Epidemiology, Clinical, and Therapeutic Aspects of Paracoccidioidomycosis

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Abstract Paracoccidioidomycosis, or PCM, was described by Adolfo Lutz 105 years ago. Since then the disease has taken a prominent position among the systemic fungal infections because it mainly affects individuals in the most productive years of their lives in various countries of Latin America. In Brazil, the disease is considered endemic in some regions. However, it is still a neglected disease. With the recent discovery that *Paracoccidioides brasiliensis* is not the only species of this genus, numerous studies have contributed to better understanding and recognition of this pathogen and its pathology in many aspects, such as the epidemiological, clinical, and therapeutic aspects.

Keywords Paracoccidioidomycosis (PCM) · Epidemiology · Clinical aspects · Therapeutics · Tropical medicine · Latin America · *P. brasiliensis* · Tropical mycosis · Systemic mycosis · Mycosis · Infectious disease

Introduction

Paracoccidioidomycosis (PCM) is a granulomatous and progressive systemic mycosis in Latin American countries, occurring mainly in Brazil, Colombia, and Venezuela [1•]. An infectious disease with high morbidity and commonly found in poor areas, it is known as South American blastomycosis, Lutz illness, and Lutz–Splendore–Almeida disease, because Splendore was the first to cultivate the pathogen and Almeida was the author of the first study of the disease [2].

PCM is caused by the cryptic species *Paracoccidioides brasiliensis* (species S1, PS2, and PS3) [3] and *P. lutzii* [4, 5•, 6•]. It is a thermally dimorphic fungus, which grows as a yeast-like structure in host tissues or when cultured at 35–37 °C and as a mycelium under saprobic conditions, producing infective asexual spores or conidia at 18–23 °C (Fig. 1) [7].

Epidemiology

PCM is acquired through inhalation of spores present in the environment and is often associated with outdoor activities and geographic exposure, but other predisposing factors, such as gender, age, tobacco use, alcohol consumption, socioeconomic conditions (poverty), and working conditions (farming and agriculture, specifically in cotton, coffee, and tobacco plantations), are associated with this pathology [8•, 9, 10].

Paracoccidioides has been repeatedly recovered from human clinical samples and tissues from some armadillo species (*Dasypus novemcinctus*) [11, 12], and the first association with these animals was observed in the Amazon region by Naiff et al. [13]. Although the *Paracoccidioides* was recovered from soil and related material in many situations, the exact places where this fungus exists in nature have not yet been determined; however, the soil continues to be an important element in the ecological study of this fungus [14].

Evidence indicates that mycelial forms occur in the soil under restrictive conditions. Propagules such as arthroconidia and aleuroconidia produced by mycelium and present in the environment may be inhaled and are subsequently transformed into yeast, which causes primary infection in the lung [15] and is then spread by blood and lymphatic vessels, reaching different organs and systems and resulting in lesions in the skin, lymph nodes, and mucous membranes [16, 17]. In addition, these propagules can induce animal infection by the respiratory route [18]. Natural infection in some domestic

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Fig. 1 Morphological characteristics of *Paracoccidioides*. **A**, Yeast in tissue host. **B**, Yeast culture. **C**, Filament form (macrocolony). **D**, Filament form with conidia and other propagules (slide culture). **E**, Yeast form (culture)

animals has been observed by intradermal and serological tests. In Brazil, seroepidemiological tests have been used in urban and rural canine populations. Enzyme-linked immunosorbent assay (ELISA) and immunodiffusion methodology were used to investigate the prevalence of anti-*P. brasiliensis* antibodies in 305 dogs from the Londrina region. The study showed positivity rates ranging from 14.5 % to 89.5 %, using the ELISA technique [19]. In addition, in 2004, the first confirmed case of paracoccidioidomycosis in a dog with a strictly urban life was reported [20].

South America has a range of climatic characteristics and rich biodiversity, which facilitate the development of various fungal pathogens in different habitats. In many countries of Latin America, principally in Brazil, there are regions with a large population of rural workers who are engaged in agricultural activities and are exposed to diverse fungal habitats in the soil [10–20, 21•].

The ecological characteristics of the endemic areas of PCM suggest that the pathogen preferentially inhabits humid environments with average annual temperatures between 18 °C and 24 °C and high annual rainfall (900–1,800 mm) [15].

In Brazil, PCM has a heterogeneous distribution, with low and high areas of endemicity. The disease has considerable public health importance, with high social and economic costs, since it occurs in individuals at their most productive age, causing frequent sequelae, and is a common cause of work disability. Although the disease remains a serious social problem, it is impossible to establish its true distribution because the disease is not notifiable in the Public Health

System in Brazil, where the status of this endemic systemic mycosis in various regions is difficult to assess [22]. On the other hand, in any Brazilian state, such as Minas Gerais, Mato Grosso do Sul, and Rondônia, PCM is considered a disease requiring compulsory notification, and in São Paulo it has been recommended that all confirmed cases of PCM be reported to the Health System [23•].

The real prevalence and incidence cannot be established precisely. Knowledge of endemic areas and prevalence, incidence, and morbidity data are based on case reports and scattered skin tests [10]. In addition, the mortality rates can be used as a tool to compare the incidence and severity of PCM with use of the regional data [24, 25•].

The prevalence of PCM varies from country to country and also, in the same country, from region to region. In Brazil, the South and Southeast regions have a high prevalence of the disease (as high as 75 %), affecting both men and women. The annual incidence is 10–30 cases per 1,000,000 inhabitants [8•, 21•, 22, 23•, 24, 25•, 26]. It is estimated that in endemic regions there are approximately 10 million people infected by *Paracoccidioides*. In regions such as Argentina, Venezuela, and Colombia, the incidence is lower (2.4 cases per 1,000,000 inhabitants) [8]. It should be stressed that in the endemic regions, the infection as measured by skin testing is far more prevalent than the disease. However, most people have no clinical symptoms of the disease, and cases like these have been reported in isolated case reports or as part of a series of patients [27].

The real number of patients with these systemic mycoses is unknown. Men are more susceptible to the disease, whereas women are infected during conditions of immunosuppression or probably as a consequence of hormonal changes [28•]. Studies have described a higher incidence in men than in women, with a ratio that ranges from 13:1 to 47:1, depending on the region [29, 30•].

Restrepo-Moreno [31] and Fava and Fava-Neto [32], utilizing intradermal tests, suggested that the incidence of PCM infection without symptoms of the disease was high in endemic areas (2–60 %).

Coutinho et al. [24] studied 3,181 deaths from PCM in Brazil over a period of 15 years, showing a high prevalence of the disease, along with its low visibility. It was notably the eighth most common cause of death among chronic diseases and had the highest mortality rate among the systemic mycoses, such as cryptococcosis, pneumocystosis, and histoplasmosis in HIV-negative patients.

Clinical Manifestations of Paracoccidioidomycosis

Forms of Paracoccidioidomycosis

PCM can have several clinical presentations. In order to establish a better way to deal with them, in 1986 the International Colloquium on Paracoccidioidomycosis, which occurred in Medellín, Colombia [33], adopted a classification combining clinical data with the disease natural course, which was adapted by the Brazilian Guidelines in Paracoccidioidomycosis in 2006 [10]. By these criteria, PCM can be classified into two basic forms: PCM infection and PCM disease. PCM infection is usually demonstrated by a positive skin test and no specific symptoms are associated with it. PCM disease can occur in three forms: acute/subacute, chronic, and residual. The chronic form can also be unifocal or multifocal, according to the presence of lesions in one or more organs, respectively. These subforms can also be classified as light, moderate, or severe, depending on the severity of the manifestations (Table 1) [34•].

The Acute/Subacute Form

The acute/subacute form is also known as juvenile-type PCM since it is the clinical form that occurs in children, although it can occasionally be seen in adults under 35 years old. The symptoms include the presence of lymphadenomegaly, gastrointestinal manifestations (including bowel obstruction or acute abdominal syndrome, which is the result of mesenteric lymph node hypertrophy [35]), cutaneous lesions, and osteoarticular symptoms [10, 34•]. In this form, which represents 3–5 % of cases of PCM, the first signs of the disease usually arise up to 12 weeks after the beginning of the

Table 1 Forms of paracoccidioidomycosis (PCM)

Basic forms	Subforms	
PCM infection		
PCM disease	Acute/subacute	
	Chronic	Unifocal
	Sequelae	Multifocal

infection [10]. Cases of subacute PCM were reported by Fonseca et al. [36] among children in the city of Belém, Pará State, Brazil, showing that the most frequent symptoms were superficial lymph node enlargement (in 100 % of cases), fever (in 92.3 %), weight loss (in 84.6 %), and increased abdominal volume (in 46 %). Other rare manifestations such as bone marrow necrosis can be seen in acute/subacute PCM, as described by Resende et al. [37] in a report of eight patients who were autopsied at Botucatu University Hospital. The most remarkable immunological aspect of acute/subacute PCM is depression of the cell-mediated response, which is important for disease control and leads to the worst prognosis, with high lethality [38].

The Chronic Form

The chronic form accounts for approximately 90 % of cases of PCM and usually occurs in male adults. It presents with a long progression and the clinical signs involve the occurrence of pulmonary lesions, with general symptoms such as weakness, weight loss, cough, fever, anorexia, and dyspnea also being present [39]. The unifocal form accounts for 25 % of chronic cases and is characterized by the presence of pulmonary lesions only. Extrapulmonary lesions are described as the multifocal form, where the fungus has disseminated to other organs, causing several different types of lesion, particularly involving the oral and nasal mucosa and the lymph nodes. But there are also other affected sites such as the gastrointestinal mucosa, liver, pancreas, central nervous system, adrenal glands, and bones [40, 41•]. Lesions in the pharyngeal and laryngeal mucosa, leading to dysphagia and odynophagia, and gingival lesions, leading to sialorrhea, are also common in this form of the disease [42].

Neuroparacoccidioidomycosis Neuroparacoccidioidomycosis is not as infrequent as it was thought to be. Medical imaging methods have allowed diagnosis of these cases, contributing to the higher incidence data shown in the literature. Prevalence rates are variable and reach up to 36 % [43]. A review of 81 papers published between 1919 and 2007 described 257 cases of neuroparacoccidioidomycosis; most of them (93 %) were males presenting with motor deficits and intracranial hypertension, and 59.1 % also presented with the pulmonary form

of PCM. Mortality was high (44.1 %) and the prevalence of sequelae after resolution, particularly motor deficits, was also elevated (50.1 %) [44].

Gastrointestinal Manifestations Gastrointestinal involvement is another chronic PCM manifestation, which has been well documented by several reports. Symptoms that have been described, beyond the general ones, are abdominal pain, diarrhea, dysentery, hepatomegaly, splenomegaly, and ascites [45]. Weight loss is also an important sign. Martinez et al. [46] reported a case of colon paracoccidioidomycosis in a 22-year-old man, who had lost 35 pounds in 5 months. Colonoscopy showed diffuse hyperemia of the mucosa and roundish reddened lesions, together with multiple ulcerations of the colon mucosa [46]. Eventually, intestinal PCM may be confused with colon cancer, as reported by Chojniak et al. [47], who described a case of an abdominal mass associated with intralesional calcifications in pseudotumoral PCM. The patient had been treated for an oropharyngeal PCM lesion 15 years before. Computed tomography imaging showed an abscessed area involving the psoas muscle, calcifications, and thickening of the bowel walls in the ileocecal area. Multiple granulomas, diffuse fibrosis, and reactive lymphoreticular hyperplasia was shown by histological study, confirming PCM [47].

Genitourinary Manifestations Genitourinary manifestations are considered rare occurrences in PCM; however, several case reports are found in the literature. Cases are mostly seen in men, since women are usually protected by feminine hormones [48]. In men, lesions can be present in the penis, scrotum, testicles, epididymis, and prostate [49, 50]. A retrospective study described 11 cases of PCM showing male genital involvement, with lesions in the testicle or scrotum being the most frequent [51]. Another study found a 1.2 % frequency of genitourinary involvement among 483 PCM patients in a 42-year period. All of them presented with lesions in the external genitalia and only one was a female patient, who had the juvenile PCM form [52]. Lopes et al. [53] described a case of PCM confused with prostatic adenocarcinoma in a 54-year-old man who had manifested palate stomatitis associated with odynophagia and dysphagia 5 years before. The patient also had dysuria, polyuria, urinary urgency, and, finally, urethral obstruction. Histological analysis revealed a diffuse chronic granulomatous inflammatory process and typical *Paracoccidioides* yeasts with multiple sprouting [53].

The Disseminated Form

Disseminated PCM is usually described in patients with immune dysfunction, not necessarily associated with HIV infection but as a consequence of other factors, such as age and habits that impair immunity (smoking, alcoholism, malnutrition). Lesions can be found in several anatomical sites and the

clinical manifestations differ from case to case. For example, Araújo et al. reported a case in a 46-year-old man presenting with disseminated plaque-like ulcerated skin lesions, associated with pharyngeal, nasal, and laryngeal mucosal lesions [54]. Another report described a 60-year-old man who lived in a rural area and had a clinical history of bloody sputum, dizziness, headache, nausea, and memory loss for 2 months. He also presented with multiple lesions in the brain and a mass in the thorax, which simulated metastatic lung cancer. An autopsy revealed central nervous system and pulmonary PCM together with pulmonary strongyloidiasis [55].

Some of the disseminated cases are associated with HIV infection and can be manifested either as acute PCM or as disseminated PCM. The clinical manifestations are usually prolonged fever, weight loss, generalized lymphadenopathy, skin lesions, splenomegaly, hepatomegaly, and pulmonary and central nervous system involvement [56]. Most of the cases are described in patients presenting with T CD4⁺ lymphocyte counts of less than 200 cells/mm³ [57]. Castro and Martinez [58] presented a case in a 32-year-old patient whose T CD4⁺ lymphocyte count was 9 cells/mm³. He had a 9-month history of weight loss, weakness, ulcerated lesions all over his body, hepatomegaly, and lytic lesions on the bones of the hands, arms, legs, feet, and skull [58]. Another case of disseminated PCM showed the occurrence of peripleuritis and subcutaneous abscesses on the chest wall and sternum associated with enlargement of cervical lymph nodes and hepatosplenomegaly. The patient also presented with prolonged fever, weight loss, anorexia, and a T CD4⁺ lymphocyte count of 8 cells/mm³ [59].

Sequelae

Residual forms or sequelae usually involve impairment of the function of the organ/tissue affected by the disease, as a result of the chronic granulomatous inflammatory process, which leads to fibrosis after resolution [60]. The most commonly

Table 2 Treatment of paracoccidioidomycosis

Drug	Dosage for adults	Period of treatment
Itraconazole	200 mg/day	Light forms: 6–9 months Moderate forms: 12–18 months
Sulfamethoxazole/trimethoprim	160–240 mg+800–1,200 mg/12 h	Light forms: 12 months Moderate forms: 18–24 months
Amphotericin B	0.5–1.0 mg/kg/day or on alternate days	Severe forms: until clinical improvement

Adapted from Shikanai-Yasuda MA, Telles Filho Fde Q, Mendes RP, et al. Guidelines in paracoccidioidomycosis. Rev Soc Bras Med Trop. 2006; 39(3):297–310

observed sequelae occur in the lungs, with the presence of chronic obstructive pulmonary disease in some cases [61]. Adrenal insufficiency can also be seen. Epilepsy, motor deficits, and hydrocephalus are observed as the result of central nervous system infection. Dysphonia, microstomia, and laryngeal obstruction are also reported [10].

Therapeutic Aspects of Paracoccidioidomycosis

The treatment of PCM requires not only the prolonged use of antifungal drugs but also global measures to stabilize the patient, i.e., treatment of comorbidities such as tuberculosis and HIV infection or the presence of nutritional problems. Patients must have their kidney and liver functions evaluated to ensure the best therapeutic choice. Cessation of smoking or drinking is recommended [34•].

Among the antifungal drugs, itraconazole is considered the drug of choice for treatment of PCM, with a dosage of 200 mg/day for 6–9 months in adults presenting with the light form of the mycosis. In moderate forms the treatment is maintained for 12–18 months. Itraconazole is usually combined with sulfamethoxazole/trimethoprim in dosages of 160–240 mg/12 h for trimethoprim and 800–1,200 mg/12 h for sulfamethoxazole. Sulfamethoxazole/trimethoprim therapy is maintained for 12 months in light forms and for 18–24 months in moderate forms. For severe forms the drug of choice is amphotericin B in a dosage of 0.5–1.0 mg/kg/day or on alternate days. For special groups such as children, pregnant women, and patients with liver or renal failure, other recommendations are necessary and must be evaluated specifically. Patients must be evaluated monthly during the first 3 months of treatment by serological, radiological, biochemical, and clinical criteria until they are cured (Table 2) [10].

Studies have been performed to investigate other kinds of therapy. The main strategies involve therapeutic vaccination using fungal antigens and the use of specific monoclonal antibodies in order to improve the cell immune response against the fungus [62•]. An immunodominant peptide called P10 [63], derived from the major antigen gp43, has been shown to be useful in eliciting the cellular immune response and was validated as a vaccine candidate [64] and proven to play a protective role in prophylactic and therapeutic experiments using infected mice [62•]. Although this and other strategies may need a long road to come into clinical use, they point to the possibility of increasing the therapeutic options in PCM treatment.

Conclusions

Since its first description, paracoccidioidomycosis has been well studied and information about the disease and its

etiologic agents have been accumulated, and so the diagnosis, treatment, and control of cases have become easier and more effective. However, many other studies are needed to better comprehend not only the biology of the fungus, with the diversity of species that have now been found, but also the host–pathogen interactions, considering this new scenario. Establishing how the cryptic species are distributed in endemic areas, what kind of immune response they stimulate, and how to deal with them in terms of diagnostic techniques may be important steps to follow in order to help clinicians and patients most effectively.

Compliance with Ethics Guidelines

Conflict of Interest Maurimélia Mesquita da Costa and Silvia Helena Marques da Silva declare that they have no conflicts of interest in connection with this work.

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

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