CASE REPORT

Palisaded neutrophilic and granulomatous dermatitis associated with the initiation of etanercept in rheumatoid arthritis: a case report

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A B S T R A C T

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is an unusual entity with variable clinical manifestations and histopathological features. It is associated with a variety of immune-mediated systemic diseases, most commonly in rheumatoid arthritis. We report a 42-year-old female with a long-standing history of rheumatoid arthritis, presenting with multiple pruritic erythematous papules and nodules on the lower legs 1 month after beginning treatment with etanercept. Microscopic examination of a fully developed lesion showed a diffuse dense interstitial lymphohistiocytic infiltrate interspersed with palisaded granulomas consisting of epithelioid histiocytes and multinucleated giant cells surrounding central zones of degenerated collagen, neutrophils and leukocytoclastic debris. A diagnosis of PNGD was made on the basis of typical histopathologic features. Withdrawal of etanercept led to gradual resolution of the skin lesions, with no new skin lesions appearing afterwards. Although the correlation between the use of tumor necrosis factor-α (TNF-α) antagonists and the development of PNGD remains controversial and warrants further investigation, PNGD should be considered in the differential diagnosis of skin eruptions within a setting of anti-TNF-α therapy.

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Introduction

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is a rare cutaneous manifestation associated with various autoimmune diseases. It represents a disease spectrum encompassing interstitial granulomatous dermatitis (IGD), arthritis and plaques, rheumatoid papules, cutaneous extravascular necrotizing granuloma, Churg-Strauss granuloma and superficial ulcerating rheumatoid necrobiosis. Recently, tumor necrosis factor-α (TNF-α) antagonists have become widely used for the treatment in a number of autoimmune-mediated inflammatory disorders with favorable effectiveness, particularly against rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis and Crohn's disease. Although TNF-α antagonists suppress only a specific area of the immune system and are considered safe and well tolerated, various adverse cutaneous reactions have been confronted. In addition to the formation of leukocytoclastic vasculitis, urticaria, lichenoid drug eruptions and lupus erythematosus-like eruptions reported during TNF-α antagonist therapy,1 it has been suggested that anti-TNF-α therapy is associated with the onset of PNGD.2,3 It is well known that RA is the most common disease associated with PNGD; however, the correlation between the use of TNF-α antagonists and the development of PNGD in patients with RA remains controversial. We report a case of PNGD following treatment with etanercept for RA, and explore possible causal links.

Case presentation

A female (age, 42 years) had a medical history of RA and hepatitis B since 2007. Her past medications included sulfasalazine 1000 mg, hydroxychloroquine 400 mg, leflunomide 10 mg and entecavir 0.5 mg per day regularly. Due to exacerbated arthralgia, injections of etanercept were added in June 2009. One month after the beginning of treatment with etanercept, the patient developed pruritic skin eruptions starting bilaterally from the lower legs, with lesions gradually spreading to the trunk and upper limbs (Figure 1A). An examination revealed multiple scattered erythematous papules and nodules with excoriations distributed symmetrically, particularly on the lower legs (Figures 1B and 1C). No ulceration, discharge, or vesiculation was found. Meanwhile, the patient showed no signs of fever, loss of body weight or lymphadenopathy. Laboratory investigation revealed abnormal liver function (AST 193 IU/L, ALT 208 IU/L), elevated rheumatoid factor

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RF; 19.9 IU/ml, normal 10–15 IU/ml), and elevated erythrocyte sedimentation rate (ESR; 32 mm/h, normal 0–20 mm/h). Blood cell count, renal function, C-reactive protein, and IgE were all within normal limits. The lesions were not alleviated following treatment with topical corticosteroids and oral antihistamine for 1 month. Therefore, an incisional skin biopsy was performed.

Pathological sections revealed a diffuse dense interstitial and perivascular inflammatory infiltrate throughout the reticular dermis, composed mainly of histiocytes and lymphocytes. Striking palisaded granulomatous inflammation comprised epithelioid histiocytes, multinucleated giant cells and large numbers of neutrophils within the mid-dermis were found (Figure 2A). Prominent palisaded histiocytes surrounded the center of basophilic degenerated collagen (piecemeal fragmentation) and leukocytoclastic debris (Figures 2B and 2C). Swollen endothelial cells, fibrinoid degeneration of vessel walls and erythrocytes extravasation were also noted. Neither dermal mucin nor leukocytoclastic vasculitis was found. Subcutaneous tissue remained intact. The

Figure 1 (A) Multiple scattered erythematous papules and nodules distributed symmetrically on both lower legs, particularly on the extensor aspect. (B) Close-up view of erythematous papules and nodules with excoriations on right shin. (C) Close-up view of left shin.

Figure 2 (A) Diffuse dense interstitial and granulomatous inflammatory infiltrate throughout the reticular dermis (H&E stain, magnification 40×). (B) Striking palisaded granulomatous inflammation consisting of epithelioid histiocytes, multinucleated giant cells and large numbers of neutrophils within the mid-dermis (H&E stain, magnification 100×). (C) Prominent palisaded histiocytes surrounding the center of basophilic degenerated collagen, numerous neutrophils with a variable number of eosinophils, fibrin and leukocytoclastic debris (H&E stain, magnification 200×).
histopathological differential diagnoses included PNGD, granuloma annulare, rheumatoid neutrophilic dermatitis, interstitial granulomatous drug reaction, mycobacterial infection and deep fungal infection. PAS staining and acid-fast staining of the skin biopsy demonstrated no microorganisms. Further investigations of a polymerase chain reaction for *Mycobacterium tuberculosis* or nontuberculous mycobacteria provided negative results (Figure 3). Therefore, a diagnosis of PNGD was made.

Following the skin biopsy, etanercept treatment was immediately withdrawn. During the 4 months follow-up, only topical corticosteroids and oral antihistamines were prescribed. The skin eruption gradually resolved with residual post-inflammatory hyperpigmentation diminishing within 4 months following the discontinuation of treatment with etanercept (Figure 4A). The numbers of erythematous papules on the lower legs decreased and pruritus was improved (Figures 4B and 4C). The patient refused to resume treatment with etanercept thereafter, and no similar skin lesions were reported during the follow-up period.

**Discussion**

This report of PNGD occurring 1 month after beginning treatment with TNF-α inhibitor in a patient with RA is of considerable importance. The mechanism behind PNGD remains poorly understood, and the relationship between PNGD and the use of TNF-α antagonists has not been well established. A number of recent studies have investigated this correlation. Bremner et al reported on three patients with RA receiving anti-TNF-α therapy developing PNGD.2 They suggested that the only common link was RA. However, Deng et al described five patients developing PNGD following the initiation of four different anti-TNF-α therapies (infliximab, etanercept, adalimumab and lenalidomide).3 Of the five patients, three had underlying RA. In addition to RA, one patient had psoriatic arthritis and the other two patients had multiple myeloma. Rashes developed within 3 months following initiation of TNF-α inhibitors in three of the patients. The eruptions cleared in three of the patients and improved in one patient within 2 months following discontinuation of the TNF-α inhibitors. The skin lesions persisted in one patient who continued receiving the TNF-α inhibitor. Deng et al inferred that TNF-α antagonists enhanced the likelihood of developing PNGD in patients with RA who also suffered from granulomatous diathesis. In our patient, we observed a close association between the development of skin lesions and the initiation of treatment with TNF-α inhibitor, as described by Deng. Our patient, who had a long-standing history of RA, did not show evidence of erythematous papules until 1 month after initiating the use of etanercept. She had severe polyarthralgia with elevated RF and ESR about 3 years prior, up to 88.6 IU/ml and 50 mm/h, respectively; however, no PNGD lesions were encountered at that time. The skin eruptions persisted for 5 months during the period of etanercept therapy despite treatment with topical corticosteroids. In addition, gradual resolution of skin lesions was observed within 4 months following discontinuing treatment of TNF-α inhibitor. Etanercept was not re-administered and the patient did not develop similar new skin lesion afterwards. The time correlation of the lesions with the initiation of etanercept supports the presumption that the TNF-α inhibitor may have played a role in this patient developing PNGD. Spontaneous resolution over a period of months to years has been reported in a number of patients presenting with PNGD. Nonetheless, rapid resolution of skin lesions in the patient in this study after discontinuing use of etanercept made this unlikely.

The mechanism behind PNGD remains unclear. In 1983, Finan and Winkelmann observed IgM and C3 in small vessels using direct immunofluorescent examination of skin lesions resulting from PNGD.4 They presumed that the cutaneous lesions were the result of immune complexes generated by underlying systemic diseases. These lesions tended to occur in patients suffering from more severe diseases and were correlated with high titers of anti-DNA antibodies, antinuclear antibodies (ANA) and RF.5,6 It is now believed that the deposition of immune complexes in dermal vessels activates the complement and neutrophils, leading to degeneration of ischemia and collagen, followed by granulomatous reaction to this damaged collagen.7 The exact mechanism by which the TNF-α antagonist is involved in the promotion of PNGD has not been confirmed. The development of autoimmunity and flares of vasculitis are well-known concerns with all TNF-α inhibitors.8 Etanercept is a fully soluble human TNF receptor fusion protein and, although it does not cause antibody-dependent cytotoxicity or trigger T-cell apoptosis like infliximab, we assumed that it alters the antigenicity of dermal collagen and elicits an immune response. It may also cause other autoantibodies to bind to RF, IgM/C3 or a preformed immune complex to reach a critical size precipitating in the blood vessels and causing vascular injury through type III immune complex reaction. After all, the development of PNGD was triggered in our patient following the initiation of treatment with etanercept.

Among the TNF-α antagonists, monoclonal antibodies to TNF-α, such as infliximab and adalimumab, were considered better able to break down granuloma than etanercept. Etanercept binds primarily to soluble TNF, whereas infliximab binds to both soluble and membrane-bound TNF and is able to fix complement and induce cell lysis and apoptosis of cells expressing membrane-bound TNF.9,10 Etanercept has not demonstrated clinical benefits in Wegener’s granulomatosis,11 Crohn’s disease12 or sarcoidosis.13 It leaves TNFRp75-mediated signaling at least partially intact, which would explain why etanercept did not completely impair the formation of palisaded neutrophilic granuloma in our patient.

PNGD is an unusual cutaneous condition found in patients with a variety of immune-mediated systemic diseases, most commonly associated with RA. Consistent with its association with immune-mediated diseases, PNGD has also been diagnosed in conjunction with systemic lupus erythematosus, Wegener’s granulomatosis, vasculitis, lymphoproliferative malignancies, Behçet’s disease, adult-onset Still’s disease and limited systemic sclerosis.14 It was first described by Dykman et al in 1965 in patients with RA developing indurated linear subcutaneous bands on the lateral aspect of the trunk.15 In recent years, various names have been proposed to designate the same entity and in 1994, Chu et al proposed the
Histopathologic spectrum of PNGD in patients with collagen vascular disease to unify the variety of names given to these conditions. The clinical manifestations of PNGD are highly diverse, including tender skin-colored erythematous papules with central crusting and umbilication, asymptomatic or pruritic erythematous plaques, indurated linear bands, linear subcutaneous indurated cordlike bands, the so-called rope sign, was first described by Ackerman in 1993 and considered pathognomonic of IGD. The polymorphous cutaneous eruption is characterized by symmetrical distribution predominantly on the trunk and extensor extremities, especially with the upper limbs, as described by Hantash et al. The appearance of these lesions often coincides with a worsening of the underlying systemic disease.

Chu proposed that, histopathologically, PNGD displays a spectrum of various characteristics dependent upon the duration of the lesions. At different stages, the histologic findings of PNGD vary from diffuse interstitial inflammation composed of lymphohistiocytes, eosinophils and little neutrophils to palisading granuloma surrounded by dense histiocytic and neutrophilic infiltrates with central degenerated collagen and leukocytoclastic debris. Mucin is usually scant or absent. In our patient, the histopathologic appearance displayed a fully developed lesion showing palisaded granulomas surrounding areas of degenerated collagen, numerous neutrophils, nuclear dust and fibrin. Leukocytoclastic vasculitis was not a feature at this stage, although vasculopathy presented with fibrinoid degeneration and plump endothelial cells. The main histopathologic differential diagnoses included granuloma annulare, rheumatoid neutrophilic dermatitis and interstitial granulomatous drug reaction. In granuloma annulare, a palisaded granuloma, necrobiosis and multinucleated giant cells are frequently observed. However, the neutrophils and eosinophils are usually scant or absent and the deposition of dermal mucin is abundant. In our patient, the absence of dermal mucin, deeply basophilic degenerated collagen in the center of histiocytic palisaded granuloma and numerous neutrophilic infiltrates were distinguishing features of PNGD. Rheumatoid neutrophilic dermatitis is characterized by heavy dermal infiltrates of neutrophils with variable degrees of leukocytoclasis without palisaded necrobiotic granuloma, which is unlike the palisaded neutrophilic granulomatous inflammation in our case. The histopathologic features of interstitial granulomatous drug reaction are characterized by changes in the vacuolar interface and often by epidermotropism of the lymphocyte, in addition to diffuse lymphohistiocytic infiltrate and piecemeal fragmentation of collagen. The absence of neutrophils is a cardinal feature differentiating PNGD. Other forms of palisaded granulomatous dermatitis, including Churg-Strauss disease and Wegener’s granulomatosis, should also be considered. Churg-Strauss disease typically reveals abundant eosinophils in the centers of granulomas. In Wegener’s granulomatosis, there are often many foci of active vasculitis concurrent with palisaded extravascular granulomas. Furthermore, it is well known that patients receiving anti-TNF-α therapy face a significant increase in the risk of infection from Mycobacterium tuberculosis. Therefore, tuberculosis should be considered (with caution) in the differential diagnosis.

The clinical course of PNGD tends to be self-limiting. Most cases resolve spontaneously, while others may persist for several months or years. In our patient, significant clinical improvement was observed following the withdrawal of etanercept. Several treatments have shown variable improvements in PNGD, including topical corticosteroids, low-dose prednisolone, dapsone, colchicine, cyclosporin, cyclophosphamide and hydroxychloroquine.

**Conclusion**

In conclusion, we report a case of PNGD developing after the initiation of treatment with etanercept, subsequently subsiding following the discontinuation of treatment. PNGD should be considered in the differential diagnosis of skin eruptions in the setting of anti-TNF-α therapy. The TNF-α antagonist could play a role in triggering PNGD via autoimmunity in patients with immune-mediated diseases. Further studies are indicated to clarify the association and identify the precise mechanism between TNF-α inhibitors and PNGD.

**References**