Acute Coronary Syndrome due to In-Stent Neoatherosclerosis 14 years after Bare-Metal Stent Implantation: Findings of Intravascular Imaging Modalities

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In recent years, neoatherosclerosis and very late stent thrombosis in the extended follow-up period after bare-metal stent (BMS) implantation have been recognized. We experienced a case of in-stent restenosis (ISR) detected in a BMS implanted 14 years prior. An 86-year-old man who had a history of BMS implantation because of angina pectoris in the proximal left anterior descending coronary artery (LAD) 14 years previously was referred to our hospital because of worsening chest pain on exertion for 1 month. A coronary angiogram revealed severe stenosis in the previously implanted BMS. Seven days later, percutaneous coronary intervention (PCI) for the LAD lesion was performed. Prior to intervention, intravascular ultrasound (IVUS), optical coherence tomography (OCT), and intracoronary angioscopy were performed, which showed diffuse heterogeneous plaque throughout the stent, various types of imaging in plaques including thrombi and fibrous plaque, and yellow plaques with respective imaging devices. We deployed two drug-eluting stents to cover all the plaque using a filter device in order to protect from distal embolism, and verified the good result by final angiography. From observations obtained with intracoronary imaging modalities in this case and knowledge that some past studies revealed, this case was considered as an acute coronary syndrome since neoatherosclerosis rupture in the BMS lesion happened in the extended follow-up period. Therefore we emphasize that physicians have to follow patients who have undergone BMS implantation carefully, even if ISR is not detected in the post early phase.

Key words: bare-metal stent, in-stent restenosis, neoatherosclerosis, intravascular imaging modalities, acute coronary syndrome

Background

Percutaneous coronary interventions (PCIs) with stenting are widely performed in order to treat symptomatic coronary artery disease; and bare-metal stent (BMS) implantation is one of the standard therapies in interventional cardiology.

Although it is well known that late and very late (VL) stent thrombosis can be seen after the drug-eluting stent (DES) implantation; some studies revealed the late and VL thrombosis after the BMS implantation also increased mortality, and the luminal narrowing presenting with restenosis was significantly associated with clinical events such as myocardial infarction during extended follow-up periods, which might be due to plaque rupture within the neointima.

Several studies have tried to elucidate qualitative features inside the BMS over an extended period after their implantation, using various imaging modalities.

We here report a case of in-stent restenosis (ISR) detected in an extended period after BMS implantation, and present some intracoronary images—intravascular ultrasound (IVUS), intracoronary optical coherence tomography (OCT), and intracoronary angioscopic images—from a patient suffering from acute coronary syndrome (ACS).
Case

An 86-year-old man was referred to our hospital because of worsening chest pain on exertion for 1 month. His coronary risk factors were hypertension, dyslipidemia, chronic kidney disease, and a past history of smoking. He also had a history of angina pectoris and had undergone PCI for the proximal left anterior descending coronary artery (LAD) and received a BMS implantation at another hospital 14 years previously. After that, his blood pressure control and medication adherence had been good.

Electrocardiogram on admission revealed biphasic T waves in the anterior chest leads as compared with that of 28 months ago (Fig. 1). Blood tests revealed elevated levels of blood urea nitrogen (27.4 mg/dL), serum creatinine concentration (1.3 mg/dL), and Troponin I (0.123 ng/mL). His LDL cholesterol level was 110 mg/dL on admission.

He underwent coronary angiography, showing a diffuse and moderate- to-severe stenosis in the LAD, which was the culprit lesion within the BMS implanted 14 years before (Fig. 2).

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Fig. 1  Comparison of electrocardiograms (ECGs) on admission and 28 years previously. ECG on admission revealed biphasic T waves in the anterior leads (V3–V5) as compared with 28 months ago.

Fig. 2  Coronary angiogram of right coronary artery (upper) and left coronary artery (lower) before intervention. They show a severe in-stent restenosis of the BMS implanted before in the left anterior descending artery (arrowhead). RAO: right anterior oblique, LAO: left anterior oblique, AP: anterior-posterior
Seven days later, PCI for the proximal LAD was performed. Prior to intervention, IVUS with a 2.7 French (Fr) IVUS catheter (Atlantis Pro 2; Boston Scientific, Natick, Massachusetts) and OCT with a 0.014-inch wire-type imaging catheter (Image Wire; Light Lab imaging, Westford, Massachusetts) in association with a 3 Fr over-the-wire type occlusion balloon catheter (Helios, Goodman, Nagoya, Japan) and intracoronary angioscopy (Vecmova, Clinical Supply, Gifu, Japan) were performed.

IVUS showed diffuse heterogeneous plaque throughout the BMS, which contained both high and low echoic plaques (Fig. 3A). OCT showed various types of imaging in plaques—lipid-laden intima, red thrombi, thin-cap fibroatheroma (TCFA), plaque rupture, and high intensity fibrous layered pattern plaques (Fig. 3B). Angioscopic imaging clarified the yellow plaques (color grade 3) and thrombosis in this in-stent restenosis lesion (Fig. 4).

After these imaging examinations, a filter device (Filtrap, NI-PRO, Osaka, Japan) for preventing distal embolism was inserted in the distal LAD following predilation with a 2.0 mm balloon. We deployed a 3.0×28 mm (distally) and a 3.0×18 mm (proximally) Nobori stent (Terumo, Tokyo, Japan), slightly overlapping each other to cover all the plaques and post-dilated with a 3.5 mm noncompliant balloon. Postprocedural OCT and angioscopy imaging showed protrusions from the stent strut (Fig. 5A, B). A filter device was removed, and then the final angiography was performed, which revealed a good result without slow flow (Fig. 5C).

After the procedure, we tried to evaluate the retrieved materials.
in the filter device histopathologically; however this was impossible because the pieces of material were too small to be fixed and stained.

**Discussion**

In this case, we performed PCI on a patient with unstable angina. This coronary event happened in the extended late-phase after BMS implantation. Characteristics of plaque in the ISR obtained with intravascular imaging modalities included (1) diffuse heterogeneous echo with IVUS; (2) red thrombi, TCFA, plaque rupture, fibrous plaque, and protrusion after stent deployment with OCT; and (3) yellow plaques with angioscopy. These imaging findings were quite different from those of intimal hyperplasia that could be observed in an ISR lesion during the early period after BMS deployment.

In 2002, a serial angiographic evaluation of the BMS segments revealed a triphasic luminal response characterized by an early narrowing phase during the course of 6 months, a medium-term regression phase from 6 months to 3 years, and a late narrowing phase beyond 4 years8). Previously, the early lumen narrowing and medium-term regression were interpreted as neointimal thickening by cell proliferation and thinning by neointimal remodeling, respectively9).

Meanwhile, over 4 years, angioscopic observations for BMS5) demonstrated that vulnerable atherosclerotic plaque containing thrombus usually healed as white neointima within 1 year of BMS implantation, however white neointima replaced into lipid-laden yellow plaque, in other words, atherosclerotic transformation might occur beyond 4 years. Similarly, Habara, et al.7) compared the morphological characteristics of VL ISR (>5 years) to those of early (E) ISR (<1 year) with OCT. Restenotic tissue mainly observed in the VL-ISR was heterogeneous, while that in the E-ISR was homogeneous.

Although not only BMS but also DES implantation can lead to later in-stent neoatherosclerosis, neoatherosclerosis has been found more frequently in DES and occurs earlier than in BMS. The median stent duration with neoatherosclerosis was 420 days in DES and 2,160 days in BMS80).

In this case, a clinical history of worsening angina, ECG changes, and morphological in-stent plaque features allowed us to diagnose this case as ACS following in-stent neoatherosclerosis. A retrospective study of 4,503 consecutive patients treated with BMS11) revealed that the cumulative incidences of BMS thrombosis and of myocardial infarction caused by BMS restenosis at 10 years were 2.0% and 2.1%, respectively. As a result, clinical events like these significantly decreased survival during long-term follow-up. Although whether or not use of BMS instead of DES is safer has been debated in recent years, these data may explain BMS will not resolve this safety issue. Therefore, clinical decision-making should be considered on the basis of lesion- and patient-specific variables.

Why do these vascular responses occur in stents over the years? Inoue et al.12) performed histopathological and immunohistochemical studies from autopsied patients after Palmaz-Schatz coronary stenting. In stented lesions, chronic inflammatory cells including T lymphocytes and macrophages around the stent strut were observed and they speculated that these chronic inflammatory responses to the strut itself might cause accelerated indolent atherosclerotic changes and plaque vulnerability. Although we tried to collect in the filter device some plaque de-
bris drifting distally in the LAD, the specimen was not adequate for evaluation.

We considered that the morphological characteristics of the plaques in the ISR lesion observed in this case were consistent with those of previous studies and reports that mentioned VL phase neoatherosclerosis after BMS implantation. Intravascular imaging modalities revealed characteristics of in-stent plaques precisely, which was useful for diagnosing ACS even in ISR cases. Previously, we experienced a similar case comparing the IVUS and OCT images of ruptured plaque in a BMS implanted 8 years before\(^{13}\). In this presenting case, the strength of angioscopy was clearly shown by the direct visualization of yellow plaque in the BMS. Although the quality of the angioscopic pictures might not be adequate, we think that at least yellow plaque can be easily detected. It was reported that yellow color intensity of plaque determined by angioscopy might be a marker of plaque vulnerability\(^{14}\) and patients with two or more yellow plaques had a 2.2-fold higher incidence of an ACS event than those with no or a single yellow plaque\(^{15}\). Therefore a direct observation of plaque color has a possibility to estimate the patient’s prognosis. Each intravascular imaging modality has its own advantage and disadvantage. Thus, the multi-modality imaging to assess neoatherosclerosis provides synthetic several information which includes some amount of plaque, appearance of vascular remodeling by IVUS, quantitative assessments of thickness of TCFA by OCT, plaque color by angioscopy, and so on. From these observations, we may be able to consider, for instance, a necessity of distal protection device on PCI, the stent type (BMS or DES), and the period of dual antiplatelet therapy.

Because when we treated this patient, drug-coating balloon (DCB) was off-label for coronary artery disease in Japan, we selected DES to cover the plaque. The question as what type of device we should use, BMS or DES or DCB, to treat neoatherosclerosis has not been clearly elucidated. Future studies about treatment strategy for in-stent neoatherosclerosis will be needed for better patient outcome.

In conclusion, when clinicians encounter patients with VL phase ISR in BMS, who undergo PCI, careful strategy planning using intracoronary imaging modalities such as IVUS, OCT, and intracoronary angioscopy could be quite useful for discriminating ACS.

The authors declare that there are no conflicts of interest regarding the publication of this article. The authors obtained written informed consent from the patient regarding the therapy and publication of this case.

Disclosure

None of the authors have conflicts of interest to disclose.

References

4) Chen MS, John JM, Chew DP, et al: Bare metal stent restenosis is not a benign clinical entity. Am Heart J 2006; 151: 1260–1264