

Paracoccidioidomycosis: clinical and epidemiological profile of hospitalized patients in Passo Fundo - RS

Paracoccidioidomicose: perfil clínico e epidemiológico de pacientes internados em Passo Fundo - RS

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ABSTRACT: Paracoccidioidomycosis (PCM) is not a notifiable disease despite its relevance in Latin America, and therefore estimates of the prevalence, incidence, and associated morbidity of this mycosis are based on reports of epidemiological surveys, case series, hospitalization records, and mortality data. The objective of this study was to describe aspects related to the patient, disease evolution, diagnostic confirmation, and treatment of confirmed cases of PCM treated at a teaching hospital in southern Brazil. Information was collected from the medical records of 27 patients diagnosed with PCM, confirmed in the period from 2010 to 2019. The prevalent profile was a male patient, with a mean age of 53 years, who was involved in various work activities, of urban origin, immunocompetent and without comorbidities, and a smoker, but not an alcoholic. For most cases, the initial involvement was pulmonary, with significant involvement of the lymphatic system during the course of the disease. Microscopic observation of pathognomonic fungal structures in biopsy samples, lymph node aspirates, and sputum was the most common method to confirm the clinical suspicion. Itraconazole was the first treatment option, followed by amphotericin B.

Keywords: Paracoccidioidomycosis; Endemic disease; Lung disease, fungal.

RESUMO: A paracoccidioidomicose não é uma doença de notificação obrigatória apesar de sua relevância na América Latina, por isso as estimativas de prevalência, incidência e morbidade dessa micose são baseadas em relatórios de levantamentos epidemiológicos, séries de casos, registros de hospitalização e dados de mortalidade. O objetivo desse trabalho foi descrever aspectos relacionados com o paciente, evolução da doença, confirmação diagnóstica e tratamento de casos confirmados de paracoccidioidomicose atendidos em um hospital de ensino do sul do Brasil. Foram coletadas informações de prontuários de 27 pacientes com diagnóstico de paracoccidioidomicose confirmado no período de 2010 até 2019. O perfil prevalente foi de um paciente do sexo masculino, com idade média de 53 anos, envolvido com atividades laborais diversas, de procedência urbana, imunocompetente e sem comorbidades, tabagista, mas não etilista. Para a maioria dos casos o acometimento inicial foi pulmonar, com importante envolvimento do sistema linfático no percurso da doença. A observação microscópica das estruturas fúngicas patognomônicas em amostras de biópsia, aspirado linfonodal e escarro foi o método mais utilizado para confirmar a suspeita clínica. O itraconazol foi a primeira opção de tratamento, seguido da anfotericina B.

Palavras-chave: Paracoccidioidomicose; Doenças Endêmicas; Pneumopatias Fúngicas.

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INTRODUCTION

Paracoccidioidomycosis is a systemic mycosis caused by *Paracoccidioides* spp. that mostly affects non-immunosuppressed patients in Brazil and South America and is the most prevalent mycosis in hospitals in Brazil. The southern region of the country has the highest levels of hospitalization (6.9%)^{1,2}. This microorganism is found in the soil in a filamentous form and infects humans via the inhalation of sporulated structures that are easily dispersed in the air. Therefore, individuals who work directly with the soil, such as rural workers, construction workers, or gardeners are more likely to contract this disease^{3,4}. Clinical manifestations of the infectious process can occur years after exposure to the pathogen. Immunosuppression, alcoholism, and alcohol consumption are associated with the appearance of clinical signs owing to an imbalance in microorganism control by the host's immune system³. The disease has a chronic granulomatous characteristic with primary pulmonary infection owing to the mode of transmission. From the lungs, it spreads mainly to the lymph nodes, oral mucosa, larynx, skin, digestive tract, and central nervous system⁴. Confirmation of clinical suspicion can be carried out by diagnostic imaging or laboratory tests. The gold standard is the visualization of *Paracoccidioides* spp. in clinical samples^{4,5,6}.

From a taxonomic perspective, paracoccidioidomycosis is caused by dimorphic fungi of the genus *Paracoccidioides*, from the Ajellomycetaceae family^{7,8}. Its dimorphism is associated with temperature, developing at 25 °C as a filamentous fungus and 37°C as a yeast, which modulates its ability to adhere to and invade host tissues, in addition to evasion of the immune response⁸. The species *Paracoccidioides brasiliensis* presents as a complex of five phylogenetic clusters classified as the phylogenetic species S1a, S1b, PS2, PS3, and PS4, whereas the species *Paracoccidioides lutzii* contains PS3 and PS4; therefore, owing to significant genetic heterogeneity, some of the studied strains were regrouped and became the distinct species *P. lutzii*, with its own characteristics, such as geographical distribution, virulence, and laboratory diagnosis^{4,8}. Thus, the *P. brasiliensis* and *P. lutzii* were determined to cause this mycosis.

Fungi of the genus *Paracoccidioides* can maintain saprophytic cycles in the soil, preferably clay or sandy soils rich in organic matter and uric acid, where they form mycelia typical of molds and forming inhalable infecting arthroconidia that produce parasitic cycles in animal hosts, such as humans. This can lead to this systemic mycosis, through the production of granulomatous lesions for which evolution is directly related to the patient's cellular immunity, the inoculum, and the geographical distribution

of those affected^{5,8,9}. The virulence of *P. brasiliensis* and *P. lutzii* is associated with the synthesis of α -(1 3)-glucan, which protects the fungal cell from the activity of lysosomal enzymes in neutrophils and macrophages, as well as the presence of several adhesins and the production of proteases, lipases, and phospholipases, capable of providing the mechanisms for tissue adhesion and invasion. One of these enzymes is gp43, an immunogenic protein capable of degrading collagen, casein, and elastin, in addition to being bound to laminins. In fact, determining the presence of this protein or antibodies targeting it is a more frequent strategy for the serological diagnosis of this disease. The change from a filamentous fungus to a yeast also contributes to the expression of virulence genes and avoidance of the host response^{8,9}.

Paracoccidioidomycosis is not a mandatory notification disease; therefore, epidemiological data are scarce. Estimates of its prevalence, incidence, and associated morbidity are based on reports of epidemiological surveys, case series, hospitalization records, and mortality data⁴. This is the most relevant systemic mycosis in Brazil and Latin America, responsible for 51.2% of deaths linked to deep mycoses in this country. Its occurrence is 1–3 cases/100,000 inhabitants/year, with a mortality of approximately 0.14–4.49 cases/100,000 inhabitants/year⁸. The most affected Brazilian states are São Paulo, Rio Grande do Sul, Paraná, Goiás, and Rondônia⁴. The collection of data and information to help in the formulation of a clinical hypothesis, the request for confirmatory diagnostic tests, and the search for appropriate means/treatments could provide a more adequate management plan to deal with this problem and thus motivated this study.

MATERIALS AND METHODS

This was an observational and quantitative study, following a descriptive, analytical, and cross-sectional design, performed from records obtained at the São Vicente de Paulo Hospital (*Hospital São Vicente de Paulo* - HSVP) in Passo Fundo, Rio Grande do Sul, Brazil, of patients with a report in the medical file of paracoccidioidomycosis. The inclusion criteria were as follows: medical records of patients with a clinical and laboratory diagnosis of paracoccidioidomycosis confirmed in the period from 2010–2019. The sample size was 27 patients. The data were read and analyzed by a data collection instrument designed by the author, containing variables such as sex, age, occupation, origin, smoking habits, alcohol consumption habits, comorbidities, and immunological status, as well as data on initial disease involvement, sites of dissemination and initial signs and symptoms. In addition, the methods used to confirm the diagnosis and radiographic alterations present were analyzed. Finally, a therapeutic approach

taken, and the outcome of each case was described. The variables found were tabulated using Microsoft Excel 2010 to describe means, frequency distribution, and percentage values, as well as to generate charts and tables.

Ethical aspects: The work followed the precepts of resolution 466/12 of the National Health Council on the participation of people in research. The project was approved by the Research Ethic Committee of the University of Passo Fundo (Opinion Number: 2.893.223; CAAE 90706218.9.0000.5342).

RESULTS

The data indicated the following profile as the most common for patients with paracoccidiomycosis diagnosed in Passo Fundo - RS: a male patient, with a mean age of 53 years, involved in various work activities, of urban origin, immunocompetent and without comorbidities, and a smoker but not an alcohol consumer (Table 1).

Table 1 - Epidemiological profile of patients diagnosed with paracoccidiomycosis in the municipality of Passo Fundo - RS

N=27 patients	
Sex	Female 6 (22.22%) Male 21 (77.78%)
Average age	53 years (ranging from 29 to 81 years)
Occupation	Rural worker 11 (40.74%) Construction 1 (3.7%) Another 15 (55.56%)
Origin	Urban 17 (62.96%) Rural 10 (37.04%)
Alcohol consumption	Yes 7 (25.93%) No 20 (74.07%)
Smoker	Yes 16 (59.26%) No 11 (40.74%)
Comorbidities	Absent 18 (66.66%) HIV 2 (7.41%) Oncology 5 (18.52%) COPD 2 (7.41%)
Immune status	Immunocompetent 20 (74.07%) Immunocompromised 7 (25.93%)

Clinically, the involvement was initially pulmonary, followed by the spread of the disease to the lymph nodes, central nervous system, oral mucosa, larynx, pharynx, and adrenal glands (Table 2).

Confirmation of the clinical hypothesis for 96.30% of the cases evaluated was performed via microscopic observation of the pathognomonic fungal structures in the following biological samples: biopsy (85.18%), lymph node aspirate (3.71%) and sputum (7.40%). Itraconazole was the first treatment option, used in 81.5% of the cases, followed by amphotericin B (18.5%). Of the cases evaluated in this study, three patients (11.11%) died of the disease.

Table 2 - Clinical manifestations of patients diagnosed with paracoccidiomycosis in the municipality of Passo Fundo - RS

N=27 patients	
Initial involvement	Lungs 19 (70.37%) Lymph nodes 1 (3.70%) Other 7 (25.93%)
Early signs and symptoms	Pulmonary 16 (59.25%) Anorexia 7 (25.93%) Localized lymph node enlargement 6 (22.22%) Gastrointestinal manifestations 6 (22.22%) Mucosal lesions 3 (11.11%) Generalized lymph node enlargement 1 (3.70%) Fever 1 (3.70%) Osteoarticular involvement 1 (3.70%)
Dissemination	Lymph nodes 8 (26.63%) CNS 7 (25.92%) Other 7 (25.92%) Oral Mucosa 5 (18.52%) Larynx 4 (14.81%) Adrenal glands 3 (11.11%) Pharynx 3 (11.11%)

DISCUSSION

Some of the results obtained are similar to those of other studies, which describe a predominance of cases in males (75% to 95% of cases), although women are equally exposed to the fungus. This reinforces the hypothesis that the disease predominates in males owing to the protection conferred by female hormones, in particular β -estradiol, which inhibits the transition from the mycelial to the fungal state in the lungs, preventing development of the infection^{8,10}. Another study that evaluated 184 patients reported an age range between 4 and 94 years, with a median of 48 years, very close to the average age found in this study^{10,11}. They observed a predominance of PCM among individuals aged 30–59 years.

The smoking profile of the patients with PCM observed in our study has also been described by other authors^{10,12}, and the chronic form of the infection is strongly associated with smoking¹³. Smoking increases the risk of pulmonary PCM by 10-fold and reduces the patient's average age by 8 years at the onset of symptoms¹¹. Approximately 40% of patients diagnosed with PCM in this study had some involvement in agricultural activity, a similar percentage observed in other studies¹⁰. Several studies also show that PCM has been identified in recent decades more frequently in urban areas, including in individuals who have never left large population centers¹⁴. Just over 25% of the patients were considered alcohol consumers. According to Martinez¹³, alcohol intake in amounts greater than 50 g per day favors the onset of PCM,

but this was not the predominant profile found in patients diagnosed in Passo Fundo (RS).

Populations at a high risk for lung fungal infections include individuals with solid or hematological malignancies, those undergoing organ or bone marrow transplantation, and HIV-infected patients (15). Unlike other mycoses, such as cryptococcosis, disseminated histoplasmosis, and candidiasis, PCM is generally not related to immunosuppressive diseases. However, cases of the disease associated with HIV infection, neoplasia, and more rarely, organ transplants, chronic obstructive pulmonary disease (COPD), and immunobiological use have been reported^{4,16}. Although the data collection occurred in a health center that assists cancer patients and transplant patients, these individuals were not the most affected.

For most patients, the initial involvement was pulmonary, consistent with the route of microorganism entry into the host. From that anatomical site, the fungus spreads through the lymphatic vessels to the paratracheal and parabrachial lymph nodes, resulting in the cases of lymph node enlargement observed¹¹. Fever, weight loss, and anorexia appear in the acute form of the disease and as a complaint of patients^{4,11}. In our study, anorexia and gastrointestinal involvement were more evident than fever, which is considered a sign of greater severity of the disease¹¹. Mucosal lesions, highlighted in the literature after the spread of the disease, were uncommon in our study. The percentage of neuro-PCM cases observed in this study matches the literature records, which describe a rate of 20–30% neuro-PCM cases¹¹.

Regarding the method of confirmation of clinical suspicion, although it is invasive and traumatic to the patient, biopsy histopathology is highly sensitive for the diagnosis of PCM. This technique allows for the fragmentation of biopsy tissue and can reveal micromorphology and tissue reactions, with visualization of fungal cells with rounded, spherical, or oval buds with double birefringent membranes attached to the mother cell and with vast compact granuloma, filled with fungal-containing epithelioid cells⁸. Imaging also reveals alterations, such as the observation of nodules on chest tomography.

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Itraconazole has an efficacy of 96%, and patients with the chronic form treated with this antifungal attain serological cure after 6 months of treatment on average¹¹. Antifungal treatment of mild and moderate cases usually depends on itraconazole or the combination of trimethoprim/sulfamethoxazole. Severe and disseminated infections might require the use of amphotericin B formulations, followed by consolidation therapy with itraconazole or trimethoprim/sulfamethoxazole. Patients are usually treated for 12–24 months, depending on the clinical presentation¹⁸. For mild-to-moderate disease, the first treatment option is itraconazole at a dose of 100–400 mg orally per day, lasting for 6 months. This drug is considered superior to ketoconazole because of its shorter treatment cycles, lower relapse rates (3–5%), and lower toxicity¹⁹. In severe cases, refractory to other forms of treatment, amphotericin B is the drug of choice. Doses range from 1 to 2 g, based on the clinical response. However, its use is limited owing to its toxicity. Formulations such as amphotericin B lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersions are associated with lower toxicity and better tolerance¹⁹. PCM has a high morbidity rate but relatively low lethality (7.6% for adults and 9.3% among children), except in immunosuppressed patients or cases with CNS involvement, in which the prognosis is poor¹⁹.

CONCLUSION

The most common profile among patients with PCM evaluated in this study was a male individual, with a mean age of 53 years, involved in various work activities, of urban origin, immunocompetent and without comorbidities, and a smoker but not an alcohol consumer. For most cases, the initial involvement was pulmonary, with important involvement of the lymphatic system during the course of the disease. Anorexia and gastrointestinal involvement were more evident than fever. Mucosal lesions were uncommon in our study. The microscopic observation of pathognomonic fungal structures in biopsy samples, lymph node aspirate, and sputum was the most common method to confirm clinical suspicion. Itraconazole was the first treatment option, followed by amphotericin B.

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