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CASE REPORT

Fulminant necrotizing eosinophilic myocarditis after COVID-19 vaccination survived with mechanical circulatory support

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Abstract

A 69-year-old man was hospitalized for heart failure 7 days after coronavirus disease 2019 (COVID-19) mRNA vaccination. Electrocardiography showed ST-segment elevation and echocardiography demonstrated severe left ventricular dysfunction. Venoarterial extracorporeal membrane oxygenation and Impella 5.0 were instituted because of cardiogenic shock and ventricular fibrillation. Endomyocardial biopsy demonstrated necrotizing eosinophilic myocarditis (NEM). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) PCR test was negative. He had no infection or history of new drug exposure. NEM was likely related to COVID-19 vaccination. He was administered 10 mg/kg of prednisolone following methylprednisolone pulse treatment (1000 mg/day for 3 days). Left ventricular function recovered and he was weaned from mechanical circulatory support (MCS). Follow-up endomyocardial biopsy showed no inflammatory cell infiltration. This is the first report of biopsy-proven NEM after COVID-19 vaccination survived with MCS and immunosuppression therapy. It is a rare condition but early, accurate diagnosis and early aggressive intervention can rescue patients.

Keywords Necrotizing eosinophilic myocarditis; COVID-19 vaccination; Older adult; Mechanical circulatory support

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Introduction

Eosinophilic myocarditis (EM) is a rare form of myocardial inflammatory disease, which is caused by immune-mediated diseases, hypereosinophilic syndrome, parasitic infection, hypersensitivity reaction, or cancer.[1] The disease course ranges from asymptomatic to fulminant myocarditis, or chronic restrictive cardiomyopathy, so-called Löffler endmyocarditis.[1] Several cases of myocarditis after coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccination have been reported.[2–5] However, previous reports have shown that this complication frequently occurs in young patients and that its severity is relatively mild. Recently, an autopsy case of necrotizing eosinophilic myocarditis (NEM) after COVID-19 vaccination has been reported.[6] We experienced a survival case of biopsy-proven fulminant NEM after COVID-19 mRNA vaccination requiring mechanical circulatory support (MCS) with venoarterial extracorporeal membrane oxygenation (VA-ECMO) and Impella 5.0. The patient was recovered by immunosuppression therapy with corticosteroid and could be weaned from MCS.

Case report

A 69-year-old man visited the prior hospital complaining of chill and peripheral coldness 7 days after COVID-19 mRNA vaccination (BNT162b2, first dose). He had no history of

infection or new drug exposure during this period. His past medical history included hypertension and peripheral artery disease (PAD), but no cancer, haematologic disorders, or immune-mediated diseases. He did not report dyspnoea, and a PCR test was negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) RNA. His body temperature was 36.4°C. His blood pressure was 120/80 mmHg, and pulse rate was 100 b.p.m. Electrocardiography (ECG) showed wide QRS in all leads and ST-segment elevation in leads II, III, aVF, and V1 through V4 (*Figure 1A*). Chest X-ray showed cardiac enlargement with mild pulmonary congestion (*Figure 1C*). Laboratory examination revealed the elevation of myocardial biomarkers such as serum troponin T, creatine kinase (CK), and CK-MB and inflammatory biomarkers including white blood cell count C-reactive protein (CRP) (*Table 1*). Serum eosinophilic count was mildly elevated to 746 cells/μL (normal value 30–350 cells/μL). The serum antibody titres against popular myocarditis-causing viruses including echoviruses, coxsackieviruses, and influenza viruses did not rise, while the antibody titre against SARS-CoV2 was mildly elevated to 0.90 U/mL (normal value <0.80 U/mL). Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) and cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) were negative. There was no recent new drug exposure except COVID-19 mRNA vaccine. Blood cultures were all negative. A transthoracic echocardiography demonstrated severe global hypokinesia, while left ventricular dimensions were not dilated (*Figure 2A,B*, *Table 1*). Pericardial effusion

Table 1 Laboratory test results and echocardiographic parameters

	Day 1	Day 3	Day 25	Normal values
Laboratory tests				
White blood cells (cells/μL)	13 090	18 030	12 660	3300–8600
C-reactive protein (mg/dL)	3.89	31.58	0.81	<0.14
Creatine kinase (CK) (U/L)	1318	12 636	2065	59–248
CK-MB (U/L)	114	108	7	<12
Troponin T (ng/mL)	5.86	10.09	0.041	<0.014
BNP (pg/mL)	1082.9	705.6	121.5	0–18.4
Echocardiography				
LVIDd (mm)	44	42	45	40–56
LVIDs (mm)	40	40	33	20–38
LVEF (%)	17	10	56	45–90
IVS (mm)	14	15	9	7–11
PW (mm)	13	15	8	7–11

Abbreviations: IVS, interventricular septum thickness; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension at diastole; LVIDs, left ventricular internal dimension at systole; PW, posterior wall thickness.

Figure 1 Electrocardiographic and chest X-ray images at admission and after the treatment with mechanical circulatory support and corticosteroid. Electrocardiography showed widening of QRS duration and ST-segment elevation in leads II, III, aVF, and V1 through V4 at admission (A). These findings were almost normalized except first-degree atrioventricular block after the treatment (B). Chest X-ray at admission demonstrated enlargement of cardiac silhouette and pulmonary congestion (C). Cardiac silhouette enlargement and pulmonary congestion were improved after the treatment (D).

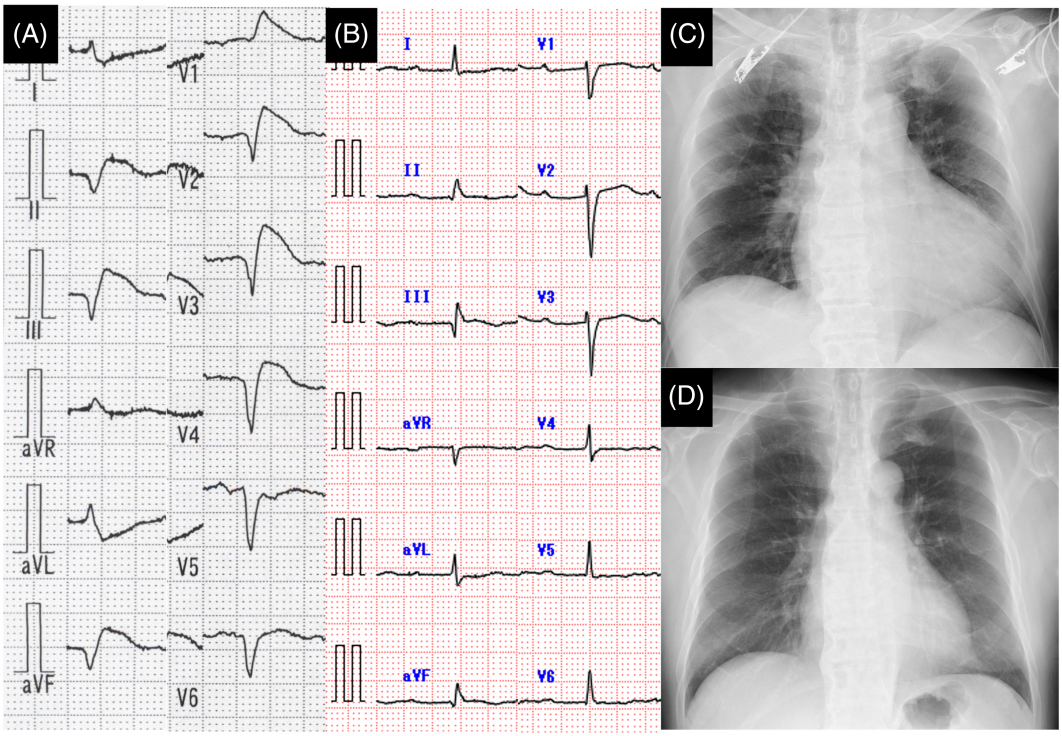
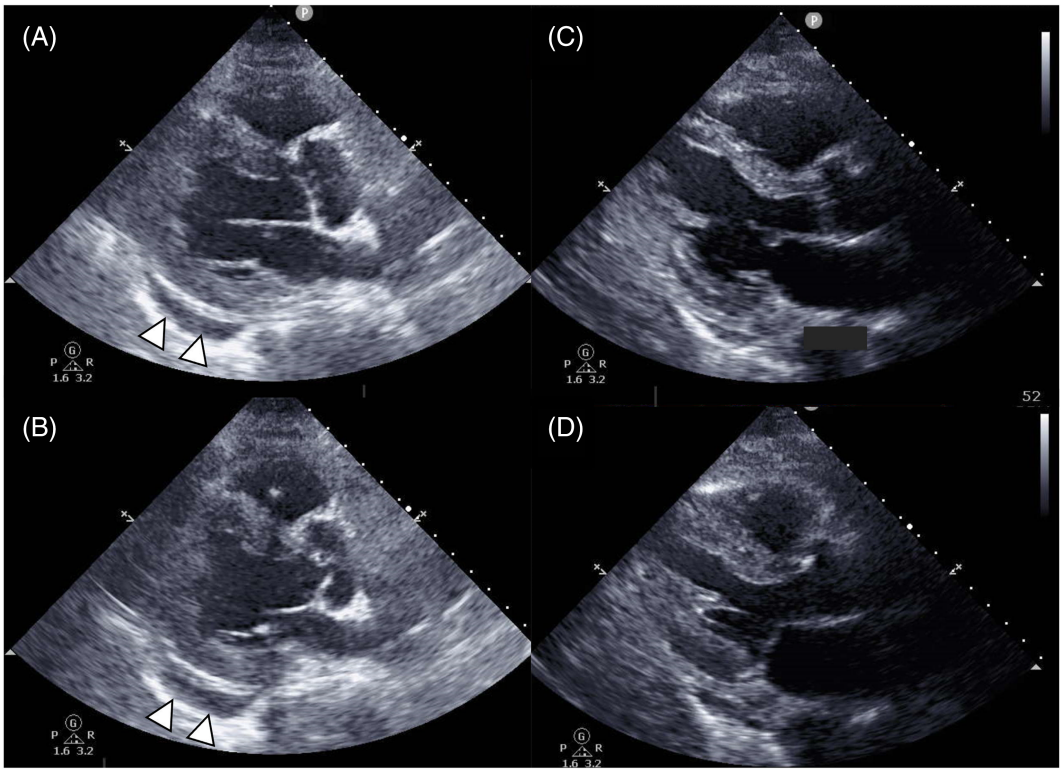


Figure 2 Echocardiographic images at admission and 1 month after the onset of fulminant myocarditis. Parasternal long-axis views of transthoracic echocardiography at diastole (A) and systole (B) at admission. Left ventricular (LV) systolic function was severely impaired, but dilatation of the LV dimension was not observed. Pericardial effusion was noticeable (arrowheads). Parasternal long-axis views at diastole (C) and systole (D) after the weaning from mechanical circulatory support and inotropes demonstrated the shortening of LVIDs suggesting recovery of systolic function.



was also observed (arrowheads in *Figure 2A,B*). Coronary angiography revealed no obstructive coronary artery disease. Invasive haemodynamics by right heart catheterization showed elevated right atrial pressure of 24 mmHg, pulmonary artery wedged pressure of 29 mmHg, and cardiac index of 1.63 L/min/m^2. Since myocarditis was suspected from above findings, endomyocardial biopsy was performed. Histopathology of myocardial tissue showed cardiomyocyte necrosis and exaggerated infiltration of inflammatory mononuclear cells and eosinophils associated with degranulation (*Figure 3A–C*). No parasitic organisms or giant cells were detected. He was diagnosed with NEM based on these findings.

Soon after admission to the intensive care unit, he experienced cardiogenic shock and refractory ventricular fibrillation. He was immediately resuscitated and peripheral VA-ECMO and intra-aortic balloon pump (IABP) were instituted, but cardiac contractility was almost absent and the aortic valve kept closed. In addition, he developed complete atrioventricular block (AVB). He was transferred to our hospital for further treatment. Impella 5.0 pump (Abiomed Inc., Danvers, MA) was placed through the right subclavian artery. Because of right ventricular failure, infusion of milrinone and inhalation of nitric oxide (NO) were also required. Immunosuppressive therapy with corticosteroid was simultaneously initiated. After methylprednisolone pulse treatment with 1000 mg/day for 3 days, 1 mg/kg of prednisolone was administered as maintenance therapy. Cardiac contractility partially recovered and the patient was successfully weaned from Impella and V-A ECMO 7 days after the onset of myocarditis. IABP was placed instead for prolonged haemodynamic support. Complete AVB persisted, and thus, temporary transvenous pacemaker was placed. Corticosteroid was weaned by 10 mg every week. As cardiac function restored and the haemodynamics was stable, the patient was weaned from IABP, infusion of inotrope, and inhalation of NO on Day 14. He was also weaned from mechanical ventilation on Day 17. Since conduction defect was partially recovered to second-degree AVB (Wenckebach type 2), temporary pacemaker was removed on Day 21. QRS widening and ST-T change on ECG were also recovered (*Figure 1B*). Inflammatory and myocardial biomarkers such as CRP, CK, and troponin T gradually declined (*Table 1*). Chest X-ray showed regression of cardiac silhouette enlargement (*Figure 1D*). Echocardiography on Day 25 showed almost normal left ventricular systolic function (*Figure 2C,D, Table 1*). Repeat endomyocardial biopsy on Day 30 demonstrated no apparent

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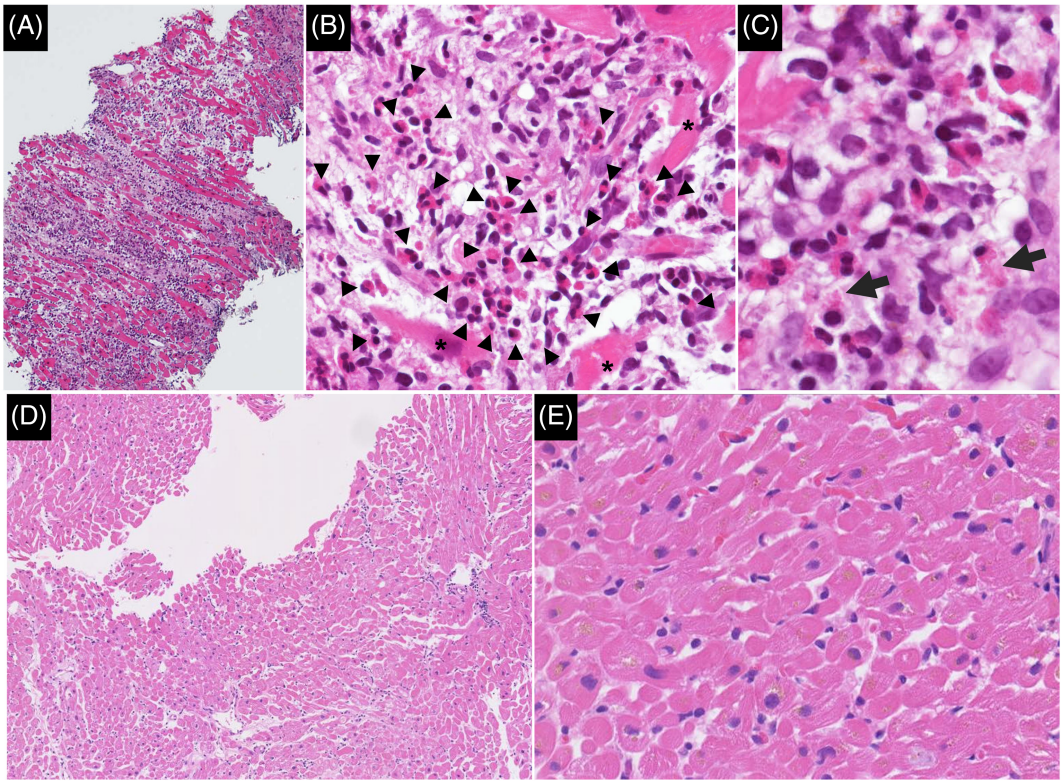
Figure 3 Histopathological findings of endomyocardial biopsy specimens stained with haematoxylin–eosin at admission and 1 month after the onset of fulminant myocarditis. Low power magnification (×100) showed diffuse infiltration of mononuclear cells in the entire myocardial tissue at the initial biopsy (A). Marked infiltration of eosinophils (arrowheads) with severe tissue injury and cardiomyocyte necrosis (asterisks) were noticeable at high power magnification (×400) (B), and degranulation of eosinophils was also observed (arrows) (C). There was no apparent infiltration of inflammatory cells in the myocardium and tissue injury was repaired at the repeat biopsy after treatment with mechanical circulatory support and immunosuppression therapy; low (×100) (D) and high power magnification (×400) (E) are shown.



infiltration of inflammatory cells including eosinophils and no myocyte necrosis (*Figure 3D,E*). Since he had the worsening PAD, he was discharged home after endovascular therapy at the department of vascular surgery. He did not experience relapse of heart failure or any other cardiovascular events in the following 6 months.

Discussion

Myocarditis is progressive inflammation of the myocardium associated with myocardial injury provoked by infection of viruses, bacteria, fungi, and protozoa, cardiotoxic drugs, and immune-mediated systemic diseases.[7] EM is a relatively rare form of myocarditis, which is often accompanied by eosinophilla.[8] It has been reported that almost one-third of EM was caused by hypersensitivity reaction.[1] Frequent causes of hypersensitivity-associated EM include antibiotics, anti-tubercular agent, antiretroviral drugs, anticonvulsants, allopurinol, calcium channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), and vaccines.[8,9] Eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES) also causes EM.[1] Other causes include infection, pregnancy-related, malignancies, and idiopathic.[1] Up to 19% of cases of hypersensitivity-associated EM has been reported to develop fulminant phenotype requiring haemodynamic support with MCS, and their in-hospital mortality rate was quite high (36%).[1]

Viral myocarditis is characterized by progressive myocardial injury triggered by inflammatory processes. Viruses from the Coronaviridae family including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV2 are also known to cause myocarditis.[10] Cardiovascular complication of COVID-19 includes acute coronary syndrome, arrhythmia, venous thromboembolism, and heart failure.[11,12] The mechanisms of cardiovascular injury associated with COVID-19 have not been fully elucidated and are likely multifactorial. It has been proposed that myocardial injury is caused by direct cardiotoxicity, hypoxaemia-mediated injury, supply–demand mismatch, cytokine storm, disseminated intravascular

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coagulation (DIC), myocarditis, and stress-induced cardiomyopathy.[12] In a systematic review of 14 cases of COVID-19-associated myocarditis, around 40% of all patients either presented in acute respiratory distress syndrome (ARDS) or developed it during the course; and nearly two-thirds of the patients were in shock (71% cardiogenic and 29% mixed cardiogenic and septic shock), requiring vasopressors or inotropes (50%) and/or MCS (17%), with the mortality rate of 19%.[13] As the PCR test for SARS-CoV2 RNA was negative, COVID-19-related myocarditis was unlikely in the present case.

Cases of vaccine-associated myocarditis following influenza, tetanus toxoid, and smallpox vaccination have been reported.[14] COVID-19 vaccination has also become known to cause myocarditis.[2–5] The possible mechanisms of COVID-19 vaccination-related myocarditis include multiple cytokines, autoantibodies, and natural killer (NK) cells.[15] In previous reports, diagnosis of COVID-19 vaccination-associated myocarditis was determined based on the ECG change, depressed left ventricular function, elevated cardiac enzymes, and cardiac MRI findings of myocardial oedema and injury in almost all cases. In a review including 17 cases of myocarditis after COVID-19 vaccination, all patients were male, and most cases were age of 10s through 30s.[5] Other groups also reported the same characteristics of patients.[3,4] Almost all patients with myocarditis after COVID-19 vaccination were haemodynamically stable without need for inotropes or MCS, and the disease course was mild.[2,3] Abbate *et al*. reported two young patients with fulminant myocarditis requiring VA-ECMO after COVID-19 mRNA vaccination, and one case with trisomy 21 died.[16] Patients of COVID-19 vaccination-associated myocarditis in older ages have been reported to progress to fatal outcome.[5,6] There have been only one report of NEM after COVID-19 vaccination, in which the patient was found deceased at home and the autopsy confirmed the diagnosis.[6]

In the present case, the patient did not show the evidence of infection of any viruses or other microorganisms and did not have a history of exposure to any new drugs potentially causing hypersensitivity reaction. It was highly suspected that vaccination was causally associated with myocarditis based on the clinical course of developing myocarditis soon after COVID-19 vaccination. Histopathological finding of NEM in the present case further supports the causal relationship between COVID-19 vaccination and myocarditis since EM is often accompanied by hypersensitivity reaction. The patient was in critical condition requiring MCS during the early phase in accordance with previous cases of myocarditis after COVID-19 vaccination in older patients. This is the first case report of an older adult patient with biopsy-proven NEM after COVID-19 vaccination successfully treated with MCS and immunosuppression therapy. The appropriate evaluation and rapid intervention are necessitated if COVID-19 vaccination-associated myocarditis is suspected especially in high-risk cases. Aggressive therapeutic strategy may warrant the survival even in such severe condition as in the present case.

Conflict of interest

None declared.

Funding

None.

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