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Cryptococcosis in Acquired Immunodeficiency Syndrome Patients Clinically Confirmed and/or Diagnosed at Necropsy in a Teaching Hospital in Brazil

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Abstract. Cryptococcosis occurs in acquired immunodeficiency syndrome (AIDS) patients with poor compliance to antiretroviral therapy or unaware of their human immunodeficiency virus status who present severe immunosuppression at admission. Consequently, high mortality rates are observed due to disseminated fungal infection. This report presents clinical and postmortem data of AIDS patients with cryptococcosis in a teaching hospital in Brazil. Retrospectively, medical and necropsy records of AIDS patients with cryptococcosis clinically confirmed and/or postmortem verified were reviewed. Clinical data were compared with those of patients presenting a good outcome to evaluate disseminated fungal infection and the agreement between clinical and postmortem diagnosis. At admission, most of the 45 patients with cryptococcal meningitis who died, presented more altered consciousness ($P = 0.0047$), intracranial increased pressure ($P = 0.047$), and severe malnutrition ($P = 0.0006$) than the survivors. Of 29 (64.4%) patients with cryptococcal meningitis, 23 died before week 2 on antifungal therapy, and the other six during the next 3 months. The remaining 16 (35.6%) cases had other diagnoses and died soon after. At necropsy, 31 (68.9%) presented disseminated infection involving two or more organs, whereas 14 (31.1%) cases had meningeal or pulmonary localized infection. The agreement of 64.4% between clinical and postmortem diagnosis was similar to some studies. However, other reports have shown figures ranging from 34% to 95%. Currently, a progressive worldwide decrease of autopsies is worrying because the role of postmortem examination is pivotal to verify or identify the death causes, which contributes to improve the quality of clinical diagnosis and medical training.

INTRODUCTION

According to the recent World Health Organization (WHO) estimates, at least 1 million cases of cryptococcal meningitis are yearly diagnosed worldwide mostly in acquired immunodeficiency syndrome (AIDS) patients. Commonly, cryptococcosis occurs as the first AIDS-defining disease in patients presenting advanced immunodeficiency who present poor compliance or did not receive antiretroviral therapy (ART). As a consequence, 625,000 of these individuals die during the first week on therapy due to severe and disseminated fungal disease in poor-resource settings from Asia, Latin America, and mainly sub-Saharan Africa where the mortality rate related to cryptococcosis overcomes that of tuberculosis.[1–3]

Cryptococcosis has been considered the second most prevalent central nervous system (CNS) infection, and one of the commonest opportunistic infection in human immunodeficiency virus (HIV) patients at necropsy studies performed elsewhere and the second cause of mortality among systemic mycosis in Brazil.[4–7]

At admission, most patients present subacute meningitis that often evolves to meningoencephalitis with several clinical and laboratory features associated to a poor prognostic. Among them, increased intracranial pressure, altered consciousness, cerebrospinal fluid (CSF) low cell count (< 20 cells $\times$ μL), capsular antigen titers higher than 1:1024 and elevated fungal burden are the most consistent.[8–10]

Disseminated fungal infection occurs in 30% of severely immunocompromised AIDS patients with cryptococcosis. Besides, meningeal and respiratory symptoms, fever, weight loss, anemia, lymph-node-enlargement, and hepatosplenomegaly are also observed.[11–14] The involvement of several organs such as adrenal gland, heart, skin, gut, thyroid gland, and prostate among others have been reported at necropsy studies carried out elsewhere.[6,15]

Some reports have shown discrepancies between clinical and postmortem cryptococcosis diagnosis whereas others have pointed out some concerns with the decreasing rate of postmortem examination in teaching hospitals around the world.[13,16–18] The aim of this study is to present clinical and epidemiological data of AIDS patients with cryptococcosis diagnosed and/or confirmed at necropsy in a teaching hospital in Brazil.

METHODS

Medical and necropsy records of 45 AIDS individuals with confirmed cryptococcosis at the Teaching Hospital of Triângulo Mineiro Federal University, in Uberaba, Minas Gerais, Brazil, from 1989 to 2008 were reviewed. An AIDS-associated cryptococcosis case was defined by two positive anti-HIV enzyme-linked immunosorbent assay tests confirmed by western blotting test together with clinical features and/or blood or CSF positive culture, positive cryptolatex test, positive Nankin stain, or histopathological evidence of *Cryptococcus neoformans* infection at necropsy. The main demographic, epidemiological, clinical, and laboratorial features of these patients were reviewed and registered. Intracranial increased pressure was diagnosed through clinical features, evidence of papilledema, skull computed tomography findings, and a fast CSF dropping. Malnutrition was defined by the body mass index and other specific measurements performed by nutrology specialist. To compare these data, medical records of 24 AIDS patients with cryptococcal meningitis diagnosed during the same period and presented good outcome after antifungal therapy were reviewed as well.

Data analysis was performed using χ^2 and Kruskal–Wallis test. Values of $P \leq 0.05$ were considered statistically

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significant. This study was approved by the Research Ethical Board of the Triângulo Mineiro Federal University under protocol number 2526.

RESULTS

From 1989 to 2008, a total of 1,785 necropsies were performed at the teaching hospital. Of these, 284 (15.9%) were of AIDS patients of whom 45 (15.8%) had cryptococcosis as definitive diagnosis. Thirty-five (77.8%) were male, mean age of 31.7 years; 15 (33.3%) developed cryptococcosis as the first AIDS-defining condition and 25 (55.6%) had the HIV diagnosis confirmed during the same year. The $CD4^+$ T cell baseline values were less than 100 cell/mm^3 in 13 of 15 (86.7%) evaluated cases. Of the 45 cases, 18 (40%) were diagnosed before 1997 and did not receive ART or started it with one or two of the formerly nucleoside analogs. The remaining 27 died before starting ART.

At admission, most of the 45 patients who died, presented more altered consciousness ($P = 0.0047$), intracranial increased pressure ($P = 0.047$), and severe malnutrition ($P = 0.0006$) than survivors. No other relevant epidemiological or clinical differences were observed between the groups (Table 1).

Twenty-nine (64.4%) individuals with confirmed cryptococcal meningitis received amphotericin B. Of these, 23 died before week 2 on therapy, and the other six during the next 3 months. The remaining 16 (35.5%) cases had other clinical diagnosis such as toxoplasmosis encephalitis (five), bacterial pneumonia (four), *Pneumocystis jirovecii* pneumonia (three), sepsis (five), bacterial meningitis (one), meningeal tuberculosis (two), and meningeal syndrome (three). At necropsy, cryptococcal infection was evidenced in all of them. According to this figure, the disagreement rate between clinical and postmortem diagnosis was 34.5%.

Of the 45 individuals who underwent necropsy, 31 (68.9%) presented a disseminated cryptococcosis involving two or more organs: CNS in 24 (77.4%) cases, lungs in 31 (100%), lymph nodes in 25 (80.6%), kidney in 22 (79.9%), and liver and spleen in 21 (67.7%) each, among others. Of 29 patients with confirmed cryptococcosis, 22 (75.8%) had clinical suspicion of disseminated fungal infection and three (10.3%) of them also had positive *Cryptococcus* blood culture, whereas of the 24 survivors, only three (12.5%) presented cryptococcemia. A similar proportion of disseminated cryptococcosis was found between those who had cryptococcosis diagnosis and received antifungal therapy, 20 (69.0%), and those with postmortem diagnosis, 11 (68.75%). The remaining 14 (31.1%) cases presented localized cryptococcal infection of meninges (11) or lung (three) (Table 2).

Other opportunistic infections were also concomitantly observed such as toxoplasmosis in 13 (28.9%) cases, candidiasis in 7 (15.6%) cases, and cytomegalovirus and mycobacterial disease in 5 (11.1%) cases each.

DISCUSSION

Recently, WHO global estimates pointed out that of nearly 35 million people living with HIV, 1,600,000 live in Latin America and Caribbean region.[20] From around 1 million worldwide cases of HIV-associated cryptococcosis reported yearly, 70,000 occur in the Caribbean region that presents the third most prevalence of cryptococcosis after sub-Saharan Africa and Asia.[21] According to several authors, a late HIV diagnosis was performed in 45–76% of cases in two great case series of cryptococcosis reported from that region contrasting with the figures of 15–38% from Europe.[22–24]

Nowadays, the epidemiological scenario in poor-resource settings exhibits an unacceptable and high mortality rate of 63% directly related to cryptococcosis. Most of these patients are unaware of their HIV status or do not receive or present poor compliance to ART. At admission, disseminated fungal infection and advanced immunodeficiency at admission are often seen.[23,24] Unfortunately, the ideal antifungal therapy for this disease is not available in most places due to its high cost, which also contributes to the poor outcome. In contrast, the reports from Europe and the United States have shown an impressive decrease of prevalence and mortality rates related to cryptococcosis and other opportunistic infections after the introduction of ART in 1995.[6,22]

This report shows clinical and necropsy data of 45 (15.8%) cases of AIDS-associated cryptococcosis selected among 284 HIV-infected individuals necropsied along 19 years. Of these,

TABLE 1
Comparative epidemiological, clinical, and laboratory data of patients with AIDS-associated cryptococcosis

	Deaths ($N = 45$; mean age = 31.7)			Survivors ($N = 24$; mean age = 29.9)			
	Yes	No	%	Yes	No	%	*P* value
Epidemiological features							
Male	35	–	77.8	23	–	95.8	–
Female	10	–	57.9	1	–	4.2	–
Alcoholism	28	17	75.7	21	3	87.5	0.0275
Illicit drug user	15	30	41.7	16	8	66.6	0.0080
$CD4^+$ T count < 100 cell/mm^3	13	2	86.7	23	1	95.8	0.2959
First AIDS defining condition	15	30	33.3	6	18	25.0	0.4736
Clinical and laboratorial features							
Signs/symptoms < 10 days	22	23	48.9	14	10	56.5	0.4544
Fever	39	6	86.7	20	4	83.3	0.7070
Weight loss	34	11	75.6	8	16	33.3	0.0006
Altered consciousness	23	22	52.3	4	20	16.7	0.0047
Intracranial increased pressure	23	22	52.3	6	18	25.0	0.0407
CSF low cell count	17	28	54.9	16	8	66.7	0.4175
CSF low glucose	28	17	90.3	17	7	70.8	0.6680

AIDS = acquired immunodeficiency syndrome; CSF = cerebrospinal fluid.

TABLE 2
Comparative organ involvement in AIDS-associated disseminated cryptococcosis cases at necropsy

	Present study		Klock and others[15]		Antinori and others[19]	
Organ involvement	*n*	%	*n*	%	*n*	%
Central nervous system	38	84.4	45	100	52	84
Lungs	35	77.7	17	38	25	40
Lymph nodes	25	55.6	NA	NA	21	34
Kidney	22	48.9	17	38	19	31
Liver	21	46.7	17	38	18	29
Spleen	21	46.7	22	49	18	29
Gut	13	28.8	20	45	NA	NA
Adrenal gland	10	22.2	NA	NA	8	13
Pancreas	10	22.2	8	18	NA	NA
Prostate	9	20.0	NA	NA	NA	NA
Bone marrow	9	20.0	NA	NA	NA	NA
Thyroid	8	17.8	7	16	NA	NA
Heart	7	15.5	NA	NA	8	13
Hypophysis	4	8.9	NA	NA	NA	NA
Esophagus	3	6.7	NA	NA	NA	NA
Stomach	3	6.7	NA	NA	NA	NA
Gallbladder	2	4.4	NA	NA	NA	NA
Testicle	2	2.2	NA	NA	NA	NA
Breast	1	2.2	NA	NA	NA	NA
Eye	1	2.2	NA	NA	NA	NA
Bladder	1	2.2	NA	NA	NA	NA
Subcutaneous nodule	1	2.2	NA	NA	NA	NA

AIDS = acquired immunodeficiency syndrome; NA = not available.

29 (64%) presented cryptococcal meningitis as first clinical diagnosis at admission and they died during the first week on antifungal therapy. Most of them had late cryptococcal meningitis and HIV diagnoses and two or more of the clinical and laboratorial markers associated to a poor outcome, evidencing a severe and disseminated fungal infection together with advanced immunodeficiency.[8,9,25]

The remaining 16 (36%) patients had other clinical diagnoses, and they died a few days later. A disseminated fungal infection involving two or more organs was evidenced in most of them but a similar proportion of disseminated infection was also evidenced among the 29 cases who had started antifungal therapy. The necropsy findings in the present report are in line with several authors who included different years and number of cases and showed that the CNS, lungs, spleen, liver, kidney, gut, and lymph nodes were the sites most frequently involved (Table 2).[12,15,19,26]

Although cryptococcal meningitis is the most usual clinical picture observed among AIDS patients with cryptococcosis, a disseminated fungal infection to two or more organs seems to be a common condition at postmortem examination as observed in 69% of cases in the present report. This figure is in accordance with the 50%, 66.6%, and 63% cases reported by others, respectively.[15,17,19]

Because of the severity and fast progression of cryptococcosis in patients seriously immunocompromised, who can simultaneously present other opportunistic diseases, the diagnosis of disseminated fungal infection can be missed or even raised leading to variable discrepancy rates between clinical and postmortem diagnosis.[27,28] The agreement rate of 64.4% herein found differs from other author's results who reported 46%, 34.7%, and 95%, respectively.[16,17,19] To improve the global scenario, the WHO recommends the wide use of serum cryptococcal antigen screening that can detect cryptococcal infection several weeks before the appearance of clinical symptoms in HIV-infected individuals presenting severe immunodeficiency.[29]

A progressive decline of cryptococcosis and other opportunistic infections rates in most places where ART is available has been observed, especially in patients with good compliance, which permits to evaluate its true impact on AIDS mortality rates.[6,9,30,31] Despite ART availability in public health services in Brazil since 1997, the prevalence of cryptococcosis is 6–12% and the associated mortality rate is currently 55%.[32–34] This mycosis was considered the second most important cause of mortality among systemic mycoses according to Brazilian study based on public health registers.[4] This figure is similar to that of Latin American countries where most HIV-infected patients are also severely immunocompromised when they start the ART or discover their HIV status and/or are hospitalized.[23,24]

Probably, a high and unknown number of AIDS patients die before cryptococcosis diagnosis is performed or antifungal therapy started, and the lack and/or a progressive decrease of necropsy performance in most teaching hospitals hinder a definitive postmortem diagnosis in these cases. The prevalence of this mycosis associated to AIDS in necropsy reports from teaching hospitals around the world during the last years showed rates ranging from 3.8% to 22.8% (Table 3).[13–19,28,35–39]

In fact, according to recent reports, the progressive decrease in postmortem examination in many teaching hospitals is

TABLE 3
Update of AIDS-associated cryptococcosis in case series necropsy reports

No. of autopsies	No. of AIDS cases (%)	Time of study (years)	Cryptococcosis cases	Cryptococcosis rate	No. of disseminated cases (%)	Author
4,824	NA	9	30*	–	10 (33)	Colombo and others[35]
1,785	284 (15.9)	19	45	15.8	31 (68.8)	Present report
1,630	1,630 (100)	18	62	3.8	39 (62.9)	Antinori and others[19]
1,478	92 (6.2)	7	4	4.3	2 (50.0)	Cury and others[36]
395	395 (100)	13	21	5.3	NA	Hofman and others[14]
387	387 (100)	14	45	11.6	45 (100)	Klock and others[15]
281	16 (5.6)	5	3	18.7	2 (75.0)	Eza and others[37]
250	250 (100)	7	22	8.8	NA	d'Armino Monforte and others[16]
236	236 (100)	19	18	7.6	17 (94.4)	Lanjewar[38]
216	216 (100)	5	17	7.8	11 (64.7)	Klatt[28]
129	129 (100)	7	7	5	NA	Souza and others[39]
59	35 (59)	1	8	22.8	1	Cox and others[13]
52	52 (100)	7	6	11.5	4	Borges and others[17]

AIDS = acquired immunodeficiency syndrome; NA = not available.
*AIDS patients.

worrying.[19,40,41] Several factors would account, for example, economic factors, lack of professional training, loss of academic interest, difficulties to obtain familiar consent, new paradigms in medical education, and better legislation about this matter. As a consequence, the teaching hospitals lose a valuable tool to improve the quality of clinical diagnosis and medical training. Therefore, it is very important to encourage students and professors of medical schools to make a postmortem examination a remarkable practice.[37,42]

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