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CASE REPORT

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A case of acquired hemophilia caused by factor VIII inhibitor with rheumatoid arthritis, successfully treated with immunosuppressive treatment and recombinant activated factor VII

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Abstract We report the case of a patient who presented with acquired hemophilia associated with rheumatoid arthritis. The patient's factor VIII activity was less than 1% and factor VIII inhibitor was detected. Based on the blood analysis, the patient was diagnosed as having the factor VIII inhibitor. She was successfully treated with prednisolone, cyclophosphamide, and gammaglobulin to suppress the factor VIII inhibitor, and the administration of recombinant activated factor VII was effective in controlling severe bleeding episodes.

Key words Acquired hemophilia · Factor VIII · Intramuscular hemorrhage · Recombinant activated factor VII (rFVIIa) · Rheumatoid arthritis (RA)

Introduction

Acquired hemophilia caused by the clotting factor VIII inhibitor is rare, but occasionally develops in nonhemophiliac patients with malignancy, drug reactions, and autoimmune diseases, in postpartum nonhemophiliac patients, or in healthy individuals.[1] Corticosteroid and cyclophosphamide were administered to suppress the factor VIII inhibitor,[2] and plasma-derived clotting factors were administered to treat hemorrhages due to acquired hemophilia caused by the factor VIII inhibitor.[3] Recently, recombinant activated factor VII (rFVIIa) has been used for the treatment of hemorrhage because of its safety and fast action.[3,4]

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We report the case of a patient with acquired hemophilia caused by the factor VIII inhibitor associated with rheumatoid arthritis (RA) who was successfully treated by the administration of prednisolone, cyclophosphamide, gammaglobulin, and rFVIIa.

Case report

A 71-year-old Japanese woman who had had a history of RA for 31 years was admitted to our hospital on December 24, 2002, because of swelling and pain in her left lower extremity. Bloody synovial fluid was drawn from her left knee joint. The swelling and pain developed suddenly on December 18, 2002, without any previous episodes. During examination on admission, cloudy consciousness and anemic palpebral conjunctiva were noted. In addition, marked intramuscular swelling and discoloration of the lower part of the left leg due to bleeding were noted. She had no family history of a bleeding tendency, and both platelet counts and coagulation study results were normal when she was admitted to our hospital because of renal failure due to alfacalcidol in September 2002.

Laboratory results were as follows: total leukocyte count 8.7×10^9/l; hemoglobin level 24 g/l; platelet count 241×10^9/l. The serum liver transaminase level was normal. The C-reactive protein level was 9.5 mg/dl and the erythrocyte sedimentation rate (ESR) was 130 mm/h. The rheumatoid factor was 27 U/ml (normal range 0–15). The anti-agalactosyl IgG antibody was 179.0 AU/ml (normal range 0–6.0). The blood urea nitrogen level was 65 mg/dl and the serum creatinine level was 1.9 mg/dl. The blood coagulation study results were as follows: prothrombin time (PT) and PT-international normalized ratio (INR) were 12.6 s (control 11.3 s) and 81% (normal range 80%–130%), respectively. Activated partial thromboplastin time (APTT) was 86.9 s (control 31.2 s). Prolonged APTT was not corrected by the addition of normal plasma, indicating the presence of a clotting factor inhibitor (Table 1). An assay of clotting factors and inhibitors revealed that the factor VIII activity

Table 1. Plasma mixing test using the plasma of the patient. Prolonged APTT was not corrected by the addition of normal plasma in vitro

Mixing ratio Normal : patient	APTT immediately after mixing (second)	APTT after 60-min incubation at 37°C (second)
1 : 1	54.7	77.5
1 : 4	67.4	87.4

The APTT of the patient was 78.8 s (control 31.2 s)
APTT, activated partial thromboplastin time

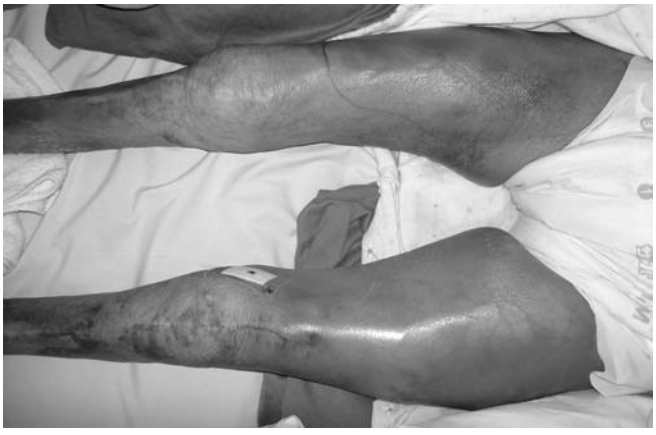

Fig. 1. Intramuscular hemorrhage in the lower extremities of the patient

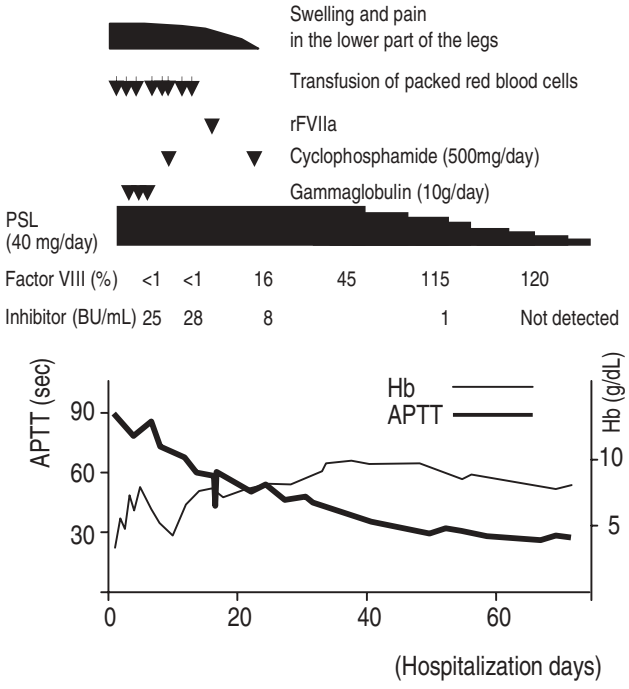

Fig. 2. Clinical course of the patient. The initial dose of prednisolone was 40 mg/day (1 mg/kg body weight/day). *rFVIIa*, recombinant activated factor VII; *PSL*, prednisolone; *BU*, Bethesda unit; *APTT*, activated partial thromboplastin time; *Hb*, hemoglobin

was less than 1% and the factor VIII inhibitor titer was 28 Bethesda units/ml. The β_2-glycoprotein I-dependent anticardiolipin antibody and lupus anticoagulant were not detected. The results of the urinalysis were normal. An X-ray of the hands revealed dislocations and marginal osseous erosions of the finger joints and ankylosis of the carpal bones.

On day 2 of hospitalization, severe intramuscular hemorrhage and pain developed in the patient's right thigh (Fig. 1) and both forearms without any such episodes previously. Based on the laboratory data and clinical manifestations, she was diagnosed as having acquired hemophilia caused by the factor VIII inhibitor. She was treated with a total 12 units of blood by transfusion from day 1 to day 13 of hospitalization, 40 mg/day of prednisolone (1 mg/kg body weight/day), and 10 g/day of gammaglobulin (250 mg/kg body weight/day) for 3 days. In addition, 500 mg/day of cyclophosphamide was administered because the bleeding did not improve even after the administration of prednisolone and gammaglobulin. However, the swelling of the lower part of the left leg was not improved by these treatments; the factor VIII activity was less than 1%, and the factor VIII inhibitor titer was 28 Bethesda units/ml on day 14 of hospitalization. Therefore, a bolus intravenous injection of 4.8 mg rFVIIa (120 μg/kg body weight) was administered three times for 3 h on day 16 of hospitalization.[5] The patient provided informed consent before the administration of rFVIIa. After the rFVIIa administration, the prolonged APTT decreased transiently (Fig. 2), and both the hemorrhage and the pain in her extremities disappeared. After the rFVIIa administration, a stomachache developed transiently. On day 24 of hospitalization, cyclophosphamide (500 mg/day) was readministered. After these treatments, the APTT and factor VIII activity gradually became normal and the factor VIII inhibitor disappeared completely. A reduction in the prednisolone dose was possible with time at a rate of 10% per week. To date, the patient has had no relapse of the acquired hemophilia caused by the factor VIII inhibitor.

Discussion

We report the case of a patient with acquired hemophilia caused by the factor VIII inhibitor associated with RA. The incidence of acquired hemophilia caused by the factor VIII inhibitor in nonhemophiliac patients is very rare, and is

reported to be 1 in 1 000 000 per year.[1] This disease usually develops idiopathically (46%) and 7.9% of the cases are associated with RA.[1]

Corticosteroid, cyclophosphamide, and gammaglobulin have been used in treating acquired hemophilia caused by the factor VIII inhibitor.[6–9] Among these, gammaglobulin has a rapid effect.[10] In our case, a combination therapy using these drugs appeared to normalize the prolonged APTT and factor VIII activity, and finally to decrease the factor VIII inhibitor titer. However, clinical manifestations such as intramuscular hemorrhage and pain did not improve immediately after the combination therapy. Therefore, rFVIIa was administered. rFVIIa is considered to activate factor X by bypassing factors VIII and IX,[11] thereby exerting hemostatic effects. rFVIIa has been a safe and effective treatment for bleeding in patients with hemophilia A and B with inhibitor antibodies. Recently, Hay et al.[12] reported that rFVIIa is also safe and effective as first-line and salvage therapy in patients with acquired hemophilia by factor VIII inhibitor. In that study, a good response was obtained in all bleeds for which rFVIIa was used as first-line therapy, and the response rate after 24 h of rFVIIa salvage therapy was good in 75% of cases, partial in 17%, and poor in 8%. The bolus intravenous injections of rFVIIa were effective in managing intramuscular hemorrhage and muscular pain in the present case, indicating that both immunosuppressive agents and rFVIIa should be administered in controlling hemorrhage in acquired hemophilia caused by the factor VIII inhibitor.

However, transient stomachache was observed in our patient. rFVIIa sometimes induces gastrointestinal thrombosis in patients with atherosclerosis or infections.[13,14] Careful monitoring of thrombosis is necessary after rFVIIa administration because the appearance of transient thrombosis should not be overlooked. At present, we consider that rFVIIa should be administered, with informed consent, to a patient who has severe pain due to hemorrhage, life-threatening hemorrhage, or surgical intervention.

In conclusion, immunosuppressive treatment and rFVIIa administration should be considered as a first-line therapy in the treatment of severe hemorrhage or surgical interventions in acquired hemophilia caused by the factor VIII inhibitor in patients with RA. rFVIIa should be administered with careful monitoring of thrombosis, especially in a patient with a risk factor of thrombosis such as one with atherosclerosis or infections.

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