A rare presentation of cryptococcal meningoencephalitis in an immunocompetent individual

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Abstract

Cryptococcal meningoencephalitis is a leading of morbidity and mortality in immunocompromised individuals worldwide. However, there are few documented cases in immunocompetent patients. We present a rare case of disseminated Cryptococcus with progression to meningoencephalitis in an immunocompetent patient, with a possible atypical presentation. Magnetic resonance imaging of the brain and electroencephalogram to rule out brain metastasis were negative. Lumbar puncture resulted positive for *Cryptococcus neoformans* antigen at titers of 1:2048 and a detailed history later revealed occupational exposure to bird dander by cleaning floors and cages. Diagnosis is challenging, with delays often resulting in increased morbidity and mortality. Cerebrospinal fluid and serum *Cryptococcus* antigen play a key role in both diagnosis and determining treatment efficacy. Furthermore, current treatment guidelines are used for immunocompromised individuals. Due to the significant side effects of these medications, further research is needed to determine the optimal treatment duration for immunocompetent patients to minimize the need for unnecessary therapy.

Introduction

Cryptococcal meningoencephalitis (CM) is a leading cause of morbidity and mortality among immunocompromised patients, and HIV/AIDS-associated cases having a worldwide incidence of over one million cases and 600,000 mortalities per year. Cryptococcus is an encapsulated saprophytic yeast that is transmitted through environmental spores. In the lung, they are phagocytosed and survive in alveolar macrophages where it can cause pulmonary disease. In patients with compromised immune systems, the organisms can reactivate and disseminate to the central nervous system.[1,2]

Two separate species, *Cryptococcus neoformans* and *Cryptococcus gattii*, account for the majority of disease burden. *C. neoformans* serotypes A and D are the virulent pathogens in most immunocompromised patients. In contrast, cryptococcus gattii serotypes B and C, endemic in Australia and Papua New Guinea, are more frequently reported in immunocompetent individuals.[3]

Current literature identifies the following risk factors for CM: AIDS, organ transplant recipients, patients with recent corticosteroid use, cancer, and patients with idiopathic $CD4^+$ lymphocytopenia.[4] While approximately one million cases of HIV-associated cryptococcus are reported annually worldwide, the incidence in immunocompetent subjects with co-morbid cancer is more likely to present with disseminated disease or lung involvement.[5] Herein, we share an atypical presentation of CM in an immunocompetent patient with newly diagnosed metastatic lung cancer. We highlight our diagnostic approach with the utility of the lumbar puncture (LP) to not only aid in diagnosis, but also to evaluate the efficacy of the treatment course and response.

Case Report

A 63-year-old male (75 kg, BMI 33.3) with no known past medical history presented for further management of hip pain. The patient was recently diagnosed with poorly differentiated adenocarcinoma of the lung with metastasis to the liver and right iliac bone. The patient had not received medical care in over twenty-years and denied surgical history or use of medications. He denied intravenous drug use, alcohol use, and tobacco history. The patient worked as a part-time bird-cage cleaner and had no travel history. The patient denied a recent history of fevers, chills, nausea, vomiting, and weakness, shortness of breath, confusion, vision changes, headache, or sick contacts.

Physical exam and neurologic exam were unremarkable without focal deficits. The patient was alert and orientated to time, location, and situation. Labs on admission showed no leukocytosis, neutrophilia, eosinophilia, or monocytosis. Orthopedic surgery consultation recommended medical management of bone metastases. A plan for palliative radiation therapy to right hemipelvis was planned. On day two of the hospitalization, prior to initiating radiation therapy, the patient was observed to be confused, and unable to follow commands. The patient was lethargic with intermittent episodes of agitation and hallucinations. No focal neurological deficits were present. An EEG and MRI brain were unremarkable without evidence of interictal discharges or metastases. An LP was performed to rule out carcinomatous meningitis.

Cerebrospinal fluid (CSF) fluid analysis yielded high protein, low glucose, pleocytosis with monocyte predominance, and gram stain with many *C. neoformans* fungi. The Cryptococcal antigen titer was strongly positive - 1:2048 and paired with positive serum cryptococcal antigen titer - 1:4096 (Table 1). Further testing showed negative HIV serology, RPR serology, and a normal CD4/CD8 count.

The patient was initiated on anti-fungal therapy with Flucytosine 2000-mg IV every 6-hours and amphotericin 200-mg IV daily with plan for a repeat LP on day fourteen of treatment to help determine treatment duration and efficacy. The patient's mental status improved after four days of anti-fungal therapy and the patient fully returned to baseline mental status after twelve days. Repeat LP on day fourteen of treatment revealed a normal opening pressure, elevated protein, lymphocyte predominate pleo-

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Table 1. Summary of initial lumbar puncture results versus repeat lumbar puncture results.

	CSF Description xanthochromia	White blood cells, red blood cells	Percent of neutrophils, mononuclears, eosinophils	CSF protein glucose	CSF culture results	Cryptococcal antigen titer CSF *vs* serum
Initial LP	Colorless, clear, no xanthochromia	165 3	1% 99% 0%	179.5 31	Moderate white blood cells seen; many Cryptococcus neoformans seen	CSF - 1:2048 Serum - 1:4096
Repeat LP	Pink, hazy, no xanthochromia	166 3000	2% 97% 1%	176.4 57	No white blood cells seen; no fungus seen	CSF - 1:640 Serum - 1:1280

cytosis, and negative CSF cultures for Cryptococcus, with a downtrend in CSF cryptococcal antigen titer - 1:640, paired with a downtrend in serum Cryptococcal antigen titer of 1:1280 (Table 1). A plan for four weeks of induction therapy, to be followed by eight weeks of consolidation therapy, and six months of suppression therapy was set forth.

The patient's hospital course was complicated by severe neutropenia and significant electrolyte abnormalities attributed to the flucytosine therapy, along with moderate hyponatremia attributed to SIADH in the setting of adenocarcinoma. Flucytosine was stopped indefinitely after nineteen days and the induction phase was completed with 28 days of amphotericin single-therapy. The consolidation phase with eight weeks of high-dose fluconazole, 400 mg PO daily, was started and tolerated well. While on consolidation therapy, the patient completed a full course of ten-fractions of palliative radiation without further complications.

Ultimately, in the setting of a metastatic lung cancer, the patient was discharged to home with low-dose fluconazole, 100mg PO daily, for one-year to achieve chronic suppression.

Discussion and Conclusions

We describe a case of Cryptococcal neoformans meningoencephalitis in an immunocompetent patient with newly diagnosed metastatic lung cancer. The finding was unexpected given patient was not neutropenic, not acutely ill appearing (*i.e.*, afebrile with stable vital signs) and was not initiated on radiation, chemotherapy, or immunosuppressive medications. The infection was initially occult and progressed insidiously.

The patient presented with the sole symptoms of delirium and altered mental status, without abnormalities on MRI brain.[6] Notably, this case lacked the common manifestations of cryptococcal meningitis presenting with fever, frontal headache, and neck stiffness or the unilateral or bilateral visual disturbances, ophthalmoplegia, seizures, or focal sensorimotor deficits typically associated with cryptococcal encephalitis.[7] In the absence of such findings, a clinician faces great difficulty identifying an underlying CM infection, which has a poor prognosis if not discovered early.

A diagnostic lumbar puncture is pivotal in this elusive setting. However, a negative LP cannot exclude cryptococcal encephalitis infection limited to the brain.[8] As a result, we also highlight the utility of systematically searching for the *C. neoformans* antigen titer when there is high clinical suspicion for a cryptococcal infection.

Patients with CM are susceptible to a variety of medical complications, most commonly increased intracranial pressure, immune reconstitution inflammatory syndrome (IRIS), drug-resistant Cryptococcal infection, and Cryptococcomas causing intracerebral mass effects. While a swift inflammatory response may worsen intracranial edema and mass effect, an intact immune system is likely more able to control the fungal pathogen and partially eliminate the primary disease burden.[4] Such factors underscore the fact that cases of CM with subtle presenting symptoms present a major challenge in determining how aggressive to be in pursuing treatment strategies, with different treatment paradigms needed for cases of CM in immunosuppressed *versus* immunocompetent individuals.

The optimal treatment regimens for CM rely on the aggressive administration of antifungal agents in three phases: induction, consolidation, and maintenance, with supplemental therapeutic relief of increased intracranial pressures as needed by serial LP's.[9] Recent studies have shown that combination antifungal therapies, specifically with amphotericin and flucytosine compared to amphotericin B monotherapy, increases yeast clearance and confers a significant survival benefit to patients, with fewer deaths both at 14 and 70-day benchmarks after the initiation of treatment.[10,11]

In practice, the recommended timeline for treatment includes an induction period of two-weeks, usually followed by an eight-week consolidation period and up to one-year of maintenance therapy.[4] However, there is no specific considerations for cases of CM in the immunocompetent population.

Patient tolerance of the side effects and administration methods is a major challenge in treatment. Amphotericin must be administered intravenously and is associated with side effects including anemia, renal injury, electrolyte abnormalities such as hypokalemia, and phlebitis. Flucytosine is also typically administered intravenously and carries a similar side effect profile. Most patients also carry a high risk of developing rebound IRIS, a severe inflammatory response that affects the CNS best controlled by incorporation of anti-TNFα agents such as adalimumab into the regimen to reduce the inflammatory response.[9]

In summary, this case addresses the diagnostic challenge posed by an atypical presentation of CM without classical risk factors and signs/symptoms. While current treatments guidelines are geared towards removing the infectious pathogen and controlling the ongoing immune response in the CNS, we believe future strategies should consider the characterization of a patient's immunophenotype in devising a drug regimen for both immunosuppressed and immunocompetent patients. We believe our patient most likely acquired CM due to a combination of very high fungal load in his occupational exposure combined with a recent diagnosis of cancer.

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