Case report

Pemphigus foliaceus 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 foliaceus. (Fig 3).

Fig.1

Fig.2.2a-2d

Fig.3.

Fig. 1 Erythrodermic stage of pemphigus foliaceus

Fig 2a- Mild epidermal acanthosis with focally stripped off 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.

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

Fig.5.

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 foliaceus 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 foliaceus 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 foliaceus 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)

Table 1

S.No	Author	Journal	Year	Age of patient	Location of lesion
1	Grunwald MH et al [14]	International Journal of Dermatology 1986;25(6):392-393	1986	39 years, male	Oral lesion
2	Brown P et al [15]	Journal of the American Academy of Dermatology, Volume 21, Issue 5, 1126-1128	1989	55 years, male	Oral lesion
3	Prendiville JS et al [16]	Paediatric Dermatology 1994;11:145-50.	1994	11 years, female	Oral lesion
4	Takahashi I et al [17]	Diagnostic Cytopathology 1998;19:446-50	1998	53 years, female	Oral lesion
5	Hale EK et al [18]	Journal of European Academy Dermatology and Venereology 1999;13:221-3	1999	69 years, female	Oral lesion
6	Kalajian AH [19]	Australas J Dermatol. 2007;48:242-7	2007	57 years, female	Erosive Genital lesion
7	Brandão ML et al [20]	Rev Inst Med Trop Sao Paulo. 2011 Mar-Apr;53(2):113-7.	2011	50 Years, female	Eyelid

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.^[1]

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.^{6,7,8,9,12} 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] (Table 2)

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

1. Marzano AV, Tournalaki A, Merlo V, Spinelli D, Venegoni L, Crosti C. Herpes simplex virus infection and pemphigus. *International Journal of Immunopathology and Pharmacology*. 2009;22(3):781-6
2. Connelly EA, Aber C, Kleiner G, Nousari C, Charles C, Schachner LA. Generalized erythrodermic pemphigus foliaceus in a child and its successful response to rituximab treatment. *Paediatric Dermatology*. 2007; 24(2):172-6.
3. Freedberg, et al. (2003). Fitzpatrick's Dermatology in General Medicine. (6th ed.). Page 558-562. McGraw-Hill
4. Hong Wu, Schapiro B, Harrist TJ. Noninfectious Vesiculobullous and Vesiculopustular Diseases. Lever's Histopathology of the Skin, 9th ed, 2005;258
5. Krain LS. Pemphigus: epidemiologic and survival characteristics of 59 patients, 1955-1973. *Archives in Dermatology*. 1974;110:862-5
6. Schlupen EM, Wollenberg A, Hänel S, Stumpfenhausen G, Volkenandt M. Detection of herpes simplex virus in exacerbated pemphigus vulgaris by polymerase chain reaction. *Dermatology*. 1996; 192:312-6.
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. *British Journal of Dermatology* 1999;141:1033-9
8. F. Z. Belgnaoui, K. Senouci, H. Chraïbi et al., "Predisposition to infection in patients with pemphigus. Retrospective study of 141 cases," *La Presse Medicale* 2007; 36(11); 1563–1569.
9. Nikkels AF, Delvenne P, Herfs M, Pierard GE. Occult herpes simplex virus colonization of bullous dermatitides. *American Journal of Clinical Dermatology* 2008;9:163-8
10. Caldarola G, Kneisel A, Hertl M, Feliciani C. Herpes simplex virus infection in pemphigus vulgaris: clinical and immunological considerations. *European Journal of Dermatology* 2008;18:440-3.
11. Esmaili N, Hallaji Z, Abedini R, Soori T, Mortazavi H, and Chams-Davatchi C, "Pemphigus vulgaris and herpesviruses: is there any relationship?" *International Journal of Dermatology* 2010; 49 (11);1261–5.

12. Esmaili N, Mortazavi H, Noormohammadpour P, Boreiri M, Soori M, Farahani IM,5 and MitraMohit M, "Pemphigus Vulgaris and Infections: A Retrospective Study on 155 Patients," *Autoimmune Diseases* 2013, Article ID 834295. doi:10.1155/2013/834295
13. Banihashemi M, Maleki M, Pezeshkpoor F, Jafarian AH, Sharghi MR, Hashemzadeh S. Incidence of herpes family viruses in skin lesions of pemphigus patients. *Iran Journal of Dermatology* 2013; 16(64): 53-6.
14. Grunwald MH, Katz I, Friedman-Birnbaum R. Association of pemphigus vulgaris and herpes simplex infection. *International Journal of Dermatology*. 1986;25:392-3.
15. Brown P, Taylor B. Herpes simplex infection associated with pemphigus vulgaris. *Journal of the American Academy of Dermatology*, 1989 ; 21 (5) , 1126 – 1128
16. Prendiville JS, Israel DM, Wood WS, Dimmick JE. Oral pemphigus vulgaris associated with inflammatory bowel disease and herpetic gingivostomatitis in a 11-year-old girl. *Pediatric Dermatology*. 1994;11:145-50
17. Takahashi I, Kobayashi TK, Suzuki H, et al. Coexistence of pemphigus vulgaris and herpes simplex virus infection in oral mucosa diagnosed by cytology, immunohistochemistry, and polymerase chain reaction. *Diagnostic Cytopathology* 1998;19:446-50
18. Hale EK, Bystryn JC. Atypical herpes simplex can mimic a flare of disease activity in patients with pemphigus vulgaris. *Journal of European Academy Dermatology and Venereology*. 1999; 13:221-3.
19. Kalajian AH, Callen JP. Atypical herpes simplex infection masquerading as recalcitrant pemphigus vulgaris. *Australasian Journal of Dermatology*. 2007;48:242-7
20. Brandao, Maria Luiza Figueiredo Braga et al. Refractory pemphigus vulgaris associated with herpes infection: case report and review. *Rev. Inst. Med. trop. S. Paulo* 2011; 53 (2);113-17
21. Cheng HF, Lam MS, KH Tsang KH, HoWC, Ng WF, Kwan WK. Pemphigus foliaceus complicated by disseminated cutaneous herpes simplex virus infection in an elderly man. *Hong Kong Journal of Dermatology and Venereology*. 2013;21;73-77