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Case and Review

Bullous Pemphigoid Associated with Acquired Hemophilia A: A Case Report and Review of the Literature

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Keywords
Bullous pemphigoid · Acquired hemophilia A · Factor VIII inhibitor

Abstract
Acquired hemophilia A (AHA) is a rare autoimmune disorder with high morbidity and mortality. It results from the development of circulating autoantibodies against factor VIII. AHA can be seen in association with autoimmune vesiculobullous diseases, autoimmune diseases, malignancy, pregnancy, and medications. We report a 68-year-old Thai woman diagnosed and treated for bullous pemphigoid (BP) for 11 months who recently presented with a 3-day history of extensive hemorrhagic bullae and large intra-oral buccal hematoma. Laboratory investigations confirmed a prolonged activated partial thromboplastin time, a low factor VIII level, a high factor VIII inhibitor level, and elevated anti-BPAG180 and anti-BPAG230 titers, confirming the diagnosis of BP associated with AHA. Immunosuppressive therapy with systemic corticosteroids and cyclophosphamide combined with bypassing agents for bleeding control resulted in significant clinical improvement and subsequent negative antibody levels. There was no recurrence after a 7-month follow-up period. Due to life-threatening bleeding in severe AHA cases, early diagnosis and effective treatment in this condition are essential.

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Introduction

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by autoantibodies directed against factor VIII. Factor VIII is composed of a heavy chain (A1-a1-A2-a2 domain) and a light chain (a3-A3-C1-C2 domain). Autoantibodies in AHA are typically polyclonal in the immunoglobulin G (IgG) 4 subclass and bind to A2, A3, or C2 domains, thus affecting the binding of FVIII to other clotting factors, von Willebrand factor, membrane phospholipid, and activated C protein, which finally results in an abnormal coagulation cascade. The incidence of AHA is one person per million per year [1–4].

AHA is more common in the elderly population. In approximately 50% of the cases, no underlying disease is identified. The remaining cases have coexisting conditions, such as autoimmune diseases, solid organ and/or hematologic malignancy, pregnancy, and medications [5]. The autoimmune diseases reported to be associated with AHA include systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, multiple sclerosis, cryoglobulinemia, pemphigus vulgaris, and bullous pemphigoid (BP).

We present a case of BP associated with AHA and a literature review of 17 cases with this rare condition (Table 1).

Case Report

A 68-year-old Thai female presented with tense bullae on the extremities. Initial investigations, including histology and direct immunofluorescence, were performed in another hospital prior to this admission. Histopathology showed subepidermal vesicles, well-preserved dermal papillae, and a dense inflammatory cell infiltrate, predominantly eosinophils (Fig. 1). Direct immunofluorescence demonstrated linear IgG and C3 deposition along the dermoepidermal junction. The patient was diagnosed with BP. For treatment of BP, she was prescribed oral prednisolone 20 mg/day, nicotinic acid 150 mg/day, and topical 0.05% clobetasol propionate cream, which resulted in clinical improvement. Her skin lesions have been stable for 10 months with a maintenance dose of oral prednisolone 5 mg/day and nicotinic acid 200 mg/day.

Her past medical history included hypertension, dyslipidemia, and type 2 diabetes mellitus. Her medications included hydrochlorothiazide 25 mg/day, losartan 50 mg/day, and neutral protamine hagedorn/regular insulin (70/30) 36 U/day for 10 years. She has not received any new medications. She denied a previous bleeding tendency in her personal and family history.

One month prior to presentation at our hospital, she developed new tense bullae on the trunk and extremities. She was treated at another hospital, where her oral prednisolone dose was increased to 15 mg/day without clinical improvement.

Three days before she was seen at the otorhinolaryngology outpatient department of our hospital, she developed a large hematoma on the right buccal mucosa with extensive new tense bullae that became hemorrhagic on her trunk and extremities. The patient was admitted to our hospital in the otorhinolaryngology department for close monitoring of upper airway obstruction. She had no signs of gastrointestinal bleeding, such as hematemesis, melena, hemoptysis, and hematuria.

Dermatological examination revealed multiple hemorrhagic and few clear tense bullae on the trunk and extremities (Fig. 2, Fig. 3) involving approximately 20% of the body surface area. Complete blood count showed moderate anemia (hemoglobin level of 7.9 g/dL) and normal white blood cell and platelet count. International normalized ratio was normal, but activated partial thromboplastin time (aPTT) was prolonged at 75.1 s (normal range: 22–33 s). The mixing test showed failure to correct aPTT, indicating that this patient had a factor inhibitor in the intrinsic pathway. Factor VIII level was 0% (normal: 50–150%), and factor VIII inhibitor level was 28 BU/mL (normal: negative), which thus confirmed the diagnosis of AHA. Enzyme-linked immunosorbent assays (ELISAs) for anti-BPAG180 and anti-BPAG230 were both more than 200 RU/mL, correlating to high activity of BP.

After consultation with hematology, anemia from blood loss was corrected with blood transfusion, and bleeding was controlled with activated prothrombin complex concentrate APCC (factor eight bypassing activity [FEIBA VH, Baxter BioScience, Westlake Village, CA, USA]) and tranexamic acid. To suppress antibody production, she received intravenous dexamethasone 20 mg daily for 1 week. The aPTT gradually decreased from 75.1 to 52.6 s. Factor VIII inhibitor level also decreased from 28 to 5.68 BU/mL. Her cutaneous eruptions and intraoral hematoma resolved in 3 weeks. Oral prednisolone 30 mg/day (0.5 mg/kg/day) in combination with cyclophosphamide 50 mg/day were prescribed as maintenance therapy.

At 1-month follow-up, aPTT and factor VIII level returned to normal. Factor VIII inhibitor level was also undetectable. The patient did not develop any further bleeding event. She still continues on a tapering dose of oral prednisolone 5 mg/day and cyclophosphamide 50 mg/day to control BP and AHA up to 7 months after the onset of AHA.

Discussion

BP is an autoimmune blistering skin disease, characterized by subepidermal blister formation on the skin and rarely the mucous membrane. The pathogenesis is the presence of circulating IgG autoantibodies against BP180 and BP230 antigen.

BP has been reported in association with many diseases, including neurodegenerative disorders (Parkinson's disease, stroke, and dementia) [6]; however, there are few case reports of BP associated with AHA. The pathophysiologic mechanism remains unclear. Despite the possibility of BP and AHA as merely coexisting conditions, it has been postulated that there may be a possible relation between these 2 autoimmune diseases. One hypothesis is the cross-reactivity of antibodies due to sequence homology between epitopes on factor VIII and the BP180 collagen XVII domain [7]. There are few case reports that demonstrate the activity of IgG subclass (IgG4 and IgG1, IgG4 predominantly) against the 44 kDa (A2 domain) of factor VIII using immunoblotting and immunonephelometric method [8].

Based on our review of the 17 cases of BP associated with AHA, the age distribution varied from 24 to 88 years old, and there was no gender predisposition. The ethnicities, including this case, were 11 Caucasian and 7 Asians. To the best of our knowledge, there has been no significant predilection in ethnicity; however, more case reports should be collected to find some genetic bridge between these cases, if any. Most patients developed AHA after the onset of BP, as in this patient. The longest reported duration was 3 years.

AHA is a rare autoimmune bleeding disorder occurring in about one per million per year. It is caused by the production of IgG autoantibodies targeting endogenous factor VIII [9]. The most common presentation of AHA is subcutaneous bleeding (ecchymosis) followed by hematoma, gastrointestinal, genitourinary (hematuria), and retroperitoneal bleeding. However, hemarthrosis, which is a common symptom in congenital hemophilia, rarely occurs [10].

In approximately 50% of AHA patients, no underlying disease is identified. The remaining 50% are associated with autoimmune diseases, malignancy, pregnancy (post-partum period), and medications. The drugs reported to be associated with AHA include penicillin, sulfonamide, quinolone, phenytoin, methyldopa, hydralazine, antidepressant, clopidogrel, and interferon-alpha [4]. This patient suffers from hypertension, dyslipidemia, and type 2 diabetes; however, after reviewing her medication history, we could not find any culprit drug that could cause either drug-induced BP or AHA. Cases of AHA associated with autoimmune disease typically have high inhibitor titers, while malignancy-, pregnancy-, and medication-induced cases have low inhibitor titers [11].

Prognosis of AHA depends on the severity of hemorrhage and response to immunosuppressive drugs. Poor prognosis is associated with old age, comorbidity, and high inhibitor titers (>20 BU/mL) [11]. The mortality rate resulting from severe bleeding ranges from 7.9 to 22.2% [11].

To date, treatment of AHA is based on anecdotal case reports which focus on the eradication of autoantibodies with immunosuppressive drugs and bleeding control with bypassing agents [12, 13]. For the eradication of autoantibodies, corticosteroid alone or in combination with cyclophosphamide is considered the first-line therapy (Table 2). Rituximab has been reported to be successfully used as a second-line treatment of AHA [14]. Other immunosuppressive drugs used in the literature include cyclosporine, azathioprine, vincristine, high-dose immunoglobulins (IVIg), and mycophenolate mofetil [2, 4]. Relapse is common after discontinuing immunosuppressive therapy.

Bypassing agents are the first-line therapy for bleeding control due to their high effectiveness and rapid action. Available bypassing agents are recombinant activated factor VII (rFVIIa or Novoseven®) or activated prothrombin complex concentrate (aPCC or FEIBA®) [15]. In this case, we used FEIBA® which contains various activated clotting factors that bypass steps in blood clot formation. The dosage of aPCC is 50–100 U/kg every 8–12 h (not exceeding 200 U/kg/day) [9].

Human factor VIII replacement can also be used to control bleeding but is not effective in patients with high factor VIII inhibitor titers. In cases with low factor VIII inhibitor levels (<5 BU/mL), the replacement dose should be adjusted to suppress the inhibitor [9, 16].

Furthermore, invasive procedures or surgery should be avoided. In cases of emergency where surgery cannot be postponed, effective hemostatic therapy should be achieved before as well as after the procedure [4].

In conclusion, AHA associated with BP is rare and should be suspected in BP patients presenting with hemorrhagic bullae, hematoma, ecchymosis, and systemic bleeding with no personal or family history of a bleeding tendency. Life-threatening conditions, such as massive bleeding and upper airway obstruction, can occur; therefore, early diagnosis and effective treatment are important. Treatment involves both suppression of autoantibody production with immunosuppressive drugs and bleeding control with bypassing agents. Long-term follow-up is essential even after complete remission due to the possibility of relapses.

Statement of Ethics

The authors confirm that the patient was fully informed, and she agreed to the report of her case.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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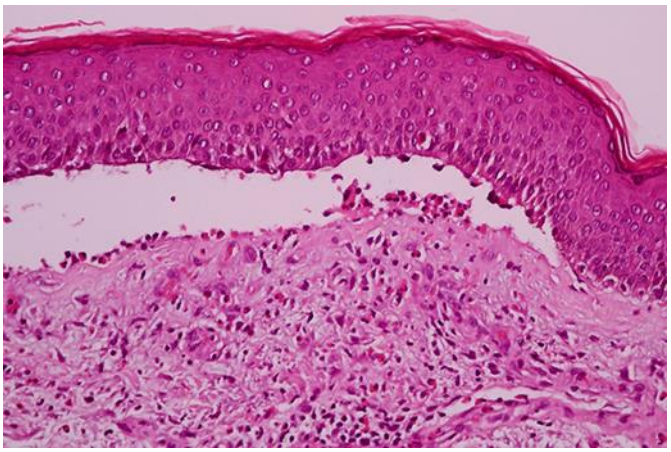

Fig. 1. Histopathology shows subepidermal separation and dense inflammatory cell infiltration, predominantly eosinophils.

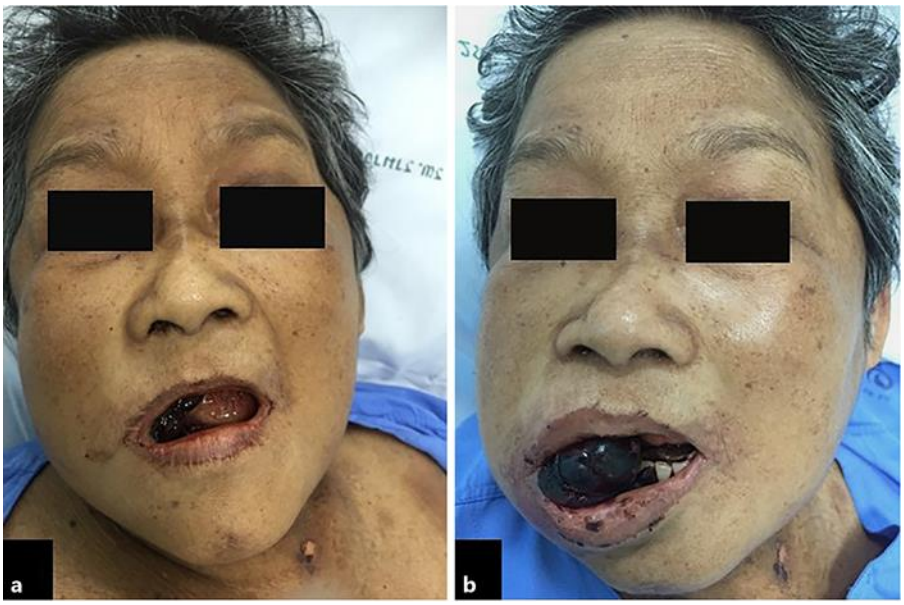

Fig. 2. **a** Large hematoma on the right buccal mucosa and floor of the mouth on the day of admission. **b** Progression of the hematoma within 1 day after admission.

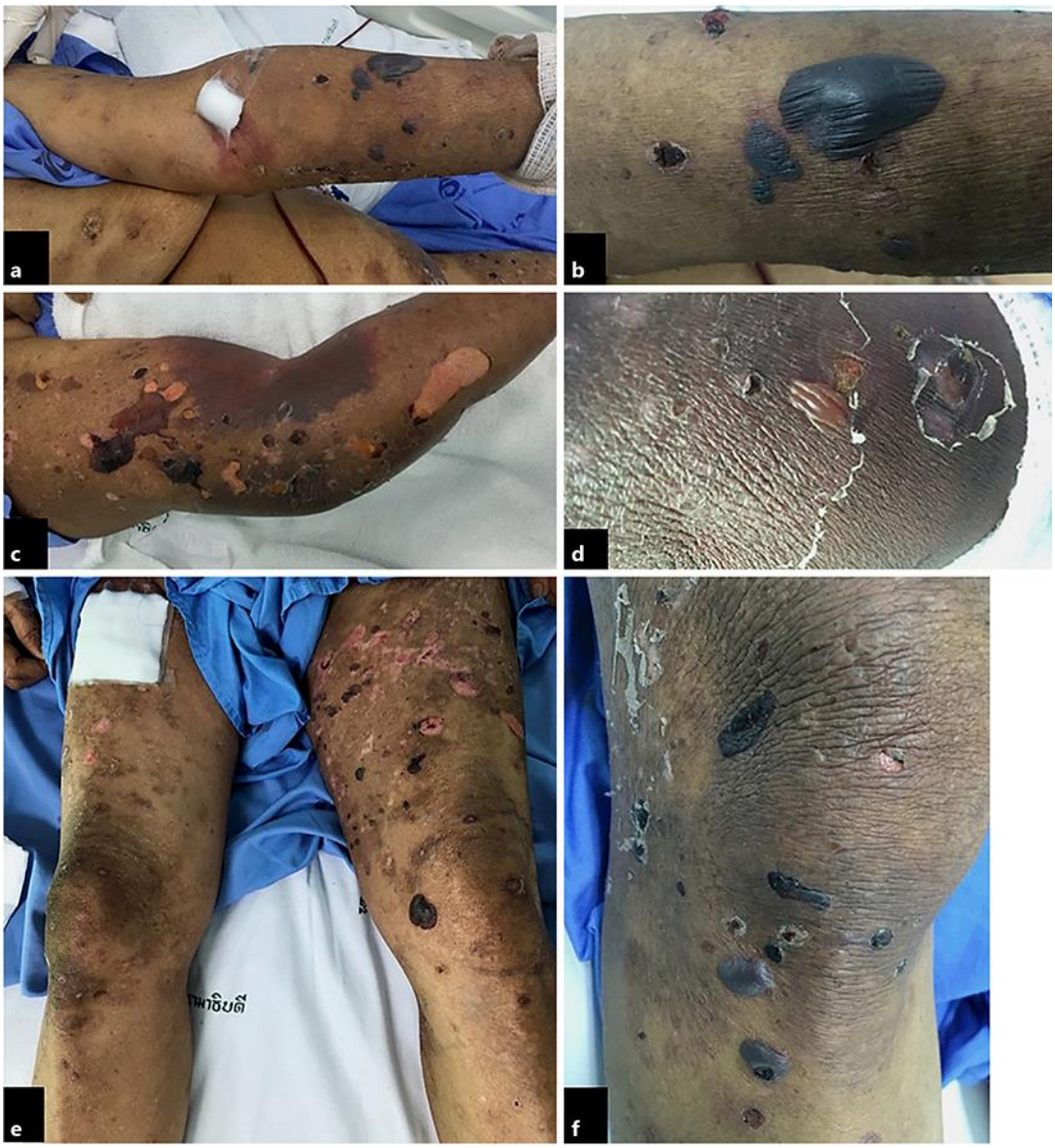

Fig. 3. **a** Multiple tense hemorrhagic bullae with erosion on the left forearm. **b** Large tense hemorrhagic bullae on the left forearm. **c** Ecchymosis and multiple tense hemorrhagic bullae with erosion on the right forearm and arm. **d** Clear fluid-filled bullae on the right arm. **e** Multiple tense hemorrhagic bullae with dry hemorrhagic crusts and erosions on both thighs. **f** Tense hemorrhagic bullae on the right thigh.

Table 1. Reported cases of bullous pemphigoid associated with acquired hemophilia A in the literature

Case No.	First author [ref.]	Gender/age, years (ethnicity)	U/D autoimmune-disease	Response to treatment of BP	Onset (before AHA)	IgG subclass	Inhibitor titer, BU/mL	Treatment of AHA	Response to treatment of AHA
1	This case	F/68 (Thai)	–	Resolved with CS, nicotinamide	11 months	NA	28	CS, CPA, FEIBA	Complete remission
2	Chen [1]	M/24 (Taiwanese)	–	Resolved with CS	2 years	NA	256	mPSL, CPA, PP, rituximab, rFVIIa	Improved after 2 months
3	Aljasser [2]	M/73 (Canadian)	–	Minimal response with CS	1 month	NA	25	CS, IVIg, CPA, rituximab, rFVIIa, FEIBA	Complete remission
4	Caudron [7]	F/68 (French)	–	Resolved with topical CS	Concurrently with AHA	NA	1.4	FEIBA	Improved after 3 months
5	Zhang [8]	F/49 (Chinese)	–	Resolved with CS and CPA	7 months	IgG4 (predominant), IgG1	148	CS, PP, FFP	Complete remission
6	Patel [11]	M/78 (English)	Rheumatoid arthritis, vitiligo	Resolved with CS	4 months	NA	839	CS, CPA, FEIBA	Relapsed 3 months after discontinuation of CPA due to severe neutropenia and sepsis; remission with CS alone for 12 months
7	Qiu [12]	F/60 (Chinese)	–	NA	Concurrently with AHA	NA	NA	CS, CPA, IVIg, rFVIIa	Complete remission
8	Makita [13]	F/80 (Japanese)	–	Resolved with CS	8 months	IgG4	28	CS	Complete remission
9	Ly [17]	M/68 (French)	–	Resolved with topical CS	6 months	NA	>2	CS	Complete remission
10	Binet [18]	M/75 (Belgian)	–	Controlled with CS, AZA/MMF	21 months	NA	25	CS, rituximab, rFVIIa	Complete remission
11	Lightburn [19]	M/74 (French)	–	NA	Concurrently with AHA	NA	110	CS, CsA, AZA, CPA, IVIg, FVIII, rFVIIa	Complete remission
12	Kluger [20]	M/72 (French)	–	Resolved with MTX and topical CS	9 months	NA	200	CS, rituximab, rFVIIa	Complete remission
13	Soria [21]	F/83 (French)	–	Controlled with topical CS but relapsed	3 years	NA	17	CS, rFVIIa	Died due to severe hemorrhage
14	Gupta [22]	F/84 (Caucasian)	–	NA	2 months	NA	29.4	CS, CPA, rFVIIa, FEIBA	Improved but died with sepsis and multi-organ failure
15	Zhang [23]	F/88 (Chinese)	–	Not improved with CS	4 months	NA	7	mPSL, rituximab	Complete remission but died with severe pneumonia and multi-organ failure
16	Ammannagari [24]	M/69 (Caucasian)	–	Resolved with CS	1 month	NA	34	CS, rituximab, rFVIIa	Complete remission
17	Rodprasert [25]	M/71 (Thai)	–	NA	Concurrently with AHA	NA	219	CS, IVIg, cryoprecipitate, rFVIIa	NA due to transfer to another hospital
18	Nguyen [26]	F/49 (Latina)	–	Minimal response to CS and IVIg	4 months	NA	17	CS, CPA, FEIBA	Complete remission

AZA, azathioprine; BP, bullous pemphigoid; CPA, cyclophosphamide; CS, corticosteroid; CsA, cyclosporin; FEIBA, factor eight inhibitor bypassing agents; FFP, fresh frozen plasma; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; mPSL, pulse methylprednisolone; MTX, methotrexate; NA, not available; PP, plasmapheresis; rFVIIa, recombinant human factor VII; U/D, underlying disease.

Table 2. Recommended dosage of immunosuppressive agents

Immunosuppressive agents	Dosing and clinical recommendations
First-line treatment	
Prednisolone alone or in combination with cyclophosphamide	Prednisolone (1 mg/kg/day) or/and cyclophosphamide (1–2 mg/kg/day) between 3 and 5 weeks
Second-line treatment	
Rituximab	375 mg/m^2 weekly for 4 weeks
Other (less used) drugs	
Cyclosporine	200–300 mg/day
High-dose intravenous immunoglobulin (IVIg)	0.4 g/kg/day for 5 days or 1 g/kg/day for 2 days
Plasmapheresis, immunoadsorption	Rapid but transient action (used in severe bleeding)