

# Pulmonary Paracoccidioidomycosis

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## ABSTRACT

Paracoccidioidomycosis is a subacute or chronic systemic mycosis caused by *Paracoccidioides brasiliensis*, a soil saprophyte and thermally dimorphic fungus. The disease occurs mainly in rural workers in Latin America and is the most frequent endemic systemic mycosis in many countries of South America, where almost 10 million people are believed to be infected. Paracoccidioidomycosis should be regarded as a disease of travelers outside the endemic area. The primary pulmonary infection is subclinical in most cases, and individuals may remain infected throughout life without ever developing clinical signs. A small proportion of patients present with clinical disease. The lungs are frequently involved, and the pulmonary clinical manifestations must be differentiated from many other infectious and noninfectious conditions. Diagnosis should be based on epidemiological, clinical, and microbiological data. Effective treatment regimens are available to control the fungal infection, but most patients develop fibrotic sequelae that may severely hamper respiratory and adrenal function and the patient's well-being.

**KEYWORDS:** Paracoccidioidomycosis, South American blastomycosis, *Paracoccidioides brasiliensis*, systemic mycosis

Systemic endemic mycoses are frequently found throughout the American continent, where they have an important impact on public health. These mycoses include blastomycosis, histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis (PCM). The latter, previously named South American blastomycosis, is a systemic endemic granulomatous mycotic disease caused by *Paracoccidioides brasiliensis*, a thermodimorphic fungi. The disease was first described by Adolpho Lutz in the city of São Paulo, Brazil, in 1908.<sup>1,2</sup>

Paracoccidioidomycosis occurs in most Latin America countries, with the endemic zone extending South from Tampico, Mexico, to Buenos Aires, Argentina.<sup>3,4</sup> It is considered to be the most important systemic fungal infection affecting countries in South America, with a higher incidence in Brazil (80% of the

cases), Colombia, and Venezuela, followed by Argentina, Peru, Ecuador, Uruguay, and Paraguay (Fig. 1).<sup>2,5,6</sup> Outside Latin America, PCM may also be regarded as a disease of travelers because of several nonautochthonous cases observed in countries outside Latin America, all represented by infected individuals who had previously lived for an extended time in the endemic area.<sup>5,6</sup> These cases have been reported, mostly in the United States, Europe, the Middle East, and Asia. The time between visiting the endemic area and the onset of overt disease is highly variable (range, 0.5 to 37 years; mean 15 years).<sup>4</sup>

It is estimated that ~10 million people in Latin America are infected with *P. brasiliensis*, of which only ~1 to 2% will develop clinical forms of the disease.<sup>2,7,8</sup> PCM is a systemic pathological process that may involve many different organ sites, especially the lungs, mucous

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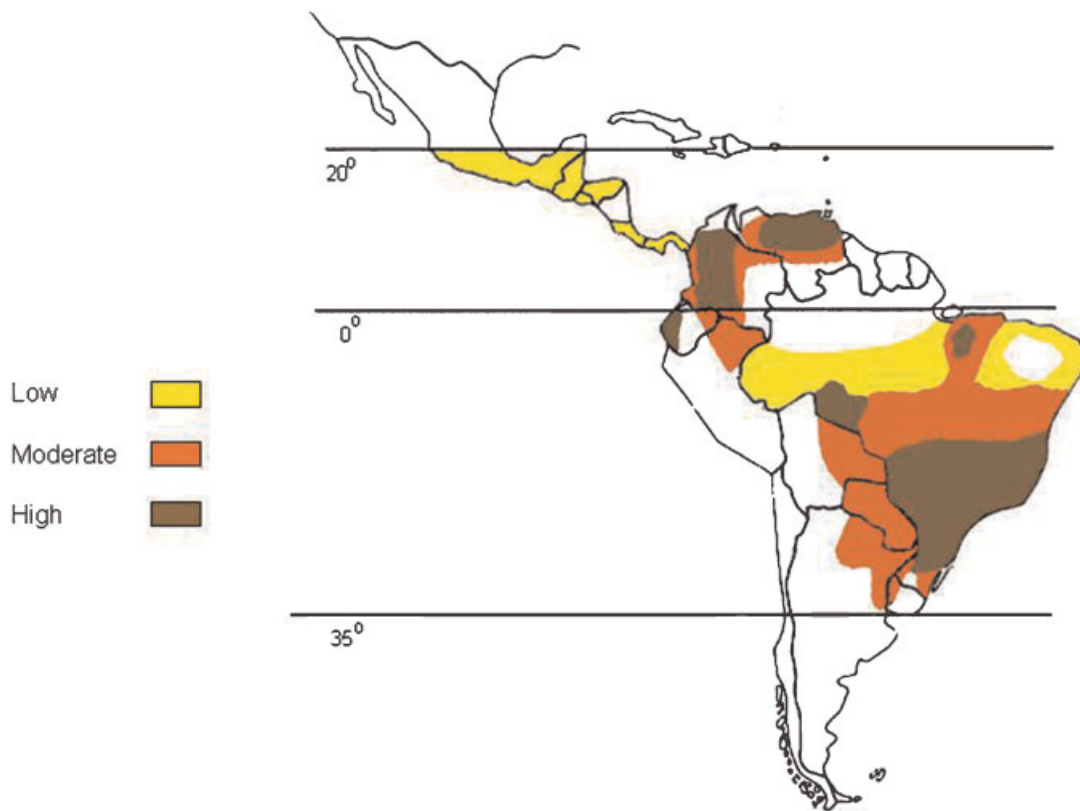
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**Figure 1** Geographic distribution of paracoccidioidomycosis in Latin America. Adapted from Colombo, Queiroz-Telles.<sup>5</sup> (With kind permission of Springer Science + Business Media.)

membranes, skin, lymph nodes, central nervous system (CNS), adrenal glands, and virtually all organs and tissues.<sup>4,5,9–11</sup> Like other endemic systemic mycoses, PCM is an airborne infection. It commences following inhalation of fungal conidia from free-living mycelial forms. The fungal propagules are small enough to reach the alveoli, where they are ingested by alveolar macrophages and over the course of a few days convert to the parasitic forms and begin to reproduce. The lung is the port of entry and the organ primarily affected.<sup>4,5,11–14</sup>

## MYCOLOGY

*P. brasiliensis* is a soil fungus that undergoes a dimorphic switch following host inhalation. Dimorphism appears to be regulated by temperature, oxygen, and nutrients.<sup>4,5,15</sup> According to recent molecular data, *P. brasiliensis* is taxonomically related to the family Onygenaceae (order Onygenales, Ascomycota), which is the same common group of most of the agents of the endemic systemic mycoses (*Blastomyces dermatitidis*, *Coccidioides immitis*, and *C. posadasii*, and *Histoplasma capsulatum*).<sup>16–19</sup> In addition, a distinct clade from Onygenaceae *sensu lato* has been proposed as a new family, Ajellomycetaceae, to encompass the monophyletic group Ajellomyces, which includes the anamorph

genera *Blastomyces*, *Emmonsia*, *Histoplasma*, and *Paracoccidioides*.<sup>18–20</sup>

Molecular phylogenetic and phylogeographic studies have also indicated that the several species members of the Onygenaceae family may have originated in the Americas around 3 to 20 million years ago.<sup>21</sup> These agents are biologically related to a fungal group that phylogenetically evolved in association with mammalian hosts.<sup>18</sup> Recently, the use of molecular methods showed that *P. brasiliensis* is not a single species but rather a species complex comprising at least three cryptic species: S1 (present in Brazil, Argentina, Paraguay, Peru, and Venezuela); PS2 (*P. lutzii*; from Brazil and Venezuela); and PS3 (restricted to Colombia).<sup>2,9,19</sup> The clinical and therapeutic impacts of this genotypic diversity have not been evaluated, but the identification of an association of each species type with distinct profiles of clinical manifestation, response to treatment, and epidemiological patterns seems to be just a question of time.<sup>2,9</sup>

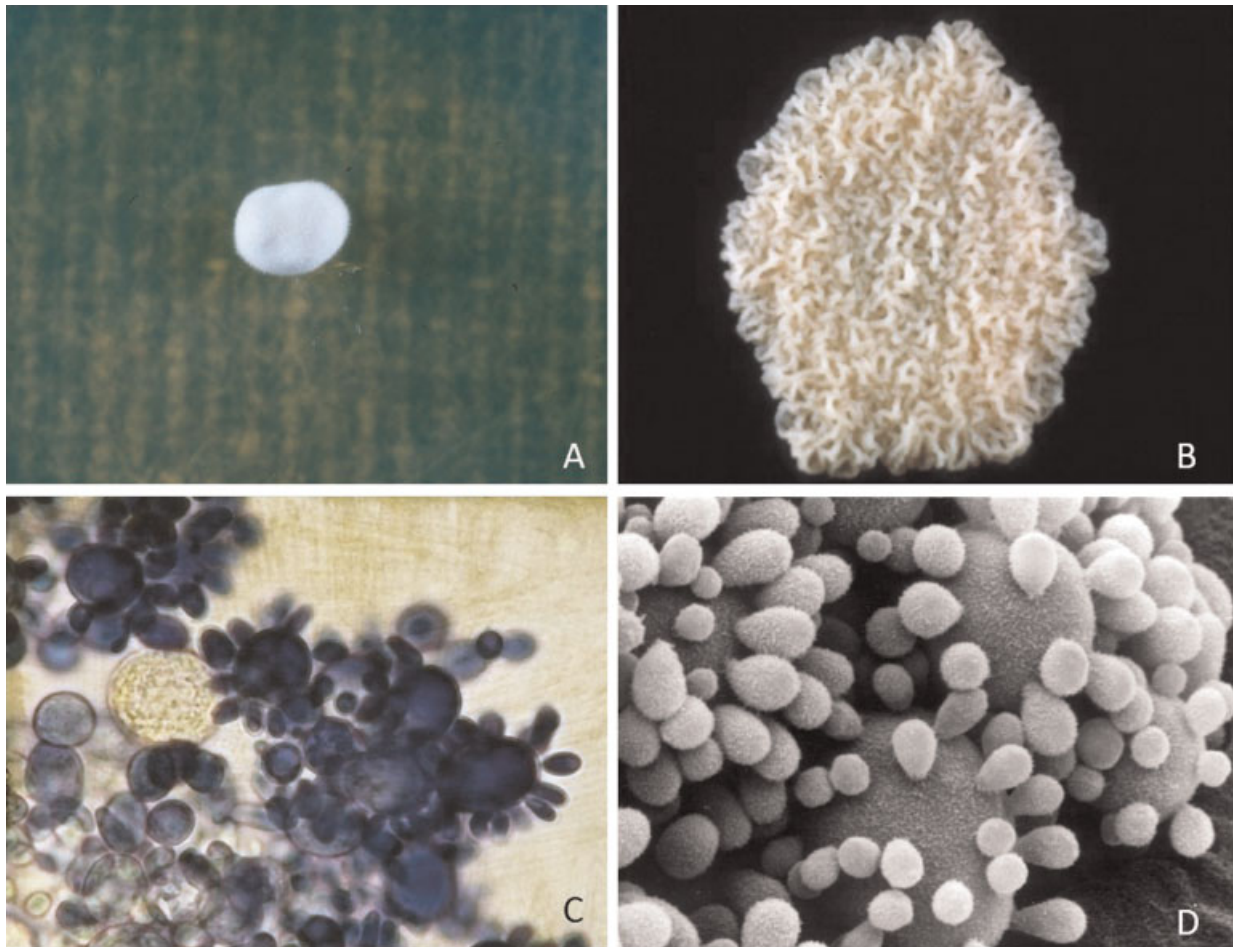
Although the precise ecological niche of *P. brasiliensis* has not been determined, it is thought that this fungus is a soil microbiota member that produces several types of conidia acting as propagule cells.<sup>4,11,14</sup> In cultures maintained at room temperature (<28°C), the fungus grows in the mycelial form, which is represented by septate and dichotomously branching hyaline hyphae.<sup>4,5</sup>

Mycelia may form different types of conidia, including chlamidoconidia, terminal conidia, and arthroconidia. The latter are believed to be the infectious propagule. The yeast form (5 to 30  $\mu\text{m}$  in diameter) is found in cultures incubated at 28° to 37°C as well as in tissue and body fluids. The characteristic morphology of the yeast phase of *P. brasiliensis* is a mother cell surrounded by several blastoconidia.<sup>4,5,22</sup> In vitro and in vivo, the hallmark fungal elements are represented by globose large cells surrounded by narrow-necked multiple budding yeasts (resembling a “pilot well” or a “floating mine”) or mother cells presenting only two buds (resembling a “Mickey Mouse” head) (Fig. 2). Pathogenicity appears to be linked to morphogenesis because strains unable to undergo the morphological transition are not virulent.<sup>4,3,22,23</sup>

### ECO/EPIDEMIOLOGY

Some epidemiological aspects of PCM are less well understood than those of other systemic mycoses. The

natural habitat of *P. brasiliensis* and related fungi probably consists of soil from the several tropical and subtropical humid areas of the endemic regions in Latin America.<sup>3,4</sup> This evidence comes from sporadic fungal isolations from soil samples and internal organs from armadillos. The fungus ecological niche remains hypothetical.<sup>24–30</sup> Reporting the fungal disease to the health authorities is not required in Latin American countries; consequently, there are few data on the incidence of PCM in endemic areas. Epidemiological surveys with a paracoccidioidin intradermal test show a high prevalence of reactors individuals, including in humans, sheep, cows, and horses.<sup>3,4,31–33</sup> These data suggest that the prevalence rate of *P. brasiliensis* human infection in endemic areas may be as high as 50 to 75% in the adult population.<sup>4–7</sup> Estimates of the incidence of PCM vary from one to three new cases per 100,000 inhabitants of endemic areas with an estimated mortality rate of 1.45 deaths per million inhabitants, according to data from the Brazilian Ministry of Health.<sup>4–7,34,35</sup> The infection is more prevalent in rural dwellers, but recent epidemiological data



**Figure 2** Mycological aspects of *Paracoccidioides brasiliensis*. (A) Colonies at mycelial phase at room temperature and (B) at the yeast phase, at 37°C. (C) Several multibudding yeast cells in lymph node aspirate stained by Grocott-Gomori stain. (D) In scanning electron microscopy, the yeast cells may resemble a “floating mine” aspect. (A), (B), and (C) adapted from Colombo, Queiroz-Telles.<sup>5</sup> (With kind permission of Springer Science + Business Media.)

suggest that changes in agricultural practices such as extensive use of agricultural pesticides, especially azole derivatives, and the progressive mechanization of the plantations may result in a reduction in the incidence of infection in some areas.<sup>2,9,36,37</sup> One of the characteristics of PCM is its distribution according to gender: the chronic form of the disease is more prevalent in males aged 30 to 60 years. The average male to female ratio is 13:1, but it may be as high as 150:1 in Colombia, Ecuador, and Argentina.<sup>3,4,7</sup> It was experimentally demonstrated that *P. brasiliensis* has  $\beta$ -estradiol membrane receptors that inhibit the transition of conidia-mycelial propagules to the yeast form, a critical step in the pathogenesis of the disease.<sup>38</sup> For this reason adult women are protected from developing the disease but not from infection. Furthermore, the high male to female ratio is not observed in prepubescent individuals who may present with the acute or juvenile clinical form.<sup>3-5,38,39</sup> The influence of tobacco and alcohol consumption on chronic PCM may play a role in the development of the chronic form of the disease. In a case-control study, the risk of becoming ill was 14 times greater among smokers and 3.6 times greater among individuals with an alcohol intake of more than 50 g/d.<sup>2,5,40</sup> PCM is controlled by cell-mediated immunity, and cases have been only scarcely reported among patients with acquired immune deficiency syndrome (AIDS) or cancer or those who have undergone organ transplantations.<sup>4,24,41-43</sup> Like other systemic mycoses, there is no human-to-human transmission of *P. brasiliensis*, but unlike most of the systemic mycoses, no outbreaks have been reported to date.<sup>4,7,14</sup>

## CLINICAL MANIFESTATIONS

Paracoccidiomycosis infection is usually acquired early in life. Both humans and animals are thought to be infected by the respiratory route. Although the clinical forms of the disease are mostly observed in humans, sporadic cases in domestic animals have been reported.<sup>12,44</sup> After being inhaled *P. brasiliensis* usually causes a benign and transient pulmonary infection that may be recognized by a positive paracoccidin intradermal test.<sup>31-33</sup> The primary pulmonary infection is subclinical in most cases, and individuals may remain infected throughout life without ever developing clinical signs of PCM infection.

After infection, most patients are able to block the fungal growth and prevent dissemination of infection with the help of neutrophils and activated macrophages. In a minority of infected individuals, the disease may evolve in two patterns: the acute or subacute (juvenile type) form and the chronic form (adult type).<sup>4,5,7-12</sup> The acute or subacute form represents fewer than 10% of the cases, runs a more rapid course, and is more severe than the chronic form. Acute PCM occurs in children of both genders at the prepubescent phase, in youths, and in

adults under 30 years of age. It may progress to a disseminated disease.<sup>4,5,7-12</sup> The monocytic phagocytic system is involved in this form of the disease, and the most common clinical manifestations are fever, weight loss, lymphadenopathy, osteolytic lesions, hepatosplenomegaly, intestinal involvement, and sometimes bone marrow dysfunction.<sup>7-12,45</sup> Lung involvement is frequent in the chronic form but not in the acute form. After a long period of time (years), following loss of immune balance due to conditions not clearly defined, the infection may progress and give rise to full-blown disease. The chronic form of PCM usually results from the reactivation of pulmonary latent foci formed during the primary infection, but reinfection may also occur.<sup>12,13</sup> Chronic PCM is usually a slow progressive process affecting mostly adult males, but postmenopausal females may also present with the disease. In most cases, patients do not ask for medical assistance until systemic or lymphatic dissemination has occurred.<sup>5,10,14</sup> After dissemination, secondary lesions can affect numerous tissues, including the mucous membranes, lymph nodes, skin, adrenal glands, CNS, and other organs. The frequent involvement of the oral mucosa prompts patients to seek dental or medical consultation when the diagnosis is made.<sup>4,5,10-14</sup> Lesions occurring in the oropharyngeal mucous membranes may begin as a nonspecific gingivitis, with local bleeding and loose teeth. With time, typical painful granulomas, "mulberry-like" ulcers, may appear and may extend to the lips, tongue, gums, and the hard and soft palate. The larynx and vocal chords may present the same pattern of lesions, leading to different degrees of dysphonia or even aphonia. Most patients respond to therapy, but incapacitating residual lesions frequently occur.<sup>7,10</sup> Uncontrolled disease may culminate in death.

When associated with human immunodeficiency virus (HIV), most cases of PCM exhibit clinical features of disseminated disease, sometimes with characteristics of both chronic and acute forms of the disease. Clinical manifestations include prolonged fever, weight loss, lung involvement, generalized lymphadenopathy, splenomegaly, hepatomegaly, and skin rash.<sup>46-48</sup> In HIV-positive patients, the infection may be documented in patients with early or advanced stages of the disease. It is important to mention that the drop in the CD4 cell count in patients coinfecting with HIV and *P. brasiliensis* may be a result not only of advancing viral infection but may also be caused by the imbalance between the host and *P. brasiliensis*, as reported with tuberculosis in the setting of HIV.<sup>46-48</sup>

## THE LUNGS IN PARACOCCIDIOIDOMYCOSIS

The respiratory system is the most common primary site of PCM. It is assumed that, initially, the lung involvement is usually asymptomatic or, if present, symptoms are mild and cannot be differentiated from those of

bacterial or viral pulmonary infections.<sup>11–13</sup> The intensity and severity of the lung lesions present at the moment of the diagnosis predict the chance of developing residual lesions. Lung sequelae in pulmonary paracoccidioidomycosis are reported in more than 50% of patients in advanced stages of the disease and may severely impair respiratory function.<sup>4,13</sup>

With progression, the disease usually runs a course of a continuous or recurrent respiratory infection with cough, mucoid or purulent sputum, and several degrees of dyspnea. Unlike the clinical picture of the acute clinical form, pulmonary manifestations are depicted by 90% of the patients with chronic PCM.<sup>4,11–13</sup> Respiratory complaints are not the main reason for medical consultation. The unifocal pulmonary involvement is observed in ~25% of the cases. In most of the cases, medical advice is sought only after dissemination

to extrapulmonary sites or multifocal disease.<sup>12,13</sup> Pulmonary signs and symptoms are nonspecific and include dry or productive cough, shortness of breath, anorexia, and weight loss. Hyperthermia is usually associated with comorbidities such as viral or bacterial lung infections, especially pulmonary tuberculosis.<sup>2,4,11</sup> Chronic pulmonary paracoccidioidomycosis may mimic tuberculosis, and both may coexist in the same host in 10 to 15% of the cases (Table 1). Although the association between the two diseases has been documented in the literature, misdiagnosis is common due to the superimposition of and the similarity between their clinical and radiographic presentations.<sup>49</sup> There are other pulmonary chronic conditions that may resemble PCM, such as pulmonary mycoses (histoplasmosis, coccidioidomycosis, blastomycosis, and cryptococcosis), idiopathic interstitial fibrosis, Wegener granulomatosis (granulomatosis with

**Table 1 Differences and Similarities between Pulmonary Tuberculosis and Paracoccidioidomycosis**

	Tuberculosis	Paracoccidioidomycosis
EPIDEMIOLOGY		
Age	Wide range	Restricted (30–60 years old)*
Gender	Indistinct	Prevalent in males (13:1)*
Prevalence	1–3/100,000	45/100,000
Mortality	5%	1.45/million
Geographic distribution	Worldwide, more urban	Latin America, rural zones
MICROBIOLOGY		
Etiologic agent	<i>Mycobacterium tuberculosis</i>	<i>Paracoccidioides brasiliensis</i>
Source of infections	Human/animal	Soil
Infection	Contagious disease	Noncontagious
Cultivation	Fastidious	Fastidious
CLINICAL ASPECTS		
Signs and symptoms Weight loss	Well defined ++/++++	Nonspecific ++/++++
Fever	++++	+/-**
Cough	++++	+/-
Hemoptoic sputum	+/++++	+/-
Pleural involvement	Yes	No
Association	Paracoccidioidomycosis (10–15%)	Tuberculosis (10–15%)
RADIOLOGY		
Image localization	Prevalent in upper zone	Prevalent in middle zone
Cavities	+++ /++++	++ /++++
Pleural images	Yes	No
Dissemination	Uni-/multifocal	Uni-/multifocal
LABORATORY CHANGES		
Red blood cells	Normocytic Normochromic anemia	Normocytic Normochromic anemia
White blood cells	Leukocytosis/leukopenia	Leukocytosis/leukopenia
Erythrocyte sedimentation rate	+++ /++++	+/++
Serum proteins	Normal/low	Normal/low
NATURAL EVOLUTION		
Consumption	Yes	Yes
Anergy	Yes	Yes
Death	Yes	Yes

\*Exceptionally, lung involvement may occur in acute/subacute paracoccidioidomycosis. In these cases younger individuals from both genders can be affected.

\*\*Fever may occur in patients with associated infections.

polyangiitis), sarcoidosis, neoplasia, and other infectious and noninfectious chronic diseases.

Active pulmonary involvement and residual fibrotic lesions are observed, respectively, in 80% and 60% of patients with PCM. Consequently the lungs are a significant site of morbidity and mortality in patients with PCM.<sup>12,13,49</sup>

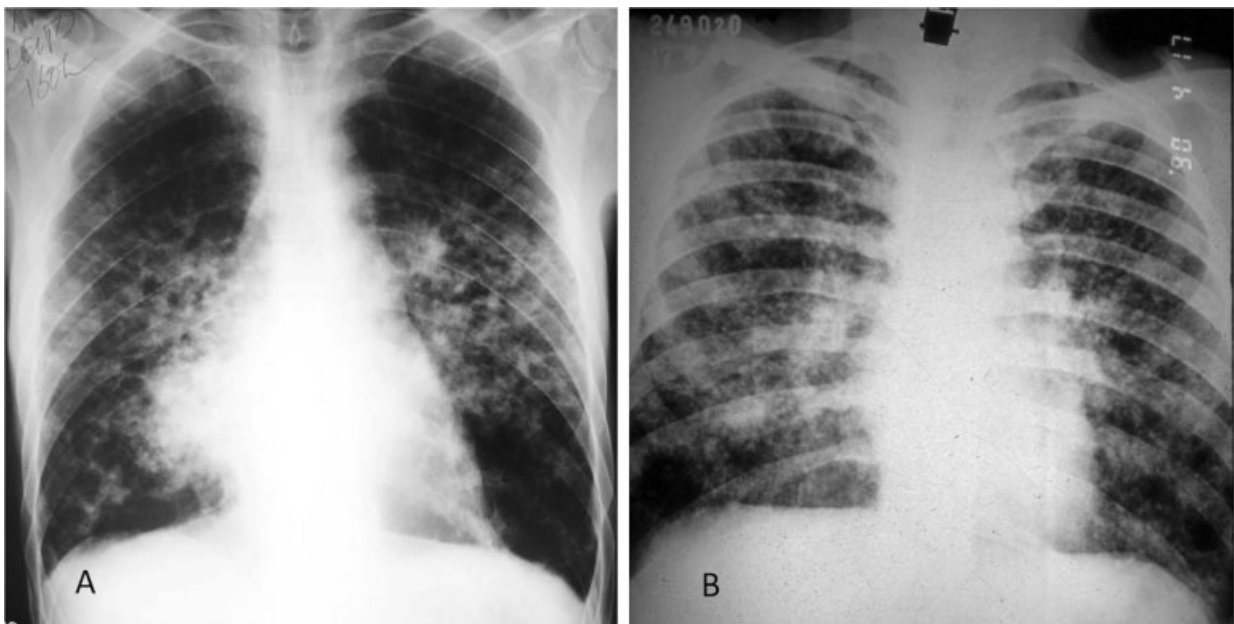
## RADIOLOGY

Many of the radiological findings are nonspecific, including diffuse micronodular infiltrates, tumoral mass, and cavitations. However, mixed infiltrates distributed in the median zone (bat or butterfly wing image) is strongly suggestive<sup>11,14,50</sup> (Fig. 3). In spite of the high proportion of lung involvement and the nonspecific clinical picture, in chronic pulmonary PCM a clear clinical–radiological dissociation is a common feature.<sup>51</sup> The chest radiographic findings in patients with pulmonary PCM are most commonly interstitial opacities (reticular or nodular), or mixed alveolar and interstitial lesions. When observed, the cavitory images must be differentiated from tuberculosis and other cavitating lung diseases. Radiographic and computed tomographic (CT) findings correlate with the pathological features. The ground-glass attenuation correlates to inflammation or fibrosis of the alveolar septa. Air space consolidations and large nodules correlate pathologically to acute alveolar inflammatory exudates, with areas with necrosis and cavitation. Small random pulmonary nodules correspond to granulomas. Interlobular septal thickening represents inflammatory infiltration or fibrosis.<sup>52–54</sup>

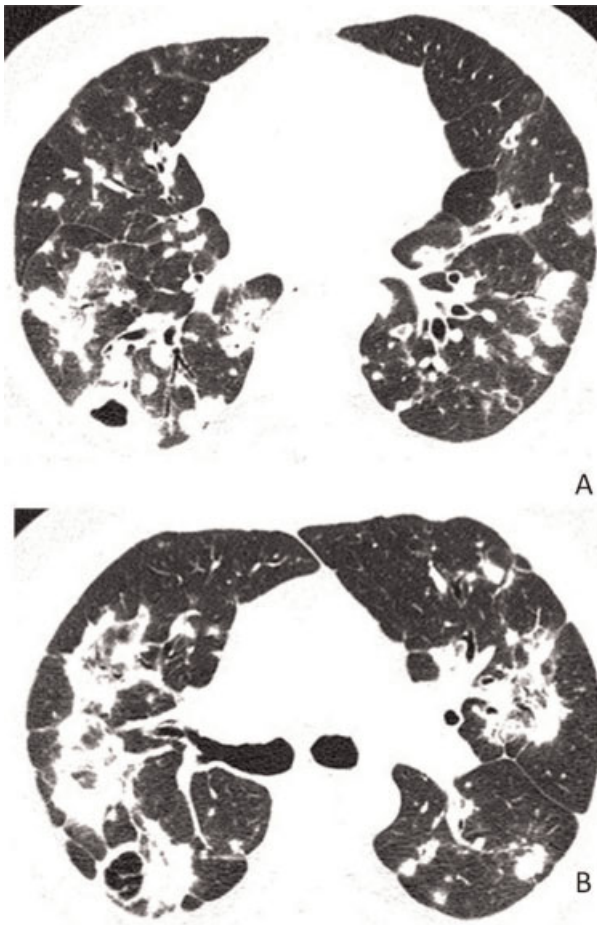
The residual abnormalities after treatment in patients with PCM are characterized by alveolar and interstitial opacities, enlarged and calcified hilar and mediastinal lymph nodes, distortion of the pulmonary parenchyma, and pseudotumoral masses. Although the association between PCM and tuberculosis (TB) has been documented, misdiagnosis is common due to the overlap of radiographic findings. The high-resolution CT (HRCT) findings of patients with untreated pulmonary PCM consist mainly of ground-glass attenuation areas associated with small centrilobular nodules, cavitary nodules, large nodules, parenchymal bands, and areas of cicatricial emphysema. These lesions are seen predominantly in the posterior and peripheral regions of the lungs. There is a discrete predominance in the middle lung zones.<sup>52–54</sup> The reversed halo sign is seen in ~10% of patients and reflects a central area of predominantly interstitial inflammation surrounded by air-space infiltration. The pulmonary abnormalities seen in patients after treatment are characterized as interlobular septal thickening, nodular opacities, traction bronchiectasis, peribronchovascular interstitial thickening, areas of cicatricial emphysema, and centrilobular nodular opacities. These HRCT findings have a predominant bilateral and symmetric distribution affecting all lung zones<sup>55</sup> (Fig. 4).

## RESIDUAL FORMS

PCM is a granulomatous infectious process that heals after therapy and leads to several grades of fibrosis, regardless of the involved organ.



**Figure 3** Chronic paracoccidioidomycosis. (A) Anteroposterior chest radiograph in a man with pulmonary paracoccidioidomycosis shows bilateral consolidations with butterfly wing distribution. (B) Anteroposterior chest radiograph in a 59-year-old man shows multiple small pulmonary nodules. Confluence of the nodules is seen in the right lung.



**Figure 4** High-resolution computed tomographic scans of patients with chronic paracoccidioidomycosis. (A) Image at level of inferior pulmonary veins shows multiple nodules and masses in a 59-year-old man. Associated cavitated mass is seen in right lung. (B) Image at level of carina shows opacities with the reversed halo sign in a 55-year-old man.

Lung fibrosis is associated with morbidity and mortality in patients with PCM, even after successful treatment. Almost 60% of patients display respiratory sequelae due to lung fibrosis. The principal related clinical findings are progressive dyspnea and cor pulmonale that may alter the respiratory function, leading to the patient's incapacitation so that normal activities become a burden.<sup>56</sup> With respect to extrapulmonary sequelae, microstomia, dysphonia, and several grades of stenosis of the glottis and trachea have also been reported.<sup>5,9,56</sup>

## DIAGNOSIS

Suspicion of PCM is based upon clinical and epidemiological data and confirmed by microbiological demonstration of the etiologic agent. Evaluation for PCM is warranted in patients from endemic regions who have weight loss, respiratory symptoms, oral or cutaneous

lesions, and lymph node enlargement associated or not with Addison syndrome.<sup>5,14</sup>

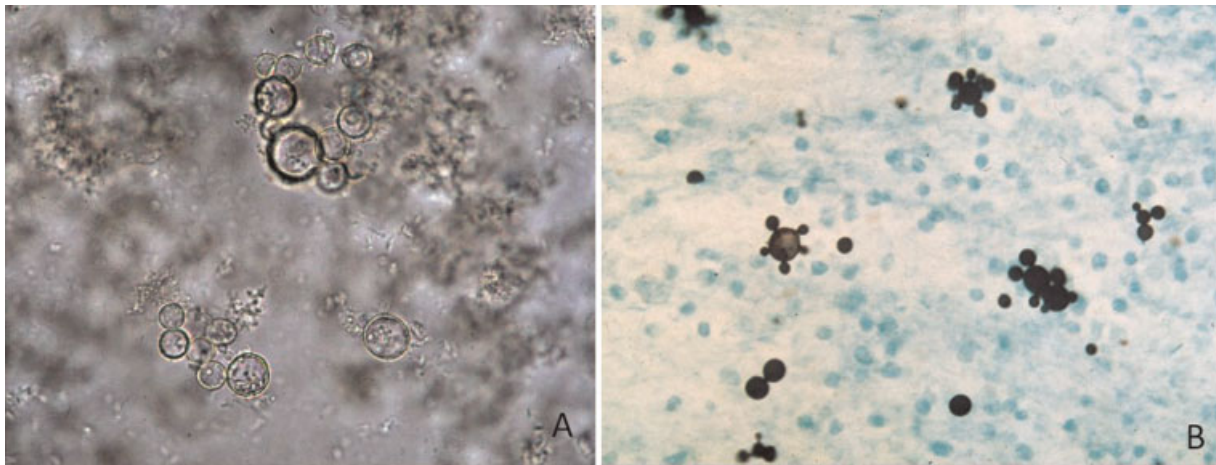
## Microbiological Diagnosis

The definitive diagnosis of PCM, including the pulmonary disease is based on the microscopic visualization of fungal structures of *P. brasiliensis* in the yeast phase or by isolating the fungus from any clinical specimen. Characteristically the yeast cells may look birefringent under the light microscope because they have a thick mucopolysaccharide cell wall (Fig. 4). Morphology consists of globose large cells surrounded by narrow-necked multiple budding yeasts or mother cells presenting only two buds, respectively, the forms that resemble a "pilot well" and a "Mickey Mouse head." Sometimes small round to oval nonbudding or single-budding cells can be found, but they are not considered typical of PCM. The fungal elements are easily documented by routine methods, including potassium hydroxide (KOH) or calcofluor for wet mounts and Grocott-Gomori stain or periodic acid-Schiff (PAS) for smears (Fig. 5).<sup>5,14</sup> Digested and concentrated sputum can be positive in 60 to 70% of the subjects with the chronic pulmonary form. Because of the high rates of tuberculosis coinfection, respiratory samples should also be stained by the Ziehl-Nielsen method. Samples can be obtained from any affected tissue or organic fluid such as sputum, bronchoalveolar lavage (BAL), lymph node aspirate, and the like.<sup>14,49</sup>

*P. brasiliensis* is a fastidious organism and cultures usually take 20 to 30 days to grow from clinical specimens on Sabouraud dextrose agar, or agar containing chloramphenicol and cycloheximide. If isolation is made at room temperature, the demonstration of the fungus dimorphism is mandatory because the mycelia phase morphology is nonspecific (Figs. 2A, B).

## Nonmicrobiological Tests

In clinical practice serological methods are usually used to monitor the patient's response to therapy.<sup>57</sup> However, in some cases, the microbiological documentation of PCM is not feasible because patients with the chronic pulmonary form of the disease may have minimal sputum with negative BAL and lung biopsy.<sup>14</sup> For such cases, the detection of specific antibodies or antigens is the best diagnostic tool. Quantitative immunodiffusion tests are the most reliable and suitable methodology to detect anti-*P. brasiliensis* antibodies.<sup>57,58</sup> Other serological tests include immunoenzymatic assays and counter-immunoelectrophoresis. Ninety percent of patients may exhibit specific antibodies before therapy using the gp43-glycoprotein exoantigen in the immunodiffusion reaction.<sup>4,14</sup> This test is highly sensitive and specific, but it may cross-react with serum from patients with histoplasmosis.<sup>59</sup> Antigen detection is also a valuable tool in



**Figure 5** Microbiological diagnosis of paracoccidioidomycosis. (A) Wet mount of a fresh sputum examination from a patient after clarification with potassium hydroxide. (B) Grocott silver methenamine staining of a smear from lymph node aspirate. Adapted from Colombo, Queiroz-Telles.<sup>5</sup> (With kind permission of Springer Science + Business Media.)

the diagnosis and prognosis of patients with PCM, including those with CNS involvement, but these methods have not yet been standardized.<sup>60–63</sup>

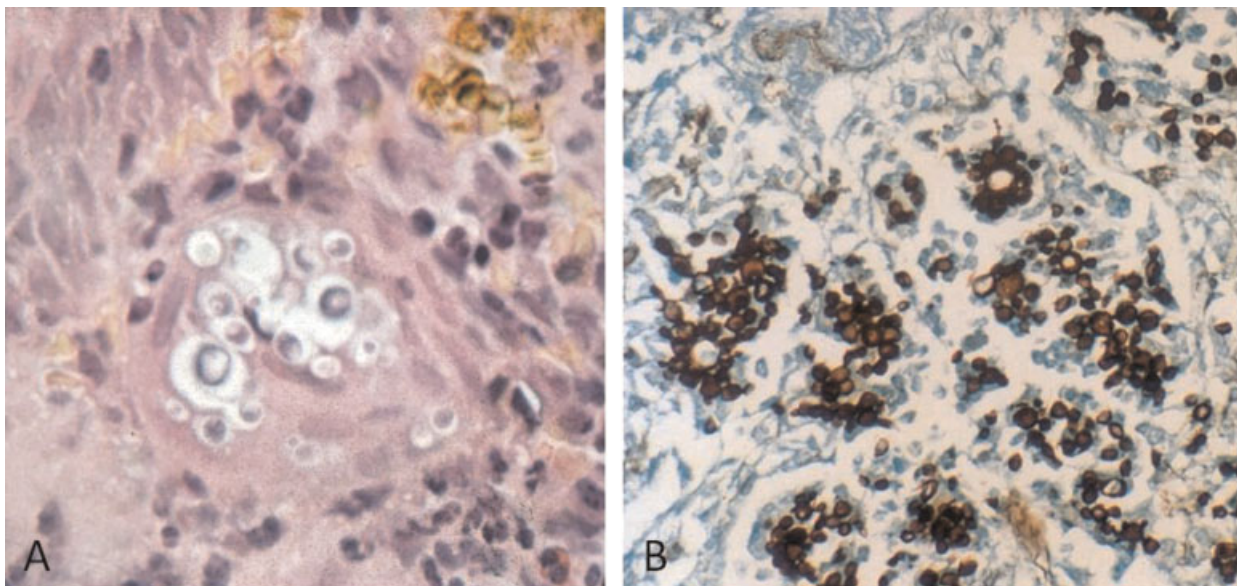
### Histopathology

Tissue sections can be stained by hematoxylin-eosin, Grocott-Gomori stain, or PAS (Fig. 6). The tissue reaction is similar to those of other systemic mycosis. *P. brasiliensis* yeast cells may be observed in granulomatous or mixed granulomatous and suppurative infiltrates.<sup>2,63</sup> Unlike *Blastomyces dermatitidis*, yeasts are multibudded and have a thin neck for daughter cells. Sometimes *P. brasiliensis* predominantly produces mi-

nute forms in its parasitic life. These elements may not show the typical multibudding aspect and may be mistaken as yeast cells of *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Sporothrix schenckii*, *Coccidioides immitis* endospores, and capsule-deficient *Cryptococcus neoformans*.<sup>3,14</sup>

### TREATMENT

*P. brasiliensis* differs from other pathogenic fungi because it is a very sensitive organism when exposed to antifungal drugs; even sulfonamides can inhibit its growth.<sup>64</sup> So a large therapeutic armamentarium is available for patients with PCM, including sulfonamide



**Figure 6** Histopathology of paracoccidioidomycosis. (A) Multibudding yeast cells of *P. brasiliensis* in a Langerhans giant cell stained by periodic acid-Schiff. (B) Globose cells surrounded by multiple budding yeasts depicting the typical "pilot-wheel" shape of the fungus. Adapted from Colombo, Queiroz-Telles.<sup>5</sup> (With kind permission of Springer Science + Business Media.)



**Table 2 Most Used Drugs in Paracoccidioidomycosis**

Drug	Dosage	Duration of Treatment
Itraconazole	200 mg per day	6–18 months
Cotrimoxazole	Trimethoprim, 160 mg Sulfamethoxazole, 800 mg (by mouth or intravenous, two or three times a day)	18–24 months*
Amphotericin B	1.5–2 g total dose	30–90 days**

\*Extended therapy with central nervous system involvement.

\*\*Require maintenance therapy with itraconazole or cotrimoxazole.

derivatives (sulfadiazine, sulfadoxine, sulfamethoxypropyridazine, cotrimazine, and trimethoprim-sulfamethoxazole), amphotericin B, azoles (eg, ketoconazole, itraconazole, fluconazole, voriconazole, and posaconazole), and terbinafine.<sup>4,5,10,65–71</sup> Despite the fact that PCM has a high incidence and high morbidity rate in South America, very few studies have been conducted to define optimal treatment. Currently, itraconazole is considered the standard treatment for mild and moderate clinical forms of PCM. The scientific evidence is supported by a single-center, open, noncomparative clinical trial and two randomized, unblinded, comparative clinical trials. Unfortunately these studies lacked sufficient power to assess response or cure rates.<sup>68</sup> For severe and disseminated forms of paracoccidioidomycosis an intravenous formulation of antifungal drug is usually required. Conventional or lipid formulations of amphotericin B are indicated to treat severe disseminated cases in patients who are intolerant of other agents or who have refractory infections. To avoid relapses, patients who were treated with amphotericin B must receive maintenance therapy for long periods, with either sulphonamides or itraconazole (Table 2). Among the second-generation azoles, both voriconazole and posaconazole have been evaluated in patients with PCM. In a pilot randomized clinical trial, oral voriconazole was as effective as itraconazole for treating patients with chronic PCM. Voriconazole penetrates well into the CNS and has a potential indication in patients with neuroparacoccidioidomycosis).<sup>70,71</sup> With respect to posaconazole, preliminary results suggest that this drug is also effective in treating chronic and subacute forms of PCM.<sup>72</sup> All patients must remain on therapy until clinical signs and symptoms of the infection are resolved, complete clearance of fungal elements has occurred, and a significant decrease and stabilization in the antibody titers is documented.<sup>56,73</sup>

The main therapeutic challenges in the management of PCM are the long periods of treatment and the high frequency of relapses and sequelae (particularly pulmonary fibrosis). In experimental models of chronic pulmonary PCM, itraconazole combined with pentoxifylline exhibited antifibrotic effects. In the future this new therapeutic strategy may be evaluated in patients.<sup>74</sup>

A second and valid strategy is the use of vaccines as a potential adjunct to antifungal therapy. Peptide P10 (a derivative of GP43) has been tested in animal models. This strategy protected mice against intrathecal infection, induced interferon- $\gamma$  and interleukin-12-rich immune responses, and reduced fungal burden in challenged immunosuppressed animals.<sup>75</sup> This strategy should be evaluated in humans in clinical trials.

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