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Case Report

A case of newly demonstrated coronary spasm 4 months after paclitaxel-eluting stent implantation for in-stent restenosis

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Summary A 56-year-old woman with hypertension and hypercholesterolemia was admitted to our hospital with acute inferior myocardial infarction. The patient had total occlusion of the right coronary artery (RCA) segment 2, and bare-metal stents were placed. Four months later, plain old balloon angioplasty was performed for in-stent restenosis. Follow-up coronary angiography (CAG) 6 months later showed in-stent total occlusion, so a stent-in-stent procedure was performed using paclitaxel-eluting stents (PESs). Four months later, the patient began complaining of early morning chest pain at rest. CAG showed no in-stent restenosis, so coronary spastic angina was suspected. Intracoronary infusion of ergonovine to the right and left coronary arteries revealed spasm of the RCA with total occlusion just proximal to the PES in segment 1. Her chest pain was reproduced with ST-elevation in leads II, III, and aVF, so the diagnosis of coronary spastic angina was made. Treatment with a Ca-channel blocker and nitrates relieved the symptoms. The PES was the probable cause of the coronary spasm.

Case report

A 56-year-old woman with hypertension and hypercholesterolemia was admitted to our hospital in September 2006 with an acute inferior myocardial infarction. She had menopause when she was 43 years old. Coronary angiography (CAG) showed total occlusion of the right coronary artery (RCA) segment 2. A Multilink Vision stent (3.5 mm × 18 mm; Abbott, Tokyo, Japan) and a Driver stent (3.5 mm × 24 mm; Medtronic, Minneapolis, MN, USA) were overlapped and placed. The left circumflex artery (LCX) was also significantly stenosed, so sirolimus-eluting stents (SESs) (Cypher; Johnson & Johnson, Cordis Corporation, Miami, FL, USA) were placed in segment 11 (3.5 mm × 18 mm) and segment 13 (2.5 mm × 18 mm) before hospital discharge.

Four months later, the patient was hospitalized for exertional chest pain. CAG showed in-stent restenosis of segment 2, so plain old balloon angioplasty (POBA) was performed. Six

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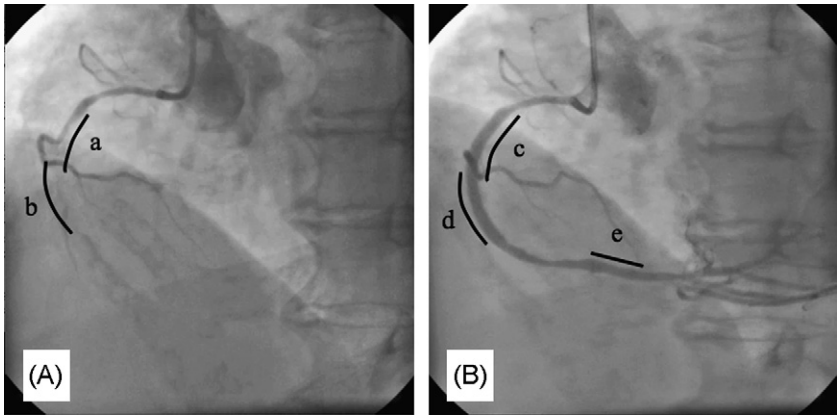

Figure 1 Third percutaneous coronary intervention. (A) Coronary angiography shows in-stent total occlusion in the right coronary artery. (B) Paclitaxel-eluting stents (PESs) were placed in the bare-metal stents (BMSs). The BMSs were fully covered by the PESs. A PES was also placed at the segment 3 90% new lesion (a: Multilink Vision stent; b: Driver stent; c, d, and e: PES).

months later, follow-up CAG revealed in-stent total occlusion of segment 2 (Fig. 1A). Because this was the second restenosis, a stent-in-stent procedure using a paclitaxel-eluting stent (PES; Taxus, Boston Scientific, San Diego, CA, USA) was performed. Two PESs (3.5 mm × 24 mm) were overlapped and placed, completely covering the bare-metal stent (BMS). After reperfusion, a new 90% lesion in segment 3 was detected, so a PES (3.0 mm × 12 mm) was placed. The procedure was completed with good results (Fig. 1B).

However, 4 months later, the patient experienced early morning chest pain at rest for the first time. We performed CAG without an exercise test and without stopping oral vasoactive agents before CAG, because we were concerned about the possibility of unstable angina due to the presence of resting chest pain. CAG showed 75% stenosis just proximal to the PES in segment 1 (Fig. 2C). No other significant lesions were present to account for the resting chest pain. Thus, a spasm provocation test using ergonovine was per-

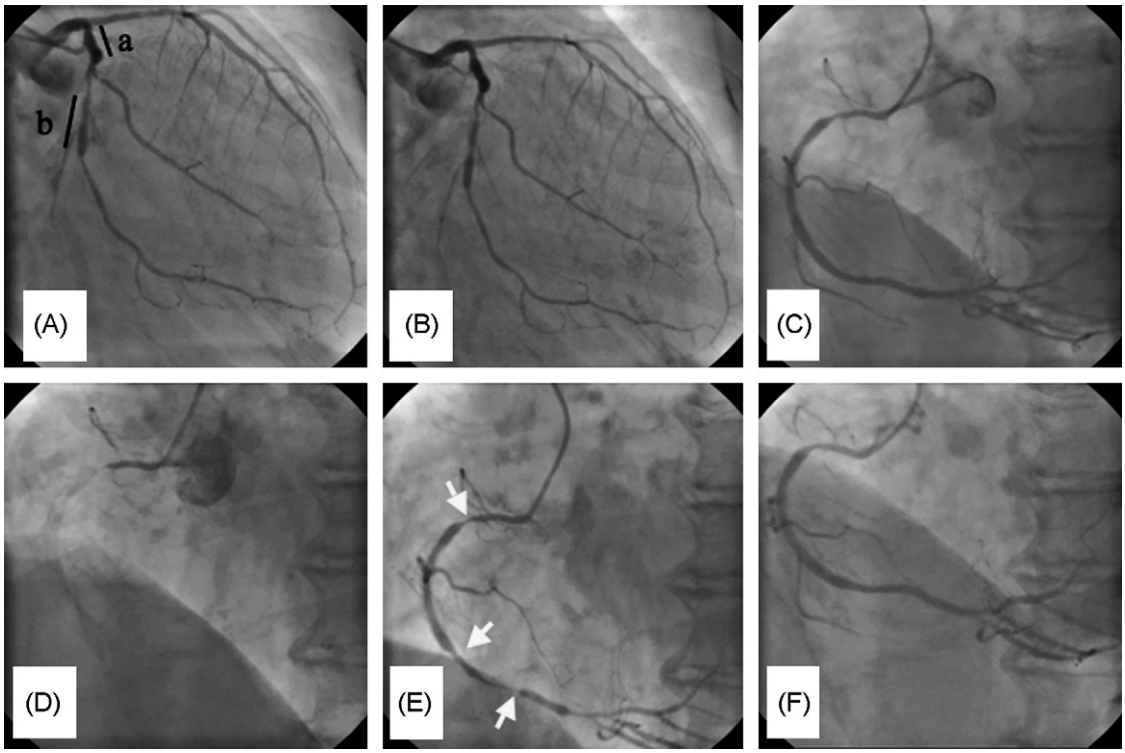

Figure 2 Left coronary angiograms both (A) pre- and (B) post-ergonovine infusion (a and b: sirolimus-eluting stent). (C) Right coronary angiogram pre-ergonovine infusion. (D) Total occlusion of segment 1 is observed after infusion. (E) Coronary spasm remains just proximal to the paclitaxel-eluting stent (PES) in segments 1 and 3 and just distal to the PES in segment 2 after infusion of isosorbide dinitrate 2.5 mg (arrows). (F) Following additional intracoronary infusion of isosorbide dinitrate, the coronary spasm has resolved completely.

formed. First, ergonovine was infused into the left coronary artery at a rate of 8 μg/min for 5 min, but only slight vasoconstriction was noted (Fig. 2A and B). Then, ergonovine was similarly infused into the RCA, and within 4 min, the patient began to complain of her usual chest pain with ST-elevation in leads II, III, and aVF. CAG revealed that the stenotic lesion of segment 1 was totally occluded (Fig. 2D). Though intracoronary infusion of 2.5 mg of isosorbide dinitrate achieved reperfusion, coronary spasm remained just proximal to the PES in segment 1 and segment 3 and just distal to the PES in segment 2 (Fig. 2E). Again, with intracoronary infusion of 2.5 mg of isosorbide dinitrate, the coronary spasm, including the chest pain and the electrocardiogram changes, resolved completely (Fig. 2F).

The patient had taken aspirin 200 mg/day, ticlopidine 200 mg/day, amlodipine 5 mg/day, bisoprolol 5 mg/day, lisinopril 10 mg/day, and atorvastatin 10 mg/day. Because coronary spasm was demonstrated, long-acting isosorbide dinitrate 40 mg/day and benidipine 8 mg/day were added. On follow-up, the patient has had no recurrence of chest pain at rest.

Discussion

A case of newly demonstrated coronary spasm 4 months after PES implantation was described. Ergonovine did not provoke coronary spasm in the LCX with SES, but clearly provoked it with total occlusion just proximal to the PES in the RCA.

Although drug-eluting stents (DES) effectively prevent restenosis and are now widely used in percutaneous coronary intervention (PCI), late stent thrombosis has been reported as a major concern of DES implantation [1]. As the cause, delayed endothelialization has been reported in DES cases as compared to BMS cases from a histopathological perspective [2]. Furthermore, as compared to BMS, endothelial dysfunction has been more often reported with DES [3,4]. The underlying mechanism of endothelial dysfunction due to DES includes: (1) direct endothelial injury and hypersensitivity reactions to the stent system (drug and polymer coating) and (2) delayed recovery of endothelial function due to delayed re-endothelialization [5].

Coronary spastic angina was first reported by Prinzmetal et al. [6] in 1959 as variant angina. During the 1970s, coronary artery spasm as the underlying etiology was documented by CAG [7]. A major cause of coronary artery spasm is endothelial cell dysfunction due to a variety of factors, such as oxidative stress, endothelial nitric-oxide synthase (e-NOS) gene polymorphism, and chronic inflammation [8].

Consequently, this has been raising concerns about coronary spasm due to endothelial injury associated with DES implantation, and there have actually been some reports of newly demonstrated coronary spasm after DES implantation. Based on our literature search, 13 cases of coronary spasm after SES or PES implantation, including our case, have been reported (Table 1) [5,9—11]. Coronary spasm in all 3 branches has been described, and time of onset has varied from during PCI to 6 months post-PCI. The site of coronary spasm also varies from diffuse to proximal or distal to the stent.

Table 1 Case reports of coronary spasm associated with drug-eluting stent implantation.

Case	Type of stent	Indication for stent	Location of stent	Method of spasm identification	Location of spasm	Time to spasm (after PCI)
Present report	PES	AP	ISR in RCA	CAG	RCA stent proximal	4 months
El-Bialy et al. [9]	PES	uAP	LAD	Chest pain, ECG, CAG (patent stent)	Unknown	Same day
Kim et al. [10]	PES	Acute MI	RCA, LAD, LCX	Sudden cardiac arrest CAG	Diffuse narrowing of three coronary arteries	10 h
Maekawa et al. [11]	SES	Recent MI	LAD	CAG	LAD stent distal	6 months
Brott et al. [5]	SES	uAP	LAD & diagonal	Chest pain, ECG, CAG	Diffuse, LAD&LCX	3 h
Brott et al. [5]	SES	AP	ISR in LAD	Chest pain, CAG	Diffuse LAD&LCX	1 week
Brott et al. [5]	SES	Acute MI	LAD	CAG	Distal to stent	4 weeks
Brott et al. [5]	SES	uAP	LCX distal	Chest pain, ECG, CAG	Proximal to stent	12 h
Brott et al. [5]	SES	N/A	LAD via LITA	CAG	Proximal and distal	3 h
Brott et al. [5]	PES	N/A	LAD	CAG	Entire LAD&LCX	During procedure
Brott et al. [5]	PES	N/A	RCA, OM	CAG	RCA, OM	During procedure
Brott et al. [5]	SES	AP	LAD	MI, chest pain, ECG, CAG (patent stents)	Unknown	11 days
Brott et al. [5]	SES	N/A	RCA	Chest pain, CAG (patent stents)	Unknown	11 days

AP, angina pectoris; CAG, coronary angiography; ECG, electrocardiogram; ISR, in-stent restenosis; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LITA, left internal thoracic artery; MI, myocardial infarction; N/A, not available; OM, obtuse marginal branch; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; RCA, right coronary artery; SES, sirolimus-eluting stent; uAP, unstable angina pectoris.

Table 1 lists cases of coronary spasm associated with DES implantation, based on the absence of any prior symptoms suggesting coronary spastic angina. The present patient also first experienced early morning chest pain at rest after PES implantation, and, with the spasm provocation test, total occlusion just proximal to the PES in segment 1 was observed. Moreover, the spasm remained just proximal and distal to the PES after infusion of isosorbide dinitrate. These findings suggest coronary spasm related to PES implantation. However, objective evaluation of whether DES implantation indeed caused coronary spasm was limited, because the spasm provocation test (with negative results) was not performed beforehand in any of the cases, including the present case. In the present case, the presence of coronary spasm was confirmed by the spasm provocation test. Therefore, we consider that the spasm provocation test should be done in patients who complain of resting chest pain after DES implantation, although spontaneous attacks may not be proven to be the same as the induced attack.

The present patient also had SES in the LCX, but coronary spasm did not develop at this site. There are more case reports of coronary spasm with SES than with PES, but this may be influenced by their period of availability and number used. It would be interesting to know whether SES and PES differ in their ability to provoke spasm. Individual differences in reactivity to drugs may exist. However, the details are unclear, because, unlike the present case, there are no reports that involved implantation of both SES and PES and that mentioned differences between the stents in their ability to provoke spasm.

Brott et al. [5] reported, in addition to DES cases, 3 cases of coronary spasm after BMS implantation. Their findings suggest that PCI itself may also cause endothelial injury, leading to coronary spasm. In the present case, the patient had already undergone PCI 3 times for the PES implantation site in segment 2, so the proximal endothelium might have been injured by repeated PCI. In segment 3, however, PCI was performed only once, and PES was easily deployed after balloon predilation. Thus, we consider there was no significant endothelial injury due to PCI itself in segment 3.

With the additional oral medications mentioned previously, further chest pain at rest did not develop, so drug therapy provided good control. In conclusion, coronary spasm must always be kept in mind as a potential cause of resting chest pain after DES implantation. However, further investigation is necessary to determine whether drug therapy to prevent coronary spasm is required in all patients with DES implantation.

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