

[CASE REPORT]

Successful Treatment of Acute Fulminant Eosinophilic Myocarditis in a Patient with Ulcerative Colitis Using Steroid Therapy and Percutaneous Cardiopulmonary Support

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Abstract:

A 47-year-old man with ulcerative colitis was transferred to our hospital due to progressive dyspnea. Electrocardiography on admission showed ST elevation in leads II, III, aVF, and V5-V6. Coronary angiography revealed no remarkable coronary stenosis, and left ventriculography showed a depressed left ventricular ejection fraction (EF) of 23%. Although the patient received percutaneous cardiopulmonary support, his EF progressively decreased (7-15%), and both ventricular tachycardia (VT) and high-degree atrial-ventricular block occurred. An endomyocardial biopsy showed eosinophilic infiltration in the myocardium. Steroid therapy improved the patient's EF. However, his severe inferior wall hypokinesis and non-sustained VT remained after the abovementioned treatment.

Key words: fulminant myocarditis, eosinophilic myocarditis, ventricular tachycardia, atrial-ventricular block, percutaneous cardiopulmonary support, steroid therapy

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Introduction

Eosinophilic myocarditis (EM) is a relatively rare disorder, characterized by eosinophilic infiltration. EM can be caused by infections or allergic diseases (1, 2). The disease is often fatal, and a particularly high in-hospital mortality rate has been reported when EM presents in the fulminant form (also known as acute necrotizing EM) (3, 4). Myocarditis associated with ulcerative colitis (UC) is also a rare disorder with a serious risk of mortality (5, 6). An endomyocardial biopsy facilitates the definite diagnosis of EM (7, 8), and steroid therapy has been used for the treatment of EM (9). In this report, we describe the case of a 47-year-old man who had fulminant EM complicated with UC. He also experienced ventricular tachycardia (VT) and high-degree atrial-ventricular (A-V) block. He was ulti-

mately treated with steroid therapy which improved the patient's left ventricular function.

Case Report

A 47-year-old man was referred to our hospital from another medical clinic with progressive dyspnea and left ventricular dysfunction on echocardiography (UCG). He had been treated for UC with 5-aminosalicylic acid (5-ASA) (Asacol, 2,400 mg/day) for 15 years at the hospital. He complained of a common cold two days before he was transported to our hospital due to worsening of his dyspnea at rest.

Upon arrival at the emergency room, he was alert with a blood pressure of 127/88 mmHg and body temperature of 37.3°C. An electrocardiogram (ECG) showed sinus rhythm with a heart rate of 103 beats per minute, ST elevation in

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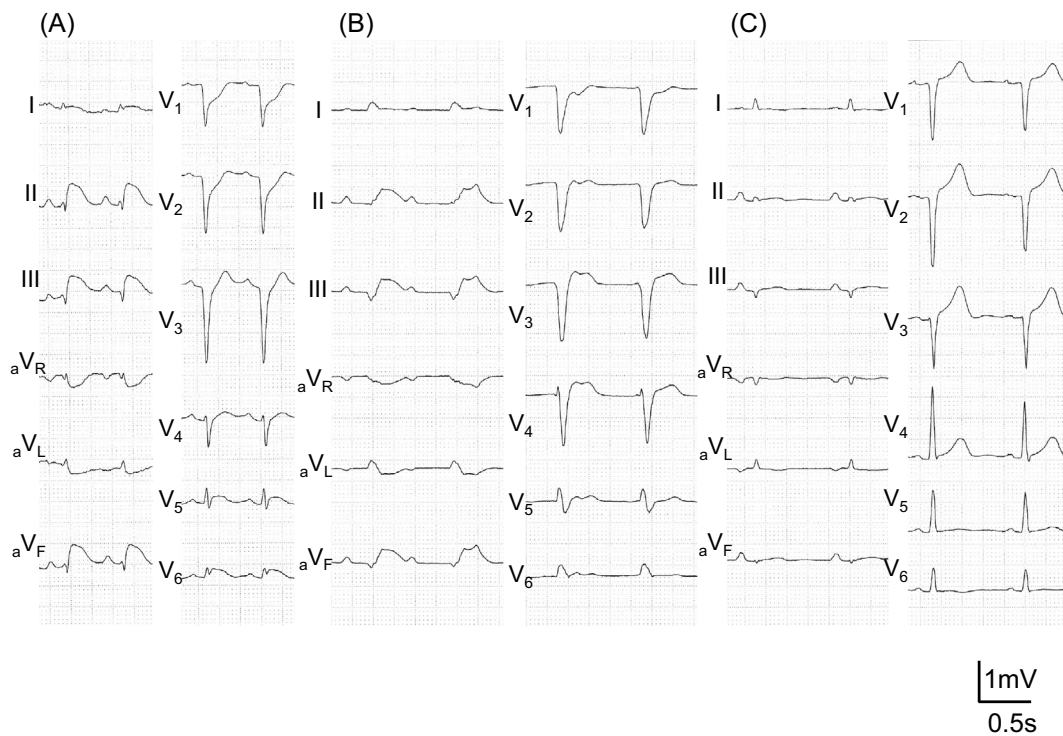


Figure 1. Electrocardiogram (ECG) changes during admission. (A) ECG obtained on admission shows a sinus rhythm with a heart rate of 103 beats per minute, ST elevation in leads I, II, III, aVF, and V5-V6, and ST depression in leads V1-V2. (B) ECG performed on day 4 after admission shows complete left bundle branch block (CLBBB) and intermittent I-III-degree atrioventricular (A-V) block intermittently. (C) ECG performed after recovery shows improvement in the poor R voltages and wide QRS. Abnormal Q waves in leads III, and aVF and inverted T wave in leads in II, III, aVF, and V6 remain.

leads I, II, III, aVF, and V5-V6, and ST depression in leads V1-V2 (Fig. 1A). The hematological and serological examination results demonstrated positive troponin T and elevated levels of alanine transaminase (ALT) and lactate dehydrogenase (LDH). The patient's creatine kinase (CK), creatine kinase-muscle/brain (CPK-MB), and brain natriuretic peptide (BNP) levels were elevated (CK: 2,255 IU/L, CPK-MB: 178 IU/L, and BNP: 1,342.04 pg/mL). His C-creative protein (CRP) level was also elevated (9.90 mg/dL). In contrast, count of both leukocytes [white blood cells (WBCs)] and eosinophils were within the normal ranges (WBC: 5,290/ μ L, eosinophils: 30/ μ L). Chest radiography revealed cardiomegaly [Cardio-Thoracic ratio (CTR)=56.2%] without lung congestion. UCG showed a normal-sized left ventricle (LV), diffuse hypokinesis of the LV with an ejection fraction (EF) of 30%, particularly severe hypokinesis lateral to the posterior wall, and mild hypertrophy of the LV wall.

After obtaining informed consent, we performed cardiac catheterization. The right ventricular pressure and LV end diastolic pressure (EDP) were evaluated [pulmonary artery=34/21 (26) mmHg; LV=112/EDP 34 mmHg]. The cardiac index (CI) was 1.58 L/min/m². Coronary angiography revealed no remarkable coronary stenosis. Left ventriculography showed a depressed LVEF of 23.0% with diffuse hypokinesis and particularly severe hypokinesis with inferior to the posterior wall (Fig. 2A). We suspected fulminant myo-

carditis and performed an endomyocardial biopsy. Intra-aortic balloon pump (IABP) support was then initiated. Immunoglobulin therapy (60 g/day) and continuous intravenous heparin infusion (15,000 μ /day) were started to prevent LV thrombosis.

On the day after admission, the patient's dyspnea had progressed, and his systolic blood pressure had decreased to 80 mmHg. His CI decreased from 3.0 to 0.7-1.2 L/min/m² with IABP support. An ECG revealed abnormal Q waves in leads II, III, and aVF. Percutaneous cardiopulmonary support (PCPS) and temporary pacing were initiated under ventilator support. Administration of 5-ASA (Pentasa 3,000 mg/day) was continued with a nasotracheal tube to prevent worsening of UC.

On days 3-5 after admission, the patient's systolic blood pressure was decreased to 60 mmHg, and his cardiac function deteriorated (CI=0.5-0.7 L/min/m²) despite PCPS, IABP (Fig. 3), and intravenous administration of dopamine and dobutamine. An ECG revealed complete left bundle branch block (CLBBB) and intermittent I-III-degree A-V block (Fig. 1B). Chest radiography revealed cardiomegaly and progressive lung congestion (Fig. 4A). UCG showed that the patient's LV function had decreased (EF=8-11%), and the LV wall had become thick (13.6-15.2 mm) (Fig. 2B). Furthermore, non-sustained to sustained monomorphic VT occurred frequently, necessitating electrical cardioversion to si-

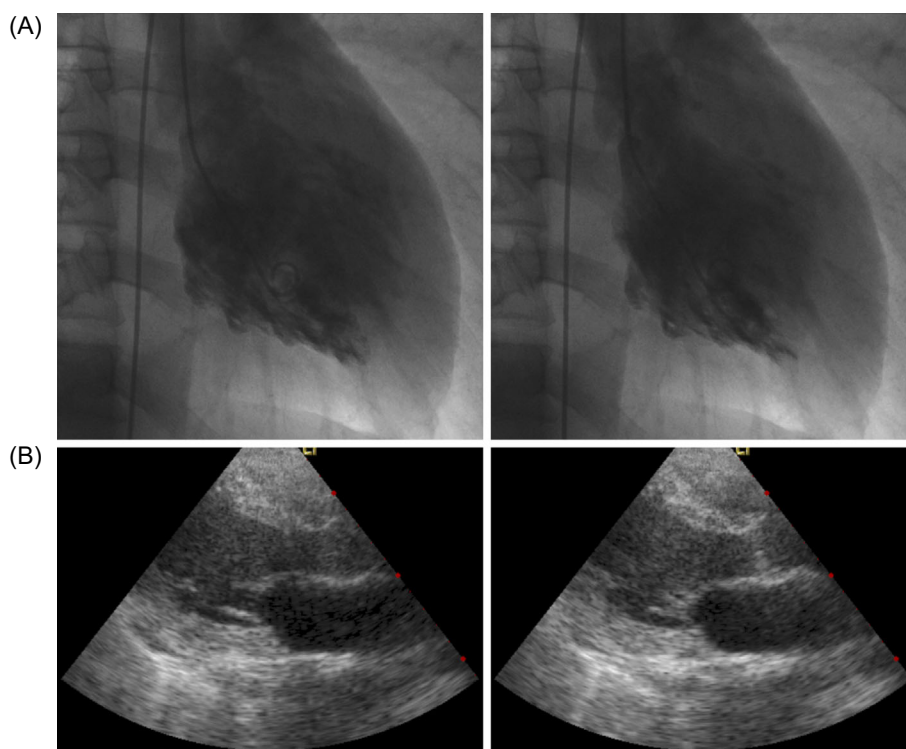


Figure 2. Left ventriculography (LVG) performed on admission and echocardiography (UCG) performed on day 3 after admission. (A) Left ventricle angiography showing a depressed left ventricular ejection fraction (LVEF) of 23.0% with diffuse hypokinesis, with particular severe inferior-to-posterior wall hypokinesis. (B) UCG on day 3 after admission showing that the left ventricular (LV) function was decreased, with an ejection fraction of 15%. Thickening of the LV wall can be seen.

nus rhythm (Fig. 5). The CK and CPK-MB levels were consistently evaluated (CK: 786-2,262 IU/L, CPK-MB: 33-178 IU/L). The patient's eosinophil count remained within the normal ranges (10-30/ μ L) (Fig. 3).

On day 5 after admission, the histological results of the endomyocardial biopsy revealed inflammation caused by eosinophilia, degranulation of eosinophil granules and damage to the myocardial muscles (Fig. 6). These findings were compatible with fulminant EM (acute necrotizing EM). Steroid pulse therapy (methylprednisolone 1,000 mg/day \times 3 days) was initiated, followed by intravenous administration of methylprednisolone at 125 mg/day. Administration of 5-ASA acid was discontinued.

After starting the patient on steroid therapy, his blood pressure improved to 90 mmHg. On day 7 after admission, his ST-T elevation in leads II, III, aVF, and V5-V6, CLBBB, and A-V block improved. In contrast, non-sustained and sustained VT reproducibly occurred but were suppressed by intravenous administration of amiodarone.

The patient's LV dysfunction remained consistently decreased (EF=21-23%, CI=0.7-0.8 L/min/m²) until day 11 after admission. PCPS support was needed for 15 days in total (Fig. 3). To discontinue PCPS support, intravenous administration of milrinone (0.125 μ g/kg/min) was started for 2 days. IABP was also discontinued on day 18 after admission.

The patient's cardiac function improved from this point.

An ECG showed that the patient's poor R voltages and wide QRS had improved. However, abnormal Q waves in leads III and aVF and inverted T wave in leads in II, III, aVF, and V6 remained (Fig. 1C). The patient's cardiomegaly and lung congestion had improved on chest radiography (Fig. 4B). UCG revealed improvement in the LV function but severe hypokinesis with inferior-to-posterior thinning of the LV wall (Fig. 7B). We started the patient on anticoagulant treatment. We switched him from intravenous methylprednisolone to oral prednisolone (60 mg/day), which was tapered carefully to 17.5 mg/day at discharge, and the outpatient maintenance dose was tapered to 10 mg/day. Although a low dose of beta-blocker (carvedilol at 1.25 to 2.5 mg/day) was also started to prevent heart failure and VT, the beta-blocker was discontinued because of the patient's decreased blood pressure and heart rate. Therefore, oral amiodarone (200 mg/day) was started to prevent VT recurrence.

After the patient provided his informed consent, we performed cardiac catheterization on day 82 after admission. The right ventricular pressure and LV EDP were normalized (pulmonary artery=24/9 mmHg (12); LV=101/EDP 7 mmHg). His CI was 3.59 L/min/m². Left ventriculography revealed an LVEF of 40.5% with severe hypokinesis and aneurysmal changes to the inferior-to-posterior wall (Fig. 7A). The histological results of the endomyocardial biopsy revealed no infiltration of eosinophils. The patient did not agree to the treatment of an implantable cardioverter de-

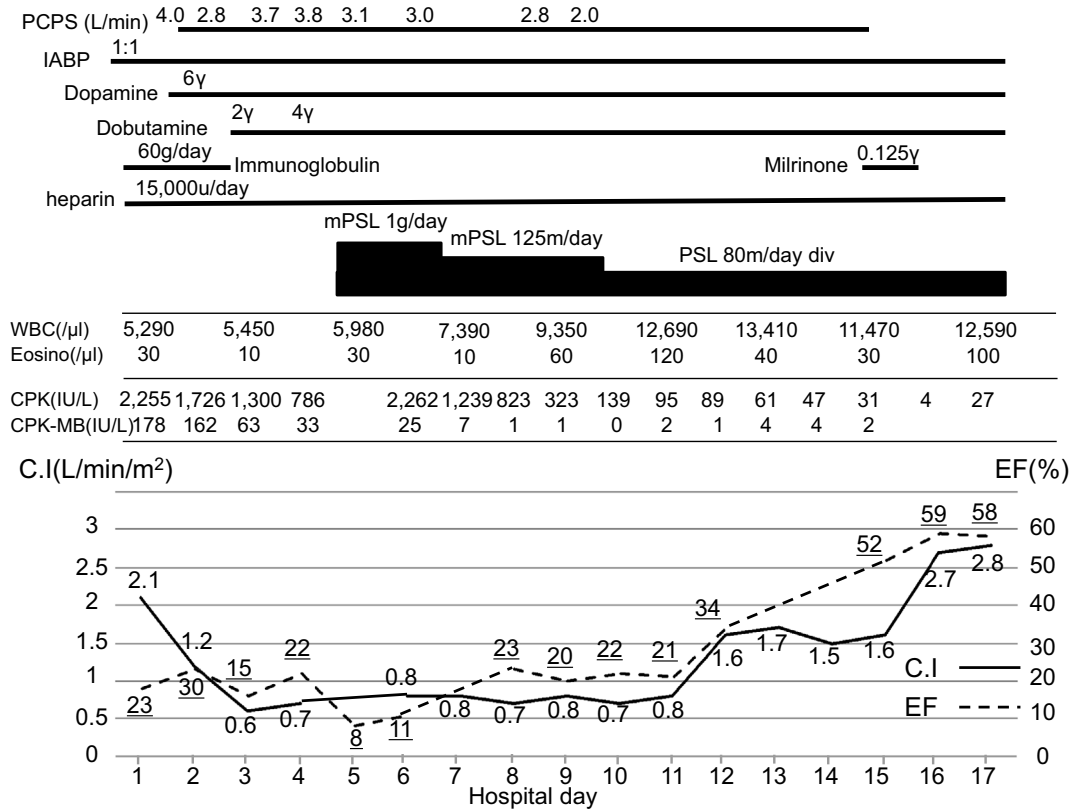


Figure 3. The clinical course of the acute phase. The CI and EF via two-dimensional echocardiography decreased after admission despite PCPS, IABP, and intravenous catecholamine infusion. The CI and EF improved with steroid treatment. LV dysfunction lasted until day 11 after admission; PCPS support was used for 15 days. The peripheral eosinophilia count is within the normal range. CI: cardiac index, EF: ejection fraction, WBC: leukocyte, Eosino: eosinophil, CK: creatine kinase, CPK-MB: creatine kinase-muscle/brain, PCPS: percutaneous cardiopulmonary support, IABP: intra-aortic balloon pumping, mPSL: methylprednisolone, PSL: prednisolone

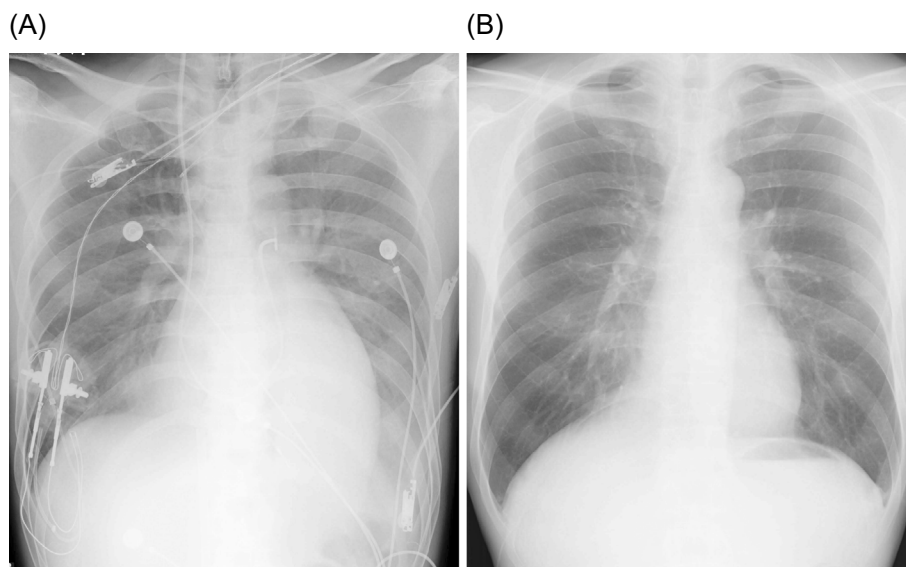


Figure 4. Chest radiography performed during admission. (A) Chest radiography performed on day 4 after admission showing cardiomegaly and progression of lung congestion. (B) Chest radiography performed after recovery showing a decrease in the cardiothoracic rate and the disappearance of lung congestion.

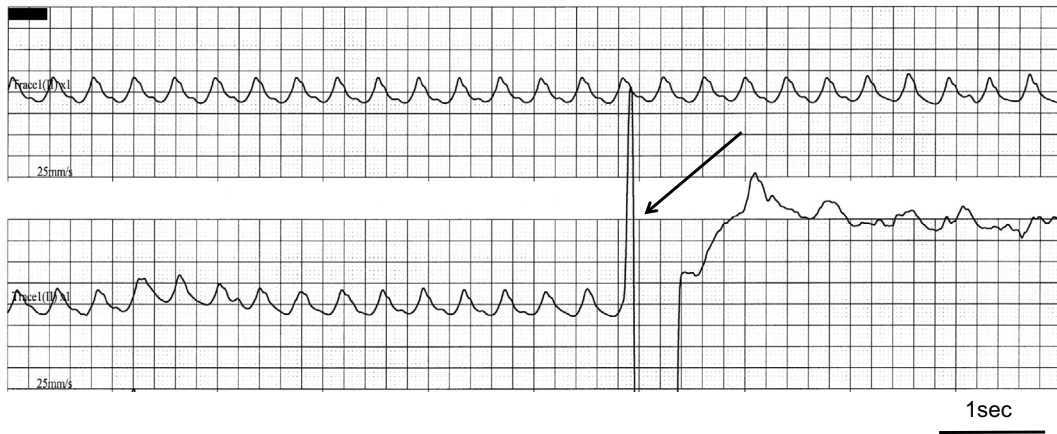


Figure 5. Electrocardiography results. ECG showing monomorphic sustained ventricular tachycardia (VT) with a rate of 150 beats per minute on day 4 after admission. The patient's blood pressure decreased to 40-50 mmHg with sustained VT. Electrical cardioversion (which was allowed in the present case) was needed to recover to sinus rhythm.

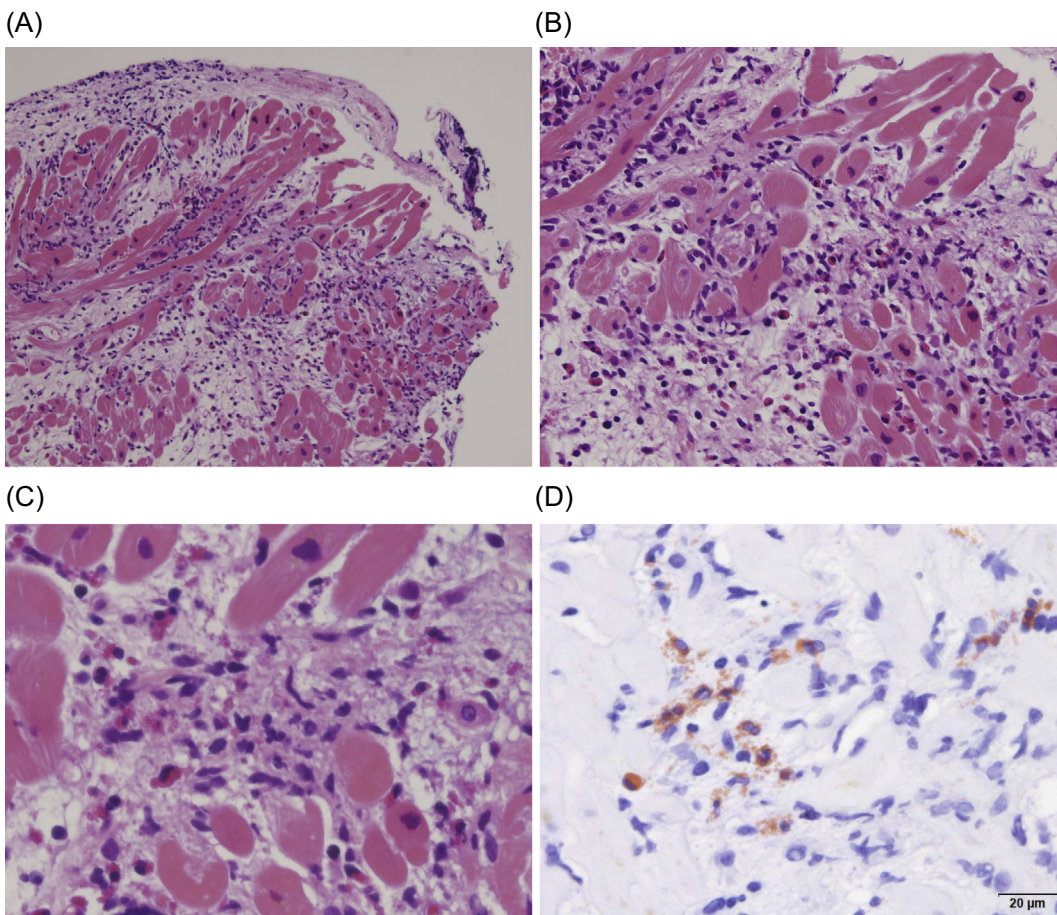


Figure 6. Histological images of an endocardial biopsy. (A, B) Eosinophilia and lymphocyte infiltration and damage to the myocardial muscles (Hematoxylin and Eosin (H&E) staining) (A: $\times 100$, B: $\times 400$). (C, D) Infiltration of eosinophils and degranulation of eosinophil granules (C: H&E staining, $\times 600$, D: direct fast scarlet stain, $\times 600$).

fibrillator (ICD). Myocarditis, congestive heart failure, and ventricular arrhythmic attack did not occur as a result of treatment during a follow-up period of 61 months.

Discussion

In the present case, severe LV dysfunction in addition to

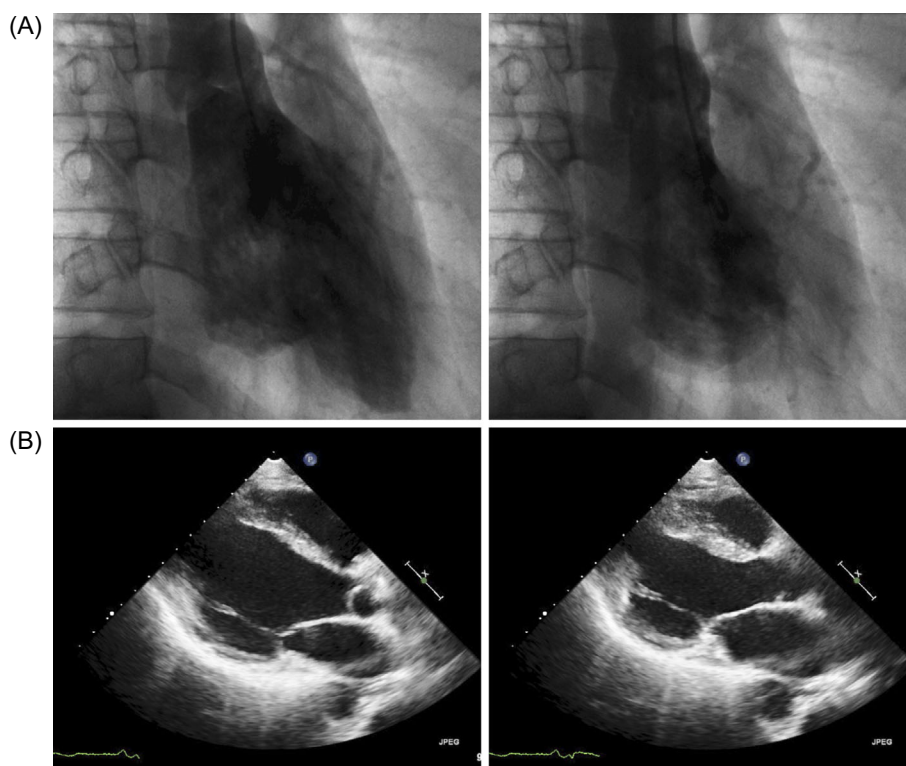


Figure 7. Left ventriculography (LVG) and echocardiography (UCG) performed after recovery. (A) LVG showing a left ventricular ejection fraction (LVEF) of 40.5% with severe inferior-to-posterior wall hypokinesia associated with aneurysmal changes. (B) UCG showing improvement in the LV function. Inferior to posterior wall hypokinesia remains associated with the thinning of the LV wall.

episode of VT and high-degree A-V block continued for several days despite IABP and PCPS support due to acute fulminant EM. Steroid therapy after the histological diagnosis of EM improved the LV function. However, severe hypokinesia with thinning of the inferior-to-posterior wall of the LV and non-sustained VT remained in the long term.

As mentioned previously, EM is a rare form of myocardial inflammation characterized by eosinophilic infiltration that is often accompanied by peripheral eosinophilia (1, 2, 10, 11). The disease is often fatal, with high in-hospital mortality rates, particularly when it presents in the fulminant form (1, 3, 4, 12). Patients with fulminant myocarditis have an increased risk of mortality compared to patients with non-fulminant myocarditis and often require mechanical circulatory support, including PCPS and ventricular assist devices, as well as heart transplantation (13). The present patient had a decreased blood pressure and cardiac function despite receiving IABP and PCPS. Furthermore, both VT and A-V block occurred frequently. Although we had treated him under the diagnosis of fulminant myocarditis, his clinical course was very serious.

Despite this serious clinical course, the patient's peripheral eosinophil count was within the normal range (14, 15). This meant that we were unable to arrive at a diagnosis of EM until a histological analysis of his myocardial biopsy sample revealed eosinophilic infiltration into the myocardium. Brambatti et al. reported that peripheral eosinophilia is absent in up to 25% of the patients with EM and that this

fact probably contributes to the underdiagnosis of EM without an endomyocardial biopsy and the high rate of a diagnosis only after sudden death (1). In that report, only 5 of 39 (12.8%) patients without eosinophilia at admission developed peripheral eosinophilia between the second and sixth days of hospitalization (1). Morimoto et al. also reported that the initial eosinophil count was $<500/\text{mm}^3$ in 50% of the patients with EM, and the reason why eosinophilia is not present in the peripheral blood in some patients with EM may be that peripheral blood eosinophils migrate into the tissues, with the bone marrow unable to respond immediately with increased production (14). In addition, the steroid therapy administered after days 5 might have reduced the percentage of peripheral eosinophils and thereby masked the elevation of the eosinophil count in the present case (4, 16).

An endomyocardial biopsy is the gold standard for diagnostic testing (7, 8, 17). Indeed, an endomyocardial biopsy revealed EM in the present case, leading to steroid therapy that ultimately improved the patient's LV dysfunction. In the long term, a histological analysis of an endomyocardial biopsy sample revealed no eosinophilia.

UC is a severe disease with many extra-colonic manifestations, such as skin involvement, rheumatic problems, and ocular complications. The frequency of myocarditis associated with UC has been studied only rarely, but there appears to be a high risk of mortality in these patients (5, 6). The mechanisms of myocarditis associated with UC have not

been fully elucidated. Controversy surrounds whether steroid therapy is always necessary for the treatment of EM (1). In contrast, some reports have shown that the treatment of myocarditis with and without eosinophilia associated with UC is focused and effective for the management of UC, often using steroid therapy and/or immunosuppression therapy along with heart failure therapy (6, 18). Previous reports have also demonstrated that steroid therapy is a frequently used and effective treatment for EM patients with UC (6). In the present case, steroid therapy may have been effective for the treatment of both EM and UC. A prompt diagnosis and treatment can lead to the resolution of cardiac dysfunction in these cases.

Eosinophilic infiltration to the myocardium has been described as a hypersensitivity response induced by a variety of causes, including drugs, parasitic infections, and neoplasia (1). EM is frequently encountered in autoimmune disorders, such as Churg-Strauss syndrome and Löffler's disease (19). 5-ASA, also known as mesalamine or mesalazine, and its derivatives remain key in the treatment of UC and provide disease-free maintenance therapy (20). However, some reports have revealed that the use of medications containing 5-ASA may cause a rare but potentially lethal side effect involving inflammation in the form of myocarditis or pericarditis (21, 22). In the present case, the patient had previously been treated with 5-ASA, and we were unable to completely rule out the possibility of 5-ASA-associated EM. However, before admission, the patient had been treated with 5-ASA for 15 years without experiencing any 5-ASA-induced complications. The key distinguishing feature of 5-ASA-induced inflammation is the appearance of symptoms and signs shortly after the initiation of 5-ASA therapy (21). It should also be noted that the discontinuation of treatment for UC can induce severe complications, such as the bleeding from the colon seen in the present case. Furthermore, the UC had not worsened under treatment with 5-ASA and steroid therapy. The patient had cold-like symptoms 2 days before the onset of the remaining symptoms, and his symptoms had failed to resolve by 11 days after admission despite the discontinuation of 5-ASA administration. These facts suggested the possibility that the EM was triggered by an infection and associated with UC rather than hypersensitivity to 5-ASA.

Intravenous immunoglobulin has been used to treat several autoimmune or inflammatory diseases. Some reports have demonstrated the effectiveness of intravenous immunoglobulin therapy against fulminant myocarditis (23). Although intravenous immunoglobulin was also used in some cases with EM, its effectiveness in this respect is still unclear (16, 17). The present patient was diagnosed with fulminant myocarditis, and intravenous immunoglobulin was started on the admission day. However, there was no obvious improvement of the LV dysfunction. Therefore, whether or not intravenous immunoglobulin is effective for EM should be investigated in the future.

EM often present in the fulminant form, with abrupt im-

pairment of the LV function and a high risk of malignant arrhythmia (1). Many of these patients experience complete recovery of their cardiac function before discharge (1, 24). In the present case, the patient's myocardial damage persisted, and non-sustained VT occurred. The patient's LV dysfunction lasted for 15 days after admission, resulting in potentially severe myocardial damage due to inflammation. In patients complicated with LV dysfunction due to myocarditis, it is important to determine whether or not chronic myocarditis remains.

In conclusion, the details of this case report suggest that patients with EM should be carefully treated and followed-up to ensure that the long-term outcomes are satisfactory.

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

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