

## Paracoccidioidomycosis in the northern region of Rio Grande do Sul

*Paracoccidioidomicose na região norte do Rio Grande do Sul*

*Paracoccidioidomycosis en la región norte del Rio Grande do Sul*

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### ABSTRACT

**Background and Objectives:** Paracoccidioidomycosis (PCM) is a systemic disease caused by the dimorphic fungus *Paracoccidioides brasiliensis* found in the tropical and subtropical regions of Latin America. This study aimed to perform a retrospective analysis of PCM cases from the northern region of Rio Grande do Sul, Brazil. **Methods:** A total of 200 records of PCM cases diagnosed at the local reference pathology laboratory from 1995 to 2015, were analyzed. **Results:** Of the patients, 185 were male and 15 female. Patients ranged in age from 31 to 80 years, the largest proportion (35,5%) being aged between 51 and 60 years and living or working in the countryside. Clinical samples were mostly obtained from the oral cavity, followed by the oropharynx, lungs, brain, skin, and prostate. **Conclusion:** PCM is endemic in the south of Brazil, as the local economy is largely based on agricultural activities, favoring the contact of the population with *P. brasiliensis*. Due to the great similarity between PCM symptoms and other respiratory diseases, the differential diagnosis is essential for the correct treatment of the disease and to avoid its progression.

**Keywords:** Paracoccidioidomycosis. Pbmycosis. epidemiology, *P. brasiliensis*.

### RESUMO

**Justificativa e Objetivos:** A paracoccidioidomicose (PCM) é uma doença sistêmica causada pelo fungo dimórfico *Paracoccidioides brasiliensis*, o qual é encontrado nas regiões tropicais e subtropicais da América Latina. Este estudo objetivou realizar uma análise retrospectiva dos casos de PCM na região norte do Rio Grande do Sul, Brasil. **Métodos:** Foram analisados 200 prontuários relativos aos casos de PCM de 1995 até 2015 diagnosticados pelo laboratório de patologia referência na região. **Resultados:** Destes pacientes, 185 eram homens e 15 mulheres. Os pacientes tinham idade variando de 31 a 80 anos, sendo que a maior proporção (35,5%) tinha entre 51 e 60 anos e viviam ou trabalhavam na zona rural. Os materiais clínicos eram provenientes em sua maioria da cavidade oral,

seguido da região orofaríngea, pulmão, cérebro, pele e próstata. **Conclusão:** O sul do Brasil é região endêmica de PCM, devido a sua economia estar centrada na agricultura, o que propicia o contato do homem com o fungo. Devido à grande semelhança dos sintomas da PCM com outras doenças respiratórias, o diagnóstico diferencial é relevante para que seja realizado o tratamento correto da doença e para que seu avanço seja evitado.

**Descritores:** *Paracoccidioidomycosis*. *Pbmicosose*. *Epidemiologia*. *P. brasiliensis*.

## RESUMEN

**Justificación y objetivos:** La paracoccidioidomycosis (PCM) es una enfermedad sistémica causada por el hongo dimorfo *Paracoccidioides brasiliensis*, que se encuentra en las regiones tropicales y subtropicales de América Latina. Este estudio tuvo como objetivo realizar un análisis retrospectivo de casos de PCM en la región norte de Rio Grande do Sul, Brasil. **Métodos:** se analizaron 200 registros médicos relacionados con casos de PCM de 1995 a 2015, diagnosticados por el laboratorio de patología de referencia en la región. **Resultados:** De estos pacientes, 185 eran hombres y 15 mujeres. Los pacientes tenían edades comprendidas entre 31 y 80 años, con la mayor proporción (35.5%) entre 51 y 60 años y viviendo o trabajando en el campo. Los materiales clínicos provenían principalmente de la cavidad oral, seguidos de la región orofaríngea, pulmón, cerebro, piel y próstata. **Conclusión:** El sur de Brasil es una región endémica de PCM, debido a que su economía se centra en la agricultura, que proporciona el contacto del hombre con el hongo. Debido a la gran similitud de los síntomas de PCM con otras enfermedades respiratorias, el diagnóstico diferencial es relevante para el tratamiento correcto de la enfermedad y para evitar su progreso.

**Palabras clave:** *Paracoccidioidomycosis*. *Pbmicosis*. *Epidemiology*. *Epidemiología*. *P. brasiliensis*.

## INTRODUCTION

Paracoccidioidomycosis (PCM) is a systemic disease of granulomatous nature caused by thermodimorphic fungi of two species: *Paracoccidioides brasiliensis* e *Paracoccidioides lutzii*.<sup>1</sup> The infection is autochthonous and restricted to the American continent, being found in the tropical and subtropical regions of Latin America. In Brazil, this disease is responsible for 51.2% of deaths related to deep mycoses, with the highest occurrence described in the states of São Paulo, Rio Grande do Sul, Paraná, Rio de Janeiro, Goiás, Rondônia, Espírito Santo, Minas Gerais, Mato Grosso do Sul, Mato Grosso, Amazonas and Maranhão.<sup>2-6</sup>

PCM was first described, in 1908, as a mucocutaneous infection in which the agent is introduced into the skin or oral mucosa by trauma with plant fragments.<sup>7</sup> However, in 1959, Mackinnon confirmed the hypothesis, through tests in mice, that the mucocutaneous infection indicates symptoms secondary to a lung infection.<sup>8</sup> Nowadays, the most accepted route of transmission is through the inhalation of conidia of the fungus *P. brasiliensis* dispersed in the environment, which reaches the pulmonary alveolar epithelium and differentiates into its yeast form.<sup>9</sup>

The degree of infection and symptomatology depend on fungal virulence and the host's immune response. PCM cases may vary from asymptomatic to acute or chronic, with clinical manifestations involving the respiratory system and mucocutaneous lesions, leading to death if not properly treated. Chronic paracoccidioidomycosis is the classic clinical form of the disease, affecting predominantly rural workers, although its incidence has progressively increased in suburban and urban areas.<sup>1,10</sup>

The acquisition of the infection is closely related to the occupation. Professionals who work with contamina-

ted soil management are more susceptible to infection. Thus, men over 50 years old constitute the population most diagnosed with PCM, considering, in addition to the profession, other factors such as smoking, alcoholism and the hormonal protective factor against infection in women.<sup>1,3,8,10</sup>

Three studies carried out in the last five years, in Pelotas, Capão do Leão, Bagé and the metropolitan region of Porto Alegre, demonstrated the contamination of dogs, horses and wild mammals by *Paracoccidioides* sp.<sup>11-13</sup> These publications encourage the discussion about new forms of transmission and contagion in humans, especially in urban areas, where domestic dogs can represent an intermediary host between contaminated soil and humans.<sup>13</sup>

Until the beginning of the year 2020, no systemic mycoses was included in the national list of diseases and conditions of compulsory notification in Brazil. Without epidemiological surveillance, knowledge about endemic areas, prevalence, incidence and morbidity is based on case studies. In February 2020, PCM became part of the list of diseases and conditions of compulsory notification, together with cryptococcosis, human sporotrichosis and chronic Chagas disease.<sup>14</sup> In this way, a few years from now, there will be a better estimate of the epidemiology of PCM.

Taking into account the higher prevalence of PCM among rural workers, farmers, and construction workers, people living in the northern region of Rio Grande do Sul (RS) are susceptible to this disease since the local economy is based on these activities. However, because it did not integrate, for a long time, the range of diseases with compulsory notification, it is difficult to establish its real prevalence. The present study aimed to describe PCM cases through a survey of medical records from the database of the Pathology Institute of Passo Fundo, in order to measure disease incidence in this region.

## METHODS

A survey of PCM-positive cases diagnosed at the Pathology Institute of Passo Fundo, Passo Fundo, RS, Brazil, the main laboratory of pathology in the northern region of the state, was performed. This region has a subtropical climate and an average annual temperature of 17.5 °C. Frost formation is common during the colder months. Rainfall is well distributed throughout the year, with September having the highest volume of precipitation (197.9 mm) and April the lowest (99.7 mm). On average, humidity is about 70%.

PCM-positive cases diagnosed from January 1995 to December 2015 were analyzed, totaling 200 cases. The histopathological diagnosis was confirmed by the presence of *P. brasiliensis* yeast cells in surgical specimens evidenced by Grocott staining. The analyzed patient data comprised gender, age, city of origin, occupation, and location of biopsy.

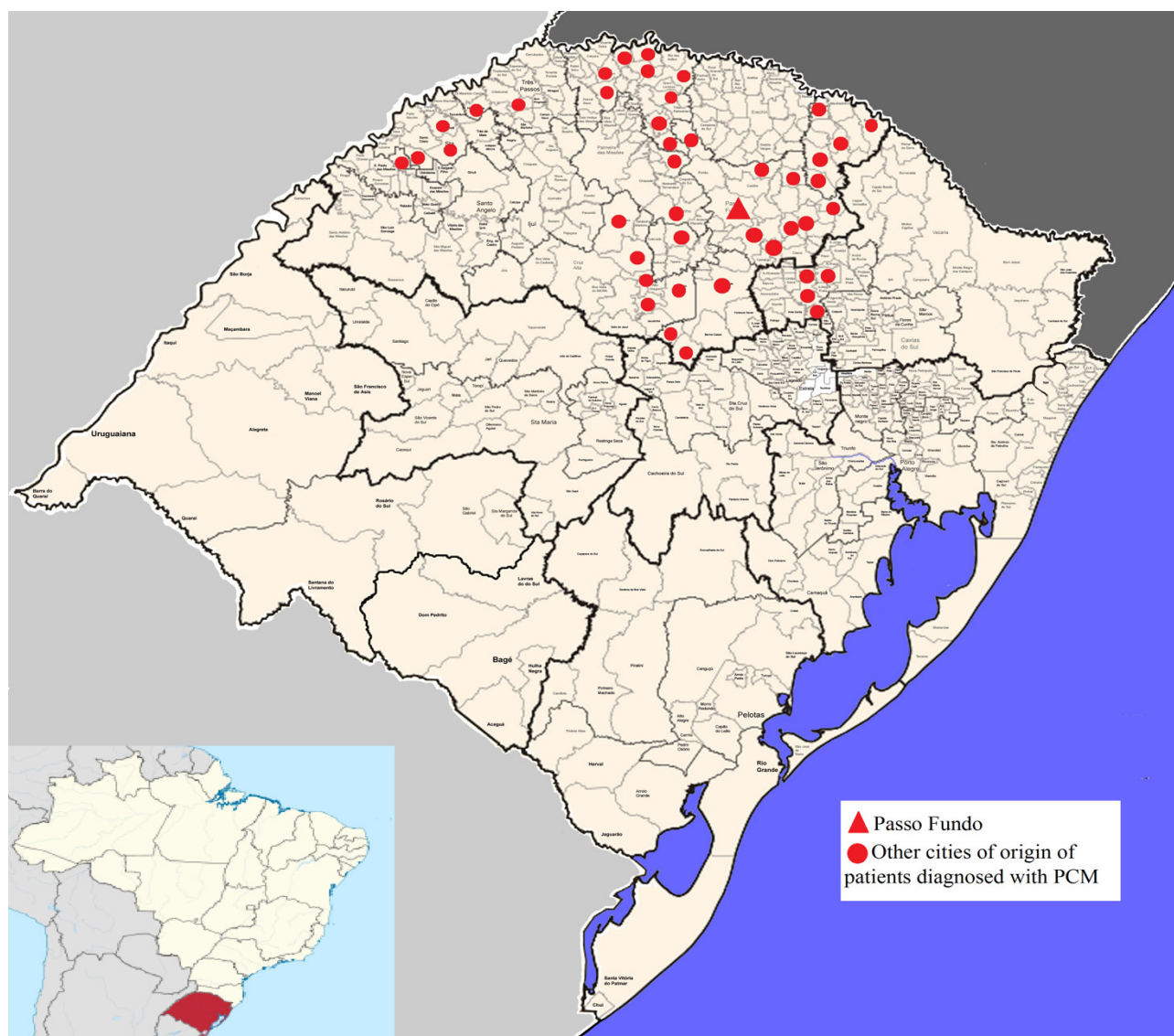
Data analysis was performed using descriptive

statistics. This study was approved by the research ethics committee of Imed College, Passo Fundo, RS, Brazil.

## RESULTS

Two hundred medical records of PCM cases registered from 1995 to 2015 (20 years) were analyzed (Table 1). The male:female ratio was 185:15. Patients ranged in age from 31 to 80 years. Fourteen (7%) patients were of the 31–40 years age group, 57 (28.5%) of the 41–50 years, 71 (35.5%) of the 51–60 years, 44 (22%) of the 61–70 years, and 14 (7%) of the 71–80 years age group.

One hundred and sixteen patients (58%) were residents of Passo Fundo and 84 patients (42%) resided in other cities of the northern region, with cases ranging from 1 to 10 in number in each city (Figure 1). Information on the place of origin (whether rural or urban) and/or occupation was available for 85 patients. Of these, 63 (74%) lived in rural areas and/or had worked in agriculture and



**Figure 1.** Cities of origin of patients diagnosed with PCM at the Pathology Institute of Passo Fundo, RS, Brazil. Source: Adapted from [https://pt.wikipedia.org/wiki/Ficheiro:RioGrandedoSul\\_MesoMicroMunicip.svg](https://pt.wikipedia.org/wiki/Ficheiro:RioGrandedoSul_MesoMicroMunicip.svg).

22 (26%) lived in urban areas and had occupations such as bricklayer, logger, gardener, military, general services or household activities.

Clinical samples were obtained from the oral cavity (n = 106), oropharynx (n = 47), lungs (n = 15), brain (n = 8), skin (n = 7), and prostate (n = 3).

**Table 1.** Distribution of PCM cases according to sex, age group and injury site.

	Total	%
<b>Sex</b>		
Man	185	92.5%
Woman	15	7.5%
<b>Age group (years)</b>		
31-40	14	20.5%
41-50	57	28.5%
51-60	71	35.5%
61-70	44	22%
71-80	14	7%
<b>Injury site</b>		
Brain	8	4%
Lung	15	7.5%
Oral cavity	106	53%
Oropharyngeal	47	23.5%
Prostate	3	1.5%
Skin	7	3.5%

## DISCUSSION

This is the first retrospective study to report PCM cases in the northern region of Rio Grande do Sul, Brazil. We analyzed 200 cases of PCM diagnosed histopathologically in patients from Passo Fundo and other cities in the northern region of Rio Grande do Sul over a period of 20 years.

The majority of patients diagnosed with PCM were male, aged between 51 and 60 years, and had lesions located predominantly in the oral cavity or oropharyngeal region.

The region of Passo Fundo has its economy based mainly on agriculture, which favors the infection of agricultural workers with *P. brasiliensis*. Verli et al. (2005) described positive cases of PCM in a stomatology service in Porto Alegre, RS, and showed that 73.7% of the patients diagnosed between 1976 and 2004 were from the northern region of Rio Grande do Sul.<sup>10</sup>

Although RS has low winter temperatures, several studies report endemic PCM cases in cities of this state, such as Santa Maria, Porto Alegre, and Pelotas.<sup>15</sup> In addition, the fungus that causes PCM was also found in the soil of the Pampa biome, in the city of Bagé and in urban areas of the municipality of Rio grande.<sup>16,17</sup>

Similar to other epidemiological studies on PCM, in this study, the number of men affected by the disease was greater than that of women, in the ratio of 18:1.<sup>1</sup> This observation can be explained by the higher number of men working as farmers and by the fact that men are more frequently in contact with the sources of infection. Another explanation is the protection conferred to

women by hormonal factors, possibly by the action of estrogen as a potentiator of the immune cellular response.<sup>18</sup> After menopause, estrogen levels drop dramatically. From the age of 35, a decrease in estrogen secretion by female follicular cells begins. Possibly for this reason, in this study, women with PCM were over 40 years old. Similar data are found in the literature, with reports of women with PCM in childhood or in the post menopausal period.<sup>1</sup> In addition, men are more prone to smoking and alcoholism, factors related to the disease.<sup>19</sup>

Several studies describe agricultural activities as the most predominant occupations of PCM patients.<sup>10,15</sup> However, there are also consistent reports of a high incidence of the disease among construction workers.<sup>10</sup> This can be explained by their contact with aerosols (from soil and wood) or, mostly, by rural workers who left the field, where they probably acquired the infection, and manifested the clinical symptoms years later, when they were already integrated into the urban population.<sup>1,20</sup> This characteristic of PCM cases was confirmed in the present study: the majority of patients (74%), for whom this information was available on medical records, were from rural areas and worked in agriculture, whereas the others (26%) lived in urban areas but worked in activities that made them susceptible to *P. brasiliensis* infection, as masons, loggers, gardeners, among others.

In the present study, the largest proportion of patients were aged between 51 and 60 years, which agrees with previous PCM reports from RS and other countries, but differs from data from other regions of Brazil, where lower age groups are more prevalent.<sup>15,21,22</sup>

Most individuals infected with *Paracoccidioides* spp. do not develop the disease, exhibiting a pattern of immune response by T-helper cells type 1 (Th-1), characterized by the synthesis of cytokines that activate macrophages and TCD4+ and TCD8+ lymphocytes, resulting in the formation of compact granulomas and control of fungus replication. Patients with chronic unifocal or multifocal PMC exhibit depression of the Th-1 response, but to a lesser extent than in patients with the acute or severe disseminated chronic form. In patients with mild or moderate chronic PCM, the loss of Th-1 function seems to be compensated by the Th-17 and Th-22 responses, which promote inflammatory mucosal response with intense neutrophil participation.<sup>23</sup> This mechanism explains the involvement of mucous membranes, especially the respiratory tract.

Oral lesions were present in 106 patients, in different anatomical sites (tongue, lip, soft palate, gingiva, and jugal mucosa), similar to those found in other studies.<sup>10,24</sup> Extrapulmonary manifestations appear in the chronic phase of the disease after the fungus has spread through the bloodstream. Data from the literature have already shown that in the southern region of Brazil there is a predominance of the chronic form of PCM.<sup>15</sup> These data may be underestimated since in the medical records there were only annotations restricted to the site of biopsy but no reports of other anatomical sites possibly involved.

PCM was classified as a compulsory notification

disease in Brazil only in February 2020, by Decree No. 254 of the Ministry of Health, however, the non-mandatory notification until then, may have generated a large number of unreported or unidentified cases.<sup>14</sup> The epidemiological data on PCM reported in this study highlight the importance of performing the differential diagnosis, since the most common manifestation of this infection is a productive cough with mucopurulent expectoration, also the main manifestation of tuberculosis.<sup>1</sup> In addition, the differential diagnosis should include histoplasmosis, leishmaniasis, squamous cell carcinoma, syphilis and Hodgkin's lymphoma (in lymphatic form).<sup>1</sup> In rural areas, where there are few investments in healthcare, PCM is commonly not considered during diagnosis, leading to the patient's death and its record under incorrect causes.<sup>25</sup> Another factor that seems to influence the difficulty in obtaining more accurate numbers of PCM is the non-adherence to treatment. Because, once the clinical cure (that is, the disappearance of symptoms such as: reduction of dyspnea and mucocutaneous lesions) precedes the immune recovery, the patient tends to discontinue pharmacotherapy, thus leading to disease recurrences.<sup>26</sup>

Other factors that reinforce the importance of PCM notification and control are the social and economic costs of the disease, affecting individuals in their most productive life phases and requiring prolonged treatment as well as frequently causing sequelae that may permanently prevent workers from executing their activities.<sup>3</sup>

It can be mentioned as limitations of the study, the lack of data in the patients' medical records, such as scholarship and comorbidities. Regarding comorbidities, even with the existence of other diseases in these patients, unlike other systemic mycoses, such as histoplasmosis, PCM is not usually related to immunosuppressive diseases.<sup>1</sup>

PCM incidence among men aged more than 50 years agrees with data from the literature. Men are more frequently in contact with the fungal agent due to their occupations and are more exposed to risk factors for the disease, such as smoking and alcoholism. These data highlight the importance of healthcare professionals in the correct diagnosis and treatment of PCM cases. Early diagnosis is of high relevance due to the high cost of the disease, its prolonged treatment, and to prevent its progression.

## CONFLICT OF INTEREST

The authors state that there was no conflict of interest to declare.

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## CONTRIBUIÇÕES DOS AUTORES

**Débora Nunes Mario, Daniela Schwingel e Lygia Maria Mouri Malvestio** contribuíram para a concepção, planejamento, delineamento do artigo, análise, redação do artigo e aprovação final do artigo.

**Luiza Paloma dos Santos Giroto, Paulo Josué da Silva Jaques e Gabriel Krieser Biolowons** contribuíram para o delineamento do artigo, coleta dos dados e revisão e redação do artigo.

Todos os autores aprovaram a versão final a ser publicada e são responsáveis por todos os aspectos do trabalho, incluindo a garantia de sua precisão e integridade.