Red crusty plaques in a young man

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Abstract

Pemphigus foliaceus is a superficial blistering disorder characterized by erosions and scaling in a seborrheic distribution. The condition typically occurs in healthy individuals but issues arise from delayed diagnosis. Many cases remain undiagnosed or misdiagnosed due to the lack of awareness of the condition. With use of common diagnostic tools, pemphigus foliaceus can be easily identified and monitored. Histological analysis exhibits "chicken wire" patterning along keratinocytes in the upper epidermis, whereas immunofluorescence study displays subcorneal acantholysis. Pemphigus foliaceus is confirmed via ELISA studies revealing the presence of autoantibodies against desmoglein 1. Once correctly diagnosed, typically the condition is responsive to corticosteroid therapy. However in recalcitrant cases such as in ours, adjunctive immunosuppressive therapy with dapsone or rituximab may be indicated.

Keywords: blister, desmoglein, pemphigus, rituximab, seborrheic, superficial

Introduction

Pemphigus foliaceus is a superficial blistering disorder with sebaceous distribution. The condition typically presents as erythematous scaly, crusted erosions due to the fragile nature of the superficial blisters [1]. Blistering is often accompanied with a burning sensation. In contrast to pemphigus vulgaris, mucosal surfaces are spared. The condition is relatively uncommon, but similar to its other pemphigus counterparts, the pathogenesis of pemphigus foliaceus relates to the presence of autoantibodies and in pemphigus foliaceus these are specifically directed against the epidermal desmosome protein, desmoglein 1, resulting in subcorneal acantholysis [2]. Individuals affected are generally not severely ill, unless the blistering rapidly progresses to generalized involvement and subsequently into potentially life-threatening exfoliative erythroderma [1]. To prevent such an occurrence and to avoid ineffective medical treatments, it is vital to diagnose pemphigus foliaceus promptly. Once diagnosed, typically pemphigus foliaceus is responsive to corticosteroid therapy. However in recalcitrant cases such as ours, adjunctive immunosuppressive therapy may be indicated. We present a patient with pemphigus foliaceus and give guidance on how to recognize and correctly diagnose the condition as well as discuss protocol for treatment resistant cases.

Case Synopsis

A 28-year-old man presented to the dermatology clinic for a treatment-resistant rash located on his face for the past month. He reported that the rash had been accompanied by a constant burning sensation, but denied any other symptoms. According to the patient, the rash began as flaccid blisters which subsequently ruptured with ease, leaving behind yellow crusting. He denied involvement of other regions or any worsening with sun exposure.

On examination, an erythematous plaque with an overlying yellow scaling crust and surrounding scattered small erosions were noted on the left malar

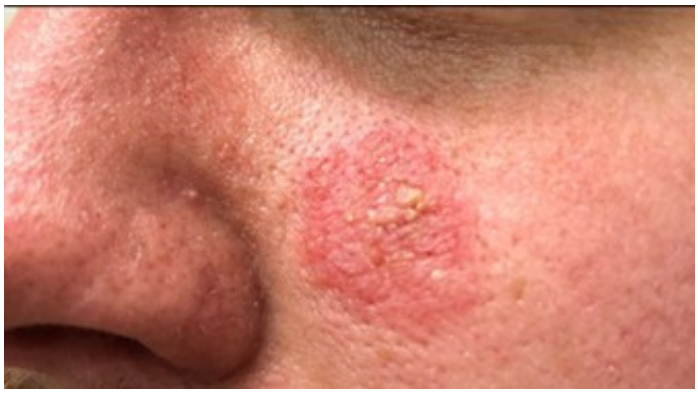

Figure 1. *A singular well-demarcated pink patch present within seborrheic distribution on the left side of the face. Overlying yellow scaling present in the center of the patch with no visible blistering.*

cheek (**Figure 1**). The right malar cheek displayed smaller ill-defined pink macules coalescing into patches. Mucosal membranes were spared and the Nikolsky sign was negative. Previous KOH scrapings were negative for fungus.

Bloodwork results included an unremarkable blood count and biochemistries. Antinuclear antibody, glucose-6-phosphate dehydrogenase, and creatinine values were all within normal limits.

Lesional and peri-lesional skin were biopsied for H&E staining (**Figure 2**), and direct immunofluorescence studies. H&E stain of the early blisters demonstrated superficial intra-epidermal separation (acantholysis) between the stratum granulosum and stratum spinosum and the presence of neutrophils. Direct immunofluorescence of the adjacent normal skin showed positive intercellular deposition of IgG autoantibodies. Indirect immunofluorescence on monkey esophagus was positive for IgG desmoglein 1 antibodies, confirming the diagnosis of pemphigus foliaceus.

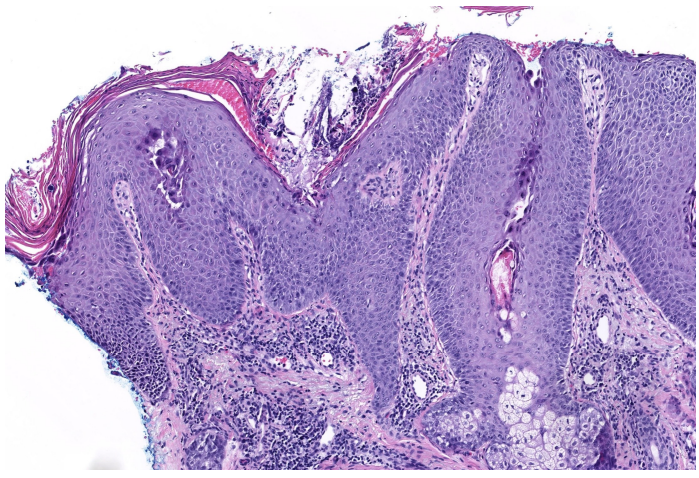

Figure 2. *Histopathologic section revealed acantholysis prominent in the granular layer. H&E, 100×.*

The rash was initially believed to be fungal or seborrheic in nature, resulting in the patient undergoing multiple antifungal therapies including topical ketoconazole, topical miconazole, and a week trial of oral terbinafine. All provided no alleviation. Subsequent trials of sodium sulfacetamide, topical hydrocortisone, and topical clobetasol were initiated with minimal changes in condition.

Upon diagnosis of pemphigus foliaceous, the patient was placed on a prednisone taper, initial dosing at 60mg, with 10mg increment decreases every five days. Concurrently, patient was prescribed topical tacrolimus ointment 0.1% BID for three months. There was no alleviation in symptoms with these treatments, leading to initiation of dapsone 25mg BID, which proved to be efficacious. After two weeks of successful treatment, elevated liver enzymes led to discontinuation of medication before complete remission. Extensive literature review guided treatment toward rituximab infusions, which ultimately led to full remission of the condition. Rituximab treatment was administered as two doses 1000mg IV given two weeks apart and a single dose 6 months later, with no current plans of further treatment.

Case Discussion

We present a treatment resistant case of pemphigus foliaceus, a benign superficial blistering disorder, to serve as a reminder to consider a wide differential diagnosis when managing facial rashes in order to avoid extraneous medical burdens. Difficulty in diagnosis of pemphigus foliaceus begins with the lack of medical provider knowledge of the condition, especially in comparison to its counterparts such as pemphigus vulgaris or other more common similarly presenting facial eruptions. Disparity exists in part due to pemphigus foliaceus occurring less commonly but the condition is quite relevant in certain populations, depending on the presentation.

Pemphigus foliaceus presents in two forms—sporadic and endemic. The endemic form of this rash is heavily observed in South America and North Africa, with the peak incidence occurring between the second and third decades of life [3]. In contrast, in non-endemic areas, pemphigus foliaceus typically presents between the fourth and six decades of life [4].

Even with pemphigus foliaceus in mind, diagnosis can remain difficult due to its resemblance to many other more common conditions. As mentioned prior, pemphigus foliaceus causes well-demarcated superficial blisters in a seborrheic distribution on the upper trunk, face, and scalp [2]. These blisters do not occur on mucosal surfaces, but the cutaneous findings are similar to pemphigus vulgaris, a widely recognized superficial blistering condition. Similar to pemphigus vulgaris, the blisters of pemphigus foliaceus may not be visualized due to their fragile nature, leading to extensive crusted erosions and scaling by the time the patient presents to the medical provider. Once the rash transitions to its crusted state, it begins to resemble other common conditions such as impetigo. Additionally, pemphigus foliaceus has no key identified associated symptoms. At times, the skin rash is associated with generalized burning, but this is a common, nonspecific symptom. Typically, the patient is healthy, as they are with many similarly presenting facial rashes.

There are many conditions in the differential diagnosis for erosions in sebaceous distributions. The following conditions are the common misdiagnoses for pemphigus foliaceus. Upon presentation, bullous impetigo very closely resembles pemphigus foliaceus due to the toxin associated targeting desmoglein 1 cleavage. However, it presents more commonly in pediatric populations and staphylococcus should be easily demonstrated. Direct immunofluorescence and H&E would be sufficient to differentiate the two, as bullous impetigo demonstrates linear IgG and C3 deposits and autoantibodies against the basement membrane. Seborrheic dermatitis is a very common diagnosis that presents with yellow hyperkeratosis, sometimes with crust. However, early superficial blisters are not typical of seborrheic dermatitis. Tinea faciei is a fungal infection that presents with erythema with central clearing and annular borders with leading scale. Our patient was initially considered to have a condition of fungal etiology but KOH analysis yielded negative findings and antifungal treatments from multiple classes provided no alleviation. Another relatively uncommon condition, facial discoid dermatosis, can present as red, orange plaques with variable scale [5]. This condition is relatively novel in the literature, with first description in 2010. Physical appearance of the condition can resemble the crusted state of pemphigus foliaceus. However, histological analysis would display dermal lymphocytic infiltrate in addition to other findings that may resemble pityriasis rubra pilaris [5].

Histological evaluation in conjunction with direct and indirect immunofluorescence is essential to definitively diagnose pemphigus foliaceus. Histology of early blisters display subcorneal acantholysis, although earlier blisters may only demonstrate neutrophilic spongiosis with limited acantholysis [6]. These histological findings are identical to those of staphylococcal scalded skin syndrome and bullous impetigo. Pemphigus vulgaris presents with similar histological findings except acantholysis is more prominent in the suprabasilar layer in contrast to in the granular layer as seen in pemphigus foliaceus [6]. Direct immunofluorescence studies display positive IgG fluorescent staining around keratinocytes predominantly occurring in the upper epidermis region, resembling "chicken wire" patterning in both pemphigus foliaceus and pemphigus vulgaris [2]. However, enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescence studies can be performed to distinguish the two. The presence of only desmoglein 1 antibodies confirms the diagnosis of pemphigus foliaceus. Any presence of desmoglein 3 antibodies points to the diagnosis of pemphigus vulgaris, even with desmoglein 1 antibody positivity. Once successfully diagnosed, ELISA can be utilized for objective monitoring of pemphigus foliaceus with increasing antibody titers demonstrating associations with flares [4].

Treatment for pemphigus foliaceus varies with the severity of its presentation. For localized disease, high potency topical corticosteroids are typically efficacious [7]. Remission is achieved when no new lesions are noted for two weeks and the majority of present lesions are healed [4,7]. Interestingly, our patient with localized disease found no improvement with high-potency topical corticosteroids. First-line treatment for those who fail topical corticosteroids or those with more diffuse presentations is systemic corticosteroid therapy of 0.5-1.0mg/kg/day prednis[ol]one [2]. Adjunctive immunosuppressant agents can be pursued such as mycophenolate mofetil, azathioprine, or dapsone [2,4,8]. If a patient continues to fail treatment, guidelines vary in recommendations for next steps. Possible next steps include addition of another immunosuppressive drug; others recommend sole treatment with an alternative immunosuppressant agent [2,4]. In our patient, the corticosteroid-sparing agent dapsone was initiated at starting dosage of 25mg twice a day, with plans to titrate up to 300mg/day if needed. However, within two weeks of dapsone initiation, elevated liver enzymes led to discontinuation of the drug. Ultimately, rituximab was initiated and our patient received two doses of 1,000mg IV, two weeks apart which resulted in full remission. Rituximab is a monoclonal antibody synthesized to bind specifically to CD20, a transmembrane protein present on B cells. Given the pathogenesis of pemphigus foliaceus is centered around the desmoglein 1 autoantibody, the therapy has been popular for pemphigus foliaceus as well as for other forms of pemphigus. Of note, recent literature supports the idea of utilizing rituximab earlier in the course of treatment, given its lower side effect profile than systemic corticosteroids and possible higher efficacy of the therapy in preventing and/or elongating time between relapses of the condition [2,4,7].

Conclusion

Pemphigus foliaceus can often present as a non-specific rash that may go undiagnosed. Although typically mild, the rash can rapidly progress to potentially life-threatening exfoliative erythroderma or can lead to patients receiving extraneous unnecessary treatments. Histologic evaluation in conjunction with direct indirect immunofluorescence, indirect immunofluorescence, and/or ELISA are necessary for definitive diagnosis. Therefore, pemphigus foliaceus must be considered in the differential diagnosis.

Potential conflicts of interest

The authors declare no conflicts of interest.

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