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Case Report

Pemphigus foliaceus complicated by disseminated cutaneous herpes simplex virus infection in an elderly man

一名患有落葉性天皰瘡與及廣泛性單純皰疹病毒皮膚感染的長者個案

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Pemphigus foliaceus is an immunobullous disease which commonly presents with erosions, ulcerations and crusting. In immunocompromised hosts, disseminated cutaneous herpes simplex infection may also present in a similar fashion. It may be difficult to distinguish between them on clinical grounds alone and their co-existence poses both a diagnostic and therapeutic challenge. We report a case of pemphigus foliaceus complicated by disseminated cutaneous herpes simplex infection. Systemic acyclovir plus systemic steroids hastened the clinical recovery within a month. The clinical features will be discussed together with a literature review.

落葉型天疱瘡是一種免疫大皰病，通常表現爲皮膚糜爛、潰瘍和結痂。在免疫功能低下的病人，播散性單純疱疹病毒感染發生在皮膚時，也可出現類似病徵。臨床上要區分兩者存在一定困難，若果兩者同時發生，更是診斷和治療上的一大挑戰。我們報告一例落葉型天疱瘡併發廣泛性皮膚單純疱疹病毒感染，在同時接受全身性阿昔洛韋及類固醇治療後，一個月內得以快速痊癒。此病的臨床特徵及其文獻回顧將會在此文中一併討論。

Keywords: Disseminated herpes simplex virus infection, pemphigus foliaceus

關鍵詞：播散性皮膚單純疱疹病毒感染、落葉型天疱瘡

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Introduction

Pemphigus foliaceus (PF) usually presents with flaccid blisters, tender erosions and crusting. Epidermal damage from autoimmune antibodies leading to subcorneal blistering and acantholysis is responsible for the morphology. Cutaneous herpes simplex virus (HSV) infection presents with localised grouping of vesicular lesions with surrounding erythema. This is due to balloon degeneration of keratinocytes, leading to

reticular alteration of epidermis.[1] However, in immunocompromised individuals, HSV infection could also present with widespread erosions, erythema, haemorrhagic crusting and ulcerations. As treatment of PF requires immunosuppression, while eradication of HSV infection requires anti-viral therapy, it is important to treat both conditions appropriately.

Case report

An 89-year-old old age home resident who had a past medical history of hypertension, asthma, paroxysmal atrial fibrillation, alpha thalassaemia trait, peptic ulceration, old stroke and borderline level of vitamin B12 was admitted into the medical ward for worsening of his skin rash which had persisted for three decades. He had been admitted for the same complaint four months previously. Topical emollients and 0.0125% fluocinolone cream were given at that time.

On examination there was widespread erythema, erosions and haemorrhagic crusts (Figure 1) with yellowish scales. The lesions were found over the face, upper trunk and proximal extremities. A few shallow and punched-out ulcers with round regular edges were noted (Figure 2). Vesiculobullous lesions were not present. The mucosa, scalp and nails were spared and a keloid was noted over the anterior chest wall. The clinical differential diagnoses were PF, drug eruption, vasculitis and arthropod bite reaction. Skin swabs for viral and bacterial culture were taken from the chest wall region. Blood tests showed a leucocytosis, normal eosinophil count and mild renal impairment from dehydration. A dermatology consultation was requested.

While waiting for dermatology assessment, a 2 mm punch biopsy was performed on a lesion over the left lateral leg. Direct immunofluorescence (DIF) could not be performed due to limitations of the specimen. An incisional skin biopsy was subsequently taken from the right upper chest

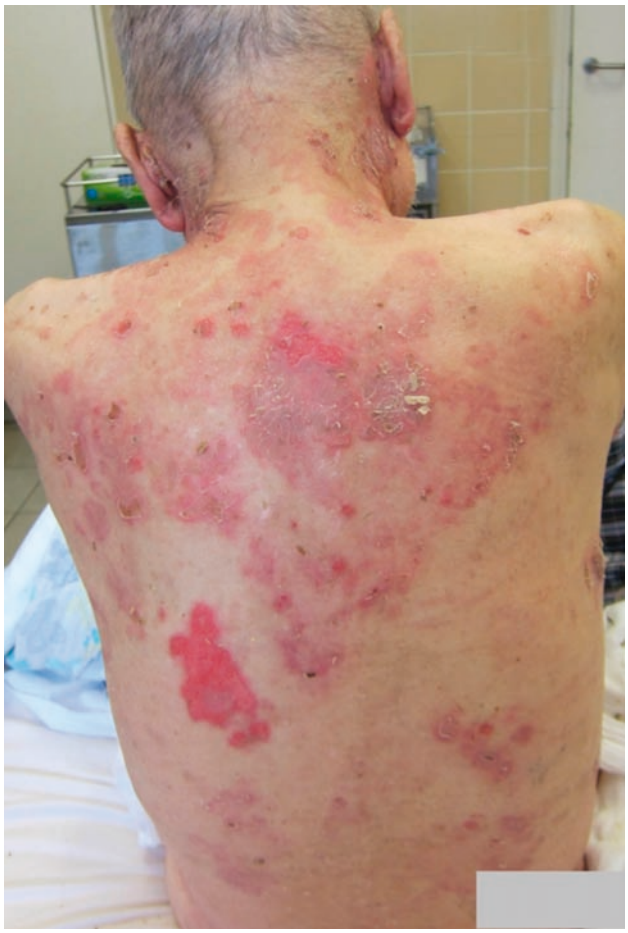

Figure 1. Diffusely-distributed lesions over the trunk.

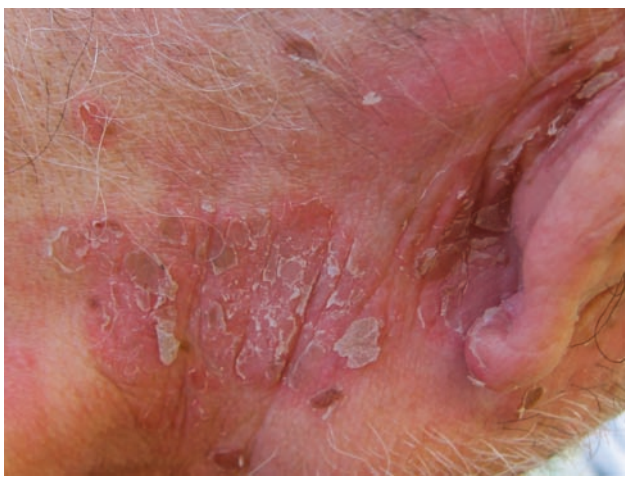

Figure 2. Close-up view of the lesions showing yellowish scaling and round-edged ulcerations in places.

wall. An elliptical piece of skin measuring 1.6x1.0x0.6 cm was sent for examination. Histopathology showed subcorneal blistering and acantholytic dyskeratosis (Figure 3). Aggregates of neutrophils were noted within the parakeratotic layers. Cytopathic changes from herpesvirus infection were seen over the ulcer base (Figure 4a). DIF showed full-thickness intercellular IgG deposition in the epidermis (Figure 4b). The diagnosis of pemphigus foliaceus was made based on clinico-pathological correlation. Immunohistochemical staining with HSV markers showed a strong nuclear and cytoplasmic positivity in those virally infected cells. Skin swab culture revealed both HSV type 1 and methicillin-resistant *Staphylococcus aureus* (MRSA).

After dermatological review, it was suggested that dermatophytosis and scabies should be excluded. As systemic steroids were required, it was also recommended to screen for diabetes and chronic viral hepatitis B infection. These conditions were subsequently excluded. After correction of renal

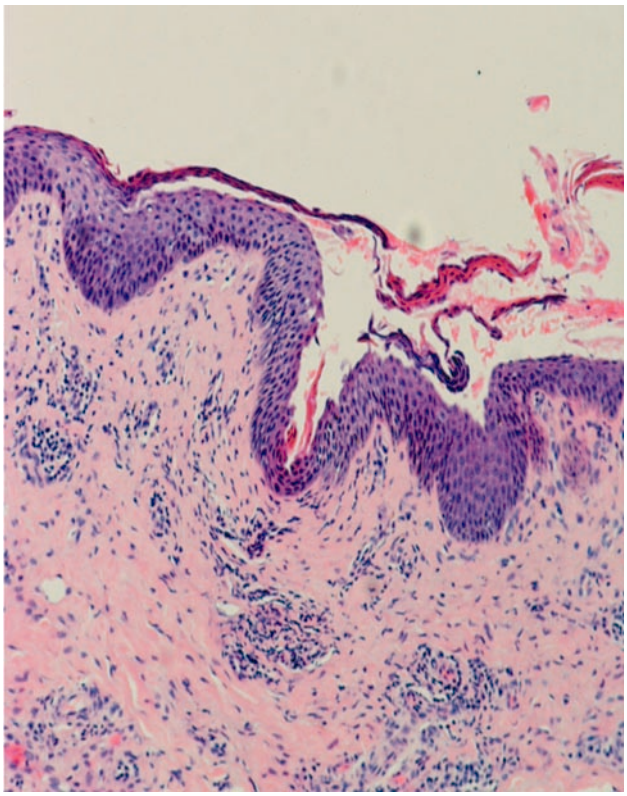

Figure 3. Low power view showing subcorneal splitting and streaks of parakeratosis. (H&E, Original magnification x10).

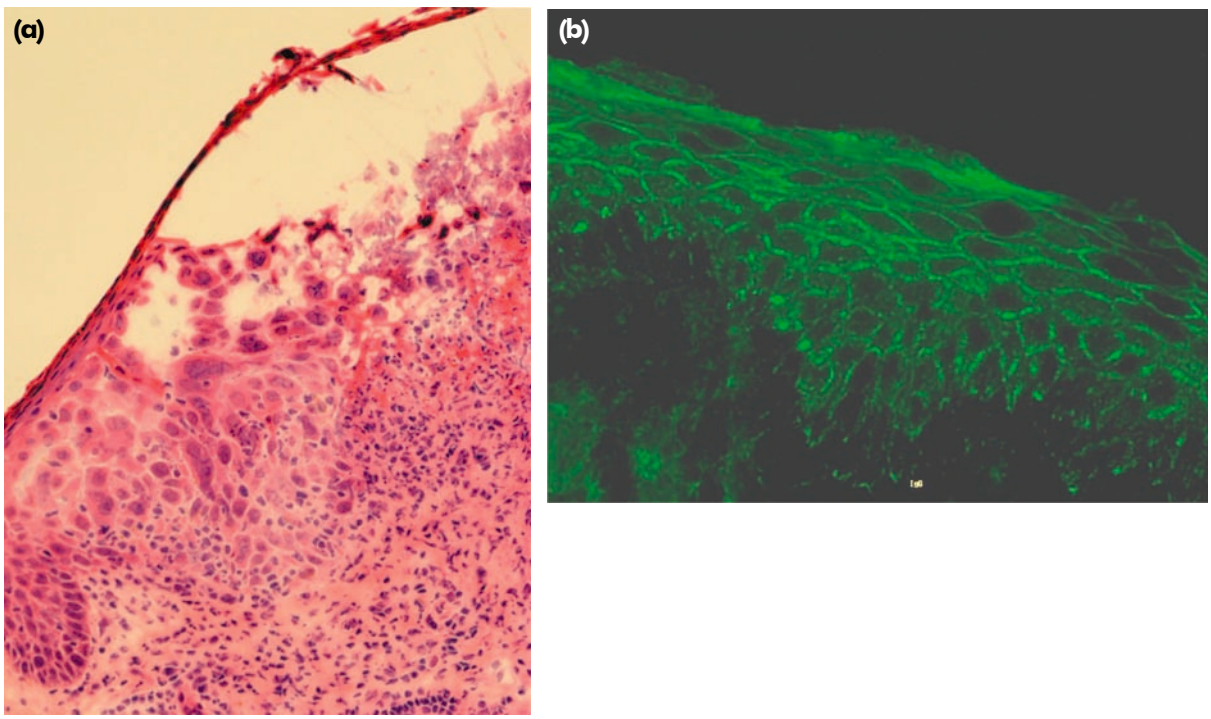

Figure 4. (a) Higher power view showing subcorneal acantholysis and an ulcer base with viral cytopathic changes (H&E, Original magnification x 20). (b) Direct immunofluorescence showing intercellular IgG deposits (Magnification x 10).

impairment by rehydration, oral prednisolone 40 mg daily (1 mg/kg/day), oral acyclovir 400 mg five times daily, and intravenous vancomycin infusion 500 mg once every 12 hours were started. Fucidin cream was applied over the yellowish scaly areas. Within a week, the erosions and erythema had resolved with postinflammatory hyperpigmentation. The yellowish scaling also resolved gradually. Post-treatment skin swabs for viral studies from different body regions were negative. The skin condition remained stable one month after systemic steroids were started. There was no history of prior orolabial or genital herpes infection.

Discussion

Pemphigus foliaceus is traditionally considered as benign and superficial form of pemphigus. The erosion, scaling and erythema represent partial denudation of epidermis, parakeratosis and effect of active superficial perivascular inflammation respectively. It is a clinico-pathological diagnosis. Topical therapies are helpful in general but systemic steroids are often required. Complications are mainly infection or steroid-related. Herpes simplex infection may complicate other dermatoses such as Darier's disease, pemphigus vulgaris, atopic eczema, ichthyosis vulgaris, mycosis fungoides and burns. The morphology and distribution of HSV infection in the immunosuppressed may be atypical. Disseminated HSV infection is associated with mortality; lethal cases from fulminant hepatitis or necrotising encephalitis have been reported.[2-4] Apart from sun exposure and thiol-containing medication, HSV is also a well known trigger of pemphigus.[5] The possible mechanisms include interruption of T-cell tolerance, up-regulation of pro-inflammatory factors in those genetically pre-disposed, structural damage to keratinocytes resulting in exposure of endogenous antigens and epitope spreading.[5]

Theoretically, the co-expression may be those of an active pemphigus with superimposed HSV infection, isolated HSV infection with quiescent pemphigus or HSV infection causing flare-up of pemphigus. Studies have been performed in an attempt to elucidate their association. Nikkels et al demonstrated asymptomatic carriage of HSV in acantholytic dermatoses. The occult HSV colonisation was revealed only by immunohistochemistry.[6] However, there was no follow-up study to show if the occult HSV had fully established itself as clinical infection before subsequent exacerbation of the acantholytic dermatoses. Tufano et al had shown that HSV viral DNA could be retrieved in both skin samples and peripheral blood mononuclear cells in selected populations of pemphigus vulgaris.[7] There was no mention of active clinical HSV infection or corresponding histology in the recruited subjects during the course of study. The author proposed that the viral infection may be an occasional trigger for pemphigus. So far, it is still unclear whether pemphigus and HSV infection bear a causal or casual relationship.

In practice, this poses a diagnostic and therapeutic challenge. As mentioned, the morphology of PF and HSV infection could closely resemble each other. Furthermore, localised HSV infection per se could mimic immunobullous disease.[8] If extensive enough, HSV infection may simulate an active flare of the immunobullous disease.[9] Without biopsy and culture, it may be difficult to make a definitive diagnosis in ambiguous situations. While it is prudent to distinguish HSV infection from immunobullous disease, it will be essential to exclude HSV co-infection. A high index of suspicion is needed especially when the pemphigus is refractory to immunosuppression, or when the clinical course is rapidly deteriorating.[4,5,10,11] So far, there are no studies on the prevalence of their co-existence or genetic predisposition leading to this particular form of expression.

In our patient, the combination of advanced age and months of topical steroid therapy increased the susceptibility to infection. The protracted clinical course raised suspicion of additional

element such as infection. No skin swabs or biopsies were taken prior to admission; hence one cannot ascertain when the HSV infection started. Furthermore, whether the HSV infection triggered PF or it was a superimposed infection on a partially-treated PF remains unknown. The MRSA infection was co-incidental and was treated successfully. The clinical differential diagnosis of vasculitis was excluded, based on the absence of serum autoimmune markers and primary vasculitic changes on histological section. Arthropod bite reaction and drug eruption were excluded based on histopathology and DIF findings. Pemphigus erythematosus could mimic PF, but the demographic profile and morphology were incompatible. The histopathologic differential diagnoses of subcorneal splitting include staphylococcal scalded skin syndrome (SSSS), bullous impetigo, subcorneal pustular dermatosis (SPD), Grover's disease and drug-induced pemphigus. The clinical history was against SSSS and SPD. The presence of yellowish scales likely represented secondary impetiginisation rather than bullous impetigo. The DIF findings lent support to the diagnosis of PF rather than pemphigus erythematosus. The absence of itchiness, a protracted clinical course, a relatively monomorphic histology and the presence of immune deposits helped to exclude Grover's disease. Drug-induced pemphigus is a diagnosis of exclusion and clinico-pathological correlation is required. In our patient, there was no recent introduction of thiol-group medications such as penicillamine or captopril, or sulphur-containing drugs.

In summary, we have reported an elderly man with PF complicated by disseminated HSV infection. From the above discussion and literature review, management of difficult-to-treat or atypical pemphigus requires exclusion of alternative diagnoses or additional pathology. Timely management improves patient well-being and saves lives. Further research is required to study the exact mechanisms and actual prevalence of their co-existence.

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References

1. Ackerman AB, Ragaz A. The lives of lesions, Chronology in Dermatopathology. USA: Masson Publishing; 1983. Chapter 10, Herpesvirus infection; p. 83-93.
2. Wilde C, Sheehan W, Shepherdson A, Patwardhan A. Disseminated mucocutaneous herpes simplex in an atopic individual. JRSM Short Rep 2011;2:80.
3. Tischendorf JJ, Grosse V, Flik J, Verhagen W, Manns MP, Trautwein C. Fulminant course of herpes simplex virus reactivation in an apparently immunocompetent woman. Int J Infect Dis 2003;7:160-2.
4. Demitsu T, Kakurai M, Azuma R, Hiratsuka Y, Yamada T, Yoneda K. Recalcitrant pemphigus foliaceus with Kaposi varicelliform eruption: report of a fatal case. Clin Exp Dermatol 2008;33:681-2.
5. Brandao MLFB, Fernandes NC, Batista DPO, Santos N. Refractory pemphigus vulgaris associated with herpes infection: case report and review. Rev Inst Med Trop Sao Paulo 2001;53:113-7.
6. Nikkels AF, Delvenne P, Herfs M, Pierard GE. Occult herpes simplex virus colonization of bullous dermatitides. Am J Clin Dermatol 2008;9:163-8.
7. Tufano MA, Baroni A, Buommino E, Ruocco E, Lombardi M, Ruocco V. Detection of herpesvirus DNA in peripheral blood mononuclear cells and skin lesions of patients with pemphigus by polymerase chain reaction. Br J Dermatol 1999;141:1033-9.
8. Lecluse ALY, Bruijnzeel-Koomen CAFM. Herpes simplex virus infection mimicking bullous disease in an immunocompromised patient. Case Rep Dermatol 2010;2:99-102.
9. Hale EK, Bystryn JC. Atypical herpes simplex can mimic a flare of disease activity in patients with pemphigus vulgaris. J Eur Acad Dermatol Venereol 1999;13:221-3.
10. Kalajian AH, Callen JP. Atypical herpes simplex infection masquerading as recalcitrant pemphigus vulgaris. Aust J Dermatol 2007;48:242-7.
11. Caldarola G, Kneisel A, Hertl M, Feliciani C. Herpes simplex virus infection in pemphigus vulgaris: clinical and immunological considerations. Eur J Dermatol 2008;18:440-3.