Fulminant Acute Cellular Rejection With Negative Findings on Endomyocardial Biopsy

Rajeshkumar Bhalodolia, MD,[a] Cherise Cortese, MD,[b] Michael Graham, MD,[b] and Paul J. Hauptman, MD[a]

We present a case of a heart transplant recipient who had new-onset heart failure, repeatedly unremarkable endomyocardial biopsies, a negative evaluation for humoral rejection, and subsequently autopsy findings of severe sub-epicardial myocyte necrosis with classic cellular rejection. The sub-endocardial layer was free from rejection. The implications for clinical management, in the context of a diagnosis of "biopsy-negative rejection with hemodynamic compromise," include the need to consider intensification of immunosuppression with regimens similar to those used for biopsy-proven rejection. J Heart Lung Transplant 2006;25:989–92. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

Endomyocardial biopsy has been considered the gold standard for diagnosis of acute rejection.[1] To minimize the risk of a false-negative biopsy based on sampling error, multiple specimens are required.[2–4] Nevertheless, the possibility of a false-negative result exists. Several studies have suggested that there can be discordance between findings on endomyocardial biopsy and autopsy, although the incidence is not known.[5,6] Furthermore, patients who present with hemodynamic compromise in the absence of biopsy-proven acute cellular rejection ("biopsy-negative rejection")[7,8] could have classic acute cellular rejection as opposed to humoral or vascular rejection if sampling error has occurred.

We report a case of a cardiac transplant recipient who presented with new-onset heart failure and demonstrated severe allograft rejection morphology limited to the epicardial half of the myocardium. No evidence of significant cellular rejection was observed in multiple endomyocardial biopsy specimens. Immunofluorescence studies performed on multiple biopsies showed no evidence of humoral rejection. The lack of findings in the subendocardial layer in the setting of classic cellular rejection has implications for clinical management.

CASE REPORT

A 54-year-old white male with a history of hypertension, dyslipidemia, atrial flutter and familial cardiomyopathy underwent uncomplicated orthotopic heart transplant while on an intra-aortic balloon pump. In the early post-transplant period, monoclonal antibody induction therapy was not used and serial echocardiograms showed normal left ventricular function. Twelve endomyocardial biopsies (EMBs) performed on Days 10 through 236 post-operatively did not show any evidence of acute allograft rejection (Table 1). The patient was successfully weaned off corticosteroids but maintained on azathioprine and cyclosporine at appropriate levels based on 12-hour trough measurements.

The patient was admitted to the hospital 312 days after transplantation with complaints of new-onset fever, chills, weakness and dizziness. An echocardiogram showed a right ventricular volume overload pattern with an estimated left ventricular ejection fraction of 50%. An emergent EMB demonstrated an endocardial plasma cell infiltrate with eosinophils and some lymphocytes. There was evidence of associated myocyte damage but no significant inflammatory infiltrates were seen in the deeper portions of the specimens; most of the inflammatory activity was seen sub-adjacent to the endocardial surface and was interpreted to be consistent with tissue adjacent to or at a previous biopsy site. Viral inclusions, abnormalities of the microvasculature and ischemic changes were not seen. Nevertheless, the patient was treated with pulse methylprednisolone 1 g/day for 3 days and a regimen of angiotensin-converting enzyme inhibitor and beta-adrenergic antagonist was initiated.

The next biopsy performed 20 days later revealed no evidence of rejection and no plasma cell infiltrate. A second repeat biopsy performed 24 days later revealed International Society for Heart and Lung Transplantation (ISHLT) Grade 0 rejection, a Quilty A effect, an occasional plasma cell and lymphocyte, and negative immunofluorescence for IgG, C1q, C3 and IgA. Nonspecific punctate foci of IgM positivity were seen in the interstitium. Mycophenolate mofetil was added on an empiric basis to the regimen and azathioprine was

From the Departments of [a]Medicine and [b]Pathology, Saint Louis University School of Medicine, St. Louis, Missouri.

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Reprint requests: Paul J. Hauptman, MD, Saint Louis University School of Medicine, 3635 Vista Avenue, St. Louis, MO 63110. Telephone: 314-577-8896. Fax: 314-268-5138. E-mail: hauptmpj@slu.edu

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Table 1. Endomyocardial Biopsy Results

Days from transplant	Endomyocardial biopsy findings
10	0
17	0
24	1A
32	1A (Quilty A)
46	0 (Quilty B)
63	0
90	1A (Quilty A)
118	0
146	0
178	1A
207	QNS (0 on 3 fragments)
236	0
313	0[a]
334	0
357	0 (Quilty A) with negative immunofluorescence
388	1A

[a]Plasma cell infiltrate noted (see text for details). QNS, quantity not sufficient.

withdrawn. Cardiac catheterization performed at the same time revealed angiographically normal coronary arteries, moderately elevated filling pressures with mild pulmonary hypertension, and a left ventricular ejection fraction on left ventriculography estimated at 30%. Given the ongoing heart failure and low ejection fraction, discussions were initiated about possible re-transplantation.

Shortly thereafter, on Day 388 post-operatively, the patient was re-admitted to the hospital with complaints of fatigue, weakness and pre-syncope. An echocardiogram showed an ejection fraction of 15% to 20% with global hypokinesis. The repeat biopsy showed a focal mild mononuclear perivascular cellular infiltrate consistent with ISHLT Grade 1A rejection. An immunofluorescence panel showed negative staining for C1q, IgM and IgA. IgG and fibrinogen showed background staining; Cd4 was negative with appropriate controls. The usual histologic findings of humoral rejection (perivascular leukocyte accumulation, arteriolitis and endothelial swelling) were not seen. Plans were initiated for the administration of intravenous monoclonal antibody therapy, but during the early part of the third hospital day the patient developed cardiac arrest with pulseless electrical activity; extracorporeal membrane oxygenation (ECMO) was used to resuscitate the patient. However, allograft function did not improve and the patient rapidly developed multisystem organ failure. Ventricular assist device therapy as a bridge to repeat transplantation was not considered a viable option and, after discussion with the family, the decision was made to withdraw ECMO support.

At autopsy, the patient had anasarca with bilateral pleural effusions and heavy, congested lungs. The heart weighed 740 g with biventricular hypertrophy. There was mild coronary artery disease. Microscopically, a diffuse, intense infiltrate of small, mature lymphocytes was seen in the myocardium with marked edema and severe myofiber damage. The infiltrates were predominantly seen in the mid-myocardium and the myocardium adjacent to the epicardium (Figure 1) and occurred in a similar pattern in the right ventricle, left ventricle and septum. The endocardium was mildly affected, with a few small infiltrates without myocyte necrosis noted in scattered areas (Figure 2). In addition, dense infiltrates of lymphocytes were noted in the pericardial tissue. These infiltrates were composed of densely packed, small, mature lymphocytes with scattered plasma cells and histiocytes and a rare eosinophil. No lymphoid follicles or viral inclusions were observed. The infiltrates did not extend into and were not contiguous with the myocardial infiltrates; there was a demarcation between the epicardium and the myocardium with a

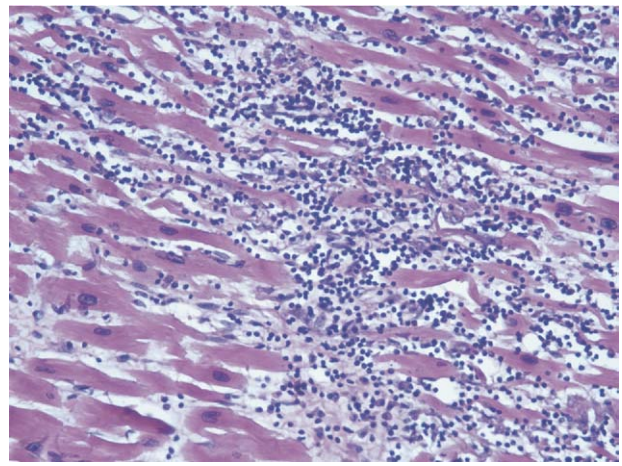

Figure 1. Mid-myocardial lymphocytic infiltrate with myocyte damage (hematoxylin–eosin stain; original magnification ×100).

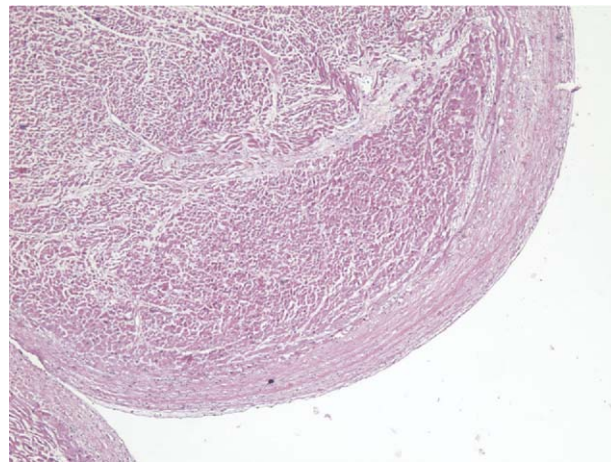

Figure 2. Endomyocardium at autopsy showing absence of lymphocytic infiltrates (hematoxylin–eosin stain; original magnification ×40).