Treatment of Refractory Ulcerative Necrobiosis Lipoidica Diabeticorum With Infliximab

Report of a Case

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Background: Necrobiosis lipoidica diabeticorum (NLD) is a rare, granulomatous inflammatory skin disease of unknown origin, sometimes associated with diabetes mellitus. Skin lesions usually develop on the lower extremities and can progress toward ulceration and scarring. Many treatments have been proposed, but few have demonstrated consistent efficacy, and no standard regimens have emerged to date.

Observations: An 84-year-old woman with type 1 diabetes mellitus presented with a 3-year history of chronic right-lower-extremity erythematous papules and plaques that had developed into confluent ulcers with prominent granulation tissue and an orange-yellow hue. The results of a biopsy of the lesion was consistent with a diagnosis of NLD. The wound did not respond to 4 months of intensive local wound care. After the first intravenous infusion of infliximab (5 mg/kg), there was rapid reduction in wound size, pain, and drainage. There was complete wound healing with excellent cosmesis at 6 weeks (total of 3 infusions).

Conclusions: Infliximab should be considered in the treatment of refractory, ulcerative NLD. Its anti–tumor necrosis factor activity may underlie its efficacy in targeting this granulomatous process, and further investigation should be undertaken to confirm these results.


REPORT OF A CASE

An 84-year-old woman had a 3-year history of chronic right-lower-extremity erythematous papules and plaques, some of which developed into confluent ulcers, extending from the right knee to the medial malleolus, punctuated with islands of normal-appearing skin. Prominent granulation tissue was present at the base of the ulcers, and healed areas harbored an orange-yellow hue. The results of a biopsy of a leg lesion taken during the initial onset of the disease showed an ulcerated epidermis and necrotic collagen with sclerosis and palisaded granulomas in the dermis (Figure 1). The dermal interstitial infiltrate consisted of histiocytes, multinucleated giant cells, lymphocytes, and plasma cells. These findings were consistent with a diagnosis of NLD. Her medical history was significant for type 1 diabetes mellitus, 2 prior strokes, idiopathic thrombocytopenic purpura (status post splenectomy), mild renal insufficiency, and hypertension. She also had a history of cho-
lecystitis with subsequent granulomatous inflammation, but no evidence of sarcoidosis.

During the 1-month period before her initial presentation at the Angiogenesis & Wound Healing Center, Brigham and Women’s Hospital, the patient experienced a fulminant expansion and ulceration of the lesions, with the ulcers extending over her shin and calf (Figure 2). She was initially treated with intralesional triamcinolone acetonide (5 mg/mL) and intensive local wound management, which included sharp debridement, papain-urea enzymatic debriding ointment, cadoxem-iodine antiseptic gel, Prisma Promogran (1% silver-ORC [oxidized regenerated cellulose]-collagen, Johnson & Johnson Wound Management, Somerville, New Jersey) bioactive dressing, and compression strapings. The wounds remained open and inflamed despite 4 months of this treatment regimen.

Given the lack of response to intensive local wound care, we theorized that the underlying pathogenic process of NLD might respond to an anti-TNF approach, and we decided to treat the patient with intravenous infliximab at a dose of 5 mg/kg. Before the initiation of anti-TNF treatment, a negative purified protein derivative (tuberculin) test result was confirmed. She received a total of 5 infusions (at weeks 0, 2, 6, 12, and 21). At her first posttreatment visit (week 2), the surface area of the larger ulcerations had decreased by approximately 50%, and the smaller lesions had almost completely reepithelialized (Figure 3). She also reported decreased pain and drainage in the involved areas. Complete wound healing was achieved at week 6 of infliximab therapy, with excellent cosmesis. The patient experienced no adverse effects from infliximab and no recurrence of the lesions during clinical follow-up more than 1 year.

**COMMENT**

Necrobiosis lipoidica diabeticorum is a chronic granulomatous disease of unknown origin, occurring 3 times more frequently in women than in men, particularly in patients aged 30 to 40 years, and often on the shins, back of the hands, or the forearms. Seventy-five percent of patients with NLD have or will develop diabetes mellitus (type 1 more often than type 2), although only approximately 0.3% of diabetic patients develop NLD. Although ulceration has been reported in 13% to 35% of cases, usually in the setting of trauma, spontaneous rapid and fulminant ulceration is uncommon. Spontaneous remission has been reported in approximately 20% of patients.

To our knowledge, there is currently no standardized, effective treatment of NLD in clinical practice. First-line therapies include topical and intralesional corticosteroids. Smoking cessation and diabetic control may also be effective because reports have documented the beneficial effects of thiazolidinediones in NLD; however, treatment of a patient’s diabetes has not been shown to improve the cutaneous lesions. Other therapies that have been tried, with varying degrees of success, include systemic corticosteroids, topical retinoids, pentoxifylline, aspirin and dipyridamole, clofazimine, hyperbaric oxygen, fumaric acid esters, thalidomide, topical tacrolimus, mycophenolate mofetil, cyclosporine, and sometimes excision in the case of recalcitrant ulcers. Topical psoralen–UV-A and photodynamic therapy have been effective, and pulsed dye lasers can improve the appearance of telangiectasias. Recently, 7 in a series of 8 patients were reported to show clinical improvement with antimalarial therapy.
Infliximab is a monoclonal antibody that binds to TNF and is currently approved for the treatment of inflammatory bowel disease, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis. Infliximab blocks soluble and transmembrane-bound TNF and leads to a number of anti-inflammatory effects and cytolysis of inflammatory cells expressing TNF receptors. Tumor necrosis factor is a pro-inflammatory cytokine, and blockade results in amelioration of inflammatory conditions, which includes the reduced formation of granulomas. As such, infliximab has been shown to be beneficial in chronic cutaneous granulomatous diseases, such as disseminated granuloma annulare and sarcoid.

In both cases of ulcerative NLD, a dose of 5 mg/kg was used. In the article by Drosou et al., a 32-year-old woman with extensive ulcerative NLD, who did not respond to 40 mg per day of prednisone, showed complete healing after 2 infusions of infliximab. In the case reported by Kolde et al., a 33-year-old man experienced substantial clinical improvement after infliximab therapy; however, treatment was terminated because of reactivation of tuberculosis resulting from the therapy. This highlights the importance of screening for prior exposure to tuberculosis before initiating treatment with infliximab.

Interestingly, one case of an NLD lesion in a 35-year-old woman with well-controlled type 1 diabetes mellitus was previously reported to be treated successfully with etanercept, another TNF antagonist in the form of a dimeric fusion protein that binds the cytokine. Initial improvement was seen by the first month of intradermal etanercept injections (25 mg) into the dermis, with complete resolution after 8 months. Mechanistically, inhibition of the granulomatous process underlying NLD may serve as the basis for the efficacy of other agents as well: both thalidomide and pentoxifylline have been shown to antagonize this TNF.

Given the marked response of infliximab therapy in our patient with recalcitrant ulcerative NLD, we believe that an anti-TNF approach holds promise in the treatment of this disease, and infliximab should be considered as a therapeutic option for patients with this condition. Because the current literature on therapy of this disease lacks controlled studies, further investigation is warranted to establish the efficacy of the anti-TNF approach (infliximab or other anti-TNF agents) in NLD and to better define the optimal dose and duration of treatment.

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