

Palisaded Neutrophilic and Granulomatous Dermatitis/ Interstitial Granulomatous Dermatitis Overlap: A Striking Clinical and Histologic Presentation With “Burning Rope Sign” and Subsequent Mirror-Image Contralateral Recurrence

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Abstract: Palisaded neutrophilic and granulomatous dermatitis and interstitial granulomatous dermatitis are uncommon granulomatous dermatoses that often arise in association with rheumatoid arthritis. These 2 entities have overlapping features and may exist on a spectrum. We report an intriguing case of a 53-year-old man with advanced rheumatoid arthritis who presented with a large indurated painful truncal plaque with a palpable cord in addition to a papulonodular eruption on his dorsal hands. Furthermore, our patient had a recurrence in a near-identical mirror-image pattern on the contralateral trunk. The constellation of clinical and histopathological findings in our patient further suggests that palisaded neutrophilic and granulomatous dermatitis and interstitial granulomatous dermatitis exist as overlapping disease entities on a continuum. In addition, we propose that recurrence of skin findings may be indicative of the severity of the underlying systemic disease process.

Key Words: palisading neutrophilic and granulomatous dermatitis, rheumatoid arthritis, palisading granulomas, disease-modifying antirheumatic drugs, interstitial granulomatous dermatitis

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INTRODUCTION

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is a rare neutrophilic dermatosis that commonly presents as a tender, erythematous papulonodular eruption on the extensor surface of extremities including the digits and elbows. Relatedly, interstitial granulomatous dermatitis (IGD) classically presents with the pathognomonic “rope sign”—an erythematous linear cord coursing along the lateral trunk to mid-axillary flank—as well as annular

erythematous to violaceous papules or plaques on the lateral trunk and proximal limbs. Overlapping clinical and histopathological findings between these dermatoses have led to debate on whether these 2 entities are the same disease, similar diseases on a spectrum, or 2 separate entities altogether. Their classification is further complicated by potential alternate or synonymous terminology that exists in the literature, including Churg–Strauss granuloma, cutaneous extravascular necrotizing granuloma, IGD with cutaneous cords and arthritis, and rheumatoid papules.^{1–5}

We report an intriguing case of PNGD in a 53-year-old man with advanced rheumatoid arthritis (RA) who presented with a large indurated painful truncal plaque with a palpable cord in addition to a papulonodular eruption on his dorsal hands. Furthermore, our patient had a recurrence in a near-identical pattern on the contralateral trunk. The constellation of clinical and histopathological findings in our patient presents evidence in favor of PNGD and IGD as overlapping disease entities on a continuum and highlights the importance of clinicopathological correlation for this challenging diagnosis. In addition, we propose that recurrence of skin findings may be indicative of the severity of the underlying systemic disease process.

CASE REPORT

A 53-year-old white man with a history of advanced refractory RA and associated interstitial lung disease presented with a 6-week history of a steadily expanding nontender plaque on his left back. Numerous tried antibiotics resulted in no improvement. He reported a “burning” type of pain in association with his cutaneous plaque. He had no history of fevers, chills, or weight loss. His RA medications included abatacept, hydroxychloroquine, and leflunomide. Physical examination revealed a 28 × 24 cm, erythematous-to-purple, smooth dermal plaque with ill-defined borders and no overlying epidermal change on the left upper lateral back. Cord-like extension onto the mid-axillary trunk was observed (Fig. 1A). The plaque was markedly warm on palpation. In addition, papulonodules were noted overlying his right metacarpophalangeal joints and volar pads (Fig. 1B). Laboratory evaluation including complete blood count, metabolic panel, and liver function tests were all within normal limits.

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IRB approval is not required

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FIGURE 1. Palisaded neutrophilic and granulomatous dermatitis/interstitial granulomatous dermatitis overlap. A, Violaceous plaque on the left upper lateral back with cord-like extension onto the mid-axillary trunk. B, Papulonodular eruption noted overlying bilateral dorsal hands and fingers.



Incisional wedge biopsy of the truncal plaque revealed extensive palisading necrobiotic granulomatous inflammation in the deep dermis (Fig. 2). Broad zones of necrobiosis composed of tightly packed dead collagen bundles surrounded by dense layers of palisading histiocytes were observed (Fig. 3). Immunostains showed the histiocytic component to express CD68 with negative S100 protein, pancytokeratin, and CD31 staining. Most of the zones of necrobiosis showed scattered neutrophils (Fig. 4). Denser neutrophil aggregates were seen within necrotizing granulomas focally, as well (Fig. 5), but obvious leukocytoclastic vasculitis was not appreciated. Abundant plasma cells were present in the infiltrate (Fig. 6). Despite the palisading granulomas, the presence of numerous neutrophils and plasma cells raised concern for the possibility of an infectious etiology. However, no fungal or acid-fast organisms were identified on periodic acid–Schiff, Grocott's methenamine silver, Mucicarmine, Fite, or Kinyoun acid-fast bacilli-stained sections. Microbial tissue cultures were also negative. Given the immunosuppressive effects of abatacept and the histologic appearance, the case was sent to the Centers for Disease Control (CDC; Atlanta, GA) to more thoroughly exclude the possibility of infection by molecular analysis. Per report

from the CDC, no special stain, immunohistochemical, or molecular evidence of *Mycobacterium* species or fungal organisms were identified. In light of multiple data points arguing against infectious etiology, a diagnosis of exuberant PNGD was favored histologically.

A biopsy was also performed on one of the papulonodules from the skin overlying the right fifth metacarpophalangeal joint. It showed features suggestive of a re-epithelialized vesicle with a necrotic blister roof and mixed dermal inflammation. No granulomas were seen. The findings were clinically and histologically suspected to be nonspecific changes overlying a deeper unsampled process. Thus, the biopsy was regarded as likely being not representative of the actual lesion itself. Repeat biopsy of the hand lesions was not performed.

Considering an approximately 1-year history of abatacept and numerous reports in the literature of PNGD associated with immunosuppressive disease-modifying anti-rheumatic drugs including tumor necrosis factor- α inhibitors, abatacept was discontinued and the patient was started on an 8-week course of a high-dose prednisone taper. At his 2-month follow-up, the plaque

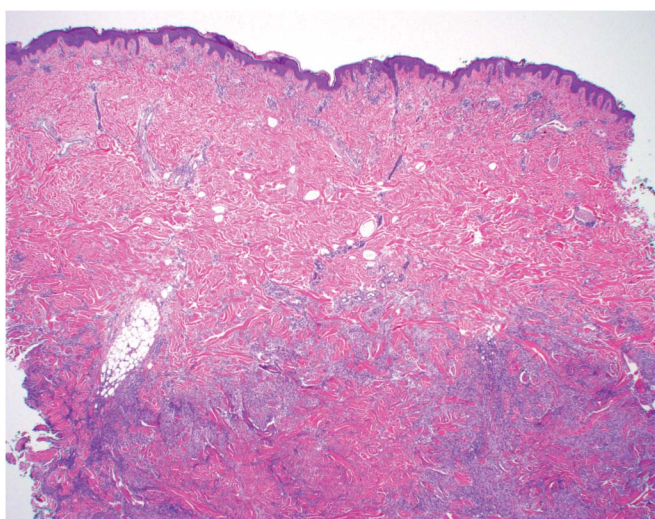


FIGURE 2. Palisaded neutrophilic and granulomatous dermatitis/interstitial granulomatous dermatitis overlap. The large incisional wedge biopsy showed striking palisading granulomas in the deep dermis.

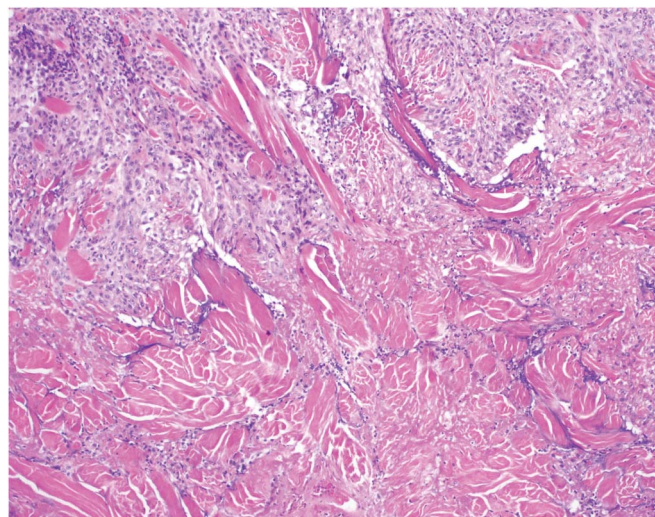


FIGURE 3. Palisaded neutrophilic and granulomatous dermatitis/interstitial granulomatous dermatitis overlap. The granulomas displayed with central zones with numerous necrobiotic collagen bundles surrounded by dense zones of palisading histiocytes.

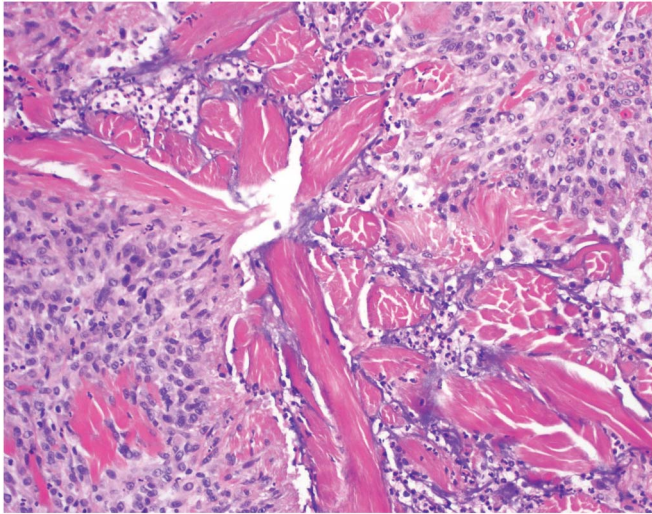


FIGURE 4. Palisaded neutrophilic and granulomatous dermatitis/interstitial granulomatous dermatitis overlap. Neutrophils were associated with necrobiotic collagen bundles.

had resolved and the nodules on his hands had shown marked improvement.

The patient returned to clinic 3 months later with a 4-day history of a nearly identical plaque to the one seen previously—this time on the contralateral side of his trunk. Physical examination revealed a mirror-image plaque on his right upper lateral back with cord-like extension onto the proximal arm and mid-axillary flank (Fig. 7). On the dorsal aspect of the digits were numerous erythematous deep-seated papulopustular nodules. The patient was again started on an 8-week high-dose prednisone taper with the addition of dapsone. At his 3-month follow-up, the patient had mild-to-moderate improvement of the plaque on his right back and the nodules on his hands. Since the patient had discontinued abatacept and still had a recurrence, a diagnosis of PNGD in association with RA

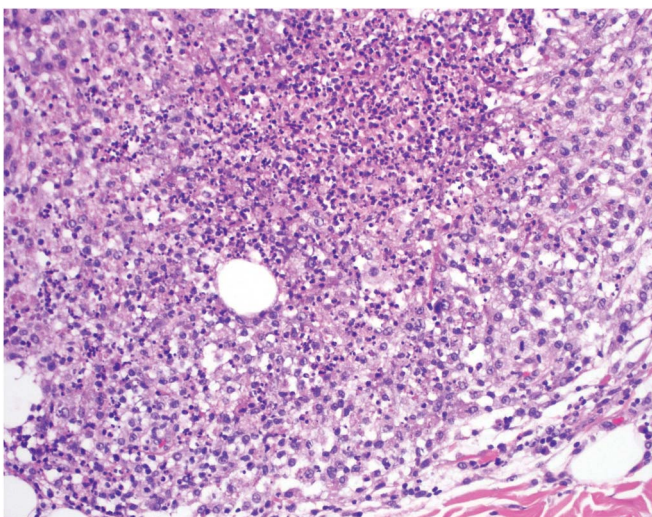


FIGURE 5. Palisaded neutrophilic and granulomatous dermatitis/interstitial granulomatous dermatitis overlap. Aggregates of neutrophils were seen within some of the granulomas.

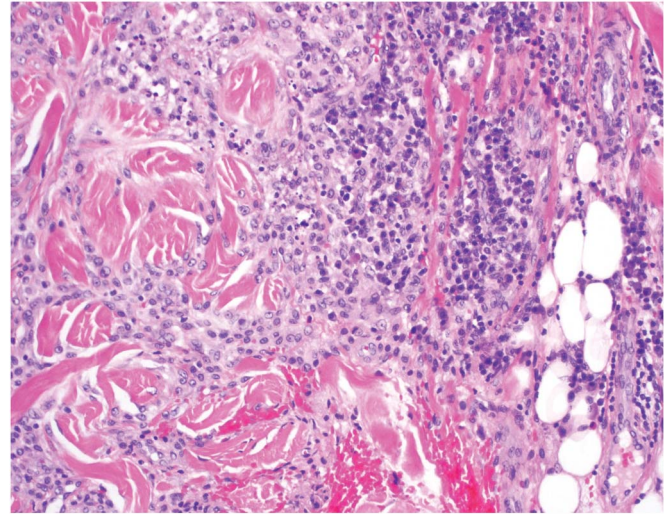


FIGURE 6. Palisaded neutrophilic and granulomatous dermatitis/interstitial granulomatous dermatitis overlap. Numerous plasma cells were present in the infiltrate.

without contribution from immunosuppressive disease-modifying anti-rheumatic drugs was favored.

DISCUSSION

PNGD is most commonly associated with systemic diseases such as RA and systemic lupus erythematosus (SLE). However, reports in the literature suggest an association with a variety of other systemic diseases including sarcoidosis, systemic sclerosis, ankylosing spondylitis, inflammatory bowel disease, vasculitides, and lymphoproliferative disorders.^{6–11} Recently, immunosuppressive drugs including tumor necrosis factor- α inhibitors such as infliximab and adalimumab have been implicated in PNGD with resolution of lesions after discontinuation of the drug.^{12,13} Similarly, IGD is also associated with collagen vascular diseases such as RA and SLE in addition to an array of other systemic diseases, malignancies, and immunosuppressive medications.¹⁴

Given the overlapping clinical presentations, systemic disease associations, and histopathological findings, some have considered PNGD and IGD to be part of a clinicopathological spectrum while others have considered them to be mutually exclusive. Histologically, PNGD is characterized by early leukocytoclastic changes, palisaded granulomas, and collagen degeneration. IGD, however, is typified by an interstitial granulomatous infiltrate with foci of degenerated collagen.^{14–17} However, coexisting interstitial and palisaded inflammatory patterns can be frequently seen in the same case with no consistently specific histologic finding to distinguish PNGD from IGD.^{18,19} In addition, late lesions for both can demonstrate collagen degeneration—further confounding the histologic picture. Those that have favored a distinction between these dermatoses have highlighted a paucity of tissue neutrophilia and an absence of vasculitic changes in IGD. However, multiple case series have recently found that tissue neutrophilia can occur regardless of the predominant



FIGURE 7. Palisaded neutrophilic and granulomatous dermatitis/interstitial granulomatous dermatitis overlap. The recurrent lesion showed very similar findings to the initial presentation but in a mirror-image pattern on the contralateral back with a cord-like extension onto the proximal arm and mid-axillary trunk.

inflammatory pattern (interstitial vs. palisaded).^{16,19} Furthermore, some authors have suggested that the absence of vasculitic changes in IGD are due to the transient and early nature of vascular destruction in the histologic evolution of the lesions (like in that of PNGD) and therefore, are not observed in late lesions of IGD.¹⁹ Regardless, given that vasculitic changes are not observed in late lesions of either PNGD or IGD, this histologic feature may not be a reliable distinction between these dermatoses.

The unique case presentation in our patient provides additional evidence in support of the clinicopathological overlap between these 2 inflammatory dermatoses. Our patient with advanced RA presented with the axillary “rope sign”—which is classically pathognomonic for IGD—in addition to the papulonodular eruption classically seen with PNGD. Biopsy of the axillary lesion in our patient showed palisading granulomatous inflammation with numerous neutrophils consistent with PNGD. We find it intriguing that the pathognomonic “rope sign” in IGD is seen in a lesion with histopathologic changes corresponding to that of PNGD. We interpret this finding as further evidence supporting the notion that there is clinicopathological overlap between PNGD and IGD. In our review of the literature, we found a case similar to ours in which the “rope sign” was found in association with

PNGD in a patient with SLE. This patient also reported a “burning” type of pain leading Gulati et al²⁰ to name this as the “burning rope sign.”

In addition, we report our case to highlight the recurrence of the “burning rope sign” in our patient on the contralateral trunk after resolution of the initial plaque. While PNGD and IGD can be self-limiting in some patients, improvement of lesions has been observed with a variety of treatments including topical and systemic steroids, dapsone, cyclophosphamide, mycophenolate mofetil, and cyclosporine.^{20–24} Although persistence of lesions despite therapy can occur, recurrence is relatively rare.^{20,25–27} Specifically, recurrence of this severity in a near-identical pattern and cutaneous distribution has not been reported in the literature to date. We propose that this recurrence may reflect the severity and refractory nature of our patient’s RA. The patient has had greater than a 10-year history of seropositive erosive RA (+rheumatoid factor, +anti-cyclic citrullinated peptide) and associated interstitial lung disease. Since the diagnosis of RA, our patient has been on a variety of drugs including leflunomide, hydroxychloroquine, abatacept, methotrexate, etanercept, adalimumab, sulfasalazine, and rituximab. Unfortunately, he has had a poor response to these treatment regimens including the newer biologics. In light of a complicated history of RA in our patient, we interpret a possible association between PNGD/IGD and the severity of RA. Given that an immune complex deposition phenomenon is hypothesized to be the mechanism behind these 2 reactive granulomatous dermatoses, we find a correlation between recurrence and severity to be a likely possibility. However, more clinical cases will need to be analyzed to observe if such a correlation is consistent.

In infectious diseases such as leprosy and syphilis, the balance between 2 different forms of immune response, namely delayed-type hypersensitivity (DTH) and humoral immunity, seems to play a crucial role in the severity of disease and duration of the infection. Strong DTH, including effective granulomatous host response, is associated with clearance of the infectious organisms, whereas weak DTH in the setting of strong humoral immune response is associated with persistence of the organism, prolonged infection, and eventual disease progression.²⁸ The inflammatory response seen in RA is similar to that seen in leprosy, and indeed patients with leprosy sometimes develop a form of chronic arthritis that closely resembles RA. This arthritis is not necessarily a direct result of mycobacterial organisms within the joint but may actually be a form of autoinflammatory host response stimulated by *Mycobacterium leprae* infection. Even patients with paucibacillary leprosy or previously treated leprosy may still develop this form of arthritis.²⁹ In our patient, who had relatively severe RA with refractory disease course, there was not only robust granulomatous immune response but also an influx of neutrophils into the infiltrate. Perhaps this partially neutrophil-mediated response is a surrogate marker of suboptimal DTH in our patient. If the theories above hold true, this may suggest that the more severe and persistent disease course in our patient could be related not merely to an overactive autoimmune response, but rather to an inappropriate form of immune response where the balance

is swinging away from DTH and toward humoral immunity. It has been previously shown that decreased DTH immune response in RA patients may be associated with greater disease activity; perhaps that is the case here.³⁰

Although the immune response in leprosy or syphilis is targeting antigens derived from infectious organisms, the autoimmune response seen in RA is driven by unknown antigen/s. In both cases, the general goal of host immune response is to eradicate the antigen or at least decrease the load of antigens present. To mount an appropriate cell-mediated immune response, antigen must be removed from tissue and transported to regional lymph nodes through lymphatic channels. Obstruction of lymphatic flow, may be seen in lymphedema, for example, will thus result in regional immune suppression.³¹ Although we cannot exclude the possibility, we do not see any definitive evidence to support this mechanism in our patient. To our knowledge, he had no history of lymphedema in this area, and although we observed some dilated vessels in the dermis overlying the granulomatous infiltrate, these vessels appeared to be dilated venules or capillaries rather than lymphatics. Further investigation into the role of DTH versus humoral immunity, as well as the possible role of lymphatic dysfunction, may be worthwhile areas of study in attempting to further elucidate the exact mechanisms underlying PNGD and IGD.

Given that the diagnosis of this entity is challenging for both dermatologists and dermatopathologists alike, we stress the importance of clinicopathological correlation in an attempt to arrive at the correct diagnosis. In our case, the clinical presentation of the patient's axillary plaque was initially favored to be an infectious etiology because of its erythema, progressive expansion, and marked warmth on palpation—all features which can be seen in cellulitis. Although an infectious cause is possible and cannot be excluded without negative microbial stains and cultures, it is important to consider a reactive granulomatous process such as PNGD/IGD in a patient with a history of systemic disease—especially, RA or SLE. We recommend a high index of clinical suspicion in patients with underlying connective tissue disease presenting with papulonodular eruptions on the extremities or an axillary truncal plaque. Considering the importance of promptly recognizing the characteristic findings in these reactive dermatoses, we would also like to raise awareness of the “burning rope sign” as part of the clinicopathological spectrum of PNGD/IGD. In conclusion, the combination of clinical and histopathological features in our case support the notion that IGD and PNGD are actually the same entity or 2 entities on a spectrum with overlapping features, and the very rare incidence of disease recurrence may be reflective of the severity and refractory nature of the underlying systemic disease.

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