Case report

Pemphigus foliaceous associated with Herpes simplex virus infection

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Introduction

Pemphigus is a group of autoimmune blistering diseases of the skin and/or mucous membranes caused by the presence of antibodies against adhesion molecules on the cell surface of keratinocytes.[¹] Most cases are localized to the face and trunk and are characterized by recurrent crops of flaccid bullae that readily rupture, resulting in shallow crusted erosions which heal leaving behind hyperpigmentation. Rarely can it also present as erythroderma.[²] Management requires immunosuppressive therapy.

In rare cases, herpes simplex virus infection can develop as a consequence of immunosuppressive therapy in these patients and cause a clinical diagnostic dilemma. Definite diagnosis is essential as the management then requires immunosuppressive therapy with antiviral drugs.

Case report

We report a case of a 48 year old male who presented with complaints of on and off itching along with scaly lesions over the face and the entire body for 3 years (Fig. 1). He had taken treatment from elsewhere with partial relief. There were no complaints of photosensitivity, malar rash, discoid rash and other systemic complaints. There were no blisters, eye or oral mucosal involvement. The patient was a known diabetic and had undergone left orchidectomy in the past.

On examination, the patient was having erythroderma with scaling more prominent over the face and trunk. Conjunctival, oral and genital mucosae were normal. Systemic examination did not reveal any abnormality. There was no palpable lymphadenopathy.

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Haematological investigations including complete blood count, renal and liver function tests were normal except for a total leucocyte count and ESR which were 17,200 /cumm and 25 mm/ hour respectively. Fungal smears taken from the skin were negative. Ultrasonography of the abdomen showed mild hepatomegaly. Antinuclear antibodies were detected in a primary dilution of 1:40. Histopathological evaluation of the skin biopsy showed mild irregular epidermal acanthosis with a focally stripped off corneal layer (? blister base) showing scattered dyskeratotic granular keratinocytes. Dermis showed a mildly increased perivascular lymphocytic infiltrate. As the features suggested pemphigus foliaceus (Fig 2), direct immunofluorescence was done and it showed a lace like positivity for IgG at the intercellular junction in the full thickness of epidermis consistent with pemphigus foliaceous. (Fig 3).

Fig. 1 Erythrodermic stage of pemphigus foliaceous
Fig 2a- Mild epidermal acanthosis with focally stripped of corneal layer (H&Ex4). Fig 2b- Stipped-off area show occasional dyskeratotic keratinocytes (H&Ex20). Fig 2c- Foci showing dyskeratotic keratinocytes (H&Ex40). Fig 2d- Dyskeratotic keratinocytes (H&EX100)

Fig. 3. Direct immunofluorescence (DIF) showing lace like positivity for IgG
The patient was treated with oral steroids along with azathioprine. Following the treatment, the patient’s lesions partially subsided. However fresh lesions appeared around the lips, eyes and the chest and a repeat skin biopsy was taken. (Fig.4.)

![Fig.4.](image)

**Fig. 4.** Fresh blisters around eyes, oral cavity and chest wall

**Fig. 5.**  **Fig.5a** Moderate epidermal acanthosis with sub corneal acantholytic blister (H&Ex4).  **Fig.5b**-Subcorneal acantholytic blister (H&Ex20).  **Fig.5c** A focus with surface ulceration and enlarged nuclei (H&Ex20).  **Fig 5d**- Enlarged nuclei with eosinophilic inclusions. Multinucleate cells (inset) [H&Ex100]

Sections from the lesion showed acantholysis in the upper epidermis, within and adjacent to granular layer. Focally detached stratum corneum with several dyskeratotic granular keratinocytes and eosinophilic spongiosis was also noted. Another focus in the biopsy showed ballooning degeneration of cells, homogenous eosinophilic inclusions and ground glass nuclei. Occasional multinucleate cells were also seen. (Fig 5)

Histopathological features were suggestive of pemphigus foliaceous with herpetic infection.

Serological tests for HSV Type 1 and type 2 IgG were positive with values of 6.05 and 3.31 respectively. The patient was started on injectable antiviral therapy along with continuation of the immunosuppressive therapy for pemphigus.

**Discussion**

Pemphigus foliaceous is an autoimmune disease having a chronic generalized course.
It clinically presents with flaccid bullae that usually arise on an erythematous base or as scaling patches without evident blisters.[3] Erythema, oozing, and crusting can be present. Because of their superficial location, the blisters break easily, leaving shallow erosions. Mucosal involvement is absent even with widespread disease. It may rarely present as an exfoliative dermatitis. The Nikolsky sign is positive and Tzanck smear preparation reveals acantholytic granular keratinocyte.[4]

Serologically, it is characterized by the formation of antibodies against desmoglein 1, which is present mostly in the upper layers of the epidermis.

Histological evaluation of the skin lesion shows superficial epidermal/sub corneal acantholytic blisters. Presence of dyskeratotic granular keratinocytes is very characteristic. In our case, though there was no definite blisters, the presence of dyskeratotic keratinocytes in the first biopsy specimen were clues to the diagnosis.

Direct immunofluorescence in patients with pemphigus foliaceous show intercellular deposition of IgG either in the superficial portion or full thickness of the epidermis as seen in our case.

Whether HSV infection represents an aetiopathogenic factor for pemphigus or a consequence of the immunosuppressive treatment has long been debated. The associations of herpes with pemphigus have been studied by several groups.[5-21] (Table1)

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Few believe that the presence of herpes acts as an aetiological triggering agent for pemphigus whereas others believe that it is a result of the immunosuppressive drugs used for pemphigus.

The role of HSV in the aetiopathogenesis of pemphigus was first described by Krain in 1974 in a study of 59 patients where they found that two patients had developed pemphigus after severe herpetic infection.[5]

Nikkels et al studied the presence of HSV in acantholytic disorders, including 19 patients with pemphigus vulgaris for possible occult viral colonization. No cytopathic signs suggestive of HSV were seen. However, immunohistochemistry (IHC) revealed HSV antigens in pemphigus vulgaris in one patient (1/19, HSV-I). They concluded that occult HSV colonization may occur in pemphigus vulgaris. Given the frequent use of immunosuppressive treatment for primary bullous disorders, greater awareness of the possibility of HSV colonization and infection is required.[9]

Marzano et al tried to evaluate the association of herpes with pemphigus in his study. Skin and/or mucosal swabs from 35 patients with pemphigus vulgaris or pemphigus foliaceus were tested for HSV by polymerase chain reaction (PCR). With their findings, they concluded that HSV is unlikely to be a triggering factor for pemphigus but its presence in pemphigus lesions seems to be a frequent and early complication of immunosuppression.[11]

Esmaili N et al tried to detect the presence of HSV 1 and 2 and human herpes virus (HHV8) (8) in patients suffering from pemphigus vulgaris by using PCR. They could not detect these viruses in any of these patients and concluded that herpes viruses may be only occasional factors in the development or exacerbation of pemphigus vulgaris.[11]

Co-existence of herpetic infection in pemphigus patients has been studied widely. All these studies found herpes virus in their subjects with pemphigus with the percentage varying from 9.68% to 19%.

In a recent study, Mahnaz Banihashemi et al analysed 30 diagnosed cases of pemphigus for the presence of HSV1, EBV, HSV2 and HHV8 by immunohistochemistry. They found a significant prevalence of HSV1 in lesions of pemphigus patients, especially in pemphigus foliaceus.[13]

There have been several case reports of pemphigus with associated herpes virus infection which were mostly seen as a complication of immunosuppressive therapy as in our case.[14-21]
Conclusion

With the above studies, it seems to appear that the immunosuppressive therapy for pemphigus results in a flare up of typical or atypical herpetic lesions. However, more randomized studies on a larger number of patients are required on screening for occult herpes in erythrodermic pemphigus patients for substantiating the findings. For the practicing dermatologist, herpetic infection should be considered in pemphigus patients with lack of improvement under adequate immunosuppressive therapy or the development of fresh lesions after a partial response.

References


