Pemphigus Foliaceus, An Uncommon Presentation with Erythroderma: A Case Report

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ABSTRACT:

Pemphigus foliaceus (PF) is an autoimmune blistering disease, which is typically characterized by scaly, crusted skin lesions and flaccid blisters that can evolve into cutaneous erosion, distributed to the seborrheic areas of the scalp, face, and trunk, but lacking mucosal involvement. Exfoliative erythroderma is an uncommon feature of PF that tends to resist conventional treatment, such as corticosteroids. We report the case of a 69-year-old man who presented with exfoliative dermatitis and ectropion both eyes. An incisional skin biopsy was done at the left forearm revealing subcorneal separation with acantholytic keratinocytes and direct immunofluorescence consistent with PF.

The patient was treated with two infusions of 1 gram rituximab two weeks apart accompanied by 30 mg oral prednisolone daily. After rituximab infusion, significant clinical improvement was observed. Rituximab is an alternative treatment for moderate to severe PF, including exfoliative PF, and leads to clinical improvement.

Key words: Pemphigus Foliaceus, Erythroderma

Introduction

Pemphigus foliaceus (PF) is an autoimmune blistering disease caused by immunoglobulin G (IgG) autoantibodies action against desmoglein-1 (Dsg1) transmembrane glycoproteins, an intercellular adhesion protein that presents on the surfaces of keratinocytes in the granular layer of the epidermis, causing a loss of intercellular connections between the keratinocytes. PF is characterized by two clinical variants: sporadic (non-endemic) and endemic PF. Both variants of PF present with superficial and flaccid blisters that can be seen on histopathological evaluation as subcorneal acantholysis[1]. Patients with PF typically develop scaly, crusted lesions and flaccid blisters that evolve into cutaneous erosion, distributed to the seborrheic areas of the scalp, face, and trunk, but lacking mucosal involvement[2]. Erythroderma accounts for about 6% of PF cases, which are usually cases of fogo selvagem ("wildfire", endemic pemphigus foliaceus), causing a burning sensation and pain, exacerbated by exposure to the sun[3]. Exfoliative erythroderma can occur during non-endemic PF that does not respond to treatment, and is even more unusual[4].

There are various diagnostic studies that can be performed to support a clinical diagnosis of PF. Generally, the diagnosis of PF is based on three criteria assessments: 1) overall clinical characteristics, including history and physical examination; 2) histopathological findings; and 3) the presence of immunoglobulin (Ig) G and complement 3 (C3) autoantibodies as detected by direct immunofluorescent study (DIF) and indirect immunofluorescent study (IIF) [5].

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The worldwide incidence and prevalence of exfoliative PF is low, making it a rare condition. We report the case of a patient who presented with exfoliative erythroderma, which was ultimately diagnosed as PF based on the clinical characteristics, histopathological features, and direct immunofluorescence study.

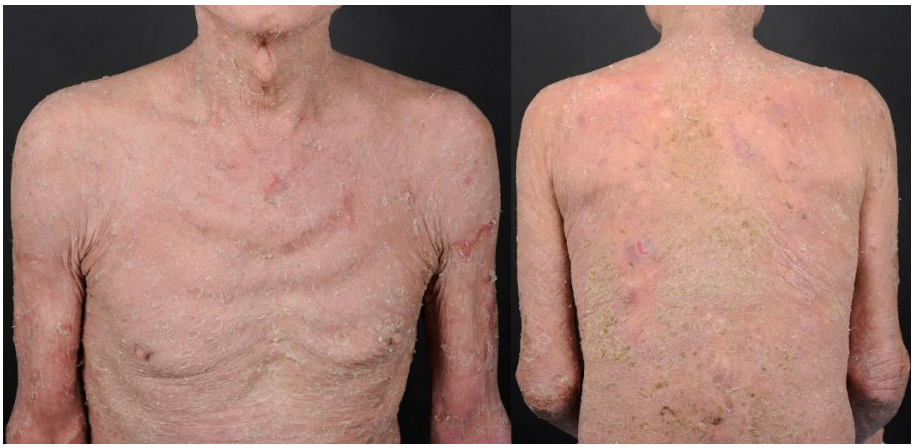

Figure 1 Clinical presentation at the first visit to our hospital showed generalized erythroderma with desquamation, crusted yellow scales, and some erosions involving over 90% of the total body surface area with bilateral ectropion

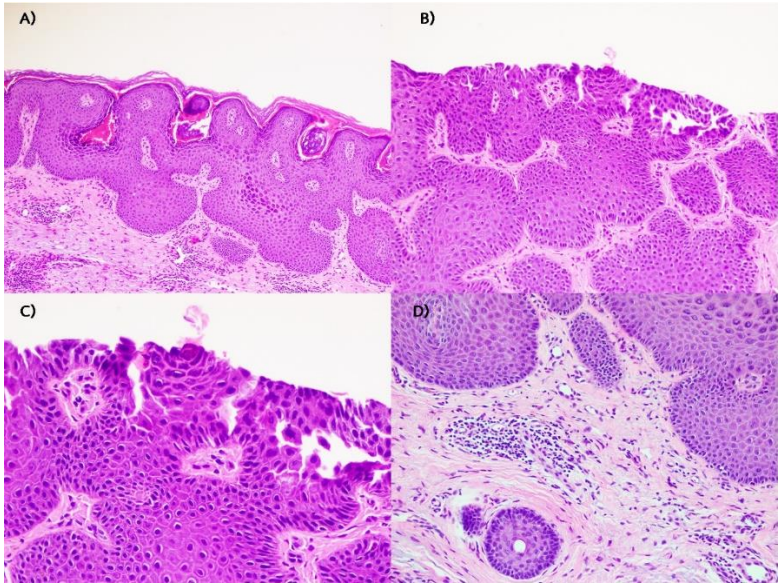

Figure 2 Incisional skin biopsy was performed at the left forearm and demonstrated subcorneal separation with acantholytic keratinocytes (A. hematoxylin-eosin stain, X10 magnification; B. hematoxylin-eosin stain, X20 magnification; C. hematoxylin-eosin stain, X40 magnification) and lymphocyte infiltration with scattered melanin incontinence and melanophages at the upper dermis (D. hematoxylin-eosin stain, X40 magnification)

Case report

A 69-year-old man with underlying hypertension and chronic kidney disease presented with exfoliative dermatitis and ectropion both eyes. Initially, he had developed erythematous patches with some tiny erythematous papules present on the trunk for 9 months. Before visiting our hospital, he was previously investigated by IIF study. The results revealed positive circulating IgG intercellular antibodies at the titer of 1:80. He was diagnosed as autoimmune bullous disease. After that, the lesions became more widespread and gradually progressed to erythroderma with desquamation and yellow crusted lesions and erosions on the face and trunk without mucosal involvement over 5 months. The patient denied taking any recent medications before the symptoms arose. The patient had tried using alternative medicine, taking various herbal medications with partial improvement.

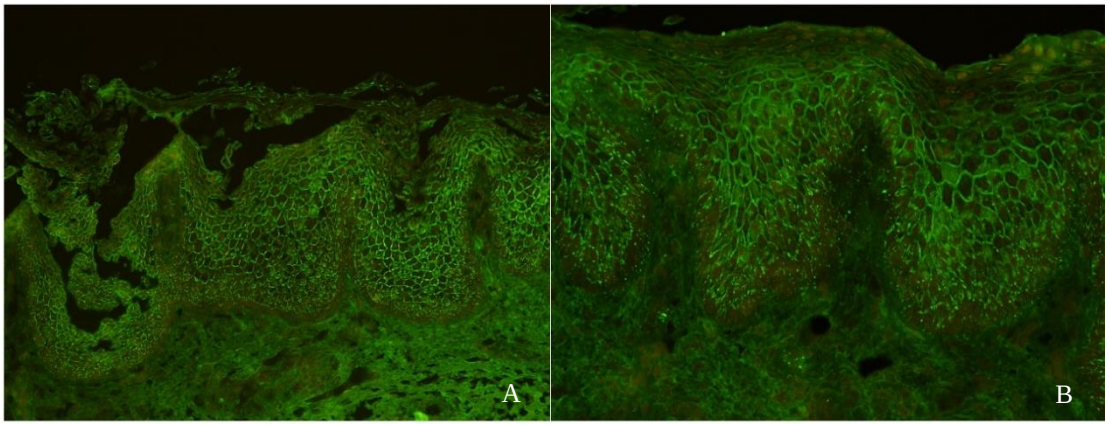

Figure 3 Direct immunofluorescence showing the deposition of immunoglobulin G in the intercellular space within the epidermis (A. X20 magnification, B. X40 magnification)

Upon physical examination, generalized erythroderma was noted with desquamation and crusted yellow scaling with some erosions involving over 90% of the total body surface area without definite tense or flaccid blisters (Figure 1). Bilateral ectropion was observed. Nikolsky's sign was positive. There was no mucosal involvement. Lymph node examination was performed, identifying no superficial lymphadenopathy. Incisional skin biopsy was done at the left forearm revealing subcorneal separation with acantholytic keratinocytes and lymphocyte infiltration with scattered melanin incontinence and melanophages at the upper dermis (Figure 2). DIF showed an intercellular deposition of IgG within the epidermis. IIF showed circulating IgG intercellular antibodies at the titer of 1:320 (Figure 3). Both the histopathology and immunofluorescent studies were consistent with PF. Complete blood count showed hypereosinophilia (absolute eosinophils count of 1992/ul). An examination was performed to test for occult infection, including parasitic infection, hepatitis B and C virus infection, and HIV infection. The hepatitis B core antibodies test was positive without evidence of active infection; here, lamivudine prophylaxis was prescribed before giving a systemic immunosuppressant. The other laboratory tests were normal. After a multidisciplinary approach, the patient was treated with systemic corticosteroid, comprising intravenous dexamethasone 10 mg/day for 3 days, then switched to 40 mg oral prednisolone daily for 2 weeks after discharge from the hospital. There

was no significant clinical improvement. Generalized erythroderma with yellow crusted lesions, especially on the face and trunk, could still be observed. Since the disease was refractory to the initial treatment, rituximab was an alternative treatment. The patient was treated with two infusions of 1 g rituximab two weeks apart accompanied by 30 mg oral prednisolone daily. For the bilateral ectropion, ophthalmology consultation was provided. Supportive treatment, comprising artificial tear eye drops and lubricant eye gel (Vidisic® gel), was given to the patient. After rituximab infusion, significant clinical improvement was observed.

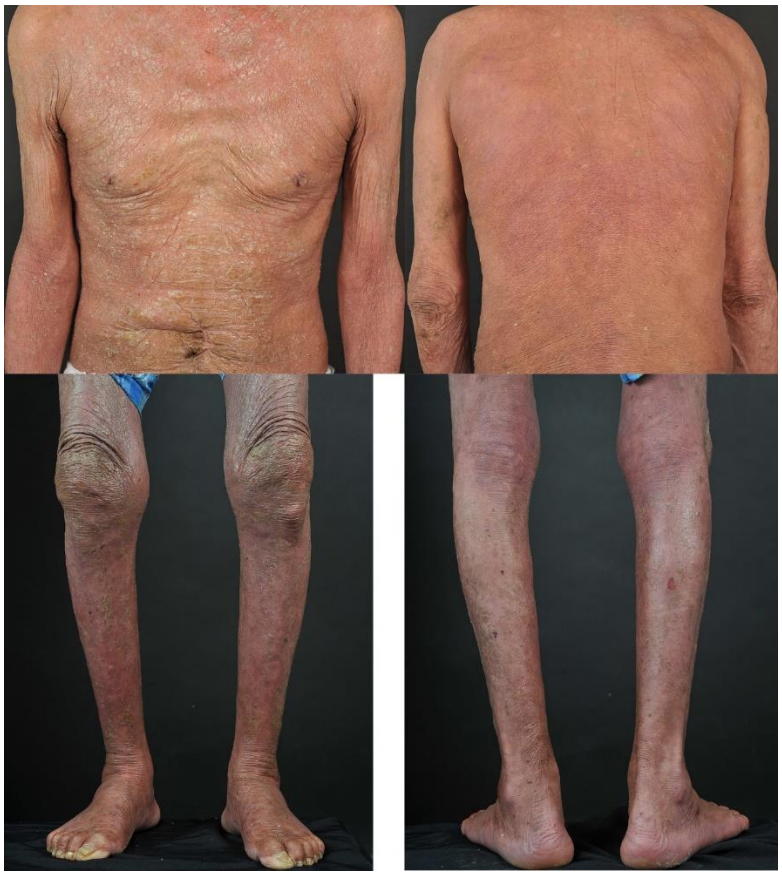

Figure 4 Clinical presentations after the 1st cycle of rituximab (2 doses) showing no yellow crusted lesion and a marked improvement of erythroderma within 4 weeks

At follow-up 2 weeks after discharge, the patient had developed right herpes zoster ophthalmicus, which was treated with oral valacyclovir and ganciclovir eye ointment for 2 weeks, and then the lesions of herpes zoster ophthalmicus were resolved as well as the PF lesion. Overall, his skin demonstrated significant clinical improvement after rituximab therapy at 4-weeks follow-up. There was no yellow crusted lesion, suggesting an improvement of the erythroderma (Figure 4). Oral prednisolone was slowly tapered without flaring of the PF symptoms. On the latest visit, his disease was controlled by prednisolone 10 mg/day. The treatment planning in this patient was to reduce the prednisone dose by 10%–25%

every 2–4 weeks. In cases showing no disease control, it is considered that the dose of prednisone should be increased to up to 1.5 mg/kg/d or intravenous corticosteroids pulses should be administered or other immunosuppressants added, i.e., azathioprine 1 to 2.5 mg/kg/d or mycophenolate mofetil 2 g/d[6]. Following the standard guideline, the infusion of 500 mg or 1 g of rituximab at month 6 is suggested in patients with severe pemphigus who are on complete remission on/off therapy. On the contrary, patients without complete remission on/off therapy at month 6 should be treated by two infusions of 1 g two weeks apart (2 g in total)[6]. Unfortunately, our patient was lost to follow-up after 4 months of treatment (2 months after rituximab treatment).

Discussion

Erythroderma occurs when the skin becomes erythema and inflamed on more than 90% of the body surface. PF is one of the less frequently considered entities in the differential diagnosis of patients with erythroderma[3]. As in previous studies, exfoliative PF in patients is typically reported in middle age and equally between men and women[7]. The clinical presentations of exfoliative PF consist of a progressive bullous eruption complicated by several flares of erythroderma. Patients with PF, as well as exfoliative erythrodermic PF, rarely develop mucosal lesions, unlike pemphigus vulgaris[4]. The unusual history of our patient suggested the need for a more detailed history of the timing of the symptoms, as erythroderma caused by autoimmune diseases generally progresses slowly.

In exfoliative erythrodermic PF, the findings of the skin biopsy and DIF and IIF studies will appear to be the same as for other variants of PF[4]. The histopathology of early lesions of PF demonstrate subcorneal acantholysis just below the stratum corneum and adjacent to the granular layer, and eosinophilic spongiosis may be found. With the extension of the lesions, the vacuoles coalesce and form subcorneal blisters within the upper epidermis. The bullae contain fibrin, neutrophils, and scattered acantholytic keratinocytes. These histologic features of superficial blisters are undifferentiated from staphylococcal scalded skin syndrome or bullous impetigo, as Dsg1 is the antigen in both these diseases. Late lesions of PF show acanthotic, papillomatous, and hyperkeratotic tiers with focal parakeratosis. Dyskeratotic cells in the granular layer of late lesions distinguish pemphigus foliaceus from pemphigus vulgaris[1].The degree of inflammatory infiltrate is varied, depending on the age of the lesions[1]. Immunofluorescence studies are correlated with the pathogenesis. DIF study can demonstrate the intercellular substance deposition of IgG localized to the superficial epidermis. C3 may also stain at the intercellular space in PF. According to the DIF result, IIF study can show intercellular staining in the upper epidermis. IgG4 subclass autoantibodies are predominant in PF[8].

Autoantibodies action against Dsg1 is responsible for the pathogenesis of PF, as well as exfoliative erythrodermic PF. Dsg1 is weakly present in mucosae, and mucosal involvement is rarely seen in all variants of PF. The disease activity of PF, including the exfoliative erythrodermic variant, is known to correlate with the titer of the autoantibodies[5]. In a recent study, vascular endothelial growth factor (VEGF) and soluble receptors vascular endothelial growth factor 1 (sVEGFR-1) levels in the serum of PF patients with erythroderma were found to be increased, indicative of a role of the blood vascular endothelium. A positive correlation between the sVEGFR-1 and anti-Dsg1 antibodies indicates a suppressive response to VEGF upregulation during the erythrodermic phase of PF. The most common abnormal peripheral blood laboratory finding is eosinophilia, accounting for 22% of PF patients[9].

The treatment of PF varies depending on the severity of the disease, including treatment with topical steroids for localized disease. Patients with extensive involvement or erythroderma may be treated with systemic corticosteroids followed by various steroid sparing agents, such as mycophenolate mofetil or cyclophosphamide[6]. Alternative treatment modalities for patients resistant to conventional treatments include rituximab, intravenous immunoglobulin, or plasmapheresis[6]. At present, there are few case reports of non-endemic erythrodermic PF effectively treated with rituximab[4,7]. Rituximab is a monoclonal antibody that targets CD20, which is expressed on pre-B lymphocytes and activated mature B lymphocytes surfaces. Although a low dose of rituximab is an effective and safe treatment for all variants of PF, adverse events have been reported, including infections (flared hepatitis B infection, erysipelas, herpes simplex infection, herpes zoster infection), gastrointestinal tract disturbance, fever, and rash. Aggravated herpes zoster infections after rituximab administration have been reported in previous studies and was found in this case[7]. The increased risk of infection after rituximab infusion could be related to hypogammaglobulinemia and neutropenia[10]. For this reason, all patients should be screened for infections before rituximab injection and the side effects monitored.

Conclusion

Exfoliative erythroderma is an uncommon feature of PF that tends to resist conventional treatment, such as corticosteroids. Rituximab is an alternative treatment for moderate to severe PF, including exfoliative PF, and leads to clinical improvement.

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