

Amicrobial pustulosis of the folds: report of two cases

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Authors declare no conflict of
interests for this article and
received no specific grant from
any funding agency in the public,
commercial, or not-for-profit
sectors.

Recibido el 20 de diciembre de
2021, aceptado el 15 de marzo
de 2022.

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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.

(Rev Med Chile 2022; 150: 256-260)

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 neutrofilica crónica, recurrente y poco común. Se caracteriza por lesiones pápulo-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 corticoides 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.

Amicrobial Pustulosis of the Folds (APF) is a relapsing, chronic and rare neutrophilic dermatoses, characterized by papulopustular, eczematous and aseptic lesions on skin folds, perioral region, scalp and external auditory meatus^{1,2}. It occurs commonly in female patients, with an average age of 30 years. Its association with various autoimmune diseases is frequent, mainly with systemic lupus erythematosus (SLE)³.

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

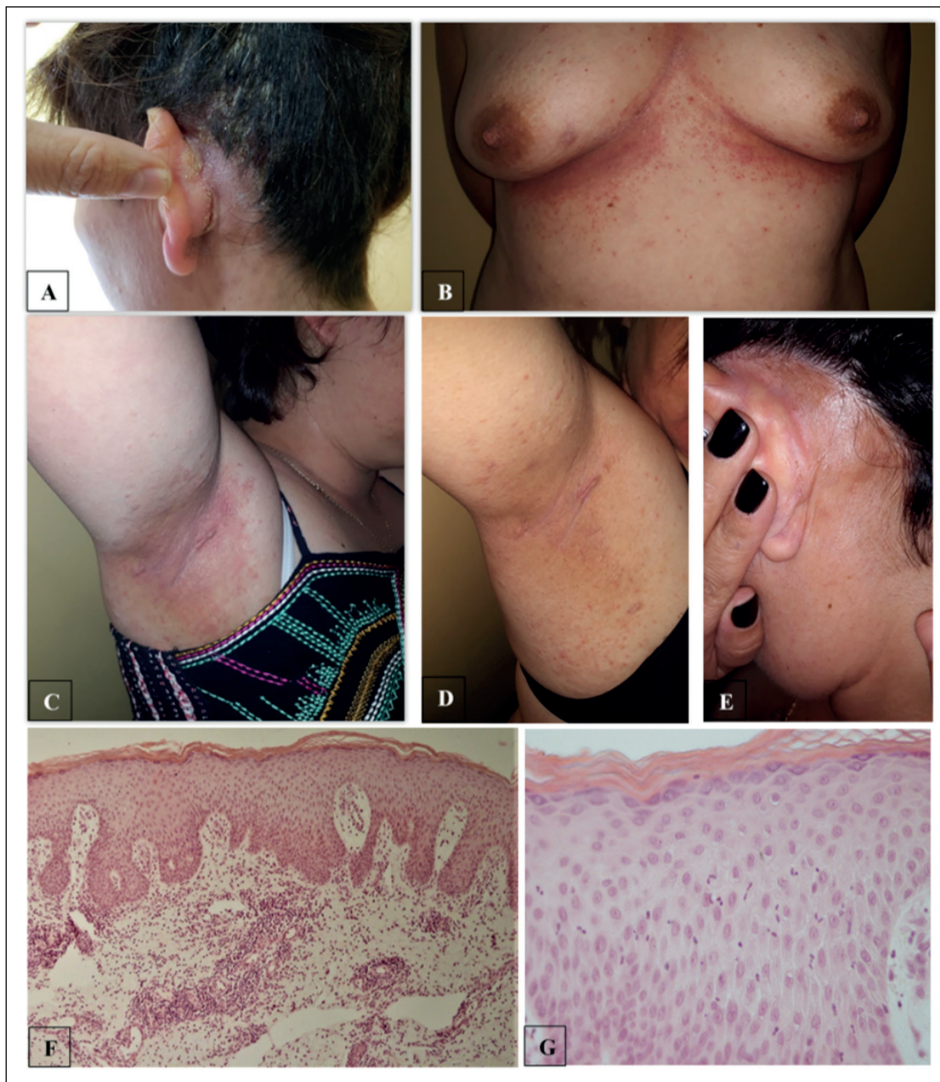


Figure 1. **A.** Erythematous crusted plaques in the scalp and left retroauricular region. **B** and **C.** Erythematous papules and pustules coalescing into plaques on the submammary folds and right axilla. **D** and **E.** After 3 month treatment with doxycycline. Almost full resolution of the lesions in right axilla and left retroauricular region. **F** and **G.** Punch biopsy, hematoxylin-eosin staining (x 40 and x 200 respectively). Spongiotic and pustular psoriasiform dermatitis, with marked neutrophilic epitheliotropism and a mixed perivascular infiltrate of neutrophils and lymphocytes in the upper dermis.

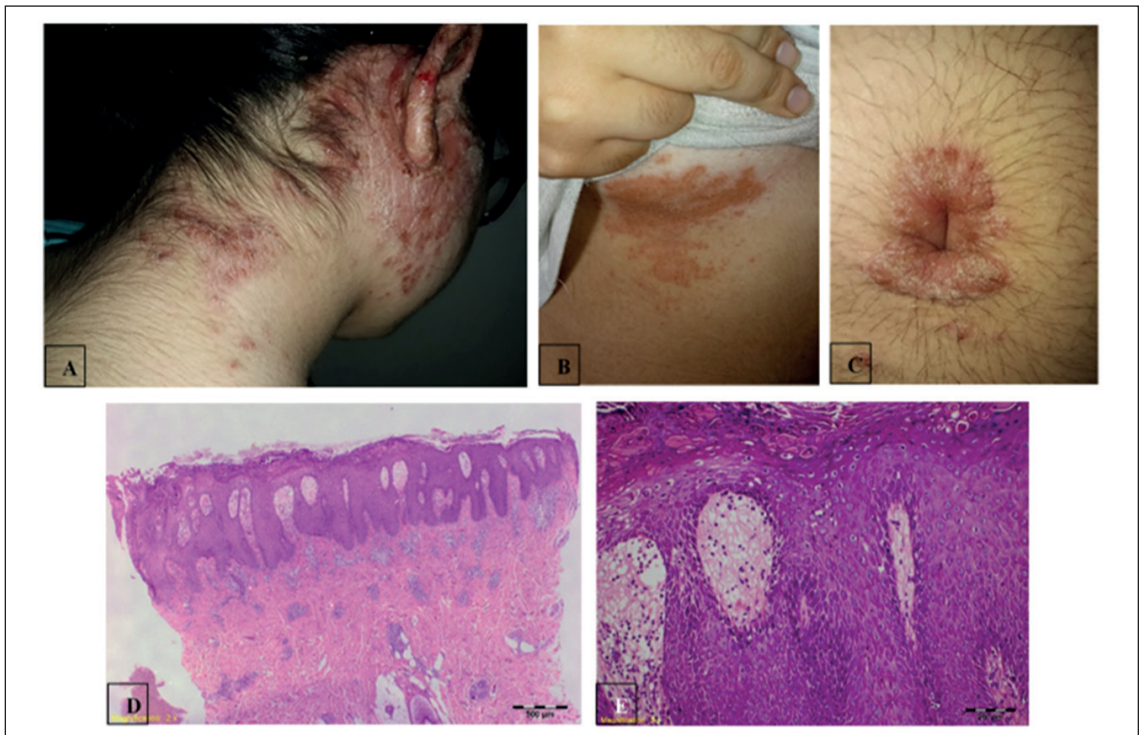


Figure 2. **A.** Large erythematous confluent plaques with superficial fissures, crusting and scattered pustules on the periphery involving the right temporal scalp, ear and cheek, with a smaller similar plaque involving the posterior neck. **B** and **C.** Papulopustular lesions and crusted plaques localized on the right submammary fold and navel. **D** and **E.** Punch biopsy, hematoxylin-eosin staining. Psoriasiform epidermal hyperplasia, focal spongiosis, parakeratosis and intraepidermal and subcorneal pustules. Moderate superficial and deep perivascular lymphocytic infiltrate, with intense perivascular edema in the papillary dermis. The pustules were negative for fungal and bacterial microorganisms on stain testing.

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-1e).

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 months 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 literature⁴. 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-1 β) IL8, IL-7, CXCL 1/2/3, TNF alpha and its receptors, RANTES (regulated on activation, normal T cell, expressed and secreted), matrix metalloproteinases (MMP)-2 and MMP9, which would support the autoinflammatory 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 alpha (infliximab and adalimumab) in patients with inflammatory bowel disease^{6,7}. The mechanisms of this is unknown, but it is believed that the inhibition of TNF alpha, increases the concentration of INF alpha 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 described^{3,8}. It tends to present a chronic evolution, with periods of remission and frequent relapses, generally associated with the decrease or suspension of therapy^{3,6} but not with the activity of the underlying autoimmune disease.

Microbiological examination of the pustules is negative, but secondary bacterial colonization of erosive and macerated lesions is frequent^{3,6}. Regarding biochemical alterations, elevation of acute phase reactants such as HSV and CRP is usually found^{4,6}.

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 folliculitis^{1,3,4}.

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 case⁹. The use of cimetidine, ascorbic acid and zinc supplements have been anecdotally described^{3,8}. 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 response^{3,4,7}. 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 alpha, IL-1b, IL-6¹¹ and dapsone by acting against neutrophilic functions inhibiting its chemotaxis¹².

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