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# Case reports in general cardiovascular medicine 2023

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# Case reports in general cardiovascular medicine: 2023

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# Editorial: Case reports in general cardiovascular medicine: 2023

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Editorial on the Research Topic
Case reports in general cardiovascular medicine: 2023

Cardiovascular diseases (CVD), a big threat to public health worldwide, have been considered as a leading noninfectious killer to individuals. Understanding the mechanisms and developing effective treatments for CVD is a top priority (1–3).

In this editorial, we took insight into case reports featured in the Frontiers in Cardiovascular Medicine Research Topic "Case Reports in General Cardiovascular Medicine: 2023." This special issue collects over 20 cases that cover diagnosis, management and outcomes of complex and rare CVD. This special issue has garnered widespread attention with more than twenty-five thousand views and including more than four thousand downloads. Table 1 presents the Case Reports published in the General Cardiovascular Medicine Section in the year 2023. By sharing these unique experiences, the authors contributed to enhancing medical knowledge and improving clinical care.

Pulmonary embolism (PE) is a life-threatening condition resulting from a blockage in the pulmonary arteries with big challenges, which has been the focus of several compelling cases (4). Different with the typical symptoms such as chest pain, rapid breathing, hemoptysis, and syncope, Ma et al.'s exceptional case report described a rare occurrence of PE by which manifested with third-degree atrioventricular block and ST-segment elevation. The patient's history of cerebral hemorrhage led to a complexity of diagnosis, emphasizing the importance of a comprehensive assessment of all clinical findings to decrease misdiagnosis rates. Šačić et al. presented a case of woman with an implanted pacemaker by which led to infective endocarditis, affecting the right atrium and ventricle, further complicated by pulmonary embolism. This case highlighted the growing incidence of endocarditis associated with cardiac devices, particularly in patients with complex medical backgrounds requiring immunosuppressive therapy. An additional striking case shared by Li et al. depicted a sudden and severe PE episode that resulted in cardiac arrest in a 59-year-old male undergoing a routine femoral fracture reduction procedure under general anesthesia. Prompt diagnosis facilitated by computed

TABLE 1 Metrics (on July 8, 2024) of the articles published in case reports in general cardiovascular medicine: 2023.

| Title | Authors | Views | Downloads |
|---|---|---|---|
| Case report: The presence of third-degree atrioventricular block caused by pulmonary embolism masquerading as acute ST-segment elevation myocardial infarction | Ma et al. | 633 | 322 |
| Successful cardiopulmonary resuscitation of cardiac arrest induced by massive pulmonary embolism under general anesthesia: a case report | Li and Cai | 1,713 | 417 |
| Tale of two hearts: a TNNT2 hypertrophic cardiomyopathy case report | Pham et al. | 3,200 | 482 |
| A case report of multiple artery pseudoaneurysms associated with SARS-CoV-2 | Zhang et al. | 1,200 | 359 |
| Coronary artery mycotic aneurysm in a patient suffering from subacute endocarditis: a case report and literature review | Hali et al. | 902 | 440 |
| Cardiac pacemaker–related endocarditis complicated with pulmonary embolism: Case report | Šačić et al. | 1,400 | 267 |
| Case Report: Postmortem brain and heart pathology unveiling the pathogenesis of coexisting acute ischemic stroke and electrocardiographic abnormality | Hattori et al. | 1,150 | 516 |
| A novel compound heterozygous variant in ALPK3 induced hypertrophic cardiomyopathy: a case report | Li et al. | 1,326 | 548 |
| Case Report: Hypertrophic cardiomyopathy with recurrent episodes of ventricular fibrillation and concurrent sinus arrest | Hamidi et al. | 1,195 | 358 |
| Case Report: Early diagnosis and bevacizumab-based chemotherapy for primary pericardial mesothelioma: a case with occupational asbestos exposure history | Wang et al. | 1,025 | 279 |
| Case Report: Flurbiprofen-induced Type I Kounis syndrome | Tang et al. | 811 | 286 |
| Subacute hemorrhagic pericardial tamponade after COVID-19 infection mimicking carcinomatous pericarditis: a case report | Yamamoto et al. | 1,900 | 240 |
| A case report on pheochromocytoma mimicking as fulminant myocarditis—a diagnostic challenge | Cheng et al. | 667 | 237 |
| Case Report: Thrombus aspiration and *in situ* thrombolysis via a Guidezilla guide extension catheter in a patient with high-risk pulmonary embolism | Ding et al. | 706 | 105 |
| Case Report: Three cases of clinically suspected viral myocarditis with recovery of left ventricular dysfunction | Brown et al. | 519 | 129 |
| Venoarterial extracorporeal membrane oxygenation for vasoplegic shock after treprostinil refill of an implanted intravenous pump: a case report | Valencia et al. | 1,200 | 435 |
| A Case Report of Mycoplasma pneumoniae-induced fulminant myocarditis in a 15-year-old male leading to cardiogenic shock and electrical storm | Zhu et al. | 746 | 133 |
| Case Report: A case of Kounis syndrome induced by iodine contrast agent during coronary angiography | Sun et al. | 722 | 261 |
| Sudden death associated with delayed cardiac rupture: case report and literature review | Tinzin et al. | 520 | 102 |
| Old woman with Sheehan's syndrome suffered severe hyponatremia following percutaneous coronary intervention: a case report and review of literature | Gao et al. | 657 | 179 |

tomography pulmonary angiography (CTPA) and subsequent thrombolytic therapy proved pivotal in successful resuscitation, underscoring the critical need for timely intervention in acute PE situations. Moreover, Ding et al. introduced an innovative approach utilizing catheter-directed thrombolysis and thrombus aspiration with the Guidezilla guide extension catheter to manage a massive PE case ineligible for systemic thrombolysis. This novel intervention strategy holds significant potential, particularly in resource-constrained settings. Collectively, these case studies illuminated the landscape of PE management, emphasizing the need for personalized care, advanced diagnostic techniques, and innovative therapeutic interventions to optimize patient outcomes.

The research topic on hypertrophic cardiomyopathy (HCM) illuminates the intricate and multifaceted nature of this heritable cardiac disorder, which is predominantly driven by pathogenic mutations in sarcomeric proteins (5). The remarkable case described by Pham et al. involving a mother and daughter, both harboring the same mutation in the cardiac Troponin T (TNNT2) gene, demonstrates the incomplete penetrance and variable expression within TNNT2-positive HCM families. Despite their shared genetic background, the strikingly different disease presentations in these individuals underscore the challenges in predicting clinical outcomes based solely on genotype. In a separate case, Li et al. described a 14-year-old girl with HCM and sudden cardiac arrest, whose whole-exome sequencing demonstrated a novel heterozygous ALPK3 gene variant with severe clinical implications. This emphasizes the pivotal role of genetic testing in diagnosing HCM and guiding familial screening protocols. The report emphasizes the importance of closely monitoring, assessing risks, and evaluating genetic background to effectively manage HCM, particularly in identifying modifiable risk factors and necessitating timely interventions such as implantable cardioverter defibrillator (ICD) placement. Furthermore, Hamidi et al. presented an intriguing case of an 18-year-old woman with non-obstructive HCM who experienced sudden cardiac arrest due to ventricular fibrillation (VF) and subsequent sinoatrial node (SAN) arrest during VF episodes. Identifying a MYH7 gene variant as causative underscores the rarity of SAN arrest in HCM cases and highlights the crucial role of comprehensive electrophysiological assessment in managing complex arrhythmic presentations in HCM patients. This case serves as a reminder of the need for appropriate ICD selection in such scenarios. In summary, these case reports emphasized the importance of recognizing the variability in disease expression and the need for comprehensive risk assessment and management approaches to improve outcomes in HCM patients.

Myocarditis is a significant contributor to non-ischemic cardiomyopathy, ranging from acute heart failure to cardiogenic shock and ventricular arrhythmias (6). The unpredictable nature of this condition underscores the importance of early detection and appropriate management to improve patient outcomes. In a study by Brown et al., three cases of viral myocarditis suspected to be caused by coxsackievirus B were highlighted. Despite the

initial concern for cardiogenic shock, all three patients showed positive outcomes with significant clinical improvement and restoration of left ventricular ejection fraction. This underscores the potential for a favorable short-term prognosis in cases of coxsackie myocarditis with appropriate treatment and close monitoring. Zhu et al. presented a case of a young man who faced fulminant myocarditis and cardiogenic shock due to M. pneumoniae infection. The case emphasizes the importance of atypical pathogens consideration, like M. pneumoniae, in patients with cardiac complications, especially in younger individuals. The successful utilization of intra-aortic balloon pump and veno-arterial extracorporeal membrane oxygenation in this case highlights the critical role of advanced cardiac support measures in managing severe manifestations of myocarditis. Cheng et al. reported a female with 53-year-old who initially misdiagnosed with fulminant myocarditis but later identified as pheochromocytoma. The successful treatment through alpha-blockade therapy and laparoscopic adrenalectomy showcased the importance of tailored management approaches in achieving significant clinical improvement. These cases illustrated the diverse presentations and challenges in diagnosing and managing myocarditis-related complications. They underscored the importance of considering various etiological factors, utilizing advanced cardiac support strategies, and maintaining clinical vigilance to optimize outcomes in patients with myocarditis-related cardiac issues.

The emergence of the coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has sparked a worldwide pandemic (7–9). Among the extrapulmonary manifestations of COVID-19, two intriguing cases shed light on the diverse spectrum of unexpected cardiovascular abnormalities linked to SARS-CoV-2 infection, emphasizing the critical importance of vigilant monitoring and comprehensive understanding of such complications. Yamamoto et al. unraveled a unique instance of COVID-19-related acute pericarditis evolving into subacute hemorrhagic pericardial tamponade, initially masquerading as malignancy-induced cardiac distress. The intricate diagnostic journey underscores the challenging nature of identifying pericardial involvement in post-COVID-19 patients and the significance of exploring varied cytomorphological and histological features to reach a precise diagnosis. Zhang et al. delved into the rare occurrence of arterial pseudoaneurysms associated with SARS-CoV-2 infection, shedding light on the potential complexities of vascular abnormalities in the COVID-19 context. This study presented a patient developing pulmonary and gallbladder artery pseudoaneurysms after SARS-CoV-2 infection, serving as a crucial step in understanding the enigmatic pathophysiological mechanisms underlying SARS-CoV-2-associated artery pseudoaneurysms. Early diagnosis and prompt surgical intervention can greatly improve the long-term outlook for patients.

Two highlighted case reports underscored the complexity of Kounis syndrome (KS), characterized by the confluence of an allergic or hypersensitivity reaction and acute coronary syndrome. A clear consensus on diagnosing and treating KS remains elusive, with challenges in effectively identifying and managing KS patients in a timely manner. Sun et al. demonstrated the diagnostic challenge in a patient without coronary artery disease or allergies-related disease history, emphasizing the importance of recognizing KS in such scenarios. A Type II KS diagnosis was confirmed by a significant allergic reaction and widespread peripheral vasodilation during angiography. Tang et al. further illustrated the life-threatening potential of KS, where a patient developed severe symptoms after receiving intravenous flurbiprofen. The lack of significant stenosis or thrombus on coronary angiography, leading to a diagnosis of Type I KS, highlights the heterogeneity of this syndrome. These cases underscored the need for heightened clinical awareness and a multidisciplinary approach in managing KS, as timely recognition and appropriate treatment can be crucial for patient outcomes.

The collection of case reports presented in this research topic offers invaluable insights into the diagnosis and management of several rare and complex cardiovascular conditions, further expanding our clinical knowledge and improving patient care. Wang et al. highlighted the diagnostic challenge of primary pericardial mesothelioma (PPM), a rare malignant cancer with a poor prognosis. The case underscored the importance of a multidisciplinary approach, with consideration of the patient's occupational asbestos exposure history and a prompt biopsy leading to an early diagnosis. The successful use of a bevacizumab-based chemotherapy regimen as the first-line treatment is a promising development. Hali et al. emphasized the importance of recognizing coronary artery mycotic aneurysms (CAMA) in the context of infective endocarditis. While mycotic aneurysms are well-known in the cerebrovascular system, CAMA remains a rare but critical complication that deserves greater clinical attention. The case described a 42-year-old man with diabetes, cerebellar infarction and endocarditis caused by Viridans Streptococci. Diagnostic imaging revealed aneurysmal dilatation of the left main coronary artery, confirming CAMA. Due to high surgical risk, the patient was managed conservatively with prolonged antibiotic therapy, leading to a favorable 1-year outcome. Hattori et al. shed light on a rare and perplexing condition of cardiocerebral infarction (CCI), where simultaneous cerebral and coronary artery embolism occur, often with a fatal outcome. The autopsy findings in this 92-year-old patient revealed a critical role of atrial fibrillation-induced left atrial appendage thrombi as the common etiology for the cerebral and coronary artery embolism. Another pathological study was warranted to establish pathological mechanisms and Intervention strategies of CCI. Tinzin et al. reported the importance of recognizing the risk of delayed cardiac rupture following thoracic trauma, even in patients who seem to be recovering well initially. This rare complication can lead to sudden death, emphasizing the need for heightened vigilance and appropriate management strategies in such cases. Valencia et al. described a successful use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) as a rescue for refractory vasoplegic shock following an accidental treprostinil overdose in a patient with pulmonary arterial hypertension. ECMO helps maintain organ perfusion and allows for rapid recovery similar to drug elimination. It's

important to continuously monitor the patient to determine the best time to remove them from ECMO to avoid complications. Gao et al. reported an elderly patient with Sheehan's syndrome, who developed severe hyponatremia after a percutaneous coronary intervention, requiring prompt hydrocortisone administration to rapidly alleviate symptoms. This highlights the critical importance of stress-dose glucocorticoid supplementation before such procedures, especially in patients with adrenal insufficiency. Comprehensive endocrinological management is crucial for this patient population.

In summary, case reports in this special issue provided invaluable insights into the diagnosis and management of rare and complex cardiovascular conditions, emphasizing the importance of a multidisciplinary approach and evidence-based interventions to improve patient outcomes in these challenging scenarios.

## Author contributions

HW: Writing – original draft, Writing – review & editing. QW: Writing – original draft, Writing – review & editing. WC: Writing – original draft, Writing – review & editing. LR: Writing – original draft, Writing – review & editing. PL: Writing – original draft, Writing – review & editing. JX: Writing – original draft, Writing – review & editing.

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## Conflict of interest

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

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# Tale of two hearts: a TNNT2 hypertrophic cardiomyopathy case report

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Hypertrophic cardiomyopathy (HCM) is a heritable cardiomyopathy that is predominantly caused by pathogenic mutations in sarcomeric proteins. Here we report two individuals, a mother and her daughter, both heterozygous carriers of the same HCM-causing mutation in cardiac Troponin T (*TNNT2*). Despite sharing an identical pathogenic variant, the two individuals had very different manifestations of the disease. While one patient presented with sudden cardiac death, recurrent tachyarrhythmia, and findings of massive left ventricular hypertrophy, the other patient manifested with extensive abnormal myocardial delayed enhancement despite normal ventricular wall thickness and has remained relatively asymptomatic. Recognition of the marked incomplete penetrance and variable expressivity possible in a single *TNNT2*-positive family has potential to guide HCM patient care.

KEYWORDS

hypertrophic cardiomyopathy, TNNT2, cardiac troponin T, familial cardiomyopathy, incomplete genetic penetrance, variable genetic expressivity, case report

## Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular hypertrophy (LVH) in the absence of other explanatory causes such as systemic hypertension, valvular disease, or infiltrative disease. In clinical practice, HCM is diagnosed through noninvasive cardiac imaging, typically echocardiography or magnetic resonance imaging (MRI), and defined by unexplained left ventricular wall thickness ≥15 mm in adults, or ≥13 mm in adults who have a first-degree relative with HCM (1).

HCM is believed to affect 1 out of every 500 adults in the general population, with the majority of cases being familial, following an autosomal dominant pattern of inheritance (2–4). The genetic basis of HCM is heterogenous, with over 1,400 disease-causing variants identified that have varying effects on a wide array of sarcomeric and Z-disc proteins in cardiomyocytes (5). Pathogenic alterations of myofilament proteins account for the majority of HCM cases and are associated with a high degree of phenotypic heterogeneity (6).

Approximately 4% of HCM cases are attributable to pathogenic alterations of the myofilament protein cardiac troponin T (1). Cardiac troponin T is a regulatory protein that functions as the tropomyosin-binding subunit of the thin filament troponin complex in the sarcomere and is encoded by the gene *TNNT2* (7, 8). As such, it plays an important role within myofilaments and is necessary for normal contractile function within cardiomyocytes. Over 30 distinct pathogenic/likely pathogenic variants affecting *TNNT2* gene products have been associated with HCM, with individual mutations being unique and private to individual families (3).

In the present study we report two individuals with HCM, a mother and her daughter, who both carry the same familial *TNNT2* mutation. Despite their genetic background, they presented with very different phenotypic manifestations of HCM, spanning clinical presentation, symptomatology, and cardiac imaging. This variable intra-familial phenotypic expressivity highlights the importance of genetic testing as a means of identifying susceptible individuals in families that carry HCM-causative genetic variants, especially considering most of the pathogenic mutations that cause HCM do not reliably predict clinical presentation, disease course, or prognosis (9–11). Furthermore, because of the vast phenotypic heterogeneity associated with HCM, many mutation carriers do not present with the typical finding of LVH and may be asymptomatic, going undiagnosed (9, 10).

## Family genetic history

This report focuses on two individuals of Caucasian descent, a woman presenting at age 18 (Patient A) and her mother (Patient B). Both were found to have a c.275 G > A mutation (p.Arg92Gln-TNNT2) in the gene *TNNT2* through genetic testing (GeneDx Laboratories, Gaithersburg, MD). No additional HCM-associated gene variants were reported in either patient.

Family pedigree is shown as **Figure 1**. Of note, five additional family members are known to have HCM, including one of patient A's brothers (IV-2), both of patient B's siblings (III-3, III-IV), patient B's mother (II-2), and one of patient B's maternal aunts (II-3). These additional family members have not yet undergone genetic testing with confirmed results. At present, patients A and B are the only confirmed carriers of the *TNNT2* variant in this family.

## Case presentation of patient A

Patient A was initially referred for cardiac evaluation when she experienced a sudden out-of-hospital cardiac arrest at age 18. She was swing dancing with friends when she suddenly lost consciousness and was found to be pulseless. Bystander

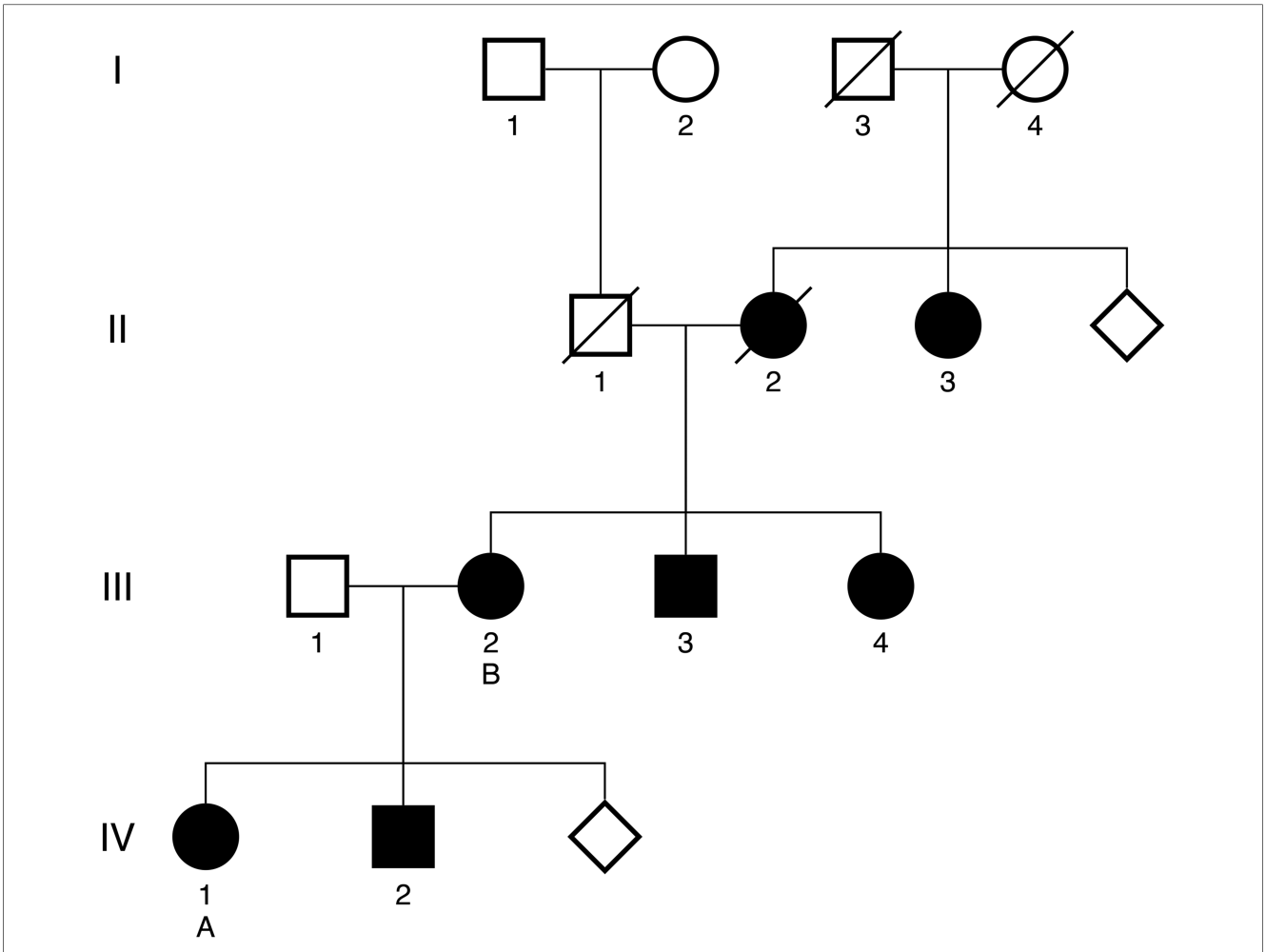


FIGURE 1
Targeted family pedigree. Family members with a confirmed diagnosis of HCM are denoted by solid dark shapes. Patient A and patient B are denoted by the letters A and B, respectively. Deceased family members are denoted with a diagonal line. Diamonds represent the presence of additional family members within a generation who have not been diagnosed with HCM.

cardiopulmonary resuscitation was performed for eight minutes. On-site automatic external defibrillator advised no shock. She regained full neurological function during hospitalization with a hypothermic protocol. Serial 12-lead electrocardiograms (ECGs) demonstrated left ventricular hypertrophy with ST-T depression in the anterolateral leads, with an initial QTc interval of 510 msec that normalized throughout the course of hospitalization. Transthoracic echocardiography revealed HCM with massively hypertrophied left ventricular septum (33 mm) with a reverse curve septal contour (**Figure 2A**). There was no outflow tract obstruction at rest or with Valsalva maneuver. She underwent single-lead implantable cardioverter-defibrillation (ICD) placement and was started on metoprolol succinate 25 mg daily.

ECG treadmill stress testing was performed two months following the initial hospitalization, which demonstrated a blunted blood pressure response from 80/58 mmHg to 90/46 mmHg and a peak $VO_2$ of 25.3 ml/kg/min (66% of predicted). She then experienced three separate ambulation-associated syncopal episodes in the following months, all with appropriate ICD discharges. ICD interrogation revealed sinus tachycardia at 140–150 bpm preceding ventricular tachycardia that quickly degenerated into ventricular fibrillation, with rates above 300 bpm by the time the shocks were delivered. She was started on amiodarone at 400 mg per day in addition to her metoprolol therapy.

Following these events, she underwent repeat ECG treadmill stress testing and developed polymorphic ventricular tachycardia 4 min and 20 s into exercise. Her ICD did not discharge due to rates below the detection zone (detection zone 290 to 310 msec, whereas the event was at 280 msec). Manual chest compressions and 150 mg of IV amiodarone were administered with resultant return to sinus rhythm. She was directly admitted and electrophysiology (EP) study was performed, but no clinically inducible arrythmia could be found. The ICD was reprogrammed to detect ventricular tachycardia at a lower threshold, and she

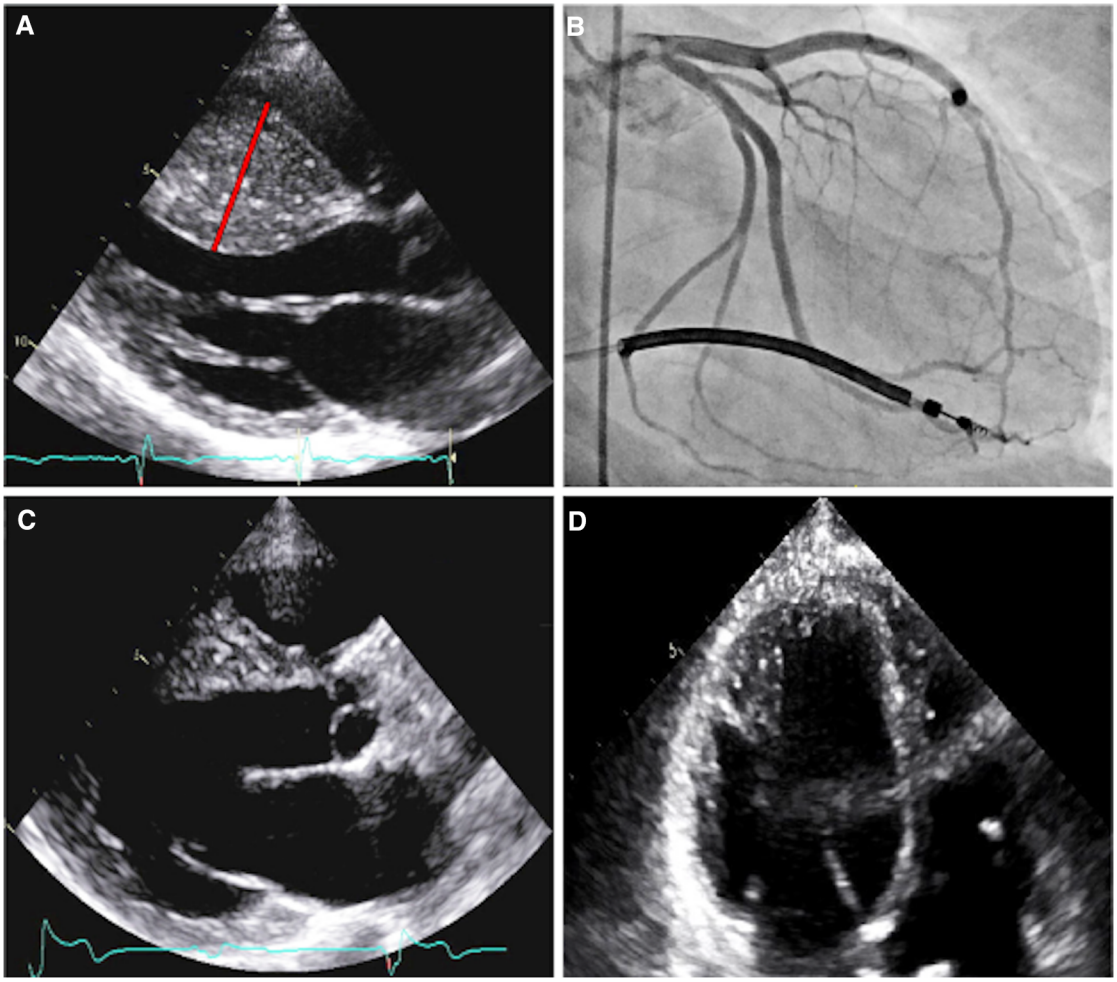


FIGURE 2
Imaging of patient A. Parasternal long axis echocardiogram prior to septal myectomy (**A**). The interventricular septum has reverse curve morphology, with a septal thickness measurement of 33 mm (red line) during diastole and a patent left ventricular outflow tract. Right anterior oblique caudal angiogram with prominent myocardial bridging of the large first and second septal perforators (**B**). Parasternal long axis echocardiogram, status-post septal myectomy (**C**). Four-chamber echocardiogram, with increased apical cavity size following septal myectomy (**D**).

was transitioned to monotherapy with sotalol (80 mg twice daily). Thoracoscopic sympathectomy of the left sympathetic chain (T1–T4) was performed. During a subsequent ECG treadmill stress test she developed global ST depression with ventricular tachycardia approximately four minutes into exercise, followed by ventricular fibrillation and loss of consciousness with ICD discharge. She regained a normal sinus rhythm and consciousness shortly thereafter. Sotalol was discontinued and she was started on flecainide (100 mg twice daily).

Coronary angiography revealed marked myocardial bridging of large septal perforators (**Figure 2B** and **Supplementary Video S1**). She ultimately underwent coronary artery unroofing and extended septal myectomy through combined transaortic and transapical approaches to improve diastolic function and debulk her arrhythmogenic substrate (**Figures 2C**, **D**). Pathology demonstrated histological features consistent with HCM, including moderate to marked myocyte hypertrophy, mild to focally moderate myocyte disarray, and mild to focally moderate interstitial fibrosis. Flecainide was discontinued and sotalol (120 mg twice daily) was resumed on post-operative day four.

A follow up EP study was pursued four months post-operatively for ventricular arrythmia substrate modification. Substrate mapping was performed in the right and left ventricles with endocardial radiofrequency ablation of fragmented potentials in the right ventricular septum, left ventricular septum, and lateral mitral annular region. She continued sotalol and did not have any peri-procedural ventricular tachyarrhythmias. Five months later her ICD discharged once more, though this was determined to be an inappropriate shock. Atrial fibrillation with a rapid ventricular response was suspected. She was asymptomatic during the episode aside from mild chest discomfort. The ICD detection zone was increased to 205–210 bpm, which has prevented further inappropriate discharges.

One year after the ablation, she sustained an occlusion of the right posterior cerebral artery at the P2–P3 segment, suggestive of a cardioembolic source. A transesophageal echocardiogram revealed a highly mobile mass on the pacemaker lead in the high right atrium but no left heart masses. There was no intracardiac shunt to facilitate paradoxical embolism. It was ultimately thought that a thrombus could have formed within the left ventricular apex, where apical dyskinesia could predispose to thrombus formation. She was started on warfarin (5 mg daily) with bridging enoxaparin and monitored with a goal INR of 2–3. She experienced a transient ischemic attack approximately three years later when her INR was subtherapeutic (1.8). Her INR goal was empirically increased to 2.5–3.5.

Given the development of lower extremity edema and worsening diastolic function, she was placed on furosemide 20 mg daily and was transitioned to a cardiac resynchronization therapy device. She remained hemodynamically stable and following diuresis, right heart catheterization demonstrated normal right atrial pressure (6 mmHg), right ventricular systolic pressure (21 mmHg), mean pulmonary artery pressure (14 mmHg), and pulmonary capillary wedge pressure (12 mmHg). Serial echocardiographic surveillance has demonstrated preserved left ventricular systolic function, with stable low-normal ejection fraction of 54%. Her functional capacity has remained reduced but stable, with peak exercise capacity ranging between 31% and 39% of predicted, and peak $VO_2$ of 12.7 (36% of predicted).

## Case presentation of patient B

Patient B was first referred at age 46 for genetic evaluation shortly after patient A began workup for HCM, as per familial screening guidelines, and was revealed to be a carrier of the pathogenic *TNNT2* variant. Her initial transthoracic echocardiogram revealed a maximal wall thickness of 11 mm with hypokinesis in the basal to mid inferior wall and basal to mid anteroseptal walls, with no evidence of obstruction (**Figure 3A**). ECG demonstrated baseline ST and T wave abnormalities. Prior to this evaluation she had experienced chronic episodic chest pain without other cardiac symptoms or clear precipitating factors, though cardiac diagnostic evaluation had never been pursued. Holter monitoring revealed a 7-beat run of nonsustained ventricular tachycardia at 129 bpm. A treadmill stress echocardiogram with maximal exertion resulted in no symptoms of chest pain. Electrocardiographic findings were within normal limits aside from baseline ST and T wave abnormalities. There was normal augmentation of left ventricular function with an increase in ejection fraction from 55% at rest to 65% during peak stress. No new regional wall motion abnormalities were identified. No further coronary evaluation was pursued.

She remained well from a cardiovascular standpoint until 8 years thereafter, when she presented to an outside emergency department with palpitations and intermittent chest discomfort. Newly identified atrial tachycardia was present with a ventricular rate of 130–150 bpm. She developed significant bradycardia (30 s bpm) with first-degree AV block after 3.5 mg of intravenous metoprolol tartrate. Her troponin I level was also noted to be mildly elevated to 1.352 ng/ml (reference range $\leq$0.013 ng/ml) and NT-proBNP to 260 pg/ml (reference $\leq$100 pg/ml). Coronary angiography revealed normal variant anatomy with a diminutive LAD (**Figure 3B**). She was monitored overnight with no further tachyarrhythmia or chest discomfort and discharged on dual anti-platelet therapy and high-intensity statin therapy.

Subsequent outpatient cardiac MRI demonstrated wall thinning and akinesia of the mid inferior and inferior septal segments with near transmural delayed enhancement hypoperfusion, and focal myocardial delayed enhancement of the mid anterior septal wall segment (**Figures 3C–F**). Repeat transthoracic echocardiography demonstrated a severely enlarged left atrium, left ventricular ejection fraction 54%, and ventricular septal thickness of 11 mm. Ambulatory Holter monitoring thereafter demonstrated low ectopic burden with self-limiting runs of atrial tachycardia and two 4-beat runs of nonsustained ventricular tachycardia.

Overall, she has remained NYHA class I on medical therapy with metoprolol succinate (25 mg daily) and is scheduled to undergo ICD implantation in the future given her family history,

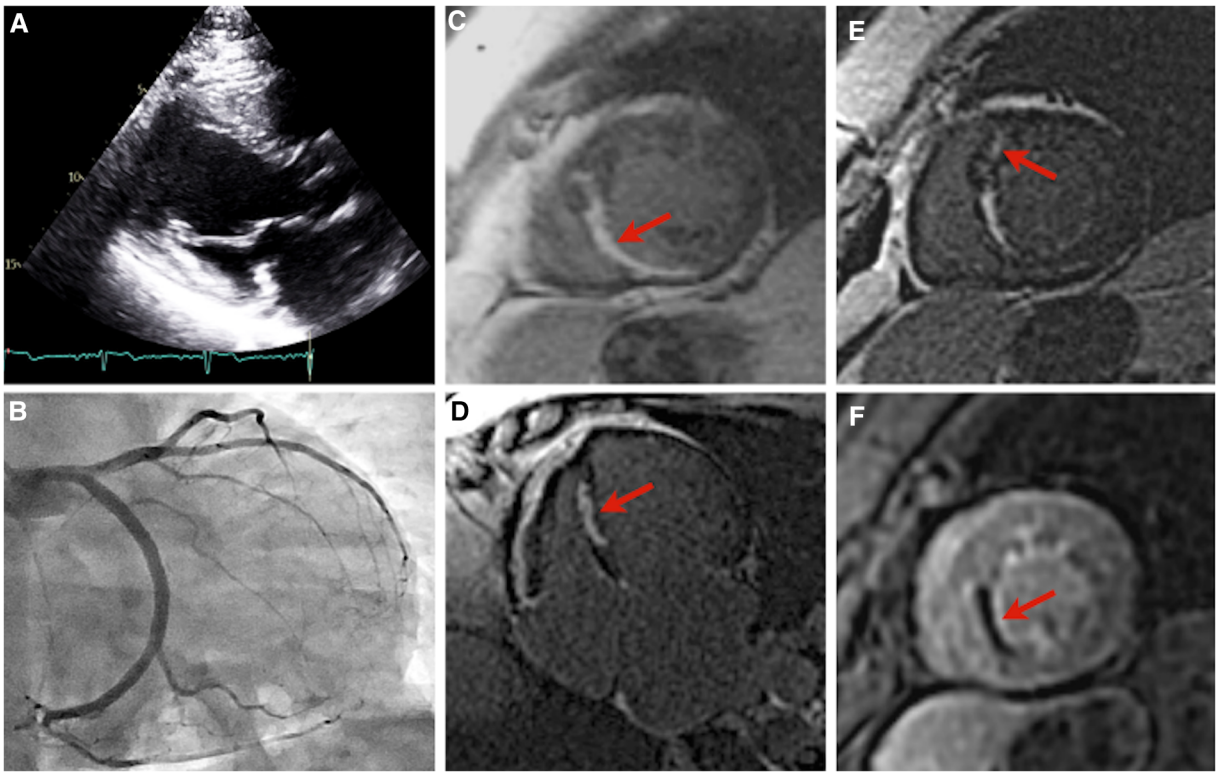


FIGURE 3
Imaging of patient B. Parasternal long axis echocardiogram, with an interventricular septal thickness measurement of 11 mm during diastole, and a patent left ventricular outflow tract (A). Right anterior oblique caudal angiogram demonstrating a diminutive left anterior descending artery (B). Images (C–F): cardiac magnetic resonance imaging of patient B. Near-transmural delayed gadolinium enhancement of the mid inferior and inferoseptal wall segments, short-axis view (C). Near-transmural delayed gadolinium enhancement of the mid inferior and inferoseptal wall segments, four-chamber view (D). Focus of mid-myocardial delayed gadolinium enhancement in the mid anteroseptal wall segment, short-axis view (E). Near-transmural septal hypoperfusion, short-axis view (F).

scarring on cardiac MRI, and non-sustained ventricular tachycardia. Her troponin T level has remained stably elevated on serial outpatient measurements (19–20 ng/dl, reference range ≤10 ng/L).

## Discussion

Not all carriers of *TNNT2* mutations will present with HCM. Furthermore, pathogenic alterations to cardiac troponin T often present with marked incomplete genetic penetrance and variable expressivity (6). Previous cases have been reported in which *TNNT2* mutations are associated with only minor or subclinical left ventricular hypertrophy but carry a high risk of arrhythmia (12). *TNNT2* mutations have additionally been implicated in other myocardial diseases including dilated cardiomyopathy, restrictive cardiomyopathy, and left ventricular noncompaction (13–15). The profound variability in clinical presentation and patient outcomes associated with *TNNT2* mutations can complicate the diagnosis and treatment of the diseases they cause.

Patient A carried a high disease burden with treatment-resistant ventricular arrhythmia, even following coronary artery unroofing, septal myectomy, and left sympathectomy. It is possible that myocardial ischemia may have contributed to her arrhythmia, particularly in the case of her second treadmill stress test; however, she did not describe angina and no definite ischemic findings were present on cardiac imaging. Ranolazine has recently shown promise in reducing ventricular arrhythmic burden in select patients with HCM and could have been considered (16). Given her borderline ejection fraction, worsening diastolic function, and reduced functional capacity, close cardiovascular clinic follow-up of patient A is needed, with cardiac transplantation a potential future outcome.

Patient B had milder LV hypertrophy with evidence of microvascular angina. Overall, her presentation was more consistent with the typical phenotype seen in thin-filament HCM (17, 18). She had no functional limitations in her daily life and remained relatively asymptomatic until presenting to the emergency department with palpitations. Serial lab work in the outpatient setting revealed a chronically elevated baseline troponin level, consistent with HCM (19). Together, these findings suggest HCM rather than an acute infarct as the cause of her initial presentation. The pattern of patchy mid-wall late gadolinium enhancement involving the interventricular septum observed on her MR imaging (**Figures 3C–E**) is attributable to myocardial fibrosis and occurs in approximately 60% of HCM

patients with LVH (20). A similar distribution of late gadolinium enhancement was previously documented in another p.Arg92Gln-TNNT2-positive individual who presented without symptoms or echocardiographic evidence of HCM (21). The functional implications of late gadolinium enhancement in the setting of HCM remain unclear. Previous studies have found it to be inconsequential, whereas others have demonstrated associations with increased myocardial stiffness, regional wall motion abnormalities, and diminished LV systolic function (20). Regions of fibrosis may also serve as arrhythmogenic substrates and the extent of scarring has been correlated with sudden cardiac death and major adverse cardiovascular events (21, 22). Because of this, the 2020 ACC/AHA guidelines have highlighted the clinical utility of late gadolinium enhancement evaluation in HCM sudden cardiac death risk stratification (23).

The genetic locus of *TNNT2* is 1q32.1 and its transcript contains 17 exons (11). The p.Arg92 codon within this gene has been described as a "hot spot" for mutation, and an p.Arg92Gln-TNNT2 pathogenic variant was determined to be the genetic culprit for the family in the current study. Other documented TNNT2 HCM-causative pathogenic/likely pathogenic variants include p.Arg278Cys-TNNT2, p.Arg92Leu-TNNT2, p.Arg92Trp-TNNT2, p.ΔGlu163-TNNT2, p.Ala104Val-TNNT2, and p.Arg278His-TNNT2 (24). Pathogenic variants of *TNNT2* gene product variants account for a relatively small subset of HCM cases compared to other myofilament genes such as *MYBPC3* and *MYH7* (2, 25). Though both patients in this report presented with nonobstructive HCM, it should be noted that both obstructive and nonobstructive phenotypes can arise from *TNNT2* mutations (24).

A growing body of work in the past few years has shown that the high degree of phenotypic heterogeneity observed in HCM may be due, at least in part, to the additive effects of pro-hypertrophic common genetic variants across the genome. Recent genome-wide association studies have jointly identified over a dozen common (minor allele frequency >0.01) genetic variants that contribute to HCM risk and severity (26, 27). These common variants are distinct from the rarer sarcomeric genes (e.g., *TNNT2*) traditionally associated with HCM, but have been correlated with increased HCM risk in both carriers and noncarriers of pathogenic sarcomeric protein variants (27). Polygenic risk score metrics have been constructed to calculate the additive genetic effects that these common variants have on an individual's HCM

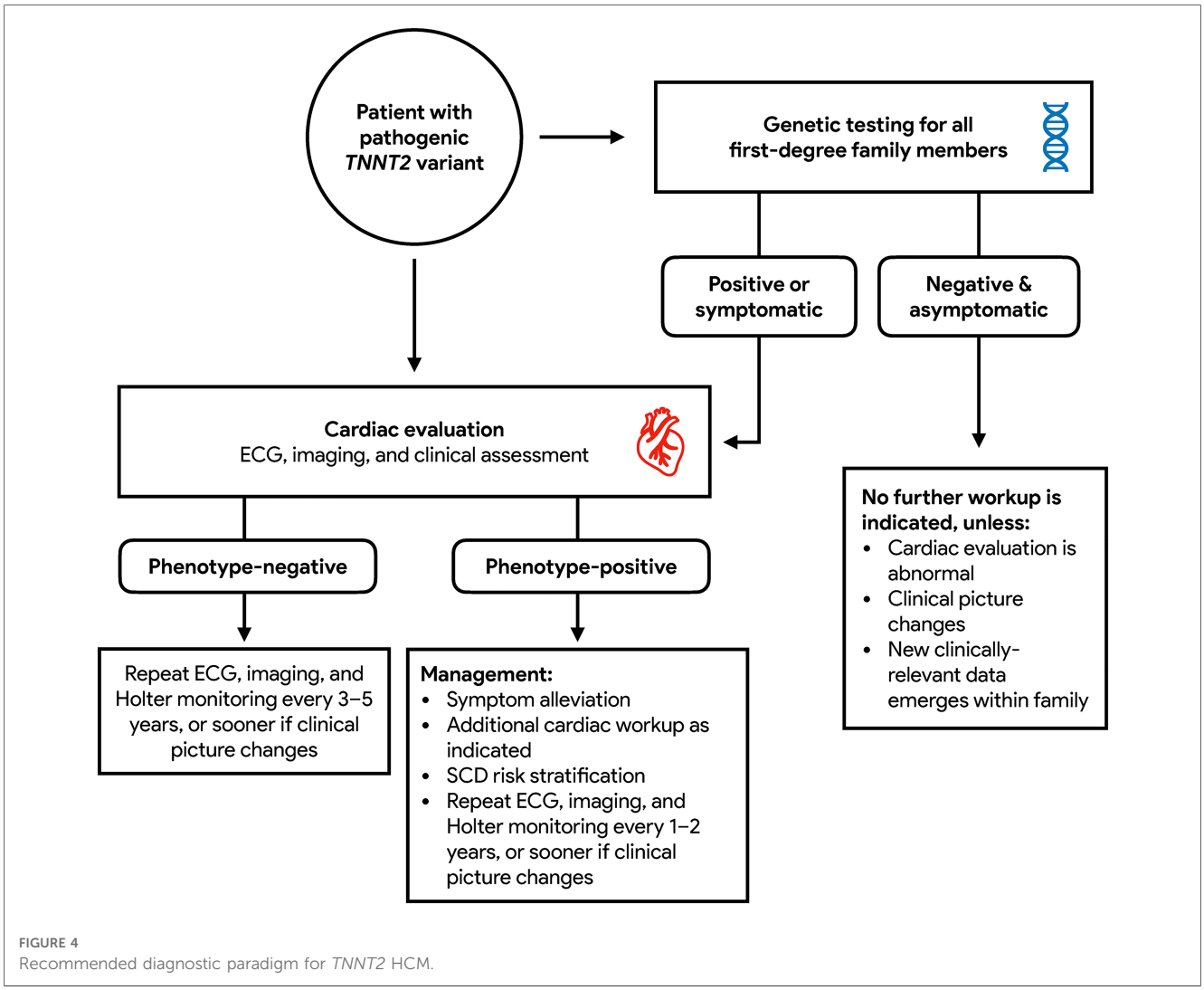


FIGURE 4
Recommended diagnostic paradigm for *TNNT2* HCM.

risk. Importantly, an upper quintile PRS has been linked to a relative increase in disease severity, measured through adverse clinical events and degree of LVH, while a lower score has protective effects (26). Thus, interindividual differences in "genetic background" may contribute to differences in expressivity between two carriers of the same pathogenic *TNNT2* variant. Additionally, modifiable risk factors such as hypertension have similarly been correlated with increased disease risk and severity in both carriers and noncarriers of pathogenic sarcomeric protein variants (27, 28). These findings suggest the potential benefit in assessing polygenic burden status and modifiable risk factors for HCM prognostication (28).

Genetic testing should be considered in any patient who fulfills diagnostic criteria for HCM, as genetic testing is the preferred method of family screening when a causative mutation is identified (23). Due to the genetic heterogeneity of HCM, a comprehensive panel should be used for screening that covers not only the main sarcomeric culprits (e.g., *TNNT2*, *MYH7*, *MYBPC3*, *TNNI3*, *ACTC*), but also other causes including RASopathies, mitochondrial proteins, and glycogen storage diseases (29). Although important for family screening, genetic analysis does not typically alter therapeutic decision-making in the management of HCM.

In general, patients who test positive for pathogenic variants of *TNNT2* are recommended to undergo cardiac evaluation due to their increased risk for the development of HCM (30). Mutation carriers who are symptomatic or phenotype-positive should continue ongoing monitoring inclusive of ECG, transthoracic echocardiography, and ambulatory Holter monitoring every 1–2 years (23). Risk assessment for sudden cardiac death, inclusive of stress testing and cardiac MRI should also be performed, with a low threshold for additional diagnostic cardiac workup as indicated. The frequency of follow up beyond general guidelines should be further tailored to individual patients on the basis of symptomatology, additional genetic results, functional capacity, changes in clinical status, and course of disease progression (31). For patients in whom there is concern for HCM but echocardiography is inconclusive, cardiac MRI should be performed for diagnostic clarification. Mutation carriers who are asymptomatic or phenotype-negative should repeat screening every 3–5 years (23). First-degree relatives of mutation carriers who undergo genetic testing and are found not to be mutation carriers themselves are still recommended to have cardiac evaluation done. If cardiac workup returns negative and these patients are asymptomatic, they may be discharged from further follow-up but advised to seek re-assessment in the event that their clinical picture changes or new clinically relevant data emerges within the family (9). These recommendations are summarized as **Figure 4**.

## Conclusion

Though they account for a relatively small subset of HCM cases, pathogenic variants in *TNNT2* exemplify the marked incomplete penetrance and variable phenotypic expressivity seen in genetic cardiomyopathies. As we have reported, a single genotype can give rise to a wide range of presentations, from mild symptoms to sudden cardiac death. The two patients presented herein had very different phenotypic expressions of the same p.Arg92Gln-TNNT2 pathogenic variant, manifesting at different stages in their lives. One individual carried a relatively high burden of HCM manifesting as massive left ventricular hypertrophy and recurrent tachyarrhythmia. The other had an overall milder presentation with subclinical to minimal left ventricular hypertrophy. This report adds to the ever-growing body of documentation that highlights the highly heterogenous phenotypes of *TNNT2* cardiomyopathies.

## Data availability statement

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

## Ethics statement

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

## Author contributions

JP and JBG made significant contributions to the composition of the manuscript. The manuscript was written by JP. The treatment and follow-up of the patients were managed by MT and DN. The final written manuscript was reviewed, revised, and approved by all authors. All authors contributed to the article and approved the submitted version.

## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1167256/full#supplementary-material.

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# A case report of multiple artery pseudoaneurysms associated with SARS-CoV-2

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Arterial pseudoaneurysms are rare vascular abnormalities that can occur as a complication of infections. Artery pseudoaneurysms associated with SARS-CoV-2 are a rare occurrence in COVID-19 patients, and their rupture can result in significant hemorrhage and sudden death. Few cases of SARS-CoV-2-associated artery pseudoaneurysms have been reported, and their underlying pathophysiological mechanisms remain unclear. This study presents the first reported case of a patient who developed both pulmonary and gallbladder artery pseudoaneurysms following SARS-CoV-2 infection. We investigate the potential pathogenesis of these pseudoaneurysms and aim to improve the understanding of this rare complication.

KEYWORDS

SARS-CoV-2, pseudoaneursym, pulomary artery, gallbladder artery, case report, pathogensis

## 1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been known to cause damage to organs and tissues containing angiotensin-converting enzyme 2 (ACE2) receptors, resulting in various complications (1). Direct damage to vascular endothelial cells can cause thrombosis, leading to pulmonary embolism or coronary heart disease (2). Although such events have been reported, reports on *de novo* pseudoaneurysms during coronavirus disease 2019 (COVID-19) infection are limited. This study presents a case of an 80-year-old male patient with chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus who developed both pulmonary and gallbladder artery pseudoaneurysms one week after SARS-CoV-2 infection. The study aims to analyze the potential pathogenesis of these pseudoaneurysms to improve the understanding of this rare SARS-CoV-2-related complication.

## 2. Case report

The patient experienced symptoms such as fatigue, muscle soreness, chills, fever, and unsteady gait three days prior to admission. Upon admission, laboratory tests showed

Abbreviations
SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease; HRCT, high-resolution computed tomography; CTA, computed tomography angiography.

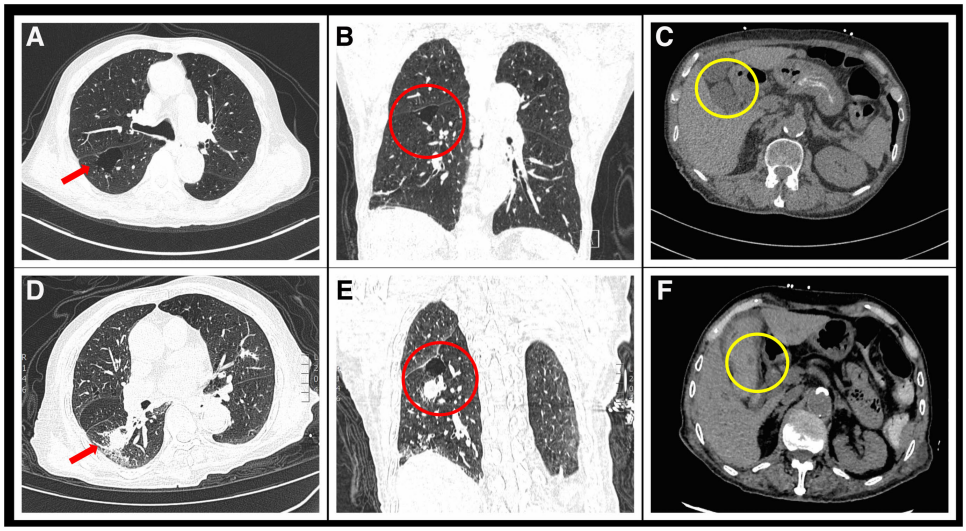


FIGURE 1
Comparison of chest and abdominal CT scans before and after admission. (A) Transverse section of chest HRCT upon admission shows a large bulla in the red arrow region due to COPD. (B) Coronal section image of the chest before hemoptysis shows a newly developed solid nodule in the right lung. (C) Abdominal CT at admission shows no abnormalities in the gallbladder artery. (D) Follow-up chest HRCT image 1 week after admission shows a new solid nodule with a diameter of 21 × 18 mm in the posterior segment of the right lower lobe (red arrow). (E) Coronal section image of the chest after hemoptysis shows a newly developed solid nodule in the right lung. (F) Emergency abdominal CT image taken after abdominal pain and vomiting shows a newly appeared circular low-density dark area at the gallbladder artery (yellow circle).

significantly elevated levels of cardiac enzymes, transaminases, bilirubin, creatinine, erythrocyte sedimentation rate and procalcitonin. High-resolution computed tomography (HRCT) of the lungs showed multiple pulmonary cysts (Figure 1B), while abdominal CT revealed no significant abnormalities (Figure 1C). Sputum culture identified white Candida, but no bacteria or fungi were found in the bronchoalveolar lavage fluid. The initial diagnosis was acute myocarditis and liver and kidney failure following a novel coronavirus infection. Considering that the patient was positive for COVID-19, significantly elevated procalcitonin and inflammatory markers, paxlovid was given to inhibit viral replication, ceftriaxone and meropenem for infection, intravenous methylprednisolone succinate to reduce inflammation, and dibutyl cyclic adenosine calcium for injection to protect the heart and glutathione for injection to protect the liver. The patient had acute renal insufficiency, and his overall condition improved significantly after routine hemodialysis treatment.

On the seventh day after admission, the patient experienced four sudden and unexpected episodes of hemoptysis, with each episode producing approximately 30–50 ml of blood. Hemostatic medication, i.e., etamsylate, hemocoagulase bothrops atrox and tranexamic acid, was administered immediately, and a repeat HRCT scan of the lungs revealed the presence of a newly formed solid nodule in the posterior segment of the right lower lobe (Figure 1D). Further contrast-enhanced CT imaging confirmed the diagnosis of a pseudoaneurysm of the pulmonary artery in the same location (Figure 2).

After the cessation of hemoptysis, the patient developed severe right upper abdominal pain and recurrently vomited fresh blood. Emergency abdominal CT scan revealed acute cholecystitis with biliary bleeding (Figure 1F). With the assistance of interventional doctors, percutaneous cholecystocentesis and drainage were performed, resulting in the extraction of approximately 150 ml of bloody fluid. To identify the cause of abdominal pain and vomiting, we conducted computed tomography angiography (CTA) of the entire aorta, which revealed a newly formed pseudoaneurysm in the gallbladder artery (Figure 3).

A multidisciplinary consultation was organized to discuss further treatment options. Considering the patient's current physical condition, which was no longer suitable for surgical intervention, the experts recommended an interventional approach with balloon occlusion of the pseudoaneurysm. However, the patient subsequently experienced massive gastrointestinal bleeding with hemorrhagic shock, and due to the critical condition of the patient, he was transferred to the intensive care unit for further treatment. Ultimately, surgical intervention was abandoned in favor of conservative treatment.

## 3. Discussion

The formation of arterial pseudoaneurysms is characterized by the destruction of the arterial wall, leading to an extravascular hematoma surrounded by a thin layer of connective tissue. Pseudoaneurysms typically occur due to the focal dilation of arterial branches, and they are commonly associated with infections caused by pathogens like staphylococci, streptococci, or Mycobacterium tuberculosis (3). Although rare, arterial pseudoaneurysms have been reported as a complication of COVID-19, and their rupture can cause massive bleeding and

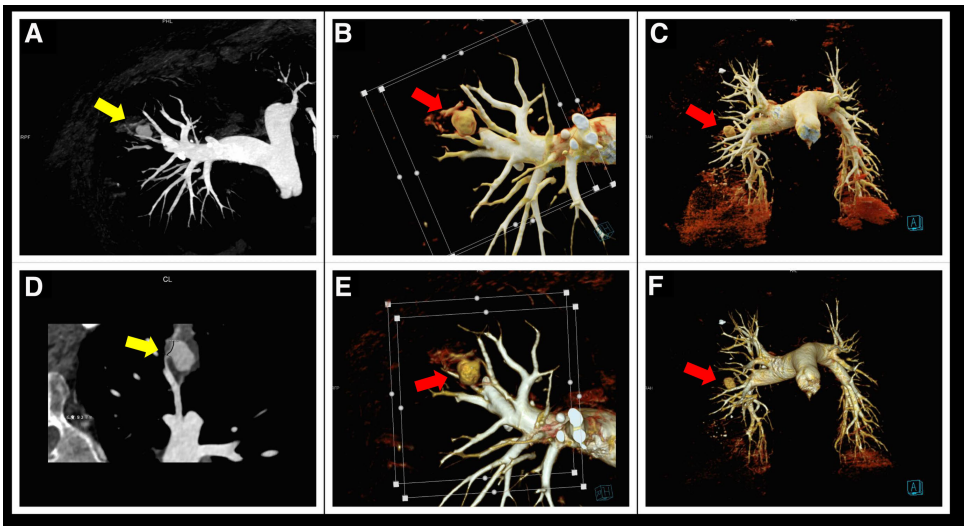


FIGURE 2
Contrast-enhanced CT scan of the patient's lungs. (**A,D**) Curved planar reconstruction images reveal the dilation of the pulmonary artery at its distal end, forming a pseudoaneurysm (yellow arrow). (**B,C,E,F**) Volume rendering technology images clearly show a nearly spherical mass pseudoaneurysm at the distal end of the right pulmonary artery (red arrow).

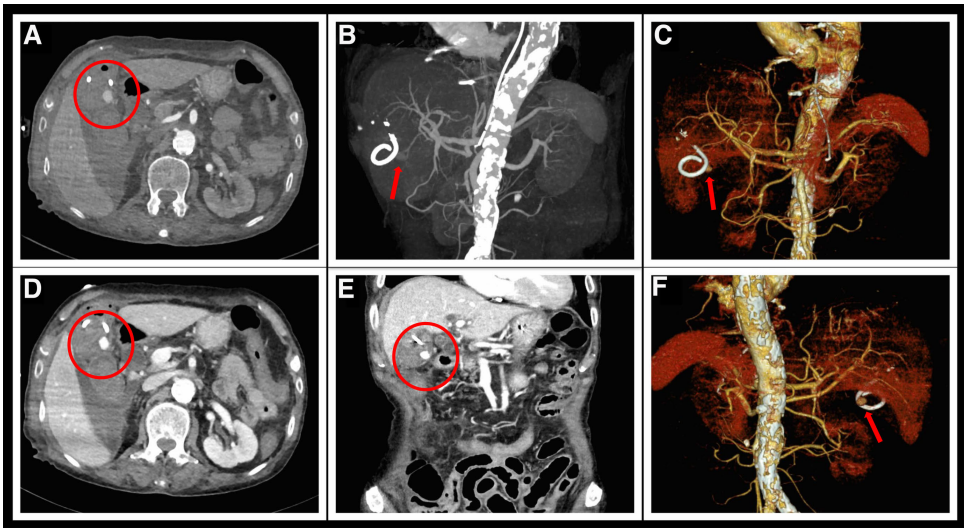


FIGURE 3
Aortic CTA examination after hematemesis. (**A,D**) Delayed enhancement of the pseudoaneurysm of the gallbladder artery (encircled in red) during the arterial phase of CTA. (**B,C,E,F**) Reconstructed three-dimensional images clearly show a spherical pseudoaneurysm at the exit of the gallbladder artery. (**E**) Reconstructed coronal section image shows an enhanced pseudoaneurysm image below the gallbladder.

hemorrhagic shock, which is a significant cause of death in patients with SARS-CoV-2 infection (**Table 1**).

The specific mechanisms that lead to the formation of pseudoaneurysms following SARS-CoV-2 infection remain unclear. However, existing evidence suggests that the virus can attack endothelial cells in blood vessels, and cause multisystem inflammatory syndrome, which can exacerbate vascular injury (2). The disruption of the endothelial layer can initiate the formation of pseudoaneurysms by increasing local wall stress and causing the tearing and rupture of the vessel wall. In some cases, severe inflammatory response to the virus, such as "cytokine storm", may also induce the formation of the pseudoaneurysms. In addition, recent studies suggested that abnormal presence of autoantibodies and endothelial damage may also be cornerstones of COVID-19 disease (4, 9), but more clinical evidence is still needed.

Research indicates that patients recovering from SARS-CoV-2 infection may develop iatrogenic and noniatrogenic pulmonary cysts, which can rupture and merge to form lung bullae or spontaneous pneumothorax (5). Slow airflow within these cysts creates a conducive setting for the colonization of bacteria or fungi, which can worsen the intensity of pulmonary infections and inflammatory responses. This process is similar to the

TABLE 1 Pathophysiological mechanism of artery pseudoaneurysms associated with SARS-CoV-2.

| Mechanism | Detail | Reference |
|---|---|---|
| Virus | Attack endothelial cells in blood vessels | (2) |
| Immune response | Multisystem inflammatory syndrome or "cytokine storm", which can exacerbate vascular injury | (2) |
| Pulmonary cysts | Slow airflow within these cysts creates a conducive setting for the colonization of bacteria or fungi, which can worsen the intensity of pulmonary infections and inflammatory responses | (4) |
| Infection | Secondary mucormycosis infection | (5) |
| | The use of glucocorticoids during treatment can further suppress immune function, facilitating fungal invasion and pseudoaneurysm development | (6) |
| Complication | Diabetes is a chronic metabolic inflammatory disorder that activates serine kinases and leads to insulin resistance | (7) |
| | Prolonged diabetes and fluctuations in blood glucose can exacerbate endothelial damage and cardiovascular complications | (8) |

formation of cavities and pulmonary artery pseudoaneurysms after tuberculosis infection (6). In this case, the patient had a history of COPD and suboptimal baseline lung function. A large lung bulla is visible above the pulmonary artery pseudoaneurysm, and this structural anomaly could potentially contribute to the development of the pseudoaneurysm.

In addition, secondary mucormycosis infection following SARS-CoV-2 infection may also be an important mechanism for the formation of pseudoaneurysms (7, 8). Although there are few reports of this disease, it is plausible that SARS-CoV-2 infection can impair immune system, while the use of glucocorticoids during treatment can further suppress immune function, facilitating fungal invasion and pseudoaneurysm development. Notably, this condition appears to be more prevalent in elderly diabetic patients (10), as diabetes is a chronic metabolic inflammatory disorder that activates serine kinases and leads to insulin resistance (11). Prolonged diabetes and fluctuations in blood glucose can exacerbate endothelial damage and cardiovascular complications (12), increasing the risk of developing pulmonary artery pseudoaneurysms.

Although there have been no reports of SARS-CoV-2-related pseudoaneurysms in the gallbladder artery, the virus can damage organs that have ACE2 receptor (1), which may include the gallbladder artery, increasing the risk of pseudoaneurysm formation. If a patient presents with pseudoaneurysms in multiple locations, Behçet's disease, a chronic autoimmune disease characterized by vasculitis should be considered. However, in the case presented, the patient had developed pseudoaneurysms in both the pulmonary and gallbladder arteries but had no oral or genital ulcers, and the antibodies associated with rheumatic immunity were negative, ruling out Behcet's disease. Instead, the patient was diagnosed with multiple pseudoaneurysms that were likely related to SARS-CoV-2 infection, given the explosive inflammatory response observed and the rapid emergence of these pseudoaneurysms.

## 4. Conclusion

In conclusion, we present a case of pulmonary artery and gallbladder artery pseudoaneurysms that developed during SARS-CoV-2 infection and investigate the underlying mechanism of SARS-CoV-2-associated artery pseudoaneurysms. Elderly diabetic patients experiencing sudden hemoptysis or hematemesis during the recovery phase following SARS-CoV-2 infection should be evaluated for rare complications such as artery pseudoaneurysms. Early diagnosis and surgical intervention can significantly improve the long-term prognosis of patients with this condition.

## Data availability statement

The original contributions presented in the study are included in the article, 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

QL and CL: treated the patient and conceived the study. ZZ: drafted the manuscript, and YX and QL: critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# Case Report: Postmortem brain and heart pathology unveiling the pathogenesis of coexisting acute ischemic stroke and electrocardiographic abnormality

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Electrocardiography abnormalities have been occasionally reported at the onset of stroke. Simultaneous electrocardiographic abnormalities and stroke require a rapid differentiated diagnosis among several diseases. However, direct causal relationships remain unclear. A 92-year-old woman presented to our emergency department in a sudden-onset coma. The patient suffered from huge acute ischemic stroke with bilateral internal carotid artery occlusion assessed by brain magnetic resonance imaging, and her electrocardiography showed ST-segment elevation at II, III, aVF and V4–6, and atrial fibrillation (AF). However, the etiology of the medical condition was clinically unknown. Eventually, the patient died on day 4 of hospitalization before the diagnosis could be completed. Therefore, an autopsy was performed to investigate pathological findings after obtaining informed consent from the family. A postmortem pathological evaluation demonstrated that fibrin mural thrombi in the left atrial appendage (LAA), and the cerebral and coronary arteries possessed CD31-positive endothelial cells, and CD68-positive and CD168-positive macrophages in a similar fashion, suggesting the fibrin thrombi observed in the three sites implicated to be identical. We concluded that nearly concurrent cerebral and coronary artery embolism because of the fibrin thrombi in LAA developed by AF. Simultaneous cerebral infarction and myocardial infarction are referred to as cardiocerebral infarction (CCI), a rare disorder for which clear pathomechanisms remain unknown, although several mechanisms of CCI have been proposed. We first revealed the clear pathology of CCI using the autopsy. Additional pathological studies are warranted to establish clear pathomechanisms and preventive strategies of CCI.

KEYWORDS

cardiocerebral infarction, cardioembolic stroke, myocardial infarction, atrial fibrillation, coronary artery embolism

## 1. Introduction

Bidirectional interactions between the cardiovascular and nervous systems have gotten more attention and are becoming increasingly important (1). Electrocardiography (ECG) abnormalities have been occasionally detected at the onset of stroke. Insular cortical damage such as stroke is linked to QT dispersion (2), negative T-waves (3), and atrial fibrillation (AF) (4, 5). Regarding ST-segment changes among ECG abnormalities, we must consider

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the following as differential diagnoses: (i) cardiac changes induced by stroke such as takotsubo cardiomyopathy or other cardiac conditions due to insular stroke, and (ii) cardioembolic stroke induced by intraventricular thrombi due to acute myocardial infarction (AMI) or takotsubo cardiomyopathy, and concurrent coronary-cerebral artery embolism induced by intra-atrial thrombi due to AF.

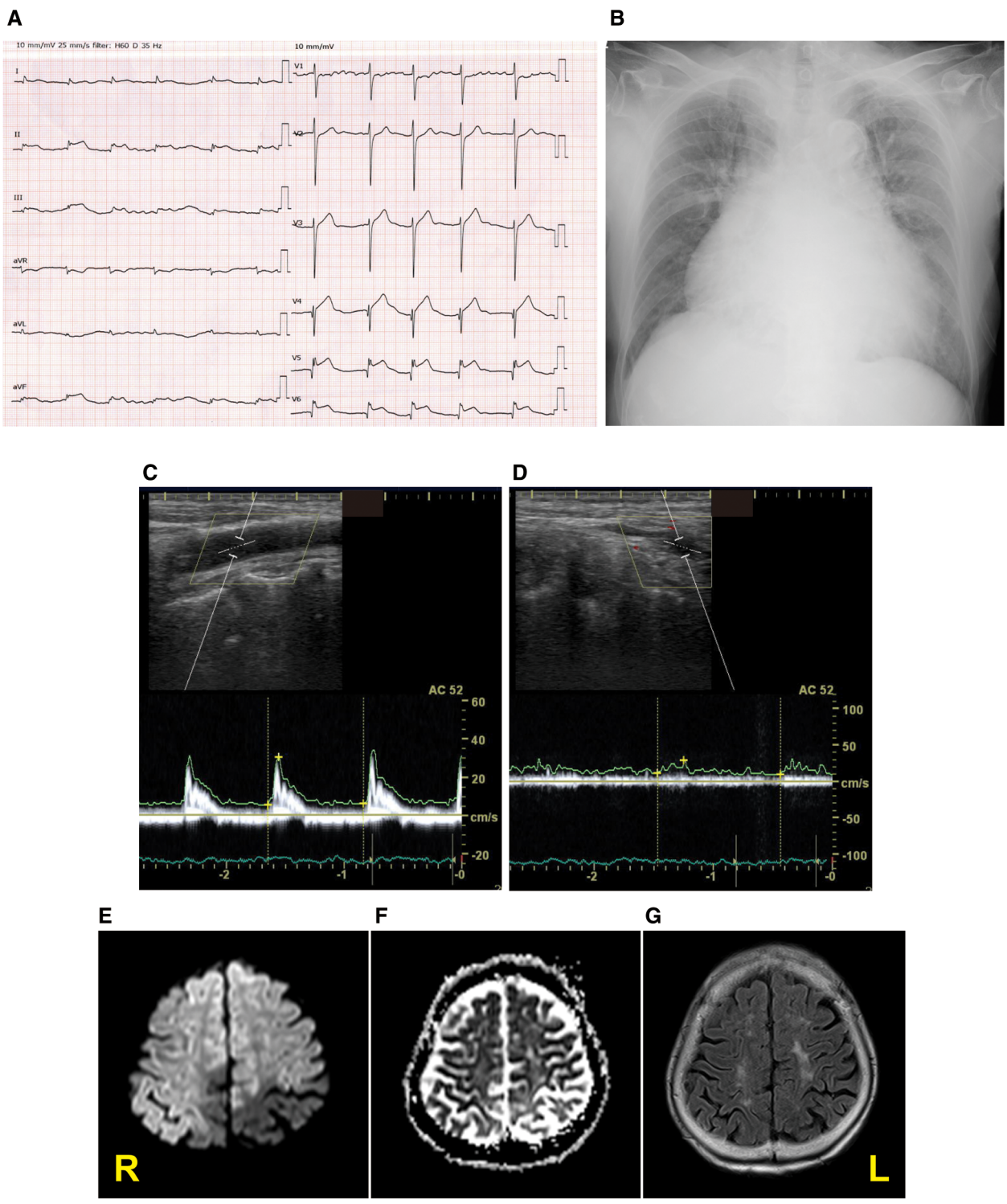


FIGURE 1
Diagnostic testing performed on admission. Twelve-lead electrocardiography (**A**), chest x-ray (**B**), pulse-wave carotid ultrasonography with Doppler in the left common carotid artery (**C**) and internal carotid artery (ICA) (**D**), and the diffusion-weighted magnetic resonance imaging (MRI) (**E**), apparent diffusion coefficient map (**F**), and fluid-attenuated inversion recovery MRI (**G**) displaying acute bilateral ICA territory infarction. R stands for right; L stands for left.

Among the abovementioned differential diagnoses in patients with acute stroke and ST-segment changes, cardiocerebral infarction (CCI) is one of the representative diseases. The simultaneous occurrence of AMI and acute ischemic stroke (AIS) is rare in CCI (6, 7). There are several possible mechanisms of CCI, which can be classified into four categories: (i) conditions causing concurrent cerebral–coronary infarction, (ii) cardiac conditions such as intraventricular thrombi due to wall akinesis or hypokinesis causing cerebral infarction, (iii) cerebral infarction causing AMI due to brain–heart axis dysregulation (8), and (iv) systemic prothrombotic state with hematologic disorders such as polycythemia vera and high plasma factor VIII levels (9). However, the clear pathomechanisms of CCI have not been studied with pathological findings.

Here we successfully revealed a part of causal relationships in a patient with AIS and ST-segment elevation via a postmortem autopsy.

## 2. Case presentation

A 92-year-old woman presented to our emergency room with a sudden-onset coma. A family member witnessed that she suddenly fell down on the floor while they were talking. Her eyes were closed, and she had lost consciousness. Although her medical history included chronic AF, hypertension, and aortic valve stenosis, but she did not take any anticoagulants. Her blood pressure was 205/102 mmHg. Neurological examination revealed severe disturbance of consciousness. The patient was mute and could not follow any command. Her Glasgow Coma Scale score was 6 (E1V2M3). The pupil size was normal (3/3 mm), and the oculocephalic reflex showed a positive response; however, roving eye movement was noted. This indicated that the cerebral cortex was impaired while the brainstem was functionally preserved. The pupillary light reflex was prompt bilaterally. Motor assessment revealed flaccid tetraplegia, and the Babinski reflex was bilaterally positive. The National Institutes of Health Stroke Scale score was 34. Blood test revealed 7,600/μl in white blood cell, hemoglobin was 13.4 g/dl, aspirate transaminase was 22 IU/L, alanine aminotransferase was 9 IU/L, sodium was140 mEq/L, glucose was 116 mg/dl, serum creatinine was 0.88 mg/dl, C-reactive protein was 0.04 mg/dL, brain natriuretic peptide was1035.5 pg/mL, and D-dimer was 18.5 μg/mL. A chest x-ray showed cardiomegaly, 72.0% in cardio–thoracic ratio, and ECG revealed AF with ST-segment elevation at II, III, aVF and V4–6 (**Figures 1A,B**). Echocardiography showed hypokinesis of the anterior and inferior walls. Carotid ultrasonography exhibited a reduction in the end-diastolic velocity (right, 4.9 cm/s; left, 6.3 cm/s) and increased pulsatility index (2.2;2.3) at the bilateral common carotid arteries and did not detect pulse-wave Doppler in the bilateral internal carotid artery (ICA), suggesting that the bilateral ICA was occluded (**Figures 1C,D**). On brain non-contrast magnetic resonance imaging (MRI), diffusion-weighted MRI (**Figure 1E**) and apparent diffusion coefficient map (**Figure 1F**) showed almost the same signal intensity in the infarcted lesions of the bilateral ICA territories, whereas fluid-attenuated inversion recovery revealed no such lesions with a high signal intensity (**Figure 1G**), demonstrating acute cerebral infarction in the bilateral ICA territories with a nearly simultaneous onset. These clinical findings suggested that acute massive ischemic stroke due to near-simultaneous bilateral ICA occlusion occurred. Following admission, we carefully explained

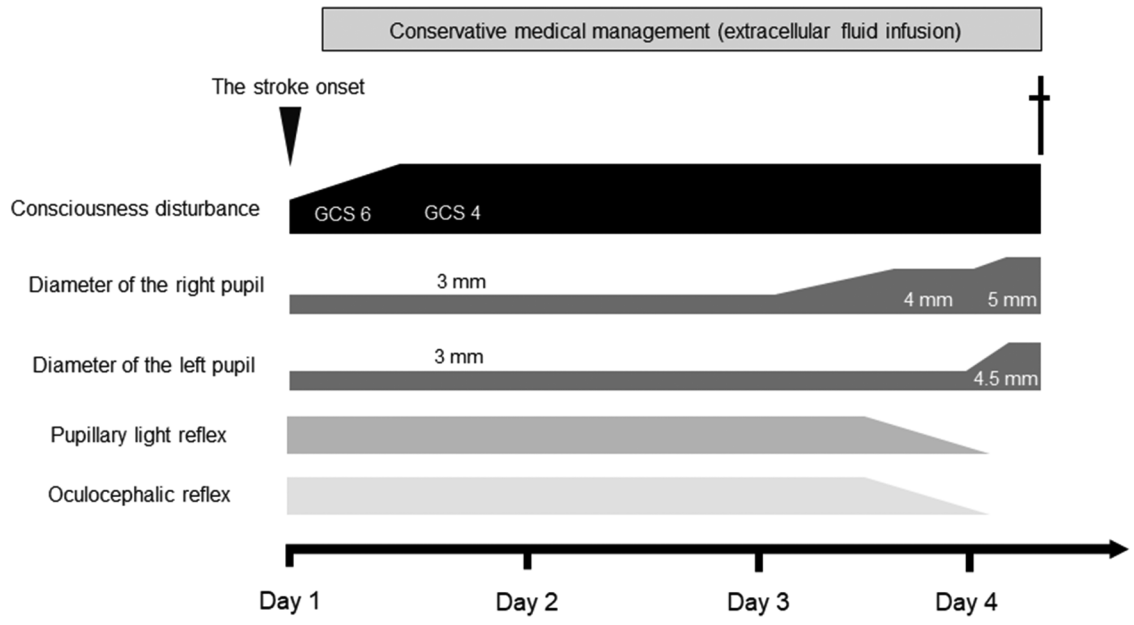


FIGURE 2
Clinical course of the patient after stroke onset. GCS, Glasgow Coma Scale.

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to the family members that reperfusion therapy such as the administration of recombinant tissue-type plasminogen activator, or mechanical thrombectomy was not suitable for the massive cerebral infarction because of the risk of hemorrhagic transformation. Moreover, coronary angiography could not be performed because her neurological prognosis was poor, and the condition would unfortunately be irreversible. Accordingly, conservative medical management was recommended. The family members understood our explanations, and agreed on conservative management after deep deliberation. No reperfusion therapy or coronary angiography was performed. On day 3, her right pupil dilated to 4 mm. On day 4, the patient vomited once. Her pupils further dilated bilaterally to 5.0/4.5 mm, and the oculocephalic and pupillary light reflexes were absent. Her blood pressure and heart rate also gradually decreased. Eventually, the patient died on day 4 of hospitalization before the diagnosis was completed (**Figure 2**). Clinical differential diagnoses included three categories: (i) conditions leading to concurrent cerebral–coronary infarction in which AF could induce both cardioembolic stroke and coronary artery embolism; (ii) cardiac conditions leading to cerebral infarction, such as intraventricular thrombi due to ST-elevation myocardial infarction or takotsubo cardiomyopathy with ST elevation; and (iii) cerebral infarction leading to AMI through brain–heart axis dysregulation (e.g.,

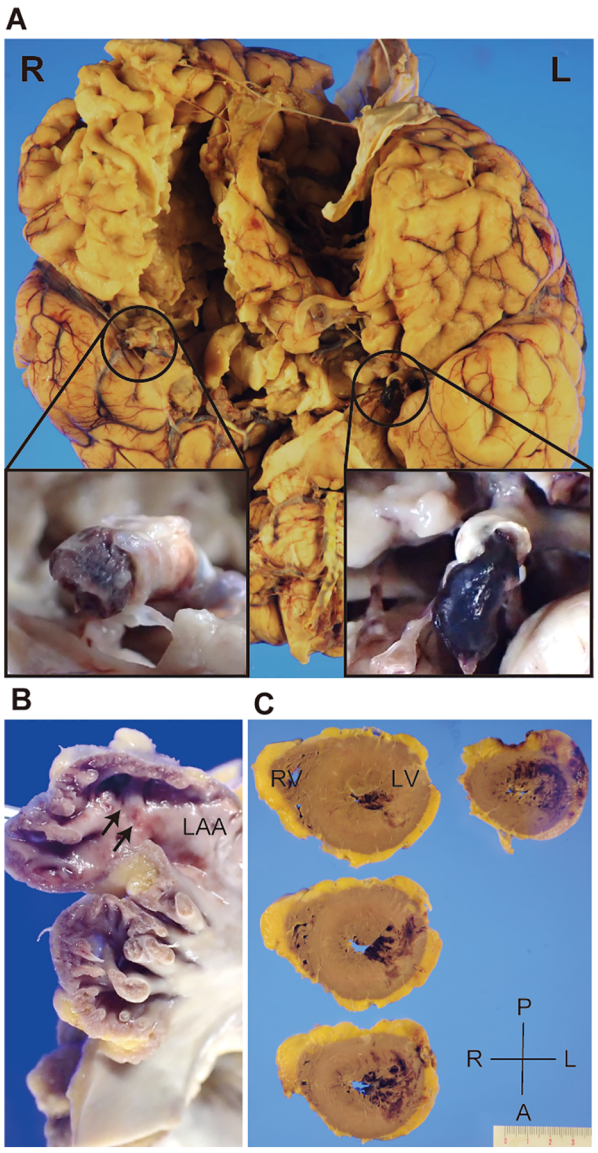


FIGURE 3
Gross appearance of the patient's brain and heart during autopsy. Representative pictures depicting bilateral internal carotid artery (ICA) filled with thromboemboli (**A**), mural thrombi in the left atrial appendage (LAA) (**B**, arrows), and acute myocardial hemorrhagic infarcts in the lateral-posterior wall of the left ventricle (**C**). R, right; L, left; A, anterior; P, posterior; RV, right ventricle; LV, left ventricle.

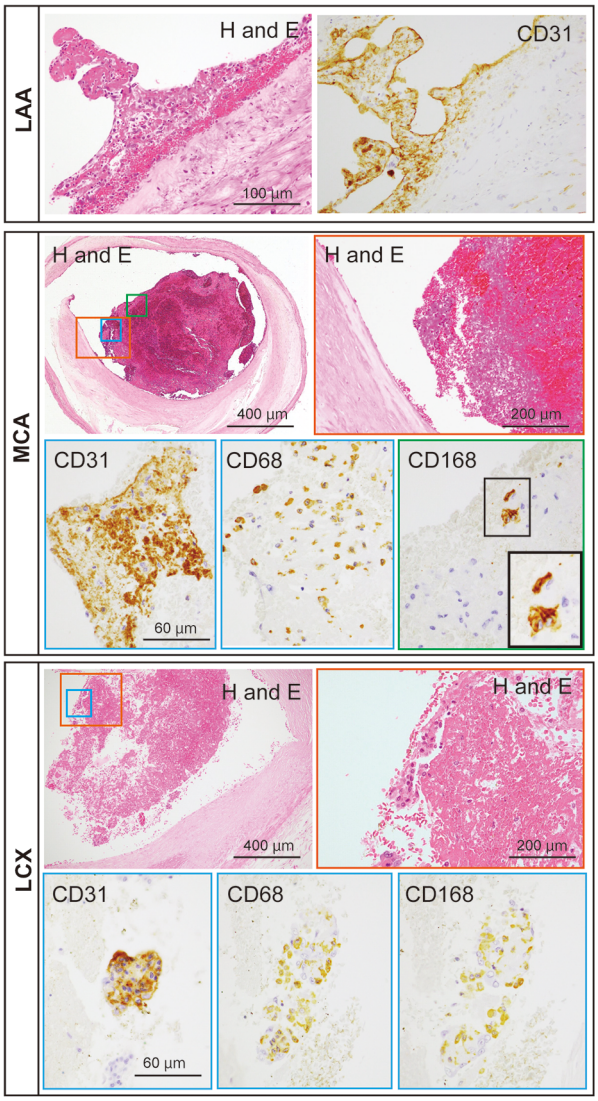


FIGURE 4
Representative microscopic images of the thromboemboli at the patient's left atrial appendage (LAA), middle cerebral artery (MCA), and left circumflex artery (LCX). The thromboemboli in the LAA, MCA, and LCX were stained with hematoxylin and eosin (H and E), for CD31, CD68, and CD168. Colored rectangles with lowest magnification in the MCA and LCX are magnified to the pictures surrounded with each colored rectangle. Inset in CD168 of the MCA represents the enlargement of the area outlined by the black rectangle.

insular ischemic stroke). Thus, the etiology of the thrombi and the relationship between AIS and cardiac dysfunction with ST-segment elevation were unclear.

An autopsy was performed to explore pathological findings after informed consent was obtained from the family. Macroscopic autopsy examination revealed bilateral ICA occlusion with red thrombi (**Figure 3A**), mural thrombi in the left atrial appendage (LAA) (**Figure 3B**), and acute myocardial hemorrhagic infarcts in the lateral-posterior wall (**Figure 3C**), which suggested the occurrence of coronary artery embolism and recanalization. Microscopic examination revealed thrombi with abundant cell-lytic changes on the wall of the LAA, in the middle cerebral artery (MCA), and in the left circumflex artery (LCX) (**Figure 4**). In these three sites, the thrombi included CD31-positive cells, and those in the MCA and LCX included CD68- and CD163-positive cells similarly (**Figure 4**). The autopsy results suggested that the fibrin thrombi observed in the three sites were identical. We eventually concluded CCI where the fibrin thrombi in the LAA developed by AF nearly simultaneously migrated into the bilateral ICA and coronary arteries, leading to near-concurrent cardioembolic stroke and coronary artery embolism.

## 3. Discussion

The patient was conclusively diagnosed as near-concurrent cardioembolic stroke and coronary artery embolism because of AF. A total of 5,953 patients with AIS had been admitted to our hospital between January 2011 and March 2020. Of them, six patients were identified with CCI (0.1%, 71–94 years old, five women) (**Table 1**). Five patients had cardioembolic stroke. All five patients diagnosed as cardioembolic stroke had AF, but no patients had received oral anticoagulation before the events. Some associations between AMI and/or AF, and AIS were implicated, however, precise associations regarding CCI were not evident. Shibata et al. proposed diagnostic criteria for a clinical diagnosis of coronary artery embolism attributing to AMI (10). According to the criterion, only Patient 1 was equivalent to definite coronary artery embolism, whereas most of the patients, including Patient 6 (the current case) were dissociated with the clinical diagnoses as CCI with coronary artery embolism (**Table 1**). Thus, the criterion was still inappropriate to precise diagnosis as CCI subtype of concurrent cerebral and coronary artery embolism, suggesting that pathological findings are of importance for precise diagnosis.

In the autopsied case, the thrombi with CD31-positive endothelial cells adhered to the LAA wall and were also found inside the lumens of the MCA and LCX, implying that the thrombi with endothelial cells of the LAA wall occluded both the MCA and LCX. Furthermore, in the MCA and LCX, CD68-, and CD163-positive macrophages were found inside the thrombi, indicating that the thrombi formed at the similar time (11). Thus, it was clear that the current case had a near-concurrent cerebral–coronary artery embolism. How fibrin thrombus age is determined has been assessed in animal and human studies. Macrophages rises in experimental fibrin thrombi in rats (12), in mice (13), and in rabbits (14) in the chronic phases. Furthermore, a human study found that the majority of macrophages expressed CD163 in aspirated fibrin thrombi from patients. Furthermore, the number of CD163 macrophages in fibrin thrombi was correlated with the time after onset. As a result, expression of CD163 macrophages may be a marker of fibrin thrombus age (11). CD163 has been proposed as a marker for assessing M2 macrophages distribution (15). Interleukin (IL)-6, IL-10, and glucocorticoids also increase the expression of CD163 in monocytes/macrophages. CD163-expressing macrophages may help to suppress an inflammatory response (16). That is, CD163-positive M2 macrophages should increase when acute inflammatory responses subside in the subacute and chronic inflammatory phases.

This case report has a limitation. As coronary angiography was not performed, the clinical diagnosis of ST-elevation myocardial infarction was presumptive.

In conclusion, the postmortem pathological evaluation successfully unveiled the clear pathophysiology of CCI, where intra-atrial thrombi due to AF induced concurrent cerebral-coronary artery embolism, although clear diagnosis in AIS and ST segment elevation in ECG was not completed. Further

TABLE 1 Clinical data on patients suffering from a cardiocerebral infarction.

| Patient | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Age | 73 | 71 | 84 | 68 | 94 | 92 |
| Sex | F | M | F | F | F | F |
| Premorbid ATA | None | ASA | None | ASA, CLP | None | CLS |
| Clinical diagnosis of CI subtype | CES | LAA | CES | CES | CES | CES |
| Clinical diagnosis of AMI subtype | CE | Atherosclerosis | CE | CE | CE | CE |
| AF | + | – | + | + | + | + |
| ECG findings | STEMI | non-STEMI | STEMI | non-STEMI | non-STEMI | STEMI |
| Treatment for CI | rt-PA, MT | ASA | Conservative treatment | rt-PA, MT | rt-PA, MT | Conservative treatment |
| Treatment for MI | Heparin | Heparin | Conservative treatment | ASA | rt-PA | Conservative treatment |
| mRS at discharge | 2 | 4 | 5 | 4 | 3 | 6 |
| Definite CE (10) | + | – | – | – | – | – |

AF, atrial fibrillation; ATA, anti-thrombotic therapy; CI, cerebral infarction; AMI, acute myocardial infarction; ECG, electrocardiography; mRS, modified Rankin scale; CES, cardioembolic stroke; CE, coronary artery embolism; ASA, acetylsalicylic acid; LAA, large-artery atherosclerosis; CLP, clopidogrel; rt-PA, recombinant tissue plasminogen activator; MT, mechanical thrombectomy; STEMI, ST-segment elevation myocardial infarction; CLS, cilostazol.

pathological examinations are required to establish clear pathomechanisms and preventive strategies of CCI.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of National Cerebral and Cardiovascular Center.

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

## Author contributions

YH and MI conceived the study. MM and KH conducted the autopsy and pathological evaluation. YH, SI, and NT extracted the cases from the electronic medical chart. YH, SI, and MI wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# A novel compound heterozygous variant in *ALPK3* induced hypertrophic cardiomyopathy: a case report

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**Background:** Malignant hypertrophic cardiomyopathy (HCM) phenotypes have potential risks of severe heart failure, fatal arrhythmia, and sudden cardiac death. Therefore, it is critical to predict the clinical outcomes of these patients. It was reported recently that the alpha kinase 3 (*ALPK3*) gene was involved in the occurrence of HCM. Herein we reported a girl with HCM, while whole-exome sequencing found novel compound heterozygous variants in *ALPK3* gene, which identified a potential association.

**Case presentation:** We reported a 14-year-girl who suffered from clinical manifestations of cardiac failure, with sudden cardiac arrest before admission. The heartbeat recovered after cardiopulmonary resuscitation, though she remained unconscious without spontaneous breath. The patient stayed comatose when she was admitted. Physical examination indicated enlargement of the heart boundary. Laboratory results revealed a significant increment of myocardial markers, while imaging demonstrated hypertrophy of the left heart and interventricular septum. Whole-exome sequencing (WES) identified a compound heterozygous variant in *ALPK3* gene consisting of c.3907_3922del and c.2200A>T, which was inherited from her parents. Both variants (p.G1303Lfs*28 and p.R734*) were disease-causing evaluated by MutationTaster (probability 1.000). The crystal structure of the complete amino acid sequence is predicted and evaluated by AlphaFold and SWISS-MODEL software (July, 2022), which revealed three domains. Moreover, both variants resulted in a wide protein-truncating variant and damaged protein function. Thus, a novel compound heterozygous variant in *ALPK3* associated with HCM was diagnosed.

**Conclusion:** We described a young patient with *ALPK3*-associated HCM who experienced sudden cardiac arrest. Through WES, we identified a compound heterozygous variant in the *ALPK3* gene, c.3907_3922del and c.2200A>T, which were inherited from the patient's parents and resulted in a truncated protein, indirectly causing the symptoms of HCM. In addition, WES provided clues in evaluating potential risks of gene variants on fatal clinical outcomes, and the nonsense and frameshift variants of *ALPK3* were related to adverse clinical outcomes in HCM patients, which required implantable cardioverter defibrillator (ICD) timely.

KEYWORDS

*ALPK3*, hypertrophic cardiomyopathy, novel variant, case report, whole-exome sequencing

# 1. Introduction

Cardiomyopathies constitute a diverse group of disorders with clinical and genetic heterogeneity that primarily affect the ventricular myocardium, resulting in impaired cardiac function and heightened morbidity and mortality. According to existing practice and guidelines, cardiomyopathies can be classified into five subtypes based on their clinical phenotypes, including morphologic and functional features: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathy (1). Among children, HCM and DCM are the most frequently encountered cardiomyopathy phenotypes (2). HCM is distinguished by symmetric or asymmetric left ventricular hypertrophy, particularly in the interventricular septum, obstructing the left ventricular outflow tract (3). Additionally, HCM is an inherited disease, with a predicted prevalence of 1/500 in adulthood (4). Given the high prevalence of HCM, it is crucial to differentiate between benign and malignant phenotypes and predict the risk of cardiac failure and sudden cardiac death, as some patients may be asymptomatic. In contrast, others present with atrial fibrillation, dyspnea, chest pain, fatigue, or syncope (4–6). The challenge of HCM diagnosis lies not only in making a definitive diagnosis but also in predicting or assessing the heterogeneity of phenotypes and associated clinical outcomes that may require implantable cardioverter defibrillator (ICD) implantation or heart transplantation (7–9). Although the etiology of HCM is highly diverse, it can be summarized as genetic or environmental factors (10). With the rapid development of genetic sequencing, over 900 genes have been identified as involved in the pathogenesis of HCM, with dominant molecules in the sarcomere or sarcomere-associated proteins being implicated in an autosomal dominant manner (11). Recent research has utilized genetic or polygenetic scores to predict clinical risks of HCM on a molecular level, aiding in the clinical management of high-risk patients and guiding the administration of ICD implantation or interventional treatment. The decreasing cost of next-generation sequencing has significantly promoted the application of genetic assessments in cardiomyopathies. Furthermore, hundreds of newly identified HCM-related genes or variant sites have been recorded, providing evidence of the association between rare genetic variants and strategies for diagnosis or treatment.

The alpha kinase 3 (*ALPK3*) gene, located on chr15:85360587-85416710, is a member of the family of atypical protein kinases (12), recently has been implicated in some cases of HCM, highlighting its potential role in the disease (10, 13, 14). In previous studies, *ALPK3* has been identified as a potential factor associated with myocardial cell differentiation, and mice with functional deficiency of *ALPK3* exhibit significant ventricular hypertrophy (15, 16). The *ALPK3* protein consists of two immunoglobulin (Ig)-like domains and an alpha-type protein kinase domain. Although its specific function in the heart remains unclear, it is believed to play a critical role in cardiac development and transcriptional regulation (10, 17). In this report, we present a case of a 14-year-old female with HCM who initially presented with symptoms of heart failure and experienced multiple cardiac arrests. Whole-exome sequencing (WES) revealed novel compound heterozygous variants on the *ALPK3* gene, underscoring the importance of ICD placement in *ALPK3*-related HCM patients. Furthermore, we provide a comprehensive review of the existing literature and discuss the molecular function of the *ALPK3* protein.

# 2. Case presentation

## 2.1. History of illness and physical examination

The study was approved by the ethics committee of the West China Second Hospital of Sichuan University (approval no. 2014–034). In addition, we obtained written, informed consent from the patient's parents prior to performing WES and for the inclusion of the patient's clinical and imaging details in publications.

The proband was a 14-year-old female who presented with a two-year history of reduced tolerance to physical exertion and subsequently experienced severe dyspnea, respiratory distress, and fatigue following exertion. The patient suffered a sudden cardiac arrest 2 h before arrival at the hospital, during which carotid pulsation and respiratory movement were absent. CPR and defibrillation were promptly administered by first-aid personnel, resulting in the return of heartbeats after 15 min and restoration of sinus rhythm. Nevertheless, the patient remained unconscious and exhibited no spontaneous breathing. The patient was transferred to the emergency department while receiving laryngeal mask ventilation and subsequently underwent tracheal intubation, positive pressure ventilation, fluid infusion, sedation, and analgesia. The patient was later transferred to the cardiac intensive care unit one hour after the cardiac arrest. The patient's parents denied any history of illness, especially cardiovascular disorders, and any family history of cardiac arrest or cardiovascular disease. Notably, no family member had a history of hypertension or coronary artery disease.

Upon arrival at the cardiac intensive care unit, the patient's blood pressure was approximately 92/63 mmHg, and arterial oxygen saturation was maintained at 97% through mechanical ventilation. Physical examination revealed the patient to be comatose with significant cardiac enlargement, thoracolumbar scoliosis, and muscle weakness.

## 2.2. Laboratory and imaging evaluation

The results of the blood gas analysis indicated extremely severe respiratory alkalosis (pH = 7.52, PCO2 = 24 mmHg, PO2 = 155 mmHg), electrolyte disturbance ($K^+$ = 4.0 mmol/L, $Na^+$ = 136 mmol/L, $Cl^-$ = 104 mmol/L, and $Ca^{2+}$ = 0.99 mmol/L), and high lactate levels (4.8 mmol/L). Peripheral blood counts revealed an increased leukocyte count of 13.2 × 109/L. Blood biochemical

tests demonstrated an elevated level of lactic dehydrogenase [494 U/L; normal range (NR) 109–245 U/L], while other renal and hepatic function parameters showed no apparent abnormalities. Thyroid function test results showed a decreased free triiodothyronine level at 3.2 pmol/L (NR > 4.3 pmol/L). Myocardial markers revealed significantly increased levels of troponin I (0.791 μg/L; NR < 0.2 μg/L), creatine kinase MB isoenzyme (11.75 μg/L; NR < 5 μg/L), and b-type natriuretic peptide (>5,000.00 pg/ml; NR < 100 pg/ml).

The electrocardiogram (ECG) revealed right axis deviation, biventricular hypertrophy, and ventricular escape beats (**Figure 1A**). Transthoracic echocardiography revealed significant hypertrophy of the left ventricular wall, particularly the interventricular septum (IVS) and left posterior ventricular wall

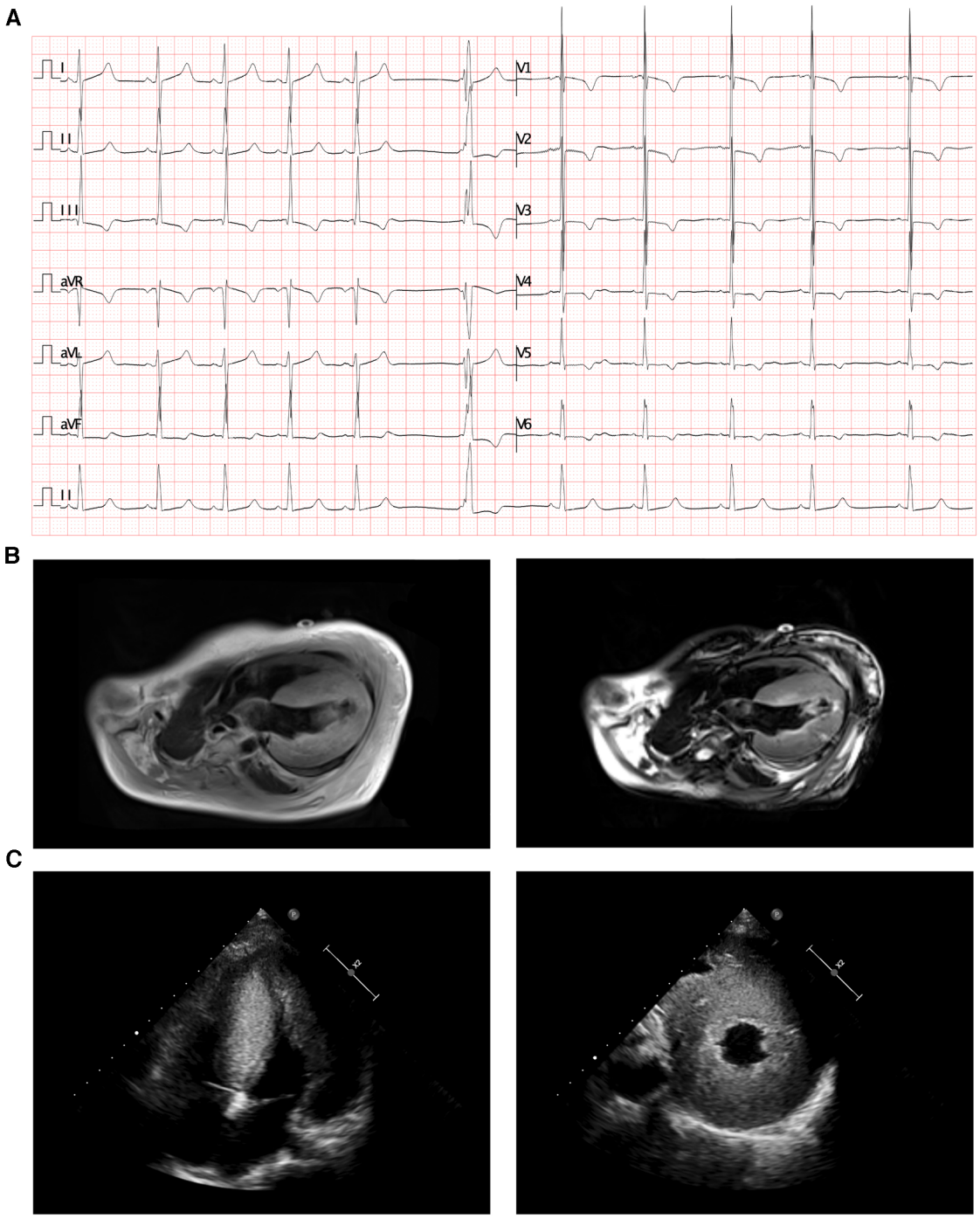


FIGURE 1
Radiology manifestation in the current proband. (**A**) Electrocardiographic examination demonstrated right axis deviation, enlargement of bi-ventricles and ventricular escape (arrow). (**B**) Cardiac magnetic resonance (CMR) demonstrated diffuse hypertrophy of ventricular myocardium, T2-weighting imaging revealed abnormal signal intensity of left ventricular subendocardial myocardium. (**C**) Transthoracic echocardiography (TTE) demonstrated significant hypertrophy of left ventricle and the interventricular septum.

(LVPW) (Figure 1C). In addition, cardiac magnetic resonance imaging (CMR) demonstrated diffuse hypertrophy of the ventricular myocardium. The thickness of each part during the diastolic period was as follows: LVPW, 28.3 mm; right ventricular anterior wall (RVAW), 8.3 mm; and IVS, 32.2 mm (Figure 1B, left panel). Additionally, the left ventricular ejection fraction (LVEF) measured by CMR was decreased (40.2%). Furthermore, the T2-weighted image revealed an abnormal signal intensity of the left ventricular subendocardial myocardium indicating myocardial ischemia (Figure 1B, right panel). It is noteworthy that the parents of the patient also underwent physical examinations and echocardiographic assessments conducted by cardiologists, revealing no indications associated with HCM.

## 2.3. Molecular results

We obtained a peripheral blood sample in an EDTA anticoagulant blood sample tube from the patient and stored it at 4°C for less than 6 h. DNA extraction was performed using the Blood Genome Column Medium Extraction Kit (Tiangen Biotech, Beijing, China) according to the instruction. Protein-coding exome enrichment was performed using the xGen Exome Research Panel v1.0. WES was performed using the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA), while primary quality control was performed using FastP, comprising process of the raw data and removement of filter low-quality reads. Variants were annotated in accordance with database-sourced minor allele frequencies (MAFs) and practical guidelines on pathogenicity issued by the American College of Medical Genetics. The sequencing data have been deposited in GSA database (http://ngdc.cncb.ac.cn/gsub/). MutationTaster software and combined annotation dependent depletion (CADD) scaled c-scores were used to predict the pathogenicity of variants, while GRCh37 reference genome was used for alignment. We searched database including gnomAD, ExAC and 1000G to identify prevalence of variants. Effects of genetic variants on protein structure were evaluated via PROVEAN protein batch software with Provean score. As there is no available protein crystal structure for *ALPK3*, AlphaFold database (https://alphafold.ebi.ac.uk/) tool is used to predict protein crystal structure. Within the structure, three important domains have been revealed with analyzed crystal structure. PyMOL software was used to annotate domains and variant sites of the protein. Then we performed modeling analysis and compared three domains with the 6c6m.2.A, 3uto.2.A, and 1ia9.1.A template via SWISS-MODEL database (https://swissmodel.expasy.org/), to visualize and analyze the altered amino acid sequence and stability of *ALPK3*. And other identified variants had been presented in Supplementary Table S1.

Based on the clinical manifestations and laboratory analyses, HCM induced by genetic anomaly was strongly suspected. Thus, WES was performed, which identified a novel compound heterozygous variant of c.3907_3922del (p.G1303Lfs*28) and c.2200A>T (p.R734*) in *ALPK3* gene, while genomic coordinates of these two variants are chr15:85401269-85401285delGG CCTCCTGGGGGCCT and chr15:85384104A>T (depth of coverage is 236.34, percent of exome captured is 98.34%). The patient's parents presented normal cardiac morphology, thus, we employed Sanger sequencing to validate the genotypes of the parents of the patient (forward primer "agcccacacactccttgacc" and reverse primer "tacatcagagctgctgctgg" for c.2200A>T and forward primer "ctgtacctcccgccgcctca" and reverse primer "tcccctggg aacttctcctc" for c.3907_3922del), which revealed that each parent carries a heterozygous variant of the *ALPK3* gene. The variant of c.3907_3922del was maternal inherit, and the variant of c.2200A>T was paternal inherit (Figures 2A,B). According to the American College of Medical Genetics, both variants have pathog enicity as PVS1+PM2_Supporting+PM3 (Trans), and both were related to familial HCM. According to updated data in gnomAD, ExAC and 1000G, these two variants have not been reported in any populations, that means it is the first report of these variants (Figure 2C). Analysis performed with MutationTaster revealed that variant of c.3907_3922del in *ALPK3* was considered pathog enic (probability 1.000) due to nonsense-mediated mRNA decay (NMD), amino acid sequence changed, frameshift, protein features affected and splice site changes, while c.2200A>T was also considered pathogenic because of NMD, acid sequence changed, and protein features affected (probability 1.000). Besides, CADD scaled c-scores of variant c.2200A>T is 36, which implies that the predicted pathogenicity of the variant is extremely high. PROVEAN protein batch software indicated that the p.R734* protein was deleterious with the PROVEAN score of −4.79, due to frameshift and NMD of p.G1303Lfs*28, PROVEAN and SIFT prediction were not applicable. While all the reported variants of *ALPK3* had been listed in Figure 2D.

The entire amino acid sequence crystal structure was predicted by AlphaFold and assigned the name AF-Q96L96-F1 (Figure 3A). Although the predicted protein covered the entire length of the amino acid sequence, only three domains demonstrated high confidence (pLDDT >70). These domains were labeled red, green, and orange (Figure 3B). Other regions displayed low confidence in the crystal structure. While all potential templates were searched, only partial parts of the protein had been analyzed previously. We picked structures with the highest predictive value, which may cause several parts do not have a specific folding. In a word, the AlphaFold-predicted structure was the only model that could be utilized. The c.2200A>T and c.3907_3922del variants would result in a protein-truncating variant, typically leading to protein denaturation. The sites of truncated sequences caused by variants were labeled in yellow (Figures 3C,D). SWISS-MODEL was then employed to present the crystal structures of the variant's three domains, including two immunoglobulin-like (Ig-like) domains and an alpha-type protein kinase domain (Figure 3B). An ig-like domain superfamily is a heterogeneous group of proteins that play the role of cell recognition. The alpha-kinase domain is an atypical protein kinase catalytic domain that exhibits no detectable similarity to conventional protein serine/threonine kinases. This protein kinase recognizes protein sequences that adopt an alpha-helical conformation by its initial members, which act as the final link and effector of intracellular information transmission. The identified *ALPK3* variants, c.3907_3922del and c.2200A>T

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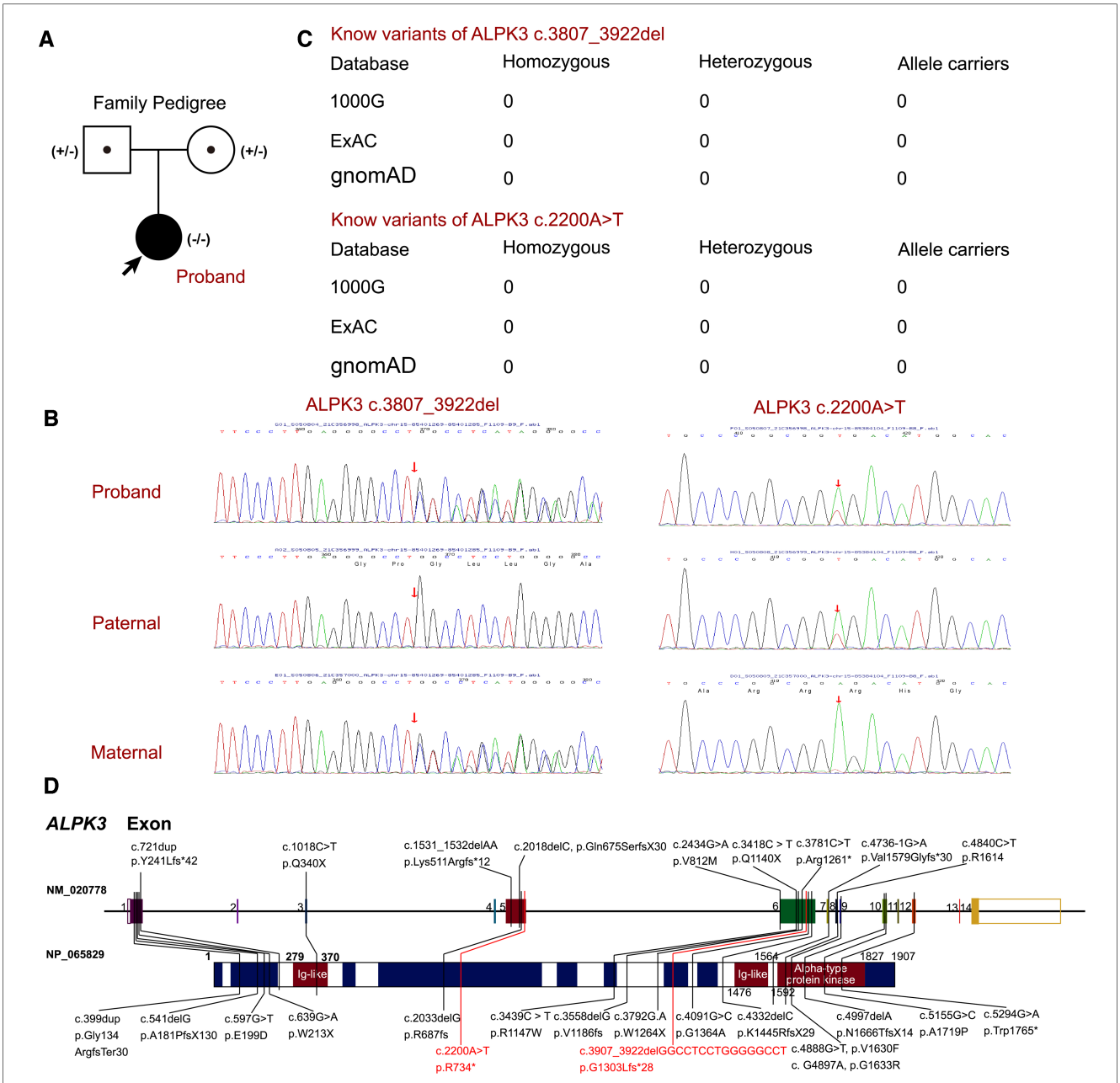


FIGURE 2
The *ALPK3* variants in this family. (**A**) Family pedigree revealed the maternal carrier of c.3907_3922del (p.G1303Lfs*28) and the paternal carrier of c.2200A>T (p.R734*). The current proband exhibited significant hypertrophic cardiomyopathy with compound heterozygous variants of *ALPK3*. circles represent females, squares represent males, and arrow indicates the proband. Black symbols indicate the clinical presentation of hypertrophic cardiomyopathy, grey symbols indicate carriers. (**B**) Sanger sequencing validation of the current proband and his parents. (**C**) The prevalence of *ALPK3* variants of c.3907_3922del and c.2200A>T. (**D**) Summary of current reports on individual *ALPK3* variants resulting in hypertrophic cardiomyopathy.

would cause truncated protein, leading to the loss of an Ig-like domain and an alpha-type protein kinase domain, resulting in the dysfunction of the *ALPK3* molecule. The aforementioned analyses suggested that both newly identified variants could alter the transcription of the *ALPK3* gene and damage the protein structures. Therefore, the compound heterozygous variant of *ALPK3* was considered to be genetically associated with HCM in this patient. In addition, several heterozygous variants were identified by WES, such as c.4639A>G in the *FBN1* gene, c.3791G>A in *ANKRD26*, and c.1123G>T in *DPYS*. However, all three genes were considered to exhibit recessive inheritance, and the pathogenicity predictions for these variants were uncertain. Furthermore, all of these variants were inherited from one of her parents, unaffected by associated diseases. Consequently, they were not considered to be associated with HCM.

## 2.4. Treatment and clinical outcome

Following comprehensive laboratory and echocardiographic assessments, the patient was diagnosed with HCM. A 6-week hospitalization period was instituted, during which the patient

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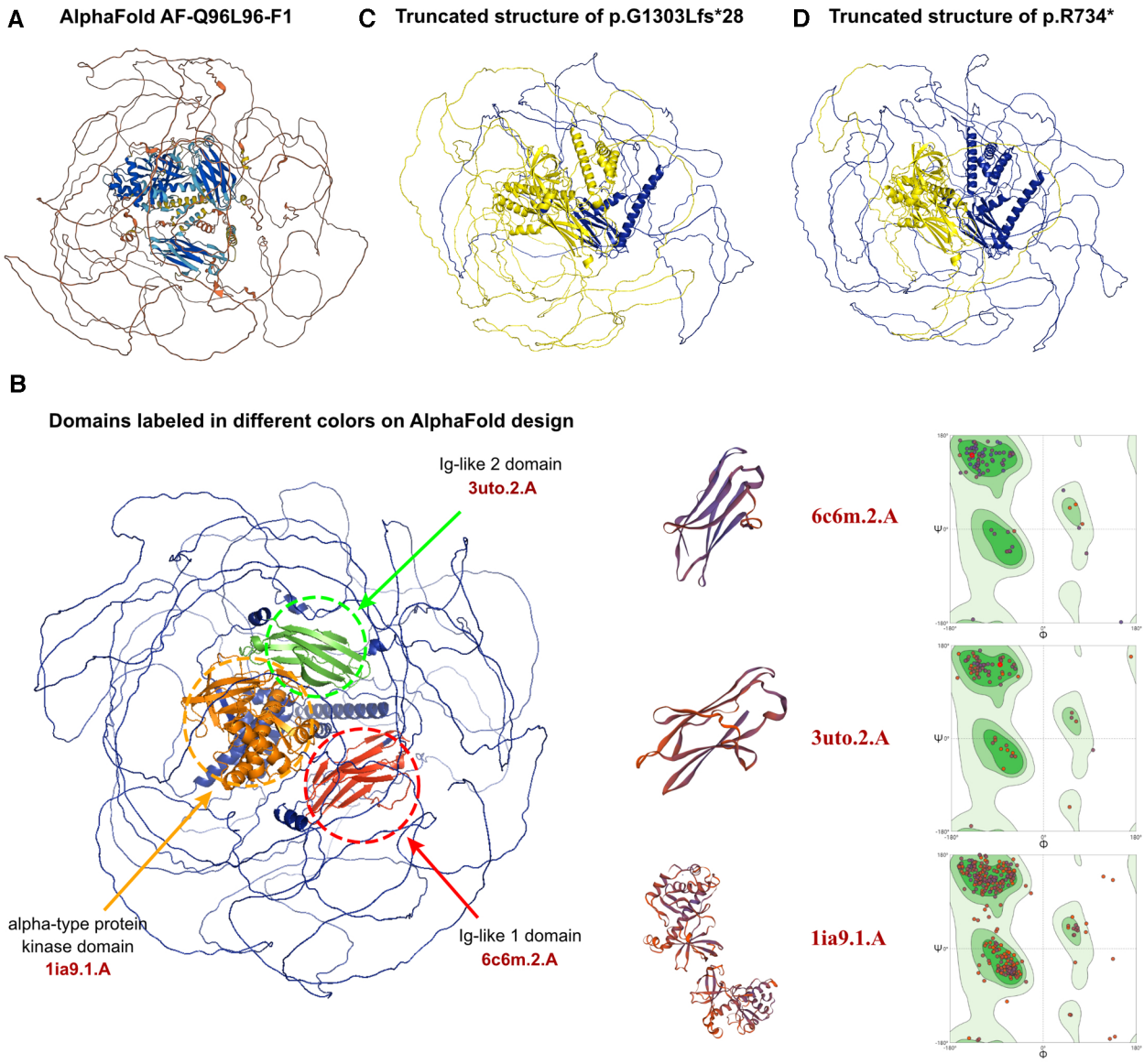


FIGURE 3
The effects of *ALPK3* c.3907_3922delGGCCTCCTGGGGGCCT and c.2200A>T variants on the molecular structure of the protein. (**A**) AlphaFold protein structure database was used to predict the *ALPK3* wild-type protein crystal structure. (**B**) Three domains of ALPK3 protein were labeled in red, green and orange individually. SWISS-MODEL presented the crystal structures of the variant's three domains, including two immunoglobulin-like (Ig-like) domains and an alpha-type protein kinase domain according to 6c6m.2.A, 3uto.2.A, and 1ia9.1.A model template. Ramachandran plots of three functional domains in wild-type sequences were displayed. (**C**,**D**) Truncating variant sites of p.G1303Lfs*28 and p.R734* caused by variants of c.3907_3922delGGCCTCCTGGGGGCCT and c.2200A>T was labelled in yellow.

received a range of medical interventions, including invasive and noninvasive mechanical ventilation, myocardial protection, anti-arrhythmia, cerebral protection, anti-infection, anti-inflammatory, diuresis, and blood transfusion. Although there was residual muscle weakness, the patient was discharged from the hospital after partial recovery from her major concerns with respect to heart rhythm control and cardiac function. However, two weeks after discharge, the patient experienced recurrent cardiac arrest during rehabilitation training and subsequently regained consciousness. The patient was subsequently readmitted to our department, where mechanical ventilation and gastrointestinal decompression were provided to alleviate symptoms. Anti-infective therapy was initiated with cefoperazone and sulbactam, while captopril and metoprolol were prescribed to address HCM and inhibit potentially lethal arrhythmias. Nutritional and rehabilitation therapies were also administered. After a month of comprehensive medical management, including fluid infusion, diuretic therapy, and vitamin supplementation, the patient was discharged with improved symptoms. However, due to the prolonged duration of the condition and recurrent cardiac arrest, the patient had not regained consciousness and experienced severe cognitive and neurological impairment. Oral medication

administration and continuous follow-up and evaluation were regularly conducted, with clinic visits scheduled every two weeks in the first month and every three months thereafter.

## 3. Discussion and conclusion

HCM is a primary cardiomyopathy that is commonly associated with a genetic variant. Its prevalence is high worldwide, but some subtypes of HCM with specific genetic variants can result in lethal arrhythmia and severe heart dysfunction, leading to sudden cardiac death (18). It is now commonly accepted that HCM is usually inherited with a complex genetic etiology. Studies and books have revealed that pathogenic variants in the core genes encoding sarcomeric proteins, including thick filament encoding genes *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, and thin filament encoding genes *TNNC1*, *TNNT2*, *TNNI3*, account for over 90% of the pathogenic variants in patients with HCM (19, 20). Additionally, variants in several genes encoding non-sarcomeric proteins with diverse functions, including *ACTN2*, *ALPK3*, *CSRP3*, *FHOD3*, *FLNC*, *JPH2*, *KLHL24*, *PLN*, and *TRIM63*, have also been considered as genetic etiology of HCM (21). Furthermore, variants in *FHL1*, *FXN*, *GAA*, *LAMP2*, and *TTR* genes have an extremely low prevalence of 1/100,000–1/20,000 but have also been reported to be associated with HCM (22).

*ALPK3* gene locates on chromosome 15q25.2 and contains 14 exons. It had been recently identified as a possible disease-causing gene of pediatric HCM, myopathic and dysmorphic skeletal features (10, 17). Initially, the Midori gene was discovered and named by Hosoda et al. through differential display analysis of the P19CL6 cell line (16), and later identified as the *ALPK3* gene. The study revealed that expression of Midori was restricted in the fetal and adult heart and adult skeletal muscle in mice. At the same time, the overexpression of Midori could promote the differentiation of P19CL6 cells into cardiomyocytes (16). A mouse model of *ALPK3* knockout by Van Sligtenhorst et al. in 2012 revealed biventricular hypertrophy in $ALPK3^{-/-}$ mice (15). Additionally, the electron microscopy showed impaired cardiomyocyte architecture characterized by reduced numbers of abnormal intercalated discs (15). The experimental data suggested *ALPK3* could regulate the transcript of cardiomyocyte differentiation and heart development, and the loss of function of *ALPK3* would lead to cardiomyopathy. Thus, the OMIM number of HCM in our manuscript is #618052, which is named familial hypertrophic cardiomyopathy-27 caused by homozygous mutation in the *ALPK3* gene (OMIM 617608) on chromosome 15q25. Indeed, several studies have reported on cardiomyopathies caused by other types of kinases. For instance, Brodehl et al. identified protein mutations p.H77Y and p.P70l in integrin-linked kinase, which were found to be associated with arrhythmogenic cardiomyopathy in both humans and transgenic zebrafish (23).

After conducting a comprehensive review of the literature, we identified 22 patients with *ALPK3*-associated HCM, involving 28 distinct variants of the *ALPK3* gene, as described in nine studies and a case report. A summary of all reported variants can be found in **Table 1** and **Figure 2D** (10, 13, 14, 24–29). Consistent with previous reports, the majority of described patients were from consanguineous families, and nearly all patients exhibited biallelic damage, as homozygous or compound heterozygous variants of the *ALPK3* gene were commonly observed (15). Notably, only patients with HCM were identified with heterozygous variants of the *ALPK3* gene, and one such patient was found to have an accompanying DSP gene and was free of lethal cardiac events (29). Thus, *ALPK3* variants appeared to demonstrate a recessive feature in inducing HCM.

The clinical presentation of *ALPK3*-associated HCM varied, with most pediatric patients presenting symptoms or positive imaging results before age 18. In addition to typical clinical manifestations and findings on ECG and echocardiography, extracardiac manifestations, such as facial and musculoskeletal abnormalities, were observed in some patients (10, 24, 25, 27). Fatal arrhythmia, such as ventricular fibrillation, was the leading cause of death, necessitating ICDs and, in some cases, heart transplantation. Notably, only nonsense and frameshift variants among the 22 reported patients resulted in death and fatal arrhythmia, necessitating ICD implantation. Conversely, missense variants were associated with mild clinical outcomes. Thus, homozygous and compound heterozygous variants of *ALPK3* with nonsense or frameshift variants were linked to adverse clinical outcomes, warranting careful follow-up and timely ICD implantation to prevent sudden cardiac death. Therefore, given the patient's clinical symptoms and history of cardiac arrest, we recommended ICD implantation. Regrettably, the patient's family declined this recommendation.

In the present study, we report the case of a 14-year-old female who suffered from *ALPK3*-associated HCM and experienced sudden cardiac arrest. Through molecular analysis, we identified a novel compound heterozygous variant (c.3907_3922del and c.2200A>T) in the *ALPK3* gene, which was inherited from her parents and resulted in truncated protein formation. WES was employed for molecular diagnosis, which has emerged as an efficient and favorable technique for HCM diagnosis and provides valuable insights for assessing sudden cardiac death risks. The entire process, from sampling to library preparation for sequencing, usually takes about five days, and subsequent analysis requires approximately one week, enabling us to produce a report within two weeks. Therefore, we recommend the utilization of WES for the timely identification of deleterious variants in HCM patients. Furthermore, our findings suggest that the nonsense and frameshift variants of *ALPK3* are associated with unfavorable clinical outcomes, and prompt implantation of an ICD is crucial for preventing sudden cardiac death.

## Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

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TABLE 1 Summarization of reported ALPK3 mutations resulting in hypertrophic cardiomyopathy.

| Reference | Mutation site | Genotype | Variant type | Amino acid change | Onset age/ gender | Symptom (s) | Extracardiac manifestations | Echo | ECG | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Almomani et al. 2016 | c.4736-1G>A | Hom | Frameshift deletion | p.V1579Gfs*30 | At birth/M | Respiratory insufficiency, cyanosis | NA | Severe biventricular dilation | Sinustachycardia, normal PR-interval and QTc, flattened T waves | Dead |
| | c.3781C>T | Hom | Nonsense mutation | p.R1261* | At birth/F | Generalized hydrops | NA | Severe concentric LV hypertrophy | Biventricular hypertrophy, prolonged QTc, repolarization abnormalities, PVCs | Alive |
| | c.5294G>A | Hom | Nonsense mutation | p.W1765* | 4 y/M | VF, cardiac arrest | Cleft palate, ptosis, low set ears, knee contractures, kyphoscoliosis, talipes equines | Severe concentric LV hypertrophy, RV hypertrophy | VF at age 7, biventricular hypertrophy, prolonged QTc, repolarization abnormalities | ICD implantation |
| Phelan et al. 2016 | c.3792G>A | Hom | Nonsense mutation | p.W1264* | Early infancy/F | Echo/ECG anomaly | Cleft palate, intraoral pterygia, knee and shoulder contractures, camptodactyly, webbed neck | Severe hypertrophy of the LV and IVS | Prolonged QT, SVT, nsVT | ICD implantation |
| Çağlayan et al. 2017 | c.2018delC | Hom | Frameshift deletion | p.Q675Sfs*30 | 21 w of gestation/M | Echo anomaly | Low set ears, high arched palate | Diffuse LV hypertrophy | NA | Alive |
| Jaouadi et al. 2018 | c.1531_1532delAA | Hom | Frameshift deletion | p.K511Rfs*12 | 7 d/M | Respiratory distress | Cleft palate, ptosis, low set ears, micrognathia, camptodactyly, webbed neck, knee stiffness | Concentric LV hypertrophy | NA | Unknown |
| Al Senaidi et al. 2019 | c.639G>A | Hom | Nonsense mutation | p.W213* | At birth/M | Tachypnea, heart failure | Low set ears, high arched palate | Biventricular hypertrophy | LV hypertrophy | Alive |
| Herkert et al. 2020 | c.1018C>T | Comp het | Nonsense mutation | p.Q340* | No.1: At birth/M No.2: At birth/M No.3: 4 m/F | Echo/ECG anomaly | No.1: Ptosis, ankyloglossia, hypertelorism, low set ears, micrognathia, knee contractures, webbed neck No.2: Hypertelorism, low set ears, micrognathia, knee contractures, webbed neck No.3: NA | No.1: Significant LV hypertrophy, mild RV hypertrophy No.2: Biventricular hypertrophy No.3: Biventricular hypertrophy | No.1: Prolonged QTc No.2: Prolonged QTc No.3: Biventricular hypertrophy, prolonged QTc, VF at age 11 | All alive |
| | c.2434G>A | Comp het | Missense mutation | p.V812M | No.1: At birth/M No.2: At birth/M | | | | | |
| | c.4332delC | Comp het | Frameshift deletion | p.K1445Rfs*29 | No.3: 4 m/F | | | | | |
| | c.541delG | Comp het | Frameshift deletion | p.A181Pfs*130 | 31 y/M | Sinus bradycardia | Hypertelorism | Biventricular dilation | Sinusbradycardia, high-voltage QRS complex, normal QTc, 2nd degree AV block | Alive |
| | c.3439C>T | Comp het | Missense mutation | p.R1147W | | | | | | |

(*Continued*)

TABLE 1 (Continued)

| Reference | Mutation site | Genotype | Variant type | Amino acid change | Onset age/ gender | Symptom (s) | Extracardiac manifestations | Echo | ECG | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| | c.4997delA | Comp het | Frameshift deletion | p.N1666Tfs*14 | 53 y/M | Echo/ECG anomaly | Spondylolysis, unilateral hearing loss (conductive) | Asymmetric LV hypertrophy | SR, LV hypertrophy, short PR without pre-excitation but increased PR dispersion, prolonged QTc at high heart frequencies, repolarization abnormalities, nsVT (once) | Alive |
| | c.4091G>C | Comp het | Missense mutation | p.G1364A | | | | | | |
| | c.5105+5G>C | Comp het | Missense mutation | p.(?) | No.1: 3 m/F No.2: 3 m/F | Echo/ECG anomaly | No.1: bilateral hearing loss (conductive) No.2: NA | Moderate progressive LV hypertrophy | SR, LV hypertrophy, short PQ interval, prolonged QTc, repolarization abnormalities | All alive |
| | c.597G>T | Comp het | Missense mutation | p.E199D | | | | | | |
| | c.4888G>T | Comp het | Missense mutation | p.V1630F | 14 y/F | Echo/ECG anomaly | Cleft palate, high arched palate, low set ears, camptodactyly, kyphoscoliosis, webbed neck | Severe concentric LV hypertrophy, moderate RV hypertrophy | Extreme septal hypertrophy, prolonged QTc, repolarization abnormalities | ICD implantation |
| | c.2023delC | Comp het | Frameshift deletion | p.Q675Sfs*30 | | | | | | |
| | c.3418C>T | Hom | Nonsense mutation | p.Q1140X | 9 y/F | Echo/ECG anomaly | Cleft palate, camptodactyly, kyphoscoliosis | Concentric LV hypertrophy | SR, biventricular hypertrophy, prolonged QTc, repolarization abnormalities | Alive |
| | c.5155G>C | Hom | Missense mutation | p.A1719P | 35 w/F | Echo/ECG anomaly | Cleft palate, hypertelorism, low set ears, micrognathia, webbed neck | Concentric LV hypertrophy, moderate RV hypertrophy | Biventricular hypertrophy, repolarization abnormalities | Alive |
| Jorholt et al. 2020 | c.2033delG | Comp het | Frameshift deletion | p.R687fs | 6 m/M | Respiratory distress, heart failure | Broad forehead, cleft palate, axial hypotonia, webbed neck, pectus excavatum, scoliosis | Asymmetric LV hypertrophy | prolonged QTc, repolarization abnormalities | Dead |
| | c.3558delG | Comp het | Frameshift deletion | p.V1186fs | | | | | | |
| | c.4897G>A | Hom | Missense mutation | p.G1633R | 21 y/F | Palpitations, dyspnea, heart failure | NA | Severe LV and IVS hypertrophy | Severe LV hypertrophy, prolonged QTc | Heart transplantation |
| Ding et al. 2021 | c.721dup | Comp het | Frameshift deletion | p.Y241Lfs*42 | 10 m/F | Echo anomaly | Cleft palate, low set ears, scoliosis, knee contractures, webbed neck | LV and IVS hypertrophy | LV hypertrophy, ST-T changes in multiple-lead, T wave inversion, prolonged QTc | Unknown |
| | c.4840C>T | Comp het | Nonsense mutation | p.R1614* | | | | | | |

(*Continued*)





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TABLE 1 (Continued)

| Reference | Mutation site | Genotype | Variant type | Amino acid change | Onset age/ gender | Symptom (s) | Extracardiac manifestations | Echo | ECG | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Carlo et al. 2022 | c.399dup | Het | Frameshift deletion | p.G134Rfs*30 | 60 y/M | Chest pain, palpitations | NA | Concentric LV hypertrophy | Left anterior hemiblock, premature atrial contractions | Alive |
| This study | c.3907_3922delGGCCTCCTGGGGGCCT | Comp het | Frameshift deletion | p.G1303Lfs*28 | 14 y/F | Respiratory distress, fatigue | Low set ears, scoliosis | Diffuse biventricular hypertrophy | Biventricular hypertrophy, ventricular escape | Alive |
| | c.2200A>T | Comp het | Nonsense mutation | p.R734* | | | | | | |

Comp het, compound heterozygous; Echo, echocardiography; ECG, Electrocardiograph; F, female; Het, heterozygous; Hom, homozygous; ICD, implantable cardioverter defibrillators; IVS, interventricular septum; LV, left ventricle; m, month(s); M, male; nsVT, non-sustained ventricular tachycardia; NA, not available; RV, right ventricle; SR, sinus rhythm; SVT, supraventricular tachycardia; VF, ventricular fibrillation; w, week(s); y, year(s).

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of West China Second Hospital of Sichuan University (2014-034). 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 individual(s) and minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

## Author contributions

TL, YJ and RL contributed equally to this work. TL, YJ, RL, SL and YL were the patient's physicians. TL and RL reviewed the literature and contributed to manuscript drafting. DZ, TL and YJ performed the variant analysis. DZ, SL and YL conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. DZ, YL and SL were responsible for the revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1212417/full#supplementary-material

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# Cardiac pacemaker–related endocarditis complicated with pulmonary embolism: Case report

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Cardiac device–related endocarditis as a device-therapy complication is a growing problem due to higher life expectancy and the increasing number of abandoned leads and subclinical symptoms. We reported a case of a 47-year-old woman with an implanted pacemaker who was admitted to the clinic for cardiology due to the right-sided device-related infective endocarditis of the pacemaker leads with vegetations, predominantly in the right atrium and right ventricle and complicated by pulmonary embolism. Several years after pacemaker implantation, she was diagnosed with systemic lupus erythematosus and started immunosuppressive therapy. The patient was treated with prolonged intravenous antibiotic therapy. The atrial and ventricular lead was extirpated, and the posterior leaflet of the tricuspid valve was shaved.

KEYWORDS

pacemaker, vegetation, endocarditis, *Staphylococcus*, embolism

## 1. Introduction

Cardiac device–related endocarditis has emerged as a serious device-therapy complication in the era of advanced medical technology and is a growing problem due to higher life expectancy, limited electrode lifetime, and an increasing number of abandoned leads and subclinical symptoms (1). We present a case of a pacemaker lead endocarditis complicated by pulmonary embolism in a female patient on immunosuppressive treatment for systemic lupus erythematosus (SLE).

## 2. Case description

A 47-year-old female was admitted to the cardiology clinic with a diagnosis of right-sided device-related infective endocarditis of the pacemaker leads with vegetations, predominantly in the right atrium and right ventricle. The patient's medical history revealed pacemaker implantation (DDDR pacemaker system RV and RA electrode St. Jude Medical 1688 T) due to a complete atrioventricular block. After 10 years, the pacemaker's elective replacement indicator mode was detected, indicating the need for a pacemaker replacement. Post-surgery, the previously implanted ventricular lead could not be disconnected from the generator and was cut and isolated as inactive. A new ventricular lead was implanted in the septal position, and the pulse generator was replaced with new DDDR mode stimulation.

The patient had a history of hypertension, diabetes, and paroxysmal atrial fibrillation prior to hospital admission. She was diagnosed with SLE 9 years after pacemaker implantation and started immunosuppressive therapy with prednisone and chloroquine.

Prior to hospital admission, the patient underwent a dental procedure, following which she exhibited indications of soft tissue inflammation within the oral cavity. Upon admission to the hospital, the patient had a fever of up to 38.3°C and was diagnosed with inflammatory syndrome based on laboratory tests that revealed an erythrocyte sedimentation rate (ESR) of 58, C-reactive protein (CRP) of 148 mg/L, and leukocytes of $16 \times 10^9$/L. Blood cultures drawn prior to starting antibiotics grew *Staphylococcus epidermidis*, and antibiotic therapy was administered accordingly (vancomycin 2 g ×1 g intravenous, gentamicin 2 mg ×80 mg, rifampicin 600 mg with antifungal fluconazole 150 mg once a week, and a probiotic). The patient tolerated the antibiotic course and received treatment for 6 weeks.

Transesophageal echocardiography (TEE) confirmed the diagnosis of right-side lead-associated endocarditis (LAE), with the presence of vegetation on the pacemaker leads, predominantly in the right atrium (maximum of 3 cm) and right ventricle (maximum of 1 cm). Tricuspid valve regurgitation of 2–3 and a small pericardial effusion were also observed (**Figure 1**).

Multi-slice CT (MSCT) coronarography revealed a massive thromboembolism at the bifurcation of the right pulmonary artery, with surrounding muscle or thromboembolism in the left lower segmental branch (**Figure 2**). Surgical extraction was performed, specifically the extirpation of the atrial and ventricular leads and shaving of the posterior leaf of the tricuspid valve. The patient received prolonged intravenous antibiotics during the treatment.

After surgery, the patient was afebrile. Her cardiac action was of a sinus rhythm with a frequency of 66 bpm, and the need for pacemaker reimplantation was ruled out. Blood cultures taken during the continuation of antibiotic treatment and after the completion of treatment were sterile, and laboratory analyses were within normal ranges. A follow-up echocardiographic examination a few days later revealed normal findings, and MSCT of the thorax showed a small amount of left-sided pleural effusion and no pulmonary consolidation or infiltration. A small thrombotic mass (8 mm × 6 mm) was present in the lower lobar branch of the right pulmonary artery and in the branch of the lower-left lobe (8 mm ×7 mm) (**Figure 3**). One month after surgery, a control MSCT of the thoracic showed the pulmonary artery without endoluminal pathological masses in the pulmonary lobar and segmental branches.

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

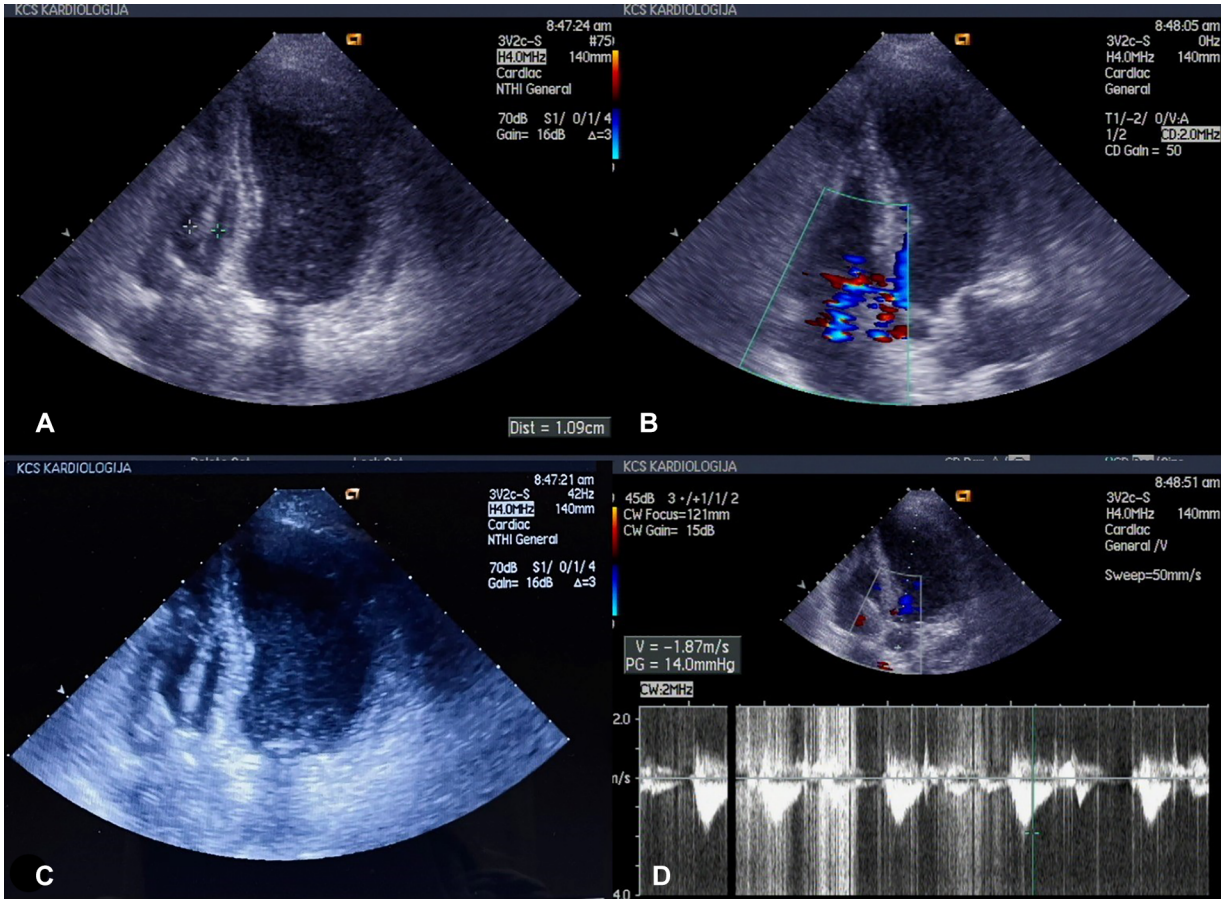


FIGURE 1
(A–D) Echonosonography showing vegetations covering the pacemaker electrode in the right ventricle.

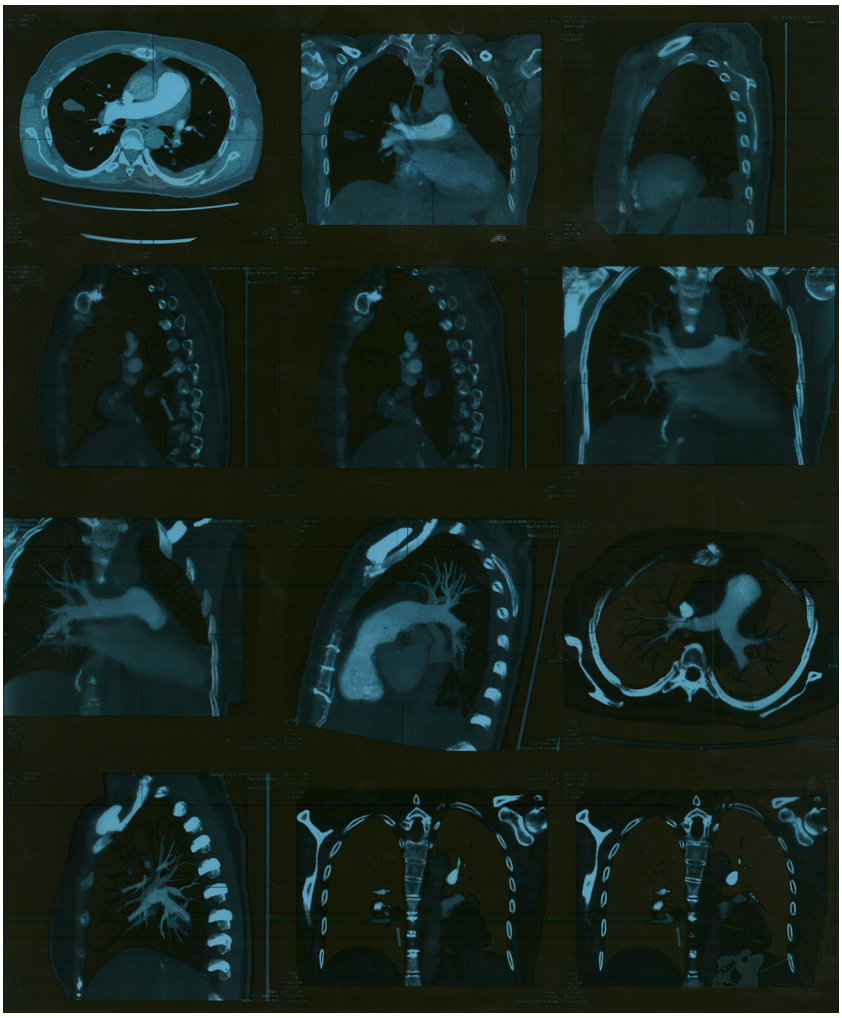

FIGURE 2
MSCT of coronary blood vessels with massive thromboembolism at the bifurcation of the right pulmonary artery. MSCT, multi-slice CT.

## 3. Discussion

The rate of cardiac implantable electronic device (CIED) infection, including permanent pacemaker and implantable cardioverter defibrillators, has increased over the past three decades (2–4) due to an aging population of CIED recipients with associated comorbidities, such as diabetes, heart, and renal failure (5). The patient, presenting with infective endocarditis as her primary diagnosis, had also the following comorbidities: diabetes, arterial hypertension, paroxysmal atrial fibrillation, lupus erythematosus systemic, and osteopenia.

Pacemaker infection may be present as either local pocket infection or bloodstream infection with or without LAE or as late-onset lead endocarditis (5, 6). When it comes to the symptoms and signs, fever is the most common symptom. Increased ESR, CRP, leukocytosis, microscopic hematuria, and anemia were the most common laboratory findings (5–9). Our patient also exhibited remarkably similar findings, including elevated levels of CRP, leukocytosis, and ESR.

In addition, this case was specific due to the inactive implanted ventricular lead that was not disconnected from the generator, so it was cut and isolated. A study that investigated the clinical failure-related events and complications of lead dislodgement showed that more deaths were reported from interventions than those from lead-related trauma or embolization (10). This indicates the importance of critical and timely decision-making on the intervention to be carried out.

Staphylococcal species are the predominant organisms responsible for pacemaker infection (9, 11, 12). However, more indolent organisms such as the coagulase-negative staphylococci are important pathogens, particularly in late-onset LAE as was a case in our patient where *Staphylococcus epidermidis* was detected (5, 13).

TEE and computed tomographic angiography (CTA) are currently the first-line imaging studies for device-related endocarditis. A fluorodeoxyglucose positron emission tomography (FDG-PET) scan can detect the site of infection earlier than anatomic findings on TEE and CTA and even earlier than surgical exploration, which is significant for clinical management (14).

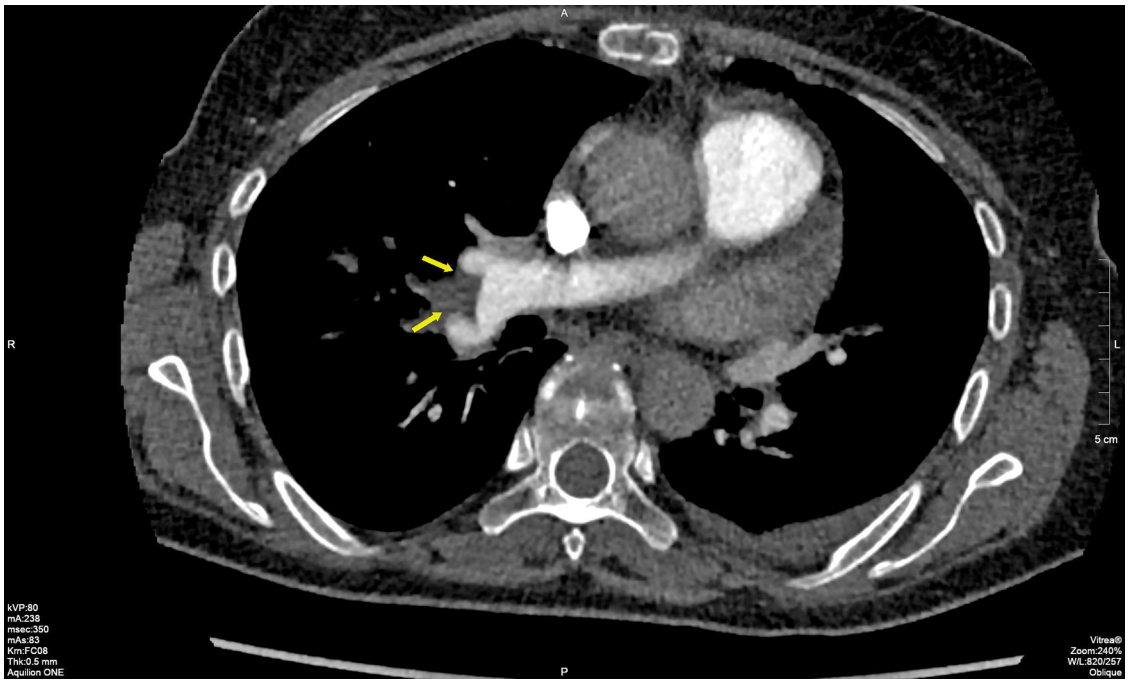


FIGURE 3
MSCT of the thorax showing small residual thrombotic masses. MSCT, multi-slice CT.

Among patients with autoimmune diseases, such as in our case where the patient underwent a dental procedure, infective endocarditis can arise due to pathogen exposure during dental or surgical interventions. It is noteworthy that corticosteroids have been shown to substantially elevate the risk of cardiovascular diseases in patients with SLE, as demonstrated in a study (15).

Studies have shown that infections with coagulase-negative staphylococci are more often associated with larger vegetations (>1 cm) than those in infections with *Staphylococcus aureus*, which more often causes smaller vegetations (<1 cm) (5). This was true in the reported case where a significant amount of pacemaker lead was observed covering the structures (maximum of 3 cm).

Treatment of pacemaker infection includes prompt removal of the device and a prolonged course of intravenous antibiotics (9). There is some concern about performing percutaneous extraction in patients with large lead vegetations due to the risk of pulmonary emboli.

The American Heart Association and Heart Rhythm Society guidelines recommend complete device removal with a prolonged course of antibiotic therapy lasting up to 6 weeks in any patient with an infection (16). Recent European guidelines have emphasized the association of vegetation size with embolic risk in endocarditis (17).

Septic pulmonary embolism may occur in a significant number of patients with LAE, ranging from 31.2% (18) to 55% of them. It was previously observed that the size of the vegetation >15 mm in diameter is a very important predictor of pulmonary embolic events (19). In accordance with the European and American recommendations for our patient, a surgical extraction was performed, i.e., the extirpation of the atrial and ventricular lead. The adequacy of this treatment was validated by Greenspon et al., who concluded that patients who underwent device removal exhibited superior outcomes compared to those who received drug therapy alone (5).

## 4. Conclusion

This case illustrates the complexity of diagnosing, investigating, and managing patients with cardiac device–associated infection that remains a rare but potentially lethal complication of device implantation.

Prompt recognition and management of LAE depend on obtaining blood cultures and echocardiography, including TEE, in all patients who present with either signs of local pocket or systemic infection.

This case underscores the role of prolonged immunosuppression, integral to the management of autoimmune disorders like SLE, as a contributory factor augmenting the susceptibility of patients with pacemaker (PM) to the development of infective endocarditis (IE). This risk is further compounded by well-recognized predisposing factors, such as dental interventions.

The consideration of septic pulmonary embolism should be prioritized in patients with LAE, particularly in cases where the size of the vegetation exceeds 15 mm, as demonstrated in our patient.

## Data availability statement

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

## Ethics Statement

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

## Author contributions

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

## Conflict of interest

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

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# Successful cardiopulmonary resuscitation of cardiac arrest induced by massive pulmonary embolism under general anesthesia: a case report

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**Background:** While pulmonary embolism (PE) is a common occurrence, a large life-threatening PE is not. Herein, we discuss the case of a patient with a life-threatening PE that occurred under general anesthesia.
**Case presentation:** We present the case of a 59-year-old male patient who was at bed rest for several days due to trauma, which resulted in femoral and rib fractures and a lung contusion. The patient was scheduled for femoral fracture reduction and internal fixation under general anesthesia. After disinfection and surgical towel laying, there was a sudden occurrence of severe PE and cardiac arrest; the patient was successfully resuscitated. Computed tomography pulmonary angiography (CTPA) was performed to confirm the diagnosis, and the patient's condition improved after thrombolytic therapy. Unfortunately, the patient's family eventually discontinued treatment.
**Discussion:** Massive PE frequently occurs suddenly, may endanger a patient's life at any point in time, and cannot be diagnosed quickly on the basis of clinical manifestations. Although the vital signs fluctuate greatly and there is insufficient time to conduct more tests, some factors such as special disease history, electrocardiography, end-tidal carbon dioxide, and blood gas analysis may help us determine the preliminary diagnosis; however, the final diagnosis is made using CTPA. Current treatment options include thrombectomy, thrombolysis, and early anticoagulation, of which thrombolysis and early anticoagulation are the most feasible.
**Conclusion:** Massive PE is a life-threatening disease that requires early diagnosis and timely treatment to save patients' lives.

KEYWORDS

pulmonary embolism, general anesthesia, electrocardiography, computed tomography pulmonary angiography, thrombolysis

## Background

While several cases of pulmonary embolism (PE) have been reported in the literature, cases of large perioperative PE are rare. The incidence of PE is one case of PE occurring in every 1,000 people in the United States every year, and the incidence of perioperative PE is five times higher than that of non-perioperative PE (1). In most cases, the embolus

Abbreviations
PE, pulmonary embolism; ECG, electrocardiography; CTPA, computed tomographic pulmonary angiography; $P_{ET}CO_2$, end-tidal carbon dioxide; $PaCO_2$, partial pressure of carbon dioxide in artery; RBBB, right bundle branch block.

of PE is small and may not even be detected or diagnosed in a timely manner owing to atypical symptoms or inadequate diagnostic conditions (2). Perioperative massive PE that occurs under general anesthesia is disastrous because it can present with varied symptoms in different patients and its diagnosis is difficult, especially in patients with hemodynamic fluctuations. If massive PE is not diagnosed quickly and patients do not receive timely treatment, death may be instant (3). Here, we report a case of sudden massive PE that occurred under general anesthesia.

## Case presentation

We report the case of a 59-year-old male patient who suffered a car accident, which caused pain in his left thigh, resulting in unconsciousness. After treatment at a local hospital, radiography revealed multiple fractures of the right ribs, mandible fracture, and brain contusions. The patient was transferred to the bone and joint trauma ward of our hospital for further treatment. A radiographic examination at our hospital revealed that the continuity of the left femoral cortex was interrupted, and there was displacement. After a partial examination, including tests for coagulation (prothrombin time,14s; activated partial thromboplastin time, 32.40 s; fibrinogen, 4.930 g/L) and D-dimer level (5.29 mg/L), the surgeon prepared the patient for internal fixation of the fractured femur. Because this patient and his family wanted the operation to be performed as soon as possible, no examination for deep venous thrombosis of the lower extremity was performed. In addition, the surgeon did not perform interventions such as anticoagulation.

The patient had no previous history of deep vein thrombosis, family history of sudden cardiac death, or cancer. He also had no comorbidities and was in a healthy state before the accident took place. Ever since the patient had been hospitalized, he had been bedridden. Owing to the pain caused by the fracture, the patient did not perform any lower limb movement in his bedridden condition.

The patient's anesthesia risk classification was American Society of Anesthesiologists grade III, cardiac function grade 2. In the operating room, arterial and internal jugular vein catheterizations were performed, and the arterial blood pressure (BP) was 140/80 mmHg. Sufentanil, etomidate, propofol, and cisatracurium were administered for routine anesthesia induction, which was performed smoothly, and tracheal intubation was successful. Propofol, remifentanil, and sevoflurane were used to maintain the depth of anesthesia, and the dosage was adjusted according to the vital signs. The surgeon then posed and sterilized the site and spread a sterile surgical towel. By the time the surgeon was ready to open the skin, the patient's BP had suddenly dropped to 45/25 mmHg, approximately 1 h after the last induction time. When he was administered a short-order treatment with ephedrine and norepinephrine, his BP did not rise but tended to decrease. At this point, end-tidal carbon dioxide ($P_{ET}CO_2$) on the anesthesia monitor decreased significantly. An arterial blood gas analysis revealed a high partial pressure of carbon dioxide in the artery ($PaCO_2$). BP continued to decrease, and the heart quickly stopped beating. Immediately after chest compressions, electrical defibrillation, and continuous high-dose epinephrine administration, the patient's BP increased to approximately 105/65 mmHg, and the heart rate was 105 beats per minute. Cardiopulmonary resuscitation was performed twice, and BP was maintained at 110/65 mmHg and heart rate at 135 beats/min. During this period, the lowest end-tidal carbon dioxide was 12 mmHg, and the highest $PaCO_2$ was 111 mmHg. Partial arterial oxygen pressure (PaO2) was 162 mmHg, the pH value was 6.99, and the lactate level was 11.7 mmol/L. Lead electrocardiography (ECG) revealed a complete right bundle branch block (RBBB), I-lead deep S wave (S1), III-lead Q wave (Q3), and T-wave negative (T3), which is called S1Q3T3. **Figure 1** shows the ECG results. Computed tomography pulmonary angiography (CTPA) showed multiple embolisms in

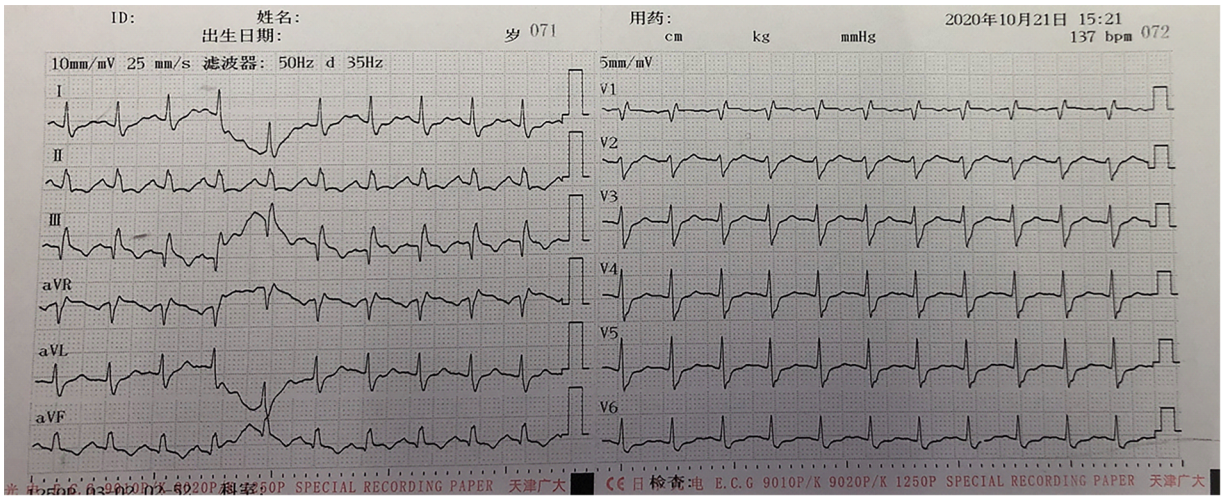


FIGURE 1
ECG of the patient after cardiopulmonary resuscitation: I-lead deep S wave (S1), III-lead Q wave (Q3), and T-wave negative (T3), which is called S1Q3T3.

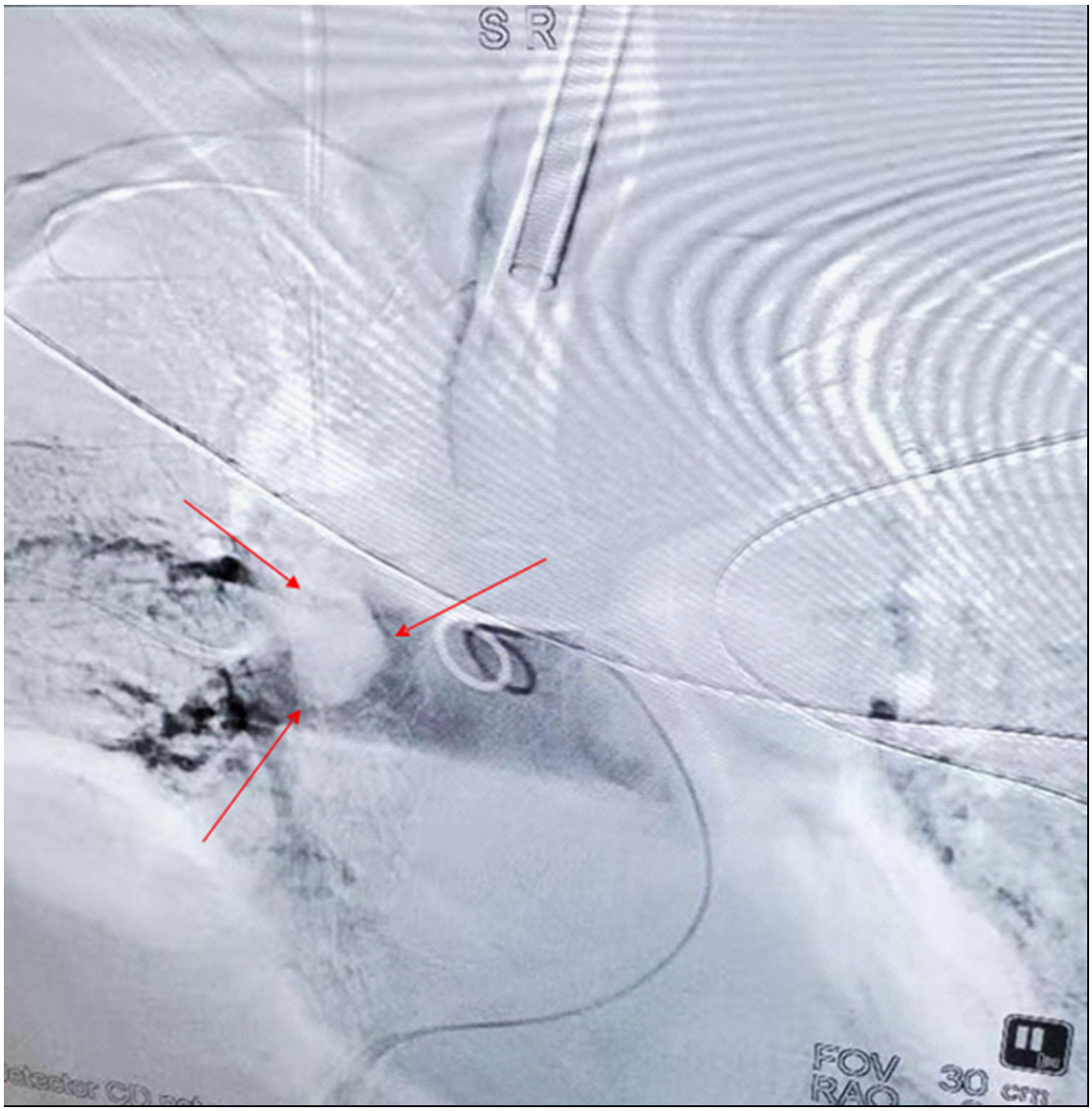


FIGURE 2.
Computed tomography angiography of the lung approximately 3 h after hemodynamic fluctuations occurred: multiple embolisms in the two main pulmonary arteries and bilateral pulmonary artery branches. The arrows denote a very large embolus.

the two main pulmonary arteries and bilateral pulmonary artery branches (Figure 2). Blood gas analyses within 5 h after onset are presented in Table 1. Because of the urgency of the situation, an Echo-fast examination for quickly assessing the heart chambers was not performed after ECG and resuscitation.

The patient underwent inferior vena cava filter implantation and thrombolysis, for which the pulmonary artery catheter was used, followed by thrombolysis for several days in the intensive care unit. The patient's vital signs gradually stabilized; follow-up on days 2, 3, and 4 showed that the patient responded correctly to their own name and simple instructions, and a gradual improvement in blood gas analysis results (Table 2). The relevant datasheet from the episode of care is given in Table 3. Unfortunately, the patient's family sought

TABLE 1 Blood gas analyses within 5 h after onset.

| | 13:02 | 14:06 | 14:27 | 14:44 | 14:56 | 15:15 | 15:44 | 16:08 |
|---|---|---|---|---|---|---|---|---|
| PH (mmHg) | 7.48 | 7.43 | 6.93 | 6.99 | 7.06 | 7.13 | 7.10 | 7.16 |
| $PCO_2$ (mmHg) | 36 | 31 | 70 | 111 | 89 | 70 | 88 | 72 |
| $PO_2$ (mmHg) | 85 | 266 | 262 | 162 | 213 | 192 | 186 | 196 |
| Lac (mmol/L) | 0.9 | 3.2 | 11.4 | 11.7 | 11.3 | 10.2 | 10.0 | 9.5 |
| BEecf (mmol/L) | 3.3 | −3.7 | −17.7 | −4.7 | −5.1 | −5.9 | −2.4 | −3.0 |

TABLE 2 Arterial blood gas analysis.

| | The first day 23:10 | The next day 7:40 |
|---|---|---|
| PH | 7.279 | 7.439 |
| $PO_2$ (mmHg) | 135 | 153 |
| $PCO_2$ (mmHg) | 50.5 | 35.9 |
| LAC (mmol/L) | 6.5 | 3.0 |
| $PO_2/FiO_2$ | 270 | 306 |

discontinuation of treatment, following which the patient was voluntarily discharged.

## Discussion

Massive PE is often sudden and harmful and may lead to a person's death at any point in time. However, the initial symptoms may be atypical. In order to make the correct diagnosis and provide timely treatment, the exclusion criteria for PE need to be understood, and its possible clinical manifestations and related procedures, such as biochemical tests and imaging examinations, should be established.

Patients with suspected PE should be assessed for the clinical likelihood of PE using a validated risk score. In an article by Kruger et al, it was reported that a low or moderate clinical probability, combined with a normal D-dimer level, can rule out PE (4). A study by Salehi et al. provided evidence of suboptimal adherence to CTPA abandonment in patients who tested D-dimer-negative before CTPA was performed (5). Yang et al. observed that older age (increasing every 10 years), delay from the time of injury to surgery (daily), and fibrinogen levels $>0.4$ g/L were independent risk factors for preoperative deep vein thrombosis (6), Therefore, it is worth considering early surgical treatment for such patients. When the dimer and fibrinogen levels increase, blood is in a hypercoagulable state. At this time, there is a high risk of thrombosis leading to serious consequences such as organ embolization; therefore, there needs to be vigilance when there is an increase in the dimer and fibrinogen levels.

Massive PE often needs to be distinguished from ST-segment elevation myocardial infarction as both conditions result in ST-segment elevation. The ECG of patients with PE can show an RBBB, leading to deep S wave (S1), III-lead Q wave (Q3), and T-wave negative (T3), called S1Q3T3, which indicates that the patient's condition is serious and is the cause of the shock (7). In contrast, the ECG of patients with ST-segment elevation myocardial infarction does not show S1Q3T3.

When thromboembolic events are suspected during surgery, echocardiography will show right ventricular dilation and dysfunction with high specificity (8). Transesophageal echocardiography can be a reliable adjunct diagnostic measure, and PE should be considered when hemodynamic instability occurs and echocardiography shows right ventricular hypertension (9). Transthoracic echocardiography and transesophageal echocardiography are effective means to evaluate cardiac function status and provide a strong basis for the diagnosis and exclusion of some diseases, especially cardiopulmonary diseases.

CTPA is considered the gold standard technique in the emergency department for diagnosing patients with suspected acute PE (10). Early diagnosis of patients with suspected acute PE using emergency CTPA helps in reducing mortality in these patients (11). CTPA is mainly applicable to the examination of pulmonary vascular diseases, such as pulmonary embolism and pulmonary hypertension.

In our patients with endotracheal intubation under general anesthesia, airway pressure increased and $P_{ET}CO_2$ decreased, whereas arterial blood gas analysis revealed a significant increase in $PaCO_2$; these results are consistent with those reported by Torres et al. (12).

The current PE management guidelines do not recommend specific treatments for patients with high-risk perioperative PE (13). However, in addition to anticoagulation, systemic and catheter thrombolysis are appropriate interventions for massive PE. Surgical pulmonary embolectomy can be performed to save patients' lives, whereas right ventricular assist devices and extracorporeal life support can provide hemodynamic support in instances when removal of the embolus from a patient with PE is difficult (14).

Pulmonary embolism still needs to be differentiated from several diseases. Coronary heart disease is characterized by myocardial ischemia. Coronary angiography shows coronary atherosclerosis and obstruction of the lumen, but there is no pulmonary vascular obstruction. Most patients with aortic dissection have a history of hypertension, chest radiographs often show mediastinum widening, and chest computed tomography angiography shows aortic dissection.

Although a definitive diagnosis and effective treatment were the strengths of this study, significant omissions in thrombosis

TABLE 3 Relevant datasheet from the episode of care.

| Date | Body temperature (°C) | Heart rate (times per minute) | Respiratory rate (times per minute) | Blood pressure (mmHg) | Oxyhemoglobin saturation (%) | Urine volume (ml) |
|---|---|---|---|---|---|---|
| The first day | 36.8 | 122 | 13 | 104/62 | 99 | 500 |
| The next day | 36.6 | 108 | 15 | 147/82 | 100 | 1,330 |
| The third day | 36.4 | 88 | 16 | 112/62 | 99 | 1,590 |
| The fourth day | 36.4 | 85 | 16 | 130/72 | 99 | 4,850 |

prevention and PE risk assessment during preoperative preparation, such as the absence of preoperative anticoagulation and lower-extremity deep vein thrombosis screening, acted as limitations. In patient cases such as ours, it is important to respect the feelings of the patient and his family, but the patient's safety should be the paramount consideration.

## Conclusions

The diagnosis of perioperative massive PE is a major challenge for clinicians. In our patient, ECG showed an RBBB, S1Q3T3, decreased $P_{ET}CO_2$, and increased $PaCO_2$. Transesophageal echocardiography showed hemodynamic instability and increased right ventricular resistance, all of which are helpful for the diagnosis of PE, which can be confirmed using CTPA when conditions permit, such as when the patient's vital signs are stable or when the hospital has sufficient resources to perform CTPA. Early and rapid diagnosis, timely treatment, and saving patients' lives are the treatment goals in patient cases such as ours.

## Data availability statement

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

## Ethics statement

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

## Author contributions

ZL analyzed and interpreted the patient data, performed the literature review, and drafted the manuscript. NC analyzed and interpreted the patient data, performed the literature review, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# Coronary artery mycotic aneurysm in a patient suffering from subacute endocarditis: a case report and literature review

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Although mycotic aneurysm is a known and important disease in the cerebrovascular system, especially the brain, there are scarce reports about coronary artery mycotic aneurysms (CAMA). CAMA can occur not only in the context of endocarditis but also as a rare adverse event of coronary artery stenting, which has been used more extensively in recent years. Accordingly, it is essential to pay greater attention to its associated presentations and clinical course. Considering the scant evidence available, reporting the disease course of each patient with CAMA can help increase the physician's knowledge about this condition, which is why we are reporting this case. A 42-year-old man with diabetes was referred to our center with embolic left cerebellar infarction 3 months earlier, as well as a 2-month history of feverishness before his referral. His blood culture was positive for *Viridans Streptococci*, and he had paraclinical signs of inflammation and two- and three-dimensional transthoracic and transesophageal echocardiography (2D & 3D TTE and TEE) signs of aortic and mitral valves' infective endocarditis with the destruction of the aortic valve, severe aortic and mitral regurgitation, severe pulmonary hypertension, and moderate biventricular systolic dysfunction. Regarding the obviously dilated left main coronary artery on TEE images, contrast-enhanced chest multidetector computed tomography was performed for better assessment of coronary arteries with suspicion of CAMA, which confirmed aneurysmal dilatation of the proximal left main coronary artery. The presence of bacteria was confirmed on staining the valvular tissue, resected during the surgical replacement of aortic and mitral valves. As the cardiac surgeon considered CAMA resection and coronary bypass grafting high risk for the patient, he received parenteral antibiotic therapy, for 6 weeks. At 1-year follow-up, he was doing well with no signs/symptoms of endocarditis and well-functioning mechanical prosthetic valves. This case shows the significance of considering CAMA in the setting of endocarditis, resistant to medical and/or surgical therapy or in patients with coronary aneurysm, simultaneous with active endocarditis. Therefore, more attention should be paid to this extravalvular complication of endocarditis, and its possibility should be considered and investigated in any patient presented with valvular endocarditis, especially involving the aortic valve.

KEYWORDS

cardiac infection, mycotic coronary aneurysm, endocarditis, anti-bacterial agents, *Viridans Streptococci*

## Introduction

A mycotic aneurysm refers to localized, irreversible vascular dilatations, because of the weakening and destruction of the vessel wall, caused by a bacterial, fungal, or viral infection. The term "mycotic" refers to the particular shape of the aneurysm in the first case described and not the underlying pathology. So, as the fungal infection is not the mere cause of this infection, "infected aneurysm" would be a more accurate term. Femoral, aorta, intracranial, and visceral arteries are the more commonly involved vessels correspondingly (1).

Infected coronary artery aneurysm or coronary artery mycotic aneurysm (CAMA) is a very rare phenomenon, mainly observed in men, caused secondary to infective endocarditis (IE), percutaneous coronary artery intervention (PCI), and extracardiac infections, during which microembolization to the vasa vasorum and direct invasion of the pathogen to the arterial wall, or immune complex deposition results in vessel's wall injury and destruction (2). Although most CAMA cases are large (average 3.4 cm, max: 9 cm in diameter) at the time of diagnosis, non-specific clinical presentations, such as feverishness, malaise, and weight loss with leukocytosis, increased level of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) makes CAMA diagnosis a challenge and includes it in the differential diagnosis of any "fever of unknown origin" (3). However, the presence of an infected aneurysm, especially with a cardiac/coronary origin, is rarely anticipated by such clinical presentations. Furthermore, most cases do not have any specific finding on the initial/routine clinical or paraclinical cardiac exam -such as cardiac auscultation or electrocardiogram-, so more accurate diagnostic methods, such as chest computed tomography (CT), are suggested for diagnosis (4).

Missed diagnosis of CAMA results in a high mortality rate because the aneurysm, especially those larger than 1–2 cm, will eventually grow and end in rupture or thrombosis frequently, even despite proper antibiotic therapy. Considering the acceptance of PCI as an appropriate therapeutic tool for several coronary diseases and its widespread use during the recent decades, it is anticipated that the incidence of CAMA has also increased (5, 6). However, few case reports available in the current literature make it difficult to estimate the rates of incidence and complications of CAMA or to determine the most accurate diagnostic tool. There is also scant evidence available in the literature in terms of the most appropriate therapeutic approach. Some experts have suggested medical treatment for smaller aneurysms and surgical treatment for larger ones (7); Even though it is (then again) not clear what precise cut-point should be considered for the surgical resection of the aneurysm or what setup should be considered. Accordingly, reporting the disease course and outcome of any patient with this condition can help increase the physician's knowledge and grow the available literature. Here, we report a case of CAMA in a 42-year-old man, who presented with a 2-month history of feverishness and was successfully diagnosed and managed at our center.

## Case presentation

A 42-year-old man with diabetes mellitus was referred with a 2-month history of feverishness and embolic ischemic left cerebellar infarction a month back. Serum tests revealed a positive blood culture for *Viridans Streptococci* organism with evidence of inflammation, including leucocytosis and increased levels of ESR and CRP. A brain CT scan without contrast was suggestive of a non-hemorrhagic stroke involving the left cerebellum (**Supplementary Figure S1**).

He had no past medical history of cardiovascular diseases and no first-degree family history of valvular or ischemic heart disease or genetic disorder. The psychological history of the patient was unremarkable.

Considering the easily audible systolic and diastolic murmurs on cardiac auscultation, two- and three-dimensional transthoracic and transesophageal echocardiography (2D & 3D TTE and TEE) were performed for better assessment, which revealed an irregularly thickened and destructed bicuspid aortic valve (fusion of non-coronary and right coronary cusps), a few small mobile vegetative lesions, and a partially ruptured left coronary cusp of the aorta, resulting in severe aortic regurgitation (**Figure 1**). The patient had no aortic ectasia or dilation in view of bicuspid aortic valve or any evidence of endarteritis elsewhere. IE involvement of the mitral valve in the base of the anterior leaflet, adjacent to the aortic valve, with severe mitral regurgitation was also evident (**Figure 2**). A tricuspid regurgitation with moderate severity and severe pulmonary hypertension (60 mmHg), and severe left ventricular dilatation, accompanied by moderate biventricular systolic dysfunction were also detected. The left main coronary artery was dilated on 2D & 3D TEE.

The vegetative lesions on both aortic and mitral valves raised the suspicion of a probable simultaneous coronary artery involvement by IE (**Figures 2**, **3**). Contrast-enhanced chest multidetector CT scan performed showed aneurysmal dilatation of the left main coronary artery (12.7 mm diameter) with an irregular border, originating from the left coronary sinus extending to the proximal LAD artery, suggestive of CAMA (**Figure 4**). The algorithmic process of diagnosis in the presented case is provided in **Supplementary Figure S2**.

Surgical replacement of aortic and mitral valves was done after 2 weeks of intravenous antibiotic therapy. Control echocardiography (repeated after 2 weeks of therapy) showed no changes in echocardiographic findings. Preoperative assessments (sestamibi dipyridamole stress test) showed no signs of coronary artery disease, requiring concomitant coronary artery bypass grafting. During surgery, the aortic and mitral valves were replaced by proper mechanical bileaflet valves (St. Jude 21 and St. Jude 30 for aorta and mitral positions, respectively) and tissue samples were sent for pathological examination. Gross observation during the operation confirmed abnormal dilatation of the left main coronary artery, which extended to the proximal LAD, in favor of CAMA. The cardiac surgeon considered CAMA resection and coronary bypass grafting to be of high risk. Therefore, the surgeon ended the surgery with mere valvular replacement and long-term antibiotic therapy was selected as the treatment of CAMA in this patient.

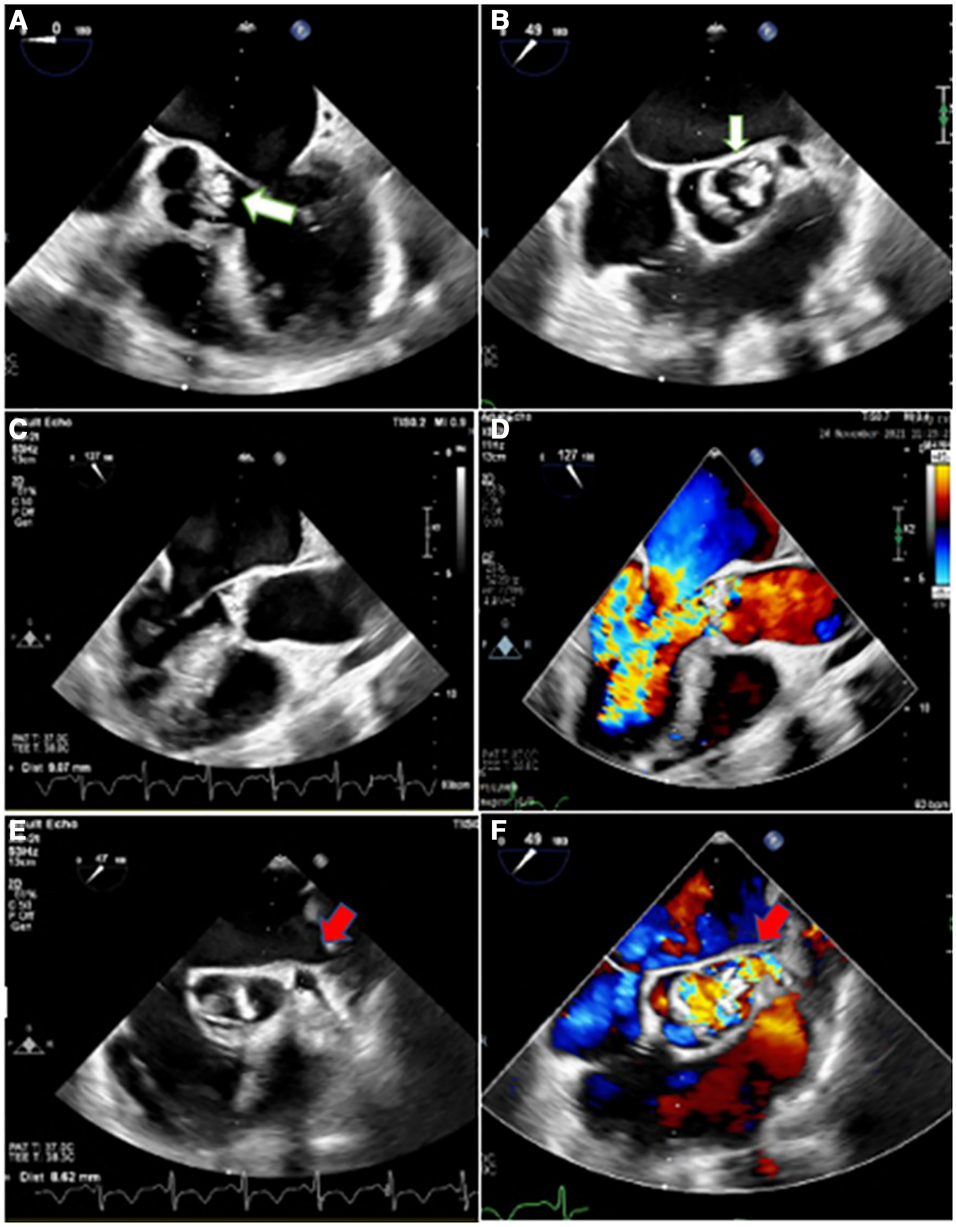


FIGURE 1
Two-dimensional transesophageal echocardiography in different views, illustrating irregularly thickened and destructed bicuspid aortic valve (non-coronary cusp and right coronary cusp fusion) with partially ruptured left coronary cusp (white arrow) and a few small mobile vegetative particles, suggestive of aortic valve involvement and destruction by infective endocarditis (A,B), heralding severe aortic insufficiency (C,D). Moreover, it shows the dilated left main coronary artery (red arrow) with turbulent blood flow inside (E,F).

Histopathological evaluation of the excised valves and surrounding tissues confirmed valvular destruction, inflammation, and infection with gram-positive cocci (**Supplementary Figure S3**). The patient was uneventful during postsurgical weaning, recovery, and admission. He was discharged after 6 weeks of combined parenteral and PO antibiotics, prescribed for 2 more weeks to complete a 2-month period of antibiotic therapy, consisting of a combination of rifampicin, Tavanex, and amikacin (selected based on the antibiogram results). At 1-year follow-up, he was doing well with well-functioning mechanical prosthetic valves on echocardiography and no change in size of coronary aneurysm on the contrast-enhanced chest multidetector CT scan (**Supplementary Figure S4**). For all diagnostic tests and selection of therapeutic procedures, the patient was informed about the risks and benefits and signed the written informed consent. After treatment, the patient was completely satisfied with the care provided.

## Discussion

CAMA is a serious clinical condition with the risk of rupture and myocardial infarction (8); short-term mortality rate of CAMA is reported at about 40%, confirming poor prognosis of this condition (9). Few cases have been reported, limited to a

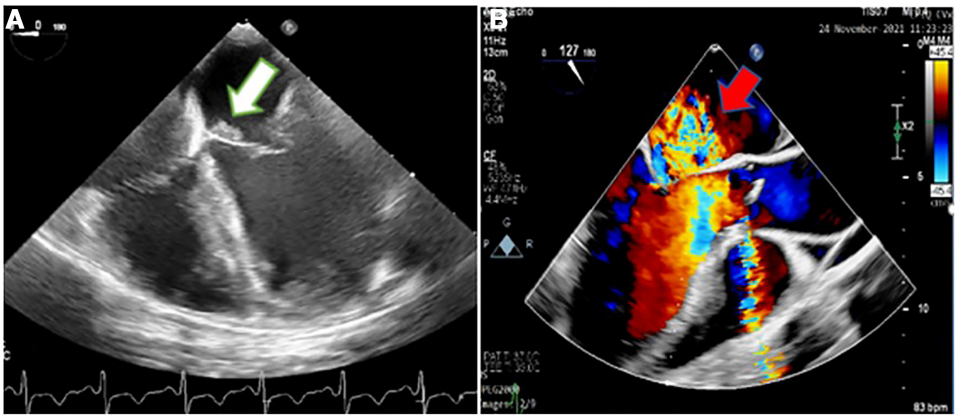


FIGURE 2
Two-dimensional transesophageal echocardiography showing an irregular thickening over the atrial side of the base of anterior mitral valve leaflet (white arrow) (A) suggestive of the involvement of the mitral valve by infective endocarditis, which caused severe mitral regurgitation, demonstrated in color Doppler flow study (red arrow) (B).

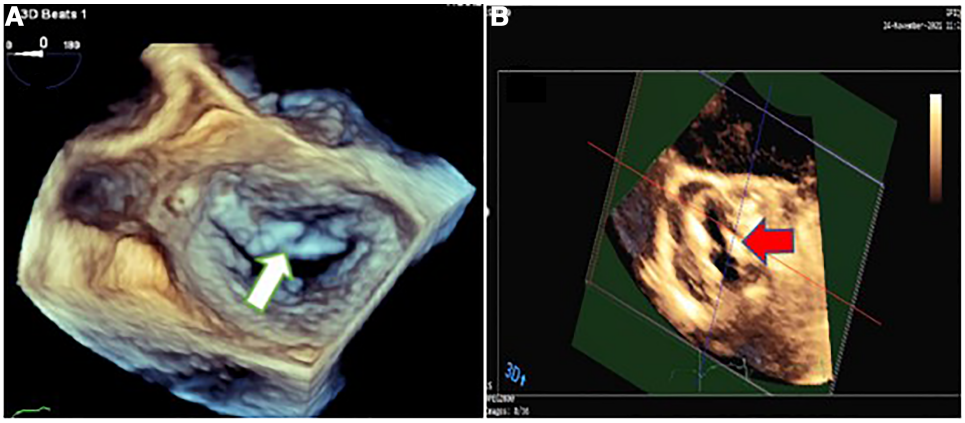


FIGURE 3
Three-dimensional transesophageal echocardiography showing mitral valve endocarditis with irregular thickening over the atrial side of the base of anterior mitral valve leaflet (white arrow) (A) and irregularly thickened and destructed bicuspid aortic valve involved by infective endocarditis (red arrow) (B).

total of <100 cases until 2017 (9); thus, more studies are required to estimate the accurate incidence of CAMA.

In view of pathophysiology, the available evidence suggests IE as the source in most cases of CAMA (5, 6, 10), which predisposes the patients to other complications, such as hemorrhagic and embolic (cerebrovascular) events (11). Stent implantation in coronary arteries is also frequently reported as an important source of bacteremia and bacterial seeding, resulting in CAMA; but our patient had no history of previous coronary stenting and neither was immunocompromised to be further predisposed to any possible systemic infection as the cause of CAMA; therefore, his coronary infection can be attributed to endocarditis because of the bicuspid aortic valve and direct extravalvular extension of IE or possible bacterial seeding of the proximal coronary artery, secondary to valvular involvement by IE.

Another important concern about CAMA, based on its cause, is the high risk of comorbidities resulting from IE-related cardiac damage, such as valvular destruction (in cases with concomitant IE) (12). As in the case presented here, concomitant IE was a probable cause of CAMA, which could have been the source of destruction of aortic valves and involvement of the mitral valve with severe regurgitation. Fortunately, this case was diagnosed on time and successfully managed before the occurrence of any severe complications or rupture of the aneurysm. Unfortunately, there are some reports available of patient's expiry, even after therapeutic measurements, mainly because of the challenging management of coronary artery rupture (8, 13).

The dubious nature of CAMA makes well-timed diagnosis an important parameter in the proper and successful management of this potentially fatal condition. Although the clinical symptoms are mainly non-specific and general (3), some patients may present with acute symptoms, such as high fever, shortness of breath, chest pain, nausea, and vomiting, associated with coronary complications itself or concomitant cardiac conditions, like

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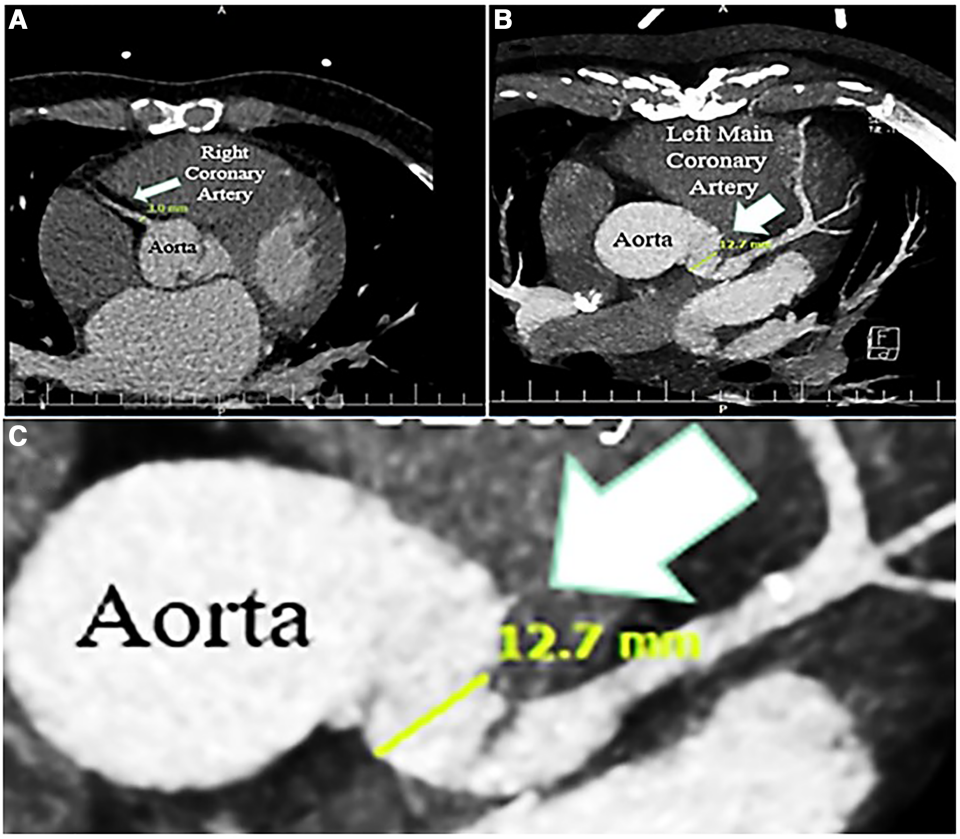


FIGURE 4
Contrast-enhanced chest computed tomography scan, showing normal caliber right coronary artery (3 mm) (A), and dilated left main coronary artery (12.7 mm); zoom out (B), and zoom in (C).

pericardial effusion (4), pericarditis (14, 15) or IE. Nevertheless, the case presented here did not have any acute or significant cardiac-related symptoms at referral, no evidence of coronary artery disease (based on the results of sestamibi dipyridamole stress test), and his mere clinical symptom was a 2-month history of feverishness with a history of recent brain ischemic embolic event, of course. As there are no clinical presentation or laboratory findings, specific to CAMA, it is important to exclude other diseases with similar presentations in clinical approach to the patients; differential diagnoses, such as reactivaltion of rheumatic fever and systemic lupus erythematosus, should be considered. Accordingly, in our case, we were able to exclude other diseases by relevant laboratory tests (16). However, the presence or source of CAMA was not predictable initially, based on clinical presentation only, in our patient, as he reported no history of any known cardiac disease or previous cardiac intervention and complained of no significant cardiac-related symptoms. In the meantime, the morphological characteristics of the coronary artery, observed on cardiac imaging, in addition to the presence of valvular involvement by IE and the suggestive paraclinical data, guided the physicians toward this diagnosis. Paraclinical data in our case showed evidence of bacteremia with *Viridans Streptococci*. *Staphylococcus aureus* and *Streptococcus viridans* have been previously described to be the two most common pathogens in CAMA (2, 17). Furthermore, our patient had high levels of inflammatory markers in the blood (leukocytosis, increased level of ERS and CRP), which are non-specific markers and were thus not helpful for diagnosis of CAMA, regarding concomitant valvular involvement with IE. So, the key diagnostic finding in our case was the unusual focal dilation of the coronary artery in the echocardiographic examination, confirmed by chest MDCT, besides valvular involvement by IE.

Cardiac imaging in CAMA can detect coronary dilation with occasional lobulated contour or saccular shape, wall thickening or mural thrombus, and also possible associated abnormalities in the pericardium or valves. We have identified the characteristics of the coronary aneurysm by contrast-enhanced chest CT scan. Some authors have used angiography for an accurate diagnosis (18), which we consider high risk for such patients, especially in cases with involvement of the very proximal portion of coronary arteries, near the ostial region; thus, we recommend the use of CT angiography as a better diagnostic tool, in case the physician requires angiographic parameters for accurate diagnosis (17). Magnetic resonance angiography, also, has several limitations, such as limited access, long examination time, and motion artifacts, and thus not preferred (3, 17). Some experts have also described the use of TEE for the diagnosis of CAMA (19). In our experience, TEE could successfully reveal the abnormalities of the proximal coronary artery and propose the probability of the presence of CAMA, in addition to valvular abnormalities.

Considering the scant evidence available and the rarity of CAMA, it is not easy to suggest one imaging tool as the gold standard. More studies are required to compare the diagnostic accuracy of different imaging modalities and suggest one as the superior method (17).

Treatment of CAMA consists of antibiotic therapy, in addition to surgical resection or de-roofing and debridement of the infected aneurysm, in combination with arterial ligation, with or without distal bypass of the artery, and vascular reconstruction; in case of rupture, endovascular therapies may be required (9, 17). The size of aneurysm, extent, and location of the coronary artery involved, morphological appearance and characteristics of the aneurysm, clinical status, and other factors may also be important for proper decision-making and therapeutic approach for each patient; although these parameters have not been defined well in literature. Other treatments, like covered stent, which can be used in other types of coronary aneurysms, are also not an appropriate choice in CAMA, considering the infection background (17, 20); apparently, long-term antibiotic therapy is the treatment of choice in CAMA. However, there is still no approved evidence-based guideline available for the treatment of CAMA, and the best therapeutic option is not defined; hitherto, it is certain that CAMA requires clinical vigilance and great attention to be diagnosed and managed appropriately.

Fortunately, our patient did not develop coronary rupture or other complications by the time he was diagnosed, and he was successfully managed by a hybrid treatment strategy (combination of surgery for treatment of valvular IE and medical therapy for CAMA), had an uneventful postoperative period, no clinical symptoms, and negative paraclinical results (no evidence of IE of the prosthetic valve) until the last follow-up (1 year); the favorable prognosis of our patient could be related to the relatively small size of the aneurysm and limited involvement of coronary artery with no visual signs of the high-risk aneurysm (which predispose the patients to complications or rupture) in preoperative imaging modalities, and gross visual observation by the surgeon at the time of surgery. For the choice between surgery and medical treatment (no surgery), in this case, the surgeon suggested a no-surgery strategy (antibiotic therapy), considering the high risk of surgical resection. Antibiogram-driven antibiotic therapy was also prescribed, and 1-year follow-up showed favorable results, which indicated that the treatment strategy applied could be appropriate in carefully selected patients.

In conclusion, the case presented here had several notes to be kept in mind. First of all, the symptoms of CAMA are non-specific, thus, diagnosis can be confounding and needs a high level of suspicion, as mycotic aneurysms are an infrequent type of aneurysms, and the coronary artery is a rare site of this condition. As CAMA has a poor prognosis and high risk of rupture, myocardial infarction, and other cardiac complications, special attention should be paid for considering CAMA in differential diagnosis, when the patient has coronary aneurysm, simultaneous with active endocarditis or in patients with endocarditis, resistant to medical and/or surgical therapy. Blood tests are helpful in determining bacteremia and inflammation. Focused imaging approaches should be considered, especially if the case is accompanied by other more obvious sources of infection (like the valvular endocarditis in our case), which makes the diagnosis doubtful. The etiology of CAMA is mainly attributed to IE or previous cardiac vascular interventions, especially in patients without immunosuppressive conditions. But, the possibility of concomitant CAMA, in the absence of these conditions, should be also kept in mind and greater attempt should be applied for detection of other sources of infection in cardiac structure. In our patient, the bicuspid aortic valve was the most probable cause of valvular IE, resulting in coronary aneurysm. The choice of treatment, antibiotic therapy and/or urgent surgical intervention, should be made based on patient's conditions; surgery is recommended in cases with large or high-risk aneurysms.

There are few case reports available in the literature about CAMA; however, we believe that the true incidence is much higher than that reported, considering the high probability of missed diagnosis. This notion has to be confirmed by further epidemiological studies.

## Data availability statement

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

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

All authors have made substantial contributions to treatment planning. RH and MS performed echocardiographies, participated in literature searching, and contributed to the preparation of this manuscript. AY was the cardiologist in charge. JB performed the surgical treatment. NS prepared and analyzed pathology specimens and provided clinical images. All authors contributed to the article and approved the submitted version.

## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1188946/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Brain computed tomogram without contrast, showing a low-density region in the left cerebellum, suggestive of non-hemorrhagic stroke.

SUPPLEMENTARY FIGURE S2
The algorithmic process of diagnosis in the presented case.

SUPPLEMENTARY FIGURE S3
The pathological specimen indicates destruction of valvular structure with overlying fibrin thrombus and mild focal infiltration of acute inflammatory cells in the setting of previous antibiotic treatment, mitral valve (H&E staining 10X objective) (A). Effacement of the valvular structure due to severe inflammation, and infiltration of acute inflammatory cells is evident, aortic valve (H&E staining 10X objective) (B). Rare gram-positive cocci (black arrowhead). (Gram staining 100X objective) (C).

SUPPLEMENTARY FIGURE S4
The results of contrast-enhanced computed tomography, illustrating the diameter of the coronary aneurysm before cardiac surgery (A), and 1 year later (B).

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# Case report: The presence of third-degree atrioventricular block caused by pulmonary embolism masquerading as acute ST-segment elevation myocardial infarction

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**Background:** Pulmonary embolism (PE) typically presents with chest pain, tachypnea, hemoptysis, syncope, and increased markers of myocardial injury. On an electrocardiogram (ECG), sinus tachycardia, right bundle branch block (RBBB), S1Q3T3 pattern, and/or precordial T-wave inversion may be observed. Despite being one of the common causes of chest pain, a third-degree atrioventricular block (III° AVB) is rare in cases of PE, which can lead to difficulties in diagnosis or even overlooking this condition.
**Case summary:** In this case report, we present a patient who was transferred to our hospital with suspected acute myocardial infarction (AMI). The patient's ECG showed ST-segment elevation in the inferior wall and a III° AVB, combined with significantly increased markers of myocardial injury. Interestingly, the patient also had a history of cerebral hemorrhage (ICH) for 7 days prior to being transferred to our hospital. After undergoing a systematic examination and evaluation, the final diagnosis for the patient was PE.
**Conclusions:** In addition to considering common symptoms, it is important not to overlook rare symptoms when diagnosing a disease. This case serves as an example of how the misdiagnosis rate for PE can be reduced by conducting a comprehensive clinical evaluation and paying attention to all clinical clues and examination results.

KEYWORDS

acute myocardial infarction, third-degree atrioventricular block, pulmonary embolism, imaging, intracerebral hemorrhage

## Introduction

Most cases of pulmonary embolism (PE) present with typical clinical manifestations such as chest pain, tachypnea, hemoptysis, and occasionally syncope. Additionally, on the electrocardiogram (ECG), characteristic changes can be seen in PE, including sinus tachycardia, right bundle branch block (RBBB), S1Q3T3 pattern, and/or precordial T-wave inversion (1). Abnormal Q waves may also appear on leads III and aVF on the ECG. However, in the case we report, none of these commonly seen features were observed. Instead, the patient presented with inferior wall ST-segment elevation, significantly increased myocardial injury markers, and a unique finding of third-degree atrioventricular block (III° AVB). Initially suspected to be experiencing acute myocardial

infarction (AMI), the patient underwent a thorough examination, which eventually led to the diagnosis of PE.

## Case presentation

A 54-year-old man was transferred from the local hospital to our hospital's chest pain center in the emergency department due to suspected AMI. The ECG obtained at the local hospital showed ST-segment elevation in the inferior wall leads (II, III, and aVF), indicating possible damage to the heart muscle in that area and a complete atrioventricular block (**Figure 1A**). When the patient arrived at our emergency department, another ECG was performed, which showed a sinus rhythm with ST-segment elevation in the inferior wall leads (**Figure 1B**). The patient did not exhibit obvious difficulty in breathing. The laboratory results showed a high percentage of neutrophils (84.3%), indicating an inflammatory response in the body. Furthermore, the results of biomarker analysis were as follows: cardiac troponin-T (cTnT) level, 474.4 ng/L; myoglobin (Mb) level, 565.30 ng/ml; creatine kinase MB (CK-MB) level, 108.00 ng/ml; and brain natriuretic peptide level, 264 pg/ml. Moreover, the patient underwent general cranial computed tomography (CT) scans (**Figures 2A–C**) and chest CT scans (**Figures 2D–F**) to assess any further complications or conditions.

Six days prior to admission to our hospital, the patient was admitted to the local hospital with symptoms of headache, right limb immobility, unclear speech, nausea, and vomiting. His blood pressure was measured at 180/120 mmHg and a cranial CT scan revealed intracerebral hemorrhage (ICH) in the thalamus. As a result, the patient was diagnosed with ICH. During his hospital stay, he experienced precordial squeezing chest pain, which lasted for approximately 1.5 h. This chest pain was accompanied by diaphoresis, palpitations, dyspnea, nausea, and vomiting. Given the symptoms and ECG changes indicating inferior wall involvement, acute inferior myocardial infarction were suspected.

Furthermore, the patient was transferred to the Cardiology Department, where an emergency bedside echocardiography was performed. The echocardiogram showed that the diameters of the aorta and pulmonary arteries were within the normal range. Additionally, in the resting state, there were no definite segmental motion abnormalities observed in the left ventricular (LV) wall. Furthermore, there was no presence of pericardial effusion. The systolic function of the LV was found to be normal. At this point, ST segments of the inferior wall leads displayed resolution (**Figure 1C**), and the patient stated that the chest pain had subsided. Due to the presence of ICH, the Department of Neurosurgery suggested that anticoagulants should not be given for two weeks As a result, instead of performing a coronary angiography (CAG), we decided to proceed with a computed tomography coronary angiography (CTCA) to assess if there was any stenosis in the coronary artery. Surprisingly, the CTCA scan showed no signs of coronary artery occlusion or severe stenosis (**Figures 3A–C**). In addition, there were no identifiable factors present in the patient that could have caused coronary artery spasm. Furthermore, conditions such as AMI resulting from inadequate blood supply to the heart due to hypotension or anemia were ruled out.

However, a coagulation function test revealed a D-dimer level of 22.48 mg/L in the patient's blood. During the patient's hospitalization, the presence of hemoptysis and deep vein thrombosis (DVT) in their lower extremity were observed. Based on these symptoms, a possible diagnosis of PE was considered. To confirm this diagnosis, a computed tomography pulmonary angiography (CTPA) was performed (**Figures 3D–F**), and the diagnosis of PE was confirmed.

After successfully managing the ICH, the patient's condition stabilized, and he was discharged. He was prescribed oral warfarin for approximately 6 months, which gradually relieved his tightness in breathing symptoms. During his second hospitalization, a series of tests were conducted including biomarkers for myocardial injury, coagulation function assessment, echocardiography, CTPA and CAG. Importantly, the CTPA scan showed no abnormalities, indicating the absence of PE. Furthermore, the CAG results revealed no significant stenosis in the coronary arteries (**Figures 3H–3J**).

## Discussion

Patients who suffer from ICH often have restricted mobility and are frequently bedridden, which increases their vulnerability to developing venous thromboembolism (VTE). Notably, the incidence of VTE is particularly high among individuals with hemorrhagic stroke. It was found that the incidence of DVT in hemorrhagic stroke patients is nearly four times higher compared to those with thromboembolic stroke (2), with around 1.37% of patients with a hemorrhagic stroke had DVT, and 0.74% exhibited PE (1). Importantly, hemorrhagic stroke itself is recognized as an independent risk factor for the development of DVT (2). Moreover, there are additional factors that contribute to the risk of DVT, including advanced age, female gender, obesity, suspected infection, the presence of a central venous catheter, and notably, immobility resulting from paralysis or mechanical ventilation restrictions (3). In the present case, the patient had limited mobility in their right limb for a duration of six days, which could predispose them to the development of lower extremity DVT. DVT is one of the underlying causes of PE, which can be confirmed through a vascular ultrasound examination.

In fact, the presence of ST-segment elevation in leads II, III, and aVF, along with an increase in cTnT levels, initially posed a challenge in distinguishing PE from acute ST-segment elevation myocardial infarction (STEMI). This was further complicated by the occurrence of III° AVB, a phenomenon that has not been previously reported in relevant literatures. Several factors may contribute to the observed ST-segment elevation. Firstly, PE-induced pulmonary artery hypertension (PAH) can cause acute right ventricular (RV) failure, resulting in impaired LV filling and subsequent hypotension (4). Secondly, the combination of hypotension, hypoxemia, PAH, and a surge in catecholamines may trigger transmural ischemia in RV. Additionally, a sudden increase in RV pressure may lead to

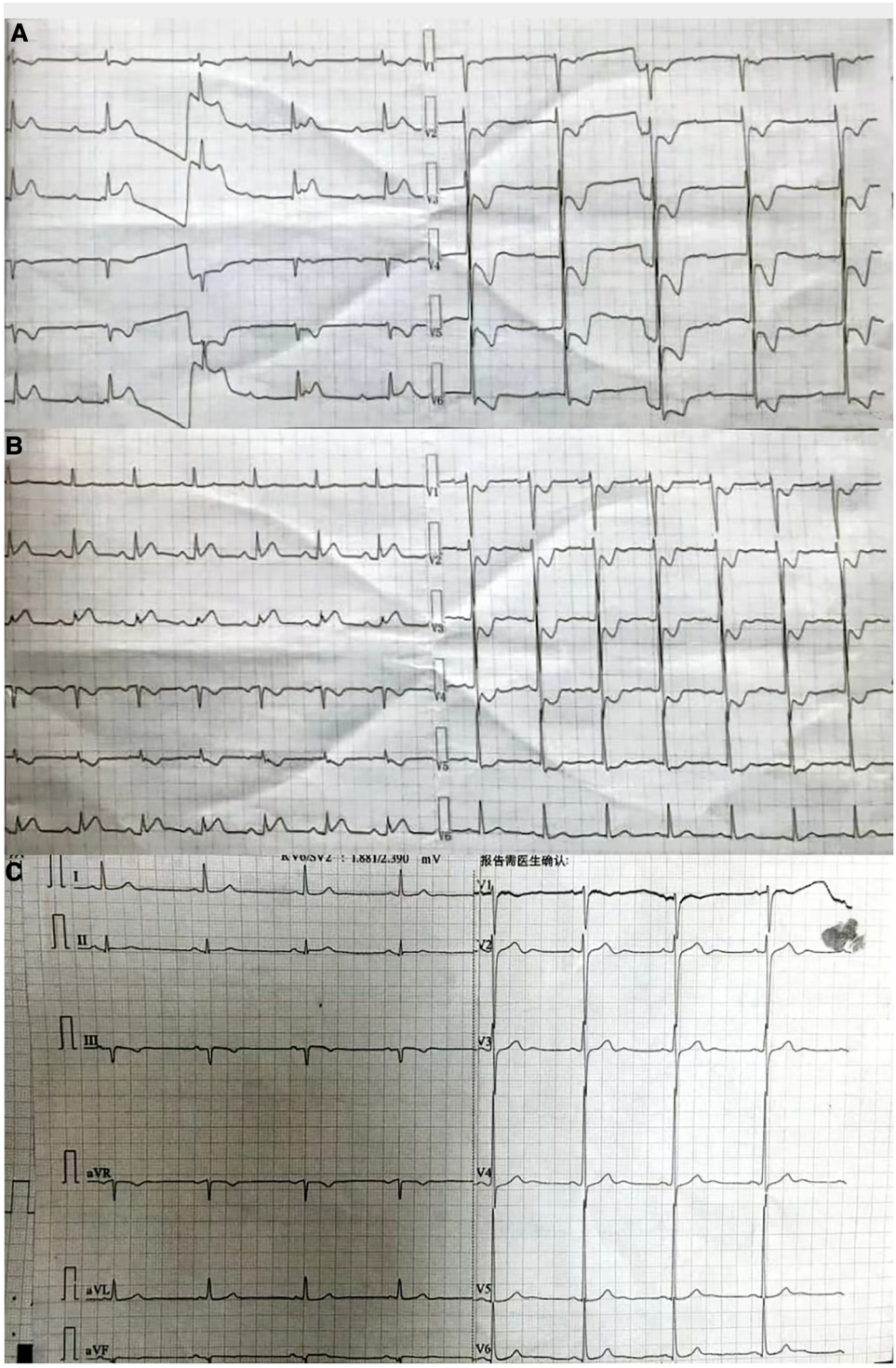


FIGURE 1
(**A**) ECG obtained at the local hospital. The findings suggest that the patient has been diagnosed with third-degree atrioventricular block. In addition, there are significant ST segment elevations observed in leads II, III, and aVF, and inverted T waves seen in leads V1–V6, accompanied by ST-segment depression. (**B**) ECG obtained at the emergency department of our hospital. The findings suggest that the patient has a sinus rhythm. There are inverted T waves observed in leads V1–V4, accompanied by a lesser degree of ST-segment depression. (**C**) ECG obtained at the Department of Cardiology of our hospital. The findings indicate left ventricular high voltage. There is a resolution observed in the ST segments of leads II, III, and aVF.

myocardial cell stretching, resulting in ischemic injury (5). Thirdly, reduced coronary artery perfusion due to hypoperfusion resulting from increased RV pressure, can induce neurohormonal activation. The release of vasoconstrictors, such as endothelin, may further contribute to coronary spasm and cardiac ischemia. Therefore, it is hypothesized that PE can lead to a more severe increase in RV pressure, subsequently causing more severe ischemic injury, as reported in this case.

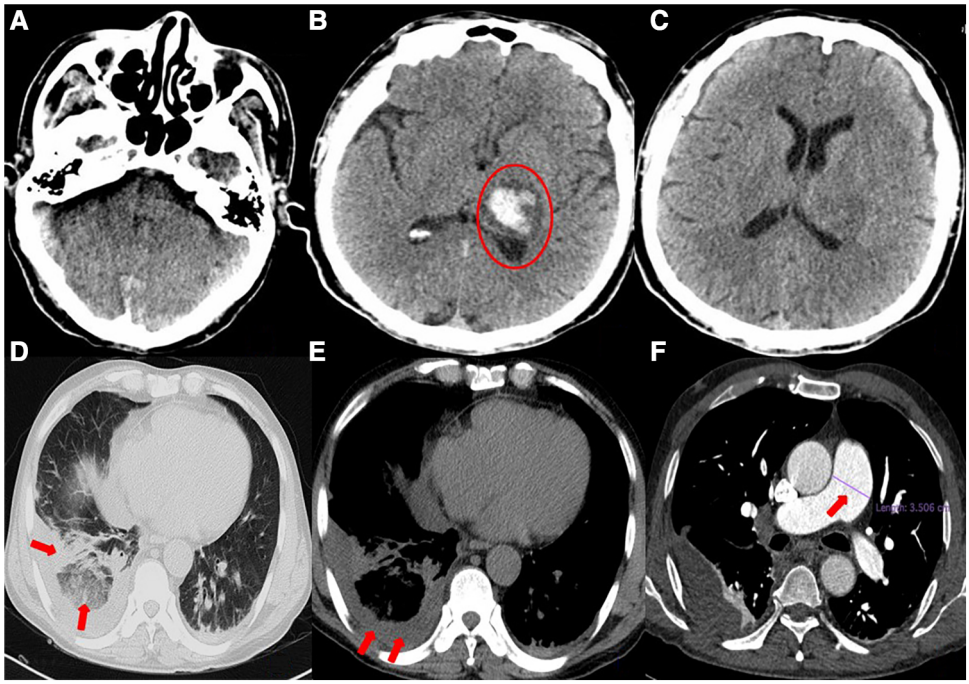


FIGURE 2
(A–C) General cranial computed tomography scan. A 3.3 × 2.3-cm left thalamic hematoma (red circle) is visible, with minimal surrounding edema. There is no evidence of midline shift. (D–F) Chest computed tomography scan. Scattered infection foci in bilateral lungs (especially in the lower lobes of both lungs), thickened bilateral pleura, right lower lobe atelectasis, right pleural effusion, and suspected pulmonary infarction can be seen. The pulmonary artery trunk is enlarged (red arrow).

ECG plays a crucial role in both differentiating PE from other conditions and distinguishing it from AMI to some extent. In the case of PE, the presence of T-wave inversions and ST-segment depressions in leads V1–V3 is indicative, whereas these ECG changes in leads V4–V6 suggest AMI. However, in the current case, T-wave inversions and ST-segment depressions were observed in leads V1–V6, making the diagnosis more challenging. The occurrence of PE with Ⅲ° AVB is rare, with only a few reported cases found in the available literature (1, 6, 7). The occurrence of Ⅲ° AVB may be attributed to a preexisting left bundle branch block (LBBB). Notably, Ⅲ° AVB is the combination of a preexisting LBBB and an emerging RBBB. In the present case, the patient had a history of hypertension, which can cause ICH and LV hypertrophy, making him more likely to develop LBBB. However, it was difficult to determine whether the patient had RBBB or LBBB. Another possible explanation for the occurrence of Ⅲ° AVB could be ischemic injury to the atrioventricular node (AVN). The AVN receives its blood supply primarily from the AVN branch of the right coronary artery in approximately 90% of individuals (8). Therefore, the low perfusion of the coronary artery and potential coronary spasm could have led to dysfunction in the AVN, further contributing to the development of Ⅲ° AVB.

Large PE, particularly in the form of pulmonary artery trunk embolism or involving the left and right proximal pulmonary arteries, can at times present solely as Ⅲ° AVB. In such cases, sudden death is often the main manifestation, making it challenging to save these patients if they do not reach the hospital in time. Consequently, encounters with cases of PE combined with Ⅲ° AVB are relatively rare in clinical settings. In the case of the patient in question, the ECG obtained upon arrival at the emergency department demonstrated a sinus heart rate and ST elevation in the inferior wall. Additionally, the Ⅲ° AVB had resolved, and the patient's dyspnea had improved. We speculated that the large embolus blocking the pulmonary artery may have turned into multiple small emboli because of bumpy transportation and that spontaneous fibrinolysis may be a possible etiology. This could explain the improvement of dyspnea and disappearance of Ⅲ° AVB.

In some cases, there is a risk of misdiagnosing AMI due to ECG findings that resemble AMI and elevated levels of cTnT. It is worth noting that the elevation of high-sensitivity cTnT (hs-cTnT) levels is the most specific and sensitive biomarker for diagnosing AMI. Therefore, it is recommended to dynamically monitor hs-cTnT levels in the management of acute coronary syndrome (9). However, it is important to recognize that any condition that causes myocardial injury can result in elevated hs-cTnT levels (10). Consequently, this factor alone cannot determine the exact cause of myocardial injury. For instance, patients with stroke and chronic kidney disease may have higher hs-cTnT levels compared to healthy individuals (11, 12). In the case of patients with PE, PAH, systemic hypotension, and hypoxia can lead to cardiac ischemia, resulting in elevated hs-cTnT levels. Therefore, it is crucial to carefully monitor and assess the dynamic changes in markers of myocardial injury.

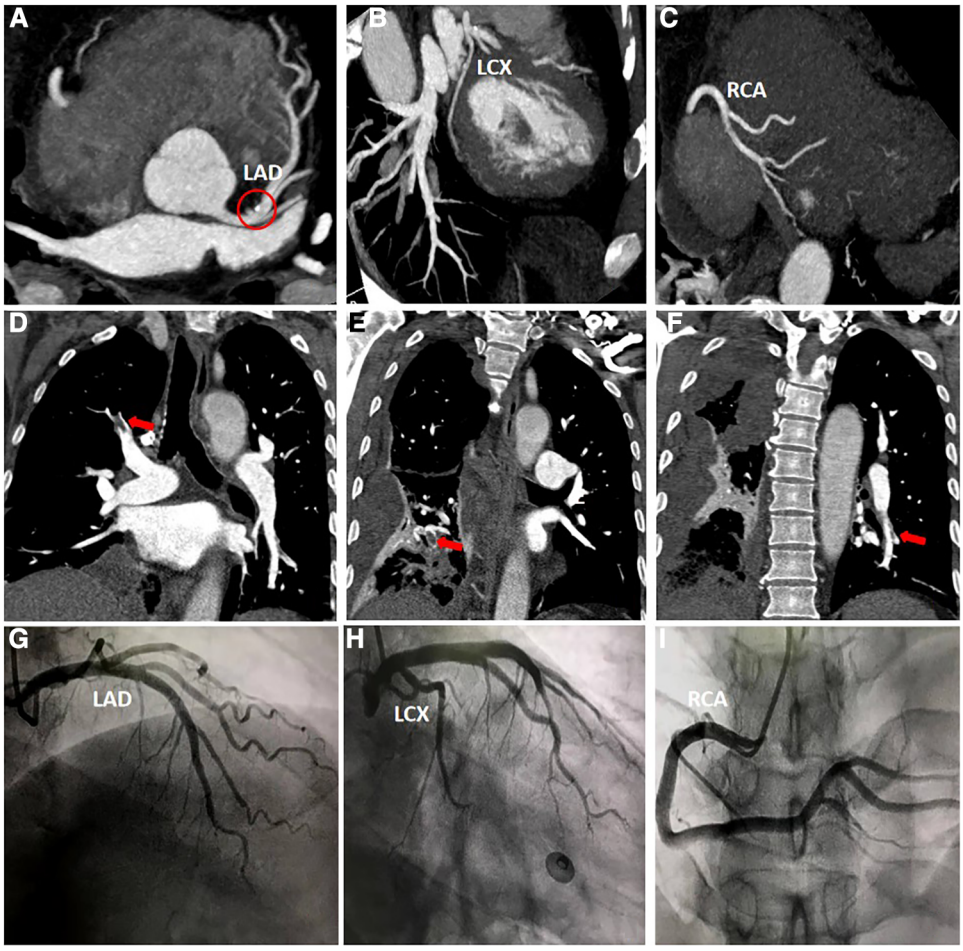


FIGURE 3
(A–C) Computed tomography coronary angiography scan. Calcification can be seen in the left anterior descending artery (red circle), and no other abnormalities were observed. (D–F) Computed tomography pulmonary angiography scan. The main findings revealed the presence of thrombi in the right upper lobe, right lower lobe, and left lower lobe. (H–J) Coronary angiography scan. The scan indicates that there are no significant narrowings or stenosis observed in either the left or right coronary arteries.

Echocardiography also plays a crucial role in the rapid and accurate diagnosis of PE. As a quick, practical, and highly sensitive method for detecting RV overload following PE, echocardiography not only aids in early risk stratification but also serves as a valuable tool in differentiating PE from other potentially fatal conditions such as STEMI, pericardial tamponade, and aortic dissection (13). By using echocardiography, regional segmental ventricular wall dyskinesia can be identified. Specifically, in PE patients, it is possible to observe RV hypokinesia and/or dilation (14). In the case of our patient, during the emergency bedside echocardiography, attention was primarily focused on LV movements and functions, inadvertently neglecting the assessment of RV movements and functions. To ensure a comprehensive evaluation in the future, it is essential to include reporting on the RV movements and functions.

## Conclusions

Despite the complexity and challenges in diagnosing PE, the prognosis for this patient was positive. By utilizing the ECG and taking into account the patient's history of ICH and results of coagulation function, echocardiography, and CTPA, the misdiagnosis rate for PE can be reduced. It is essential to emphasize comprehensive clinical reasoning, multidisciplinary collaboration, and meticulous treatment and nursing care for patients with ICH in order to significantly decrease the diagnostic delay in cases like this.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by The Biomedical Research Ethics Committee, West China Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

## Author contributions

MM and SL contributed equally to this work. They participated in the study design, data collection, imaging data analysis, and drafting of the manuscript. YH and WH provided valuable assistance in critically revising the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Notably, patient consent was obtained before writing the case report. We would like to thank the staff from departments of Cardiology and Radiology.

## Conflict of interest

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

## Publisher's note



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# Case Report: Hypertrophic cardiomyopathy with recurrent episodes of ventricular fibrillation and concurrent sinus arrest

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**Background:** Hypertrophic cardiomyopathy (HCM) is a serious hereditary cardiomyopathy. It is characterized morphologically by an increased left ventricular wall thickness and mass and functionally by enhanced global chamber function and myocellular contractility, diastolic dysfunction, and myocardial fibrosis development. Typically, patients with HCM experience atrial fibrillation (AF), syncope, and ventricular fibrillation (VF), causing severe symptoms and cardiac arrest. In contrast, sinoatrial node (SAN) arrest in the setting of HCM is uncommon. In particular, during VF, it has not been described so far.

**Case summary:** In this study, we report an 18-year-old woman patient with sudden cardiac arrest due to VF and successful cardiopulmonary resuscitation as the first clinical manifestation of non-obstructive HCM. Subsequently, a subcutaneous implantable cardioverter-defibrillator (ICD) was implanted for secondary VF prophylaxis. However, additional episodes of VF occurred. During these, device interrogation revealed a combined occurrence of VF, bradycardia, and SAN arrest, requiring a device exchange into a dual-chamber ICD. A heterozygous, pathogenic variant of the *MYH7* gene (c.2155C>T; p.Arg719Trp) was identified as causative for HCM.

**Discussion:** First published in 1994, the particular *MYH7* variant (p.Arg719Trp) was described in HCM patients with a high incidence of premature cardiac death and a reduced life expectancy. Electrophysiological studies on HCM patients are mainly performed to treat AF and ventricular tachycardia. Further extraordinary arrhythmic phenotypes were reported only in a few HCM patients. Taken together, the present case with documented co-existing VF and SAN arrest is rare and also emphasizes addressing the presence of SAN arrest (in particular, during VF episodes) in HCM patients when a distinct ICD device is considered for implantation.

KEYWORDS

hypertrophic cardiomyopathy, SAN arrest, *MYH7*, ventricular fibrillation, case report

Abbreviations

AA, atrial asystole; AF, atrial fibrillation; AS, atrial sensing; ATP, anti-tachycardic pacing; AVB, atrioventricular block; ECG, electrocardiography; ECM, extracellular matrix; HCM, hypertrophic cardiomyopathy; hiPSCs, human-induced pluripotent stem cells; HRV, heart rate variability; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVNC, left ventricular non-compaction; LVOT, left ventricular outflow tract; NGS, next-generation sequencing; SACT, sinoatrial conduction time; SAN, sinoatrial node; SCA, sudden cardiac arrest; S-ICD, subcutaneous ICD; SNRT, sinus node recovery time; SR, sarcoplasmic reticulum; TSH, thyroid-stimulating hormone; VES, ventricular extrasystoles; VF, ventricular fibrillation.

## Introduction

Hypertrophic cardiomyopathy (HCM) is a genetically determined cardiomyopathy characterized by the presence of increased left ventricular (LV) mass and wall thickness. Increasing the stiffness of the LV wall adversely affects the blood flow through the heart chamber by attenuating the tissue elasticity. Phenotypically, severe cardiac arrhythmia, heart failure, or sudden cardiac death may occur, reflecting the development of myocellular disarray and myocardial fibrosis (1). Recent data estimated an HCM prevalence of 1:200–500 (2). In familial HCM, 50%–60% of probands have pathogenic variants of genes encoding cardiac sarcomere proteins; however, the mutation frequency is quite lower in sporadic forms. In addition to the *MYBPC3* gene encoding for myosin-binding protein C, another important cardiac sarcomere protein is the myosin heavy chain beta (encoded by the *MYH7* gene). *MYH7* converts chemical energy into mechanical energy by enzymatic anti-tachycardic pacing (ATP) hydrolyses taking place at the myosin head (3).

Sinus node dysfunction (SND) has a prevalence of 1:600, mostly in cardiac patients above 65 years old with heart failure or coronary artery disease (4). SND is mainly age-dependent but rarely inherited or familial; so far, it is primarily treated by permanent pacemaker implantation (5). One of the first indicators of symptomatic SND is chronotropic incompetence and the inability of the heart rate to properly respond to stress and exercise (6). Other symptoms or ECG signs of SND are sinus bradycardia (<50 bpm), sinus arrest, sinoatrial block and tachycardia–bradycardia syndrome, and syncope or cardiac arrest (7).

With regard to the present HCM case, a concurrent occurrence of ventricular fibrillation (VF) and sinoatrial node (SAN) arrest was documented as an unusual ECG pattern. The repeated appearance of VF and survived sudden cardiac arrest (SCA) supports the severity of the HCM and the existence of the accompanying disturbed sinus node function revealed by sinus arrest at every single event. Furthermore, the resting ECG exhibits sinus bradycardia, which is one of the most common symptoms of SND (7).

## Case presentation

An 18-year-old woman survived an exercise-related SCA due to VF and immediate cardiopulmonary resuscitation. Initially, an underlying myocarditis was suspected. No indication of heart insufficiency had been detected. The patient has negated other symptoms such as angina pectoris, dyspnea, or previous arrhythmic events, like palpitations or syncopes, before the first hospitalization (**Table 1**). However, cardiac magnetic resonance imaging was not diagnostic but showed pathologic LV thickening of the anteroseptal and mid-anteroseptal and apical parts (**Figure 1**, up to 21 mm), leading to the diagnosis of non-obstructive HCM. MRI functional parameters were nearly normal [ejection fraction 53.5%, end-diastolic volume (EDV) 79.1 ml/m$^2$, end-systolic volume (ESV) 36.8 ml/m$^2$, ejection volume 42.4 ml/m$^2$, heart-minute volume 4.9 L/min, LV mass 83.3 g/m$^2$]. In addition to the diagnosed non-obstructive HCM with pathologic LV thickening of the anterior, middle, and anterior-septal and apical parts until up to 21 mm, an obstruction in the LV outflow tract (LVOT) could not be confirmed. Gadolinium application showed myocardial late enhancement and fibrosis, particularly in the hypertrophied LV sections. Ajmaline testing was negative for Brugada syndrome. Initially, a subcutaneous ICD (S-ICD) was implanted. Striking was a post-shock pacing with 22 pulses of 26 s duration. We interpret this as a depression of the sinus node due to the 65-J shock. A medication consisting of 1.25 mg/day bisoprolol and 1.25 mg/day ramipril was initiated upon discharge. The baseline ECGs showed a normal but bradycardic sinus rhythm (45 bpm; **Figure 2A**) and conduction at rest without any disturbances of repolarization or LV hypertrophy.

TABLE 1 Basic information.

| Basic information | |
|---|---|
| Sex | Female |
| Age | 18 years |
| Previous medical history | None |
| Alcohol intake | No |
| Asthma | No |
| Blood pressure (systolic/diastolic) | 98/59 mmHg |
| BMI | 24.5 |
| Chronic kidney disease | No |
| COPD | No |
| Coronary heart disease | No |
| Creatinine | 0.86 mg/dl |
| Diabetes | No |
| Dialysis | No |
| Drug abuse | None |
| Family history of stroke | None |
| Gastrointestinal bleeding history | None |
| Gout | No |
| Heart failure | No |
| Hemoglobin | 13.5 g/dl |
| History of cancer | None |
| HIV status | Negative |
| Hypertension | No |
| Liver cirrhosis | No |
| liver steatosis | No |
| Smoker | No |
| Stroke | No |

BMI, body mass index.

A stress-induced syncope event occurred 16 weeks after the first event. Interrogation of the S-ICD revealed a successful termination of VF by a single S-ICD shock, followed by a sinus node arrest of nearly 90 s hereafter. Subsequently, the S-ICD was replaced by a dual-chamber transvenous ICD system with correct positioning and regular function of the device leads. At discharge, the daily medication of the patient included 2.5 mg bisoprolol, 1.25 mg ramipril, and 300 mg magnesium and tromcardin.

After another period of 10 weeks, physical exercises again triggered another VF episode, which could be adequately terminated by the dual-chamber ICD. Subsequent device interrogation revealed adequate sensing of VF after a short period of previous ventricular tachycardia. Of note, atrial sensing (AS) showed an initially regular atrial activity aggravating into sinus bradycardia and cardiac arrest due to complete atrial

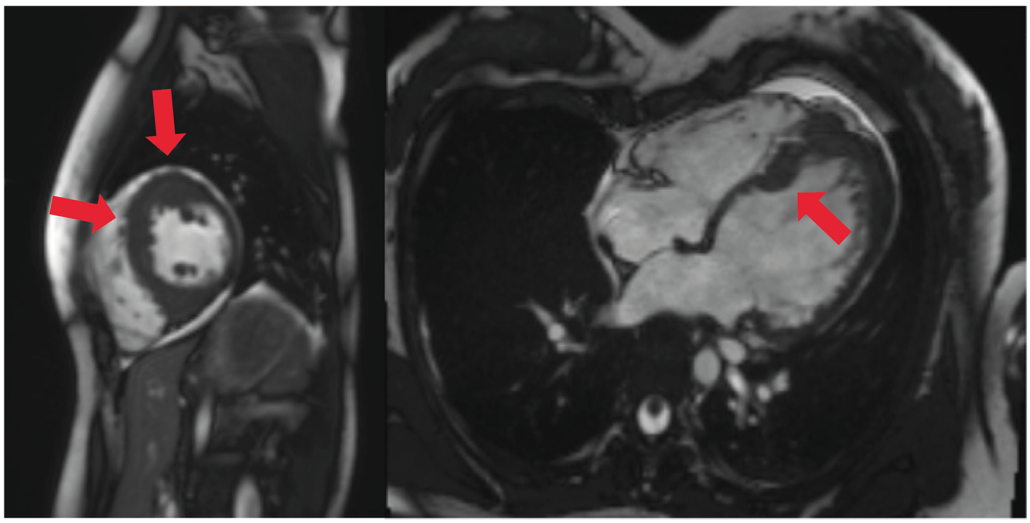

FIGURE 1
Cardiac MRI, four-chamber view. Depicted long- and short-axis cine images. Red arrows: thickened LV septal and apical wall (up to 20 mm); small apical pericardial effusion.

asystole (AA) but still concurrent VF of low amplitude. This illustrates a rare ECG registration and co-event of VF and SAN arrest or AA (**Figures 3A,B**).

Using a multi-gene-panel sequencing approach, a pathogenic and known heterozygous non-synonymous variant (p.Arg719Trp) (ACMG class 5: PS3, PS4_M, PM1, PM2, PP3) of the *MYH7* gene was identified. This variant was reported in >10 unrelated HCM patients and is nearly absent in controls (gnomAD: MAF 0.003%), further supporting its pathogenicity. Other NGS panel genes for inherited arrhythmia forms or cardiomyopathies showed no further pathogenic variant.

A beta-blocker therapy was established to prevent exercise- or stress-induced fatal arrhythmic events. Nevertheless, another exercise-induced VF episode occurred when the patient was climbing stairs, 83 weeks after the first event. Device data initially demonstrated sinus tachycardia with cycle lengths from 385 to 400 ms in addition to ventricular extrasystoles (VES). Notably, interrogated ICD data again demonstrated a co-occurrence of ventricular tachycardia degenerating into VF and accompanying a decelerating AS to sinus bradycardia followed by asystole (**Figures 4A,B**). Although this episode of VF was regularly terminated through the first ICD shock, VF re-occurred in the following minutes and was again accompanied by sinus bradycardia and finally sinus asystole. Another two ICD shocks, including ineffective defibrillation, were necessary to adequately terminate the VF/AA. However, fast shortening of the ventricular cycle length and severe degeneration of the signal amplitude in the EGM channel with partial undersensing of single events exposed an ineffective detection sensitivity. The dual-chamber ICD was reprogrammed to reduce the electrode threshold in the right ventricle to 0.3 mV because the minimum amplitude of the last VF episode was 1.4 mV.

Another VF episode occurred during a psychotherapeutic appointment 3 months later. Notably, it initially emerged during the resting phase without physical exercise, followed by inadequate termination via the ICD through several shocks. Altogether, three particular episodes of VF were registered in the ICD data. The first episode was defibrillated twice, the second one was successfully terminated through ATP, and the third was inadequately terminated by another single ICD shock. During the approximately 7 min of lasting arrhythmia episode, cardiopulmonary resuscitation was conducted until emergency physicians arrived. After intravenous administration of amiodarone (300 mg), the ICD effectively terminated the VF episode by a shock intervention, and a reprogramming of the dual-chamber ICD was conducted due to undersensing.

During hospitalization, amiodarone treatment was initiated (initial saturation treatment and then 200 mg/day). Furthermore, diltiazem therapy (2 × 60 mg/day) was initiated. No further severe cardiac arrhythmic events have been detected since then (**Table 2**).

Notably, since April 2022, the patient has suffered from the first symptoms of hyperthyroidism [thyroid-stimulating hormone (TSH) < 0.01 µIU/ml, anti-Tg-RO = 1,771.0 IU/ml, anti-TPO Roche = 312.0 IU/ml]. Although amiodarone-induced functional abnormalities in thyroid homeostasis are quite common, an autoimmune-induced hyperthyroidism could not yet be excluded. Nevertheless, thyreostatic therapy was initiated with thiamazole and Irenat. Considering the young age of the patient and the long-term toxicity of amiodarone, a transition to another less toxic antiarrhythmic medication such as sotalol would be preferable, especially to reduce the risk of hyperthyroidism. A medication change has not been conducted yet due to severe psychological concerns of the patient during the follow-up related to a replacement of amiodarone

The family history for HCM, SCD, or SCA was unremarkable; a cascade of clinical and genetic testing was offered to the family but was not completed.

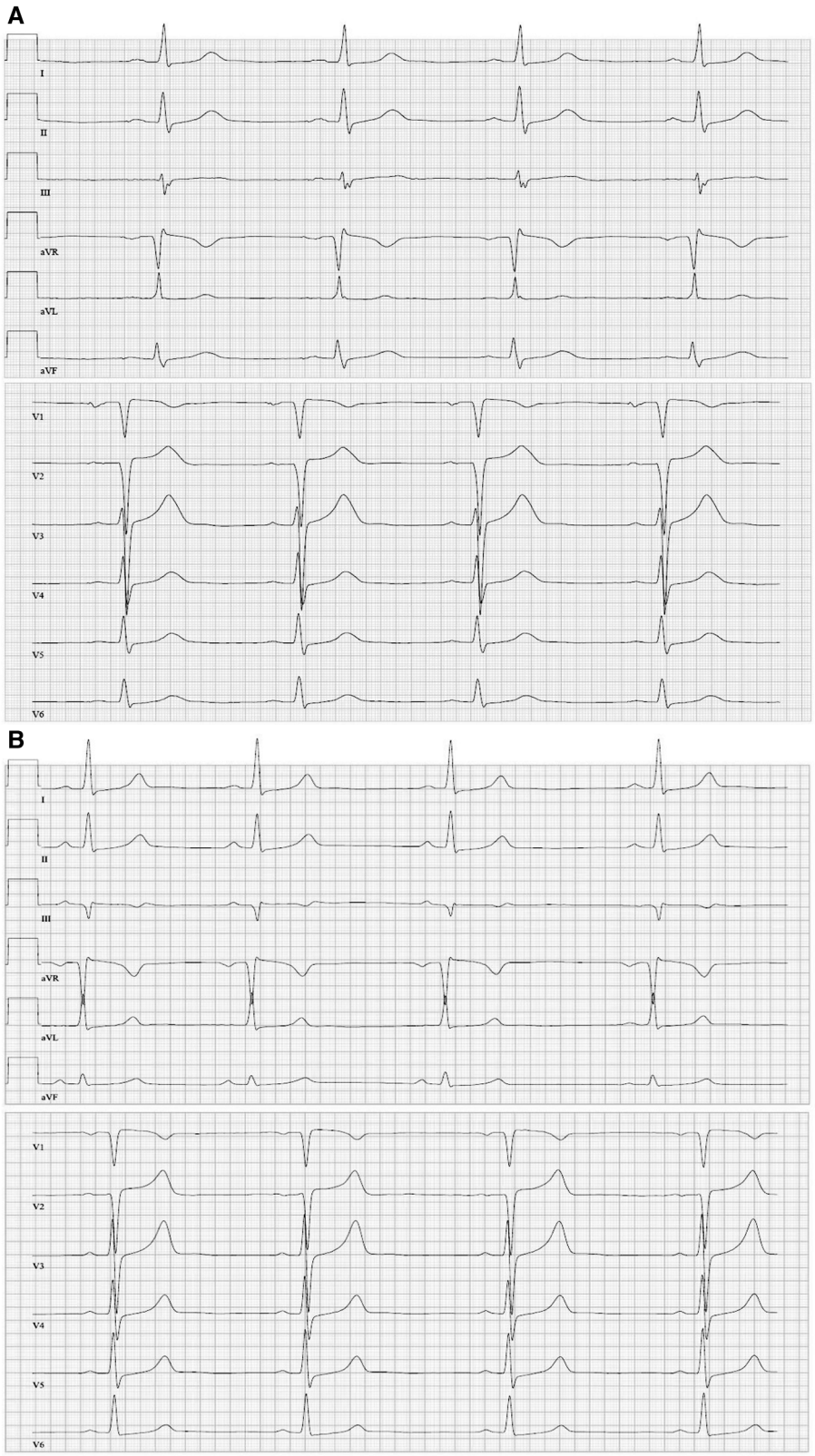


FIGURE 2
(**A**) Twelve-lead resting ECG (June 2016) (1.25 mg/d bisoprolol) before the first cardiac event depicting sinus bradycardia (45 bpm), regular conduction and repolarization, and tall *T*-waves. (**B**) Twelve-lead resting ECG (January 2018) (medication: 200 mg twice/day amiodarone, 60 mg twice/day diltiazem) with sinus rhythm and a heart rate of 50 bpm.

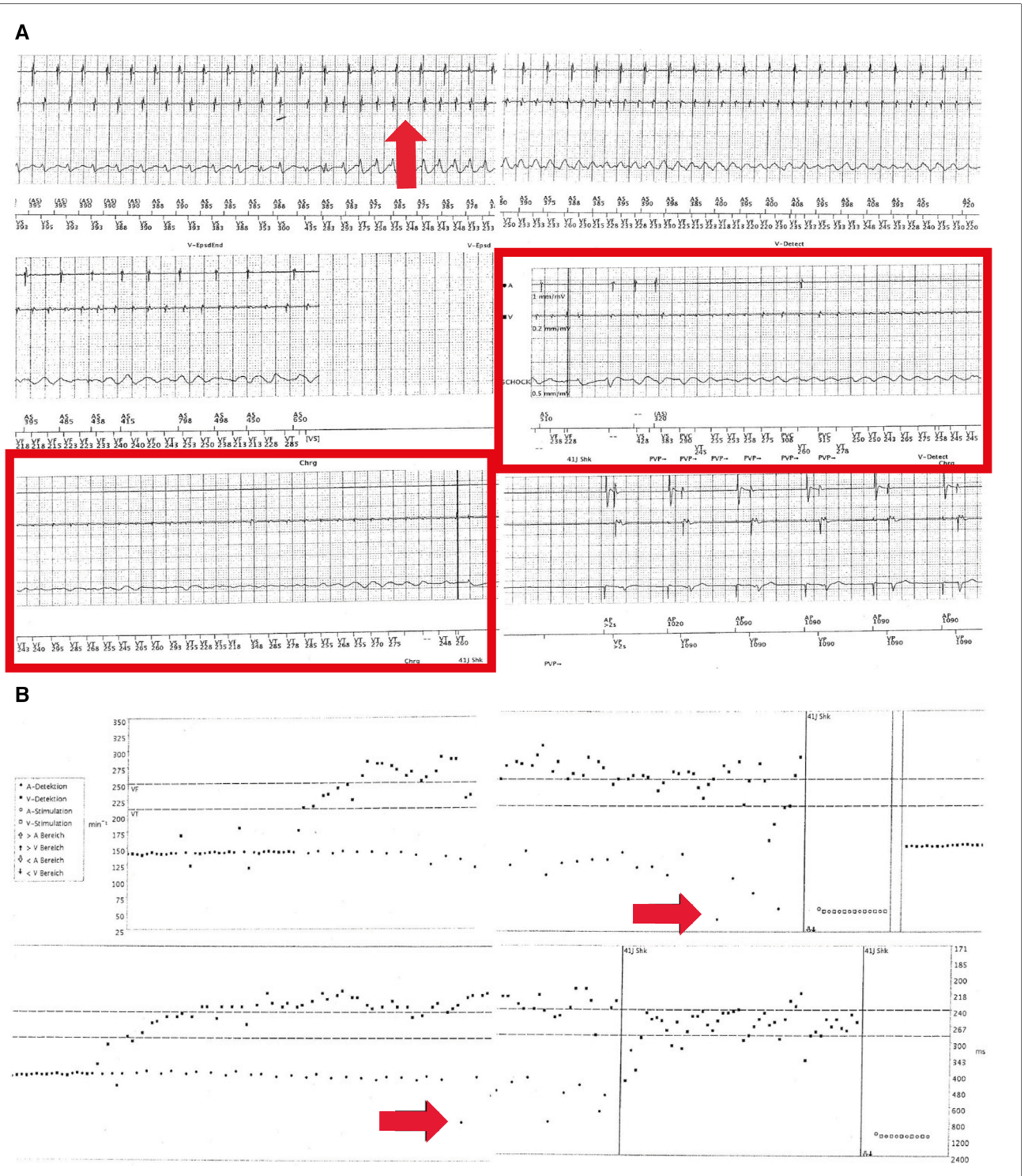


FIGURE 3
(**A**) Electrograms during the exercise of the dual-chamber ICD in August 2016. Sensing of a spontaneously occurring ventricular tachycardia (approximately 230 ms, 260 bpm, red arrow in the left upper panel) can be observed. Of note, initially regular atrial sensing (approximately 400 ms or 150 bpm; exercise-related) (upper two leads in the left upper panel) but further degeneration into VF (red arrow in the right upper panel) and sinus bradycardia and arrest (middle panels, red rectangle) can be seen. In the lower panel, ventricular shock (41 J) and hereafter atrial pacing (1,000 ms or 60 bpm) and ventricular sensing indicated a recurrence of regular ventricular activity. (**B**) Histograms corresponding to (**A**). Spontaneously occurring ventricular tachycardia and fibrillation (upper panel) arising from sinus tachycardia (exercise, 150 bpm) (red arrow in upper panel) can be observed. In the lower panel, a red arrow indicates the occurrence of sinus bradycardia and sinus node arrest during VF. Vertical lines indicate an ICD shock (41 J) and atrial stimulation.

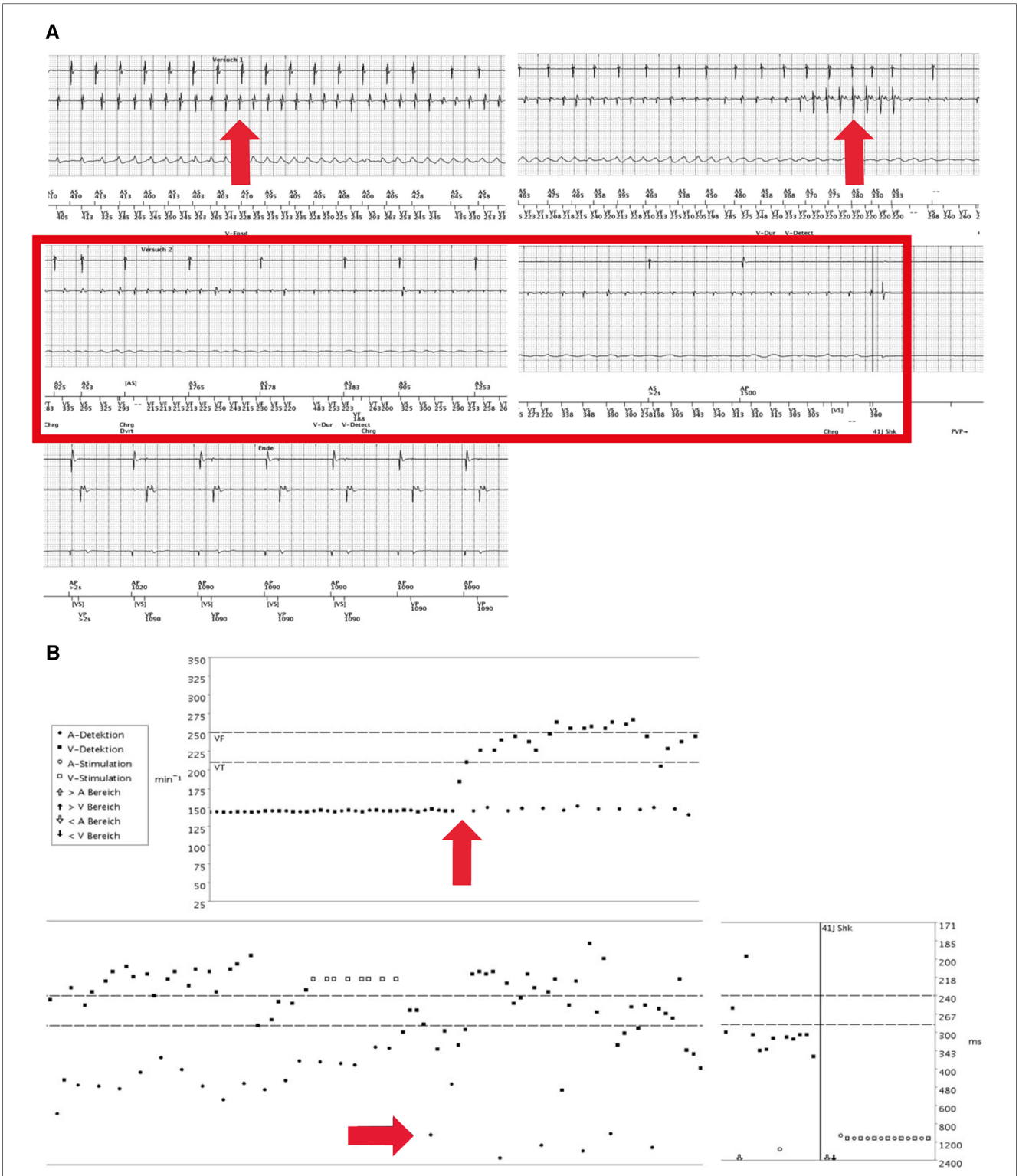


FIGURE 4
(A) First electrograms of the dual-chamber implantable cardioverter-defibrillator (ICD) (during physical exercise, September 2017). Re-occurrence of a VF episode (red arrow in left upper panel), again induced by physical exercise. Remarkably, during persisting VT, the atrial sensing aggravated again into sinus bradycardia and finally sinus node arrest until the second ICD shock, hereafter, atrioventricular pacing (right middle and left lower panels). (B) Electrograms (September 2017). ICD sensing shows a VF at the ventricular level and atrial tachycardia that further decelerates (red arrows). Vertical lines indicate ICD shock (41 J each) to restore regular and paced rhythm and rhythm restoration but re-occurrence of VF and sinus node arrest.

TABLE 2 Timeline.

| Timeline | |
|---|---|
| Week 1 | SCA due to VF as the first clinical symptom. After successful cardiopulmonary resuscitation, the diagnosis of HCM was made |
| Week 4 | S-ICD implantation for secondary SCA prophylaxis |
| Week 16 | Recurrence of a VF episode during stress, sufficiently terminated by S-ICD; subsequently, documented sinus node arrest and asystole for >90 s |
| Week 17 | Device exchange of the S-ICD to a dual-chamber (DDD-) ICD |
| Week 27 | Genetic testing revealed a pathogenic heterozygous non-synonymous variant (p.Arg719Trp) of the *MYH7* gene |
| Week 27 + 1 day | Re-occurrence of stress-induced VF episode (without beta-blocker therapy) and adequate shock termination by the ICD device (**Figures 3A,B**); documented co-existing SAN arrest during VF; initiation of beta-blocker treatment |
| Week 83 | Exercise-induced VF during beta-blocker therapy and need for three ICD interventions to restore normal rhythm; partially ineffective defibrillation with rapid shortening of the ventricular cycle length and severe degeneration and low-amplitude signaling in the EGM; subsequently, the ICD was reprogrammed to increase sensitivity and reduce the detection threshold in the right ventricle (to 0.3 mV; minimum VF amplitude: 1.4 mV) (**Figures 4A,B**) |
| Week 95 | An initial emerging VF storm event occurred during a psychotherapeutic consultation, followed by insufficient termination via the ICD; cardiopulmonary resuscitation and intravenous administration of amiodarone, together with external defibrillation to terminate VF; initiation of oral amiodarone and diltiazem |
| Follow-up | No VF recurrences have been detected over 4 years |

# Discussion

First described in 1994, the *MYH7* p.(Arg719Trp) mutation was initially associated with a high incidence of premature death and, thereby, a significant decrease in average life expectancy (8). *In silico* prediction models, particularly designed for the assessment of non-synonymous variants in HCM, confirmed the relevance of the variant. Furthermore, this underlines previous findings (9) because a significant increase in disease-associated missense variants could be localized to the spherical region where the p.(Arg719Trp) variant is located (10).

Remarkably, around 31% of patients with *MYH7* mutations have ventricular conduction system impairments (mainly bundle branch blockade). However, cases with documented concurrent decelerating AS and asystole in combination with VF are rare in the literature. This phenotypic discrepancy between atrial and ventricular rhythm represents some uniqueness in the present case and emphasizes considering SAN arrest in the setting of HCM and VF before deciding to implant a distinct ICD device. In this line, invasive electrophysiological studies of 155 HCM patients revealed an abnormal sinus node recovery time (>1,500 ms) in 7% (11). Moreover, the co-existence of HCM and SND as primary heritable diseases is rarely described; in a single, larger study, SND (including sinus bradycardia and sinus node arrest) was described in 17% of an HCM cohort of 101 enrolled patients (12).

Deleterious *MYH7* missense variants and other overlapping phenotypes, e.g., HCM with LV non-compaction (LVNC), have been reported (13). Thus, considering the heterogeneous arrhythmic cardiac phenotype in this case, it remains unresolved whether the pathogenic *MYH7* missense variant can directly result in such an extraordinary arrhythmia presentation as seen here. Of note, longer episodes of VF may lead to a high secretion of adenosine that may compromise regular SAN function. The latter may be in line with the clinical observation that aminophylline may be useful in restoring cardiac rhythm in this setting (14–16).

Pathogenic MYH7 variants, as described in the present case, belong to the most common genetic etiologies for HCM, with an involvement of about 15%–25% in all HCM patients. Clinical manifestations can also vary depending on the specific gene and causative variant. They can reach from ventricular tachycardia (VT) or supraventricular tachycardia and syncopal episodes to minor severe symptoms such as chest pain and dyspnea on exertion (17). Recently, Higuchi et al. (18) reported an association between HCM and first-degree atrioventricular block (AVB) as another symptomatic manifestation by analyzing 414 patients with HCM. Among these, 96 patients were diagnosed with AVB, representing 23% of all enrolled patients.

Taking into account the implanted dual-chamber (DDD-) ICD device, one could suggest an Atrium, Atrium, Inhibited (AAI) pacing mode for appropriate SND treatment (19). Nevertheless, this approach might not be applicable to address the SAN arrest in the described case because the episodes of SAN arrest only occur simultaneously with VT and VF, which would be inadequately treated by single atrial pacing. Further, AAI pacing was shown to be the opportune mode for patients suffering from SND and coronary heart disease, atrial fibrillation (AF), or atrioventricular (AV) block but not for HCM patients. Overall, AAI pacing was assumed to have a higher suppressive effect on atrial arrhythmias than ventricular pacing (20).

SND in the setting of VF episodes and, in particular, hereafter manifesting as SAN arrest may lead to the necessity of a dual-chamber transvenous ICD system to treat atrial and ventricular arrhythmias. The clinical severity—in contrast to the moderate LV hypertrophy—due to the extraordinary arrhythmic phenotype also required additional medical, antiarrhythmic treatment.

Remarkably, the identified pathogenic *MYH7* variant (p.Arg719Trp) has already been reported to cause unexpected arrhythmic events, e.g., in the case of a young 12-year-old girl. The patient suffered from dizziness and chest discomfort while walking around. Furthermore, she experienced syncopal attacks with a heart rate drop to 40 bpm. ECG exhibited an AVB of the third degree (AVB III°) in combination with a complete left bundle branch block. Whole exome sequencing also identified the heterozygous missense variant of *MYH7* (p.Arg719Trp) and no other variants of arrhythmia genes (21). Considering this described phenotype is related to the particular *MYH7* variant, atrial pacing might be suitable for an advanced therapeutic approach. So far, the "coupled clock" is a widely accepted model of SAN automaticity and proposes a functional interplay (coupling) between the activity of pacemaking ion channels of the cell plasma membrane and the activation of the $Na^+/Ca^{2+}$ exchanger (NCX1) by spontaneous diastolic $Ca^{2+}$ release from the sarcoplasmic reticulum (SR),

mediated by RYR2 receptors. Hsieh et al. (22) established two human-induced pluripotent stem cell (hiPSC) lines carrying an MYH7 variant (p.Arg723Cys); at mature stage, the generated derived mutant cardiomyocytes displayed HCM-consistent phenotypic characteristics, such as hypertrophy, altered calcium handling and metabolism, and also arrhythmias. Notably, hiPSC-derived cardiomyocytes investigated before emerging of known HCM characteristics exhibited dysregulated extracellular matrix (ECM) remodeling, limited formation of focal adhesion expressed by interrupted cell–ECM adhesion, and altered integrin expression. Altered intracellular calcium handling due to *MYH7* variants may also influence the $Ca^{2+}$-dependent activity of proteins involved in SAN automaticity.

### Study limitations

SAN functional parameters, in particular SNRT and SACT, HR parameters (max/min) during day and night, and HRV (e.g., before and after VF storm and successful treatment) were not available. Thus, it could not be determined whether SAN dysfunction alone led to any symptoms. Furthermore, the evaluation of SAN function upon adenosine bolus and subsequent aminophylline or theophylline treatment and also atropine treatment to restore SAN rhythm could not be analyzed because the focus was set on anti-tachycardic intervention (15, 16). Consequently, due to the lack of specific SAN function data, it must be acknowledged that SAN arrest (SAN pacemaker/automaticity arrest) from the SAN exit block and conduction impairments cannot be distinguished in this case.

### Future directions

The heterogeneous and unexpected phenotype in this case represented by episodes of VF and concurrent SAN arrest may lead to the necessity of a dual-chamber transvenous ICD system to treat atrial and ventricular arrhythmias simultaneously. Thus, when approaching patients with genetically determined cardiomyopathies such as HCM, in particular, with causative *MYH7* variants, a treatment for bradycardic arrhythmias should also be considered before deciding to implant a distinct ICD device.

## Conclusion

Although the underlying *MYH7* mutation for HCM and (recurrent) VF has been known for almost 30 years, the particular phenotype with SAN arrest has not been noted in detail. Assessing not only for ventricular but also bradycardic arrhythmias might be useful in particular HCM patients and distinct gene mutations.

## Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://www.ebi.ac.uk/ena. Study name: 877a8bc8-06ec-4f7a-a195-3b7ed94e864f. Accession numbers: PRJEB64497; ERP149670.The deposited data will become public on the 15 November, 2023.

## Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the legal guardians/next of kin of the participants in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

RW was the attending physician, and JW was the supervising professor responsible for this case at the Augusta Hospital in Düsseldorf. ES was the attending physician and the supervising professor at the Institut für Genetik von Herzerkrankungen (IfGH) in Münster, in which the genetic examination was conducted. JH is a PhD student at the IfGH who has gathered all the information about this patient and has written this case report. SD was the supervising postdoc at the IfGH, who has supported JH with this work. All authors contributed to the article and approved the submitted version.

## Conflict of interest

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

## Publisher's note

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# Case Report: Early diagnosis and bevacizumab-based chemotherapy for primary pericardial mesothelioma: a case with occupational asbestos exposure history

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**Background:** Primary pericardial mesothelioma (PPM) is an exceedingly rare malignant cancer and has a poor prognosis, which has been partly attributed to its frequently delayed diagnosis due to its nonspecific syndromes, its similar presentation to benign pericardial diseases, and its non-definitive etiology. In many PPM cases, the time from presentation to definite diagnosis may last for several months or even over one year. Unlike pleural mesothelioma, the relationship between PPM and asbestos exposure remains unsettled. To date, there is no consensus on the treatment of PPM.
**Case report:** The patient is a 57-year-old male who had nonspecific syndromes and inconclusive image findings. The occupational long-term asbestos exposure history of this patient raised our concerns regarding potential malignancy when confronted with unexplained pericardial effusion accompanied by cardiac tamponade. The heightened suspicion prompted us to perform pericardiocentesis and biopsy on the third day after admission to our department. An early diagnosis of PPM was established by the pathological and immunohistochemical evaluation of the biopsy specimen two weeks after admission. Positron emission tomography-computed tomography revealed that the lesion was localized at the anterior part of the mediastinum without distant metastasis. This patient refused to receive cardiac surgery. He subsequently underwent six cycles of chemotherapy (cisplatin plus pemetrexed) in combination with bevacizumab (a humanized anti-VEGF antibody) as the first-line treatment, resulting in complete relief of symptoms and satisfactory outcomes with no complications. Four months after the first course, the patient initiated a second course of chemotherapy with a similar regimen, but he opted to discontinue the medical treatment after the initiation of the second course. The patient was transferred to the hospice care unit and unfortunately expired one year after the initial presentation.
**Conclusion:** We present a case of an early multidisciplinary clinical approach to diagnose and manage PPM with consideration of occupational asbestos exposure history and clinical symptoms. Bevacizumab-based chemotherapy remains an option for the treatment of PPM.

KEYWORDS

primary pericardial mesothelioma, asbestos, occupational exposure, bevacizumab, chemotherapy

## Introduction

Primary pericardial mesothelioma (PPM) is an exceedingly rare malignant cancer accounting for only 0.7% of all malignant mesotheliomas, with an annual standardized incidence rate of approximately 0.36 per 10 million person-years (1–5). PPM has a poor prognosis with a median survival of less than six months (1, 4–6), which has been partly attributed to its frequently delayed diagnosis (6–8). In many PPM cases, the time from presentation to definite diagnosis may last for several months (4–7) or even over one year (6, 9–14). This slow recognition is likely due to its nonspecific syndromes, its similar presentation to benign pericardial diseases, and its non-definitive etiology (1, 6–8, 10–15). It has been suggested that early detection of this disease is the only hope for survival (2). Unlike pleural mesothelioma, the relationship between PPM and asbestos exposure remains unsettled; some investigators reported an association with asbestos exposure (3, 4, 16), while others reported no or weak correlation (6–10, 12–15, 17–19). So far, there is no consensus on the treatment of PPM, although the survival benefit of chemotherapy has been shown to be superior to that of surgery (6). In almost all reported cases with chemotherapy, a doublet regimen, cisplatin plus pemetrexed, was used as the first-line treatment (6, 7, 9–11, 17, 18, 20, 21). Here we present a case of early diagnosis of PPM promoted by the indication of the patient's occupational asbestos exposure history and clinical presentations. This patient was subsequently treated with bevacizumab (a humanized anti-VEGF antibody) (2) combined with first-line chemotherapy.

## Case presentation

A 57-year-old male patient who presented with left-sided chest tightness, frequent dry cough, progressive orthopnea, and a weight loss of 5 kg over a 4-month period was admitted to our department on 18th July 2022 (Day 0). The patient complained that he began to feel chest tightness and dry coughing at night about a month. He had an unremarkable medical history, was an active smoker consuming 1 pack of cigarettes every 3 days and had a 20-year history of occupational asbestos exposure from his work as an interior designer. He frequently came into contact with sound and heat insulation material containing high levels of asbestos and did not consistently use a face mask.

The patient's body weight and length were 73.4 kg and 173 cm, respectively, and his blood pressure, heart rate, and respiratory rate were 102/67 mmHg, 81 beats/minute, and 24 breaths/minute, respectively. The physical examination was notable for bilateral pitting edema of the lower legs. Muffled and irregular heart sounds were detected with jugular vein elevation. Electrocardiography showed sinus tachycardia without abnormal T waves or ST segment changes. The initial laboratory analysis revealed that the white blood cell count was 16,390 cells/mm$^3$, the BUN/creatinine ratio was 31/1.16, the high sensitivity troponin I level (hs-troponin I) was 4.3 pg/ml, NT-proBNP was 418.0 pg/ml, and carcinoembryonic antigen (CEA) was 1.9 ng/ml. Chest x-ray showed cardiomegaly and pericardial effusion (**Figure 1A**). Computed tomography (CT) scans revealed massive pericardial effusion with thickened pericardium and bilateral pleural effusion (**Figure 1B**).

Pericardiocentesis was performed on Day 1 to relieve the symptoms of the unexplained pericardial effusion, and the drainage of pericardiocentesis came out with a purulent and bloody effusion. In light of his history of occupational long-term asbestos exposure and clinical data, a thoracoscopic pericardial biopsy was conducted on Day 3. Subsequent cytopathology analysis of pericardial effusion showed clustered mesothelial cells (**Figure 2A**). Pathological evaluation of the biopsy specimen revealed the presence of several abnormalities, including an overgrowth of mesothelial cells, changes in the nuclei of these cells, increased collagen in the connective tissue, and the accumulation of fibrinoid exudates (**Figure 2B**). Immunohistochemistry shows positive mesothelial 183 markers (cytokeratin 5/6 and calretinin) and negative pulmonary 184 epithelial markers (thyroid transcription factor-1 and 185 carcinoembryonic antigen). The tumor cells also exhibited a loss of 186 expression of methylthioadenosine phosphorylase and retained 187 expression of BRCA1-associated protein 1 (**Figure 2C–2E**). Positron emission tomography-computed tomography (PET-CT) was then performed to detect potential metastasis on Day 10. The result showed 18F-fluorodeoxyglucose (FDG) uptake in the anterior part of the mediastinum without distant metastasis (**Figure 3**). With these pathological findings, the diagnosis of PPM was made on Day 11.

After the diagnosis, our patient was recommended to receive a combined cardiac tumor debulking surgery and palliative chemotherapy, but he opted for palliative chemotherapy only, which started on Day 33. For cycles 1–6, the patient was administered Avastin (bevacizumab) at a dose of 5 mg/kg, Cisplatin at a dose of 50–60 mg/m$^2$, and Alimta (Pemetrexed) at a dose of 400–500 mg/m$^2$. The patient tolerated the first cycle well and experienced mild appetite loss and nausea. The patient received acupuncture as an adjuvant therapy aiming to minimize the treatment-related symptoms. There were no other treatment-related side effects reported. A follow-up chest x-ray and CT scan immediately after the 6 cycles of chemotherapy on Day 149 revealed normal heart size, no pleural or pericardial effusion (**Figure 1C**), and lessened pericardial thickening (**Figure 1D**). The follow-up laboratory analysis revealed that the white blood cell count was 5.89 cells/mm$^3$, the BUN/creatinine ratio was 15/1.03, the hs-troponin I was 5.8 ng/ml, NT-proBNP was 871 pg/ml, and CEA was 1.6 ng/ml. Subsequently, the patient was discharged with minimal side effects, such as mild body weight loss, appetite loss, and fatigue. On Day 270, the patient initiated a second course of chemotherapy due to an escalation in episodes of arrhythmia and mild dyspnea. However, the patient opted to discontinue the medical treatment after the initiation of the second course due to side effects. We did fully discuss with the patient and family members regarding the treatment. The patient also received mental consultation from experts. The patient nevertheless refused to receive further treatment. Subsequently, the patient was transferred to the hospice care unit and unfortunately expired on Day 355. The timeline of the major events during the episode of care for this patient is summarized in **Figure 4**.

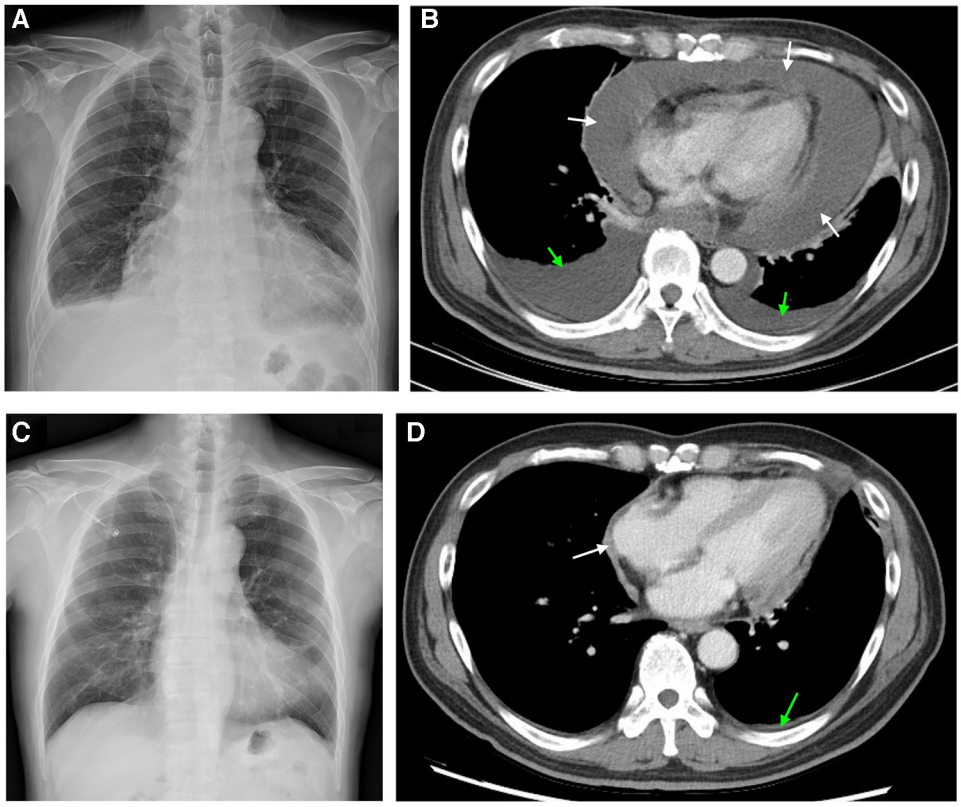


FIGURE 1
Chest image findings before and after 6 cycles of chemotherapy. (**A**) x-ray image shows cardiomegaly with pericardial effusion and blunted left costophrenic angle. (**B**) Computed tomography image shows pericardial effusion with noticeable pericardial thickening and bilateral pleural effusion. (**C**) x-ray image showed normal heart size without pleural effusion. (**D**) Computed tomography image showed subsiding pericardial effusion and lessened pericardial thickening. White and green arrows indicate the areas of pericardial and pleural effusion, respectively.

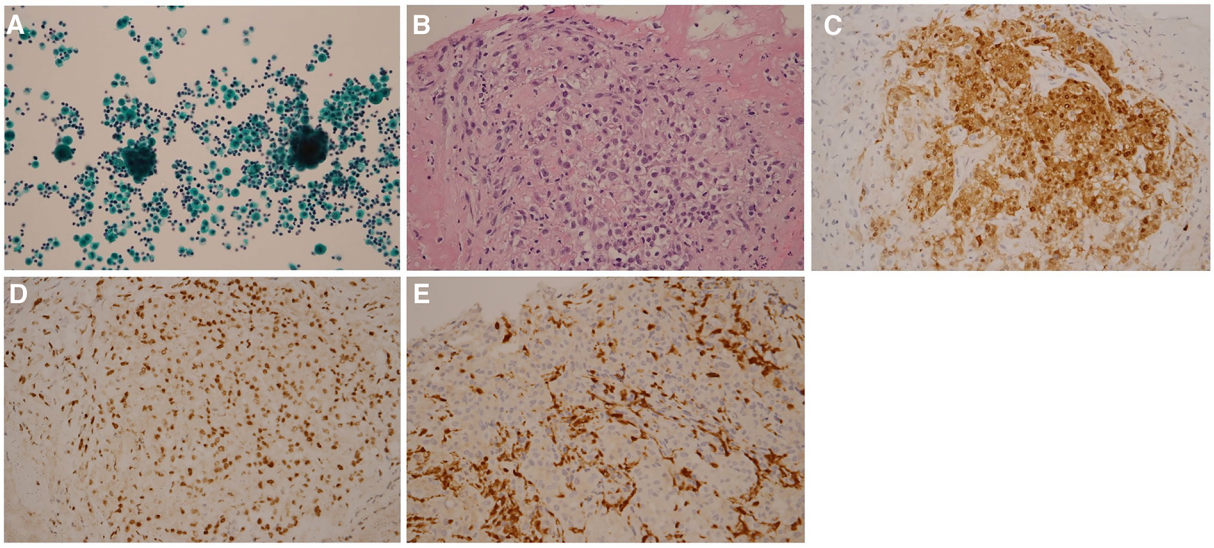


FIGURE 2
Pathology findings. Cytopathology analysis of pericardial effusion shows clustered mesothelial cells (**A**) H&E stain analysis of pericardial biopsy shows atypical mesothelioma cells (**B**) Immunohistological analysis of pericardial biopsy shows that tumor cells exhibited positive staining of cytokeratin 5/6 (**C**), retained expression of BRCA1-associated protein 1 (**D**), and loss of expression of methylthioadenosine phosphorylase (**E**) Magnifications: 10x in panel (**A**), 40x in panel (**B**), and 20x in panels (**C**–**E**).

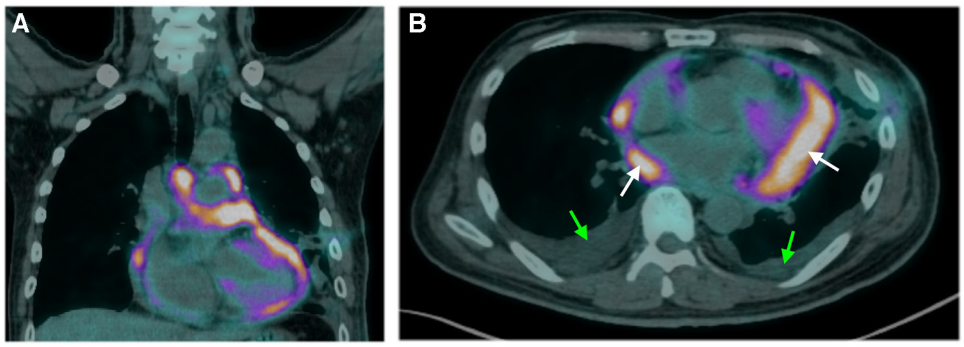


FIGURE 3
Findings of positron emission tomography-computed tomography. Sagittal (A) and axial (B) images illustrate diffuse, irregular nodular uptake of fluorodeoxyglucose in the anterior mediastinum with no metastasis. White and green arrows indicate the areas of pericardial and pleural effusion, respectively.

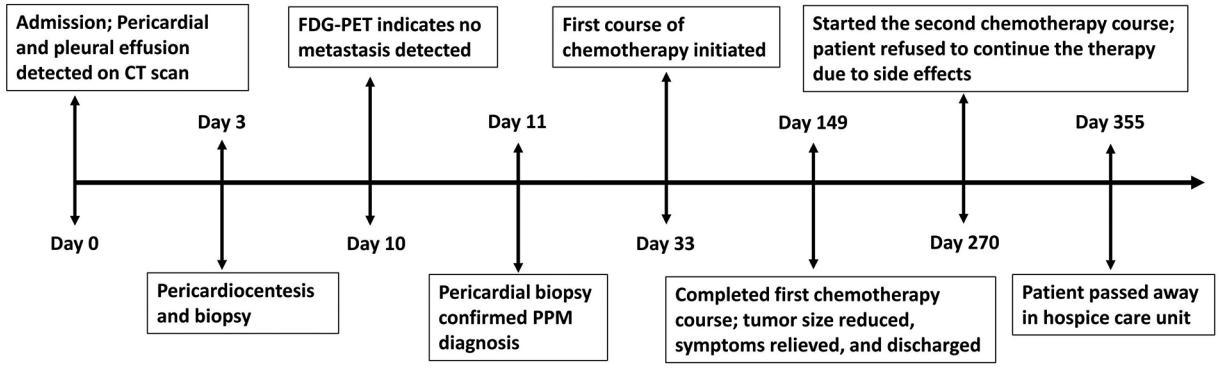


FIGURE 4
Timeline summarizing the major events during the episode of care for the patient. CT, computed tomography; FDG, 18F-fluorodeoxyglucose; PPM, primary pericardial mesothelioma.

## Discussion

This report describes a patient with PPM who had an occupational long-term asbestos exposure history and who received chemotherapy only after diagnosis resulting in satisfactory outcomes. In this case, early diagnosis of PPM and bevacizumab-based chemotherapy are two main points that deserve to be highlighted.

Our patients underwent a total of 6 cycles of chemotherapy in the first course with a combination of bevacizumab as the first-line treatment, resulting in complete relief of symptoms and satisfactory outcomes. This choice was made based on the patient's preference for palliative chemotherapy over surgical intervention following a full discussion of treatment plans. Due to its rarity, there is no consensus on the treatment of PPM (1, 2, 5, 6). Currently, treatment options for PPM are adapted from the more often studied diffuse pleural mesotheliomas (1, 2, 18); surgery is the most widely-used approach, followed by chemotherapy (5, 6, 18). However, in a review of 103 published PPM cases, it was found that chemotherapy, but not surgery, provided a statistically significant survival benefit. Of note, a doublet regimen, cisplatin plus pemetrexed, was used as the first-line treatment in almost all reported cases with chemotherapy (6, 7, 9–11, 17, 18, 20, 21). In only one reported case (14), a combination of bevacizumab, cisplatin, and pemetrexed was used as the first-line treatment for PPM, but unfortunately, the tumor remained stable after eight cycles of chemotherapy. Bevacizumab is a humanized anti-VEGF antibody that inhibits angiogenesis (2). In our case, the patient well tolerated the first course of chemotherapy in combination with bevacizumab with a satisfactory outcome. Unfortunately, the patient opted to discontinue the medical treatment after the initiation of the second course and subsequently expired. The use of bevacizumab has been shown to be promising in the treatment of malignant pleural mesothelioma (22). The addition of bevacizumab to standard-of-care chemotherapy has provided a novel therapeutic option in a range of advanced cancers (23). Several randomized controlled trials have been conducted to investigate its efficacy in different types of cancers, including colorectal cancer, lung cancer, breast cancer, renal cell carcinoma, cervical cancer, glioblastoma, and ovarian cancer (23). In light of this fact, we still suggest that bevacizumab may also be considered as an option for the treatment of PPM.

The diagnosis of PPM remains challenging, which leads to the situation that the diagnosis is usually made after surgery or at autopsy (2, 10, 15, 18, 21). The delayed diagnosis of PPM may be due to its nonspecific syndromes, its similar presentation to benign pericardial diseases, and its non-definitive etiology (1, 6–8, 10–15). Our patient also initially had nonspecific symptoms and inconclusive image findings. However, the occupational long-term asbestos exposure history of this patient raised our concerns regarding potential malignancy when confronted with unexplained pericardial effusion accompanied by cardiac tamponade. As a result, from the time of admission, it only took 11 days for us to establish a definitive diagnosis. The etiology of PPM is unclear. The relationship between PPM and asbestos exposure remains controversial (3, 4, 6–10, 12–19). Our finding regarding the early detection of PPM supports the notion that asbestos exposure plays a role in the pathogenesis of PPM. Although the mechanisms underlying this pathogenesis remain unclear, it has been proposed (24) that, after asbestos fibers are inhaled deeply into the lung and penetrate the pleural space, the interaction of asbestos fibers with mesothelial cells and inflammatory cells is thought to initiate prolonged cycles of tissue damage, repair, and local inflammation, which finally lead to carcinogenesis of malignant mesothelioma.

In conclusion, we present a case of an early multidisciplinary clinical approach to diagnose and manage PPM with consideration of occupational asbestos exposure history and clinical symptoms. Although the patient expired after the premature discontinuation of the second course of chemotherapy based on the patient's own decision, bevacizumab-based chemotherapy remains an option for the treatment of PPM.

## Data availability statement

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

## Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

## Author contributions

DW: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. YW: Conceptualization, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – review & editing. SC: Conceptualization, Resources, Supervision, Writing – review & editing.

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## Conflict of interest

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

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# Case Report: Flurbiprofen-induced Type I Kounis syndrome

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**Background:** Kounis syndrome is a specific type of acute coronary syndrome caused by allergic or hypersensitivity response. Clinical knowledge about this syndrome is insufficient. We report a case in which intravenous administration of flurbiprofen resulted in Type I Kounis syndrome.

**Case summary:** A 60-year-old female patient with no history of coronary artery disease developed limb erythema, hypotension, and chest tightness after receiving intravenous flurbiprofen. Electrocardiogram showed ST segment elevation in leads II, III, and aVF. Emergency coronary angiography revealed no significant stenosis or thrombus in the coronary arteries. Subsequent echocardiography showed no apparent abnormalities. Levels of troponin T were elevated. The diagnosis was flurbiprofen-induced Type I Kounis syndrome, presenting as acute ST segment elevation myocardial infarction.

**Conclusions:** Patients with Kounis syndrome can exhibit severe clinical symptoms, and their condition may even be life-threatening. It is important for clinicians to have a thorough understanding of this syndrome in order to develop comprehensive treatment plans.

KEYWORDS

Kounis syndrome, allergy, acute myocardial infarction, flurbiprofen, case

## Introduction

Kounis syndrome is defined as a type of acute coronary syndrome associated with the activation of various inflammatory mediators and cytokines caused by allergic reactions and the activation of mast cells and platelets (1). Myocardial injury is common in allergic patients; however, many cases of Kounis syndrome may go undiagnosed due to atypical symptoms and a lack of awareness among clinical doctors (2). Additionally, current treatment options are not standardized. In this report, we present a case of Kounis syndrome induced by flurbiprofen.

## Case presentation

A 60-year-old female patient presented to our emergency department on June 12th, 2023 with a complaint of upper abdominal pain persisting for the past two weeks. Abdominal ultrasound in an external hospital revealed cholecystitis with sandy gallbladder stones. The patient had a 10-year history of hypertension and had been managing her asthma for more than 4 years with appropriate treatment. Additionally, the patient had experienced a rash-like allergic reaction when previously using omeprazole and rabeprazole injection solutions.

In the emergency room, the patient was treated with fluids. After the first dose of intravenous infusion of flurbiprofen ester was completed, the patient developed symptoms including cold sweats, chest tightness, shortness of breath, fatigue, red rashes on the trunk, accompanied by itching, mainly on the lower extremities. This was followed by

prolonged chest pain, described as dull, and approximately 15 min later, then the patient experienced confusion and collapsed to the ground. She was immediately transferred to the resuscitation room for treatment. Upon arrival in the resuscitation room, the patient was conscious with a blood pressure of 75/49 mmHg, a heart rate of 58 bpm, peripheral oxygen saturation around 80%, and tenderness in the umbilical area. The patient was treated with intravenous administration of diluted methylprednisolone 40 mg, intravenous administration of dexamethasone 5 mg, subcutaneous injection of epinephrine 0.5 mg, and intravenous drip of metaraminol bitartrate injection.

An electrocardiogram showed ST segment elevation of 0.2–0.3 mV in leads II, III, and aVF, and depression of 0.1–0.2 mV in leads I and aVL (**Figure 1**). Arterial blood gas analysis showed a pH of 7.39, a partial pressure of carbon dioxide of 38.0 mmHg, a partial pressure of oxygen of 42.0 mmHg, an oxygen saturation of 72.1%, and a lactate level of 1.7 mmol/L. The white blood cell count was $6.0 \times 10^9$/L (normal range: $3.5–9.5 \times 10^9$/L), lymphocyte count was $2.5 \times 10^9$/L (normal range: $1.1–3.2 \times 10^9$/L), eosinophil count was $0.39 \times 10^9$/L (normal range: $0.02–0.52 \times 10^9$/L), and eosinophil percentage was 6.5% (normal range: 0.4%–8.0%). Creatine kinase isoenzyme was 1.88 ng/ml (normal range: <3.77 ng/ml), myoglobin was 25 ng/ml (normal range: 25–58 ng/ml), troponin T was 4 pg/ml (normal range: <30 pg/ml), and N-terminal pro-brain natriuretic peptide (NT-proBNP) was 174 pg/ml (normal range: <300 pg/ml). Liver and kidney function tests and coagulation tests were normal. Acute myocardial infarction was suspected, and the patient was treated with subcutaneous injection of heparin 3,000 units, oral ticagrelor tablets 180 mg, and oral aspirin tablets 300 mg. Emergency coronary angiography showed no significant stenosis or thrombus in the coronary arteries (**Figure 2**). Thrombolysis in myocardial infarction (TIMI) blood flow grade III was observed. After coronary angiography, the patients' heart rate was maintained at around 80 bpm and blood pressure around 100/60 mmHg. Post-angiography electrocardiography showed sinus rhythm, and the ST segment elevation in the inferior leads decreased (**Figure 3**). A bedside echocardiogram indicated no obvious segmental wall motion abnormalities in the left ventricle.

Based on the patient's medical history, physical symptoms, and relevant laboratory findings, coronary spasm due to flurbiprofen ester allergy (Kounis syndrome) was considered. Post-angiography, the patient was treated with cetirizine 10 mg once daily for 3 days, as well as specific treatments such as hepatobiliary drugs, anti-infection therapy, and myocardial nutrition therapy. On the third day, the patient's NT-proBNP levels significantly increased (**Figure 4**), and furosemide was administered for diuresis while controlling fluid replacement. Then the patient's condition improved, and she was discharged on the 7th day. The follow-up echocardiogram before discharge showed good motion of all segments of the left ventricular wall, with a left ventricular end-diastolic diameter of 42 mm and an ejection fraction of 65%. At the 2-month follow-up, the patient reported no recurrence of chest tightness or chest pain and expressed satisfaction with the treatment.

## Discussion

Flurbiprofen, as a nonsteroidal anti-inflammatory drug, can selectively inhibit cyclooxygenase, block prostaglandin synthesis, and produce analgesic, anti-inflammatory, and antipyretic effects. It is widely used in clinical practice but can also cause adverse drug reactions. Common adverse reactions mainly include skin

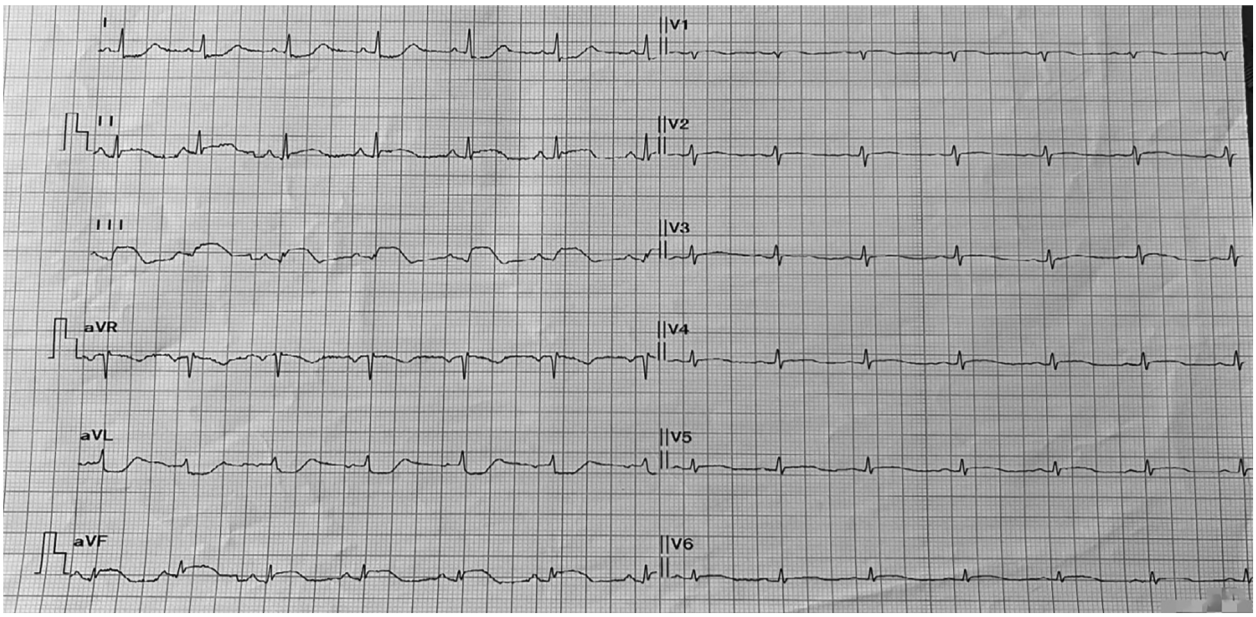


FIGURE 1
The 12-lead electrocardiogram in patient with chest tightness and discomfort showed ST segment elevation in leads II, III, and aVF.

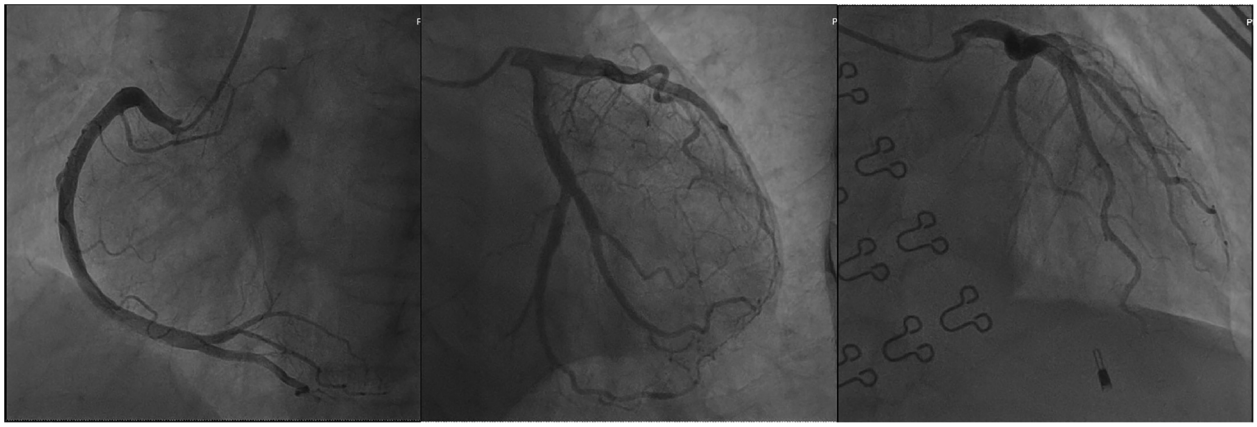

FIGURE 2
Coronary angiography revealed no significant coronary artery stenosis or thrombus formation.

damage, central nervous system damage, respiratory system damage, and gastrointestinal system damage. Studies have found that allergic reactions to nonsteroidal anti-inflammatory drugs are the main cause of Kounis syndrome (3). The article suggests that the mechanism behind the induction of Kounis syndrome by NSAIDs may involve two aspects (4). The first mechanism is related to drug-specific IgE antibodies. The second mechanism involves the inhibition of cyclooxygenase, which stimulates the lipoxygenase pathway of arachidonic acid metabolism, leading to increased production of leukotrienes. The latter is specific to NSAID-induced Kounis syndrome. To the best of our knowledge, this is the first reported case of flurbiprofen allergy-induced Kounis syndrome. The patient in this case was a middle-aged woman with no history of coronary atherosclerotic heart disease, and the initial symptoms were rash and difficulty breathing, accompanied by signs of shock, indicating a serious condition.

Since its first report in 1991, Kounis syndrome has mainly occurred in Southern Europe, with reported incidence rates of 2–19.4 cases per 100,000 inhabitants (5). Currently, there are no reported incidence rates among Asian populations, and only sporadic cases were reported in China. In our patient, coronary angiography did not reveal significant coronary stenosis or acute thrombus formation. Subsequent electrocardiogram showed resolution of ST segment elevation in the inferior leads soon, suggesting coronary artery spasm as the cause, which corresponded to the characteristics of Kounis syndrome Type I. Now, Kounis syndrome is believed to be divided into three types (6). In these three types, patients present with symptoms

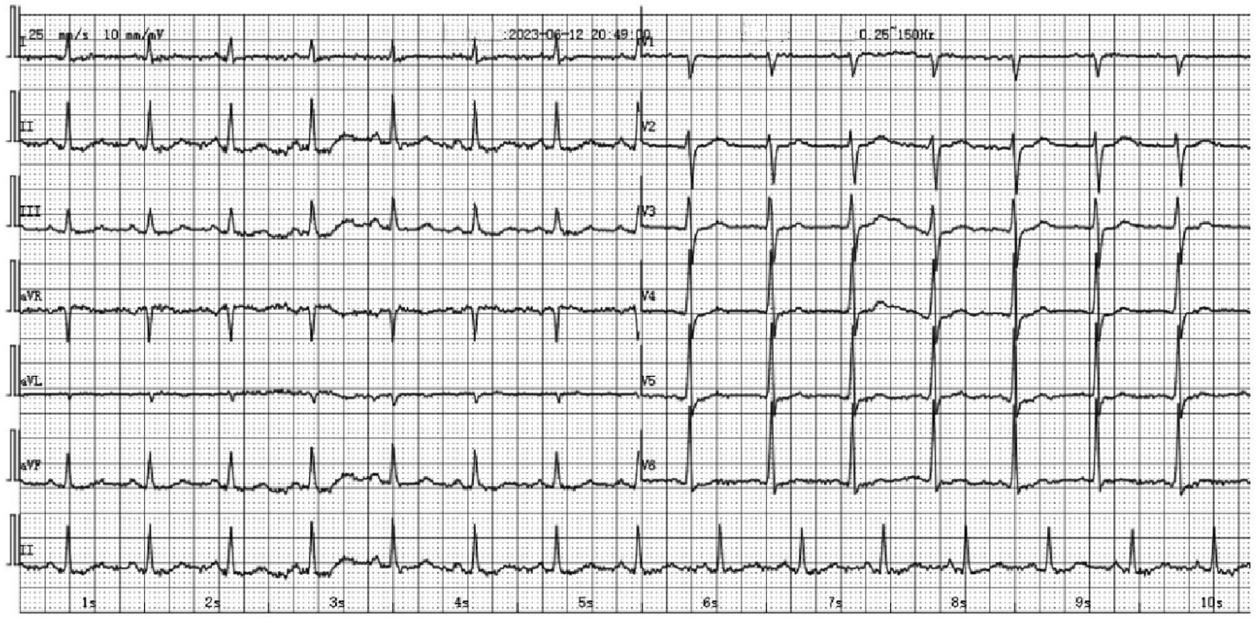


FIGURE 3
The 12-lead electrocardiogram in patient after coronary angiography showed the disappearance of ST segment elevation in leads II, III, and aVF.

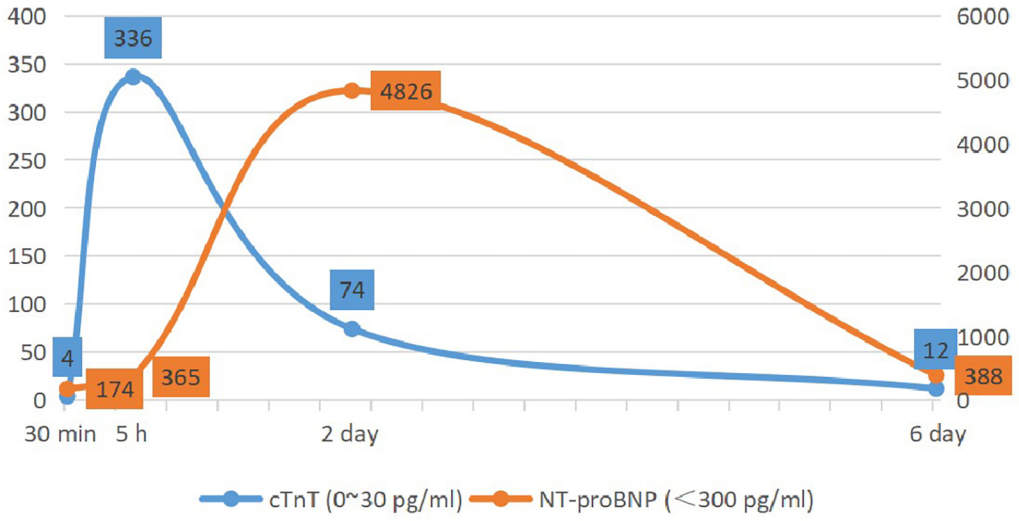


FIGURE 4
Changes in serum levels of cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP).

similar to myocardial infarction, but with varying conditions of the coronary arteries. Type I is characterized by patients having normal coronary arteries, with the coronary artery spasm being caused by an allergic reaction. It is a common cause of non-obstructive myocardial infarction (7). Type II is characterized by patients already having underlying coronary artery atherosclerosis, and the allergic reaction leading to erosion or rupture of the plaque (8). Type III refers to patients who have undergone coronary artery stenting, but experience acute thrombosis due to an allergic reaction. Type III can be further divided into two subtypes, with type IIIa being characterized by thrombus formation within the stent, while type IIIb is characterized by in-stent restenosis (9). Among all Kounis syndrome patients, Type I accounts for 72.6%, while Type II and Type III account for 22.3% and 5.1% (10). The majority of patients (68%) are between 40 and 70 years old, and pediatric cases are relatively rare (11). Males make up 74.3% of the cases.

Kounis syndrome is characterized by symptoms and signs of allergic reaction accompanied by acute coronary syndrome manifestations, such as chest pain, dizziness, nausea, vomiting, difficulty breathing, syncope, palpitations, pallor, hypotension, and bradycardia (9). It is important to note that in patients with shock, a rash may be absent, which increases the risk of misdiagnosis (12). Stress-induced cardiomyopathy should be considered in the differential diagnosis of Kounis syndrome since these two clinical conditions can coexist, forming the so-called "adrenaline-takotsubo-anaphylaxis-Kounis (ATAK complex)", and allergic myocarditis should also be distinguished (13). New imaging techniques such as dynamic contrast-enhanced cardiac magnetic resonance imaging and myocardial single-photon emission computed tomography can also assist in the diagnosis (14, 15). Additionally, research has also indicated that performing flow cytometry-based proliferation assay *in vitro* can better elucidate the association between drugs and allergic reactions (16). Previous studies have reported that the information provided by electrocardiography may be unreliable. It has been reported that ST segment changes are not consistent with spastic coronary artery discovered by coronary angiography (17). Currently, it is believed that investigating the allergen source and personal medical history is helpful in the diagnosis of Kounis syndrome, with 25.1% of patients having a history of allergies, and the usual allergens needing to be traced back to 1–6 h before the clinical onset (10).

Treating Kounis syndrome presents a challenge as there may be conflicting approaches to cardiovascular and allergic reaction treatments. In this case, aggressive fluid resuscitation can improve hypotension, but it also increases cardiac volume load and poses a risk of precipitating heart failure. Currently, it is believed that anti-allergic treatment can improve symptoms in the majority of patients with Type I Kounis syndrome. In patients with normal blood pressure, most medications, including nitroglycerin, can be used (5). For patients with Type II and Type III Kounis syndrome, treatment should be initiated with an acute coronary event protocol combined with corticosteroids and antihistamines. However, there are some specific considerations when choosing medications. β-blockers for acute coronary artery disease may exacerbate coronary artery spasm. Vasodilators, such as nitrates and calcium channel blockers, can worsen hypotension. Opiates, such as morphine, used for relieving acute chest pain, may worsen allergic reactions, making fentanyl and its derivatives preferable (5). What's more, adrenaline carries the risk of exacerbating ischemia and coronary artery vasospasm. Adrenaline without sulfite, glucagon, and methoxamine may be more effective (18). Additionally, for Type III Kounis syndrome patients, aggressive treatment for acute myocardial infarction and urgent clot aspiration from stenting are advised. Identifying the allergen and intensifying anti-allergic treatment is also crucial. If these measures fail, it seems inevitable to remove the stent (19).

## Conclusions

Kounis syndrome is not uncommon, but it is often underdiagnosed. If the underlying cause is not effectively treated, these patients may experience more coronary events or require more interventional treatments. Therefore, clinicians should pay attention to this specific coronary artery disease related to allergic response.

## 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

CT: Visualization, Writing – original draft, Writing – review & editing. YC: Investigation, Resources, Visualization, Writing – review & editing. XG: Conceptualization, Funding acquisition, Writing – review & editing.

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## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1284408/full#supplementary-material

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# Subacute hemorrhagic pericardial tamponade after COVID-19 infection mimicking carcinomatous pericarditis: a case report

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**Background:** Coronavirus disease (COVID-19)-associated acute pericarditis has recently received much attention owing to its high frequency associated with pericardial tamponade (PT), showing unfavorable prognosis. However, early diagnosis and treatment remain challenging in cases of non-specific signs and symptoms.

**Case presentation:** A 64-year-old man was admitted to our hospital for acute osteomyelitis of the toes and was properly treated with antimicrobial agents. Three days after admission, the patient developed mild COVID-19 without pneumonia, for which early anti-COVID-19 agents were initiated. Nevertheless, the patient developed hemorrhagic PT due to acute pericarditis 2 weeks later, which was confirmed by cardiac magnetic resonance, requiring an urgent pericardiocentesis. Although cytological analysis of the hemorrhagic pericardial fluid strongly suggested adenocarcinoma, the atypical cells were eventually proven to be mesothelial cells with reactive atypia. Furthermore, lymph nodes swelling with abnormal 2-[18F]-fluoro-2-deoxy-D-glucose accumulation on imaging were suggestive of malignancy. However, biopsy examination revealed multiple non-caseating granulomas in the lymph node, unlikely due to malignancy. Eventually, the temporal association of the preceding COVID-19 with the occurrence of subacute PT without other identifiable cause led to a final diagnosis of COVID-19-associated acute pericarditis. With anti-inflammatory and corticosteroids treatment, the patient's symptoms involving the pericardial structure and function were completely resolved along with improvements in size of the affected lymphadenopathies.

Abbreviations

ACE, angiotensin converting enzyme; CKD, chronic kidney disease; CT, computed tomography; COVID-19, coronavirus disease; ECG, electrocardiogram; FDG, fluoro-2-deoxy-d-glucose; LV, left ventricular; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; PF, pericardial fluid; PT, pericardial tamponade; PET, positron emission tomography; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VATS-biopsy, video-assisted thoracoscopic biopsy.

**Conclusions:** We encountered a unique case of COVID-19-associated acute pericarditis exhibiting hemorrhagic PT. This case underscores the residual risk of delayed pericardial involvement even in patients with mild COVID-19 who receive early treatment, and the recognition that COVID-19 may cause various cytomorphological and histological features. Additionally, the importance of considering this rare entity as a cause of hemorrhagic pericardial effusions should be highlighted.

KEYWORDS

COVID-19, hemorrhagic pericardial tamponade, acute pericarditis, cytology, sarcoid-like reaction

## 1 Introduction

Coronavirus disease (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a worldwide pandemic. Among extrapulmonary manifestations of COVID-19, acute pericarditis has recently gained attention owing to its high frequency associated with pericardial tamponade (PT), which is a life-threatening condition requiring prompt interventions (1–4). Acute pericarditis is diagnosed based on the following symptoms and signs: pleuritic chest pain, pericardial friction rub, typical changes in the electrocardiogram (ECG), and new-onset or worsening pericardial effusion (5). However, early diagnosis and treatment of acute pericarditis remain difficult in cases of non-specific signs and symptoms. Here, we report a unique case of subacute hemorrhagic PT after nosocomial COVID-19 infection, mimicking carcinomatous pericarditis.

## 2 Case description

A 64-year-old man was admitted to our hospital for acute osteomyelitis of the toes, presenting with left toes ulcer due to infection developed after a fall injury 3 days prior to admission. The patient had a past medical history of hypertension, chronic kidney disease (CKD), and diabetes mellitus controlled using insulin. The patient's initial vital signs were as follows: blood pressure, 189/104 mmHg; heart rate, 109 beats/min; and blood temperature, 39.8°C. Physical examination of his left great and second toes revealed ulcers with pus, swelling, and surrounding erythema. Laboratory test results revealed white blood cell count, 10,000 cells/μl (differential count, 88.9% neutrophils); elevated C-reactive protein levels, 3.09 mg/dl (normal: <0.14 mg/dl); fasting blood glucose, 316 mg/dl (normal: <110 mg/dl); and glycated hemoglobin, 12.4% (normal: <6.0%). Moderate renal dysfunction was observed. SARS-CoV-2 was undetectable using reverse-transcriptase polymerase chain reaction (RT-PCR) on a nasopharyngeal swab specimen. Magnetic resonance imaging (MRI) indicated acute osteomyelitis of the toes (Supplementary Figure S1). Subsequently, the patient underwent surgical debridement of the ulcers to enhance the healing process. Following the collection of blood and pus for cultures, the patient was intravenously administered with ampicillin-sulbactam (1.5 g every 8 h). Simultaneously, a continuous insulin infusion was initiated to strictly control hyperglycemia. On the second day after admission, nosocomial transmission of SARS-CoV-2 infection occurred. A repeated nasopharyngeal swab for RT-PCR showed negative results; however, on day 3, the patient complained of a sore throat. His vital signs were stable except for low-grade fever of 36.9°C. A follow-up RT-PCR showed positive results for SARS-CoV-2. His physical examination and chest radiograph showed unremarkable findings (Figure 1A). Serum cardiac enzyme levels were within normal ranges. ECG showed sinus rhythm and concave ST-segment elevation in precordial leads, suggestive of early repolarization (Supplementary Figure S2A). Echocardiography showed mild concentric left ventricular (LV) hypertrophy with normal contraction and enlarged left atrium suggestive of diastolic dysfunction; however, pericardial effusion was not observed (Figures 1B,C and Supplementary Videos S1, S2). After the patient was isolated, intravenous infusions of antiviral agent (remdesivir, a loading dose of 200 mg followed by 100 mg for 2 days) and SARS-CoV-2 neutralizing antibody (sotrovimab, a single dose of 500 mg) were administered for mild COVID-19 treatment. On day 7, all the cultures collected on admission yielded *Staphylococcus aureus* sensitive to cefazolin and de-escalation of intravenous cephazolin (2 g every 8 h) was performed for 4 weeks. The patient achieved improvement in glycemic control and was then switched to conventional regular subcutaneous insulin. His wound healing process was uneventful. On day 13, the patient experienced dyspnea. His vital signs were blood pressure, 134/77 mmHg; heart rate, 68 beats/min; body temperature, 36.7°C; respiratory rate, 18 breaths/min; and oxygen saturation, 85% on ambient air. A follow-up chest radiograph revealed cardiomegaly with left pleural effusion. The patient's body weight increased by 8 kg. Jugular vein distention and bilateral leg edema were noted; serum brain natriuretic peptide level was elevated (332 pg/ml, normal: <18 pg/ml). Therefore, a presumptive diagnosis of acute heart failure was made, and the patient was administered oxygen at 2 L/min and treated with intravenous loop diuretics (furosemide, 20 mg twice daily) to control volume overload. On day 15, a repeated RT-PCR confirmed SARS-CoV-2 negativity, ending isolation. On day 17, the patient's condition exacerbated (Figure 1D). Chest computed tomography (CT) revealed moderate pericardial and bilateral pleural effusions (Figure 2A). The follow-up ECG showed ST-segment normalization (Supplementary Figure S2B). The follow-up echocardiography

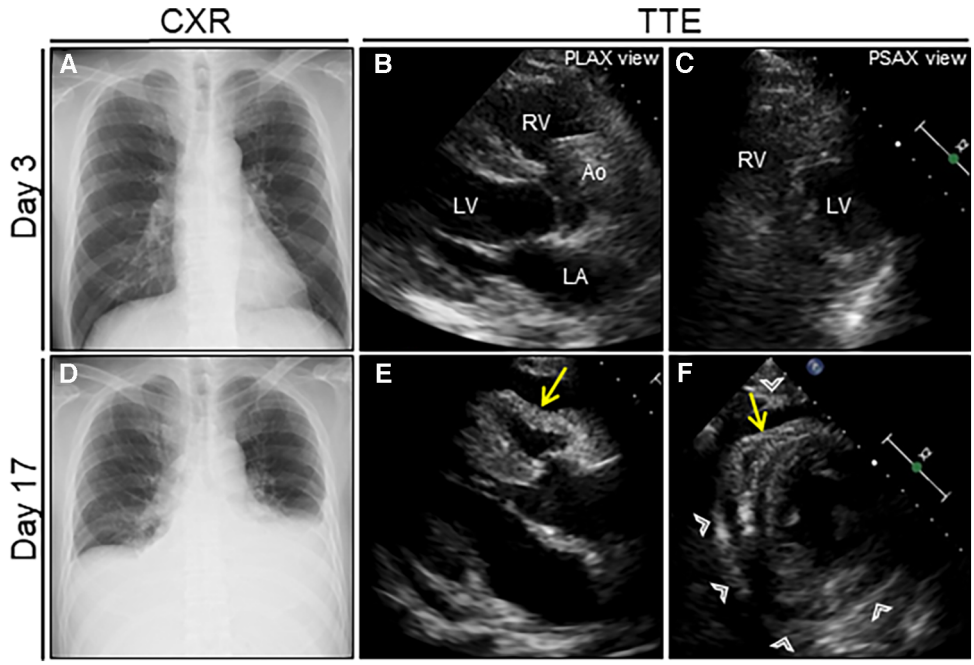


FIGURE 1
Serial chest radiograph (CXR) and transthoracic echocardiography (TTE) after nosocomial infection of COVID-19. On day 3 after admission (1 day after nosocomial infection of SARS-CoV-2), CXR (**A**) and TTE (**B, C**) are unremarkable. On day 17 (15 days after nosocomial infection of SARS-CoV-2), the follow-up CXR reveals cardiac enlargement with bilateral pleural effusions (**D**), whereas the follow-up TTE reveals a moderate pericardial effusion with pericardial thickening (arrowheads) (**E, F**). Note the right ventricular collapse during early diastole (arrows). Ao, aorta; COVID-19, coronavirus disease; LA, left atrium; LV, left ventricle; PLAX, parasternal long-axis; PSAX, parasternal short-axis; RV, right ventricle; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

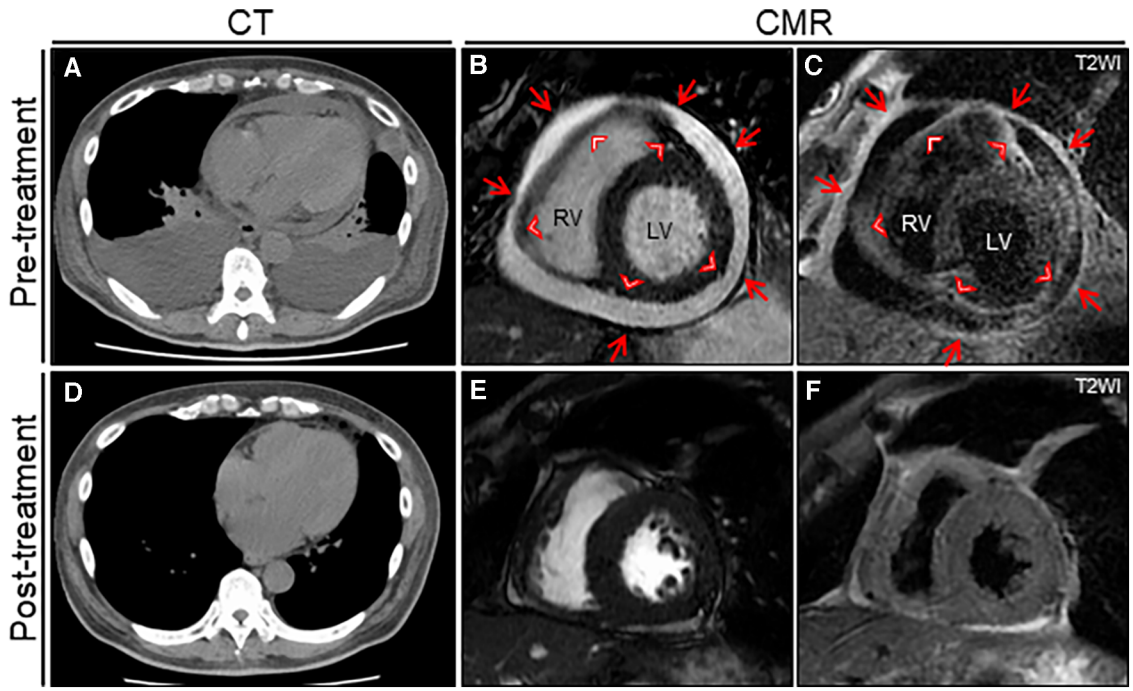


FIGURE 2
The treatment effect on chest computed tomography (CT) and cardiac magnetic resonance (CMR) findings. Chest CT reveals moderate pericardial and bilateral pleural effusions with passive atelectasis (**A**) that resolves completely at the 6-month follow-up (**D**) Cine CMR reveals a moderate pericardial effusion at baseline (**B**) that resolves significantly at the 6-month follow-up (**E**) Note the entire thickening of epicardium (arrowheads) and pericardium (arrows). T2-weighted image (T2WI) shows active diffuse pericardial edema of the epicardium (arrowheads) and pericardium (arrows) observed at baseline (**C**) that resolves significantly at the 6-month follow-up (**F**). LV, left ventricle; RV, right ventricle.

revealed a moderate pericardial effusion with tamponade physiology, suggestive of PT (Figures 1E,F and Supplementary Videos S3, S4). Cardiac MRI suggested active pericarditis (Figures 2B,C). Right heart catheterization confirmed PT with equalization of diastolic pressures across all chambers and marked hemodynamic pulsus paradoxus (Supplementary Table S1). Subsequently, the patient underwent an urgent pericardiocentesis with a placement of pericardial drainage, showing 750 ml of hemorrhagic exudate fluid (Figure 3A). Pericardial fluid (PF) analysis showed hypercytokinemia consistent with an inflammatory process (Supplementary Table S2). SARS-CoV-2 in the PF was undetectable using RT-PCR. Gram and Ziehl-Neelsen staining and bacterial and fungal cultures yielded negative results. Serologic testing for autoimmune diseases and cardiotropic viruses workup indicated negative results. Notably, PF cytology suggested adenocarcinoma cells suspecting carcinomatous pericarditis (Figure 3B), for which ibuprofen (600 mg three times daily) and colchicine (0.5 mg twice daily) were initiated. On day 18, the patient underwent bilateral thoracocentesis with drainage of serous transudate pleural fluids, which also showed hypercytokinemia (Supplementary Table S3). SARS-CoV-2 in the pleural fluids was also undetectable using RT-PCR. After confirmation of no pericardial effusion recurrence, the drain was removed. Upper endoscopy and colonoscopy for cancer screening showed unremarkable findings. CT screening revealed right paraesophageal and hilar lymph nodes swelling (Figures 4A,B). On day 26, positron emission tomography (PET)/CT with the glucose analog 2-[18F]-fluoro-2-deoxy-d-glucose (FDG) disclosed the slight hypermetabolic activities in the same lesions (Figures 4C,D). Owing to the concern for malignancy, the patient underwent video-assisted thoracoscopic biopsy (VATS-biopsy) of the FDG-avid hilar lymph node, revealing multiple non-caseating granulomas suggestive of sarcoidosis (Figure 3C). However, considering normal serum angiotensin converting enzyme (ACE) levels and the absence of pulmonary, skin, and eye involvement, the patient was diagnosed with a sarcoid-like reaction. Furthermore, re-examination of the PF cytological materials using immunohistochemistry revealed that the atypical cells were reactive mesothelial cells because they were positive for D2-40, a specific cell-marker for mesothelial cell (Figure 3D), which was unlikely due to malignancy. Therefore, based on the temporal association between preceding SARS-CoV-2 infection and the development of subacute PT without other identifiable causes, a final diagnosis of COVID-19-associated acute pericarditis was made. On day 36, the patient developed leukopenia during treatment, which was suspected to be drug-induced, that resolved with colchicine discontinuation.

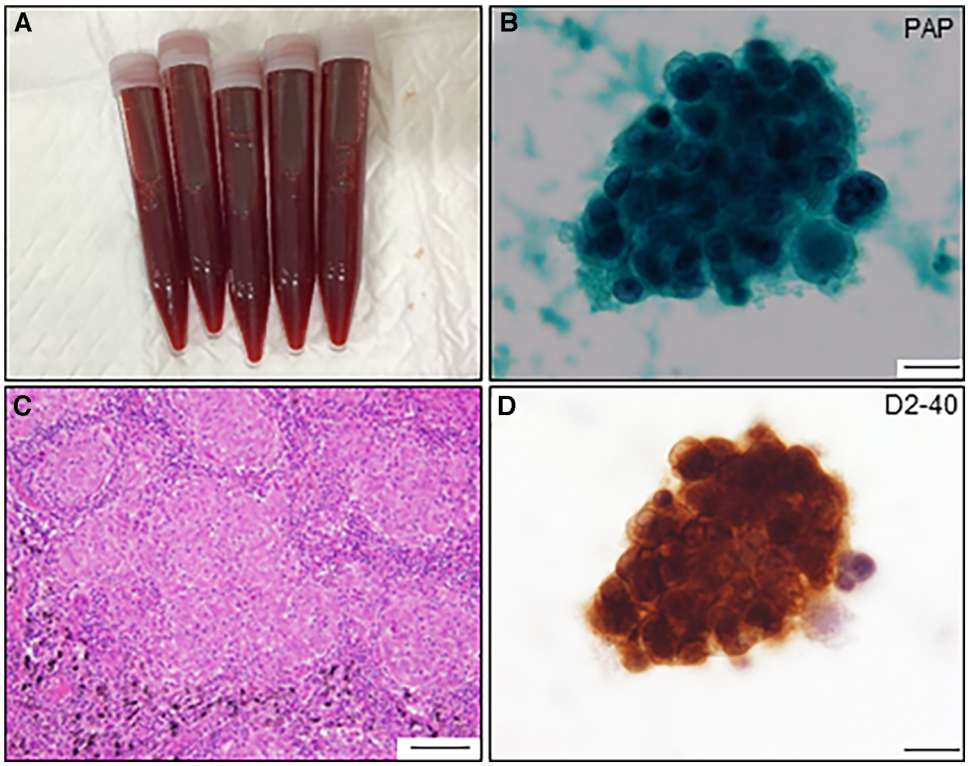


FIGURE 3
Pericardial fluid and cytological findings and histological feature of resected lymph node. (**A**) Pericardial fluid shows hematogenous appearance. (**B**) Atypical cell nest is detected in the pericardial fluid and initially diagnosed as adenocarcinoma by Papanicolaou (PAP) staining (scale bar, 20 μm). (**C**) The resected lymph node shows multiple non-caseating granulomas (scale bar, 100 μm). (**D**) The same atypical cells observed in (**B**) are positive for anti-D2-40 antibody by immunocytochemistry (scale bar, 20 μm).

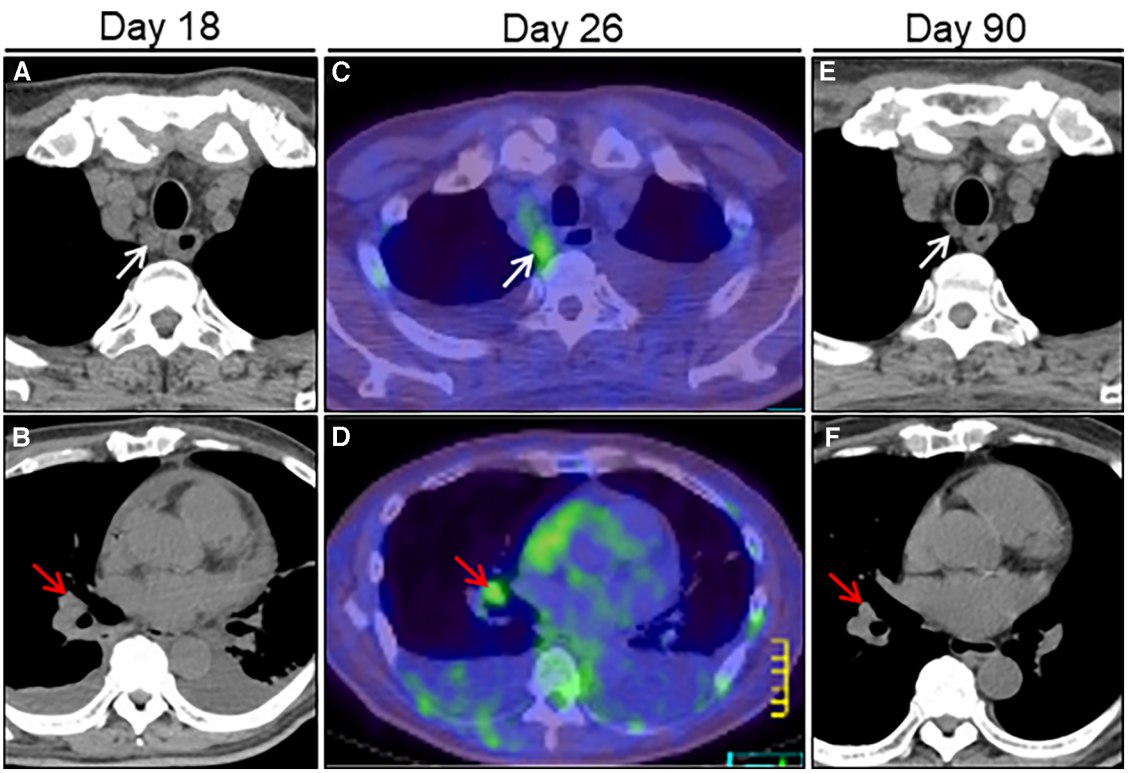


FIGURE 4
Treatment effect on lymphadenopathy on chest computed tomography (CT) imaging. Chest CT on day 18 after admission reveals right paraesophageal (white arrow) and hilar (red arrow) slight lymphadenopathies (A, B). FDG/PET-CT on day 26 reveals slight hypermetabolic activities in the same ones (C, D). Post-treatment follow-up CT on day 90 reveals a significant improvement in size of the affected lymphadenopathies (E, F). FDG/PET, positron emission tomography with 2-[18F]-fluoro-2-deoxy-D-glucose.

Alternatively, oral prednisolone (20 mg/day) was added because of residual pericardial thickening with pericardial effusion on the follow-up echocardiography. Thereafter, the patient's clinical condition improved steadily, and he was discharged on day 55. A significant improvement in size of the affected lymphadenopathies was also observed on day 90 (Figures 4E,F). Furthermore, a complete resolution of pericardial structural and functional abnormalities with concurrent pleural effusions was observed at the 6-month follow-up (Figures 2D–F). Thereafter, ibuprofen and prednisolone were tapered and discontinued over 3 months. The patient remains clinically stable during the first year of follow-up. We present a summarized illustration of the case presentation in Figure 5.

## 3 Discussion

COVID-19 was first reported in Wuhan, China, in 2019 and became a global pandemic. Although COVID-19 primarily affects the respiratory system, which commonly progresses to acute respiratory distress syndrome in severe cases, it can affect all organs (6). Regarding the cardiovascular system, pericardial involvement has increasingly gained attention with growing pieces of evidence (3). The accurate incidence of pericardial involvement remains unknown. However, a retrospective multicenter study suggested the potential high risk of acute pericarditis in patients with COVID-19 compared with those without COVID-19 (odds ratio, 1.45; 95% confidence interval, 1.07–1.97) (7). Furthermore, COVID-19-associated acute pericarditis has been presumed to exhibit a more aggressive phenotype compared with acute pericarditis in the pre-COVID-19 pandemic era owing to the higher frequency of associated pleural effusions (76%) and PT (35%), with poor prognosis (1, 8). Herein, we report a case of subacute hemorrhagic PT after nosocomial COVID-19 infection, successfully treated with pericardiocentesis followed by medical treatment. Our case may provide four valuable clinical lessons.

First, this is the first report of COVID-19-associated pericarditis mimicking malignancy. Our patient had to be differentiated from carcinomatous pericarditis based on the following three findings.

As the first finding, our case presented with hemorrhagic PT. Although causative diseases underlying hemorrhagic PT varies with the era, region, and patient population, a retrospective observational study showed that most hemorrhagic PT causes included invasive cardiac surgery-related (31%), malignancy (26%), mechanical complications of myocardial infarction (10%), and idiopathic etiologies (10%). Miscellaneous causes include tuberculosis, trauma, uremia, aortic dissection, drugs (e.g., anticoagulant or anti-TNF alpha agent), and viral infection (9–11). Generally, viruses have been considered rare etiologies for hemorrhagic pericardial effusions, with the exception of

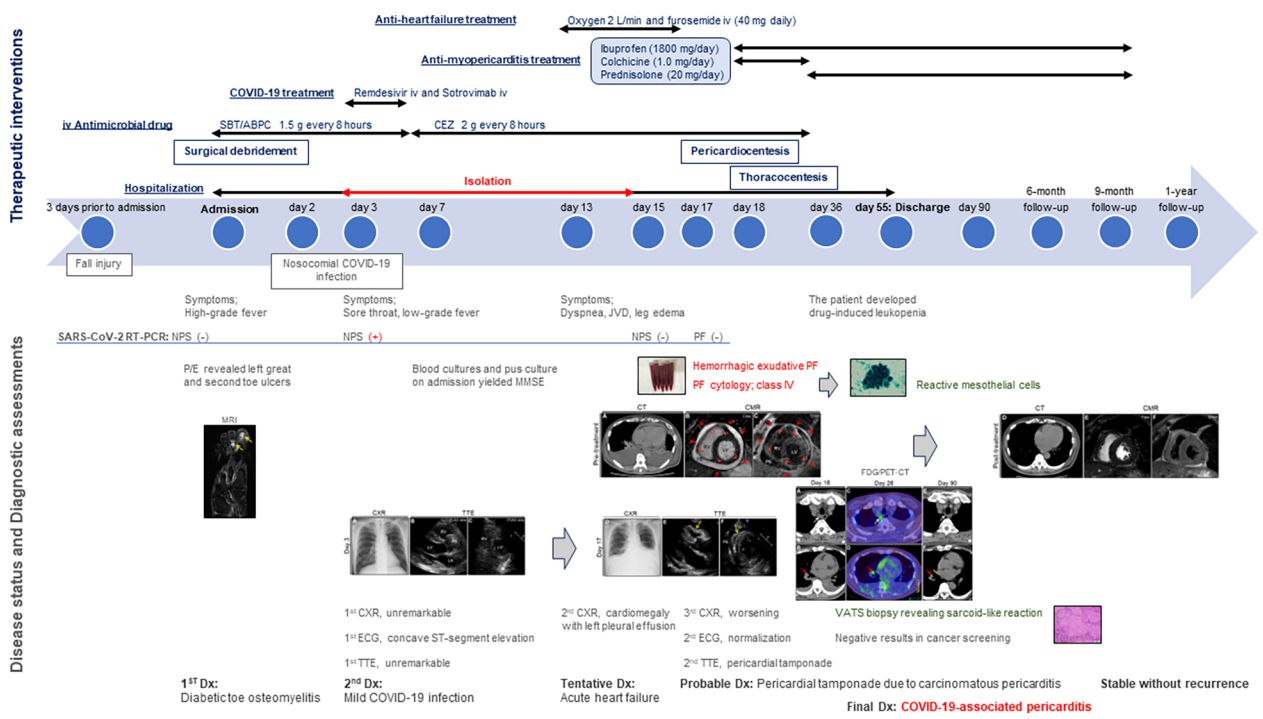


FIGURE 5
Timeline of the diagnostics, therapeutic interventions, and disease status of the present case. CEZ, cephazolin; CMR, cardiac magnetic resonance; CT, computed tomography; CXR, chest radiograph; COVID-19, coronavirus disease; Dx, diagnosis; ECG, electrocardiogram; FDG/PET, glucose analog 2-[18F]-fluoro-2-deoxy-d-glucose positron emission tomography; iv, intravenous; JVD, jugular vein distention; MMSE, methicillin-sensitive *Staphylococcus aureus*; MRI, magnetic resonance imaging; NPS, nasopharyngeal swab; P/E, physical examination; PF, pericardial fluid; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBT/ABPC, ampicillin-sulbactam; TTE, transthoracic echocardiography; VATS-biopsy, video-assisted thoracoscopic biopsy.

Coxsackievirus (12). However, given the certain incidence of previous case reports and case series with COVID-19 presenting with hemorrhagic pericardial effusion (4, 13–15), our case highlighted the significance of considering COVID-19 as an etiology of hemorrhagic pericardial effusion.

The second finding was the PF cytology result suggesting adenocarcinoma. However, re-examination of immunostaining with D2-40 revealed mesothelial cells with reactive atypia. These phenomena are most likely due to the aberrant hyperimmune response to cytokine storm during acute infection. A previous study evaluated the impact of COVID-19 on cytomorphological manifestations of mesothelial cells in body fluids. It revealed that more atypical mesothelial cells having multinucleation, bizarre nuclei, and prominent nucleoli (73.9% vs. 53.8%, $p < 0.005$), requiring more immunostains ordered (47.8% vs. 7.7%, $p < 0.014$), were found in body fluids during the active phase compared with those during the recovery phase (16), supporting this notion. Hence, this case emphasized the careful comprehension of cytomorphological changes in effusion fluid cytology associated with COVID-19.

The last finding was the presence of swollen lymph nodes on imaging. Metastatic lymph nodes associated with carcinomatous pericarditis were initially suspected based on the above two findings. However, VATS-biopsy of the FDG-avid hilar lymph nodes indicated non-caseating granulomas. Similar to the present case, there is a growing number of case reports of *de novo* sarcoidosis or sarcoid-like reactions in multiple organs induced by COVID-19 (17–19). Sarcoidosis and sarcoid-like reactions are histologically indistinguishable. Sarcoidosis is a multisystem disorder characterized by the accumulation of non-caseating granulomas with lymphocytic inflammation involving various organs including the lungs, skin, eyes, heart, and lymph nodes. Although the exact etiology and mechanism of sarcoidosis remain poorly understood, plausible mechanisms include hyperinflammatory immune-mediated responses to an antigen against infectious or environmental exposures. Previous studies have proposed a possible signal crosstalk between COVID-19 and sarcoidosis, which shared cell signaling pathways such as renin-angiotensin signaling, inhibited autophagy, and induced cell apoptosis (20). Similarly, COVID-19 might have induced sarcoid-like reaction in the lymph nodes in our case. Clinicians should recognize possible lymph node involvement after infection with COVID-19.

In summary, our case underscored characteristic cytomorphological and histological features caused by COVID-19.

As the second clinical lesson, early treatment of mild COVID-19 did not inhibit ongoing active pericarditis.

Approximately 80% of patients with COVID-19 have mild to moderate severity with or without pneumonia, and 15% of them progress to a severe or critical state without treatment (21). Given that viral load is a determinant of subsequent severity and

prognosis, early pharmacological treatment to reduce viral load has a beneficial effect not only in reducing disease severity but also in controlling infection spread to multiple organs. Our patient had a history of hypertension, diabetes mellitus, and CKD, which are well-known risk factors for COVID-19 severity; thus, drug therapy was initiated immediately after the onset of mild COVID-19. Nevertheless, the patient developed ongoing pericarditis, resulting in hemorrhagic PT. Although the exact mechanism underlying pericardial involvement remains poorly understood, several mechanisms have been proposed (3, 4, 22). First, SARS-CoV-2 can directly infect cardiovascular tissue, such as cardiomyocytes, pericytes, endothelial cells, and macrophages, which express the ACE2 receptor. This infection can activate the ACE2 signaling pathway and result in cardiovascular injury. SARS-CoV-2 has actually been detected in the PF of a COVID-19 patient with pericarditis using RT-PCR (23), although the direct causal relationship remains unknown. Second, the normal pericardium, a double-layered membrane surrounding the heart composed of an inner visceral and outer parietal layer, is relatively avascular. However, pericarditis is characterized by hypervascularity. Under situations of vascular injury and inflammation triggered by SARS-CoV-2 infection, the ensuing vascular endothelial dysfunction in the pericardium may lead to pericarditis. Third, an aberrant hyperimmune response to cytokine storm following SARS-CoV-2 infection may lead to apoptosis of epithelial or endothelial cells and vascular damage with subsequent pericarditis. Fourth, SARS-CoV-2 infection primarily affects the lungs and often complicates acute respiratory distress syndrome. Therefore, oxidative stress caused by severe hypoxia can contribute to concomitant pericardial injury, leading to pericarditis. Given hypercytokinemia in the PF despite early COVID-19 treatment, the indirect systemic hyperinflammatory response to cytokine storm may be the crucial mechanism underlying pericardial involvement in our case. Hence, this case highlighted the importance of considering the residual risk of subsequent pericardial involvement even in patients with mild COVID-19 undergoing early pharmacological treatment.

For the third clinical lesson, T2-weighted cardiac MRI was also effective in diagnosing atypical acute pericarditis as per our case.

Acute pericarditis is diagnosed based on the presence of more than two of the following: (i) typical pleural chest pain; (ii) pericardial friction rub; (iii) generalized ST-segment elevation with reciprocal ST-segment depression and PR-segment elevation in leads aVR and V1 on ECG; and (iv) new-onset or worsening pericardial effusion (24). However, our case did not meet the above criteria except for new-onset pericardial effusion. Although contrast-enhanced CT/MRI was not available owing to renal dysfunction in our case, T2-weighted cardiac MRI could characterize pericardial inflammation, leading to the correct diagnosis of acute pericarditis. However, the early repolarization pattern on ECG observed on day 3 after admission might have been the initial manifestation of acute pericarditis in our case. Cardiac MRI can provide detailed morphological and functional evaluation of the pericardium (24). Therefore, cardiac MRI may be the first screening tool in patients suspected with acute pericarditis that is inconclusive based on the above-mentioned criteria.

The fourth clinical lesson is that ibuprofen and corticosteroids were effective in treating COVID-19-associated hemorrhagic pericarditis in our case.

Untreated hemorrhagic pericarditis may pose transition risk to chronic pericarditis or constrictive pericarditis. However, there is no current guideline for managing COVID-19-associated pericarditis. Although nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen and colchicine are the first line agents for acute viral pericarditis (5), there are the following two theoretical concerns of using NSAIDs for COVID-19-associated pericarditis. As a first concern, NSAIDs may involve in the upregulation of ACE2 protein, a known cell entry receptor for SARS-CoV-2, leading to potential risks of SARS-CoV-2 re-infection or COVID-19 severity. However, there is conflicting experimental data: ibuprofen augmented ACE2 expression in a rat model with diabetes (25), whereas ibuprofen had no impact on ACE2 expression and SARS-CoV-2 viral entry in human cell cultures (26). In addition, a large observational study revealed no significant relationship between NSAIDs use and COVID-19 occurrence or severity (27). As a second concern, NSAIDs have a potential risk of promoting hemorrhagic pericardial effusion owing to its antiplatelet activity. However, such association has not been observed in previous case reports (4, 28). Based on these findings, there is currently no solid evidence to prove that NSAIDs use could have detrimental effects on COVID-19 occurrence or severity. Corticosteroids are a potential therapeutic option; however, routine administration of corticosteroids for acute viral pericarditis treatment is fundamentally not recommended because corticosteroids may delay viral clearance in host cell, resulting in ongoing inflammation (5). Nevertheless, corticosteroids may be beneficial for certain cases with recurrent or resistant to the first-line agents, in which hyperinflammatory response could be detrimental to the host. The present case had to avoid receiving the continuous use of colchicine owing to drug-induced leukocytopenia and required corticosteroids as an alternative, which was eventually effective. The guidelines for management of COVID-19-associated acute pericarditis would be established in the future.

Finally, our case presented a hemorrhagic phenotype in a pericardial lesion. Similar phenomena have been reported in several case reports and case series involving various organs and tissues including the brain, retina, pancreas, gastrointestinal tract, arteries, and muscle (29–34). These facts strongly suggest unresolved common mechanisms underlying the hemorrhagic phenotype after infection with COVID-19. Blood vessels are primarily composed of two interacting cell types: endothelial cells and perivascular cells (pericytes, vascular smooth muscle, or mural cells). Endothelial cells form the inner layers of the vessel wall, whereas perivascular cells encase the surface of the vessel wall. Importantly, endothelial cell/pericyte interactions are critical to maintain the homeostasis of the microvasculature, including vessel remodeling or angiogenesis (35).

Given the high ACE2 expression in human cardiac pericytes, these cells may be an attractive target for SARS-CoV-2. A study demonstrated that SARS-CoV-2 directly infects cardiac pericytes in patients with COVID-19-associated myocarditis, leading to the upregulation of inflammatory chemokines, cytokines, type I interferon, and vasoactive mediator genes with subsequent

endothelial inflammation, in addition to enhancing the death of infected pericytes, which is dependent on the nuclear factor-kappa B pathway (36). During SARS-CoV-2 infection, microvascular thrombosis and cytokine storm can occur frequently, causing inflammation and endothelial cell injury, as well as vascular permeability. Therefore, the failure of functional and anatomical interactions between endothelial cells and pericytes may challenge vessel integrity, resulting in serious hemorrhagic phenotype after COVID-19 infection. A case report of ongoing hemorrhagic pericarditis, requiring the complete removal of the epicardium, revealed neovascularization and inflammation on histology, suggesting spontaneous rupture of microvasculature as a possible etiology (37). Similarly, a CMR imaging study of histological analyses of excised pericardium from patients with active constrictive pericarditis emphasized the importance of chronic inflammation and neovascularization during the active phase of pericarditis (38). These findings suggest that the failure of neovascularization, caused by dysregulated endothelial cell/pericyte interactions, might be a possible etiology of hemorrhagic pericarditis associated with COVID-19 infection.

Reports have indicated that the ongoing evolution of SARS-CoV-2 variants is associated with various cardiovascular diseases (39). The acute phase of COVID-19 may involve cardiac manifestations including acute coronary syndrome, myocarditis, pericarditis, heart failure, and arrhythmias. In addition, vascular involvements include acute venous (pulmonary embolism and deep vein thrombosis) and arterial (stroke and critical limb ischemia) thromboses, bleeding, coagulopathy, or disseminated intravascular coagulation. Notably, post-acute sequelae of COVID-19 infection cause long-term adverse cardiovascular events including stroke, heart failure, and arrhythmias. Although SARS-CoV-2 variants of concern have mutations that increase transmissibility and potentially worsen disease severity, their impact on cardiovascular involvement and patient outcomes remains poorly understood. Further evidence is warranted.

The present case report had three limitations. First, the definitive diagnosis of viral pericarditis was originally established based on a histological evaluation of the pericardium and viral genomic analyses with pericardial tissue specimen using RT-PCR. In the present case, pericardiectomy was not required since pericardial involvement showed complete recovery with medical treatment. Therefore, we could not reveal the direct causal relationship between COVID-19 and the development of acute pericarditis. In addition, the hypothesized mechanism of the hemorrhagic phenotype after COVID-19 infection could not be confirmed due to the lack of histology of the resected pericardium. Second, there was no solid evidence of causal link between COVID-19 and sarcoid-like reaction owing to the lack of the imaging information on FDG/PET-CT prior to COVID-19 and detailed immunohistological examination of the lymph node in our case. Third, a COVID-19 variant was not determined by genotyping in our case. Therefore, it remains unclear whether the delayed hemorrhagic pericarditis in this case is a complication specific to SARS-CoV-2 variants of concern.

## 4 Conclusions

Herein, we describe a case of COVID-19-associated acute pericarditis complicated by hemorrhagic PT. PT can be a fatal sequela of untreated acute pericarditis. However, COVID-19-associated acute pericarditis may sometimes mimic malignancy, leading to delayed diagnosis and treatment. Therefore, clinicians should recognize the pericardium as an important target of cardiovascular involvement and cytomorphological and histological features after COVID-19 infection. Accordingly, clinicians should consider this rare clinical entity in the diagnostic workup of hemorrhagic pericardial effusion.

## Data availability statement

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

## Ethics statement

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

## Author contributions

HY: Conceptualization, Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing. NK: Data curation, Investigation, Writing – original draft. KH: Data curation, Writing – original draft. JI: Conceptualization, Supervision, Validation, Visualization, Writing – original draft. TK: Data curation, Investigation, Visualization, Writing – original draft. MN: Methodology, Supervision, Validation, Writing – original draft. HM: Data curation, Writing – original draft. TH: Data curation, Supervision, Writing – original draft. HO: Data curation, Supervision, Writing – original draft.

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## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1329952/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Magnetic resonance imaging (MRI) of the left foot. T2-weighted short tau inversion recovery MRI reveals high signal intensity spots in the left distal phalanx of first toe and the proximal phalanx of second toe (arrows).

SUPPLEMENTARY FIGURE S2
Serial electrocardiogram (ECG) on day 3 (**A**) and on day 17 (**B**) after admission (**A**) ECG shows concave ST-segment elevation in precordial leads (V1-4). Note the absence of reciprocal ST-segment depression and PR-segment elevation in leads aVR and V1. (**B**) ECG shows ST-segment normalization observed in (**A**) and T-wave inversions in leads II, III, aVF, V5, V6.

SUPPLEMENTARY TABLE S1
Right heart catheter measurements before and after pericardiocentesis.

SUPPLEMENTARY TABLE S2
Blood and pericardial fluid analyses.

SUPPLEMENTARY TABLE S3
Blood and pleural fluid analyses.

SUPPLEMENTARY VIDEO S1
Transthoracic echocardiography on day 3 after admission: parasternal long-axis view.

SUPPLEMENTARY VIDEO S2
Transthoracic echocardiography on day 3 after admission: parasternal short-axis view.

SUPPLEMENTARY VIDEO S3
The follow-up transthoracic echocardiography on day 17: parasternal long-axis view.

SUPPLEMENTARY VIDEO S4
The follow-up transthoracic echocardiography on day 17: parasternal short-axis view.

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# Venoarterial extracorporeal membrane oxygenation for vasoplegic shock after treprostinil refill of an implanted intravenous pump: a case report

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**Introduction:** Venoarterial extracorporeal membrane oxygenation (ECMO) is a rescue therapy that can stabilize patients with hemodynamic compromise. Indications continue to evolve, including drug overdose. However, the indication merely for vasoplegic shock following drug overdose is controversial.
**Case summary:** We report a case of a 57-year-old male with high-risk idiopathic pulmonary arterial hypertension treated with upfront triple combination therapy (sildenafil, bosentan, and intravenous treprostinil infusion via subcutaneous abdominal implantable pump). In one of the refills of the drug reservoir, accidental administration of 1 months's supply of treprostinil (200 mg) into the subcutaneous tissue occurred, causing refractory vasoplegic shock. He required urgent VA-ECMO for 96 h, surviving to discharge 28 days later.
**Discussion:** Treprostinil poisoning is rare due to its less frequent use but is life-threatening. ECMO may be considered in vasoplegic shock due to overdose of vasodilatory medication. It allows organ perfusion to be maintained, with the knowledge that recovery is as rapid as drug elimination.

KEYWORDS

VA-ECMO, overdose, treprostinil, vasoplegic shock, case report

## Introduction

Pulmonary arterial hypertension (PAH) remains a challenging condition to treat. In patients with high-risk status according to expected 1-year mortality, triple combination therapy can stabilize a patient's condition (1) and avoid lung transplantation which has a 5-year mortality of 41% even in proficient centers (2).

Triple therapy for PAH pulmonary vasodilator treatment target 3 potent mediators of vascular tone: nitric oxide, prostacyclin and endotelin pathway. The prostacyclin metabolic pathway is dysregulated in patients with PAH. Prostacyclin analogues and prostacyclin receptor agonists inhibit platelet aggregation and induce potent vasodilation. The most common adverse events observed are headache, flushing, jaw pain, and diarrhea.

Treprostinil is a prostacyclin analog (PGI2) used for the treatment of group 1 PAH. Treprostinil is available for subcutaneous, intravenous, inhaled, and oral administration. Inhaled or oral are not approved in Europe. Subcutaneous treprostinil improves exercise capacity and right heart function (3). However, on many occasions, the therapy is interrupted due to infusion-site pain.

Intravenous treprostinil can be an alternative for this adverse effect and may also be administered via implantable pumps, decreasing the occurrence of line infections (4). The intravenous implanted treprostinil pump comprises a drug reservoir, covered by a silicone septum for percutaneous refilling and a central venous catheter which is tunneled into the jugular vein. After implantation, treprostinil solution is injected monthly into the drug reservoir under aseptic conditions and the pump mechanism provides a constant intravenous flow. Treprostinil overdose is rare but can be catastrophic.

## Case presentation

The authors report a case involving a 57-year-old male, weight 85 kg, height 185 cm, with paroxysmal atrial fibrillation, obstructive sleep apnea, and high-risk idiopathic PAH diagnosed 5 years previously and treated with upfront triple combination therapy (sildenafil [40 mg/8 h], bosentan [125 mg/12 h], and intravenous treprostinil infusion [50 ng/kg/min] via subcutaneous abdominal implantable pump). Initially, treprostinil infusion was started subcutaneously with an external pump. Due to pain at the infusion site and repeated infections, intravenous infusion was carried out by subcutaneous implantation of the pump in the abdomen. The patient came to our hospital every 28 days to fill the pump reservoir for two years. A nurse from the Pulmonary Vascular Unit trained to fill the pump in a sterile environment proceeded to manually locate the silicone port on the top of the device (Figure 1). To ensure that the medication was injected into the reservoir, the silicone membrane was punctured, and the medication residue was removed. Once the needle position was fixed, the reservoir was progressively filled, with repeated aspirations to guarantee that the needle remained in the reservoir until the procedure was completed.

In one of the refills of the drug reservoir, accidental administration of 1 months' supply of treprostinil (200 mg) into the subcutaneous tissue occurred, causing circulatory collapse. The accident probably occurred after the needle inadvertently came out of the reservoir during one of the last control aspirations. The patient was transferred to the intensive care unit and started on perfusions of norepinephrine (up to 3 mcg/kg/min) combined with epinephrine (1 mcg/kg/min) and vasopressin (0.03 IU/min). An additional 1 mg terlipressin and 1 mg/kg methylene blue were administered. Despite multiple high-dose vasopressor infusions, the patient experienced refractory shock (blood pressure 60/30 mmHg and anuria, with a serum lactate level >15 mmol/L). Chest x-ray showed bilateral alveolar infiltrates compatible with volume-overload pulmonary edema, resulting in hypoxemia (high flow nasal cannula $FiO_2$ 70% for $SpO_2$ 96%). Physical examination

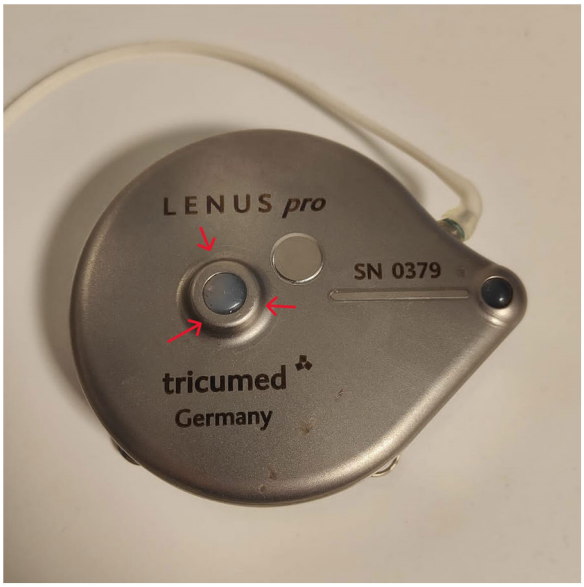


FIGURE 1
Photograph of intravenous implanted treprostinil pump. The silicone membrane where treprostinil is injected is marked with arrows.

revealed generalized vasodilation, with an erythematous and edematous area around the subcutaneous pump (Figure 2). Arterial blood gas analysis showed pH: 7.29, $pCO_2$: 30.8 mmol/L, $pO_2$: 121 mmHg, and HCO3: 16.4.

Transthoracic echocardiography revealed hypercontractile left ventricle, with anomalous movement of the septum due to pressure overload with preserved systolic function, dilated right ventricle with preserved function. Estimated pulmonary artery systolic pressure was 60 mmHg.

Attempts were made to reduce subcutaneous absorption of the drug, diluting it with peribomb injection of 100 ml of saline solution. Cold gauze was applied to cause vasoconstriction of the

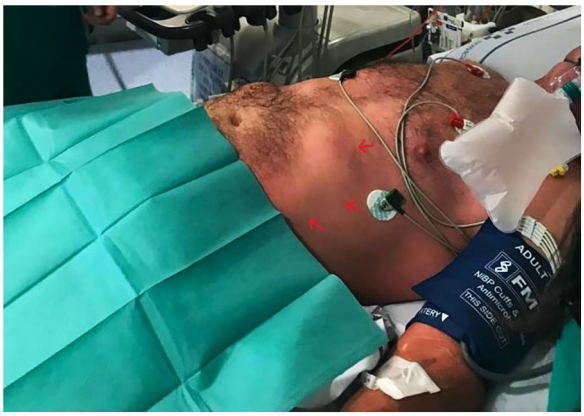

FIGURE 2
Erythematous and oedematous area around the subcutaneous pump.

subcutaneous tissue and delay the absorption of treprostinil. Also, incision and drainage of the injection site was performed to remove the treprostinil, with no clinical improvement (Figure 3).

Due to refractory shock within 2 h and, given that the terminal half-life of treprostinil is 3.5 h, peripheral venoarterial extracorporeal membrane oxygenation (VA-ECMO) was planned as the rescue therapy. Cannulation was performed with semi-Seldinger technique under general anesthesia (right femoral artery cannula 19 fr × 15 cm with distal perfusion cannula 8 fr; right femoral venous cannula 23 fr × 55 cm). Pump flow was maintained at 4.5 L/min, 3,500 revolutions per minute, sweep gas flow of 4 L/min, $FiO_2$ of 0.7 and activated clotting time of between 150 and 180 s. Baseline cerebral oximetry values was 76/70%, right and left side respectively, and remained within the normal range during ECMO therapy.

In the following hours, the patient's blood pressure increased to 90/60 mmHg. Improvement of indirect signs of cardiac output, with recovery of diuresis and normalization of lactacidemia (serum lactate level 1.8 mmol/L) was observed. After achieving hemodynamic stability 12 h post-ECMO, epinephrine was gradually withdrawn. Because of the decrease in inotropic drugs and the high afterload due to the retrograde flow of ECMO, pulseless electrical activity occurred. Transthoracic echocardiography revealed a dilated left ventricle with biventricular dysfunction without aortic valve opening. Promptly epinephrine was reintroduced up to 0.17 mcg/kg/min, and pump flow was decreased up to 2 lpm to reduce afterload. After 20 min of mechanical cardiopulmonary resuscitation [LUCAS (Physio-Control/Jolife AB, Lund, Sweden)], recovery of spontaneous circulation occurred. One day later, sildenafil and bosentan were gradually re-introduced (Figure 4). The patient was progressively weaned from pump, guided by echocardiogaphy, maintaining velocity–time integral (VTI) around 10 cm, which allowed for decannulation of the patient at 96 h and subsequent extubation.

Twenty-four hours after ECMO withdrawal, intravenous perfusion of treprostinil (2.38 ng/kg/min) was progressively titrated up to the initial dose. The patient was transferred to the intermediate respiratory care unit and 28 days later discharged.

As mentioned above, due to the possibility of pump malfunction, treprostinil perfusion was started via central venous catheter, given that the abdominal area was swollen after subcutaneous drainage. Subsequently, although the patient was reluctant, the subcutaneous implantable pump was restarted, initially with saline, and later with treprostinil, noting the decrease in infusion rate to 0.06 ml/day. Simultaneously, intravenous treprostinil perfusion with external pump was maintained at home for 4 months until it was switched to the implanted pump. Currently, the patient remains clinically stable, and satisfied with the pump's restart, with a good quality of life.

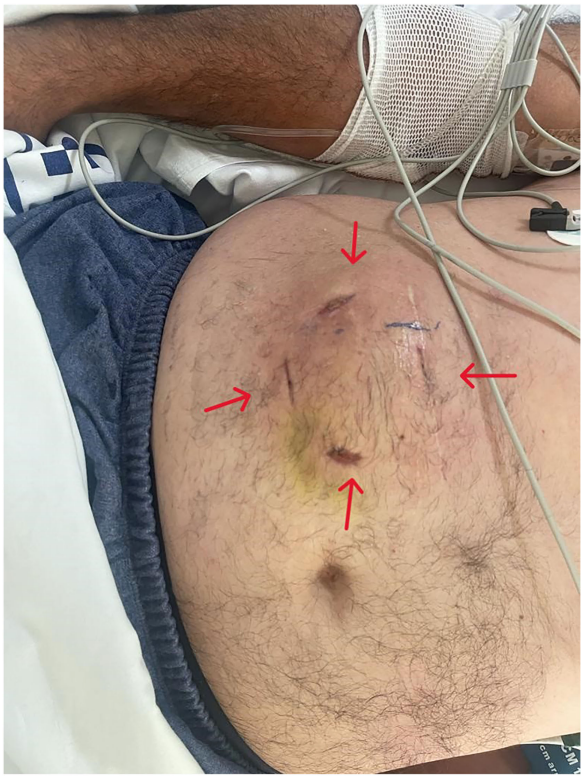

FIGURE 3
Abdominal incisions around the subcutaneous pump, 7 days later.

## Discussion

The patient described herein experienced refractory cardiocirculatory collapse and was uccessfully resuscitated using VA-ECMO even though the indication for VA-ECMO in vasoplegic shock is controversial. Vasoplegic or vasodilatory shock, is a condition defined by profound vasodilation due to persistently low systemic vascular resistance with normal or high cardiac index (5). Thus, maintaining adequate ECMO flows in this group of patients may be difficult due to relative intravascular hypovolemia. Consequently, the role of ECMO may be challenging in this condition.

Vasoplegic shock includes multiple and diverse etiologies, the most common types of this shock are septic, anaphylactic, and drug overdose. Numerous cases of septic shock in which ECMO is indicated have been reported since 2013, with a low survival rate of around 15% (6). Since then, single-center studies have emerged with a 36% improvement in survival. These studies were evaluated in a recent metanalysis of 468 patients, in which survival was higher in patients with EF <20% compared to those with EF >35% (62% vs. 32.1%) (7). Sepsis-induced cardiomyopathy is an increasingly recognized entity characterized by myocardial dysfunction in a sepsis setting. Up to half of patients with septic shock demonstrate some level of sepsis induced cardiomyopathy. The most recent Surviving Sepsis Campaign International Guidelines in 2021 do not include recommendations for VA-ECMO in cardiomyopathy refractory to inotropes. Considering all this data, the experts concluded VA-ECMO might be a reasonable treatment option in refractory septic shock when cardiac dysfunction is associated (8).

Anaphylactic shock is also characterized by arteriolar vasodilation resulting in vasoplegic shock. Additionally, in the

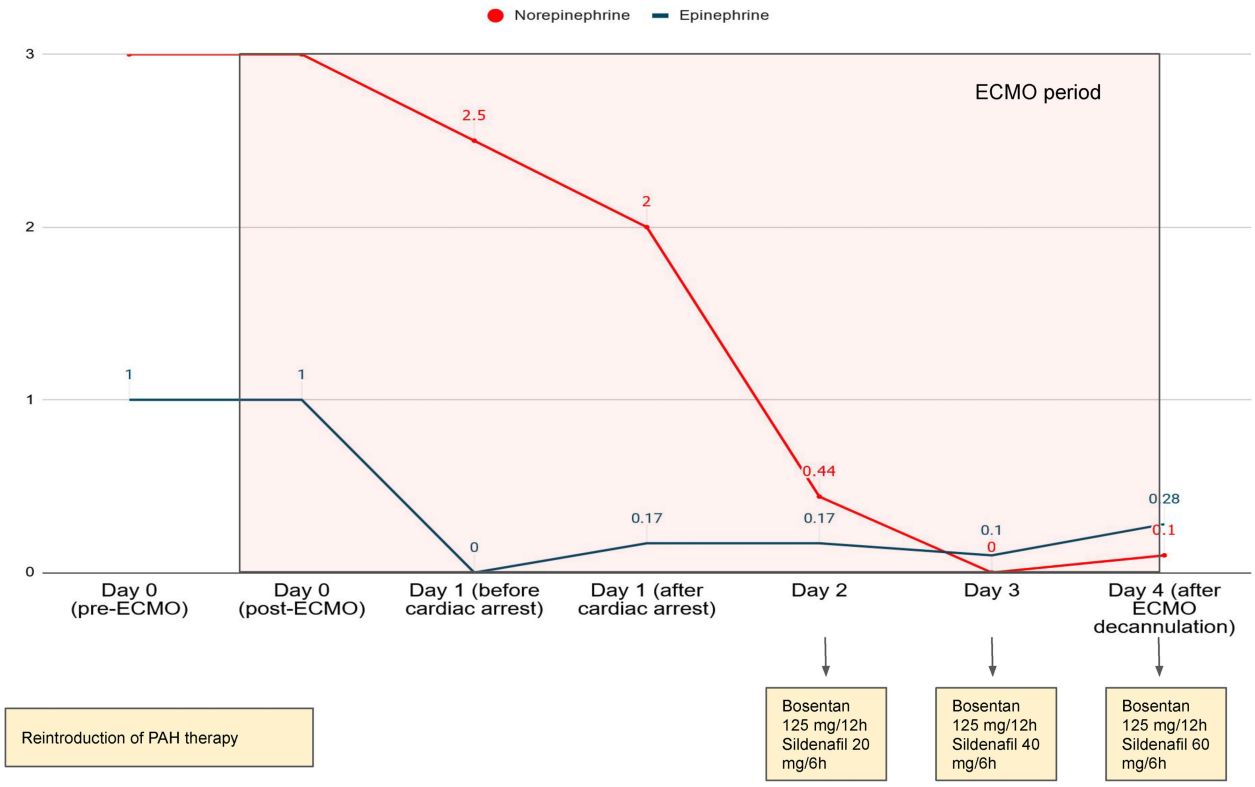


FIGURE 4
Trends in catecholamines and restart of pulmonary arterial hypertension treatment.

context of most severe anaphylactic shock requiring the need for ECMO, myocardial function is impaired. Sometimes, Kounis syndrome (coincidental occurrence of an acute coronary syndrome with hypersensitivity reactions following an allergic event) may cause myocardial dysfunction (9). There are various case reports of successful use of ECMO for anaphylactic shock (10). All of them involved severe allergic reactions, with left ventricular dysfunction (11–14), and some of them include Kounis syndrome (9, 15).

Another type of vasoplegic shock in which ECMO may be indicated is drug overdose, as in our patient. Other documented cases of VA-ECMO rescue for overdose such as amlodipine (16, 17), and metformin have been published (18). Overdose of both drugs not only cause vasoplegic shock but also cardiogenic shock. In metformin poisoning, intermittent hemodialysis or continuous renal replacement therapy is the first therapeutic rescue, but VA-ECMO support should be performed immediately when cardiac function is significantly depressed (18). On the other hand, amlodipine acts by blocking the voltage-sensitive (l-type) calcium channels 3 and thus affects not only vascular smooth muscle tone, but also myocardial contractility, automaticity, and atrioventricular conduction.

Unlike other intoxications, treprostinil overdose is strictly a vasoplegic shock with no cardiotoxic component. In our center we normally perform a transthoracic echocardiography prior to ECMO cannulation to confirm the choice of ECMO configuration. In this case, it allowed us to determine that biventricular function was not impaired. VA-ECMO was planned as desperate therapy.

Treprostinil poisoning is rare due to its less frequent use but is life-threatening. In adults, there are two published cases, without requiring ECMO, since the doses administered subcutaneously were lower than in our patient [100 mg subcutaneous (19) y 7.5 mg subcutaneous (20)]. The treatment was only hemodynamic support since treprostinil may not be reliably eliminated by hemodialysis, and no specific antidote is available. However, in refractory shock, even in merely vasoplegic shock, ECMO serves as a bridge-to-recovery by maintaining perfusion to vital organs, affording time for drug elimination.

Treprostinil does have a half-life of 3.5 h. Therefore, drug elimination should finish after 12–16 h. However, Hohenforst-Schmidt et al. (19) noticed patient experienced prolonged hemodynamic effects. In our case it was difficult to assess how long the vasodilator effect of treprostinil lasted, given that the patient was supported with ECMO but norepinephrine begins to decrease after 24–48 h. Predicting the absorption of a subcutaneous drug was difficult, after injecting saline into the area and placing cold gauze to delay absorption. Although this measure did not seem to be effective at first, it may have contributed to reducing the severity of the shock.

The use of VA-ECMO for vasodilatory shock carries the risk for cerebral hypoperfusion and aortic valve closure by exposing the heart to increased afterload due to high doses of alpha-adrenergic catecholamines. Optimal monitoring such as near-infrared spectroscopy, pulse oximetry saturation in the right hand, and serial transthoracic echocardiography is essential to avoid complications (21). Diary echocardiography is mandatory in VA-ECMO. Weaning trials are essential to assess the behavior of ventricles during increases in preload. Moreover, the pulmonary artery catheter could have helped in our case. When monitoring pulmonary artery pressures in a patient with VA-ECMO we must understand that they are not real since the cardiac output passing through the pulmonary artery is only 40%. Apart from the unreliability of the Swan–Ganz parameters resulting from suction of the venous ECMO cannula, some authors reject the use of a Swan–Ganz catheter in patients on VA-ECMO support due to safety issues such as migration of the catheter or introduction of air to the ECMO system (22). However, it plays an important role in weaning from ECMO, supporting the echocardiogram, since elevated capillary pressures support left ventricular failure. Moreover, in our case, the pulmonary artery monitoring would have helped us restart PAH medication more accurately.

To our knowledge, this is the first case of failure in treprostinil refill and vasoplegic catastrophic shock requiring VA-ECMO. ECMO may be considered in vasoplegic shock due to overdose of vasodilatory medication. It allows organ perfusion to be maintained, with the knowledge that recovery is as rapid as drug elimination. Continuous monitoring is necessary to determine the optimal time to wean the patient off ECMO to avoid complications, because in vasoplegic shock, the risk of cerebral hypoperfusion and aortic valve closure is higher than in other indications for VA ECMO.

Finally, emphasizing and reinforcing the safety of monthly pump refill is critical. In cases of difficulty in locating the entry port, ultrasound should be used to ensure the initial position of the needle. Also, it is very important that the filling of the pump is done progressively with small strokes followed by aspirations to ensure that the needle remains in the reservoir throughout the procedure. We highlight the slowing of pump infusion rate after its temporary cessation.

## Data availability statement

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

## Ethics statement

Ethical approval was not required for the studies involving humans because It is a case report, and we have the written consent from the patient. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

## Author contributions

LV: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing, Validation, Visualization. SL: Data curation, Methodology, Writing – review & editing. AO: Data curation, Methodology, Visualization, Writing – review & editing. ÁB: Data curation, Formal Analysis, Methodology, Visualization, Writing – review & editing. MA: Data curation, Methodology, Visualization, Writing – review & editing. MÉ: Data curation, Methodology, Validation, Writing – review & editing. NO: Data curation, Methodology, Visualization, Writing – review & editing. LC: Data curation, Methodology, Visualization, Writing – review & editing. AR: Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. GP: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

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

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# Case Report: A case of Kounis syndrome induced by iodine contrast agent during coronary angiography

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Kounis Syndrome (KS), a seldom-seen adverse reaction to iodine contrast agents, has an incidence that remains unclear. At present, there are no unified guidelines for managing KS either nationally or internationally. Ioversol, a new triiodinated hypotonic nonionic contrast agent, is commonly used in cardiovascular Computed Tomography (CT) and vascular imaging for diagnostic purposes. Its principal adverse reactions encompass fever, dermatological responses, convulsions, respiratory distress, hypersensitivity reactions including KS, and acute renal injury. This paper documents a case of KS induced by an iodine contrast agent during coronary angiography and, at the same time, searches for related literature and carries out a summary analysis in an attempt to provide a dependable reference for clinicians to make accurate diagnoses and treatments.

KEYWORDS

allergy, coronary spasm, ioversol, Kounis syndrome, cardiovascular system

## Introduction

As an acute coronary condition, Kounis Syndrome (KS) results from an anaphylactic reaction caused by the interaction of mast cells and inflammatory cells. It extends beyond a single-organ disorder, representing a complex, multisystem disease with considerable implications for both morbidity and mortality (1). The first case of acute myocardial infarction due to a penicillin allergy was reported by Pfister and Plice in 1950. In 1991, Greek scholars Kounis et al. established a correlation between allergic reactions, inflammatory mediators, and concurrent angina pectoris, thereby proposing the concepts of "allergic angina syndrome" and "allergic myocardial infarction" (2). Therefore, many scholars started referring to the acute coronary syndrome induced by severe allergic reactions as Kounis Syndrome in subsequent reports. KS is not a rare condition and can occur at any age. However, due to its atypical clinical manifestations and scarce clinical data, clinicians' knowledge of KS remains incomplete, resulting in frequently underdiagnosed conditions in clinical practice (3).

## Case report

A 59-year-old male was admitted to our center, complaining of persistent chest pain over three days. He reported a 40-year history of heavy smoking and sporadic alcohol consumption for 18 years. His medical, allergy, and family histories were unremarkable. On admission, myocardial injury biomarkers revealed a myoglobin level of 45.4 ng/ml

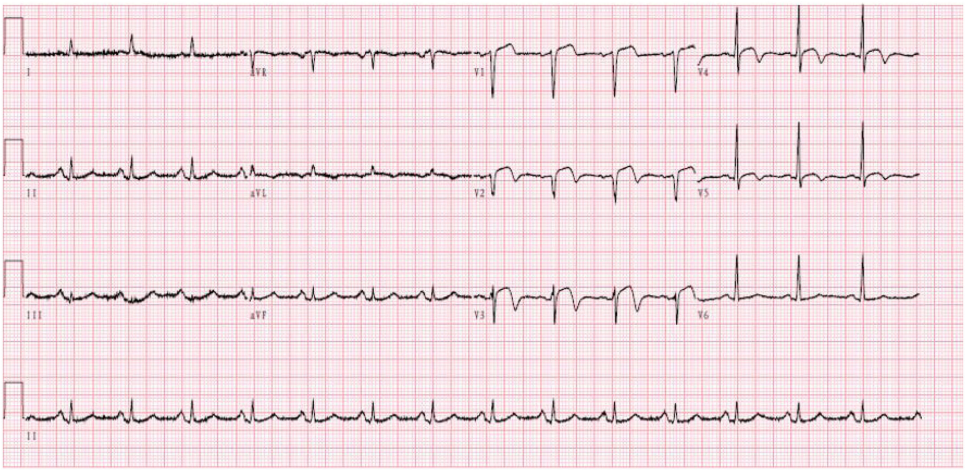

FIGURE 1
Electrocardiogram showing extensive anterior wall myocardial infarction.

(0–121 ng/ml), a CK-MB mass of 4.85 ng/ml (0–3.38 ng/ml), and an ultrasensitive troponin I level of 2.47 ng/ml (0–0.034 ng/ml). The electrocardiogram (MAC800 model, GE Company) revealed an acute, extensive anterior wall myocardial infarction (Figure 1). Further, an echocardiogram (vividE9 model, GE Company) identified a left ventricular ejection fraction amounting to 56%, coupled with segmental motion abnormalities of the ventricular wall and a decreased amplitude of the lower ventricular septal pulsation. Following the diagnosis of "coronary artery atherosclerotic heart disease, extensive anterior myocardial infarction with Killip grade I classification", a coronary angiogram was executed on the fifth day of the patient's hospital stay. Local stenosis of 95% within the proximal Left Anterior Descending artery (LAD) was evident, with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 3 (Figure 2A). Meanwhile, the Left Circumflex artery (LCX) showed non-significant stenosis, maintaining a TIMI grade of 3 (Figure 2B). Moreover, diffuse stenosis from the proximal to middle and distal segments of the Right Coronary Artery (RCA) was noted, along with greater than 90% stenosis, preserving a TIMI grade 3 flow (Figure 2C). We proposed to perform stenting for LAD, but the patient had a sudden onset of a peripheral red rash, decreased intracoronary pressure, and dyspnea during angiography. Re-evaluation angiography revealed proximal LAD occlusion, stenosis of the Obtuse Marginal artery (OM) and LCX, and diffuse RCA stenosis with distal segment occlusion (Figure 3A). The patient's blood pressure dropped to 55/35 mmHg, while his heart rate was 108 bpm. We attributed this to an allergic reaction and promptly administered adrenaline 0.1 mg, dexamethasone 10 mg, morphine injection 3 mg immediately, and norepinephrine infused to relieve the allergic reaction and maintain blood pressure. At the same time, continuous and large amounts of intracoronary nitroglycerin was given, after which the patient's symptoms gradually subsided,

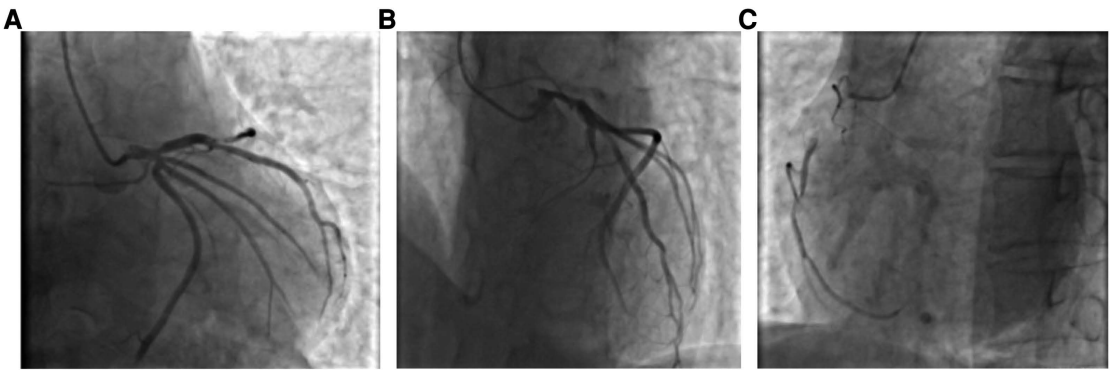


FIGURE 2
(A) Coronary angiogram showing limited stenosis in the proximal segment of the LAD, up to 95% or more, with antegrade TIMI grade 3; (B) Coronary angiogram showing no significant stenosis in the LCX, with antegrade TIMI grade 3; and (C) Coronary angiogram showing diffuse stenosis from the proximal to the middle and distal segments of the RCA, up to 90% or more, with antegrade TIMI grade 3.

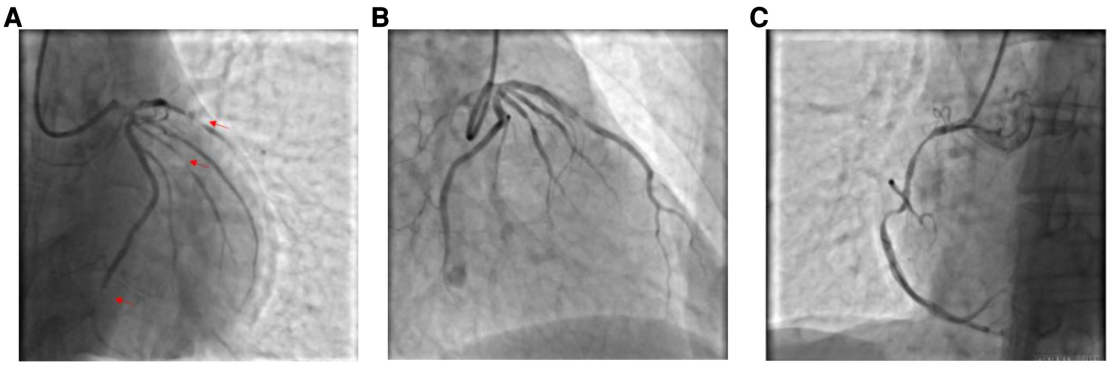


FIGURE 3
(A) Coronary angiography shows proximal occlusion of the LAD, stenosis of the OM and LCX, and diffuse stenosis of the RCA throughout, with occlusion of the distal segments. (B) Stenosis is relieved by intracoronary injection of nitroglycerin. (C) Stenosis of the RCA is markedly improved by administration of nitroglycerin for half a minute.

stenosis improved (Figure 3B), and RCA stenosis improved significantly after half a minute of nitroglycerin administration (Figure 3C). Following a mid-segment LAD stent implantation, blood flow was restored (Figure 4). Postoperatively, his heart rate was 103 bpm, his blood pressure was 107/63 mmHg, and he was transferred to the coronary care unit for further surveillance. Postoperative examination: the patient was clear and cooperative, but a generalized red rash remained. He was diagnosed with Type II Kounis Syndrome with cardiogenic shock induced by iodophorol. His management included promethazine, vitamin C, norepinephrine and dopamine, after which the patient's blood pressure was maintained at 100/60 mmHg. On the first postoperative day, his blood pressure was 106/63 mmHg, his pulse was 75 bpm, and his level of consciousness was normal. The red rash gradually faded. Laboratory studies exhibited a cardiac troponin I level of 0.582 ng/ml (0–0.034 ng/ml) and an elevated high-sensitivity C-reactive protein level of 87.52 mg/L (0–3.5 mg/L). His IgM level was normal at 0.55 g/L (0.3–2.2 g/L), and his IgE level was less than 18.80 IU/ml (<100 IU/ml). Four days after the surgical intervention, the patient reported no discomfort, and his ultrasensitive troponin I level was down to 0.159 ng/ml (0–0.034 ng/ml). He was discharged with instructions for regular antiplatelet medication and future caution with contrast agents.

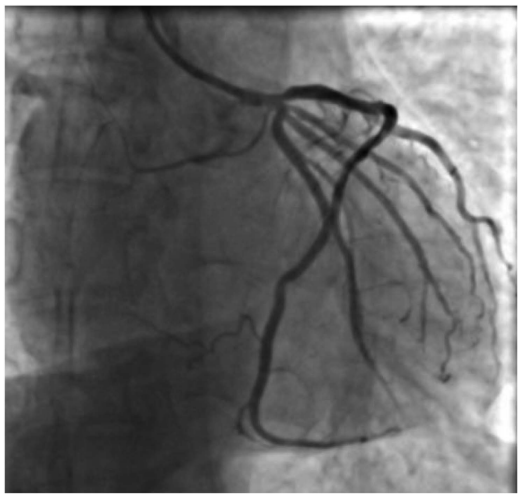

FIGURE 4
Coronary angiogram showing no residual stenosis after placement of 1 stent in the proximal segment of the LAD with anterograde flow TIMI grade 3.

## Epidemiology

A prospective study by Ayhan Akoz and colleagues suggested that the incidence of KS in the emergency department was 19.4 cases per 100,000 individuals per year among all patients admitted to the hospital. This rate reflects the under-recognition and under-reporting of this condition rather than its rarity (4). Moreover, a large epidemiological study from the U.S. revealed that among 235,420 patients admitted due to allergic or hypersensitivity reactions, 2,616 patients (1.1%) presented with acute coronary syndrome and were subsequently diagnosed with KS (5). Although KS can manifest at any age, it predominantly affects males aged 40–70 years (74.3%). Individuals with a history of allergies, hypertension, smoking, diabetes mellitus, and hyperlipidemia are at increased risk of developing KS. Of all the reported KS cases, 6% are induced by contrast medium (6).

## Etiology and pathophysiological mechanisms

The exact pathophysiological mechanisms contributing to Kounis syndrome (KS) are unknown. Mast cells, abundant in both the heart and blood vessels, are central to the pathogenesis of KS. Their excessive production and breakdown have been implicated in the pathophysiology of coronary artery vasospasm (7). The degranulation of mast cells leads to the release of

allergic inflammatory mediators such as histamine, proteases, thromboxane, prostaglandins, leukotrienes, 5-hydroxytryptophan, and various cytokines. These contribute to coronary artery constriction, plaque rupture, and platelet aggregation, all of which play an important role in KS-associated angina (8). Mast cell activation in Acute Coronary Syndromes (ACS) is considered a primary event,not a result of coronary artery spasm. There is evidence that tryptase levels are elevated in peripheral blood during spontaneous myocardial ischemia, whereas they are not elevated during drug-induced coronary artery spasm, this situation also proves it (9). Literature suggests that while any drug can potentially induce KS, common culprits include antibiotics, analgesics, anesthetics, anti-tumor drugs, herbal medicines, and contrast media (10). Notably, some studies have indicated that iodinated contrast agents applied for coronary angiography can also induce KS during secondary patient exposure (11).

## Diagnosis

The spectrum of initial symptoms in Kounis Syndrome (KS) is wide, ranging from mild indicators (e.g., flushing, nausea, vomiting, chest pain, and chest discomfort) to severe instances (e.g., hemodynamic instability and sudden death) (12). In any patient presenting with systemic allergic reactions, if these are coupled with acute myocardial ischemic symptoms reflected in clinical examinations, electrocardiograms, echocardiograms, angiographic assessments, and laboratory studies, a diagnosis of KS should be contemplated. Complementary diagnostic tests like cardiac magnetic resonance imaging, optical coherence tomography, and myocardial scintigraphy can also aid in the diagnosis. Serum trypsin-like enzymes, IgE antibodies, cardiac enzymes, Creatine Kinase (CK), CK-MB, and troponin should be tested in all cases to confirm or exclude the diagnosis of KS (13). In cases presenting with shock, the onset of an allergic reaction may be so rapid that rashes may not appear. Consequently, the absence of a rash does not exclude an allergic reaction but could be indicative of hypotensive shock (14). Now most scholars are recognized to classify KS into three types: Type I, the most prevalent, typically occurs in patients with intact coronary arteries devoid of risk indicators for coronary artery disease. This condition is triggered by allergen-induced inflammation, releasing inflammatory mediators that give rise to coronary artery spasms, occasionally accompanied by elevated myocardial enzymes and troponin levels. Type II emerges as an acute myocardial infarction induced by coronary artery spasms in patients with pre-existing coronary artery disease, frequently correlating with plaque erosion or rupture. Type III, a variant, materializes in patients with a past record of coronary artery stenting, where allergic reactions instigate acute thrombus formation within the stent (15).

## Treatment progress

The management of Kounis Syndrome (KS) must simultaneously address both acute coronary syndrome and allergic reactions. As of yet, no national or international guidelines are in place; however, an immediate stoppage of potential triggers such as medications, food, and environmental exposures can prevent further cardiac injury (16). Treatment for Type I KS often includes simple anti-allergic measures such as corticosteroids (for example, hydrocortisone) and H1 and H2 receptor antagonists, which often suffice to alleviate symptoms. For Type II KS, treatment should be with both corticosteroids and antihistamines and follow ACS treatment guidelines. In patients with type III KS, a severe myocardial infarction protocol should be followed and thrombus aspiration performed immediately, followed by histologic examination of the aspirated material and staining for eosinophils and mast cells (17). In patients who develop allergic reactions post-stent implantation, standard anti-allergic treatments can often be effective. Should these measures fail, the causative agent can be identified via patch and/or skin prick testing after implementing desensitization procedures. If an allergy to nitinol (nickel-titanium alloy), as confirmed by patch testing, is noted, stent removal may become necessary if desensitization fails (18). It's important to note that adrenaline, similar to beta-blockers, can exacerbate coronary artery spasms and deteriorate clinical conditions. Given these circumstances, glucagon, not adrenaline, should be the first-line therapy for treating allergic reactions in KS patients (10). Thus, adrenaline should only be administered in cases of severe allergic reactions, keeping in mind that adequate fluid resuscitation and oxygen therapy are crucial treatments for KS (19). The use of vasopressors and vasodilators to relieve coronary spasm is also contradictory in hypotensive patients. However, coronary angiography is a meaningful therapeutic approach in this setting. Firstly, both type II and type III KS are combined with acute thrombotic occlusion, requiring coronary intervention. Secondly, the intracoronary administration of nitroglycerin can alleviate vasospasms. However, the advantages must be weighed against the potential risk of exacerbating allergic reactions through the use of iodinated contrast agents (20). In cases of refractory KS, cardiopulmonary cerebral resuscitation proved ineffective, and the use of extracorporeal membrane oxygenation (ECMO) should be considered as early as possible for effective maintenance of coronary circulation (21).

# Discussion

For cardiologists, the presence of an acute coronary syndrome in patients with anaphylaxis is a challenging diagnostic dilemma (22). In the present case, the patient is a middle-aged man with no prior history of allergies or underlying coronary artery disease. The onset of disease is consistent with the prevailing epidemiologic pattern of previous KS. His condition developed into significant allergic reactions, abnormal volume distribution, and widespread peripheral vasodilation during angiography, leading to a diagnosis of iodophorol-induced Type II KS. After the patient developed allergy-related symptoms during coronary angiography, we found that the RCA stenosis was significantly worse than before and considered the possibility of KS. It has been shown that endothelial dysfunction can be detected in

patients with mastocytosis and that endothelial function appears to be negatively affected by mast cell proliferation (23). Mast cells are predominantly found in the cardiovascular system at coronary plaque sites and may infiltrate areas of plaque erosion or rupture. The number of cardiac mast cells is up to 200 times higher in patients with coronary plaques compared to the coronary arteries of healthy individuals (9). Therefore, it can be hypothesized that patients with severe coronary atherosclerotic plaques are at higher risk of developing KS syndrome, even if there is no previous history of allergy. Patients without a history of allergy but with extensive mast cell activation due to advanced atherosclerosis may represent a specific type of Kounis syndrome. The treatment of this patient is ambivalent, and there are currently no harmonized guidelines on KS. Nitroglycerin can relieve coronary artery spasms but exacerbate hypotension, while adrenaline and noradrenaline can reverse hypotension but intensify coronary artery spasms. Taking into account our medical center's experience in treating KS and the treatments used in some previous case reports (24), we consider that coronary artery spasm is the underlying cause of KS. To prevent further myocardial ischemia exacerbations, in addition to the standard antiplatelet therapy for coronary artery disease, we initially administered nitroglycerin intracoronary to alleviate the coronary artery spasm during the operation. Subsequently, we employed vasoconstrictors, fluid resuscitation, and adequate anti-allergic treatment to maintain stable vital signs. The significant improvement in RCA stenosis after administration of antiallergic and intracoronary nitroglycerin treatment supports the diagnosis of iophorol-induced type II KS. The patient responded well to treatment, and his prognosis was favorable.

## Conclusion

In comparison to KS caused by other allergens, contrast-induced KS during coronary angiography poses more risk due to the potential for widespread coronary artery spasms. Prior studies have indicated that contrast-induced KS can lead to severe complications, with 23.1% of cases resulting in cardiac arrest and a 7.7% mortality rate (2). Yet, there is no clear consensus on directives for diagnosing and treating KS. Not all KS patients are effectively identified and managed in a timely manner. Presently, the diagnosis and treatment methods for KS are generally derived from cumulative experience outlined in case report summaries. Therefore, it is essential to increase the number of randomized clinical trials on KS, to improve clinicians' understanding of KS, and to incorporate the standard treatment of KS into the ACS guidelines.

## Data availability statement

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

## Ethics statement

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

## Author contributions

YS: Writing – original draft, Data curation. JZ: Writing – review & editing.

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## Conflict of interest

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

## Publisher's note



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# A case report on pheochromocytoma mimicking as fulminant myocarditis—a diagnostic challenge

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We present an exceptional case of a 53-year-old female, initially misdiagnosed with fulminant myocarditis, but later correctly diagnosed with pheochromocytoma. The presentation of the patient included a spectrum of symptoms such as headache, chest discomfort, palpitations, and dyspnea, following the intake of Domperidone. Two weeks prior to admission, the patient had experienced episodes of diarrhea and a low-grade fever. Unresolved symptoms and an unmanageable surge in blood pressure despite comprehensive fulminant myocarditis treatment prompted further investigation. The discovery of an adrenal mass via a CT scan and subsequent biochemical tests led to the confirmation of pheochromocytoma. Implementation of alpha-blockade therapy and a successful laparoscopic adrenalectomy resulted in significant clinical improvement. This case underscores the diagnostic intricacies of pheochromocytoma and highlights the need for vigilance when faced with severe, unresponsive cardiovascular symptoms.

KEYWORDS

pheochromocytoma, fulminant myocarditis, Domperidone, catecholamine-induced cardiomyopathy, alpha-blockade therapy

## Introduction

Pheochromocytoma, a rare neuroendocrine tumor originating from chromaffin cells of the adrenal medulla, is notorious for its varied clinical presentations, often complicating its diagnosis (1, 2). Myocarditis, an inflammatory condition of the myocardium, has numerous etiologies, encompassing viral infections, autoimmune diseases, and drug reactions (3). It often manifests with symptoms like chest pain, shortness of breath, fatigue, and heart palpitations. In extreme cases, it can progress to heart failure, arrhythmias, or even sudden cardiac death (4). Although distinct, pheochromocytoma can display symptoms akin to myocarditis due to an overproduction of catecholamines, influencing the cardiac function (5). Such overlaps can create confusion, leading to misdiagnosis, particularly in patients with acute cardiac symptoms. We report an unusual case of a 53-year-old woman initially suspected of fulminant myocarditis but ultimately diagnosed with pheochromocytoma. This case aims to bring attention to this potentially fatal condition and offers a thorough review of similar cases documented in literature.

## Case presentation

A 53-year-old female presented to our emergency department urgently with a one-day history of headache, chest tightness, palpitations, and dyspnea. These symptoms emerged

around 15 min post Domperidone administration, taken due to a loss of appetite. There was no report of anterior chest pain but she subsequently developed dyspnea and irritability. Remarkably, the patient had endured episodes of diarrhea and low-grade fever two weeks prior to this visit, which spontaneously resolved. The patient's medical history was unremarkable, with no previous episodes of hypertension, diabetes, or coronary heart disease, and no relevant familial history was reported.

Initial assessment showed a body temperature of 36.5°C, heart rate of 117 beats per minute, respiratory rate of 24 breaths per minute, and blood pressure of 120/74 mmHg. The patient was conscious but exhibited signs of lethargy and pallor. She reported orthopnea and found relief from dyspnea in an upright position. Upon auscultation, crackles were noted in the lower lung fields. The heart rhythm was regular with no noticeable abnormalities. There was no peripheral edema observed. An immediate electrocardiogram (ECG) displayed ST-segment depression in leads II, III, AVF and V3 to V6, as well as T-wave inversions in leads II, AVF and V4 to V6 (Figure 1A). The myocardial enzyme analysis showed significantly elevated levels of myoglobin (MYO, 284.04 ng/ml; normal 0–58 ng/ml), creatine kinase isoenzyme (CK-MB, 100 ng/L; normal 0–5 ng/ml), cardiac troponin-T

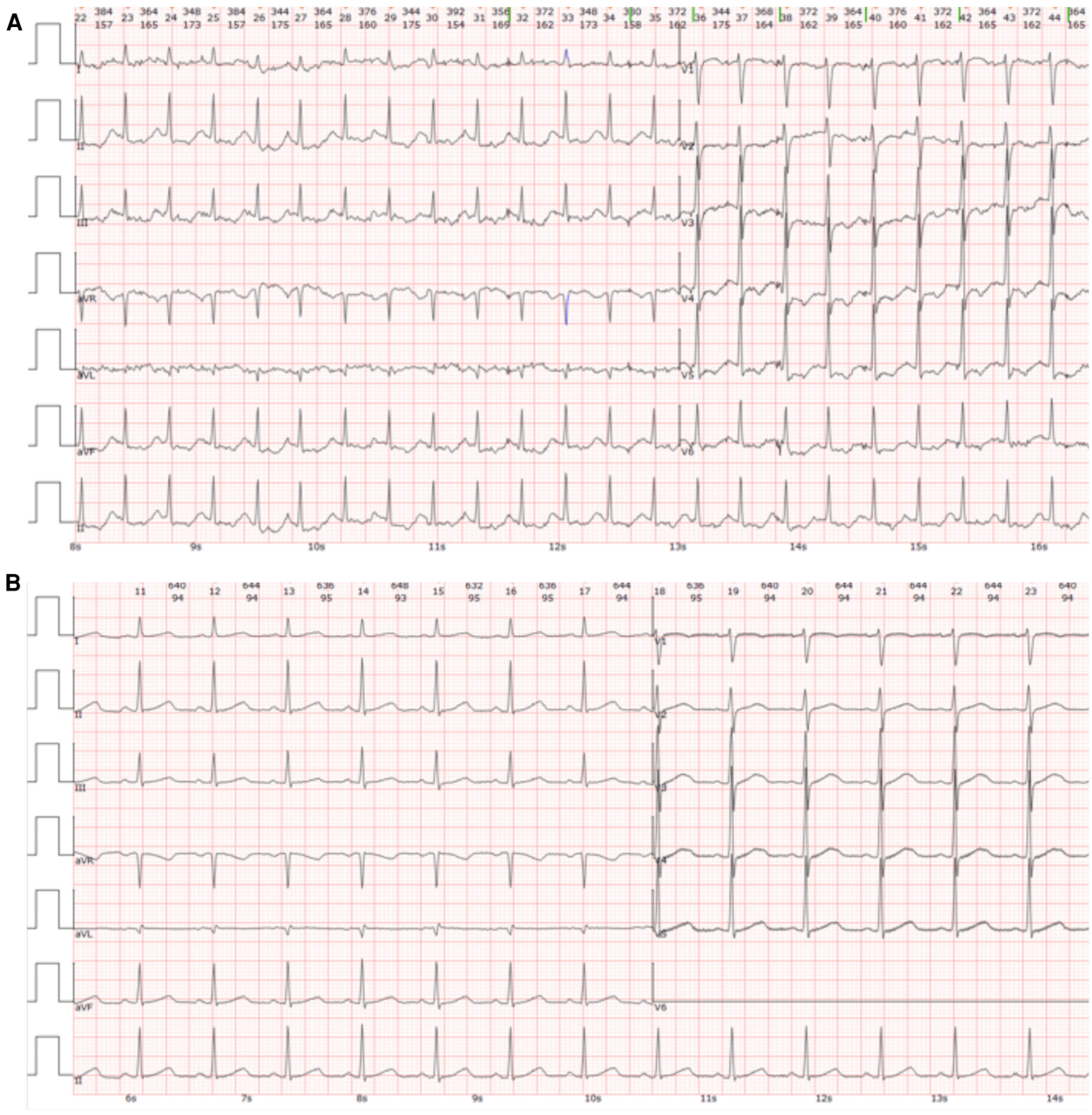


FIGURE 1
Electrocardiogram (ECG) findings. (A) The initial ECG conducted upon admission revealed ST-segment depression in leads II, III, AVF, and V3 to V6, along with T-wave inversions in leads II, AVF, and V4 to V6. (B) The ECG taken at discharge exhibited a normal sinus rhythm without significant abnormalities.

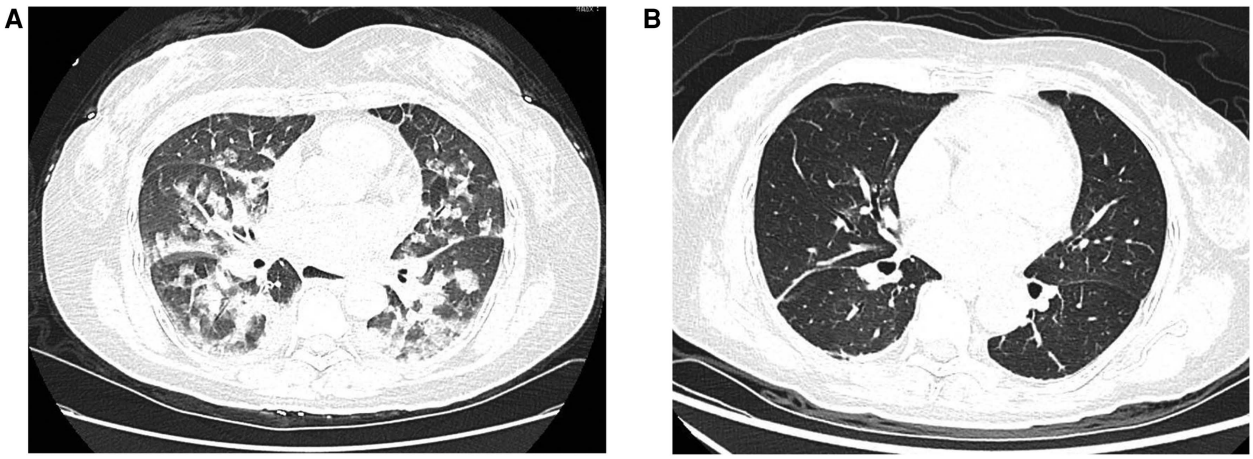


FIGURE 2
Chest computed tomography (CT) scans. (**A**) The initial chest CT scan performed upon admission demonstrated bilateral pulmonary edema. (**B**) A repeat chest CT scan at discharge showed complete resolution of the previously noted pulmonary edema.

(cTnT, 1,569 ng/L; normal 0–14 ng/L), as well as N-terminal pro-brain natriuretic peptide (NT-proBNP, 14,058 pg/ml; normal 0–300 pg/ml). Arterial blood gases analysis revealed a pH of 7.24, pO2 of 56 mmHg, pCO2 of 32.7 mmHg, $HCO3^-$ of 14 mmol/L, and lactic acid of 8.42 mmol/L. Additional laboratory tests showed leukocytosis, elevated procalcitonin, and liver enzyme abnormalities, while coagulation, electrolyte, and renal function tests remained within normal limits. An echocardiogram showed diffuse left ventricular hypokinesia with a depressed ejection fraction of 26.9% along with mild mitral and tricuspid valve regurgitation. A chest computed tomography (CT) scan suggested bilateral pulmonary edema, potentially compounded by a lung infection (Figure 2A).

Given the fulminant myocarditis suspicion, the patient was immediately transferred to the emergency intensive care unit (EICU), and a comprehensive treatment strategy was adopted, including non-invasive ventilatory support, antiviral therapy, intravenous immunoglobulin, corticosteroids, anti-infective therapy, and aggressive heart failure management. However, the patient's condition deteriorated, with persistently elevated cardiac markers, and considerations for mechanical circulatory support emerged. On the third day of hospitalization, a sudden and significant increase in blood pressure discouraged the usage of extra-corporeal membrane oxygenation (ECMO) and prompted a reassessment of the initial diagnosis. It is worth noting that despite the administration of medications such as Sodium Nitroprusside and Calcium channel blockers, the patient's blood pressure remained challenging to control. At this point, a contrast-enhanced abdominal CT scan revealed a $26 \times 26 \times 25$ mm mass in the right adrenal gland, leading to suspicion of pheochromocytoma (Figure 3A). This suspicion was supported by elevated plasma metanephrine (2.15 nmol/L; normal < 0.50 nmol/L), plasma normetanephrine (1.24 nmol/L; normal < 0.90 nmol/L), urinary metanephrine (1,954 nmol/24 h; normal < 216 nmol/24 h), and urinary normetanephrine (1,399 nmol/24 h; normal < 312 nmol/24 h). Upon further questioning, the patient stated that she had been having episodic headaches with vomiting and sweating, as well as elevated blood pressure, usually post-Domperidone administration. In light of these findings, the diagnosis was revised from fulminant myocarditis to pheochromocytoma-induced cardiomyopathy, also known as a pheochromocytoma crisis.

Following the initiation of alpha-blockade therapy, the patient's condition gradually improved, with the normalization of various clinical and biochemical markers, improvement in left ventricular ejection fraction (50.8%), and resolution of ECG (Figure 1B) and radiological findings (Figure 2B). Four weeks following alpha-blockade therapy, the patient underwent successful laparoscopic right adrenalectomy (Figures 3B,C), with the pathology report confirming adrenal pheochromocytoma (Figure 3D).

## Discussion

Our report sheds light on the intricate diagnostic conundrums that arise from the diverse presentations of pheochromocytoma, which, in this case, mimicked fulminant myocarditis, leading to a delay in precise diagnosis and intervention.

Pheochromocytoma is an infrequent neuroendocrine tumor originating from the chromaffin cells of the adrenal medulla. Its ability to mimic a multitude of cardiovascular, endocrine, and psychiatric conditions is attributed to its sporadic secretion of catecholamines (6). This attribute warrants its label as "The Great Mimic" (7, 8). Conversely, fulminant myocarditis represents an acute, severe myocardium inflammation, typically induced by viral infections, drugs, or autoimmune diseases. It can escalate swiftly to acute heart failure, shock, and possibly death if not promptly identified and managed (9). A common pathophysiological aspect of both conditions is the cataclysmic surge of catecholamines. Pheochromocytoma provokes an

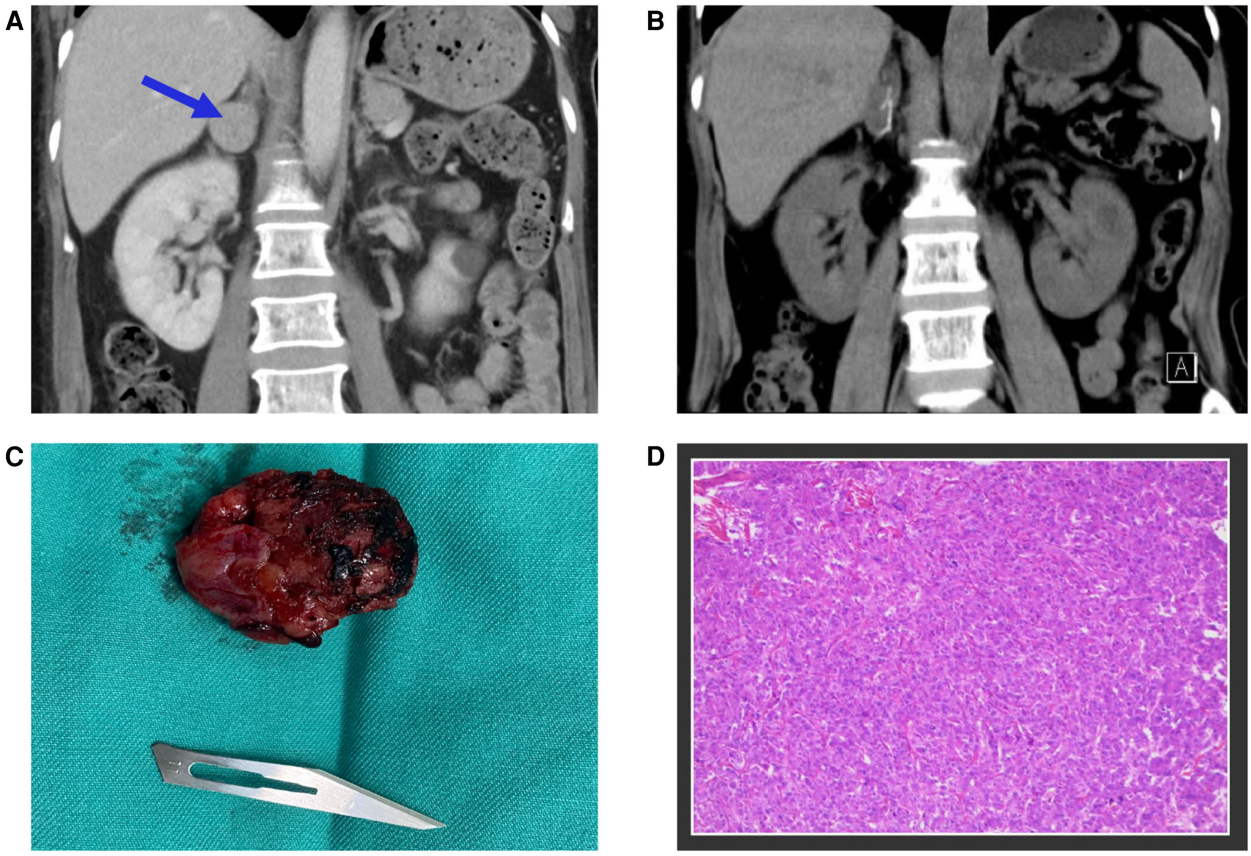


FIGURE 3
(A) The contrast-enhanced abdominal CT scan identified a 26 × 26 × 25 mm mass located in the right adrenal gland, marked with blue arrows. (B) The postoperative follow-up CT scan revealed the complete excision of the tumor mass. (C) A photograph of the surgically removed tumor during the operation. (D) Microscopic examination of the adrenal gland tumor confirmed the diagnosis of pheochromocytoma.

overproduction of catecholamines, potentially leading to catecholamine-induced cardiomyopathy (10). Simultaneously, in fulminant myocarditis, the body's stress response triggers a release of catecholamines, aggravating myocardial injury (11). The coexistence of these clinical features complicates the differentiation of these two conditions, particularly in an acute context.

Our case underscores the cruciality of harboring a high level of suspicion for pheochromocytoma in patients exhibiting severe cardiovascular symptoms. This is particularly significant when the clinical trajectory deviates from the usual course of myocarditis or proves unresponsive to conventional treatment. Clinicians must be alert to signs such as episodic hypertension, fluctuating blood pressure, or intractable hypertension, indicative of possible pheochromocytoma (12). Our case demonstrates that the initial lack of these signs might lead to an erroneous diagnosis, thus accentuating the intricacies in handling such situations. However, a meticulous examination of the patient's history revealed periodic headaches accompanied by vomiting and sweating, and escalated blood pressure post Domperidone intake. This, paired with the subsequent discovery of the adrenal mass, provoked a reconsideration of the initial diagnosis to pheochromocytoma-induced cardiomyopathy or a pheochromocytoma crisis.

The patient consistently experienced identical symptoms post Domperidone intake, prompting our exploration into a potential connection. We hypothesize that the heightened blood pressure and related symptoms observed after Domperidone administration can be attributed to the drug's influence on gastrointestinal motility. Dopamine, a neurotransmitter, naturally restrains smooth muscle contractions in the gastrointestinal tract, playing a pivotal role in motility regulation (13). In contrast, Domperidone interacts with dopamine receptors, effectively blocking dopamine's inhibitory effects (14). This disruption leads to increased smooth muscle activity, thereby amplifying gastrointestinal motility. Considering a potential complication with a pheochromocytoma, a tumor known for excessive catecholamine secretion, the stimulation caused by Domperidone-induced gastrointestinal motility may trigger an abnormal surge in catecholamines. This surge can manifest as periodic episodes of elevated blood pressure, accompanied by symptoms like headache, palpitations, and sweating. This proposed theory aligns seamlessly with the patient's clinical presentation. The symptoms emerged shortly after Domperidone intake, closely mirroring the typical manifestations of pheochromocytoma, including episodic hypertension and other

catecholamine-associated symptoms. However, to substantiate this hypothesis and establish a direct causal relationship between Domperidone-induced gastrointestinal motility and pheochromocytoma stimulation, further investigation is essential. Validation of this theory would not only deepen our understanding of the patient's condition but also contribute valuable insights into the potential risks associated with Domperidone use in cases of underlying conditions such as pheochromocytoma.

Diagnostic methods such as biochemical testing and imaging play a crucial role in diagnosing pheochromocytoma, with escalated levels of plasma or urinary metanephrines serving as the principal diagnostic indicator. Moreover, imaging tools like CT scan or magnetic resonance imaging (MRI) aid in identifying adrenal or extra-adrenal tumors (15, 16). The confirmation of a pheochromocytoma diagnosis necessitates initiating alpha-blockade therapy to manage hypertension and prepare the patient for surgical intervention, which is the ultimate treatment strategy for this condition (17). The significant improvement observed in our patient after initiating alpha-blockade and undergoing adrenalectomy reinforces the efficacy of this therapeutic regimen.

An exploration of similar case studies reveals that the singular presentation observed in our case is not an isolated phenomenon. Levin BS et al. presented a case where a patient initially diagnosed with fulminant myocarditis was later discovered to have a pheochromocytoma (18). Likewise, Wu et al. detailed a case involving two middle-aged males with acute myocarditis and cardiogenic shock, necessitating an intra-aortic balloon pump (IABP) and ECMO for life support, ultimately unmasking the presence of a pheochromocytoma (19). In the same vein, Rojbi I et al. documented a case of a 40-year-old female with symptoms suggestive of fulminant myocarditis and COVID-19 pneumonia, later attributed to a pheochromocytoma (20). These cases collectively reiterate the diagnostic hurdles posed by pheochromocytoma mimicking fulminant myocarditis. The capacity of pheochromocytoma to masquerade as other conditions underscores the necessity of considering this uncommon neuroendocrine tumor when assessing patients presenting with severe cardiovascular symptoms.

## Conclusion

In summation, our case accentuates the need for maintaining an expansive differential diagnosis in patients with severe cardiovascular symptoms, even when an initial diagnosis, like fulminant myocarditis, appears feasible. The diagnostic conundrum created by pheochromocytoma, also known as "The Great Mimic", calls for an elevated level of suspicion, especially when the clinical trajectory strays from the usual path or is unresponsive to conventional therapy. The use of biochemical testing, varied imaging techniques, and an interdisciplinary approach are pivotal for accurate diagnosis and appropriate management. This case serves as an invaluable cue for clinicians to factor in pheochromocytoma in their differential diagnosis, emphasizing the need for further research and heightened awareness of this rare, yet potentially lethal, 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.

## Ethics statement

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

## Author contributions

YC: Conceptualization, Data curation, Investigation, Writing – original draft. ND: Data curation, Writing – original draft. LW: Data curation, Validation, Writing – review & editing. LQ: Funding acquisition, Writing – review & editing.

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## Conflict of interest

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

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# Case Report: Thrombus aspiration and *in situ* thrombolysis via a Guidezilla guide extension catheter in a patient with high-risk pulmonary embolism

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Standard catheter-directed thrombolysis (CDT) and thrombus aspiration are considered potentially promising approaches for reopening the embolism-related pulmonary artery in patients with pulmonary embolism (PE) with high thrombotic burden and deteriorating hemodynamics, especially in those for whom systemic thrombolysis is contraindicated or has failed. However, the constrained accessibility of dedicated catheters has impeded the potential benefits of standard CDT in developing countries. The Guidezilla guide extension catheter (GEC) with a larger diameter and extended length is widely used in challenging coronary anatomy. Nevertheless, there have been few reports on the application of the Guidezilla GEC as a novel option for patients with massive PE when dedicated catheters and surgical thrombectomy are not available. In this case report, we demonstrated that thrombus aspiration and *in situ* thrombolysis through the Guidezilla GEC are applicable to patients with PE in whom systemic thrombolysis is contraindicated, resulting in successful reperfusion and positive clinical outcomes.

KEYWORDS

case report, pulmonary embolism, catheter-directed thrombolysis, thrombus aspiration, Guidezilla catheter

## Introduction

Pulmonary embolism (PE) is caused by intraluminal thrombosis resulting in partial or complete occlusion of the pulmonary artery (PA). The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend that the application of catheter-based techniques should be considered for patients with high-risk PE with contraindications to systemic thrombolysis (1). The current research expands the evidence supporting the use of catheter-directed thrombolysis (CDT) as a promising therapy for acute high-risk PE, demonstrating significant improvement in right heart parameters and PA pressure compared to systemic thrombolysis and anticoagulation (2). The present analysis supports the notion that individuals exhibiting a more adverse baseline right ventricle (RV) to left ventricle (LV) ratio, elevated PA systolic pressure, and increased pulmonary artery obstruction manifest the most pronounced enhancements in these specific parameters after undergoing CDT (3). A meta-analysis

of small retrospective studies has shown that CDT is associated with lower short-term mortality and exhibits a tendency toward a reduced 1-year mortality benefit compared to anticoagulation (4). Studies focusing on the enhancement of clinical endpoints through CDT are still strongly needed to advance cardiopulmonary health after PE (3).

The Guidezilla (Boston Scientific, Marlborough, MA, USA) guide extension catheter (GEC) is widely applied in complex percutaneous coronary intervention (PCI) for facilitating deep culprit vessel intubation by enhancing the additional backup support of the guiding catheter (5). As a mother-in-child catheter, the Guidezilla GEC has a larger diameter to enable various interventional devices for performing complicated procedures, which may be applicable for massive PE as an alternative in the absence of dedicated techniques and surgical thrombectomy.

Herein, we present the detailed operation of thrombus aspiration and *in situ* thrombolysis through the Guidezilla GEC for a patient with high-risk PE with absolute contraindication of systemic thrombolysis.

## Case report

A 70-year-old Chinese female patient with left hydronephrosis was admitted for a planned laparoscopic disconnection of ureteropelvic junction obstruction. For 2 days postoperatively, she developed severe dyspnea and presented with circulatory shock. She had hypotension (79/55 mmHg) on norepinephrine (0.4 μg/kg/min), sinus tachycardia (122 beats/min), tachypnea with 44 breaths/min, and her initial oxygen saturation was 93% on 3 L oxygen and worsened to 81% on 5 L. The elevated D-dimer levels (13.28 μg/mL) suggested a high suspicion of pulmonary embolism. Computed tomography pulmonary angiography (CTPA) confirmed the diagnosis of pulmonary embolism, revealing large emboli in the bilateral pulmonary arteries (Figure 1). As systemic thrombolysis was contraindicated and surgical pulmonary thrombectomy was unavailable in our hospital, the patient was transferred to the Department of Cardiovascular Medicine and taken to the operating room for percutaneous catheter-directed therapy.

After inserting a 6-French (Fr) flex introducer sheath into the right femoral route, a 6-Fr pigtail catheter was advanced over a 0.035-inch guidewire to reach the pulmonary trunk. The catheter-directed pulmonary angiogram confirmed simultaneous filling defects of the right and left pulmonary arteries, especially of the left PA with large saddle emboli (Figure 2). Since regular percutaneous catheter-directed systems of PE were unavailable in our hospital, the Export Aspiration Catheter (EAC; Medtronic Corporation, Sunnyvale, CA, USA) with 1.37 mm (0.054-inch) aspiration lumen, which is widely used in PCIs for establishing antegrade flow before culprit vessel stenting, was used to remove pulmonary large clots through aspiration mechanisms. After dilatation of the Sprinter balloon (2.5 × 20 mm; Medtronic, Inc., Minneapolis, MN, USA) in the distal part of the right middle-pulmonary artery, the EAC was inserted for thrombus aspiration. With the limited diameter of the EAC, thrombus aspiration seemed to be ineffective, and only a small amount of thrombus was removed. In total, 1 million IU of urokinase was delivered through the EAC, a significantly lower dose than the standard treatment indicated for systemic thrombolysis, with a loading dose of 4,400 IU/kg, followed by 4,400 IU/kg/h over 12–24 h (1). Thus, the Guidezilla GEC with a larger inner diameter (0.067 inches, 1.71 mm), which allows more room for aspiration, was considered to be the optimal alternative to remove the thrombosis clot. Rather unexpectedly, the Guidezilla GEC captured several fresh thrombi in the bilateral PA and successfully aspirated and brought them out from the catheter. Subsequently, 1 million IU of urokinase were bolus injected as *in situ* thrombolytics in the left main pulmonary artery through the Guidezilla GEC. The pigtail catheter-directed pulmonary

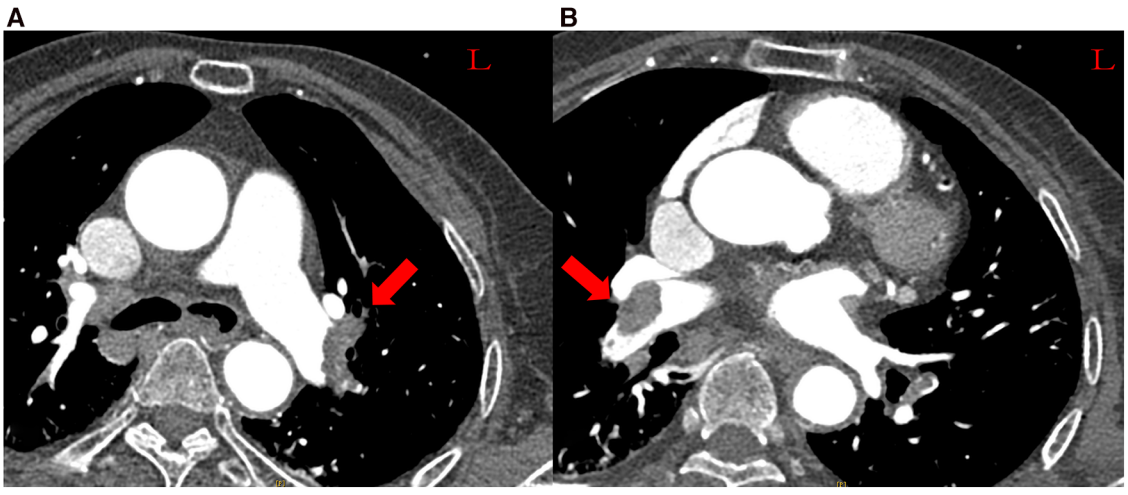


FIGURE 1
Massive pulmonary embolism. (A) Left pulmonary arteries. (B) Right pulmonary arteries.

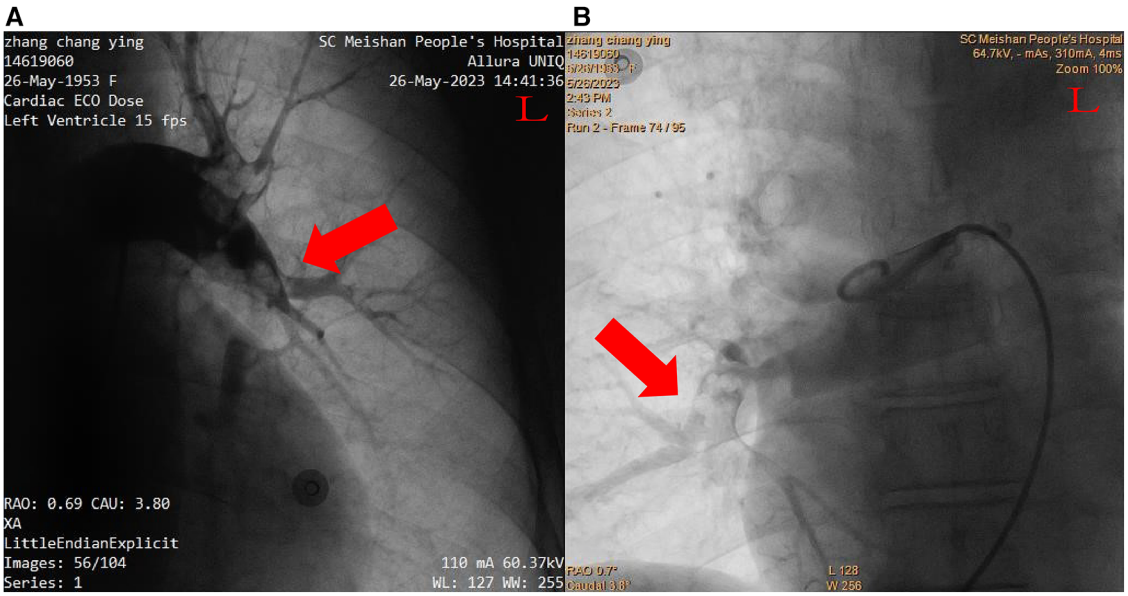


FIGURE 2
Pulmonary angiogram. (A) Left pulmonary arteries. (B) Right pulmonary arteries.

angiogram demonstrated a significant reduction in the size of the thrombus and the reperfusion in the bilateral PA was substantially improved (Figure 3).

Over the next few hours after the procedure, the patient's oxygenation gradually increased to 99% on 2 L oxygen, hemodynamic status was restored to 122/66 mmHg on significantly reduced norepinephrine and a sinus rhythm (73 beats/min) was observed. The severe dyspnea was conspicuously alleviated, and tachypnea was resolved to normal status (19 breaths/min). Five days after the thrombus aspiration and *in situ* thrombolysis through the Guidezilla GEC, the patient's clinical condition was further improved and she was finally discharged to continue her rehabilitation. A new CTPA, scheduled for 2 months later, demonstrated a significant reduction in the size of the thrombus, which was barely visible (Figure 4).

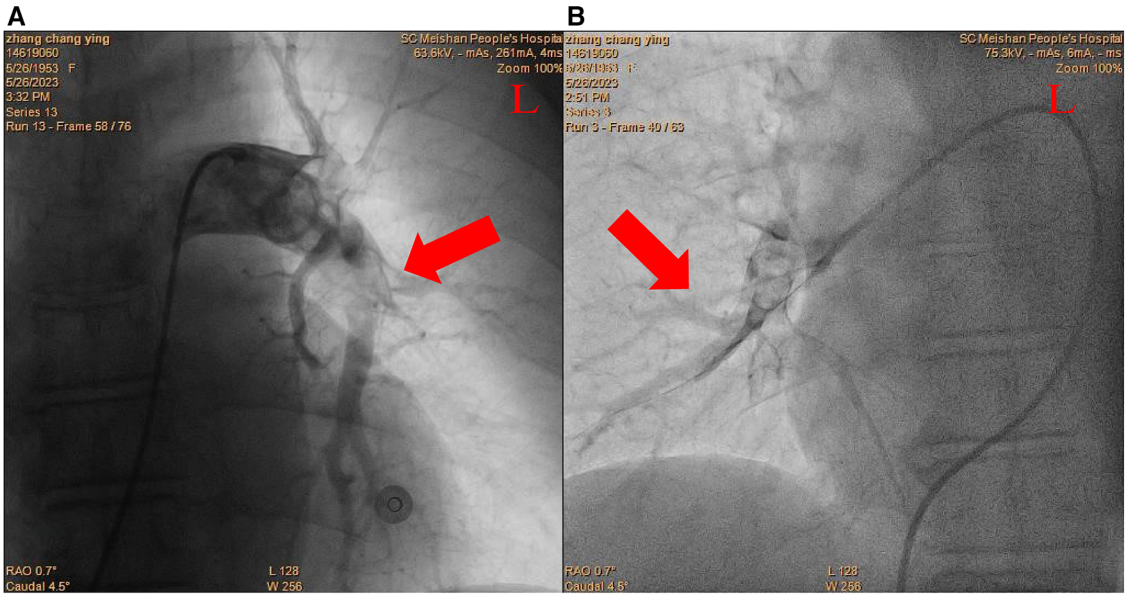


FIGURE 3
Postcatheter-related treatment. (A) Left pulmonary arteries. (B) Right pulmonary arteries.

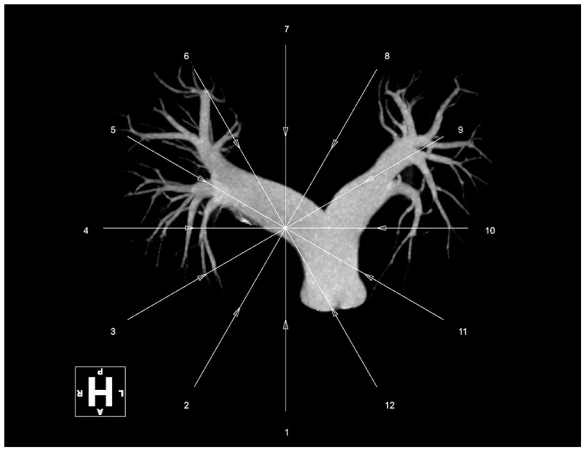


FIGURE 4
3D reconstruction of CTPA in 2 months later.

## Discussion

Although rescue thrombolytic therapy is generally recommended for patients with hemodynamic deterioration on anticoagulation treatment, the ESC/ERS guidelines have shown that systemic fibrinolysis can predispose patients to critical hemorrhage if they have undergone surgery in the previous 3 weeks (1). In this case, the elderly patient with massive PE presented an absolute contraindication to fibrinolysis due to the high risk of severe hemorrhage, indicating that the standard CDT appeared to be the preferred alternative reperfusion options.

Notwithstanding the early studies being limited, the severe complications of conventional therapy encouraged the research into novel alternative treatments for reducing the thrombolytic dose. The standard CDT involves advancing the dedicated catheters into the culprit pulmonary artery with thrombus distribution for restoration of pulmonary blood flow by delivering thrombolytics (6). Multiple studies have demonstrated the advantage of immediate thrombus removal through percutaneous catheter-directed thrombectomy and aspiration by providing strong evidence of excellent safety, which may be credited to locally administered low-dose thrombolytics (7, 8). The FLASH trial evaluated the effectiveness of percutaneous catheter-directed thrombectomy and aspiration for the treatment of intermediate to high-risk PE and showed it has a tendency toward superiority in immediate hemodynamic improvements and cardiac function recovery (9).

Different types of dedicated catheters are adopted for mechanical fragmentation, thrombus aspiration or, more commonly, a pharmacomechanical approach combining mechanical or ultrasound fragmentation of the thrombus with *in situ* reduced-dose thrombolysis (10). The UniFuse (AngioDynamics, Latham, NY, USA) and Cragg-McNamara (ev3 Endovascular, Plymouth, MN, USA) 4–5-Fr infusion catheters, with an infusion length of 10–20 cm, are recommended as currently favorable treatment options (1). The overall procedural success rates of thrombus aspiration and *in situ* thrombolysis via different catheter devices are in the range of 70.8%–83.1% (11). However, the actual value of dedicated techniques should be interpreted with caution due to the limited availability of specialized catheters in clinical practice, especially in developing countries. The utilization of dedicated catheters was confined to leading tertiary medical centers in China, potentially limiting the clinical benefits of CDT. The Guidezilla GEC is widely recognized as a frequently used support catheter in chest pain centers in China. It has been designed with a larger diameter for challenging coronary vasculature anatomy to allow the use of various interventional equipment by providing extra deep seating support during complex PCI procedures. Simultaneously, due to its flexibility and widespread utilization in China, this catheter's effectiveness as auxiliary equipment can be extended to thrombus aspiration and the delivery of thrombolytics for massive PE.

To the best of our knowledge, few cases have been reported where local thrombolytics and aspiration were successfully delivered through a Guidezilla GEC. In the present case, a total of 2 million IU of urokinase, a significantly reduced dose than the routine basis indicated for systemic thrombolysis, was delivered in bilateral pulmonary arteries equally after aspiration through the Guidezilla GEC (1). Compared with routine systemic thrombolysis, the delivery of a reduced-dose thrombolytic after thrombus aspiration by the Guidezilla GEC increases its local concentration in the culprit vessels, potentially achieving the most optimal balance between safety and efficacy. The success of the practice of the Guidezilla GEC appeared to be consistent with the dedicated equipment of standard catheter-directed treatment in terms of net clinical benefit. The Guidezilla GEC is one of the most commonly used GECs, which makes it a promising and potentially optimal substitute device from an emergency perspective for massive PE.

## Conclusion

The percutaneous catheter-directed treatment should be an imperative alternative to rescue thrombolytic therapy for patients with massive PE with deteriorating hemodynamics, in whom systemic thrombolysis has failed or is strictly contraindicated. However, the scarcity of dedicated catheters has barricaded the clinical practice of CDT, especially in developing countries. In this letter, the successful practice of the GuideZallia GEC in this particular patient suggests it could enhance the clinical benefits of treatment of PE, and the advantage of efficiency and safety may have the potential to extend to all patients with indications, serving as an easily accessible alternative. Thus, further cohort trials are required to determine whether it could become a new preferred equipment for wide application among patients with high-risk PE.

## Data availability statement

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

## Ethics statement

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

## Author contributions

J-WD: Conceptualization, Writing – original draft, Writing – review & editing, Project administration. Y-AJ: Formal Analysis, Investigation, Writing – review & editing. PL: Formal Analysis, Investigation, Writing – review & editing, Resources. H-XX: Formal Analysis, Investigation, Resources, Writing – review & editing. H-SD: Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing.

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## Conflict of interest

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

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# Sudden death associated with delayed cardiac rupture: case report and literature review

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Cardiac injury plays a critical role in the process of thoracic trauma-related fatal outcomes. Historically, most patients who suffer a cardiac rupture typically die at the scene of occurrence or in the hospital, despite prompt medical intervention. Delayed cardiac rupture, although rare, may occur days after the initial injury and cause sudden unexpected death. Herein, we present the clinical details of a young man who suffered a chest stab injury and recovered well initially, but died days later due to delayed cardiac rupture. The forensic autopsy confirmed delayed cardiac rupture as the cause of death. We also reviewed previous similar reports to provide suggestions in such rare cases in clinical and forensic practice.

KEYWORDS

pathology, autopsy, delayed cardiac rupture, cardiac tamponade, case report

## Highlights

- We report a case of sudden death due to delayed cardiac rupture.
- Delayed cardiac rupture and tamponade post chest trauma were carefully reviewed.
- The present case and literature review could provide reference in such rare cases in forensic practice.

## Introduction

Thoracic trauma is the second-leading cause of morbidity and mortality and often involves cardiac injuries that can increase the mortality rate by 15 times (1). Given the varied definitions and diagnostic criteria of cardiac injury, its exact incidence is still unknown; however, previous studies have indicated that it ranges from 3% to 71% (2–4). Specifically, the incidence of cardiac rupture in chest trauma is reported to be 0.5% and is often associated with a lethal outcome (5). In 2023, Sessa et al. reviewed the published studies focusing on penetrating cardiac injury associated with firearm from 1990 to 2022, concluded that the morality of penetrating cardiac injury was affected by the location and severity of the heart injury, the interval between injury and medical intervention, the quantity of blood lost and presence of cardiac tamponade (6).

The presence of cardiac tamponade was common in the fatal cases indicating cardiac rupture is a medical emergency. Most patients die at the scene of occurrence without prompt medical intervention. By contrast, delayed cardiac rupture is a rare phenomenon that may cause sudden unexpected death in

individuals with a history of chest trauma. It poses a significant threat to individuals who recover well at first after the initial chest injury in clinical practice. This complicates the link between the primary injury and subsequent fatal outcomes in forensic practice. However, the underlying mechanisms of delayed cardiac rupture are still debatable and require further investigation.

In this study, we present the clinical details of a young man who suffered a chest stab injury and recovered well initially, but died several days later because of delayed cardiac rupture, as confirmed by forensic autopsy.

## Case presentation

A 21-year-old man was stabbed in the left front chest with a folding fruit knife and was subsequently admitted to the hospital. Radiographic examination revealed left hemothorax. Closed thoracic drainage and blood-transfusion were performed, and the patient's condition stabilized. However, 5 days later, his condition suddenly deteriorated, and he died despite receiving timely medical intervention.

A forensic autopsy was performed one day later, which revealed bilateral hemothorax, and 800 ml and 500 ml blood were found in the left and right thoracic cavities, respectively. A 1.2-cm-long oblique strip with a sharp-edge wound was found on the right side of the pericardium and the middle of the right ventricular anterior wall. The pericardial cavity was filled with blood up to a volume of approximately 100 ml. A 1.0-cm-long wound with the same characteristics was found in the middle of the right ventricular anterior wall and pierced into the cardiac chamber.

Numerous multinucleated cells infiltrated the epicardium at the trauma site in the right ventricle. Thrombosis, degenerated and necrotic myocardium, and macrophage infiltration were also observed at the trauma sites. To further evaluate the time interval post-injury, Masson's trichome and Prussian blue staining were performed. Large amounts of blue collagen fibers distributed at the injury site were observed by Masson staining (Figure 1). Other organs showed anemia without any pathological changes.

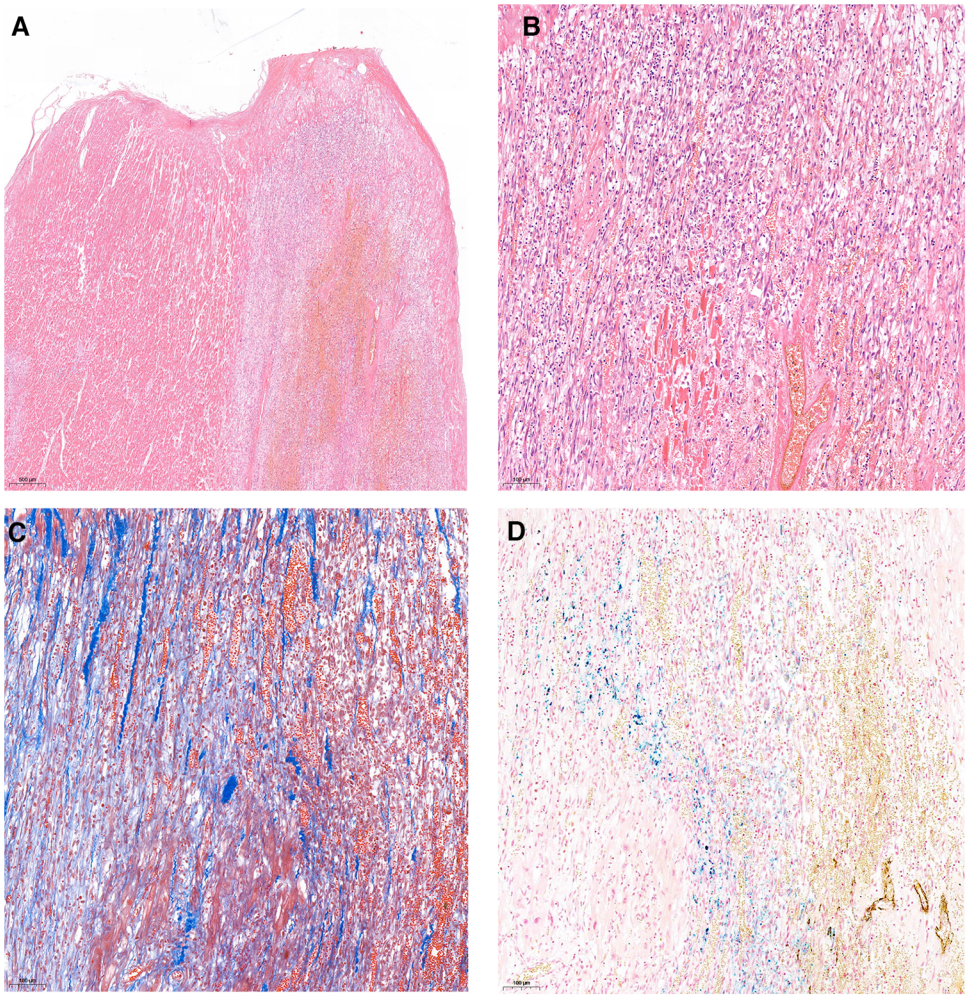


FIGURE 1
Histopathology examination of the trauma site on right ventricular anterior wall: thrombosis, degenerated and necrotic myocardium, and macrophages infiltration. (A) H&E staining, 20×; (B) H&E staining, 100×; (C) Masson's trichrome staining 100×, (D), Prussian blue staining, 100×.

## Discussion

The incidence of penetrating chest trauma has increased in urban regions in the past three decades. The cause of penetrating cardiac injuries varies according to the population and culture, and stabbing is still the leading cause in China (7, 8). Penetrating cardiac trauma is associated with immediate fatal outcomes; however, delayed cardiac rupture, although rare, can occur. To better understand the characteristics of such cases, we carefully reviewed the literature on delayed cardiac rupture in PubMed, and have summarized them in Table 1 (9–28). Delayed cardiac rupture can occur as soon as several hours post-trauma or as long as after 74 days, but most of them occur within a month, with stabbing accounting for half of the reported cases.

Table 1 shows that according to previous reports, the left ventricle is the most common site of injury with delayed cardiac rupture. However, the anatomical location of the heart causes the right ventricle to be most frequently affected by a thoracic stab injury (29). The thinner wall of the right ventricle makes it impossible to close the defect by muscle overlap and contraction. Hence, the penetrating trauma may result in copious bleeding, even with low intraventricular pressure, resulting in rapid death. By contrast, the thick muscular wall in the left ventricle may easily close a stab injury and thus seal the trauma. However, even if the persistent bleeding is slight, it may still eventually result in cardiac tamponade, even with drainage intervention. The atria are most susceptible to penetrating trauma, as they completely lack a sealing effect (30). The formed thrombosis, which adheres tightly to the wound as in Case 1 may be the origin of the delayed cardiac rupture.

The data in Table 1 indicate that non-penetrating chest trauma can cause cardiac rupture, and common blunt cardiac rupture injuries among civilians, including traffic accidents, falls, heavy impact, and even a punch, can cause fatal damage. Cardiac ruptures are not always accompanied by thoracic wall injuries or rib fractures (31). Delayed cardiac rupture is often associated with hemopericardium as bleeding into the pericardial sac. To better understand the fatal outcome of delayed chest trauma, we searched for delayed hemopericardium or cardiac tamponade in PubMed, and have summarized the literatures on negative or healed cardiac injuries in Table 2 (32–44).

The clinical manifestations of chest traumas listed in Tables 1, 2 are common in that their condition is rather stable after primary medical intervention. Moreover, other examinations such as chest radiography and computed tomography show negative findings, even with cardiac rupture and effusion. A previous study has indicated that delayed cardiac ruptures can be asymptomatic (45). The post-trauma ECG may initially be abnormal; however, ECG changes are not

TABLE 1 Delayed cardiac rupture cases.

| Authors and publication year | Age/ Gender | Mechanism of injury | Admission CT scan | Interval time (days) | Primary injury location | Cardiac injury location | Outcome |
|---|---|---|---|---|---|---|---|
| Ochi et al., 2020 (9) | 51/M | Stab | CT negative | 28 | Chest | Right ventricular-pericardial-pleural fistula | Well |
| Dokoupil et al., 2019 (10) | 47/F | Accident | Rib fracture | 34 | Chest | Left ventricle rupture | Autopsy |
| Pooniya et al., 2016 (11) | 2/M | Accident | None | 7 | Negative | Left ventricle rupture | Autopsy |
| Greene et al., 2016 (12) | 21/F | Fall | CT: negative | 10 | Chest | Left ventricle rupture | Well |
| Esfahanizadeh et al., 2013 (13) | 19/M | Stab | None | 60 | Chest | Aorto-RV Fistula | Well |
| Bartoloni et al., 2013 (14) | 29/M | Stab | Chest x-ray and CT: left hemothorax | 9 | Chest | Coronary wall rupture | Autopsy |
| Ueda et al., 2011 (15) | 75/F | Blunt chest trauma | Unknown | 74 | Chest | Left ventricular rupture | Well |
| Hermens et al., 2009 (16) | 70/M | Accident | None | 28 | Chest | Hemorrhagic myocardial defect | Well |
| Babin-Ebell et al., 2008 (17) | 25/M | Stab | Echocardiography | Sever hours | Chest | Ventral septal defect | Well |
| Eisenman et al., 2006 (18) | 18/M | Stab | None | 30 | Chest | Ventricular puncture | Well |
| Moore et al., 2006 (19) | 39/M | Stab | Chest radiograph and CT normal | 21 | Chest | Atriocaval laceration | Well |
| Murai et al., 2003 (20) | 36/M | Fall | Echocardiography: negative | 20 h | Chest | Right ventricular rupture | Autopsy |
| Murillo et al., 2002 (21) | 10/M | Accident | CT: Haemo-pneumothorax | 140 min | Chest | Left ventricular rupture | Autopsy |
| Lassus et al., 2001 (22) | 44/M | Accident | x-ray, CT: negative | 14 | Chest | Right ventricle rupture | Well |
| Klingkenberg et al., 1994 (23) | 34/F | Stab | Unknown | 3 | Chest | Right ventricle | Well |
| Pollak et al., 1991 (24) | 7/M | Fall | None | 8 | Chest | Left ventricular rupture | Well |
| Martin et al., 1986 (25) | 48/M | Stab | Unknown | 42 | Chest | Coronary arteriovenous fistula | Well |
| Lempinem et al., 1972 (26) | 38/M | Stab | Unknown | 9 | Chest | Right ventricle | Well |
| Pastor et al., 1961 (27) | 25/M | Stab | Unknown | 35 | Abdomen | Ventricle | Well |
| | 31/M | Stab | Unknown | 74 | Negative | Negative | Well |
| Cosman et al., 1958 (28) | 15/M | Stab | x-ray: right hemothorax | 5 | Chest | Right auricular | Well |

TABLE 2 Delayed hemopericardium or cardiac tamponade cases.

| Authors and publication year | Age/ Gender | Mechanism of injury | Admission CT scan | Interval time (days) | Primary injury location | Cardiac injury location | Outcome |
|---|---|---|---|---|---|---|---|
| Almehmadi et al., 2016 (32) | 23/M | Stab | Negative | 10 | Chest + right ventricle laceration | Negative | Well |
| Khidir et al., 2015 (33) | 19/M | Fall | Chest x-ray: normal | 12 | Chest | Negative | Well |
| Donahoe et al., 2013 (34) | 20/M | Stab | Echocardiography: effusion | 6 | Chest | Negative | Well |
| Kanchan et al., 2012 (35) | 71/M | Fall | Chest radiograph: multiple fractures | 8 h | Negative | Right ventricle contusion | Autopsy |
| Nijjer et al., 2010 (36) | 21/M | Stab | Chest radiograph: normal | 100 | Chest | Negative | Well |
| Liang et al., 2009 (37) | 58/M | Accident | CT: sternal fracture | 14 | Chest | Negative | Well |
| Harris et al., 2003 (38) | Median: 28 (range: 14–53) 23/M; 1/F | Stab | Unknown | 3–31 median 14.2 | Chest | Unknown | Well |
| Kelsey et al., 1999 (39) | 21/M | Fall | None | 7 | Chest | Negative | Well |
| Mechem et al., 1997 (40) | 35/M | Stab | Chest x-ray, echocardiogram: normal. | 19 | Chest | Pulmonary artery laceration | Well |
| Raney & Kennedy, 1997 (41) | 28/M | Stab | Unknown | 21 | Chest | Negative | Well |
| Bellanger et al., 1996 (42) | 35/M | Stab | Unknown | 21 | Chest | Negative | Well |
| Bowers et al., 1994 (43) | 21 months/W | Fall | None | 7 | Chest | Negative | Well |
| Aaland et al., 1991 (44) | 50/M | Stab | Unknown | 14 | Chest | Negative | Well |

specific, as they can also occur in normal autopsy findings, and delayed cardiac rupture may occur even with normal ECG post-injury (46–48). This was the same as the CK-MB level and echocardiography with respect to cardiac injury. CK-MB, echocardiography, repeated ECG, and chest radiographic examinations may play a role in suspected cardiac injury cases (22, 49).

In 2023, Sessa et al. reviewed the published studies focusing on penetrating cardiac injury associated with firearm from 1990 to 2022, and identified 38 articles, 39 cases were involved (6). Among which, 33 were males, the entrance wound is located in the anterior chest in 30 cases. Based on the study, he suggested that timely transport, resuscitation, and immediate surgery were the critical management in the therapy of penetrating cardiac injury. In 2022, Berrichi et al. reported delayed cardiac herniation after a traumatic pericardial rupture in an adult male who fall from 8m high, and the patient was rescued through timely surgery (50). In the present case, the entrance wound is on left front chest, and the decedent was given immediate surgery and he was recovered well at first. However, few days later he suffered from delayed cardiac rupture and tamponade and died. The asymptomatic of his later fatal complications delayed the diagnose of his complication and eventually resulted in his tragedy.

Although rare, delayed cardiac rupture and tamponade after chest trauma is a challenge in clinical and forensic practice. Physicians should bear in mind this rare complication to provide better medical therapy. In forensic practice, the original cause of later cardiac complications and time interval after the primary injury make the real link underlying them more complicated. Forensic pathologists should carefully document the primary injury and thoroughly investigate the patient's medical history and interval time through histopathological examination and other advanced technologies.

## Conclusion

Delayed cardiac rupture and tamponade after chest trauma are rare in clinical and forensic practice and may cause sudden death. The casual link between the primary injury and later complications remains to be elucidated.

## Data availability statement

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

## Ethics statement

The requirement of ethical approval was waived by Zhongshan School of Medicine Sun Yat Sen University for the studies involving humans. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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## Publisher's note



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# A Case Report of *Mycoplasma pneumoniae*-induced fulminant myocarditis in a 15-year-old male leading to cardiogenic shock and electrical storm

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*Mycoplasma pneumoniae (M. pneumoniae)* is a well-recognized pathogen primarily associated with respiratory tract infections. However, in rare instances, it can lead to extrapulmonary manifestations, including myocarditis. We present a case of a 15-year-old male who developed fulminant myocarditis, cardiogenic shock, and cardiac electrical storm attributed to *M. pneumoniae* infection. He underwent a combination of intra-aortic balloon pump (IABP) and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for cardiac support, ultimately surviving despite the intracardiac thrombus formation and embolic stroke. Following comprehensive treatment and rehabilitation, he was discharged in stable condition. This case underscores the importance of considering atypical pathogens as potential etiological factors in patients presenting with cardiac complications, especially in the adolescents. It also emphasizes the need for clinical vigilance and effective support for potential cardiac complications arising from *M. pneumoniae* infection.

KEYWORDS

*Mycoplasma pneumoniae*, myocarditis, cardiogenic shock, ventricular arrhythmia, case report

## 1 Introduction

*Mycoplasma pneumoniae* (*M. pneumoniae*) is one of the main pathogens of community-acquired pneumonia (CAP), accounting for 10%–40% of such instances, with children and young adults as the most susceptible group (1, 2). In the year of 2023, following the cessation of COVID-19 restrictions, there were increasing patients admitted to hospital due to *M.pneumoniae* infection in China (3). Typically, *M. pneumoniae* causes mild respiration infection, however, some patients with *M. pneumoniae* may develop severe respiratory failure requiring ICU admission (4, 5). Moreover, *M. pneumoniae* can also manifest with extrapulmonary illness, including gastrointestinal, cardiovascular, neurological, renal, musculoskeletal, skin, and hematologic syndromes (1). These complications have been reported to occur in approximately 25% of individuals infected with *M. pneumoniae* and may occur at any time during the infection (6).

The cardiac manifestations of *M. pneumoniae* are rare. The cardiac manifestations of *M. pneumoniae*, including myocarditis, pericarditis, and conduction abnormalities, occurring in only 1%–8.5% of cases. Notably, this phenomenon is more prevalent in adults than in children (6). While relatively uncommon, these cardiac complications potentially can lead to severe consequences. Moreover, *M. pneumoniae*-induced fulminant myocarditis is an exceptionally rare occurrence, with no pertinent data reported to date. Herein, we present an unusual case of *M. pneumoniae* infection presenting with CAP, acute fulminant myocarditis, leading to cardiogenic shock, electrical storm, along with left ventricular thrombi and cerebral embolism, who survived with additional cardiac support with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pump (IABP) in a 15-year-old male.

## 2 Case description

A previously healthy 15-year-old male with no prior medical history was admitted to the emergency room (ER) in July 2023, after experiencing 8 days of fever, reaching temperatures as high as 40°C, accompanied by a dry cough. He had previously received intravenous azithromycin and cephalosporin antibiotics in the local clinic. Three days prior to admission to the ER, he developed dyspnea and coughed with white and pink foam sputum.

On arrival at the ER, his vitals included a temperature of 39.5° C, heart rate of 153 beats per minute, respiratory rate of 35 breaths per minute, oxygen saturation ($SpO_2$) of 90% on room air, and blood pressure of 97/63 mmHg. His weight was 60 kg, and his height was 175 cm. The chest computed tomography (CT) scan images on admission indicated consolidation of the right lower lobe and patchy infiltrates at the left lower lobe (Figure 1A), and the ECG showed sinus tachycardia and ST-T changes (Figure 1B). In addition, echocardiography revealed poor left ventricular systolic function with global hypokinesia [ejection fraction (EF) 30%]. Laboratory findings showed an elevated troponin-T and natriuretic peptide (BNP). He was diagnosed with CAP and acute myocarditis, receiving supportive care. Alongside, piperacillin/tazobactam, as empirical antibiotics, and 40 mg methylprednisolone were administered. The next day, he was transferred to the intensive care unit (ICU) for further support.

Upon admission to the ICU, the patient presented with a high fever, reaching up to 38.9°C. He received high-flow nasal oxygen (HFNO) therapy (60 L/min, $FiO_2$ 50%), resulting in an $SpO_2$ of 100%. To alleviate cardiac preload and pulmonary edema (Figure 2A), non-invasive ventilation was intermittently employed. The patient's blood pressure remained within normal range on low-dose vasopressors (metaraminol at 0.75 ug/kg*min), while his heart rate ranged from 130 to 150 beats per minute. Urine output and lactate levels were within normal limits, although the extremities exhibited signs of coldness. Low-dose inotropes, diuretics, beta-blockers, morphine, natriuretic peptide, and anticoagulants were administrated. The extra-cardiac organ functions were almost normal (Table 1).

Cefoperazone/sulbactam and azithromycin were empirically started to cover the potential pathogens. Simultaneously, nasopharyngeal swabs and plasma samples were screened for pathogens associated with myocarditis and CAP. Additionally, blood and sputum samples were sent for metagenomic Next Generation Sequencing (NGS) assay (ID seq$^{TM}$ Ultra, Vision Medicals Co., Ltd., Guangzhou, China) to identify the causative pathogens. These results revealed a significant increase in *M. pneumoniae* antibodies [IgG > 300 AU/ml detected by chemiluminescence immunoassay commercial kits (YHLO Biotech Co., Ltd., Shenzhen, China)] and the presence of *M. pneumoniae* in both blood and sputum in two days, confirming the diagnosis of *M. pneumoniae* infection. Furthermore, in response to the positive result of *M. pneumoniae* infection, sputum sample was sent to a targeted NGS assay (KingMad Co., Ltd., Guanzhou, China) to detect macrolide-resistant genes, revealing a point mutation of A2063G on the 23S rRNA (12 reads out of 341 reads of *M. pneumoniae*). Consequently, tigecycline was administered in combination with azithromycin on ICU-day 2, as quinolones are contraindicated for patients under 18 years of age. A dosage of 40 mg/day methylprednisolone was administered during the initial five days in ICU.

The echocardiography conducted in ICU indicated prominently decreased left ventricle contractility with an EF of 26%, enlarged left atrium and ventricle [Left ventricular end-diastolic volume (LVEDV) 223 ml], along with apical thrombi in the dilated left ventricle (Figure 2B). Following that, the anticoagulant therapy was strengthened with subcutaneous injection of 4,100 IU of low molecular weight heparin (LMWH) every 12 h.

With the initial support, both lung edema and hemodynamic condition showed rapid improvement (Figure 2A, Table 1). However, at noon on the third day of ICU admission, he experienced an episode of ventricular fibrillation (VF) and Adams–Stokes syndrome. Cardiopulmonary resuscitation (CPR), defibrillation, endotracheal intubation, and brain protection were initiated, and amiodarone was infused. Spontaneous circulation was restored 20 min later under advanced cardiac life support. Nevertheless, after resuscitation, his condition significantly deteriorated, with aggravating cardiogenic shock and the presence of severe pulmonary edema. In response, IABP was immediately administered with a counter pulsation ratio of 1:1, and a counter pulsation pressure of 120 mmHg. With the IABP support, peripheral circulatory perfusion was improved, and the pulmonary edema declined. He experienced intermittent ventricular premature beats, which could be reversed by antiarrhythmic drugs. However, on the subsequent day, he experienced refractory ventricular tachycardia (VT) and VF. Unfortunately, these episodes constituted an electrical storm (ES) that could not be successfully terminated despite attempts with defibrillation, CPR, and antiarrhythmic drugs. Consequently, VA-ECMO was initiated through the femoral artery and vein cannulation, with an initial flow set at 3 L/min. To prevent distal leg ischemia, a catheter connected superficial femoral artery with femoral artery was employed. The combined support of VA-ECMO and IABP, allowed for aortic valve opening during left ventricular contraction.

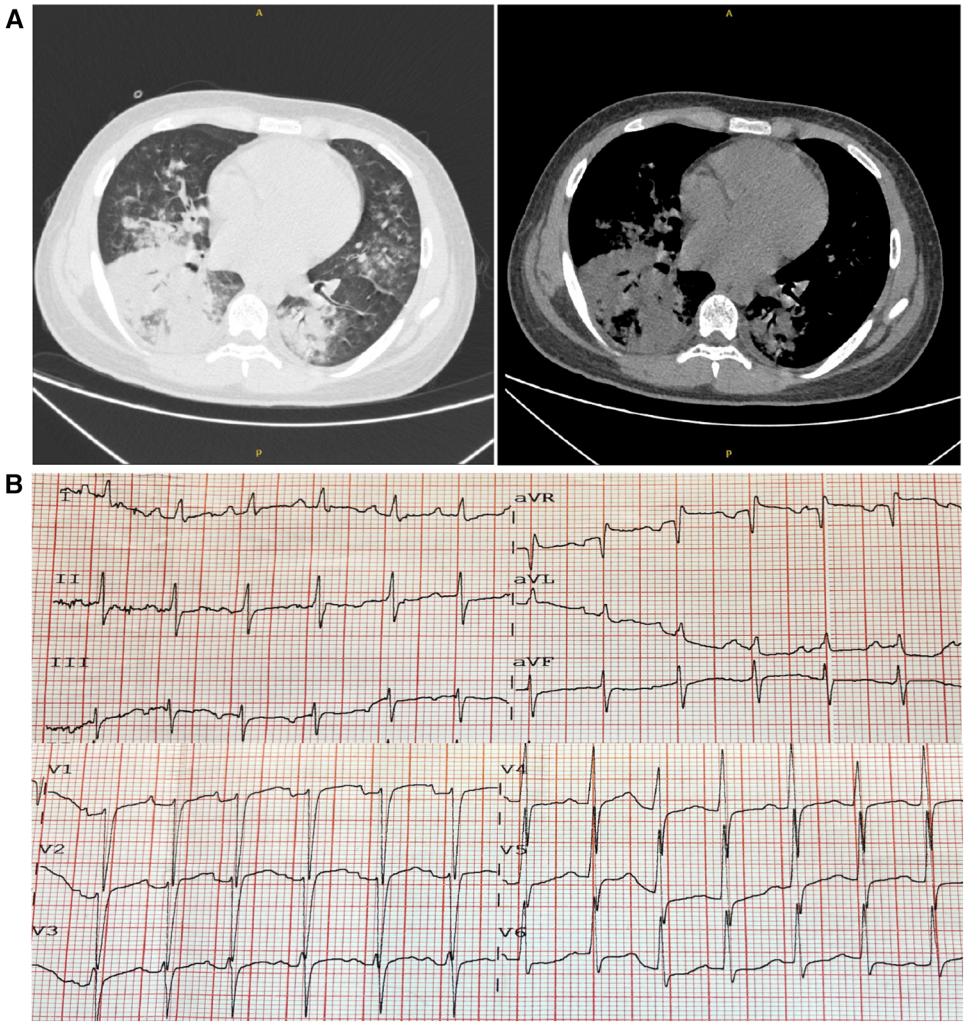


FIGURE 1
Chest computed tomography (CT) and electrocardiogram (ECG) on admission. (A) The chest CT scans revealed consolidation and patchy infiltrates within the right lower lobe and the left lower lobe. (B) The ECG showed sinus tachycardia accompanied by ST-T alterations.

After two days of ECMO initiation, he no longer exhibited malignant arrhythmia. Meanwhile, his cardiac enzyme and BNP gradually declined (Table 1). Hemodynamic stability was achieved with NE at 0.2–0.4 ug/kg*min, and daily bedside echocardiography demonstrated gradual improvement in cardiac contractility. Accordingly, the ECMO flow rate was decreased, according to the vital signs and indicators of peripheral circulatory failure. Concurrently, pharmacotherapy for heart failure, including low doses of angiotensin-converting enzyme inhibitors and beta-blockers, were administered to mitigate the risk of ventricular remodeling.

The clinical course and laboratory data during the initial 14 days in ICU were outlined in Table 1. The chest images revealed a significant resolution of pneumonia. On ICU Day 12, he was successfully weaned from ECMO, when echocardiography showed an estimated LVEF of 30% and LVEDV of 220 ml. The IABP was subsequently removed on ICU Day 16. Nevertheless, the thrombi in the left atrium persisted. Throughout the period of mechanical circulatory and ventilation support, spontaneous awakening trials were implemented, and the patient remained conscious despite prior episodes of CPR.

Unfortunately, he experienced an acute ischemic stroke resulting in right-sided hemiplegia on the 17th day of ICU stay. Brain CT revealed an acute infarction of a large area of left middle cerebral artery territory, consistent with an embolic pattern. This was likely attributed to the dislodgement of the left ventricular thrombus, a finding subsequently confirmed by magnetic resonance imaging and magnetic resonance angiography after discharged from ICU (Figure 3). The anticoagulant therapy with LMWH was continued, although thrombolysis was not administered due to the risk of secondary bleeding and a probable prolonged duration of ischemic stroke (exceeding 6 h). Furthermore, serial CT scans were performed over two weeks to monitor for potential hemorrhagic transformation.

Following continued stabilization of cardiac function and active physical rehabilitation, he was successfully weaned from

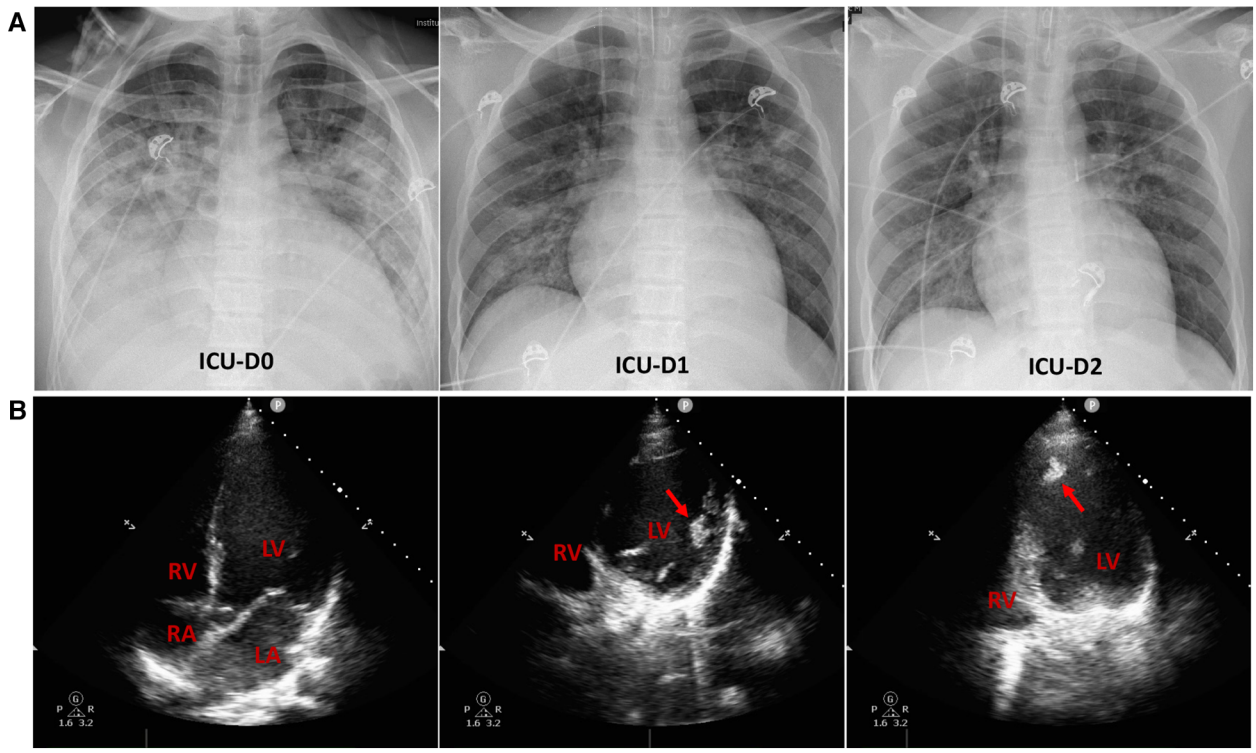


FIGURE 2
Chest radiographs and echocardiograms in the intensive care unit (ICU). (**A**) Chest radiographs on the initial three days of ICU admission. Lung edema exhibited a rapid amelioration. (**B**) On ICU admission, the apical 4-chamber views of the echocardiography indicated enlarged left atrium and ventricle, along with apical thrombi (indicated by red arrows) in the dilated left ventricle. RV, right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.

**TABLE 1** Clinical and laboratory data during the first 2 weeks of hospitalization.

| Parameters | ER | ICU-D0 | ICU-D1 | ICU-D2 | ICU-D3 | ICU-D4 | ICU-D5 | ICU-D7 | ICU-D9 | ICU-D12 | ICU-D14 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Main intervention | | | | CPR + IABP + IMV | | ECMO | | | | Withdrawal of ECMO | |
| T, °C | 39.5 | 38.9 | 38.7 | 37 | 38.4 | 37.8 | 36.8 | 37.4 | 37.3 | 37.3 | 37.2 |
| HR, bpm | 153 | 151 | 90 | 108 | 73 | 78 | 80 | 85 | 94 | 82 | 76 |
| Vasopressors, ug/kg*min | DA 3 | MA 0.75 | MA 0.5 | NE 2 | NE 1.4 | NE 1.6 | NE 1.0 | NE 0.4 | NE 0.4 | NE 0.2 | NE 0.2 |
| Urine output, ml | | 12 h: 600 | 3,910 | 3,605 | 2,600 | 5,320 | 5,570 | 3,120 | 3,055 | 1,780 | 2,420 |
| Lactate, mmol/L | 2.2 | 1.6 | 1.4 | 2–15 | 2.3–5.5 | 2.6 | 3.2 | 2.3 | 1.9 | 1.1 | 2 |
| WBC,$10^9$/L | 11.49 | 14.42 | 13.61 | 10.17 | 18.92 | 20.16 | 19.87 | 13.68 | 27.19 | 15.46 | 12.19 |
| Ly, $10^9$/L | 1.35 | 1.25 | 1.66 | 2.23 | 4.43 | 2.53 | 0.87 | 0.84 | 4.82 | 3.83 | 3.18 |
| PLT,$10^9$/L | 211 | 228 | 280 | 264 | 314 | 195 | 147 | 130 | 93 | 57 | 110 |
| PT, s | 14.3 | 15.6 | 14.8 | 14.4 | 14.3 | 16.3 | 15.7 | 15.7 | 15.7 | 17.7 | 17.2 |
| APTT, s | 38.7 | 36.8 | 39.6 | 43.2 | 39.6 | 47.1 | 58.4 | 92.5 | 159.9 | 161 | 81.7 |
| Fib, g/L | 5.12 | 5.94 | 5.47 | 5.29 | 4.31 | 4.19 | 3.55 | 2.57 | 1.75 | 1.54 | 1.6 |
| D-dimer, ug/ml | 2.57 | 9.58 | 9.57 | 9.81 | 7.26 | 2.19 | 2.87 | 2.43 | 3.01 | 10.65 | 5.72 |
| ALT, U/L | 93 | 97 | 87 | 84 | 94 | 79 | 105 | 106 | 92 | 112 | 95 |
| T-bil, μmol/L | 7 | 9.5 | 9.2 | 9.4 | 9.2 | 12.4 | 20 | 22.5 | 20.9 | 14.4 | 23.9 |
| Cr, μmol/L | 69 | 62 | 57 | 59 | 107 | 104 | 81 | 61 | 53 | 51 | 48 |
| CRP, mg/L | 77.35 | | 116.2 | | 55.8 | | | | 23.5 | | 22 |
| TnI, ng/ml | TnT 0.334 | 3.983 | 3.385 | 1.96–6.37 | 4.95–2.45 | 3.571 | 1.684 | 0.599 | 0.345 | 0.096 | 0.049 |
| NT-proBNP, pg/ml | 4,421 | 6,595 | 11,670 | 13,016 | 17,383 | 8,950 | 1,312 | | 1,102 | | BNP 211 |
| EF, % | 30% | 26% | | 20% | | 20% | 22% | | | 30% | |

The values represent the worst values observed throughout the day.
ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; BNP, b-type natriuretic peptide; CPR, cardiopulmonary resuscitation; Cr, creatinine; CRP, C-reactive protein; DA, dopamine; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; ER, emergency room; HR, heart rate; IABP, intra-aortic balloon pump; IMV, invasive mechanical ventilation; Ly, lymphocyte; T, body temperature; WBC, white blood cell; PLT, platelet; PT, prothrombin time; Fib, fibrinogen; T-bil, total bilirubin; TnI, troponin I; MA, metaraminol; NE, norepinephrine.

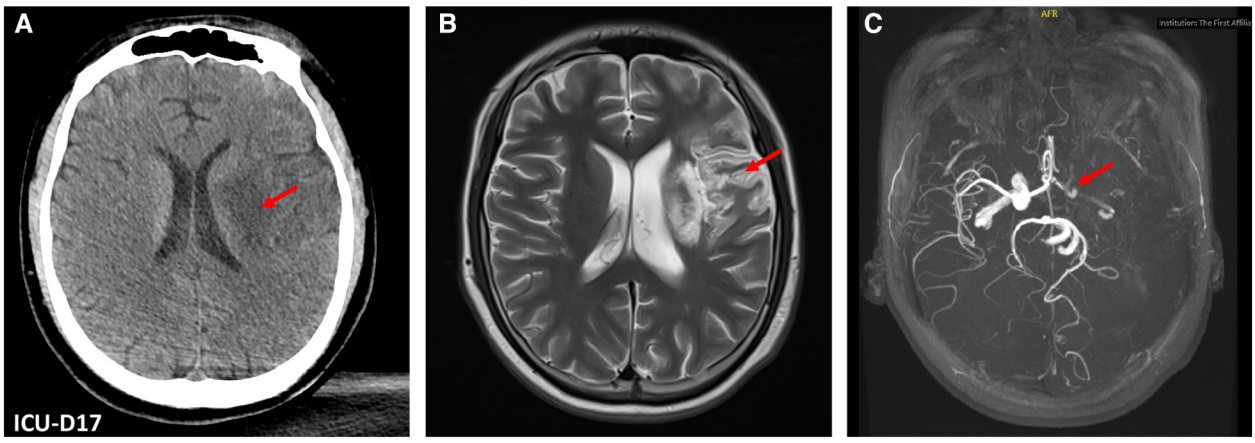


FIGURE 3
Brain computed tomography (CT) and magnetic resonance (MR) images. (**A**) Brain CT on ICU Day 17 revealed an acute infarction of a large area of left middle cerebral artery territory (red arrow). (**B**) The post-ICU discharge brain MRI showed hyperintense regions (red arrow) in the left frontotemporal and basal ganglia areas. (**C**) Brain MR angiography revealed diminished perfusion in the intracranial segment of the left cervical internal carotid artery left, along with occlusion of the left middle cerebral artery (red arrow).

mechanical ventilation on the 20th day of his ICU stay. The following bedside echocardiography demonstrated a gradual resolution and eventual disappearance of the intracardiac thrombi. Throughout the subsequent hospitalization period, there were no further complications or reports cardiac discomfort symptoms. He was ultimately discharged from the hospital on the 37th day of admission and returned home for further physical rehabilitation.

Three months after discharge, he remained free from any cardiac discomforts. However, a follow-up echocardiography persistent revealed left ventricular enlargement, albeit with a reduced LVEDV of 149 ml, and an increased EF of 42%, compared to previous measurements. Through diligent limb rehabilitation exercises, he demonstrated the ability to stand and walk independently.

## 3 Discussion

In this report, we present a complex and unusual case of *M. pneumoniae* infection characterized by the occurrence of fulminant myocarditis, cardiogenic shock, malignant ventricular arrhythmia leading to electrical storm, along with left ventricular thrombosis and subsequent embolic stroke in a healthy 15-year-old male.

Viruses are the predominant pathogens among infectious causes of myocarditis, while mycoplasma infection-induced myocarditis constitutes a minor proportion of cases. Typically, *M. pneumoniae* causes mild respiration infections with potential extra-pulmonary manifestations. However, increased clinical severity and extrapulmonary manifestations have been reported to be associated with delayed effective treatment for macrolide-resistant *M. pneumoniae* (7, 8). In this case, a low sequence number of *M. pneumoniae* with a macrolide-resistant gene, A2063G on the 23S rRNA, was detected. A2063G mutation can decrease the affinity of macrolide with *M. pneumoniae* ribosome, accounting for 99% of macrolide-resistant *M. pneumoniae* infections in China (9). The existence of macrolide-resistance in *M. pneumoniae* might partially contribute to the fulminant cardiac complications in the patients. Tigecycline was subsequently administered in combination with azithromycin, targeting the potential macrolide-resistant strains. However, due to the limited sequences of the macrolide-resistant *M. pneumoniae*, a definitive causal relationship between the fulminant clinical course and macrolide resistance cannot be established.

The *M. pneumoniae*-induced myocarditis can lead to severe consequences, as demonstrated in this case. The precise mechanisms underlying *M. pneumoniae*-induced myocarditis are multifaceted and not yet entirely elucidated. It involves the activation of the host immune response, leading to release of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α, within the cardiac tissues (6, 10). Furthermore, *M. pneumoniae*-induced myocarditis may involve autoimmune mechanisms. The cross-reaction between the *M. pneumoniae* cell components and cardiac tissues plays a role in the cardiac injury (10). Increased levels of circulating immune complexes and elevated T-cell immunoglobulin and mucin domain 1 titers have been associated with myocardial damage in *M. pneumoniae* infections (11, 12), highlighting their significance in the development of *M. pneumoniae*-induced myocarditis. Additionally, it has been suggested that *M. pneumoniae* may directly invade cardiac cells, causing cellular damage and further contributing to the inflammatory cascade (13).

While the *M. pneumoniae*-induced CAP in this case was promptly resolved with the appropriate antibiotics and supportive care, the myocarditis and the severe cardiac presentation necessitated ICU admission and advanced cardiac support

measures. During the initial two days in ICU, cardiac outputs and perfusions could be maintained with low dose of vasopressors and inotropes. However, as the patient developed ventricular arrhythmia and ES, the hemodynamic status of the patient rapidly deteriorated. ES, characterized by three or more separate episodes of ventricular arrhythmia within a 24-hour period, poses a high risk of sudden cardiac death, significant reduction in quality of life, and an overall poor prognosis (14). The ES observed in this case could be associated with the unstable cardiac electrical activity triggered by the myocardial inflammation, along with the altered electrophysiological property due to ventricular remodeling and dilation (14, 15).

Due to inadequate efficacy of pharmacological interventions, mechanical circulatory support was necessary to ensure systemic and coronary perfusion, facilitate venous drainage, and prevent multiple organ dysfunction (16). The timely application of IABP immediately following the initial episode of VF was chosen for its convenience and cost-effectiveness. By employing counterpulsation, IABP reduce left ventricular afterload and increase forward blood flow to the brain and kidney, providing approximately 20% additional circulation support (17). Indeed, this intervention substantially improved perfusion under conditions of declining cardiac output. Unfortunately, the occurrence of ES made it unable to optimize balloon inflation/deflation, resulting in inadequate perfusion. Hence, VA-ECMO were considered immediately under this circumstance. VA-ECMO, recognized as the most advanced temporary circulatory support, ensures immediate and comprehensive hemodynamic support (18). VA-ECMO decreases cardiac preload, improves systemic perfusion, reduces myocardial oxygen consumption; however, it can potentially lead to left ventricular overload and distention due to the increased afterload (18). Therefore, VA-ECMO is better employed in combination with IABP, and in a setting of low flow rate, to effectively mitigate afterload and maintain pulsatile flow. In this case, the combined application of VA-ECMO and IABP played a pivotal role in stabilizing the patient's hemodynamics, allowing for cardiac recovery and, ultimately, weaning from the circulatory supports.

In previous reports, cardiac thrombosis associated with *M. pneumonia* is extremely rare (19, 20). In the case presented, the persistence of left ventricular thrombi posed a significant challenge in clinical management. The development of left ventricular thrombi could largely be attributed to intracardiac turbulence resulting from the ventricular enlargement and the compromised systolic function. Furthermore, *M. pneumoniae* infection also leads to vascular occlusion a which may lead to subsequent cardiac thrombosis. This occlusion can result from either localized vascular injury, or a systemic hypercoagulable state mediated by cytokines (10, 21). Despite anticoagulant therapy was administered initially, the risk of embolic events persisted, ultimately leading to an acute ischemic stroke resulting in right-sided hemiplegia. This underscores the importance of anticoagulant management and vigilance for thromboembolic events and in patients with myocarditis caused by *M. pneumonia*. Management strategies for preventing coagulopathy and thromboembolic events in this case included anticoagulant therapy and monitoring to reduce thrombus propagation and the risk of recurrent events or bleeding complications. Additionally, monitoring of the left ventricular thrombus and heart failure management were employed to prevent further embolization. In some cases, thrombolysis and intracardiac thrombectomy may be considered; however, thrombolysis was not administered due to the risk of secondary bleeding and the likelihood of a prolonged duration of ischemic stroke. Gradual resolution and eventual disappearance of the intracardiac thrombi were observed, indicating a positive therapeutic response without the need for invasive procedures.

Complete cardiac recovery is common in myocarditis associated with *M. pneumonia* infection; however, long-term sequelae have been described (22, 23). In the presenting case, while the patient's cardiac recovery has been encouraging, there was persistent left ventricular enlargement three months after discharge, which could potentially lead to further cardiac complications, such as dilated cardiomyopathy, heart failure, arrhythmias, and sudden cardiac death. This discovery prompts inquiries into the long-term cardiac consequences of *M. pneumoniae*-induced myocarditis, suggesting the need for ongoing cardiological follow-up.

## 4 Conclusions

In conclusion, this case illustrates the diverse clinical manifestations of *M. pneumoniae* infection, demonstrating its potential to trigger fulminant myocarditis leading to cardiogenic shock, electrical storm, as well as the formation of left ventricular thrombi and cerebral embolism. It underscores the importance of maintaining clinical vigilance for potential cardiac complications associated with *M. pneumoniae* infection. Additionally, it emphasizes the necessity for prompt implementation of advanced cardiac support measures to ensure positive outcomes.

## Data availability statement

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

## Ethics statement

The studies involving humans were approved by Ethics board of the First Hospital of China Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

## Author contributions

CZ: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. BH: Formal Analysis, Validation, Writing – review & editing. XL: Formal Analysis, Validation, Writing – review & editing. WH: Formal Analysis, Validation, Writing – review & editing. YL: Project administration, Supervision, Writing – review & editing. MX: Conceptualization, Writing – review & editing.

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## Conflict of interest

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

## Publisher's note



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# Old woman with Sheehan's syndrome suffered severe hyponatremia following percutaneous coronary intervention: a case report and review of literature

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Glucocorticoid deficiency can lead to hypoglycemia, hypotension, and electrolyte disorders. Acute glucocorticoid deficiency under stress is very dangerous. Here, we present a case study of an elderly patient diagnosed with Sheehan's syndrome, manifesting secondary adrenal insufficiency and secondary hypothyroidism, managed with daily prednisone and levothyroxine therapy. She was admitted to our hospital due to acute non-ST segment elevation myocardial infarction. The patient developed nausea and limb twitching post-percutaneous coronary intervention, with subsequent diagnosis of hyponatremia. Despite initial intravenous sodium supplementation failed to rectify the condition, and consciousness disturbances ensued. However, administration of 50 mg hydrocortisone alongside 6.25 mg sodium chloride rapidly ameliorated symptoms and elevated blood sodium levels. Glucocorticoid deficiency emerged as the primary etiology of hyponatremia in this context, exacerbated by procedural stress during percutaneous coronary intervention. Contrast agent contributed to blood sodium dilution. Consequently, glucocorticoid supplementation emerges as imperative, emphasizing the necessity of stress-dose administration of glucocorticoid before the procedure. Consideration of shorter intervention durations and reduced contrast agent dosages may mitigate severe hyponatremia risks. Moreover, it is crucial for this patient to receive interdisciplinary endocrinologist management. In addition, Sheehan's syndrome may pose a risk for coronary atherosclerotic disease.

KEYWORDS

Sheehan's syndrome, percutaneous coronary intervention, severe hyponatremia, glucocorticoid deficiency, stress, contrast agent, coronary atherosclerotic disease

## Introduction

In developed countries, studies have revealed varying prevalence rates of Sheehan's syndrome (SHS) among women, ranging from 0.0051% (1) to 3.1% (2). There were also studies showing that the prevalence of SHS ranged from 1% to 2% among women who experienced hypotension due to blood loss of 1–2 L (3, 4). Contrastingly, in

undeveloped nations, the prevalence varies from 3.1% to 27.6% (5–7). The diagnostic journey for SHS patients spans a considerable duration of 7–19 years from symptom onset to definitive diagnosis (8). Sheehan's syndrome arises from ischemic necrosis of the anterior pituitary gland triggered by postpartum hemorrhage (8), leading to pituitary hormone dysfunction, including insufficient secretion of growth hormone, thyroid stimulating hormone, gonadotropin, prolactin, and adrenocorticotropin (ACTH) (7, 9). Predominant symptoms are associated with dysfunction of the gonads, thyroid, and adrenal cortex due to insufficient secretion of gonadotropins, thyroid stimulating hormones, and ACTH, respectively. The latter is the most prominent and sometimes life-threatening. Supplementing various deficient hormones is the primary treatment for SHS.

Glucocorticoids, pivotal adrenal cortex hormones, play crucial roles in regulating glucose metabolism, blood pressure, and electrolyte balance. Deficiency in glucocorticoids can lead to hypoglycemia, hypotension, and electrolyte disturbances. Lifetime glucocorticoid replacement therapy stands as a cornerstone in managing SHS patients. Fluctuations in neuroendocrine system activity necessitate adjustments in glucocorticoid supplementation, while metabolic disruptions from other etiologies also dictate dosage alterations. Inadequate comprehension of these dynamics among healthcare professionals may impact the prognosis of SHS patients and predispose them to risks. Surgical treatments, including interventional procedures, represent significant stressors in medical care. Failure to administer preoperative stress doses of glucocorticoids to SHS patients can engender serious consequences. To our knowledge, this article represents the first documented case of severe hyponatremia in an SHS patient following percutaneous coronary intervention (PCI).

## Case presentation

A 70-year-old female patient presented with paroxysmal exertional chest tightness persisting for one month, alleviated by a few minutes of rest. Forty years ago, the patient suffered from postpartum hemorrhage, without blood transfusion, subsequently developing lactation failure and amenorrhea. Five years later, she was diagnosed with SHS at the Affiliated Hospital of Shandong University. Management included 5 mg of prednisone acetate in the morning for secondary adrenal insufficiency, and 50 ug of levothyroxine for secondary hypothyroidism. Apart from medication adherence, the patient lacked awareness regarding adrenal insufficiency. The patient had a decade-long history of hypertension, controlled with 5 mg of telmisartan and 5 mg of amlodipine daily. This patient had a weight of 46 kl, a height of 1.57 m, and a BMI of 18.66 kg/m$^2$. Upon hospital admission, her vital signs were stable with a blood pressure of 122/58 mmHg, and a heart rate of 65 beats per minute. Physical examination revealed no pulmonary rales, cardiac murmurs, lower limb edema. Laboratory finding indicated elevated blood troponin I (0.5487 ng/ml, 0–0.0175 ng/ml), normal blood sodium (141.5 mmol/L, 137 mmol/L–147 mmol/L), and elevated fasting total cholesterol (6.28 mmol/L, 3 mmol/L–5.7 mmol/L). Thyroid function tests revealed low level of free thyroxine (FT4) (6.77 pmol/L, 7.98 pmol/L–16.02 pmol/L), with normal levels of free triiodothyronine (FT3) and thyroid stimulating hormone. Electrocardiogram indicated sinus bradycardia. We diagnosed the patient with acute non-ST segment elevation myocardial infarction (NSTEMI) and performed percutaneous coronary angiography (CAG) and intravascular ultrasound (IVUS) examination. We found that the stenosis degree was 40%, 80%, and 60%, 98%, and almost completely occluded, respectively, in the left main trunk (LM), the proximal and middle segments of the left anterior descending branch (LAD), the proximal segments of the left circumflex branch (LCX), and the middle segment of the right coronary artery (RCA) (Figures 1A–C). The minimum lumen area at the distal stenosis of the LM was 4.51 mm$^2$ (Figure 1E), the plaque load at the most severe stenosis of the proximal LAD was 80%, with a minimum lumen area of 2.88 mm$^2$ (Figure 1F). Due to the patient's refusal to undergo coronary artery bypass grafting, two stents were inserted in the middle segment of the RCA (Figure 1D). The intervention lasted for 2 h, including coronary angiography, bilateral intravascular ultrasound examination, patient involvement in treatment decision-making based on examination results, and subsequent coronary intervention treatment, utilizing 130 ml of iodixanol. The patient did not experience any chest discomfort, but was nervous and had a blood pressure rise to 190/100 mmHg, managed with sublingual nifedipine tablets and intravenous isosorbide nitrate. Following percutaneous intervention (PCI), the patient experienced a sequence of symptoms from the 12th to the 50th h, including nausea and loss of appetite, profuse sweating, mild limb twitching, and drowsiness in sequence (Table 1). Limb twitching persisited for 18 h from the 38th to the 56th h post-PCI. On the 24th h post-PCI, the patient was diagnosed with hyponatremia (Table 1), and 2%−3% sodium chloride was intermittently administered intravenously. Despite increased sodium chloride supplementation, symptoms persisted until administration of hydrocortisone, leading to symptom resolution and rapid improvement in blood sodium levels (Table 1). By the 62nd h post-PCI, symptoms of hyponatremia completely resolved, with blood sodium level increasing from 114.2 mmol/L to 132 mmol/L (Table 1). At the 86th h post-PCI, blood sodium level returned to normal. After 40 h, blood tests revealed low levels of cortisol (2.76 ug/dl, 6.7ug/dl–22.6 ug/dl), ACTH (4.26 pg/ml, 10.1 pg/ml–57.6 pg/ml), FT3 (3.41 pmol/L, 3.53 pmol/L −7.37 pmol/L), and FT4 (7.12 pmol/L, 7.98 pmol/L–16.02 pmol/L). Following discharge, the patient continued oral medication with 2.5 mg prednisone acetate and 50 ug levothyroxine sodium daily, as well as dual antiplatelet drugs, statins, and antihypertensive agents. During the next nine-month follow-up period, the patient did not experience ischemic symptoms or hyponatremia.

## Discussion

### SHS and hyponatremia

Sheehan's syndrome is characterized by insufficient secretion of ACTH due to pituitary necrosis, resulting in decreased synthesis

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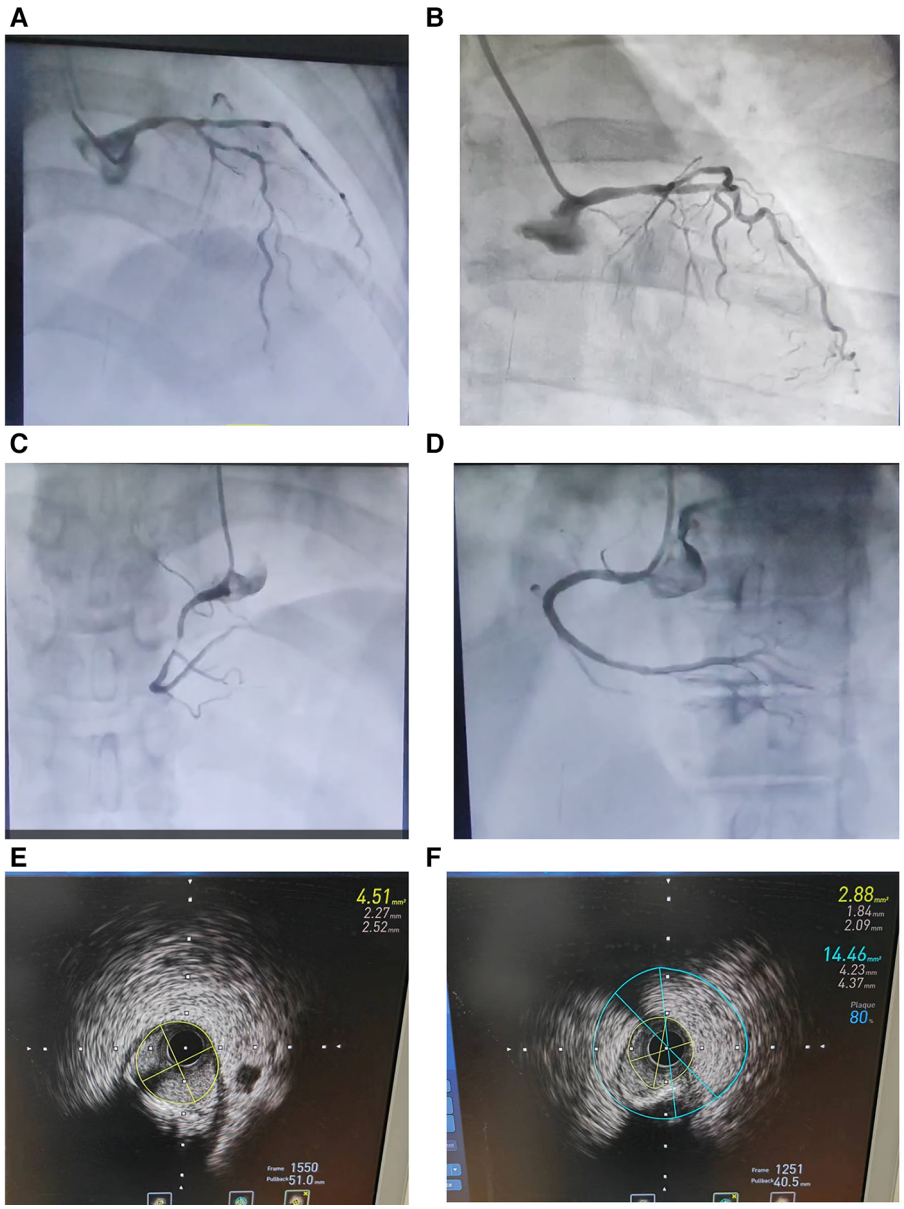


FIGURE 1
Coronary angiography (A–D) and intravascular ultrasound examination (E and F) in an elderly patient with Sheehan's syndrome. (A) The stenosis degree is 40%, 80%, and 60%, respectively, at the end of the left main trunk, the proximal and middle segments of the left anterior descending branch. (B) The stenosis degree is 98% at the proximal segments of the left circumflex branch. (C) The stenosis degree is almost completely occluded at the middle segment of the right coronary artery. (D) Two stents are inserted in the middle segment of the RCA. (E) The minimum lumen area at the distal stenosis of the left main trunk is 4.51 $mm^2$. (F) The plaque load at the most severe stenosis of the proximal left anterior descending branch is 80%, and the minimum lumen area is 2.88 $mm^2$.

and secretion of adrenocortical hormones, particularly glucocorticoids. Glucocorticoids play a vital role in regulating sodium and water excretion and maintaining electrolyte balance in the body. Insufficient glucocorticoid levels lead to diminished renal free water clearance, causing water retention and dilutional hyponatremia, resulting in reduced plasma osmolality. Furthermore, despite low osmolality, there is inappropriate secretion of antidiuretic hormone (vasopressin) due to the absence of cortisol's tonic inhibition (10).

## Clinical presentation and management

In this case, the patient had a medical history of a SHS diagnosis, presenting with secondary adrenal insufficiency and secondary thyrotrophin deficiency necessitating hormone replacement therapy. Secondary adrenal insufficiency arises from pituitary impairment, causing decreased production of ACTH and subsequent reduction in adrenal stimulation, leading to decreased cortisol production. Glucocorticoid deficiency emerged

TABLE 1 Timeline of changes in symptoms, blood sodium titers, and hyponatremia treatment in this patient at 12, 24, 38, 50, 56, 62 and 86 h after percutaneous intervention. normal titer blood sodium reference value: 137 mmol/L to 147 mmol/L.

| | Pre-operative | Post-operative | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 12 h | 24 h | 38 h | 50 h | 56 h | 62 h | 86 h |
| Nausea | | Yes | Yes | Yes | Yes | | | |
| Poor appetite | | Yes | Yes | Yes | Yes | Yes | | |
| Sweating | | | Yes | Yes | Yes | | | |
| Limb twitching | | | | Yes | Yes | | | |
| Drowsiness | | | | | Yes | | | |
| Blood sodium titers (mmol/L) | 141.5 | | 117 | 109.7 | 114.2 | | 132 | 136 |
| Intravenous treatment with sodium chloride (g) | | 4.5 | 6.5 | 17.55 | 6.25 | | 10.75 | |
| Intravenous treatment with hydroprednisone (mg) | | | | 10 | | | | |
| Intravenous treatment with hydrocortisone (mg) | | | | | 50 | | | |

as the primary mechanism of hyponatremia in this patient. During the 2-h of coronary diagnosis and treatment, the patient was anxious, had high blood pressure, and was in a severe stress state, which required additional cortisol to cope with. The specific amount could be evaluated by a specialist doctor. However, due to secondary adrenal insufficiency, the patient could not suddenly increase the secretion of glucocorticoids to copy with the stress. Additionally, glucocorticoids were not pre increased before the procedure. Therefore, the patient was at risk of acute and severe adrenal cortical hormone deficiency, leading to excessive sodium loss, water retention, and subsequent hyponatremia.

## Treatment response

Despite intravenous supplementation of 24.05 g sodium chloride within 26 h, hyponatremia persisted, accompanied limb twitching and drowsiness, indicating an exacerbation of hyponatremia and the formation of hypotonic brain edema. Administration of 50 mg hydrocortisone effectively relieved excessive sodium excretion and water retention. Even with 6.25 g sodium chloride treatment, the patient's symptoms almost disappeared after 6 h, and blood sodium increased from 114.2 mmol/L to 132 mmol/L after 12 h. The subsequent increase in blood sodium levels highlights the importance of glucocorticoid replacement therapy in managing hyponatremia secondary to SHS.

## Management considerations

The case underscores the importance of preoperative stress dose glucocorticoid therapy in SHS patients undergoing procedures such as PCI. However, we were unaware the importance. Additionally, awareness of the potential for contrast agents to induce dilutional hyponatremia and stress response caused by PCI is crucial. Lack of endocrinologist consultation before the procedure and inadequate patient education regarding adrenal insufficiency contributed to the suboptimal management of this patient. Inappropriately administered sublingual nifedipine treatment, intended to manage transient hypertension, not only increased the risk of acute cardiovascular and cerebrovascular disease, but also increased the risks of further activating the sympathetic nervous (11) and exacerbating stress. Therefore, the interdisciplinary management involving endocrinologists is crucial for optimizing the treatment for patients with complex endocrine disorders like SHS, facilitating appropriate examinations, treatment and health education to prevent adrenal crisis and improve long-term outcomes (12, 13).

## Prolonged limb twitching and sodium correction

Unlike the transient symptoms of epilepsy, the patient experienced persistent limb twitching for up to 18 h, possibly due to prolonged lower blood sodium levels. This prolonged imbalance could have led to sustained electrical instability in brain cells, resulting in repetitive abnormal electro-discharge and impaired brain function, posing significant risks to the patient. However, our approach to correcting hyponatremia may not have followed optimal guidelines. Our method of correcting hyponatremia may not have followed the best guidelines. The target value for increasing serum sodium was not set to not exceed 8–10 mmol/L/24 h (14). Our treatment rapidly increased the patient's blood sodium from 114 mmol/L to 132 mmol/L in 12 h, and then continued to supplement with hypertonic sodium chloride. Within 26 h after identifying hyponatremia, 24.05 g of sodium chloride was administered intravenously. These treatments are unreasonable, and the overly rapid correction of hyponatremia may be a risk factor for osmotic demyelination syndrome. Proper management should aim to increase blood sodium concentration gradually, with close monitoring to prevent such complications.

## Other proposed mechanisms of hyponatremia

Contrast agents have been implicated in inducing hyponatremia, particularly in women (15–18). Following administration, the contrast agents elevate the osmotic pressure

of extracellular fluid, leading to passive water transfer of intracellular to extracellular compartments and resultant diluted hyponatremia (15, 16). Sweating caused by sympathetic nerve stimulation and sweating caused by adverse reactions to iodixanol injection may also contribute to sodium loss.

### Role of hypothyroidism

The patient's thyroid hormone levels were low before and after the procedure, indicating the presence of secondary hypothyroidism. Hypothyroidism may have contributed to hyponatremia mainly through the reduced ability to excretal free water, caused by higher levels of ADH. The elevation in ADH levels is largely due to the decrease in cardiac output that stimulates the carotid sinus baroreceptors, prompting the release of ADH. In addition, hypothyroidism can promote hyaluronic acid deposition in extravascular tissues, leading to increased water retention and reduced blood volume. This not only reduces glomerular filtration, but also increases the secretion of antidiuretic hormone, thereby increasing the risk of diluted hyponatremia (19–22). Therefore, optimizing levothyroxine therapy to restore normal thyroid hormone levels may help mitigate the risk of hyponatremia in such cases.

### SHS and coronary artery disease

Previous studies have indicated a higher mortality rate in patients with pituitary dysfunction, primarily attributed to cardiovascular diseases (23–25). Due to chronic inflammation, dyslipidemia, and abdominal obesity, patients with SHS tend to develop coronary artery disease (CAD) (26). This NSTEMI patient suffered from severe coronary atherosclerosis, with traditional risk factors including hypertension and hypercholesterolemia. Long-term oral administration of glucocorticoids may be associated with hypertension and hyperlipidemia in such patients (27, 28). In addition, hypothyroidism, which is common in SHS, can also contribute to hyperlipidemia (29).

Although severe hyponatremia following PCI in SHS patients is not extensively reported, there are cases of female patients exhibiting life-threatening adrenal dysfunction post-PCI (30, 31). The lowest blood sodium level in these cases is 122 mmol/L, and there is no hypoglycemia. Glucocorticoids have good therapeutic effects. The difference is that these patients exhibit significant hypotension, shock, and even Takotsubo syndrome (30, 31).

## Conclusions

The deficiency of glucocorticoids caused by secondary adrenal insufficiency is the primary mechanism for severe hyponatremia in this patient with SHS. The stress induced by PCI exacerbates glucocorticoid deficiency. The contrast agent further contributes to dilutional hyponatremia. The preoperative stress dose of glucocorticoid is crucial to avoid this complication. Glucocorticoids were crucial in correcting severe hyponatremia in this SHS patient with secondary adrenal insufficiency. Shortening the duration of PCI and minimizing the dosage of contrast agents may be beneficial for preventing severe hyponatremia. Meanwhile, it is also crucial for this SHS patient to receive interdisciplinary management involving endocrinologists before and after the procedure. Additionally, SHS may serve as a potential risk factor for CAD.

## Data availability statement

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

## Ethics statement

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

## Author contributions

JG: Data curation, Writing – review & editing. YW: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing, Software, Methodology, Project administration, Supervision. AZ: Writing – review & editing. HP: Writing – review & editing, Data curation. FW: Writing – review & editing.

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

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# Case Report: Three cases of clinically suspected viral myocarditis with recovery of left ventricular dysfunction

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Viral myocarditis is an important cause of non-ischemic cardiomyopathy. Multiple clinical manifestations have been reported, including acute heart failure, cardiogenic shock, and ventricular arrhythmias. We present three patients with clinically suspected viral myocarditis causing acute heart failure. Serum coxsackievirus B antibodies were positive in all three patients. Each case resulted in significant clinical improvement with hemodynamic support and acute recovery of left ventricular ejection fraction. Despite an initial critical presentation concerning for cardiogenic shock, we highlight three cases of clinically suspected coxsackie myocarditis with an excellent short-term prognosis.

KEYWORDS

myocarditis, non-ischemic cardiomyopathy, coxsackievirus, heart failure, cardiogenic shock

## Introduction

Viral myocarditis is an important cause of acute cardiomyopathy resulting from inflammatory destruction of the myocardium (1). Enteroviruses, such as coxsackie B virus, are recognized as a common causal agent of acute myocarditis. Multiple clinical manifestations have been reported, including signs of acute heart failure, cardiogenic shock, and ventricular arrhythmias (2). The natural history of myocarditis is often unpredictable. Patients may experience an acute recovery of left ventricular systolic function, develop chronic and irreversible cardiomyopathy, or face fulminant disease resulting in acute cardiogenic shock and death. The diagnosis of clinically suspected myocarditis relies on a compatible clinical presentation with noninvasive diagnostic findings (3). Cardiac biomarkers including troponin I and troponin T may be elevated in cases of myocarditis, with increased levels associated with a worse prognosis (4). Electrocardiogram changes include sinus tachycardia, atrioventricular block, nonspecific ST-wave and T-wave abnormalities, and ST-segment elevation mimicking an acute myocardial infarction (5). Echocardiographic findings vary depending on the timing of the patient's presentation, often demonstrating new segmental or global wall motion abnormalities (3). Second-level investigations include cardiovascular magnetic resonance (CMR), coronary angiography to exclude ischemic cardiomyopathy, and endomyocardial biopsy (EMB). CMR serves as a highly specific, noninvasive diagnostic tool to characterize myocardial tissue, with the ability to detect inflammation, necrosis, fibrosis, and edema

(1). Limitations of CMR include its inability to detect the degree of myocardial inflammation and cannot be used to exclude viral myocarditis (1, 3). Although EMB remains the gold standard for a definitive diagnosis, it is not routinely performed in patients with a clinical suspicion of myocarditis due to the lack of clinical value for guiding treatment or determining prognosis except in unique circumstances (6). Herein, we report a series of three cases with clinically suspected viral myocarditis.

# Case presentation

## Patient 1

A 19-year-old male with no significant past medical history presented with five days of persistent nonbilious, non-bloody vomiting and worsening abdominal pain. Initial vital signs were significant for a temperature of 98.2°F, blood pressure of 80/47 mmHg, heart rate of 124/min, and oxygen saturation of 93% on room air. Electrocardiogram (EKG) showed sinus tachycardia without significant ST segment or T wave changes (Figure 1). Initial troponin was elevated at 2.15 ng/ml (*N*: < 0.012 ng/ml). Computed tomography (CT) of the abdomen without contrast was unremarkable. CT of the chest without contrast showed bilateral pulmonary edema. The patient was upgraded to the intensive care unit (ICU) due to suspected cardiogenic shock and started on vasopressors including norepinephrine and dobutamine. Echocardiogram showed a left ventricular ejection fraction (LVEF) of 20%–24% with severe global hypokinesis. Reverse transcription polymerase chain reaction for SARS-CoV-2 was negative. On day 3, the patient was weaned off vasopressors. Coronary angiography was deferred due to the absence of risk factors for coronary artery disease and the absence of ischemic changes on EKG. Serum coxsackievirus B (serotypes 1, 2, 5, and 6) IgG and IgM antibodies were positive. On day 6, the patient was initiated on a low dose of carvedilol and lisinopril. A repeat echocardiogram showed improvement of LVEF to 50%–54%. The patient had resolution of symptoms and he was stable for hospital discharge. Two weeks following hospitalization, the patient had achieved complete clinical recovery.

## Patient 2

A 20-year-old female with no significant past medical history presented with chest pain, dizziness, and epigastric pain. Initial vital signs were notable for a temperature of 98.2°F, blood pressure of 63/39 mmHg, heart rate of 106/min, and oxygen saturation of 100% on room air. Physical exam was benign except for abdominal tenderness in the epigastric region. The patient remained hypotensive and was admitted to the ICU for vasopressor support. EKG on admission showed acute ST segment elevations in leads V1 and V2 (Figure 2). Initial labs were notable for a creatinine of 4.6 mg/dl and an elevated troponin of 0.6 ng/ml (*N*: < 0.012 ng/ml). A transthoracic echocardiogram showed an LVEF of 25%–29% and diffuse hypokinesis with right ventricular dysfunction. The patient required dobutamine and norepinephrine for cardiogenic shock. Right and left heart catheterization with coronary angiography showed no significant coronary artery disease, normal pulmonary pressures, and normal cardiac output.

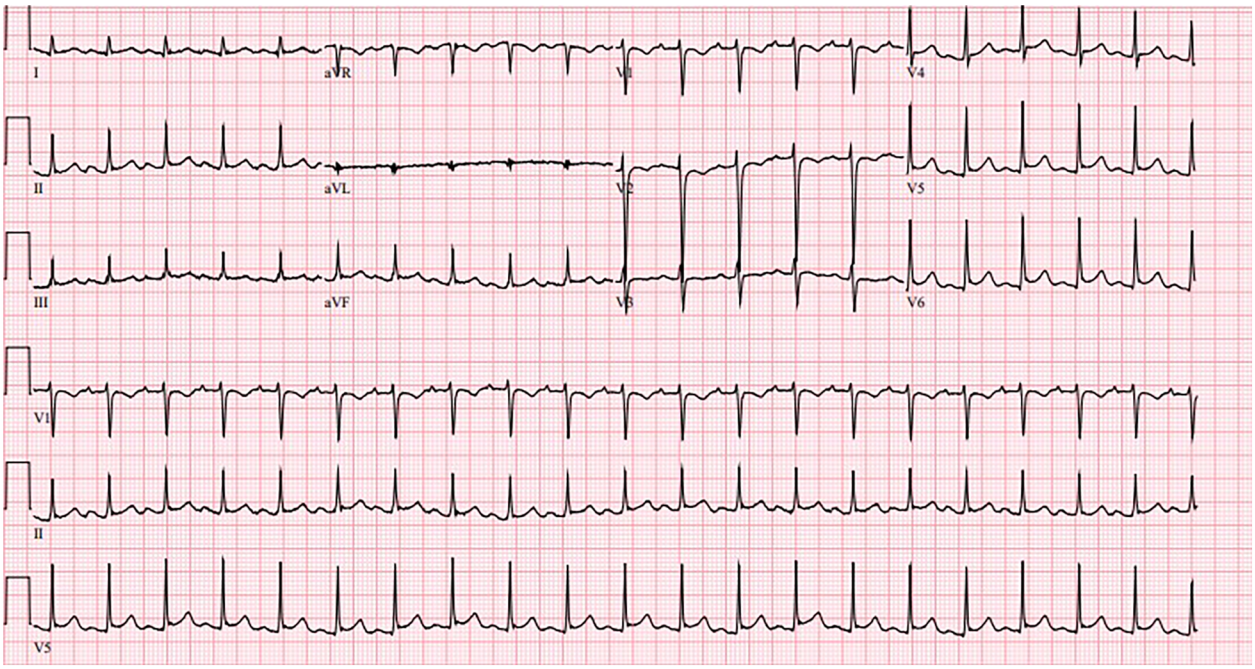


FIGURE 1
Sinus tachycardia without significant ST segment or T wave changes.

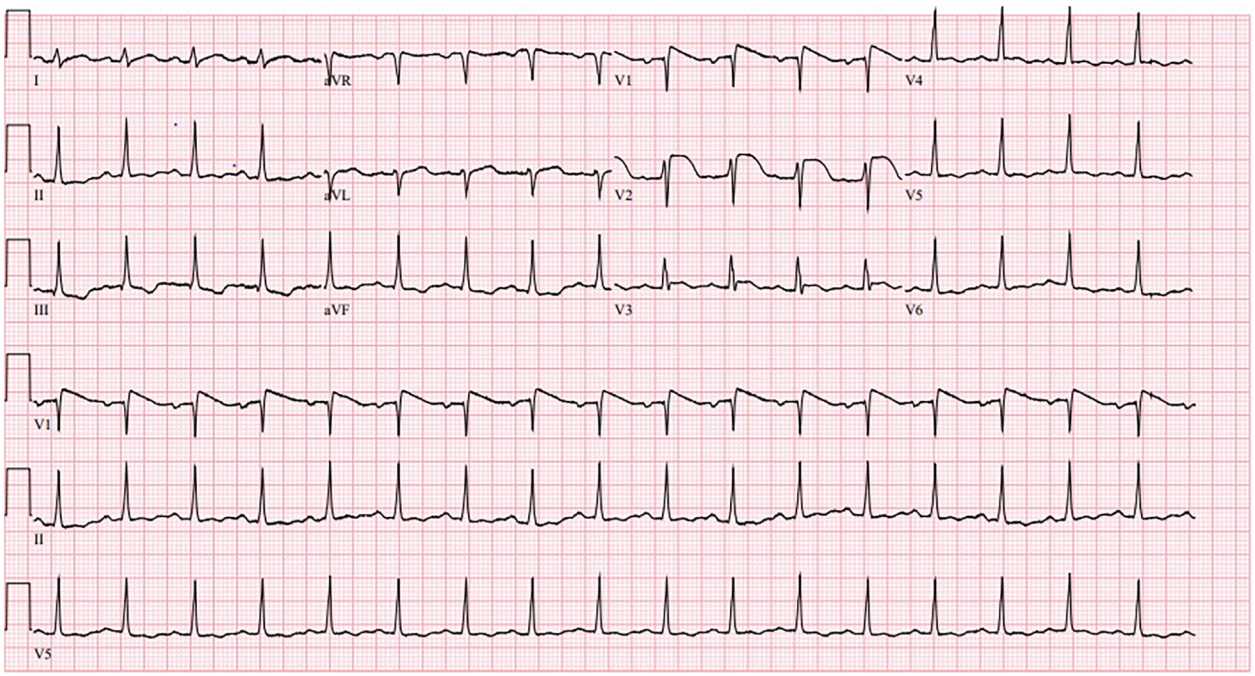


FIGURE 2
Normal sinus rhythm with ST segment elevations in leads V1 and V2.

On day 4, repeat EKG showed normal sinus rhythm with resolution of ST elevations, and the patient no longer required inotropic support. Serum coxsackievirus group B (serotypes 1–6) IgG and IgM antibodies was positive. Low dose sacubitril/valsartan and carvedilol was initiated on day 6 of hospitalization. Additional guideline directed medical therapy for heart failure was withheld due to low blood pressure measurements. She was stable for discharge on day 7 of hospitalization. Upon 1 month follow up, a repeat echocardiogram demonstrated a normal LVEF and no wall motion abnormalities.

## Patient 3

A 78-year-old female with a history of hypertension, type 2 diabetes, and chronic hyponatremia presented with new onset dizziness and weakness. On admission, vital signs were notable for a temperature of 98.9°F, blood pressure of 70/40 mmHg, heart rate of 87 /min, and oxygen saturation of 99% on room air. Physical exam was notable for bilateral lower extremity pitting edema but otherwise unremarkable. EKG showed a normal sinus rhythm with nonspecific ST-segment changes (Figure 3). Initial troponin was 10.7 ng/ml ($N$: < 0.012 ng/ml). A transthoracic echocardiogram demonstrated a reduced LVEF of 40%–44% with hypokinesis of the anteroseptal and apical myocardium. A left heart catheterization showed twenty to thirty percent proximal and mid left anterior descending artery (LAD) stenosis which did not warrant intervention. Serum coxsackievirus group B (serotype 3) IgM and IgG antibody was positive. Hypotension improved with intravenous fluids. After nine days of hospitalization, the patient reported complete resolution of symptoms. She was continued on losartan and metoprolol with close outpatient follow up. Three months following admission, a repeat echocardiogram showed recovery of ventricular function with a LVEF of 60%–65%.

# Discussion

We highlight three unique cases of clinically suspected myocarditis with positive coxsackievirus B antibodies. Despite an initial presentation of cardiogenic shock, there was rapid clinical recovery within a week of hospitalization. The diagnosis of myocarditis relies on clinical presentations resembling acute coronary syndrome, nonspecific ST segment and T wave changes on ECG, followed by unexplained left ventricular dysfunction with either regional or global wall motion abnormalities on echocardiogram. Our first two cases consisted of healthy, young patients with no cardiovascular risk factors who prompted an investigation for new onset non-ischemic cardiomyopathy (NICM). In our third case, an elderly patient with multiple cardiovascular comorbidities, highly elevated troponin and nonspecific ischemic changes on ECG highlighted the importance of excluding coronary artery disease.

There were several limitations in our cases. First, endomyocardial biopsy was not performed during hospitalization due to the resolution of symptoms and improvement in LVEF within days of starting heart failure medical therapy. EMB is generally reserved for patients with new-onset fulminant myocarditis refractory to pharmacologic therapy or unexplained heart failure associated with

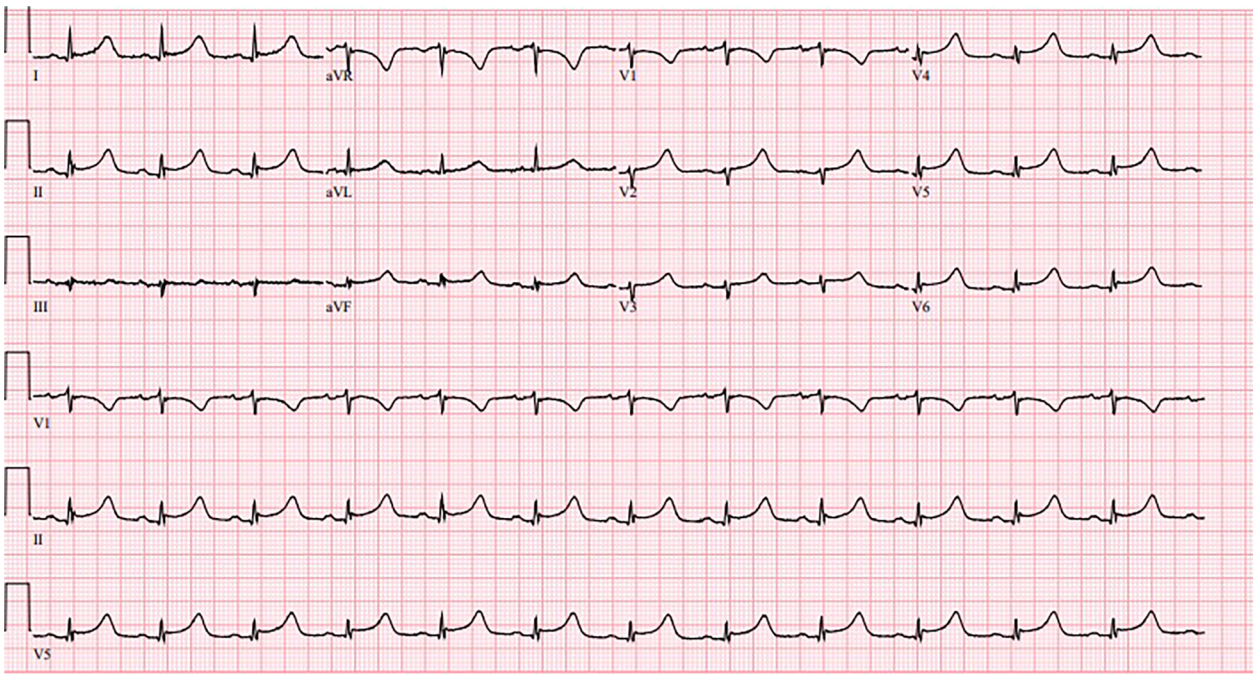


FIGURE 3
Normal sinus rhythm with nonspecific ST-segment changes.

a dilated left ventricle, ventricular arrhythmias, and atrioventricular block (6). In addition, CMR was not available at our hospital, and could have served as a valuable noninvasive tool to support the diagnosis of clinically suspected myocarditis. We recognize the limitation of serum coxsackie antibodies in the diagnosis of coxsackie myocarditis and that a definite diagnosis requires viral PCR on cardiac biopsy.

Myocarditis causes an inflammatory cardiomyopathy leading to acute heart failure with risk of hemodynamic instability, often requiring temporary inotropic and vasopressor support (7). Depending on the degree of left ventricular dysfunction, patients may experience rapid resolution, chronic dilated cardiomyopathy, or end stage heart failure with risk of sudden cardiac death (3). Myocarditis can result from multiple infectious pathogens including viruses, bacteria, fungi, and protozoans (2). Parvovirus B19, human herpesvirus 6 (HHV 6), and enteroviruses, including coxsackie B virus, are common viral etiologies of acute and chronic myocarditis (2). The pathogenesis involves introduction of the virus through the respiratory or gastrointestinal tract followed by entry into the myocardium (1). Direct infection of cardiomyocytes enables viral replication and activates immune responses, resulting in myocyte necrosis and cellular degradation (8). In addition, molecular mimicry between cardiac and viral antigens triggers an autoimmune reaction in which virus specific T cells target the myocardium. Over time, a chronic inflammatory response causes myocyte fibrosis and cardiac remodeling, resulting in dilated cardiomyopathy (2). Progressive ventricular dysfunction is associated with persistent viral infection as demonstrated from an EMB based analysis of clinically suspected viral myocarditis (9).

Echocardiography is essential in the initial work-up to exclude other causes of NICM such as amyloidosis or valvular heart disease. Echocardiographic features are nonspecific and encompass a wide spectrum of findings. They often demonstrate a reduced LVEF with global hypokinesis, as seen in two of our patients. Right ventricular dysfunction, shown to be a prognostic factor for mortality and the need for transplantation, was observed in one of our cases (2). Other potential features include increased septal thickening, regional hypokinesis, diastolic dysfunction, or pericardial effusion (10). Such findings on echocardiography cannot reliably distinguish myocarditis from acute coronary syndrome. Therefore, cardiac catheterization is warranted when coronary artery disease is suspected.

Treatment recommendations for viral myocarditis are based on expert consensus centered on guideline-directed medical therapy for heart failure. No clinically approved antiviral therapies are available for coxsackie B-related myocarditis due to the absence of randomized clinical trials in the field. However, anti-viral agents such as interferon-β (IFN-β) have gained recent attention due to cardiomyocyte protection and decreased inflammatory cell infiltration, as demonstrated in an experimental animal model (11). In addition, a phase-II study from Schultheiss et al. showed effective viral clearance, reduction in viral load, and improvement in NYHA functional class among patients receiving IFN-β in addition to standard heart failure therapy (12). The role of immunomodulatory therapy remains largely exploratory. Given the role of the coxsackievirus-adenovirus receptor for myocardial viral entry, neutralization with soluble virus receptor traps can inhibit development of chronic myocarditis and preserve cardiac function,

as demonstrated in an animal model (13). Further randomized clinical trials are required to determine the effect of antiviral and immunomodulatory therapy on multiple clinical endpoints.

## Conclusion

We reported three cases of clinically suspected myocarditis requiring hemodynamic support. Serum coxsackie antibodies were positive in all patients. Patients hospitalized for left ventricular dysfunction secondary to acute myocarditis often have significant recovery within weeks. Clinical management for viral myocarditis centers on optimizing heart failure medical therapy. Given the possibility of progressive systolic dysfunction with viral persistence, close monitoring with long term follow up is required.

## Data availability statement

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

## Ethics statement

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

## Author contributions

JB: Writing – original draft, Writing – review & editing. HR: Writing – original draft, Writing – review & editing. SS: Writing – review & editing. ST: Writing – review & editing. JK: Writing – review & editing. AS: Writing – review & editing. MD: Writing – review & editing. SR: Writing – review & editing.

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## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1345449/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Echocardiogram of patient 1, short-axis view showing reduced LVEF with severe global hypokinesis.

SUPPLEMENTARY VIDEO 2
Echocardiogram of patient 2, short-axis view showing reduced LVEF with diffuse hypokinesis.

SUPPLEMENTARY VIDEO 3
Echocardiogram of patient 3, long-axis view showing reduced LVEF with anteroseptal hypokinesis.

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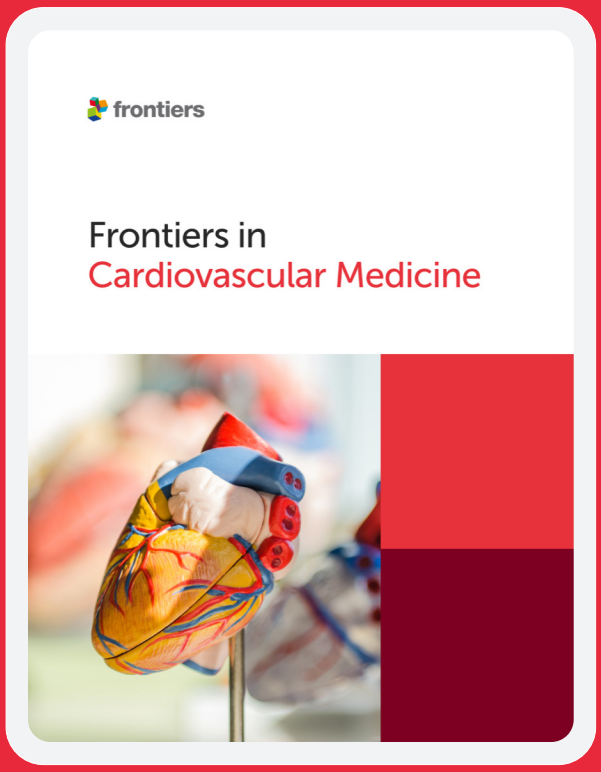


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