A diagnostic challenge in an individual with Paracoccidioidomycosis during hospitalization in times of COVID-19

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ABSTRACT

Paracoccidioidomycosis (PCM) is a deep fungal infection, endemic with considerable morbidity in South America, whose first symptoms can occur in the oral cavity. A 47-year-old male patient, leucoderma, living on the streets, presenting dyspnea, pain during the speech, and dysphagia, was referred for admission to the ICU for suspected COVID-19 infection. The intensive care physician's evaluation revealed a tongue lesion with suspected carcinoma. By dentist investigation was observed the presence of moriform lesions with high borders delimitation in the tongue. Also, granulomatous ulcers with irregular texture, suggesting moriform stomatitis, the chest tomography revealed diffuse thickening of the bronchial walls, indicating chronic bronchopathy with discrete centrilobular nodules, sometimes confluent. Incisional tongue biopsy associated with lung imaging confirmed the diagnosis of PCM, and the patient was referred to the referral center for the treatment of fungal diseases. The involvement of the oral environment as a region to the appearance of detectable first symptoms of PCM suggests the need for the oral evaluation by a specialist as a diagnostic tool.

Keywords: Fungal Infection; Paracoccidioidomycosis; Oral Diagnosis

1. Introduction

Paracoccidioidomycosis (PCM) is a systemic mycosis originally described by Adolfo Lutz in 1908, with an endemic character in Latin America, with the highest incidence recorded in countries south of the continent (Brazil, Argentina, Colombia, and Venezuela). In Brazil, most cases were reported in the south, southeast, and central-west regions[1]. It is called South American Blastomycosis being a deep fungal infection caused by *Paracoccidioidesbrasiliensis*. The main risk infection factor is contact with contaminated soil by the fungus. In most cases of PCM infection, patients were exposed to the etiological agent during agricultural activities in the first two decades of life, regardless of the clinical manifestations appearing many years later[2,3].

Considered the fungal infection with the highest morbidity in Latin America, the recognition of lesions present in the oral environment is an important opportunity for an early diagnosis, considering that usually, the appearance of clinical manifestations occurs in the oral mucosa, remaining with other latent symptoms for periods of indefinite time[4]. The fungal lesions present themselves uni and multilocular, and in most cases, multilocular dissemination predominates in the gingiva, alveolar crest, palate, buccal mucosa, and tongue, becoming the most frequent places for their appearance[5].

Due to its systemic nature, fungal infection by PCM can affect any anatomical site. However, it is extrapulmonary lesions, especially lesions in the oropharynx, which usually motivate the first consultation, even though the lung is known to be the entry point for the fungus. A significant percentage of individuals classified as chronic have significant respiratory manifestations such as cough associated with episodes of dyspnea[6].

The difficulty in diagnosing PCM is due to the picture that its symptoms are similar to those of tuberculosis (TB), which can also be confused with some carcinomas or even protozoan infections such as mucocutaneous leishmaniasis[7].In the early stages of the disease, clinical and radiological signs do not always allow a clear distinction between PCM and TB. Due to this, they can occasionally be a confounding factor in diagnosing moderate to severe COVID-19. The main symptoms of the unifocal form of PCM are weakness, emaciation, fever, cough, dyspnea, reticulonodular infiltrates, and distal bibasal hypertransparency. In the multifocal form, the disease affects other organs besides the lung, such as the skin, oral mucosa, pharyngeal mucosa, larynx, and the apex of teeth (causing pain during chewing, drooling, and odynophagia)[8].

Patients with immunological impairment or systemic changes that interfere with the immune response, such as diabetes or even depression, tend to have more severe infectious processes, and the presence of pathognomonic lesions in the oropharynx can be considered indicative of lung impairment[9]. As a rule, the risk of developing the disease in its clinical form is related to the personal characteristics and lifestyle of the infected individuals, including genetic background, age, sex, ethnicity, smoking, chronic alcohol abuse, or even occasional episodes of immunosuppression[10,11].

By the relevant details involving the episodes of infection and, above all, diagnosis, this article aims to corroborate the consolidation of the dentist and physician in the importance of clinical knowledge as a fundamental tool in the diagnosis of systemic diseases that manifest symptoms in the stomatognathic system.

2. Case Report

A 47-year-old male patient, Caucasian, homeless, was admitted to the ICU with dyspnea, complaints of pain during the speech, difficulty eating, and dysphagia, with suspicion of COVID-19. During the admission process, the patient was classified as Glasgow 12, RASS (-1), sleepy but collaborative, with isochoric and photo-reactive pupils, stable cardiocirculatory system, sinus heart rate between 60 and 80 bpm, blood glucose 145-90 mg/dl, and (+) 756 fluid balance, 1ml in 12h, respiratory rate of 17rpm, Fl02: 18% and SPO2: 94%, normotrophic muscular motor system, without edema and free calves, presenting values around 70% for the scale of Karnofsky's performance. The presence of a lesion in the tongue suggestive of carcinoma was observed by the intensive care physician, indicating the need for evaluation by the Hospital Dentistry team.

The clinical dental examination revealed the presence of well-delimited, coarse moriform lesions with raised edges all over the tongue, and granulomatous ulcers of irregular texture, with hemorrhagic spots, of the moriform stomatitis type all over the tongue (Figure 1).

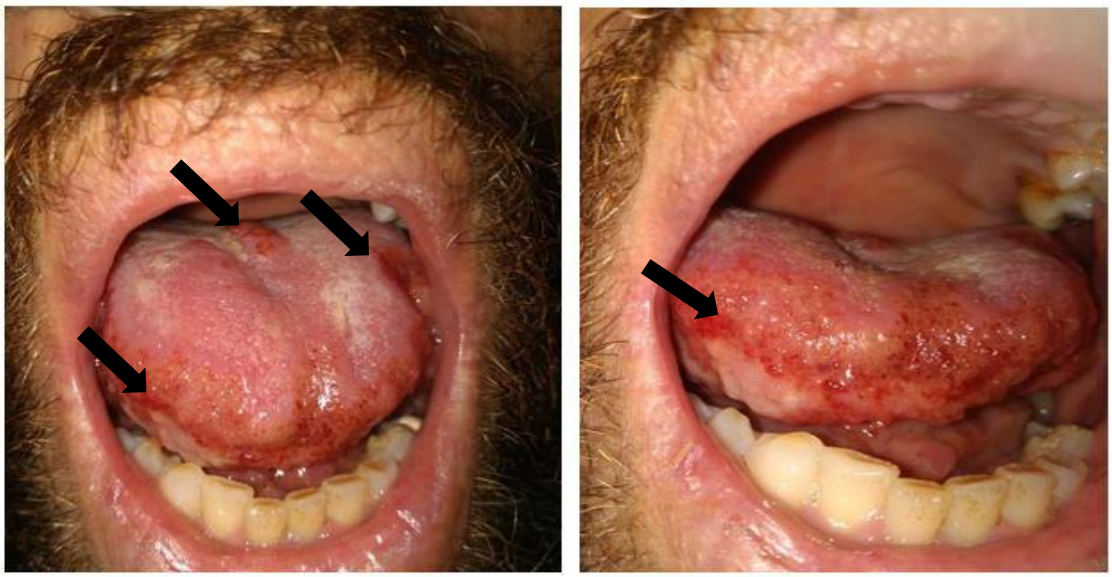

Figure 1: Well-delimited moriform lesions, coarse and with high edges throughout the tongue, granulomatous and irregular ulcers were also observed.

In view of the oral evaluation and clinical investigation, a computed tomography scan of the chest was requested (Figure 2), which revealed that the patient had diffuse thickening of the bronchial walls, indicating chronic bronchopathy and discrete centrilobular nodules, sometimes confluent, often characterizing trees in budding, possible correlation to bronchiolopathy inflammatory.

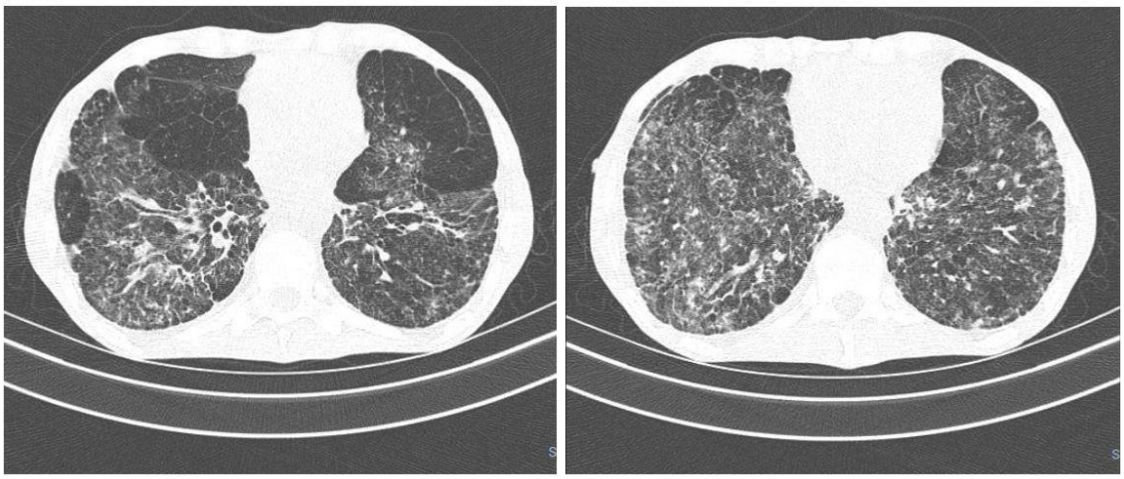

Figure 2: CT images with sections of the upper 1/3 of the lung structure showing diffuse thickening of the bronchial walls, indicating chronic bronchopathy and discrete centrilobular nodules, sometimes confluent.

After this result of the imaging exam and through the direction of the diagnostic reasoning, the presence of lesions on the hands and feet was found (Figure 3). When asked about the wounds, the patient reported that he had lived with them for approximately one year.

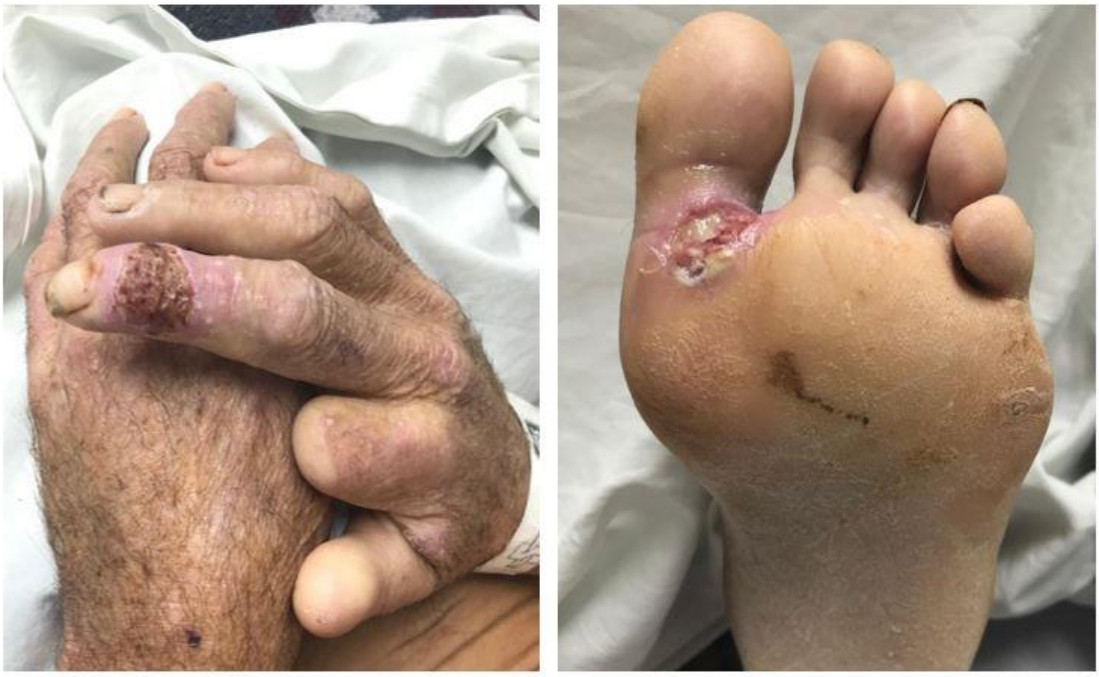

Figure 3: Ulcerated lesions on the hands and feet of an erosive character with a raised edge with hemorrhagic spots

Regarding oral health, the patient had painful symptoms and spontaneous gingival bleeding, with the absence of several dental elements and severe periodontal involvement, but no tooth mobility was identified. Through the symptoms as well as the patient's own reports, the hypothesis of a possible squamous cell carcinoma or serious oral manifestations resulting from COVID infection was raised, through incisional biopsy submitted to histopathological analysis (Figure 4) revealed the presence of dense connective tissue and granulomatous, with visible multinucleated giant cells containing microorganisms

inside, the lamina propria showed the presence of spherical fungi of varying sizes with a birefringent membrane, compatible with Paracoccidioides, more evident in PAS (Periodic acid Schiff).

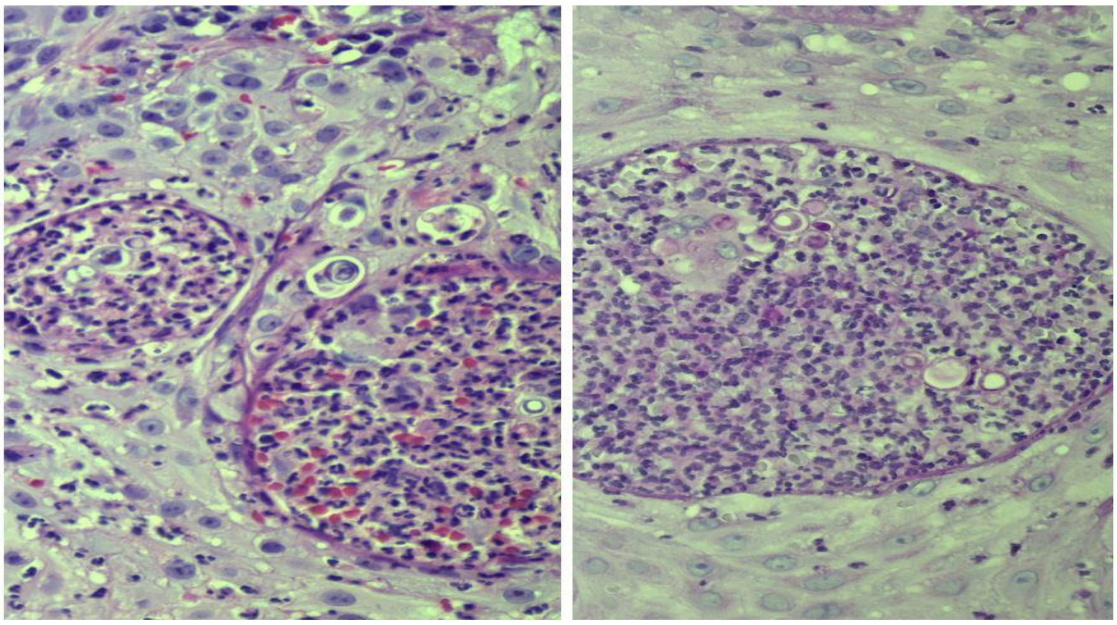

Figure 4: Histological sections showed the *Paracoccidioides brasiliensis* fungus yeast inside a multinucleated giant Langhans cell. Lamina propria showing chronic granulomatous inflammation.

In view of this information and due to the lack of confirmation of the presence of viral RNA of SARS-CoV-2, ruling out positivity for COVID, he was discharged from the ICU, and with a positive diagnosis for PCM, the patient was referred to the referral center for treatment of fungal diseases.

3. Discussion

SARS-CoV-2 develops well in the oral environment because it is the first contact area of the virus with the new host, but also because the mucosal tissue in the region presents a significant expression of the Angiotensin-converting enzyme 2 (ACE2), favoring viral replication, producing lesions and characteristic symptoms. Generally, the manifestations of COVID infection in the oral cavity are non-specific, and it is not clear whether such symptoms occur due to the disease itself or whether it arises due to the loss of the immune response[11,12]. Aphthous, herpes, and localized candidiasis lesions are the most common manifestations found in the oral mucosa, advanced age and the worsening of the clinical condition seem to be the predictors of more severe manifestations in the mouth. Lack of oral hygiene during hospitalization, opportunistic infections, stress, underlying diseases, and hyperinflammatory response secondary to COVID-19 may be considered the most important predisposing factors for the development of oral lesions in COVID-19[13] patients, a condition that can turn more difficult the differential diagnosis for other systemic diseases that have oral repercussions.

The literature frequently mentions that PCM diagnosis occurs mainly through oral lesions, epidemiological monitoring based on the resolution of oral and maxillofacial biopsies obtained in

specialized services corroborate to consolidate the oral environment as a simple and effective alternative for detecting the disease[14,15]. Upon the evaluation of about 320 PCM biopsy records analyzed in relation to the patient's gender, age, and occupation, the recurrence of lesions on the lips, gingiva/alveolar ridge, tongue, the floor of the mouth, buccal mucosa, the palate was observed and oropharynx, with the exception that the same patient may have been affected in more than one anatomical site[16](**Table 1**).

Table 01- Comparison of histopathological findings in the anatomical structures of the oral environment in individuals of both sexes who obtained a positive diagnosis for PCM via mouth biopsy.

Author & Date	Anatomical location					Sex		Diagnosis	
	Tongue	Proc. Alv	Lips	Mucosa	Palate	male	female	oral biopsy	Others
Arruda et al, 2018	1	1	1	-	-	1	-	1	-
Vicente et al, 2018	-	1	1	1	-	1	-	1	-
Tomoset al, 2020	-	1	-	-	1	1	-	1	-
Gomide et al, 2019	1	1	-	-	-	1	-	1	-
Paulo et al, 2014	1	1	-	-	-	1	-	1	-
Costaet al, 2021	-	1	-	1	-	-	1	1	-
Azenha et al, 2012	-	1	1	1	-	1	-	1	-
Yasuda et al, 2017	-	-	1	1	1	1	-	1	-
Andrade et al, 2019	-	-	-	1	-	1	-	-	1
Sanches et al, 2014	-	-	-	1	-	1	-	-	1
Trindade et al, 2017	-	1	1	1	-	1	-	1	-

Retrospective studies evaluating cases of patients known to be diagnosed with PCM observed the presence of oral lesions in all individuals evaluated, confirming the high stomatological incidence of the fungus, considering that prior to infection and impairment of the respiratory system, it tends to manifest itself in the oral structures, the importance of the presence of professionals capable of carrying out the diagnosis and early monitoring of the infectious process of patients with multidisciplinary teams is highlighted[17].

Most of those exposed to the fungus (*Paracoccidioidis brasiliensis*) develop an initial asymptomatic infection, and despite having granulomatous losses in the lungs and lymph nodes needed by primary complexes, which may remain latent in some, such nodules are concentrated before the infective strains that both may remain latent or migrate to other tissues, contaminating them, with the caveat that acute infectious processes are related to the speed of dissemination of this process[18]. Normally the evolution of PCM infection depends on the host's cellular immune response, more specifically on the activity of T cells. It is interesting to note that there is a variety of clinical manifestations, with each one being potentially associated with a specific pattern of immunity manifested by T24 cells[3]. In turn, individuals who do not develop the disease tend to exhibit a T-helper immune response pattern where the release of macrophage

activating cytokines favors the formation of compact granulomas and a reduction in the proliferative potential of the fungus[3,19].

One of the relatively frequent chronic clinical forms of the multifocal type of PCM is the cutaneous mucosal integumentary, characterized by lesions of the oral mucosa, gums, tongue, soft palate, and labial, nasal, pharyngeal, and laryngeal mucosa.[8]. Although the primary route of infection is pulmonary, through inhalation of spores or fungus particles, several anatomical sites can be affected by lymphohematogenous dissemination, including in the oral mucosa. The specificity of oral diagnosis by a specialized professional play a fundamental role in identifying these lesions, correct diagnosis and referral for appropriate treatment, careful clinical evaluation, and complementary tests, such as exfoliative cytology and incisional biopsy, are procedures of great value in the diagnosis of this disease[20,21]. It is worth remembering that surveys carried out in the first decade of the 21st century in Latin America already reported millions of patients having been tested positive for the presence of the pathogen; however, only approximately 2% of this population would develop characteristic clinical manifestations of the disease[22].

Systemic physiological impairment occurs from a chronic inflammatory process, usually evolving to the formation of fibrosis in the affected regions, capable of triggering the functional impairment of the organs affected by the infection, more specifically the lungs, adrenal glands, larynx, and central nervous system[9,23]. Due to its potential morbidity, it is highly recommended that patients with disseminated forms of PCM presenting neurological disorders, respiratory failure, nutritional status deficiency, gastrointestinal impairment, jaundice, ascites, or hemodynamic changes should be considered eligible for immediate hospitalization. Individuals with comorbidities such as Acquired Immunodeficiency Syndrome (AIDS), tuberculosis and/or neoplasms, decompensated Chronic Occlusive Pulmonary Disease (COPD), laryngeal or tracheal stenosis should also be considered for immediate admission[24]. In the period of the COVID-19 pandemic and pulmonary impairment, the diagnosis of PCM has also become a challenge, which creates the need to investigate the differential diagnoses of respiratory diseases associated with other systemic manifestations.

Currently, according to the national health policy, only cases characterized by the presence of clinical manifestations compatible with PCM and by histopathological identification of Paracoccidioides spp are considered eligible for specific drug therapy. As a rule, the choice of antifungal medication used should consider the severity of the clinical condition presented, have good rates of absorption through the gastrointestinal tract, as well as the presence of coexisting diseases. Cotrimoxazole is still the most used drug in the treatment of PCM, as it is provided free of charge to patients through the public health system.[25].

Population studies that follow the therapeutic evolution of patients affected by fungal infections report a higher rate of treatment dropout during follow-up precisely in the first four months, leading to the belief that patient adherence to long-term treatments for diseases with a chronic infectious profile is a challenge for clinical practice since the act of using prescribed medications and monitoring the therapeutic evolution consist of a behavioral profile that depends exclusively on the patient[20,17,27,28]

The literature has reinforced the need for surveillance and mandatory notification for paracoccidioidomycosis; actions capable of promoting environmental changes tend to facilitate contact with the etiological agent. Correct monitoring and geographic location of new cases would incur in

reducing the relative risks of human intervention in order to reduce and perhaps prevent future episodes of paracoccidioidomycosis infection[3,11,29].

4. Conclusion

Through the present exposure, this report aims to emphasize the importance of correct identification of oral manifestations, significantly those considered pathognomonic, so that they can help in the differential diagnosis of diseases that affect not only the stomatognathic system but the whole body. Specifically, in the case of paracoccidioidomycosis, biopsies in oral tissues are an essential tool capable of helping the medical team in the early and optimized treatment of an endemic disease with a high potential for morbidity.

6. Acknowledgement

This study was conducted without funding from any funding institutions or agencies. The execution fees were the responsibility of the researchers.

7. References

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