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Case Report of a Novel Association between Anti-p200 Pemphigoid and Acquired Haemophilia A

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Anti-p200 pemphigoid is an uncommon subepidermal autoimmune bullous disease that, unlike many other autoimmune bullous diseases, has not previously been associated with hematological diseases. The diagnosis of anti-p200 pemphigoid in a patient with congruent clinical features requires the demonstration of subepidermal blistering, with linear deposition of immunoglobulin (Ig) G and/or C3 at the dermoepidermal junction on direct immunofluorescence, and a floor-binding pattern on indirect immunofluorescence. In addition, the detection of antibodies against p200 antigen via immunoblotting is ideal but not readily accessible in many facilities, leading to a potential under-recognition and under-diagnosis of this condition. In this case report, we describe a 53-year-old gentleman with recently diagnosed acquired hemophilia A who developed a concurrent vesiculobullous eruption and was evaluated to have anti-p200 pemphigoid. Both of his conditions were controlled with immunosuppression via prednisolone and cyclophosphamide. While we acknowledge the contemporaneous occurrence of both diseases in this patient may be a mere coincidence, it is important to recognize the possibility of this association given the potential clinical significance. Whether the activity of one disease parallels the other will require further evaluation.

Keywords: Blister, Dermatoses, Factor VIII, Hemophilia, Pemphigoid

INTRODUCTION

Anti-p200 pemphigoid is a rare subepidermal autoimmune bullous disease (AIBD). There is a male predominance, with onset more commonly in sexagenarians. It is associated with psoriasis, in particular in Japanese patients[1]. A variety of other reported associations in individual patients include malignancy, immunoglobulin (Ig) A nephropathy, and glomerulonephritis with end-stage renal failure, inflammatory bowel disease, esophagitis, polyarteritis nodosa, and congenital ichthyosis[2]. Unlike other AIBDs including bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, and epidermolysis bullosa acquisita, there is no known association of anti-p200 pemphigoid with hematological disease. We report a potentially novel association of anti-p200 pemphigoid with acquired hemophilia A (AHA). The patient gave written consent for publication of his photographs in this case report.

CASE REPORT

A 53-year-old Chinese gentleman was transferred to our tertiary hospital for further care of newly diagnosed acquired hemophilia, having presented to a secondary hospital with atraumatic left knee hemarthrosis. At diagnosis of hemophilia, he had elevated activated partial thromboplastin time (APTT, 95.0 sec) and prothrombin time (PT, 9.8 sec) with partial correction on mixing study, low factor VIII (<1%), and high inhibitor assay (38 Bethesda units). Other supportive

laboratory investigations such as factor IX, factor XI, van Willebrand antigen and ristocetin factor were consistent with the diagnosis. Additionally, a contrasted computed tomography of the neck, thorax, abdomen and pelvis was performed for malignancy screening; this revealed an atrophic pancreas with coarse calcification but no suspicious lesions.

Seven months prior, the patient had developed a pruritic bullous rash over his neck. Lesional histopathology showed a subepidermal blister containing fibrin, neutrophils and eosinophils. In the adjacent dermis, significant papillary edema was present with neutrophils, eosinophils and lymphocytes concentrated in the superficial interstitial and perivascular regions (Fig. 1). Direct immunofluorescence (IF) microscopy revealed linear deposits of C3 and IgG along the dermal-epidermal junction (Fig. 2A). Indirect IF microscopy on salt-split skin showed linear deposits of IgG at the floor of the artificial blister. No serum antibodies against BP180 and BP230 were detected by enzyme-linked immunosorbent assay (ELISA; Euroimmun, Lübeck, Germany), and urine porphyrins and anti-nuclear antibodies were negative. A provisional diagnosis of epidermolysis bullosa acquisita was made and initial treatment with prednisolone and dapsone commenced. Further investigations showed no serum antibodies against collagen type VII by ELISA (Euroimmun). Immunoblotting of patient's serum with dermal extract and recombinant laminin γ1 showed IgG4 reactivity against the p200 antigen and laminin γ1, respectively (Fig. 2B). The diagnosis was revised to anti-p200 pemphigoid.

Initial treatment with prednisolone (highest dose 30 mg daily) and dapsone gave sufficient disease control, but dapsone was switched to mycophenolate mofetil due to headache. At a dose of prednisolone 20 mg daily (0.25 mg/kg daily) and mycophenolate mofetil 500 mg twice daily, the patient sustained a flare of blisters. Examination revealed tense vesicles and small bullae and associated erythematous urticated papules and plaques over his ears, jaw, neck and wrist, with a hemorrhagic blister over his left buccal mucosa. Nikolsky's sign was negative (Fig. 3).

Concurrently, the patient developed and was treated for newly diagnosed AHA. He received high dose prednisolone

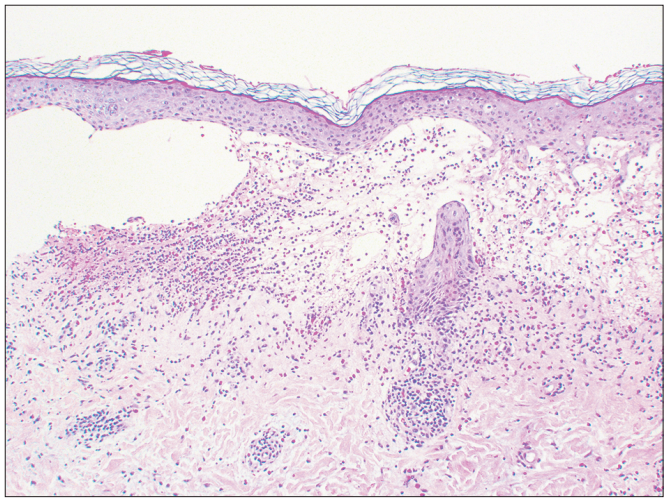

Fig. 1. Lesional skin biopsy showing a subepidermal blister. There is edema in the adjacent papillary dermis, together with a mixed superficial and perivascular infiltrate of neutrophils, eosinophils and lymphocytes (H&E, original magnification ×100).

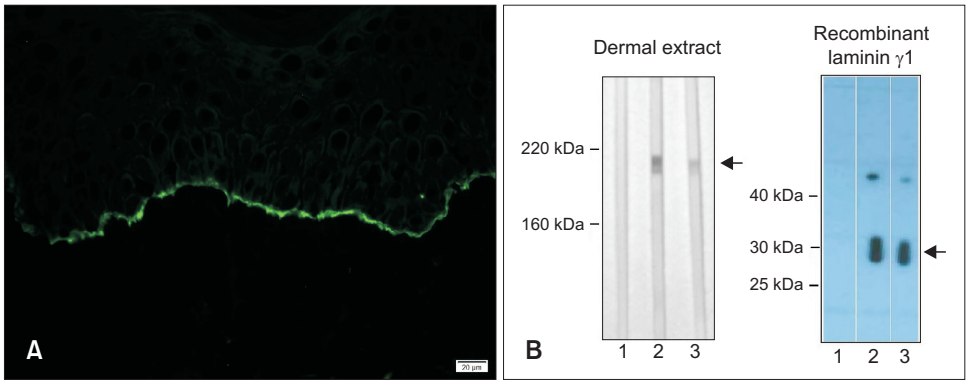

Fig. 2. (A) Direct immunofluorescence demonstrating linear deposits of immunoglobulin (Ig) G in the dermal-epidermal junction with an n-serration pattern. (B) Immunoblot with extract of human dermis (left panel) and the recombinant C-terminus of laminin γ1 (right panel) show IgG4 reactivity of the patient's serum with the 200 kD p200 protein in dermal extract and recombinant laminin γ1 (lanes 3). In lanes 1, serum reactivity of a healthy volunteer and in lanes 2, of a patient with known anti-p200 pemphigoid is shown. Arrows indicate the p200 and the recombinant laminin γ1 (28 kDa), respectively. Migration markers are shown to the left of each blot.

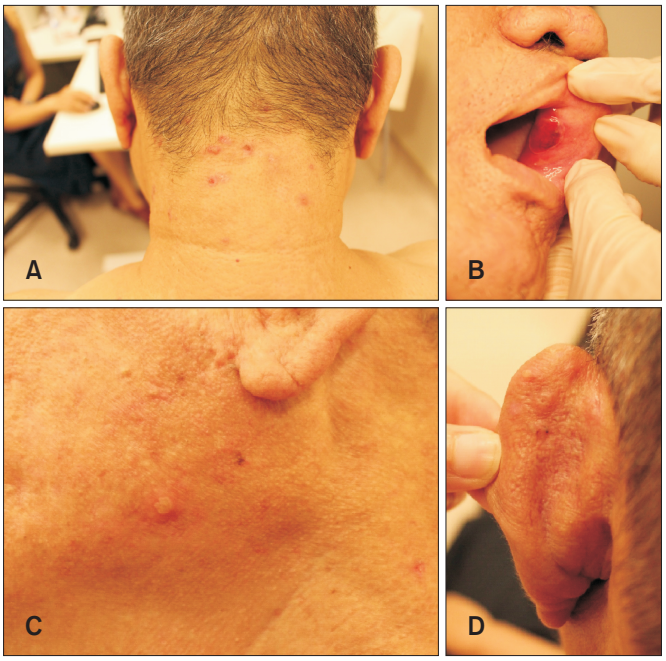

Fig. 3. (A) Nape of neck: Small tense vesicles on an erythematous base. Few erythematous erosions and papules. (B) Left buccal mucosa: hemorrhagic bulla. (C) Left angle of jaw: Small tense vesicle on an erythematous base. (D) Posterior left ear: Small tense vesicle on erythematous base over tip of helix.

at 80 mg daily (1 mg/kg/day) and cyclophosphamide 100 mg daily (1.25 mg/kg/day) for one month before tapering, in keeping with international recommendations for the treatment of AHA[3]. Cyclophosphamide was eventually stopped and prednisolone was tapered by 5 mg/week. Good cutaneous response with resolution of blisters was seen. Again, however, when prednisolone was reduced to 20 mg daily, patient had a biochemical relapse of hemophilia A (evidenced by prolongation of APTT and low factor VIII) with concomitant cutaneous relapse of plaques and blisters over his head, neck and oral cavity.

The patient's cutaneous condition remained responsive to cyclophosphamide and prednisolone. These medications were required to keep both the cutaneous and hematological diseases in remission.

DISCUSSION

AHA is an uncommon bleeding disorder due to the development of factor VIII inhibitor. Although AHA is most commonly associated with autoimmune disease such as rheumatoid arthritis and systemic lupus erythematosus, malignancy and pregnancy, an association with AIBD of which bullous pemphigoid is most frequent, has been described[4]. Less commonly associated AIBDs include pemphigus[5], other members of the pemphigoid group such as mucous membrane pemphigoid[6,7], epidermolysis bullosa acquisita[8], and linear IgA bullous dermatosis[9]. To our knowledge, this is the first reported case of anti-p200 pemphigoid co-existing with AHA.

Anti-p200 pemphigoid is a potentially under-recognized and under-reported disease. Patients demonstrate blister formation most frequently on the limbs and trunk, with occasional involvement of the head and neck, palms and soles, and mucosae. Of the reported cases to date, none has had solely mucosal disease. Urticarial plaques, scars and milia are other clinical signs. An index of suspicion is suggested for younger patients with lesions distributed over the head and neck, acral and mucosal areas.

Diagnosis of anti-p200 pemphigoid necessitates a consistent clinical picture for a subepidermal AIBD. Other AIBD must be excluded. By lesional histopathology, a subepidermal cleft is seen and by direct IF microscopy, a linear deposition of IgG and/or C3 with an n-serration pattern[1,2]. Indirect IF microscopy on salt-split skin shows a floor-binding pattern. Autoantibodies to a 200 kDa protein of the basement membrane zone are detected by immunoblotting. Recently, a large cohort of AIBD patients with floor pattern of Ig/C3 by indirect IF on salt-split skin classified about 80% as anti-p200 pemphigoid compared with 11% with epidermolysis bullosa acquisita, concluding that anti-p200 pemphigoid is by far the commonest pemphigoid disease with floor-binding pattern[10]. Since detection of antibodies against the p200 protein and laminin γ1 is only performed in few specialized laboratories, anti-p200 pemphigoid is most likely highly underdiagnosed in many places, and certain ethnicities may be underrepresented.

While there may be increasing awareness of the potential association of AHA with AIBD among physicians, the underlying mechanism for the association of AHA with AIBD is as yet unelucidated[11]. One hypothesis is that of cross-reactivity of factor VIII inhibitor with various pathogenic domains of AIBD. Concurrent biochemical or clinical worsening of both AIBD and AHA have been reported in some cases[5,6,8,9,12,13], while others do not demonstrate this relationship[7,11]. A recent retrospective evaluation of 6 patients with bullous pemphigoid and AHA did not demonstrate a temporal relationship between clinical and serological flare of bullous disease and

activity of AHA[11]. Conversely, our patient experienced simultaneous worsening control of both anti-p200 pemphigoid and AHA. Furthermore, factor VIII inhibitor is a polyclonal heterodimer usually of IgG4 subclass, targeting the factor VIII heavy chain A2 region and light chain C2 and A3 regions[7,9]. Yet, cross-reactivity between factor VIII inhibitor and respective epitopes of AIBD has not been demonstrated. The lack of consistent temporal association together with the wide variety of AIBD with associated specific antigenic sites that have been reported thus far suggest a more complex causal mechanism.

Another hypothesis is that of an underlying altered immunity driving both AHA and AIBD via autoantibody development[6]. AHA and AIBD have been reported in association with other autoimmune conditions, such as rheumatoid arthritis, vitiligo and Hashimoto's disease[14]. Chan et al.[15] reported a case of autoimmune syndrome secondary to *ZAP-70* mutations manifesting as bullous pemphigoid, AHA, minimal change disease and inflammatory colitis in a child, which resolved after allogeneic hematopoietic cell transplant. *ZAP-70* mutation affects T-cell signaling, which may be a potential area for further investigation of possible downstream effects on autoantibody-mediated autoimmunity.

We report a potentially novel association of anti-p200 pemphigoid with AHA. While we acknowledge the contemporaneous occurrence of both diseases in this patient may be a mere coincidence, it is important to recognize the possibility of this association given the potential clinical significance. Whether treatment of associated diseases would improve disease activity of anti-p200 pemphigoid and vice versa remains a conundrum.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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