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Case Report

Plaque regression associated with everolimus administration after heart transplantation

Daisaku Nakatani (MD)[a,*], Jun-ichi Kotani (MD)[b], Koichi Tachibana (MD)[a], Yasuhiro Ichibori (MD)[a], Isamu Mizote (MD)[a], Yoshihiro Asano (MD)[a], Yasushi Sakata (MD)[a], Yasuhiko Sakata (MD)[a], Satoru Sumitsuji (MD)[a], Shunsuke Saito (MD)[c], Taichi Sakaguchi (MD)[c], Norihide Fukushima (MD)[c], Shinsuke Nanto (MD, FJCC)[a], Yoshiki Sawa (MD, FJCC)[c], Issei Komuro (MD, FJCC)[a]

[a] *Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 (A8) Yamadaoka, Suita, Osaka 565-0871, Japan*
[b] *Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan*
[c] *Division of Cardiovascular Surgery, Department of Surgery, Osaka University Graduate School of Medicine, Suita, Japan*

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ABSTRACT

A 45-year-old male who had suffered from refractory non-ischemic heart failure treated with a left ventricular assist device received heart transplantation in February 2008. He underwent coronary angiography (CAG) and intravascular ultrasound (IVUS) at 3 months, and 1, 2, and 3 years after surgery. At 3 months, neither significant stenosis on CAG nor plaque on 3 coronary arteries, as assessed by IVUS were observed. However, focal eccentric plaque on proximal left anterior descending artery has developed up to 2 years, despite the fact that risk factors for cardiac allograft vasculopathy were well controlled. At 2 years, everolimus 2.5 mg/day was added to the patient's existing regimen consisting of corticosteroids, mycophenolate mofetil, and cyclosporine. Then mycophenolate mofetil was withdrawn. At 3 years, concomitant with plaque regression, a decreased plaque volume index, enlarged lumen volume index, and increased minimum lumen area were observed. We experienced a case with plaque regression associated with everolimus administration. Further investigations are needed to explore the mechanism of plaque regression associated with everolimus, as well as to confirm our observation in randomized controlled trials for patients after heart transplantation.

<**Learning objective:** We experienced a case with plaque regression associated with everolimus administration. Further investigations are needed to explore the mechanism of plaque regression associated with everolimus, as well as to confirm our observation in randomized controlled trials for patients after heart transplantation.>

Introduction

Cardiac allograft vasculopathy is an ongoing issue after heart transplantation, even though treatment regimen consisting of calcineurin inhibitors, mycophenolate mofetil and glucocorticoids has been established in patients after heart transplantation.

We report a case with plaque regression associated with Everolimis administration after heart transplantation.

A 45-year old male who had suffered from refractory non-ischemic heart failure treated with a left ventricular assist device received heart transplantation in February 2008. At 3 months, and 1, 2, and 3 years after surgery, he underwent coronary angiography (CAG) (Fig. 1) and intravascular ultrasound (IVUS) (Fig. 2) examinations to evaluate cardiac allograft vasculopathy (CAV). No significant rejection episodes, as assessed by right ventricular biopsy, were observed during the follow-up period. Although his lipid and diabetic profiles were well controlled until 2 years after heart transplantation, those parameters were worsened at 3 years, even under statin administration, subcutaneous insulin injection, and oral anti-diabetic drugs (Table 1 and Fig. 4). There was no cytomegalovirus infection during the follow-up periods.

At 3 months, neither significant stenosis on CAG nor plaque on 3 coronary arteries, as assessed by IVUS, were observed. The maximum plaque thickness at 3 months on the proximal left anterior descending (LAD) coronary artery was 0.42 mm (Figs. 2a and 3b). At 1 year, IVUS revealed that an eccentric focal plaque had developed with a maximum thickness of 1.06 mm at the same area in the LAD with an increased plaque volume index (4.6 mm^3/mm), and decreased lumen volume index (12.2 mm^3/mm) and minimum lumen area (10.9 mm^2) (Figs. 2b, 3a and 3b). At 2 years, the eccentric plaque had further

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* Corresponding author. Tel.: +81 6 6879 6612; fax: +81 6 6879 6613.
E-mail address: nakatani@cardiology.med.osaka-u.ac.jp (D. Nakatani).

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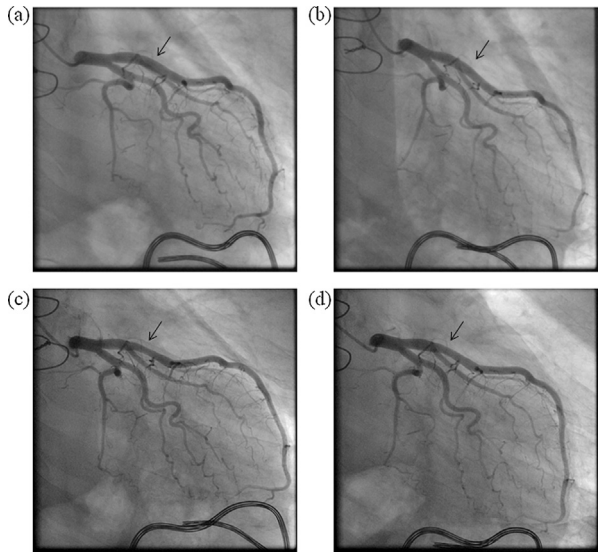

Fig. 1. Serial changes in angiogram for left coronary artery after heart transplantation. No obvious stenosis on the coronary artery tree was observed following intracoronary injection of nitrate after heart transplantation at (a) 3 months, (b) 1 year, (c) 2 years, and (d) 3 years, even though increased plaque thickness was detected up to 2 years, as assessed by intravascular ultrasound (IVUS). Arrows indicate the site corresponding to plaque progression and regression observed by IVUS.

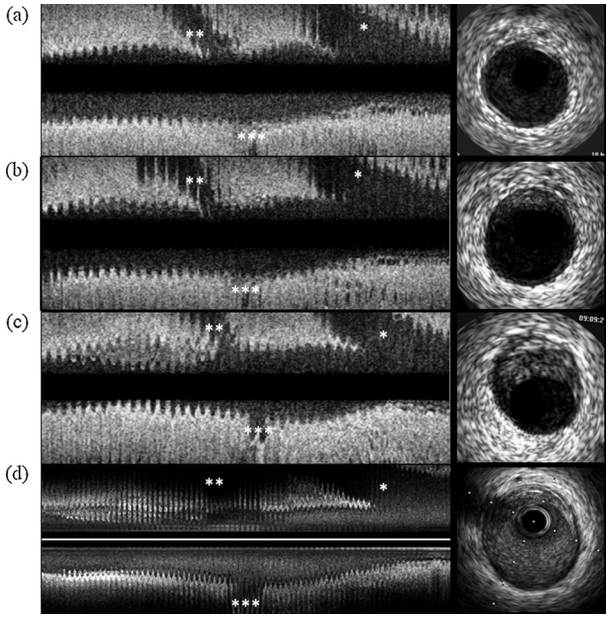

Fig. 2. Serial changes in plaque thickness in the proximal left anterior descending coronary artery assessed by intravascular ultrasound (IVUS). Single (*), double (**), and triple (***) asterisks indicate the left circumflex artery, first diagonal branch, and first septal branch, respectively. Focusing on the site between the first diagonal branch to second septal branch where plaque progression and regression took place, we measured maximum plaque thickness, minimum lumen area as well as lumen and plaque volume indices using Simpson's method. (a) No obvious plaque was detected at 3 months. (b) At 1 year, longitudinal and cross-sectional images showed that a focal eccentric plaque was observed in an area distal to first diagonal branch. (c) The plaque thickness had increased by 2 years, as shown in both the longitudinal and cross-sectional images, with decreased lumen area. (d) Although it was difficult to see the first diagonal branch due to wire artifact after transplantation, at 3 years, both the longitudinal and cross-sectional images showed decreased plaque thickness with enlarged lumen area, which was associated with everolimus administration. We note that IVUS was performed in a standard fashion using an automated and motorized 1.0 mm/s pullback with a commercially available imaging system with a 20-MHz IVUS catheter (Volcano Corp, Rancho Cordova, CA, USA) at 3 months, 1 year, and 2 years after surgery, and an automated motorized 0.5 mm/s pullback with a 40-MHz IVUS catheter (Boston Scientific Corp., Natick, MA, USA) at 3 years after surgery, respectively.

Table 1
Laboratory data after heart transplantation.

	3 months	1 year	2 years	3 years
HbA1c (%)	5.1	5.7	5.6	7.0
Total cholesterol (mg/dL)	154	193	182	219
LDL-cholesterol (mg/dL)	90	112	100	128
HDL-cholesterol (mg/dL)	36	41	49	57
Triglycerides (mg/dL)	118	190	165	134

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

developed, reaching a maximum plaque thickness of 1.79 mm, with increased plaque volume index (7.0 mm^3/mm), and decreased lumen volume index (6.9 mm^3/mm), and minimum lumen area (5.6 mm^2) (Figs. 2c, 3a, and 3b).

Subsequently, everolimus was added at an initial dose of 1.5 mg/day to the patient's existing regimen consisting of corticosteroids (2.5 mg/day), cyclosporine (450 mg/day), and mycophenolate mofetil (250 mg/day). As the patient displayed no adverse effects to everolimus in the first week of administration, the dosage was increased to 2.5 mg/day in order to maintain a drug concentration of 3–8 ng/ml and mycophenolate mofetil was withdrawn (Fig. 4). At 3 years after transplantation surgery, IVUS showed that the eccentric plaque in the proximal LAD had regressed, with a maximum plaque thickness of 1.11 mm (Figs. 2d and 3b). Concomitant with plaque regression, a decreased plaque volume index (5.1 mm^3/mm), enlarged lumen volume index (9.0 mm^3/mm), and increased minimum lumen area (8.1 mm^2) were observed (Figs. 2d and 3a). Coronary narrowing assessed by CAG exhibited marginal progression and regression during the follow-up period (Fig. 1).

Discussion

CAV has been reported to be a main cause of death after heart transplantation. Previous studies have shown that numerous recipient factors, including male sex, older age, early severe rejection, cytomegalovirus infection, diabetes, hypertension, hyperlipidemia, and higher body mass index, are associated with an increased risk of CAV [1]. Although the patient did not experience any rejection episodes or viral infection, he had several risk factors for CAV, including male sex, diabetes, and hyperlipidemia. In addition, a plaque with a thickness of >0.5 mm had developed within 1 year after transplantation, which is considered to be a surrogate value of high risk for CAV [2]. A randomized clinical trial comparing the efficacy and safety between patients assigned either to low- (1.5 mg/day) or high-dose everolimus (3.0 mg/day) or azathioprine revealed that maximal plaque thickness 12 months after transplantation, as assessed by IVUS, was significantly smaller in the two everolimus groups than that in the azathioprine group [3]. As the everolimus-treated group exhibited lower plaque progression, it is possible that everolimus potentially promotes plaque regression, resulting in a reduced risk of vasculopathy after heart transplantation. Although the mechanism underlying everolimus-related plaque regression after heart transplantation remains unknown, anti-immunosuppression [4] as well as anti-inflammatory effects [5] may play a role in the phenomenon.

In summary, we experienced a case with plaque regression associated with the administration of everolimus following heart transplantation, despite having a high risk for developing CAV. If we encounter transplantation patients with high CAV risks, we may need to consider administering everolimus. Further investigations are needed to explore the mechanism of plaque regression associated with everolimus, as well as to confirm our observation in randomized controlled trials for patients after heart transplantation.

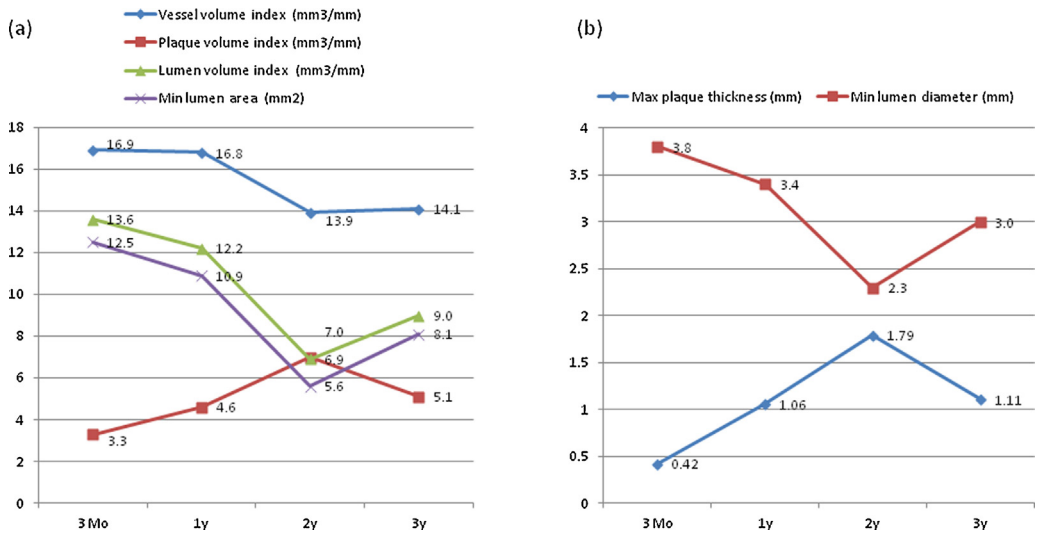

Fig. 3. Serial changes in intravascular ultrasound parameters.

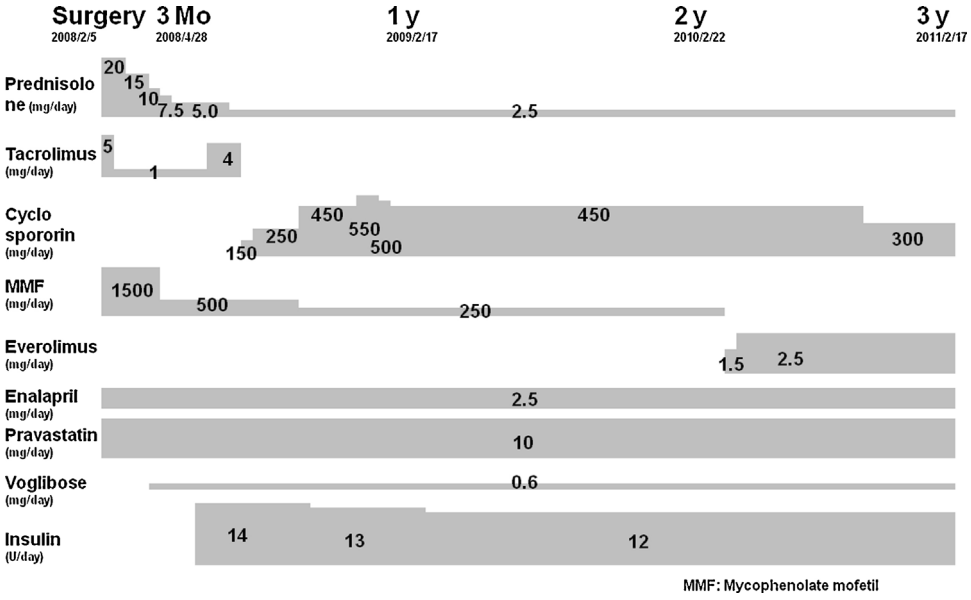

Fig. 4. Medications after heart transplantation surgery.

Conflict of interest

None of the authors have conflicts of interest that should be declared.

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