Extensive Loss of Myocardium due to Lymphocytic Fulminant Myocarditis: An Autopsy Case Report of a Patient with Persistent Cardiac Arrest for 25 Days

Kei Morikawa¹, Seiji Takashio¹, Ryota Sato¹, Eiichiro Yamamoto¹, Koichi Kaikita¹, Kenichi Tsujita¹ and Yoshihiro Komohara²

Abstract:
We herein report the histological findings of a patient who had progressed to persistent cardiac arrest for 25 days due to lymphocytic fulminant myocarditis despite mechanical circulatory support (MCS). There were few residual cardiomyocytes, and extensive replacement fibrosis was present. Therefore, improvement of the cardiac function for this patient was considered improbable. Further research is warranted to improve predictions for the recovery of the cardiac function and optimize MCS strategies for patients with fulminant myocarditis.

Key words: fulminant myocarditis, cardiac arrest, autopsy

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Introduction
Mechanical circulatory support (MCS) is recommended for patients with fulminant myocarditis who present with cardiogenic shock (1, 2). In recent years, the combination of a percutaneous left ventricular assist device (e.g. Impella® axial flow pump; Abiomed Inc., Danvers, MA, USA) and venoarterial extracorporeal membrane oxygenation (V-A ECMO) has been selected, and further improvement in the prognosis for fulminant myocarditis is expected (3).

Impella® (Abiomed Inc.) support unloads the left ventricle and mitigates inflammatory responses and myofibroblast activation. The strategy of prolonged Impella® support (the PROPELLA concept) may contribute to enhanced myocardial recovery/remission in patients with fulminant myocarditis (4). However, the prognosis is still poor, and some cases lead to heart transplantation without recovery of the cardiac function. To improve the prognosis, it is important to predict the severity of myocardial damage and immediately establish an optimal treatment strategy with MCS.

We therefore report the autopsy findings of a patient who died from persistent cardiac arrest due to lymphocytic fulminant myocarditis after receiving ECPELLA (V-A ECMO + Impella®) support for 25 days.

Case Report
A 52-year-old man presented to a nearby hospital with a fever and chest pain that had begun 2 days earlier. The patient had no medical history or medication. On an electrocardiogram (ECG), elevation of the ST segment was observed in leads I, II, aVL, and V2-6 with junctional rhythm (Fig. 1A). The patient was suspected of having acute coronary syndrome and was referred to a regional hospital. Coronary angiography showed no significant coronary stenosis. However, the creatine kinase (CK: 2,495 IU/L) and CK-myocardial band (MB) (80 IU/L) levels were elevated. Echocardiography showed mild hypokinesis in the apex, and the left ventricular (LV) ejection fraction was approximately 60%; however, the patient's hemodynamics were deteriorating. The patient was diagnosed with fulminant myocarditis and transferred to our hospital.

The patient was conscious and coherent with a heart rate...
of 84 beats per minute and blood pressure of 91/67 mmHg (under infusion of dopamine: 5.4 μg/kg/min and dobutamine: 5 μg/kg/min) on admission. A second ECG showed the loss of R waves in precordial leads with additional ST elevation and increased QRS width compared to the first ECG (Fig. 1B). Right heart catheterization was performed and showed a mean pulmonary capillary wedge pressure of 20 mmHg, right atrial pressure of 8 mmHg, cardiac output

Figure 1. Serial electrocardiogram findings for a 56-year-old man. A: A 12-lead electrocardiogram at the previous hospital. B: A 12-lead electrocardiogram upon admission to our hospital (Day 1). C: Post Impella® insertion: Complete atrioventricular block (Day 1). D: Asystole (Day 4).

Figure 2. A comparison of the biopsy and autopsy tissues using tissue staining and immunohistochemistry (IHC). Biopsy tissue sections were obtained and stained with A) Hematoxylin and Eosin (H&E) staining, B) Azan, C) anti-CD8 antibody, and D) anti-CD163 antibody. Autopsy tissue sections were stained with E) H&E staining, F) Azan, G) anti-CD8 antibody, and H) anti-CD163 antibody. The representative H&E staining section (A), and immunohistochemistry (IHC) with anti-CD8 and anti-CD163 antibodies showed increased numbers of infiltrating lymphocytes (C) (lymphocytes: 10-20 cells/high-power field) and macrophages (D). Although fibrosis was rarely observed in biopsy samples (B), severe fibrosis was observed in the autopsy sample (F). No viable cardiomyocytes were observed in the autopsy sample (E). Increased infiltration of inflammatory cells was observed in the autopsy sample (G, H). Bar scales were 50 μm for H&E staining (A), 100 μm for Azan, and 20 μm for H&E staining (E) and IHC staining.
cardiac index showed a decreasing trend (1.51 L/min/m²). Complete atrioventricular block occurred (Fig. 1C), and the left ventricular assist device (VAD; Impella 2.5; Abiomed Inc.) and temporary pacemaker were introduced. An endomyocardial biopsy of the right ventricle (RV) was performed, and infiltration of lymphocytes and macrophages without eosinophils or giant cells was observed in the tissue (Fig. 2A-D). Echocardiography showed an increase in the interventricular septal thickness (11.7 mm) with edematous changes and a decrease in LV fractional shortening (32%) (Fig. 3A). We diagnosed the patient with lymphocytic fulminating myocarditis and began immunoglobulin therapy (5,000 mg/day). Despite the introduction of Impella 2.5, ventricular pacing was not effective (Fig. 1D). The Impella 2.5 device continued to support circulation at performance level 2, and the ECMO flow was maintained at 3-4 L/min. While continuing with MCS, the patient remained in asystole. On day 14, we performed an electrophysiological study; however, no sites responded to ventricular pacing. Myocardial edema and pericardial effusion were observed until day 8, at which point these changes began to improve gradually and were not observed on day 16 (Fig. 3C-D). Without a return of spontaneous circulation, the patient died on day 28 due to bleeding and multiple organ failure. Fig. 4 shows the clinical course of this case.

An autopsy was performed to investigate the reasons for the prolongation of cardiac arrest. Macroscopic findings revealed atrophy of the heart (220 g), enlargement of both ventricles, thinning of the myocardium (LV wall: 8 mm, RV wall: 4 mm), and whitish fibrosis in the posterior wall of the LV (Fig. 5A). Microscopic findings revealed that most of the myocardium showed cardiac injury (Fig. 5B). A percutaneous left ventricular assist device (VAD; Impella 2.5; Abiomed Inc.) and temporary pacemaker were introduced. An endomyocardial biopsy of the right ventricle (RV) was performed, and infiltration of lymphocytes and macrophages without eosinophils or giant cells was observed in the tissue (Fig. 2A-D). Echocardiography showed an increase in the interventricular septal thickness (11.7 mm) with edematous changes and a decrease in LV fractional shortening (32%) (Fig. 3A). We diagnosed the patient with lymphocytic fulminating myocarditis and began immunoglobulin therapy (5,000 mg/day). Despite the introduction of Impella 2.5, complete atrioventricular block occurred (Fig. 1C), and the cardiac index showed a decreasing trend (1.51 L/min/m²).

On day 2, cardiogenic shock persisted, and systolic blood pressure fell below 80 mmHg; therefore, mechanical ventilation and V-A ECMO were introduced. Continuous hemodialysis was introduced due to acute kidney injury. On day 3, almost no thickening of the LV (LV fractional shortening: 6%) was noted, and a marked increase in the interventricular septal thickness (17.9 mm) with edematous changes was observed using echocardiography (Fig. 3B). CK and CK-MB levels peaked at 13,300 and 1,289 IU/L, respectively. From day 4, the ECG showed cardiac arrest, and ventricular pacing was not effective (Fig. 1D). The Impella 2.5 device continued to support circulation at performance level 2, and the ECMO flow was maintained at 3-4 L/min. While continuing with MCS, the patient remained in asystole. On day 14, we performed an electrophysiological study; however, no sites responded to ventricular pacing. Myocardial edema and pericardial effusion were observed until day 8, at which point these changes began to improve gradually and were not observed on day 16 (Fig. 3C-D). Without a return of spontaneous circulation, the patient died on day 28 due to bleeding and multiple organ failure. Fig. 4 shows the clinical course of this case.

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the cardiomyocytes had disappeared and been replaced by fibrous tissue with infiltration of lymphocytes and macrophages (Fig. 2E-H). The fibrous tissue was a mixture of old and new fibrosis. Viable cardiomyocytes were only observed in the free walls of the LV and RV along with eosinophilic and vacuolar changes (Fig. 5B, C). However, no viable cardiomyocytes could be found in most of the myocardium (Fig. 5D). Many lymphocyte infiltrates were found at the border area between the viable cardiomyocytes and fibrous tissue. Some macrophages showed hemosiderin accumulation. Mature collagen fibers were observed in the macroscopic whitish area, which was presumed to be an old le-
sion. No eosinophils or giant cells were found. These findings suggested that widespread myocardial injury resulted in extreme loss of myocardium, making it difficult or impossible to achieve return of spontaneous circulation.

**Discussion**

We herein report a patient with lymphocytic fulminant myocarditis who was supported by ECPELLA. The patient’s cardiac function did not improve, asystole continued for 25 days, and return of spontaneous circulation was not obtained. A majority of the cardiomyocytes were lost due to extensive myocardial damage and replaced by fibrosis. The persistent asystole was attributed to the disappearance of the working myocardium itself and not conduction disturbances. This point was consistent with the failure to obtain effective ventricular pacing at any site. To our knowledge, this is the first report confirmed by an autopsy that showed persistent cardiac arrest supported by MCS due to fulminant myocarditis and extensive loss of myocardium.

The histopathological findings suggested that resumption of self-heartbeat would have been improbable because of the extreme loss of myocardium. A VAD was also considered, but the patient’s renal function rapidly became impaired, and cardiac arrest developed. If the renal function and heartbeat had improved, the introduction of a VAD as a “bridge to candidacy” would have been considered. We previously reported a patient with fulminant myocarditis who survived after 56 hours of cardiac arrest supported by V-A ECMO (5). Therefore, in the current case, we decided to wait for the return of spontaneous circulation and improvement in the cardiac function with ECPELLA. However, no such improvement occurred, and the CK levels increased substantially, suggesting that extensive myocardial damage had occurred. Although the CK levels normalized after approximately one week, myocardial damage may have occurred in the early stage of the disease followed by extensive replacement fibrosis. High CK levels, conduction disturbances, and a lack of improvement in the cardiac function within 48 hours after ECMO induction are considered poor prognostic factors (6, 8) and were found in our case. It is necessary to discuss further regarding how to quickly determine that myocardial injury is extremely advanced and the cardiac function is not expected to improve. In this case, the hemodynamics deteriorated despite the introduction of Impella 2.5®. Escalation to ECPELLA should have been immediately considered before “crash and burn” occurred. One of the reasons for the extensive myocardial damage was that the right atrial and pulmonary diastolic pressure remained high for an extended period of time, and adequate ventricular unloading was not obtained, even after the introduction of ECPELLA. We should consider reduction of the left ventricular afterload by adjustment of the performance level of Impella 2.5® and optimization of the volume status while maintaining the hemodynamics.

Further research is warranted to improve predictions concerning the recovery of the cardiac function and optimize MCS strategies to improve prognoses and candidacy for transplantation among patients with fulminant myocarditis.

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

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