Palisaded neutrophilic and granulomatous dermatitis in rheumatoid arthritis: A case report and a review of literature.

Noppanun Chalermroj MD,
Kumutnart Chanprapaph MD,
Silada Kanokrungsee MD.

ABSTRACT:

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DIVISION OF DERMATOLOGY, DEPARTMENT OF MEDICINE, FACULTY OF MEDICINE RAMATHIBODI HOSPITAL, MAHIDOL UNIVERSITY, BANGKOK, THAILAND.

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is a rare dermatologic condition which shows various clinical and histopathological features. The classic lesions are flesh-colored to erythematous papules, with smooth, crusted or umbilicated surfaces, appearing in a symmetrical distribution on the extensor extremities. However, other locations including trunk, face and scalp have been reported. PNGD can present as pink to violaceus papules, plaques, nodules or urticarial plaques. Some of which show a linear or annular configuration. PNGD usually presents in patients with underlying diseases, such as connective tissue diseases, arthritides, malignancies and patients with administration of some medications. Diagnosis of PNGD depends mainly on histopathology, which is varied depending on the lesion's age or associated underlying diseases. Because of the recurrence or presence of PNGD usually coincides with the aggravation of underlying diseases. The main principle of PNGD management is to identify the underlying disease and target therapy to control that disorder. We report a case of an 87-year-old woman, with rheumatoid arthritis, who presented with widespread scaly erythematous papules, some

From: Division of Dermatology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University
Corresponding author: Noppanun Chalermroj MD., email: noppachalerm@gmail.com

coalescing into plaques, on the entire left leg. Histopathology showed perivascular, interstitial and nodular infiltrate of lymphocytes, histiocytes, multinucleated giant cells admixed with nuclear dust and fibrinoid material throughout the dermis**.** She was diagnosed as having palisaded neutrophilic and granulomatous dermatitis. Initially, she was treated with topical corticosteroid but the lesions progressed to her face. Cyclosporine had been therefore started and given for few weeks; however, she unfortunately developed severe hypertension. Given this, cyclosporine was discontinued and switched to oral cyclophosphamide in combination with prednisolone. Herein, we present the unusual manifestation of PNGD with asymmetrical skin involvement in a patient with rheumatoid arthritis.

Key words: cyclosporine, cyclophosphamide, Palisaded neutrophilic and granulomatous dermatitis, rheumatoid arthritis

บทคัดย่อ:

นพนันท์ เฉลิมโรจน์ กุมุทนาท จันทร์ระภาพ ศิลดา กนกรังสี รายงานผู้ป่วยโรค PALISADED NEUTROPHILIC AND GRANULOMATOUS DERMATITIS IN RHEUMATOID ARTHRITIS

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สาขาวิชาตจวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

Palisaded neutrophilic and granulomatous dermatitis เป็นโรคทางผิวหนังที่พบได้น้อย โดยมีลักษณะอาการแสดงของโรคและผลทางพยาธิวิทยาที่มีความหลากหลาย ตำแหน่งที่พบบ่อยคือบริเวณระยางค์ โดยพบแบบสมมาตร และพบพื้นผิวของผื่นได้ทั้งแบบเรียบ, เป็นแผล หรือมีรอยบุ๋มตรงกลาง นอกจากนั้นสามารถพบลักษณะผื่นที่เป็นลักษณะตุ่มนูนสีชมพูม่วง, ตุ่มนูนเป็นแนวยาว ไปจนถึงตุ่มที่ลักษณะคล้ายลมพิษ โดยส่วนใหญ่มักพบในผู้ป่วยที่มีโรคประจำตัวกลุ่มconnective tissue disease, โรคข้ออักเสบ, โรคมะเร็งและยาบางชนิด เป็นต้น การวินิจฉัยต้องอาศัยลักษณะทางพยาธิวิทยาเป็นสำคัญ ซึ่งแปรผันตามระยะของผื่นและโรคร่วมของผู้ป่วย เนื่องจากการเกิดขึ้นของผื่นมักสัมพันธ์กับการกำเริบของโรคทางกาย ดังนั้นการรักษาหลักจึงมุ่งเน้นที่การหาโรคร่วมทางกายและควบคุมการกำเริบของโรคนั้น รายงานนี้ถือเป็นการนำเสนอผู้ป่วยหญิงสูงวัยที่มีโรคประจำตัวเป็นrheumatoid arthritis มาด้วยผื่นคันบริเวณขาข้างซ้าย ได้รับการวินิจฉัยว่าเป็น Palisaded neutrophilic and granulomatous dermatitis โดยช่วงแรกผู้ป่วยได้รับการรักษาด้วยยาทาเสตียรอยด์แต่ผื่นเพิ่มปริมาณมากขึ้นบริเวณใบหน้า จึงได้เริ่มการรักษาด้วย cyclosporine แต่มีภาวะแทรกซ้อนความดันโลหิตสูงจึงได้ทำการหยุดยาและเปลี่ยนการรักษาเป็น cyclophosphamide ร่วมกับ prednisolone รายงานนี้เป็นการนำเสนอการแสดงของโรคที่พบได้น้อยในปัจจุบัน

คำสำคัญ: cyclosporine, cyclophosphamide,พาลิเสดเดด นิวโทฟิลิค แอนด์ แกรนูโลมาตัส เดอมาไททิส, รูมาตอยด์

Case report

An 87-year-old Thai female with hypertension, dyslipidemia, osteoporosis, old cerebrovascular disease, and a 3-year history of rheumatoid arthritis (RA) which had been diagnosed due to (i) the presence of polyarthritis of both wrists, elbows, knees, and ankles, (ii) high CRP and (iii) high titer of rheumatoid factor/anti-CCP. She presented to the dermatology clinic with a widespread pruritic erythematous eruption on the left extremity of 2-month duration (Fig.1). The patient has been taking multiple medications including leflunomide 20 mg daily, methotrexate 15 mg weekly, and hydroxychloroquine 200 mg daily for 3 years. The patient's review of symptoms still had neck arthralgia and high inflammatory markers. She denied any of new medication.

Dermatologic examination revealed multiple widespread scaly erythematous papules, some coalescing into plaques on the entire left leg. Since various differential diagnoses including contact dermatitis, nummular dermatitis, chronic infection, mycosis fungoides, and drug eruption were considered, a 4-mm punch biopsy was performed to aid in the diagnosis of the eruption. The hematoxylin and eosin-stained biopsy showed perivascular, interstitial and nodular infiltrate of lymphocytes, histiocytes, multinucleated giant cells admixed with nuclear dust and fibrinoid material throughout the dermis. (Fig.2A,2B). All special stains (Fite, AFB, GMS) were negative. Skin tissue culture for aerobic bacteria, mycobacteria and fungus were negative. Correlating the clinical manifestation, histopathologic findings, and the presence of RA, the diagnosis of PNGD was made.

Laboratory evaluations including complete blood count, ANA, P-ANCA and C-ANCA were unremarkable except for rising C-reactive protein and ESR (84 mm/hr). Initially, she was treated with topical corticosteroid but the lesions did not improve. She developed new lesions that extended to the face, and also reported pruritus (Fig.3). Cyclosporine was chosen due to its rapid onset of action and started at 100mg/day with titrating to 150 mg/day. Although the lesions responded dramatically, she unfortunately developed severe hypertension. Because of this, cyclosporine was withdrawn and switched to cyclophosphamide 100 mg/week in combination with prednisolone 10 mg/day. After 7-month administration, she has currently achieved satisfactory improvement.

Discussion

Rheumatoid arthritis is a chronic multisystem disease of unknown origin, characterized by polyarthritis and a broad spectrum of extraarticular manifestations. Regarding dermatologic manifestations in RA, rheumatoid nodules are most frequently observed. A rather uncommon cutaneous manifestation; however,

is the development of palisaded neutrophilic and granulomatous dermatitis (PNGD) that shows a broad clinical and histopathological spectrum.[1]

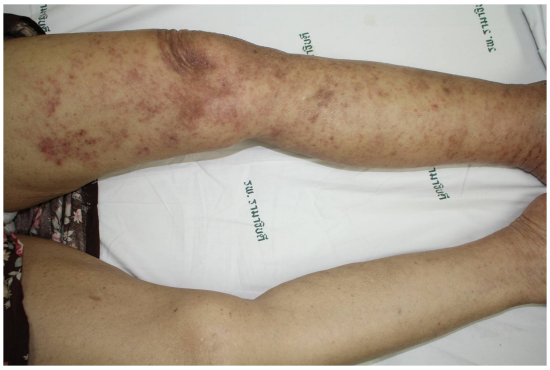

Figure 1 Multiple pruritic scaly erythematous papules and plaques on the left lower extremity

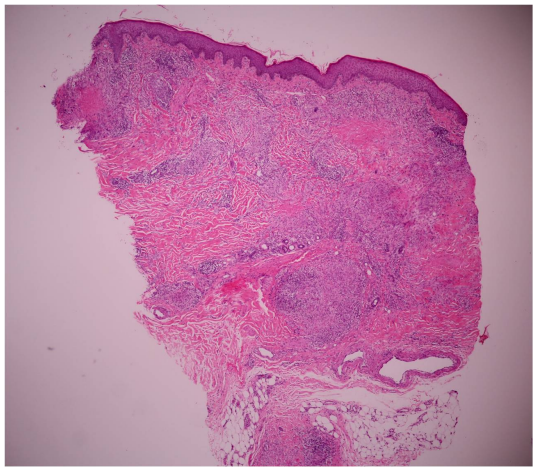

Figure 2A H&E, original magnification X 40

Tissue biopsy showing perivascular, interstitial and nodular infiltrate of lymphocytes, histiocytes, multinucleated giant cells admixed with nuclear dust and fibrinoid material throughout the dermis.

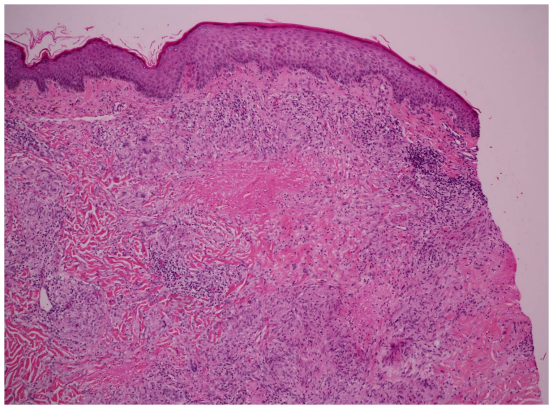

Figure 2B H&E, original magnification X 100

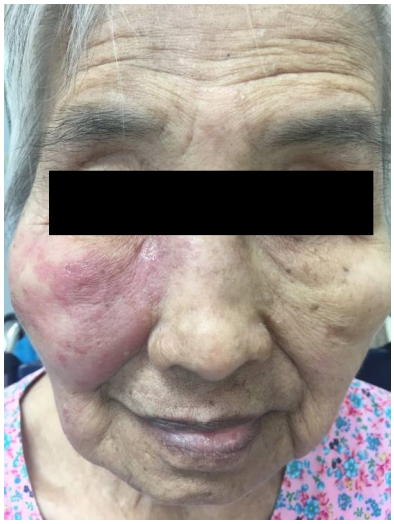

Figure 3 Multiple pruritic scaly erythematous papules and plaques on the face

PNGD is an uncommon condition that has variable clinical manifestations and histopathological features. It is usually associated with systemic diseases including connective tissue diseases (lupus, vasculitis, etc.), arthritides (rheumatoid arthritis, other inflammatory and reactive arthritides), malignancies (especially hematologic malignancy), and some medications

(TNF inhibitors, allopurinol).[2] However, previous cases with no underlying systemic diseases have been reported.[3] Recently, a literature reporting a man with hypercalcemia possibly secondary to PNGD has been published.[4]

PNGD was first described in 1965 by Dykman et al.[5]They reported 2 cases of patients with RA who developed linear cords on the lateral trunk. Later, several authors described this entity in many terms including Churg–Strauss granuloma, cutaneous extravascular necrotizing granuloma, rheumatoid papules, Winkelmann granuloma, and interstitial granulomatous dermatitis with arthritis.

In 1994, Chu et al[6] proposed the unifying term PNGD to encompass the spectrum of changes found in this disease represents merely an evolution of immune complex–mediated changes from leukocytoclastic vasculitis in early lesions, to palisaded granulomas in fully developed lesions, and finally to fibrosis in late lesions.

Patients of all ages can develop PNGD, although reports in childhood are rare. Women are affected more frequently than men (approximately 3:1 ratio), likely owing to the systemic diseases associated.[7]

The classic lesions are flesh-colored to erythematous papules, with smooth, crusted or umbilicated surfaces, appearing in a symmetrical distribution on the extensor extremities. However, other locations including trunk, face and scalp have been reported.[7,8] PNGD can present as pink to violaceus papules, plaques, nodules or urticarial plaques. Some of which show a linear or annular configuration. Early lesions are urticaria-like annular plaques, or may have a livedoid appearance. In later stages, the lesions become more infiltrative and pleomorphic (e.g. violaceous annular plaques, waxy papules, painful subcutaneous nodules, indurated linear bands etc.). Finally, fibrosis was observed.[9]

The etiology of the disease is unknown. Theories include abnormal neutrophil activation, circulating immune complex deposition[3], a delayed-type hypersensitivity reaction[10],or a low grade small vessel vasculitis.

PNGD has variable histopathological features, possibly depending on the lesion's age or associated underlying diseases. Early lesions may display intense neutrophilic inflammation, karyorrhectic debris, and frank leukocytoclastic vasculitis which typically have more neutrophils, nuclear dust, and fibrinoid change than in pure vasculitis. In evolving phase, there are piecemeal areas of collagen degeneration and palisades of histiocytes and small granulomas, finally accompanied by areas of fibrosis. Generally, we can distinguish PNGD from interstitial granulomatous dermatitis (IGD) by the presence of vasculitis and from granuloma annulare by

containing less mucin and more intense neutrophilic infiltrate and nuclear debris.[6,9,11,12]

Patients with PNGD should be evaluated for underlying internal systemic diseases. The recurrence or presence of PNGD usually coincides with the aggravation of underlying diseases. All patients warrant serologic tests, including antinuclear antibody, antineutrophilic cytoplasmic antibodies, rheumatoid factor, cyclic citrullinated peptide, complete blood count with differential, and chest radiography.

In general approximately 20% of cases may resolve spontaneously. The main principle of PNGD management is to identify the underlying disease and target therapy to control that disorder. Therefore most treatments reported in the literature are aimed at controlling the underlying systemic diseases (e.g., nonsteroidal anti-inflammatory drugs, colchicine, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, systemic corticosteroids, etanercept, infliximab, etc.).[10,13] PNGD-specific treatments include intralesional triamcinolone, dapsone, and systemic corticosteroids.[14,15] Generally, topical medications are not effective although rare reports note improvement.

In conclusion, the differential diagnosis of PNGD should be considered in all patients with a history of collagen vascular disease and/or auto-immune disorders who present with papular eruptions on the extremities. If the rash persists, a biopsy should be taken to confirm a presumptive diagnosis.

In summary, we report a case of PNGD involving in an asymmetrical fashion that occurred in an elderly woman with a history of RA who presented with widespread erythematous scaly papules, some coalescing into plaques on the entire left leg. She was initially treated with topical corticosteroid but the lesions did not improve. She developed new lesions that extended to her face. Therefore, cyclosporine was prescribed to control the lesions. Although satisfactory improvement was observed, cyclosporine was then discontinued due to severe hypertension. The lesions are currently well-controlled by the combination of oral cyclophosphamide and prednisolone.

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