CASE REPORT

Massive cerebral edema resulting in brain death as a complication of Cryptococcus neoformans meningitis

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Despite the widespread use of highly active antiretroviral therapy, cryptococcal meningoencephalitis has emerged as the second leading cause of infectious morbidity and mortality in HIV-infected patients worldwide. It presents usually as subacute or chronic disease but occasionally may be fulminant. Common clinical presentations included headache, fever, and depressed level of consciousness. The infection affects both the subarachnoid space and brain parenchyma, and is characterized by a paucity of inflammation and a large fungal burden in the cerebrospinal fluid at the time of diagnosis. Infection is usually lethal without treatment, thus the prompt diagnosis and therapy might improve the outcome. We report a case of brain death caused by Cryptococcus neoformans meningitis that was diagnosed based on clinical neurological examinations and supported by the absence of cerebral blood flow on brain angiography.

Keywords: Cryptococcus; meningitis; intracranial pressure; cerebral edema; brain death

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Cryptococcus neoformans is an encapsulated yeast that is found ubiquitously in soil, dust, and pigeon droppings. Despite the high prevalence of the organism in the environment, human cryptococcal infections are uncommon, except in patients with disorders of cell-mediated immunity such as AIDS or lymphoreticular malignancies, or in patients with immunosuppression after steroid therapy or organ transplantation (1–3). C. neoformans enters the host primarily through the respiratory tract and establishes primary infection in the lungs. Deposition in the alveoli produces an asymptomatic infection that is either cleared or controlled by a strong cell-mediated immune response leading to a dormant latent infection. From the lungs, bloodstream infection may occur through which the central nervous system (CNS), the skin and soft-tissues, and the genito-urinary tract are established as the most common sites of disseminated infection (4). Approximately 7–8% of HIV-infected patients developed cryptococcal meningitis during their lifetime (5), with a mortality of about 12% in the USA and other developed nations. In sub-Saharan Africa, the incidence per year of cryptococcal meningitis is estimated to be more than 3%, leading to a 3-month case-fatality rate of 70% (6).

Although increased intracranial pressure and cerebral edema are known clinical features of cryptococcal meningoencephalitis, cases of brain death resulting as a complication of the infection have been infrequently reported. We describe a case of C. neoformans meningitis as the cause of cerebral herniation resulting in brain death.

Case

A 50-year-old African American woman presented to the emergency department complaining of headaches, neck pain, photophobia, blurry vision, and vomiting for 4 days. Her medical history was significant for HIV/AIDS, seizure disorder, substance abuse, and asthma. She referred to having an unknown infection for which she required several lumbar punctures about 2 months prior to this presentation. Her outpatient medications included highly active antiretroviral therapy (HAART) (composed of emtricitabine, ripinavir, and tenofovir), albuterol, and levetiracetam. Her vital signs on arrival to the emergency department were as follows: blood pressure of 135/60 mmHg, heart rate of 88 beats/min, respiratory rate of 18 breaths/min, and temperature of 37°C. Her oxygen saturation was 98% while breathing room air. She was alert and oriented in time, place, and person. Her physical...
examination showed no neck rigidity, negative Kernig’s and Brudzinski’s signs, and intact cranial nerves. No skin lesions were noted, and lungs examination was unremarkable. Significant laboratory findings included a urine toxicology positive for opiates, and a CD<sub>4</sub> T-cell count of 195 cells/µL. Chest radiography showed no abnormalities. Head computed tomography (CT) demonstrated no evidence of ischemic infarcts, hemorrhage, mass, or hydrocephalus. She was admitted to the medical floor with the possible diagnosis of CNS infection. Initial empiric intravenous antimicrobial therapy with vancomycin (1 g every 12 hours), ceftriaxone (2 g every 12 hours), acyclovir (500 mg every 8 hours), and fluconazole (400 mg daily) was initiated. Cerebrospinal fluid (CSF) analysis showed a white blood cell count of 36/cu mm (81% lymphocytes, 19% neutrophils), a red blood cell count of 36/cu mm, a glucose level of 29 mg/dL (40–80), and a protein level of 120 mg/dL (12–60). Even though the diagnosis of possible *C. neoformans* meningoencephalitis was sought, opening pressure was not documented because of technical reasons. Approximately 8 hours after the lumbar puncture was performed, she was found unresponsive and apneic. She was intubated and transferred to the intensive care unit (ICU). Initial blood cultures obtained on arrival to the hospital grew yeast within 48 hours of admission, later identified as *C. neoformans* on day 5 of admission. *C. neoformans* was also isolated from the CSF cultures. Serum and CSF cryptococcal antigen were also positive at titers of 1:2048 and 1:1024, respectively. Antimicrobial therapy was narrowed to liposomal amphotericin-B (480 mg intravenously daily) and flucytosine (2 g per orogastric tube every 6 hours). ICU course was complicated by hemodynamic instability requiring vasoppressors, electrolyte imbalance (diabetes insipidus), and acute kidney injury. Repeated head CT showed diffuse edema, which progressed to massive brain edema and herniation within 12 hours of arrival to ICU. Neurological examination disclosed dilated and fixed pupils bilaterally, absence of corneal and gag reflexes, negative eye-caloric test, and no response to deep painful stimuli. A brain flow scan was performed on day 5 of admission to ICU, revealing no evidence of cerebral blood flow. Patient was pronounced brain dead.

**Discussion**

**Increased intracranial pressure is a common complication of cryptococcal meningitis.** It has been postulated that it may be secondary to outflow obstruction precipitated by aggregation of fungal polysaccharide accumulating in arachnoid villi and subarachnoid spaces thus providing the blockage of the channels for CSF drainage (7). Another important contributing factor could be cerebral edema resulting from cytokine-induced inflammation and possibly osmotic effect by fungus-induced mannitol (8). In one study, 40% of deaths during weeks 3–10 following an episode of cryptococcal meningoencephalitis were attributed to increased intracranial pressure (9). A recent autopsy study demonstrated a correlation between high concentration of viable and dead organisms in the arachnoid granulations and raised CSF pressure with the consequence of the obstruction of CSF resorption and communicating hydrocephalus (10). Cerebral herniation and brain death as a result of cryptococcal meningoencephalitis has been infrequently reported. Zhu et al. found an incidence of 19.5% of cerebral herniation in non-HIV-infected individuals with cryptococcal meningitis (11). Other cases of *C. neoformans* meningoencephalitis leading to brain herniation were found at autopsy (12–15). Several studies have demonstrated that high CSF fungal burden (expressed by elevated cryptococcal antigen titers) (16, 17), altered mental status (17), disseminated infection (manifested by the presence of fungemia) (16), symptomatic elevation of intracranial pressure (18), and low CSF leukocyte counts (19) are factors associated with poor outcome of AIDS-related cryptococcal meningoencephalitis. Blood cultures have been reported positive in 47–71% of HIV-infected patients with cryptococcal meningoencephalitis (20). The patient described in this report had several findings that might have contributed to her rapid adverse outcome: 1) CSF cryptococcal antigen was elevated, which might support the presence of a high fungal load, 2) blood cultures were positive, which evidenced the presence of disseminated disease, and 3) she had clinical evidence of increased intracranial pressure, expressed by headache and vomiting. Besides, initial empiric antimicrobial therapy did not include amphotericin-B or 5-flucytosine, which has been described as risk factor for adverse outcome (16, 21).

The optimal medical therapy of cryptococcal meningoencephalitis consists of the combination of amphotericin-B and 5-flucytosine for 2 weeks, which is known as induction phase. The consolidation phase is the subsequent 8-week treatment period with fluconazole and is followed by the maintenance phase or secondary prophylaxis in order to prevent relapses. Discontinuation of maintenance therapy is indicated after at least 12 months of antifungal therapy with undetectable HIV-viral load for >3 months, and a sustained T-cell lymphocytes count of >100 cells/µL (22). HAART should be initiated as soon as possible because its deferral is associated with further HIV-related diseases and increased mortality. However, the risk of severe or potentially lethal immune reconstitution inflammatory syndrome (IRIS) associated with an unsterilized CSF infection is an argument against an early or concomitant (with antifungal therapy) antiretroviral treatment. Nevertheless, fear of inducing IRIS-related complications of cryptococcal meningitis should not be a barrier to beginning HAART (23).

The management of increased intracranial pressure without hydrocephalus in the setting of cryptococcal
meningitis consisted of CSF drainage by lumbar puncture with or without positioning of temporary percutaneous lumbar drains for patients requiring repeated daily lumbar punctures (22). However, daily lumbar punctures, although associated with immediate relief of headache, may increase the risk of brain herniation (24). The use of permanent ventriculoperitoneal shunts can be reserved for patients with hydrocephalus or raised intracranial pressure refractory to other measures (22, 25).

It is difficult to establish whether our patient had a relapse from a possible previous infection, a persistent infection, or a cryptococcal-related IRIS. We assumed that the CNS infection she referred to on admission was probably cryptococcal meningitis. The Infectious Diseases Society of America defines persistent infection as positive CSF cultures after 4 weeks of proven antifungal therapy at established effective doses (22). It is important to differentiate relapse from persistent infection because changing cryptococcal antigen titers and the presence of positive India ink examination results are insufficient to diagnose microbiological relapse with an implied need to alter antifungal treatment strategies. Most cases of relapse are attributable to inadequate primary therapy (dose and duration) or failure of compliance with consolidation or maintenance therapy (26, 27). The authors hypothesized that this patient likely had a relapse from her possible previous infection, based on the following: 1) patient was not adherent to secondary prophylaxis, 2) CSF cultures were positive for *C. neoformans*, and 3) presence of low CSF leukocytes count, as previously suggested in one study (28).

In conclusion, high index of suspicion is required to diagnose and treat opportunistic infections among immunocompromised patients. *C. neoformans* meningoencephalitis may be lethal without appropriate antifungal therapy, which included a combination of amphotericin-B and flucytosine. Initial induction therapy with amphotericin-B, achieving CSF sterility, secondary prophylaxis with fluconazole, and adherence to HAART remains the key cornerstones of care for these patients.

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