A Case Report: Dapsone for the Treatment of Recalcitrant Generalized Pruritic Tense Bullae

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ABSTRACT:

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Anti-p200 pemphigoid is a rare subepidermal autoimmune bullous disease. The clinical presentations of anti-p200 pemphigoid are multiple bullae or vesicles with erosions localized on extremities and trunk. Mucosal involvement is reported in some patients. The lesions usually resolved without scar or milia formation. The diagnosis of anti-p200 pemphigoid is challenging. The clinical features, histopathologic findings and immunofluorescence studies of this condition are similar to other autoimmune subepidermal bullous diseases. Although the diagnosis of anti-p200 pemphigoid is confirmed by immunoblotting technique to detect 200-kDa protein autoantibodies, no laboratory service is available as routine in Thailand. Therefore, the diagnosis of anti-p200 pemphigoid should be performed by exclusion of other autoimmune blister diseases.

Key words: anti-p200 pemphigoid, subepidermal autoimmune bullous disease

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Introduction

Anti-p200 pemphigoid is a rare subepidermal autoimmune bullous disease characterized by autoantibodies against a 200-kDa protein (laminin γ1) localized within the lower part of lamina lucida. It was first described by Zillikens *et al*[1]. in 1996. The majority of patients present by tense bullae, vesicles, and erosions on trunk and extremities which are difficult to distinguish from other autoimmune bullous diseases[2].

Case report

A 33-year-old female was referred to our outpatient clinic after developing generalized pruritic tense bullae over her trunk and extremities for the past 7 months. She had no active medical problems and did not take any additional medications. Neither she nor her family had a past history of vesiculobullous diseases. She denied the history of photosensitivity rashes, alopecia, prolonged fever or arthralgia. Physical examination revealed multiple erosions on erythematous base with some pruritic bullae and hyperpigmented patches on trunk and all extremities (Figure 1). Oral, genital mucosa and conjunctiva were spared.

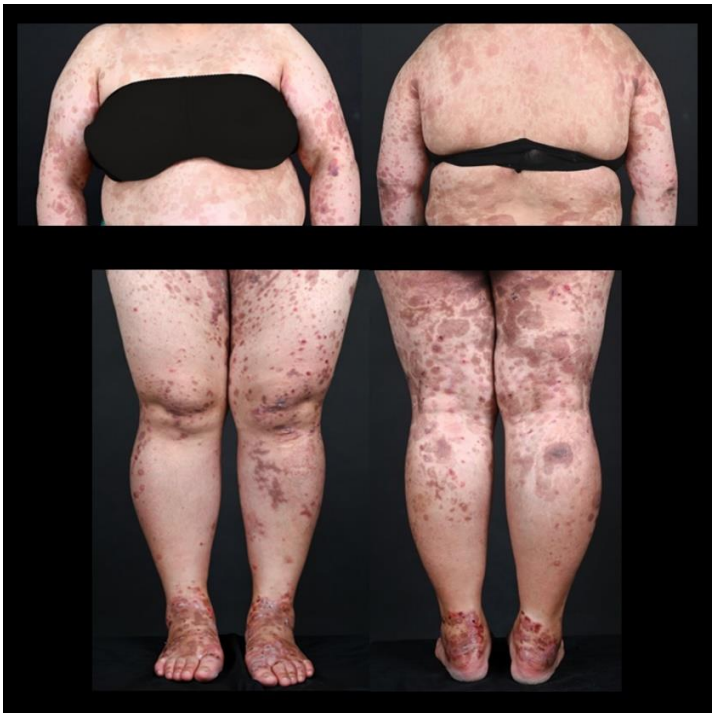

Figure 1 The clinical presentations showed multiple erosions on erythematous base with some bullae and hyperpigmented patches located on trunk and extremities

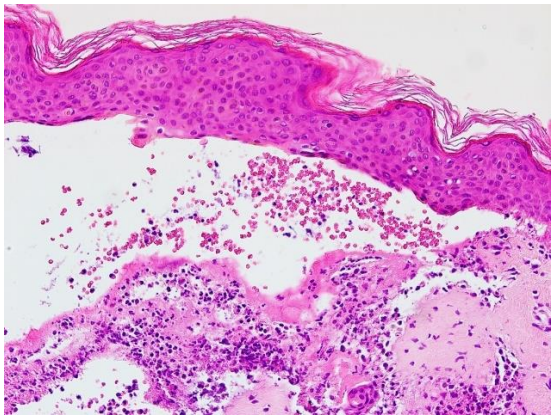

Figure 2 Histopathologic examination showed subepidermal separation with neutrophil infiltration. (Hematoxylin-eosin stain, objective X40)

The skin biopsy was performed on right arm at the blister. The histopathological examination showed an area of subepidermal blister along dermo-epidermal junction (DEJ) with an abundant infiltration of neutrophils (Figure 2). Direct immunofluorescence (DIF) study demonstrated a linear deposition of immunoglobulin (Ig) G and a granular deposition of complement 3 (C3) along basement membrane zone (Figure 3A, 3B). Salt-split skin technique by NaCl (1 mol/L) showed the deposits of IgG and C3 at the floor of the blister (Figure 3C). Indirect immunofluorescence study revealed negative result. Bullous systemic lupus erythematosus (BSLE), epidermolysis bullosa acquisita (EBA) and anti-p200 pemphigoid were included in differential diagnosis. The further investigations for other autoimmune diseases including antinuclear antibody (ANA) were negative. By clinical presentations, the distribution of bullae and erosions did not only appear at sites of trauma which was unlike EBA. In this patient, the immunoblotting analysis for 200-kDa protein autoantibodies was not performed because this investigation was not available in Thailand. Finally, a diagnosis of anti-p200 pemphigoid in this case was established by clinical presentations, histopathological findings, DIF findings and exclusion of other conditions.

Initially, she was treated by prednisolone 15 mg daily for 4 months, doxycycline 200 mg daily for 2 months, nicotinic acid 200 mg daily for 2 months, as well as topical corticosteroids before visiting our outpatient clinic. Owing to disease progression, she was given the dose of prednisolone was increased to 30 mg daily and doxycycline and nicotinic acid were removed. After the diagnosis of anti-p200 pemphigoid, dapsone 100 mg was added to her daily regimen. The disease severity was dramatically reduced within 3 weeks after the combination of prednisolone and dapsone. She continually took 100 mg of dapsone daily and gradually reduced dose of prednisolone to 10 mg weekly. All lesions were healed by post-inflammatory hyperpigmentation without scarring or milia formation.

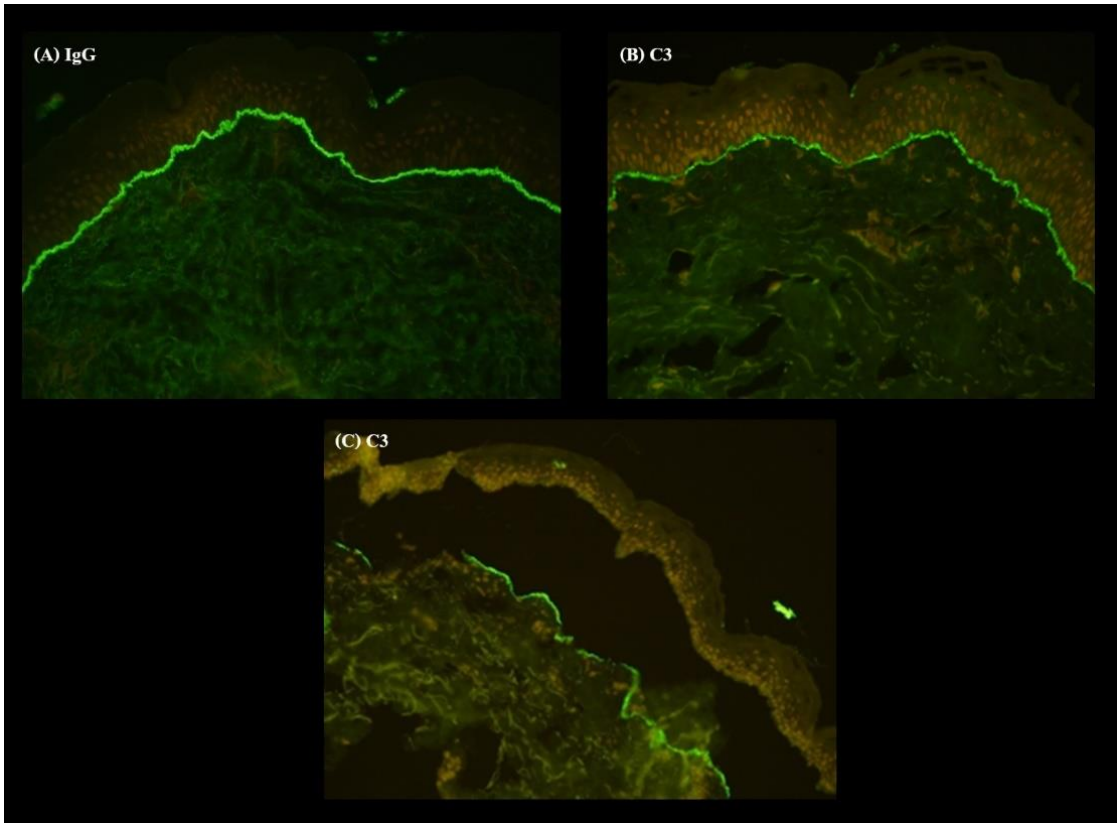

Figure 3 Direct immunofluorescence showed the deposits of immunoglobulin G at basement membrane zone (BMZ) in linear pattern (A) and the deposits of complement 3 at BMZ in granular pattern (B). Salt-split skin technique showed the staining of complement 3 at the dermal side of blisters (C). (20x magnification)

Discussion

Anti-p200 pemphigoid as called as anti-laminin γ1 pemphigoid is a rare subepidermal autoimmune bullous disease. This condition is supposed to be a variant of pemphigoid which is caused by 200-kDa protein autoantibodies localized within the lower lamina lucida of DEJ. The mean age of onset is 65.5 years[3]. This condition is reported predominantly in males[3]. The systematic review of anti-p200 pemphigoid performed by Kridin et al[3]. reveals that most patients present by bullae or vesicles following by urticarial plaques. Lesions usually resolve without scarring or the formation of milia. Ninety-five percent of patients occur multiple bullae on extremities following by trunk, palmoplantar, head, and neck areas[3]. Almost half of them present as generalize distribution[3]. Oral and genital mucosa membranes are involved in approximately 20% of patients[2]. In the aspect of

treatment, no standard treatment guideline for anti-p200 pemphigoid has been established. Based on the literature, the treatment options including systemic corticosteroid, dapsone, doxycycline, azathioprine, cyclosporine, colchicine, intravenous immunoglobulin and rituximab have been reported[2,4,5]. Dapsone, an immunomodulating agent, appears to be as an effective treatment in anti-p200 pemphigoid[6,7]. In several case reports, the addition of dapsone to systemic corticosteroid shows dramatically resolved lesions and permitted remission and withdrawal of corticosteroids in the end. However, the data of clinical presentations and course of diseases are still deficient owing to a small number of cases.

Primarily, the diagnosis of anti-p200 pemphigoid is challenging because the clinical features and histopathological characteristics are resembling other subepidermal bullous diseases such as bullous pemphigoid, anti-type IV collagen pemphigoid, BSLE, linear IgA bullous dermatosis, and mucous membrane pemphigoid (Table 1). The DIF findings of anti-p200 pemphigoid reveal linear or granular depositions of IgG and/or C3 along basement membrane zone. Moreover, salt-split skin technique by NaCl (1 mol/L) shows staining in the dermal side (floor) of the blister in anti-p200 pemphigoid. Although both of DIF study and salt-split skin technique cannot discriminate among anti-p200 pemphigoid, BSLE, anti-type IV collagen pemphigoid and EBA, the clinical features of EBA are different from anti-p200 pemphigoid and BSLE as shown in table 1. The distribution of EBA usually involves at sites of trauma such as elbows, knees, the dorsal of hands and feet with scarring formation[3]. Whereas, the lesions of anti-p200 pemphigoid commonly locate on extremities and trunk and resolve without scar or milia formation[8]. Finally, the diagnosis of anti-p200 pemphigoid is confirmed by immunoblotting technique to identify the patient's 200-kDa protein IgG autoantibodies[8]. Unfortunately, there is no laboratory service for diagnosis anti-p200 pemphigoid as routine in Thailand. Thus, the diagnosis of this condition should be performed carefully by complete history review, physical examination, histopathological examination and immunofluorescence study for exclusion of other autoimmune blister diseases.

Table 1 The clinical presentations, histological findings and direct immunofluorescence of subepidermal autoimmune bullous diseases

Diseases	Clinical features	Histologic findings	DIF findings	Salt-split skin technique	Other information
Bullous pemphigoid	Tense bullae and erosions with a symmetrical distribution on extremities and trunk	Subepidermal blisters with eosinophil infiltration	C3 and/ or IgG deposits at DEJ in linear pattern	Staining in epidermal side (roof) of the blister Staining in both sides (roof and floor) of the blister	-
Bullous systemic lupus erythematosus	Tense bullae or vesicles over normal skin of SLE patients in both sun-exposed and sun-protected areas	Subepidermal blisters with neutrophil infiltration	C3 and/ or IgG deposits at DEJ in linear or granular patterns	Staining in dermal side (floor) of the blister	Positive ANA or fulfilled criteria diagnosis of SLE
Epidermolysis bullosa acquisita	Tense bullae at sites of trauma such as the hands, feet, knees, elbows and buttocks.	Subepidermal blisters with neutrophil infiltration	C3 and/ or IgG deposits at DEJ in linear or granular patterns	Staining in dermal side (floor) of the blister	-
Linear IgA bullous dermatosis	Scattered and asymmetrical vesicles or bullae in an annular or herpetiform arrangement	Subepidermal blisters with neutrophil infiltration	IgA deposits at DEJ in linear pattern	-	-
Dermatitis herpetiformis	Pruritic papulovesicles or excoriated papules on extensor surfaces	Subepidermal blister with neutrophilic infiltration of the dermal papillae with vesicle formation	IgA deposit within the dermal papillae in granular pattern	-	History of gluten sensitivity
Mucous membrane pemphigoid	Recurrent blisters and erosions on scalp, face, neck, and upper trunk and involvement of the mucosal surfaces with subsequent scarring	Subepidermal blisters with neutrophil and eosinophil infiltration	C3 and/ or IgG deposits at DEJ in linear pattern	Staining in dermal side (floor) of the blister	-
Anti-type IV collagen pemphigoid	Non-scarring blisters and erosions in the skin	Subepidermal blisters with inflammatory cells infiltration	C3 and/ or IgG deposits at DEJ in linear pattern	Staining in dermal side (floor) of the blister	Membranous glomerulonephritis
Anti-p200 pemphigoid (anti-laminin γ1 pemphigoid)	Tense bullae and erosions on extremities and trunk	Subepidermal blisters with neutrophil infiltration	C3 and/ or IgG deposits at DEJ in linear or granular patterns	Staining in dermal side (floor) of the blister	-

Abbreviation: ANA; antinuclear antibody, C3; complement 3, DEJ; dermo-epidermal junction, DIF; direct immunofluorescence, Ig; immunoglobulin, SLE; systemic lupus erythematosus

In this case, anti-p200 pemphigoid, anti-type IV collagen pemphigoid and BSLE were included in differential diagnosis. Although negative ANA was shown, we could not exclude the condition of BSLE in this case. Because the condition of systemic lupus erythematosus (SLE) was common in middle-age women[9]. BSLE can be the early presentation of SLE.[9] Some cases may not fulfill the diagnosis of SLE from the initiation and took time to complete criteria by other detectable autoantibodies and systemic involvements[10]. In the aspect of treatment, dapsone is the first-line treatment of both BSLE and anti-p200 pemphigoid[6,7,9]. So, a good response to dapsone do not help to exclude BSLE. In term of anti-type IV collagen pemphigoid, this condition is rare and diagnosed by the immunoblotting technique[11]. The significant reported complication is membranous glomerulonephritis[11]. Although the renal function was normal in this patient, anti-type IV collagen pemphigoid could not be excluded. However, the information of anti-type IV collagen pemphigoid is limited due to small number of cases. At this point, anti-p200 pemphigoid is possible to be diagnosed in this patient owing to clinical presentations, findings of histopathology and DIF, negative ANA and a good response to dapsone. Nevertheless, we could not summarize the definite diagnosis of this patient. She required the monitoring of clinical transformation, treatment response and complication for proving the definite diagnosis.

Conclusion

Anti-p200 pemphigoid is a rare subepidermal autoimmune bullous disease. The diagnosis of this condition is challenging. This case report demonstrated a patient presented by refractory generalized pruritic bullae with erosions for 7 months. She was suspected to diagnose anti-p200 pemphigoid by exclusion and responded well to the combination of systemic corticosteroid and dapsone.

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