Oral Indicators of Ulcerative Colitis: A Rare Case Report and Review of Literature

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ABSTRACT

Ulcerative colitis (UC) belongs to the inflammatory bowel diseases (IBD), which may be divided into two major groups, ulcerative colitis (UC) and Crohn’s disease (CD). It affects part or whole of the large intestine, frequently of the lower colon and rectum, causes inflammation and ulcers. The leading initial symptom of UC is diarrhea with blood and mucus, pain, tenesmus. UC is usually associated with recurrent attacks with complete remission of symptoms in the interim. Extraintestinal manifestations including various oral lesions have been associated with UC. The oral lesions in UC are rare and commonly occurring are mucosal ulcers, aphthous ulcers, pyostomatitis vegetans, etc. at any part of the oral cavity. Microscopically the oral lesions mimic colonic crypt abscess without granulomatous inflammation, spongiotic epithelium with eosinophilic and neutrophilic intraepithelial microabscesses and submucosa shows edema with neutrophils, eosinophils and lymphocytes. The severity of the oral disease usually reflects the severity of intestinal disease; oral manifestations may be used as additional criteria to determine the severity of disease and probably response to therapy. Here, we present a rare case report with oral manifestations as indicators for intestinal disease flare-ups in a patient diagnosed with UC.

Keywords: Ulcerative colitis, Intraepithelial abscess, Lichen planus, Mucosal ulcers.

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INTRODUCTION

Ulcerative colitis (UC) is a relapsing and remitting disease characterized by acute noninfectious inflammation of the colorectal mucosa, extends proximally from the anal margin. The rectal mucosa is invariably affected. Virtually all patients with UC have rectal bleeding or bloody diarrhea and other colonic symptoms.1 These symptoms may persist for days, weeks, or months and then subside, only to recur after an asymptomatic interval of months to years or decades.2 Extraintestinal manifestations including various oral lesions have been associated with UC. The oral lesions commonly occurring in ulcerative colitis are mucosal ulcers, pyostomatitis vegetans, diffuse pustules and lichen planus at multiple oral sites.3 The oral lesions may precede or occur concomitantly with systemic disease and has been found that the oral lesions tend to regress when the intestinal disturbance is brought under control. However, exacerbations of the gastrointestinal disease frequently result in exacerbation of oral lesions.3-5

CASE REPORT

A 54-year-old male patient was referred by gastroenterologist to our institution for evaluation of red and white areas, ulcerations on left and right buccal mucosa. His chief complaint was severe burning sensation in the mouth and inability to eat food since 2 months. The patient also complained of nausea, regurgitation, acidic taste, halitosis and revealed that he was diagnosed of ulcerative colitis in 2009.

A detailed medical and dental history was taken. The patient commented that 2 years before the appearance of recurrent bloody diarrhea, he noted recurrent oral lesions, severe burning sensation, recurrent intestinal pain, diarrhea, nausea, regurgitation, acidic taste. As the frequency of bloody diarrhea increased, the patient consulted a gastroenterologist. Colonoscopy, biopsy from transverse colon and rectum diagnosed of ulcerative colitis (transverse and rectosigmoid colon up to hepatic flexure) (Figs 1 and 2).

He was treated with prednisolone 40 mg for 14 days and tapered 20 mg for 10 days and stopped. Later was kept on a mesalamine 1.2 gm/twice daily maintenance therapy which he discontinued after sometime. The patient was asymptomatic and disease-free for 1 year, but again had

Fig. 1: Colonoscopy: Friability, ulceration, loss of vascularity of colonic and rectal mucosa
severe exacerbations for every 6 months. During one of the exacerbations he was referred to us and informed that usually oral lesions, burning sensation are first to appear 1 month prior to intestinal manifestations and were severe during exacerbations. Oral lesions were more intense when the patient suffered mood variations and increased stress. There was no significant family history or any habits except increased stress levels.

Extensive general body examination, extraoral and TMJ examination were carried out which were not contributory. Intraoral examination showed erythematous areas and erosions on right and left buccal mucosa surrounded by white lacy striae which were extending onto gingiva, vestibule, hard and soft palate except tongue and floor of the mouth. Two ulcerated lesions with elevated margin, measuring around 1 and 5 mm were seen on left buccal mucosa, opposite to molars and right lower labial mucosa respectively. The marginal gingiva was erythematosus with radiating white striae and gingival abscesses, periodontitis were also observed (Figs 3 and 4).

Incisional biopsy of the left buccal mucosa at the margin of the ulcer and white striae was carried out under local anesthesia for histopathological examination. Microscopic examination of ulcer revealed spongiotic stratified squamous epithelium with intraepithelial microabscess comprised of eosinophils, neutrophils, lymphocytes and plasma cells (Fig. 5). The lamina propria was edematous with mixed inflammatory cell infiltrate consisting of neutrophils, lymphocytes, plasma cells, histiocytes and eosinophils (Fig. 6). The histopathological features were suggestive of oral manifestation of ulcerative colitis. While the histopathology of white striae revealed hyperkeratotic, acanthotic stratified squamous epithelium with basal cell degeneration, band of inflammatory cell infiltrate consisting

Fig. 2: Biopsy from transverse colon showed crypt abscess consisting of few mucosal glands showing collection of neutrophils, lamina propria consisting of lymphocytes, plasma cells, histiocytes, prominent eosinophils

Fig. 3: Ulcer with elevated border, erythematous areas and erosions, white striae on left buccal mucosa and palate

Fig. 4: Delicate white striae in gingivobuccal sulcus

Fig. 5: Photomicrograph (40x) (ulcer)—intraepithelial abscesses with neutrophils, eosinophils

Fig. 6: Ulcerative colitis with crypt abscess and inflammatory cell infiltrate
of lymphocytes, few plasma cells and prominent eosinophils which were consistent with features of lichen planus (Figs 7 and 8). A palliative treatment of topical clobetasol propionate, antioxidant, multivitamin therapy and oral prophylaxis was advised. Our observations and a recommendation for evaluation of patient for active disease and its treatment was conveyed. After 2 weeks of therapy for intestinal symptoms (oral mesalazine-1.2 gm/twice daily) patient was reviewed and he showed resolution of white striae on palate, gingivobuccal sulcus and gingival abscesses, regression of ulcers and the lesions on buccal mucosa also regressed (Fig. 9).

**DISCUSSION**

Ulcerative colitis and Crohn’s disease (CD) are two disorders known as inflammatory bowel disease (IBD). These diseases share common features but have distinctly different clinical manifestations. The origin of IBD is multifactorial but the cause remains unresolved. It is postulated that they result from unregulated and exaggerated immune responses to commensal microbes in the gut in genetically susceptible individuals.

The genetic susceptibility plays an important role and the implicated genes regulate several important biologic functions, including immunoregulation, mucosal barrier integrity and microbial clearance and/or homeostasis. There are four genes associated with CD, CARD15 (NOD2), SLC22A4 and SLC22A5, DLG5, PPARG and one gene in UC, MDR1 located on chromosome, the function is efflux transporter for drugs and, possibly, xenobiotic compounds eased in patients. In UC, the genotypes HLADRBI*0103, B*27 and B*58 are linked with extraintestinal manifestations involving the joints, skin and eyes, HLA B8/DR3 is associated with primary sclerosing cholangitis.
The existence of true autoimmunity in UC is uncertain. They are characterized by loss of tolerance to enteric commensal bacteria, enhanced recruitment and retention of effector macrophages, neutrophils and T cells into the inflamed intestine, where they are activated and release proinflammatory cytokines. It most probably looks like Th2 type disease with extensive activation of Th2 cells secretes, IL4 and IL10 ( interleukin 4 and 10) cytokines and this leads to a hyperactive response to the antigens. 

Several environmental factors in the pathogenesis of IBD are included like smoking, diet, the use of antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), stress and infection. These triggering factors alter mucosal barrier integrity, immune responses, or the luminal micro-environment, each of which have an impact on susceptibility to inflammation. Theses triggers are necessary to initiate or reactivate disease expression.

Enteric microflora can stimulate immune responses either by functioning as adjuvants or antigens. High concentrations of sulfate-reducing bacteria with concomitant elevation of hydrogen sulfide have been noted in patients with UC. Defects in barrier function of intestinal epithelium could allow luminal flora to gain access to mucosal lymphoid tissue and thus trigger immune response. 

UC is global in distribution and varies in incidence relative to Crohn’s disease, supporting the concept that they are separate diseases. The incidence/prevalence of ulcerative colitis varies not only according to geographical region but also with race and ethnicity. In the United States, Great Britain, and Scandinavia the incidence is about 4 to 12 per 100,000 populations, which is slightly greater than Crohn’s disease. Regions with a low incidence of UC include Asia, Japan, Africa and South America. Both males and females are equally affected. UC may be present at any age. It most commonly affects people between the ages of 15 and 40 years with a second peak in incidence between 50 and 80 years. Cigarette smokers have a 40% lower risk of developing ulcerative colitis than do nonsmokers.

It typically presents as a relapsing disorder marked by attacks of bloody mucoid diarrhea, lower abdominal pain, tenesmus, cramps relieved by defecation. Constipation may occur paradoxically due to disruption of normal peristalsis. A patient may have proctitis (most distal part of colon and rectum), left-sided colitis, limited or distal colitis, extensive colitis involving the transverse colon, or pancolitis (when it involves rectum and extends proximally in a retrograde fashion to involve the entire colon in severe cases). At any point in time, 50% of patients are asymptomatic, 30% have mild symptoms, and 20% have moderate to severe symptoms. UC may be insidious, with gradual onset of symptoms, or the first attack may be acute and fulminate. As the disease progresses the patient may also experience weight loss, fatigue, loss of appetite that may result in nutrient deficiencies, mucus in the stool, severe rectal bleeding, fever and anemia. In the course of colonic involvement with UC, the mucosa may exhibit slight reddening and granularity with friability, loss of vascular pattern and easy bleeding. With fully developed severe active inflammation, there may be extensive broad-based ulceration of the mucosa and pseudopolyps may be present. Serious complications are dilatation and perforation of the bowel, toxic megacolon and in longstanding cases, carcinoma of the bowel. Many patients have long periods of complete remission, but the cumulative probability of remaining free from relapse at 2 years is only 20%, decreasing to less than 5% at 10 years. Later relapses generally affect the same region of the colon as previous episodes emotional or physical stress may cause flare-ups.

IBD patients may present with comorbidities leading to symptoms and complications outside the colon. UC and CD often involve almost every organ other than those of the gastrointestinal tract. These nonintestinal affections are termed extraintestinal symptoms and may not always coincide with the underlying bowel disease. The organs most commonly involved include the skin, eyes, joints, biliary tract and lungs whereas oral lesions, gallstones, pancreatitis, nephrolithiasis and amyloidosis, are more associated with CD than with UC. Other symptoms, e.g. skin and eye manifestations are equally seen in both CD and UC. Several factors may be responsible for extraintestinal organ involvement in IBD and sometimes it can be difficult to differentiate the true extraintestinal manifestations (EIMs); i.e. primary systemic affection by the disease itself, from secondary extraintestinal complications (EICs) of the disease, caused mainly by malnutrition, chronic inflammation or side effects of therapy. The reported frequency of EIMs in patients with IBD varies from 6 to 47%. The development of one EIM appears to increase the susceptibility of developing other EIMs. An overlap of EIMs is observed with peripheral arthritis, erythema nodosum, affection of the biliary tract and the eyes, in concordance with the hypothesis of a common pathogenic pathway. Some authors discuss an autoimmune reaction toward an isofrom of tropomyosin (tropomyosin related peptide), which is expressed in eye (nonpigmented ciliary epithelium), skin (keratinocytes), joints (chondrocytes), biliary epithelium and the gut.

Extraintestinal manifestations may provide clues to the severity of the disease and physical examination should
target various systems. EIMs and EICs observed in UC are:

**Ophthalmic lesions**: Iritis or uveitis (0.5-3%, which is inflammation of the iris).

**Musculoskeletal lesions (20-30%)**: Peripheral arthritis (5-10%), ankylosing spondylitis (1-3%), arthritis of the spine, sacroiliitis, nonspecific musculoskeletal pain, TMJ arthritis. Osteoporosis and osteomalacia (EICs) mainly because of treatment and malabsorption with severe disease.

**Cutaneous lesions**: Erythema nodosum (15%, which is a panniculitis), pyoderma gangrenosum (0.5-2%), acneiform eruptions, aphthae, bullous disorders, such as bullous pemphigoid, urticaria, pyostomatitis vegetans, scarlatiniform skin lesions.

**Hepatobiliary**: The main hepatic EIM is primary sclerosing cholangitis (3%) which is a distinct disease, (inflammation of the bile ducts), gallstones, pericholangitis, cirrhosis, amyloidosis (EICs). Deep venous thrombosis (0.3%), pulmonary embolism (0.2%), autoimmune hemolytic anemia, clubbing deformity of the ends of the fingers in UC.

**Oral manifestations**: The information regarding oral involvement in UC is sparse and is mainly based on several case reports. The clinical distinction between the oral manifestations of Crohn’s disease and ulcerative colitis may be blurred with overlapping clinical features. Nonspecific clinical changes, such as dry mouth (30%), halitosis (50%), nausea (30%), vomiting (15%), regurgitation (45%), acid taste (15%), taste changes (15%) and dysphagia (15%) are seen in UC. But, these are neither diagnostic nor helpful in the differentiation of the two conditions. Several distinct types of oral lesions may be broadly divided into aphthous type ulcers, pyostomatitis vegetans, hemorrhagic ulcers of oral mucosa and pyoderma gangrenosum, diffuse pustules, lichen planus. The oral lesions may precede GI lesions but are generally present synchronously. Pyostomatitis vegetans is a rare, benign chronic mucocutaneous pustular disorder. Most common in young and middle-aged adults (average age-34 years) with male predominance (3:1). They initially form abscesses measuring 2 to 5 mm in diameter over erythematous skin or mucosa; the pustule erode, coalesce and undergoes necrosis to form ‘snail tracks’ appearance. They correspond to exophytic lesions, producing a vegetating appearance. The surface is yellow-creamy color and is covered by a pseudomembrane that easily disintegrates, facilitating the formation of small ulcers or superficial erosions. Most common site of occurrence are the labial and buccal mucosa, hard and soft palate, gums and less frequently floor of the mouth, tongue. It is thought as a good mucosal indicator of the possible existence of inflammatory intestinal disease—fundamentally ulcerative colitis, with which it is most often associated. Histologically hyperkeratosis, acanthosis, intraepithelial and/or subepithelial microabscesses with a prominent eosinophilic and neutrophilic infiltrate in the lamina propria are present. Intraepithelial dissociation suggestive of ancytholysis is also evidenced.

Pyoderma gangrenosum (PG) is a skin manifestation which appears as a tender erythematous papule evolving into a livid pustule with central necrosis and subsequent ulceration, occurring in single or multiple lesions. It occurs in 0.5 to 2% of both patients with UC and CD and may take a course independent of disease activity. Conversely, 36 to 50% of patients with PG suffer from IBD. Oral mucosal involvement has rarely been described. The peak incidence is between 30 and 50 years, with a slight female preponderance. Sites of involvement have included tongue, palate and tonsillar pillars. Oral lesions are characteristically irregularly shaped with rolled out margins and a grey-colored base. They are usually painful and develop over a period of 4 to 8 weeks. Histological findings include ulcerations with fibrinopurulent membrane, heavy infiltration of the lamina propria with chronic inflammatory cells and perivascular hyalinization and fibrin deposition. Oral aphthous type ulcers are seen in at least 10 to 25% of patients with UC. They are characteristically leathery and may be persistent. The ulcers show white necrotic center and erythematous periphery.

Lichen planus is a chronic mucocutaneous disease of unknown cause. In oral mucosa, it typically presents as bilateral white lesions. It is considered as an immunologically mediated process which is characterized by an intense CD8+ T cells against basal keratinocytes. Oral LP with UC has rarely been reported. There are doubts as to the side effects of drugs used like sulfasalazine or diltiazem could have induced LP. It seems likely that the aminosalicylic acid moiety is responsible for this reaction and that lichen planus is a true complication of mesalazine therapy. Some authors indicated that LP associated with ulcerative colitis is a drug complication and discontinuation of sulfasalazine resolved LP, whereas others contradicted and reported that discontinuation of therapy did not resolve instead became more extensive. Histologic findings of LP associated with UC are hypergranulosis, basal cell necrosis, cytoid bodies, dense infiltrate of lymphocytes at dermoepidermal junction.

Pustular lesions, acute odontogenic abscess secondary to pulp pathology, nonspecific gingivitis with periodontal disease have also been reported with outbreaks.
Temporomandibular inflammatory process, such as arthritis is also associated. Arthritis is not rheumatoid in nature but is specifically referred as colitic arthritis. Glossitis, angular cheilitis and stomatitis (EICs) are complications of vitamin, iron deficiency or drug therapy. CD and UC share common features and overlapping oral signs and symptoms. The microscopic presence of granulomas is considered diagnostic of oral Crohn’s disease; whereas microabscesses of neutrophils and eosinophils without granuloma is considered consistent with ulcerative colitis in appropriate clinical setting. In the absence of granulomas, an aggregated pattern of lymphocytic infiltration of lamina propria and the submucosa, perivascular infiltration of lymphohistocytic cells and neuronal hyperplasia are considered good indicators of oral lesions in CD.

The mainstays of UC treatment are 5-ASA (5-aminosalicylic acid) derivatives, corticosteroids (prednisone), azathioprine in resistant cases, and others are mercaptopurine, infiximab. Surgical management is indicated in severe cases with massive hemorrhage, toxic megacolon, and perforation and with dysplasia or cancer. The oral lesions can be managed with antiseptic mouthwashes, such as chlorhexidine or topical corticosteroids mouthwash. However, topical steroids have limited success instead requires systemic steroids, such as prednisolone. Alternatively, dapsone, azathioprine and sulfamethoxy-pyridazine have been effectively used. The use is limited because of drug’s side effects such as hemolytic anemia, hepatitis, agranulocytosis, bone marrow suppression and should be carefully monitored. Treatment is often based on treating the underlying gastrointestinal disease. The remission of oral disease indicates improvement of the preexisting intestinal disease.

CONCLUSION

In the present case with history of UC, exacerbations of the oral lesions (LP and mucosal ulcers) coincided with intestinal disease severity and resolved with systemic mesalamine therapy indicating that LP may have an association with UC rather than a complication of therapy. The oral lesions in our case appeared prior to initial disease presentation and also during exacerbations, indicating they may be best guide toward disease activity, response to therapy and relapse. Hence, awareness of possible association between gastrointestinal disease and oral lesions among dentists and gastroenterologists may improve early diagnosis with appropriate treatment modalities.

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