Characterization of cryptococcal meningitis in patients without human immunodeficiency virus infection hospitalized at a tertiary care hospital

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Abstract

Introduction: cryptococcosis is a relevant opportunistic fungal infection which mainly affects the central nervous system (CNS) and is highly fatal in both HIV seronegative and seropositive patients.

Methods: this was a retrospective descriptive cross-sectional chart review of adult patients hospitalized for cryptococcal meningitis who met the inclusion criteria. Measures of central tendency and dispersion were calculated for quantitative variables. Qualitative variables were grouped in frequency tables.

Results: this was a homogeneous sample of six cases with equal incidence by sex. Serum and CSF *Cryptococcus spp* antigens were positive in all cases, while the RT-PCR was diagnostic in four patients, and only two patients had a positive culture. High protein, pleocytosis, low glucose and high opening pressure were the most frequent findings on CSF tests. Neuroimaging only showed lesions compatible with infection in two patients.

Conclusions: cryptococcal meningitis has a variable presentation that requires high clinical suspicion not only in HIV seropositive patients but also in HIV seronegative patients and women. It has a highly lethal course, possibly related to chronic corticosteroid use, rheumatic diseases, kidney disease and diabetes. (Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.2859).

Keywords: *cryptococcal meningitis, Cryptococcus neoformans, HIV, immunocompromised host, serological diagnosis of AIDS.*

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Introduction

The *Cryptococcus* genus includes more than three species, of which two complexes are the most frequent: *C. neoformans* and *C. gatti*. Thanks to the advent of molecular techniques, these two have been divided into two and five species, respectively, considering the genotype (1-3). They are related to high mortality in both immunocompetent and immunosuppressed patients, mainly affecting the central nervous system. Initially, this genus of microorganisms was only related to human immunodeficiency virus (HIV) infection (4). However, for several years now, patients with primary and/or secondary immunodeficiency due to solid organ and hematological transplants, diabetes mellitus, chronic kidney disease, liver disease, autoimmunity and immunosuppressant therapy have been documented to be at risk of developing the infection (1).

The form of presentation, prognosis, diagnostic test yield and treatment plan may vary in patients with immunosuppression, depending on its etiology (4), and therefore it is essential to differentiate them. This poses a clinical challenge in the approach to these patients. The objective of this paper is to present the first description in Colombia of patients without HIV infection with crypotococcosis and central nervous system involvement.

Materials and method

We conducted a retrospective review of patients with cryptococcosis at a public tertiary care hospital in the city of Bogotá from 2012 to 2022. The search was done using the infection committee records and hospital statistics of patients diagnosed with cryptococcosis, ICD-10 code (B45X). Likewise, all patients who had received flucytosine, amphotericin B and/or fluconazole within the described time period were identified. Patients who did not have HIV infection according to the national clinical practice guidelines (Colombian Guidelines on HIV Infection) were selected.

This study was approved by the institutional ethics committee and was considered to have minimal risk for the patients. The diagnosis was made using a CSF, blood or brain tissue culture; *Cryptococcus* antigen in CSF and serum (latex agglutination), CSF FilmArray, India ink staining, and histopathological tests on brain tissue samples.

The sociodemographic, clinical, laboratory and imaging data was extracted from the medical charts, with its inherent information bias. The data gathered was entered into Excel Microsoft Office Version 16.58, the basic statistical data were analyzed in Excel Microsoft Office Version 16.58, and a descriptive table was drafted with each case and its findings.

Results

During the specified period, six patients were found who met the inclusion criteria. The characteristics are shown in Table 1, presenting three women and three men, with a mean age of 53.3 years, ranging from 32 to 83 years. In the group of women, two had a history of cardiovascular disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and hypothyroidism, one had autoimmunity and was being given immunosuppressant treatment with steroids. The third woman was on chronic prednisolone treatment for autoimmune thrombocytopenia and had also had her spleen removed. In the group of men, one had an unclear steroid use, another had advanced cancer (lymphoproliferative), and the last one had no other relevant findings.

Five patients reported headaches, two had seizures, and all had problems walking, with a feeling of instability and a widened stance (Table 2). Likewise, five had to be admitted to the intensive care unit (ICU) and 33% had a fatal outcome.

Routine laboratory tests showed that five of the six patients had fluid and electrolyte abnormalities due to mild to moderate hyponatremia, with no other type of study found in the context of differential diagnoses or secondary associations. In all cases, the *Cryptococcus spp* serum antigen was positive, as it was in the CSF; the RT-PCR multiplex FilmArray***® detected it in the four cases in which it was requested, and two cases had*** *Cryptococcus neoformans* ***growth on culture (Table 1).***

For other CSF parameters, there was a mean leukocyte count of 988 cel/dL, ranging from a minimum of 14 cel/dL to a maximum of 5,200 cel/dL; CSF proteins had a mean of 1,175 mg/dL, ranging from a minimum of 49.6 mg/dL to a maximum of 6,253 mg/dL; CSF glucose had a mean of 28 mg/dL, ranging from a minimum of 14 mg/dL to a maximum of 48 mg/dL; and opening pressure had a mean of 22 cmH_2O, ranging from a minimum of 19 cmH_2O to a maximum of 26 cmH_2O. These results indicate that elevated CSF protein, pleocytosis, low CSF glucose, and increased opening pressure were common findings in most cases.

For diagnostic imaging, cranial computed tomography only showed findings compatible with infectious central nervous system lesions in two patients, as seen in Figures 1 and 2, with no abnormalities found in the other four patients.

Treatment was given according to the institutional and international guidelines available in the literature (IDSA 2010, Colombian and institutional guidelines). Liposomal amphotericin B treatment was chosen due to its availability within the institution, along with 5-flucytosine. We are emphatic in stating that the completion of induction therapy was flawed, due to the premature death of the cases or transfer to other institutions for administrative reasons.

Discussion

Cryptococcal meningitis causes approximately one million cases and 625,000 deaths per year in patients with HIV, worldwide. Despite this, the number of cases in HIV negative patients has been increasing in developed countries (1), especially in patients who are immunocompromised due to prolonged corticosteroid treatment (28%), as was the case of three of the patients presented. To a lesser degree, it has also been associated with pulmonary disease, hematological malignancies (9%) and splenectomy (17%), comorbidities that were present in the remaining patients (5, 6).

The literature highlights the male sex as a constant risk factor for cryptococcosis in HIV-seronegative and seropositive patients (7). This phenomenon appears to be attributed to differences in the immune response due to hormonal effects. However, the similar presentation in both men and women is notable in the six cases presented here. This similarity could be attributed to the postmenopausal age of the women in this study, as it has been reported that 17-β-estradiol increases macrophage activity in response to *Cryptococcus gattii* in female rodents, improving disease control (7, 8). Consequently, we believe that, given the cases reported in the literature of infections in pregnant or postpartum women (7, 9, 10) hormonal variations could be an important susceptibility factor in the female population.

On the other hand, a group of particular interest is the population of "normal" patients who make up 17-22% of the general population in the reported studies of HIV-negative patients (1, 11), a subgroup that has been associated with more serious outcomes and greater complications (1, 7), as documented in patient number four.

Likewise, we found that 33% of the cases had a fatal outcome, probably due to chronic corticosteroid use due to rheumatological and kidney disease (1, 6). In a systematic review of patients with active lupus and cryptococcal meningitis, the use of prednisolone was associated with greater mortality, with an odds ratio (OR)=9.69 (1.54, 60.73) (1, 12). Diabetes and rheumatoid arthritis also increased mortality in this population.

As far as complications, the use of prednisolone was related to the onset of immune reconstitution inflammatory syndrome (IRIS) (1, 12, 13), and kidney disease was an independent factor for 90-day mortality (1, 6).

Table 1. *Main characteristics of the study sample*.

Characteristics	Total patients n=6 (%)	Mean (SD)	Range
Age	…	53.3 (17.9)	(32-83)
Sex			
Male	3 (50)	…	…
Female	3 (50)	…	…
Comorbidity			
Cardiovascular disease	3 (50)	…	…
COPD	2 (33.3)	…	…
Chronic kidney disease	2 (33.3)	…	…
Autoimmune disease	3 (50)		
Chronic steroid use	3 (50)	…	…
Immunomodulation	1 (16.6)	…	…
ICU admission	5 (83.3.)	…	…
Fatal outcome	2 (33.3)	…	…
Days of hospitalization	…	23.1 (9.5)	(5-35)
Complete blood count			
White blood cells (10^3) cel/mL	…	10.7 (2.5)	(7.8-15.8)
Granulocytes (10^3) cel/mL	…	8.5 (2.4)	(6.1-13.7)
Lymphocytes (10^3) cel/mL	…	1.2 (0.4)	(0.4-1.7)
Hemoglobin g/dL	…	14.7 (2.8)	(11-19.8)
Platelets (10^3) cel/mm	…	332.8 (99.6)	(244-493)
Blood chemistries			
BUN mg/dL	…	19.9 (8.11)	(11.2-32.7)
Creatinine mg/dL	…	1.1 (0.5)	(0.5-2.3)
CRP** mg/dL	…	32.6 (25.8)	(5.5-59.3)
Prolonged times *	1 (20)	…	…
VDRL	0	…	…
***Cryptococcus Neoformans* antigen in the blood**	6 (100)	…	…
Cerebrospinal fluid			
VDRL	0	…	…
Cryptococcus Neoformans antigen (latex)	6 (100)	…	…
Positive Cryptococcus Neoformans culture	2 (33.3)	…	…
India ink staining	4 (66.6)	…	…
FilmArray	4 (66.6)	…	…
Initial CSF cytochemistry			
Cloudy appearancea	1 (16.6)	…	…
Opening pressure cmH_2O	…	22.2 (2.5)	(19-26)
Glucose mg/dL	…	30.6 (12.2)	(14-48)
Proteins ¿Units ¿--- ¿ g/L mg/dL?	…	143 (98)	(49-312)
Erythrocytes*** cells	…	5000	…
Leukocytes cells	…	988 (1885)	(14-5200)
Neutrophils (%)	…	16.6 (17.8)	(4-55.7)
Lymphocytes (%)	…	82.6 (18.4)	(14.4-95)
Abnormal CAT findings	5 (83.3%)	…	…
Abnormal MRI findings	2 (33.3%)	…	…
Amphotericin B # of days of treatment *	…	15.4 (8)	(3-28)
Flucytosine # of days of treatment *	…	14.8 (8.2)	(3-28)

Continuation.... **Table 1.** *Main characteristics of the study sample.*

Characteristics	Total patients n=6 (%)	Mean (SD)	Range
Post-treatment CSF cytochemistry			
Cloudy appearance*	1 (20%)	…	…
Opening pressure	…	17.4 (7.3)	(8-27)
Glucose**	…	34.2 (17.4)	(8-54)
Protein**	…	161.6 (855)	(70.6-253)
Erythrocytes***	…	1000	…
Leukocytes**	…	72.7 (43.7)	(8-124)
Neutrophils (%)	…	6.8 (4.6)	(2.3-13.3)
Lymphocytes (%)	…	92.5 (4.6)	(86.2-97.3)

*** Data only available for five patients**.
** Data only available for four patients.
*** Data from a single patient.

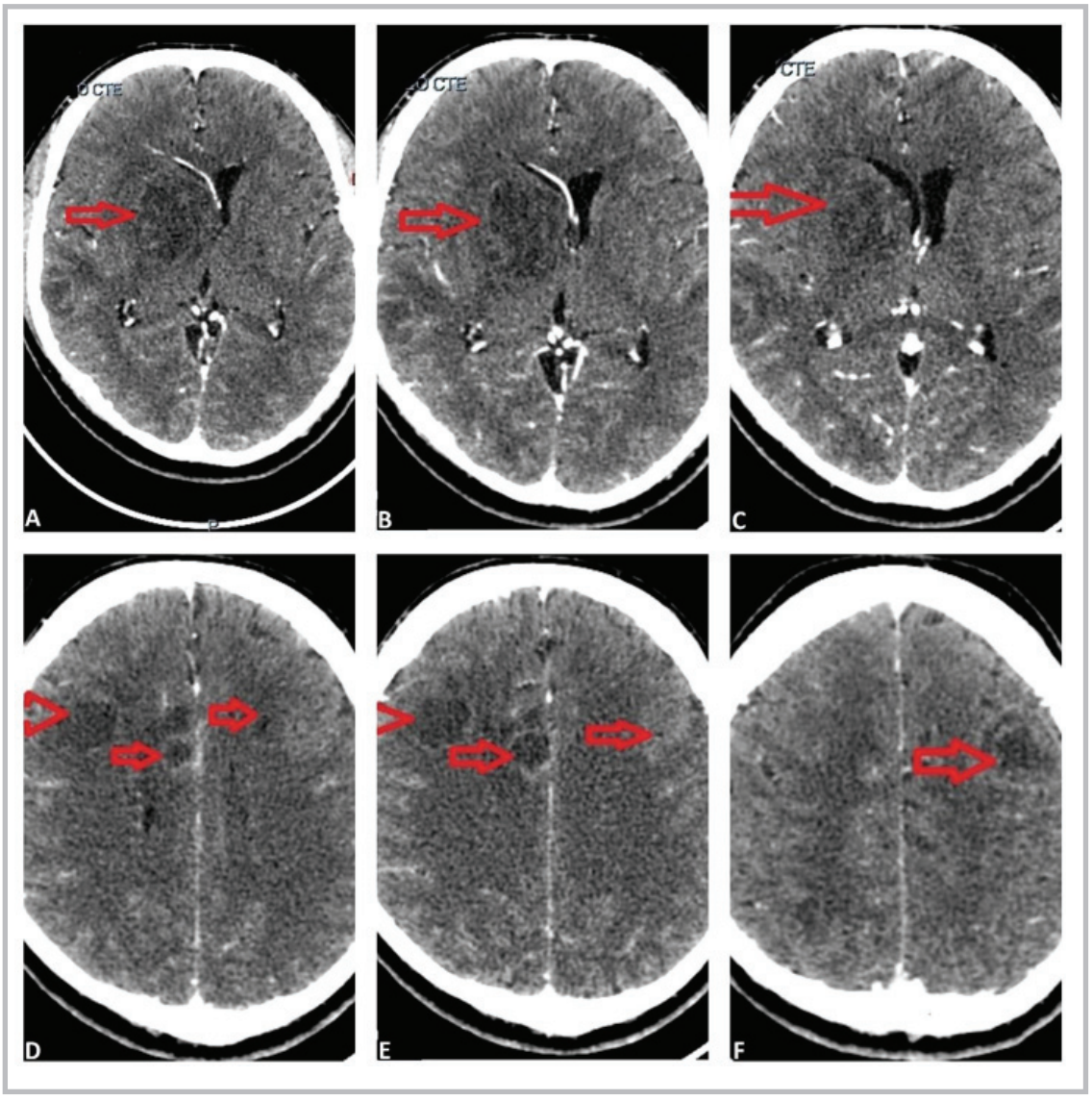

Figure 1. *A patient with multiple lesions on an axial section of the cerebral tomography with contrast; the lesions are indicated with red arrows; images A, B and C show evident basal ganglia involvement with midline shift; images D, E and F show cortical lesions with no predilection for any cerebral region.*

Cryptococcal meningitis has a varied clinical presentation in this group; up to 50% of cases debut with a fever. An association with headaches, visual problems, delirium and subacute dementia has also been described (14). On the other hand, on cerebrospinal fluid (CSF) cytochemical analysis, glucose levels under 40 mg/dL have been associated with a worse prognosis, a phenomenon that could explain the fatal outcome in two of the reported cases, who had low glucose levels, with 38 and 18 mg/dL, respectively.

Also, it is less likely for patients to have a positive India ink test (5, 6), as occurred with patients two and three. Moreover, since an opening pressure of more than 20 cmH_2O was associated with a worse prognosis, we suggest that aggressive neurosurgical interventions in cases of elevated intracranial pressure could reduce mortality (6, 15).

As far as imaging findings, magnetic resonance imaging of the brain is more sensitive than cranial computed axial tomography (CAT) for diagnosis. Up to half of head CATs can be normal (7, 16), and other cases may show hydrocephaly, convolution enhancement, single or multiple nodules, masses and acute or subacute brain infarcts (5, 14, 17), as in the reported patients. Brain magnetic resonance imaging can reveal hyperintense T2-potentiated zones that are not enhanced by the contrast medium in the T1-potentiated images of the basal ganglia or the mesen-

Table 2. *Signs and symptoms of patients with cryptococcal meningitis*

Clinical characteristics	Total patients n=6(%)
Headache	5 (83.3)
Seizure	2 (33.3)
Collapse	2 (33.3)
Syncope	1 (16.6)
Gait abnormality	5 (83.3)

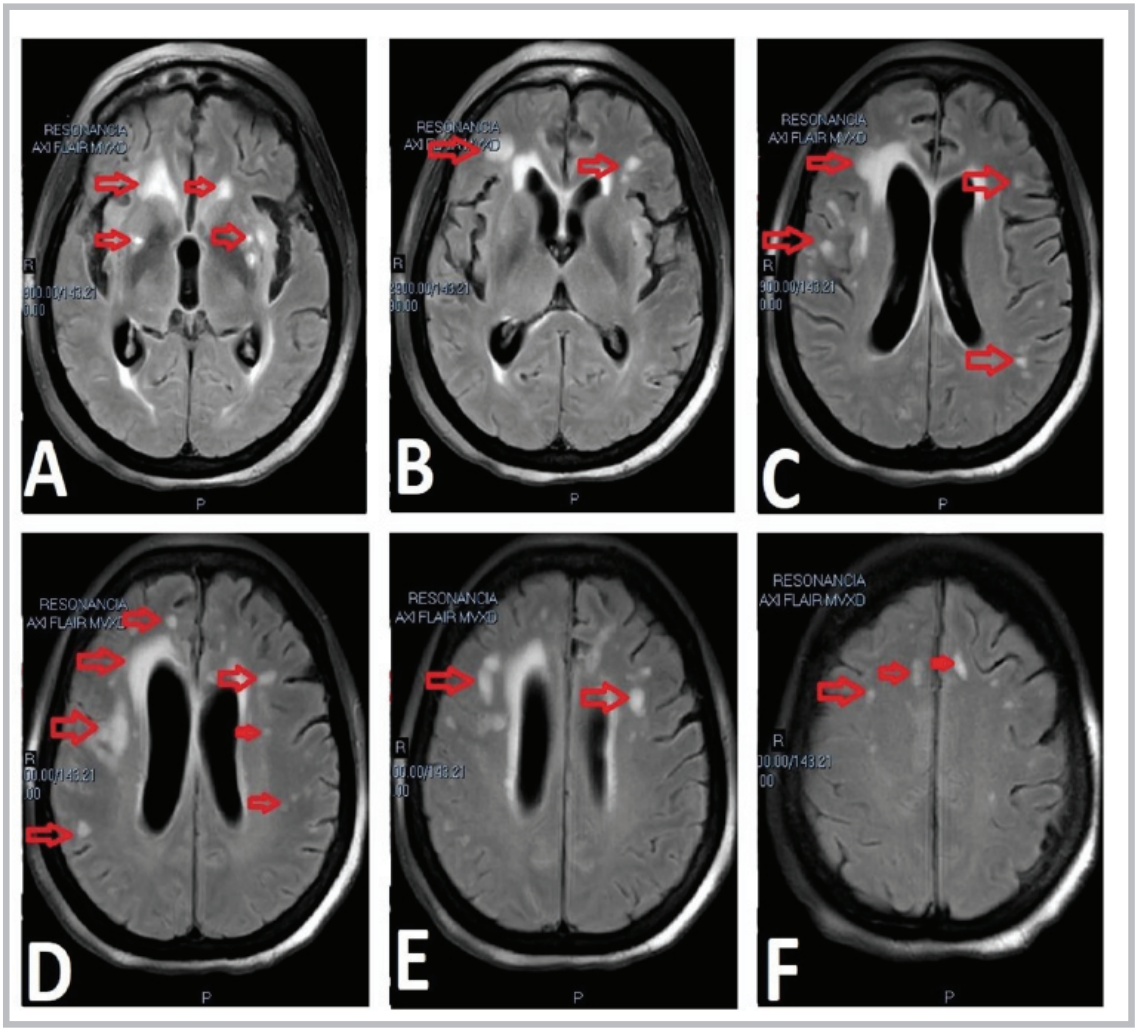

Figure 2. *A patient with multiple lesions that are enhanced in the axial section of a FLAIR sequence magnetic resonance; the red arrows identify the lesions. Images A and B show extensive enhancement and involvement of multiple basal ganglia lesions. Figures C, D and E emphasize the subependymal and white matter involvement. Finally, Figure F shows enhanced lesions resembling white matter disease.*

cephaly, and multiple miliary nodules with enhancement in the leptomeninges (14).

The recommended treatment is based on the 2010 IDSA guidelines (18), which divide the strategies according to host. There is scant evidence to establish the optimal antifungal treatment; however, the experts favor four weeks of induction treatment with liposomal amphotericin B with or without flucytosine (14, 18, 19) in HIV negative patients and those without solid organ transplant, and this should even be extended to six weeks if there are neurological complications (19). After this, reduction therapy to 400-800 mg a day of fluconazole for up to 12 months is suggested, depending on the clinical response, together with immunosuppression correction.

Conclusion

Cryptococcal meningitis has a variable presentation that requires high clinical suspicion, especially in HIV-seronegative patients and postmenopausal women, as well as pregnant or postpartum women, due to hormonal variations. There is also the hypothesis that the chronic use of prednisolone, rheumatological disease and kidney disease were significant factors in the fatal outcome of 33% of the cases in this study. These risk factors, together with low CSF glucose or an opening pressure > 20 cmH_20 could be more vulnerable to complications, perpetuating the treatment challenge presented by this disease..

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