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A case–control study of human immunodeficiency virus-negative patients with cryptococcemia and cryptococcal meningitis in a Chinese tertiary care hospital during 10 years

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Abstract

Objective: This study aimed to characterize patients with cryptococcemia and compare the clinical features of cryptococcemia and cryptococcal meningitis.

Methods: This was a retrospective, case–control study. We retrospectively identified blood cultures with *Cryptococcus* spp. growth. Controls were hospitalized patients who suffered from cryptococcal meningitis, but did not experience cryptococcemia. Controls and cases were matched by admission date, age, sex, and body weight. Clinical information was analyzed by two independent reviewers.

Results: Eight patients with cryptococcemia and eight patients with cryptococcal meningitis were included. They were all negative for human immunodeficiency virus. The most common underlying disease was primary nephrotic syndrome. All patients presented with fever. The incidence of headache, nausea/vomiting, seizures, and cough/expectoration was significantly lower in patients with cryptococcemia than in those with cryptococcal meningitis. All clinical strains of *Cryptococcus*, except for one, were sensitive to fluconazole, voriconazole, itraconazole, amphotericin B, and flucytosine *in vitro*. The rate of receiving an amphotericin B-containing regimen was significantly higher in patients with cryptococcal meningitis than in those with cryptococcemia. In-hospital mortality was significantly higher in cryptococcemia cases compared with cryptococcal meningitis cases.

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Conclusion: Cryptococcemia is an unusual infection characterized by a high mortality. Cryptococcemia requires early identification and prompt antifungal therapy.

Keywords
Cryptococcemia, *Cryptococcus neoformans*, human immunodeficiency virus, cryptococcal meningitis, amphotericin B, in-hospital mortality

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Introduction

Cryptococcosis is an opportunistic fungal infection caused by the encapsulated yeasts of the *genus Cryptococcus*. This fungus particularly affects immunocompromised individuals, especially among patients with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome. Meningoencephalitis and pulmonary infiltrates are the two most common presentations of cryptococcosis. Cryptococcemia is an uncommon, but severe form, of invasive cryptococcal disease. There have been few studies that described the full characteristics of this fulminant condition, except for some clinical case series.[1–3] Therefore, we conducted this retrospective study to analyze the clinical features and therapeutic outcomes of patients with cryptococcemia in a large tertiary care hospital in China. We aimed to determine the clinical characteristics of this unusual infection. Additionally, a group of patients with meningitis were selected as controls to compare with patients with cryptococcemia.

Methods

Hospital setting

This study was conducted at the First Medical Centre of the Chinese People's Liberation Army General Hospital (PLAGH) (Peking, China). This is a large tertiary care hospital with a 3000-bed capacity and 190,000 inpatients per year in northern China.

Study design

This was a retrospective, consecutively selected, case–control study. We searched the database of the Infection Management and Disease Control Department of the First Medical Centre of the PLAGH for *Cryptococcus* spp. that were isolated from blood during 1 January 2010 to 31 December 2019. The controls were selected from inpatients with cryptococcal meningitis at the same time. The controls were individually matched to each case by admission date, age (within a 5-year range), and sex at a 1:1 ratio. The medical records of these patients were reviewed and analyzed. The duration from disease onset to diagnosis and that from admission to diagnosis were calculated. The clinical data collected included demographics, underlying conditions, interval from collecting blood to reporting, initial clinical symptoms, risk factors, laboratory examinations, sites of involvement, Sequential Organ Failure Assessment (SOFA) score, treatment, and prognosis. All records were analyzed by two independent reviewers.

The clinical isolates were identified by Vitek 2 Compact (bioMérieux SA, Marcy l'Etoile, France) and intergenic spacer sequence analysis. Data were counted only once in blood and cerebrospinal fluid (CSF) or twice from blood in the same patient. Determination of broth dilution minimum inhibitory concentrations of antifungal agents was carried out according to the instructions of the ATB FUNGUS 3 kit (bioMérieux SA) for fluconazole, itraconazole, voriconazole, amphotericin B, and 5-flucytosine. The results of drug susceptibility were determined according to Clinical and Laboratory Standards Institute protocol M27-A3 criteria. Interpretation of minimum inhibitory concentration values was based on epidemiological cutoff values.[4,5]

Ethical statement

This study was approved by the Clinical Trial Ethics Review Committee of the PLAGH on 28 April 2014 (approval number: S2014-036-01). For this type of retrospective study, the institutional review board approved the exemption of informed consent. All personal information of patients was anonymized.

Definitions

Cryptococcemia was defined as one or more positive blood cultures growing *Cryptococcus* spp. in this study. Cryptococcal meningitis was defined as staining of India ink, one or more positive cultures growing *Cryptococcus* spp., or a positive cryptococcal antigen of CSF. The time of diagnosis was defined as the day when a positive result was reported. The SOFA score was calculated on the basis of the results of several assay tests on the day of blood collection. Antimicrobial therapy was considered empirical when an antibiotic was used before the results of an antimicrobial susceptibility test were returned. Pulmonary involvement was considered if the patient had a compatible abnormal computed tomography (CT) scan or chest X-ray presentation. Effective anti-cryptococcal treatment was defined as when a patient received fluconazole, itraconazole, voriconazole, or amphotericin B for longer than 72 hours.

Statistical analysis

Analyses were performed using IBM SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistic data are shown as the median, range, and standard deviation for continuous variables, and as frequency and percentage for categorical variables. The chi-square test was used for comparison of two proportions. All statistical tests were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Cases and controls

During 10 years, we screened 10,211 blood stream infections and 8 patients with cryptococcemia were identified. Eight controls were randomly selected from the 372 patients who were admitted with cryptococcal meningitis. These controls were matched to the eight patients with cryptococcemia at a 1:1 ratio.

Characteristics of the patients

Table 1 shows the characteristics of the patients with cryptococcemia and those with cryptococcal meningitis, including demographic features, underlying diseases, history of immunosuppressive therapy, and close contact with pigeons.

All patients were HIV-negative. The median age of patients with cryptococcemia and those with cryptococcal meningitis was approximately 40 years. Most (62.5%)

Table 1. Demographic and clinical characteristics of patients with cryptococcemia and those with cryptococcal meningitis.

Characteristics	Patients with cryptococcemia (n = 8)	Patients with cryptococcal meningitis (n = 8)	p value
Patients' demographics			
Age (years)	42 ± 13.1 (23–72)	43 ± 11.1 (32–68)	0.98
Male sex	3 (37.5)	3 (37.5)	1.00
BMI (kg/m^2)	22.8 ± 3.47 (17.1–28)	22.5 ± 2.83 (18–26)	0.88
Underlying condition			
Malignancy	1 (12.5)	1 (12.5)	1.00
Lung/kidney transplantation	1 (12.5)	1 (12.5)	1.00
Systemic lupus erythematosus	2 (25)	2 (25)	1.00
Primary nephrotic syndrome	3 (37.5)	4 (50)	0.48
Viral myocarditis	1 (12.5)	–	
Risk factors			
History of pigeon contact	0	0	
Glucocorticoid treatment	6 (75)	6 (75)	1.00
Prednisolone ≥15 mg/day	5 (50)	5 (50)	1.00
Prednisolone <15 mg/day	1 (25)	1 (25)	1.00
Immunosuppressants treatment	2 (50)	2 (50)	1.00
Multiple antibiotic therapy	8 (100)	8 (100)	1.00
Symptoms			
Fever	8 (100)	8 (100)	1.00
Headache	2 (25)	8 (100)	<0.01
Nausea/vomiting	1 (12.5)	7 (87.5)	<0.01
Confusion	4 (50)	6 (75)	0.10
Seizures	1 (12.5)	4 (50)	0.03
Cough/expectoration	1 (12.5)	4 (50)	0.03
Sites of involvement			
Central nervous system	6 (75)	8 (100%)	0.52
Lungs	2 (25)	4 (50)	0.16
Diagnostic related information			
Days from disease onset to diagnosis of cryptococcemia	45.5 ± 15.3 (25–75)	42.5 ± 5.9 (34–54)	0.34
Days from admission to diagnosis of cryptococcemia	15.5 ± 6.02 (7–25)	13.5 ± 3.98 (9–22)	0.65
Results of a cryptococcal antigen test	2/2 (100)	3/3 (100)	1.00
Interval of sample submission to a blood culture report (days)	8 ± 1.73 (4–10)	7.5 ± 1.56 (6–11)	0.78
Polymicrobial bloodstream infection	2 (25)	3 (37.5)	0.47
SOFA score	3.25 ± 3.8 (0–11)	2.5 ± 3.3 (0–10)	0.95
Treatment			
Triazole antifungal agents	6 (75)	8 (100)	0.52
Amphotericin B-containing regimen	1 (12.5)	6 (75)	<0.01
Outcome			
Survived	2 (25)	6 (75)	<0.01

Values are mean ± SD, range, or n (%).

SD, standard deviation; BMI, body mass index; SOFA, Sequential Organ Failure Assessment.

cases occurred in women. The distribution of age, sex, and body mass index was similar between patients with cryptococcemia and those with cryptococcal meningitis.

The most common underlying disease was primary nephrotic syndrome in patients with cryptococcemia cases and those with cryptococcal meningitis, followed by systemic lupus erythematosus. The pattern of underlying conditions was not significantly different between those with cryptococcemia and those with cryptococcal meningitis. All patients presented with fever. The incidence of headache, nausea/vomiting, seizures, and cough/expectoration in patients with cryptococcemia was significantly lower than that in those with cryptococcal meningitis (all $p < 0.05$). All patients received multiple antibiotic therapy and six (75%) in each group received glucocorticoid treatment before identification of cryptococcal infection. No patients had a history of pigeon contact. Polymicrobial bloodstream infection occurred in two (25%) patients with cryptococcemia and in three (37.5%) patients with cryptococcal meningitis.

All patients received a chest CT scan or X-ray examination. Two (25%) patients with cryptococcemia and four (50%) with cryptococcal meningitis showed consolidation and reticular opacity on CT imaging. In cryptococcemia cases, two patients received a brain magnetic resonance imaging (MRI) scan and two received a brain CT scan, but they showed no signs of meningeal infection. Another four patients did not receive any brain imaging examination. One (12.5%) patient received a lumbar puncture examination and *C. neoformans* was identified in CSF culture. Although most patients did not receive a lumbar puncture examination, six showed symptoms of the central nervous system (CNS), such as headache, and confusion due to other reasons/diseases was excluded. These six (75%) patients were considered as having meningeal involvement. All of the patients with cryptococcal meningitis received a brain MRI scan and showed considerable signs of meningeal infection. Two (25%) patients with cryptococcemia and three (37.5%) patients with cryptococcal meningitis received a serum cryptococcal antigen test, respectively, and all of them showed a positive result. The interval from disease onset to diagnosis was approximately 45 days and the interval from admission to diagnosis was approximately 15 days. The interval of a blood culture report was 8 days.

Antifungal susceptibility test

Sixteen clinical isolates were all identified as *C. neoformans* var. *grubii* by intergenic spacer sequence analysis. The results of an antifungal susceptibility test of one isolate were lost. Therefore, only 15 isolates were available for antimicrobial susceptibility analysis. Fifteen clinical strains of *Cryptococcus* were sensitive to fluconazole, voriconazole, itraconazole, amphotericin B, and 5-flucytosine *in vitro* (Table 2).

Treatment and prognosis

Six (75%) patients with cryptococcemia and eight (100%) with cryptococcal meningitis received triazole antifungal agents (Table 1). The rate of receiving an amphotericin B-containing regimen was significantly higher in patients with cryptococcal meningitis than in those with cryptococcemia ($p < 0.01$). Additionally, in-hospital mortality was significantly higher in patients with cryptococcemia than in those with cryptococcal meningitis ($p < 0.01$).

Among patients who had cryptococcemia, one (patient 1) died before establishment of the diagnosis of cryptococcemia and did not receive any antifungal treatment. One patient (patient 6) was diagnosed 1 day before she died. Furthermore, three

Table 2. Susceptibilities of *Cryptococcus neoformans* var. *grubii* to antifungal drugs, and anti-cryptococcal therapy and prognosis of patients with cryptococcemia and those with cryptococcal meningitis.

Patient	Sex	Age (y)	MIC range (mg/L)					Underlying disease	GCS or immunosuppressant therapy	Site of involvement	Anti-cryptococcal therapy before a blood culture report	Anti-cryptococcal therapy after a blood culture report	Prognosis
1	F	41	FCZ	ICZ	VRC	AMB	5-FC	SLE	GCS	Lungs	–	–	Died
2	F	41	<1	<0.125	<0.06	<0.5	<4	VMC	–	CNS	VRC	FCZ	Died
3	F	23	2	<0.125	<0.06	<0.5	<4	PNS	GCS	CNS	–	VRC	Died
4	M	46	2	0.5	0.25	<0.5	<4	PNS	GCS+ISD	CNS	–	VRC	Died
5	F	33	N/A	N/A	N/A	N/A	N/A	SLE	GCS	CNS	–	VRC+5-FC	Died
6	F	72	2	0.25	0.125	<0.5	<4	EOC	–	CNS	–	VRC	Died
7	M	43	2	<0.125	<0.06	<0.5	<4	PNS	GCS	CNS	CAS/VRC	VRC/FCZ	Survived
8	M	36	<1	0.25	0.125	<0.5	<4	LTX	GCS+ISD	lung	VRC/CAS	FCZ+AMB	Survived
9	F	39	2	<0.125	<0.06	<0.5	<4	SLE	GCS+ISD	CNS+lungs	FCZ	FCZ+AMB	Survived
10	M	45	2	<0.125	<0.06	<0.5	<4	KTX	GCS+ISD	CNS+lungs	FCZ	FCZ	Died
11	F	29	<1	0.25	0.125	<0.5	<4	PNS	GCS	CNS	VRC	FCZ+AMB	Survived
12	M	47	2	0.25	<0.06	<0.5	<4	PNS	GCS	CNS	–	FCZ+AMB	Survived
13	F	32	<1	<0.125	<0.06	<0.5	<4	SLE	GCS	CNS+lungs	VRC	FCZ+AMB	Survive
14	F	68	<1	<0.125	0.125	<0.5	<4	CRC	–	CNS	VRC	FCZ	Died
15	M	42	2	0.5	<0.06	<0.5	<4	PNS	GCS	CNS+lungs	FCZ	FCZ+AMB	Survived
16	F	44	2	0.25	0.125	<0.5	<4	PNS	GCS	CNS	FCZ	FCZ+AMB	Survived

The antifungal susceptibility of patient 4 could not be obtained.

y, years; MIC, minimum inhibitory concentration; GCS, glucocorticoid; F, female; FCZ, fluconazole; ICZ, itraconazole; VRC, voriconazole; AMB, amphotericin B; 5-FC, 5-flucytosine; SLE, systemic lupus erythematosus; VMC, viral myocarditis; CNS, central nervous system; PNS, primary nephrotic syndrome; M, male; ISD, immunosuppressive drug; N/A, not available; EOC, endometrioid ovarian cancer; CAS caspofungin; LTX, lung transplantation; KTX, kidney transplantation; CRC, colorectal carcinoma.

patients received antifungal treatment with voriconazole for 10, 14, and 47 days until they died. One patient received combination antifungal treatment with voriconazole and 5-flucytosine. He died after 2 months because of multiple organ failure. One patient received voriconazole and was then treated with fluconazole for 1.5 years. He has been followed for 3 years without relapse. Another patient received combination antifungal treatment with fluconazole and amphotericin B. He is continuing oral fluconazole for maintenance treatment at present. Of the two surviving patients, none developed neurological sequelae.

Among the patients who had cryptococcal meningitis cases, all of them who received an amphotericin B-containing regimen survived.

Discussion

In this study, we retrospectively analyzed the clinical features of eight patients with cryptococcemia and eight patients with cryptococcal meningitis who did not experience cryptococcemia. Cryptococcemia is different from *Cryptococcus,* which is most likely to invade the meninges. Cryptococcemia is a rare blood stream infection. To the best of our knowledge, this is the first study of cryptococcemia reported in North China. The incidence of cryptococcosis in North China is less than that in South China.[6–8] Our study examined the characteristics of patients in whom cryptococcemia was the initial diagnostic proof of cryptococcosis. We also provided information about the microbial features of *Cryptococcus* spp. that were isolated from blood and clinical characteristics of cryptococcemia, which were different from cryptococcal meningitis.

Similar to cryptococcal meningitis, cryptococcemia mostly develops in immunocompromised hosts, especially in patients with late-stage HIV infection.[1] In addition to HIV infection, solid organ transplantation, immunosuppressive medication treatment, chronic renal failure, hematological malignancy, severe hepatic diseases, and rheumatological disorders can also predispose individuals to cryptococcemia.[1–3] In our study, most patients had predisposing conditions. Most patients had also been treated with corticosteroids or immunosuppressants for various reasons before identification of cryptococcal infection. Notably, one patient with cryptococcemia and viral myocarditis was apparently immunocompetent in this study. The potential of *Cryptococcus* spp. to cause endovascular infection and endocarditis is low. Interestingly, cryptococcosis occurs more frequently in immunocompetent patients than in immunocompromised patients in China.[9–12] The mechanism of this finding is unclear. There might be immune function abnormalities in patients with cryptococcosis that cannot be recognized by laboratory tests at present. Notably, the patient with cryptococcemia and viral myocarditis suffered from multiple deep vein catheterizations, which does not exclude the probability of iatrogenic bloodstream infection. *Cryptococcus* is common in excretions from certain birds, such as pigeons. None of the patients in our study had a history of pigeon contact. Many clinicians only consider the diagnosis of cryptococcosis based on the contact history with pigeons, which greatly delays the diagnosis of cryptococcosis.

The symptoms of cryptococcemia are usually nonspecific and atypical. These symptoms are sometimes mistaken for manifestations of primary disease. This problem poses considerable diagnostic challenges for clinicians. Fever was found in all eight patients with cryptococcemia in our study. Because of the unique propensity of CNS invasion of *Cryptococcus*, approximately 80% of patients with cryptococcemia are complicated by meningitis.[1,13]

Clinical manifestations of CNS involvement include headache, nausea/vomiting, altered consciousness, and signs of meningeal irritation. Interestingly, in our study, most patients with cryptococcemia lacked typical symptoms of headache and nausea/vomiting. Four (50%) patients with cryptococcemia had subtle confusion. The incidence of headache, nausea/vomiting, seizures, and cough/expectoration was significantly higher in patients with cryptococcal meningitis than in those with cryptococcemia. The mild symptoms of headache and nausea/vomiting in cryptococcemia cases may be ignored in medical daily inquiries or not described in the medical records. Therefore, the incidence of symptoms of meningitis in patients with cryptococcemia is likely to be underestimated.

The imaging manifestations in the early stage of cryptococcal meningitis were not obvious in our study. MRI/CT scans of the brain were performed in four patients with cryptococcemia in our study. None of them showed evidence of cryptococcal infection. Therefore, negative brain imaging cannot preclude development of disseminated cryptococcal infection. Rather than an imaging examination, a test of cryptococcal polysaccharide capsular antigen in serum or CSF is highly sensitive and specific for disseminated *Cryptococcus* infection.[14] In the current study, two (25%) patients with cryptococcemia and three (37.5%) patients with cryptococcal meningitis received a serum cryptococcal antigen test, respectively, and all of them showed a positive result. This is a good method for early diagnosis of cryptococcosis. Additionally, the cryptococcal antigen test took less time than a blood culture of *Cryptococcus*. Introduction of the point-of-care lateral flow cryptococcal antigen assay has greatly facilitated a lower cost and better sensitivity than earlier serological tests.[15,16] However, regrettably, the serum cryptococcal antigen assay was not performed in most patients in our study. Therefore, the diagnosis of opportunistic infections, including cryptococcosis, should be considered as early as possible in immunocompromised patients. Performing a serum cryptococcal antigen test in routine diagnostic work-up in high-risk individuals might be necessary, especially with fever of unknown origin.

C. neoformans and *C. gattii* are the two main pathogenic cryptococcal species in humans.[16] The 16 *Cryptococcus* spp. isolates in our study were all *C. neoformans* var. *grubii*. These data are consistent with a multicenter investigation, which showed that *C. neoformans* var. *grubii* accounted for 97.1% of all the *C. neoformans* spp. complex in China.[17] In our study, 15 clinical strains of *Cryptococcus* were sensitive to fluconazole, voriconazole, itraconazole, amphotericin B, and 5-flucytosine *in vitro*. These results provide information about the microbial features of *Cryptococcus* spp. isolated from blood. However, drawing conclusions about the overall microbiology and antifungal drug sensitivity is difficult because of the small sample size.

Cryptococcemia is an extremely severe form of invasive cryptococcosis with a poor prognosis. Cryptococcemia showed a high mortality rate of 30% to 40% in previous studies.[1,2,18] Effective antifungal therapy is the cornerstone for treating disseminated cryptococcosis, including cryptococcemia. Induction therapy is recommended for disseminated cryptococcosis using fungicidal regimens, such as a polyene and flucytosine, followed by consolidation and maintenance therapy using suppressive regimens with fluconazole.[19] The other triazoles, including itraconazole, voriconazole, and posaconazole, are active against cryptococcal isolates *in vitro*. However, because of the differences in bioavailability,

CSF permeability, drug interactions, cost-benefit ratio, and lack of strong studies on cryptococcosis, these agents are not recommended as first-line agents for consolidation or maintenance therapy. These agents were used clinically in salvage situations. Furthermore, echinocandins have no *in vivo* activity against *Cryptococcus* species. In our study, six patients with cryptococcemia received antifungal treatment. However, only one patient received an amphotericin B-containing regimen and one received a flucytosine-containing regimen. Most patients did not receive appropriate antifungal therapy. However, six patients with cryptococcal meningitis received an amphotericin B-containing regimen and they all survived. These findings suggest that amphotericin B should be the first choice as long as the bloodstream is involved (even if there is no other site involved). Most clinicians agree that voriconazole is an effective treatment for cryptococcosis, but neglect it being insufficient for treating disseminated cryptococcosis. Additionally, many clinicians prefer conservative regimens rather than being concerned about the side effects of amphotericin B and flucytosine. Both of these reasons led to the inadequacy of early induction of treatment of the disease in our study.

Although cryptococcemia itself may have contributed to the fatal outcome, we believe that the delay in diagnosis and improper treatment were the main contributing factors in our study. Patients who were first diagnosed by blood cultures had mild and neglected symptoms of meningitis, which may have led to the delayed diagnosis. These patients also had less access to effective antifungal treatment, which caused a poor outcome. However, patients with cryptococcal meningitis presented with more serious clinical symptoms than those with cryptococcemia. This situation might have caused vigilance and attention by doctors for these patients, and therefore, more active treatment was performed. Consequently, the clinical prognosis of patients with cryptococcal meningitis was relatively good.

Our findings suggest the need to identify this rare infectious disease and its clinical presentations at an early stage, especially in immunocompromised patients. These results further highlight the importance of prompt aggressive interventions in improving the outcome of cryptococcemia. However, our study has several limitations. Although we collected 10-year data of cryptococcemia in the PLAGH, the sample size of this study was small because of the low incidence of cryptococcemia. Another limitation is the lack of use of latex agglutination and the lateral flow assay for determination of cryptococcal polysaccharide capsular antigen. Furthermore, the antifungal susceptibility of *Cryptococcus* may vary among different hospitals, especially those in different regions. Therefore, prospective studies involving a larger sample size and more hospitals are required in the future to provide more information about cryptococcemia.

Conclusion

This study identified the prevalence of *C. neoformans* var. *grubii* causing cryptococcemia in Peking, North China. This rare infection usually occurs in immunocompromised patients and is characterized by a high mortality rate. The diagnosis of cryptococcemia should be considered early in these patients, especially with a fever of unknown origin. A cryptococcal polysaccharide capsular antigen test should be more commonly used in these patients presenting with a fever of unknown origin. Insightful, effective, anti-cryptococcal therapy is crucial for the prognosis of patients with cryptococcemia.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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