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A case of pemphigus herpetiformis with excellent response to mycophenolate mofetil

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Abstract

Pemphigus herpetiformis (PH) is a rare and unique clinical form of pemphigus foliaceus and pemphigus vulgaris. Patients show autoantibodies against desmoglein 1 and less frequently against desmoglein 3 and desmocollins. We report a 24-year-old woman with a 3-year history of recurrent intensely pruritic erythematous papules and annular plaques localized on the trunk and extremities. In recent months she developed small vesicles around the annular lesions. The histological features showed eosinophilic spongiosis, and direct immunofluorescence demonstrated typical staining of the epidermal intercellular spaces characteristic for pemphigus. There was no mucosal involvement, and hence a diagnosis of PH was established. This patient was unresponsive to dapsone and methotrexate, but she finally experienced remission with prednisone and mycophenolate mofetil.

Keywords: pemphigus herpetiformis, autoantibodies, autoimmune disease

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Introduction

Pemphigus herpetiformis (PH), initially described in 1975 by Jablonska et al. (1), is an atypical clinical variant of pemphigus that develops in patients with pemphigus foliaceus or pemphigus vulgaris (1–5). Approximately 158 cases have been reported in the literature (2–5), with an estimated prevalence of 6.5% among cases of pemphigus worldwide, without predominance by sex or ethnicity. The age of presentation ranges from 30 to 80 years, and it is less frequent in children (3). The etiology of PH remains unknown, although in endemic pemphigus foliaceus (Portuguese *fogo selvagem*) the etiology may be environmental (6, 7).

PH is characterized by annular and vesiculopustular skin lesions and histologically by eosinophilic spongiosis (5, 6, 8). This disease is caused by IgG autoantibodies against desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3). However, additional factors, such as Fcy-dependent neutrophil activation (2) or release of cytokines and chemokines (9), may be relevant in the pathogenesis of the disease. Therapy for PH includes systemic steroids, dapsone, and immunosuppressive drugs.

Case report

We present the case of a 24-year-old female patient from Trujillo, La Libertad, Peru, a housewife with no comorbidities or pathological family history. She came to the hospital in August 2017 with a 3-year history of an intensely pruritic papular eruption on the lower extremities that had evolved in recent months into annular plaques with small blisters.

She was initially diagnosed with urticarial vasculitis and drug reaction, and she received treatment with colchicine, antihistamines, methotrexate, prednisone, and dapsone with unfavorable results. Physical examination revealed erythematous-violaceous plaques with small vesicles and secondary scaliness and excoriations on the trunk and lower limbs (Fig. 1).

A complete blood count showed peripheral eosinophilia of 31%. A skin biopsy showed acantholysis and eosinophilic spongiosis (Fig. 2). Direct immunofluorescence (IF) of the perilesional skin was positive, showing epidermal intercellular staining with IgG. Indirect IF and ELISA studies of the patient's serum were not performed because they were not available and this patient could not afford to pay privately for testing. A diagnosis of PH was established. Treatment with prednisone 1 mg/kg/day and dapsone 100 mg/day produced minimal improvement. Dapsone was discontinued and mycophenolate mofetil 3 g/day was introduced. The patient experienced complete clinical remission and has now been free of skin lesions for 2 years (Fig. 3).

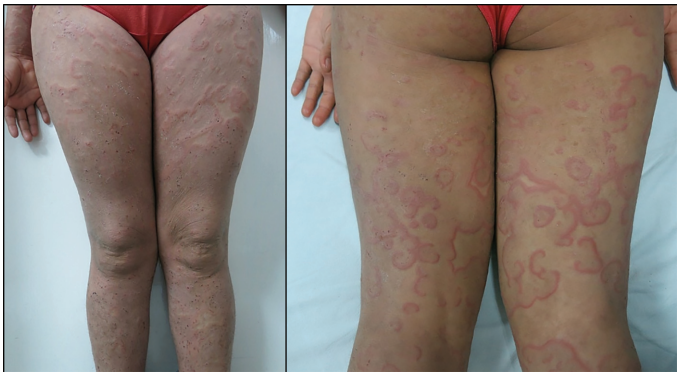

Figure 1 | Arcuate, scaly, and excoriated purplish plaques spread across the legs.

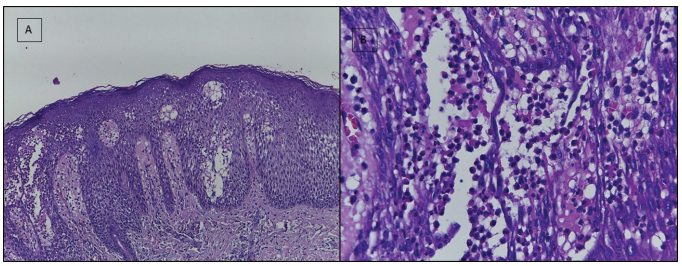

Figure 2 | a) Epidermis with acantholysis, dermis with superficial perivascular inflammatory infiltrate with eosinophils; b) spongiosis with neutrophils and eosinophils.

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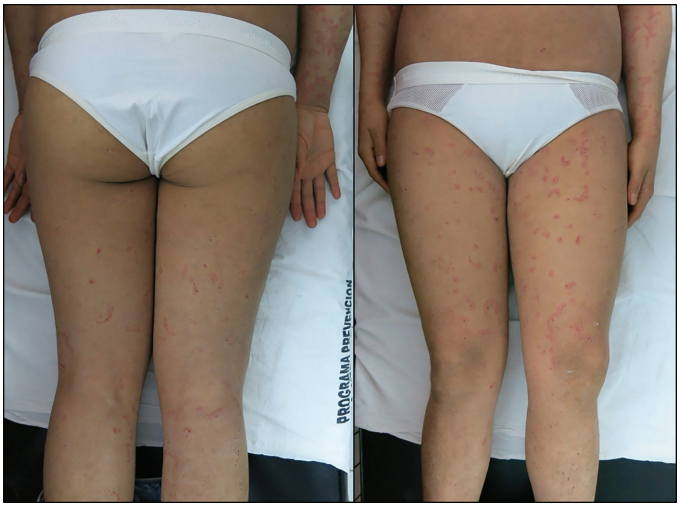

Figure 3 | Evolution of excoriated plaques on the legs after 7 days of treatment.

Discussion

PH is an unusual and atypical presentation of pemphigus foliaceus in most cases, and sometimes pemphigus vulgaris. PH may appear before or after pemphigus foliaceus or pemphigus vulgaris (1–6). Clinically, it is characterized by the presence of a polymorphic eruption of inflammatory papules and plaques, some of them annular and studded with small vesicles. These lesions may be located on the trunk and extremities. Oral or scalp lesions are seen in cases of previous pemphigus vulgaris lesions (1–6). The target antigens for PH are generally Dsg1 and, less commonly, Dsg3 or desmocollins (2, 5). Histologically, there is dermal-epidermal interface inflammation with neutrophils and eosinophils, which may invade the epidermis, producing eosinophilic spongiosis. There may be areas of acantholysis (10). Autoantibodies in PH induce the release of pro-inflammatory cytokines in keratinocytes, especially interleukin-8, which leads to the recruitment and stimulation of inflammatory cells, predominantly eosinophils and/or neutrophils, which produce spongiosis and focal intercellular edema, and finally the blistering process typical of the disease (9). The diagnosis of PH is made taking into account the presentation of at least one clinical, histopathological, and immunological characteristic. Clinical manifestations include intact herpetiform pruritic bullae or pruritic urticarial or annular skin plaques with or without erosions. In pathological studies, intraepidermal eosinophils or intraepidermal division with or without acantholysis are found, and in immunological studies the detection of antibodies against Dsg1, Dsg3 and/or desmocollins through IF (5).

The differential diagnosis is broad due to the various manifestations of eosinophilic spongiosis, and it includes various diseases such as bullous pemphigoid, linear IgA disease, erythema multiforme, and IgA pemphigus (3–5).

PH is distinguished from pemphigus foliaceus and vulgaris in its presentation, which consists of erythematous, rotating, annular, and edematous lesions, with accumulations of vesicles and/or small or abortive pustules, frequently in a herpetiform pattern. In addition, the histopathology shows eosinophilic spongiosis, unlike pemphigus foliaceus and vulgaris, which show a suprabasal and granular cleft, respectively (11–12).

The diagnosis of PH in our patient was established based on the clinical presentation, the histological features of eosinophilic spongiosis, and the direct IF findings of IgG in the epidermal intercellular spaces, as previously described in the literature (3–5, 8, 10).

Historically, dapsone has been used to treat PH with unpredictable outcomes. Because PH falls within the autoimmune group of blistering diseases of the skin, systemic steroid and immunosuppressive drugs have been routinely employed (2, 5).

Our patient was initially treated with prednisone 50 mg/day (patient weight 58 kg) and dapsone 100 mg/day, which led to some improvement; however the itching and skin rash continued. We discontinued dapsone and maintained prednisone at 20 mg/day, and we began treatment with mycophenolate mofetil 3 g/day. Our patient gradually experienced complete clinical remission. This case report stresses the relevance of clinical, histological, and immunological findings for the diagnosis of PH and establishes that mycophenolate mofetil is an immunosuppressive drug that may be useful in treating these patients.

To conclude, PH is a very uncommon autoimmune skin disease that is often misdiagnosed. The clinical and histological criteria described in the literature and encountered in our patient were extremely useful in the diagnosis of PH. Therapy that includes systemic steroids, immunosuppressive drugs, and dapsone in some cases can control this disease.

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