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Central nervous system cryptococcosis in solid organ transplant recipients: clinical relevance of abnormal neuroimaging findings

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Abstract

Background—Prognostic implications of cryptococcal antigen and outcomes associated with CNS cryptococcal lesions in solid organ transplant (SOT) recipients have not been fully defined.

Methods—Patients were derived form a cohort of 122 SOT recipients with cryptococcosis in a multicenter study from 1999–2006.

Results—CNS cryptococcosis was documented in 61 patients. Serum or CSF antigen titers did not correlate with mortality at 90 days or CSF sterilization at 2 weeks. CNS lesions were identified in 16 patients and included leptomeningeal lesions in 8, parenchymal lesions in 6 and hydrocephalus in 2. Overall, 13/16 CNS lesions were present at the time of diagnosis. One parenchymal and 2 hydrocephalus lesions however, developed after diagnosis and fulfilled the criteria for immune reconstitution syndrome (IRS). CSF antigen titers were higher with meningeal vs. parenchymal lesions, and hydrocephalus (p=0.015). Mortality was 50% (3/6) for patients with parenchymal, 12.5% (1/8) for those with leptomeningeal, and 0/3 for patients with hydrocephalus. Mortality was 31% (4/13) for patients with CNS lesions at baseline and 0/3 in those with new onset lesions.

Conclusions—Despite a greater antigen titer with meningeal lesions, outcomes tended to be worse with parenchymal compared to meningeal lesions or hydrocephalus. New onset CNS lesions may represent IRS and appeared to be associated with better outcome.

Keywords

Cryptococcosis; central nervous system infection; transplants; *C.neoformans*; cryptococcal antigen

Background

C. neoformans is a significant opportunistic pathogen in organ transplant recipients. An average of 2.6%, and up to 5% of the transplant recipients develop cryptococcosis. Central nervous system (CNS) involvement has been documented in 25–72% of organ transplant recipients with cryptococcal disease (1–3). Mortality in patients with cryptococcosis ranges from 10–25%, and approaches 40% in those with CNS disease (1–3).

Detection of cryptococcal polysaccharide capsular antigen in the cerebral spinal fluid (CSF) has proven to be a valuable diagnostic assay for CNS cryptococcosis. CSF antigen titers have also been shown to be a prognostic factor for poor outcomes in HIV-infected patients and other immunocompromised hosts primarily in non-transplant setting (4–8). High CSF antigen titers correlated with death and microbiologic failure in these patients (7,8). Some studies have also shown an association between serum antigen titers and long-term outcomes in patients with cryptococcosis (9). The value of cryptococcal antigen in predicting clinically relevant outcomes in organ transplant recipients has not been fully defined.

Cryptococcal meningitis is by far the most frequently encountered clinical presentation of cryptococcosis. Although CNS lesions detectable on neuroimaging studies occur less commonly (10–18), they are a significant complication of cryptococcal disease and were independently associated with lower survival in one study (8). CNS lesions due to cryptococcosis in SOT recipients have largely been reported as case reports or case series comprising a small number of patients (1,2,19). Outcome of these lesions and their effect on prognosis in transplant recipients with cryptococcosis has not been fully assessed. The goals of this study were to determine variables influencing serum and CSF cryptococcal antigen positivity and its prognostic implications in SOT recipients with CNS cryptococcosis. We also discuss clinical characteristics and outcome of cryptococcal CNS lesions in these patients.

Methods

Patients for this study were derived from a cohort of 122 organ transplant recipients with cryptococcosis in a prospectively conducted multicenter study between 1999 and 2006. A detailed description of this cohort has been reported elsewhere (20). None of the patients were HIV-infected. CNS cryptococcosis (meningitis or meningoencephalitis) was defined per criteria proposed by the European Organization for Research and Treatment in Cancer and the Mycosis Study Group (21). Patients were considered to have CNS cryptococcosis if they had positive CSF culture for cryptococcus or positive CSF cryptococcal antigen. CSF or serum cryptococcal antigen titer ≥ 1:512 was considered to represent high fungal load as previously reported (8,9). Disseminated infection was defined as CNS infection or fungemia or involvement of ≥2 noncontiguous organ sites (20). Abnormal neurologic symptoms recorded at presentation included headache, visual symptoms, and altered mental status. Mortality was assessed at 90 days (20).

Patients were considered to have CNS cryptococcal lesions if any of the following previously reported abnormalities were found on neuroimaging studies patchy or diffuse leptomeningeal enhancement, hydrocephalus, parenchymal mass lesions or cryptococcomas, gelatinous pseudocysts, and dilation of the perivascular (Virchow-Robin) spaces (13,15,17,22). Interpretation of the imaging studies was per the radiologists at each center. Cryptococcal antigen testing was performed as part of standard clinical care at that institution. For the purpose of this study, antigen titer at baseline (i.e. at the time of diagnosis of cryptococcosis and before employment of antifungal therapy was considered).

Statistical analyses were performed using Intercooled Stata version 9.2 (College Station, TX). Categorical data were compared using the Chi-square test. The Fisher's exact test was used for contingency tables with expected cell values less than 5. Antigen titers were log transformed and compared using the t test. The Kruskal-Wallis test was use for 3 way comparisons. The time of onset of disease post transplant was evaluated using the Wilcoxon rank sum test.

Results

Of 122 patients with cryptococcosis, 86% (105 /122) had CSF analysis performed and 58% (61/105) had CNS cryptococcosis as defined in the Methods. CSF antigen was positive in 98.2% (55/56) and serum antigen in 97.5% (39/40) of the patients with CNS disease who had this test performed. Fungemia was present in 35.6% (21/59) of the patients with CNS cryptococcosis. Patients with CNS disease had higher serum antigen titers (median 1:512 vs. 1:32, p=.0.02) and were more likely to be fungemic (35.6% vs. 4.8%, p=.0002) than those without CNS disease. CSF cultures were positive in 85% (52/61) of the patients with CNS cryptococcosis. Those with positive CSF cultures had median serum antigen titers of 1:512 versus 1:64 (p=0.10), and median CSF antigen titers of 1:128 versus 1:4 (p=0.06) compared to patients with negative CSF cultures.

Cryptococcal antigen positivity and outcomes

We assessed the association between antigen positivity and clinical (mortality rate), and microbiologic outcome (CSF sterilization at 2 weeks). Mortality rate was 20% (12/61) in patients with CNS cryptococcosis vs. 5% (2/44) in those without CNS involvement (p=0.038). In patients with CNS involvement, serum cryptococcal antigen titer in patients who died was 1:1024 vs. 1:512 in those who lived (p=0.63). Mortality also did not correlate with CSF antigen titer (1:128 in patients who died vs. 1:64 in those who lived, p=0.91). Mortality did not correlate with antigen titer ≥1:512 vs. <1:512 in the serum (19% and 11%, p=0.38),) or in the CSF (31% and 50%, p=0.58), respectively.

Repeat CSF results at 2 weeks were available in 41% (25/61) patients with CNS cryptococcosis. This group did not differ with regards to the frequency of headache (68% vs. 67%, p=0.91), abnormal mental status (48% vs. 40%, p=0.54), renal failure at beseline (28% vs. 34%, p=0.61), fungemia (36% vs. 35%, p=0.96), positive CSF culture (91% vs. 85 %, p=0.47), or the presence of CNS lesions (32% vs. 27%, p=0.66) from the group that did not have repeat CSF. In all, 40% (10/25) of the patients with repeat CSF remained culture positive at 2 weeks. Serum (p=0.70) or CSF (p =0.89) antigen titers at baseline did not predict CSF sterilization at 2 weeks following antifungal therapy. Rate of CSF sterilization did not correlate with fungal burden (antigen titer ≥1:512 vs. <1:512) in the serum (69% vs.50%, p=0.58) or in the CSF (67% vs.55%, p=0.68), respectively.

CNS lesions

Neuroimaging studies (CT and/or MRI) were performed for 90% (55/61) of the patients with CNS disease; 6 patients who did not have neuroimaging study performed had normal neurologic examination. In all, 27 patients had CT only, 17 had MRI only, 7 had both imaging studies performed, and in 4 the type of imaging performed was not specified (all 4 of were normal). Abnormal neuroimaging findings consistent with cryptococcal lesions as defined in the Methods were documented in 29% (16/55) of the patients and included leptomeningeal lesions in 50% (8/16), parenchymal lesions in 37.5% (6/16), and hydrocephalus in 12.5% (2/16). Five of 6 parenchymal and all meningeal lesions were present at baseline or diagnosis. One parenchymal and both hydrocephalus lesions however, were not present at baseline and developed a median of 18 days (range 14–21 days) after initiation of antifungal therapy; all 3 cases fulfilled the criteria for immune reconstitution syndrome (IRS) (23,24).

The frequency of headache (60%, 9/15 versus 80%, 31/39, p=0.14), altered mental status at presentation (50%, 8/16 versus 41%, 16/39, p=0.54), and visual symptoms (25%,4/16 versus 7.7%,3/39,p=0.10) was not significantly different for patients with or without CNS lesions. Fifty percent (4/8) of the patients with leptomeningeal, 17% (1/6) with parenchymal lesions, and none (0/2) of those with hydrocephalus had fungemia (Table 2). CSF antigen titers were significantly higher with leptomeningeal vs. parenchymal lesions, and hydrocephalus (p=0.015)(Table 2). CSF opening pressure was recorded in 68.8% (11/16) of the patients with CNS lesions. Opening pressures were not significantly different for patients with various types of CNS lesions (Table 2).

Mortality in patients with CNS lesions was 25% (4/16). Deaths occurred a median of 19 days (range 5–53 days) after diagnosis and were deemed attributable to cryptococcosis by site investigators in all 4 cases. Mortality rate was 50% (3/6) in patients with parenchymal, 12.5% (1/8) in those with leptomeningeal, and 0/2 in patients with hydrocephalus. Mortality rate was 31% (4/13) in patients with cryptococcal lesions at baseline and 0/3 in those with new onset lesions consistent with IRS. Except one patient with leptomeningeal lesions who received fluconazole, antifungal therapy comprised amphotericin B formulations in 15/16 patients with CNS lesions. Eleven of 16 patients (3/6 with parenchymal lesions, 7/8 with leptomeningeal lesions, and 1/2 with hydrocephalus) also received 5-flucytosine concurrently. Mortality was 2/11 in patients with CNS lesions who received 5-flucytosine, and 2/5 in those who did not receive this agent (p=0.55). Antifungal therapy in patients without CNS lesions also comprised amphotericin B formulations in 92% (36/39) of the patients;11 patients received 5- flucytosine concurrently.

Discussion

Cryptococcal meningitis is frequently associated with infection of the subarachnoid space and involvement of the underlying brain parenchyma to a variable extent in most cases (25). However, CNS lesions manifesting as abnormal neuroimaging findings occur infrequently.

Previous studies of neuroimaging abnormalities in CNS cryptococcosis have documented focal parenchymal masses in 11–25%, hydrocephalus in 9–11%, meningeal enhancement in 15%, and cerebral edema in 3% of the patients (16,17,22,26,27). CNS lesions were observed in 33% (3/9) of SOT recipients with CNS cryptococcal disease in a prior report (1).To our knowledge however, our study represents the first in depth analyses of CNS lesions in SOT recipients with cryptococcosis. Leptomeningeal lesions, mass lesions, and hydrocephalus were observed in 14%, 12%, and 4% of the patients with cryptococcal disease, respectively. Whereas a majority of the lesions were documented at baseline,19% of the CNS lesions developed after initiation of antifungal therapy and patients with new CNS lesions met the proposed criteria for IRS (23,24). A previous report of intracranial cryptococcosis in non-HIV infected immunocompromised patients has described a renal transplant recipient who had a negative CT scan at baseline and who subsequently developed hydrocephalus (22). Although not recognized as IRS, hydrocephalus in this case and in our patients likely represents IRS resulting from an enhanced inflammatory response due to reversal of cryptococcal induced immunosuppression, initiation of antifungal therapy, and reduction of immunosuppression (23,24). New onset or worsening CNS lesions, hydrocephalus or aseptic meningitis have also been identified as manifestations of IRS in HIV-infected patients with cryptococcal meningitis following initiation of antiretroviral therapy (28–31).

Outcome in our patients varied depending upon the type of lesion. Whereas the mortality was 50% in patients with parenchymal lesions, those with leptomeningeal lesions despite a higher cryptococcal antigen titer had mortality rate of 12.5%. Previous reports mainly in non transplant setting have also documented poor outcomes in patients with CNS cryptococcal lesions with mortality rates ranging from 20–50% (8,17,22,27,32). Deaths in patients with CNS parenchymal lesions in our study occurred early; 3 of 4 patients who died succumbed to their infection within 30 days of diagnosis thus raising the possibility that adjuncts to antifungal therapy such as immune augmentation strategies may have a potential role in this setting (33–35). Outcomes in general were better in our patients with new onset cryptococcal lesions ensuing on therapy than those with lesions documented on presentation. It is plausible that proinflammatory responses associated with IRS may have contributed to better outcomes in the former group as proposed previously (36). We however, note that due to small number of patients with IRS-related lesions, our data should be interpreted with caution.

A number of studies largely in other immunocompromised hosts have evaluated the prognostic value of cryptococcal antigen in patients with CNS cryptococcosis. High CSF and serum cryptococcal antigen titers have been associated with lack of sterilization and death in patients with cryptococcosis in some, but not all studies (8,37). A recent study comprising 230 patients with cryptococcosis of whom 77% (177) were HIV-positive and 6% (11) were organ transplant recipients documented that high CSF antigen titers ($\geq$ 1: 512) correlated with lack of CSF sterilization at 2 weeks (8). Overall, 88% of the total study population, but only 9% of the transplant recipients in this study had CSF antigen titer $\geq$ 1:512 (8). In our study, CSF antigen titers $\geq$1:512 were present in 33% of the patients with CNS cryptococcosis (Table 1). Thus it appears that organ transplant recipients tend to have lower antigen titers than other immunocompromised hosts such as HIV-positive patients with cryptococcosis. Further, since antigen titers did not correlate with CSF sterilization at 2 weeks or mortality in our patients suggests that outcomes in diverse hosts may be influenced by specific immune deficits, host-fungal interactions (38,39) or other yet undetermined factors.

Our study has limitations that deserve to be acknowledged. The cryptococcal antigen assay was performed locally thus leading to the possibility of interlaboratory variability in test results. We however, note that cryptococcal antigen is a widely employed standardized assay and previous reports using local laboratory results in multicenter studies have yielded valuable and valid data (8). Second, although standard terminology was used for the description of imaging

findings, radiographic studies were interpreted by radiologists at each site. Finally, repeat CSF analysis was performed in 40% of the patients and therefore we were unable to determine the evolution of antigen titers or the role of monitoring antigen in patients with CNS cryptococcosis. Antigen monitoring has been of limited value in the management of HIV-infected patients with cryptococcosis in some studies (40,41). In others however, persistently high cryptococcal antigen titers correlated with the risk of relapse (9).

In summary, CNS lesions were documented in ~30% of the SOT recipients with CNS cryptococcosis. Despite a higher fungal burden in patients with meningeal lesions as indicated by fungemia and higher CSF antigen titers, outcomes tended to be worse for patients with parenchymal as compared to meningeal lesions or hydrocephalus. New onset CNS cryptococcal lesions in these patients may represent IRS and potentially portend better outcome.

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Table 1

Demographic and clinical characteristics of patients with central nervous system cryptococcosis

Variable	Patients with CNS cryptococcosis (n=61)	Patients without CNS cryptococcosis (n=44)
Age, mean (range)	50 years (19–74)	52 (26–77)
Gender, male	73.8% (44/61)	68.8% (31/44)
Female	26.2% (16/61)	29.6% (13/44)
Type of transplant		
Kidney	57.4% (35/61)	38.6% (17/44)
Liver	26.2% (16/61)	25.0% (11/44)
Heart	5% (3/61)	15.9% (7/44)
Lung	3.3% (2/61)	11.4% (5/44)
Kidney-pancreas	3.3% (2/61)	9.1%(4/44)
Kidney-liver	1.6% (1/61)	0/44
Kidney-heart	3.3% (2/61)	0/44
Small bowel	0/61	0/44
Immunosuppressive agents		
Tacrolimus	64% (39/61)	79.5% (35/44)
Cyclosporine A	16% (10/61)	15.9% (7/44)
Azathioprine/mycophenolate mofetil[1]	18% (11/61)	4.5% (2/44)
Prednisone	97% (59/61)	79.5% (35/44)
Time to onset of cryptococcosis post-transplant (months) [2,3]	28 (10–73)	17(9–25)
Fungemia[5]	35.6% (21/59)	4.8% (2/42)
CSF Characteristics[3]		
Opening pressure, mm H_2O	27 (12–36)	15 (14–18)
White blood cell count	79 (20–160)	2 (0–4)
Protein (mg/dL)	95 (58–114)	45 (32–61)
Glucose (mg/dL)	54 (33–69)	63 (54–78)
CSF antigen	1:64 (1:2 – 1:1024)	--
Antigen≥1:512	33.9%(19/56)	--

[1] p=.04.

[2] p=.027.

[3] Numbers represent median and range.

[5] p=.0002

Table 2

Cerebrospinal fluid characteristics in patients with central nervous system cryptococcal lesions

Variable *	Parenchymal lesions (n=6)	Meningeal lesions (n=8)	Hydrocephalus (n=2)	Significance level (3-way)
Serum antigen titer	1:256	1:512	1:64†	0.08
	(1:128–1:1024)	(1:64 –1:1024)		
CSF characteristics				
CSF antigen titer	1:32	I:768	1:2†	0.015
	(1:16–1:64)	(1:256–1:1,024)		
Opening pressure	21 (16 –25)	24 (13– 29)	19†	0.95
WBC per mm^3	130 (25 – 210)	119 (67 – 172)	194 (58–330)	0.93
Protein mg/dL	164 (60 – 227)	204 (87 – 479)	125 (110 –191)	0.72
Glucose mg/dL	41 (31 – 59)	32 (19 – 41)	61 (61 – 81)	0.22
Positive culture	83% (5/6)	100% (8/8)	50% ¶ (1/2)	0.11

*Values represent median and interquartile range

CSF= Cerebrospinal fluid, WBC= White blood cell count

†Serum cryptococcal antigen was available in 1/2 patients. CSF antigen level was 1:2 in both patients

¶Number reflects culture positivity at baseline. Both patients had negative CSF cultures at onset of hydrocephalus.