

## Case Report

# Case of Recurrent Paracoccidioidomycosis in Female 10 Years after Initial Treatment

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## Abstract

This report describes a case of recurrence of chronic paracoccidioidomycosis 10 years following the initial diagnosis. A 56-year-old female was admitted to the Dental Clinic of the Pontifical Catholic University of Paraná complaining of oral soreness. Mulberry-like ulcerations were observed on the gingiva, right labial commissure, and vermilion of the lip. The patient reported persistent chronic cough, weight loss, appetite loss and fever. The anamnesis revealed that the patient had developed and been treated for paracoccidioidomycosis 10 years earlier. A biopsy was performed and microscopic examination revealed microabscesses, collections of macrophages organized into granulomas, multinucleated giant cells and *Paracoccidioides brasiliensis*. The patient was treated with Itraconazole and, the oral lesions disappeared within 3 months. Persistent follow-up examination in patients with a history of paracoccidioidomycosis is essential in the management of this disease.

Key words: Paracoccidioidomycosis—Mouth mucosa—Gingival—Stomatitis—Pathology

## Introduction

Paracoccidioidomycosis (PMC) is a chronic granulomatous infectious disease caused by a thermally dimorphic fungus, *Paracoccidioides brasiliensis*. Fungi may grow in soil, water and on plants in rural areas, and reach the human host through the inhalation of airborne prop-

agules. Infection typically occurs after inhalation of dry airborne spores, fungal propagules or mycelium fragments, which they settle in the airways, followed by the thermally regulated transition to the parasitic yeast phase<sup>21</sup>.

From the lungs, this particular disease can disseminate to several organs, giving rise to a variety of clinical signs<sup>6,21</sup>. One of the early



Figs. 1 and 2 Mulberry-like ulcerations on gingival and buccal mucosa

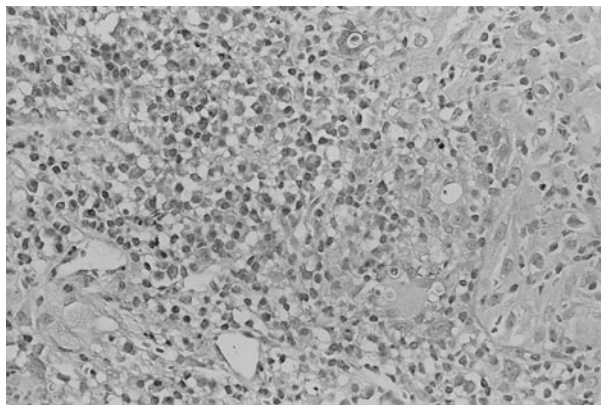


Fig. 3 Chronic inflammatory infiltrates, macrophages and giant cells HE staining at high magnification (original magnification  $\times 200$ ).

and more evident manifestations of the disease is the presence of mulberry-like ulcers on the oral mucous membranes<sup>5,22,23,26</sup>. PMC is the most important systemic mycosis in Brazil, the country with the most endemic areas for this disease in the world. It is the eighth most common cause of death among chronic/recurrent infectious and parasitic diseases<sup>10</sup>. It occurs more frequently in males than in females, with an overall ratio of prevalence of 13:1<sup>6</sup>. PMC is controlled effectively by anti-fungal therapy, but recurrences are frequent and may cause sequels or death. This report describes a case of recurrent PMC in a female patient, 10 years following initial treatment.

### Report of Case

A 56-year-old female was admitted to the Clinic of Stomatology at the Dental School of the Pontifical Catholic University of Paraná (Curitiba-PR/Brazil) complaining of oral soreness. Ten years earlier, the patient and her husband lived in Cantagalo, an agricultural city in the south of Brazil. They developed and were treated for PMC involving their lungs. The patient exhibited a white lesion on the right labial commissure, together with progressive dyspnea and chronic cough. Oral biopsy, hemogram, blood platelet count and chest X-rays were performed. Histopathologic

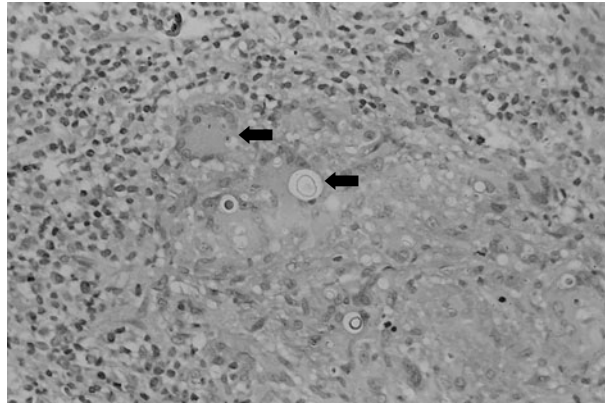


Fig. 4 Phagocytosis of *Paracoccidioides brasiliensis* levedures by Giant cells (arrows) HE staining at high magnification (original magnification  $\times 400$ ).

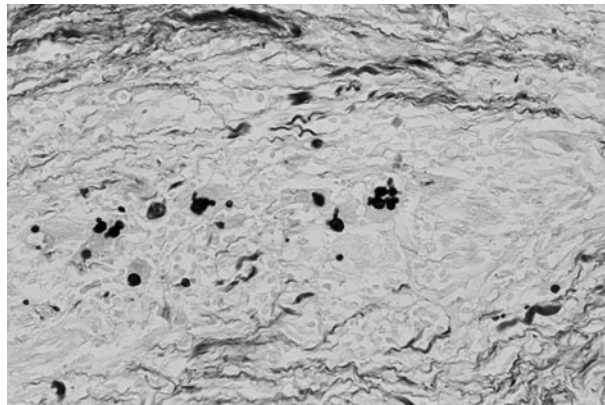


Fig. 5 Globulous yeasts of *Paracoccidioides brasiliensis* cells Grocott-Gomori staining at high magnification (original magnification  $\times 400$ )

examination confirmed a diagnosis of PMC. The husband died during the course of his treatment. The patient was treated with anti-fungal medication (a combination of sulfamethoxazol-trimethoprim) for 8 months and moved to Curitiba (Capital of the State of Paraná, Brazil).

During clinical examination at the Clinic of Stomatology, the patient complained of chronic cough, weight loss, appetite loss and daily cycles of fever. Intraoral examination revealed mulberry-like ulcerations on the gingiva (teeth #31, 32, 41, 42), right labial comissura and vermillion of the lip (Figs. 1 and

2). The anamnesis revealed that oral lesions initially appeared next to labial comissura 2 months ago. The patient was diabetic and a heavy smoker. Biopsy, hemogram, blood platelet count, rate of glycemia and hemosedimentation,  $17\text{-}\beta\text{-estradiol}$  hormone dosage, double immunodiffusion (IDD) and chest X-rays were obtained. Microscopic examination of lesional tissue revealed microabscesses, collections of macrophages organized into granulomas and multinucleated giant cells (Figs. 3 and 4). *Paracoccidioides brasiliensis* was identified in the routine H&E-stain and confirmed by the Grocott-Gomori methenamine silver

method (Fig. 5). Posteroanterior and lateral chest X-rays revealed opacities and a thick-walled cavity containing a prominent air-fluid level projecting into the superior segment of the left lower lobe. The IDD revealed positive reaction (1:1). The patient was referred to the Department of Infectious Diseases at the Hospital of Clinics of the Federal University of Paraná (Curitiba-PR/Brazil) for specialized treatment. The patient showed satisfactory progress becoming asymptomatic 2 months following the introduction of oral Itraconazole 200 mg (2 tablets per day) therapy and the oral lesions disappeared completely.

### Discussion

PMC is the most prevalent systemic mycosis in many countries in Latin America. Its distribution is limited to subtropical regions of Central and South America, where it is endemic. Studies have shown that certain ecological variables such as altitude (800–2,110 m), temperature (17–24°C) and minimal precipitation rates of 2,000 mm/year are related to PMC incidence. A striking feature of its epidemiology is its increased frequency in males, tobacco users, and restriction to people who have been in close contact with rainforests or agricultural regions<sup>7</sup>.

The majority of case reports on PMC concern males, and there are few case reports available on PMC in females<sup>9,11–14,17,18,25,28</sup>. In this case, the patient was a female smoker who had worked in an agricultural region 10 years prior to moving to a metropolitan region.

Which hormonal factors play a critical role in the pathogenesis of PMC has been established. Estrogens inhibit the transformation of mycelium into yeast. According to Restrepo *et al.*<sup>20</sup>, this inhibition in the lungs of females at the portal of infection explains the resistance of females to this disease. Therefore, sexually immature individuals and females during menopause can develop PMC. This explains the recurrence of PMC in this particular case.

Clinically, two forms of the PMC are distin-

guished: acute juvenile and chronic adult. The disease progresses slowly, and may take months or even years to become fully established. In the chronic multifocal form, the symptoms are variable and may affect to more than one organ or system. Most frequently, PMC lesions affect the lungs, oral mucosa, skin, lymph nodes, spleen, liver and adrenal glands in adult individuals<sup>5,6</sup>. Oral involvement was initially described by Lutz in 1908<sup>1</sup>. Head and neck lesions include inflammatory lesions of the lips, tongue, gingival, palate, pharyngeal mucosa, epiglottis, aryepiglottic folds, vestibular and vocal folds<sup>8</sup>. In this case, the patient developed several oral lesions and infection of the lungs. The chronic form is considered to be a reactivation of quiescent foci. Reactivated pulmonary foci spread via the regional lymphatic circulation, and may cause lesions in many different sites throughout the respiratory tract. A low expression of nitric oxide synthase enzymes by macrophages, together with decreased CD4<sup>+</sup> T cells and higher numbers of viable yeast cells, may be associated with local fungal multiplication and maintenance of active oral lesions<sup>3</sup>. Head and neck involvement is a frequent manifestation of PMC, and is usually associated with high morbidity: patients may present with poor nutritional status due to dysphagia and/or impairment of mastication<sup>8</sup>.

PMC is usually diagnosed on the basis of clinical examination, X-rays to detect pulmonary lesions, and lesional biopsy or exfoliative cytology<sup>2,23</sup>. The differential diagnosis of PMC includes mainly squamous carcinoma, tuberculosis, Wegener's granulomatosis and sarcoidosis<sup>4</sup>. The best and speediest way to establish the diagnosis of this fungal disorder is by direct examination of clinical specimens, which allows detection of *Paracoccidioides brasiliensis* cells. Identification of the fungus in histological sections or smears can be performed by using hematoxylin-eosin, but the most useful methods include Grocott's silver-methenamin and Papanicolaou's and Schiff's periodic acid<sup>1</sup>. PMC is characterized by granulomatous inflammation and pseudoepitheliomatous hyperplasia. In tissue sections such as

smears obtained from lesions, *Paracoccidioides brasiliensis* cells appear as globulous yeasts, with a birefringent wall and multiple budding (the 'Mickey-Mouse' and 'ship's steering wheel' forms). Young cells have diameters ranging from 1 to 10  $\mu\text{m}$ , while mature cells can reach up to 60  $\mu\text{m}$ <sup>6)</sup>. Expression of cytokeratins in the basal layer of the epithelium in pseudoepitheliomatous hyperplasia in PMC is similar to that in normal oral mucosa, except for cytokeratins 1, 10 and 14<sup>16)</sup>. Both chest X-rays and microscopy were decisive in diagnosis of this case.

Detection of specific antibodies in serum is also a major tool in the diagnosis of this disease, and may be useful in monitoring its evolution and response to treatment<sup>19)</sup>.

The treatment of PMC is lengthy, starting with an aggressive dosage of antifungal agents, after which, maintenance treatment must continue for months or even years<sup>15)</sup>. Imidazoles (ketoconazole) and triazoles (fluconazole, saperconazole, and particularly itraconazole) have been extensively used in the treatment of PMC<sup>20)</sup>. Most adult patients respond to specific therapy with antifungal, and especially imidazole derivatives, but recurrence is frequent, and may cause sequels or death. Nevertheless, the clinical appearance of oral lesions with PMC is fairly typical, and is highly suggestive of such a diagnosis when the index of suspicion is high. The various different modalities of treatment can decrease fungal load and permit the recovery of cellular immunity and balance between parasite and host<sup>24)</sup>. For this reason, the patients should be clinically accomplished after the ending of the treatment and, once, cure parameters is gotten<sup>27)</sup>. Probably, the term "cure" can never be attributed to patients with PMC due to the impossibility of eradicating *Paracoccidioides brasiliensis*. Patients always carry the risk of reactivation. Therefore, women who have developed PMC may exhibit recurrence. It is postulated that, after menopause, women are more susceptible to this disease. This disease should be suspected in patients with an appropriate travel history and who experience weight loss and pulmonary, mucosal or

cutaneous lesions.

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