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TROPICAL DISEASES IN COLOMBIA (A RESTREPO, SECTION EDITOR)

# Paracoccidioidomycosis: Global Vision of a Forgotten Endemic Mycosis

Lina María Rodríguez Molina[1] · Angela María Tobón Orozco[2]

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**Abstract**

**Purpose of Review** This review aims to evaluate the disease globally from its immunopathogenesis to clinical manifestations and treatment. We would like to call attention to an infectious disease, restricted to some countries in Latin America and with serious sequelae mainly at the pulmonary level.

**Recent Findings** Paracoccidioidomycosis is a systemic fungal infection caused by a complex of thermal dimorphic fungi named *Paracoccidioides brasiliensis* and *P. lutzii*. It is the second most prevalent endemic mycosis in Latin America and is usually restricted to this geographical area. It is characterized by a primary pulmonary infection from where it disseminates to the oropharyngeal mucosa, lymph nodes, skin, and other organs. There are a great number of people infected but just a few develop clinical manifestations. Azoles are used for the treatment of the disease. Itraconazole is preferred in mild to moderate disease, and amphotericin B products are reserved for patients with severe or disseminated disease.

**Summary** There are new clinical, epidemiological, and laboratory aspects that allow an opportune diagnosis of this disease. Also, we would like to advance in the knowledge of the immunopathogenic process initiated by the fungal infection, to find mechanisms that prevent infection and the development of the fibrosis produced by it.

**Keywords** Paracoccidioidomycosis · Mycoses · Endemic diseases

## Introduction

Paracoccidioidomycosis, also called South American blastomycosis, is almost exclusive in Latin America. It is a systemic mycosis that enters the body through the lungs and can affect almost any organ with predilection for the mucosa [1].

## Causative Organism

Paracoccidioidomycosis is caused by fungi species belonging to the genre *Paracoccidioides*. There are two well-known species: *Paracoccidioides brasiliensis* and *P. lutzii*. *P. brasiliensis* has a complex of at least five phylogenetic species: S1a, S1b, PS2, PS3, and PS42. *P. lutzii* has only one species [2]. It is a thermally dimorphic fungus that grows as mycelium in nature at 71–78 °F, and as yeast in human tissue at 98.6 °F [3].

## Route of Entry

*P. brasiliensis* and *P. lutzii* enter the body through the respiratory tract, developing an asymptomatic or subclinical disease, followed by dissemination to the skin and other organs. Less frequently, the fungus can also be inoculated after trauma especially by workers from rural areas, which they do teeth cleaning as well as anal cleaning with vegetal material [4••].

## Epidemiology

Paracoccidioidomycosis is the second most prevalent endemic mycosis in Latin America after histoplasmosis. Brazil is the country with the highest incidence of the disease with approximately 80% of cases. The notification of this disease is not mandatory, reason why there is no precise data on its

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✉ Angela María Tobón Orozco
atobon@ces.edu.co

[1] Universidad Pontificia Bolivariana, Medellín, Colombia

[2] Instituto Colombiano de Medicina Tropical-Universidad CES, Medellín, Colombia

incidence. It is estimated that there are approximately 10 million people infected, of those only 1–2% develop clinical disease [4••].

The infection is usually acquired in the first two decades of life, with a peak incidence between the ages of 10 and 20 years. A low percentage of affected individuals develop clinical manifestations in adulthood between the ages of 30 and 50 years, after reactivation of a latent infection [5]. The disease is more common in males than females with a male to female reported ratio of 13:1. This fact could be possibly explained by estrogens, which are considered to be a protective factor in females [4••].

Regarding epidemiological distribution of phylogenetic species, it has been seen that S1a and A1b are mainly located in southern regions of South America: south and southeast of Brazil, Argentina, and Paraguay. PS2 species have sporadic distribution with fewer cases reported. PS3 is endemic in Colombia and PS4 in Venezuela. *P. lutzii* is distributed in the Middle West area: amazon region of Brazil and Ecuador [2, 6].

In 2000 in Colombia, they did a study to determine the endemic regions of the disease. Seven regions belonging to the Andeans region were found: Antioquia, Santander, Cundinamarca, Meta, Norte de Santander, Caldas, Boyacá, and Tolima. And there is only one located in the Sierra Nevada of Santa Marta in the Magdalena region [7].

Other study identified ecological independent variables related to the presence of the fungus: altitudes between 1000 and 1499 m above sea level, annual rainfall between 2000 to 2999 mm, and the presence of humid forests. However, the identification of the natural habitat of *Paracoccidioides* spp. has not been found [8].

Paracoccidioidomycosis is more prevalent among rural area workers, particularly coffee-, cotton-, or tobacco-growing farmers. This explains why most of the endemic regions in Colombia belong to the Andean region where coffee crops are common. These epidemiological scenarios might change with the new farming practices. Places with sugar cane plantations have a lower incidence of the disease because these crops require the use of potent pesticides and extensive burns to grow the cane [9].

In general, the disease does not affect animals living in the endemic regions. There are only a few reports of dogs, squirrel monkeys, and nine-banded (*Dasypus novemcinctus*) and seven-banded (*D. septemcinctus)* armadillos, infected with the fungus [5].

## Immunopathogenesis

Most of the infected individuals who do not develop apparent clinical disease exhibit Th1 immune response characterized by the activation of T CD4 and T CD8 lymphocytes which once activated, release cytokines that activate macrophages. Additionally, compact granulomas are formed by the collection of activated mononuclear cells, macrophages, histiocytes, and neutrophils. These structures help control fungal replication and dissemination.

On the contrary, people who develop the disease have a deficient Th1 immune response. More severe forms of the disease such as the acute and subacute forms and the chronic or disseminated form develop a mixed Th1 and Th9 immune response not capable of forming compact granulomas but capable of activating B lymphocytes, followed by hypergammaglobulinemia with high levels of specific antibodies including IgE and eosinophilia. Patients with chronic disease with low fungal loads have a low Th1 response, but it is enough to favor granuloma formation partially avoiding fungal replication. The loss of Th1 response is partially replaced by Th17 and Th22 responses. They both generate severe inflammatory responses in the mucous membranes mediated mainly by neutrophils which are the true responsible for tissue damage. In fact, a typical characteristic of patients with chronic disease is the mucous membrane involvement, especially the pulmonary and the oropharyngeal mucosa [2, 10].

Once conidia are inhaled, there is a morphological change to the yeast form in the pulmonary alveoli and this is a determinant factor for the development of the disease [11]. Among the involved mechanisms in this morphological change is the fungal synthesis of polyamines, which are macromolecules required for the appropriate growth and cellular differentiation in eukaryotes derived from the decarboxylation of ornithine by ornithine decarboxylase (ODC). In vitro, high levels of ODC have been seen during morphological change in *P. brasiliensis* [12].

Another pathway involved in the transition to yeast at 98.6 °F is the signaling regulated by the DRK1 (dimorphism-regulating kinase-1). Mutant strains for DRK1 lack virulence because they grow as mycelium even at 98.6 °F. It has been seen that DRK1 is expressed mainly in the pathogenic phase of *Paracoccidioides* spp. Ras and heterotrimeric G protein signaling controls multiple processes that include cAMP signaling, morphogenesis, differentiation, progression of the cellular cycle, and the expression of genes associated with pathogenicity, as well as calcium signaling through heat shock protein 90 (HSP90) that binds to and stables calcineurin controlling cellular differentiation. This protein increases the fungal capacity to adapt to the host when it grows in acid environments [12, 13].

Some studies have demonstrated that estrogens, more specifically 17β-estradiol (E2), alter morphological transition to yeast which could explain why it is more prevalent in males. The exact mechanism is not clear but it has been associated with cellular wall remodeling, energetic metabolism, and cellular signaling during the transition [14].

Another important virulence factor of *Paracoccidioides* spp. is the change in the composition of the cell wall in the mycelial phase. The cell wall is constituted by β-1,3-glicans as the main glucose polymer. Multiple budding yeasts reduce this polysaccharide and replace it for α-1,3-glicans. These reduction and replacement of β-glucans diminish the capacity of the host's phagocytic cells to recognize yeasts, protecting them against the host's immune response [12, 15].

It is considered that *Paracoccidioides* spp. are fungi that have developed multiple mechanisms to compensate nutritional and oxygen deficiencies needed for the morphological transition to yeast in the macrophage. The fungus is able to increase the number of specific copper, iron, hexose, and monosaccharide transporters for its survival [16].

*P. brasiliensis* produces melanin in the presence or absence of L DOPA, which promotes fungus virulence inhibiting phagocytosis and neutralizing oxygen radicals generated by the host's cells [17].

During the process of invasion, *Paracoccidioides* spp. require the interaction with the epithelial cells of the host to assure its intracellular survival. This phenomenon is facilitated by multiple adhesins. The 43-kDa glycoprotein (gp43) was the first described adhesin in *P. brasiliensis*. It adheres to extracellular matrix laminin and fibronectin. Once the fungus is in the pulmonary epithelial cell, degradation of cytokeratin and cell apoptosis is induced [11].

## Clinical Features

There are different forms of presentation of the disease that are classified according to what was stablished by the international paracoccidioidomycosis colloquium held in Medellin, Colombia, in 1986 [18] (Table 1).

**Table 1** Clinical classification

| Paracoccidioidomycosis international colloquium (1986) |
|---|
| I. Paracoccidioidomycosis infection. |
| II. Paracoccidioidomycosis disease: |
| A. Acute/subacute form (juvenile) |
| B. Chronic form (adult) |
| III. Residual paracoccidioidomycosis |

### Infection

Representing the first contact with the host, it usually occurs two decades before symptoms begin. Usually, the only response to infection is the cellular immune response to fungal antigens. Infection is diagnosed with intradermal reaction to specific antigens or in autopsies of individuals coming from endemic areas. It can be limited or progress to a disease [19].

### Acute/Subacute Disease

It is also known as the juvenile form of the disease. It is responsible for up to 5–25% of the cases; it is more frequent in children and teenagers but it can also affect young adults (under 35 years of age). It has an acute course with rapid evolution of the disease and dissemination to multiple organs. It is characterized by the involvement of the mononuclear phagocytic system [19–21].

Symptoms include fever, weight loss, mild to moderate anemia for 2–3 months, and cervical, axillary, and inguinal adenopathy. Jaundice might be present as well as hepatomegaly and splenomegaly. Bone marrow involvement might be seen sometimes. Half of the cases present with involvement of the gastrointestinal tract. Eosinophilia has also been described. Even though the fungus enters the body through the lung, pulmonary symptoms in this form of the disease are usually absent [3, 13].

Skin lesions are more frequently seen in adults than in children. They are usually developed in patients with severe systemic and disseminated disease. At early stages, acneiform papules in the face might be seen in patients with HIV [18].

### Chronic Disease

Chronic disease or adult form of the disease represents 90% of the cases. It has a chronic and insidious course. Lungs are the most affected organs, followed by mucocutaneous involvement. Intestines, central nervous system, bones, spleen, eyes, adrenal glands, genitourinary tract, and cardiovascular system may also be involved [19].

Pulmonary paracoccidioidomycosis is characterized by dry cough and dyspnea. Productive cough, hemoptysis, and chest pain have also been described [20]. Chest X-ray show mixed pulmonary bilateral infiltrates mainly in the lower and middle lobes. An important clinical characteristic is clinical-radiological discordance. Even though chest X-ray shows extensive pulmonary involvement, the patient might not be seen severely ill [22]. Up to 13% of patients can have concomitant tuberculosis. It should be suspected when there are apical lesion involvement and cavitation found at chest X-ray [23].

The oral cavity and pharynx are the most common affected mucous membranes. Ulceration with a red granulomatous or berry-like surface with multiple hemorrhagic dots has been described. Even though inoculation might be traumatic, the most common form of transmission is through contact with bronchial secretion [3]. The most commonly affected areas are the lower lip, tongue, hard palate, and sublingual area. The supraglottic larynx and epiglottis might also be affected [24•]. Gastrointestinal mucosa is the second most affected mucous membrane; less frequently, the tarsal conjunctiva and genital mucosa are involved [25]. By the time patients complain of

**Table 2** Paracoccidioidomycosis remission criteria

| Remission criteria | |
|---|---|
| Clinical | • Absence or resolution of signs and symptoms (including weight stabilization) |
| | • Healing of skin lesions and adenopathy |
| Mycological | • Negative direct mycological smear and negative culture |
| Radiological | • Scarring |
| Serological | • Double immunodiffusion: negative or stabilization of dilutions 1:2. |
| | • CF title stabilization in two consecutive measurements |

tooth and facial pain, tooth loss is common, making the mouth look like a tapir mouth [26].

Cutaneous lesions have different morphologies, usually ulcers or verrucous plaques that might become infected with bacteria. They can have hemorrhagic dots on the surface similar to the ones on mucous membranes. The commonly affected areas are the face, extremities, and trunk [27]. There is a less common form of the disease characterized by sarcoid-like infiltrative lesions usually in the face [28].

Central nervous system involvement is present in 9 to 25% of the patients with systemic disease. Clinical manifestations depend of the location of the lesions. They usually develop when cerebral hemispheres are involved. Seizures, hemiparesis, cerebellar symptoms, migraine, and hydrocephalus are some of the most common signs and symptoms [19].

Adrenal gland involvement can affect both the cortex and the medulla. It can be asymptomatic or manifest with diminished function of the gland (15–40%) which usually disappears with antifungal therapy. Less frequently, it can be manifested as Addison's disease in about 3% of the cases [29]. Recent autopsy studies have shown that half of the patients presented variable degrees of adrenal involvement.

### Residual Disease

There are two important sequelae: chronic respiratory insufficiency secondary to residual pulmonary fibrosis, which affects between 60 and 80% of the patients, and adrenal insufficiency in a lower percentage of patients. Other less frequent sequelae include hoarseness, microstomia, and tracheal and glottal stenosis [2].

## Diagnosis

Direct observation of *Paracoccidioides* spp. in sputum and other samples has a high sensibility and is considered the gold standard for the diagnosis of the disease. With a sensibility of 90%, it can be performed using 10% KOH or fresh smear [30]. At direct observation in the microscope, multiple budding yeasts composed by a thin wall stem cell with multiple buds around can be observed. This finding is pathognomonic of the disease, and according to the number and distribution of blastoconidia, different forms might be seen; the most representative one is the "ship's wheel" configuration [31]. To increase sensibility, it is recommended to take serial sputum samples [30].

Cultures have a sensitivity of 95% and *P. brasiliensis* can be cultured from sputum, tissue, or abscesses. Being a dimorphic fungus, to obtain the filamentous form, it should be cultured in Sabouraud agar at 28 °C, Sabouraud agar with antibiotic, and yeast extract agar. At 37 °C, the yeast form is grown. The time needed to grow is variable; colonies are usually observed after 3 to 4 weeks and up to 2 to 3 months of incubation [31].

Multiple budding cells can also be observed in skin biopsy specimens using fungal stains such as the Grocott stain. Pseudoepitheliomatous hyperplasia with epidermal hyperkeratosis might be seen, as well as foreign body and epithelioid granulomas, lymphocytic inflammatory infiltrate, and microabscesses with polymorphonuclear cells [31].

Serological tests to determine the presence of antibodies have a sensitivity of 70–95%. Currently, the following serological tests are available for the diagnosis of the disease: agar gel immunodiffusion (AGID), complement fixation tests (CF), counter-immunoelectrophoresis, ELISA, and immunoblots. AGID remains the test of choice. It is easy to perform and cost effective and has a high sensitivity (80%) and specificity (90%) allowing the detection of two precipitation bands, 1 and 2.

CF is capable of detecting titers of antibodies against the yeast form of the fungus. Titers over 1:8 are considered diagnostic with a sensitivity between 75 and 77% but it has a lower specificity compared to AGID given the possibility of cross reacting with *Histoplasma capsulatum.* It is useful for the monitoring of therapy and the evaluation of recurrence. To assure adequate follow-up during therapy, the serological response must be always evaluated using the same laboratory technique [2, 32].

Antibody titers against *P. brasiliensis* correlate with the severity of the disease and clinical presentations. Higher titers are detected in disseminated, acute, and subacute disease, while there is no data available regarding antibody titers against *P. lutzii* [2].

Molecular biology tests such as protein chain reactions (PCR) have recently become available for the diagnosis.

Genes encoding for different proteins and molecules: gp43, Hsp70, and ribosomal subunit 5.8s, are some of the ones used for the molecular diagnosis, recognizing minimal quantities of fungus [33, 34].

## Treatment

For the treatment of mild to moderate disease (chronic disease), itraconazole 200–400 mg once daily is the drug of choice. It should be given for up to 6 to 9 months until clinical and serological responses are achieved [2]. There are some cases reported of patients treated with voriconazole with good responses, especially with CNS involvement [31]. There are no reports of patients treated with posaconazole. Trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg bid or tid has also been reported as an effective therapy; being a fungistatic agent, it requires longer therapy of up to 24 months. It has been associated with recurrence of the disease given low adherence, treatment abandonment, and resistance [2]. For severe and disseminated disease (acute/subacute disease), amphotericin B deoxycholate (0.5–0.7 mg/kg/day) and lipid complex amphotericin (3–5 mg/kg/day) are the drugs of choice, followed by itraconazole or TMP/SMX once clinical improvement is achieved, which is usually 2 to 4 weeks after the initial dose [35, 36].

## Follow-up

Both clinical and serological responses must be monitored at least monthly for the first 3 months. If the response is satisfactory, patient follow-up is indicated every 3 months for the first year. Complete blood count, renal and liver function tests, and electrolyte count should be performed for the first month of treatment and then every 3 months for the first year, and every 6 months the second year. Radiological follow-up should be performed every 6 months for the first year. Treatment could be stopped once remission criteria are achieved (Table 2) and follow-up is required for at least 2 years. If after this period of time the patient keeps meeting remission criteria, they could be released with instructions of possible signs and symptoms to consult again [2].

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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