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ORIGINAL ARTICLE

Different presentations and outcomes between HIV-infected and HIV-uninfected patients with Cryptococcal meningitis

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Background and Purpose: Cryptococcus species are the most common causative agents of fungal meningitis. Different populations may show different clinical manifestations and outcomes. In this retrospective study, we investigated these differences in patients with and without HIV infection.
Methods: From 1995 to 2009, we collected data from HIV-infected or HIV-uninfected patients aged 18 years or over who had cryptococcal meningitis (CM) in a medical center in Taiwan. We reviewed and analyzed their demographic data, clinical manifestations, therapeutic strategies and outcomes.
Results: Among the 72 patients with CM, 19 HIV-infected patients were predominantly younger males, and all of them had AIDS status when CM was diagnosed. In contrast, the 53 HIV-uninfected patients were mostly older males with underlying diseases. The time from initial symptoms to diagnosis was shorter in HIV-infected patients (median 10 vs. 18 days, $p = 0.048$). The HIV-infected patients presented with less pleocytosis ($p = 0.003$) and lower protein levels in the cerebrospinal fluid (CSF), but a higher proportion had positive results for cryptococci in the CSF (90% vs. 60%, $p = 0.02$) and blood (53% vs. 21%, $p = 0.009$) cultures. Surgical drains and repeated lumbar punctures for the management of increased intracranial pressure were performed in 47% of the HIV-infected patients and 38% of the HIV-uninfected patients. A lower mortality rate was observed in the HIV-infected patients ($p = 0.038$). On

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multivariate analysis, initial CD4 count $\leq 20/mm^3$ was an indicator of death or relapse in HIV-infected patients. In the HIV-uninfected group, the initial high cryptococcal antigen titer in the CSF ($\geq$1:512) and hydrocephalus were related to unsatisfactory outcomes.
Conclusion: In addition to well-known differences, we found a lower mortality in HIV-infected patients than in HIV-uninfected patients. Cryptococci and inflammation in the central nervous system may play important roles in the pathogenesis of CM. Low intensity of inflammation and effective surgical CSF drains for increased intracranial pressure and cryptococci removal may contribute to lower mortality in HIV-infected patients.

Introduction

Cryptococci are environmental fungi that can cause infectious diseases in humans. *Cryptococcus neoformans* and *Cryptococcus gattii* are the most common pathogenic species across the worldwide and can be classified into five serotypes.[1,2] Risk factors for cryptococcal infections, including infection with HIV, liver cirrhosis, diabetes mellitus, solid organ transplantation, malignancies, rheumatologic diseases, corticosteroid use and chronic kidney disease, are well-documented.[2,3] Occasionally, these pathogens also infect immunocompetent patients.[4]

The central nervous system (CNS) is a common site for cryptococcal infection. Cryptococcal meningitis (CM) is one of the most common opportunistic infections in HIV-infected patients.[5,6] Similarly, the pathogen can also infect HIV-uninfected patients causing severe meningitis.[4] This type of infection causes high mortality rates in HIV-infected (9%—55%) and HIV-uninfected patients (15%—44%), even with appropriate treatment.[4,6—8] Therefore, the diagnosis and treatment of CM remains challenging for clinicians.

Different clinical presentations of CM in HIV-infected and HIV-uninfected patients have been described.[4,5,7] Some researchers have compared mortality the rates of HIV-infected and HIV-uninfected patients,[8—12] but the results have been inconsistent and this prompted us to investigate this controversial issue.

Methods

Patients and definitions

From 1995 to 2009 we conducted a retrospective study at China Medical University Hospital (CMUH, 2000 beds in mid-Taiwan), a tertiary hospital. We enrolled all CM patients aged 18 years or over. CM was defined as isolation of *Cryptococcus* species from cerebrospinal fluid (CSF) culture, positive CSF India ink or positive CSF cryptococcal antigen (CrAg) titer, and consistent clinical features of meningitis. The diagnosis and classification of HIV infection, AIDS status and opportunistic infection/malignancy were performed on the basis of the standard criteria proposed by the US Centers for Disease Control and Prevention in 1993.[13] Predisposing factors of CM were identified in all of our patients.[2,3] Corticosteroid use encompassed that those who could not withdraw from corticosteroids or those who required at least prednisolone 20 mg daily. The Charlson comorbidity score was used to evaluate comorbidity status. The time from the initial symptoms to the time of definite diagnosis was considered the symptom duration.[11]

Clinical symptoms and all laboratory data were recorded on presentation to our hospital. For treatment classification, the patients who received initial antifungal therapy for at least 7 days were divided into different groups (amphotericin B dosage: 0.5—1.0 mg/kg daily; fluconazole dosage: 400—800 mg daily; flucytosine dosage: 100 mg/kg daily; lipid amphotericin B dosage 3—5 mg/kg daily). Flucytosine and lipid amphotericin B had been available since 2007.[14,15] Repeated lumbar punctures and temporary drains like Ommaya reservoirs, lumbar drains or external ventricular drains for increased intracranial pressure (IICP) control were also analyzed. Permanent shunts for long-term CSF drainage were collected separately.

All patients were followed up until death or for at least 6 months after discontinuation of antifungal therapy. Outcomes[4,16] were categorized as:

- cure/success: a drug-free interval >1 year, and no reappearance of symptoms;
- improved: the same definition for cure/success but the last follow-up examination or death occurred within a year;
- fail: death due to first treated CM;
- relapse: defined as for improved, but with reappearance of symptoms with CSF culture/India ink proof after therapy had been stopped; and
- indeterminate: death due to causes other than CM, and the treatment course was incomplete.

The outcomes were further classified as satisfactory (cure/success or improved) and unsatisfactory (death, relapse or indeterminate).[4] Patients in the satisfactory group were evaluated further for sequelae.

Laboratory methods

In cases of CM, an initial lumbar puncture was performed in each patient and open pressure was recorded. CSF and blood samples were collected for complete blood cell counts and differential counts, glucose, protein, culture and CrAg tests; a CSF staining with India ink was also

performed. The titers of CrAg in serum and CSF were measured using the CALAS® Cryptococcal Antigen Latex Agglutination System (Meridian Bioscience Inc. Cincinnati, Ohio, USA). All laboratory data and microbiological examinations were performed at the CMUH laboratory. All images, including chest film and computed tomography (CT) or magnetic resonance imaging (MRI) images of the brain, were analyzed according to the reports of radiologists.

Statistical analysis

Continuous data were presented as mean and standard deviation or median and range. Continuous variables were calculated using the Student *t* test, and categorical variables were analyzed using the Chi-squared test or Fisher's exact test if any expected value was below five. Kaplan-Meier analysis was used to obtain the survival curve. A *p*-value <0.05 was considered statistically significant.

For outcome analysis, clinical presentations, laboratory data and treatment methods were all analyzed as factors using logistic regression in both groups. Variables with $p < 0.15$ were entered into further multivariate analysis with forward stepwise regression, leaving only variables with $p < 0.05$. All analyses were two-sided and performed using the Statistical Package for the Social Sciences version 17.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Demographic data

During the study period, 72 patients with CM (19 HIV-infected and 53 HIV-uninfected patients) were identified, and the male sex was predominant in both groups (Table 1). Compared to the HIV-uninfected group, those with HIV were younger (mean age: 33.3 years vs. 55.3 years, $p < 0.001$). Individuals in the HIV-infected group all had CD4 counts $<200/mm^3$. The majority of HIV-infected patients had concurrent opportunistic infections (74%) and two patients had AIDS-related malignancies. Among those with HIV, 14 patients had been diagnosed with HIV infection before the presentation of CM and 11 had received antiretroviral therapy (ART) at some point (five patients without regular ART; and six patients with ART for <4 months). The median CD4 count among these 11 patients was $37/mm^3$ (range: 10–140/mm) and their median viral load was 5.3 log copies/mL (range: 2.6–5.7 log copies/mL). Five patients were newly diagnosed with HIV infection on the presentation of CM. In the HIV-uninfected group, 35 patients (66%) had at least one predisposing factor and 18 patients (34%) had more than one factor for CM. The Charlson comorbidity score was significantly higher among the HIV-infected patients than among the HIV-uninfected patients (6.7 vs. 4.7, $p = 0.014$).

Presentations and laboratory data

As shown in Table 2, headache and fever were the most common clinical presentations in patients with CM. More HIV-uninfected patients presented with visual symptoms ($p = 0.031$) and were more likely to present with altered mental status, seizures and auditory symptoms than the HIV-infected patients. Three HIV-infected patients without neurological symptoms were diagnosed after lumbar puncture for previous cryptococcal fungemia or antigenemia. The duration of symptoms was shorter in the HIV-infected patients than in the HIV-uninfected patients (median duration: 10 days vs. 18 days, $p = 0.048$).

In the patients with recorded open pressure during lumbar puncture, increased pressure ($\geq$20 cmH_2O) was

Table 1 Demographics and characteristics

	HIV-infected	HIV-uninfected	*p*
Male/Female, *n*/*n*	17/2	37/16	0.125
Age, mean no. years ± SD[#]	33.3 ± 7.4	55.3 ± 15.7	<0.001*
Predisposing factors			
Corticosteroid use, *n* (%)	0/19 (0%)	13/53 (24.5%)	0.015*
Diabetes mellitus, *n* (%)	0/19 (0%)	12/53 (22.6%)	0.028*
Liver cirrhosis, *n* (%)	0/19 (0%)	12/53 (22.6%)	0.028*
Chronic kidney disease, *n* (%)	0/19 (0%)	9/53 (17.0%)	0.100
Autoimmune disease, *n* (%)	0/19 (0%)	5/53 (9.5%)[a]	0.316
Solid organ transplant, *n* (%)	0/19 (0%)	2/53 (3.8%)	>0.999
Malignancy, *n* (%)	2/19 (10.5%)[b]	6/53 (11.3%)[c]	>0.999
Concurrent opportunistic infections, *n* (%)	14/19 (73.7%)[d]	NA	NA
CD4,/mm^3, median (range)	28.5 (6–140)	NA	NA
HIV viral load, log_{10} copies/mL, mean ± SD[#]	4.84 ± 0.81	NA	NA
Charlson comorbidity index, mean ± SD[#]	6.7 ± 1.1	4.7 ± 3.4	0.014*

CM, cryptococcal meningitis; NA, not applicable; SD, standard deviation.
* $p < 0.05$; [#]student's t test.
[a] Systemic lupus erythematosus (2/53), autoimmune hemolytic anemia (2/53), rheumatoid arthritis (1/53).
[b] Kaposi's sarcoma of the lungs (1/19) and duodenal lymphoma (1/19).
[c] Lymphoma (2/53), hematological malignancy (2/53), prostate cancer (2/53).
[d] Opportunistic infection: *Pneumocystis jiroveci* pneumonia (5/19), candidiasis (4/19), tuberculosis (3/19), nontuberculosis mycobacterium (2/19), herpes simplex (2/19), cytomegalovirus (1/19).

Table 2 Presenting clinical symptoms and laboratory data

	HIV-infected	HIV-uninfected	*p*
Fever, *n* (%)	7/19 (36.8%)	24/53 (45.3%)	0.524
Headache, *n* (%)	11/19 (57.9%)	25/53 (47.2%)	0.114
Altered mental status, *n* (%)	5/19 (26.3%)	25/53 (47.2%)	0.422
Visual symptoms, *n* (%)	0/19 (0%)	11/53 (20.8%)	0.031*
Auditory symptoms, *n* (%)	0/19 (0%)	6/53 (11.3%)	0.331
Seizure, *n* (%)	1/19 (5.3%)	7/53 (13.2%)	0.672
No neurologic symptoms, *n* (%)	3/19 (15.8%)	0/53 (0%)	0.016*
Symptoms duration, days, median (range)[#]	10 (0—60)	18 (3—110)	0.048*
Symptoms duration <30 days	13/16 (81.3%)	32/45 (71.7%)	0.428
Open pressure ≥ 20 cmH2O, *n* (%)	9/13 (69.2%)	26/35 (74.3%)	0.728
CSF WBC,/μL median (range)[#]	2 (0—167)	107 (0—1080)	0.003*
Mononuclear cells predominant, *n* (%)[a]	6/7 (85.7%)	31/41 (75.6)	>0.999
CSF protein, mg/dL median (range)[#]	37 (0—173)	106 (1—4500)	0.054
CSF glucose, mg/dL median (range)[#]	45 (6—65)	35 (1—173)	0.806
CSF culture positive, *n* (%)	17/19 (89.5%)	32/53 (60.4%)	0.020*
CSF CrAg titer ≥1:512, *n* (%)	8/17 (47.1%)	20/47 (42.6%)	0.748
CSF India Ink positive, *n* (%)	12/18 (66.7%)	28/46 (60.9%)	0.667
Cryptococcemia, *n* (%)	10/19 (52.6%)	11/53 (20.8%)	0.009*
Serum CrAg titer ≥1:512, *n* (%)	8/14 (57.1%)	13/34 (38.2%)	0.230
Other site culture positive, *n* (%)	1/19 (5.3%)[b]	4/53 (7.5%)[c]	>0.999
Chest film: mass or nodule lesion, *n* (%)	8/19 (42.1%)	11/49 (20.8%)	0.105
infiltrates, *n* (%)	3/19 (15.8%)	12/49 (24.5%)	0.530
Brain image: hydrocephalus, *n* (%)	4/14 (28.6%)	15/49 (30.6%)	0.553
hypodense lesions, *n* (%)	5/14 (35.7%)	13/49 (26.5%)	0.986
meningeal enhancement, *n* (%)	3/14 (21.4%)	4/49 (8.2%)	0.177

CrAg, cryptococcal antigen.
* $p < 0.05$. [#]student's t test.
[a] Differential counting was only performed as the result of white blood cell count ≥10/μL.
[b] Sputum culture.
[c] Ascites: 1 patient; urine: 3 patients.

common in both groups. Higher pleocytosis ($p = 0.003$) and protein levels ($p = 0.054$) in the CSF were observed among the HIV-uninfected patients than in the HIV-infected patients. No intergroup difference in the proportion of blood CrAg titers ≥1:512, CSF CrAg titers ≥1:512 or positive CSF staining with India ink was observed between the groups. More HIV-infected patients, however, yielded cryptococci in their blood (53% vs. 21%, $p = 0.009$) and CSF (90% vs. 60%, $p = 0.02$) than the other group. The most common presentation on chest films of HIV-infected patients with CM was mass lesion (42%). In the brain images, hydrocephalus, hypodense lesions and meningeal enhancement were commonly reported.

Treatment and outcomes

Excluding the three HIV-uninfected patients who died in the first 7 days, patients from the two groups who received each regimen showed no significant differences (Table 3). The median time to therapy from the time of admission for HIV-infected and -uninfected patients was 2 days (range: 0—10 days) and 6 days (range: 0—45 days), respectively ($p = 0.048$). Fluconazole was prescribed for consolidation and maintenance therapy for all patients with complete induction therapy. For the management of IICP during admission, six HIV-infected patients (32%) with higher open pressure (mean 36.5 ± 7.6 cmH_2O) received temporary drains, which released pressure by performing frequent and smaller amounts of CSF drainage several times a day until the symptoms improved. Other patients (26%) with mild IICP symptoms received lumbar punctures (2.6 ± 0.9 times). Temporary drains were also inserted in 25% of the HIV-uninfected patients (mean open pressure: 39.2 ± 17.2 cmH_2O) and repeated lumbar punctures (mean 2.8 ± 1.3 times) were administrated in 21% of the patients. For long-term CSF drainage, permanent shunt devices were inserted in 26% of the HIV-infected patients and in 19% of the HIV-uninfected patients. Adjuvant corticosteroid therapy was prescribed in about one-third of the patients in both groups.

The mortality rate on day 30 in the HIV-infected patients was lower than that in the HIV-uninfected patients (0% vs. 18.9%, $p = 0.054$), and that on day 90 was significantly lower than that in the HIV-uninfected group (5.3% vs. 30.8%, $p = 0.029$). The Kaplan-Meier survival curves are shown in Fig. 1 (hazard ratio: 4.45; confidence interval [CI]: 1.04—18.98; $p = 0.038$).

One HIV-infected patient and one HIV-uninfected patient were lost to follow-up (Table 4). Antifungal therapy was successfully discontinued for at least 1 year in 13 HIV-infected patients (72%) and 27 HIV-uninfected patients (52%). Three HIV-uninfected patients had

Table 3 Treatment and mortality

	HIV-infected	HIV-uninfected	*p*
Treatment as antifungal therapy			
Amphotericin B alone	10/19 (52.6%)	21/50 (42%)	0.428
Amphotericin B + flucytosine	1/19 (5.3%)	6/50 (12%)	0.664
Lipid amphotericin B alone	0/19 (0%)	1/50 (2%)	>0.999
Lipid amphotericin B + flucytosine	0/19 (0%)	1/50 (2%)	>0.999
Fluconazole alone	7/19 (36.8%)	18/50 (36%)	0.948
Fluconazole + flucytosine	1/19 (5.3%)	3/50 (6%)	>0.999
Treatment for IICP	9/19 (47.4%)	20/53 (37.7%)	0.463
Repeated LP, *n* (%)	5/19 (26.3%)	11/53 (20.7%)	0.749
Numbers of LP, mean ± SD[#]	2.6 ± 0.9	2.8 ± 1.3	0.835
Temporary drains, *n* (%)	6/19 (31.6%)	13/53 (24.5%)	0.550
Permanent shunt device, *n* (%)	5/19 (26.3%)	10/53 (18.9%)	0.521
Adjuvant therapy- corticosteroid	6/19 (31.6%)	17/53 (32.1%)	0.968
Mortality			
Day 30 mortality, *n* (%)	0/19 (0%)	10/53 (18.9%)	0.054
Day 90 mortality, *n* (%)	1/19 (5.3%)	16/52 (30.8%)	0.029*

CM, cryptococcal meningitis; IICP, increased intracranial pressure; LP, lumbar puncture.
*$p < 0.05$. [#]student's t test.

improved outcomes. Five HIV-infected patients had unsatisfactory outcomes, with:

- two patients relapsing (whose CD4 counts were 150/mm^3 and 105/mm^3, respectively, when antifungal therapy was discontinued after maintenance antifungal therapy for 320 days and 1302 days, but both died of CM);
- one death due to CM; and
- two deaths from other causes.

Of the 22 HIV-uninfected patients with unsatisfactory outcome, 16 died of CM. In patients with satisfactory outcomes, visual symptoms were only observed in the HIV-uninfected patients with CM (double vision 3/7; blindness 2/7; blurred vision 2/7). Less than one-third of patients recovered from CM without any sequela.

On the analysis of the indicators of unsatisfactory outcomes (Table 5), we found that an initial CD4 count $\leq$20/mm^3 was a significant indicator of unsatisfactory outcomes in the HIV-infected patients (odds ratio [OR]: 18.0; 95% CI: 1.19-271.46; p = 0.037). On the other hand, corticosteroid use, advanced liver cirrhosis, altered mental status, cryptococcemia, CSF CrAg $\geq$ 1:512 and hydrocephalus, however, were significant indicators of unsatisfactory outcomes in HIV-uninfected group among univariate

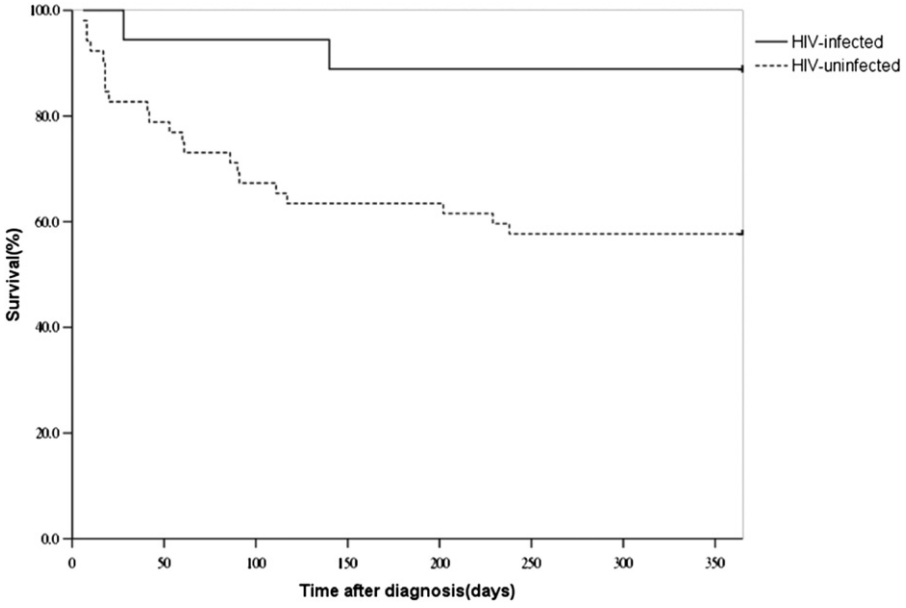

Figure 1. Kaplan-Meier survival curve of HIV-infected patients and HIV-uninfected patients with CM.

Table 4 Treatment outcomes and sequelae

	HIV-infected	HIV-uninfected	*p*
Lost to follow-up, *n* (%)	1/19 (5.3%)	1/53 (1.9%)	0.461
Satisfactory outcomes, *n* (%)	13/18 (72.2%)	30/52 (57.7%)	0.275
Cure/success, *n* (%)	13/18 (72.2%)	27/52 (51.9%)	0.134
Improved, *n* (%)	0/18 (0.0%)	3/52 (5.8%)	0.564
Unsatisfactory outcomes, *n* (%)	5/18 (27.8%)	22/52 (42.3%)	0.275
Fail, *n* (%)	1/18 (5.6%)	16/52 (30.8%)	0.052
Relapse, *n* (%)	2/18 (11.1%)	0/52 (0.0%)	0.063
Indeterminate, *n* (%)	2/18 (11.1%)	6/52 (11.5%)	>0.999
Sequelae, *n* (%)	9/13 (69.2%)	22/30 (73.3%)	>0.999
Headache, *n* (%)	5/13 (38.5%)	3/30 (10%)	0.042*
Dizziness/vertigo, *n* (%)	2/13 (15.4%)	4/30 (13.3%)	>0.999
Hemiparesis, *n* (%)	2/13 (15.4%)	5/30 (16.7%)	>0.999
Visual, *n* (%)	0/13 (0.0%)	7/30 (23.3%)	0.082
Auditory, *n* (%)	1/13 (7.7%)	5/30 (16.7%)	0.649
Seizure, *n* (%)	1/13 (7.7%)	3/30 (10%)	>0.999

CM, cryptococcal meningitis.
*$p < 0.05$.

analysis. Hydrocephalus (OR: 8.7; 95% CI: 2.23—28.98; $p = 0.003$) and CSF CrAg ≥1:512 (OR: 16.2; 95% CI: 1.36—192.02; $p = 0.027$) were significant indicators in the multivariate analysis.

Discussion

Our results demonstrated some differences between HIV-infected and HIV-uninfected patients with CM. HIV-infected patients were significantly younger and easily yielded cryptococci in the blood and CSF. More HIV-uninfected patients presented with visual symptoms, a higher degree of pleocytosis and higher protein levels in the CSF. In addition to receiving repeated lumbar punctures, temporary drains and permanent shunts were frequently administrated in both groups for CSF drainage. HIV-infected patients had significantly lower mortality rate. Finally, different groups showed different indicators of unsatisfactory outcomes.

In contrast to earlier reports,[12,17,18] we found that old age and a high proportion of predisposing factors were common to our HIV-uninfected patients with CM. These findings were also reported by Lee et al from Taiwan.[11] Like others,[3,6,8—11] we found that HIV-infected patients with CM were mostly young males with AIDS status, consistent with the age distribution of HIV-infected patients in Taiwan. Similar to the findings in prior reports,[4,7,11,12] fever and headache were the most common initial symptoms in both groups, but a trend towards more altered mental status was observed in the HIV-uninfected group. Although more HIV-infected patients presented with subtle neurological

Table 5 Indicators of unsatisfactory outcomes after treatment of HIV-infected and HIV-uninfected patients with cryptococcal meningitis

Factors	Univariate		Multivariate	
	OR (95%CI)	*p*	OR (95%CI)	*p*
HIV-infected with CM				
CD4 ≤ 20/mm^3 at CM presentation	18.0 (1.19—271.46)	0.037*	18.0 (1.19—271.46)	0.037*
Altered mental status	8.25 (0.79—85.56)	0.077		
CSF CrAg ≥1:512	9.0 (0.75—108.31)	0.118		
HIV-uninfected with CM				
Age ≥60	2.4 (0.78—7.44)	0.129		
Corticosteroid use	4.5 (1.16—17.41)	0.031*		
Advanced liver cirrhosis	10.86 (1.20—98.47)	0.034*		
Altered mental status	4.29 (1.32—13.88)	0.015*		
CSF CrAg ≥1:512	5.31 (1.51—18.69)	0.009*	16.2 (1.37—192.02)	0.027*
Cryptococcemia	9.69 (1.83—51.35)	0.008*		
Hydrocephalus	13.00 (2.92—57.85)	0.001*	8.7 (2.23—28.98)	0.003*

CM, cryptococcal meningitis; CSF, cerebrospinal fluid; CrAg, cryptococcal antigen.
*$p < 0.05$.

symptoms, the symptom duration in these patients was shorter than that in the HIV-uninfected patients. This may result from clinicians' higher degree of suspicion on opportunistic infection in HIV-confirmed patients.

In agreement with the literatures,[8,11,19] HIV-uninfected patients had a higher degree of pleocytosis and higher protein levels in the CSF, but fewer patients yielded cryptococci in CSF and blood, which might be explained by the higher severity of inflammation and lower fungal burdens in the HIV-uninfected patients.[2,8] Pulmonary cryptococcosis with CNS involvement was identified in more immune-compromised patients[20,21] and concurrent pulmonary infections might be an alternative suspicion in these individuals. Hydrocephalus, hypodense lesions and meningeal enhancement were common presentations in brain images, with varying proportions in the literature [11,18,22] and in our study.

For treatment of CM, amphotericin-B-based therapy is the first choice, as recommended in the guideline,[14,15] but this drug was not used exclusively in our study or others.[8,9,11,17] A higher proportion of predisposing factors and intolerable side-effects may influence clinicians to choose or change a regimen.

For managing IICP, repeated lumbar punctures or surgical drains are suggested as a therapeutic option by the guidelines[15] and literature.[8,11,23,24] In many studies, patients received lumbar punctures rather than drains,[8,11,19,25] as surgeons might be less disposed to perform surgical interventions in HIV-infected patients.[8] In our study, a high proportion of drains or shunts were inserted in both groups, and this may be attributed to the adequate support of neurosurgeons.

A lower mortality rate was observed in HIV-infected patients. Similar results were also noted in a prospective multicenter study, which summarized that a more intact immune response may contribute to increased CNS-related morbidity and overall mortality,[8] but this was not compatible with the findings of other retrospective studies.[11,12] Earlier diagnosis and intensive treatment of IICP in our HIV-infected patients might be the reason for the reduced mortality in our group. High intracranial pressure was an important factor associated with early mortality in HIV-infected patients.[26] In a histopathological study of HIV-infected patients with high open pressure, larger amounts of cryptococci and greater inflammation response were observed over arachnoid granulations, which might impair CSF reabsorption.[27] A prominent immune response in the CNS might contribute to more severe obstruction of CSF outflow and higher mortality, but AIDS patients with CM would have little inflammatory response in the CSF.[8,28] Their IICP is associated with a higher fungal load, and mechanical drainage of CSF may be helpful to decompress the obstruction and remove fungal polysaccharides.[24] In some situations, however, brain herniation might be a concern when a large volume of CSF has been drained through lumbar punctures for extremely high pressure.[29] Frequent lumbar punctures for CSF drainage may increase the suffering of patients and reduce the likelihood of procedure performance by clinicians. In our study, temporary drains and permanent shunts were often used in patients with higher intercranial pressure. None of the HIV-infected patients with IICP died within 10 weeks. High mortality rates were, however, observed at 2 weeks (2/13, 15%) and 10 weeks (7/13, 58%) among the HIV-uninfected patients who had received temporary drains. Although aggressive decompression was performed for these patients, prominent inflammation may have been ongoing, thereby leading to more complications, irreversible brain damage and higher mortality.[8,28] This inference needs to be confirmed by larger multicenter randomized studies.

Prolonged antifungal therapy until immune restoration with ART to reduce relapse was recommended in patients with HIV.[15,21,30] In two patients, however, relapses occurred after antifungal therapy was discontinued although their CD4 counts were $>100/mm^3$ after ART, and this has been previously reported.[31]

Twenty-two HIV-uninfected patients had unsatisfactory outcomes, but without relapse. A combination of brain lesions and inflammation may contribute to most sequelae. Uncontrolled IICP was also mentioned and may be associated with visual or auditory impairment[32,33] but these sequelae were still observed, even after intensive treatment for IICP, and may be attributed to delayed intervention and irreversible damage.

Indicators of unsatisfactory outcomes in HIV-uninfected patients with CM are well described and include corticosteroid use, fungemia, semicoma and initial CSF CrAg $\geq$1:512.[4,16] Liver cirrhosis and advanced age are also associated with poor prognoses for patients with cryptococcemia.[9] In addition, hydrocephalus may be attributed to CSF malabsorption and had poor outcome in patients.[18] We obtained similar results in our multivariate analysis, and these results suggest that this condition may result from prolonged inflammation in the CNS and delayed diagnosis. In HIV-infected patients, a CD4 count $\leq 20/mm^3$ at CM presentation was associated with death or relapse in multivariate analysis. The mean CD4 counts were also significantly different (satisfactory outcomes vs. unsatisfactory outcomes: 16.6 ± 10.1 vs. 65.7 ± 44.7, $p = 0.031$). An initial low CD4 count was an important poor prognostic factor for all AIDS patients, regardless of whether in the pre-ART or post-ART era.[34–36] Patients with extremely low CD4 counts may have a higher risk of early death because of concurrent complicated problems, and they may show a higher probability of contracting new infections during a longer immune restoration period.[36]

There are some limitations in our study. First, the low use of lipid amphotericin B and flucytosine in our patients made it difficult to investigate their influences on outcomes. Second, the variant presentations and prognoses of different serotypes of *Cryptococcus* were documented,[37] but further identification was not pursued in our study. Third, the small sample size in our study may have led to the under-estimation of some of the significant factors.

There are differences in the clinical presentations and mortality rates of CM between patients with and patients without HIV infection. Extremely low CD4 cell counts ($\leq 20/mm^3$) in HIV-infected patients and marked hydrocephalus in HIV-uninfected patients was associated with unsatisfactory outcomes. In addition to these, both cryptococci and intensity of inflammation in the CNS may also play important roles in the pathogenesis of CM. Early diagnosis to prevent the formation of marked hydrocephalus and surgical intervention to drain the cryptococci and release

IICP may improve the outcome of patients with CM, especially those with HIV infection.

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