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Case Study

ATYPICAL CLINICAL PRESENTATION OF THROMBOTIC THROMBOCYTOPENIC PURPURA JUST AFTER PERCUTANEOUS CORONARY INTERVENTION

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Abstract Thrombotic thrombocytopenic purpura (TTP) is a life-threatening illness associated with cardiovascular surgery, infection and medications. We report a case of a 77-year-old female patient with acute myocardial infarction (AMI) treated with percutaneous coronary intervention and suffered TTP immediately afterwards. This was successfully treated with plasma exchanges. Differential diagnosis of the thrombocytopenia was important and assays for the activities of von Willebrand Factor-cleaving protease, its inhibitor and heparin-induced thrombocytopenia (HIT) antibody were helpful to differentiate TTP from other conditions, including HIT and disseminated intravascular coagulation. Intensivists should be aware of an atypical presentation of TTP associated with AMI.

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Key words: thrombocytopenia; thrombotic thrombocytopenic purpura; heparin induced thrombocytopenia; ADAMTS13; plasma exchange.

症例研究

経皮的冠動脈形成術後に発症し非典型的臨床所見を呈した血栓性血小板減少性紫斑病の１例

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抄録　急性心筋梗塞に対する経皮的冠動脈形成術後に急激な血小板の減少を来たし，血漿交換により救命した血小板減少性紫斑病（thrombotic thrombocytopenic purpura：TTP）の症例を経験したので報告する．

症例は77歳女性．急性心筋梗塞の診断により経皮的冠動脈形成術を施行されICUに入室した．ICU入室直後より血小板減少（13.3×10^4/μl→1.9×10^4/μl）を来たし，ヘパリン誘発性血小板減少症が疑われた．高度凝固線溶障害，肝・腎機能障害を認めた．明らかな溶血性貧血，精神症状は認めなかった．ヘパリン投与中止後も血小板の改善を認めず，第６，７病日に血漿交換を施行した．血漿交換施行当日より血小板の増加を認め，第９病日一般病棟へ帰室となった．血漿交換施行以前に採取した血液よりADAMTS13活性の低下およびADAMTS13 inhibitor活性の上昇が判明し，TTPと診断した．

TTPは急激な血小板の減少を来たすが凝固能障害は軽度にとどまるとされ，本症例の検査結果と矛盾したため診断に難渋した．ADAMTS13およびADAMTS13 inhibitorの測定がTTPと血小板減少をきたす疾患との鑑別に有用であった．

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening illness associated with infection, medication, and cardiovascular surgery. In a patient who suffered acute myocardial infarction (AMI), platelet count was markedly decreased immediately after an emergent percutaneous coronary intervention (PCI) under systemic heparinization. We initially diagnosed the thrombocytopenia as heparin-induced thrombocytopenia (HIT), but this was subsequently re-diagnosed as TTP during the clinical course.

Case

A 77-year-old woman presented to our Emergency Department, complaining of a 4-day history of chest pain. Electrocardiographic examination revealed ST-segment elevations and abnormal Q waves in V1-V6. Blood concentration of creatine kinase (CK), CK isoenzyme with muscle and brain subunits and troponin T were elevated. Following the diagnosis of AMI, aspirin and ticlopidine were administered as anti-platelet therapies just before coronary angiography. Emergent coronary angiography revealed total occlusion in the middle segment of the left anterior descending artery (LAD). Subsequently, bare metal stent was successfully deployed and intra-aortic balloon pumping (IABP) was required. Thereafter, a low cardiac output state (cardiac index 1.2 l/min/m^2), associated with a high cardiac filling pressure (pulmonary capillary wedge pressure 18 mmHg), was recognized.

Following PCI, the patient was transferred to the intensive care unit (ICU). There was no symptom to suspect TTP such as purpura, thrombocytopenia or neurological abnormalities. However, the platelet count had markedly decreased from 13.3×10^4/μl to 1.9×10^4/μl over 12 hours in the ICU. HIT was suspected because the patient had received a bolus injection of 8000 units of heparin during PCI and subsequent continuous intravenous infusion of heparin (400 U/hr). Therefore, we discontinued administration of heparin, and argatroban therapy (20 mg/day) was started.

Apparent pericardial effusion due to oozing type cardiac rupture was detected by transthoracic echocardiography and five units of concentrated platelets were transfused on the 2nd day in the ICU. In addition, acute renal failure, severe liver damage and coagulopathy were present (table 1). Continuous hemodiafiltration was commenced on the 3rd day and continued for the subsequent 7 days because of oliguria (<0.2 ml/kg/hr) and elevation of plasma creatine (3.4 mg/dl). Five units of fresh frozen plasma had been transfused for 3 days for treatment of the coagulopathy since the 3rd day. In spite of the discontinuation of heparin, platelet counts did not increase, with the lowest value of 0.1×10^4/μl in the 3rd day, and the coagulopathy did not improve even 5 days after discontinuation (Figure 1 and Table 1). As the treatments based on the diagnosis of HIT had not been effective, plasma exchange (PE) on the 6th and 7th day was performed according to several case reports demonstrating the effectiveness of PE on HIT[1-3]. Platelet counts increased dramatically in response to PE. However, on the 6th day it was found that the antibody for complexes of platelet factor 4 (PF4) and heparin (HIT antibody) were not detectable. IABP could be removed without complication on the 9th day. The patient was moved to the ward from ICU on the 13th day. On the 16th day, from analysis of day 6 blood, it was found that there was a deficiency in von Willebrand factor (vWF) -cleaving protease ADMATS13 (A Disintegrin-like And Metalloprotease with Thrombospondin type I repeats-13) activity, with the activity of less than 0.5%. Moreover, the activity of its

Table 1 laboratory data during the clinical course

	Day1	Day 2	Day 5	Day 12	Day 23
Hb (g/dl)	10.7	9.3	9.2	7.9	8.4
Ht (%)	33.0	28.1	29.0	24.6	24.7
Platelet (/μl)	$13.3x10^4$	$0.5x10^4$	$1.0x10^4$	$5.9x10^4$	$27.6x10^4$
PT (sec)/INR		15.9/1.96	29.2/5.83	12.0/1.20	11.7/1.15
APTT (sec)		82.4	101.7	43.8	27.8
Fibrinogen (mg/dl)		247	289	305	257
FDP (μg/ml)		11.9	28.9	74.3	16.1
ATIII (%)		64	98	62	66
D-dimer (μg/ml)		5.3	19.0	-	15.2
TAT (μg/ml)		97.3	64.8	-	9.7
BUN (mg/dl)		42	49	43	-
Cre (mg/dl)		1.7	2.4	2.6	0.8
AST (U/l)		2904	4298	50	28
ALT (U/l)		2127	892	12	13
LDH (U/l)		3661	2461	-	244
CK (U/l)		2976	708	135	23
CK-MB (U/l)		184	378	23	5

PT: prothrombin time, APTT: activate partial thrombin time,
FDP: fibrinogen and fibrinogen degradation products, AT III: antithrombin III,
TAT: thrombin/antithrombin complex, BUN: blood urea nitrogen,
Cre: creatinine, AST: aspartate aminotransferase, ALT: alanin aminotransferase,
LDH: lactate dehydrogenase, CK: creatine phosphokinase,
CK-MB: isoenzyme of creatine phosphokinase with muscle and brain subunits.

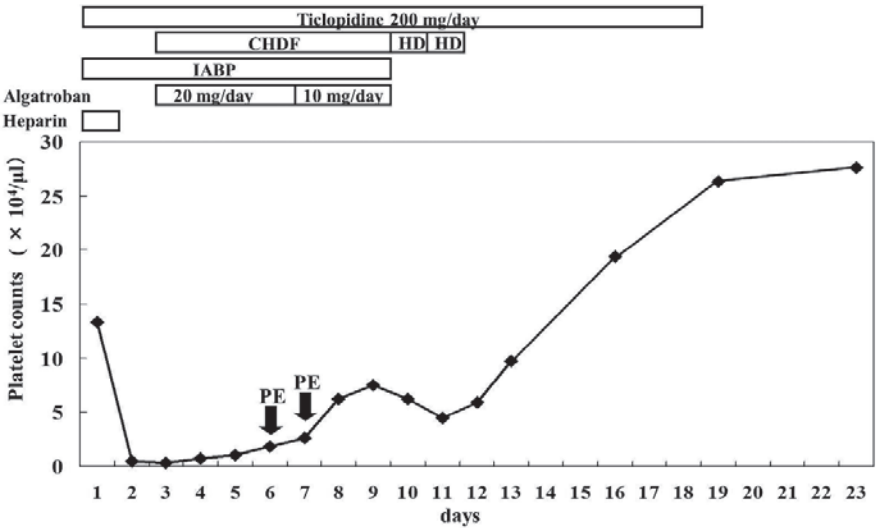

Figure 1 Changes in platelet counts and the clinical course

Platelet count was markedly decreased just after the percutaneous coronary intervention, and the thrombocytopenia persisted until plasma exchange (PE) was initiated. Ticlopidine was administered to the patient as an anti-platelet therapy. CHDF: Continuous hemodiafiltration, HD: Hemodialysis, IABP: Intra-aortic balloon pumping

inhibitor was elevated to 115.2 Bethesda.U/ml. Thrombocytopenia was finally diagnosed as TTP. By the 16th day, her platelet counts had already increased to the normal range, and additional PE was not required. ADAMTS13 and its inhibitor returned to the normal range (ADAMTS13 106.6% and its inhibitor <0.5 Bethesda.U/ml) in blood taken on the 23rd day.

She was discharged from our hospital without complication on the 71st day.

Discussion

We report a patient who had an acute episode of thrombocytopenia following PCI for AMI. Although this was finally diagnosed as TTP, HIT was suspected at the beginning of her clinical course because of heparin usage during and after the PCI. Assays for the activity of ADAMTS13 and its inhibitor were useful in the diagnosis of TTP. Coincidentally, PE was performed before diagnosis of TTP was made. This was very effective and probably saved the patient.

TTP is an acute syndrome characterized by abnormalities in multiple organ systems. Identification of the first episode of TTP is considered very challenging because of the great variation in presenting features and the potential confusion with other diseases such as HIT and DIC[4]. It has been known that TTP patients express five clinical signs: thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, renal dysfunction and fever. However, the full range is observed in only 20% of TTP[5]. In this case, thrombocytopenia, renal dysfunction and microangiopathic hemolytic anemia were detectable. The peripheral blood smear showing microangiopathic hemolysis with schistocytes could suggest TTP, but schistocytes are also seen somewhat in patients with IABP.

There are two types of HIT. Type I HIT is caused by non-immune mechanisms as a result of the physical and biological features of heparin. Type II HIT is caused by an immune mechanism in which a heparin-specific auto-antibody of the IgG class (HIT antibody) is involved. HIT antibody recognizes complexes of PF4 and heparin, and activates platelets. Type II HIT typically occurs approximately 10 days after the commencement of heparin therapy[6]. However, earlier onset of HIT can be seen in type II HIT if the patient was treated with heparin in the previous three or four months. We suspected the present thrombocytopenia as a HIT, though it was found several days after the admission to the ICU that the patient did not have any past history of heparin treatment. In addition, use of a pretest-scoring system to diagnose HIT[7], yielded just one diagnostic criteria for HIT. In retrospective consideration, we should have suspected other causes of thrombocytopenia such as TTP.

DIC was another possible etiology consistent with her symptoms of thrombocytopenia and coagulopathy. Usually coagulation studies are helpful in differentiating TTP from DIC because TTP tends to show normal levels of the coagulation components and little or no prolongation of the PT or APTT[8]. However, her coagulation studies were far from the normal range making it difficult to diagnose TTP. Severe liver damage following cardiogenic shock would have a significant impact on her pathology.

Assays for the activity of ADAMTS13 and its inhibitor were useful to differentiate TTP from other conditions in the present case. ADAMTS13 activity is typically absent or severely decreased in patients with TTP, and its inhibitor has been found at varying titers among a high percentage of patients with idiopathic TTP who have severe ADAMTS13 decrease[9]. However, a decrease in ADAMTS13 is not specific for TTP, since it is also found in DIC[10], thrombocytopenic disorders different from TTP[11], various acute inflammatory conditions, liver cirrhosis, uremia, late stages of pregnancy and in the newborn[12]. Bianch and the colleagues suggested that severe decrease in ADAMTS13 (< 5% of normal range) was about 90% sensitive and specific for TTP[13]. However, assays adaptable in clinical laboratories are no available yet. It also took about five days to measure

activities of ADAMTS13 and its inhibitor in this case. Therefore, a delayed ADAMTS13 activity measurement and testing for its inhibitors would be performed in order to retrospectively document the definitive diagnosis.

One third of TTP cases are considered idiopathic, and etiologies of the other TTP cases are related to various clinical situations such as cardiovascular surgery, malignant disease, autoimmune disorders, infection and several medications[14]. Ticlopidine is one of the suspected medications. The present patient received this immediately after AMI diagnosis. Ninety percent of ticlopidine-induced TTP is reported to occur within 2 weeks of initiation of ticlopidine therapy with the remaining 10% occurring within 12 weeks[15]. Ticlopidine was unlikely to be the pathogen of TTP in this patient because of its continuous administration over this clinical course of TTP even after PE treatment.

Several case reports have described AMI as a possible complication in patients with TTP[16-17]. TTP can occur following coronary artery bypass graft surgery[18-19] and percutaneous coronary intervention[5]. As we could not find any causes of TTP before AMI in this case, AMI and procedures related to PCI were suspected to be involved in the onset of TTP.

Platelet transfusion for thrombocytopenia is theoretically considered as a contraindication in patients with TTP or HIT because of deteriorating thrombotic complications. However, 5 units of concentrated platelets were administered to it following echocardiographic examination. Indications for platelet transfusion must be carefully considered with respect to the complication of bleeding.

Conclusion

We experienced a case in which TTP occurred just after PCI for AMI under systemic heparinization. It was difficult but important to differentiate TTP from HIT because of their differing treatments and indications for platelet transfusion. Assays for HIT antibodies and activities of ADAMTS13 and its inhibitor were useful to diagnose TTP. Intensivists should be aware of atypical presentation of TTP around AMI.

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