Acquired Hemophilia A in a Patient with Systemic Lupus Erythematosus

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Abstract

A patient with systemic lupus erythematosus (SLE) developed acquired hemophilia A. The patient, a 24-year-old Japanese woman, was referred to our hospital because of uncontrollable bleeding following a tooth extraction. Laboratory examination revealed prolonged APTT (116 seconds), reduced factor VIII activity (2.8%) and the presence of factor VIII inhibitor at a titer of 46.5 Bethesda units/ml. Transfusion of prothrombin complex concentrate and activated prothrombin complex concentrate followed by administration of prednisolone and cyclophosphamide successfully arrested bleeding and reduced the factor VIII inhibitor level. Acquired hemophilia A is a rare but lethal condition. Rapid diagnosis and introduction of adequate therapies are critical.

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Key words: Factor VIII inhibitor, SLE, prednisolone, cyclophosphamide

Introduction

Acquired hemophilia A is a rare but life-threatening bleeding diathesis caused by autoimmune depletion of factor VIII. Underlying conditions are autoimmune diseases, pregnancy, malignancy, and a drug reaction. In this report, we describe a patient with quiescent SLE who developed acquired hemophilia A. Prednisolone and cyclophosphamide were effective in suppressing factor VIII inhibitor.

Case Report

A 24-year-old Japanese woman consulted a hospital complaining of butterfly rash, oral ulcer, and edema in 1994. Laboratory data were total protein 3.7 g/dl, potassium 5.98 mEq/l, blood urea nitrogen (BUN) 61.2 mg/dl, creatinine (Cr) 2.6 mg/dl, urinary protein excretion 4.0 g/day, anti-nuclear antibody titer \times 640, anti-DNA antibody 188 U/ml, and CH50 13.8 U/ml. There was no abnormality of bleeding or coagulation time; PT was 130% and APTT 22.5 seconds. Renal biopsy revealed diffuse proliferative lupus nephritis, and a diagnosis of SLE was made. She was treated with intravenous methylprednisolone pulse therapy followed by oral prednisolone administration. After treatment, her laboratory data improved; BUN 24.6 mg/dl, Cr 0.7 mg/dl, and CH50 33.2 U/ml. Anti-DNA antibody became negative, and urinary protein excretion was reduced to 0.4 g/day. The patient remained in good condition for a prolonged time period with prednisolone at 10 mg/day. In October 1997, she developed skin eruptions on her arms when cefdinir was given after surgery on her nail. In June 1998, she had nasal bleeding which was difficult to stop. In February 1999, the patient noticed widespread subcutaneous bleeding when she had gone skiing.

In October 1999, the patient had bleeding following a tooth extraction which persisted for three weeks despite sutures. Her hemoglobin (Hb) fell to 6.7 g/dl. After receiving red cell concentrate transfusions, she was transferred to our hospital. On physical examination, her general condition was good except for swelling of the submandibular region due to coagula in her oral cavity. Laboratory findings were Hb 9.7 g/dl, white blood cell count (WBC) 4.5×10⁹/l, platelet count 301×10⁹/l, coagulation time 20 minutes, APTT 116 seconds, PT 119%, and factor VIII activity 2.8%. Factor VIII inhibitor was positive at a titer of 46.5 Bethesda units/ml. Neither lupus anticoagulant nor anticardiolipin antibody was detected. BUN was 10 mg/dl, Cr 0.7 mg/dl, total protein 6.0 g/dl, and albumin 4.1 g/dl. Urinalysis did not reveal any abnormality. CH50 was 31.7 U/ml, and anti-DNA antibody was negative. These data suggested that SLE was quiescent.

She underwent suture and received 9,600 units of prothrombin complex concentrate (PCC) and 8,000 units of activated prothrombin complex concentrate (aPCC) transfusion. Through this therapy, bleeding ceased within 24 hours after admission, but the fibrin degradation products (FDP) level was temporarily elevated up to 101.9 µg/ml. On the third hospital day,
prednisolone (30 mg/day) and cyclophosphamide (100 mg/day) were started. The inhibitor level was gradually reduced. When the patient was discharged in December 1999, factor VIII inhibitor was 0.95 Bethesda units/ml, factor VIII activity 30% and APTT 43.5 seconds. There has not been any recurrence of the disease, and the patient is now being treated with prednisolone (10 mg/day) and azathioprine (50 mg).

**Discussion**

Inhibitor against factor VIII was detected in our SLE patient while searching for the cause of uncontrollable bleeding following tooth extraction. In a survey of 215 non-hemophilic patients demonstrating factor VIII inhibitor, the underlying diseases were rheumatoid arthritis (7.9%), SLE (5.7%), other autoimmune disorders (4.5%), malignant tumors (6.7%), postpartum (7.3%), and drug reaction (6%), no underlying disorders was found in approximately 50% of the patients. Almost the same population has been reported in other series (2, 3), but there is little information to date about the activity of underlying disorders in which factor VIII inhibitor was detected (1-4). It is noteworthy that, in the present case, factor VIII inhibitor was detected though SLE remained well controlled. The patient also had a history of drug allergy to cefdinir in October 1997. There were some reports describing penicillin allergy as a cause of factor VIII inhibitors (1, 5). In some cases, factor VIII inhibitors were detectable for more than one year after causative drugs were discontinued. Although coagulation data were lacking, our patient had two episodes implying hemorrhagic diathesis (nasal bleeding and subcutaneous bleeding) which occurred after allergy to cefdinir. Thus, in our case, cefdinir might have played a causative role in triggering production of factor VIII inhibitor against the background of SLE.

While the mortality rates are decreasing with time (6), management of bleeding is still critical. Administration of PCC and aPCC was quite effective in stopping bleeding in the present case (7), but temporal elevation of FDP was observed. One of the problems in PCC and aPCC is that they sometimes cause DIC and thrombosis. This may be because a large administration is repeatedly required in the treatment of bleeding. In addition, there is no reliable test to monitor the response and efficacy of PCC and aPCC (7). In this respect, recombinant activated factor VII (rFVIIa) is thought to directly activate Xa, and to generate thrombin locally at the site of vessel injury, which reduces the risk of thromboembolic complications. rFVIIa is expected to efficiently control bleeding caused by acquired hemophilia A (7, 8).

To reduce or eliminate factor VIII inhibitor, several therapeutic interventions have been tried. These include 1) plasmapheresis, 2) combined administration of glucocorticoids and...
immunosuppressive agents such as cyclophosphamide, azathioprine and cyclosporine, 3) intravenous gammaglobulin (7). Prednisolone and cyclophosphamide are generally used to treat acquired hemophilia A. A prospective randomized trial indicated that glucocorticoids are recommended as an initial treatment of non-hemophilic patients with factor VIII inhibitor, and that cyclophosphamide is effective as second-line therapy for many of those who are steroid resistant (9). This indicates that cyclophosphamide provides a degree of immunosuppression not available with prednisolone alone. Plasmapheresis is recommended when patients fail to respond to immunosuppressive therapies (10). Intravenous gammaglobulin therapy benefits only a minority of patients with acquired inhibitors (11, 12). However, it offers an alternative mode of treatment for patients who do not respond to or become refractory to immunosuppressive therapies (12).

Although acquired factor VIII inhibitor is a rare condition, its hemorrhagic complications are sometimes lethal. The underlying causes vary, but it should be noted that the factor VIII inhibitor level is not always correlated with underlying disease activity. To save patients with potentially fatal bleeding, rapid recognition of the inhibitor is critical, and immediate administration of rFVIIa rather than PCC or aPCC, followed by prednisolone alone or in combination with cyclophosphamide is recommended.

References