Acquired Haemophilia in a Patient with Systemic Lupus Erythematosus

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Abstract: Acquired haemophilia is a rare bleeding disorder caused by production of autoantibodies directed against coagulation factor VIII (FVIII), with high morbidity and mortality. Systemic lupus erythematosus (SLE) is one of the known associated underlying conditions. We report a case of life threatening bleeding in a patient with acquired haemophilia caused by FVIII inhibitor and underlying SLE. The patient presented with spontaneous bruises over right calf and ankle. Coagulation studies showed isolated prolonged activated partial thromboplastin time, reduced FVIII level, and high FVIII inhibitors. The coagulopathy did not improve despite pulse methylprednisolone followed by oral steroid, azathioprine and intravenous immunoglobulin. One and a half year later, she developed massive, life-threatening haemorrhage refractory to pulse cyclophosphamide, corticosteroid, and plasmapheresis. Finally, combination therapy with rituximab, cyclosporine A, cyclophosphamide, and corticosteroid resulted in clinical and biological remission.

Keywords: Acquired haemophilia, Factor VIII, Systemic lupus erythematosus

Introduction

Acquired haemophilia is a rare bleeding disorder with high morbidity and mortality. According to the United Kingdom registry, the reported incidence of acquired haemophilia is 1.48 cases per million/year. Approximately 50% of cases are associated with underlying medical conditions, such as autoimmune disease, postpartum, and malignancy. Systemic lupus erythematosus (SLE) is one of the known associated conditions. We reported a life-threatening bleeding case of SLE with acquired haemophilia caused by acquired factor VIII (FVIII) inhibitor.

Case Report

A 45 year-old lady was diagnosed to have SLE 7 years ago with photosensitive rash, polyarthralgia, pleuritic chest pain, lymphopenia, positive ANA (titer 1: 25 600), positive anti-double stranded DNA and anti-Ro antibodies. She underwent clinically quiescent disease while maintained on 10 mg of prednisolone per day. In July 2005, she was admitted to United Christian Hospital for spontaneous bruises over the right calf and ankle. There was no epistaxis, haemoptysis, haematuria, tarry or bloody stool. She had not taken any anticoagulants and there was no family history of bleeding disorder. On examination, there was no other bruising or active bleeding noted except for the extensive bruises over right calf and ankle. Laboratory tests revealed haemoglobin of 10.5 g/dl with platelet count of 242 x 10^3/µL. Coagulation studies revealed normal prothrombin time and international normalized ratio, but prolonged activated partial thromboplastin time (APTT) of 93 seconds (normal: 26-35.2 seconds) which was not corrected by incubating for 2 hours at 37°C equal volumes of patient and normal plasma (mixing study). Quantitative assays showed that Factor VIII level was less than 0.01 IU/ml (normal, 0.50-1.50 IU/ml) and FVIII inhibitors were at a level of 82.71 Bethesda units (BU). Factor IX level was normal. Both lupus anticoagulant and anti-cardiolipin antibody were
negative. Her complement and anti-ds DNA levels were normal. From this clinical and laboratory findings, the diagnosis of SLE with acquired haemophilia caused by the FVIII inhibitors was made. She was treated with pulse intravenous methylprednisolone (1 g/day for 3 days) followed by oral corticosteroid (1 mg/kg/day) with azathioprine (100 mg/day) and intravenous immunoglobulin. However, the coagulation test parameters did not improve and recurrent ecchymoses persisted. She declined cyclophosphamide therapy for worry of toxicity.

In April 2007, she developed multiple ecchymoses again over the limbs and right lower abdominal wall after a fall. Ultrasound pelvis and thigh revealed haematoma involving right iliacus muscle, lateral aspect of right-sided lower abdominal wall and right upper thigh. In addition to ecchymoses, tender left cervical swelling appeared. It increased in size rapidly within one day, and resulted in difficulty in swallowing. Computed tomography (CT) of thorax and neck showed left cervical haematoma with extension across midline with trachea and esophagus displaced to the opposite side (Figure 1). Drainage was necessitated to relief the airway. FVIII inhibitor level rose to 425 BU. Repeated courses of recombinant activated factor VII (rFVIIa) and FVIII inhibitor bypassing agent (FEIBA) were administrated. Concomitantly, pulse methylprednisolone and intravenous cyclophosphamide (500 mg monthly) were started. However, bleeding persisted. Plasmapheresis was given but stopped shortly after 3 courses because of lack of adequate response. In view of ongoing active bleeding from cervical wound and epistaxis, 4 weekly doses of rituximab (375 mg/m² per week) and oral cyclosporin A (75 mg BD) were given. No more bleeding was observed eight weeks after the fourth dose of Rituximab. APTT value was markedly reduced to 80 seconds (Figure 2). Two months later, the patient developed headache and vomiting. CT brain showed right intracranial haemorrhage (Figure 3). Oral cyclophosphamide (50 mg daily) was added on top of oral corticosteroid and cyclosporin A. The coagulation test parameters gradually normalized. Figure 4 summarizes the patient’s clinical course together with treatment administration. There has been no recurrence of the haematological disorder after 3.5 years of follow-up (Figure 4).

![Figure 1. CT scan of neck. A large haematoma (arrowheads) was seen in the left side of the neck causing displacement of the trachea to the opposite side.](image)
Figure 2. Graph showing the clinical course of the patient during the life-threatening haemorrhagic episode in 2007.

Figure 3. CT scan of brain. CT scan demonstrated a haematoma over right cerebral hemisphere.
Acquired Haemophilia in a Patient with SLE

Discussion

Acquired haemophilia is a rare life-threatening bleeding disorder caused by production of autoantibodies directed against coagulation factor, most commonly FVIII. Major bleeding occurs in 85% of affected patients and the mortality was 8-22%.\(^2\)\(^3\) SLE associated with acquired haemophilia is well recognized but uncommon. In a case series of 215 non- haemophilic patients with inhibitors to FVIII, up to 50% of cases had an identifiable underlying disease, and 5.6% of patients had SLE.\(^2\)

Bleeding in acquired haemophilia usually occurs in skin, soft tissue, muscle or mucosal membranes and may present as epistaxis, melaena, haematuria, retroperitoneal haematomas or postpartum haemorrhage. Unlike congenital haemophilia, haemarthroses are uncommon.\(^4\) Catastrophic haemorrhage has been reported.

The diagnosis of acquired haemophilia should be suspected in patients with SLE who experience sudden onset of spontaneous bleeding associated with an isolated prolonged APTT. The most common cause of prolonged APTT in patients with SLE is due to the presence of antiphospholipid antibodies, but these antibodies are responsible for thrombosis, rather than bleeding. In order to delineate the cause of prolonged APTT, a mixing study should be performed. It indicates the presence of an acquired inhibitor when mixture of equal volume of patient's plasma and normal plasma after incubation for 2 hours at 37°C cannot correct the abnormality. Once a mixing test suggests the presence of an inhibitor, subsequent identification of a reduced FVIII level with evidence of FVIII inhibitor activity titrated using the Bethesda assay should be carried out.\(^5\)

As illustrated in our case and previous case reports, acquired haemophilia can occur in patients when the underlying SLE is not active.\(^6\)\(^-\)\(^8\) It indicates that the presence of FVIII inhibitor does not always correlate with the general disease activity of lupus. Moreover, the inhibitor level may not correlate with the severity of bleeding.\(^9\)

The fundamental management strategies for acquired haemophilia include the control of bleeding, eradication of the inhibitor, and treating the underlying disorders.\(^10\)

The first line treatment for acute bleeding is with bypassing agents including rFVIIa and FEIBA. The effectiveness of both

**Figure 4.** Follow up progress of the patient.
agents in the treatment of bleeding events for patients with acquired haemophilia has been well documented. The recommended dosage for rFVIIa is 90 mcg/kg every 2-6 hours and the dosage for FEIBA is 50-100 IU/kg every 8-12 hours. The duration of therapy depends on the site and severity of the bleeding and the clinical response. If either rFVIIa or FEIBA is ineffective, the other agent should be tried. There are no comparative studies to suggest that either agent has superior haemostatic effect. Human FVIII concentrates usually have inadequate haemostatic response unless the inhibitor level is low (i.e., less than 5 BU).

To eliminate the inhibitor, immunosuppressive therapy should be initiated once the diagnosis is established. Prednisolone therapy (1 mg/kg/day for 4-6 weeks) remains the first-line treatment. More than 50% of patients respond to corticosteroid. For steroid resistant patients, combination with cyclophosphamide (1.5-2 mg/kg/day) is considered as second line therapy. Cyclosporine A (200-300 mg/day), high dose intravenous immunoglobulin and plasmapheresis are also used as salvage therapy for refractory cases.

Recently, increasing evidence in literature suggested that rituximab, an anti-CD 20 monoclonal antibody, appeared to be a promising alternative for those who failed the 1st-line therapy. The commonly used regime was 375 mg/m² once weekly for 4 consecutive weeks. The respond rate was over 90% from a systemic review on uncontrolled studies. Repeated courses of rituximab or combination with prednisolone and/or cyclophosphamide can improve the response.

Literature on the management of acquired haemophilia associated with SLE was scanty. Most of the experience came from small case series or case report. According to the series by Green et al, autoimmune related haemophilia required treatment with alkylating agents. They reported a decrease or complete disappearance of factor inhibitors after treatment with alkylating agents in 40% of patients. Other authors also proposed using the combination of cyclophosphamide and corticosteroid in the induction therapy. Our patient initially did not respond to corticosteroid and azathioprine. Patient refused cyclophosphamide for worry of toxicity. In the catastrophic and stormy stage, clinical improvement and long-lasting remission was only achieved after combination treatment with rituximab, cyclosporine A, cyclophosphamide and steroid. This case illustrated the stormy and catastrophic course; and daunting difficulties in the management of patients with acquired haemophilia associated with SLE.

In conclusion, we reported a young lady with stable lupus disease who developed life-threatening complications due to acquired factor VIII inhibitor. The existence and clinical severity of factor VIII inhibitor does not necessarily correlate with the general lupus activity. Acquired haemophilia frequently can cause fulminant and potentially fatal bleeding complications refractory to standard immunosuppressive therapy especially in patients with high inhibitor titer. Early recognition and effective treatment are important in reducing morbidity and mortality. Combination therapy with rituximab, cyclosporine A, cyclophosphamide and corticosteroid may be life saving. Aggressive supportive treatment is imperative during the critical periods.

References