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CASE REPORT

Recurrence of in-stent restenosis in cardiac allograft vasculopathy following implantation of a sirolimus-eluting stent

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Summary

Coronary lesions in patients with advanced cardiac allograft vasculopathy (CAV) are frequently treated with percutaneous coronary intervention. Despite high primary success rates, long-term outcome is significantly impaired by a high incidence of restenosis. In nontransplanted patients, the use of drug-eluting stents (DES) significantly decreases the rate of coronary in-stent restenosis. We report a case treated for cardiac allograft coronary in-stent restenosis with a sirolimus-eluting stent presenting with recurrent in-stent restenosis at follow up. However, the pattern of in-stent restenosis changed from diffuse proliferative disease in the bare-metal stent to a focal pattern in the sirolimus-eluting stent concordant with observations in nontransplanted patients. This case highlights the need for further studies addressing the effect of DES for the prevention of restenosis both in *de novo* as well as in-stent restenotic lesions in patients with CAV.

Introduction

Cardiac allograft vasculopathy (CAV) is the most common cause for morbidity and graft failure in patients receiving heart transplantation [1]. Thus, it constitutes the predominant obstacle for long-term survival after cardiac transplantation. Risk factors for CAV include hyperlipidemia [2,3], active or recurrent human cytomegalovirus (CMV) infection [4] as well as immunologic risk factors [5]. Interventional therapy to treat coronary artery stenosis in heart-transplanted patients with CAV is complicated by a high rate of in-stent restenosis [6]. In nontransplanted patients, drug-eluting stents have shown in landmark clinical trials that they significantly decrease the need for reintervention caused by restenosis [7,8]. Despite the lack of controlled clinical trials, it is tempting to speculate that usage of these stents may also allow for a better long-term outcome in CAV patients undergoing percutaneous coronary intervention.

Case report

A 57-year-old male Caucasian received a heart transplant in 1994 because of end-stage dilated cardiomyopathy and was first diagnosed with CAV in 2000. He had a negative CMV serostatus prior transplantation and no clinical nor laboratory evidence for previous or acute CMV infection (negative titre for anti-CMV IgG and IgM antibodies). Risk factors included arterial hypertension; the renal function was impaired (creatinine 2.6 mg/dl). Since 1995, the patient received continuous statin therapy (pravastatin); total cholesterol at admission was 155 mg/dl, LDL cholesterol 75.4 mg/dl, triglycerides 68.1 mg/dl. In addition, he received an angiotensin receptor blocker (valsartan), diuretics (furosemid and hydrochlorothiazide), ß-blocker (bisoprorol) as well as a calcium channel blocker (amlodipine). Immunosuppressive therapy included no cortisone but cyclosporine A with plasma levels maintained at a minimum of 150 ng/ml and azathioprin 25 mg per day. Repeated cardiac muscle biopsies collected over

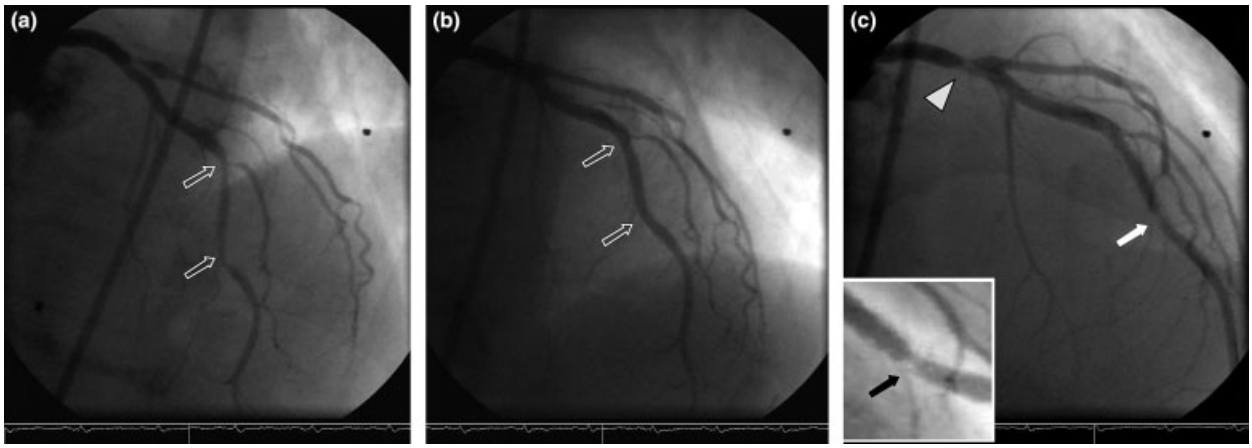

Figure 1 Right anterior oblique (RAO) cranial view of the left anterior descending artery of the patient with cardiac allograft vasculopathy. A diffuse pattern of in-stent restenosis (a) was detected 6 months after implantation of a bare metal stent and was treated with placement of a sirolimus-eluting Cypher stent with adequate immediate postprocedural result (b); (c) focal in-stent restenosis recurred 6 months after Cypher stent implantation (white arrow and black arrow in the magnified view of the restenotic stent segment). Progression of allograft vasculopathy is concurrently detectable (grey triangulated arrow).

the years revealed no significant histological signs of transplant rejection requiring additional therapy. According to the International society for heart transplantation (ISHT) guidelines [9], biopsies were categorized from grade 0 to 1A. As a result of progression of CAV as recorded by scheduled annual coronary angiography, the patient received a 28-mm bare-metal stent in August 2003 to treat a long left anterior descendent artery stenosis with an adequate immediate postprocedural angiographic result and was maintained on low dose aspirin and clopidogrel since then. Diffuse in-stent restenosis (Fig. 1a) was diagnosed during scheduled follow up and treated in February 2004 with a 33-mm long Cypher^{TM} (Cordis, J&J, Miami Lakes, FL, USA) sirolimus-eluting stent (Fig. 1b). In August 2004, coronary angiography revealed progression of transplant vasculopathy outside the previously stented segment (Fig. 1c, triangle) as well as focal in-stent restenosis within the sirolimus-eluting stent (Fig. 1c, white arrow and black arrow on the magnified picture on the lower left). In-stent restenosis was treated by implantation of another drug-eluting stent (DES) as there is evidence that repeated DES implantation is superior to mere balloon angioplasty in restenotic DES [10].

Discussion

Similar to coronary in-stent restenosis occurring in non-transplanted patients, CAV is characterized by concentric intimal thickening, predominantly caused my intimal smooth muscle cell proliferation [11]. Therefore, systemic or local anti-proliferative therapeutic regimens are likely to improve therapeutic outcomes and decrease the rate of restenosis. Although CAV typically involves diffuse narrowing of coronary arteries rather than more focal lesions as commonly observed in conventional coronary atherosclerosis [11], percutaneous coronary intervention (PCI) is frequently performed in these patients. Despite the high primary success rate of over 90% and a low peri-procedural complication rate, long-term outcome is limited by the high incidence of restenosis [12]. As in the general population [13], stent placement in cardiac allograft disease limits the rate of restenosis after PCI compared with balloon angioplasty alone [6]. Local inhibition of smooth muscle cell proliferation, the major underlying mechanism of in-stent restenosis, by DES has dramatically decreased the rate of in-stent restenosis in native coronary arteries in nontransplanted patients [7]. Implantation of sirolimus-eluting stents is regarded as an efficient therapy for in-stent restenosis [14] and has been shown to decrease the rate of recurrent in-stent restenosis when compared with balloon angioplasty alone [15].

In-stent restenosis is very common in coronary allograft vasculopathy with a rate of over 30% within 6 months of PCI [6], however, no experience is available yet for the treatment of these lesions with DES in this particular population. Interestingly, the focal pattern of in-stent restenosis observed in our case resembles what is commonly observed in nontransplanted patients presenting with Cypher^{TM} in-stent restenosis. Nondrug-eluting, bare-metal stents tend to display a diffuse pattern of in-stent restenosis (defined as a longitudinal dissemination of >10 mm) in the majority of cases, whereas sirolimus-eluting stents reveal generally a focal pattern of in-stent restenosis [16]. Apparently, treatment of in-stent

restenosis in this patient with advanced CAV had a beneficial effect in limiting the diffuse proliferative response compared with previous conventional treatment but the occurrence of focal in-stent restenosis suggests that currently available DES may not entirely eliminate the problem of recurrent restenosis in this particular population. To define the status of DES for the local treatment of *de novo* and in-stent restenosis in CAV, prospective clinical trials are needed that address these particular clinical problems. Importantly, systemic administration of both sirolimus [17] or its close relative everolimus [18] have been shown to effectively inhibit the progression of coronary vasculopathy in heart-transplanted patients. Together with the encouraging results from numerous DES trials involving the nontransplanted population, DES may enable a new era for the local treatment of coronary allograft disease by presumably attenuating the high rate of restenosis observed with conventional PCI in patients suffering from heart transplant vasculopathy.

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