CASE REPORT

Renal hemorrhage caused by acquired inhibitors to coagulation factors VIII and V in a hemodialysis patient

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Abstract Acquired coagulation factor deficiency is a rare bleeding disorder caused by the inhibitors to coagulation factors. We report a case of an elderly hemodialysis patient who presented with the intermittent hematuria and anemia, associated with the prolonged activated partial thromboplastin time and prothrombin time. Laboratory examination revealed undetectable factor VIII activity, decreased factor V activity, and the presence of inhibitors to these coagulation factors. The patient was diagnosed to have inhibitors to coagulation factors VIII and V simultaneously. In addition, hematuria was found to be caused by the right renal hemorrhage. Renal extravasation was treated by transcatheter arterial embolization. Oral prednisolone successfully eradicated the inhibitors. The present case highlights the importance to consider acquired coagulation factor inhibitors for bleeding symptoms, because they are sometimes life-threatening.

Keywords Acquired hemophilia A · Kidney · Hemodialysis · Coagulation factors

Introduction

Acquired coagulation factor deficiency is a rare bleeding disorder caused by the development of autoantibodies against coagulation factors. Autoantibodies against all coagulation factors have been reported [1–3]. Of these, factor VIII inhibitor, also known as acquired hemophilia A, is the most common type of antibody-mediated coagulation factor deficiency, with an incidence of 1.5 per million individuals per year [4]. Factor V inhibitor is even rarer, and the literature on this condition is limited to less than 200 cases [3]. These disease conditions are sometimes life-threatening, and the diagnosis must be made promptly. We herein report a case of an elderly hemodialysis patient who presented with the intermittent hematuria and anemia caused by the acquired inhibitors against coagulation factors VIII and V simultaneously.

Case report

An 82-year-old man, who started his maintenance hemodialysis 17 years ago due to diabetic nephropathy, had been suffering from the intermittent gross hematuria and lower abdominal pain for a month. Besides hematuria, he had no symptoms related to bleeding tendency. Because he had a past history of transurethral resection of the bladder tumor, the bleeding by recurrent bladder cancer was first suspected at the dialysis clinic. However, no abnormal findings were detectable in his bladder. Deterioration of anemia was observed during the month, and he was thus referred to our hospital for admission.

On admission, the patient was 157 cm tall and weighed 53.8 kg. He had a good appetite, and body weight loss was not observed. He had no past personal or family history of

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bleeding diathesis and had no exposure to medications known to cause hemorrhagic complications. Physical examination revealed a blood pressure of 184/83 mmHg, heart rate of 74 beats/min, and body temperature of 36.8 °C. He was anemic, but no other abnormal physical signs were noted. Laboratory data was summarized in Table 1. The hemoglobin level was 7.7 g/dL, and platelet count was 270,000/ μ L. Coagulation studies showed an activated partial thromboplastin time (APTT) of 149.3 s and prothrombin ratio (PT-INR) of 1.87. Because of the prolonged APTT and PT, cross-mixing studies were performed using sera from the patient and a healthy volunteer. The results showed that the APTT and PT curves both were upward convex in shape, indicating the presence of inhibitors to coagulation factors (Fig. 1). Individual factor assays revealed that a factor VIII level was <1 % and the level of factor V was 7 % (Table 2). Moreover, the

inhibitor of factor VIII was 32.7 Bethesda units (B.U.), whereas the inhibitor of factor V was 2.8 B.U. The patient was diagnosed to have inhibitors to factor VIII and factor V simultaneously.

Contrast-enhanced computed tomography and renal angiography were performed to identify the cause of hematuria. The right kidney was enlarged (Fig. 2a), and extravasation from the branch of the right renal superior capsular artery was detected by angiography (Fig. 2b). Extravasation was treated by the transcatheter arterial embolization.

To eradicate the inhibitors against factors VIII and V, the patient took 1.0 mg/kg/day of prednisolone (PSL) orally. As shown in Fig. 3, APTT and PT were gradually recovered, and the titers of inhibitors to factors VIII and V also decreased. Oral PSL was tapered, and the patient was discharged home 66 days after the admission.

Table 1 Laboratory findings at admission

White blood cells (/ μ L)	5600
Red blood cells (/ μ L)	2.47×10^6
Hemoglobin (g/dL)	7.7
Hematocrit (%)	24.6
Mean corpuscular volume (fL)	100
Mean corpuscular hemoglobin (pg)	31.2
Mean corpuscular hemoglobin concentration (g/dL)	31.3
Platelet (/ μ L)	270×10^3
APTT (s)	149.3
PT-INR	1.87
Fibrinogen (mg/dL)	333
Fibrin/fibrinogen degradation products (μ g/mL)	11.6
D-dimer (μ g/mL)	8.3
Total protein (g/dL)	6.1
Albumin (g/dL)	2.6
Urea nitrogen (mg/dL)	16.3
Creatinine (mg/dL)	3.14
Na (mEq/L)	144.6
K (mEq/L)	5.1
Cl (mEq/L)	109
Ca (mg/dL)	8.6
IP (mg/dL)	1.7
Glucose (mg/dL)	96
Lactate dehydrogenase (IU/L)	267
Aspartate transaminase (IU/L)	51
Alanine transaminase (IU/L)	38
Alkaline phosphatase (IU/L)	602
Creatine phosphokinase (IU/L)	48
Iron (μ g/dL)	15
Total iron binding capacity (μ g/dL)	176
Ferritin (ng/mL)	190
C-reactive protein (mg/dL)	3.41

Discussion

We experienced a maintenance hemodialysis patient who exhibited the intermittent hematuria and anemia due to renal hemorrhage caused by the acquired inhibitors against coagulation factors VIII and V. It took about a month from the time when the patient became aware of hematuria to the time to be diagnosed. During this period, anemia was deteriorated and the right kidney was enlarged. The diagnosis was somewhat delayed because of the following reasons. First, hemodialysis patients have a relatively higher incidence of bleeding complications, because heparin is routinely used for the dialysis therapy. Simple adjustment of heparin doses sometimes improves the bleeding symptoms. Second, the patient had a past history of bladder cancer, and the relapse was suspected initially. He spent 1 or 2 weeks before undergoing cystoscopy. Third, hematuria was intermittent and not persistent. Even in these conditions, it is important to consider a rare bleeding disorder, such as acquired coagulation factor deficiency, to avoid non-essential invasive procedures.

Acquired inhibitors are known to be associated with autoimmune diseases, malignancies, pregnancy, organ transplant, bacterial infections, and the exposure to the drugs, such as penicillin, sulfonamides, methyl dopa, and interferon alpha [1, 2]. In addition, factor V inhibitor is often seen in association with the use of topical bovine thrombin in surgical patients [3]. In some groups of patients, there are no apparent causes. In the present case, the cause of acquired inhibitors against factors VIII and V is unknown. The patient had been taking several medications, including valsartan, nifedipine, doxazosin, calcium carbonate, cinacalcet, and lansoprazole. However, these drugs are unlikely to be the cause of the development of

Fig. 1 Cross-mixing tests. Sera from the patient and a healthy volunteer were mixed at the indicated ratio. The APTT (a) and PT (b) were measured 2 h after incubation at 37 °C

Table 2 Laboratory findings for coagulation factors and inhibitors

vWF: Ag (%)	310
vWF: RCo (%)	287
Factor II (%)	69
Factor V (%)	7
Factor VII (%)	128
Factor X (%)	61
Factor VIII (%)	<1
Factor IX (%)	42
Factor XI (%)	42
Factor XII (%)	37
Factor XIII (%)	115
Factor V inhibitor (Bethesda unit)	2.8
Factor VIII inhibitor (Bethesda unit)	32.7

acquired inhibitors, because they had been prescribed for a certain period. In addition, although the patient did not present with any symptoms related to autoimmune diseases, serum tests might be useful to rule out the possibility of co-existing autoimmune diseases. Moreover, the patient had undergone the maintenance hemodialysis therapy. The relationship between the hemodialysis therapy and acquired inhibitors is unclear, because only a few cases of acquired inhibitors in hemodialysis patients have been reported previously [5].

In this case, it is considered that the inhibitors to factor VIII and factor V both contributed to renal hemorrhage. Although the level of factor V was still detectable as 7 %, PT-INR was prolonged, and the PT curve in cross-mixing study was only partially corrected by the addition of normal serum. These laboratory findings cannot be explained by the single deficiency of factor VIII. Indeed, factor VIII and factor V are homologous cofactors for intrinsic Xase complexes (factor IX, factor VIII, Ca^{2+} , and anionic membranes) and the prothrombinase (factor X, factor V, Ca^{2+} , and anionic membranes), respectively [6]. Amino acid identity between factor VIII and factor V is over 40 %. Although speculative, an autoantibody against the homologous domain between these factors might be generated in the patient.

Treatment of acquired inhibitors consists of hemostatic management and eradication of inhibitors [1–3]. In case of acute bleeding episodes, bypassing agents, such as recombinant activated factor VII and plasma-derived activated prothrombin complex concentrate are used as the hemostatic therapy. In our case, these agents were not used, because the bleeding in the patient was not urgent. Alternatively, transcatheter arterial embolization was performed to treat the extravasation in the kidney. To eradicate the inhibitors, it is recommended to use steroids alone or steroids and cytotoxics against acquired hemophilia [1, 2].

Fig. 2 Contrast-enhanced computed tomography (a) and angiography (b). **a** Arrowheads indicate the enlarged right kidney. **b** Arrows indicate the catheter. Arrowheads indicate the extravasation

Fig. 3 Clinical course of the patient with acquired inhibitors to factors VIII and V. APTT (circle) and PT-INR (triangle) during the admission are shown. APTT over 150 s was plotted as 150 s. The titers of inhibitors to factors VIII and V were measured three times during the admission. The patient was treated with PSL, starting at admission day 7

Recent studies have demonstrated that rituximab, an anti-CD20 antibody used to treat B cell malignancies, is also effective for a number of acquired inhibitors. However, it should be noted that there is a general consensus that asymptomatic patients with factor V inhibitor should not be treated regardless of their inhibitor titer and residual factor V level, whereas acquired hemophilia A should be treated immediately. In our case, because the patient had inhibitors to both factor VIII and factor V, he was treated with steroids immediately after the diagnosis.

Acquired inhibitors are sometimes life-threatening, and the relapse has been reported in 20 % of patients [4]. It is important to carefully follow-up the patient for a long period.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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