**Case Study**

**Retransplantation in a 26-Year-Old Woman With Dilated Cardiomyopathy**

John Conte, MD

**June 2003**

A 26-year-old woman with dilated cardiomyopathy was evaluated and listed for transplantation. Despite maximum medical therapy (including a β blocker, angiotensin-converting enzyme [ACE] inhibitor, diuretics, and intravenous milrinone) she had progressive deterioration.

**August 2003**

A left ventricular assist device (VAD) was implanted, and she did well initially, but after a few months she developed complications; driveline infections were treated with antibiotics and debridements.

**May 2004**

The patient was transplanted (Figure 1) with daclizumab induction and then started on cyclosporine, mycophenolate mofetil, and prednisone.

**Figure 1. Transplant for Dilated Cardiomyopathy and Progressive Heart Failure (May 2004)**

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Donor</th>
</tr>
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<tbody>
<tr>
<td>Blood type O Rh-</td>
<td>Blood type O Rh+</td>
</tr>
<tr>
<td>HLA A: 24,32</td>
<td>A: 2,3</td>
</tr>
<tr>
<td>B: 7,60</td>
<td>B: 7,35</td>
</tr>
<tr>
<td>BW: 6</td>
<td>BW: 6</td>
</tr>
<tr>
<td>C: 3,7</td>
<td>DR: 11</td>
</tr>
<tr>
<td>DR: 4,11</td>
<td>DRw: 52,53</td>
</tr>
<tr>
<td>DRw: 52,53</td>
<td>DQ: 8,7</td>
</tr>
<tr>
<td>DQ: 8,7</td>
<td>CMV, EBV+</td>
</tr>
<tr>
<td>CMV, EBV-</td>
<td></td>
</tr>
<tr>
<td>Donor ischemic time, 270 min</td>
<td></td>
</tr>
<tr>
<td>PRA &gt;10%; crossmatch performed: negative</td>
<td></td>
</tr>
<tr>
<td>Retrospective crossmatch 5/17/04: negative</td>
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**May 2005**

She did well for 1 year before 2 sequential grade 3A biopsies were found. Both rejection episodes were successfully treated with methylprednisolone boluses, leading to grade 1 biopsies after each event. As planned, she was then converted to tacrolimus. Steroid-induced diabetes required treatment with insulin.

**July 2005**

She developed recurrent grade 3B/3R rejection. The hematoxylin and eosin showed significant grade 3 rejection with diffuse cellular infiltrates, and the CD8 immunoperoxidase staining showed a large number of cytotoxic T lymphocytes, representative of a high-grade rejection episode. She was treated with methylprednisolone and antithymocyte globulin (ATG). Right heart catheterization at that time revealed significantly elevated filling pressures, and echocardiography revealed severe left ventricular dysfunction. She was discharged on furosemide and an ACE inhibitor.

**August 2005**

At follow-up, the ejection fraction was persistently low (30%). She was euvoletic on a right heart catheterization with a reasonable cardiac index of 3 L/min/m². Her left heart catheterization at that time showed no significant coronary disease, but she had developed class III heart failure symptoms (ie, dyspnea on exertion, 2-pillow orthopnea, and occasional palpitations).

**September 2005**

She worsened and was admitted with heart failure and syncope. Right heart biopsy showed low degrees of cellular rejection (1R/1A), but very significant elevations of her filling pressures with a pulmonary capillary wedge pressure of 30 mm Hg, a right atrial pressure of 18 mm Hg, but again, a

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**CMV** = cytomegalovirus; **EBV** = Epstein-Barr virus; **HLA** = human leukocyte antigen; **PRA** = panel-reactive antibody.
maintained cardiac index of 3 L/min/m² on right heart catheterization. Echocardiography at this point was 20%. Based on a clinical diagnosis of humoral rejection, she was treated with muromonab-CD3, plasmapheresis, and immunoglobulin G. During the follow-up period she developed cytomegalovirus pneumonitis and a urinary tract infection. Frequent follow-up with fluid management with diuretics was required.

**November 2005**

She developed recurrent cellular rejection. There was continued depression of her ejection fraction (10%–15%) and markedly diminished cardiac index (1.4 L/min/m²). She was treated with methylprednisolone and a prednisone taper and had persistent problems with fluid management. Over the next several months, she had class IV symptoms, and her right heart catheterization showed persistently low ejection fraction and elevated filling pressures.

**June 2006**

After continued decline, patient was discharged on milrinone and re-listed for heart transplantation. One month later a donor became available, and she was successfully transplanted (Figure 2) and did generally well. She was discharged approximately 2 weeks after her repeat transplantation. The explanted heart showed evidence of ongoing mild-to-moderate cell rejection, with a mixture of T lymphocytes, CD3 and CD8 positive, and macrophages. Interestingly, there was no evidence of graft coronary disease.

**January 2008**

All biopsies since retransplantation have been grade 0-1, and at her last visit the patient continues to do well clinically with no limitations.

**Discussion**

**Dr Conte:** When we reached that decision point in June 2006, our discussions included possible repeat transplantation, placement of a VAD, inotropic therapy, and hospice therapy. I would be interested in your thoughts on retransplantation and other options.

**Dr Rogers:** I commend you on this aggressive approach. Generally, I have concerns about retransplanting patients with graft dysfunction related to acute rejection. Commonly, these patients continue to have significant rejection with their second graft, and their risk of dying is higher than patients retransplanted for coronary disease.

**Dr Kobashigawa:** This is a transplant patient with a VAD history and one that has experienced a form of smoldering rejection. We certainly would have employed ATG and steroids as you did. Retransplantation is also feasible but I might have first considered starting photopheresis 1 year after the initial transplant. Photopheresis is helpful in patients with recurrent or recalcitrant cellular rejection. Even noncellular rejection seems to improve. We have had at least a dozen patients of this nature go through photopheresis, and even those with ejection fractions of 20% have improved over a period of time.

**Dr Eisen:** I agree that photopheresis may have a role in the recalcitrant, ongoing cellular rejections, and perhaps to some extent in antibody-mediated rejections. This is based mostly on observational studies. It is interesting to note that this patient’s immune response was so robust to the first heart but not to the

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**Table 1. Retransplantation (July 2006)**

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**HLA**

A: 24,32 A: 23,34  
B: 7,60 B: 44,58  
CW: 6 CW: 4,6  
DR: 4,11 DR: 11,15, 52, 53  
DRw: 52,53  
DQ: 8,7 DQ: CMV, EBV-

Donor ischemic time, 110 min
PRA >10%; crossmatch performed: negative
Retrospective crossmatch 7/11/06: negative

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HLA = human leukocyte antigen; PRA = panel-reactive antibody.
second heart and to wonder if this is due to attenuated immune responses due to her ongoing immunosuppression.

**Dr Conte:** Do you think her immune system was revved up due to the infected VAD at the time of the first transplant?

**Dr Eisen:** Infected VADs are associated with elevated panel-reactive antibodies and, even more troubling, with specific antibodies that are difficult to deal with by plasmapheresis. Thus specific antigens might have indeed played a role in the beginning of this case.

**Dr Kobashigawa:** In some patients like this one, you may see an entity called restrictive cardiac physiology with extremely stiff myocardium possibly due to small vessel cardiac allograft vasculopathy. There may also be scar tissue developing around the heart, which can lead to more restrictive cardiac physiology. In these cases there may be no alternative but to evaluate for retransplantation.

**Dr Conte:** We have also used twice weekly low-dose methotrexate to clean up these smoldering rejections. Has anyone else?

**Dr Eisen:** That is possible. It is an older strategy with an inexpensive and readily available drug. However, patients just do not ever seem to clear up and you need to watch for hepatic toxicity. Also, it has been used most often for patients with no hemodynamic compromise, thus, you may need more dramatic therapies, such as photopheresis, for this type of patient.

**Dr Rogers:** One problem with photopheresis is that it is a short-lived treatment and this person had a protracted course of recurrent rejections. You still might end up needing adjuvant oral therapy.

**Dr Kobashigawa:** Methotrexate, cyclophosphamide, vincristine, and other oncology-related drugs have been used to try to shut down the immune system, but they are mainly still for indolent-type rejections. More recently, we have used alemtuzumab for those who have failed photopheresis. Rituximab might even be of value in ongoing humoral rejection.

**Dr Russell:** Would you feel comfortable placing a VAD in somebody that was chronically immunosuppressed?

**Dr Conte:** Most of us would try to avoid implanting prosthetic material into an immunosuppressed patient because of the increased risk for infection and complications. That being said, we have used mechanical circulatory support devices to support people through treatment of severe rejection or as a means to bridge to another transplant.

**Dr Kobashigawa:** True rejection episodes are all more or less potentially reversible. That is why I would rather see rejection than severe transplant vasculopathy, where there is essentially no choice but to consider retransplant. With severe rejection, you still have a chance. We have gone to the intra-aortic balloon pump and then right on to extracorporeal membrane oxygenation (ECMO) and even to VAD placement. By decompressing the ventricle you allow more blood flow, and potentially more of the antirejection medications to get into the donor heart. Thus, even though we have patients on ECMO or the VAD, we will give intense regimens of antirejection medications in the hope of turning the rejection around. We have been successful for example in giving ATG, plasmapheresis, ATG immediately after the plasmapheresis, and then finishing with intravenous immunoglobulin and even rituximab if we are convinced it is humoral rejection—which it often is in cases of hemodynamic compromise. Thus, an intense broad-spectrum treatment may be justified to get return of function.