A Case of Intraprocedural Thrombotic Events During Percutaneous Coronary Intervention Due to Acquired Antithrombin Deficiency-related Heparin Resistance Successfully Treated with Antithrombin Gamma Supplementation

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Abstract:
A 75-year-old man receiving treatment for necrotizing pancreatitis developed septic disseminated intravascular coagulation and acute coronary syndrome (ACS). During percutaneous coronary intervention (PCI), a large amount of fresh thrombi appeared after balloon dilatation for the ACS-culprit lesion. Given the low plasma AT activity and poorly prolonged activated clotting time (ACT), we suspected that acquired AT deficiency-related heparin resistance (HR) was responsible for the thrombus formation. Administration of AT gamma markedly improved ACT, and we successfully completed PCI. We suggest that AT gamma be considered a treatment option for AT deficiency-related HR and subsequent intraprocedural thrombotic events.

Key words: antithrombin deficiency, heparin resistance, antithrombin gamma, intraprocedural thrombotic event, percutaneous coronary intervention

Introduction
Intraprocedural thrombotic events (IPTEs), the unexpected thrombus formation during percutaneous coronary intervention (PCI), is a rare but serious complication associated with a poor prognosis (1). Among possible mechanisms of IPTEs, heparin resistance (HR) is clinically important, as unfractionated heparin (UFH) is the most standard anticoagulation agent during PCI (2). Antithrombin (AT) deficiency, which can complicate patients requiring PCI under some conditions, is a representative cause of HR (3). Although IPTEs with AT deficiency-related HR have been documented (4, 5), appropriate management has not been established.

We herein report a case of an IPTE due to acquired AT deficiency-related HR successfully treated with AT gamma, a recombinant form of human AT.

Case Report
A 75-year-old Japanese man was transferred from a local hospital to our intensive-care unit with a diagnosis of necrotizing pancreatitis. He had smoked 40 cigarettes per day for 50 years. Despite having no medical history of cardiovascular disease, his initial electrocardiogram (ECG) showed reversed R-wave progression in precordial leads, indicating old anterior myocardial infarction (Fig. 1A). After admission, he was treated with antibiotics and endoscopic catheter drainage of pancreatic necrosis.

On day 8 of admission, he suddenly presented with bradycardia and dyspnea. His vital signs were as follows: a body temperature of 38.2 °C, blood pressure of 74/52 mmHg, pulse rate of 50 beats per minute, and oxygen saturation of 91% on 5 L/min oxygen. Laboratory tests revealed elevated values for the white blood cell count (10,900/μL),...
Figure 1. (A) Initial electrocardiogram (ECG) findings on admission showing reversed R-wave progression in precordial leads, indicating the presence of old anterior myocardial infarction. (B) On day 8 of admission, an ECG revealed new-onset ST elevation in the inferior leads and complete atrioventricular block.

Figure 2. Emergent coronary angiography showed sub-occlusion of the proximal right coronary artery (A). Intravascular ultrasound (IVUS) revealed a hypoechoic plaque with attenuation, suggesting a vulnerable plaque (asterisk) at the culprit lesion without visible thrombus (B). Although coronary flow was temporarily improved after balloon dilatation (C), the culprit lesion became reoccluded only a few minutes later (D). Repeated IVUS detected the appearance of a lobulated hypoechoic mobile mass (asterisk), indicating fresh thrombi (E). After antithrombin gamma supplementation, we obtained an appropriate anticoagulation status and implanted a stent without secondary thrombus formation (F).

C-reactive protein level (12.8 mg/dL), and presepsin level (1,342 pg/mL), implying the presence of sepsis. Furthermore, elevated fibrin degradation products (45.8 μg/mL), a high prothrombin time-international normalized ratio (1.41), and low AT activity (49%) indicated coagulation disorder, although the platelet count was within the normal limit.

An ECG showed new-onset ST elevation in inferior leads and complete atrioventricular block (Fig. 1B). Transthoracic echocardiography visualized a reduced left ventricular ejection fraction of 25% with local hypokinesia in the inferior wall and local dyskinesia in the anterior wall. Based on these findings, he was diagnosed with acute inferior and old anterior myocardial infarction, complicated by cardiogenic shock and septic disseminated intravascular coagulation (DIC) following necrotizing pancreatitis.

To stabilize the hemodynamics, we inserted an intra-aortic balloon pump (IABP) and a temporary pacemaker. Coronary angiography revealed sub-occlusion of the proximal right coronary artery (RCA) (Fig. 2A); we then started emergent PCI for the RCA. Just prior to PCI, dual antiplatelet agents (200 mg of aspirin and 20 mg of prasugrel) and a bolus of 8,000 units of UFH were administered. Intravascular ultrasound (IVUS) showed a hypoechoic plaque with deep ultrasound attenuation, suggesting a vulnerable plaque at the culprit lesion without visible thrombus (Fig. 2B). Following 3.0-mm balloon dilatation, thrombolysis in myocardial in-
A timeline showing the temporal changes in the activated clotting time, anticoagulation therapy, intravascular thrombi, and procedure during percutaneous coronary intervention.

Discussion

Despite advances in the development of PCI devices, techniques, and antithrombotic therapy, IPTEs still occur, resulting in high morbidity and mortality (1). Therefore, understanding the mechanism and management of IPTEs is a clinically essential issue. To our knowledge, this is the first case report of IPTEs occurring during PCI due to acquired AT deficiency-related HR that were successfully treated with AT gamma supplementation.

IPTEs have been defined as developing a new or increasing thrombus, acute vessel closure, no-reflow/slow flow phenomenon, or distal embolization occurring during the PCI procedure (1). In this case, fresh thrombi appeared unexpectedly soon after balloon dilation, and several mechanisms were considered to potentially have led to IPTEs. First, vulnerable atherosclerotic plaques that cause acute coronary syndrome (ACS) typically contain a large amount of tissue factor, a trigger of the coagulation cascade (6). In our case, the mechanical destruction of the prothrombotic factor-rich plaque by balloon dilation may have induced a massive coagulative reaction. Second, platelet aggregation may not have been adequately inhibited because dual antiplatelet therapy was initiated just before the PCI procedure. Finally, the patient had ineffective anticoagulation due to HR with low plasma AT activity. In the emergent PCI to vulnerable plaques without antiplatelet pretreatment, a sufficient anticoagulation status should be obtained before balloon dilatation or stenting to prevent IPTEs.

UFH is the most widely used anticoagulation agent during PCI. However, HR, defined as a poor anticoagulation response to a standard therapeutic dose of heparin (70-100 units/kg initial bolus and additional 2,000-5,000 units if necessary to achieve an ACT of 300-350 seconds in Hemochron devices (2, 3)), can be observed under several conditions. In our case, we suspected that acquired AT deficiency due to septic DIC was the primary pathophysiology. AT is a natural inhibitor of the coagulation cascade, and heparin expresses the AT-dependent anticoagulation effect; therefore, decreased
AT activity can be a cause of HR (3). As a cause of AT deficiency, septic DIC before PCI was considered. Septic DIC consumes AT by activating the coagulation cascade and promoting fibrin precipitation, resulting in HR and an increased risk of IPTEs (7). When we encounter a case of IPTEs with a poorly prolonged ACT, AT deficiency-related HR should be considered as a differential diagnosis.

While there is no consensus regarding the optimum treatment of AT deficiency-related HR during PCI, two reasonable choices have been proposed: AT-independent thrombin inhibitors, such as argatroban, or AT supplementation therapy (3). Argatroban is a direct thrombin inhibitor commonly used to treat HIT, which can be another cause of IPTEs. Although a previous report documented the effectiveness of argatroban for stent thrombosis in a similar situation (4), there has been little evidence regarding AT deficiency-related HR thus far. Therefore, argatroban may be more suitable in IPTE cases with definite or suspected HIT. In contrast, the efficacy and safety of AT supplementation therapy for AT deficiency-related HR have been evident, especially in cardiovascular surgery (8). Furthermore, AT supplementation therapy was developed as a standard treatment for septic DIC in Japan (7, 9). Because of the extremely low plasma AT level in our patient, we selected AT supplementation therapy as a first-line strategy and considered argatroban as the next treatment option. On reviewing the patient’s condition since admission, it is apparent that the patient was susceptible to septic DIC before PCI; we therefore should have predicted and prepared for AT deficiency-related HR and subsequent IPTE beforehand. If we can recognize DIC and/or AT deficiency before PCI, preoperative AT supplementation, careful ACT monitoring, and preparation of argatroban might be effective in preventing cardiac events due to IPTE.

In the present case, AT gamma proved very effective in increasing the AT activity, improving the heparin response, and preventing subsequent thrombus formation. AT gamma is a novel recombinant AT characterized by a pathogen-free, long-active, stable supply and has an equivalent therapeutic effect to plasma-derived AT (10). This report focused on a unique AT deficiency-related HR case with a special background including septic DIC, so whether or not this AT gamma supplementation strategy can be applied to other situations is unclear. While the further accumulation of experience is needed, we suggest that AT gamma be considered as a treatment option for AT deficiency-related HR and subsequent IPTEs during PCI.

In conclusion, we experienced a rare case of IPTEs during PCI due to acquired AT deficiency-related HR successfully treated with AT gamma. When we cannot achieve an ideal coagulation level during PCI despite using a sufficient dose of UFH, HR and underlying AT deficiency should be considered. AT gamma may aid in treating AT deficiency-related HR and subsequent IPTEs.

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

References