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【 CASE REPORT 】

Massive Biventricular Myocardial Calcification in a Patient with Fulminant Myocarditis Requiring Ventricular Assist Device Support

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Abstract:
The natural course of myocardial calcification is unclear. We herein report a case of massive biventricular myocardial calcification associated with fulminant myocarditis and present its natural course. The patient was a 15-year-old boy. Massive calcification was detected in both ventricles on computed tomography several months after left ventricular assist device placement. Although the calcification gradually regressed, the patient's cardiac function did not recover, and he underwent heart transplantation after a waiting period of 3 years. A histological examination revealed severe fibrosis in both ventricles of the original heart. Myocardial calcification might suggest severe myocardial inflammation and injury in cases of fulminant myocarditis.

Key words: myocardial calcification, myocarditis, heart transplantation

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Introduction

Myocardial calcification caused by fulminant myocarditis has been previously reported, especially in pediatric patients (1). However, the natural course of myocardial calcification has not been fully elucidated thus far. We herein report a case of massive biventricular myocardial calcification associated with fulminant myocarditis. Due to severe myocardial damage, the patient required biventricular assist device (BiVAD) support, followed by implantable left ventricular assist device (LVAD) support as a bridge to transplantation (BTT). Thus, we performed serial follow-up of myocardial calcification for 3 years and a detailed pathological evaluation of the entire heart after heart transplantation. We herein present the natural course of myocardial calcification.

Case Report

A 15-year-old previously healthy boy, who had flu-like symptoms for 4 days, was referred to our institution due to deteriorating hemodynamic conditions. On admission, electrocardiography revealed complete atrioventricular block with an elevated ST segment on all leads. Furthermore, the biventricular contractility was severely reduced [left ventricular ejection fraction (LVEF), 18%]; this was accompanied by a thickened left ventricular wall (inter-ventricular septal thickness, 14 mm; left ventricular posterior wall thickness, 15 mm). Moderate pericardial effusion was detected on echocardiography. Lymphocytic fulminant myocarditis was diagnosed based on the pathological examination of myocardial biopsy specimens. Elevated cardiac enzyme levels [peak creatine kinase (CK), 7,819 U/L; CK-

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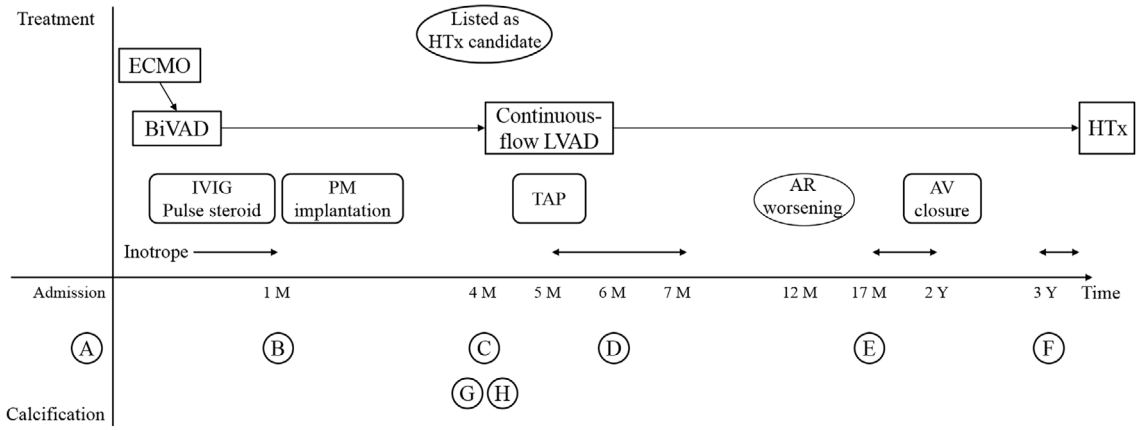

Figure 1. **The relationship between the time course of treatment and myocardial calcification. Circles A-H indicate the timing of myocardial calcification in Fig. 2. AR: aortic regurgitation, AV: aortic valve, BiVAD: biventricular assist device, ECMO: percutaneous veno-arterial extracorporeal membrane oxygenation, HTx: heart transplantation, IVIG: intravenous injection of immunoglobulin, LVAD: left ventricular assist device, M: month, PM: pacemaker, TAP: tricuspid annuloplasty, Y: year**

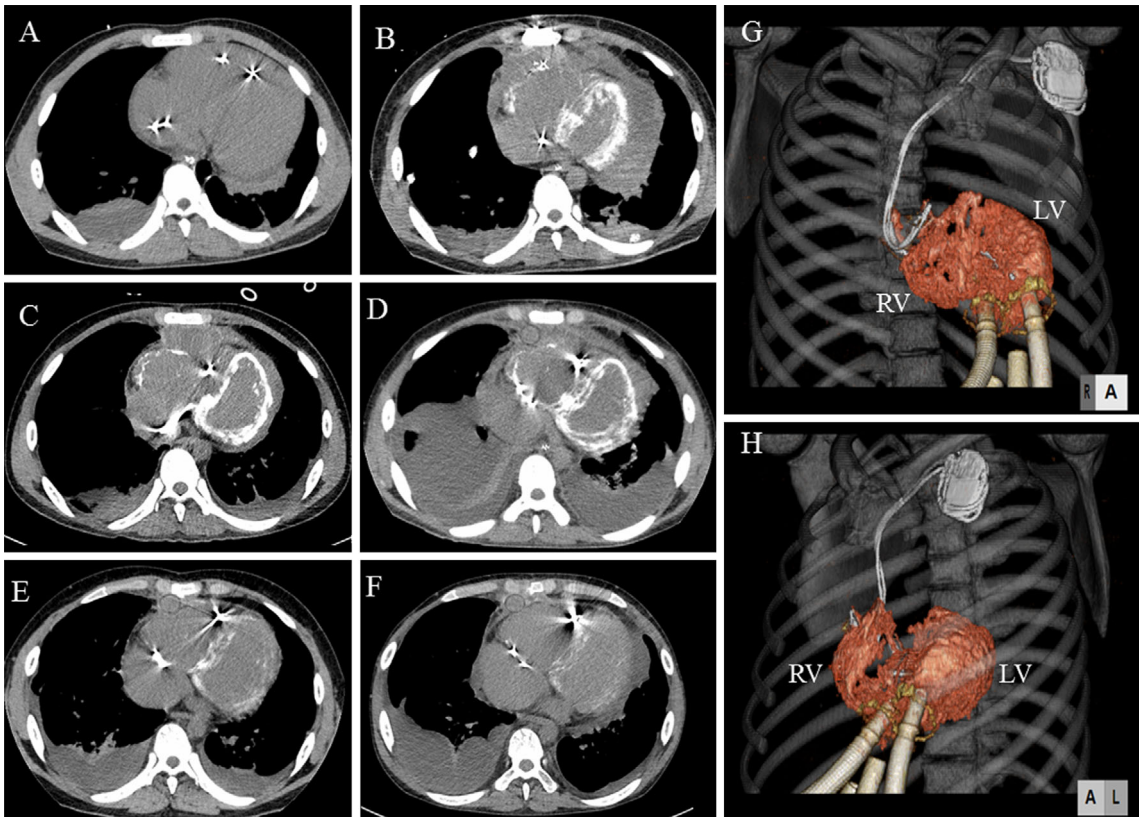

Figure 2. **(A-F) The time course of myocardial calcification on chest computed tomography (CT) at admission (A) and 1 month (B), 4 months (C), 6 months (D), 17 months (E), and 3 years after admission (F). (G, H) Myocardial calcification in both ventricles on three-dimensional reconstructed CT at 4 months after admission (G: right anterior oblique, H: left anterior oblique).**

MB, 704 U/L; and troponin-T, 54.2 ng/mL] were noted, indicating severe myocardial damage. Both intra-aortic balloon pumping and percutaneous veno-arterial extracorporeal membrane oxygenation (ECMO) were performed. However, his cardiac hemodynamic conditions did not improve (mean pulmonary artery pressure, 20 mmHg; mean right atrial pressure, 23 mmHg; and cardiac index, 2.1 L/min/m^2), and his multi-organ failure progressed [aspartate aminotransferase (AST) level, 11,114 U/L; alanine aminotransferase (ALT) level, 5,727 U/L; total bilirubin (T-Bil) level, 1.0 mg/

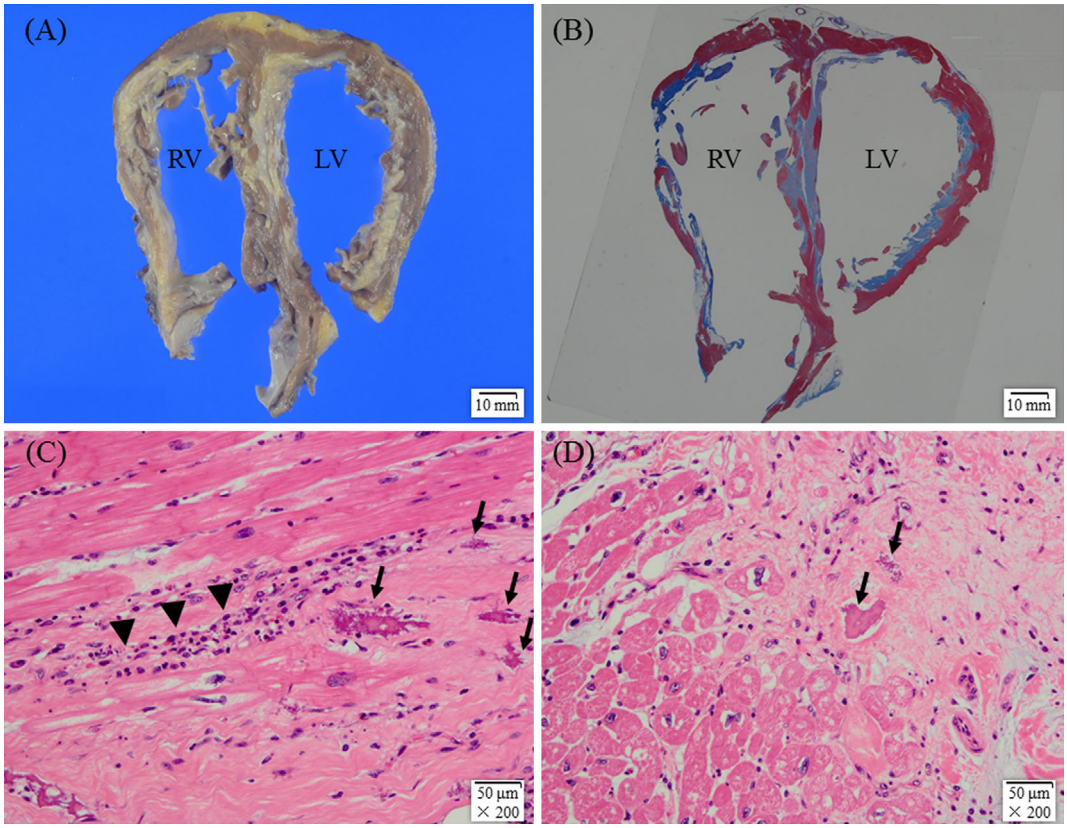

Figure 3. **(A) The gross examination of a transverse section (mid-ventricular level) of the explanted heart. Both ventricles appear enlarged. (B) The endocardium shows thickening with remarkable fibrosis on Masson-trichrome staining. (C, D) Microscopically, the cardiomyocytes in both ventricles disappear and are replaced by severe fibrotic tissue on hematoxylin-eosin staining. The residual myocardium shows disarrangement with a perinuclear halo and vacuolation. Inflammatory cells partially infiltrate the perivascular lesion (arrowhead), and some calcification is noted in the cardiac interstitial tissue (arrow) (C: right ventricle, D: left ventricle).**

dL; and creatinine (Cr) level, 2.37 mg/dL]. Thus, ECMO was changed to para-corporeal BiVAD support to obtain better circulatory support. His renal and liver functions improved within 2 months (AST level, 45 U/L; ALT level, 36 U/L; T-Bil level, 0.9 mg/dL; and Cr level, 0.88 mg/dL). However, despite aggressive immunomodulation treatment with the intravenous injection of immunoglobulin, pulse steroid therapy, and mechanical unloading, his cardiac function had not recovered at 4 months after the onset of myocarditis. In addition to left ventricular dysfunction (LVEF, 10%), his right heart function was severely reduced (right ventricular stroke work index, 0.92 g/m/beat/m^2) with mild-to-moderate tricuspid regurgitation. Thus, he was listed as a candidate for heart transplantation, and an implantable continuous-flow LVAD (DuraHeart®) was placed as a BTT, along with tricuspid annuloplasty. During LVAD support, he experienced right heart failure requiring the administration of inotrope and underwent aortic valve closure to treat aortic regurgitation. However, he continued to experience bilateral heart failure requiring prolonged hospitalization. He successfully underwent heart transplantation after a waiting period of 3 years, and he was discharged 2 months after heart transplantation (Fig. 1).

The natural course of myocardial calcification

With respect to the properties of the myocardium, massive calcification was detected in both ventricles on computed tomography (CT) 1 month after the development of myocarditis, which was not observed on admission (Fig. 2A and B). Myocardial calcification became obvious 4 months after admission (Fig. 2C). The calcification was diffuse in both ventricles on three-dimensional reconstructed CT (Fig. 2G and H). It subsequently regressed at 6 months after admission (Fig. 2D). Furthermore, the right ventricular calcification was found to have almost disappeared at 17 months after admission (Fig. 2E), and the left ventricular calcification had almost completely regressed at 3 years after admission (Fig. 2F).

The pathological findings of the explanted heart

On gross examination of the explanted heart, both ventricles were enlarged and weighed 347 g (Fig. 3A). Both ventricles showed remarkable endocardial fibrotic thickening and left ventricular septal wall calcification focally on Masson-trichrome staining (Fig. 3B). Microscopically, the biventricular myocardium was replaced by severe fibrotic

tissue with lymphocytic infiltration and calcification on hematoxylin-eosin staining (Fig. 3C and D).

Discussion

Myocardial calcification involves two different mechanisms, namely metastatic and dystrophic calcification (2, 3). Metastatic calcification results from impaired calcium metabolism and elevated serum calcium levels associated with chronic renal failure and hyperparathyroidism (2). Dystrophic calcification results from severe myocardial damage with cellular necrosis caused by myocardial infarction, myocardial fibrosis, infection, sarcoidosis, hemorrhage, or myocarditis (2-4). Calcium accumulates in the injured myocardium during the healing process (3).

In previous articles, myocardial calcification occurred a few months after the onset of acute myocarditis and showed regression 6 months later (4, 5). However, the prolonged natural course of myocardial calcification has not been fully elucidated because of the poor outcomes of these patients. In our case, the patient's right ventricular calcification, which was less developed than the left ventricular calcification, decreased first. Thereafter, the left ventricular calcification almost completely disappeared on chest CT over a period of 3 years. This finding suggests that massive myocardial calcification can completely regress within several years.

Myocardial calcification can cause focal wall motion abnormalities, diastolic dysfunction, arrhythmia, and congestive heart failure (3, 6, 7). Additionally, myocardial calcification with pediatric myocarditis has been reported to be a predictor of poor outcomes (8). In our case, the patient's cardiac function did not recover after the regression of calcification, and right heart failure was noted after LVAD placement. This is because prolonged subclinical inflammation was present in both ventricles and the healthy cardiac myocytes were almost completely replaced by fibrotic tissue with some histological calcification. Myocardial calcification might suggest severe myocardial inflammation and injury during the acute phase of myocarditis. Additionally, the regression of myocardial calcification might not indicate a good prognosis, such as recovery of the cardiac function.

In conclusion, we clearly presented the time course of myocardial calcification in both ventricles that occurred in association with fulminant myocarditis. Myocardial calcification can occur several months after myocardial damage, and will gradually regress over several years independently of treatment. The cardiac function might not recover after the regression of myocardial calcification in both ventricles, as the myocytes are replaced by severe fibrotic tissue. Myocardial calcification might suggest severe myocardial inflammation and injury in cases of fulminant myocarditis.

The authors state that they have no Conflict of Interest (COI).

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References

1. Benettoni A, Berton E. Echocardiographic detection of early myocardial calcification in acute neonatal myocarditis due to Coxsackie virus type B. Pediatr Cardiol **32**: 1068-1069, 2011.
2. Lin A, Greaves S, Kingston N, Milne D, Ruygrok P. Myocardial calcification after orthotopic heart transplantation. J Heart Lung Transplant **33**: 219-221, 2014.
3. Ananthakrishna R, Moorthy N. Dystrophic myocardial calcification. Indian Heart J **68**: S180-S181, 2016.
4. Díez-Delhoyo F, Zatarain-Nicolás E, Pérez-David E, Sánchez-Alegre ML, Fernández-Avilés F. Extensive myocardial calcification after acute myocarditis. Eur Heart J Cardiovasc Imaging **16**: 690, 2015.
5. Wada A, Nakata T, Tsuchihashi K, et al. Massive myocardial calcification of right and left ventricles following acute myocarditis complicated with rhabdomyolysis-induced acute renal failure. Jpn Circ J **57**: 567-572, 1993.
6. Ito S, Endo A, Okada T, et al. Myocardial calcification with a latent risk of congestive heart failure in a patient with apical hypertrophic cardiomyopathy. Intern Med **54**: 1627-1631, 2015.
7. El-Bialy A, Shenoda M, Saleh J, Tilkian A. Myocardial calcification as a rare cause of congestive heart failure: a case report. J Cardiovasc Pharmacol Ther **10**: 137-143, 2005.
8. Stallion A, Rafferty JF, Warner BW, Ziegler MM, Ryckman FC. Myocardial calcification: a predictor of poor outcome for myocarditis treated with extracorporeal life support. J Pediatr Surg **29**: 492-494, 1994.