Case Presentation

A diagnostically challenging case of pemphigus foliaceus without histologic evidence of acantholysis

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Keywords: acantholysis, autoimmune bullous dermatosis, pemphigus foliaceus

Dermatology Online Journal

Vol. 32, Issue 1, 2026

Abstract

A 77-year-old woman presented with pruritic, scaly, erythematous papules and plaques on the face, which subsequently spread to the trunk. Over nearly 2 years, 5 skin biopsies were performed, consistently suggesting a subacute to chronic eczematous process without acantholysis or intraepidermal bullae. After 2 years of unsuccessful treatment, enzyme-linked immunosorbent assay demonstrated elevated anti–desmoglein-1 IgG and normal anti–desmoglein-3 IgG. Direct immunofluorescence of a skin biopsy revealed IgG and C3 deposition in the intercellular spaces. A diagnosis of pemphigus foliaceus was established, and the patient was treated with rituximab, resulting in significant clinical improvement. This case illustrates a diagnostically challenging presentation of pemphigus foliaceus in which multiple biopsies failed to demonstrate acantholysis or intraepidermal bullae (classic histologic features) highlighting the importance of immunologic testing in the evaluation of suspected autoimmune blistering disorders.

Introduction

Pemphigus foliaceus is an uncommon autoimmune bullous dermatosis mediated by antibodies against the intercellular adhesion molecule desmoglein-1 (Dsg1),[1,2] for which early treatment can alter disease course. Although lesional histology classically demonstrates granular layer acantholysis and subcorneal bullae, definitive diagnosis requires immunologic testing showing circulating anti-Dsg1 IgG and epidermal intercellular deposition of IgG and/or C3.[1-3] We report a diagnostically challenging case of pemphigus foliaceus in which multiple skin biopsies failed to reveal acantholysis or intraepidermal bullae, resulting in a diagnostic dilemma and delayed definitive treatment.

Case Synopsis

A 77-year-old woman presented to the dermatology clinic with a 5-month history of pruritic, scaly, erythematous papules and plaques on the face, concentrated in the nasolabial folds and nasal bridge. The rash subsequently progressed to involve the bilateral cheeks, nose, upper eyelids, forehead, and scalp (**Figure 1**). The patient also developed pruritic, violaceous, scaly, crusted nummular plaques on the chest, abdomen, and back (**Figure 1**).

An initial skin biopsy revealed spongiotic, irregular psoriasiform dermatitis with a predominantly lymphohistiocytic perifollicular and perivascular inflammatory infiltrate (**Table 1**). Over the next 23 months, 4 additional biopsies were performed, showing varied reaction patterns, with most featuring a spongiotic/psoriasiform dermatitis suggestive of a subacute to chronic eczematous process (**Figure 2** and **Table 1**). During this period, the patient received multiple courses of low-dose oral prednisone, oral doxycycline, intralesional triamcinolone, oral hydroxychloroquine, subcutaneous dupilumab, topical corticosteroids, topical ketoconazole, and topical tacrolimus, without significant or sustained improvement.

After 2 years of unsuccessful treatment, enzyme-linked immunosorbent assay (ELISA) revealed elevated IgG to Dsg1 at 167 U/mL (positive: > 20 U/mL) and normal IgG to desmoglein-3 (Dsg3). Direct immunofluorescence (DIF) of a skin biopsy demonstrated intercellular IgG, IgG4, and C3 deposition in the epidermis (**Figure 3**), confirming a diagnosis of pemphigus foliaceus. Initial treatment with mycophenolate mofetil was insufficient, and significant clinical improvement was achieved only after

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Table 1. *Histopathologic Findings of Skin Biopsies Performed Over the Course of 23 Months.*

Biopsy Location	Findings
Right cheek	• Spongiotic, irregular psoriasiform dermatitis with overlying mild parakeratosis and neutrophilic crust • Superficial dilated blood vessels with a perifollicular and perivascular lymphohistiocytic inflammatory infiltrate, scattered plasma cells, and rare neutrophils
Back	• Spongiotic, slightly psoriasiform dermatitis, eroded and ulcerated, with superficial perivascular lymphocyte-predominant inflammatory infiltrate and some neutrophils • PAS and PAS-D negative for fungal organisms • Alcian blue and colloidal iron demonstrate no increase in dermal mucin
Right cheek	• Superficial perivascular and periadnexal dermatitis • Focal interface change with pigment incontinence
Left lateral cheek	• Spongiotic, perivascular, mixed dermatitis with eosinophils and plasma cells
Right forehead	• Irregular psoriasiform, spongiotic dermatitis with superficial perivascular lymphohistiocytic inflammatory infiltrate and scattered plasma cells • PAS and PAS-D negative for fungal organisms • Alcian blue and colloidal iron negative for increased mucin

Abbreviations: PAS, periodic acid–Schiff; PAS-D, periodic acid–Schiff with diastase.

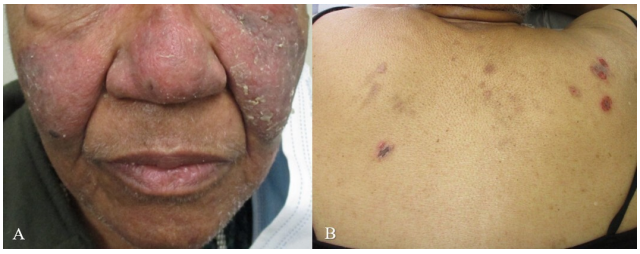

Figure 1. *Erythematous and hyperpigmented scaly papules and plaques on the **(A)** nose and cheeks and **(B)** upper back.*

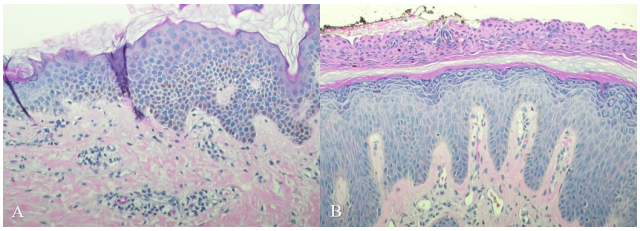

Figure 2. *Two separate biopsies showing **(A)** spongiotic dermatitis with lymphocytic perivascular inflammation and **(B)** psoriasiform dermatitis with lymphohistiocytic perivascular inflammation (hematoxylin-eosin, original magnification ×20).*

rituximab therapy, administered as two 1000 mg intravenous doses separated by 2 weeks. Following the first course, truncal lesions resolved predominantly, but facial lesions persisted. Two additional rituximab courses were administered at 6-month intervals, resulting in eventual improvement of the facial rash and a corresponding decrease in anti-Dsg1 titers.

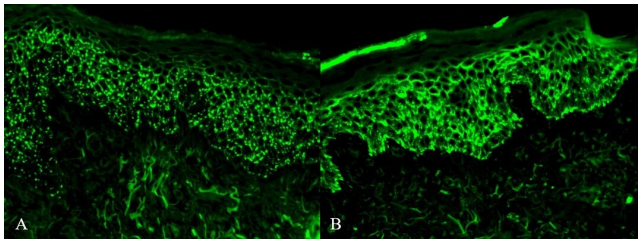

Figure 3. *Intercellular epidermal staining for **(A)** IgG and **(B)** C3 (direct immunofluorescence, original magnification ×400).*

Case Discussion

Pemphigus foliaceus is a member of the pemphigus family of autoimmune bullous dermatoses, mediated by autoantibodies that disrupt intercellular adhesion structures between keratinocytes, resulting in intraepidermal bullae.[1,2] In pemphigus foliaceus, the antigenic target is Dsg1, predominantly expressed in the upper epidermis, whereas Dsg3, localized mainly to the lower epidermis and targeted in pemphigus vulgaris, is unaffected.[4]

Clinically, pemphigus foliaceus presents with crusted, eroded, scaly, erythematous plaques in a seborrheic distribution, including the head and trunk, without significant mucosal involvement; intact bullae may be absent.[1,2] Classic histopathologic features include granular layer acantholysis, subcorneal blisters, and scattered eosinophils and neutrophils.[2] DIF of perilesional skin remains the gold standard for diagnosis, showing an intercellular staining pattern of IgG and/or C3 concentrated in the upper epidermis.[2,3] Circulating autoantibodies can be assessed via indirect immunofluorescence, which demonstrates a similar IgG pattern, and ELISA, which

typically shows elevated anti-Dsg1 IgG with normal anti-Dsg3 IgG.[2,3]

We report a diagnostically challenging case of pemphigus foliaceus initially presenting as a facial rash, in which extensive histopathologic analysis repeatedly failed to demonstrate acantholysis or intraepidermal bullae. The differential diagnosis included seborrheic dermatitis, eczematous dermatitis, pemphigus vulgaris, nutritional deficiency, and connective tissue disease. Immunologic testing via DIF and ELISA ultimately confirmed the diagnosis. One variant considered in the differential is pemphigus erythematosus (Senear-Usher syndrome), an overlap disorder with lupus erythematosus.[5] Our patient was evaluated by rheumatology, with an overall negative workup for underlying connective tissue disease, including a negative antinuclear antibody test, although a later repeat test showed a titer of 1:80. DIF did not demonstrate prominent immunoglobulin or complement deposition at the dermal-epidermal junction, as described in pemphigus erythematosus;[6] notably, the biopsy was obtained from a photoprotected site.

Although eosinophilic spongiosis can represent an early histologic feature of pemphigus prior to the development of classic acantholysis,[7,8] our patient underwent 5 skin biopsies over nearly 2 years, none of which demonstrated appreciable acantholysis or bullae. Absence of acantholysis has been reported previously in pemphigus,[9] particularly when spongiosis is prominent.[10] Recent studies suggest that the presence of eosinophils and neutrophils, along with the absence of Langerhans cell microabscesses, may help distinguish pemphigus-associated spongiosis from non-pemphigus spongiotic dermatitis.[10] Nevertheless, definitive diagnosis of pemphigus foliaceus ultimately requires immunologic testing.

Conclusion

This case highlights the importance of ongoing clinicopathologic correlation in patients with unclear diagnoses or inadequate treatment response and underscores the essential role of immunologic testing in the diagnosis of autoimmune bullous dermatoses.

Potential conflicts of interest

The authors declare no conflicts of interest.

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