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Andrej Spec
Washington University School of Medicine

Krunal Raval
St. Lukes Hospital

William G. Powderly
Washington University School of Medicine

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MAJOR ARTICLE

End-Stage Liver Disease Is a Strong Predictor of Early Mortality in Cryptococcosis

Andrej Spec,[1] Krunal Raval,[2] and William G. Powderly[1]

[1]Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, and [2]Department of Medicine, St. Lukes Hospital, St. Louis, Missouri

Background. Cryptococcosis in the setting of end-stage liver disease (ESLD) has been associated with high mortality. We sought to compare the outcome of cryptococcal disease in patients with ESLD to that of human immunodeficiency virus (HIV)-positive patients and to those patients without HIV or ESLD.

Methods. We assembled a retrospective cohort of 232 consecutive cases of cryptococcosis in our institution, from 2002 to 2014, inclusively. We analyzed the cases for comorbidities, type of infection, and survival. Data were analyzed with *t* tests, Fishers Exact test, and Kaplan-Meyer analysis.

Results. Twenty-five (10.8%) patients with cryptococcal infection had concomitant ESLD; of these, 5 (20%) presented with peritonitis. Most (17 of 25, 68%) did not have any other cause of immunocompromise that has been more classically associated with cryptococcosis. Patients with ESLD had a significantly higher mortality than HIV-positive patients and HIV-negative patients without ESLD (HIVNE) (80% vs 13.6% and 22.7%, respectively; $P < .001$). In addition, fatal outcome in ESLD patients occurred more rapidly than in HIVNE patients, with a median survival of 6 days (vs 17), despite a comparable time to diagnosis (6.2 vs 6.6 days).

Conclusions. Cryptococcosis is an important morbidity in patients with ESLD. Patients with ESLD who are infected with *Cryptococcus* have a high and rapid mortality. This suggests that a high level of vigilance for cryptococcal infection should be kept in patients with ESLD.

Keywords. adult; *Cryptococcus*; end-stage live disease (ESLD); prognosis.

Cryptococcosis is one of the most common and important invasive fungal infections worldwide, infecting predominantly immunocompromised patients. Known predisposing conditions include receipt of an organ transplant, being positive for human immunodeficiency virus (HIV), and other causes of immunocompromise, such as use of glucocorticoids [1, 2]. Worldwide, it is estimated that there are 1 million cases and 625 000 deaths annually due to cryptococcal meningitis in HIV-infected individuals alone [3]. In the United States, other predisposing conditions account for the majority of cases of cryptococcosis [4], suggesting that the burden of disease is considerable.

Although considerable improvements have been made to treatment, mortality associated with cryptococcosis is dependent on the underlying predisposing condition [4, 5]. Several studies have found a trend to improved survival amongst patients who are HIV positive and a worse outcome in patients who are HIV negative and do not have a transplant [4, 6].

Cryptococcal infections have been previously associated with end-stage liver disease (ESLD). Case reports of cryptococcal infection as a complication of cirrhosis date back as far as at least 1967 [7]. Mortality in these case reports exceeds 80%, with 92% of the mortality attributed to the cryptococcal infection [5]. In a recent review, "liver failure", autoimmune hepatitis, and ESLD have been associated with 6.1-, 10-, and 2.8-fold increase in relative prevalence of cryptococcal meningitis compared with the general population, respectively [1].

Therefore, we evaluated the cases of cryptococcosis occurring in a large tertiary care hospital from 2002 to 2014 with the specific aim of describing the epidemiology and outcome of cryptococcosis in ESLD.

METHODS

Cohort Construction

Data were collected from patients admitted to Barnes-Jewish hospital, a 1315-bed tertiary referral hospital located in an urban environment, with a significant suburban and rural referral base. The study was approved by the Washington University (St. Louis, MO) Institutional Review Board.

Cases of cryptococcosis from January 1, 2002 to December 31, 2015 were studied. Cases were identified by either a positive cryptococcal antigen or a culture positive for *Cryptococcus* spp. Due to limitations of the informatics system, cases of cryptococcosis identified by histopathology alone could not be retrieved. If histopathology was available in addition to antigen and

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Correspondence: A. Spec, Infectious Disease Fellow, Division of Infectious Disease, 4523 Clayton Ave., Campus Box 8051, St. Louis, MO 63110-0193 (aspec@dom.wustl.edu).

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culture, it was used for defining location of disease. A standardized data collection tool was used to collect data on age, sex, survival, immune status, presentations, laboratory, and treatment.

Patients were then divided into 3 separate groups: HIV^+ patients, patients with ESLD, and HIV-negative without ESLD (HIVNE). The patients who met criteria for both the HIV and the ESLD group were classified in the ESLD group for the purposes of data analysis.

Definitions

Sites of infection were classified as follows: (1) central nervous system (CNS), defined by presence of *Cryptococcus* by histology, antigen, or culture within the meninges or brain parenchyma, or a positive cerebrospinal fluid culture or antigen for *Cryptococcus*; (2) pulmonary, defined by microbiologic or histologic isolation of *Cryptococcus* from the lung or presence of pulmonary infiltrates compatible with cryptococcal disease (nodules, interstitial pattern, lobar consolidation, and acute respiratory distress syndrome) and isolation of *Cryptococcus* from another source; (3) blood, which was defined by a positive blood culture, either on routine bacterial cultures or dedicated fungal culture; and (4) other, defined by histological or microbiologic isolation of *Cryptococcus* from a source other than lung, blood, or CNS, such as ascitic fluid. Patients could have multiple locations of infection; for example, a case of cryptococcemia and meningitis would be classified as CNS and bloodstream.

The causes of possible immunocompromise examined were as follows: HIV infection, solid organ transplant, hematopoietic stem cell transplant, diagnosis of cancer, recent (<30 days) receipt of chemotherapy, diabetes, ESLD, and receipt of immunosuppressants (such as glucocorticoids, antimetabolites, and monoclonal antibodies). End-stage liver disease was defined if a liver biopsy was performed and showed cirrhotic changes or if there was evidence of nodularity and fibrosis on ultrasound or computed tomography and there was evidence of synthetic liver dysfunction, as defined by elevated bilirubin (>5.0 mg/dL) and increased international normalized ratio (>1.5) on admission.

End-stage renal disease was defined as receipt of renal replacement therapy or persistent glomerular filtration rate ≤10 mL/min in the 90 days before admission. Immunosuppression due to medications was defined as receipt of cytotoxic chemotherapy, antimetabolite, monoclonal antibody, or glucocorticoid (≥5 mg of prednisone equivalent) in the 30 days before diagnosis.

Time to diagnosis was defined as the time from admission until the time the cryptococcal antigen or culture results indicating the presence of *Cryptococcus* or encapsulated yeast were first available. Worsening renal failure was defined by at least a doubling in creatinine. A worsening of clinical status was defined as a new transfer to a higher level of care (such as intensive care unit), a new institution of vasopressors, or decrease in mean arterial pressure more than 15 mmHg.

Statistical Analysis

Data were stored in Microsoft Access, and statistics were performed using SPSS V23 (IBM, Armonk, NY). Fisher's exact test and Students *t* test were used for the descriptive statistics and crude mortality. For survival analysis, mortality past 90 days was censored, because it was deemed less likely to be related to the cryptococcal infection and more related to the underlying disease. Survival analysis comparing ESLD patients to HIVNE was performed using Kaplan-Meier survival analysis. All statistical tests were 2-tailed and assessed significance at $\alpha = 0.05$.

RESULTS

Two hundred forty-seven cases of possible cryptococcosis were identified. Fifteen cases were excluded from analysis; 5 lacked any clinical data, 3 represented false-positive antigen tests that were of low titer, not repeatable, and the patients were not treated; and 7 were cases of non-*neoformans Cryptococcus*. This included 2 cases of *Cryptococcus laurentii*, 1 case each of *Cryptococcus luteolus*, *Cryptococcus albidus*, *Cryptococcus uniguttulatus*, *Cryptococcus humicolus*, and 1 non-*neoformans Cryptococcus* where a species could not be identified. Ultimately, 232 cases were analyzed. Of those, 25 (10.8%) were classified as ESLD, 87 (37.5%) as HIV, and 120 (51.7%) as HIVNE.

Baseline demographics were different between groups related to the epidemiology of the underlying diseases (Table 1). The ELSD and HIVNE groups were quite similar, but they differed significantly from the HIV group. The HIV-positive patients were more likely to be African American (77.3%) vs ESLD (16%) and HIVNE (12.6%). They were also younger, 41 vs 61.8 and 59.5 years, respectively.

Seventeen of 25 did not have another cause of immunocompromise classically associated with *Cryptococcus*. One patient had both HIV and ESLD. The remaining 7 patients had multiple additional causes of immunocompromise, including cancer, chemotherapy, ESLD, renal and lung transplant, and receipt of glucocorticoids, cyclosporine, mycophenolic acid, and tacrolimus (Table 2). All patients were classified in the ESLD group regardless of other conditions. The mean time to diagnosis was similar between the ESLD (6.2 days) and HIVNE (6.6 days) patients, but it was much more rapid in the HIV-positive patients (2.2 days) (Table 1).

The percentage of patients with meningitis was similar between HIVNE (41.2%) and ESLD (44%) groups, but it was much higher in HIV-positive patients (70.5%). Positive blood cultures were more common in ESLD (56%) than in HIVNE (33.6%), but they were comparable to the HIV patients (58%). However, sites other than cerebrospinal fluid, blood, and lungs were much more common in ESLD patients (20%) compared with HIVNE (6.7%) and HIV (2.3%) (Table 1). This was due to positive peritoneal cultures in all 5 patients, and biopsy confirmed skin lesions in 1 patient.

Table 1. Baseline Characteristics and Outcomes of 232 Patients With Cryptococcosis by Underlying Disease, 2002–2014

	HIV N = 88 (%)	ESLD N = 25 (%)	HIVNE N = 119 (%)	*P* Value	Total Cohort N = 232 (%)
Mean age (±SD), years	41.0 (9.4)	61.8 (11.8)	59.5 (16.0)	*P* < .001	52.7 (16.3)
Mean time to diagnosis (±SD), days	2.2 (7.0)	6.2 (9.6)	6.6 (11.5)	*P* = .006	4.9 (9.9)
Male gender (%)	67 (76.1)	23 (92)	75 (63.0)	*P* = .006	161 (71.1)
Race					
White (%)	18 (20.5)	20 (80.0)	94 (79.0)	*P* < .001	132 (56.9)
African American (%)	68 (77.3)	4 (16)	15 (12.6)	*P* < .001	87 (37.5)
Other (%)	2 (2.3)	1 (4)	10 (8.4)	*P* < .001	13 (5.6)
Site of Infection					
CNS (%)	62 (70.5)	11 (44.0)	49 (41.2)	*P* < .001	122 (52.6)
Pulmonary (%)	11 (12.5)	7 (28.0)	49 (41.2)	*P* < .001	67 (28.9)
Bloodstream (%)	51 (58)	14 (56.0)	40 (33.6)	*P* = .001	105 (45.3)
Other (%)	2 (2.3)	5 (20.0)	8 (6.7)	*P* = .006	15 (6.5)
90-d mortality (%)	12 (13.6)	20 (80)	27 (22.7)	*P* < .001	72 (31)

Abbreviations: CNS, central nervous system; ESLD, end-stage liver disease; HIV, human immunodeficiency virus; HIVNE, HIV-negative, without ESLD; SD, standard deviation.

The HIV-positive patients had the lowest 90-day mortality at 13.7%, followed by HIVNE (22.7%), in contrast to the 80% mortality experienced in the ESLD group. This was significant ($P < .001$) when comparing ESLD group with HIVNE using Kaplan-Meier analysis (Figure 1).

In addition to the overall mortality, the time to death in the ESLD group was significantly more rapid. The median survival from admission in the HIV and HIVNE groups were 11 and 17 days, respectively, compared with 6 days in the ESLD group ($P < .001$).

Amongst the patients with ESLD, 7 of 25 (28%) died before administration of any antifungal therapy. Sixteen (64%) received liposomal amphotericin B (LAB) and 13 of 16 (81.25%) of those that did died, with 11 of 16 (68.8%) dying with at least a doubling in serum creatinine before death. The 2 patients who received fluconazole for an isolated pulmonary cryptococcosis survived.

Furthermore, patients with ESLD experienced a worsening in their hemodynamic status. Of the 20 that died, 17 met at least 1 criterion for worsening clinical status. Fifteen had a decrease in their mean arterial pressure (MAP) of more than 15 mmHG, 10 required a transfer to the intensive care unit (ICU), and 4 had a new institution of vasopressors after starting therapy.

CONCLUSIONS

With the improvements in antiretroviral therapy over the last 20 years, there has been a shift in the epidemiology of cryptococcal infection away from HIV as the predominant predisposing cause

Table 2. Other Comorbid Conditions of 232 Patients With Cryptococcosis by Underlying Disease, 2002–2014

Immune Status	HIV N = 88 (%)	ESLD N = 25 (%)	HIVNE N = 119 (%)
Immunocompetent	0 (0)	0 (0)	31 (26.1)
Pregnant	1 (1.1)	0 (0)	2 (1.7)
Chemotherapy	4 (4.5)	2 (8.0)	27 (22.7)
Solid Tumor	8 (9.1)	3 (12.0)	22 (18.5)
Hematologic Malignancy	0 (0)	1 (4.0)	23 (19.3)
Diabetes Mellitus	4 (4.5)	6 (24.0%)	22 (18.5)
End-Stage Renal Disease	4 (4.5)	2 (8.0)	8 (6.7)
Heart Transplant	0 (0)	0 (0)	4 (3.4)
Lung Transplant	0 (0)	2 (8.0)	7 (5.9)
Kidney Transplant	0 (0)	2 (8.0)	2 (1.7)
Liver Transplant	0 (0)	0 (0)	3 (2.5)
Bone Marrow Transplant	0 (0)	0 (0)	3 (2.5)
Graft-vs-Host Disease	0 (0)	0 (0)	2 (1.7)
Glucocorticoid Therapy	3 (3.4)	5 (20)	39 (32.8)
Biologic Therapy	0 (0)	2 (8.0)	9 (7.6)
Other Immunosuppressants	0 (0)	3 (12.0)	22 (19.1)

Abbreviations: ESLD, end-stage liver disease; HIV, human immunodeficiency virus; HIVNE, HIV-negative, without ESLD.

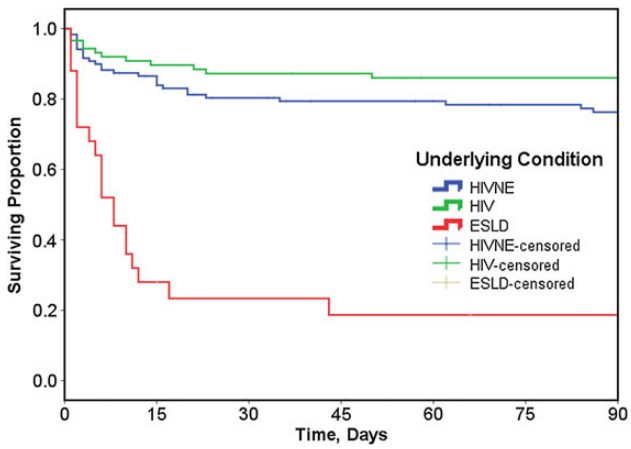

Figure 1. Kaplan-Meier survival curve of 232 patients with cryptococcosis by underlying condition, 2002–2014. Patients with end-stage liver disease (ESLD) had the lowest survival, most dramatically expressed in the first 15 days of the infection. Mortality was censored after 90 days because it was less likely to be related to cryptococcosis; $P < .001$. Abbreviations: HIV, human immunodeficiency virus; HIVNE, HIV-negative, without ESLD.

in the United States [1]. Similar to our study, others have found a trend to improved survival amongst patients who have HIV infection, but none achieved statistical significance [4, 6].

In particular, ESLD has emerged as an important risk factor for developing cryptococcal meningitis [1]. Liver failure, autoimmune hepatitis, and ESLD were associated with 6.1-, 10-, and 2.8-fold increase, respectively, in relative prevalence of cryptococcal meningitis compared with the general population [1]. In our data set, ESLD was present in 10.8% of the cohort, and 68.0% of those patients had no other cause of immunocompromise.

Decompensated ESLD in Taiwan was associated with an odds ratio of 8.5 of developing cryptococcal meningitis and an odds ratio of 23.8 of developing cryptococcemia compared with other underlying conditions [8]. Patients with ESLD have been found to have a 5.3-fold higher rate of dissemination than other non-HIV patients [9]. Even after liver transplant, cryptococcosis appears to have a higher risk of dissemination and a more severe presentation than patients with other solid organ transplants [10].

This increased risk may be related to previously demonstrated deficiencies in cell-mediated immunity amongst patients with ESLD [11–13]. Liver functions as an important organ in clearing infections because it contains the majority of the reticuloendothelial cells, and it is thus instrumental in clearing of cytokines, bacteria, and endotoxin from the circulation [11]. A total of 70%–96% of radiolabeled Gram-negative bacteria injected into healthy volunteers are localized to the liver within 10 minutes of injection [14]. The efficiency of this critical portion of immunity is diminished by portosystemic shunting of blood. In addition, monocyte, neutrophil, macrophage, and lymphocyte chemotaxis and function have been shown to be diminished in ESLD [11]. Patients with alcoholic liver disease have a hyperactive B-cell response and a decreased lymphocyte transformation [12] as well as a blunted T-cell response [13].

In addition to having an increased predisposition to cryptococcal infection, patients with ESLD have a much higher than expected mortality. In our study, the overall mortality was 80%. Furthermore, their mortality appears to be early in the course of their disease, with a mean survival of only 6 days, despite a comparable time to diagnosis. In a case series of 5 patients, with a systematic review of 28 cases in published literature [5], a similar mortality of 81% (26 of 32) was observed. Of the 26 deaths, 24 (92%) were attributed to *Cryptococcus* [5]. In a recent multicenter analysis of patients with cirrhosis and liver transplant, a mortality of 57.1% was observed [15]. End-stage liver disease was associated with a 7.5-fold increase in unsatisfactory outcomes amongst patients infected with hepatitis B in China [16] and a 100% mortality in a small Taiwanese cohort of 33 HIV-negative patients [17].

The findings of increased prevalence and early mortality could be explained by several possible mechanisms. It is possible that patients with ESLD are infected by a different strain of *Cryptococcus* due to their specific host immune defects. However, we have no evidence to date that strain differences among *C neoformans* contribute to outcome.

It is also possible that patients with ESLD are diagnosed very late in the course of their disease due to low suspicion on the part of the clinician. However, the time to diagnosis was same in the ESLD group compared with HIVNE group (6.2 vs 6.6 days, respectively). This was much longer than the time to diagnosis in HIV^+ patients (2.2 days), which is probably due to a very high index of suspicion for cryptococcal disease in patients living with HIV. Patients with ESLD were no more likely than HIV patients to have a positive blood cultures and were no more likely than HIVNE patients to have meningitis.

Mortality differences could be further explained by antifungal toxicity in this patient group. Liposomal amphotericin B and/or flucytosine treatment may be too toxic in patients with ESLD, because it can lead to renal or hepatic failure, which has a high mortality in the setting of ESLD. Of the 16 patients with ESLD who received LAB and flucytosine, only 2 survived. Of the 14 that died after receiving at least 1 dose of LAB, 11 (78.6%) died with at least a doubling in creatinine. This could be related to worsening renal function from LAB toxicity. A worsening of renal function has been observed in 66% of renal transplant recipients infected with *Cryptococcus* who later developed immune reconstitution inflammatory syndrome (IRIS) [18].

In our study, 15 patients had a decrease in their MAP of more than 15 mmHG, 10 required a transfer to the ICU, and 4 had a new institution of vasopressors after starting therapy. This raises the possibility that treatment itself may trigger a response that the precarious homeostatic balance in patients with ESLD is rapidly worsened by the release of antigen during the treatment with antifungal agents, resulting in hemodynamic instability, reminiscent of a Jarisch-Herxheimer reaction. This has not been demonstrated in other patient groups, but it may be comparable to IRIS and warrants further study.

CONCLUSIONS

In conclusion, in our cohort of 232 patients with cryptococcosis over 11 years, approximately 11% had underlying ESLD. In these patients, the course of the disease is dramatically different, because they exhibit much higher and more rapid mortality compared with other populations. In view of the high and rapid mortality in patients with ESLD, cryptococcosis should be considered early in patients with ESLD presenting with possible infection.

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