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【 CASE REPORT 】

Successful Treatment of Life-threatening Bleeding Caused by Acquired Factor X Deficiency Associated with Respiratory Infection

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Abstract:
Acquired factor X deficiency (AFXD) is a very rare coagulation disorder. A 40-year-old man with no comorbidities suffering from a fever, malaise, and severe hemorrhagic symptoms, including massive hematuria, was emergently admitted. His platelet count was normal, but his prothrombin time and activated partial thromboplastin time were markedly prolonged, which was thought to be due to autoantibody against a coagulation factor in the common pathway. Despite severe massive hematuria resulting in transient renal failure, he was successfully treated with urgent immunosuppressive therapy. Computed tomography revealed bronchopneumonia, which improved with antibiotic administration. AFXD without evidence of amyloidosis was subsequently diagnosed.

Key words: acquired factor X deficiency, pneumonia, severe hematuria

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Introduction

The blood coagulation system is composed of many factors, and the balanced activity of those factors is required for normal coagulation and fibrinolysis. Among them, factor X (FX) plays a crucial role in the coagulation cascade as the first enzyme in the common pathway of thrombus formation (1). Acquired FX deficiency (AFXD) is a very rare phenomenon that is partly associated with amyloidosis. AFXD develops in approximately 10% of patients with systemic light-chain amyloidosis, and in such cases, it is probably caused by absorption of FX by amyloid fibrils (2-4). In contrast, AFXD without amyloidosis is extremely rare, and only a small number of cases have been described in the literature (5-11). In the majority of cases AFXD is presumed to be caused by autoimmunity towards FX, and a specific FX inhibitor has been identified in some cases (5, 8). Some AFXD patients exhibit severe hemorrhagic symptoms requiring therapeutic intervention.

We herein report a case of AFXD associated with respiratory infection in which there was no amyloidosis. Despite severe subcutaneous hematoma and massive hematuria leading to renal failure, the patient was successfully treated with immunosuppressive therapy. Immediate therapeutic intervention with immunosuppressive agents may be life-saving in AFXD patients with severe hemorrhagic complications.

Case Report

The patient was a 40-year-old man who had suffered from a fever and malaise for two weeks without cough or sputum. He had previously been healthy and had not experienced any prior hemorrhagic episodes, and there was no known familial history of any hereditary coagulation disorder. Three days prior to the current presentation subcutaneous hematoma, epistaxis, and hematuria had developed, prompting him to visit the hospital. He was immediately admitted and transferred to our institution the next day due to periodic severe hemorrhaging.

On presentation he was critically ill with a fever and hemorrhagic symptoms, including hematoma in the bilateral

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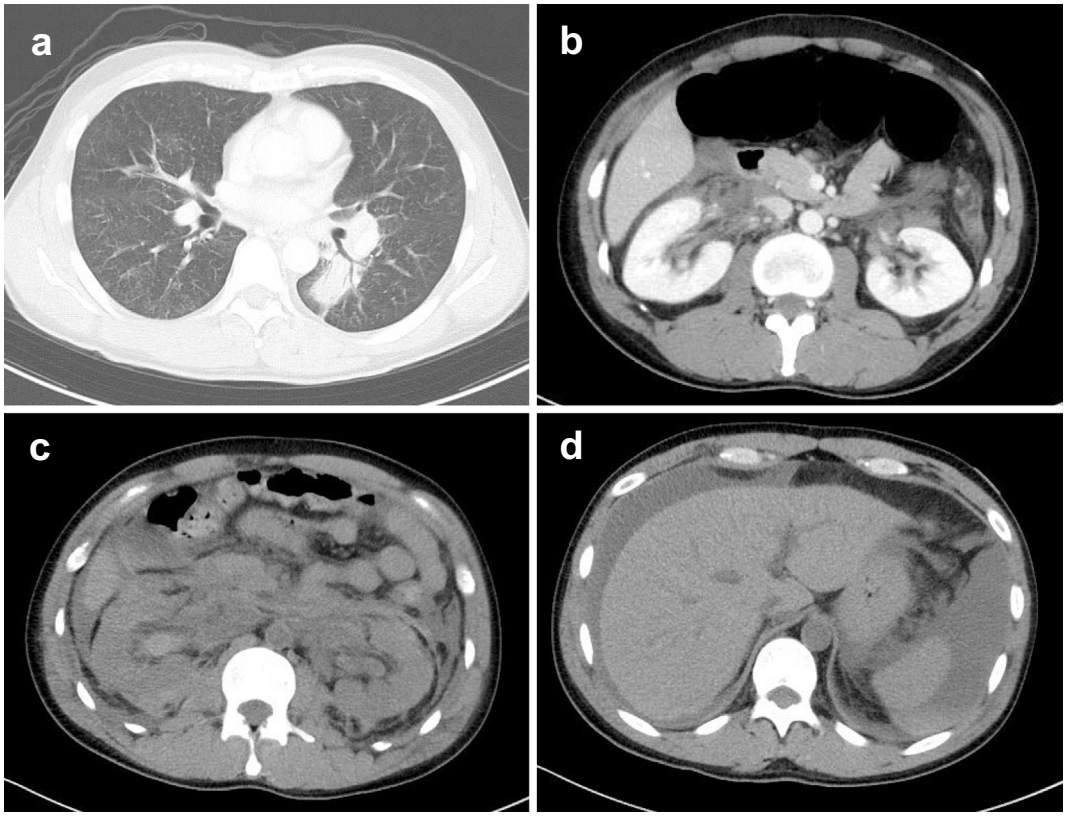

Figure 1. **Computed tomography findings on admission (a, b), and on the third admission day (c, d).**

eyelids, conjunctival hemorrhaging, epistaxis, oral mucosal hemorrhaging, and massive hematuria. He was febrile (body temperature, 38.0°C), but his vital signs were stable (blood pressure, 126/88 mmHg; pulse rate, 83/min) without depression of percutaneous oxygen saturation (98% in room air). A complete blood count revealed anemia (hemoglobin 9.8 g/dL) and a normal platelet count (32.0×10^4/μL). Biochemistry tests revealed elevated C-reactive protein levels (5.69 mg/dL) but no other abnormalities. The renal function was normal at that time.

In coagulation tests, the prothrombin time (PT) was extremely prolonged (170.0 s), as was the activated partial thromboplastin time (APTT; 127.5 s), but fibrin degenerative product (<2.5 μg/mL) and D-dimer (0.5 μg/mL) levels were within normal ranges. The fibrinogen concentration was elevated (435 mg/dL). Computed tomography (CT) depicted consolidation with an air bronchogram in the left lower lobe and diffuse microgranular shadowing with ground-glass opacity in both lungs, which were respectively suggestive of infectious pneumonia and alveolar hemorrhaging (Fig. 1a). There were also conspicuous bilateral perirenal soft tissue shadows with partially high density, which may have been associated with hematoma (Fig. 1b).

The clinical course is shown in Fig. 2. Further examinations could not be performed promptly at the time of presentation due to long public holidays. It was assumed that the prolongation of PT and APTT, accompanied by severe hemorrhagic symptoms, had been caused by the emergence of autoantibody against a clotting factor of the common pathway, such as fibrinogen, prothrombin, factor V, or FX. Accordingly, 70 mg/day prednisolone (PSL) was initiated in addition to transfusion of fresh-frozen plasma (FFP) and red blood cells. For acute pneumonia, the antibiotics dripenem (500 mg/8 h) and minocycline (100 mg/8 h) were initiated, as was intravenous immunoglobulin. Massive hematuria and subcutaneous hematoma persisted, however, and the anemia worsened despite the transfusions. Tranexamic acid was not administered because macroscopic hematuria is a contraindication for its use (12). Abdominal distention also developed. On the third admission day, the urine volume was reduced, the serum creatinine level was elevated, and CT depicted swelling of the bilateral kidneys with high-density areas in the renal pelvis, which was considered to reflect post-renal obstruction of the ureter via sustained hematuria (Fig. 1c). CT also revealed retention of bloody ascites (Fig. 1d).

Further immunosuppression was considered necessary in order to ameliorate the life-threatening hemorrhaging, so pulse methylprednisolone was initiated (1,000 mg for 3 days, tapered thereafter). Recovery of urination and the renal function ensued, and the hematuria subsided over the subsequent three days. The total amount of infused FFP was 40 units. The abdominal distension and subcutaneous hematoma also improved. PT and APTT improved, but not sufficiently, so pulse cyclophosphamide (500 mg) was administered on the 10th admission day. Pneumonia improved with dripenem and minocycline, although the causative pathogen could not

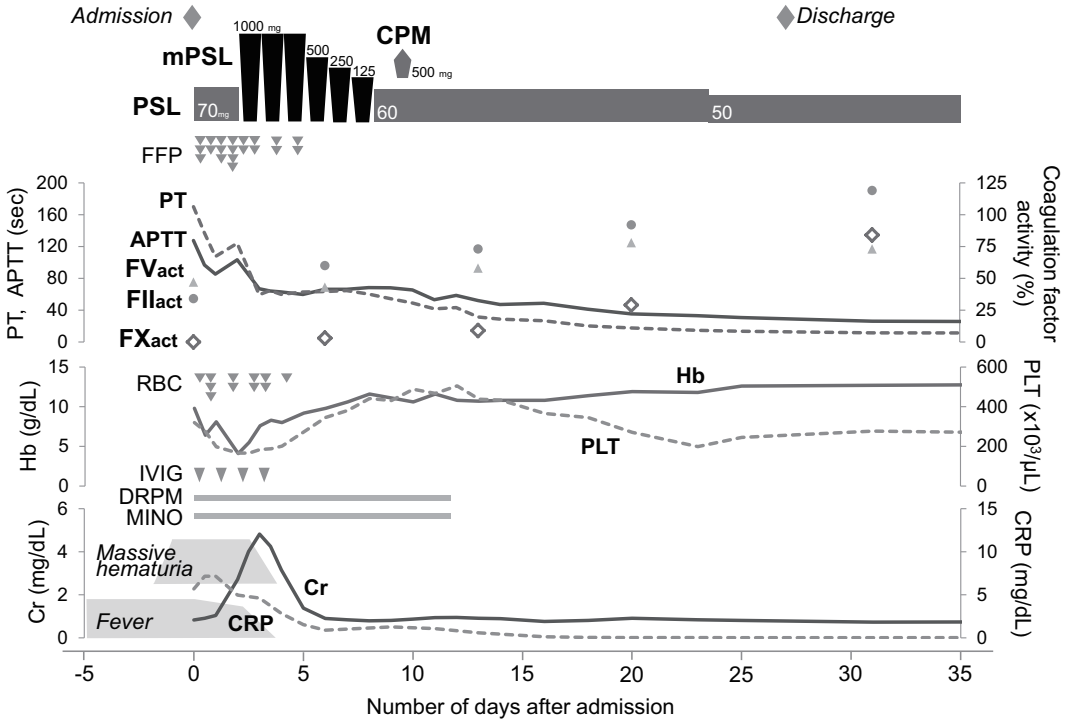

Figure 2. **Clinical course. APTT: activated partial thromboplastin time, CPM: cyclophosphamide, Cr: creatinine, CRP: C-reactive protein, DRPM: dripenem, FIIact: factor II activity, FVact: factor V activity, FXact: factor X activity, FFP: fresh frozen plasma, Hb: hemoglobin, IVIG: intravenous immunoglobulin, MINO: minocycline, mPSL: methylprednisolone, PLT: platelet, PSL: prednisolone, PT: prothrombin time, RBC: reb blood cell**

be identified via blood culture on admission or serological tests for *Mycoplasma* and *Chlamydophila*. Sputum culture could not be performed due to the absence of respiratory symptoms.

Mixing tests with normal pooled plasma were performed on the fifth admission day and revealed correction of PT and APTT (Table 1 and Fig. 3). The results of coagulation function examinations performed using plasma preserved on admission are shown in Table 1. The FX activity was profoundly depressed. Factors II, V, and VII exhibited mildly reduced activity, and the other factors exhibited normal activity. AFXD was diagnosed based on the above results. Inhibitors of factors II and X were detected, but their titers were low (both 1 Bethesda unit/mL). No M-proteins were detected in serum or urine via immunofixation. With the exception of positivity for lupus anticoagulant (LAC), no other immunological abnormalities were identified.

After pulse methylprednisolone and cyclophosphamide, the administration of PSL was continued. Gradual normalization of PT and APTT ensued, as did recovery of the FX activity. Hemorrhagic symptoms, including hematuria, did not recur, and the renal function normalized. The patient's general condition also improved markedly, and he was discharged four weeks after admission. PSL was tapered gradually without recurrence of a reduced FX activity, and the low-titer inhibitors of factor II and X disappeared. The patient also converted to LAC sero-negative status. He has been well without hemorrhagic symptoms for the six months since his admission.

Discussion

AFXD is an uncommon coagulation disorder, and AFXD without AL amyloidosis is even rarer, with no more than 50 cases having been reported in the literature to date. In 2012, Lee et al. (5). reviewed 34 cases of non-amyloid AFXD. In those cases, AFXD was frequently preceded by respiratory infection, and marked prolongation of both PT and APTT was seen in almost all patients. Initial presentations were variable, however, ranging from no bleeding to severe hemorrhaging, such as musculoskeletal bleeding. A specific inhibitor of FX was identified in approximately a quarter of the cases. Various treatments were administered, including corticosteroids, plasma exchange, and intravenous immunoglobulin. All patients eventually recovered completely, and in some of them, the coagulopathy resolved spontaneously.

The clinical course in the present case was relatively typical of AFXD without amyloidosis. There was complicating pneumonia, extreme PT/APTT prolongation, and a favorable outcome that ensued after immunosuppressive therapy. The case is conspicuous, however, because of the life-threatening hemorrhagic symptoms, including massive hematuria causing life-threatening acute renal failure-possibly due to ureter obstruction-and its complete improvement following the administration of corticosteroids. This suggests that the prompt initiation of immunosuppressive therapy may be life-saving

Table 1. The Coagulation Function and Immunological Examination Findings.

	Results	Normal range
Coagulation function examinations		
PT*	59.2 s	9.9-11.8
1:1 mix (0 h/2 h)*	16.4/16.7 s	
APTT*	63.6 s	26.9-38.1
1:1 mix (0 h/2 h)*	32.3/34.0 s	
Thrombotest*	7.5%	70-130
Thrombin-antithrombin complex	<1.0 ng/mL	<3.0
Plasmin-alpha 2-antiplasmin complex	0.7 μg/mL	<0.8
Factor II activity	34%	74-146
Factor V activity	47%	70-152
Factor VII activity	58%	63-143
Factor VIII activity	102%	62-145
Factor IX activity	99%	74-149
Factor X activity	<1%	71-128
Factor XI activity	79%	73-136
Factor XII activity	56%	46-156
VWF activity	256%	50-150
Factor II inhibitor	1 BU/mL	Not detected
Factor V inhibitor	Not detected	Not detected
Factor VIII inhibitor	Not detected	Not detected
Factor IX inhibitor	Not detected	Not detected
Factor X inhibitor	1 BU/mL	Not detected
Immunological examinations		
Lupus anticoagulant	2.4	0-1.3
Anti-cardiolipin Ab	9.0 U/mL	0-9.9
Anti-cardiolipin/β2 glycoprotein 1 complex Ab	<1.3 U/mL	0-3.4
Antinuclear Ab	×40	0-79
Anti-MPO-ANCA Ab	<1.0 IU/mL	<1.0
Anti-PR3-ANCA Ab	<1.0 IU/mL	<1.0

*The tests were performed on the fifth admission day.

Ab: antibody, ANCA: anti-neutrophil cytoplasmic antibody, APTT: activated partial thromboplastin time, MPO: myeloperoxidase, PR3: proteinase 3, PT: prothrombin time, VWF: von Willebrand factor

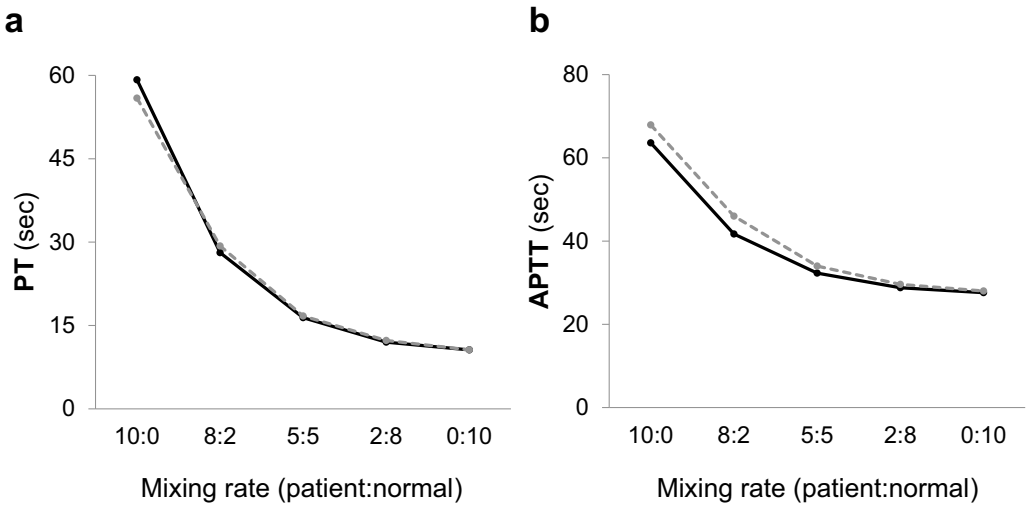

Figure 3. Results of mixing tests for the (a) prothrombin time and (b) activated partial thromboplastin time performed on the fifth admission day.

Table 2. Recent Reports Describing Cases of Non-amyloid Acquired Factor X Deficiency.

Ref.	Age/ Sex	Symptoms	Associated conditions	FX activity	FX inhibitor	Mixing study	Immunosuppressive therapy	Time to recovery
(6)	52/M	Hematuria, epistaxis	Pneumonia	<1%	Negative (BA)	Corrected	CS	~3 wk
(10)	59/M	Subcutaneous bleeding, intestinal bleeding, epistaxis	Upper respiratory infection	16%	Not mentioned	Partially corrected	CS, PE, IVIG, CPM, RTX	~6 wk
(11)	72/M	Skin bruise, ecchymosis, hematoma, oral bleeding, perisplenic hemorrhaging	Upper respiratory infection	13%	Positive (Ca-dependent)	Partially corrected	CS, PE, IVIG, RTX	~3 wk
(9)	81/M	Hematoma	Marginal zone lymphoma	3-4%	Negative (BA) Positive non-neutralizing Ab	Corrected	CS, CB, RTX	~3 wk
(7)	62/M	Malaise, hematuria, orbital hemorrhaging, extensive ecchymosis	Fever	<1%	Negative (BA)	Not corrected	CS, PE	~3 wk
(8)	89/F	Vaginal bleeding, subcutaneous bleeding, intestinal bleeding, hematuria	Not documented	<1%	Negative (BA) Positive non-neutralizing Ab	Corrected	CS	~1 mth
Present case	40/M	Hematoma, epistaxis, mucosal hemorrhaging, massive hematuria, bloody ascites	Pneumonia	<1%	Low titer (BA)	Corrected	CS (pulse), CPM	~1 mth

Ab: antibody, BA: Bethesda assay, CB: chlorambucil, CS: corticosteroid, CPM: cyclophosphamide, IVIG: intravenous immunoglobulin, NA: not applicable, PE: plasma exchange, RTX: rituximab

in cases with severe hemorrhagic symptoms in which AFXD is suspected.

Since the aforementioned review by Lee et al. (5) was reported, several novel cases of AFXD without amyloidosis have been described (6-11) (Table 2). Consistent with the cases reviewed by Lee et al. (5), complicating respiratory infections were present in some of those subsequently described cases. In most of the cases, the FX activity was markedly reduced (<5%), and there were multiple hemorrhagic symptoms. Notably however, almost all patients recovered within one month. In most cases, FX autoantibody was not detected via the Bethesda assay, or it was only detected at a low level, and mixing tests with normal pooled plasma indicated correction of PT and APTT. Among autoantibodies for coagulation factors, it is assumed that in addition to neutralizing antibodies that bind the functional regions, non-neutralizing antibodies that bind nonfunctional regions also promote clearance (13, 14). To our knowledge, only two cases of AFXD in which non-neutralizing antibody was demonstrated have ever been reported (8, 9). Neutralizing antibodies were not detected via the functional Bethesda assay in either of those cases. Non-neutralizing antibodies were detected in immunological antibody detection assays, and they disappeared after improvements in the hemorrhagic symptoms and FX activity. In the present case, a low titer of functional FX antibody was detected, but it was too low to have caused the prominent reduction in FX activity and severe hemorrhagic symptoms observed. In addition, mixing tests with PT and APTT showed the factor deficiency pattern. That is why the existence of non-neutralizing antibodies for FX is sufficiently estimated in this case; however, it could not be demonstrated due to technical limitations.

LAC is reported to become transiently positive in the course of various infectious diseases (15-17), which may have been applicable to this case. In addition, given the LAC positivity and the fact that the activities of factors II and V were mildly depressed in conjunction with a low titer of factor II inhibitor, the emergence of LAC may have been associated with the emergence of inhibitors of multiple coagulation factors (18). It is also reported that an inhibitor of a single factor can interfere with the assays of other factors, selectively reducing the target factor, although there may be some apparent reduction in other factor levels due to an inhibitory effect on the factor-deficient plasma used in the assay (19). In the present case, the transient LAC caused by respiratory infection may have been associated with depression of the activities of factors II and V.

In summary, an AFXD patient with severe hemorrhagic symptoms was successfully treated via urgent therapeutic interventions including steroid pulse in the present case. In cases involving patients with acute progression of hemorrhagic symptoms with prolongation of both PT and APTT, the possibility of acquired coagulation diseases including AFXD should be considered, even if the mixing test yields a factor deficiency pattern. In addition, the combination of immunosuppressive therapy may play a key role in the successful treatment of AFXD. Because of the rarity of the disease, the further accumulation of clinical reports is necessary in order to facilitate a better comprehension of the clinicopathological features of AFXD.

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

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