Oral Manifestations of IBD

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Definition

Inflammatory bowel disease (IBD) comprises chronic heterogeneous disorders of unknown etiology, resulting from multifactorial environmental precipitants in genetically susceptible individuals. IBD are distinguished in two main phenotypes, Crohn's disease (CD) and ulcerative colitis (UC), characterized by inflammation of the intestinal mucosa. While UC affects the rectum and a variable extent of the colon, CD can involve any location of the gastrointestinal (GI) tract, from the oral cavity to the anus. Furthermore, up to 36% of patients with IBD may have extra-intestinal manifestations (EIM) which can affect almost any organ of the body (eyes, joints, liver, pancreas, skin, blood, and mouth).

1. Oral Lesions in Patients with IBD

The first cases of oral IBD manifestations were described in 1969 in two patients with CD [1]. In the last 50 years, the prevalence of oral lesions in patients with IBD has been reported to range from 5% to 50%, according to heterogeneous studies [2][3]. This wide range could be due to various reasons: first, the heterogeneity of the studies, including patients of different ages, ethnicities, and genetic backgrounds; second, the authors' level of experience; third, the variability in the definition of lesions. The latter, in fact, could be a specific IBD lesion, but could also have iatrogenic origin, due to the drugs used to treat IBD.

The prevalence of oral manifestations is higher in males and in children [3]. The higher incidence of upper GI tract involvement in children with CD, compared to adults, could explain the higher prevalence of oral lesions in pediatric CD [4]. Although oral lesions are generally more prevalent in CD (20%–50%) [5] than in UC (8%) patients, in some studies a significant difference was not observed [6]. Moreover, in adult CD patients, the prevalence rate of oral manifestations is higher in those with upper GI tract involvement and perianal disease [7].

Oral manifestations can occur either concomitantly with intestinal symptoms or before the presentation of IBD. In 60% of these patients, oral lesions may be the primary presenting sign, preceding GI manifestations [8][9]. Although the oral mucosa lesions and oral symptoms can be more severe during disease activity period, the correlation is not universal, and up to 30% of affected patients continue to suffer active oral manifestations (especially in the pediatric age group) despite remission of IBD [10]. Oral IBD manifestations can be divided into specific and not-specific lesions (Table 1), according to the presence of granulomas noted on the histopathology examinations [6][11]. It should be highlighted that some of these lesions can be considered an oral location of IBD while others are the result of nutritional deficiencies secondary to intestinal malabsorption.

Table 1. Specific oral lesions in patients with inflammatory bowel disease (IBD).

Lesion	Location	Features
Cobblestoning	Posterior buccal mucosa	Fissured swollen mucosa with corrugation and hyperplastic
Indurated tag-like lesions	Labial and buccal vestibules; retromolar region	Hyperplastic edge firm or boggy
Mucogingivitis	Whole gingiva	Gingiva edematous, granular and hyperplastic

Lesion	Location	Features
Others: Lip swelling with vertical fissures Deep linear ulceration Edema of the face	Lips, tongue, buccal sulci, face	

For IBD, and for its oral manifestations, the pathogenesis remains unclear. Parallel to what has been reported on the potential role of microbiota in the pathogenesis of IBD and its oral location, it has been proposed that dysbiosis (term that means imbalance within the bacterial community) of salivary microbiota (with relative abundance of Streptococcus, Prevotella, Haemophilus, and Veillonella) may play a crucial role [12].

2. Specific Oral Lesions

Specific oral lesions are less common than non-specific ones. The main feature of specific lesions is the presence of non-caseous granulomas, observed only in patients with CD (CD with concomitant orofacial granulomatosis) [13]. Granulomas consist of a core of activated macrophages, some of which merge to form giant cells, surrounded by lymphocytes and fibrotic tissue. Granulomas are found in only 24%–61% of patients with CD, whereas in those with orofacial granulomatosis, granuloma formation in the oral lesions occurs in 70%–100% of cases, irrespective of coexisting CD. It has been reported that CD with concomitant orofacial granulomatosis is frequently associated with perianal lesions; furthermore, children with CD and concomitant orofacial granulomatosis show a more extensive disease phenotype and proximal GI tract involvement than CD patients with intestinal inflammation only [14].

The differential diagnosis should consider that granulomatous oral lesions can also occur in other diseases, including orofacial granulomatosis, sarcoidosis, mycobacterial infection, and foreign-body reactions.

The specific oral lesions include indurated tag-like lesions, cobblestoning, mucogingivitis, lip swelling with vertical fissures, and deep linear ulcerations (Table 1).

2.1. Clinical Characteristics

In cobblestoning, fissured swollen buccal mucosa with corrugation and hyperplastic appearance of the mucosa resemble a “cobblestone”. These lesions are usually detected in the posterior buccal mucosa and consist of mucosal-colored papules that produce firm plaques on the buccal mucosa and palate. In addition, indurated polypoid fringe-like lesions can be observed in the vestibule and in the retromolar region. Such lesions may cause pain and make speaking and eating difficult [15].

Mucosal tags and deep linear ulcerations (lip and tongue fissures) have hyperplastic edges, which can be firm or boggy to palpation. Attached gingiva and alveolar mucosa can become granulated, swollen, and hyperplastic with or without ulcerations. These lesions are mostly present in the labial and buccal vestibules and in retromolar regions.

In the setting of specific lesions, edema of the face, of one or both lips, and of the buccal mucosa has been described. The lips are the most commonly affected, and they are usually painless, tender, and firm to palpation [16]. Painful vertical fissures can occur in numerous patients with swollen lips; many microorganisms can be isolated in lip fissures [17].

Mucogingivitis can be present. The gingiva appears edematous, granular, and hyperplastic in CD, with or without ulcerations. The whole gingiva up to the mucogingival line might be involved [18].

A rare manifestation of CD could be represented by autoimmune changes of the minor salivary glands and dry mouth [19]. Chronic inflammatory processes near the parotid duct result in partial to total duct

obstruction and cause dilated ducts and cyst formation, which can lead to the formation of cutaneous fistulas. All these changes can also lead to a reduction in saliva production and dry mouth [20].

Other specific manifestations include granulomatous cheilitis, macrocheilia, and palatal ulcer. In case of granulomatous cheilitis the main change is a chronic granulomatous inflammation, with edema and lumpy swelling of the lips.

2.2. Diagnosis

The differential diagnosis of specific oral lesions includes syndromes presenting with multiple mucosal swellings, such as multiple hamartoma syndrome (Cowden disease), multiple endocrine neoplasia (MEN) 2B/III, neurofibromatosis, and idiopathic orofacial granulomatosis.

In the case of histologically confirmed oral granulomatous, the differential diagnosis includes foreign body reaction, allergic reaction to benzoate or cinnamon, and idiopathic orofacial granulomatosis. Systemic conditions associated with granulomatous inflammation include deep fungal infections, mycobacterial infections, sarcoidosis, and tertiary syphilis.

3. Non-Specific Oral Lesions

Non-specific oral lesions (Table 2) occur more frequently than specific lesions, so differential diagnosis can be difficult. These lesions may occur as result of chronic inflammation, malnutrition and malabsorption syndrome, or as a side effect of pharmacological treatment.

Table 2. Non-specific oral lesions in patients with IBD.

Lesion	Location	Features
Aphtous stomatitis	Anywhere in the oral cavity	Shallow round ulcerations with central fibrinous exudate surrounded by an erythematous border
Pyostomatitis vegetans	Labial gingiva, buccal and labial mucosa; less common: tongue, soft and hard palate	Erythematous and thickened oral mucosa with multiple pustules and superficial erosions
Angular cheilitis	Corner of the oral cavity	Erythema at the corners of the mouth with or without painful fissures and sores
Others: Glossitis Periodontitis and dental caries Perioral dermatitis Recurrent buccal abscesses Submandibolar lymphoadenopathy Salivary duct fistula	Oral mucosa, gingiva, tongue, teeth, periodontal tissue, alveolar bone, perioral skin, palate, lips, lymph nodes, salivary glands	

Patients with IBD and EIM may suffer from recurrent aphthous stomatitis more often than others; these lesions may occur in up to 10% of patients with UC and up to 20%–30% of patients with CD [21]. Apthae are shallow, round ulcerations with central fibrinous exudate surrounded by an erythematous border (“halo”). Aphthous stomatitis are not specific for IBD and may be observed in several other disorders including celiac sprue, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome, autoimmune rheumatic disease (lupus, Bechet’s disease and Reiter’s syndrome), infections (herpes virus, cytomegalovirus), autoimmune bullous diseases, and common aphthae seen in the normal population.

Angular cheilitis is characterized by erythema at the corners of the mouth with or without painful fissures and sores. It can be a consequence of anemia or fungal and bacterial infections [22].

Pyostomatitis vegetans (PV) is a rare, benign, chronic, mucocutaneous ulcerative disorder, considered the oral equivalent of pyodermatitis vegetans of the skin [23]. There is a frequent association between PV and IBD; it occurs in patients with UC more commonly than in those with CD and, in the former, is considered a specific marker of disease activity [24]. PV is characterized by erythematous and thickened oral mucosa with multiple pustules and superficial erosions. Multiple white or yellow pustules may rupture, and form folded, fissured appearances resembling a “snail-track”. The most affected areas are the labial gingiva, buccal and labial mucosa, and soft and hard palate. PV may present with oral ulcers (with possibly oral malodor). The differential diagnosis includes autoimmune pemphigoid diseases and infections [25]. The diagnosis of PV is based on the result of biopsy specimen obtained from the affected area. Microscopic sections show intraepithelial clefting and acantholysis. Within the spinous layer, the accumulation of eosinophils (intraepithelial abscesses) are also seen. The underlying connective tissue demonstrates the infiltration of mixed inflammatory cells [26]. Some authors have suggested that PV belongs to the spectrum of neutrophilic dermatoses or even represents an oral form of pyoderma gangrenosum [27].

In patients with IBD, caries and periodontal disease occur with a higher prevalence than in those without IBD. This is supported by the results of a meta-analysis, reporting that the risk of periodontitis is significantly increased in IBD compared to the control group and that it is more pronounced in UC than in CD [28]. In addition, the severity and extent of periodontitis is greater in IBD patients when compared to healthy controls [29], probably in association with the high expression of interleukin (IL)-18 in the serum of IBD patients with periodontitis [30]. The pathogenesis of periodontal disease, similar to that of IBD, involves local pathogens and the host immune-inflammatory response, and is influenced by genetic and environmental factors [31]. The increase in dental caries risk is thought to be associated to dietary habits, changes in saliva and microbiological conditions of the oral cavity, and deficient intestinal absorption of food substances. The malabsorption of vitamin D, which is common in IBD patients [32], may possibly be related to the complex multifactorial etiopathology of dental caries [33].

Other non-specific oral manifestations of IBD include stomatitis, glossitis, odynophagia and dysphagia, perioral dermatitis, diffuse pustules and non-specific gingivitis, lichenoid reactions, candidiasis, gingival hyperplasia, papillomatosis of the oral mucosa, pemphigus vegetans, persistent submandibular lymphadenopathy, recurrent buccal abscesses, and metallic dysgeusia [34].

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Keywords

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