Palisaded Neutrophilic and Granulomatous Dermatitis Associated with Lupus Profundus: A Case Report and Literature Review

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ABSTRACT:
Palisaded neutrophilic granulomatous dermatitis (PNGD) is an uncommon histological pattern of reactive granulomatous dermatitis, characterized by distinctive cutaneous manifestations. The primary histological features include localized collagen degeneration and palisading lymphohistiocytic infiltration, with or without vasculitis and mucin deposition. Although its etiology remains elusive, PNGD is frequently associated with systemic underlying conditions, such as autoimmune connective tissue disorders, lymphoproliferative diseases, and infections. It can precede the onset of underlying disorders or develop concurrently. Furthermore, certain medications can precipitate this condition. This report discusses the case of a 63-year-old woman who exhibited numerous painful erythematous papules and plaques on both extensors of the lower extremities, which were histologically consistent with palisaded neutrophilic and granulomatous dermatitis. The patient demonstrated improvement following eight months of dapsone treatment. Upon discontinuation of dapsone for two months, new skin lesions recurred on both knees, accompanied by the onset of non-scarring alopecia in the frontal and right temporal areas. A skin biopsy from the frontal area of the scalp revealed lupus profundus. The patient was subsequently administered dapsone and hydroxychloroquine, resulting in a favorable clinical response.

Key words: Palisaded Neutrophilic Granulomatous Dermatitis, Lupus Profundus, Leukocytoclastic Vasculitis, Neutrophilic Skin Disease, Autoimmune Connective Tissue Disease

Introduction

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is histopathologically characterized by unique granulomatous inflammation patterns with or without vasculitis. The diagnosis of PNGD relies primarily on distinctive histopathological characteristics, with the condition exhibiting a diverse range of clinical manifestations. The precise pathogenesis of PNGD remains incompletely elucidated, despite an increased incidence of reported cases. It is predominantly associated with systemic diseases characterized by immune-reactive conditions, such as systemic lupus erythematosus. In these conditions, immune complexes within the cutaneous vasculature are hypothesized to be the initiating factor. This elicits the activation of complement systems as well as neutrophils, which subsequently induce dermal collagen degradation, eventually leading to granulomatous formations.

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Received: 30 March 2024 Revised: 21 April 2025 Accepted: 8 July 2025

Case presentation

A case of a 63-year-old female with underlying essential hypertension, primarily presented with numerous non-blanchable erythematous edematous papules on both lower extremities for ten days. The patient exhibited no constitutional symptoms, gastrointestinal symptoms, or arthralgia. Dermatological examination revealed bilateral well-defined non-blanchable edematous erythematous papules and plaques with crusted ulcers on both lower legs and feet. (Figure 1) No oral ulcer was observed. A punch biopsy was performed, indicating leukocytoclastic vasculitis. The patient was given oral prednisolone, and topical betamethasone valerate cream was applied, resulting in a partial remission.

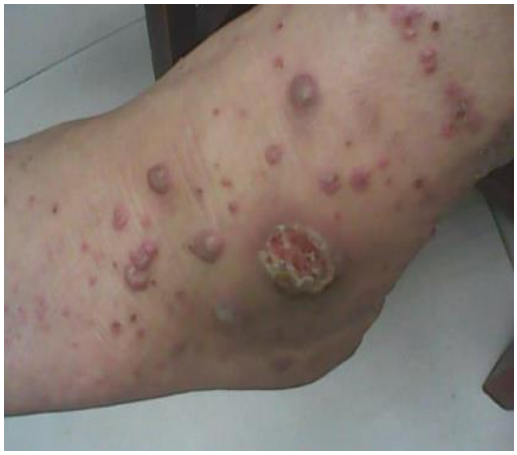

Figure 1 Bilateral well-defined non-blanchable erythematous edematous papules and plaques with crusted ulcers on both lower legs and feet

Eight months later, the patient presented with numerous painful erythematous papules located on both lower legs and soles. Consequently, the patient was treated with oral prednisolone 30 mg/day, colchicine, and indomethacin, leading to marked clinical improvement. Following the gradual tapering of prednisolone, several painful erythematous to purplish plaques with scales appeared on both lower extremities. (Figure 2) A skin biopsy from the left knee revealed palisaded neutrophilic and granulomatous dermatitis. (Figure 3) Dapsone was prescribed to the patient for six months, achieving a complete resolution.

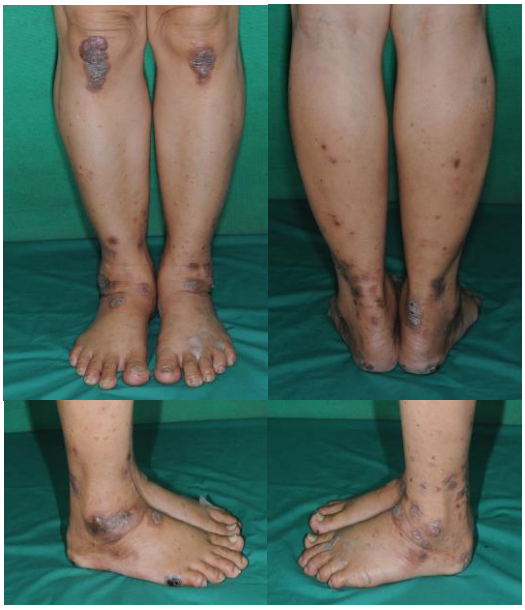

Figure 2 Multiple painful scaly erythematous to violaceous infiltrative papules and plaques developed on both knees, lower legs, and feet

Two months after discontinuing medication, the patient developed new lesions on both knees, along with alopecia on the scalp. (Figure 4) There were no malar rash, photosensitivity, or oral ulcers. There were no clinical signs of arthritis or serositis. Punch biopsy from the left temporal region demonstrated superficial and deep perivascular as well as periadnexal infiltration with lymphocytes and plasma cells in the dermis. Additionally, fibrosis and sclerosis were noted in the reticular dermis. Focal areas of fat necrosis accompanied by hyalinization and hemorrhage were identified. (Figure 5) Direct immunohistochemistry showed weakly positive C3 in a granular pattern at the dermal-epidermal junction. Based on clinical and histopathological findings, the patient was diagnosed with lupus profundus.

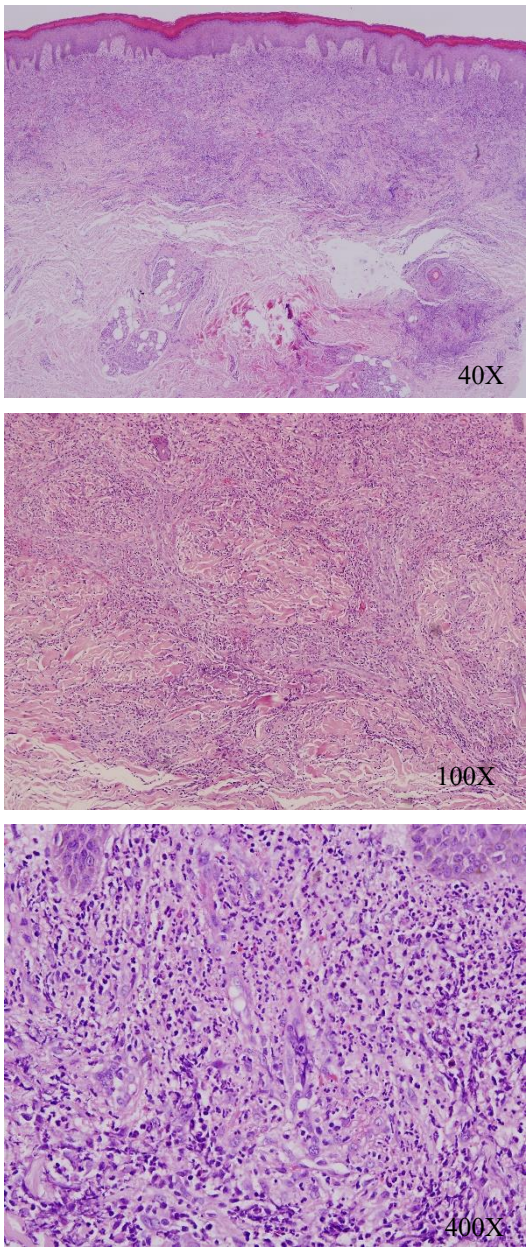

Figure 3 Palisading granulomatous formation with neutrophil infiltration (H&E, 40X, 100X and 400X, respectively)

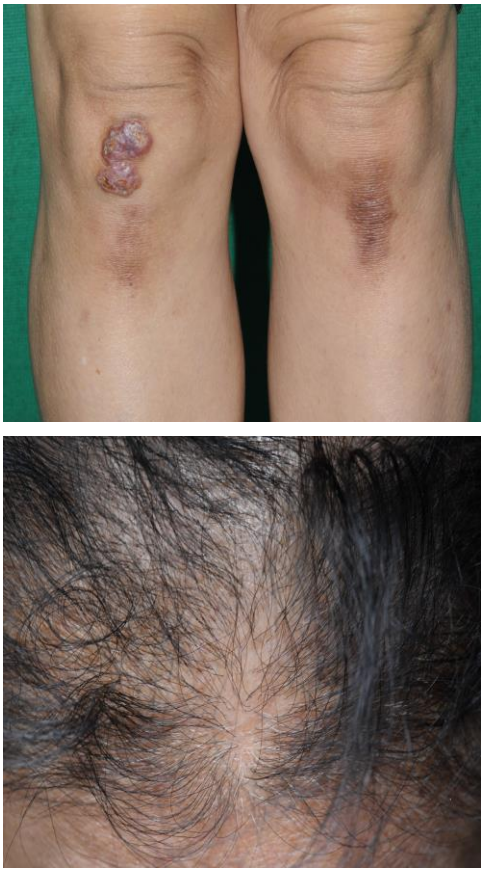

Figure 4 A. New scaly erythematous to violaceous plaques on both knees **B.** Non-scarring alopecia on frontal and both temporal areas

Complete blood count with differential was within normal limits. Antinuclear antibody testing yielded positive results at a titer of 1:160 with a homogeneous pattern. Rheumatoid factor was also positive at a titer of 1:32. However, other autoimmunity panel tests, including anti-dsDNA antibodies, anti-Smith antibody, antiphospholipid antibodies, complement, and antineutrophilic cytoplasmic antibodies were negative. According to the clinical manifestation and laboratory investigations, the patient was diagnosed with palisaded neutrophilic and granulomatous dermatitis associated with lupus profundus. A daily

combination of hydroxychloroquine 100 mg and dapsone 100 mg were prescribed, resulting in a favorable clinical response.

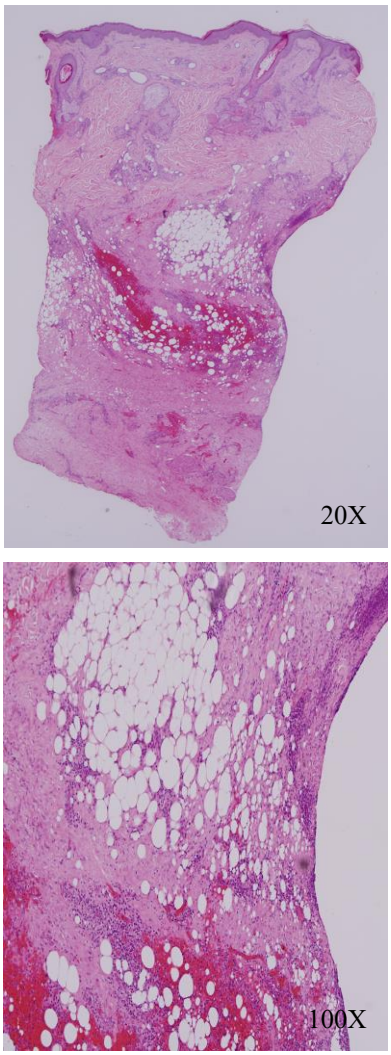

Figure 5 Superficial and deep perivascular and periadnexal infiltration of lymphocytes and plasma cells in the dermis, with focal fat necrosis, hyalinization and hemorrhage (H&E, 20X and 100X, respectively)

Discussion

Palisaded neutrophilic and granulomatous dermatitis (PNGD) represents a cutaneous reaction pattern linked to various systemic causes. PNGD exhibits a broad spectrum of clinical appearances and histopathological subtypes[1]. Systemic conditions commonly associated with PNGD comprise autoimmune diseases, with systemic lupus erythematosus being particularly prevalent. Other triggers include inflammatory arthritis, lymphoproliferative disorders, and less commonly, infections or drugs. Among medications known to induce PNGD are TNF-inhibitors and allopurinol[2].

While the precise etiology of this disease remains incompletely understood, its association with autoimmune-related systemic conditions suggests that immune complex deposition may play a role in initiating the pathological process. Several hypotheses have been advanced to explain the disease's etiopathogenesis, including dysregulated neutrophil activity, vasculitis affecting small vessels, and a delayed-type hypersensitivity response. These theories contribute to our evolving understanding of the disease's underlying mechanisms, though further research is needed to fully elucidate its pathogenesis[3].

Typical skin manifestations appear as symmetrical, painful skin-colored to erythematous papules, plaques, or nodules, with an umbilicated or crusted appearance. These lesions primarily occur on the extensor surfaces of the extremities. The mucous membranes are generally unaffected. PNGD is more prevalent in adults, with a female predominance at an approximate 3:1 ratio[3,4]. The histological findings vary based on the lesional stage, ranging from clear leukocytoclastic vasculitis to neutrophilic granulomatous inflammation. In early stages, lesions may show neutrophil infiltration, with or without leukocytoclastic vasculitis and degraded collagen. Well-established lesions display palisading granulomas with trapped collagen and neutrophil infiltrates[5].

According to PNGD associated with systemic disorders, a comprehensive diagnostic approach is necessary. This includes performing serologic tests for all patients, encompassing rheumatoid factor, cyclic citrullinated peptide, antinuclear antibodies (ANA), and antineutrophilic cytoplasmic antibodies, either proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). A complete blood count with differential should also be conducted. Radiological assessments, particularly chest imaging, are crucial. Furthermore, evaluating for paraproteinemia is important when suspected. Depending on the specific systemic manifestations presented by individual patients, additional targeted investigations may be required[6,7].

Regarding management strategies, the fundamental approach involves identifying the underlying disorder and customizing therapeutic interventions to address it effectively. The extant scientific literature predominantly emphasizes therapeutic strategies targeting the management of the underlying systemic condition. These approaches primarily involve the administration of anti-inflammatory agents, including systemic corticosteroids, nonsteroidal anti-inflammatory drugs, and colchicine. Additionally, immunosuppressive medications such as methotrexate, cyclosporine, and cyclophosphamide are considered preferred treatment options. Notably, there exists documentation regarding the utilization of hydroxychloroquine or tumor necrosis factor (TNF) inhibitors, specifically etanercept and infliximab.

Cutaneous manifestations necessitate specific interventions, such as intralesional steroid administration, dapsone, and systemic corticosteroids. Although topical medications generally demonstrate limited efficacy, some reports of improvement exist. Spontaneous resolution occurs in approximately 20% of cases, occasionally within a period as brief as 1 week[8,9].

This case exhibited an intriguing clinical manifestation. Initially, the patient exhibited clinical and histopathological features consistent with leukocytoclastic vasculitis. Subsequently, several painful erythematous to purplish plaques developed on both extensor surface of lower extremities, with histopathological findings indicating palisaded neutrophilic and granulomatous dermatitis.

Initially, PNGD may present with clinical manifestations that resemble those of leukocytoclastic vasculitis. However, histopathological and immunopathological characteristics facilitate their differentiation. PNGD is characterized as a granulomatous process that generally lacks true vascular destruction, whereas leukocytoclastic vasculitis is identified as neutrophilic vasculitis. Furthermore, leukocytoclastic vasculitis is associated with immune deposits in the vessel walls, in contrast to PNGD, which does not exhibit significant immune complex deposition upon direct immunofluorescence analysis.

Upon establishing a diagnosis of PNGD, it is imperative to assess patients for underlying systemic diseases. Despite initial tests failing to reveal any systemic disease involvement in this case, the emergence of new scalp lesions was later confirmed through histological examination to be consistent with lupus profundus. Photoprotection, topical corticosteroids and antimalarials remain the primary treatments for cutaneous lupus erythematosus. Alternative systemic medications include methotrexate, oral retinoids, dapsone, and thalidomide, among others. As our understanding of the disease's pathogenesis has advanced, new therapeutic approaches have been developed, such as belimumab targeting B-cells, interferon receptor blockers, and JAK inhibitors, which focus on the various identified immune activation pathways. Our patient received

treatment with a combination of hydroxychloroquine and dapsone, resulting in substantial improvement.

Based on literature reviews, palisaded neutrophilic granulomatous dermatitis exhibits associations not only with systemic lupus erythematosus, but also with cutaneous lupus erythematosus, particularly discoid lupus erythematosus, as reported in several cases[10]. To the extent of current medical knowledge, this case represents the first documented instance of PNGD in conjunction with lupus profundus. This finding illuminates an additional rare manifestation of cutaneous lupus erythematosus linked to PNGD, which medical practitioners should be cognizant of in their diagnostic considerations.

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