JACC: CASE REPORTS VOL. 24, 2023

CASE REPORT

ADVANCED

CLINICAL CASE

Very Late Stent Thrombosis Complicating Immune Thrombocytopenia

Insights From Optical Coherence Tomography and Thrombopathology

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ABSTRACT

Immune thrombocytopenia (ITP) carries bleeding and thrombotic risks; however, thromboses associated with ITP have not been histologically examined. This report presents optical coherence tomography images of the culprit lesion and histology of coronary aspirates in very late stent thrombosis complicating severe ITP, providing evidence of platelet-rich thrombus formation. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;24:102017) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

An 89-year-old man with a history of inferior wall myocardial infarction and multiple percutaneous coronary interventions (PCIs) for multivessel disease presented worsening intermittent chest pain for months, suggesting the recurrence of acute coronary syndrome (ACS). Because the patient had immune thrombocytopenia (ITP) as a comorbidity, multidisciplinary management for ACS after transfer to our hospital, which involves hematology and cardiology departments, was required. On admission, blood pressure was 122/68 mm Hg, heart rate was 72/min, oxygen saturation was 97% (room air), and bleeding signs were absent.

LEARNING OBJECTIVES

- To recognize the high risk of thrombosis in patients with ITP.
- To demonstrate platelet thrombus formation in ITP-associated thrombosis.
- To understand the management of coronary thrombosis in patients with severe ITP.

PAST MEDICAL HISTORY. The patient had been diagnosed with ITP 6 months prior and was prescribed eltrombopag, a thrombopoietin receptor agonist (TPO-RA). However, due to frequent chest pain, another TPO-RA, romiplostim, was prescribed, failing to relieve the chest symptoms.

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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 July 28, 2023; revised manuscript received August 10, 2023, accepted August 17, 2023.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2023.102017

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BMS = bare-metal stent(s)

Cit-H3 = citrullinated histone H3

DES = drug-eluting stent

ISR = in-stent restenosis

ITP = immune thrombocytopenia

LAD = left anterior descending artery

NETs = neutrophil extracellular traps

OCT = optical coherence tomography

PCI = percutaneous coronary interventions

TPO-RA = thrombopoietin receptor agonist

VLST = very late stent thrombosis

DIFFERENTIAL DIAGNOSIS

Considering the history of myocardial infarction, multiple PCIs, and chest pain, ACS was a high-priority differential diagnosis.

INVESTIGATIONS

Elevated cardiac troponin T level (0.109 ng/mL, normal reference value: <0.014 ng/mL) on blood test, ischemic changes on electrocardiography (Supplemental Figure 1), and wall motion abnormalities on echocardiographic examination (Video 1) strongly indicated ACS; however, blood test showed extremely low platelet counts (9000/μL). Emergency coronary angiography via the radial artery was performed under temporary platelet transfusion and subsequent heparin administration. Coronary angiography revealed a contrast-filling defect inside a second-generation drug-eluting stent (DES) implanted 9 years prior for in-stent restenosis (ISR) of the bare-metal stent (BMS) in the middle left anterior descending artery (LAD), along with the associated delayed coronary flow (TIMI flow grade 1) (Video 2). Longitudinal (**Figure 1A**) and cross-sectional (**Figure 1B**) images and a video (Video 3) of the culprit lesion obtained using optical coherence tomography (OCT) revealed layered, low-attenuation thrombi in the DES, diagnosing that ACS was due to very late stent thrombosis (VLST). However, OCT provided no evidence of the typical scaffolds for VLST (eg, rupture of in-stent neoatherosclerotic plaque, uncovered strut, and stent malapposition or evagination), except for partially insufficient DES expansion (minimal stent area: 3.97 mm^2).

Consistent with the white appearance of the aspirated clots (**Figure 1C**), histological evaluation (**Figure 1D**) confirmed platelet-rich thrombi with fibrin and a limited percentage of red blood cells. Neutrophils showing partial lytic changes were locally accumulated in the thrombus, suggesting a mixture of subacute thrombi. Citrullinated histone H3 (Cit-H3) staining was observed at the site of neutrophil accumulation, suggesting the presence of neutrophil extracellular traps (NETs). No atherosclerotic plaque component was observed in the aspirated thrombus, similar to the OCT images of the culprit lesion. OCT imaging and histopathology of coronary thrombi showed that platelet-rich thrombi could be formed even in platelet counts below 10,000/μL (fatal bleeding-prone threshold).

MANAGEMENT

After the aspiration of the thrombus in the DES, coronary blood flow improvement was insufficient. PCI using a cutting balloon was performed with a Filtrap (Nipro) to prevent distal thromboembolism, followed by prolonged inflation using a perfusion balloon to improve LAD flow. A drug-coated balloon was used to avoid further stenting. Finally, LAD flow was improved with these procedures (TIMI flow grade 3) (Video 4).

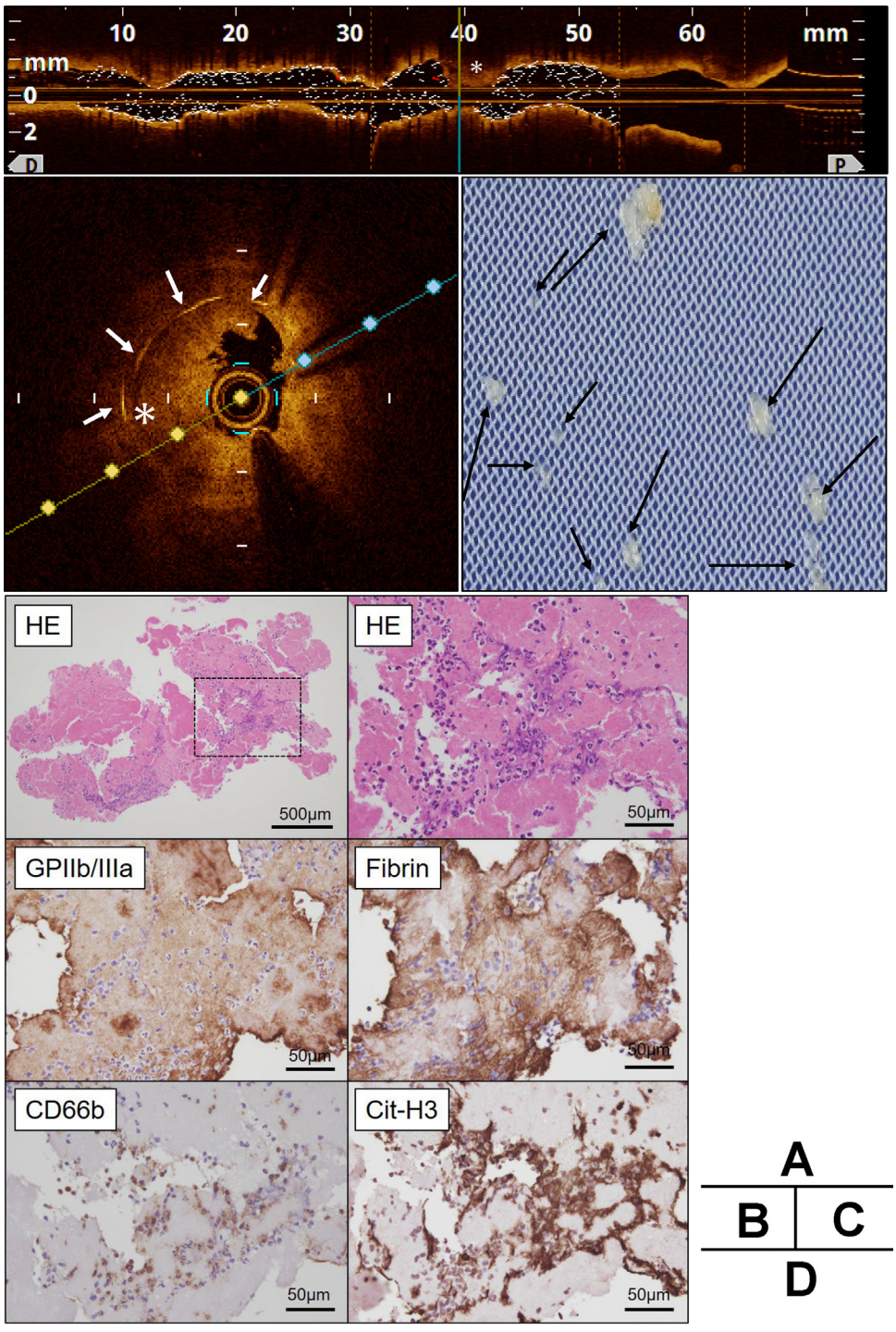
After PCI, TPO-RA was discontinued, and the patient received oral prednisolone 30 mg/d for ITP. By monitoring activated partial thromboplastin time, heparin was continuously administered, and a $P2Y_{12}$ inhibitor was added to aspirin after confirming an increase in platelet counts.

DISCUSSION

ITP is associated with bleeding and thrombotic risks;[1] thus, ITP cases complicated by thrombotic events often present therapeutic dilemmas.[2,3] However, histological evidence is lacking to understand the mechanism of thrombosis in ITP. We herein presented OCT images of the culprit lesion and histopathologic findings of the aspirated coronary thrombi in a patient with VLST complicating severe ITP.

OCT imaging and histopathologic examination revealed the presence of platelet-rich thrombi in a VLST complicated by severe ITP. DES had an insufficient expansion, which partly met the OCT criteria for underexpansion,[4] but there were no other scaffolds for VLST. OCT images of VLST lesions in 33 patients showed that 70% and 42% of patients with VLST had in-stent neointimal ruptures and stent malappositions, respectively, whereas 22% of patients had both, and only 6% of patients did not exhibit those anatomies.[5] Therefore, our patient lacked the major VLST scaffolds. Furthermore, VLST occurred in a second-generation DES, where stent thrombosis is rarely complicated compared to first-generation DES.[6] Additionally, this patient had no apparent coronary events until the onset of ITP 9 years after DES implantation. These results suggest that VLST occurred primarily due to thrombotic changes in the circulating blood caused by the direct effects of ITP (or ITP treatment) and not just an intracoronary scaffolding problem.

FIGURE 1 **Optical Coherence Tomography Imaging and Histopathology of Very Late Stent Thrombosis**



The longitudinal (A) and cross-sectional (B) optical coherence tomography images of culprit thrombotic lesion inside the drug-eluting stent (layered and low-attenuated thrombus indicated as white asterisks; white arrows show the struts of previously implanted drug-eluting stents); the white appearance of aspirated thrombus (C, black arrows indicate clots on the mesh). Histopathology of aspirated coronary arterial thrombus (D). In hematoxylin and eosin (HE) stains, the square corresponds to high magnification. Immunohistochemistry was performed using glycoprotein (GP) IIb/IIIa (a platelet marker), fibrin, CD66b (a marker of neutrophil), and citrullinated histone H3 (Cit-H3) (a marker of neutrophil extracellular traps).

TPO-RA is currently used as a second-line treatment for ITP when steroid therapy is ineffective or burdensome. Therefore, TPO-RAs may be selected for older patients vulnerable to the adverse effects of steroids. However, recent studies reported an increased risk of thrombosis associated with TPO-RA, particularly in older patients.[7] Therefore, balancing the efficacy and safety of TPO-RA requires careful consideration.

Histologic evaluation of the coronary aspirates revealed an accumulation of neutrophils with positive Cit-H3 staining, indicating the possible involvement of NETs in ITP-associated thrombosis. And also, compared to our colleague's previous pathologic analysis of late/very late stent thrombosis in non-ITP cases,[8] the aspirated thrombus, in this case, was more platelet-rich. These results indicate that the increased thrombotic risk in ITP may be due to the increased platelet aggregation via nonplatelet factors, including NETs, or to the altered quality of platelet itself. Although NETs formation occurs in non-ITP coronary thrombi,[9] and may not be specific to ITP-related thrombosis, coronary thrombosis in ITP may develop differently from that in non-ITP, and the thrombotic process, including the interactive contributions of platelets, fibrin, neutrophils, and NETs in patients with ITP, should be further explored. In this study, coronary occlusion with platelet counts below 10,000 (fatal bleeding threshold) suggested that sufficient platelets are not essential for the local formation of a platelet-rich thrombus.

FOLLOW-UP

The peak cardiac troponin T level was 0.505 ng/mL (normal reference value: <0.014 ng/mL), and electrocardiography at discharge is shown in Supplemental Figure 2. The patient has no further chest symptoms and remains under observation while the oral prednisolone dosage gradually decreases.

CONCLUSIONS

OCT and histopathologic examination revealed platelet-rich thrombi in the VLST that developed in patients with severe ITP. ITP-related thrombosis likely includes platelet thrombus formation, even in patients with severe thrombocytopenia.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS drug-eluting stent, immune thrombocytopenia, thrombopoietin receptor agonist, very late stent thrombosis

APPENDIX For supplemental figures and videos, please see the online version of this paper.