Giant cell myocarditis in the explanted heart of an orthotopic heart transplant recipient – a case report

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Abstract

Giant cell myocarditis (GCM) is an unusual cause of cardiomyopathy. Because of its fulminant clinical course and specific treatment, it should be taken into consideration in patients with a new onset of left ventricular heart failure, which is difficult to treat with standard therapy. Giant cell myocarditis may present as an atrioventricular block as well. The outcome is fatal, unless the patient undergoes a heart transplantation. Mean survival time from the first symptoms to end-point (transplantation or death) is 5.5 months. We would like to present a case of a patient who was successfully treated with heart transplantation for cardiomyopathy caused by GCM, which was revealed in the explanted heart.

Key words: giant cell myocarditis, cardiomyopathy, heart transplantation.

Streszczenie

Olbrzymiokomórkowe zapalenie mięśnia sercowego jest rzadko spotykaną przyczyną kardiomiopatii. Ze względu na swój gwałtowny przebieg i nieliczne opcje lecznicze rozpoznanie to powinno być brane pod uwagę u wszystkich chorych ze świeżo rozpoznaną niewydolnością lewokomorową, niepoddającą się standardowemu leczeniu. Inna prezentacja kliniczna tej choroby to blok przedsionkowo-komorowy. Rokowanie co do przeżycia jest niekorzystne: średnie przeżycie od pierwszych objawów do śmierci (lub przeszczepu serca) wynosi 5,5 miesiąca. Jedynym znanym sposobem leczenia jest przeszczep serca. W niniejszym artykule prezentujemy przypadek kliniczny chorego, któremu z powodzeniem przeszczepiono serce z powodu olbrzymiokomórkowego zapalenia mięśnia sercowego, rozpoznanego na podstawie badania histopatologicznego eksplantowanego serca.

Słowa kluczowe: olbrzymiokomórkowe zapalenie mięśnia sercowego, kardiomiopatia, przeszczep serca.

Introduce

Giant cell myocarditis (GCM) is a rare but very serious disease of the heart, which is mediated by autoimmune reactions. It affects usually young and previously healthy individuals. The outcome is fatal, unless the patient undergoes heart transplantation. Even then there is a risk that the GCM will develop in the transplanted heart. The mean survival time from presenting symptoms to death is quite short – about 5.5 months [1]. The majority of patients present with symptoms of congestive heart failure, such as dyspnoea, decreased exercise tolerance, orthopnoea, and peripheral oedema or those of heart block, e.g. palpitations, syncope, sudden death [2].

GCM represents a specific pathological entity. Its frequency in a series of 2300 biopsies was below 0.08% [3]. The pathological changes are dispersed in myocardial tissue and consist of dense, active lymphocytic infiltrates with the presence of multinucleated giant cells, resembling specific inflammation [2].

We would like to present a case of a patient who was successfully treated with heart transplantation for cardiomyopathy caused by GCM, which was revealed in the explanted heart.

Case description

A 48-year-old, white man with past cardiac medical history underwent a heart transplantation due to heart failure and GCM was recognized during histological examination of the explanted heart.

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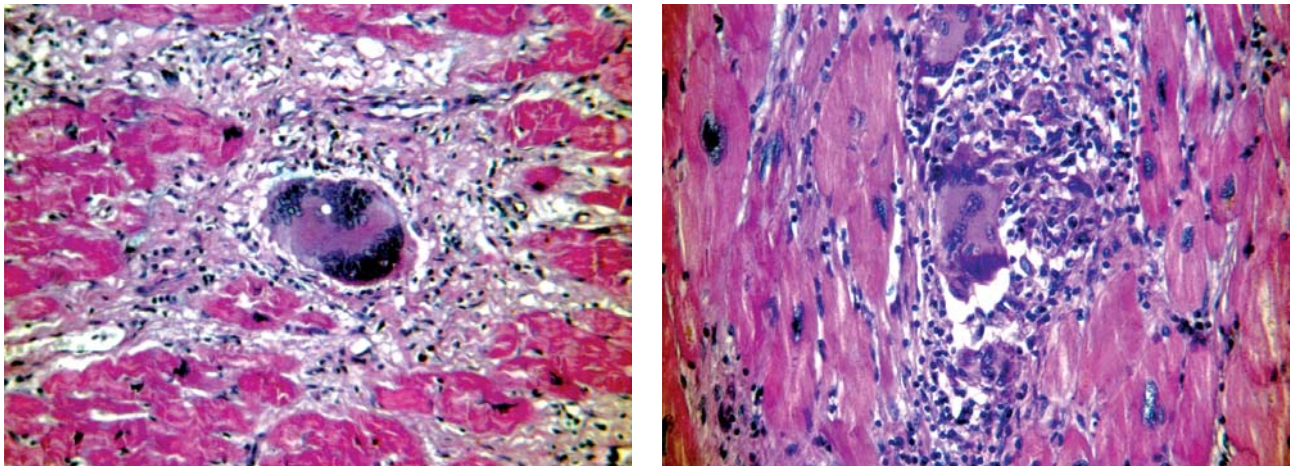

Fig. 1. Fusion cells – the most characteristic finding for GCM

The patient suffered from rheumatic fever in childhood and had aortic valve insufficiency diagnosed at the age of 24, but otherwise he was enjoying good health and was even a football player in a school team. However, as his valve defect progressed, his clinical condition gradually deteriorated and heart failure developed. Eventually he received an aortic valve replacement when he was 36. Since then he had remained in a good physical condition with LVEF of 45%. However, at the age of 47 his clinical condition declined substantially as a result of a rapid onset of congestive heart failure with several episodes of pulmonary oedema. The LVEF lowered to 12% at this point. There was no evidence either of heart block or ventricular tachyarrhythmia. The patient was listed for a heart transplantation, which was performed 11 months after the onset of symptoms. Following the operation immunosuppressant therapy was initiated, consisting of high-dose steroids, cyclosporine and azathioprine, and maintenance immunosuppression was performed with cyclosporine, mycophenolate mofetil and prednisone respectively, in a gradually reducing dose scheme.

During the short post-operative period, there were 2 episodes of ISHLT grade 3A acute rejection of the heart transplant. Other biopsy specimen rejection results varied from ISHLT grade 0 to grade 2. Four and half years after the operation the patient has remained asymptomatic, with excellent exercise tolerance.

Histopathology

Gross examination of the patient's heart revealed enlargement of the heart (dimensions: 110 mm, 100 mm, 80 mm), with dilation of the chambers and slight fibrosis of the endocardium. The ventricular musculature showed slight hypertrophy (left ventricle 14 mm, right ventricle 2 mm) and the presence of delicate myocardial fibrosis with punctiform disseminated scars. The coronary vessels showed no abnormalities or atherosclerotic lesions. The histological examination of the left ventricular tissue revealed the presence of focal active lymphocytic infiltrations with myocardial necrosis, granulomas with giant cells and polymorphonuclear cells including eosinophils, macrophages and plasma cells, and focally small fibrotic scars with remnant inflammatory cells (Fig. 1). In the right ventricular myocardium only lymphocytic infiltrations were present, without granulomas. The eosinophil admixture was evident mainly in granulomas. The pericardial and pericoronary tissues were free of inflammatory infiltrations.

The post-transplant biopsies showed the absence of specific inflammatory infiltrations, suggesting the lack of recurrent GCM.

Discussion

GCM is an unusual cause of cardiomyopathy. Because of its rapid and fatal clinical course and specific treatment it should be taken into consideration in patients with a new onset of left ventricular heart failure, which is difficult to treat with standard therapy. In contrast to primary lymphocytic myocarditis (PLM), which is another cause of inflammatory cardiomyopathy, the mean time elapsing between the definite diagnosis to the end-point (death or transplantation) in GCM is between 3 months and 1-2 years [4, 5], whereas in PLM this period is much longer and estimated at about 5.9 years [6]. Another difference between GCM and PLM is that GCM may respond to a treatment consisting of a combination of immunosuppressive drugs [1]. GCM affects usually young and previously healthy people, with an average age of 42 [1]. The rates in men and women are equal. There is no difference among races. The symptoms are those of heart failure or heart block. Ventricular tachyarrhythmia is common [1, 7].

Multicentre studies have revealed the coexistence of GCM with autoimmunological and inflammatory disorders in up to 20% of cases [7], especially with inflammatory bowel diseases [1, 7], but also with thymoma [8, 9], autoimmune hepatitis, discoid lupus [10] and coeliac disease [11]. The giant cell response may also be the result of hypersensitivity [12], may accompany stem cell transplantation, or may develop following interleukin administration [13].

The experimental and clinical data suggest the role of T lymphocytes in GCM. In an experimental model, GCM in rats was induced by immunization to cardiac myosin [14]. The infiltrates in greater part consisted of T lymphocytes. They could be identified in human heart affected by GCM as well. This indicates that treatment aimed at attenuating T cell function may be useful [7].

From the histological point of view, GCM resembles cardiac sarcoidosis [15]. The most striking difference between sarcoidosis and GCM is the lack of myocyte damage in cases with sarcoidosis. In cases of GCM three histological phases could be distinguished: the acute phase with the absence of typical granulomas, the *healing* phase with the presence of typical granulomas, and the healed phase without giant cells. All phases may be identified in the heart with GCM, often in a single heart chamber [15]. The giant cells in the acute phase present the macrophage phenotype, whereas in the healing and healed phases its myogenic immunophenotype is predominant. The clinical and epidemiological studies indicate, over the pathological similarities, the more rapid progression of heart failure, the higher percentage of atrioventricular block and syncope, and the shorter transplant-free survival in GCM than in sarcoidosis [16].

Multicentre studies indicate that immunosuppressive therapy with cyclosporine, azathioprine combined with steroids, muromonab, or OKT 3 may prolong the transplant-free life over one year [7, 17]. It should be noted that the use of etanercept, a TNF-α p75 receptor antagonist, gave complete resolution of the cardiac symptoms in a patient with GCM [18]. A frequently used and accepted therapeutic model includes cardiac transplantation or mechanical circulatory support as a bridge to transplantation [19]. Post-transplantation survival is additionally complicated by a 25% rate of GCM recurrence in the donor heart [7]. Scott et al. reported 38 patients who received a cardiac transplant for GCM [20]. The GCM was a recurrent disease in 9 patients among these, and one of the 9 recurrences was a subject of the study. In this patient vascular and cellular rejection was observed in the early postoperative period, and the authors could not exclude the presence of GCM in the donor heart. The cited article could evoke more complicated diagnostic problems: are GCM recurrences a specific rejection reaction in autoimmune patients [21]? The biopsy studies of GCM recurrences in transplanted hearts indicate that efficient immunosuppression therapy causes complete regression of the GCM [22].

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