When Should We Consider the Diagnosis of Giant Cell Myocarditis? Revisiting “Classic” Echocardiographic and Clinical Features of This Rare Pathology

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Abstract

Objectives: Giant cell myocarditis is a rare and often fatal disorder. According to the American Heart Association, the American College of Cardiology Foundation, and the European Society of Cardiology scientific statements, an endomyocardial biopsy should be done to exclude giant cell myocarditis in unexplained new-onset heart failure of 2 weeks to 3 months duration associated with dilated left ventricle and new ventricular arrhythmias, or Mobitz type II second-degree, or third-degree atrioventricular heart block.

Case Presentations: Two hundred thirty-five heart transplants were performed since May 1993 at the Institut universitaire de cardiologie et de pneumologie de Quebec, Canada. Giant cell myocarditis was found in the explanted hearts of 5 patients. The preoperative diagnosis of giant cell myocarditis was done by endomyocardial biopsy or at the installation of a left ventricular-assisted device. Patients had symptoms of progressive heart failure of subacute onset. Patients consulted at a mean 32 days after the onset of symptoms. Two patients neither had ventricular arrhythmia nor heart block. Two patients had ventricular arrhythmias and heart block; the other patient had symptomatic heart block. All patients had at least 2 echocardiographies. Two patients had an increase in left ventricular size, enough to reach the criteria of left ventricular dilatation according to the American Society of Echocardiography. During this time, left ventricular ejection fraction showed a rapid decline (mean 37% to 16%).

Conclusions: Ventricular arrhythmia, heart block, and left ventricular dilatation initially can be absent in many patients having giant cell myocarditis with symptoms of progressive heart failure. Endomyocardial biopsy should be quickly considered in patients with a rapid and dramatic decline of left ventricular ejection fraction, even in the absence of classic clinical and echocardiographic features of giant cell myocarditis to rapidly obtain the diagnosis of this rare but lethal disease.

Key words: Giant cell myocarditis, Cardiomyopathy, Heart failure, Echocardiography, Endomyocardial biopsy

Introduction

Giant cell myocarditis is a rare autoimmune subtype of myocarditis that shows an aggressive clinical evolution with high mortality rate.1 The clinical course is characterized by refractory congestive heart failure of subacute onset. Half of the time, it is associated with refractory ventricular arrhythmias or high-degree atrioventricular block.1,2 In patients without arrhythmias or block, a high index of suspicion is required for diagnosis. The histologic hallmark of giant cell myocarditis is a polymorphous inflammatory response manifested by many multinucleated giant cells and extensive necrosis.2,3 It is assumed to be a dilated cardiomyopathy.4 To exclude giant cell myocarditis, an endomyocardial biopsy should be done to exclude this rare disease.
biopsy is indicated for patients with refractory heart failure of subacute onset in the presence of left ventricular dilatation, especially if one or more of the following are present: ventricular arrhythmias, malignant atrioventricular block, or failure to respond to usual care within 1 to 2 weeks. Once the diagnosis is made, treatment with immunosuppressive medications may be started. This treatment may be associated with increased survival. However, in most patients, a heart transplant remains the only effective therapy.

In this case series, we review our experience with 5 patients who underwent a heart transplant for giant cell myocarditis. We emphasize their initial echocardiographic findings and clinical presentation.

**Case Presentations**

**Case 1**
A 62-year-old woman presented with heart failure symptoms of 2 months duration. An electrocardiogram showed a right bundle branch block. A heart catheterization showed normal coronary arteries. A transthoracic echocardiography showed a depressed left ventricular ejection fraction (LVEF) of 40%, with normal left ventricular end diastolic dimension (LVEDD) of 43 mm (normal value for women ≤ 53 mm). Eight days after, the LVEF declined to 15%, with no significant LVEDD dilatation (46 mm). She did not experience any ventricular arrhythmias or atrioventricular block. An endomyocardial biopsy was performed, demonstrating an inflammatory infiltrate with giant cells, eosinophilia, and necrosis, diagnostic for giant cell myocarditis. Her worsening clinical status necessitated initiation of extracorporeal membrane oxygenation, and she underwent a successful heart transplant 5 days later. On follow-up, there was no evidence of recurrence on endomyocardial biopsies. Unfortunately, 1.5 years after the transplant, she died from severe pneumonia with multiorgan failure.

**Case 2**
A 53-year-old woman with a history of a biliopancreatic bypass for morbid obesity was admitted with a 3-week history of dyspnea. On initial evaluation, we found a right bundle branch block. A heart catheterization demonstrated chronic total occlusion of the right coronary artery. A transthoracic echocardiography showed a depressed LVEF of 40% without an LVEDD dilatation (43 mm). Two days later, the LVEF worsened to 15% in absence of an LVEDD dilatation (47 mm). Her condition deteriorated to cardiogenic shock and multiorgan failure. Right and left ventricular-assist devices were implanted (HeartMate II, Thoratec Corporation, Pleasanton, CA, USA). A cardiac biopsy was performed, showing polymorphic inflammatory infiltrates with multinucleated giant cells, eosinophilia, and necrosis, which was diagnostic for giant cell myocarditis. Five months after admission, she underwent a successful heart transplant. Six months after the allograft, she had a fatal sudden death at home. The autopsy showed lesions just beside the bifurcation of the bundle of His, in the superior part of the interventricular septum. In one of the lesions, there was the presence of granulation tissue with small lymphocytes and a few giant cells, which was compatible with a recurrence of giant cell myocarditis. Most of the lesions were inactive or scarred. The last endomyocardial biopsy, done 1 month before the patient’s death, was normal.

**Case 3**
A 55-year-old man with type 2 diabetes consulted in a peripheral medical center for dyspnea, diaphoresis, and light-headedness of 2 days duration. During hospitalization, he developed a complete atrioventricular block and was implanted with a permanent DDDR pacemaker. Heart catheterization showed nonsignificant stenosis of the left anterior descending artery. Transthoracic echocardiography revealed a mild systolic left ventricular dysfunction, with normal LVEDD of 53 mm (normal value for men ≤ 59 mm). He was given medical treatment for coronary artery disease and was discharged.

One month later, he was seen for retrosternal chest pain, heart palpitations, and progressive heart failure. On heart monitoring, there were frequent episodes of nonsustained ventricular tachycardia. A control echocardiography showed a decrease of LVEF from 50% to 20% with similar LVEDD. An endomyocardial biopsy was performed, showing inflammatory infiltrates with giant cells, eosinophilia, and necrosis, diagnostic for giant cell myocarditis. The patient was treated with methylprednisolone (1 g intravenous × 3 days), rabbit anti-thyroglobulin, tacrolimus, and mycophenolate mofetil. The patient received a biventricular implantable cardioverter defibrillator. Despite immunosuppression, the patient...
experienced persistent and symptomatic ventricular arrhythmias. He underwent a successful heart transplant less than 1 month after the beginning of treatment. There was no recurrence of the disease on follow-up biopsies, and the patient is well 2.5 years after the heart transplant.

Case 4
A 49-year-old man with a history of type 2 diabetes, vitiligo, and Hashimoto’s thyroiditis, was seen for dyspnea of 2 months duration. The results of an initial electrocardiogram were normal. A transthoracic echocardiography showed a depressed LVEF at 20% with an LVEDD of 56 mm. Heart catheterization revealed normal coronary arteries. The patient developed a complete atrioventricular block and was implanted with a cardioverter-defibrillator. An endomyocardial biopsy showed a massive inflammatory infiltrate with giant cells and eosinophilia, diagnostic for giant cell myocarditis. The patient subsequently developed cardiogenic shock and multiorgan failure. One week after admission, there remained severe alteration of the LVEF (20%) and significant progressive LVEDD dilatation (62 mm). The patient underwent a successful heart transplant several days later. There was no sign of recurrence on follow-up biopsies, and 4 years after the transplant the patient is well.

Case 5
A 44-year-old man with no significant medical history was seen for dyspnea, palpitations, and orthopnea of 1 month duration. An echocardiography revealed an LVEF of 35% and an LVEDD of 57 mm. The results of left heart catheterization were normal. The patient’s hospitalization was complicated by episodes of ventricular tachycardia and intermittent complete atrioventricular block. A temporary pacemaker was implanted along with an intra-aortic balloon counterpulsation device. An echocardiography performed 1 week later showed a decreased LVEF of 15% with an LVEDD of 62 mm. A left ventricular assist device (Thoratec Corporation) was implanted. A pathological analysis of the excised heart samples obtained during left ventricular assist device implantation showed polymorphic inflammatory infiltrates with numerous giant cells and eosinophilia, diagnostic for giant cell myocarditis. The patient underwent a successful heart transplant 3 months after his admission. There were no signs of recurrence on follow-up biopsies and 10 years after the heart transplant, the patient is well.

Discussion
Giant cell myocarditis is a rare but frequently fatal pathology. Initially included under the more general term granulomatous myocarditis, in 1956 Tesluk first distinguished it from sarcoidosis. Since then, a little more than a 100 cases have been reported in the literature. Giant cell myocarditis is believed to be an autoimmune disease. This is supported by animal experimental models, and by the fact that about 20% of patients have an associated autoimmune condition: mainly inflammatory bowel diseases (8%), thymoma, myasthenia gravis, Hashimoto’s thyroiditis, and rheumatoid arthritis. In humans, some cases have been attributed to the adverse events of drugs.

In this case series, 1 patient had a clear autoimmune background (patient 4 had vitiligo and Hashimoto’s thyroiditis). Most of what we know about this disease comes from experimental animal models obtained by immunizing Lewis rats against myosin. They suggest a central effect of T lymphocytes, but the precise mechanism is unclear.

Giant cell myocarditis usually presents with heart failure of subacute onset (1-3 months) that deteriorates despite medical treatment. Other frequent clinical features include high degree atrioventricular block and ventricular malignant arrhythmias, but these may absent up to 50% of the time. In patients without arrhythmias or a block, a high index of suspicion is required for making the diagnosis. In accordance with previous studies, 40% of the patients included in our report did not experience any arrhythmias or high degree atrioventricular blocks that could have suggested the presence of giant cell myocarditis. Rapid decline of the LVEF over a few days is an important clue when suspecting giant cell myocarditis (Figure 1). One study used contrast ventriculography and radionuclide to compare the evolution of biopsy-proven giant cell myocarditis and lymphocytic myocarditis in 10 patients. In that study, patients with giant cell myocarditis showed a rapid decline in LVEF over several days, which was uncommon in patients with lymphocytic myocarditis.
From a clinical perspective, immunosuppressive treatment is lifesaving for some patients but also can cause severe adverse effects. Accordingly, the diagnosis must be confirmed by endomyocardial biopsy before immunosuppressive treatment is started. Actual guidelines for endomyocardial biopsy in patients with refractory subacute heart failure symptoms requires the presence of left ventricular dilatation. However, in our case series, left ventricular dilatation was absent in a significant proportion of patients (60%).

Recurrence of giant cell myocarditis in the cardiac allograft causes left ventricular dysfunction in one third of all cases. It is usually cured by increasing the patient’s immunosuppression. The prognosis of patients with a heart transplant for giant cell myocarditis is good and similar to that of patients that had an allograft for other indications.

In conclusion, in presence of refractory subacute heart failure, we believe that it is reasonable to perform endomyocardial biopsy in the absence of left ventricular dilatation, especially if the clinical course is marked by a subsequent rapid deterioration of the LVEF, occurrence of malignant ventricular arrhythmias, or atrioventricular blocks.

References