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Thrombosis in Left Ventricle of a Dog Remains with Anticoagulant Therapy

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SUMMARY

Thromboembolism commonly occurs in cats with heart disorders, but is rare in the dogs. We describe a dog with suspected thromboembolism, with the thrombus in the peripheral artery and left ventricle. A border collie suddenly presented with astasia on hind legs, and a peripheral arterial thrombus embolism was suspected. We started anticoagulant therapy with the administration of heparin, but a mass (20.6 × 18.5 mm) that was projected inside the apex of the left ventricle was found in echocardiography. The prescription was changed to dalteparin sodium, ozagrel hydrochloride, and cephalexin. Seven days after changing the treatment, the mass was reduced to 13.1 × 4.9 mm. We suggest that replacing thrombolysis with antithrombotic therapy suppressed the thrombus formation.

—— Key words : low-molecular weight heparin, myocardial infarction, ozagrel hydrochloride, thrombosis.

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CASE REPORT

A case of active peri-stent inflammation after sirolimus-eluting stent implantation

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Abstract We report an autopsy case of a coronary aneurysm with massive adventitial inflammation post-percutaneous coronary intervention with sirolimus-eluting stent (SES) insertion in the left circumflex (LCX) coronary artery for ischemic heart disease 3 years prior to death. The internal elastic membrane was disrupted opposite the site of the eccentric LCX plaque due to injury during stenting, and the adventitia showed massive inflammatory cell infiltration, mainly consisting of eosinophils. The LCX showed aneurysmal dilatation with inflammatory cell infiltration. Inappropriate SES implantation attracted chronic inflammation. Chronic inflammation can lead to the development of coronary artery aneurysms.

Keywords Drug-eluting stent · Inflammation · Pathology · Percutaneous coronary intervention

Introduction

Use of the first-generation drug-eluting stent (DES) has resulted in a considerable decrease in the restenosis rate following coronary angioplasty compared to bare metal stents (BMS), although with concerns about very late stent thrombosis (VLST), localized chronic inflammatory reactions in the coronary arteries and late catch-up due to delayed healing over the long term [1–4]. A recent report demonstrated that visualization of peri-stent contrast staining (PSS) on angiogram might be associated with VLST [5]. On the other hand, it has not been clarified whether delayed healing is associated with structural abnormalities in the late phase.

We experienced a case in which the index percutaneous coronary intervention (PCI) procedure [sirolimus-eluting stent (SES) implantation] caused chronic inflammation of peri-stent segment.

Case report

An 83-year-old Japanese woman with a history of hypertension, chronic atrial fibrillation and ischemic stroke had a history of aortocoronary bypass surgery 12 years prior to her death due to critical limb ischemia related to sepsis. She had undergone PCI with SES implantation in the left circumflex coronary artery (LCX) for cardiac ischemia 3 years prior to her death. Final IVUS showed no stenotic lesion, but incomplete expansion of the SES. Since the patient was receiving three anti-thrombotic drugs (aspirin 162 mg, clopidogrel 75 mg and warfarin 1.5 mg), there were no ischemic events since the last PCI. Postmortem pathological investigation demonstrated no acute ischemic changes in the myocardium, although there was intense lymphocytic and eosinophilic infiltration in the coronary artery around the area of the SES (2.5 × 18 mm), especially in the adventitia. However, systemic blood examination did not reflect them throughout the process. The maximum counts of each corpus were 968 μ/l in lymphocyte, 32 μ/l in eosinophil and 752 μ/l in monocyte (all did not exceed normal range). Disruptions of the elastic membrane (open arrows) opposite the site of the calcified

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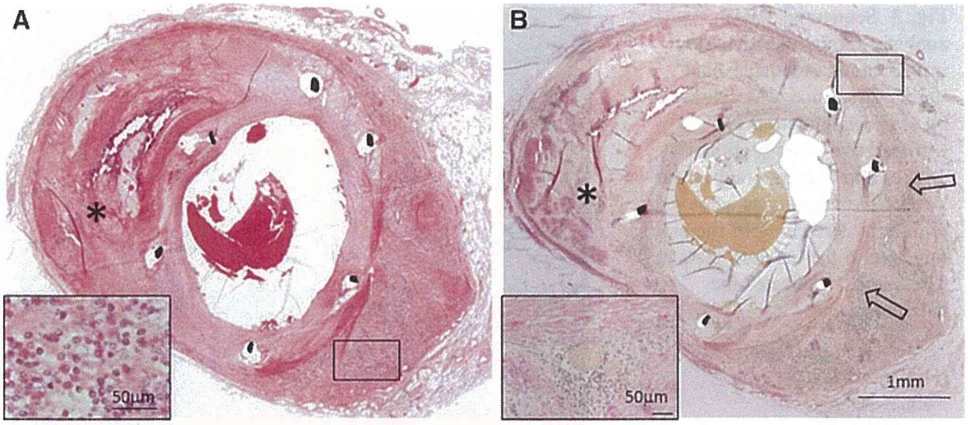

Fig. 1 Hematoxylin–eosin staining (**a**), and elastic van Gieson staining (**b**) of the *left* circumflex coronary artery showing the sirolimus-eluting stent (SES). Intense lymphocytic and eosinophilic infiltration (**a** *inset*) was present around the SES (2.5 × 18 mm), together with disruption of the elastic membrane (**b** *inset*, *open arrows*) opposite to the site of the calcified plaque (*asterisk*)

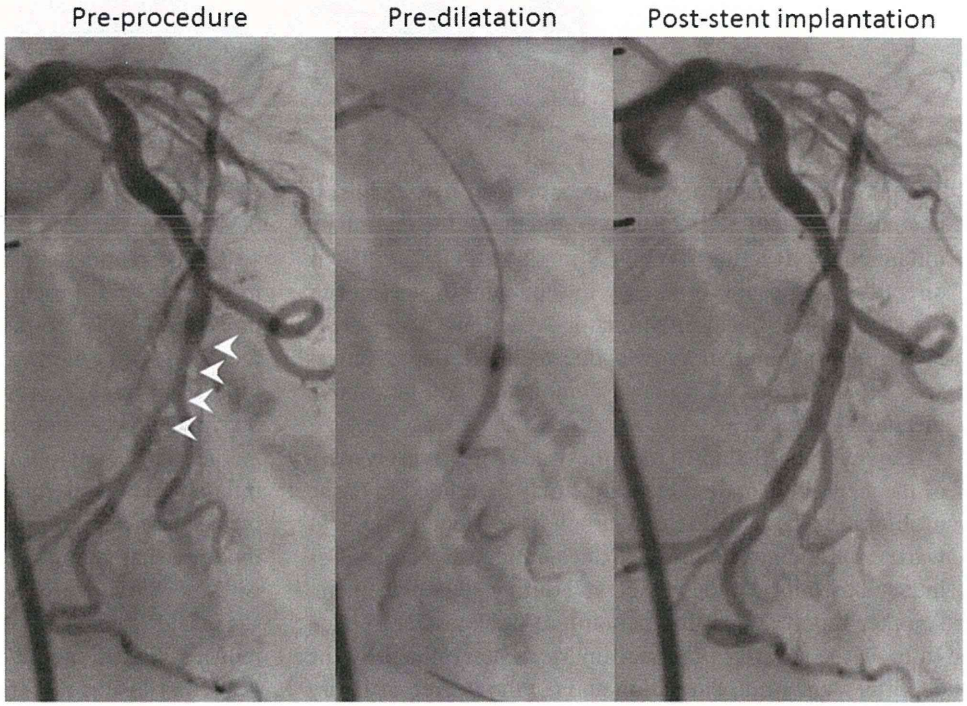

Fig. 2 Angiogram during the index procedure. Balloon indentation was solved by repetitive dilatation with a non-compliant balloon (2.75 × 10 mm) before and after stent implantation

plaque (asterisk) were also observed [Fig. 1a: hematoxylin-eosin staining (inset indicates eosinophils), and Fig. 1b: elastic van Gieson stain]. There was thinning of the medial layer consisting of smooth muscle cells, due to vascular injury following stent deployment. The crescentic space in the mid-LCX corresponded to the area of the reconstruction, which was created by high-pressure dilatation with a 2.75 × 10 mm non-compliant balloon inflated to a pressure of 22 atmospheres (Figs. 2, 3).

Discussion

Angiographic aneurysmal/localized lumen dilatations have been reported in the BMS era [6–8], although the exact underlying pathological mechanism responsible for positive remodeling (an increase in vessel dimensions) remains unknown. The pathology in the present case may have resulted from persistent inflammatory reactions, including a hypersensitivity reaction, following SES implantation.

The mechanism of development of a space between the stent strut and vessel wall is either positive remodeling without an equal amount of underlying residual atheromatous plaque formation or intimal hyperplasia, so that the vessel pulls away from the stent or plaque, or thrombus dissolution, resulting in formation of a gap between the stent and the vessel wall (primarily in patients presenting with acute coronary syndromes) [6–12]. After DES insertion, late incomplete stent apposition appears to be more frequent compared with that after BMS implantation [13]. Especially, coronary aneurysm formation was a rare

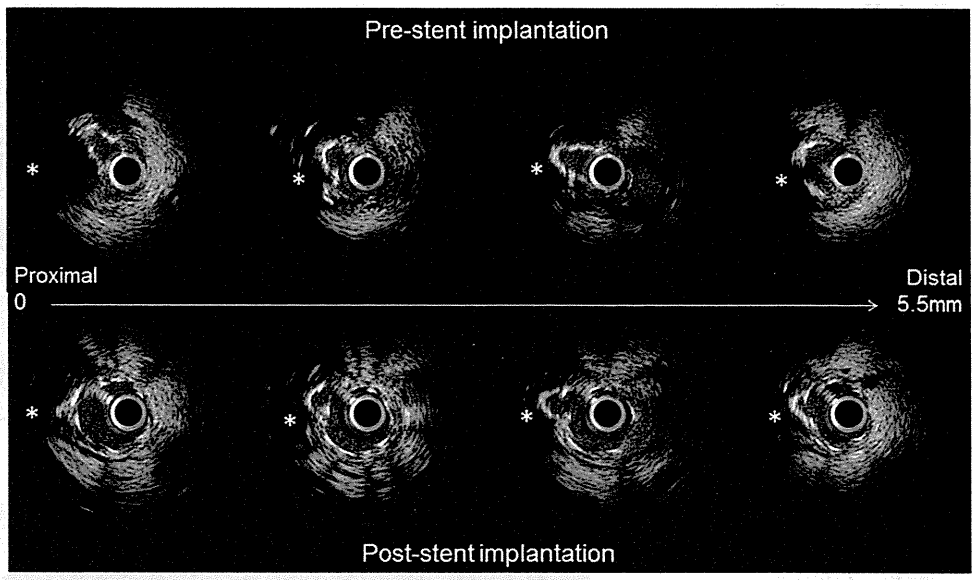

Fig. 3 Sequential IVUS analysis before and after stent implantation. Adequate final lumen dimension was achieved by stent implantation. Comparative cross-sectional images showed that gain in the size of the lumen was achieved mainly by stretching of the side opposite to the calcium plaque. The *asterisk* indicates the calcium plaque

complication in the BMS era. Several possible mechanisms have been considered for development of the sustained inflammatory reaction after DES implantation. The first is direct drug exposure, or allergy to the metal or polymer of the strut causing local inflammatory reactions. The next is incomplete neointimal growth due to the strong suppressive effect of the DES, or a combination of the above mechanisms.

Previous IVUS studies hypothesized that aggressiveness of the stent implantation technique may be related to tissue proliferation both inside and around the stent [14]. Schwartz et al. demonstrated that thick intimal hyperplasia is induced by injury to the vessel wall during stent placement. Another report stated that neointimal thickness correlated with (1) the severity of vessel injury as determined by the depth of stent strut penetration and (2) the degree of injury adjacent to the stent wire sites [15]. In our case as well, the stent implantation was aggressively performed, such that lack of neointima, which is usually composed of smooth muscle cells, and poor endothelialization were seen even 3 years after stent implantation. Neointimal proliferation usually stops within 6 months after BMS implantation. DES, however, leads to persistent healing impairment and active inflammation. Our patient did not have diabetes, which predisposes to excess neointima formation, and was receiving three anti-thrombotic drugs; this might also have delayed the filling and healing of the residual space between the stent and vessel. Another hypothesis is that the reaction to vessel trauma, such as overstretching and reactive aggregative neointimal growth, may be a natural healing response. Our patient was over 80 years old. Because of senile changes in the vessels, the healing process might have been delayed. Therefore, inhibition of the biological reaction by DES may exacerbate the healing delay, especially after aggressive stent implantation.

The current case suggested that disruption of the elastic membrane and the enlarged vessel during the index PCI procedure had led to the chronic inflammation; this kind of localized, long-lasting inflammation with eosinophilic infiltration might represent potential DES failure, although our patient did not have any ischemic complications. Additionally, previous reports suggest that delayed healing, inflammation and hypersensitivity might play a role in incomplete stent apposition [2, 3]. Previous IVUS studies reported that calcified lesions tend to dissect the vascular wall more frequently [14], while other IVUS observations suggested that use of rotational ablation significantly reduces dissection and/or vessel injury [16–18]. This suggests that lesion modification with rotational atherectomy prior to DES may be an ideal strategy in patients with calcified lesions.

Conclusions

In our patient, serial observation of the index PCI procedure by IVUS and postmortem histologic findings suggested persistent and intense inflammation of the LCX secondary to vascular injury and a hypersensitivity reaction, resulting in aneurysm formation. An inflammatory reaction was still recognized even 3 years after the index DES implantation, probably because aggressive stenting might have delayed healing. Hence, to avoid vascular injury and subsequent intense inflammation, the procedural strategy for DES deployment in severely calcified lesions should be carefully considered.

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