Successful Treatment of Recalcitrant Pemphigus Vulgaris and Pemphigus Vegetans With Etanercept and Carbon Dioxide Laser

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 26-year-old woman presented with a 5-month history of painful oral erosions and a 1-month history of widespread flaccid vesicles over her face and torso. A biopsy specimen of a skin lesion revealed suprabasal acantholysis. The diagnosis of pemphigus vulgaris (PV) was confirmed by a positive intercellular (IC) antibody titer. The patient was treated with prednisolone (30-45 mg/d) combined with other immunosuppressive agents, including azathioprine (100 mg/d), cyclophosphamide (100 mg/d), methotrexate sodium (15 mg/wk), mycophenolate mofetil (1 g/d), and dapsone (100 mg/d), at different times over a 2-year period. The clinical course was complicated by episodes of severe flare, with hemorrhagic paronychia and onychomadesis that required pulse therapy with methylprednisolone, with or without cyclophosphamide, and intravenous immunoglobulin therapy. The disease proved to be recalcitrant to all these medications. The circulating IC antibody titer was 1:640. The treatments were associated with severe adverse effects, including iatrogenic Cushing syndrome, depression, severe infectious mononucleosis–like reaction with acute hepatitis, and cutaneous bacterial and fungal infections. The erosions on the face were particularly unresponsive to treatment, even with the addition of potent topical corticosteroids to the regimen.

THERAPEUTIC CHALLENGE

The patient was extremely distressed and depressed because of the unremitting disease activity with recurrent severe flares and disfiguring caused by the persistent facial lesions and moon facies (Figure 1). Various potent regimens had been used, but they were either ineffective or poorly tolerated, so the patient was in desperate need of an effective and tolerable new therapy.

SOLUTION

Recent reports indicate that tumor necrosis factor α (TNF-α) is involved in the pathogenesis of PV. These findings prompted us to try therapy with etanercept, a competitive inhibitor of TNF-α, in our patient. Treatment with subcutaneous injections of etanercept (25 mg twice weekly), in combination with prednisolone (30 mg/d) and azathioprine (100 mg/d) therapy, was initiated in December 2003. The lesions began to heal in 3 weeks, and the number of new blisters was greatly reduced to fewer than 1 per day. The dosage of prednisolone was reduced to less than 20 mg/d for the first time after 2 weeks of etanercept therapy. By week 16, the skin lesions had almost completely healed, except for the hypokeratotic plaques over the chin, which were pathologically shown to be pemphigus vegetans (Figure 2). Despite our recommendation of a gradual tapering of the immunosuppressant therapy, the patient accelerated the tapering process by lowering the dosage to 5 mg/d of prednisolone and 30 mg/d of azathioprine by March 2004, and she was no longer taking either medication by May 2004. The titer of IC antibody was reduced to 1:80 by April 2004 and to 1:20 by August 2004. Although the blistering of PV was successfully controlled by etanercept therapy, the vegetative lesions on the patient's face per-
Pemphigus vulgaris is an autoimmune bullous disease of the skin and mucosa that leads to flaccid blisters and erosions. It is caused by IgG autoantibodies primarily against desmogleins 1 and 3, which are adhesion molecules in the desmosomes of keratinocytes. Treatment of severe PV often poses great problems. Systemic corticosteroid therapy is still the mainstay of treatment for pemphigus. However, the therapy is limited by various adverse effects. To decrease these adverse effects, steroid-sparing agents, such as azathioprine, cyclophosphamide, cyclosporine, mycophenolate, and dapsone, are often used. Recent advances suggest that cholinergic control of keratinocytic adhesion and proinflammatory cytokines, particularly TNF-α, is involved in the pathogenesis of PV. Nguyen et al reported that nondesmoglein autoantibodies to cholinergic receptors can also induce clinical features of PV. These cholinergic receptors regulate adhesion and motility of keratinocytes, and their activation by autoantibodies may trigger intracellular signals and result in disassembly of desmosomes and acantholysis. The role of cholinergic control of keratinocytic adhesion was further supported by the successful control of PV with the acetylcholinesterase inhibitor pyridostigmine bromide (360 mg/d).

Tumor necrosis factor α is an important proinflammatory cytokine and plays a critical role in activating innate and acquired immune responses. Several lines of evidence indicate that TNF-α as well as interleukin (IL)-6 and IL-1 are mediators in the blistering process of pemphigus. Ameglio et al reported that serum levels of TNF-α and IL-6 correlate with the disease activity and titers of IgG antibody. The levels of TNF-α and IL-6 were shown to be increased in serum as well as in blister fluid. Feli ciani et al reported in vitro as well as in vivo expression of TNF-α and IL-1α in PV. They also reported that C3 messenger RNA expression is increased by TNF-α and IL-1α.

Recently, anti–TNF-α therapy has been reported to be effective in treating various inflammatory diseases, most notably rheumatoid arthritis, psoriasis, and psoriatic arthritis. Its efficacy has been confirmed by randomized control studies. Two different agents have been developed to neutralize TNF-α activity, ie, a neutralizing antibody (infliximab and adalimumab) and a fusion protein of TNF-α receptor (etanercept). The latter is a recombinant fusion protein that consists of the extracellular ligand-binding domain of the human 75-kDa TNF-α receptor and the Fc portion of human IgG1. Etanercept acts as a competitive inhibitor of TNF-α by binding TNF-α and preventing its interaction with the cell surface receptor.

Etanercept therapy was very effective in our patient. The blisters began to heal in about 3 weeks. The disease was controlled for the first time in 2 years. Etanercept therapy also allowed smooth tapering and discontinuation of treatment with prednisolone and azathioprine. It has been used successfully in other inflammatory diseases, including Behçet disease, Wegener granulomatosis, sarcoidosis, scleroderma, and a single case of cicatricial pemphigoid. In the reported case of cicatricial pemphigoid, the disease was resistant to treatment with oral prednisolone, azathioprine, mycophenolate, and topical cyclosporine. After the third dose of etanercept, oral blistering ceased and the dosage of prednisolone was quickly reduced from 60 mg/d to 7 mg/d. A total of 6 injections were administered, and the patient remained disease-free for 8 months at a prednisolone dosage of 1 mg/d.

Etanercept therapy is well tolerated. The adverse effects include injection site reaction (37%) in the first month, usually in the first 3 to 5 days, respiratory tract infections (35%), headaches (20%), and rash (10%). Central nervous system demyelinating disorders, sepsis, aplastic anemia, pancytopenia, and lupuslike conditions also have been reported. There were no adverse effects in the present case.

Interestingly, although etanercept was effective in treating the blistering of PV, it did not have any obvious effect...
on the vegetative lesions of pemphigus vegetans. The lesions were treated by carbon dioxide laser, with excellent result. The outcome suggests that the carbon dioxide laser may be an effective treatment option for recalcitrant pemphigus vegetans.

In summary, we report a case of recalcitrant PV and pemphigus vegetans that was successfully treated by etanercept and carbon dioxide laser. To the best of our knowledge, this is the first case report of such treatment for pemphigus. The present case illustrates that etanercept therapy can be an effective adjunct in treating severe cases of PV that are resistant to potent immunosuppressant therapy. Etanercept therapy also allowed smooth and rapid tapering and discontinuation of immunosuppressant therapy. Etanercept therapy also allowed smooth and rapid tapering and discontinuation of immunosuppressant therapy in our patient. The therapeutic effect of etanercept observed in our patient is encouraging, but further clinical study is warranted to confirm efficacy and to optimize treatment protocol. Vegetative lesions of pemphigus vegetans may not respond to etanercept therapy but can be treated with carbon dioxide laser.

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