CLINICAL AND EPIDEMIOLOGICAL STUDY OF HIV CO-INFECTION AND PARACOCCIDIOIDOMYCOSIS IN A BRAZILIAN TEACHING HOSPITAL

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ABSTRACT

Introduction: Paracoccidioidomycosis (PCM) is the most prevalent systemic mycosis in Latin America. Despite this, the association with the Human Immunodeficiency Virus (HIV) is poorly described. HIV infection has been recognized as a factor that modifies the natural history of fungal diseases, among which PCM is included, with clinical particularities and greater severity being observed. Methods: The clinical, epidemiological, and evolutionary findings of PCM in 21 patients co-infected with HIV, treated at a Brazilian teaching hospital, between January 2000 and December 2023, were evaluated. Results: Of the 21 patients studied, 14 (66.7%) were men. The mean age was 37.04 years. Thirteen (61.9%) patients reported living in a rural area, current or previous, and 5 (23.8%) of them performed agricultural activities at the time of diagnosis. Thirteen (61.9%) patients were smokers and 7 (33.3%) were alcoholics. For 57.14% of the cases, PCM was the first manifestation of AIDS. The mean CD4+ T lymphocyte count was 90.8 cells/mm3. Most patients (12; 57.14%) presented concomitant manifestations of the two classic clinical forms of PCM. Amphotericin B was the most commonly used treatment, in single, combined or sequential therapy (14 patients; 66.7%). Eighteen patients (85.7%) had a good evolution with the treatment administered. Mortality was 14.3% of the cases, with 2 deaths (9.5%) attributed to PCM. Conclusions: This study corroborates the existence of particularities in HIV-PCM co-infection, with greater severity and overlapping of clinical forms, in addition to a wide differential diagnosis in our setting, requiring early diagnosis and treatment.

Keywords: Paracoccidioidomycosis. AIDS. HIV. Coinfection.

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INTRODUCTION

It is estimated that since the beginning of the Acquired Immunodeficiency Syndrome (AIDS) epidemic, 74.9 million people have been infected by the human immunodeficiency virus (HIV)[1]. Brazil is the country with the highest detection rate of new cases of the disease in Latin America, accounting for more than 40% of all new HIV infections in the region2,3.

As HIV infection progresses and the CD4+ T lymphocyte count drops to values below 200 cells/mm3, patients become predisposed to the emergence of opportunistic diseases, caused by fungi, viruses, protozoa, and bacteria, in addition to other comorbidities, with systemic mycoses being considered one of the main causes of morbidity and mortality in these patients.

Among the endemic mycoses in Brazil, Paracoccidoidomycosis (PCM) is one of the most prevalent, but its association with HIV is little described. Endemic throughout the country, where it predominates in the states of the Southeast, Midwest, and South, it is a systemic infection caused by fungi of 2 main species: *Paracoccidioides brasiliensis and Paracoccidioides lutzii*, being the eighth cause of death due to chronic infectious-parasitic diseases in the country, which allows us to infer its great magnitude4,5.

PCM is clinically classified into 2 forms: acute or subacute (juvenile type), responsible for 5% to 25% of cases; and chronic (adult type), found in 74% to 96% of cases. The first preferentially affects young patients, up to 30 years of age, with rapid dissemination of the fungus, predominantly compromising the phagocytic-mononuclear system. The chronic form, frequently observed in male adults between 30 and 50 years of age, arises from a quiescent focus, with a slow course of evolution, affecting a single organ (unifocal) or multiple organs (multifocal), with pulmonary involvement in approximately 90% of cases5,6.

HIV-induced CD4+ T-cell lymphocytopenia has been recognized as one of the factors that modify the natural history of fungal diseases, among which PCM is included. This may be the first manifestation of AIDS, usually in patients with CD4+ T lymphocyte counts below 200 cells/mm3. Overlap of the two clinical forms is observed in the few published studies on PCM-HIV co-infection, with disseminated disease, generally consisting of bilateral reticulonodular pulmonary infiltrate, lymphadenomegaly, skin lesions, hepatosplenomegaly, ulcerations of the oral mucosa, and other less frequent visceral lesions6-11.

PCM-HIV co-infection is rarely reported in the literature. This may be partly explained by the use of trimethoprim-sulfamethoxazole or azoles for prophylaxis or treatment of opportunistic infections, since these medications also act on *Paracoccidioides sp*. In

addition, HIV and PCM have different epidemiological profiles, with the former predominating in urban centers, and the latter in rural areas. However, there has been a progressive spread of HIV infection to small and medium-sized municipalities and rural areas, places with high prevalence of PCM. Therefore, a significant increase in the number of cases of this co-infection would be expected8-13. However, apparently, this has not yet been observed.

The objective of this study was to evaluate the clinical, epidemiological and evolutionary findings of PCM among AIDS patients, reporting its particularities.

PATIENTS AND METHODS

This study retrospectively evaluated, through the review of medical records, the clinical and laboratory data of patients co-infected with PCM-HIV, over 18 years of age, of both sexes, assisted from 01/01/2000 to 12/31/2023, at the Hospital das Clínicas of the Federal University of Uberlândia – Minas Gerais, Brazil.

The case definition of co-infection was established by evidence of HIV infection, by a positive ELISA test, confirmed by Western Blot test or quantification of viral RNA, and observation of fungal structures similar to Paracoccidioides sp by direct examination, histopathology or culture of fluids, secretions or tissues, from patients with clinical suspicion of PCM.

Data were collected on: gender, age, place of birth, origin, profession, contact with rural areas (current or previous), lifestyle habits (smoking and alcoholism), duration of symptoms, clinical forms, diagnostic methods, date of diagnosis of HIV infection, CD4+ T lymphocyte count and viral load, treatment used, and evolution of cases, considering hospital discharge as a favorable outcome.

The project was submitted to analysis and approved by the Research Ethics Committee of the Federal University of Uberlândia.

RESULTS

In the period analyzed, 21 cases of HIV-PCM co-infection were diagnosed.

Males accounted for 66.7% of the total cases (14/21), with a ratio of 2 men for every woman, with a mean age of 37.04 years, with sexual intercourse being the main form of HIV acquisition, in 95.2% of cases (n: 20). Four of these (20.0%) reported the use of inhaled illicit drugs, and 1 (5.0%) reported injecting drugs.

Thirteen (61.9%) patients stated that they had lived in a rural area or had never had contact with a rural area (4.8%). Five (23.8%) patients were performing agricultural

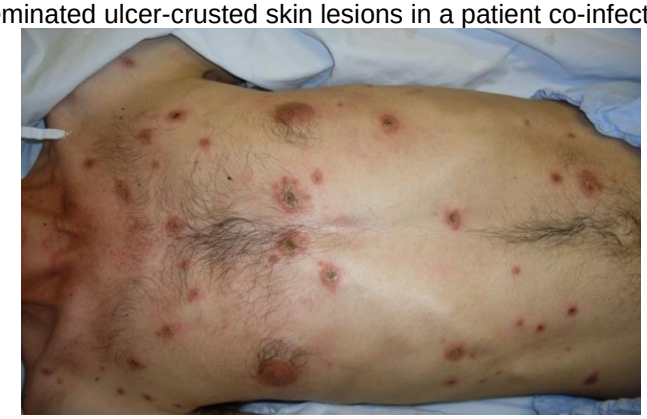
activities at the time of diagnosis. Chronic smoking was reported by 13 patients (61.9%) and 7 reported chronic alcoholism (33.3%).

The mean time elapsed between the onset of symptoms and treatment was 114.21 days, and most patients (12; 57.14%) had an association of the two classic clinical forms of Paracoccidioidomycosis, characterizing a mixed form of the disease (Table 1).

The main clinical manifestations were fever (17; 80.95%), weight loss (14; 66.7%), lymph node enlargement (13; 61.9%), hepatomegaly (14; 66.7%), cough (12; 57.14%), splenomegaly (10, 47.6%) and disseminated skin lesions (7; 33.3%).

The skin lesions were disseminated, described as papular or ulcer-crusted (Figure 1).

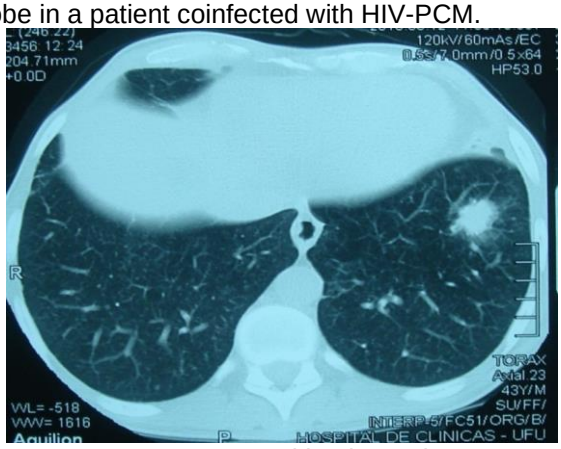
Figure 1 – Disseminated ulcer-crusted skin lesions in a patient co-infected with HIV-PCM



Source: Prepared by the authors

Pulmonary involvement was observed in 12 patients (57.14%). The radiological alterations described were varied, with a predominance of micronodular infiltrate associated with cavitated consolidations (25%); bilateral interstitial infiltrate (16.7%); diffuse interstitio-nodular infiltrate (16.7%); and diffuse micronodular infiltrate (16.7%). (Figure 2).

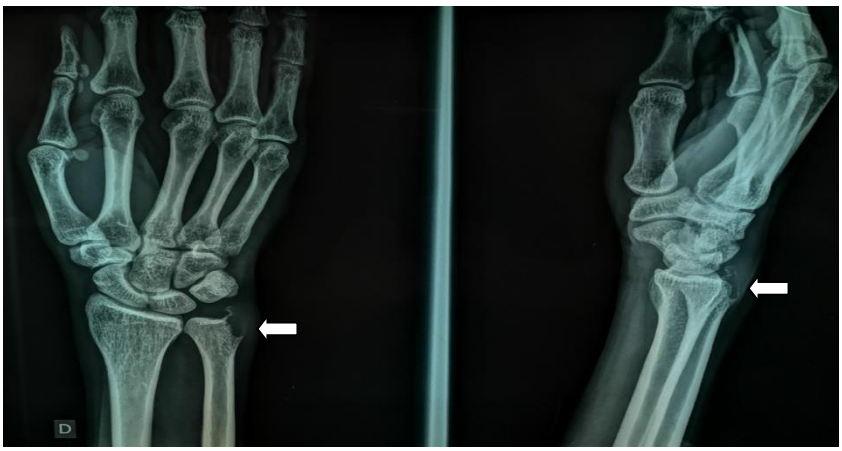
Figure 2 – Computed tomography scan of the chest showing diffuse micronodular infiltrate and nodular consolidation in the left lower lobe in a patient coinfected with HIV-PCM.



Source: Prepared by the authors

Bone involvement occurred in 1 patient (4.76%) whose plain X-ray showed an osteolytic lesion in the ulna head and the biopsy confirmed osteomyelitis. The fungus was identified through direct histopathological and mycological examinations, as well as in the culture of the bone fragment (Figure 3).

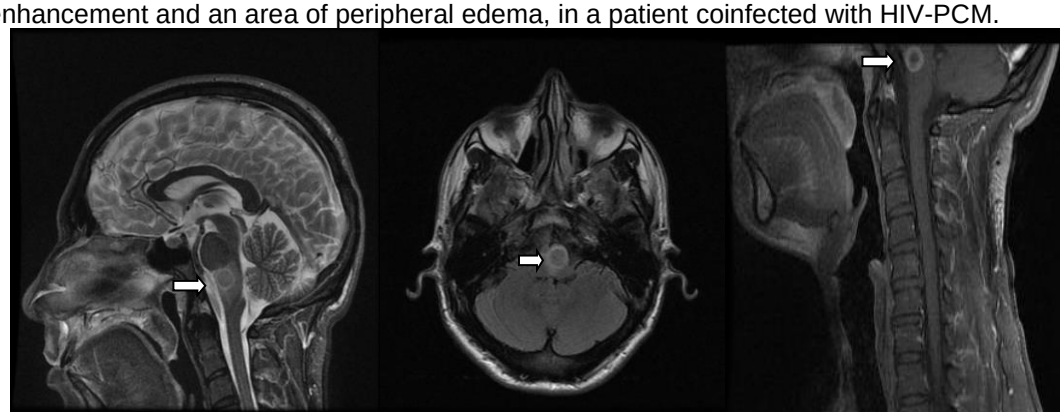
Figure 3 – Plain X-ray of the right wrist, showing an osteolytic lesion in the ulna head, in a patient co-infected with HIV-PCM.



Source: Prepared by the authors

Another patient (4.76%) presented clinical manifestations of central nervous system involvement, with focal signs, whose cranial magnetic resonance imaging is shown in Figure 4.

Figure 4 – Magnetic resonance imaging of the skull, showing a rounded medulla oblongata lesion with ring contrast enhancement and an area of peripheral edema, in a patient coinfected with HIV-PCM.



Source: Prepared by the authors

Gastrointestinal manifestations were reported by 2 patients (9.5%), clinically characterized by abdominal pain, diarrhea, with and without blood, nausea and vomiting. His endoscopic examinations revealed lesions in the colon, cecum, duodenum, stomach and esophagus.

Most patients (16; 76.2%) had other opportunistic infections, either at admission or developing them during hospitalization. Oral moniliasis/esophageal (8; 38.1%),

cryptococcosis (2; 9.5%), histoplasmosis (2; 9.5%), and genital herpes (2; 9.5%) were the most frequent co-infections in this series.

Nonspecific laboratory abnormalities evidenced at the time of diagnosis were anemia, hypoalbuminemia, and elevated liver enzymes, with a predominance of canalicular enzymes.

In 12 patients (57.14%), Paracoccidioidomycosis was the first manifestation of AIDS and the mean CD4+ T lymphocyte count at the time of diagnosis was 90.8 cells/mm3, ranging from 1 to 368 cells/mm3. Only 2 patients (9.5%) had values above 200 cells/mm3. The mean quantification of HIV viral load was 106,732.2 copies/ml (254 to 641,183.0 copies/ml).

Regarding antiretroviral treatment (ART), among the 14 patients (66.7%) with a previous diagnosis of HIV infection, 2 (14.3%) had recently started using the medications (1 week, and 2 weeks before hospitalization); 3 (21.4%) were abandoned; 1 (7.1%) in irregular use; 1 (7.1%) who had been in regular use for 3 months, with an undetectable viral load and 205 TCD4+ lymphocytes/mm3 at the time of PCM diagnosis; 1 (7.1%) in regular use for 7 months, with an increase in TCD4+ lymphocytes from 14 cells/mm3 to 88 cells/mm3, and suppression of viremia (from 171,666 copies/ml to undetectable); and 1 (7.1%) had been in regular use for 6 months, with immune recovery from 73 TCD4+ lymphocytes/mm3 to 367 cells/mm3, and reduction in viremia from 310,329 copies/ml to 291 copies/ml.

The mean time elapsed from the patient's admission to the diagnosis of Paracoccidioidomycosis was 12 days (1 – 39 days), which was established through mycological and/or histopathological examination of samples obtained by biopsy, puncture, lesion scraping, bronchoscopy, sputum samples, and serological testing (radial immunodiffusion).

Amphotericin B was the most commonly used treatment, in single, combined or sequential therapy (14 patients; 66.7%). Other medications used were sulfamethoxazole-trimethoprim, itraconazole, and ketoconazole.

Most patients (18; 85.7%) had a favorable outcome, and were discharged from the hospital in good condition after a variable period of treatment. Three patients (14.3%) died during hospitalization, 2 of them (9.5%) were directly attributed to Paracoccidioidomycosis.

DISCUSSION

In the present study, thirteen (61.9%) patients reported contact with rural areas, current or previous. Chronic smoking and alcoholism were reported by thirteen (61.9%) and 7 (33.3%) patients, respectively. These findings reinforce the evidence that the

management of soil contaminated by the fungus favors the acquisition of the infection, as well as the habits mentioned can contribute to the emergence of the disease4,5.

Regarding the clinical presentation, we observed the coexistence of manifestations of the two classic clinical forms of PCM in most cases (57.14%), such as symptoms of involvement of the phagocytic-mononuclear system, in association with pulmonary, cutaneous, and mucosal involvement, characterizing a more severe form of clinical presentation of this mycosis, as an opportunistic disease. This reinforces the idea of including PCM associated with immunosuppression as a third clinical form, called mixed, as previously suggested by some authors7,8,10,13,14.

Most patients (14; 66.7%) had CD4+ T lymphocyte counts below 100 cells/mm3 at the time of diagnosis of Paracoccidioidomycosis. For 12 patients (57.14%), PMC was the first manifestation of AIDS, and concomitance with other opportunistic infections was observed in most cases (76.2%). This data, together with the fact that most patients (57.14%) did not perform activities related to the risk of infection by *Paracoccidioides sp.* at the time of diagnosis, reinforce the hypothesis that mycosis results from reactivation of latent infection7,8,10,14.

In this study, only 2 patients had CD4+ T lymphocyte counts above 200 cells/mm3 at the time of PCM diagnosis. One of them, with a CD4 count: 368 cells/mm3 and viral load: 291 copies/ml, had already been on ART for 6 months when generalized adenomegaly appeared. The CD4+ T lymphocyte count and viral load prior to the initiation of ART were, respectively, 73 cells/mm3 and 310,329 copies/ml. The other patient had a CD4 count: 205 cells/mm3 and viral load: undetectable, and had been on ART for 3 months. She already had skin lesions at the time of the start of ART, which worsened concomitantly with the onset of fever, cough, oral lesions, hepatomegaly and lymph node enlargement. In another case, the patient had been diagnosed with HIV and Histoplasmosis 7 months before the onset of PCM symptoms. The CD4+ T lymphocyte count at the time of HIV diagnosis was 14 cells/mm3, with a viral load of 171,666 copies/ml. ART was started in the same month of diagnosis. Three months later, the CD4+ T lymphocyte count was 42 cells/mm3 and the viral load was undetectable, and at the time of PCM diagnosis, the CD4+ T lymphocyte count was 88 cells/mm3 and the viral load remained undetectable. Immunological recovery and virological response, coinciding with the onset or recrudescence of mycosis symptoms, strongly suggests the diagnosis of Inflammatory Immune Reconstitution Syndrome (IRIS) associated with PCM. Only one case of IRIS associated with PCM was retrospectively defined based on a review of a report of neuroparacoccidioidomycosis in an HIV-positive patient published by other authors15.

In this study, PCM was diagnosed through histopathological analysis in 18 patients (85.7%). The direct mycological test had a yield of 47.6%, while the culture had a yield of 33.3%. Serological tests were performed in only 2 patients, with 100% positivity.

Amphotericin B was the most commonly used treatment, in single, combined or sequential therapy (14 patients; 66.7%), with a favorable outcome in 85.7% of the cases. The lethality attributed to co-infection varies among the few national reports, ranging from 12.2% to 66.66%[7,8,10,14,16]. In the present series, mortality attributed to PCM was relatively low, 9.5%.

The association between PCM and AIDS is rarely reported in the literature, unlike what has been observed with other endemic mycoses in our country, such as histoplasmosis and cryptococcosis. This finding, as already mentioned, may be a consequence of epidemiological differences between infections, as well as the use of active drugs against the fungus, for other purposes7,8,10,11,13,14.

The present study corroborates the existence of particularities in HIV-PCM co-infection, such as systemic dissemination, greater severity, and overlapping clinical forms, which, as already mentioned, together with other findings, suggest another form of clinical presentation of PCM.

Table 1 – Clinical presentation, diagnosis and evolution of patients with HIV-Paracoccidioidomycosis co-infection.

PATIENTS	GENDER	AGE (YEARS)	CLINICAL FORM	CD4 (cells/mm3)	DIAGNOSIS	TREATMENT	EVOLUTION
# 1	Male	46	Chronicle	146	Skin biopsy	Amphotericin B	Good
# 2	Female	34	Acute/ Subacute	122	Phygate biopsia	Amphotericin B/ Sulfametoxa-zol-trimetropim	Good
# 3	Male	29	Mixed	45	Lymph node biopsia; Direct mycological and culture (sputum and lymph node aspirate)	Amphotericin B/ Ketoconazole	Good
# 4	Male	57	Chronicle	57	Laryngeal biopsy	Amphotericin B/ Itraconazole	Good

# 5	Male	27	Mixed	Not carried out	Mycological direct skin and sputum; Blood culture	Amphotericin B/ Sulfametoxa-zol-trimetropim	Death
# 6	Male	34	Aguda/ Subaguda	26	Biopsy, direct mycology and lymph node culture; Radial immunodiffusion reagent	Amphotericin B/ Itraconazole	Good
# 7	Female	48	Chronicle	96	Bronchial mucosa and lung biopsy	Amphotericin B/ Sulfametoxa-zol-trimetropim	Good
# 8	Male	28	Acute/ Subacute	21	Cholon and liver biopsy	Amphotericin B	Death
# 9	Male	43	Mixed	1	Skin and bone biopsy; Direct mycology and culture (gas-tric aspirate, skin and bone fragment)	Sulfametoxa-zol-trimetropim	Good

PATIENTS	GENDER	AGE (YEARS)	CLINICAL FORM	CD4 (cells/mm3)	DIAGNOSIS	TREATMENT	EVOLUTION
# 10	Male	35	Chronicle	82	Lung biopsy	Sulfametoxa-zol-trimetropim	Good
# 11	Female	28	Acute/ Subacute	368	Lymph node biopsia	Itraconazole	Good
# 12	Male	43	Chronicle	96	Skin biopsy	Amphotericin B/ Sulfametoxa-zol-trimetropim	Good
# 13	Female	31	Mixed	29	Tracheia biopsia	Sulfametoxa-zol-trimetropim	Good
# 14	Female	51	Mixed	112	Biopsy of oral lesion and esophageal, gastric and duodenal mucosa	Amphotericin B	Death
# 15	Female	33	Mixed	35	Biopsy and Mycological direct skin	Amphotericin B/ Itraconazole	Good

# 16	Male	34	Mixed	32	Biopsy direct mycological and oral mucosal culture; Radial immunodiffusion reagent	Amphotericin B/ Itraconazole	Good
# 17	Male	29	Mixed	133	Biopsy and Mycological direct lymph node	Amphotericin B/ Itraconazole	Good
# 18	Male	39	Mixed	2	Biopsy, direct mycological and skin fragment culture	Sulfametoxa-zol-trimetropim	Good
# 19	Male	32	Mixed	205	Direct mycological and skin lesion scraping culture	Sulfametoxa-zol-trimetropim	Good

PATIENTS	GENDER	AGE (YEARS)	CLINICAL FORM	CD4 (cells/mm3)	DIAGNOSIS	TREATMENT	EVOLUTION
# 20	Female	45	Mixed	120	Mycological direct sputum	Sulfametoxa-zol-trimetropim	Good
# 21	Male	32	Mixed	14	Lymph node biopsia	Anfotericina B/Itraconazol	Good

Source: Prepared by the authors

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