Rapidly Progressive Cardiac Allograft Vasculopathy in Early Onset Regressed With Everolimus Treatment in an Adult Cardiac Recipient

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SUMMARY

A 60-year-old man with severe heart failure underwent an orthotopic heart transplant. Maintenance immunosuppression consisted of a calcineurin inhibitor, mycophenolate mofetil (MMF), and a glucocorticoid. Six months after the transplantation, coronary angiography (CAG) and intravascular ultrasound sonography (IVUS) showed rapidly progressive cardiac allograft vasculopathy (CAV) along with acute cellular rejection. Methylprednisone pulse therapy resulted in the resolution of acute rejection. MMF was exchanged for everolimus (EVL) and 6 months after EVL therapy, CAG and IVUS revealed the regression of CAV. EVL can improve established CAV as well as prevent the progression of CAV. (Int Heart J 2012; 53: 388-390)

Key words: Heart transplantation, Intravascular ultrasound sonography, Rejection

Cardiac allograft vasculopathy (CAV) is often observed after heart transplantation and involves the entire length of the transplanted arterial vasculature. The clinical symptoms of ischemia are not useful for detecting early CAV, because transplanted hearts are denervated. CAV remains the major cause of long-term mortality in heart transplant recipients. There is no established treatment for CAV, but it is noteworthy that EVL, an immunosuppression agent for solid organ transplantation, has been reported to at least partially prevent the development of CAV. Regimens containing EVL are currently indicated mainly in patients with evident CAV, but it remains unclear whether EVL causes regression of CAV or not. Herein we describe a case of a post-heart transplant patient with rapidly progressive CAV, which regressed with EVL.

CASE REPORT

The patient was a 60-year-old man who had received a diagnosis of dilated cardiomyopathy 17 years before on the basis of coronary angiography and endomyocardial biopsy. He had no history of hypertension, diabetes mellitus, dyslipidemia, or smoking. He had been repeatedly hospitalized for worsening heart failure, and underwent left ventricular assist device (LVAD, EVAHEART) implantation as a bridge to cardiac transplantation 5 years earlier. He subsequently underwent an orthotopic heart transplant 2 years after implantation of the LVAD. The immunosuppressive regimen started with cyclosporine (CyA), mycophenolate mofetil (MMF), and prednisone. The initial clinical course after the transplant was unventful and the levels of plasma B-type natriuretic peptide (BNP) decreased from 118 pg/mL 3 months posttransplant to 85 pg/mL 5 months posttransplant (Figure 1). He had a normal electrocardiogram (ECG) (Figure 2) and a normal coronary angiogram 3 months after the transplant (Figure 3A). Six months after the transplant, however, plasma BNP levels increased to 315 pg/mL (Figure 1) and his ECG showed ST depression in leads I, aVL, and V5-6 (Figure 2). Although he remained asymptomatic without any sign of heart failure on chest X-rays, endomyocardial biopsy disclosed grade 3A acute rejection. He had had no evidence of antibody-mediated rejection throughout the clinical course. There were no significant immunostainings of IgG, IgM, C1q, C3, C4 or C4d in his biopsy samples, nor were there any increases in the levels of donor-specific antibodies. Coronary angiography (CAG) showed subtotal occlusion of the high lateral branch (HL) and diffuse stenotic lesions in the left circumflex artery (LCx), the left anterior descending artery (LAD), and the first diagonal branch (Figure 3B). Intravascular ultrasound (IVUS) with a Volcano system (Volcano Corporation, Rancho Cordova, CA, USA) revealed a diffuse neointimal hyperplasia in the LAD and vascular narrowing associated with negative remodeling in the LCx. The neointima, which was histologically assessed with virtual histology-IVUS (VH-IVUS), was mainly composed of fibrous plaque. We started methylprednisone pulse therapy (1 g/day for 3 days), which was followed by EVL 1.5 mg/day therapy in exchange for MMF. Methylprednisone pulse therapy resulted in considerable resolution of allograft rejection (grade 2). At 8 months posttransplant, because the trough concentrations of
CyA and EVL had been fluctuating. CyA was switched to tacrolimus (TAC), which stabilized the trough concentrations of TAC and EVL. Twelve months after the transplant, plasma BNP levels gradually decreased, ST-segment depression in the ECG disappeared, and CAG also revealed the regression of the diffuse stenotic lesions in the LCx and LAD and no significant progression of the stenosis of HL (Figure 3C). IVUS findings for the LAD at 9 months and 12 months posttransplant were compared (Figure 4A, 4B, 4C). The ratio of plaque area to vessel area was decreased from 52% to 43%, from 63% to 56%, and from 57% to 41% at sites located 13 mm, 33 mm, and 47 mm from the bifurcation of the LAD and LCx, respectively, which exhibited attenuation of plaque burden. VH-IVUS revealed that fibrous components were significantly decreased and that calcium components partially emerged. The lumen cross-sectional areas (CSA) were, on the other hand, increased from 4.1 to 4.9, from 4.3 to 4.8, and from 2.8 to 3.3 mm² at each site described above.

**Discussion**

We have described a case with rapidly progressive CAV. EVL was significantly effective to change the clinical course in this patient.

The management and prevention of CAV is very important, because CAV determines major morbidity and mortality late in the transplant natural history. To assess CAV, IVUS is a more sensitive tool than CAG and multislice computer tomography. Therefore, we have routinely performed IVUS studies to evaluate CAV.

Risk factors for CAV can be divided into two broad categories: (i) classic cardiovascular risk factors, such as smoking, obesity, diabetes, dyslipidemia, and hypertension, and transplant-associated risk factors, such as cytomegalovirus (CMV) infection, number of HLA mismatches, number and duration of rejection episodes, donor-age, and recipient-age. Actually, this case had no risk factors for CAV other than recipient-age.

Early CAV, diagnosed within 1 year of transplantation, is an independent predictor of mortality at 5 years. Moreover, rapidly progressive CAV, one of the most severe forms of CAV, is defined as a lesion > 70% within 1 year of a benign angiogram (< 30% previously) and can portend a poor prognosis. Thus, the speed of CAV development and the time after the transplant are the primary determinants of adverse outcomes. In this case, rapidly progressive CAV, which was detected 6 months posttransplant, indicated a poor prognosis.

Today standard immunosuppressive regimens after heart
transplant consist of calcineurin inhibitors (CNIs; CyA or TAC), inhibitors of de novo nucleotide synthesis (usually MMF or azathioprine), and glucocorticoids. More recently, proliferation signal inhibitors (sirolimus or EVL) instead of MMF or azathioprine are sometimes used for maintenance immunosuppression. Imamura, et al reported that EVL reduced the prevalence of CMV infection compared with MMF, which will be favorable for managing the development of CAV. 19 There has been no proven regimen for established CAV. Both CyA and TAC have been considered to be equally ineffective for the prevention of CAV development. 20 Glucocorticoids are not directly effective in the treatment of CAV; although these standard drugs may be partially beneficial to prevent CAV development since CAV has been known to be worsened by repetitive acute rejection. 21 In contrast, recent reports suggested that EVL reduced the severity and incidence of CAV 20 and that sirolimus treatment slowed disease progression in patients with CAV. 23 It is considered that the antiproliferative and antiganglionic actions of these drugs may possibly have direct effects on CAV. Surprisingly, VH-IVUS demonstrated that the plaque volume, especially fibrous components in the neointima, was reduced in this case. When EVL was administered in combination with CNIs, a drug interaction with CyA was noted. 25 On the other hand, TAC appears to have a minimal interaction with EVL. 24 In this case, CyA was switched to TAC because the trough concentrations of CyA and EVL had fluctuated, and consequently the trough levels of TAC and EVL became stabilized. In some observational studies, plaque regression of CAV was associated with usage of angiotensin-converting enzyme inhibitors 31 and statins. 32 Enalapril and pravastatin had been prescribed for this patient since the transplantation, but these drugs might not be effective enough to prevent CAV in this case. In addition, revascularization procedures for CAV are only palliative with no long-term survival benefit, because CAV diffusely affects vessels. 26 In this case, early detection of CAV allowed us early intervention with EVL. To the best of our knowledge, this is the first case report that established CAV had regressed with EVL treatment. In conclusion, EVL treatment can improve established CAV as well as delay the progression of CAV. Considering recent findings, EVL may be recommended in patients at high risk for the development of CAV.

References