CASE REPORT

IT LOOKS LIKE, BUT IT IS NOT: ORAL PARACOCCIDIOIDOMYCOSIS AS A DIFFERENTIAL DIAGNOSIS OF ORAL CANCER

PARECE, MAS NÃO É: PARACOCCIDIOIDOMICOSE ORAL COMO DIAGNÓSTICO DIFERENCIAL DO CÂNCER ORAL

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ABSTRACT

South American blastomycosis, also known as paracoccidioidomycosis, is a systemic mycosis caused by the fungus *Paracoccidioides brasiliensis* that grows in the soil feeding on decomposing organic matter and it is considered the most important fungal infection in Latin America, with Brazil being an endemic center. The infection initially involves the lungs through inhalation of the fungal spores with possible spread to other regions of the body, including the mouth. In the oral cavity, lesions usually manifest with a granular, erythematous, and ulcerated appearance. Other diseases can have similar characteristics, such as squamous cell carcinoma. The objective of this study is to report a clinical case of a patient with paracoccidioidomycosis that mimicked the clinical features of squamous cell carcinoma. A 57-year-old male patient presented with a lesion in the lower labial mucosa region extending to the gingiva and floor of the mouth. The lesion exhibited a moriform, ulcerated appearance with ill-defined borders. The diagnostic hypotheses were paracoccidioidomycosis and squamous cell carcinoma. Histopathological examination showed pseudoepitheliomatous hyperplasia and multinucleated giant cells with *Paracoccidioides brasiliensis* yeasts inside, which is consistent with the definitive diagnosis of paracoccidioidomycosis. It is concluded that paracoccidioidomycosis and squamous cell carcinoma have similar clinical and microscopic characteristics, which may lead to a mistaken clinical diagnosis. Thus, the definitive diagnosis can only be established after confirmation of the presence of the fungus.

Keywords: Paracoccidioidomycosis; Blastomycosis; Squamous cell carcinoma; Oral cancer; Differential diagnosis; Microscopy.

RESUMO

A blastomicose sul-americana, também conhecida como paracoccidioidomicose, é uma micose sistêmica causada pelo fungo *Paracoccidioides brasiliensis,* que cresce no solo, nutrindo-se de restos de matéria orgânica em decomposição. É considerada a infecção fúngica mais importante da América Latina, sendo o Brasil um centro endêmico. A infecção envolve inicialmente os pulmões, por meio da inalação do fungo, com possível disseminação para outras regiões do corpo, incluindo a boca. Clinicamente, na mucosa oral, as lesões geralmente se manifestam com aspecto granular, eritematoso e ulcerado. Outras doenças podem apresentar características semelhantes, como o carcinoma de células escamosas. O objetivo deste trabalho é relatar um caso de paracoccidioidomicose que mimetiza as características do carcinoma de células escamosas. Trata-se de um paciente de 57 anos, do sexo masculino, com lesão na região da mucosa labial inferior, estendendo-se para gengiva e assoalho bucal, e apresentando aspecto clínico moriforme, ulcerado e sem limites precisos. As hipóteses diagnósticas foram de paracoccidioidomicose e de carcinoma de células escamosas orais. O exame histopatológico exibiu epitélio pseudoepiteliomatoso e células gigantes multinucleadas com leveduras de *Paracoccidioides brasiliensis* em seu interior, sendo compatível com o diagnóstico definitivo de paracoccidioidomicose. Conclui-se que o paracoccidioidomicose e o carcinoma de células escamosas apresentam características clínicas e microscópicas semelhantes, o que pode acarretar um diagnóstico clínico equivocado. Dessa forma, o diagnóstico definitivo é feito por meio da confirmação da presença do fungo.

Palavras-chave: Paracoccidioidomicose; Blastomicose; Carcinoma de células escamosas; Câncer bucal; Diagnóstico diferencial; Microscopia.

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INTRODUCTION

South American blastomycosis, also known as paracoccidioidomycosis (PCM), is a systemic mycosis caused by the dimorphic fungus *Paracoccidioides brasiliensis*. It is estimated that 10 million people in Latin America are infected with PCM, and Brazil is an endemic center of this disease, with a higher concentration in the South, Southeast, and Central-West regions (1). However, due to the lack of disease notification, even though it has recently been included in the National List of Compulsory Notifiable Diseases, the number of PCM cases may be underestimated. Moreover, this condition is considered the third leading cause of death from chronic infectious diseases in the country (2).

People are infected by inhaling the fungus in its yeast form, which is found in the soil. Rural workers or residents of the region can have contact with the fungus directly or indirectly (2). Most PCM cases affect men with chronic tobacco and alcohol use between 30 and 50 years of age, who have poor nutrition and hygiene, as well as socioeconomic vulnerability (3). The lungs are generally the primary site of involvement, with symptoms including cough, dyspnea, and weight loss. Nevertheless, dissemination may occur to various regions of the body, such as lymph nodes, skin, mucous membranes, and adrenal glands (3,4).

In most cases, PCM is diagnosed by the dental surgeon or otolaryngologist, as the head and neck region is an important area of disease manifestation (1). In the oral cavity, lesions usually manifest with a granular, erythematous, and ulcerated appearance. The most affected sites are the lips, buccal mucosa, floor of the mouth, tongue, and pharynx (3). It is important to note that other diseases may have clinical and even microscopic characteristics similar to those of this infection, and differential diagnosis between these conditions is essential. This study aims to report a case of PCM that mimics the characteristics of squamous cell carcinoma (SCC).

CASE REPORT

This research was submitted to and approved by the Research Ethics Committee under CAEE 69783923.0.0000.5578.

A 57-year-old pheoderma Black man attended the School Clinic of Faculdade Independente do Nordeste (Fainor), located in the city of Vitória da Conquista (Bahia), to evaluate an extensive lesion in the lower lip mucosa region. During the anamnesis, he reported being a farmer and a chronic smoker for about 30 years, smoking 20 cigarettes a day. He denied the presence of previous systemic diseases and alcoholism.

During the clinical examination, the presence of a vegetating lesion with granulomatous and ulcerated surface was observed, with hemorrhagic areas, characterized as moriform stomatitis. The lesion stretched throughout the lower lip mucosa, and the same clinical pattern was present in the anterior gingival region and floor of the mouth, without delimited margins (Figure 1a). Hardened and bloody edges (Figure 1b) were observed on palpation. The patient did not report any pain. Based on clinical presentation, two main diagnostic hypotheses were proposed: SCC and PCM.

The area with hardened and irregular edge, along with the ulcerated region, was chosen for incisional biopsy, considering that there would be more morphologically altered cells in connective tissue and in the tissue deployment area. The intraoperative and the postoperative period passed without complications. The patient received a prescription of 500 mg of sodium dipyrone to be taken every six hours for three days, and all postoperative instructions were delivered both verbally and in written form.

The surgical specimen was sent to the Oral Pathology Laboratory of the Nova Friburgo Health Institute at Universidade Federal Fluminense (ISNF/UFF), in the state of Rio de Janeiro. Partial loss of epithelial integrity and pseudoepitheliomatous hyperplasia were observed microscopically in some areas. In connective tissue, a granulomatous appearance was noted, with the presence of epithelioid macrophages and multinucleated giant cells with *Paracoccidioides brasiliensis* inside, which led to the final diagnosis of PCM (Figure 2a and B).

Prescribed treatment was the use of 200mg itraconazole once daily for nine months. However, the patient reported that, on his own, he suspended the use of the medicine after completing six months of treatment and that he no longer had medical follow-up.

The patient returned to FAINOR School Clinic to undergo intraoral physical examination again. The loss of the lower right lateral incisor was observed, probably caused by periodontal disease. In addition, clinical evaluation of the labial mucosa, gingiva, and floor of the mouth revealed complete remission of PCM.

Figure 1 - Clinical features of the oral lesion. (A) Vegetative lesion with a superficial appearance of moriform stomatitis, with loss of epithelial continuity in the lower labial mucosa region (arrow). (B) A more pronounced pattern is seen in the intraoral region, but with erythematous color and diffuse appearance in the inserted gingiva extending to lingual region, which appears hemorrhagic upon palpitation.

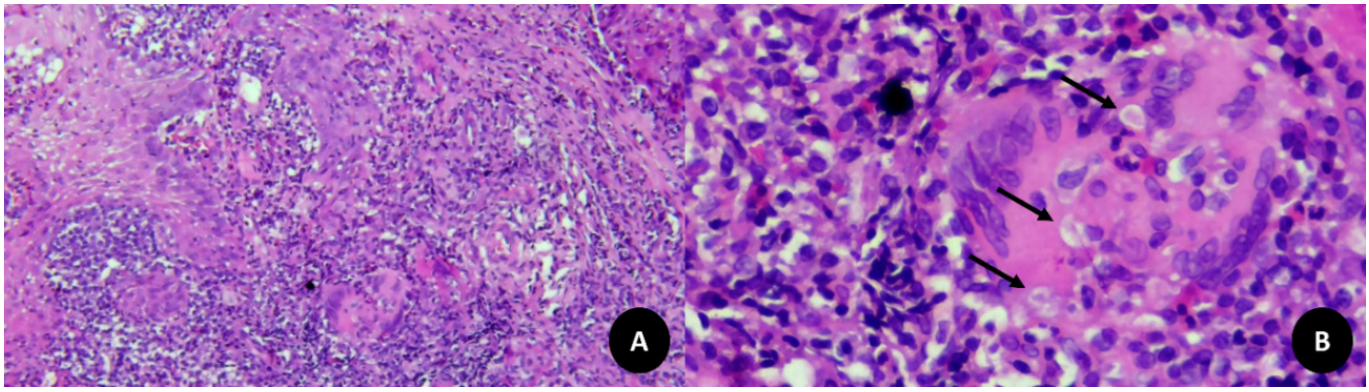

Figure 2 - Microscopic characteristics. A) Pseudoepitheliomatous invasion and intense inflammatory subepithelial infiltrate with the presence of multinucleated giant cells and dispersed epithelioid macrophages in connective tissue (hematoxylin and eosin staining, X50). (B) In the magnified image, the presence of yeast of Paracoccidioides brasiliensis (arrow) was observed inside a multinucleated giant cell (hematoxylin and eosin staining, X400).

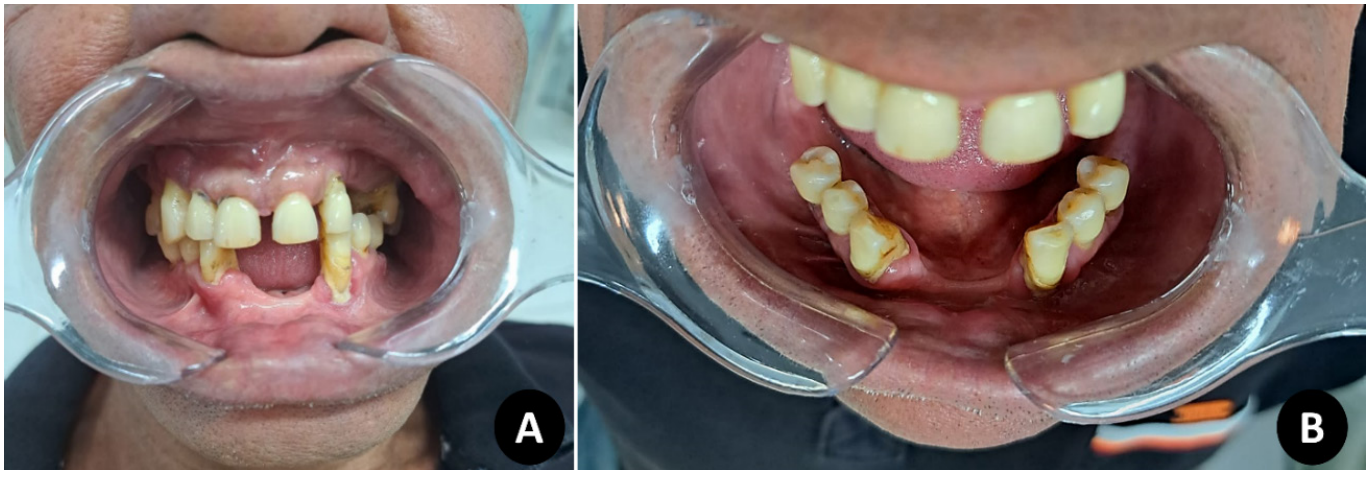

Figure 3 - Clinical characteristics after treatment for PCM. (A) and (B) Intact and normocolored mucous membranes after antifungal treatment prescribed by the infectologist. It is noteworthy that the patient did not complete the nine months of treatment with itraconazole.

DISCUSSION

PCM is a systemic mycosis caused by the dimorphic fungus *Paracoccidioides brasiliensis*, which preferably affects the rural population due to occupational exposure and the inhalation of conidia present in the soil (5). States with an agricultural lifestyle such as Rio Grande do Sul, Minas Gerais, Paraná, Espírito Santo, and São Paulo record more cases of oral PCM (2). The disease is predominant in men (5,6) due to greater occupational exposure in agriculture and the influence of estrogen, which provides women with hormonal protection by inhibiting the transition from the fungus to its pathogenic form (9,10).

In addition, the most affected patients are adults, between 30 and 50 years of age, chronic smokers and/or alcohol users, residing in rural areas, with precarious hygiene and a low socioeconomic status (10-12). These characteristics are present in the case reported, because the patient is older, chronic smoker, and lives in adverse conditions in rural area.

The main sites affected by PCM are the lungs, lymph nodes, and skin. Nevertheless, there is a high incidence in the oral cavity regions in South America, especially in Brazil, Mexico, and Venezuela, with rates ranging from 29.3% to 66.0% (9,.13-15). The most commonly affected places in the oral cavity include the gingiva/alveolar ridge, palate, lips, and buccal mucosa (13).

Clinically, the chronic manifestation of PCM in the oral cavity is characterized by one or multiple surface lesions that vary from granulomatous to ulcerated, often presenting hemorrhagic petechiae, known as moriform stomatitis (13). These lesions are frequently painful (9), although the analyzed patient has denied this symptom. Other systemic signs, such as a non-productive cough, fever, hemoptysis, dysphagia, and dyspnea may arise concomitantly (5), but were not reported by the patient. Studies suggest that the use of plant-based materials, such as toothpicks, may be a source of infection (9-10). In addition, according to Brazão-Silva et al. (9), inflammatory mediators from pre-existing periodontal disease may favor the installation of *Paracoccidioides brasiliensis*, although further studies are needed to prove this relationship.

Differential diagnoses of PCM include SCC, syphilis, histoplasmosis, leishmaniasis, tuberculosis, and lymphoma (9,10). Among malignant neoplasms, SCC is the most common and can affect the same regions or adjacent tissues affected by the PCM. Azevedo et al. (16) reported a case of coexistence of PCM and SCC, highlighting similarities in clinical characteristics, sex, age, and social behaviors of the patients. This justifies the inclusion of SCC as a diagnostic hypothesis in this case, since the patient was a middle-aged male chronic smoker.

PCM diagnosis is based on the clinical characteristics of the lesion, microscopic analysis of tissue samples, and chest radiography (2). However, not all these exams are promptly available to the requesting professional. Techniques such as incisional biopsy and oral exfoliative cytopathology can be easily performed by the stomatologist (2). In the Unified Health System, incisional biopsy in the oral cavity is performed in patients referenced to the Dental Specialty Centers (17).

Microscopically, the oral PCM has pseudoepitheliomatous hyperplasia, which can mimic the true carcinomatous invasion observed in SCC. The main histopathological feature of PCM is the presence of *Paracoccidioides brasiliensis* inside multinucleated giant cells, often linked to the mother cell, giving the characteristic aspect known as “Mickey Mouse ears” or “steering wheel” (18). Special staining methods such as Grocott-Gomori’s methenamine silver (GMS) and Periodic Acid-Schiff (PAS) can facilitate fungus visualization (3,16,18). Nevertheless, in the case reported, hematoxylin and eosin (HE) staining was sufficient to identify the microorganism.

According to Shikanai-Yasuda et al. (2017) (19), itraconazole at the 200mg/day dose for nine to 12 months is the recommended treatment for the moderate clinical manifestations of PCM, as performed in the case studied. At advanced stages or in immunosuppressed patients, amphotericin B can be used. Other azole antifungals derived from sulfonamide and amphotericin B are effective for different clinical forms of the disease (20-22). Photodynamic therapy (PDT) can be used as a complementary treatment, assisting in the healing and decontamination of the region (20-22).

Relapses are common, especially when the patient discontinues treatment, which is a possibility in the case reported, given that the patient reported abandoning medical follow-up and the use of medication. Furthermore, the disease may manifest decades after the initial infection (23). The prognosis is favorable with early diagnosis and proper treatment. Nonetheless, in cases of late diagnosis or inadequate treatment, the prognosis becomes unfavorable and may evolve to severe impairment of vital organs and death (5).

CONCLUSION

PCM and SCC share similar clinical and microscopic characteristics, which may result in misdiagnoses. Considering that the oral cavity is a region often affected by PCM, it is essential that health professionals, especially in endemic areas, recognize the clinical profile of the disease and include it among diagnostic hypotheses. Biopsy plays a crucial role in confirming the final diagnosis. The prognosis is directly related to the severity of the disease, the time to establish the diagnosis, and the adequacy of the prescribed treatment. It is noteworthy that the treatment for PCM is prolonged and demands continuous follow-up by infectologists and stomatologists, both during and after its completion, to minimize the risk of relapse and complications.

The authors have no conflict of interest to declare.

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