Cryptococcaemia: clinical features and prognostic factors

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Summary

Background: Limited data are available on the clinical significance of cryptococcaemia, which occurs in 10–30% of patients with cryptococcal diseases.

Aim: To describe the clinical features of cryptococcaemia and identify its prognostic factors.

Study design: Retrospective cohort study.

Methods: All adult patients with Cryptococcus neoformans isolated from blood culture at the National Taiwan University Hospital, Taipei, 1981–2001, were included. Demographic and clinical information was obtained from medical records.

Results: Fifty-two patients were diagnosed and treated for cryptococcaemia. Acquired immunodeficiency syndrome (24/52, 46%), immunosuppressive therapy (12/52, 23%) and decompensated liver cirrhosis (11/52, 21%) were the three major predisposing conditions. Forty-two patients (81%, n = 52) had sepsis, including four patients with septic shock, when blood cultures were obtained. Of the 38 patients in whom lumbar puncture was done, cerebrospinal fluid culture showed meningeal involvement in 32 (84%). The 30-day fatality rate was 37%. Liver cirrhosis, septic shock at presentation, an initial APACHE II score > 20, age > 60 years and female gender were associated with mortality under univariate analysis. Starting antifungal therapy within 48 h after blood culture was associated with improved survival. Under multivariate analysis, liver cirrhosis remained a strong independent predictor of mortality at 30 days after blood culture (HR 16.3, 95% CI 2.6–101.7, p = 0.003).

Discussion: Patients with cryptococcaemia have a high risk of mortality within 30 days. Sepsis and meningeal involvement are common. Those with liver cirrhosis have a particularly poor prognosis.

Introduction

Cryptococcus neoformans, an encapsulated fungus found worldwide as a soil organism, is an important opportunistic pathogen causing chronic meningitis in immunocompromised patients.1–11 C. neoformans can be isolated from blood in 10–30% of patients with cryptococcal disease.8–11 Limited data are available about the clinical significance of cryptococcaemia. Among patients with cryptococcal meningitis, the presence of cryptococcaemia is associated with a poor prognosis.11,12 Besides some anecdotal case reports,13–18 the only clinical study focused on cryptococcaemia was a case series involving 15 patients diagnosed and treated before 1983.19 It concluded that the progress of underlying diseases and the outcome of concomitant infections due to other pathogens were more important determinants of survival than the cryptococcaemia itself.19 Thus, the clinical significance of cryptococcaemia

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remains uncertain. There are no data about the clinical features and natural history of cryptococcaemia in the era of acquired immunodeficiency syndrome (AIDS). It is also unclear whether cryptococcaemia, like candidaemia, can cause sepsis and septic shock.

To clarify the clinical significance of cryptococcaemia, we sought to characterize its clinical features and outcome through a retrospective cohort study. Survival analysis was used to identify the determinants of prognosis.

Methods

Patients

All adult patients (aged ≥ 16 years) with C. neoformans isolated from blood culture at National Taiwan University Hospital (NTUH) (Taipei, Taiwan) from January 1981 through December 2001 were included in this retrospective cohort study. NTUH is a university-affiliated medical centre with a 2000-bed capacity that provides both primary and tertiary referral care, including a bone-marrow and solid-organ transplantation service. The numbers of annual admissions increased steadily from 18 729 in 1981 to 56 341 in 2001. Culture and identification of C. neoformans were by standard microbiological methods. All fungal blood culture samples were routinely incubated for 30 days before ‘no growth’ was reported. The automatic fungal blood culture system BACTEC 9240 was used from 1999 onwards to facilitate rapid reporting. The list of patients in whom C. neoformans had been isolated from blood was obtained from the computer database of clinical fungal isolates.

Data

In each of the included cases, demographic and clinical information, including age, sex, underlying diseases, initial symptoms, physical and laboratory findings, treatment, clinical course, concomitant infections, and outcome, were obtained from medical records.

Definitions

The severity of infection on the day of blood culture sampling was assessed by both systemic inflammatory responses syndrome and Acute Physiology and Chronic Health Evaluation (APACHE) II score. Sepsis and septic shock were defined according to the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee definition. A scoring system, which assigns 2 points to patients with septic shock, 1 point to those with sepsis but without shock, and 0 points to those without sepsis, was used to evaluate the severity of sepsis. APACHE II scores were calculated by the original scoring system, but to enhance the applicability of the scoring system to the present patient group, a modification allowed zero points to be assigned to the items ‘PaO2’ and ‘pH’ if the attending physicians did not perform arterial blood gas analysis due to an absence of cyanosis or respiratory distress. The severity of underlying disease was classified as non-fatal, ultimately fatal, or rapidly fatal, according to McCabe-Jackson criteria. AIDS was defined according to the Centers for Disease Control and Prevention (CDC) 1993 revised classification system for human immunodeficiency virus (HIV) infection.

Statistical analysis

Day 1 was defined as the day of the first positive blood culture sampling of C. neoformans. A Kaplan-Meier survival curve was used to characterize the survival probability of patients with cryptococcaemia after day 1. Survival of patients with different demographic and clinical factors was analysed using Cox’s proportional hazards model. The proportions and medians were compared by Fisher’s exact test and the Mann-Whitney test, respectively. The statistical software used for computation was S-PLUS 2000 for Windows (MathSoft). Two-tailed p values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 52 adult patients with cryptococcaemia were diagnosed during the period from January 1981 through December 2001. The temporal trend over the years was shown in Figure 1. Numbers of cases increased in 1990s, due to both the increase of AIDS patients and the increase in service amount. There was no statistically significant change in incidence of non-HIV cases per 10 000 admissions over the years (data not shown). The 52 patients accounted for 23% (52/228) of the total 228 patients with cryptococcosis diagnosed during the study period.

Of the 52 patients, 24 (46%, n = 52) were HIV-infected, and all of them already had AIDS and a CD4 count < 200/μl when cryptococcaemia occurred. None was under prophylaxis with fluconazole or other antifungals regimen. These 24 accounted for 60% (24/40) of the total 40
HIV-infected patients with cryptococcosis diagnosed during the study period. Of the remaining 28 patients, immunosuppressive therapy (12 patients), and decompensated liver cirrhosis (11 patients) were the two major predisposing conditions. The regimens of immunosuppressive therapy (Table 1) included cytotoxic chemotherapy for leukaemia or lymphoma, and corticosteroid therapy for autoimmune diseases and other disorders. None of the patients receiving immunosuppressive therapy was a recipient of a bone-marrow or solid-organ transplant. All of the patients with liver cirrhosis were in Child class B or C, and had physical signs of portal hypertension. HIV-infected patients (median age 34 years, range 25–57) were significantly younger than non-HIV-infected patients (median age 52 years, range 18–88) ($p = 0.001$, Mann-Whitney test). By McCabe-Jackson criteria, the severity of underlying diseases was classified as ultimately fatal in 47 patients, and non-fatal in five patients. Demographic features and underlying medical conditions of these patients are summarized in Table 1.

**Clinical manifestations**

Forty-two patients (81%, $n = 52$) had sepsis, including four with septic shock, when blood cultures were obtained. Eighteen (43%, $n = 42$) had concomitant symptoms or signs of meningitis, including headache, vomiting, altered consciousness, neck stiffness or seizures. Of the ten patients without sepsis at presentation, the main initial manifestations were symptoms or signs of meningitis ($n = 7$), fever $\geq 38$ °C ($n = 2$), and pleural effusion on chest X-ray ($n = 1$). There was no significant difference in clinical manifestations between HIV-infected and non-HIV-infected patients. Patients with liver cirrhosis (3/11, 27%) were more likely to have septic shock at presentation than patients without liver cirrhosis (1/41, 2%) ($p = 0.03$, Fisher’s exact test). The clinical manifestations were summarized in Table 2.

**Meningeal and extrameningeal involvement**

Meningeal involvement was confirmed by cerebrospinal fluid culture in 32 patients (84%, $n = 38$) of the 38 patients who had received lumbar puncture. Of the 20 (38%, $n = 52$) with abnormal chest X-ray, *C. neoformans* was isolated from pleural

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of 52 patients with cryptococcaemia</th>
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<tr>
<td></td>
<td>HIV-infected ($n = 24$)</td>
</tr>
<tr>
<td><strong>Demographic features</strong></td>
<td></td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>24:0</td>
</tr>
<tr>
<td>Age* (years)</td>
<td>34 (25–57)</td>
</tr>
<tr>
<td><strong>Predisposing conditions (n)</strong></td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>24 (100%)</td>
</tr>
<tr>
<td>Immunosuppressive therapy**</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Decompensated liver cirrhosis</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Others***</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>None</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Median (range). **Cytotoxic chemotherapy for leukaemia ($n = 3$) or lymphoma ($n = 2$); and corticosteroid therapy for systemic lupus erythematosis ($n = 3$), rheumatoid arthritis ($n = 1$), panniculitis ($n = 1$), bronchial asthma ($n = 1$) or myelofibrosis ($n = 1$). ***Bronchiectasis and adrenal insufficiency ($n = 1$), diabetes mellitus and end-stage renal disease ($n = 1$).
effusion in four, and from sputum in another two.

Two patients had culture-proved cryptococcal peritonitis, and both had pre-existing liver cirrhosis. Another three patients had C. neoformans isolated from urine. One patient developed culture-proved cryptococcal lymphadenitis on the neck. There was no significant difference in the proportions of meningeal and extrameningeal involvement between HIV-infected and non-HIV-infected patients.

**Initial antifungal therapy**

Seven (13%, n = 52) patients, including five patients with liver cirrhosis, one patient with AIDS, and one patient receiving corticosteroid therapy for autoimmune disease, died before blood culture results became available and never received antifungal therapy. All of the remaining 45 patients were treated with appropriate antifungal therapy. The initial regimens included amphotericin B 0.7–1.0 mg/kg/day alone (24 patients), amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day (1 patient), amphotericin B 0.8 mg/kg/day plus intravenous fluconazole 400 mg/day (1 patient), intravenous fluconazole 400 mg/day alone (11 patients), amphotericin B 0.3 mg/kg/day plus flucytosine 100–150 mg/kg/day (5 patients), amphotericin B 0.4–0.5 mg/kg/day alone (2 patient), and intravenous fluconazole 400 mg/day plus flucytosine 100 mg/kg/day (1 patient). HIV-infected patients (18/24, 75%) were more likely to receive high-dose (0.7–1.0 mg/kg/day) amphotericin-B-based regimens than were non-HIV-infected patients (7/28, 25%) (p < 0.001, Fisher’s exact test). Only one of the patients with liver cirrhosis received a high-dose amphotericin-B-based regimen.

**Timing of antifungal therapy**

The median interval from blood culture sampling to reporting was 4 days (range 3–17 days). The median interval from blood culture sampling to the start of antifungal therapy was 2.5 days (range 0–17 days). The antifungal therapy was started empirically in 15 patients before the blood culture results were reported, under the presumptive diagnosis of cryptococcal meningitis. Twenty-three patients (44%) received antifungal therapy within 48 h after blood culture. Patients with liver cirrhosis (1/11, 9%) were significantly less likely to receive antifungal therapy within 48 h than were those without cirrhosis (22/41, 54%) (p = 0.014, Fisher’s exact test). In contrast, patients with HIV infection (14/24, 58%) were more likely, although not significantly so, to receive antifungal therapy within 48 h than non-HIV-infected patients (9/28, 32%) (p = 0.09, Fisher’s exact test).

**Duration of antifungal therapy**

Intravenous antifungal therapy was continued until a successful response to treatment was obtained, if the patient survived. The median duration of intravenous antifungal therapy was 21 days (range 2–183 days). After discontinuation of intravenous antifungal therapy, prolonged oral fluconazole 400 mg/day was prescribed for 18 of the HIV-infected patients and 13 of the non-HIV-infected patients. The median duration of the entire course (intravenous plus oral) of antifungal therapy in patients who survived >14 days was 146 days (range 14–1320 days). There was only one case of relapse in an HIV-infected patient during the one-year follow-up period, which was successfully treated with intravenous amphotericin B followed by oral fluconazole.

**Concomitant infections due to other pathogens**

Four HIV-infected patients had concomitant non-typhoid Salmonella bacteraemia when blood culture was obtained. None had septic shock. The Salmonella bacteraemia was successfully treated with third-generation cephalosporins in all of these patients. One AIDS patients had concomitant miliary tuberculosis, and another AIDS patient had concomitant pulmonary tuberculosis. Two non-HIV-infected patients, both of whom developed respiratory failure after the onset of cryptococcaemia,
acquired methicillin-resistant *Staphylococcus aureus* pneumonia in intensive care units. Both patients received vancomycin in addition to antifungal therapy, but one died on day 7, and the other died on day 8.

**Outcome and prognostic factors**

The Kaplan-Meier survival curve for all 52 patients is shown in Figure 2. Acute mortality was high: case fatality rate was up to 31% (16/52) on day 14, and as high as 37% (19/52) by day 30. The majority of deaths (19/28, 68%) occurred within 30 days after blood culture. Of the three main groups of patients, those with liver cirrhosis had a particularly high 30-day mortality (9/11, 82%), compared to patients with AIDS (5/24, 21%) or patients receiving immunosuppressive therapy (4/12, 33%). Of the patients who survived >30 days, four had persistent neurological sequelae secondary to cryptococcal meningitis: two had hydrocephalus and sensorineural hearing loss, one diplopia and impaired mentality, and one both vision and hearing loss.

In the univariate analysis, predictors of 30-day mortality included liver cirrhosis (p = 0.003), septic shock at presentation (p = 0.009), an initial APACHE II score ≥ 20 (p < 0.001), age ≥ 60 years (p = 0.001) and female gender (p = 0.007) (Table 3a). HIV-infected patients had a lower 30-day mortality than non-HIV-infected patients (21% vs. 50%, p = 0.037). Culture-proven meningeal involvement, concomitant infection due to other pathogens, ultimately fatal underlying diseases by McCabe-Jackson classification and use of immunosuppressive therapy were not associated with 30-day mortality. Start of antifungal therapy within 48 h after blood culture was associated with improved survival (30-day mortality 16% vs. 48%, p = 0.02). Analysis of the subgroup of patients receiving antifungal therapy (n = 45) showed that 30-day mortality was 23% (6/26) in patients treated with amphotericin B 0.7–1.0 mg/kg/day; lower than the 31% (6/19) in patients treated with amphotericin B 0.3–0.5 mg/kg/day or fluconazole 400 mg/day, although the difference was not statistically significant (p = 0.73).

In the multivariate analysis, after adjusting for the effect of other variables, liver cirrhosis remained a strong independent predictor of 30-day mortality (HR 16.3, 95% CI 2.6–101.7, p = 0.003). Severity of sepsis was another strong independent predictor of 30-day mortality (HR 7.0, 95% CI 1.6–23.8, p = 0.010). HIV-infection was no longer associated with a lower 30-day mortality after adjusting for the effect of age, timing of antifungal therapy, severity of sepsis syndrome, and other variables. Female gender also became non-significant in the multivariate analysis. The results of the multivariate analysis are summarized in Table 3b.

**Discussion**

This study shows that patients with cryptococcaemia have a high acute mortality rate, especially those with liver cirrhosis. The 14-day mortality was up to 31%, much higher than the 11% among patients with cryptococcal meningitis from the same institute during the same study period. Furthermore, as many as 13% of the patients died before culture results became available. Beginning antifungal therapy within 48 h of blood culture was associated with an improved survival. These findings suggest that cryptococcaemia signifies a fulminant form of cryptococcal disease, and requires early diagnosis and prompt antifungal therapy.

Sepsis, as defined by the 1992 American College of Chest Physicians and Society of Critical Care Medicine Consensus, was the most common manifestation of cryptococcaemia. In the majority

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**Table 3a** Univariate analysis of factors predicting 30-day mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis</td>
<td>0.003*</td>
</tr>
<tr>
<td>Septic shock at presentation</td>
<td>0.009*</td>
</tr>
<tr>
<td>APACHE II score ≥ 20</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Concomitant infection due to other pathogens</td>
<td>0.460</td>
</tr>
<tr>
<td>McCabe-Jackson classification</td>
<td>0.500</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.007*</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>0.001*</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>0.560</td>
</tr>
<tr>
<td>Lack of antifungal therapy within 48 h</td>
<td>0.020*</td>
</tr>
</tbody>
</table>

*Statistically significant.
of patients, sepsis could not be attributed to concomitant infection by other pathogens. *C. neoformans* was the only identifiable pathogen among 38 out of the 42 patients who had sepsis at presentation. Further, none of the four patients who developed septic shock at presentation had concurrent bacteraemia. These observations indicate that, as with bacteraemia or candidaemia, cryptococcaemia is able to induce systemic inflammatory responses, including septic shock.

In addition to sepsis, concurrent cryptococcal meningitis with increased intracranial pressure and cerebral herniation may also contribute to early mortality.²⁶,²⁷ Although in this study culture-proved meningitis was not associated with 30-day mortality, it should be noted that the impact of meningeal involvement on prognosis may be underestimated, because lumbar puncture was not performed in the seven patients who died before blood culture reports became available. Among those who did receive lumbar puncture, as many as 82% had meningeal involvement. The percentage of meningeal involvement among patients who died without lumbar puncture is unknown, because autopsy was not performed in these cases. Nevertheless, concurrent meningeal involvement should be routinely sought in patients with cryptococcaemia; and increased intracranial pressure, if present, should be aggressively managed.

Since this was a retrospective study, not every non-HIV-infected patient had their HIV status checked, especially those diagnosed in the early 1980s and those who died before their blood culture result became available. However, none of the 28 patients classified as non-HIV-infected had other AIDS-defining illnesses such as *Pneumocystis carinii* pneumonia, Kaposi’s sarcoma, oesophageal candidiasis or wasting syndrome, before or after the episode of cryptococcaemia. Thus, the likelihood of undetected HIV infection is low in these patients.

Patients with AIDS or under immunosuppressive therapy are at increased risk for development of cryptococcal diseases.¹⁻⁶ It is worth noting that, in our study, liver cirrhosis was the predisposing condition in up to 21% of the patients when cryptococcaemia developed. Liver cirrhosis has been identified as a predisposing factor for cryptococcal peritonitis.²⁸ Patients with decompensated liver cirrhosis have impaired host defence in several important aspects, including deficiency of serum complement;²⁹ defects in chemotaxis;³₀ and lymphocyte hyporesponsiveness.³¹ Portal-systemic shunting of blood flow, which bypasses hepatic Kuppfer cell scavenging, also facilitates the entry of bowel organism into the systemic circulation in these patients. The impaired host defence and portal-systemic shunting are likely to predispose patients with liver cirrhosis to the invasion of *C. neoformans* from the respiratory or gastrointestinal tract into bloodstream.

Transplant recipients under immunosuppressive regimens are another group susceptible to cryptococcal diseases,¹ although cyclosporine, a immunosuppressive agent commonly used in transplant recipients, has an anticytotoxic effect via its inhibition of fungal calcineurin.³² The use of cyclosporine in these patients may therefore have provided some protective effect against *C. neoformans*. As of the end of December 2001, 164 heart transplantation (since 1987), 71 liver transplantation (since 1988), 29 lung transplantation (since 1995), and more than 500 kidney transplantation (since 1968) had been performed at our hospital. Cyclosporine is almost always used as a component in the immunosuppressive regimens for these patients. Interestingly, none of our patients were transplant recipients. This is in contrast to the report that two cases of cryptococcaemia, accounting for 5% of bloodstream infections, occurred in 136 consecutive liver transplant recipients receiving tacrolimus-based immunosuppression.³³,³⁴

Under survival analysis, the 30-day mortality for cryptococcaemia was much higher in patients with liver cirrhosis than in those with AIDS. Patients with liver cirrhosis were also more likely to develop septic shock when cryptococcaemia occurred. Multiple factors may have adversely affected the outcome of cryptococcaemia among patients with liver cirrhosis. Patients with AIDS were typically younger, and more likely to receive prompt

### Table 3b Multivariate analysis of factors predicting 30-day mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis</td>
<td>16.3 (2.6–101.7)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Severity of sepsis</td>
<td>7.0 (1.6–23.8)</td>
<td>0.010*</td>
</tr>
<tr>
<td>APACHE II score ≥ 20</td>
<td>0.8 (0.2–3.5)</td>
<td>0.720</td>
</tr>
<tr>
<td>Concomitant infections</td>
<td>1.8 (0.5–7.3)</td>
<td>0.390</td>
</tr>
<tr>
<td>McCabe-Jackson classification</td>
<td>1.9 (0.2–23.7)</td>
<td>0.620</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.5 (0.3–6.2)</td>
<td>0.680</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>3.7 (0.9–19.6)</td>
<td>0.089</td>
</tr>
<tr>
<td>HIV infection</td>
<td>3.8 (0.4–39.4)</td>
<td>0.270</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>4.1 (0.7–24.1)</td>
<td>0.110</td>
</tr>
<tr>
<td>Antifungal therapy within 48 h</td>
<td>0.3 (0.07–1.2)</td>
<td>0.095</td>
</tr>
</tbody>
</table>

*Statistically significant.
diagnosis and therapy due to the alertness of physicians. In contrast, patients with liver cirrhosis were older, and less likely to receive prompt antifungal therapy because physicians often did not include cryptococcal infection in the list of differential diagnosis in this group of patients. However, even after adjusting for the effect of age, timing of antifungal therapy, initial APACHE II score and initial severity of sepsis syndrome, liver cirrhosis remains a strong independent predictor of 30-day mortality. It remains to be clarified whether the immune deficits in liver cirrhosis have a more profound impact than those of AIDS on the host defence mechanism against cryptococcaemia.

The optimal antifungal regimen for cryptococcaemia remains unclear, due to a lack of systematic research. Our patients, with or without concurrent meningitis, were usually treated with regimens for cryptococcal meningitis. The regimens were heterogeneous, however, due changes in therapeutic recommendation over time. In the past 20 years, the recommended therapy for cryptococcal meningitis has evolved from amphotericin B 0.3 mg/kg/day plus flucytosine 150 mg/kg/day to amphotericin B 0.7–1.0 mg/kg/day plus flucytosine 100–150 mg/kg/day plus flucytosine 150 mg/kg/day to amphotericin B 0.3 mg/kg/day plus flucytosine 100–150 mg/kg/day and initial severity of sepsis. Further prospective randomized study is needed to determine the optimal therapeutic regimen for cryptococcaemia.

In conclusion, patients with cryptococcaemia have a high risk of acute mortality, and require early diagnosis and prompt antifungal therapy. AIDS, immunosuppressive therapy, and liver cirrhosis are the three main predisposing conditions. Sepsis syndrome and meningeal involvement are common. Those with liver cirrhosis have a particularly grave prognosis, even after adjusting for the effect of age, timing of antifungal therapy, initial APACHE II score, and severity of sepsis.

References


