Amicrobial pustulosis of the folds: report of two cases

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ABSTRACT

Amicrobial Pustulosis of the Folds is a relapsing, chronic and rare neutrophilic dermatosis, characterized by papulopustular, eczematous and aseptic lesions on skin folds. This disorder usually occurs predominantly in females (30 years of age average) with a history of an autoimmune disorder, especially systemic lupus erythematosus. There is no standard therapy, but systemic corticosteroids, alone or in combination with other immunosuppressive drugs, are usually the first-line therapy. We report two females aged 37 and 20 years with the disease but without associated autoimmune diseases. They were successfully treated with non-steroidal treatments.

Key words: Autoimmune Diseases; Doxycycline; Skin Diseases.

Pustulosis amicrobiana de los pliegues. Informe de dos casos

La pustulosis amicrobiana de los pliegues es una dermatosis neutrofílica crónica, recurrente y poco común. Se caracteriza por lesiones púpulo-pustulosas, eczematosas y asépticas de los pliegues cutáneos. Este cuadro se presenta predominantemente en mujeres de alrededor de 30 años con enfermedades autoinmunes, especialmente lupus eritematoso sistémico. No existe un tratamiento estándar pero los corticoideas solos o con inmunosupresores se usan de primera línea. Informamos dos mujeres de 27 y 20 años sin patología autoinmune, con la enfermedad. Ellas fueron tratadas exitosamente sin usar esteroides.

Palabras clave: Enfermedades de la Piel; Enfermedades Autoinmunes; Inmunología.

Case Reports

Case 1

A 37-year-old female patient, without personal or family medical history, who refers a 5-year history of recurrent outbreaks of erythematous papulopustular lesions that converge forming painful eczematous plaques (burning) in the axillae scalp, external ear canal, retroauricular area, inguinal and submam-
Mary folds. She also presented isolated pustular lesions in the anterior trunk, abdomen (with navel involvement), neck, face and thighs. Nail pitting was observed. The mucous membranes were not affected, there were no systemic symptoms or fever. Prior to the consultation, she had received multiple systemic corticosteroids treatments, with partial and temporary remission, presenting new outbreaks when treatment was stopped (Figure 1a-c).

Patient’s immune profile, blood count, and liver function tests were normal. Histopathological evaluation showed spongiotic psoriasiform dermatitis, epidermal lichenification, and prominent neutrophil epitheliotropism (Figure 1f-g). Direct immunofluorescence, bacterial and mycological culture were negative. Based on the clinical and histological characteristics of the lesions, the diagnosis of amicrobial pustulosis of
the folds was established. It was decided to restart oral corticosteroids (daily dose of prednisone at 0.5 mg/kg/day with gradual suspension). After 3 months of treatment, the patient showed a partial remission, therefore it was indicated doxycycline 100 mg every 12 hours. After a 3 month of this treatment, the patient showed a significant reduction of lesions (Figure 1d-e).

The patient has consented to the submission of the case report and pictures to the journal.

**Case 2**

20-year-old, otherwise healthy female, consulted for a 7-year history of small pustules in an erythematous surface in her occipital scalp, retroauricular area and external ear meatus, submammary fold, umbilicus, and groin area, with erosions and exudation (Figure 2a-c). Most of these lesions were painful. No nails or mucous membranes were compromised, and no other symptoms were reported. She was treated with systemic corticosteroids with partial response but full rebound after suspension. Multiple lesion cultures were negative. Biopsy was compatible with APF (Figure 2d-e) and no other findings were reported in blood tests. Dapsone 50 mg/d was started and after 1 month the dose was increased to 50 mg BID with good clinical response and no significant side effects.

The patient has consented to the submission of the case report and pictures to the journal.

**Discussion**

APF is a recently described neutrophilic dermatosis, with few case reports in the literature\(^4\). Its etiology is unknown, but it has been suggested...
that autoinflammation would be part of the pathogenesis, as in other neutrophilic dermatoses. Marzano et al. showed the overexpression of various pro-inflammatory cytokines, chemokines, and inflammation-amplifying molecules in skin samples from patients with APF, such as Interleukin (IL-1β) IL8, IL-7, CXCL 1/2/3, TNF alfa and its receptors, RANTES (regulated on activation, normal T cell, expressed and secreted), matrix metalloproteinases (MMP)-2 and MMP9, which would support the autoimmune inflammatory and the inflammasome component of this disease5.

It is frequently associated with several autoimmune diseases (generally diagnosed prior to APF), particularly with SLE6, but its association with Hashimoto’s thyroiditis, mixed connective tissue disease, celiac disease, myasthenia gravis, autoimmune hepatitis, rheumatoid arthritis, among others. Recently, cases of amicrobial pustulosis have been reported as secondary complications to the use of anti-TNF alfa (infliximab and adalimumab) in patients with inflammatory bowel disease6,7. The mechanisms of this are unknown, but it is believed that the inhibition of TNF alfa, increases the concentration of INF alfa on the skin making it prone to the apparition of lesions because of its role in neutrophil recruitment and chemotaxis10.

From the clinical point of view, it is characterized by the sudden appearance of aseptic papulopustular lesions on skin folds, with symmetrical distribution, which coalesce to form extensive eczematous, eroded and crusted plaques, usually painful3. Other frequently involved areas are the anogenital region, scalp, external ear canal, navel and interdigital region. Nail involvement is frequently observed as onychodystrophy with vegetative paronychia. Although systemic compromise is rare, cases of generalized pustulosis associated with compromise of general condition and fever have been described3,6. It tends to present a chronic evolution, with periods of remission and frequent relapses, generally associated with the decrease or suspension of therapy3,6 but not with the activity of the underlying autoimmune disease.

Histopathology reveals the presence of spongiform intraepidermal or subcorneal pustules with a predominantly polymorphonuclear dermal inflammatory infiltrate, without vasculitis elements. In respect of direct immunofluorescence (DIF), Schissler et al. described the presence of positive DIF in 8 cases, in which a lupus band was observed, while in 26 cases it was negative and in 29 cases it was indeterminate3.

The diagnosis of APF is based on clinical and histopathological criteria. Differential diagnosis should be made with other pustular disorders, such as pustular psoriasis, subcorneal pustular dermatosis, acute generalized exanthematous pustulosis (AGEP), pemphigus foliaceus, pemphigus IgA, vegetative pyoderma, and infectious pathologies such as impetigo and folliculitis13,4.

Due to the limited number of cases in the literature and the rarity of APF, there is no standard therapy to date. Systemic corticosteroids (prednisone) in doses of 0.5-1 mg/kg/day are effective in most cases and are generally considered to be the mainstay of treatment, but they usually have recurrences when the dose is reduced, or the treatment is suspended. Other treatments described (associated or not with systemic corticosteroids) with variable efficacy are cyclosporine, colchicine, dapsone, mycophenolate mofetil, methotrexate, hydroxychloroquine, and systemic antibiotics. Among the latter, the use of doxycycline in doses of 100 mg every 12 hours has been described with a good response, as in our first case8. The use of cilomethine, ascorbic acid and zinc supplements have been anecdotally described3,8. More recently, the use of biological therapies such as the antagonist of the receptor of interleukin (IL)1 (Anakinra), anti-TNF (infliximab, adalimumab) and anti-IL 12/23 (ustekinumab) has been described with good response3,4,7. In the cases described, both dapsone and doxycycline were used because of their anti-inflammatory rather than its antimicrobial properties: doxycycline acts reducing pro-inflammatory cytokines like TNF alfa, IL-1b, IL-611 and dapsone by acting against neutrophilic functions inhibiting its chemotaxis12.

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