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【 CASE REPORT 】

The Assessment of the Platelet Function During the Acute Phase of ST-segment Elevation Myocardial Infarction in Essential Thrombocythemia

Shinnosuke Kikuchi[1], Kiyoshi Hibi[1], Kouichi Tamura[2] and Kazuo Kimura[1]

Abstract:
We encountered a case of ST-segment elevation myocardial infarction (STEMI) as the first clinical manifestation of essential thrombocythemia (ET). Platelet function tests revealed high thrombogenicity during primary percutaneous coronary intervention compared with general cardiovascular patients, whereas the platelet function two weeks after admission was effectively suppressed by dual antiplatelet therapy. The patient, who lacked cytoreduction, suffered from recurrent STEMI because of poor compliance with antiplatelet drugs. The risk of acute coronary occlusion may be high during the acute phase of STEMI in ET patients because of high thrombogenicity. Insufficient antiplatelet therapy and no cytoreduction are also risk factors for recurrent coronary events.

Key words: platelet function, ST-segment elevation myocardial infarction, essential thrombocythemia, case report

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Introduction

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm characterized by increased platelet counts with platelet dysfunction (1). Patients with ET are at a high risk for paradoxical complications of thrombosis and hemorrhaging. Thrombotic complications are caused by platelet dysfunction, and hemorrhagic complications occur secondary to acquired von Willebrand syndrome (AvWS). Acute myocardial infarction (AMI) is a rare but life-threatening complication of ET (2).

The incidence of ET is 1.0 to 2.5 individuals per 100,000 annually (3), and the incidence of AMI in patients with ET has been reported to be 2% to 9.4% (4, 5). The management of AMI with ET remains unclear because of its rarity. In particular, few studies have focused on the platelet function during the acute phase of ST-segment elevation myocardial infarction (STEMI) in patients with ET.

We herein report a patient who developed STEMI as the first clinical manifestation of ET. We evaluated the platelet function during the acute phase of STEMI using multiple tests [with the VerifyNow system and Total thrombus-formation analysis system (T-TAS)] in the present case.

Case Report

First hospitalization

A 76-year-old man with current smoking presented to our hospital with upper back pain. An electrocardiogram showed ST-segment elevation in leads II, III, and aVF, and an echocardiogram detected hypokinesis of the inferior wall, resulting in a diagnosis of STEMI.

The platelet count at admission was $57.7\times10^4/\mu L$. After the administration of a loading dose of 200 mg of aspirin and unfractionated heparin, an emergency coronary angiogram (CAG) revealed occlusion of the proximal right coronary artery (RCA) with a crab-like filling defect, suggesting a thrombus (Fig. 1A). We performed primary percutaneous

[1]Division of Cardiology, Yokohama City University Medical Center, Japan and [2]Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Japan
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Correspondence to Dr. Shinnosuke Kikuchi, skikuchi@yokohama-cu.ac.jp

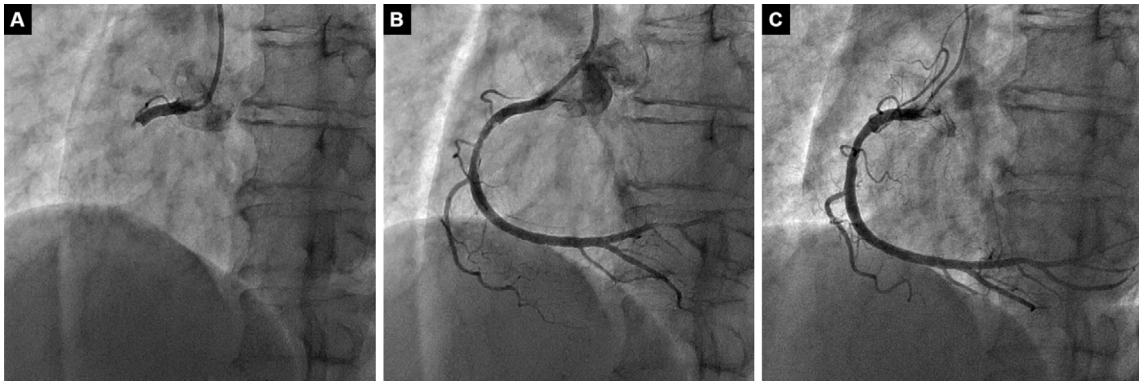

Figure 1. **The coronary angiogram at the first hospitalization. (A) An emergency CAG revealed occlusion of the proximal RCA with a crab-like filling defect. (B) PPCI was performed with thrombus aspiration and perfusion balloon dilatation. Although the final TIMI flow was grade 3, intraluminal multiple filling defects (suggestive of thrombus) were observed. (C) CAG on day 11 confirmed the disappearance of intraluminal filling defects. CAG: coronary angiogram, RCA: right coronary artery, TIMI: thrombolysis in myocardial infarction**

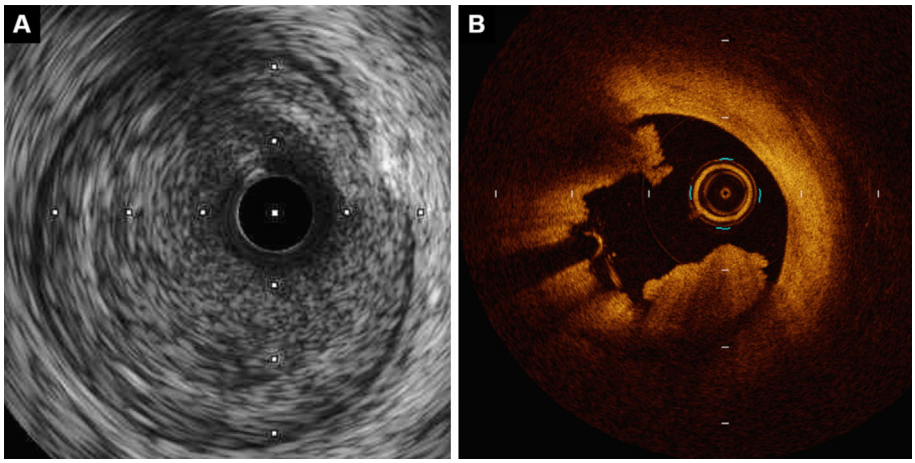

Figure 2. **Intracoronary imaging at the first hospitalization (after prolonged balloon dilatation). (A) IVUS demonstrated concentric fibrous plaque with a large amount of thrombus. (B) OCT confirmed mixed (white and red) thrombus partially with low signal attenuation. There was no plaque rupture in the culprit lesion. IVUS: intravascular ultrasound, OCT: optical coherence tomography**

coronary intervention (PPCI) without any P2Y12 inhibitors, considering the non-stenting strategy. Thrombolysis in myocardial infarction (TIMI) 3 flow was restored after thrombus aspiration and perfusion balloon dilatation, although multiple intraluminal filling defects (suggestive of thrombus) were observed (Fig. 1B). Intravascular ultrasound demonstrated concentric fibrous plaque and a large amount of thrombus, which was observed as mixed (white and red) on optical coherence tomography (Fig. 2). The intracoronary imaging findings revealed no plaque rupture.

After PPCI, we performed dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in addition to continuous intravenous heparin infusion for four days. The patient was discharged after CAG on day 11, confirming the disappearance of the multiple intraluminal filling defects (Fig. 1C). During hospitalization, the platelet count increased to 105.5×10^4/μL. A bone marrow biopsy showed marked increases in megakaryocytes. ET with a positive JAK2-V617F mutation was diagnosed after discharge.

Second hospitalization

After one month, the patient, who had poor compliance with antiplatelet drugs, suffered from recurrent inferior STEMI, and the RCA was found to be once again totally occluded at the proximal segment. ET treatment had not yet been performed, and the platelet count on admission was 71.2×10^4/μL. After administration of a loading dose of 200 mg of aspirin and 20 mg of prasugrel (Japanese standard dose) and unfractionated heparin, PPCI without stent implantation was successfully performed using thrombus aspiration and a perfusion balloon. After that, the patient received treatment with hydroxycarbamide.

Platelet function test

At each hospitalization, serial changes in the platelet function were measured by the T-TAS during the acute

Table. Platelet Function Tests Results.

1st/2nd hospitalization	On arrival	During PPCI	2 weeks
PL-AUC	483/473	473/458	7/11
AR-AUC	1,747/1,823	1,024/1,692	1,799/1,727
PRU (% inhibition)	249 (0%)/185 (0%)	146 (0%)/185 (0%)*	85 (38%)/57 (73%)**
ARU	660/661	662/660	447/434
General STEMI patients	On arrival	During PPCI	2 weeks
PL-AUC, median	402	110	97
AR-AUC, median	1,865	10	1,690

PPCI was performed after administration of a loading dose of aspirin and unfractionated heparin. * The patient did not receive a loading dose of any P2Y12 inhibitors in the 1st hospitalization and received a loading dose of prasugrel in the 2nd hospitalization. ** In the 1st and 2nd hospitalization, the patient received maintenance doses of clopidogrel and prasugrel, respectively.

PL-AUC and AR-AUC were tested at flow rates of 18 μL/min and 10 μL/min, respectively. For the purpose of comparison, previous data on general STEMI patients are shown in the lower part (10).

AR-AUC: area under the flow-pressure curve for the AR-chip, ARU: aspirin reaction unit, PL-AUC: area under the flow-pressure curve for the PL-chip, PPCI: primary percutaneous coronary intervention, PRU: P2Y12 reaction unit, STEMI: ST-segment elevation myocardial infarction.

phase of STEMI [on arrival, during PPCI (1 hour after loading of antiplatelet drugs), and 2 weeks after admission]. The VerifyNow system allows for the assessment of the responsiveness to antiplatelet drugs. The results are reported as P2Y12 reaction units (PRU) and aspirin reaction units (ARU). The ARU and PRU measured by VerifyNow reflect platelet reactivity through the thromboxane A2 and P2Y12 receptors. High on-treatment platelet reactivity is defined as PRU > 208 (6), and aspirin resistance is defined as ARU >550 (7). T-TAS enables the quantitative analysis of the thrombus formation process under blood flow conditions using two types of microchips: PL and AR chips (8, 9). The PL chip is designed for the analysis of platelet-derived thrombogenicity, and the AR chip is designed for the analysis of thrombogenicity, including platelets and the coagulation system. Thrombogenicity is evaluated by measuring the area under the flow-pressure curve (AUC). T-TAS can enable the evaluation of total thrombogenicity, reflecting not only the effects of antithrombotic drugs but also the patient characteristics and the complex status of STEMI. We previously reported serial changes in the platelet function measured by the VerifyNow system and T-TAS in general patients with STEMI undergoing PPCI (10). We compared the platelet function in the present ET patient with the function in general STEMI patients.

The results of platelet function tests are shown in Table. At each hospitalization, the platelet function on arrival was similar to that in general STEMI patients, except for the slightly higher PL-AUC levels in our ET patient [1st, 482.6; and 2nd, 473.4 vs. general, 402 (median)]. The PL-AUC levels during PPCI in this ET patient remained high [1st, 472.8; and 2nd, 457.7 vs. general, 110 (median)], although the PL-AUC level decreased from arrival to during PPCI in general patients. The AR-AUC levels during PPCI were also higher in our ET patient [1st, 1,023.5; and 2nd, 1,692.4 vs. general, 10 (median)]. The PRU levels during PPCI were relatively low [1st (no P2Y12 inhibitor), 146; and 2nd (prasugrel), 185], but both inhibition rates were 0%. The ARU levels during PPCI indicated aspirin resistance (1st, 662; and 2nd, 660). The PL-AUC levels 2 weeks after admission were acceptably low [1st, 7.1; and 2nd, 11.3 vs. general, 97 (median)]. The PRU and ARU levels after two weeks also indicated sufficient effects of antiplatelet drugs.

Discussion

The most appropriate antithrombotic (antiplatelet and anticoagulant) therapy in AMI patients with ET remains unclear. Several studies have reported that the platelet function measured by the VerifyNow system is effectively suppressed after a sufficient DAPT duration in patients with ET, as well as in general cardiovascular patients (11, 12). However, to our knowledge, no data are available concerning the platelet function during the acute phase of STEMI in patients with ET.

The present case revealed that a patient with ET had high thrombogenicity during PPCI compared with general patients. In general, in STEMI patients, platelet-derived thrombogenicity (PL-AUC) decreases from arrival to during PPCI. The decreased levels of PL-AUC during PPCI can be explained by the effect of fast-acting antithrombotic agents, such as aspirin and unfractionated heparin (10). However, in the present ET patient, the PL-AUC levels remained high during PPCI. This ET patient also had high ARU and AR-AUC levels during PPCI, unlike general patients, suggesting that the effects of aspirin and heparin were insufficient. Thrombocytosis has been reported to cause aspirin and heparin resistance (13, 14). The effect of prasugrel during PPCI was insufficient, as with general STEMI patients (10). In patients with ET, it is necessary to be alert for acute coronary occlusion during the acute phase of STEMI because of its high thrombogenicity. T-TAS-based high throm-

bogenicity in STEMI patients with ET may reflect high thrombogenicity in ET itself and resistance of antithrombotic drugs accompanying ET. T-TAS might be useful for evaluating thrombogenicity for patients with a special pathophysiology showing an abnormal platelet function (e.g. ET). However, the PL-AUC, PRU, and ARU levels two weeks after admission were acceptably low, suggesting that antiplatelet therapy was effective. These results were consistent with those of previous reports regarding the responsiveness to antiplatelet therapy in patients with ET (11).

Several important points concerning treatment strategies in AMI patients with ET should be mentioned. First, stent implantation in patients with ET carries a higher risk of stent thrombosis than usual (2). Patients with ET often suffer from AMI caused by thrombus formation without associated coronary atherosclerosis. The mechanism has been reported to be based on endothelial dysfunction, a reduced coronary flow reserve, and adenosine diphosphate (AD)-induced platelet aggregation (15, 16). In this situation, aspiration thrombectomy or intracoronary thrombolysis without stent implantation might be optimal. In the present case, we did not perform stent implantation based on the angiographic and intracoronary imaging findings (17, 18). A recent study suggested that percutaneous coronary intervention (PCI) with drug-eluting stents (DES) may be effective and safe even in patients with ET (11). Second, cytoreduction is crucial for preventing recurrent thrombotic events in high-risk patients with ET (19). According to the International Prognostic Score of Thrombosis for Essential Thrombocythemia (age >60 years old, cardiovascular risk factors, previous thrombosis, and a JAK2-V617F mutation) (19), this patient was at an extremely high risk of thrombotic events. In addition to poor compliance with antiplatelet drugs, the absence of cytoreductive drugs resulted in recurrent STEMI. However, the administration of antiplatelet drugs can promote bleeding in the setting of AvWS with extreme thrombocytosis (11). Therefore, adequate cytoreduction is an important step for preventing hemorrhagic events in addition to thrombotic events in ET patients receiving DAPT. In the second DES era, stent implantation and DAPT may be effective and safe in ET patients with adequate cytoreduction (11).

Conclusions

The treatment of AMI in patients with ET remains challenging. The present case suggested that PL-AUC and AR-AUC during PPCI measured by T-TAS were not effectively suppressed in STEMI patients with ET, despite the administration of antiplatelet and anticoagulant therapy. A T-TAS might be useful for evaluating thrombogenicity in patients with an abnormal platelet function, such as ET. We should be alert for acute coronary occlusion during the acute phase of STEMI in patients with ET. In the chronic phase, the responsiveness to antiplatelet therapy in patients with ET may be similar to that in general cardiovascular patients; however, insufficient antiplatelet therapy and no cytoreductive therapy are risk factors for recurrent coronary events.

The authors state that they have no Conflict of Interest (COI).

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