CASE REPORT

DISSEMINATED HISTOPLASMOSIS WITH ORAL MANIFESTATION IN A PATIENT WITH CROHN'S DISEASE

HISTOPLASMOSE DISSEMINADA COM MANIFESTAÇÃO ORAL EM PACIENTE COM DOENÇA DE CROHN

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ABSTRACT

Histoplasmosis and Crohn's Disease (CD) can resemble each other in clinical characteristics, thus complicating the diagnosis by the doctor or dentist. Through a clinical case, this work aims to demonstrate the diagnostic challenge of a single histoplasmosis lesion in the oral cavity in a patient with chronic granulomatous disease. The histopathological examination found it to be an oral lesion resulting from a specific granulomatous process, subsequently diagnosed as histoplasmosis after microbiological culture of the lesion. The systemic medical evaluation did not identify lesions compatible with histoplasmosis in other organs. After appropriate therapy, the fungal infection was remission, and therapeutic follow-up of the autoimmune disease was performed. The co-occurrence of histoplasmosis in patients with CD is a possibility to be considered, especially due to the potential state of immunosuppression associated with this condition. Although the anatomopathological examination may not detect the microorganism in the tissue sample, this case demonstrated that microbiological culture should be considered an essential complementary examination for diagnosing deep mycoses.

Keywords: Histoplasmosis, Disseminated fungal infection, Oral diseases, Autoimmune disease, Crohn's disease.

RESUMO

A Histoplasmose e a Doença de Crohn (DC) são enfermidades que podem se assemelhar em características clínicas e, assim, dificultar o diagnóstico por parte do médico ou cirurgião-dentista. O objetivo deste trabalho é demonstrar, através de um caso clínico, o desafio diagnóstico de uma lesão única de histoplasmose na cavidade oral em paciente com doença crônica granulomatosa. No exame histopatológico, verificou tratar-se de lesão oral decorrente de processo granulomatoso específico, diagnosticado em seguida como histoplasmose mediante cultura. A avaliação médica sistêmica não identificou lesões compatíveis com histoplasmose em outros órgãos. Após terapia apropriada, houve a remissão da infecção fúngica e o seguimento terapêutico da doença autoimune. A co-ocorrência de histoplasmose em pacientes com Doença de Crohn é uma possibilidade a ser considerada, especialmente em virtude do potencial estado de imunossupressão associado a essa condição. Este caso demonstrou que, embora o exame anatomopatológico possa não detectar o microrganismo na amostra de tecido, a cultura microbiológica deve ser considerada um exame complementar essencial para o diagnóstico de micoses profundas.

Palavras-chave: Histoplasmose, Infecção fúngica disseminada, Doenças bucais, Doença Autoimune, Doença de Crohn.

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INTRODUÇÃO

Crohn's Disease (CD) is a chronic inflammatory and granulomatous condition widely affecting the gastrointestinal system. Its etiology is not fully understood, but it is believed to involve an immunologically mediated hypersensitivity, influenced by environmental factors such as smoking, in genetically susceptible individuals (1-7).

The pathophysiology of the disease is associated with abnormalities in helper-T cells, which differentiate into Th1 and Th17 lymphocytes. These anomalies trigger the overproduction of cytokines, such as IL-12, interferon-gamma, and tumor necrosis factor-alpha (8). The probable disease-associated antigens include enteric bacteria and/or autoantigens of the intestinal tract, which may be targets of an autoimmune response. This response compromises the affected tissues, causing changes, remodeling, and forming inflammatory granulomas (9-11). The disease can affect the entire gastrointestinal tract, with a higher incidence in the terminal ileum and colon. However, about 50% of affected individuals may present non-intestinal manifestations before the appearance of enteric lesions in areas such as skin, eyes, mouth, joints, and lungs (12). The signs and symptoms of the disease are diverse and include abdominal pain, diarrhea, fever, renal bleeding, intestinal lumen stenosis, peptic ulcers, diverticulitis, abscesses with fistulae, vomiting, weight loss, loss of appetite, enterorrhagia, occasional nasal obstruction, and epistaxis (13).

The diagnosis of CD is based on a combination of clinical and histopathological findings. Among the clinical findings, the physical examination performed by the healthcare professional stands out, identifying typical signs and symptoms of the disease (13-14). Complementary exams include endoscopy, imaging, and laboratory tests. Among the laboratory tests are the complete blood count, C-reactive protein, erythrocyte sedimentation rate, albumin dosage, IgG and IgA antibody testing against *Saccharomyces cerevisiae*, and the detection of anti-neutrophil cytoplasmic antibodies (13,15-16). From the histopathological point of view, the biopsy of the lesions by CD is important. In particular, in gastrointestinal lesions, non-necrotizing granulomas are expected to be found on microscopic examination (1). The definitive diagnosis is usually established after excluding other diseases and conditions that can cause similar granulomatous inflammation, such as tuberculosis, sarcoidosis, and fungal diseases (14).

Treating CD generally involves using drugs from the following classes: glucocorticoids, immunomodulators, biologics, and elemental diets. These treatments aim to control the adverse manifestations of the disease, reduce inflammation, and improve patients' quality of life (17). Among the frequently used drugs are aminosalicylates, prednisolone, mercaptopurine, azathioprine, thiopurines, and methotrexate (18). In addition to drug therapy, nutritional control plays an important role in treatment, and dietary supplementation may be necessary (7,19-20). In some cases, surgical procedures may be necessary, especially during disease exacerbation, such as in cases of intestinal obstruction with abscesses and fistulas (21). Maintaining an excellent quality of life is essential to minimize the adverse effects of the disease and treatment. This includes following a balanced diet and regular physical activity (17,19,22-23).

In the differential diagnosis of CD, it is essential to consider histoplasmosis, a severe fungal infection that can present similar symptoms. It occurs endemically in the Americas and is caused by the fungus *Histoplasma capsulatum*. The disease mainly develops in moist soils rich in bird and bat droppings, from where the spores are carried by the air and inhaled into the lungs (24). The disseminated form of the disease is characterized by spreading to extrapulmonary sites, such as the spleen, liver, and gastrointestinal tract. In the oral cavity, the tongue is the most frequently affected site. This form of the disease tends to affect immunosuppressed individuals, the elderly, and AIDS virus carriers more severely. If not treated properly, the disseminated form becomes fatal (25). Usually, the diagnosis of Histoplasmosis is made through a histopathological examination resulting from an incisional biopsy of the lesion, which shows a non-caseating chronic granulomatous inflammatory lesion (26), similar to the microscopy of CD and other diseases, in addition to performing histochemical assays with special stains such as PAS and Grocott-Gomori methenamine silver to highlight the fungal yeasts (27). The performance of fungal cultures and serological tests also contributes to the diagnosis. This work aims to demonstrate the diagnostic challenge of a single histoplasmosis lesion in the oral cavity in a patient with chronic granulomatous disease through a clinical case.

CASE REPORT

A 59-year-old man, caucasian, asymptomatic, attended the stomatology clinic at the Dental School of the Federal University of Uberlândia, complaining about the appearance of a lesion on the tongue that originated after the placement of a titanium osseointegrated implant in the region of the first lower left molar, with one month of evolution, and which bothered him especially during speech and

chewing. According to the patient, after the dental surgery, their tongue touched a part of the exposed metal component of the implant, triggering the injury. During the anamnesis, the patient showed some difficulty in articulating words due to the mentioned tongue alteration and reported having had CD for twelve years, initially with manifestations of colitis and proctitis, under periodic medical follow-up and with the autoimmune disease under control. He reported being a resident of an urban area and not having contact with rural or forested regions. Routinely, the patient used the immunosuppressants adalimumab and mesalazine to control CD, which his gastroenterologist doctor prescribed. A week prior, the same professional also prescribed the ointment for topical administration on the tongue lesion. The ointment AdMuc 100mg - an extract of *Chamomilla recutita*- was indicated for various oral conditions. The patient carried various laboratory tests, including a complete blood count, lipid parameters, sodium, potassium, liver transaminases, renal function indicators, vitamin B12, C-reactive protein, and erythrocyte sedimentation rate (ESR). Among all verified, only the ESR was elevated (46 mm - 60 minutes). According to the patient, it was an expected and frequent finding in their routine exams, given the inflammatory condition typical of CD.

In the extraoral examination, there was nothing noteworthy. However, in the oroscopy, good overall oral hygiene was identified and a relatively well-defined lesion, approximately 2.5 cm in diameter, with erythematous and white fibrinoid exudative areas, showing central ulceration, located on the left anterior lateral border of the tongue, with a generally increased volume (Figure 1A, 1B). Some diagnostic hypotheses were considered after the clinical examination was completed, the main one being an oral manifestation related to CD; the secondary ones included a traumatic ulcer resulting from trauma to the recently performed implant, a lesion from some granulomatous infection, or even a possible squamous cell carcinoma. Thus, an incisional biopsy was performed in the same session for a conclusive diagnosis and to institute appropriate treatment, removing three small lesional fragments from distinct areas. After a week, the patient returned with the lesion showing a greater increase, with an aspect of worsening (Figure 2). The histological fragments stained with hematoxylin and eosin showed a tissue fragment characterized by extensive fibrinoid necrosis associated with vascular neoformation, mixed mononuclear and polymorphonuclear inflammatory infiltrate, and discrete neofibrogenesis. The conclusion after microscopy was fibrinoid necrosis of connective tissue and granulation reaction, with findings inconclusive for the hypothesis of CD or squamous cell carcinoma. Given the obtained anatomopathological report, the stomatologist responsible for the case informed the patient and contacted the involved gastroenterologist, reporting the findings and suggesting that the lingual lesion was possibly a nonspecific oral lesion resulting from the autoimmune hypersensitivity that characterizes CD. Thus, the doctor decided to suspend the use of Adalimumab for thirty days, understanding that the medication, potentially immunosuppressive, could delay the healing process of the ongoing lesion. In addition, the stomatologist prescribed two new topical medications: the betamethasone elixir 0.5 mg/5ml for rinsing two to three times a day and the triamcinolone acetonide ointment 1mg/g once a day, both corticosteroids, in daily alternation with the AdMuc 100 mg already in previous use, while the lesion was present. After another week, an improvement in the appearance of the lesion was noted, and the patient continued with the same medications and care regarding the lesion, with weekly follow-up at the stomatology clinic. After another two months of follow-up, the patient remained asymptomatic, but the lesion showed some morphological changes that justified the need for a new investigative incisional biopsy. The microscopy of the second biopsy was compatible with stratified squamous epithelium with pseudocarcinomatous hyperplasia, permeated by varying degrees of spongiosis and leukocytic exocytosis, forming occasional microabscesses. In the lamina propria and submucosa, a mononuclear inflammatory infiltrate was also noted, predominantly histiocytic, with multinucleated giant macrophages, lymphocytes, plasma cells, eosinophils, and neutrophils, characterizing a chronic granulomatous sarcoid-type inflammatory infiltrate, suggesting a specific CD lesion (Figure 3).

It is also important to highlight that histochemical stains PAS, Ziehl-Neelsen, and Grocott's methenamine silver, performed in the evaluation of the first and second microscopy, did not show any signs of fungal or bacterial parasites in the intra or extracellular inflammatory environment, with the pathologist noting that the definitive exclusion of the possibility of infectious diseases would require further evaluations, such as culture from the lesion tissue and serology for specific microbial antigens.

The patient continued clinical follow-up with the stomatology team, which decided to use low-power laser therapy. The established protocol was following the manufacturer through 100mW of power, with 1J every 10 seconds on each of the six chosen points on the lingual lesion, for two weeks and with two weekly sessions, using the Therapy XT device from DMC (Figure 4). Simultaneously, in conjunction with the gastroenterology medical team, it was decided

to perform a culture for microbiological purposes with samples from the oral lesion to confirm the absence of microorganisms, as indicated by previous histochemical stains. The culture revealed the growth of the fungus *Histoplasma capsulatum*, the causative agent of histoplasmosis. Based on this result, the patient was referred to the infectious disease department of the same hospital. During a 9-day hospitalization, he received treatment with Amphotericin B, prescribed at a dose of 3 mg/kg per day. After discharge, the treatment was adjusted to Itraconazole, initially with 200 mg every 8 hours for three days, later changed to every 12 hours. Three years later, the patient continues to use Itraconazole prophylactically and is being monitored by the infectious disease team. Chest imaging exams did not show pulmonary involvement, and 20 days after the start of antifungal treatment, the lingual lesion showed complete remission (Figure 5).

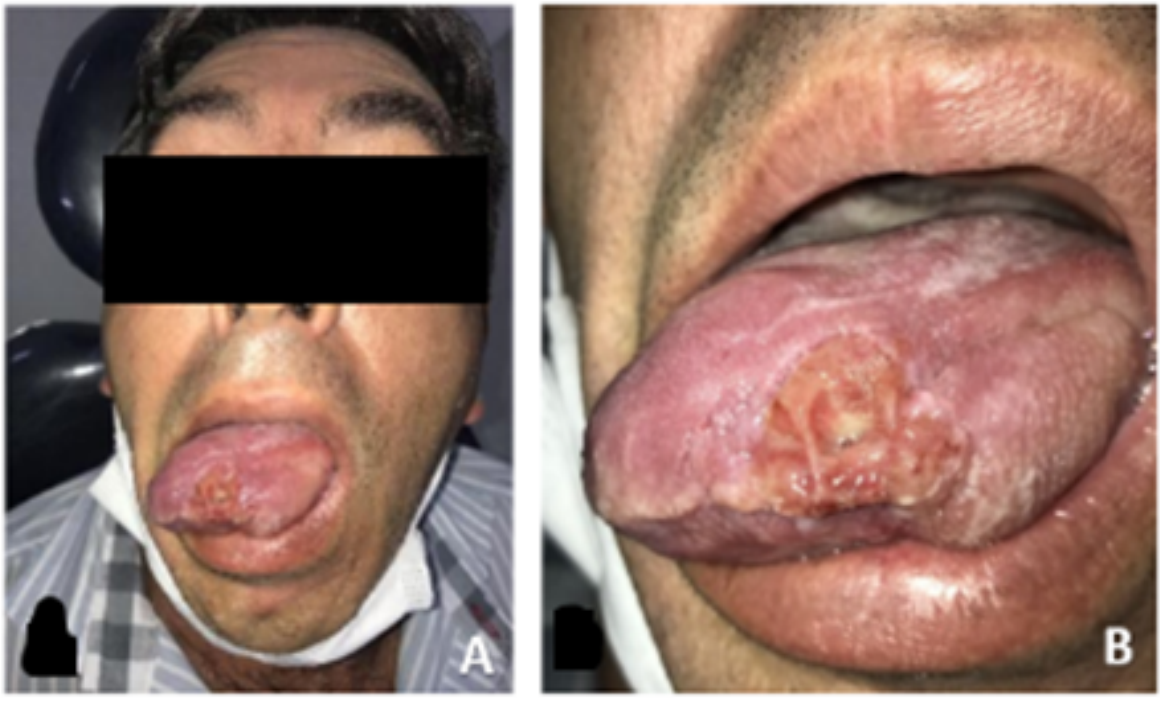

Figure 1: **A**- Frontal view of the patient exposing the tongue with the lesion. **B**- Granulomatous and ulcerated lesion approximately 2.5 cm in length on edematous tongue.

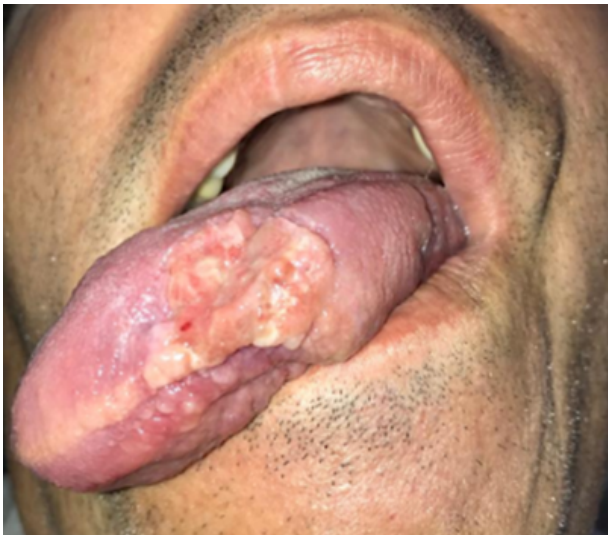

Figure 2: The aspect of the tongue after the incisional biopsy showed a modified appearance and general volume increase.

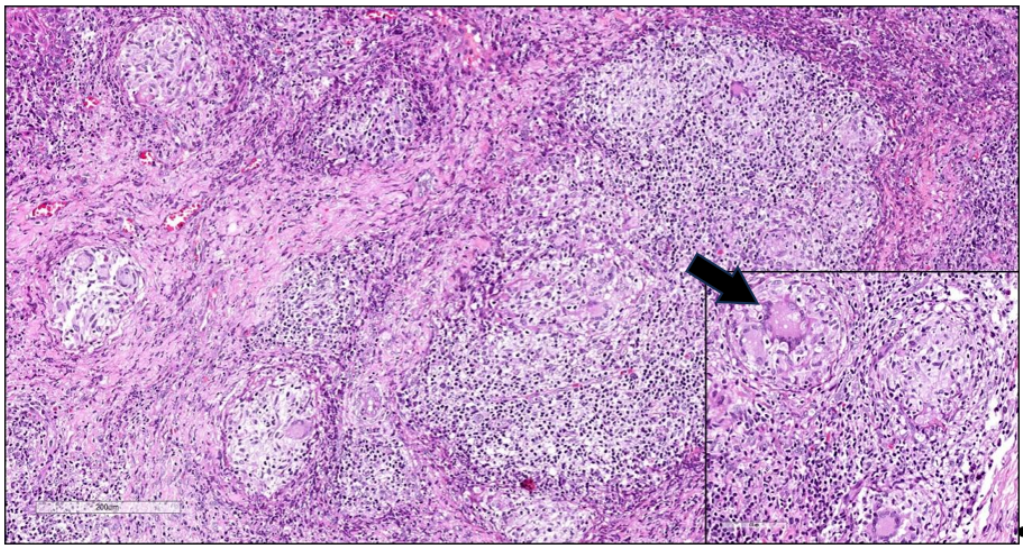

Figure 3: Histopathology revealed diffuse granulomatous inflammation, well-defined non-necrotizing granulomas, and numerous Langhans giant cells. Some of these cells showed vacuoles (uncertain), but no inclusion bodies or infectious agents were found. (Hematoxylin-eosin staining).

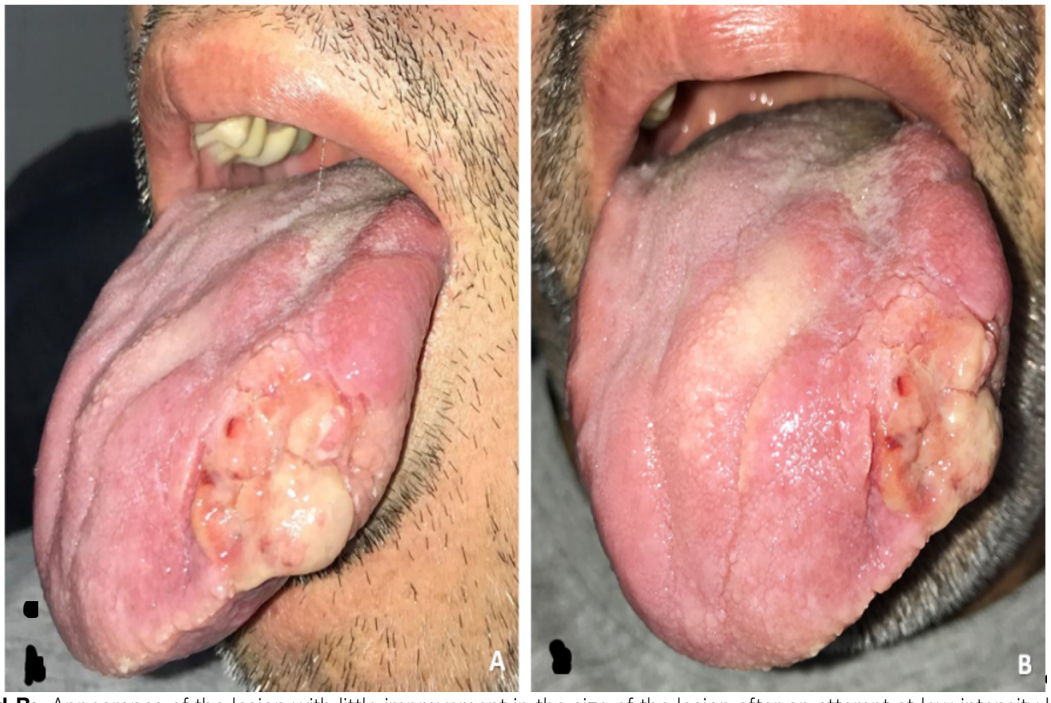

Figure 4 A and B: Appearance of the lesion with little improvement in the size of the lesion after an attempt at low-intensity laser therapy.

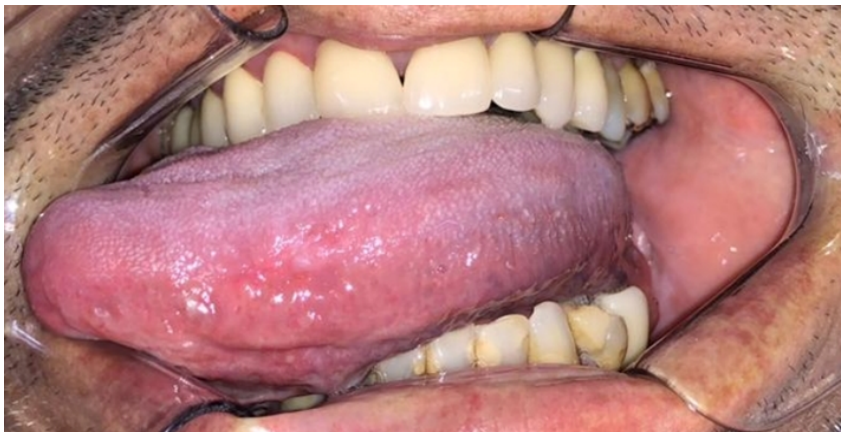

Figure 5: The final appearance of the tongue with total remission of the lesion.

DISCUSSION

The CD is currently understood as a type IV autoimmune hypersensitivity, characterized by a large infiltration of TH1 and TH17 lymphocytes in association with an overproduction of local cytokines, such as tumor necrosis factor, interleukin 12, and gamma interferon, which act on the tissues remodeling them in favor of the constitution of local granulomas (10). Clinically, it is a disease with inflammatory intestinal manifestations located in various sites, such as the ileum, ascending colon, transverse colon, descending colon, and sigmoid colon, triggering cases of intestinal diverticulitis, abscesses that may eventually fistulize, and a series of possible signs and symptoms, including diarrhea, abdominal pain, skin ulcers, and oral lesions (23,28).

The oral manifestations of CD are characterized by sporadic non-intestinal involvement in patients but are of great importance in the course of the disease (23). The case of a patient with CD for 12 years was evidenced, without intestinal manifestations due to a successful ongoing treatment, who developed a granulomatous oral lesion, initially suggestive of an oral manifestation of the disease. Specific histochemical stains were performed on the biopsied specimen, with no identification of microorganisms in the lesion. Nevertheless, subsequent tissue cultures revealed the presence of the fungus *Histoplasma capsulatum* in the tissue. This changed the initial hypothesis of an oral manifestation of CD to disseminated histoplasmosis with oral involvement. The disseminated form of histoplasmosis is the one that most affects the oral cavity, and the oral lesion may be the first manifestation of the disease, as evidenced in this case. Furthermore, oral manifestations of histoplasmosis can resemble malignant neoplasms, a feature also observed in this report.

Histoplasmosis is a relatively common fungal disease in immunocompromised individuals that usually shows a significant state of organic debility in this group (29). Commonly, the Disseminated variant of the disease has an extrapulmonary systemic repercussion, with the oral cavity being a possible site of involvement, with a higher incidence on the tongue (30). For various reasons, immunocompromised patients are most commonly affected by the Disseminated variant of Histoplasmosis. The patient affected by CD presents an unequivocal immunological imbalance because, even though the chronic autoimmune disease is under control, there is a daily need for immunomodulatory drugs. The use of drugs for controlling CD for more than a decade by the patient in the case now reported possibly made him susceptible to fungal colonization by *Histoplasma capsulatum*, determining the coexistence of two concomitant pathological entities, CD and Histoplasmosis.

Interestingly, this case report raises challenging questions regarding the sequence of events. Would there have been a fungal colonization after the histopathological analysis that would justify that microorganisms were not identified in the histochemical stains? Would the lingual lesion be an oral manifestation of CD that was later colonized by *Histoplasma capsulatum*? Would this be a case of opportunistic Disseminated Histoplasmosis in an immunocompromised patient due to an ongoing CD for 12 years? These are all intriguing questions from the study, and it is understood that the best characterization of the case is the advent of an oral manifestation of Disseminated Histoplasmosis in a patient with immunologically unbalanced CD due to long-term therapy. It is noteworthy that both nosological entities pose life-threatening risks and that, in addition to the fact that CD still does not have a definitive cure and thus requires continuous therapeutic control, Disseminated Histoplasmosis often requires patient hospitalization and long intravenous and oral antifungal treatments.

CONCLUSION

The management of oral manifestations of CD requires the dentist to perform a differential diagnosis with various lesions, including deep mycoses, which demands a comprehensive and detailed approach. The manifestation of histoplasmosis in patients with CD is a relevant possibility, considering the potential immunosuppression of these patients, and should always be considered in the diagnosis. Furthermore, this case demonstrates that although the anatomopathological examination may not detect the microorganism in the tissue sample, the microbiological culture should be considered an essential complementary examination for diagnosing deep mycoses.

The authors declare no conflicts of interest.

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