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Malignant lymphoma in the donor heart after heart transplantation

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A case of post-transplant lymphoproliferative disease (PTLD) with donor heart involvement is reported. The 49-year-old patient presented with heart failure initially ascribed to acute graft rejection. The treatment with high doses of immunosuppressive agents was unsuccessful and the outcome rapidly fatal. This case suggests that cardiac failure occurring after high doses of immunosuppressive therapy could be a sign of early PTLD in heart transplant recipients.

Introduction

The incidence of a lymphoproliferative disorder is 28 times higher in transplanted patients than in the general population[1]. Extranodal development is frequent and organs mostly involved by post-transplant lymphoma (PTLD) are the central nervous system, small bowel, lungs and liver[2]. Involvement of the grafted organ is rarely reported but is believed to occur in as many as 18% of the renal transplant recipients who develop PTLD[3]. We report a case of PTLD involving a transplanted heart which was misdiagnosed and assumed to be acute rejection.

Case history

A 49-year-old man was admitted to our institution with primitive dilated cardiomyopathy at an advanced stage (left ventricle ejection fraction of 17%). An orthotopic heart transplantation was indicated and the operation was performed on 3 June 1989. The donor was a 21-year-old male without any history of previous disease. Immunosuppression was obtained with methylprednisolone starting with 500 mg . day^{-1} and decreasing to 1 mg . kg^{-1} . day^{-1} on the 5th day as well as anti-lymphocyte globulins (175 mg . day^{-1} over 5 days). At the 5th postoperative day azathioprine and cyclosporine were added. A daily dose of 1 mg . kg^{-1} of prednisolone was maintained during the first month.

The initial postoperative period was uncomplicated and the patient was discharged on the 20th postoperative day. He was rehospitalized on the 27th day for an acute rejection episode confirmed by endomyocardial biopsy. During the next 50 days, two other rejection episodes occurred leading to a total of three acute rejections, all of which were qualified as mild to moderate rejection according to histological grading[4]. Transthoracic echocardiographic imaging during each acute episode demonstrated an important shortening of the isovolumic relaxation time (IVRT) and a decrease in the pressure half time (PHT), associated with impairment of left ventricular diastolic function. The IVRT and the PHT consistently returned to normal values between the rejection episodes. The two first rejections were treated with methylprednisolone (1 g . day^{-1} for 3 days) and anti-lymphocyte globulins (175 mg . day^{-1} for 7 days). The third rejection was treated with monoclonal CD3 antibody, at a dose of 5 mg . day^{-1} for 10 days and methylprednisolone (1 g . day^{-1} for 3 days).

On the 85th postoperative day, 10 days after the last rejection episode, the patient presented with cardiac failure, oliguria and fever. Echocardiographic examination showed significant thickening of the left ventricular wall with dilation of the right ventricle and severe impairment of the systolic and diastolic functions of the left ventricle. The diagnosis of continuing acute rejection was established. Despite new treatment with monoclonal CD3 antibody, the clinical condition of the patient worsened resulting in intractable congestive heart failure. The patient died on the 88th postoperative day. The total dose of monoclonal CD3 antibody administered to the patient during the clinical course was 65 mg. Unfortunately, Epstein Barr Virus (EBV) serology was not performed in this patient. The post-mortem examination showed hypertrophic and dilated cardiopathy. The heart weighed 820 g and demonstrated concentric hypertrophy. The liver and the spleen weighed 2250 g and 1210 g, respectively; right and left lungs weighed 670 g and 590 g, respectively. The central nervous system was normal.

Lymph nodes appeared normal and were not harvested. The bone marrow was not examined. Histological examination showed lymphomatous destructive infiltration of the left ventricular wall with tumour necrosis. The lymphomatous elements were polymorphic with immunoblasts. Histology of the liver showed lymphomatous portal infiltration with few foci of necrosis, and diffuse immunoblastic infiltration. The spleen tissue was completely replaced by immunoblastic cells. Immunohistological examination was obtained on paraffin embedded material

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and was positive for common leukocyte and MB2 antigen, confirming the diagnosis of B-type non-Hodgkin's lymphoma. An IgM immunoglobin linked to the light chain kappa was expressed. According to the Kiel classification and to the working formulation for clinical usage, the lymphoma could be classified as immunoblastic with plasmocytic differentiation (group H). However, PTLD are usually classified according to criteria defined by Frizzera *et al.*[5] and our case would there be a polymorphic diffuse B-cell lymphoma. Endomyocardial biopsies performed before death were reexamined with immunohistological markers and were found negative for MB2 (B cells) and positive for UCHL1 and CD3 (T cells). The paraffin embedded material was studied for Epstein–Barr Virus (EBV) DNA by the immunocytochemical method and was found positive.

Discussion

Cardiac involvement by a malignant lymphoma is uncommon. The rate of occurrence is described to range from 8·5%[6] to 26%[7] in cases of disseminated lymphoproliferative disease. In transplant organ receivers, and particularly since the introduction of cyclosporine A, lymphomas are the most frequently encountered tumours. Moreover, recent developments in immunosuppressive therapy with monoclonal CD3 antibody have been associated with an increased occurrence of lymphoproliferative disorders[8], but the rate of cardiac localization of PTLD is very difficult to assess. We were able to find eight cases of cardiac involvement by post-transplant lymphomas in the English literature, six in renal transplant recipients[9–12] and two in cardiac transplant recipients[13]. Only one patient presented with an isolated localization of the lymphoma in the heart[11]. All others had a disseminated, multi-organ form of the disease. The time of occurrence after transplantation was very short, less than 12 months, apart from the isolated form, in which the time interval was 13 years. The shortest time of occurrence of PTLD reported to date is 0·7 months after transplant[12]. Clinical symptoms, when existing, were cardiac failure[11] or heart block[9]. In one of the cardiac transplant recipients, the diagnosis was considered before death through an endomyocardial biopsy. No patient survived. All lymphomas were of B-type. The responsibility of EBV could be assumed in only one patient with a primary infection[9].

The development of a lymphoproliferative disorder in a transplanted heart is of particular interest because, as in our case, the clinical symptoms could mimic an episode of acute rejection. We can assume that what was diagnosed as a persistent acute rejection was, in fact, the clinical signs of the cardiac lymphoma. Endomyocardial biopsy could have permitted the diagnosis but was not performed due to the poor condition of the patient. The positive result of immunocytochemical examination for EBV on autopsy material confirms the role of EBV oncogenesis in this case, in spite of the absence of serologic data.

Although the total dose of monoclonal CD3 antibody administered to our patient was only 65 mg, the case is consistent with the findings of Swinnen *et al.*[8] who reported an increased incidence of post-transplant lymphoma after a total dose of 75 mg. Lastly, involvement of the donor organ raises the question of a donor-transmitted lymphoproliferative disease. In bone marrow transplanted patients[14] the transmission of lymphoma by donor cells has been documented. However, other authors reported that cancer transmission by a donor organ is an unlikely event: among the 164 cases of donor-transmitted cancers collected over a 21-year-period, lymphomas were the exception[15,16]. In our case, the short time interval of occurrence would substantiate the hypothesis of a donor-transmitted disease, although early endomyocardial biopsies could not detect the lymphoproliferative elements which would confirm this hypothesis. Furthermore, these endomyocardial biopsies were found positive with only T-cell markers, thus supporting the hypothesis that the lymphoma appeared very late in the clinical course of our patient. In our opinion, the short time interval is due to deep immunosuppression induced by the association of high doses of powerful agents such as cyclosporine and monoclonal CD3 antibody during rejection episodes and not to a donor transmission.

In conclusion, the diagnosis of cardiac lymphoma should be suspected when rejection signs worsen after high doses of immunosuppressive drugs, and endomyocardial biopsy should be performed even in cases of severe heart failure.

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