LETTER TO THE EDITOR

Atypical presentation of idiopathic granulomatous myocarditis mimicking idiopathic giant cell myocarditis: diagnostic, therapeutic and prognostic insights

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Myocarditis is the cause of up to 8% of heart transplants [1]. Specific types of myocarditis as idiopathic giant cell myocarditis (IGCM) and cardiac sarcoidosis (or granulomatous myocarditis, GM) require different management because of the risk of recurrence after transplantation. IGCM and GM are sometimes grouped together, but recently there has been a distinction made between the two on clinical and pathological bases [2]. We describe a case with a clinical course mimicking IGCM, but with histopathological findings of GM in the explanted heart.

A 39-year-old man was referred for cardiac transplantation in September 2004 for severely dilated cardiomyopathy with refractory heart failure.

In 1987 he was treated successfully with mesalazine for ulcerative proctocolitis. Cardiac examination, in 2002, showed no pathological findings. In May 2004, the patient began complaining of asthenia, fatigue and ankle edema with paresthesia of the arms; in June, congestive heart failure was diagnosed because of severely dilated cardiomyopathy with depressed ejection fraction (EF, 20%) and a small amount of pericardial fluid. The coronary arteries were normal. Electrocardiogram (ECG) showed sinus rhythm with low voltage in all leads and incomplete right bundle branch block. He was treated with angiotensin converting enzyme (ACE) inhibitors, diuretics, betablockers and spironolactone. Episodes of sustained ventricular tachycardia were treated with an implantable cardioverter defibrillator, resynchronization therapy, and amiodarone. Laboratory exams showed elevated creatinine phosphokinase (CPK), elevated hepatic markers and lymphocytopenia T. A muscle biopsy excluded peripheral myopathy. The clinical situation deteriorated rapidly and he was transplanted in October 2004. The explanted heart weighted 350 g; the ventricles were dilated; the ventricular walls were 12 mm thick on the left and 7 mm on the right. The myocardium appeared diffusely marbled and multiple irregular greyish-white areas were noted on both the ventricular walls and interventricular septum. The papillary muscles, chordae tendinae, orifices, ostia, valves and coronary vessels were unremarkable. Sections taken from the ventricular walls, septum and atria showed myocyte necrosis, inflammatory cell infiltration comprising lymphocytes, histiocytes, some eosinophils and some giant cells. The inflammatory infiltrates formed noncaseating granulomas with rare giant cells surrounded by B and T (CD8 lymphocytes). The same histopathological pattern was observed in the right ventricle and atria. The histopathology was consistent with GM with features of lymphocytic and histiocytic myocarditis (Fig. 1).

The immediate post-operative course was uneventful and the patient was started on standard immunosuppressive therapy with cyclosporin, mycofenolate and corticosteroids. Echocardiograms performed on day one and five after transplant were within normal limits, although the patient was beginning to develop hypotension and oliguria. Endomyocardial biopsy on the sixth day was grade 0. The symptoms worsened and the patient was treated with infusions of furosemide, dopamine and dobutamine, and pulsed, supplemental high-dose intravenous prednisolone along with the standard immunosuppressive maintenance regimen. The next day the patient had to be intubated, ventilated and started on noradrenaline because of

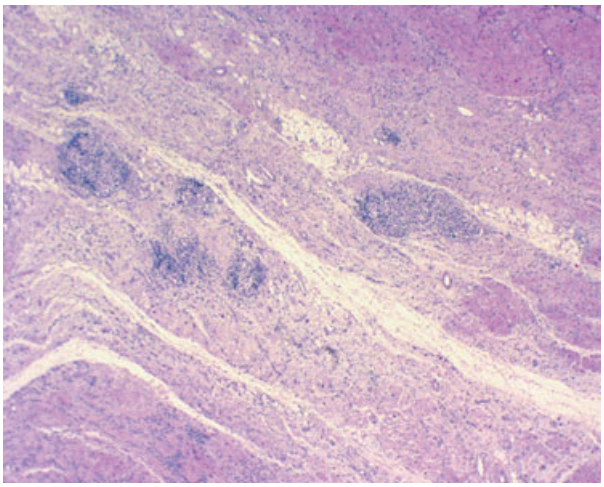

Figure 1 Myocyte necrosis and diffuse inflammatory infiltrates in the left ventricular myocardium (hematoxylin-eosin; original magnification, ×100).

cardiogenic shock. Echocardiogram showed diastolic dysfunction and hypertrophy, an enlarged right ventricle with reduced contractility, moderate tricuspid insufficiency and pericardial effusion with compression of the right atrium. Five hundred milliliters of pericardial fluid were drained. Humoral rejection was suspected on the basis of morphological evidence and CD4 positivity of the small vessel walls. He underwent three cycles of plasmapheresis and was treated with cyclophosphamide 2 mg/kg/day. The results of subsequent biopsies were as follows: 1A persistent, 1B with a humoral component and 3B with a humoral component. Immunofluorescence studies revealed negative staining of IgA, IgM, IgG, c1q, c3, c4 and fibrinogen in the first endomyocardial biopsy. Cytomegalovirus infection complicated the course and was treated with antiviral therapy. Clinical status improved gradually and, two months later, the patient was discharged on triple immunosuppressive therapy. Three years after transplant, he remains asymptomatic and the regularly scheduled follow-up biopsies have been negative.

The present case shows how difficult it is to make a definitive diagnosis differentiating between IGCM and GM. In this case, the clinical presentation was typical of IGCM because of rapidly worsening heart failure, history of ulcerative colitis, and no extra-cardiac involvement suggesting systemic sarcoidosis or tuberculosis. However, the histological findings of the explanted heart were consistent with idiopathic GM. There is still an open debate as to whether IGCM and GM are separate disorders. The question has also being raised of whether IGCM is part of the spectrum of GM [2]. In addition, in experimental myocarditis, IGCM and GM have the same inflammatory response [3,4].

Recently Okura *et al.* [2] demonstrated, in a large series of patients, histological differences between GM and IGCM: the first has more granulomas and fibrosis, while the second one more necrosis, foci of lymphocytic myocarditis and eosinophils. The number of giant cells is equivalent in GM and IGCM. These authors also make a clear, clinical distinction between GM and IGCM: the first is characterized by a presentation with advanced heart block or with symptoms lasting longer than nine weeks, whereas the presence of heart failure predicts IGCM. The authors also underscore how the prognosis in IGCM and GM is markedly different: the transplant-free 5-year survival probability from the beginning of the symptoms is 10% vs. 60.5% ($P < 0.001$) respectively [1]. Moreover, IGCM recurrence in the donor heart is about 25% [5–7], while in the literature there are only two cases of GM recurrence after transplantation [8,9].

However, in cases like the present one, GM can also have an aggressive course with histopathological findings of myocyte destruction, myocarditis and granulomas. Post-transplantation, the patient underwent episodes of severe humoral and cellular rejection, but no recurrence of the disease, as would have been expected with IGCM. For some authors [1,10] the risk of rejection for patients with myocarditis could be higher than for others, but the data are still controversial.

This case shows that GM can mimick the malignant clinical course of IGCM and only the endomyocardial biopsy allowed us to make the differential diagnosis. We therefore recommend this procedure in all candidates for transplant with recent onset cardiomyopathy for proper diagnosis and management.

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