Coexistence of acquired hemophilia A and epidermolysis bullosa acquisita: Two case reports and published work review

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ABSTRACT

Epidermolysis bullosa acquisita (EBA) is a rare chronic subepidermal bullous autoimmune disease. The occurrence of acquired hemophilia A (AHA) is low and so the coexistence of EBA and AHA is extremely rare. We herein described a case of EBA coexisting with AHA and a case of EBA coexisting with AHA and hepatitis B. These EBA may be related to the pathogenesis of AHA. In this study, we analyzed the clinical features in the two Chinese cases of EBA coexisting with AHA, and found esophageal hemorrhage and hematemesis were the main symptoms of both patients. Cyclosporin, prednisone and lamivudine effectively control EBA with AHA and hepatitis B. The dose of cyclosporin should be more than 4 mg/kg per day and the period of treatment should be longer than 5 months to reduce the risk of EBA co-occurring with AHA.

Key words: acquired hemophilia A, cyclosporin, epidermolysis bullosa acquisita, hepatitis B, lamivudine.

INTRODUCTION

Epidermolysis bullosa acquisita (EBA) is a rare chronic subepidermal bullous disease characterized by an autoimmune response to type VII collagen. The occurrence of acquired hemophilia A (AHA) is also low and is caused by antibodies to factor VIII (FVIII). The coexistence of EBA and AHA is rare. Using PubMed, a review of the English-language published work since January 1900 revealed three case reports of EBA coexisting with AHA. However, hematemesis has not been reported in these cases. Here, we report two cases of EBA coexisting with AHA, which exhibited characteristic features of EBA with AHA on biopsy, immunofluorescence and laboratory studies. Esophageal hemorrhage and hematemesis were the main symptoms of both patients.

CASE REPORTS

Case 1

A 29-year-old man presented with a 5-day history of hematemesis and 2-year history of tense blisters and erythema on his trunk and extremities. His past medical history was unremarkable except for 10 years of hepatitis B. His family members had no similar conditions. Physical examination showed bullae and hemorrhagic crusting on his trunk and extremities that left no milia or scars after healing (Fig. 1). No ocular or oral lesions were observed.

Laboratory studies revealed the following: the activated partial thromboplastin time (aPTT) was markedly prolonged at 105.1 s (normal range, 22.7–31.8) and was not corrected by incubation of patient’s plasma with normal plasma at 37°C for 2 h; a low activity of FVIII (0.3%; normal, 50.0–150.0%); and high titers of FVIII inhibitors (64 BU/mL plasma; normal, <0.6 BU/mL plasma). Virus tests revealed active hepatitis B virus (HBV) infection with positive of hepatitis B surface antigen, hepatitis B e-antigen and anti-hepatitis B core antibodies. Liver and renal functions were normal. Gastrointestinal endoscopy revealed esophageal varices and esophageal hemorrhage. A biopsy of the lesion revealed subepidermal blister formation in the papillary dermis infiltrated with neutrophils and lymphocytes (Fig. 2). Direct immunofluorescence (DIF) showed immunoglobulin (Ig)G and C3 deposition along the basal membrane zone (BMZ). Indirect immunofluorescence showed anti-BMZ antibodies, which reacted with the dermal side of 1 mol/L sodium chloride-split skin (Fig. 3). Immunoblotting of normal human dermal extract exhibited IgG reactivity with 290-kDa proteins. Autoantibodies against type VII collagen were positive by enzyme-linked immunosassay.

From those findings, we diagnosed the patient as having EBA, coexisting with AHA and hepatitis B. The patient was
Case 1 treated with 0.8 mg/kg per day of prednisone and 100 mg of cyclophosphamide daily to eradicate the acquired inhibitor and EBA lesions. At the same time, 0.1 g lamivudine daily was prescribed to treat the hepatitis B. Seven days later, the bullous lesions gradually disappeared. The hematemesis also resolved but the aPTT remained prolonged (96.2 s). Cyclosporin was prescribed at a dose of 4 mg/kg per day and cyclophosphamide was stopped due to side-effects. One month later, the dose of cyclosporin was increased to 5 mg/kg per day because of poor effect. After 7 months of treatment, the conditions improved and the activity of FVIII increased gradually to 5.8% and the titer of FVIII inhibitor was 28.8 BU/mL plasma. The dose of prednisone was tapered to 0.5 mg/kg per day and cyclosporin 5 mg/kg per day was continued. Liver and renal functions remained normal.

Case 2
A 45-year-old man presented with a 10-month history of widespread cutaneous erythema and blistering on the trunk and extremities along with a 6-month history of intermittent hematemesis. During the previous 6 months, hematemesis had intermittently developed on two occasions with at approximately 150 mL every time. He was transfused with packed red blood cells each time. His family members were healthy and his past medical history was unremarkable. Physical examination revealed sparse blisters on the trunk with erosions, scarring and milia formation. Nikolsky’s sign was negative. The oral mucosa, scrotum and perineum were not

Figure 1. Vesicles and bullae on his (a) left hand and (b) forearm.

Figure 2. Biopsy of the lesion showing subepidermal blister formation in the papillary dermis infiltrated with neutrophils and lymphocytes (hematoxylin–eosin, original magnifications: [a] ×40; [b] ×400).

Figure 3. Immunofluorescence showing immunoglobulin G anti-basement membrane zone antibodies, which reacted with the dermal side of 1 mol/L sodium chloride-split skin (original magnification ×40).
involved. Upper gastrointestinal endoscopy demonstrated extensive esophageal hemorrhage.

A skin biopsy showed a neutrophil and eosinophil-rich subepidermal blister and indirect immunofluorescence analysis of 1 mol/L sodium chloride-split skin revealed linear dermal side staining of IgG at a titer of 1:160. During the treatment, the skin biopsy presented with persistent bleeding. Thorough investigation revealed that aPTT was markedly prolonged at 51.4 s and this was not corrected by incubation of the patient’s plasma with normal plasma at 37°C for 2 h, with low activity of FVIII (6.9%), and high titer of FVIII inhibitor (>296 BU/mL plasma). He was diagnosed as having EBA coexisting with AHA and was treated with 1.2 mg/kg per day of prednisone and 4 mg/kg per day of oral cyclosporin daily. After 5 months of treatment, his aPTT was normal and titer of FVIII inhibitor were decreased to undetectable levels. The dose of prednisone was tapered regularly and the patient remains in follow up.

DISCUSSION

Epidermolysis bullosa acquisita is characterized by the presence of autoantibodies against type VII collagen, and these antibodies were correlated with disease severity. Clinically, two major types, mechanobullous (non-inflammatory or classical) and inflammatory variants, can be differentiated. The first two major types, mechanobullous (non-inflammatory or classical) and the other was considered classical. AHA is caused by an autoantibody directed against circulating coagulating FVIII. Patients are prone to life-threatening hemorrhage because of an underlying disease, typically another autoimmune disorder. The two cases reported here were diagnosed with AHA coexisting with EBA. To our knowledge, only three cases of EBA coexisting with AHA were reported in the published work. The coexistence of EBA and AHA was not merely coincidental, although the common mechanism is not known. We hypothesize that VII collagen and FVIII share some common antigens. Antibodies against collagen VII or FIII were decreased to undetectable levels. The dose of prednisone was tapered regularly and the patient remains in follow up.

EBA coexisting with AHA

For the two patients reported here, esophageal hemorrhage and hematemesis were the main symptoms except for tense blisters. Our findings support the fact that patients with both EBA and AHA often suffer from gastrointestinal hematemesis. If an EBA patient presents with recurrent hematemesis, AHA should be suspected.

Cyclosporin proved to be effective when the EBA and AHA failed to respond to conservative therapy. The two patients presented here were treated successfully with cyclosporin and prednisone without any detectable therapeutic side-effects. For the first patient, the dose of cyclosporin was 5 mg/kg per day. After treatment for 7 months, his condition improved (the activity of FVIII increased to 5.8% and the titer of FVIII inhibitor was 28.8 BU/mL plasma) but these indicators did not return to normal levels. At the time of reporting, the patient is still in follow up. For the second patient, the dose of cyclosporin was 4 mg/kg per day. After 5 months of treatment, his aPTT was normal and titers of factor VIII inhibitor were not detectable. Maize et al. reported a case of AHA with EBA. Cyclosporin 100 mg twice daily (4 mg/kg per day) for 3 weeks controlled both disease processes though the patient was resistant to prednisone, colchicine and pulse cyclophosphamide. The EBA relapsed when the cyclosporin was tapered to 100 mg daily (2 mg/kg per day) but it cleared after 3 weeks when the dose was increased to 100 mg twice daily. Cyclosporin has since been decreased gradually to 50 mg daily (1.0 mg/kg per day) without relapse of either condition or detectable side-effects.

Another challenge in the first patient was HBV infection because corticosteroid and cyclosporin has the potential to activate HBV. After treatment with cyclosporin for 1 year, the hepatitis B did not worsen. At the follow up after a year and 3 months, the patient was free of discomfort and his liver function remained stable. Unfortunately, we did not detect HBV DNA copies prior to treatment for comparison.

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CONFLICT OF INTEREST: None declared.

REFERENCES


