Very Late In-stent Restenosis due to Neoatherosclerosis in the Second-generation Everolimus-eluting Stent

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Implantation of metallic stents in the atherosclerotic lesions resolved the lumen stenosis or obstruction of a coronary artery and myocardial ischemia. The phenomenon of transformation of proliferating neointima into atheromatous intima is now recognized as neoatherosclerosis that can lead to stent failure including restenosis or thrombosis at the late phase after stent implantation. Although neoatherosclerosis in the second-generation drug-eluting stent (DES) had been found by the proper signal patterns of optical coherence tomography, there is no certification by direct visualization using angioscopy. An 85-year-old woman with dyslipidemia and hypertension, chronic kidney disease admitted to our hospital suffered from recurrent angina pectoris of effort. She had a history of successful stent implantation for stable angina pectoris two years ago. Cobalt chromium everolimus-eluting stent was implanted into the mid left anterior descending artery. Coronary angiography showed focal restenosis in the stent segment. Coronary angioscopy identified intense yellow plaque at the same lesion. In this case, late stent failure presented as restenosis in the second-generation EES was caused by neoatherosclerosis. To the best of our knowledge, this is the first report of neoatherosclerosis in the second-generation everolimus eluting stent validated by angioscopy.

Key words: neoatherosclerosis, restenosis, drug-eluting stent

Introduction

The principle pathogenesis of atherosclerosis is inflammation caused by infiltration of foamy macrophages through impaired endothelium into the vessel wall. Metallic coronary stents are deployed into the atherosclerotic lesions in order to preserve wide coronary lumen and dissolve myocardial ischemia. Transformation of proliferating neointima derived from medial smooth muscle cells into the atheromatous lesion is now called neoatherosclerosis which can lead to stent restenosis or thrombosis at the late phase. In the DES (drug-eluting stent) era, the second-generation DESs have launched and they have new technologies, such as biocompatible (or biodegradable) polymer to inhibit the inflammatory response for reducing endothelial damage compared to the first-generation DES. Although the second-generation DESs of everolimus-, zotarolimus-, and biolimus-eluting stents actually reduce the incidence of very late stent thrombosis according to large-scale clinical trials, neoatherosclerosis plays an important role of late (or very late) DES failure. However, there are few reports showing neoatherosclerosis in the second-generation DESs.

A Case Report

An 85-year-old woman with dyslipidemia and hypertension, chronic kidney disease admitted to our hospital complaining of chest pain on exertion. Her serum low-density lipoprotein cholesterol was 103mg/dl and eGFR level was 29ml/min/1.73m², respectively. She took statin and angiotensin II receptor blocker. She had received stent
implantation for stable angina pectoris and the culprit lesion of the mid left anterior descending artery was treated by cobalt chromium everolimus-eluting stents (EESs) 5 and 2 years before the current symptom (XIENCE V® 2.5/15mm and XIENCE PRIME® 2.25/12mm, Abbott, Santa Clara, California, U.S.A., respectively). Focal in-stent restenosis in the distal stent was found by coronary angiogram (Fig. 1). Coronary angioscopy (CAS; FULLVIEW NEO®, FiberTech, Tokyo, Japan) showed complete stent coverage by an intense yellow plaque at the restenosis lesion (Fig. 2). Then, we treated the lesion with non-slip element balloon (Lacrosse NSE ALPHA® 2.0/13mm, Goodman, California, U.S.A.) and adjunctive angioplasty using drug coated balloon (SeQuent® Please 2.5/30mm, Goodman, California, U.S.A.) to avoid stent-in-stent that may lead to lumen narrowing due to two layers of struts. Her chest pain completely disappeared and her clinical course has been good until now.

**Discussion**

Neoatherosclerosis emerges as an important mechanism of stent-related vascular failure. The phenomenon of neoatherosclerosis in the bare-metal stent (BMS) and the first-generation DES is well known. It is understood that the mechanisms of neoatherosclerosis of BMS is chronic inflammation as a foreign body reaction to metallic stent struts and that of the first-generation DES is impaired barrier function of endothelium by polymer induced hypersensitive reaction and thick struts which interfere migration of endothelial cells. Anyway, activated macrophages can form progressive atherosclerotic lesions which cause lumen stenosis and thrombosis following their disruption.

The concept of second-generation DESs have improved stent

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**Fig.1** The findings of coronary angiography
A. The proximal and distal stents (XIENCE V® 2.5/15mm and XIENCE PRIME® 2.25/12mm, Abbott, Illinois, U.S.A.) were successfully deployed 2 and 5 years ago respectively. The two stents overlapped, and there was no stent gap. The two stents overlapped, and there was no stent gap. The two stents overlapped, and there was no stent gap.
B. Focal in-stent restenosis in the distal stent was found.

**Fig.2** The findings of angioscopy in the stents
2: Stent struts were invisible, instead intense yellow plaque were found at the in-stent restenosis lesion.
3: Thin neointima around struts was seen at the overlapped stent segment.
4: White neointima moderately covered struts at the proxymal stent.
polymer to inhibit inflammation and thin strut to promote re-endothelialization subsequently protect against the occurrence of neoatherosclerosis comparing with the first-generation DES.\textsuperscript{13)\textsuperscript{15}) Although angiographic late loss or restenosis reduced in the second-generation DES,\textsuperscript{16)\textsuperscript{16) intracoronary imaging such as OCT and CAS disclosed the participation of neoatherosclerosis associated with catastrophic stent thrombosis.\textsuperscript{17}) A basic study showed neoatherosclerosis occurs rapidly in DES might be due to the eluted drug prevents endothelial cell proliferation and viability, migration which allows infiltration of lipid-laden foamy macrophage into the vessel accelerating atherosclerotic change.\textsuperscript{18–21) According to human autopsy, neoatherosclerosis can arise in the second-generation DES. The duration after stenting is 270 days of EES, and that is longer than the first generation DES (sirolimus- and paclitaxel-eluting stents of 120 and 70 days, respectively).\textsuperscript{22) Although angiography identified neatherosclerosis 2 years after EES implantation because of recurrent angina, exact time of onset is unknown.

There is speculation why the neoatherosclerosis appears only in the distal stent of the same individual. The geometric effect may drive neoatherosclerosis as follows. Stent implanted in the bifurcated lesion may cause endothelial damage according to in vitro study.\textsuperscript{12)\textsuperscript{12) The distal stent was located in bifurcation of left anterior descending artery and large septal branch. Moreover, the size of the distal stent was smaller than the proximal stent. Smaller stent is prone to suffer from neoatherosclerosis than larger stent should be addressed in another study.\textsuperscript{23)\textsuperscript{23) To avoid stent-in-stent that may lead to lumen narrowing, we selected the treatment with DCB. There has not been established treatment for the neoatherosclerosis, so further study is needed to treat the neoatherosclerosis.

Regarding patients' background as systemic factors of neoatherosclerosis, conventional coronary risk factors, statin, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker usage were associated with the presence of neoatherosclerosis.\textsuperscript{24)\textsuperscript{24) Another OCT study showed that chronic kidney disease and > 70mg/dl of low-density lipoprotein cholesterol were independent predictors of neoatherosclerosis.\textsuperscript{19)\textsuperscript{19) In clinical follow-up at 9 years revealed neoatherosclerosis in the stent was parallel to progression of native coronary atherosclerosis, and the above findings may suggest two phenomena have similar pathophysiological mechanisms.\textsuperscript{25)\textsuperscript{25) Statin and angiotensin II receptor blocker were administered in this case. However, her low-density lipoprotein cholesterol was > 70mg/dl and chronic kidney disease might contribute to the development of neoatherosclerosis.

For the first time, neoatherosclerosis in the second-generation of DES was confirmed by CAS. CAS-derived yellow plaque formation at one year after DES implantation is one of the predictive factors of very late stent failure.\textsuperscript{26)\textsuperscript{26) The part of restenosis and late loss of DES is related with neoatherosclerosis as this case, and angioscopic identification of neoatherosclerosis may have clinical significance to predict cardiovascular events caused by stent failure.

Conflict of Interest

The authors have declared that there is no conflict of interest.

References

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