ORAL MANIFESTATIONS OF GASTROINTESTINAL DISEASE, AN INDICATOR FOR EARLY DIAGNOSIS: AN OVERVIEW

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ABSTRACT
Diagnosis of the disease by dentists and other clinicians through the evaluation of oral clinical findings is a rare incident. Mucocutaneous and granulomatous lesions of the oral cavity alert the clinician to investigate the gastrointestinal tract. This review highlights oral manifestations of gastrointestinal disorders, how various diseases and their presentations are integrated and intertwined. Oral manifestations include stomatitis, glossitis, cheilitis, aphthous ulceration, pyostomatitis vegetans, macrocheilia, cobblestoning of oral mucosa, deep linear ulcers of buccal vestibule and polypoid mucosal tags.

Key words: Inflammatory Bowel Disease, Chron’s Disease, Ulcerative Colitis, Pyostomatitis Vegetans, Aphthous Stomatitis, Cobblestoning, Mucogingivitis etc.

INTRODUCTION
Inflammatory bowel diseases (IBD) include Crohn’s disease (CD), ulcerative colitis (UC) and an ill-defined group of medical conditions known as indeterminate colitis. These are characterised by the chronic and recurrent inflammation of different parts of the gastrointestinal tract. In CD, chronic inflammation may affect any part of the gastrointestinal tract, whereas in UC, mucosal inflammatory changes are confined to the colon. The term indeterminate colitis should be reserved only for those cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either CD or UC after full examination, and the term IBD type unclassified is suggested for patients in whom there is clinical and endoscopic evidence of chronic IBD affecting the colon, without small bowel involvement, and with no definitive histological or other evidence to favour either CD or UC (Rowland et al., 2010).

Chron’s Disease
Patients with intestinal CD who have involvement of the oral cavity typically are described as having oral CD (OCD). Oral lesions of CD may proceed abdominal symptoms and do not necessarily correlate with intestinal disease activity. An oral biopsy will often confirm the nature of the lesions in the presence of a granulomatous inflammation. The histopathological analysis in Crohn's disease bears conspicuous resemblance in intestinal and oral lesions. It is characterized by the triad of deep focal fissuring of the mucosa, formation of noncaseating granuloma deep into the superficial mucosa and the presence of Langhan-type giant cells. Lymphedema of the upper corium and a diffuse or peri-lymphatic lymphocytic infiltrate are also often observed.

An oral biopsy will often confirm the nature of the lesions in the presence of a granulomatous inflammation. The pathogenesis of CD is unknown and
the role of genetic, infectious, immune and environmental factors continues to be debated. Oral localization of CD raises more acutely the question of the role of environmental factors. Toothpaste has been proposed as a causal factor of CD, but this hypothesis was not confirmed. Smoking clearly increases the risk for CD and worsens its course, but it is not associated with particular localization (Galbraith et al., 2005; Freysdottir et al., 2007).

Although the etiology of CD is not known, experimental data suggests that CD4+ T cells play a role. The inflammatory process is characterized by increased production of pro inflammatory cytokines. Tumour necrosis factor (TNF-α) plays a central role in the pathogenesis of the disease. The crucial pathogenic role of TNF in CD has been verified experimentally in mice that bear the genetic deletion of the TNF AU-rich regulatory elements (ARE) that leads to defective post-transcriptional regulation of tnf expression and chronic TNF overproduction. Further, chronically overproduce TNF and spontaneously develop CD8+ T lymphocyte-dependent Crohn-like inflammatory bowel disease pathology in the ileum. Restricting TNF over expression in myeloid cells or T lymphocytes suffices for the induction of intestinal pathology, indicating the pathogenic potential of TNF derived from innate or adaptive effectors (Basu et al., 1975).

Mucocutaneous changes of CD in the orofacial region include granulomatous changes of oral CD caused by direct extension of intestinal inflammation, or those of metastatic CD affecting a distant cutaneous site non-contiguous with the bowel. The prevalence of oral CD varies between 0.5 and 80% and oral findings may precede onset of intestinal disease in up to 60% patients (Harty et al., 2005).

Clinical manifestations of oral CD include specific and non-specific changes. Changes considered specific and pathognomonic for CD are cheilitis granulomatosa, cobblestoning of oral mucosa, mucosal tags and linear ulcerations, and hyperplastic folds of buccal vestibule. Non-specific changes are angular cheilitis, aphthous stomatitis and pyostomatitis vegetans. Dental erosion, halitosis, odynophagia, dysphagia, high prevalence of caries, granulomatous and autoimmune like changes in minor salivary glands, and reduced salivation have also been reported (Bangsgaard et al., 2011).

Cobblestoning Mucosa and Mucosal Tags
Cobblestoning refers to nodular granulomatous swellings that result in a cobblestone appearance of the oral mucosa, particularly on the labial and buccal mucosa. Along with mucosal tags, cobblestoning is highly suggestive of CD (Chi et al., 2007).

Deep Linear Ulcers with Hyperplastic Folds: These ulcerations may cause pain on touch or when eating acidic, spicy or hot foods. These ulcers, which are typically persistent linear and deep, should not be confused with aphthous ulcers, which are shallow, round to oval shaped lesions that heal spontaneously in approximately seven to 14 days.

Pyostomatitis Vegetans
Although IBD may precede the onset of oral or cutaneous lesions by months or years, sometimes the symptoms may be minimal and not sufficient to make an early diagnosis. In these cases the identification of PV could represent a reason to encourage diagnostic investigations intended to reveal subclinical intestinal diseases. Clinically PV is characterised by multiple pustules on an erythematous base (Hegarty et al., 2004).

The friable pustules have a grey to yellow necrotic appearance; they erode and form shallow ‘snail-track’ ulcers which may affect all areas of oral mucosa, although the most commonly affected sites are the labial and buccal mucosa, hard and soft palate, gingiva and sulci, while the least affected sites are the tongue and floor of mouth. Vegetations in areas of erythema can be seen especially on the gingiva and palate. As vegetating lesions progress the mucosa may be thrown into verrucous folds, particularly the lesions of buccal and labial mucosae which are soft and oedematous. Pain is not prominent even when there is extensive oral involvement (Cataldo et al., 1981). Microscopically, the lesions mimic the crypt abscesses of colonic lesions, without evidence of granulomatous inflammation. The oral submucosa shows edema with neutrophils, eosinophils and lymphocytes, while the epithelium shows spongiosis with neutrophilic and eosinophilic abscesses. The primary objective in the treatment of PV must be identifying and/or controlling the associated bowel disease. Lesions frequently improve when the colitis is controlled; likewise, an exacerbation of colitis usually is followed by a similar flare in oral lesions. Oral lesions are often treated effectively with topical corticosteroids in a gel or mouthwash formulation. However, systemic corticosteroids, dapsone and other immunosuppressive therapy may be suggested for moderate-to-severe symptomatic lesions in the oral cavity that are recalcitrant to topical therapy (Ali and Duerksen, 2008).

Aphthous Ulcers
Aphthous ulcers are considered by many to be non-specific, as they can be seen in up to 20% of the general population; however aphthae are usually more extensive and persistent when associated with IBD. If a patient develops IBD during adulthood but has a history of recurrent aphthous ulcerations since adolescence, it is likely that the aphthous ulcers represent a coincident process that may be exacerbated by IBD or its management. For example, anti-inflammatory medications such as 5-aminosalicylates, the mainstay of
IBD treatment, are excreted in saliva and are known to cause aphthous ulcers in some patients. Aphthous ulcerations are a primary component of Behçet syndrome, which has also been implicated in inflammation of the large bowel, and also of Sweet’s syndrome, which is a rare cutaneous manifestation of ulcerative colitis or Crohn’s disease. In the past, it was believed that the association between an uncommon disorder like Sweet’s syndrome and a relatively common disease like IBD was coincidental, but given the increasing number of case reports on Sweet’s syndrome and IBD (IBD is now the third most common disease associated with Sweet’s syndrome), this is unlikely. The other factor supporting a true association between Sweet’s syndrome and IBD is that Sweet’s syndrome is from the same family of cutaneous disorders as erythema nodosum and pyoderma gangrenosum, suggesting a possible common pathogenesis (Katz et al., 2003).

Other Associations
It is difficult to determine which oral manifestations are expressions of IBD, which represent pre-existing and/or coincidental findings, and which result directly from medical treatment of bowel disease. Although candidosis is often associated with IBD patients, it probably represents either a reaction to the bacteriostatic effect of sulfasalazine or an impaired ability of neutrophils to kill this granuloma provoking organism, rather than a primary manifestation of the disorder. Likewise, some anti-inflammatory and sulf-containing preparations used to manage IBD patients are reported to cause lichenoid drug reactions (Grave et al., 2009).

Orofacial Granulomatosis
It comprises a group of diseases characterized by noncaseating granulomatous inflammation affecting the soft tissues of oral and maxillofacial regions. This term was first introduced by Wiesenfeld in 1985, encompasses Melkerson-Rosenthal syndrome and cheilitis granulomatosa of Miescher. In addition, oral granulomas can occur in such systemic conditions such as tuberculosis, Crohn’s disease and sarcoidosis. Oral granulomatosis is a common manifestation in patients with IBD and is typified by recurrent or persistent swelling of the lips, cheeks, gingivae or oral mucosa with characteristic noncaseating granulomas on histologic examination. The lips are the most frequent site of involvement; the labial tissues demonstrate a nontender, persistent swelling that may involve one or both lips. Many patients with orofacial granulomatosis do eventually develop gastrointestinal disease consistent with Crohn’s disease.

Beclamethasone mouthwashes (0.5 mg dissolved in water, up to 6 times a day) bring symptomatic relief. However, there is considerable risk of systemic steroid absorption with attendant side effects, thereby mitigating against prolonged use of this form of treatment. Lip swelling is sometimes helped by topical tacrolimus. Intralesionial injection of steroid into swollen lips has been reported. However, this form of treatment appears to bring only short-term benefit and can be painful. In patients with persistent pain, swelling and cosmetic disfigurement, the use of immunosuppression can be considered at an early point. Recently, other forms of treatment such as methotrexate and biologic treatment using anti-TNF antibodies have been reported to be useful. However, the potential risks of immune suppression, which includes malignancy, must be weighed up carefully in such patients (Tysk et al., 1997).

Ulcerative Colitis
Mucosal changes of UC in the oral cavity include stomatitis, glossitis, cheilitis, aphthous ulceration, and pyostomatitis vegetans, which represent a specific marker of ulcerative colitis even if the nature of this association is not clear. Erosive temporo-mandibular joint disease secondary to ulcerative colitis-associated spondyloarthropathy has also been reported (Satsangi et al., 1997).

Dental Management of Patients with IBD
Patients with IBD are at increased risk of developing dental caries and oral infections. The causes of the increased incidence are multiple, but they appear to be related to either the patient’s altered immune status or to diet. It is also important to recognise the risk of adrenal gland suppression in patients receiving corticosteroids to manage their IBD. It may be necessary to augment the steroid regimen during some dental treatments, especially for anxious patients in whom preoperative or postoperative pain management is difficult or when a complicated or stressful procedure is anticipated. Oral inflammatory and granulomatous lesions associated with IBD may respond to topical steroid therapy but should not be used indefinitely due to the risk of mucosal atrophy and systemic absorption (Shivananda et al., 1996).

Dental Management of Patients with IBD Should Include the Following
• Frequent preventive and routine dental care to prevent destruction of hard and soft tissue.
• Evaluation of hypothalamic/pituitary/adrenal cortical function to determine the patient’s ability to undergo extensive dental procedures.
• Avoid prescribing non-steroidal anti-inflammatory drugs (NSAID), as they can trigger a flare-up. The use of paracetamol is recommended, although it can also adversely affect patients.
• Early diagnosis and treatment of oral infections to enhance the gastroenterologist’s ability to manage the IBD.
• Diagnosis (biopsy if necessary) and treatment of oral inflammatory, infectious, or granulomatous oral lesions (Hill et al., 2005).

Celiac Disease

It is a permanent intolerance to gluten (a protein present in wheat, rye and barley) that results in damage to the small intestinal mucosa caused by an autoimmune mechanism in those who are genetically susceptible to the disease. The villous atrophy that ensues can lead to malabsorption of a variety of macro- and micronutrients including iron, calcium, folate and fat-soluble vitamins. Celiac disease was thought to be a rare malabsorptive disorder of infancy and childhood; however, it is now considered to be a common, chronic, multi-system disorder that can present at any age when gluten is present in the diet. It is one of the most common chronic gastrointestinal disorders in the world affecting both children & adults. It is hereditary. Both first- and second-degree relatives of the patient have a significant (5%-15%) risk of developing the disorder. Other high-risk groups include patients with autoimmune disorders, e.g., type I diabetes mellitus, thyroiditis and Down syndrome. Population-based serologic studies estimate that 1% of North Americans may have it, and about 90% of these cases remain undiagnosed. Celiac disease is a “clinical chameleon” (AGA Institute, 2006).

Typical symptoms are abdominal pain, diarrhea and weight loss. However, many people present with non-gastrointestinal symptoms including anaemia, extreme weakness, short stature, osteoporosis, lymphomas, menstrual irregularities and infertility. Additional symptoms in children include delayed growth and puberty, vomiting and dental enamel defects. Dermatitis herpetiformis is “celiac disease of the skin.” It presents with a chronic, severely itchy, blistering rash that is poorly responsive to conventional therapies. Serologic screening is recommended for all those at high risk for celiac disease (Cranney et al., 2007).

Serologic screening of minimally symptomatic patients or those with atypical/non-gastrointestinal complaints can significantly increase the rate of diagnosis. Highly sensitive and specific serologic tests are available to screen for celiac disease. Those currently recommended are the serum immunoglobulin A (IgA), tissue transglutaminase (TTG) antibody test and the IgA-endomysial antibody (EMA) test. These tests have a sensitivity and specificity greater than 90%. The TTG antibody test is currently the test of choice and is widely available. IgA deficiency is common in celiac disease and, hence, total serum IgA level must also be measured to avoid a false-negative result. These serologic tests are less reliable in children under 3 years of age. Also, a negative test does not rule out celiac disease. Patients with a positive TTG antibody test should be referred for an endoscopic small intestine biopsy for confirmation of the diagnosis. It can be effectively treated by strict, lifelong adherence to a gluten-free diet. However, a gluten-free diet should not be started before a biopsy is done, as the diet will heal intestinal lesions, thus affecting interpretation of the biopsy and making confirmation of the diagnosis difficult. Awareness of celiac disease among health professionals remains poor, and delays in diagnosis are common (Rashid et al., 2005).

Oral Manifestations

Celiac disease can develop at any age when solid foods are introduced into the diet; however, if it appears in children while the permanent teeth are developing i.e., before 7 years of age, abnormalities in the structure of the dental enamel can occur. These defects are seen most commonly in the permanent dentition and tend to appear symmetrically and chronologically in all quadrants, with more defects in the maxillary and mandibular incisors and molars. Both hypoplasia and hypomineralization of the enamel can occur. A band of hypoplastic enamel, often with intact cusps is common. A hiatus in enamel and dentin formation can occur at a developmental stage corresponding to the onset of gastrointestinal symptoms. Dental enamel defects are common in children who develop symptoms of celiac disease before 7 years of age (Catassi et al., 2007).

Such defects are not seen as frequently in adults with celiac disease, as they may have developed symptoms at a later age or have had severely affected abnormal teeth altered or extracted. The exact mechanism leading to these defects is not clear, but immune-mediated damage is suspected to be the primary cause. Nutritional disturbances, including hypocalcaemia, may also play a role. Stimulation of naïve lymphocytes by gluten in the oral cavity has also been hypothesized. The overall prevalence of systemic dental enamel defects in celiac disease patients with mixed or permanent dentition ranges from 9.5% to 95.9% (mean 51.1%); in patients with deciduous teeth, prevalence is 5.8% to 13.3% (mean 9.6%). This difference can be explained by the fact that the crowns of permanent teeth develop between the early months of life and the seventh year (i.e., after the introduction of gluten in the diet) whereas the development of deciduous teeth occurs primarily in utero (Priotrovou et al., 2004).

The involvement of deciduous teeth in some cases supports the hypothesis that immunologic and genetic factors are more important in the etiology of the defects than nutritional deficiencies. Dental enamel defects are also found in healthy first-degree relatives of patients with celiac disease, further supporting an immunogenetic basis for causation. Enamel defects include pitting, grooving and sometimes complete loss of enamel (Aine et al., 1990).
A classification of these defects in celiac disease was developed by Aine and colleagues (Amato and Small, 1970).

**Classification of Systemic Dental Enamel Defects in Celiac Disease** (Adapted from Aine et al., 1990):

- **Grade I**: Defects in colour of enamel: single or multiple creams, yellow or brown opacities.
- **Grade II**: Slight structural defects: rough enamel surface, horizontal grooves and shallow pits.
- **Grade III**: Evident structural defects: deep horizontal grooves, large vertical pits.
- **Grade IV**: Severe structural defects: shape of the tooth may be changed.

Recurrent aphthous ulcers can also occur in celiac disease (Fig 1) and may provide another clue to the possible presence of the disorder. In a large survey of a Canadian population with biopsy-proven celiac disease, 16% of children (< 16 years of age) and 26% of adults reported having recurrent oral ulcers. The exact cause of aphthous ulcers in celiac disease is unknown; however, it may be related to hematinic deficiency, with low serum iron, folic acid and vitamin B12 due to malabsorption in patients with untreated celiac disease.

**Gardner Syndrome**

An autosomal dominant disorder, Gardner syndrome (GS) is a well-recognized variant of familial adenomatous polyposis. It is characterized by the presence of colonic polyposis; osteomas; and numerous soft-tissue tumors, such as epidermal cysts, desmoid tumors and lipomas. In addition to the polyposis, patients with GS may have various extraintestinal manifestations, including multiple jaw osteomas (Fig 2), odontomas, impacted teeth and supernumerary teeth. Unless the osteomas interfere with normal function or are deemed cosmetically unacceptable, they typically require no treatment. Development of the osteomas precedes that of the premalignant polyps, which usually start to appear during puberty. Patients become symptomatic in their early 20s. If not treated, intestinal polyps will become malignant. Therefore, diagnosis of this syndrome early in life is imperative so the patient can have a prophylactic colectomy and siblings can be evaluated for the disease (Rodu and Martinez, 1984).

**Peutz-Jeghers Syndrome (PJS):**

It is an inherited autosomal dominant disease characterized by gastrointestinal hamartomatous polyposis associated with mucocutaneous melanin pigmentation. Peutz [1921] first reported the entity, associating the mucocutaneous pigmentation with the intestinal polyps. It is rare, with a frequency of encounter from polyposis registries one tenth that of familial adenomatous polyposis. This would place the frequency from 1 case per 60,000 people to 1 case per 300,000 people. This disorder is characterized by oral and perioral ephelides, oral melanotic macules and intestinal polyposis. The polyps are typically found in the small intestine and are thought to be hamartomas, benign polyps with an extraordinarily low potential for malignancy. The pigmentation present as dark blue to brown macules, ranging in size from 1 to 5 mm, predominately found on the vermillion border of the lip, buccal mucosa, hands, feet & genital region (Hemminki et al., 1997).

The lesions resemble freckles, but they do not wax and wane according to sun exposure, as true freckles does. The oral pigmentations appear first and thus play an important part in early diagnosis. Ideally, early recognition of the characteristic mucocutaneous melanosis would lead to a thorough medical workup and the diagnosis of PJS. In reality, most cases of PJS are diagnosed subsequent to the onset of GI complaints, such as abdominal pain, obstruction and bloody stools, typically between the ages of 10 and 30 years. Microscopically; the pigmented macules are characterized by slight acanthosis of the epithelium with elongation of the rete ridges. The melanocytes may have elongated dendritic processes, although no apparent increase in melanocyte number is detected. However, intraoral macules tend to persist. Localization in the oral mucosa is typical of patients with Peutz-Jeghers syndrome and does not happen with other types of dermatologic pigmented lesions, such as common lentigo. Freckles also do not localize in the buccal mucosa (Bartlett et al., 1996).

**Gastroesophageal Reflux Disease**

One GI disorder with oral manifestations is gastroesophageal disease (GERD), which affects 15%-40% of the population. A chronic disorder, GERD results from continual passage of acid from the stomach up into the esophagus which damages the mucosal lining. Common symptoms include heartburn, dysphagia and regurgitation, especially while the patient is lying flat. Reflux esophagitis, esophageal hemorrhage, stricture, Barrett esophagus, and adenocarcinoma have all been linked to untreated GERD. Potential oral manifestations of GERD include a burning or itching sensation affecting the oral mucosa, oral ulcers, erosion of tooth structure, halitosis, altered salivary flow and a bad taste in the mouth. Additionally, the teeth may be affected, becoming sensitive to thermal insult and prone to fracture as the underlying dentin becomes exposed (Deschler and Benjamin, 1989).

Eventually, the acid erosion can lead to exposure of the tooth pulp and impaired chewing. Erosion also occurs in hiatus hernia, wine drinking, chronic alcoholism and bulimia. Dental enamel consists
primarily (almost 97 percent by weight) of a calcium phosphate mineral in the form of carbonated hydroxyapatite (CHA). CHA is insoluble in an alkaline medium. However, its solubility increases with a decrease in the oral pH17-18. This effect was first noted as a result of direct contact of the tooth surface with acids from extrinsic sources such as beverages. Erosion is most often observed on the palatal surfaces of the maxillary dentition (Fig 3), lingual surfaces of mandibular anterior teeth and the occlusal surfaces of the mandibular posterior teeth. Regular dental care and medical control of acid production help decrease the prevalence of erosion. The eroded enamel is smooth, shiny and hard. If it becomes thin enough, the yellowish colour of the dentin becomes visible and the teeth may become sensitive to temperature changes. However, once the erosion occurs, it is irreversible and can be treated only with dental restorative procedures. Therefore, early recognition and patient education are the most effective treatment approach (Armstrong et al., 2004).

**Sarcoidosis**

This multisystem granulomatous disorder of unknown cause affects young adults and is more common in women and blacks. Some of the systemic manifestations most often seen include bilateral hilar lymphadenopathy, pulmonary fibrosis, erythema nodosum on the skin, ocular inflammation, hepatic involvement, parotid gland swelling, gingival inflammation (Fig 4) and fever. Acute sarcoidosis manifests with abrupt onset of erythema nodosum, which is characterized by non-tender, elevated purple areas on the skin, whereas chronic sarcoidosis demonstrates a slow onset with progressive pulmonary fibrosis and multisystem involvement. Acute sarcoidosis often undergoes spontaneous resolution. In addition to the skin lesions; patients may demonstrate oral manifestations as well (Newman, 1887).

The clinician may notice painless, non-ulcerating, maculopapular, dark-red to brown lesions, occurring most often on the buccal mucosa and hard palate. One-fourth of all intraoral sarcoidosis cases are located in bone and identified on x-ray by an ill-defined radiolucency with no expansion. In the majority of reported cases of sarcoidosis with intraoral involvement, the oral lesion was the first sign of the disease. Recognizing the oral manifestations of sarcoidosis is important because they may lead to a definitive diagnosis of systemic disease.
CONCLUSION
One of major significance of a study of oral presentations of GI pathologies is that often, they are the first signs and symptoms of the underlying disorder. Hence the oral clinician might be the first to diagnose or at least, to provide a clue for the recognition of such a disease. An alert oral diagnostician therefore can serve as much more than just addressing the oral and maxillofacial region. A single clinical entity like an ulcer or a swelling in the oral mucosa should alert the physician to a plethora of possibilities. Only a studied approach to every individual patient will provide for a successful diagnostic and therapeutic modality. In dental management of patients with gastrointestinal diseases, it is important that they undergo frequent dental revisions and preventive care to avoid oral infections and hard and soft tissue destruction; it is also important to diagnose and treat all inflammatory, infectious or granulomatous 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. Oral manifestations of gastrointestinal disorders present with numerous challenges and loopholes for successful diagnosis and management. They present with a bizarre array of clinical presentations, most of which are almost identical in nature with minute variations. The difficulties are compounded by the fact that various pathologies which are native to the oral mucosa, may present with similar manifestations.

Hence, a thorough knowledge of the various disorders as well as correlation with an extensive history of the patient is mandatory for arriving at a correct diagnosis.

REFERENCES