

# Paracoccidioidomycosis disease (Lutz-Splendore-Almeida): etiology, epidemiology, and pathogenesis

## *Paracoccidioidomicose (doença de Lutz-Splendore-Almeida): etiologia, epidemiologia e patogênese*

Alfredo Miranda de Góes<sup>1</sup>, Lillian da Silva Santos Silva<sup>2</sup>, Stanley de Almeida Araújo<sup>2</sup>, Samuel Gonçalves da Cruz<sup>2</sup>, Weverton César Siqueira<sup>2</sup>, Enio Roberto Pietra Pedroso<sup>3</sup>

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### ABSTRACT

Paracoccidioidomycosis (PCM) is a polymorphic systemic granulomatous mycosis determined by *Paracoccidioides brasiliensis* and *P. lutzii* and constitutes one of the 10 leading causes of morbidity and mortality by the parasitic diseases endemic in Brazil. The need for updates on the etiology, epidemiology, and pathogenesis is a for routinely including this disease in the differential diagnosis of current medical practice, recognizing it early and treating it properly, so as to avoid progression with sequelae and death.

**Key words:** Paracoccidioidomycosis; Mycosis; Paracoccidioides.

### RESUMO

*A paracoccidioidomicose (PCM) é uma micose granulomatosa sistêmica, polimórfica, determinada pelos Paracoccidioides brasiliensis e P. lutzii e constitui-se em uma das 10 causas de morbimortalidade entre as doenças endêmicas parasitárias no Brasil. A atualização do conhecimento sobre sua etiologia, epidemiologia e patogênese constitui estímulo para que seja incluída no espectro do diagnóstico diferencial da prática médica rotineira, reconhecida com precocidade e tratada convenientemente, evitando-se que evolua com sequelas e morte.*

**Palavras-chave:** Paracoccidioidomicose; Micose; Paracoccidioides.

### INTRODUCTION

Paracoccidioidomycosis (PCM) is the most important deep mycosis in Latin America, described initially in Brazil in 1908 by Adolfo Lutz, with relevant later contributions by Splendore and Almeida.<sup>1,2</sup> It was named in various ways such as: South American blastomycosis, Lutz-Splendore-Almeida disease, paracoccidioides granulomatosis, paracoccidioides granuloma, tropical blastomycosis granuloma, and malignant ganglionic granuloma of blastomycosis origin.<sup>3</sup>

The disease can affect people of all ages, with acute-subacute or chronic evolution observed mainly in children-teenagers or adults 30 years and older, respectively; and clinical manifestations from benign to serious with risk of death. Its anatomopathological presentation has a granulomatous and suppurative character, affecting mainly the lungs, mucous membranes of the upper airways and mouth, skin and lymph nodes; however it can affect all organs and systems.<sup>4-14</sup>

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Institution:

Institute of Biological Sciences; Graduate Program in Health Sciences: Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Medical School from UFMG Belo Horizonte, MG – Brazil

Corresponding Author:

Enio Roberto Pietra Pedroso  
E-mail: enio@medicina.ufmg.br

## ETIOLOGY

PCM is caused by the fungi *Paracoccidioides brasiliensis* and *P. lutzii* (Onygenales, Onygenaceae, *Paracoccidioides*) dimorphic, which at room temperature (4 to 28 °C), presents the mycelial form and at 37 °C develops as a yeast. The mycelial forms (multicellular) found in the environment, and mycelium in the yeast (unicellular) differentiate by giving the fungus increased resistance and pathogenicity in infected organisms, respectively. They present spherical shape in human tissues, double-walled refringent, measuring 2 to 30 micrometers or more in diameter. Its multiple sporulation results in the typical aspect of “wheel” or “boat wheel” considered as pathognomonic (Figure 1).<sup>1, 3, 4-14</sup>



**Figure 1** - *P. brasiliensis* in tissue sample, budding and with the pathognomonic aspect of 'boat wheel'. Source: Grocott technique, silver impregnation, 1000X magnification.

The exocellular components of *P. brasiliensis* with more reactivity in immuno-diffusion tests are glycoproteins with molecular weights of 43 (gp43), 55, and 72 kDa. Gp43 is the component with the best reaction with specific rabbit antiserum.

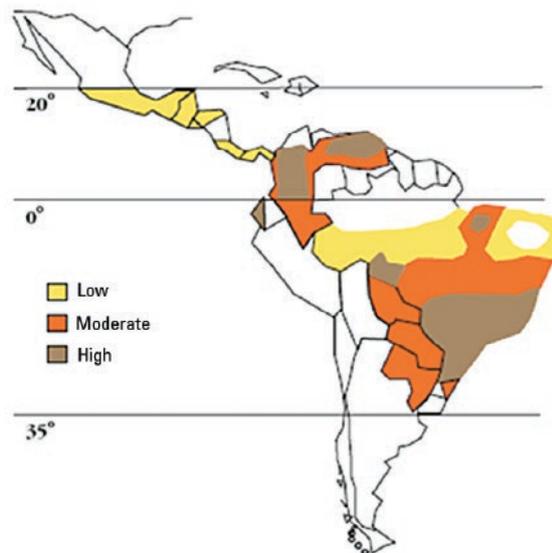
The habitat of *P. brasiliensis* in nature is unknown; the mycelium seem to be its saprophytic life form, and the production of infective spores occurs in soil and plant debris.<sup>7-13</sup>

The definitive hosts are humans, armadillos (*Dasypus novemcinctus*), and probably dogs.

## EPIDEMIOLOGY

Endemic areas are located in regions of tropical or subtropical forests, with average temperatures between 14 and 20 °C, precipitation between 800 and 2,000 mm, and high relative air humidity. Brazil shows the highest number of PCM cases described, followed by Colombia, Venezuela, and Guatemala.<sup>14-16</sup> Their regional distribution is heterogeneous, with higher prevalence in the States of Rio Grande do Sul, Paraná, São Paulo, Rio de Janeiro, Espírito Santo, Minas Gerais, Goiás, Mato Grosso do Sul, Mato Grosso, and Amazon. Increased records of cases in the states from the Midwest and Northern regions have been observed in the recent years associated with the advance of agricultural frontiers at the edge of the Amazon rainforest.<sup>6-10,17</sup>

The actual prevalence of the PCM-disease is not established because its notification is not mandatory in most Brazilian States.<sup>15, 16, 18</sup> The estimate of its incidence is between 1 and 3/ 100,000 inhabitants in endemic areas in Latin America (Figure 2).<sup>15,17</sup>



**Figure 2** - Geographic distribution of paracoccidioidomycosis.

Source: Brazilian Ministry of Health.

PCM composes the group of neglected infectious diseases because it does not receive the attention from institutions involved in public health policies and the pharmaceutical industry does not invest in the development of new antifungals. In Brazil, it is not included among neglected diseases.<sup>3,18-23</sup>

Studies based on intradermal reaction with paracoccidioidin reveal prevalences in endemic areas between 11.0 and 43.8% with contact with the fungus, being similar between genders. Among adults, there is involvement in the ratio of 5.4 to 10 men for each woman; however, a significant difference between genders does not occur in the childhood. Involvement in women over 50 years old is described as similar to that in childhood.

The severity of PCM has been linked to genetic factors in the host. It is more frequent in patients with HLA-B and in Asian descendants. The use of immuno-suppressants such as glucocorticoids, and immunosuppression such as in the acquired immunodeficiency syndrome (AIDS) relate to a higher frequency of PCM. However, this association is less significant than that with pneumocystosis, histoplasmosis, and cryptococcosis.<sup>4,8,9,11,13,19-22</sup>

PCM is associated to professions and activities that involve soil management such as agriculture (rice, coffee, maize, and sugarcane crops), transport of plant products, earth-moving, and gardening. It mainly affects rural (44.3 to 76.2%) and construction workers (5 to 20%), who are in general, from rural areas. PCM has been identified, in recent decades, at higher frequencies in urban areas, even in individuals who never left major population centers.<sup>21-24</sup>

The mortality rate stands at about 1.45 per 1,000,000 inhabitants, becoming the eighth cause of mortality among chronic infectious parasitic-chronic diseases. The lethality rate is between 2 and 23%, and up to 30% if associated with AIDS.<sup>16-21</sup> Social and economic costs are high when affecting individuals at productive stages, determining secondary permanent sequelae, and often preventing the patient to return to their original work.<sup>12,25-27</sup>

## PATHOGENESIS

The paracoccidioidomycosis infection is acquired by inhalation or inoculation of spores in solution of continuity in the skin or mucous membranes, especially in the oral or anal region. It does not show inter-human transmission.<sup>6-11,13</sup>

The spores or infective particles easily reach the bronchiole alveolar units, where they transform into yeasts and multiply by multiple budding. Next, the fungus can cause alveolitis with migration of neutrophils, which are later replaced by lymphocytes and macrophages (parenchymal pole). The process is followed by lymphatic spread with lymphangitis and regional

ganglia reaction (ganglionic pole). These changes constitute the paracoccidioides primary complex, similar to tuberculosis. The formation of epithelioid granuloma occurs, which is the most typical form of inflammatory tissue reaction to *P. brasiliensis*.<sup>8-14</sup>

The granuloma that forms around the yeast consists of giant cells and epithelioid cells with suppuration and coagulation necrosis in its central area.

The host immune response determines the evolution of the primary complex, from asymptomatic to intense symptoms and severe, affecting gateway organs or becoming systematized, depending on the extent and intensity of the inflammatory reaction, load of infective particles inhaled, and virulence of the *P. brasiliensis* strain. In most cases, spontaneous involution will occur, although fungemia can occur at any time with the development of metastatic focus in any organ. The scars resulting from the initial lesions may be sterile, with fungal destruction if the inflammatory response is effective. *P. brasiliensis* persists alive in many cases with the formation of a latent or quiescent focus that can last for years or for life in the host, identified only by the host skin reaction to paracoccidioidin, becoming active if favored by some immunosuppression factor.<sup>6-11,13, 19-23</sup>

The fungal spread by lymphatic and hematogenous pathways (air and digestive ways) to various organs and systems occurs exceptionally after the initial contact with *P. brasiliensis* probably due to ineffective defense responses. The development of this type of evolution characterizes the acute or sub-acute form of PCM observed mainly in children and adults up to 30-year-olds and from both genders.<sup>12, 13, 19, 24</sup>

The majority of cases evolves, usually to prolonged latency, after involution of lesions of the primary complex, and can last for many years; the disease only appear in its chronic form, through reactivation of quiescent outbreaks (endogenous reactivation), when the fungi remained viable, spreading to other organs. The factors involved in reactivation of the residual or quiescent focus are not yet established. They may result from an imbalance of defense mechanisms responsible for the maintenance of fungal quiescence (endogenous reinfection). Exogenous reinfection can still occur in people in permanent contact with the fungal source leading to the development of the chronic form of the disease.<sup>4,6-10,13, 25-32</sup>

Every organ can be affected with often involvement of mucous-cutaneous (especially mouth and upper airways), pulmonary lymphatic, nervous, adrenal, spleen, liver, bones, and joints.

The evolution of PCM may be to healing, sequel, or death. The scars can promote lung function, upper airways, or digestive alterations in addition to promoting serious mucous-cutaneous aesthetic retractions.<sup>4-6,12,24-26</sup>

The initial establishment period of *P. brasiliensis* is asymptomatic, although the development of humoral and cellular immune response is observed.

Humans are a host that is resistant to *P. brasiliensis* because the number of people exposed (PCM-infection) to the fungus is much higher than that of patients with PCM (PCM-disease). Some factors such as age, gender, or genetics can relate to the process of reactivation of the initial infection. The higher prevalence among men seems associated with the female protection afforded by estrogen, which inhibits the transformation of mycelium into yeast. This conception is reaffirmed by the similar prevalence between genders in the first and after the sixth decades of life. The inhibitory action of estrogen on the transformation of mycelium into yeasts can be associated with the apparent female resistance to PCM.<sup>20-34</sup>

*P. brasiliensis*, despite being pathogenic, sometimes acquires an opportunistic character associated with the severe forms and disseminates with immunodeficiency factors such as leukemia, lymphoma, drug-related immunosuppression, post-transplant occurrences, and acquired immunodeficiency syndrome. In these cases, the clinical evolution tends to be acute or sub-acute, febrile and systemic, with loose granulomas, rich in fungi, detected through histopathology.<sup>6-10</sup>

## IMMUNOPATHOGENESIS

The factors involved in the rupture of the host-parasite balance, favorable to the parasite, are not yet identified. The evolution of paracoccidioidomycosis infection into the disease in individuals living in endemic areas seems to depend on factors in the parasite and the host's immune response against *P. brasiliensis*. There seems to be a difference in the pattern of responses between individuals, expressed as disease with acute or chronic evolution or with spontaneous healing, as well as change in the immune profile, in same individual who achieves apparent healing by means of specific treatments.<sup>6-10,34-43</sup>

The immune response in the *P. brasiliensis* host seems to be at the origin of these differences, being mainly cellular and under the influence of the cytokines involved (humoral response). The fungus anti-

gens, located in the infectious focus, are initially recognized by macrophages and dendritic cells, which activate the complement system, release cytokines, and promote the chemotaxis of neutrophils circulating toward this focus; and with the evolution of inflammatory processes, are replaced by mononuclear cells.<sup>33-38</sup>

Neutrophils and macrophages, once reaching the infectious focus, cannot digest the fungus and prevent its multiplication, however, they are able to promote fungal debugging if they are activated by interferon-gamma (IFN- $\gamma$ ) and alpha tumor necrosis factor (TNF- $\alpha$ ). TNF- $\alpha$  is able to activate T lymphocytes (L); and IFN- $\gamma$ , through NK cells and LTCD4<sup>+</sup>, activates macrophages, which results in the inhibition of *P. brasiliensis* replication. The antibodies do not appear to protect against infection by *P. brasiliensis*. Worsened PCM is observed associated with impaired cellular immunity and presence of elevated serum A, E, and G immunoglobulin titers, possibly associated with a predominance of LTh2 stimulation. LTh1, which produces IL-2, TNF- $\alpha$ , and INF- $\gamma$  promotes macrophages activation. LTh2 releases IL-4, IL-5, IL-6, and IL-10, which inhibits cellular immunity. These interleukins can inhibit LTh1 activity through the suppressor cytokines IL-4 and IL-10, and promote the synthesis of antibodies. The repressed response of LTh1 promotes the decrease of LT, NK cells activity, production of INF- $\gamma$ , TNF- $\alpha$ , and IL-2 (and its receptor), and consequent decreased proliferative response from lymphocytes, favoring the establishment of the PCM-disease.<sup>33-38</sup>

## PATHOLOGY

The initial contact of the host with the fungus is reflected by nonspecific inflammation around one or more fungi, characterized by vascular congestion, edema, and the predominance of polymorphonuclear cells (neutrophils and eosinophils). Subsequently, mononuclear cells, macrophages, auxiliary LTs, and histiocytes replace many of the polymorphonuclear cells. The immune reaction is specific with the formation of granulomas and transformation of macrophages in multinucleated giant cells and epithelioid cells that organize the granuloma, which shows supuration and coagulation necrosis at its center featuring the tuberculoid pattern.<sup>6-10,13</sup>

Granulomas can present different forms, from compact and with few fungi (hyperergic pole) to loose and suppurative with extensive necrosis and many fungi

(anergic pole), which are, respectively, associated to effective immune defense or compromised.

Intensive involvement of the monocytic-phagocytic system is observed in necropsies represented by lymphadenomegaly (95.4%), hepatomegaly (40%), and splenomegaly (23%); lungs and oropharynx are affected in 96 and 66% of cases, respectively.<sup>43</sup>

The evolution in the acute-subacute form (15.4%) predominates in the second and third decades of life (average of 22.2 years), with male-female ratio of 3:1; whereas the chronic form (84.6%) is more incident on the fourth, fifth, and sixth decades of life (average of 47.3 years), with a male/female ratio of 15:1. The chronic/multifocal form represents 46.4% of cases, with higher incidence in the third and fourth decades of life, age varying between 24 and 58 years (average of 41 years old), male/female ratio of 2.2:1, and involvement of 84.2, 73.7, 47.4, and 42.1% of lymph nodes, lungs, spleen, and cutaneous-mucosal, respectively.<sup>6-10,36-43</sup>

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