frontiers | Research Topics

Case reports in cardiovascular therapeutics 2022

Edited by
Jun Yu and Baohui Xu

Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-8325-3747-3
DOI 10.3389/978-2-8325-3747-3

About Frontiers

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

Frontiers journal series

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

Dedication to quality

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

What are Frontiers Research Topics?

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

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

Case reports in cardiovascular therapeutics: 2022

Topic editors

Jun Yu — Temple University, United States

Baohui Xu — Stanford University, United States

Citation

Yu, J., Xu, B., eds. (2023). *Case reports in cardiovascular therapeutics: 2022*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3747-3

Table of contents

frontiers | Frontiers in Cardiovascular Medicine

CASE REPORT
published: 12 May 2022
doi: 10.3389/fcvm.2022.895627

Hydrogen Gas Inhalation Regressed Coronary Artery Aneurysm in Kawasaki Disease-Case Report and Article Review

Ho-Chang Kuo [1,2,3,4,5]*

[1] Kawasaki Disease Center, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [2] Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [3] College of Medicine, Chang Gung University, Taoyuan, Taiwan, [4] Department of Respiratory Therapy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [5] Taiwan Association for the Promotion of Molecular Hydrogen, Kaohsiung, Taiwan

Kawasaki disease (KD) is a systemic vasculitis that primarily affects children under the age of 5 years old and is among the most common acquired heart disease in developed countries, particularly in Asia. No effective treatment is currently available for aneurysm formation in KD. In this report, we showed a KD patient with an aneurysm over the right coronary artery with a size of 6.08 mm in diameter and 35 mm in length, which completely regressed to within normal range after hydrogen inhalation within 4 months after disease onset. This 10-year-old KD patient was diagnosed on the 12th day of disease onset with incomplete presentation of KD symptoms. Intravenous immunoglobulin was prescribed after KD diagnosis was confirmed by the formation of a coronary artery aneurysm. Once discharged from the hospital, the family used hydrogen inhalation (77% hydrogen and 23% oxygen) at home with nasal cannula 1 h per day. The aneurysm was found to be completely regressed at the 4-month follow-up (day 138 of the illness). The follow-up laboratory data showed complete blood cell count, differential count, electrolytes, liver enzyme, and renal function to all be within normal range. This is the first study to report an aneurysm from KD with regression under supplementary therapy with hydrogen gas inhalation and no other complications. Therefore, hydrogen gas inhalation may be an alternative anti-free radical or anti-oxidant therapy for KD, but further study is still required.

Keywords: Kawasaki disease, hydrogen gas, inhalation, aneurysm, regression

OPEN ACCESS

Edited by:
Baohui Xu,
Stanford University, United States

Reviewed by:
Makoto Samura,
Yamaguchi University, Japan
Gang Li,
Shandong Provincial Hospital, China
Jingjing Wei,
Shanxi Medical University, China

***Correspondence:**
Ho-Chang Kuo
erickuo48@yahoo.com.tw;
dr.hckuo@gmail.com

Specialty section:
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

Received: *14 March 2022*
Accepted: *22 April 2022*
Published: *12 May 2022*

Citation:
Kuo H-C (2022) Hydrogen Gas Inhalation Regressed Coronary Artery Aneurysm in Kawasaki Disease-Case Report and Article Review. Front. Cardiovasc. Med. 9:895627. doi: 10.3389/fcvm.2022.895627

INTRODUCTION

Kawasaki disease (KD) is the most common acquired heart disease among children in many countries, especially Asian ones. This acute febrile systemic vasculitis was first reported by Dr. Tomisaku Kawasaki in 1967 in Japanese and 1974 in English (1). Initially referred to as mucocutaneous lymph node syndrome (MCLS), it was later renamed Kawasaki Disease (KD) or Kawasaki syndrome after Dr. Kawasaki (1925–2020) in memory of his contribution. KD mainly affects young children under the age of 5 years old, especially those of Asian descent in Japan, Korea, China, and Taiwan. Currently, the etiology of KD remains unknown (2–4), but both genetic background and environmental impacts have been shown to be important for disease susceptibility.

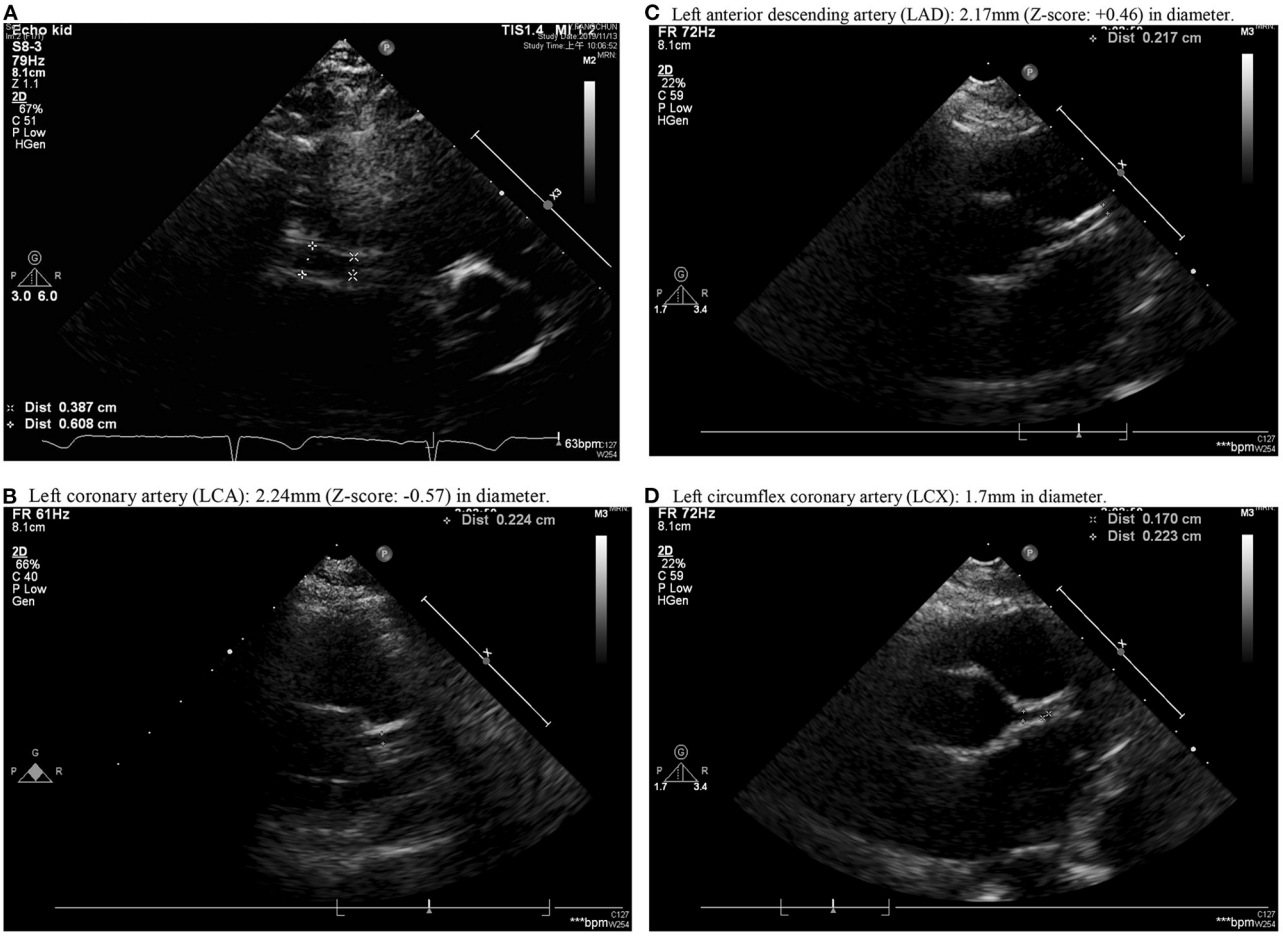


FIGURE 1 | Aneurysm formation over middle right coronary artery (RCA) with a diameter of 2.9 mm near the ostia, gradual dilation to maximum diameter of 6.08 mm near the middle 1/3 of RCA with length of 3.5 cm and distal RCA diameter of 3.11 mm (posterior AV groove) **(A)**. **(B–D)** showed Left coronary artery (LCA), Left anterior descending artery (LAD) and Left circumflex coronary artery (LCX). **(B)** Left coronary artery (LCA): 2.24 mm (Z-score: −0.57) in diameter. **(C)** Left anterior descending artery (LAD): 2.17 mm (Z-score: +0.46) in diameter. **(D)** Left circumflex coronary artery (LCX): 1.7 mm in diameter.

Aneurysm formation is considered the most severe complication of KD survivors since IVIG treatment was introduced in 1983. According to the American Heart Association (AHA) statement for 2017, a large or giant aneurysm (> 8 mm in diameter) does not "resolve," "regress," or "remodel." Friedman et al. (5) reported a total of 2,860 KD patients and found that 17% had aneurysm; the probability of regression of a moderate size aneurysm was 0.3 at 4 months after disease onset and 0.5 at 24 months. Kato et al. (6) reported outcomes in 598 KD patients and found that aneurysms were diagnosed in 25%, with 49% reducing to a normal luminal dimension 6 to 18 months later.

According to the standard treatment for KD suggested by AHA, no effective anti-inflammatory treatment for aneurysm formation is available after the acute stage. When a KD patient with aneurysm formation after acute stage treatment, antiplatelet or anticoagulation medication is most likely to be prescribed. However, no treatment is available for the inflammation of vasculitis. Nevertheless, considerable evidence has shown ongoing inflammation in the coronary artery of KD. Serological evidence of ongoing systemic inflammation has been noted in those patients with persistent aneurysms, with higher levels of serum amyloid A and interleukin-6, high sensitivity C-reactive protein, hypermethylation of FcγR2B in leukocytes, and imaging evidence by PET scanning (7). Additional anti-inflammation treatment may be needed for KD patients with aneurysm formation. In this study, we reported on a KD patient with regressed moderate aneurysm formation after hydrogen gas inhalation and reviewed the revelant literature.

CASE

A previously healthy 10-year-old Taiwanese boy presenting with a high fever for 12 days was admitted to another hospital in year 2019. Prior to admission to our hospital, he showed

bilateral conjunctival injection, erythema of the lips and neck, and lymphadenopathy. No BCG site induration was observed, nor was skin rash or limbs induration found. After the patient was admitted to our pediatric ward, the laboratory analysis revealed evidence of mild leukocytosis (10,600/μl), thrombocytosis (557,000/μl), and high C-reactive protein (CRP) (132.22 mg/L), without acute liver or kidney injury. A two-dimensional echocardiography on day 1 of admission (day 12 of illness) revealed a 4.12 mm aneurysm (BSA-adjusted Z score = 3.17) of the right coronary artery (RCA) with general dilatation of the RCA and LCA. High-dose intravenous immunoglobulin (IVIG, 2 g/kg) infusion was prescribed during admission (day 12 of illness). After being discharged, the RCA still progressed to a mid-sized aneurysm 6.08 mm (Z score: 4.85) in diameter and 35 mm in length (day 20 of illness) (**Figure 1**). Parents were directed to give hydrogen gas inhalation at least 1 h per day for the patient (77% hydrogen with 23% oxygen, 70∼75 liter/hour) at home by themselves until aneurysm regression. The follow-up echocardiography showed regression in the aneurysm, which was then 5.37 mm in diameter and 12 mm in length of RCA (day 34 of illness) and 4.56 mm × 8.68 mm (day 48 of illness), then 4.16 mm (day 62 of illness). The mid-sized aneurysm regressed to within normal range with 2.91 mm in diameter (Z score = 1.46) on day 138 of illness (**Figure 2**). The following laboratory data showed normal liver enzyme (aspartate aminotransferase/ alanine aminotransferase: 24/17 U/L), renal function (blood urine nitrogen/creatinine: 18.0/0.52 mg/dl, estimated glomerular filtration rate: >60 ml/min), total white blood cell count: 11,800/ul (leukocytosis), hemoglobin: 14.2 g/dl, platelet: 258,000/ul, segment: 67%, lymphocyte: 26%, monocyte: 5%, eosinophil: 0%, basophil: 0%, sodium: 143 mEq/L, potassium: 3.7 mEq/L, chloride: 107mEq/L, albumin: 4.6 g/dl, calcium: 9.7 mg/dl, eosinophil cationic protein: <2.0 microgram/L and total immunoglobulin E: 107 KU/L. The laboratory data from acute and chronic stage (after hydrogen gas inhalation) were showed in **Table 1**. We reported on this case using a medical chart review retrospective, and the institutional review board (IRB) of Chang Gung Memorial Hospital approved this study (IRB No.: 201900827B0).

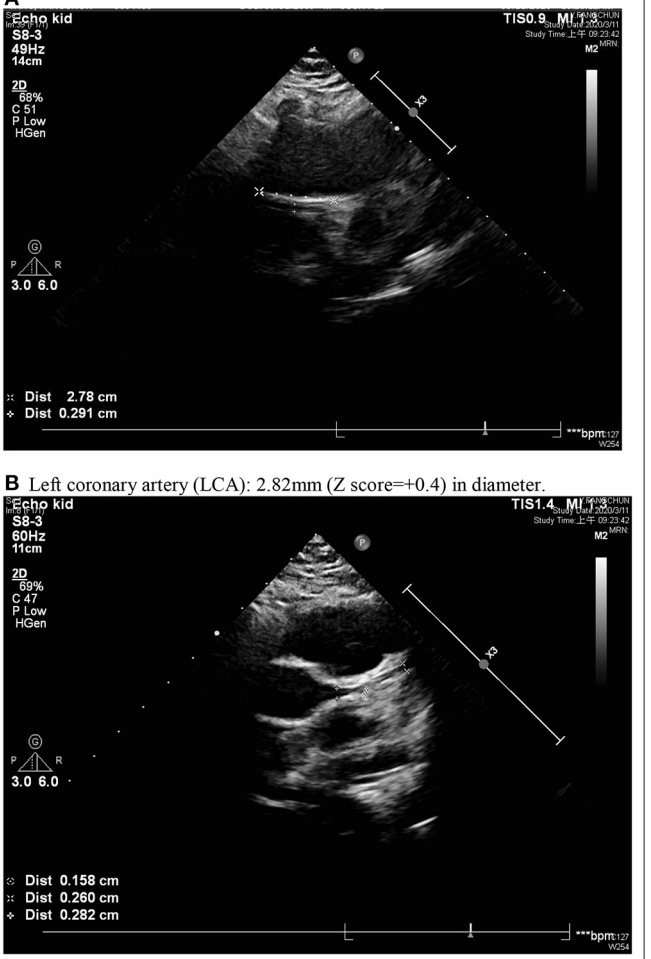


FIGURE 2 | Normal inner diameter and origin of coronary arteries; regressed right coronary artery with a diameter of 2.91 mm **(A)** and normal left coronary artery (LCA) **(B)**. **(B)** Left coronary artery (LCA): 2.82 mm (Z score = +0.4) in diameter.

DISCUSSION AND REVIEW

Coronary artery aneurysm formation is the most severe complication of KD and may have life-long implications. Currently, no effective treatment is available for KD patients with aneurysm formation after the acute stage of IVIG treatment, and it is even worse when the patient has a progressed aneurysm. Only antiplatelet and anticoagulant medications are prescribed for KD patients with aneurysm formation, and these agents had no effect on anti-inflammation for coronary vasculitis. Additional anti-inflammatory agents, including steroids, tumor necrosis factor blocker, and immunomodulatory agent have been suggested for KD patients with IVIG resistance in the acute stage during admission at the hospital. However, these anti-inflammatory agents have not been prescribed for KD patients with an already formed coronary aneurysm.

Wang et al. reported that nitric oxide (NO)-mediated inflammatory responses play a very important role in the pathogenesis of coronary artery lesions of KD (8). Yahata et al. (9) reported that inflammation and oxidative stress are closely related to a variety of diseases. Oxidative stress plays an important role in the pathology of KD and even multi-systemic inflammatory syndrome (MIS-C) (10, 11). The excessive production of reactive oxygen species (ROS) increases oxidative stress, which triggers an endless and vicious cycle of inflammation reactions and ROS metabolites. Oxidative stress has been shown to have an important role in the development of arteriosclerosis of KD patients and is strongly associated with endothelial dysfunction in early childhood patients with KD (12). Furthermore, simultaneous oxidative and nitrative stress occurrences in KD patients may lead to cardiovascular complications (13). IVIG treatment in KD can effectively reduce oxidative stress that provokes vasculitis. The urinary level of 8-iso-prostaglandin F2alpha (8-iso-PG) is a useful marker of the

TABLE 1 | Laboratory data from acute stage and chronic stage (after hydrogen gas inhalation) of Kawasaki disease.

Laboratory data	First day of admission (day 12 of illness)	Followed-up (day 138 of illness)
White blood cell count (/ul)	10,600	11,800*
Hemoglobin (g/dl)	11.6*	14.2
Platelet (/ul)	557,000*	258,000
Segment (%)	67.2	67
Lymphocyte (%)	22.5	26
Monocyte (%)	8.2	5
Eosinophil (%)	1.6	0
Basophil (%)	0.5	0
Aspartate aminotransferase (U/L)	25	24
Alanine aminotransferase (U/L)	27	17
Blood urine nitrogen (BUN) (mg/dl)	10.0	18.0
Blood creatinine (mg/dl)	0.63	0.52
Estimated glomerular filtration rate (ml/min)	>60	>60
Sodium (mEq/L)	139	143
Potassium (mEq/L)	3.9	3.7
Chloride (mEq/L)	102	107
Albumin (g/dl)	3.69	4.6
C-reactive protein (mg/L)	132.22*	<5

**indicate data not within normal range.*

effectiveness of IVIG on oxidative stress of KD (14). The risk factors for the development of atherosclerosis in adults, such as CRP, oxidative stress, and inflammatory cytokines are also increased in both the remote phase of KD and the acute stage (15). Taken altogether, oxidative stress and nitrative stress play important roles in the pathogenesis of vasculitis and coronary artery lesions of KD.

Ohsawa et al. (16) reported that hydrogen gas, an inert gas, is an effective antioxidant that contributes to the regulation of oxidative stress and inflammation response. Their study demonstrated that H2 reduced oxidants of the detrimental ROS, thus protecting against oxidant-induced cell injury. Hydrogen gas inhalation has been reported to decrease the levels of inflammatory cytokines including TNF-α, IL-1β, IL-6, and hypoxia-inducible factor 1 alpha (17), which were found to be elevated in KD and even higher in KD with CAL formation. Long et al. reported that hydrogen gas had protective effects in a rat model of branch retinal vein occlusion via decreasing Vascular endothelial growth factor (VEGF)-α expression (18). Local VEGF-α and its signaling pathway are associated with the development of LCWE-induced CAL in mice model of KD (19). Zhang et al. also reported that post-conditioning with hydrogen gas ameliorated subarachnoid hemorrhage (SAH)-induced, which is predominantly caused by a ruptured aneurysm, neuronal pyroptosis in part through the mitochondrial ATP-sensitive K+ channels/ERK1/2/p38 MAPK signaling pathway (20). These evidences support that hydrogen gas may be effective on rupture or occlusion of vasculitis associated with KD. Cole et al. showed that inhalation of hydrogen gas does not appear to cause clinically significant adverse effects in healthy adults. Although these data suggest that inhaled hydrogen gas may be well tolerated, future studies need to be powered to further evaluate safety especial in children (21).

Altogether, oxidative stress and inflammatory cytokines that were elevated in KD and CAL formation may benefit from hydrogen gas inhalation. The correlation between aneurysm regression and suppression of inflammatory cytokines after hydrogen gas inhalation in KD also need future investigation. After performing the literature review, we determined that we retrospectively reported the first case of a KD patient with coronary aneurysm formation to regress after hydrogen gas inhalation.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chang Gung Memorial Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics.* (1974) 54:271–6. doi: 10.1542/peds.54.3.271
2. Wang C-L, Wu Y-T, Liu C-A, Kuo H-C, Yang KD. Kawasaki disease: infection, immunity and genetics. *Pediatr Infect Dis J.* (2005) 24:998–1004. doi: 10.1097/01.inf.0000183786.70519.fa
3. Burns JC, Glode MP. Kawasaki syndrome. *Lancet.* (2004) 364:533–44. doi: 10.1016/S0140-6736(04)16814-1
4. Kuo HC, Yang KD, Chang WC, Ger LP, Hsieh KS. Kawasaki disease: an update on diagnosis and treatment. *Pediatr Neonatol.* (2012) 53:4–11. doi: 10.1016/j.pedneo.2011.11.003
5. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, Tang A, Berry E, Tremoulet AH, et al. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse

cardiac events in the US Population. *J Am Heart Assoc.* (2016) 5:e003289. doi: 10.1161/JAHA.116.003289
6. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation.* (1996) 94:1379–85. doi: 10.1161/01.CIR.94.6.1379
7. Chang LS, Yu HR, Chu CL, Chen KD, Huang YH, Guo MM, et al. Long-term hypermethylation of fcgammar2b in leukocytes of patients with Kawasaki disease. *J Clin Med.* (2021) 10:2347. doi: 10.3390/jcm10112347
8. Wang CL, Wu YT, Lee CJ, Liu HC, Huang LT, Yang KD. Decreased nitric oxide production after intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr.* (2002) 141:560–5. doi: 10.1067/mpd.2002.127505
9. Yahata T, Hamaoka K. Oxidative stress and Kawasaki disease: how is oxidative stress involved from the acute stage to the chronic stage? *Rheumatology.* (2017) 56:6–13. doi: 10.1093/rheumatology/kew044
10. Graciano-Machuca O, Villegas-Rivera G, Lopez-Perez I, Macias-Barragan J, Sifuentes-Franco S. Multisystem inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: role of oxidative stress. *Front Immunol.* (2021) 12:723654. doi: 10.3389/fimmu.2021.723654
11. Chen KD, Lin WC, Kuo HC. Chemical and biochemical aspects of molecular hydrogen in treating Kawasaki disease and COVID-19. *Chem Res Toxicol.* (2021) 34:952–8. doi: 10.1021/acs.chemrestox.0c00456
12. Ishikawa T, Seki K. The association between oxidative stress and endothelial dysfunction in early childhood patients with Kawasaki disease. *BMC Cardiovasc Disord.* (2018) 18:30. doi: 10.1186/s12872-018-0765-9
13. Straface E, Marchesi A, Gambardella L, Metere A, Tarissi de Jacobis I, Viora M, et al. Does oxidative stress play a critical role in cardiovascular complications of Kawasaki disease? *Antioxid Redox Signal.* (2012) 17:1441–6. doi: 10.1089/ars.2012.4660
14. Takatsuki S, Ito Y, Takeuchi D, Hoshida H, Nakayama T, Matsuura H, et al. IVIG reduced vascular oxidative stress in patients with Kawasaki disease. *Circ J.* (2009) 73:1315–8. doi: 10.1253/circj.CJ-07-0635
15. Fukazawa R, Ogawa S. Long-term prognosis of patients with Kawasaki disease: at risk for future atherosclerosis? *J Nippon Med Sch.* (2009) 76:124–33. doi: 10.1272/jnms.76.124
16. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, et al. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med.* (2007) 13:688–94. doi: 10.1038/nm1577
17. Liang IC, Ko WC, Hsu YJ, Lin YR, Chang YH, Zong XH, et al. The anti-inflammatory effect of hydrogen gas inhalation and its influence on laser-induced choroidal neovascularization in a mouse model of neovascular age-related macular degeneration. *Int J Mol Sci.* (2021) 22:12049. doi: 10.3390/ijms222112049
18. Long P, Yan W, He M, Zhang Q, Wang Z, Li M, et al. Protective effects of hydrogen gas in a rat model of branch retinal vein occlusion via decreasing VEGF-alpha expression. *BMC Ophthalmol.* (2019) 19:112. doi: 10.1186/s12886-019-1105-2
19. Lin IC, Sheen JM, Tain YL, Chou MH, Huang LT, Yang KD. Vascular endothelial growth factor-a in lactobacillus casei cell wall extract-induced coronary arteritis of a murine model. *Circ J.* (2014) 78:752–62. doi: 10.1253/circj.CJ-13-0612
20. Zhang CS, Han Q, Song ZW, Jia HY, Shao TP, Chen YP. Hydrogen gas post-conditioning attenuates early neuronal pyroptosis in a rat model of subarachnoid hemorrhage through the mitoKATP signaling pathway. *Exp Ther Med.* (2021) 22:836. doi: 10.3892/etm.2021.10268
21. Cole AR, Sperotto F, DiNardo JA, Carlisle S, Rivkin MJ, Sleeper LA, et al. Safety of prolonged inhalation of hydrogen gas in air in healthy adults. *Critical care explorations.* (2021) 3:e543. doi: 10.1097/CCE.0000000000000543

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

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

frontiers | Frontiers in Cardiovascular Medicine

CASE REPORT
published: 13 May 2022
doi: 10.3389/fcvm.2022.882817

Extensive Aortic Thromboembolism in a Patient With Erdheim-Chester Disease: A Case Report

Jiangping He[1], Xin Fang[2], Xianfeng Zhang[1], Kuang Chen[3] and Jiao Huang[1]**

[1] Department of Rheumatology, Affiliated Hangzhou First People's Hospital, School of Medicine, Zhejiang University, Hangzhou, China, [2] Department of Vascular Surgery, Affiliated Hangzhou First People's Hospital, School of Medicine, Zhejiang University, Hangzhou, China, [3] Department of Hematology, Affiliated Hangzhou First People's Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Background: Erdheim-Chester disease (ECD) is a rare disease that affects multiple systems and is characterized by non-Langerhans cell histiocytosis. Classic clinical signs include long bone infiltration, central nervous system involvement, diabetes insipidus, and sheathing of the entire aorta. However, thrombosis is not recognized as a typical cardiac manifestation of ECD. Here, we report the case of an ECD patient with extensive arterial thrombus formation and embolism in several sections of the aorta.

Case: A 36-year-old woman was admitted due to recurrent fever and left finger cyanosis for 20 days. Laboratory tests revealed that her C-reactive protein and interleukin-6 levels were significantly elevated. Thoracic computed tomographic angiography (CTA) revealed thrombosis from the aortic arch to the left subclavian artery accompanied by severe stenosis of the left subclavian artery. Abdominal CTA revealed splenic infarction due to splenic artery embolism and thrombus formation in multiple abdominal arteries. She underwent emergent arterial thrombectomy. During hospitalization, she complained of polyuria. The desmopressin test and pituitary magnetic resonance imaging findings suggested diabetes insipidus. Furthermore, positron emission tomography-computed tomography and bone emission computed tomography showed long bone impairment, and pathological examination of the bone samples confirmed ECD. Steroids and tocilizumab were selected as the initial therapies; however, thrombosis continued to develop. After replacement of tocilizumab with interferon-α, her condition became stable.

Conclusion: Although extremely rare, fatal thrombosis may be a significant cardiovascular manifestation of ECD.

Keywords: aortic thromboembolism, Erdheim-Chester disease, non-Langerhans cell histiocytosis, splenic infarction, lipogranulomatosis

OPEN ACCESS

Edited by:
Xiaofeng Yang,
Temple University, United States

Reviewed by:
Yung-Wei Chi,
University of California, Davis, United States
Guangzhi Cong,
General Hospital of Ningxia Medical University, China

****Correspondence:***
Jiao Huang
huangjiao2001@163.com
Kuang Chen
124974406@qq.com

Specialty section:
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

Received: *25 February 2022*
Accepted: *26 April 2022*
Published: *13 May 2022*

Citation:
He J, Fang X, Zhang X, Chen K and Huang J (2022) Extensive Aortic Thromboembolism in a Patient With Erdheim-Chester Disease: A Case Report. Front. Cardiovasc. Med. 9:882817. doi: 10.3389/fcvm.2022.882817

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare disease that refers to a series of clinical manifestations caused by non-Langerhans cell histiocytosis. Since it was first described by anatomopathologist Erdheim and his student Chester in 1930, no more than 2,000 cases have been reported worldwide.

ECD can lead to fatal outcomes, especially when it affects multiple systems. The main clinical signs include bone impairment (79%), diabetes insipidus (48%), coated aorta (40%), and hairy

kidney appearance on computed tomography (CT) scan (63%) (1). Only one case was reported wherein ECD was associated with arterial thromboembolism (2).

Herein, we report a rare case, in which the patient was diagnosed with ECD following extensive aortic thrombosis and splenic infarction.

CASE DESCRIPTION

A 36-year-old woman was admitted due to recurrent fever and left finger cyanosis for 20 days. She had undergone a cesarean section 26 days prior. The patient also complained of abdominal pain and nausea. Body temperature was 38.3°C, and other vital signs were stable. Physical examination showed that the fingers of her left hand were pale and her skin temperature was much lower than that on the right side. A murmur in the left subclavian artery was auscultated.

DIAGNOSTIC ASSESSMENT AND THERAPEUTIC INTERVENTION

Diagnostic Assessment

Routine blood test showed a white blood cell (WBC) count of 12.7×10^9/L, C-reactive protein (CRP) level of 60.2 mg/L, and erythrocyte sedimentation rate (ESR) of 36 mm/h. Blood biochemistry was within the normal range, and serological examinations, including autoimmune antibodies and antiphospholipid antibodies, were negative. CTA of the thoracic and abdominal aorta showed thrombosis starting from the aortic arch to the left subclavian artery, accompanied by severe stenosis of the left subclavian artery, diffuse splenic infarction due to embolism of the splenic artery, and thrombosis in several arteries, including the common hepatic artery, left common iliac artery, and proximal to the femoral artery (**Figure 1**). The patient was diagnosed with extensive arterial embolism secondary to unknown reasons and presented a risk of thrombus drop, which would lead to embolism in other vital organs. Therefore, emergent catheter-based arteriography and thrombectomy in the left subclavian artery was performed, while balloon block in the superior mesenteric and renal arteries was adopted to prevent thrombus drop.

Surgery was successful; however, the patient's fever persisted. Laboratory examinations revealed elevated levels of blood CRP at 108 mg/L, serum sodium at 163 mmol/L, and serum interleukin-6 (IL-6) at 198.69 pg/mL. The blood culture results were negative. She also complained of thirst and polyuria, and her urine volume collected for 24 h was 7,000 mL. Pituitary enhanced magnetic resonance imaging (MRI) revealed nodular thickening of the pituitary stalk (**Supplementary Figure 1**) and the desmopressin test result was positive, which were supportive of a diagnosis of diabetes insipidus. Sex hormones were assessed, and the levels of follicle-stimulating hormone and luteinizing hormone were found to be extremely low, suggesting anterior pituitary hypofunction. Positron emission tomography (PET)-CT suggested inflammatory-reactive changes in superficial lymph nodes, slight interstitial pneumonia, and most importantly, multiple bone changes in the scanned area. For further confirmation, bone emission computed tomography (ECT), knee CT, and knee MRI were performed, which showed diffuse bone infiltration in bilateral distal femurs and proximal tibias (**Supplementary Figures 2A–C**).

A multidisciplinary discussion was conducted, and considering the pituitary lesion and the long bone infiltration, the diagnosis of ECD was proposed. Further examination was performed. Brain enhanced MRI revealed thickening of cerebral falx, which is a typical change in ECD (**Supplementary Figure 3**), while the cardiac MRI examination did not show a coated aorta. Bone puncture was finally approved, and the results showed a large number of foamy cells surrounded by fibrosis and few multinucleated giant cells (**Figure 2**). Immunohistochemistry (IHC) revealed CK [−], CD68 [+], CD163 [+], Langerin [−], CD1a [−], and S100 [+], in accordance with the changes in ECD. In addition, a circulating $BRAF^{V600E}$ mutation was identified, further confirming the diagnosis of ECD.

Therapeutic Intervention

Upon diagnosis, the following medications were administered: methylprednisolone 40 mg intravenously twice a day, rivaroxaban 20 mg and aspirin 100 mg orally every day as anticoagulant therapy, and Minirin (desmopressin) 0.05 mg orally three times a day to reduce the urine volume. Her body temperature returned to normal immediately after treatment. Because of the elevated IL-6 levels, we used tocilizumab 8 mg/kg to suppress the inflammatory state, and the dosage of methylprednisolone was gradually reduced to 20 mg orally per day as maintenance. A repeat blood test performed 1 week after therapy showed normal WBC count, CRP, ESR, and IL-6 levels.

However, 1 month later, when the patient was admitted for review, enhanced CT of the thoracic aorta showed fresh thrombus formation in the brachiocephalic trunk (**Figure 3A**). Laboratory tests showed that CRP was elevated at 28 mg/L, although there were no symptoms according to the patient. This CT finding suggested progression of the disease; therefore, tocilizumab administration was discontinued and replaced by interferon-α 60 μg *via* subcutaneous injection three times every week. After 2 months of treatment, repeat CT scan showed disappearance of the thrombus in the brachiocephalic trunk (**Figure 3B**), and her vital signs and laboratory test results returned to normal.

DISCUSSION

ECD is a rare disease first reported in 1930. The diagnosis of ECD is based on typical clinical manifestations, radiological findings, and histological results, excluding other mimics. In our case, the patient had diabetes insipidus, long bone infiltration, and meningeal thickening. Bone histopathology demonstrated foamy histiocytes admixed with fibrosis, and IHC confirmed non-Langerhans histiocytosis. Although the $BRAF^{V600E}$ mutation was not detected in her bone sample, which may be attributed to decalcification during sample preparation, the circulating $BRAF^{V600E}$ mutation was identified. After specialist treatment, the patient's symptoms resolved, and the laboratory results

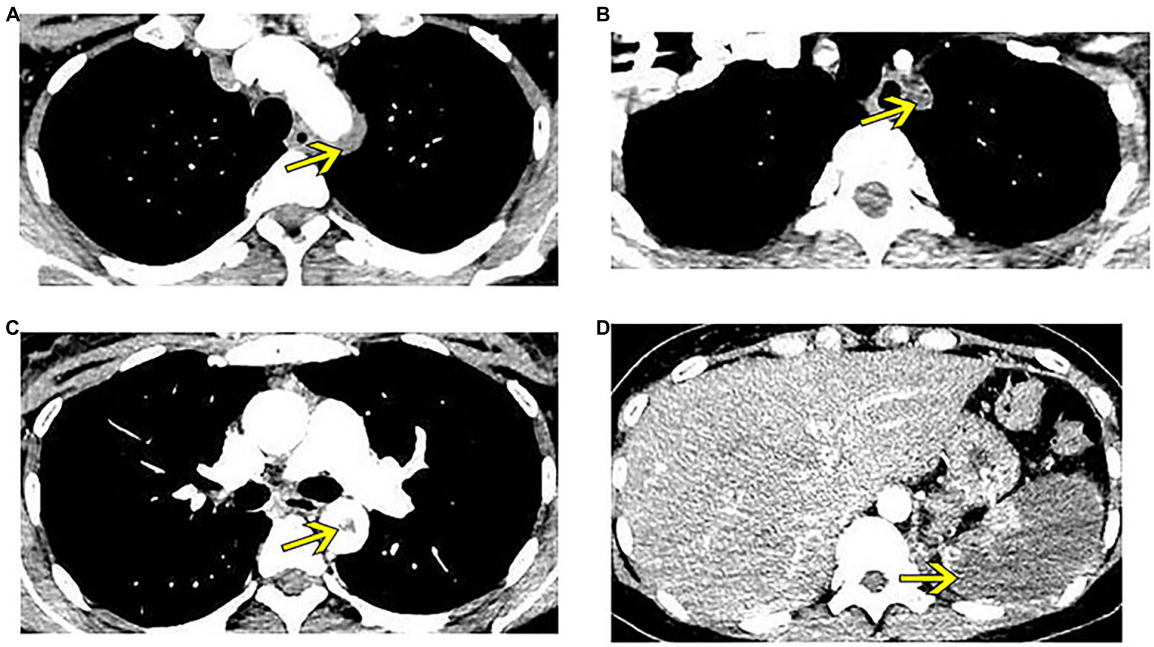


FIGURE 1 | Enhanced computed tomography shows thrombus formation in several arteries (yellow arrows). **(A)** Thrombus at the aortic arch. **(B)** Thrombus crosses to the left subclavian artery, leading to embolism of this artery. **(C)** Thrombus at the thoracic aorta. **(D)** Splenic infarction.

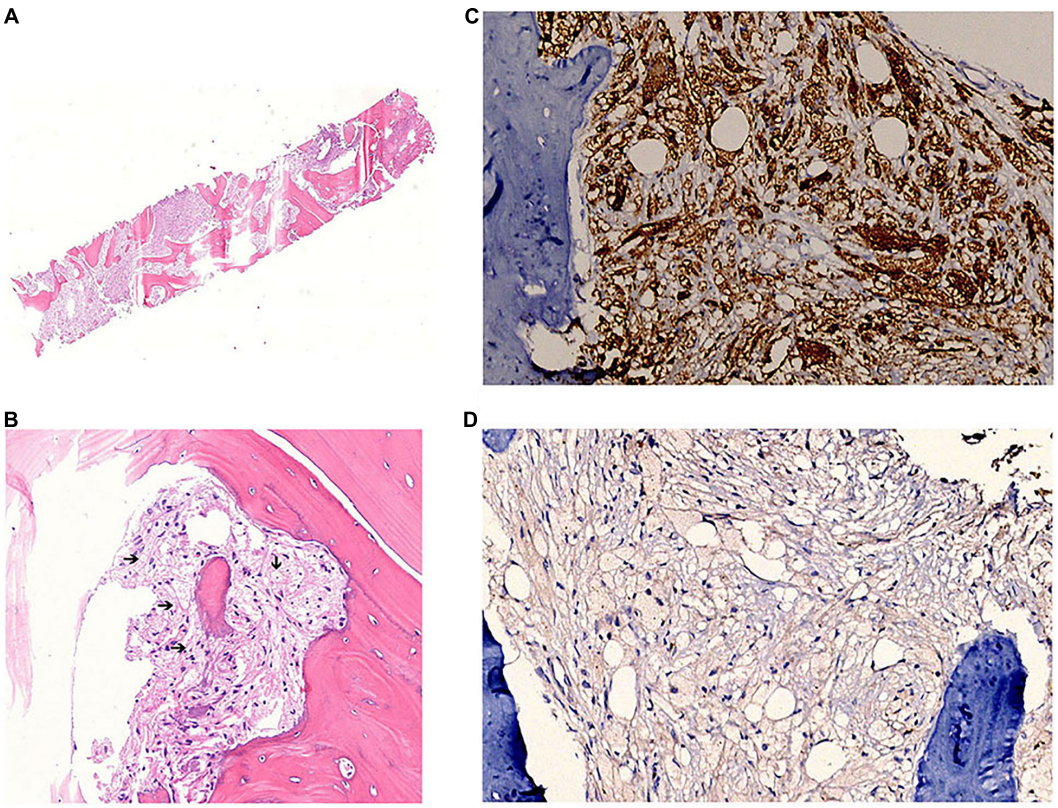


FIGURE 2 | Bone sample pathology and immunohistochemistry confirms the diagnosis of ECD. **(A)** Hematoxylin and eosin staining of the bone sample. **(B)** Foamy cells surrounded by fibrosis (black arrows). **(C)** CD68 staining is positive. **(D)** CD1a staining is negative.

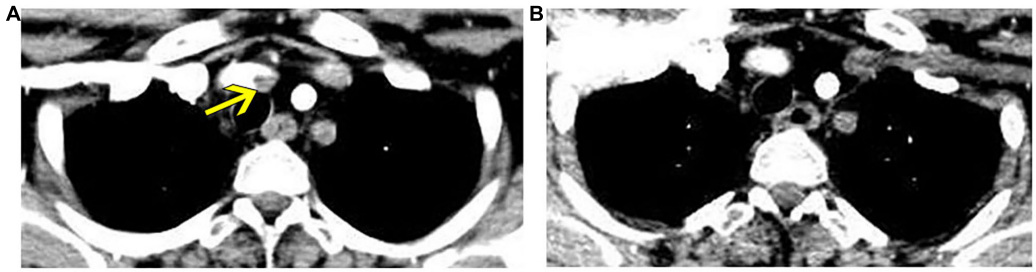


FIGURE 3 | Enhanced thoracic computed tomography reveals fresh thrombus formation in the brachiocephalic trunk, which regressed after interferon-α treatment. **(A)** Fresh thrombus in the brachiocephalic trunk (yellow arrow). **(B)** Regression of thrombus in a reviewed computed tomography after 2 months of interferon-α treatment.

became normal. Collectively, these findings established the diagnosis of ECD.

Among the clinical features of ECD, thrombosis is extremely rare, with only one case reported. In our patient, extensive thrombosis was observed in different sections of the aorta, including the aortic arch, left subclavian artery, aorta ventralis, common hepatic artery, and the splenic artery. It is regrettable that we did not obtain the thrombus sample for physiological examinations to elucidate the relationship of the thrombus and ECD. Nevertheless, the onset of thrombosis formation was in accordance with the activity of ECD verified by blood tests, radiological findings, and pathological results. Other possible causes of thrombosis, such as autoimmune diseases and malignancies, were also excluded. Moreover, during the course, the patient developed progression of thrombosis, accompanied by an elevated CRP level; after changing her therapy to interferon-α, the CRP levels returned to normal and neonatal thrombosis disappeared. These findings suggested that in our patient, thrombus formation was closely related to the activity of ECD, and the treatment of ECD was also effective for treating thrombosis, indirectly suggesting the possibility that thrombosis was formed secondary to ECD.

ECD can result in fatal outcomes, and spontaneous regression is rare. In a retrospective review, 10.1% of patients with ECD had overlapping myeloid neoplasms (3). Therapeutic regimens for ECD include immunosuppressive therapy (interferon-α, IL-6 inhibitor, and IL-1 inhibitor), nucleoside analog (cladribine), and targeted therapy (vemurafenib and cobimetinib). Interferon-α is recognized as the best initial choice for ECDs (4). In recent years, promising advances have demonstrated that BRAF and MEK inhibitors have robust efficacy, especially in multi-system and refractory ECD (5, 6). In mild cases, biological agents, such as anakinra (7) tocilizumab (8), infliximab (9), or steroids plus sirolimus (10) can be used. In our case, we started treatment with steroids and tocilizumab; however, the disease was not well controlled. After adjustment with interferon-α, the patient achieved remission. With the advent of targeted therapies, even severe manifestations of ECD have become a chronic, rather than fatal, illness (11). In our patient, thrombosis was the major and unusual manifestation. In the subsequent follow-up examinations, despite the classical lesion of ECD, we should especially consider thrombosis formation. If no further fatal thrombus is formed after treatment, the longevity of the patient may be optimistic. Given that interferon treatment is relatively long-term and may have adverse effects, such as fatigue and depression, targeted therapy may be attempted in the future.

PATIENT PERSPECTIVE

ECD is a rare but fatal disease; therefore, early and correct diagnosis is important for improving patient outcomes. According to reported cases and studies, thrombosis is not recognized as a clinical feature of ECD. However, in our case, extensive thrombosis and embolism of vital arteries produced the main life-threatening symptoms of the patient. Although we have no direct evidence on the relationship between thrombosis and ECD, the patient's symptoms resolved with interferon therapy and her thrombosis has been stable. This case suggests that the understanding of ECD is not comprehensive; fatal thrombosis may be a significant cardiovascular manifestation of ECD, and other clinical signs may emerge if we continue to explore this condition.

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

AUTHOR CONTRIBUTIONS

JH, KC, JPH, and XF contributed in patient diagnosis, treatment, and follow-up. JPH collected the data and drafted

this manuscript. JH and XZ revised the final version of the manuscript. All authors agreed to be accountable for the content of the work.

FUNDING

This work was supported by grants from the National Natural Science Foundation of China (Grant No. 81900785) and the Medical Science and Technology Project of Zhejiang Province (Grant No. 2020KY686).

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.cn) for English language editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.882817/full#supplementary-material

REFERENCES

1. Haroche J, Cohen-Aubart F, Amoura Z. Erdheim–Chester disease. *Blood.* (2020) 135:1311–8.
2. Razanamahery JM, Malakhia A, Guillon B, Humbert S, Magy-Bertrand N. Multiple arterial thrombosis and pericarditis revealing histiocytosis successfully treated with MEK-inhibitor cobimetinib. *Clin Exp Rheumatol.* (2020) 38:173–4.
3. Papo M, Diamond EL, Cohen-Aubart F, Emile JF, Roos-Weil D, Gupta N, et al. High prevalence of myeloid neoplasms in adults with non-Langerhans cell histiocytosis. *Blood.* (2017) 130:1007–13. doi: 10.1182/blood-2017-01-761718
4. Arnaud L, Hervier B, Néel A, Hamidou MA, Kahn JE, Wechsler B, et al. CNS involvement and treatment with interferon-alpha are independent prognostic factors in Erdheim–Chester disease: a multicenter survival analysis of 53 patients. *Blood.* (2011) 117:2778–82. doi: 10.1182/blood-2010-06-294108
5. Haroche J, Cohen-Aubart F, Emile JF, Arnaud L, Maksud P, Charlotte F, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim–Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. *Blood.* (2013) 121:1495–500. doi: 10.1182/blood-2012-07-446286
6. Diamond EL, Durham BH, Ulaner GA, Drill E, Buthorn J, Ki M, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. *Nature.* (2019) 567:521–4. doi: 10.1038/s41586-019-1012-y
7. Cohen-Aubart F, Maksud P, Saadoun D, Drier A, Charlotte F, Cluzel P, et al. Variability in the efficacy of the IL1 receptor antagonist anakinra for treating Erdheim–Chester disease. *Blood.* (2016) 127:1509–12. doi: 10.1182/blood-2015-09-672667
8. Berti A, Cavalli G, Guglielmi B, Biavasco R, Campochiaro C, Tomelleri A, et al. Tocilizumab in patients with multisystem Erdheim–Chester disease. *Oncoimmunology.* (2017) 6:e1318237. doi: 10.1080/2162402X.2017.1318237
9. Cohen-Aubart F, Maksud P, Emile JF, Benameur N, Charlotte F, Cluzel P, et al. Efficacy of infliximab in the treatment of Erdheim–Chester disease. *Ann Rheum Dis.* (2018) 77:1387–90. doi: 10.1136/annrheumdis-2017-212678
10. Gianfreda D, Nicastro M, Galetti M, Alberici F, Corradi D, Becchi G, et al. Sirolimus plus prednisone for Erdheim–Chester disease: an open-label trial. *Blood.* (2015) 126:1163–71. doi: 10.1182/blood-2015-01-620377
11. Goyal G, Heaney ML, Collin M, Cohen-Aubart F, Vaglio A, Durham BH, et al. Erdheim–Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. *Blood.* (2020) 135:1929–45. doi: 10.1182/blood.2019003507

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

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

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 22 July 2022
DOI 10.3389/fcvm.2022.931590

OPEN ACCESS

EDITED BY
Jun Yu,
Temple University, United States

REVIEWED BY
Fang Liu,
Children's Hospital, Fudan University, China
Sanaz Hatami,
University of Alberta, Canada

*CORRESPONDENCE
Chengming Fan
fanchengming@csu.edu.cn
Jinfu Yang
yjf19682005@csu.edu.cn

SPECIALTY SECTION
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 29 April 2022
ACCEPTED 28 June 2022
PUBLISHED 22 July 2022

CITATION
Tang M, Wu X, Hu S, Wu Q, Yang D, Iroegbu CD, Fan C and Yang J (2022) A case of rare pulmonary sequestration complicated with congenital heart disease treated by arterial embolization and atrial defect closure: A case report and review of literature. *Front. Cardiovasc. Med.* 9:931590. doi: 10.3389/fcvm.2022.931590

A case of rare pulmonary sequestration complicated with congenital heart disease treated by arterial embolization and atrial defect closure: A case report and review of literature

Mi Tang[1], Xun Wu[1], Shijun Hu[1], Qin Wu[1], Danni Yang[2], Chukwuemeka Daniel Iroegbu[1], Chengming Fan[1]* and Jinfu Yang[1]*

[1]Department of Cardiovascular Surgery, The Second Xiangya Hospital, Central South University, Changsha, China, [2]Hunan Agricultural University, Changsha, China

Pulmonary sequestration with congenital heart disease is a rare congenital malformation. Herein, we report a 19-month-old toddler diagnosed with right lower pulmonary sequestration, right pulmonary artery dysplasia, right lower pulmonary venous ectopic drainage, and a right-sided heart with an atrial septal defect. The pulmonary sequestration had a rare blood supply, such as confluent arteries with the renal vessels draining into the hepatic veins. Arterial embolization and atrial defect closure were used to treat the rare congenital malformation with satisfactory results.

KEYWORDS

pulmonary sequestration, atrial septal defect, atrial septal occlusion, interventional therapy, pulmonary vein drainage

Introduction

Pulmonary sequestration, categorized as intralobar or extralobar isolation, is a rare congenital anomaly thought to arise from the accessory lung buds (1). The intralobar lesion's arterial supply typically arises from the thoracic aorta, while it's venous drainage via the pulmonary veins. On the other hand, the extralobar lesions drain (venous) via the systemic circulation, including the azygos, hemiazygos, or vena cava (2). Notably, extralobar sequestration, less common than intralobar sequestration, presents early in life with respiratory distress or feeding difficulties, is often associated with other congenital malformations, and accounts for 25% of reported cases.

In pulmonary sequestration, confluent arteries with the renal vessels draining into the hepatic veins are extremely rare. Traditional treatments include surgical resection and supplying artery ligation (3). Notwithstanding, transarterial embolization has since been proposed (4). Some reports using supplying artery embolization to treat pulmonary isolation have reported that the embolic lesions eventually become muscled or even disappeared due to ischemia (5–7).

Case report

A 19-month-old toddler was admitted to the hospital following a heart murmur discovery. During the fetal period, a routine prenatal color Doppler ultrasound examination at a local hospital detected a congenital cardiac anomaly. However, the examination results were lost by the patient's family. The patient had recurrent pneumonia after birth. After admission, auscultation revealed a heart murmur and weak breath sounds in the right lung. There was no other notable clinical findings during physical examination and no medical, family, and psychosocial history including genetic information about cardiovascular disease. Cardiac ultrasound examination showed: (i) a dextrorotatory heart; (ii) atrial septal defect (iii) right inferior pulmonary venous drainage; (iv) right pulmonary artery dysplasia; and (v) moderate pulmonary hypertension. The patient was delivered at term with a birth weight of 3.5 kg.

Chest X-ray showed a large area of high density in the lower right lung. Chest CT showed a 9 mm defect in the atrial septum (**Figure 1A**), a significantly small right pulmonary artery (∼5 mm) and a significantly small right superior pulmonary vein (**Figures 1B–D**), a small and sparsely branched right lung, and the venous of sequestration lung return to the hepatic vein (**Figure 2**). Considering the patient's young age and inability to tolerate cardiac and pulmonary surgery, isolated pulmonary embolism and atrial septal occlusion were performed under general anesthesia. Digital subtraction angiography (DSA) and CT 3D reconstruction (**Supplementary Video**) showed an abnormal blood vessel branching from the right renal artery opening (∼4 mm; **Figures 3A–C**), and arching toward the right lower lung for blood supply. During the operation, nine coils of equal size were applied to completely block the abnormal blood supply to the right lower lung. Under transthoracic ultrasound guidance, a 14 mm atrial septal occluder was placed through the delivery sheath and ascertained to be adequately fixed, with no residual shunt and intact valvular apparatus (**Figure 3D**).

The patient recovered well after the operation. Pulmonary infection was controlled with no obvious abnormality following blood examination. Three days postoperatively, echocardiography showed that the occluder was well fixed and there was no residual shunt. The patient had no special discomfort and was discharged 4 days later. No adverse and unanticipated events were indicated during the one-month follow-up period, the patient was strongly advised to come back to the hospital for echocardiography and chest CT reexamination 6 months and 1 year after that.

Discussion

Pulmonary sequestration refers to the abnormal connection of the lung tissue (part) to the trachea and bronchial tree, with an abnormal vascular supply. Some studies have also suggested that the sequestered lung is a congenital disorder that results from the growth of parapulmonary buds during development. This lung bud is pinched from the caudal foregut, develops its blood supply, and remains independent of the normal tracheobronchial tree (8). However, other authors have suggested that intralobar sequestration can be acquired via bronchial obstruction causing distal infection. It thus stimulates angiogenesis, which utilizes the existing small systemic arteries from the pulmonary ligaments to form a new arterial supply (9).

The presented patient was diagnosed with right lower pulmonary sequestration, right pulmonary artery dysplasia, right lower pulmonary venous ectopic drainage, and a right-sided heart with an atrial septal defect. Pulmonary sequestration occurs in 0.15–6.6% of all pulmonary malformations. Two types can be distinguished: intra-leaf (ILS) and extra-leaf (ELS) isolation. With ILS, the abnormal lung tissue is located within the normal lung and visceral pleura, with venous drainage to the pulmonary veins. Its arterial supply is 73% from the thoracic aorta, 20% from the abdominal aorta, and 3.7% from the intercostal arteries. With ELS; however, the mass is located outside the normal lung and within its visceral pleura, with venous drainage to the systemic venous system. Approximately 80% of its arterial supply comes from the thoracic or abdominal aorta, while 15% arises from the subclavian artery, brachiocephalic, spleen, stomach, and intercostal arteries, and 5% from the pulmonary artery (10). In the present case, the arterial supply arose from a confluent right renal artery (**Figure 4A**), while the venous drainage was to the hepatic vein (**Figure 4B**), a form of blood supply and drainage that has never been reported.

Extra-leaf (ELS) patients are often accompanied by acute respiratory distress or feeding difficulties after birth. Approximately 60% of children with ELS have congenital malformations, including diaphragmatic hernia, congenital heart disease, elbow syndrome, congenital cyst-adenomatoid malformation (CCAM), or pulmonary dysplasia (11). In the case herein, the patient was born with recurrent episodes of pneumonia and concomitant atrial septal defect.

Traditional treatment is with surgical excision (3). Currently, less invasive endovascular treatments have been reported to prevent complications (12). Platinum coils and polyvinyl alcohol granules are the most frequently used in transcatheter vascular embolization (13). Also, hybrid surgery has been performed for patients with large lung disease and multiple or large feeding arteries or aneurysmal abnormal arteries (14–17). Patients with larger feeding arteries may be at high risk for incomplete embolism, which may require reoperation due to recanalization and symptom recurrence as described in our previous work (18–21). In the present case, the patients feeding artery opening was 4 mm, and the possibility of incomplete embolization was low. Nine platinum coils were placed.

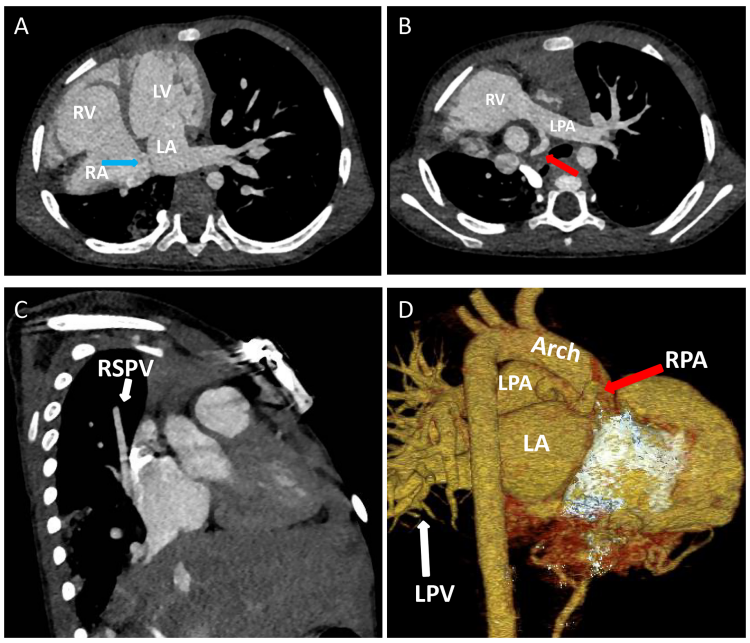


FIGURE 1
Contrast-enhanced CT of the chest and three-dimensional cardiac computed tomography angiography: **(A)** Atrial septal defect location, ~9 mm in size (blue arrow). **(B–D)** The right pulmonary artery (red arrow) and right superior pulmonary vein are hypoplastic (white arrow). LA, left atrium; LPA, left pulmonary artery; LPV, left pulmonary vein; LV, left ventricle; RA, right atrium; RPA, right pulmonary artery; RSPV, right superior pulmonary vein; RV, right ventricle.

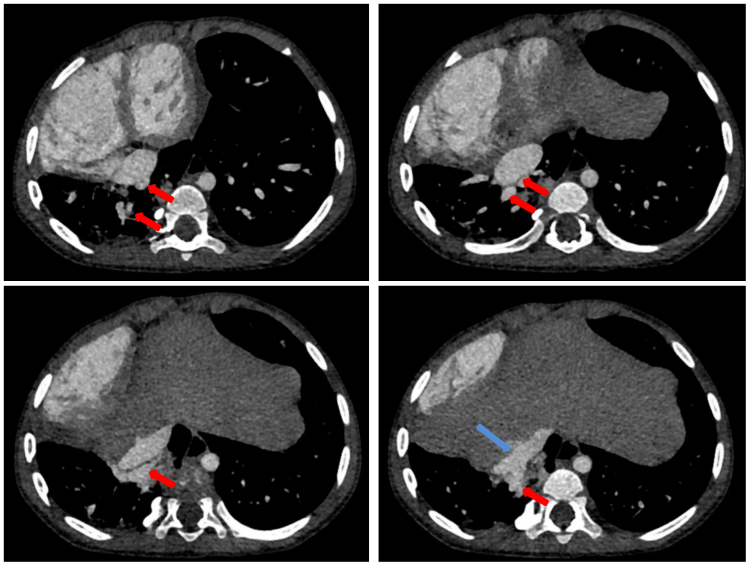


FIGURE 2
Contrast-enhanced CT of the chest: contrast-enhanced CT shows the isolated pulmonary venous draining (red arrow) into the hepatic vein (blue arrow).

Notably, patients reported having received endovascular therapy recovered better, faster, and had lower complication rates. Given that the abnormal lung parenchyma has not been resected, recurrent hemoptysis and secondary pulmonary infection are the primary complications. Other complications include chest pain and low-grade fever, which might be due to pulmonary infarction after embolization. The patient experienced no postoperative complications, spontaneously

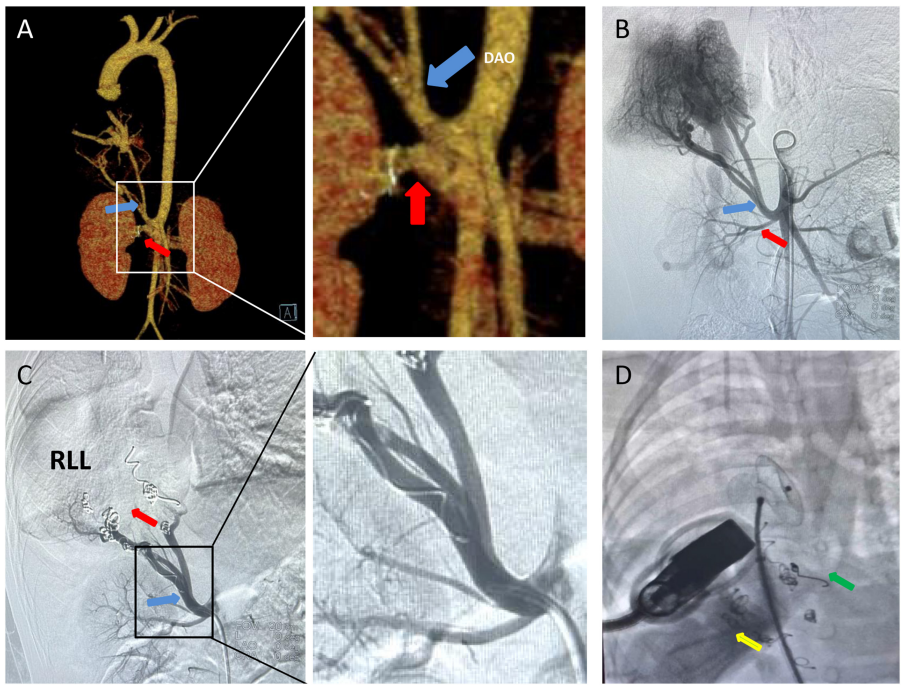


FIGURE 3
CT 3D reconstruction and Aortic DSA: **(A,B)** A isolates the pulmonary supplying artery (blue arrow) and the renal artery (red arrow) to the abdominal aorta, and isolates the pulmonary supplying artery by approximately 4 mm. **(C)** Nine platinum coils were placed in the isolated pulmonary supplying artery (blue arrow), and no contrast agent entered the distal end of the infarct (red arrow). **(D)** Placement of atrial septal defect occluder (green arrow) under co-guided echocardiography (yellow arrow) and DSA. DAO, decending aorta; RLL, right lower lobe.

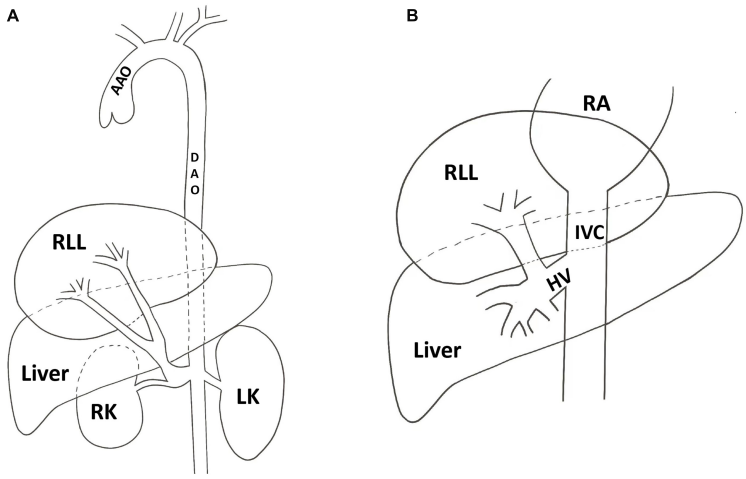


FIGURE 4
Schematic figure shows the presented case of pulmonary sequestration: **(A)** The arterial supply of the sequestration lung arose from a confluent right renal artery. **(B)** The venous of sequestration lung return to the inferior vena cava via the hepatic vein. AAO, ascending aorta; DAO, decending aorta; HV, hepatic vein; IVC, inferior vena cava; LK, left kidney; RA, right atrium; RK, right kidney; RLL, right lower lobe.

recovered after surgery, and was discharged from the hospital 4 days later.

Take-home points: 1. Pulmonary sequestration occurs in 0.15–6.6% of all pulmonary malformations; 2. Pulmonary sequestration can be congenital or acquired via bronchial obstruction causing distal infection; 3. Approximately 80% of its arterial supply comes from the thoracic or abdominal

aorta; 4. Transcatheter vascular embolization and hybrid surgery are the most frequently used strategies for the treatment.

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.

Author contributions

MT, XW, CF, and JY contributed to the conception and design of the study. JY, XW, MT, CI, and CF wrote sections of the manuscript. DY draw the schematic figure. All authors contributed to the manuscript revision, read, and approved the submitted version.

Funding

This study was supported by the Natural Science Foundation of Changsha City (kq2014231).

Conflict of interest

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

Publisher's note

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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.931590/full#supplementary-material

SUPPLEMENTARY VIDEO
Three-dimensional great artery computed tomography angiography and the kidneys.

References

1. Savic B, Birtel FJ, Tholen W, Funke HD, Knoche R. Lung sequestration: report of seven cases and review of 540 published cases. *Thorax.* (1979) 34:96–101.

2. Gamillscheg A, Beitzke A, Smolle-Jüttner FM, Zach M, Stein JI, Steinbrugger B, et al. Extralobar sequestration with unusual arterial supply and venous drainage. *Pediatr Cardiol.* (1996) 17:57–9. doi: 10.1007/bf02505815

3. Yucel O, Gurkok S, Gozubuyuk A, Caylak H, Sapmaz E, Kavakli K, et al. Diagnosis and surgical treatment of pulmonary sequestration. *Thorac Cardiovasc Surg.* (2008) 56:154–7. doi: 10.1055/s-2007-965572

4. Zhou H, Tang S, Fu Q, Yu L, Liu L. Hybrid surgery in treatment of pulmonary sequestration with abdominal aorta feeding vessel: a case report. *J Cardiothorac Surg.* (2018) 13:44. doi: 10.1186/s13019-018-0733-6

5. Borzelli A, Paladini A, Giurazza F, Tecame S, Giordano F, Cavaglià E, et al. Successful endovascular embolization of an intralobar pulmonary sequestration. *Radiol Case Rep.* (2018) 13:125–9. doi: 10.1016/j.radcr.2017.10.003

6. Qian X, Sun Y, Liu D, Wu X, Wang Z, Tang Y. Pulmonary sequestration: a case report and literature review. *Int J Clin Exp Med.* (2015) 8:21822–5.

7. Szmygin M, Pyra K, Sojka M, Jargiełło T. Successful endovascular treatment of intralobar pulmonary sequestration – an effective alternative to surgery. *Polish J Radiol.* (2021) 86:e112–4. doi: 10.5114/pjr.2021.103975

8. Gezer S, Taştepe I, Sirmali M, Findik G, Türüt H, Kaya S, et al. Pulmonary sequestration: a single-institutional series composed of 27 cases. *J Thorac Cardiovasc Surg.* (2007) 133:955–9. doi: 10.1016/j.jtcvs.2006.11.003

9. Bolca N, Topal U, Bayram S. Bronchopulmonary sequestration: radiologic findings. *Eur J Radiol.* (2004) 52:185–91. doi: 10.1016/j.ejrad.2004.03.005

10. Corbett HJ, Humphrey GM. Pulmonary sequestration. *Paediatr Respir Rev.* (2004) 5:59–68. doi: 10.1016/j.prrv.2003.09.009

11. Pikwer A, Gyllstedt E, Lillo-Gil R, Jönsson P, Gudbjartsson T. Pulmonary sequestration – a review of 8 cases treated with lobectomy. *Scand J Surg.* (2006) 95:190–4. doi: 10.1177/145749690609500312

12. Park ST, Yoon CH, Sung KB, Yoon HK, Goo DE, Kim KS, et al. Pulmonary sequestration in a newborn infant: treatment with arterial embolization. *J Vasc Int Radiol.* (1998) 9:648–50. doi: 10.1016/s1051-0443(98)70337-9

13. Leoncini G, Rossi UG, Ferro C, Chessa L. Endovascular treatment of pulmonary sequestration in adults using Amplatzer§vascular plugs. *Interact Cardiovasc Thorac Surg.* (2011) 12:98–100. doi: 10.1510/icvts.2010.246546

14. Hewett L, Kwon J, Adams JD, Denlinger CE, Klapper JA. Intralobar pulmonary sequestration with aneurysmal feeding vessel: use of hybrid surgical management. *Ann Thorac Surg.* (2016) 102:e533–5.

15. Sridhar P, Hardouin S, Cheng T, Farber A, Suzuki K, Jones DW. Endovascular exclusion and open resection of aberrant pulmonary artery aneurysm associated with intralobar pulmonary sequestration. *J Vasc Surg.* (2019) 70:1328–9. doi: 10.1016/j.jvs.2019.06.182

16. Sakai M, Ozawa Y, Konishi T, Watanabe A, Shiigai M. Endostapling the aberrant artery filled with embolized coils for intralobar pulmonary sequestration: a report of two cases. *J Thorac Dis.* (2018) 10:E304–8. doi: 10.21037/jtd.2018.04.21

17. Petty L, Joseph A, Sanchez J. Case report: pulmonary sequestration in an adult. *Radiol Case Rep.* (2018) 13:21–3. doi: 10.1016/j.radcr.2017.09.029

18. Guan Q, Li J, Deng K, Wu X, Tang S, Fan C, et al. Clinical study to individual treatment for major aortopulmonary collaterals of tetralogy of fallot. *Biomed Res Int.* (2019) 2019:1603712. doi: 10.1155/2019/1603712

19. Fan C, Cheng J, Wu S, Tang S, Chen W, Yang J. Pulmonary arteriovenous malformation detected by three-dimensional computed tomographic angiography. *Heart Lung Circ.* (2017) 26:e59–61. doi: 10.1016/j.hlc.2017.02.016

20. Cheng J, Fan C, Tang M, Shu Y, Yang J. Initial research on postoperative management of tetralogy of fallot with major aortopulmonary collaterals. *Cardiology.* (2016) 134:406–10. doi: 10.1159/000445046

21. Fan C, Zhou Z, Yin N, Yang J. Detection of pulmonary arteriovenous fistula with three-dimensional computed tomographic angiography. *Eur Heart J.* (2016) 37:3210. doi: 10.1093/eurheartj/ehv763

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 22 July 2022
DOI 10.3389/fcvm.2022.905189

OPEN ACCESS

EDITED BY
Xiaofeng Yang,
Temple University, United States

REVIEWED BY
Bernhard Maisch,
University of Marburg, Germany
Paul C. Tang,
University of Michigan, United States

*CORRESPONDENCE
Lun Li
allan7579@163.com

SPECIALTY SECTION
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 26 March 2022
ACCEPTED 23 June 2022
PUBLISHED 22 July 2022

CITATION
Li H and Li L (2022) Successful treatment of fulminant myocarditis with intra-aortic balloon pump counterpulsation combined with immunoglobulin and glucocorticoid in a young male adult. *Front. Cardiovasc. Med.* 9:905189. doi: 10.3389/fcvm.2022.905189

Successful treatment of fulminant myocarditis with intra-aortic balloon pump counterpulsation combined with immunoglobulin and glucocorticoid in a young male adult

Huanhuan Li and Lun Li*

Department of Cardiology, Wuhan Fourth Hospital, Wuhan, China

Background: Fulminant myocarditis (FM) is a serious non-specific inflammatory disease of the myocardium. FM tends to occur in adolescents and the course of the disease progresses rapidly. It is prone to cardiogenic shock (CGS) and multiple organ failure (MOF) with high mortality. We report a case of FM with CGS and MOF in a young male who was successfully treated with intra-aortic balloon pump counterpulsation (IABP) combined with intravenous immunoglobulin (IVIG) and glucocorticoid (GC).

Case summary: A 21-year-old previously healthy man presented with fever, headache, and chest tightness. He came to the hospital for emergency treatment. The laboratory data showed that the levels of serum cardiac troponin I (cTnI), N-terminal B-type natriuretic peptide (NT-proBNP), myocardial zymogram, and neutrophils increased. Echocardiography showed pericardial effusion and decreased left ventricular systolic function. ECG showed diffuse ST-segment elevation. He was clinically diagnosed with FM and admitted to the intensive care unit for treatment. Within 48 h of admission, the clinical course of the patient deteriorated rapidly, with CGS accompanied by MOF, high atrioventricular block (AVB), and ventricular tachycardia (VT). After using mechanical circulatory support (MCS) therapy with IABP, IVIG, GC, continuous renal replacement therapy (CRRT), and mechanical ventilation complicated with a temporary cardiac pacemaker, he recovered normal cardiac function. He made a full recovery and was discharged home on day 21.

Discussion: For patients with FM, early diagnosis, close monitoring, timely use of MCS devices, and active comprehensive treatment are very important. MCS devices such as IABP can become lifesaving tools for the treatment of FM.

KEYWORDS

fulminant myocarditis, intra-aortic balloon counterpulsation pump, immunoglobulin, glucocorticoid, cardiogenic shock, multiple organ failure, case report

Introduction

Fulminant myocarditis (FM) is a sudden and life-threatening myocardial disease, which is characterized by atypical clinical symptoms, rapid disease progression, and a high risk of death without timely treatment (1–3). Viral infection is the most common cause of FM (4). When FM occurs, the virus causes direct damage to the myocardium and a secondary immune response causes indirect damage to the myocardium. These cause rapid and serious damage to the heart, resulting in the rapid decline in cardiac function and serious hemodynamic disorders (5, 6). Mechanical circulatory support (MCS) devices are recommended for patients with FM with poor response to drug therapy (3, 7). We describe a young male FM case of cardiogenic shock complicated with multiple organ failure (MOF), which was successfully treated with intra-aortic balloon pump counterpulsation (IABP) combined with intravenous immunoglobulin (IVIG) and glucocorticoid (GC).

Case presentation

On 17 August 2018, a previously healthy 21-year-old man living in Wuhan developed fever, headache, and chest tightness after catching a cold, with a maximum temperature of 39.0°C. He also developed symptoms of dry cough, nausea and vomiting. He did not suffer from syncope, abdominal pain, diarrhea, jaundice, black stool, frequent urination, urgent urination, pain, and other discomforts. He went to the community hospital to see a doctor and was treated with mezlocillin, sulbactam, and diclofenac sodium. The symptoms of headache and chest tightness could not be relieved. At the same time, he had dyspnea and decreased activity. For further treatment, he came to Wuhan Fourth Hospital at 5 p.m. on 21 August 2018. He had no history of heart disease, no family history of heart disease, and no history of food or drug allergies. He did not smoke or drink alcohol and had not undergone any major surgery, trauma, blood transfusion, or intravenous drug abuse before onset.

In the emergency department, his vital signs and physical examination were as follows: body temperature (T) 38.4°C, respiratory rate (RR) 23 beats/min (bpm), blood pressure (BP) 106/72 mm Hg, pulse (P) 98 bpm, oxygen saturation (SpO_2) 98% (indoor air), pupil diameter 2 mm, and sensitive bilateral light reflex. No swelling of superficial lymph nodes is found in the whole body. The breath sounds of both the lungs were thick during auscultation and no dry and wet rales were heard. The heart rate (HR) was 98 bpm, the heart sound was low and dull, and there was no murmur in each valve area. The abdomen was flat and soft, the Murphy sign was negative, the liver, spleen, and subcostal were not reached, there was no edema in both the lower limbs, and the pathological sign was negative. Admission laboratory tests showed (**Supplementary Table 1**): leukocyte count 6.75 × 10^{Λ} 9/L, neutrophils 68.2%, lymphocytes 18.7%, eosinophils 0.3%, amylase 24 U/l, total bilirubin 27.6 μmol/l, direct bilirubin 13.3 μmol/l, blood potassium 3.5 mmol/l, creatinine 107.5 μmol/l, random blood glucose 7.51 mmol/l, cardiac troponin I (cTnI) 38.678 ng/ml, N-terminal B-type natriuretic peptide (NT-proBNP) 8,480 ng/ml, creatine kinase (CK) 1,203 U/l, creatine kinase-MB (CK-MB) 55 U/l, lactate dehydrogenase (LDH) 406 U/l, alanine aminotransferase (ALT) 21 U/l, aspartate aminotransferase (AST) 114 U/l, and procalcitonin (PCT) 0.47 ng/ml. ECG showed: sinus rhythm, right bundle branch block, and ST-segment elevation in leads II, III, aV_F, and V_2–V_6 (diffuse) (**Figure 1A**). Transthoracic echocardiography showed pericardial effusion [the maximum anterior–posterior diameter of the posterior dark area of the left ventricular posterior wall was 0.8 cm (**Figure 2A**), the maximum anterior–posterior diameter of the dark area of the left ventricular inferior wall was 1.2 cm (**Figure 2B**), and the anterior–posterior diameter of the dark area of the xiphoid process was 2.5 cm (**Figure 2C**)] and the left ventricular systolic function decreased [left ventricular ejection fraction (LVEF) = 42%]. Brain CT showed no abnormality. Chest CT showed a few fibrous foci in both the lungs (**Figure 2G**). Massive pericardial effusion and blurred pericardial fat space are also present, considering the possibility of inflammatory lesions (**Figure 2J**). Abdominal CT showed intrahepatic bile duct calculi.

As a result of these clinical findings, he was suspected of being diagnosed with FM and was admitted to the intensive care unit. Anti-infective (piperacillin and sulbactam) and antiviral (astragalus and oseltamivir) treatments were given; vitamin C and coenzyme Q10 were started to be taken. Then, we screened the viruses that may cause myocarditis, namely, coxsackievirus (CV) B3, CV B5, enterovirus, and cytomegalovirus, which were negative. The antimyocardial virus antibody test was negative. Other viral screening tests, such as hepatitis antibody, HIV antibody, and syphilis antibody, were negative (**Supplementary Table 1**).

His clinical course was as follows (**Figure 3**). His body temperature gradually decreased 24 h after admission, but he still had headache, nausea, and vomiting. The output was significantly less than the input. The vital signs monitoring showed that: temperature 36.5°C, RR 24 bpm, BP 90/60 mm Hg, HR 110 bpm, and SpO_2 92% (nasal catheter oxygen inhalation). The results of myocardial zymogram and cardiac injury markers increased further: cTnI 36.2786 ng/ml, NT-proBNP 13,427 ng/ml, CK 1,694 U/l, CK-MB 90 U/l, LDH 491 U/l, ALT 47 U/l, AST 154 U/l, creatinine 102.3 μmol/l, total bilirubin 25 μmol/l, direct bilirubin 11.6 μmol/l, PCT 0.6 mg/dl, and arterial blood gas [pH 7.46, partial pressure of arterial carbon dioxide ($PaCO_2$) 29 mm Hg, partial pressure of arterial oxygen (PaO_2) 268 mm Hg, bicarbonate (HCO_3^-) 20.6 mmol/l, alkali residue (BE^-) 2.2, and lactic acid (Lac) 2.1 mmol/l]. Combined with laboratory examination, FM combined with

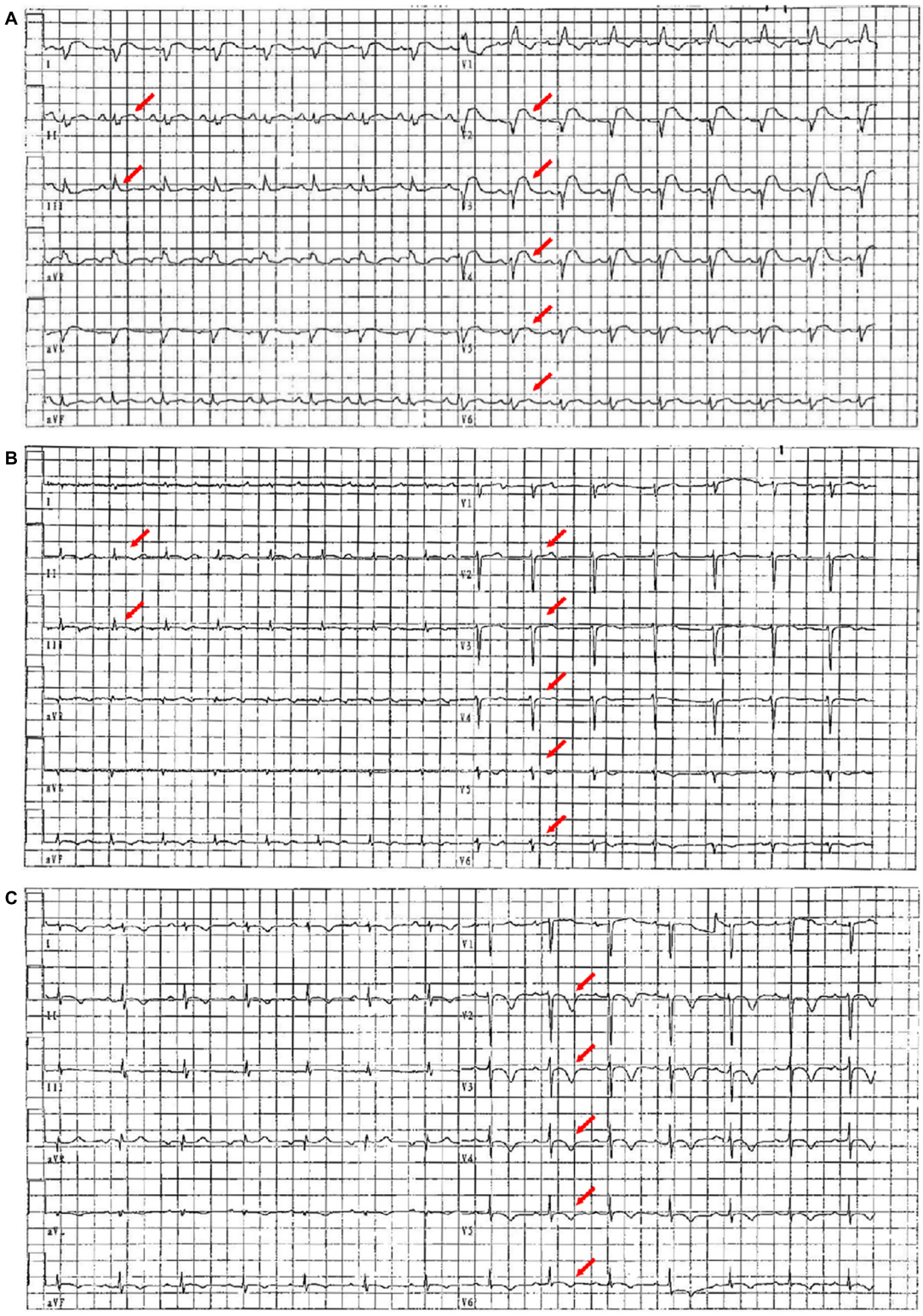


FIGURE 1
ECG images on the first day, the seventh day, and the 20th day of admission. **(A)** On the first day of admission, ECG showed sinus rhythm, right bundle branch block, and diffuse ST-segment elevation (red arrow). **(B)** On the seventh day of admission, ECG showed sinus rhythm and diffuse ST-segment elevation that improved significantly (red arrow). **(C)** On the 20th day of admission, ECG showed sinus rhythm with extensive anterior wall T-wave inversion (red arrow).

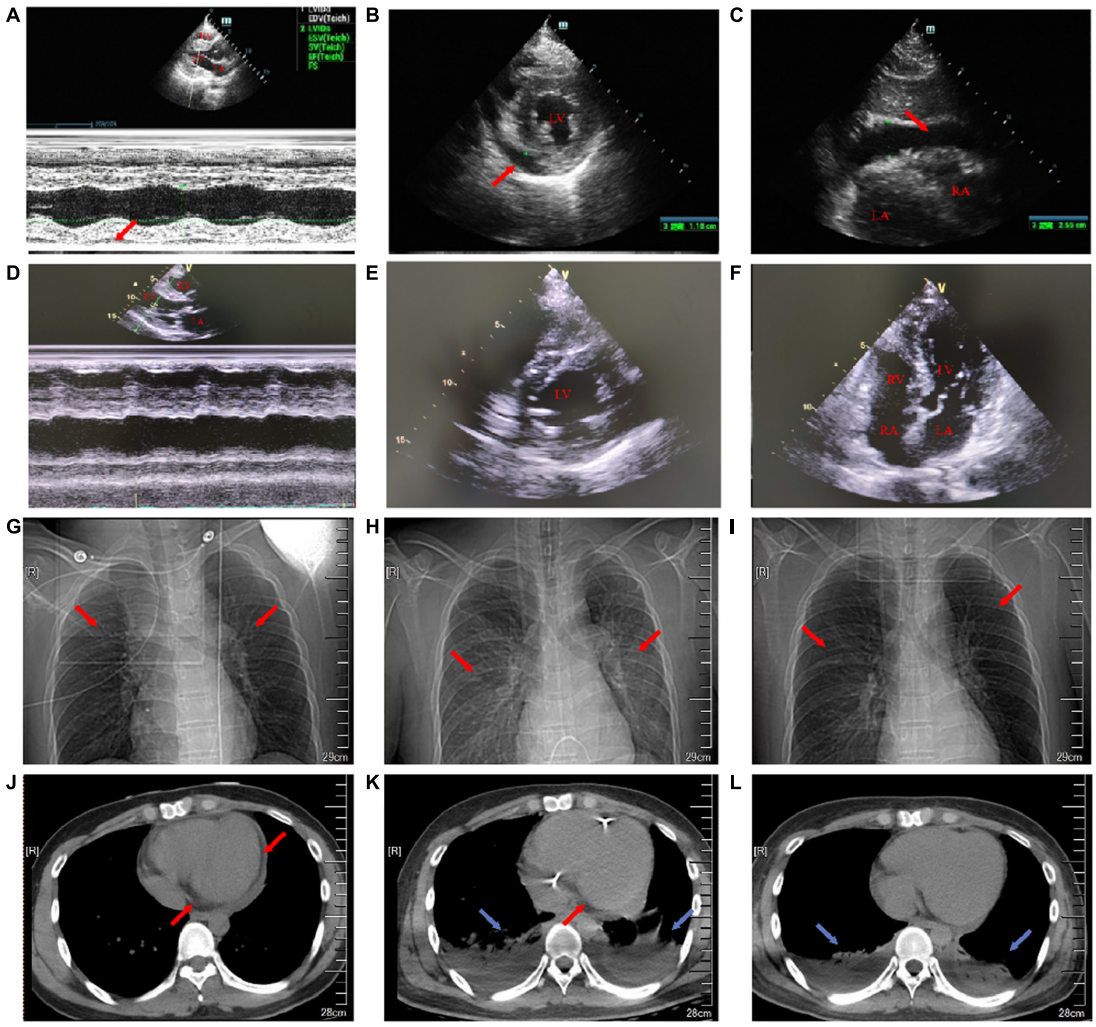


FIGURE 2
Transthoracic echocardiography on the first day and the 18th day of admission. Chest X-ray and chest CT images on the first, eighth, and 15th day of admission. **(A)** On the first day of admission, the maximum anterior–posterior diameter of the posterior dark area of the left ventricular posterior wall on the long-axis view of transthoracic echocardiography was 0.8 cm (red arrow). **(B)** On the first day of admission, the maximum anterior–posterior diameter of the dark area of the lower wall of the left ventricle on the short-axis view of transthoracic echocardiography was 1.2 cm (red arrow). **(C)** On the first day of admission, transthoracic echocardiography showed that the anterior–posterior diameter of the dark area under the xiphoid process was 2.5 cm (red arrow). **(D)** On the 18th day after admission, the pericardial effusion on the long-axis view of transthoracic echocardiography was less than that before. **(E)** On the 18th day after admission, the pericardial effusion on the short-axis view of transthoracic echocardiography was less than that before. **(F)** On the 18th day of admission, transthoracic echocardiography four-chamber view. **(G)** On the first day of admission, a chest X-ray showed a few fibrous foci in both the lungs (red arrow). **(H)** On the eighth day of admission, the chest X-ray showed inflammation in the upper lobe of the left lung and the middle lobe of the right lung (red arrow). **(I)** On the 15th day of admission, the chest X-ray showed a little inflammation of the left upper lung (red arrow). **(J)** On the first day of admission, the cross-section of the chest CT soft-tissue window showed that the pericardial fat space was blurred and there was a large amount of pericardial effusion (red arrow). **(K)** On the eighth day of admission, the cross-section of the chest CT soft-tissue window showed bilateral pleural effusion with bilateral lower lung insufficiency (blue arrow) and a small amount of pericardial effusion (red arrow). **(L)** On the 15th day of admission, the cross-section of the chest CT soft-tissue window showed bilateral pleural effusion and bilateral lower lung insufficiency (blue arrow).

acute left heart failure and upper respiratory tract infection was considered. Non-invasive ventilator-assisted respiration (continuous positive airway pressure under 12 cm H_2O to maintain adequate tissue oxygenation) was given and circulating agonists (dopamine 7.5 μg/kg/min) were added to maintain blood pressure. At the same time, IVIG (40 g/day in the first 2 days and gradually decrease in the next few days) and intravenous GC (200 mg/day of methylprednisolone in the first 3 days and gradually decreasing in the next few days) treatment started. Furosemide was injected intravenously to optimize intravascular volume.

On the 42nd h of admission, he developed irritability, panting, sitting up, and breathing and the output was still less than the intake. Physical examination suggested: temperature

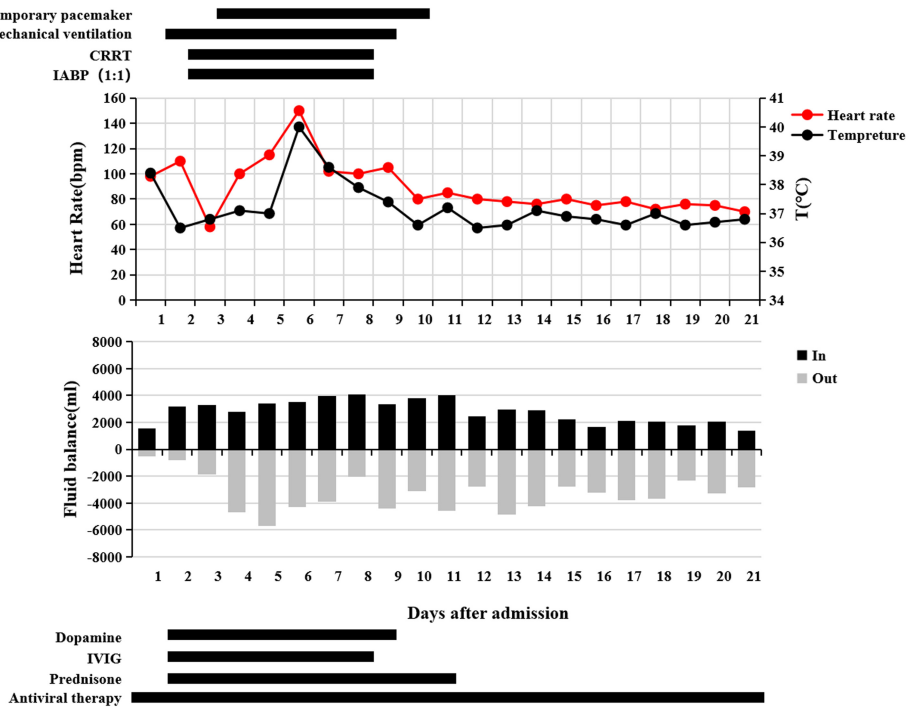


FIGURE 3
Clinical course of the patient during 21 days of hospitalization. Heart rate and body temperature changes. Daily liquid inflow and outflow. Use mechanical support therapy and medication.

36.8°C, RR 36 bpm, BP 90/42 mm Hg (maintained by 10 μg/kg/min of dopamine), HR 118 bpm, SpO_2 90% (non-invasive ventilator-assisted respiration), low respiratory sounds in both the lungs, and audible moist rales. Laboratory tests became worse: NT-proBNP 16,163 ng/ml, CK 1,809 U/l, CK-MB 110 U/l, LDH 1,469 U/l, ALT 47 U/l, AST 154 U/l, and the level of anaerobic metabolism in arterial blood is very high (pH 7.20, $PaCO_2$ 26 mm Hg, PaO_2 73 mm Hg, HCO_3^- 10.2 mmol/l, BE^- 13.6, and Lac 10.9 mmol/l). Echocardiography showed pericardial effusion (small to medium volume, the maximum anterior–posterior diameter of the dark area of the lower wall of the left ventricle was 2.0 cm, and the anterior–posterior diameter of the dark area of the inferior xiphoid process was 1.0 cm) and the left ventricular systolic function decreased further (LVEF = 38%). Color Doppler ultrasound of the thoracic cavity showed bilateral pleural effusion (5.9 cm on the left and 6.8 cm on the right). Surgical pericardium and pleural puncture were not performed because there was no safe puncture space. The patient was considered to have CGS combined with MOF and had a poor response to vasoactive drugs. After obtaining informed consent, we immediately gave IABP (counterpulsation pressure 110 mm Hg, counterpulsation ratio 1:1), continuous renal replacement therapy (CRRT), and endotracheal intubation with ventilator-assisted respiration (continuous positive airway pressure under 15 cm H_2O to maintain sufficient tissue oxygenation) and then the upper gastric tube was given to ensure intestinal nutrition. He developed Adams–Stokes syndrome during CRRT and developed a third-degree atrioventricular block (AVB) after rescue. We gave him temporary pacemaker implantation. Continuous administration of heparin through an infusion pump maintained an activated partial thrombin time of 70–100 s to prevent left ventricular thrombosis. Intermittent transfusion ensured that a hemoglobin level was greater than 90 g/l.

The subsequent days of treatment were maintained using a combination of IABP, CRRT, mechanical ventilation, a temporary pacemaker, and drug support. The patient's body temperature was normal, the urine output also continued to increase, and the water balance gradually tended to be negative (**Figure 3**). Cardiac injury markers such as cTnI (**Figure 4A**), NT-proBNP (**Figure 4B**), and myocardial zymogram tended to improve (**Figures 4C,D**), leukocyte count (**Figure 4E**), liver function (**Figure 4F**), and renal function (**Figure 4G**). Echocardiography indicates gradual improvement of LVEF (**Figure 4H**) and the level of anaerobic metabolism in arterial blood decreased (pH 7.40, $PaCO_2$ 30 mm Hg, PaO_2 77 mm Hg, HCO_3^- 18.6 mmol/l, BE^- 5.4, and Lac 5.0 mmol/l).

On the sixth day of admission, the patient had a fever again, with a temperature of 40.0°C. Three cases of ventricular tachycardia (VT) and ventricular fibrillation were corrected by electrocardiography and amiodarone.

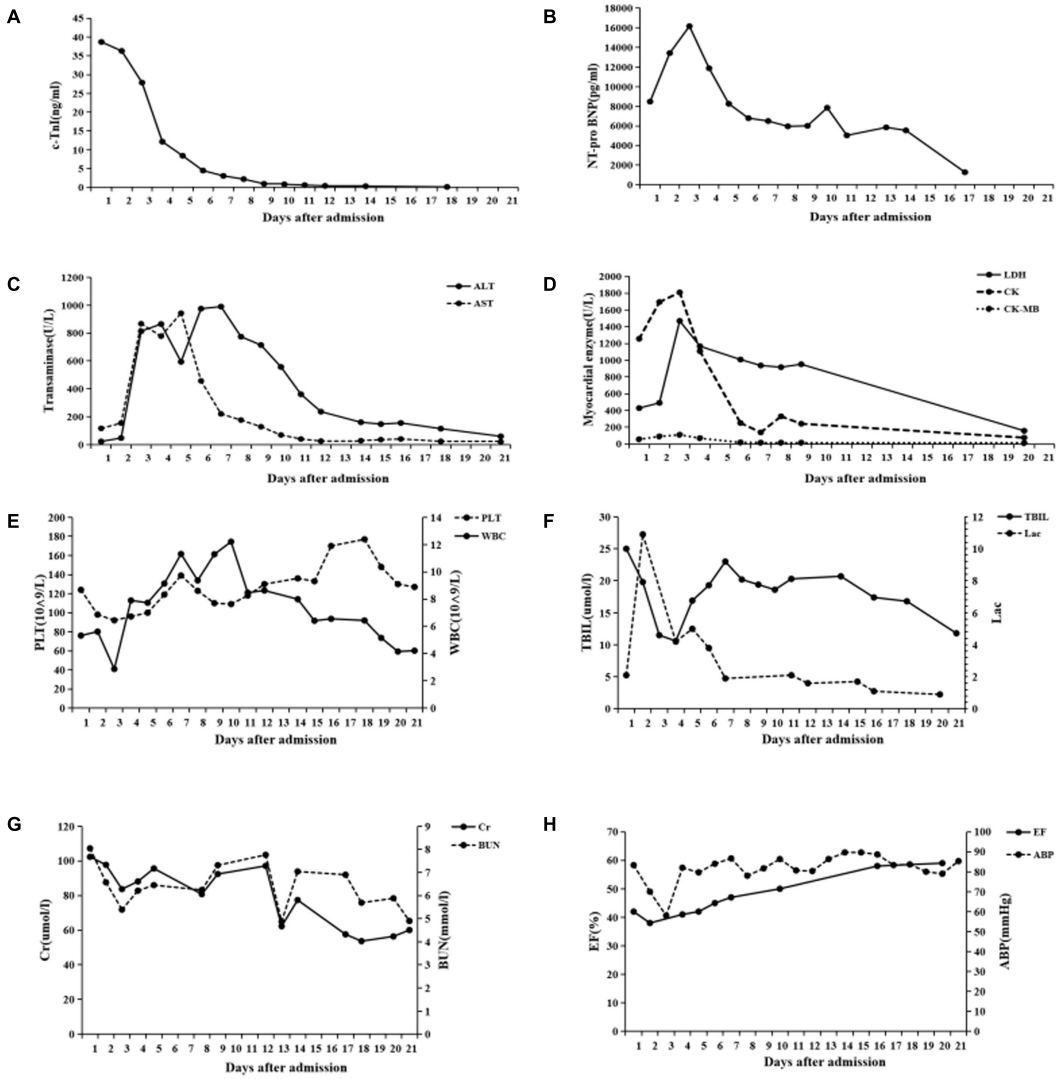


FIGURE 4
Changes of various indexes during 21 days of hospitalization. **(A)** cTnI. **(B)** NT-pro BNP. **(C)** ALT and AST. **(D)** Myocardial zymogram. **(E)** Platelet (PLT) and leukocyte count (WBC). **(F)** Total bilirubin (TBIL) and arterial blood gas lactate (Lac) levels. **(G)** Creatinine (Cr) and blood urea nitrogen (BUN). **(H)** Ejection fraction (EF) and average blood pressure (ABP) in transthoracic echocardiography.

On the seventh day of admission, the patient's body temperature decreased and the level of anaerobic metabolism in arterial blood further decreased (pH 7.43, $PaCO_2$ 33 mm Hg, PaO_2 90 mm Hg, HCO_3^- 21.9 mmol/l, BE^- 1.9, and Lac 1.9 mmol/l), suggesting that organ perfusion was improved and relevant laboratory indexes tended to be improved (**Figure 4**). ECG showed that sinus rhythm and diffuse ST-segment elevation were significantly improved (**Figure 1B**). Echocardiography showed that the pericardial effusion decreased gradually (less to medium, the maximum anterior–posterior diameter of the dark area of the lower wall of the left ventricle was 0.8 cm) and the left ventricular systolic function was higher than that of front (LVEF = 47%). Color Doppler ultrasound of the thoracic cavity showed bilateral pleural effusion (2.6 cm on the left and 4.3 cm on the right). Brain CT showed no abnormality. Chest CT showed inflammation in the upper lobe of the left lung and the middle lobe of the right lung (**Figure 2H**), bilateral pleural effusion and bilateral lower lung insufflation (**Figure 2K**), and a small amount of pericardial effusion. Abdominal CT showed changes in peritoneal exudation and pelvic effusion. Considering the reduced demand for mechanical support, they stopped CRRT support.

On the ninth day of admission, IABP was pulled out, endotracheal intubation was pulled out, and ventilator treatment was stopped. The patient had no wheezing, dyspnea, and chest tightness. Physical examination showed: temperature 37.4°C, RR 19 bpm, BP 95/52 mm Hg, HR 105 bpm, SpO_2 97%

(nasal catheter oxygen inhalation), the low respiratory sound of both the lungs, and no dry and wet rales. The rest of the physical examination is the same as before. Stop vasoactive pressor drugs and start using low-dose β-receptor blockers (metoprolol 12.5 mg/day) that were used to prevent heart failure and VT.

On the tenth day of admission, the temporary pacemaker and gastric tube were removed. Low doses of angiotensin converting enzyme inhibitors (Astat 2 mg) were added to prevent ventricular remodeling. Subsequently, the patient gradually received active physical rehabilitation and comprehensive oral nutrition.

Before discharge, the patient's body temperature was normal and there was no discomfort such as headache and chest tightness. Re-examination of ECG suggested sinus rhythm and ST-T changes (**Figure 1C**). Echocardiography indicated that the size of each cardiac cavity was normal, the movement of the ventricular wall was normal, and the ventricular systolic function was normal (LVEF = 59%) (**Figures 2D–F**). The patient's chest CT showed little inflammation in the upper left lung (**Figure 2I**), bilateral pleural effusion, and bilateral lower lung insufficiency (**Figure 2L**). He was discharged from the hospital on the 21st day of admission and returned home without apparent complications. During the 3-year follow-up period, he had no deterioration of cardiac function, recurrent myocarditis, congestive heart failure, or episodes of ventricular arrhythmias.

During the 21 days of hospitalization, to determine the microbial cause of fever, blood culture, urine culture, stool culture, and fungal D-glucan test were negative and there were no signs of elevated eosinophils and lymphocytes. However, we did not perform an endomyocardial biopsy (EMB) and coronary angiography (CAG) because we failed to obtain the consent of the patient. Due to claustrophobia, the patient failed to undergo a cardiac MR examination. He was diagnosed as an FM case with CGS and MOF.

Discussion

The precursor symptoms of FM, such as fatigue, fever, cough, dyspnea, and chest pain, are usually not significantly different from the common cold (8). The condition deteriorates rapidly within 2 days to 2 weeks after the onset of prodromal symptoms, namely, severe heart failure, refractory arrhythmia, CGS, and MOF. Hemodynamic disorders need to be treated with vasoactive drugs and MCS devices (6, 9). Studies have shown that in adult patients, FM accounts for about 10% of all the cases of myocarditis, but the mortality rate is more than 50% (10, 11). These characteristics make an early diagnosis, close monitoring, and comprehensive treatment that are very important in the diagnosis and treatment of FM.

The most common causes of FM are viral infections, namely, adenovirus and enterovirus (common CV B serotype) (12–14), cytomegalovirus (15, 16), herpes simplex virus (17), parvovirus B19 (18), H1N1 influenza virus (19), and HIV (20). Due to the lack of specificity and sensitivity, negative serological results cannot exclude possible viral infections. Antiviral therapy is still an important part of FM therapy. Evidence showed that early use of antiviral drugs in patients with viral myocarditis caused by H1N1 could reduce mortality and have a better prognosis (21). Some case reports have shown that antiviral drugs such as oseltamivir and zanamivir had encouraging therapeutic effects (22, 23). The Chinese Society of Cardiology recommended that antiviral treatment can be started as soon as possible for patients with FM (3). In this case, we continued antiviral treatment.

The European Society of Cardiology (ESC) guidelines recommend that the detection of the virus genome by PCR through EMB should be used as the gold standard for the diagnosis of myocarditis (4). EMB could be used to determine specific myocarditis types (such as lymphocytic myocarditis, giant cell myocarditis, and eosinophilic myocarditis) and ruled out cardiac sarcoid, which is of guiding significance for the selection of treatment plan and prognosis of FM (24, 25). A multicenter study showed that only 38% of patients with myocarditis were able to find the viral genome in their EMB samples (26). EMB was at risk of arrhythmia and ventricular perforation due to invasive procedures (27). In this case, due to unstable hemodynamics and lack of available facilities and clinical experience in the early stage of the disease, we decided not to conduct EMB. After the disease was stable, the patient refused to undergo EMB. The ESC myocardial and pericardial disease working group recommends that all the patients with clinically suspected myocarditis should consider CAG. Especially, in the case of CGS, CAG can help guide management strategies (28). In this case, CAG was not performed. The patient had no typical cardiovascular risk factors, no previous history of cardiovascular disease, and extracardiac causes that could explain the symptoms. His left ventricular systolic function and cTnI returned to normal without coronary intervention. In this case, even without available EMB and CAG results, the patient's clinical manifestations met the diagnostic criteria of FM (ECG/cTnI/echocardiography) (29).

In patients with FM with CGS, appropriate vasopressor and mechanical ventilation can ensure adequate perfusion pressure and oxygenation (7). For patients with FM with poor drug treatment effect, it is recommended to use a temporary MCS support device in time (30). The main purpose of using a temporary MCS support device is to prevent multiple organ dysfunction and death through biventricular unloading, ensure systemic and coronary perfusion and venous dredging, and provide a safe bridge for rehabilitation or durable auxiliary device implantation (31). The most common temporary MCS implantation devices are IABP and venous arterial extracorporeal membrane oxygenator (VA-ECMO)

with peripheral cannula (32, 33). IABP inflates and deflates synchronously with systolic and diastolic rhythm through the balloon, which can reduce left ventricular afterload and increase blood flow to the brain and kidney. Compared with the total circulation demand, IABP can provide about 15% additional circulation support. It is the most commercial MCS device for the treatment and the first-line device recommended by some researchers (34, 35). Low-dose inotropic drugs and vasodilators and/or IABP implantation are the most common strategies to reduce cardiac afterload. If IABP cannot sufficiently improve the cycle, VA-ECMO should be considered immediately. VA-ECMO is the preferred temporary MCS option when oxygenation is poor. VA-ECMO can ensure rapid and comprehensive cardiopulmonary assistance. It is an effective method to restore cardiac output and organ perfusion in patients with FM (36). However, VA-ECMO may lead to left ventricular overload and dilation. The increase of left ventricular end-diastolic pressure can reduce coronary blood flow and cause a cardiac electrical storm (37). Therefore, VA-ECMO is best used in combination with IABP, especially for those patients with CGS whose cardiac index is less than 2 l/min/m^2 or whose blood lactic acid is more than 2 mmol/l. IABP can decrease left ventricular afterload and increase coronary blood flow (38). According to previous reports, the median duration of ECMO was 5–9 days and the therapeutic discharge rate was 55–66% (30, 33, 39). After VA-ECMO implantation, bedside echocardiography was performed everyday to determine whether the ventricular systolic function was restored. Trials of discontinuation could be carried out once there was lasting evidence of cardiac recovery (40, 41). If the cardiac function of patients with FM cannot improve, no matter how many days VA-ECMO supports, durable MCS such as HeartMate II, Heartware HAVAD, and HeartMate 3 LV assist device (VAD) should be considered for treatment. VAD is beneficial to reduce left ventricular load and is a better device to prevent and improve MOF, including liver failure (42, 43). Relevant studies suggested that VAD should be used to replace VA-ECMO when the bilirubin cases rapidly reached more than 3.0 mg/dl (44). In this case, CGS and hypoxia were gradually relieved after using IABP combined with mechanical ventilation and an echocardiographic indication of EF did not decrease further. VA-ECMO was not used.

Whether to use IVIG and steroids in FM is controversial. The position statement of the ESC suggested that immunosuppression therapy should not be started until EMB eliminates viral infection by PCR (4). Studies had shown that early immunosuppression of FM might be the key to hindering the inflammatory process and reduced in-hospital mortality (45, 46). IVIG could eliminate myocardial virus infection faster by targeting specific virus antibodies and reduce cardiac inflammation by regulating the immune response. In the animal model of viral myocarditis, the free immunoglobulin light chain showed antiviral and anti-inflammatory effects, which supported the clinical application of IVIG (47). IVIG could be used for lymphocytic myocarditis in children (48). Several studies have reported that IVIG treatment was effective in the treatment of acute myocarditis and FM (49–51). High-dose intravenous IVIG could significantly improve LVEF and left ventricular end-diastolic diameter (LVEDD) in adult patients with acute myocarditis and FM, reduce the incidence of ventricular tachycardia or fibrillation, and reduce mortality (52–54). Some studies suggested that due to GC-induced immunosuppression, virus infection might worsen and spread and adult lymphocyte FM was a contraindication to immunosuppression (55, 56). A meta-analysis published in 2013 showed that there was no increase in viral replication or disease severity in patients with viral myocarditis treated with GC (57). At the same time, in patients with inflammatory cardiomyopathy and myocarditis with persistent PVB19, the use of immunosuppressive drugs did not aggravate virus replication (58). Studies have shown that the use of GC reduced virus titer by stimulating interferon secretion. In some cases of myocarditis, patients responded well to GC treatment (46, 59). These were evidence of the safety of GC in the treatment of FM. The American Heart Association recently said that if there is a high suspicion of immune-mediated FM, 1 g of methylprednisolone can be taken urgently before biopsy diagnosis or further diagnostic test (7). Ammirati et al. (60) proposed that the combination of immune regulation and MCS using IVIG and GC in FM could help improve circulatory dysfunction and reduce cytokine storm. In this case, we clinically diagnosed the patient as FM, started IVIG and GC treatment for the first time, and the patient responded well to the treatment. It is necessary to carry out large-scale prospective studies to explore the role of immunosuppression in acute and FM, so as to provide evidence for standardized treatment.

In this case, the patient had obvious precursor symptoms of the upper respiratory tract or gastrointestinal virus infection and the symptoms of severe heart failure (rapid deterioration of LVEF and new conduction block) occurred rapidly within 2 weeks of onset. The development of hemodynamic damage was rapid, which required positive inotropic drugs and temporary MCS device implantation support. During hospitalization, his blood bacterial culture and fungal test results were always negative, excluding bacterial or fungal myocarditis. Because eosinophil levels did not rise during hospitalization, he was also less likely to have eosinophilic myocarditis. His left ventricular systolic function and cTnI returned to normal without coronary intervention, which suggests that his myocardial injury was not caused by acute myocardial infarction. Combined with an auxiliary examination (ECG/serum troponin/echocardiography), the patient met the diagnosis of FM. For this FM case, we believe that IABP implantation combined with IVIG, GC, CRRT, and mechanical ventilation is the key to successful treatment.

Conclusion

For young patients with a history of proinfection and no basis of heart disease, who develop heart failure in a short time, doctors should consider the possibility of FM and improve ECG, echocardiography, and blood biochemical examination as soon as possible. Once FM is suspected, we should be alert to the deterioration of symptoms and hemodynamics caused by acute heart failure or CGS. If there are early signs of circulatory failure, it is recommended to transfer to a tertiary medical center with MCS devices and multidisciplinary teams as soon as possible. The improvement of EMB and CAG has a guiding significance for the treatment and differential diagnosis of FM classification. After the diagnosis of FM, actively use antiviral drugs and drugs to improve circulation. Immunosuppressants can be considered. MCS devices such as IABP are recommended as early as possible before the onset or progression of MOF to maintain stable hemodynamics and perfusion of vital organs. If temporary MCS is invalid, VAD therapy and heart transplantation should be actively considered. Temporary MCS can serve as a bridge for resuscitation or heart transplant transport. The prognosis of patients with FM can be improved by carrying out individualized comprehensive treatment to help patients with FM successfully overcome the acute stage.

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.

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

HL and LL made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all the aspects of the manuscript. Both authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Foundation of Wuhan, Hubei Province, China (grant no. WX21Q35).

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.905189/full#supplementary-material

References

1. Ammirati E, Veronese G, Cipriani M, Moroni F, Garascia A, Brambatti M, et al. Acute and fulminant myocarditis: a pragmatic clinical approach to diagnosis and treatment. *Curr Cardiol Rep.* (2018) 20:114. doi: 10.1007/s11886-018-1054-z

2. Maisch B, Ruppert V, Pankuweit S. Management of fulminant myocarditis: a diagnosis in search of its etiology but with therapeutic options. *Curr Heart Fail Rep.* (2014) 11:166–77. doi: 10.1007/s11897-014-0196-6

3. Wang D, Li S, Jiang J, Yan J, Zhao C, Wang Y, et al. Chinese society of cardiology expert consensus statement on the diagnosis and treatment of adult fulminant myocarditis. *Sci China Life Sci.* (2019) 62:187–202. doi: 10.1007/s11427-018-9385-3

4. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European society of cardiology working group on myocardial and pericardial diseases. *Eur Heart J.* (2013) 34:2636–48. doi: 10.1093/eurheartj/eht210

5. Yajima T. Viral myocarditis: potential defense mechanisms within the cardiomyocyte against virus infection. *Future Microbiol.* (2011) 6:551–66. doi: 10.2217/fmb.11.40

6. Gupta S, Markham DW, Drazner MH, Mammen PP. Fulminant myocarditis. *Nat Clin Pract Cardiovasc Med.* (2008) 5:693–706. doi: 10.1038/ncpcardio1331

7. Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American heart association. *Circulation.* (2020) 141:e69–92. doi: 10.1161/CIR.0000000000000745

8. Wang Z, Wang Y, Lin H, Wang S, Cai X, Gao D. Early characteristics of fulminant myocarditis vs non-fulminant myocarditis: a meta-analysis. *Medicine.* (2019) 98:e14697. doi: 10.1097/MD.0000000000014697

9. Schubert S, Opgen-Rhein B, Boehne M, et al. Severe heart failure and the need for mechanical circulatory support and heart transplantation in pediatric patients with myocarditis: results from the prospective multicenter registry "MYKKE". *Pediatr Transplant.* (2019) 23:e13548. doi: 10.1111/petr.13548

10. McCarthy RR, Boehmer JP, Hruban RH, Weigelt A, Wagner R, Muller G, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med.* (2000) 342:690–5. doi: 10.1111/petr.13548

11. Lee EY, Lee HL, Kim HT, Lee HD, Park JA. Clinical features and short-term outcomes of pediatric acute fulminant myocarditis in a single center. *Kor J Pediatr.* (2014) 57:489–95. doi: 10.3345/kjp.2014.57.11.489

12. Peretto G, Sala S, Della BP. Diagnostic and therapeutic approach to myocarditis patients presenting with arrhythmias. *G Ital Cardiol.* (2020) 21:187–94. doi: 10.1714/3306.32767

13. Seko Y, Shinkai Y, Kawasaki A, Yagita H, Okumura K, Yazaki Y. Evidence of perforin-mediated cardiac myocyte injury in acute murine myocarditis caused by Coxsackie virus B3. *J Pathol.* (1993) 170:53–8. doi: 10.1002/path.1711700109

14. Iwasaki T, Monma N, Satodate R, Segawa I, Oyama K, Kawana R, et al. Myocardial lesions by Coxsackie virus B3 and cytomegalovirus infection in infants. *Heart Vessels Suppl.* (1985) 1:167–72. doi: 10.1007/BF02072386

15. Roubille C, Brunel AS, Gahide G, Vernhet KH, Le Quellec A. Cytomegalovirus (CMV) and acute myocarditis in an immunocompetent patient. *Intern Med.* (2010) 49:131–3. doi: 10.2169/internalmedicine.49.2313

16. Vanstechelman F, Vandekerckhove H. Cytomegalovirus myocarditis in an immunocompetent patient. *Acta Cardiol.* (2012) 67:257–60. doi: 10.1080/ac.67.2.2154221

17. Fukae S, Ashizawa N, Morikawa S, et al. A fatal case of fulminant myocarditis with human herpesvirus-6 infection. *Intern Med.* (2000) 39:632–6.

18. Spartalis M, Tzatzaki E, Spartalis E, et al. Parvovirus B19 Myocarditis of Fulminant Evolution. *Cardiol Res.* (2017) 8:172–5. doi: 10.14740/cr580w

19. Lobo ML, Taguchi A, Gaspar HA, Yano K. Fulminant myocarditis associated with the H1N1 influenza virus: case report and literature review. *Rev Bras Ter Intensiva.* (2014) 26:321–6. doi: 10.2169/internalmedicine.39.632

20. Aletti M, Lecoules S, Kanczuga V, Soler C, Maquart M, Simon F, et al. Transient myocarditis associated with acute Zika virus infection. *Clin Infect Dis.* (2017) 64:678–9. doi: 10.1093/cid/ciw802

21. Rodriguez A, Alvarez-Rocha L, Sirvent JM, Zaragoza R, Nieto M, Arenzana A, et al. Recommendations of the INFECTIOUS DISEASES WORK GROUp (GTEI) of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) and the Infections in Critically Ill Patients Study Group (GEIPC) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) for the diagnosis and treatment of influenza A/H1N1 in seriously ill adults admitted to the Intensive Care Unit. *Med Intensiva.* (2012) 36:103–37. doi: 10.1016/j.medin.2011.11.020

22. Mazzitelli M, Garofalo E, Bruni A, Barreca GS, Quirino A, Giancotti A, et al. Severe myocarditis due to influenza A(H1N1)pdm09 viral infection in a young woman successfully treated with intravenous zanamivir: a case report. *Clin Case Rep.* (2019) 7:2336–40. doi: 10.1002/ccr3.2499

23. Morioka I, Nonoyama S, Tanaka-Taya K, Ihara T, Sugaya N, Ueta I, et al. Survey of Japanese infants younger than 3 months who were treated with oseltamivir for influenza: safety of oseltamivir treatment. *Scand J Infect Dis.* (2012) 44:605–9. doi: 10.3109/00365548.2012.669844

24. Murphy L, McGuckin M, Giblin G, Keogh A, McGovern B, Fabre A, et al. The role of endomyocardial biopsy in suspected myocarditis in the contemporary era: a 10-year National Transplant Centre experience. *Cardiovasc Pathol.* (2021) 54:107366. doi: 10.1016/j.carpath.2021.107366

25. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation.* (2007) 116:2216–33. doi: 10.1161/CIRCULATIONAHA.107.186093

26. Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, McCarthy R, et al. Detection of viruses in myocardial tissues by polymerase chain reaction. evidence of adenovirus as a common cause of myocarditis in children and adults. *J Am Coll Cardiol.* (2003) 42:466–72. doi: 10.1016/s0735-1097(03)00648-x

27. Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol.* (1992) 19:43–7. doi: 10.1016/0735-1097(92)90049-s

28. Pankuweit S, Maisch B. Etiology, diagnosis, management, and treatment of myocarditis. Position paper from the ESC working group on myocardial and pericardial diseases. *Herz.* (2013) 38:855–61. doi: 10.1007/s00059-013-3988-7

29. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J.* (2019) 40:237–69. doi: 10.1093/eurheartj/ehy462

30. Asaumi Y, Yasuda S, Morii I, Kakuchi H, Otsuka Y, Kawamura A, et al. Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. *Eur Heart J.* (2005) 26:2185–92. doi: 10.1093/eurheartj/ehi411

31. Esposito ML, Kapur NK. Acute mechanical circulatory support for cardiogenic shock: the "door to support" time. *F1000Res.* (2017) 6:737. doi: 10.12688/f1000research.11150.1

32. Okai I, Inoue K, Maruyama M, Maruyama S, Komatsu K, Nishizawa H, et al. Transbrachial intra-aortic balloon pumping for a patient with fulminant myocarditis. *Heart Vessels.* (2012) 27:639–42. doi: 10.1007/s00380-012-0231-z

33. Lorusso R, Centofanti P, Gelsomino S, Barili F, Di Mauro M, Orlando P, et al. Venoarterial extracorporeal membrane oxygenation for acute fulminant myocarditis in adult patients: a 5-year multi-institutional experience. *Ann Thorac Surg.* (2016) 101:919–26. doi: 10.1016/j.athoracsur.2015.08.014

34. Unverzagt S, Buerke M, de Waha A, Haerting J, Pietzner D, Seyfarth M, et al. Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock. *Cochr Datab Syst Rev.* (2015) 2015:D7398.

35. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* (2012) 367:1287–96. doi: 10.1056/NEJMoa1208410

36. Nakamura T, Ishida K, Taniguchi Y, Nakagawa T, Seguchi M, Wada H, et al. Prognosis of patients with fulminant myocarditis managed by peripheral venoarterial extracorporeal membranous oxygenation support: a retrospective single-center study. *J Intens Care.* (2015) 3:5. doi: 10.1186/s40560-014-0069-9

37. Israel CW, Manegold JC. Electrical storm: definition, prevalence, causes and prognostic implications. *Herzschrittmacherther Elektrophysiol.* (2014) 25:59–65. doi: 10.1007/s00399-014-0321-y

38. Stretch R, Sauer CM, Yuh DD, Bonde P. National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis. *J Am Coll Cardiol.* (2014) 64:1407–15. doi: 10.1016/j.jacc.2014.07.958

39. Hsu KH, Chi NH, Yu HY, Wang CH, Huang SC, Wang SS, et al. Extracorporeal membranous oxygenation support for acute fulminant myocarditis: analysis of a single center's experience. *Eur J Cardiothorac Surg.* (2011) 40:682–8. doi: 10.1016/j.ejcts.2010.12.050

40. Pozzi M, Banfi C, Grinberg D, Koffel C, Bendjelid K, Robin J, et al. Veno-arterial extracorporeal membrane oxygenation for cardiogenic shock due to myocarditis in adult patients. *J Thorac Dis.* (2016) 8:E495–502. doi: 10.21037/jtd.2016.06.26

41. Diddle JW, Almodovar MC, Rajagopal SK, Rycus PT, Thiagarajan R. Extracorporeal membrane oxygenation for the support of adults with acute myocarditis. *Crit Care Med.* (2015) 43:1016–25. doi: 10.1097/CCM.0000000000000920

42. Aoyama N, Izumi T, Hiramori K, Isobe M, Kawana M, Hiroe M, et al. National survey of fulminant myocarditis in Japan: therapeutic guidelines and long-term prognosis of using percutaneous cardiopulmonary support for fulminant myocarditis (special report from a scientific committee). *Circ J.* (2002) 66:133–44. doi: 10.1253/circj.66.133

43. El-Banayosy A, Arusoglu L, Kizner L, Tenderich G, Boethig D, Minami K, et al. Predictors of survival in patients bridged to transplantation with the thoratec VAD device: a single-center retrospective study on more than 100 patients. *J Heart Lung Transplant.* (2000) 19:964–8. doi: 10.1016/s1053-2498(00)00174-1

44. Adachi Y, Kinoshita O, Hatano M, Shintani Y, Naito N, Kimura M, et al. Successful bridge to recovery in fulminant myocarditis using a biventricular assist device: a case report. *J Med Case Rep.* (2017) 11:295. doi: 10.1186/s13256-017-1466-1

45. Barrie M, McKnight L, Solanki P. Rapid resolution of acute fulminant myocarditis after IVIG and steroid treatment. *Case Rep Crit Care.* (2012) 2012:262815. doi: 10.1155/2012/262815

46. Li S, Xu S, Li C, Ran X, Cui G, He M, et al. A life support-based comprehensive treatment regimen dramatically lowers the in-hospital mortality of patients with fulminant myocarditis: a multiple center study. *Sci China Life Sci.* (2019) 62:369–80. doi: 10.1007/s11427-018-9501-9

47. Matsumori A, Shimada M, Jie X, Higuchi H, Groot KT, Redegeld FA. Effects of free immunoglobulin light chains on viral myocarditis. *Circ Res.* (2010) 106:1533–40. doi: 10.1161/CIRCRESAHA.110.218438

48. Yen CY, Hung MC, Wong YC, Chang CY, Lai CC, Wu KG. Role of intravenous immunoglobulin therapy in the survival rate of pediatric patients with acute myocarditis: a systematic review and meta-analysis. *Sci Rep.* (2019) 9:10459. doi: 10.1038/s41598-019-46888-0

49. Kato S, Morimoto S, Hiramitsu S, Uemura A, Ohtsuki M, Kato Y, et al. Successful high-dose intravenous immunoglobulin therapy for a patient with fulminant myocarditis. *Heart Vessels.* (2007) 22:48–51. doi: 10.1007/s00380-006-0923-3

50. Shioji K, Matsuura Y, Iwase T, Kitaguchi S, Nakamura H, Yodoi J, et al. Successful immunoglobulin treatment for fulminant myocarditis and serial analysis of serum thioredoxin: a case report. *Circ J.* (2002) 66:977–80. doi: 10.1253/circj.66.977

51. Ozyigit T, Unal Z, Ozben B. Successful intravenous immunoglobulin therapy in a case of acute fulminant myocarditis. *Turk Kardiyol Dern Ars.* (2011) 39:59–63.

52. Goland S, Czer LS, Siegel RJ, Tabak S, Jordan S, Luthringer D, et al. Intravenous immunoglobulin treatment for acute fulminant inflammatory cardiomyopathy: series of six patients and review of literature. *Can J Cardiol.* (2008) 24:571–4. doi: 10.1016/s0828-282x(08)70638-x

53. Kishimoto C, Shioji K, Hashimoto T, Nonogi H, Lee JD, Kato S, et al. Therapy with immunoglobulin in patients with acute myocarditis and cardiomyopathy: analysis of leukocyte balance. *Heart Vessels.* (2014) 29:336–42. doi: 10.1007/s00380-013-0368-4

54. Yu DQ, Wang Y, Ma GZ, Xu RH, Cai ZX, Ni CM, et al. Intravenous immunoglobulin in the therapy of adult acute fulminant myocarditis: a retrospective study. *Exp Ther Med.* (2014) 7:97–102. doi: 10.3892/etm.2013.1372

55. Blagova OV, Nedostup AV, Kogan EA, SulimovV A. [Efficiency of immunosuppressive therapy in virus-negative and virus-positive patients with morphologically verified lymphocytic myocarditis]. *Ter Arkh.* (2017) 89:57–67. doi: 10.17116/terarkh201789857-67

56. Matsumori A, Tomioka N, Kawai C. Viral myocarditis: immunopathogenesis and the effect of immunosuppressive treatment in a murine model. *Jpn Circ J.* (1989) 53:58–60. doi: 10.1253/jcj.53.58

57. Chen HS, Wang W, Wu SN, Liu JP. Corticosteroids for viral myocarditis. *Cochr Datab Syst Rev.* (2013) 2013:D4471. doi: 10.1002/14651858.CD004471.pub3

58. Tschope C, Elsanhoury A, Schlieker S, Van Linthout S, Kuhl U. Immunosuppression in inflammatory cardiomyopathy and parvovirus B19 persistence. *Eur J Heart Fail.* (2019) 21:1468–9. doi: 10.1002/ejhf.1560

59. Nakamura H, Kunitsugu I, Fukuda K, Matsuzaki M, Sano M. Diverse stage-dependent effects of glucocorticoids in a murine model of viral myocarditis. *J Cardiol.* (2013) 61:237–42. doi: 10.1016/j.jjcc.2012.11.006

60. Ammirati E, Veronese G, Brambatti M, Merlo M, Cipriani M, Potena L, et al. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol.* (2019) 74:299–311. doi: 10.1016/j.jacc.2019.04.063

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 04 August 2022
DOI 10.3389/fcvm.2022.934489

OPEN ACCESS

EDITED BY
Jun Yu,
Temple University, United States

REVIEWED BY
Manel Sabate,
Hospital Clinic of Barcelona, Spain
Enrico Romagnoli,
Agostino Gemelli University Polyclinic (IRCCS), Italy

*CORRESPONDENCE
Shihao Zhao
765595720@qq.com
Li Fan
fl6698@163.com
Jinwen Tian
tjwsqr.2000@163.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 02 May 2022
ACCEPTED 11 July 2022
PUBLISHED 04 August 2022

CITATION
Shen M, Lu H, Liao Y, Wang J, Guo Y, Zhou X, Nong Y, Fu Z, Wang J, Guo Y, Zhao S, Fan L and Tian J (2022) Intracoronary artery retrograde thrombolysis for ST-segment elevation myocardial infarction with a tortuous coronary artery: A case report and review of the literature. *Front. Cardiovasc. Med.* 9:934489. doi: 10.3389/fcvm.2022.934489

Intracoronary artery retrograde thrombolysis for ST-segment elevation myocardial infarction with a tortuous coronary artery: A case report and review of the literature

Mingzhi Shen[1,2†], Haihui Lu[1†], Yichao Liao[1†], Jian Wang[1], Yi Guo[1], Xinger Zhou[1,2], Yingqiao Nong[1,2], Zhenhong Fu[3], Jihang Wang[1], Yuting Guo[1,2], Shihao Zhao[1*], Li Fan[4*] and Jinwen Tian[1,2*]

[1]Department of Cardiology, Hainan Geriatric Disease Clinical Medical Research Center, Hainan Branch of China Geriatric Disease Clinical Research Center, Hainan Hospital of Chinese PLA General Hospital, Sanya, China, [2]The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China, [3]Department of Cardiology, Sixth Medical Center, PLA General Hospital, Beijing, China, [4]Department of Cardiology, Second Medical Center, PLA General Hospital, Beijing, China

Background: How to deal with large thrombus burdens of culprit's blood vessel remains a great challenge in the treatment of acute myocardial infarction.

Case presentation: A 32-year-old Chinese man was diagnosed with ST-segment elevation myocardial infarction (STEMI). Coronary angiography revealed that the distal end of a tortuous left circumflex was completely occluded by a large amount of thrombus. Cutted balloon-directed intracoronary artery retrograde thrombolysis (ICART) with urokinase led to the restoration of coronary blood flow. Because there was no obvious plaque rupture or artery stenosis in the coronary artery, it was only dilated, and no stent was implanted.

Conclusion: Cutted balloon-directed ICART can be performed effectively and safely in some STEMI patients with tortuous coronary vessels and large thrombus. (REST or named ICART ClinicalTrials.gov number, ChiCTR1900023849).

KEYWORDS

myocardial infarction, tortuous coronary artery, intracoronary retrograde thrombolysis, thrombosis, reperfusion preconditioning

Background

Intracoronary thrombosis is a great challenge and can cause no-reflow, slow-flow, malignant arrhythmia, and other adverse cardiac events in patients with ST-segment elevation myocardial infarction (STEMI) (1–3). Without a benefit and with even increased stroke risk, the recommended level of routine thrombus aspiration has been reduced or even not recommended (4–6). There is still a long way to go to solve the problem of intracoronary thrombosis, especially in patients with large thrombus burdens. In 2013, we began to use the intracoronary artery retrograde thrombolysis (ICART) technique combined with primary percutaneous coronary intervention in treatment of STEMI (7). This process produced microblood flow and microperfusion, which could be defined as reperfusion pre-adaptation and characterized by reduced reperfusion injury and improved blood flow. Here, we report a case of a young patient with STEMI with a tortuous coronary artery who was not suitable for thrombus aspiration or primary balloon dilation. For this patient, ICART was successfully performed to realize coronary reperfusion without stent implantation.

Case presentation

A 32-year-old young man was transferred to the emergency department with sudden chest pain lasting for 80 min. He has had high blood pressure for 4 years but on no medication, and had a blood pressure of 174/113 mmHg and a pulse rate of 78 beats per minute. Electrocardiography showed ST-segment elevations in leads II, III, aVF, V3R, V4R, and V5R (**Figures 1A,B**). Serum creatinine was 73 μmol/L, and serum troponin T was 7.97 ng/ml. Killip classification was class I. Aspirin 300 mg and ticagrelor 180 mg were chewed just before the coronary angiography (CAG) was performed, followed by a routine antithrombotic therapy of oral DAPT (aspirin 100 mg qd, ticagrelor 90 mg bid) lasting for 1 year. The treatment was approved by Hainan Hospital of PLA General Hospital ethics committee, and informed consent was signed. The CAG showed that the left circumflex (LCX) was completely occluded by a large amount of thrombus in the distal portion (**Figure 2A**). A bolus of unfractionated heparin (11,250 IU) was administered intravenously. A Runthrough guidewire was advanced through the thrombus to the distal end of the occluded LCX. The distal end of a 2.5 mm × 15 mm Sprinter Legend balloon was cut off, leaving a metal marker at the tip. Then, the balloon was inserted

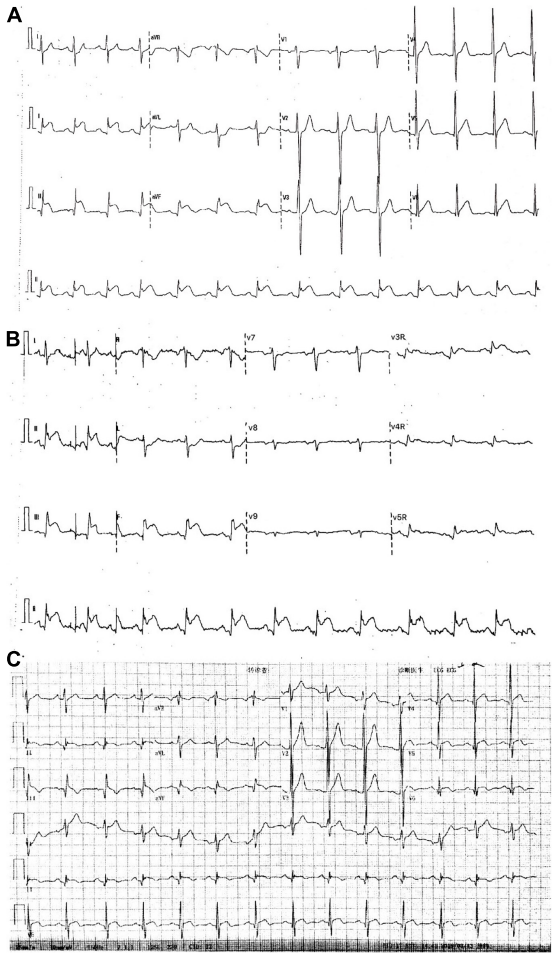


FIGURE 1
Electrocardiograms. **(A,B)** In the emergency room. **(C)** After intracoronary artery retrograde thrombolysis (ICART).

over the Runthrough guidewire and through the stenotic section of the occluded coronary artery (**Figure 2B**).

A total of 300,000 units of urokinase, 15 ml physiological saline, and 5 ml iopromide were mixed, forming a 20-ml cocktail. Following this, 1 ml of the cocktail was bolus-injected through the cut balloon, which was repeated every 30 s (**Figure 2B**). After injection, the mixture of contrast agents and thrombolytic agent retained in the distal end of the occluded lumen, exerted its thrombolytic effect while visualizing the occluded vessels during this process. After 7 min of ICART, the thrombus in the proximal segment disappeared, but the thrombus in the distal location still existed. An aspiration catheter was used for thrombus aspiration, but it was unable to pass through the lesion because of the tortuosity of the blood vessels. The occluded segment was dilated up to 5 atm with a 2 mm × 20 mm Sprinter Legend compliant balloon (**Figure 2C**) at the distal portion of the LCX. Blood flow improved to TIMI grade 2. Diltiazem 200 μg was given through

Abbreviations: STEMI, ST-segment elevation myocardial infarction; ICART, intracoronary artery retrograde thrombolysis; PCIs, percutaneous coronary interventions; CAG, coronary angiography; PLA, People's Liberation Army; LCX, left circumflex; TIMI, thrombolysis in myocardial infarction.

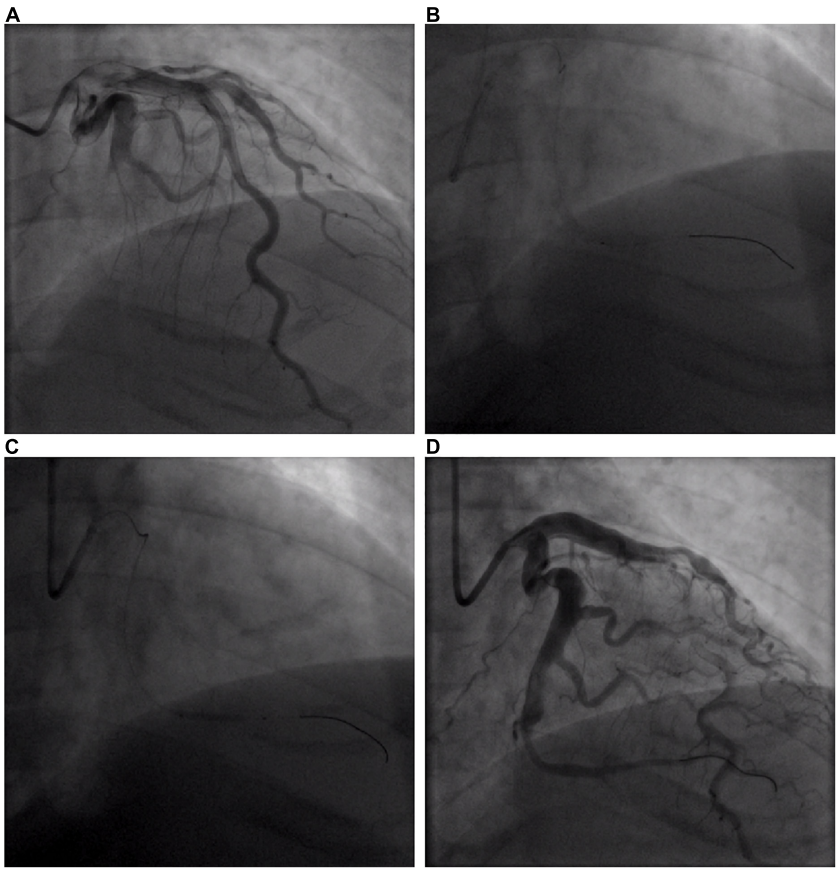


FIGURE 2
Coronary angiogram of acute circumflex artery occlusion. **(A)** Basal angiogram showing total occlusion of the left the circumflex artery (LCX) distal segment with thrombus image. The arrow shows the occlusion. **(B)** Procedure of intracoronary artery retrograde thrombolysis (ICART) through the cut balloon. The distal thrombus was gradually dissolved. The fine arrow shows the tip of the cut balloon, and the coarse arrow indicates the thrombolytic agent with contrast agent to fill the occluded lumen. **(C)** The distal end of the LCX was dilated up to 5 atm with a 2 mm × 20 mm compliant balloon. **(D)** Revascularization was achieved at the distal end of the LCX without stent implantation.

the intracoronary artery. The blood flow in the coronary artery was restored to TIMI grade 3 (**Figure 2D**). The chest pain was completely relieved, and the ST-segment elevation was resolved (**Figure 1C**). Intravenous infusion of tirofiban was maintained for 36 h after PCI. Oral administration of aspirin (100 mg/day), ticagrelor (180 mg/day), rosuvastatin (10 mg/day), bisoprolol (5 mg/day), nicorandil (15 mg/day), and perindopril (2 mg/day) was continued. Low molecular-weight heparin was administered subcutaneously after stopping tirofiban. No significant bleeding complications occurred after ICART. The patient was discharged 10 days after ICART. At a follow-up time of 1 year, there was no recurrent myocardial infarction, re-hospitalization, or death happened.

Discussion and conclusion

Management of intracoronary thrombus is a great challenge of PPCI. Large thrombus burden is associated with poor prognosis, including procedural failure, abrupt vessel closure, recurrent myocardial infarction and death (8, 9). It is widely acknowledged that the primary responsibility of physicians is to clear a thrombus quickly and open occluded vessels (10–12). Although great progress has been made in antithrombotic therapy and PCI technology, a large intracoronary artery thrombus is still a nightmare for interventional cardiologists.

In order to reduce the thrombus load of patients with STEMI, many methods such as distal protection device, thrombus aspiration, and glycoprotein IIb/IIIa antagonists are used during a PPCI procedure (13–15). However, some studies, including the EMERALD, PROMISE, and AIMI trials (16), have found that distal protection devices have no protective effect or are even harmful on myocardial perfusion and final infarct area.

Intravenous thrombolysis is simple and convenient, but the vascular opening rate is relatively low. At the same time, large doses of thrombolytic drugs increase the risk of hemorrhagic events (17). Transcatheter antegrade thrombolysis of coronary artery has been tried on patients with myocardial infarction (18).

The head of a thrombus is mainly composed of white thrombi; at the same time, the thrombolytic agent cannot be retained, and transcatheter antegrade thrombolysis effect is poor. Similarly, the dose of the thrombolytic agent needs full amount, which causes a large possibility of hemorrhage.

Thrombus aspiration is one of the most frequently used thrombectomy methods to deal with a thrombus in the coronary artery (6). However, studies reveal that patients with STEMI does not benefit from routine thrombus aspiration (5). Routine thrombus aspiration showed no benefits for death from any cause or the composite of death from any cause, rehospitalization for myocardial infarction, or stent thrombosis at 1 year either (19). Moreover, thrombus aspiration even increased stroke rate (4). As such, the recommended level of routine thrombus aspiration has been reduced to grade III.

We first invented the ICART technology in 2013 to treat patients with myocardial infarction in the world (7). We amazingly found that ICART can produce reperfusion pre-adaptation characterized by microblood flow and microperfusion. It is more feasible than ischemic pre-adaptation; and when compared with post ischemic treatment, it is supposed to cause less debris, thus preventing slow blood flow and no-reflow phenomena. ICART can produce microblood flow and microperfusion, which can reduce reperfusion injury. Therefore, we summarized the following experience for myocardial infarction: urgent transport (shortening the time from symptoms to balloon opening), slow opening (by ICART rather than sudden opening of blood vessels with thrombus aspiration, so as to reduce reperfusion injury), 10 minutes of reperfusion (we found that any urgent opening is harmful, whether it is ischemic pretreatment or post ischemic treatment). We speculate that ICART will reduce malignant arrhythmia, myocardial stunning, myocardial microcirculation occlusion, intracardiac hemorrhage, and myocardial infarction area, which are related to reperfusion injury.

In this case, the blood vessel was tortuous, which is different from the cases selected in our previous article (7), the proximal part was very thick, and the distal part was completely occluded, and it had a high-load thrombus. Thrombus aspiration should be performed according to the guidelines. However, the blood vessel was very tortuous, the aspirating catheter could not pass through the tortuous lesion, which was confirmed by subsequent operation. If balloon dilatation was performed directly, there would be slow blood flow or no reflow due to high thrombus load at the distal end. The following operation also confirmed this idea. We ingeniously cut off the head of the balloon (in our previous research, we used cutted balloons, they were made by ourselves and were similar to a double lumen microcatheter), put the balloon to the end through the wire, and formed a very high concentration of thrombolytic agent locally to dissolve the thrombus, which received very amazing results. There was no thrombus in the distal vascular bed. At the same time, according to the tortuous, distal, suddenly thinning vascular structure, a stent could not be implanted, which was also the prominent feature of this case (different from our previous case). In this case, ICART successfully exposed the lesion and revealed the occluded vessel before any other intervention was taken, thus guiding the following strategies including the choice of balloons. Our present case is a supplement to our previous ICART article, which shows that the ICART method is very feasible and much safer to use even in the variant occlusive vessels.

Intracoronary thrombolysis was previously conducted on patients with an ectatic coronary artery (20). The disadvantages of this method were that the blood vessel wall was destroyed during suction, the thrombus was pushed to the far end of the coronary artery, forming slow blood flow, and no reflow. The thrombus may fall to the aorta, leading to stroke. At the same time, the reperfusion injury was very obvious. After that, antegrade thrombolysis was carried out; because the thrombus structure was destroyed, the thrombolytic agent could not be retained, and the thrombolytic efficiency was greatly reduced. At the same time, the dosage of the thrombolytic agent was very large, which significantly increased the risk of bleeding. Therefore, if ICART is performed, the thrombolytic agent will first make contact with a red thrombus and stay for a long time, so the thrombolysis efficiency will be greater. ICART is an effective, feasible, and simple approach for management of patients with STEMI. Small amounts of thrombolytics may cause very high local blood drug concentrations in an occluded section, so as to open the occluded blood vessel. The process of gradually opening occluded blood vessels produces reperfusion preadaptation, which reduces the occurrence of malignant arrhythmia. By relatively thorough removal of a thrombus, the incidence of slow-flow or no-reflow was reduced. Because the occluded segment was relatively small, no stent was implanted in this case.

In conclusion, microcatheter-directed ICART may be a safe and effective alternative reperfusion strategy in the culprit vessel for STEMI associated with massive thrombosis in small and tortuous coronary arteries.

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 patient for publication of this case report and any accompanying images.

Author contributions

HL, YL, JW, XZ, and YN carried out patient management and data collection. YTG, ZF, and JHW drafted the manuscript and edited the figures. JT, MS, and SZ performed the angioplasty. JT and LF critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Funding

This study was supported by the Hainan Science and Technology Project (ZDYF2020123, ZDYF2020027, ZDYF2017096, and ZDKJ2019012), the National Key R&D Plan (2020YFC2004706), the National Natural Science Foundation of China (81500202), and the Open Subject of National Clinical Research Center of Geriatrics Disease (NCRCG-PLAGH-2018014) to MS. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

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

Publisher's note

References

1. Ndrepepa G, Tiroch K, Fusaro M, Keta D, Seyfarth M, Byrne RA, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol.* (2010) 55:2383–9. doi: 10.1016/j.jacc.2009.12.054

2. Napodano M, Dariol G, Al Mamary AH, Marra MP, Tarantini G, D'Amico G, et al. Thrombus burden and myocardial damage during primary percutaneous coronary intervention. *Am J Cardiol.* (2014) 113:1449–56. doi: 10.1016/j.amjcard.2014.01.423

3. Jaffe R, Dick A, Strauss BH. Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: a systematic approach. *JACC Cardiovasc Interv.* (2010) 3:695–704. doi: 10.1016/j.jcin.2010.05.004

4. Jolly SS, Cairns JA, Yusuf S. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med.* (2015) 372:1389–98. doi: 10.1056/NEJMoa1415098

5. Frobert O, Lagerqvist B, Gudnason T, Thuesen L, Svensson R, Olivecrona GK, et al. Thrombus aspiration in ST-elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale. *Am Heart J.* (2010) 160:1042–8. doi: 10.1016/j.ahj.2010.08.040

6. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GFH, Fokkema ML, de Smet BJGL, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial in-farction Study (TAPAS): a 1-year follow-up study. *Lancet.* (2008) 371:1915–20. doi: 10.1016/S0140-6736(08)60833-8

7. Tian JW, Zhu M, Wang FQ, Li K, Zhou CF, Li B, et al. Intracoronary arterial retrograde thrombolysis with percutaneous coronary intervention: a novel use of thrombolytic to treat acute ST-segment elevation myocardial infarction. *J Geriatr Cardiol.* (2019) 16:458–67.

8. Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF. *Braunwald's heart disease: A textbook of cardiovascular medicine*. 7th ed. Singapore: Elsevier Medicine (2007). p. 1068–90.

9. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart As-sociation Task Force on Practice Guidelines: Developed in collaboration with the Canadian Cardiovascular Society en-dorsed by the American Academy of Family Physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction, writing on behalf of the 2004 writing committee. *Circulation.* (2008) 117:296–329. doi: 10.1161/CIRCULATIONAHA.107.188209

10. Antman EM. Time is muscle: Translation into practice. *J Am Coll Cardiol.* (2008) 52:1216–21. doi: 10.1016/j.jacc.2008.07.011

11. Gibson CM, de Lemos JA, Antman EM, Timi Study Group. Time is muscle in primary PCI: The strength of the evidence grows. *Eur Heart J.* (2004) 25:1001–2. doi: 10.1016/j.ehj.2004.04.029

12. Muñoz D, Roettig ML, Monk L, Al-Khalidi H, Jollis JG, Granger CB, et al. Transport time and care processes for patients transferred with ST-segment-elevation myocardial infarction: The reperfusion in acute myocardial in-farction in Carolina emergency rooms experience. *Circ Cardiovasc Interv.* (2012) 5:555–62. doi: 10.1161/CIRCINTERVENTIONS.112.968461

13. Kushner FG, Hand M, Smith SC Jr., King SB, Anderson JL, Antman EM, et al. 2009 focused updates:ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focusedupdate) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol.* (2009) 54:2205–41. doi: 10.1161/CIRCULATIONAHA.109.192663

14. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: Description of the current situation in 30 countries. *Eur Heart J.* (2010) 31:943–57. doi: 10.1093/eurheartj/ehp492

15. Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med.* (2015) 372:1389–98. doi: 10.1056/NEJMoa1415098

16. Limbruno U, De Caterina R. EMERALD, AIMI, and PROMISE: Is there still a potential for embolic protection in primary PCI? *Eur Heart J.* (2006) 27:1139–45. doi: 10.1093/eurheartj/ehi755

17. Thiele H, Schindler K, Friedenberger J, Eitel I, Fürnau G, Grebe E, et al. Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: The randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST elevation myocardial infarction

trial. *Circulation.* (2008) 118:49–57. doi: 10.1161/CIRCULATIONAHA.107.747642

18. Eitel I, Wöhrle J, Suenkel H, Meissner J, Kerber S, Lauer B, et al. Intracoronary compared with intravenous bolus Abciximab application during primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: Cardiac magnetic resonance substudy of the AIDA STEMI trial. *J Am College Cardiol.* (2013) 61:1447–54. doi: 10.1016/j.jacc.2013.01.048

19. Lagerqvist B, Fröbert O, Olivecrona GK, Gudnason T, Maeng M, Alström P, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med.* (2014) 371:1111–20. doi: 10.1056/NEJMoa1405707

20. Lee Y, Kim E, Kim BK, Shin JH. A case of successful reperfusion through a combination of intracoronary thrombolysis and aspiration thrombectomy in ST-segment elevation myocardial infarction associated with an ectatic coronary artery. *BMC Cardiovasc Disord.* (2017) 17:94. doi: 10.1186/s12872-017-0527-0

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 07 September 2022
DOI 10.3389/fcvm.2022.913391

OPEN ACCESS

EDITED BY
Xiaofeng Yang,
Temple University, United States

REVIEWED BY
Lou Bezold,
University of Kentucky, United States
Yiwei Shi,
First Hospital of Shanxi Medical University, China

*CORRESPONDENCE
Kuo-Yang Wang
wky830@gmail.com

SPECIALTY SECTION
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 05 April 2022
ACCEPTED 04 August 2022
PUBLISHED 07 September 2022

CITATION
Tai I-H, Shyu T-C, Hsieh K-S, Chen K-W, Tsai W-J and Wang K-Y (2022) Case report: The impact of percutaneous atrial septal defect closure in pulmonary hypertension with co-existing cor triatriatum sinister and multiple cardiac comorbidities. *Front. Cardiovasc. Med.* 9:913391. doi: 10.3389/fcvm.2022.913391

Case report: The impact of percutaneous atrial septal defect closure in pulmonary hypertension with co-existing cor triatriatum sinister and multiple cardiac comorbidities

I-Hsin Tai[1,2,3], Tsung-Cheng Shyu[1,2,3], Kai-Sheng Hsieh[1,2,3], Ke-Wei Chen[3,4], Wan-Jane Tsai[3] and Kuo-Yang Wang[1,3,4]*

[1]Department of Medicine, College of Medicine, China Medical University, Taichung, Taiwan, [2]Department of Pediatric Cardiology, China Medical University Children's Hospital, China Medical University, Taichung, Taiwan, [3]Pulmonary Hypertension and Pulmonary Vascular Disease Center, China Medical University, Taichung, Taiwan, [4]Department of Cardiology, China Medical University Hospital, China Medical University, Taichung, Taiwan

Cor triatriatum sinister is a rare congenital anomaly characterized by the left-sided triatrial form of the heart. Diverse theories have been proposed regarding its formation, and the failure of incorporation of the common pulmonary vein into the left atrium (LA) during embryogenesis is the most widely accepted theory. Accordingly, cor triatriatum sinister may be associated with pulmonary venous obstruction and post-capillary pulmonary hypertension in the setting of restricted fenestration. A high proportion of patients with cor triatriatum sinister also have an associated secundum atrial septal defect. Pre-capillary pulmonary hypertension, which is unusual in patients with small atrial septal defects (<2 cm), is probably not as rare as some reports indicate, especially when combined with complex comorbidities. The conventional treatment strategy of atrial septal defect closure in patients with pulmonary hypertension, whether associated with cor triatriatum sinister or co-existing multiple cardiac anomalies, involves simultaneous repair with other cardiac surgical procedures. To the best of our knowledge, there is no reported clinical experience of percutaneous atrial septal defect closure in the literature. Herein, we present the case of an elderly female with pulmonary hypertension and coexisting cor triatriatum sinister, secundum atrial septal defect, and multiple cardiac anomalies. Despite optimal medical therapy, the biventricular failure deteriorated, and clinical stabilization could not be achieved. Transcutaneous atrial septal defect closure was then performed. Subsequent investigations showed an initial improvement (perhaps due to elimination of the left-to-right shunt) from this intervention, but the long-term impact did not appear

favorable, likely due to multiple uncorrected cardiac anomalies. To the best of our knowledge, this is the first clinical report showing that partial treatment of combined pre- and post-capillary pulmonary hypertension by eliminating the pre-capillary component may have an initial benefit; thus, total surgical correction should be considered a definite therapeutic strategy unless contraindicated.

KEYWORDS

chronic heart failure, pulmonary hypertension, transcutaneous ASD closure, cor triatriatum, case report

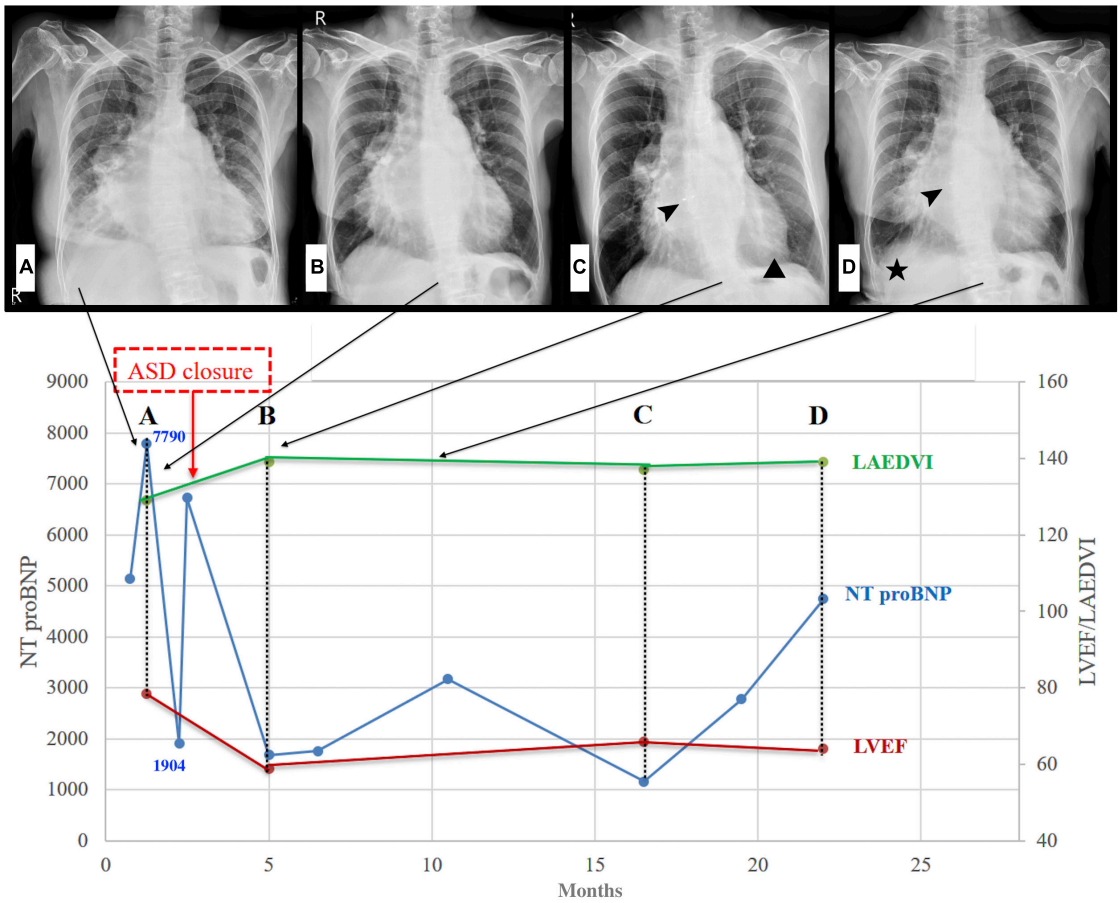
Introduction

Pulmonary hypertension (PH) due to left heart disease (PH-LHD) caused by elevated left-sided filling pressures is the most common etiology of PH. PH-LHD is further classified into two subsets according to the presence of a pre-capillary component [combined pre- and post-capillary PH (Cpc-PH) or isolated post-capillary PH (Ipc- PH)] (1). Cpc-PH is considered a more serious subset than Ipc-PH (2). Previous research has pointed out that patients with PH-LHD have a worse clinical prognosis than those without PH-LHD (3), which may be because the diagnosis is delayed and there are no existing optimal treatments. The current ESC/ERS PH guidelines define PH as a mean pulmonary artery pressure (mPAP) of > 25 mmHg and define the two subsets of PH-LHD according to the diastolic pressure gradient (DPG) [the difference between diastolic PAP and pulmonary artery wedge pressure (PAWP)] and/or pulmonary vascular resistance (PVR). Previous studies have investigated whether Cpc-PH, as defined by current guidelines, predicts clinical outcomes, although the results have varied widely among patient groups (4). Categorizing two subsets of PH-LHD using DPG has been considered too restrictive (5); hence, comprehensive hemodynamic evaluation should always be performed for Cpc-PH diagnosis in case of clinical suspicion. Due to the absence of uniform consensus on the criteria for the diagnosis of Cpc-PH, effective treatment options have not yet been developed. Herein, we report a patient with Cpc-PH and co-existing multiple cardiac comorbidities partially treated by eliminating one of the suspected causes of Cpc-PH.

Abbreviations: Af, Atrial fibrillation; AFL, atrial flutter; Cpc-PH, combined pre- and post-capillary PH; DPG, diastolic pressure gradient; Ipc- PH, isolated post-capillary PH; LA, large left atrium; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; NT-pro BNP, N-terminal pro-brain natriuretic peptide; NYHA class, New York Heart Association functional classification; PAWP, pulmonary artery wedge pressure; PH, Pulmonary hypertension; PH-LHD, Pulmonary hypertension due to left heart disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; ASD, secundum atrial septal defect; CTS, triatriatum sinister.

Case presentation

A 62-year-old woman with long-term PH, valvular heart disease, atrial fibrillation (Af), and atrial flutter (AFL) on amiodarone, spironolactone, and valsartan/hydrochlorothiazide was admitted to the intensive care unit because of progressive dyspnea and bilateral lower limb edema for over 2 weeks. On physical examination, she was found to have bilateral basal rales, orthopnea, and grade IV bilateral lower-limb edema. The clinician-assessed New York Heart Association functional classification (NYHA class) was Grade III-IV. Chest radiography revealed an enlarged cardiac profile and lung congestion (**Figure 1**, Panel A). Electrocardiography revealed an AFL with biatrial enlargement. The N-terminal pro-brain natriuretic peptide (NT-pro BNP) level was 7,790 pg/ml on the day of admission. Transthoracic echocardiography revealed a hyperdynamic heart (ejection fraction >70%) with moderate aortic-mitral regurgitation and a large left atrium (LA). Additionally, the LA was bisected by a membranous structure into two distinct chambers (proximal and distal chambers) without a transmembrane pressure gradient on color Doppler, which suggested a non-obstructive cor triatriatum sinister (CTS) and secundum atrial septal defect (ASD) underneath. Subsequent three-dimensional transesophageal echocardiography confirmed the presence of a 1.5 cm secundum ASD in the distal LA chamber. Nuclear imaging and computed tomographic pulmonary angiography excluded the possibility of chronic thromboembolic disease. After heart failure was controlled with intravenous diuretic medication, cardiomegaly improved (**Figure 1**, Panel B), NT-pro BNP levels decreased (**Figure 1**, 7,790 to 1,904 pg/mL), and lower limb edema reduced. Hemodynamic evaluation with right heart catheterization (RHC, **Table 1**) showed moderate PH, probably because of the prevalent systemic-to-pulmonary shunt, without a significant pressure gradient between the proximal and distal chambers of the LA. This improvement in the clinical condition after intensive care with diuretic agents, however, was not long-lasting. After 1 week of follow-up, NT-pro



Time stamp	LVEF (%)	MV E/A , DecT (ms)	LVID d / s (mm)	LAEDVI (ml/cm²)	NYHA Fc
A	78.34	1.19, 225	50.90/26.87	129	III-IV
B	58.73	2.71, 196	52.47/36.04	139	II
C	65.88	1.78, 133	56.50/35.75	137	II
D	64.03	NA, 154	49.46/32/16	139	II

FIGURE 1
Left heart disease progression after ASD closure. Serial chest radiographs (arrows indicated the timeline of CXR) and heart failure markers (NT proBNP & Echocardiography) before and after ASD closure. **(A)** CXR: cardiomegaly, moderate right-side pleural effusion, and bilateral lung congestion **(B)** CXR: pleural effusion and lung congestion improved after diuretics **(C)** CXR: minimal pericardial effusion (triangle) 2.5 months after closure, arrowhead: ASD occluder **(D)** CXR: evident right pleural effusion (asterisk) with increased lung congestion 8 months after closure, arrowhead: ASD occluder. NT-pro BNP initial drop following ASD closure, gradually re-climbed 14-20 months later. Note that the climbing velocity is slower than that seen before ASD closure. In addition to the improving hyperdynamic LVEF and progressive enlarged LA volume, the other echocardiography parameter seems to have no significant change during the 20-month follow-up. ASD denotes atrial septal defect; CXR, chest X-ray; NT-pro BNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; LAEDVI, left atrial end-diastolic volume index; MV, mitral valve; DecT, deceleration time; LVID, left ventricular internal diameter; NYHA Fc, New York Heart Association Functional class.

BNP levels had increased to pre-treatment levels (1,904–67,25 pg/mL). Total surgical structural correction (CTS resection, ASD closure, and mitral and aortic valvular repair) was planned; however, the patient declined to undergo this procedure. The patient eventually underwent transcutaneous ASD closure using an 18-mm Amplatzer septal occluder, following which trivial residual interatrial shunting was detected on color Doppler echocardiography (Figure 2). The patient's condition improved significantly for several months after transcutaneous closure of the ASD. However, with time, the heart failure worsened (Figure 1, NT proBNP).

TABLE 1 Right heart catheterization after heart failure control.

PAP (s/d/m), mmHg	69/20/36
PAWP (s/d/m), mmHg	15/15/12
LVP (s/d/m), mmHg	152/12/21
RAP (s/d/m), mmHg	13/10/7
LAP (s/d/m), mmHg	16/13/11
PVR, WU	4.06
TPG, mmHg	24
DPG, mmHg	8
Qp, L/min	5.91
Qs, L/min	2.74
Qp:Qs	2.16

Discussion and conclusions

Hemodynamic evaluation and correlation in the presence of multiple cardiac comorbidities

The RHC data ostensibly fulfilled the criteria for pre-capillary PH (6). However, when interpreting these values, we need to take into consideration that the patient's volume status may have influenced the pulmonary hemodynamics and the subsequent measurements. As the patient had undergone diuretic treatment before right heart catheterization, the measured pulmonary arterial wedge pressure (PAWP) may have been erroneously reduced to < 15 mmHg (1, 7). Left ventricular end-diastolic pressure (LVEDP), a more reliable surrogate for left atrial pressure, was 21 mmHg; however, in the presence of mitral and aortic valve disease, PAWP and LVEDP may not be assumed to be interchangeable (7, 8). Furthermore, the patient's diastolic pressure gradient (DPG) and transpulmonary pressure gradient (TPG) were 8 and 24 mmHg, respectively, which implied the combined presence of passive and reactive PH (1, 3, 9), making Cpc-PH the most likely assessment.

Role of atrial septal defect closure

The key indication to close ASD in PH is the value of pulmonary vascular resistance (PVR) or pulmonary vascular resistance index (PVRI) (1). The ESC recommendations (1) for the correction of prevalent systemic-to-pulmonary shunts in PH are a PVR < 2.3 Wood units (WU) (PVRI < 4 WU.m^2) for it to be correctable, > 4.6 WU (PVRI > 8 WU.m^2) for it to be not correctable, and between 2.3 and 4.6 WU (PVRI 4–8 WU.m^2) to require individualized evaluation, which was the case in our patient. In patients with a 1.5-cm isolated ASD, who are likely to be asymptomatic, the magnitude of the left-to-right shunt with multiple structural anomalies and arrhythmia remains unclear, for it is unknown whether the left-sided filling pressure is also increased (10). Recently, a prospective study used baseline

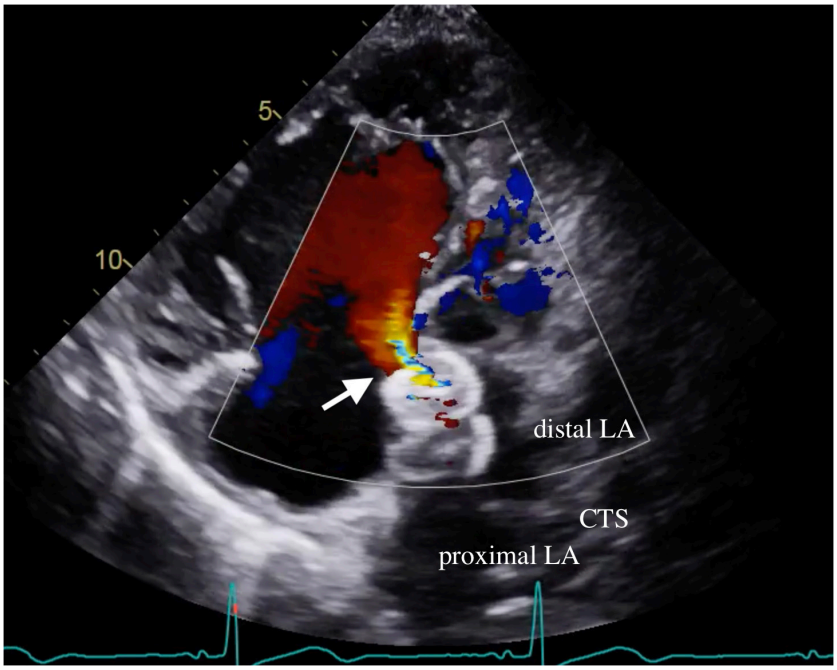


FIGURE 2
Residual ASD shunt. Transthoracic echocardiography demonstrated residual shunting (arrow) through the waist of the ASD device. ASD denotes atrial septal defect; CTS denotes cor triatriatum sinister; LA denotes left atrium.

PAPm to predict whether PAPm could further decrease after ASD closure in 209 patients with PH (11). The optimal cutoff value of baseline PAPm without PAH-specific medication was 35 mmHg (the area under the curve was 0.919, $p < 0.001$), which is nearly equal to that of our patient (PAPm:36 mmHg). ASD closure may block the left-to-right shunt, but the long-term effect of the absence of decompression for irreversible PH (12) warrants future research.

Strengths and limitations of management

Transcutaneous closure has significant benefits in ASD patients with PH owing to its minimal invasiveness and low complication rates. However, if a patient is undergoing other cardiac surgeries, the surgeries are typically performed together. CTS is a rare congenital cardiac anomaly in which a fenestrated fibromuscular membrane subdivides the LA into two chambers. When the fenestration is small, the obstruction mimics mitral stenosis, which may further aggravate Af (13) and increase the risk of stroke (14). Surgical resection of the CTS membrane seems curative; however, our experience indicates that transcutaneous balloon dilatation can also achieve clinical improvement (15). Given that Doppler color flow mapping with RHC data showed no transmembrane pressure gradient in our patient, surgical resection was probably not the ideal choice. According to the American Heart Association guidelines on valvular heart disease, valve replacement is a reasonable approach in patients with moderate AR or MR undergoing other cardiac surgeries (16).

The serial quantitative echocardiography demonstrated normalized hyperdynamic left ventricular ejection fraction (from 78.34 to 58.73%) and functional class. Concerning the absence of sepsis or any other form of non-traumatic shock, ASD-related significant systemic pulmonary shunting might be a reasonable explanation for hyperdynamic left ventricular ejection fraction. The severity of aortic regurgitation represented by the left ventricular volume seemed unchanged compared with that before ASD closure. Notably, the left atrial volume increased one month following percutaneous ASD closure. With multifactor such as poorly controlled atrial fibrillation/flutter or perhaps worsened mitral regurgitation, making it hard to differentiate from effect after ASD closure. It seems that the rate of worsening heart failure, as represented by NT-pro BNP (**Figure 1**), is slower after ASD closure than before. The long-term outcome of intra-atrial shunt blockade in our patients with combined pre- and post-capillary PH remains unknown, and to the best of our knowledge, no relevant investigations have been conducted. However, the current evidence of persistent PH with ongoing worsening of LV function suggests that partial repair of Cpc-PH may be achieved by eliminating the pre-capillary component in a short period of palliation. This suggests that total correction of structural anomalies should be considered in the management planning of Cpc-PH due to the complex hemodynamic situation.

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.

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

W-JT and K-SH collected the clinical data and help complete the manuscript. I-HT analyzed and interpreted the patient data regarding the right heart catheterization and was a major contributor to writing the manuscript. T-CS and K-WC performed the diagnostic and therapeutic intervention procedure and made critical revisions to the manuscript. K-YW designed the research and made critical revisions to the manuscript. All authors read and approved the final manuscript.

Funding

The investigation was funded by China Medical University DMR-111-067.

Conflict of interest

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

Publisher's note

References

1. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), International society for heart and lung transplantation (ISHLT). *Eur Heart J.* (2016) 37:67–119. doi: 10.1093/eurheartj/ehv317

2. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail.* (2013) 1:290–9. doi: 10.1016/j.jchf.2013.05.001

3. Vachiery JL, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol.* (2013) 62:D100–8. doi: 10.1016/j.jacc.2013.10.033

4. Rezaee ME, Nichols EL, Sidhu M, Brown JR. Combined Post- and Precapillary Pulmonary Hypertension in Patients With Heart Failure. *Clin Cardiol.* (2016) 39:658–64. doi: 10.1002/clc.22579

5. Vachiery JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, et al. Pulmonary hypertension due to left heart disease. *Eur Respir J.* (2019) 53:1801897. doi: 10.1183/13993003.01897-2018

6. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* (2004) 126:14S–34S. doi: 10.1378/chest.126.1_suppl.14S

7. Naeije R, Chin K. Differentiating Precapillary From Postcapillary Pulmonary Hypertension. *Circulation.* (2019) 140:712–4. doi: 10.1161/CIRCULATIONAHA.119.040295

8. Reddy YNV, El-Sabbagh A, Nishimura RA. Comparing Pulmonary Arterial Wedge Pressure and Left Ventricular End Diastolic Pressure for Assessment of Left-Sided Filling Pressures. *JAMA Cardiol.* (2018) 3:453–4. doi: 10.1001/jamacardio.2018.0318

9. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* (2009) 30:2493–537.

10. Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. *Circulation.* (2006) 114:1645–53. doi: 10.1161/CIRCULATIONAHA.105.592055

11. Pan W, Zhang Y, Guan L, Zhang X, Zhang L, Yang L, et al. Usefulness of mean pulmonary artery pressure for predicting outcomes of transcatheter closure of atrial septal defect with pulmonary arterial hypertension. *EuroIntervention.* (2020) 16:e1029–35. doi: 10.4244/EIJ-D-19-00172

12. Akseer S, Horlick E, Vishwanath V, Hobbes B, Huszti E, Mak S, et al. Prevalence and outcomes of pulmonary hypertension after percutaneous closure of atrial septal defect: a systematic review and meta-analysis. *Eur Respir Rev.* (2020) 29:200099. doi: 10.1183/16000617.0099-2020

13. Chen Y, Zheng M, Lin K, Cui K. Mapping and surgical ablation of persistent atrial fibrillation in cor triatriatum sinister. *Eur Heart J.* (2016) 37:2868. doi: 10.1093/eurheartj/ehw093

14. Ullah W, Sattar Y, Rauf H, Roomi S, Shah MI. A Systematic review of a long-forgotten cause of atrial fibrillation and stroke: cor triatriatum. *Cureus.* (2019) 11:e6371. doi: 10.7759/cureus.6371

15. Huang TC, Lee CL, Lin CC, Tseng CJ, Hsieh KS. Use of Inoue balloon dilatation method for treatment of Cor triatriatum stenosis in a child. *Catheter Cardiovasc Interv.* (2002) 57:252–6. doi: 10.1002/ccd.10334

16. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* (2014) 129:2440–92.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 20 September 2022
DOI 10.3389/fcvm.2022.996072

OPEN ACCESS

EDITED BY
Baohui Xu,
Stanford University, United States

REVIEWED BY
Daniele Ronco,
Maastricht University Medical Centre, Netherlands
Francesco Patanè,
Azienda Ospedaliera Ospedali Riuniti Papardo Piemonte, Italy

*CORRESPONDENCE
Xiajun Hu
husteduhxj@163.com
Yumiao Wei
yumiaowei@qq.com

SPECIALTY SECTION
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 17 July 2022
ACCEPTED 26 August 2022
PUBLISHED 20 September 2022

CITATION
Shuai X, Hu X and Wei Y (2022) Case report: Spontaneous closure of ventricular pseudoaneurysm post-acute myocardial infarction with non-surgical therapy.
Front. Cardiovasc. Med. 9:996072.
doi: 10.3389/fcvm.2022.996072

Case report: Spontaneous closure of ventricular pseudoaneurysm post-acute myocardial infarction with non-surgical therapy

Xinxin Shuai, Xiajun Hu* and Yumiao Wei*

Department of Cardiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Left ventricle (LV) pseudoaneurysm is a rare disorder post-acute myocardial infarction (AMI). Resection or closure of the pseudoaneurysm by surgery is recommended due to the high propensity of pseudoaneurysm rupture while surgery has also high risks. Conservative therapy could be acceptable in small pseudoaneurysms or patients with high surgical risks. Nevertheless, the risk evaluation and grasp of indication are not clear. This case reported an acute cyst-like LV pseudoaneurysm formation post-AMI-induced myocardial free wall rupture (MFWR), and the patient recovered with spontaneous closure of the fissure and shrinkage of the LV pseudoaneurysm through non-surgical therapy. Based on the observations in the echocardiogram, we proposed that intermittent closing of the fissure and interruption of the blood flow between the LV and the pseudoaneurysm due to LV contraction alleviated stress change on the pseudoaneurysm. The narrow fissure, small pseudoaneurysm, and intermittently interrupted blood flow that benefit fissure healing and pseudoaneurysm stabilization could indicate the prognosis of this patient. Drugs like β-blocker that decreased the stress on the pseudoaneurysm also led to the risk reduction of pseudoaneurysm rupture. To our knowledge, this is the first case that reports a spontaneous closure of LV pseudoaneurysm. The size of the fissure and the pseudoaneurysm, as well as the corresponding hemodynamic state, could be valuable to evaluate the risk and prognosis of the pseudoaneurysm. Optimized medical management was also helpful to pseudoaneurysm stabilization.

KEYWORDS

ventricular pseudoaneurysm, myocardial infarction, shape, hemodynamic, conservative therapy, outcomes

Introduction

Left ventricle (LV) pseudoaneurysm formation is a rare complication of acute myocardial infarction (AMI) with a poor prognosis (1). It is a consequence of myocardial free wall rupture (MFWR), followed by pericardial adhesions, enclosing the fissure to form a fibrous chamber, and keeping interflow with the ventricular chamber.

Pseudoaneurysm commonly occurs in the posterior or lateral wall of LV, with an incidence of 0.1% in MI (2). A pseudoaneurysm is more dangerous than a true aneurysm because of the high propensity to rupture and sudden death (3). Other symptoms could be congestive heart failure, arrhythmia, or thrombosis. Some patients could be asymptomatic and the illness can be discovered by imaging examination. Pseudoaneurysm resection or closure through surgical intervention (3) is the major therapeutic strategy; meanwhile, conservative therapy is also observed in some cases. However, a detailed information about risk evaluation, strategy making, long-term management, and associated outcomes is not clear. Here, we firstly reported an acute cyst-like LV pseudoaneurysm formation post-AMI; the patient recovered with spontaneous closure of the fissure and shrinkage of the pseudoaneurysm through non-surgical therapy. The width of the fissure that determines whether the fissure could be closed, and the blood flow could be interrupted during myocardial contraction could be an important parameter to evaluate the pseudoaneurysm risk and prognosis of the patient. The case will be presented in accordance with the CARE reporting checklist.

Case description

A 53-year-old male patient was admitted to CCU because of sudden syncope for 8 h, which was preceded by intermittent chest pain for 3 days, while the patient did not seek medical attention. He had a history of hypertension and diabetes mellitus for 2 years without medical intervention, his home blood pressure (BP) was about 160/80 mmHg, and his blood glucose was not monitored. He also had a smoking history of 20 years. No family history or psychosocial history was declared. The electrocardiogram (ECG) of the patient showed ST segment elevation in leads II, III, aVF, V5-V6, and V7-V9, which suggested inferior-, posterior-, and lateral-wall AMI (Figure 1A). Primary percutaneous coronary intervention (PCI) of the occlusive proximal segment of the left circumflex (LCX) coronary artery (Figure 1B) was successfully performed (Figure 1C). The blood pressure of the patient was 96/60 mmHg, and the resting heart rate (HR) was 118 beats per minute (bpm). He had impaired hepatic function, with alanine aminotransferase (ALT) raised to 3,751 U/L (normal < 40 U/L), and aspartate aminotransferase (AST) elevated to 6,804 U/L (normal < 40 U/L). Creatinine was elevated to 393.8 μmol/L (normal 44–133 μmol/L). Arterial blood gas analysis showed decreased pH level (7.27) and elevated lactate level (5.7 mmol/L). The patient performed typical symptoms of shock that cannot be attributed to simple LCX proximal segment occlusion. A bedside transthoracic echocardiography (TTE) was urgently performed and found mild pericardial effusion. Chest CT (CT) further confirmed that the pericardium effusion was bloody (Figure 1D). Subacute cardiac rupture and pericardial tamponade were highly suspected. Emergency pericardiocentesis and drainage of bloody effusion were subsequently performed. The BP of the patient rapidly raised to 168/90 mmHg, the HR reduced to 90-100 bpm, and shock-associated symptoms were also relieved. A cardiac surgeon was called for an emergency consultation. The surgical department estimated that surgery was recommended, while the postoperative risk was high in this patient. After adequate notification of the therapeutic strategies and associated prognosis, the patient and his family finally chose conservative intervention instead of surgery. However, subsequent TTE reexamination revealed the presence of a 2.1*1.1 cm pseudoaneurysm with a width of 0.3 cm fissure in the lateral wall that connected the LV and the pseudoaneurysm (Figures 1E,F), while cardiac magnetic resonance (CMR) also demonstrated the LV pseudoaneurysm formation (Figure 1G). Interestingly, during diastole, the blood flowed between the LV and pseudoaneurysm (Figure 1E, Supplementary Video 1); while during systole, the fissure was closed due to myocardial contraction, and the blood flow was subsequently interrupted (Figure 1F). Comprehensively considering the risk of the disease and the willingness of the patient, we carried out a conservative strategy. Aspirin and ticagrelor were continuously prescribed. Betaloc was also used in sufficient doses, aiming to decrease the stress on the fissure and the pseudoaneurysm. A low dose of diuretics was reserved to gently reduce volume overload. Twenty-eight days later, the patient was discharged without any symptoms, such as dyspnea or chest pain. The pre-discharge TTE still observed a 1.5*1. pseudoaneurysm with a 0.3 cm-wide fissure, and the ejection fraction of LV was 55%. One month after discharge, the patient came for a follow-up. TTE showed that the LV pseudoaneurysm was reduced to 1.7*.7 cm, and the fissure was 0.2 cm. Mild pericardial effusion was still observed without any symptoms. One year later, TTE reexamination revealed that the LV pseudoaneurysm was only about 0.3*0.5 cm, and the fissure was closed without blood flow between the ventricle and the pseudoaneurysm (Supplementary Figure 1, Supplementary Video 2). Meanwhile, pericardial effusion was not observed anymore. The clinical diagnosis and treatment timeline of the patient was summarized in Figure 2.

Discussion

Pseudoaneurysm is fatal because of the risk of rupture. According to previous literature (Table 1), most patients accepted surgical therapy. The outcomes were diverse in different clinical centers, operation associated mortality ranged from 0 to 35.7% (1–3, 5–11), mortality during follow-up ranged from 0 to 31% (1–6, 8–11), and patients with acute pseudoaneurysm or high surgical risks had higher mortality (3). The mortality of conservative therapy was also discussed in some studies with a small sample size, which appeared to be higher than surgical therapy (1, 4, 5, 7, 11). Meanwhile,

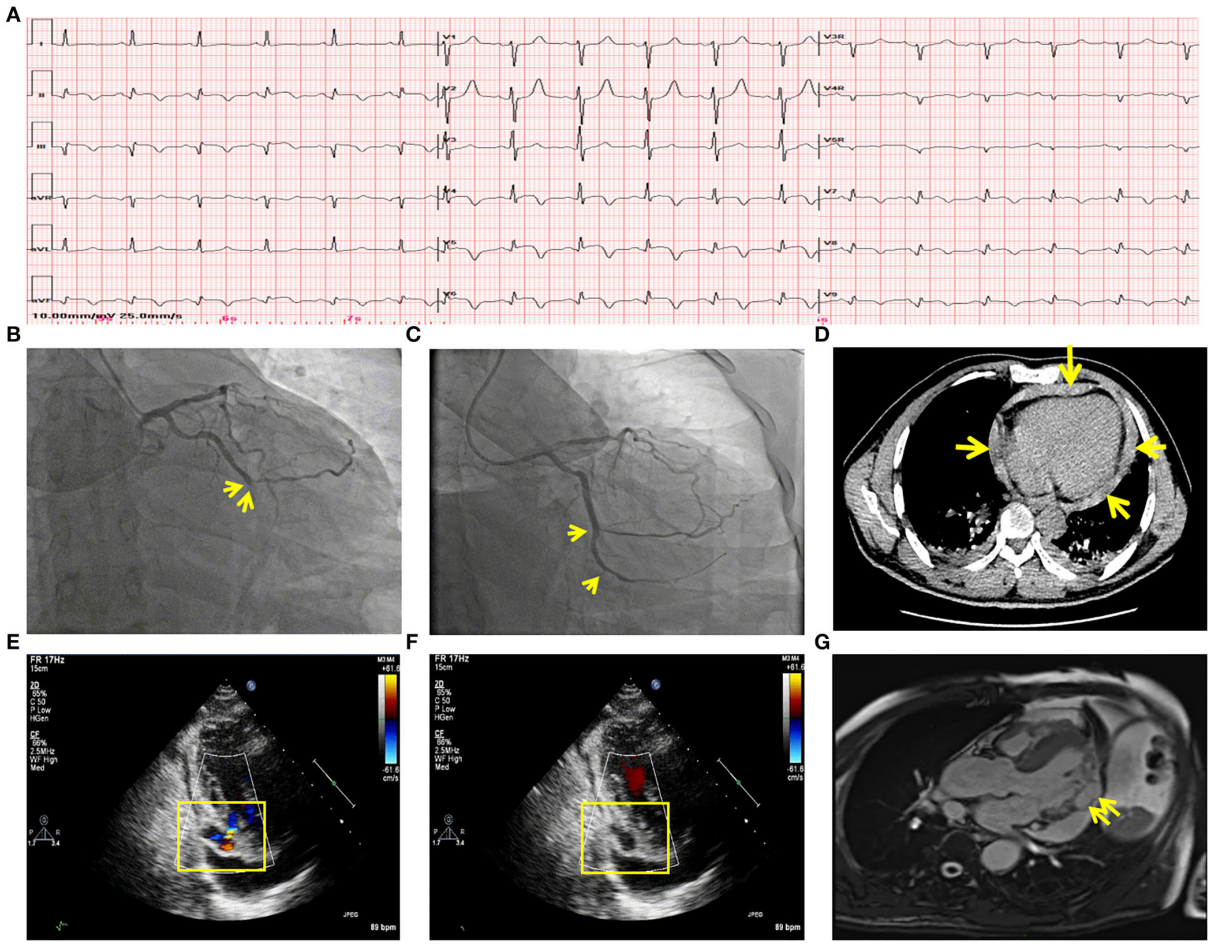


FIGURE 1
Clinical data of the patient with LV pseudoaneurysm post-acute myocardial infarction. **(A)** ECG showed acute inferior-, posterior- and lateral wall myocardial infarction. **(B)** Coronary angiography showed LCX acute occlusion. Yellow arrows indicated the occluded point of the LCX. **(C)** The primary percutaneous coronary intervention of LCX. A yellow arrow marked the revascularization of the proximal segment of the LCX. **(D)** CT demonstrated hemopericardium which was marked by yellow arrows. **(E)** TTE showed an LV pseudoaneurysm formation and blood between the pseudoaneurysm and LV during the diastolic period. **(F)** TTE showed blood flow interruption during the systolic period. **(G)** CMR confirmed LV pseudoaneurysm formation in the lateral wall, which is marked by the yellow arrow. LV, left ventricle; ECG, electrocardiogram; LCX, left circumflex; TTE, transthoracic echocardiography; CMR, cardiac magnetic resonance imaging.

some retrospective studies reported patients with chronic small (<3 cm in size) LV pseudoaneurysm or patients with high surgical risks could be managed conservatively (12). Based on these data, surgery should be the first choice for patients with pseudoaneurysms, while conservative therapy could be acceptable in some special situations. The question is how to evaluate the risk and prognosis for each patient. Our patient surprisingly underwent a spontaneous closure of the pseudoaneurysm without surgery, which was not reported since. Several case reports also gave detailed information about patients with non-surgical therapy (13–15), while all these pseudoaneurysms kept the same or expanded size. The factors that participated in the closure of pseudoaneurysm in our case is worthy of discussion. Since ventricular anatomy is important in maintaining cardiac function (16), the anatomic and corresponding hemodynamic change due to pseudoaneurysm formation in the LV could give some indications.

Pseudoaneurysm keeps blood flow with LV, bearing stress from the ventricular chamber and pericardial cavity. With the movement of LV, altering stress could result in pseudoaneurysm expansion or even rupture. Through TTE and CMR, we observed a specific cardiac movement pattern in our patient with a small pseudoaneurysm, which is dissimilar from a big pseudoaneurysm that continuously keeps a connection with LV (17, 18). We made a schematic diagram to illustrate the hemodynamic state. In a small pseudoaneurysm with a narrow fissure, the fissure relaxes and blood flows between LV and the pseudoaneurysm during the ventricle diastole.

Time point	First visit 2020.10.26	Second stage 2020.10.27	Third stage 2020.11.12	One-month follow-up 2020.12.23	One-year follow-up 2021.11.26
Symptom	Chest pain Synope	Chest tightness Dyspnea	Fatigue	None	None
Diagnosis and observation	STEMI	Acute tamponade Cardiac shock	Pseudoaneurysm formation （2.1*1.1cm with a 0.3cm fissure）	Pseudoaneurysm shrunk （1.7*0.7cm with a 0.2cm fissure）	Pseudoaneurysm closure （0.3*0.5cm without fissure）
Intervention	• Primary PCI	• Pericardiocentesis • Surgeon consultation	• Surgeon consultation • DAPT • Tatin • β blocker • Diuretic	• DAPT • Tatin • β blocker • Diuretic	• SAPT • Tatin • β blocker • ARNI

FIGURE 2
Clinical diagnosis and treatment timeline of the patient. STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; DAPT, dual-antiplatelet therapy; SAPT, single antiplatelet therapy; ARNI, angiotensin receptor, and neprilysin inhibitor.

In this period, LV pressure is low, and stress endured by the pseudoaneurysm is small. Meanwhile, the pressure from the pericardial due to the presence of effusion provides centripetal force in the pseudoaneurysm, offsetting the pressure from the ventricle. During cardiac systole, the fissure is tightened because of ventricular wall contraction, resulting in a temporary partition between the pseudoaneurysm and the LV. Pressure in the pseudoaneurysm was not influenced by sharply increased LV pressure (Figure 3A, Supplementary Video 1). As with a big pseudoaneurysm with a wide fissure, the pseudoaneurysm keeps blood transfer with LV, the stress and shape change are continuously influenced by the changing LV pressure (Figure 3B), resulting in worse cardiac function and pseudoaneurysm instability. Therefore, we conclude that for small pseudoaneurysms with narrow fissures, LV contraction tends to promote the rupture healing by tightening the fissure, and patients with conservative therapy may survive under this condition. While a big pseudoaneurysm keeps consistent and unstable blood flow with LV, conservative management is associated with higher mortality. This is an uncommon case that reported a spontaneous closure of ventricular pseudoaneurysm, while similar cases or clinical studies are not retrieved. Torchio et al. also recently mentioned that the size of the pseudoaneurysm could partly determine the intervention strategy (19), while due to the limited case, further observations are needed to promote our cognition.

Concerning to medical therapy, long-term medication of ACEI/ARB or β-blocker was observed in some conservative cases (13–15). Some studies retrospected clinical characteristics of MFWR and a summarized higher ACEI/ARB and β-blocker coverage was associated with lower in-hospital incidence and mortality (20). Nonetheless, there is no evidence-based medicine supporting the efficiency in pseudoaneurysm formation post-MFWR. For patients who suffered acute pseudoaneurysms without surgical therapy, promoting rupture repair could be more important. ACEI/ARB was avoided in the early stage because of their inhibition of blood pressure and cardiac fibrosis. Oral β blocker is prescribed because β-blocker can block catecholamine adrenergic receptors-mediated cardiotoxicity in MI. In this patient, β-blocker prolonged ventricular diastolic time to increase returned blood volume. On the other hand, the negative inotropic effect reduced the myocardial stretch on the fissure and the pseudoaneurysm. Through these methods, the pseudoaneurysm was placed in a relatively stable mechanical environment, which reduced the risk of rupture and strove for the opportunity of myocardial wound healing.

In some cases, or small retrospective analysis, mechanical circulatory support (MCS) could be beneficial in stabilizing the hemodynamic conditions in patients with mechanical complications post-AMI and building a bridge to a safer timing of surgery. For example, La Torre et al. (21) described their first experience in the use of Impella in patients with cardiogenic shock due to acute ventricular septal defect (VSD) post-AMI. Patanè et al. (22) also confirmed the advantages of Impella in improving patients' hemodynamic state and survival rate. Extracorporeal membrane oxygenation (ECMO) support

TABLE 1 Summary of clinical investigations about LV pseudoaneurysm.

Ref/Year	Size of pseudo-aneurysm (cm)	Patients with surgery	Operation related mortality	Follow up mortality in surgical patients	Patients with conservative therapy	Follow up mortality in conservative patients
Frances et al. (4)/1998	6.0 (1.5, 20.1)	193	/	23%	31	48%
Tiong et al. (5)/1998	/	42	7%	31%	10	60%
						No cardiac rupture
Yeo et al. (1)/1999	4.53 ± 2.03	16	13%	50%	6	83%
						No cardiac rupture
Prêtre et al. (6)/2000	/	10	30%	30%	/	/
Moreno et al. (7)/2003	9.8 ± 6.9	1	0%	0%	10	20%
						No cardiac rupture
Lafci (8)/2006	/	8	12.5%	1 CHF	/	/
Eren et al. (2)/2007	4.7 ± 0.48	14	35.7%	1 sudden death	/	/
				1 cancer		
Fernando et al. (9)/2007	/	30	20%	27%	/	/
Narin et al. (10)/2008	/	5	0%	0%	/	/
Prifti et al. (3)/2017	4.2 ± 0.7	12	30.8%	15%	/	/
Zhong et al. (11)/2022	/	10	0%	0%	7	42.9%

Ref, reference; CHF, chronic heart failure.

10.3389/fcvm.2022.996072

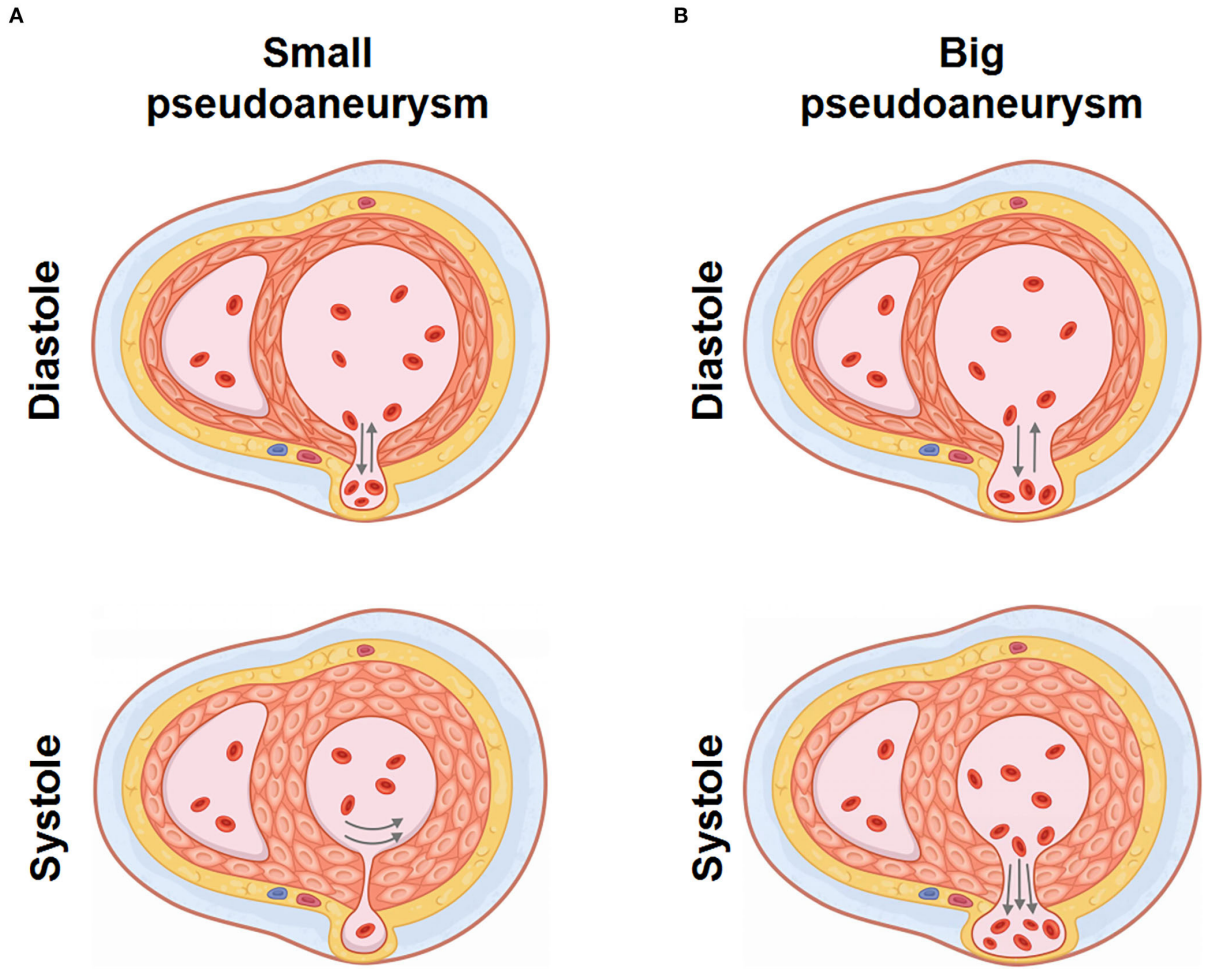


FIGURE 3
Hemodynamic characteristics of LV pseudoaneurysm with different shapes. **(A)** Hemodynamic diagram of small LV pseudoaneurysm with narrow fissure. **(B)** Hemodynamic diagram of big LV pseudoaneurysm with wide fissure.

in patients with MFWR was also reported as a single case (23, 24), although the anticoagulation strategy was not clearly described. Compared with Impella and ECMO, Intraaortic balloon counterpulsation (IABP) is a more available device. Even though IABP-SHOCK trials concluded that IABP did not reduce short and long-term mortality in patients with cardiogenic shock (25, 26), IABP is still commonly used in acute VSD post-AMI, while the usage in patients with MFWR or LV pseudoaneurysm was not reported (27). Meanwhile, the adverse effects of mechanical device implantation should be noticed. Further trials are needed to optimize the MCS strategy. In our patient, hemodynamic instability was rapidly relieved after pericardiocentesis, we evaluated that MCS was unnecessary after weighing the benefits and risks of this approach.

Conclusion

This is the first case report of spontaneous closure of a pseudoaneurysm post AMI with non-surgical therapy. The shape and movement pattern of the pseudoaneurysm could promote rupture healing. Careful conservative management based on stress control and wound healing synergistically facilitated the healing process. This case highlights the importance of shape characteristics and hemodynamic state of a pseudoaneurysm in the risk and prognosis evaluation. With the limitation of the number of cases, whether the experience can be expanded or even provide information for clinical decision need to be further investigated.

Data availability statement

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

Ethics statement

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

Author contributions

XS designed the case report, analyzed the patient data, and revised the manuscript. XH analyzed the patient data and drafted the manuscript. YW designed the case report and collected the patient data. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Nos. 31901004 and 82070376).

Acknowledgments

We thank the patient for providing his information for this case report.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.996072/full#supplementary-material

References

1. Yeo TC, Malouf JF, Reeder GS, Oh JK. Clinical characteristics and outcome in postinfarction pseudoaneurysm. *Am J Cardiol.* (1999) 84:592–95. doi: 10.1016/s0002-9149(99)00385-9

2. Eren E, Bozbuga N, Toker ME, Keles C, Yakut C. Surgical treatment of post-infarction left ventricular pseudoaneurysm: a two-decade experience. *Tex Heart I J.* (2007) 34:47–51.

3. Prifti E, Bonacchi M, Baboci A, Giunti G, Veshti A, Demiraj A, et al. Surgical treatment of post-infarction left ventricular pseudoaneurysm: case series highlighting various surgical strategies. *Ann Med Surg.* (2017) 16:44–51. doi: 10.1016/j.amsu.2017.03.013

4. Frances C, Romero A, Grady D. Left ventricular pseudoaneurysm. *J Am Coll Cardiol.* (1998) 32:557– 61.

5. Tiong CY, Joe FM, Jae KO, James BS. Clinical profile and outcome in 52 patients with cardiac pseudoaneurysm. *Ann Intern Med.* (1998) 128:299–305. doi: 10.7326/0003-4819-128-4-199802150-00010

6. Prêtre R, Linka A, Jenni R, Turina MI. Surgical treatment of acquired left ventricular pseudoaneurysms. *Ann Thorac Surg.* (2000) 70:553–7. doi: 10.1016/s0003-4975(00)01412-0

7. Moreno R, Gordillo E, Zamorano J, Almeria C, Garcia-Rubira JC, Fernandez-Ortiz A, et al. Long term outcome of patients with postinfarction left ventricular pseudoaneurysm. *Heart.* (2003) 89:1144–6. doi: 10.1136/heart.89.10.1144

8. Lafci B, Ozsyler I, Emrecan B, Gktogan T, Gürbüz A. Surgical treatment of postinfarction left ventricular pseudoaneurysms. *Heart Surg Forum.* (2006) 9:e876–9. doi: 10.1532/HSF98.20061042

9. Fernando AA, Jose LN, Pablo RV, Gonzalo VG, Joan MA, A. Marc G, et al. Surgical treatment of postinfarction left ventricular pseudoaneurysm. *Ann Thorac Surg.* (2007) 83:526–31. doi: 10.1016/j.athoracsur.2006.06.080

10. Narin C, Ege E, Ozkara A, Tanyeli O, Sarkilar G, Soylu A, et al. Surgical treatment of postinfarction pseudoaneurysms of the left ventricle. *J Cardiac Surg.* (2008) 23:294–8. doi: 10.1111/j.1540-8191.2007.00544.x

11. Zhong Z, Song W, Zheng S, Liu S. Surgical and conservative treatment of post-infarction left ventricular pseudoaneurysm. *Front Cardiovasc Med.* (2022) 9:801511. doi: 10.3389/fcvm.2022.801511

12. Alapati L, Chitwood WR, Cahill J, Mehra S, Movahed A. Left ventricular pseudoaneurysm: a case report and review of the literature. *World J Clin Cases.* (2014) 2:90–3. doi: 10.12998/wjcc.v2.i4.90

13. Inayat F, Ghani AR, Riaz I, Ali NS, Sarwar U, Bonita R, et al. Left ventricular pseudoaneurysm: an overview of diagnosis and management. *J Investig Med High Impact Case Rep.* (2018) 6:1–6. doi: 10.1177/2324709618792025

14. Hung MJ, Wang CH, Cherng WJ. Unruptured left ventricular pseudoaneurysm following myocardial infarction. *Heart.* (1998) 80:94.

15. Jiang C, Zhao R, Yang X. Six-year follow-up of a left ventricular pseudoaneurysm without surgical repair. *Can J Cardiol.* (2007) 23:739–41. doi: 10.1016/s0828-282x(07)70821-8

16. Ballester-Rodés M, Flotats A, Torrent-Guasp F, Carrió-Gasset I, Ballester-Alomar M, Carreras F, et al. The sequence of regional ventricular motion. *Eur J Cardio-Thorac.* (2006) 29Suppl:S139–44. doi: 10.1016/j.ejcts.2006.02.058

17. Hinton J, Hunter G, Dissanayake M, Hatrick R. Acute respiratory distress secondary to a huge chronic left ventricular pseudo-aneurysm. *Echo Res Pract.* (2019) 6:K19–22. doi: 10.1530/ERP-19-0018

18. Matteo M, Andrea M, Bettina C, Nicola G. Giant left ventricular pseudoaneurysm following coronary artery bypass graft surgery. *Eur J Cardiothorac Surg.* (2012) 41:e21. doi: 10.1093/ejcts/ezr226

19. Torchio F, Garatti A, Ronco D, Matteucci M, Massimi G, Lorusso R. Left ventricular pseudoaneurysm: the niche of post-infarction mechanical complications. *Ann Cardiothorac Surg.* (2022) 11:290–8. doi: 10.21037/acs-2022-ami-25

20. Lou B, Luo Y, Hao X, Sun L, Deng Y, Guo M, et al. Clinical characteristics and protective factors in patients with acute myocardial infarction undergoing in-hospital myocardial free wall rupture: a single-center, retrospective analysis. *J Investig Med.* (2019) 67:1097–102. doi: 10.1136/jim-2019-001070

21. La Torre MW, Centofanti P, Attisani M, Patanè F, Rinaldi M. Posterior ventricular septal defect in presence of cardiogenic shock: early implantation of the impella recover LP 50 as a bridge to surgery. *Tex Heart Inst J.* (2011) 38:42–9.

22. Patanè F, Grassi R, Zucchetti MC, Ceresa F, Amata AD, Zingarelli E, et al. The use of Impella Recover in the treatment of post-infarction ventricular septal defect: a new case report. *Int J Cardiol.* (2010) 144:313–5. doi: 10.1016/j.ijcard.2009.03.042

23. Abedi-Valugerdi G, Gabrielsen A, Fux T, Hillebrant CG, Lund LH, Corbascio M. Management of left ventricular rupture after myocardial infarction solely with ECMO. *Circ Heart Fail.* (2012) 5:e65–7. doi: 10.1161/CIRCHEARTFAILURE.111.965764

24. Anastasiadis K, Antonitsis P, Hadjimiltiades S, Karapanagiotidis G, Foroulis C, Argiriadou H, et al. Management of left ventricular free wall rupture under extracorporeal membrane oxygenation support. *Int J Artif Organs.* (2009) 32:756–8. doi: 10.1177/039139880903201008

25. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* (2012) 367:1287–96. doi: 10.1056/NEJMoa1208410

26. Thiele H, Zeymer U, Thelemann N, Neumann FJ, Hausleiter J, Abdel-Wahab M, et al. Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction: long-term 6-year outcome of the randomized IABP-SHOCK II Trial. *Circulation.* (2019) 139:395–403. doi: 10.1161/CIRCULATIONAHA.118.038201

27. Liebelt JJ, Yang Y, DeRose JJ, Taub CC. Ventricular septal rupture complicating acute myocardial infarction in the modern era with mechanical circulatory support: a single center observational study. *Am J Cardiovasc Dis.* (2016) 6:10–6.

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 11 October 2022
DOI 10.3389/fcvm.2022.975871

OPEN ACCESS

EDITED BY
Mohammed Idhrees,
SIMS Hospitals, India

REVIEWED BY
Randolph Wong,
Prince of Wales Hospital, China
Martin Rouer,
Hôpital Privé de Villeneuve d'Ascq, France

*CORRESPONDENCE
Xiao-Qiang Li
vasculars@126.com
Min Zhou
zhouminnju@nju.edu.cn

SPECIALTY SECTION
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 22 June 2022
ACCEPTED 20 September 2022
PUBLISHED 11 October 2022

CITATION
Li W-D, Wu G-Y, Song B, Zhao J, Li X-Q and Zhou M (2022) Case report: Remedial surgical treatment of aorto-duodenal fistula with infected aneurysm after endovascular aortic repair.
Front. Cardiovasc. Med. 9:975871.
doi: 10.3389/fcvm.2022.975871

Case report: Remedial surgical treatment of aorto-duodenal fistula with infected aneurysm after endovascular aortic repair

Wen-Dong Li, Guang-Yan Wu, Bin Song, Jie Zhao, Xiao-Qiang Li* and Min Zhou*

Department of Vascular Surgery, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

Aorto-duodenal fistula (ADF) is a rare cause of upper gastrointestinal bleeding, but it is associated with high mortality. It usually occurs in patients with prior aortic surgery or who have undergone aortic graft placement. Abdominal aortic aneurysm (AAA) might be a cause of primary ADF, which could develop into sudden shock. Because ADF is difficult to diagnose, surgery to correct it has a poor outcome. We here report the successful treatment of an ADF complicated with infected AAA after endovascular repair of a ruptured aneurysm of the iliac artery.

KEYWORDS

aorto-duodenal fistula, infected aneurysm, endovascular aortic repair complications, aortic abdominal aneurysm, ruptured iliac artery aneurysm

Case report

A 71-year-old man underwent two rounds of endovascular repair treatment for rupture of an aneurysm of the right iliac artery 6 months prior to the index operation. He presented with recurrent hematemesis, melena, and intermittent fever. He was treated with antibiotics according to the findings of the bacteriology examination of blood samples. PET-CT suggested a gastrointestinal stromal tumor surrounding the abdomen. Emergency endoscopy revealed a fistula of duodenum and minor hemorrhage. The fistula was found in the horizontal part of duodenum. Computed tomography angiography (CTA) scan had revealed an infected abdominal aortic aneurysm (iAAA) with low-density image surrounding the AAA and the right iliac artery (**Figure 1**). However, there was no evidence of contrast leakage into the intestinal tract. Blood tests at the time of the patient's arrival revealed severe anemia, renal dysfunction, elevated white blood cell count, and high levels of serum procalcitonin and C-reaction protein. Blood culture found *Escherichia coli*, which was sensitive to

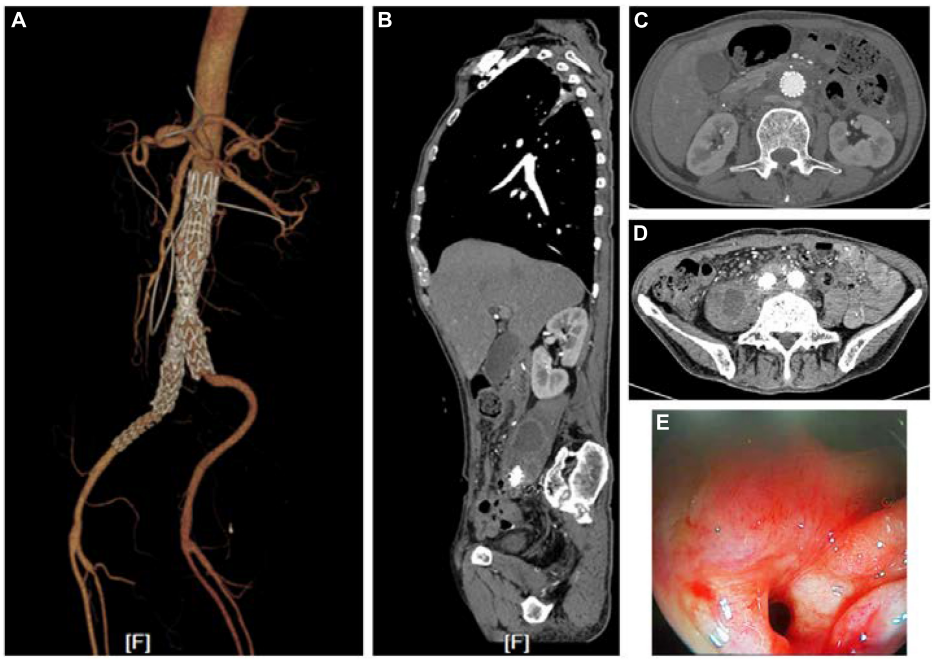


FIGURE 1
Images of CTA and endoscopy before treatments. **(A)** Endovascular repair and drainage had been performed when the patient was hospitalized. **(B–D)** A low-density shadow hinting at an abscess in the right psoas major muscle and around the stenting. **(E)** Fistulae in the horizontal part of duodenum found via endoscopy.

vancomycin. Based on these findings, aorto-duodenal fistula (ADF) and iAAA were suspected.

After a week of antibiotic therapy with vancomycin (500 mg), the fever was controlled. Then, a series of surgeries were performed. The stents in the aneurysm were removed using an injector and supra (**Figure 2**) or infrarenal aortic cross-clamping technique. First, the artery was clamped at the suprarenal aortic site. The primary purpose of this was to reduce blood loss, but it also rendered the endograft easier to remove. After the graft was removed, we clamped the infrarenal aortic site to restore the blood flow to the kidney and prevent renal failure. The aortic aneurysm was replaced *in situ* with an artificial blood vessel made in-house using bovine pericardium biological mesh. The distal end of this artificial blood vessel was sutured to the left common iliac artery. The right common iliac artery and right internal iliac artery were surrounded with pus, which was removed carefully. The stumps of the two arteries were ligated. Femoral artery bypass grafting was performed to restore circulation in the right lower extremity.

There were two 3-mm-wide fistulas between the anterior wall of the AAA and the horizontal part of the duodenum. This was consistent with the findings of endoscopy. The perforated region of the duodenum was resected. A gastrojejunal Roux anastomosis was performed. The cavity was irrigated with 10 L of saline. The momentum was placed between the aorta and duodenum. Many scattered nodules were found around the abdomen. The results of the histological examination showed that chronic inflammatory cells had focally infiltrated into the aneurysmal wall, and that the nodules, which PET-CT suggested could be gastrointestinal stromal tumors, were verified as Schistosoma eggs. Bacterial culture of the pus in the aneurysm showed *Escherichia coli* infection, as in the blood culture before

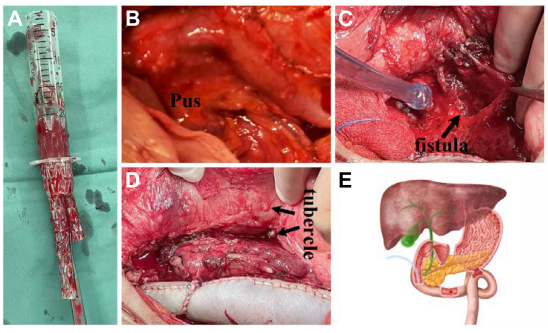


FIGURE 2
Images taken during the operation. **(A)** The stent in the abdominal artery was removed using an injector. **(B,C)** Pus and fistula were found surrounding the horizontal part of duodenum. **(D)** The infected abdominal aortic artery was replaced with a bovine pericardium biological mesh. There were many small masses around the abdomen. Pathological analysis showed this mass to be Schistosoma eggs. **(E)** A schematic diagram of the surgery in the horizontal part of duodenum.

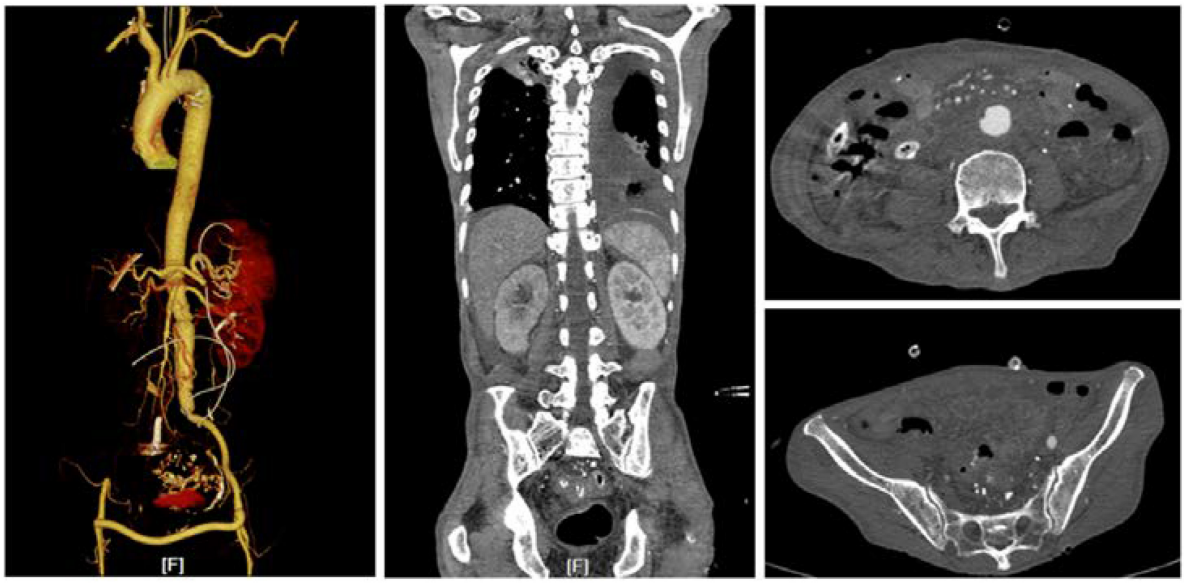


FIGURE 3
CTA result at 1 month after the operation. Abscesses in the abdomen were cured. The bypass vessels and the lumen were unobstructed.

surgery. Antibiotic therapy was maintained postoperatively for at least 6 months with no evidence of recurrent infection as of 6 months into follow-up. There was no blockage of the aorta and femoral artery bypass graftings at CTA 3 months after the indexed operation.

Discussion

Aorto-duodenal fistula is the most common aorto-enteric fistula (1). It most commonly originates from an atherosclerotic AAA (2). It usually involves at the third or fourth duodenal segment, presenting with upper gastrointestinal bleeding but not obstructive syndrome. This may be primary caused by spontaneous communication between the lumen of aortic aneurysm and the intestinal loop, or secondarily caused by surgical repair of aneurysms, becoming detectable months or even years after surgery (1, 3). ADF should be considered for patients with upper gastrointestinal bleeding and a history of surgery with artificial blood vessels or stents in the aorta. Endoscopy combined with CT angiography or arteriography could confirm a definitive diagnosis (4). Delay in diagnosis and treatment has been historically associated with extremely high mortality (5).

Aorto-duodenal fistula management goals include maintaining distal perfusion after controlling the hemorrhage and preventing recurrent infection (6). Once ADF is diagnosed, preventive measures, such as antibiotic therapy, delicate surgery for eradication of septic focus with thorough debridement of infected and devitalized tissue, and reconstruction of the excised aorta by extra-anatomic or an *in situ* route, are required (7, 8). For patients with hemodynamic instability, EVAR can serve as a bridging therapy in cases with problematic bleeding. It can seal the fistula and stop bleeding rapidly (9, 10). For patients with severe purulent infection in AAA and periaortic tissue, extra-anatomic bypass was suggested to be an alternative approach for treatment (11). However, results have shown this method to have a high mortality rate because of high risk of limb loss and aortic stump blowout. *In situ* reconstruction could be performed by homograft, antibiotic-impregnated prosthetic graft, or autologous femoral vein graft. The results of this treatment might depend on the patient's condition, the extent of vascular disease, and the virulence of the bacteria (8, 12, 13). In this case, the infected aortic artery was replaced *in situ* with an artificial blood vessel made by bovine pericardium biological mesh. It also produced good results in the reconstruction of the infected aorta. For the duodenal fistula and infection in the abdomen, gastrojejunal Roux anastomosis was performed. This treatment also produced good results in the repair of the duodenal fistula (**Figures 2**, **3**).

Conclusion

We here reported a case of ADF complicated with iAAA. Diagnosis was made via CTA and endoscopy. Explorative laparotomy, including removal of stents and AAA placement of an artificial blood vessel made of bovine pericardium with biological mesh, grafting of the femoral artery bypass, removal of pus from the right iliac artery, resection of the perforated

region of the duodenum, and gastrojejunal Roux anastomosis, was performed with excellent results.

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

W-DL: manuscript writing. X-QL and MZ: final approval of the manuscript. All authors participate in the treatments of this case.

Acknowledgments

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Conflict of interest

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

Publisher's note

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

References

1. Geraci G, Pisello F, Li Volsi F, Facella T, Platia L, Modica G, et al. Secondary aortoduodenal fistula. *World J Gastroenterol.* (2008) 14:484–6.

2. Keunen B, Houthoofd S, Daenens K, Hendriks J, Fourneau I. A case of primary aortoenteric fistula: review of therapeutic challenges. *Ann Vasc Surg.* (2016) 33:230.e5–13. doi: 10.1016/j.avsg.2015.11.033

3. Honjo O, Yamada Y, Arata T, Matsuno T, Kurokawa T, Kushida Y. A primary aorto-duodenal fistula associated with an inflammatory abdominal aortic aneurysm: a case report. *Acta Med Okayama.* (2005) 59:161–4.

4. Ichita C, Sasaki A, Sumida C, Kimura K, Nishino T, Tasaki J, et al. Clinical and endoscopic features of aorto-duodenal fistula resulting in its definitive diagnosis: an observational study. *BMC Gastroenterol.* (2021) 21:45. doi: 10.1186/s12876-021-01616-9

5. Bissacco D, Freni L, Attisani L, Barbetta I, Dallatana R, Settembrini P. Unusual clinical presentation of primary aortoduodenal fistula. *Gastroenterol Rep (Oxf).* (2015) 3:170–4.

6. Miura S, Kurimoto Y, Ujihira K, Masuda T, Yanase Y, Iba Y, et al. Emergency endovascular aneurysm repair coupled with staged omentopexy for primary aorto-duodenal fistula. *Ann Vasc Dis.* (2020) 13:183–6. doi: 10.3400/avd.cr.19-00104

7. Kavanagh DO, Dowdall JF, Younis F, Sheehan S, Mehigan D, Barry MC. Aorto-enteric fistula: changing management strategies. *Ir J Med Sci.* (2006) 175:40–4. doi: 10.1007/BF03168999

8. Savlania A, Tripathi RK. Aortic reconstruction in infected aortic pathology by femoral vein "neo-aorta". *Semin Vasc Surg.* (2019) 32:73–80. doi: 10.1053/j.semvascsurg.2019.07.002

9. Baril DT, Carroccio A, Ellozy SH, Palchik E, Sachdev U, Jacobs TS, et al. Evolving strategies for the treatment of aortoenteric fistulas. *J Vasc Surg.* (2006) 44:250–7.

10. Lonn L, Dias N, Veith Schroeder T, Resch T. Is EVAR the treatment of choice for aortoenteric fistula? *J Cardiovasc Surg (Torino).* (2010) 51:319–27.

11. Pagni S, Denatale RW, Sweeney T, McLaughlin C, Ferneini AM. Primary aorto-duodenal fistula secondary to infected abdominal aortic aneurysms: the role of local debridement and extra-anatomic bypass. *J Cardiovasc Surg (Torino).* (1999) 40:31–5.

12. Brown PM Jr., Kim VB, Lalikos JF, Deaton DH, Bogey WM, Powell CS. Autologous superficial femoral vein for aortic reconstruction in infected fields. *Ann Vasc Surg.* (1999) 13:32–6. doi: 10.1007/s100169900217

13. Thrush S, Watts A, Fraser SC, Edmondson RA. Primary autologous superficial femoral vein reconstruction of an emergency, infected, ruptured aortic aneurysm. *Eur J Vasc Endovasc Surg.* (2001) 22:557–8. doi: 10.1053/ejvs.2001.1518

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 18 October 2022
DOI 10.3389/fcvm.2022.991886

OPEN ACCESS

EDITED BY
Xiaofeng Yang,
Temple University, United States

REVIEWED BY
Gopal Chandra Ghosh,
Rabindranath Thakur Diagnostic and Medical Care Center, India
Wuqiang Zhu,
Mayo Clinic Arizona, United States

*CORRESPONDENCE
Ratko Lasica
drlasica@gmail.com

SPECIALTY SECTION
This article was submitted to Cardiovascular Therapeutics, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 12 July 2022
ACCEPTED 23 September 2022
PUBLISHED 18 October 2022

CITATION
Lasica R, Spasic J, Djukanovic L, Trifunovic-Zamaklar D, Orlic D, Nedeljkovic-Arsenovic O and Asanin M (2022) Case report: Acute toxic myocardial damage caused by 5-fluorouracil—from enigma to success.
Front. Cardiovasc. Med. 9:991886.
doi: 10.3389/fcvm.2022.991886

Case report: Acute toxic myocardial damage caused by 5-fluorouracil—from enigma to success

Ratko Lasica[1]*, Jelena Spasic[2], Lazar Djukanovic[1], Danijela Trifunovic-Zamaklar[3], Dejan Orlic[3], Olga Nedeljkovic-Arsenovic[4] and Milika Asanin[1]

[1]Department of Cardiology, Emergency Center, University Clinical Center of Serbia, Belgrade, Serbia, [2]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia, [3]Department of Cardiology, University Clinical Center of Serbia, Belgrade, Serbia, [4]Center for Radiology and Magnetic Resonance, University Clinical Center of Serbia, Belgrade, Serbia

Considering the pandemic of both cardiovascular diseases and oncological diseases, there is an increasing need for the use of chemotherapy, which through various pathophysiological mechanisms leads to damage to heart function. Cardio toxicity of chemotherapy drugs can manifest itself in a variety of clinical manifestations, which is why establishing a valid diagnosis is a real mystery for clinicians. Acute systolic heart failure (AHF) due to the use of 5-fluorouracil (5-FU) is a rare occurrence if it is not associated with myocardial infarction, myocarditis or Takotsubo cardiomyopathy. Therefore, we decided to present a case of an 52-year-old male who was diagnosed with stage IV RAS wild-type adenocarcinoma of the rectum and in whom the direct toxic effect 5-FU is the main reason for the appearance of toxic cardiomyopathy.

KEYWORDS

cancer, 5-fluorouracil, toxic myocardial damage, cardiomyopathy, acute coronary syndrome

Introduction

The application of both chemotherapy and targeted therapy has greatly improved the outcome of cancer patients, however, there is a large amount of evidence that indicates potential cardiotoxic complications of their use (1–3). Manifestation of the cardiotoxic effect of the administered drug can endanger the patient's life in two ways, both by direct impact on cardiac function and by the indicated discontinuation of the antineoplastic drug, which can worsen the prognosis of the oncology patient. Diagnosing cardiotoxicity is a difficult differential diagnostic task, because despite the well-known time correlation between receiving antineoplastic therapy and damage to heart function, the clinical picture of patients can be different. The cardiotoxic effect of specific therapy can be accompanied by minimal symptoms to severe AHF.

Fluoropyrimidines (5-fluorouracil and capecitabine) are antineoplastic drugs that have the most negative effect on the cardiovascular system, leading to anginal complaints such as stable angina pectoris, acute coronary syndrome (ACS) or the development of

heart failure (4–6). Acute systolic heart failure due to 5-FU administration is rare unless associated with myocardial infarction, diffuse coronary vasospasm, toxic myocarditis, or Takotsubo cardiomyopathy (7). The most common adverse reaction caused by oxalipatin include nausea, vomiting, acute and cumulative peripheral sensory neuropathy and allergic reactions (8). As for cardiotoxicity, QT prolongation and ventricular arrhythmias have been reported after oxaliplatin (9), but direct toxic effect to the heart has rarely been described (10, 11). In order to prove the exclusive cardiotoxic effect of drugs as the cause of cardiac disease, in addition to the basic diagnostic methods [electrocardiogram (ECG), echocardiographic examination, and laboratory biomarkers of heart damage (brain natriuretic peptide- BNP; NT pro BNP)] for establishing a final diagnosis, it is recommended coronary angiography and cardiomagnetic resonance of the heart (CMR) (12). Not infrequently, intravascular ultrasound (IVUS) is performed which is an intravascular imaging modality primarily used in interventional cardiology to characterize lesion morphology, quantify plaque burden, guide stent sizing, assess stent expansion, and identify procedural complications. IVUS assessment can distinguish between calcified plaque, lipid, and neointimal proliferation.

According to the consensus of experts of the European Association of Cardiologists (ESC), Cancer therapeutics–related cardiac dysfunction (CTRCD) is defined as a decrease in the left ventricle ejection fraction (LVEF) of > 10 percentage points, to a value below the lower limit of normal (13). The presence of atherosclerotic plaques on angiography requires an assessment of their functional significance. Also, the possibility of existence an acute myocardial infarction (AMI) without obstruction of the blood vessels of the heart -MINOCA requires additional evaluation of the patient and the application of more sophisticated methods of proving myocardial damage. It is very important to differentiate these conditions in oncology patients, not only because of the application of different therapeutic modalities, but also because of the continuation of the treatment of the primary disease.

Case report

A 52-year-old male, current heavy smoker, with no known comorbidities, was diagnosed with stage IV RAS wild-type adenocarcinoma of the rectum, with metastases in the liver and retroperitoneal lymph nodes in April 2022. About 2 weeks prior to the start of chemotherapy, he had been seen by a cardiologist due to asymptomatic ventricular extra systoles seen on routine ECG. At that time echocardiogram was unremarkable with LVEF of 65%; LV had normal end-diastolic diameter (EDD) and end-systolic diameter (ESD) (EDD/ESD−52 mm/33 mm). No disturbances were registered in segmental LV kinetics. LV diastolic function was preserved.

Upon admission to the Department of Oncology, he was started on FOLFOX-6 chemotherapy with planned administration of panitumumab, as per current guidelines (14). Panitumumab infusion was planned on day 3 of treatment, for technical reasons. He received 85 mg/m^2 of oxaliplatin, followed by 400 mg/m^2 leucovorin, 400 mg/m^2 5-FU i.v.bolus and 2400 mg/m^2 continuous infusion of 5-FU over 46 h. Approximately 24 h into the continuous 5-FU infusion he started complaining of pain in the epigastrium that propagated toward the lower third of the sternum and slight nausea, with no shortness of breath, palpitations or dizziness. Infusion of 5-FU was stopped immediately. At this time, panitumumab had not yet been administered.

Upon examination he was hypertensive at 180/100 mmHg, slightly tachycardic with HR of 115/min, afebrile. ECG initially showed peaked T waves with no ST changes (Figure 1A). Initial values of high sensitivity Troponin (Hs-cTn) were in the reference range.

Due to persisting symptoms and evolution of ECG changes he was transferred to cardiac intensive care unit (ICU).

Upon admission to the ICU, the patient continued to complain of pain in the epigastrium spread to the lower third of the sternum, nausea and sweating. Vital signs on admission showed a heart rate of 95 beats/min, arterial blood pressure 110/80 mmHg on both arms, respiration rate 20/min, arterial oxygen saturation 96%. During the examination, the patient was conscious, oriented without focal neurological outbursts and cyanosis. Signs of heart failure (gallop rhythm—present third heart sound) and symptoms of heart failure (dyspnea, tachypnea, orthopnea) with the appearance of late-inspiratory crackles in the lower lung fields were registered.

In the ECG, after 10 h from the initial ECG, an evolution was registered in relation to the previous finding (concave elevation of the ST segment in the inferior and lateral series of leads with frequent single VES) (Figure 1B) and at 15 h from the initial ECG ST elevation is registered in the same series of leads with the appearance of terminally negative T waves (Figure 1C).

On the first therapeutic day, an ECHO of the heart was performed, where an enlarged LV was registered (EDD/ESD LV- 65/51 mm), with the presence of segmental wall motion abnormalities of the LV. Akinesia of the apical and medial third of the left ventricle as well as the basal segment of the interventricular septum was registered, while the remaining segments of the LV were hypokinetic. No signs of left ventricular apex ballooning were observed. Estimated EF using Simpson's Biplane method was 15–20%. There were no signs of valve disease or pericardial effusion. In laboratory analyses, non-significant increase in Hs-cTnT values was registered (12...168. . . 64..12 ng/L; ref. range < 14 ng/L). A slight increase in Hs-cTnT was not accompanied by elevated values of creatinine kinase (CK) (64...40...20 U/L; ref. range 0.0-200 U/L), MB fraction of CK (CK-MB) (2 U/ L; ref. range < 25 U/L) nor lactate dehydrogenase (LDH) [340...328 (ref. value 220-460

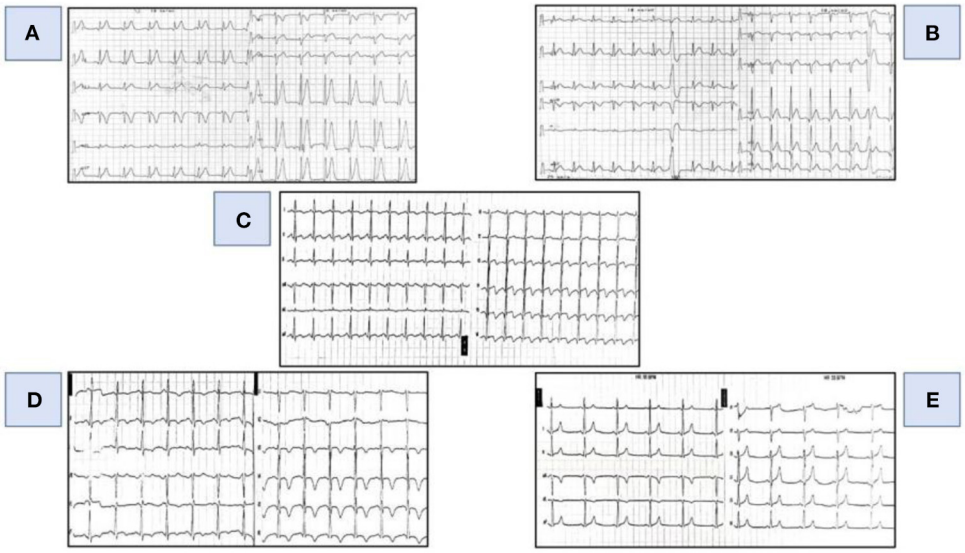


FIGURE 1
Evolutionary changes in the ECG. **(A)** (First day-07.14 AM: ECG at initial presentation): tall, spiky T waves diffusely in the ECG. **(B)** (First day-07.57 PM): concave ST elevation in the inferior and lateral series of leads. **(C)** (First day- 22.09 PM): ST elevation in the inferior and lateral series of leads with terminally negative T waves. **(D)** (Second day- 06.50 AM)**:** negative T waves in the inferior and lateral series of leads. **(E)** (Fifth day- 07.00 AM): normal electrocardiogram.

U/L)]. Although we knew that Hs-cTnt can be easily elevated in patients with AHF, such as our patient, we suspected that it was an acute coronary syndrome. There was no increase in inflammatory markers (CRP, leukocytes and procalcitonin) as well as nitrogen substances and D-dimer.

In view of the clinical picture, ECG changes as well as the findings of echocardiography, the patient underwent cardiac catheterization, which did not register angiographically significant narrowing of the large blood vessels of the heart. Coronary artery vasospasm was not visualized during coronary angiography. Considering the findings of the coronary angiography, a working diagnosis of myocardial infarction without obstruction of the blood vessels of the heart was made—MINOCA (15).

In order to establish/exclude the diagnosis, the patient underwent in the second act automated intravascular ultrasound (IVUS) system, pull/back interrogation (0.5 mm/s) of all three coronary arteries. IVUS showed normal trilaminar appearance of vessel wall and absence of atherosclerotic disease. In addition, signs of plaque rupture, plaque erosion or thrombus were not found in either of all three coronary arteries (Figure 2).

Medical treatment continued (coronary vasodilators, calcium channel blockers, ACE- inhibitors, beta-blockers, low-molecular-weight heparin, diuretics with the use of antiarrhythmic—amiodarone) in the ICU, where he was monitored all the time. Rapid evolutionary changes on daily basis were still registered in the ECG, and on the 2nd day of therapy negative T waves were registered in the inferior and lateral leads (Figure 1D) while, on the 5th day of therapy, a normal ECG was registered (Figure 1E).

During the next 7 days, control echocardiographic examinations were performed on several occasions. Given that we still did not have a clear diagnosis, in order to eliminate the differential diagnostic dilemma between myocardial infarction without changes in the blood vessels of the heart (MINOCA) and toxic cardiomyopathy caused by 5-FU, the patient underwent CMR. It was performed on the seventh therapeutic day from the onset of symptoms according to ESC recommendations (16). Cardio magnetic resonance should have considered the presence of scar in the endocardium/myocardium, the presence of micro- vascular obstructions, the presence of hemorrhage in the myocardium, myocardial edema and the detection of the so-called "gray zone"—the zone at risk or to prove signs of the presence of dilated cardiomyopathy caused by 5-FU.

Examination of the heart was performed in standard planes using functional True FISP sequences and TSE morphological sequences in three planes without contrast medium application, as well as after contrast application with IR sequence and T1 and T2 maps using Modified Look Locker inversion recovery (MOLLI) sequence. Reduced LV systolic function was registered (EF 40%); LV was dilated (EDD/ESD- 62/47 mm), normal wall thickness, enlarged EDV (202 ml; ref 77–195 ml) and ESV (121 ml; ref 19–72 ml), overall hypo contractile without segmental LV wall abnormalities.

Post-contrast, a smaller linear zone of late gadolinium accumulation (LGE) was observed—septal fibrosis

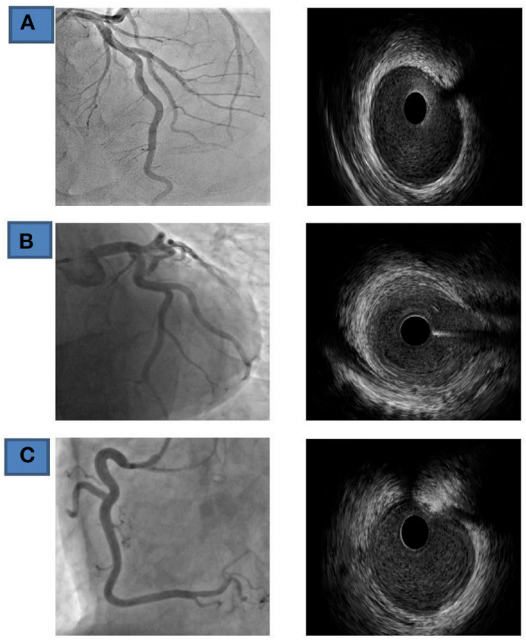


FIGURE 2
Coronary findings and IVUS (Fifth day of admission) **(A)** LAD, left anterior-descending coronary artery. **(B)** Cx, circumflex coronary artery; **(C)** RCA- right coronary artery.

intramyocardially in the basal part of the septum with inhomogeneous opacification of the entire myocardium, primarily as part of the post-therapeutically altered myocardium (cardio toxicity). No signs of localized edema or necrosis of LV were registered. According to radiologists and CMR findings, changes in the myocardium first correspond to changes in cardiotoxicity (Figure 3).

During hospitalization, a drop in TnT was registered in the laboratory with the normalization of natriuretic peptides.

Transthoracic echocardiography (TTE) on the fifth day of admission revealed an enlarged LV (EDV 182 ml, ESV 113 ml), severely hypokinetic, with depressed EF (30%) and spontaneous contrast within the cavity. Global longitudinal function was significantly reduced (GLS-9.5%) with prominent mechanical dispersion (PSD 80.5 ms), detected by 2D speckle tracking echocardiography.

Thirteen days after, TTE confirmed the presence of enlarged LV (EDV 168 ml, ESV 71 ml), but with significantly better LV EF (58%), improved global longitudinal function (−17.6%), and significantly more synergic intraventricular contractions (PSD 44.6 ms) (Figure 4).

The patient was discharged home in good general condition. Frequent check-ups by a cardiologist are advised. Further oncological treatment was advised based on the opinion of the cardiology-oncology council (Supplementary Figure 1).

Discussion

Thanks to the recommendations of the ESC and the American Heart Association (AHA), it would be logical that the diagnosis of AMI based on the clinical picture of the patient, ECG changes and elevated troponin values is very easy (16–18). However, we are faced with the fact that we also have a certain number of patients in whom the diagnosis is difficult or in whom the diagnosis of AMI is incorrectly established. According to a systematic review by Kwok, Chun Shing et al., which included 15 studies, it was shown that the diagnosis of AMI is missed in 1–2% of patients (19).

Reasons for missed AMI diagnosis include incorrect electrocardiogram interpretation and failure to order appropriate diagnostic tests. Navi et al. showed that patients with cancer have a 3-fold higher risk of AMI compared to patients without cancer (20). The prothrombogenic state and hyper viscosity of blood in patients with cancer can lead to the formation of arterial thrombosis, while the use of drugs as part of chemotherapy can lead to endothelial cell damage predisposing to erosion and rupture of the atherosclerotic plaque and thus lead to AMI type I. On the other hand, AMI Type II can be provoked by tachycardia, hypotension, hypoxia or anemia, as well as vasospasm due to the use of chemotherapy drugs (21).

In our patient, the presence of pain in the epigastrium with propagation in the lower third of the sternum, changes in the ECG and new changes in the echocardiography, which he did not have before chemotherapy, as well as slightly elevated values of Hs-cTnT raised suspicion that it is AMI. However, elevated values of Hs-cTnT in AHF may be due to non-ischemic events (e.g., increased afterload, increased preload, oxidative stress, etc.) (22). Studies have shown that in patients with AHF, a certain pathological stimulus can cause the release of troponin directly from the cytosol of otherwise intact myocytes, which are called the cytosolic pool (22). Also, the effects of stretching, increased volume, and pressure overload that occur with AHF should not be overlooked. Numerous stressors, such as inflammatory mediators and neurohumoral stimulation may also have an effect on increasing cTn values in patients with AHF. In the ADHERE study, 75% of patients hospitalized with AHF (67 924) had detectable levels of cTn (cTnI >0.4 ng/ml or cTnT >0.01 μg/l). When a higher threshold for cTn values was used (cTnI of 1.0 ng/ml or cTnT of 0.1 g/l), about 6.5% of patients with AHF had values above this level (23). Similar data were shown by the study of Logeart D. and colleagues in a patient with heart failure of non-ischemic etiology (24). In the study by You JJ and colleagues in which 2025 AHF patients were analyzed, the prevalence of cTnI values above the 99th percentile was registered in 34.5% of patients (25). Increased troponin values can be detected early in chemotherapy administration, long before LV functional damage is detected by

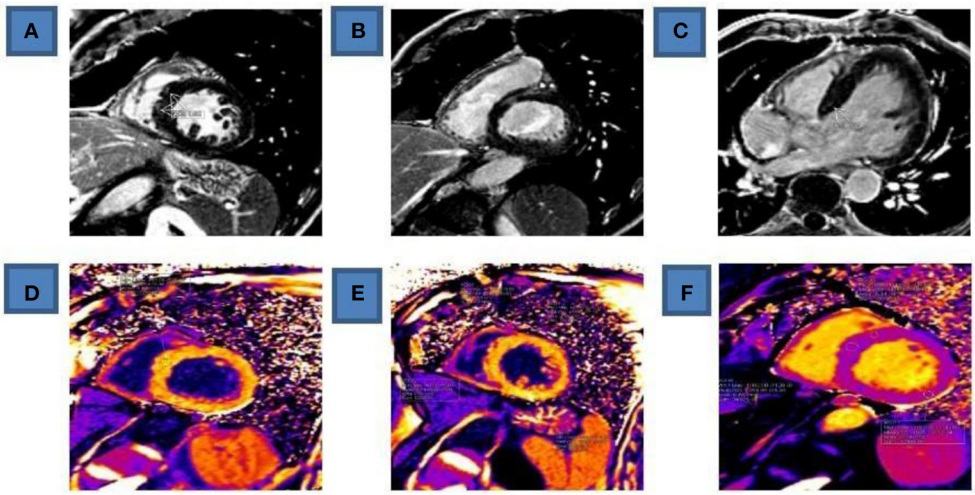


FIGURE 3
CMR of the heart (Fifth day of admission). **(A)** Postcontrast LGE in medial septum on PSIR sequence, SAX. (**B**) Basal anteroseptal postcontrast LGE on PSIR sequence, SAX. **(C)** Basal septum LGE phenomenon as well as pericard LGE in basal and medial lateral wall on PSIR sequence, four chamber view. **(D)** Pathological postcontrast T1 mapping (values > 500 ms) in basal septum, on MOLLI sequence, SAX. (**E**) Pathological postcontrast T1 mapping (values > 500 ms) in medial segments of all walls, circumferentially, on MOLLI sequence, SAX. **(F)** Pathological precontrast T1 mapping (values > 1100 ms) in basal septum and lateral wall. LGE, Postcontrast late gadolinium enhancement; PSIR, Phase sensitive inversion recovery; SAX, short axis view; MOLLI, Modified Look Locker inversion recovery.

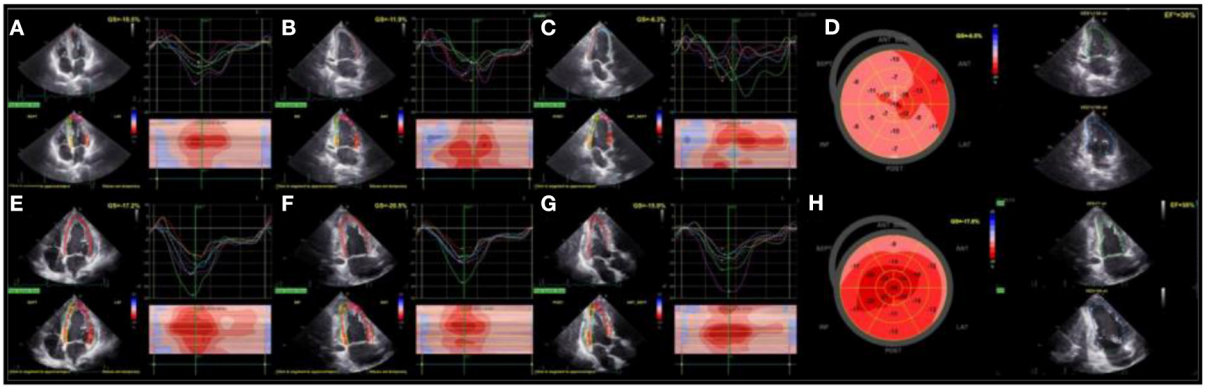


FIGURE 4
Assessment of LV function with TTE (On the fifth day of admission): LV systolic function was severely impaired, including impaired and asynergic longitudinal deformations that can be appriciated from speckle tracking analysis of apical 4- chamber **(A)**, 2-chamber **(B)**, and 3-chamber **(C)** views and globally from polar map **(D)**. During the follow-up (eighteenth day), LV EF and longitudinal deformations significantly improved **(E–H)**. LV, left ventricle; TTE, transthoracic echocardiography; EF, left ventricular ejection fraction.

available techniques. Cardinale et al. by serial measurement of cTnI levels in serum during the administration of chemotherapy showed that elevated TnI values are associated with a progressive decrease in LVEF (26).

In relation to AMI with obstruction of blood vessels (> 50% obstruction), myocardial infarction with non-obstructive coronary arteries (MINOCA) is a heterogeneous clinical entity, characterized by clinical evidence of myocardial infarction (MI) with non-obstructive coronary arteries on angiography (≤50% stenosis) (27). The prevalence of MINOCA is 3.5–15% (27). When MINOCA is suspected in most cases, additional invasive and non-invasive tests are needed to establish its diagnosis. IVUS often diagnoses the presence of plaque rupture or ulceration, which is a frequently missed finding in women who have had MINOCA (28). The presence of plaque rupture or ulceration in the coronary arteries in patients with MINOCA is diagnosed with IVUS in about 40% of cases (29, 30). Based on the aforementioned research, we first performed IVUS and then

CMR in our patient. ESC recommendations suggest the use of CMR in all patients with suspected MINOCA, as it identifies its underlying cause in 87% of patients (17). In our patient, the application of CMR helped to resolve this differential-diagnostic dilemma.

The occurrence of cardiac dysfunction, depending on the manifestations of the disease after the administration of chemotherapy, can be acute, subacute and chronic (31). Changes in cardiac function can be reversible or irreversible (32). Our patient had acute cardiac dysfunction that was reversible. AHF, cardiogenic shock, and even sudden cardiac death if not explained by coronary vasospasm can be caused by myocardial inflammation or the presence of Takotsubo cardiomyopathy as a consequence of the action of 5-FU (33–36).

Anthracyclines are a group of drugs that most often lead to cardiotoxicity (AHF occurs in 2–4% of patients), followed by 5-FU pyrimidine analog, which is widely used for the treatment of many solid tumors, including colorectal, breast and head and neck cancers (33, 37). Incidence of cardio toxicity after application 5-FU moves from 1 to 35% in various studies and mortality from 2 to 13% (38–41). The incidence of the development of myocardial damage depends on the administered dose, the distribution of the drug and the method of its administration. The greatest risk of developing cardiotoxicity is during the first administration of the drug (33, 40). However, there is a schedule-dependent difference, with a higher risk of developing cardiac toxicity when using continuous infusion of 5-FU in comparison to bolus infusion, possibly related to the short half-life of 5-FU, which is 15–20 min (39, 42).

The most frequently documented symptom of cardiotoxicity with 5-FU administration is chest pain. However, care should be taken in patients with cancer because the symptoms of AMI can be atypical, with some authors stating that dyspnea (and not chest pain) is the most common presentation of the disease (43). In a study by Jensen et al., during treatment of colorectal cancer patients with the FOLFOX regimen, the incidence of chest pain was found to be about 8.5% (44). In our patient, the cardio toxicity of 5-FU manifested itself during the continuous infusion of 5-FU and was accompanied by pain in epigastrium with propagation in the lower third of the sternum. In patients treated with 5-FU, anginal complaints occur in 45% of patients, and heart failure in 2% of patients (45). Oxaliplatin, unlike 5-FU, more often leads to gastrointestinal complaints, hypersensitivity reactions, even anaphylactic shock (46) and far less often has cardiac side effects in the form of disturbances in the electrical activity of the heart, which can be manifested by the appearance of arrhythmias or conduction blocks (9, 47).

A marked heterogeneity has been shown in terms of ECG changes in patients treated with 5-FU (48–50). Changes in the ECG can easily mislead physicians when it comes to cardio toxicity with 5-FU. Ischemic changes in the ECG are found far more often in patients with previously proven coronary disease (51). Changes in the form of hyper acute T waves have also been described (52). Mizuno et al. reported a case of 5-FU-induced cardiomyopathy, which presented with chest pain, ECG-changes in the form of diffuse ST-elevation, diffuse LV kinetic disturbances with normal coronary arteries on angiography. The aforementioned authors considered that coronary vasospasm was not the cause of cardiomyopathy in this patient (53). The changes in the electrocardiogram in our patient could indicate a possible pericardial affection caused by the toxic effect of the drugs. It is recommended that all patients who receive 5-FU and develop chest pain with ischemic changes in the ECG undergo angiography. Most often, the findings are normal, and transient changes in the form of ST elevation are explained by transient vasospasm, which is registered angiographically (7, 54).

In some cohorts, coronary artery vasospasm was directly visualized during coronary angiography, but this was not the case in our patient. Although no vasospasms were registered during coronary angiography, shorter vasospasms could not be ruled out. Our patient could not have diffuse vasospasms because their occurrence would be followed on CMR by myocardial edema and late accumulation of gadolinium in the subendocardial part of the myocardium. Even the application of nitroglycerin and calcium blockers in our patient did not lead to the resolution of changes in the ST segment, which would otherwise happen if it were really about vasospasm. Various studies have shown different coronary angiography findings, from clear vessels to the presence of significant occlusions (39, 55, 56). In our patient, IVUS did not show the presence of plaque rupture, plaque erosion, thrombosis, i.e., significant stenoses on the blood vessels of the heart.

Sudden HF in our patient is not a consequence of Takotsubo cardiomyopathy, not only because of the absence of echocardiographic criteria (LV ballooning), but also because the Gothenburg criteria exclude the diagnosis of Takotsubo syndrome if there is suspicion of drug-induced cardiotoxicity (57). Nor were the 2008 Mayo criteria for the diagnosis of Takotsubo cardiomyopathy met (58). The use of CMR excluded the existence of segmental abnormalities in kinetics, myocardial edema (which would be in favor of toxic myocarditis) as well as microvascular obstructions, all of which were in favor of acute dilated toxic cardiomyopathy. We also consider it almost impossible that LV changes caused by acute myocarditis and consequent severe dilated cardiomyopathy on echocardiography are completely reversible and that in such a short period of time as in our patient. In patients with myocarditis and severely impaired cardiac function (<25%) who were treated with immunomodulatory drugs, it was shown that the recovery of cardiac function usually occurs between 6 and 14 weeks after the start of therapy. In about a third of patients, that recovery begins only between the 2nd and 4th months (59). In acute myocarditis, the left ventricle is damaged for a long time with reduced systolic function. A possible pathophysiological cause of acute toxic impairment of LV function after 5-FU administration could be a

sudden decrease in the level of adenosine triphosphate, which is also described in the literature (7, 60).

Conclusions

In addition to the very great therapeutic effect of 5-FU in the treatment of patients with rectal cancer, its use is often associated with heart diseases. Fluoropirimidines are amongst the most commonly-used cardiotoxic antineoplastic drugs, with cardiotoxic effects ranging from asymptomatic ECG changes to sudden cardiac death, suspected to be caused by coronary vasospasm. Although the literature states that coronary vasospasms, thrombosis and toxic myocarditis are the most common causes of AHF LV in patients treated with 5-FU, it can often occur due to the direct toxic effect of the drug. Our case report presents an uncommon clinical manifestation of 5FU cardiotoxicity. Summarizing the knowledge available in the world literature so far, we have differentially considered all cardiac diseases that can occur due to the toxic effect of 5-FU. If rapid reversibility of changes on the electrocardiogram and rapid echocardiographic recovery of heart function is registered, this would be in favor of the fact that the disease is not of ischemic origin. Newly diagnosed acute dilated cardiomyopathy followed by heart failure in the absence of angiographically significant stenosis on the blood vessels of the heart and CMR criteria for ischemic or inflammatory myocardial disease should always raise the suspicion of toxic reversible cardiomyopathy caused by 5-FU. In the case of our patient, the most modern diagnostic methods were used to rule out differential-diagnostic dilemmas and establish a diagnosis. Taught by our experience, we recommend a mandatory ECHO strain for every patient before chemotherapy, and if there are cardiac complications, during or after the application of chemotherapy, a serious cardiological-oncological approach, both in the administration of an interventional therapeutic regimen and in order to continue the adequate treatment of an oncological patient.The fact that the mechanisms by which 5- FU leads to myocardial damage are still not fully explained requires the implementation of new clinical studies that will resolve this dilemma.

Data availability statement

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

Author contributions

Conceptualization, methodology, investigation, data curation, writing, and original draft preparation: RL and LD. Original draft preparation: JS and MA. Investigation: DT-Z, DO, and ON-A. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

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

Publisher's note

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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.991886/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Values of laboratory parameters and results of diagnostic methods in relation to the time period of hospitalization.

References

1. Adhikari A, Asdaq SMB, Al Hawaj MA, Chakraborty M, Thapa G, Bhuyan NR, et al. Anticancer drug-induced cardiotoxicity: insights and pharmacogenetics. *Pharmaceuticals (Basel).* (2021) 14:970. doi: 10.3390/ph14100970

2. Dong J, Chen H. Cardiotoxicity of anticancer therapeutics. *Front Cardiovasc Med.* (2018) 5:9. doi: 10.3389/fcvm.2018.00009

3. Morelli MB, Bongiovanni C, Da Pra S, Miano C, Sacchi F, Lauriola M, et al. Cardiotoxicity of anticancer drugs: molecular mechanisms and strategies for cardioprotection. *Front Cardiovasc Med.* (2022) 9:847012. doi: 10.3389/fcvm.2022.847012

4. Karakulak UN, Aladag E, Maharjan N, Övünç K. Capecitabine-induced coronary artery vasospasm in a patient who previously experienced a similar episode with fluorouracil therapy. *Turk Kardiyol Dern Ars.* (2016) 44:71–4. doi: 10.5543/tkda.2015.36005

5. Jurczyk M, Król M, Midro A, Kurnik-Łucka M, Poniatowski A, Gil K. Cardiotoxicity of fluoropyrimidines: epidemiology, mechanisms, diagnosis, and management. *J Clin Med.* (2021) 10:4426. doi: 10.3390/jcm10194426

6. Yuan C, Parekh H, Allegra C, George TJ, Starr JS. 5-FU induced cardiotoxicity: case series and review of the

literature. *Cardiooncology.* (2019) 5:13. doi: 10.1186/s40959-019-0048-3

7. Fakhri Y, Dalsgaard M, Nielsen D, Lav Madsen P. 5-Fluorouracil-induced acute reversible heart failure not explained by coronary spasms, myocarditis or takotsubo: lessons from MRI. *BMJ Case Rep.* (2016) 2016:bcr2015213783. doi: 10.1136/bcr-2015-213783

8. Oxaliplatin package insert and prescribing information. Available online at: https://www.drugs.com/pro/oxaliplatin.html

9. Chen X, Wang H, Zhang Z, Xu Y, An X, Ai X, et al. Case report: oxaliplatin-induced third-degree atrioventricular block: first discovery of an important side-effect. *Front Cardiovasc Med.* (2022) 9:900406. doi: 10.3389/fcvm.2022.900406

10. Weidner K, Behnes M, Haas J, Rusnak J, Fuerner P, Kuska M, et al. Oxaliplatin-induced acute ST-segment elevation mimicking myocardial infarction: a case report. *Oncol Res Treat.* (2018) 41:52–6. doi: 10.1159/000480661

11. Chang PH, Hung MJ, Yeh KY, Yang SY, Wang CH. Oxaliplatin-induced coronary vasospasm manifesting as Kounis syndrome: a case report. *J Clin Oncol.* (2011) 29:e776–8. doi: 10.1200/JCO.2011.36.4265

12. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* (2014) 27:911–39. doi: 10.1016/j.echo.2014.07.012

13. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. ESC Scientific Document Group. (2016) ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J.* (2016) 37:2768–01. doi: 10.1093/eurheartj/ehw211

14. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol.* (2016) 27:1386–422. doi: 10.1093/annonc/mdw235

15. Mukherjee D. Myocardial infarction with nonobstructive coronary arteries: a call for individualized treatment. *J Am Heart Assoc.* (2019) 8:e013361. doi: 10.1161/JAHA.119.013361

16. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393

17. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* (2021) 42:1289–67. doi: 10.1093/eurheartj/ehab088

18. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* (2013) 61:e78–e140.

19. Kwok CS, Bennett S, Azam Z, Welsh V, Potluri R, Loke YK, et al. Misdiagnosis of acute myocardial infarction: a systematic review of the literature. *Crit Pathw Cardiol.* (2021) 20:155–62. doi: 10.1097/HPC.0000000000000256

20. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV, et al. risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol.* (2017) 70:926–38. doi: 10.1016/j.jacc.2017.06.047

21. Costa IBSDS, Andrade FTA, Carter D, Seleme VB, Costa MS, Campos CM, et al. challenges and management of acute coronary syndrome in cancer patients. *Front Cardiovasc Med.* (2021) 8:590016. doi: 10.3389/fcvm.2021.590016

22. Harrison N, Favot M, Levy P. The role of troponin for acute heart failure. *Curr Heart Fail Rep.* (2019) 16:21–31. doi: 10.1007/s11897-019-0420-5

23. Peacock WF. 4th, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, et al.; ADHERE investigators. Cardiac troponin and outcome in acute heart failure. *N Engl J Med.* (2008) 358:2117–26. doi: 10.1056/NEJMoa0706824

24. Logeart D, Beyne P, Cusson C, Tokmakova M, Leban M, Guiti C, et al. Evidence of cardiac myolysis in severe nonischemic heart failure and the potential role of increased wall strain. *Am Heart J.* (2001) 141:247–53. doi: 10.1067/mhj.2001.111767

25. You JJ, Austin PC, Alter DA, Ko DT, Tu JV. Relation between cardiac troponin I and mortality in acute decompensated heart failure. *Am Heart J.* (2007) 153:462–70. doi: 10.1016/j.ahj.2007.01.027

26. Cardinale D, Sandri MT, Martinoni A, Borghini E, Civelli M, Lamantia G, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. *Ann Oncol.* (2002) 13:710–5. doi: 10.1093/annonc/mdf170

27. Tamis-Holland JE. Jneid H. Myocardial infarction with nonobstructive coronary arteries (MINOCA): it's time to face reality! *J Am Heart Assoc.* (2018) 7:e009635. doi: 10.1161/JAHA.118.009635

28. Reynolds HR, Srichai MB, Iqbal SN, Slater JN, Mancini GB, Feit F, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation.* (2011) 124:1414–25. doi: 10.1161/CIRCULATIONAHA.111.026542

29. Rioufol G, Finet G, Ginon I, André-Fouët X, Rossi R, Vialle E, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. *Circulation.* (2002) 106:804–8. doi: 10.1161/01.cir.0000025609.13806.31

30. Ouldzein H, Elbaz M, Roncalli J, Cagnac R, Carrié D, Puel J, et al. Plaque rupture and morphological characteristics of the culprit lesion in acute coronary syndromes without significant angiographic lesion: analysis by intravascular ultrasound. *Ann Cardiol Angeiol (Paris).* (2012) 61:20–6. doi: 10.1016/j.ancard.2011.07.011

31. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio- oncological prevention. *J Natl Cancer Inst.* (2010) 102:14–25. doi: 10.1093/jnci/djp440

32. Florescu M, Cinteza M, Vinereanu D. Chemotherapy-induced Cardiotoxicity. *Maedica.* (2013) 8:59–67.

33. More LA, Lane S, Asnani A. 5-FU Cardiotoxicity: vasospasm, myocarditis, and sudden death. *Curr Cardiol Rep.* (2021) 23:17. doi: 10.1007/s11886-021-01441-2

34. Joy G, Eissa H, Al Karoudi R, White SK. Fluorouracil-induced Takotsubo cardiomyopathy causing cardiogenic shock: a case report of clinical and acute cardiac magnetic resonance imaging features. *Eur Heart J Case Rep.* (2019) 3:1–6. doi: 10.1093/ehjcr/ytz146

35. Kabach M, Ghumman W, FOLFOX. Induced takotsubo cardiomyopathy treated with impella assist device. *Case Rep Cardiol.* (2017) 2017:8507096. doi: 10.1155/2017/8507096

36. Amraotkar AR, Pachika A, Grubb KJ, DeFilippis AP. Rapid extracorporeal membrane oxygenation overcomes fulminant myocarditis induced by 5-fluorouracil. *Tex Heart Inst J.* (2016) 43:178–82. doi: 10.14503/THIJ-15-5100

37. Agunbiade TA, Zaghlol RY, Barac A. Heart failure in relation to anthracyclines and other chemotherapies. *Methodist Debakey Cardiovasc J.* (2019) 15:243–9. doi: 10.14797/mdcj-15-4-243

38. Grem JL. 5-Fluorouracil: forty-plus and still ticking. A review of its preclinical and clinical development. *Invest New Drugs.* (2000) 18:299–313. doi: 10.1023/A:1006416410198

39. Sara JD, Kaur J, Khodadadi R, Rehman M, Lobo R, Chakrabarti S, et al. 5- fluorouracil and cardiotoxicity: a review. *Ther Adv Med Oncol.* (2018) 10:1758835918780140. doi: 10.1177/1758835918780140

40. Shiga T, Hiraide M. Cardiotoxicities of 5-Fluorouracil and Other Fluoropyrimidines. *Curr Treat Options Oncol.* (2020) 21:27. doi: 10.1007/s11864-020-0719-1

41. Mishra T, Shokr M, Ahmed A, Afonso L. Acute reversible left ventricular systolic dysfunction associated with 5-fluorouracil therapy: a rare and increasingly recognised cardiotoxicity of a commonly used drug. *BMJ Case Rep.* (2019) 12:e230499. doi: 10.1136/bcr-2019-230499

42. Ng M, Cunningham D, Norman AR. The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC). *Eur J Cancer.* (2005) 41:1542–6. doi: 10.1016/j.ejca.2005.03.027

43. Yusuf SW, Daraban N, Abbasi N, Lei X, Durand JB, Daher IN. Treatment and outcomes of acute coronary syndrome in the cancer population. *Clin Cardiol.* (2012) 35:443–50. doi: 10.1002/clc.22007

44. Jensen SA, Sørensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. *Cancer Chemother Pharmacol.* (2006) 58:487–93. doi: 10.1007/s00280-005-0178-1

45. Steger F, Hautmann MG, Kölbl O. 5-FU-induced cardiac toxicity–an underestimated problem in radiooncology? *Radiat Oncol.* (2012) 7:212. doi: 10.1186/1748-717X-7-212

46. Yu Z, Huang R, Zhao L, Wang X, Shangguan X, Li W, et al. Safety profile of oxaliplatin in 3,687 patients with cancer in china: a post-marketing surveillance study. *Front Oncol.* (2021) 11:757196. doi: 10.3389/fonc.2021.757196

47. Chang RY, Lee MY, Kan CB, Hsu WP, Hsiao PC. Oxaliplatin-induced acquired long QT syndrome with torsades de pointes and myocardial injury in a

patient with dilated cardiomyopathy and rectal cancer. *J Chin Med Assoc.* (2013) 76:466–9. doi: 10.1016/j.jcma.2013.05.001

48. Koca D, Salman T, Unek IT, Oztop I, Ellidokuz H, Eren M, et al. Clinical and electrocardiography changes in patients treated with capecitabine. *Chemotherapy.* (2011) 57:381–7. doi: 10.1159/000331645

49. Wacker A, Lersch C, Scherpinski U, Reindl L, Seyfarth M. High incidence of angina pectoris in patients treated with 5-fluorouracil. A planned surveillance study with 102 patients. *Oncology.* (2003) 65:108–12. doi: 10.1159/000072334

50. Lestuzzi C, Vaccher E, Talamini R, Lleshi A, Meneguzzo N, Viel E, et al. Effort myocardial ischemia during chemotherapy with 5-fluorouracil: an underestimated risk. *Ann Oncol.* (2014) 25:1059–64. doi: 10.1093/annonc/mdu055

51. Dyhl-Polk A, Schou M, Vistisen KK, Sillesen AS, Serup-Hansen E, Faber J, et al. Myocardial ischemia induced by 5-fluorouracil: a prospective electrocardiographic and cardiac biomarker study. *Oncologist.* (2021) 26:e403–13. doi: 10.1002/onco.13536

52. Ben-Yakov M, Mattu A, Brady WJ, Dubbs SB. Prinzmetal angina (Coronary vasospasm) associated with 5-fluorouracil chemotherapy. *Am J Emerg Med.* (2017) 35:1038.e3–1038.e5. doi: 10.1016/j.ajem.2017.02.046

53. Mizuno Y, Hokamura Y, Kimura T, Kimura Y, Kaikita K, Yasue H, et al. case of 5-fluorouracil cardiotoxicity simulating acute myocardial infarction. *Jpn Circ J.* (1995) 5:303–7. doi: 10.1253/jcj.59.303

54. Alter P, Herzum M, Schaefer JR, Maisch B. Coronary artery spasm induced by 5- fluorouracil. *Z Kardiol.* (2005) 94:33–7. doi: 10.1007/s00392-005-0159-8

55. Moriyama S, Yokoyama T, Irie K, Ito M, Tsuchihashi K, Fukata M, et al. Atrial fibrillation observed in a patient with esophageal cancer treated with fluorouracil. *J Cardiol Cases.* (2019) 20:183–6. doi: 10.1016/j.jccase.2019.08.005

56. Sorrentino MF, Truesdell AG. 5-Fluorouracil-induced coronary thrombosis: A case report and review of the literature. *J Cardiol Cases.* (2012) 6:e20–2. doi: 10.1016/j.jccase.2012.03.011

57. Redfors B, Shao Y, Lyon AR, Omerovic E. Diagnostic criteria for takotsubo syndrome: a call for consensus. *Int J Cardiol.* (2014) 176:274–6. doi: 10.1016/j.ijcard.2014.06.094

58. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J.* (2008) 155:408–17. doi: 10.1016/j.ahj.2007.11.008

59. Schultheiss HP, Kühl U, Cooper LT. The management of myocarditis. *Eur Heart J.* (2011) 32:2616–25. doi: 10.1093/eurheartj/ehr165

60. Patel H, Madanieh R, Kosmas CE, Vatti SK, Vittorio TJ. Reversible Cardiomyopathies. *Clin Med Insights Cardiol.* (2015) 9:7–14. doi: 10.4137/CMC.S19703

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 25 January 2023
DOI 10.3389/fcvm.2023.1100425

OPEN ACCESS

EDITED BY
Jun Yu,
Temple University, United States

REVIEWED BY
Jia Guo,
First Hospital of Shanxi Medical University, China
Martin Borggrefe,
Universität Heidelberg, Germany
Xianxi Huang,
Stanford University, United States

*CORRESPONDENCE
Li Liu
✉ liulibwh@163.com
Chengwei Liu
✉ whlcw60@126.com

SPECIALTY SECTION
This article was submitted to Clinical and Translational Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine

RECEIVED 16 November 2022
ACCEPTED 09 January 2023
PUBLISHED 25 January 2023

CITATION
Yi D, Li L, Han M, Qiu R, Tao L, Liu L and Liu C (2023) Case report: Mechanical-electric feedback and atrial fibrillation–Revelation from the treatment of a rare atrial fibrillation caused by annular constrictive pericarditis. *Front. Cardiovasc. Med.* 10:1100425. doi: 10.3389/fcvm.2023.1100425

Case report: Mechanical-electric feedback and atrial fibrillation–Revelation from the treatment of a rare atrial fibrillation caused by annular constrictive pericarditis

Dong Yi[1], Lei Li[1], Min Han[1], Rujie Qiu[1], Liang Tao[2], Li Liu[1]* and Chengwei Liu[1]*

[1]Division of Cardiac Care Unit, Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan, Hubei, China, [2]Department of Cardiac Surgery, Wuhan Asia Heart Hospital, Wuhan, Hubei, China

Atrial fibrillation (AF) is one of the most common arrhythmias encountered in clinical practice. The pathophysiological mechanisms responsible for its development are complex, vary amongst individuals, and associated with predisposing factors. Here, we report a case of AF caused by annular constrictive pericarditis (ACP), which is extremely rare due to its unusual anatomical form. In our patient, AF was refractory to multiple antiarrhythmic medications; however, spontaneous conversion to sinus rhythm occurred when the ring encircling the right and left ventricular (RV and LV) cavities along the atrioventricular (AV) groove was severed. This suggests that atrial stretch due to atrial enlargement and increased left atrial (LA) pressure may contribute to the initiation and maintenance of AF. This report highlights the importance of the careful investigation of rare predisposing factors for AF using non-invasive diagnostic approaches and mechanical-electric feedback (MEF) as a pathophysiological mechanism for AF initiation and maintenance.

KEYWORDS

atrial fibrillation, annular constrictive pericarditis, mechanical-electric feedback, predisposing factors, atrioventricular groove

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias encountered in clinical practice (1, 2). The pathophysiological mechanisms responsible for initiating AF are complex and often vary among individuals (1, 3, 4). Predisposing factors, such as obesity, pericardial fat, obstructive sleep apnea, pre-hypertension, hyperthyroidism, excessive endurance exercise, cardiomyopathies, channelopathies, and heart failure (HF) play an important role in triggering the development of AF (1, 2, 5–9). The regulation of these factors is essential for AF management, such as pharmacological control of HF, however, specific triggers may not be easily identifiable in clinical practice.

Constrictive pericarditis (CP) is a disease characterized by progressive fibrosis, thickening, and/or calcification of the pericardium, which limits heart expansion and leads to symptoms and signs of HF. It may be caused by primary (idiopathic, tuberculosis, posterior viral or

bacterial pericarditis, and connective tissue disease-related) or secondary factors (pericardial injury syndrome or radiation therapy) (10, 11). AF was thought to be a part of the natural history of CP; however, it has been reported in only 20–30% of patients with CP (12, 13), and more frequently in those with pericardial calcification (9). Pericardial thickening and/or calcification can be observed in patients with CP using echocardiographic or radiological imaging, although approximately 18% of patients were reported to have a normal pericardium (9). Annular CP (ACP), an extremely rare form of localized CP, is easily missed or misdiagnosed due to its unusual anatomical form. It is a thickened and/or calcified pericardial ring that encircles the right and left ventricular (RV and LV) cavities at the level of the atrioventricular (AV) groove, which leads to cardiac strangulation. As it is very rare and easily missed, AF caused by ACP can become refractory to antiarrhythmic medicines.

Here, we report a case of AF caused by ACP, wherein the diagnosis was complicated, leading to a misdiagnosis for many years. The AF was refractory to multiple antiarrhythmic medications; however, spontaneous conversion to sinus rhythm occurred when the AV groove ring was surgically severed. In this report we highlight the importance of careful investigation of a rare cause of AF and discuss the mechanical-electric feedback (MEF) as a possible pathophysiological mechanism in AF initiation and maintenance.

Case presentation

A 29-year-old man presented to the hospital with progressively worsening dyspnea and palpitations for 7 years, and intermittent lower extremity edema and abdominal distension for 12 years. He

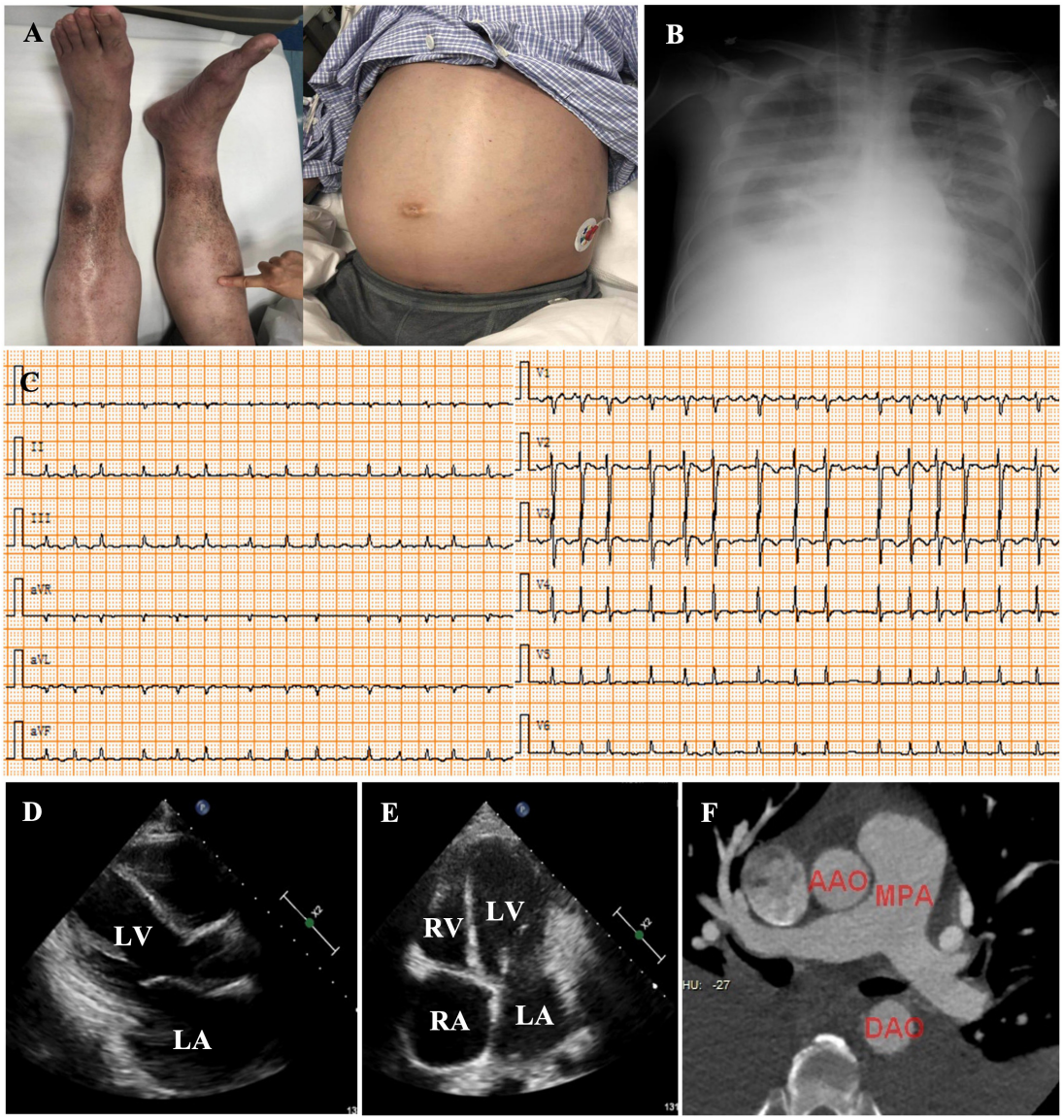


FIGURE 1
Physical examination revealed pitting edema of the lower extremities and abdominal distension **(A)**. Chest radiology showed a pleural effusion **(B)**. Electrocardiography (ECG) at admission indicated the diagnosis of atrial fibrillation (AF) [heart rate (HR), 134 bpm] with low voltage in all leads **(C)**. Echocardiography showed left **(D)** and RA enlargement **(E)**, and a normal LV chamber. Cardiac computed tomographic angiography of the pulmonary arteries excluded pulmonary embolism **(F)**. LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; AAO, ascending aortic artery; MPA, main pulmonary artery; DAO, descending aortic artery.

denied chest pain, had no history of hypertension and diabetes, and no family history of heart disease. Personal habits included a small amount of alcohol intake and no smoking. He was diagnosed with bilharziasis, a nephrotic syndrome, approximately 10 years previously, and AF 3 years previously at a local hospital.

On admission, he was hypotensive [blood pressure (BP), 95/60 mmHg] and weak. A physical examination revealed distended jugular veins, abdominal distension, pitting edema of both lower extremities (**Figure 1A**), decreased breath sounds in the right lower lung, and a grade II/VI systolic murmur at the apex of the heart. Routine blood, renal function, plasma electrolyte concentration, troponin, and inflammatory and tumor marker tests were normal. He had mild liver dysfunction and elevated D-dimer (19.20 g/ml) and plasma B-type natriuretic peptide (NT-proBNP, 1,987 pg/ml). Chest radiology revealed a right-sided pleural effusion and cardiac enlargement (**Figure 1B**). AF [heart rate (HR), 154 bpm] without ST-segment and T-wave changes was confirmed on electrocardiography (ECG) (**Figure 1C**). Transthoracic echocardiography (TTE) revealed left atrial (LA) and right atrial (RA) enlargement (LA, 51 mm; RA, 53 mm), mild mitral and

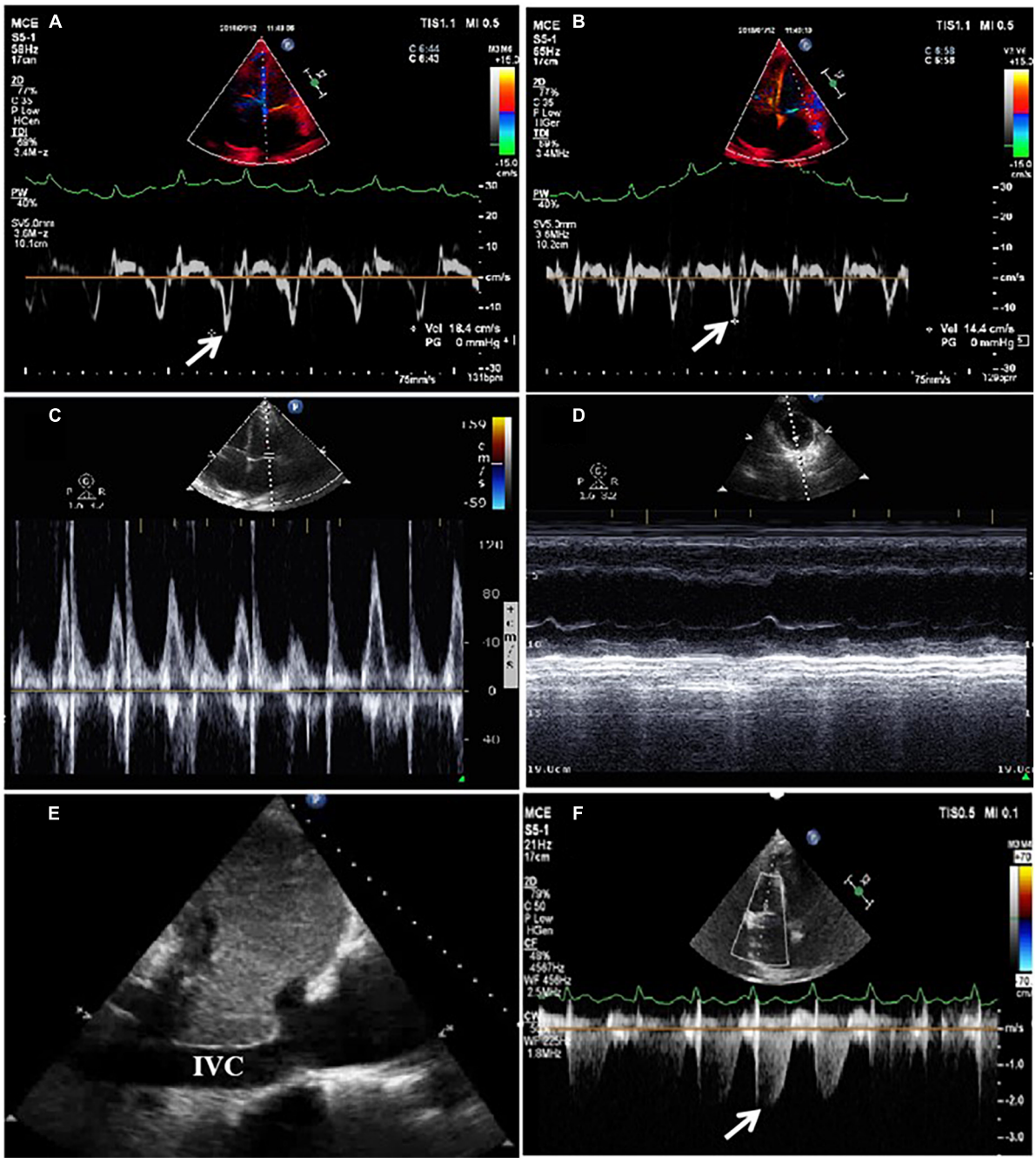


FIGURE 2
Tissue Doppler imaging (TDI) using echocardiography revealed that e' = 18.4 m/s (medial) > 14.4 m/s (lateral) in the mitral valve **(A,B)**. Significant respiratory variation of mitral or tricuspid peak E velocity was indeterminable due to atrial fibrillation (AF) **(C)**. Paradoxical septal motion during respiration was not observed **(D)**. The inferior vena cava (IVC) was dilated without inspiratory collapse **(E)**. Pulmonary artery pressure was elevated according to the velocity of tricuspid regurgitation **(F)**.

tricuspid regurgitation, decreased LV systolic function (LVEF, 45%), diastolic dysfunction, and a normal LV size (42 mm) (**Figures 1D, E**). Abdominal ultrasonography revealed a large amount of abdominal fluid, liver congestion, and inferior vena cava (IVC) distention. Pleural and abdominal effusion analyses indicated transudative fluid. Tuberculosis and rheumatism were excluded based on laboratory test results and effusion fluid analysis. Pulmonary embolism was excluded using computed tomography angiogram (CTA) (**Figure 1F**). Chemical cardioversion was attempted unsuccessfully using several antiarrhythmic medications (amiodarone and nifekalant). A repeat TTE revealed mitral lateral annulus e' velocity (14.4 cm/s) < mitral medial annulus e' velocity (18.4 cm/s) using tissue Doppler imaging (TDI) (**Figures 2A, B**). We were unable to determine significant respiratory variation of mitral and tricuspid peak E velocity due to the AF (**Figure 2C**). Paradoxical septal motion during respiration was not observed (**Figure 2D**). The IVC was dilated without inspiratory collapse (**Figure 2E**). The pulmonary artery pressure (~30 mmHg) was elevated according to the velocity of the tricuspid regurgitation

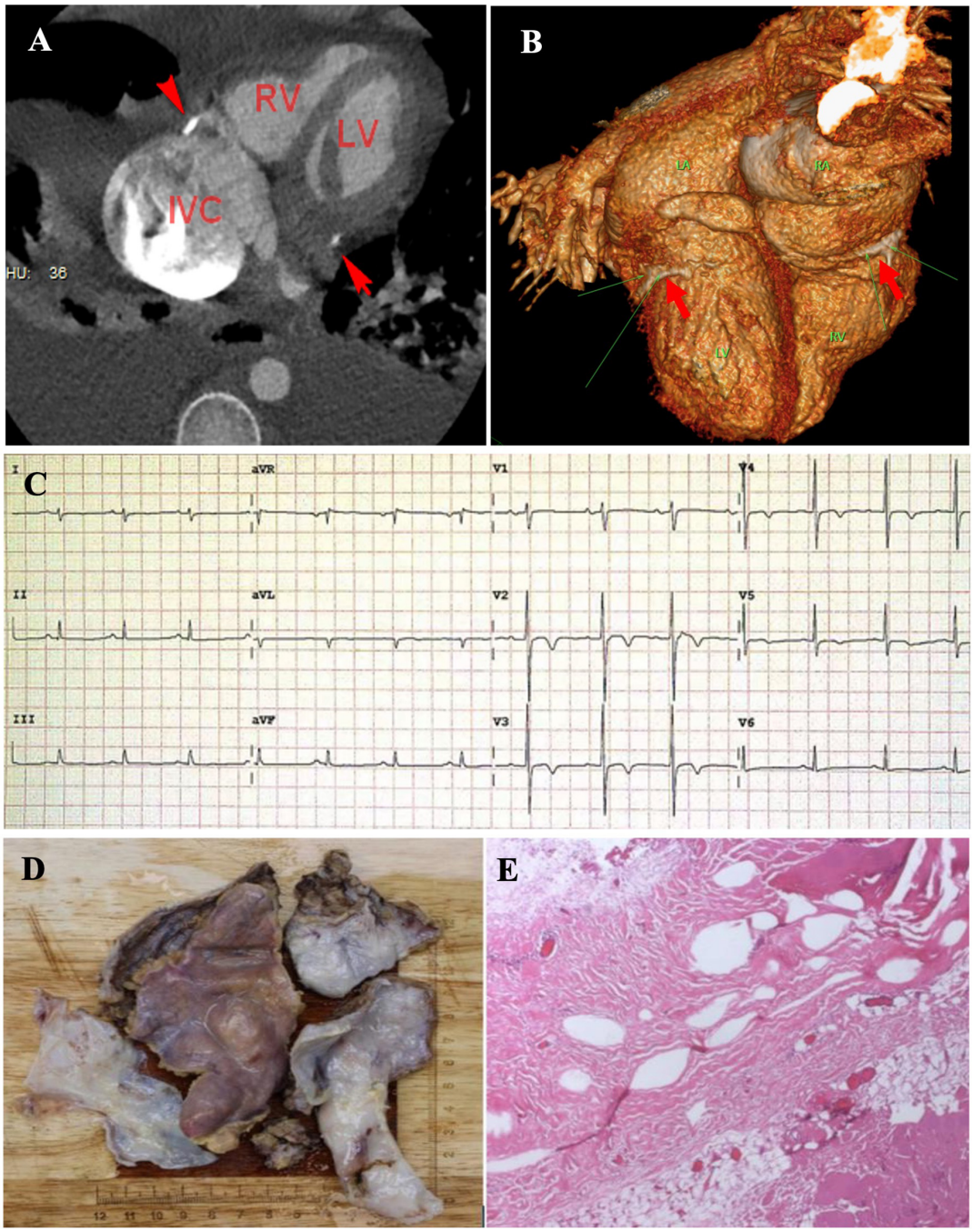


FIGURE 3
Cardiac computed tomographic angiogram of four-chamber view **(A)** and volume rendering views **(B)** showed calcified annular constrictive pericarditis (ACP) trapping both ventricles (red arrows). Spontaneous conversion from atrial fibrillation (AF) to sinus rhythm as the calcified pericardial ring was severed **(C)**. Complete pericardiectomy was performed and revealed a thickened pericardium with calcification embedded in the atrioventricular (AV) groove **(D)**. Pathological examination of the pericardial tissue indicated fibrotic tissue with calcification **(E)**.

(Figure 2F). Careful review of the echocardiographic images showed nodular thickening of the pericardium in the AV groove, without significant thickening of the whole pericardium. We then measured the peripheral venous pressure, which was elevated (43 cm H_2O). These findings supported but did not confirm the diagnosis of CP. ACP was diagnosed using further CT scan analysis, which showed a thickened and calcified pericardial ring around each AV groove with minimal pericardial calcification; however, radiological pericardial thickening and calcification were not observed on chest X-ray (CXR) (Figures 3A, B). Intraoperatively, a calcified pericardial ring encircling the RV and LV cavities at the level of the AV groove was revealed. As the calcified pericardial ring was severed, spontaneous conversion to sinus rhythm was observed (Figure 3C). Pathological examination of the pericardial tissue revealed pericardial thickening, fibrous tissue hyperplasia, and hyaline degeneration, in which a large number of capillaries and few inflammatory cells were observed. A large amount of fat was observed on the surface, confirming the diagnosis of ACP (Figures 3D, E). Post-operatively, the patient's symptoms and vital signs improved significantly. The lower extremity edema, pleural effusion, and ascites subsequently subsided, and the pulmonary congestion and cardiac enlargement mitigated, indirectly indicating a reduced constrictive pattern. The patient was followed up on an outpatient basis and remained in good clinical condition. The echocardiographic assessment at the 1-month follow-up showed that the enlarged atria became smaller (LA, 39 mm; RA, 38 mm) and LV ejection fraction (LVEF) significantly improved (from 45% pre-operation to 57%). The patient management timeline during hospitalization is summarized in Table 1. This study was approved by the local Ethics Committee, and written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Discussion

Annular constrictive pericarditis is an extremely rare form of localized CP. Anatomically, a thickening fibrous band, with or without calcification, encircles the right and left cavities at the level of the AV groove, and strangulates the heart. HF symptoms, such as exertional dyspnea and edema, are commonly reported by patients with ACP (10, 14). The diagnosis is easily missed due to the absence of a thickened/calcified pericardium, which is commonly seen in CP. TTE may reveal some characteristics of cardiac constriction, such as interventricular dependence, changes in mitral TDI velocity, respiratory variation in transmitral flow, and dilation of the IVC without inspiratory collapse (10, 15); however, these characteristics are non-specific and seen in other disorders, such as cardiomyopathy. In our patient, TTE revealed a normal LV size and systolic function, paradoxical septal motion during respiration was not observed, and the respiratory variation of mitral and tricuspid peak E velocity was indeterminable due to AF, although bi-atrial enlargement and dilation of the IVC were observed. Due to the rarity and anatomical form of ACP, careful examination of the AV groove was required to make a diagnosis; therefore, radiological imaging was another useful diagnostic modality for detecting pericardial thickening and/or calcification. In our patient, a thickened/calcified band in the AV groove was initially missed and ACP was diagnosed using further CT scan analysis based on suspicion, and the diagnosis was confirmed surgically. Cardiac catheterization is the gold standard for diagnosing CP, and can be used to differentiate it from other diseases with restrictive physiology. Typically, elevation and equalization of diastolic pressures in all four chambers can be observed. The RV and LV waveforms exhibit a "dip and plateau (or square root)" sign (16). However, we did not perform cardiac catheterization prior to surgery due to the patient's condition (very weak), which could have provided diagnostic evidence of CP.

The precise pathophysiological mechanisms of AF remain elusive; however, the following two different mechanisms have been proposed: abnormal impulse formation and reentrant activity. Most sustained atrial arrhythmias have been ascribed to the reentrant mechanism (17). AF frequently occurs in patients with atrial dilatation (18, 19). Atrial dilatation and/or elevated atrial pressure induces local or global changes in cardiac electrophysiology by increasing the atrial surface, shortening the refractory period, and/or slowing the conduction velocity (20, 21). This phenomenon suggests the role of MEF in atrial arrhythmogenesis. Both experimental and clinical studies have confirmed that atrial stretch induces the onset of atrial arrhythmias through the modulation of myocardial electrophysiological properties (i.e., refractory period (RP) and conduction velocity) (21, 22). In contrast to CP, which limits expansion and filling of all four chambers, ACP mainly affects atrial structure and function through strangling the outflow tract of the atria, leading to atrial dilation and dysfunction. In such situations, drug-therapy is usually ineffective if the mechanical stretch is unresolved. The spontaneous conversion from AF to sinus rhythm and the resection of the annular ring in our patient confirmed this opinion, suggesting the role of MEF as a possible pathophysiological mechanism in ACP -induced AF.

Annular constrictive pericarditis is an extremely rare form of localized CP, which is easily missed or misdiagnosed due to its unusual anatomical form. Careful examination of the AV groove using radiological imaging should be performed in patients with clinical suspicion of underlying CP, without evidence of pericardial thickening. ACP-induced AF is usually refractory to antiarrhythmic medications and surgical resection of the connective ring is imperative. MEF was a possible pathophysiological mechanism in ACP-induced AF.

TABLE 1 The timeline of patient's management during hospitalization.

Timeline of the case management	
Day 1	• Admission • Lab tests • Management with medications
Day 2	• Chest X-ray • Echocardiography
Day 3	• CTA • Diagnostic thoracocentesis and abdominocentesis and fluid analysis
Day 4	• Repeated Echocardiography and Color Doppler • Review results of lab test, echocardiography, radiological Imaging
Day 5	• Heart team consultation including cardiac surgeons • Reached the diagnosis of ACP
Day 7	• Pericardiectomy • Transferred to ICU
Day 12	• Discharge

CTA, computed tomographic angiogram; ACP, annular constrictive pericarditis; ICU, intensive care unit.

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 patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

DY, LeL, MH, RQ, LT, LiL, and CL contributed to the patient diagnosis, treatment, and follow-up. DY and LeL drafted this manuscript. LiL and CL revised the final version of the manuscript. All authors agreed to be accountable for the content of the work and approved the submitted version.

Acknowledgments

We thank Xuan He for help in preparing some of the material.

Conflict of interest

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

Publisher's note

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

References

1. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res.* (2014) 114:1453–68. doi: 10.1161/CIRCRESAHA.114.303211

2. Feinberg W, Blackshear J, Laupacis A, Kronmal R, Hart R. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med.* (1995) 155:469–73. doi: 10.1001/archinte.155.5.469

3. Peters N, Schilling R, Kangaratnam P, Markides V. Atrial fibrillation: strategies to control, combat, and cure. *Lancet.* (2002) 359:593–603. doi: 10.1016/S0140-6736(02)07748-6

4. Chugh S, Havmoeller R, Narayanan K, Narayanan K, Singh D, Rienstra M, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation.* (2014) 129:837–47. doi: 10.1161/CIRCULATIONAHA.113.005119

5. Kannel W, Wolf P, Benjamin E, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol.* (1998) 82:2N–9N. doi: 10.1016/S0002-9149(98)00583-9

6. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. *Europace.* (2008) 10:618–23. doi: 10.1093/europace/eun071

7. El-Battrawy I, Lan H, Cyganek L, Maywald L, Zhong R, Zhang F, et al. Deciphering the pathogenic role of a variant with uncertain significance for short QT and Brugada syndromes using gene-edited human-induced pluripotent stem cell-derived cardiomyocytes and preclinical drug screening. *Clin Transl Med.* (2021) 11:e646. doi: 10.1002/ctm2.646

8. El-Battrawy I, Cammann V, Kato K, Szawan K, Di Vece D, Rossi A, et al. Impact of atrial fibrillation on outcome in takotsubo syndrome: data from the international takotsubo registry. *J Am Heart Assoc.* (2021) 10:e014059. doi: 10.1161/JAHA.119.014059

9. Li Y, Lang S, Akin I, Zhou X, El-Battrawy I. Brugada syndrome: different experimental models and the role of human cardiomyocytes from induced pluripotent stem cells. *J Am Heart Assoc.* (2022) 11:e024410. doi: 10.1161/JAHA.121.024410

10. Welch T. Constrictive pericarditis: diagnosis, management and clinical outcomes. *Heart.* (2018) 104:725–31. doi: 10.1136/heartjnl-2017-311683

11. Welch T, Oh J. Constrictive pericarditis. *Cardiol Clin.* (2017) 35:539–49. doi: 10.1016/j.ccl.2017.07.007

12. Talreja D, Edwards W, Danielson G. Constrictive pericarditis in 26 patients with histologically normal pericardial thickness. *Circulation.* (2003) 108:1852–7. doi: 10.1161/01.CIR.0000087606.18453.FD

13. Rezaian G, Poor-Moghaddas M, Kojuri J, Rezaian S, Liaghat L, Zare N. Atrial fibrillation in patients with constrictive pericarditis: the significance of pericardial calcification. *Ann Noninvasive Electrocardiol.* (2009) 14:258–61.

14. Ling L, Oh J, Schaff H, Danielson G, Mahoney D, Seward J, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. *Circulation.* (1999) 100:1380–6. doi: 10.1161/01.cir.100.13.1380

15. Welch T, Ling L, Espinosa R, Anavekar N, Wiste H, Lahr B, et al. Echocardiographic diagnosis of constrictive pericarditis: mayo clinic criteria. *Circ Cardiovasc Imaging.* (2014) 7:526–34. doi: 10.1161/CIRCIMAGING.113.001613

16. Talreja D, Nishimura R, Oh J, Holmes D. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. *J Am Coll Cardiol.* (2008) 51:315–9. doi: 10.1016/j.jacc.2007.09.039

17. Brugada P, Wellens H. Early afterdepolarizations: role in conduction block, prolonged repolarization-dependent reexcitation, and tachyarrhythmias in the human heart. *Pacing Clin Electrophysiol.* (1985) 8:889–96. doi: 10.1111/j.1540-8159.1985.tb05908.x

18. Sanfilippo A, Abascal V, Sheehan M, Oertel L, Harrigan P, Hughes R, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. *Circulation.* (1990) 82:792–7.

19. Schotten U, Neuberger H, Allessie M. The role of atrial dilatation in the domestication of atrial fibrillation. *Prog Biophys Mol Biol.* (2003) 82:151–62.

20. Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. *Circulation.* (1997) 96:1686–95. doi: 10.1161/01.cir.96.5.1686

21. Satoh T, Zipes D. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. *J Cardiovasc Electrophysiol.* (1996) 7:833–42. doi: 10.1111/j.1540-8167.1996.tb00596.x

22. Shibata E, Drury T, Refsum H, Aldrete V, Giles W. Contributions of a transient outward current to repolarization in human atrium. *Am J Physiol.* (1989) 257:H1773–81. doi: 10.1152/ajpheart.1989.257.6.H1773

frontiers | Frontiers in Cardiovascular Medicine

TYPE Case Report
PUBLISHED 19 May 2023
DOI 10.3389/fcvm.2023.1130552

OPEN ACCESS

EDITED BY
Baohui Xu,
Stanford University, United States

REVIEWED BY
Ahmet Karabulut
Department of Cardiology, Acibadem Atakent Hospital, Turkey
Nagwa Ali Sabri,
Ain Shams University, Egypt

*CORRESPONDENCE
Guangping Li
✉ tjcardiol@126.com

RECEIVED 23 December 2022
ACCEPTED 02 May 2023
PUBLISHED 19 May 2023

CITATION
Li Y, Qiu J, Gao Y and Li G (2023) Case report: reuse of tirofiban leads to very severe thrombocytopenia.
Front. Cardiovasc. Med. 10:1130552.
doi: 10.3389/fcvm.2023.1130552

Case report: reuse of tirofiban leads to very severe thrombocytopenia

Yuqing Li, Jiuchun Qiu, Yi Gao and Guangping Li*

Tianjin Key Laboratory of Logic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, the Second Hospital of Tianjin Medical University, Tianjin, China

Background: Telofiban is a class of small molecule non-peptide tyrosine derivatives containing RGD sequences. It is the only platelet surface glycoprotein (GP) IIb/IIIa receptor antagonist (GPI) currently marketed in China. In patients with ST-segment elevation myocardial infarction(STEMI) who receive percutaneous coronary intervention (PCI) with a heavy thrombotic load, postoperative intravenous tirofiban can prevent complications of myocardial ischemia due to sudden coronary artery occlusion. With the increase in the clinical use of tirofiban, the number of adverse reactions related to thrombocytopenia induced by tirofiban has gradually increased. Still, most of them have thrombocytopenia after the first use. We report one case of very severe thrombocytopenia following the reuse of tirofiban.

Case summary: A 65-year-old man of Han nationality, 170 cm in height, 85 kg in weight, and 29.4 BMI, suffered from cerebral infarction 13 years ago and left with right limb movement disorder. Five days before this hospitalization, the patient underwent PCI, and three stents were implanted. After the operation, anti-platelet tirofiban and nadroparin calcium were given, and no thrombocytopenia was found. The patient still retains 80% stenosis due to anterior descending branches and plans to undergo PCI again half a month later. The patient with a history of hypertension, type 2 diabetes, diabetic nephropathy, and cerebral infarction usually took 100 mg of aspirin and 75 mg of clopidogrel, antiplatelet therapy, and had no history of food and drug allergy. One day after discharge, the patient suddenly felt chest tightness and wheezing. The laboratory showed hypersensitivity troponin 2.85 ng/ml (normal 0–0.0268 ng/ml), and the admission ECG showed ST-T changes in leads I, aVL, V5-V6. On the 6th day of hospitalization, PCI was performed, a stent was implanted in the proximal section of the anterior descending branch opening, and tirofiban(10 ug/kg, 3 min bolus, then 0.1 ug/kg/min) antiplatelet therapy was given after surgery. About 10 min after the tirofiban infusion, the patient suddenly shivered, accompanied by convulsions, accompanied by elevated body temperature (up to 39.4°C), accompanied by epistaxis and microscopic hematuria. An urgent blood test showed that the platelets dropped to 1×109/L, tirofiban and aspirin stopped immediately, and the antiplatelet therapy of clopidogrel was retained. After infusion of methylprednisolone sodium succinate and gamma globulin, the patient's platelets gradually recovered, and the patient was successfully discharged seven days later in stable condition.

Conclusion: This case is typical of severe thrombocytopenia caused by reusing tirofiban. This case may provide new insights into: 1. Patients who did not have thrombocytopenia after the first use of tirofiban may still have extremely severe thrombocytopenia after re-exposure to tirofiban. Routine platelet count monitoring and early identification of thrombocytopenia are the essential links. 2. Thrombocytopenia caused by re-exposure to tirofiban may have a faster onset, deeper degree, and slower recovery due to antibodies retained after the first exposure to tirofiban; 3. Platelet transfusions may not be necessary for

patients with severe thrombocytopenia; 4. Immunosuppressants help suppress the body's immune response, promote platelet recovery, and can be reduced or discontinued when platelets rise and may be safe; 5. After tirofiban for PCI, continuing the maintenance dose of clopidogrel may be safe if the patient has no significant bleeding events.

KEYWORDS

tirofiban, thrombocytopenia, severe, anaphylaxis, case report

Introduction

Coronary angiography (CAG) and PCI have become standard methods for evaluating and treating coronary artery lesions. Patients undergoing CAG routinely take antiplatelet and anticoagulant drugs (1). Platelet aggregation inhibitors have better clinical benefits in patients at high risk of coronary artery disease with a heavy thrombus burden who undergo emergency PCI (2). As the only GPI currently marketed in China, tirofiban reduces the risk of thrombosis by inhibiting platelet aggregation. However, tirofiban can cause severe thrombocytopenia in rare cases (3).

The glycoprotein IIb/IIIa receptor aggregates platelet by linking the vWf factor and fibrinogen. As a small non-peptide tyrosine derivative, tirofiban competes for glycoprotein IIb/IIIa receptors. When administered intravenously, platelet aggregation is inhibited in a concentration-dependent manner (4). Current studies have found that typical GPI-induced thrombocytopenia is mainly divided into five modes: (1) Occurs within 12 h after the first contact; (2) Within 12 h of the second contact; (3) Delayed thrombocytopenia: 5–7 days after treatment; (4) Pseudothrombocytopenia: platelet aggregation; (5) Allergic reactions secondary after exposure (5). With the widespread clinical use of tirofiban, reports of thrombocytopenia have gradually increased (6). Most cases are thrombocytopenia after the first exposure, and thrombocytopenia due to the second exposure is rare.

Here, we report a very severe thrombocytopenia caused by reusing tirofiban.

Timeline: See **Table 1**.

Case presentation

A 65-year-old man of Han nationality, 170 cm in height, 85 kg in weight, and 29.4 BMI, suffered from cerebral infarction 13 years ago and left with right limb movement disorder. Coronary angiography performed one year before hospitalization showed three-vessel disease, and no stent was implanted. The patient underwent CAG five days before hospitalization, three stents were planted during the operation, and 80% of the lesions with the preservation of the anterior descending branch were opened later. The patient had a history of hypertension, type 2 diabetes mellitus, diabetic nephropathy, and cerebral infarction and had no history of food or drug allergy or thrombocytopenia. After hospitalization, the laboratory showed that hypersensitivity troponin was 2.85 ng/ml. The ECG on admission showed ST-T changes in leads I, aVL, V5-V6 (**Figure 1**), and non-ST-segment elevation myocardial infarction(NSTEMI) was initially considered. Blood tests did not show apparent thrombocytopenia. Cardiac examination reveals no prominent murmurs, friction rubs, or galloping rhythms.

On the 6th day after admission, the patient was admitted to the cardiac catheterization laboratory for PCI. During the operation, 80% stenosis of the proximal section of the anterior descending branch opening was found, the occlusive lesion was opened, one stent was implanted, and the patient returned to the ward after the operation. Because of the severe thrombus burden of the patient, tirofiban (10 ug/kg, 3 minute bolus, followed by 0.1 ug/kg/min [the guidelines recommend the dose] (7)) instillation was started. Ten minutes after the tirofiban infusion, the patient suddenly shivered, accompanied by a continuous increase in body temperature, up to 39.4°C, with heavy sweating. It was considered that the patient had a high possibility of sudden

TABLE 1 Timeline of major events before and after the patient's hospitalization.

5-Days before	Coronary angiography was performed, a total of 3 stents were implanted, and 80% of the lesions presentation were opened on a later date before retention. Postoperative application of tirofiban and calcium natracalcin showed no thrombocytopenia
Day 0	A 65-year-old male patient, emergency laboratory test: hypersensitive troponin 2.85 ng/ml, admitted ECG: I, AVL, V5-V6 LEAD ST-T changes, again due to severe chest tightness and asthma admitted to the cardiovascular department of our hospital
Day 1	Initially considering non-ST-segment elevation myocardial infarction(N-STEMI), aspirin and clopidogrel dual antiplatelet therapy, and natreparin calcium anticoagulation therapy, no obvious thrombocytopenia was seen
Day 6	Coronary angiography was performed before opening the descending branch and implanted with one stent, and after surgery, ticrofiban was given symptomatic anti-plate therapy. After 10 min of tirofiban infusion, the patient suddenly shivered, accompanied by high fever and sweating, and the emergency blood routine showed that platelets dropped to 1 × 109/L. Discontinue all anticoagulant and antiplateau drugs and retain clopidogrel alone
Day 7–10	The patient had scattered ecchymosis with subcutaneous bleeding points, microscopic hematuria, and epistaxis, and methylprednisolone sodium succinate 40 mg bid for 4 days and gamma globulin 10 g/d for 2 days. On the 10th day of admission, platelets were rechecked and recovered to 18 × 109/L
Day 13	The ecchymosis gradually subsided, and no bleeding spots were visible to the naked eye. The platelets recovered to 84 × 109/L and the patient recovered and was discharged from the hospital
1-Month post-discharge	The patient's platelets returned to normal

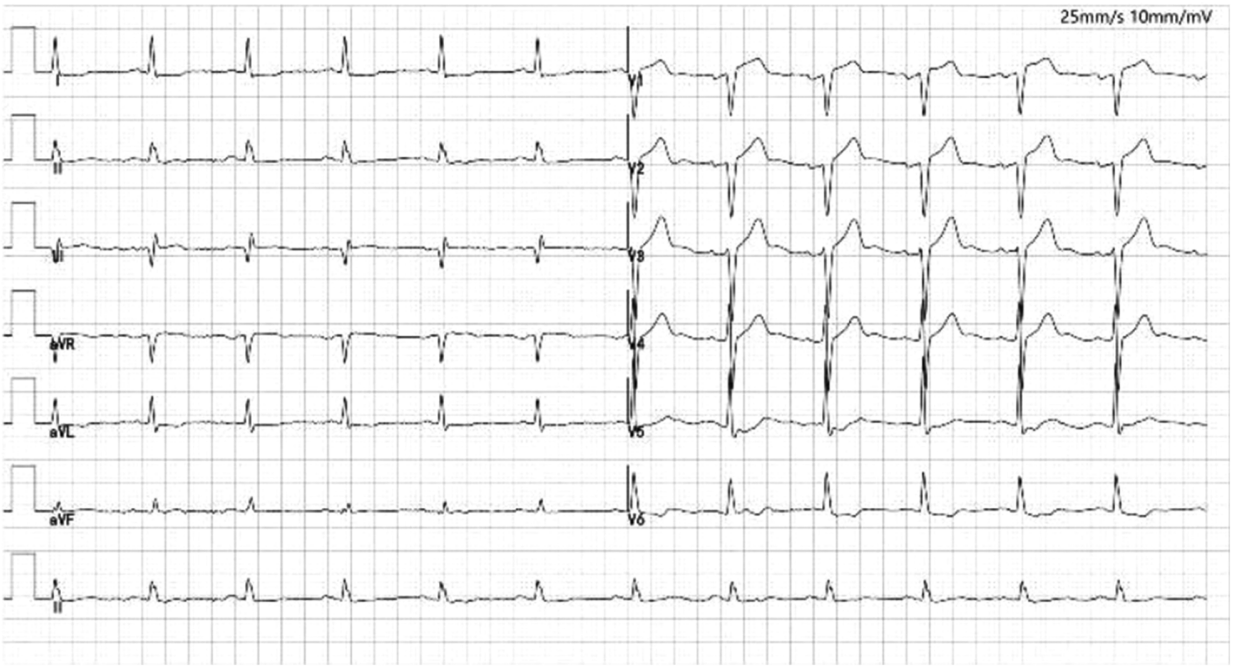


FIGURE 1
Electrocardiogram of the patient with I, AVL, V5-V6 lead ST-T changes. There is pathological Q waves (lead III, V1-V2). Poor increase of R waves in thoracic leads.

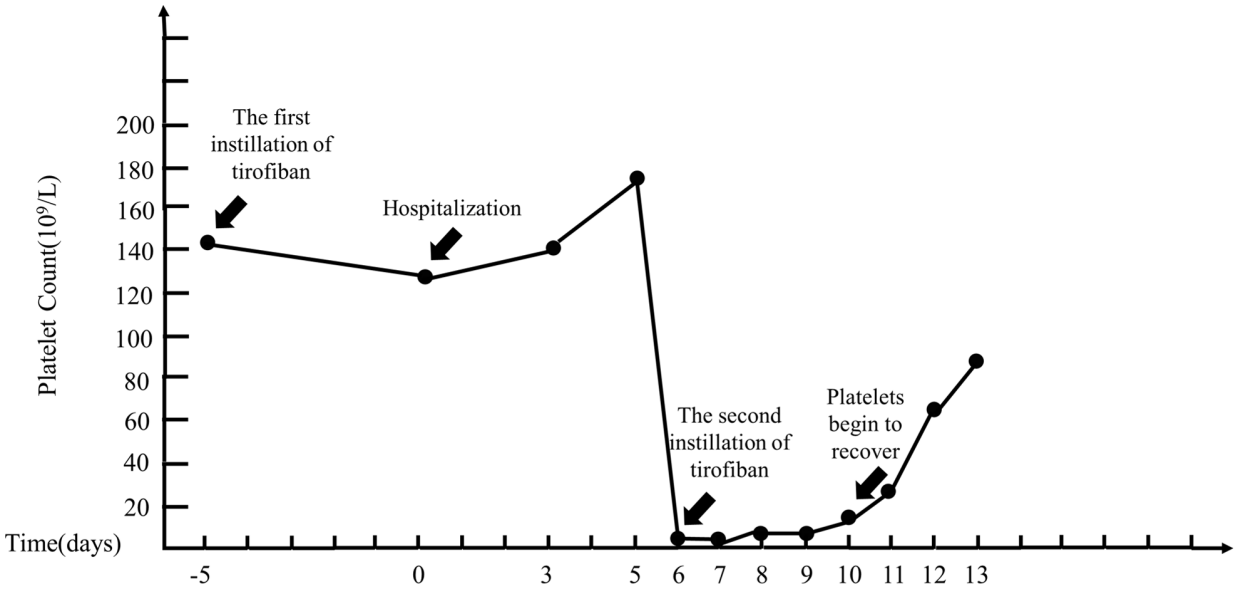
hypersensitivity reaction, and the allergen was not known, so transient bacteremia and infusion reaction could not be ruled out. Blood routine examinations and blood cultures were taken urgently. Diphenhydramine hydrochloride injection (1 ml; 20 mg) by intramuscular injection for symptomatic anti-allergic treatment. It was found that the platelet count decreased to 1×10^9/L, but the blood was drawn again to exclude the test error, and the reexamination was still 1×10^9/L. The laboratory physician performed a blood-smear examination of the peripheral-blood sample, confirming a profound platelet deficiency with no platelet aggregation. The smear results were reported to the attending physician.

All antiplatelet and anticoagulant drugs were discontinued immediately. Given the patient's severe thrombotic burden, clopidogrel antiplatelet therapy was still retained. On the 7th day after hospitalization, the patient gradually developed scattered ecchymosis with subcutaneous bleeding spots, microscopic hematuria, and epistaxis. Other standard laboratory tests include prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, and D-dimer. Haptoglobin, reticulocyte count, and lactate dehydrogenase (LDH) are also expected. Methylprednisolone sodium succinate 80 mg for four days and gamma globulin 200 mg/kg/day for two days for symptomatic anti-inflammatory treatment, daily blood routine (**Figure 2**), and occult blood tests, including urine and stool samples. On the 10th day of hospitalization, the patient's platelets recovered to 18×10^9/L. On the 13th day of hospitalization, the ecchymosis throughout the patient's body gradually subsided, and no visible bleeding points were seen. The re-examination showed that platelets recovered to 84×10^9/L, and the patient was discharged. One month after discharge, the patient's repeated blood routine showed that platelets had returned to normal.

Discussion

Tirofiban-induced thrombocytopenia(TIT) gradually increases in clinical practice with the widespread use of tirofiban, and the severity usually ranges from mild to severe. Classification according to the degree of thrombocytopenia: mild ($50–99 \times 10^9$/L), severe ($20–49 \times 10^9$/L), very severe (20×10^9/L). Very severe thrombocytopenia ($Plt < 20 \times 10^9$/L) is rare and should be considered an emergency, usually requiring platelet transfusion. In some reported cases, patients developed thrombocytopenia with symptoms such as chills, fever, and hypotension (8). Tirofiban has a half-life of approximately 2 h and a rapid onset of action. For TIT, platelet count generally recovered 2.1 days after drug withdrawal. According to the current reports, the incidence of severe thrombocytopenia ($Plt << 50 \times 10^9$/L) ranges from 0.2% to 0.5% of tirofiban (9). The combination of GPI and PCI has been shown to reduce mortality after revascularization in patients with STEMI and NSTEMI (10). Thrombocytopenia is one of the main adverse effects of tirofiban, but thrombocytopenia has primarily been reported after initial application. Rapid thrombocytopenia with re-exposure to tirofiban has only been reported in a few cases (3, 6).

Drug-mediated immune thrombocytopenia (DITP) is a spontaneous immune-mediated response in which anti-platelet



Platelet(10^9/L)	142	130	141	178	1	1	5	4	18	31	63	84
Fecal occult blood	-				±					-		
Urine occult blood	±				2+					-		

FIGURE 2
Evolution of the platelet count (days before and after stopping tirofiban infusion).

antibodies generally appear 1–2 weeks after using a new drug or re-exposure to a drug after a previous exposure history. TIT belongs to a species of DITP. At present, it is believed that the mechanism of tirofiban-induced thrombocytopenia is roughly divided into two types: one is the antigen-antibody reaction in the patient's body, resulting in platelets being cleared by the body's immune system (11); The second is that tirofiban induces the conformational change of glycoprotein receptor on the platelet surface, and the new antigenic determinants are produced and recognized by the liver and eventually eliminated (12). Acute platelet destruction after GPI use suggests that non-immune factors may play a role. Still, recent studies have confirmed that drug-dependent antibodies may be the leading cause of platelet destruction (8). The detection of antibodies recognizing the GPIIb/IIIa site in the blood of patients with thrombocytopenia further verified the possibility of immune factors. However, there is still no precise mechanism to explain the cause of thrombocytopenia (11).

Like other DITPs, TIT is also an exclusive diagnosis and other drug-induced thrombocytopenia needs to be excluded from making a definite diagnosis. In addition to intravenous tirofiban infusion after PCI, the patient received intravenous nadroparin calcium 4000 IU during the whole treatment and long-term oral antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg before CAG. These factors could not be excluded from participating in the patient's thrombocytopenia. Pseudo-thrombocytopenia due to laboratory testing was also included as one of the leading differential diagnoses. Pseudo-thrombocytopenia usually refers to using the anticoagulant EDTA in sample tubes that may cause platelets to clump, resulting in artificially low platelet counts. The diagnosis of pseudo-thrombocytopenia can be excluded by performing a peripheral blood smear without platelet aggregation and repeating the platelet count (13). HIT is caused by a combination of heparin and platelet factor 4 (PF4) autoantibodies, and platelets are widely activated, eventually leading to thrombosis and thrombocytopenia. The "4Ts score (14)"(**Figure 3**) is a pre-test scoring system for HIT designed to play a suggestive role in the clinical diagnosis of HIT. The "4Ts score" has a high sensitivity and negative predictive value for diagnosing HIT. HIT can be ruled out in patients with low clinical likelihood, and HIT-antibody testing and continuous platelet count monitoring are unnecessary. HIT is divided into two types. Type I mainly occurs within five days after the application of heparin and is related to the direct activation of platelets by heparin. Most of them are transient platelet decline, to a lesser extent, and are non-immune thrombocytopenia. Type II occurs 5 to 15 days after heparin application, is associated with PF4 and heparin forming heparin/PF4 complexes, and is an immune response with thrombosis rather than bleeding. The patient had been exposed to heparin for coronary angiography one year before and for the first PCI five days before hospitalization, and no thrombocytopenia was observed. The lowest platelet count was 1×10^9/L. No clinical symptoms related to thromboembolism were found. The final "4Ts score" was only two, indicating that the probability of HIT was very low and HIT could be ruled out (15). The previous "CAPRIE" study (16) showed that aspirin and

Project	Score:		
	Two points	One point	Zero point
Quantitative characteristics of thrombocytopenia	both of the following: (1) thrombocytopenia >50%, (2) the lowest value ≥20×10^9/L	one of the following: (1) thrombocytopenia of 30%-50%; (2) the lowest value was between (10-19)×10^9/L	one of the following: (1) thrombocytopenia of not more than 30%, (2) a nadir of less than 10×10^9/L
Temporal characteristics of decreased platelet counts	one of the following: (1) use of heparin for 5 to 10 days; (2) re-exposure to heparin for ≤1 day (exposure within the past 30 days)	one of the following: (1) use heparin for >10 days (2) use heparin for ≤1 day (exposure to heparin in the past 30 to 100 days)	Use of heparin <5 days (no recent exposure to heparin)
Type of thrombosis	newly formed venous and arterial thrombosis; skin necrosis; acute systemic reactions following a loading dose of heparin	progressive or recurrent thrombosis, skin erythema; suspected thrombosis that has not yet been demonstrated	nothing
Other causes of thrombocytopenia	nothing	maybe	sure

Score 0-3→mild suspicion: the probability of HIT diagnosis is very low;
Score 4-5→moderate suspicion: the probability of HIT diagnosis was 0.6% in antibody-negative patients and 58.2% in antibody-positive patients;
Score 6-8→high suspicion: the probability of HIT diagnosis is 16% for antibody negative and 98% for antibody positive.

FIGURE 3
Scoring system for heparin-induced thrombocytopenia (H IT 4T's score).

clopidogrel had a good effect on the prognosis of CAG patients, and thrombocytopenia was rare in both groups. Although very rare, clopidogrel can also cause DITP, and the mechanism is currently believed to be the production of IgG-type autoantibodies against ADAMTS13 induced by the drug (17). So far, no extremely severe thrombocytopenia caused by aspirin or clopidogrel alone has been reported. Long-term antiplatelet therapy with aspirin and clopidogrel was initiated one year earlier, and thrombocytopenia was not observed, so this diagnosis can be ruled out. Based on the clinical presentation, laboratory tests, and timeline of events during hospitalization, thrombocytopenia in patients is likely due to immune thrombocytopenia mediated after reusing tirofiban.

As a kind of DITP, TIT follows the general treatment principles of DITP. Still, its treatment should be adjusted according to the degree of thrombocytopenia and bleeding, even if the degree of thrombocytopenia is not necessarily proportional to the degree of bleeding. The details were as follows: (1) Patients with platelet count decreased to 50–99 × 10^9/L were generally maintained under observation, and tirofiban infusion would be stopped if the platelet count decreased continuously; (2) Patients whose platelet count decreased to less than 50 × 10^9/L. There is a strong rationale for first withholding tirofiban in treating very severe thrombocytopenia since tirofiban is cleared from the circulation within one hour after discontinuation (18). For TIT, corticosteroid or immunoglobulin infusion may be considered without long-term platelet recovery. Unfortunately, there is no clinical trial or basic research to confirm that corticosteroids and immunoglobulin play a decisive role in promoting platelet recovery. More empirical treatment exists in clinical reports (19, 20). Switching to another antiplatelet agent, such as bivalirudin, may be considered if the patient is at high risk for thrombosis. Bivalirudin has fewer bleeding events and 30-day net adverse clinical events than tirofiban (21); (3) For patients with thrombocytopenia <10 × 10^9/L and patients with severe bleeding, it is recommended to stop all anticoagulants and antiplatelet drugs. Platelet transfusion is recommended (22). For life-threatening bleeding (brain, lung, or pericardium), hemodialysis or plasmapheresis may facilitate the rapid metabolism of tirofiban in the body. For details, see **Figure 4**. On the one hand, considering the patient's economic factors, a half-dose of gamma globulin (200 mg/kg/d) combined with methylprednisolone sodium succinate (80 mg/d) was used for anti-immune treatment, and the drug was stopped in time when the patient's platelet showed a recovery trend. On the other hand, clopidogrel antiplatelet therapy has been retained to prevent the risk of thrombosis caused by the rapid rise of platelets. Ultimately, the patient did not have prominent bleeding events, and the platelet gradually returned to normal.

Thrombocytopenia due to this case is rare compared with patients with thrombocytopenia after the first exposure to tirofiban. The onset of the disease is shorter (10 min after administration; The standard time is from a few hours to seven days after starting the infusion), symptoms are more typical at the beginning (platelets drop to 1 × 10^9/L), Platelet recovery time is longer (platelet levels do not recover until about one week after discontinuation of tirofiban, much longer than the half-life of tirofiban by two hours). Therefore, it is essential to design a concise and straightforward procedure to prevent the occurrence of highly severe TIT. (1) Screening high-risk patients before tirofiban administration: the PRISM-PLUS study found that older age, lower body weight, female gender, and limited creatinine clearance (<30 ml/min) were associated with a higher risk of bleeding (23). Not coincidentally, Yi et al. designed a clinical preoperative risk model by reviewing the clinical features of patients with tirofiban-induced thrombocytopenia, identifying

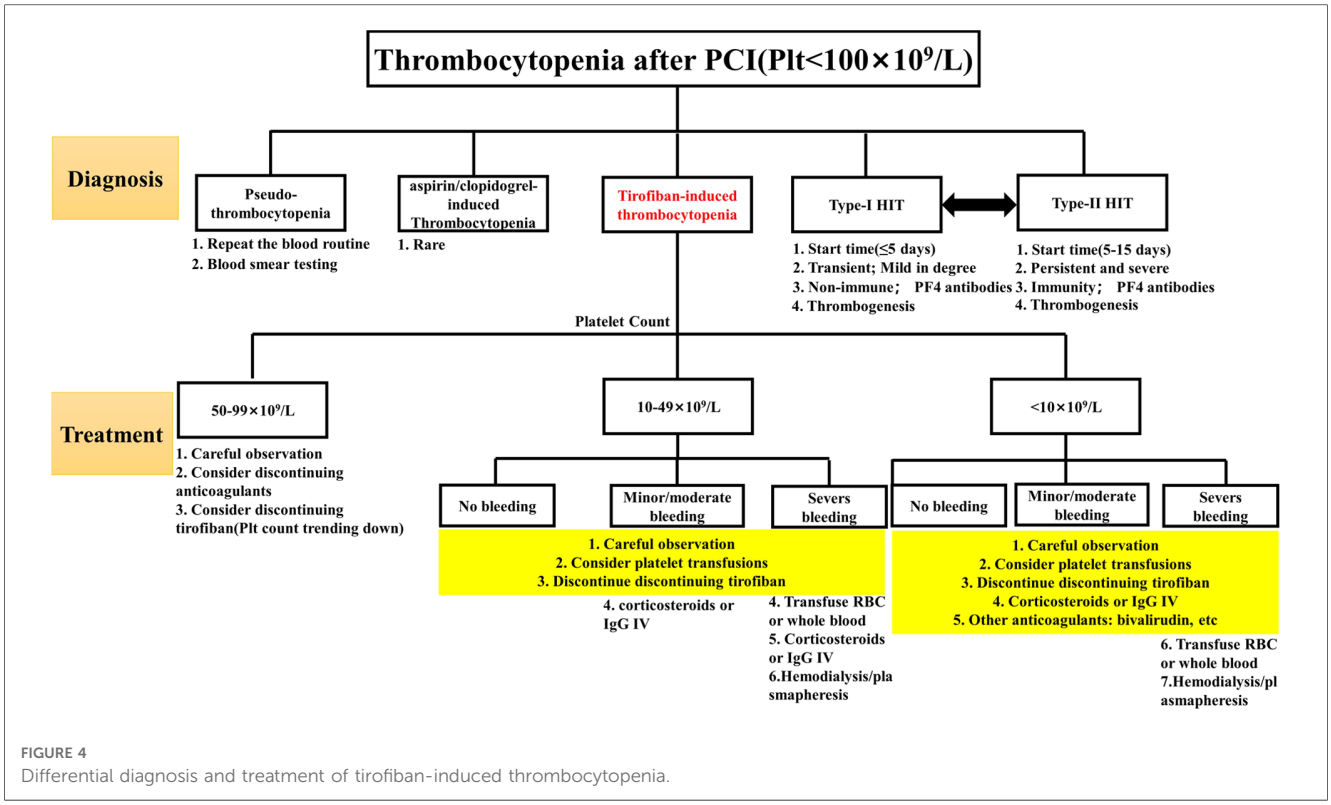


FIGURE 4
Differential diagnosis and treatment of tirofiban-induced thrombocytopenia.

five independent risk factors: age ≥ 65 years, white blood cell ≥ 12×10^9/L, diabetes, congestive heart failure, and chronic kidney disease. Applying preoperative risk models allows us to assess the risk of thrombocytopenia in patients and then adopt instillation dose reduction or alternative drug methods to improve patient safety (24); (2) Selection of infusion dose during the application of tirofiban: Wang et al. conducted a safety study on different amounts of tirofiban instillation, showing that high-dose tirofiban instillation was associated with a significant reduction in the incidence of major cardiac adverse events but was accompanied by a higher bleeding rate and thrombocytopenia. It suggests that the dose of tirofiban should be adjusted reasonably according to the patient's condition and bleeding risk (25); (3) Routine monitoring after tirofiban application: routine blood tests should be rechecked at two, six, twelve, and twenty-four hours after tirofiban application, and regularly rechecked once a day after tirofiban withdrawal until discharge to prevent failure to detect thrombocytopenia in time (19, 20); (4) Early identification after TIT: when the patient's blood routine shows extremely severe thrombocytopenia, it is essential to analyze the related drugs that may cause thrombocytopenia in the patient, conduct related laboratory tests to confirm/exclude the diagnosis, and finally determine the causative drug.

Data availability statement

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

Ethics statement

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

Author contributions

LYQ is involved with the patient's management and the manuscript's write-up. GY made significant contributions to writing, proofreading, and submitting the manuscript. QJC and LGP are involved in treating the patient, mentoring, and making suggestions in preparing the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82100342) and the Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-029A).

Acknowledgments

We want to thank Dr. Wang Weiding, and Dr. Zhang Zizhao, the Second Hospital of Tianjin Medical University, for

providing patient information and helping with manuscript writing.

Conflict of interest

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

Publisher's note

References

1. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention*. (2022) 17: e1371–96. doi: 10.4244/EIJ-D-21-00904

2. Safley DM, Venkitachalam L, Kennedy KF, Cohen DJ. Impact of glycoprotein IIb/IIIa inhibition in contemporary percutaneous coronary intervention for acute coronary syndromes: insights from the national cardiovascular data registry. *JACC Cardiovasc Interv*. (2015) 8:1574–82. doi: 10.1016/j.jcin.2015.04.031

3. Eryonucu B, Tuncer M, Erkoc R. Repetitive profound thrombocytopenia after treatment with tirofiban: a case report. *Cardiovasc Drugs Ther*. (2004) 18:503–5. doi: 10.1007/s10557-004-6228-9

4. Vayne C, Guéry EA, Rollin J, Baglo T, Petermann R, Gruel Y. Pathophysiology and diagnosis of drug-induced immune thrombocytopenia. *J Clin Med*. (2020) 9 (7):2212. doi: 10.3390/jcm9072212

5. Aster RH, Curtis BR, Bougie DW, Dunkley S, Greinacher A, Warkentin TE, et al. Thrombocytopenia associated with the use of GPIIb/IIIa inhibitors: position paper of the ISTH working group on thrombocytopenia and GPIIb/IIIa inhibitors. *J Thromb Haemost*. (2006) 4:678–9. doi: 10.1111/j.1538-7836.2006.01829.x

6. Guo sj, Qi xq, Zhao ym. Analysis on the repeat administration of tirofiban induced severe thrombocytopenia in six patients. *Chin Circ J*. (2021) 36:6. doi: 10.3969/j.issn.1000-3614.2021.06.004

7. Sullivan AE, Nanna MG, Wang TY, Bhatt DL, Angiolillo DJ, Mehran R, et al. Bridging antiplatelet therapy after percutaneous coronary intervention: jACC review topic of the week. *J Am Coll Cardiol*. (2021) 78:1550–63. doi: 10.1016/j.jacc.2021.08.013

8. Aster RH. Immune thrombocytopenia caused by glycoprotein IIb/IIIa inhibitors. *Chest*. (2005) 127:53s–9s. doi: 10.1378/chest.127.2_suppl.53S

9. Tcheng JE, Kereiakes DJ, Lincoff AM, George BS, Kleiman NS, Sane DC, et al. Abciximab Readministration: results of the ReoPro readministration registry. *Circulation*. (2001) 104:870–5. doi: 10.1161/hc3301.094533

10. Gumina RJ, Yang EH, Sandhu GS, Prasad A, Bresnahan JF, Lennon RJ, et al. Survival benefit with concomitant clopidogrel and glycoprotein IIb/IIIa inhibitor therapy at ad hoc percutaneous coronary intervention. *Mayo Clin Proc*. (2008) 83:995–1001. doi: 10.4065/83.9.995

11. Bougie DW, Wilker PR, Wuitschick ED, Curtis BR, Malik M, Levine S, et al. Acute thrombocytopenia after treatment with tirofiban or eptifibatide is associated with antibodies specific for ligand-occupied GPIIb/IIIa. *Blood*. (2002) 100:2071–6. doi: 10.1182/blood.V100.6.2071

12. Estevez B, Shen B, Du X. Targeting integrin and integrin signaling in treating thrombosis. *Arterioscler Thromb Vasc Biol*. (2015) 35:24–9. doi: 10.1161/ATVBAHA.114.303411

13. Lardinois B, Favresse J, Chatelain B, Lippi G, Mullier F. Pseudothrombocytopenia-A review on causes, occurrence and clinical implications. *J Clin Med*. (2021) 10:594. doi: 10.3390/jcm10040594

14. Linkins LA, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. *Chest*. (2012) 141:e495S–530S. doi: 10.1378/chest.11-2303

15. Arepally GM, Padmanabhan A. Heparin-Induced thrombocytopenia: a focus on thrombosis. *Arterioscler Thromb Vasc Biol*. (2021) 41:141–52. doi: 10.1161/atvbaha.120.315445

16. Markham A, Coukell AJ 1. Clopidogrel. *Drugs*. (1997) 54:745–50. doi: 10.2165/00003495-199754020-00009

17. Lian EC. Pathogenesis of thrombotic thrombocytopenic purpura: aDAMTS13 deficiency and beyond. *Semin Thromb Hemost*. (2005) 31:625–32. doi: 10.1055/s-2005-925468

18. Kondo K, Umemura K. Clinical pharmacokinetics of tirofiban, a nonpeptide glycoprotein IIb/IIIa receptor antagonist: comparison with the monoclonal antibody Abciximab. *Clin Pharmacokinet*. (2002) 41:187–95. doi: 10.2165/00003088-200241030-00003

19. Giugliano RP. Drug-Induced thrombocytopenia: is it a serious concern for glycoprotein IIb/IIIa receptor inhibitors? *J Thromb Thrombolysis*. (1998) 5:191–202. doi: 10.1023/A:1008887708104

20. Said SM, Hahn J, Schleyer E, Müller M, Fiedler GM, Buerke M, et al. Glycoprotein IIb/IIIa inhibitor-induced thrombocytopenia: diagnosis and treatment. *Clin Res Cardiol*. (2007) 96:61–9. doi: 10.1007/s00392-006-0459-7

21. Han Y, Guo J, Zheng Y, Zang H, Su X, Wang Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *Jama*. (2015) 313:1336–46. doi: 10.1001/jama.2015.2323

22. Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, et al. Guidelines for the use of platelet transfusions. *Br J Haematol*. (2017) 176:365–94. doi: 10.1111/bjh.14423

23. Huynh T, Piazza N, DiBattiste PM, Snapinn SM, Wan Y, Pharand C, et al. Analysis of bleeding complications associated with glycoprotein IIb/IIIa receptors blockade in patients with high-risk acute coronary syndromes: insights from the PRISM-PLUS study. *Int J Cardiol*. (2005) 100:73–8. doi: 10.1016/j.ijcard.2004.07.014

24. Yi YH, Yin WJ, Gu ZC, Fang WJ, Li DY, Hu C, et al. A simple clinical Pre-procedure risk model for predicting thrombocytopenia associated with periprocedural use of tirofiban in patients undergoing percutaneous coronary intervention. *Front Pharmacol*. (2018) 9:1456. doi: 10.3389/fphar.2018.01456

25. Wang H, Feng M. Influences of different dose of tirofiban for acute ST elevation myocardial infarction patients underwent percutaneous coronary intervention. *Medicine (Baltimore)*. (2020) 99:e20402. doi: 10.1097/MD.0000000000020402

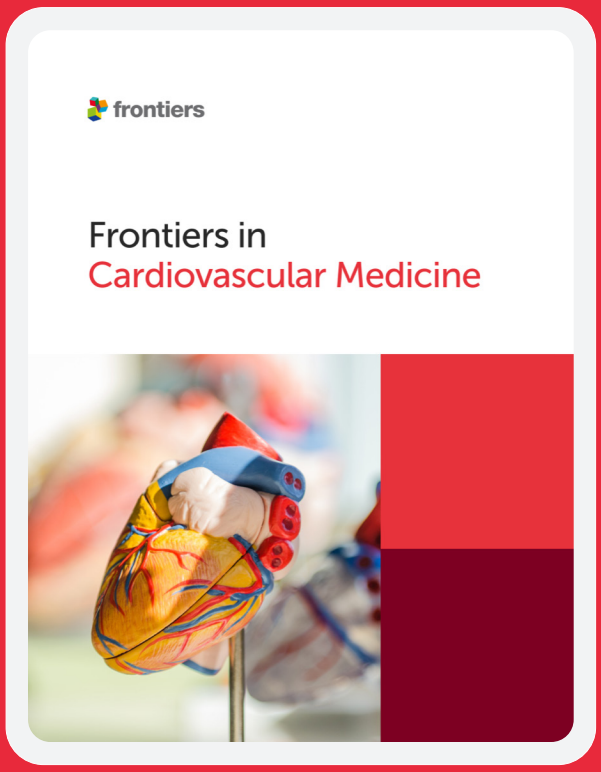
Frontiers in
Cardiovascular Medicine

Innovations and improvements in cardiovascular treatment and practice

Focuses on research that challenges the status quo of cardiovascular care, or facilitates the translation of advances into new therapies and diagnostic tools.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact