

CLINICAL DILEMMAS

## Behcet's disease and heart transplantation: A word of caution

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Behcet's disease is a rare autoimmune disease characterized by oral and genital ulcers, and by multisystem disease, including arthritis, neurologic complications and vasculitis. Large-vessel and coronary artery aneurysms are often an indication for surgery, but the return of aneurysms, thrombosis, and the tendency to exhibit an exaggerated inflammatory response at puncture sites (*pathergy*) complicate surgical recovery. As such, cardiac transplantation, which requires atrial and large-vessel anastomoses, has not been reported in patients with Behcet's disease. We report the first orthotopic heart transplant with >1-year survival in a patient with Behcet's disease despite major complications. The investigators remain pessimistic about cardiac transplantation in patients with Behcet's disease until advances in preventing recurrent vascular pathology ensue.

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Behcet's disease (BD) is a rare autoimmune disease characterized by painful oral and genital ulcers, eye and skin lesions as well as large- and small-vessel vasculitis. Vascular disease may manifest as deep venous thrombosis of large vessels or with systemic arterial aneurysms, often involving the great vessels and coronary arteries. Mortality attributable to arterial involvement ranges from 28% to 70%. BD patients exhibit a phenomenon known as *pathergy*, an erythematous, often pustular response to local skin injury, after a skin prick by a needle, or at anastomotic sites after vascular surgery.<sup>1</sup> As such, the

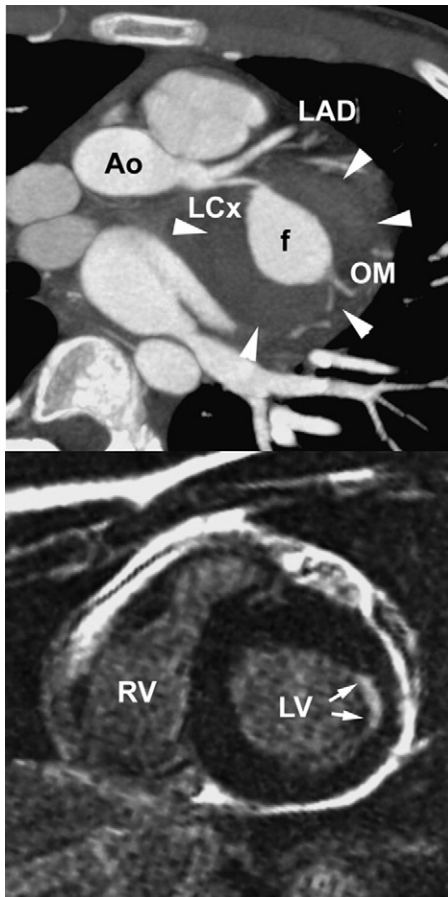
risk factors associated with solid-organ transplantation in this patient population are myriad. There are only a few case reports of renal transplantation in BD patients, the first of which was performed in 1999.<sup>2,3</sup> Due to the risk of performing the required vascular and atrial anastomoses in the presence of this underlying pathology, cardiac transplantation has generally been considered to be contraindicated in BD. To our knowledge, this is the first report of an orthotopic heart transplant with >1-year survival in a patient with BD.

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### Case report

A 17-year-old African American male presented in 2005 with fever, weight loss, aphthous ulcers, hematochezia and



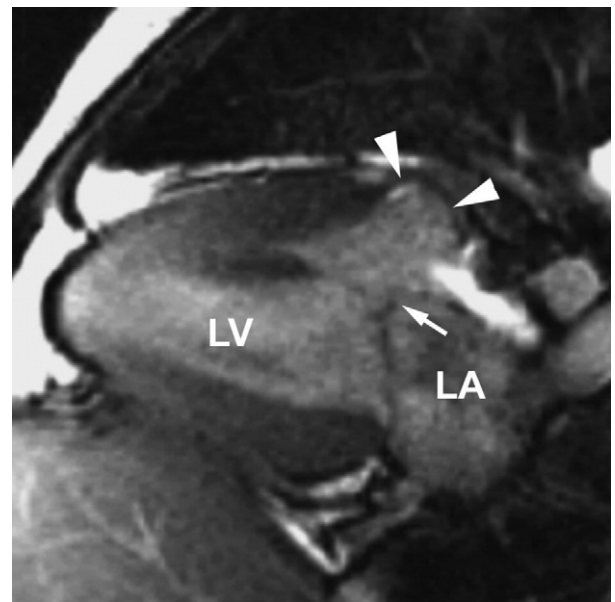
**Figure 1** (Top) An axial maximal intensity projection image from a cardiac-gated, contrast-enhanced CT angiogram of the heart shows a large coronary aneurysm (arrowheads). (Bottom) A short-axis view from a delayed enhancement cardiac MRI shows endocardial hyperenhancement (arrows) of the lateral wall of the left ventricle (LV), consistent with a small region of myocardial infarction.

elevated inflammatory markers consistent with a diagnosis of Behcet's disease.<sup>4</sup> The patient later presented with new-onset cardiac symptoms that included chest pain, dyspnea, elevated cardiac enzymes and a myocardial infarction in the circumflex distribution. Cardiac imaging studies revealed a giant aneurysm of the left circumflex artery, smaller aneurysms of the right coronary artery at its origin, and an endocardial infarction at the lateral wall of the left ventricle (LV) (Figure 1). He was initially treated medically with prednisone, cyclophosphamide and metoprolol; anti-coagulation included aspirin, heparin and eptifibatid. Over time, the patient developed mitral annulus disruption with severe mitral insufficiency, and LV aneurysm recurrence (Figure 2). Despite several interventions between 2005 and 2008, including mitral valve repair and replacement, exclusion of aneurysms and catheter placement of occlusion devices in aneurysmal communications, the patient developed end-stage heart failure with symptoms consistent with New York Heart Association (NYHA) heart failure Class 3 or 4. After much discussion, he was listed for transplant. The patient underwent orthotopic heart transplantation in January 2008. Pre-operative panel-reactive antibody measure-

ments showed no evidence of Class I or Class II HLA antibodies according to a Luminex flow cytometry-based method. Induction therapy consisted of daclizumab (1 mg/kg) every other week for 5 doses. Maintenance therapy included cyclosporine, mycophenolate mofetil and prednisone. He was discharged 17 days post-operatively.

The post-transplant course was complicated by periodic episodes of renal failure, recurrence of painful mouth ulcers and hypertension requiring 4-drug therapy (enalapril, clonidine, diltiazem and amlodipine). Biopsies during the first post-transplant year consistently showed Grade 1A/1R rejection, with the last biopsy at 1-year post-transplant negative for both cellular and antibody-mediated rejection. Cardiac magnetic resonance imaging (MRI) 1 month after transplant showed no evidence of aneurysm formation at the anastomosis sites, or elsewhere. Ventricular function remained normal by echocardiography.

Approximately 18 months after transplant the patient developed severe chest pain and several large pseudoaneurysms were found in the ascending aorta at the site of the surgical anastomosis, the largest measuring  $5.5 \times 7.5 \times 4.7$  cm (Figure 3). At the time of their discovery, prednisone had been weaned to 10 mg/day orally. These lesions represented the first manifestation of recurrent vascular pathergy since transplantation. Emergency surgical re-anastomosis and exclusion of the aneurysm was performed without complication. Colchicine and Anakinra, an interleukin-1 receptor antagonist (IL-1RA) that has been shown in animal models to blunt IL-1-mediated inflammatory and immune responses, were initiated post-operatively. Follow-up computed tomography (CT) with angiography has shown no evidence of re-formation of aneurysms. The patient is now >2 years post-transplant.



**Figure 2** A systolic, vertical long-axis image from a cardiac-gated, bright-blood MRI cine shows a detachment of the mitral valve (arrow) from the ventricular wall (arrowheads). This disruption causes severe mitral regurgitation as represented by the peripheral regurgitant jet. LV, left ventricle; LA, left atrium.



**Figure 3** A maximum-intensity projection image from a contrast-enhanced MR angiogram shows a large false aneurysm (A) that developed after a rupture at the anastomosis between the donor aorta below and the recipient aorta above.

## Discussion

Large-vessel vasculitis is present in up to one third of patients with Behcet's disease and is the leading cause of death in this group.<sup>5,6</sup> In patients with BD who undergo cardiac transplantation, aggressive immunosuppression appears necessary. Despite frequent surveillance with echocardiography, CT angiography and MRI, we were unable to predict the evolution of a rapid and catastrophic aortic anastomotic dehiscence necessitating emergency surgical

intervention. The addition of an IL-1RA may prevent further vascular pathology, but the risks associated with their use in the transplanted human heart remain unclear.

In BD patients who undergo cardiac transplantation, recurrent cardiac and non-cardiac disease remains a significant challenge. In our patient, it is unclear whether increased immunosuppression would have prevented recurrent vascular disease, meriting the attendant risk for infectious complications and post-transplant lymphoproliferative disorders. Despite this patient's survival to date, we remain pessimistic about cardiac transplantation in BD patients until there is a better understanding of the mechanisms that lead to recurrent vascular pathology as well as more effective strategies to prevent adverse sequelae.

## Disclosure statement

The authors have no conflicts of interest to disclose.

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