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Palisaded neutrophilic granulomatous dermatitis in a patient with HLA-B27–negative axial spondyloarthritis: a case report and literature review

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Abstract

Palisaded neutrophilic granulomatous dermatitis (PNGD) is a rare histopathological pattern belonging to a group of cutaneous granulomatous eruptions that typically manifests with asymptomatic skin-colored, erythematous, or violaceous papules or nodules. PNGD can be triggered by various systemic conditions, including medications and autoimmune and autoinflammatory disorders, as well as malignancies; for example, lymphoproliferative disorders. Therefore, in patients with PNGD an extended diagnostic workup is mandatory as well as follow-up in the case of idiopathic PNGD. To the best of our knowledge, this is the first reported case in the literature of PNGD causally related to a relapse of HLA-B27–negative axial spondyloarthritis.

Keywords: palisaded neutrophilic granulomatous dermatitis, granulomatous dermatitis, neutrophilic dermatoses, axial spondyloarthritis

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Introduction

Palisaded neutrophilic granulomatous dermatitis (PNGD) is a rare histopathologic pattern belonging to a group of cutaneous granulomatous eruptions and neutrophilic dermatoses (1, 2). Although patients of all ages may be affected, PNGD most commonly develops in the 5th decade of life (mean age 47.3 years) and shows a female predominance (female:male = 3:1) (3). PNGD can be triggered by various systemic conditions (1). Here we present an interesting case of PNGD triggered by a relapse of HLA-B27–negative axial spondyloarthritis (axSpA) in an adult male. To the best of our knowledge, this causal relationship is reported for the first time. The case report is followed by a review of the literature on PNGD and a presentation of the characteristics of the main differential diagnoses.

Case report

A 49-year-old male was referred to the dermatology department because of multiple asymptomatic bump-like changes above the elbows and knees of 6 months' duration that appeared few weeks after a relapse of HLA-B27–negative axSpA, which the patient has had since 2012. AxSpA had successfully been treated with adalimumab until 2014, which was then discontinued at the patient's request. The patient did not have any checkups with rheumatologists and did not receive any treatment in the meantime. However, a few months before the referral, the patient's condition worsened with the onset of fatigue, unintentional loss of 18 kg over a 2-month period, and severe low back pain, causing awakening in the middle of the night and morning stiffness. Moreover, peripheral arthritis with pain in the joints of the shoulder girdle, knees, and hands also developed, along with an episode of acute scleritis in the right eye. The patient denied other systemic symptoms. On physical examination there were multiple violaceous papules with a firm consistency and slightly hyperkeratotic surface located above the elbows and knees (Fig. 1). No other abnormalities were noticed except reduced spine mobility.

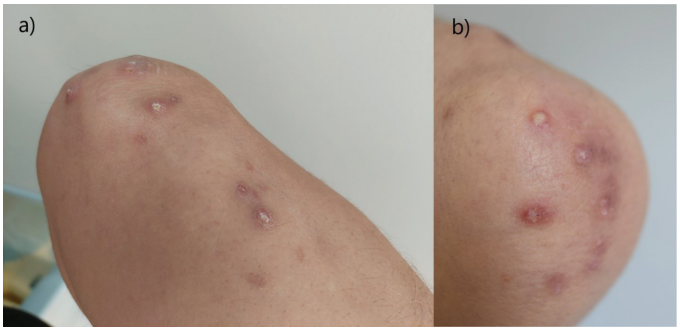

Figure 1 | (a) Typical clinical presentation of palisaded neutrophilic granulomatous dermatitis with multiple firm violaceous papules over the elbows with slightly hyperkeratotic surface; (b) note the yellowish discoloration when the lesion is stretched (the same is visible on diascopy).

An H&E stain of a biopsy specimen from a papule on the right elbow revealed the presence of palisading granulomas surrounding neutrophilic debris, mucin, and collagen throughout the dermis, also extending into the subcutaneous fat. In addition, transepidermal elimination of granulomas was also present (Fig. 2). Based on clinical and histopathological features, a diagnosis of PNGD was made. Despite the apparent causal relationship between axSpA and PNGD, and in particular due to a history of weight loss, extensive investigations to exclude other potential triggers for PNGD followed. All laboratory results—including complete blood count, biochemistry, urinalysis, lactate dehydrogenase, angiotensin convertase enzyme, rheumatoid factor, anti-nuclear antibody, extractable nuclear antigen, anti-dsDNA, C and P anti-neutrophil cytoplasmic antibody, complement C3 and C4, tumor markers, hematests, quantiferon test, serum protein electrophoresis, and serology for hepatitis B and C virus—were completely normal, negative, or nonreactive, except for mildly elevated leukocytes, C-reactive protein, and erythrocyte sedimentation rate. Abdominal ultrasound and chest X-ray were without pathological abnormalities.

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Magnetic resonance imaging of the sacroiliac joints showed subchondral sclerosis with slight bone marrow edema.

Topical betamethasone was initiated for PNGD. The patient was also referred to a rheumatologist, who prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), which did not have a satisfactory effect. Therefore, treatment with a biological drug from the group of tumor necrosis factor (TNF)-α inhibitors was indicated. Unfortunately, therapy was again refused by the patient. As a result, peroral methylprednisolone with gradual tapering was initiated. The doses were as follows: 16 mg a day for 2 weeks, followed by a reduction of 4 mg every 3 weeks. However, this tapering scheme was unsuccessful because the low back pain was under control only when the patient had been taking 16 mg of methylprednisolone per day, and so the patient never tried to reduce the dose below 12 mg daily. Moreover, at follow-up 3 months after the introduction of methylprednisolone, the inflammatory parameters increased slightly with additional signs of synovitis of the metacarpophalangeal and proximal interphalangeal joints of the right hand with dactylitis of the middle fingers as well as epicondylitis of the left elbow. The patient again had an episode of scleritis. There were still some firm violaceous papules on the elbows, whereas on the knees they regressed with residual post-inflammatory macules. Due to the progression of HLA-B27–negative axSpA, at the time of writing the patient finally agreed to re-treatment with a biological drug.

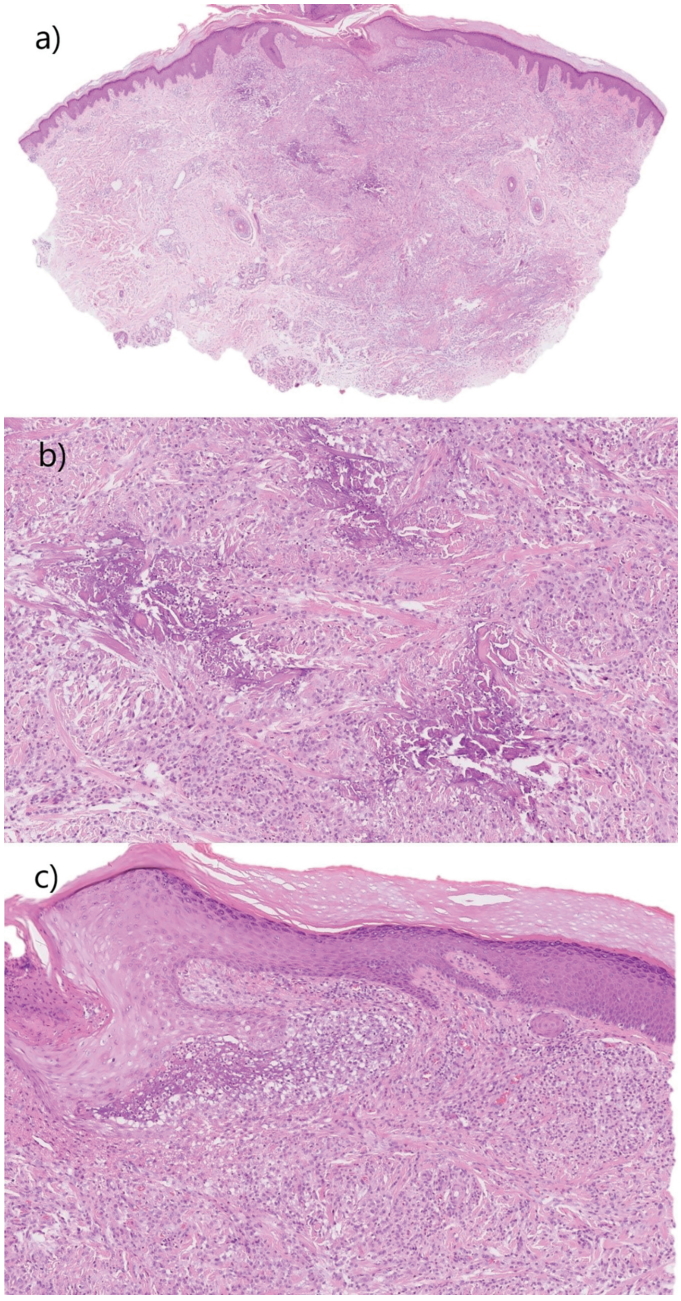

Figure 2 | Histology showing features of palisaded neutrophilic granulomatous dermatitis: (a, b) palisading granulomas surrounding neutrophilic debris, mucin, and collagen can be seen throughout the dermis and subcutaneous fat; (c) note transepidermal granuloma elimination (a–c, H&E, original magnification).

Discussion and literature review

Many other names have been used in the literature for PNGD, thus creating much unnecessary confusion. These names include *rheumatoid papules*, *eosinophilic granulomatosis with polyangiitis* (*Churg–Strauss granuloma*), and *cutaneous extravascular necrotizing granuloma* (1).

The pathogenesis of PNGD has not been completely elucidated. However, based on underlying systemic diseases with an immunoreactive nature and leukocytoclastic vasculitis sometimes present in early lesions, it is considered to be caused by the deposition of immune complexes in dermal vessels followed by complement activation, chronic inflammation, fibrosis, and granulomatous infiltrate (1, 4).

Clinically, PNGD typically manifests with multiple asymptomatic or rarely tender skin-colored, erythematous, or violaceous papules or nodules that may coalesce into plaques or annular configurations (5). They are located on the extensor extremities, especially the elbows, whereas disseminated lesions or lesions on the trunk, buttocks, and head are rare. Other morphologies reported are urticarial, linear, ulcerated, and necrotic (5–7).

Differential diagnosis of PNGD on clinical grounds is shown in Table 1 and includes frictional lichenoid dermatitis, acute febrile neutrophilic dermatosis (Sweet's syndrome), erythema elevatum et diutinum, and particularly some other cutaneous non-infectious granulomatous skin diseases, including granuloma annulare, cutaneous sarcoidosis, rheumatoid nodules, interstitial granulomatous dermatitis (IGD), and interstitial granulomatous drug reaction (IGDR). However, considerable overlap exists between clinical features and the histological picture in PNGD, IGD, and IGDR, suggesting a possible relationship between the three conditions. Therefore, the unifying term *reactive granulomatous dermatitis* has been proposed to encompass PNGD, IGD, and IGDR (1).

The diagnosis of PNGD is based on clinicopathological correlation. Histologic features of PNGD are diverse, depending on the stage of the lesions. Early forms are characterized by neutrophilic infiltrate, leukocytoclastic vasculitis, and collagen degeneration. As the lesions evolve, interstitial and/or palisaded granulomatous infiltrates surrounding leukocytoclastic debris and collagen degeneration can be seen, which was also evident in the patient presented (1). To aid in diagnosis, lesions typically become yellowish on diascopy (8).

PNGD is a reaction pattern that can occur a few years prior to diagnosis, concomitantly with or many years after numerous lymphoproliferative, autoimmune, and autoinflammatory diseases, including Hodgkin's lymphoma, non-Hodgkin's lymphoma, chronic myelomonocytic leukemia, ulcerative colitis, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, systemic vasculitides (i.e., microscopic polyangiitis and granulomatosis with polyangiitis), and Behçet's disease (4–7, 9–14). An association of PNGD with HLA-B27–negative axSpA has not been reported in the literature so far, making our case unique. There is only

one similar case of a woman with ankylosing spondylitis, rheumatoid arthritis, and a history of treatment with TNF-α inhibitors, which could also trigger PNGD as a paradoxical side effect (15–17). In addition to TNF-α inhibitors, PNGD can also be triggered by allopurinol and ledipasvir/sofosbuvir (18, 19). However, the last association of PNGD with antiviral drugs is questionable because the hepatitis C in that case report could also have been a cause of PNGD (19). Because of many possible triggers of PNGD, patients' history, physical examination, extensive laboratory tests, and age-appropriate malignancy screening are mandatory to exclude any underlying disease. In the case of idiopathic PNGD, it is advised to follow-up a patient regularly (6). We excluded other potential PNGD triggers and confirmed a causal relationship with axSpA in our patient. Weight loss and mildly elevated inflammatory parameters were thus caused by a relapse of axSpA.

It is primarily important to treat the causative disease when PNGD manifests. However, PNGD-specific treatment options are dapsone and topical, intralesional, and systemic corticosteroids, whereas NSAIDs, methotrexate, cyclosporine, cyclophosphamide, hydroxychloroquine, colchicine, and TNF-α inhibitors have been prescribed in the literature because of underlying diseases and have shown various success in remitting skin lesions. Regression of skin changes is spontaneous in 20% (1). In a case series involving 52 patients with either PNGD (11.6%) or IGD (88.4%), cutaneous lesions completely disappeared in 76.9% of patients, but it was not specified how many of these received treatment (20). However, in our case PNGD only partially regressed after systemic and local corticosteroid therapy. Moreover, axSpA progressed despite methylprednisolone treatment. Therefore, treatment with adalimumab was initiated.

To conclude, PNGD is a rare granulomatous reaction pattern that can occur concomitantly with several systemic disorders that must be excluded during the patient's diagnostic workup. Because PNGD can manifest before systemic disease occurrence, in the absence of triggers, regular patient monitoring is recommended.

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Table 1 | **Differential diagnosis of palisaded neutrophilic granulomatous dermatitis with references.**

	Palisaded neutrophilic granulomatous dermatitis (1)	Interstitial granulomatous dermatitis (1)	Interstitial granulomatous drug reaction (1)	Granuloma annulare (8)	Rheumatoid nodules (8)	Cutaneous sarcoidosis (21)	Sweet's syndrome or acute febrile neutrophilic dermatosis (22)	Frictional lichenoid dermatitis (23)	Erythema elevatum et diutinum (24)
Patient age	More common in adults, F:M = 3:1	More common in adults, F:M = 3:1	More common in adults	Younger patients, 2/3 under 30 years old, F:M = 1:2	15–20% of adult patients with RA	Bimodal age distribution with two peaks in 30s and 50s	Most frequently adults 30–60 years, F > M	Usually children and young adults	More common in adults, M > F
Clinical features	Typically multiple skin-colored, erythematous, or violaceous papules or nodules that may coalesce into plaques or annular configurations	Erythematous to violaceous patches or plaques, papules and subcutaneous nodules also possible	Erythematous to violaceous, often annular plaques, also subcutaneous nodules, erythema nodosum-like lesions	Localized form in 75%, erythematous flesh-colored annular plaques and within them small firm papules, rarely subcutaneous nodules	Deep dermo-hypodermic nodules that are adherent to periosteum	Nonspecific: erythema nodosum, specific: red, brown, or violaceous maculopapular lesions, plaques, subcutaneous nodules, lupus pernio, scars, etc.	Abrupt onset of erythematous, edematous plaques or nodules with possible targetoid appearance, rarely vesiculobullous, subcutaneous or necrotizing lesions	Lichenoid grouped papules	Violaceous to red-brown papules, nodules
Location of the lesions	Extensor extremities, especially elbows, rarely trunk, buttocks, head	Proximal trunk and proximal limbs, rarely proximal thighs, buttocks, abdomen	Proximal thighs, proximal trunk, inner arms, rarely scalp, face	Back of the hands, feet, rarely face, disseminated form on the trunk and extremities	Extensor parts of the large joints or at pressure points (i.e., elbows), even above the tendons	Papules often on the face, plaques on extensor surfaces of the extremities, face, back, buttocks	Head, neck, extremities	Extensor surfaces of the extremities, especially elbows, knees, rarely face	Extensor surfaces of joints, legs, head/ears, rarely trunk, buttocks
Symptoms	Usually none, rarely tender	Usually none	Usually none	Usually none	Usually none, when ulcerating, possible pain or discomfort	Cutaneous lesions are usually asymptomatic, numerous possible extracutaneous manifestations	Lesions are painful, concomitant constitutional symptoms	Usually none, pruritus in 33%	Usually asymptomatic, possibly pruritic, painful
Laboratory findings	Depending on the underlying systemic disorders	Depending on the underlying systemic disorders	–	Depending on the underlying systemic disorders	RF and anti-CCP more commonly positive	Anemia, leukopenia, lymphopenia, hypercalcemia, elevated liver and kidney function tests, ESR, CRP, ACE	Leukocytosis, elevated CRP and ESR	–	IgA ANCA in 77.8%, IgG ANCA in 22.2%
Concomitant autoimmune and autoinflammatory diseases	UC, SLE, RA, axSpA, sarcoidosis, systemic vasculitides (i.e., microscopic polyangiitis, granulomatosis with polyangiitis), Behçet's disease	SLE, RA, seronegative arthritis, AI hepatitis, uveitis, chronic demyelinating polyneuropathy, AI thyroiditis, antiphospholipid antibody syndrome, vitiligo	–	Sarcoidosis, AI thyroiditis, AI hepatitis, primary biliary cholangitis	Associated with RA and is a clinical predictor of its extraarticular involvement	–	IBD, erythema nodosum, sarcoidosis, SLE, relapsing polychondritis, vasculitis, PG, multifocal sterile osteomyelitis, Behcet's disease, AS, RA, SCLE, AI thyroiditis, AI hepatitis, MS, AI cholangitis, DM, etc.	–	RA, relapsing polychondritis, celiac disease, SLE, IBD, PG, etc.
Concomitant lympho-proliferative disorders	Hodgkin's lymphoma, non-Hodgkin's lymphoma, CML	Lymphoma, MDS, myelodysplasia with leukemic progression, leukemia	–	Possible in disseminated form	–	–	MDS, AML, CML, multiple myeloma, hairy cell leukemia, etc.	–	Paraproteinemias, lymphoma, multiple myeloma, MDS

Table 1 | **Continued.**

	Palisaded neutrophilic granulomatous dermatitis (1)	Interstitial granulomatous dermatitis (1)	Interstitial granulomatous drug reaction (1)	Granuloma annulare (8)	Rheumatoid nodules (8)	Cutaneous sarcoidosis (21)	Sweet's syndrome or acute febrile neutrophilic dermatosis (22)	Frictional lichenoid dermatitis (23)	Erythema elevatum et diutinum (24)
Concomitant solid organ malignancies	–	Uncommon (breast, endometrial, lung, esophageal)	–	Possible in disseminated form	–	–	Breast, prostate, oral, cervical, gastric, lung cancer, melanoma, etc.	–	Lung, breast
Concomitant infections	HC	Pulmonary coccidiomycosis, *B. burgdorferi* infection	–	VZV	–	–	RTI, GI, non-tuberculosis mycobacteria, HIV, TB, UTI, HC, HB, VZV, CMV, bacterial endocarditis	–	HIV, TB, HB, HC, streptococcal infection, rarely others
Other possible underlying triggers	–	Diabetes, pulmonary silicosis	–	Diabetes, dyslipidemia	–	–	Pregnancy, trauma, radiation therapy	May be a minor morphologic variant of AD, but possibly not; UV light	Diabetes
Drug-induced variant	TNF-α inhibitors, allopurinol, ledipasvir/ sofosbuvir	TNF-α inhibitors, furosemide, ACEi	CCB, BB, lipid-lowering agents, ACEi, brompheniramine, ranitidine, bupropion, furosemide, trastuzumab, thalidomide, allopurinol	Vaccines, allopurinol, topiramate, gold, TNF-α inhibitors, IFN-α	–	–	G-CSF, azathioprine, all-trans retinoid acid, hydralazine, bortezomib, TMP-SMX, tetracyclines, NSAID, vaccination, etc.	–	–
Histology	Early lesions: neutrophilic infiltrate, leukocytoclastic vasculitis, and collagen degeneration; older lesions: interstitial and/or palisaded granulomatous infiltrates surrounding collagen degeneration	Interstitial histiocytes surrounding foci of degenerated collagen that can lead to clefting named "floating sign", the histiocytes may form small granulomas, vasculitis is absent, mucin is generally absent	Interface dermatitis, diffuse interstitial histiocytes with granulomas, surrounding foci of degenerated collagen, prominent tissue eosinophilia	Interstitial and palisaded granulomatous infiltrate, necrobiosis, mucin deposition	Palisaded granulomas with central massive necrosis with fibrin deposits	Specific manifestations: naked or sarcoidal non-caseous granulomas, commonly multinucleated giant cells within granulomas; non-specific: reactive process	Diffuse dermal neutrophilic infiltrate, usually with superficial dermal edema, sometimes also vasculitis	Nonspecific perivascular lymphocytic infiltrate	Early lesions: leukocytoclastic vasculitis; late lesions: perivascular fibrosis, extracellular lipid deposits

ACE = angiotensine convertase enzyme, ACEi = angiotensine convertase enzyme inhibitors, AD = atopic dermatitis, AI = autoimmune, AML = acute myeloid leukemia, ANCA = anti-neutrophil cytoplasmic antibody, anti-CCP = cyclic citrullinated peptide antibody, axSpA = axial spondyloarthritis, BB = beta adrenergic blockers, CCB = calcium channel blockers, CML = chronic myelogenous leukemia, CMV = cytomegalovirus, CRP = C-reactive protein, DM = dermatomyositis, ESR = erythrocyte sedimentation rate, F = female, GI = gastrointestinal infection, G-CSF = granulocyte colony-stimulating factor, HB = hepatitis B, HC = hepatitis C, HIV = human immunodeficiency virus, IBD = inflammatory bowel disease, IFN = interferon, Ig = immunoglobulin, M = male, MDS = myelodysplastic syndrome, MS = multiple sclerosis, NSAID = non-steroidal anti-inflammatory drug, PG = pyoderma gangrenosum, RA = rheumatoid arthritis, RF = rheumatoid factor, RTI = respiratory tract infection, SCLE = subacute cutaneous lupus erythematosus, SLE = systemic lupus erythematosus, TB = tuberculosis, TMP-SMX = trimethoprim/sulfamethoxazole, TNF = tumor necrosis factor, UC = ulcerous colitis, UV = ultraviolet, UTI = urogenital tract infection, VZV = varicella zoster virus.