Successful Treatment of Granulomatous Cheilitis With Thalidomide

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 39-year-old woman presented with a 5-month history of painless, nonitching swelling of the upper lip (Figure 1). In addition, she had a symptomless lingua plicata. A biopsy specimen revealed cheilitis with edema and perivascular lymphohistiocytic infiltrates (Figure 2) pointing to an early stage of cheilitis granulomatosa (CG). There was no neurologic abnormality such as facial palsy. Also, there were no findings or history of previous infection or local contact allergy. Systemic clofazimine therapy was started at 200 mg/d but discontinued after 2 weeks because of a morbilliform eruption. Over the following 4 months, dapsone therapy at 50 mg/d had no effect. Thereafter, prednisone treatment at 40 mg/d for 10 days reduced the lip swelling but was followed by an immediate recurrence on discontinuing the treatment.

THERAPEUTIC CHALLENGE

Cheilitis granulomatosa by itself or as part of the Melkerson-Rosenthal syndrome is characterized by a chronic course. In our patient this could not be controlled by clofazimine, dapsone, or prednisone. Another therapeutic option was needed.

SOLUTION

Since tumor necrosis factor alpha (TNF-α) is a key chemokine in most types of acute and chronic inflammation,1,2 thalidomide was considered as an alternative therapeutic approach. Treatment consisting of 100-mg/d oral thalidomide was initiated. Over the next 6 months, the lip swelling almost completely disappeared (Figure 3). Thalidomide treatment was then reduced to 100 mg every other day for 2 months, and no recurrence was observed. Therapy was then stopped. One year after discontinuation of the therapy, the patient’s condition was still stable without any signs of a relapse.

In view of the potential adverse effects, most notably teratogenicity and peripheral neuropathy, absence of pregnancy, effective contraception, and a normal neurological status were ascertained prior to treatment. Routine laboratory parameters including red and white blood cell counts and liver transaminase levels, neurological status, and clinical findings were regularly monitored during administration of thalidomide. The treat-
Cheilitis granulomatosa is clinically characterized by painless soft to firm swelling of one or both lips. Histologically, lymphedema, perivascular lymphocytic infiltration, and to a varying degree nonnecrotizing granulomas are seen.3,4 The undefined etiology of this inflammatory disorder has led to a variety of anti-inflammatory treatment strategies. Glucocorticosteroid therapy, either systemic or intralesional, generally may reduce the macrocheilia. But the response is temporary in most patients, and therapy requires multiple injections or repeated treatment cycles.5 The antileukocyte drug clofazimine has been reported to reduce the inflammatory lip swelling with remissions lasting for at least several months after treatment.6,7 However, in our patient, clofazimine had to be discontinued owing to a morbilliform eruption. Despite promising results reported by some authors using the immunomodulatory agent dapsone, the value of this drug for treatment of CG is still unclear.8 Similar anti-inflammatory and immunoregulatory properties are ascribed to antimalarial agents (eg, hydroxychloroquine). A treatment alternative that has not been evaluated for CG therapy is thalidomide.

Initially promoted as a sedative agent, thalidomide was withdrawn from the market because of its teratogenicity.9 This drug has since been reintroduced selectively for the treatment of diseases with an underlying autoimmune or inflammatory mechanism.10 Thalidomide has been found useful for the treatment of diseases such as erythema nodosum leprosum,11,12 sarcoidosis,13 prurigo nodularis,14 discoid lupus erythematosus,15,16 aphthous manifestations including Behcet syndrome,17,18 pyoderma gangrenosum,19 rheumatoid arthritis, and graft-vs-host disease.20,21 These observations and the postulated inhibitory action of thalidomide on TNF-α production prompted us to consider thalidomide therapy in our patient as well.

With regard to the mechanism of action, multiple effects of thalidomide have been demonstrated in vivo and in vitro.10,22-24 Thalidomide exerts specific inhibitory action on TNF-α. It decreases the responsiveness of polymorphonuclear cells to chemotactic factors and is associated with a reduction of monocyte phagocytosis and fibroblast growth factor–induced angiogenesis. However, many of these effects may be secondary to the inhibition TNF-α. With regard to adverse effects, most notably teratogenicity and the possibility of severe and irreversible neurotoxic effects, baseline evaluation and follow-up monitoring of patients is required.20 By treatment with anti–TNF-α antibodies (such as infliximab) and administration of soluble TNF receptors (such as etanercept), a significant benefit can be produced in patients with severe rheumatoid arthritis.25 Since both of these therapies are likely to be used in conjunction with methotrexate and questions of safety and efficacy over the long term still need to be resolved, we have not yet considered this approach for treatment of CG.

In summary, we describe the effectiveness of thalidomide in a patient with CG resistant to all of the conventional therapies published. In the follow-up 1 year after discontinuation of medical treatment, the patient remained free of disease in contrast to the prior relapse following corticosteroid therapy. We presume that the strong anti-inflammatory effects of thalidomide cleared the underlying inflammation to such an extent that the result was a prolonged disappearance or even cure of her CG.

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REFERENCES


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