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Case Report Open Access

Cryptococcal Meningitis in a Patient with Idiopathic CD4 Lymphocytopenia

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Abstract

A 49 year-old man with a past medical history of hypertension and tobacco use presented to the emergency department after being found by family with altered mental status. Over the previous few months he had experienced progressive fatigue and slurred speech. More recently over a period of days he had experienced flu-like illness with upper respiratory infection, nausea, vomiting and diarrhea with subjective hearing loss. He was subsequently diagnosed with *Cryptococcus neoformans* meningitis with fungemia due to idiopathic CD4 lymphocytopenia.

Case Presentation

A 49 year-old Caucasian man presented to the emergency department with altered mental status. His family reported that he had not felt well for several months and they had noticed slurring of his speech over this time. They urged him to seek medical evaluation but he declined. He had been able to continue his daily activities including working a manual labor job installing flooring until the past week although he was experiencing progressive fatigue over the previous month. He had no unusual chemical exposures and had not been out of the country. He had no pets and had no exposure to any exotic animals or birds. He had no significant HIV risk factors. Family reported he had developed bizarre behavior over the past week including answering the door partially undressed. He would not allow family members to come into his home but persisted in stating he was fine. Family reported he had flu like symptoms with cough, upper airway congestion, nausea and vomiting over four to five days prior to presentation. However, these symptoms had now resolved. In addition, he complained of decreased hearing in bilateral ears for the previous two to three days along with imbalance.

In the emergency department he was alert and oriented, but noted to be impulsive and removed medical appliances. He requested to sign out against medical advice and tried to leave but was unsteady on his feet and unable to maintain balance, and subsequently agreed to stay. Neurology was consulted for admission. On exam he had generalized weakness, bilateral hearing loss, incoordination, truncal ataxia, nystagmus, a positive Romberg sign, severe gait ataxia, and he was unable to maintain an upright posture. His bilateral horizontal nystagmus was non-fatigable. Deep tendon reflexes (DTRs) were absent but a right Babinski sign was present. Skin exam revealed Condyloma on his penis. Initial work up included CT of the head, Complete blood count, Metabolic panel, Liver function test, blood and urine cultures were obtained. LP was attempted but initially was unsuccessful due to his body habitus.

CT of the head was unremarkable. Chest radiograph was normal. Flu, Respiratory virus panel and Syphillis serologies were negative. White blood cell count was elevated at 15,000 cell/mcL with 87.2 % neutrophils and no bands. BMP, LFTs, Ammonia, Vitamin B 12, Folate and TSH and Ammonia were unremarkable. Urinalysis showed moderate ketones. CRP was elevated at 90.7 mg/L.

Differential diagnosis included posterior circulation ischemia, alcohol withdrawal, meningitis, and subarachnoid space inflammatory process, an infectious process such as encephalitis, paraneoplastic syndrome, or vitamin deficiency such as Wernicke's encephalopathy.

The morning following admission the patient developed symptoms that were thought to possibly be related to alcohol withdrawal including hallucinations, diaphoresis, hypertension and tachycardia. The family reported patient alcohol use of five to six beers per day. He was given folic acid and thiamine supplementation and the Neuro ICU was then consulted for transfer. The patient underwent endotracheal intubation for altered mental status and oxygen desaturation. He was initiated on propofol infusion. A lumbar puncture was performed and cloudy appearing fluid was obtained. Opening pressure was not recorded. He was started on empiric antibiotic and antiviral therapy with for presumed bacterial meningitis or viral encephalitis.

EEG showed diffuse slowing with no epileptiform abnormalities. CSF was sent for lyme, west nile and encephalitis panel. CSF analysis showed 100 RBCs, 35 WBCs with lymphocytic predominance, glucose 4 and protein 74. Gram stain of CSF showed yeast suggestive of Cryptococcus. HSV, Enterovirus, VDRL were negative. The CSF cryptococcal antigen returned with a positive result of >1:1024. Blood cultures also grew out *Cryptococcus neoformans*. Urine culture and respiratory cultures were unrevealing.

Treatment with Amphotericin B, Flucytosine and Fluconazole were initiated. A CD4 count was obtained which showed lymphocytopenia with reduced absolute CD4 cells with a count of 95 cells/ul consistent with immunodeficiency. HIV -1 RNA Viral Load was not detected and HIV 1 and 2 Reflex Confirmatory test was negative. Hepatitis panel was negative. Patient was also initiated on prophylaxis with atovaquone for pneumocystis jiroveci pneumonia (PCP) prophylaxis. ANA, Quantiferon Gold, was negative. Rheumatoid factor was positive with titer of 1:16.

MRI of the brain with and without contrast showed multiple foci of high T2 FLAIR signal in the subcortical and deep white matter with

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diffuse high FLAIR signal in the subarachnoid space and a single focus of enhancement which was thought to be sequela of patient's known cryptococcal meningitis.

LP was repeated in 48 hours with elevated opening pressure of >54 cm H_20. Ophthalmology evaluation showed optic disc edema but no evidence of chorioretinitis. Serial daily lumbar punctures were done with persistently elevated opening pressures. Subsequently a lumbar drain was placed for management of intracranial hypertension.

His ICU course was complicated by non-oliguric acute kidney injury as a result of Amphotericin B and exacerbated by fluid losses from C –difficile colitis-negative diarrhea and amphotericin B induced diabetes insipidus. During his initial ICU stay he experienced a deteriorating exam with intermittent agitation, inability to follow commands and generalized weakness. Sedation was ultimately discontinued as agitation improved.

CSF cultures continued showing yeast on gram stain but cultures became negative as of day 14. The patient was successfully extubated on hospital day 16. His mental status and wakefulness slowly improved so those by day 18 he inconsistently would mimic and intermittently verbalize. He indicated difficulty with hearing. ENT evaluation was done; CT of the temporal bones was unrevealing. Bedside audiogram was unable to be performed due to mental status. ICP normalized and the lumbar drain was removed on hospital day 29. He was transferred to the Intermediate care unit after a 28 day ICU course and later transferred to long term rehabilitation.

He concluded induction treatment with Amphoterecin B and Flucytosine and treatment with Fluconazole continued. Repeat CSF examination at 6 weeks revealed negative smear and culture. At 3 months patient's CD4 count remained at 150. Further testing revealed no known cause of immunodeficiency consistent with the diagnosis of Idiopathic CD4 Lymphocytopenia.

Discussion

Cryptococcal meningitis occurs mainly in immune-compromised hosts with the diagnosis of HIV/AIDS and has an increased frequency in patients with autoimmune disease such as Sarcoidosis, malignancy or immunosuppression. However, after increasing reports of cryptococcal disease and other opportunistic infections in patients without any known disease process but with low CD4 counts, this syndrome was termed Idiopathic CD4 Lymphocytopenia (ICL). It was first recognized by the CDC in 1992 [1]. Case reports of ICL with opportunistic infections have since continued to appear in case studies throughout medical literature. ICL is defined by the CDC as having depressed number of CD4 +T- lymphocytes at less than 300 cells per cubic millimeter or less than 20 percent of total T cells on more than one occasion three months apart and in the absence of HIV type 1 or 2 as well as any other immunodeficiency that may cause depressed levels such as Sarcoidosis, HTLV1, HTLV2 infection, or immunosuppressive therapies. Patients with ICL may range from asymptomatic to life threatening infections [2]. The condition is more commonly seen in adults but is reported in children through the elderly. There is a male predominance with a range reported of 1.2:1 to 1.8:1 [3,4]. There are no known causative agents, however, there is some suspicion of autoimmune etiology with the development of T cell antibodies [5]. Other hypothesis include decreased T cell precursor generation, increased apoptosis of T cells or alteration by decreased production of cytokines [6].

In a review of 53 cases by Zonios et al., patients with Cryptococcus and ICL they described the most common opportunistic infections seen as dermatomal zoster, mycobacterium, and human papilloma virus, with zoster being most common. PCP infection was rare with only one reported case. There appears to be a lower rate of PCP in ICL patients compared to HIV patients so the need for prophylaxis in unclear but trends to follow the current HIV guidelines [2,3,6]. As opposed to HIV patients, those with ICL tend not to have the progressive overall decline in health and CD4 counts tend to maintain a stable level. Recurrence of infection is also less common in ICL than HIV [4].

A review of 259 cases found in a review of ICL case studies by Ahmad et al. found that cryptococcal infection was the most common opportunistic infection [4]. This review revealed that 9.3% of patients died because of their opportunistic infection and 77.5% survived whether infection, malignancy or autoimmune disease and 13.2% were not documented. This review revealed that 85% had more than one opportunistic infection.

It is suspected that *Cryptococcus neoformans* may exist in a chronic form as the autopsy on one patient who went undiagnosed. He had ICL and developed cognitive impairment, gait ataxia and mild pleocytosis but unrevealing CSF analysis. Post mortem he was found to have infiltration of CD8+ and macrophages in the base of the brain phagocytizing but not efficiently digesting *Cryptococcus neoformans* suspecting that it enabled a chronic intracellular infection [7]. It can be hypothesized that this may explain the changes this selected patient experienced for several months prior to presentation. An additional case report describes a patient with a symptomatic lung mass that revealed *Cryptococcus neoformans* in the setting of ICL. Further workup ensued and he was found to have at that time asymptomatic cryptococcal meningitis [8].

Learning Points/Take Home Message

1. Although a rare diagnosis, Cryptococcal meningitis can occur in the otherwise immune-competent host and testing should still be considered.
2. Immunodeficiency is not necessarily related to HIV and testing in patients with unusual infections should be done.
3. Low CD4 counts should not be presumed as a diagnosis of HIV in patients suspected of having HIV infection.

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