Contrast Staining Outside the Sirolimus-Eluting Stent Leading to Coronary Aneurysm Formation
A Case of Very Late Stent Thrombosis Associated With Hypersensitivity Reaction

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A 69-year-old man with prior myocardial infarction (hypertension; dyslipidemia; smoking; no diabetes; and no history of allergy, autoimmune disease, or vasculitis) underwent sirolimus-eluting stent (SES) implantation (3.0 mm in diameter; 33 mm in length) for chest pain on exertion with chronic total occlusion of the left anterior descending coronary artery (LAD) (Figure 1A through 1C and Video 1). Intravascular ultrasound examination after SES implantation demonstrated well-expanded stent struts without evidence of incomplete stent apposition (ISA) (Figure 1D through 1F).

Follow-up angiography at 8 months after initial SES implantation demonstrated multifocal contrast staining outside the stent contour with no evidence of angiographic restenosis (Figure 2A and Video 2). Subsequently, at 16 months after stenting, coronary angiography showed that the areas of contrast staining outside the stent contour increased in size (Figure 2B and Video 3). At 23 months after stenting, coronary artery aneurysm (CAA) formation was demonstrated in the midportion of the SES (Figure 2C and Video 4). The first 8-month angiography was a protocol-driven follow-up study for the index LAD lesion. The second 16-month angiography was also a protocol-driven follow-up study for the circumflex coronary artery lesion treated 8 months before. Similarly, the third 23-month angiography...
was also a protocol-driven follow-up study for the right coronary artery lesion treated 7 months before. The patient had been free of cardiac symptoms throughout the follow-up period. The patient continued taking aspirin at a dose of 100 mg/d; however, ticlopidine had been discontinued because of hemoptysis related to pneumoconiosis.

The patient underwent surgery for squamous cell carcinoma of the lung at 35 months after stenting. Aspirin had been stopped 7 days before surgery and restarted 2 days after surgery. Fifty days after the lung operation (36 months after SES implantation), the patient had acute myocardial infarction with cardiogenic shock. Coronary angiography revealed occlusion of the LAD at the site of previously documented CAA inside the SES (Figure 2D and Video 5). After thrombus aspiration, TIMI 3 flow was obtained without evidence of significant stenosis in the stent region. The procedure was completed with high-pressure dilatation of the previously placed SES, using a noncompliant balloon catheter (3.5 mm in diameter). Despite good angiographic results and intensive treatment of heart failure, the patient died of heart failure and pneumonia 87 days after acute myocardial infarction.

An autopsy demonstrated that the wall of the stented segment of the artery showed aneurysm-like focal dilatation (Figure 3A). ISA was found in the region of aneurysmal dilatation caused by collapse and loss of the intimal tissue. The separated part between the strut and the vessel wall was filled with blood and a large amount of fibrin (Figure 3B). Marked inflammatory cell infiltration, mainly by lymphocytes and monocytes but also eosinophils, was seen in the stented segment slightly distal to the segment of aneurysmal dilatation (Figure 3C through 3E). Occasional giant cells were also visible. These inflammatory cells diffusely infiltrated the media, causing medial disruption and destruction (Figure 3D). These pathological findings were consistent with a localized hypersensitivity vasculitis. The inflammatory reaction with eosinophilic infiltrate was not present in circumflex coronary artery and right coronary artery.

**Discussion**

Association between late acquired ISA and very late stent thrombosis (VLST) of drug-eluting stent (DES) has been suggested by several intravascular ultrasound studies demonstrating very high prevalence (73% to 77%) of ISA in the setting of VLST. More recently, Alfonso et al conducted systematic evaluation of CAA at the site of DES implantation in which CAA was identified in 15 patients (1.3%) of 1197 consecutive patients; 3 patients with CAA had VLST at the time of or during follow-up after diagnosis of CAA. However, the underlying mechanisms of development of ISA and CAA after DES implantation remain unknown. Virmani et al demonstrated localized hypersensitivity vasculitis of the arterial wall within the stent segment in a patient who died of

![Figure 2.](image-url) A. Follow-up angiography at 8 months after initial SES implantation demonstrated multifocal contrast staining outside the stent contour with no evidence of angiographic restenosis (arrows). B. At 16 months after stenting, the areas of contrast staining outside the stent contour increased in size (arrows). C. At 23 months after stenting, CAA formation was demonstrated in the midportion of the SES (arrows). D. At 36 months after stenting, VLST of the SES occurred at the site of previously documented CAA inside the SES (arrow).

![Figure 3.](image-url) Histopathology of cross sections of middle (A) and slightly distal (C) portions of the SES-implanted coronary artery segment. A, Focal strut malapposition with aneurysmal dilatation (double arrows); B (boxed area in A), collapse and loss of intimal tissue are present. The separated part between the struts and vessel wall is filled with blood components, which consist mainly of fibrin. C through E (D, boxed area in C; E, boxed area in D), At the region of the stent slightly distal to the aneurysmal dilatation portion, extensive inflammatory infiltrate consisting predominantly of lymphocytes and monocytes but also some eosinophils (arrows) was present involving intima, media, and adventitia. Hematoxylin and eosin stain; original magnification: A, ×3.43; B, ×14.1; C, ×4.37; D, ×18.1; and E, ×94.5.
late SES thrombosis. On histopathologic examination, chronic inflammation and aneurysmal dilatation with ISA were confirmed in the stent segment. The hypersensitivity reaction to the polymer was suspected to have been responsible for the vasculitis. To our knowledge, the current case report is the first one with VLST demonstrating serial changes in contrast staining outside the stent border leading to aneurysm formation as well as histopathologic evidence of hypersensitivity vasculitis in the stented segment. These 2 pathological cases suggest that chronic inflammation and hypersensitivity vasculitis might be an important underlying mechanism of ISA and CAA. The current case also demonstrated that inflammatory cells diffusely infiltrated the media, causing medial disruption and destruction, which might result in loss of elastic integrity of the vessel wall leading to aneurysm formation.

It has not yet been clarified whether thrombosis in lesions with ISA and CAA is causally related to the flow turbulence as the result of aneurysm formation or of inflammatory responses underlying the aneurysm formation. Although the real clinical significance of contrast staining outside the stent contour would only be clarified by long-term follow-up evaluation in a large number of patients, very close clinical follow-up should be mandatory when this angiographic abnormality is found during follow-up after DES implantation.

Disclosures
Dr. Kimura serves as an advisory board member for Cordis Cardiology and has received honoraria from Cordis Cardiology.

References

Key Words: intravascular ultrasound ▪ pathology ▪ stent thrombosis
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SUPPLEMENTAL MATERIAL

Video Legends

Video 1. Post-procedural coronary angiography after implantation of a sirolimus-eluting stent (3.0mm in diameter; 33 mm in length) in the LAD.

Video 2. Coronary angiography at 8 months after stenting; Three areas of contrast staining outside the stent contour were observed with no evidence of angiographic restenosis.

Video 3. Coronary angiography at 16 months after stenting; the areas of contrast staining outside the stent contour increased in size.

Video 4. Coronary angiography at 23 months after stenting; Coronary artery aneurysm formation was demonstrated in the mid-portion of the stent, where the contrast staining outside the stent contour was seen previously.

Video 5. At 36 months after stenting, very late stent thrombosis of sirolimus-eluting stent occurred at the site of previously documented coronary artery aneurysm inside the stent.