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CASE REPORT
Heart failure

Cardiac sarcoidosis preceded by sick sinus syndrome presenting as biventricular involvement and intracardiac giant thrombus: a case report

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Background Sarcoidosis is a granulomatous disorder characterized by the formation of non-necrotizing granulomas in various organs. Cardiac sarcoidosis presents with various clinical, anatomical, and electrophysiological manifestations. As cardiac involvement is related to adverse outcomes, the early diagnosis of cardiac sarcoidosis is crucial and sometimes challenging.

Case summary A 65-year-old woman was initially treated for sick sinus syndrome (SSS) with normal cardiac function. Cardiac conduction defects and biventricular dysfunction continued to progress over a short clinical course, and the patient was eventually referred to our hospital for further investigation and treatment of cardiogenic shock due to pacemaker pacing failure. An echocardiography revealed a large thrombus formation in the right ventricle and atrium. An urgent thrombectomy was performed, and myocardial biopsy confirmed the diagnosis of cardiac sarcoidosis. Steroid pulse therapy was initiated and was effective in treating the cardiogenic shock. One year after discharge, the patient manifested with sustained ventricular tachycardia and ultimately died of severe cardiac pump failure. On autopsy, diffuse fibrotic tissues were noted in both ventricles and atria.

Discussion While conduction abnormalities, such as right bundle brunch block and atrioventricular block, are common clinical manifestations, SSS is rarely reported as a primary manifestation of cardiac sarcoidosis. Thus, clinicians should ensure that sufficient investigations are carried out when diagnosing idiopathic SSS.

Keywords Case report • Cardiac sarcoidosis • Sick sinus syndrome • Thrombus • Cardiomyopathy • Pathology

ESC curriculum 5.7 Bradycardia • 6.5 Cardiomyopathy

Learning Points

- Sick sinus syndrome can precede atrioventricular block and/or apparent ventricular dysfunction in patients with cardiac sarcoidosis.
- Clinicians should be aware of SSS as a possible primary manifestation of cardiac sarcoidosis.
- Steroid pulse therapy may be considered for patients with inflammatory-active cardiac sarcoidosis who require the intravenous administration of catecholamines and/or mechanical circulatory support.

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Introduction

Sarcoidosis is a granulomatous disorder characterized by the formation of non-necrotizing granulomas in various organs.[1] Cardiac sarcoidosis presents with various clinical, anatomical, and electrophysiological manifestations. Conduction abnormalities, such as right bundle brunch block and atrioventricular block, are common clinical manifestations of cardiac sarcoidosis, while sick sinus syndrome (SSS) is a rare primary manifestation of the disease. As cardiac involvement is related to adverse outcomes, the early diagnosis of cardiac sarcoidosis is crucial.

Summary figure

Time	Events
2015	Patient was diagnosed with uveitis by an ophthalmologist.
September 2016	Patient was diagnosed with sick sinus syndrome. Pacemaker implantation was performed at the referring hospital.
November 2016	Patient experienced progressive dyspnoea with minimal activity and was treated with diuretics and angiotensin receptor antagonists.
10 January 2018	Patient complained of leg oedema. Device interrogation revealed progressive atrioventricular conduction defect.
24 January 2018	Patient was hospitalized for worsening heart failure. Pacemaker interrogation and electrocardiogram revealed junctional escape rhythm due to complete atrioventricular block with atrial and ventricular pacing failure. Echocardiography revealed biventricular systolic dysfunction and giant right ventricular thrombus formation. Pacemaker re-programming was unsuccessful; the junctional escape rate was 50–60 b.p.m. An additional pacemaker lead had not been inserted yet.
30 January 2018	Patient went into cardiac arrest as the escape contraction suddenly disappeared and a temporary pacing electrode was inserted into the coronary sinus.
2 February 2018	Patient was transferred to our hospital for further investigation and treatment.
3 February 2018	An urgent thrombectomy was performed. Endomyocardial biopsy confirmed cardiac sarcoidosis.
6 February 2019	Patient was re-admitted due to sustained ventricular tachycardia and had refractory ventricular electrical storm.
20 March 2019	Patient died from severe biventricular pump failure and sepsis.

Case presentation

A 65-year-old woman first presented with palpitations and dizziness in September 2016. She had no family history of cardiomyopathy, arrhythmia, or sudden death. Her medical history included diabetes mellitus and bilateral cataracts. She was diagnosed with uveitis 1 year prior, which was relieved by the administration of eye drops. A 12-lead electrocardiogram (ECG) showed a sinoatrial block (SSS) and right bundle branch block (*Figure 1A*). Further sinus arrest (up to 3.9 s) with dizziness was detected on 24-h Holter ECG. No abnormal findings were observed on physical examination, laboratory tests, or echocardiography [left ventricular ejection fraction (LVEF) 62%]. Cardiac magnetic resonance imaging was not performed at the time. The patient underwent a dual-chamber pacemaker implantation.

Two months later, the patient experienced progressive dyspnoea with minimal activity. Electrocardiogram showed atrial pacing rhythm (*Figure 1B*), and laboratory tests revealed abnormal liver function and an elevated level of brain natriuretic peptide (BNP; 291 pg/mL; Supplementary material online, *Table S1*). Echocardiography showed that the LVEF decreased from 62% to 51% in December 2017. She was clinically diagnosed with heart failure with preserved ejection fraction and treated with diuretics and angiotensin receptor antagonists to relieve the signs and symptoms of congestion.

In January 2018, the patient presented with leg oedema. Device interrogation showed a complete atrioventricular block with atrial-paced and ventricular-paced rhythm (*Figure 2A*). Two weeks later, she was hospitalized for worsening heart failure. Pacemaker interrogation and 12-lead ECG showed junctional escape rhythm due to a complete atrioventricular block with atrial and ventricular pacing failure (*Figure 2B*). Echocardiography showed biventricular systolic dysfunction and giant right ventricular thrombus formation. In response to this finding, anti-coagulant therapy with heparin and warfarin was started promptly. Pacemaker re-programming was unsuccessful; the junctional escape rate was 50–60 b.p.m., without additional pacemaker lead insertion. During hospitalization, the patient went into cardiac arrest, as the escape contraction suddenly disappeared. Cardiologists at the referring hospital did not re-insert an additional right ventricular electrode because of the large thrombus formation in the right ventricle (RV). As a result, a temporary pacing electrode was inserted into the coronary sinus, and the patient was transferred to our hospital for further investigation and treatment.

On admission, ECG revealed ventricular pacing rhythm (see Supplementary material online, *Figure S1*). Serum levels of angiotensin converting enzyme [upper reference limit (URL), 29.4 IU/L] and calcium (URL, 10.2 mg/dL) were within normal limits at 16.3 IU/L and 8.9 mg/dL, while soluble interleukin-2 receptor (URL, 500 U/mL) and BNP levels were remarkably elevated at 677 U/mL and 844.7 pg/mL, respectively. Coronary angiography revealed no significant stenosis. Echocardiography revealed severe biventricular dysfunction. Left ventricular ejection fraction was moderately to severely reduced (~30% by visual assessment), and the anteroseptal, inferoseptal, and inferior walls of the left ventricle were severely hypokinetic and regionally dyskinetic due to ventricular aneurysm. The RV was severely dilated, and the basal and longitudinal diameters of the RV were 51 mm (normal range; 25–41 mm) and 88 mm (normal range; 59–83 mm), respectively.[1] Tricuspid annular plane systolic excursion (TAPSE) was reduced to 8 mm. The tricuspid annulus was dilated, and tricuspid valve coaptation was reduced, resulting in severe tricuspid regurgitation. The right ventricular thrombus was thought to be caused by severe stasis flow due to right ventricular dysfunction. Furthermore, it was clinically suspected that inflammation due to cardiac sarcoidosis or eosinophilic myocarditis may have contributed to thrombus formation. A large thrombus formation was also observed in the RV (47 × 26 mm in the apical four-chamber view) and right atrium (RA; see Supplementary material online, *Video 1*). Preoperative contrast-enhanced computed tomography (CT) was performed to obtain accurate anatomical information confirming thrombus formation in the RA and RV (*Figure 3A and B*). There were no other organ findings.

Following discussions within our heart team, it was determined that the patient's condition posed a significant risk for acute pulmonary

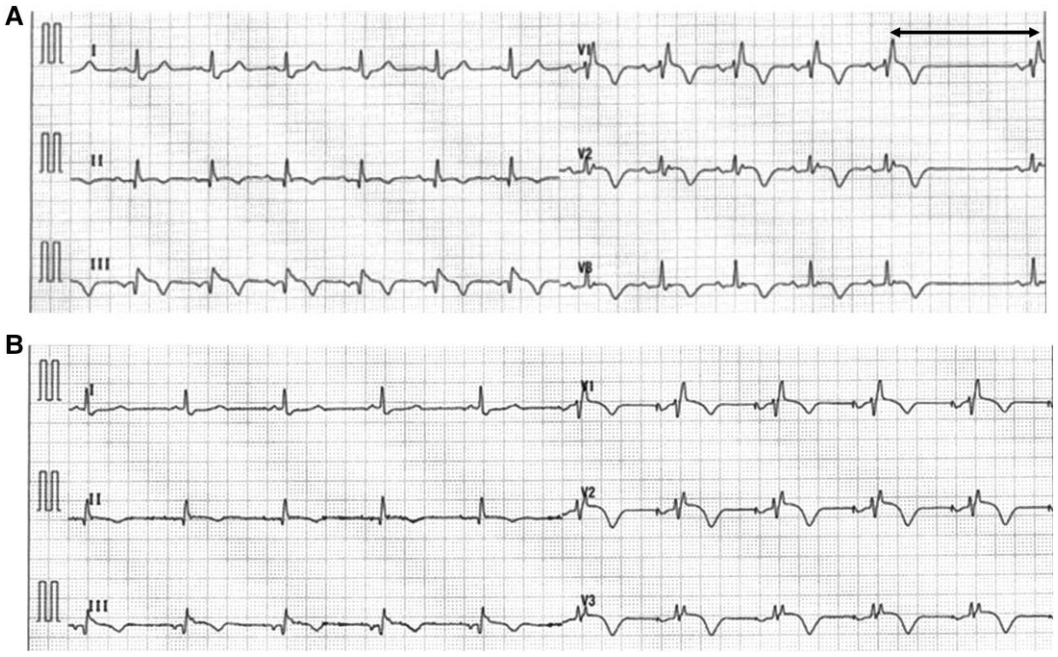

Figure 1 Electrocardiogram taken before versus after pacemaker implantation. (*A*) Electrocardiogram showing a sinoatrial block (double-headed arrow) and a complete right bundle branch block. (B) Electrocardiogram showing atrial pacing rhythm.

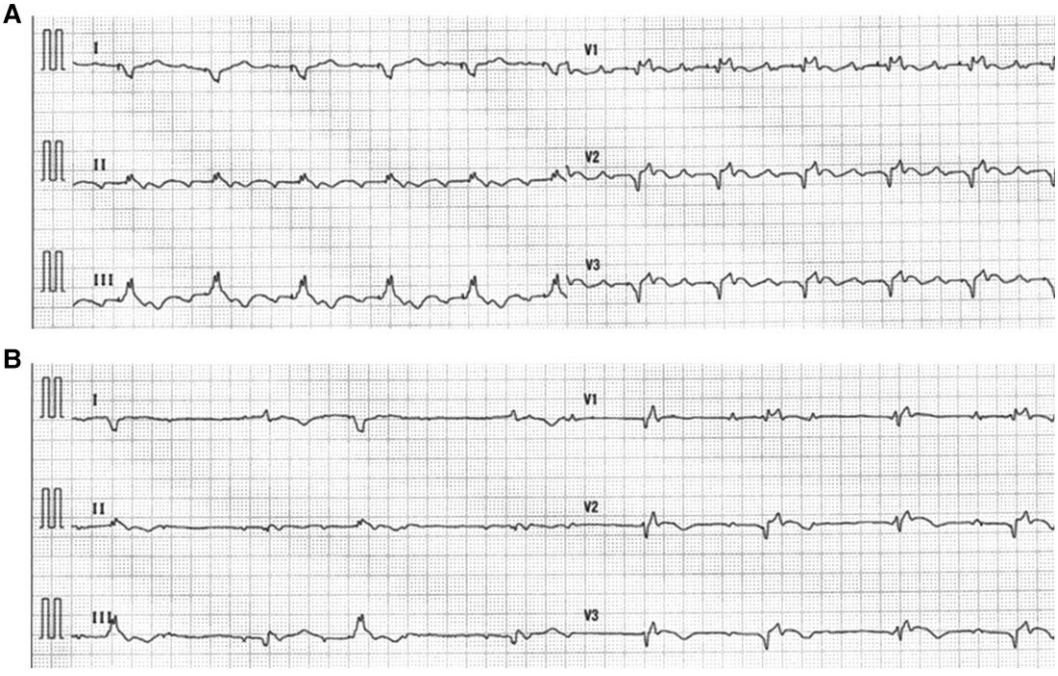

Figure 2 Electrocardiogram taken after the patient developed heart failure. (*A*) Electrocardiogram showing atrial and ventricular pacing rhythm. (*B*) Electrocardiogram showing junctional escape rhythm because of complete atrioventricular block with atrial and ventricular pacing failure.

thromboembolism, and the efficacy of thrombolytic therapy alone was deemed limited. Additionally, the extent of RV wall thinning and severe RV dysfunction rendered the use of cardioprotective agents, such as beta-blockers and renin–angiotensin–aldosterone system inhibitors, unlikely to improve tricuspid regurgitation. The patient underwent an urgent thrombectomy of the RA and RV to prevent pulmonary

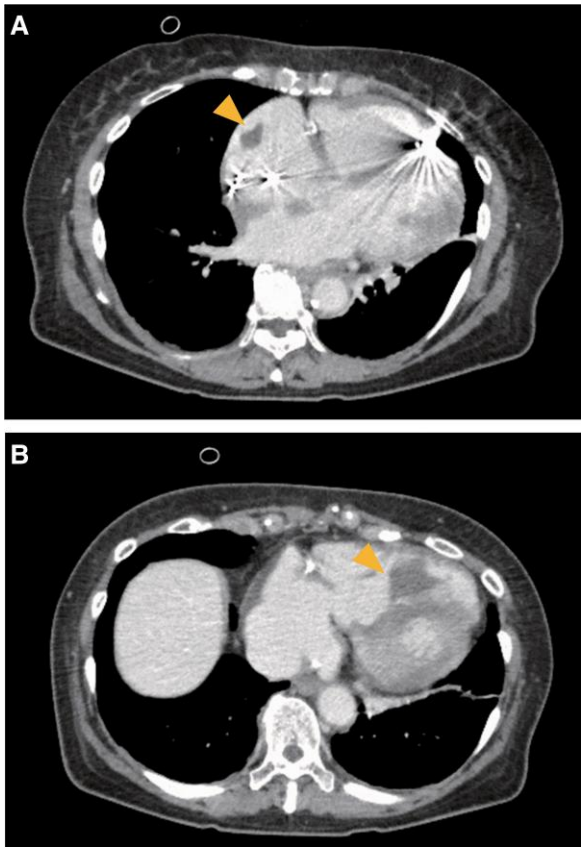

Figure 3 Contrast-enhanced computed tomography. Contrast-enhanced computed tomography showing thrombus formation in the right atrium (*A*, arrow) and right ventricle (*B*, arrow).

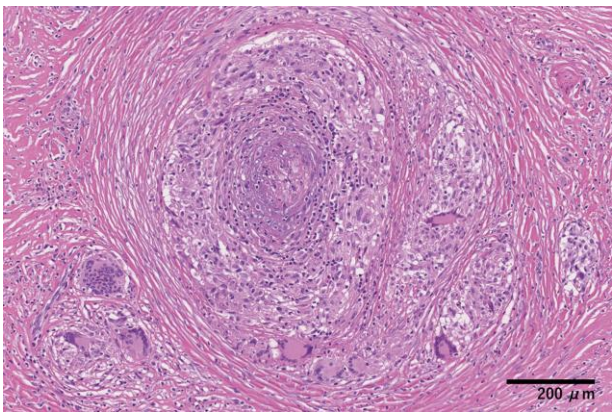

Figure 4 Biopsy specimen. The biopsy specimen shows infiltrative inflammatory cells and non-caseating epithelioid granulomas including multinucleated giant cells (haematoxylin and eosin stain; scale bar, 200 μm).

thromboembolism, as well as the removal of the jugular vein pacemaker leads. Epicardial pacemaker implantation was also carried out simultaneously with tricuspid annuloplasty. Endomyocardial biopsy revealed infiltrative inflammatory cells and epithelioid cell granulomas, including multinucleated giant cells (*Figure 4*). Consequently, the patient was diagnosed with cardiac sarcoidosis. After open-heart surgery, the patient experienced cardiogenic shock due to severe biventricular dysfunction with a LVEF of 26% 10 days post-operatively, which was dependent on the intravenous administration of dobutamine and noradrenaline. We initiated immunosuppressive therapy with corticosteroids, including steroid pulse therapy (1000 mg for 3 days) and subsequent maintenance therapy. Notably, the patient's LVEF improved to 35% following a course of immunosuppressive therapy, including a steroid pulse, and intravenous catecholamine support was eventually withdrawn. The patient was discharged on Day 79 of hospitalization. Guideline-directed medical therapy for heart failure with a reduced ejection fraction was provided (bisoprolol 0.625 mg/day, enalapril 2.5 mg/day, spironolactone 25 mg/day, and empagliflozin 10 mg/day). However, further titration of these drugs was difficult due to symptomatic hypotension. Anti-coagulation therapy with warfarin was continued, and prednisolone was administered at 10 mg/day after discharge. Six months after initiation of steroid therapy, positron emission tomography (PET)-CT detected no uptake of ^{18}F-fluorodeoxyglucose in the myocardium (see Supplementary material online, *Figure S2*). To prevent recurrence of active inflammation, oral prednisolone 10 mg/day was continued as the maintenance dose.

During outpatient follow-up, our patient presented with gradually worsening symptoms of heart failure. On September 2018, she presented symptomatic sustained ventricular tachycardia (SVT), which prompted upgrading of her pacemaker to an implantable cardioverter defibrillator. However, she was re-admitted with recurrent SVT on 6 February 2019. The patient had refractory ventricular electrical storms shortly after admission. With mechanical ventilation, deep sedation, and intravenous administration of the anti-arrhythmic agents amiodarone and lidocaine, we were able to save her from this life-threatening situation. However, despite intensive care, she became progressively weaker owing to severe biventricular pump failure. The patient developed fever, arterial hypotension, and leukocytosis. Bacteraemia caused by methicillin-resistant *Staphylococcus epidermidis* and *Candida albicans* was detected, resulting in a diagnosis of sepsis. The source of the infection was unclear, with catheter-related infection or bacterial translocation from the skin or gastrointestinal tract suspected as potential causes. Treatment was initiated with appropriate antibiotics and catecholamines, along with a maintenance dose of glucocorticoid therapy, but the patient ultimately died of multiple organ failure on 20 March 2019, which was attributed to the combination of severe pump failure and sepsis. On autopsy, there was no evidence suggestive of an infectious source in the implantable devices, leads, heart valves, or elsewhere in the body. Diffuse fibrotic tissues were noted in both ventricles. In particular, the myocardium in the RV was substantially replaced with fibrotic tissues without inflammatory cell infiltration (*Figure 5A* and *B*). Significant fibrotic changes, including those in the anatomical sinus node, were also observed in the RA (*Figure 5C*). Clinicopathological correlation indicated that cardiac sarcoidosis involving the RA and RV initially caused SSS and thrombus formation in the RA and RV, ultimately resulting in biventricular heart failure.

Discussion

Cardiac sarcoidosis presents with various clinical, anatomical, and electrophysiological manifestations.[2] This case is uncommon in that SSS preceded an advanced atrioventricular block. A retrospective cohort study reported that 32 of 100 patients with cardiac sarcoidosis had supraventricular arrhythmias as follows:[3] atrial fibrillation (18%), atrial tachycardia (7%), atrial flutter (5%), and other supraventricular arrhythmias (2%). Sick sinus syndrome is a rare primary manifestation of

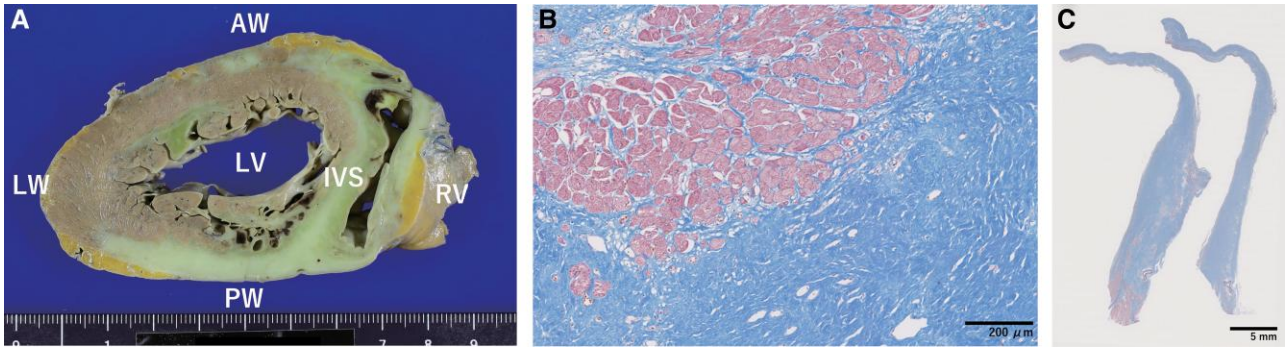

Figure 5 Findings on autopsy. (*A*) Diffuse fibrosis that was particularly abundant from the IVS to the right ventricular free wall (gross, scale bar 10 mm) and (*B*) depicted microscopically (Masson's trichrome stain; scale bar, 200 μm). AW, anterior wall; IVS, interventricular septum; LV, left ventricle; LW, lateral wall; PW, posterior wall; RV, right ventricle. (*C*) Remarkable fibrotic changes in the right atrium and the anatomical sinus node are visible.

cardiac sarcoidosis and has only been reported in case reports.[4,5] In this case, upon the diagnosis of SSS, a right bundle branch block was noted on ECG with no abnormal structural findings on echocardiography. However, biventricular dysfunction developed over 1 year. The autopsy imaging revealed extensive fibrosis in both the RV and LV, which is not typically observed within such a short period of time with RV pacing. Additionally, the pacemaker was initially implanted for SSS, and as the heart failure progressed, the pacemaker transitioned from ventricular sensing failure to ventricular pacing failure. This process differed from the typical course of LV dysfunction associated with RV pacing.[6,7] To the best of our knowledge, there are currently no reports of patients with cardiac sarcoidosis initially presenting SSS, following by a progression from ventricular sensing failure to ventricular pacing failure, accompanied by concurrent RV and LV systolic dysfunction.

Positron emission tomography has high diagnostic power for the detection of active cardiac sarcoidosis but is not readily available in all facilities. There are no specific serological markers, ECG, echocardiography, or imaging findings that can confirm the diagnosis of cardiac sarcoidosis.[8] While a pattern of late gadolinium enhancement on cardiac magnetic resonance imaging can be suggestive of cardiac sarcoidosis, arrhythmogenic ventricular cardiomyopathy and myocarditis can mimic similar patterns.[8,9] Myocardial biopsy is key to the definite diagnosis of cardiac sarcoidosis but has a low sensitivity (35%).[10] Thus, the early diagnosis of cardiac sarcoidosis is difficult for clinicians.

Current guidelines for the treatment of cardiac sarcoidosis recommend long-term immunosuppressive treatment,[2] while investigations of steroid pulse therapy for patients with inflammatory-active cardiac sarcoidosis who require intravenous administration of catecholamines and/or mechanical circulatory supports are scarce.[11] In the present case, steroid pulse therapy led to successful withdrawal of intravenous catecholamine support, as seen in some types of myocarditis (e.g. eosinophilic myocarditis). Further studies are needed to assess the association between steroid therapy and haemodynamics and prognosis in haemodynamically unstable patients with cardiac sarcoidosis.

This case showed unique clinical features in that symptomatic SSS preceded an advanced atrioventricular block and severe fibrosis in the RA and RV was pathologically confirmed. Given this information, clinicians should diagnose idiopathic SSS, as well as atrioventricular block, only after performing sufficient investigations. Steroid pulse therapy may be an effective treatment option for active inflammatory cardiac sarcoidosis in severely ill patients with haemodynamic impairment.

Lead author biography

Akeo Hirai graduated from Jikei University School of Medicine in 2014. After 2 years of junior residency, he completed his senior residency at the Department of Cardiology, Keio University School of Medicine. He has been working as a general cardiologist at the Akashi Medical Centre since April 2021.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Consent: The authors obtained verbal consent from the patient's husband for submission and publication of this case report, accompanying images, and associated text as per hospital policy in accordance with the Committee on Publication Ethics (COPE) guidelines.

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