Characteristics and Management of Autoimmune Bullous Disease in Psoriasis Patients

Dear Editor,

Psoriasis is a common chronic inflammatory skin disease. On the other hand, autoimmune bullous diseases (AIBD) are less prevalent. Several case reports and studies have documented AIBD in patients with psoriasis.[1,2] However, their causative factors are unclear. It has been hypothesised that certain antipsoriatic treatments such as ultraviolet irradiation, psoralen and coal tar could have triggered off the development of autoantibodies that cause AIBD.[3] Treatment of AIBD in patients with psoriasis is challenging since systemic corticosteroids may potentially cause flares of pustular psoriasis. We report our experience in the management of psoriasis patients with AIBD in the National Skin Centre, a tertiary dermatology institution, in Singapore.

This retrospective case series included 17 patients who were clinically diagnosed with "psoriasis" and either "pemphigoid" or "pemphigus" according to the International Classification of Diseases between 1 January 2003 and 31 July 2017 (Fig. 1). The diagnosis of AIBD was confirmed by histopathological examination (Fig. 2), immunofluorescence studies and/or serological tests. The clinical records of the patients were reviewed and details including demographics, disease severity, AIBD onset and treatment were extracted and analysed. This study was approved by the Institutional Review Board (Protocol 2017/00572).

The demographics and clinical findings of our patients are shown in Table 1. There were 15 Chinese and 2 Malay patients. Male (70.6%) patients vastly outnumbered female (29.4%) patients. Mean age at AIBD onset was 72 years. Psoriasis preceded AIBD in all patients (94.1%) except for 1 case. Mean duration between psoriasis and AIBD onset was 14 years. More than half of them (64.7%) had moderate psoriasis, defined as having body surface area (BSA) involvement of between 5-10%. Three (17.6%) patients had mild psoriasis (BSA <5%) and another 3 (17.6%) patients had severe psoriasis (BSA >10%).

All patients had a single type of AIBD. Bullous pemphigoid (BP) was the most prevalent form and it affected 13 (76.5%) patients. Three patients had pemphigus foliaceus and 1 had pemphigus vulgaris (PV). Our cohort did not include patients with antilaminin gamma-1 (p200) pemphigoid.

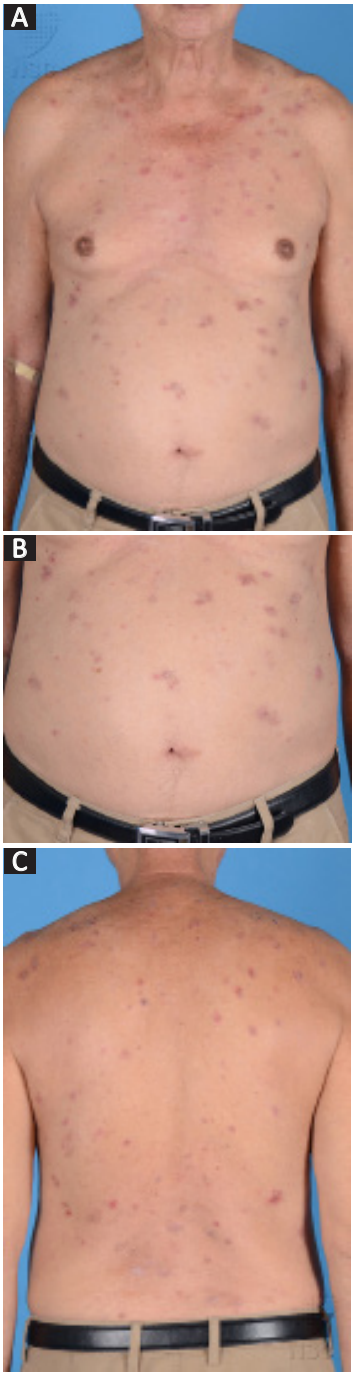

Fig. 1. Patient with pre-existing psoriatic lesions. A: Blisters and vesicles are seen on the anterior trunk. B: Vesicles overlie thin psoriasiform plaques. C: Blisters and vesicles are visible on the posterior trunk.

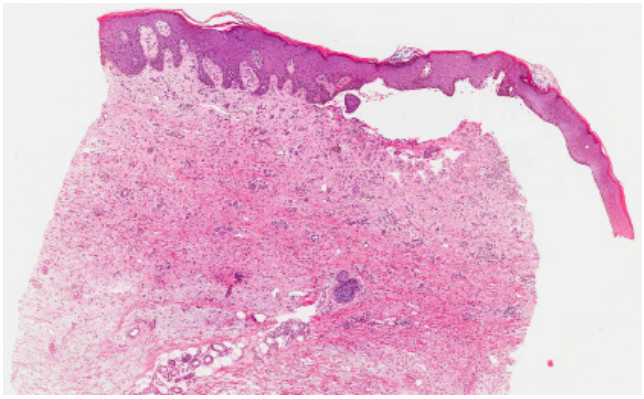

Fig. 2. Subepidermal blister with eosinophils and adjacent psoriasiform dermatitis.

Fourteen (82.4%) patients were on only topical steroids during AIBD onset. The 3 remaining patients developed AIBD while they were being treated with cyclosporine, hydroxyurea and narrow-band ultraviolet B (NBUVB) phototherapy, respectively. In the patient who was on cyclosporine, treatment ceased due to cost issues. In the other 2 patients, hydroxyurea and NBUVB ceased after methotrexate was started.

As part of their AIBD treatment, 13 (76.5%) patients received systemic corticosteroids with or without other immunomodulators such as mycophenolate mofetil. Two (11.8%) patients were treated with only methotrexate and another 2 (11.8%) were conservatively managed with highly potent topical corticosteroids (Table 2). Clinical improvement and disease control were seen in all patients. In patients who were on systemic corticosteroids, prednisolone was initiated with a mean dose of 0.47 ± 0.24 mg/kg/day and it was tapered over a mean period of 17.0 ± 11.3 months with no exacerbation of psoriatic lesions.

In a recent pooled analysis of case-control studies, a significant association between BP and psoriasis was reported.[2] However, the precise mechanisms responsible for the development of AIBD in patients with psoriasis are not known. Researchers have speculated that exogenous factors such as systemic antipsoriatic treatment and UV exposure can possibly precipitate bullous eruptions by stimulating antibody release or promoting expression of prior subclinical bullae.[3] Since most of our patients had no prior exposure to known exogenous factors, our study did not support previous findings of psoriasis as a cause or trigger for the development of AIBD.

In our study, psoriasis preceded bullous eruptions by a mean of 10 years. This suggests that the endogenous pro-inflammatory environment in psoriasis may promote a phenomenon known as "break of immune tolerance" when antigens and cytokines are released and upregulated. This may expose and induce autoimmunity against basement membrane zone components such as BP antigens that lead to autoimmune bullous lesions.[4,5] Other factors that may play an important role in epidermal splitting include downstream factors such as complement activation, mast cell degranulation, macrophage activation and neutrophilic chemotaxis.[6] These mechanisms cannot be measured by the levels of antibodies against BP antigens 180 (BP180) and 230 (BP230) and desmogleins 1 (DSG1) and 3 (DSG3).

A recent review had discussed a possible relationship between psoriasis and pemphigoid diseases that included local inflammation and upregulation of neutrophils and matrix metalloprotease.[7] The presence of neutrophil elastase in psoriasis[8] may play a role in the degradation of dermoepidermal junction and the formation of blisters. It was also reported that BP lesions have increased expression of interleukin-17,[9] a cytokine important to the development of psoriasis.

Interestingly, 1 patient who had PV (which was consistent on histology as well as direct and indirect immunofluorescence assays) also had antibodies to BP180 and BP230 in addition to DSG1 and DSG3. BP antigens and desmogleins are not known to be closely related, and the coexistence of BP and PV in a patient is rare.[10] Currently, the mechanisms responsible for the production of multiple autoantibodies in a patient are not known. As such, more research is needed on them in mixed bullous diseases.

A limitation of our study is that none of the patients were subjected to a complete diagnostic test. Additionally, immunoblot analysis was not performed in any of them. Some patients also did not undergo a complete serological and direct immunofluorescence evaluation (Table 2). However, histology and immunofluorescence features characteristic of antilaminin gamma-1 (p200) pemphigoid and epidermolysis bullosa acquisita were not seen in any of them. In their study, Ohata et al had demonstrated an association between psoriasis and antilaminin gamma-1 pemphigoid in 145 Japanese patients.[1] In comparison, our study is limited to a much smaller patient cohort. It is, however, the first study that examined an association between AIBD and psoriasis in a multiracial population that included the Chinese and Malays in Southeast Asia. It also describes, in detail, the management and outcomes in these patients that were not highlighted in other reported case series.

Management of psoriasis patients with AIBD is challenging. Initiation and withdrawal of systemic corticosteroids in patients with extensive psoriasis can expose them to the risk of developing serious sequelae of pustular or erythrodermic psoriasis. Despite the absence and discouragement of systemic corticosteroids in most psoriasis management guidelines, they remain the most common systemic treatment prescribed by dermatologists

Table 1. Demographics and Clinical Characteristics of Subjects

Variable	Aggregate (%)
Gender	
Male	12 (70.6)
Female	5 (29.4)
Race	
Chinese	15 (88.2)
Malay	2 (11.8)
Median age at AIBD onset (range, years)	72 (59 – 77)
40 – 49	3 (17.6)
50 – 59	2 (11.8)
60 – 69	1 (5.9)
70 – 79	9 (52.9)
80 – 89	1 (5.9)
≥90	1 (5.9)
Median duration from psoriasis to AIBD onset (range, years)	14 (8 – 20)
<0	1 (5.9)
0 – 9	5 (29.4)
10 – 19	6 (35.3)
20 – 29	5 (29.4)
Body surface area of psoriasis (%)	
<5	3 (17.6)
5 – 10	11 (64.7)
>10	3 (17.6)
Psoriasis type	
Plaque	16 (94.1)
Guttate	1 (5.9)
Pustular	–
AIBD type	
Bullous pemphigoid*	13 (76.5)
Pemphigus foliaceus†	3 (17.6)
Pemphigus vulgaris†	1 (5.9)
Therapy at AIBD onset	
Topical steroids only	14 (82.4)
Cyclosporine	1 (5.9)
Hydroxyurea	1 (5.9)
Narrow-band ultraviolet B phototherapy	1 (5.9)

AIBD: Autoimmune bullous diseases
*Patients with bullous pemphigoid (BP) showed subepidermal bullae with eosinophils on histology, linear immunoglobulin G (IgG) and complement 3 (C3) in basement zone membrane on direct immunofluorescence assay and had circulating autoantibodies directed against BP antigens 180 and/or 230.
†Patients with pemphigus showed intraepidermal vesicles with acantholysis on histology and intracellular IgG and C3 in epidermis on direct immunofluorescence assay. Patients with pemphigus foliaceus and pemphigus vulgaris had serum IgG autoantibodies against desmoglein 1 and 3, respectively.

Table 2. Descriptive Analysis of Subjects

AIBD Type, Severity and Patient Number	Bullae Histology	Direct IF Assay	Indirect IF Assay	Autoantibody Serology	Psoriasis Management	AIBD Management	Outcome
Bullous pemphigoid							
Mild (<5% of BSA)							
1	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	BP180/BP230 positive	Topical corticosteroids	Prednisolone 0.42 mg/kg/day	Improved
2	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/40	BP180 positive	Topical corticosteroids	Prednisolone 0.25 mg/kg/day	Improved
3	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/80	No data	Topical corticosteroids	Prednisolone 0.33 mg/kg/day	Improved
Moderate (5 – 10% of BSA)							
4	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	No data	Topical corticosteroids	Prednisolone 0.67 mg/kg/day, methotrexate 10 mg/week	Improved
5	Erosion with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/20	No data	Topical corticosteroids	Prednisolone 1.00 mg/kg/day	Improved
6	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	No data	Topical corticosteroids	Prednisolone 0.50 mg/kg/day, methotrexate 7.5 mg/week	Improved
7	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	BP180 positive	Topical corticosteroids	Prednisolone 0.50 mg/kg/day, methotrexate 10 mg/week	Improved
8	Subepidermal bullae with eosinophils	No data	Split skin substrate; roof pattern, 1/160	BP180 positive	Topical corticosteroids	Prednisolone 0.25 mg/kg/day	Improved
9	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/20	No data	Topical corticosteroids	Prednisolone 0.50 mg/kg/day	Improved
10	Subepidermal bullae with eosinophils	Linear C3 in BMZ	No data	BP180 positive	Topical corticosteroids	Prednisolone 0.33 mg/kg/day	Improved
Severe (>10% of BSA)							
11	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	No data	No data	Topical corticosteroids	Methotrexate 5 mg/week	Improved
12	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	No data	No data	Topical corticosteroids	Topical corticosteroids	No change
13	Subepidermal bullae with eosinophils	Linear IgG and C3 in BMZ	Split skin substrate; roof pattern, 1/160	BP180/BP230 positive	Hydroxyurea	Methotrexate 5 mg/week	Improved
Pemphigus foliaceus							
Mild (<5% of BSA)							
14	Psoriasiform hyperplasia with eosinophils	Intercellular IgG and C3 in epidermis	Normal skin substrate; intercellular pattern, 1/160	DSG1 positive	Cyclosporine	Prednisolone 0.50 mg/kg/day, mycophenolate mofetil 500 mg	Improved
Moderate (5 – 10% of BSA)							
15	Intraepidermal vesicle with acantholysis and eosinophils	Intercellular IgG and C3 in epidermis	Normal skin substrate; intercellular pattern, 1/160	DSG1 positive	Topical corticosteroids	Prednisolone 0.50 mg/kg/day	Improved
16	Intraepidermal vesicle with acantholysis and eosinophils	Intercellular IgG and C3 in epidermis	Normal skin substrate; intercellular pattern, 1/160	DSG1 positive	NBUVB phototherapy	Prednisolone 0.67 mg/kg/day, methotrexate 12.5 mg/day	Improved
Pemphigus vulgaris							
Moderate (5 – 10% of BSA)							
17	Intraepidermal bullae with neutrophils	Intercellular IgG and C3 in epidermis	Normal skin substrate; intercellular pattern, 1/160	BP180/BP230/DSG1/DSG3 positive	Topical corticosteroids	Topical corticosteroids	No change

AIBD: Autoimmune bullous diseases; BMZ: Basement membrane zone; BP180: Bullous pemphigoid antigen 180; BP230: Bullous pemphigoid antigen 230; BSA: Body surface area; C3: Complement 3; DSG1: Desmoglein 1; DSG3: Desmoglein 3; IF: Immunofluorescence; IgG: Immunoglobulin G; NBUVB: Narrow-band ultraviolet B

for psoriasis patients.[11] The use of systemic corticosteroids in immunobullous disease is well documented in the literature and clinical practice. Although methotrexate monotherapy may be useful in psoriasis patients with AIBD, the use of systemic corticosteroids appeared to be more common in our study. This may be attributed to rapid resolution of bullous lesions with systemic corticosteroids and physician preference after considering the comorbidities of patients.

In our study, most patients achieved good disease control of both AIBD and psoriasis after they were initiated on systemic corticosteroids. None of them developed pustular flares during or after steroid taper. Additionally, no improvement was seen in their bullous lesions in the absence of systemic corticosteroids. As such, systemic corticosteroids may be a safe treatment option in these patients. More research is needed to establish the unique pathogenetic relationship between psoriasis and concomitant AIBD before a review of the therapeutic guidelines for these patients can be undertaken.

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