Transition from Pemphigus Vulgaris to Pemphigus Foliaceus
- Report of Two Cases

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Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are two different subtypes of the pemphigus group with distinct clinicopathologic features. Clinically, PV presents with mucosal, mucocutaneous, or cutaneous lesions whereas PF lesions are primarily cutaneous. Histopathologically, intraepidermal acantholysis is located at the granular layer in PF and suprabasally in PV. Traditionally, these differences are used for basis of treatment selection and prognostic estimation. However, infrequent transition between the subtypes has been reported. Herein we describe two cases of PV with transition into PF and discuss the proposed mechanism for this phenomenon. (Dermatol Sinica 27: 52-58, 2009)

Key words: Pemphigus, Desmoglein, Subtype transition, Epitope spreading

INTRODUCTION

Pemphigus is one of the prototypical autoimmune bullous diseases. It has been divided into two distinct groups depending on the location of the vesicle in the epidermis.1 Traditionally, this simplified dichotomous classification into pemphigus vulgaris (PV) and pemphigus foliaceus (PF) by histopathology can be reflected clinically in their differing presentation, lesional distribution, expected disease prognoses, and treatment protocols. Despite these differences, the mechanisms of disease are believed to be similar. Concurrent presentation or transition between pemphigus phenotypes have been reported previously, but is a relatively infrequent phenomenon.1-8 As of 2006, less than 25 cases had been reported.7 Herein we report two cases of pemphigus vulgaris with transition into pemphigus foliaceus.

CASE REPORT

CASE 1

A 38-year-old man with hepatitis B virus-related liver cirrhosis, Child class C, presented in March 2002 with recurrent eruptions over the trunk and limbs of 6 months’ duration. Family history and contact history were unremarkable. These itchy vesicles and erosions over the trunk and limbs had been treated at a local medical clinic, but did not improve significantly (Fig. 1A). New oral ulcers then occurred. A skin biopsy was performed on his back under the clinical
diagnosis of bullous dermatosis, favoring PV. Histopathologic examination revealed suprabasal acantholysis with formation of an intraepidermal vesicle and mild perivascular
mononuclear cell infiltrates with occasional eosinophils in dermis (Fig. 1B). Direct immunofluorescence revealed positive intercellular IgG and C3 staining, further supporting the diagnosis of PV.

Treatment was initiated with oral prednisolone 75 mg/day (equal to 1 mg/kg/day) and topical betametasone 0.12% + gentamicin 0.1% cream b.i.d. The dose was tapered gradually to 5 mg/day (0.067 mg/kg/day) over a year’s time. This maintenance dose was further tapered to 5 mg q.o.d. two months later. However, persistent cough was noted, and after thorough laboratory examination, pulmonary tuberculosis (TB) infection was diagnosed 16 months after initial onset of skin lesions. Anti-TB drugs were added, but toxic hepatitis was noted (ALT: 1296 U/L, AST: 791 U/L) two months later, and thus TB treatment was changed to monotherapy with ciprofloxacin, which lasted for one month. Thereafter, the patient was only followed in gastroenterology clinic; another episode of acute hepatitis due to hepatitis B virus reactivation was noted one year later (November 2004).

In July 2006, some itchy facial lesions appeared, but no new treatment was sought. By August 2006, he was admitted to gastroenterology again for liver function impairment and deepening jaundice, under the impression of impending liver decompensation, possibly due to HBV-reactivation, and growth of *Aeromonas hydrophilia* in blood culture), systemic corticosteroids were contraindicated. Moderate-potency topical corticosteroid therapy was chosen due to the localized involvement and non-progressive nature of the PF lesions. By follow-up in March 2007 later, the lesions had completely resolved (Fig. 1E).

**CASE 2**

A 48-year-old woman admitted for diabetic ketoacidosis presented in March 1992 for evaluation of relapsing blisters on the entire body for more than one year’s duration. These generalized blisters had been treated at another hospital as bullous pemphigoid, although no skin biopsy had been performed for definitive diagnosis. On physical examination, there were flaccid vesicles over the central abdomen, erythematous patches with tiny patches over the thighs, post-inflammatory hyperpigmentation on wrists and one new tense vesicle over the left forearm. Severe itching was complained. There were no oral ulcers or other skin lesions. A skin biopsy of the left forearm vesicle was performed under the clinical impression of bullous pemphigoid or linear IgA dermatosis. Histopathologic examination revealed an intraepidermal vesicle containing acantholytic...
cells and many eosinophils with fibrinous fluid. Eosinophils and mononuclear cells were also noted in dermis (Fig. 2A). Direct immunofluorescence revealed positive intercellular IgG staining, and the diagnosis of PV was made. Anti-ICS Ab was also checked; it was 1:160 (+). High-dose systemic corticosteroids were initiated (prednisolone 90 mg/day, equal to 1.5mg/kg/day). The corticosteroid dose had been tapered down to a maintenance dose of 25 mg/day three months later when she was once again admitted due to diabetic ketoacidosis. From this admission onward, skin biopsies from 6 different locations over the next 6 years, all revealed superficial acantholysis of granular cells (Fig. 2B) and PF diagnosed each time. During this span, only one anti-ICS Ab examination (in June 1992) showed low titers (1:20); the subsequent 13 examinations showed consistently elevated titers ranging from 1:160–1:1280. This correlated with the progressively intractable disease despite aggressive treatment with high dose of systemic corticosteroids (up to dexamethasone 12 mg/day; equivalent to prednisolone 1.25mg/kg/day), and adjuvant immunotherapy with azathioprine, vibramycin, and multiple courses of plasmapheresis. She was lost to follow-up 2 months after her last admission in February 1998.

**DISCUSSION**

Although both PV and PF are characterized by intraepidermal acantholysis with vesicle formation, they can be distinguished clinically and histopathologically. Clinically PV involves both the epidermis and/or the mucosa while PF affects only the skin. The differing sites of involvement noted clinically can be elegantly explained by the theory of desmoglein compensation. Desmogleins (Dsg) along with desmocollins are the two groups of cadherins or desmosome-cell specific adhesion molecules which comprise the keratinocytic desmosomes. Dsg 3 is believed to be the main cadherin present in mucosa, whereas Dsg 1 is likely the major component of the epidermal desmosomes, although Dsg 3 probably also plays a role in skin adhesion. Therefore it has been proposed that the profile of autoantibodies to desmogleins is the primary determinant of clinical phenotype with antibodies to Dsg
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3 being associated with mucosa-dominant pemphigus, whereas the presence of both anti-Dsg 3 and anti-Dsg 1 is associated with mucocutaneous pemphigus.\(^1\) Although minor cutaneous involvement was observed in most anti-Dsg3+/Dsg1- patients, severe cutaneous involvement was seen only in anti-Dsg3+/Dsg1+ patients.\(^1\) PF, by similar logic, is associated with an anti-Dsg3-/Dsg1+ profile and presents primarily with skin lesions.\(^1\) This has been confirmed by large scale studies using enzyme-linked immunosorbent assay (ELISA),\(^13-18\) suggesting anti-Dsg ELISA testing may be a viable alternative diagnostic tool in conjunction to the histopathological analysis. The role of desmoglein antibodies have further been supported by recent reports of altering desmoglein titers in patients with transition in pemphigus phenotypes.\(^3-9\) Serial testing of anti-Dsg 1 and Dsg 3 antibody titers in patients with PV transitions into PF have revealed decreasing anti-Dsg 3 antibody level with relatively stable levels of anti-Dsg 1 antibody titers.\(^3, 6\) Nevertheless, a delay of about one year between conversion of PV to PF phenotype and the decrease of anti-Dsg 3 antibodies levels to sub-threshold levels was observed in one patient.\(^3\) In the reported cases, a change from PV to PF is more common than a change from PF to PV.\(^7\) Nevertheless, antibody profiles in observed PF shifts into PV revealed antibody profile transition from anti-Dsg3-/Dsg1+ to anti-Dsg3+/Dsg1+, in concordance with the proposed mechanism.\(^4, 5\) The mechanism for such an acquisition of new autoantibodies has been termed “epitope spreading” in continuous transitions and “epitope shift” in patients with prolonged inactive disease states\(^7\) by which transitions between different pemphigus phenotypes as well as into bullous pemphigoid have been explained.\(^19-21\) Namely, tissue damage caused by an autoimmune or inflammatory skin disease exposes a previously sequestered antigen normally undetectable by the immune system, leading to the production of autoantibodies against the exposed protein components and formation of another autoimmune skin disease.\(^20, 21\)

In our first patient, systemic corticosteroids were clearly contraindicated considering his Aeromonas septicemia, impending liver decompensation, and suspected hepatitis B virus reactivation. Given his limited involvement and the phenotype of PF topical betamethasone and gentamicin cream was selected. Clinical resolution was noted at 6 months’ follow-up. In our 2\(^{nd}\) patient, the elevated activity and widespread involvement of PF necessitated the use of systemic immunosuppressants, and even then, clinical progression was seen. Thus the optimal therapeutic route and dose may depend a variety of factors, although the extent of involvement (indicative of disease activity) is probably the most important.

Thus while systemic glucocorticoids are the mainstay of therapy for pemphigus as a whole, in select patients with localized PF, moderate-to-high potency corticosteroids can be used as an initial therapy.\(^11\) As prognosis between the different subtypes have been shown to be of little significance, some localized PV may likely be treatable, at least initially, via the topical route. In terms of the prognostic implications of pemphigus with subtype transition, further study may be needed since this phenomenon may be a manifestation of selective inhibition or epitope spreading.

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REFERENCES

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尋常性天疱瘡轉換至落葉性天疱瘡
-兩個病例報告

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尋常性天疱瘡及落葉性天疱瘡是天疱瘡疾病群中具有獨特的臨床病理變化之兩種次分類。臨床上，尋常性天疱瘡可以黏膜病灶、黏膜皮膚病灶或皮膚病灶表現，而落葉型天疱瘡則以皮膚病灶為主。病理上，落葉性天疱瘡的表層內棘層鬆解位於顆粒細胞層裡，而尋常性天疱瘡則位在基底層之上。傳統上這些不同的特徵可用於治療選擇及預後評估的依據。不同表現型之間的轉換則不常見。我們報告兩個由尋常性天疱瘡轉換至落葉性天疱瘡的病例，並提出可以解釋這個現象的機制加以討論。（中華皮誌: 27: 52-58, 2009）