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Antibody-Mediated Rejection After Orthotopic Heart Transplantation: A 9-Year Single-Institution Experience

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ABSTRACT

Objective. Over the past decade, antibody-mediated rejection (AMR) continues to be recognized as one of the major obstacles in cardiac transplantation, yet its clinical outcome has been reported only in small series studies. This investigation reviews our experience in treating 11 patients with AMR after heart transplantation.

Methods. We retrospectively analyzed a total of 11 patients who underwent cardiac transplantation from 2004 to 2012 at a single medical institute. The diagnosis of AMR was made according to criteria set by the International Society for Heart and Lung Transplantation (ISHLT) 2011 working formulation.

Results. The average age among the 11 patients was 50.4 ± 16.9 years. The overall mortality rate was 54.5%. Five patients (45.4%) developed hemodynamic compromise in an average of 5 days after transplantation, presenting with sudden onset of fatal arrhythmia (n = 4; 80%) and immediate heart failure (n = 1; 20%). All 5 patients underwent immediate resuscitation and extracorporeal membrane oxygenation (ECMO) support, and 3 patients died (60%); in contrast, the other 6 patients suffered from progressively worsening cardiac function during long-term follow-up. Three patients (50%) died in this group.

Conclusions. Clinical presentation of AMR varies. Long-term postoperative follow-up in the form of endomyocardial biopsy is recommended with immunohistochemistry C4d staining, with the anticipation of the possibility of future recurrence.

CARDIAC allograft rejection involves cell-mediated and antibody-mediated immunologic mechanisms. Thanks to the advances in immunosuppression, incidence of acute cellular rejection (ACR) has been decreased and attention has now shifted toward the entity recognized as antibody-mediated rejection (AMR), or acute humoral rejection, which was first described by Herskowitz et al and subsequently recognized as a distinct rejection entity by the International Society for Heart and Lung Transplantation (ISHLT) [1,2]. AMR is defined as all allograft rejection caused by antibodies directed against donor-specific human leukocyte antigen (HLA) molecules, blood group antigen (ABO)-isoagglutinins, or endothelial cell antigens. Over the past decade, AMR has been recognized as a significant risk factor for poor outcomes, poor survival, increased graft loss, and accelerated allograft coronary disease [3–5]. An update consensus was reported in 2011, shifting the diagnosis of AMR from clinical to pathological criteria [6]. This study reports our clinical experience in AMR, including diagnosis, management, and treatment, and evaluates cardiovascular mortality among heart transplant recipients with AMR.

METHODS

Patient Population

Between January 1, 2004 and August 31, 2012, we performed a total of 306 orthotopic heart transplantations at the National Taiwan University Hospital. Among them, 11 patients diagnosed with AMR were selected and evaluated using retrospective chart review. All of

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these patients met the criteria set out by the ISHLT 2011 working formulation [7], which included histological parameters, such as activated endothelial cells and intravascular macrophages, and immunophenotypic evidence of capillary C4d deposition.

Clinical Data

The collected clinical and biological parameters included age, gender, etiology of heart failure, and comorbidities. Any mechanical support devices implanted before heart transplantation, including left ventricular assist device (LVAD) or extracorporeal membrane oxygenation (ECMO), are summarized in Table 1. All patients were regularly followed up at a special cardiac transplantation clinic with appropriate post-transplantation evaluation for evidence of rejection and for coexisting hyperlipidemia, hyperuricemia, and hyperglycemia. Five patients (45%) developed acute symptomatic AMR (less than 30 days after heart transplantation) during the same admission. Any precipitated symptoms, date of onset, date of transvenous endomyocardial biopsies for diagnosis, and application of post-transplantation mechanical devices, including ECMO, were noted. The remaining 6 patients diagnosed with AMR in relative chronic status were also enrolled. Any mortality occurring during the study period was recorded for retrospective analysis.

Immunosuppressive Protocols

The maintenance immunosuppression after heart transplantation has been described in a previous study [8]. In brief, our protocol was based on triple-drug regimens of cyclosporine, azathioprine, and prednisolone. Rabbit antithymocyte globulin immuno-induction was routinely administered immediately after the operation. Tacrolimus and mycophenolate mofetil were used for the long-term regimen of rejection prevention.

Rejection Surveillance Protocols

Transvenous endomyocardial biopsies for the surveillance of rejection were performed weekly for the first month, then every 3 months for the first year, and then yearly afterward. The frequency of biopsies could be altered depending on the clinical symptoms and rejection histories. Treatment for AMR was initiated by steroid pulse therapy with methylprednisolone 500–1000 mg/d for 3 days. The decision for initiation of treatment was mainly based on the clinical suspicion of AMR followed by immediate biopsy for pathological proof. All episodes of treated rejection mandated the follow-up biopsy 1 week later for the documentation of resolution or regression to a lower rejection grade.

Table 1. Baseline Demographic and Clinical Characteristics of Patients

Patient No.	Gender	Age (y)	Diagnosis	HTN	DM	Pre-HTx LVAD	Pre-HTx ECMO
1	M	65	ICMP	+	+	−	−
2	F	52	VHD	−	−	+	+
3	M	66	ICMP	+	+	−	−
4	M	61	ICMP	+	+	−	−
5	M	50	ICMP	+	−	−	−
6	M	69	ICMP	+	+	−	−
7	M	63	DCMP	−	−	−	−
8	M	49	DCMP	+	−	−	−
9	M	13	DCMP	−	−	+	−
10	M	27	DCMP	−	−	+	+
11	M	39	DCMP	−	−	−	−

Abbreviations: M, male; F, female; ICMP, ischemic cardiomyopathy; VHD, valvular heart disease; DCMP, dilated cardiomyopathy; HTx, heart transplantation; HTN, hypertension; DM, diabetes mellitus.

Plasma Exchange Protocols

Concomitant plasma exchange or plasmapheresis followed by intravenous immunoglobulin (IVIG) infusion was given over a 5-day treatment basis if severe hemodynamic compromise occurred under the suspicion of rejection. The dosage of IVIG was administered according to body weight. With concurrent plasmapheresis, IVIG 0.4 g/kg was given after each course of plasmapheresis for 5 days, otherwise IVIG 2 g/kg for a single dose without plasmapheresis was given.

HLA

The total number of HLA-A, B, and DR mismatches between donors and recipients were recorded. Patients with only 1 HLA antigen identified at a given locus were presumed to be homozygous for that antigen. HLA mismatch score was calculated based on OPTN/Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) Policy 3.5.11.2 [9].

RESULTS

A total of 11 among 306 patients (3.6%) undergoing cardiac transplantation from 2004 to 2012 were diagnosed with AMR. The baseline demographic and clinical characteristics of the patients are summarized in Table 1. In brief, the average age was 50.4 ± 16.9 years. Of note, there were 3 patients who underwent left ventricular assist device (LVAD) implantation and 2 patients who underwent ECMO before heart transplantation. The clinical outcomes are summarized in Table 2. Among the 11 AMR patients, the overall mortality rate was 54.5%. Five patients (45.4%) developed hemodynamic compromise in an average of 5 days after transplantation, presenting with sudden onset of fatal arrhythmia (n = 4; 80%) and immediate heart failure (n = 1; 20%). All 5 patients underwent immediate resuscitation and ECMO support. Prompt transvenous endomyocardial biopsies were performed in an average of 7 days after transplantation (range, 1–14), and the in-hospital mortality rate was 60% in this group. In contrast, the remaining 6 patients suffered from progressively worsening cardiac function during long-term follow-up, with 3 patients (50%) dying. With all 11 patients, prompt treatment of plasma exchange, plasmapheresis, or double-filtration plasmapheresis was given, with 5 patients undergoing additional IVIG administration. Regarding the HLA mismatching, the total A, B, DR mismatch numbers are 4.8 ± 0.4 and 4.2 ± 1.1 in the acute and chronic AMR groups, respectively. Typical transvenous endomyocardial biopsies pathological finding are demonstrated (Fig 1; patient no.4). Under immunochemistry staining, the major component of the AMR diagnostic criteria was scattering C4d over the endothelial linings of the interstitial capillaries, with scant positive staining of either pan T-cell marker (CD3) or pan B-cell marker (CD20).

DISCUSSION

Early allograft failure accounts for 20% of perioperative deaths of heart transplant recipients [10]. The etiologies