Paracoccidioidomycosis Epidemiological Features of a 1,000-Cases Series from a Hyperendemic Area on the Southeast of Brazil

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Abstract. Paracoccidioidomycosis has been known for over 100 years, and until now, there were only few estimates of the disease's incidence. We aim to analyze 1,000 cases treated between 1960 and 1999 at Ribeirão Preto city, São Paulo, Brazil, where the disease's incidence range detected was 1.6 to 3.7 cases per 100,000 habitants per year (mean = 2.7 cases/year). We observed a male to female ratio of 6:1 and an age distribution from 3 to 85 years. The acute/subacute form of the disease accounted for 25.4% of cases. Most of the patients (93.5%) had lived or worked in rural areas before the disease development. Smoking and alcoholism were reported by 64.7% and 37.2% of patients, respectively. Comorbidities identified included tuberculosis (8.3%), Chagas' disease (8.6%), and human immunodeficiency virus/acquired immunodeficiency syndrome (4.2%). The present study revealed an area in Brazil where paracoccidioidomycosis is hyperendemic (has the highest reported incidence of this disease); this endemic area is probably caused by geological and climatic conditions as well as intensive agriculture.

INTRODUCTION

Paracoccidioidomycosis (PCM) is the most prevalent systemic fungal infection in Brazil as well as in many South American countries,¹ but its impact on public health has not been fully evaluated because of a lack of available data.² Despite being endemic, about 100 years after its discovery, there are only estimates of the disease's incidence, varying from 1 to 3 new cases per 100,000 habitants in endemic areas.¹ Fatality and mortality rates attributed to PCM make it possible to estimate that 3,360 new cases occur annually in Brazil.³ Epidemiological surveys conducted by intradermal reaction with paracoccidioidin and case series reports suggest that *Paracoccidioides brasiliensis* infection occurs in the entire Brazilian territory.⁴ However, it is rare to identify cases with acute infection by this fungi⁵ or isolate *P. brasiliensis* from nature,⁶ making it difficult to fully recognize areas of fungi acquisition. Alternatively, epidemiological studies of large series of cases may be useful for demarcation of endemic areas. In this regard, a study of cases in children and young adults is more valuable, because their social mobility is limited and fungal disease may progress soon after infection in this population.⁷

Because case notification is not mandatory at the national level, PCM epidemiology was constructed considering regional data. Epidemiological differences were observed among Brazilian regions, including a higher prevalence in the Southeast and Midwest, and there was heterogeneity in the age and gender distribution.⁴ In the current study, we present new data about PCM occurring in the Ribeirão Preto region in southeast Brazil. The 1,000 patients received medical care in a single public university hospital over four decades, and this series represents the second largest case series ever reported.

MATERIALS AND METHODS

Study setting. The Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo

(HC FMRP-USP) is a public university tertiary care hospital with 713 beds located in Ribeirão Preto city, São Paulo State, Brazil. Beyond admitting patients for acute care, it also provides ambulatory care for a reference population of 3 million people living as far as 150 km from Ribeirão Preto city. Indeed, the HC-FMRP USP is a reference facility for the diagnosis and management of patients with PCM.

Ribeirão Preto is located on the Northeast of São Paulo, Brazil (21°12'42"S, 47°48'24"W) and is the main city of a state district that contains 26 cities. The geographic area is generally flat and predominantly composed of purple latossol, but dark red latossol, yellow red latossol, lithosol, and hydromorphic soil are also found. The mean annual temperature is 22.6°C, the mean air humidity is 71.8%, and annual precipitation is about 1,500 mm/year, most of the rain falling between November and March. The air humidity and temperature decreases between May and August, reaching monthly averages as low as 48.8% and 19.2°C, respectively.⁸

Throughout the region, there are intensive agricultural and livestock activities resting on the little part of the native vegetation. In Ribeirão Preto city, the urban area comprises 17.9% of the total city area (651 km²); 6.9% of the city area is remnant native forest or river borders, 59.8% is occupied by sugar cane culture, 10.9% is occupied by pastures, and 3.9% of the area is occupied by other agriculture activities. In the other cities of the region, sugar cane culture is now becoming more common, but coffee culture and pastures were predominant during the period of data collection.⁸

Data collection. We analyzed the data from 1,000 patients with confirmed PCM whose diagnoses were made based on the clinical picture, serology (counterimmunoelectrophoresis), and mycological and histopathological results. Data were retrospectively collected from medical records of patients who received care from 1960 to 1999.

Knowing that the HC FMRP-USP consolidated its role as a regional reference on the diseases' management since 1980, we used data from the 1980 to 1999 period to estimate the PCM incidence in the Ribeirão Preto district. All cases diagnosed in this period in people residing in Ribeirão Preto state district were included. The population estimates for each city of the region on the period were obtained from a Brazilian government website (DATA SUS).⁹

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FIGURE 1. Geographic area where most of the 1,000 patients with paracoccidioidomycosis lived (Brazil 1960–1999). The grey mark delimits Ribeirão Preto State district. MG = Minas Gerais State; SP = São Paulo State.

Beyond demographic data, we investigated past medical and epidemiological history, with emphasis on the association with other infectious diseases or cancer, exposure to rural ambient, and alcohol or tobacco consumption. According to clinical presentation, patients were classified into the acute/subacute form (juvenile type) and chronic form (adult type).¹⁰

Statistics. Data were digitized in a bank data of the Epi-Info program (CDC, version 3.5.1), Atlanta City, NJ and analyzed in the same program.

RESULTS

During the study period, we included 1,000 patients with PCM. From this whole population, 497 new cases living in Ribeirão Preto district were detected from 1980 to 1999, whereas the cumulative population of the district reached 18,393,197 habitants over 20 years, leading to a mean incidence of 2.7 cases per 100,000 habitants. The mean incidence of the acute/subacute form of the disease was 0.6 cases per 100,000 habitants in the same period. Figure 1 shows the area from where most of the patients studied came, whereas Figure 2 describes the annual incidence of the disease in the Ribeirão Preto district.

Table 1 presents the laboratorial diagnostic findings of the patients studied; it shows that most of them had a positive

serological result (97.2%) and/or a positive histopathological exam (64.7%), whereas mycological cultures were positive only in 25.3% of the patients.

Table 2 shows the state and district where patients were current living at the time of first attendance. Franca district and municipalities of the southwest of the Minas Gerais state had more elevated prevalence of the acute/subacute form of PCM than the Ribeirão Preto district or other regions. In Table 3, we present the seasonal variation of the first attendance at HC FMRP-USP. August and July presented a discrete increase in the number of cases. December must be excluded, because the medical service was partially closed in this month.

Table 4 describes some demographic characteristics of the studied patients: most of them were male (85.8%), and the mean age was 40.8 years old (standard deviation = 15.9 years). White skin color was most common (79.0%), which is also the most common in the whole population, and most of the patients had worked or lived or were still living on a country area (93.5%). Figure 3 describes the age distribution of patients according to the clinical form presented.

In Table 5, we show the patient's occupation before disease development. Almost one-half of the cases (47.2%) were farm workers, including employees and owners of the land. Building worker was the second most common occupation, with 8.2% of these patients.

FIGURE 2. Paracoccidioidomycosis incidence per 100,000 habitants on Ribeirão Preto State district from 1980 to 1999.

TABLE 1

Laboratory diagnostic findings of 1,000 patients with paracoccidioidomycosis (Brazil, 1960–1999)

Laboratory test	n evaluated	Positive result n (%) [*]
Counterimmunoelectrophoresis	939	913 (97.2)
Mycological culture	775	196 (25.3)
Histopathological exam	784	507 (64.7)

^{*} Absolute number of patients and percentage.

Table 6 reveals some clinical aspects of the disease presented by these patients, where one can see that the majority of them were classified as having a chronic form of the mycosis. Most of them were current or past smokers (64.7%), and more than one-third related current or past alcoholism (37.2%). Coinfections with tuberculosis (8.3%), human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS; 4.2%), Chagas' disease (8.6%), and strongyloidiasis (9.1%) were detected among others. About 10.7% of patients presented with clinical signs and symptoms of chronic obstructive pulmonary disease (COPD), and 6.4% had a malignant neoplastic disease confirmed by histopathology.

DISCUSSION

The present study revealed that Ribeirão Preto, São Paulo, Brazil, is the geographic area with the highest ever reported incidence of PCM. Data on incidence of this fungal disease are scarce, but the average incidence of 2.7 new cases per 100,000 habitants per year is in the presumed range of incidence for endemic areas, which is estimated to be from 1 to 4 new cases per 100,000 habitants per year.¹ A study of 937 patients evaluated between 1953 and 1978 pointed that the Central and North parts of the São Paulo state had an incidence of 0.3–0.4 cases per 100,000 habitants per year.¹¹ Another study among 260 patients from the state of Rio Grande do Sul revealed an incidence of 0.9 cases per 100,000 habitants per year,¹² whereas in other South America countries, it has been estimated an average incidence of 0.5 cases per 100,000 habitants per year,^{13–15} with lower rates being described in Colombia.¹⁶

It is probable that the incidence detected here is underestimated, because it is known that a small portion of patients receives medical care from other medical services. The estimate was done on the basis of a period when a stable and continuous influx of patients was observed, and it used only the

TABLE 2

State and district where patients with paracoccidioidomycosis were currently living at the time of first attendance at the study institution according to the clinical form presented (Brazil, 1960–1999)

Current residence (state/district)	Clinical form N (%)		
	Chronic	Acute/subacute	Total
State of São Paulo			
Ribeirão Preto	394 (78.3)	109 (21.7)	503 (100)
Franca	88 (66.2)	45 (33.8)	133 (100)
Araraquara	68 (78.2)	19 (21.8)	87 (100)
São João da Boa Vista	43 (76.8)	13 (23.2)	56 (100)
Barretos	30 (75.0)	10 (25.0)	40 (100)
Other cities	30 (81.1)	7 (18.9)	37 (100)
State of Minas Gerais (southwest)	73 (59.8)	49 (40.2)	122 (100)
Other states	16 (88.9)	2 (11.1)	18 (100)
Total	742 (74.5)	254 (25.5)	996 (100)

TABLE 3

Seasonal variation of the first attendance of 1,000 patients with paracoccidioidomycosis at the study institution (Brazil, 1960–1999)

Month	N (%)
January	82 (8.2)
February	88 (8.8)
March	92 (9.2)
April	77 (7.7)
May	77 (7.7)
June	65 (6.5)
July	95 (9.5)
August	113 (11.3)
September	87 (8.7)
October	84 (8.4)
November	88 (8.8)
December	52 (5.2)

data from the Ribeirão Preto district, which brought more accuracy to the numbers obtained. A small annual variation observed here may be because of climatic changes that encourage or discourage the growth of *P. brasiliensis* in the soil and also, temporal changes in intensity and type of agricultural activity.¹⁷

The large area where the 1,000 patients lived included Northeastern São Paulo state and Southwestern Minas Gerais state and was roughly bounded by latitudes 20° North and 22° South and longitudes 47° East and 49° West. It is adjacent to other endemic areas that have, as regional poles, the cities of Campinas in the State of São Paulo¹⁸ and Uberaba in the State of Minas Gerais.¹⁹ *P. brasiliensis* was isolated from soil of a coffee plantation in the Ibiá city in the region of Uberaba.⁶ The high endemicity of PCM in the study area is probably related to geological and climatic conditions that favor the development of the saprobe fungi and intensive agricultural activity that exposes people to the microorganism. The rainfall is enough to keep the soil moist for several months each year, which should stimulate the growth of *P. brasiliensis*.¹⁷ Besides that, Latosol soil has been associated with higher incidences of PCM in other studies.²⁰

The small increase in the number of patients with PCM observed in July and August may be related to the coffee harvest, typically occurring in the first one-half of the year, or the sugar cane harvest, which extends from the first to second one-half of the year. Another possible factor is the low air humidity in July and August, which could stimulate the formation and spreading of *P. brasiliensis* propagules. However, the duration of the disease before medical treatment varies from weeks to months, and the long latency period between infection and chronic disease is enough to disturb the analysis of seasonality of infection and fungal disease.

TABLE 4

Demographic characteristics of 1,000 patients with paracoccidioidomycosis (Brazil, 1960–1999)

Parameters	n evaluated	n [*]
Mean age in years (range)	998	40.8 (3–85)
Male sex (%)	1,000	858 (85.8)
Ratio of male to female	1,000	6:1
White color (%)	991	783 (79.0)
Black color (%)	991	81 (8.2)
Mulatto (%)	991	127 (12.8)
Had lived or is still living in the country (%)	758	709 (93.5)

^{*} Data presented are absolute numbers of cases and percentages unless otherwise indicated.

FIGURE 3. Age distribution of 1,000 patients with paracoccidioidomycosis according to the clinical form presented (Brazil 1960–1999). ● = acute/subacute form; ■ = chronic form; ▲ = all patients.

Among the cases reviewed, there were 121 children or adolescents 3–20 years old and 132 adults 21–30 years old, most of them residing in Ribeirão Preto district, which represents additional evidence of the endemicity of this area. It is known that the acute/subacute disease presented by most of the younger patients occurs shortly after infection with *P. brasiliensis*, which makes it likely that the patient is still near the microniche where he was infected.⁷

In this sense, it is interesting to note that the highest proportion of cases with the acute/subacute disease was living in Southwestern Minas Gerais State and the neighboring Franca city. In these areas, there were numerous and extensive coffee plantations, and coffee cultivation has been associated with acquiring PCM.^{7,21} The manual harvesting of coffee requires large numbers of workers, and even children and young people were being recruited for this task. The increased exposure of young individuals to *P. brasiliensis* is possibly the cause of the higher rate of cases with the acute/subacute form in subareas with the highest prevalence of coffee growing.

Cases included in the study received care from different medical specialties at the HC-FMRP-USP, to which patients had free access. These conditions and the large number of cases suggest that the data are representative of the epidemiology of PCM. We confirmed the predominance of patients aged 20–50 years old as well as the most prevalent forms of acute/subacute and chronic disease in the first three decades of life and after 30 years of age, respectively.²² The male to female ratio observed here (6:1) is similar to that observed in large series of cases in the Southeast¹⁸ and Midwest of Brazil²² (respectively, 5.4:1 and 10:1). In these regions, the involvement of women is proportionately larger than in other areas of

Brazil and other countries of South America, probably because of increased participation of the women in agricultural work. Ethnicity does not seem associated with PCM, because the distribution of patients is comparable with the population of the area of Ribeirão Preto regarding skin color. Previous studies have shown a higher prevalence in mulattos²³ and Asians,¹² but these results may be because of increased contact with the rural environment.

The high rate of agricultural workers, as in other studies,^{18,24} characterizes PCM as an occupational disease of people who directly handle the soil or expose themselves to a rural environment. This disease also seems to affect the drivers, many of whom work on farms or travel between cities in the Ribeirão Preto area. Many patients who worked or resided in urban areas reported having lived or worked in a rural area in the past years. The high rate of patients with prolonged exposure to rural areas in the present or past (93.5%) makes it clear that PCM is a rural disease.

Smoking was very common among the PCM patients²⁵ studied, and it is known to be a pre-disposing factor for various pulmonary infections because of the changes in lung microstructure caused by smoke. Alcoholism was associated with the chronic form of PCM,²⁶ and this finding may be related to the changes on the immune system produced by abusive alcohol consumption.

The coinfections presented by patients, including tuberculosis, Chagas' disease, leprosy, and strongyloidiasis, probably resulted from the same conditions of life that pre-disposed then to PCM, such as low socioeconomic and educational

TABLE 5

Occupation before disease development of 1,000 patients with paracoccidioidomycosis (Brazil, 1960–1999)

Occupation	n (%)
Farm worker (employee)	403 (40.3)
Farm worker (owner)	69 (6.9)
Building worker	82 (8.2)
Student or underage children	69 (6.9)
House maid	64 (6.4)
Professional driver	51 (5.1)
Industrial worker	39 (3.9)
Others	146 (14.6)
Unknown	47 (4.7)
Total	1,000 (100)

TABLE 6

Relevant clinical characteristics of 1,000 patients with paracoccidioidomycosis (Brazil, 1960–1999)

Clinical form and comorbidities	n evaluated	n (%)
Acute/subacute form	1,000	254 (25.4)
Chronic form	1,000	746 (74.6)
Smoking	782	506 (64.7)
Alcoholism	782	291 (37.2)
TB coinfection	783	65 (8.3)
HIV/AIDS coinfection	782	33 (4.2)
Hansen's disease coinfection	782	12 (1.5)
Chagas' disease coinfection	782	67 (8.6)
Strongyloidiasis coinfection	782	71 (9.1)
COPD	782	84 (10.7)
Malignant neoplastic diseases	782	50 (6.4)

TB = tuberculosis; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; COPD = chronic obstructive pulmonary disease.

status, alcoholism, malnutrition, and exposure to rural and suburban areas.² Tuberculosis is relatively common among patients with PCM²⁷ and was diagnosed before, after, or simultaneously with the fungal disease.

The HIV/AIDS epidemic hit the Northeast of São Paulo state severely, causing this region to report the highest number of cases of *P. brasiliensis* coinfection in Brazil. Coinfected patients usually exhibit a different epidemiology related to the lower age and increased urbanization.²⁸ Neoplasia located mainly in the respiratory tract and tegument occurred during the treatment period or at the next post-treatment of patients with mycosis. This comorbidity may not be causally related to PCM, but it is also possibly associated with the age, lifestyle, and smoking habits of patients.²⁹

In conclusion, this study revealed that the geographic area of Ribeirão Preto, Southeast Brazil, is hyperendemic for PCM, which was shown by the high incidence rate, the high proportion of young patients with acute/subacute disease, and also, the significant percentage of patients coinfecting with HIV/AIDS. Epidemiological data of patients, distribution among the clinical forms of disease, and comorbidity were similar to several other series of contemporary cases from the Southeast and Midwest regions of Brazil.

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