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Heart transplantation in a highly sensitised patient

Przeszczep serca u pacjenta ze znacznie zmodyfikowaną odpornością

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Abstract

Some patients awaiting heart transplantation may develop positive panel reactive antibodies (PRA). Several reports have demonstrated that pre-transplant sensitisation is associated with decreased survival and a higher rejection rate, and leads to the development of cardiac allograft vasculopathy. We describe our experience with a highly sensitised transplant recipient. To reduce sensitisation, three courses of immunoadsorption were administered. The PRA level decreased effectively and actual cross-match was negative. The patient underwent successful heart transplantation, and desensitisation treatment continued with immunoadsorption and intravenous immunoglobulin for five courses. Graft function remains normal at 12 months post-operatively and the clinical status of the patient is stable.

Key words: allograft rejection, allograft vasculopathy, immunoadsorption, heart transplantation

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INTRODUCTION

The proportion of patients with elevated panel reactive antibodies (PRA) is gradually increasing and poses a high risk of antibody-mediated rejection and graft failure [1]. In the pre-transplant period, it is one of the causes of the development of antibodies against leukocyte antigens [2, 3]. The commonest reasons are blood transfusions, previous surgical revascularisation and/or the use of a ventricular assist device [4, 5]. In women, antibodies may develop during pregnancy, labour or abortion. Suppression of antibody formation is a complex task. It comprises suppression of the activity of both T and B lymphocytes, and predominantly, elimination of the circulating antibodies. This case report illustrates the complex management of a highly sensitised heart transplantation (HTx) candidate.

A 51 year-old patient with multiple risk factors for coronary artery disease, including arterial hypertension, diabetes mellitus controlled by diet, and cigarette smoking, experienced a cerebral vascular stroke ten years ago with transient left-sided hemiparesis. In April 2008, he was admitted to the local hospital with a diagnosis of extensive anterior myocardial infarction with ST elevation. Early coronary angiography documented multi-vessel disease, including the involvement of the left main coronary artery. Left ventricular systolic function was impaired (LVEF 25%). The patient was selected for early surgical myocardial revascularisation and this was performed in May 2008. During cardiac surgery, the patient received blood derivatives. No significant improvement in LVEF was observed post-operatively. He was discharged in June 2008 and re-admitted for acute left heart failure in the July and again in the August. In August, repeated coronary angiography was performed which documented patency of all aortocoronary bypasses. In September 2008, the patient was transferred to our department with bilateral heart failure. The-

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rapy with inotropic support (dopamine and dobutamine) combined with continuous diuretic treatment was established. Echocardiographic examination confirmed significant left ventricular systolic dysfunction (LVEF 20–25%). Right-sided catheterisation revealed severe postcapillary pulmonary hypertension (mean pulmonary artery pressure of 51 mm Hg and pulmonary arterial resistance 4.1 Wood units). After stabilisation of clinical status, mean pulmonary artery pressure decreased to 39 mm Hg, and arterial resistance to 1.7 Wood units. The patient was enlisted for HTx in October 2008. In the set of immunological examinations, high PRA levels were repeatedly identified, reaching 92%. This finding necessitated desensitisation therapy before HTx could be performed.

The elimination method of immunoadsorption, using affinity chromatography, was employed to remove antibodies. The Citem 10 immunoadsorption system and staphylococcal protein A column were used. Three immunoadsorption rounds were applied between 18 November and 2 December, 2008. As a result, immunoglobulin levels and PRA decreased from 92% to 36% (Fig. 1). On 16 December, a cross-match test was performed with a negative result and the patient underwent successful HTx. After uneventful surgery, the patient had temporary pacing due to complete atrioventricular (AV) block. Because of persistence of AV block, a permanent pacemaker was implanted ten days later.

In the early post-operative period, inotropic support was progressively discontinued, and renal function temporarily decreased although it was promptly restored. Prophylactic therapy with anti-thymocyte globulin was administered after surgery. Immunosuppression took the form of tacrolimus, mycophenolate and steroids. Another course of immunoadsorption was performed 48 hours after HTx. The initial biopsy on day seven was grade 0R and immunofluorescence was negative. A total of four endomyocardial biopsies were performed during the first four post-operative weeks, with no signs of allograft rejection. The patient was discharged on January 15, 2009. However, one week later, a fifth endomyocardial biopsy showed early antibody-mediated rejection — slight positivity of C4d (+/-) in the blood vessel wall. This finding was associated with positivity of cross-match test. Two urgent courses of immunoadsorption were applied and intravenous immunoglobulin was administered after each round at a dose of 1 g/kg and 0.5 g/kg. As a result, there were significant drops in the IgG, IgA and IgM levels. There were decreases in immunoglobulin subclasses IgG1 (from 7.7 to 2.4 g/L) and IgG2 (from 4.9 to 2.3 g/L) as shown in Figure 2. Other plasma proteins (albumin, coagulation factors, antithrombin III) remained unchanged. A further eight endomyocardial biopsies showed no signs of antibody-mediated and/or cellular rejection. The final biopsy was performed in October 2009. The patient remains haemodynamically stable with preserved left ventricular systolic function.

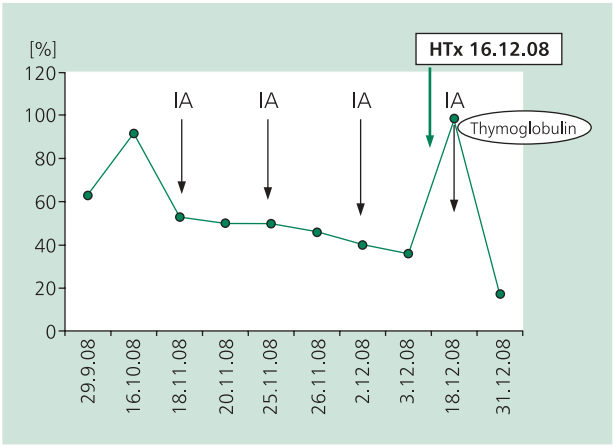

Figure 1. Immunoadsorption (IA) reduced panel reactive antibodies levels; HTx — heart transplantation

DISCUSSION

In recent years, the number of candidates for HTx awaiting a donor has markedly increased. The waiting time for highly sensitised patients is even longer, as these individuals develop antibodies against the tissues of the majority of the general population. The presence of high values of PRA in the HTx candidate increases the risk of positive cross-match. A high percentage level of PRA can be the result of previous blood transfusions, surgical revascularisation, pregnancy and/or the use of ventricular assist devices. Such pre-transplant sensitisation may lead to decreased survival, increased incidence of antibody-mediated rejection and the development of graft cardiac allograft vasculopathy after HTx [6, 7]. In recent reports, a PRA > 25% has been associated with poor survival after HTx [8]. However, the indication and strategy of desensitisation therapy before HTx remain inconsistent. Some transplant centres [9] perform pre-transplant desensitisation treatment in patients with PRA > 50%. The desensitisation protocol consists of a combination treatment, including immunoadsorption or plasmapheresis and intravenous immunoglobulin [9–13]. Compared to plasmapheresis, immunoadsorption has some important advantages. Firstly, there is no significant depletion of plasma components such as albumin or clotting factors. Secondly, adverse effects such as allergic reaction, viral contamination and hypotension are less frequently observed. Immunoadsorption is also more specific and therefore more effective. Intravenous immunoglobulin is effective in reducing anti-HLA antibodies and also has an anti-inflammatory effect. It modulates the cellular and humoral mechanisms of immune response, induces long-term immunosuppression and eliminates reactive T and B cells. Intravenous infusion of immunoglobulins has also been observed to neutralise circulating antibodies. Other centres use monoclonal antibodies against CD20 antigen-rituximab [14, 15]. It inhibits CD20 positive B cell proliferation and induces apoptosis by antibody-dependent cytotoxicity and by com-

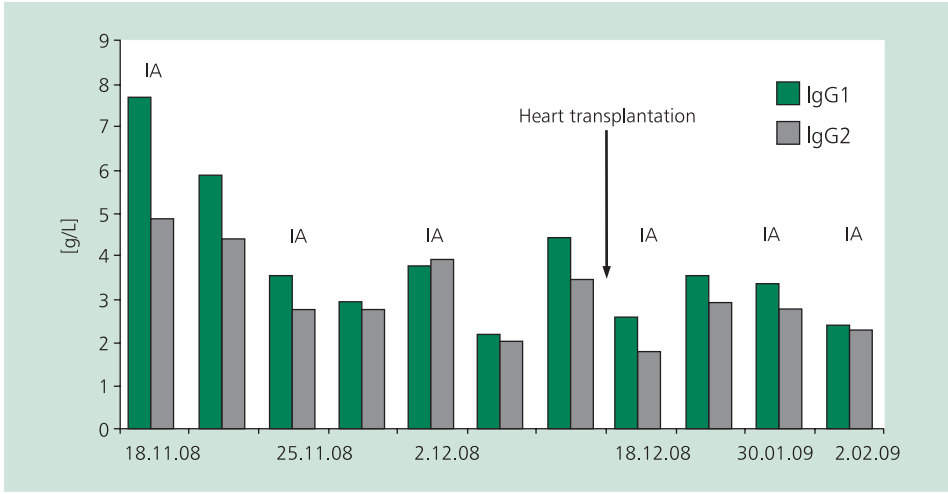

Figure 2. Elimination of immunoglobulin G1 (IgG1) subclass and immunoglobulin G2 (IgG2) subclass after immunoadsorption (IA)

plement-dependent cellular toxicity. Rituximab has been proven effective in the treatment of haemodynamically significant humoral rejection refractory to conventional therapy [16]. The timing of desensitisation therapy is also an issue. Some centres use it just prior to HTx, while others treat it pre-transplant [17, 18]. The threshold PRA level for initiation of treatment also differswith some centres treating patients with PRA > 10% and others with PRA > 80% [9].

Our patient was probably sensitised after myocardial revascularisation and secondary to blood product exposure. We applied pre-transplant desensitisation using immunoadsorption which led to a significant decrease in circulating antibodies. Repeated courses of immunoadsorption and administration of intravenous immunoglobulin post-operatively after HTx suppressed antibody-mediated rejection, as confirmed by endomyocardial biopsy. Thus, this strategy proved to be successful and could be adopted in similar cases of high level sensitisation before HTx.

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