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CASE REPORT

ADVANCED

CLINICAL CASE

Biopsy-Proven Lymphocytic Myocarditis With Heart Failure in a Middle-Aged Female Patient With Mixed Connective Tissue Disease

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ABSTRACT

A 56-year-old woman with mixed connective tissue disease, who was on maintenance immunosuppression, developed asymptomatic left ventricular dysfunction, ventricular arrhythmia, and high troponin I. Heart catheterization showed normal coronaries and biopsy-proven, virus-negative lymphocytic myocarditis. A biopsy-guided immunosuppression upgrade effectively treated autoimmune myocarditis, which resulted in ventricular function recovery, resolution of arrhythmia, and of troponin release. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2019;1:171–4)

Cardiac involvement in mixed connective tissue disease (MCTD) is common, with an estimated prevalence of 13% to 65%; it is associated with poor prognosis (1–3). Leading mortality causes include accelerated coronary atherosclerosis and myocarditis, which probably reflects the myositis-like features of MCTD (3). The distinction between infectious myocarditis versus noninfectious myocarditis is key, dictating a downgrade or an upgrade of chronic immunosuppression, respectively (1–5).

LEARNING OBJECTIVES

- To be able to make a differential diagnosis of infectious and autoimmune myocarditis in SIDs.
- To identify an etiology-directed therapeutic regimen.

HISTORY OF PRESENTATION

A 56-year-old woman with MCTD was hospitalized due to sudden onset of abdominal pain, vomit, and diarrhea. Standard 12 lead electrocardiography revealed new-onset negative T-waves in the inferolateral leads (**Figure 1A**), increased high-sensitivity troponin I (2,800 ng/l), and mildly elevated brain natriuretic peptide (110 ng/l). No cardiac murmurs were present. Echocardiography showed moderate left ventricular dilation, a severely depressed left ventricular ejection fraction (LVEF) (27%) with diffuse hypokinesis, and mildly reduced right ventricular function, but no valvular dysfunction or pericardial effusion.

MEDICAL HISTORY

Six years before, she had presented with fatigue, arthralgia, Raynaud's phenomenon, and high titer

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ABBREVIATIONS AND ACRONYMS

AHA = anti-heart autoantibodies

AIDA = anti-intercalated autoantibodies

CMR = cardiac magnetic resonance

EMB = endomyocardial biopsy

HRCT = high-resolution chest computed tomography

LVEF = left ventricle ejection fraction

MTP = methylprednisolone

MCTD = mixed connective tissue disease

MMF = mycophenolate mofetil

SID = systemic immune mediated disease

(1 of 1,280) centromere antinuclear, anti-SSA, and anti-U1 ribonucleoprotein autoantibodies. High-resolution chest computed tomography (HRCT) revealed diffuse ground glass areas; pulmonary function was mildly depressed. A diagnosis of MCTD was established; she was treated with oral methylprednisolone (MTP) and intravenous cyclophosphamide (6 500-mg pulses, on weeks 0, 1, and 3, and then monthly for 3 months). Symptoms resolved, and HRCT showed normal findings. The patient was put on maintenance low-dose MTP and hydroxychloroquine. Yearly echocardiographic assessments showed borderline (52%) stable LVEF over the following 5 years. At a subsequent routine cardiology follow-up, a few weeks before hospital admission, echocardiographic LVEF unexpectedly dropped to 34%. Routine 24-h continuous electrographic Holter monitoring, used to detect asymptomatic arrhythmia that is frequent and associated with accelerated coronary atherosclerosis, revealed nonsustained ventricular tachycardia and high premature ventricular ectopic beat burden (Lown grade 4). The patient was apparently asymptomatic, and her cardiovascular physical examination was normal, but coronary angiography was planned. Therapy was not changed due to her stable clinical status and lack of cardiac symptoms.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses included non–ST-segment elevation myocardial infarction in a MCTD patient on long-term steroid therapy and myocarditis with pseudo-infarct presentation, which was either infectious due to background immunosuppression or infectious-negative autoimmune.

INVESTIGATIONS

The patient refused to undergo cardiac magnetic resonance (CMR) due to claustrophobia. Heart catheterization showed severe left ventricular systolic dilation (end-diastolic volume: 164 ml/m^2) and dysfunction (LVEF: 32%), diffuse hypokinesis, normal coronary arteries at selective coronary angiography, mild mitral regurgitation, normal pulmonary artery (peak: 22 mm Hg; mean: 11 mm Hg) and capillary pressures (mean capillary wedge: 9 mm Hg), and a normal cardiac index (3.04 l/min/m^2). Right ventricular endomyocardial biopsy (EMB) showed focal active lymphocytic myocarditis (CD43+, CD3+, and CD68+ lymphomonocyte infiltrates, and focal nonischemic necrosis) with mild interstitial and perivascular fibrosis. Cardiomyocyte hypertrophy and vacuolization with irregular-shaped nuclei and perinuclear halos were also observed (**Figures 1D and 1E**). Polymerase chain reaction for cardiotropic viruses (4) was negative, confirming the diagnosis of chronic active virus-negative lymphocytic myocarditis evolving towards dilated cardiomyopathy. C-reactive protein was elevated. Serum organ-specific antiheart autoantibodies (AHAs) and anti-intercalated autoantibodies were detected by standard indirect immunofluorescence on human heart and skeletal muscle as previously described (6,7), and were strongly positive (**Figures 1B and 1C**), in keeping with the diagnosis of autoimmune myocarditis.

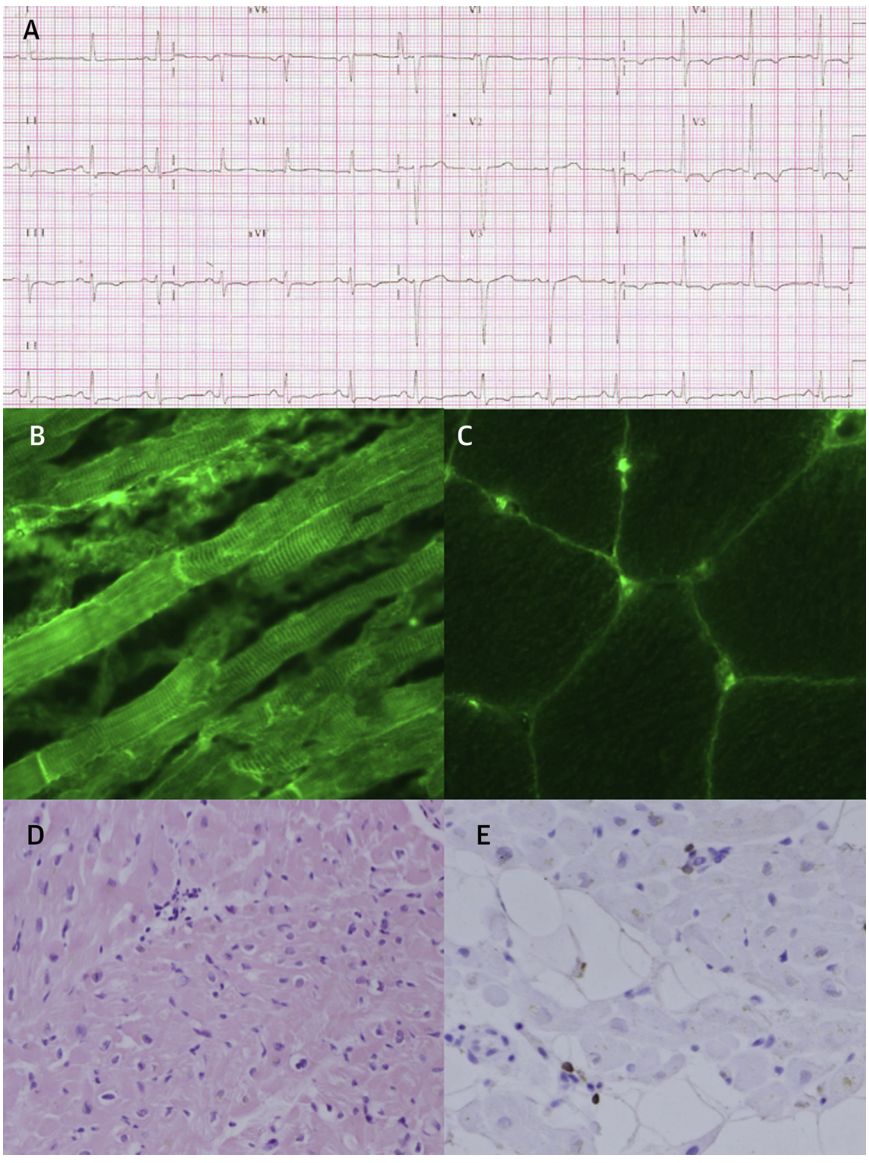
MANAGEMENT

Standard heart failure therapy at discharge included carvedilol 6.25 mg twice daily, ramipril 5 mg twice daily, furosemide 25 mg, eplerenone 50 mg, and amiodarone 200 mg. Immunosuppressive therapy with oral prednisone, 1 mg/kg daily, and mycophenolate mofetil (MMF), 1 g twice daily, was started.

DISCUSSION

In MCTD, as in other systemic immune-mediated diseases (SIDs), the distinction between infectious myocarditis versus noninfectious myocarditis is key, because many patients are already immunosuppressed and susceptible to infectious complications (1). Thus, although autoimmune myocarditis in SIDs requires intensification of immunosuppression, infectious myocarditis warrants reduction and/or discontinuation of immunosuppressive drugs and prompt introduction of targeted anti-infectious therapy (1). This case exemplifies some key diagnostic issues of myocarditis in SIDs. First, its clinical presentation mimicked an acute coronary syndrome, but the rapid clinical deterioration following the acute gastrointestinal syndrome was also compatible with superimposed viral myocarditis (e.g., by enterovirus). EMB in this setting was crucial to confirm clinically suspected myocarditis and to exclude the presence of a viral genome (4,5). Hydroxychloroquine-induced cardiomyopathy was ruled out by EMB histopathological findings. Furthermore, this rare and late complication, which develops an average of 13 years after continuous therapy, seemed unlikely in our patient, who was treated for only 5 years (8). In contrast, latent myocarditis could have been

FIGURE 1 **Key Diagnostic Profile**



(A) Electrocardiogram showing sinus rhythm and negative T waves in inferior and lateral leads. **(B)** Standard indirect immunofluorescence of patient's serum on human heart (×400) and on **(C)** skeletal muscle tissues (×400), giving organ-specific antiheart (AHA) and anti-intercalated disk (AIDA) autoantibody patterns: positive cytoplasmic and fine striational staining of cardiac myocytes (AHA), and strong linear staining of the intercalated disks (AIDA) that were negative on human skeletal muscle tissue. **(D and E)** Right ventricular endomyocardial biopsy showing focal active lymphocytic myocarditis (**D**, hematoxylin eosin ×200; **E**, lymphomonocyte infiltrates CD3+ ×200) with mild interstitial and perivascular fibrosis, cardiomyocyte hypertrophy, and vacuolization with irregular-shaped nuclei.

responsible for the early echocardiographic findings of borderline LVEF. Unfortunately, the patient refused to undergo CMR, which could have provided useful noninvasive clues to distinguish between an ischemic etiology and nonischemic etiology before EMB.

FOLLOW-UP

The patient entered outpatient follow-up. Stable and complete recovery of LVEF (59%) was achieved after 2 years of immunosuppression; the patient remained asymptomatic, without ventricular arrhythmias or an

increase in troponin I. After 2 years, MMF was stopped, leaving the patient on maintenance oral MTP, 2.5 mg/day, carvedilol 6.25 mg twice daily, and ramipril 5 mg twice daily. Amiodarone was stopped because LVEF recovered, no arrhythmia was detected on Holter monitoring, and to avoid potential long-term, drug-induced pulmonary fibrosis. The patient is on regular follow-up as an outpatient. A follow-up EMB was not considered clinically indicated, due to stable clinical and echocardiographic findings and normal troponin levels.

CONCLUSIONS

Myocarditis in MCTD, similar to other SIDs, critically affects prognosis and may be infectious or autoimmune. EMB differentiates between these distinct etiologies and directs the appropriate therapeutic approach. Our case confirmed that the detection of serum AHA was a specific cardiac autoimmunity biomarker in both isolated organ-specific (4,6,7) and SIDs-associated myocarditis (1). To the best of our knowledge, this was the first report of AHA in biopsy-proven autoimmune myocarditis in MCTD. However, AHA can be absent in cell-mediated disease; thus, in myocarditis, the diagnosis of certainty and of its etiology can only be established by EMB.

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KEY WORDS autoimmune, cardiomyopathy, chronic heart failure