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Case Report

Pathological findings of late stent thrombosis after paclitaxel-eluting stent implantation for superficial femoral artery disease

Yoshimitsu Soga (MD)[a,*], Katsumi Inoue (MD)[b], Sosei Kuma (MD)[c]

[a] Department of Cardiology, Kokura Memorial Hospital, Japan
[b] Laboratory Medicine, Kokura Memorial Hospital, Japan
[c] Department of Vascular Surgeon, Kokura Memorial Hospital, Japan

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ABSTRACT

A 76-year-old man presented with right critical limb ischemia. An angiography revealed right SFA occlusion. Therefore, two paclitaxel-eluting stents (Zilver PTXs 6.0 mm × 120 mm stents; Cook Medical, Bloomington, Indiana) were placed, which promoted good blood flow. Follow-up angiography at 6 months also showed no restenosis. However, 10 months later, the patient suddenly visited with acute-onset pain in the right leg. Computed tomography showed the acute occlusion at the stented SFA. Eventually, above-knee amputation was performed due to the poor general condition and progressive limb ischemia. As the pathological finding, heterogeneous neointima formation at the stented site was mainly found. Although neointimal layer consisting of smooth muscle cell (SMC) was partly observed, necrotic tissue was evident in the remaining portion. At the necrotic tissue site, the majority of the components of the material covered by the stent strut were fibrin deposits. The findings of regenerative endothelial cells were not observed at the luminal surface. Nuclei of medial SMCs were also lost between the arterial media and the stent strut.

Late stent thrombosis after paclitaxel-eluting stenting for SFA lesion has not been sufficiently evaluated. Here, we report a case of late stent thrombosis with a review including pathological findings.

<**Learning objective:** We reported that a 76-year-old man received paclitaxel-eluting stent for femoropopliteal disease. Ten months later, stent thrombosis was occurred and above-knee amputation was performed. As the pathological finding, heterogeneous neointima formation was mainly found and the regenerative endothelial cells were not observed. Our report suggested that delayed healing and uncovered strut caused by paclitaxel-exposure resulted in late stent thrombosis.>

Introduction

Superficial femoral artery (SFA) lesions are generally long segment stenoses with many chronic occlusions. Paclitaxel-eluting stents show superiority to conventional procedures [1] and are likely to provide higher therapeutic efficacy. However, the influence stent thrombosis after paclitaxel-eluting stenting for SFA lesion has not been sufficiently evaluated. Here, we report a case of major amputation due to late stent thrombosis after implantation of a Zilver PTX, with a review including pathological findings.

Case report

A 76-year-old man presented with right critical limb ischemia. An angiography revealed right superficial artery (SFA) occlusion (Fig. 1A), and endovascular therapy (EVT) was performed. Two Zilver PTXs 6.0 mm × 120 mm stents (Cook Medical, Bloomington, Indiana) were placed to cover the whole lesion (Fig. 1B). Postoperative imaging confirmed good runoff of below-the-knee arteries. The patient was discharged with prescriptions for the oral anticoagulant (warfarin) for atrial fibrillation and antiplatelet agents of aspirin 100 mg and clopidogrel 75 mg.

Wound healing without restenosis was confirmed at 3 and 6 months (Fig. 1C).

At 10 months after EVT, the patient visited our hospital with sudden-onset pain in the right leg. Computed tomography showed the acute occlusion from the origin to the distal part of the right SFA (Fig. 1D). Above-knee amputation of the right limb was

* Corresponding author at: Department of Cardiology, Kokura Memorial Hospital, 1-2-3 Asano, Kokurakita-ku, Kitakyushu 802-0001, Japan. Tel.: +81 93 511 2000; fax: +81 93 511 2029.
E-mail address: sogacchy@yahoo.co.jp (Y. Soga).

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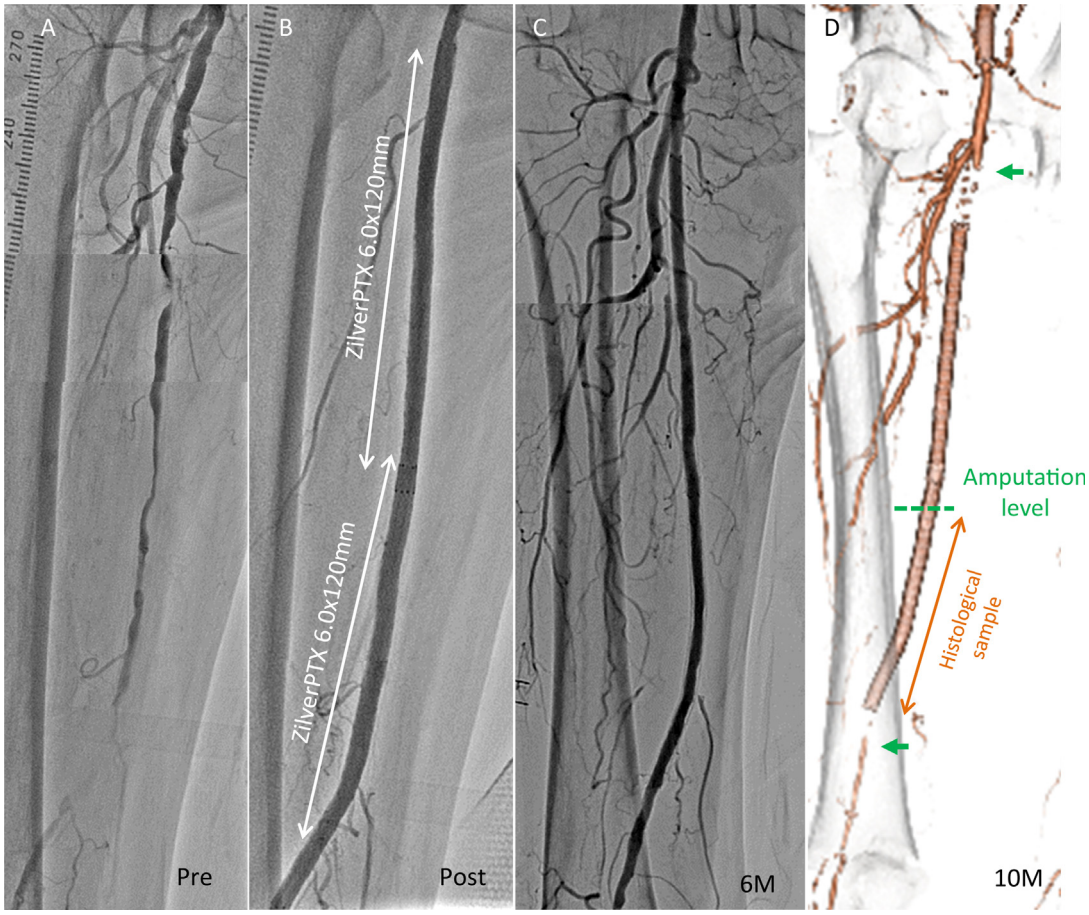

Fig. 1. Endovascular treatment for right superficial femoral artery. (A) Pre-angiogram; (B) Final angiogram; (C) 6-months follow-up angiogram; (D) Acute-onset limb ischemia at 10 months three-dimensional computed tomography for superficial femoral artery (SFA) in acute occlusion. Occlusive lesion was found from proximal SFA to distal SFA (green arrow).

undergone due to the poor general condition, progressive limb ischemia, and insufficient narcotic pain control.

Pathological findings

The sample was fixed in 10% buffered formalin and embedded in paraffin. The paraffin block was stained with hematoxylin and eosin. There were entirely necrotic tissues in the intimal side of the stent struts, where almost no circumferential viable smooth muscle cell (SMC) proliferation (Fig. 2A). The majority of the components of the material covered by the stent strut were necrotic tissue with fibrin deposition. Furthermore, the findings of regenerative endothelial cells were not observed at the luminal surface. Nuclei of medial SMCs were also lost between the arterial media and the stent strut, where necrotic tissues were observed. In the stented regions, expansion of the stent strut forced the struts contiguous to the medial layer, and remarkable loss of nuclei of medial SMCs was obvious (Fig. 2B). The heterogeneous neointima formation is shown (Fig. 2C). Although neointimal layer consisting of SMCs was partly observed, necrotic tissue was evident in the remaining portion. A low-power field image showed SMC proliferation including necrotic tissues near the superficial layer (Fig. 2D). The thrombotic occlusion site is shown in Fig. 2E. Massive thrombus formation was observed mainly on the intimal side of the uncovered stent struts. Tissue reaction at the stented site including mainly fibrin deposits, were partly observed around the stent strut, but most of these portions were consisted of necrotic tissue. The stent strut had squeezed the median smooth muscle layer (Fig. 2F).

Discussion

The Zilver PTX stent incorporates a self-expanding nitinol stent platform with a 3 mg/mm^2 polymer-free coating of paclitaxel on its outer surface. These stents deliver approximately 95% of the total paclitaxel within 24 h after deployment, and the plasma paclitaxel level becomes undetectable at 10 h. Local paclitaxel levels in the artery wall may be sustained for 56 days [2].

Paclitaxel from the Zilver PTX is eliminated within 2 months and the general duration of dual-antiplatelet therapy (DAPT; aspirin + clopidogrel) is also 2 months. However, the case reported here was interesting because stent thrombosis developed despite continuation of DAPT due to placement of a drug-eluting coronary stent and anticoagulant therapy for atrial fibrillation (PT-INR = 3.13 at the time of acute occlusion).

A coronary bare metal stent is almost fully covered by neointima consisting of SMCs and extracellular matrix 1 month after stent implantation. In contrast, in this study, the Zilver PTX placement area showed heterogeneity, with regions with and without neointimal proliferation (Fig. 2C). Heterogeneous neointimal coverage after paclitaxel-eluting coronary stenting is already reported. This pathological heterogeneity after Zilver PTX implantation might be the possible effects of the types of techniques and blood flow on the local distribution of the drug [3]. The possible

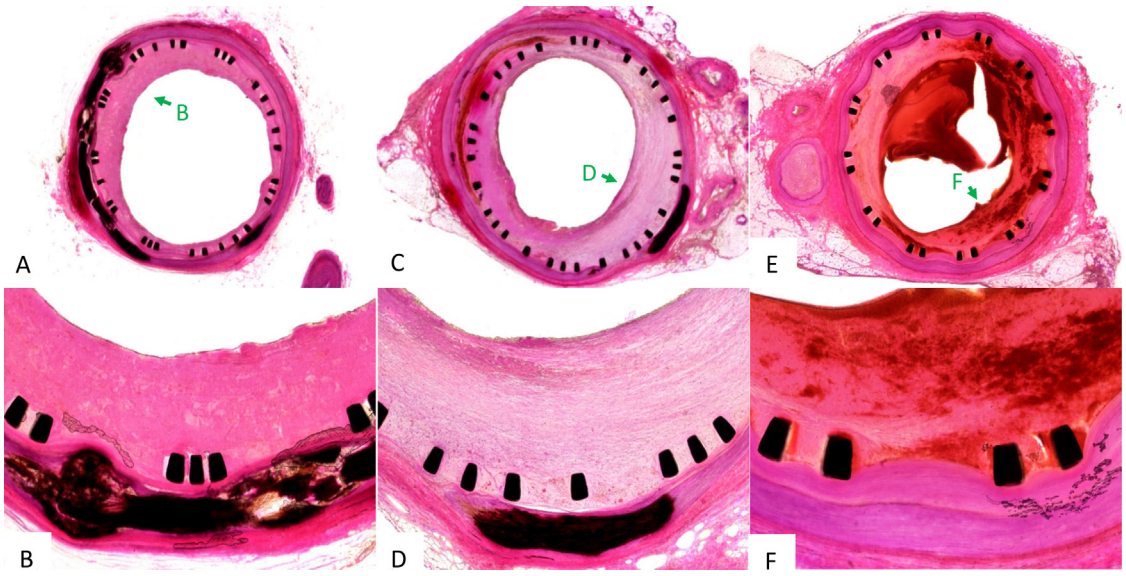

Fig. 2. Pathological findings (H&E stain). (A) Necrotic tissue site. Remarkable calcification of the medial wall (Mönckeberg'scalcinosis) was evident in the 5 O'clock and 7–11 O'clock directions are shown. (B) Low-power field indicated by arrow B; endothelialization was not observed at the luminal surface. Necrotic tissue with fibrin depositions was entirely observed. (C) Heterogeneous neointima site Necrotic tissues were observed in the 6–12 O'clock direction. In the other area, neointimal layer was found. (D) Low-power field indicated by arrow D. (E) Massive thrombus site Thrombi were extruding into the lumen and these thrombi were attached to the stent strut in the 1–6 O'clock direction. (F) Low-power field indicated by arrow F. Thrombus formation was observed on the surface of these nectotic portions. Stent strut was surrounded by thrombotic components and necrotic tissues and it was attached by a very small number of smooth muscle cells.

acute and late stent thrombosis was already reported [4,5]. Ishihara et al. reported angioscopy findings of a large red thrombus and an uncovered stent strut in a patient with stent thrombosis 6 months after placement of Zilver PTX [4]. An uncovered stent strut and heterogeneity of healing have been shown to cause late stent thrombosis in the coronary artery [6] and our pathologic findings also indicated thrombi directly attached to an uncovered stent strut and heterogeneity of healing. This suggests that these findings may be risk factors for late stent thrombosis in cases with SFA lesions.

Mechanism of late stent thrombosis after SFA stenting remains unclear and the optimal medical therapy has not been established. The efficacy of DESs for SFA is likely to increase, including additional indications for treatment of complex lesions, but further investigation is needed to examine the trade-off between the risk of stent thrombosis, which may directly cause serious limb events, and the efficacy of restenosis inhibition.

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Conflict of interest

None declared.

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