

CASE REPORT

Cobblestoning soft palate lesion: case report of a difficult diagnosis

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ABSTRACT

Oral lesions are often the first sign of an Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC). Oral manifestations are not always accompanied by intestinal inflammation's symptoms. For this reason, many times, ENT specialist is the first doctor who receives the patient. Diagnosis and treatment of the patients affected by IBD associated with several extra-intestinal manifestations requiring a multidisciplinary management. Endoscopic examination allows us to diagnose the disease but non-invasive markers of intestinal inflammation, like fecal calprotectin, may be used to select which patients need to undergo endoscopic examination, thereby avoiding unnecessary investigations. The therapeutic choice, currently available, to treat oral lesions associated with IBD includes topical or systemic corticosteroids, immunosuppressive agents, and biologic drugs.

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KEY WORDS: Inflammatory bowel diseases; Crohn disease; Oral manifestations.

Inflammatory bowel disease (IBD) comprises chronic heterogeneous disorders of unknown etiology, resulting from multifactorial environmental precipitants in genetically susceptible individuals.^{1,2}

Crohn's disease (CD) and ulcerative colitis (UC) belong to the group of chronic inflammatory bowel diseases (IBD).³

UC generally affects the rectum and the colon while CD can involve all the gastrointestinal (GI) tract, from the oral cavity to the anus.¹

The etiology of these diseases has not been completely ascertained but it is well known that the factors contributing to disease pathogenesis

include environmental aspects, intestinal microflora, genetic predisposition and pathological immune responses.^{1,3} Common genetic background is represented by IBD1 gene, MHC allele HLABR1*0103, ABCB1 gene.⁴

Probably "western" lifestyle and diet are factors that predispose to IBD's development. Besides gastrointestinal tract's manifestations, there are a series of extraintestinal manifestations (EIM).³ About 36% of subjects affected by IBD present extraintestinal manifestations that involve any organ of the body (eyes, joints, liver, pancreas, skin, blood, and mouth).^{1,2,5} The pathogenesis of EIMs is still not fully identified.

It appears that the inflamed intestinal mucosa can trigger immunological responses by sharing common epitopes (*e.g.*, intestinal bacteria and synovia). Bacteria that can translocate because of greater permeability of the intestinal mucosa trigger an acquired immune response that does not distinguish between a bacterial epitope and a joint or skin epitope.⁶

Case report

In October 2019, a 28-years old female reported to have seen a strange lesion on her soft palate. She didn't report odynophagia, or dysphagia or other systemic symptoms.

During the anamnesis story she reported idiopathic thrombocytopenia (WBC: 5200/ μ L; HB: 13.6 g/dL; PLT 67000 / μ L) in February 2018. After one-month physical abdomen's examination was negative. She repeated blood count with WBC: 6820/ μ L; HB: 14.0 g/dL; PLT 94000 / μ L and an increase in eosinophil (EOS: 900 / μ L). The patient's evaluation continues with:

- abdominal US: negative for lymphadenomegaly or splenomegaly;
- bone marrow aspirates to research: TCR gene's rearrangement (negative) and the modification of t(9;22) interesting BCR/ABL (negative);
- Stool Test: negative.

The patient was discharged in good general conditions; without specific symptoms and she was invited to continue follow up.

In the April 2018, the patient was referred to hospitalization in the emergency room due to perianal abscess treated by surgical drainage with a complete symptomatology's remission.

The patient was admitted to our Federico II University ENT unit to study her oral lesion. Oral examination evidenced soft palate's cobblestoning lesion (Figure 1). The lesion appeared smooth and raised.

Oral endoscopy with Narrow Band Imaging (NBI) showed interconnected thin, oblique and arborescent vases. Intrapapillary capillary loops were almost invisible (Type 1 – Ni Classification).⁷ (Figure 2). This NBI pattern oriented for a benign lesion of the oral cavity.

Blood count showed HB: 10.6 g/dL; WBC:



Figure 1.—Cobblestoning lesion involving soft palate.



Figure 2.—NBI pattern: type 1.

37900/ μ L; PLT 114000/ μ L. She practiced biopsy and the pathological report showed hyperplastic squamous epithelium with notes of dyskeratosis. At corion's level there was a predominantly plasmacell inflammatory infiltrate. Immunohistochemical staining (PASS and Grocott) showed coccoid microbial share at intraepithelial site and lymphocytes (CD3+and CD 20+) (Figure 3).

The patient practiced research of fecal calprotectin with results of 109,5 μ g/g of stools.

She was sent for gastroenterological consultancy. The overall clinical conditions and the tests carried out led to the diagnosis of CD.

She practices periodic follow up, the disease is in remission and the lesion of the soft palate has completely disappeared.

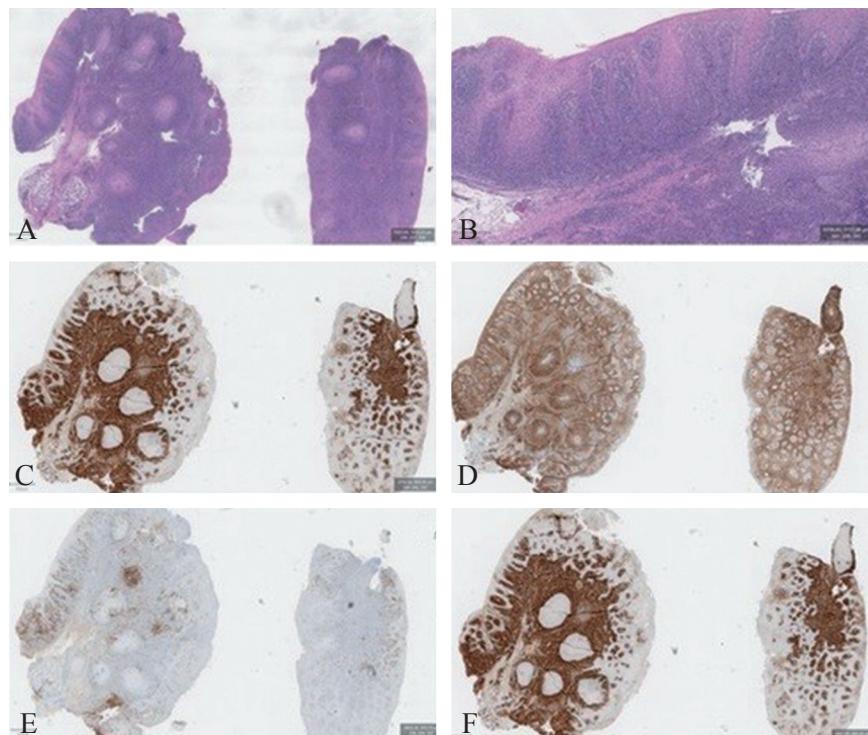


Figure 3.—A, B) Histopathological examination revealed two polypoid lesions. A severe chronic, non granulomatous inflammation was present in the stroma. The surface squamous, non keratinizing epithelium was hyperplastic with intraepithelial neurotrophils (H&E 2x and 10x respectively); C-F) At the immunohistochemical examination the infiltrate resulted predominantly composed of plasma cells, CD79a and CD138 positive (C and D respectively). A small number of B and T lymphocytes was highlighted by CD 20 (D) and CD3 (F) immunostaining (2x).

Discussion

The first cases of oral IBD manifestations were described in 1969 in two patients with CD.⁸ The prevalence of oral manifestations is higher in males and in children. It is more frequent when the upper gastrointestinal tract or the perianal tract are involved. Oral manifestations can occur either concomitantly with intestinal symptoms or before the presentation of IBD.¹ Oral manifestations of CD can be specific or non-specific, according to the presence of granulomas noted on the histopathology reports.^{2, 9}

Specific oral lesions are less common than non-specific ones. Characteristics of specific lesion include the presence of non-caseous granu-

loma characterized by a core of activated macrophages, giant cells and peripheral lymphocytes and fibrotic tissue. Oral manifestation is often associated with perianal lesions. We could have: Cobblestoning lesion that interested posterior buccal mucosa who appeared hyperplastic like a “cobblestone”; mucosal tag that interested vestibules and retromolar region with hyperplastic edge firm or boggy to palpation; mucogengivitis. Other less frequent manifestations are swelling of the lips characterized by painful vertical fissures of lips and buccal sulci; edema of the face who cause facial deformations. When we have an oral granulomatous lesion we need to exclude other pathologies besides CD such as: orofacial granulomatosis, sarcoidosis, my-

TABLE I.—*Specific oral lesion in patients with inflammatory bowel disease (IBD).*

Lesion	Location	Features
Cobblestoning	Posterior buccal mucosa	The mucosa of oral cavity is hyperplastic like a “cobblestone”
Mucosal tags	Vestibules and retromolar region	Hyperplastic edge firm or boggy to palpation
Mucogengivitis	Whole gingiva	Gingiva edematous, granular and hyperplastic
Others		
Swelling of the lips	Lips, buccal sulci	Painful vertical fissures
Edema of the face	Face	Facial deformation

cobacterial infection and foreign-body reactions (Table I).^{1-3, 6}

Non-specific oral lesions are the most frequent and this makes differential diagnosis difficult. In fact, these lesions can occur as a result of chronic inflammation, malnutrition and malabsorption syndrome, or as a side effect of pharmacological treatment. We have: aphthous stomatitis who appeared like shallow round ulcerations surrounded by an erythematous ring with a central fibrin membrane and interested all oral cavity; pyostomatitis vegetans characterized by multiple pustules in labial gingiva, buccal ad labial mucosa, tongue, soft and hard palate; angular cheilitis who presented erythema with or without painful fissures at the corner of the mouth. Other non-specific oral lesions are glossitis, lichen planus, periodontitis and dental caries, perioral dermatitis, recurrent buccal abscesses, submandibular lymphadenopathy, salivary duct fistula (Table II).^{1-3, 6}

If an oral manifestation occurs, the presence of IBD should be suspected, even in absence of GI symptoms. Because oral lesions can be the first sign of IBD, a cooperation between specialists in oral medicine and gastroenterologists is required to allow an early diagnosis. It is important to diagnose the underlying disease early because there is a possible association between IBD and oral cavity's cancer and it is described in the literature.^{1-3, 5}

Clinical, laboratory, radiological, endoscopic, and pathological data are needed for the diagnosis of IBD. However, the gold standard is colonoscopy with multiple biopsies.^{1, 9, 10}

Non-invasive investigation includes non-specific parameters of inflammation like erythrocyte sedimentation rate and C-reactive protein, and serologic markers of CD like: anti-neutrophil cytoplasmic antibodies (ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA). These markers are very important for the diagnosis and prognostic stratification of CD patients.¹

Fecal calprotectin is a very accurate marker to distinguishing patients with an inflammatory disease compared to those without.¹¹

Calprotectin is a 36-kDa protein which is a member of the S100 family. Calprotectin is derived predominantly from neutrophils, with a lesser contribution from monocytes and macrophages and it accounts for about 60% of the cytosolic protein in neutrophils. Calprotectin has a direct antimicrobial effect: this protein is able to chelate metal ions and thus sequester them from pathogenic organisms.^{11, 12}

Calprotectin is found in various body fluids but its concentration in feces is six times that of the normal plasma. Moreover, its concentration increases during inflammatory process. Thanks to these correlation with inflammation, fecal calprotectin is useful to distinguishing patients with inflammatory bowel disease (IBD) from those with irritable bowel syndrome selecting patients to undergo to endoscopy.¹¹

Based on a literature study, a fecal calprotectin of >200 µg/g permits the detection of CD in 50% of suspected cases. On the contrary, when it is <100 µg/g, further tests should be ruled out be-

TABLE II.—*Non-specific oral lesion in patients with inflammatory bowel disease (IBD)*.

Lesion	Location	Features
Aphthous stomatitis	Anywhere in the oral cavity	Shallow round ulcerations surrounded by an erythematous "halo" with a central fibrin membrane
Pyostomatitis vegetans	Labial gingiva, buccal and labial mucosa; less common: tongue, soft and hard palate	Erythematous oral mucosa with multiple pustules of an unknown etiology
Angular cheilitis	Corner of the oral cavity	Erythema with or without painful fissures and sores at the corners of the mouth
Others		
Glossitis	Tongue	
Lichen planus	Oral mucosa, gingiva	
Periodontitis and dental caries	Teeth, periodontal tissue, alveolar bone	
Perioral dermatitis	Perioral skin	
Recurrent buccal abscesses	Palate, lips	
Submandibular lymphadenopathy	Lymph nodes	
Salivary duct fistula	Salivary glands	

cause the possibility of finding an inflammatory disease is low.¹³

Fecal lactoferrin is 76-kDa iron-binding glycoprotein and it is a member of transferrin family's proteins. It is released by activated neutrophils. Like calprotectin lactoferrin is another important marker to identify patients affected to IBD with a sensitivity and specificity of 82% and 93%, respectively.

However, the dosage of fecal lactoferrin is more used in disease monitoring rather than diagnosis.¹⁴

Conclusions

Certainly, oral lesions' biopsy is important to confirm diagnosis; in fact, many studies have shown that 50% of all patients with oral lesions had signs of intestinal mucosa inflammation, discovered on ileo-colonoscopy, in absence of specific GI symptoms. However, in absence of gastrointestinal manifestations, it remains difficult to diagnose UC from the oral lesion alone.^{15, 16} The advantage of using non-invasive markers (such as serological markers of IBD and fecal calprotectin) in patients with suspected IBD is certainly their low cost and lack of radiation.¹

Drug therapy currently available includes topical or systemic corticosteroids, immunosuppressive agents, and biologic (mainly anti-Tumor necrosis factor α). Topical treatment includes intralesional injections, mouthwashes, and ointments. The therapy's goal is to induce remission and control of disease, improving clinical symptoms and endoscopic sign. Generally the first line of treatment starts with corticosteroid ointments and/or mouthwashes and non-steroidal anti-inflammatory pastes.¹ In severe cases (for example fistulizing oral CD) treatment with biologic drugs has obtained satisfactory results.⁹

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

All authors read and approved the final version of the manuscript.

History

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