Eosinophilic Cellulitislike Reaction to Subcutaneous Etanercept Injection

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Background: Injection site reactions are well recognized in patients treated with etanercept. Previous reports describe histologic findings of a cell-mediated TH1 reaction, with CD8+ T cells composing the majority of the dermal infiltrate.

Observations: A pruritic, erythematous, edematous patch occurred on the right thigh of a 57-year-old white woman treated for rheumatoid arthritis within 12 to 24 hours after her second dose of subcutaneous etanercept. The patient had a similar reaction to adalimumab injection 2 weeks prior to presentation. While benzyl alcohol is present in the etanercept preparation, and mannitol in both drugs, dermal injection revealed no reaction to these additives. Biopsy specimens from the etanercept injection site demonstrated papillary dermal edema accompanied by a brisk polymorphous infiltrate with a predominance of eosinophils and scattered flame figures.

Conclusions: Histologic features of eosinophilic cellulitis as a response to etanercept have not been reported to date. Although most injection site reactions contain T cells and represent a TH1 immune response, the findings we report suggest a TH2-mediated phenomenon.

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Wells syndrome or eosinophilic cellulitis (EC) was initially described by George Wells in 1971 in 4 patients who demonstrated pruritic, erythematous to violaceous papules, plaques, and occasionally bullae in 1 or more locations. Since its elucidation, EC has been described in association with a wide array of conditions including urticaria, dental abscess, myelofibrosis, hypothyroidism, bullous pemphigoid, pemphigoid gestationis, tinea pedis, arthropod bite reactions, myelosclerosis, onchocerciasis, ascariasis, toxocariasis, and herpes simplex viral infection, as well as being the result of an adverse drug reaction to many medications, both prescription and over the counter.

Histologic evaluation shows prominent dermal edema, specifically papillary dermal, perivascular and interstitial infiltration of eosinophils, and flame figure formation. With resolution, palisading histiocytes surround areas of eosinophilic, damaged collagen.

Immunophenotypically, the infiltrate of eosinophilic cellulitis is composed of eosinophils in addition to CD8+ T lymphocytes. These T lymphocytes are presumably responsible for mitigating and maintaining the reaction. Why these T cells cause infiltration of a large number of eosinophils is unknown; however, production of interleukin (IL)-5 and eosinophil-specific chemotactic signals and adhesion molecules are likely implicated.

Injection site reactions (ISRs) are relatively common, occurring in up to 37% of patients treated with etanercept. Typically, these reactions consist of mild to moderate erythema, pain, pruritus, and edema; occur within 1 to 2 days of the injection; and resolve in 3 to 5 days. The majority of the dermal infiltrate in these ISRs is composed of CD8+ T cells, indicating a cell-mediated TH1 reaction. We present a patient who developed an eosinophilic cellulitislike reaction at the site of etanercept injection.

REPORT OF A CASE

Clinical Review

A 57-year-old white woman had a history of rheumatoid arthritis diagnosed 8 months prior to presentation. After 5 months of therapy with prednisone, methotrexate, and hydroxychloroquine sulfate, the patient still had active arthritis, and adalimumab, 40 mg subcutaneously every other week, was added to her treatment regimen with rapid...
improvement. Within 24 to 48 hours of her fourth dose of adalimumab, she developed an ISR initially composed of faint, erythematous macules, which rapidly evolved into an erythematous, indurated plaque surmounted by a bulla (Figure 1). Adalimumab therapy was discontinued, the patient was treated with antibiotics and rest, and the ISR resolved. No biopsy was performed.

Two weeks later, the patient began treatment with etanercept, 25 mg subcutaneously twice weekly. Within 24 hours of her first dose, the patient developed an evanescent, pruritic, slightly indurated, erythematous plaque surrounding the injection site. Within 12 to 24 hours after her second injection, a much larger ISR developed.

On presentation to our clinic, 3 days after her second injection of etanercept, the patient reported that the reaction had continued to increase in size. Physical examination revealed a healthy-appearing white woman with a faintly erythematous, slightly raised plaque encompassing nearly two thirds of her right thigh, with extension inferiorly and medially from the injection site. Within this large plaque, and surrounding the actual injection site, was a more inflamed and indurated red plaque measuring 8 cm in diameter (Figure 2). The remainder of the examination revealed only an 8-cm faintly erythematous patch on the right side of her abdomen, at the site of her first etanercept injection. Notably, the patient had no history of an arthropod bite, and a full body examination failed to reveal bites elsewhere.

A skin biopsy was performed, and the patient was treated with oral antihistamines and prednisone (40 mg daily), with complete resolution of the ISR over the next 2 days. At no time did the patient report symptoms of shortness of breath, hypotension, or fever. Results from a complete blood cell count and basic chemistry panel demonstrated no significant abnormalities.

**HISTOLOGY**

Routine histologic examination of the specimen obtained on day 3 of the ISR revealed a normal epidermis with moderate dermal edema, a superficial and deep perivascular and interstitial lymphocytic infiltrate, and numerous eosinophils (Figure 3). Eosinophils were observed in a dense interstitial pattern throughout the mid and deep reticular dermis. Areas of hyper eosinophilic collagen surrounded by eosinophils were seen in multiple foci throughout the dermis (inset, Figure 3). These features, combined with the clinical history, led to the diagnosis of eosinophilic cellulitis in response to etanercept injection.

**DERMAL TESTING**

Etanercept and adalimumab preparations contain mannitol at concentrations of 0.04% and 0.0096%, respectively. To rule out the possibility of mannitol hypersensitivity, skin testing was undertaken. Results from scratch tests using dilutions of 0.01%, 0.1%, and 1% were all negative (compared with a positive histamine control; histamine base, 1.8 mg/mL), and an intradermal test using 0.05 mL of a 1% mannitol solution also had a negative result. Because the etanercept required the addition of preserved saline for reconstitution, intradermal testing to benzyl alcohol was also performed and had negative results.
Injection site reactions are the most common adverse event associated with etanercept administration. They are generally mild, diminish with successive doses of drug (the so-called hardening response), cease within the first 2 months of therapy, and do not necessitate discontinuation of the drug. Up to 40% of patients with ISRs may develop a “recall ISR” at previous injection sites. The typical histopathologic findings in an etanercept ISR consist of mild dermal edema with a superficial perivascular infiltrate of lymphocytes and eosinophils.

In their immunohistochemical analysis of skin biopsies from etanercept ISRs, Zeltser et al. demonstrated that the majority of the dermal infiltrate is composed of mature CD4⁺/CD8⁺ cytotoxic T lymphocytes. On this basis, they proposed that etanercept ISRs may represent a delayed-type hypersensitivity reaction, an example of a T₄₁ reaction. Although delayed-type hypersensitivity reactions are typically mediated by CD4⁺ memory T cells, delayed-type hypersensitivity reactions mediated by CD8⁺ T cells via the endogenous pathway have also been recognized, most notably in allergic contact dermatitis, but also in drug eruptions.

In the present case, the histologic findings differ considerably from the well-characterized etanercept ISRs reported in the literature. First, the dermal changes in our case are those of eosinophilic cellulitis, unlike the lymphocyte-rich infiltrate seen in typical etanercept ISRs. Second, the history of worsening ISRs with subsequent injections is at odds with the usual “hardening” response seen in etanercept ISRs. These 2 observations suggest that the underlying immune mechanism in the present etanercept ISR may differ from the delayed-type hypersensitivity mechanism proposed by Zeltser et al. The predominance of eosinophils points to a role for IL-5 and a mechanism more akin to a T₄₁₂ reaction. Indeed, a correlation between disease severity and levels of both IL-5 and eosinophil cation protein has been characterized in patients with Wells syndrome.

It is not known whether ISRs to etanercept are to the active drug or to a component of the vehicle, and in the present case, the target of the ISR remains unclear. Interestingly, the patient developed a clinically similar pattern of reactions to both adalimumab and etanercept, which are molecularly distinct biologic agents. The similarity of the reactions suggested that the patient may have had an allergic reaction to mannitol, the only common excitant in the administered forms of the drugs. Results from prick and dermal testing to mannitol were negative, but we cannot exclude the possibility of false-negative test results given the patient’s immunosuppressive therapy. A possible reaction to the other excipients in the etanercept solution cannot be excluded either because these were not tested. Alternatively, the ISRs may have been directed at the drugs themselves. In their discussion of etanercept ISRs, Werth and Levinson have suggested that neo–self-antigens may be created at the point of fusion of the tumor necrosis factor α receptor and FcγR proteins. The ISRs in this patient, however, may be explained by the rheumatoid factor autoantibody binding to the FcγR component found in both etanercept and adalimumab.

In conclusion, we present a case of an unusual ISR to etanercept with the histologic features of eosinophilic cellulitis. The histologic findings support an immunologic response that differs from the usual T₄₁ profile of ISRs reported in the literature to date. If differing immunologic mechanisms underlie various ISRs after etanercept injection, continued treatment may not always be advisable.

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