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Amicrobial pustulosis of the folds associated with thyroperoxidase antibodies

Amicrobial pustulosis of the folds związany z przeciwciałami przeciwko peroksydazie tarczycowej

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ABSTRACT

Amicrobial pustulosis of the folds is a rare neutrophilic dermatosis, co-existing with autoimmune disorders, especially with systemic lupus erythaematosus. The disease is characterised by the presence of sterile pustules localised in the skin folds, intraepidermal pustules with mainly neutrophilic infiltrate on histology, negative microbial cultures from an unopened pustule and the presence of circulating autoantibodies or autoinflammatory diseases. Due to its rare incidence, data on effective therapeutic options are limited to individual clinical cases. We present a 69-year-old man with disseminated pustular lesions in the main skin folds, focusing on the clinical, histopathological and immunological characteristics of the disease. Based on the clinical presentation and laboratory investigation, amicrobial pustulosis of the folds was diagnosed with an accompanying increased concentration of anti-thyreoperoxidase antibodies with compensated thyroid hormones. After two weeks of the treatment with local glucocorticosteroids, skin lesions disappeared, leaving the post-inflammatory discoloration. The patient remains without recurrence of any skin lesions during the five-month observation period.

To conclude, in the diagnosis of this rare disease, the clinicopathological correlation plays a crucial role, as well as the investigation for the co-existing autoimmune disorders.

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Key words: amicrobial pustulosis of the folds, aseptic pustulosis, neutrophilic dermatosis, pustular dermatosis

STRESZCZENIE

Amicrobial pustulosis of the folds (APF) jest rzadką dermatozą neutrofilową, współistniejącą z zaburzeniami autoimmunologicznymi, zwłaszcza toczniem rumieniowatym układowym. Choroba charakteryzuje się obecnością: 1. jałowych śródnaskórkowych krost zlokalizowanych w fałdach skórnych, 2. odczynów zapalnych neutrofilowych w skórze właściwej, przy negatywnych posiewach mikrobiologicznych oraz 3. obecnością krążących autoprzeciwciał lub współistnieniem chorób autozapalnych. W związku z rzadkim występowaniem, dane dotyczące skutecznych opcji terapeutycznych ograniczają się do opisów pojedynczych przypadków klinicznych.

Prezentujemy przypadek 69-letniego mężczyzny z rozsianymi zmianami krostkowymi w fałdach i ich otoczeniu, skupiając się na obrazie klinicznym, histopatologicznym oraz immunologicznym choroby. Na podstawie wykonanych badań, w oparciu o obraz kliniczny, u pacjenta rozpoznano *amicrobial pustulosis of the folds* z towarzyszącym wzrostem stężenia przeciwciał przeciwko tyreoperoksydazie, przy wyrównanych hormonach tarczycy.

Po dwutygodniowej terapii miejscowymi glikokortykosteroidami uzyskano ustąpienie zmian skórnych, z pozostawieniem przebarwień pozapalnych. Pacjent pozostaje w remisji w trakcie 5-miesięcznego okresu obserwacji.

W podsumowaniu, w rozpoznaniu tej rzadkiej jednostki chorobowej dużą rolę odgrywa korelacja kliniczno-patologiczna i poszukiwanie współistniejących zaburzeń autoimmunologicznych.

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Słowa kluczowe: dermatoza krostkowa, dermatoza neutrofilowa, choroby autozapalne

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INTRODUCTION

Amicrobial pustulosis of the folds is a rare clinical condition, which has been reported in association with autoimmune diseases and is classified within the spectrum of neutrophilic dermatoses. It is characterised by the relapsing pustular lesions consisting of small follicular and non-follicular sterile pustules, usually grouped on inflammatory, erythaematous plaques and involving mainly the cutaneous folds, anogenital region and scalp. The course is often chronic, with relapses. Its underlying pathogenic mechanism remains controversial [1–3].

We present a case of 69-year-old man with hypertension and asthma, who presented to our department with a three-week history of escalating pustular eruption of major skin folds with co-existing pruritus. The patient presented diffuse pustular lesions in axillary and mammary regions (Fig. 1), anogenital area (mainly scrotum and inguinal folds), as well as the posterior neck. The pustules were well demarcated, unrelated to hair follicles, arising on the erythaematous skin background. In addition, erosions (partially covered with haemorrhagic crusts) and inflammatory papules were observed. The appearance of lesions was not preceded by any infection or new medication taken. Before, due to the suspicion of disseminated herpes zoster, the lesions were treated with acyclovir without significant improvement.

Histopathological examination of the biopsy taken from the lesion of the arm pit showed the presence of subcorneal pustules, psoriasiform epidermal hyperplasia with granular layer preserved, as well as dilatation and congestion of the dermal papillae (Fig. 2). Periodic Acid-Schiff (PAS) staining of the biopsy specimen gave a negative result. Histological findings in correlation with clinical presentation suggested the diagnosis of amicrobial pustulosis of the folds (APF).

In order to verify the diagnosis, a number of additional tests were performed. Tissue examination of the healthy looking skin surrounding the lesion gave a negative result for IgG, IgA, IgM and complement component C3 in the direct immunofluorescence (DIF) method. Analysis of the blood serum by the means of indirect immunofluorescence (IIF) did not show evidence of antinuclear, anticardiolipin or antineutrophil cytoplasmic antibodies. The laboratory results, including full blood cell count, electrolytes, glycaemia, renal and hepatic function and tumour markers were within normal limits. The only abnormality in the routine laboratory tests was an increased concentration of antibodies against thyreoperoxidase (ATPO; 48 IU/mL; laboratory standard: < 9 IU/mL) without any thyroid hormones disturbances (TSH 1.61 mcIU/mL; fT3 3.11 pg/mL, fT4 0.92 ng/dL). There were no clinical symptoms of autoimmune thyroiditis observed.

Based on the clinical and histopathological findings, the patient was diagnosed with APF. An improvement lead-

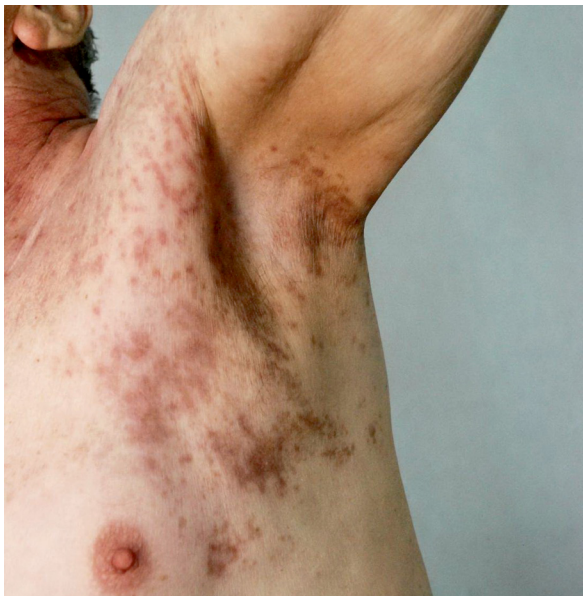

Figure 1. The patient presented diffuse pustular lesions in axillary and mammary regions as presented on the picture

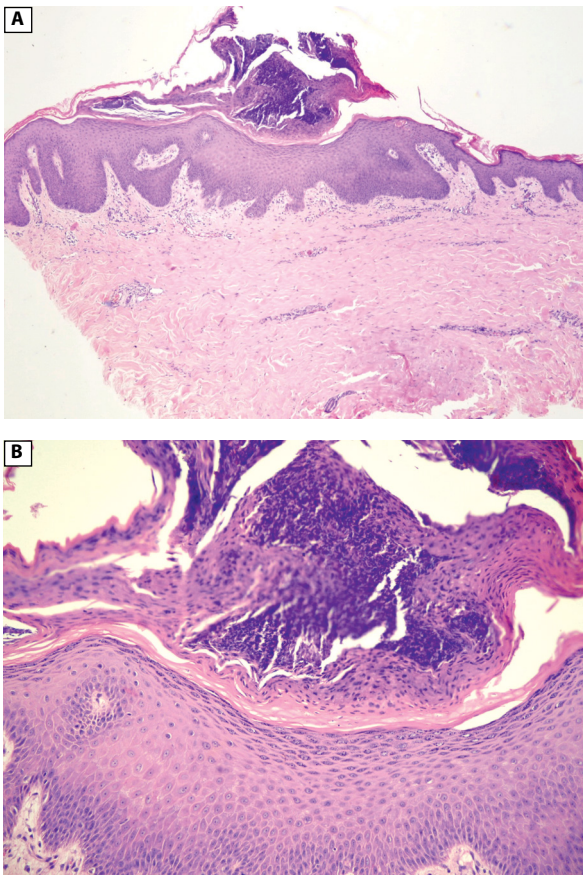

Figure 2. Histopathologic features detected with haematoxylin-eosin stain (H&E). **A**. Psoriasiform epidermal hyperplasia with granular layer preserved, intracorneal neutrophilic large pustule not associated with hair follicle, papillary dermal oedema with inflammatory perivascular inflammation are visible (H&E, 100×). **B**. Magnified intracorneal neutrophilic pustule with preserved granular layer below in an hyperplastic, psoriasiform epidermis (H&E, 400×)

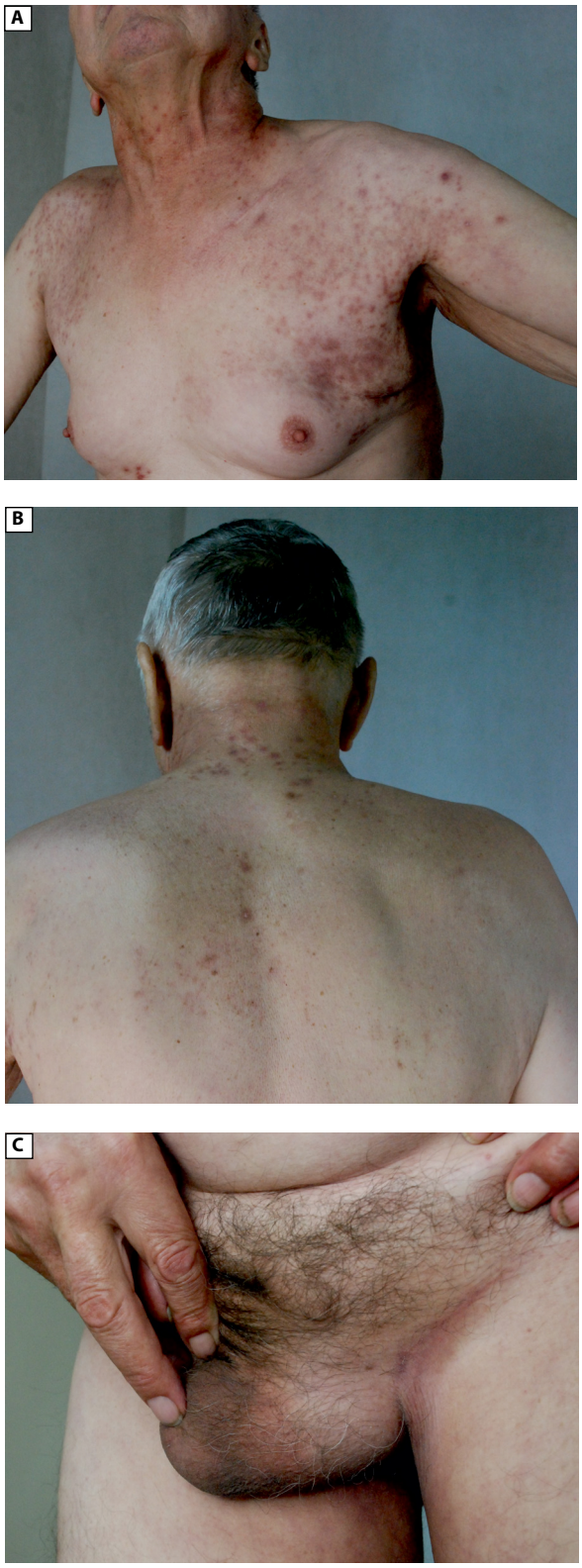

Figure 3. Resolution of pustular lesions with post-inflammatory discoloration involving intertriginous and extra-intertriginous anatomical locations. **A**. Chest and neck. **B**. Nape. **C**. Groin

ing to resolution of almost all cutaneous lesions was observed after two-week treatment with high-potency topical glucocorticosteroids (betamethasone dipropionate, fluticasone propionate) twice a day and oral bilastine. After the treatment, only post-inflammatory discoloration was observed (Fig. 3). Currently, during the five-month observation, the patient remains without recurrence of any skin lesions. Control laboratory tests revealed, however, even higher ATPO antibodies concentration of 59,70 IU/ml, as well as elevation of fT3 concentration (4.27 pg/mL; laboratory standard: 2.5–3.9 pg/mL) and stable fT4 and TSH (0.83 ng/dL and 2.38 mcIU/mL respectively). The patient still did not manifest any signs of thyroiditis. Further endocrinological care, as well as thyroid ultrasonography was recommended.

The disease was first reported in 1991 by Crickx and colleagues [4] in two young women with systemic lupus erythaematosus (SLE) and outbreaks of amicrobial pustules. Since its first description, over 60 cases have been described in the literature, with only 10% of them affecting men and mostly involving young population (mean age, 30 years). The patients with APF exhibit a wide spectrum of autoimmune abnormalities. Whilst the SLE co-occurrence is the most common among the autoimmune diseases associated with APF (27%), over one third of all the cases involves antinuclear antibodies (ANA) or soluble extractable nuclear antibodies (ENA) with no autoimmune disease established. There are also several cases concerning Sharp's syndrome, Sjoegren's syndrome or Crohn's disease, as well as single reports on various autoimmune diseases co-existence [2]. Reports showing an association between the thyroid disease and pustular and neutrophilic dermatoses are rare. There were reports of five cases revealing APF in the course of thyroiditis so far [5–7]. Our case is, to our knowledge, the second one reported with no ANA or ENA and the first one in a male patient. The characteristics of APF with co-existing thyroiditis cases are presented in Table 1. Further studies are needed to clarify the pathways responsible for the pathogenesis of APF in association with both thyroid disease and other autoimmune diseases. High levels of IL-1α, IL-1β and IL-17 were detected in the skin lesions of APF [8].

Our patient had characteristic clinical and histopathological features of APF, with erosive areas surrounded by isolated pustules and papules. Typical histological features involve subcorneal and intraepidermal spongiform pustules in an acanthotic epidermis and a dermal inflammatory infiltrate, predominantly consisting of neutrophils, without vasculitis. In older plaques, psoriasiform hyperplasia with parakeratosis is observed. Direct immunofluorescence studies including the lupus band test are usually negative [1–3].

As the disease shares common clinical and histopathological features with other pustular dermatoses, differential diagnosis might be problematic. The following entities should be taken into consideration while differentiating the condition: pustular psoriasis, mainly its inverse type

Table 1. Characteristics of patients with APF and thyroiditis

Characteristics	Case 1 — our patient	Case 2 [5]	Case 3 [5]	Case 4 [5]	Case 5 [7]
Age of onset (years)	69	54	65	30	36
Sex, ethnicity	Male, White	Female, Indian	Female, White	Female, Mexican	Female
ANA	Negative	Strongly positive	Strongly positive	Strongly positive	Negative
ENA	Negative	dsDNA	Anticentromere	Ds-DNA, Sm, SS-A, SS-B, RNP	Negative
Associated autoimmune diseases	Unspecified thyroiditis	Hyphothyroiditis, undifferentiated connective tissue disease	Hyphothyroiditis	SLE, Hashimoto thyroiditis	Hashimoto thyroiditis
Diagnosis of thyroiditis	At the time of APF diagnosis	No data	Before diagnosis of APF	Before diagnosis of APF	1 month before diagnosis of APF
Pustule locations	Both intertriginous and extra-intertriginous	Both intertriginous and extra-intertriginous	Mainly extra-intertriginous + neck	Mainly intertriginous + limbs	Both intertriginous and extra-intertriginous
PAS-staining and DIF	Negative	Negative	Negative	Negative	Negative
Histopathologic findings	Subcorneal and intracorneal pustules, psoriasiform epidermal hyperplasia with granular layer preserved, dilatation and congestion of blood vessel in the dermal papillae	Intracorneal neutrophilic pustules, epidermal neutrophils with spongiosis, perivascular and interstitial neutrophils, papillary dermal oedema, leukocytoclasis and scattered eosinophils vasculitis, pustules overlying ostium of eccrine ducts and hair follicles, perifollicular neutrophils	Intracorneal neutrophilic pustules, epidermal neutrophils with spongiosis, perivascular and interstitial neutrophils, papillary dermal oedema, perifollicular neutrophils intracorneal pustules overlying the follicular ostium, leukocytoclasis without vasculitis	Intracorneal neutrophilic pustules, spongiform subcorneal and intraepidermal pustules, superficial dermal oedema, perivascular, eccrine and interstitial neutrophils, leukocytoclasis without vasculitis, pustules overlying follicular ostium	Peri- and intrafollicular neutrophilic infiltrates, perivascular neutrophilic infiltrate in the superficial dermis without vasculitis; parakeratosis, intraepidermal spongiform pustules, acanthotic epidermis without acantholytic cells
Disease duration, effective regimen	5 weeks, 2 weeks of topical corticosteroids	6 years, systemic colchicine and prednisone	4 weeks, 5 days of topical corticosteroids	No data, long-term prednisone	12 months, systemic prednisone, methotrexate + prednisone

(minor folds involvement is less characteristic; usually the presence of psoriatic lesions outside the skin folds), Sneddon-Wilkinson disease (different course of the disease, higher mean age of the patients, characteristic appearance of the pustules: half-and-half blisters, fine scaling after relapse, less characteristic psoriasis-like appearance of epidermis in histopathology), pemphigus foliaceus (positive DIF), IgA pemphigus (intraepidermal IgA deposits in DIF), acute generalised exanthaematous pustulosis (more severe course of the disease), impetigo herpetiformis and bacterial and candidal dermatoses [2–3]. Clinicopathologic correlation plays an important role, that is why Marzano et al. [1] in 2008 proposed some diagnostic criteria providing both for clinical manifestations of the disease (pustulosis affecting one or more major folds; aseptic pustules), histological pattern (intraepidermal spongiform pustulosis with neutrophil infiltrate in the dermis) — obligate criteria; as well as immunological deviations (so called 'minor criteria': the association with one or more autoimmune disorders, ANA titters of 1:160 or more, or the presence of additional autoantibodies).

The therapy of APF is not well standardised. Due to low incidence of APF, data on effective therapeutic options are limited to solitary cases. Several cases of topical corticosteroids clinical effectiveness in monotherapy in APF have been described to date [9–10]. In most cases however, systemic treatment was utilised, with oral corticosteroids (0.5–1 mg/kg/day of prednisone dose equivalent) given in most cases in monotherapy or in combination [2]. In individual cases, cyclosporine A and dapsone, hydroxychloroquine, and methotrexate have successfully been used in addition to systemic corticosteroids. There are also some reports on good response to colchicine, as well as healing with zinc and ascorbic acid supplementation [3]. In more resistant cases, cytokine inhibitors such as anakinra, infliximab and ustekinumab might be useful, as their efficacy was recently shown in a couple of cases [3, 10, 11]. We obtained a complete response without noticeable relapse lasting 5 months of follow-up, until the time of writing. Relapses of APF following tapering or discontinuation of treatment are common. However, long-term remissions of the disease have been reported only rarely [12].

In conclusion, amicrobial pustulosis of the folds is a rare neutrophil dermatosis, co-existing with autoimmune disorders. The diagnosis of this entity can be difficult and it should always be taken into consideration in cases of neutrophillic infiltrate of the skin. Most importantly, a clinicopathological correlation plays a crucial role in making an accurate diagnosis. Finally, as most cases of APF are associated with other diseases, screening and monitoring particularly for autoimmune diseases is necessary. We consider taking into account the possibility of asymptomatic autoimmune thyroiditis co-existence, as it was in case of our patient and another one described previously [6]. The cases of such subclinical immunological disturbances need further monitoring, even though they might not evolve into treatment-requiring disease.

REFERENCES

1. Marzano AV, Ramoni S, Caputo R. Amicrobial pustulosis of the folds. Report of 6 cases and a literature review. Dermatology. 2008; 216(4): 305–311, doi: 10.1159/000113942, indexed in Pubmed: 18230977.
2. Schissler C, Velter C, Lipsker D. Amicrobial pustulosis of the folds: Where have we gone 25years after its original description? Ann Dermatol Venereol. 2017; 144(3): 169–175, doi: 10.1016/j.annder.2016.10.018, indexed in Pubmed: 28242094.
3. Marzano AV, Borghi A, Wallach D, et al. A comprehensive review of neutrophilic diseses. Clinic Rev Allerg Immunol. 2017 Jul 7.
4. Crickx B, Diego ML, Guillevin L, et al. Pustulose amicrobienne et lupus érythémateux systémique. Journées Dermatologiques de Paris 1991; Mar: Communication n. : 11.
5. Wang MZ, Camilleri MJ, Guo R, et al. Amicrobial pustulosis of the folds: Report of 4 cases. J Cutan Pathol. 2017; 44(4): 367–372, doi: 10.1111/cup.12873, indexed in Pubmed: 28000249.
6. Claeys A, Bessis D, Cheikhrouhou H, et al. Amicrobial pustulosis of the folds revealing asymptomatic autoimmune thyroiditis. Eur J Dermatol. 2011; 21(4): 641–642, doi: 10.1684/ejd.2011.1406, indexed in Pubmed: 21697048.
7. López-Navarro N, Alcaide A, Gallego E, et al. Amicrobial pustulosis of the folds associated with Hashimoto's thyroiditis. Clin Exp Dermatol. 2009; 34(8): e561–e563, doi: 10.1111/j.1365-2230.2009.03370.x, indexed in Pubmed: 19549241.
8. Marzano AV, Tavecchio S, Berti E, et al. Cytokine and chemokine profile in amicrobial pustulosis of the folds: evidence for Autoinflammation. Medicine (Baltimore). 2015; 94: e2301.
9. Lagrange S, Chosidow O, Piette JC, et al. A peculiar form of amicrobial pustulosis of the folds associated with systemic lupus erythematosus and other auto-immune diseases. Lupus. 1997; 6(6): 514–520, doi: 10.1177/096120339700600607, indexed in Pubmed: 9256309.
10. Inui S, Azukizawa H, Asada H, et al. Amicrobial pustulosis with antinuclear antibodies and rheumatoid factor. Br J Dermatol. 2006; 154(3): 568–569, doi: 10.1111/j.1365-2133.2005.07095.x, indexed in Pubmed: 16445803.
11. Amazan E, Ezzedine K, Mossalayi MD, et al. Expression of interleukin-1 alpha in amicrobial pustulosis of the skin folds with complete response to anakinra. J Am Acad Dermatol. 2014; 71(2): e53–e56, doi: 10.1016/j.jaad.2013.12.041, indexed in Pubmed: 25037815.
12. Kerl K, Masouyé I, Lesavre P, et al. A case of amicrobial pustulosis of the folds associated with neutrophilic gastrointestinal involvement in systemic lupus erythematosus. Dermatology. 2005; 211(4): 356–359, doi: 10.1159/000088508, indexed in Pubmed: 16286747.