Giant Cell Myocarditis Responding to Immunosuppressive Therapy*

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An unusual case of giant cell myocarditis presenting with cardiogenic shock that dramatically responded to conventional dose of steroids and azathioprine is reported. Cardiac recovery was rapid, complete (left ventricular ejection fraction rose to 55% from 10%), and was accompanied by the disappearance of the inflammatory infiltrates including giant cells in the control endomyocardial biopsy. Maintenance of the recovery at 16 months of follow-up on a low dose of azathioprine suggests that giant cell myocarditis might be a heterogeneous disease having either a negative untreatable trend necessitating cardiac transplantation, or a curable substrate responding to immunosuppressive drugs.

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Key words: giant cell myocarditis; heart failure; immunosuppressive therapy

Abbreviations: EF = ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction

Giant cell myocarditis is a progressive disease of unknown cause that has been reported in subjects aged 6 months to 70 years. This entity has a grim prognosis, as conventional immunosuppressive therapy is usually ineffective and affected patients die in a short time unless a heart transplant is rapidly done. Causes of death include progressive heart failure and sudden death. The authors report the unusual case of a young patient presenting with cardiogenic shock due to giant cell myocarditis that responded dramatically to a combination of steroids and azathioprine maintaining a complete recovery for a long period.

CASE REPORT

A 23-year-old girl was admitted because of rapidly worsening shortness of breath. Two months before, she had a flu-like syndrome. On admission, she was stable. Tachycardia was present (heart rate, 130 beats/min) with a gallop rhythm; BP was 130/80 mm Hg. The ECG showed low voltages, left anterior bundle branch block, and diffuse ST-T wave abnormalities. Chest radiograph was normal. Routine laboratory tests including glucose, creatinine, BUN, serum electrolytes, and urinalysis were within normal limits. Erythrocyte sedimentation rate was 108 mm/h at the first hour. C-reactive protein was 187.5 mg/L. Blood cell count revealed a leukocyte count of 10.9 × 10^9/L with 80% neutrophils. The echocardiogram showed normal cardiac dimensions and mild reduction of left ventricular [LV] contractility (ejection fraction [EF] of 45%).

Three days later, the patient had a clinical deterioration with worsening of dyspnea and severe hypotension (BP 70/40 mm Hg). A new echocardiogram revealed LV dilatation of 61 mm, with marked impairment of LV contractility (EF, 10%). The patient underwent an invasive cardiac study including cardiac catheterization, LV (Fig 1, left) and coronary angiography, and LV endomyocardial biopsy with extraction of three good-sized tissue samples that were processed for histology following standard techniques and stains (hematoxylin-eosin, Miller’s elastic Van Gieson, and Masson’s trichrome). Coronary angiography was normal.
normal, LV end-diastolic pressure was elevated (25 mm Hg), and LV function was extremely compromised. The histology showed in all samples the presence of extensive inflammatory infiltrates mainly represented by lymphocytes, histiocytes, eosinophils, and multinucleated giant cells in close apposition to injured myocytes (Fig 2, top). No epithelioid histiocytes or distinct granulomas were observed on several sections so that sarcoid and granulomatous myocarditis were ruled out, while a diagnosis of giant cell myocarditis was established. At immunohistochemistry, giant cells stained for the macrophage marker CD68 but not for the muscle markers actin and desmin, suggesting the macrophage origin of giant cells. Serologic tests for cardiotropic viruses (echovirus, Coxsackievirus B, cytomegalovirus, adenovirus, influenza, and parainfluenza viruses) were negative. Antinuclear, anti-DNA, anticiardioplin, antineutrophil cytoplasmic antibody, anti-extractable nuclear antigens antibodies, circulating immune complexes, C3c, and C4 were within the normal range. Patient serum was also tested for cardiac autoantibodies by standard indirect immunofluorescence as previously described, showing a strong positivity with diffuse cytoplasmic immunofluorescence staining of myocytes (antibodies titer, 1/40). The patient received IV prednisolone, 7 mg/kg for 3 days, followed by prednisone, 1.5 mg/kg/d orally for 2 weeks tapered to 1 mg/kg/d for 4 weeks. On day 7 after the beginning of therapy, the patient had a visible improvement of symptoms, with reduction of heart rate to 70 beats/min and disappearance of gallop rhythm. The echocardiogram showed an increase of LV function (left ventricular ejection fraction [LVEF], 30%). After 6 weeks of therapy, the ECG showed an increase of voltages with disappearance of conduction and repolarization abnormalities, the echocardiogram revealed a reduction of LV dimension (LV dilatation, 56 mm), and a marked improvement of LV contractility (LVEF, 55%). A new cardiac catheterization including LV angiography and endomyocardial biopsy was performed. LV end-diastolic pressure (10 mm Hg) and LV function (Fig 1, right) normalized, and biopsy showed a healed myocarditis with the disappearance of inflammatory infiltrates, including giant cells, and focal replacement fibrosis (Fig 2, bottom). On the basis of hemodynamic and histologic findings, prednisone was reduced to 0.33 mg/kg/d and azathioprine, 2 mg/kg/d, was included in the treatment. After 6 months, steroids were tapered and withdrawn. Azathioprine from the sixth month was reduced to 1 mg/kg/d. At 16 months of follow-up, the patient is receiving maintenance low doses of azathioprine, and is still asymptomatic with normal cardiac volumes and function.

**Discussion**

Giant cell myocarditis is a rare disorder presenting with progressive heart failure or in up to 50% of cases with sudden cardiac death. It is usually an untreatable disease, and affected patients are rapidly forwarded to cardiac transplantation as soon the diagnosis is established through endomyocardial biopsy. Unfortunately, the disease recurs in the transplanted heart in as many as 24% of cases, although it may respond to augmentation of immunosuppression, suggesting an autoimmune pathogenetic mechanism.

Successful treatment of severe heart failure due to giant cell myocarditis has been rarely reported, while no histologic study after clinical recovery has ever been obtained in the responders. Indeed, histologic confirmation of myocarditis being healed is crucial to tapering of the immunosuppression dose, lessening the risk of inflammatory recurrences.

In this report, the authors describe a dramatic recovery of cardiac volume and function (LVEF, 55% from 10%) in a young patient with cardiogenic shock and giant cell
myocarditis who was treated by a conventional immuno-suppressive treatment. In particular, steroids and azathioprine were administered at the usual dose while cyclosporine, an additional component of the immunosuppressive regimen normally unable to control the disease, was not included in the treatment. Moreover, patient recovery was accompanied by the disappearance of inflammatory infiltrates including giant cells at a repeated cardiac biopsy, and finally a full cardiac recovery was maintained on a low dose of azathioprine at 16 months of follow-up. These observations suggest giant cell myocarditis might be a heterogeneous disease having either a curable or an untreatable substrate. It can be argued that a sarcoid or a granulomatous myocarditis (such as Wegener’s disease or Churg-Strauss syndrome, commonly more susceptible to immunosuppression than giant cell myocarditis) might have been missed. However no systemic manifestation, such as vasculitis, renal and lung disease, nor hematologic (ie, eosinophilia for Churg-Strauss) nor immunologic (ie, antineutrophil cytoplasmic antibody for Wegener’s disease) abnormalities, usually associated with these entities, were documented in our patient. Finally neither epithelioid histiocytes nor distinct granulomatous lesions were observed on several histologic sections of three cardiac biopsies.

On the other hand, additional reports of giant cell myocarditis responding to immunosuppression are currently available.

In conclusion, conventional doses of steroids and azathioprine may relieve in some cases the severe cardiac compromise of a giant cell myocarditis, avoiding the need for a heart transplantation.

References


The Surgical Management of Severe Gastroparesis in Heart/Lung Transplant Recipients*

Olufemi A. Akindipe, MD; John L. Faul, MD; Mark A. Vierra, MD; George Triadafilopoulos, MD; and James Theodore, MD, FCCP

This article describes the use of gastric bypass surgery for severe gastroparesis in two lung transplant recipients. In addition to feeding intolerance, both our patients suffered from severe erosive esophagitis, transfusion-dependent upper GI hemorrhage, and recurrent aspiration pneumonia. They responded poorly to promotility agents and were eventually treated with Roux-en-Y esophagojejunostomy.

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