A CASE OF PEMPHIGUS VULGARIS TRANSFORMED INTO PEMPHIGUS FOLIACEUS MANIFESTED WITH A SINGLE, RECURRENT LESION WITH SUPRAINFECTION

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Summary

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are bullous dermatoses with multiple similarities. The transition between these pemphigus subtypes rarely occurs and the underlying pathophysiological and molecular mechanism has been widely debated in many studies. The desmogleins are abundant in the hair follicles, which are frequently affected by acantholysis. The humid environment which is specific to the lesions promotes bacterial colonization.

We present the case of a 49-year old patient diagnosed with PV in 2006, treated chronically with prednisone, who attended a consultation due to the appearance of an erosive lesion on the vertex of the scalp. The medical history shows the presence of a recurrence with an unchanged characteristic, which was triggered by the disruption of the treatment. The microbiologic culture of the secretion has confirmed the presence of Staphylococcus aureus each time the patient had a consultation. The anti-desmoglein 1 antibodies (anti-Dsg1) were found positive, and the histopathology exam revealed acantholysis at the subcorneal level, and in the granular layer. The flare was treated by increasing the dosage of the prednisone.

Although the scalp involvement is common in PV, the recurrent unilateral injury together with the appearance of nonscarring alopecia, while concomitant with a suprainfection, is specific to our case. We suspect the transition from PV to PF with an unchanged, recurrent nature, and discuss the role of suprainfection in the development of nonscarring alopecia.

Key words: *pemphigus vulgaris, pemphigus foliaceus, desmogleins, alopecia, epitopes, autoantibodies.*

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Introduction

Intraepidermal blistering dermatoses group includes several clinical entities, namely PV, PF, paraneoplastic pemphigus, with Ig A and drug induced. The similarities between these often make differential diagnosis a challenge for the clinician.

The two main subtypes, PV and PF, are differentiated clinically, through the histology and immunological profile. This is marked by the presence of antibodies directed towards calcium-dependent cell adhesion molecules belonging to the cadherin family. The transition between the subtypes has rarely been reported.

PV is normally associated with generalized skin lesions. Often patients develop mucosal involvement and flaccid bullae, and its presence can be justified histologically by suprabasal epidermal acantholysis, a consequence of an autoimmune process directed towards the desmoglein 3 (Dsg3), although over half of these patients also have anti-desmoglein 1 (Dsg1) antibodies.[1]

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The scalp's involvement can be frequently observed, however the development of nonscarring alopecia is unusual, and the role of concomitant suprainfection in the development of anagen effluvium is disputed. [1,2]

PF is characterized by the appearance of erosive, crusty plaques, as a result of acantholysis at the level of the subcorneal epidermal layers, with circulating and tissue antibodies directed against Dsg1.

Case presentation

A 49-year-old female patient was admitted into our clinic in 2020 due to the appearance of an erosive lesion with a tendency to ulcerate, located on the vertex of the patient's head, as well as local sensitivity, which had appeared approximately two months prior to the patient's visit.

Her past medical history shows that the patient was diagnosed with PV in 2006 based on the clinical manifestations (mouth ulcers and blisters on the face and trunk) and investigations, for which she had received immunosuppresive treatment with prednisone and azathioprine. The patient achieved a complete remission during this time, however she had experienced two relapses after she interrupting the treatment on her own accord.

In 2011, the patient presented a solitary lesion, located on the vertex of the head, which looked similar to the one previously described, and which was initially interpreted as follicular pyoderma, however the antibiotic treatment was ineffective.

Skin examination shows a poorly defined, round-shaped erosive plaque on the vertex of the head, 7 cm in diameter, partially covered by an epithelium which peels off easily through friction, with clear, serous fluid, almost completely devoid of hair, as shown in figure 1. Nikolsky sign was positive.

The assesment through the PDAI score (Pemphigus Disease Area Index) showed a moderate activity of the disease (10 points).

Routine blood tests were normal. Cultures from the lesions' secretion were performed, highlighting the presence of *Staphylococcus aureus*.

The Tzanck smear test from the serous fluid revealed numerous placardes of parabasal cells.

Histopathological examination of tissue material obtained by biopsy described acantholysis at the subcorneal level and in the granular layer, with numerous acantolytic cells, neutrophils and discrete fibrin. There are some remnants of follicles that have a cleavage space (Figure 3).

Suspecting a change in the phenotype of the antibodies based on the clinical appearance, we requested the determination of the titer of anti-Dsg 1 and anti-Dsg 3 antibodies via enzyme linked immunosorbent assays (ELISA) method. Antibodies specific for PV were within normal limits, and those characteristic of foliaceous were positive, in a titer of 1:40. Direct immunofluorescence test was not available when the patient arrived at our clinic.

After we confirmed the diagnosis of PF, we reinitiated the therapy with prednisone 0,75 mg/kg body/day in association with azathioprine 0,5 mg/kg body/day. Antiseptical solutions and silver sulfadiazine cream were applied topically until reepithelialization. The evolution was quickly favorable, which allowed the reduction of prednisone dosage to 0,2mg/kg body and azathioprine 0,5 mg/kg (1 tablet/day) during a period of six weeks. After the complete epithelialization, the growth of new hairs was observed, as seen in Figure 2, and the maintenance dose treatment was continued.

Discussions

The persistent scalp lesions without the consecutive appearance of skin lesions in other locations for a long period of time, and the tendency of the pemphigus to be rather generalized than localized, suggests a transition from PV, which the patient was previously diagnosed with, towards PF. This hypothesis is supported both by the presence of the anti-Dsg1 antibodies, lack of specific PV antibodies, and the clinical manifestations.

The transition from PV towards PF is an unusual medical event, explained by qualitative changes in the antibody profile. The mechanism of transition is unclear but could be explained through the phenomenon of epitope spreading, which occurs as a result of a secondary

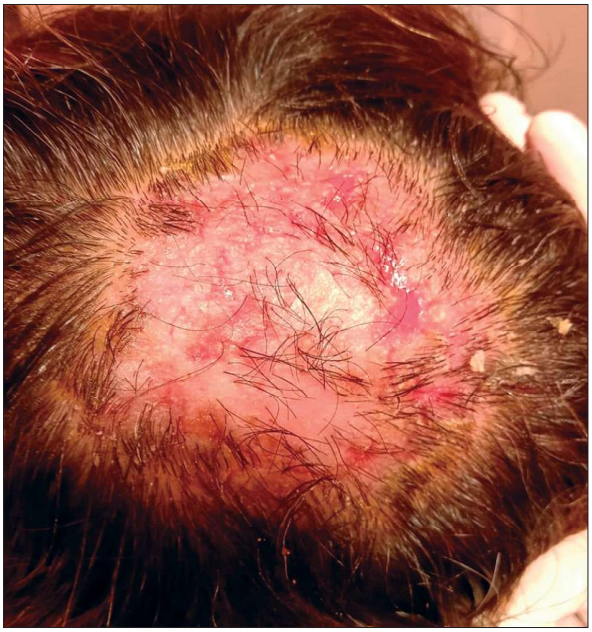

Figure 1. Clinical presentation of PF. A poorly defined, round-shaped erosive plaque on the vertex of the head partially covered by an epithelium.

autoimmune response after the exposure of cryptic antigens following a primary immune response.[3,4]

This process has been researched through studies on both patients with autoimmune diseases and animals, and it involves diversification of the immune response from a dominant epitope to a secondary one as the disease evolves, with the aim of increasing the efficiency of the immune system. As it was shown by Didona and Di Zenzo, the transition between these subtypes is not always permanent, a possible explanation to that being the temporary suppression of anti-Dsg3 antibodies by immunosuppressive therapy. The authors noted that the transition was rarely reported in patients without this type of treatment included in their study.[5] The most probable mechanism, in the case of our patient, is the intermolecular epitope spreading, as the secondary antigen, Dsg 1, is a different molecule and has the same anatomical site as the main antigen Dsg 3.[3]

The appearance of lesions localized on the scalp is an event frequently encountered during the progression of PV, being observed in up to 60% of cases in the literature.[1] However, the

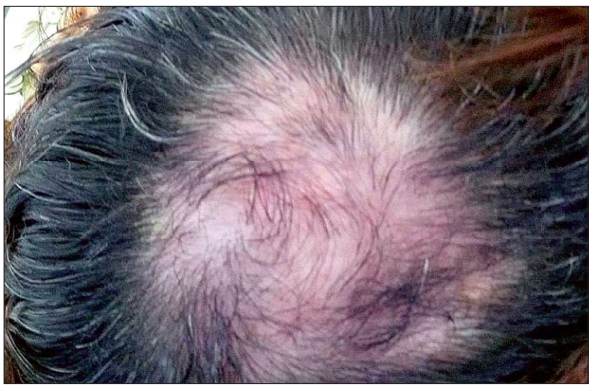

Figure 2. Patient's clinical evolution after six weeks of treatment. Complete reepithelialization with growth of new hairs.

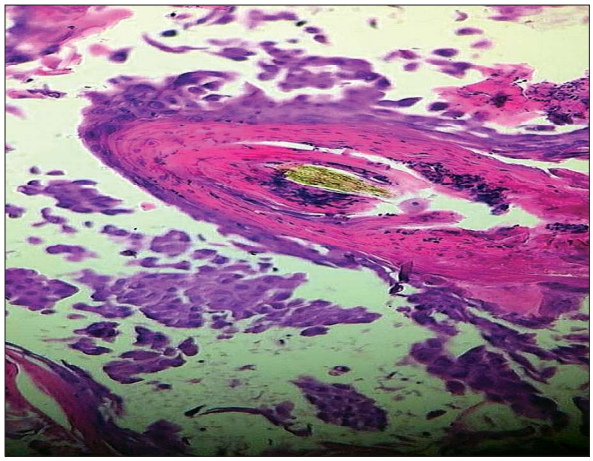

Figure 3. Histopatologic features. Pemphigus foliaceus: Acantholysis at the subcorneal level and in the granular layer, with numerous acantolytic cells. There are some remnants of follicles that have a cleavage space. Haematoxylin and eosin staining, original magnification x40.

presence of nonscarring alopecia is a rare phenomenon.

The psychological impact of hair loss within the lesional area was the decisive factor that caused the patient to seek medical help.

The humid microclimate which is specific for the lesions of the patients with pemphigus promotes the selection of pathogenic bacterial strains. In our patient's lesion, the growth of one single pathogen was exposed, i.e. Staphylococcus aureus.

The role of bacterial suprainfection in the development of alopecia in patients with PV is

debated in literature. Although the effect it has on the affected skin is not yet well established, some authors have disputed the hypothesis that it is an additional factor that, along with acantholysis, causes a decrease in the anchoring of the hair.[2]

Another peculiarity of our case is the unchanged location of the relapses. Localized forms are rarely described in both PV and PF. PV of the scalp was described in two cases, both after surgery, one after cochlear implant and the other after hair transplant. As both procedures involved trauma of the scalp, the Koebner phenomenon can be considered a reasonable explanation.[1,6]

The history of local trauma is excluded in the case of our patient, which supports the presence of another mechanism.

Follicular acantholysis can be explained through the abundance of the antigens at this level.[1] As it was previously proven by Wu et al., that their distribution is dependent on both the degree of cell differentiation and the type of keratinization. Dsg1 can be found in the deep layers of the outer root sheath (ORS) and in the inner root sheath (IRS) of the hair, these being made up of well differentiated cells. The distribution of Dsg3 in the infundibulum is similar to the epidermal one. In the follicular isthmus, in the presence of trichilemmal keratinization, is expressed in all the layers of the ORS. As the authors have shown Dsg1 is missing from the protuberance (bulge), this area being responsible for epidermal regeneration, a possible argument for the favorable evolution with the rapid regeneration of the hairs shortly after the increase of the dose of immuno-suppressant in the presented case.[7] Also, in the case of PV acantolysis, Ig G deposits can be spotted between keratinocytes in the ORS, from the infundibular to the suprabulbar level, at a deeper level than in the PF that occurs at the infundibular level.[1,2]

We highlight the role of the Dsg1 in the maintenance of the epidermal integrity, proven by the studies on animals which are missing this desmosomal component, developing lethal lesions through the loss of the epidermis in the first day of life.[8]

After an increase in the dosage of the prednisone, the evolution in the case of our patient has became quickly positive, allowing a decrease in the dosage during 6 weeks of maintenance treatment of 0,2 mg/kg body prednisone and 0,5 mg/kg body of azathioprine, and obtaining a clinical remission of the disease up until now. Our case confirms that a relatively decreased dosage of corticosteroid treatment, associated with an imunosupresor is sufficient for restoring the skin balance and inducing the remission of the disease.

Conclusions

Our case illustrates the transition from PV to PF, confirmed by the elevated titer of anti-Dsg1 antibodies, which could be explained through the epitope spreading phenomenon. The existence of the solitary recurrences with unmodified and localized character, together with the development of the nonscarring alopecia are the particularities of this case.

As the alopecia is an unusual clinical manifestation of pemphigus, the role of the concomitant suprainfection has to be taken into consideration, some future investigations being necessary, as the mechanism which leads to the loss of the hair is still obscure.

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Conflict of interest
NONE DECLARED

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