

Oral manifestation in inflammatory bowel disease: A review

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Abstract

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis, not only affect the intestinal tract but also have an extraintestinal involvement within the oral cavity. These oral manifestations may assist in the diagnosis and the monitoring of disease activity, whilst ignoring them may lead to an inaccurate diagnosis and useless and expensive workups. Indurated tag-like lesions, cobblestoning, and mucogingivitis are the most common specific oral findings encountered in CD cases. Aphthous stomatitis and pyostomatitis vegetans are among non-specific oral manifestations of IBD. In differential diagnosis, side effects of drugs, infections, nutritional deficiencies, and other inflammatory conditions should also be considered. Treatment usually involves managing the underlying intestinal disease. In severe cases with local symptoms, topical and/or systemic steroids and immunosuppressive drugs might be used.

reserved.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Extra-intestinal manifestations; Pyostomatitis vegetans; Aphthous stomatitis; Cobblestoning; Mucogingivitis; Oral manifestation

Core tip: Although the gastrointestinal tract is the primary site of involvement in inflammatory bowel disease (IBD) patients, some cases might present with non-intestinal manifestations, such as oral lesions. These oral manifestations may aid in the diagnosis and the monitoring of disease activity, whilst ignoring them may lead to an inaccurate diagnosis and useless and expensive workups. Indurated tag-like lesions, cobblestoning, mucogingivitis, aphthous stomatitis, and pyostomatitis vegetans are the main oral presentations of IBDs. With the growing incidence of IBDs and the increased likelihood of encountering these particular manifestations, this review summarizes various oral findings seen in IBD cases by describing their unique morphologic description, treatment recommendations, and probable differential diagnosis.

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INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases with primary intestinal involvement^[1-5]. Although the exact underlying pathogenesis of IBD has not been clearly elucidated, it is postulated that dysregulated immunity is its basis^[4,6-12]. Generally, it is assumed that IBD is a multifactorial disease in which immune system, genetics, and environmental factors all have a

role^[2,8,13-17]. Other than the expected symptoms of gastrointestinal involvement, IBD patients may exhibit a wide range of non-intestinal signs and symptoms known as extraintestinal manifestations (EIMs), with prevalence rates ranging from 6%-47%^[2,8,18,19]. Approximately one third of IBD patients develop EIMs in the course of their disease^[1,20-25]. Joints, skin, eyes, and the biliary tract are among the most common organs involved in EIMs^[22,26-28]. Oral involvement with different presentations may also be seen in IBD. Oral manifestations could also occur in these patients due to other causes, such as drug reactions, infections, and unrelated diseases^[1,2,6,8,20,21]. Patients with IBD may present with these oral manifestations years before the appearance of intestinal disease^[1,6]. Recognizing these patterns may assist physicians and other care givers in making a timely diagnosis of IBD while avoiding unnecessary workups^[29]. The scope of this review is to describe various oral presentations in IBD and their differential diagnosis and treatment.

EPIDEMIOLOGY OF ORAL MANIFESTATIONS IN IBD

In 1969, Dyes and colleagues initially described oral lesions in two patients with CD^[7,30]. This was followed in the same year by Dudeney's report of another patient suffering from CD who had oral manifestation^[51]. Oral lesions in the absence of intestinal findings in CD were initially described in 1972 by Varley^[32], and there have since been various reports on the incidence of oral lesions in CD^[1-3,23,30,33-39]. The highest rate was reported from a study in a pediatric age group, indicating a rate of 48%^[33]. The prevalence rate is estimated to be between 50% and 20% in most publications^[1,33,38].

This variation in rate might be related to the different ages of patients studied, their ethnicity and genetic background, whether they were receiving treatment while being investigated, the experience level of the examiners, and the variation in definition of specific lesions^[34].

In the majority of cases, intestinal involvement precedes the oral lesion^[1]. Oral lesions are more common in CD compared to UC, more prevalent in children compared to adults, and with a male dominance^[1,8,21,33,34,37,40,41]. The prevalence is also higher in CD patients with proximal gastrointestinal tract and/or perianal involvement^[2,33,42].

Oral lesions may be the primary presenting signs preceding gastrointestinal symptoms^[43,44] in 5%-10% of affected patients^[39]. This figure has been reported to be as high as 60% in patients with CD^[37].

Although the lesions might be more severe at the time of active disease, the correlation is not universal, and up to 30% of affected patients may continue to manifest oral lesions (especially in the pediatric age group) despite disease control^[34,45].

ORAL LESIONS IN CROHN'S DISEASE

Dudeney's report of oral Crohn's disease in 1969 de-

scribed it as a raised, edematous, pink granulation tissue in the buccal mucosa^[31]. It is now known that the lips are the most frequent site of oral Crohn's disease (OCD) lesions^[37]. Oral lesions may be painful, impair proper oral function, or lead to psychological disorders due to disfigurement^[8,46]. Oral manifestations of CD can be specific or non-specific, based on the presence of granulomas noted on the histopathology reports^[1].

SPECIFIC ORAL CROHN'S DISEASE LESIONS

These specific lesions contain granulomatous changes noted upon histopathological examination. They are less common than non-specific lesions, and can occur either concomitantly with intestinal symptoms or before gut presentation by several years^[47,48]. The most affected portions in the mouth are the buccal mucosa, gingiva, lips, vestibular, and retromolar areas^[32]. There are four main lesions, as described below and shown in Table 1.

INDURATED TAG-LIKE LESIONS

These are white reticular tags^[35] referred to as mucosal tags, epithelial tags, or folds^[49]. These lesions are mostly discovered in the labial and buccal vestibules, and in the retromolar regions^[21]. Up to 75% of these lesions may show non-caseating granulomas on histopathology^[33,42]. There has been no specific direct association of these lesions with intestinal CD activity reported^[1]. Treatment is described in the later section on general treatments of OCD lesions.

COBBLESTONING

Fissured swollen buccal mucosa with corrugation and hyperplastic appearance of the mucosa are called cobblestoning^[1,42,50,51]. These lesions are usually seen in the posterior buccal mucosa and may be associated with succulent mucosal folds with normal epithelium^[21]. The lesions usually consist of mucosal-colored papules that produce firm plaques on the buccal mucosa and palate. Such lesions may cause pain and make speaking and eating normally difficult^[52]. These lesions, along with mucosal tags, are considered pathognomonic for CD^[35], but are not associated with intestinal CD activity^[1]. Treatment consists of topical steroids in addition to the treatment of intestinal involvement. In more severe presentations, systemic steroids could be used^[53].

MUCOGINGIVITIS

The gingiva may become edematous, granular, and hyperplastic in Crohn's disease, with or without ulceration. The whole gingiva up to the mucogingival line might be involved^[7,30]. As with other specific lesions of the oral cavity, this lesion has no association with intestinal CD activity. Treatment is discussed in the section on general

Table 1 Summary of specific and non-specific oral lesions in Crohn's disease

	Lesion	Relation with CD activity	Frequency	Treatment options
Specific oral lesions	Indurated tag-like lesions	No specific direct association reported	Common in OCD patients	See general points on the treatment of OCD in the text
	Cobblestoning	No specific direct association reported	Common in OCD patients	Topical steroids for less severe cases and systemic steroids for others
	Mucogingivitis	No specific direct association reported	Common in OCD patients	See general points on the treatment of OCD in the text
	Others: Lip swelling with vertical fissures Deep linear ulcerations	No specific direct association reported		Topical tacrolimus, intra-lesional injection of steroids, immunosuppressive agents Topical analgesics, 5-ASA, or steroids, intra-lesional steroids, topical tacrolimus, other medications used in PV treatment
Non-specific oral lesions	Aphthous stomatitis	No specific direct association reported	10% of patients with UC and 20%-30% of those with CD	Topical agents (lidocaine 2%, triamcinolone 0.1%, dexamethasone elixir), non-steroidal anti-inflammatory pastes, systemic steroids, intra-lesional steroids
	Pyostomatitis vegetans	Associated with active CD	Rare	Antiseptic mouthwashes/topical steroids (though less effective), systemic steroids, azathioprine and sulfamethoxypyridazine, dapsone, cyclosporine A, injections of infliximab pursued by maintenance therapy with MTX, adalimumab, surgical colectomy in UC
	Others: Angular cheilitis	No specific direct association reported	Unknown	5-ASA mouthwashes, topical steroids (1% hydrocortisone), vitamin supplements, intra-lesional steroids
	Persistent submandibular lymphadenopathy Recurrent buccal abscesses Perioral erythema with scaling Glossitis			See general points on the treatment of OCD in the text Antibiotics, infliximab, methotrexate, thalidomide

CD: Crohn's disease; OCD: Oral Crohn's disease; MTX: Methotrexate; UC: Ulcerative colitis.

treatments of OCD lesions below.

OTHER SPECIFIC LESIONS

Lip swelling with vertical fissures, deep linear ulcerations (usually in the buccal sulci with hyperplastic folds), and midline lip fissuring may also occur in CD^[1,2,7,8,22,30,33,35,39,42,49,54]. These lesions also have no association with intestinal CD activity^[1].

While these lesions may be very incommensurate for patients, they can be treated with topical tacrolimus at low concentration (0.5 mg/kg) and intra-lesional steroid injection with or without mandibular blockade^[34,55,56]. In more severe cases with persistent pain and cosmetic disfigurement, more aggressive therapy with immunosuppressive agents is recommended^[34].

NON-SPECIFIC ORAL LESIONS IN CD

Table 1 provides details of various non-specific oral lesions that occur with Crohn's disease.

APHTHOUS STOMATITIS

Aphthae are shallow round ulcerations with central fi-

brinous exudate and an erythematous border^[23,57]. These lesions may occur in 20%-25% of the general population^[3,58], up to 10% of patients with UC, and 20%-30% of those with CD that have oral aphthosis^[4]. In a survey conducted in Iran, oral aphthous lesions were found in approximately 13% of CD *vs* 6% of UC patients^[13]. The association of oral aphthosis and disease activity is not clear. While it may become more severe in active disease, its presence does not correlate with disease activity.

Patients with IBD and other EIMs may suffer recurrent aphthous stomatitis more often than others^[4]. Aphthous stomatitis has been associated with ankylosing spondylitis, uveitis, peripheral arthritis, and erythema nodosum^[59]. Aphthous eruptions are not specific for IBD and may be observed in several other disorders including celiac sprue, HIV/AIDS, Behçet's disease, and Reiter's syndrome, as well as common aphthae seen in the normal population^[23,60-66].

Management of CD is usually sufficient for control of oral aphthosis. For control of pain, topical agents (such as lidocaine) and/or topical steroids (such as triamcinolone 0.1%) up to three times per day can be used. Dexamethasone elixir (0.5 mg/5 mL spit or swish) or ointment up to three times per day is also efficacious. Non-steroidal anti-inflammatory pastes are effective in

relieving pain and promoting healing. Systemic or intra-lesional steroids should be reserved for severe refractory and/or persistent cases^[4,13,21,32,67-70].

PYOSTOMATITIS VEGETANS AND OTHER NON-SPECIFIC LESIONS

Pyostomatitis vegetans can occur in both UC and CD, but is more common in the former and will be discussed in more detail in the later section addressing oral manifestations of UC.

Other non-specific oral findings of CD include angular cheilitis, persistent submandibular lymphadenopathy, sicca syndrome and reduced salivation, halitosis, dental caries and periodontal involvement, candidiasis, odynophagia, dysphagia, minor salivary gland enlargement, perioral erythema with scaling, recurrent buccal abscesses, glossitis, mucosal discoloration, lichen planus, and metallic dysgeusia^[2,7,21,32,34,35,40,54,71]. For the management of angular cheilitis, 5-ASA mouthwashes, topical steroids (1% hydrocortisone), vitamin supplements, and intra-lesional steroids may be effective. Antibiotics are the first step in treating recurrent buccal abscesses. For more severe cases, immunomodulating agents including chimeric anti-tissue necrosis factor (TNF) alpha monoclonal antibody-infliximab, methotrexate, and thalidomide have been used^[7,21].

GENERAL POINTS ON THE TREATMENT OF OCD

In the majority of patients with OCD, the oral findings are asymptomatic and clinically silent. In these patients, no peculiar treatment is needed for oral lesions and the latter will resolve over time in association with the treatment of gastrointestinal disease using anti-inflammatory drugs (5-ASA), immunosuppressive agents, and finally biological agents, whichever are indicated^[8,21,34,40,72].

The treatment armamentarium includes topical and systemic steroids, 5-ASA compounds, immunosuppressive agents, biologic treatments, and even antibiotics such as tetracycline^[2,73].

The first and foremost step in treating oral lesions is to control colonic disease^[74]. Food restriction, which is discussed later in the management of orofacial granulomatosis (OFG), could also be tried in OCD^[75,76].

ORAL LESIONS IN UC

There are many similarities between the oral manifestations of CD and UC. Although oral lesions are more common in CD, almost all of the so-called non-specific oral lesions described in CD can also occur in UC. Among these lesions, pyostomatitis vegetans occurs more commonly in UC than in CD and will be discussed here in more detail^[1,2,74,77,78].

The term pyostomatitis vegetans (PV) was first in-

troduced by McCarthy in 1949^[38], but its association with IBD was not initially recognized^[38]. PV is a chronic mucocutaneous ulcerative disorder consisting of multiple milium white or yellow pustules with an erythematous and edematous mucosal base^[1,23,77,79]. The pustules can rupture and coalesce to form linear or “snail-track” ulcers^[1,23,38,77,78,80]. The most frequently involved regions of the oral cavity are the labial gingiva, labial, and buccal mucosa^[78]. The least damaged portions are the tongue and floor of the mouth^[1], but pustules can involve almost all parts of the oral cavity^[78].

PV can be seen at any age, but is more prevalent in patients aged between 20 and 59 years, with an average age of 34 years. Males are affected more frequently than females, with a ratio of 2:1-3:1^[81,82]. PV is considered to be the oral equivalent of pyodermitis vegetans on the skin^[77,78]. There is a strong association between PV and IBD, and the former is a specific marker of disease activity in UC^[1,2,38,39,78,83,84]. Intestinal involvement usually predates the onset of PV in IBD, although this could be asymptomatic and mild^[23,85]. Despite every effort, no bacterial, fungal, or viral cause has yet been found for this manifestation and its pathogenesis remains obscure^[77]. The principal histological features on microscopy are intra-epithelial and/or sub-epithelial micro-abscesses with neutrophils and eosinophils. Furthermore, hyperkeratosis, acanthosis, and acantholysis are seen in histology examination^[1,38,40,78,86]. Direct immunofluorescence in PV is negative for deposits of IgA, IgG and C3 and this result is helpful in distinguishing PV from pemphigus vulgaris^[1,87]. Clinically, the patient may have fever, enlarged and tender submandibular lymph nodes, and pain. Pain intensity is variable; some patients with extensive oral lesions may not have any pain^[78]. Peripheral eosinophilia is seen in up to 90% of cases and is the main laboratory finding in many patients^[87].

The diagnosis of PV is based on a constellation of clinical features that include concurrent IBD, peripheral eosinophilia, histological study, and negative culture results of the lesion exudate. As mentioned above, a negative immunofluorescence study is also helpful^[1,77,87].

The main differential diagnoses of PV include vesicular disorders involving both the skin and oral cavity; similar to pemphigus vulgaris in particular, as well as other diseases like bullous pemphigoid, acquired epidermolysis bullosa, bullous drug eruptions, herpetic infection, Behçet's disease, and erythema multiforme^[1,77,80,88]. Herpetic infections should be excluded by Tzanck smear, antigen detection, and culture of the virus, or PCR for HSV virus^[23]. The mainstay in the management of PV is the treatment of underlying IBD. Topical steroids and antiseptic mouthwashes alone are effective in only a few instances. Systemic steroids are usually prescribed for these patients and are considered as the treatment of choice. Azathioprine and sulfamethoxypyridazine can be used in parallel with steroids as sparing agents^[3,21,23,38,77,78]. Dapsone is another option, but should be used as a second line agent, especially in relapsing cases. Hemolytic ane-

mia, hepatitis, agranulocytosis, and drug-induced allergic reactions are the major side effects of dapsone requiring attention^[3,78].

Calcineurin blockers like cyclosporine A have been successfully used, as described in case reports in the treatment of PV^[89]. Injections of infliximab followed by maintenance therapy with methotrexate have been also effective, especially in PV associated with CD^[77]. Systemic use of newer humanized anti-TNF agents like adalimumab has also proven effective in inducing remission of both oral and gastrointestinal manifestations^[77]. Surgical colectomy produces promising results in PV associated with UC^[3,78,90].

Other non-specific findings in UC include oral aphthae, glossitis, cheilitis, stomatitis, lichen planus, mucosal ulcers, diffuse pustules, and non-specific gingivitis^[1-3,23,42].

In a report of patients with UC, 4.3% had aphthous stomatitis during intestinal disease flare-ups^[2], thus the presence of this non-specific manifestation may have some correlation with disease activity in UC.

DIFFERENTIAL DIAGNOSES

Because CD is a granulomatous disorder, all other diseases capable of inducing granulomatous reaction in the oral cavity are included in the differential diagnosis (DDX) list. The most common cause of developing oral granulomas is a response to foreign bodies, primarily dental materials such as retained amalgams or endodontic sealers^[91]. The second important DDX to be considered is tuberculosis bacilli. Special staining processes for acid-fast bacilli, PPD skin test, sputum culture, and chest X-ray are often used to diagnose oral tuberculosis^[2,80,92].

Fungal infections such as candidiasis, histoplasmosis, cryptococcosis, paracoccidioidomycosis, and blastomycosis can all trigger granulomatous involvement of the mouth. The presence of these infections could be confirmed by special stains including applying PAS or Gömöri trichrome stain and, more specifically, with molecular studies^[2,21,80].

Oral sarcoidosis should always be considered in DDX, and an appropriate workup should include measuring serum angiotensin converting enzyme, IL-2 receptor level, IL-8 level, and chest X-ray in suspected cases^[2,6,21,39,93].

Leprosy, cat scratch disease, tertiary syphilis, orofacial granulomatosis, T-cell lymphoma, and Wegener's disease can all produce a granulomatous reaction in the oral cavity, but are much rarer and usually have other prominent features leading to diagnosis^[21,39].

Considering the role of nutritional deficiencies is of utmost importance as stomatitis, glossitis, aphthous ulcers, cheilitis, or perioral dermatitis may occur with nutrient deficiencies resulting from an insufficient supply of the vitamin B family, albumin, iron, folate, zinc, niacin, and/or other essential elements^[8,41,94-97]. Nutrient deficiencies may be the result of intestinal involvement or may be caused by the medications used in the treatment of

IBD^[98,99]. Sulfasalazine and azathioprine, for instance, may cause folate and niacin deficiency, respectively^[2].

Other non-specific oral manifestations may also be related to the side effects of drugs. As an example, oral aphthosis has been reported in association with non-steroidal anti-inflammatory agents, nicorandil^[100], and bupropion^[101]; gingival hyperplasia with cyclosporine^[102], amlodipine^[103], and anticonvulsants such as phenytoin^[104]; and reversible lichen planus with sulfasalazine^[54].

OROFACIAL GRANULOMATOSIS

Gibson *et al.*^[40] used the term OFG in 1985 to define a constellation of oral signs similar to those seen in OCD, but in the absence of evidence of intestinal CD. In this rare syndrome, chronic swelling of the lips and lower half of the face is prominent, in association with oral ulcers and hyperplastic gingivitis. Granulomatous cheilitis is the most common sign seen in OFG^[105]. The most frequent sites of involvement in OFG are the lips, which may be individually or both involved^[80]. Lip swelling usually leads to painful vertical fissures^[2]. Three forms of ulcers are found in OFG: deep buccal ulcers with raised peripheral mucosa, aphthous-type ulcers, and micro-abscesses located commonly on the gingival margin or soft palate^[21]. In general, the ulcers are mainly superficial and the gingivae are erythematous with patchy distribution, mostly affecting the anterior portion. These alterations extend from the free gingival margin to the non-keratinized mucosa of the sulci, developing a full-thickness gingivitis pattern^[40].

In the largest series of studies involving OFG reported to date, the mean age of those affected at presentation was 20 years with no gender predilection. With the pathogenesis unknown, allergic, infectious, and genetic causes have also been postulated^[40,106]. Unlike OCD in which Th1 CD4⁺ lymphocytes are the dominant population, in OFG the overstimulation of Th2 CD4⁺ lymphocytes is detected in biopsy specimens, where it is shown as infiltrating cells^[21].

Granulomas noted upon histology examination are the hallmark in both OFG and OCD. The only way to exclude CD is by clinical presentation^[21]. As mentioned previously, oral manifestations may precede gastrointestinal involvement in CD for many years. Thus, cases labeled as OFG may later progress to being diagnosed as CD^[21,34]. Recently, it has been reported that 4 out of 6 children with OFG in early childhood were reported as having developed CD on follow-up^[34].

A rare presentation of OFG seen in adults is Melkersson-Rosenthal syndrome; a triad of orofacial swelling, intermittent facial paralysis, and a fissured tongue^[21,34,107].

Observational studies in pediatric patients with OFG have demonstrated that dietary elimination of some triggering elements (encompassing cinnamaldehyde, benzoate additives, carnosine, monosodium glutamate, cocoa, and sunset yellow) are effective in the treatment of oral lesions^[75,76]. Analgesia and topical agents like beclomethasone mouthwash and 5-ASA spray or ointments can be

used as basic therapies. In unresponsive cases, treatment with systemic steroids and immunosuppressive medications can be used^[21]. Clofazimine, a drug used in the treatment of leprosy, is occasionally effective in OFG^[37].

CONCLUSION

Oral manifestations of inflammatory bowel diseases are diverse. Although they are generally more common in patients with Crohn's disease, specific manifestations like PV occur more commonly in ulcerative colitis, which is associated with disease activity in most instances. Most other manifestations have no correlation with disease activity. In differential diagnosis of these oral manifestations, side effects of drugs, nutritional deficiencies, infections, as well as other granulomatous diseases with oral involvement should all be considered. There is usually no need for specific treatment for these lesions, but when indicated it may comprise topical and systemic steroids, immunosuppressive drugs, antibiotics, and even biological treatment in more severe cases.

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