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CASE REPORT

Rituximab in recurrent idiopathic giant cell myocarditis after heart transplantation: a potential therapeutic approach

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Summary

Giant cell myocarditis (GCM) is a very aggressive form of myocardial inflammation. While immunosuppressive therapy is usually able to keep under control the disease and prolong the average transplant-free survival in many patients, effective therapeutic strategies to prevent or treat the recurrence of GCM in transplanted organs are still to be defined. We report the case of a young woman with idiopathic GCM who, despite immediate aggressive immunosuppressive therapy, rapidly progressed to irreversible heart failure and required urgent heart transplantation. Yet, 2 months later, the disease recurred in the transplanted heart, despite an intensive four-drug antirejection regimen. The introduction of rituximab, an anti-CD20 monoclonal antibody, 375 mg/m^2/week i.v. for four consecutive weeks and then every 4 months as maintenance therapy, determined a complete and steady clinical remission of the disease. After nineteen months since rituximab administration, the patient is doing well and repeated follow-up endo-myocardial biopsies confirmed the complete resolution of myocardial inflammation. Our experience seems to suggest that rituximab can be a reasonably effective and safe therapeutic option in GCM recurring in transplanted organs.

Introduction

Giant cell myocarditis (GCM) is an uncommon and very aggressive myocardial disease of unknown origin [1]. While timely and well-calibrated immunosuppressive therapy is usually able to keep under control the disease in many patients, effective prevention and treatment of recurrences in transplanted organs are still to be defined [2]. We herein describe the case of a young woman with idiopathic GCM recurrence in the cardiac allograft successfully treated with rituximab, an anti-CD20 monoclonal antibody [3].

Case report

A previously healthy 38-year-old Caucasian woman was admitted to the coronary intensive care unit of our hospital for the onset of rapidly worsening dyspnea, hypotension, and anuria. In the previous 3 weeks, she manifested abdominal pain associated with fever, diarrhea, and nausea and she began to experience chest pain, cough, and increasing dyspnea. At admission, heart function was severely depressed with a LVEF of 17%. As first line treatment, she received diuretics, ACE inhibitors, beta-blockers, antibiotic therapy, dobutamine, and dopamine. Cardiac MRI was planned, but not performed since the occurrence of two episodes of ventricular fibrillation, requiring CPR and DC-shock resuscitation. An urgent endo-myocardial biopsy (EMB) was performed. The histology showed a massive inflammatory cell infiltration, extensive myocyte necrosis, and numerous giant cells, in the absence of caseating necrosis, epithelioid cells, and asteroid bodies, consistent with the diagnosis of idiopathic GCM (Fig. 1a–d). Molecular

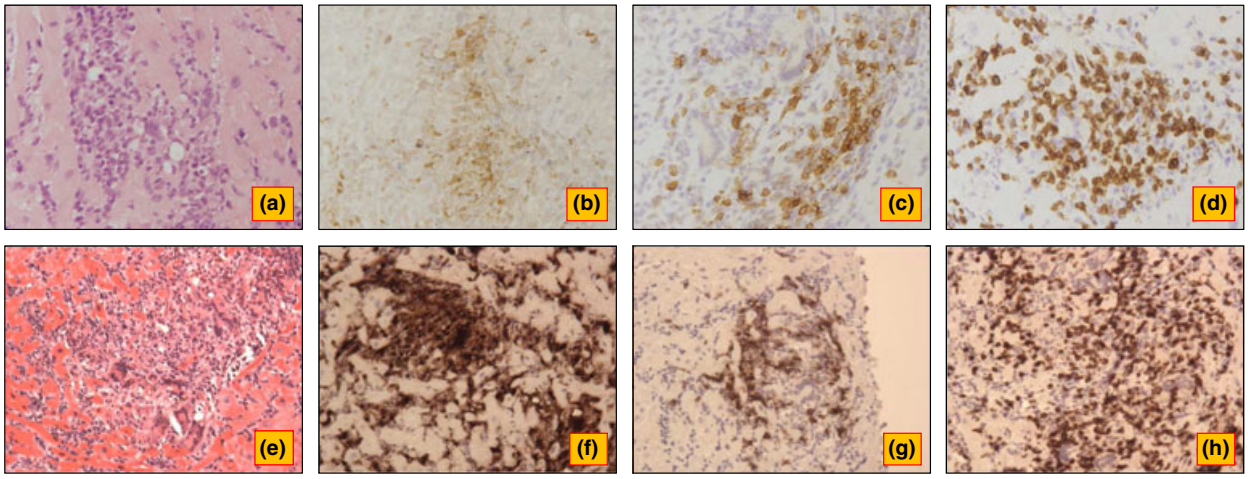

Figure 1 Histological and immunohistochemical pictures. (a–d) Endo-myocardial biopsy (EMB) performed at the onset of the disease on native organ: (a), H&E staining (200× of magnification) showed massive inflammatory infiltration, giant cells, lymphocytes, eosinophils, and myocardial necrosis; (b), CD68 staining (200× of magnification) identifies giant cells and macrophages; (c), CD20 staining (200× of magnification) showed diffuse B-cell infiltration; (d), CD3 staining (200× of magnification) confirmed the massive presence of T cells. (e–h) EMB performed on transplanted heart showed the recurrence of non-granulomatous giant cell myocarditis: (e), H&E staining (100× of magnification) showed severe myocardial damage; (f), CD68 staining (200× of magnification) confirmed the presence of a large number of giant cells; (g), CD20 staining showed B-cell population; (h), CD3 staining showed numerous T lymphocytes.

analyses were negative for EBV, CMV, influenza viruses A and B, parvovirus B19, enterovirus, and herpes virus 6. Other systemic granulomatous diseases were excluded. Immunosuppressive therapy with methylprednisolone, 1.5 mg/kg/Day, azathioprine, and cyclosporine A was immediately started. Nevertheless, despite treatment, the clinical conditions worsened and the patient underwent continuous veno-venous hemofiltration (CVVH) and then extra-corporeal membrane oxygenation (ECMO) stabilized patient hemodynamic condition. The patient was placed on the "Status One" list for emergency HTx which was carried out on day fifteen since onset of symptoms. After transplantation, the patient underwent regular follow-up including monitoring EMBs according to our protocol [4]. The sixth biopsy, 2 months after HTx, revealed a diffuse lympho-monocytic infiltration (40% CD3+ T cells, 5% CD20+ B lymphocytes, 10% CD138+ plasma cells, and 45% CD68+ cells) together with many giant cells, eosinophilic granulocytes, and diffuse myocyte necrosis, consistent with the recurrence of idiopathic GCM (Fig. 1 e–h). Troponin I evaluation showed a mild increase 2 weeks after transplantation (3.64 μg/l). As the EMBs performed 2 weeks later showed resolution of the process, the decision was to continue with immunosuppression therapy for 7 months. Six EMBs performed subsequently, 5 months after the first recurrence, were negative for moderate rejection (<2R) and recurrence. The patient was stable with preserved ejection fraction. Second recurrence episode (EMBs XIII-XIV) occurred 8 months after transplantation (i.e., 6 months after the first episode) requiring infusion of rabbit antithymocyte globulin (rATG) and increase in cyclosporine and prednisone dosages (Fig. 2). Troponin I was in normal range. Cardiac MRI showed focal edema localized to apex (Fig. 3). Despite the following three EMBs (XV, XVI, XVII at 1, 2, 3 months, respectively) were negative, hemodynamic condition progressively deteriorated in the following months (LVEF reduction). On the XVIII EMB, 13 months after HTx, there was a third recurrence episode of GCM. Immunosuppressive therapy was immediately integrated with the addition of everolimus (0.25 mg) and a pulse of methilprednisolone (1 g).

Despite this aggressive therapy, EMBs XIX, XX, XI performed 15, 16, 17 months after HTx (Fig. 2) did not show any regression of GCM. LVEF remained low, with the development of a left ventricle thrombotic stratification and frequent ventricular extra-systolic beats (ESB). Given the rapidly deteriorating clinical condition of the patient, according to its reported safety and efficacy in some systemic granulomatous diseases [5–10], we made a therapeutic attempt with rituximab, an anti-CD20 monoclonal antibody, even if not supported by international guidelines nor randomized studies. Rituximab was given at the dose of 375 mg/m^2/week i.v. for four consecutive weeks, in combination with the aforementioned standard immunosuppressive treatment. We observed a rapid recovery of the EF, together with the resolution of the left ventricle thrombotic stratification, the reduction in ventricular ESB and the resolution of myocardial inflammation at monitoring EMBs

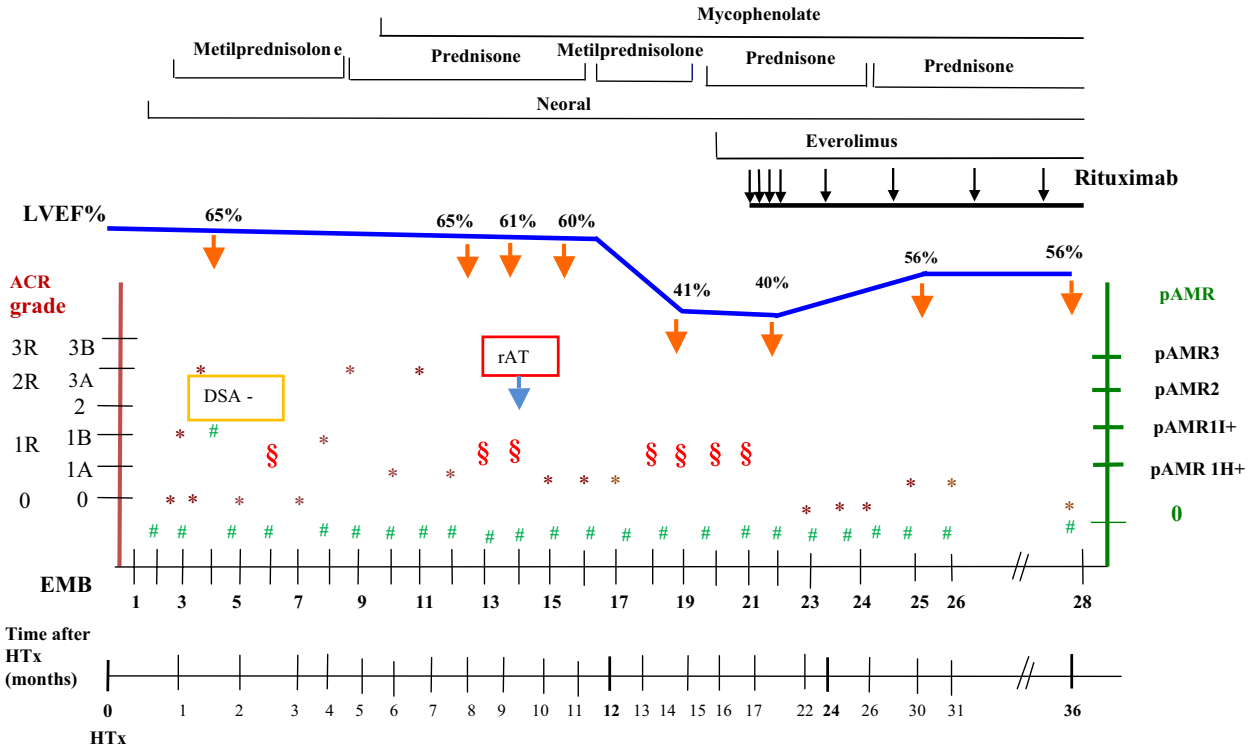

Figure 2 Clinical course in terms of endo-myocardial biopsies (EMBs), acute cellular rejection, antibody-mediated rejection, recurrence of idiopathic giant cell myocarditis (GCM), pharmacologic treatment hemodynamic status. *ACR grade: we reported the two ISHLT classification (1990 and 2005). #pAMR classification: we reported the pAMR grade according to ISHLT 2011. IV EMB C4d was positive and DSA were negative. §Recurrence of idiopathic giant cell myocarditis (idiopathic GCM) after heart transplantation. Rituximab (375 mg/m^2) administered once a week for 4 weeks and then every 4 months. The patient had three episodes of recurrence of idiopathic GCM. At the third episode, we introduced rituximab and the hemodynamic conditions improved, and at nineteen months after HTx, they are stable and no recurrence occurred.

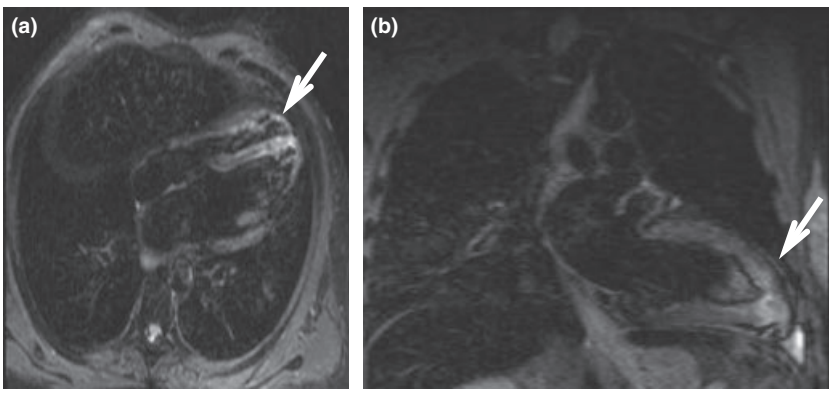

Figure 3 Cardiac MRI images (obtained without contrast due to concomitant renal failure) of the first recurrence of giant cell myocarditis. Myocardial inflammation and edema of the apical septum and apex (a) seen as high myocardial intensity on triple inversion recovery (TIRM) T2-weighted delayed enhancement images with fat saturation in four cardiac chambers and (b) edema of apical segments seen in two cardiac chambers view.

(Fig. 2) [11]. Rituximab, 375 mg/m^2 i.v., was then given as maintenance therapy every 4 months. All the following routine EMBs confirmed the complete resolution of the disease in the graft and patient clinical and hemodynamic condition remains steadily good.

Discussion

To the best of our knowledge, the use of rituximab in the treatment of idiopathic GCM, both in primary onset and transplanted heart, has never been reported before and

there are no randomized studies in literature. Non-granulomatous GCM represents a particularly aggressive form of myocarditis with a rapid and fatal clinical evolution. It usually affects young adult patients (mean age 42.6 ± 12.7 years); there is a strong association with autoimmune disorders (20%), mainly inflammatory bowel disease (8%), thyroiditis, and thymoma [12]. Its exact prevalence is unknown while medical literature only reports small series and single cases. Compared to lymphocytic myocarditis, GCM has a markedly worse prognosis with a median survival of 5.5 months from the onset of symptoms with 89% of patients requiring HTx [1]. Diagnosis of idiopathic GCM is based on EMB. The histological feature is characterized by the presence of diffuse myocardial inflammatory infiltration of lymphocytes, plasma cells, eosinophils, and multinucleated giant cells associated with myocyte necrosis, in the absence of any viral etiology and of typical giant cell granuloma. The pathogenesis of idiopathic GCM is currently attributed to a T lymphocyte-mediated inflammation of myocardial tissue [13]. A rapid and accurate differential pathological diagnosis is then crucial to establish a prompt and effective therapy. The clinical onset of idiopathic GCM is usually characterized by sudden onset of congestive heart failure (75% of cases), frequent ventricular arrhythmias (14–50%), acute myocardial infarction (6%), and complete heart A–V block (5%) [1]. Patients with idiopathic GCM should receive the same guideline-based treatment for heart failure and arrhythmias of patients with heart failure from different causes. However, digoxin should generally be avoided because it increases the risk of A–V block and arrhythmia due to myocardial inflammation [2]. Immunosuppressive therapy includes a combination of cyclosporine and corticosteroids with or without azathioprine and/or anti-CD3 murine Moab (muromonab) and is associated with a median transplant-free survival of 12.3 months compared to 3 months in patients who do not receive immunosuppression [3,14]. The reduction or discontinuation of immunosuppressive therapy up to 8 years after initial diagnosis has been followed by the recurrence of the disease [15,16]. However, idiopathic GCM can have a rapidly progressive evolution to irreversible cardiac failure despite immunosuppressive treatment, requiring emergency HTx or mechanical assisted device [13]. The efficacy of HTx has been questioned because, as in our case, the disease may recur in transplanted organ with a fatal outcome. Indeed, despite the introduction of a classical post-heart-transplant four-drug immunosuppressive regimen, our patient did not show any clinical improvement or benefit. Given the histological evidence of a recurrent idiopathic GCM, the deep immunosuppression of T-cell-mediated immunity (high risk of infection), and the critical hemodynamic condition of the patient, we did not introduce muromonab, whose efficacy is not uniformly observed [17,18]. Despite idiopathic GCM is recognized as a T-cell-mediated autoimmune disease, the immunophenotypic characterization on EMB showed the massive presence of B lymphocytes (CD20+; Figure 1). Granulomatous GCM is characterized by the presence of giant cells, epithelioid cells, necrosis, and vasculitis[5–8]; in granulomatous GCM, there is also a strong evidence of the pathogenic role of B cells expressing CD20, as in idiopathic GCM. Rituximab, a chimeric mouse–human monoclonal antibody that binds to CD20, leads to B-cell depletion by a complement-mediated pathway (antibody dependent cellular cytotoxicity) [19,20]. Rituximab acts against B cells in CD20+ lymphoproliferative diseases and blocks B-cell-mediated immunity in antibody-mediated autoimmune disease without producing any major imbalance of T-cell-mediated immunity. Although the initial rationale for the use of rituximab in granulomatous diseases was based on the evidence of autoantibody production in antineutrophil cytoplasmic antibodies (ANCA) positive diseases, it is likely that it has a more complex mechanism of action involving also T-cell-mediated immunity [10]. Indeed, rituximab showed to be effective and safe in the treatment of systemic sarcoidosis and WG with cardiac involvement [7,8]. Moreover, rituximab acts also by an immunomodulatory mechanism and not only by a B-depleting action; then rituximab can also be used in the absence of a histological massive infiltration of B cells. This single experience seems to suggest that rituximab could be a reasonably safe and effective therapeutic option in GCM refractory to standard therapeutic measures, both when it recurs in transplanted organs but, possibly, also at its onset in native organs. However, as there are neither randomized studies nor guidelines supporting the use of rituximab in GCM, this therapeutic option must be carefully evaluated in every single patient.

Authorship

GT: performed clinical management and wrote the paper. PT: collected data and wrote the paper. MF: collected data, performed histological examination and wrote the paper. AA: performed histological examination and reviewed the paper. RM: conceived and planned the treatment, wrote and reviewed the paper.

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