Pathological assessment of very late bare metal stent thrombosis in the left main coronary artery: a case report

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Background
Late catch-up phenomenon following stent implantation is a well-known complication. However, no report has evaluated thrombosis after 9 years with multi-modality and pathological evaluation.

Case summary
A 71-year-old man with stable angina underwent elective percutaneous intervention of the left main coronary artery with implantation of a bare metal stent (BMS) 9 years ago. At the 9-year follow-up, coronary computed tomography (CCT) and coronary angiography (CAG) findings revealed a thrombus-like structure in the BMS slightly protruding into the sinus of Valsalva. Therefore, the previously prescribed double-antiplatelet therapy was replaced with an anticoagulant and clopidogrel, and a potent statin treatment was initiated. After the changes in drug treatment, follow-up examinations with CCT at 1 and 3 months suggested a decrease in the size of the thrombus; however, it appeared to increase after 6 months. Subsequently, the patient underwent surgical intervention. Pathological assessment of the explanted stent showed a proteoglycan-dominated extracellular matrix with few smooth muscle cells suggesting an organized thrombus.

Discussion
It should be emphasized that multiple factors might be responsible for very late stent thrombosis, such as peri-stent strut chronic inflammation involving proteoglycans, stent protrusion, and poorly controlled type 2 diabetes mellitus, possibly further inducing inflammatory cells.

Keywords
Case report • Very late stent thrombosis • Left main coronary artery • Pathology • Proteoglycan

Introduction
The later occurrence of restenosis (‘late catch-up phenomenon’) after bare metal stent (BMS) implantation is a well-known complication. However, no published reports are available on very late thrombosis in the left main coronary artery (LMCA) of surviving patients with silent ischaemia. Herein, we report a rare case of very late thrombosis in the LMCA along with multiple modalities, including...
5 years did not reveal any significant restenosis (Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) revealed an arteriosclerotic lesion with an organized thrombus (Figure 2E and F, and Videos 2 and 3). Hence, our heart team recommended coronary artery bypass grafting (CABG) to avoid the risk of embolization during repeat PCI. However, the patient refused this procedure as he was asymptomatic. Therefore, the previously prescribed double-antiplatelet therapy was replaced with an anticoagulant (apixaban 10 mg/day) and clopidogrel, and the standard statin therapy was replaced with a combination of high-intensity statin and ezetimibe. In addition, intensive glycaemic control with additional drugs was provided. After a change in drug treatment, follow-up CCT examination at 3 months showed a decrease in thrombus size (Figure 3B). However, thrombus size appeared to increase after 6 months (Figure 3C). Echocardiography showed preserved left ventricular systolic function (LVEF = 65%) over time. Subsequently, surgical removal of the stent, LMCA ligation, and CABG including left internal mammary artery anastomosed to left anterior descending artery, saphenous venous graft anastomosed to obtuse marginal, and posterior lateral artery were performed. Pathological assessment of the extracted stent revealed a proteoglycan-rich extracellular matrix on the lumen side with few smooth muscle cells, indicating an organized thrombus (Figure 1A and B). The patient was asymptomatic to date, approximately 1 year after surgery.

### Timeline

| Date       | Event                                                                 |
|------------|-----------------------------------------------------------------------|
| 29 December 2008 | Drug-eluting stent (3.5 mm × 23 mm Cypher™ Cordis, Johnson & Johnson) implantation in the left main coronary artery (LMCA) to the left anterior descending artery for stable angina. |
| 29 June 2009  | Bare metal stent (4.0 mm × 8 mm Vision™ Abbott Vascular) implantation in LMCA ostium for stable angina. |
| 11 June 2014  | Coronary angiography (CAG) was performed for routine follow-up purpose, and it did not reveal any significant in-stent thrombosis. |
| July 2018     | Due to the positive result of exercise stress electrocardiogram test, coronary computed tomography (CCT), CAG, intravascular ultrasound, and optical coherence tomography were performed. These findings suggested stent thrombosis. |
| July 2018 to April 2019 | Patient refused invasive therapy because he was asymptomatic. Therefore double-antiplatelet therapy was replaced with an anticoagulant and clopidogrel, and high-intensity statin and ezetimibe were conducted. In addition, intensified glycaemic control treatment was provided. |
| 04 October 2018 | CCT at 3 months after changing drugs suggested a decrease in the size of the thrombus. |
| 28 February 2019 | CCT at 6 months after changing drugs suggested re-growth of the thrombus. |
| 01 April 2019  | Surgical removal of the LMCA stent and coronary artery bypass grafting. |

### Case presentation

A 71-year-old man with stable angina underwent elective percutaneous coronary intervention (PCI) of the LMCA with implantation of a BMS (4.0 mm × 8-mm Vision™), due to proximal restenosis of a drug-eluting stent (3.5 mm × 23-mm Cypher Stent) implanted (Figure 2A). Routine follow-up coronary angiography (CAG) after 5 years did not reveal any significant restenosis (Figure 2B). Coronary computed tomography (CCT) and CAG were performed at 9 years due to a positive exercise stress electrocardiogram test performed in the routine (Figures 2C, D and 3A, and Video 1). The patient had no abnormal findings on physical examination. He had no history of myocardial infarction but had a history of poorly controlled diabetes mellitus (DM) (haemoglobin A1c 8.7%) treated with oral medicine. Coronary computed tomography and CAG revealed a thrombus-like structure in the BMS slightly protruding into the sinus of Valsalva. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) suggested atherosclerotic plaque in the LMCA ostium. However, the patient was asymptomatic due to a positive exercise stress electrocardiogram test performed in the routine, approximately 1 year after surgery.

### Discussion

Very late stent thrombosis (VLST) is an extremely rare phenomenon, and it is even rarer with a BMS. To the best of our knowledge, no study has assessed thrombosis at 9-year follow-up with multiple modalities and pathological examination. A previous study indicated that VLST after BMS implantation might be caused by thrombus formation after the rupture of a calcified atherosclerotic plaque. However, we would like to emphasize that multiple factors...
such as peri-stent strut chronic inflammation involving proteoglycans,6,7 stent strut protrusion,8 and poorly controlled type 2 DM involving induction of inflammatory cells9 might be responsible for VLST.

Proteoglycans
Proteoglycan-rich tissue, observed as an echolucent zone on IVUS10 and a relatively signal-poor region on OCT,11 is observed in the vascular wound healing process, including thrombus absorption.12 Its presence has been reported to be associated with early in-stent restenosis (ISR).6,7 In our case, both intravascular imaging modalities suggested the presence of proteoglycans, which was confirmed by pathological examination. Therefore, we hypothesize that a process similar to early ISR, in which a thrombus is adhered and absorbed, occurred over the 9 years.

Stent protrusion/malapposition
Stent strut malapposition and late-acquired stent malapposition have been suggested as probable aetiologies for VLST after BMS implantation.8 A study reported that flow disturbance, especially the occurrence of non-streamlined flow along the malapposed stent struts, is relevant to stent thrombogenicity.13 In our case, IVUS and OCT confirmed that the major portion of the thrombus was in the stent, protruding from the LMCA. The flow disturbance due to stent protrusion may have contributed to stent thrombosis in a manner similar to that due to malapposed stent strut.

Poorly controlled diabetes mellitus
Core metabolic defects occurring in DM are impaired glucose tolerance, insulin resistance, and proinflammatory and prothrombotic states. These defects may lead to endothelial dysfunction and accelerated atherogenesis.9 A study reported that high-mobility group box 1 (a thrombus-promoting factor) protein was more abundant in patients with type 2 DM than in patients without DM.14 Other studies assessing the coronary atherectomy specimens of stenotic lesions from symptomatic patients with DM revealed that the total area percentage occupied by the thrombus was larger in specimens from patients with DM than in those without DM.15 Therefore, patients
Figure 3  Coronary computed tomography images of changes at treatment site over time. (A) Coronary computed tomography image just before the thrombosis was identified on coronary angiography. (B) Coronary computed tomography image at 3-month follow-up. The thrombus size decreased after treatment with an anticoagulant (apixaban 10 mg/day) and clopidogrel, a high dose of strong statin and ezetimibe, and DDP-4 and metformin hydrochloride. (C) Coronary computed tomography image at 6-month follow-up. Regrowth of the thrombus was observed after previous decrease in size. CCT, coronary computed tomography; CAG, coronary angiography.

Video 1  Coronary angiography at 9 years after stent implantation.

Video 2  OCT images.
with poorly controlled DM, as in our case, may be more prone to thrombosis. Hence, morphological and functional evaluation follow-up should be considered in addition to risk control in such cases.

Lead author biography

Dr Yuki is a medical doctor working in the cardiology field for two years now. I want to become a cardiologist with specific interest in imaging in cardiology.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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