A 50-year-old woman presented with a 24-year history of recurrent aphthous stomatitis. Nine to 12 new lesions usually appeared weekly, resolving in approximately 2 weeks. She experienced associated pain, dysphagia, and swelling of the lips and tongue with a subjective pain severity of 9 (scale, 1-10). Symptoms were exacerbated before menstrual periods and were unchanged with use of oral contraceptives and after menopause. There was no association with food or oral trauma, but she reported flares with emotional stress. She denied associated fever, genital ulcers, skin lesions, or ocular complaints.

On physical examination, there were small erosions (<5 mm) on the left lateral part of the tongue, gingival mucosa, and nonkeratinized labial mucosa, surrounded by erythematous halos (Figure 1). A complete blood cell count, levels of serum urea nitrogen, creatinine, electrolytes, vitamins B₁, B₂, B₆, B₁₂, folate, zinc, ferritin, serum iron, thyrotropin, and antinuclear antibodies, and herpes simplex virus culture were within normal limits or negative. Patch testing for sensitivity to mercury chloride amalgams was also negative. A biopsy specimen showed a mucosal ulceration with acute and chronic inflammation.

Frequent tapered courses of oral prednisone resulted in improvement of pain and healing of ulcers. Intramuscular and topical corticosteroids, viscous lidocaine, acyclovir, oral erythromycin, doxycycline, clotrimazole troches, and mouthwashes consisting of diphenhydramine hydrochloride, tetracycline hydrochloride, and prednisone provided only minimal and transient improvement of symptoms. Dapsone was started November 1995 but discontinued because of angioedema. Colchicine was started March 1996 but not tolerated because of diarrhea. Minocycline, doxycycline, and acyclovir were not effective.

Thalidomide, 50 to 100 mg daily, was started in November 1998, with significant improvement in the patient’s symptoms. However, thalidomide was discontinued because of a sensory peripheral neuropathy in her toes. She started treatment with gabapentin, which resulted in an improvement in her neuropathic symptoms. On discontinuation of thalidomide, she experienced flares consisting of 9 to 12 new erosions every 2 weeks with a subjective pain severity of 8, once again requiring systemic corticosteroids.

Treatment options for recurrent aphthous stomatitis include topical, intralesional, and systemic corticosteroids, azathioprine, dapsone, colchicine, pentoxifylline, oral tetracycline, and thalidomide. In our patient, her aphthous stomatitis was successfully controlled with thalidomide. However, she developed a sensory neuropathy that required its discontinuation. Other treatment options were either not tolerated or ineffective.

Etanercept (Enbrel), 25 mg subcutaneously twice weekly, was started in May 2001, resulting in significant improvement in the patient’s aphthous stomatitis within 1 month (Figure 2). After 7 months of treatment, the patient’s condition continued to flare, but...
with decreased frequency, severity, and duration. Flares occurred only once per month, usually with 3 erosions and a subjective pain severity of 3 to 4. Flares resolved in 3 to 5 days (as opposed to 2 weeks before therapy) and were treated with prednisolone syrup, swished and expectorated. The patient has not required systemic corticosteroids since that time. During one severe flare (pain severity, 6) in October 2001, the patient added 1 additional dose of etanercept (25 mg, 3 times per week instead of twice per week) for 1 week, and the flare resolved the next day.

The only adverse effects of etanercept in our patient have been mild erythema, induration, and tenderness at etanercept injection sites. These injection site reactions occur the day after administration of etanercept and resolve within 3 days, leaving postinflammatory hyperpigmentation and mild induration. She has treated these areas with topical hydrocortisone valerate cream. A complete blood cell count and differential count after etanercept administration are within normal limits.

Recurrent aphthous stomatitis is the most common inflammatory ulcerative condition of the oral mucosa in North America. The lesions are localized, painful, shallow ulcers typically on nonkeratinized or poorly keratinized mucosa, often covered by a gray fibromembranous slough and surrounded by an erythematous halo. Sites of predilection include the ventral surface of the tongue, floor of the mouth, and buccal, labial, soft palatal, and oropharyngeal mucosa. Lesions are classified into 3 groups: minor, major, and herpetiform ulcers. Minor aphthous ulcers are most common, less than 1.0 cm, and resolve within 3 to 5 days without scarring. Herpetiform ulcers are the least common variant, with numerous 1- to 2-mm grouped ulcers that coalesce, healing in 7 to 30 days. Most patients have infrequent recurrences, 2 to 4 times per year (simple aphthosis), while a few have almost continuous disease activity, large and deep ulcers, marked pain or disability, and occasional genital or perianal ulcers (complex aphthosis). A prodrome of burning or tingling at the site may occur. The lesions are usually noted in childhood or adolescence and recur with decreasing frequency and severity with age. The prevalence of recurrent aphthous stomatitis varies from 5% to 50% in the general population. Women are affected more commonly than men.2

The cause is unclear, with many possible predisposing factors, including trauma, emotional stress, hormonal state, family history, food hypersensitivity, viruses, bacteria, and immune dysregulation.2,3 Smokers have aphthous stomatitis less often and with less severity than nonsmokers, possibly secondary to the increased keratinization due to tobacco irritation.4 Evidence suggests a cytotoxic effect of peripheral blood lymphocytes toward oral epithelial cells. Depressed or reversed CD4/CD8 cell ratios, and increased T-cell receptor-γδ+ cells have been found in patients with active recurrent aphthous ulcers compared with control subjects and patients with inactive disease.7 Elevated levels of interleukin (IL) 2, interferon γ, tumor necrosis factor (TNF) α, IL-4, and IL-5 messenger RNA and lower levels of IL-10 messenger RNA have been detected in aphthous stomatitis lesions compared with healthy controls.8 The high expression of TNF-α in recurrent aphthous ulcers may contribute to the activation and recruitment of leukocytes in these lesions.7

Associated systemic diseases or correctable causes, such as Behçet disease; mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome; fever, aphthosis, pharyngitis, and adenitis (FAPA) syndrome; Reiter syndrome; cyclic neutropenia; human immunodeficiency virus disease; inflammatory bowel disease; celiac disease; and vitamin (B1, B2, B6, B12, folate, zinc, and iron) deficiencies, must be excluded. However, most patients have no associated condition.2,8-10

The most effective treatment options include topical, intralesional, and systemic corticosteroids11-13; azathioprine14; dapsone15; colchicine16,17; pentoxifylline18; and thalidomide.19-21 Patch testing to food additives and flavoring agents also may be of value.22 A gluten-free diet has been reported to be successful in some patients even in the absence of demonstrable celiac disease.23 Thalidomide remains the most effective agent at doses of 100 to 300 mg/d in healing minor and major recurrent aphthous stomatitis.19,21 Thalidomide inhibits the production of TNF and reduces its activity by accelerating the degradation of its messenger RNA.24,25 The teratogenicity, sedation, and peripheral sensory neuropathy associated with thalidomide unfortunately limit its use.26

Etanercept (Enbrel) is a recombinant TNF-soluble receptor composed of a dimeric fusion protein consisting of the extracellular portion of the human TNF receptor (p75) linked to the Fc portion of human immunoglobulin (IgG). The primary action of etanercept is competitive inhibition of TNF binding to cell surface TNF receptors, preventing TNF-mediated cellular responses.27 Etanercept is effective in reducing disease activity of rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, and psoriatic arthritis,27-30 and is currently being studied in other disorders, such as chronic heart
failure, sarcoidosis, ankylosing spondylitis, and Wege-
ner granulomatosis.27

Etanercept is well tolerated, and the most com-
monly reported events are mild to moderate injection site
reactions that do not result in ulceration or discontinua-
tion of treatment. The only adverse effect experienced
by our patient was injection site reactions, which have been
reported in 20% to 49% of patients within the first 2 months
of treatment and subsequently decrease in frequency. In-
jection site reactions are characterized by erythema, pain,
pruritus, or edema; occur 1 to 2 days after an injection;
and last 3 to 5 days. More than 90% of injection site re-
actions resolve without treatment; the rest are treated with
oral or topical antihistamines or topical corticoste-
roids.31-34 Injection site reactions may be an example of a
T-lymphocyte-mediated delayed-type hypersensitivity re-
action, with waning over time because of eventual induc-
tion of tolerance. Recall reactions, reactions at previous
injection sites after the last injection, may also occur with
continued etanercept treatment.33 There have been few re-
ports of unusual complications. Brion et al33 reported dis-
coid lupus and necrotizing vasculitis in patients with rheu-
matoid arthritis taking etanercept. Few patients (0.4%-
3%) develop antibodies to etanercept, but these antibodies
are sporadic and nonneutralizing and not correlated with
clinical response or adverse events.29,36 Etanercept has been
associated with upper respiratory tract infections, but se-
vere infections did not exceed those observed in control
groups.31,34,37 The frequency of nonlymphoid malignan-
cies is similar to the expected frequency in the age-
matched controls. However, long-term follow-up is nec-
essary.37 The numbers of observed tuberculosis cases to
date in patients receiving etanercept is similar to the ex-
pected background incidence. Unlike experience with anti-
TNF monoclonal antibodies, there is no temporal asso-
ciation between introduction of etanercept and onset of
clinical tuberculosis. Tuberculin skin testing has not been
required in etanercept clinical trials, but may be war-
ranted in patients with tuberculosis risk factors.36 The cost
of etanercept, 25 mg subcutaneously twice weekly, is ap-
proximately $1500 per month.

Etanercept has not been previously reported, to our
knowledge, for the treatment of recurrent aphthous stom-
atitis, but it has provided marked disease improve-
ment with minimal adverse effects in our patient, who
was unable to tolerate thalidomide. We propose that her
improvement is due to the inhibition of TNF-mediated
cellular responses by etanercept. This finding may offer
improvement is due to the inhibition of TNF-mediated

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Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in “Instructions for Authors.” Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017.

ARCHIVES Web Quiz Winner

Congratulations to the winner of our July quiz, Sultan Al-Khenaizan, MBBS, FRCPC, consultant dermatologist and pediatric dermatologist, King Fahad National Guard Hospital, Riyadh, Saudi Arabia. The correct answer to our July challenge was **leishmaniasis**. For a complete discussion of this case, see the Off-Center Fold section in the August ARCHIVES (Bradley VR, Liu V, Haynes HA. Rash with regional lymphadenopathy. Arch Dermatol. 2003;139:1075-1080).

Be sure to visit the Archives of Dermatology World Wide Web site (http://www.archdermatol.com) to try your hand at the Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of the The Art of JAMA II.