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Case Report

Oral Lesions as the First Clinical Sign of Multifocal Paracoccidioidomycosis: A Case Report

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Abstract: To report a multifocal case of paracoccidioidomycosis (PCM) with oral, pulmonary, and adrenal involvement, highlighting diagnostic challenges and the role of dental professionals in early detection. A 50-year-old Brazilian man, smoker, and alcohol user presented with oral ulcers, weight loss, and respiratory symptoms. Clinical, histopathological, and imaging analyses confirmed PCM by Paracoccidioides brasiliensis with pulmonary and adrenal dissemination. Treatment included liposomal amphotericin B, hydrocortisone replacement, and photodynamic therapy (PDT) for oral lesions, followed by sulfamethoxazole-trimethoprim maintenance. Combined therapy led to resolution of oral and cutaneous lesions, respiratory improvement, and adrenal stabilization. After 10 months, the patient showed weight gain and no recurrence. Despite Brazil's high PCM prevalence, delayed diagnosis remains common due to non-mandatory reporting and limited professional awareness. Oral manifestations preceded systemic symptoms, emphasizing the dentist's role in early diagnosis. PCM is an underdiagnosed systemic mycosis with potentially severe outcomes. Recognition of oral lesions as early indicators enables timely intervention and prevents systemic complications. Strengthening awareness among dental and medical professionals, along with improved epidemiological surveillance, is essential to enhance prognosis and reduce morbidity.

Keywords: Paracoccidioidomycosis; Oral Ulcer; Prevalence; Delayed Diagnosis.

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1. Introduction

Paracoccidioidomycosis (PCM) is an endemic fungal infection in the tropical regions of Latin America, caused by the fungus *Paracoccidioides brasiliensis* [1-3]. This etiological agent was first described in Brazil by the researcher Adolpho Lutz in 1908, marking an important milestone in the understanding of systemic mycoses.[4] PCM is considered an occupational disease, as it is closely associated with activities involving soil disturbance, such as agricultural practices, deforestation, and earthworks. In addition to environmental sources such as soil and dust particles, which may carry the fungus in suspension, current evidence points to the nine-banded armadillo (*Dasypus novemcinctus*) as a likely natural reservoir for the pathogen [3-5].

A higher prevalence is observed in men, since the transformation of *P. brasiliensis* into its pathogenic yeast form is inhibited by the female hormone 17-β-estradiol, which plays a crucial role in disease development [6, 7]. The disease primarily affects individuals be-

tween 30 and 50 years of age. Clinically, PCM is characterized by cutaneous lesions, lymphadenopathy, and pulmonary involvement. Oral manifestations often include superficial ulcers with a tendency to bleed, displaying a mulberry-like appearance [3, 6, 8].

Although PCM is classically restricted to endemic areas in Latin America, several studies have reported imported cases in non-endemic regions, particularly in Europe and North America, due to migration, tourism, or occupational exposure abroad [9-11]. These cases highlight the growing global relevance of neglected tropical mycoses, which often pose diagnostic challenges in countries unfamiliar with their epidemiology [12]. Misdiagnosis and delayed recognition are frequent in these scenarios, potentially leading to severe systemic complications.[13] Therefore, increasing awareness of PCM beyond its endemic regions is crucial for early detection and appropriate therapeutic management [14].

This report presents a case of paracoccidioidomycosis with muco-cutaneous, pulmonary, and adrenal involvement in a 50-year-old man with a 5-year clinical course of the disease. In addition, we discuss the main clinical features and therapeutic management of the case.

2. Case Report

A 50-year-old Black Brazilian man from a rural area, with a long-standing history of tobacco and alcohol use, presented with painful, ulcerated, mulberry-like lesions in the oral cavity that had progressively worsened over the past five years. The patient reported that the COVID-19 lockdown significantly hindered his ability to seek medical care in the city, delaying diagnosis and treatment. He also described an unintentional weight loss of 13 kg over the previous two months, primarily due to difficulty swallowing solid foods and even water. Additional symptoms included a dry cough, fatigue, and episodes of nocturnal fever. Extraoral examination revealed crusted lesions in the perioral region and on the glabella, along with inflammatory cervical lymphadenopathy, trismus, sialorrhea, and impaired speech (Figure 1).

Based on clinical presentation and patient history, a provisional diagnosis of paracoccidioidomycosis (PCM) was established. This was confirmed by an incisional biopsy of the lateral border of the tongue, which revealed a chronic granulomatous inflammatory process characterized by multinucleated giant cells and numerous yeast-like fungal structures (Figure 2). Imaging studies demonstrated bilateral adrenal thickening. Laboratory tests revealed elevated ACTH levels associated with low morning cortisol, a hormonal profile consistent with primary adrenal insufficiency secondary to fungal infiltration of the adrenal cortex, as commonly reported in disseminated PCM.

The patient was hospitalized for 20 days and received hydrocortisone replacement therapy along with liposomal amphotericin B. As an adjunct to systemic antifungal therapy, photodynamic therapy (PDT) was administered to reduce local pain and fungal burden in the oral cavity. PDT was performed using methylene blue (0.01%) as a photosensitizer, activated by red and infrared laser light at an energy dose of 6 J per point. Although PDT is not considered standard of care for deep fungal infections such as PCM, its use has been reported in other subcutaneous mycoses. The patient received detailed information regarding its experimental nature and signed a specific informed consent form. No adverse events were observed. Clinical improvement of the oral lesions occurred in parallel with systemic antifungal therapy during hospitalization.

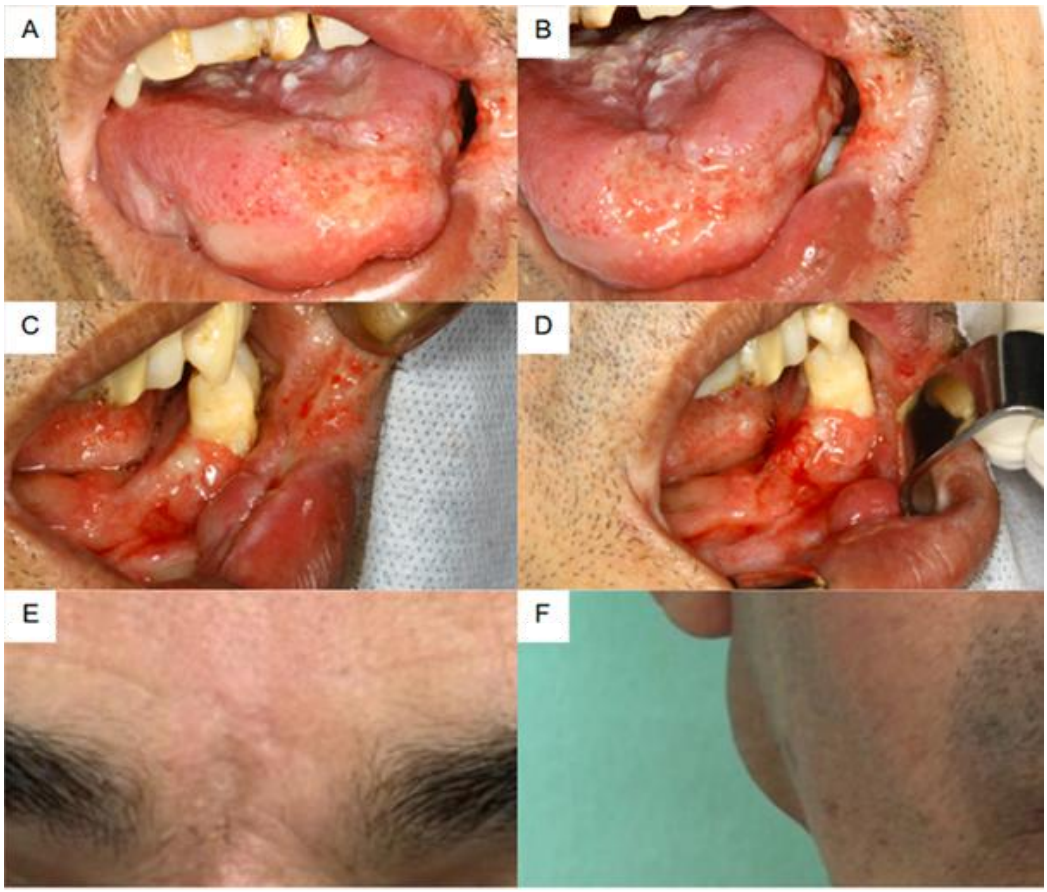
After discharge, treatment was continued at home with hydrocortisone and Bactrim® (sulfamethoxazole 800 mg + trimethoprim 160 mg), leading to significant clinical improvement, including near-complete regression of the oral lesions and a 20 kg weight gain after 10 months of follow-up.

3. Discussion and Conclusion

PCM remains a neglected tropical disease in Brazil, despite its significant prevalence in endemic regions such as the Southeast, South, and Center-West of the country [10, 15].

Its status as a non-mandatory notifiable disease hampers robust epidemiological surveillance, contributing to underdiagnosis and delayed treatment [16]. This public health gap is particularly concerning given the disease's potential for systemic dissemination, chronicity, and impact on quality of life. Consistent with epidemiological trends reported in the literature, PCM predominantly affects adult males between the third and fifth decades of life, a pattern also reflected in the clinical profile of the patient in this case [17-19].

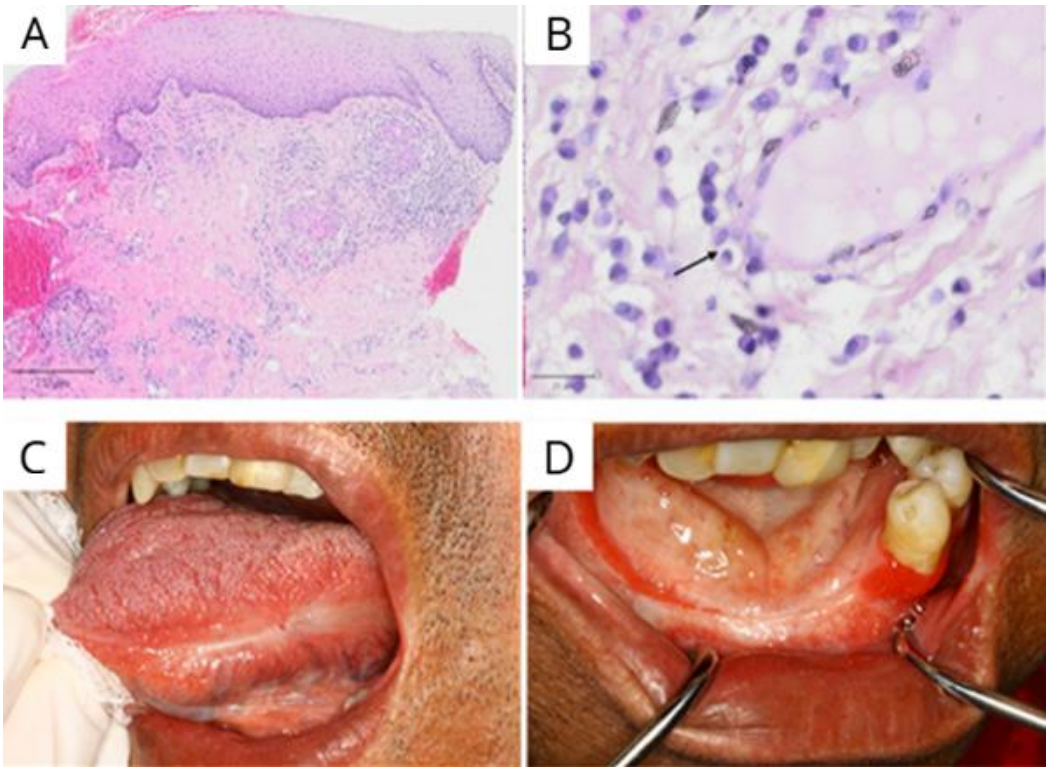
Figure 1. A to D. Mulberry-like lesions affecting tongue, oral commissure, buccal mucosa, and gingiva. E. Cutaneous lesion located in the glabellar region. F. Volumetric enlargement in the submandibular region, consistent with inflammatory lymphadenopathy.



The oral clinical manifestations of PCM are well established in the literature and are like the results described in our investigation. They are characterized by multiple or isolated lesions, with mulberry-like morphological features, exhibiting a granular surface, erythematous coloring and irregular margins. These lesions are often found on the lips, gums, alveolar ridge, and hard palate, although reports also point to occurrences in other areas of the oral. In addition, symptoms such as pain, difficulty in chewing, and halitosis are related [3, 17, 20].

Although the patient lived with oral lesions for approximately five years, the transition to systemic involvement likely evolved gradually and went unnoticed because of multiple barriers. He sought care from various professionals during this time, yet the diagnosis remained elusive. The onset of the COVID 19 pandemic further restricted access to healthcare services, leading to delays in follow up and diagnosis, a phenomenon well documented among neglected tropical diseases [21]. Despite negative serologic testing for HIV and absence of diabetes or liver dysfunction, his prolonged alcohol and tobacco use may have impaired immune defense and facilitated deeper fungal invasion. These factors taken together contributed to the shift from a localized to a disseminated clinical presentation of PCM.

Figure 2. A. Photomicrograph showing epithelial hyperplasia and a chronic granulomatous inflammatory process in the oral lesion tissue (Hematoxylin & Eosin [H&E] stain). B. Section stained with the Periodic Acid–Schiff (PAS) method reveals a large Paracoccidioides yeast cell (arrow) with daughter buds resembling the classic "Mickey Mouse ears" morphology, phagocytosed within the cytoplasm of a multinucleated giant cell. C to D. Patient follow-up after 10 months of treatment showing significant regression of the lesions.



Once diagnosed, the patient underwent a combined therapeutic approach with liposomal amphotericin B, indicated for severe and disseminated cases due to its reduced nephrotoxicity compared to the conventional formulation, and Bactrim® (sulfamethoxazole 800 mg + trimethoprim 160 mg; SMX-TMP), a synergistic antimicrobial combination also effective against Paracoccidioides spp. This regimen was selected for maintenance therapy over itraconazole due to the patient's history of chronic alcohol use and the associated risk of hepatotoxicity. This choice is supported by the Brazilian Ministry of Health guidelines for PCM, which recommend SMX-TMP as a suitable alternative in cases with potential hepatic comorbidities. The treatment regimen proved effective in controlling the infection, leading to significant lesion regression and overall clinical improvement.

In addition to systemic antifungal therapy, the patient received PDT to manage extensive oral lesions. Although not currently considered standard of care for PCM, PDT was applied under an institutional protocol as an adjunctive local treatment aimed at reducing fungal burden and symptomatic discomfort. This decision was supported by literature highlighting the potential of PDT in fungal infections, particularly those involving superficial or mucocutaneous sites. A recent review reported its effectiveness in oral candidiasis, onychomycosis, and tinea infections, and described benefits in deeper mycoses such as chromoblastomycosis and mucormycosis when used in combination with systemic antifungal agents [22]. Given its favorable safety profile and localized mechanism of action through reactive oxygen species generation, PDT may serve as a supportive therapeutic option in selected cases of disseminated fungal disease affecting the oral cavity.

Adrenal involvement in PCM occurs when *Paracoccidioides brasiliensis* disseminates beyond the lungs, reaching endocrine structures through hematogenous or lymphatic

spread [23,24]. The adrenal glands are particularly vulnerable due to their high local steroid concentrations, which create an immunosuppressed microenvironment that facilitates fungal persistence [22,26]. These glands are considered potential "sanctuaries" where the pathogen may evade antifungal activity, even after systemic therapy [23,25].

While autopsy studies have reported adrenal invasion in up to 85–90% of fatal cases [23, 27, 28], functional insufficiency is observed in 44–48% of patients based on serum cortisol levels [23]. Imaging modalities such as CT, ultrasound, and nuclear medicine can also reveal subclinical involvement [29], reinforcing the importance of thorough endocrine evaluation in suspected disseminated cases.

In the present case, adrenal dysfunction was confirmed through hormonal and imaging findings, highlighting a chronic and severe clinical manifestation of PCM [3]. Early diagnosis and intervention are essential to prevent endocrine-related complications. Additionally, the submandibular lymphadenopathy observed reflects lymphatic dissemination of the fungus [9], underscoring the importance of differential diagnosis, particularly to distinguish PCM from other infectious or neoplastic diseases.

This case underscores the critical role of dental professionals in the early recognition of oral lesions as potential indicators of systemic mycoses such as PCM. The five-year diagnostic delay, exacerbated by socioeconomic vulnerability and restricted healthcare access during the COVID-19 pandemic, illustrates how systemic barriers can contribute to disease progression and severe clinical outcomes. The use of PDT as an adjunct to systemic antifungal treatment demonstrated promising local effects and highlights the potential value of supportive, site-specific interventions in managing extensive mucosal involvement. Overall, this case reinforces the importance of integrated, multidisciplinary care and suggests that individualized therapeutic strategies, guided by both clinical presentation and patient context, can significantly improve outcomes in disseminated PCM.

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Research Ethics Committee Approval: The patients provided written informed consent to participate in the study, which was conducted in accordance with the ethical principles of the Declaration of Helsinki.

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