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LETTER TO THE EDITOR

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Is the endomyocardial biopsy in giant cell myocarditis of some help for the rapid indication for heart transplantation?

To the Editor,

We describe the case of a 49-years-old-man hospitalized at the Policlinico Hospital of Bari, with sudden onset of acute heart failure requiring venoarterial extracorporeal membrane oxygenation implant for circulatory support for suspicion of acute myocarditis. His clinical history was unremarkable for cardiovascular and immune diseases.

The patient was submitted to an endomyocardial biopsy (EMB) and the subsequent histological diagnosis documented a diffuse inflammatory lympho-plasmocytic and eosinophilic infiltrate with the occurrence of numerous multinucleated giant cells, areas of myocyte necrosis and focal fibrosis. The morphological appearance was consistent with giant cell myocarditis (GCM).

The patient was treated with immunosuppressive therapy. After 20 days, he received a cardiac transplant for biventricular heart failure due to giant cell myocarditis unresponsive to immunosuppressive therapy.

Macroscopically, the explanted heart weighted 331 g and measured cm $10 \times 10 \times 7$ in longitudinal, transverse and antero-posterior diameters respectively, with right ventricular wall 2 mm thick and left ventricular wall 8 mm thick. On cut section, it was characterized by ill-defined brown-reddish areas at the postero-septal wall of the right ventricle with extension to the posterior wall of the left ventricle; similar appearance was found affecting the anterior wall of the left ventricle. Septal myocardium and lateral free wall showed large confluent pale-white areas (Figure 1a).

Microscopically, the heart was characterized by a diffuse inflammatory lymphoplasmacytic and eosinophilic infiltrate with the presence of numerous multinucleated giant cells (Figure 1b) associated with areas of myocyte necrosis and diffuse fibrosis (figure 1c) with hypertrophic and regressive aspects of myocardiocytes.

The inflammatory infiltrate and the diffuse fibrosis extended transmurally from the endocardium to the subepicardial myocardium.

Immunohistochemistry was strongly and diffusely positive for CD68 in histiocytes and giant cells (Figure 1d); mononuclear cells resulted CD3 (Figure 1e) and CD8 positive (Figure 1f) and focally positive for CD4 and CD20.

10 days after heart transplantation, the patient was submitted to a EMB with no signs of acute cellular rejection and focal immunohistochemical expression of C4d in the capillary endothelium diagnosed as WF: 0; ISHLT'04: 0; AMR: 1 (i). Subsequent EMB were unremarkable. The patient died three months later because of septic peritonitis. Autopsy was not performed.

GCM was first described in 1905 and the role of immunosuppression was reported only in 1987.[1]

GCM is a rare and a rapidly progressive inflammatory disease targeted at cardiac myocytes, frequently fatal diagnosis, affecting young and middle-aged adults. The incidence of GCM has been reported to range from 0.007% to 0.051%[2] in larger autopsy series and the incidence of 6% in pediatric cases.[2]

The pathogenesis of GCM is unknown, but it has been postulated a T-cell-mediated pathogenesis, characterized by infiltration made of lymphocytes, histiocytes, multinucleated giant cells, eosinophils with necrosis of cardiomyocytes, and notable absence of granulomas.[3]

It is associated with autoimmune disorders reported in the medical literature such as myasthenia gravis, inflammatory bowel disease, idiopathic generalized myositis, orbital myositis, systemic lupus erythematosus, common variable immunodeficiency syndrome, autoimmune hepatitis, Sjogren syndrome, vitiligo, and Hashimoto thyroiditis.

Clinical diagnosis of GCM is often difficult due to the symptoms mimicking other pathological conditions, so it is important to perform a myocardial biopsy for the differential diagnosis especially with cardiac sarcoidosis and fulminant lymphocytic myocarditis.

Cardiac sarcoidosis is characterized histologically by non-necrotizing granulomas with central giant cells with cytoplasmic Schaumann or asteroid bodies, few eosinophils, occasional myocyte necrosis and prominent fibrosis.

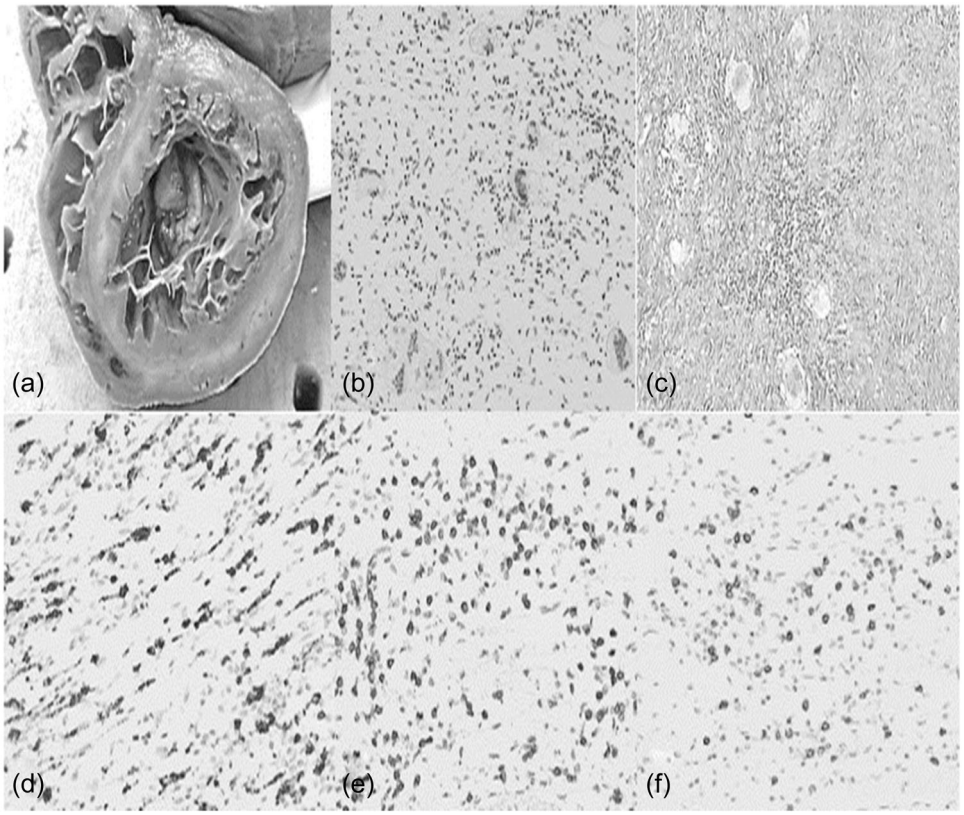

FIGURE 1 GCM. (a) Grossly, the heart is characterized by ill-defined brown-reddish foci and diffuse intramural pale-white area. (b) Diffuse lymphoplasmacytic infiltrate with the occurrence of numerous multinucleated giant cell (Hematoxylin-Eosin, 20×). (c) Extensive fibrosis (trichrome stain, 10×). (d) CD68 immunostaining (20×) was strongly and diffuse positive. (e) CD3 (20×) was strongly and diffuse positive in mononuclear cells. (f) CD8 immunostaining (20×) was also positive in some lymphocytes.

Fulminant lymphocytic myocarditis is characterized by a diffuse lymphocytic infiltrate with myocyte necrosis and rare giant cell.

In most cases, GCM is characterized by rapidly progressive myocarditis to a fulminant state of cardiogenic shock but can be characterized predominantly by arrhythmia such as atrioventricular block or ventricular arrhythmias,[4] with death occurring within weeks or months from initial submission.[2,4] However, in some series, more indolent presentations of GCM have been described.[4]

The disease is largely responsive to immunosuppressive therapy, but in few cases cardiac transplantation is required. There are no data available in Italy on the indication for heart transplant in cases of fulminant myocarditis.

It is reported that patients with GCM have excellent posttransplant survival with the use of rabbit antithymocyte globulin and triple drug immunosuppressive therapy (tacrolimus, mycophenolate, and prednisone); however, some patients remain at risk for recurrence of GCM after transplantation, which may respond to increased immunosuppression.[5]

The gross examination of the heart is nonspecific, but the myocardium may appear pale or slightly yellow with multiple whitish foci of fibrosis[2]; cardiomegaly has been described in one series; the average heart weight in GCM is reported as 476 g ranging from 405 to 580 g.[2]

Microscopically the GCM is histologically characterized by a diffuse and heterogeneous leukocyte infiltration consisting of prominent multinucleated giant cells, abundant small lymphocytes, some eosinophils and plasma cells, occasional neutrophils, and large areas of necrosis.

Giant cells are immunohistochemically mostly CD68+ (macrophages) and lymphoid cells are predominantly T lymphocytes CD3+ with CD8 positive immunophenotype.

In the presented case, the patient presented an acute and rapidly progressive clinical presentation, and was unresponsive to immunosuppressive therapy, so he underwent to cardiac transplantation.

Macroscopic examination of the heart demonstrated the occurrence of alternating ill-defined brown-reddish and extensive pale-white areas. The histological observation showed, beside the presence of the typical features of GCM, a diffuse transmural fibrosis in various stages of organization. In particular, the latter strongly suggests the hypothesis of a disease characterized, at least in our case,

by a long subclinical course whose acute presentation could represent the final event of a persistent necrotizing inflammation that would lead to an extensive remodeling of the myocardium. The extension of consolidated fibrotic tissue well beyond the inflamed areas and the poor response to immunosuppressive therapy would support the view of a myocarditis with subacute/chronic course and a sudden frequently fulminant clinical presentation. The persistence in the explanted heart of large areas of necrosis and inflammation would be indicative of resistance to the immunosuppressive therapy and of the possible role of biopsy to orientate to heart transplantation in not respondent patients.

AUTHOR CONTRIBUTIONS

Writing—original draft preparation: Andrea Marzullo and Cecilia Salzillo. *Devised and collected the pathological and clinical information*: Cecilia Salzillo, Gerardo Cazzato, Marialessandra Capuzzolo, and Carla Nardelli. *Writing—review and editing*: Andrea Marzullo and Gabriella Serio. All authors have read and agreed to the published version of the manuscript.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

None declared.

ETHICS STATEMENT

The project was approved by an institutional ethics committee.

For human subjects, the investigation was conducted in accordance with the Declaration of Helsinki of 1975.

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