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Jacobs Journal of Clinical Case Reports

Case Report

Cryptococcal Meningitis in the Immunocompetent Host: A Case Report and Review of the Literature

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Received: 02-26-2016

Accepted: 04-07-2016

Published: 04-14-2016

Abstract

A 79-year-old previously healthy male presented to the emergency department with a three-month history of headaches, falls, and personality changes. No acute changes were evident upon computed tomography scan of the head. Blood cultures grew yeast, and the patient was treated empirically for candidemia with fluconazole. The cultures were finalized seven days later, revealing *Cryptococcus neoformans.* A nucleated cell count of 97 cells/μL was found on lumbar puncture. The patient was diagnosed with CM and treated with amphotericin B + flucytosine. His hospital stay was complicated by several transfers to the intensive care unit, severe hypokalemia, anemia requiring multiple blood transfusions, methicillin-resistant *Staphyloccocus aureus* septic arthritis and bacteremia, possible endocarditis, vancomycin-resistant *Enterococcus* bacteremia, health care-associated pneumonia, and *Clostridium difficile* colitis. Four months later, he was discharged to a long-term care facility. CM is commonly diagnosed in immunocompromised patients, but infection of patients with no obvious immune deficits is rare. Compared to immunocompromised patients, immunocompetent hosts often suffer worse outcomes of infection due to delays in diagnosis and less robust response to treatment. Here we present a case report and review of the available literature regarding treatment of CM in an immunocompetent host. Prompt diagnosis and aggressive treatment is key for optimal outcomes.

Keywords: Amphotericin B; Antifungal Therapy; Cryptococcosis; Cryptococcal Meningitis; Immunocompetent; Meningitis

Abbreviations:

CM: Cryptococcal Meningitis;

CT: Computerized Tomography;

CSF: CEREBROSPINAL FLUID;

LAmB: Liposomal Amphotericin B;

ART: Antiretroviral Therapy ;

IDSA: Infectious Diseases Society of America ;

AmBd: Amphotericin B Deoxycholate;

ICP: Intracranial Pressure

Introduction

Immuncompromised hosts, including those with HIV, transplants, and malignancies, have an increased risk of acquiring cryptococcal meningitis [CM][1]. Factors associated with cryptococcal infection in HIV(-) patients include immunosuppressive drug therapy, diabetes mellitus, chronic renal failure, liver failure or cirrhosis, Cushing's syndrome, sarcoidosis, and lupus erythematous[2-7]. However, 17-33% of patients with cryptococcosis have no identifiable immune dysfunction[2,6,8]. Sparse published data on risk factors and management of these patients exists. In this article we discuss differences in clinical presentation, diagnosis, treatment, and outcomes of CM in immunocompetent versus immunocompromised patients.

Case presentation

A 79-year-old previously healthy male presented to the hospital for a three-month history of headaches, personality changes, and gait disturbance with falls. On exam he was noted to have impaired judgement and executive function; alert and oriented only to name and place. Cranial nerves were intact, without ocular abnormalities or nystagmus, neck was supple. While gait was noted to be wide based and unsteady, strength and coordination was intact and reflexes were 2/4 throughout. A computerized tomography [CT] scan of the head revealed dilated cerebral ventricles with hypodense lesions. Subsequent magnetic resonance imaging [MRI] with contrast MRI showed diffuse atrophy, prominent ventricles, and scattered signal changes in the subcortical white matter with small enhancing vessels thought to be due to a vascular malformation. Magnetic resonance angiogram [MRA] suggested chronic microvascular disease. A lumber puncture was attempted but aborted due to inability to obtain any cerebrospinal fluid [CSF]. Despite this, the patient's mental status improved with hydration and he requested to be discharged home. Ten days later he experienced further mental status deterioration, falls, decreased appetite, and dehydration and was readmitted. Upon repeat CT, perivascular abnormalities were unchanged from the study done at prior admission and were attributed to cerebrovascular ischemia. Blood cultures revealed yeast, and he was empirically started on fluconazole—which was later switched to micafungin—for presumed candidemia.

On hospital day 7, the yeast was identified as *Cryptococcus neoformans*. A serum cryptococcal antigen was reported as >1:512. CSF analysis yielded a nucleated cell count of 97 cells/μL with lymphocytic predominance and neutrophils of 3%. A diagnosis of CM was made and induction therapy was initiated with intravenous liposomal amphotericin B [LAmB] at 4mg/kg/day plus flucytosine 100mg/kg/day. The CSF cultures later grew *Cryptococcus neoformans.* Immunocompromising conditions including transplant, malignancy, autoimmune disorders, receipt of immunosuppressive medications, and HIV were ruled out. The patient did report living on a ranch and having contact with pigeons.

Hydrocephalus was untreated as there was a low suspicion for increased intracranial pressure (ICP) after the first LP due difficulties in obtaining an adequate volume of CSF during the procedure. After 5 weeks, opening pressure on repeat LP was 10 cm H_20. The hospital course was complicated by severe hypokalemia, acute kidney injury, and anemia requiring blood transfusions. It was suspected that these side effects were due to amphotericin B/flucytosine therapy, and the flucytosine dose was reduced. After six weeks of induction, he was transitioned to fluconazole consolidation (8 weeks) and maintenance therapy. A final CT scan revealed periventricular low-density lesions that were diffusely worsened from previous imaging, and his cryptococcal antigen remained elevated at 1:128. Mental status continued to wax and wane, and after 4 months, he was transferred to a long-term care facility where he ultimately expired one month later. Autopsy was declined.

Literature Review

Demographics and Diagnosis

In studies comparing HIV (+) to HIV (-) patients with cryptococcosis (not exclusively CNS disease), infected HIV(+) patients were younger than HIV(-) patients (mean age 36-39 versus 54-56 years, respectively) [7,8]. HIV(+) patients were more frequently African American (60%), and HIV(-) patients were more likely to be white (66%)[7].

Presenting symptoms and imaging in HIV (-) patients vary from those of HIV(+) patients with the majority of patients overall presenting as ours did with non-specific symptoms of headache and altered mental status (Table 1)[2,9]. In one retrospective chart review, 43% of HIV(-) patients with CM were asymptomatic [2]. Differences in serum laboratory markers also exist (Table 2)[8-10]. In one study of cryptococcosis in patients with and without HIV, serum antigen was positive in 97% of HIV(+) patients with CM, versus 86% of HIV(-) patients (p=0.027)[8]. In HIV(-) patients, serum antigen was undetectable in 16% with disseminated disease and 33% with fungemia. However, all HIV(+) patients with similar presentation had detectable serum antigen levels. Surprisingly, six patients with a positive CSF culture had negative serum antigens (2 HIV(+) patients, 4 HIV(-) patients). These results indicate that discrepancies between serum and CSF antigen exist, and a negative serum antigen titer cannot definitively rule out CM. Additionally, insensitive serological testing may contribute to delayed diagnosis and treatment of CM in immunocompetent hosts.

Table 1. Differences in presenting symptoms between HIV+ and HIV- patients with CM [2,8,9].

Symptom	Incidence in HIV- patients	Incidence in HIV+ patients
Headache	89% (n=8/9)	55% (n=6/11)
Hearing disturbances	22% (n=2/9)	0
Fever	22% (n=2/9)	73% (n=8/11)
Altered mental status	33% (n=3/9)	46% (n=5/11)
Dyspnea	11% (n=1/9)	36% (n=4/11)
Insomnia	0	18% (n=2/11)
Asymptomatic	43% (n=6/14)	N/A
Mean time between symptom onset and hospitalization	6.0 ± 7.4 weeks	3.3 ± 3.3 weeks

Table 2. Differences in laboratory markers between HIV+ and HIV- patients with CM [8-10].

Laboratory value	Incidence in HIV- patients	Incidence in HIV+ patients
Positive India ink test*	52-78%	88-100%
CSF *Cryptococcus* cultures*	69-78%	89-91%
CSF antigen titers*	Lower	Higher
Serum WBCs^ (cells/uL)	7880	3800
Serum cryptococcal antigen^	86%	97%

*statistical significance not assessed

^$p<0.05$ for difference

The concentrations of pro- and anti-inflammatory mediators also differ between the two groups. TNF-a, IL-8, and IL-10 are found in higher concentrations in the CSF of HIV(-) patients than HIV(+) patients[11]. HIV(+) patients taking highly-active antiretroviral therapy [ART] have similar IL-8 concentrations when compared to HIV(-) patients, indicating that ART partially restores immune response against Cryptococcus. Compared to HIV(-) patients, cryptococcal meningitis in HIV(+) patients is associated with lower CNS inflammatory response and higher intracranial pressure. HIV(+) patients are also less likely to have mass lesions [12]. The underwhelming inflammatory response in HIV(-) associated CNS cryptococcosis is likely responsible for higher fungal burdens and poorer outcomes.

A typical presentation of CM in HIV (-) hosts may be responsible for delays in diagnosis and treatment. In one case study of cryptococcosis in HIV(-) patients, CM presentation is described as subacute, with symptoms developing over several weeks or months [6]. In another study, HIV(+) patients were hospitalized on average 3.3 weeks after symptom presentation, while HIV(-) patients were hospitalized after an average of 6.0 weeks (p=0.0019)[8]. A case review identified the median time from onset of symptoms to diagnosis in immunocompetent patients as 44 days (range: 7 days – 1 year), with three quarters of patients requiring three or more physician visits before diagnosis [13]. CNS cryptococcosis was commonly misdiagnosed as migraine/cluster headache, stroke, carcinoma, chronic infection, or sinusitis.

In recent years, it was discovered that the species formally referred to as *Cryptococcus neoformans* is actually comprised of two variants: *C. neoformans* and *C. gattii. C. neoformans* tends to infect immunocompromised hosts and often responds to treatment more readily. In contrast, *C. gattii* tends to infect immunocompetent hosts, and is associated with a higher incidence of neurological symptoms and inflammatory lesions in the brain. Patients tend to require longer durations of antifungal treatments and have worse overall prognosis. *C. gattii* is currently considered an endemic species of the Pacific Northwest, but is expected to continue spreading across the United States. Currently, most microbiology laboratories are unable to distinguish between the two variants due to antiquated technology[1,14].

Treatment and Prognosis

Few studies examining the most appropriate treatment for CM in HIV(-) hosts exist. The Infectious Diseases Society of America [IDSA] guideline recommendations are based on a few landmark trials, many of which were retrospective, included small sample sizes, and were conducted before ART was readily available. Thus, most recommendations are extrapolated from data in HIV(+) patients prior to the ART era.

In 1979, Bennet and colleagues conducted a prospective study of HIV(-) patients in the U.S. with CM. They compared amphotericin B deoxycholate [AmBd] monotherapy to AmBd plus flucytosine[15]. Patients received either AmBd 0.4 mg/kg/day for 42 days followed by 0.8 mg/kg every other day for 28 days (ten weeks total treatment), or AmBd 0.3 mg/kg + flucytosine 150 mg/kg divided in four doses for six weeks. The trial was discontinued early because the investigators felt the primary endpoint, non-inferiority of combination therapy vs. AmBd alone, had been met. Sixty-eight percent of patients in the combination therapy arm and 47% in the monotherapy arm improved or were cured ($p>0.05$). Twenty-four percent of combination therapy and 47% of monotherapy patients died ($p<0.05$). CSF cultures converted from positive to negative more rapidly in the AmBd + flucytosine arm ($p<0.001$). Treatment non-adherence and discontinuation was frequently due to flucytosine toxicity. Additionally, renal toxicity occurred more frequently in the monotherapy arm ($p<0.05$), presumably due to increased AmBd drug exposure. This trial was criticized for the low dose of AmBd chosen for the monotherapy

arm. Regardless, combination therapy is now considered standard of care for CM.

In 1987, Dismukes and colleagues sought determine the appropriate AmBd + flucytosine length of therapy for CM. Ninety-one non-transplant patients, only two of which had HIV, were randomized to receive combination therapy (AmBd 3mg/kg/day + flucytosine 150mg/kg/day in four equal doses for either four or six weeks)[5,16]. The 4-week and 6-week regimens resulted in cure rates of 62% and 70%, and relapse rates of 25% and 15%, respectively. The authors could not determine that a 4-week regimen was non-inferior to a 6-week regimen.

In both the Bennett and Dismukes trials, flucytosine caused substantial toxicity, and the drug was discontinued altogether in 18% of patients in Bennett's trial[5,15]. These trials also predated the era of triazole antifungal agents, which would soon become a mainstay of CM treatment.

In the 1990's, Dromer and colleagues retrospectively assessed the efficacy of fluconazole in HIV(-) cryptococcosis[17]. Patients who received AmBd (with or without flucytosine) were compared to patients who received fluconazole for initial treatment. Doses and treatment duration varied; AmBd doses ranged from 0.5-1mg/kg/day, averaged 24 days of treatment, did not differ based on site of infection, and were combined with flucytosine in 91% of cases. Fluconazole doses averaged 384 $\pm$ 55mg daily in CM. After initial therapy 74% of AmBd and 78% of fluconazole treated patients were cured, and the authors concluded that fluconazole was as effective as AmBd in the treatment of *Cryptococcus*. When CM patients were examined separately, similar numbers of AmBd (74%) and fluconazole (68%) patients were cured. However, 9% of AmBd patients did not receive flucytosine, which had proven superior efficacy over AmBd monotherapy at the time of the study. Additionally, patients who received AmBd for CM may have been sicker at baseline, as AmBd patients were numerically more likely to have altered mental status (57% vs. 44%), higher serum and CSF antigen titers, and extrameningeal infection than those who received fluconazole.

In 2001, a retrospective case series of HIV(-) patients better described the role of fluconazole in the treatment of cryptococcosis[6]. Sixty-eight percent of patients received AmBd + flucytosine, 17% received AmBd monotherapy, and 5% received AmBd + fluconazole as initial therapy. The median duration of AmBd was 27 days. Seventy-eight percent of patients received fluconazole consolidation therapy, usually after substantial clinical improvement, at a median of 400 mg daily for 70 days. Overall, treatment success rates were comparable to previous studies (81%), but relapse rates were lower than previously observed (4%), indicating that fluconazole consolidation therapy may significantly reduce cryptococcosis recurrence rates in HIV(-) patients. Additionally, a shorter duration of AmBd therapy (4 vs. the previously established 6 weeks), may be sufficient in treating CM in HIV(-) hosts, and may mitigate some drug toxicity.

The IDSA first released guidelines for CM in HIV(-) patients in 2000, and the guidance was updated in 2010. These guidelines recommend AmBd 0.7-1.0 mg/kg/day plus flucytosine 100mg/kg/day in four equal doses for induction therapy (for at least 4 weeks), then consolidation with fluconazole 800mg (12mg/kg) orally daily (for 8 weeks), followed by maintenance therapy with fluconazole 200mg (3mg/kg) daily for 6-12 months[1]. The flucytosine dose recommended is lower than the doses studied in the Bennett and Dismukes trials to mitigate toxicity[5,15]. Durations for induction therapy vary based upon patient prognostic factors: two weeks for patients with an early diagnosis, no underlying immunocompromising conditions, and excellent clinical response to treatment; four weeks for patients without neurological complications or positive CSF yeast cultures after two weeks of treatment; and six weeks for patients with neurological complications [1]. Notably, most immunocompetent patients will receive a longer course of induction therapy than HIV(+) patients if treated according to the guidance.

The use of steroids for the management of CM is controversial and has not been endorsed in published treatment guidelines [1]. However, clinical deterioration after successful clearance of *Cryptococcus gatti* from the CSF has been reported in HIV (-) patients and thought to be similar to the immune reconstitution syndrome seen in HIV (+) patients with CM who begin antiretroviral therapy [20,21]. A retrospective review of 4 patients with *C. gattii* meningitis who developed worsening mental status changes and inflammatory lesions on imaging despite clearance of fungus from the CNS reported clinical improvement in symptoms and imaging with use of dexamethasone in conjunction with serial LPs +/- shunt placement for management of increased intracranial pressure [22]. Another case report describes an HIV (-) male with *C. gattii* CM who experienced clinical deterioration and evidence of cerebral infarction five weeks after treatment initiation despite maintaining clearance of organisms from his CSF. Prednisone was started in conjunction with a ventriculoperitoneal shunt with clinical improvement, however he deteriorated again once the prednisone was discontinued. Ultimately he was maintained on prednisone until successfully tapered off 9 months later [20].

Conclusions

Atypical presentation and practitioner bias regarding which patients are at risk for CM likely contributes to delayed diagnosis and treatment of the disease in immunocompetent hosts. As highlighted by our case, cryptococcosis should be considered in immunocompetent patients who describe an indolent onset of headache and mental status changes in the setting of enhancing lesions, ventricular enlargements, or subacute vascular changes on brain imaging, particularly if fungus is identified from blood or CSF. For HIV (-) patients who present with

classic signs or symptoms of meningitis, cryptococcosis should remain in the differential due to discrepancies between serum and CSF antigen tests in immunocompetent patients.

Acknowledgements

This was an un-funded project.

Table 3. Prognostic factors and associated outcomes for immunocompetent patients with CM[2-6,17-19].

Favorable Outcome	Unfavorable Outcome
• Normal mental status at baseline • Presence of headache • CSF WBCs >20/mL • Presence of idiopathic CD4 lymphocytopenia versus no apparent immune dysfunction	• Pre-treatment serum antigen titers ≥1:32 • Serum antigen titers ≥1:8 one month after the completion of therapy • High CSF fungal burden (CSF antigen ≥1:32 to ≥1:512) • Abnormal neurology at baseline • Abnormal imaging • Peripheral WBC >10,000/mL • Positive *Cryptococcus* blood cultures or cultures at other sites • High opening pressures, low CSF glucose initially and at ≥4 weeks after treatment initiation • Age >60 years • Male sex • Organ failure • Continued prednisone treatment at doses ≥20mg/day after CM treatment discontinuation

Immunocompetent patients diagnosed with CM have a poorer prognosis as compared to HIV (+) patients (Table 3). The profound inflammatory response mounted by the immune system along with delayed detection due to an atypical presentation and lack of apparent risk factors may help explain this phenomenon. Our patient described a 3-month history of symptoms upon initial presentation to the healthcare system with further delay of nearly 3 weeks to an accurate diagnosis. Possible paradoxical deterioration after treatment initiation due to an intact immune system may have further complicated his case. Prompt detection and aggressive treatment are key interventions in treating immunocompetent patients with CM.

Most immunocompetent patients will require a longer induction regimen for CM, which imparts an increased risk of treatment-related complications. The role of steroids for adjunctive management of *C. gattii* CNS infections remains unclear.

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