

## Restenosis Developing Over One Year After Implantation With a Sirolimus-Eluting Stent: Two Case Reports

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### Abstract

A 68-year-old man with familial hypercholesterolemia developed effort angina and received a sirolimus-eluting stent (SES) to treat 99% stenosis in segment 6 of the left anterior descending coronary artery in January 2005. A further stent was implanted 14 months later to treat 99% restenosis at the proximal stent edge. A 66-year-old man with diabetes developed acute anterior myocardial infarction and underwent SES implantation to treat 90% stenosis in segment 4 atrioventricular node artery branch of the right coronary artery in April 2006. Heart failure developed 14 months later. Another stent was implanted to treat 100% obstructive stenosis of the proximal stent site. Late stent restenosis may occur over 1 year after SES implantation, so longer follow-up is required compared to bare metal stent.

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### Key Words

Restenosis

Stent( sirolimus-eluting )

Coronary artery disease

### INTRODUCTION

Randomized, double-blind trials have shown that sirolimus-eluting stent (SES) implantation markedly decreases restenosis rates compared with bare metal stent (BMS)<sup>1,2)</sup> and the beneficial effect persists at mid-term follow-up.<sup>3-5)</sup> However, late stent restenosis is a potential risk after implantation of a drug-eluting stent because of the delayed healing response.<sup>6,7)</sup> Here we describe two patients with late stent restenosis 14 months after SES implantation, requiring target lesion revascularization (TLR).

### CASE REPORT

#### Case 1

A 68-year-old man with familial hypercholesterolemia, hypertension and obesity was referred to our hospital in December 2004 for further examination of frequent chest pain on mild exertion that had

persisted for 1 month. Atorvastatin (40 mg/day) and colestimide (1.5 g/day) had been administered for familial hypercholesterolemia, but details of his family history were unknown. Coronary angiography revealed 99% stenosis in segment 6 of the left anterior descending artery (LAD). He underwent percutaneous coronary intervention (PCI) on January 28, 2005. After pre-dilation with a balloon (Kongou 3.0 × 15 mm, Terumo), a SES (Cypher 3.5 × 18 mm, Cordis) was deployed initially with an inflation pressure of 12 atm followed by the second dilation up to 18 atm with the same balloon at a rather proximal site from the stent (Figs. 1 - A, B). Although follow-up coronary angiography at 8 months after stenting revealed no restenosis, he frequently experienced chest pain on mild exertion from March 2006. He was admitted to our hospital under a diagnosis of unstable angina on March 17, 2006.

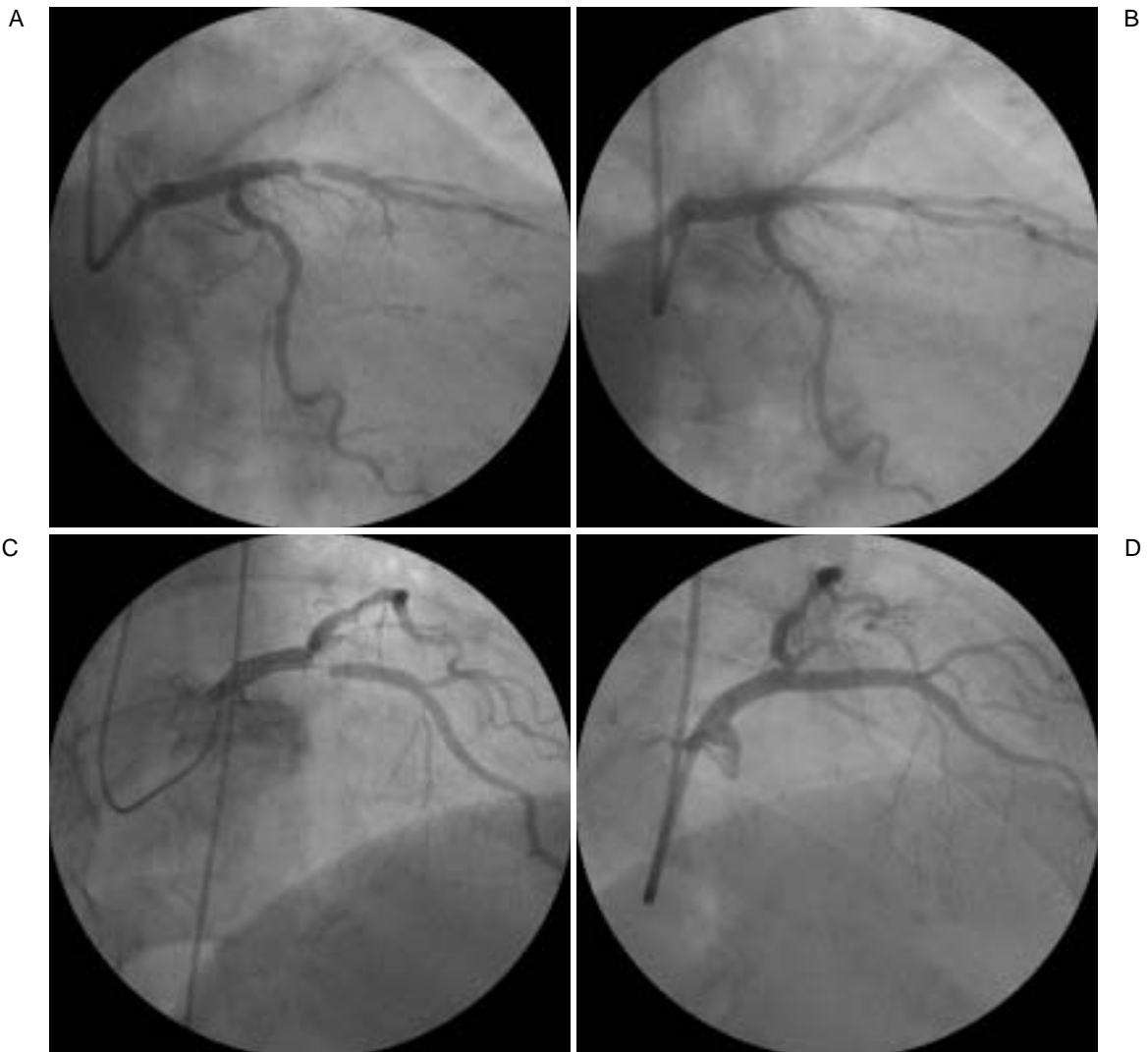
Physical examination on admission revealed

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**Fig. 1 Left coronary angiograms of Case 1**

- A: Segment 6 of the left anterior descending artery showed 99% stenosis.
- B: A sirolimus-eluting stent was implanted for the target lesion.
- C: The proximal stent edge developed 99% restenosis 14 months after the first stenting.
- D: A sirolimus-eluting stent was implanted to cover the proximal site of the previous stent.

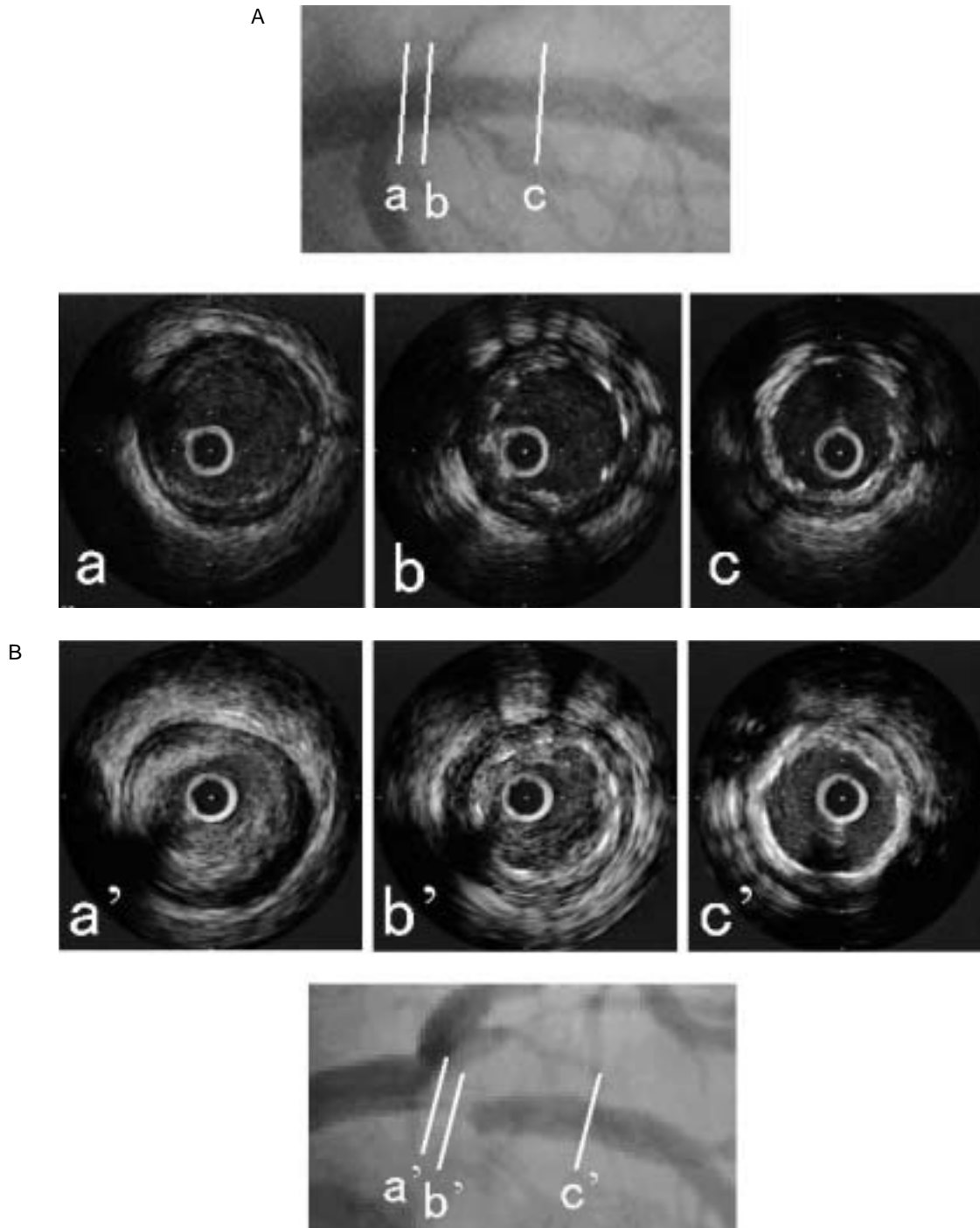
body mass index of 27.6 kg/m<sup>2</sup>, mildly high blood pressure of 152/86 mmHg and thick bilateral Achilles tendons. Lipid profile showed the following: total cholesterol, 194 mg/dl; high-density lipoprotein cholesterol, 36 mg/dl; low-density lipoprotein cholesterol, 131 mg/dl; and triglyceride, 127 mg/dl. None of the myocardial enzyme levels were elevated. Electrocardiography and chest radiography revealed no unusual findings. Echocardiography revealed mild hypokinesia in the anteroseptal apex area of the left ventricle.

Coronary angiography showed 99% stenosis in the proximal stent edge in segment 6 of the LAD

on March 20, 2006. Therefore, ad hoc PCI was performed (Figs. 1 - C, D). After pre-dilation with a balloon (Rosso 2.5 × 15 mm, Kaneka), a SES (Cypher 3.5 × 18 mm, Cordis) was implanted with an inflation pressure of 18 atm at the proximal site of the previous stent. Intravascular ultrasound (IVUS) revealed obvious intimal proliferation in the proximal stent edge with a partial low echoic area 14 months after stent implantation (Fig. 2).

#### Case 2

A 66-year-old male former smoker with untreated



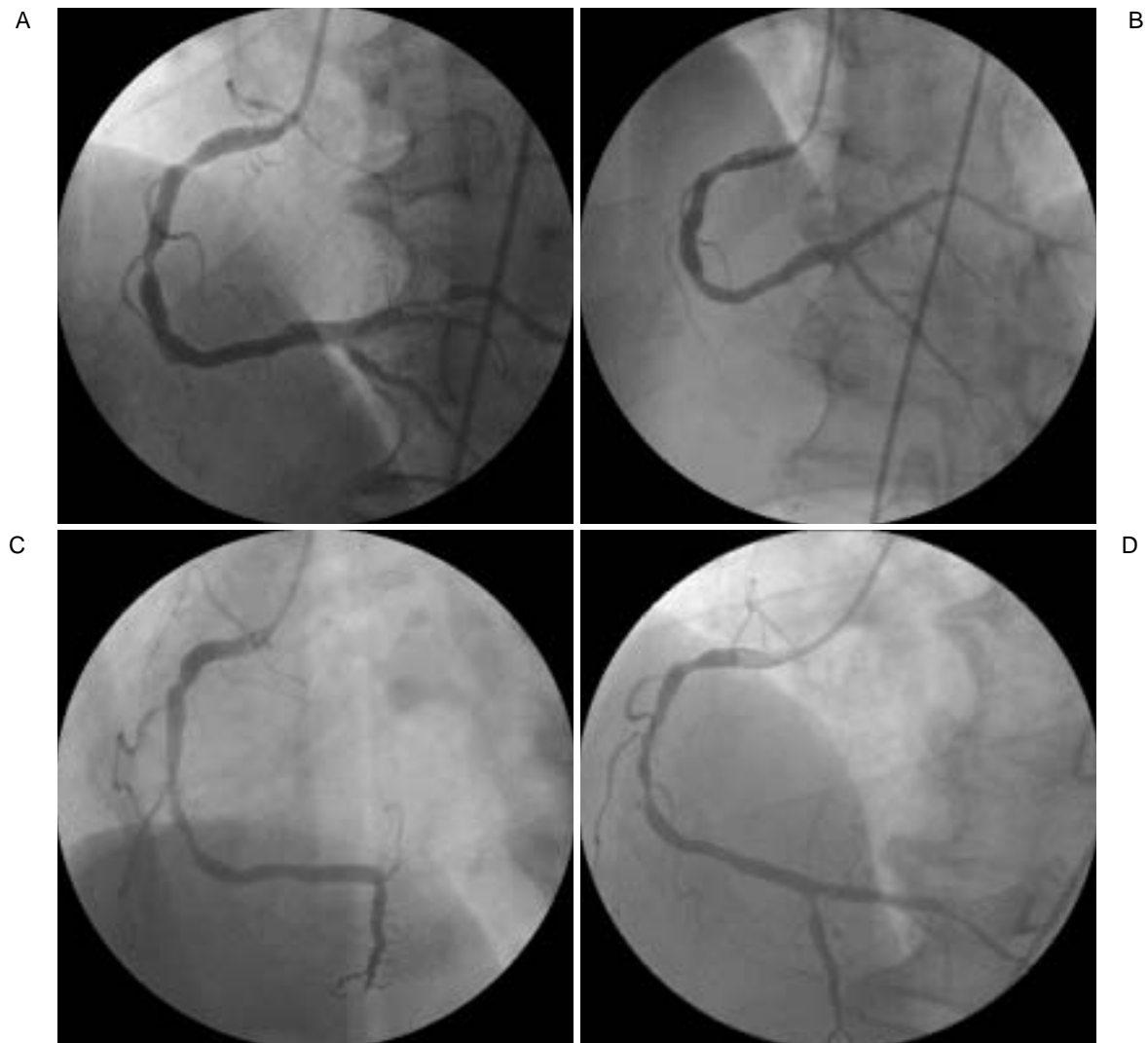
**Fig. 2 Intravascular ultrasound and angiography findings in Case 1**

*A*: Left coronary angiogram showing the sites corresponding to the following intravascular ultrasound frames after the first stenting.

*a*: Proximal site to the stent. *b*: Proximal stent edge. *c*: First culprit lesion.

*B*: Left coronary angiogram 14 months after the first stenting showing the sites corresponding to the following intravascular ultrasound images.

*a'*: Proximal site to the stent showing intimal proliferation with isoechoic area. *b'*: Proximal stent edge showing intimal proliferation with partial low echoic area. *c'*: First culprit lesion.



**Fig. 3 Right coronary angiograms of Case 2**

*A:* Segment 4 atrioventricular node artery branch (AV) of right coronary artery showed 90% stenosis.

*B:* A sirolimus-eluting stent was implanted for the target lesion.

*C:* The ostium of segment 4 AV developed 100% obstructive restenosis 14 months after the first stenting.

*D:* A sirolimus-eluting stent was implanted in the proximal site of the first stent crossing the posterior descending branch.

ed diabetes was admitted to our hospital to treat an acute anterior myocardial infarction (Killip's classification class 1; peak creatine kinase, 8,294 IU/l) on March 11, 2005. He underwent emergency PCI to treat total occlusion of segment 7 of the LAD, and a SES (Cypher 3.5 × 23 mm, Cordis) and a BMS (Driver 3.0 × 24 mm, Medtronic) were implanted. Insulin (30R of 30 U/day) was administered to treat diabetes after admission. Additional PCI for stenotic lesions of the right coronary artery was performed before discharge on April 12, 2005, and a BMS (Driver 4.0 × 15 mm, Medtronic) for 75% stenosis in segment 2 and a SES (Cypher 3.5 × 23 mm,

Cordis) for 90% stenosis in segment 4 atrioventricular node artery branch (AV) were implanted (Figs. 3 - A, B). The SES for segment 4 AV was deployed initially with an inflation pressure of 12 atm followed by a second dilation up to 18 atm with the same balloon at a rather proximal site from the stent. Although follow-up coronary angiography 10 months after stenting to the right coronary artery revealed 75% restenosis for the BMS (distal to the stent in segment 2 and in-stent site in segment 7), PCI was not performed. He experienced shortness of breath on exertion since June 2006. Chest radiography indicated congestive heart failure. He was

admitted to our hospital again on June 16, 2006.

Physical examination on admission showed slightly low blood pressure of 96/58 mmHg and slight pretibial pitting edema in the legs. No significant findings were evident in the chest. Oxygen saturation was normal. Laboratory tests revealed the following: hemoglobin, 11.1 g/dl; total protein, 6.6 g/dl; creatine kinase, 364 IU/l; creatine kinase-MB, 16 IU/l; C-reactive protein, 2.46 mg/dl; high-density lipoprotein cholesterol, 34 mg/dl; hemoglobin A<sub>1c</sub>, 6.7%; and troponin-T, 0.36 ng/ml.

Electrocardiography showed sinus tachycardia with a heart rate of 100 beats/min, a QS pattern in leads I, aL and <sub>5</sub>, poor R progression in precordial leads and a strain ST-T pattern in leads <sub>5</sub> and <sub>6</sub>. Chest radiography showed a cardiothoracic ratio of 54%, thickening in the minor fissure and dullness in the bilateral costophrenic angles. Echocardiography revealed severe hypokinesis in the inferior wall of the left ventricle in addition to akinesis in the anterior wall, left ventricular end-diastolic diameter of 61 mm and ejection fraction reduced to 31%.

Coronary angiography revealed 100% obstructive stenosis of Thrombolysis in Myocardial Infarction (TIMI) grade 1 from the ostium of segment 4 AV with a collateral vessel arising from segment 13 of left circumflex coronary artery on June 20, 2006. Therefore, ad hoc PCI was performed (Figs. 3 - C, D). After passing a mildly stiff wire (Miracle Primo, Asahi Intecc) through the lesion and dilation with an over-the-wire balloon (Maverick 2.0 × 15 mm, Boston Scientific), an SES (Cypher 3.5 × 23 mm, Cordis) was implanted in the proximal site of the previous stent, crossing the posterior descending branch. IVUS showed obvious intimal proliferation in the proximal stent edge with a low and heterogeneous echoic area 14 months after implantation (Fig. 4). In addition, positive remodeling (external elastic membrane-cross sectional area enlarged from 18.3 to 23.2 mm<sup>2</sup>) and incomplete stent apposition were evident in the previous culprit lesion.

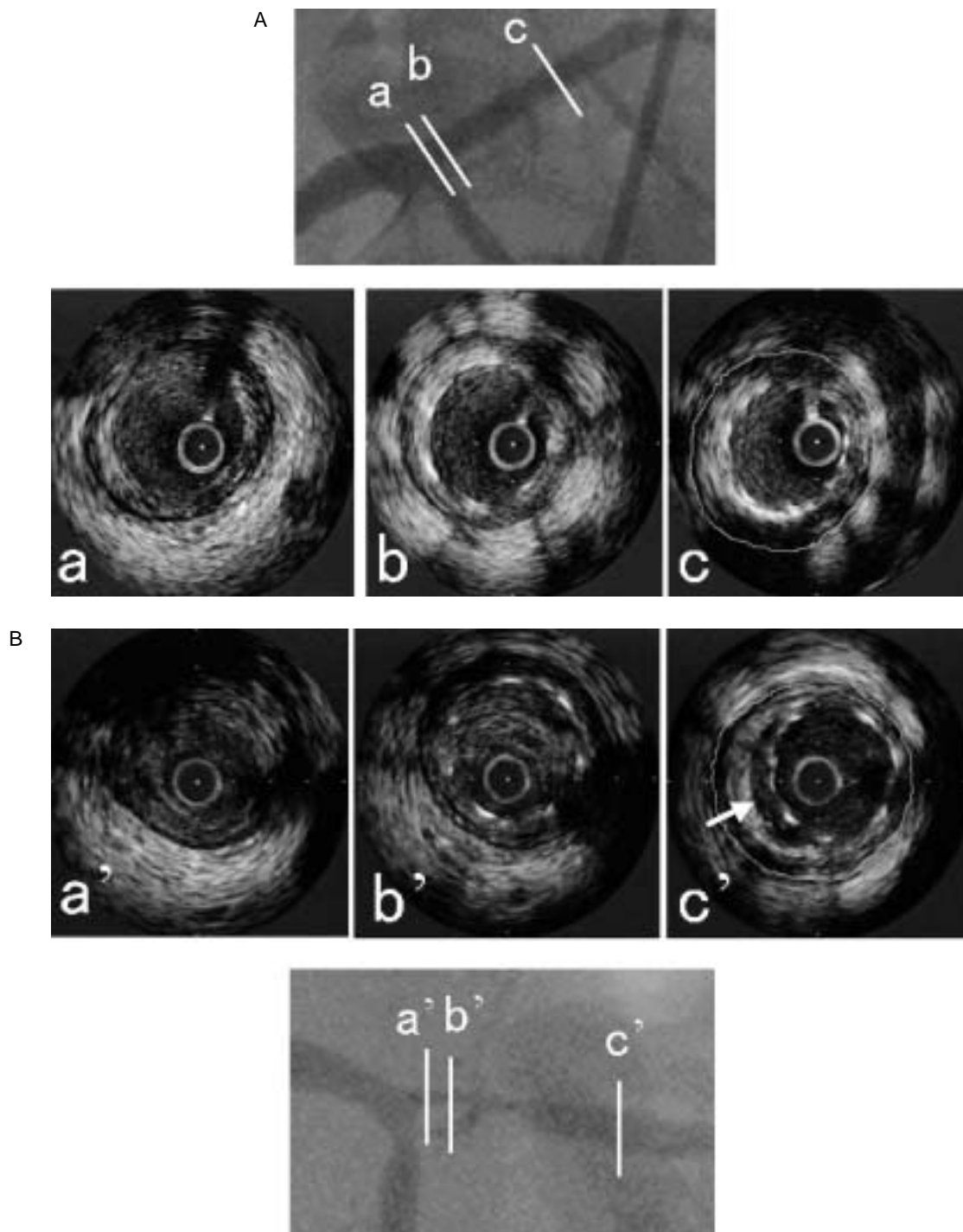
## DISCUSSION

The key issue in both of these patients is that stent restenosis occurred at over 1 year after SES implantation. The 2-year follow-up outcomes of the largest randomized double-blind SIRIUS trial<sup>4)</sup> showed that most TLR were performed within 1 year after SES implantation, so the present cases

are quite rare. Intimal proliferation occurring in the late phase after implantation of a drug-eluting stent in an animal model was equivalent to that for a BMS over the long term, or the late 'catch up' phenomenon.<sup>6)</sup> Therefore, late restenosis was initially involved in the clinical application of drug eluting stent, whereas mid-term follow-up results of a few SES trials showed that the rate of TLR was significantly smaller in the SES than in the BMS group.<sup>3-5)</sup> The RAVEL trial<sup>3)</sup> included 6 patients with TLR between 12 and 36 months after SES implantation, but none in the BMS group. This result might be the late 'catch up' effect. However, the risk factors of late stent restenosis were not reported.

The present two patients had some key features for the mechanism of restenosis. Restenotic lesions developed in the proximal stent edge and were located distally from the bifurcation with the large branch vessels. In addition, the new lesions were different from the first culprit lesions. The first stent did not completely cover the region from the proximal site of the stent to the bifurcation and post-dilation was performed rather proximally from the stent deployment site. Since restenosis in the proximal stent edge was rather noticeable in the SIRIUS trial,<sup>2)</sup> avoiding unnecessary balloon injury and full coverage of the plaque beside the culprit lesion with a longer stent have been recommended for SES implantation. Balloon injury induced by post-dilation might have caused intimal proliferation at the proximal stent edge in the present two patients. Hypercholesterolemia or diabetes is commonly related to vascular endothelial dysfunction,<sup>8-11)</sup> and our patients probably had worse disease such as familial hypercholesterolemia or diabetes with insulin therapy. In fact, vascular endothelial dysfunction is associated with stent restenosis<sup>12,13)</sup> and diabetes is widely accepted as a representative factor of stent restenosis.<sup>14,15)</sup> In the setting of these illnesses, endothelial dysfunction promoted by procedural vascular injury that persists even after the end of sirolimus release from a stent strut might cause late intimal proliferation as in the animal model.

The proposition that the stent thrombosis was related to obstructive stenosis in the second patient is difficult to exclude without endoscopic or pathologic evaluation. However, we supposed that the mechanism of obstructive stenosis was mainly restenosis due to intimal proliferation, because the progress of the lesion was not acute, electrocardio-



**Fig. 4 Intravascular ultrasound and angiography findings in Case 2**

A: Right coronary angiogram showing the sites corresponding to the following intravascular ultrasound frames immediately after the first stenting.

a: Proximal site to the stent. b: Proximal stent edge. c: First culprit lesion with external elastic membrane cross-sectional area (EEM-CSA) of 18.3 mm<sup>2</sup> (circle).

B: Right coronary angiogram showing the sites corresponding to the following intravascular ultrasound frames 14 months after the first stenting.

a': Proximal site to the stent showing intimal proliferation with low echoic area. b': Proximal stent edge showing intimal proliferation with low and heterogenous echoic area. c': First culprit lesion with EEM-CSA enlarged to 23.2 mm<sup>2</sup> (circle). Positive remodeling and acquired incomplete stent apposition with crescent echo-free space (arrow) had occurred.

graphy showed no significant change in the ST-T segment, and IVUS revealed increased intimal area in the proximal lesion to the stent. IVUS of the patient also revealed positive in-stent remodeling and incomplete stent apposition 14 months after SES implantation. Late incomplete apposition after SES implantation was not associated with cardiac events at mid-term follow-up.<sup>16, 17)</sup> We considered

that incomplete stent apposition was not related to stent restenosis in this patient, because the apposition site differed from that of the intimal proliferation.

The present two patients required TLR due to late stent restenosis that occurred over 1 year after SES implantation. Longer follow-up is required for drug-eluting stent than for bare metal stent.

### 要 約

#### シロリムス溶出性ステント留置1年以上後に再狭窄をきたした2例

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症例1は68歳, 男性, 家族性高脂血症あり. 2005年1月, 労作性狭心症により左前下行枝分節6の99%狭窄にシロリムス溶出性ステントを留置した. 14ヵ月後にステント近位端に99%狭窄をきたし, 再度ステント留置した. 症例2は66歳, 男性, 糖尿病あり. 急性前壁心筋梗塞を発症し, 2005年4月に残存する右冠動脈分節4房室結節動脈枝(AV)の90%狭窄に対してシロリムス溶出性ステントを留置した. 14ヵ月後に心不全となり, 4AVのステント近位部が100%閉塞となっていたため, 再度ステント留置した. シロリムス溶出性ステント留置例では遅延性再狭窄を生じる可能性があり, 通常の金属ステントよりも長期間の経過観察が必要である.

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### References

- Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346**: 1773 - 1780
- Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators: Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349**: 1315 - 1323
- Fajadet J, Morice MC, Bode C, Barragan P, Serruys PW, Wijns W, Constantini CR, Guermontprez JL, Eltchaninoff H, Blanchard D, Bartorelli A, Laarman GJ, Perin M, Sousa JE, Schuler G, Molnar F, Guagliumi G, Colombo A, Ban Hayashi E, Wulfert E: Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: Three-year results of the RAVEL trial. *Circulation* 2005; **111**: 1040 - 1044
- Weize G, Leon MB, Holmes DR Jr, Kereiakes DJ, Clark MR, Cohen BM, Ellis SG, Coleman P, Hill C, Shi C, Cutlip DE, Kuntz RE, Moses JW: Two-year outcomes after sirolimus-eluting stent implantation: Results from the Sirolimus-Eluting Stent in de Novo Native Coronary Lesions(SIRIUS) trial. *J Am Coll Cardiol* 2006; **47**: 1350 - 1355
- Daemen J, Ong AT, Stefanini GG, Tsuchida K, Spindler H, Sianos G, de Jaegere PP, van Domburg RT, Serruys PW: Three-year clinical follow-up of the unrestricted use of sirolimus-eluting stents as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. *Am J Cardiol* 2006; **98**: 895 - 901
- Carter AJ, Aggarwal M, Kopia GA, Tio F, Tsao PS, Kolata R, Yeung AC, Llanos G, Dooley J, Falotico R: Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. *Cardiovasc Res* 2004; **63**: 617 - 624
- Park DW, Hong MK, Mintz GS, Lee CW, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Weissman NJ, Park SW, Park SJ: Two-year follow-up of the quantitative angiographic and volumetric intravascular ultrasound analysis after nonpolymetric paclitaxel-eluting stent implantation: Late "catch-up" phenomenon from ASPECT Study. *J Am Coll Cardiol* 2006; **48**: 2432 - 2439
- Berliner JA, Heinecke JW: The role of oxidized lipoproteins in atherogenesis. *Free Radic Biol Med* 1996; **20**: 707 - 727
- de Jongh S, Lilien MR, op t Roodt J, Stroes ES, Bakker HD, Kastelein JJ: Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 2002; **40**: 2117 - 2121
- Aronson D, Bloomgarden Z, Rayfield EJ: Potential mechanisms promoting restenosis in diabetic patients. *J Am Coll Cardiol* 1996; **27**: 528 - 535

- 11) Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA: Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1996; **27**: 567 - 574
- 12) Piatti P, Di Mario C, Monti LD, Fragasso G, Sgura F, Caumo A, Setola E, Lucotti P, Gallucio E, Ronchi C, Origgi A, Zavaroni I, Margonato A, Colombo A: Association of insulin resistance, hyperleptinemia, and impaired nitric oxide release with in-stent restenosis in patients undergoing coronary stenting. *Circulation* 2003; **108**: 2074 - 2081
- 13) Patti G, Pasceri V, Melfi R, Goffredo C, Chello M, D'Ambrosio A, Montesanti R, Di Sciascio G: Impaired flow-mediated dilation and risk of restenosis in patients undergoing coronary stent implantation. *Circulation* 2005; **111**: 70 - 75
- 14) Kastrati A, Schomig A, Elezi S, Schuhlen H, Dirschinger J, Hadamitzky M, Wehinger A, Hausleiter J, Walter H, Neumann FJ: Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 1997; **30**: 1428 - 1436
- 15) West NE, Ruygrok PN, Disco CM, Webster MW, Lindeboom WK, O'Neill WW, Mercado NF, Serruys PW: Clinical and angiographic predictors of restenosis after stent deployment in diabetic patients. *Circulation* 2004; **109**: 867 - 873
- 16) Ako J, Morino Y, Honda Y, Hassan A, Sonoda S, Yock PG, Leon MB, Moses JW, Bonneau HN, Fitzgerald PJ: Late incomplete stent apposition after sirolimus-eluting stent implantation: A serial intravascular ultrasound analysis. *J Am Coll Cardiol* 2005; **46**: 1002 - 1005
- 17) Hong MK, Mintz GS, Lee CW, Park DW, Park KM, Lee BK, Kim YH, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ: Late stent malapposition after drug-eluting stent implantation: An intravascular ultrasound analysis with long-term follow-up. *Circulation* 2006; **113**: 414 - 419