Successful Treatment of Cardiogenic Shock Caused by Humoral Cardiac Allograft Rejection

Shunsuke Saito, MD; Goro Matsumiya, MD; Norihide Fukushima, MD; Taichi Sakaguchi, MD; Tomoyuki Fujita, MD; Takayoshi Ueno, MD; Shuji Miyagawa, MD*; Amane Yamauchi, MD**; Yoshiki Sawa, MD

The progress of immunosuppressive therapy has made heart transplantation the standard therapy for end-stage heart failure. However, humoral rejection of the cardiac allograft is still a challenging problem associated with high incidence of graft loss and patient mortality. The present patient developed profound cardiogenic shock requiring extracorporeal life support on the 8th day after heart transplantation. Endomyocardial biopsy revealed no cellular rejection, and complement component C4d was positively stained on the capillary endothelium. The patient was successfully treated with repeated plasmapheresis and administration of anti-CD20 monoclonal antibody, rituximab, as well as with steroid pulse and increased standard immunosuppressive medication. (Circ J 2009; 73: 970–973)

Key Words: Anti-CD20 monoclonal antibody; Anti-donor antibody; Heart transplantation; Humoral rejection; Plasmapheresis

Because of progress in immunosuppressive therapy, heart transplantation is now the most effective treatment for end-stage heart failure. However, humoral rejection of the cardiac allograft is still a challenging problem associated with high incidence of graft loss and patient mortality. We present a patient who developed severe cardiogenic shock from humoral rejection and who was successfully treated with a combination therapy consisting of plasmapheresis and pharmacological treatment including the anti-CD20 monoclonal antibody.

Case Report

A 45-year-old gentleman with dilated cardiomyopathy who had been supported by a Novacor left ventricular assist device (WorldHeart Corp, Oakland, CA, USA) for 709 days underwent orthotopic heart transplantation. Although he had received a transfusion of packed red blood cells and platelets at the time of left ventricular assist device implantation, his pretransplant panel reactive antibody (PRA) was 0% and the prospective direct crossmatch was negative. On the day of extubation, the patient suddenly developed profound cardiogenic shock, which required the re-establishment of the IABP and ECMO support (Figure 1). Echocardiography revealed diffuse severe hypokinesis (LVEF <10%) and the thickening of the wall of both ventricles. Humoral rejection was highly suspected, so intravenous steroid pulse therapy and plasmapheresis were started immediately. Endomyocardial biopsy revealed no cellular rejection (International Society of Heart and Lung Transplantation grade 0), but there was severe interstitial edema (Figures 2A, B). Complement component C4d was positively stained on the endothelium of the capillaries (Figures 2C, D). PRA after the 1st plasmapheresis was 34% and anti-donor specific antibodies were detected by flow cytometry analysis (Figure 3B). The diagnosis of humoral rejection was confirmed by these findings, and we treated the patient with a single administration of rituximab at a standard dose of 375 mg/m² and a total of...
Humoral Cardiac Allograft Rejection

Figure 1. Post-transplant course. LVEF, left ventricular ejection fraction; EMB, endomyocardial biopsy; P, plasmapheresis; PRA, panel reactive antibody.

Figure 2. Endomyocardial biopsy at the time of humoral rejection (8th post-transplant day) shows no cellular infiltration but significant interstitial edema (A, B). Immunofluorescence (C) and immunoperoxidase (D) staining show dense deposition of C4d in the capillary endothelium (A: hematoxylin and eosin, ×400, B: Masson’s trichrome, ×100, C: anti-C4 FITC conjugate, ×100, D: immunoperoxidase, ×400).
Humoral rejection of a cardiac allograft is a well-recognized, yet still challenging entity, that was first reported by Hammond and coworkers. The reported frequency ranges from 4% to 20%. Humoral rejection is mediated by antibody and complement deposition in the vasculature of the transplanted heart, and it is associated with decreased graft and patient survival, as well as an increased and earlier risk of cardiac allograft vasculopathy. Although cellular rejection has significantly decreased during the past 2 decades because of improved immunosuppressive therapies, the incidence of humoral rejection is reportedly unchanged. In the most cases of humoral rejection, the characteristic findings in the endomyocardial biopsy and routine staining are interstitial edema and capillary endothelial swelling only, which represent a marked influx of macrophages into the injured capillaries. Complement component C4d is demonstrated on the capillary endothelium by immunostaining, and is considered to be a significant diagnostic finding of humoral rejection. Reported risk factors in heart transplant patients for developing humoral rejection include high levels of PRA, positive pre- or post-transplant crossmatch, induction therapy with OKT3, female gender, malignancy, and preceding infection. The present patient had received a transfusion of packed red blood cells and platelets at the time of left ventricular assist device implantation, and this may have caused sensitization to human leukocyte antigens. Current options for treatment of humoral rejection include plasmapheresis, immunoadsorption, intravenous immunoglobulin and cyclophosphamide administration, increasing doses of immunosupression, and rituximab. Rituximab is a genetically engineered monoclonal antibody directed against the pan-B cell surface molecule CD20, inhibiting B-cell proliferation and inducing apoptosis by antibody and complement-dependent cellular toxicity. T-cells are unaffected by rituximab, and consequently, opportunistic infections rarely occur in association with its administration.

The present patient experienced 2 episodes of profound cardiac allograft dysfunction. The 1st occurred immediately after reperfusion of the graft. As hyperacute rejection was unlikely to occur in a patient with negative pretransplant direct crossmatch, it was considered to be primary graft dysfunction, which we treated with mechanical circulatory support, and the graft’s function recovered in a few days. The 2nd episode occurred on the 8th post-transplant day and humoral rejection was strongly suspected from the timing and the sudden onset of cardiogenic shock without other obvious reasons. The diagnosis was confirmed by demonstrating C4d deposition on the capillary endothelium. PRA, which was 0% preoperatively, turned positive and increased up to 55%. The titer decreased after treatment with plasmapheresis and rituximab. Newly detected antibodies against human leukocyte antigen after heart transplantation are known to be associated not only with humoral rejection but also with cellular rejection, and with poor outcomes. However, in our experience of a total of

700 mg, followed by 4 sessions of plasmapheresis. Cyclosporine was switched to tacrolimus, and the dose of mycophenolate mofetil was doubled. The cardiac allograft’s function gradually recovered with these treatments (LVEF 49%) and IABP and ECMO were removed again. C4d was still positive on the endomyocardial biopsy specimen of the 2nd postoperative week, so another session of plasmapheresis and administration of rituximab was performed, and C4d turned negative in the 3rd postoperative week. Although the patient’s hemodynamic condition was stable thereafter, PRA (12%), C4d staining and donor specific antibodies (Figure 3C) became positive again 1 month after transplantation.
15 cases of heart transplantation, none of the patients has experienced significant increase in PRA titer without humoral rejection.

Humoral rejection accompanying hemodynamic compromise is known to be often fatal. In previous case reports in which humoral rejection accompanying hemodynamic compromise was successfully treated, the EF of the cardiac allografts was 20–40% at the time of diagnosis of humoral rejection. Cardiogenic shock so profound as to necessitate mechanical circulatory support with ECMO and IABP is rare, but many cases of early graft loss that were previously diagnosed as primary graft failure with unknown cause would have been the consequence of humoral rejection.

In conclusion, the possibility of humoral rejection should be considered in case of early allograft dysfunction. Monitoring of antibody levels and immunohistochemical staining are useful for the diagnosis. Plasmapheresis and rituximab are effective treatments, even for severe humoral rejection causing cardiogenic shock.

References