Development of Alveolar Hemorrhage in a Patient with Acute Myocardial Infarction Complicated with Essential Thrombocythemia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient:	**Male, 75-year-old**
Final Diagnosis:	**Alveolar hemorrhage**
Symptoms:	**Hemoptysis**
Medication:	**—**
Clinical Procedure:	**—**
Specialty:	**Cardiology • Hematology**

**Objective:** Unusual or unexpected effect of treatment

Background: Essential thrombocythemia (ET) is a risk factor both for bleeding caused by abnormal platelet function and for thrombus formation caused by excessive platelet proliferation. We present a rare case of alveolar hemorrhage after dual antiplatelet therapy (DAPT), a serious bleeding complication of antithrombotic therapy, in a patient with an acute myocardial infarction complicated by ET.

Case Report: A 75-year-old man was treated for ET. He experienced an acute myocardial infarction, and an emergent percutaneous coronary intervention was subsequently performed. DAPT was started just before stent implantation. Because a left ventricular thrombus was suspected in spite of DAPT, anticoagulant therapy with heparin was added. On day 7, a large amount of hemoptysis was observed, and alveolar hemorrhage was diagnosed. Although the antithrombotic treatment was de-escalated from DAPT to single antiplatelet therapy, no stent thrombosis or recurrence of alveolar hemorrhage was observed.

Conclusions: In ET patients, reduced platelet function due to thrombocytosis and strong antithrombotic therapy may cause an excessive bleeding risk. Switching from DAPT to antiplatelet monotherapy at the early stage of stent implantation is a treatment option in situations in which excessive bleeding risk is a concern.

Keywords: Hemorrhage • Platelet Aggregation Inhibitors • Risk Assessment • Thrombocythemia, Essential

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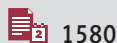
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Background

Antiplatelet therapy for chronic hematological diseases such as thrombocytopenia and thrombocytosis creates a dilemma in clinical practice. Essential thrombocythemia (ET) is a chronic myeloproliferative disease that is characterized by excessive platelet proliferation and can cause thrombus formation. However, patients with ET often have a higher bleeding risk because the increased platelets deplete von Willebrand factor, leading to acquired von Willebrand syndrome [1]. Dual antiplatelet therapy (DAPT) is typically necessary after stent implantation, but in patients with ET, the bleeding risk may be excessive owing to abnormal platelet function. Herein, we report a case of acute myocardial infarction complicated by ET that was successfully treated, without thrombotic complications, by switching from DAPT to single antiplatelet therapy at an early stage of stent implantation.

Case Report

A 75-year-old man with sudden chest pain was admitted to the Emergency Department of our hospital. The patient had a prior medical history of ET, which was treated with oral anagrelide to prevent thrombosis. Before anagrelide was administered, the patient's white blood cell count was 14 070/μL, hemoglobin was 13.6 g/dL, and platelet count was 1 027 000/μL. Other coronary risk factors of the patient were hypertension and current smoking. The patient's vital signs at the time of admission were blood pressure, 96/76 mm Hg; heart rate, 75 beats/min;

peripheral capillary oxygen saturation, 98%; and body temperature, 36.3°C. No abnormal findings were observed on physical examination, and his body weight was 60.4 kg. His white blood cell count was 21 600/μL, hemoglobin was 12.8 g/dL, and platelet count was 631 000/μL. Prothrombin time and activated partial thromboplastin time were normal. An electrocardiogram revealed ST-segment elevation in I, aV_L, and V1-5.

After loading doses of aspirin (200 mg) and clopidogrel (300 mg) were administered, emergent coronary angiography was performed and a total occlusion of the proximal left anterior descending artery was confirmed. Subsequently, percutaneous coronary intervention (PCI) was performed with heparin (**Figure 1**). Intravascular ultrasound revealed the presence of plaque rupture at the culprit lesion. A drug-eluting stent (Xience Alpine 3×15 mm) was implanted at the lesion site, and the procedure was completed at Thrombolysis in Myocardial Infarction grade 3. Postoperative maximal creatine kinase increased to 1864 U/L. Maintenance doses of aspirin 100 mg/d and clopidogrel 75 mg/d were started. In addition, the patient continued to receive anagrelide for ET.

Immediately after PCI, pulmonary edema was observed; therefore, noninvasive positive pressure ventilation was required. Diuretics were also administered, and pulmonary edema was improved the following day. On day 3, because echocardiography results were suggestive of left ventricular thrombus in spite of DAPT, heparin administration was started at a dosage of 10,000 U/d. However, on day 5, a chest computed tomography revealed ground-glass opacity in the bilateral lung field,
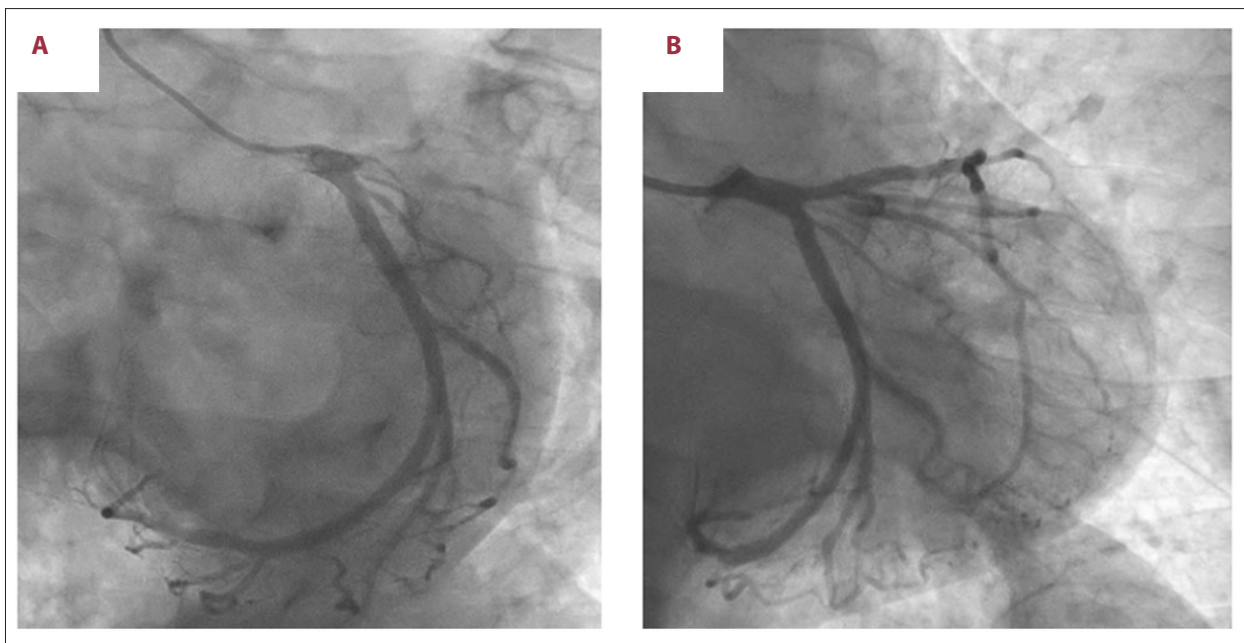

Figure 1. Left coronary angiography. (**A**) Emergent coronary angiogram showed total occlusion in the proximal left anterior descending artery. (**B**) Successful coronary angioplasty with a drug-eluting stent.
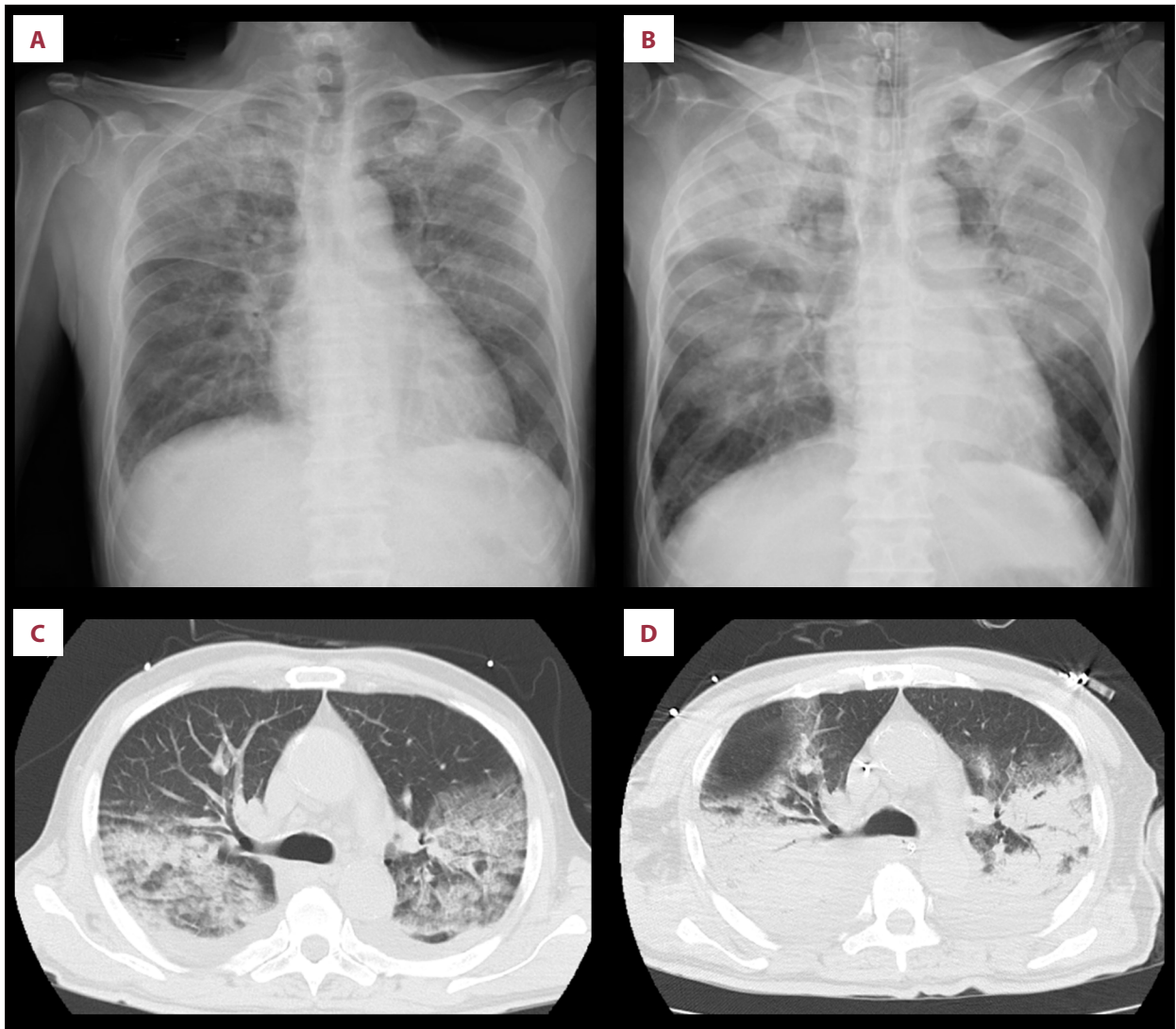
Figure 2. (**A**) The X-ray on day 5 showed decreased permeability in the pulmonary apex region predominance. (**B**) The decreased permeability worsened on day 7. (**C**) Chest computed tomography revealed ground-glass opacity with partial consolidation in the bilateral lung field on day 5. (**D**) The ground-glass opacity effect was even more pronounced on day 7.

and recurrent pulmonary edema or alveolar hemorrhage was suspected (**Figure 2**). Heparin administration was subsequently discontinued because of the possibility of alveolar hemorrhage. The diuretics were continued and noninvasive positive pressure ventilation was restarted in order to improve the patient's respiratory condition. A large amount of hemoptysis occurred on day 7, and tracheal intubation and ventilator management were required. Bronchoscopy also revealed tracheal bleeding (**Figure 3**). The deterioration of his respiratory status was caused by alveolar hemorrhage. In addition to abnormal platelet function due to ET, platelet activity seemed to be strongly suppressed by administration of DAPT plus anagrelide. Given the resultant susceptibility for bleeding, the anticoagulant action of heparin was suspected to have caused the alveolar hemorrhage. We investigated whether the patient had

any other diseases, such as vasculitis, that could cause alveolar hemorrhage, but none was found. Despite the risk of stent thrombosis, we judged that it was impossible to continue DAPT in this patient due to the abnormal platelet function. Aspirin was discontinued, and antithrombotic therapy was switched to clopidogrel monotherapy (**Figure 4**). Anagrelide was also temporarily discontinued. Steroid pulse therapy was administered to address alveolar hemorrhage. Afterward, the patient's respiratory status gradually improved, and he was extubated on day 14. There was no occurrence of stent thrombosis or recurrence of alveolar hemorrhage. The patient was discharged on day 41.
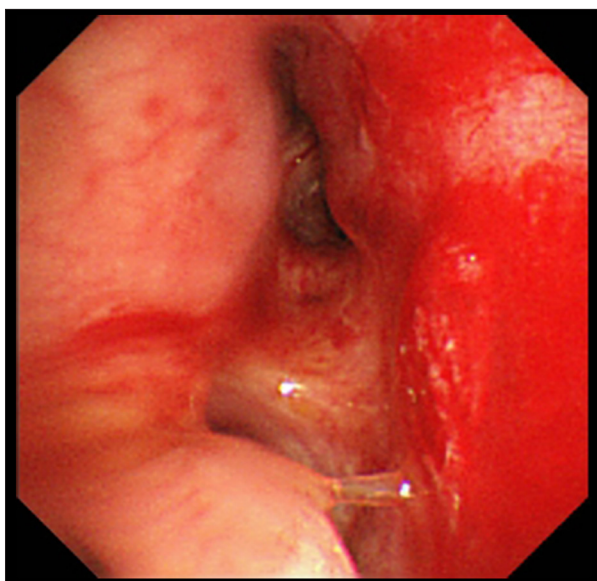
Figure 3. The bronchoscopy image at the time of hemoptysis on day 7. Intratracheal bleeding was observed.

Figure 4. The clinical course of the patient after hospitalization. LV – left ventricular; Plt – platelets; APTT – activated partial thromboplastin time; WBC – white blood cells; Hb – hemoglobin; NPPV – noninvasive positive pressure ventilation.

Discussion

ET is classified as one of the chronic myeloproliferative diseases. Symptoms include thrombus formation due to excessive platelet proliferation, but bleeding can also develop because of platelet activity abnormalities. The incidence of thrombotic events and bleeding events in ET was previously reported to be 11-25% and 3.6-37%, respectively [2]. In particular, it was reported that ET patients with high platelet counts (>1000×109/L=1 000 000/μL) had more hemorrhagic complications than thrombotic complications [3]. However, the risk of bleeding or embolism cannot be predicted by conventional platelet function tests in patients with ET. The preventive effects of thrombosis by anagrelide are due to its platelet-reducing effect and antiplatelet effect [4,5]. Selective action of anagrelide on megakaryocytes inhibits platelet production [4]. The antiplatelet action of anagrelide arises from its effects on a type III phosphodiesterase [5]. Anagrelide possibly promotes bleeding by enhancing the antiplatelet effect. Although the hematologist advised us to continue anagrelide for the treatment of ET, it is possible that anagrelide should be stopped at the start of DAPT for acute myocardial infarction. In the present case, in addition to the increase in left atrial pressure accompanying myocardial infarction, alveolar hemorrhage was thought to have occurred as a result of decreased platelet activity caused by the concurrent administration of DAPT, anagrelide, and heparin, with a high bleeding risk due to ET. Because left ventricular thrombus was suspected in spite of DAPT, adding anticoagulation therapy with heparin was necessary. We should have considered the de-escalation of antiplatelet therapy at this point. It is extremely rare for alveolar hemorrhage to occur following antiplatelet drugs after
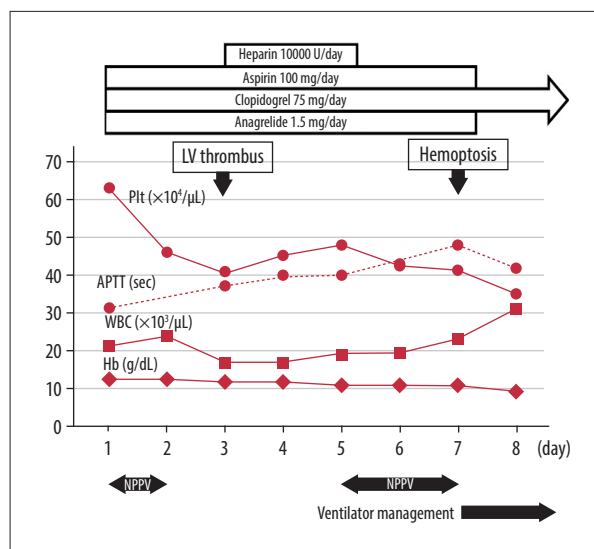
PCI. Glycoprotein IIb/IIIa inhibitors, in combination with other antiplatelet drugs, were the drugs most commonly associated with alveolar hemorrhage, and the frequency of alveolar hemorrhage was reported to be 0.27% of all patients who underwent coronary angiography and received abciximab [6]. Therefore, in the present case, it seemed that the susceptibility for bleeding due to ET also significantly influenced the development of alveolar hemorrhage.

The mutations in patients with ET have been reported to be associated with thrombogenicity. In particular, the JAK2V617F mutation is associated with a high risk of thrombosis and represents one of the predictors of thrombosis [7,8]. It was also reported that ET patients with a CALR mutation have a lower risk of thrombosis than with other mutations [7]. Unfortunately, we have no data about mutations in our patient; however, the detection of mutation might have been useful in deciding the antithrombotic therapy.

Both the European Society of Cardiology guidelines [9] and the American College of Cardiology/American Heart Association guidelines [10] recommend administering DAPT for 6-12 months following an acute coronary event. However, shortening the DAPT period is necessary when the bleeding risk is high. Recently, the Academic Research Consortium noted high bleeding risks in patients undergoing PCI [11]. Furthermore, the Japanese guidelines indicated additional factors for high risk of bleeding such as low body weight and/or frailty, heart failure, and peripheral vascular disease [12]. Our patient met 2 minor criteria for a high risk of bleeding (age over 75 years and hemoglobin 11-12.9 g/dL)

and 1 Japanese major criterion (heart failure); therefore, he was judged to have a high bleeding risk. In the Academic Research Consortium white paper [11], moderate or severe baseline thrombocytopenia (platelet count <100×10^9/L=100,000/μL) is considered indicative of a major high bleeding risk. However, a bleeding risk due to thrombocytosis that causes platelet dysfunction is not mentioned. When antithrombotic therapy is being decided after PCI, it is necessary to recognize that patients with thrombocytosis caused by a chronic myeloproliferative disease have an additional bleeding risk. Although there have been several case reports of stent thrombosis in patients with acute myocardial infarction complicated by ET [13,14], we found no reports on serious bleeding complications, including alveolar hemorrhage, after stent implantation in patients with ET. Spontaneous bleeding events were reported to worsen mortality risk after PCI, and that risk was comparable to that due to myocardial infarction [15]. The mortality rate of diffuse alveolar hemorrhage was reported to be 24.7% [16]. Additionally, in the STOPDAPT-2 study conducted in Japan, 1 month of DAPT significantly reduced the rate of combined cardiovascular and bleeding events compared with 12 months of DAPT without an increase of thrombotic events [17]. The study revealed that the incidence of definite or probable stent thrombosis was 0.27% in the 1-month DAPT group. Because the risk of stent thrombosis associated with the implantation of a second-generation

drug-eluting stent is low, it may be more important to focus on managing the risk of bleeding. It is necessary to pay attention to the risks of both thrombotic and hemorrhagic complications when deciding on antithrombotic therapy and to consider factors such as whether the patient has a high risk of bleeding, whether additional antithrombotic therapy such as heparin is needed, and what is the thrombotic risk if DAPT is stopped. When considering the risk of bleeding, it is important to remember that excessive thrombocytosis is one of the additional risk factors for bleeding. In the present case, we switched from DAPT to an antiplatelet monotherapy 1 week after PCI, and the patient had no thrombotic complications such as stent thrombosis and no recurrent bleeding events.

Conclusions

It is necessary to make careful judgments based on individual background with respect to how to prevent the onset of stent thrombosis without hemorrhagic complications in patients with chronic myeloproliferative disease such as ET.

Conflict of Interest

None.

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