

## Orofacial Crohn's Disease: An Oral Enigma

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**SUMMARY** Crohn's disease is a chronic, relapsing, inflammatory disorder which may involve any segment of the bowel from mouth to anus. The mucocutaneous manifestations of Crohn's disease in the orofacial region are multiple, including oral Crohn's disease, metastatic Crohn's disease in sites non-contiguous with the bowel system, and reactive disorders such as pyoderma gangrenosum. Clinicians should be familiar with these extraintestinal manifestations and include this important and often serious disease in the evaluation of patients with selected orofacial disorders. The recognition of these manifestations may help prevent misdiagnosis and unnecessary treatment, and facilitates timely diagnosis, palliation and definitive therapy.

**KEY WORDS:** Crohn's disease, pyoderma gangrenosum, oral disease

### INTRODUCTION

Crohn's disease (CD) is a chronic, transmural inflammatory bowel disease which may involve any segment of the gut, including oral cavity (1-3). First described by Crohn *et al.* in 1932 as regional ileitis (4), the disease primarily affects whites, often in early adulthood, and has a slight predilection for females (5-8). The precise etiology is unknown, but is thought to be multifactorial and include potential aberrations in the immune system, heredity, infectious and environmental factors (9,10). A number of factors contribute to missed or delayed diagnosis of CD. These include mild or nonspecific symptoms, relapsing pattern of the disease and pres-

ence of extraintestinal manifestations which may obscure the underlying bowel involvement (11).

Extraintestinal manifestations may occur prior to the onset or throughout the course of CD and have been reported in 25%-36% of patients (5,12,13). Examples include anemia, inflammatory arthropathies, hepatobiliary disease, metabolic osteopathy, ocular problems, renal disorders, and mucocutaneous lesions. (8,14,15). We present a case of a 49-year-old male with a history of CD who developed right-sided face and lip swelling and mucocutaneous ulcers unresponsive to administration of multiple antibiotics. The patient's

cutaneous findings improved with corticosteroid therapy. Orofacial presentations of CD are discussed and inclusion of a systemic disease in the differential diagnosis of these orofacial manifestations is emphasized.

### CASE REPORT

A 49-year-old African-American male information technologist was admitted to the University Hospital for evaluation of a sudden onset right-sided tender face and lip swelling. The onset was 5 days prior to admission with right lower lip swelling, which gradually progressed to involve the chin and cheek, resulting in limitation of mouth opening as he developed fever, light headedness and fatigue throughout that time.

His past medical history was significant for anemia and minimally active left-sided CD diagnosed by intestinal biopsy 10 years earlier. There was no history of Crohn's-related complications or surgeries. His last endoscopy and colonoscopy were performed 1.5 years prior to admission. During his last flare-up three months before, he developed abdominal pain, diarrhea and fresh bright red blood *per rectum* which responded to therapy with systemic corticosteroids. He was taking mesalamine 400 mg *bid* for maintenance of remission. He had a baseline Hg of 12-13 g/dL, prior history of rectal bleeding, poor compliance with medical therapy and follow-up. He was a lifelong resident of his area and denied a history of foreign travel. He denied tobacco, alcohol and drug abuse, weight loss, trauma, recent dental work, visual changes or yellowing of the eyes, abdominal pain or bright red blood *per rectum* at presentation.

On initial examination, he had a fever of 102.9 F, but was not in acute distress. The patient had a tender, non-fluctuant, right-sided facial edema extending from the right mandibular angle to the right lower lip, submandibular and submental area. There was cervical lymphadenopathy and trismus with maximal interincisal opening of 30 mm. Limited intraoral examination revealed that the patient was dentate with no obvious dental caries. Notable was a firm, dark, adherent patch extending from the right posterior buccal and vestibular mucosa to the lower lip midline. There was no elevation of the floor of the mouth. His laboratory values showed significant anemia (Hemoglobin (Hg)=6.2 g/dL, nl=13.8-17.2 g/dL and hematocrit (Hct)=17.9%, nl=42-52%), elevated liver function tests, high C-reactive protein (CRP=208 mg/L, nl=0-9 mg/L), renal insufficiency (elevated BUN/creatinine), and positive stool guaiac.

Potential etiologies for sudden onset facial swelling were considered and included infectious and drug-related disorders. The work up for sepsis was initiated with the patient empirically started on intravenous vancomycin and piperacillin-tazobactam for cellulitis and possible abscess. After transfusion with 2 units of packed red blood cells, hemoglobin increased to 9.0 g/dL with improvement in the symptoms of weakness and fatigue, but following an episode of melena a day after admission it dropped again to 7.9 g/dL. The anemia was considered to be related to bleeding from the oral ulcer and most likely the cause of melena. Endoscopy under sedation to rule out upper gastrointestinal bleeding was deferred due to trismus, risk of bleeding from oral ulcer and anticipated pharyngeal swelling until when the patient stabilized or deemed suitable for endoscopy under general anesthesia. However, he was closely monitored with sequential CBC for the status of anemia and possible blood loss.

Clinical examination and panoramic radiography ruled out dental pathology as the cause of right-sided facial swelling. The head and neck imaging with contrast was suggestive of cellulites and extensive inflammation, but no abscess cavity formation in the right mandibular subcutaneous soft tissues was observed. Nevertheless, the facial swelling persisted and lower lip fissuring and cheilitis became more prominent (Fig. 1). The discolored, intraoral patch progressed to form surface corrugations, focal erosions and necrosis on the buccal mucosa (Fig. 2), along with a tender, deep, linear ulceration with raised borders on the lower right vestibule (Fig. 3). In addition, a solitary aphthous-like ulcer developed on the right floor of



**Figure 1.** Right sided facial swelling and lower lip macrocheilia. Note mild cheilitis and fissuring of the lower lip.



**Figure 2.** Erythematous, boggy left buccal mucosa with corrugated surface features, focal erosions and necrosis.

the mouth, and localized hyperplastic gingivitis in the canine-premolar region became apparent. A few days after admission, the patient also developed a pustule on his left cheek which gradually enlarged to form a tender, indurated, grey plaque of nearly 4 cm in diameter with superficial ulceration at the center (Fig. 4). The patient reported a prior incidence of ingrown hair, but denied recent insect bites, or a history of exaggerated scarring. The differential diagnosis of the cutaneous ulcer included atypical pyoderma gangrenosum, deep fungal infection and atypical mycobacterial infection.

Biopsy specimens were obtained from both cutaneous and vestibular ulcers and submitted for histopathologic evaluation and culture studies. The left cheek biopsy specimen revealed massive neutrophil infiltration of the dermis with negative staining with periodic acid-Schiff, Gomori, Gram, and acid fast stains for microorganisms. Incisional biopsy of vestibular ulcer demonstrated granulation tissue and abscess formation, while special stains were negative for fungal organisms. The abscess culture failed to grow any microorganism including fungi and bacteria or demonstrate any ova or parasite. The urine and blood cultures were also negative.

In spite of broad spectrum antibiotic therapy, facial swelling and oral ulceration persisted. The cutaneous ulceration continued to expand through the course of hospitalization. The absence of obvious fluid collections on the head and neck imaging, the histopathologic findings on biopsy and negative growth on culture of collected specimens were all supportive of a noninfectious etiology. Follow-up blood work revealed normalized transaminase



**Figure 3.** Deep linear ulceration with raised borders on the right mandibular vestibule and focal hyperplastic gingivitis.

levels and return of normal renal function. The high index of suspicion for relapse of CD and re-evaluation of presumptive diagnosis led to a consideration that the patient's orofacial changes may have represented extraintestinal manifestations of CD. The patient was started on 60 mg of oral prednisone daily. Over the four ensuing days, facial swelling, mucocutaneous findings and diarrhea improved, and hemoglobin stabilized. The patient was subsequently discharged to be followed up by his gastroenterologist.

## DISCUSSION

Mucocutaneous changes are the most common type of extraintestinal manifestations in CD. Their prevalence varies between 15% and 75% (8,12,16-20). In a quarter of patients, dermato-



**Figure 4.** Crusted ulcerative lesion on the lower left cheek.

logic changes may precede Crohn's diagnosis by 3-8 years (21). They may be solitary or multiple and often associated with minimal symptoms (8). Although mucocutaneous changes may occur independently of the activity or quiescence of the intestinal disease, they are more common in the context of colonic CD (12,13,22,23).

There are three types of mucocutaneous findings in CD depending on the origin: 1) granulomatous oral and perianal changes caused by direct extension of intestinal disease as well as granulomatous skin findings non-contiguous with gastrointestinal tract (8,15); 2) reactive conditions in association with CD such as pyoderma gangrenosum, erythema nodosum, Sweet's syndrome, erythema multiforme, and cutaneous vasculitis (8,15,16,24,25); and 3) changes related to therapy directed against CD or disease-induced nutritional deficiencies such as acrodermatitis enteropathica and marasmic striae (12,14,16).

### **Metastatic Crohn's disease (MCD)**

Metastatic CD refers to rare skin changes, with non-caseating granulomas on histology, separated and distant from the intestinal tract in patients with known intestinal disease (26,27). MCD may develop independently of the status of intestinal disease activity and even prior to the onset of bowel symptoms; however, they occur more frequently when colon is involved by CD (22,23,28,29). MCD may affect genital and non-genital sites. Although cutaneous ulcerations are the most common form of MCD, cutaneous plaques, papules, nodules and chronic edematous infiltration affecting different body regions have also been reported (30,31). These cutaneous changes are hard to heal and have a predilection for the intertriginous areas (26,32).

In adults, MCD usually appears following CD diagnosis and is frequently evident as plaques with or without ulcerations on extremities (8). In contrast, MCD in children often develops at the onset of intestinal disease, is of shorter duration, and frequently affects genitalia (8). Genital changes in MCD are distinct from perineal and parastomal changes caused by direct extension of intestinal lesions (33). Perianal changes develop in and around anus as fissures, fistulas, abscesses, ulcers and chronic edematous infiltration affecting children and females (8,34,35).

Genital changes are also more common in children (19), often presenting as vulvar swelling, induration, fissures, fistulas, abscesses, skin tags or

ulcerations (36). Edema and ulceration may also affect subcoronal penis and scrotum, although less frequently (37). Nearly a quarter of patients experience genital changes prior to the onset of bowel symptoms (19). MCD may rarely cause disfiguring facial lesions with attendant psychosocial stress (22,28,31,32). Although the etiology of MCD is not well-defined, cutaneous immune complexes and cell-mediated hypersensitivity reactions have been implicated in the pathogenesis of granulomatous inflammation and vascular damage (38,39).

The clinical spectrum of MCD is varied and shared by many other skin disorders (40). This often leads to diagnostic delay and mandates prompt evaluation of cutaneous lesions in patients with CD (40). When MCD is suspected, a biopsy specimen should be obtained, with special stains such as Gram, periodic acid-Schiff, and acid fast and evaluated for the presence of granulomatous inflammation, perivascular lymphocytes, monocytes and necrobiosis (26,38-42). Additional work up may include tissue culture, polarized microscopy, tuberculin skin test, and chest radiography to exclude other causes of granulomatous inflammation such as tuberculosis, deep fungal infections, sarcoidosis, erysipelas and foreign body reactions (8,40). Reactive cutaneous conditions such as pyoderma gangrenosum, erythema nodosum and erythema multiforme associated with CD should also be considered (12,16). In addition, when evaluating genital manifestations of MCD, sexually transmitted diseases with similar clinical features should be excluded (8,40).

### **Oral manifestations of Crohn's disease**

Oral Crohn's disease comprises a variety of cutaneous manifestations in the orofacial region associated with CD (18,43). The involvement of oral cavity in CD may occur in all age groups, but is more common in pediatric population (44). Oral changes may occur prior to, concurrently with or following the onset of bowel disease and independently of the extent and severity of intestinal symptoms (8,45-47). They may precede intestinal disease in up to 60% of patients (18). The reported symptoms associated with oral Crohn's include pain, difficulty with oral functions, cosmetic concerns and psychological stress (18,22). The prevalence of oral manifestations in the context of CD ranges from 0.5% to 80% (3,12,18,44,48-52). This variability may be related to specific and nonspecific oral changes reported in the context of CD. Table 1 lists a variety of oral findings associated with CD including gingivitis, mucosal tags,

**Table 1.** Oral manifestations of Crohn's disease

<p><b>Pathognomonic:</b></p> <ul style="list-style-type: none"><li>• Macrocheilia with/without fissuring</li><li>• Cobblestoning of oral mucosa</li><li>• Linear ulcerations of oral vestibules</li><li>• Mucosal tags</li></ul> <p><b>Non-pathognomonic:</b></p> <ul style="list-style-type: none"><li>• Facial swelling</li><li>• Perioral erythema</li><li>• Angular cheilitis</li><li>• Aphthous stomatitis</li><li>• Pyostomatitis vegetans</li><li>• Diffuse oral edema</li><li>• Hyperplastic granular gingivitis</li></ul>
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Based on references 3,9,14,16,18,43,44,50,54-56,58,60

aphthous ulceration, labial swelling, cobblestoning of buccal mucosa, and linear ulcers of oral vestibules (3,9,14,16,18,43,44,50,54-56,58,60). The subtle and nonspecific nature of many of these findings, especially when developed prior to the onset of intestinal symptoms, often creates a diagnostic dilemma (57). Although recurrent, severe aphthous stomatitis does affect Crohn's patients, aphthous ulcers are frequently seen in general population and are not considered a specific oral finding for CD (50). Another nonspecific oral finding in Crohn's patients is pyostomatitis vegetans. This condition is more often associated with ulcerative colitis and is characterized by multiple oral pustules, erosive vegetations, labial and gingival erythema and mucosal folds (58,59). In contrast to the above findings, oral changes such as labial swelling linear fissures, mucosal tags and cobblestoning are considered specific and pathognomonic for CD (3,58,60). "Cobblestoning" is characterized by nodular, granulomatous swellings of labial and buccal mucosa resulting in a specific clinical appearance. (58) Deep, linear ulcers of oral Crohn's often develop in oral vestibules and have hyperplastic extensions at the edges (58).

The descriptive term orofacial granulomatosis (OFG) is often used to describe a variety of conditions in which granulomatous inflammation affects oral cavity and face (61). The spectrum of OFG is broad and includes Melkersson-Rosenthal syndrome (MRS), cheilitis granulomatosa, foreign body reaction, certain infections, and systemic diseases such as Crohn's disease, tuberculosis, sarcoidosis, and granulomatous processes of unknown etiology, all of which share similar clinical

and histopathologic features (57,61). In nearly 10% of patients with signs and symptoms of OFG, CD is the underlying etiology (55,61).

Diagnostic work up includes tissue sampling of the involved orofacial region for histopathologic examination (57). Microscopic features of orofacial CD resemble those identified in intestinal CD and include non-caseating granulomas in the setting of acute and chronic inflammation (38,62). Evaluation with special stains helps rule out other causes of granulomatous inflammation and establish the definitive diagnosis.

### Facial pyoderma gangrenosum

Pyoderma gangrenosum (PG) is an uncommon, noninfectious, inflammatory, neutrophilic dermatosis (63). It often starts as a follicular pustule which enlarges rapidly to form a painful, necrotic ulcer with mucopurulent or hemorrhagic exudate and peripheral erythema (63,64). The condition often affects the lower extremity, but may occur on other body areas, including the face (63,64). It was initially thought to be infectious in nature, but cultures have been repeatedly found to be sterile. Aberrations in humoral or cell-mediated immune response to an unknown antigen may be responsible (65). PG often affects patients with an associated systemic illness, of which inflammatory bowel disease is the most frequent culprit (63,64,66-68). PG has been reported in 1%-2% of CD patients (12,69,70), in whom cross-reaction of cutaneous and intestinal antigens may lead to reactive dermatosis such as PG (68).

Diagnosis depends on thorough medical history unraveling the underlying systemic disease, clinical signs and symptoms, histopathology and exclusion of similar ulcerative conditions (63,64). Although histopathologic findings in PG are not diagnostic and vary with stage of the disease, a skin biopsy for culture and staining is essential to exclude bacterial, fungal, viral and mycobacterial infections (64). On microscopic examination, PG resembles an abscess or cellulitis (71), as it contains dense neutrophil infiltration, hemorrhage and epidermal necrosis (63-65). Local wound care, topical antibiotics, and corticosteroids are palliative, prevent superinfection and accelerate healing; however, these strategies do not address the underlying systemic disease (64). Immunosuppressive therapy is often necessary to manage extensive or progressive pyoderma gangrenosum (63,64,68,72).

In our patient, the oral biopsy specimen demon-

strated ulceration, granulation tissue and abscess formation. The culture from the abscess failed to grow any microorganism. Special stain for fungus was negative. The failure to detect granulomas histologically does not exclude CD and may be consequence of size of the sample (9,18,43,57). In analogy with the skip region of intestinal CD, the distribution of oral findings is patchy, so the sampling may reflect normal rather than diseased mucosa (73). Also, the incidence of granuloma is variable in different tissues (9). Non-caseating granulomas have been reported in 60% of the gut tissue resected (74,75). In contrast, giant cell granulomas have been reported in 67%-85% of oral findings associated with CD (18,44,55,58,60). The skin biopsy in our patient revealed massive neutrophil infiltration of the dermis with staining negative for microorganisms, indicating that the ulcer was not infectious in nature and that an acute neutrophilic dermatosis such as PG in the context of CD was a potential diagnosis.

The patient presented was the first one seen with a combination of two extraintestinal cutaneous manifestations affecting the orofacial region, namely oral findings and a reactive cutaneous ulcer, i.e. PG. Macrocheilia, linear fissuring of the vestibule, and cobblestoning of the buccal mucosa noted in this patient are pathognomonic cutaneous manifestations of CD in the orofacial region. The failure to establish an infectious etiology for the abscess identified on both oral and facial tissue biopsy specimens, as well as the resolution of orofacial findings with corticosteroid therapy, further supported this notion.

Mucocutaneous manifestations of CD may also be related to nutritional deficiency. The latter may result from chronic diarrhea, reduced oral feeding, overgrowth of bowel flora, intestinal resection, malabsorption, or drug therapy (76-80). Specific mucocutaneous changes such as stomatitis, aphthous ulceration, glossitis, cheilitis, perioral dermatitis and acrodermatitis enteropathica have been linked to low levels of albumin, zinc, folic acid, niacin, vitamin B-12 and other essential nutrients (76-78,81,82). Deficiency of folic acid, niacin and fat-soluble vitamins has also been reported in association with medications such as sulfasalazine/sulfapyridine, azathioprine, and cholestyramine, respectively (76-78). In addition, patients undergoing corticosteroid or immunosuppressive therapy are at risk for acneiform eruptions and opportunistic mucocutaneous infections (82).

The role of CD-induced malabsorption in the etiology of the patient's mucocutaneous findings

could not be entirely ruled out. He was anemic on admission and his baseline Hg hovered around 12-13 g/dL. Nevertheless, he was not taking any vitamin, iron or other types of supplements. On admission, his methylmalonic acid level was normal (MMA= 0.1  $\mu\text{mol/L}$ , nl <0.4  $\mu\text{mol/L}$ ), which did not support vitamin B-12 deficiency as an etiology for his mucocutaneous symptoms.

The patient was taking mesalamine daily for maintenance for months prior to admission. Although possible, mesalamine is not known to cause nutritional deficiency, hematologic or hepatic alterations leading to the mucocutaneous manifestations observed in our patient. On admission, the patient had elevated liver function tests and renal insufficiency both of which normalized with hydration, transfusion and supportive medical care, indicating that renal and liver abnormalities were likely acute rather than chronic (i.e. changes caused by CD or toxic effect of drugs used to treat it).

Reactivation of CD in this case may have reflected suboptimal maintenance therapy or the patient's lack of compliance with taking his medications. In our opinion, the addition of corticosteroids to the patient's maintenance therapy helped resolve the ulcerative, bleeding oral ulcer (presumably the source of melena and anemia) and aborted a full relapse with resolution of gastrointestinal symptoms (i.e. diarrhea, rectal bleeding). He had responded favorably to steroid therapy during his previous flare-ups of CD. This case illustrates the importance of historical data in the evaluation of current orofacial findings. A positive history of CD and prior relapses in spite of medical therapy in a patient with specific orofacial findings should alert the clinician to the possible reactivation of intestinal disease. In patients with ongoing gastrointestinal complaints, weight loss and fatigue, detection of pathognomonic orofacial lesions unresponsive to routine therapy should also prompt a thorough diagnostic work up, including endoscopy to exclude underlying CD (12,57,83).

Orofacial CD may develop prior to the onset or throughout the course of intestinal disease, often independently of disease activity (55,58,60,84,85). A diagnosis of CD prompted by oral manifestations was first reported by Varley *et al.* in 1972, followed by others (86,87). The predictive value of orofacial findings to the future onset of CD is subject to controversy (88). However, even in the absence of gastrointestinal complaints, certain orofacial findings should raise sufficient suspicion to warrant tissue biopsy from this easily accessible area. It is also warranted to question patients about intes-

tinal complaints, to examine them for genital and perianal changes or presence of occult blood in the stool, to perform screening blood work (CBC, iron levels, ESR, albumin), and to closely follow them for potential development of CD in the future (8,58).

### Management strategies

Medical therapy aimed at the underlying CD often results in resolution of extraintestinal signs and symptoms (45,89). A variety of systemic anti-inflammatory drugs, immunomodulators, and biological agents have been used, with variable success, in the treatment of orofacial CD. TNF-alpha has been implicated in the pathogenesis of CD (90). Anti-TNF agents such as infliximab and thalidomide have been utilized in the treatment of refractory CD and its orofacial manifestations (27,31 53,59,85,90-99).

It is unclear whether benefits of infliximab, a chimaeric monoclonal anti-TNF-alpha antibody, is the result of its inhibitory effect on TNF- $\alpha$  or indirect consequence of improvement in CD (59). Concurrent administration of methotrexate may diminish the incidence of anti-infliximab antibodies and extend remission in responsive patients (53). While highly efficacious, infliximab therapy may be associated with serious complications such as hypersensitivity reactions, opportunistic infections, lymphoproliferative disorders and reactivation of latent tuberculosis (53,100). Adalimumab, a newer non-chimeric monoclonal antibody against TNF-alpha, may be an alternate biological agent in patients who are intolerant or unresponsive to infliximab (101,102).

The efficacy of thalidomide in the treatment of CD and its orofacial manifestations may be

**Table 2.** Therapeutic approaches to orofacial Crohn's disease and patient response

Ref. No.	Orofacial manifestation	Therapy	Response
45	Gingival bleeding, metallic dysguesia	Tetracycline + steroid mouthwash	Yes
110	Cobblestoning, mucosal tags	Intralesional steroid injection	Yes
111	Lip swelling and fissuring	Topical tacrolimus	Yes
112	Oral swelling and ulceration	Prednisone	Yes
113	Palatal ulceration	Steroids + mesalamine	Yes
92	Lingual ulceration	Steroids + mesalamine Infliximab	No Yes
85	Oral vestibule cobblestoning	Steroids + antibiotics Infliximab + azathioprine	No Yes
115	Oral pyostomatitis vegetans and tongue lesions	Prednisone + zinc supplementation	Yes
58	Oral ulcers, hyperplastic gingival folds	6-Mercaptopurine	Yes
58	Lip swelling, gingival edema	6-Mercaptopurine + metronidazole Infliximab	No Yes
58	Lip swelling and discoloration	Prednisolone + metronidazole +6-MP	Yes
31	Perioral erythema, labial swelling and ulceration	Infliximab + topical steroids	Yes
27	Facial swelling and oral ulceration	Systemic steroids + mesalamine Infliximab + azathioprine	No Yes
59	Oral pyostomatitis vegetans	Infliximab + methotrexate	Yes
53	Lip swelling and mucosal tags Fistulizing oral Crohn's	Prednisolone + azathioprine Infliximab + methotrexate	Yes Yes
115	Labial and gingival swelling, oral aphthous ulcers	Total enteral nutrition	Yes
116	Oral cobblestoning and esophageal ulcers	Prednisone + 6-MP + Infliximab Adalimumab + 6-MP + dapsone	No Yes
90	Oropharyngeal ulcerations	Prednisolone, topical steroids Thalidomide	No Yes
95	Peritonsillar, oropharyngeal and esophageal ulcers	Infliximab Thalidomide + steroids	No Yes
98	Oral aphthous ulceration	Thalidomide	Yes

related to its inhibitory effect on TNF- $\alpha$  (90), its antiphagocytic (103) and antiangiogenic actions (104), or its influence on cell-mediated immunity (90). The well-known side effects of thalidomide include teratogenicity, peripheral neuropathy and severe somnolence (90,103), mandating appropriate counseling prior to administration.

Cutaneous CD is potentially responsive to topical therapy and application of topical steroids, tacrolimus and cyclosporine, for this purpose has been described. The immunosuppressive agents tacrolimus and share the same mechanism of action, but differ in potency and cutaneous absorption (45,105-107,111). Each drug dampens generation of cytokines and activation of T cells (108); however, cyclosporine is not as efficacious as tacrolimus for the management of cutaneous changes in CD (109).

Table 3 provides a summary of therapeutic approaches to orofacial CD (27,31,45,53,58,59,90,92,95,98,110-116). Patients at risk for opportunistic infections related to immunosuppressive therapy may also benefit from preventive or therapeutic antimicrobial interventions. Nutritional support, elimination of exacerbating factors and palliative measures should also be considered in the management on individual basis.

## Overview

The clinician should be familiar with the spectrum of CD manifestations in the orofacial region, include CD in the differential diagnosis of specific lesions affecting oral cavity, and initiate a thorough diagnostic work up, particularly in the presence of prior or current gastrointestinal complaints and lack of response to routine therapy. Even in the absence of bowel symptoms, biopsy specimens should be obtained from oral changes and patient closely followed for possible development of intestinal disease.

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