

## Paracoccidioidomycosis in a 64-year-old man: a case report

### Paracoccidioidomicose em um homem de 64 anos: relato de caso

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## ABSTRACT

Paracoccidioidomycosis (PCM) is a systemic mycosis caused by the thermo-dependent dimorphic fungus *Paracoccidioides spp*, limited to the American continent, but with a high incidence in Brazil, mainly in the Midwest, South and Southeast regions. This is a case report of a 64-year-old male patient that was referred at a hospital, complaining of pain in the mouth and dysphagia. The patient presented multiple and finely granular hemorrhagic pinpoint erosions with a mulberry-like appearance in oral mucosa. The patient underwent an incisional biopsy, and the histopathological analyses confirmed the presence of the fungus and the diagnosis of PCM. Lesions in oral mucosa may be the first visible clinical manifestation of PCM; so, a meticulous evaluation of oral cavity and well-conducted diagnostic techniques are indispensable for a correct diagnosis and an appropriate therapy of PCM.

**Keywords:** Paracoccidioidomycosis, systemic mycosis, mulberry-like lesion.

## RESUMO

A paracoccidioidomicose (PCM) é uma micose sistêmica causada pelo fungo dimórfico termo-dependente *Paracoccidioides spp*, limitado ao continente americano, mas com alta incidência no Brasil, principalmente nas regiões Centro-Oeste, Sul e Sudeste. Trata-se de um relato de caso de um paciente do sexo masculino, 64 anos, encaminhado a um hospital, com queixa de dor na boca e disfagia. O paciente apresentou múltiplas e finamente granulares, erosões hemorrágicas pontuais com aspecto de amora na mucosa oral. O paciente foi submetido a biópsia incisional, e as análises histopatológicas confirmaram a presença do fungo, culminando no diagnóstico de PCM. Lesões na mucosa oral podem ser a primeira manifestação clínica visível da PCM, portanto, uma avaliação meticulosa da cavidade oral e técnicas diagnósticas bem conduzidas são indispensáveis para um diagnóstico correto e uma terapia adequada da PCM.

**Palavras-chave:** Paracoccidioidomicose, micoses sistêmicas, estomatite moriforme.

## 1 BACKGROUND

Paracoccidioidomycosis (PCM) is a systemic mycosis caused by a thermo-dependent dimorphic fungus that mostly affects individuals of Latin America<sup>1,2</sup>. About 80% of the PCM cases are registered in Brazil while other cases are observed in other South American countries, mainly Colombia, Venezuela, Argentina, and Ecuador<sup>3</sup>. This disease is observed in practically all Brazilian territory as in states of the South, Southeast, Midwest and North, with sporadic cases recorded in the Northeast region<sup>4</sup>.

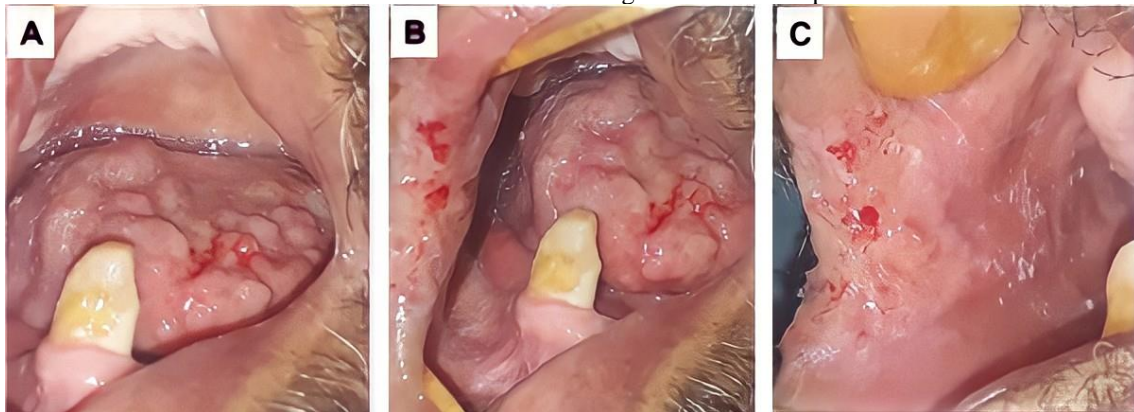
PCM affects mostly males with a male to female ratio of 15.5:1, with ages ranging from 7 to 89 years (mean age 50 years)<sup>5-7</sup>. In relation to occupation, farmers and construction workers are more affected by PCM<sup>7</sup>. PCM is acquired when conidia or mycelial fragments present in the soil are inhaled and deposited in the pulmonary alveoli. After the fungus is inhaled it shifts to a pathogenic yeast phase<sup>8</sup>. PCM is classified as a

systemic disease since multiple organs are affected. Oral manifestations can be the first noticeable clinical signs of this disease<sup>9</sup>. Clinically, PCM presents in two forms: the acute / subacute form (juvenile form) that affects patients under 30 years old, and corresponding to 5% to 25% of the cases; and the chronic form (adult form) that affects males between 30 and 60 years of age and corresponds to most PCM cases with a prevalence of 74 to 96%<sup>2</sup>. The purpose of this case report is to highlight the importance of knowledge about the clinical manifestations of oral PCM.

## 2 CASE REPORT

A 64-year-old male patient was referred at Hospital Municipal Moacyr Rodrigues do Carmo in Duque de Caxias (Rio de Janeiro, Brazil), complained of a constant cough, pain in his mouth and dysphagia. He also reported weight loss and weakness. Clinical examination revealed ulcerated areas and finely granular hyperplasia with pinpoint hemorrhages (mulberry-like appearance) in his tongue, buccal mucosa, and gums (Figure 1A-C).

Figure 1. Clinical aspects of oral Paracoccidioidomycosis (PCM): (A) and (B) ulcerated and granular lesions with hemorrhagic specks in tongue and buccal mucosa; (C) Note the mulberry-like lesion in right buccal mucosa close to the right commissure lip.



Based on the anamnesis and in the clinical aspects, the initial diagnostic proposed was PCM. To confirm this hypothesis the patient underwent an incisional biopsy of buccal mucosa, using local anesthesia (Lidocaine 2% with Epinephrine). The specimen was submitted to histopathological analyses. Complementary tests were also requested, such as complete blood count, EAS exam and chest radiography (Figure 2). The patient's complete blood count showed the presence of anemia, neutrophilia, and a discreet increase in the number of platelets. The chest X-ray study revealed areas of pulmonary

consolidation, bilateral and diffuse lung lesions, predominating the middle zone. Due the presence of lung disease and a debilitated physical state the patient was hospitalized.

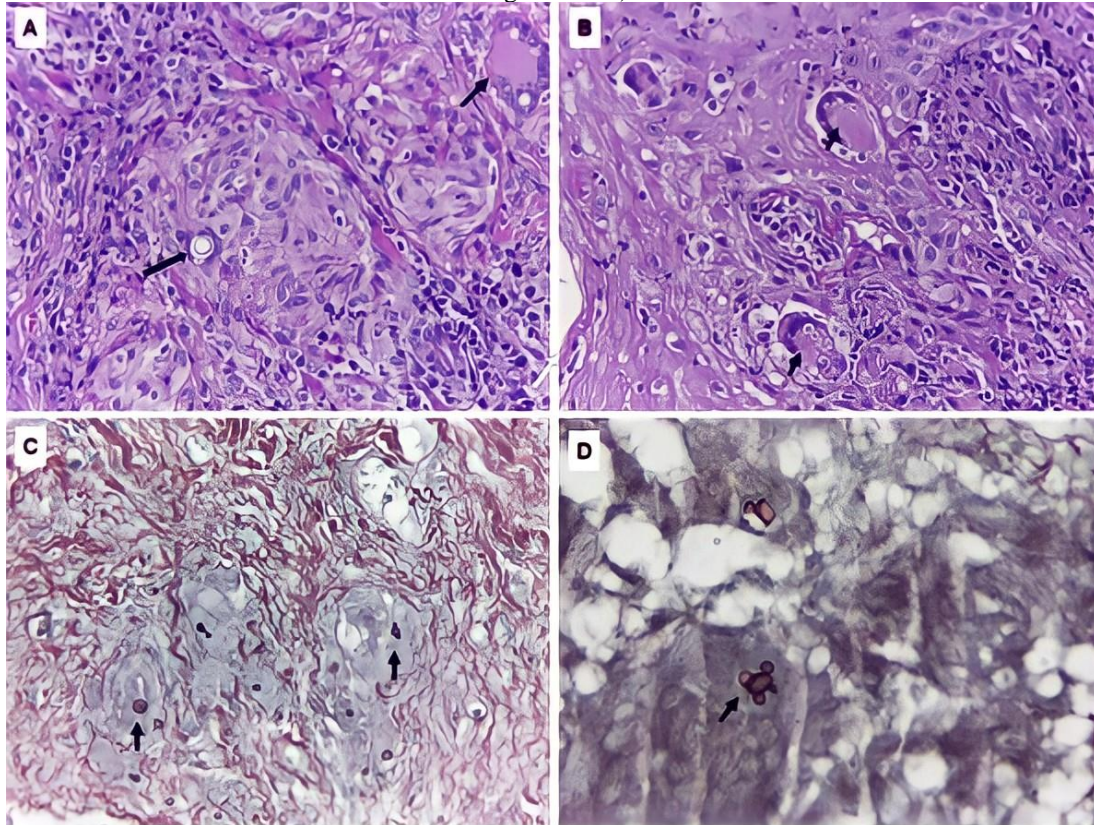
Figure 2. Pulmonary Paracoccidioidomycosis. Anteroposterior chest radiograph in a 64-Year-Old Man.



The clinical diagnostic of PCM was confirmed by the histopathological evaluation of H&E-stained tissues and special PAS and Gomori staining. It was observed chronic inflammatory infiltrate and multinucleated giant cells detected in the lamina propria. The identification of *P. brasiliensis*, described as resembling “Mickey Mouse ears” or the spokes of a ship’s steering wheel (“mariner’s wheel”) was observed using the Grocott-Gomori staining (Figure 3A-3C). Therapy with intravenous Amphotericin B was performed for 15 days. The patient was followed up until showing improvement of the disease.



Figure 3. Histologic aspects of oral Paracoccidioidomycosis: (A) and (B) Oral mucosa revealed a granulomatous chronic inflammatory infiltrate in connective tissue. Multinucleated giant cells exhibit numerous rounded structures surrounded by a clear halo (birefringent) in the cytoplasm representing yeast cells of *Paracoccidioides brasiliensis* (arrows). (C-D) Grocott-Gomori staining illustrating the appearance of budding yeasts of *P. brasiliensis* with characteristics of “mariner’s well” or “Mickey Mouse ears” (inset) (hematoxylin and eosin staining: A-B  $\times 40$  magnification; Grocott-Gomori staining: C-D,  $\times 40$  magnification).



### 3 DISCUSSION

PCM is registered in practically all Brazilian territory, being considered an endemic disease. There are no precise data related to the incidence about this disease because PCM is not a compulsory notification disease in Brazil<sup>2</sup>. We presented a case report of a 64-year-old male patient resident of Baixada Fluminense presenting PCM. A study published by Valle et al. demonstrated a 5.7-fold increase in cases of PCM expected for the Baixada Fluminense, a region composed of 12 municipalities in the Metropolitan Area of Rio de Janeiro during December 2015 to December 2016<sup>10</sup>. According to these authors, the outbreak of this disease was observed one year after the deforestation and massive earth removal during the construction of the Raphael de Almeida Magalhães Highway (2008-2014), popularly known as Arco Metropolitano, and located in Metropolitan Area of Rio de Janeiro.

At least five species of fungi have already been linked to the etiology of PCM: *Paracoccidioides brasiliensis*, *Paracoccidioides lutzii*, *Paracoccidioides americana*,

*Paracoccidioides restrepiensis* and *Paracoccidioides venezuelensis*)<sup>1,11-13</sup>. Theodoro *et al.* in a biogeographic study demonstrated a map of distribution of each species of genus *Paracoccidioides* in South America<sup>11</sup>. According to these authors, *Paracoccidioides lutzii* (*P. lutzii*) is more prevalent in the central region of Brazil, *Paracoccidioides brasiliensis* (*P. brasiliensis*) is vastly distributed in South America and *Paracoccidioides restrepiensis* (*P. restrepiensis*) is restricted to Colombia. De Macedo *et al.* conducted phylogenetic analysis of 54 *Paracoccidioides spp.* clinical strains. These authors demonstrated that the etiological agent of PCM in patients from Rio de Janeiro- Brazil were *P. brasiliensis* (n = 48) and *P. americana* (n = 6)<sup>13</sup>.

PCM presents in the acute / subacute (juvenile) and in the chronic form<sup>2</sup>. The acute/subacute form mostly has a rapid progression (few weeks after exposition to the fungus) affecting mostly children and young adults with an inadequate Th2 type cell immune response to the pathogen. The clinical manifestation of this “juvenile” form generally involves intra-abdominal lymphadenomegaly often associated to lesions of the skin, the bone, intestinal and oral mucosa and hepatosplenomegaly<sup>3</sup>. The chronic form affects individuals between 30 and 60 years of age. This form presenting a slow progression and a symptomatology that begins in four to six months, but in some cases the symptomatology manifests over one year<sup>2</sup>. The lung and upper airways are involved in this “adult” form as well as lesions in the face and oral mucosa and on the skin adjacent to the mouth and nose<sup>3</sup>. In the mildest cases, the patient presents weight loss (around 5% of normal weight) and without tissue and organ dysfunction. In most cases, the patient loses 10% of his usual weight, respiratory failure, adrenal dysfunction, neurological syndrome, or acute abdomen<sup>2</sup>. The chronic form mainly affects males. This difference in incidence observed between the sexes seems to be attributed to hormonal factors. Adult women are protected against the progression of *P. brasiliensis* by their sex hormones.  $\beta$ -estradiol receptors are present on the cell membrane of *Coccidioides* species<sup>14</sup>. In the endocrinologically mature woman with adequate levels of estrogens, estradiol prevents the transformation of the filamentous phase into yeast form in *P. brasiliensis*, blocking a crucial step of infectious process of this parasite, thus suggesting a protective role for female hormones<sup>14</sup>.

In this present study the patient presented ulcerated areas and finely granular hyperplasia with pinpoint hemorrhages in his oral mucosa as described in the literature<sup>6,7,15</sup>. In the oral mucosa, the sites commonly affected by PCM are gingival/alveolar ridge,

lips, buccal mucosa, hard and soft palate, floor of the mouth and tongue<sup>5-7</sup>. Oral PCM presents multiple and finely granular hemorrhagic pinpoint erosions with a “mulberry-like” appearance, ulcerative lesions and macrocheilia are also observed<sup>6,9,15</sup>. Oral manifestations of PCM are frequent and can be the first noticeable clinical signs of this disease<sup>9</sup>. The diagnosis of PCM consists to detect the *Paracoccidioides spp.* in sputum samples and/or fragments of organ biopsies<sup>2</sup>. Yeasts of *P. brasiliensis* can be identified by using special PAS and Grocott-Gomori staining. The microorganisms often are observed as rounded, birefringent and multi-budded structures, with the daughter cells (buds) attached to the parental cell and “Mickey Mouse ears” or “mariner’s wheel” appearance<sup>6,7</sup>. However, it is particularly important to emphasize that, initially, one should not ignore differential diagnoses in oral cavity, such as tuberculosis, leishmaniasis, histoplasmosis and squamous cell carcinoma<sup>7</sup>.

Due to the scope of affected organs, the treatment is multidisciplinary, and may involve professionals of different specialties. It is recommended that patients who have changes in the larynx and trachea should be referred to the otorhinolaryngologist. Patients with persistent dyspnea, cicatricial pulmonary disease and Addison's syndrome should be referred to the pulmonologist and endocrinologist for confirmation and treatment of pulmonary disease and its systemic manifestations<sup>2</sup>. Antifungals are effective in different clinical forms and for severe cases, The itraconazole has been widely used for the treatment of mild and moderate forms of PCM, with high rates of efficacy and safety<sup>2</sup>. Amphotericin B is an antifungal of natural condition, of the class of polyenes, widely used in the control of severe systemic fungal infections<sup>16</sup> besides having important activity in the combat of protozoa (*Leishmania* species) and amoeba (species of *Naegleria*)<sup>17</sup>. The mechanism of action of amphotericin B, which is common to polyenes in general, is based on the binding of its hydrophobic portion to ergosterol present in the cell membrane of fungi<sup>18</sup>. Its use is mainly by intravenous administration, which becomes inconvenient for long periods due to the need for hospitalization and the need for prolonged venous access, in addition to the adverse effects and toxicity related to the continuous use of Amphotericin B<sup>19</sup>.

#### 4 CONCLUSION

PCM is the main systemic mycosis in Brazil. This disease can compromise any system or organ, and their treatment is multidisciplinary. The professionals must be

attentive and vigilant in relation to clinical manifestations, differential diagnosis, and treatment of PCM because lesions in oral mucosa may be the first visible clinical manifestation of PCM. This report highlights that a meticulous evaluation of oral cavity and well-conducted diagnostic techniques are indispensable for a correct diagnosis and an appropriate therapy of PCM.

### **CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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### **ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

The study was approved by the Ethics Committee of the Grande Rio University (Approval number 4.364.512), and the patient gave written informed consent to participate.



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