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Increased cryptococcal meningitis mortality among HIV negative, non-transplant patients: a single US center cohort study

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Abstract

Cryptococcal meningitis (CM) is an opportunistic fungal infection associated with human immunodeficiency virus (HIV) and other forms of immunosuppression. We lack a clear understanding of CM associated mortality among HIV-negative, non-transplant patients in the United States (US). This article compares clinical features and outcomes across HIV status in patients with laboratory-confirmed CM.

Methods: A retrospective cohort study was performed that included adult patients with laboratory-confirmed CM treated at an academic tertiary hospital between January 2000 and September 2018. Those with a history of organ transplant or non-meningeal infections were excluded. Data were gathered on demographics, HIV status, clinical presentation, cerebrospinal fluid (CSF) profiles, neurological outcomes, hospital course, and mortality.

Results: A total of 70 patients with cryptococcal disease were identified. Our final sample included 36 CM patients, mean age was 48.8 ± 13.2 years; of this group, 66.7% ($n = 24$) had HIV. Median [interquartile range (IQR)] absolute CD4 count for the HIV group was 35 cells/μl (10–80 cells/μl). Non-HIV/non-transplant patients were significantly older ($p < 0.001$) and had higher rates of altered mental status (AMS) on presentation (58.3% *versus* 25%, $p = 0.05$). Non-HIV patients/non-transplant patients had significantly higher CSF white blood cell (WBC) count ($p = 0.02$), lower CSF glucose ($p = 0.005$), and higher CSF protein ($p < 0.001$) compared with HIV patients. There was no significant variation in temperature, blood pressure, WBC count, serum sodium, CSF opening pressure, length of stay, intensive care unit admission, or neurological outcomes. Overall, 90-day all-cause mortality was 19.4%: mortality rates were significantly higher in non-HIV/non-transplant patients at both 90 days (41.7% *versus* 8.3%, $p = 0.017$) and 1 year (41.7% *versus* 12.5%, $p = 0.047$).

Conclusion: Compared with HIV-infected individuals, non-HIV/non-transplant CM patients have a higher CSF WBC count at the time of diagnosis, higher rates of AMS on presentation, and higher rates of 90-day and 1-year all-cause mortality. Further prospective research is needed to identify the hallmarks of CM in non-HIV/non-transplant patients to facilitate early identification and intervention.

Keywords: cerebral cryptococcosis, cryptococcal meningitis, *Cryptococcus neoformans*, human immunodeficiency virus

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Introduction

Cryptococcal meningitis (CM) is an opportunistic fungal infection associated with human immunodeficiency virus (HIV) and other forms of immunosuppression, including solid organ transplantation, malignancy, sarcoidosis, systemic lupus erythematosus, and cirrhosis.[1,2] Cryptococcus exhibits high mortality in patients with

HIV and other forms of immunosuppression.[3] Each year, approximately one quarter of a million cases of CM occur among persons living with HIV around the world, causing nearly 181,100 deaths.[4] In the United States (US), cryptococcal infections account for almost 3400 hospitalizations every year, and age-adjusted mortality close to 0.07 per 10,000 persons.[5,6] CM often goes unrecognized, or has a delayed diagnosis, among HIV-negative patients. This often translates to worse outcomes in non-HIV/non-transplant patients.[7] Recent retrospective population-based studies in Colorado, Florida, and California found the incidence of cryptococcosis among HIV-negative patients to be close to half of the overall cases reported (between 44% and 55%).[8,9]

We lack a clear understanding of CM-associated mortality among HIV-negative/non-transplant patients in the US. We aim to compare clinical features and outcomes across HIV and solid-organ status in patients with laboratory-confirmed CM.

Methods

This protocol was approved by the Colorado Multiple Institutional Review Board (COMIRB) (Protocol ID number: 15-1340) and received an exemption to obtain a written informed consent). We conducted a retrospective, cohort study of all patients aged 18 years and over with laboratory-confirmed cryptococcal disease treated at an academic tertiary care center from January 2000 to September 2018. Patients were identified *via* local laboratory and TrinetX datasets. Laboratory confirmation was defined as either a positive culture or antigen test for *Cryptococcus* in serum or cerebrospinal fluid (CSF). Electronic medical reports were accessed to collect clinical and laboratory variables for all patients. The following data were collected: demographics (sex, gender, and race), HIV status, clinical presentation, CSF profiles (CSF white blood cell count, CSF glucose, CSF protein, and opening pressure), ventricular shunt insertion, neurological outcomes (stroke, cognitive deficits, hearing impairments, speech difficulties, and muscle weakness), hospital course, and 90- and 360-day mortality. Patients with a history of organ transplant or non-meningeal infections were excluded from the analysis.

Definitions

Cryptococcus infection was identified through Immuno-Mycologics Inc. (IMMY, OK, USA) serum and CSF cryptococcal antigen tests (CrAg® LFA —Cryptococcal Antigen Lateral Flow Assay) using semi-quantitative enzyme immunoassay. Confirmation was performed through regular fungal culture. These tests, unfortunately, cannot distinguish the species or the genotype of the isolate. Blood cultures were processed using the BACTEC 9240 automated culturing system (Becton Dickinson, Franklin Lakes, NJ, USA). All laboratory data were obtained at the time of diagnosis of cryptococcal infection. CM was defined as a positive cryptococcal CSF antigen, positive CSF culture, or positive blood cryptococcal culture with endophthalmitis, or known history of CM. Other meningeal co-infections were ruled out clinically during initial evaluation. Ventriculoperitoneal shunt insertion in this setting were inserted for intracranial pressure control management regardless of HIV status. Standard treatment for CM was defined as at least 14 days of liposomal amphotericin B plus flucytosine. Cryptococcus-attributable death was defined as mortality with cryptococcus infection considered to be the direct cause of death.

Statistical analysis

Continuous variables were summarized with the sample median and range and compared between the groups using Mann–Whitney *U* test, or two-sample *t* tests depending on the distributions of the variables of interest. Categorical variables were summarized with the number and percentage of patients and compared using Chi-square tests. p values <0.05 were considered statistically significant. All statistical tests were 2-sided. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Data access

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

A total of 70 patients with cryptococcal disease were identified. Our final sample included 36 CM patients with a mean age of 48.8 ± 13.2 years; of

Table 1. CM: clinical features and outcomes in HIV and non-HIV/non-transplant patients.

Characteristic	HIV ($n=24$)	Non-HIV/non-transplant ($n=12$)	Total ($n=36$)	p value
Age (years), mean (±SD, years)	42.2 ± 9.9	62.2 ± 7.4	48.8 ± 13.2	<0.001*
Sex, Male	21 (87.5)	9 (75)	30 (83.3)	0.343
White (%)	16 (66.7)	7 (58.3)	23 (63.9)	0.624
Clinical variables				
Median CSF WBC count/μL (IQR)	27.5 (12–63)	84 (53–265)	53 (14–118)	0.02*
Mean CSF glucose (±SD, mg/dl)	44 ± 17.2	25.6 ± 16.1	37.4 ± 18.8	0.005*
Median CSF protein (IQR, mg/dl)	57 (47–89)	171 (101–292)	89 (51–171)	0.001*
Opening pressure (cm H_2O)	30 (24–37)	29 (17–41)	30 (25–35)	0.8
Altered mental status (%)	6 (25)	7 (58.3)	13 (36.1)	0.05
ICU admission (%)	5 (20.8)	5 (41.7)	10 (27.8)	0.188
Mortality rate				
90-days (%)	2 (8.3)	5 (41.7)	7 (19.4)	0.017
1-year (%)	3 (12.5)	5 (41.7)	8 (22.2)	0.047

*Mann–Whitney because skewed distribution.
CM, cryptococcal meningitis; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartil range; SD, standard deviation; WBC, white blood cell.

Table 2. CM: ventricularperitoneal shunts and neurological outcomes in HIV and non-HIV/non-transplant patients.*

Characteristic	HIV ($n=24$)	Non-HIV/non-transplant ($n=12$)	Total ($n=36$)	p value
VPS (%)	3/23 (13.0)	1/12 (8.3)	4/35 (11.4)	0.678
Stroke (%)	3/19 (15.8)	4/9 (44.4)	7/28 (25.0)	0.102
Cognitive deficitis (%)	7/21 (33.3)	4/10 (40.0)	11/31 (35.5)	0.717
Hearing impairments (%)	3/20 (15.0)	2/9 (22.2)	5/29 (17.2)	0.634
Speech difficulties (%)	2/22 (9.1)	1/9 (11.1)	3/31 (0.1)	0.863
Muscle weakness (%)	8/21 (38.1)	3/9 (33.3)	11/30 (36.7)	0.804

*Frequencies vary in some neurological characteristics according to the availability of neurological outcome information in both groups.
CM, cryptococcal meningitis; VPS, ventriculoperitoneal shunt.

this group, 66.7% ($n=24$) had HIV (Table 1). Median [interquartile range (IQR)] absolute CD4 count for the HIV group was 35 cells/μl (10–80/μl). The other 34 patients had non-meningeal forms of cryptococcal disease and we excluded them. Non-HIV/non-transplant patients were significantly older ($p<0.001$) and had higher rates of altered mental status (AMS) on presentation (58.3% *versus* 25%, $p=0.05$). Risk factors identified among non-HIV/non-transplant were use of

corticosteroids, smoking, malignancy, history of lung disease, and diabetes mellitus. There was no significant variation in temperature, blood pressure, white blood cell (WBC) count, or serum sodium. No significant difference was observed in CSF opening pressure (28.8 *versus* 30.4 cm H_2O, $p = 0.8$); analysis *via* Mann–Whitney test revealed that non-HIV/non-transplant patients had significantly higher CSF cell count ($p = 0.02$) and protein ($p < 0.001$) compared with HIV patients. CSF glucose, however, was significantly lower in non-HIV/non-transplant patients ($p = 0.005$). This study did not include subspecies of Cryptococcus. The frequency of neurological outcomes and insertion of ventriculoperitoneal shunts for CSF drainage were similar in both groups (Table 2). Non-HIV/non-transplant patients had a higher frequency of stroke compared with non-HIV/non-transplant patients, although non statistically significant (44.4% *versus* 15.8%, $p = 0.102$). There was no significant variation in the length of stay or rates of intensive care unit admission. Overall, 90-day all-cause mortality was 19.4%. Mortality rates were significantly higher in non-HIV/non-transplant patients at both 90 days (41.7% *versus* 8.3%, $p = 0.017$) and 1 year (41.7% *versus* 12.5%, $p = 0.047$).

Discussion

In this retrospective cohort of 36 patients with CM over 18 years at our tertiary care center, we found that non-HIV/non-transplant patients were older and had increased rates of 90-days and 1-year mortality compared with HIV patients.

We reported increased rates of AMS, CSF, WBC count, and protein, and lower CSF glucose in non-HIV patients/non-transplant compared with HIV patients. Bratton *et al.* described similar findings in AMS and CSF WBC count in a retrospective cohort, but reported no differences in CSF protein or glucose among groups.[10]

No differences in CSF opening pressures were observed in this study, which differs from other studies. In a multi-center study, Nguyen *et al.* described significantly increased opening pressures in immunocompetent patients compared with the HIV-infected and the immunocompromised groups.[11] On the contrary, Bratton *et al.* reported a higher proportion of HIV-patients with elevated opening pressures, followed by non-HIV and transplant patients.[10]

In our cohort, non-HIV/non-transplant patients were older and had increased mortality rates at 90-days and 1-year, which is similar to previous studies.[8,10,11] A recent retrospective study by Hevey *et al.* found increased mortality in non-HIV/non-transplant patients and a higher frequency of cryptococcosis in those patients compared with HIV and transplant patients.[7]

We found no significant variation in the length of stay or ICU admission rates. Few studies have evaluated specifically these two variables in patients with CM. A recent study by Fang *et al.* reported a more extended duration of hospitalization in non-HIV patients compared with HIV patients (112.3 days *versus* 52.6 days).[12] Although Hevey *et al.* did not evaluate length of stay, they observed that time to diagnosis from hospitalization was significantly longer for non-HIV/non-transplant patients compared with HIV-patients (2.0 days *versus* 1.0 day), and duration of symptoms was longer for non-HIV/non-transplant patients than for HIV patients (19.0 days *versus* 14.0 days).[7] Bratton *et al.* also reported longer symptom duration for the non-HIV/non-transplant patients (mean 44 days) than for HIV and transplant patients (mean 19 days).[10]

There was no significant variation in temperature, blood pressure, WBC count, or serum sodium. These findings differ from previous reports where a fever was significantly more common in HIV-patients.[7,11] Although low CSF WBC associates with worse outcomes in HIV positive patients, we found higher CSF WBC among our non-HIV/non-transplant patients compared with the HIV positive ones. The irreversibility of immunosuppression among HIV negative patients can partially explain the linked worse outcomes of this population.

There were no statistically significant differences in neurological outcomes between the two groups. Ventriculoperitoneal shunts for CSF drainage were frequently performed in both groups. Similarly, a cohort from Taiwan reported comparable frequencies of ventriculoperitoneal shunts among HIV patients and non-HIV/non-transplant patients (26% *versus* 19%).[13]

Non-HIV/non-transplant patients had a greater frequency of strokes, cognitive deficits, hearing impairment, and speech difficulties compared with HIV patients, although not statistically

significant. We previously reported an increased risk of lacunar stroke and neurological disability in patients with CM.[14]

The increased frequency and mortality of CM in non-HIV/non-transplant patients may have multiple explanations. In the last decade the widespread implementation of potent antiretroviral therapy has led to decreased Cryptococcus incidence and mortality among HIV patients.[3,7,8,10] This trend was also evident in our study, non-HIV/non-transplant group accounted for one-third of the total population despite including patients over the past 18 years. Multiple studies have demonstrated that non-HIV patients suffer significant delays in diagnosis and experience higher mortality.[3,10,13]

In addition, other factors such as severe comorbidities, advanced age, irreversibility of immunosuppression, and clinical inexperience have been proposed to contribute to the delayed diagnosis and treatment of cryptococcosis in non-HIV patients.[8] In our study, non-HIV/non-transplant patients were older, and required more intensive care than patients with HIV.

The limitations of this study include its retrospective nature, the small sample size in a single center, and the lack of data regarding cryptococcus species as *C. gatti* often occurs in immunocompetent hosts and is associated with worse neurologic outcomes. We lacked timing from symptoms onset to diagnosis, which could be potentially important. The results of the present cohort may not be generalized to patients with CM elsewhere. Further prospective research is needed to identify the hallmarks of CM in non-HIV/non-transplant patients to facilitate early identification and intervention.

Author declaration

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Conflict of interest statement

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