Letter to the Editor

An alternative immunosuppressive regimen to prolong transplant free survival in a patient with giant cell myocarditis

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A 60-year-old man was referred to our hospital for reevaluation of progressive heart failure in January, 2011. Two months before admission, a permanent cardiac pacemaker had been implanted because of third degree atrioventricular block. At that time, the patient had a normal left ventricular ejection fraction which decreased in the following weeks. On admission to our hospital, 2-dimensional echocardiography showed a severe decrease in left ventricular ejection fraction (EF ~ 20%) but no peri-cardial effusion. Laboratory data on admission showed a highly elevated Troponin I with 41.3 ng/ml (reference value < 0.05), elevated d-dimers of 2.8 μg/ml (<0.5), a moderate elevation of C-reactive protein up to 7.7 mg/dl (<0.5) and a slight anemia. CK and CK-MB values were within the normal range, and peripheral eosinophils were of normal count. Serological analyses showed no hint for acute or subacute systemic infections with cardiotropic viruses, bacteria, fungi or parasites.

The patient was put on beta blocker, ACE inhibitors and diuretics. Due to a further rise in troponin I right ventricular myocardial biopsy was performed two days after admission. Ventriculography confirmed the severely reduced left ventricular function with an ejection fraction of 22%, a severely reduced cardiac index with 1.5 ml/min/m² (norm > 2.5 ml/min/m²) and a dilated left ventricle (EDV 122 ml/m²). The micropathological evaluation of the myocardial biopsies showed a distinct interstitial fibrosis with multiple areas of fresh necrosis surrounded by CD3-positive T cells and CD68-positive macrophages. Furthermore, multiple eosinophilic granulocytes and one single CD68-positive giant cell were detected (Fig. 1). A histopathological diagnosis of giant cell myocarditis (GCM) was made. Due to the rapid progression of myocarditis and inefficiency of standard therapy regimen (then including betablockers, ACE-inhibitors, diuretics and aldosterone antagonists) an interdisciplinary decision was made to place the patient on the waiting list for heart transplantation. In parallel an immunosuppressive therapy was started comprising cyclosporine (200 mg/day for 2 days, then according plasma levels, goal 150–200 ng/ml) and anti-thymocyte globulin (ATG) (300–320 mg/d for 4 days) combined with high dose steroid infusions (250 mg SDH for 2 days with subsequent tapering to a maintenance dose of 7.5 mg/day) based on treatment protocols recently published by Cooper et al. [1] (dosages differ slightly from the study protocol, for the exact dosages recommended please see the original article by Cooper et al.). Longitudinal echocardiographic follow up studies over the next 5 months revealed a rapidly increasing left ventricular ejection fraction to only mild depression in cardiac function (EF 55%) with a subsequent clinical improvement (functional NYHA stage I). The patient was removed from the transplant list and was kept on an immunosuppressive regimen with cyclosporine (level 150–200 ng/ml) and prednisolone (maintenance dose of 7.5 mg/d).

9 months after initial admission, the patient was readmitted to our hospital with progressive signs of cardiac decompensation such as exertional dyspnea (NYHA II–III), nocturia and weight gain. Laboratory findings again showed an elevation of Troponin I (1.43 ng/ml) and echocardiography revealed a decreased left ventricular ejection fraction of 35%. The patient underwent myocardial biopsy again, which revealed an ongoing inflammation with the infiltrate merely consisting of lymphocytes. A therapy with ATG was reintiated but had to be interrupted due to a severe allergic reaction. The immunosuppressive regimen was therefore switched to tacrolimus and MMF, the prednisolone dose was maintained and the patient slowly recovered. Another ten months later the patient was in NYHA stage I–II with a stable left ventricular ejection fraction of 40%, but referred to our hospital one year after initiation of our alternative immunosuppressive regimen for ICD-CRT-implantation because of exertional dyspnea and a decrease in left ventricular ejection fraction up to 32%.
Giant cell myocarditis (GCM) is a usually fulminant disease that leads to severe heart failure within a few weeks. In addition, GCM is often accompanied with malignant cardiac arrhythmias such as ventricular tachycardia (14%) or heart block (5%) [2].

In our patient, development of a heart block preceded a rapid progressive heart failure, which did not improve clinically despite intensive treatment. This resistance to heart failure medication is often observed in GCM patients [3]. On the other hand, GCM has been reported to be efficiently treated by immunosuppressive agents [2]. These findings are based on animal models of GCM, single case reports, a multicenter giant cell myocarditis registry [2] and a prospective multicenter study [1]. Whereas the therapy with corticosteroids alone seemed not to be effective in various cases [2], the combined use of immunosuppressive agents such as cyclosporine, azathioprine, methylprednisolone/predisolone and antibodies against T lymphocytes (muromonab-CD3 or ATG) was reported to prolong overall and transplant free survival [2,4]. We therefore treated our patient with the above regimen. Initially, this combined immunosuppression yielded a dramatic improvement of clinical symptoms and left ventricular ejection fraction increased to 55%. We continued an immunosuppressive regimen with prednisone (7.5 mg/day) and cyclosporine (target plasma level 150–200 ng/ml) in our patient as suggested by the latest prospective trial [1]. However, ten months after initiation of the therapy, the cardiac status of the patient decreased and he was admitted for recurrent myocarditis despite continuation of immunosuppressive therapy. Therefore, and due to additional allergic reactions upon ATG treatment, the standard immunosuppressive regimen had to be stopped and we sought for alternative immunosuppressive approaches. Azathioprine plus prednisolone could have been such an alternative, as it has been described in GCM treatment [2], but does not appear to be as efficient as cyclosporine combinations [2]. On the other hand, GCM can be cured by heart transplantation and recurrence under standard immunosuppressive regimen for heart transplantation occurs only in one out of four patients [2]. Based on this consideration we placed the patient on a combination of tacrolimus, MMF and prednisolone, a treatment regimen often successfully used as immunosuppression after heart transplantation. Nearly one year after initiation of this therapy, the patient was under stable cardiac conditions (EF 40%).

This therapeutic regimen, so far has not been described before for the treatment of giant cell myocarditis and our case suggests that a change to Tacrolimus/MMF and prednisolone could prolong transplant free survival in cases refractory to cyclosporine/azathioprine combination therapies. The fact that the patient’s LVEF recently decreased outlines the necessity of new therapeutic approaches to fight progression of this aggressive autoimmune disease.

Fig. 1. (a) shows HE staining of the myocardial biopsy with an area of fresh necrosis (*) and a giant cell (**). (b) Giemsa staining reveals interstitial fibrosis and multiple eosinophilic granulocytes (↗). (c) Immunohistochemical staining shows CD68+ macrophages (⇦) including a single CD68+ giant cell (↘). (d) Immunohistochemical staining for CD3+ cells.

References