LETTER TO THE EDITOR

ORAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

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Received July 5, 2017 – Accepted August 2, 2017

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, have important extraintestinal manifestations, notably in the oral cavity. These oral manifestations can constitute important clinical clues in the diagnosis and management of IBD, and include changes at the immune and bacterial levels. Aphthous ulcers, pyostomatitis vegetans, cobblestoning and gingivitis are important oral findings frequently observed in IBD patients. Their presentations vary considerably and might be well diagnosed and distinguished from other oral lesions. Infections, drug side effects, deficiencies in some nutrients and many other diseases involved with oral manifestations should also be taken into account. This article discusses the most recent findings on the oral manifestations of IBD with a focus on bacterial modulations and immune changes. It also includes an overview on options for management of the oral lesions of IBD.

To the Editor,

Extra intestinal manifestations (EIM) of inflammatory bowel disease (IBD) have been reported to affect several systems including those cardiovascular, skin and skeletal. These manifestations also involve the oral cavity, with inflammation being a common denomination. Inflammation, in a well-controlled immune system, is a normally exhibited physiological reaction in intestinal mucosa as a response to microbial antigens. Gastrointestinal microbiota is, however, very complex and rich in antigenic determinants. Once these offending agents are eliminated, the inflammation disappears. However, in the case of abnormal conditions and diseases, the inflammation persists and becomes chronic, thus leading to functional and anatomical alterations. The inflammatory bowel diseases, including Crohn's disease (CD) and ulcerative colitis (UC), are examples of chronic relapsing inflammatory disorders of the gastrointestinal tract. IBD has wide and non-pathognomonic clinical characteristics which can usually mislead the clinician. Therefore, in addition to the clinical presentation, histological and radiological findings as well as endoscopic, serological and anatomo-pathologic evaluations constitute important elements for establishing an accurate diagnosis. Recently, stool markers were detected and seemed helpful for

Key words: Crohn's disease, dysbiosis, IBD, Inflammation, ulcerative colitis

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0393-974X (2017)

diagnosis (1). On the other hand, the oral cavity is a large reservoir of bacteria profoundly relevant to host health and disease. Current studies highlighted various oral symptoms such as aphthous stomatitis, lip swelling, oral ulcer and pyostomatitis vegetans (PV) that are frequently seen in IBD patients (2). These oral findings are manifestations of the underlying disease process. Since saliva-producing cells are part of the digestive system, the assessment of this body fluid was conducted in many studies. For instance, elevated interleukin-6 (IL-6) was found in saliva of patients with IBD, indicating that the general involvement of the gastrointestinal tract is extending to the oral cavity. Therefore, measuring IL-6 can be a convenient tool to monitor disease activity and progression. This minireview sheds the light on the oral manifestations of IBD. Relevant findings in the literature for the past 15 years or so on bacterial modulations and immune changes were evaluated. Management of the oral lesions of IBD is also covered.

Prevalence of oral manifestations in IBD

Oral lesions have been reported to occur in up to 50% of IBD patients. They are more prevalent in CD patients and are more likely to occur in males and in children (3). The prevalence of oral lesions in CD reportedly ranges from 20% to 50% (2). However, a recent systematic review on pediatric CD revealed that the prevalence of oral manifestations ranged between 10% and 80%, based on 28 papers published between 2000 and 2015 (4). On the other hand, oral lesions have been also reported to occur in only 8% of UC patients (5). Some studies, however, noted no statistically significant differences between the two diseases (6).

Immune changes in the oral cavity

The exact pathogenesis of IBD has not been clearly elucidated, however, it is thought to be caused by a dysregulated immunity (7). Generally, it is assumed that IBD is a multifactorial disease involving the immune system (abnormal self-recognition and autoantibodies against organ-specific cellular antigens shared by the gastrointestinal tract and other organ systems) (7), genetic susceptibility, and environmental factors such as smoking, diet, use of antibiotics or nonsteroidal anti-inflammatory drugs and the presence of enteric infections (2).

It is well documented that the most widely accepted mechanism of IBD pathogenesis includes inflammation due to altered host immune response in association with continuous stimulation from the resident gut microbiota and consequent secretions of an array of proinflammatory entities and reactive oxygen species (ROS) (1). IL-6 seems to have an important role in the regulation of IBD chronic inflammatory process. The overproduction of IL-6 by immunocompetent cells is thought to contribute to the development of the inflammatory condition. Patients with CD and UC have higher concentrations of IL-6 in the saliva compared to plasma. This could be expected and may indicate that the inflammatory process in the bowel causes a higher release of IL-6 in the saliva since the saliva-producing cells are greatly involved with the functions of the digestive tract, the inflamed organ. Further analysis of immunological biomarkers in the saliva of IBD patients showed higher levels of many inflammatory cytokines, immunoglobulin A, IL-1β and IL-8 as well as a lower lysozyme level (8). Additionally, saliva contains a variety of components such as cytokines, immunoglobulins, hormones and antimicrobial proteins involved in host defense mechanisms for maintaining oral and systemic health. Levels of many salivary cytokines and IgA were significantly higher in both CD and UC patients than those observed in healthy patients, documenting that inflammatory responses are triggered in the oral cavity of the patients (8). As mentioned above, increased salivary IL-1β, and tumor necrosis factor-α (TNF-α) levels in CD patients and an elevated IL-8 level in the saliva of patients with bowel disease were also reported (9). On the other hand, IBD patients demonstrate autoimmune changes affecting the minor salivary glands, leading to dry mouth (5). This results in significantly reduced salivary lysozyme levels as compared with those of healthy controls (8). Lysozyme is an antimicrobial protein expressed by various cells including epithelial cells, neutrophils and macrophages. It plays a major role in the host constitutive defense mechanisms and is abundant

in saliva. Salivary lysozyme was reported to be significantly lower in patients with gingivitis and periodontitis as compared with healthy subjects (10).

Bacterial changes in the oral cavity

Alterations in the oral microbiota were described among IBD patients. Analysis of salivary microbiota of IBD patients as compared to healthy controls revealed that *Bacteroidetes* were significantly increased with a concurrent decrease in Proteobacteria. The dominant genera, including *Streptococcus*, *Prevotella*, *Neisseria*, *Haemophilus*, *Veillonella*, and *Gemella*, were found to be significantly contributing to dysbiosis (dysbacteriosis) observed in the salivary microbiota of IBD patients. Other reports have noted a significant increase of the genus *Prevotella* in the salivary microbiota of IBD patients, with a relative abundance almost equivalent to the reduction of *Streptococcus*, the latter being most abundant in healthy salivary microbiota.

It is worth noting that there was a strong correlation between lysozyme and IL-1β levels and the relative abundance of *Streptococcus*, *Prevotella*, *Haemophilus* and *Veillonella* (8). Interactions among these organisms and other species could be involved in the dysbiosis of salivary microbiota of IBD patients (11).

Oral pathologies

Oral manifestations are divided into two categories, specific lesions, and more commonly, non-specific lesions. CD is characterized by both specific and non-specific oral lesions, while only non-specific lesions are seen in UC.

Specific oral lesions in patients with CD include cobblestoning of the oral mucosa, deep linear ulcerations, mucosal tags, mucogingivitis as well as face and lip swelling (5). "Cobblestoning" lesions present as nodular granulomatous swellings that affect the oral mucosa, more specifically the labial and the posterior part of buccal mucosa, and result in a cobblestone appearance. They are characterized by thickened, firm, and pinkish areas mostly on the labial and jugal mucosa, which may be multifocal, linear, polypoid, or diffuse. Although they are considered pathognomic lesions for CD, their presentation is not directly associated with the activity of intestinal IBD (25). Mucosal tags are indurated, polypoid, tag-like lesions that are mainly seen in the labial and buccal mucosa as well as in retromolar regions. Mucogingivitis lesions are characterized by gingival redness, swelling and easy bleeding in addition to having a hyperplastic and edematous appearance (2). In a prospective 3-year study conducted by Harty et al., up to 60% of CD patients had mucogingivitis (12). Furthermore, patients usually complain of swelling of the face and the lips. These lesions may impair proper oral function, or lead to psychological disorders due to disfigurement (13). Histological examination of these lesions typically show non-caseous granulomatous inflammation. Many studies reported an increased rate of granuloma detection in oral biopsies, reaching up to 77% (14); granulomas were found in 14/16 patients biopsied in two different cohorts (12). In a prospective cohort study, the presence of oral granulomas was the most important diagnostic criterion used for classifying the patient as having CD as opposed to UC (14).

Non-specific oral lesions associated with CD and UC include aphthous stomatitis, angular cheilitis, pyostomatitis vegetans, glossitis, halitosis, caries, persistent submandibular lymphadenopathy, and lichen planus (5, 15).

Aphthous stomatitis presents as shallow, round ulcers surrounded by an erythematous border with a central fibrinous membrane. The lesions occur in up to 10% of patients with UC, and 20%-30% of those with CD (7). Angular cheilitis manifests as erythema in the presence or absence of painful fissures at the corners of the mouth. It can occur due to anemia or as a manifestation of a fungal or bacterial infection (5). *Pyostomatitis vegetans* is a rare benign chronic inflammatory mucocutaneous disorder characterized by pustules of an unknown etiology. It is the only condition that is more prevalent in UC patients compared to those with CD, and is more common in male patients. It represents a specific inflammatory marker of UC. Macroscopically, the disease manifests as small exophytic lesions with an erythematous border and a creamy white or yellow surface. The lesions are covered with vulnerable membranes and their cracking results in small superficial erosions

or ulcers. The confluence of these lesions results in the characteristic morphology sign of a "snail track". The alterations occur in the upper and lower frontal vestibule, on the tongue and gingiva, as well as on the soft and hard palate.

Management of the oral manifestations in IBD

Oral manifestations in IBD are mostly self-limited and have a good prognosis. Remission can be slow and may take weeks to months to have a total recovery. In most cases, supportive measurements and symptomatic pain relief may be sufficient. However, in more severe and advanced situations, a drug should be used. In such cases, management can be divided into two types. The first is based on treating the lesions. This can be carried out with topical or intralesional therapies and are usually common to all lesions. As examples, we have the hydroacting dressing, foam dressing and laminate dressing which are the most common local therapies. If still persisting, topical steroids can be used with successful results. It must be noted that wound management should always be carried out simultaneously to prevent any secondary infections.

Nonetheless, if lesions persist regardless of topical treatments, systemic drugs should be used. In this case, steroids are most commonly used and are considered as the drug of choice. Moreover, other less common systemic treatments include colchicine and hydroxychloroquine. The second is based on treating the underlying disease, which in this case is IBD. Since oral lesions are present secondary to IBD, treating it may be helpful. In fact, these lesions will resolve once the IBD is controlled, but may recur in case of exacerbations.

CONCLUSIONS

Oral manifestations in patients with IBD are part of the extraintestinal manifestations of the disease. They can also occur as complications of the disease and treatment. Although they occur more often in CD patients, some oral manifestations are largely seen in UC patients especially *Pyodermatitis vegetans*. Their presentations vary considerably and might be well diagnosed and distinguished from other oral lesions. Among these, infections, drug side effects, deficiencies in some nutrients and many other diseases involved with oral manifestations should be taken into account. For this reason, collaboration of different specialists, including gastroenterologists, coloproctologists, dermatologists and dental experts, should be implemented for a better diagnosis and management of IBD.

While their management is usually limited to symptomatic treatment, some cases may require the use of antibiotics, steroids or immunosuppressive drugs. Given the fact that IBD is usually caused by the upregulation of expression of inflammatory cytokines, TGF-β, TNF-α, ROS and other signaling molecules leading to an imbalance in the intestinal microflora, further studies must focus on a treatment targeting this imbalance to prevent the occurrence of this inflammatory disease.

ACKNOWLEDGEMENTS

The Authors acknowledge the partial support of the grant PHC CEDRE code project 34974PE.

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