Aortic dissection and cytomegalovirus activation: a possible link?

Introduction

Aortic dissection in cardiac allograft recipients is rare with reported incidences in case series of 0.9% (Rothenburger et al, 2005). However, following cardiac transplantation in patients with Marfan syndrome, the incidence rises to between 30 and 40% (Knosalla et al, 2007). Aortic dissection in these patients is promoted by immunosuppressive therapy, hypertension and an improved cardiac output. This article describes a case of aortic dissection in a cardiac transplant recipient with Marfan syndrome and cytomegalovirus activation and reviews the literature.

Discussion

There are a number of case reports describing aortic dissection in cardiac transplant recipients, both with (Kesler et al, 1994; Botta et al, 2006) and without (Coppola et al, 1993; Defraigne et al, 1997; Caffarelli et al, 2005) Marfan syndrome. Outcomes have been variable with some cases being diagnosed post-mortem (Coppola et al, 1993) and others treated successfully by surgical (Caffarelli et al, 2005), endovascular (Botta et al, 2006) and medical strategies (Defraigne et al, 1997).

Aortic dissection in non-Marfan cardiac transplant recipients is rare (Rothenburger et al, 2005) but when it does occur, is commonly limited to the donor aorta (Caffarelli et al, 2005). However, aortic dissection is frequent in cardiac transplant recipients with Marfan syndrome and the first case series in this group demonstrated a 40% incidence (Kesler et al, 1994). Survival in this series was poor with 45% mortality in less than 3 years follow-up (Kesler et al, 1994). Consequently, there is concern regarding listing of patients with Marfan syndrome for cardiac transplantation (Kesler et al, 1994), although Knosalla and colleagues (2007) demonstrated post-cardiac transplant survival in 10 patients with Marfan syndrome to be equivalent to patients without Marfan. This is despite a 40% (n=4) incidence of aortic dissection or aneurysmal complications including two deaths and two surgical abdominal aortic aneurysm replacements.

The reasons for the high incidence of aortic complication following cardiac transplantation in patients with Marfan syndrome are multifactorial. Immunosuppression with steroids may further weaken vascular connective tissue while both steroids and calcineurin inhibitors may cause hypertension. Furthermore, fol-

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Case Report

A 48-year-old man with Marfan syndrome was referred to the authors' unit for urgent consideration for a cardiac transplant. Marfan syndrome had been diagnosed at another unit based on a number of characteristic features which fulfilled the Ghent diagnostic criteria (De Paepe et al, 1996); the patient and his family had declined genetic screening. The features included dilatation of the ascending aorta, abdominal aortic aneurysm, severe scoliosis with kyphosis, pes planus, arm span-to-height ratio >1.05, joint hypermobility, a high arched palate and previous ectopia lentis. He was referred for cardiac transplantation following decompensation of severe heart failure and left ventricular dilatation secondary to valvular heart disease. At the age of 33 years he had received a 27 mm Medtronic composite aortic valve replacement and aortic root repair for severe aortic regurgitation associated with an 82 mm aortic root. His other medical history included a left nephrectomy at the age of 6 years for an unknown reason. His father had died of abdominal aortic aneurysm rupture, aged 27 years.

During assessment for transplantation, computed tomography scanning confirmed a 36 mm abdominal aortic aneurysm and revealed aneurysms of the right common iliac, both popliteal and both internal mammary arteries. He underwent orthotopic cardiac transplantation and standard induction immunosuppression with anti-thymocyte globulin and methylprednisolone. He received standard maintenance immunosuppressive therapy with mycophenolate mofetil 2.25 g/day, ciclosporin 375 mg/day and prednisolone tapered from 1 to 0.2 mg/kg/day at discharge on day 25.

Three days later he presented with severe, burning chest pain radiating to the right lumbar region. On arrival, examination revealed heart rate 90 beats per minute, blood pressure 156/94 mmHg, normal heart sounds and mild right-sided abdominal tenderness. A contrast computed tomography scan revealed a type A aortic dissection arising from the aortic arch, involving the proximal portion of the left subclavian artery and extending to the left common iliac artery (*Figure 1*). All major vessels including coeliac, superior mesenteric, right renal and right common iliac arteries arose from the true lumen which was patent. The patient was managed medically and started on intravenous labetolol with prompt blood pressure control. His maintenance antihypertensive regimen consisted of oral nebivolol, amlodipine and ramipril and his prednisolone dose was tapered further to 0.1 mg/kg/day.

Cytomegalovirus activation occurred on day 24 with blood log values rising from 3.49 (3109 copies/ml) to 5.7 (505781 copies/ml) on day 45. Viral replication responded slowly to intravenous ganciclovir and subsequent genotype studies revealed A594V mutation in the UL97 gene, consistent with ganciclovir resistance. In this setting, treatment options are limited but high dose ganciclovir (7mg/kg twice daily) can be used, which was used in this patient. Cytomegalovirus titres slowly responded to high-dose ganciclovir and the patient was converted to oral therapy and discharged on day 63 post transplant. Follow-up computed tomography at 6 months demonstrated stable appearances of the dissection.

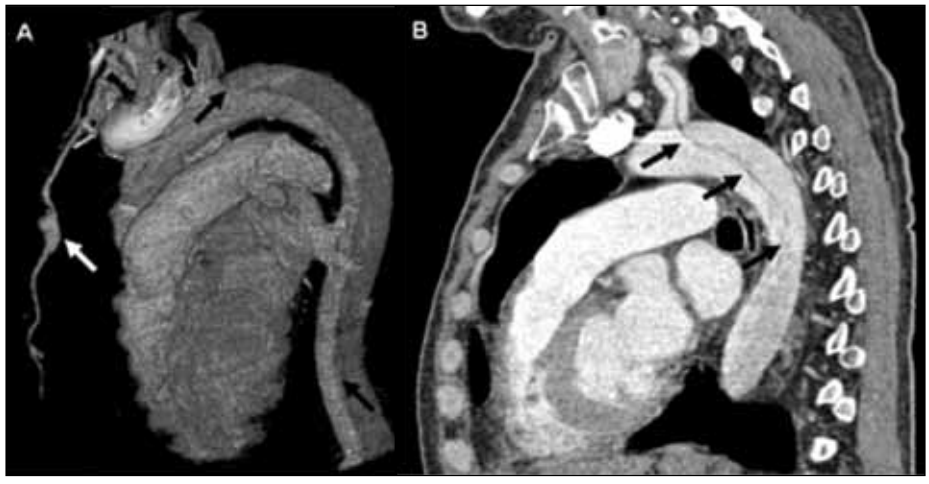

Figure 1. a. Three-dimensional reconstruction and (b) sagittal section computed tomography demonstrating aneurysm of the right internal mammary artery (white arrow) and Stanford type A aortic dissection involving the left subclavian artery (black arrow).

lowing cardiac transplant, the native aorta is exposed to greater wall stresses secondary to improved cardiac output. In this patient systolic blood pressures increased from 100 mmHg to 130 mmHg immediately post-transplant because of the improved cardiac output of the graft. Certainly, aortic diameters in non-Marfan patients increase post-cardiac transplant with the greatest increases seen in patients with greater percentage increases in ejection fraction pre- to post-transplant (Bull et al, 1994).

Established abdominal aortic aneurysms also progress at a more rapid rate following both cardiac and non-cardiac solid organ transplantation (Englesbe et al, 2003). Pre-transplant vasculopathy has also been shown to be a risk factor for vascular morbidity, including dissection and abdominal aortic aneurysm in cardiac transplant recipients (Takayama et al, 2007).

A further potential contributory factor in this patient is cytomegalovirus activation which had a temporal association with his aortic dissection. Cytomegalovirus is associated with a number of vascular disorders including vasculitis (Golden et al, 1994). Cytomegalovirus DNA has been detected by polymerase chain reaction in macroscopically normal aorta taken from patients undergoing aortic valve replacement (Reszka et al, 2008).

Cytomegalovirus aortitis, characterized by the presence of cytomegalovirus antigen and mononuclear cells in intima and media layers, has also been demonstrated in the native aorta of wild-type mice infected with cytomegalovirus (Presti et al, 1998). Furthermore, in a rat model systemic cytomegalovirus infection causes inflammatory cell infiltration and perivascular inflammation in aortic allografts (Li et al, 1996). Therefore, it is plausible that cytomegalovirus activation may have contributed to the development of aortic dissection in this patient.

In this setting, treatment options are limited. High dose ganciclovir (7mg/kg twice daily) can be used, which was used in this patient. Foscarnet is also an option but as this patient was taking ciclosporin and only had a single kidney, foscarnet was avoided because of the high risk of renal impairment with multiple nephrotoxic agents. The use of leflunomide and cidofavir has also been described in patients with human immunodeficiency virus and ganciclovir-resistant cytomegalovirus infection. However, these were not felt appropriate because of the co-prescription of immunosuppressants and concerns regarding renal toxicity.

Conclusions

This case demonstrates successful medical management of a type A aortic dissection 30 days after orthotopic cardiac transplantation in a patient with Marfan syndrome. Cautious β-blocker use has been advocated in cardiac transplant recipients because of dependence on catecholamines to preserve cardiac function during exercise. However, this patient tolerated both intravenous and oral β-blockade therapy without significant impairment of exercise tolerance. Contributory factors for aortic dissection in cardiac transplant recipients include improved cardiac output, increasing systolic blood pressure, immunosuppressive medications and possibly cytomegalovirus activation. Given the high vascular complication rate, active surveillance is prudent post-cardiac transplant in patients with Marfan syndrome. **BJHM**

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