Acquired Factor V Inhibitor

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Abstract

Inhibitors directed against factor V rarely occur, and the clinical symptoms vary. We herein report the case of a patient who presented with a decreased factor V activity that had decreased to <3 %. We administered vitamin K and 6 units of fresh frozen plasma, but she thereafter developed an intracerebral hemorrhage. It is unclear whether surgery >10 years earlier might have caused the development of a factor V inhibitor. The treatment of acquired factor V inhibitors is mainly the transfusion of platelet concentrates and corticosteroids. Both early detection and the early initiation of the treatment of factor V inhibitor are thus considered to be important.

Key words: acquired factor V inhibitor, intracerebral hemorrhage

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Introduction

Inhibitors directed against factor V occur rarely. However, they can occur at any age, and the clinical symptoms vary, ranging from asymptomatic laboratory abnormalities to life-threatening bleeding. The presence of life-threatening factor V inhibitor cases underscores the need for prompt diagnosis and treatment (1). Various causes of factor V inhibitors have been reported, and most of the cases described in Japan developed after exposure to bovine thrombin preparations, which have been used frequently as topical hemostatic agents in various types of surgery. However, due to the increasing surgical use of recombinant human or bovine forms of thrombin, at least in developed countries, the number of factor V inhibitor cases associated with these products appears to be in decline. In parallel, attention has lately been focused on other possible causes of factor V inhibitor development (2).

We herein report the case of a patient who developed idiopathic acquired factor V inhibitor and died due to an intracerebral hemorrhage.

Case Report

A 79-year-old Japanese woman presented herself to another hospital with left pedal edema. Furosemide was started, but the pedal edema did not improve. She also received oral cefcapene pivoxil hydrochloride hydrate to treat her lower urinary tract symptoms. She was transferred to our hospital because a routine coagulation panel revealed a markedly prolonged prothrombin time of 60 s and an activated partial thromboplastin time of 120 s.

Her medical history included hypertension, diabetes mellitus, and coronary artery disease (CAD). The CAD first manifested as angina in June 2001, at which time her coronary angiography demonstrated triple vessel disease. In July 2001, she underwent coronary artery bypass grafting. In December 2012, she was re-admitted to our hospital because of a worsening angina, and she underwent percutaneous coronary intervention. Subsequently, she underwent percutaneous coronary intervention with a drug-eluting stent in November 2013. Thereafter, she had been administered clopidogrel sulfate and aspirin. No previous bleeding tendency was noted, and she had no significant family history of bleeding disorder. Her medication included clopidogrel sulfate, aspirin, cilnidipine, lisinopril hydrate, pravastatin sodium, and nicoran-
On admission to our hospital in October 2014, her height was 143 cm and weight was 43.1 kg; her body temperature was 37.2°C, blood pressure 109/47 mmHg, pulse 83/min, clear consciousness, no conjunctival pallor, and no icterus. There were no palpable superficial lymph nodes. Left pedal tender swelling was observed and it was thought to be a hematoma.

The laboratory findings at the time of admission are shown in Table. The measurement of the coagulation factor profile revealed a marked decrease in factor V activity to ≤3% and somewhat reduced activities of factors II, IX, X, XI, and XII. The test for coagulation factor V inhibitor was positive (18 Bethesda U/mL).

She was given vitamin K and six units of fresh frozen plasma, while the administration of clopidogrel sulfate was stopped, but her coagulation panel did not improve. On day 3 after admission she slipped into a coma, and an emergent brain computed tomography (CT) scan demonstrated she had suffered an intracerebral hemorrhage (Fig. 1). Because platelets contain factor V, we transfused 10 units of platelets. In addition, prednisone 1 mg/kg daily was initiated in an attempt to suppress possible autoantibody production against coagulation factor(s). Despite these treatments, her coagulation profile was not corrected and she died on day 7 after admission.

### Discussion

The patient’s plasma demonstrated prolonged phospholipid-dependent in-vitro clotting tests, such as APTT. Mixing studies with pooled normal plasma failed to correct the abnormal APTT, in which the incubation time was two hours (Fig. 2), suggesting the presence of an inhibitor. The levels of phospholipid-dependent clotting factors (factors II, V, IX, X, XI, and XII) were low, and we evaluated the possibility of lupus anticoagulant hypoprothrombinemia syndrome, but the dilute Russell viper venom time dil.

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**Table.** Laboratory Data.

| Biochemistry          | Coagulation |
|-----------------------|-------------|
| AST 7 U/L             | PT ≥60.0 sec|
| ALT 6 U/L             | PT activity <5 % |
| γ-GTP 18 U/L          | PT(INR) ≥7.00 |
| LDH 186 U/L           | APTT ≥120.0 sec |
| BUN 34 mg/dL          | Fib 333 mg/dL |
| Cr 1.54 mg/dL         | ATIII 79 % |
| UA 10.2 mg/dL         | FDP 3.3 μg/mL |
| Na 133 mmol/L         | D-dimer 1.19 μg/mL |
| K 3.8 mmol/L          | TT ≥150 % |
| Cl 103 mmol/L         | HPT 103 % |

**CBC**

- WBC 6,800 /μL
- RBC 242 x 10⁶/μL
- Hb 7.1 g/dL
- Hct 20.4 %
- Plt 13.3 x 10⁹/μL

**vitamin k1 0.88**

**k2 3,362.8**

**PIVKA-II 19 mAU/mL**

**Coagulation factor assay**

- Factor II activity 23 %
- Factor V activity ≤3 %
- Factor VII activity 68 %
- Factor IX activity 53 %
- Factor X activity 58 %
- Factor XI activity 35 %
- Factor XII activity 15 %
- Factor II inhibitor 1 BU/mL
- Factor V inhibitor 18 BU/mL
- Factor X inhibitor negative

**Immuno-serological findings**

- Lupus AC (dRVVT) not determinable

AST: aspartate-aminotransferase, ALT: alanine-aminotransferase, γ-GTP: γ-glutamyl transpeptidase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Hct: hematocrit, Plt: platelets, PIVKA-II: protein induced by vitamin K absence-II, PT: prothrombin time, PT(INR): prothrombin time international normalized ratio, APTT: activated partial thromboplastin time, Fib: fibrin, ATIII: antithrombin III, FDP: fibrin/fibrinogen degradation products, TT: thrombotest, HPT: heparplastin test, Lupus AC: lupus anticoagulant

Figure 1. CT of the head of the patient, a 79-year-old woman, obtained on day 3 after admission.
tor because concomitant antibiotic therapy was also present, however, it is difficult to establish whether these latter conditions were recorded in 31% and 23%, respectively. How- ever, it is difficult to establish whether these latter conditions were recorded in 31% and 23%, respectively. How- ever, it is difficult to establish whether these latter conditions were recorded in 31% and 23%, respectively. How- ever, it is difficult to establish whether these latter conditions were recorded in 31% and 23%, respectively. However, the level of factor V activity was remarkably low, which was in- consistent with criterion (iv). In addition, the positivity of factor II inhibitor might be a false-positive result, due to cross-reactivity with factor V inhibitor.

According to the review by Franchini and Lippi (2), among the conditions associated with the development of factor V inhibitors, autoimmune disorders were present in 13% of the cases examined, whereas 22% were associated with cancer. The most common associated condition was the use of antibiotics, such as β-lactams, aminoglycosides (espe- cially streptomycin), cephalosporins, tetracyclines and fluoroquinolones (especially ciprofloxacin), which accounted for 42% of the reported cases. Surgical procedures and infections were recorded in 31% and 23%, respectively. However, it is difficult to establish whether these latter conditions play a causative role in the development of the inhibi- tor because concomitant antibiotic therapy was also present in almost all cases (2). Cases of an acquired factor V inhibitor due to medications, such as rifaximin, dabigatran etex- ilate methanesulfonate and warfarin have been de- scribed (1, 4, 5). However, our patient’s medications, except for furosemide and cefcapene pivoxil hydrochloride hydrate, had been continually taken for many years without developing any inhibitors. Furthermore, furosemide and cefcapene pivoxil hydrochloride hydrate were initiated after the develop- ment of symptoms. Bovine factor V acts as a potent im- munological stimulus for the development of anti-bovine factor V inhibitors, which can then cross-react with human factor V. Most patients with bovine thrombin-induced autoantibodies showed only coagulation laboratory abnor- malities without any hemorrhagic complications, and the antibodies were frequently transient (2). Our patient underwent coronary artery bypass grafting about 10 years earlier, and it

Figure 2. Cross mixing test of the patient, a 79-year-old woman.

was not measurable in this case. A laboratory diagnosis of LA requires careful adherence to the following criteria: (i) the prolongation of at least one phospholipid-dependent clot- ting test, (ii) a failure to correct prolonged screening coagu- lation test upon mixing with pooled normal plasma, (iii) evi- dence that an inhibitory activity is dependent on phospholi- pids, and (iv) ruling out any other coagulopathies (such as factor VIII inhibitor, heparin) (3). Our patient’s laboratory data were consistent with criteria (i), (ii) and (iii), but the level of factor V activity was remarkably low, which was in- consistent with criterion (iv). In addition, the positivity of factor II inhibitor might be a false-positive result, due to cross-reactivity with factor V inhibitor. The early recognition and initiation of treatment for factor V inhibitor are thus important to achieve a better prognosis in such cases. We herein presented a case of factor V inhibitor that re- sulted in fatal intracranial bleeding. The earlier recognition of this condition and timely initiation of treatment therefore appear to be of critical importance. The authors state that they have no Conflict of Interest (COI).

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