Crohn’s disease (CD) is a chronic inflammatory condition that is able to affect any portion of the digestive tract from the mouth to the anus. Oral Crohn’s disease (OCD) is a well-documented extra-intestinal manifestation of CD, first described in 1969 by Dudney and Todd (1). Numerous published case reports and series have documented this condition’s inconsistent and often disappointing response to traditional CD treatment modalities. More recently, several case reports have documented success in the treatment of OCD with infliximab, a chimeric monoclonal antibody against tumor necrosis factor alpha (2–8) (TNF-α). Here we report a case of severe OCD successfully treated with infliximab.
In 1999, the patient was referred to a gastroenterologist. The patient’s history also included a long history of relapsing and remitting lower gastrointestinal (GI) symptoms including diarrhea, constipation, anorectal bleeding, as well as daily fevers up to 39°C. In addition to the oral lesions, the physical exam of the patient was significant for a wasted appearance and rectal scarring. Laboratory values were significant for an erythrocyte sedimentation rate of 113, an albumin of 3.2, a white blood cell count of 12.3, and a hemoglobin of 11.2. An iron panel revealed a serum iron of 29, total iron binding capacity of 241 and serum ferritin of 153.

Endoscopy of the upper GI tract revealed a 1 x 0.5 cm esophageal ulcer with sharp margins and a gray-white base (Figure 1). Multiple biopsies were performed with histologic findings that were consistent with acute and chronic inflammation. Colonoscopy showed anorectal ulceration, scarring and inflammation with scattered areas of colitis. Significant involvement of the right proximal ascending colon, cecum and ileocecal valve was noted with multiple 30mm to 2cm well-circumscribed gray-white ulcers with intervening normal-appearing mucosa (Figure 2). Colonic biopsies showed chronic inflammation, reactive lymphoid hyperplasia and crypt distortion.

A diagnosis of Crohn’s disease was made at this time. The patient initially received treatment with oral prednisone, azathioprine, and repeated courses of antibiotics. While this resulted in resolution of the patient’s gastrointestinal involvement clinically and endoscopically, the oral lesions persisted.

In August 2001, infliximab therapy was initiated. Following an initial infusion of 5 mg/kg, 30%–40% healing of the large ulcers occurred. However, three to four weeks later, the patient reported a self-limiting episode of myalgia and arthralgia. A complete physical and laboratory evaluation was conducted with no abnormalities or long-term effects noted. After communication with the manufacturer, infliximab treatment was restarted with 5 mg/kg at 0, 2, and 6 weeks. Due to the previous reaction, prednisone 40 mg daily was also initiated and slowly tapered with no recurrence of disease symptoms or adverse effects. After the second infusion, complete healing of all lesions was observed. After completion of the third dose, no recurrence was noted. The patient returned to work and regained previously lost weight, returning every 8 weeks for maintenance infliximab infusions. The patient was last seen January 2005 with no recurrence of his oral lesions.

**DISCUSSION**

Orofacial manifestations are reported in the literature to occur in 0.5%–17% of patients with CD, depending
A CASE REPORT

Treatment of Oral Crohn’s Disease with Infliximab

on diagnostic criteria used (9–13). Orofacial Crohn’s disease typically displays a marked male predominance and is associated with a young age of onset of CD (13,14). Oral lesions regarded as specific to CD include mucosal tags, deep linear ulcers coursing through edematous buccal mucosa giving a “cobblestone” appearance, angular cheilitis, induration and swelling of the lips, pyostomatitis vegetans, and multiple deep ulcerations of the palate (13–16). Recurrent superficial aphthous stomatitis is not a specific finding in CD (13) and was not more common compared to controls in one series (17). These can occur as a result of poor nutrition or can represent adverse effects of medications and thus are a complication of the disease, not a direct manifestation of the disease (13,14).

The relationship between OCD and the intestinal manifestations of CD is varied. OCD can occur at any point in the course of CD and is not uncommonly the initial presentation (13). Rates of asymptomatic gastrointestinal disease in patients with oral manifestations have been reported to be between 16%-37% (13,15,16). Just as OCD appears to be independent from that of the gastrointestinal component temporally, the severity of the oral disease is not reflective of the activity of gastrointestinal disease (7,13,14,17,18). OCD does not appear to be completely independent from disease elsewhere in the body—it tends to be more prevalent in patients with other extra-intestinal manifestations (19). Additionally, as observed in our patient, Dupuy, et al observed that there is a higher incidence of concomitant esophageal and anal involvement in patients with oral disease, perhaps pointing to a form of CD with a predilection toward squamous epithelium (13).

Noncaseating granulomas are encountered in biopsies of the oral mucosa between 17%-89% of the time, and may be missed by more superficial biopsies (12, 20–22). However, the presence of granulomas does not confirm the diagnosis of OCD, as several other granulomatous conditions present similarly. Melkersson-Rosenthal syndrome (MRS) describes the classic triad of orofacial swelling, a fissured tongue, and facial palsy, yet often these signs do not present concurrently (7). When orofacial swelling occurs alone, this monosymptomatic form is called chelitis granulomatosa (2). Other diseases presenting with oral granulomatous inflammation include sarcoidosis and mycobacterial infections (20). The potential for OCD to present in the absence of intestinal symptoms and the differential diagnoses discussed above presents a diagnostic dilemma in many cases. To allow time for patients’ disease processes to present themselves without prematurely labeling them, the term orofacial granulomatosis (OG) was proposed by Wiesenfeld, et al. (20). Following the recommended nomenclature, a patient with CD presenting only with orofacial involvement will carry the general label of OG until more specific symptoms or signs become apparent.

Traditional treatment for Crohn’s-related oral lesions has largely mirrored treatments for intestinal CD. OCD has an unpredictable response to systemic steroids, with or without azathioprine, with literature reports ranging from no response to complete remission (13,14,16,22). However, relapse is very common upon steroid withdrawal. Success with topical steroid preparations has been documented in minor cases while intralesional steroids are very painful to administer and generally not very effective (13,16).

In light of its relative resistance to traditional treatment modalities, other therapies for OCD have been proposed and include thalidomide, topical tacrolimus, and infliximab. To date, however, no large trials exist. Thalidomide use has been documented in two case reports, both of which were children with severe steroid refractory oral lesions (23,25). One report describes an 8-year-old male who was treated with daily thalidomide and achieved complete remission that lasted for several months after his thalidomide was discontinued. The patient’s relapses would respond to repeat courses of thalidomide. The second report involves a 13-year-old female who enjoyed complete remission but continued to require chronic maintenance therapy at the conclusion of that report. Similar to infliximab, thalidomide’s effect on OCD is presumably mediated through its antagonism of the effects of TNF-α, inhibiting its production in the case of the latter. While both patients responded nicely, no larger trials exist. Furthermore, disadvantages of thalidomide therapy include difficulties obtaining the medication, side effects including an irreversible peripheral neuropathy, and inability to use in patients of child-bearing potential.

(continued on page 94)
Topical tacrolimus therapy for OCD was described in one series of eight children (24). All patients responded, while remission was achieved only in the patients (6/8) that underwent a slow weaning off the medication. Relapses responded to repeat courses. The advantages of this treatment option include good response rates in this small series, ease of use, and lack of any systemic absorption. The authors pointed to cost as a major disadvantage, although the topical solution was prepared at their institution specifically for this study. An obvious disadvantage would be the fact that this treatment modality would have no effect on CD elsewhere in the body.

Infliximab is a chimeric monoclonal antibody that binds specifically to TNF-α. In Crohn’s disease, infliximab is indicated for the induction and maintenance of remission in luminal disease and for reducing the number of enterocutaneous and rectovaginal fistulas and for maintaining fistula closure in patients with fistulizing Crohn’s disease. It is also indicated for the treatment of rheumatoid arthritis and ankylosing spondylitis. Its efficacy is attributed to its ability to bind to and neutralize TNF-α while transmembrane-bound, while soluble, and when it is bound to receptors. In addition, infliximab promotes lysis of activated cells through antibody dependant cellular cytotoxicity and possible complement activation. To date, three case reports and two small series (3 and 4 patients each) describe the use of infliximab in Crohn’s patients with oral manifestations (2–6). Two case reports detail its use in patients with laryngeal manifestations (7,8). Induction regimens varied from a single infusion (6,7) to 3 infusions at weeks 0, 2, and 6 (2–5). All patients experienced significant improvement after the first infusion and at the end of the induction phase most patients enjoyed complete remission of their oral and laryngeal lesions subjectively and objectively. However, in the reports describing a single-dose induction regimen, only 2 week and one month follow-ups were documented (6,7). In one, laryngeal manifestations improved dramatically but swelling persisted at the last follow-up visit, although this report did not describe the treatment regimen or follow-up in detail (8). Follow-up ranged from 8 weeks to 22 months in the reports that described using a three-dose induction phase (7 patients total), with the ultimate outcome being complete remission (2–5). All of these patients were placed on a maintenance regimen in some form, one used infliximab infusions every 3 months (5), methotrexate was used in another (4) and azathioprine in another (2). One patient began maintenance on 6-MP but following a relapse of both the oral and intestinal symptoms, the patient was given a fourth dose of infliximab and a maintenance regimen of infliximab infusions every 10 weeks was begun with no recurrence at one year (3). No adverse effects were mentioned.

Our patient’s dramatic initial response to infliximab was similar to those described above. As such, our case adds additional evidence to suggest that infliximab is a safe and effective treatment strategy for oral manifestations of CD. Furthermore, only two previously published reports describe regular infliximab infusions in the maintenance of remission of OCD (3,5), and our case lends additional support to this strategy. To date, our case documents the longest published follow-up of successfully treated OCD in complete remission at over 4 years. Also of note is the lack of serious adverse reactions. While the etiology of our patient’s self-limiting episode of myalgia and arthralgia four weeks after the initial infusion is not known, it seems unlikely to be a true infusion reaction. While patients can experience delayed-type hypersensitivity reactions after infliximab, they usually occur 3–12 days post infusion and are typically more severe, presenting with a serum-sickness picture (26). Furthermore, delayed-type hypersensitivity reactions are more common in patients who are reintroduced to infliximab following missed doses, or after a prolonged period of time without infliximab therapy. As described, the symptoms followed the first dose of infliximab with no prolonged lapse in treatment.

In summary, orofacial involvement is a well-described extraintestinal manifestation of Crohn’s disease and is not uncommonly observed in the absence of intestinal symptoms. Thus, the diagnosis of Crohn’s disease should be entertained in cases where severe stomatitis (lip swelling, mucosal tags, buccal cobblestoning, or deep ulcerations) is encountered even in the absence of typical Crohn’s symptoms. Conversely, recurrent superficial aphthae are not a specific finding in orofacial Crohn’s disease.
Treatment of Oral Crohn’s Disease with Infliximab

A CASE REPORT

(continued from page 94)

While there is a paucity of data to support any treatment strategy for a patient presenting with oral manifestations of Crohn’s disease, our case supports the use of infliximab in the induction and maintenance of remission in patients with this extra-intestinal manifestation. Topical tacrolimus may be considered in patients without clinical evidence of Crohn’s disease elsewhere in the body while infliximab may be a reasonable first line treatment option for the remainder of patients.

Acknowledgment
Special thanks to Nancy Rayhorn for assisting in the preparation of this manuscript.

References
26. Remicade (infliximab) current prescribing information.