

Oral Pathology unmasking Gastrointestinal Disease

Review Article**Abstract**

Different gastrointestinal disorders, such as Gastroesophageal Reflux Disease (GERD), Celiac Disease (CD) and Crohn's disease, may manifest with alterations of the oral cavity but are often under and misdiagnosed both by physicians and dentists. GERD can cause dental erosions, which are the main oral manifestation of this disease, or other multiple affections involving both hard and soft tissues such as burning mouth, aphthous oral ulcers, erythema of soft palate and uvula, stomatitis, epithelial atrophy, increased fibroblast number in chorion, xerostomia and drooling. CD may be responsible of recurrent aphthous stomatitis (RAS), dental enamel defects, delayed eruption of teeth, atrophic glossitis and angular cheilitis. Crohn's disease can occur with several oral manifestations like indurated tag-like lesions, clobbestoning, mucogingivitis or, less specifically, with RAS, angular cheilitis, reduced salivation, halitosis, dental caries and periodontal involvement, candidiasis, odynophagia, minor salivary gland enlargement, perioral erythema with scaling, recurrent buccal abscesses, glossitis, mucosal discoloration, lichen planus, and metallic dysgeusia. A prompt detection of the oral signs of these systemic diseases allows an early diagnosis and treatment and could prevent related long-term complications.

Keywords: Dental erosion; Gastroesophageal reflux; GERD; Celiac Disease; Stomatitis; RAS; IBD; Crohn's Disease; oral pathology

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Abbreviations: CREST: Calcinosis Raynaud Phenomenon Esophageal Dismotility Sclerodactyly Teleangiectasia; GERD: Gastro Esophageal Reflux Disease; CD: Celiac Disease; RAS: Recurrent Aphthous Stomatitis; MiRAS: Mikulicz's Aphthae; MaRAS: Sutton's Aphthae; HeRAS: Herpetiform Aphthae; PFAPA: Periodic Fever Aphthous Stomatitis Pharyngitis and Adenitis; IBD Inflammatory Bowel Diseases; EIMs: Extraintestinal Manifestations

Introduction

A careful and recurrent assessment of the oral cavity is essential to recognize dental and gum problems but also to early detect signs of a systemic pathology. During the inspection of the oral cavity signs and symptoms like persistent pain, halitosis, ulcerations (and related features such as type, frequency, recurrence, numbers), mass, bleeding may rise the suspect of thrombocytopenia, ptyalism, xerostomia, cancer, nutritional problems, chronic inflammation, immunodeficiency, diabetes, renal or gastrointestinal diseases. Systemic pathologies which affect the oral cavity could be divided into infectious diseases (HIV, syphilis, mononucleosis, herpes zoster), neoplastic diseases (lymphoma, melanoma), inflammatory diseases (chronic Inflammatory Bowel Diseases), autoimmune diseases (systemic lupus erythematosus, CREST syndrome, celiac and Reiter's disease), hepatic diseases (hepatic cirrhosis), vitamins deficiency diseases (Moeller Hunter's glossitis). Besides, the oral inspection may be a precious underestimated treasure that reveals other different important problems: chronic periodontal disease related to vascular problems, malocclusion as a result of a prognathism due to acromegaly, delayed tooth eruption due to hypopituitarism, crown alterations with enamel hypoplasia due

to vitamins deficiency, rickets and hypoparathyroidism; dental discoloration related to fetal erythroblastosis, porphyria and congenital liver disease. Furthermore, enamel defects have been connected with gastroesophageal reflux Disease, but also with bruxism, self-induced vomiting and bulimia; a periodontitis with teeth loss could be caused by Chèdiak-Higashi's disease, whereas localized edentulism has been reported in Papillon-Léfevre's syndrome, Kaposi's sarcoma, Burkitt's lymphoma, Histiocytosis X and hypophosphatasia, and, a strawberry gingivitis can be a manifestation of Wegener's granulomatosis. The focus of this paper is on gastrointestinal disorders that could cause oral alterations in children.

Gastroesophageal reflux (GER)

GER is the return of gastric content into the esophagus and up or out the oral cavity. When GER cause troublesome symptoms or complications it is defined as GER-disease (GERD). The contact of gastric juice, pepsin and acid outside the stomach may determine esophageal and extra-esophageal inflammation, erosions or ulcers, resulting in pain, heart or oral burn, laryngitis, dysphonia, pharyngitis, respiratory and oral disorders such as dental erosions and soft tissue lesions [1].

Dental erosions

Pindborg defines dental erosion as the loss of tooth structure caused by a chemical process with no involvement of the bacterial flora [2]. In patients with GERD, the chronic or recurrent exposure to acid gastric juice on dental enamel can be recognized by the presence of dental erosion, whose severity depends on the duration of the disease, the quantity and quality of reflux and the individual resistance [3,4]. Young children and patients with

neurologic impairment show the greatest risk [4]. Case series and a recent systematic review reported a causative association between GERD and dental erosion [5]. A study in adolescents showed that reflux was associated with an increased incidence of erosion of enamel on the lingual surfaces of the teeth [6]. On the other hand, another study did not report an increased incidence of dental erosions in adolescents with abnormal esophageal pH monitoring [7]. Besides reflux, other conditions that may cause similar dental erosions should be considered and included juice drinking, bulimia, racial and genetic factors affecting the characteristics of enamel and saliva [4]. The demineralization of dental hard tissues due to the dissolution of apatite crystals can cause the total destruction of teeth. The location of this damage in patients with GERD is usually in the occlusal and palatal surfaces of upper teeth and in the buccal and lingual/occlusal surfaces of lower teeth, because the acid is led to these surfaces by the position of the tongue [8]. The pattern of erosion severity is established by assessing the extent of the loss of tooth substance. The most widely used classification is the Erosion Index proposed by Eccles and Jenkins [9], which considers four grades:

- a) Grade 0: No erosion.
- b) Grade 1: Loss of enamel without exposure of dentin.
- c) Grade 2: Loss of enamel with exposure of dentin in less than a third of the tooth surface.
- d) Grade 3: Loss of enamel with exposure of dentin in more than a third of the tooth surface.

The clinical appearance of dental erosion includes broad concavities within smooth surface enamel, cupping of occlusal surfaces with dentin exposure, increased incisal translucency, wear on non-occluding surface, “raised” amalgam restorations, clean and non-tarnished appearance of amalgams, loss of surface characteristics of enamel in young children, preservation of enamel “cuff” in gingival crevice, hypersensitivity and pulp exposure in deciduous teeth [10]. The real prevalence of dental erosions in patients with GERD is unclear and dependent on several factors (Table 1).

Table 1: Variables connected with the different prevalence reported for dental erosions.

Variables connected with the patient	Variables Connected With the Operator
Frequency of regurgitation	Type of classification used for dental erosions
Duration of GERD	Number of patients included
Salivary Buffer	Difficulty in the detection of dental erosions
Swallow	Exclusion of dental attrition and abrasion
Phoniatric problem	Presence of dental implants
Individual resistance	
Lingual Clutch	

Soft tissue lesions

Studies analyzing the relationship between oral pathology and GERD are mainly focused on hard tissue lesions, where as little attention is paid to the implication of soft tissues. Järvinen et al. [11] correlated burning mouth, aphtous oral ulcers and hoarseness of the voice with GERD. Other authors supported the relationship between eating disorders and burning mouth syndrome [12], Silva et al. [13] investigated the effects of GERD on dentition, salivary function and oral mucosa by using salivary test (sialometry, buffer capacity and pH), biopsy and morphometry of the palatal mucosa. No relationship between GERD and changes in the oral cavity was shown by saliva tests, oral clinical examination and histology of the palatal mucosa. However, morphometric analysis of the palatal epithelium showed a significant difference between the patients with GERD and the control group. The authors concluded that GERD is associated with microscopic alterations in the palatal mucosa such as epithelial atrophy and increased fibroblast number which could only be detected by morphometry. Despite oral mucosa insult, symptoms may be mild because of the protective role of saliva (the salivary flow and the quantity of swallowed saliva) stimulated, through a salivary reflex, by acid GER [14]. The oral manifestations related to GERD are summarized in the following table (Table 2)

Table 2: Oral findings associated with GERD [13].

Oral signs of GERD
Dental Erosions
Burning mouth
Aphtous oral ulcers
Erythema of soft palate and uvula
Stomatitis
Epithelial atrophy
Increased fibroblast number in chorion
Xerostomia
Drooling

Celiac disease (CD)

Celiac disease is defined as an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals [15]. It’s characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies (against transglutaminase, endomysium and deamidated forms of gliadin peptides), HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy [15]. CD ranges from a gluten-sensitive small bowel disorder with only gastrointestinal symptoms to a systemic disease with a broad spectrum of intestinal and/or (just) extra intestinal symptoms or signs, including oral manifestations [15]. The most common oral signs of CD are recurrent aphtous stomatitis (RAS), dental enamel defects, delayed eruption, atrophic glossitis and angular cheilitis [16].

Dental enamel defects

The cause of dental enamel defects in celiac patients still needs to be fully clarified. Malabsorption of both macro- and micro-nutrients (such as iron, calcium, folate and fat-soluble vitamins) [17,18] and the critical period of interruption of amelogenesis [19] have all been suggested, although the immune-mediated damages have been recently considered as the leading cause [20]. In detection of CD, the presence of enamel defects in permanent teeth could be a fundamental clue for clinicians with increasing sensitivity and specificity with more severe lesions. The overall prevalence of dental enamel defects in celiac patients ranges from 9.5% to 95.9% (mean value of 51.1%). In children with deciduous teeth, the prevalence of dental enamel defects is reported in a range of 5.8-13.3% (mean value of 9.6%) of patient with CD [20]. Enamel defects are most commonly seen in the permanent dentition and they tend to appear symmetrically and chronologically in all four quadrants, with more defects in the maxillary and mandibular incisors and molars. Both hypoplasia and hypo mineralization of the enamel can occur and a band of hypo plastic enamel, often with intact cusps, is common [21,22].

Recurrent Aphthous stomatitis (RAS)

Recurrent aphthous stomatitis (RAS) belongs to the group of chronic, inflammatory, ulcerative diseases of the oral mucosa. The pathogenesis of this condition is complex and multifactorial [23]. The most characteristic sign is the recurrent onset of single or multiple painful erosions and ulcers that appear mainly on unattached oral mucosa of the lips, cheeks and tongue [24]. The eruptions are surrounded by a characteristic erythematous halo and covered with fibrous coating. Three main types of recurrent aphthae can be distinguished: minor aphthae (Mikulicz's aphthae; MiRAS), major aphthae (Sutton's aphthae; MaRAS)

and herpetiform aphthae (HeRAS) (Table 3). The prevalence of RAS in general population ranges between 5% and 25%. The second life decade is considered as a peak period of RAS whilst MaRAS more frequently appears in younger patients and HeRAS usually affects adults. Generally, the severity and frequency of the episodes vary individually, but they usually decrease with age. The reduced incidence of RAS in elderly may partially result from age-dependent alterations in the immune innate and adaptive components, described as immunosenescence and "inflamm-aging" [25]. This condition is found three times more often in Caucasians than in Afro-Americans, with a higher prevalence in females rather than males [23]. The potential triggers of RAS are: genetic predisposition, bacterial and viral infections (Streptococcus oralis, Helicobacter pylori, HSV, Varicella-Zoster virus, CMV, Adenovirus), vitamin and micronutrient deficiencies (iron, zinc), food allergies, hormonal level fluctuations (pregnancy, menopause, use of oral contraceptives), mechanical injuries, increased oxidative stress, systemic disease (IBD, CD, HIV, Behçet's disease, IgA deficiency), and anxiety [23-26]. In CD patients the prevalence of RAS ranges from 9.7% to 40.9% (mean value of 20%). CD patients, especially before starting gluten-free diet show higher RAS prevalence (44%) than healthy control [27]. The higher prevalence of RAS in chronic IBDs (Crohn's disease, ulcerative colitis) and celiac disease may be related to nutrient deficiencies and/or immune mechanisms including preponderance of proinflammatory Th1-type cytokines, limited expression of anti-inflammatory cytokines, hyper-reactivity of neutrophils, increased number of T γ and B lymphocytes and NK cells, and decreased activity of regulatory cells [23]. An increased activity of the Th1 type immune response was observed in Crohn's disease, celiac disease and PFAPA (periodic fever, aphthous stomatitis, pharyngitis and adenitis) syndrome [28].

Table 3: Clinical characteristics of RAS.

Type of RAS	Size (mm)	Number of Lesions	Depth	Scar	Peak Onset	Localization
Mi RAS	05-10	< 10	Shallow	No	2° life decade	Non keratinized oral mucosa involving lips, buccal regions, tongue margins
Ma RAS	>10	1 - 3	Deep	Yes	1°-2° life decade	Keratinized and non-keratinized oral mucosa, often involving soft palate
He RAS	< 5	>10	Shallow	No	3° life decade	Non keratinized oral mucosa involving mouth floor and ventral surface of the tongue

Crohn's disease

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are chronic inflammatory diseases with primary intestinal involvement [29-33]. Although the exact underlying pathogenesis of IBD has not been clearly elucidated, it is postulated that dysregulated immunity represents its basis [34]. Generally, it is assumed that IBD is a multifactorial disease in which immune system, genetics and environmental

factors all play a role [35]. Besides the expected symptoms of gastrointestinal involvement, IBD patients may show a wide range of non-intestinal signs and symptoms known as extraintestinal manifestations (EIMs), with prevalence rates ranging from 6%-47% [36,37]. Oral manifestations could represent a significant part of EIMs, especially in Crohn's Disease and they can occur either concomitantly with intestinal symptoms or several years before gut presentation [38,39]. The pathognomonic feature of

Crohn's disease is transmural inflammation and the presence of granulomas in the histology reports [29]. The most affected portions in the mouth are: buccal mucosa, gum, lips, vestibular and post-molar areas [40].

Specific oral lesions

Specific oral lesions include indurated tag-like lesions, clobbestoning and mucogingivitis. Indurated tag-like lesions consist of white reticular tags referred as mucosal tags, epithelial tags, or folds. These lesions are mostly located in the labial and buccal vestibules and in the post-molar regions. Up to 75% of these lesions may show non-caseating granulomas on biopsy [41,42]. Cobblestoning is a fissured swollen buccal mucosa with corrugation and hyperplastic appearance. These lesions are usually seen in the posterior buccal mucosa often associated with succulent mucosal folds with normal epithelium. The lesions usually consist of mucosal-colored papules that produce firm plaques on the buccal mucosa and palate. Such lesions may cause pain deterring speaking and eating difficult. These lesions, along with mucosal tags, are considered specific for Crohn's disease, but are not associated with intestinal Crohn's disease activity. [43] Mucogingivitis appears as an edematous, granular, and hyperplastic gingiva with or without ulceration. Other specific lesions are lip swelling with vertical fissures, deep linear ulcerations (usually in the buccal sulci with hyperplastic folds) and midline lip fissuring, all with minimal or no association with intestinal Crohn's disease activity [29-48].

Non-specific oral lesions

Other non-specific oral lesions that occur in Crohn's disease mainly include pyostomatitis vegetans, stomatitis, salivary and periodontal problems, caries and abscesses. Pyostomatitis vegetans is a chronic mucocutaneous ulcerative disorder consisting of multiple miliary white or yellow pustules with an erythematous and edematous mucosal base. The pustules can rupture and coalesce forming linear or "snail-track" ulcers. The most frequently involved regions of the oral cavity are the labial gingiva, labial and buccal mucosa. The less damaged portions are the tongue and the mouth floor, but pustules can involve almost all parts of the oral cavity [49-51]. Moreover Crohn's disease has been associated with: RAS, 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 [40-54].

Conclusion

Both pediatricians and dentists should be aware of different oral manifestations unmasking Crohn's disease, Celiac Disease and GERD. An increased awareness may provide an early diagnosis and treatment and prevent related long-term complications including persistent gastrointestinal problems, nutritional deficiency, impaired growth, delayed puberty, reproductive and autoimmune disorders and possible malignancy. The practical implication of emphasizing the role of dentists in identifying oral pathology related to gastrointestinal diseases consists in increased diagnosis in children and in selecting patients for screening.

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