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Amicrobial Pustulosis-Like Rash in a Patient with Crohn's Disease under Anti-TNF-Alpha Blocker

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Key Words
Amicrobial pustulosis · Lupus erythematosus · Infliximab · Neutrophilic dermatoses · Cutaneous lupus · Tumor necrosis factor-α inhibitor

Abstract
Amicrobial pustulosis of the folds (APF) is a recently described entity characterized by relapsing pustular lesions predominantly involving the cutaneous flexures and scalp. This disease typically occurs in association with systemic lupus erythematosus and a variety of other autoimmune diseases. We here describe an APF-like pustular eruption predominantly affecting the scalp, face and trunk, occurring during long-term infliximab treatment for Crohn's disease. Immunohistochemical staining of skin biopsy specimens for myxovirus resistance protein A, a marker for type 1 interferon-inducible proteins, showed increased staining in the epidermis and dermal mononuclear inflammatory infiltrate. Our observation further extends the spectrum of cutaneous adverse reactions potentially related to anti-tumor necrosis factor-α, the clinical context in which APF can occur as well as its clinical presentations.

Introduction

Amicrobial pustulosis of the folds (APF) is a recently described entity that is characterized by relapsing pustular lesions affecting mainly the cutaneous folds and scalp. Since the initial report of APF occurring in association with systemic lupus erythematosus (LE) by Crickx [1] in 1991, there have been further reports of its association with systemic and cutaneous LE as well as other dysimmune diseases [2–10].

We here report a case of a pustular eruption closely mimicking APF that occurred under long-term therapy with infliximab for Crohn's disease expanding the spectrum of cutaneous complications occurring under anti-tumor necrosis factor-α (TNF-α) blockers.

Report of a Case

A 22-year-old female patient was referred for evaluation of a recurrent pustular and crusted eruption of 5 months' duration involving predominantly the scalp and the face with isolated lesions of the trunk and extremities. She had a history of severe Crohn's disease and had been receiving infusions of infliximab every other month for the past 4 years, which resulted in complete disease remission. She had no prior history of eczema, psoriasis, systemic LE or other autoimmune diseases. She was seen initially by her primary physician and was treated with topical emollients and several courses of oral antibiotics (amoxicillin-clavulanic acid) without any improvement.

On examination, there were multiple erythematous, weepy, erosive and pustular lesions in the occipital area of the scalp, coalescing into large plaques with extensive hair loss. She also had isolated pustular and eroded lesions along the hairline of the scalp, in the retroauricular regions, external auditory canals and nares. On the trunk and limbs, there were isolated papulopustules and discrete eczematous lesions (fig. 1).

Light microscopy studies of a skin biopsy specimen obtained from the scalp showed neutrophilic folliculitis and perifolliculitis with mild spongiosis, dermal edema with an inflammatory infiltrate of lymphocytes and neutrophils (fig. 2a, b). In another biopsy specimen obtained from the thigh, there was a spongiform subcorneal pustule with interface changes of basal vacuolar degeneration and a superficial and deep dermal infiltrate of neutrophils

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and lymphocytes with increased mucin deposition (fig. 2c, d). The periodic acid-Schiff staining did not demonstrate fungi, and Gram staining for bacteria was also negative. Repeated cultures from pustules were either sterile or revealed the presence of *Staphylococcus aureus*. Direct immunofluorescence microscopy studies of lesional skin were negative. Complete blood count, electrolytes, renal, liver function tests and urine sediment analysis were within normal limits. Antinuclear antibodies, anti-double-stranded DNA and antinucleosome antibodies were negative, whereas antihistone antibodies were positive (1.9 units; normal <1).

The patient was started on both topical and systemic corticosteroids (prednisolone 0.5 mg/kg) as well as on oral amoxicillin-clavulanic acid. Based on its potential triggering role, infliximab was discontinued, and the patient was switched to sulfasalazine for her Crohn's disease. Within 1 week of initiation of systemic corticosteroid therapy, there was significant improvement with no new lesions. On follow-up 2 months later, there was complete resolution of the pustules and scaly plaques with almost regrowth of hair on the scalp.

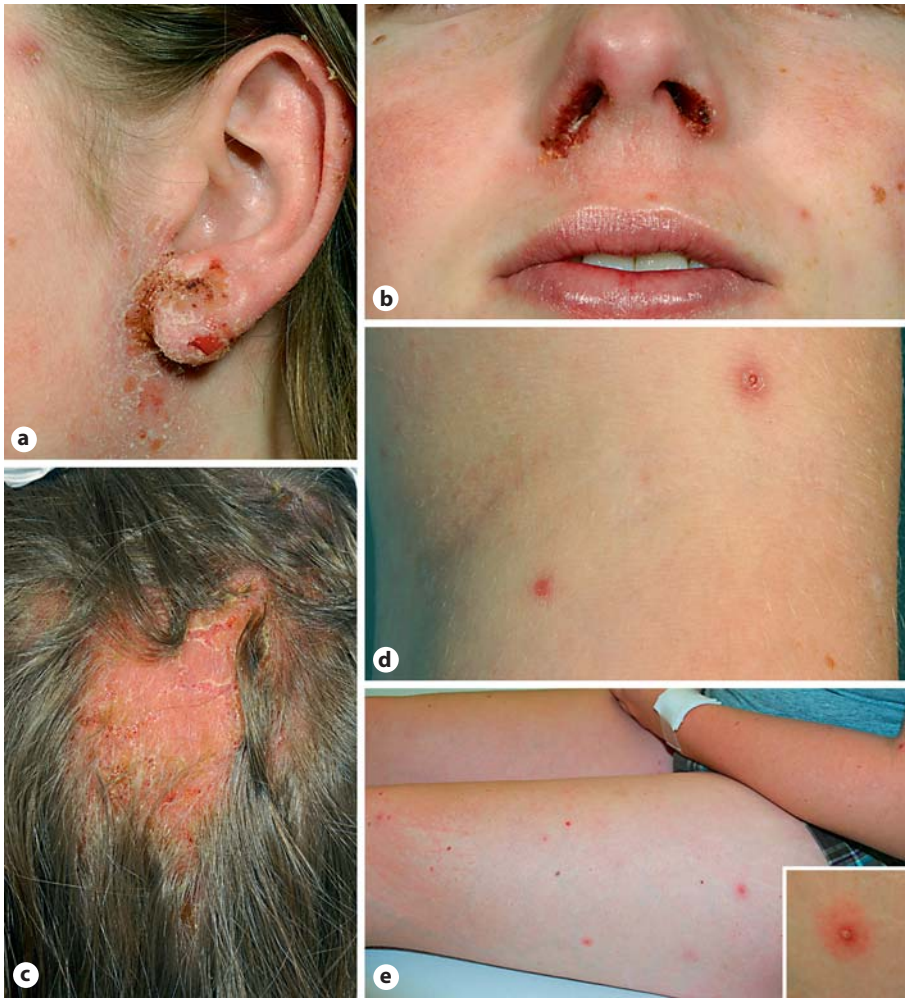


Fig. 1. a–c Erythematous, crusted plaques affecting the ears, nares and scalp with scarring alopecia. **d**, **e** Scattered papulopustules distributed over the limbs. **Inset** Close-up of a pustule.

Immunohistochemical Methods

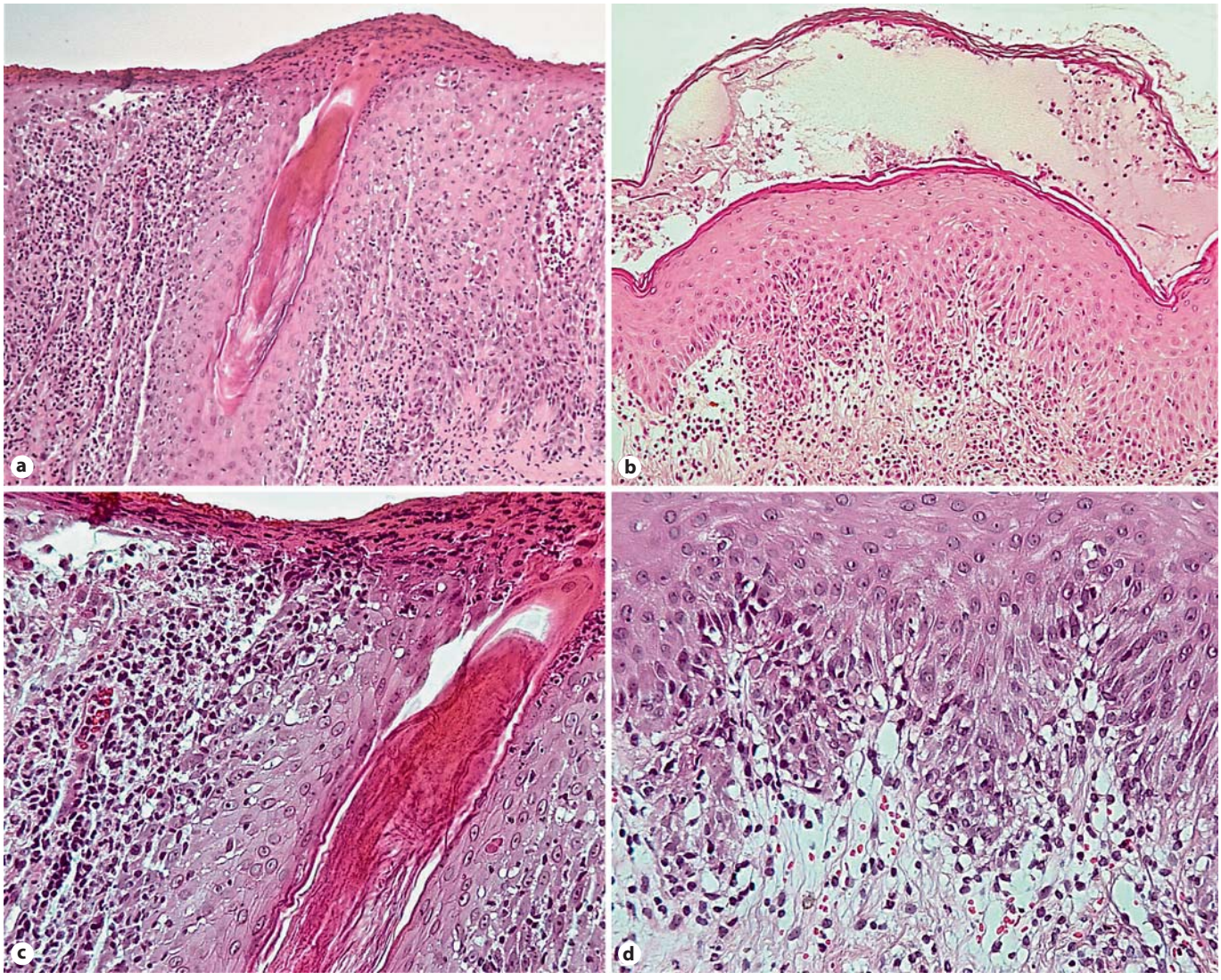
Formalin-fixed paraffin-embedded skin specimens from our patient were further processed after informed consent. Sections were deparaffinized and stained with standard hematoxylin-eosin for routine histological examination. In addition, type 1 interferon (IFN) signaling was evaluated by immunostaining for myxovirus resistance protein A (MxA), using a streptavidin-biotin peroxidase system. Antigen retrieval was performed using a citrate buffer at pH 6 in a pressure cooker. Tissue sections were incubated overnight with rabbit polyclonal antibody to human MxA (1:700; Gene Tex, Irvine, Calif., USA) followed by biotinylated goat anti-rabbit immunoglobulin antiserum (1:200 dilution; Dako, Glostrup, Denmark) for 1 h. Sections were subsequently incubated with a streptavidin-biotin complex/alkaline phosphatase (1:200 dilution; Dako) and then developed with new fuchsin-naphthol AS-BI (Sigma, St. Louis, Mo., USA) for 10 min, counterstained with hematoxylin and mounted. As negative controls, we replaced the primary antibody with the antibody dilution buffer. Finally, we carried out immunohistological staining with MxA on skin sections obtained from patients with active psoriasis as positive control and from healthy individuals.

Results

Representative stainings from lesional skin and a normal control are shown in figure 3. In our case, immunostaining with MxA used as surrogate marker for type 1 IFN-inducible protein demonstrated intense epidermal staining, particularly in areas corresponding to the interface changes as well as cytoplasmic staining of the dermal inflammatory mononuclear and vascular endothelial cells. Polymorphonuclear leukocytes were not positively stained.

Discussion

We here report the unusual and striking case of a patient under long-term treatment with infliximab for Crohn's disease who developed a pustular eruption with clinical and histological features mimicking APF. APF is an uncommon entity that has gained increasing attention in the dermatological literature [1–10]. Invariably all cases have been described in young women in the context of dysimmune diseases.



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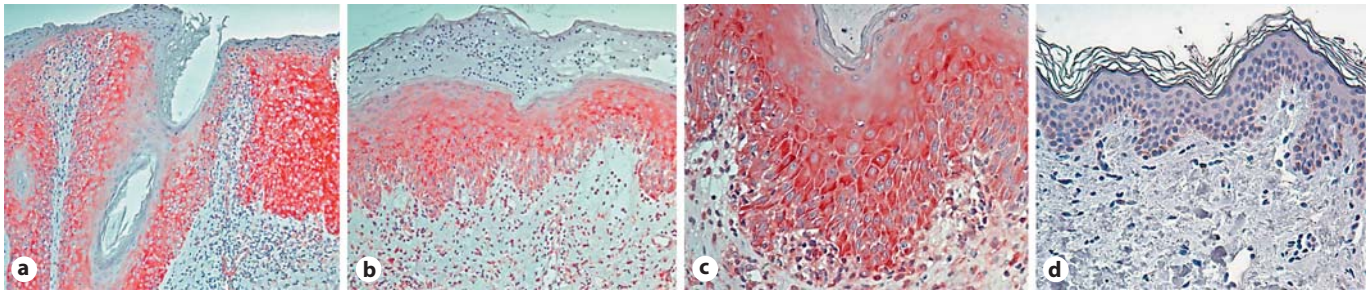

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Fig. 2. a Scalp biopsy: folliculitis and perifolliculitis. Hematoxylin-eosin. Original magnification ×10. **b** Scalp biopsy: perifollicular infiltrate of neutrophils. Hematoxylin-eosin. Original magnification ×20. **c** Biopsy from pustule on the thigh: subcorneal pustule with papillary edema. Hematoxylin-eosin. Original magnification ×10. **d** Biopsy from pustule on the thigh: spongiosis with interface dermatitis. Hematoxylin-eosin. Original magnification ×20.

Fig. 3. a Scalp biopsy: increased epidermal staining of MxA. Original magnification ×10. **b** Biopsy from pustule on the thigh: increased epidermal staining of MxA with sparing of neutrophils. Original magnification ×10. **c** Biopsy from pustule on the thigh: prominent staining of the epidermis and dermal mononuclear infiltrate corresponding to the interface changes. Original magnification ×20. **d** Normal skin: negative staining for MxA. Original magnification ×20.

Table 1. Major differential diagnoses considered in our patient

	Amicrobial pustulosis of the folds [1–10]	Pustular psoriasiform eruptions associated with anti-TNF [12–18]	Pustular Crohn's disease/ vesiculopustular eruption of IBD/pustular variant of pyoderma gangrenosum [19–21]
Epidemiology	Affects females 3rd decade	Female:male ratio 2:1 Mean age 45 ± 15 years	Unknown
Clinical features	Symmetrical eruption of pustules, erosive macerated areas and crusts involving the folds (axilla, groins, external auditory meatus, nares, retroauricular flexures, interdigital spaces) Isolated pustules over the body Pustular and crusted lesions over the scalp	Localized pustulosis of the palms/soles, frequently Other forms: guttate psoriasis, plaque psoriasis, nail psoriasis	Pustules and papulopustules distributed on the trunk and limbs Occasionally progression to pustular pyoderma gangrenosum
Disease associations/ triggers	Systemic and cutaneous LE Anecdotal cases: scleroderma, mixed connective tissue disease, sicca syndrome, celiac disease, idiopathic thrombocytopenia, myasthenia gravis and Hashimoto's thyroiditis	Use of TNF blockers in RA, JRA, AS, SA, IBD, psoriasis	IBD
Histology	Intraepidermal, subcorneal spongiform abscesses; neutrophilic dermal inflammatory infiltrate; negative DIF	Psoriasiform changes: epidermal hyperplasia, parakeratosis, dilated capillaries, intraepidermal pustulosis Less commonly: lichenoid pattern; neutrophilic folliculitis	Neutrophilic folliculitis; dermal neutrophilic infiltrate
Treatment	Systemic steroids, cyclosporine A, dapsone, cimetidine with ascorbic acid	Topical treatment In severe cases: systemic treatment, anti-TNF-α withdrawal	Systemic steroids, cyclosporine, metronidazole, minocycline, dapsone, methotrexate

AS = Ankylosing spondylitis; DIF = direct immunofluorescence; IBD = inflammatory bowel disease; JRA = juvenile rheumatoid arthritis; RA = rheumatoid arthritis; SA = seronegative arthropathy.

Besides systemic and cutaneous LE, anecdotal cases occurring in association with scleroderma, mixed connective tissue disease, sicca syndrome, celiac disease, idiopathic thrombocytopenia, myasthenia gravis and Hashimoto's thyroiditis have been reported [1–10]. The disease is characterized by relapsing pustular lesions and predominantly involves major and minor body folds, including the retroauricular region, the external ear canal and nares as well as the face and the scalp [1, 2]. Furthermore, the upper and lower extremities, the trunk and the buttocks may also be affected with pustular and/or eczematous lesions. The primary lesions consist of small follicular and nonfollicular sterile pustules coalescing into erosive plaques. Histological features include intraepidermal spongiform abscesses with a neutrophilic dermal inflammatory infiltrate [6]. Direct immunofluorescence microscopy studies including the lupus band test are usually negative [2, 6]. This pustulosis is considered amicrobial as microbiological cultures from recent, closed pustules are always negative although *Staphylococcus* and *Streptococcus* can be isolated from older and eroded lesions because of secondary colonization, as observed in our case [4].

Based on the frequent association with systemic LE, cutaneous LE and other autoimmune diseases, the appealing term of neutrophilic cutaneous lupus has been suggested for APF by some authors [3]. Other authors have rather proposed to include the condition within the spectrum of neutrophilic dermatoses. In analogy to other neutrophilic diseases, extracutaneous involvement such as colonic ulcerations has also been described in APF [2].

Marzano et al. [5] proposed a set of diagnostic criteria for APF, which include as one of the obligate criteria a pustulosis involving 1 or more major folds, 1 or more minor folds and the anogenital area. Based on these as yet unvalidated criteria, our patient does not have a definite diagnosis of APF. However, our patient although lacking major fold and anogenital involvement exhibited lesions of the face and nares identical to those of patient 5 as described by Marzano et al. [5]. Furthermore, she had other typical features of APF such as severe scalp and retroauricular involvement and isolated pustular lesions of the trunk and extremities. Hence, we think

Table 2. Cutaneous side effects associated with anti-TNF treatment

Cutaneous side effects of anti-TNF	Estimated incidence
Inflammatory	
Psoriasiform/pustular reactions	<1% of all patients
Palmar plantar	
Plaque psoriasis	
Guttate psoriasis	
Nail psoriasis	
Mixed patterns	
Granulomatous	0.04–5% of all patients
Sarcoidosis	
Interstitial granulomatous dermatitis	
Granuloma annulare	
Eczematous	unknown; 20 cases in a prospective
Pompholyx-like	cohort of 289 RA patients on anti-TNF
Nummular eczema-like	
Atopic dermatitis-like	
Nonspecific papular lesions	
Lichenoid	unknown; about 20 cases reported
Lichen planus-like	
Lichen planopilaris	
Psoriasiform	
Nonspecific macules/papules	
Neutrophilic	anecdotal case reports
Pyoderma gangrenosum	
Autoimmune	
Vasculitis	<0.5–4% of all patients
Lupus erythematosus	<1.0% of all patients
Dermatomyositis/polymyositis	anecdotal case reports
Autoimmune bullous skin diseases	anecdotal case reports
Bullous pemphigoid	
Pemphigus foliaceus	
Pemphigus vulgaris	
Others	
Infections (skin)	overall (8%)
Viral	0.8–5%
Bacteria	0.1–7%
Atypical mycobacteria	anecdotal
Fungal	1–7%
Malignancies	
NMSC	0.3–1.4%; relative risk of NMSC: 2.0
Infusion reactions	
Acute	10% of infusions
Late	2.5% of infusions
Injection site reactions	10–20% of patients

NMSC = Nonmelanoma skin cancers; RA = rheumatoid arthritis.

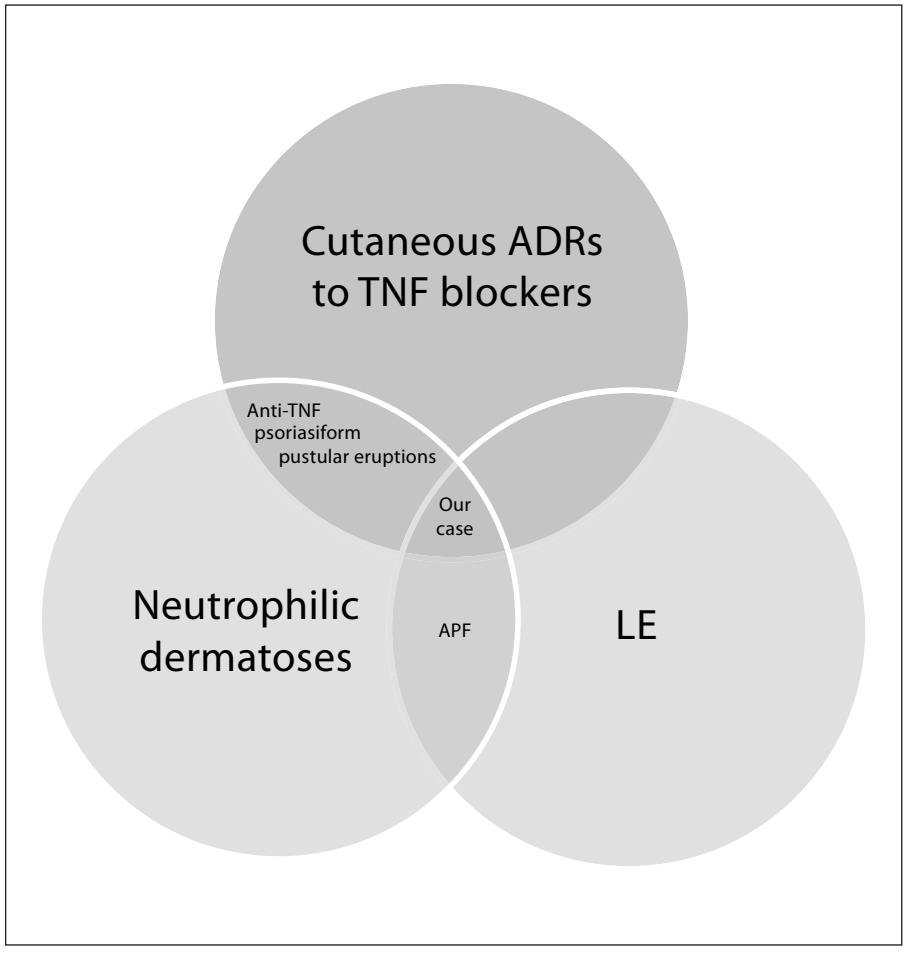

Fig. 4. Schematic representation tentatively illustrating the potential overlap and relation between the groups of neutrophilic dermatoses, cutaneous manifestation of LE and cutaneous side effects associated with anti-TNF blockers. ADRs = Adverse drug reactions.

that both distribution and severity of APF are much more variable than assumed so far.

The pathogenesis of APF is unclear; however, it is believed to involve autoinflammatory pathways [11]. Previous cytokine analysis has shown increased expression of matrix metalloproteinase 9 and Siglec-5 (CD 170) compared to normal skin as well as increased expression of cytokines such as interleukin 1α, interleukin 2 receptor α, macrophage colony-stimulating factor and TNF-α [3].

The list of other differential diagnoses of aseptic pustular diseases to be considered in our case is summarized in table 1 [12–19]. The presence of an interface dermatitis with increased dermal mucin in one of the biopsy samples obtained from our patient together with the detection of positive antihistone antibodies raised the possibility of a peculiar form of drug-triggered LE. Nevertheless, the occurrence of pustular, crusted and scaly lesions was also reminiscent of the paradoxical cutaneous reactions observed under anti-TNF-α therapy although in the latter, it usually affects the palms and soles [16]. Therefore, there seems to be an overlap between APF, neutrophilic disease and TNF-induced lupus and psoriasiform pustular reactions as tentatively illustrated in figure 4. This clinical overlap is plausible based on the common pathogenic pathway of type 1 IFN upregulation. Upregulation of IFN-α following TNF blockade has been proposed as a mechanism for pustular/psoriasiform eruption, as well as TNF-induced LE. This 'type-1 IFN signature' is also characteristic of the interface dermatitis found in several conditions, such as cutaneous LE, dermatomyositis, lichen planus and lichenoid drug eruptions [20]. Evidence has been recently provided indicating the importance of type 1 IFNs in neutrophil recruitment and chemotaxis [21], possibly accounting for the preponderance of pustular cutaneous reactions associated with anti-TNF therapy. In line with these observations, the immunohistochemical studies of our patient's skin sections revealed a staining pattern for MxA (an antiviral protein specifically induced by type 1 IFNs) similar to that found in psoriasiform eruptions associated with TNF blockers [12], while the discrete interface dermatitis observed mimicked that of cutaneous LE [19].

Since the introduction of anti-TNF treatment, an increasing number of cutaneous adverse reactions have been recognized including psoriasiform and pustular eruptions, lupus-like disorders, dermatomyositis, vasculitis, granulomatous reactions, infections, infusion and injection site reactions and malignancies [21–38]. These entities have been summarized in table 2.

In conclusion, we now report a novel observation of APF-like or incomplete form of APF following anti-TNF therapy, expanding not only the clinical context during which APF may occur, but also the spectrum of cutaneous complications potentially associated with anti-TNF therapy.

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