Acta Cardiol Sin 2021;37:542–545
Letter to the Editor
doi: 10.6515/ACS.202109_37(5).20210518A

Refractory Coronary Stent Thrombosis in a Patient with Chronic Immune Thrombocytopenia on Eltrombopag

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INTRODUCTION

Immune thrombocytopenia (ITP) is a rare autoimmune disorder, caused by immunologic destruction and insufficient compensatory production of platelets. The management and treatment of ITP depends on estimated risks including platelet count, symptomatic severity, and duration of disease.[1] One of the more recent second-line therapies for enhancing platelet production in patients with ITP is the use of thrombopoietin receptor agonist (TPO-RA), such as eltrombopag.[1] However, some randomized controlled trials have reported severe adverse effects of arterial and venous thromboembolic events from using TPO-RA, but the pathophysiology and risk factors have not been well elucidated.[2] Regarding thromboembolic events, a clinical dilemma arises when a patient with acute coronary syndrome (ACS) presents with ITP from TPO-RA treatment because a balance must be maintained between bleeding events and thromboembolism. Here, we report a case of recurrent fatal coronary thrombosis in a middle-aged woman with chronic ITP on eltrombopag.

CASE

A 61-year-old woman, presented to our emergency department with sudden onset of chest pain. Suspecting inferior ST-elevation myocardial infarction (STEMI), she was taken immediately to the cardiac catheterization laboratory. She had a history of ITP with Evans syndrome and underwent regular medical follow-up for 4 years. She did not have any history of congenital or acquired thrombophilia state. She received glucocorticoid therapy intermittently and subsequently subjected to danazol medication, immunosuppressive therapies, and splenectomy. She was prescribed eltrombopag four times for relapsed thrombocytopenia, and each treatment course ranged from 30 to 90 days. The dose was reduced or treatment was terminated once her platelet counts normalized. The last treatment course had started 15 days ago after observing significant thrombocytopenia (27,000/μL). Primary percutaneous coronary intervention (PCI) revealed a high thrombus burden in the proximal right coronary artery (RCA), thrombolysis in myocardial infarction (TIMI) thrombus grade 4. We immediately performed a manual aspiration thrombectomy (MAT), and deployed one sirolimus-eluting cobalt chromium stent (3.5 mm × 35 mm) at the RCA and one everolimus-eluting platinum chromium stent (2.5 mm × 48 mm) at proximal left anterior descending (LAD) artery due to 80-90% stenosis (Figure 1). Her condition gradually stabilized without any sequalae. We were overly concerned about her bleeding tendency while combing dual antiplatelet therapy (aspirin and clopidogrel), heparinization, and refractory thrombocytopenia. After discussing with the hematologist, we decided to prescribe dual antiplatelet therapy (DAPT) with aspirin and clopidogrel instead of ticagrelor, retain the same dosage of eltrombopag (25 mg QD), and closely monitor her platelet counts. She recovered uneventfully and was then discharged.

Five days later, she returned with chest pain. We soon diagnosed anterolateral STEMI, and the laboratory data revealed a marked increase in platelet counts (542,000/

Received: January 21, 2021 Accepted: May 18, 2021
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μL). Upon activating the primary PCI, we found LAD artery contained a large burden of stent thrombosis (TIMI thrombus grade 5) complicated with total occlusion in its middle portion. Balloon dilation and MAT were used sequentially and a TIMI grade 3 flow was obtained. Coronary angiography of RCA similarly revealed stent thrombosis with concomitant coronary spasm. Intravascular ultrasound (IUVS) revealed a patent stent expansion without malposition (Figure 1), and the activated clotting time was confirmed to be over 300 seconds. Sudden cardiac arrest occurred during the procedure. Even after timely resuscitation and mechanical support, the patient died because of prolonged myocardial stunning and uncontrollable bleeding.

DISCUSSION

We illustrated an unusual case of recurrent STEMI with devastatingly endless stent thrombosis in a patient with ITP on eltrombopag. Although We successfully performed IVUS-guided primary PCI with optimal medical treatment, the patient succumbed to the lethal coronary thrombotic events the second time around. To the best of our knowledge, this is the first case report of a fatal coronary stent thrombosis involving eltrombopag.

Patients with ITP were reported to have not only problematic thrombocytopenia but also thromboembolic events, with higher relative risks for arterial and venous thrombosis of 1.5 and 1.9, respectively, compared with normal controls.[3] Inflammatory conditions elevated procoagulant microparticles, and antibody-mediated endothelial damage were documented to be involved.[4] ITP treatment such as corticosteroids, intravenous immunoglobulin, or splenectomy also can be a contributory factor for thromboembolism.[5]

TPO-RA therapy predominantly promotes platelet production in ITP, but it may increase the occurrence of thromboembolism without known mechanism. Some studies have reported the incidence rate to be from 1.5% to 2.5%.[1] Thrombocytosis may be involved, but was reportedly related to only one-third of thromboembolic events on TPO-RA.[6] Alternatively, although absolute platelet counts may not directly correlate with thromboembolism, a rapid platelet increase may lead to thrombogenicity in patients, especially among those with a risk

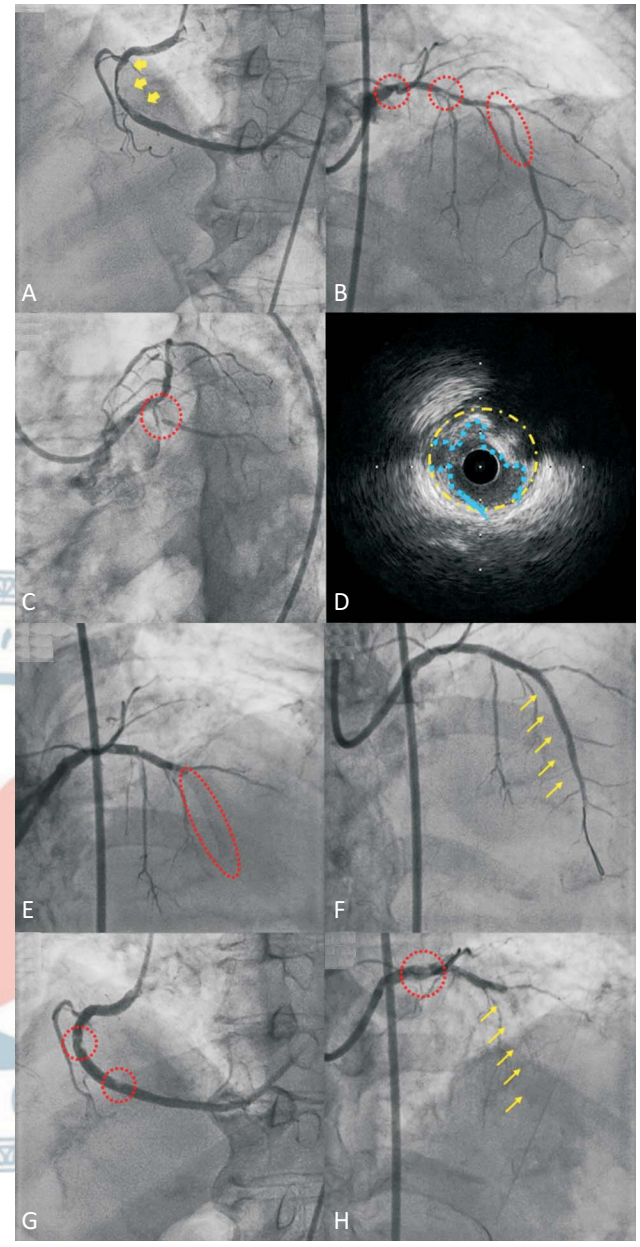


Figure 1. *(A) Primary percutaneous coronary intervention (PCI) at the first ST-elevation myocardial infarction (STEMI) event: right coronary artery (RCA) showed a high thrombus burden (yellow arrows). (B) left anterior descending (LAD) showed diffuse atherosclerosis with 80%-90% segmental stenosis (red circles). (C) Left circumflex artery, a nondominant and small-caliber artery (red circle). (D) Intravascular ultrasound (IUVS) at LAD revealed unstable plaques (blue dash) within the vessel (yellow dash circle) with critical stenosis. (E) Primary PCI at the second STEMI event: LAD showed a large burden of stent thrombosis and total occlusion below the middle part (red circle). (F) LAD showed successful reperfusion (yellow arrows) after balloon dilation and MAT. (G) RCA showed stent thrombosis (red arrows). (H) LAD stent thrombosis recurred soon (red circle) with total occlusion again (yellow arrows).*

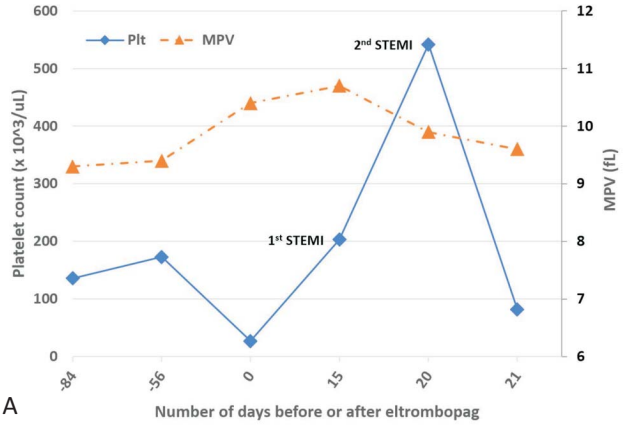
of comorbidity.[7] Our case encountered severe coronary thrombosis events both times with platelet counts rising from 27,000/μL to 203,000/μL within 15 days and surging up to 542,000/μL in only 5 days (Figure 2).

Elevated mean platelet volume (MPV) and accelerated thrombopoiesis imply increased generation of large platelets with high granular content and high enzymatic activity. MPV was believed to be a younger platelet population with enhanced aggregability.[7] Our patient's MPV level was within the normal limits, with the exception of the first day on eltrombopag treatment and day 15 when the first STEMI event occurred. On those days, it slightly increased to 10.4 and 10.7 fL, respectively (Figure 2).

Eltrombopag transiently increases P-selectin and platelet monocyte aggregates. A pooled data analysis documented that it exhibited an overall thromboembolism rate of 4.5% compared with none in placebo groups.[8] Five coronary thrombotic events involving eltrombopag in patients with ITP have been documented in total. Of them, three were in men, aged 31-67, with treatment durations of 1-12 months and platelet counts from 10,000 to 437,000/μL.

Keeping eltrombopag could be a key of recurrent coronary thrombosis. The thing of the case presented by Satoh. T, et al.[9] and our case in common is that both cases were kept eltrombopag. All the other cases without recurrence did not continue eltrombopag after the first event.

Another dilemma over managing complex cases of ITP is the safety concern of the DAPT strategy following PCI with stent implantation, as platelets play a dominant role in the atherosclerotic process and stent endothelization.[5] Our case showed recurrent STEMI with repetitive stent thrombosis even under DAPT, indicating that DAPT may not be effective in counterbalancing activated platelets. Previous studies have reported that major bleeding was rare in PCI strategy for patients with ITP even in severe thrombocytopenia.[5] We suggest it might be reasonable to keep DAPT and taper down or stop eltrombopag for patients in peri-myocardial infarction phase unless any contraindications, such as active bleeding exist.



A

Platelet count (x 10^3 / uL)	Dosage adjustment
Initial	50 mg QD (25 mg QD for Asians), Max: 75 mg/day
< 50	Increase daily dose by 25 mg (If 12.5 mg QD, increase to 25 mg QD)
≥ 50	Use the lowest dose to achieve Discontinue if not response to the level (after 4 weeks at maximum of 75 mg/day)
200 to 400	Reduce daily dose by 25 mg (If 25 mg QD, decrease to 12.5 mg QD) Reassess in 2 weeks
> 400	Withhold dose (assess twice weekly) When < 150, resume with daily dose reduced by 25 mg Still > 400 after 2 weeks: discontinue treatment

B

Figure 2. *(A) Trend of the patient's platelet count with the mean platelet volume (MPV) level and the two ST elevaiton myocardial infaction (STEMI) episodes marked on the number of days before and after taking eltrombopag, with the day of starting eltrombopag labeled as day zero. (B) Eltrombopag drug information for persistent or chronic immune thrombocytopenia (ITP).[10] Adapted from reference 10 and Promacta (eltrombopag) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2021.*

LEARNING POINTS

- According to prior reports and the details of the present case, it is imperative to make a careful balance between the risk of thrombosis and bleeding for IPT patients.
- We suggest that it may be reasonable to keep DAPT, taper down or stop eltrombopag unless any active bleeding event or extremely low platelet counts, and much more closely monitor platelet counts for ITP patients in peri-myocardial infarction phase.
- An unexpected surge in platelets is a warning sign in such patients. Further investigation is required to explore the optimal strategy of medications for ITP patients with ACS.

CONFLICT OF INTEREST

All authors do not have any conflict of interest or financial disclosure.

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