Erythema multiforme major following treatment with infliximab

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Background. The growth in the use of anti–tumor necrosis factor α (TNF-α) agents for treatment of inflammatory conditions has led to increased recognition of the side effects associated with this class of drugs.

Case description: We report a case of a patient who developed erythema multiforme (EM) major with characteristic oral and cutaneous lesions following treatment with the anti-TNF-α medication infliximab therapy for Crohn's disease (CD).

Clinical implications: To our knowledge, this is the first reported case of infliximab-induced EM secondary to the treatment of CD. It is important for dental clinicians evaluating patients using anti-TNF-α agents to be aware of this possible complication. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:e36-e40)

The number of patients treated with medications that neutralize tumor necrosis factor α (TNF-α such as infliximab (Remicade) and adalimumab (Humira) has increased over the past decade because of the long-term efficacy and effectiveness of these agents.[1] This number includes patients with chronic inflammatory diseases such as Crohn's disease (CD), rheumatoid arthritis, and ulcerative colitis. Although anti-TNF-α therapy is generally well tolerated,[2-5] adverse serious cutaneous and oral reactions have been reported with the use of the fully humanized monoclonal adalimumab, including hypersensitivity reactions, demyelinating disease, a lupus-like reaction, Stevens–Johnson syndrome (SJS), and erythema multiforme (EM) major.[6,7] Colombel et al.[5] reported an incidence of 4% to 22% infusion reactions to infliximab. The majority of patients discontinued further infliximab drug therapy. In a safety and efficacy study of infliximab for treatment of ankylosing spondylitis,[2] 4 patients in the infliximab arm (N = 201) developed serious adverse reactions. One developed drug-induced systemic lupus erythematosus, and a second patient discontinued treatment because of pleurisy, pericarditis, pulmonary embolism, systemic lupus erythematosus, and antiphospholipid syndrome. Two additional patients developed uveitis after dose escalation of infliximab. Clearly, these drugs, although efficacious and safe for the vast majority of patients suffering from immune-related inflammatory conditions, have a significant risk for secondary immune reactivity.

As noted above, SJS and EM major have been associated with anti-TNF-α use. As of 2008, the Food and Drug Administration (FDA) had received 21 reports of adult patients with severe cutaneous adverse reactions associated with infliximab, including EM (15 cases), SJS (5 cases), and toxic epidermal necrolysis (TENS).[8] Also, severe cutaneous reactions have been reported with etanercept and adalimumab.

Although EM/SJS/TENS reactions to anti-TNF-α agents are well documented by the FDA, the literature is sparse with regard to the publication of such cases related to infliximab and negligible with regard to oral lesions. Although there have been 21 infliximab-induced EM/SJS/TENS cases reported to the FDA, a review of the literature did not reveal the publication of such cases within the medical literature. Only Ahdout et al.[6] and Salama and Lawrance[7] noted the issue of major oral involvement, and all previous such cases were reported within medical journals with the focus upon the cutaneous lesions. Both of the above-mentioned case reports[6,7] noted oral involvement of EM/SJS reactions to adalimumab therapy. To our knowledge, this is the first reported case of infliximab-induced EM secondary to the treatment of CD. This report details the presentation of a woman who appeared with oral mucosal and cutaneous lesions consistent with EM major following treatment with infliximab for CD.

CASE REPORT

A 39-year-old Caucasian female, diagnosed with CD in 1996, was referred for evaluation of oral ulcerations that developed after a dental prophylaxis 4 weeks earlier. She reported that this was the second time she had developed oral lesions after visiting the dentist. Unlike the outbreak following the first dental visit, new oral ulcerations continued to erupt after the initial lesion development. The intraoral le-

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Received for publication May 30, 2012; returned for revision July 24, 2012; accepted for publication August 4, 2012.
Published by Elsevier Inc.
2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2012.08.001

sions increased in number, size, and severity compared with the first eruption and involved the buccal mucosa, labial mucosa, and tongue. There was a corresponding increase in her pain level. The oral lesions worsened after she received an infusion of infliximab 1 week later for the treatment of CD. That infliximab infusion would end up being her last, approximately 1 month prior to her examination by the National Institutes of Health dental clinic.

The patient's CD was diagnosed in 1996 and treated with azathioprine (Imuran) until 2006, with good control of her symptoms. In 2006, azathioprine was discontinued for an anticipated pregnancy. Postpartum, the drug was restarted, but the patient was subsequently hospitalized on 2 occasions for extreme "flares" of the gastrointestinal tract and joints symptoms believed to be rheumatoid arthritis. Sixty-five milligrams daily of prednisone was started, but discontinued because of side effects. In late 2008, the patient began treatment with 285 mg of (intravenous) infliximab every 2 months. Prior to the onset of her oral and cutaneous symptoms, she did not have any known complications during 2 years of infliximab treatment. When she appeared there was no history of Crohn's-associated oral ulcerations. No other significant medical history or allergies were noted.

Oral ulcerations (Fig. 1, a, b, and c) developed after the second dental visit. The oral presentation included shallow ulcerations with an erythematous halo and pseudomembrane on the labial mucosa and larger (1-cm) ulcerations on the tongue. Nikolsky's sign was negative. Furthermore, multiple cutaneous lesions were noted demonstrating small (less than 1 cm in diameter) erythematous papules on the hands, forearms, and plantar feet (Fig. 2, a–e). Several of the papules had a central dusky appearance. The patient's oral pain level was 7 out of 10. She was afebrile and without signs or symptoms of upper or lower respiratory tract infection. The differential diagnosis included viral infection, EM, SJS, allergic reaction, erosive lichen planus, pemphigus vulgaris, and mucosal pemphigoid. The histopathological appearance (Fig. 1, d) of the labial lesion revealed an acutely and chronically inflamed benign ulcer with marked spongiosis as well as intracellular edema with occasional necrotic keratinocytes. The histopathologic features were not consistent with diagnoses of oral CD, lichen planus, pemphigus, pemphigoid, or malignancy. The cutaneous biopsy demonstrated necrotic keratinocytes and perivascular lymphocytic infiltrate of the dermis without eosinophils, consistent with EM. Coxsackievirus A and B antibodies were negative/weakly positive, oral cultures and polymerase chain reaction for herpes simplex virus (HSV) were negative, and the patient did not respond to empiric treatment with oral acyclovir.

A diagnosis of EM major was made based upon the minimal cutaneous lesion presentation, the patient's history, the temporal relation to infliximab infusions, the histopathologic evaluations, and a negative evaluation for active HSV disease. The patient's treatment consisted of 5 mL dexamethasone rinse (0.5 mg/5 mL), swish and spit, every 6 hours for 7 days. The oral lesions resolved in 7 days without recurrence (Figure 1, e, f, and g). Skin lesions were treated concurrently with 40 mg prednisone, systemically for 1 week, with tapered doses in subsequent weeks. The patient's skin lesions gradually resolved in 5 weeks. Taking into consideration the lack of CD symptoms, the patient was not challenged with infliximab.

In subsequent 6-month and 1-year recalls, the patient had not had another oral flare-up. This seemingly can be attributed to the fact that the patient was taken off infliximab and once again placed on a daily dose of 125 mg of Imuran (not accompanied with any corticosteroid) for management of the patient's CD.

DISCUSSION

There were several challenges in the diagnosis of this case. First, CD may manifest as oral lesions (oral CD). Typically, oral CD presents as indurated taglike lesions, described as deep linear ulcers with hyperplastic margins; labial, buccal, or gingival swelling with induration; and cobblestone or hyperplastic appearance of the buccal mucosa.[9] EM is noted for its multiple ulcerations of the oral mucosal surfaces, often with prominent involvement of the lips. Multiple papules and vesicles are preceded by erythematous macules. The vesicles tend to rupture, leaving multiple areas of superficial erosions that are usually covered by a yellow fibrinous pseudomembrane.[10-13]

Another challenge in this case was to decide whether the patient had EM or SJS because both are reported to occur after anti-TNF-α therapy. In the past 20 years, a number of authors have reviewed the categorization of the diagnostic categories of EM major, SJS, and TENS and highlighted relatively new delineations and consensus regarding these terms.[11,14-17] EM major is highly variable with regard to its episodic frequency and the severity with oral mucosal lesions that occur in more than 70% of cases. Skin lesions, which may or may not be present, are characterized by atypical targetoid papules and plaques that are limited to $<$10% of the skin. There is a strong association with HSV, other infections including mycoplasma pneumoniae, and candidiasis in over 70% of cases, although medications are sometimes implicated.[11-16] Oral lesions are often painful, but in general the oral lesions associated with EM are less severe than those of SJS. EM lesions heal without scarring and have a negative Nikolsky sign, and medical complications are rare.[11,14-16] EM's histopathology tends to demonstrate inflammation with an abundance of lymphocytic infiltrate and necrotic keratinocytes.[11,14-17] Immunofluorescence was not utilized because the hematoxyin and eosin biopsy was sufficient, given the history and clinical appearance. Furthermore, HSV or other microbial infections may elicit further EM episodes, and antiviral suppression therapy may be necessary.[11,14-16]

SJS also demonstrates variability. It usually occurs within 45 days after a drug exposure, and reexposure to the same pharmacotherapy may result in secondary episodes with greater severity. A prodrome may occur