# Giant-Cell Myocarditis: A Rare Cause of Rapidly Evolved Stenosis of the Mitral Valve

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An aged anemic woman was operated on for mitral valve stenosis that had rapidly progressed in a few months. Surgical and histological findings of the replaced valve proved the unexpected diagnosis of giant-cell myocarditis. This atypical clinical presentation of mitral stenosis associated with systemic manifestations must raise suspicions for other underlying illnesses. In such cases, a preoperative endomyocardial biopsy can be helpful. The patient succumbed few days later from low cardiac output syndrome. Repair or replacement of an infiltrated by giant-cells myocardium and mitral valve should not be attempted. Instead, combined immunosuppression or mechanical support and heart transplantation should be applied to save these patients.

**M**itral valve stenosis of origin other than rheumatic fever is a rare entity. Giant-cell myocarditis is an extremely rare, with poor prognosis, probably autoimmune, granulomatous disease of the heart. Progressive congestive heart failure, intraventricular conduction defects and ventricular arrhythmias, which in many cases can be fatal, are the usual manifestations of this disease[1]. On the contrary, mitral valve stenosis has not been observed as an initial clinical presentation of giant-cell myocarditis. The present case report regards a patient with the clinical presentation of a rapidly evolved mitral valve stenosis, due to giant-cell infiltration of the myocardium and the mitral apparatus.

## Case report

A 71-year old female patient, (married and mother of five children), was referred for surgical correction of a critical mitral valve stenosis. The patient's medical record reported hypothyroidism diagnosed 25 years ago, for which she was receiving replacement therapy. There was no history of rheumatic fever during childhood or adolescent years. The symptoms began 7 months earlier with a dyspnea on exertion, moderate fever, substernal aches, and anemia (Ht=23%). The echocardiogram revealed normal cardiac function, a well functioning mitral valve, and only minor accumulation of pericardial fluid. The clinical findings were attributed to a viral pericarditis, and the anemia treated as pernicious. Four months later, the symptoms relapsed. The findings of a new echocardiogram were interesting: mitral valve stenosis with a valve area of 1.65 cm$^2$ (Figure 1) and pulmonary hypertension with a systolic pulmonary artery pressure of 57.6 mmHg. Relief of the symptoms was observed after administration of digitalis and diuretics, and blood transfusions. Two months later, the patient presented with orthopnea and severe anemia. The echocardiogram that was immediately performed showed critical mitral stenosis with an impressive decrease of the valve
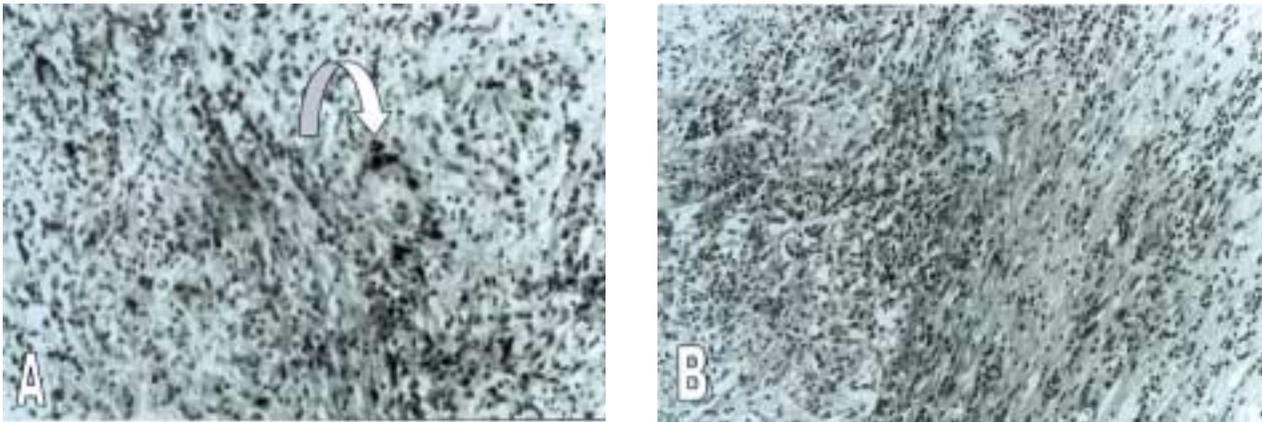
**Figure 1.** Calculation of the mitral valve area by the pressure half-time technique. At the *A* echocardiogram the mitral valve area was measured to 1.65 cm$^2$. At the *B*, two months later, the area was decreased to 1.04 cm$^2$. There are also E>A and blood flow indicating mitral damage.

area to 1.04 cm$^2$ (Figure 1b). The mean left atrioventricular pressure gradient was measured to 16.8 mmHg and the pulmonary artery systolic pressure was increased to 67.6 mmHg. Preoperative cardiac catheterization confirmed the diagnosis of severe stenosis of the mitral valve, pulmonary hypertension and right heart failure. No lesions were observed in the coronary angiography. Physical examination revealed a pale skin, distension of the jugular veins, absence of a mitral face, tachycardia, diastolic rumbling murmur, and signs of stasis at both lung bases. Electrocardiogram showed sinus node tachycardia with 1$^{st}$ degree AV block, without right ventricular hypertrophy, mitral or pulmonary P waves. Chest x-rays revealed an enlargement of the cardiac silhouette and pulmonary congestion without any other abnormal findings from the lung parenchyma.

The patient was operated on with the indication of replacement of the stenosed mitral valve. Intraoperatively, there was an active pericardial inflammation, loose adhesions and moderate accumulation of pericardial fluid. The mitral valve was approached via the traditional left vertical atriotomy. The inspection through the small left atrium revealed a heavy invasion of the mitral apparatus by a white firm tissue, which resulted in a total destruction of its architecture. The tissue extended from the mitral annulus to the basis of both papillary muscles, creating a solid tubular mass, thus obstructing the atrioventricular opening. This tissue and the infiltrated native mitral valve were removed with great difficulty. The diseased valve was replaced with a mechanical Sorin– No 27 valve, sutured with multiple mattress sutures of Ethybond– 2-0, reinforced with Teflon– pledgets. Cardiopulmonary bypass weaning was achieved with high inotropic support. A few hours later acute pulmonary edema emerged necessitating reintubation, mechanical respiratory support and increased doses of inotropes. The patient succumbed on the 12$^{th}$ postoperative day from low cardiac output syndrome. Mechanical circulatory assistance as a bridge to heart transplantation was not attempted, due to the patient's age, and the rarity of donor hearts in our country.

A limited autopsy confined to the thorax was performed which revealed that, the heart weighed 700 gr and was hypertrophic. The prosthetic mechanical valve was intact with no paravalvular leaks or limitations at the movement of its leaflets. The other valves were normal and there was no thrombus in any of the cardiac chambers. Multiple cross sections of the heart revealed notable hypertrophy of the left ventricle with a severe limitation of its cavity. Many white global lesions of various diameters diffusely occupied the myocardium. There were no atheromatic lesions in the coronary arteries. The pericardium was edematous and thickened.

The surgical specimen with the mitral valve was fixed in buffered formalin and after dehydration was embedded in paraffin. The specimen was studied by light microscopy. Sections were stained with hematoxylin-eosin, Masson trichrome, Pas, Giemsa, Ziehl-Nielsen, and Grocott stains, as well as immunohistochemically with the ABC method. The antibodies utilized were against T cells (CD3), B cells

**Figure 2.** Active granulomatous process of giant-cell myocarditis with *(A)* scattered giant-cells (white arrow, H+E×200), and *(B)* interstitial inflammation with focal development of collagen fibers (H+E×100).

(CD20) and CD68 antigen (myelomonocytic marker – Dako). The histological examination showed active granulomatous process with multiple giant-cells, scattered foci of necrosis and a mild increase in collagen deposition (Figure 2). In addition to the granulomatous lesions, there was a heavy interstitial inflammation (lymphocytes, mononuclear and plasma cells) with degeneration of the myofibers. Results of the special stains with CD68 antibodies (myelomonocytic marker) were positive for multinucleate giant cells. The interstitial lymphocytic population was composed mainly of CD3+ (T) and few CD20+ (B) lymphocytes. These histological findings established the diagnosis of giant-cell myocarditis.

Histological examination of the explanted heart revealed the same findings, in addition to focal development of fibrous collagen tissue. The degree of inflammation and the extent of the granulomatous process were more severe in the left ventricle, especially in the vicinity of the mitral annulus (Figure 3). The study of the lungs showed congestion, a finding compatible with the clinical picture of pulmonary edema. No granulomata or other pathological lesions were observed in the pulmonary parenchyma.

## Discussion

Mitral valve stenosis is the result of the rheumatic fever in almost all adult patients. Between acute rheumatic fever during the adolescent years and the appearance of symptoms from leaflet calcification and fusion, there is a latent period of about 20 years.

Therefore, the mean age of patients undergoing surgery for symptomatic mitral stenosis is approximately 40-50 years[2]. In this case report, the advanced age, the absence of rheumatic history during childhood and adolescent years, the absence of calcifications of the mitral apparatus, the functional and pathological integrity of the other valves, and the rapidly evolved stenotic process based on the echo findings (no stenosis observed seven months before surgery, and mitral valve area of 1.65 cm$^2$ and 1.04 cm$^2$ before four and two months) does not favor the rheumatic origin of the disease.

Rare causes, other than rheumatic fever, can lead to functional or anatomical stenosis of the mitral valve. These include myxoma[3], sarcoma[4], or free-floating thrombus of the left atrium[5], hydatid cysts[6], vegetations from infective endocarditis[7], mu-
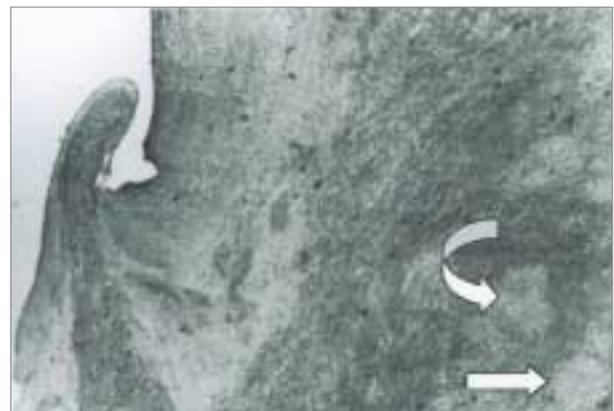


**Figure 3.** Granulomata (white arrows) in the vicinity of the mitral annulus (H+E ×40).

copolisaccharidoses[8], or antiphospholid antibodies deposition[9], hypereosinophilic infiltrations[10], or post-radiation reactions[11].

Giant-cell myocarditis is a rare with a of poor prognosis, probably autoimmune, granulomatous disease of the heart. The multicenter, international Giant-Cell Myocarditis Study Group in 1997 reported only 63 cases[1]. Since this study, seven other cases have been published[12-18]. Apart from the idiopathic form of giant-cell myocarditis, the etiology of which is unclear, granulomatous involvement of myocardium has been associated with a wide variety of systemic diseases such as sarcoidosis, a well known cause of lung and heart granulomata, infective endocarditis, rheumatoid arthritis, Wegener's disease, Takayasu's arteritis, tuberculosis, fungal infections, syphilis, foreign body reaction, or drug hypersensitivity (secondary giant-cell myocarditis)[19,20]. On the other hand, various auto-immune manifestations, such as hypothyroidism[1], or pernicious anemia[21] have been reported in association with idiopathic giant-cell myocarditis.

Progressive congestive heart failure, intraventricular conduction defects and malignant arrhythmias characterize the clinical course of this, frequently fatal, type of myocarditis[1,19]. Most patients have died within a few months, but some survived for a longer period, after immunosuppressive treatment or heart transplantation. In the Giant-Cell Myocarditis Study Group, the mortality rate or cardiac transplantation was 89%, with a median survival of 5.5 months from the onset of symptoms to the time of death or heart transplantation[1]. Combined immunosuppressive therapy may prolong the time to transplantation or death in these patients[1,13,15,17]. Thirty-eight patients of the above study were transplanted with or without mechanical assistance as a bridge to heart transplantation. Nevertheless, recurrence of giant-cell myocarditis in the transplanted heart is another serious problem[1,22]. Recurrence was observed in 9 of the 38 cases (23.6%) who were transplanted. Interestingly, these 9 transplanted patients had a better clinical course, perhaps due to early diagnosis from the endomyocardial biopsies or the immunosuppressive therapy.

The patient we present had replacement of the critically stenosed mitral valve, without knowing the nature of the underlying pathology and its relation with the pericarditis or the pernicious anemia. Perhaps, a preoperative endomyocardial biopsy would have led to the right diagnosis and to a different therapeutic approach based on immunosuppression[23]. The mitral valve stenosis "covered' the infiltrated and diseased left ventricle. With the replacement of the mitral valve and the enlargement of the effective orifice area, the preload of the left ventricle was increased and "unmasked" its insufficiency dramatically. Surgical and histological findings during the operation revealed the diagnosis of giant-cell myocarditis, which was confirmed by autopsy. The absence of pulmonary granulomata abolished the diagnosis of sarcoidosis. Moreover, there were not any of the previously mentioned illnesses of secondary giant-cell myocarditis. All this evidence sets the diagnosis of idiopathic giant-cell myocarditis.

Only three cases of idiopathic giant-cell myocarditis associated with mitral valve stenosis or insufficiency were found in the literature. In the first cases, published 30 years ago, the mitral stenosis was due to rheumatic fever and the granulomata were an additional finding[24]. In the second case, giant-cell myocarditis was an autopsy finding from a 22-year old man after an unsuccessful mitral valve replacement for mitral valve prolapse[25]. In 1996, El Gamel et al, reported the third and more interesting case of a young woman with mitral valve dysfunction and congestive heart failure[26]. The attempt of mitral valve repair was followed by inability to wean from cardiopulmonary bypass. Emergency mechanical biventricular assistance with centrifugal blood pumps was instituted and successful heart transplantation was performed later. Histology of the explanted heart revealed granulomata and infiltration of the myocardium and the mitral anterior papillary muscle by giant-cell myocarditis.

The rapidly evolving stenosis of the mitral valve in an aged patient rather excludes the rheumatic origin of the disease. On the contrary, it must raise suspicions, especially when associated with systemic manifestations, for other underlying illnesses. In such cases, a preoperative endomyocardial biopsy, followed by immunosuppressive treatment when the diagnosis of giant-cell myocarditis is confirmed, can be helpful. Based on the clinical course of our case and on the literature, surgery of the infiltrated with giant-cells mitral valve should be attempted only if there are facilities for mechanical circulatory support and heart transplantation. Otherwise, any attempt to repair or replace an in filtrated by giant-cell myocarditis mitral valve, is condemned to failure.

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