JACC: CASE REPORTS VOL. 28, 2023

CASE REPORT

CLINICAL CASE

Mechanism of Drug-Eluting Stent Thrombosis Diagnosed by Histopathological Evaluation of Directional Coronary Atherectomy Specimen

Kazuki Ito, MD,[a] Shinya Fujita, MD,[a] Atsushi Sakamoto, MD, PhD,[b] Hayato Ohtani, MD, PhD,[b] Masahiro Muto, MD,[a] Yuichiro Maekawa, MD, PhD[b]

ABSTRACT

An 89-year-old man with a history of percutaneous coronary intervention using a sirolimus-eluting stent presented with recurrent in-stent occlusion. Pathological assessment of the neointima resected via directional coronary atherectomy revealed a double-layered thrombus. Clopidogrel resistance and limited antithrombotic regimen owing to high bleeding risk likely resulted in the in-stent thrombotic occlusion. (J Am Coll Cardiol Case Rep 2023;28:102123)

HISTORY OF PRESENTATION

An 89-year-old man with dyspnea at rest was brought our hospital by ambulance. The patient was afebrile, with a blood pressure of 180/110 mm Hg, heart rate of 110 beats/min, and respiratory rate of 30 counts/min with an oxygen saturation of 90% (10 L/min of oxygen). Laboratory examinations revealed increased B-type natriuretic peptide (1,757.5 pg/mL) and troponin I (818.7 pg/mL) levels. No apparent elevation in creatine kinase/creatine kinase-MB was observed at admission or subsequent testing. Electrocardiogram revealed atrial fibrillation (AF) without ST-segment elevation. A chest radiograph revealed pulmonary congestion. Transthoracic echocardiography revealed hypokinetic motion of the left ventricular anteroseptal wall. The patient was diagnosed with non-ST-segment elevation myocardial infarction, accompanied by acute decompensated heart failure (ADHF). On the second day of admission, electrocardiogram showed inverted T waves in leads I, aVL, V_2, and V_3, which were compatible with myocardial ischemic changes.

LEARNING OBJECTIVES

- To understand the usefulness of resection of neointima by DCA and its pathological assessments for estimating the underlying mechanisms of coronary in-stent restenosis/occlusion.
- To recognize the potential thrombotic risk of: 1) clopidogrel resistance resulting from *CYP2C19* polymorphism; 2) local paclitaxel toxicity; and 3) limited antithrombotic regimen owing to high bleeding risk for the in-stent thrombus formation.

From the [a]Department of Cardiology, Hamamatsu Medical Center, Hamamatsu, Japan; and the [b]Division of Cardiology, Internal Medicine III, Hamamatsu University School of Medicine, Hamamatsu, Japan.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 21, 2023; revised manuscript received October 16, 2023, accepted October 18, 2023.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2023.102123

ABBREVIATIONS AND ACRONYMS

ADHF = acute decompensated heart failure

AF = atrial fibrillation

CAG = coronary angiography

DCA = directional coronary atherectomy

ISR = in-stent restenosis

IVUS = intravascular ultrasound

PCB = paclitaxel-coated balloon

PCI = percutaneous coronary intervention

SES = sirolimus-eluting stent(s)

PAST MEDICAL HISTORY

The patient had diabetes, hypertension, dyslipidemia, paroxysmal AF, and chronic kidney disease. Twelve years before the current admission, he was diagnosed with angina pectoris and underwent a percutaneous coronary intervention (PCI) to the severe stenosis in the left anterior descending coronary artery with a sirolimus-eluting stent (SES) (Cypher, Johnson & Johnson). Following SES implantation, the patient underwent dual antiplatelet therapy (aspirin 100 mg/d and clopidogrel 75 mg/d) for 12 months, followed by continuation of aspirin and dabigatran (220 mg/d).

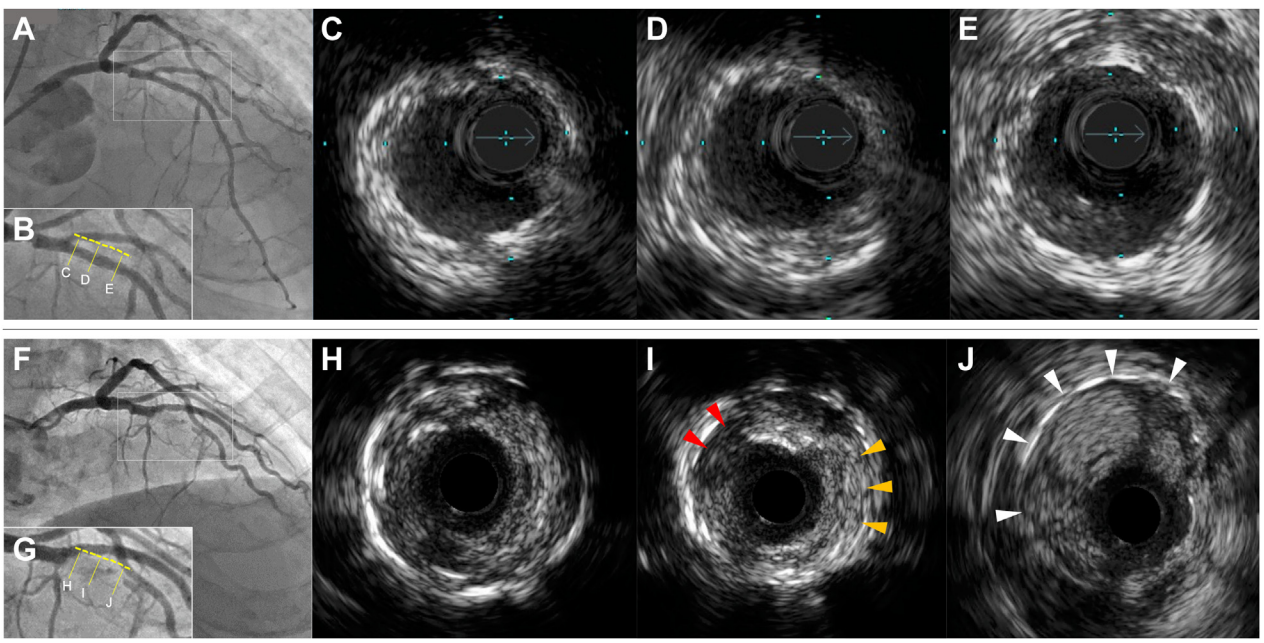
Fourteen months before the current admission, he was referred to our department with unstable angina. Coronary angiography (CAG) revealed an in-stent occlusion at the SES-implanted segment. Balloon dilatation and subsequent paclitaxel-coated balloon (PCB) (SeQuent Please, B. Braun) treatment were performed (Figures 1A to 1E). The patient was initially treated with triple-antithrombotic therapy (aspirin, clopidogrel, and dabigatran) for 10 days after admission, followed by dual-antithrombotic therapy with clopidogrel (75 mg/d) and dabigatran (220 mg/d) thereafter.

Seven months after PCB treatment, clopidogrel was discontinued to minimize the risk of bleeding complications, and dabigatran monotherapy was continued. However, 3 months later, the patient experienced gastrointestinal bleeding from a colon adenoma; therefore, the antithrombotic regimen was changed to edoxaban monotherapy (15 mg/d).

DIFFERENTIAL DIAGNOSIS

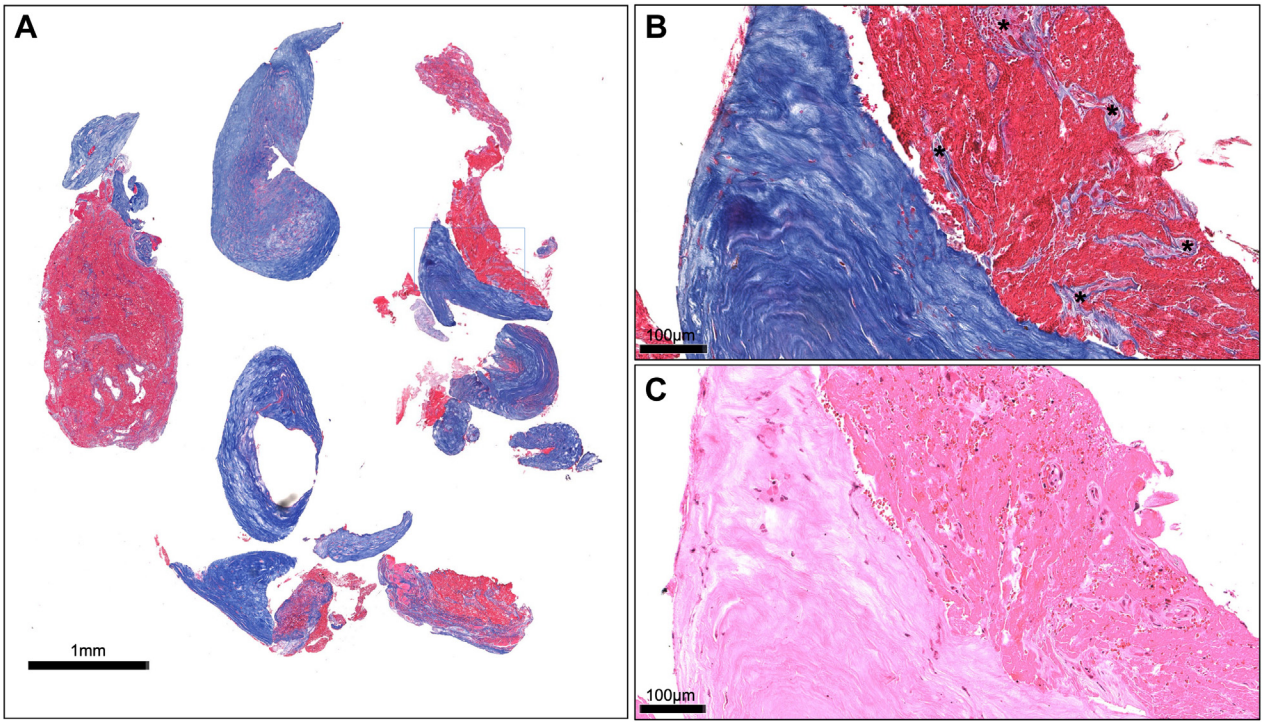
The differential diagnosis was ADHF accompanied by coronary artery disease, including progression of native coronary artery stenosis or in-stent restenosis (ISR) of the PCB-treated segment.

FIGURE 1 CAG and IVUS Findings at Prior PCB and Current DCA Treatment for In-Stent Reocclusion



(A to E) Images of the prior paclitaxel-coated balloon (PCB) treatment for very late sirolimus-eluting stent reocclusion (post-percutaneous coronary intervention). Coronary angiography (CAG) image of the left coronary artery (right anterior oblique-cranial view) (A). B represents the white-rectangular field in A. The in-stent segment was successfully dilated. The dotted line represents the stented segment. C to E represent intravascular ultrasound (IVUS) images of the in-stent segment corresponding to the positions in B. No neointimal tissue was apparent in the segment. (F to J) Images of the current percutaneous coronary intervention (pre-directional coronary atherectomy [DCA]). CAG image of the left coronary artery (F). G represents the white-rectangular field in F. The dotted line represents the stented segment. H to J represent IVUS images of the in-stent segment corresponding to the positions in G. Before DCA treatment, double-layered neointima with low and isoechoic patterns were observed (red and orange arrows). White arrows represent the lotus root patterns, suggesting partial thrombus recanalization.

FIGURE 2 **Pathology of In-Stent Neointima Resected by DCA**



(A) Low-power image of the directional coronary atherectomy (DCA)-resected neointima stained with Masson's trichrome (A). (B and C) High-power images with Masson's trichrome (B) and hematoxylin and eosin staining (C) corresponding to the rectangular field in A. Adjacent tissue showing a fibrin-rich organizing thrombus with microvessel formation (asterisk) and collagen-rich fibrous tissue characteristic of organized thrombus. No inflammatory cell aggregation, foamy macrophage infiltration, or necrotic core formation was observed.

INVESTIGATIONS

Following improvement of the ADHF with oxygenation and medical therapy, CAG revealed recurrent occlusion in the PCB-treated in-stent segment (Figures 1F and 1G). Therefore, re-PCI of the occluded in-stent segment was performed. A tapered guidewire, supported by a microcatheter, was passed through the occluded segments. Intravascular ultrasound (IVUS) revealed a layered-pattern with low and isoechoic neointima (Figures 1H to 1J). A directional coronary atherectomy (DCA) was performed to reduce the volume of the in-stent neointima. After the DCA procedure, additional PCB treatment was conducted, and an acceptable forward coronary flow was achieved.

Histopathology of the neointima revealed a fibrin-rich organizing thrombus and adjacent collagen-rich fibrous tissue characteristic of an organized thrombus (Figure 2). Based on our observations (ie, age of thrombus), the fibrin-rich organizing thrombus appeared to have formed around the time of ADHF (2 weeks before the DCA procedure), and the collagen-rich organized thrombus likely formed after initial PCB treatment for the in-stent occluded segment. No evidence of inflammatory cell aggregation, foamy macrophage infiltration, or necrotic core formation (evidence of neoatherosclerosis) was observed in the 5 dissected samples.

Although the patient had AF, there was no evidence of left atrial thrombus (by transesophageal echocardiography) or systemic embolism. No sign of persistent inflammation against the SES component was confirmed in pathological or coronary computed tomography (ie, positive vessel remodeling) analyses. Because a collagen-rich organized thrombus was confirmed pathologically, we expected the presence of an intrinsic local prothrombotic status such as clopidogrel resistance. Indeed, genetic testing confirmed a *CYP2C19* polymorphism (*1/*2 allele; intermediate metabolizer), which could be one of the contributors to recurrent in-stent occlusion.

MANAGEMENT

To avoid further in-stent thrombotic restenosis/occlusion, prasugrel (2.5 mg/d) instead of clopidogrel and edoxaban (15 mg/d) were continued following the present PCI.

DISCUSSION

In the present case, DCA was performed to reduce the neointimal tissue of the recurrent in-stent occlusion. Pathological assessment of the resected tissue revealed double-layered neointima with fibrin-rich organizing and collagen-rich organized thrombi (**Figure 2**). In general, the critical contributors for drug-eluting stent restenosis/occlusion include biological, mechanical, and procedural factors.[1] According to CAG and IVUS findings in this case, no evidence of the aforementioned mechanical or procedural factors was confirmed. Coronary computed tomography and IVUS did not show positive vascular remodeling in the SES-implanted segment, and pathological assessment of the DCA specimens did not reveal any inflammatory cell aggregation. Therefore, hypersensitivity and allergic reactions to the SES components were excluded as likely contributors to recurrent occlusion. Furthermore, in-stent neoatherosclerosis, another potential mechanism of late in-stent failure, is unlikely to be the reason for recurrent in-stent reocclusion. Although multiple in-stent tissue resections with DCA (5 times circumferential cutting) were conducted, no foamy macrophage infiltration or the presence of a necrotic core were observed in the specimens.

Because atherosclerotic coronary disease and AF are common comorbidities in elderly patients, appropriate management of antithrombotic therapy to minimize both thrombotic and bleeding risk is vital in this subpopulation. Because coronary heart disease, AF, and gastrointestinal bleeding were comorbidities in the patient in this case report, antiplatelet therapy (clopidogrel 75 mg/d) was discontinued 7 months after the in-stent PCB treatment, and only the anticoagulation therapy (edoxaban 15 mg/d) was continued thereafter. Therefore, discontinuation of the antiplatelet therapy may have contributed to the silent in-stent thrombotic occlusion. Moreover, paclitaxel loaded in drug-coated balloons is known to have local cytotoxicity and delayed healing effect with excessive fibrin aggregation.[2] Thus, local thrombotic occlusion in this case might be, in part, affected by PCB treatment itself.

Thienopyridine antiplatelet agents are key drugs for preventing subacute stent thrombosis following coronary stent implantation; however, a greater risk for early and late cardiovascular events, including stent thrombosis, has been reported in patients with at least 1 reduced-functional allele of *CYP2C19*, an enzyme related to clopidogrel metabolism.[3,4] Thus, the antiplatelet effect of clopidogrel was potentially attenuated in this case, and the local thrombotic status may have exacerbated during the local healing process at the PCB-treated segment, leading to recurrent restenosis/occlusion caused by subclinical thrombosis (type I collagen-rich organized thrombus). Subsequently, the deteriorated coronary hemodynamic status during ADHF may have contributed to further thrombotic occlusion (fibrin-rich organizing thrombus). The pathological findings of the lesion with double-layered neointimal tissue support the aforementioned mechanisms of in-stent re-occlusion. To achieve greater antithrombotic effects, prasugrel (instead of clopidogrel) was administered following the current PCI procedure.

FOLLOW-UP

Follow-up CAG, 4 months after the DCA treatment, revealed no evidence of ISR. The patient's clinical course was uneventful, without any late thrombotic or bleeding complications.

CONCLUSIONS

Histopathological examination of the DCA specimen revealed double-layered thrombus formation as the underlying cause of the recurrent ISR. Clopidogrel resistance due to *CYP2C19* polymorphism, PCB treatment, and the limited antithrombotic regimen owing to the patient's high-bleeding risk likely led to the in-stent thrombotic occlusion. DCA is useful for pathological evaluation of neointima to estimate the underlying mechanisms of ISR and to determine a better antithrombotic strategy.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by a JSPS KAKENHI grant (No. 22K08122), and a grant from the Alumni Association of Faculty of Medicine, Kagawa University (No. R4-1) (Dr Sakamoto). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Atsushi Sakamoto, Division of Cardiology, Internal Medicine III, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan. E-mail: asakamo@hama-med.ac.jp. @AtsSakamo.

REFERENCES

1. Sakamoto A, Sato Y, Kawakami R, et al. Risk prediction of in-stent restenosis among patients with coronary drug-eluting stents: current clinical approaches and challenges. *Expert Rev Cardiovasc Ther*. 2021;19:801-816.

2. Nakazawa G, Finn AV, Vorpahl M, et al. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. *J Am Coll Cardiol*. 2011;57:390-398.

3. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360:354-362.

4. Lee CR, Sriramoju VB, Cervantes A, et al. Clinical outcomes and sustainability of using CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. *Circ Genom Precis Med*. 2018;11:e002069.

KEY WORDS **directional coronary atherectomy, drug-eluting stent, in-stent restenosis, in-stent thrombosis**