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CASE REPORT
Cardiovascular imaging

Ultra-early myocardial calcification secondary to fulminant myocarditis with 4 years of follow-up: a case report

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Background Early myocardial calcifications secondary to fulminant myocarditis (FM) are rare, and their natural evolution and effects on cardiac function are poorly understood. Here, we followed the patient for 4 years to observe the development of cardiac calcification and its impact on heart function.

Case summary A 16-year-old man was hospitalized with a fever and cough for 1 day. The patient was previously healthy and had no history of heart disease or specific family conditions. The patient was positive for anti-Epstein–Barr virus IgG and IgM. The computed tomography (CT) scan showed no coronary lesions. Cardiogenic shock and recurrent ventricular fibrillation developed on the third day after admission, and the patient received rescue therapy such as endotracheal intubation, defibrillation, extracorporeal membrane oxygenation, and corticosteroids. On the 13th day of admission, a CT scan revealed significant calcification in the left ventricular wall. The patient was discharged after 30 days in the hospital. After discharge, his left ventricular calcification peaked at 6 months and gradually subsided after that, and his left ventricular function slowly returned to normal at 12 months.

Discussion In younger patients, myocardial calcifications secondary to FM may occur as early as 13 days and affect cardiac function. After proper treatment and rehabilitation, the patient's myocardial calcification can gradually subside and the cardiac function can gradually recover. For FM patients, timely and comprehensive intensive treatment, including heart, lung, and kidney replacement therapy and early administration of hormone preparations, may be beneficial to the early recovery of patients.

Keywords Fulminant myocarditis • Myocardial calcification • Case report

ESC Curriculum 7.3 Critically ill cardiac patient • 6.4 Acute heart failure • 2.4 Cardiac computed tomography • 6.5 Cardiomyopathy • 7.1 Haemodynamic instability

Learning points

- In young patients, myocardial calcification secondary to fulminant myocarditis may occur as early as 13 days and affect cardiac function. The myocardial calcification peaked at approximately the sixth month.
- Fulminant myocarditis patients should take comprehensive and powerful treatment measures as soon as possible, and patients may recover completely.
- Myocardial calcification can be reduced or even disappeared. Vascular ageing and calcification may be halted or even reversed.

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Introduction

Acute myocarditis is caused by many cardiotropic viruses, including enteroviruses, parvovirus B19, human herpesvirus type, adenovirus, cytomegalovirus, Epstein–Barr, hepatitis C, herpes simplex type 2, and influenza and parainfluenza viruses.[1] Fulminant myocarditis (FM), an acute form of myocarditis, is an inflammatory disease of myocardium and is associated with sudden onset and severe haemodynamic disturbance.[2] In severe cases, it may lead to heart failure, cardiogenic shock, and even sudden death.[3] Fulminant myocarditis is a clinical diagnosis rather than a histological or pathological diagnosis.[4] Definite diagnosis of viral myocarditis can only be implemented after finding evidence of active viral infection, using histological or serological identification of the virus.[5] Patients with acute myocarditis may develop chronic myocarditis or dilated cardiomyopathy.[6] However, early myocardial calcification secondary to acute myocarditis is rare, and its natural evolution and impact on cardiac function remains poorly understood.[7] We herein report the early onset of myocardial calcification in a young patient with FM who had no history of underlying heart disease or family history after cardiopulmonary resuscitation (CPR) and extracorporeal membrane oxygenation (ECMO) treatment. We followed up on the patient for 4 years to monitor myocardial calcification and cardiac function evolution, and we observed a gradual decrease in the degree of myocardial calcification over the period. In addition, we observed a gradual improvement in cardiac function.

Case presentation

A 16-year-old male presented to the department of emergency, with fever and cough for 1 day. The patient had no history of heart disease, no history of drug use, no history of specific familial diseases, and no history of drug allergies. At admission, the patient body temperature was 38.0°C, and blood pressure was 100/64 mmHg, heart rate was 110 b.p.m., and breathing rate was 30/min. There was no jaundice in the sclera, wet rales could be heard in the lungs, the heart rhythm was regular, and there was no murmur in the precordial area. In addition, there was no tenderness in the abdomen, no liver or spleen edge was palpable, no palmar erythema, and no telangiectasia. Skin examination showed no rash. During hospitalization, the patient coughed pink foamy sputum and could not lie on his back. Blood tests revealed that the creatine kinase (CK) level was 1089 U/L (reference value 30–135 U/L), and the CK-myocardial band (MB) level was 127 U/L (reference value 0.0–16.0 U/L). Cardiogenic shock and recurrent ventricular fibrillation occurred on the third day of admission. Endotracheal intubation (total time 188 h), 150 J or 200 J bidirectional asynchronous defibrillation (27 defibrillations in total), and then venoarterial (VA) ECMO combined with intra-aortic balloon pump (IABP), continuous renal replacement therapy (CRRT), and corresponding drugs were administered to the patients. The patient's condition gradually improved and the vital signs were stable. Extracorporeal membrane oxygenation and IABP treatments were withdrawn after 5 days, and CRRT

Timeline

Timeline	Symptoms and treatment	Left ventricular ejection fraction (LVEF, echocardiography)	Left ventricular calcification [computed tomography (CT) scan]	Right ventricular calcification (CT scan)
1 day	Fever and cough for one day	44%	No ventricular calcification	No ventricular calcification
13 days	Cardiogenic shock lasted for 3 days. Patient was given endotracheal intubation, defibrillation, and ECMO and related drugs. The vital signs were stable.	38%	Marked calcification of the left ventricular inner wall and papillary muscle	No ventricular calcification
1 month	The patient was discharged after 30 days. 47.5 mg of betaloc sustained-release tablets once a day	42%	Myocardial calcification increased	No ventricular calcification
3 months	The patient was in stable condition and continued to take 47.5 mg of betaloc sustained-release tablets once a day	43%	Myocardial calcification increased again	Slight calcification in the right ventricular septum and free wall
6 months	The patient was in stable condition and continued to take 47.5 mg of betaloc sustained-release tablets once a day	45%	Myocardial calcification reached the peak	and calcification in the right ventricle decreased
12 months	The patient was in stable condition and continued to take 47.5 mg of betaloc sustained-release tablets once a day	67%	Myocardial calcification was stable	Might ventricular calcification resolved
24 months	Overall good condition, continued to take 47.5 mg of betaloc sustained-release tablets once a day	61%	Myocardial calcification subsided	No ventricular calcification
36 months	Overall good condition, continued to take oral 47.5 mg of betaloc sustained-release tablets once a day	66%	Only residual left ventricular muscle calcification was observed	No ventricular calcification
48 months	Overall good condition, continued to take 47.5 mg of betaloc sustained-release tablets once a day	64%	Only stable residual left ventricular muscle calcification was observed	No ventricular calcification

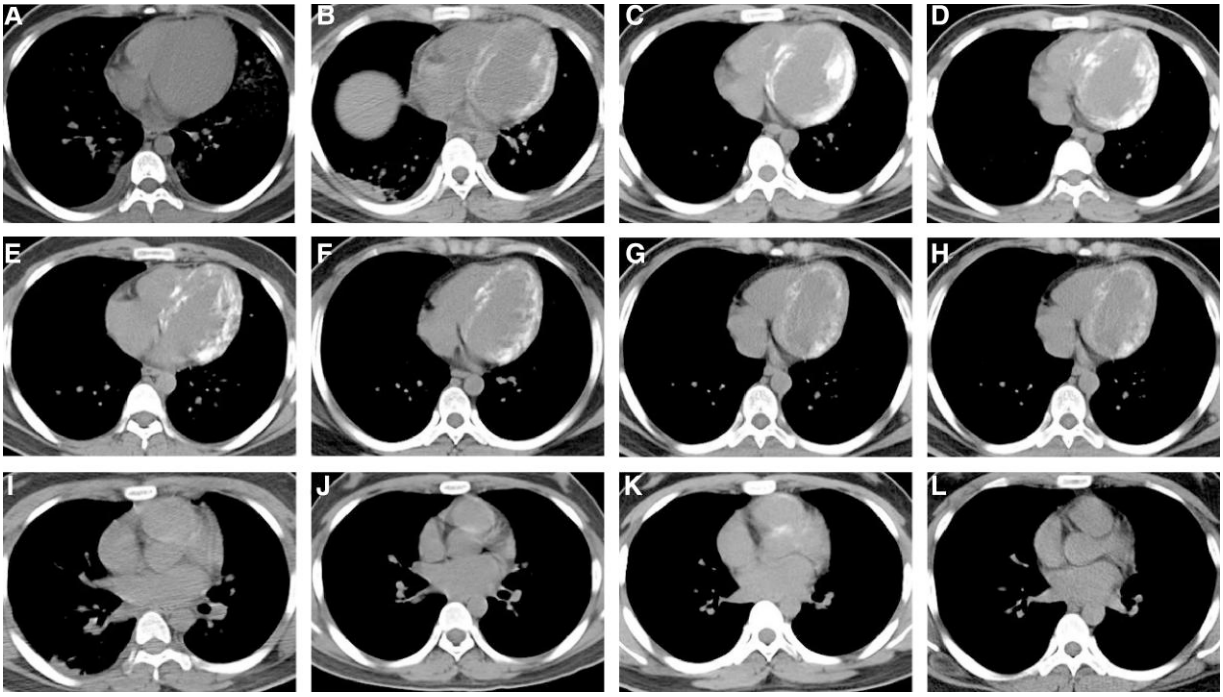

Figure 1 A series of computed tomography scans of this patient showing the evolution of myocardial calcification. (*A*) The patient did not have any signs of myocardial calcification on computed tomography scan at admission. (*B*) Annular dense shadow appeared on the inner wall of left ventricle and papillary muscle of left ventricle on the 13th day of admission. (*C*)–(*H*) showed the changes of myocardial calcification (at third, sixth,12th, 24th, 36th, and 48th month). (*I*) showed on the 13th day of admission, no myocardial calcification was seen in the right ventricle. (*J*)–(*L*) showed slight calcification in the right ventricular septum and free wall (third month), and calcification in the right ventricle decreased (sixth month), and right ventricular calcification resolved (12th month).

was retained until 7 days. During hospitalization, the patient received glucocorticoids (methylprednisolone 200 mg daily for 3 days, then changed to 80 mg daily for 3 days, and then 40 mg daily for 7 days) and immunoglobulin 10 g daily for 10 days. The patient took orally 12.5 mg of betaloc twice a day during hospitalization and 47.5 mg of betaloc sustained-release tablets once a day after discharge.

Laboratory tests demonstrated extremely high inflammation and abnormal cardiac biomarkers: CK was 12 000U/L, was CK-MB 2880 U/L, blood lactate was 2.60 mmol/L (reference value 0.50–1.60 mmol/L), and blood procalcitonin was 36.48 ng/mL (reference value <0.50 ng/mL). FT3 was 4.93 pmol/L (reference value 3.39–6.47 pmol/L), FT4 was 13.80 pmol/L (reference value 10.29–21.88 pmol/L), parathyroid hormone (PTH) was 4.78 pmol/L (reference value 1–10 pmol/L), troponin I was 4.01 ng/mL (reference value <0.30 ng/mL), blood–brain natriuretic peptide (BNP) increased (5022 pg/mL, reference value 0–300 pg/mL), and anti-Epstein–Barr virus antibodies IgG and IgM were positive. There was no bacterial growth in the blood culture. On Day 7, the C-reactive protein level was significantly reduced (from 36.0 to 5.09 mg/L). Thoracic CT plain scan showed pleural infection and pleural effusion, and coronary CT scan showed no coronary lesions. An electrocardiogram (ECG) showed an ST-elevation at I and augmented vector left (AVL) lead and an ST-depression at II, III, and augmented vector foot (AVF) lead. Echocardiography [ultrasonic cardiogram (UCG)] showed decreased left ventricular wall motion, significantly reduced left ventricular systolic function with LVEF 38%. Based on all the data, the clinical diagnosis was FM. After 30 days of hospitalization, the patient's general condition and cardiopulmonary function gradually improved, and he was discharged. Cardiac MRI showed left ventricular high signal shadow indicating cardiac fibrotic changes and myocardial oedema on the 37 days.

With regular outpatient follow-up, serial chest CT was performed to observe the evolution of myocardial calcification in the patient (see *Figure 1*): No myocardial calcification was observed in the left ventricle on the first day of admission (*Figure 1A*). On the 13th day, the left ventricular wall and left ventricular papillary muscle showed dense annular shadow, suggesting myocardial calcification (*Figure 1B*). There was increased calcification in the left ventricular lateral wall and apex around the 3 months (*Figure 1C*). At approximately 6 months, the calcification had spread to the entire left ventricular wall and papillary muscles, as well as parts of the right ventricle, aorta, and pericardium (*Figure 1D*). Left ventricular calcification peaked at approximately 6 months (*Figure 1E*). At the 24- and 36-month follow-up, the left ventricular calcification further subsided (*Figure 1F and G*). At the 48-month follow-up, the left ventricular myocardial calcification had significantly diminished (*Figure 1H*). As described above, myocardial calcification was observed on the left ventricular wall on the 13th day of admission but was not seen in the right ventricle (*Figure 1I*). At the third month, there was slight calcification in the right ventricular septum and free wall (*Figure 1J*); at 6-month follow-up, the calcification in the right ventricle decreased (*Figure 1K*); and at 12-month follow-up, right ventricular calcification resolved (*Figure 1L*).

Subsequently, at the 3-month follow-up, UCG demonstrated myocardial motion distortion and calcification of both the anterior and posterior leaflets of the mitral valve, accompanied by a decline in left ventricular systolic function, and LVEF was 43%. At 6-month follow-up, UCG showed enhanced left ventricular wall echo and uncoordinated apex movement, and LVEF was 45%. Similarly, at 12-month follow-up, UCG showed enhanced left ventricular wall echo, left ventricular systolic function was normal, LVEF was 67%, the ventricular cavity size was standard, and the ventricular wall activity was not different.

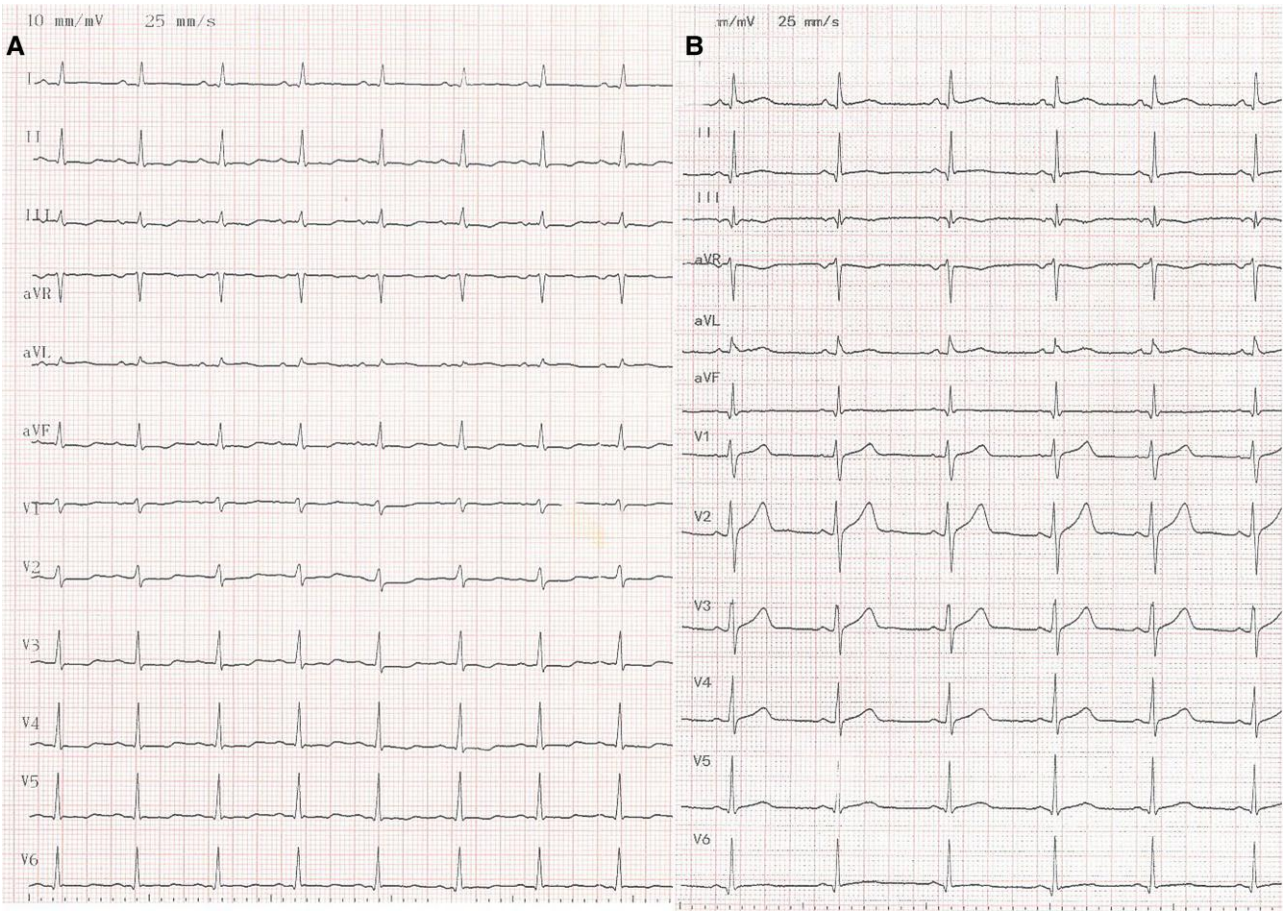

Figure 2 Electrocardiogram changes of the patient. (*A*) The patient's electrocardiogram showed sinus tachycardia, ST changes at admission. (*B*) At the 12th month of follow-up, electrocardiogram showed sinus rhythm, short PR interval, and partial ST segment changes.

Finally, at 24-, 36-, and 48-month follow-ups, UCG showed that myocardial echo enhancement gradually subsided, and cardiac function returned to the normal range (LVEF more than 60%). During the follow-up in the 12th month, ECG showed sinus rhythm, short PR interval, and partial ST segment changes (*Figure 2B*).

Discussion and conclusion

Based on the patient's age, incidence, clinical pictures and laboratory, and imaging examination, we believed that the clinical diagnosis of 'FM' can be established. Endomyocardial biopsy (EMB) can show pathological changes in the myocardium and confirm the diagnosis.[8] Endomyocardial biopsy used to be required to define myocarditis according to the Dallas criteria.[9,10] Giant cell myocarditis (GCM), as we know, is a rare, often rapidly progressive, and frequently fatal disease. The diagnosis of this patient does require consideration of GCM. Unfortunately, due to several factors, we could not perform EMB on this patient.

In recent years, in addition to the standard clinical measures, treating acute severe myocarditis is a comprehensive step on life support. In this case, we applied equipment that we thought was appropriate and available, including a temporary cardiac pacemaker (heart rhythm support), tracheal intubation, IABP, ECMO (breathing and circulatory support), blood purification, inflammatory factor adsorption (renal clearance), and immunomodulatory therapy and corticosteroid. At present, ECMO is gradually popularized in rescuing clinically critical patients. Moreover, treatments such as immunomodulatory therapies, including immunosuppression with corticosteroids, intravenous immunoglobulin (IVIG), azathioprine, and corticosteroid, have also been tried with some success.[11]

Although acute diffuse myocardial calcification in young adults has been reported clinically, it is rare.[12,13] As early as 1949, Gore *et al.*[14] proposed that myocardial calcification can be divided into metastatic and dystrophic calcifications. Metastatic calcification is often the result of systemic hypercalcemia and/or abnormal calcium homoeostasis and can occur in normal or diseased tissue. Clinically, it is more common in end-stage renal disease, hypercalcaemia, PTH, and poisoning, and the process is slow and usually takes several years.[15] Dystrophic calcification mainly occurs in damaged tissues, suggesting local tissue damage and cell necrosis. Generally, it progresses rapidly, without systemic calcium metabolism disorders, and the serum calcium level is usually average.[16] The mechanism of the rapid and extensive myocardial calcification following acute myocarditis in our patient is unclear. Such rapid myocardial calcifications have been reported in patients with acute respiratory distress syndrome and patients treated with ECMO, patients with sepsis, patients with viral myocarditis, and patients with long-term use of catecholamines.[17,18] We tend to think that this patient may be classified as having malnourished myocardial calcification. The related inducing promoting factors include

myocardial infection; multiple defibrillations; acute respiratory distress syndrome; impairment of the heart, liver, and kidney; hyperlactatemia; and application of ECMO.[12] As for which one or two factors are more important and have greater weight, there is no sufficient evidence, and it is not easy to conclude.

Confusing and thought-provoking, this patient had evidence of myocardial calcification on a chest CT scan as early as the 13th day. This was an early onset of myocardial calcification on the left ventricle after myocarditis. The myocardial calcification peaked at approximately the sixth month; myocardial calcification gradually weakened and subsided over time. Residual calcification was seen in the fourth year. Furthermore, the patient's cardiac function also gradually stabilized and recovered as the myocardial calcification decreased 6 months after the onset suggesting that the diffuse myocardial calcification of this patient significantly affected the left cardiac function. We did not observe evidence of significant changes in left diastolic function, and there was no sign or evidence of RV dysfunction during multiple echocardiographic examinations throughout treatment and follow-up. This case also suggests that the myocardial calcification secondary to infection may subside, and the affected cardiac function may recover. This case suggests that myocardial calcification can be reduced or even disappeared. Arterial aging is considered an unstoppable process, and vascular calcification is also considered a sign of plaque stabilization.[19] This long-term follow-up case may give us more thoughts that vascular calcification can also be stopped or even reversed in the future.

Lead author biography

Bingyin Wang, MD, PhD., received his MD from Zhejiang University in 1983 and his PhD from Peking University in 1989, Postdoctoral Research Fellow, 1993.1-96.10: the Division of Cardiovascular Medicine, Cardiovascular Research Center, Stanford University School of Medicine, Stanford, CA, USA. With more than 30 years of clinical work experience, he has published more than 100 academic papers.

Consent: The authors confirm that necessary consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE and HIPPA guidance.

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Data availability

The authors confirm that the data, ECG and all imaging data published in this case report are true and correct and have been obtained with the written consent of the patient and his/her family. When needed, we can provide it at any time.

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