WHAT DO DENTISTS NEED TO KNOW ABOUT CROHN'S DISEASE?

O QUE O CIRURGIÃO-DENTISTA PRECISA SABER SOBRE A DOENÇA DE CROHN?

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Resumo

A doença de Crohn é descrita como uma doença inflamatória intestinal de alta complexidade, caracterizando-se por apresentar lesões e inflamações transmurais que podem acometer todo o trato gastrointestinal. A doença de Crohn pode apresentar manifestações bucais, tais como lesões na mucosa, alterações do fluxo salivar e envolvimento periodontal. Para este artigo de revisão, foi realizada uma busca de literatura nas bases de dados PubMed, Scielo e Academic Google, com espaço temporal de 2010 a 2020, utilizando palavras-chaves obtidas de acordo com o descritor em ciência da saúde. Foi encontrado que as lesões bucais estão presentes em cerca de 46,75% dos pacientes jovens e 22% dos pacientes idosos com doença de Crohn, podendo ser bastante incômodas, persistentes e de difícil tratamento. Apresentam-se com diversos aspectos clínicos como: ulcerações lineares ou aftosas, nodularidades da mucosa e aumento de volume labial. Essas lesões estão diretamente relacionadas com a doença, mas algumas lesões podem surgir de forma indireta, como complicação da doença de Crohn ou como efeitos adversos do tratamento. As manifestações bucais podem ser os primeiros sinais da doença de Crohn, logo, o reconhecimento de seus aspectos clínicos pode contribuir para um diagnóstico precoce. Cabe ao cirurgião-dentista reconhecer, diagnosticar e tratar, junto a uma equipe multiprofissional, as manifestações bucais da doença de Crohn, promovendo melhoras no quadro clínico dos pacientes.

Palavras-chave: Doença periodontal, Doenças inflamatórias intestinais, Doença de Crohn, Manifestações orais, Inflamação.

Abstract

Crohn's disease is described as a complex inflammatory bowel disease, characterized by transmural lesions and inflammation that can affect the entire gastrointestinal tract. Crohn's disease can present oral manifestations, such as mucosal lesions, changes in salivary flow rates and periodontal involvement. For this review, a literature search was carried out using PubMed, Scielo and Scholar Google platforms, within the time range from 2010 to 2020, using keywords obtained according to the Health Science Descriptor. We found that oral lesions are present in approximately 46.75% of young patients and 22% of elderly patients with Crohn's disease, which can be uncomfortable, persistent and difficult to treat. They are associated with various clinical aspects such as: linear or aphthous ulcers, mucosal nodularities and increased lip volume. These lesions are directly related to the disease, but some lesions may appear indirectly, as a complication of Crohn's disease or as adverse effects of the treatment. Oral manifestations can be the first signs of Crohn's disease, so the recognition of its clinical aspects can contribute to an early diagnosis. Dentists should be able to recognize, diagnose and treat, along with a multidisciplinary team, the oral manifestations of Crohn's disease, promoting improvements in the patient's clinical condition.

Keywords: *Periodontal disease, Inflammatory bowel diseases, Crohn's disease, Oral manifestations, Inflammation.*

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How to cite this article:
Chagas FGA, Leão ATT, Torres SR. What do dentists need to know about crohn's disease? Nav Dent J. 2021; 48(2): .37-44.

Received: 04/05/2021
Accepted: 09/07/2021

INTRODUCTION

Inflammatory bowel disease (IBD) is a set of complex diseases, in which interactions between both exogenous and endogenous factors occur. It mainly comprises two pathological conditions of the gastrointestinal (GI) tract: Crohn's disease (CD) and ulcerative colitis (UC) (1-3). Crohn's disease can present oral manifestations, such as mucosal lesions, changes in salivary flow rates and periodontal involvement. Although they can occur at any stage of the disease, oral manifestations can be the first signs of CD, so the recognition of its clinical aspects can contribute to an early diagnosis (4).

CD oral lesions can be very uncomfortable, persistent and difficult to treat. These lesions may be associated with different clinical aspects, such as ulcers, mucogingivitis, hyperplasia of the oral mucosa, and swelling of face and lips due to granulomatous (3-5). The treatment of these lesions is not specific and involves systemic control of the disease and sometimes topical medication with corticoids may be indicated (4).

Periodontal disease (PD) is a multifactorial inflammatory disease of periodontal tissues. Periodontal pathobionts have been studied as causal roles in the onset or exacerbation of certain diseases, either by direct invasion or by stimulating excessive immune-inflammatory responses (4). PD has been associated with CD, being more prevalent in individuals with this disease than in the general population (4).

The frequency of IBD cases is increasing worldwide. However, the literature on the oral manifestations of CD is not abundant (5). Therefore, this study aimed to review the literature on the oral manifestations of CD and its possible interaction with periodontal disease.

MATERIALS AND METHODS

An electronic search for publications was carried out in the PubMed, Scielo and Google Scholar platforms with the following keywords obtained according to the Health Science Descriptor (DeCS): periodontal diseases; inflammatory bowel diseases; Crohn's disease; oral manifestations; and inflammation. Articles and clinical studies on mucosal and periodontal manifestations of CD were reviewed. The time range for the search was from 2010 to 2020, only articles in English were selected. After the first selection, according to the descriptors, abstracts were analyzed to define their relevance. Following this step, the full appreciation of the article was conducted. The selected studies met the following inclusion criteria: must be an original article, written in the English language, to have a study topic of interest to this review, and have been published in the last ten years. Exclusion criteria were studies presented as theses or dissertations. A total of 40 articles were included in this literature review.

LITERATURE REVIEW

Epidemiology

CD is more common in white individuals, with both sexes equally affected. The disease peaks between the ages of 13 and 35 but has been described in all age groups (1). The incidence of CD is, on average, 30 cases per thousand inhabitants, and the prevalence is 2 cases per thousand inhabitants (1). In Brazil, prevalence and incidence data are unknown. There is a familial incidence of IBD with possible gene transmission, both vertical and horizontal, in which 2 to 5% of individuals will have one or more relatives affected by the disease (1). The incidence of the disease increases in eastern nations, possibly due to environmental changes (6-9).

Etiopathogenesis

The etiopathogenic mechanism of CD is still not clear, though it is known that there is an interaction of genetic, microbial, and environmental factors, causing chronic inflammation of the intestinal tract (3,10). In addition, there is a range of 150 genes that increase the risk of IBD. Also, environmental factors acting on a genetically susceptible individual favor the development of the disease (11,12).

Signs and symptoms of Crohn's disease

The main signs and symptoms of CD are chronic diarrhea (with blood), abdominal pain, weight loss, fever, secondary anemia and

fistulas, and extraintestinal manifestations (1). Manifestations of the disease can occur at any stage of one's life (1). However, it is hard to establishing a definitive diagnosis due to the varied clinical presentation (1). Some extraintestinal manifestations, such as granulomatous lesions and ulcers of the oral mucosa, are more indicative of CD, while pyostomatitis vegetans is more associated with UC (8).

Oral manifestations of Crohn's disease

The prevalence of oral manifestations of CD varies from 0.5% to 37% across different studies and geographic areas (13,14). The variability in the prevalence of oral manifestations of CD, reported among various studies, may be due to the different design of the studies, number and type of population and the lack of experience of certain professionals in finding and accurately classifying oral manifestations (1). Furthermore, the lack of an adequate classification of the oral alterations in CD, using different parameters, can make it difficult to compare the different results (1).

Oral lesions can be painful and harmful to oral functionality, and may affect the patient's psychological state, causing daily problems (15,16). In addition to lesions in the oral mucosa, dysgeusia, halitosis and xerostomia may occur (1,17). These manifestations are often due to pharmacological therapy (Table 1). Subjective data must be carefully evaluated, since they are based on questionnaires filled out by the patients and, consequently, may be biased (1).

Oral lesions may be present in approximately 46.75% of young patients and 22% of elderly patients with CD (17,19,20). These manifestations can be products of the disease itself, pharmacological therapy or a result of the patient's nutritional deficiency. The most affected areas of the oral mucosa are gingiva, lips, vestibular and retromolar regions. Two main types of oral lesions can be observed in CD: granulomatous and ulcerated lesions (1,17,19-22). Granulomatous lesions may appear as a cobblestone appearance (nodularities) in the mucosa or as granulomatous cheilitis (15,19,20). Ulcerated lesions may present a linear, deep or aphthous appearance (15).

The treatment of oral lesions associated with CD aims to reduce the discomfort caused by them, in addition to accelerating the wound healing process and preventing secondary infections (9). Thus, the choice of treatment depends on the etiology and severity of the lesions. They usually regress along with the patient's intestinal manifestations (9). When the lesions come with symptoms and there is no remission response to systemic treatment, the topical use or intralesional application of steroids, tacrolimus, aminosalicylic acid (5-ASA) or topical anesthetics is indicated (9).

Specific lesions of Crohn's disease

Specific oral lesions, in some cases, precede gastrointestinal lesions. These manifestations include granulomatous lesions and ulcerated lesions (3). Histopathologically, they are characterized by granulomatous alterations with small granulomas consisting of multinucleated giant cells.

Granulomatous lesions

CD may appear associated with orofacial granulomatosis, and some authors consider the latter a disease-specific lesion due to histological similarities (23,24). Orofacial granulomatosis is mainly characterized by oral lesions such as: increased labial and facial volume, generalized gingivitis, erosions, erythemas, hypertrophy of the oral mucosa and ulcers with microabscesses that are usually located in the gingival margin or in the soft palate region (25).

In addition to CD, orofacial granulomatosis has been associated with allergic reactions and different pathological conditions, such as: sarcoidosis, angioedema, amyloidosis, leprosy, tuberculosis, fungal infections and anaphylaxis (26,27). The etiopathogenesis of orofacial granulomatosis is not well understood. Genetic factors, infections and allergic reactions could be associated with this inflammatory disorder (3). Treatment for mild cases can be done with corticosteroids and calcineurin inhibitors, such as topical pimecrolimus and tacrolimus (3). Systemic or intralesional corticosteroids are used for the most severe conditions.

Mucosal nodularities are granulomatous lesions of the oral mucosa with a cobblestone appearance (17). These nodularities may have a pleated appearance, similar to the intestinal mucosa, located mainly in the posterior region of the buccal mucosa (17). Clinically, the lesions are firm to the touch and may be painful, interfering with the physiological processes of speech and mastication (17). The treatment consists of using topical corticosteroids and treating the intestinal condition. In severe cases, systemic corticosteroids can be administered (17).

Lesions similar to granulomatous cheilitis are characterized by the presence of localized lasting, recurrent and painless increase in lip volume, which are part of the orofacial granulomatoses group (3,22-26,28). It may be a single or early manifestation of CD (24,25). Histologically characterized by the presence of non-caseating granulomatous inflammation, with possible formation of epithelioid giant cell granulomas (24,25). The association between orofacial granulomatosis and Crohn's disease is based on histological similarity and on the occurrence of manifestations of granulomatous cheilitis as the initial presentation of CD.

The gingival mucosa can also become edematous, granular and hyperplastic in CD, with or without ulcers (3,23). Herein, the entire region from the gingiva to the mucogingival line can be involved.

Deep and linear ulcers

Deep and linear ulcers of the oral mucosa are painful, often occurring in the deep regions of the vestibule, usually with high margins. In addition, secondary fibrosis can cause polyps or nodules (3,26). These injuries can be uncomfortable for the patient.

They can be treated with topical low-concentration tacrolimus (0.5 mg/kg), which is an immunosuppressive drug of the calcineurin inhibitor class, and intralesional steroid injection with or without local anesthesia by mandibular nerve block (21). In severe cases, with persistent pain and cosmetic disfigurement, a more aggressive therapy is recommended, with the use of immunosuppressive agents (21).

Aphthous ulcers

Recurrent aphthous stomatitis affects, on average, 25% of patients with CD (25). Although it can become more severe in active disease, its presence does not correlate with CD activity (29).

The management of CD is usually sufficient to control oral aphthous lesions. Thus, to control pain, topical agents based on lidocaine or steroids, such as triamcinolone 0.1%, can be used up to three times a day (21,27). Dexamethasone elixir or cream (0.5 mg/5 mL) used topically three times a day is also effective. Moreover, non-steroidal anti-inflammatory drugs are effective in relieving pain and healing wounds (21,27). Importantly, the use of systemic or intralesional steroids should be reserved for refractory cases or severe persistent injuries.

Pyostomatitis vegetans

Pyostomatitis vegetans is considered the cutaneous counterpart of pyodermatitis vegetans, which is an idiopathic lesion consisting of multiple pustules with an erythematous base, both of which can occur simultaneously (30). Pyodermatitis vegetans is a vegetative form of pyoderma gangrenosum. Pyostomatitis vegetans lesions are rare, affecting less than 1% of patients with CD (30). Clinically, they are characterized by presenting swollen mucosa covered by multiple whitish or yellowish pustules, in which ruptures can occur, resulting in elongated superficial erosions compared to a "snail track" (30,31). Changes occur in the superior and inferior frontal vestibule, tongue and gingiva, as well as in the soft and hard palate. Histopathologically, there are no granulomas in the lesions (9).

Other oral manifestations

Oral changes associated with nutritional deficiencies

Oral manifestations caused by deficiency in the essential absorptive process of vitamins and nutrients, such as zinc, vitamin B12, potassium, calcium, magnesium, vitamin A, vitamin C and others, can lead to the development of cheilitis, xerostomia, desquamative plaques, and erosive

or blistering lesions (32). In addition, iron deficiency anemia causes angular cheilitis and painful depapillation of the dorsal surface of the tongue (32).

Changes in salivary glands and salivary flow rates

Changes in the salivary glands associated with CD are caused by an inflammatory mechanism of the granulomatous type, occurring inside the ducts of the minor salivary glands (25). Salivary flow has been shown to be reduced in 29 to 38% of patients with CD, and there may be alterations in salivary compositions and increased levels of pro-inflammatory cytokines, especially when the disease is active (33–36). An increase in salivary levels of IL-6, IL-1β, and TNF-α in patients with active CD has also been demonstrated (4). There is a need for studies quantifying salivary flow rates, in addition to showing whether changes in it and in its composition are caused by the disease itself or the medications used in the treatment.

Oral changes resulting from pharmacological therapy

Oral changes resulting from pharmacological therapy depend mainly on the drug concentration, dose and use time span. A range of drugs can be used to treat CD: antibiotics, biological agents, immunosuppressants, antidiarrheal agents, among others. Table 1 shows some drugs commonly used in the treatment of CD and its adverse oral effects. No adverse oral effects of azathioprine and mycophenolate mofetil have been reported.

Periodontal disease

PD is one of the most prevalent chronic diseases in humanity, classified as: periodontitis, necrotizing periodontitis, and periodontitis as a manifestation of systemic diseases (37,38). In its most severe form, PD can lead to bone loss and, consequently, tooth loss, negatively affecting the patient's health (4). According to the WHO, around 20 to 50% of the world's population suffers from PD. Therefore, PDs are the most common chronic inflammatory diseases in humans. However, periodontitis alone (with exception for gingivitis) has a prevalence ranging from 13 to 57% (4,7).

Periodontitis is characterized as a chronic inflammatory disease, multifactorial, induced by bacterial biofilm (4). The components of microbial action, such as lipopolysaccharides, peptidoglycan and proteases, can induce inflammatory responses (4,39). These host inflammatory responses are mediated primarily by neutrophils, monocytes/macrophages and T and B lymphocytes, resulting in the production of inflammatory mediators, which include cytokines, chemokines, and proteolytic enzymes, contributing to tissue degradation and bone resorption (4). The mechanisms of immunophysiological and inflammatory responses are important for the control of bacterial biofilm to occur (4,33). These responses can lead to the destruction of periodontal tissues, in which immune system cells, such as neutrophils and macrophages, play important roles (4,33).

The pathogenesis of periodontal disease has some factors similar to CD, involving a complex interaction between pathogens and host immune-inflammatory responses, strongly influenced by genetic and environmental factors (4). Although microorganisms are necessary, they are not enough for the onset of the disease (40). Instead, it is the unbalanced and persistent inflammatory reaction of the host against pathogens that results in the destruction of periodontal tissues (34).

PD has been associated with several chronic inflammatory diseases, including CD (35). There is a higher prevalence of PD in patients with CD than in the general population, with a greater bone attachment loss and more periodontal pockets (41). In addition, the severity and extension of PD is greater in patients with CD, when compared to healthy patients (4). The reason for this may be related to an increased expression of IL-18 in the serum of CD patients with periodontitis (4). Nevertheless, different patterns of cytokine clustering were observed in gingival tissues similar to those found in intestinal tissue (4). In this sense, considering the complexity of both periodontal disease and CD, it is challenging to understand the possible mechanisms involved in their coexistence.

The pathogenic characteristics of PD and CD are similar, as both diseases present an

Table I - Orofacial changes resulting from drug therapy used in the treatment of Crohn's disease.

MEDICINE	ADVERSE ORAL EFFECTS
Adalimumab (biological)	infections and angioedema
Budesonide (oral steroid)	glossitis, tongue swelling and xerostomia
Certolizumab (biological)	Stevens-Johnson syndrome / toxic epidermal necrolysis and angioedema
Cholestyramine (anion exchange resin)	tongue irritation, sour taste, gingival bleeding, caries disease, tooth enamel erosion and tooth discoloration
Cyclosporin (calcineurin inhibitor)	gingival hyperplasia
Ciprofloxacin (antibiotic)	oral candidiasis, angioedema, Stevens-Johnson syndrome / toxic epidermal necrolysis and dysgeusia
Colestipol (anion exchange resin)	difficulty in swallowing
Diphenoxylate and atropine (antispasmodics)	xerostomia, lip swelling, changes or dysgeusia
Infliximab (biological)	infections and angioedema
Loperamide (antidiarrheal)	xerostomia, Stevens-Johnson syndrome / toxic epidermal necrolysis, angioedema
Mesalazine (anti-inflammatory)	sore throat, oral thrush, xerostomia, stomatitis and dysgeusia
Methotrexate (folic-acid antagonist)	stomatitis, gingivitis and pharyngitis
Metronidazole (antibiotic)	metallic taste, glossitis, stomatitis, oral candidiasis and xerostomia
Prednisolone (oral steroid)	oral candidiasis (candidiasis)
Propantheline (antispasmodic)	xerostomia, angioedema and dysgeusia
Sulfasalazine (anti-inflammatory)	stomatitis and Stevens-Johnson syndrome / toxic epidermal necrolysis, dysgeusia and impaired folic-acid absorption
Tacrolimus (calcineurin inhibitor)	oral candidiasis, aphthous mouth ulcers, Stevens-Johnson syndrome / toxic epidermal necrolysis and angioedema

Source: Delwyn Dyall-Smith, 2015 (18).

excessive inflammatory response with increased production of free radicals (4). However, longitudinal clinical studies in patients with IBD with adequate samples are needed to establish the clinical implications for the management of periodontitis.

CONCLUSION

Oral tissues can be directly or indirectly affected by CD. Dentists, as part of a multidisciplinary team, should be able to recognize, diagnose, and treat oral manifestations of CD, promoting an early diagnosis and, consequently, improving the clinical status of patients.

The authors declare no conflicts of interest.

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