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Pathological Analyses of Very Long-term Sirolimus-Eluting Stent Implantation in Human Coronary Artery

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Text

A 73-year old man with prior myocardial infarction (hypertension; dyslipidemia; smoking; and no history of allergy, autoimmune disease, or vasculitis) underwent sirolimus-eluting stent (SES) implantaion for chest pain on exertion with left anterior descending coronary artery (LAD) (3.0 mm in diameter; 23 mm in length, 3.0 mm in diameter; 13 mm in length and 3.0 mm in diameter; 28 mm in length) and left circumflex coronary artery (LCX) (2.5 mm in diameter; 23 mm in length) (Figure 1A and 1B).

Follow-up angiography at 10 months after initial SES implantation demonstrated no evidence of angiographic restenosis (Figure 1C). At 21 months after stenting, coronary angiography showed the restenosis of just proximal lesion of LAD (Figure 1D) and subsequently coronary intervention for ostial LAD lesion was underwent by SES implantation (3.5 mm in diameter; 18mm in length and 3.5 mm in diameter; 13 mm in length) (Figure1E). After 53-month after stenting, coronary angiography was observed with no evidence of restenosis at any lesions (Figure 1F).

The first 10-month angiography was a protcol-driven follow-up study for the index LAD and LCX lesion. The second 21-month angiography and subsequent coronay intervention was due to cardiac symptoms with effort angina. The third 53-month angiography was due to preoperative study with endovascular therapy for abdominal aortic aneurysm (AAA). The patient continued taking aspirin at dose of 81mg/d; however, thienopyridine had been discontinued for over 1 year after stenting.

The patient underwent endovascular therapy for AAA at 57 months after stenting. Four days after the endovascular therapy (57 months after SES implantation), the patient had acute severe abdominal pain with rapid progression of acidemia. Computed tomography revealed intestinal gas reservoir with no evidence of intestinal perforation and strangulation ileus. Rapid progression of acidemia and abdominal distention suggested non-occlusive mesenteric ischemia and selective angiography for superior mesenteric artery showed multiple spastic mesenteric artery. Despite selective infusion of papaverine hydrochloride for the prevention of spasm, the patient died of multiple organ failure due to mesentric ischemia 5 days after endovascular therapy.

An autopsy demonstrated that the lesions of stented site at LAD and LCX (Figure 2A) was histopathologicaly similar images. In short, only mild neointimal formation with enough patent lumen was observed in all stented sites with no evidence of restenosis (Figure2B). In addition, complete coverage of endothelial cells in the surface of neointima was visible and smooth muscle cell group forming matured small spindle-shaped under endothelium was observed with abundant of collagen fiber (Figure 2C). However, many amount of multinucleated foreign body giant cells and infiltration of foamy macrophages were seen around the stent struts (Figure2D). In addition, fine calcified deposition in the cytoplasm of these cell groups was observed and partly those calcium deposits distributed in small mass with fusion. Furthermore, necrotic core formation with a lot of circumferential cholesterol clefts was evident around the struts (Figure 2E). Rather, more pronounced infiltration by lipid-laden foamy macrophages were also observed at the overlapped stented region. In spite of these findings, observations of neointimal rupture and stent thrombosis were not found in this very late period autopsy study.These findings were almost same in LCX stented lesion.

Discussion

Neoatheroscrelosis after DES implantation has been reported by several reports including autopsy study and there is emerging evidence suggesting that chronic inflammation induce late de novo neoatheroscrelosis inside both BMS and DES, which may be an important mechanism of the late phase luminal loss and thrombosis. Atherosclerosis of the neointima within the stent (ie. Neoatheroscrelosis) was defined as peri-strut foamy macrophage clusters with or without calcification, fibroatheromas, thin-cap fibroatheromas, and plaque ruptures but no communications with the underlying native atherosclerotic plaque. Sousa et al reported first histological examination 4-years after SES implantation with widely patent stented segment showing thin neointima with foamy macrophages localized around stent struts and necrotic core with numerous cholesterol clefts[1]. These findings were also confirmed in the clinical setting in recent report concerning BMS VLST. Yamaji et al showed that aspiration of the thrombus in 42 patients with very late ST after BMS thrombosis showed fragments of atherosclerotic plaques and suggested that disruption of in-stent neoatherosclerosis could play a role in VLST[2]. Inoue postulated the possible mechanism of late ST that neointimal formation occurs after metallic stent implants is subject to the same atherosclerotic forces that affect native stented vessels, and that macrophages mediated degradation of collagen eventually could result in necrotic core formation, and possible neointimal rupture followed by thrombosis.[3] These observations suggest that neoatherosclerosis around stent struts, which expressed metallproteinases that induce disruption of neoatherosclerotic neointima may be an important background for very late thrombotic events after both DES and BMS. Neoatherosclerosis in DES is more frequent and occurs earlier than in BMS, likely different from pathogenesis, indicating that presence of durable polymer may influence on progression of neoatherosclerosis.

To our knowledge , the current case report is the first one with very long term course after SES implantation over 4 years and 9 months. In this histopathological examination, although neointimal coverage with enough lumen was observed , accumulation of extracellular lipid and cholesterol crystal was shaping necrotizing core, in short neoatherosclerosis. A recent study conducted by Kimura et al confirmed that late adverse events such as VLST are the continuous hazard lasting at least up to 5 years after implantation of the first generation drug-eluting stents (SES)[4] . Although it has not yet been definitely clarified whether thrombosis in lesions with neoatheroscrelosis is causaly related to stent thrombosis, close clinical follow-up should be mandatory after SES implantation. In the future, biocompatible DES which is not induced inflammation to the arterial wall post stenting should be appropriately addressed by the future development of improved coronary stents.

Disclosures

Dr Kimura served as an advisory board member for Cordis Cardiology, Abbott Vascular, and Terumo.

The remaining authors report no conflicts of interest.

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Figure legends

Figure 1. Baseline angiographic and post procedure findings. A, Diffuse stenosis from proximal to mid LAD lesions and moderate stenosis at mid LCX lesion. B, LAD and LCX after SES (LAD; 3.0 mm in diameter; 23mm in length, 3.0 mm in diameter; 13mm in length and 3.0 mm in diameter; 28mm in length, LCX; 2.5 mm in diameter; 23mm in length) implantation (arrows). C, Follow up angiography performed at 10-months after implantation of SES in the LAD and LCX lesion. D, Restenosis at proximal LAD lesion at 1-year 9-months after SES implantation (arrow). E, LAD after SES (3.5mm in diameter; 13mm in length and 3.5mm in diameter; 18mm in length) implantation (arrow). F, Follow up angiography 4-year 5-months after implantation of initial SES with no restenosis.

SES=sirolimus-eluting stent, LAD=left anterior descending coronary artery and LCX=left circumflex coronary artery.

Figure 2. Morphological appearance of a 4-year SES implantation

Radiograph in A shows a well-expanded stent

B, Histological sections of proximal portion of the SES-implanted coronary artery segment reveals a thin neointimal formation with enough patent lumen in stented site with no evidence of either restenosis or thrombosis. In addition, complete coverage of endothelial cells in the surface of neointima was seen.

C, D, E; High power views of the same portion in B. Complete neointimal coverage only mature regenerating endothelial cells was observed. Smooth muscle cells had become atrophic and abundant proliferation of collagen fibers was evident. Note early necrotic core formation with pronounced foamy macrophages and circumferencial cholesterol clefts around the struts.

F, G; In the region of overlap, neointimal thickness and extent of necrotic core formation were similar to those in non-overlapping segments.

Figures

Figure 1.

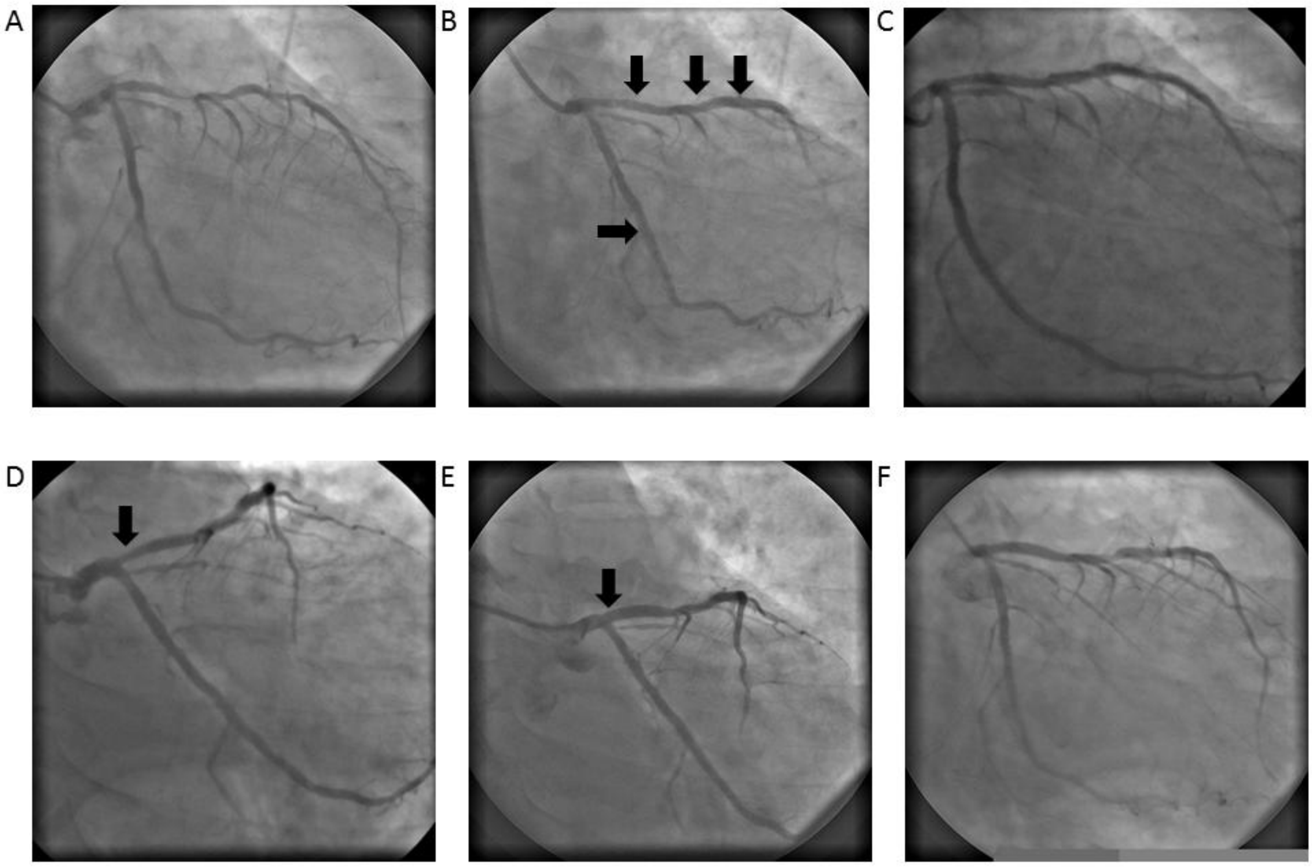

Figure 2.