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Oral paracoccidioidomycosis and pulmonary tuberculosis co-infection: relevance of oral biopsy in establishing the diagnosis and therapeutic approach

We report herein a case of concomitant oral paracoccidioidomycosis (PCM) and pulmonary tuberculosis (TB) infection in a Brazilian patient. This paper highlights the relevance of clinical and laboratory evaluation of oral lesions in the prevention, early diagnosis, and treatment of pulmonary diseases. Oral lesions are usually more accessible for sampling and can be an important marker for pulmonary fungal and bacterial illnesses.

A 47-year-old Caucasian male patient was referred to the Oral Medicine Reference Unit by his infectious disease specialist, due to a medical history of a 5-month painful oropharyngeal ulcer associated with recent weight loss, coughing, and difficulty swallowing. Physical examination revealed a bilateral submandibular lymph node enlargement, and during intra-oral examination, an extensive erythematous and granulomatous soft palate ulcer involving the uvula and the oropharynx was observed (Figure 1).

The patient reported smoking (20 cigarettes/day for 25 years) and occasional weekly alcohol consumption, but no other drug use. He reported taking part in rural activities, mainly agricultural, from 14 to 35 years of age. An initial



Figure 1 Initial clinical presentation. Extensive oropharyngeal ulcer and uvula destruction.

diagnosis of oral squamous cell carcinoma or paracoccidioidomycosis was established. An oral biopsy was immediately performed of the soft palate ulcer. Acid-fast bacilli (AFB) sputum investigation, anti-HIV antibodies by ELISA testing, and a chest radiograph were also requested. Radiograph images confirmed the diagnosis of tuberculosis with pulmonary involvement (Figure 2), and the sputum AFB was positive. The anti-HIV test was negative.

Tuberculosis treatment was initiated with daily administration of rifampin, isoniazid, and pyrazinamide (RIP). Histological analysis of the oral sample performed after initial



Figure 2 Evidence of parenchymatous infiltrate compatible with tuberculosis on chest X-ray, confirmed by acid-fast bacilli (AFB) sputum analysis.

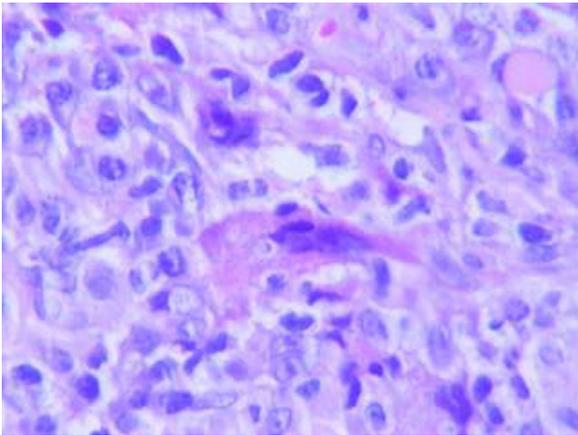


Figure 3 Oral sample: hematoxylin–eosin stain of granulomatous reaction, giant multinucleated cells, and *Paracoccidioides brasiliensis* (400×).

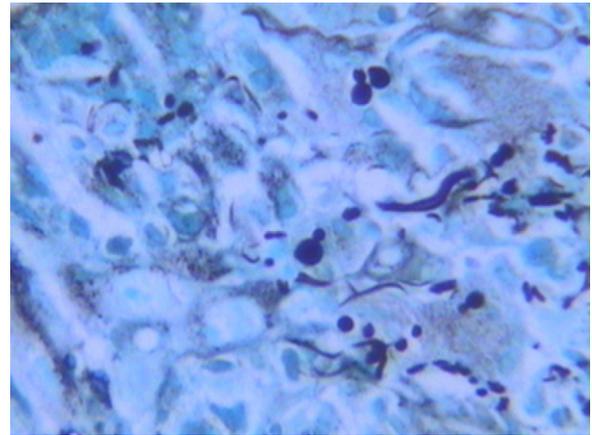


Figure 5 Grocott–Gomori staining; evidence of *Paracoccidioides brasiliensis* in the oral sample.

tuberculosis diagnosis identified a *Paracoccidioides* infection (Figure 3). The oral specimen was tested using periodic acid–Schiff's reaction (PAS) and Grocott–Gomori and Ziehl–Neelsen stains; PAS and Grocott–Gomori staining were positive for fungal infection (Figures 4 and 5), while Ziehl–Neelsen staining was negative.

Mycobacterium tuberculosis and *Paracoccidioides brasiliensis* were not cultured nor identified by PCR. These are not routine tests for pathogen identification in the Brazilian public health system. Oral examination results were sent to an infectious disease specialist who prescribed itraconazole in addition to the tuberculosis regimen. However, itraconazole was discontinued after two weeks due to interaction with RIP and was substituted with trimethoprim–sulfamethoxazole (TMP–SMZ). Partial regression of the oral lesion was observed within one month (Figure 6), with no further symptoms and with complete healing of the oral lesion within three months (Figure 7).

PCM and TB co-infection is rarely reported in the English literature, probably due to the fact that the endemic PCM deep fungal infection is prevalent mostly in Latin America,

particularly in the subtropical regions of Brazil and Argentina.^{1–3} However, PCM and TB co-infection has been described in greater numbers in regional and local medical journals.^{4–8} A retrospective study published in Brazil found that 36 out of 227 PCM patients had previously been treated for TB, while only 18 had positive direct smear microscopy for *Mycobacterium tuberculosis*.⁵ In a recent Brazilian cohort study, 23 of 422 PCM patients were diagnosed with TB.⁶ Another study found that 28 of 147 PCM-confirmed patients were TB-positive.⁷ Case reports on the association between PCM and TB have also been published for AIDS patients,⁹ as well as an unusual case of both infections in a child with multiple osseous lytic lesions and hypercalcemia.¹⁰ European authors have reported cases of 'imported' PCM that had been previously misdiagnosed as TB or other pulmonary diseases, stressing the relevance of differential diagnosis.^{11–13} The present case illustrates a co-infection of PCM and TB where oral lesion investigation was decisive for treatment choice.

Oral granulomatous lesions are very common in PCM active infected patients presenting pulmonary involvement.^{14,15} Although it is well known as a frequent pulmonary fungal disease among South Americans, it is less frequently observed than TB at primary care services, even in this endemic region. This could explain why healthcare workers worldwide are

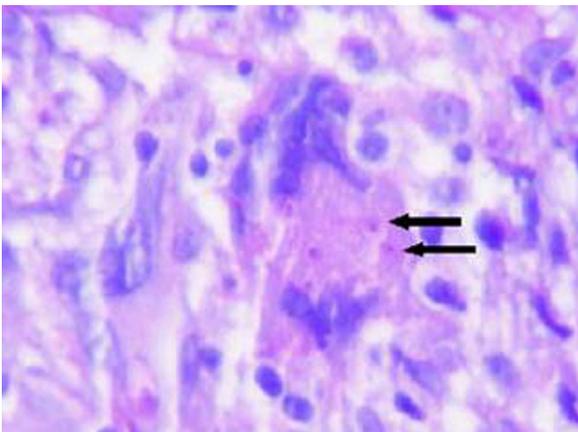


Figure 4 Periodic acid–Schiff's (PAS) positivity of fungal infection of oral sample. *Paracoccidioides brasiliensis* (arrows) (hematoxylin–eosin stain, 400×).



Figure 6 Clinical presentation at 1-month post-treatment.



Figure 7 Clinical presentation at 3-months post-treatment.

much more aware of TB than a PCM diagnosis when diagnosing a patient presenting with a history of weight loss, dry cough, and opacities visible on chest radiograph.¹² Oral manifestations are considered rare in primary or secondary TB. Lesions are described more frequently in the tongue, floor of the mouth, and hard palate.¹⁶ Both diseases can show similar oral manifestations, including non-healing extensive ulcers with indurate borders and a granulomatous aspect. An important confounding factor is that PCM has also been reported in HIV-infected patients.^{11,13} Although PCM is more frequently associated with oral lesions, usually present in approximately 50% of cases,¹⁵ its lower prevalence and the difficult recognition of oral manifestations often lead to a delay in correct diagnosis. Previous research has suggested that the low prevalence of oral lesions could be problematic in the diagnosis of TB.¹⁶ Clinicians, particularly those unfamiliar with oral mucosa lesions, tend not to include diagnoses of TB and PCM in their differential hypotheses for oral lesions.^{11,16} Oral biopsy and oral cytology are considered diagnostic for PCM infection, and samples can be collected utilizing low invasive procedures compared to other tissue samples, such as lungs or lymph nodes.¹⁵

The present case highlights the importance of investigating oral lesions in the presence of signs, symptoms, and laboratory tests compatible with TB. Oral tissue investigation has the advantage of easy accessibility to sampling procedures, either cytological or histological. Thus accessibility can facilitate diagnosis of mixed infections, particularly PCM, in patients arriving from or living in Latin American countries.

Conflict of interest: No conflict of interest to declare.

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