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【 CASE REPORT 】

Acquired Factor V Inhibitor Complicated with Immune Thrombocytopenia

Fuka Mima[1], Ryota Minami[1], Mizuki Asako[1], Hitomi Matsunaga[1], Yuri Fujita[2], Yoshimi Takimoto[2], Sonoko Senda[2], Wataru Nakahara[1], Mako Ikeda[1] and Shuji Ueda[1]

Abstract:
We herein report a patient with a high bleeding tendency as a result of acquired factor V inhibitor and immune thrombocytopenia (ITP). The administration of prednisolone increased the platelet count, but a fatal bleeding event occurred before platelet levels had sufficiently increased. Factor V is stored in not only plasma but also platelets, and platelet-derived factor V might play a local hemostatic role. Bleeding tendency may be high in rare cases where factor V inhibitor is complicated with severe thrombocytopenia. In such patients, physicians should consider aggressive hemostatic therapy, including plasma exchange, in addition to immunosuppressive therapy.

Key words: acquired factor V inhibitor, immune thrombocytopenia, platelet-derived factor V, fatal hemorrhaging

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Introduction

Acquired factor V inhibitor is a rare coagulation disorder. The associated hemorrhagic manifestations vary and range from asymptomatic to life-threatening bleeding (1, 2). The reasons for this range of symptoms are gradually being clarified, but the details remain to be elucidated (3).

Functionally important factor V is found in not only plasma but also the alpha granules of platelets, and platelet-derived factor V may play a local hemostatic role in patients with factor V inhibitor (4). Comorbid thrombocytopenia in patients with factor V inhibitor might exacerbate bleeding symptoms.

We herein report a patient with acquired factor V inhibitor and immune thrombocytopenia (ITP) who died of intracranial hemorrhaging.

Case Report

A 71-year-old Japanese woman was referred to our hospital with numerous petechiae and ecchymoses, as well as melena. Her medical history included hypertension, hyperlipidemia, and cerebral infarction. She had no history of bleeding tendency and no significant family history of a bleeding disorder. A hematological examination performed five months before admission showed no abnormal changes, but the patient experienced progressive fatigue and weight loss in the two months before admission. A few days after noticing petechiae and ecchymoses over her entire body, she consulted her family physician. A blood examination revealed anemia and severe thrombocytopenia, and the patient was immediately admitted to our hospital.

On admission, she was conscious, and her vital signs were unremarkable; however, a physical examination revealed conjunctival pallor and numerous petechiae on her limbs and trunk. A peripheral blood analysis showed a white blood cell count slightly above the reference range (8.8×10^9/L), with a normal differential cell count and a hemoglobin level and platelet count below the reference range (7.0 g/dL and 3×10^9/L, respectively; Table). The reticulocyte count was 2.4%. Routine coagulation tests revealed both a prolonged prothrombin time (international normalized ratio) (PT-INR; 2.68) and a prolonged activated partial throm-

[1]Department of Hematology, Hyogo Prefectural Nishinomiya Hospital, Japan and [2]Department of Clinical Laboratory, Hyogo Prefectural Nishinomiya Hospital, Japan
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Correspondence to Dr. Shuji Ueda, ueda0904@hp.pref.hyogo.jp

Table. **Laboratory Values on Admission.**

Biochemistry		Reference range	Coagulation		Reference range
T-bil, mg/dL	0.46	0.40-1.50	PT, s	33.3	10.5-13.5
AST, U/L	15	13-30	PT (INR)	2.68	0.90-1.10
ALT, U/L	6	7-23	aPTT, s	136.3	24.0-35.0
γGTP, U/L	34	9-32	Fib, mg/dL	556.1	200.0-400.0
LDH, U/L	190	124-222	ATIII, %	90.7	80.0-130.0
CRP, mg/dL	2.92	0.00-0.14	FDP, μg/mL	17.4	<5.0
BUN, mg/dL	21.5	8.0-20.0	D-dimer, μg/mL	8.4	<1.0
Cr, mg/dL	1.03	0.47-0.79	TAT, ng/mL	3.9	<3.0
UA, mg/dL	5.6	2.6-5.5	HPT, %	127	70-130
Na, mEq/L	136	138-145	TT, %	98	≥70
K, mEq/L	3.8	3.6-4.8	**Coagulation factor assay**		
Cl, mEq/L	105	101-108	Factor XII activity, %	49	50-150
Complete blood count			Factor XI activity, %	77	75-145
WBC, 10^9/L	8.8	3.3-8.6	Factor IX activity, %	118	70-130
Hb, g/dL	7.0	11.3-15.2	Factor VIII activity, %	87	60-150
Hct, %	21.0	33.4-44.9	Factor VII activity, %	115	75-140
Plt, 10^9/L	3	150-350	Factor X activity, %	81	70-130
Immunoserology			Factor V activity, %	<3	70-135
Lupus AC (dRVVT)	≥1.68	<1.3	Factor II activity, %	67	75-135
Before adding PL	≥150 s		Factor XIII activity, %	75	70-140
After adding PL	89.5 s		Factor V inhibitor, BU/mL	8	
aCL-IgG, U/mL	15	<10	Factor XII inbibitor, BU/mL	Negative	
aCL-β2GPI, U/mL	<1.2	<3.5	Factor II inbibitor, BU/mL	Negative	

AST: aspartate-aminotransferase, ALT: alanine-aminotransferase, γGTP: γ-glutamyl transpeptidase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, WBC: white blood cells, Hb: hemoglobin, Hct: hematocrit, Plt: platelets, Lupus AC: lupus anticoagulant, dRVVT: diluted Russell's viper venom time, PL: phospholipids, aCL: anti cardiolipin, IgG: immmunoglobulin G, β2GPI: β2 glycoprotein-I, PT: prothrombin time, PT (INR): prothrombin time/international normalized ratio, aPTT: activated partial thromboplastin time, Fib: fibrinogen, ATIII: antithrombin III, FDP: fibrin/fibrinogen degradation products, TAT: thrombin-antithrombin complex, HPT: hepaplastin time, TT: thrombotest

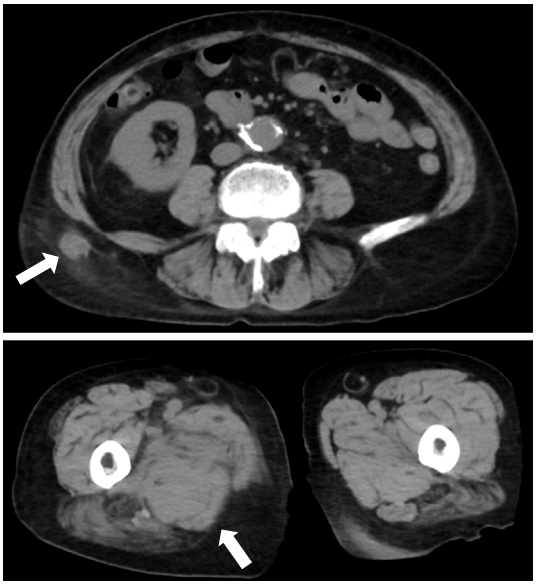

Figure 1. **A computed tomography scan showed subcutaneous hematoma in the right hip (a) and intramuscular hematoma in the right thigh (b).**

boplastin time (aPTT; 136.3 seconds). The plasma levels of fibrin/fibrinogen degradation products (FDP) and D-dimer were elevated (17.4 μg/mL and 8.4 μg/mL, respectively). Antithrombin III (AT III) activity levels were normal, but the thrombin-antithrombin complex (TAT) levels were slightly above the reference range (3.9 ng/mL). A biochemical analysis showed a slight elevation of serum C-reactive protein (CRP; 2.92 mg/dL). Laboratory tests found no indication of hemolysis, such as elevated lactate dehydrogenase (LDH) or total bilirubin. Computed tomography of the whole body showed subcutaneous bleeding in the right hip and intramuscular bleeding in the right thigh (Fig. 1). Gastroduodenoscopy showed oozing blood containing hematin (Fig. 2).

To determine whether the prolonged PT and prolonged aPTT were due to a coagulation factor deficiency or circulating anticoagulant, we performed a mixing study with plasma from the patient and a healthy volunteer. Both PT and aPTT improved to near the reference range immediately after the reaction but were prolonged at two hours after the reaction, indicating the presence of a delayed-type inhibitor. Lupus anticoagulant testing with a dilute Russell's viper venom time (dRVVT) assay was positive (Table), but anticardiolipin β2 glycoprotein-I complex antibodies were negative. In addition, we performed the hepaplastin test (HPT) and thrombotest (TT). The results were within the reference range (Table). Given the discrepancy with the PT test result, this finding was taken to indicate a factor V defi-

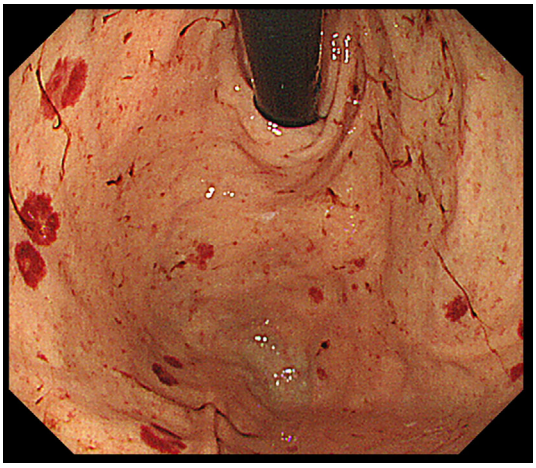

Figure 2. Gastroduodenoscopy revealed oozing blood containing hematin.

ciency (5, 6). We checked the coagulation factor activity profile of factors II, V, X, VII, VIII, IX, XI, XII, and XIII and found no detectable factor V activity. The test for coagulation factor V inhibitor was positive (8 Bethesda U/mL) (Table). Furthermore, to examine the cause of thrombocytopenia we performed bone marrow aspiration, which showed normocellular marrow with a nucleated cell count of 151×10^9/L and a megakaryocyte count of 83×10^6/L without dysplasia or hemophagocytosis. A biopsy also revealed a normal bone marrow. The platelet-associated IgG (PA-IgG) level was elevated at 249 ng/10^7 cells. A test for *Helicobacter pylori* infection was negative, and autoimmune disease-related antibodies, such as antinuclear antibody and rheumatoid factor, were not detected. The patient had neither cirrhosis nor splenomegaly. Overall, these findings were compatible with ITP.

While awaiting the results of the coagulation factor activity profiles and inhibitor titers, the patient received regular, daily transfusion of fresh-frozen plasma and platelet concentrates and was administered red blood cells as required. However, her coagulation panel and bleeding tendency showed no significant improvements.

After diagnosing her with factor V inhibitor with concomitant ITP, we started the intravenous administration of prednisolone 1 mg/kg/day on admission day 10 to suppress factor V inhibitor and increase the platelet count. However, on day 12 the patient complained of headache and nausea, and emergent brain CT showed intracranial hemorrhaging. The platelet count began to rise on day 13, but the coagulation profile did not improve. Additional transfusions of fresh-frozen plasma and platelet concentrates and antihypertensive therapy slowed down the initial bleeding, but the cerebral hemorrhaging expanded, and the patient died on day 16. Fig. 3 presents the patient's clinical course.

Discussion

Acquired inhibitors of coagulation factors are antibodies that either inhibit the activity of coagulation factors or increase their clearance, and hemorrhagic diathesis is one of the main clinical manifestations in affected patients. The clinical manifestations associated with factor V inhibitor range from asymptomatic laboratory abnormalities to life-threatening bleeding and thromboembolic events (1, 2, 7). About 20% of patients with factor V inhibitor are asymptomatic; in symptomatic patients, the most common manifestation is mucosal bleeding, such as urinary and gastrointestinal bleeding, followed by subcutaneous bleeding and epistaxis (2, 8). Fatal bleeding, such as intracranial hemorrhaging, has been reported in about 5% to 10% of patients (2, 8).

In contrast with the titers of other coagulation factor inhibitors, the titer of factor V inhibitor does not always correlate with clinical symptoms, and the same is true for factor V activity (2). Studies have suggested that at least two factors may contribute to the variability of bleeding tendency in factor V inhibitor. First, besides being found in plasma (80%), factor V is also stored in the alpha granules of platelets (20%) (9). Plasma factor V is internalized by bone marrow megakaryocytes via specific receptor-mediated processes and then undergoes several modifications that make platelet factor V structurally and functionally different from plasma factor V (4, 10, 11). Platelet-derived factor V might play a local hemostatic role at sites of vascular injury. Patients with congenital factor V deficiency with undetectable plasma factor V seldom experience major bleeding, as residual platelet factor V allows sufficient thrombin to be generated to prevent severe bleeding (10, 11). Thus, hemorrhagic manifestations in factor V inhibitor might be influenced by whether or not the inhibitor affects platelet factor V (12, 13). For example, a patient with factor V inhibitor who did not have a severe bleeding disorder was reported to have a type of inhibitor that neutralized plasma factor V but not the less accessible platelet factor V (12). Second, the bleeding phenotype depends on which factor V epitope is recognized by the inhibitor. Inhibitory anti-factor V antibodies that recognize the C2 domain of the factor V light chain have been reported to be associated with hemorrhagic manifestations (3, 14). Factor V inhibitors from asymptomatic patients both impaired the activated protein C (APC) cofactor activity of factor V in mechanisms that inactivate activated factor VIII and delayed APC-catalyzed cleavage of factor V, indicating that APC resistance helps prevent bleeding in asymptomatic patients (3). Furthermore, activated platelet factor V is proteolyzed more slowly than activated plasma factor V and not completely inactivated by APC (4, 15, 16). These findings strongly suggest that platelet factor V might contribute to the suppression of bleeding in factor V inhibitor. Accordingly, factor V inhibitor combined with thrombocytopenia is likely to increase the bleeding tendency.

Our patient had acquired factor V inhibitor complicated with ITP. Factor V inhibitors are autoantibodies and are associated with various autoimmune diseases (2, 17). How-

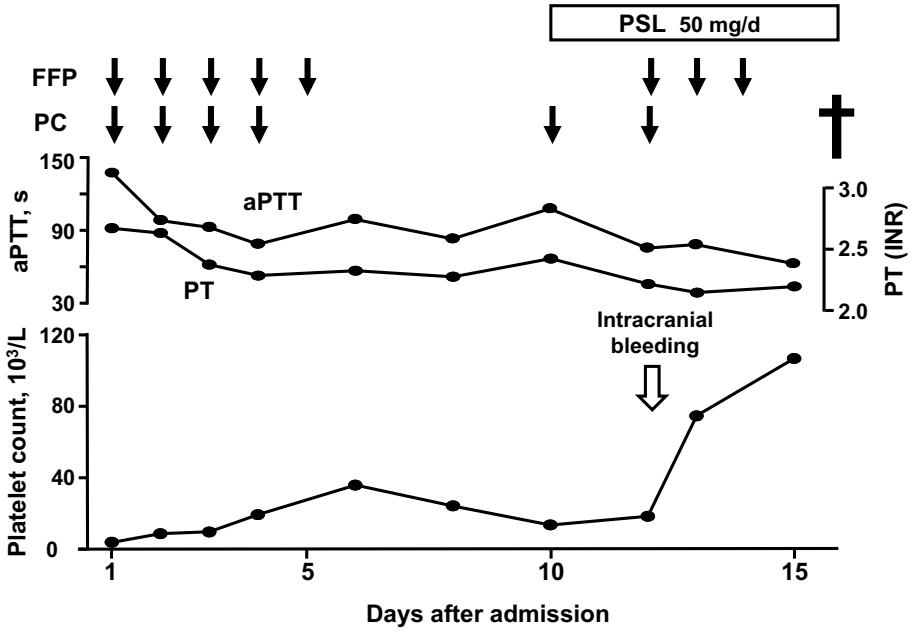

Figure 3. **Clinical course of a patient with acquired factor V inhibitor and immune thrombocytopenia. aPTT: activated partial thromboplastin time, FFP: fresh-frozen plasma, PC: platelet concentrate, PT (INR): prothrombin time (international normalized ratio), PSL: prednisolone**

ever, to our knowledge, only two case reports have described factor V inhibitor complicated with ITP (18, 19). The clinical course of a female patient with acquired factor V inhibitor described by Higuchi et al. (18) is interesting: although the patient initially presented with deep vein thrombosis from the right superficial femoral vein to the popliteal vein, after one week in the hospital, she developed immune thrombocytopenia, which resulted in decreased platelet count and hemorrhaging. Both that patient and the patient described by Takaku et al. (19) were successfully treated with steroids, which suppressed inhibitor production and increased platelet count. We also administered steroids to our patient; however, while the steroids increased the platelet count, they did not suppress the production of factor V inhibitor. Her hemostasis did not improve, and after a few days, the patient developed intracranial hemorrhaging and died.

While we had hoped that the elevated platelet count might reduce the patient's bleeding tendency by increasing the availability of platelet-derived factor V, the fatal hemorrhaging occurred before the platelet count had increased sufficiently. In such rare cases where factor V inhibitor is complicated with an extremely low platelet count, patients can have a high bleeding tendency, and physicians should consider aggressive hemostatic therapy, including plasma exchange, in addition to immunosuppressive therapy with drugs, such as prednisolone, cyclophosphamide, and rituximab (20-22).

Along with suppressing the factor V activity, the factor V inhibitor in our patient had lupus anticoagulant characteristics. Similar cases have been reported in the past (23-25). Many factor V inhibitors appear to target the C2 domain of factor V and result in impaired binding of factor V to phospholipids; therefore, the presence of excess phospholipids may partially correct clotting times and show activity similar to lupus anticoagulant (26). Other authors have reported that factor V inhibitors with lupus anticoagulant properties are rarely associated with significant bleeding (24), but fatal hemorrhaging has also been reported (23, 25). No consensus has been reached concerning the association of bleeding or thrombosis risk in factor V inhibitor with lupus anticoagulant properties, and further investigations are warranted.

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

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