Neo-atherosclerosis in very late stent thrombosis of drug eluting stent

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Background: Recent studies have described neo-atherosclerosis, developing inside the stent, as cause of very late stent thrombosis.

Case report: A 59-year-old man, with family history of coronary artery disease, presented to our Department because of anterior ST-segment elevation myocardial infarction. Two years before he had underwent percutaneous coronary intervention with multiple drug-eluting stents (DES) implantation on proximal-mid left anterior descending artery (LAD), and mid-right coronary artery (RCA), respectively. The angiogram revealed stent thrombosis with total occlusion of proximal LAD. Multiple passages with manual thrombus-aspiration catheter were successfully performed with improvement in TIMI flow. Optical Coherence Tomography (OCT) imaging revealed fully expanded stents without areas of inappropriate apposition to vessel wall; and mild to moderate intimal hyperplasia throughout the stented segment, with full covered stent struts; areas of ulcerated and ruptured plaque within the proximal struts of stented segment was depicted with intraluminal protruding material. Thus, an additional bare metal stent (BMS) was deployed inside and overlapping the previous in order to seal this plaque. OCT post procedure revealed optimal stent expansion and apposition, without residual protruding material. At 9-month follow-up patient was alive and free from symptoms. Coronary angiogram revealed patency of implanted stents without significant restenosis.

Conclusions: Neo-atherosclerosis with thrombosis on top of ruptured necrotic plaque core may play a role in the pathophysiology of very late stent thrombosis in both BMS and DES. Our report highlights the role OCT to assess the mechanism of VLST.

Keywords: Optical Coherence Tomography, Very late stent thrombosis, Neo-atherosclerosis

Background

Percutaneous coronary intervention (PCI) with stent implantation is the most widely performed procedure for the treatment of acute coronary syndromes. Mechanisms of late stent thrombosis (LST) and very late stent thrombosis (VLST) have been described and are mainly linked to delayed or incomplete stent strut endothelization, local hypersensitivity reactions, and late stent malapposition [1–3]. Neo-atherosclerosis inside a previously implanted coronary stent has...
recently been identified as an additional entity potentially linked to the development of very late in-stent restenosis and very late thrombosis [4].

Case report

A 59-year-old man with a family history of coronary artery disease presented to our department because of anterior ST-segment elevation myocardial infarction. Two years previously he underwent percutaneous coronary intervention of left anterior descending artery (LAD) and right coronary artery (RCA) with multiple sirolimus-eluting stents (SES) implantation on proximal-to-mid LAD (Cypher 3.0/12, 3.0/18, 2.5/18 mm; Cordis Corp, Warren, NJ, USA), and on proximal RCA (Cypher 3.5/38 mm), respectively. At presentation, 250 mg IV aspirin and prasugrel 60 mg orally, were administered. Coronary angiography was promptly accomplished by right radial artery. The angiogram revealed stent thrombosis with total occlusion of proximal LAD (TIMI 0) (Fig. 1a–c). After guide-wire advancement in the distal vessel, multiple passages with manual thrombus-aspiration catheter were successfully performed (Export AP 6F; Medtronic Inc. Minneapolis, MN, USA).

Significant reduction in thrombus burden with improvement in TIMI flow was achieved. Optical Coherence Tomography (OCT) (C7 Dragonfly, LightLab Imaging Inc. Westford, MA, USA) imaging was applied in order to investigate the stent struts-to-vessel boundary and to identify the mechanisms of stent thrombosis. OCT revealed fully expanded stents without areas of inappropriate apposition to vessel wall; and mild to moderate intimal hyperplasia throughout the stented segment with fully covered stent struts.

Interestingly, in the proximal segment of the stents, areas of ulcerated and ruptured plaque with intraluminal protruding material were seen (Figs. 2 and 3). Thus, an additional bare metal stent (BMS) (Multi-link Vision 3.0 x 23 mm; Abbott Vascular, Santa Clara, CA, USA) was deployed inside, and overlapping the previous one, in order to seal the plaque. OCT post-procedure revealed

![Figure 1. Diagnostic angiogram demonstrates VLST of proximal LAD in direct AP view (a); caudal RAO view (b); and cranial AP view (c). Nine months’ follow-up angiogram in cranial AP view (d).](image-url)
optimal stent expansion and apposition. At nine months’ follow-up, the patient was alive and free from symptoms. Coronary angiogram revealed patency of implanted stents without significant restenosis (Fig. 1d).

Discussion

Although first generation sirolimus and paclitaxel drug-eluting stents (DES) have radically reduced restenosis rates at short and mid-term, late stent thrombosis (LST) and very late stent thrombosis (VLST) as well as late catch-up, have emerged as important drawbacks of this technology [5]. Definitions of stent thrombosis (ST) range from ‘angiographically proven’ to ‘clinically suspected’ ST with the inclusion of myocardial infarction (MI) involving the target vessel to unexplained death (within 30 days or anytime).

The Academic Research Consortium has proposed a new standardized definition of ST based on two principles. The first is the level of certainty that ST is the underlying mechanism of adverse event and time of adverse event relative to index procedure. Definite ST (highest level of certainty) requires either angiographic or post-mortem evidence of thrombotic stent occlusion. Probable ST encompasses any unexplained death within 30 days of stent implantation or any MI in the territory of the implanted stent regardless of time. Possible ST includes any unexplained death beyond 30 days until the end of follow-up. The second classification principle is based on the time of the adverse event relative to the index procedure. Early ST refers to the first 30 days after stent implantation and is further stratified into acute (24 h) and sub-acute (24 h to 30 days). Late ST defines the time interval between one month and one year after stent implantation; very late ST includes any event beyond one year [6,7].

Premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction, total stent length, total stent number, and small stent size were identified as predictors of early, late, and very late stent thrombosis events [8,9]. Moreover, it is reported that drug-eluting stent is the only independent predictor of very late ST [10]. Studies have demonstrated that
incomplete neointimal coverage, local hypersensitivity reactions, and late stent malapposition due to positive remodelling may be possible mechanisms for LST and VLST after DES implantation [1–3]. More recently, the growth of neointimal atherosclerosis (neo-atherosclerosis) inside a previously implanted coronary stent has been identified as a new entity potentially linked with the development of late catch-up and late thrombosis [4]. Neo-atherosclerosis has been reported in both BMS and DES; however, after DES implantation, neo-atherosclerosis has been observed at an earlier time-point than that of BMS. The underlying mechanisms responsible for the development of neo-atherosclerosis following stent implantation are likely multifactorial, and related to lack of functional endothelialized luminal surface within the stented segment [4]. Neo-atherosclerosis is characterized by infiltration of foamy macrophage clusters within the neointima, and thin-cap fibroatheroma (TCFA). Studies demonstrate that neointimal rupture during an extended period contribute to late stent failure [11,12]. In-stent development of TCFA neointima with neointimal rupture has been associated with thrombotic events and clinical sequelae after stent implantation [13]. Optical Coherent Tomography (OCT) is able to detect late catch-up phenomena, as well as TCFA, neointimal rupture, neovascularization and intramural thrombi after DES implantation [14]. OCT constitutes an emergency, be it early, late, or very late, just like any acute MI. Primary PCI is the therapy of choice, the goal being to mechanically recanalize the thrombosed stent. Procedural success in >90% of patients has been reported. Most thrombotic stent occlusions can be treated with balloon angioplasty alone, perhaps aided by thrombus aspiration. Additional stent implantation should be limited to significant residual stenosis/dissections [7].

Our report highlights the relevance of OCT in assessing the pathological basis and mechanisms of very late stent thrombosis and the choice of appropriate management of stent failure. Accordingly, in the present case, OCT imaging clearly detected TCFA within the struts of previously implanted DES, with areas of ruptured plaque and superimposed thrombus, as a correlate of VLST. Our case reflects the findings recently reported by Kang and colleagues that VLST is mostly associated with neointimal rupture and area of lipid core, and that it is less associated with mechanical trouble like uncovered stent struts, frames malapposition or stent fracture. The authors concluded that neointimal rupture more likely contributed to the thrombotic event due to the spatial relationship of the intracoronary thrombus to the site of neointimal rupture [13]. Furthermore, our case appears in agreement with the recent findings of Habara et al. who described different OCT patterns of in-stent restenosis according to different time-points. Particularly, they found that TCFA-like patterns and intraluminal material were more frequently observed in very late in-stent restenosis than in patients with early in-stent restenosis, suggesting that neo-atherosclerosis contributes not only to VLST but also to late catch-up phenomena [15]. Interestingly, we performed a BMS in-stent implantation in order to seal a ruptured plaque, and to reduce further recurrence of late stent failure. However, in this regard, it is important to consider that definite treatment of VLST, due to neo-atherosclerosis, is still under debate, and that no data supports the

![Figure 3. Image magnification of Fig. 1d–e, showing stent struts, yellow arrow (a); ulcerated plaque with thrombus protruding into lumen, white arrows (a and b); and plaque rupture at thin cap, black arrow (b).](image-url)
type of stent to be implanted. In fact, although drug-eluting stents are attractive in this setting, the consequences of the eluted drug on the vessel wall healing process remain unresolved.

Conclusions

Neo-atherosclerosis with thrombosis on top of ruptured necrotic plaque core seems to play a role in the pathophysiology of very late stent thrombosis in both BMS and DES. Our report highlights the role of OCT to assess the mechanism of VLST.

Conflict of interest

There is no conflict of interest to declare.

References