Paracoccidioidomycosis: Epidemiological and Clinical Aspects in 546 Cases Studied in the State of Espírito Santo, Brazil

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Abstract. Paracoccidioidomycosis (PCM) is an endemic disease in the southeast region of Brazil, which includes the state of Espírito Santo (ES). This historic case series analyses 546 patients treated in this state from 1978 to 2012. Patients aged from 7 to 83 years, 509 males and 37 females, yielding a ratio of 13.7:1. Most of the patients (81.4%) originated from rural areas in ES, 71.0% being farmers. A higher concentration of cases was observed in municipalities located along the western range of the state. Sixty patients (11.0%) had an acute/subacute form of the disease, 485 (88.9%) had a chronic form, and one had a subclinical form. The most affected organs included the lungs, oropharyngeal mucosa, lymph nodes, skin, and larynx. The diagnosis was confirmed by histopathology in 252 (46.2%) cases, direct examination in 168 (30.7%), both exams in 111 (20.3%) and serology in 15 (2.8%). Tuberculosis, acquired immune deficiency syndrome, leishmaniasis, and intestinal parasites were the most frequently associated infectious diseases. From 328 patients followed up, total regression of the lesions was observed in 17.4%, partial regression in 77.4%, and no regression in 17 (5.2%) cases. Regarding the number of cases in this series, ES emerges as an important endemic area for PCM in Brazil.

INTRODUCTION

Paracoccidioidomycosis (PCM) has been recognized as a disease for more than 100 years. It was described by Lutz, Splendore, and Almeida, and its causal agent is *Paracoccidioides* sp. PCM constitutes the most important systemic endemic mycosis in South America and Brazil; however, its impact on public health is not completely understood. In fact, accurate information is lacking because it is not a mandatory reportable disease in the states and in the country.^{1,2} The prevalence of PCM varies between countries, and within these countries, it may vary from one region to another.³ Brazil is the “heart of the endemics,”⁴ accounting for 80% of reported cases. In the southeast of the country, one of the regions with the highest PCM prevalence, studies were conducted that generated publications describing long series of cases.^{1,5–7} In the state of Espírito Santo (ES), the mortality rate for PCM is cited as the highest in the southeast region.⁸ However, few studies have been conducted to date in this state,^{9,10} wherein the epidemiological profile of PCM remains almost unknown and where environmental conditions for disease transmission are assumed to be present. Considering the scarcity of information on this disease in the state of ES, a more comprehensive study of the disease that includes epidemiological, clinical, and therapeutic aspects in a historical series of the last 34 years was warranted.

MATERIALS AND METHODS

Study location. The Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo (HUCAM–UFES) is a public tertiary care hospital with 310 beds located in Vitória, the capital of the state of ES; it provides care

in inpatient units for complex cases and outpatient care for various specialties and is a reference hospital for the diagnosis and treatment of PCM.

The state of ES is located in the southeast region of Brazil, sharing a border with Bahia State to the north, Minas Gerais State to the west, and the state of Rio de Janeiro to the south, with its entire eastern extension bordered by the Atlantic Ocean. ES occupies an area of 46,814.1 km² with 40% of the territory in the coastal plain range and 53% of the territory residing in the interior mountainous region; the average altitude is 758 m. The climate is tropical humid–coastal, and the rainy season predominately occurs during the summer. The mean temperature ranges between 22°C and 24°C, and the annual rainfall is between 1,000 and 1,500 mm. The mountainous region is traversed by numerous permanent waterways, supplied by regular rainfall throughout the year. The rivers run through the base of the valleys and frequently create waterfalls, generating a distinctive relief, which requires the farmers who exploit the mountain slopes to have intensive contact with the land.

According to the demographic census conducted by Instituto Brasileiro de Geografia e Estatística (IBGE) in 2010, the state of ES had 3,512,672 inhabitants, representing 1.8% of the Brazilian population; of these, 2,928,993 inhabitants lived in urban areas and 583,679 lived in rural areas. The last IBGE census also indicated the racial demographic as being 46.6% mulatto, 42.2% white, and 8.4% black.

Agriculture is the third largest economic activity, accounting for 15% of revenue in ES and generating 800,000 jobs. The main product produced is coffee, which accounts for 60% of agricultural revenues and 576,000 hectares planted. With 360,000 jobs, this agricultural activity is the largest single source of employment, and its production continues to grow. Family farming accounts for 80% of rural properties in the state, which is the second largest coffee producer in the country.¹¹

Data collection. This is a descriptive study, reporting a series of 546 cases of PCM, consisting of patients treated at HUCAM from 1978 to 2012 who were diagnosed with

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acute/subacute or chronic forms of the disease based on epidemiological and clinical history and confirmed by laboratory tests.

Patient demographics were analyzed including age, gender, race, occupation, and primary agricultural activities if they were farmers. The evaluation of the patients' origins was based on information regarding the patients' first two decades of life, deferring to the concept established in the Brazilian Consensus,¹² that it is during this period that the infection is acquired.

The municipalities of origin of the patients from ES were recorded to define the regions with the highest prevalence of PCM in the state. Information about risk factors including smoking and alcohol consumption were obtained from the patients at diagnosis. Patients were considered alcoholics if they consumed 50 g or more of ethanol/day.

Based on the information concerning the clinical, radiological, and laboratory manifestations, the clinical form of the disease was defined for each case according to the classification system proposed in the Brazilian Consensus.¹²

The diagnosis was confirmed by the direct examination of sputum, bronchoalveolar lavage fluid, lymph node fine needle aspiration material, and skin or mucosal lesion scrapings in which structures consistent with *Paracoccidioides* sp. could be observed. Biopsies with histopathology findings consistent with PCM and positive serology for the disease were also used as criteria to confirm a diagnosis.

Serology was performed at the Mycology Laboratory at the Health Sciences Center—UFES. In the period from 1978 to 1987, the precipitation technique was used. Subsequently, the double immunodiffusion (ID) method was used using antigen produced in the laboratory from samples isolated in the state of ES.

Diagnostic imaging was based on an analysis of chest radiographs. Computed tomography (CT) scans were performed during more recent years for patients with more extensive involvement.

Bone and central nervous system (CNS) lesions were analyzed during the first 10 years using scintigraphy and in recent years using CT and magnetic resonance imaging.

Associated diseases were diagnosed using specific methods, and the patients were treated and received follow-up for as long as needed.

All data were recorded on standardized protocols and entered into a database that helped consolidate the information.

The study was approved by the Research Ethics Committee at the Health Sciences Center at UFES on December 15, 2011.

Statistical analysis. A database was established with the epidemiological and clinical characteristics of the patients, using the program Epi Info TM, version 7.0 (Centers for Disease Control and Prevention, Atlanta, GA). The χ^2 statistical test was used to compare proportions. A significance level of 5% was considered statistically significant ($P < 0.05$).

RESULTS

In the population studied, 444 (81.4%) patients were from ES and 102 (18.6%) were from other states, including 10.6% from Minas Gerais, which shares the longest border with ES to the west; 5.5% from Bahia, which shares a narrower border to the north; and three patients from the state of Rio de Janeiro to the south.

Among the 546 patients studied, ages ranged from 7 to 83 years, averaging 46.5 years. By gender, 509 (93.2%) patients were male and 37 (6.8%) were female, yielding a ratio of 13.7:1. By race, from 383 patients with registered information, 51% were white, 39% were mulatto, and 10% were black.

Regarding occupation, 388 (71.0%) were farmers, followed by various other professions such as building workers, general service workers, traders, drivers, and domestic service workers, with students represented among younger patients (Figure 1). The occupation for 46 (8.4%) patients was not disclosed. Among the farmers, 95.4% noted that coffee cultivation was their primary agricultural activity.

Besides ES state, patients came also from neighbor states, as listed in Table 1.

Most of the patients from ES came from more inland municipalities, primarily located on the western border with a predominantly hilly terrain, tropical climate in the lowlands,

FIGURE 1. Distribution by occupation of patients with paracoccidioidomycosis treated at Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo between 1978 and 2012. This figure appears in color at www.ajtmh.org.

TABLE 1

Place of origin of the patients with paracoccidioidomycosis divided into federative units treated at HUCAM/UFES from 1978 to 2012

Federative units	N (%)
Espírito Santo (ES)	444 (81.4)
Minas Gerais (MG)	58 (10.6)
Bahia (BA)	30 (5.5)
Rio de Janeiro (RJ)	3 (0.5)
São Paulo (SP)	1 (0.2)
Other	5 (0.9)
No Information	5 (0.9)
Total	546 (100)

HUCAM/UFES = Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo.

and high-altitude tropical climate in the mountainous region. The prevailing rainy season in this region occurs in the summer, which helps maintain a strong agricultural environment, mainly sustained by coffee production. Notably, the municipality of Colatina had a significant concentration of patients, accounting for 37 (8.4%) patients (Figure 2). In contrast, few patients were from the coastal region.

An analysis of the number of patients diagnosed with PCM indicated that during the period from 1980 to 1985, an average of 20 new cases/year were treated at HUCAM, and between 2007 and 2012, 25 cases/year were seen at the hospital, in spite of 20% reduction of the population living in rural areas in the state during those 30 years.

Regarding the clinical presentation, 485 (88.9%) patients presented with the chronic form of PCM, 60 (11.0%) presented with the acute/subacute form, and one patient presented with the subclinical form.

For the chronic form, the patients' ages ranged from 20 to 83 years with an average of 49.3 years, with the majority of patients in their 30s–60s (Figure 3). The male/female ratio was 22:1 (Table 2). The age distribution of female patients ranged from 7 to 77 years old, with an average of 36.7.

For the acute/subacute form, the patients' ages ranged from 7 to 45 years with a mean of 22.7 years and the majority of patients in their 20s. The male/female ratio among patients older than 18 years was 4.5:1. For patients younger than 18 years (16/60), the male/female ratio was equal.

Tobacco use was reported by 91.0% of 367 patients surveyed and alcohol consumption by 57.5% of 341 respondents.

The primary manifestations associated with the clinical forms of PCM are shown in Table 3. General symptoms include weight loss, observed in 64% of patients, and fever, observed in 66.7% of acute/subacute and 27.2% of chronic cases.

The group with the acute/subacute form had generalized lymphadenopathy (91.6% of the patients), hepatomegaly (46.6%), and splenomegaly (41.6%). Cutaneous lesions were present in 48.3% of cases. All of these clinical manifestations differed significantly between the acute/subacute and chronic forms.

FIGURE 2. Map of the (A) geographical location of Espírito Santo State in Brazil and South America –and (B) distribution of paracoccidioidomycosis cases based on the place of origin of 444 patients treated at Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo, Espírito Santo, from 1978 to 2012. This figure appears in color at www.ajtmh.org.

FIGURE 3. Age distribution and clinical presentation of patients with paracoccidioidomycosis treated at Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo between 1978 and 2012. This figure appears in color at www.ajtmh.org.

The impairment of intestinal and abdominal lymph tissue by PCM was evident based on various manifestations such as abdominal pain in 24 (40%) of acute/subacute patients, palpable masses and jaundice in nine (15%) patients, and bloody diarrhea in four patients. Jaundice was likely due to compression of the extrahepatic bile ducts; however, in four patients, a liver biopsy was also positive for *Paracoccidioides* sp. Of 60 patients presenting acute/subacute form, 48 had chest radiographs registered. From these, 36 (75%) presented no lesions, nine presented inspecific infiltrates, and three presented bilateral perihilar pulmonary infiltrates, suggestive of PCM; *Paracoccidioides* sp. was isolated from the sputum of two of these patients.

In patients with the chronic form of PCM, the disease was primarily located in the lungs, affected in 91.0% of cases, and the oropharyngeal mucosa, affected in 75.5%. Other clinical manifestations are shown in Table 3.

Chest radiographs were obtained for 488 (89.4%) patients, with changes evident in 408 (83.6%) of them. In the 439 patients with the chronic form, 90.0% presented with lung lesions, which predominantly manifested an interstitial-alveolar pattern in the middle third of both lungs (55.4%). Isolated lung lesions were observed in 55 patients (11.3%).

CT of the chest was performed on 67 patients. Of the 62 patients with the chronic form thereby examined, 60 (96.8%) presented with pulmonary changes, whereas two of five patients with the acute/subacute form also presented with lesions, which had a bilateral distribution, predominately located in the middle and lower third of both lungs.

Adrenal involvement was recorded in 27 (5.0%) patients based on clinical and laboratorial examinations or imaging; in 18 (66.6%) of these patients, with multifocal disease, CT scan showed images suggestive of adrenal involvement by PCM.

TABLE 2
Gender distribution of patients with various manifestations of paracoccidioidomycosis treated at HUCAM/UFES between 1978 and 2012

Gender	Chronic form N (%)	Acute/subacute form ≥ 18 years N (%)	Acute/subacute form ≤ 18 years N (%)	Total N (%)
Male	464 (85.1)	36 (6.6)	8 (1.5)	508 (93.2)
Female	21 (3.8)	8 (1.5)	8 (1.5)	37 (6.8)
Total (%)	485 (88.9)	44 (8.1)	16 (3.0)	545 (100)*
Proportion M/F	22.1/1	4.5/1	1/1	13.7/1

HUCAM/UFES = Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo; M/F = male/female.

* One male patient with subclinical form of the disease was not included in the table.

TABLE 3

Organ impairments and clinical manifestations related to paracoccidioidomycosis in patients treated at HUCAM/UFES between 1978 and 2012

Organs and clinical manifestations	Clinical form						P
	Chronic		Acute/subacute		Total		
	N = 485	%	N = 60	%	N = 545	%	
Lungs	441	90.9	8	13.3	449	82.4	< 0.001
Oropharyngeal mucosa	366	75.5	9	15.0	375	68.8	< 0.001
Cough	319	65.8	18	30.0	337	61.8	< 0.001
Weight loss	302	62.3	47	78.3	349	64.0	< 0.05
Dyspnoea	219	45.2	11	18.3	230	42.2	< 0.01
Expectoration	210	43.3	13	21.7	223	40.9	< 0.01
Localized adenomegaly	147	30.3	5	8.3	152	27.9	< 0.001
Generalized adenomegaly	42	8.7	55	91.6	97	17.8	< 0.001
Fever	132	27.2	40	66.7	172	31.6	< 0.001
Skin	130	26.8	29	48.3	159	29.2	< 0.001
Larynx	101	20.8	0	0	101	18.5	< 0.001
Haemoptysis	67	13.8	1	1.7	68	12.5	< 0.005
Adrenals	26	5.4	1	1.7	27	5.0	0.34
Central nervous system	22	4.5	2	3.3	24	4.4	1.00
Hepatomegaly	21	4.3	28	46.6	49	9.0	< 0.001
Amygdalas	12	2.5	0	0	12	2.2	0.38
Genitals	8	1.7	1	1.7	9	1.7	1.00
Eyelid	8	1.7	0	0	8	1.5	0.61
Splenomegaly	6	1.2	25	41.6	31	5.7	< 0.001
Osteoarticular	4	0.8	3	5.0	7	1.3	< 0.05
Jaundice*	–	–	9	15.0	–	–	–
Abdominal pain*	–	–	24	40.0	–	–	–
Abdominal mass*	–	–	9	15.0	–	–	–

HUCAM/UFES = Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo.

* Only present in the acute/subacute clinical form.

CNS involvement was detected in 24 (4.4%) patients, two of whom had the acute/subacute form. There were no significant differences from CNS involvement between patients with the acute or chronic form. CT of the skull was performed on 46 patients who presented with some neurological issues, and lesions (single or multiple) were found in 22 (47.8%) of these patients, which had nodular patterns and were more frequent in the cerebral hemispheres. Two patients presented with spinal cord injuries with resultant paraplegia, despite treatment. In all cases, the disease was multifocal, and the diagnosis was confirmed by the isolation of *Paracoccidioides* sp. in the integument, lungs, or lymph nodes. In two patients, the diagnosis was based on neurosurgical results, as the intervention was for a suspected brain tumor.

Genital involvement was documented in nine (1.7%) patients, all of whom were male. One presented with the acute/subacute form of PCM and eight with the multifocal chronic form. Eyelid lesions were found in eight (1.5%) patients, all with the multifocal chronic form of the disease. Osteoarticular involvement was evident in seven (1.3%) patients, four of whom presented with the chronic form of the disease and three with the acute/subacute form.

Laboratory diagnostics. The diagnosis of PCM was confirmed by direct microscopic examination of various patient samples, biopsy with histopathology of the lesion or serology, as shown in Table 4. In 15 (2.8%) patients, the diagnosis was confirmed only via serology, associated with the clinical/epidemiological condition of the disease and imaging exams.

Serological tests were performed on 419 patients at the time of diagnosis, and 303 (72.3%) showed positive results. No significant difference was observed in the positivity of patients with the acute/subacute form (70.5%) versus the chronic form

(72.5%). Moreover, no difference was observed in the positivity between the chronic form located in the skin and/or mucosa (73.3%) and cases with multifocal disease (72.5%).

A complete blood count was performed on 406 (74.4%) patients, and anemia was evident in 141 (34.7%) of these patients. This finding was more frequent among patients with the acute/subacute form of the disease, that is, 52/59 (88.1%) patients ($P < 0.001$). An analysis of the leukocyte count showed eosinophilia in 13 (21.7%) of these patients.

Comorbidities. Associated pathologies are shown in Table 5. The most frequent associated diseases were worm infections, affecting 148 (27.1%) patients, 55 of whom presented with strongyloidiasis. Of the nine patients with PCM/acquired immune deficiency syndrome (AIDS) association, five presented the acute/subacute form and four the multifocal chronic form of PCM.

Treatment. Sulfamethoxazole + trimethoprim was used in 355 (65.0%) patients and other sulfonamides in 97 (17.8%) patients, particularly sulfamethoxypyridazine during the 1980s. Ketoconazole was used by 32 (5.9%) patients in the 1980s and 1990s and itraconazole by 39 (7.1%) patients in

TABLE 4

Diagnostic methods used to confirm paracoccidioidomycosis in 546 patients treated at HUCAM/UFES between 1978 and 2012

Examination methods	N (%)
Histopathology	252 (46.2)
Direct microscopy	168 (30.7)
Direct microscopy + histopathology	111 (20.3)
Serology	15 (2.8)
Total	546 (100)

HUCAM/UFES = Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo.

TABLE 5

Diseases associated with paracoccidioidomycosis among the 546 patients diagnosed at HUCAM/UFES between 1978 and 2012

Associated diseases	N (%)
Tuberculosis	31 (5.7)
Neoplasm	14 (2.5)
Leishmaniasis	10 (1.8)
HIV	9 (1.6)
Helminthiasis	148 (27.1)
Strongyloidiasis	55 (10.1)
Hookworm	40 (7.3)
Ascariasis	31 (5.7)
Schistosomiasis	24 (4.4)

HIV = human immunodeficiency virus; HUCAM/UFES = Hospital Universitário Cassiano Antônio Moraes of the Universidade Federal do Espírito Santo.

more recent years. Amphotericin B was used in 130 (23.8%) patients in cases of acute/subacute PCM, severe chronic multifocal forms, PCM/human immunodeficiency virus (HIV) coinfections and in patients with intolerance or resistance to sulfa drugs or the inability to use azoles. In patients who received amphotericin B, maintenance treatment was extended with sulfonamides or azoles in subsequent months. In some patients, the treatment schedule was changed during treatment due to intolerance or adverse events.

In 328 patients analyzed, the treatment resulted in total regression of lesions in 57 (17.4%) patients. In 254 (77.4%) patients, partial regression ensued with the persistence of some type of clinical or radiological sequelae. In 17 (5.2%) patients, premature death from severe illness did not allow the treatment regimen to be evaluated.

The most common sequelae were residual pulmonary lesions of varying sizes, resulting from mild dyspnoea on effort to chronic respiratory failure; scars on the mucosa and skin, including severe microstomia. Laryngeal lesions leading to persistent dysphonia or even the need for permanent tracheostomy were seen in three patients.

DISCUSSION

In our series of cases, the geographic distribution primarily reflects the infection as being more closely related to topographic conditions, climate, and the occupations these patients shared rather than the geographical boundaries between states and, secondarily, that patients sought treatment in reference centers nearest their residences, which were not necessarily in their home state.

During the 1950s–1970s, the municipality of Colatina, the main location of origin of the patients in the state, was not only the state's main coffee producer but also the leading producer in Brazil. Another fact is that ES, unlike other states in Brazil,¹³ has been maintaining and even expanding coffee plantations to become the second largest domestic producer at present. The cultivation of coffee is still the state's main agricultural activity, involving 77 of the 78 municipalities and accounting for 360,000 jobs per year.¹¹ Rural farms are generally small and located in mountainous regions, requiring farmers to engage in activities that involve significant contact with the soil. This would account for the continually high numbers of PCM cases in the state, estimated in between 70 and 108 new cases/year for a population of 3.6 million inhabitants (two to three per 100,000 inhabitants/year) in a high endemic area such as the southeast region of Brazil.¹² In contrast, in states

in southern Brazil, the flat topography has allowed for the use of mechanized agriculture and the replacement of coffee cultivation, wherein a reduction in the PCM incidence has thus been observed.^{2,13}

The age of the patients was similar to other groups studied,^{1,5,14} consisting primarily of adult men, farmers, and mostly coffee plantation workers, as cited by other investigators,^{1,4,15} and who presented with the chronic form of the disease. The male/female ratio of 13.7:1, which is similar to the ratio observed in the neighboring state of Rio de Janeiro,⁵ is within the provisions of the Brazilian Consensus,¹² but higher than that recorded in other states.^{1,14} The ratio of 4.5:1 for the acute/subacute form, which is 1:1 in patients under 18 years old, reinforces the hypothesis that female hormones offer protection after puberty, which has already been documented in the literature.¹⁶

Regarding race, the disease is known to show no predilection for certain ethnicities.^{2,12} The latest IBGE census (2010) shows that in ES state, the population of mulatto individuals (48.6%) is higher than the population of white (42.6%) and black (8.4%) individuals. However, in our study, white patients represented 51% of the total. This may reflect the predominate role that European immigrants have played in traditional family farming in the patients' municipalities of origin.

Approximately 91% of patients surveyed here used tobacco, which is similar in frequency to the 90.3% already reported.¹⁴ The percentage found in our study increases to 96.4% (318 of 330 patients) if only the patients with the chronic form of PCM are included, showing the importance of this risk factor in the population studied and confirming data previously reported in this same Hospital Service.⁹ Alcohol use was reported by 57.5% of the 341 patients surveyed, a proportion close to the 55.3% reported at Hospital Universitário de Brasília.¹⁷ In addition to the effects of alcohol on a patient's immune response,¹⁸ the lack of compliance to treatment by alcoholic patients was also noteworthy.

The proportion of acute/subacute cases in our series was similar to that referenced in other publications^{3,12,19,20} and the main signs and symptoms had similar frequencies to those observed in other series.^{14,17,21,22} Skin lesions were found at a higher frequency in our population than in other series.^{14,17} These lesions arouse a high degree of disease suspicion, and because they offered easy access to direct examination and biopsy, they significantly contributed to the diagnosis. In patients with the acute/subacute form who underwent radiography and chest CT, the findings were comparable to other series.^{14,17}

The most frequent lesions found in patients with the chronic form of PCM were in the lungs and oropharyngeal mucosa, following the standards described in the literature.^{4,19} Approximately 65.8% of chronic patients reported having a cough, and of these, 13.8% presented with hemoptysis. This finding has been more satisfactorily explained in recent years using chest CT, which was conducted on 67 study patients with more severe disease in whom cavitated lesions were clearly evident. Additional observable changes were similar to those described in other studies.^{19,23} Dyspnoea was reported by 45.2% of the patients. The presence of these respiratory symptoms in over half of the patients should have allowed an earlier diagnosis; however, the high association with tobacco use became a confounding variable obscuring possible

explanations for the symptoms. In addition, difficulties in accessing health care in rural areas and the low degree of awareness of PCM by physicians have contributed to delays in diagnosing the disease. The great majority of patients with the chronic form of the disease presented with an abnormal chest radiograph, in stark contrast to the low frequency found in patients with acute disease, consistent with previous reports in the literature.^{19,24} In some patients, apparent clinical benignity masked extensive radiological lesions, characterizing the clinical and radiological dissociation of the disease as described for the chronic form of PCM.²⁵ In patients with isolated pulmonary lesions, the differential diagnosis with tuberculosis was crucial.

The frequency of adrenal involvement (5.0%) was only lower than lesions observed in the respiratory tract, integument, and lymph nodes.^{26,27} Advancements in imaging technologies, as CT, led to the description of more adrenal lesions, with no correlation to hormonal disfunction.²⁸ Some patients developed adrenal insufficiency during treatment, probably due to scars resulting from the healing process.

CNS involvement in PCM has been increasingly described lately as a result of evolution in diagnostic imaging technologies. The percentage of cases in our series (4.4%) is similar to the number of cases observed at FIOCRUZ, Rio de Janeiro²⁹ and lower than the 9.9–27% reported in other series.^{30,31} Most patients had multifocal disease, allowing proper diagnosis without CNS invasion as already mentioned in the literature.³²

The number of patients with genital lesions is relevant due to the low incidence of this disease manifestation, as also noted in literature review in 2012,³³ reporting a total of 33 cases. Eyelid lesions are rare in PCM^{34,35} and are generally associated with systemic disease, as also observed in our cases.

We additionally observed osteoarticular lesions in a frequency that is comparable to other publication.¹⁴ The patients presented with lytic lesions in their ribs, scapulae, and upper limbs, similar to observations in other case series.^{25,27}

Diagnostic methods, direct microscopic examination and histopathology, used in confirmations of PCM in this series are considered the gold standard by the Brazilian Consensus.¹² Serological tests were positive within the sensitivity range of 65–95% described in the literature.^{12,23} No significant differences were found between the positivity in patients with acute/subacute and chronic forms of the disease or between comparisons of the chronic localized and multifocal forms of the disease. We have found, however, that if double ID reactions with titration, available only in more recent years, are performed, patients with acute/subacute and multifocal PCM have higher titers, as noted in other publications.^{12,14}

The cases of tuberculosis associated with PCM in this series (5.7%) is within the expected range established by the Brazilian Consensus, which is 5–10%.¹² Our value is quite similar to 5.5% found in Mato Grosso do Sul State,¹⁴ but lower than the values observed in the series reported in states of São Paulo and Rio de Janeiro,^{1,7} who respectively reported values of 8.3% and 12.9%. In our series, although the association between these two diseases was not at the higher end, some confusion pertained to the diagnosis, as previously cited in the literature,^{19,24} often resulting in delayed diagnosis and treatment of PCM.

The PCM/AIDS association was consistent with the prevalence rate of approximately 1.4% estimated for this coinfection in Brazil³⁶ but is below the levels reported in other

series.^{1,14,17} The form of disease presentation was consistent with that reported in the literature.^{36,37} Furthermore, disease evolution also improved after the introduction of highly active antiretroviral therapy but the patients required longer periods of antifungal therapy.³⁶ Another previously described aspect that was also confirmed in this series was the low opportunistic propensity of PCM compared with other systemic mycoses such as histoplasmosis, cryptococcosis, and candidiasis, which are often associated with AIDS.^{20,36} Recent experimental findings have shown an important role of CD8 T cells in the immunoprotection of pulmonary PCM. This could explain the low frequency of PCM among AIDS patients once CD8 T cells are less depleted in HIV infection.³⁸

Associated neoplasms occurred in 2.5% of patients. A literature review showed a wide variation in the frequency of this association, between 0.16% and 14.1%.³⁹ Tobacco use, which has a high association in patients with the chronic form of PCM, certainly contributed to the frequency of this comorbidity.

Cutaneous leishmaniasis and schistosomiasis mansoni are found in the same endemic areas as PCM in ES, which may explain the association observed here. The high frequency of intestinal parasites reflects the socioeconomic and hygienic conditions of the population studied here and is consistent with similar observations in other series that have been examined.^{1,5,12} Strongyloidiasis was the most prevalent, reflecting changes in the immune response of these patients, as reported by other authors.^{1,5,14}

Patient treatments followed the classic guidelines accepted in the literature, which involves the use of sulfonamides or azoles in mild to moderate forms of the disease and amphotericin B in severe forms of PCM.^{12,40–42}

The most important sequelae were related to respiratory function due to their increased potential for morbidity and mortality among the studied patients. In our series, besides early mortality of 5.2% of patients studied, we have to consider that even patients that finished their treatment, eventually maintained pulmonary sequelae associated with chronic respiratory failure that contributed to mortality attributed to PCM, referred as the highest in the southeast region of Brazil.⁸ It was evident among our patients that prolonged treatment led to abandonment, as also observed in other series that have been examined.^{5,14} This finding increases the interest in proposals for the use of azoles, particularly itraconazole, as the first drug of choice because it may reduce the treatment time to 9 months for the mild and moderate forms of PCM.^{12,40}

Factors limiting this study, inherent in most descriptive studies, were nonadherence to treatment by the study population, preventing more precise conclusions about the therapeutic response, relapse, and mortality attributed to the disease. The use of different serological techniques throughout the historical series did not allow for a more precise definition of the sensitivity and specificity of the tests in the first 10 years of the study. Similarly, the acquisition of new diagnostic imaging equipment prevented the accurate comparison of results over the time course of the series.

These series of cases reflects what happened with PCM during 34 years in our state and Hospital. Nowadays, the incidence of PCM seems to be maintained, since at least 25 new cases come to the hospital every year. The proportion of acute/subacute cases is also maintained (2–3 cases a year), showing that new patients are being infected.

In conclusion, it is important to recognize that the number of cases presented in this series definitively recognizes the state of ES as part of the PCM map. Our results reinforce the theory that the intensive use of the land, such as the work performed on coffee plantations, favors the onset of disease. The mapping of the origin of patients will allow for more specific measures to control this disease in the state of ES.

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