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Amicrobial pustulosis of the folds: long-term remission achieved with low dose dapsone and topical pimecrolimus

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To the Editor:

A 65-year-old woman presented with asymptomatic erythematous plaques with pustules and crusts involving the popliteal and antecubital fossae bilaterally, recurring for more than a decade principally during spring months. She did not report any systemic symptoms or arthralgias and her medical history included arterial hypertension and thalassemia minor; there was no history of atopy.

Clinical examination revealed papules and pustules on erythematous base coalescing into plaques in the above-mentioned body sites (**Figure 1A**, **B**). Comedones or sinus tracts suggesting an early stage of hidradenitis suppurativa were absent. Dermoscopy revealed an erythematous plaque with yellow scaling and peripheral pustules (**Figure 1C**). Due to the initial diagnosis of superinfected eczema the patient was treated with a short course of oral amoxycillin/clavulanic acid and a monthly course of topical methylprednisolone cream, experiencing resolution of the primary plaques but development of similar lesions inframammary.

Laboratory investigation revealed elevated antinuclear antibodies (1:160 [normal, <1:80]) and HbA1c (6.5% [normal, <5.6%]), negative anti-Ro, anti-La, anti-Sm, anti-RNP, anti-dsDNA antibodies and normal thyroid function tests. The bacterial and fungal cultures, which were performed four weeks after cessation of oral antibiotics, were negative. Histopathological examination showed an extensive intraepidermal cleft with subcorneal pustules, epidermal spongiosis, dermal dense infiltrate consisting of neutrophils and eosinophils,

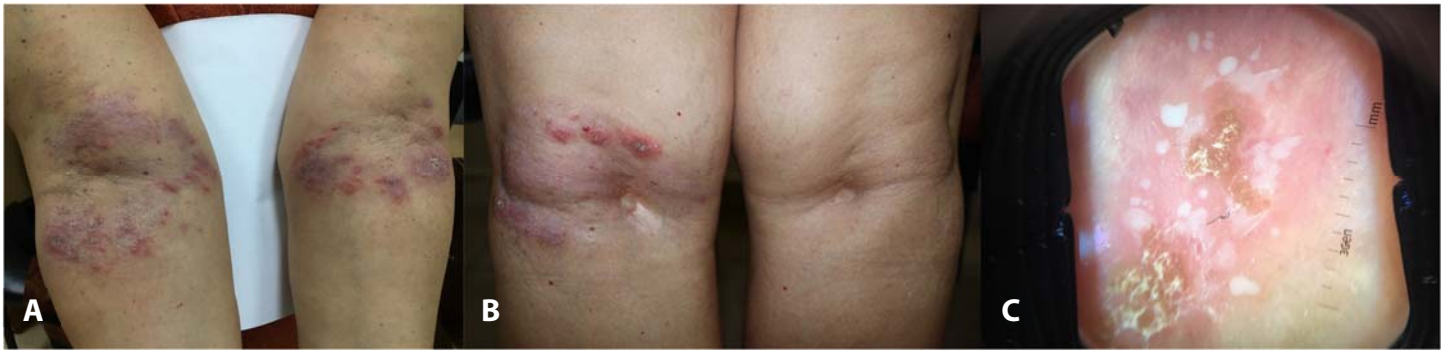

Figure 1. *A 65-year-old female patient with amicrobial pustulosis of the folds:* ***A)*** *elbows, and* ***B)*** *popliteal fossa at initial presentation.* ***C)*** *Dermoscopic findings revealing an erythematous plaque with yellow scaling and peripheral pustules.*

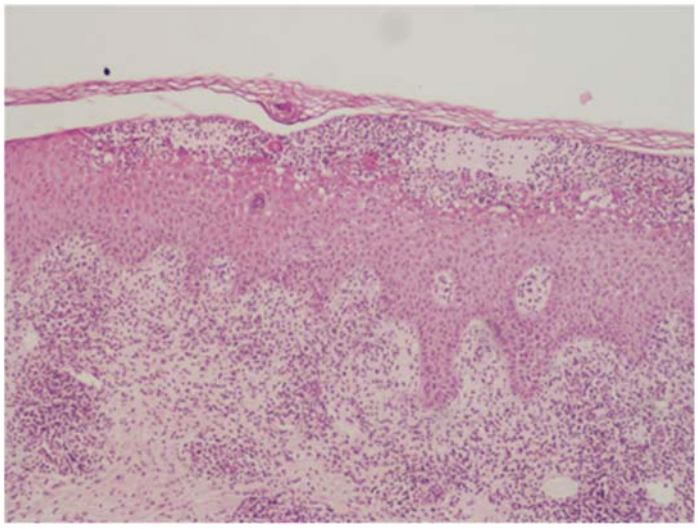

Figure 2. *Histopathological findings revealing an extensive intraepidermal cleft with subcorneal pustules, epidermal spongiosis, dermal dense infiltrate consisting of neutrophils and eosinophils, exocytosis and mild vasculitis.*

exocytosis, and mild vasculitis (**Figure 2**). Direct immunofluorescence (DIF) showed linear deposition of IgA and IgM along the basement membrane zone.

The diagnosis of amicrobial pustulosis of the folds (APF) was made based on the suggested diagnostic criteria for the diagnosis of APF (**Table 1**), [1]. Although intercellular or rarely linear IgA distribution in the subcorneal zone has been described in patients with superficial neutrophilic dermatoses, the AFP has been principally associated with negative DIF [2]. The observed linear deposition of IgA and IgM along the basement membrane zone could be correlated with the presence of a variant of linear IgA dermatosis affecting the folds and suggest that these entities may share common clinical and histopathological characteristics, making the differential diagnosis challenging (**Table 2**), [3]. This

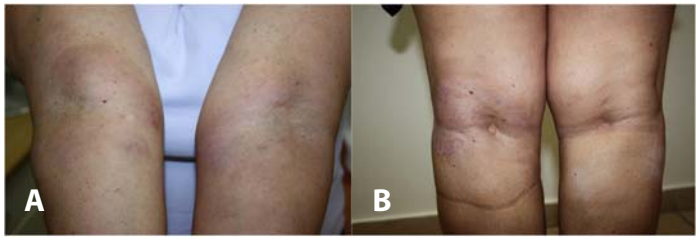

Figure 3. *Clinical presentation after therapy with low-dose dapsone and topical pimecrolimus 1% cream:* ***A)*** *elbows,* ***B)*** *popliteal fossa.*

is further complicated by the therapeutic response to dapsone that characterizes both entities. In all, even though the diagnosis of a localized linear IgA dermatosis could not be definitely excluded, APF was favored based on the histopathological characteristics (subcorneal and not subepidermal blisters and spongiosis) and distribution of the lesions exclusive in the folds. The DIF findings could even constitute a finding of an indolent lupus erythematosus, considering the frequent association of the latter with APF and the elevated ANA titer.

The patient was initially treated with dapsone 50mg/day. However, due to the development of subclinical methemoglobinemia, the dose was reduced to 25mg daily alternating on a weekly basis with 25mg every other day. Topical therapy included intermittent topical corticosteroids followed by pimecrolimus 1% cream as long-term treatment. A long-lasting clinical improvement could be maintained for over 36 months, with no further adverse effects observed thus far (**Figure 3**).

Amicrobial pustulosis of the folds is a chronic recurrent dermatosis, characterized by pustules and erosions affecting mainly the intertriginous areas and exhibiting intraepidermal pustules, spongiosis,

Table 1. *Diagnostic criteria of amicrobial pustulosis of the folds, as suggested by Marzano et al. in 2008 [1].*

Major criteria	Minor criteria
Clinically pustulosis in one or more major folds, one or more minor folds and the anogenital area	Association with one or more autoimmune disorders
Intraepidermal spongiform pustules and a mainly neutrophilic dermal infiltrate on histopathology	Positive ANA at a titer of at least 1/160
Negative culture from an intact pustule	Presence of one or more of the following serum autoantibodies (anti-ENA, anti-dsDNA, anti-smooth-muscle,anti-mitochondrial, anti-gastricparietal-cell, anti-endomysial)
The diagnosis of APF can be ascertained if all major criteria and one minor criterion are fulfilled	

ANA, antinuclear antibodies; APF, amicrobial pustulosis of the folds; ENA, extractable nuclear antigens.

Table 2. *Differential diagnosis of amicrobial pustulosis of the folds.*

Diagnosis	Clinical characteristics	Histopathology	DIF/IIF
Amicrobial pustulosis of the folds	Sterile pustules with erythema on folds and anogenital area	Intraepidermal pustules, spongiosis and neutrophilic infiltrate	Usually negative
Superficial pustular dermatosis (Sneddon-Wilkinson disease)	Hypopyon pustule (primary lesion); annular/polycyclic lesions with central clearing and peripheral pustules	Subcorneal pustules filled with neutrophils and occasionally eosinophils, mixed superficial perivascular inflammatory infiltrate	Negative
IgA pemphigus Superficial pustular dermatosis (SPD) type Intraepidermal neutrophilic dermatosis (IND) type	Pruritic, painful pustules on an erythematous base that quickly rupture to form annular crusts over the plaque	Intraepidermal blisters with massive neutrophilic infiltration and with a mild loss of cohesion between keratinocytes (spdtype in upper epidermis, IND-type in entire or lower epidermis)	SPD type: intercellular IgA against desmocollin-1 (upper epidermis) IND type: IgA autoantibodies against desmoglein 1,3 (lower epidermis)
Pyoderma vegetans	Large verrucus plaques with numerous pustules	Pseudoepitheliomatous hyperplasia, intraepidermal and dermal neutrophilic microabscesses	DIF negative
Linear IgA dermatosis (in children a.k.a. "chronic bullous disease of childhood")	Annular erythematous lesions with a ring of vesicles (children) Widespread tense bullae on non-inflamed skin (adults)	Subepidermal blistering, predominately neutrophilic infiltrate	Linear IgA in the dermo-epidermal junction
Pustular psoriasis	Yellowish pustules on erythematous base diffuse or localized	Features of psoriasis vulgaris and additional neutrophilic infiltrate in the papillary dermis and epidermis and superficial microabscesses	Negative
Dermatitis herpetiformis	Small, pruritic papules and vesicles predominately on the elbows, knees buttocks and back	Dense clusters of neutrophils and scattered eosinophils in the papillary dermis forming microabscesses	Granular IgA in dermal papillae

a.k.a., also know as; DIF, direct immunofluorescence; IgA, immunoglobulin A; IIF, indirect immunofluorescence; IND, intraepidermal neutrophilic dermatosis; SPD, superficial pustular dermatosis.

and neutrophilic infiltrate on histopathology [4,5]. Published literature support an association of APF with various immunological disorders, including either established autoimmune diseases or solely positive serum autoantibodies. Studies demonstrate an overexpression of different cytokines and chemokines, reinforcing the idea that APF is an autoinflammatory disorder like other neutrophilic dermatoses and may accompany a systemic autoimmune disorder or precede the diagnosis of an autoimmune disease by years [6,7]. Generally, the course of the skin lesions is not related to the activity of the associated autoimmune disorder [2].

Due to the rarity of the disease therapeutic data are limited. Most patients respond to oral corticosteroids, although relapses commonly occur after dose reduction. Other agents like colchicine, cyclosporine, hydroxychloroquine, methotrexate, systemic antibiotics, zinc sulphate, cimetidine and ascorbic acid, apremilast, anakinra, anti-TNF and anti-IL12/23 agents have been reported to be effective in limited number of patients [1,4,5,8-11].

In our case, long-term remission was achieved by low doses of dapsone and topical pimecrolimus 1% cream. As an anti-inflammatory agent, dapsone is employed primarily to treat chronic skin diseases characterized by an accumulation of neutrophils and/or eosinophils. For the management of APF, it has been employed in doses 50-100mg/day [4,12].

On the other hand, calcineurin inhibitors suppress the synthesis and release of pro-inflammatory cytokines. Due to their high affinity for the receptor and lower absorption through skin, they do not exhibit certain adverse events of topical glucocorticosteroids, including skin atrophy, telangiectasia, striae, and hyper- and hypopigmentation. Thus, they are especially indicated for long-term treatment or areas such as the face, skin folds, and genital region where penetration through skin is many times higher [13].

Considering the disease chronicity and the adverse events of systemic and topical corticosteroids, we suggest that the combination of low dose dapsone and topical calcineurin inhibitors may represent an effective and safe therapeutic option for long-term disease control in APF patients.

Potential conflicts of interest

The authors declare no conflicts of interest.

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