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Clinical Letter

Non-endemic erythrodermic pemphigus foliaceus: a case with delayed diagnosis and response to rituximab

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Dear Editors,

Pemphigus foliaceus (PF) is an autoimmune blistering disorder with two clinical variants: sporadic and endemic PF [1]. Pemphigus foliaceus typically presents with crusted lesions on seborrheic areas of the scalp, face and trunk [1]. In the majority of cases the target antigen is desmoglein-1 (160 kDa), an intercellular adhesion protein that connects epidermal keratinocytes [2, 3]. Erythroderma accounts for about 6 % of PF cases, which are usually cases of fogo selvagem (endemic pemphigus foliaceus) [4]. Exfoliative erythroderma can occur during non-endemic PF that does not respond to treatment, and is even more unusual [5]. These cases of erythrodermic PF may initially be misdiagnosed as psoriatic erythroderma or staphylococcal scalded skin syndrome (SSSS). Immunofluorescence is mandatory to establish the correct diagnosis and guide appropriate management [2, 3]. Here we present a rare case of erythrodermic PF that was misdiagnosed for months, refractory to classic treatment procedures and only responsive to rituximab.

A 53-year-old woman visited our department due to exfoliative dermatitis and ectropion. She initially developed a papular eruption accompanied by some tiny pustules on her trunk. This exanthema gradually progressed to erythroderma over a period of nine months. In the meantime, the patient was admitted to another hospital (five months beforehand) with the diagnosis of SSSS. At that point a complex intravenous antibiotic treatment resulted in partial improvement. Since then the patient has been treated with various antibiotics as well as low doses of systemic prednisone and cyclosporine without complete remission of erythroderma.

At admission to our department (Figure 1a, b), tissue and blood samples were taken for histology and immunofluorescence investigation. Histology revealed acantholysis in the granular layer of the epidermis (Figure 2). Immunofluorescence techniques, both direct and indirect, gave positive results and revealed an intercellular reaction with IgG and C3. High titers of circulating anti-DSG-1 autoantibodies were also detected (>200). The molecular weight of DSG-1 (160 kDa) was captured by Western blot. Pemphigus foliaceus was confirmed by all the above procedures as the cause of erythroderma in our patient.

After a multidisciplinary collaboration, we treated the patient with a combination regimen of plasmapheresis and prednisolone in intravenous pulses. A significant improvement was observed after seven weeks in hospital, and the patient was released (Figure 1c). Two months later, while the patient was still treated with 40 mg prednisone and 100 mg azathioprine and had no erythroderma, many circinate erythematosquamous lesions were observed on the face and

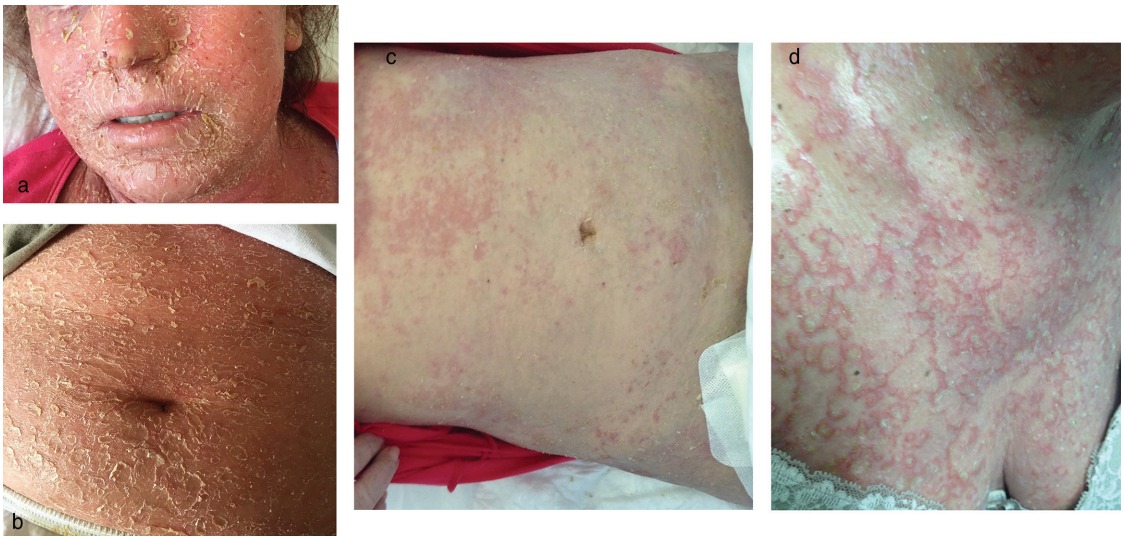

Figure 1 Patient at the time of her admission to our department (a, b). Significant improvement of the patient was observed after seven weeks of hospitalization (c). Two months later, many circinate erythematosquamous lesions were observed on the patient's trunk (d).

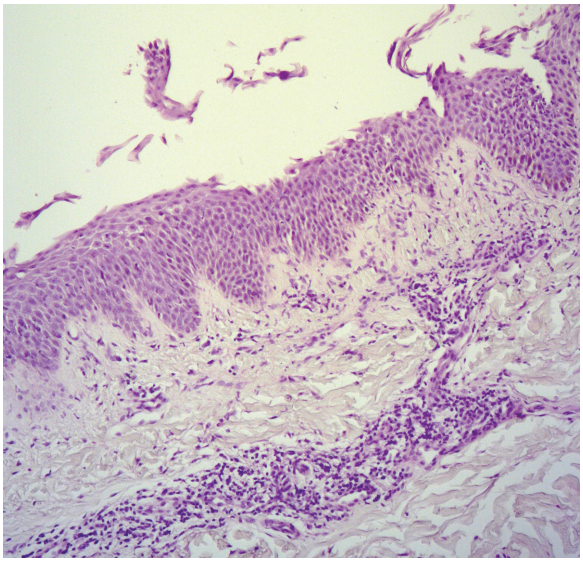

Figure 2 Acantholysis in the upper layers of the epidermis (hematoxylin-eosin stain, original magnification x 10).

trunk (Figure 1d). Since the disorder was refractory to the initial treatment, rituximab was the next therapeutic option. After approval of the health authorities (as rituximab is still considered off-label for pemphigus) the patient was treated with two infusions of 375 mg/m^2, two weeks apart and two infusions of 500 mg every six months. Rituximab led to prolonged remission of the disease.

By definition, erythroderma results when the skin becomes red and inflamed on more than 90 % of the body surface. The SCALPID mnemonic (*S*eborrheic dermatitis, *C*ontact dermatitis, *A*topic dermatitis/Autoimmune disease, *L*ymphoma/Leukemia, *P*soriasis/PRP, *I*nfections/Ichthyosis, *D*rug reactions) includes PF in the autoimmune diseases which can cause erythroderma. When a clinician encounters a patient with erythroderma, PF is one of the less frequently considered entities in the differential diagnosis. The unusual history of our patient underlines the need for a detailed history of the timing of symptoms, as erythroderma caused by autoimmune diseases generally progresses slowly [6]. In addition, erythrodermic PF should be suspected particularly in patients without a history of psoriasis, or if there is no response to conventional antipsoriatic therapies [5]. Furthermore, great caution should be exercised, since concurrence of annular psoriasis and PF has been reported [7].

Autoimmune, infectious and inflammatory skin diseases may have a common pathogenesis resulting in the clinical picture of erythroderma, possibly due to a common pathway and involving the expression of adhesion molecules, chemokines and cytokines. Recently, it was demonstrated that serum levels of VEGF and sVEGFR-1 are increased in erythrodermic PF patients, underlining a role of the blood vascular endothelium. A positive correlation between the sVEGFR-1 and anti-Dsg-1 antibodies indicated a suppressive response to VEGF upregulation during the erythrodermic phase of PF [8].

Rituximab is a monoclonal antibody that targets CD20, which is expressed on the surface of pre-B lymphocytes and activated mature B lymphocytes. Its role in the treatment of the pemphigus spectrum has been extensively demonstrated in the literature [2, 9, 10]. However, there are few case reports (four including the present case) on non-endemic erythrodermic PF successfully treated with rituximab [5, 11]. With the present case, we would like to emphasize the difficulties in the initial diagnosis of erythrodermic PF and expand the published body of evidence on the efficacy of rituximab in cases that are refractory to conventional treatment of PF.

Conflict of interest

None.

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