CASE REPORT

Chest Pain without Significant Coronary Stenosis after Implantation of Sirolimus-Eluting Stents

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Abstract

We encountered a case of exercise-induced chest pain after the implantation of sirolimus-eluting stents (SESs). She had no history of previous chest pain, and an exercise stress test just after the implantation of the SESs was negative without any symptoms. However, six months after the implantation of the SESs, she began to experience frequent episodes of severe chest pain on effort in spite of there being no significant coronary stenosis. Interestingly, severe coronary vasoconstriction was induced by an intracoronary administration of acetylcholine, and exercise stress testing revealed positive findings with chest pain and ST-T segment depression on ECG. An intensive treatment with two types of calcium channel blockers could readily and completely abolish the exercise-induced chest pain and ST-T segment depression on the ECG. In view of these findings, we presumed that coronary microvessel dysfunction and/or exercise-induced coronary vasoconstriction leading to myocardial ischemia had appeared 6 months after the implantation of the SESs. Although the pathogenesis of this phenomenon could not be completely elucidated, the anatomical and functional abnormalities of the coronary arteries associated with the implantation of the SESs may have been one of the most important mechanisms.

Key words: coronary intervention, exercise, coronary vasoconstriction, microvessel dysfunction

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Introduction

Sirolimus-eluting stents (SESs) have gained widespread use due to the extraordinarily low rates of restenosis (1). Despite these generally superior clinical outcomes, some adverse effects (2) associated with SES implantations including coronary vasoconstriction (3, 4) and endothelial dysfunction (5) have been reported. We describe a case of exercise-induced chest pain without any significant coronary stenosis 6 months after the implantation of SESs.

Case Report

A 59-year-old woman was admitted to our hospital with increasing episodes of chest pain on effort. She had no history of prior chest symptoms. Her coronary risk factors included a family history of ischemic heart disease, arterial hypertension, and dyslipidemia. Both the electrocardiogram (ECG) and echocardiogram on admission were normal (Fig. 1A). Since the coronary angiogram (CAG) revealed 1 vessel disease with a long, diffuse narrow, and severe stenosis of the proximal and mid left anterior descending (LAD) coronary artery (Fig. 2A), two SESs (Cypher3 3.5×23, 3.0×28 mm, Cordis Corporation, Miami Lakes, FL) were implanted just proximal to the mid LAD lesions (Fig. 2B). After that procedure, she was free of any symptoms and had no significant ECG changes observed during exercise stress testing (Fig. 1B), while being treated with medications including aspirin, ticlopidine, statin, and the calcium channel blocker (CCB), 5 mg per day of amlodipine. Six months after the implantation of the SESs, she began to have frequent episodes of severe chest pain on effort, and then, she was emergently readmitted to our hospital. However, the CAG revealed no restenosis at the SES implantation sites and no significant stenosis of any of the coronary arteries (Fig. 2C).

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In order to evaluate her coronary vasoconstriction, an intracoronary administration of 30 μg of acetylcholine was performed, yielding severe coronary vasoconstrictions (Fig. 2D) at the distal portion of the site of the implantation of the SES, associated with significant ST depression in the surface ECG leads II, III, aVF, and V3-6 (Fig. 1C) and severe chest pain, even though she had been receiving an oral administration of 5 mg per day of amlodipine. No vasoconstrictive responses were observed in any other coronary artery but LAD. A repeated intracoronary administration of isosorbide dinitrate was able to relieve the coronary vasoconstrictions in accordance with the disappearance of the ST depression in the ECG and chest pain symptoms. With a diagnosis of vasospastic angina, the oral administration of 8 mg per day of benidipine, which has a stronger effect for preventing coronary vasoconstrictions than amlodipine (6) was started in place of amlodipine. However, since she continued to have chest pain associated with significant ST segment depression on the ECG during exercise stress testing (Fig. 1D), intensive CCB treatment with the oral administration of 8 mg per day of benidipine and 100 mg per day of diltiazem was started. The exercise stress test after the intensive CCB treatment, revealed no significant ECG changes or symptoms (Fig. 1E). Since both the exercise stress test and acetylcholine provocation test were positive without significant stenosis in coronary arteries, we presumed that coronary microvessel dysfunction (7, 8) and/or exercise-induced coronary vasoconstrictions leading to myocardial ischemia appeared 6 months after the implantation of the SESs (4). She was completely free of any symptoms thereafter, and has remained well without any symptoms under intensive CCBs treatment for more than 2 years after the implantation of the SESs.

Discussion

We encountered a case of exercise-induced chest pain without significant coronary stenosis 6 months after the implantation of the SESs. The syndrome of chest pain without significant coronary stenosis, but with coronary vasocon-
Figure 2. The left coronary angiography in the right (RAO; left panels) and left (LAO; right panels) anterior oblique views obtained before a percutaneous coronary intervention (PCI) (A), just after PCI (B), 6 months after PCI (C), and during an intracoronary administration of acetylcholine (D). The black and white arrows indicate the stent implantation sites and coronary vasoconstriction sites, respectively.

strictions which are induced by acetylcholine or ergonovine maleate, is diagnosed as vasospastic angina. On the other hand, the syndrome of chest pain with a normal CAG is referred to as microvessel dysfunction, the so-called cardiac syndrome X (7). The former condition appears to remain common in Japan, and sometimes causes myocardial infarction and cardiac sudden death (9). Both conditions must be rare complications associated with SES implantations, because few case reports have covered that before (4).

Although the pathogenesis of the coronary microvessel dysfunction and vasospastic angina cannot be completely elucidated, endothelial and/or vascular smooth muscle cell
dysfunction has been suggested (10-12). It has been reported that the implantation of the SESs caused both anatomical (13, 14) and functional (5, 15) abnormalities of the coronary arteries. In the angiographic findings at 6 months after the SES implantations, an incomplete re-endothelialization was observed (14), indicating the existence of impaired endothelial function. Furthermore, the pathologic examination after the implantation of the SES revealed drug or polymer-induced localized vascular inflammatory reactions and/or impaired vessel healing (13, 16, 17). Moreover, an in vitro study showed that sirolimus impairs the endothelium-derived nitric oxide production leading to endothelial dysfunction and hinders the cell viability (5, 15). Finally, enhanced sympathetic nerve stimulation during exercise may accelerate the vasoconstrictor response (smooth muscle cells dysfunction) under the condition of reduced nitric oxide bioavailability (endothelial dysfunction) leading to myocardial ischemia and chest pain. These findings may be one of the important potential mechanisms of exercise-induced coronary microvessel dysfunction and/or vasoconstrictions especially in the late phase after implantation of the SES.

In the present case, the exercise-stress test was negative in the early phase, but became positive, even without significant coronary stenosis, 6 months after the implantation of the SESs. Furthermore, an intracoronary administration of acetylcholine induced coronary vasoconstrictions leading to myocardial ischemia 6 months after the implantation of the SESs. Interestingly, recent clinical trials demonstrated that exercise-induced coronary vasoconstrictions occurred at the adjacent vessel segments of the SES implantation site 6 months after an SES implantation (3), but not in the early phase after SES implantations (18). Although it might have been difficult to observe vasoconstriction at the proximal site of the SES, because the stent was positioned just proximal to LAD, these findings seem to be similar to the clinical course of the present case, and may support the hypothesis that the exercise-induced vasoconstrictions leading to myocardial ischemia had begun to occur 6 months after the SES implantation, in the present case. These conditions may be somewhat drug-refractory, since two types of CCBs were needed to treat it. Moreover, these phenomena were not observed after a biolimus A9-eluting stent (BES) implantation (19). Thus, they may be a specific phenomenon of the SESs. The more complete stent re-endothelialization with BES rather than with SES (19) may be one of the important factors in these phenomena.

Recent clinical trials also have demonstrated that SESs have been associated with an increased rate of myocardial infarctions and death, as compared to the bare metal stents, and this tendency tended to appear 6 months after the SES implantation (20, 21). These results suggest that the coronary vasoconstrictions observed after SES implantations may be one of the important factors in the increased rate of myocardial infarctions and death after the SES implantation, because it has been reported that coronary vasoconstrictions, the so-called “vasospastic angina” sometimes causes myocardial infarctions and cardiac sudden death (9).

To the best of our knowledge, there have been no reports on the exercise-induced chest pain associated with significant ST segment depression on ECG resulting from myocardial ischemia, without significant coronary stenosis after an SES implantation as in this present case. Although the frequency of these abnormalities may be low, physicians should be aware of this condition when examining patients, especially after SES implantation. An intensive CCB treatment may be one of the useful therapeutic strategies for these conditions. Supporting data from clinical and basic trials, however, are required before such conclusions can be made.

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References


