Interstitial Granulomatous Dermatitis in a Patient With Rheumatoid Arthritis on Etanercept

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Tumor necrosis factor-α (TNF-α) has been implicated in the pathogenesis of numerous inflammatory conditions, possibly facilitating the induction and maintenance of these diseases through lymphocyte activation and cytokine production. Inhibitors of TNF-α have proven efficacious in the treatment of autoimmune diseases such as psoriasis, rheumatoid arthritis, inflammatory bowel disease, and lymphoproliferative disorders. However, recent cases of adverse cutaneous reactions have been reported in anti–TNF-α therapy, most notably those of granulomatous morphology.

We report a patient with rheumatoid arthritis who had been treated with etanercept (50 mg/wk) for 6.5 years. The patient subsequently developed pink and red papules on large areas of the upper and lower extremities. Skin biopsy specimens revealed both poorly formed and well-circumscribed nonnecrotizing epithelioid granulomas in the superficial dermis. Application of clobetasol propionate ointment 0.05% without discontinuation of anti–TNF-α therapy led to complete resolution of the skin lesions.

While the precise mechanisms of physiologic and pathologic TNF activity remain to be determined, it is clear that granulomatous lesions may emerge as a complication of anti–TNF-α therapy. Treatment with topical corticosteroids may be sufficient to eliminate such lesions.

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Case Report

A 52-year-old woman with a 15-year history of rheumatoid arthritis was seen at the Center for Skin and Related Musculoskeletal Diseases, Brigham and Women's Hospital, Boston, Massachusetts. The patient had been treated with etanercept (50 mg/wk) for 6.5 years. She reported an 8-month history of a rash that began as flat red spots on her forearm, becoming raised and gradually spreading to involve large areas of her upper and lower extremities. The trunk was relatively spared. On physical examination, pink and red papules, some coalescing into annular plaques, were noted on the arms and legs. The red papules could not be completely blanched with compression using a glass slide and a residual reddish brown discoloration was observed. Notably, none of the papules were purpuric. A biopsy was performed and revealed skin with multifocal, well-circumscribed, nonnecrotizing epithelioid granulomas in the superficial dermis (Figure). Findings from repeat purified protein derivative testing were negative and a chest x-ray was normal. The eruption remained asymptomatic and the lesions cleared after treatment with clobetasol propionate ointment 0.05% applied twice daily without occlusion over 2 weeks. The patient has remained on etanercept for the past 10 months for her rheumatoid arthritis based on her rheumatologist's recommendation and the eruption has not recurred.

Comment

The eruption of cutaneous granulomatous lesions while being treated for rheumatoid arthritis with a tumor necrosis factor-α (TNF-α) inhibitor is surprising because of the role of this cytokine in inducing

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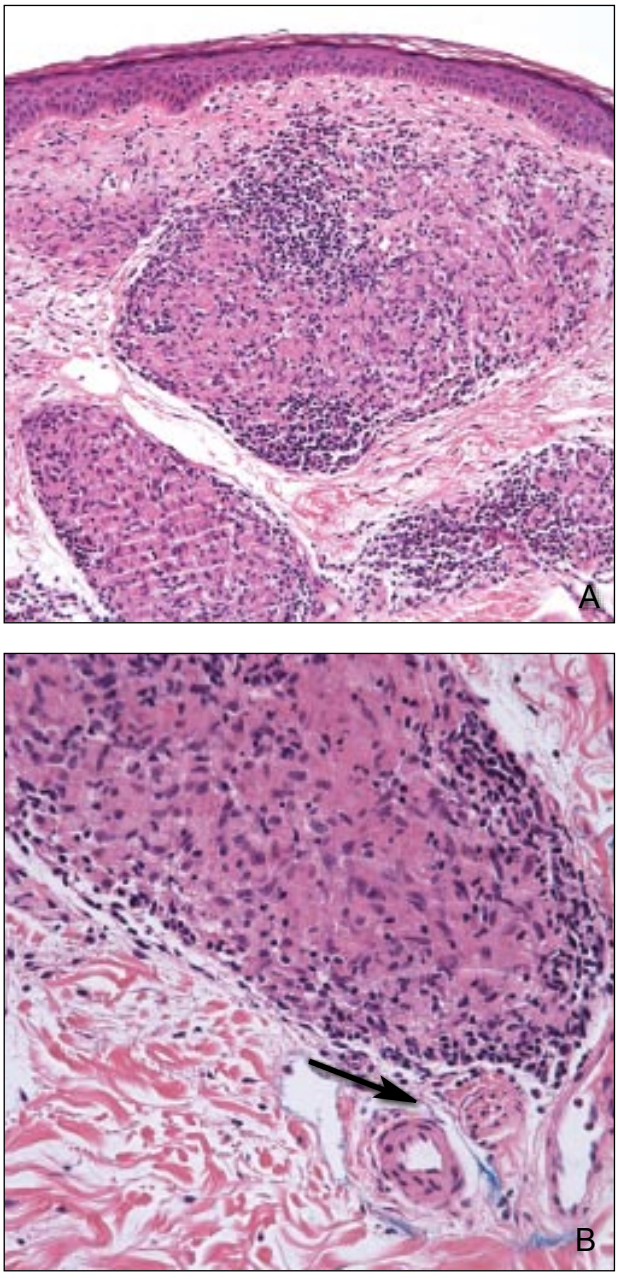
granuloma formation. In recent years, TNF-α has emerged as one of the principal cytokines involved in the pathogenesis of rheumatoid arthritis as well as several other autoimmune diseases. TNF-α is produced in monomeric and trimeric soluble and transmembrane forms by macrophages, lymphocytes, and endothelial cells, as well as keratinocytes, Langerhans cells, and melanocytes in the skin.[1] There are 2 TNF-α receptors (TNFRs), TNFRp55 and TNFRp75. The soluble forms of TNF-α (monomeric or trimeric) bind to both receptors, whereas the transmembrane form predominantly binds to TNFRp75.[2,3] Interestingly, TNF-α has been found to induce both proinflammatory and immunosuppressive processes.[4] For example, the cytokine is known to participate in the induction and maintenance of protective granulomas at multiple steps. It also induces antimycobacterial activity in macrophages and promotes the migration of various types of cells to the site of infection; however, under certain circumstances, TNF-α can promote apoptosis in T cells as part of the host defense response.[3] In general, high serum levels of TNF-α are associated with many inflammatory and autoimmune conditions.[4,5]

Although TNF-α inhibition is effective in treating inflammatory conditions such as rheumatoid arthritis, psoriasis, and psoriatic arthritis, the precise mechanism of action is still not well-understood. Kassiotis and Kollias[6] utilized murine models of multiple sclerosis to demonstrate that blocking TNFRp55 function led to the inhibition of TNF proinflammatory effects, whereas the immunosuppressive and immunomodulatory effects of the cytokine (ie, down-regulating or inactivating a potentially detrimental autoimmune T-cell response against myelin antigens) remained intact. Moreover, in TNF-deficient mice, myelin-specific T-cell reactivity failed to regress, while activated memory T-cell expansion lengthened abnormally, leading to exacerbated experimental autoimmune encephalomyelitis (EAE), a mouse model for multiple sclerosis. Remarkably, immunoregulation by TNF and protection against EAE did not require TNFRp55, while the same receptor was shown to be necessary for the detrimental effects of TNF during the acute phase of the disease. This finding has led to the association of TNFRp55 with proinflammatory and tissue-damaging activity and TNFRp75 with immunosuppressive effects, suggesting that blocking the function of TNFRp55 in autoimmune processes may inhibit the proinflammatory activities of TNF without compromising its immunomodulatory properties.[6]

As TNF-α plays a critical role in granuloma induction and maintenance, it is not surprising that inhibiting its function in the body may act as a double-edged sword. While lower levels of the cytokine are beneficial in the suppression of inflammatory disorders, they also may depress cell-mediated immunity to various pathogens and disrupt the integrity of the protective granulomatous response. In fact, adverse events have been reported following anti-TNF therapy, including the reactivation of granulomatous infectious diseases such as tuberculosis and histoplasmosis.[3,5,7] Interestingly, treatment



Well-circumscribed nonnecrotizing epithelioid granulomas rimmed by lymphocytes in the superficial dermis (H&E, original magnification ×10)(A). At higher magnification, the abundant eosinophilic cytoplasm of the epithelioid histiocytes is apparent as well as sparing of neurovascular bundles (arrow)(H&E, original magnification ×40)(B).

with infliximab, a chimeric human-murine monoclonal antibody against the soluble and transmembrane forms of TNF-α, has been associated with a higher incidence of reactivation of granulomatous infections than treatment with etanercept, a dimeric fusion protein of the extracellular ligand-binding portion of human TNFRp75 linked to FcγI.

While the molecular mechanism for the occurrence of cutaneous granulomatous events during TNF blockade remains unclear, Wallis and Ehlers[3] have proposed 3 mechanisms for the different effects on granuloma maintenance with infliximab and etanercept. The first mechanism relates to the differential inhibition of TNF signaling events. While infliximab blocks the ability of TNF to signal through both TNFRs, etanercept leaves TNFRp75 signaling partially intact, allowing the immunomodulatory effects of TNF to persevere and preserving the integrity of granulomatous lesions. The second mechanism calls attention to the distinct power of neutralizing TNF bioavailability. Infliximab binds TNF quickly and irreversibly, but etanercept has both high-on and high-off binding kinetics; etanercept sheds approximately 50% of soluble TNF and 90% of transmembrane TNF within 10 minutes of binding, which may result in a lower degree of TNF blockade with etanercept that is compatible with its greater level of granuloma maintenance. Lastly, the differential induction by infliximab and etanercept of target cell death is a possible mechanism. Apoptosis induction has not been reported for etanercept, but infliximab may induce apoptosis of memory T cells specific for mycobacterial agents, thus leading to reactivation of latent granulomatous infections.[3] These mechanisms may underlie the appearance of granulomatous eruptions in our patient who had received treatment with etanercept for rheumatoid arthritis for 6.5 years.

Deng et al[1] reported 5 cases of interstitial granulomatous dermatitis in patients treated with various TNF-α inhibitors, including infliximab; etanercept; adalimumab; and lenalidomide, a derivative of thalidomide that may have an effect in the treatment of multiple myeloma. While these lesions occurred in a similar presentation to our patient, the lesions in these 5 patients cleared only after the withdrawal of TNF-α blockade.[1] Our patient responded to clobetasol propionate ointment, a high-potency synthetic corticosteroid, without the need to withdraw necessary therapy for rheumatoid arthritis.

Cutaneous granulomatous lesions can appear in patients with arthritis even without TNF-α antagonist therapy and seem to arise as manifestations of systemic autoimmune diseases themselves, not their treatment. For example, interstitial granulomatous dermatitis with arthritis was first described by Ackerman et al[8] in 1993. In contrast to our patient, the arthritis accompanying interstitial granulomatous dermatitis with arthritis skin lesions may appear before, during, or many years after the onset of the cutaneous lesions, and joint involvement is characteristically symmetric, often including the fingers, wrists, elbows, and shoulders. Cases of clearance of these cutaneous lesions with hydroxychloroquine therapy has been reported; this antimalarial agent also is commonly used in the treatment of systemic lupus erythematosus and rheumatoid arthritis.[9]

While the precise molecular mechanisms of action of TNF-α remain under investigation, it is clear from this case and previous reports that cutaneous granulomatous reactions can occur with the use of TNF-α inhibitors. In all cases, it is recommended that patients undergo careful work-up to rule out an infectious process and a skin biopsy should be performed to confirm the diagnosis, along with long-term follow-up. Topical corticosteroids may be considered while maintaining the patient on anti–TNF-α therapy.

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