Silicone Granulomas Treated With Etanercept

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

A 47-year-old Hispanic woman was referred for evaluation of “recurrent cellulitis” of her lower extremities. Ten years previously, the patient had received a series of subcutaneous injections of “pure silicone” into the calves and buttocks for cosmetic purposes. These were performed in the home of a nonprofessional in the Dominican Republic. Four years before consultation, the patient developed an abscess of the right buttock that healed with cephalaxin. One year before coming to us, the patient sustained minor trauma to the right lower extremity in a motor vehicle crash. No laceration or fracture occurred. Six months later, the patient developed 3 abscesses in the right calf. The lesions were incised and drained by the surgery service, and the patient was empirically started on a combination of intravenous piperacillin and tazobactam. Multiple cultures were negative except for 1, which grew Nocardia asteroides complex. Treatment was changed to a combination of trimethoprim and sulfamethoxazole. The patient developed an anaphylactoid reaction and was subsequently given a 2-month course of intravenous amikacin and imipenem. The abscesses slowly healed, but during treatment the patient developed recurrent episodes of pain, erythema, and swelling of both legs associated with low-grade fever and malaise. Following discontinuation of therapy with amikacin and imipenem, the patient was treated with 2 weeks of linezolid for possible cellulitis, without benefit. The patient was referred to our dermatology clinic.

Physical examination revealed marked erythema, swelling, induration, and tenderness of the anterior and posterior legs and ankles (Figure 1A). There was mild erythema and edema of the posterior thighs. There were well-healed scars at the sites of prior abscesses and no fluctuant lesions or ulcers (Figure 2A). There was no lymphadenopathy, and the patient was afebrile. Histopathologic examination of a biopsy specimen of the left posterior thigh, an area that had not been injected, showed lipidlike material within the subcutis surrounded by histiocytes, consistent with silicone granuloma. Bacterial, deep fungal, and atypical mycobacterial tissue cultures were negative.

Minocycline treatment was stopped, and both patients were started on a regimen of 25 mg of etanercept subcutaneously twice weekly after negative purified protein derivative (tuberculin) results were confirmed. This treatment resulted in a dramatic improvement in pain and

2 weeks. However, after 2 months of therapy, the patient’s clinical condition deteriorated to baseline. She was severely depressed and had difficulty ambulating secondary to pain.

CASE 2

A 37-year-old Hispanic woman presented with a 3-month history of painful, exquisitely tender, erythematous nodules and induration of the buttocks (Figure 3A). The lesions developed 5 months after she received a series of 3 injections of “silicone” into her buttocks at 2-week intervals at a neighborhood spa in upper Manhattan, New York, NY. The patient was severely depressed, complained of pain in her buttocks not relieved by high doses of nonsteroidal anti-inflammatory drugs and hydrocodone, and could not sit, sleep, or work. She was afebrile and had no lymphadenopathy. Histopathologic examination of a biopsy specimen of the buttock showed a granulomatous inflammatory infiltrate of lymphocytes, histiocytes, and multinucleated giant cells surrounding lipidlike material, consistent with silicone granuloma. Bacterial, deep fungal, and atypical mycobacterial tissue cultures were negative. The patient was started on treatment with 100 mg of minocycline twice daily, with decreased erythema of the buttocks after 1 month of treatment but no improvement in pain. The patient complained of intolerable, constant pain and was suicidal.

Treatment of silicone granulomas is difficult and often unsuccessful. Modalities have included intralesional and systemic corticosteroids, minocycline, imiquimod cream, liposuction, lasers, and local resection. Surgical excision is difficult because of migration of silicone to distant sites, resulting in incomplete removal or requiring wide excision.

Minocycline treatment was stopped, and both patients were started on a regimen of 25 mg of etanercept subcutaneously twice weekly after negative purified protein derivative (tuberculin) results were confirmed. This treatment resulted in a dramatic improvement in pain and
tenderness in both patients within 2 weeks. In patient 1, there was decreased erythema, swelling, and tenderness of the ankles (Figure 1B) and legs (Figure 2B) after 1 month of etanercept and almost complete resolution after 2 months of treatment. The induration had diminished slightly. The patient was ambulating well and reported that she had gone dancing for the first time in a year. Etanercept was discontinued after 2 months of treatment. On follow-up 1 month later, the patient was still in remission. However, 2 months after stopping etanercept, the patient redeveloped pain and tenderness in her legs but to a lesser extent than she had experienced previously. The physical examination findings were otherwise unchanged. Etanercept was restarted at the previous dosage, with resolution of symptoms within 2 weeks. Our plan is to treat disease flares with etanercept, with the goal of inducing a long-term remission.

After 1 month of treatment, patient 2 had resumed her job and was able to sit and sleep comfortably. There was no change in induration or nodularity of her buttocks, but the erythema and tenderness had resolved (Figure 3B). She was no longer depressed. At 2-month follow-up, the patient remained in remission.

**COMMENT**

Liquid silicone (dimethyl polysiloxane) has been used for soft tissue augmentation for more than 50 years. Pure liquid silicone is nontoxic, noncarcinogenic, chemically inert, and does not support the growth of microorganisms. It is easily injectable, permanent, and inexpensive. It has never been approved for use as a soft tissue filler in the United States but is approved by...
the Food and Drug Administration for intraocular injection and is being used off-label as a filler for facial rhytides and in investigational protocols for human immunodeficiency virus–related lipoatrophy and severe facial deformities.8,9

There is enormous controversy regarding the safety of silicone.8,9 There have been numerous reports of severe complications following liquid silicone injection for soft tissue augmentation. Most of these problems have occurred following the injection of massive volumes of impure, questionable-grade, adulterated silicone (or other viscous fluids purported to be silicone) into the breasts, buttocks, hips, and legs performed by unqualified laypersons in nonmedical facilities. Proponents argue that liquid silicone is a “time bomb” and that disastrous, uncorrectable complications can occur despite good technique, good material, and small amounts injected.8,9

Serious reactions to silicone injections have been reported, occurring 3 weeks to 23 years after treatment.10 They are unpredictable and often uncorrectable. They include granulomas, cellulitis, abscesses, draining sinuses, nerosis, scarring, contractures, and deformities.11 Silicone granulomas manifest clinically as recurrent cellulitis-like reactions with pain, induration, nodules, ulceration, and local lymphadenopathy.12 Systemic complications have also been reported, including acute pneumonitis, granulomatous hepatitis, organ compression, and sudden death secondary to intravascular embolization.3

The pathogenesis of silicone granulomas is unknown, although it is believed to involve T-cell activation, possibly triggered by infectious processes, adulterants added to silicone to enhance fibroplasia, or denaturing host proteins adsorbed to silicone. Silicone granulomas are associated with elevated levels of tumor necrosis factor α (TNF-α).11 Tumor necrosis factor α is a proinflammatory cytokine that plays an important role in granuloma formation in many diseases, including sarcoidosis and Crohn disease.11 The TNF inhibitors infliximab and etanercept have been used successfully in patients with these diseases.13,14 These agents would thus appear to be a promising treatment for silicone granulomas. We chose to use etanercept rather than infliximab because of its ease of administration.

Etanercept is a human fusion protein of 2 p75-soluble TNF receptors and IgG1. It binds to both the soluble and transmembrane form of TNF-α and blocks its interaction with cell surface receptors, rendering it biologically inactive. It is approved by the Food and Drug Administration for use in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis and may soon be approved for psoriasis. It is being tested in clinical trials for a variety of inflammatory disorders15 and has been used with dramatic, rapid success for treatment-refractory pain due to cancer metastases to bone16 and for discogenic neck pain.17 Etanercept is administered by the patient subcutaneously twice weekly. The drug is well tolerated and has a good safety profile.18 The most common adverse effects are minor injection site reactions. There have been rare reports of serious infections and sepsis, reactivation of tuberculosis, lupuslike syndromes, new onset or exacerbation of demyelinating disorders, aplastic anemia, and new onset or worsening of congestive heart failure.19,20 It has not yet been established whether there is an increased risk of lymphoproliferative disease, but this is being closely monitored.

Both patients’ pain, tenderness, and erythema responded dramatically to etanercept within 2 weeks of treatment. Induration decreased slightly after 2 months. Neither patient experienced any untoward effect while taking etanercept. Placebo effect and spontaneous improvement cannot be excluded.

To our knowledge, the present cases indicate for the first time that a TNF inhibitor could be of benefit for silicone granulomas, a condition that has proved recalcitrant to therapy in the past. Further data and experience are needed, and the long-term safety of etanercept must be monitored.

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REFERENCES


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