Severe Refractory Erythema Nodosum Leprosum Successfully Treated with the Tumor Necrosis Factor Inhibitor Etanercept

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Erythema nodosum leprosum (ENL), or type II reaction, is a common complication of lepromatous leprosy that can cause significant patient debility. First-line therapy includes prednisone and thalidomide, with clofazimine reserved for patients who do not respond to first-line treatment. We present the case of a 33-year-old woman with ENL that failed to respond adequately to conventional therapy over a 6-year period. Because of the severe nature of her disease and the adverse effects of therapy that she experienced, a trial of etanercept was undertaken, which led to full resolution of her ENL. The rationale behind our choice of therapy and its future implications are discussed.

Leprosy is an ancient infectious disease caused by Mycobacterium leprae that affects the skin and peripheral nerves. A wide clinical spectrum of disease exists, from the tuberculoid pole (associated with a vigorous Th1 response, relatively few bacilli, and limited well-defined lesions) to the lepromatous pole (associated with aggressive Th2 response, many bacilli, and diffuse symmetric lesions) [1]. The global burden of leprosy remains significant, with over 200 000 registered cases at the beginning of 2008 and over 250 000 new cases detected during 2007. Areas of high endemicity remain in several countries, including Brazil, India, Mozambique, and Nepal [2].

Erythema nodosum leprosum (ENL), or type II reaction, can occur before, during, or after treatment for leprosy and is a significant cause of morbidity in this patient population. It is a complex immune-mediated phenomenon secondary to the presence of the leprosy bacillus, which manifests clinically as tender erythematous subcutaneous nodules, together with a variable degree of systemic involvement. Fever, arthritis, lymphadenitis, neuritis, iridocyclitis, and nephritis may be present [3]. Although mild episodes of ENL can be treated symptomatically with anti-inflammatory agents and usually resolve spontaneously, more severe cases (ie, those with nerve involvement) require systemic therapy to prevent permanent complications.

Prednisone and thalidomide have been traditionally employed in the treatment of ENL in the absence of contraindications, with clofazimine reserved as a second-line agent [4]. Thalidomide is teratogenic and should not be given to women of child-bearing age without reliable forms of birth control, and clofazimine is associated with a cosmetically problematic deposition of pink-brown pigments in the skin and eyes that can take months to years to resolve after discontinuation of the drug. Long-term glucocorticoid therapy can cause serious complications.

Although most patients with ENL respond well to conventional therapy, a small number may be refractory to these agents. We present a patient with ENL recalcitrant to conventional therapy that was successfully treated with etanercept, a tumor necrosis factor alpha (TNF-α) inhibitor.

CASE REPORT

A 33-year-old woman born in the Philippines presented to our department in 2000 with a two-week history of pruritic erythematous papules and nodules over her face, wrists, forearms, buttock, calves, and dorsal feet accompanied by inguinal lymphadenopathy (Figure 1). She had thickened nontender right radial cutaneous and median nerves and signs of old ulnar neuropathy. Both earlobes were thickened. Slit skin smears showed the presence of acid-fast bacilli ranging from 2+ to 4+ at 6 different sites. She received a diagnosis of mild ENL accompanying lepromatous leprosy and initiated therapy with rifampin (600 mg administered once monthly), ofloxacin (300 mg administered once daily), and dapsone (100 mg administered once daily, after documenting a normal G6PD level). Two full years of multidrug therapy were planned.

However, within 2 months of initiating therapy, the patient developed new erythematous tender lesions of ENL associated...
with malaise and fever that initially improved with prednisone but then recurred. Despite multiple extended courses of prednisone (40–80 mg daily) and thalidomide (100 mg daily), over the next 6 years she had very few symptom-free intervals and experienced many adverse effects caused by the medication. Attempts to taper her prednisone dose below 40 mg led to a recurrence of ENL lesions, neuritis, and severe systemic symptoms. As a result of long-term steroid therapy, she developed Cushingoid features, hypertension, and osteoporosis leading to toe fractures and recurrent soft-tissue infections. Treatment with thalidomide likely contributed to the large femoral deep-vein thrombosis that she developed after foot surgery. A trial of clofazimine caused hyperpigmentation of her facial ENL lesions, resulting in significant psychological distress.

Six years after the onset of her ENL lesions, the patient was approved for treatment with etanercept at a dosage of 50 mg per week administered subcutaneously. After receiving etanercept for 6 weeks, the patient had improved significantly, allowing for a slow taper and eventual discontinuation of her prednisone. Thalidomide was continued for 6 months after the initiation of etanercept treatment, at which point it was also successfully discontinued. The patient ultimately received etanercept therapy for 2 years. She remained symptom-free until 1 year after completion of therapy, at which point she required an additional 3-month course of thalidomide (100 mg once daily) for a recurrence of ENL lesions. Other than this single recurrence, she has remained asymptomatic over 2.5 years after completing her course of etanercept and has experienced no residual lesions or scarring.

**DISCUSSION**

The underlying immunologic mechanisms for ENL remain unclear. Beginning with the pioneering work of Wemambu et al in 1969, ENL has traditionally been considered an immune complex–mediated phenomenon with an accompanying vasculitis [5–7]. However, high levels of TNF-α and interleukin-6 are consistently found in patients with more severe disease, which suggests that a cell-mediated immune response also plays a role [8].

The consistent over-expression of TNF-α in patients with severe ENL provided the rationale for the use of TNF-inhibitory agents reported by Faber et al (who used infliximab) [9] and in treating our patient (who received etanercept) when conventional treatment options had been unsuccessful in controlling symptoms.

Although infliximab is a human-murine chimeric monoclonal antibody against TNF-α itself, etanercept is a dimeric fusion protein that consists of the extracellular portion of the p75 TNF receptor coupled to the immunoglobulin (Ig) G1 portion of human IgG1 (a soluble TNF-α receptor). Both are effective at reducing TNF-α levels. Studies have revealed an increased risk of reactivation of latent tuberculosis infection with infliximab (which is an antibody), compared with etanercept (which is a soluble receptor), explained by several hypotheses [10–11]. First, infliximab appears to have a higher affinity for transmembrane-bound TNF-α than does etanercept; it is suggested that infliximab-mediated lysis of granuloma macrophages bearing TNF-α may lead to release of bacilli into the bloodstream [12–14], with subsequent tuberculosis reactivation. Second, infliximab inhibits the transmembrane TNF-mediated signaling required as part of host immune responses more completely than does etanercept [14]; infliximab binds and forms more stable complexes with TNF-α than does etanercept [12], and its smaller size may allow increased penetration into granulomas [14]. The unstable and reversible complexes formed between etanercept and TNF-α allow the host to maintain some degree of immune response to TB and other infections. Third, infliximab has also been shown in vitro to inhibit IFN-γ production, which is part of the host defense against tuberculosis infection, whereas etanercept does not [12, 15]. These differences have been used to explain why etanercept therapy presents less of a risk of tuberculosis [14, 16] and granulomatous disease [10, 12] than does infliximab. We chose to use etanercept, because we extrapolated that it causes less host immunosuppression than does infliximab. Additional advantages of etanercept are patient convenience and decreased cost, because the patient can be trained to self-administer injections.

Not all studies support the role of TNF-α in ENL. One prospective study involving 20 patients who were treated with...
thalidomide for ENL showed that TNF-α levels were not elevated at baseline and increased only moderately during treatment, although the variable severity of ENL in the cohort could account for the findings [17]. A Philippine trial of thalidomide for ENL conducted in a cohort of 22 men in 2005, found no elevated pre- or post-treatment TNF levels in any of the participants, although patients with severe neuritis and incapacitating ENL were excluded from the study [18].

The impressive clinical response of our patient to etanercept, along with the similarly impressive clinical response of the patient reported by Faber et al [9] to infliximab, provides additional evidence to support an important role of TNF-α in severe ENL. Further basic studies are needed to determine the role of TNF-α in the pathogenesis of ENL. In conjunction, randomized controlled trials are necessary to clarify the role of inhibition of TNF-α in treating patients who have severe ENL that is unresponsive to standard therapy.

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References