**Fulminant Myocarditis With Prolonged Active Lymphocytic Infiltration After Hemodynamic Recovery**

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**Summary**

Fulminant myocarditis is a highly mortal syndrome. Meanwhile, the clinical course of fulminant myocarditis in surviving patients is generally self-limiting. This is a rare case of fulminant myocarditis with prolonged lymphocytic infiltration after hemodynamic recovery. A 64-year-old man was diagnosed with fulminant myocarditis and required intensive care with veno-arterial extracorporeal membrane oxygenation. Left ventricular function gradually improved but complete atrioventricular block (CAVB) persisted. Follow-up endomyocardial biopsies (EMBs) showed prolonged active infiltration of lymphocytes along with $^{18}$F-FDG uptake in $^{18}$F-FDG PET/CT until about 70 days after the onset. Therefore, he underwent immunosuppressive therapy for 3 months. Follow-up EMB revealed no evidence of infiltration of lymphocytes and no abnormal $^{18}$F-FDG uptake despite irreversible CAVB. Although repeated EMB and $^{18}$F-FDG PET/CT was not a standard strategy, it played an important role in the treatment decision in the present case. (Int Heart J 2017; 58: 294-297)

**Key words:** Chronic myocarditis, Endomyocardial biopsy, $^{18}$F-FDG PET/CT

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Fulminant myocarditis is a highly mortal syndrome characterized by clinical manifestations with signs of acute heart failure, cardiogenic shock, or life-threatening rhythm disturbances in the context of acute myocarditis. Meanwhile, the clinical course of fulminant myocarditis in surviving patients is self-limiting and the long-term prognosis is favorable. Therefore, there are few individual case reports of fulminant myocarditis with prolonged lymphocytic infiltration after hemodynamic recovery.

**Case Report**

A 64-year-old man complained of chest discomfort and low-grade fever for two days, and was admitted to a domestic hospital with suspected acute myocarditis. A 12-lead electrocardiogram showed complete atrioventricular block (CAVB) with ST elevation in the inferior leads, and echocardiography showed reduced left ventricular ejection fraction (LVEF) with LV dilation. Serum creatine kinase was elevated to 512 IU/L, and qualitative troponin-T test was positive. Emergent coronary angiography revealed no significant lesions in the coronary arteries. He was diagnosed with acute heart failure caused by non-ischemic heart disease, and continuous infusion of carperitide and dobutamine was started. On the next day, he suddenly developed ventricular fibrillation and was immediately defibrillated. He was then transferred to our hospital after insertion of a temporary transvenous pacemaker (day 1). On arrival, he collapsed into a cardiogenic shock-state so veno-arterial extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pumping (IABP) were immediately started (Figure 1A). An endomyocardial biopsy (EMB) from the right ventricular septum was performed, and the biopsy specimens showed massive lymphocytic infiltration associated with myocytolysis without obvious myocardial fibrosis (Figure 1B and C). Strong immunostaining for tenascin-C, a marker of active inflammation, was seen around cardiomyocytes (Figure 1D). His troponin-I level was 31.3 ng/mL. The serum viral titers were not increased. The LVEF worsened, falling to 15% on day 3, but his cardiac function gradually recovered and he was successfully weaned off the ECMO and IABP on days 7 and 9, respectively, despite persistent CAVB with junctional escape rhythm. The temporary pacemaker lead was removed because of pacing failure on day 8 with his intrinsic heart rate of 70 bpm, and then he suddenly developed ventricular fibrillation with successful resuscitation on day 14. A temporary pacemaker was immediately re-inserted and a second EMB was performed. The specimens still showed abundant lymphocyte infiltration and myocytolysis. Life-threatening arrhythmias did not occur subsequently, and the LVEF gradually improved. A permanent pacemaker was implanted on day 36 for sustained CAVB. The follow-up EMBs were performed on days 48 and 69, and which still showed active inflammation with involvement of predominantly CD8(+) T-cells and CD68(+) macro-
Figure 1. Clinical course (A) and series of endomyocardial biopsy (EMB) specimens (B-D, E-G and I-K) and 18F-fluoro-2-deoxyglucose (18F-FDG) PET/CT images (H and L). The EMB specimen on day 1 shows severe inflammatory cell infiltration associated with myocytolysis and interstitial edema (B), no collagen fiber depositions (C), and strong immunostaining for tenascin-C around cardiomyocytes (D). The EMB specimen on day 69 shows marked infiltration of inflammatory cells and active tissue destruction (E), increased myocardial fibrosis (F), and extensive staining for tenascin-C in newly formed fibrotic lesion as well as around cardiomyocytes (G). 18F-FDG PET/CT image on day 60 shows increased 18F-FDG uptake in the inferior wall of the left ventricle (H-a: coronal view; H-b: short axis view). The EMB specimen on day 239 shows few inflammatory cells (I) and mature replacement fibrosis (J) with only patchy deposition of tenascin-C at the periphery of fibrotic lesions (K). 18F-FDG PET/CT image on day 281 shows no 18F-FDG uptake (L-a: coronal view; L-b: short axis view). BNP indicates brain natriuretic peptide; CRP, c-reactive protein; CK, creatine kinase; LVEF, left ventricular ejection fraction; Vf, ventricular fibrillation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; HE, hematoxylin-eosin; Sirius Red, picrosirius red staining; and Tenascin-C, immunostaining for tenascin-C. Scale bar, 50 μm.
phages (Figure 1E-G and 2) whereas only modest infiltration of CD4(+) T-cells and a few CD20(+) B-cells were observed. $^{18}$F-fluoro-2-deoxyglucose ($^{18}$F-FDG) positron emission tomography/computed tomography (PET/CT) on day 60 showed an increased $^{18}$F-FDG uptake in the inferior LV wall (Figure 1H a-b) while the troponin-T level was only slightly elevated (day 56: 0.023 ng/mL). At the same time, anti-myocardial antibody testing was positive. In accordance with the statement of European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases, oral administration of prednisolone was started at an initial dose of 0.5 mg/kg once daily on day 106 after ruling out active viral infection by multivirus real-time polymerase chain reaction (PCR) using the specimen obtained from the fourth EMB (day 69). Prednisolone was gradually reduced and then withdrawn 3 months after initiation. Follow-up EMB (Figure 1I-K) and $^{18}$F-FDG PET/CT (Figure 1L a-b) revealed no evidence of infiltration of lymphocytes in the specimen and no abnormal $^{18}$F-FDG uptake. His troponin-T levels returned to normal values (days 134 and 239: 0.010 and 0.005 ng/mL, respectively) and the LVEF improved to almost the normal range (Figure 1A), but CAVB was irreversible. Because of LV wall motion dyssynchrony due to right ventricular pacing, adequate head-to-head comparisons of LV regional abnormalities between echocardiography and $^{18}$F-FDG PET/CT were not possible during the clinical course.

**Figure 2.** Profile of inflammatory cells. Predominantly CD8(+) T-cells and CD68(+) macrophages were found in the EMB specimen on day 69. In contrast, only modest infiltration of CD4(+) T-cells and a few CD20(+) B-cells were observed. Scale bar, 50 μm.

**DISCUSSION**

The clinical course of fulminant myocarditis is generally self-limiting, and the long-term prognosis of patients who survive is favorable. In this case, active lymphocytic infiltration persisted for over 70 days until the induction of immunosuppressive therapy after hemodynamic and functional recovery. Only a few case reports of persistent active lymphocytic infiltration in patients with fulminant myocarditis have been published. Hiramitsu, et al reported an autopsy case of fulminant myocarditis with prolonged inflammation of the myocardium caused by herpes simplex virus. In the present case, the serum titers and the specimens by EBMs revealed no specific pathogen and the etiology of the myocarditis was not discovered. We performed a multivirus real-time PCR before the initiation of immunosuppressive therapy according to the statement from the ESC Working Group. This PCR system has the potential to detect 163 human viruses (47 DNA viruses and 116 RNA viruses) in a 96-well plate simultaneously. The diagnostic accuracy of this method for detecting the presence of virus in the myocardium warrants further investigation. Although the precise mechanisms underlying the persistent inflammation remain unidentified, the positive anti-myocardial antibody test and the favorable effect of immunosuppressive therapy suggested a contribution of immunologic responses.

Persistent CAVB was one of the distinctive features of the
present case. A national survey of fulminant myocarditis in Japan comprising 52 patients reported that CAVB occurred in 35.4%, but permanent pacemaker implantation is rarely required after survival.

Repeated EMB combined with $^{18}$F-FDG PET/CT played an important role in evaluating the activity of myocarditis in the present case. EMB is the gold standard for the diagnosis of myocarditis, but it is an invasive method and has a potential risk of sampling error. Repeated EMB is not generally recommended as a routine follow-up strategy after the recovery of LV systolic function. However, follow-up EMB is indicated when unexpected clinical worsening occurs, for reassessment of pathological burden prior to modification of treatment. It can also be useful to monitor the response to etiology-directed therapy. Although there is no systematic research examining whether $^{18}$F-FDG PET/CT is useful for the diagnosis and follow-up of myocarditis, it can detect the presence and the location of active inflammation in the heart. Since $^{18}$F-FDG PET/CT could not detect the inflammation in the septum despite a positive finding by EMBs in the present case, the diagnostic accuracy of $^{18}$F-FDG PET/CT in the detection of active inflammation warrants further investigation. The second $^{18}$F-FDG PET/CT after the termination of prednisolone revealed no evidence of $^{18}$F-FDG uptake, which was consistent with the last EMB. Therefore, the combination of EMB and $^{18}$F-FDG PET/CT can help clinicians better manage individual patients with myocarditis.

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