Pathological Finding of Sirolimus-Eluting Stent (SES) Restenosis Lesion With Black Hole Appearance on Intravascular Ultrasound

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Restenosis still occurs, even with the sirolimus-eluting stent (SES), and the precise mechanisms have not yet been elucidated. In the present case, focal in-stent stenosis was discovered on angiography 16 months after SES implantation. Intravascular ultrasound revealed an echolucent homogeneous zone, which has been termed “black hole”. A sample of stenotic tissue retrieved by aspiration revealed neointimal hyperplasia, composed of proteoglycans and smooth muscle cells with scanty cellularity. Furthermore, infiltration of many macrophages and T lymphocytes coexisted in the restenotic tissue. These findings suggest that delayed healing is 1 of the mechanisms of SES restenosis. (*Circ J* 2009; 73: 1969–1971)

Key Words: Atherectomy; Drug-eluting stent; IVUS; Pathology; Restenosis

Since the introduction of the drug-eluting stent (DES) to interventional procedures, several studies have clearly shown it reduces the rate of restenosis and target vessel revascularization.^{1,2} However, in-stent restenosis (ISR) in DESs still occurs, although to a limited extent. Some mechanisms, such as stent fracture, damage to the DES polymer, low local drug concentrations based on local stent geometry, or chronic inflammation, have been reported.^{3–6}

The precise pathological mechanisms responsible for restenosis in DESs remain unclear. We present here a patient with focal restenosis occurring 16 months after sirolimus-eluting stent (SES) implantation, and the tissues retrieved from the restenosis were examined histologically.

Case Report

A 79-year-old man with a history of bare metal stent (BMS) implantation in the mid left anterior descending artery (LAD) was admitted with unstable angina. Coronary angiography and intravascular ultrasound (IVUS; Atlantis™ 40MHz, Boston Scientific Corp, Natick, MA, USA) revealed a tight stenosis of the left main trunk (LMT) and just proximal of the LAD (**Figure 1A**). After prophylactic placement of an intra-aortic balloon pump, predilatation was undertaken with a 2.5-mm diameter balloon (Maverick 2.5×15 mm, Boston Scientific), and a SES (3.0-mm diameter, 33 mm long; Cypher, Cordis Corporations, Miami Lakes, FL, USA) was implanted successfully from the LMT into the LAD. After deployment of the stent, it was postdilated at a pressure of 20 atm with a Quantum 3.0×30 mm balloon (Boston Scientific) in the LAD and a Quantum 3.5×12 mm balloon (Boston Scientific) in the LMT. Finally, the kissing

balloon technique was used wherein a 3.5-mm diameter balloon (Quantum 3.5×12 mm, Boston Scientific) was placed in the LAD, together with a 2.0-mm diameter balloon (Maverick 2.0×15 mm, Boston Scientific) placed in the left circumflex artery. Final angiography and IVUS confirmed satisfactory results (**Figure 1B**). The patient received oral aspirin (100 mg) and ticlopidine (200 mg) daily and remained asymptomatic after stenting. Follow-up angiography performed 3 months later showed good patency of the SES (**Figure 2A**). However, 16 months after stent deployment, evidence of asymptomatic myocardial ischemia was detected by nuclear stress test. Angiography and IVUS examination revealed focal ISR with a homogeneous echolucent intraluminal area, which was termed a “black hole” (**Figure 2B**).⁷ This lesion was dilated with a 3.0×9 mm NC Sprinter® balloon (Medtronic Inc, Minneapolis, MN, USA) at 14 atm. After dilatation, IVUS revealed persistence of the intimal flap with echolucent tissue (**Figure 2C**), from which we sampled a yellowish fragment with an aspiration device (Thrombuster™, Kaneka Corp, Osaka, Japan). Final angiography and IVUS images confirmed a decrease in the area of the “black hole” and satisfactory results (**Figure 2D**). The aspirated specimen was analyzed histologically, and comprised predominantly intimal hyperplasia with hypocellular smooth muscle cells and abundant extracellular matrix such as proteoglycans (**Figures 3A–E**). In the adjacent areas, there were many T lymphocytes and macrophages, some of them with a foamy cell appearance (**Figures 3F, G**).

Discussion

A “black hole” on IVUS has been defined as a homoge-

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Figure 1. Coronary angiography and IVUS images reveal a tight stenosis of the left main trunk, just proximal of the LAD (A). Percutaneous coronary intervention successfully performed with a SES (3.0-mm diameter, 33 mm long). Final angiographic and IVUS results are good (B). IVUS, intravascular ultrasound; LAD, left anterior descending artery; SES, sirolimus-eluting stent.

Figure 2. Three-month follow-up angiograms show good patency of the SES (A), whereas 16-month follow-up angiogram and IVUS images reveal a tight ISR in the proximal LAD lesion with an echolucent and homogeneous mass (arrows) (B). After ballooning, a hazy area is visible by IVUS (arrows) (C). After aspiration of the contents, the hazy area has decreased in size (arrow) and satisfactory angiography and IVUS images are obtained (D). ISR, in-stent restenosis. See Figure 1 for other abbreviations.

neous black-appearing image that produces no attenuation of the ultrasound signal and can be delineated from the lumen.⁷ Black holes are frequently recognized in patients who have undergone SES implantation after failed brachytherapy. This phenomenon is also observed, although less frequently, in non-irradiated patients treated with a SES, but not after BMS implantation.^{8,9}

In general, the majority of restenotic tissue after DES consists of smooth muscle cells and proteoglycan-rich tissue,

which is similar to that after BMS implanting.^{10,11} On the other hand, histologic assessment of tissue from a black hole showed predominance of hypocellular matrix with areas of proteoglycans.^{12–15} The predominance of proteoglycans could be related to general vascular wound-healing delay,¹⁶ which can occur as late as 2 year following SES implantation.¹⁷

In the present case, restenosis occurred from 3 to 16 months after SES implantation. The histology of the re-

Figure 3. Micrographs of an aspirated specimen taken from the ISR site, 16 months after SES implantation. Hematoxylin-eosin staining reveals coexistence of a relatively hypocellular region and adjacent hypercellular area (A; original magnification: $\times 4$) (B; original magnification: $\times 45$). Alcian blue staining (C: $\times 4$, D: $\times 45$) shows accumulation of proteoglycans especially in the hypocellular area. SMCs with scanty cellularity are visible (E: anti SMC α -actin stain). Immunostaining of serial sections for CD68 (F) and MT1 (G) clearly reveals remarkable infiltration of macrophages and T lymphocytes adjacent to the area of SMCs. SMC, smooth muscle cell. See Figures 1 and 2 for other abbreviations.

notic tissue showed remarkable infiltration of T lymphocytes and foam cell macrophages, as well as abundant proteoglycans almost exclusively. From these findings, we cannot suggest hypersensitivity to the polymer-based DES caused this response, because we did not find any evidence of eosinophilic infiltrates. Our findings suggest that SES-induced delayed healing could result in the proliferation of smooth muscle cells, which might be a cause of ISR.

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