

Case Report

Persistent Cryptococcal Meningitis Treated with Antiretroviral Therapy and Alternative Antifungals

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Abstract

Because of the relative lack of information surrounding persistent cryptococcal meningitis, treatment presents a clinical dilemma. We report two patients who developed persistent cryptococcal meningitis that was nonresponsive to induction therapy over the course of several weeks. In the first patient, induction therapy with amphotericin and flucytosine was extended. Because of persistently high opening pressures (OPs) and cryptococcal antigen titers at 10 weeks, antiretroviral therapy with the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide was initiated, and the patient's OP and cryptococcal titers normalized within a week. This patient was well at his 2-week visit but was lost to follow-up after that. In the second patient, induction therapy with amphotericin and flucytosine was continued for 6 weeks due to persistently elevated OPs and cryptococcal antigen titers. At that time, high-dose fluconazole was added. This patient steadily improved and was discharged on fluconazole consolidation therapy. After hospital discharge, this patient was lost to follow-up. Published risk factors for persistent infection that these patients shared were positive human immunodeficiency virus status, elevated cryptococcal antigen titers, and persistently high OP. After initiation of unique, nonstandard therapy of antiretrovirals and high-dose fluconazole, both patients improved. Other potential treatment options for persistent cryptococcal meningitis include voriconazole, posaconazole, interleukin 2, acetazolamide, and the placement of cerebrospinal fluid shunts, but these were not selected because of a variety of relative contraindications or limitations of these agents. With limited data to favor one agent over another, it is important to evaluate case-by-case for treatment decisions.

Keywords: Amphotericin, fluconazole, flucytosine, fungal infections, human immunodeficiency virus

INTRODUCTION

While amphotericin resistance among cryptococcal species is rare and routine susceptibility testing is not recommended, persistent infection has been recognized and defined as "persistently positive results of cultures of cerebrospinal fluid (CSF) after 4 weeks of proven antifungal therapy at an effective dose" by the Infectious Diseases Society of America (IDSA).^[1] This definition is somewhat arbitrary, and there may be other clinical indicators of failure in the treatment of cryptococcal meningitis. Currently, there are no recommendations for treatment in this setting. We present two such cases here.

CASE REPORTS

Patient 1

A 29-year-old male with a diagnosis of human immunodeficiency virus (HIV) not on antiretroviral therapy was transferred with fatigue, weakness, and headache. At another facility (13 days

before current admission), he had a CD4 of 34 cells/cmm, positive blood cultures for *Cryptococcus neoformans*, and a positive CSF cryptococcal antigen, for which he received 14 days of amphotericin B and fluconazole.

Laboratories revealed a CD4 of 52 cells/cmm, viral load of 366,444 copies/mL, and white blood cell (WBC) of 2.8 thousand/cmm. Although he presented with no CNS symptoms at our institution, the opening pressure (OP) was high and CSF culture was positive for *C. neoformans*. CSF WBC was 22 cells/cmm, protein was 141 mg/dL, and glucose was 6 mg/dL. Infectious diseases (ID) initially recommended

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14 days of amphotericin B lipid complex 5 mg/kg IV daily and flucytosine 25 mg/kg PO every 6 h and repeated lumbar punctures (LPs) until the OP was <20 cmH₂O.

Due to the consistently high OP and cryptococcal titers on LP over the next 7–8 weeks, induction therapy with amphotericin and flucytosine was extended [Figure 1]. During this time, the patient became encephalopathic (day 5); seized, coded, and was transferred to the intensive care unit (day 13); received empiric therapy for herpes simplex virus and bacterial meningitis (day 22); and had diagnostic tests performed (days 22–55) for bacterial, fungal, and viral pathogens. All additional tests resulted as negative.

Although susceptibilities for amphotericin, flucytosine, voriconazole, itraconazole, and fluconazole were ordered on day 45, these could not be obtained because older cultures were unavailable and newer cultures did not yield testable isolates. Amphotericin and flucytosine were continued with no improvement in the CSF titers and minimal improvement in the OP. On day 55, the ID team recommended starting elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide. Six days later (day 61), the patient had improved clinically and was changed to high-dose fluconazole 800 mg PO daily for consolidation therapy. He was discharged on hospital day 63. In total, the patient had received 75 days of amphotericin plus either flucytosine or high-dose fluconazole. The patient was doing well at his 2-week follow-up visit but had no follow-up after that.

Patient 2

A 50-year-old male with the past medical history of hypertension, diabetes mellitus, and HIV with a history of noncompliance presented with a 2-week history of headache and blurry vision. Physical examination revealed no focal deficits neurologically. An LP in the emergency department was positive for *Cryptococcus* spp. and revealed a high OP [Figure 1]. CSF WBC was 14 cells/cmm, protein was 109 mg/dL, and glucose was 16 mg/dL. Laboratory examination showed an absolute CD4 of 1 cell/cmm, a viral load of 62,147 copies/mL, a WBC of 2.0 thousand/cmm, and a positive cryptococcal antigen titer of $>1:2048$. He was initiated on conventional amphotericin B 0.5 mg/kg/day and flucytosine 25 mg/kg every 6 h, then subsequently changed to amphotericin B lipid complex 5 mg/kg daily once available.

Over the next several weeks, repeated LPs revealed high OP and elevated cryptococcal titers [Figure 1]. ID recommended continuing amphotericin and flucytosine until OP was <20 mmH₂O for two consecutive LPs and until cryptococcal titers decreased. On day 11, amphotericin susceptibilities were ordered, and those were confirmed on day 28 as susceptible (amphotericin MIC = 0.5 mcg/mL; flucytosine MIC = 1 mcg/mL). Although ID also suggested a temporary CSF shunt to help manage high OP, the patient was found to be a poor candidate by the surgical team.

On day 42, ID suggested further susceptibilities to amphotericin plus alternative antifungals, since the prolonged course of amphotericin and flucytosine had failed to sterilize the CSF to date. At this point, high-dose fluconazole 800 mg PO daily was added. On day 51, ID suggested stopping amphotericin and flucytosine, given that the patient had negative CSF cultures (despite continued high OP). On day 62, the OP fell below the desired threshold, and it was recommended to continue high-dose fluconazole for 8 weeks before transition to maintenance therapy. In total, the patient received 51 days of amphotericin and flucytosine and 21 days of high-dose fluconazole. He was discharged on hospital day 63. The patient was lost to follow-up after discharge.

DISCUSSION

Despite not meeting the IDSA definition of persistent cryptococcal meningitis, both patients presented here demonstrated meningitis symptoms, yielded *Cryptococcus* spp. from the CSF and had persistently high OP on LP procedures. With minimal data to guide decision-making, these patients received either antiretroviral therapy or high-dose fluconazole in addition to their amphotericin and flucytosine due to the lack of clinical and laboratory response. Both patients responded to these alternative therapies, potentially providing evidence to support their utility for patients not responding to standard-of-care therapy.

Comparisons of clinical features and mortality in 88 patients with or without HIV was conducted in Taiwan.^[2] Interestingly, HIV status was not a predictor of mortality in this patient

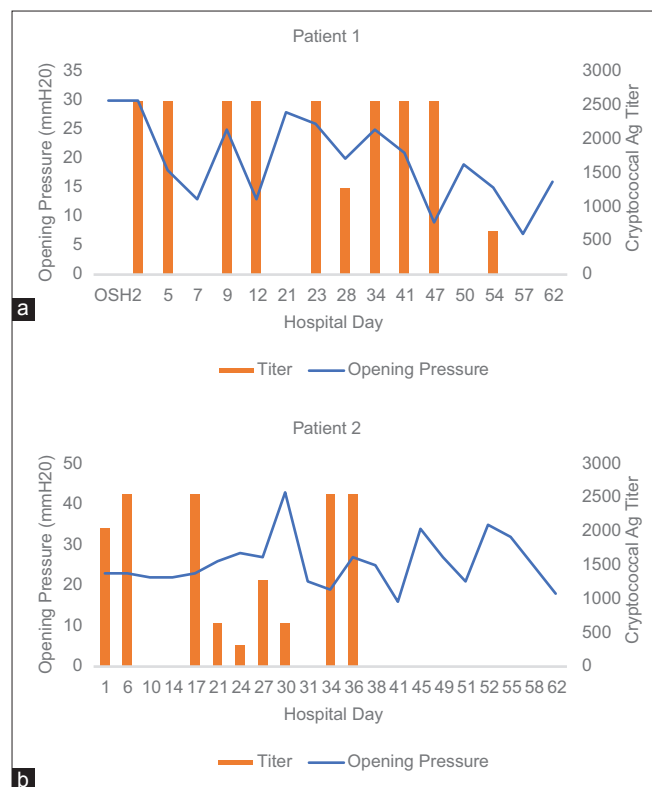


Figure 1: Cerebrospinal fluid opening pressures and cryptococcal antigen titers for the duration of the hospital stays of patient 1 (a) and patient 2 (b)

population. However, serum white count $>11,000/\mu\text{L}$, Charlson comorbidity score >6 , and the absence of normal brain images were independent risk factors for death at 90 days. A study in China evaluating features of cryptococcal meningitis in 106 patients identified HIV infection, stiff neck, serum potassium $<2.7\text{ mmol/L}$, and an ICP $>400\text{ mmHg}$ ($>29.4\text{ mmHg}$) as independent risk factors for persistent infection.^[3] Similarly, both of our patients were positive for HIV and had elevated ICP though neither complained of nuchal rigidity. Latex agglutination cryptococcal antigen titers of CSF $>1:1024$ was another characteristic identified more frequently in patients with persistent versus nonpersistent cryptococcal meningitis. In both patients presented, CSF titers $>1:2560$ were initially observed corresponding with the findings from the Xu evaluation. An important difference to note between our patients and the Lee or Xu studies is the different therapeutic management. Patients in the Lee study received monotherapy with amphotericin B initially due to the lack of availability of flucytosine.^[2] Patients in the Xu evaluation received either amphotericin B or voriconazole for 8–12 weeks with some patients additionally receiving either flucytosine or fluconazole.^[3] However, the patient outcomes were not assessed between treatment regimens. Following the guidelines set forth by the IDSA, both of our patients received initial therapy of amphotericin B plus flucytosine.^[1]

While amphotericin B and flucytosine or high-dose fluconazole are traditional therapy recommended for cryptococcal meningitis, alternative strategies, particularly the usage of voriconazole, has been employed. A total of 55 patients with cryptococcal meningitis were evaluated, assessing in-hospital mortality rates and response rates between those treated with either amphotericin B plus flucytosine, amphotericin B plus fluconazole, or voriconazole.^[4] Of the 16 patients who received voriconazole, no (0%) treatment failures were observed compared to 73% and 21% in the amphotericin B plus flucytosine or fluconazole groups ($P < 0.01$). It is important to note that the OP was numerically lower in the voriconazole treated patients. In our patients, voriconazole was not selected because of variable pharmacokinetics, cost, and potential for drug interactions.

In patients not responding to previously mentioned antifungal agents, varying approaches have been utilized. A case-series of two patients provides evidence for posaconazole in cryptococcal meningitis.^[5] One patient did not achieve either clinical or laboratory improvement after a prolonged course of amphotericin B and fluconazole so was switched to amphotericin B plus flucytosine. However, improvement was still not observed; therefore, posaconazole was added and ultimately led to clinical improvement and normalization of CNS fluid. The other patient initially received amphotericin B

plus flucytosine for 15 days without appreciable improvement, so posaconazole was added to therapy. Both symptomatic and microbiological remission were observed after 30 days. Interleukin 2 (IL 2) is another approach that has demonstrated success for persistent cryptococcal meningitis utilized in a pediatric patient after repeated admissions of dual amphotericin plus flucytosine therapy.^[6] Finally, success with the addition of acetazolamide in a single patient with persistently elevated ICP has been documented.^[7] Nonpharmacologic therapy has also been utilized for persistent cryptococcal meningitis. Specifically, elevated ICP has been managed through the placement of CSF shunts and ventriculoperitoneal shunts.^[8]

Few antifungal agents are available for the treatment of persistent cryptococcal meningitis. With no data in existence to favor one agent over another, it is important to evaluate patients on a case-by-case scenario for treatment preference, side effect profile, and drug-drug or drug-laboratory reactions.

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Conflicts of interest

There are no conflicts of interest.

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