



Misdiagnosed takotsubo syndrome: a case report

Qiuzhen Lin^{1,2,3,4#}, Yan Fu^{1,2,3,4#}, Yanqiao Chen^{1,2,3,4}, Xueyan Zang^{1,2,3,4}, Ling Liu^{1,2,3,4}

¹Department of Cardiovascular Medicine, the Second Xiangya Hospital, Central South University, Changsha, China; ²Research Institute of Blood Lipid and Atherosclerosis, Central South University, Changsha, China; ³Modern Cardiovascular Disease Clinical Technology Research Center of Hunan Province, Changsha, China; ⁴Cardiovascular Disease Research Center of Hunan Province, Changsha, China

#These authors contributed equally to this work.

Correspondence to: Ling Liu. #139 Middle Renmin Road, Changsha 410011, China. Email: feliuling@csu.edu.cn.

Abstract: Takotsubo syndrome (TTS) is characterized by acute and transient dysfunction of the apical segment of the left ventricle. In recent years, there have been increasing numbers of case reports about TTS; however, it is still being neglected and misdiagnosed in many primary hospitals in China. We present a case of a 68-year-old female who presented to our hospital with one month of paroxysmal cough. Here severe cough would sometimes induce headache, chest pain, nausea, and vomiting. She had an unexplained cardiogenic shock approximately 4 months prior and gradually developed orthopnea. Cardiac biomarkers were mildly elevated, and electrocardiogram (ECG) displayed diffuse and deep T-waves inversion in leads I, II, AVL, and V2–V9, like acute myocardial infarction. However, coronary angiography was performed and showed the absence of obstructed coronary atherosclerosis or acute plaque rupture. The patient was successively treated in four hospitals and was eventually diagnosed with TTS in our hospital (the fourth hospital) due to noncardiogenic discomfort. Physicians at some primary hospitals require additional clinical experience to deeply understand TTS. Many doctors could learn about TTS from a medical textbook but remain unfamiliar with the disease. We hope that through analysis of this case, primary doctors will have a deeper understanding of TTS, avoid misdiagnosing the typical cases that occur in their patients.

Keywords: Takotsubo syndrome (TTS); primary hospital; misdiagnosed; case report

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Introduction

Takotsubo syndrome (TTS) is a type of acute and reversible heart failure syndrome (1). It is most frequently triggered by an acute emotional or physical stressor and mimics acute myocardial infarction; however, it is characterized by the absence of obstructive coronary disease (2). TTS was first described in Japan in 1991, and its original name is derived from the typical shape of the left ventricular apex, which mimics a traditional Japanese octopus's trap called a Takotsubo (3). In recent years, there have been increasing numbers of case reports describing TTS. According to the statistical results, TTS is estimated to account for approximately 1–3% of all patients with suspected acute coronary syndrome, and this percentage can increase up to 5–6% if only female patients are considered (4,5). However,

it is still being neglected and misdiagnosed in many primary hospitals in China. In this report, we described a case of TTS that was misdiagnosed in several hospitals for 4 months, and was finally diagnosed in our hospital. This report may promote a better understanding of TTS for primary hospitals and have great implications in clinical practice. We present the following case in accordance with the CARE reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-855/rc>).

Case presentation

A 68-year-old female presented to our hospital with one month of paroxysmal cough without dyspnoea and fever. She was diagnosed with bronchitis at a local hospital. Severe cough sometimes induced headache, chest pain,

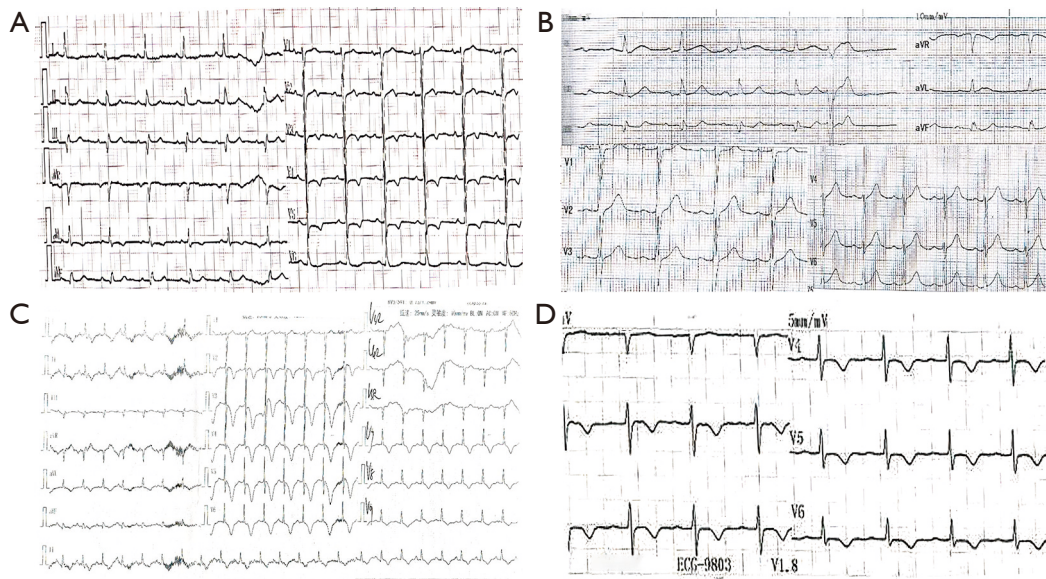


Figure 1 Dynamic ECG changes from the beginning of the onset to 4 months. (A) ECG on 4 months after onset; (B) ECG on the 1st day of onset; (C) ECG on the 3rd day of onset; (D) ECG on the 8th day of onset. ECG, electrocardiogram.

nausea, and vomiting. She had a medical history of cervical spondylosis and underwent an operation five years prior. On admission, the vital signs were stable: temperature 36.5 °C, blood pressure 106/52 mmHg, pulse rate 78 beats/min, and respiration rate 12 breaths/min. Auscultation of the heart revealed a grade 2 systolic murmur in the apex. No other abnormalities were found. The electrocardiogram (ECG) showed sinus tachycardia, shallow T-waves inversion in leads V2–V5, and a Q-wave visible in lead III (Figure 1A). Routine laboratory tests showed N-terminal pro-brain natriuretic peptide (NT-proBNP) level of 339 pg/mL (normal reference range, 0–125 pg/mL), troponin T (cTnT) level of 14.59 pg/mL (normal reference range, 0–14 pg/mL), creatine kinase (CK) level of 92.5 μ L (normal reference range, 50–310 μ L), and creatine kinase-MB (CK-MB) level of 13.8 μ L (normal reference range, 0–24 μ L). Chest radiography was normal. Transthoracic echocardiography (TTE) revealed left atrial enlargement (41 mm), normal left ventricle (48 mm), uneven thickening of the interventricular septum (11–14 mm), slight mitral valve regurgitation, ejection fraction of 59%, and fair coordination of left ventricular wall motion (Figure S1). She was diagnosed with chronic pharyngolaryngitis and quickly recovered well according to consultation with an otolaryngologist. However, her family reported that she had an unexplained cardiogenic shock approximately 4 months prior. By collecting her medical data over the

prior 4 months, she was diagnosed with TTS in our hospital. We recorded the out-of-hospital diagnosis and treatment process as follows.

Four months prior to her presentation, she had sudden dizziness while walking, accompanied by transient amaurosis, slight neck pain, profuse sweating, and fatigue. She rested for several minutes but still felt chest distress, nausea, vomited, and soon lost consciousness, without incontinence or any seizure-like activity. After ten minutes, she regained consciousness and again vomited several times. She was sent to the nearest local hospital (the first hospital) on the first day with blood pressure 88/52 mmHg and an active position. A few wet rales were heard in the bottom of the lungs. The ECG shows sinus rhythm, occasional ventricular premature beats, and Q-waves visible in lead III (Figure 1B). Laboratory evaluation revealed elevated brain NT-proBNP of 426.94 pg/mL (normal reference range, 0–250 pg/mL), CK of 175 μ L (normal reference range, 0–190 μ L), and CK-MB of 34 μ L (normal reference range, 0–24 μ L). She was diagnosed with shock of unknown origin and suspected heatstroke and treated with fluid infusion and the vasopressors dopamine and dobutamine. After treatment, her blood pressure was increased to 90–110/60–70 mmHg; however, she gradually developed orthopnea and was transferred to a municipal hospital (the second hospital) on the third day.

On admission, she presented with pained facial

appearance, blood pressure 120/70 mmHg, heart rate 95 beats/min, and orthopnea. Diffuse inspiratory crackles and expiratory wheezing sounds were heard over both lung fields. Auscultation of the heart revealed a grade 2 systolic murmur in the apex. The ECG showed diffuse and deep T-waves inversion in leads I and II, AVL, V2–V9, and Q-waves visible in lead III (*Figure 1C*). Laboratory evaluation revealed a white blood cell count of $11.2 \times 10^9/L$, of which 75.4% were polymorphonuclear leukocytes, normal levels of CK and CK-MB, TNT 387.4 pg/mL (normal reference range, 0–14 pg/mL), and NT-proBNP 5,646 pg/mL (normal reference range, 0–125 pg/mL). She was diagnosed with acute coronary syndrome and treated with recombinant human BNP, dual anti-platelet therapy with aspirin and clopidogrel, low-molecular-weight heparin sodium (one time) anticoagulation, cholesterol modulation, and anti-ventricular remodelling. Five days later, she no longer felt dyspnoea or chest distress. The ECG revealed that the previously deep T-waves inversion in leads V2–V6 had become shallow (*Figure 1D*). Chest X-ray showed bilateral pulmonary congestion and enlarged heart shadows (*Figure S2*). On the 12th day of onset, she underwent TTE and cardiac catheter examinations. TTE revealed left atrial enlargement (41 mm), normal left ventricle (47 mm), local interventricular septum hypertrophy at the basement (17.8 mm), normal thickness of left ventricle posterior wall (9 mm), left ventricular outflow tract (LVOT) narrow (9.6 mm) with increased blood flow velocity (335 cm/s), slight mitral valve regurgitation, decreased ejection fraction of left ventricle (40%), and poorly coordinated left ventricular wall movement. Coronary angiography showed unsmoothed endothelium in the left anterior descending artery and right coronary artery, supporting atherosclerosis (*Figure 2A,2B*). The conclusion on the left ventriculography report form revealed ‘no’ abnormality (*Figure 2C,2D*). She was then discharged on the 14th day with an uncertain diagnosis: suspected cardiomyopathy, left atrial enlargement, acute left heart failure, and cardiogenic shock.

To make a definite diagnosis, she was recommended to undergo TTE again in an affiliated hospital (the third hospital, a provincial hospital) of a university of traditional Chinese medicine. TTE on the 19th day showed an almost normal size of cardiac chambers (left atrium 35.7 mm, left ventricle 48.2 mm, right atrium 27.6 mm, right ventricle 26.9 mm), mildly thick interventricular septum (11.7 mm), left ventricle posterior wall (11.7 mm), a normal ejection fraction of left ventricle (60%), and left ventricular wall motion that remained uncoordinated. A summary of the timeline was shown in *Figure 3*.

All procedures performed in this study were in

accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

A significant emotional or physical stressor typically precedes the development of TTS (2). For this patient, cervical spondylopathy probably led to cerebral ischaemia and secondary vagal excitation, presenting as sweating, nausea, and repeated vomiting, which caused the excessive loss of body fluid and hypotension, followed by high sympathetic tone and finally the manifestations of TTS presenting as further hypotension and orthopnea.

The most commonly discussed possible mechanism for TTS is stress-induced catecholamine release from sympathetic activation. Endogenous catecholamine is toxic to and subsequently causes stunning of the myocardium, mainly in the apex and sometimes in the midsegment of the left ventricle. As previously stated, TTE can provide a quick method to diagnose the typical wall-motion abnormalities of TTS, specifically hypokinesis or akinesis of the mid and apical segments of the left ventricle, with low ejection fraction (6). Moreover, dynamic LVOT obstruction can be induced by high catecholamine levels in circulation due to the intensive contraction of normal myocardium without stunning in some elderly patients, or in hypertensive females with sigmoid deformity of the intraventricular septum (1). Although this patient denied a previous medical history of hypertension, local hypertrophy of the intraventricular septum was still detected after approximately 4 months. LVOT obstruction detected by TTE when she became stable supported the diagnosis for TTS; however, it was neglected by doctors who were seemingly unaware of TTS and even confused by the result of the second TTE after 8 days.

The diagnosis of TTS may be difficult upon presentation. TTS often masquerades as acute myocardial infarction (7). This patient was treated based on a diagnosis of acute non-ST-elevation myocardial infarction in the second hospital. The ECG revealed diffuse T-wave inversions in most of the leads, while cardiac enzymes were negative, with slightly elevated TNT levels. This indicates an evident disparity between widely dysfunctional myocardium and limited myocardial necrosis, which is a classical clinical performance

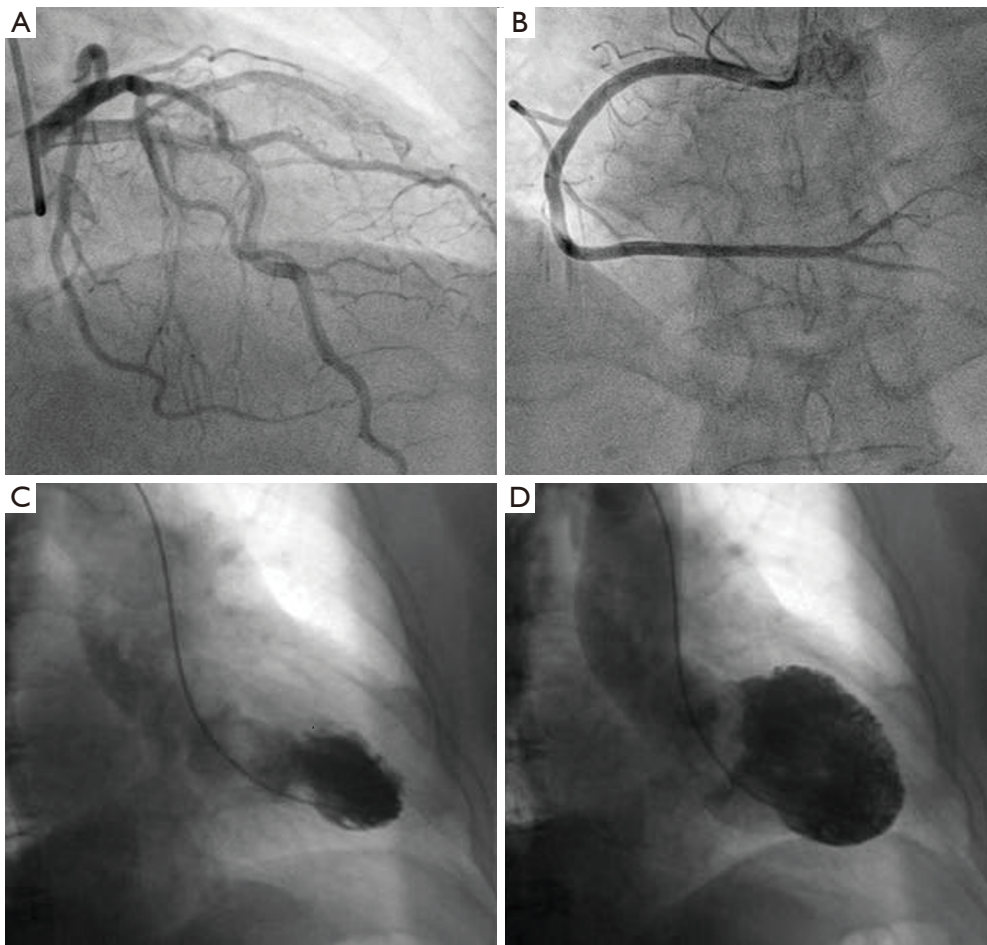


Figure 2 Coronary angiography and left ventriculography on the 12th day of onset. (A,B) Coronary angiography showed unsmoothed endothelium in the left anterior descending artery and right coronary artery, supporting atherosclerosis; (C,D) left ventriculography showed the left ventricular outflow tract obstruction.

of TTS (1). Moreover, this was accompanied by the lack of significant coronary artery stenosis that would explain the extensive involvement of the myocardium, which is another clinical characteristic of TTS (1). Patients with TTS tend to visit the hospital later and miss the opportunity for emergency coronary angiography, and are often misdiagnosed with myocardial infarction, leading to early revascularization with dual antiplatelet therapy and anticoagulant therapy given, increasing the economic burden of patients and the incidence of bleeding events. TTS has many similarities with acute myocardial infarction; however, the prognosis of TTS is relatively better. There are many differences between the treatment and prognosis, so attention should be given to the identification between the two diseases in the diagnosis process to avoid misdiagnosis and delayed treatment.

In most confirmed cases, suspected patients accepted coronary angiography and left ventriculography early on, which is immensely beneficial to confirm diagnosis and give further treatment. Due to limited medical resources, acute coronary angiography and even bedside TTE are not available in several primary hospitals in China. Although apical ballooning has been classically described as the manifestation of TTS by angiography and TTE, it has been shown that left ventricular dysfunction in TTS includes not only classic apical ballooning but also different morphologies, such as mid-ventricular ballooning and, rarely, local ballooning of other segments (8). In this patient, apical ballooning was not as obvious as her LVOT obstruction, which might be associated with the rapid improvement of apical akinesis (9). When the image of left

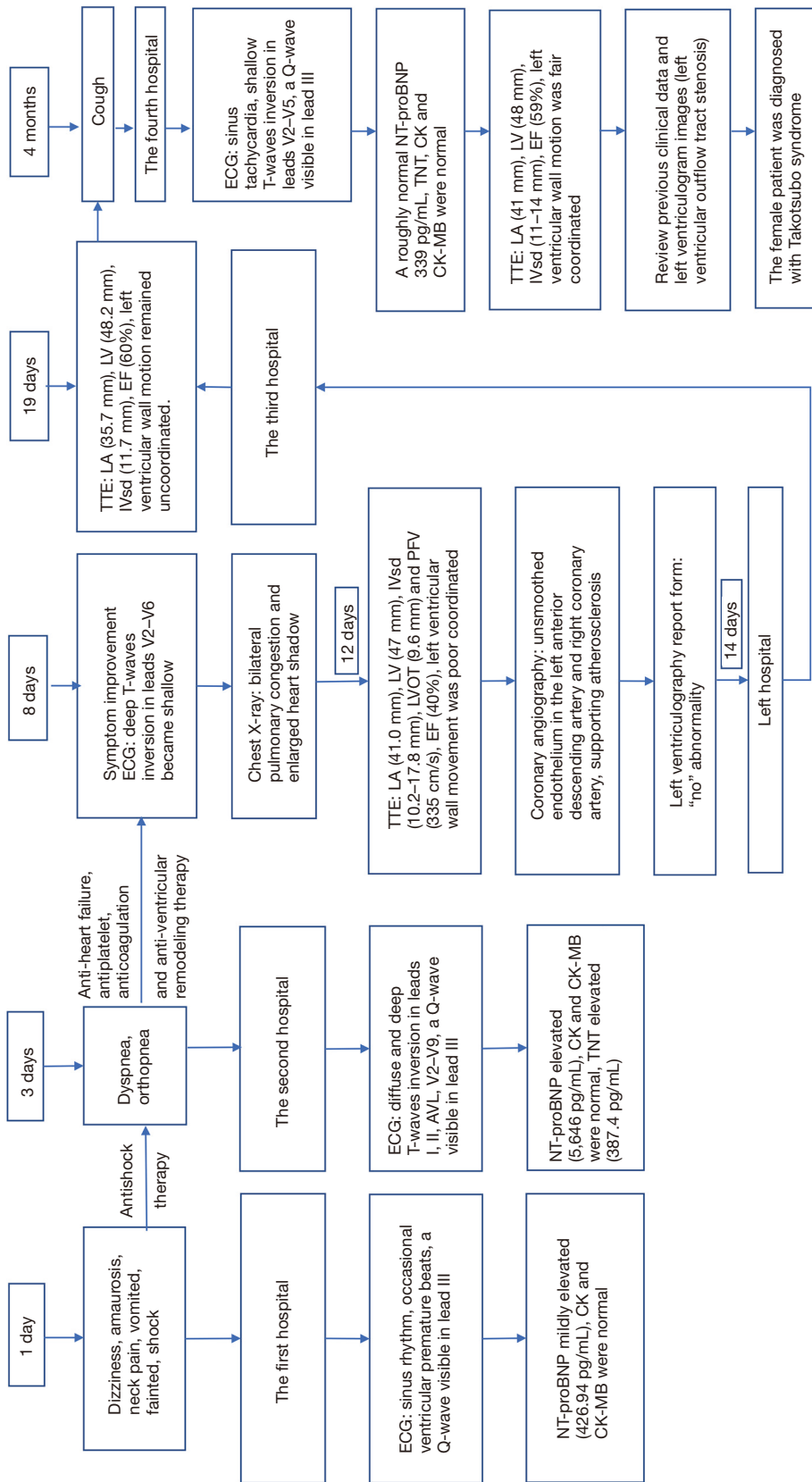


Figure 3 The timeline of the patient's medical historical. ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; CK, creatine kinase; CK-MB, creatine kinase-MB; TTE, transthoracic echocardiography; LA, left atrium; LV, left ventricle; IVsd, interventricular septal thickness at diastole; EF, ejection fraction; LVOT, left ventricular outflow tract; PFV, peak flow velocity of left ventricular outflow tract.

ventriculography was reviewed, it was found that the left ventricular apex did not demonstrate a typical ballooning morphology like other cases, and the distinct coarctation of LVOT was overlooked by previous operators.

Animal evidence showed that TTS was induced in rats exposed to physical stress and, in some instances, was prevented by pretreatment with an alpha-blocker or beta-blocker (10). Considering the catecholamine theory for TTS, a beta-blocker or selective alpha-blocker is recommended to treat patients with haemodynamically significant LVOT obstruction (LVOT pressure gradients >40 mmHg and systolic blood pressure <110 mmHg) by associated ESC guidelines (1,8). However, inotropic agents to manage haemodynamic instability could increase LVOT pressure gradients in some susceptible individuals and lead to deepening of shock and worse outcomes (11). If physicians did not realize the existence of TTS and had no evidence of LVOT obstruction, they would likely not consider the use of beta-blockers. This patient benefitted from fluids and anti-ventricular remodelling treatment, including beta-blockers, in the second hospital.

In conclusion, this case indicates that physicians in some primary hospitals require additional clinical experience to deeply understand TTS. Many doctors could learn about TTS from a medical textbook but remain unfamiliar with the disease. Thus, it would be relatively difficult to diagnose a typical patient with TTS in time. We hope that through analysis of this case, primary doctors will have a deeper understanding of TTS and avoid misdiagnosing the typical cases that occur in their patients.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist Available at <https://apm.amegroups.com/article/view/10.21037/apm-21-855/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-855/coif>).

The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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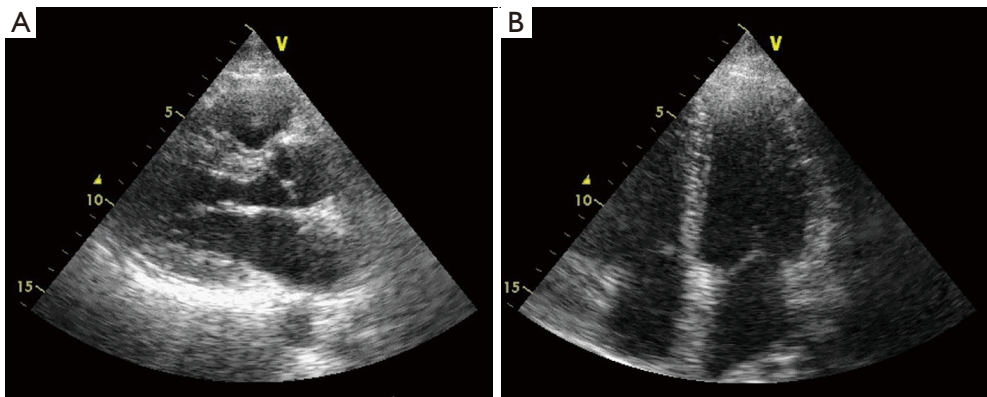


Figure S1 TTE on 4 months after onset. TTE revealed left atrial enlargement (41 mm), normal left ventricle (48 mm), uneven thickening of the interventricular septum (11–14 mm), slight mitral valve regurgitation, ejection fraction of 59%, and fair coordination of left ventricular wall motion. TTE, transthoracic echocardiography.

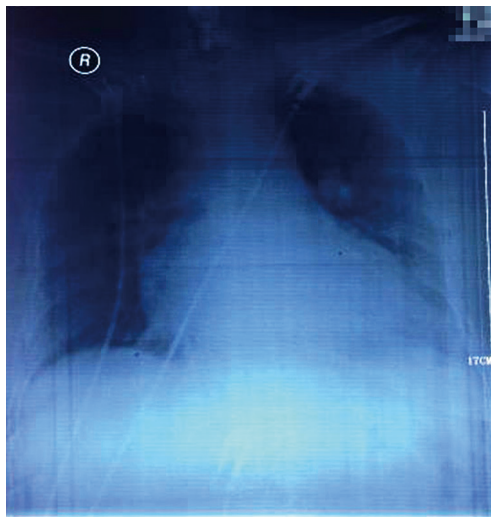


Figure S2 Chest X-ray on the 8th day of onset. A Chest X-ray showed bilateral pulmonary congestion and enlarged heart shadow with the possibility of an enlarged left ventricle.