Bullous pemphigoid associated with acquired hemophilia

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Case report

A 24-year-old man had bullous pemphigoid confirmed by histopathology, direct immunofluorescence, and a salt-split skin immunofluorescence examination in another hospital. He was treated with prednisolone 15 mg per day and was stable for 2 years. The patient was then admitted to our hospital for simple fasciotomy of an extensive and painful intramuscular hematoma over the right thigh with impending compartment syndrome from a machine injury over the right wrist and right thigh. Extensive bruising combined with swelling and tenderness over the right radial part, the right thigh and some scattered bean-sized dark-red purpura over the back and abdomen were revealed during a physical examination (Figure 1). The patient's history showed that there was no previous personal or family history of bleeding tendency. Preoperative clotting tests showed prolongation of an activated partial thromboplastin time of 43.5 seconds and a normal prothrombin time. Postoperatively, there was extensive wound bleeding that required massive blood transfusion. The factor VIII inhibitor level was 256 Bethesda units/mL (normal: <1 Bethesda units/mL) and the coagulant activity of factor VIII was reduced to 8% (normal: 60–150%). The skin lesions progressed to a diffuse nonblanchable confluent dusky-red ecchymosis over an erythematous-edematous base on the trunk and extremities (Figure 2). Under the impression of acquired hemophilia type A, the patient was treated with recombinant human factor VII (NovoSeven; Novo Nordisk Inc., Bagsvoerd, Denmark) and immunosuppressive therapy was subsequently administered to inhibit antibody production. After replacement therapy with NovoSeven for 24 days, the wound gradually stopped bleeding. Plasmapheresis (once daily for 1 week), pulse therapy with methylprednisolone (1000 mg/day for 3 days) and rituximab (100 mg/week for 2 weeks) were initially used for correcting the coagulopathy. Prednisolone (1 mg/kg/day) and cyclophosphamide (100 mg/day) were prescribed as maintenance therapy. The coagulatory disorder improved after 2 months of treatment associated with reduction of factor VIII inhibitor to 35 Bethesda units/mL with concomitant improvement of ecchymosis (Figure 3). A subsequent reduction in the factor VIII inhibitor level was observed and it was 3 Bethesda units/mL after 3 months of follow-up.

Discussion

Acquired hemophilia, as showed by mucous-cutaneous bleeding, is an uncommon disease due to spontaneous development of autoantibody to factor VIII in patients with no family history of bleeding diathesis. Its annual incidence is one per million with a biphasic mode of age distribution, presenting a small peak between 20 years and 30 years and a major peak between 68 years and 80 years without sex predilection. More than 80% of patients with factor VIII autoantibody experience hemorrhage to the skin, muscles, soft tissues and mucous membranes (e.g. epistaxis, gastrointestinal and urological bleeding, retroperitoneal hematomas), whereas hemarthroses, typical of congenital factor VIII deficiency, are unusual. The mortality rate of acquired hemophilia is 7.9–22%, with most hemorrhagic deaths occurring within the first few weeks after presentation.

Bullous pemphigoid associated with acquired hemophilia is extremely rare and several hypotheses have been proposed to explain the relationship between these two diseases. There is sequence homology between epitopes on factor VIII and the BPAG2 collagen XVII domain because the serum anti-factor VIII antibody may interact with the central collagen-like part of the BPAG2 protein. Maczek et al reported a 47-year-old patient with circulating antibodies against factor VIII
Figure 1  (A) Extensive bruising combined with swelling and tenderness over the right radial part of the wrist, (B) right thigh (C) and some scattered bean-sized dark-red purpura over the back (D) and abdomen are shown.

Figure 2  Diffuse nonblanchable confluent dusky-red ecchymosis over an edematous erythematous base on the trunk and limbs was observed 1 day after simple fasciotomy. (A) The trunk, (B) the medial side of the right leg, (C) the left upper arm and shoulder, and (D) the left lower leg are shown.
who suffered from bullous pemphigoid associated with acquired hemophilia, and direct and indirect immunofluorescent microscopy showed discrete tissue-bound and circulating immunoglobulin G (IgG) reactive with the epidermal basement membrane in a pemphigoid-like fashion. Furthermore, atypical IgG reactivity against a central portion of the extracellular domain of the BP180 antigen was found using immunoblot analysis of the patient’s serum.4 Zhang et al5 found that purified IgG from a patient who had bullous pemphigoid was able to inhibit factor VIII of normal pooled human blood. Moreover, the factor VIII inhibitor was an IgG (IgG4 and IgG1, but predominantly IgG4) directed against the factor VIII A2 domain, and IgG4 and IgG1 concentrations in this patient were higher than normal.5 Ryman et al6 observed the same phenomenon in a case of bullous pemphigoid with factor V deficiency because of the presence of a homologous sequence in factor VIII and V molecules.6

A review of the published literature in English (abstracts included) showed that acquired hemophilia is associated with several autoimmune bullous diseases, such as bullous pemphigoid (10 reported cases), pemphigus vulgaris, acquired epidermolysis bullosa, and cicatricial pemphigoid.3 Among those 10 cases associated with bullous pemphigoid, the age distribution was 38–93 years old. Acquired hemophilia occurring earlier than bullous pemphigoid is yet to be reported. The longest reported duration between the diagnosis of bullous pemphigoid and acquired hemophilia is 3 years.3 Two cases presented were bullous pemphigoid and acquired hemophilia occurring at the same time. Recombinant factor VII was used in the treatment in 5 of the abovementioned 10 cases. Systemic corticosteroids combined with different types of immunosuppressive agents were prescribed in seven cases. Two patients died because of hemorrhagic shock, multiple organ failure and sepsis, and both of them were older than 80 years old.3

It is difficult to screen for the possible association between bullous pemphigoid and acquired hemophilia because many low-titer inhibitors may be unrecognized and underestimated unless patients undergo surgery or trauma. Diagnosis is based on (1) prolongation of activated partial thromboplastin time, (2) activated partial thromboplastin time cannot be corrected by incubating the patient’s plasma with equal volumes of normal plasma, (3) factor VIII inhibitor positivity, and (4) no previous personal or family history of bleeding tendency. Patients with low titers of inhibitor (<5 Bethesda units/mL) can be treated with desmopressin alone or in combination with concentrates of human factor VIII. When the inhibitor titer is higher than 5 Bethesda units/mL in acute bleeding episodes, either heterologous porcine factor VIII concentrates, activated prothrombin complex concentrates, or recombinant activated factor VII can be used. Concentrates of human factor VIII are not recommended because cross-reactivity with anti-human factor VIII antibody may occur and this anamnestic response may increase the amount of anti-human factor VIII antibody. Therapeutic plasmapheresis or immunoabsorption of immunoglobulins to staphylococcal protein A or to polyclonal sheep antibodies against human immunoglobulins can be used as temporary extracorporeal removal of the autoantibody. Methods to eradicate the autoantibodies include (1) immunosuppressive agents (such as corticosteroids, cyclophosphamide, azathioprine, 6-mercaptopurine, vincristine, high dose immunoglobulins or cyclosporine), and (2) rituximab, an anti-CD20 monoclonal antibody, which has been shown to be effective in immune disorders caused by autoantibodies, including acquired hemophilia A.7

Figure 3  Resolution of ecchymosis after 2 months of treatment. (A) The back, (B) left upper arm and shoulder, and (C) the medial side of right leg are shown.
Old age, comorbidity with other diseases and high inhibitor titers are poor prognostic factors in this disease as shown from a meta-analysis on treatment and prognostic markers in acquired hemophilia. Published data had shown that there were only two cases where factor VIII inhibitor was higher than 100 Bethesda units/mL, our patient is the third case. Moreover, our patient had no comorbidity with other diseases and he is the youngest case to present with bullous pemphigoid associated with acquired hemophilia to date. These were favorable factors for his treatment even though there was a supranormal level of factor VIII, which increased the patient’s potential for recurrent thrombosis.

In conclusion, a rapid diagnosis and effective treatment of bullous pemphigoid associated with acquired hemophilia are imperative. To avoid relentless bleeding and to achieve a favorable outcome, multiple combined treatments such as coagulation factor supplement, additional immunosuppressive agents (e.g. cyclophosphamide) or rituximab may be needed. However, significant adverse effects resulting from the therapy should also be closely monitored.

References