Paracoccidioidomycosis: Report Case

Paracoccidioidomicose: Relato de Caso

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ABSTRACT

Paracoccidioidomycosis is a fungal systemic disease with involvement of lungs and buccal mucosa.

Purpose: A clinical case report. **Case report:** A 48-year-old male (former smoker, alcoholic and drug user) was attended at the Stomatology Service, at Lins School of Dentistry (Lins – SP, Brazil), with ulcerated lesions in the perioral and intraoral regions, with painful symptomatology, weight loss, and severe cough. The patient was clinically evaluated with suspected paracoccidioidomycosis and submitted to complementary tests, including tongue biopsy, for evidence of the *Paracoccidioides brasiliensis* yeast form. Complementary exams and biopsy were conclusive for paracoccidioidomycosis, with primary pulmonary involvement and secondary buccal mucosae involvement. The patient was submitted to antifungal treatment, with excellent result after thirty days. **Conclusion:** The dental surgeon must know how to diagnose and treat systemic diseases with oral involvement, such as paracoccidioidomycosis in a multidisciplinary perspective. Periodic patient follow-up is important, since the lesions may relapse due to exacerbation of the clinical condition, drug resistance or even patient negligence regarding treatment and even adverse drug effects.

Keywords: Paracoccidioidomycosis; Mycoses; Pneumopathies; Oral Diseases.

RESUMO

A paracoccidioidomicose é uma doença sistêmica fúngica com envolvimento pulmonar e da mucosa bucal. **Objetivo:** Relato de caso clínico. **Caso clínico:** Paciente do sexo masculino, com 48 anos de idade (ex-fumante, ex-etilista e ex-usuário de drogas) foi atendido no Serviço de Estomatologia, da Faculdade de Odontologia de Lins (Lins – SP, Brasil), com lesões ulceradas na região peribucal e intrabucal, com sintomatologia dolorosa, perda de peso e tosse acentuada. Foi avaliado clinicamente com forte suspeita de paracoccidioidomicose e submetido a exames complementares, incluindo biópsia de língua, para evidência da forma leveduriforme do *Paracoccidioides brasiliensis*. Os exames complementares e biópsia foram conclusivos para paracoccidioidomicose, com envolvimento primário pulmonar e secundário na mucosa bucal; o paciente foi submetido a tratamento antifúngico, com excelente resultado em trinta dias. **Conclusão:** O cirurgião-dentista deve ter conhecimentos para diagnosticar e tratar doenças sistêmicas com envolvimento bucal, como a paracoccidioidomicose, inclusive em caráter multidisciplinar, com preservação periódica do paciente, visto que as lesões podem recidivar, por exacerbção do quadro clínico, resistência ao medicamento, negligência do paciente em relação ao tratamento, ou ainda devido a efeitos adversos de medicamentos.

Unitermos: Paracoccidioidomicose; Micoses; Pneumopatias; Enfermidades da boca.

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INTRODUCTION

Paracoccidioidomycosis (PCM) is a fungal disease caused by the fungus *Paracoccidioides brasiliensis*, which presents the characteristics of a thermally dimorphic fungus, usually acquired via respiratory tract, through inhalation.^{1,2,3} This type of microorganism is typically found in Latin America, being endemic in Brazil, Argentina, Venezuela and Colombia.^{4,5}

The etiology of PCM is still uncertain; it is known that *P. brasiliensis* is prone to terrestrial, tropical and subtropical climates.^{1,6,7,8} Previous studies reported the armadillo as one of the disseminators of the fungus in the soil; however, the specific habitat of the fungus is not exactly known.^{9,10,11,12} Individuals who perform agricultural activities, such as rural workers or people who have gardening and plant cultivation habits, present a higher risk of contamination due to their intimate contact with the soil. The highest prevalence of the disease is in men, in the fourth to fifth decade of life; however, the fungus may present long periods of inactivity after host infection.^{3,12,13,14} The reduced incidence among women occurs due to the hormonal barrier, since *P. brasiliensis* has receptors for 17- β estradiol. This estrogen inhibits mycelium-to-yeast transformation, which justifies resistance to infection.^{13,15,16,17,18}

Several forms of entry are suggested for *P. brasiliensis*, comprising the skin, gastrointestinal tract, mucosa and lungs.^{18,19} However, recent studies report that the lung is the main route of entry, through inhalation of the fungus. Once installed, this agent is disseminated throughout the body, via lymphatic and blood vessels, from a pulmonary focus.^{6,17,18,20} Patients with PCM are associated with frequent tobacco and alcohol use.²¹ The disease is not typically associated with immunosuppressed individuals; however, there are a few reports of patients with HIV infection, transplantation and concomitant malignant neoplasms.⁹

After fungus infection, a host-parasite imbalance occurs due to conditions not yet

completely defined, and infection can progress and cause signs and symptoms of the disease, but with long latency periods after the initial contact. The lungs are the most affected organs, demonstrating clinical manifestations very similar to other alterations, such as cough, dyspnea and purulent sputum, but these are not the main signal for diagnosis.^{6,17,20,22}

PCM commonly presents oral lesions during disease evolution. Thus, dentists need to be aware of this disease, in order to make a correct diagnosis and possible treatment, avoiding further disease complications.^{7,23,24,25} The morphology of oral lesions and their dimensions are quite variable, and often easily confused with possible neoplasms. However, the most common pattern is an infiltrative and ulcerative lesion, with presence of hemorrhagic spots known as strawberry-like stomatitis. PMC results in multiple lesions in the buccal and peribuccal mucosa, gingiva and in the dorsal surface of the tongue, with poor pain symptomatology. Usually, there are multiple lesions and with painful lesions.²⁶

Serological exams, lung radiographs or computed tomography scan (CT scan) are important for the diagnosis of the disease. However, histopathological biopsy analysis, searching for fungal infection, is fundamental for a conclusive diagnosis.^{3,27,28}

The treatment of PCM consists of antifungal therapy. Azotic drugs are those of choice and its administration will depend on the degree of commitment of the patient. Itraconazole, fluconazole and ketoconazole are the most easily marketed and used drugs, available for oral or intravenous therapy. Amphotericin B is intravenous and used for cases resistant to other drugs.^{1,2,3,4,26}

The early diagnosis and appropriate treatment of PCM is essential, since it is prolonged and may present resistance to different fungal agents.^{17,18, 26}

Considering the importance of PMC in dental clinics, the aim of the present study was

to carry out a brief bibliographic survey and present a clinical case report of PMC.

CLINICAL CASE

The patient signed the Free and Informed Consent Form, according to Resolution 466/2012 of the National Health Council, allowing the use of clinical data and photographs, while attending at the Lins School of Dentistry, Methodist University of Piracicaba (Lins, SP, Brazil).

A 48-year-old male, black, single and retired patient was attended at the referred Stomatology Clinic, complaining of difficulty swallowing and painful symptoms in the dorsal and left lateral border of the tongue, for approximately two months. The patient was sent by a dental surgeon and reported continuous treatment with a psychiatrist, as well, as continuous use of Diazepam, Haldol, Cinetol and Carbamazepine. He mentioned weight and hearing losses over the recent months and a persistent cough. The patient is a cigarette smoker (30 per day), for 30 years. He was a marijuana and alcohol user, quitting both addictions 20 years ago. He did not know the duration of his alcohol addiction. According to his family history, his great-grandmother and great-aunt had cancer; one aunt had diabetes.

The physical examination was normal, with hearing impairment and the orofacial examination showed an ulcerated lesion with approximately 1 cm diameter, exhibiting raised borders and erythematous halo, in the lateral region of the mental protuberance (Figure 1-1a). The patient mentioned that this lesion had mild painful symptomatology. In the intraoral inspection, two ulcerated lesions were present in the tongue region. The first observed lesion was in the dorsal region of the tongue with approximately 2.0 cm of diameter, with raised and hardened edges on palpation, with pseudomembrane covered fundus and some erythematous spots, a large erythematous halo and intense painful symptomatology. The

patient reported its onset and feeding difficulty at approximately two months. Two smaller plate-like lesions, of approximately 0.5 cm each and another one, smaller than 0.3 cm were also visible on the dorsal surface of the tongue, more anterior to the first described lesion (Figure 1- 1a). The second lesion, also an ulcer, in the left lateral border region, had a round shape with approximately 3.0 cm, a pseudomembrane covered fundus with discreet and hardened edges on palpation, with extreme pain symptomatology (Figure 1-1b). On physical examination, the left submandibular lymph nodes chain presented acute lymphadenopathy.

At the first visit, the patient presented blood pressure of 106/72 mmHg, heart rate of 74 bpm and complained of local pain at clinical examination. Hematological tests, purified protein derivative (PPD) skin test and chest X-ray were requested for possible diagnosis assistance.

In the blood count, slight macrocytosis, normal platelet count, and leukogram with discreet relative eosinophilia were observed. PPD was negative for *Mycobacterium tuberculosis*. The posteroanterior and lateral chest radiographs showed pulmonary lesions with possible fungal involvement and characteristic "butterfly wing" image (Figure 2-2a and 2b). The patient returned six days later for an incisional biopsy of both buccal lesions. Frozen section examination showed typical granuloma formation, represented by a set of epithelioid macrophage and multinucleated giant cells containing yeast of *Paracoccidioides brasiliensis*. The staining method used was Hematoxylin-Eosin (HE) (Figure 3-3a, 3b, 3c and 3d) and periodic-Schiff acid (PAS) (Figure 4- 4a 4b and 4c).

The histopathological result was of PCM. Therefore, the patient was treated with Sulfadiazine 500 mg three times per day uninterruptedly. He was also referred to the pulmonary physician for lung impairment analysis.

Figure 1: 1 – Ulcerated cutaneous lesion in right region of mental protuberance, with a slightly crusty bottom, 1 cm, raised borders and discrete erythematous halo (small black arrow). Endophytic ulcer in region of tongue dorsal surface with approximately 2.0 cm (large black arrow), with high and hardened borders on palpation, fundus with pseudomembrane and discrete red spots (white arrow) and great erythematous halo). 1b- Ulcerated round shaped lesion, with a pseudomembrane covered fundus and discrete borders, approximately 3 cm long, extremely painful.

Figure 2- 2a Posteroanterior chest radiograph showing areas of calcification in middle and basal third of lungs, compatible with pulmonary involvement by PCM. 2b- lateral chest radiograph with evident focus of pulmonary involvement by PCM.

Figure 3- 3a- Paracoccidioidomycosis in tongue: A remarkable presence of multinucleated giant cells together with intense subepithelial inflammatory reaction (HE, 200x). 3b- Typical granuloma formation, represented by a set of epithelioid macrophages and multinucleated giant cells (HE, 200x). 3c- Detail of collection of epithelioid macrophages of granulomatous inflammation (HE-X400). 3d- Detail of collection of epithelioid macrophage and multinucleated giant cell of granulomatous inflammation (HE, 400x).

Figure 4- 4a, 4b and 4c- Paracoccidioidomycosis in tongue: multinucleated giant cell containing *Paracoccidioides brasiliensis* yeast (arrows) (PAS-X1000).

After 30 days of initial treatment and evaluation by the pulmonary physician, the patient returned reporting absence of the lesion (Figures 5- 5a and 5b) and symptomatology. The patient was then treated with Itraconazole 20 mg/400mg/day. In the intraoral examination, it was verified the complete disappearance of both lesions and absence of lymphadenopathy.

Figure 5 – Clinical appearance after 30 days of treatment with sulfadiazine. 5a Reparative lesions on dorsal surface of tongue. 5b- Lateral border lesion completely repaired, with presence of healed atrophic mucosa, with areas of painless fissures.

DISCUSSION

PCM has been studied since 1908, when it was described by Adolpho Lutz, due to the high complexity of the microorganism and its multiple self-limiting sequelae.^{8,10,11,12} After extensive studies, researchers believed that fungus contamination occurs in the buccal mucosa through the habit of chewing tobacco and cleaning teeth with pieces of twig.²⁹⁻³² Other studies reported that contamination occurred through the mucosa of the gastrointestinal tract, through contaminated food.¹⁸⁻¹⁹ It is now known that this fungus is acquired through inhalation, with primary pulmonary involvement.^{6, 17, 20,22}

The lungs provide adequate conditions for the parasite to host and proliferate; once inhaled the propagules differentiate into yeast forms of the fungus that will form their parasitic form in the host's tissues, followed by lymphatic and/or blood vessels dissemination, reaching other tissues of the body.^{6,12,17,22,33,34,35,36}

The highest prevalence, over 90%, occurs in males between 40 and 50 years old, who have direct contact with agrarian activity, such as rural workers, gardeners, stonemasons and

carpenters.^{15,29,30,31,32,36} Similar to our clinical case, the patient was male and 48 years old at the time of diagnosis. Epidemiological data report that the low rate of infection of women by the parasite occurs due to of the lower incidence of gender in the agricultural work.³⁷⁻³⁸ However, researchers reported that, in addition to the lower exposure of women in areas of higher risk, the restricted occurrence is due to the hormonal barrier.^{13,15-18} Experimental studies in animals have demonstrated that 17 β -estradiol provides a supporting role in the innate resistance of females to PCM.^{13,17,39,40,41} Therefore, the concept that women are not infected is erroneous. It is important to emphasize that women present the estrogen that affects the transition yeast and the mycelium, which will increase levels of IFN- γ and Th1, as well, as reduce IL-10 levels secreted by the defense cells, as demonstrated in experimental models.^{41,42,43,44,45}

Environmental factors are directly related to the progression of the disease in each individual, being therefore specific for each PCM patient. The factor that may influence pathogenicity is closely related to the parasite-

host relationship, lower or higher exposure to endemic areas, alcoholism and smoking, pre-existing diseases, among other causes that can interfere with the immune response of the organism, favoring or disfavoring the pathogenicity of the fungus.^{40, 46, 47, 48}

Among all factors that trigger disease progression, some epidemiological surveys and experimental studies have shown that smoking and alcoholism are associated with the disease, when exposure occurs over a long period of time.^{40,46,47,48,49} It is believed that smoking influences and/or facilitates the development of the disease, due to the aggression of the pulmonary mucosa. Such damage due to the toxic effects of tobacco causes a change in the mucociliary clearance activity and decreasing the macrophage capacity for an appropriate immune response.^{48,49} Alcoholism is a risk cofactor for smoking. It is very interesting to mention that previous studies pointed out high positivity for paracoccidioidin skin test in patients addicted to both alcohol and nicotine.^{50,51,52} Thus, these harmful habits possible contribute to PCM development.

Knowing that the lung is the main entryway^{6,17,20,22}, pulmonary lesions are primary in PCM, with clinical and radiographic characteristics similar to tuberculosis, impairing the initial diagnostic.³⁷ The primary involvement of the lungs is noticeable in cases of PCM.⁵² The involvement of the oral cavity in patients with PCM is also observed.⁵³ The patient's main complaint, however, is not usually of pulmonary involvement, such as coughing or bloody sputum, but rather of the symptomatology in secondary mucosal lesions.⁵³ Complementary exams allow the diagnosis of the primary pulmonary lesion, and it is mandatory to make the differential diagnosis of tuberculosis, obtained with the PPD test. Another means of differential diagnosis is by sputum or gastric lavage, which identifies autoimmune changes in the vascular wall and hemoptysis. In the

present case, there was similarity between the studies, the patient reported the presence of oral lesions and did not know about the pulmonary involvement, however, in the chest radiographs, the presence of the fungus lodged in the lungs was evidenced. That is, initial diagnosis was made through the oral lesions. The lesion in the identified peribuccal region pointed to a suspected paracoccidioidomycosis, along with weight loss, cough, loss of appetite and oral lesions. Usually, lesions on the buccal mucosa present with a very typical aspect, such as ulceration strawberry-like stomatitis. In the case presented, however, the lesions were not so characteristic, remaining covered by pseudomembranes. The raised borders and the large erythematous halo could clinically give the impression of tuberculosis lesions.^{46,51}

The diagnosis should be based on complementary tests, including pulmonary evaluation, revealing diseases with similar clinical conditions, such as tuberculosis,^{37,52} differentiating them by specific tests, such as PPD and paracoccidioidin, the latter is not available in smaller diagnostic centers, therefore making it unfeasible. The buccal findings, however, are extremely important for the final diagnosis, where the histopathological analysis evidences the fungus very well, mainly in PAS staining method.^{15,53.}

Typically, H&E staining method in histopathological samples from immunocompetent patients reveals multiple well-formed granulomas composed of clusters of histiocytes and centrally organized with peripheral lymphocytes. These histiocytes are also characterized by a large foamy cytoplasm called the epithelioid, and giant cells are occasionally observed in their inflammatory infiltrate^{2,10,15,53}. Both cells can encompass a relatively small number of *P. brasiliensis*, in granulomas; however, they can also be seen freely, within the connective tissue. In addition, other staining methods such as PAS and

Grocott-Gomori methenamine silver (GMS) may evidence the presence of yeasts, such as observed in the histopathological test described in both HE and PAS.^{15,53}

The initial response of the established treatment demonstrates the importance of an effective diagnosis, with multidisciplinary evaluation and alteration of medication when there is recurrence of lesions in the oral mucosa or drug non-availability as happened with sulfadiazine, which is no longer offered in public agencies.

CONCLUSION

The dentist should be able to identify and diagnose oral lesions originated from systemic diseases. A multi-professional approach is important in the case of PCM with primary pulmonary involvement. It is crucial that the dentist and the pulmonary physician work together to improve not only the oral conditions, but also the pulmonary and general condition of the patient. The PCM treatment lasts a minimum of six months and requires periodic patient follow-up, since the lesions may relapse due to exacerbation of the clinical condition, drug resistance or even negligence of the patient regarding the adverse effects of the drugs.

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