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The prevalence and clinical course of HIV-associated pulmonary cryptococcosis in Uganda

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Abstract

Background—The prevalence and clinical course of pulmonary cryptococcosis in Sub-Saharan Africa are not well-described.

Methods—Consecutive HIV-infected adults hospitalized at Mulago Hospital (Kampala, Uganda) between September 2007 and July 2008 with cough ≥ 2 weeks were enrolled. Patients with negative sputum smears for acid-fast bacilli were referred for bronchoscopy with bronchoalveolar lavage (BAL). BAL fluid was examined for mycobacteria, *Pneumocystis jirovecii*, and fungi. Patients were followed two and six months after hospital discharge.

Results—Of 407 patients enrolled, 132 (32%) underwent bronchoscopy. Of 132 BAL fungal cultures, 15 (11%) grew *Cryptococcus neoformans*. None of the patients were suspected to have pulmonary cryptococcosis on admission. The median CD4 count among those with pulmonary cryptococcosis was 23 cells/μL (IQR 7–51). Of 13 patients who completed six-month follow-up, four died and nine were improved, including five who had started antiretroviral therapy (ART) but had not received antifungal medication.

Conclusions—Pulmonary cryptococcosis is common in HIV-infected TB suspects in Uganda. Early initiation of ART in those with isolated pulmonary infection may improve outcomes, even without anti-fungal therapy. This finding suggests that some HIV-infected patients with *C. neoformans* isolated from respiratory samples may have colonization or localized infection.

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Keywords

Pulmonary Cryptococcosis; HIV/AIDS; Bronchoscopy

INTRODUCTION

Cryptococcosis is caused by *Cryptococcus neoformans*, a thin-walled non-mycelial budding yeast that is characterized by a thick polysaccharide capsule best seen on India ink stain.[1] As one of the most common opportunistic infections, cryptococcal infection affects approximately one million HIV-infected patients worldwide each year, and is associated with high mortality.[2, 3] In Sub-Saharan Africa, cryptococcal disease has been associated with 17% of all deaths among HIV-infected patients[4] and 75% of deaths from opportunistic infections in men with pulmonary tuberculosis.[5]

Most HIV-infected individuals with cryptococcosis present with meningitis and, less commonly, with meningitis and pneumonia or isolated pneumonia. Although the lungs are the portal of infection, few studies have addressed the clinical significance of isolating *C. neoformans* from pulmonary specimens in persons with HIV infection. In particular, there have been no studies from Sub-Saharan Africa since the introduction of antiretroviral therapy (ART). We describe the prevalence, clinical features and outcomes of HIV-infected Ugandans hospitalized with pneumonia who had *C. neoformans* isolated from bronchoalveolar lavage (BAL) fluid.

MATERIALS AND METHODS

Participants

Consecutive HIV-infected adults admitted to Mulago Hospital in Kampala, Uganda between September 2007 and July 2008 were screened for study eligibility and enrolled after written informed consent. Patients were eligible for inclusion if they had cough ≥ 2 weeks and a clinical diagnosis of pneumonia. Patients were ineligible if they had cough for > 6 months or were receiving anti-tuberculosis treatment.

Data Collection

Clinical and demographic information was collected using a standardized questionnaire. HIV infection was confirmed and CD4+ T-lymphocyte counts were measured. Standardized work-up for pneumonia included chest radiography and acid-fast bacilli (AFB) smear examination of two sputum specimens. Two board-certified radiologists interpreted chest radiographs while blinded to clinical information and using a standardized data collection form. Laboratory technicians at the Uganda National Tuberculosis and Leprosy Programme (NTLP) Reference Laboratory examined sputum specimens for AFB by direct light microscopy and concentrated fluorescence microscopy according to standard protocols and as described previously.[6] Processed sputum specimens were inoculated on two Lowenstein-Jensen slants. Cultures were read weekly and considered positive if any growth (≥ 1 colony forming unit) was identified within eight weeks. Patients were referred for bronchoscopy with BAL if both sputum examinations were negative for AFB.

Bronchoscopy

Two pulmonologists performed bronchoscopy according to standard protocol, which included monitoring with continuous pulse oximetry and provision of supplementary oxygen as needed. After administering nebulized and topical 1% lidocaine for airway anesthesia, and intramuscular midazolam for anxiolysis, the bronchoscopists conducted a thorough

bronchoscopic inspection of all visible airways for lesions consistent with Kaposi's sarcoma. Then, the bronchoscopists performed bronchoalveolar lavage in a subsegment of the lobe with the greatest infiltration on chest radiography or in a subsegment of the right middle lobe if the radiographic infiltrates were diffuse. Sterile, normal saline (0.9%) was instilled into an occluded subsegmental bronchus in serial 25 mL aliquots (up to a maximum of 125 mL) and then aspirated until at least 50 mL of BAL fluid were returned. BAL fluid was sent for microbiologic tests, three mL of which were sent for fungal studies.

BAL Specimen Analysis

Trained laboratory technicians analyzed BAL fluid for *Mycobacterium tuberculosis* (AFB smear and Lowenstein-Jensen culture), *Pneumocystis jirovecii* (modified Giemsa stain), and other fungi (potassium hydroxide (KOH) stain, India ink stain, and culture on Sabouraud's agar). Fungal stains and culture were performed in the Microbiology Department of Mulago Hospital using a standardized method. In brief, BAL fluid was concentrated at 450 relative centrifugal force (RCF) for five minutes, and the supernatant then poured out. A loopful of the sediment was inoculated onto Sabouraud's media for up to 30 days, and the remainder was smeared on two slides for India ink and KOH.[7] Growth of *C. neoformans* was identified by presence of mucoid, cream-colored colonies and confirmed using the urease test and India ink stain.

Patient Follow-up

Vital status was assessed in all patients either by telephone or in-person two months after hospital discharge. Patients who returned in-person were administered a standardized clinical questionnaire and underwent physical examination. In addition, patients who had *C. neoformans* isolated from BAL fluid were interviewed by telephone at four and six months after hospital discharge to determine vital status.

Statistical Analysis

We first performed bi-variate analyses comparing patients who had pulmonary cryptococcosis with those who did not, using the chi-squared or Fisher's exact test for dichotomous variables, and the Mann-Whitney rank-sum test for non-normally distributed continuous variables. We calculated the diagnostic accuracy of fungal stain for pulmonary cryptococcosis with exact binomial confidence intervals. All statistical analyses were performed using STATA 10.0 (Stata Corporation, College Station, Texas, USA), with the level of significance specified in reference to a two-tailed, type-I error (p-value) < 0.05.

Ethical Issues

The Makerere University Faculty of Medicine Research and Ethics Committee, the Mulago Hospital Institutional Review Board, the University of California, San Francisco Committee on Human Research, and the Uganda National Council for Science and Technology approved the protocol. Some of these patients have been previously included in a published study focused on diagnosis of tuberculosis.[8]

RESULTS

Of 407 HIV-infected adult patients enrolled, 218 (54%) were eligible for bronchoscopy and the 132 (32%) patients who underwent the procedure were included in the analysis (Figure 1). Demographic and clinical characteristics were similar between those who did and did not undergo bronchoscopy (data not shown).

BAL fluid fungal cultures from 15 (11%) patients who underwent bronchoscopy grew *C. neoformans*. Pulmonary tuberculosis (39%), bacterial pneumonia (23%), pulmonary Kaposi sarcoma (5%), and *Pneumocystis jirovecii* pneumonia (3%) were the principal final diagnoses among the remaining patients. Demographic characteristics, presenting clinical symptoms, and physical findings were not significantly different between patients who did and did not have *C. neoformans* isolated from BAL fluid, except that those with *C. neoformans* were less often short of breath (p=0.01) (Table 1). In addition, those with *C. neoformans* isolated had lower median CD4+ T-lymphocyte counts (23 vs. 93 cells/μL, p=0.007) and tended to be less likely to be taking antiretroviral therapy (ART) (0% vs. 19%, p=0.06).

Clinical Presentation

The most frequent presenting symptoms among the 15 patients who had *C. neoformans* were fever (93%) and weight loss (93%) (Table 1). The median duration of cough was four weeks (IQR 3–8 weeks). Most patients had tachypnea (median respiratory rate, 26 breaths/minute), but only three of them had room air oxygen saturations below 93%. The majority of patients (80%) had crepitations on auscultation of the chest.

Chest Radiographic Findings

Chest radiographs were available in 14 of 15 patients who had *C. neoformans* isolated from BAL fluid. The most common radiographic patterns were interstitial infiltrates (N=4, 29%), lobar consolidation (N=3, 21%), or a mixed pattern (N=3, 21%) (Table 2). The distribution of parenchymal infiltrates was diffuse in 55% of patients.

Diagnostic Accuracy of Fungal Staining

India ink staining of BAL fluid was positive in seven of 15 patients with positive *C. neoformans* cultures (sensitivity 47%, 95% confidence interval (CI) 21–73%) and negative in 116 of 117 patients with negative cultures (specificity 99%, 95% CI 95–100%). The positive predictive value of India ink staining was 88% (95% CI 47–100%) and the negative predictive value of staining was 94% (95% CI 88–97%).

Clinical Course

Pulmonary cryptococcosis was not suspected by ward physicians in any of the 15 patients in whom *C. neoformans* was isolated from BAL. At the time of admission, pulmonary tuberculosis was suspected in six of those patients, bacterial pneumonia in six, pulmonary Kaposi's sarcoma in one, cryptococcal meningitis in one, and tuberculous meningitis in one. During their hospital admission, eight (53%) patients had a second pulmonary process identified: six had pulmonary tuberculosis, one pulmonary Kaposi's sarcoma, and one *Pneumocystis* pneumonia (Table 3). Six (40%) patients were diagnosed with accompanying cryptococcal meningitis. Meanwhile, of 117 patients who did not grow *C. neoformans* from BAL fluid, two patients had cryptococcal meningitis without pulmonary cryptococcosis.

All 15 patients with pulmonary cryptococcosis were initially treated with antibiotics for presumed bacterial pneumonia. Of the six patients with both pulmonary cryptococcosis and cryptococcal meningitis, three were treated with amphotericin B (50 mg/day for two weeks) and then fluconazole (400 mg daily for eight weeks). Three were treated with fluconazole (400 mg daily for 10 weeks) alone. Of the nine patients with isolated pulmonary cryptococcosis without meningitis, two received fluconazole (200 mg daily for two weeks) for oral candidiasis and seven were not prescribed any anti-fungal medications. All 15 patients improved clinically and were discharged from the hospital (median hospitalization 8 days, IQR 5–16 days).

Of 15 patients with pulmonary cryptococcosis, nine (60%) survived six months, four died, and two were lost to follow up. Of four patients who died, two were known to have died within two months after discharge; one who had cryptococcal meningitis diagnosis during hospital admission and was treated with fluconazole (Patient 1) and one who had pulmonary Kaposi's sarcoma and was treated with two weeks of fluconazole (200 mg) (Patient 2). Two additional patients who were alive at two-month follow up died before six-month follow up, both after developing severe gastroenteritis. Of the two lost to follow up, one person was known to have survived at least two months after discharge.

Of the seven patients who were not prescribed antifungal medicine at hospital discharge, five survived, one was lost to follow up, and one died at six-month follow-up. All five survivors who remained asymptomatic at six-months had started ART after discharge, but the one patient who died had not started ART (Patient 3).

DISCUSSION

In this paper, we present the first detailed review of HIV-infected patients with pulmonary cryptococcosis reported since the widespread introduction of ART in Sub-Saharan Africa. We found that the prevalence of pulmonary cryptococcosis among all HIV-infected patients hospitalized with pneumonia who underwent bronchoscopy was 11%. The diagnosis of pulmonary cryptococcosis was not suspected in any of these 15 patients prior to diagnostic testing, and known survival of the patients with pulmonary cryptococcosis was low (9/15, 60% at six months). However, 33% of the patients with pulmonary cryptococcosis improved without anti-fungal therapy up to six-month follow-up. This finding was unexpected and suggests that some HIV-infected patients with *Cryptococcus* isolated from respiratory samples may have localized infection or colonization.

In previous clinical studies from Sub-Saharan Africa prior to ART introduction, the prevalence of pulmonary cryptococcosis ranged from 0 to 13% in HIV-infected patients with respiratory symptoms.[9–11] While the number of cryptococcosis cases has declined significantly in the United States following the introduction of ART, cases continue to be diagnosed in individuals with limited access to health care.[12] In our study, only 22 (17%) patients overall and none of the 15 patients who had *C. neoformans* isolated from BAL fluid were receiving ART at the time of hospital admission. Moreover, the median CD4+ T-lymphocyte count of our study sample indicates an advanced level of immunosuppression. Since access to ART remains limited in Uganda despite the initiatives to scale up distribution, it is not surprising that the prevalence of pulmonary cryptococcosis among HIV-infected patients with pneumonia remains high.

In spite of its high prevalence in this population sample, the diagnosis of pulmonary cryptococcosis was not suspected in any patient at the time of hospital admission. Many clinicians in Sub-Saharan Africa may be unaware of the epidemiology of pulmonary cryptococcosis. In South Africa, clinicians suspected the diagnosis of pulmonary cryptococcosis prior to death in only one percent of patients who had pulmonary cryptococcosis confirmed by autopsy.13 We found, as have others, that the clinical symptoms, physical exam findings, and radiographic manifestations of pulmonary cryptococcosis are non-specific and similar to those of other opportunistic pulmonary diseases, reinforcing the importance of establishing a confirmed microbiologic diagnosis whenever possible.[14–18] Therefore, clinicians should maintain a high index of suspicion for pulmonary cryptococcosis, particularly among patients with very advanced immunosuppression (CD4+ T-lymphocyte count < 50 cells/μL).

In our study, five of 13 patients had improved at six-months without anti-fungal treatment, and all five had initiated ART. One potential explanation for this unexpected finding is that ART-associated immune reconstitution enabled clearance of *C. neoformans* from the lungs. ART and the resulting immune reconstitution has been shown to be successful and is recommended as first-line therapy for several opportunistic infections such as cryptosporidiosis, microsporidiosis, and progressive multifocal leukoencephalopathy (PML) for which effective antimicrobial therapies are lacking. Zolopa et al reported that early ART was associated with fewer deaths or progressions to AIDS at 48 weeks compared to deferred ART in HIV-infected patients presenting with an acute opportunistic infection.[19] However, three mortality studies done in Uganda on cryptococcosis after initiation of ART have shown disappointing results. One study found that the mortality of cryptococcal meningitis remained high despite the availability of ART.20 Another study found that asymptomatic cryptococcal antigenemia was an independent risk factor associated with an increased mortality during the first 12 weeks of ART.21 A third study reported that five out of five HIV infected patients with CD4+ T-lymphocyte counts ≤ 100cells/μL and asymptomatic cryptococcal antigenemia died within two months after starting ART without fluconazole treatment.22 Taken together, these data suggest that ART alone is insufficient to eradicate disseminated *C. neoformans* infection from patients with advanced immunosuppression but that it may be sufficient for *C. neoformans* infection limited to the lungs.

We assume that the five patients who improved without antifungal medicine in spite of their low CD4+ T lymphocyte counts in our study did not have disseminated disease, but instead had localized infection or colonization of the airway by *Cryptococcus*. Another possibility is that the fungal cultures were false positive and represent laboratory contamination. We cannot rule out the possibility of precipitation of *Cryptococcus* from the environment on to the plates during the procedure of inoculation because *C. neoformans* has been isolated from house dust in Central Africa.[23, 24] However this possibility is unlikely because dust collection for *Cryptococcus* culture needs large amounts (200–283 liters) of air exchange[25] and the inoculation time was short.

While isolating *C. neoformans* from cerebrospinal fluid has been shown to be highly specific for cryptococcal meningitis[1], the significance of isolating *C. neoformans* from respiratory specimens has not been well established. Because the lungs are the portal of entry, *C. neoformans* organisms may be found in the airways in the absence of disease. A definitive diagnosis of cryptococcal pneumonia may require identification of the organism in tissue obtained from a biopsy or a surgical specimen.[26, 27] In practice, experts advocate treatment whenever respiratory specimens grow *C. neoformans* in the setting of a compatible clinical syndrome in HIV-infected patients.[28, 29] However, the potential presence of co-infections in HIV-infected patients makes it difficult to define a “compatible clinical syndrome.” Of 15 pulmonary cryptococcosis patients in our study, eight (53%) had two pulmonary processes. In these patients, it is unclear whether the clinical and radiographic findings were due to cryptococcosis, the other pulmonary process, or both. No study has proved the presence of colonization of C. *neoformans* in the airways of HIV-infected patients, though colonization of the nasopharynx has been documented.[30] Further studies and expert consensus are needed to define the significance of isolating *C. neoformans* from respiratory specimens.

The possibility of localized infection or colonization of C. *neoformans* in the airway of HIV-infected patients calls into question the principle that all HIV-infected patients with pulmonary cryptococcosis need antifungal treatment. Whether to “treat or observe” is a difficult decision in HIV-negative patients with pulmonary cryptococcosis because of the difficulty in distinguishing infection from colonization.[31, 32] This decision is more difficult in HIV-infected patients, given the high mortality associated with cryptococcosis in this population. CD4+ T

lymphocyte counts and serum cryptococcal antigen test may be of help in making a right decision.

There are some limitations to our study. First, we did not perform serum cryptococcal antigen testing, which might have helped us differentiate between isolated pulmonary disease and disseminated disease. Second, we did not determine the serotype of *C. neoformans* isolates obtained during our study. A previous study from Uganda showed that all 36 cryptococcal isolates causing disease were confirmed *C. neoformans var grubii*, serotype A.[4] Last, the small number of patients in this series limited our statistical power to identify clinical and radiographic characteristics that might differentiate those with pulmonary cryptococcosis from those with other respiratory infections.

In summary, pulmonary cryptococcosis is common in HIV-infected TB suspects in Uganda and should be considered in the differential diagnosis of HIV-infected individuals with pneumonia. Additional studies should determine whether initiation of ART without antifungal therapy is sufficient treatment for patients with pulmonary cryptococcosis without evidence of disseminated disease.

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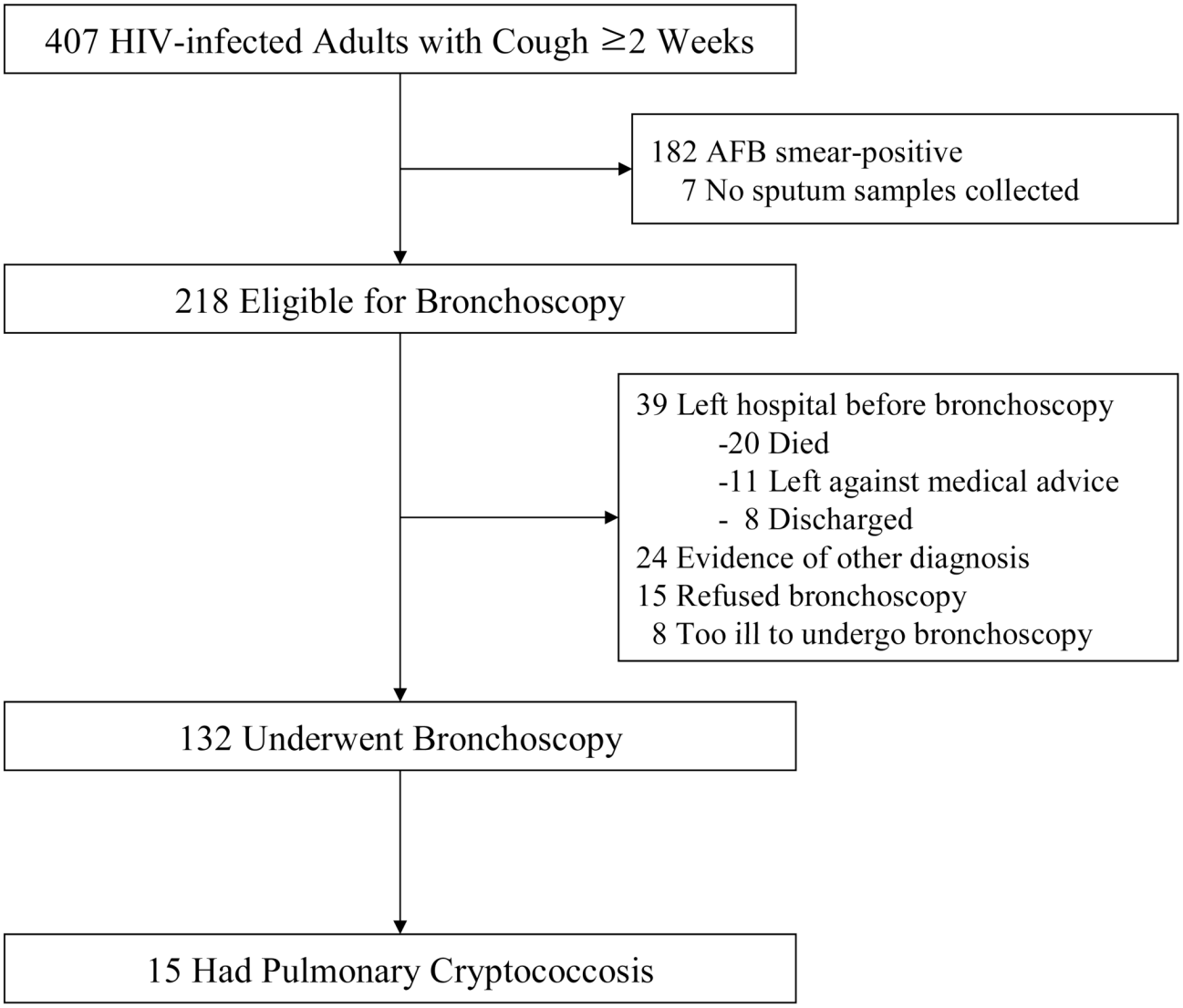

Figure 1.
Numbers of patients screened, eligible, and enrolled

Table 1

Baseline Characteristics

Characteristics	Overall (N=132)	Pulmonary Cryptococcosis (N=15)	Other Diagnosis (N=117)	p-value
Median age (IQR)	32 (28–38)	33 (28–40)	32 (27–38)	0.60
Female, (%)	76 (58)	9 (60)	67 (57)	0.53
HIV status known (%)	96 (73)	11 (73)	85 (73)	0.61
ART on admission (%)	22 (17)	0 (0)	22 (19)	0.06
Median CD4, cells/μL (IQR)	67 (17–191)*	23 (7–51)	93 (23–206)†	0.007
Fever (%)	129 (98)	14 (93)	115 (98)	0.23
Median duration of fever, weeks (IQR)	4 (2–8)	6 (4–8)	4 (2–8)	0.16
Weight loss (%)	124 (94)	14 (93)	110 (94)	0.92
Median duration of cough, weeks (IQR)	4 (3–8)	4 (3–8)	4 (3–8)	0.98
Shortness of breath (%)	83 (63)	5 (33)	78 (67)	0.01
Median duration of shortness of breath, weeks (IQR)	2 (1–4)	1 (1–2)	2 (1–4)	0.06
Chest pain (%)	88 (67)	12 (80)	76 (65)	0.25
Hemoptysis (%)	41 (36)‡	7 (50)§	34 (34)¶	0.20
Median respirations/minute (IQR)	25 (20–32)	26 (18–32)	24 (20–30)	0.64
Median % SpO_2 (IQR)	97 (93–98)	97 (94–98)	97 (92–98)	0.48
Lung examination				0.81
Normal (%)	38 (29)	3 (20)	35 (30)	
Rhonchi (%)	5 (4)	0	5 (4)	
Crepitations (%)	87 (66)	12 (80)	75 (64)	
Bronchial breath sounds (%)	2 (2)	0	2 (2)	

*n=130,

†n=115,

‡n=113,

§n=14,

¶n=99

IQR=interquartile range

SpO_2 = oxygen saturation

Table 2

Chest Radiographic findings of 14 patients with pulmonary cryptococcosis

Radiographic pattern	N (%)
Interstitial infiltrates	4 (29)
Lobar consolidation	3 (21)
Hilar /Mediastinal lymphadenopathy	3 (21)
Cavitary infiltrates	2 (14)
Pleural effusion	2 (14)
Normal (no abnormality)	2 (14)
Mixed *	3 (21)
Distribution of parenchymal infiltrates †	
Diffuse	6 (55)
Focal	5 (45)

* combination of : consolidation/linear opacity, consolidation/pleural effusion, or cavity/consolidation

† 3 cases excluded because of a lack of parenchymal infiltrates

Table 3

Summary of 15 patients with pulmonary cryptococcosis

No	Sex	Age	CD4	Co-morbid illness	Meningitis	Antifungal therapy	ART	2-month status	6-month status
1	F	36	9	-	+	Fluconazole	U	**Died**	-
2	F	29	37	PKS	−	Fluconazole for oral candidiasis	−	**Died**	-
3	M	48	165	-	−	-	−	Improved*	**Died**
4	M	33	4	-	+	Fluconazole	−	Improved	**Died**†
5	F	29	29	Culture-positive PTB	+	Fluconazole	+	Improved	Improved
6	F	54	7	Culture-negative PTB‡	+	Amphotericin B + Fluconazole	+	Improved	Improved
7	F	33	23	Culture-negative PTB‡	+	Amphotericin B + Fluconazole	+	Improved	Improved
8	F	28	7	-	+	Amphotericin B + Fluconazole	+	Improved	Improved
9	M	38	51	-	−	-	+	Improved	Improved
10	F	18	54	-	−	-	+	Improved	Improved
11	M	52	10	PCP	−	-	+	Improved	Improved
12	M	33	41	Culture-negative PTB‡	−	-	+	Improved	Improved
13	F	18	11	-	−	-	+	Improved	Suspected PCP
14	M	33	4	Culture-positive PTB	−	Fluconazole for oral candidiasis	+	Improved	**Lost to follow-up**
15	F	41	226	Culture-positive PTB	−	-	U	**Lost to follow-up**	**Lost to follow-up**

*Respiratory symptoms improved, but gastrointestinal symptoms (diarrhea and vomiting) developed.

†Died during readmission due to gastrointestinal symptoms.

‡All of them were AFB smear-negative, but improved with anti-TB medication.

B/P=Bacterial pneumonia; PKS=pulmonary Kaposi's sarcoma; PTB=pulmonary tuberculosis; CM=cryptococcal meningitis; TBM=Tuberculous meningitis; ART=antiretroviral therapy after discharge; U = unknown