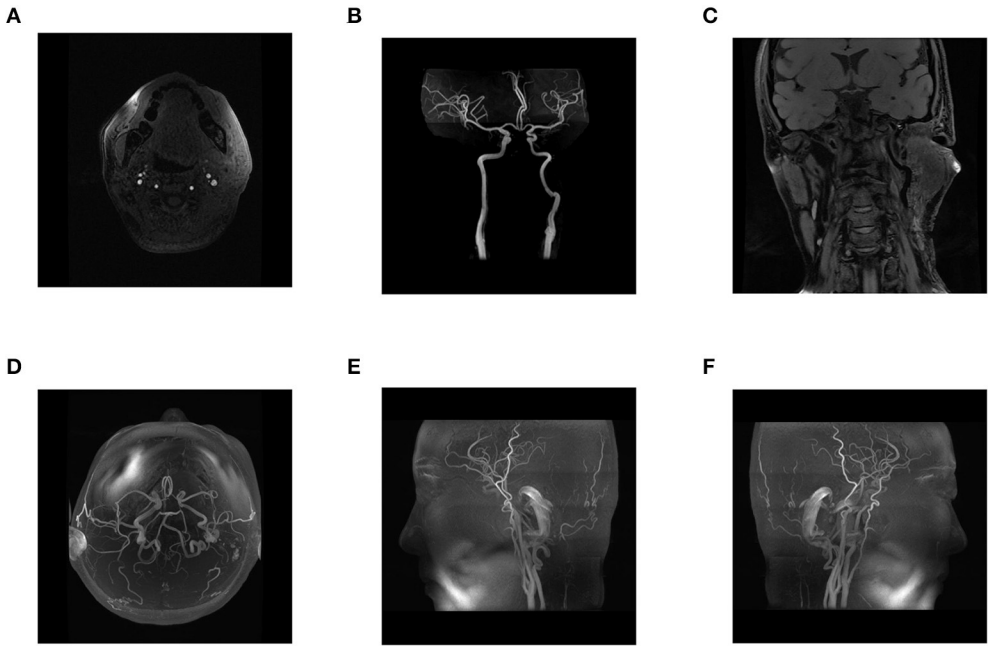

FIGURE 4
(A–F) Postoperative head and neck MRA, three-dimensional reconstruction of head and neck MRA, and blood flow assessment. After surgery, head and neck MRA showed recanalization of the left internal carotid artery.

desquamating the arterial endothelium and stiffening the arterial wall. In addition, the structural changes in the vascular wall induced by HIFU are the foundation for subsequent stenosis or obliteration of the artery.

Prior literature has proposed the possible damaging effect of HIFU on non-target tissues, including blood vessels, as a consequence of inadequate treatment depth caused by improper transducer positioning (9). Moreover, according to a previous study, the depth of the thermal coagulation point in HIFU treatment depends not only on the power settings and exposure time but also on the types of transducers used and the thickness of the skin (14). Compared with a 4.0-mm transducer, a 6.0-mm transducer could induce a more profound and significant thermally injured area in the subcutaneous fat layer for a fixed power setting and exposure time (35 W and 90 ms, respectively). In comparison, an 8.0-mm transducer could cause unintended tissue damage under the subcutaneous skin layer (14). For the purpose of skin tightening and lifting, the appropriate focal depth of HIFU is 4.5 mm, which allows HIFU to reach the SMAS layer without penetrating beyond the SMAS layer (15–17). However, HIFU devices currently used for skin lifting and adipose reduction, including 7D HIFU devices, usually support transducers that emit various HIFU frequencies ranging from 2 to 7.5 MHz (4, 16–18). A 2-MHz HIFU transducer could penetrate to a depth of 13 mm, which increases the risk of damaging non-target tissues below the SMAS layer (18). Hence, in addition to transducer positioning, the power setting of the HIFU device, the time of exposure to HIFU, and the selection of a transducer need to be carefully considered to prevent unwanted damage to deeper layers below the SMAS layer, especially in anatomic regions, including cervical skin, where the epidermis is relatively thin and the subcutaneous layer contains less fatty tissue. In the case of carotid artery dissection, the off-target damaging heat effect of 7D HIFU on the carotid artery was the primary etiology of carotid artery dissection. Hence, we propose that image guidance and rigorous operator training are essential to ensure the safety of HIFU treatment.

Conclusion

Previously, 7D High-Intensity Macro- and Micro-Focused Ultrasound has been considered a safe and effective non-surgical cosmetic procedure for skin lifting and wrinkle removal because no severe complications of 7D HIFU have been reported in prior literature studies. However, we report a case in which carotid artery dissection was most likely a complication of the damaging heat effect of 7D HIFU. We are the first to report that 7D HIFU has a potential risk of triggering carotid artery dissection. We propose that better visualization systems in 7D HIFU and more rigorous operator training are necessary to improve the accuracy of targeting treatment areas, thereby preventing off-target damage to adjacent tissues.

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

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

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Conflict of interest

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

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Giant left coronary artery diagonal branch left ventricular fistula: A case report and review of literature

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A 37-year-old Chinese man was admitted to the department of cardiology of the First Hospital of Jilin University for intermittent palpitation for 9 months, aggravating with chest pain for 3 days. After several examinations, he was diagnosed with giant left ventricular fistula of the diagonal branch of the left coronary artery. After routine treatment, which included improving circulation and administration of dual antiplatelet as well as hypolipidemic drugs among others, the patient's symptoms did not improve. The fistula was too big for transcatheter occlusion to be performed. A multi-disciplinary suggestion was that the patient be subjected to "surgical closure treatment"; however, for personal reasons, he refused the operation. After discharge, oral beta-blockers were prescribed for the patient. Incidences of congenital coronary arterial fistula in congenital cardiovascular disease are rare, and incidences of the giant fistula being located in the left heart system are even rarer. We report an adult male with a giant left anterior descending diagonal coronary artery left ventricular fistula and show various accessory examination results. Non-invasive ultrasonic cardiography was the first diagnostic option for the disease and pre-admission evaluation. Auxiliary diagnosis and exclusion value of cardiovascular magnetic resonance (CMR) were revealed for the first time. Invasive coronary angiography (ICA) was demonstrated to be the gold standard method again and it was also found that computed tomography angiography (CTA) might be used instead of ICA for determining the exact relationships among anatomic structures. Furthermore, we performed a literature review on the diagnosis and treatment of patients with this condition.

KEYWORDS

congenital cardiovascular disease, coronary artery fistula, diagnosis, review, case

Introduction

Coronary artery fistula (CAF) refers to an abnormal coronary artery that bypasses the myocardial capillary network and terminates into any cardiac lumen or large vessel. It is characterized depending on the number, origin, course, termination, and presence of an aneurysm or stenotic lesion (1). It is a very rare coronary artery anomaly whose prevalence in the general population is estimated to be 0.002% (2). Even very small CAFs in children require close attention as they may develop with age (3). Our case was an adult male with intermittent palpitation and chest pains due to the left coronary artery diagonal branch left ventricular fistula.

Case report

A 37-year-old Chinese man presenting with untreated palpitation, nausea, and fatigue for 9 months and with worsening palpitation symptoms accompanied by precordial pain was admitted to our hospital. The pain radiated to both shoulders, lasted about 30 min, and improved by itself. The patient used to be physically healthy and had no family history of genetically related diseases, history of trauma and surgery, and no record of drinking. He had a history of smoking for more than 10 years, 1 pack a day, which he never quit until hospitalization. Physical examination revealed: temperature, 36.2°C; pulse, 93 beats/min; breathing, 18 times/min, and blood pressure, 132/78 mmHg. The rest of physical examination did not show any obvious abnormalities. The primary laboratory data are shown in **Table 1** according to the time line of the patient's admission. The patient's electrocardiogram on admission was normal (**Figure 1**). Ultrasonic cardiography (UCG) showed left ventricular ectasia (**Figure 2**). The patient underwent computed tomography angiography (CTA) examination, which suggested a diagonal branch of coronary artery-left ventricular fistula (**Figure 3**), and was admitted to the cardiology department.

TABLE 1 The patient's laboratory data according to the time line of the admission.

Parameter	Value	References value	Unit	Time
Creatine kinase isoenzyme	1.20	0–4.3	ng/mL	DAY1
Myoglobin	88.40	0–107	ng/mL	DAY1
D-dimer	<100	100–600	ng/mL	DAY1
B-type natriuretic peptide	<5	0–100	ng/mL	DAY1
Troponin	<0.05	0–0.05	ng/mL	DAY1
Creatinine	78.9	57–97	umol/L	DAY1
Urea	7.09	3.1–8.0	mmol/L	DAY1
Serum potassium	3.66	3.5–5.3	mmol/L	DAY1
White blood cell	9.59	3.50–9.50	10^9/L	DAY1
Absolute neutrophil count	6.11	1.80–6.30	10^9/L	DAY1
Hemoglobin	186	130–175	g/L	DAY1
Platelet	243	125–350	10^9/L	DAY1
Activated partial thromboplastin time	25.1	21–33	s	DAY1
Urinary protein	1 +	negative	–	DAY2
Urine ketone	1 +	negative	–	DAY2
Urine specific gravity	1.033	1.010–1.025	–	DAY2
Fecal occult blood	negative	negative	–	DAY2
Aspartate aminotransferase	24.5	15.0–40.0	U/L	DAY2
Alanine transaminase	27.1	9.0–50.0	U/L	DAY2
Albumin	45.1	40.0–55.0	g/L	DAY2
Uric acid	407	210–430	umol/L	DAY2
Cholesterol	5.71	2.6–6.0	mmol/L	DAY2
Triacylglycerol	1.04	0.28–1.80	mmol/L	DAY2
High-density lipoprotein cholesterol	0.97	0.76–2.1	mmol/L	DAY2
Low-density lipoprotein cholesterol	3.83	Low risk-target value <4.14 Medium risk-target value <3.37 High risk-target value <2.59 Extremely high risk-target value < 2.07	mmol/L	DAY2
Fasting blood glucose	5.30	3.9–6.1	mmol/L	DAY2
Thyroid stimulating hormone	1.344	0.35–4.94	uIU/mL	DAY2
Free triiodothyronine	4.27	2.43–6.01	pmol/L	DAY2
Free thyroxine	16.23	9.01–19.05	pmol/L	DAY2
Immunoglobulin quantitation-IgE	<17.10	<100.00	IU/mL	DAY5

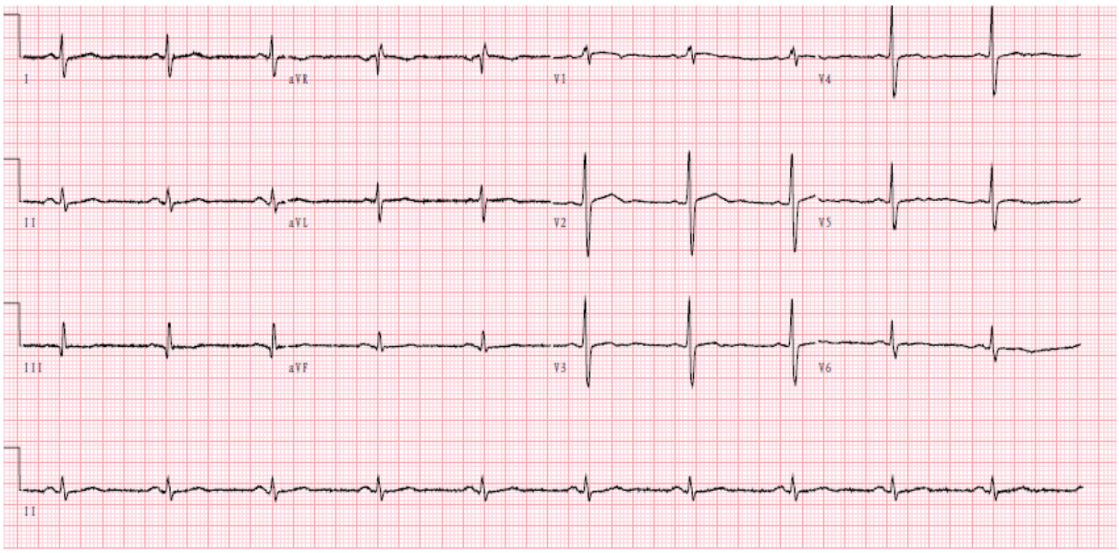

FIGURE 1
Electrocardiogram: normal, sinus rhythm.

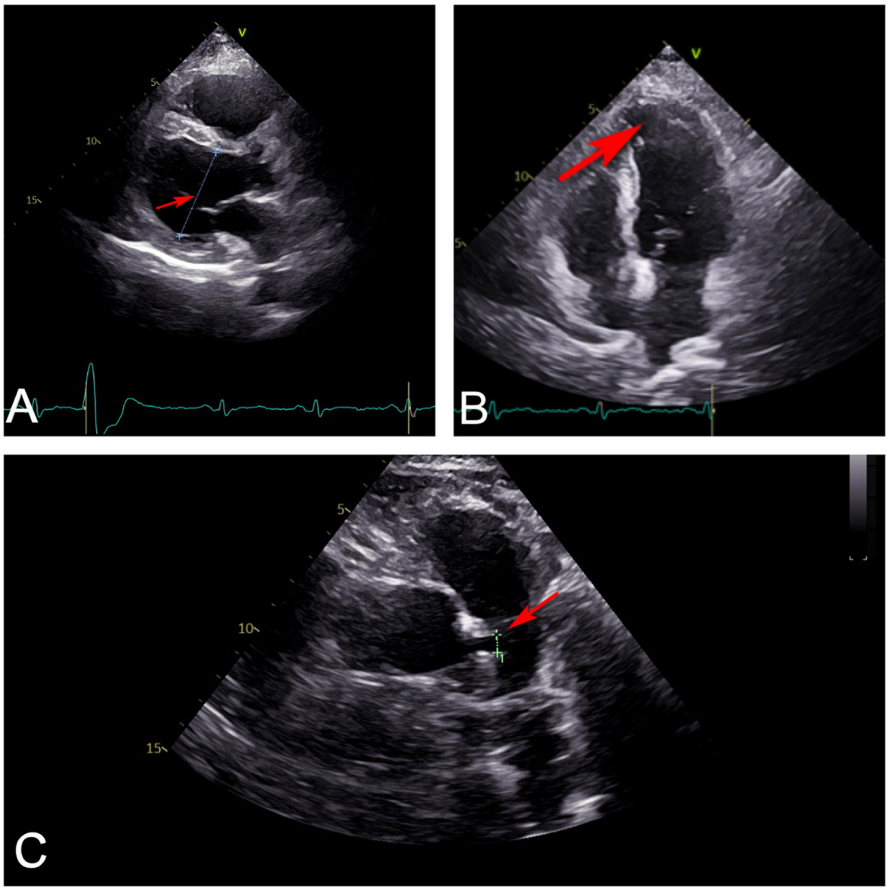

FIGURE 2
Ultrasonic cardiography showed that **(A)** left ventricle (red arrow) slightly enlarged from the parasternal long axis section view. **(B)** Apex of left ventricle (red arrow) bulged slightly outward from four-chamber view. **(C)** Left main coronary artery (red arrow) widened from random view.

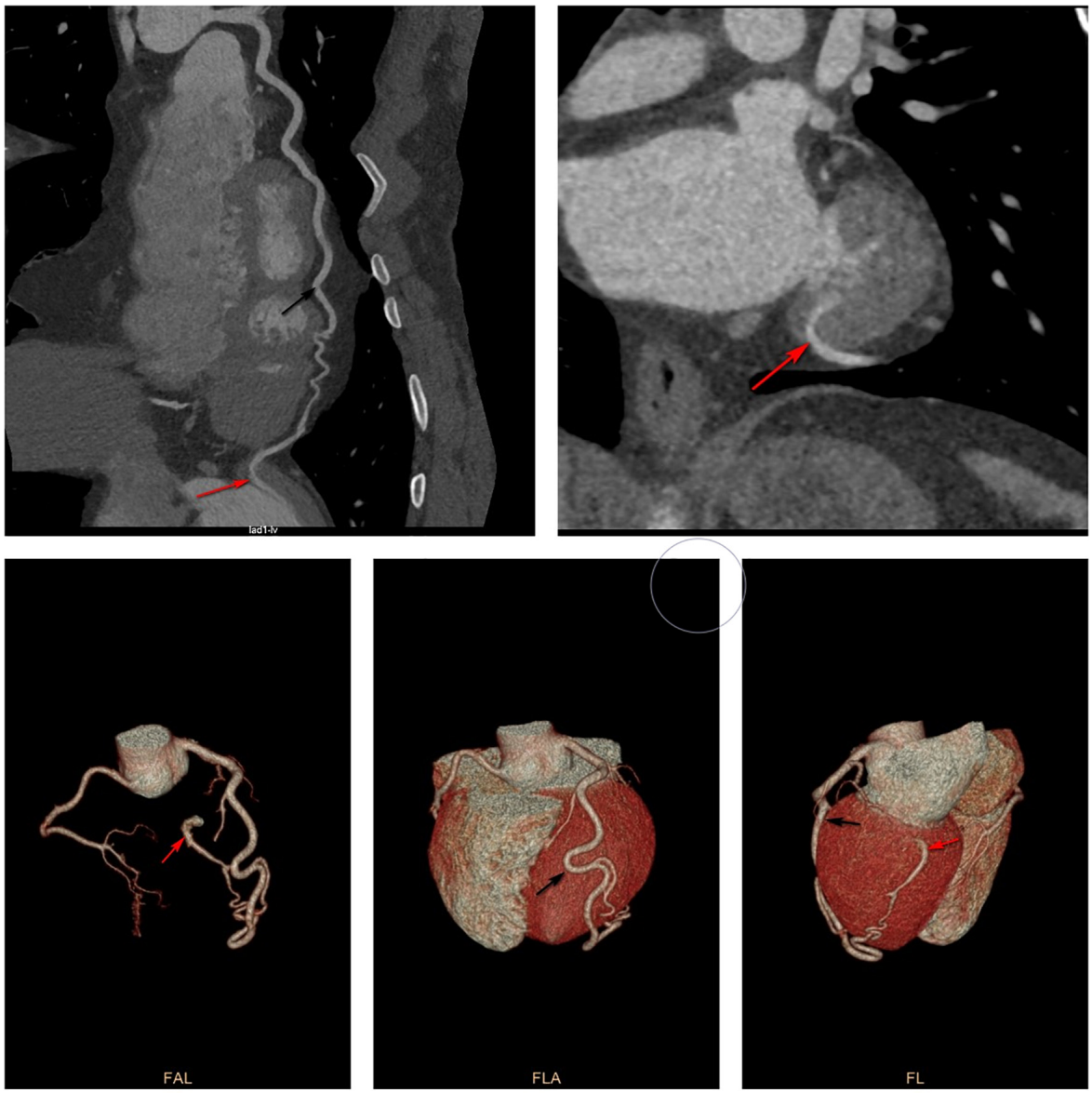

FIGURE 3
Computed tomography angiography showed that the diagonal branch of the left coronary artery was twisted, lengthened, expanded, extended along the left heart margin, and its distal end penetrated the myocardium from the basal segment of the left ventricular posterior edge into the left ventricle. Black arrow shows the thick diagonal branch; red arrow shows coronary artery-left ventricular fistula.

After admission, cardiovascular magnetic resonance (CMR) imaging and invasive coronary angiography (ICA) were performed. CMR of the heart showed suspicious fistula at the base of the inferior lateral wall (**Figure 4**) while ICA showed similar findings as CTA (**Figure 5**).

Treatment plans were: after admission, the patient was treated with papaverine, 120 mg, one time a day (QD), intravenous (I.V.); nicotinamide, 400 mg, QD, I.V.; shensongyangxin, 0.8 g, three times a day (TID), by mouth (P.O.); atorvastatin, 20 mg, QD, P.O.; aspirin, 100 mg, QD, P.O. and clopidogrel, 75 mg, QD, P.O. After treatment, there was no obvious improvement in patients' symptoms. A multi-disciplinary team suggested "surgical closure treatment" under general anesthesia. However, for personal reasons, he refused the operation. After discharge, the patient was prescribed oral beta-blockers.

Discussion and literature review

Clinically, CAF is a rare cardiac abnormality that should always be considered during differential diagnosis of chest

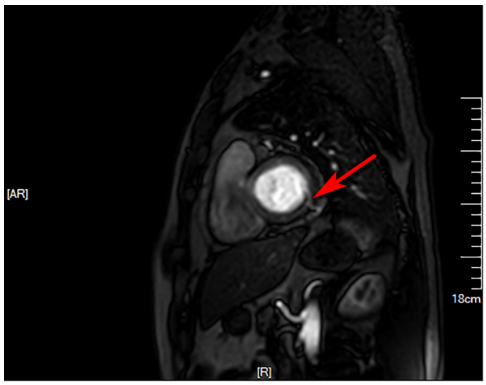

FIGURE 4
Cardiovascular magnetic resonance. Suspicious fistula at the base of the inferior lateral wall (red arrow) was seen from the left ventricular short axis at 4 o'clock direction.

pain and dyspnea, particularly in patients without significant risk factors for acquired heart disease. The etiologies and pathophysiological mechanism of CAF have not been fully established. However, it has been hypothesized that when there is no closure between the trabeculae connecting the coronary arteries, veins, and ventricles, a persistent sinus trabeculation may develop into CAF. As the flow increases, there is a significant increase in coronary branches proximal to the shunt site (4). Due to its hemodynamic consequences or complications, it is associated with various symptoms (5).

In the proximal segments of coronary arteries, CAFs are more likely to form aneurysms, which shows the significance of early diagnosis as early treatment can prevent rupture (3). The diagnostic methods, their advantages, and disadvantages in CAF are summarized in **Table 2**. Various non-invasive techniques, such as CTA, play a vital role in the diagnosis of these vascular anomalies. The CTA approach is excellent at revealing the origin, course, size, and termination site of CAF as well as its relationship with adjacent anatomic structures (6). We showed non-invasive UCG as the first diagnostic tool and the pre-admission evaluation value for the disease. The auxiliary diagnostic and exclusion values of CMR were assessed for the first time, and the gold standard value of

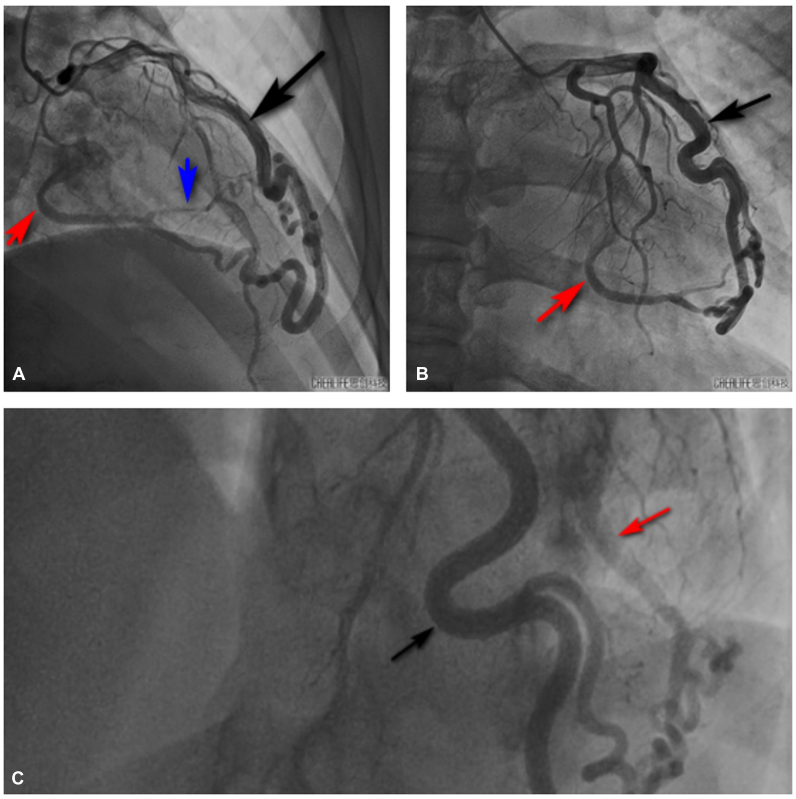

FIGURE 5
Invasive coronary angiography also showed that the diagonal branch of the left coronary artery was twisted, lengthened, expanded, extended along the left heart margin, and its distal end penetrated the myocardium from the basal segment of the left ventricular posterior edge into the left ventricle. Black arrow shows the thick diagonal branch; red arrow shows the coronary artery-left ventricular fistula; blue arrow shows the branch of coronary artery fistula that supplies the left ventricular posterior wall myocardium. **(A)** Right cranial view. **(B)** Anteroposterior view. **(C)** Left cranial view.

TABLE 2 The main diagnostic methods of CAF.

Main diagnostic methods of CAF	Advantages	Disadvantages
Ultrasonic cardiography (UCG)	·Showing abnormal vascular communication in the coronary arteries (6). ·Non-invasive. ·Measuring shunt flow in selected patients with CAF (7). ·Providing excellent qualitative and quantitative assessment of proximal coronary arteries (8).	·Dependending on the operator's skill (6). ·The quality of the acoustic window is poor and the quality of imaging is often limited (6). ·Cannot determine whether a coronary fistula is flowing from the posterior atrioventricular sulcus into the right atrium or right ventricle (8).
Transthoracic echocardiography (TTE)	·It has an important complementary role to ICA in depicting the proximal course and flow pattern of abnormal coronary arteries (9). ·Useful in accurately depicting the origin, proximal course and flow pattern of anomalous coronary arteries (9). ·Helping to determine the precise site of drainage of CAF (10). ·The effectiveness of intraoperative TEE in guiding the surgical closure of CAF (10).	·Not indicated in overweight patients (11).
Computed tomography angiography (CTA)	·Negative results could rule out coronary artery disease (12). ·Non-invasive (12). ·Identification of anomalous origin and course of coronary arteries, assessment of fistula complexity, and preoperative evaluation (13, 14). ·Defining the relationship between the details of the coronary vessels and the mediastinal structures (2).	·Renal insufficiency caution. ·Contraindication of contrast agent allergy. ·Poor image quality due to lower spatial and temporal resolution, motion and blooming artifacts, and adequate image acquisition (15). ·Depending on a low and stable heart rate (15). ·The amount of radiation (2).
Cardiovascular magnetic resonance (CMR)	·In addition to assessing the anatomy of the fistula, it is possible to further measure the blood flow in its lumen (16). ·To provide accurate measurements of cardiac output, shunt flow, turbulent floating jet areas, and even regurgitation (16). ·Velocity phase contrast images of the transverse aortic plane can provide the most accurate measurements of cardiac output, shunt, aortic or pulmonary regurgitation, and indirect mitral regurgitation (16).	·Regurgitant valves or severely stenosed aortic valves, which may fragment and are not suitable for accurate velocity measurements by CMR (16).
Multidetector computed tomography (MDCT)	·Acquisition of abnormalities in the aorta, pulmonary arteries, other vascular structures, and cardiac chambers (17). ·High temporal and spatial resolution without additional radiation exposure and contrast agents, and the ability to assess the precise anatomical relationship of coronary-pulmonary artery fistulas (17). ·Non-invasive (18). Much faster than CMR and can be done in a single breath hold (2). ·Higher temporal and spatial resolution than MR imaging (2). ·Providing an excellent overview of cardiac and vascular anatomy and helping surgeons understand the complexity of the anatomy prior to surgery (13).	·The amount of radiation (2). ·The inability to directly measure pressure in the blood vessels or ventricles is a limitation of all imaging modalities.
Invasive coronary angiography (ICA)	·Outlining the proximal course of the involved coronary artery and fistula (2). ·Remains the gold standard for describing the anatomy and collateral circulation of the involved coronary artery, the course of the fistula, the lumen of the receiving heart, and the exact site of communication (19).	·If it is a low-pressure room, it may not show up well (2). ·It is usually not possible to adequately fill an aneurysmal CAF with contrast, and it is challenging to clarify the distal site of the CAF and the relationship between the CAF and other cardiac structures (17). ·Invasive techniques that require patients to be hospitalized (20). ·Only the intraluminal route of the lesion is shown and may prevent a full assessment due to the overlap between tortuous fistulas and adjacent cardiovascular structures (21).

ICA for determining the origin and course of coronary fistula was proven. In this study, CTA showed similar results to ICA. ICA is the commonly used tool, but it is invasive. CTA might be an alternative method for determining the exact relationships among anatomic structures, because of its excellent spatial resolution.

When considering clinical treatment indications and options for CAF, an accurate assessment of the clinical presentation and morphology, including anatomic origin and course, drainage site, as well as possible aneurysm is necessary (1). The American College of Cardiology and American Heart Association guidelines for managing congenital heart disease (CHD) in adults (2008) emphasizes that large CAFs should be closed after their course has been determined, regardless of symptoms (Class I, Level of Evidence: C); small or medium-sized fistulas should be closed if the patient presents with symptoms such as myocardial ischemia, arrhythmias, ventricular dilatation, or dysfunction of unknown origin, or if the fistula is complicated with endocarditis (Class I, Level of Evidence: C); Patients with small asymptomatic fistulas should not be treated but managed by clinical follow-up, including UCG every 3–5 years (Class III, Level of Evidence: C) (22). Symptomatic patients and those with large diameter CAF, whether symptomatic or not, should have their fistulas closed surgically or with transcatheter closure (5). There is consensus regarding the surgical treatment of patients with symptomatic CAF (23). Intracardiac surgical closure of CAF is appropriate for patients with late-onset, large fistulas, coronary arteries with aneurysms, and those who are not candidates for transcatheter treatment (23). Surgical

or transcatheter treatments are linked to many risks and operative complications, such as procedural ST-T changes, and postoperative fever (5). Long-term follow-up is required to assess the effectiveness of management, recurrence, and late outcomes (23). Untreated large fistulas might lead to congestive heart failure and premature coronary arterial disease in affected vessels (24). There is no consensus regarding treating asymptomatic adult patients without significant shunts to prevent fistula-related complications (1). Although most patients with such anomalies are asymptomatic, early treatment is recommended to prevent the onset of complications, such as ventricular wall tumor, heart valve disease, cardiomyopathy, and infective endocarditis (25). Armsby et al. (26) performed transcatheter occlusion in 33 of 39 asymptomatic patients with a typical murmur and reported that all patients who accepted interventional therapy had good long-term prognostic outcomes. Researchers are still investigating suitable drugs for the disease. According to Karazisi et al. (5), antiplatelet or warfarin therapies should be considered, especially in coronary artery dilatation. For patients subjected to interventional operation, anticoagulation should be administered after operation. There are various drugs for different symptoms, such as drugs (beta-blockers or calcium channel blockers) for angina and those for treating high-risk factors (hyperlipidemia, hypertension, and diabetes among others). However, these recommendations are mostly empiric (5). Lifelong follow-up is always necessary to ensure that patients with CAF have no disease progression or further cardiac complications. In addition, the risk of infective endocarditis in those patients is also higher than that of ordinary people (11). At present, the patient demanded for conservative treatment and was informed of the above risk. He was also advised to receive regular UCG examination. Most cases of CAF are congenital. CHD is associated with many genes, such as chromatin modifiers, cilia, cilia transduction cell signaling, and maternal factors (27). Cilia and chromatin modifiers may drive the complex genetics of CHD (27). There are many hypotheses regarding the congenital etiologies of CAF. However, the specific molecular mechanisms underlying CAF pathogenesis have not been fully established. Targeted or causative therapies should be investigated through genomics, particularly the study of genes and receptors.

All of the above-mentioned diagnostic methods and treatment options have their merits and demerits. The best diagnostic and treatment plans should be selected based on patient condition and hospital facilities. UCG could be used for preliminary disease screening, CTA might be used instead of ICA for determining the exact relationships with anatomic structures, whereas CMR can be used to exclude other diseases hence help in the diagnosis. In terms of treatment plans, studies should aim at assessing various treatments to inform on the accurate treatment of CAF.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the First Hospital of Jilin University Ethics Committee. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

JW conceived the idea and conceptualized the case. JW and QW collected the data. JW and HZ analyzed the data and drafted the manuscript. QT and QW reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Case report: Ultrasound-Assisted endovascular therapy for carotid artery floating thrombus

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Background: Carotid free-floating thrombus (CFFT) is a rare but sometimes emergent condition. There has been controversy over the optimal treatment strategy. Emerging evidence suggests that endovascular thrombectomy (EVT) may be an alternative to surgery. Accurate alignment of the aspiration catheter and thrombus during EVT is critical but has, so far, remained unresolved.

Case summary: This is a rare case of CFFT presenting with acute right-sided facial droop and moderate dysarthria in a 77-year-old man. He was in sinus rhythm with a blood pressure of 110/82 mmHg. Both non-contrast CT (NCCT) and head CT angiography (CTA) were unremarkable, while whole-brain CT perfusion (WB-CTP) suggested left hemisphere core infarction. Delayed imaging of the left internal carotid system by 4D-CTA suggested severe proximal obstructive disease, as confirmed by carotid CTA and ultrasonography. The initial two aspirations under DSA were invalid due to the challenging anatomical angle between the thrombus and the catheter. The success of CFFT removal was achieved with a pressure-assisted ultrasound-guided approach that helps to compress the catheter tip toward the thrombus.

Conclusion: We innovatively report a successful ultrasound-guided EVT for CFFT. Ultrasound assistance can provide quick and effective guidance and may guide tailored aspirations during EVT.

KEYWORDS

free-floating thrombus of the carotid, endovascular thrombectomy, carotid endarterectomy, carotid angioplasty and stenting, ultrasound-guided intervention

Introduction

Carotid free-floating thrombus (CFFT) has been reported as a rare entity but may present with emergent symptoms (1). In cases that are refractory to anticoagulation therapy, carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS) may be effective. However, there has been controversy regarding the optimal treatment strategy (1). Evidence suggests that endovascular thrombectomy (EVT) is emerging

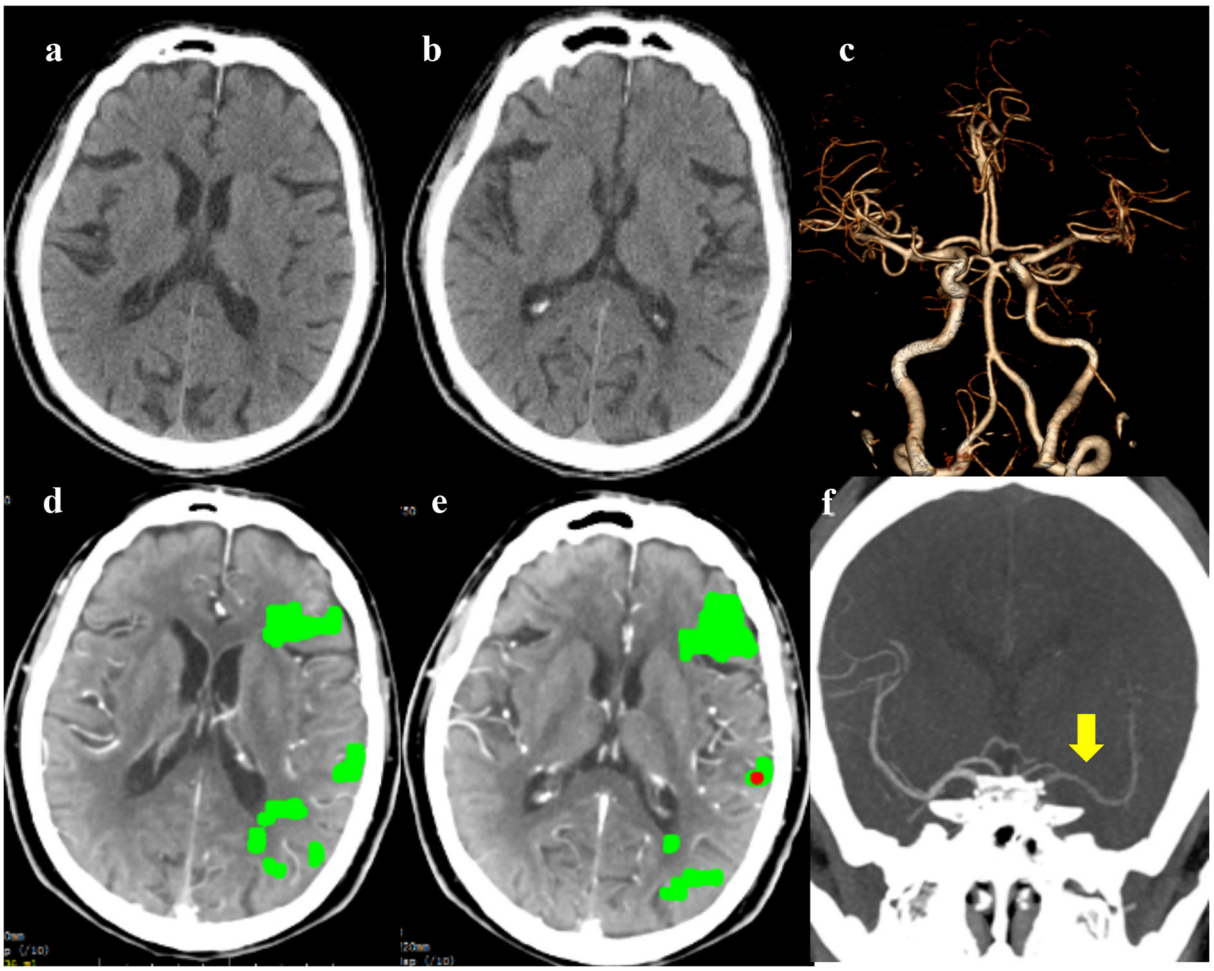

FIGURE 1
The emergency non-contrast CT (NCCT) **(a,b)** and cranial CT angiography (CTA) **(c)** did not show obvious cranial abnormalities; whole-brain CT perfusion (WB-CTP) indicated the left hemisphere core infarction **(d,e)**; The 4D-CTA reconstruction showed delayed imaging of the left middle cerebral artery [**(f)**, yellow arrow].

as an alternative to CFFT surgery and may yield good long-term outcomes (2, 3). Notably, accurate alignment of the aspiration catheter to the thrombus is critical during EVT, which has not been addressed to date. We innovatively report the successful intraoperative pressure-assisted ultrasound-guided direct aspiration of CFFT in the presence of technical obstacles caused by the anatomical angle between the plaque and catheter tip.

Case description

A 77-year-old Chinese male with only a medical history of hypertension was transferred to our hospital with acute right-sided facial droop and moderate dysarthria. About 16 h before admission, he experienced a gradual onset of weakness and numbness of the right upper extremity, followed by slurring of speech. On admission, he was in sinus rhythm with a blood pressure of 110/82 mmHg. His National Institute of Health Stroke Scale (NIHSS) was 6, Modified Rankin Scale (MRS) was 3, and Water-Swallow Test Score was 2. Only D-dimer (1,030 μg/L) and prothrombin time (12.5 s) were elevated in laboratory tests. He is a non-smoker and has no other medical history or alcohol addiction. There was no evidence of primary or acquired hypercoagulability, such as cancer or thrombotic disorders.

Diagnostic assessment

There were no obvious abnormalities in emergency NCCT and CTA, and the Alberta Stroke Program Early CT Score (Aspects) was 10 points. However, the WB-CTP indicated the left hemisphere core infarction was 1 ml with a penumbra zone of 35 ml (MIStar, Apollo Medical

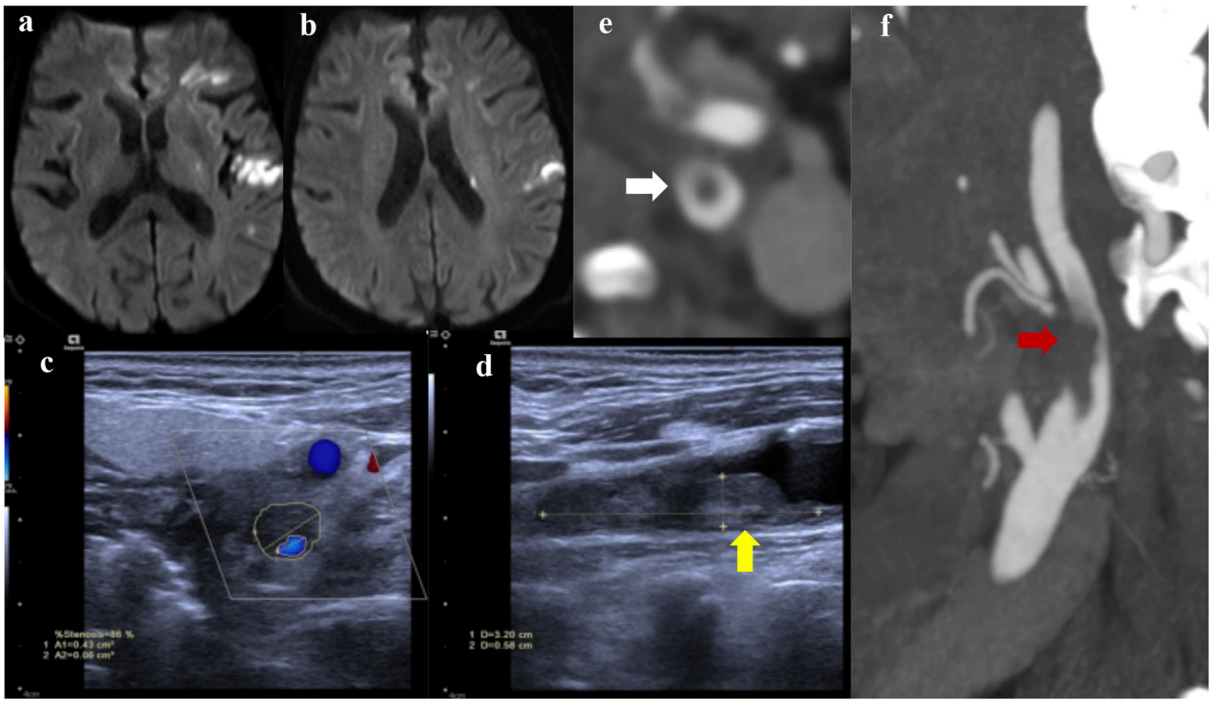

FIGURE 2
Diffusion-weighted imaging (DWI) showed multiple infarctions in the left hemisphere **(a,b)**; Carotid ultrasound **(c,d)** indicated a culprit plaque with local floating thrombus (yellow arrow), resulting in obvious stenosis of the left internal carotid artery; carotid CTA **(e,f)** presented the floating thrombus (red arrow) with a typical cross-sectional "donut sign" (white arrow).

Imaging Technology, Melbourne, Australia). The 4D-CTA reconstruction showed delayed imaging of the left internal carotid system, suggesting severe proximal obstructive disease (Figure 1). During hospitalization, daily prescriptions included enteric-coated aspirin 100 mg in combination with clopidogrel 75 mg and atorvastatin 40 mg. Diffusion-weighted imaging (DWI) showed multiple infarctions in the left hemisphere, and carotid ultrasound showed 85% stenosis of the left internal carotid artery with local floating thrombus. Two days after admission, there was no obvious change in the ultrasound review, and the carotid CTA presented a typical "donut sign," indicating a CFFT rather than only a vulnerable plaque (Figure 2).

Considering the onset-to-admission time (16 h) and evidence of CFFT on CTA, medical therapy may be invalid, and, in the shortest time, EVT was recommended according to the guidelines for the treatment of acute ischemic stroke with large vessel occlusion (4). A bilateral femoral artery approach was adopted to insert the 8F arterial sheath. One 8F balloon guide catheter (FlowGate² Balloon Guide Catheter, Stryker Neurovascular, USA) entered the left common carotid artery. Afterward, a Nav6 umbrella (Emboshield NAV6, Abbott Vascular, USA) was inserted through the catheter and placed in the distal segment of the internal carotid artery further than the floating thrombus. This help prevents distal embolization events from thrombus falling during the operation. Another 8F guide catheter (Mach1, Boston Scientific, USA) was inserted to aspirate the CFFT. However, only a small amount of thrombus was aspirated during the first two local aspirations. The Mach1 could not accurately head to the thrombus during aspiration with only the longitudinal imaging information of the thrombus identified under DSA. Therefore, an ultrasound-guided approach was initiated to visualize the location of the CFFT. The ultrasound illustrated the reason for the first two invalid aspirations by showing that the Mach1 could not head toward the thrombus due to the vascular anatomy and residual eccentric lumen. Based on the transverse view of the internal carotid artery, while viewing the Mach1 tip above the thrombus, we gently pressed the probe (1 mm/s) to reduce the distance between Mach1 tip and the thrombus. During the procedure, real-time ultrasound recorded the aspiration process and the vibrating performance of the CFFT (Supplementary Video 1), and color Doppler flow imaging confirmed CFFT removal after a single ultrasound-guided aspiration (Supplementary Video 2). We saw the thrombus aspirated from Mach1, and repeated DSA also confirmed the removal of the thrombus. There was no escape thrombus in the protective umbrella during surgery, and post-operative DWI showed no evidence of a

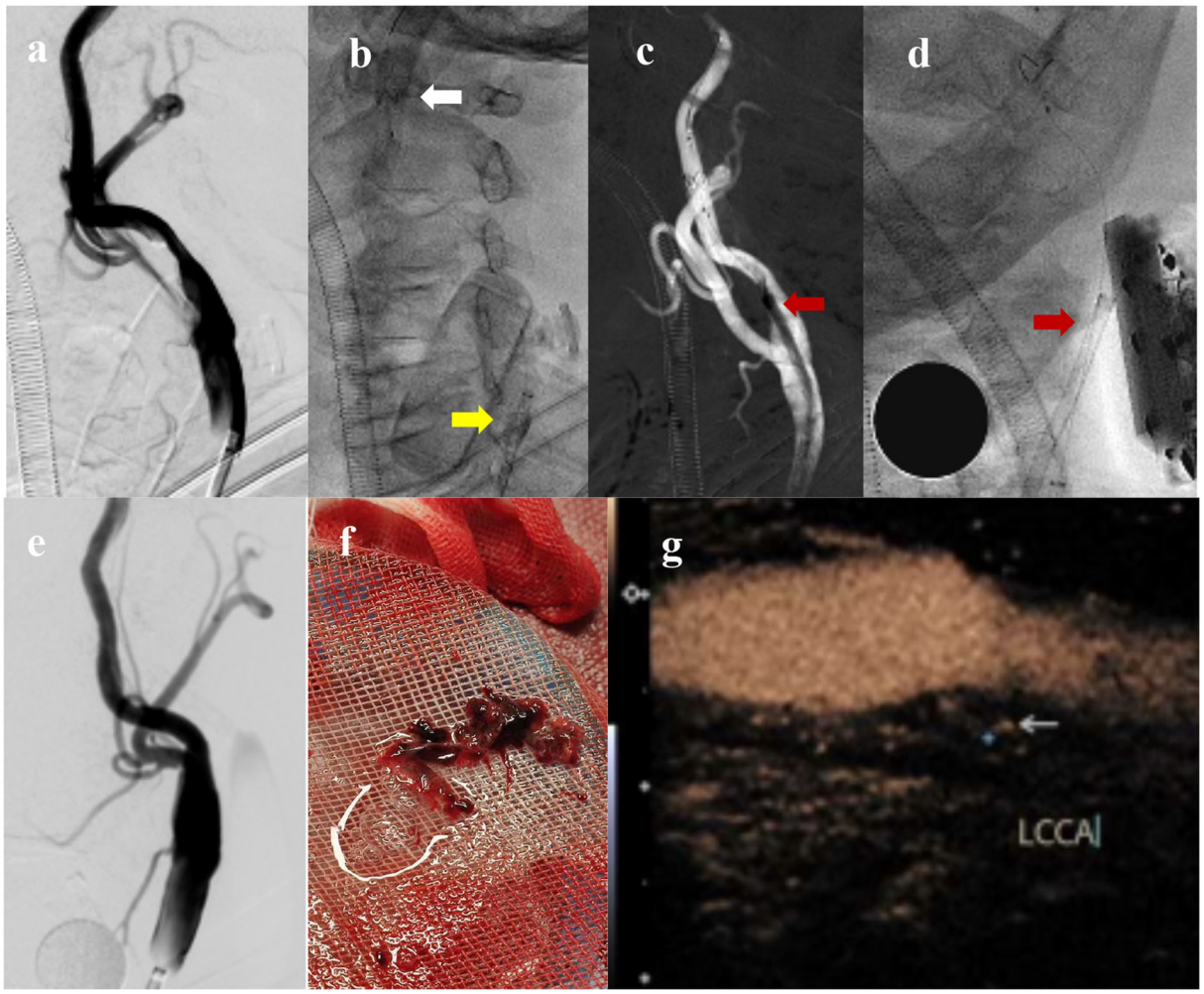

FIGURE 3
Carotid DSA before aspiration **(a)**; The FlowGate² balloon guide catheter (yellow arrow) is placed in the left common carotid artery and the Emboshield NAV6 embolic protection system (white arrow) is placed in the distal segment of the internal carotid artery **(b)**; The Mach1 guide catheter (red arrow) is inserted to aspirate CFFT **(c)**; Ultrasound probe depressing Mach1 tip (red arrow) to face the thrombus **(d)**; Carotid DSA after aspiration **(e)**; Massive thrombus has been aspirated **(f)**; Postoperative contrast-enhanced ultrasound showed unstable plaque with no evidence of CFFT **(g)**.

new infarct. On the next day, contrast-enhanced ultrasound (CEUS) showed only an unstable plaque in the region of CFFT (Figure 3). Pathological examination revealed fresh thrombi, rich in red blood cells and platelets (Figure 4). During the initial 2-week follow-up, the patient was asymptomatic and remained clinically stable. Contrast-enhanced ultrasonography of the carotid artery is recommended after 2 weeks to see if further anticoagulation is required.

Discussion

The ischemic event may have resulted from the rupture of vulnerable atherosclerotic plaques of the internal carotid artery in the patient's hypertensive setting. CFFT was reported as early as 1905 (5), and subsequent reports were mostly found in surgical operations (6). With the improvement of CTA diagnostic technology, the incidence rate has increased from 0.4 to 1.5% based on catheter angiography to 3.2%, especially owing to the proposed "donut sign" (7). A literature review has emphasized the importance of the "donut sign" and discussed the etiology and treatment of CFFT, pointing out that it was mostly atherosclerotic disease (82%), and recommending heparin combined with an antiplatelet drug for treatment (8). However, there is still a 7.5% stroke recurrence rate and a 3.5% mortality rate, with a median event time of 2 days (IQR 1–8 days). Therefore, early identification of medication refractory

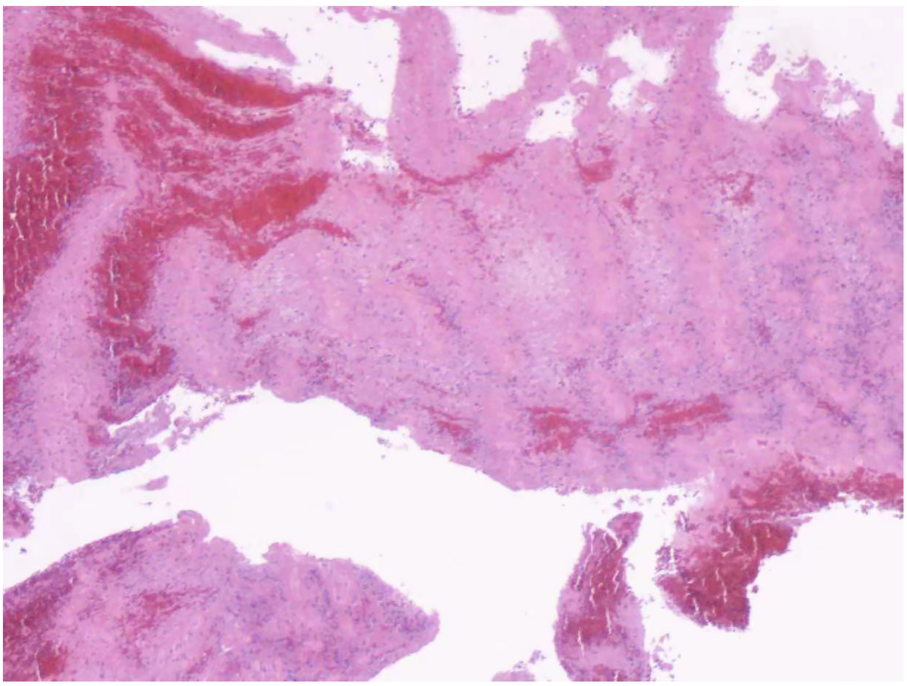

FIGURE 4
Hematoxylin and eosin stain presented a fresh thrombus that was rich in red blood cells and platelets.

and effective selection of alternative treatment options are extremely important.

Some scholars have reported that CEA is safe and effective in the treatment of CFFT (9). There are also reports of CAS in the treatment of CFFT (10). Recently, with the development of endovascular treatment of acute ischemic stroke with intracranial large artery occlusion and the introduction of minimally invasive and non-implantation concepts, more centers begin to try mechanical thrombectomy to treat CFFT (11). However, procedures of direct aspiration are extremely rare (12); there are limited reports regarding an ultrasound-guided approach to resolving CFFT. Otawa et al. (13) and Giragani et al. (14) have reported that ultrasonography helped localize CFFT during endovascular therapy. In our case, the major technical barriers include the small diameter of the catheter and the limited angle of the catheter tip, resulting in it being extremely difficult to accurately head toward the body of the thrombus. Thus, we innovatively performed a pressure-assisted ultrasound-guided aspiration. Our experience highlights that the carotid ultrasound may provide a simple and effective approach to the accurate aspiration of CFFT, which is recommended in the management of such difficult cases during the EVT treatment of CFFT.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Zhejiang Provincial People's Hospital, Affiliated People's Hospital of Hangzhou Medical College. The patients/participants provided their written informed consent to participate in this study and for the publication of this case report.

Author contributions

PW performed the EVT and wrote the main part of the manuscript. ZW performed the ultrasound scan during the intervention and revised the manuscript. JP and KL were assistants during the operation. LS and YG were directors of this research and program. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.961760/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Ultrasound-guided aspiration of CFFT. On transverse view of the left internal carotid artery, a Mach1 guide catheter was placed facing the plaque under gentle pressure from the ultrasound probe. The thrombus was vibrating when the aspiration was initiated.

SUPPLEMENTARY VIDEO 2
Color Doppler flow imaging confirmed the removal of the CFFT.

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Case report: Cement entrapped in the inferior vena cava filter after pedicle screw augmentation

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Background: Cement leakage into the inferior vena cava (IVC) is one of the most common complications associated with cement vertebroplasty, and can lead to potentially life-threatening complications such as pulmonary cement embolism (PCE). Implantation of an IVC filter is effective in the prevention of fatal pulmonary embolism. Here, we present an extremely rarely case of cement entrapped in an IVC filter after pedicle screw augmentation, and discuss all similar cases reported in the literature.

Case presentation: A 70-year-old female presented with significant back and lower extremities pain and was unable to walk. MRI of the lumbar spine revealed an osteoporotic compression fracture of the L1–L3. She underwent cement-augmented pedicle screws implanted at the L1 and L3 vertebral bodies. A retrievable IVC filter was implanted due to the presence of calf vein thrombosis before cement vertebroplasty. Cement leaked into the IVC and was trapped by the filter, rendering the filter unretrievable using a conventional method. The asymptomatic patient received rivaroxaban 20 mg daily for anticoagulant postoperatively and lifelong anticoagulation was administered to prevent secondary IVC and cemented filter thrombosis.

Methods: A literature search was conducted utilizing the PUBMED/MEDLINE using the following terms: "vertebroplasty," "complication," "bone cement," and "inferior vena cava (IVC)," or "inferior vena cava (IVC) filter." All relevant articles published in English or in other languages with English abstracts since 1962 were included.

Results: A total of 36 articles were retrieved according to the search strategy. Only 6 out of these 36 studies contained information regarding the

inferior vena cava filter and cement. Of the patients, 85.7% (36/42) reported in the literature whose gender was known were female and 14.3% were male. 28.5% (45/158) patients with pulmonary arterial and cardiovascular complications.

Conclusion: Cement embolization occurring in the IVC filter is rare. Accurate knowledge about the lumbar vertebral venous anatomy and skillful operation during vertebral cementoplasty should be required in clinical practice.

KEYWORDS

vertebroplasty, bone cement, inferior vena cava, inferior vena cava filter, complication

Introduction

Bone cement has been widely injected into diseased or fractured vertebral bodies to provide an expected increase in the stabilization and strength of the vertebral and pedicle screws, and is especially suitable for the management of osteoporotic compression fractures (1). However, spillage of cement frequently occurs in the process of vertebroplasty and may result in serious sequelae. Cement leakage into the venous plexus is the most frequent complication, and can lead to severe and potentially life-threatening complications such as pulmonary cement embolism (PCE) or myocardial perforation (2). Here, we present a case that underwent cement augmentation for improving fixation of pedicle screws, in which the cement leaked into the peripheral venous system causing large masses extending to the IVC that were eventually captured in the previously implanted IVC filter. This case study is significant because it illustrates the rare occurrence of cemented filter, making clinicians aware of the potential possibility of cement leakage into the IVC in patients with cement-based augmentation of vertebroplasty. We discuss this case and all similar cases reported in the literature.

Case presentation

There was a 70-year-old female patient who had significant back and lower extremities pain and was unable to walk. An outpatient MRI of the lumbar spine showed an osteoporotic compression fracture of the L1–L3. She had cement- (polymethylmethacrylate) augmented pedicle screws implanted at the L1 and L3 vertebral bodies after hospital admission. A total of 5.8 ml of "tooth-paste-like" bone cement was injected to provide stabilization and pain relief within 5 min after mixing, and the procedure was performed under the guidance of C-arm X-ray fluoroscopy. Before cement vertebroplasty, a retrievable IVC filter (Aegisy, LifeTech, Shenzhen, China) was implanted into the IVC to prevent pulmonary embolism (PE) since the routine preoperative ultrasound revealed an isolated distal deep vein thrombosis in the vein of her left calf. The patient received rivaroxaban 20 mg daily for anticoagulant postoperatively.

Thereafter, X-ray examination showed paravertebral venous cement leak and cement entry into the IVC, resulting in the deposition of a cement cast in the IVC filter, and CT images demonstrating cement leaking out of the vertebral body (**Figure 1**). An inferior vena cavography prior to retrieval of the filter showed that cement had migrated into the IVC and attached to the caval wall at the level of the IVC filter tip and was trapped within the filter (**Figure 2**), resulting in the IVC filter failing to be retrieved in the conventional way.

Bone cement injection was performed by spinal surgeons with more than 10 years of clinical experience, and cavography and DSA image judgment were performed by interventional radiologists with more than 10 years of clinical experience. The asymptomatic patient continued with rivaroxaban 20 mg daily and was discharged from the hospital, and close follow-up and lifelong anticoagulation was administered to prevent secondary IVC and cemented filter thrombosis.

Methods

A literature search was conducted utilizing the PUBMED/MEDLINE using the following terms: "vertebroplasty," "complication," "bone cement," and "inferior vena cava (IVC)," or "inferior vena cava (IVC) filter." All relevant articles published in English or in other languages with English abstracts since 1962 were included.

Results

The literature search yielded 36 articles whose clinical reports contained information regarding the coexistence of

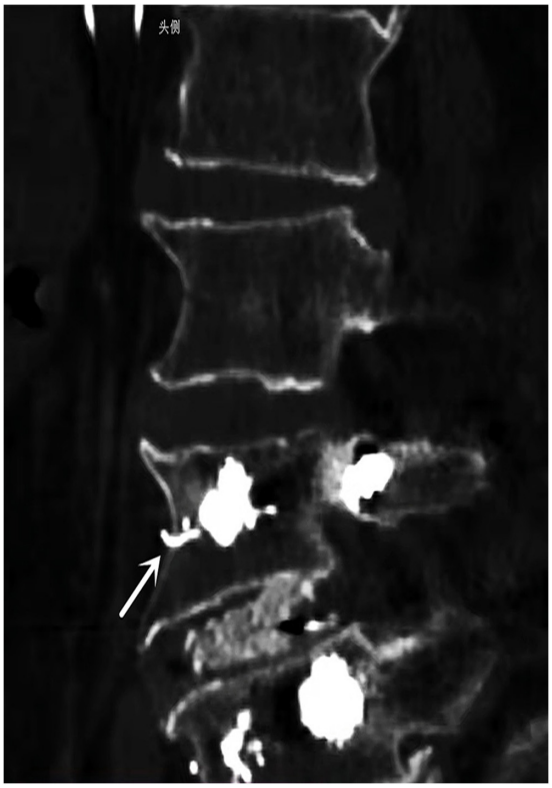

FIGURE 1
CT scans revealed strip-like high density cement extravasation (arrows) in vertebra bone.

cement and inferior vena cava or inferior vena cava filter. Of these patients, 85.7% (36/42) of individuals whose gender was known were female (n = 36) and 14.3% (6/42) were male (n = 6). Cement leakage into the IVC that primarily resulted in pulmonary arterial and cardiovascular complications despite the majority of the patients being asymptomatic accounted for 45 of 158 cases. Only 6 out of these 36 studies contained information regarding the inferior vena cava filter and cement.

Our personal experience includes one unpublished female patient seen and followed-up at our institutions. In addition, another earlier and similar case to this has been accepted for publication in a future issue of CardioVascular and Interventional Radiology, but has not been fully edited. The clinical features of those 36 previously reported are presented in **Tables 1**, **2**.

Discussion

Cement augmentation with polymethylmethacrylate is a reliable method for increasing the compressive strength of vertebral bodies, and it is an accepted treatment for osteoporotic compression fracture and reinforcement of vertebral pedicle screws fixation. Perivertebral cement leakage is a frequently reported complication following pedicle screw augmentation and it could potentially be a life-threatening condition; the leaked cement may migrate into IVC and pulmonary arterial circulation with varying incidence rates of 0.9–26% (3–5). However, it is often the case that there were no routine chest CT examinations before or after vertebroplasty. The true incidence of PCE is unknown and may even be underestimated. In addition, the mortality data related to cement leakage was not systematically documented in the literature (6, 7). Although a number of patients have bone cement leakage into the azygos vein or IVC, most cases remain asymptomatic (8). Despite this, some catastrophic outcomes, such as fatal PCE, cardiovascular collapse, and myocardial perforation, have still been documented in the literature (6, 9, 10). Kim found that cement leakage into the IVC showed a statistically significant correlation with PCE (p = 0.03) (11).

It is well known that implantation of IVC filter is effective in the prevention or reduction of the risk of fatal PE in patients with high risk of lower extremity deep vein thrombosis (12). In rare cases, some IVC filters have also

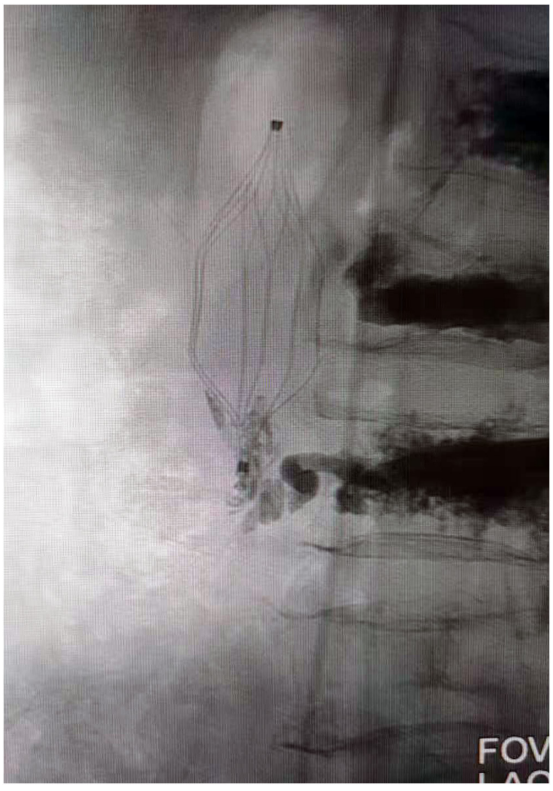

FIGURE 2
Venography showed cement attached to the IVC filter hook and trapped in the filter. IVC, inferior vena cava.

TABLE 1 Cases of cement leakage extended into the inferior vena cava reported in literature.

Authors	Year	Numbers	Gender	Outcome
Prater et al. (15)	2021	1	F	IVC filter trapped
Hu et al. (1)	2021	1	F	PCE and iliac vein thrombus
David et al. (28)	2021	1	F	PCE
Kong et al. (9)	2019	12	11F/1M	1 cardiac embolus and 11 PCE
Izumi et al. (29)	2019	1	F	PCE and shock
Ishak et al. (24)	2019	14	N/A	PCE (4)
Frenk et al. (30)	2019	1	M	Stent placement and anchor to IVC
Yuan et al. (10)	2018	1	F	PCE
Saranteas et al. (7)	2018	2	1F/1M	1 died/1 cardiac embolus
Park et al. (31)	2018	1	F	Intra-cardiac embolism
Majunke et al. (32)	2018	1	F	PCE and successful retrieval
Isaak et al. (33)	2018	1	N/A	PCE
Elens et al. (34)	2018	1	F	Anchor to IVC
Suwan et al. (35)	2017	1	N/A	Anchor to IVC
Janssen et al. (8)	2017	94	N/A	13 PCE (2 died)
Riesner et al. (2)	2016	2	N/A	No PCE
Shen et al. (36)	2015	1	F	PCE and Cardiac perforation
Edwards et al. (16)	2015	1	F	IVC filter trapped
Schmid et al. (37)	2014	1	M	PCE
Lee et al. (38)	2014	1	F	Cardiac tamponade and died
Vallabhajosyula et al. (39)	2013	1	F	PCE
Li et al. (17)	2013	1	F	IVC filter trapped
Sun et al. (40)	2012	1	F	IVC thrombosis
Schulz et al. (41)	2012	3	N/A	PCE
Kim et al. (42)	2012	1	M	IVC thrombosis and PCE
Czesla et al. (43)	2012	1	F	PCE and Cardiac perforation
Dash et al. (44)	2011	1	F	PCE and Right atrial-IVC thrombus
Agko et al. (14)	2010	1	F	IVC filter trapped
Kim et al. (11)	2009	2	1M	PCE
Athreya et al. (18)	2009	1	F	IVC filter trapped
Kao et al. (27)	2008	1	F	IVC thrombosis and PCE
Lim et al. (45)	2007	1	F	PCE and intraatrial thrombus
Herbstreit et al. (19)	2006	1	F	IVC filter trapped and cavotomy
Baumann et al. (46)	2005	1	F	PCE
Prymka et al. (47)	2003	1	F	N/A
Padovani et al. (48)	1999	1	F	PCE

IVC, inferior vena cava; PCE, pulmonary cement embolism.

been used as a prevention strategy against cement emboli in IVC, which may migrate into the pulmonary circulation (13, 14). However, it appears to be quite rare for leaked cement to become entrapped in an IVC filter. So far as we know, only six cases of cemented filters have previously been reported in the literature (**Table 2**) (14–19). In our case, cement leaked into the IVC and was trapped by the filter, preventing cement cast migration to the pulmonary arterial circulation. However, it is extremely difficult to retrieve the cemented filter into the outer sheath by utilizing conventional endovascular procedures. Management guidelines vary because of the rare nature of this event. In our case, careful observation and long-term anticoagulation were recommended. Nevertheless, with secondary events, IVC foreign bodies serve as a nidus for thromboembolism and should be taken into consideration.

Therefore, do we need to implant an IVC filter to prevent PCE before vertebral cementoplasty? The only randomized trial regarding pulmonary complications during the cementoplasty procedure is the VERTOS II trial, and 26% (14/54) of the

TABLE 2 Cases of cement trapped by inferior vena cava filter reported in literature.

Authors	Year	Age (y)	Gender	Filter brand	Outcome
Prater et al. (15)	2021	77	F	N/A	Unremoved
Edwards et al. (16)	2015	45	F	N/A	Removed
Li et al. (17)	2013	58	F	OptEase	Unremoved
Agko et al. (14)	2010	51	F	Greenfield	Removed
Athreya et al. (18)	2009	61	F	Guenther Tulip	Removed
Herbstreit et al. (19)	2006	66	F	N/A	Cavotomy

patients with PCE were confirmed by chest CT scans after the vertebral cementoplasty despite none of the patients having related symptoms due to the small size of the cement embolus and its random distribution in the pulmonary vascular endings (20). Among the 158 patients with cement leakage into the IVC after vertebral cementoplasty of all relevant retrieved articles by 2021 in our study, 45 (28.5%) had cardiopulmonary complications despite the majority presenting as mild cases, but severe complications such as cardiac perforation and circulatory failure did occur (**Table 1**). However, some cardiopulmonary complications were not well documented, and the incidence appeared to be underestimated. Apparently, the risk–benefit ratio for IVC filter implantation is far from certain. Therefore, decisions need to be made on a case-by-case basis.

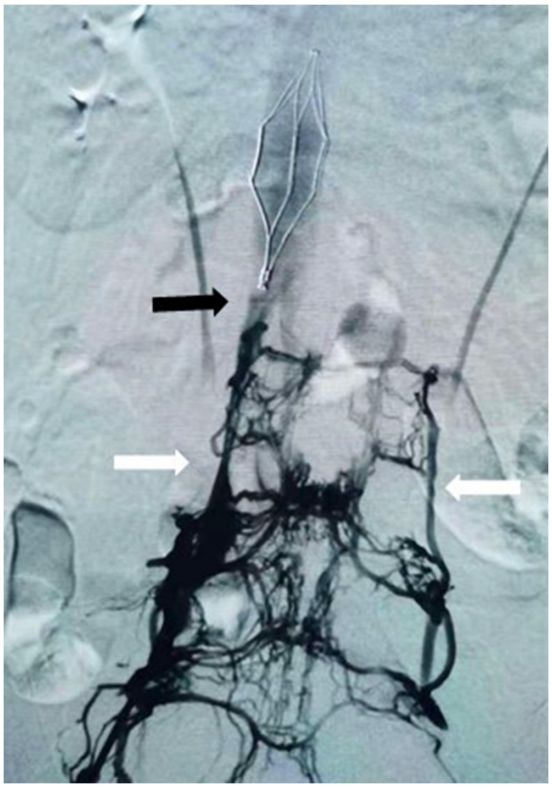

FIGURE 3
Venography showed collateral drainage veins between inferior vena cava (black arrow) and paravertebral venous (white arrow).

The reasons why cement embolization occurs in the IVC during cementoplasty procedure have been much discussed in the literature. It is known to all that lumbar vertebral veins enter the IVC at L1-L5 vertebral levels, and numerous connections exist with basivertebral vein and segmental vein (**Figure 3**) (5, 21). Iwanaga found that latex or air can flow into the IVC at the internal/external vertebral plexus through anatomical location (5). This is the anatomic risk factor for the occurrence of cement venous leakage. However, it should be noted that there may be other reasons, such as incompletely polymerizing cement, the proximity of the needle to the vertebral venous plexus, or the higher volume and faster pushing of the cement (22). Additionally, intraoperative X-ray fluoroscopy may also be helpful to reduce cement leakage (23). But Ishak, who found that 55 of 86 patients had venous cement leakage despite 52 of them having no symptoms, suggested that using CT navigation for screw placement did not reduce the cement leakage risk (24). This may be in part related to a non-radiologist operator with C-arm fluoroscopy (11). Phillips found that injection of contrast medium into the vertebral body could also predict and reduce the occurrence of bone cement leakage (25). Post-procedure chest CT scans may be useful in guiding early diagnosis and treatment. In all literature reports, the proportion of females is significantly higher than that of males. It is not clear why cement leakage into the IVC is more likely to occur in females, although Zhan found no significant association between gender and cement leakage after vertebroplasty or kyphoplasty in a recent systematic review (26).

Conclusion

These interesting cases illustrate that the IVC filter could capture cement that leaks into the IVC and prevent fatal pulmonary arterial and cardiovascular complications. The present study, as with any other (27), contributed to making clinicians aware of the potential occurrence of cement leakage into the IVC during vertebroplasty procedures. In other words, surgeons should be aware of the possibility of cement leakage

when patients develop clinical symptoms of PE, such as decreased blood pressure, tachycardia, and dyspnea.

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 this case report and the publication of any potentially identifiable images or data included in this article.

Author contributions

XH, YZ, and MZ: study concept, acquisition of data and figures, and writing of the manuscript. MZ and ZW: critical revision of manuscript for intellectual content. All authors cared for the patient and contributed to writing of the report.

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Conflict of interest

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

Publisher's note

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Case report: Unusual persistent hypotension and acute occlusion after peripheral paclitaxel balloon angioplasty

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Background: Paclitaxel-coated balloon (PCB) angioplasty is a mainstream treatment for peripheral artery disease; however, the safety of PCB remains controversial.

Case presentation: We confirmed acute occlusion during PCB angioplasty in a patient with femoropopliteal artery occlusion. The occluded vessels were revascularized completely after endovascular medical therapy and bailout stenting angioplasty. Then, the patient experienced persistent post-procedure orthostatic hypotension (30 days) and received hydration and vasoactive agents with a target mean arterial blood pressure of 75–85 mmHg. The patient's blood pressure gradually recovered over the 30 days after the procedure, and there was no recurrence of symptomatic hypotension during the follow-up.

Conclusions: This rare complication is helpful to evaluate the safety of the PCB device.

KEYWORDS

paclitaxel-coated balloon, no-reflow phenomenon, femoropopliteal artery occlusion, persistent hypotension, complication

Introduction

Percutaneous balloon angioplasty is an effective strategy for femoropopliteal artery occlusion; however, restenosis occurs in 40–60% of patients within 1 year, leading to therapeutic failure and reintervention (1–4). Paclitaxel-coated balloon angioplasty (PCB) is a relatively newer endovascular therapy strategy that has been designed to limit the intimal proliferation of target lesions and has been proven to be effective for the treatment of peripheral artery disease (5–7). However, a recent report showed an increased long-term risk of death following the application of paclitaxel-coated balloon angioplasty (8). Paclitaxel is a cytotoxic drug that inhibits smooth muscle proliferation and has potential adverse effects, such as hypotension and arrhythmia (9). Moreover, PCB angioplasty might cause a no-reflow phenomenon or acute occlusion in the target vessel, which is often reported in percutaneous coronary interventions (10, 11); however, there is still no literature reporting persistent hypotension after paclitaxel-coated balloon angioplasty for peripheral artery disease.

Case presentation

A 63-year-old man with femoropopliteal artery occlusion was admitted to the hospital with intermittent right lower limb claudication for 13 years and exacerbation of ulcers for 5 months. Local ultrasound indicated that the middle of the superficial femoral artery was occluded; the popliteal artery and artery below the knee had severe stenosis. The patient had no history of hypertension, diabetes or cardiovascular disease. He had suffered an ischemic stroke 2 years ago and had experienced mild weakness in the left lower limb; the other risk factor identified was that the patient had smoked for 30 years (20–40 cigarettes/day). Physical examination revealed that the ulcers in the foot and ankle with exudation were categorized as Rutherford V, and the clinical classification of the patient was Fontaine 4. The patient was intolerant of ischemic pain and experienced difficulty lying supine (he was administered flurbiprofen and pethidine); thus, he refused computed tomography angiography. Drug gene sensitivity tests before the procedure suggested that the aspirin genes GPIIIaP1A2 (T > C), PTGS1 (−842A > G), and PEAR1 (G > A) were homozygous wild type, and the clopidogrel gene PON1 (G > A) was homozygous mutant CYP2C19 * 2 (G > A) and homozygous wild-type CYP2C19 * 3 (G > A), suggesting that the patient was sensitive to aspirin and had clopidogrel resistance. The statin gene 67SLCO1B1 * 5 (T > C) was homozygous wild type, suggesting that statins could be used normally. After the necessary preparations and drug therapy (aspirin 100 mg/day, cilostazol 200 mg/day, and statin 20 mg/day), the patient underwent angiography and angioplasty under general anesthesia. Heparin was used during the procedure at an initial dose of 100 U/kg, followed by additional doses as necessary.

Initial angiography showed that the long occlusion of the femoropopliteal artery (∼45 cm) and the outflow below the knee were acceptable (Figure 1A). With the support of a long sheath, a 4F catheter and a V-18 (Boston Scientific, Natick, Mass) wire were passed through the occlusion lesion into the distal true lumen. Then, predilation was performed with a plain balloon (Cordis Savvy Long 2, 3, and 4–220 mm and ev3 Evercross 5–200 mm), and angiography indicated revascularization of target vessels without obvious dissection (Figure 1B). Finally, the target vessels were dilated with a PCB (Acotec 5–200 and 5.5–300 mm, 8 atm, 90 s), and acute occlusion occurred after deflation (Figure 1C). Since this was the first case in western China, the reported experience of treating acute occlusion in coronary lesions was used as a basis for treatment. Prior to treatment, we vacuumed the blood from the sheath and found mixed paste-like components of drug debris, plaque and thrombosis (Figure 2), and then rapid injection of urokinase (300,000 units), papaverine (60 mg), and heparin saline (250 ml) through the arterial catheters was performed; this strategy was repeated after 15 min. Thereafter, angiography confirmed that the lesion was reopening, but a flow-limiting dissection was detected distal to the femoral artery; thus, a bailout stent (Cordis Smart Control, 6–100 mm) was placed (Figure 1D). Final angiography showed that the dissection had disappeared and that the blood flow had returned to normal (Figure 1E). The patient was transferred to the intensive care unit.

The patient's systolic blood pressure (SBP) fluctuated between 80 and 95 mmHg following the procedure (Figure 3A). Dopamine (DA, 40–75 ml/l) was administered to maintain the patient's blood pressure in the first week, and then the DA concentration was gradually reduced (Figure 3B). However, the patient suffered sudden orthostatic hypotension (DA, 30 ml/l) when arising from bed and was immediately given resuscitation therapy (DA, 70 ml/l). The patient recovered completely after 2 min, and his SBP gradually stabilized at 90 mmHg (Figure 3A). To avoid the side effects of DA, the concentration was reduced at post-procedure day 9, and noradrenaline (NE) was administered (starting concentration: 8 ml/h, Figure 3B). NE (8 ml/h) and posterior pituitary hormone (PT, 10 ml/h) were administered on day 12. When the patient's SBP stabilized, the concentrations of NE and PT were gradually reduced to 3 and 1.5 ml/h, respectively (day 20). Owing to the vasoconstrictive effect of PT, the skin at the infusion site darkened, and then the PT and NE were replaced with DA (concentration, 30 ml/h−100 ml/l); however, the patient's SBP was still difficult to control, and NE was reintroduced after 3 days (day 23). The patient's SBP gradually stabilized between 90 and 100 mmHg, and all vasoactive drugs were stopped on day 30. Interestingly, the heart rate and body temperature of the patient remained stable during the entire therapeutic process (Figures 3C,D).

Although the blood culture (blood samples and ulcer secretions) was negative, biochemical results confirmed the inflammatory status indicated by ulcer exudation. After the initiation of treatment, the levels of the indicators decreased and stabilized (Table 1). The patient developed transient elevation of myocardial enzyme levels, although the patient had no symptoms of cardiovascular disease, and the levels of the indicators improved after therapy. The platelet counts of the patients were normal during the whole process, the antibody of heparin-induced thrombocytopenia was negative (Table 1), and no deep vein thrombosis occurred under ultrasound examination.

Discussion

A previous report demonstrated that PCB angioplasty results in a lower rate of target lesion revascularization at 24 months compared with traditional balloon angioplasty (17 vs. 52%) (10). The case confirmed mid-term patency for up to 2 years, and restenosis then occurred beyond the distal primary stent.

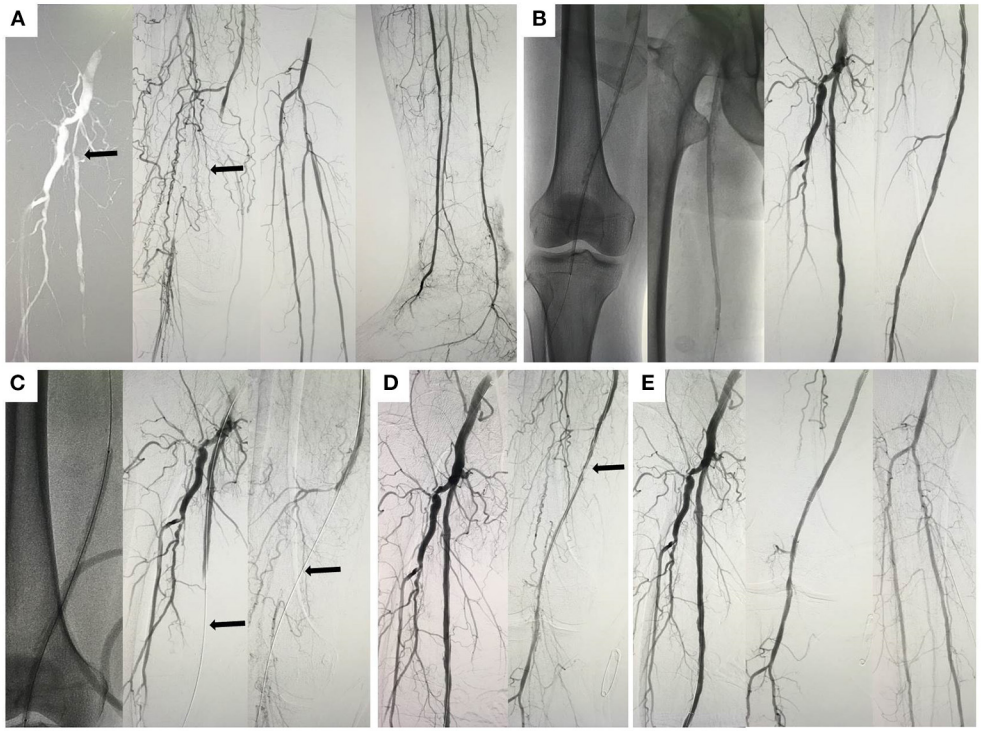

FIGURE 1
Angiographic images of the patient. **(A)** Initial angiography of the target lesion (black arrow); **(B)** predilation of the lesion and post-dilation images; **(C)** paclitaxel-coated balloon and the no-reflow phenomenon (black arrow); **(D)** angiographic images after intravascular therapy (black arrow); **(E)** final images and blood flow revascularization.

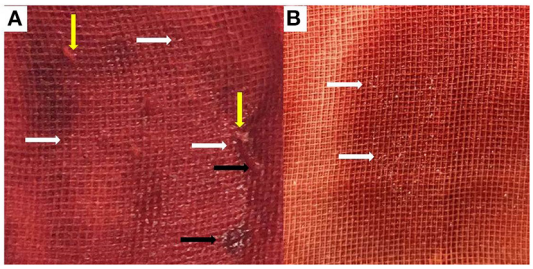

FIGURE 2
The mixed components of drug debris, thrombosis, and plaque. The mixed components include drug debris [**(A,B)**, white arrow], plaque debris [**(A)**, yellow arrow], and thrombosis debris (black arrow).

The most important prerequisite for PCB angioplasty is the preparation of the target vessels. No flow-limiting dissection or elastic retraction was detected post-dilation, and PCB angioplasty was performed. These points were closely related to the outcome of PCB.

This patient suffered from acute occlusion after PCB angioplasty following adequate vessel preparation, and this was the first case in Western China; we treated the patient according to the cardiologists' experience and reconstructed the blood flow. Thereafter, we reviewed the images from the procedure and related literature pertaining to coronary artery disease. The potential reasons for acute occlusion in this patient are as follows: (I) thrombosis: Pathological studies in coronary artery disease have reported that the fibrous cap can rupture, leading to the formation of a thrombus and acute occlusion (11). In this case, the plaque lesion might have ruptured following PCB angioplasty, thus explaining why thrombolytic therapy was effective. Furthermore, inadequate anticoagulation or antiplatelet therapy may lead to acute thrombosis occlusion during the procedure. Therefore, we recommend that sufficient heparinization and appropriate antiplatelet drugs be used according to the results of the drug genetic tests. (II) Plaque debris embolization: The microembolization of debris is an important factor in the pathogenesis of acute occlusion (12, 13). Due to the different features of lesions, especially in mixed plaques, distal embolism may be caused during dilation, leading to acute occlusion and secondary thrombosis, which may occur in the distal vessel bed. (III) Dissection: A previous report indicated that severe dissection was found in 42% of cases after dilation, and flow-limiting dissection could cause acute occlusion and

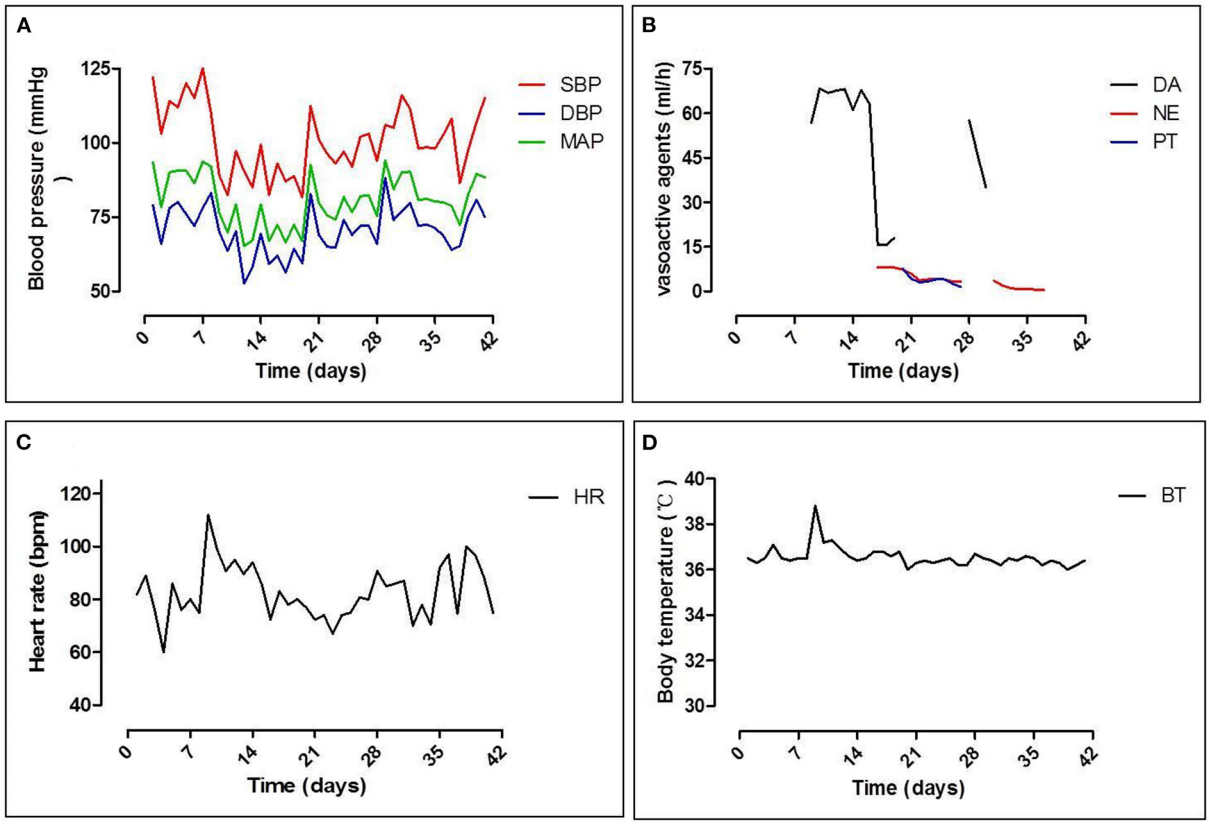

FIGURE 3
Dynamic changes in vital signs. **(A)** Changes in systolic pressure (SBP), diastolic pressure (DBP), and mean arterial pressure (MAP); **(B)** vasoactive agents used during hypotension: dopamine (DA), norepinephrine (NE), and posterior pituitary hormone (PT); **(C)** changes in heart rate; and **(D)** body temperature.

affect the outcome of PCB (14). In this patient, dissection was confirmed and treated with a self-expandable stent after endovascular therapy. (IV) Microvascular ischemia and edema and arterial endothelium were stimulated by paclitaxel or the allergic reaction to paclitaxel/excipient, which may have resulted in prolonged ischemia, endothelium edema and impaired microcirculation. (V) Crushed ice effect: The balloon was coated with paclitaxel and low levels (∼1%) of an excipient (magnesium stearate) during the manufacturing process (15). In this case, the level of magnesium stearate was 2%. A higher level would result in improper lubrication and decrease the rate of dissolution of the drug (16). Paclitaxel acts on the vessel wall during inflation, which may produce debris, and debris is dissolved in a process similar to how crushed ice gradually melts in warm water. The mixed components might produce a paste-like consistency, and acute occlusion may occur (Figure 2).

The patient presented with persistent hypotension for 30 days following PCB angioplasty and persistent orthostatic hypotension. The systolic pressure of the patient recovered to 90–100 mmHg after 30 days of intravenous therapy, and the patient was then discharged from the hospital. The patient's blood pressure did not return to the pre-procedure average level within 1 year. Obviously, the patient developed drug-induced autonomic nervous system dysfunction. This rare complication has not yet been reported in patients undergoing PCB angioplasty; it has been reported in only one patient who underwent chemotherapy with paclitaxel and cisplatin (9). Compared with the large dose of paclitaxel (200 ± 250 mg/m^2) used in chemotherapy patients, the amount of paclitaxel used in PCB angioplasty is very small (3.3 ug/mm^2) (15); however, the lower dose of paclitaxel could still potentially affect the sympathetic control of blood pressure (17, 18). This severe complication may be a potential danger posed by the application of PCB angioplasty for peripheral artery disease and partially explain the increase in all-cause mortality caused by PCB angioplasty (8). However, the mechanism of this rare complication still requires further investigation, especially the effect or allergic reaction of paclitaxel/excipients on the arterial endothelium system.

Our limited experience with one patient cannot be extrapolated to all patients undergoing PCB angioplasty. However, pre-procedure drug genetic testing, aggressive

TABLE 1 Clinical laboratory results.

Items	Reference range	Day 0	Day 1	Day 7	Day 15	Day 22
White-Cell count (10^9/l)	3.5–9.5	14.78	17.13	10.15	10.36	9.72
Red-Cell count (10^{12}/l)	4.3–5.8	4.01	3.44	3.25	3.45	3.43
Absolute neutrophil count (10^9/l)	1.8–6.30	12.53	15.04	8.58	10.36	6.77
Absolute lymphocyte count (10^9/l)	1.1–3.2	1.4	1.01	0.94	1.55	1.81
Platelet count (10^9/l)	125–350	460	350	363	445	320
Hemoglobin (g/l)	130–175	124	104	101	103	101
Sodium (mmol/l)	137–147	134	145	138	144	144
Potassium (mmol/l)	3.5–5.3	4.05	3.69	2.98	3.43	3.08
Chloride (mmol/l)	96–108	89.8	105.1	98.4	106.9	102.6
Calcium (mmol/l)	2.11–2.52	2.02	1.83	1.81	2	1.94
Carbon dioxide (mmol/l)	22–29	17	21.6	22.2	15	20
Anion gap (mmol/l)	–	34.2	24.7	23	28.5	27.3
Glucose (mmol/l)	3.9–6.1	3.41	4.51	6.97	4.81	4.17
Blood urea nitrogen (mmol/l)	3.6–9.5	5.69	2.21	3.64	3.85	3.31
Creatinine (umol/l)	57–111	54	45	46	66	44
Total protein (g/l)	65–85	68.2	47.1	54.4	63.9	59.3
Albumin (g/l)	40–55	36	25.3	27.1	34.7	33.6
Total bilirubin (umol/l)	3.4–17.1	6.8	8.1	7.2	4.2	5.9
Procalcitonin (<0.5 ng/ml)	<0.5	0.093				
Alanine aminotransferase (U/l)	9–50	115	88	105	62	71
Aspartate aminotransferase (U/l)	15–40	51	55	70	33	31
Alkaline phosphatase (U/l)	45–125	286	215	280	206	162
Fibrinogen (g/l)	2–4	6.83	5.4	7.52	8.12	4.43
Lactate dehydrogenase (U/l)	120–250	–	256	229	–	–
Prothrombin time (s)	11–14	12.4	16.8	13.8	13.7	12.4
International normalized ratio	0.94–1.30	0.95	1.38	1.08	1.07	0.94
Creatine kinase (U/l)	50–310	–	454	68	–	–
C-Reactive protein (mg/l)	0–10	168	–	100	70	–
Antibody of heparin-induced thrombocytopenia	(–)	NA	(–)	(–)	(–)	NA

intravenous hydration and vasoactive agent therapy are essential for recovery from acute occlusion and hypotension in patients treated with PCB angioplasty.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Xi'an Jiaotong University Review Board. The patients/participants provided their written informed consent to participate in this study and for the publication of this case report.

Author contributions

LY, JL, and CL: data analysis, interpretation, data collection, writing, and literature search. LY and CL: data analysis, interpretation, study design, and data collection. LY: data collection, data analysis, writing, reviewing, and study design. All authors have read and approved the final manuscript.

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Conflict of interest

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

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Degos disease with multiple intestinal perforations: A missed-opportunity case report and literature review

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Introduction: Degos disease, also known as malignant atrophic papulosis (MAP), is a rare systemic obstructive vascular disease with unknown pathophysiology, which can affect multiple systems, especially gastrointestinal tract and central nervous system. Intestinal perforations with MAP is associated with high mortality rate and ambiguous treatment outcomes.

Case presentation: Here we report a missed-opportunity case of Degos disease characterized by generalized skin eruption and multiple intestinal perforations. Definite diagnosis of Degos disease was finally concluded after two exploratory laparotomy operations and skin biopsies. Due to the delayed diagnosis and treatment, the patient died after being discharged automatically in spite of application of aspirin and low-dose subcutaneous heparin. In view of such circumstances, we searched the Pubmed using "Degos [Title] OR Malignant Atrophic Papulosis [Title]" AND "perforation [Title] OR perforations [Title]" and make a detailed analysis of the result.

Conclusions: Degos disease is a rare systemic obstructive vascular disease with unknown pathologic mechanism and unavailable treatment methods. Diagnosis is usually based on the presence of pathognomonic skin lesions and tissue biopsy. Gastrointestinal involvement can cause serious and lethal conditions with high mortality. Currently, how to achieve a satisfying prognosis of MAP with intestinal perforations becomes the most urgent problem in front of medical staff.

KEYWORDS

Degos disease, malignant atrophic papulosis, intestinal perforations, skin eruption, case report

Introduction

Degos disease, also known as malignant atrophic papulosis (MAP), is a rare systemic obstructive vascular disease with unknown pathophysiology, which can affect multiple systems, mainly involving gastrointestinal tract and central nervous system, leading to high mortality (1). Here we report a missed-opportunity case of Degos disease characterized by generalized skin eruption and multiple intestinal perforations and make a literature review of other analogous cases.

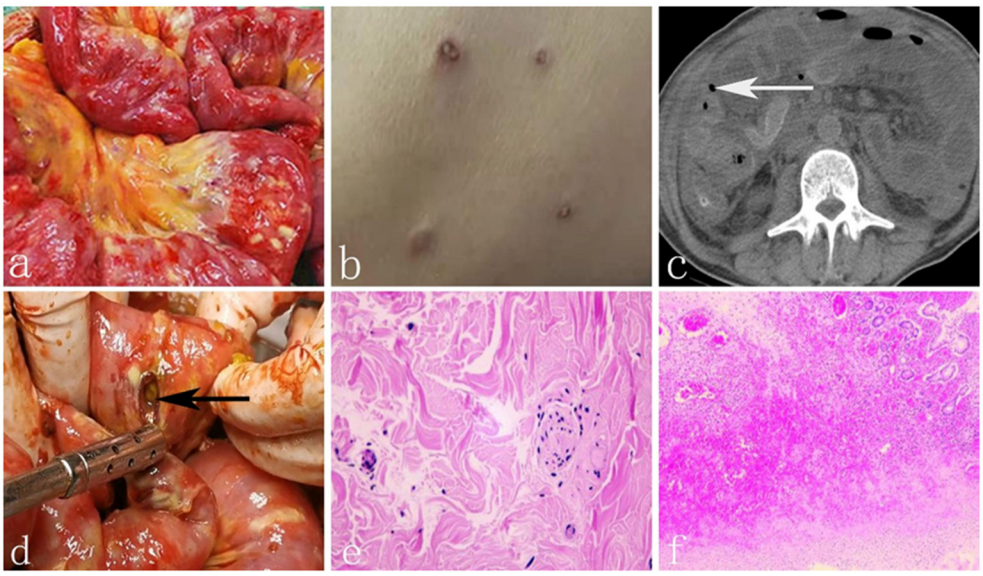

FIGURE 1
(a) Numerous yellow-white tubercles were interspersed on the surface of small intestine. **(b)** Generalized skin emption with porcelain - white centers surrounded by erythematous borders. **(c)** The white arrow shows free air around the intestine. **(d)** The black arrow shows one of the perforations of the small intestine. **(e)** The biopsy of skin eruption showed atrophy of epidermis, hyperplasia and collagen of dermal fibrous tissue. **(f)** Histopathologic result of the resected intestine showed acute and chronic inflammatory cell infiltration.

Case presentation

A 48-year-old man was admitted to our hospital's emergency department with a 2-month history of recurrent abdominal pain and a 2-week history of aggravation. He underwent an exploratory laparotomy for acute diffuse peritonitis 50 days ago at the local hospital. Intraoperative findings revealed that numerous 0.2–0.4 cm yellow-white tubercles were interspersed on the surface of congestive small intestine, colon, appendix, greater omentum and mesenterium, especially the distal ileum (Figure 1a), without apparent perforation. Rapid pathology of appendix and omentum showed acute nonspecific inflammation and intestinal tuberculosis was suspected initially. Therefore large amount of saline and metronidazole was used for irrigation and abdominal drainage was placed. The patient discharged from hospital with intermittent slight abdominal pain on the 15th day after operation.

Twenty days later, the patient developed severe abdominal pain suddenly with nausea and vomiting accompanied by fever (39°C). He was admitted to the local hospital again and transferred to our intensive care unit (ICU) for deterioration of his condition. Physical examination showed evident abdominal tenderness and rebound tenderness with weakened bowel sounds. Meanwhile, generalized skin eruptions with an atrophic porcelain-white center surrounded by erythematous rim were visible over trunk and extremities, measuring 0.2–1.2 cm (Figure 1b). No chronic diseases, no alcohol use, no family history, no herbal agents, or no suspected drug use were reported. Relevant laboratory tests and radiographic results were as follows: WBC $8.65*10^9$ ($3.5–9.5*10^9$), NEUT% 0.938↑ (0.40–0.75), procalcitonin 171.45 (0–0.05 ng/ml), HBV-DNA 9.15E+08↑ (<5.0E+02 IU/ml). Tuberculin test, Widder test, anti SS-A, and SS-B antibodies were negative. ANA was 1:100 weakly positive and Anti Ro-52 antibodies was positive too. Computed tomography showed a small amount of free air bubble, edema and thickening of the small bowel wall and massive seroperitoneum (Figure 1c). An exploratory laparotomy was performed on account of primary diagnosis of Crohn's disease with intestinal perforations. In the operation, we found more than 100 whitish-yellow plaques, dozens of intestinal perforations and purulent materials (Figure 1d). We resected 2 meters of the perforated small bowel and sutured the seromuscular layer in the wafery areas followed by enterostomy and abdominal drainage tube placement. The diagnosis of Crohn's disease was doubtful for the eccentric appearance of the intestine conditions, but there was still no definite diagnosis.

On the 5th day after operation, intestinal contents drained again, which signified recurrence of perforation. At this point, we eventually started to pay attention to the correlation between the perforation and skin lesions. Biopsy of skin eruption was conducted and the pathology showed atrophy of epidermis,

Abbreviations: MAP, malignant atrophic papulosis; BAP, benign atrophic papulosis; ICU, intensive care unit; WBC, white blood cell; NEUT, neutrophil; HBV-DNA, hepatitis B virus-DNA; ANA, antinuclear antibodies.

TABLE 1 Previous case reports of MAP and intestinal perforations.

Author/year	Age/sex	Number of intestinal perforations	Surgery (yes or no)	Operation frequency	Operation method	Postoperative treatment	Prognosis	Survival period or follow-up period
M Kanai/1988 (10)	47M	3	Yes	1	Enterectomy	Not mentioned	Alive	10 months
FMG Valverde/2003 (11)	56M	1/multilple necrotic lesions	Yes	2	Perforation repair	Not mentioned	Death	Several days
Shahshahani MM/2008 (12)	47F	1	Yes	1	Enterectomy	Antiplatelet/anticoagulant/ pentoxifylline	Death	A few months
M Beuran/2009 (13)	29F	2/not mentioned/not mentioned/not mentioned	Yes	4	Not mentioned	Not mentioned	Death	3 months
XY Zheng/2010 (14)	37M	diffuse plaque lesions/2	Yes	2	Omentectomy/ Jejunostomy	Methylprednisolone/ immunoglobulin/ anticoagulation	Death	3 months
Ahmadi/2011 (15)	15F	2/1/2	Yes	3	Enterectomy/Ileostomy/ Right hemicolectomy	Aspirin/Dipyridamol	Death	3 months
Yeung/2013 (16)	50M	Multiple perforations/Multiple perforations/Multiple perforations	Yes	3	Enterectomy	Palliative care	Death	Not mentioned
Zhu/2014 (17)	46F	1	Yes	1	Enterectomy	Heparin heparin/Cefodizime/dipyridamole	Alive	7 years and 10 months
Hu/2018 (18)	30M	Not mentioned	No	No	No	Bayaspirin/Dalteparin sodium/alprostadil/methylprednisolone	Death	Not mentioned
Day/2019 (19)	7M	Not mentioned	Yes	multiple surgeries	Not mentioned	Cyclophosphamide/rituximab	Alive	23 months
Present case	48M	>10	Yes	1	Entetectomy and jejunostomy	Aspirin/heparin	Death	16 days

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hyperplasia and collagen of dermal fibrous tissue, degeneration of elastic fibers, significantly reduction and partial necrosis of skin appendages, fibrinoid necrosis in small vessels of the deep dermis and thrombosis in local lumen (Figure 1e). Histopathology of the resected intestine showed edema and hyperaemia, thrombus organization of both tiny artery and veins lumen with acute and chronic inflammatory cell infiltration (Figure 1f). Finally, definite diagnosis of Degos disease was concluded. The patient was given aspirin (100 mg/day) and low-dose subcutaneous heparin (5,000 U/dy), but his body condition went from bad to worse because of the severe abdominal inafection. He requested automatic discharge and died 3 days later.

TABLE 2 Demographic and clinical data of four previous studies.

	Burg/ 1989 (20)	Assier/ 1995 (21)	Theodoridis/ 2014 (5)	Hu/ 2018 (18)
Study cohort size	106	15	39	80
Male/female (ratio)	63:43	6:9	16:23	37:43
Age at diagnosis	35	34	36.5	37.9
BAP/MAP (ratio)	39:67	6:9	11:27	28:52
Total mortality	51/106 (48.1)	Not mentioned	8/38 (21%)	34/80 (42.5%)
BAP mortality	1/39 (3%)	Not mentioned	0/27 (0%)	0/28 (0%)
MAP mortality	50/67(75%)	Not mentioned	8/11(73%)	34/52 (65.3%)
Survival time with systemic presentation	<5 years	Not mentioned	0.9 year	Not mentioned

Discussion and conclusions

Malignant atrophic papulosis (MAP) was first described by Köhlmeier in 1941 (2) and defined by Degos in 1942 (3), which usually occurs in the 20–50 age group with a slight male dominance (4). Previous appellation way of MAP was chaotic until Theodoridis et al. (5) renamed and divided it into two categories in 2014: benign atrophic papulosis (BAP) and malignant atrophic papulosis (MAP). The former is more common and characterized by cutaneous form, with atrophic porcelain-white center in size of 0.2–1 cm, distributed over the trunk and extremities, rarely on the face and scalp. The papules are red in early stage and expand gradually with atrophy in the center and leave white scars after deflorescence. The latter is characterized by involvement of internal organs, especially gastrointestinal tract (50%) and central nerves system (20%) (1). Median survival time of MAP is 2–3 years and five-year survival rate is less than 50% (6). However, these two forms can't be easily distinguished because involvement of inner organs may occur with skin lesions simultaneously or not (7).

Intestinal perforations with MAP is an uncommon phenomenon with a rate of 2.1% reported (8). We searched the Pubmed using "Degos [Title] OR Malignant Atrophic Papulosis [Title]" AND "perforation[Title] OR perforations[Title]" and found 11 cases. Nevertheless, the detailed data of 1 case reported by G H Evans (9) couldn't be enquired, so only the 10 cases were exhibited in Table 1 (10–19). As shown in the literature, the median age was 41.5 (range 7–56) with a male 60% proportion and only three of them were alive at follow-up. Table 2 showed four case study series ever published (5, 18, 20, 21). The age at diagnosis ranges from 34 to 37.9 years old and MAP accounts for 65% of the total cases (155:239). Two studies (5, 18) reported 0% mortality and another (20)reported 3% mortality for BAP while the mortality for MAP is 65.3–75%. Given MAP's high mortality rate, Theodoridis et al. (5) put forward a follow-up plan: whole-skin examination and skin biopsy for histological examination for BAP and colonoscopy/gastroscopy/laparoscopy if organ symptomatology suspected, the follow-up frequency was twice yearly for 0–7 years and once yearly for 7–10 years.

Etiology of Degos disease remains unknown up to now. Viral infection, autoimmune disease, coagulopathy, collagen vascular disorders and genetic defects may be some of the underlying causes (12). In this case, the level of patient's HBV-DNA may be an explanation of MAP since it is 9.15E+08↑ IU/ml, significantly higher than normal. Autosomal dominant trait of MAP is hypothesized in view of reports of clusters of patients among members of the same family and first-degree relatives (22). Diagnosis of MAP depends mainly on presence of pathognomonic skin lesions and tissue biopsy pathology containing wedge necrosis of superficial and deep dermis, with arteriolar wall inflammatory cell infiltration, epidermal atrophy and dermal collagen rigidification. Dermoscopy reveals dendritic vessels, loop and irregular vessels, with central unstructured area but it lacks specificity (23).

At present, there is still no clear guideline for the treatment of MAP. Immuno-suppressor, such as azathioprine and cyclophosphamide are proved to be invalid (24). Antiplatelet drugs (aspirin or clopidogrel) or anticoagulants (warfarin or heparin) may be helpful (25). In 2011 Magro CM reported the pathologic findings of extensive deposits of C5b−9 within the cutaneous vasculature, and proposed that inhibition of C5 might be a therapeutic approach (26), and in 2013 he discovered the use of eculizumab as salvage therapy in critically ill patients with thrombotic micro angiopathy (27). Shapiro LS thought that treprostinil may offer a second effective treatment approach to individuals with MAP or rescue therapy to those in whom eculizumab treatment has failed (28). Unfortunately, large sample

data results are still lacking, especially for gastrointestinal tract perforations.

In conclusion, Degos disease is a rare systemic obstructive vascular disease with unknown pathologic mechanism and unavailable treatment methods. Diagnosis is usually based on the presence of the pathognomonic skin lesions and tissue biopsy. Gastrointestinal involvement can cause serious and lethal conditions with high mortality (29).The patient's diagnosis was delayed because we ignored the relation between skin changes and peritonitis. Although current pharmacological treatments have limited value for MAP with intestinal perforations, early diagnosis and treatment play an important role in improving prognosis and survival rate.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the participant/s for the publication of this case report. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

WA wrote the manuscript. ZL and FL searched literatures. HY revised and approved the final manuscript. All authors have read and approved the manuscript.

Conflict of interest

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

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Compression syndromes of the popliteal artery due to intramuscular ganglion cyst of the biceps femoris: A case report and literature review

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Intramuscular ganglion cyst (IMGC) is a very rare lesion with an unidentified pathogeny that originates within the muscle. We encountered a case of 49-year-old man who complained of intermittent claudication in the right lower limb for 2 months. An intramuscular ganglion cyst in the biceps femoris muscle was diagnosed and located by Computed tomography angiography (CTA) and magnetic resonance imaging (MRI), which compressed the popliteal artery and resulted in ischemia in the right lower limb. Six months after surgical resection, there was no recurrence of the cyst and the popliteal artery was patency. We describe this case with a review of the relevant literature.

KEYWORDS

ganglion cyst of knee joint, intramuscular (IM), biceps femoris long head, popliteal artery (PA), entrapment syndrome

Introduction

A ganglion cyst is a common tumor-like lesion arising from various soft tissues that is generated by mucoid degeneration of the joint capsule, tendon, or tendon sheath (1). It usually occurs near the joints and ligaments of the extremities, especially the dorsal wrists and ankles, and occurs in young women between 20 and 40 years old (2, 3). However, an intramuscular ganglion cyst which originates within the muscle belly itself and generates symptoms of arterial compression concomitantly is a rare lesion (4, 5). As previously reported, diagnosis, localization, and complete resection of intramuscular tendon sheath cysts are challenging, and surgical exploration and pathological diagnosis are also necessary (6). Computed tomography angiography (CTA) and magnetic resonance imaging (MRI) can distinguish ganglion cysts from other soft tissue tumors and tumor-like lesions and provide particular information to determine the location of lesions. As far as we know, this is the first case report of an intramuscular ganglion cyst arising from the biceps femoris.

Case presentation

A 49-year-old male was admitted to hospital with intermittent claudication of the right lower limb for 2 months, with a limping distance of 100 m and no resting pain (Rutherford III), which is an indication for surgery (7). His past medical history includes coronary artery disease and hyperlipidemia.

Physical examination revealed that the popliteal, dorsalis pedis, and posterior tibial arteries were not observed. His skin color, skin temperature, and lower limb appearance were basically normal, and the capillary filling time of the bilateral toes was < 2 s.

Ultrasound showed reduced flow velocity in the right lower limb artery, superficial femoral artery (34 cm/s), popliteal artery (24 cm/s), anterior tibial artery (20 cm/s), posterior tibial artery (17 cm/s), and peroneal artery (24 cm/s), with absent triphasic waves (**Figure 1**). CTA suggests severe stenosis and almost complete occlusion of the P1 segment of the popliteal artery (**Figures 2A–C**). MRI suggested that the popliteal artery was compressed by an oval cyst with high signal intensity on T2-weighted, which is 1.7*2.5*3.1 cm in volume (**Figures 2D–G**). A diagnosis of popliteal artery entrapment syndrome is proposed.

Exploration of the right popliteal artery and cystectomy were performed under epidural anesthesia. The popliteal artery was connected to a tendon sheath cyst on the medial aspect of the long distal head of the biceps femoris tendon with a smooth, tough wall, and jelly-like contents (**Figure 3A**). After cyst removal, blood flow of popliteal artery and triphasic waves were restored (**Figures 3B,C**). Postoperative pathology suggests a ganglion cyst (**Figure 4**).

At the 6-month postoperative follow-up, the patient had no intermittent claudication, good arterial pulsation in the lower limbs and no significant ultrasound abnormalities.

Discussion

Ganglion cyst (GC) is a common and frequent clinical condition, but cases of tendon cysts compressing the surrounding blood vessels are rarely reported. Ganglion cysts that occur within the muscle belly and are associated with popliteal artery compression are extremely rare. Limited data available make them prone to misdiagnosis and underdiagnosis, and preoperative imaging to determine their origin and nature can be difficult. Moreover, previous studies were unable to generate valuable research to develop a uniform and effective treatment due to the small number of cases included (6, 8–14).

Entrapment neuropathy is a frequent clinical symptom because of its anatomical location. Also, the popliteal vascular components are subject to compression, including the vein, which is next most medially located and easily compressible compared with the artery, which is most lateral and least frequently involved (15). The popliteal artery is deeper and stiffer than the vein and requires greater force to produce compression, so the incidence of this syndrome is minimal. Only in rare cases, when the popliteal artery is compressed by the cyst in a pulsatile manner, the patient may develop lower limb claudication due to intermittent ischemia of the lower limb (16–20). Venous compression is not mentioned in reported cases of arterial occlusion, but the vein may also be compressed and ignored because the symptoms of arterial compression are of more clinical importance. After the removal of cysts, the pressure on any of the blood vessels is relieved.

The primary differential diagnosis is cystic adventitial disease (CAD), which typically occurs in otherwise healthy,

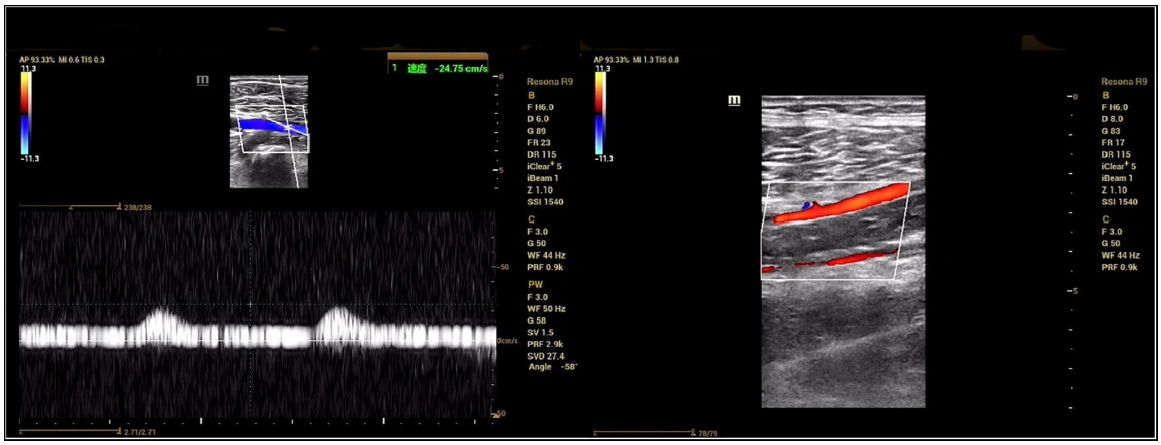

FIGURE 1
Preoperative ultrasonography. The spectral pattern was changed and triphasic waves were absent.

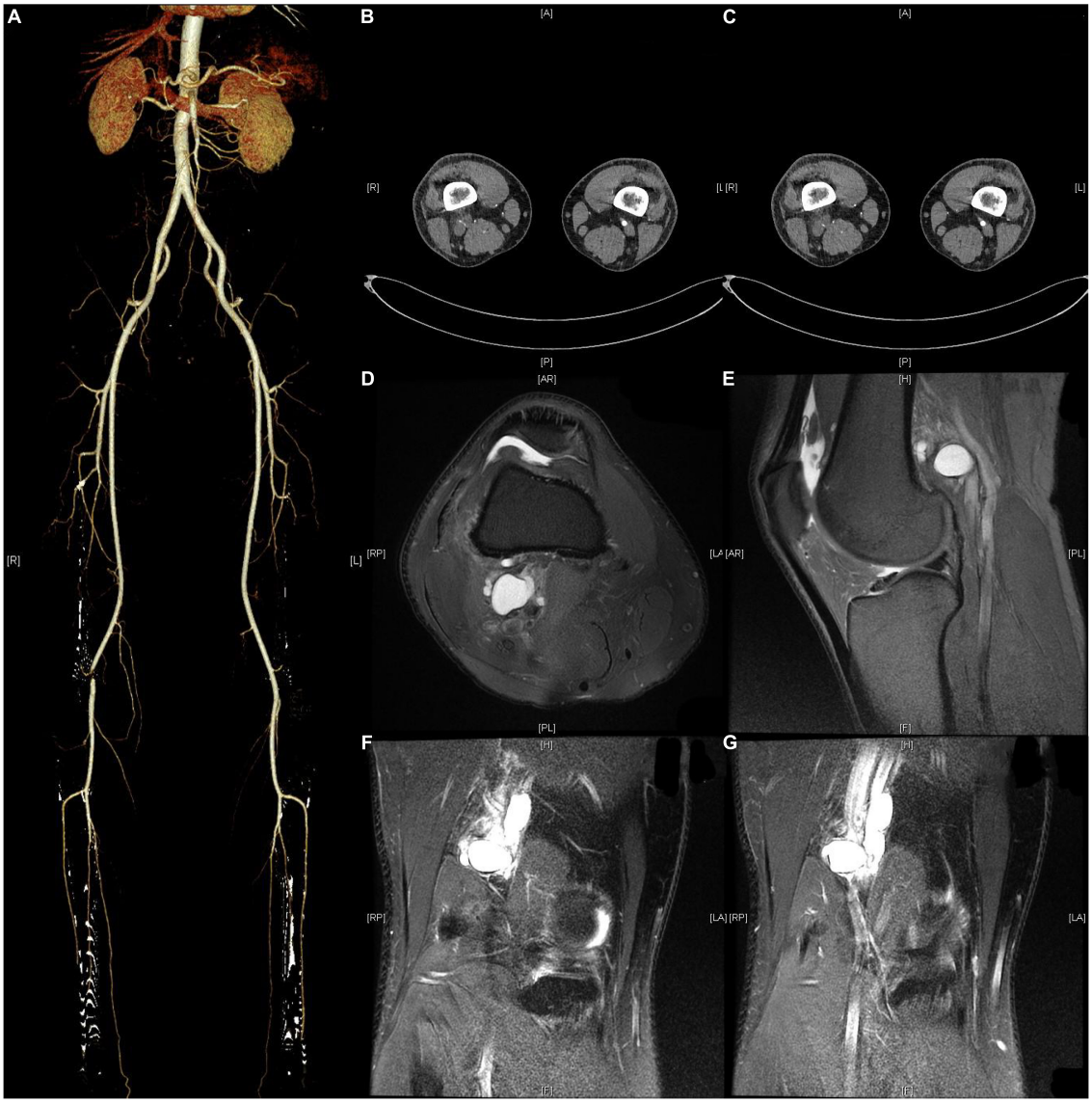

FIGURE 2
Preoperative CTA and MRI. **(A–C)** CTA showed severe stenosis of the popliteal artery in the right lower extremity. **(D–G)** MRI suggested that the popliteal artery was compressed by an oval cyst with high signal intensity on T2-weighted, which is 1.7*2.5*3.1 cm in volume.

middle aged male patients, causing symptoms of sudden-onset progressive intermittent claudication. Although four theories have been proposed, the etiology of CAD is still not fully understood (21, 22). During vascular embryonic development, undifferentiated mesenchymal cells are incorporated into the arterial wall. It is these mucin-secreting mesenchymal cells that subsequently produce mucoid material, from which epitaxial cysts arise. This hypothesis is considered to be the most reasonable explanation for CAD. Also, the etiology of intrasynovial ganglion cysts is unknown. Repeated damage to the tendon sheath with subsequent cystic changes may be the cause of intrathecal ganglion cysts, as tenosynovitis or associated tendon tears are often seen around ganglion cysts (9). During the operation, it was clear that the cyst originated from the muscle belly rather than the popliteal artery, supporting the final diagnosis.

There is controversy regarding the final diagnosis of the disease. Popliteal artery depression syndrome (PAES) is defined as a group of symptoms in which there is a congenital anatomical abnormality between the popliteal artery and its surrounding muscles or bundles of tendons and fibrous tissues (23). Classification of PAES, currently used and widely accepted, was proposed by Love and Whelan (24) and revised by Rich et al. (25). In terms of this system, type I is associated with an

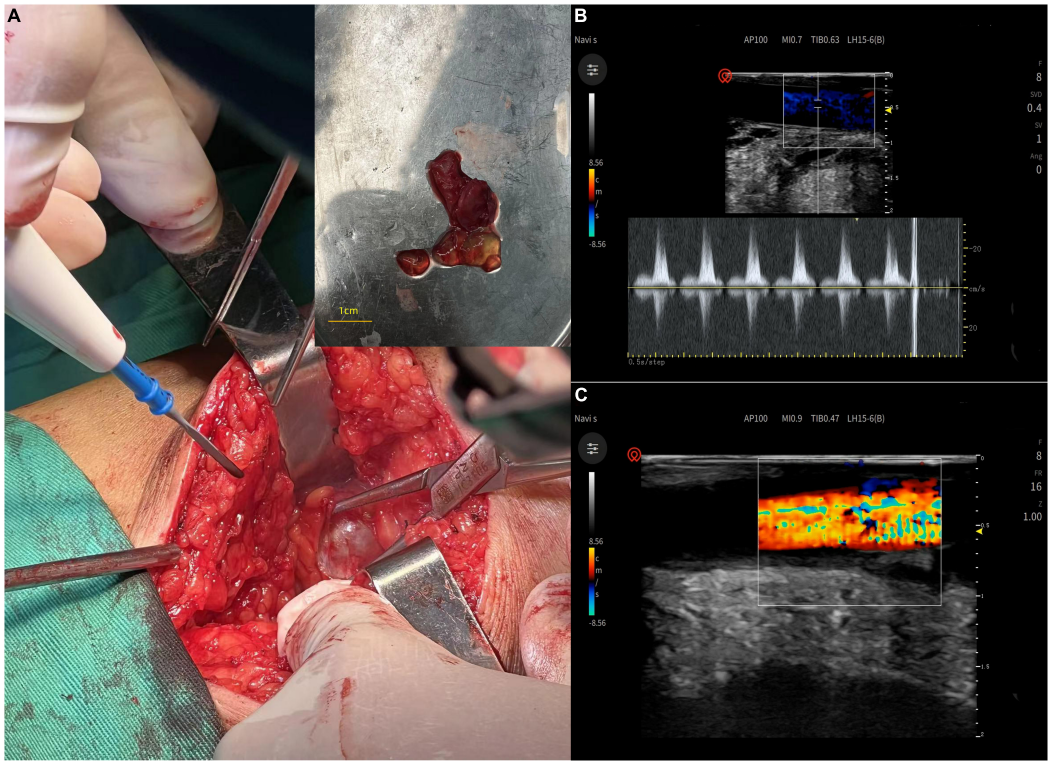

FIGURE 3
(A) The popliteal artery was connected to a tendon sheath cyst on the medial aspect of the long distal head of the biceps femoris tendon with a smooth, tough wall, and jelly-like contents. **(B,C)** After cyst removal, blood flow of popliteal artery and triphasic waves were restored.

aberrant medial arterial course around the normal medial head of the gastrocnemius muscle. In type II, an abnormal medial head of the gastrocnemius inserts laterally on the distal femur and displaces the popliteal artery medially. Type III is depicted by an aberrant accessory slip from the medial head of the gastrocnemius muscle that wraps around the popliteal artery. In type IV, the popliteal artery is entrapped by the popliteus muscle. In type V, the popliteal vein is also involved. Type VI is considered functional and is recognized in the presence of a normally positioned popliteal artery that is entrapped by a normally positioned but hypertrophied gastrocnemius muscle. Characteristics of this patient do not conform to any types of PAES.

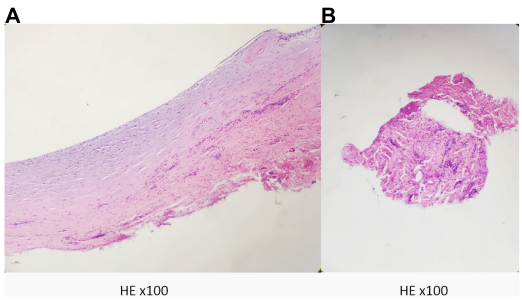

FIGURE 4
Postoperative pathology suggests a fibrous cyst wall. **(A)** The wall of the cyst. **(B)** The contents of the cyst.

Popliteal cysts are also known as Baker cysts, a general term for synovial fluid cysts in the popliteal fossa that occur in the medial head of the semimembranosus bursa (gastrocnemio-semimembranosus bursa, GSB). Secondary popliteal cysts are most often seen in adults and the cysts tend to be connected to the knee joint cavity. Sansone et al. performed a retrospective analysis of 1,001 cases of MRI for various reasons and found popliteal cysts in 4.7–37% of these cases, all of which communicated with the joint cavity. The patient in this case originated within the biceps femoris muscle belly and was not a synovial bursa of the medial head of the semimembranosus and gastrocnemius muscles and did not communicate with the joint cavity and was not strictly a popliteal cyst (26).

Several treatment options are available if the diagnosis of PAES has been made, with the treatment objective being to release the popliteal artery from compression and preserve popliteal arterial flow (27). Conventional surgery, endovascular surgery, thrombolysis, or a combination of these modalities are all reasonable treatment options depending on the patient's

clinical symptomology and anatomy (28). If the artery is occluded, stenotic, or aneurysmal, vascular reconstruction is mandatory in addition to the division of any entrapping structure (29). In this patient, after intraoperative resection of the cyst, the popliteal artery blood flow was confirmed by ultrasound, and no further vascular repair or autograft of the great saphenous vein was performed.

Conclusion

Here we describe a patient with an IMGC of the biceps femoris muscle compressing the popliteal artery, which could not be diagnosed preoperatively and highlighted the necessity and difficulty of differential diagnosis. Intraoperative exploration and postoperative histopathology are key to the diagnosis of IMGC. In our case, intraoperative ultrasound did not reveal any abnormality in the popliteal artery and there were no clinical symptoms at the 6-month follow-up, and the follow-up ultrasound was normal. In cases where the popliteal artery has been compressed for a short period of time and where there is no thrombosis, intimal thickening, or aneurysm formation, intraoperative ultrasound can be used to determine the flow velocity and flow in the popliteal artery, and if the flow is normal, decompression of the popliteal artery alone can be performed without wall repair or saphenous vein grafting.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the participant/s for the publication of this case report. 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

KZ, WY, WZ, and CL contributed to conception and design of the study. KZ wrote the first draft of the manuscript and drew the illustrative figures. WY, HR, SW, and MS had the acquisition, analysis or interpretation of clinical data for the work. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

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

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Case report: Multiple arterial stenoses induced by autosomal-recessive hypophosphatemic rickets type 2 associated with mutation of ENPP1: a case study

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Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)-related multiple arterial stenoses is a rare clinical syndrome in which global arterial calcification begins in infancy, with a high probability of early mortality, and hypophosphatemic rickets develops later in childhood. The vascular status of an ENPP1-mutated patient when they enter the rickets phase has not been thoroughly explored. In this study, we presented a case of an adolescent with an ENPP1 mutation who complained of uncontrolled hypertension. Systematic radiography showed renal, carotid, cranial, and aortic stenoses as well as random calcification foci on arterial walls. The patient was incorrectly diagnosed with Takayasu's arteritis, and cortisol therapy had little effect on reducing the vascular stenosis. As a result, phosphate replacement, calcitriol substitution, and antihypertensive medication were prescribed, and the patient was discharged for further examination. This research presented the vascular alterations of an ENPP1-mutanted patient, and while there is less calcification, intimal thickening may be the primary cause of arterial stenosis.

KEYWORDS

arterial stenosis, ENPP1, autosomal-recessive hypophosphatemic rickets-2, hypertension, childhood

1. Introduction

ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1) is a key regulator of skeletal and soft tissue mineralization (1). It is a prominent producer of extracellular inorganic pyrophosphate (PPi) and an inhibitor of fibroblast growth factor 23 (FGF23) (2); hence, biallelic loss-of-function mutations in ENPP1 are associated with two primary clinical stages: generalized arterial calcification of infancy (GACI) and autosomal-recessive hypophosphatemic rickets type 2 (ARHR2) (3). GACI caused by ENPP1 mutations may go unrecognized due to clinically insignificant vascular calcification and stenoses. ARHR2 could develop if GACI patients survived. ENPP1 also has a role in a variety of diseases such as diabetes, cancer, cardiovascular disease, and osteoarthritis (1).

ENPP1 variants were reported in 154 patients with 72.5% being demonstrably disease-causing (4), and ENPP1 deficiency prevalence was estimated approximately 1 in 64,000 pregnancies (5). It is hypothesized that both GACI and ARHR2 pathogenic theories could result in cardiovascular involvement, with distinct dominant manifestations at different ages. GACI is defined by calcification of large- and medium-sized arteries, which is coupled with intimal proliferation, and results in arterial stenosis and reduced blood flow (3, 6, 7). It has a high infant mortality rate, and affected patients may develop neonatal heart failure, arterial hypertension, and die within the first 6 months of life (8). While most children who survive to adolescence develop hypophosphatemic rickets later in childhood, and spontaneous clearance of arterial calcifications can be observed in such patients (9, 10), elevated iFGF23 levels and ARHR2 hypophosphatemia have been related to enhance survival (9). To date, it is unclear what determines whether a patient develops clinical signs of GACI or ARHR2, or both (3). Here, we present a rare instance of multiple arterial stenoses and calcification caused by an ENPP1 genetic mutation and conduct a literature review.

2. Case presentation

An 11-year-old Chinese boy with rickets was hospitalized to PUMCH with uncontrolled hypertension for 1 year. The boy's parents discovered his lower extremity bone abnormalities manifesting as "X-shaped legs" in 2014 (3 years old). He was also diagnosed with right renal dysplasia. Laboratory tests revealed low serum phosphorus levels and elevated ALP levels. He was, therefore, diagnosed with hypophosphatemic rickets and began treatment with oral phosphate solution and calcitriol as well as orthopedic orthosis to repair the skeletal defects. However, the treatment was ineffective. The patient, in 2021 (10 years old), requested to turn up the volume while watching TV, and a hearing test revealed bilateral hearing loss (left side worse). In July 2021 (10 years old), he had spinal kyphosis, a dragging and swinging stride, and underwent epiphyseal fixation for both knees. Prior to surgery, the brachial blood pressure was 100–110/70–80 mmHg; however, it increased to 190–200/100–110 mmHg shortly after the procedure. Palpitations, dizziness, and other discomfort symptoms were denied. Treatment with sodium nitroprusside, esmolol, and captopril could keep blood pressure at 130–140/90–100 mmHg. He was subsequently referred to have a computed tomography angiography (CTA) of renal artery, which revealed a slim right renal artery (diameter of around 1 mm) and right renal atrophy (right kidney size: 4.4 × 1.5 cm and left kidney size: 10.2 × 4.4 cm, as assessed by renal ultrasound). The left renal artery has severe stenosis in the beginning and proximal sections as well. Renal function imaging revealed that the total glomerular filtration rate (GFR) of both kidneys was 79.0 ml/min, with GFRs of 76.3 ml/min and 2.7 ml/min for the left and right kidneys, respectively. Following that, the patient was evaluated for systemic angiography, which revealed various degrees of stenosis in the right internal carotid artery (C4–7 and cervical segment) and the lower segment of the abdominal aorta (**Table 1**). In July 2021, the patient underwent whole exome sequencing using the next-generation sequencing method to confirm the diagnosis. The results revealed an ENPP1 mutation (c.313 + 1G > A, c.783C > G), but no mutation was detected in the ABCC6 locus. The patient was subsequently diagnosed with ARHR2. It was unclear, however, whether the multiple arterial stenoses were related to ARHR2. The patient was subsequently examined for inflammation markers at a local clinic, which revealed a minor increase ([C-reactive protein (CRP) 8.6 mg/L and erythrocyte sedimentation rate (ESR) 26 mm/h] and was suspected of having Takayasu's arteritis. As a result, he began treatment with prednisone 75 mg q.d. and azathioprine 25 mg q.d. to slow the progression of inflammation. His antihypertensive regimen included amlodipine besylate 5 mg q.d., benazepril 5 mg b.i.d., and hydrochlorothiazide 20 mg b.i.d. Aspirin 100 mg q.d. was added for antiplatelet treatment to prevent possible thrombosis. Calcitriol 0.25 μg q.d., + calcium carbonate 0.5 g b.i.d. + vitamin D3 200 U b.i.d. were used as anti-rickets therapy. The blood pressure fluctuated between 120 and 140/70–80 mmHg while on such medication.

In December 2021, the prednisone dosage was gradually reduced to 5 mg q.d. and thereafter maintained at that level. Multiple CRP and ESR testing were normal. However, the blood pressure remained elevated at 130–140/70–80 mmHg. The patient next underwent angiography, which revealed a constricted ostial left renal artery. As a result, angioplasty was performed, and his blood pressure was decreased to 120–130/70 mmHg shortly after the procedure. While it increased to 140–150/60–70 mmHg on day 5 postoperatively. The patient was required to resume antihypertensive therapy in which the blood pressure ranged between 140 and 150/80–90 mmHg.

The patient was transferred to PUMCH in June 2022, and retested inflammatory markers were normal [ESR 6 mm/h and high sensitivity C reactive protein (hsCRP) 0.07 mg/L; complement and immunoglobulin tests, antiphospholipid antibody (APLs), antineutrophil cytoplasmic antibodies (ANCAs), and anti-nuclear antibody (ANAs) were negative]. He was measured at a height of 139 cm, which is −1 standard deviation from the average height for his age group. His weight was 38 kg, which is at 0 standard deviation from the average weight for his age group. His upper circumference was 71 cm and lower circumference was 68 cm. During examination, a systolic murmur was heard in the left renal artery but no murmur was detected in the right renal artery. There was no indication of pectus carinatum or wrist sign. His knees were

TABLE 1 Clinical presentations and multisystem involved in the patient.

Systems	Manifestations	Symptoms
Vascular system	Multiple vascular stenosis	Hypertension
Urinary system	Right renal atrophy	Hypertension
Bone metabolism	Hypophosphatemia	Rickets
Skeletal system	Scoliosis	Motor dysfunction
	Double genu valgum	
Auditory system	Deformity of ossicular chain	Bilateral hearing loss

valgus, and his teeth were aligned without any abnormalities in enamel development. He did not show any signs of bone tenderness throughout his body. The costo-iliac distance was measured at 4 finger widths. He was in Tanner Stage I for pubic hair development and did not exhibit any edema in both lower extremities. Right brachial artery blood pressure (156/80 mmHg) was substantially higher than other sites (left brachial artery: 133/66 mmHg, left ankle artery: 138/71 mmHg, right ankle artery: 138/64 mmHg). Laboratory tests regarding calcium and phosphorus revealed hypophosphatemia and lower but normal level of serum calcium, increased levels of alkaline phosphates, type I collagen carboxy terminal peptide β special sequence (β-CTX), hyperphosphaturia, and normal parathyroid hormone (PTH) and 25-hydroxyvitamin D (T-25OHD) (**Table 3**).

He was reexamined in July 2022 for an aorta and head CTA, which revealed calcification of the aortic arch, right subclavian artery, and right internal carotid artery (**Figure 1**). The descending and abdominal aortas were both thin, with numerous vascular thickening and stenosis. Severe stenosis was found in the distal segment of the right common carotid artery, the bilateral internal carotid artery (C1 segment), the proximal and middle segments of the bilateral vertebral arteries, the bilateral middle cerebral arteries (M2 segment), (**Figure 2**) the beginning of the left renal artery, celiac trunk, superior and inferior mesenteric arteries, and the entire course of the right renal artery. As a result, the Riolan arterial arch opened (**Figure 3**) (**Table 2**). Renal blood flow showed that the left kidney was 87.6 ml/min·1.73 m^2 and that the right kidney did not function. Diaphragmatic ultrasound revealed that the inner diameter of the first segment of the celiac trunk did not vary significantly during the respiration process (inhale: 0.29 cm, exhale: 0.27 cm). Temporal bone CT revealed bilateral jugular bulbs reaching the cochlea, indicating ossicular chain abnormality.

The theory that arterial mineralization and calcification and proliferative alterations of arterial wall were caused by hydroxyphosphate deposition, pyrophosphate, and phosphate imbalance induced by ARHR2 could explain the arterial calcification and stenosis of various vessels. We also noticed that the inflammatory markers were not considerably elevated throughout the patient's medical history, and prednisone treatment was ineffective. Following the discussion with the multidisciplinary team (MDT), it was presumed that ARHR2 might be able to formulate an explanation for the full scope of the condition. The patient then reduced the cortisol dose until it was no longer needed. The patient was discharged and closely monitored after the antihypertension and phosphorous supplement strategy was adjusted.

3. Discussion

ENPP1-related disease is rarely documented globally, and it has a particular manifestation modality in which GACI develops in infants with a high rate of early mortality due to uncontrolled heart failure and arterial events, followed by hypophosphatemic rickets caused by ARHR2 (3). However, the disease's cardiovascular profile varies greatly. The underlying mechanism could be attributed to a transition from calcification to intimal

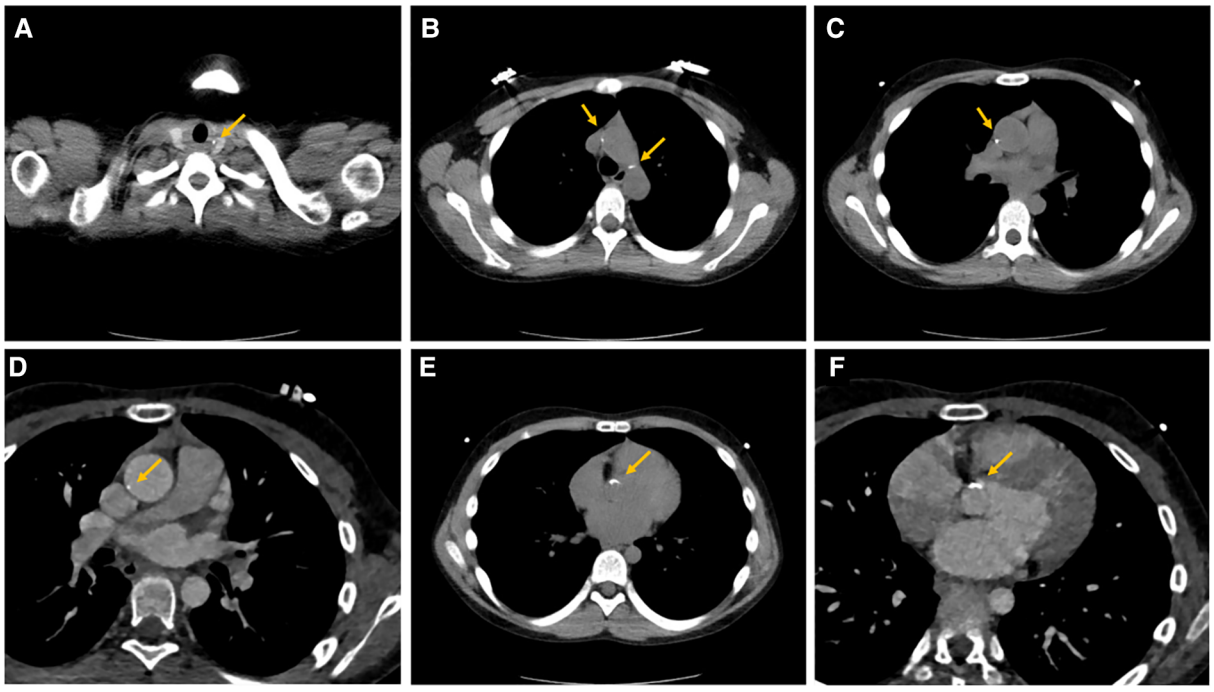

FIGURE 1
Calcifications of multiple vascular walls. Calcification foci of the aortic arch (A,B) and ascending aorta (C–F) disseminated in the arterial walls.

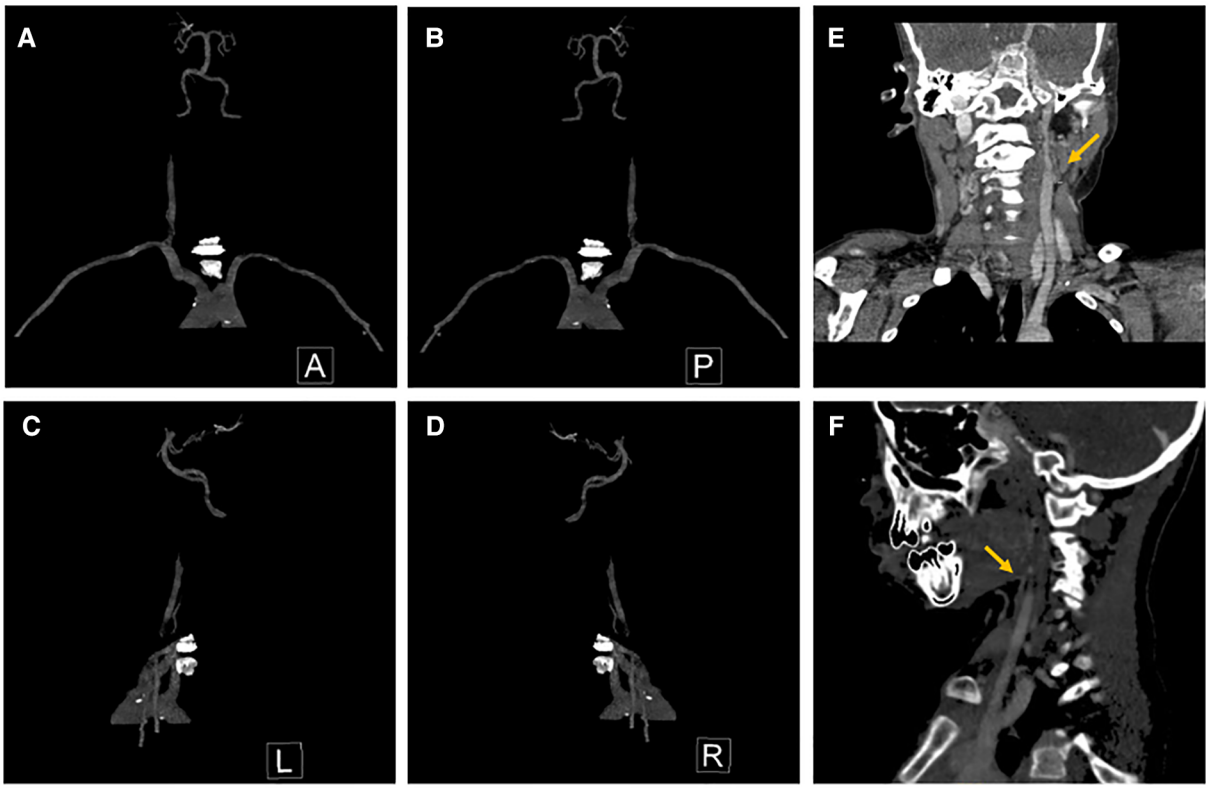

FIGURE 2
Stenosis of cranial and carotid arteries. (**A**) Anterior view, (**B**) posterior view, (**C**) lateral view (left side), (**D**) lateral view (right side), (**E**) stenosis of left ICA, and (**F**) stenosis of right ICA. ICA, internal carotid arteries.

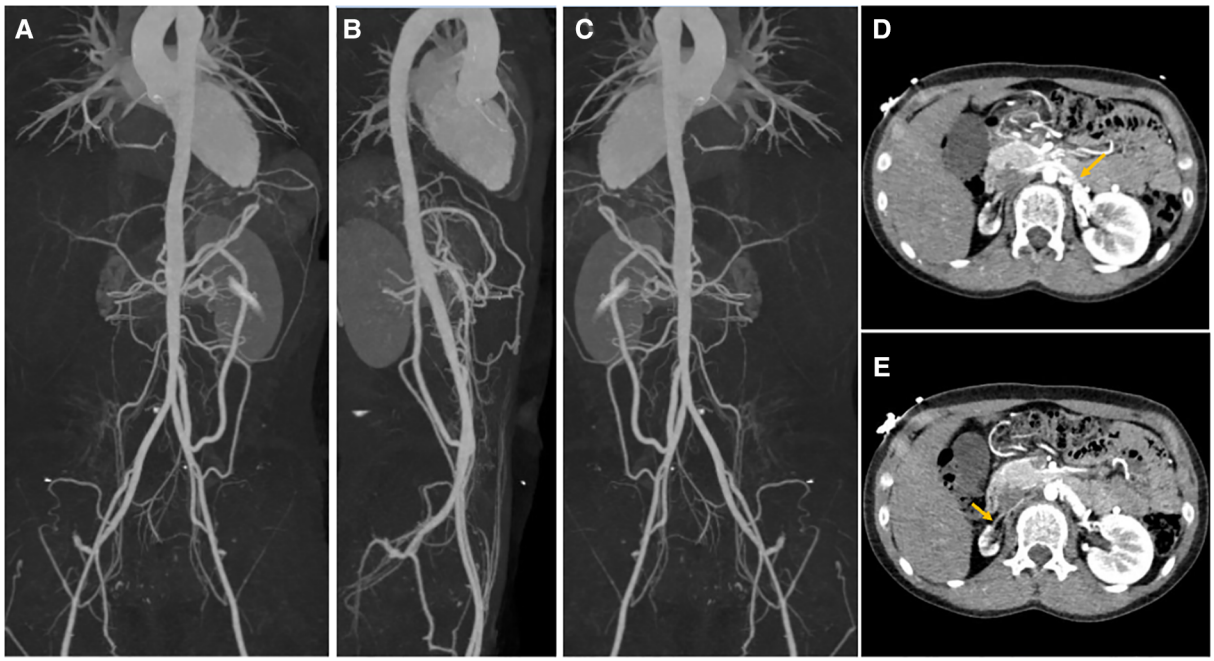

FIGURE 3
Stenosis of major and renal arteries in systematic CTA. The whole course of aorta was slender with multiple vascular thickening and stenoses. The diameter of the ascending aorta and was thoracic aorta about 21 and 12 mm, respectively. The wall of the aortic trunk and segments were thickened with calcification. Slim right renal artery was present with a diameter of about 1 mm and thickened renal arterial intima. (**A**) Anterior view, (**B**) lateral view, (**C**) posterior view of systematic CTA, (**D**) stenotic lesions of the left renal artery ostia, and (**E**) stenotic lesions of the right renal artery ostia. CTA, computed tomography angiography.

TABLE 2 Stenotic arteries and calcification conditions in the patient.

Arteries	Location	Stenosis	Collateral circulation	Calcification
Left renal artery	Beginning and proximal part	Moderate-severe		Yes
Right renal artery	Whole parts	Severe (diameter = 1 mm)		
Left internal carotid artery	C1 segment	Moderate		
Right internal carotid artery	C1 segment	Occlusion	Yes	Yes
	C4–C7 segment	Mild-moderate		
Right common carotid artery	Distal part	Occlusion	Yes	
Right subclavian artery				Yes
Bilateral vertebral arteries	Medium part	Occlusion	Yes	
Bilateral middle cerebral arteries	M2 segment and distal part	Slim		
Aorta arch				Yes
Aorta. Descending	Whole parts	Slim		
Aorta. Abdominal	Whole parts	Slim	Riolan arch	
Celiac trunk	Beginning part	Severe		
Superior mesenteric artery	Beginning part	Severe		
Inferior mesenteric artery	Beginning part	Moderate		

TABLE 3 Laboratory tests regarding calcium and phosphorus.

Item	Value	Normal range	Unit
PTH	54.1	15.0–65.0	pg/ml
ALP	429	42–390	U/L
P	0.93	0.81–1.45	mmol/L
Ca	2.46	2.13–2.70	mmol/L
T-25OHD	35.6	>30	ng/ml
β-CTX	3.08	0.26–0.51	ng/ml
24hUP	29.07	—	mmol/L/24 h
24hUCa	1.01	—	mmol/L/24 h

thickening or intimal thickening may be the primary cause of multiple arterial stenoses instead of calcification, and the specific regulation of this process is still unclear. In this case, only sporadic minor calcification foci were found. After reviewing the patient's medical records and discussion with the multidisciplinary team, we believe that at least in the adolescent period, intimal thickening, rather than calcification, was the primary cause of multiple arterial stenoses in this case.

There are few case studies and survival analyses that examine the cardiovascular changes and phosphatemic metabolisms (7–12); however, the intimal thickening changes were less noted when the patient entered the ARHR2 stage of the disease's natural history. Dlamini et al. reported three siblings with different heterozygous ENPP1 mutations from their parents (7). At 14 months, one boy had hypertension, and an arch aortogram revealed severe stenosis of the celiac axis, superior mesenteric artery, renal arteries, and both internal (ICA) and external carotid arteries, while brain CT revealed just a small region of cerebral arterial calcification. The other two siblings died perinatally due to severe cardiac and aortic calcification. This case would show that calcification is not universal and fibrointimal proliferation with subsequent vascular stenosis may occur in locations lacking calcification. Thomas et al. documented a case with prolonged survival until 11 years old and the patient also displayed discordance between the amount of vascular calcification and various arterial luminal occlusions. No phosphorus treatment was undertaken, and no genetic testing was performed (9). Ciana et al. also described two ENPP1-mutanted siblings who had numerous arterial stenoses and spontaneous clearance of arterial calcifications as they aged (10). Ferreira et al. reported an ENPP1-related newborn GACI with coronary artery blockage and calcification of the descending aorta, renal, splenic, superior mesenteric, brachial, and coronary arteries (12). Phosphate was repleted for more than 7 years and there was no progression of vascular calcification in this case (12); a retrospective observational study of 55 patients with GACI found that bisphosphonates demonstrated a trend toward benefit of improving survival (8). These cases may suggest that ENPP1-related vascular stenosis is associated with intimal thickening rather than calcification, but perinatal vascular calcification is fatal. In the children who survive to adolescence will develop hypophosphatemic rickets later and spontaneous clearance of arterial calcifications can be observed in some patients.

ENPP1 is an enzyme that converts adenosine triphosphate (ATP) to adenosine monophosphate (AMP) and PPi (13). It also suppresses FGF23 production, which is responsible for decreasing phosphate reabsorption by downregulating the expression of sodium-phosphate cotransporter in the renal proximal tubule and decreasing 1-hydroxylase activity and 1,25-dihydroxyvitamin D synthesis (14). Individuals with ENPP1 deficiency have lower amounts of PPi in their blood, which predisposes calcium and phosphorous precipitation to form calcium phosphate, notably in the vascular internal elastic lamina, cartilage, and other soft tissues (1). According to Nitschke et al., neointimal proliferation is caused by a decrease in ATP clearance and adenosine synthesis caused by ENPP1 deficiency (15), while increased FGF23 levels may be an organism's response to reduce ectopic calcification (3, 8).

In clinical practice, patients diagnosed with GACI demonstrate markedly reduced levels of systemic PPi in both their urine and plasma, with values frequently approaching zero, in contrast to the reference range documented in published studies (16). Thereafter, Bernhard et al. introduced the ATP sulfurylase method as a diagnostic tool to measure PPi levels in plasma as a potential biomarker for pediatric patients. The study examined plasma samples from 200 children between 1 day and 18 years old, who had undergone blood testing for unrelated medical

conditions. The researchers established a standard range of PPi in the blood plasma of children and adolescents, aged 0–18 years, ranging from 2.36 to 4.44 μM, with a median of 3.17 μM, which did not differ by age or sex in the pediatric cohort (17).

Initially, the treatment for this condition was contentious. Since the 1960s, phosphate and calcitriol substitution have been used in conventional hypophosphatemic rickets (HR) therapy (18). Bisphosphonates, which are synthetic PPi counterparts, are used to treat bone disorders caused by excessive bone resorption and phosphate loss (19). Besides phosphate supplement to the organism, treatment with calcitriol in most forms of FGF23-dependent HR is important to balance the suppression of 1α-hydroxylase by FGF23, which usually results in low serum levels of 1,25-OH-D3. Clinicians have been wary of phosphate substitution because of the protective effect of FGF23 and the avoidance of additional calcification, and the traditional view sees it as a protective effect with increased survival through low phosphate levels in ENPP1 deficiency. However, phosphate treatment has been tested in animal experiments and for certain patients, with longer survival rates. In the Enpp1asj mouse model of GACI and ARHR2, the administration of bisphosphonates reduced mineralization of the epidermis and the aorta and restored the bone microarchitecture (20) Ferreira et al. reported a case of a patient with GACI who was treated for more than 7 years with phosphate (and calcitriol) to compensate for phosphate wasting with no deterioration of vascular calcification (12). Recent ARHR2 studies show that phosphate and even calcitriol substitution do not induce calcification in patients with ENPP1 impairment (11, 12). These studies revealed that phosphate treatment may be beneficial for the treatment of ENPP1 decidecncy with prolonged survival without impairing vascular calcification control.

ENPP1 enzyme replacement therapy which used recombinant Enpp1-Fc protein has been developing as a novel treatment for ENPP1-related HR and vascular lesion. ENPP1 coupled to the Fc fragment of human IgG1 has been shown in animal tests to reduce mortality and vascular calcification (21), as well as improve blood pressure and cardiac function (22). Ferreira et al. discovered that recombinant Enpp1-Fc protein replacement was beneficial for correcting low bone mass in ARHR2 mice without raising the risk of nephrocalcinosis, albeit its vascular effect has not been well investigated (23). In human research, there is currently an ongoing phase 1/2, open-label, multiple ascending dose study testing enzyme replacement therapy in adults with ENPP1 deficiency (NCT04686175) to investigate and evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics.

Surgical intervention has been rarely documented in GACI patients. The most common reason for surgery was a rapidly progressing cardiovascular event, and just a few cases were documented. Samyn et al. reported a 2-year-old child with live-born GACI-related congenital heart disease who underwent operative right ventricular outflow tract (RVOT) reconstruction and restored excellent biventricular systolic function (24). Giovannoni et al. described a case of a 4-year-old Italian kid who underwent a heart transplant at the age of 18 months due to end-stage heart failure caused by severe myocardial infarction of the left ventricle and diffuse coronary calcifications (25). To date, no surgical or interventional procedure in renal artery stenosis associated in GACI- or ENPP1-related disorders has been reported. For patients with renal artery stenosis, we have three therapeutic options: medical therapy, percutaneous therapy [including percutaneous angioplasty (PTA) and stenting], and surgical therapy (including aortorenal bypass surgery, splanchnorenal bypass surgery, and endarterectomy) (26). A clinician can select between open surgery and PTA when the treatment goal is to open a stenotic lesion (27). Percutaneous revascularization is recommended for patients of any age who have resistant or malignant HTN (26, 27). Surgical treatment may be suggested in some patients having aortic revascularization if renal revascularization cannot be performed by percutaneous procedures or has failed (27). Back to our case, the patient displayed slender right renal artery (diameter was around 1 mm) with right renal atrophy and had a history of PTA, while it did not exert the antihypertensive impact for a long time. As a result, we did not do another PTA on the patient and instead advised medical treatment.

GACI had a 54.7% overall mortality rate, with a 50.4% likelihood of death before the age of 6 months, and mortality was greater for ENPP1 variations vs. ABCC6 variants (40.5% vs. 10.5%, respectively; $p = 0.0157$) (28). In ENPP1-deficient individuals, the main morbidity in adults was related to enthesis calcification (11). Previous research in children with GACI discovered an association between hypophosphatemia and hyperphosphaturia and increased survival (8). Ferreira et al. performed a prospective long-term follow-up of 20 GACI patients (16 with homozygous ENPP1 mutation) and discovered higher iFGF23 levels in the majority of surviving GACI patients, sometimes even in the absence of clinical indications of rickets (11). These research studies demonstrated that hypophosphatemia may be a protective factor for ENPP1-deficient patients. Despite the fact that studies have demonstrated that phosphate substitution is not required to promote vascular calcification, certain patients have been reported to have a long-term survival (12, 20).

In conclusion, we present a rare case of multiple arterial stenoses in which renal artery stenosis was the primary clinical manifestation, with rickets phenotype of ARHR2 caused by genetic alterations in the ENPP1 gene and a long survival. Arteritis was effectively ruled out, and medical therapy was adjusted accordingly. We first reviewed the artery stenosis involved and verified that the stenosis of these arteries is not necessarily caused by calcification but more connected with intimal thickening. Comprehensive evaluation is required to avoid the misdiagnosis of Takayasu's arteritis, especially when CRP and ESR disclosed modest elevation. Although it might be tried, percutaneous revascularization for renal artery stenosis was unable to lower the blood pressure in our case. Open surgery should be considered if necessary while there is no case recorded up to date. Conventional therapy including phosphate and calcitriol substitution should be taken in the ENPP1-related vascular disease and the use of ENPP1 enzyme replacement therapy (recombinant Enpp1-Fc protein) remains to be trialed in children 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 human participants were reviewed and approved by the Ethics Committee of Peking Union Medical College Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JL: writing—original draft (lead), review and editing, and formal analysis (lead). XS: writing—original draft (supporting) and validation. DZ: radiology and methodology (supporting). YJ, MM, and ZQ: supervision and methodology (supporting). WX: conceptualization (supporting) and resources. YC: conceptualization (lead), review, and resources. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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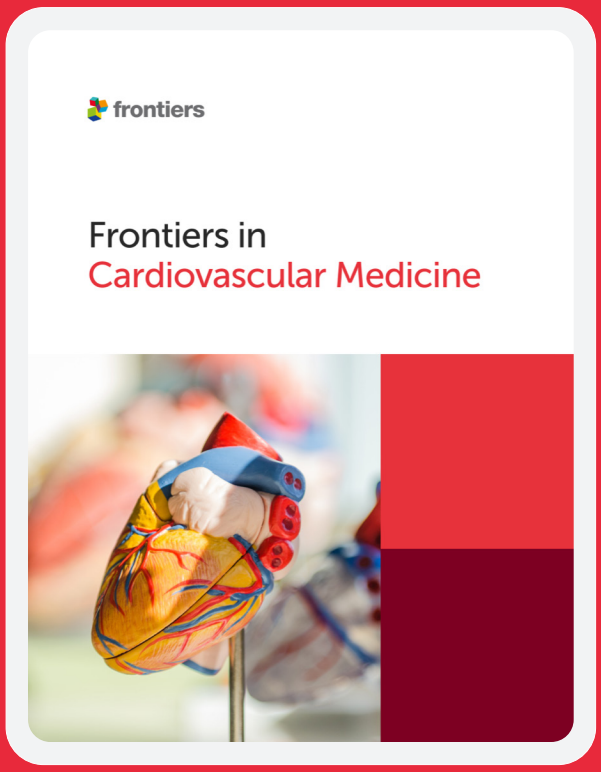

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