

Combined immunosuppressive treatment for giant cell myocarditis: a case report

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ABSTRACT

Giant cell myocarditis (GCM) is a rare and often fulminant autoimmune disease. The immune-mediated pathogenesis of GCM is also supported by animal models, association with other immunological diseases and therapeutic efficacy of immunosuppressive drugs. The diagnosis of GCM is based on endomyocardial biopsy. GCM is an orphan disease. Heart transplantation is effective but up to 25% of transplanted patients experience disease recurrence. Immunosuppressive drugs have been shown to be potential therapeutic agents for GCM. In the present case report, the prescription of cyclosporine, azathioprine and prednisone resulted in a rapid and prolonged remission in support of the role of a combined immunosuppressive regimen in improving the long-term prognosis of this cardiac pathology.

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Introduction

Idiopathic giant cell myocarditis (GCM) is a very rare immune-mediated cardiomyopathy with an often rapid and fatal course due to heart failure, ventricular arrhythmia and/or cardiogenic shock.^{1,2}

The most widely accepted pathogenetic model is dominated by the dysregulation of T-cell immunity and the involvement of anti-myosin autoantibodies. The immune-mediated pathogenesis of GCM is also supported by animal models, association with other immunological diseases, and therapeutic efficacy of immunosuppressive drugs. The diagnosis of GCM is based on endomyocardial biopsy.

GCM is an orphan disease. Heart transplantation is effective but up to 25% of transplanted patients experience disease recurrence.

Immunosuppressive drugs have been shown to be potential therapeutic agents for GCM. The therapeutic regimen associated with a higher probability of response and better long-term prognosis is cyclosporine in dual therapy with corticosteroid or triple therapy with corticosteroid and another immunosuppressant.³

Open questions are the optimal dosage of the individual drugs and especially the optimal duration of combination immunosuppressive therapy.

In the present case report, we experienced the efficacy of a triple combination of cyclosporine-prednisone-azathioprine in the therapeutic management of a patient with idiopathic GCM.

Case report

A young 30-year-old Italian man presented to the emergency department for sudden, intense, fixed retrosternal pain and severe asthenia. The patient reported a family history (mother) of chronic thyroid disease, tonsillectomy for recurrent pharyngotonsillitis at the age of 7-8 years and surgery for

varicocele on the left at the age of 22 years. On admission to the emergency department, the patient presented with a fever with a body temperature of 37.3°C, a slight rise in troponin I (6.75 ng/ml, normal value <0.05), and no changes in the electrocardiogram. The patient was subsequently transferred to the intensive care unit.

An initial echocardiogram (Figures 1A-C) showed minimal pericardial dislodgement, left ventricle with reduced cavity dimensions, concentric parietal hypertrophy with maximum parietal thickness of 20 mm at the level of the septum and middle anterolateral wall, middle anterior wall hypokinesia with initial ejection fraction (FE) of 50%.

There was a progressive increase in troponin I up to a maximum value, on the fifth day, of 27 ng/ml (normal value <0.05) and a moderate rise in C-reactive protein, from an initial normal value to a maximum, on the fifth day, of 2.17 mg/dl (normal value <0.6 mg/dl). Electrocardiographic monitoring demonstrated an evolution of the picture with the appearance of diffuse negative/diphase T waves.

The clinical course was complicated on day 5 by congestive heart failure with reduced left ventricular systolic function (FE 35%) and bilateral pleural effusion. Serologic tests for potential systemic infectious or immunologic causes of the picture were negative.

A cardiac nuclear magnetic resonance imaging (MRI) performed on day 5 documented overall a picture indicative of acute-phase myocarditis: increased left ventricular parietal thickness with a reduced global Chinese with FE measurement of 44%, global signal hyperintensity in T2-weighted sequences acquired in the short axis, an expression of oedematous myocardial involvement, a modest circumferential pericardial effusion, and a modest bilateral posterior-basal pleural effusion. Coronarography was normal.

Given the picture indicative of acute myocarditis and the negativity of diagnostic investigations aimed at recognizing potential recognizable causes of myocarditis, endomyocardial biopsy of the right ventricle was performed. Histological examination showed the presence of a massive interstitial inflammatory infiltrate consisting mainly of lymphocytes, plasma cells, neutrophils, eosinophils with evidence of scattered multinucleated giant cells in the context of the inflammatory infiltrate without figures referable to granulomas. The presence of myocellular necrotic-degenerative changes, marked interstitial edema, and multiple foci of granulation tissue were also documented in multiple locations. The histological findings described allowed the diagnosis of idiopathic GCM.

Given the severity of the clinical picture, as soon as the diagnosis of GCM was formulated and the absence of contraindications to immunosuppressive therapy was confirmed, with the negativity of chest X-ray, hepatitis B markers, anti-HCV antibodies and quantiferon tuberculosis gold, immunosuppressive combination therapy was immediately prescribed with the combination of prednisone (at an initial dosage of 1 mg/kg/day in the morning with subsequent gradual reduction in dosage of 5 mg every week), azathioprine (at an initial dosage of 2 mg/kg/day in the morning, after lunch) and cyclosporine (at an initial dosage of 3 mg/kg/day divided into two daily doses, every 12 hours).

The start of immunosuppressive therapy in addition to cardiologic therapy for heart failure, unchanged from the time of admission to the intensive care unit, was followed by a rapid, significant, and progressive improvement in the state

of compensation, with improvement in symptoms as early as the second day of treatment.

Progressive improvement to normalization of left ventricular contractility was documented, with normalization after 6 days from the start of immunosuppressive therapy of ejection fraction (53%) and reduction of parietal thicknesses. The improvement in echocardiographic findings is illustrated in Figures 1D-F.

Fever regressed as early as 1 day of therapy, polymerase chain reaction became negative as early as 24 hours, and troponin I rapidly improved to normalized after 3 days.

The patient remained asymptomatic, afebrile and in good hemodynamic compensation: 21 days after admission he was discharged and subsequently followed up on an outpatient basis at the Clinical Immunology and Cardiology operating units.

After 3 months after the onset of GCM, nuclear MRI was repeated and demonstrated complete remission of the inflammatory myocardial picture, normal biventricular function, and minimal pericardial dislodgement (Figure 2).

During immunologic, echocardiographic, electrocardiographic, and clinical follow-up, which reached seven years of observation, the myocarditis persistently remained in remission (no recurrences), and the patient remained asymptomatic at all times and tolerated the combination immunomodulatory treatment well.

The patient continued triple immunosuppressive therapy with cyclosporine, azathioprine and prednisone for about 9 months, then reduced the drug load by continuing dual therapy with cyclosporine and azathioprine until 30 months of follow-up, then continued cyclosporine monotherapy. The dosage of prednisone was progressively reduced by 5 mg per week until maintenance of 5 mg on alternate mornings for 5 months and was then definitively discontinued after 9 months from the start of treatment. The dosage of azathioprine was reduced to 1.5 mg/kg/day after 4 months of treatment and, given the persistent remission of the picture,

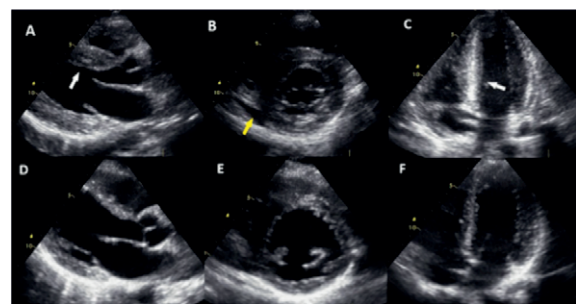


Figure 1. Two-dimensional transthoracic echocardiogram. The echocardiographic images (A, B, and C, respectively parasternal long axis, short axis, and four apical chambers) in the acute phase show the presence of a moderate increase in left ventricular parietal thicknesses with increased echogenicity, especially at the septal site (white arrow) and minimal pericardial dislodgement (yellow arrow). The corresponding images below (D, E, and F) correspond to the pre-discharge echocardiographic control and show the almost complete regression of parietal pseudohypertrophy and pericardial disconnection.

definitively discontinued after 30 months. The dosage of cyclosporine was progressively reduced to 2 mg/kg divided into two daily doses, as monotherapy for seven years after remission and was definitively discontinued after seven years of remission.

During the follow-up, the patient also took ramipril 2.5 mg/day, as prescribed by a cardiologist. During the follow-up the patient was asymptomatic.

Discussion and Conclusions

Idiopathic GCM is a very rare disease even if likely underestimated. The autopsy incidence estimated in the literature ranges from 0.007% to 0.051%. It prefers the young adult age with maximum incidence between 40 and 60 years. Pediatric and older age onset, greater than 70 years, has been described but is exceptional. No significant differences in incidence between female and male sexes have been found. The etiology is unknown. The pathogenesis of idiopathic GCM is immune-mediated and is characterized by a strong dysregulation of the T-cell compartment and an important role of anti-myosin antibodies.

The immunological genesis of idiopathic GCM is also supported by studies on animal models and by the simultaneous presence of other autoimmune diseases: about 20% of pa-

tients with GCM suffer from another associated immune-mediated disease: the most frequent associations are with rheumatoid arthritis, autoimmune thyroiditis, celiac disease, myasthenia gravis, lymphomas, thymomas, chronic inflammatory bowel disease.

The typical clinical picture of idiopathic GCM is characterized by sudden onset in previously healthy subjects, generally rapid course and potentially and frequently fatal outcome of acute heart failure with cardiogenic shock and/or arrhythmias; more rarely, in a percentage varying between 0.5 and 1.3% idiopathic GCM has an exclusive atrial involvement. By far the most frequent disorder at onset (three-fourths of cases) is acute heart failure to cardiogenic shock, followed by ventricular arrhythmias; cardiac arrest at onset is rarer.^{4,5}

Idiopathic GCM is an acute immune-mediated disease, potentially serious and fatal, and therefore it requires a complex and challenging multidisciplinary management in order to save lives of patients in the acute phase of the disease and to ensure them, subsequently, a significant increase in life expectancy and quality of life in the maintenance phase.

The achievement of these goals justifies and supports the use of prolonged immunosuppressive combination therapy regimens.

The diagnostic gold standard is an endomyocardial biopsy, in the absence of other specific diagnostic markers. The differential diagnosis must be made with other forms of

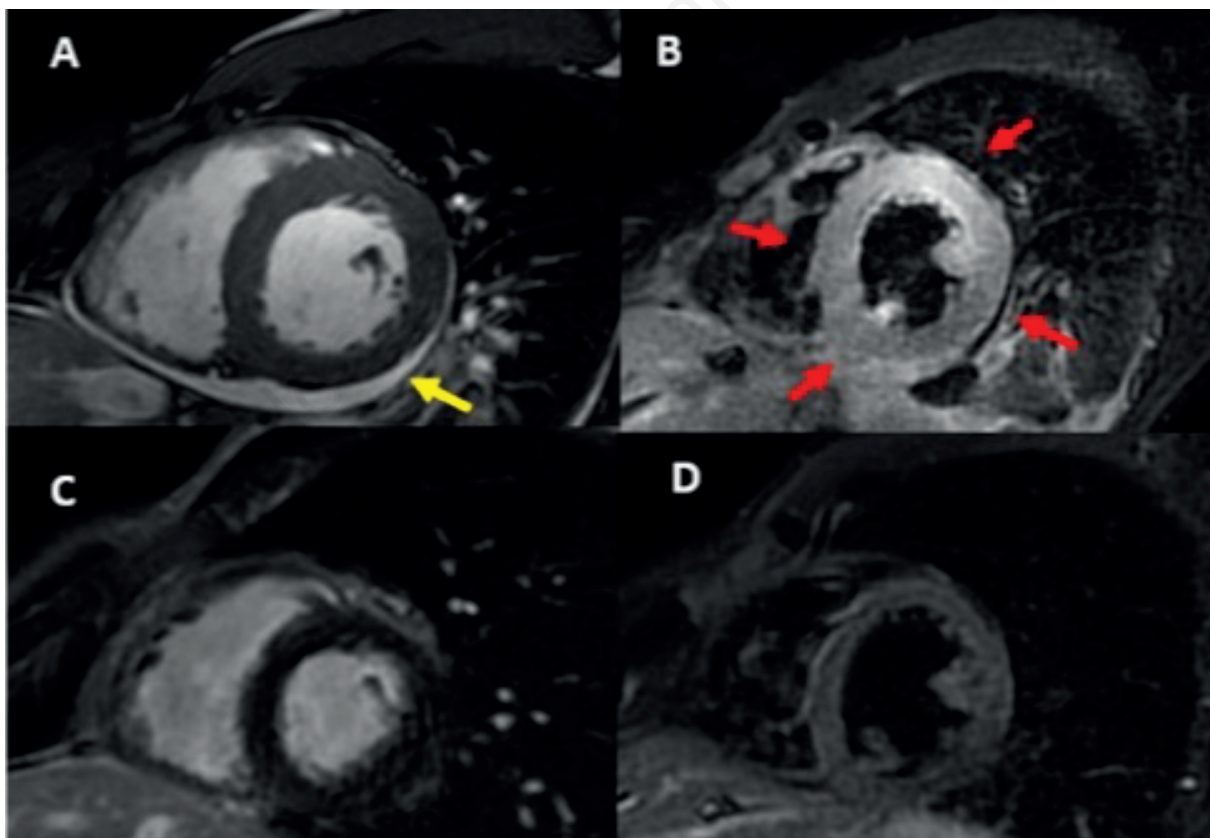


Figure 2. Cardiac magnetic resonance. In the acute phase (bottom-up images) increased wall thickness of left ventricle with pericardial effusion in the fast imaging employing steady-state acquisition sequences (A, yellow arrow) and widespread myocardial edema in T2-weighted sequences (B, red arrows). Cardiac magnetic resonance after three months of therapy showed normalized left ventricular wall thickness, with total regression both of pericardial effusion (C) and myocardial oedema (D).

mycardiopathy, for example, sarcoidosis and other autoimmune myocarditis.

Idiopathic GCM has a rapidly and frequently severe prognosis. Survival without cardiac transplantation is unlikely: there is epidemiological evidence that only up to 10% of patients, in the absence of cardiac transplantation, are still alive at 5 years after onset. Cardiac transplantation may be followed by relapses on the transplanted heart, in some cases up to a quarter of cases.

The therapeutic management is therefore essentially but not constantly based on cardiac transplantation in combination with antiarrhythmic and/or anti decompensation drugs and prescription of immunosuppressive drugs with a potential control of the course of the disease without recourse to transplantation. Systemic immunosuppressive combination therapy has been shown to be more effective than monotherapy. Immunosuppressive therapy based on the early and prolonged use of cyclosporine in a double combination with corticosteroids or in a triple combination with corticosteroids and azathioprine has been shown to have the potential to determine complete and prolonged remission of GCM and to significantly reduce the need for transplantation: up to about half of patients on combination immunosuppressive therapy remain transplant-free at 5 years.

A critical open question in the management of GCM with combination immunosuppressive drugs is the optimal duration of immunosuppressive treatment.

The occurrence of recurrences of GCM upon discontinuation of immunosuppressive drugs even after 8 years of uninterrupted therapy has been described.

This observation of the scientific literature has significant repercussions in the management of patients with GCM because it supports the hypothesis of an immunosuppressive therapeutic regimen indefinitely and without interruptions with obvious and stringent issues related to tolerability and

the risk of emergence of infections, neoplasms, allergy or other diseases from immune dysregulation directly related to immunosuppressive activity.

This case report confirms the rapidity of efficacy of the immunosuppressive triple therapy cyclosporine-azathioprine-prednisone, the persistent ability of this therapeutic regimen to maintain GCM in prolonged remission without relapses and supports the possibility of a gradual transition to a dual combination regimen and, finally, the possibility of gradually reducing the immunosuppressive drug load up to a monotherapy regimen with cyclosporine and, after some years of remission, discontinuation of immunosuppression. The significance and relevance of these conclusions should be further investigated and confirmed with the help of large randomized controlled trials.

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