Letter to the Editor

Acta Hæmatologica

Acta Haematol 2019;141:148–150
DOI: 10.1159/000496080

Received: May 17, 2018
Accepted after revision: December 7, 2018
Published online: February 15, 2019

Acquired Factor V Inhibitor with Symptoms and Titer of Inhibitor Differences: Report of Two Cases

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Dear Editor,

A 51-year-old man with normal coagulation underwent surgery because of skull trauma. After the procedure, ceftriaxone was intravenously administered at 2.0 g every 12 h to prevent a postoperative infection. Nevertheless, computed tomography revealed a pulmonary infection 2 weeks later. Consequently, he was treated with an extra antibiotic ceftazidime. In the 21 days of anti-infective treatment, the patient was found to have oral mucosal bleeding and abnormal coagulations: the activated partial thromboplastin time (APTT) was 167.5 s (normal range 30–45 s) and the prothrombin time (PT) was 30 s (normal range 12–15 s). His biochemical and immune examinations were normal (Table 1). Subsequently, he was injected with vitamin K (VK) and prothrombinase complex. However, there was no significant improvement in his coagulations even after transfusing fresh frozen plasma (FFP; Fig. 1a). Coagulation factor assay showed that the factor V activity was only 2% (normal 50–150%), FVII and FXII activity reduced slightly, while other coagulation factor activities were within normal limits (Table 1). A mixing study manifested that neither PT nor APTT could be corrected (Fig. 1c). The factor V inhibitor test was positive and showed the titer of inhibitor was 128 Bethesda units (BU). Thus, the patient was diagnosed with acquired factor V deficiency and the coagulation times reduced after injection with prednisone at 10 mg for 2 days (Fig. 1a).

Another patient, a 78-year-old man with intracranial hemorrhage, was administered several months ago. His PT (normal range 12–15 s) and APTT (normal range 30–45 s) were prolonged, at 23 and 61 s, respectively. His biochemical and immunologic tests were both regular (Table 1), but brain computed tomography scanning showed a right temporal brain hemorrhage. After removal of intracranial hematoma with anything to correct coagulation, surgical wound bleeding was detected. Coagulation assay showed the factor V activity was only 13%. Factor XII also reduced slightly (Table 1). After mixing with normal plasma (Fig. 2d), the prolonged PT and APTT were partially corrected. Furthermore, VK and FFP could not alleviate the coagulations (Fig. 1b). Thus, we suspected that the abnormity was due to the factor V inhibitor, which was later confirmed by the Bethesda method. Although the patient only had a low titer of inhibitor (2 BU), his bleeding symptoms were obvious. However, we did not provide other treatment than FFP, and the patient was discharged 2 months later without symptoms. As with the first case described above, we did not find any mutation at the factor V gene in this case.

Acquired factor V deficiency is mainly caused by a factor V inhibitor, which results in low factor V activity and is associated with various factors, such as antibiotics [1], surgery, malignancy [2], autoimmune disease, blood transfusions, and exposure to bovine thrombin [3]. In the study by Franchini and Lippi [4], antibiotics like β-lactam aminoglycosides showed the most common risk, accounting for 42% of the risk cases, yet surgery and infection accounted for 31 and 23%, respectively. This may offer an interpretation to the first

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Table 1. Laboratory findings

	Case 1	Case 2
Complete blood count		
WBC, $\times 10^9$/L	9.1 (4–10)	6.0 (4–10)
RBC, $\times 10^{12}$/L	3.31 (4–5.5)	3.42 (4–5.5)
Hb, g/L	98 ↓ (120–150)	108 (120–150)
HCT	0.31 ↓ (0.4–0.54)	0.325 (0.4–0.54)
MCV, fL	93.9 (80–100)	95 (80–100)
MCH, pg	29.6 (26–32)	31.6 (26–32)
PLT, $\times 10^{12}$/L	373 ↑ (100–300)	141 (100–300)
Coagulation test		
PT, s	45.6 ↑ (12–15)	23 ↑ (12–15)
PT-INR	4.82 ↑ (0.85–1.15)	2.17 ↑ (0.85–1.15)
APTT, s	167.5 ↑ (30–45)	61 ↑ (30–45)
Fbg, g/L	5.97 ↑ (2–4)	2.91 (2–4)
D-dimer	0.83 ↑ (0–0.5)	1.12 ↑ (0–0.5)
Coagulation factor assay		
Factor II, %	132 ↑ (50–150)	78 (50–150)
Factor V, %	2 ↓ (50–150)	13 ↓ (50–150)
Factor VII, %	44 ↓ (50–150)	69 (50–150)
Factor VIII, %	166 ↑ (50–150)	243 ↑ (50–150)
Factor IX, %	70 (50–150)	97 (50–150)
Factor X, %	68 (50–120)	79 (50–120)
Factor XI, %	100 (50–150)	104 (50–150)
Factor XII, %	35 ↓ (50–120)	52 (50–120)
Factor V inhibitor, BU	128	2
Biochemistry		
AST, U/L	70 ↑ (9–50)	51 ↑ (9–50)
ALT, U/L	53 ↑ (15–40)	17 (15–40)
γ-GTP, U/L	62 ↑ (10–60)	4 (10–60)
T-Bil, μmol/L	7.9 (6.8–34.2)	12.5 (6.8–34.2)
BUN, mmol/L	3.75 (2.8–8.2)	7.73 (2.8–8.2)
Cr, μmol/L	37.4 (53–106)	59.2 (53–106)
Immuno findings		
Antinuclear antibody	Negative	Negative
Anticardiolipin IgG	Negative	Negative
Lupus AC	Negative	Negative

↑ and ↓ indicate values higher and lower than normal ranges, respectively. Normal ranges are shown in parentheses.

case reported here. Many new factors have also been reported as being related to factor V inhibitors, such as warfarin [5], amiodarone [6], dabigatran etexilate [7], and liver transplantation. However, we did not know why hemorrhage and factor V inhibitor emerged without any determined risks in case 2. The mechanism behind the production of inhibitors was a mystery.

The clinical symptoms of patients with factor V inhibitor can range from asymptomatic hematological laboratory abnormalities to life-threatening hemorrhage. Remarkably, Franchini and Lippi [4] also referred to 4 cases associated with thrombotic complications instead of hemorrhage. In our cases, the first had 2% factor V activity and a high inhibitor titer, but only suffered oral mucosal bleeding, while the other case, with 13% factor V activity, presented serious hemorrhage. We speculated that this was owing to the detecting principles. The laboratory tests are based on poor platelet plasma, ignoring the factor V derived from platelets. Nevertheless, the factor V derived from platelets is also pivotal and has sufficient capability to ensure the normal coagulation function. Thus, factor activity cannot exactly reflect a patient's actual clotting status [8]. Besides, antibiotics, surgery, and infection may have resulted in the high titer of inhibitor that emerged in case 1, but we could not find these risks in case 2. In other words, the inhibitor resulting from drugs and stimulus probably caused mild symptoms,

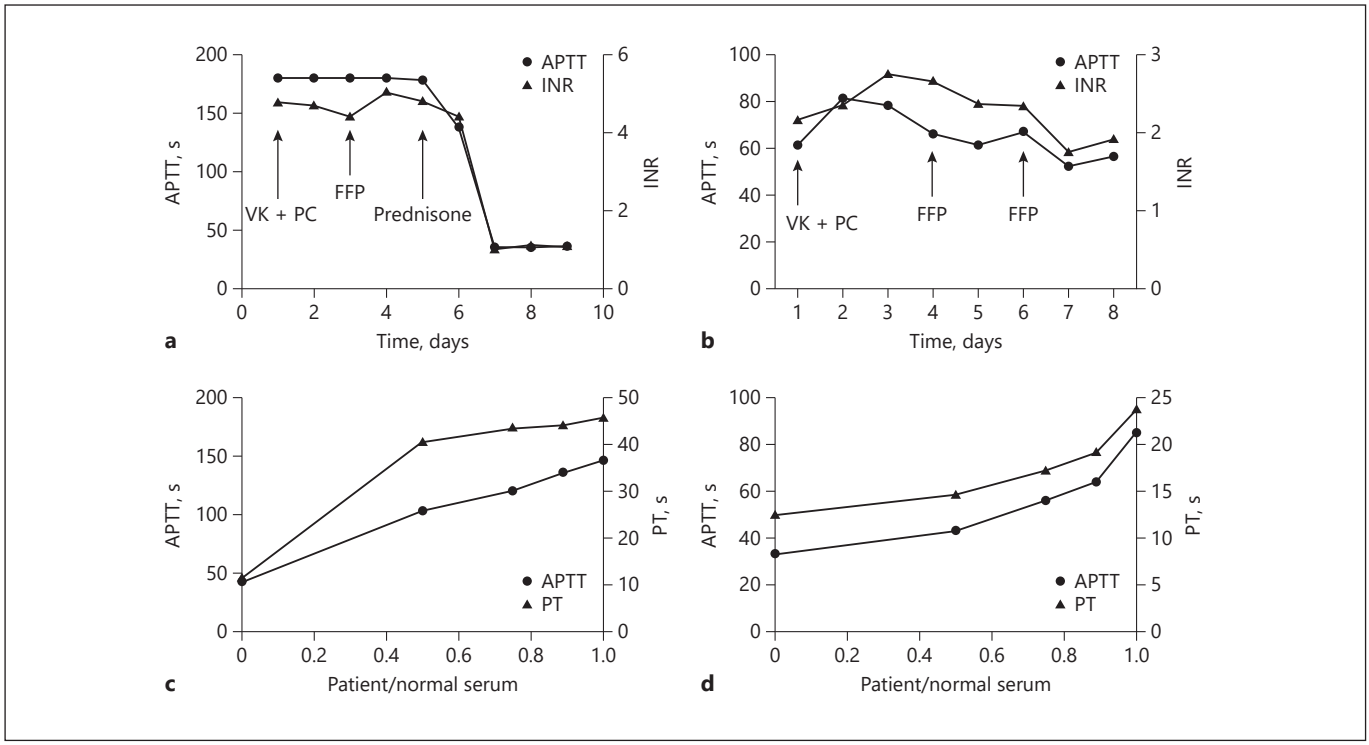

Fig. 1. INR (International Sensitivity Index) and APTT profiles of case 1 (**a**) and case 2 (**b**). Mixing test: sera from patient 1 (**c**) and patient 2 (**d**) and a healthy normal subject were mixed at the indicated ratios.

while the inhibitor generating spontaneously or caused by unknown reasons could cause a serious manifestation.

Herein, we have reported 2 rare cases of acquired factor V inhibitor that were comparable but differently induced, probably leading to opposite hemorrhagic manifestations.

Statement of Ethics

The patients gave their informed consent for the writing of this letter.

Disclosure Statement

The authors have no conflicts of interest to declare. The work has no funding sources.

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