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Case Report

Acquired haemophilia A in a patient with pemphigus vulgaris: A case report on a rare coexistence.

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Introduction

Acquired haemophilia A (AHA) is a rare bleeding disorder due to acquired inhibitors against coagulation factor VIII [1]. Compared to congenital haemophilia, AHA is rare with 1.5 cases per million population per year. The disease occurs in all ethnic groups, with equal male to female ratio and 85% of cases are above the age of 60 years [2]. Cutaneous, retroperitoneal, muscular, gastrointestinal and urogenital bleeding are common manifestation of acquired haemophilia whereas haemarthrosis is rare, in contrast to congenital haemophilia [3]. The bleeding severity in AHA varies; although 30% of patients do not require any haemostatic support, others having a risk of life threatening or limb threatening bleeding [4]. The mortality associated with AHA has been reported to be between 8-42% and studies revealed that 16% of deaths were due to the effects of immunosuppression and infection whilst 3–8% were attributed to bleeding manifestations [1,4]. AHA is often associated with autoimmune conditions, malignancy, lymphoproliferative disorders, dermatological conditions, drugs and pregnancy; 50% of cases are idiopathic [1,3]. Autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, cryoglobulinemia, Sjogren's disease, bullous pemphigoid, pemphigus foliaceous and pemphigus vulgaris are known to associated with AHA [6]. Here we present a case report of a male patient with AHA with underlying pemphigus vulgaris which is an autoimmune dermatological condition and has a rare association with AHA with very few case reports in the literature [7,8].

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Case history

A 64-year-old male with type 2 diabetes mellitus presented to the local hospital with progressively enlarging discolouration in the left thigh with worsening thigh pain and restriction of movement of the limb, over 5 days duration. There was no preceding history of trauma, fever or swelling of the affected limb. A clinical diagnosis of thigh haematoma was made and he was transferred to National Hospital, Kandy for further evaluation and management. There was no history of loss of appetite or loss of weight or night sweats. He denied any joint pain, hair loss or photosensitive rashes or high risk sexual behavior. He did not have any personal or family history of bleeding disorders. Few months prior to this bleeding manifestation, he was evaluated for generalized blistering lesions and diagnosed to have pemphigus vulgaris but defaulted follow up.

He was severely obese with a BMI of 36 kg/m^2. He was afebrile, mildly pale and not icteric; there were generalized pustular and vesicular rashes compatible with his underlying dermatological condition. He had a large left thigh haematoma but no other petechiae or purpuric lesions and no evidence of gum bleeding or epistaxis. There was no lymphadenopathy or hepatosplenomegaly and other system examination was unremarkable.

His FBC revealed a haemoglobin level of 9.9 g/dL with a platelet count of 315 x 10^3/µL and WBC count of 7.3 x 10^3/µL. His coagulation profile was normal except for isolated prolongation of APTT which was 94 seconds. Failure of correction of the prolonged APTT with mixing of pooled normal plasma suggested the presence of an inhibitor. Factor assay revealed a factor VIII level of 0.5% with normal factor IX and XI levels. The Bethesda assay to quantify inhibitory antibodies was done and the titre was 691 BU. Based on the clinical and laboratory findings, a diagnosis of acquired haemophilia A was made, where acquired IgG antibodies against factor VIII leads to inactivation causing abnormal bleeding manifestations.

Ultrasound scan of the left thigh revealed a large psoas haematoma measuring 12.5cm x5.8 cm with no evidence of neurovascular compression. Ultra sound scan of the abdomen did not revealed hepatosplenomegaly or para-aortic or intra-abdominal lymphadenopathy or other masses suggestive of underlying malignancy. Further his ESR and LDH levels were within the normal range.

For the management of acute severe bleeding, intravenous tranexamic acid along with Factor Eight Inhibitor Bypassing Activity (FEIBA) at 50 U/kg given 12 hourly was started. Oral prednisolone 1mg/kg/day and cyclophosphamide 1.5 mg/kg/day were initiated as the immunosuppressive regimen. The patient did not respond to initial treatment and the size of the haematoma increased accompanied by severe pain in the affected limb. He also developed new onset of painless haematuria with a rapid haemoglobin drop to 6.6 g/dL, which required red cell transfusion. Considering the possibility of steroid resistance, prednisolone was rapidly tailed off and cyclophosphamide was withheld. Due to the rapid clinical deterioration of the patient, intravenous rituximab 375mg/m^2, was

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given weekly for 4 weeks. Following the first dose of rituximab, there was a significant reduction in bleeding with resolving haematoma and cessation of haematuria. At the end of the rituximab course patient achieved complete remission with factor VIII level of 98% and negative Bethesda test. His long term management was planned along with the help of a multidisciplinary team. Physiotherapy, dietary and nutritional care and long term haematological and dermatological follow up were arranged.

Discussion

Acquired haemophilia A (AHA) is an abnormal bleeding disorder due to the formation of autoantibodies against factor VIII. Most acquired factor VIII inhibitors are IgG1 and IgG4 autoantibodies directed towards the epitopes in the A2, A3 and C3 domains of the factor VIII molecule [5]. Literature revealed that 11.6% of cases of AHA are associated with an underlying autoimmune condition [6]. Pemphigus vulgaris is a chronic autoimmune dermatological condition and one of the rare coexisting conditions with AHA [7,8]. It is a mucocutaneous blistering disorder characterised by the loss of keratinocytes in the epithelium of skin and mucous membrane. It results from autoantibody formation against skin proteins desmoglein 1 and 3, which are transmembrane glycoproteins involving cell-to-cell adhesion [8]. Pemphigus vulgaris is a potentially life threatening disease with a mortality rate of 5-15% (9). The widespread loss of the epidermal barrier leads to loss of fluid and proteins, electrolyte imbalance, increased catabolism and increased risk of local and systemic infections. There is a good response to systemic glucocorticoids and rituximab as first line therapy and azathioprine and mycophenolate mofetil are beneficial as steroid sparing agents [10,11]. A hypothesis suggests that development of autoantibody cross reactivity between anti desmoglein 1 and 3 antibodies and factor VIII epitopes leads to the development of AHA with pemphigus vulgaris [8].

The diagnosis of AHA is based on, new onset abnormal bleeding with isolated prolongation of APTT which is not corrected with pooled normal plasma and the presence of inhibitors. Further clinical assessment and investigations should be done to identify the underlying coexisting condition even though 50% of cases are idiopathic [1,3].

Management of AHA includes achieving haemostasis in a bleeding patient and eradicating the inhibitor. For the acute bleeding, bypassing agents including Factor Eight Inhibitor Bypassing Activity (FEIBA) which contains activated factors VII, IX, and X or recombinant activated factor VII can be used; there are no data to suggest superiority of one over another of these haemostatic agents, even though the latter has viral safety [1,3,12]. Recent studies revealed the beneficial effect of recombinant B domain deleted porcine factor VIII in AHA [3,13]. Use of human factor VIII for acute bleeding can increase the inhibitor titre leading to inactivation of human factor VIII, which makes it ineffective. But for patients with low titre inhibitors (<5 BU) initial therapy with human factor VIII can be considered, if the bypassing agents are not available [1,3,12,13].

For the eradication of inhibitors, immunosuppressive therapy with glucocorticoid alone or in combination with a cytotoxic agent is considered as the first line therapy, where

some studies show superior effect with combination therapy [12,13]. Based on this, our patient was treated with prednisolone with cyclophosphamide as the first line therapy but failed to achieve a remission. The success rate for steroid monotherapy and a combination of steroid/cyclophosphamide are 35.2% and 80% respectively [14]. Rituximab, a monoclonal antibody against CD 20 antigen on B cell surface has a rapid clinical response with increased remission rate and is recommended in patients with refractory AHA with poor response to steroids [1,3,13]. In studies, rituximab has been used in patients with AHA as monotherapy or in combination with other immunosuppressive drugs or steroids [14,15]. There is a significant clinical response, with around 85% of complete response and 12% of partial response in patients treated with rituximab-based therapy [15]. Further, cyclosporine, mycophenolate mofetil and vincristine have also been showed to be effective in AHA in steroid resistant cases [16,17]. Immuno-adsorption therapy and immune tolerance protocols showed some beneficial effects in the management of AHA [3,13]. However, current evidence does not recommend the use of immunoglobulin in antibody eradication [3,13]. The goal of immunosuppressive therapy in AHA is to reduce the time duration taken to achieve remission and to decrease the bleeding severity thus reducing life-threatening complications.

Emicizumab a biphasic factor VIII mimetic antibody which prevents recurrence of bleeding, used widely for congenital haemophilia A, was recently found to be effective in the management of AHA reducing the side effects of immunosuppressive regimens and risk of thromboembolic complications compared to other bypassing agents [18]. Nevertheless, further studies are ongoing prior to recommendation of emicizumab in clinical practice.

Our patient who had a history of pemphigus vulgaris, was initially treated with prednisolone and defaulted follow up while awaiting rituximab therapy. Persistence of autoantibody could be the precipitating event in developing AHA in this patient which was managed as a steroid resistant case.

Conclusion

Even though acquired haemophilia A is a rare entity, it should be considered as one of the causes of adult onset abnormal bleeding, especially in a patient with underlying autoimmune disorder. Early clinical suspicion, diagnosis and prompt management of the severe refractory form of acquired haemophilia A is lifesaving.

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