Pathology of Neointimal Calcification in Very Late Restenosis After Bare Metal Stent Implantation for Superficial Femoral Artery

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Summary

A 60-year-old man, who had claudication in his right limb due to total occlusion of the right superficial femoral artery, received bare metal stents. Although the bare metal stents in the superficial femoral artery did not show restenosis 5 years after stent implantation, angiography revealed significant in-stent restenosis when he developed right critical limb ischemia at 8 years post implantation. Ballooning for in-stent lesions did not result in full expansion. His right limb was amputated above the knee due to progressive limb ischemia. In the pathological findings in the superficial femoral artery, marked calcification was observed in the entire circumference of the luminal surface of the neointima. However, lipid core formation was not identified in the neointima. Although several cracks following balloon angioplasty were observed at the superficial calcified layers, injury to neointimal tissue such as compression was not observed. The neointima exhibited heavy calcification in the very late phase of in-stent restenosis after bare metal stent implantation in superficial femoral artery. Therefore, balloon angioplasty in the very late phase of in-stent restenosis potentially results in underexpansion. (Int Heart J 2017; 58: 641-644)

Key words: Endovascular therapy, Neoatherosclerosis, Peripheral artery

Endovascular therapy (EVT) for superficial femoral artery (SFA) stenosis has become a common treatment.1 When performing EVT for SFA lesions, bare metal stents (BMSs) are often implanted.2 The efficacy of primary stenting using self-expanding nitinol stents has been widely reported and the clinical outcomes of EVT for SFA lesions have been improved by the use of self-expanding nitinol stents.3 Even if early restenosis within 1 year can be prevented, there is still the potential for restenosis in the late and very late phases after BMS implantation. However, late and very late vascular responses have not been evaluated. Here, we report a case of major amputation with very late restenosis after BMS implantation for SFA and also present the pathological findings.

Case Report

A 60-year-old man, who was on hemodialysis due to diabetes and had a past history of angina and cerebral infarction, had claudication of Rutherford class 3 in his right lower limb due to peripheral artery disease. Angiography showed chronic total occlusion (CTO) of the right SFA (Figure 1A). Because his symptom continued at the same level despite appropriate medical therapy, he underwent EVT for right SFA. Two BMSs (Zilver [Cook Medical, Bloomington, Indiana] 6.0 mm*60 mm stent in the proximal lesion and Zilver 6.0 mm*80 mm stent in the distal lesion) were implanted (Figure 1B). After performing EVT, his ankle-brachial index improved from 0.32 to 0.89 and his symptom disappeared. Five years after BMS implantation, his symptom recurred due to a new and short de novo stenosis that was situated at a proximal site in the right SFA segment that received a BMS. Therefore, he underwent balloon angioplasty (POBA) for the de novo lesion. At that time, the BMSs in the SFA did not show restenosis (Figure 1C). At 8 years after implantation of the two BMSs, he developed right critical limb ischemia (CLI). Angiography at that time revealed significant restenosis of a site distal to the BMS placement (Figure 1D), and there was a de novo lesion proximal to the site of the BMS implant. Another BMS was implanted for the de novo lesion at a site proximal to the previous BMS, and we performed POBA for all in-stent lesions. However, balloononing for the stents implanted 8 years before did not result in full expansion. Therefore, he developed sepsis due to the lack of improvement of his CLI. In addition, his right limb was amputated above the knee due to progressive limb ischemia and the lack of infection control.

Pathological findings: The sample was fixed in 10% buffered formalin, and film-based radiographs (high-resolution fixation
Figure 1. Endovascular treatment for the right superficial femoral artery. A: Before endovascular treatment, B: Final angiography after implanting bare-metal stents, C: Angiography at 5 years after stenting, D: Angiography at 8 years after stenting, E: Film-based radiograph. The yellow arrows are proximal and distal edges of the stents implanted in the superficial femoral artery. The red arrow shows the stent overlap segment. The green arrow shows the amputation level. The histological sample was taken from the green to distal yellow arrow.

Figure 2. Pathological findings (H&E stain). A: Marked calcification was evident in the entire circumference of the in-stent neointima. Eccentric fibrocalcific plaque with massive calcification and significant osteoid metaplasia (red asterisk) are shown outside the stent. B, C and D: Low-power field indicated by the arrows B, C, and D. The yellow asterisks are calcified lesions. The yellow arrows show cracks at the superficial calcified layers caused by balloon angioplasty.
images) were taken to determine the stented segments for analysis by comparison to angiograms (Figure 1E). The vessel was then embedded in Spun resin, sectioned into 5-μm thick slices, and stained with hematoxylin and eosin. We evaluated 5 sections of the stented specimen and these sections showed similar histopathological findings. Figure 2 shows one of these sections. Figure 2A represents the entire image of the section. The stent was implanted over the eccentric fibrocalcific plaque with massive calcification. The stent struts were expanded to almost a rounded shape. In addition, a heavily calcified region showed significant osteoid metaplasia. More than moderately thickened neointimal formation was observed, and remarkable calcification was evident in the entire circumference of the luminal surface of the neointima. However, lipid core formation was not clearly observed around the struts. Several cracks were observed at the superficial portions of these calcified layers caused by balloon angioplasty (Figure 2B, C). Figure D shows the thickest calcification region in the entire circumferential calcified layers. However, injury to neointimal tissue, such as compression, by ballooning was not clearly observed. In the neointima, smooth muscle cells were spindle-shaped and ordered along the luminal surface, and the intracellular space still contained a relatively abundant proteoglycan component.

**Discussion**

Neointima in the long-term phase after BMS implantation has been described by imaging devices and histopathology studies of the coronary arteries. In a pathological study, neointimal modifications changes occurred beyond 2 years, and were frequently identified > 6 years after BMS implantation in coronary arteries. However, in the lower limb arteries, the neointimal modifications in the neointima over the long-term after BMS implantation still remain unclear. In addition, pathological analyses after EVT have not been undertaken. To the best of our knowledge, this is the first case report that includes a pathological evaluation in the long-term phase after EVT.

In this case, we reported that marked calcification occurred and there was no necrotic core formation in neointima in the very late phase after BMS implantation. Previous studies of coronary arteries demonstrated that neointimal calcification was observed in the long-term phase after BMS implantation based on imaging analysis, and there was marked calcification in patients who were on hemodialysis. In contrast to coronary and internal carotid arteries, the lower limb arteries have a slow progression of intimal thickening and heavy calcification, and little necrotic core plaque. Recently, we also reported that neointimal formation in the lower limb arteries after BMS implantation might be slower than that in coronary arteries. Therefore, it may be possible that late progression of neointima after BMS implantation for SFA lesions occurs at a slow rate, and neointima has heavier calcification in comparison with the coronary arteries.

CTO lesions can result in a worsening of the initial procedural success rate. Because of difficulty in penetrating CTO lesions with marked calcification, special devices are required in some cases. Even if the initial procedure is successful, CTO is recognized as one of the factors affecting in-stent restenosis (ISR) and the long-term outcome of EVT for CTO lesions in SFA is one of the remaining issues. Therefore, we need sufficient consideration of the treatment strategy for ISR. Imaging modalities such as intravascular ultrasound or optical coherence tomography that provide insight into the ISR mechanism can detect neointimal calcification and predict underexpansion after POBA secondary to recurrent ISR lesions of coronary arteries. If under-expansion secondary to recurrent ISR is predicted, other treatment choices such as the use of a debulking device like directional atherectomy and rotational atherectomy should be considered. In the very late phase of ISR, imaging modalities might be useful for selecting a treatment strategy even in lower extremity artery lesions.

**Disclosure**

Conflict of interest: The authors declare that they have no conflict of interest.

**References**