In-Stent Restenosis with “Inflammatory” Neointima Following Everolimus-Eluting Stent Implantation

In Vivo Optical Coherence Tomography and Histopathological Assessment

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Summary

A 53-year-old male presented with acute myocardial infarction and was subsequently implanted with a 4.0 × 28 mm everolimus-eluting platinum chromium stent in his proximal left anterior descending artery. Eight months after the implantation, he developed exertional angina and underwent coronary angiography, which revealed significant in-stent restenosis (ISR). Percutaneous coronary intervention was performed 1 month later, and the pre-procedural optical coherence tomography (OCT) revealed a diffusely bordered and rapidly attenuated signal-poor region with invisible stent struts at ISR site, potentially indicating a “lipid-laden” neointima. The ISR lesion was excised using a novel directional coronary atherectomy catheter. The histological analysis of the retrieved restenotic tissues revealed substantial inflammation characterized by abundant foamy macrophages and T-cell infiltration. This “inflammatory” neointimal tissue with numerous macrophages (without a necrotic core) detected on OCT was not expected owing to the absence of a known feature of macrophages on OCT (i.e., high backscattering with remarkable attenuation). The current histological confirmation of in vivo OCT findings of restenotic neointima indicated that a “lipid-laden” neointima on OCT may not necessarily reflect necrotic core accumulation, and this could be attributed to substantial inflammation with abundant macrophages.

Key words: Neoatherosclerosis, Directional coronary atherectomy, Drug-eluting stent, Lipid-laden neointima

In-stent restenosis (ISR) is an issue involving multiple underlying etiologies that continues to occur even in the era of new-generation drug-eluting stents (DESs). Optical coherence tomography (OCT) allows characterization of the morphological features of restenotic neointima,1,2 this has been pathologically confirmed only in a limited number of ex vivo studies.3

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Here, we report a case of ISR following second-generation DES placement, in which in vivo OCT findings were directly compared with histopathological findings of neointimal tissues retrieved using a novel directional coronary atherectomy (DCA) catheter.

Case Report

A 53-year-old man who had a medical history of cerebral hemorrhage, hyperlipidemia, and diabetes and being an asymptomatic hepatitis B virus carrier presented with acute myocardial infarction. He received a 4.0 × 28 mm platinum chromium everolimus-eluting stent (Promus Premier™, Boston Scientific, Marlborough, MA, USA) in the proximal left anterior descending artery. Thereafter, the optimal medication based on clinical guidelines containing aspirin and prasugrel was sequentially administered. Eight months after the DES implantation, he developed exertional angina and underwent coronary angiography, which revealed significant ISR. His lipid profile improved by continuing 2.5 mg of rosuvastatin daily from the first hospitalization to the second hospitalization; his low-density lipoprotein cholesterol level decreased from 174 to 70 mg/dL, high-density lipoprotein cholesterol level decreased from 32 to 31 mg/dL, and triglyceride level decreased from 199 to 159 mg/dL. His C-reactive protein level at the second hospitalization was 0.44 mg/dL. Percutaneous coronary intervention was performed 1 month later, and pre-procedural OCT assessment showed a diffusely bordered and rapidly attenuated signal-poor re-
Figure 1. A-D: Coronary angiography before the first percutaneous coronary intervention for acute myocardial infarction (A), just after stent implantation (B), and before revascularization for in-stent restenosis (ISR) 9 months after stent implantation (C and D). Severe stenosis in the proximal left anterior descending artery at the initial angiography (white arrow in A) and 9 months after the implantation (white arrowhead in C and D). E: Cross-sectional intravascular ultrasound images just after stent implantation at the index procedure (corresponding with B). There are no apparent protruding tissues within the stent, and the underlying plaques (outside the stent) exhibit substantial ultrasound attenuation (white asterisks in E-2, E-3, and E-4), potentially indicating the presence of a large necrotic core. F: Cross-sectional optical coherence tomography (OCT) images of the stented segment before revascularization showing ISR with a diffusely bordered and rapidly attenuated signal-poor region (yellow asterisks in F-3 and F-4). F: correspond with the dotted lines in (D'). G: Cross-sectional OCT images of the stented segment after directional coronary atherecomy (DCA) for ISR. A substantial part of the attenuated region of the restenotic tissues is successfully excised with DCA (yellow arrows in G-3 and G-4). E and G are co-registered with F.

Discussion

These histological findings indicated the involvement of inflammation in ISR development. However, the absence of eosinophils and giant cells suggested that ISR may not have been associated with hypersensitivity reactions. The pathological findings in the present case at least partly resembled those observed in cases of bare metal stent placement, in which penetration of stent struts into the necrotic core and inflammatory cell infiltration were considered to be pathological predictors of ISR. Although pathological information on the deeper neointima was limited, the location of the current ISR, which was the same as that of the original culprit site, suggested that the underlying necrotic core possibly affected the inflammatory reaction and smooth muscle cell growth following DES placement. The presence of focal fibrin and red blood cells in the neointima indicated the potential involvement of intraplaque hemorrhage or thrombus formation, which may be associated with inflammation. If ISR is considered to be derived from thrombosis, one possible explanation would be underlying plaque rupture. Another
Figure 2. Histological images of four restenotic neointimal tissue pieces (A-D) retrieved by directional coronary atherectomy. Serial histological cross sections are shown in A1-4, B1-4, C1-4, and D1-4. Abundant foamy macrophage infiltration is confirmed by immunostaining for CD68 (red arrowheads in A-3, B-3, C-3, D-3, and D-7), whereas no apparent necrotic core is identified. Substantial smooth muscle cell growth is determined by immunostaining for alpha-smooth muscle actin (α-SMA) (A-4, B-4, C-4, and D-4), with surrounding collagen (blue in Masson’s trichrome). T-cell infiltration is also identified by immunostaining for CD3 (black arrowheads in A-5, B-5, C-5, and D-5). Most of the macrophages are observed with collagen in between, as highlighted in D-6 and D-7. Focal fibrin deposition (black arrowheads in D-8 and D-9) and the presence of small amounts of RBCs (blue arrowhead in D-10) are also detected on immunohistochemistry. Green arrowheads in parts A and B indicate the potential luminal side of the specimen. H&E, hematoxylin and eosin; RBCs, red blood cells. Black scale bars = 100 μm; red scale bars = 50 μm; green scale bars = 20 μm.

possibility is in-stent neatherosclerosis, although it remains unclear whether the numerous macrophages could have newly infiltrated from the luminal side within several months after stent implantation.

On OCT, low backscattering without sharp borders is generally considered to indicate lipid, fibrin, or an organized thrombus. In this case, low backscattering was accompanied by signal attenuation, suggesting a “lipid-laden” neointima. However, pathological analysis did not identify a lipid pool or necrotic core but showed abundant macrophages, which was unexpected because of the absence of a known feature of macrophages on OCT (i.e., high backscattering with remarkable attenuation). In this case, the loaded cholesterol ester in the cytoplasm of numerous macrophages may have caused the low backscattering.

The current first histological confirmation of “in vivo” OCT findings of restenotic neointima in a new-generation DES indicated that a “lipid-laden” neointima on OCT may not necessarily reflect necrotic core accumulation, and this could be attributed to substantial inflammation with abundant macrophages. These findings might have some impact on the future consensus document of intravascular OCT imaging.

Acknowledgments

The authors thank all members of the Department of Pathology at the National Cerebral and Cardiovascular Center, Osaka, Japan, for their technical support.

Disclosures

Conflicts of interest: Dr. Otsuka has received speaking
honorarium from Abbott Vascular and Terumo Corporation.

References