Successful Management of Severe Intraperitoneal Hemorrhage by Platelet Transfusion in a Patient with Acquired Factor V Inhibitor

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ABSTRACT. A 68-year-old Japanese woman was admitted to our hospital because of macroscopic hematuria and intraperitoneal bleeding. There was no history of coagulopathy or blood transfusion. Factor V activity was markedly decreased to less than 1.0 per cent and the corrected prothrombin time test suggested the presence of an inhibitor to Factor V. Her intraperitoneal bleeding was eventually controlled by transfusion of platelet concentrate, after transfusion of fresh frozen plasma and administration of prednisolone had shown no effect. No underlying disease, such as malignancy or autoimmunity, was found in this patient. Bleeding is reported to be mild in the majority of patients with acquired Factor V inhibitor, but it is also sometimes fatal, so prompt diagnosis and treatment of this condition are necessary. Platelet transfusion may be useful for controlling severe hemorrhage in these patients.

Key words : Acquired Factor V inhibitor — intraperitoneal hemorrhage — platelet transfusion

Acquired inhibitors of blood coagulation Factor VIII are a well-known clinical problem, but inhibitors of Factor V are very rare.[1] In Japan, only 25 cases of acquired Factor V inhibitor were reported from 1977 to 2001 including those only reported at conferences.[2] Here we report a patient with acquired Factor V inhibitor that caused severe intraperitoneal hemorrhage, which was controlled by platelet transfusion, and review the previously reported cases.

CASE REPORT

Patient : A 68-year-old woman.

Chief complaint : Abdominal distension.

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History: There was no history of hemorrhagic disease or transfusion. She had not suffered abnormal bleeding when delivering her first and second children.

Family history: There was no history of a bleeding tendency.

History of the present illness: She noted macroscopic hematuria on March 1, 1998 and was admitted to a local hospital on March 4. On admission, cystoscopy plus ureteroscopy showed fresh bleeding from the left kidney, but the source of the hemorrhage could not be identified. Anemia and abdominal distension showed progression after this examination. Although intraperitoneal hemorrhage was suspected, the bleeding time and the platelet count were normal. She was transferred to the emergency department of this hospital on March 8. Since a coagulation factor abnormality was suspected from her prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), she was referred to our department for assessment and treatment.

Physical findings on admission: Her height was 161 cm, weight was 60 kg, blood pressure was 140/90 mmHg, pulse rate was 100/min, and temperature was 36.5°C.

She had marked conjunctival pallor that suggested severe anemia, but showed no jaundice. No lymph nodes were palpable. Phonocardiography showed an increase of the first heart sound. The abdomen was markedly distended (abdominal circumference: 95 cm), but was not tender. Bowel sounds were muffled. Edema of both legs was also present.

Laboratory findings on admission (Table 1): She had severe anemia with a hemoglobin of 5.8 g/dl, but the platelet count was normal. Serum albumin was reduced to 2.3 g/dl. Antinuclear antibody was negative. Examination of coagulation parameters showed prolongation of the PT and APTT to 74.3 sec and 237.3 sec, respectively. Measurement of the activity of each coagulation factor showed a marked reduction of Factor V activity alone (decreased to less than 1 per cent). When plasma from the patient and normal plasma were mixed at different ratios and let stand at room temperature for 30 min before measuring the PT and APTT with each mixture (Table 2), the results suggested that the patient did not have a defect of Factor V, but that her plasma contained an inhibitor of this factor. When the potency of this inhibitor was determined by the Bethesda method, it was 4 Bethesda units (BU)/ml. Abdominal computed tomography (Fig 1) and abdominal paracentesis confirmed the occurrence of intraperitoneal hemorrhage.

Clinical course (Fig 2): Since a Factor V inhibitor was considered to be responsible for her bleeding, prednisolone was started at 60 mg/day on the 4th day after admission (hospital day 4). She received daily transfusion of packed red cells stored in mannitol/adenine phosphate (MAP) (a total of 30 units) and fresh frozen plasma (a total of 130 units) after admission, but the intraperitoneal hemorrhage was not controlled. Abdominal paracentesis was performed twice and removed about 3,000 ml of bloody ascites, but the hemorrhage persisted. Then platelet concentrate was transfused to achieve hemostasis, after which there was gradual resolution of her ascites and

TABLE 1. Laboratory data on admission

−Hematology tests−		−Coagulation system−	
WBC	8,500 /μl	Bleeding time	4.5 min
RBC	188×10⁴ /μl	Prothrombin time	74.3 sec
Hb	5.8 g/dl	(control 9.7~12.2 sec)	
Ht	16.5 %	APTT	237.3 sec
Plt	19.0×10⁴ /μl	(control 26.1~35.8 sec)	
−Biochemistry tests−		Fibrinogen	463 mg/dl
Alb	2.3 g/dl	Antithrombin III	89.5 %
Glb	2.2 g/dl	FDP	5 μg/ml
T-Bil	0.5 mg/dl	Factor II	86 %
LDH	293 IU/l	Factor V	less than 1 %
ALT	8 IU/l	Factor VII	83 %
AST	15 IU/l	Factor VIII	92 %
Crn	0.7 mg/dl	Factor IX	72 %
BUN	13 mg/dl	Factor X	74 %
CRP	11.7 mg/dl	Factor XI	83 %
−Urinalysis−		Factor XII	61 %
Red color		Factor XIII	66 %
Protein	(3+)	vWF	178 %
Occult blood	(3+)	Hepaplastintest	104.3 %
RBC	numerous	Thrombotest	65.1 %

TABLE 2. Corrected PT and APTT measured by mixing patient plasma with normal plasma at various ratios

	PT (sec)	APTT (sec)
Patient plasma	73.4	237.3
Patient plasma (80%)+Normal plasma (20%)	72.7	117.3
Patient plasma (50%)+Normal plasma (50%)	49.8	101.2
Patient plasma (20%)+Normal plasma (80%)	14.8	36.9
Normal plasma	10.8	28.9

hematuria, with no further need for blood transfusion. Treatment with an immunosuppressant (azathioprine 100 mg/day) was started on hospital day 18 and the dose of prednisolone was gradually reduced. On hospital day 30, the PT, APTT, and Factor V activity were 22.1 sec, 54.7 sec, and 10 per cent, respectively. However, the level of Factor V inhibitor increased again at 10 days after the dose of prednisolone was reduced to 5 mg/day, so that tests performed on hospital day 60 showed a PT of 58.1 sec, APTT of 152.5 sec, and Factor V activity less than 1 per cent. Therefore, the prednisolone dose was increased to 25 mg/day and was subsequently tapered more gradually. The Factor V inhibitor was no longer detectable after hospital day 70. Imaging examinations performed after intraperitoneal hemorrhage had ceased showed no malignancy or other lesions and laboratory findings did not indicate any autoimmune disease. Furthermore,

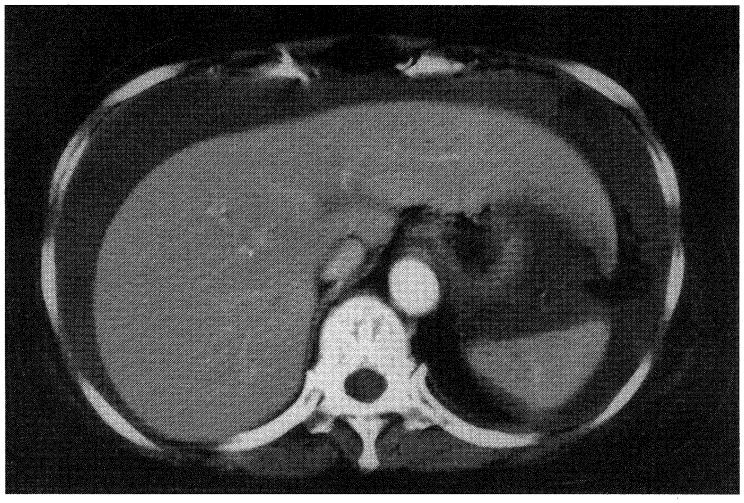

Fig 1. Abdominal CT shows massive intraperitoneal bleeding.

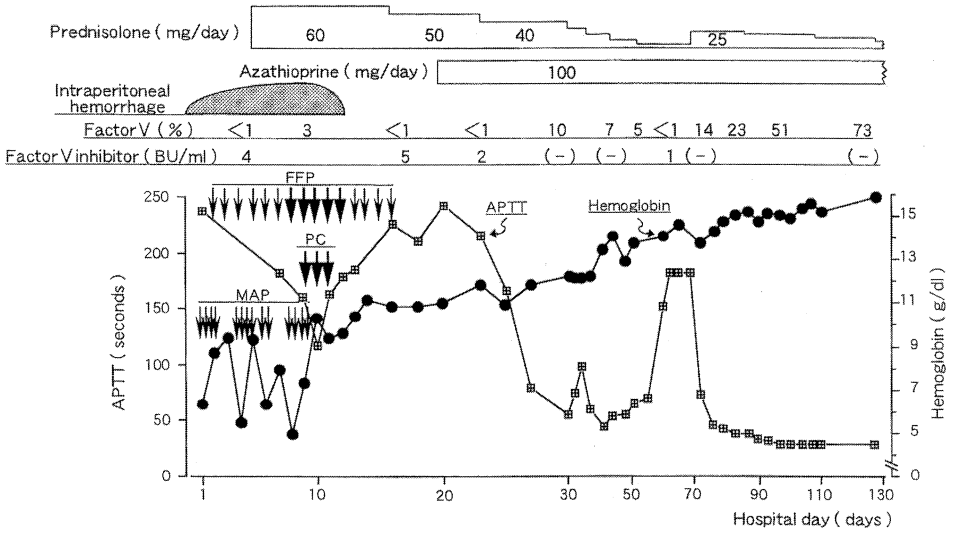

Fig 2. Summary of the clinical course. The abbreviations used in this figure are as follows. APTT: activated partial thromboplastin time, MAP: packed red cells stored in mannitol-adenine phosphate (each arrow indicates two units of red blood cells), PC: platelet concentrate (each arrow indicates 10 units), FFP: fresh frozen plasma (small arrows indicate 4 units, and large arrows indicate 10 units).

no lesion that might have caused her hematuria was detected. Screening of family members (her oldest son and daughter) showed that their coagulation profile was normal. Accordingly, the final diagnosis was hemorrhage due to idiopathic acquired Factor V inhibitor. Over the 5 years since discharge from hospital, her Factor V activity has remained between 40 and 70 pre cent, without any recurrence of bleeding.

DISCUSSION

Coagulation abnormalities related to Factor V are relatively infrequent and rarely cause severe hemorrhage like that observed in the present patient. When we reviewed the previous cases reported by Nesheim *et al* and Japanese authors,[1-8] the following characteristics were revealed.

1) Factor V inhibitor often develops in relatively old persons.
2) Many patients with this inhibitor have underlying diseases, including tuberculosis, malignancy, and collagen diseases, although it can also be associated with aging alone.
3) Drug therapy (particularly with an aminoglycoside), blood transfusion, or surgery often precedes detection of the inhibitor.
4) The inhibitor manifests suddenly and transiently, often disappearing again with 2 months.
5) Treatment with immunosuppressants and/or steroids is often needed to suppress the inhibitor and improve the bleeding tendency, although spontaneous disappearance of the inhibitor sometimes occurs.
6) The inhibitor is often an immunoglobulin (usually immunoglobulin G).

Since 1990, the detection of Factor V inhibitors has been reported in patients treated with fibrin sealants (including bovine-derived thrombin) to achieve hemostasis during surgery,[9,10] and it has been suggested that antibodies produced against bovine Factor V from these sealants might cross-react with host Factor V to act as an inhibitor. However, the detection of a Factor V inhibitor after use of fibrin glue containing human thrombin was recently reported.[11] This suggests that the etiopathogenesis of these inhibitors may vary among patients. The bleeding tendency associated with Facor V inhibitors is usually mild and severe intraperitoneal hemorrhage like that observed in the present patient is very rare. Our patient was initially hospitalized for investigation of hematuria, and intraperitoneal hemorrhage occurred after she underwent cystoscopy/ureteroscopy plus antimicrobial therapy, so her examination and treatment may have promoted the bleeding.

Acquired Factor V inhibitors can be classified into alloantibodies that develop during replacement therapy for congenital coagulation factor deficiency and autoantibodies that arise spontaneously as observed in the present patient. Immunosuppressants are often effective against acquired Factor V inhibitors because these are antibodies produced by the host immune system.[12,13] In the present case, prednisolone was started at 60 mg/day. However, since it often took 4 to 10 weeks for the inhibitor to disappear in previous patients,[14] transfusion with platelet concentrate was performed to control her hemorrhage and was successful in stemming the bleeding. Platelet α-granules contain about 25 per cent of all the Factor V in the body and these granules are exposed on the membrane surface when platelets are activated, a process that is considered important for proper prothrombin activation on platelets and subsequent hemostasis.[5] Factor V in the platelet granules may be protected from neutralization by anti-Factor V antibodies. A previous study showed that Factor V derived from platelets was effective for promoting hemostasis, so this may have

contributed to hemostasis in the present patient.[15] Knobl *et al*[14] found that a total of 105 cases of Factor V inhibitor were reported between 1955 and 1997, and that platelet transfusion was effective for acute hemorrhage in 8 of the 22 patients (36 per cent) treated in this way. The present case also confirmed the efficacy of platelet transfusion for severe hemorrhage associated with a Factor V inhibitor. Improvement of the APTT preceded that of the PT in our patient, which suggested that Factor V in the transfused platelets may have played an important role in achieving hemostasis. However, platelet transfusion does not stop the bleeding in many patients, so it seems that the Factor V stores in platelets alone are often insufficient for hemostasis, and that a mechanism based on the activation of Factor VIIa by tissue factor and activated platelets at the site of bleeding may also be involved. It has been reported that recombinant Factor VIIa is effective for the control of bleeding when platelet transfusion fails,[16] suggesting that the combination of activated Factor VIIa and platelets may be important in certain cases.

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