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Paracoccidioidomycosis in Brazilian Patients with and without Human Immunodeficiency Virus Infection

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Abstract. Paracoccidioidomycosis (PCM) is endemic to Latin America, where 10 million people may be infected with *Paracoccidioides brasiliensis*/*Paracoccidioides lutzii* and 1,600,000 individuals live with human immunodeficiency virus (HIV) infection. An epidemiological overlapping of these infections occurred early in acquired immunodeficiency syndrome era with nearly 180 published cases. This study presents epidemiological, clinical, and outcome profiles for 31 PCM patients with HIV infection diagnosed in a teaching hospital in Brazil, and includes an update of previously reported cases. Medical records were reviewed and data compared with 64 PCM patients without HIV infection. Of the 31 PCM patients with HIV infection, 23 (74.1%) were male, with a median age of 36.7 years, whereas of the 64 PCM, 45 (70.3%) were male, with a median age of 35.1 years. Both groups presented similar proportions for smoking and alcoholism. PCM patients with HIV infection presented more fever, weight loss, and the acute clinical form than the PCM patients who had more mucosal and respiratory involvement characterizing the chronic form. Most PCM patients with HIV infection exhibited overlapping symptoms from both clinical forms with median symptom duration of 4.5 months compared with 8.3 months for the PCM control. Patients received sulfonamides and/or itraconazole for a median of 15.7 and 16.7 months for PCM/HIV-infected and PCM, respectively. Relapses occurred more in PCM (12 [30%]) than PCM/HIV-infected (4 [14.8%]) patients, whose mortality rate was higher (10 [32.8%]) than PCM patients (8 [20%]). The cases of PCM/HIV infection confirm that HIV can interact with some endemic diseases without increasing their frequency, while changing their natural history, clinical presentation, and outcome. The data presented here are in agreement with those observed in other studies.

INTRODUCTION

Paracoccidioidomycosis (PCM) is one of the most prevalent endemic mycoses in Latin America, an area where 604,000,000 people reside. A study on prevalence showed that nearly 10,000,000 people would be infected by *Paracoccidioides brasiliensis*/*Paracoccidioides lutzii*, its etiologic agents.[1,2] Unfortunately, public health records of mycoses are scarce or null in this region, which limits understanding the magnitude of PCM. PCM is considered the first cause of mortality among systemic mycoses and the eighth cause of death among chronic infectious diseases in Brazil.[3] Compared with many other endemic diseases, this mycosis has been neglected. According to the largest case study of PCM, its incidence rate ranges from 1.6 to 3.7 cases per 100,000 inhabitants per year.[2,4,5] In addition, in 2015, the World Health Organization estimated that 1,700,000 individuals are living with human immunodeficiency virus (HIV) in Latin America and the Caribbean regions, where PCM is endemic.[6]

After 1950, Latin American demographics became more urban than rural. PCM often affects farmers and individuals performing activities related to agriculture, whereas the HIV epidemic began in large cities and progressively reached small towns and rural areas. This allowed the overlapping of PCM and HIV infection during the early years of the acquired immunodeficiency syndrome (AIDS) era.[7–9] Similar situations also occurred with other endemic mycoses such as histoplasmosis and coccidioidomycosis, whose frequencies soared and were included as AIDS-defining criteria illnesses.[10,11] However, present evidence shows that the number of PCM/HIV-infected cases did not increase compared with PCM non-HIV-infected individuals, despite several changes related to epidemiology, clinical presentations, and outcomes.[7,12–15] In accordance with these numbers, the PCM/HIV-infected rate can be hypothetically estimated at 0.33 cases per million people based on nearly 200 cases of this coinfection, which is reported mostly in Brazil.

PCM in immunocompetent hosts presents two different clinical forms. The acute/subacute form, seen in children and young adults a few weeks or months after infection, presents lymphohematogenic dissemination as evidenced by the mononuclear-phagocytic system and skin and bone lesions without respiratory involvement in most cases. The chronic form affects mainly adult males 30–50 years of age and occurs as reactivation of quiescent foci or as an exogenous reinfection; respiratory and mucosal lesions are commonly found, although other organs can also eventually be affected.[12,16]

Clinical findings related to PCM in HIV-infected patients are similar to those observed in the acute presentation of endemic PCM. PCM occurs as the first opportunistic disease in individuals who present advanced immunodeficiency defined by a $CD4^+$ T-cell count < 200 cells/mm^3.[12–15] In addition, patients exhibit exuberant lymphatic involvement, high frequency of polymorphic cutaneous lesions, more severe and disseminated infection, and pulmonary symptoms rarely observed among immune competent hosts. The mortality rate for this coinfection was high among the first reported cases, but a decreasing tendency was noticed during the last years (38%). Likely this is explained by early diagnosis and specific treatment together with the antiretroviral therapy (ART).[14]

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Clinicians in PCM-endemic areas often have difficulty defining the accurate PCM clinical form associated with AIDS, understanding its opportunistic character, and knowing the frequency of coinfection. This report presents epidemiological, clinical, and outcome aspects of PCM patients with HIV infection in a tertiary teaching hospital in Brazil and includes an update of cases published elsewhere to highlight the relevance of this coinfection in the context of PCM as a neglected disease.[4,12–14]

POPULATION AND METHODS

Medical records of 164 patients admitted with PCM at the Teaching Hospital in Uberaba, Brazil, from 1993 to 2014 were anonymously reviewed to identify those who presented confirmed PCM associated with HIV infection (defined by two reactive enzyme-linked immunosorbent assays plus a positive Western blot test). Among them, 31 cases presented this coinfection, and all were included in this study. Partial data of 10 of these patients have been previously published; they were included to improve the description and comparative analyses.[13]

PCM cases were defined by clinical history together with a positive smear of sputum, a swab of mucosal or cutaneous lesions, histopathological evidence, and/or a positive culture presenting birefringent and multiple budding yeasts similar to *P. brasiliensis*/*P. lutzii.* Variables such as age, gender, smoking and alcohol habits, onset and duration of symptoms, clinical presentation, diagnosis, $CD4^+$ T-cell counts, viral load values if available, therapy and patient outcomes were registered. These data were compared with those from a group of 64 PCM patients without HIV infection observed during the same period, who were randomly selected and matched by age and gender from among a group of PCM patients who are regularly seen at the infectious diseases outpatient service of the teaching hospital.

Patients were classified within the acute or chronic clinical forms according to the definitions of several authors.[2,12,16] Relapses were defined in patients who presented clinical and laboratorial evidence of PCM after having completed the antifungal therapy and remained asymptomatic for several months or years previously. Alcoholism was defined by the CAGE score, and tobacco use was evaluated by the Fagerstrom score.

Data analysis was performed using the software SPSS 17.0 (SPSS, Chicago, IL, 2008), classical χ^2, or χ^2 with Yates correction tests. Odds ratio and intervals of 95% were defined. P values < 0.05 were considered statistically significant.

ETHICS

This project was approved by the ethical board at Triângulo Mineiro Federal University in Uberaba, Minas Gerais, Brazil, under register number 928. The clinical data obtained from medical records were anonymized.

RESULTS

Thirty-one HIV-infected patients with PCM were admitted at the teaching hospital between 1993 and 2014. Of these, 23 (74.1%) were males, and the median age was 36.7 years. Twenty-four (77.4%) were born or were living in rural areas or small towns of the Minas Gerais state. Both infections were simultaneously diagnosed in 15 (48.3%) of the cases, whereas PCM was the first opportunistic illness in 18 (58.0%) individuals. Prior to PCM diagnosis, 10 (32.2%) patients had already presented one or more opportunistic infections, and for 13 (41.9%), at least one other infection was concomitantly evidenced at admission.

Most patients presented overlapping symptoms of the two classical PCM clinical forms, which consisted of history of fever, weight loss, lymph-node enlargement, pulmonary symptoms, and cutaneous lesions, among others (Table 1). Chest X-rays showed interstitial bilateral infiltrates in 16 (51%) cases. $CD4^+$ T-cell count was available in 26/31 (83.8%) patients, of whom 17 (65.3%) had values from 7 to 90 cells/mm^3, five from 113 to 125, and the remaining four presented values from 211 to 258 CD4 cells. Viral load assessment was performed in 16 patients, of whom 14 presented values from 4.61 to 6.89 logs RNA viral/mL. Fungal diagnosis was confirmed by a positive smear and/or a biopsy showing

TABLE 1
Comparison of clinical and outcome features of patients with PCM with or without HIV infection

Clinical data		PCM HIV+ *N* (%)	PCM HIV− *N* (%)	OR (95% CI)	*P* value
Fever	Yes	21 (67.8)	25 (39.1)	3.28 (1.33–8.10)	**0.010**
	No	10 (32.2)	39 (60.9)	1.00	
Weight loss	Yes	20 (64.5)	31 (48.4)	1.94 (0.80–4.69)	0.143
	No	11 (35.5)	33 (51.6)	1.00	
Respiratory symptoms	Yes	16 (51.6)	32 (50)	1.07 (0.45–2.52)	0.883
	No	15 (48.4)	32 (50)	1.00	
Mucosal involvement	Yes	10 (32.2)	37 (57.8)	0.35 (0.14–0.86)	**0.022**
	No	21 (67.8)	27 (42.2)	1.00	
Lymph node enlargement	Yes	17 (54.8)	36 (56.3)	0.57 (0.23–1.43)	0.232
	No	14 (45.2)	17 (56.7)	1.00	
Skin lesions	Yes	13 (41.9)	26 (40.6)	1.06 (0.44–2.52)	0.903
	No	18 (58.1)	38 (59.4)	1.00	
Clinical forms	Acute	19 (61.2)	15 (21.9)	5.17 (2.05–13.05)	**< 0.001**
	Chronic	12 (38.7%)	49 (75.0%)	1.00	
Outcome	Cured	15 (55.5%)	20 (50%)	1.07 (0.42–2.79)	0.213
	Relapsed	4 (14.8%)	12 (30%)	1.00 (Relapsed + died)	
	Died	10 (32.2%)	8 (20.0%)		

CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio; PCM = paracoccidioidomycosis. The bold values indicated the statistical significant values.

TABLE 2
Diagnosis of PCM in HIV-infected patients and PCM controls

Diagnosis method		PCM HIV$^+$ *N* (%)	PCM HIV$^-$ *N* (%)	*P* value
Biopsy	+	22 (95.5)	54 (98.2)	1
	–	1 (4.5)	1 (1.8)	
Culture	+	6 (35.3)	3 (8.6)	**0.046**
	–	11 (64.7)	32 (91.4)	
Smear	+	13 (59.1)	21 (39.6)	0.123
	–	9 (40.9)	32 (60.4)	
Chest plain	A	16 (64.0)	22 (66.7)	0.913
	N	9 (36.0)	11 (33.3)	

A = abnormal; HIV = human immunodeficiency virus; N = normal; PCM = paracoccidioidomycosis. The bold values indicated the statistical significant values.

birefringent yeasts with multiple budding similar to *Paracoccidioides* spp. (Table 2).

Of 31 patients, 27 received amphotericin B and/or itraconazole or sulfamethoxazole–trimethoprim. Fifteen (55.5%) were considered clinically cured after 12–18 months of therapy and four relapsed after remaining asymptomatic for several months and were successfully retreated. Ten of 31 patients died before or at the early stages of antifungal therapy. Of these, five died as a direct consequence of PCM, three of severe cryptococcal meningitis, and two of bacterial sepsis. Upon postmortem examination, four of these cases exhibited disseminated PCM in several organs. Of the remaining two cases, one missed the follow-up, and the second is still under treatment.

Currently, 14 (45.1%) of these patients are alive and on ART and six died at during the HIV infection as a consequence of other illnesses. The mortality rate of PCM/HIV-infected cases in the years surrounding 2000 did not show a significant decrease (7/13 [53.8%] and 9/18 [50%], respectively).

Of 64 PCM patients without HIV infection 45 (70.3%) were male and the median age was 35.1 years. A similar proportion of smoking and alcoholism was observed in both groups. PCM patients with HIV infection presented more fever, weight loss, and the acute clinical form than the PCM patients who presented more mucosal involvement and the chronic clinical form (Table 1). However, most PCM patients with HIV infection had overlapping symptoms related to both clinical forms with a median duration of symptoms of 4.5 months compared with 8.3 months for the PCM patients. Antifungal therapy was performed with sulfonamides and/or itraconazole for a median of 15.7 and 16.7 months for PCM/HIV-infected and PCM patients, respectively. Relapses were more common among the PCM patients (12 [30%]) than for the PCM/HIV-infected group (4 [14.8%]). The mortality rate (due to all reasons) was higher for coinfected patients (10 [32.8%]) than for PCM control patients (8 [20%]). Of the PCM control patients who died, three died during treatment, and five died due to obstructive pulmonary disease that was worsened by PCM-caused fibrosis (Table 1).

DISCUSSION

Since the first reported cases of coinfections of PCM and HIV, a different pattern of symptoms has been observed, characterized by a more acute and severe clinical picture with overlapping of symptoms and features observed in both clinical forms, with a predominance of skin, lymphatic, and lung involvement. Therefore, it may be difficult for a clinician to differentiate which clinical category these patients belong to.[12–15] In accordance with several authors, HIV infection can influence the natural history of endemic diseases by facilitating the infection, increasing the ratio of disease to infection, changing the clinical presentation, or exacerbating the course of the disease.[12,17]

This study describes the main epidemiological and clinical aspects of 31 PCM patients with HIV infection. Of these, 48% presented PCM as the first clinical event leading to HIV suspicion, due to the severity and/or atypical clinical picture. The history of previous or concomitant opportunistic diseases, together with CD4$^+$ T-cell count < 100 cells/mm^3 and high viral load observed in most of the patients to whom these tests were available, confirm the advanced immunodeficiency favoring the reactivation of fungal infection. Similar figures have been reported by several authors elsewhere.[12–15]

These patients exhibited a significantly high fever, less mucosal lesions, and high but no significant difference in skin, lymphatic, and pulmonary involvement compared with PCM control patients. The largest case study of this coinfection found a significant difference in fever, skin and lymphatic involvement, but a similar proportion of pulmonary symptoms between PCM/HIV-infected and PCM controls.[14] Considering these symptoms, patients often presented lymphatic and skin features related to the acute classical PCM form and pulmonary and mucosal involvement as it happens in the chronic form. These observations of a mixed clinical form are in agreement with other studies.[12–15]

TABLE 3
Update of the main epidemiological and clinical aspects of PCM/HIV-infection case reports

		Gender			Site of the lesions					Clinical form	
Author, year	No. of cases	M	F	Age range	Pulmonary	Skin	Lymphatic	Mucosal	CD4$^+$ < 200	Acute	Chronic
Bernard and Duarte, 2000* [12]	79	56	17	15–62	31	34	41	38	25/29	56	17
Silva-Vergara and others, 2003[13]	10	8	2	22–53	7	4	7	3	5/7	7	3
Paniago and others, 2005[15]	12	12	0	27–49	7	6	10	5	1/2	10	2
Marchiori and others, 2007[18]	5	4	1	35–57	5	†	†	†	3/5	0	5
Morejon and others, 2009[14]	53	43	10	16–57	39	32	40	11	36/43	27	26
Several authors,[19–35] 2000–2014	19	13	6	13–59	10	6	10	5	14/19	8	11
Present report	21	15	6	27–55	9	9	10	7	15/19	12	9
Total	199	151	42	13–62	108	91	118	69	99/124	120	73

HIV = human immunodeficiency virus; PCM = paracoccidioidomycosis.
*Six patients were excluded.
†Data unavailable.

Patients with PCM presented more relapses than the PCM/HIV infected, which could be attributed to better follow-up for the HIV-infected patients. They are observed monthly in the outpatient service to evaluate the adhesion to ART, whereas PCM patients are seen within three to 6 months depending on clinical evaluation.

Taken from the literature, we compiled data for 178 coinfected patients of whom 79 were reviewed by others,[12] four case studies which included 10, 12, five, and 53 patients, respectively,[13–15,18] with the remaining being isolated case reports.[19–35] There was large variability in the quality and precision of the clinical data in some of these reports due to the focus of the publication. Studies were often restricted to a particular anatomical site, specific clinical presentation, or PCM organ involvement. Consequently, it was difficult to accurately determine which clinical form the patient presented (Table 3).

Although PCM is not a notifiable disease in endemic areas, its incidence rate in HIV-infected patients seems not to differ from that of PCM non-HIV individuals.[12,14] This assertion is based on the 178 cases already published plus the 21 presented here which occurred during 35 years of the AIDS era. Epidemiological overlapping of the two infections has taken place since the first years of the HIV epidemic and can be supported by two facts. First, most HIV patients live in large and middle-sized cities with an unknown number of asymptomatic PCM individuals who migrated from rural areas during the last decades. Second, HIV incidences reached the small towns and rural PCM-endemic areas of Latin American countries.[4,8,9]

Currently, there are no concrete facts to help understand why HIV/*P. brasiliensis* overlapping did not favor an increase in the number of PCM cases such as those of other endemic mycoses. Histoplasmosis and coccidioidomycosis incidence rates increased in HIV-infected individuals and were used early as AIDS-defining illnesses criteria.[10,11] Sulfonamide and azole derivatives are commonly prescribed for HIV-infected patients as prophylaxis or therapy for opportunistic diseases, including toxoplasmosis, candidiasis, and *Pneumocystis* pneumonia, among others. Several authors have hypothesized that these drugs could prevent the reinfection or clinical reactivation of latent foci of *P. brasiliensis*, particularly because these drugs are also used to treat *P. brasiliensis* infection.[2,36] This assertion is very difficult to prove. Moreover, PCM patients with HIV infection might also be inadvertently treated because other opportunistic infections in HIV-infected patients present many clinical similarities.

Because most cases of PCM patients with HIV infection have been reported as isolated cases or a small case series in endemic areas, the recruitment of a reasonable number of cases to evaluate the impact of ART on the incidence of PCM is a challenge. The biology of *P. brasiliensis* and its interaction with HIV may be more endemic than opportunistic fungi such as *Histoplasma capsulatum* and *Coccidioides immitis*.[10,11]

Despite the advanced immunosuppression observed in most of these patients, the frequency of PCM is similar to that observed in non-HIV individuals in endemic areas.[12,14] PCM in HIV-infected patients presents characteristics of a unique clinical form of opportunistic PCM different from the two classical forms formerly defined. This supports a review of the clinical classification of PCM to define a new clinical category of this mycosis. Publication and notification of all cases of this coinfection must be highly encouraged among clinicians and public health services in PCM-endemic countries of Latin America, to gain a better understanding of the real magnitude and dynamics of PCM/HIV infection overlapping.

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