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The Journal of
Heart and Lung
Transplantation

http://www.jhltonline.org

Hypersensitivity myocarditis and outcome after heart transplantation

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KEY WORDS:
eosinophils;
myocarditis;
heart transplantation;
acute cellular rejection

BACKGROUND: Hypersensitivity myocarditis (HSM) is associated with the use of multiple drugs and has been occasionally observed in patients awaiting heart transplantation (HTx). However, whether HSM at the time of HTx affects long-term prognosis, including acute cellular rejection (ACR) and antibody-mediated rejection (AMR), after HTx remains unclear.

METHODS: Between 2000 and 2010, 759 consecutive patients underwent de novo HTx at Columbia University Medical Center and were retrospectively reviewed. Clinical characteristics and pathologic findings of patients with a pre-HTx HSM diagnosed by histologic evaluation of the explanted heart were analyzed. Prognosis after HTx was compared between patients with and without pre-HTx HSM.

RESULTS: HSM was observed in 21 patients (2.7%), but in no case was HSM clinically diagnosed. Twelve patients (57%) had received dobutamine infusions. HSM patients had varying degrees of perivascular or interstitial eosinophilic infiltrates with rare necrosis in the explanted heart. The number of biopsy specimens diagnosed with ACR (International Society for Heart and Lung Transplantation Grade $\geq$2R) was 11 (3.9%) in HSM patients and 197 (2.2%) in patients without HSM ($p = 0.06$) during the first year post-HTx, and 11 (3.8%) in HSM patients and 78 (1.5%) in patients without HSM ($p = 0.006$) after the second year post-HTx. Post-HTx survival did not differ in patients with or without pre-HTx HSM.

CONCLUSIONS: HSM at the time of HTx is associated with an increased frequency of late ACR after HTx. Post-HTx survival is not influenced by pre-HTx HSM.

J Heart Lung Transplant 2013;32:553–559

Hypersensitivity myocarditis (HSM) is a well-known cardiac manifestation of a delayed-type hypersensitivity response caused by a variety of drugs, including inotropes, vasodilators, diuretics, and antibiotics.[1,2] The incidence is reported to be 0.5% in autopsy series and up to 23% in the explanted heart for heart transplantation (HTx).[3]

Patients with advanced cardiac failure are generally treated with multiple medications; therefore, the incidence of HSM is elevated in HTx candidates. HSM can cause heart failure,[4,5] but most patients are clinically asymptomatic and are frequently diagnosed as an incidental finding at HTx. HSM in HTx candidates is more frequent with inotropic support with dobutamine.[6–8] HSM is usually resolved by drug withdrawal and corticosteroid therapy, but not all patients with severe hemodynamic compromise can be successfully weaned from inotropic support, even if HSM is clinically diagnosed. Therefore, it may be difficult to exclude patients with HSM from the HTx list.

Generally, the benefits of HTx for any type of myocarditis have been challenged because of the possibility of recurrence and poor prognosis and high rejection rate after HTx.[9–11]

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2013.01.1052

However, little has been reported on the prognosis of patients with HSM in end-stage heart failure. Takkenberg et al[8] showed that 8-year survival after HTx was similar in patients with and without HSM. They did not include data on acute cellular rejection (ACR) or antibody-mediated rejection (AMR), but other studies have shown that pre-transplant HSM had no effect on ACR during 6 months to 1 year after HTx in small cohorts of patients.[7] However, whether HSM at the time of HTx affects long-term prognosis including ACR and AMR after HTx remains unclear. In the present study, we addressed the occurrence, clinical and pathologic characteristics, and prognosis after HTx of patients with HSM at HTx.

Methods

The data collection protocol was approved by the Columbia University Institutional Review Board. The protocol complied with the Health Insurance Portability and Accountability Act and all ethical guidelines outlined by the 1975 Declaration of Helsinki.

Study design

We retrospectively reviewed 759 patients (582 men, 177 women) who underwent de novo heart-only transplantation at Columbia University Medical Center between 2000 and 2010. The analysis excluded patients whose biopsy data after transplant were not available. HSM was diagnosed in 21 patients by histologic evaluation of the explanted heart. Pre-HTx clinical characteristics and post-HTx prognosis in HSM group were compared with the other HTx recipients without HSM (non-HSM group: $n = 738$). Post-HTx endomyocardial biopsies were performed weekly for 1 month, every 2 weeks for 2 months, monthly for 3 months, and every 2 months for 6 months. In second year, the patients undergo biopsy typically at 15, 18, and 24 months; thereafter, biopsies are performed every 6 months or annually, depending on their rejection history.

Histologic evaluation of the explanted heart

The diagnosis of HSM was based on the presence of a mixed eosinophil-rich infiltrate with lymphocytes, macrophages, and plasma cells but little myocyte necrosis.[1,7,8] Routinely sampled regions included the base, middle, and apex from the left and right ventricles and the interventricular septum. For each patient, 9 hematoxylin and eosin stained sections of myocardium were analyzed according to a modified Takkenberg's method.[8] The density of eosinophils/0.1 mm^2 microscope field were evaluated at the most severely inflamed lesion in each location within the heart: epicardium, perivascular, interstitial, and endocardium. These results were graded as 0 (<5 eosinophils/0.1 mm^2), 1+ (5–100 eosinophils/0.1mm^2), 2+ (101–300 eosinophils/0.1 mm^2), 3+ (>300 eosinophils/0.1 mm^2) and the pathologic scores expressed as the sum of grades in 4 locations.

The distribution of eosinophils was classified as localized perivascular, interstitial, epicardium, and endocardium. The form of eosinophilic infiltration was classified as focal or diffuse type. Biopsy grading of ACR was performed according to the 2004 International Society for Heart and Lung Transplantation (ISHLT) classification.[12] Pathologic diagnosis of AMR was made based on the diffuse, strong staining for C4d in capillaries by paraffin immunohistochemistry.[13] Left ventricular (LV) core specimens obtained at the time of LV assist device (LVAD) implantation before the HTx were also investigated.

Statistical analysis

Data are presented as mean ± standard deviation and frequency (percentage). Variables were compared between the groups with Student's unpaired two-tailed *t*-test or Mann-Whitney's *U*-test, as appropriate. Categoric variables were compared using the chi-square test or Fisher's exact tests, as appropriate. The correlation between pathologic score and eosinophil count was explored using Spearman's rank correlation coefficient. A p-value of <0.05 was considered statistically significant. Post-HTX survival was compared using Kaplan-Meier methods with log-rank test. All statistical analyses were performed using SPSS 13.0J software (SPSS Inc, Tokyo, Japan).

Results

Of the 759 transplant recipients, 21 (2.7%; 16 men, 5 women) showed histologic HSM in the explanted heart at the time of HTx. HSM was unsuspected in all patients before HTx. The rate of pre-HTx HSM in our hospital has been decreasing during the study period in inverse relation to the rate of LVAD implantation before HTx (Figure 1). Analysis of demographic characteristics of both groups showed no statistically significant differences, except in the follow-up period, which was longer in the HSM group (Table 1) because HSM was more frequently diagnosed early in the study period. It was unlikely that HSM played a causative role for heart failure in view of their clinical history.

As reported in Table 2, 12 patients (57%) had received dobutamine infusions. Seven (33%) had a history of drug allergy; however, none had signs of drug sensitivity before HTx. Peripheral blood eosinophilia before HTx was observed in 19 patients (90%). The percentage and counts of eosinophil in the HSM group were higher than in the non-HSM group (% eosinophils: HSM vs non-HSM = 9.5 ±

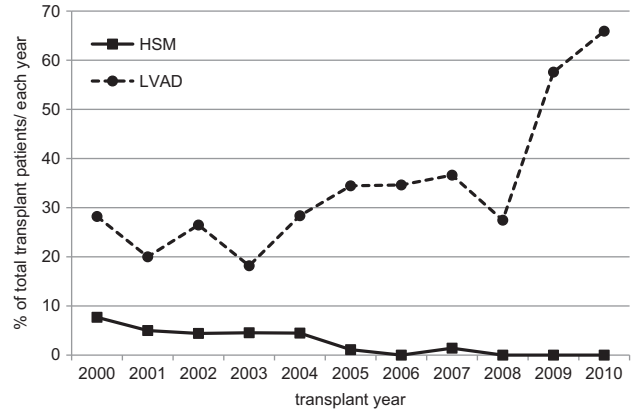

Figure 1 The rates of pre-transplant hypersensitivity myocarditis (HSM) and left ventricular assist device (LVAD) implantation before transplant. The rate of pre-transplant HSM in our hospital has been decreasing as the rate of LVAD implantation before transplant has increased.