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Editorial

Pathogenesis of late in-stent thrombosis after treatment with drug-eluting stents

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Advantages of drug-eluting stents (DES) for coronary artery diseases are widely accepted because of their significant reduction of restenosis and of target lesion revascularization compared to bare-metal stents (BMS) [1]. However, in-stent thrombosis (IST), a rare but unpredictable and tragic event, has been reported after DES implantation. IST often leads to a catastrophic outcome and overall prognosis from IST is poor: 10–30% of patients with IST will die [2]. No difference between DES and BMS is seen for the incidence of early IST (<30 days) or late IST (30 days to 1 year); however, significantly higher rates of very late IST (>1 year) are seen with DES [3]. Data from several registries have indicated that the risk of very late IST persists at an annual rate of 0.36–0.6% per year to at least 5 years after DES implantation [4,5]. The current on-label indications for DES are limited to simple lesions and off-label indications represent a higher risk population with complex morphology. Thus, the risk of IST is higher for the patients treated with DES for off-label indications compared with on-label indications.

The pathogenesis of IST is probably multi-factorial and numerous factors have been implicated in increasing the risk of an IST event [6]. Precipitants of IST include patient factors, such as acute coronary syndrome lesion, diabetes mellitus, renal dysfunction, low left ventricular output, and early cessation of dual anti-platelet therapy (DAPT). Lesion characteristics, such as severe calcified lesion, bifurcation lesion, and chronic total occlusion may contribute the pathogenesis of IST. Procedural factors, such as incomplete stent apposition, stent deployment over the lipid rich necrotic core, multiple stent implantation, long target lesion, and stent undersizing have been also shown to be important in the development of IST.

Histological observation indicates that foreign body reaction against DES is clearly different from the corresponding lesions occurring after BMS implantation. In our experience of autopsy cases, first-generation DES suppresses the early immune response of the treated artery compared to BMS [7]. Furthermore, delayed arterial healing processes, such as incomplete endothelial cell covering, lack of intimal thickening, and persistent fibrin deposition have been identified after DES implantation (Fig. 1). These phenomena may play an important role in IST development. In preclinical experiments at 28 days after treatment with DES, the delayed arterial healing compared to BMS was overlooked. Rapid endothelial covering after DES deployment in animal models contrasts with the delayed healing processes after DES implantation in human coronary arteries. Furthermore, the influence of advanced atherosclerotic lesion on the healing processes after DES implantation should be taken into account. Plaque components, such as lipids, inflammatory cells, necrotic debris, extracellular matrix, and thrombus, may influence drug release, retention, absorption, and distribution. In fact, DES implantation after acute myocardial infarction results in apparently delayed vascular healing, compared to DES treatment in patients with stable angina.

One of our autopsy cases has shown the complete stent strut coverage with re-endothelialization after 6 months of sirolimus-eluting stent (SES) implantation (Fig. 2). In contrast, a previously reported case at 15 months after SES deployment has shown minimal coverage of the struts by fibrin with rare endothelial cells. In addition, incomplete strut coverage is demonstrated by coronary angioscopy persisting as late as 24 months after SES implantation [8]. This discrepancy indicates that the response to DES deployment in human coronary artery is heterogeneous. There is no doubt that DES resulted in delayed arterial healing compared to BMS, whereas it appears difficult to evaluate the chronologic evolution of changes after DES implantation. The local responses to DES deployment may be affected by a variety of factors, such as stent length, apposition of struts, anatomical location, histological features of the underneath plaque, blood flow speed and turbulence, and immune reactivity of each individual. Therefore, the optimal duration of DAPT after DES implantation remains controversial. Whereas we need to keep it in mind that discontinuation of DAPT at less than 1 year after stent implantation is one of the most significant independent predictors of IST along with poor compliance, surgery, bleeding complications, and allergy to clopidogrel [9].

An analysis of the lesions in 32 autopsy cases shows a mean $55.8 \pm 26.5\%$ of struts with re-endothelialization after a mean DES implantation of 223 ± 253 days; in contrast to DES, 36 BMS lesions showed $89.9 \pm 20.9\%$ strut re-endothelialization at 299 ± 360 days [6]. Studies using optical coherency tomography (OCT) have shown that the rate of uncovered stent struts is lower in the second generation of zotarolimus-eluting stent, when compared with SES [10]. A comparative study of stents with biodegradable polymer versus stents with durable polymer using OCT images indicates significantly higher rate of stent coverage with biodegradable polymer stent [11]. This result suggests that not only eluting drug itself, but also polymer may participate in the endothelial cell coverage over stent struts.

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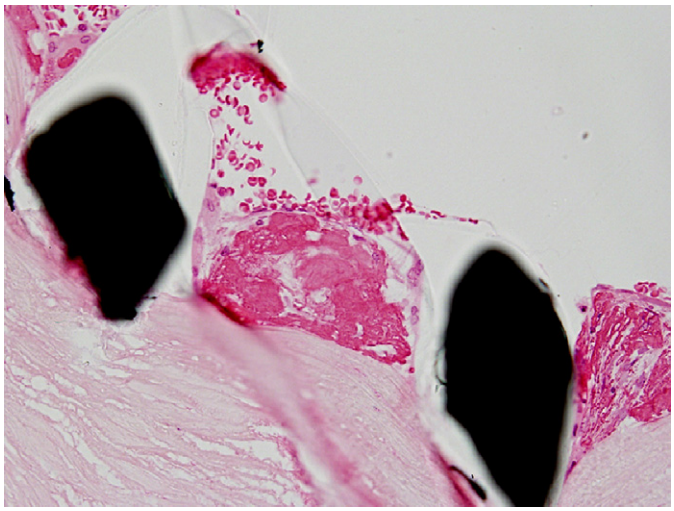

Fig. 1. Local reactions against sirolimus-eluting stent at 2 months after implantation. Stent struts apparently exposed to the blood flow and fibrin deposits on the luminal surface between the stent struts. Few inflammatory cells except several foreign body giant cells infiltrate near stent struts. No endothelial cell coverage over stent struts is apparent (hematoxylin–eosin, 200×).

The ability to induce hypersensitivity reactions through the presence of a polymer deserves additional consideration. Permanent polymer facilitates drug release and remains after complete drug elution. Histopathological studies have shown that the polymers induce localized vascular inflammation, hypereosinophilia, thrombogenic reactions, and apoptosis of smooth muscle cells [12]. The Cypher SES (Cordis, Bridgewater, NJ, USA) is coated in a durable polymer, which has been shown to induce hypersensitivity in human. The Taxus paclitaxel-eluting stent (Boston Scientific, Natick, MA, USA) also has a durable polymer that has been shown to be associated with positive remodeling. These device concerns need to be improved for the development of next generation DES. The possibility of IST according to a permanent polymer led to the development of second-generation DESs with biocompatible and biodegradable polymers. These new polymers have been shown to have a greater degree of re-endothelialization compared to first-generation DESs.

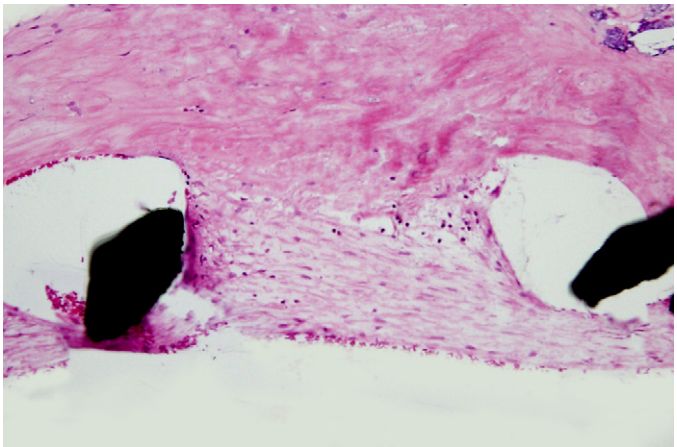

Fig. 2. Complete stent strut coverage with re-endothelialization after 6 months of sirolimus-eluting stent implantation. Minimal but sufficient intimal thickening completely covers the stent struts. A few lymphocytes infiltrate around stent struts without destructive reaction to the vessel wall (hematoxylin–eosin, 100×).

Sonoda et al. [13] have demonstrated intravascular ultrasound (IVUS) images and histopathology of a very late IST case. They have observed late-acquired stent malapposition with positive remodeling at the level of SES implantation by IVUS imaging. Histology indicates fibrin thrombi formation at the level of malapposed stent struts. Inflammatory cell infiltration is prominent around stent struts and arterial wall has shown the destructive reaction. They have shown that multinucleated giant cells, B-lymphocytes, plasma cells, and eosinophils were identified around the stent struts. These pathological alterations are similar to the previously reported hypersensitivity induced IST cases. In spite of the massive inflammatory reaction against DES struts, the lack of clinical evidence of hypersensitivity vasculitis, such as hypereosinophilia, high serum IgE value, and elevated high sensitive C-reactive protein level is noteworthy. Furthermore, we need to learn from this patient that marked positive remodeling and stent malapposition by vascular imaging may represent a massive inflammatory reaction with vessel wall destruction: lesion with extremely high thrombogenic potential.

Observation of alterations occurring after DES implantation by imaging techniques, such as IVUS, OCT, and coronary angioscopy, may furnish important information on the conditions of DES-treated vessels. In order to achieve more accurate diagnosis in vivo, comparative data between vascular imaging and histopathology findings is required to improve interpretation of imaging. Furthermore, our understanding of IST pathogenesis should be facilitated by the knowledge of pathological alterations present in coronary arteries treated with DES devices. From this viewpoint, accumulation of information concerning histopathology at the level of the DES implanted artery is imperative.

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