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Case Reports

Fulminant Myocarditis in Patients With Autoimmune Disease That Requires Extracorporeal Membrane Oxygenation Support

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Abstract

Myocarditis is a potentially life-threatening inflammatory disease of the myocardium, often resulting from infectious and immune-mediated responses. Clinical presentation in severe cases often results in a devastating illness requiring extracorporeal membrane oxygenation support as a result of cardiogenic shock. Although endomyocardial biopsy is still considered the gold standard for diagnosis, it often reveals nonspecific lymphocytic infiltration. Because the precise cause is usually unknown, the initial treatment typically involves immunosuppression and frequent assessment of myocardial contractility. This report presents 3 rare cases of autoimmune diseases (polymyositis, immunoglobulin G4–related disease, and systemic lupus erythematosus) that require extracorporeal membrane oxygenation support as a result of fulminant myocarditis, including their follow-up periods.

Keywords: myocarditis; autoimmunity; extracorporeal membrane oxygenation; immunosuppression therapy; connective tissue diseases; polymyositis; lupus erythematosus, systemic; immunoglobulin G4-related disease

Introduction

Myocarditis is an inflammatory condition of the heart muscle that can be caused by various infectious or noninfectious factors, including autoimmune reactions. Though most cases present with mild, nonspecific symptoms, some patients may experience severe acute heart failure (HF) and require extracorporeal membrane oxygenation (ECMO) support.[1] This article describes 3 unusual cases of autoimmune-mediated myocarditis, exploring their unique symptoms, clinical progression, diagnostic challenges, and subsequent treatment.

Case 1: Polymyositis

A 44-year-old male patient who was a professional soldier and had a body mass index of 28 presented with progressive muscle weakness in his lower extremities that progressed to whole-body weakness over the next 3 months. During his initial examination, the laboratory results showed only a minor increase in hepatic enzymes. Because of this unusual clinical presentation, the patient was scheduled for cardiac magnetic resonance imaging, and a biopsy of the quadriceps muscle was suggestive of polymyositis. The diagnosis was confirmed by laboratory findings,

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which showed strong positivity of antinuclear antibodies and anti–signal recognition particle autoantibodies. To rule out malignancy, investigations were conducted, including positron emission tomography, which did not confirm paraneoplastic syndrome.

Despite first-line immunosuppression (prednisone and azathioprine), the patient's condition worsened, and he began to experience progressive dysphagia and persistent fevers. He was admitted to the emergency department 3 months after immunosuppression because of chest pain and dyspnea and was diagnosed with acute HF. Initial transthoracic echocardiography revealed a dilated left ventricle, with an end-diastolic diameter of 69 mm and a left ventricular ejection fraction (LVEF) of 15%. Despite supportive treatment, he soon progressed to cardiogenic shock and needed cardiopulmonary resuscitation, with the return of spontaneous circulation after 10 minutes. He was quickly transferred to an ECMO center, where peripheral venoarterial ECMO was initiated. Following a massive lymphocytic infiltration observed in the endomyocardial biopsy, the patient was prescribed methylprednisolone (1.5 g for 3 consecutive days for a total of 4.5 g) (Fig. 1A, Fig. 1B). Despite early immunosuppression, his LVEF remained at 15%

Key Points

- Despite the presence of chronic autoimmune disease and cardiogenic shock, the prognosis for patients with myocarditis appears to be favorable.
- For young patients with systemic autoimmunity who are not suitable candidates for heart transplantation—that is, patients for whom LVEF does not improve with immunosuppression—LVAD destination therapy can be offered.
- Repeated endomyocardial biopsy should be considered in patients for whom the initial endomyocardial biopsy result was inconclusive despite high clinical suspicion of myocarditis.

Abbreviation/Acronym, Full Term

ECMO, extracorporeal membrane oxygenation
HF, heart failure
IgG4, immunoglobulin G4
IVIG, intravenous immunoglobulin
LVAD, left ventricular assist device
LVEF, left ventricular ejection fraction
OHT, orthotopic heart transplantation
RV, right ventricle; right ventricular
SLE, systemic lupus erythematosus
VT, ventricular tachycardia

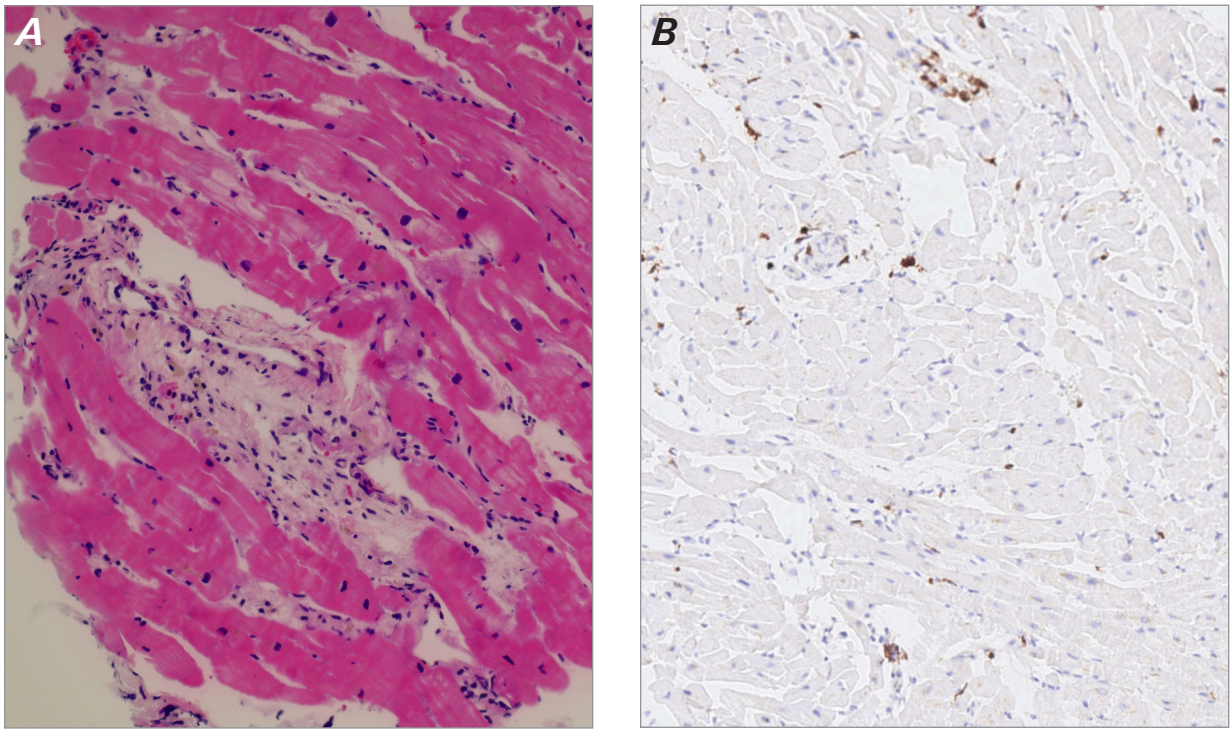

Fig. 1 Images related to case 1 include (**A**) endomyocardial biopsy photomicrographs obtained from right ventricle showing lymphocytic infiltration (33/mm^2) (hematoxylin-eosin, original magnification ×40) and (**B**) immunohistochemical staining demonstrating CD3-positive T lymphocytes consistent with lymphocytic myocarditis (hematoxylin-eosin, original magnification ×25).

after 10 days, rendering ECMO weaning impossible. Following the advice of his specialist, the patient was given intravenous immunoglobulins (IVIG) at a dose of 10 g/kg per day for 2 consecutive days. Gradual clinical improvement was observed, starting with the return of muscle strength and followed by a slow resolution of dysphagia with decreasing myoglobin levels.

Following IVIG treatment, weaning from ECMO was successful on day 23, with an LVEF of 37%. Eleven months after being discharged, the patient is doing well and has resumed his routine daily activities. Because of HF and physical weakness, however, he no longer serves as an active-duty soldier.

Case 2: Immunoglobulin G4–Related Disease

A 34-year-old male patient (body mass index = 18) with type 2 myotonic dystrophy and a 10-year history of immunoglobulin G4 (IgG4)–related disease presented at the emergency department with recurrent ventricular tachycardia (VT). His IgG4-related disease primarily involved his liver, biliary tract, and pancreas and was successfully controlled with 5 mg oral prednisone. His father and grandfather had hereditary type 2 myotonic dystrophy, manifesting only as prolonged muscle fatigue after exercise.

In 2022, the patient began to experience recurrent VT that required multiple hospital admissions; these episodes were initially terminated using various antiarrhythmic agents, including amiodarone, sotalol, and flecainide, though without long-term success (Fig. 2A). Multiple attempts to use radiofrequency catheter ablation to terminate VT were unsuccessful. A stellate ganglion block was also attempted, but it was not adequate to prevent recurring VT. As a result, a primary prevention implantable cardioverter-defibrillator was placed. At each hospitalization for VT, the patient's LVEF was initially substantially reduced (LVEF, 25%) and returned to normal within 2 days, suggesting tachycardia-induced cardiomyopathy.

Despite multiple readmissions over the next 2 years, the patient's VT remained poorly controlled. The last episode of VT became unresponsive to internal or external defibrillation and resulted in cardiac arrest requiring extracorporeal cardiopulmonary resuscitation, initially considered a bridge to recovery. Peripheral venoarterial ECMO was initiated, followed by endomyocardial biopsy, which revealed multiple areas of fibrosis but was inconclusive for myocarditis at the time. As part of the differential diagnosis, IgG4-related disease was also considered as a cause of acute HF, but endomyocardial biopsy revealed only occasional IgG4 deposition in plasmatic cells and was therefore negative (Fig. 2B). After not meeting echocardiographic criteria and negative findings on previous magnetic resonance imaging (showing preserved right ventricular [RV] ejection fraction without regional RV dyskinesia or dyssynchronous RV contraction), RV arrhythmogenic dysplasia was also improbable (Fig. 2C). The present fibrosis on endomyocardial biopsy could be explained by scarification as a result of repeated radiofrequency catheter ablation. Initial echocardiography revealed severe biventricular failure while the patient was on ECMO. There was no pericardial involvement at any time during hospitalization. Despite combined inotropic support, ejection fraction did not improve for either ventricle by day 14.

The patient was therefore transferred to the National Institute for Cardiovascular Diseases in Slovakia, and escalation to a biventricular assist device was undertaken. He was deemed ineligible for heart transplantation because of the presence of IgG4-related disease and was offered an LV assist device (LVAD) as destination therapy, instead. Before the LVAD surgery, another endomyocardial biopsy showed massive chronic lymphocytic infiltration consistent with lymphocytic myocarditis (Fig. 3A, Fig. 3B). The HeartMate 3 (Abbott Laboratories) LVAD was ultimately implanted (Fig. 3C). The patient spent an additional 6 months in the intensive care unit as a result of multiple complications related to long-term intensive care stays and was released from the hospital after 9 months. He has been alive for a year since leaving the hospital and is now able to walk and perform basic daily activities independently.

Case 3: Systemic Lupus Erythematosus

A 36-year-old female patient (body mass index = 19) with a 9-year history of primary Raynaud phenomenon affecting the fingers of both hands presented at the hospital with progressive dyspnea for the previous 2 days. No previous rheumatologic investigation of the patient's case of Raynaud phenomenon had been carried out. She did not report taking any chronic medications.

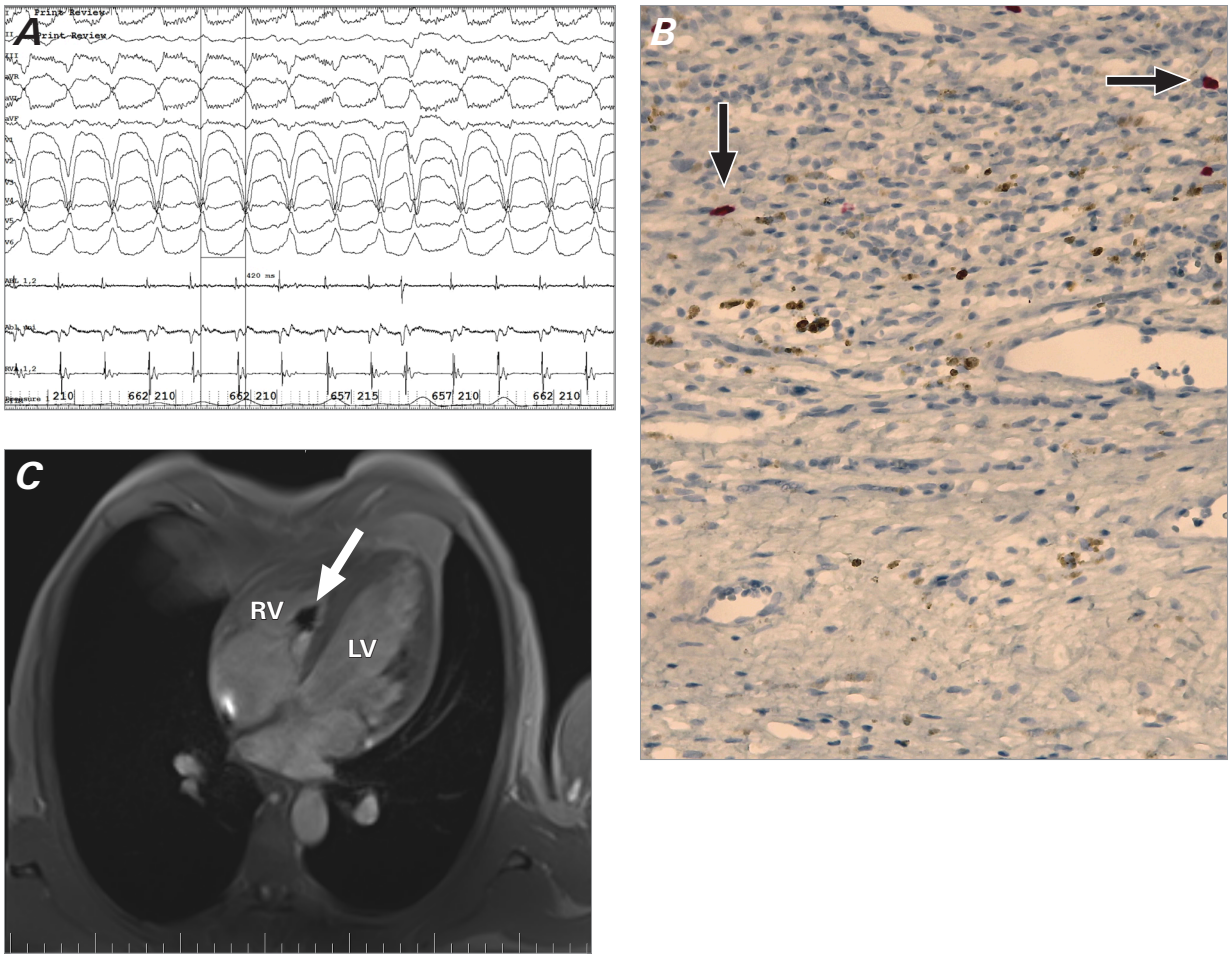

Fig. 2 Images related to case 2 include (**A**) an electrocardiogram showing induced monomorphic ventricular tachycardia during repeated radiofrequency catheter ablation; (**B**) endomyocardial biopsy photomicrographs obtained from the right ventricle showing occasional IgG4 positivity in plasma cells (red chromogen, original magnification ×25), with arrows pointing at scarce IgG4 deposition in the ventricle; and (**C**) a cardiac magnetic resonance T2-weighted image (4-chamber view) 3 years before development of cardiogenic shock, showing borderline left ventricular dilatation with preserved ejection fraction, with an arrow showing implantable cardioverter-defibrillator electrode.

IgG4, immunoglobulin G4; LV, left ventricle; RV, right ventricle.

Upon admission to the hospital, she tested positive for COVID-19. A polymerase chain reaction test revealed a high viral load, with a cycle time of 17. Two years before this hospital admission, the patient had been vaccinated with 2 doses of messenger RNA SARS-CoV-2 vaccine (Pfizer-BioNTech). At admission, her vital signs revealed sinus tachycardia of 100/min; blood pressure of 92/50 mm Hg; and peripheral saturation of 95% while breathing room air, with chest auscultation revealing bilateral crackles suggestive of pulmonary edema. Echocardiography showed a substantially reduced LVEF of 15%, with a normal LV end-diastolic diameter of 48 mm (Fig. 4). Right ventricular function was preserved, with an RV end-diastolic diameter of 26 mm and a tricuspid valve annular plane systolic excursion of 20 mm.

Within 24 hours, the patient's hemodynamics rapidly deteriorated, and she soon required mechanical ventilation and peripheral venoarterial ECMO support. Endomyocardial biopsy showed that there was myocytic necrosis along with lymphocytic infiltration, as demonstrated in Figure 5A and 5B. COVID-19–related myocarditis was initially suspected but not probable because her interleukin 6 levels were normal (10.6 pg/mL). Remdesivir was therefore not administered because the only symptoms present were related to cardiovascular failure. Instead, pulse methylprednisolone

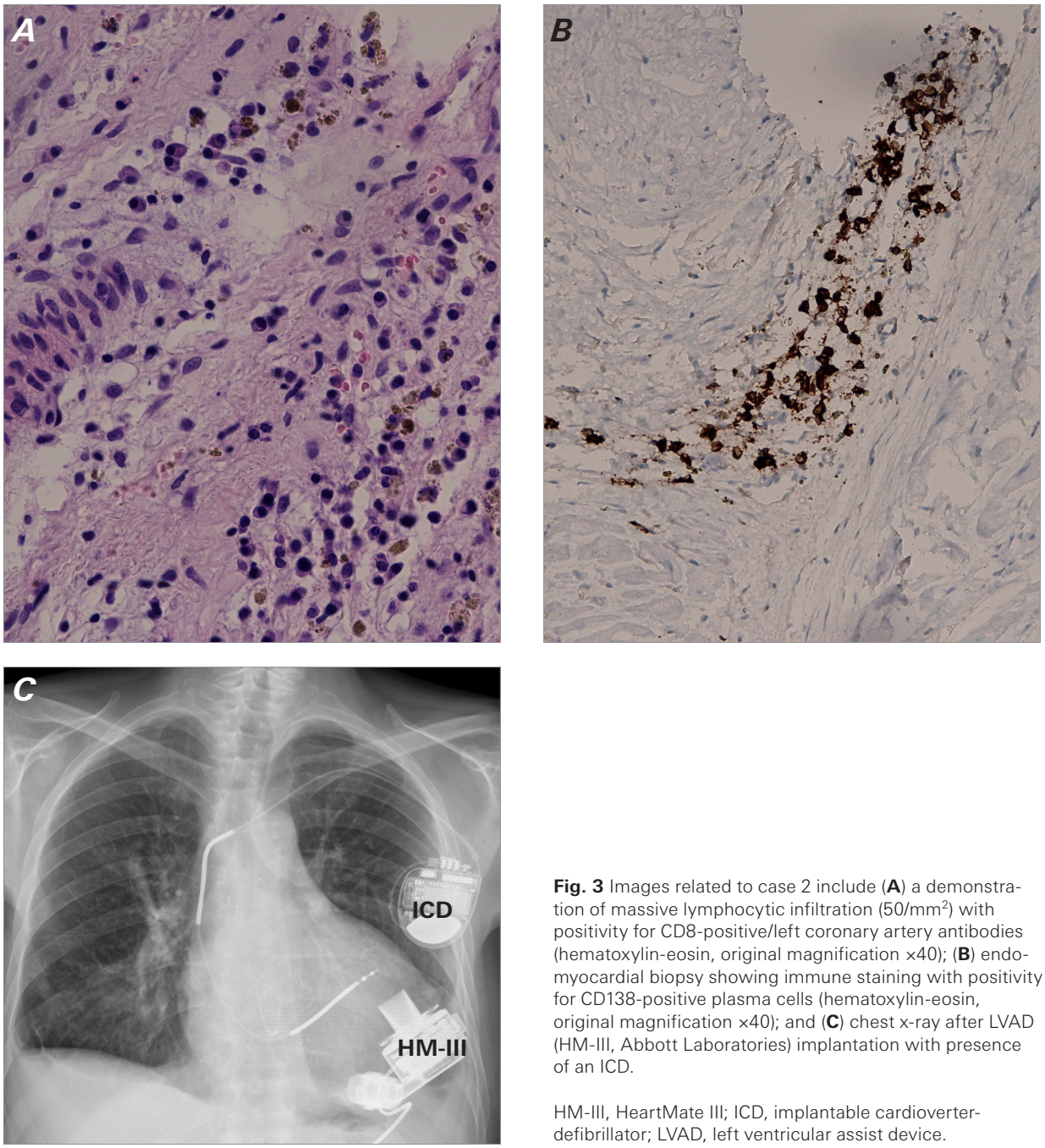

Fig. 3 Images related to case 2 include (**A**) a demonstration of massive lymphocytic infiltration (50/mm^2) with positivity for CD8-positive/left coronary artery antibodies (hematoxylin-eosin, original magnification ×40); (**B**) endomyocardial biopsy showing immune staining with positivity for CD138-positive plasma cells (hematoxylin-eosin, original magnification ×40); and (**C**) chest x-ray after LVAD (HM-III, Abbott Laboratories) implantation with presence of an ICD.

HM-III, HeartMate III; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device.

treatment (1 g/d over 3 days) was given soon after the endomyocardial biopsy. With this treatment, the patient's LVEF improved substantially, from an initial 15% to 50% within the next 7 days. Afterward, she was successfully weaned off ECMO without experiencing any further complications. Her laboratory results were positive for antinuclear antibodies and anti–double-stranded DNA antibodies, indicating systemic lupus erythematosus (SLE). Oral immunosuppression therapy (prednisone and azathioprine) was introduced, and the patient was discharged from the hospital after 7 days. During her 1-year follow-up, she reported only mild exertional fatigue.

For all patients, a polymerase chain reaction screening for infectious agents yielded negative results for common pathogens, including adenovirus, borreliosis, enterovirus, Epstein-Barr virus, human herpesvirus

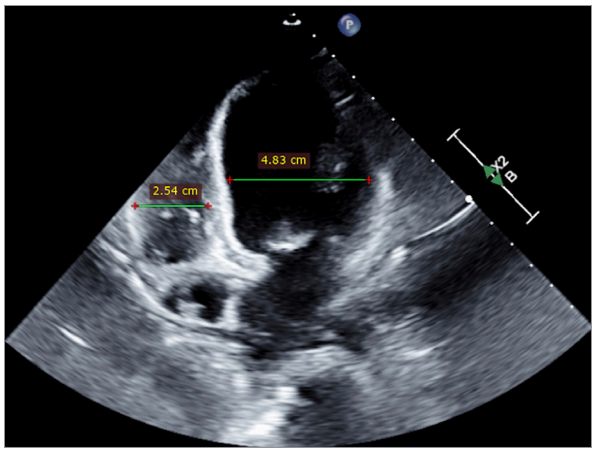

Fig. 4 A transthoracic echocardiogram with an apical 4-chamber view for case 3 shows a left ventricular end-diastolic diameter of 48 mm, with a poor left ventricular ejection fraction of 15% and preserved right ventricular function before initiation of venoarterial extracorporeal membrane oxygenation.

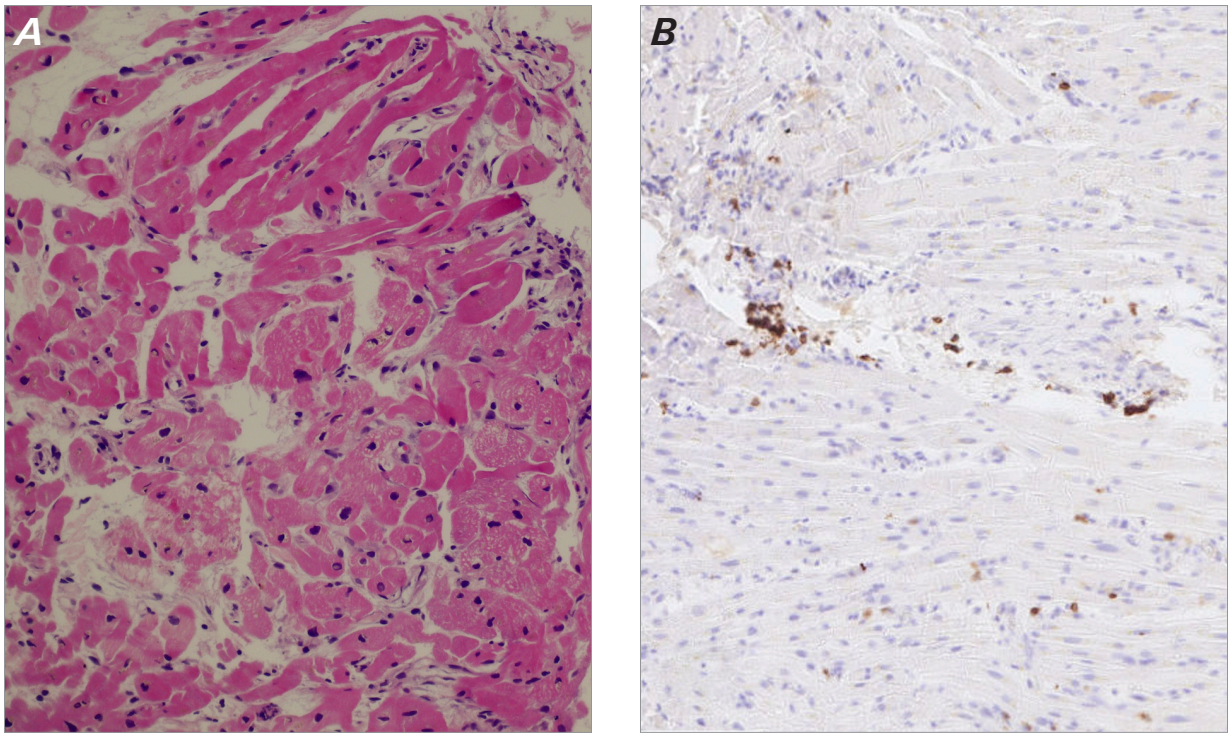

Fig. 5 Images related to case 3 include (**A**) endomyocardial biopsy photomicrographs obtained from the right ventricle, showing lymphocytic infiltration (hematoxylin-eosin, original magnification ×40) and (**B**) immunohistochemical staining demonstrating CD3-positive T lymphocytes consistent with lymphocytic myocarditis (hematoxylin-eosin, original magnification ×25).

type 6, herpes simplex virus types 1 and 2, and parvovirus B19. Laboratory parameters, hemodynamics, and results from endomyocardial biopsy for all patients are presented in Table I. The timeline for all 3 cases is shown in Figure 6.

Discussion

Myocarditis is an inflammatory process of the myocardium; it has an incidence of up to 10 cases per 100,000 persons per year, involving predominantly younger adults.[1] Its clinical presentation can vary from cold-like symptoms to severe HF and even death. Although the precise etiology is often unknown, histologic evidence of autoimmunity was present in 9% to 16% of unexplained dilated cardiomyopathies.[2] Although favorable outcomes have been reported for patients with SLE that requires ECMO support, literature on patients with polymyositis and IgG4-related disease that requires ECMO support is scarce.[3]

TABLE I. Laboratory and Hemodynamic Parameters for All 3 Patients

	Case 1: polymyositis	Case 2: IgG4-related disease	Case 3: SLE
Parameter			
Troponin I, ng/L	5.610	83	14.690
Creatine kinase, μkat/L	41	2	28
Creatine kinase dimer of M and B chains, μg/L	150	5	161
Aspartate aminotransferase, μkat/L	123	1.7	22
Alanine aminotransferase, μkat/L	77	4	16
Myoglobin, μg/L	2.246	–	–
C-reactive protein, mg/L	251	–	1.9
Procalcitonin, μg/L	4.7	0.7	0.1
White blood cell count, $\times 10^9$/L	16	17	21
Autoantibodies			
Type of autoantibody	Antinuclear antibody ++	IgG4 +++	Antinuclear antibody +++
	Anti–signal recognition particle +++	(18 g/L)	Anti–double-stranded DNA +
Hemodynamics			
Cardiogenic shock	Yes	Yes	Yes
LVEF at admission, %	15	10	15
LVEF at ECMO weaning, %	37	–	50
Recovery	Yes	No	Yes
Extracorporeal cardiopulmonary resuscitation	Yes	Yes	No
ECMO runtime, d	23	16	14
Histopathology			
Infiltration	Lymphocytic	Lymphocytic[a]	Lymphocytic
Subtype	CD3 positive	CD8 positive/leukocyte common antigen	CD3+
		CD138	
Lymphocyte count, /mm^2	33	50	N/A
Eosinophils	No	No	No
Giant cells	No	No	No
Conclusion	Lymphocytic myocarditis	Lymphocytic myocarditis	Lymphocytic myocarditis

ECMO, extracorporeal membrane oxygenation; IgG4, immunoglobulin G4; LVEF, left ventricular ejection fraction; N/A, not applicable; SLE, systemic lupus erythematosus.

SI conversion factor: To convert ng/L to μg/L, multiply by 0.001. To convert μg/L to nmol/L, multiply by 0.05814.

[a] Chronic lymphocytic infiltration confirmed on second endomyocardial biopsy.

The gold standard in diagnosing myocarditis remains endomyocardial biopsy, which usually shows nonspecific lymphocytic infiltration with associated cardiomyocytic injury. As part of the differential diagnosis for the case report of the patient with IgG4-related disease, it was important to rule out HF caused by IgG4 deposition in the myocardium. Red chromogen staining, however, revealed only occasional IgG4 positivity in plasma cells, indicating a negative result. The first endomyocardial biopsy was negative for myocarditis because of insubstantial lymphocytic infiltration along with abundant fibrosis. This fibrosis was most likely the result of repeated radiofrequency catheter ablation leading to scarification across the RV endomyocardium.

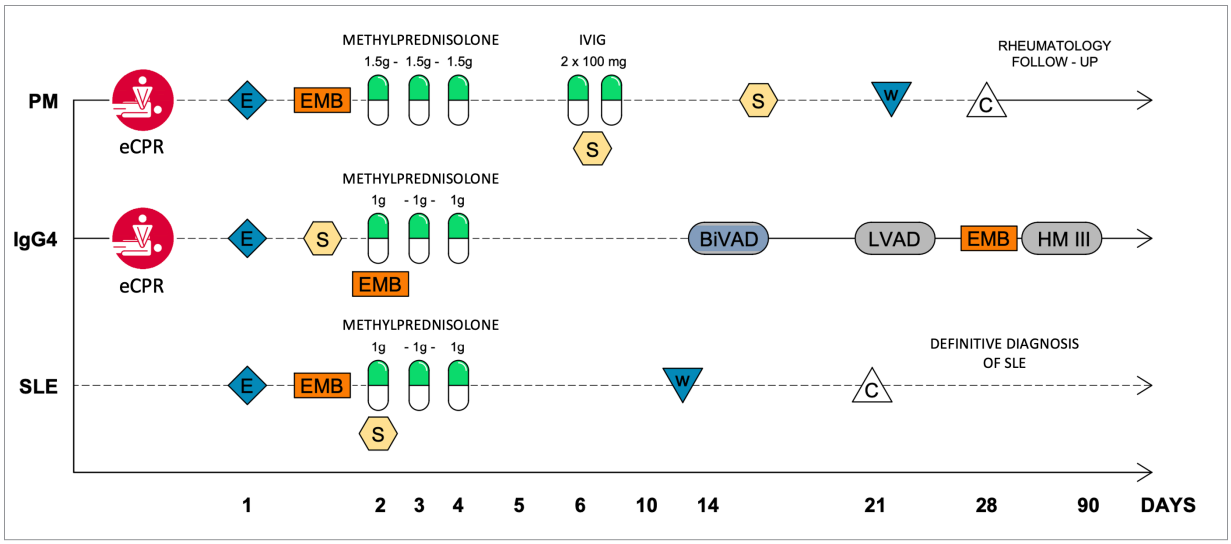

Fig. 6 A timeline shows major interventions and management for all 3 cases.

BiVAD, biventricular assist device; C, transfer to cardiology ward; E, ECMO start; ECMO, extracorporeal membrane oxygenation; eCPR, extracorporeal cardiopulmonary resuscitation; EMB, endomyocardial biopsy; HM III, HeartMate 3 (Abbott Laboratories); IgG4-RD, immunoglobulin G4–related disease; IVIG, intravenous immunoglobulin; LVAD, left ventricular assist device; PM, polymyositis; S, levosimendan; SLE, systemic lupus erythematosus; W, ECMO weaning.

Despite negative findings from the initial endomyocardial biopsy, myocarditis was still strongly suspected because of unexplained acute HF; it was confirmed only on the second endomyocardial biopsy. It is therefore possible that an earlier diagnosis of myocarditis could have been established if repeated endomyocardial biopsy had not been delayed until LVAD surgery.

It is assumed that the primary problem in fulminant myocarditis is the host cytokine storm and the extensive cellular infiltration of heart tissue by the patient's immune system. Immunosuppression as treatment for severe myocarditis is still not well established.[4] The American Heart Association suggests administering methylprednisolone if immune-mediated fulminant myocarditis is suspected, even before biopsy, to improve outcomes.[5] The decision to use corticosteroids alone or in combination with IVIG is also controversial, but studies show that the combination of the 2 may limit excessive immune response better than single agents alone and may improve recovery.[6,7] In the case report of the patient with known polymyositis, combined immunosuppression was associated with successful ECMO weaning. The presence of anti–signal recognition particle antibodies is linked to a poor prognosis in patients with polymyositis. If combined pharmacologic immunosuppression, including IVIG, is not successful, therapeutic plasma exchange to remove pathogenic antibodies remains the last line of treatment.[8]

Although fulminant myocarditis in patients with SLE is rare, it has been reported with favorable outcomes in known and de novo cases.[9] Most cases of severe myocarditis in the COVID-19 pandemic era appear to be associated with messenger RNA vaccination.[10] The patient with SLE whose case was discussed in this report presented with acute HF 2 years after receiving the messenger RNA SARS-CoV-2 vaccine; her myocarditis was therefore likely unrelated to vaccination. Two years ago, she had had COVID-19 but did not require hospitalization; her second COVID-19 episode triggered lymphocytic myocarditis and the appearance of positive SLE autoantibodies.

A combination of active autoimmune disease and fulminant myocarditis that requires ECMO support often precludes these patients from being eligible for orthotopic heart transplantation (OHT). It was found that fulminant onset of acute myocarditis, lower LVEF at presentation, and high-titer organ-specific antibodies were independent predictors of death and OHT, suggesting that autoimmune features predict worse prognosis.[11] Although reports of OHT in patients with autoimmune disease are scarce and clear recommendations are missing, favorable long-term survival for these patients suggests that select candidates can be considered for OHT.[12,13]

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