

Another case of cryptococcal meningitis in a person without HIV who injects drugs: A possible risk factor in need of further investigation

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ABSTRACT

Cryptococcal meningitis is a fungal central nervous infection typically occurring in patients with severe immunocompromise. We present a case of cryptococcal meningitis occurring in a patient with active injection drug use (IDU) but no immunocompromising condition. This is the seventh case in the recent literature of cryptococcal central nervous involvement in an otherwise healthy young person with IDU, suggesting a possible association in need of further exploration.

1. Introduction

Cryptococcus is a fungus that typically causes opportunistic infections among people living with advanced HIV or with significant immunosuppression or compromise such as those with hematologic malignancies, autoimmune diseases or solid organ transplant. Transmission is thought to occur via inhalation of the organism from an environmental source like soil or bird feces. In the United States, there are two predominant disease-causing species of the fungus – *C. neoformans*, typically occurring in individuals with severe T cell deficiencies, and less commonly *C. gattii*, which can occur in healthy individuals. Cryptococcosis in general however remains rare among seemingly immunocompetent hosts, and in non-HIV and non-transplant patients with cryptococcal meningitis, diagnosis and treatment may be delayed due to lower suspicion for this disease entity and atypical presentations.

Intravenous injection of heroin, fentanyl and methamphetamine are thought to have immunosuppressive effects and recent case series by Polk et al. (2020) and Shorman et al. (2016) describe several recent cases of Cryptococcal meningitis in the US among immunocompetent patients with injection drug use (IDU). In this report, we describe an additional case of cryptococcal meningitis in an otherwise healthy patient who injects drugs, adding to the limited body of literature suggesting IDU as a potential risk factor for cryptococcal CNS disease.

2. Case

A 28-year-old female with a past medical history of polysubstance use disorders including severe opioid use disorder with ongoing IV heroin use and chronic Hepatitis C without cirrhosis presented with 2 weeks of progressive headache, nausea, vomiting and subjective fever. She initially presented to a local detoxification center on Day 0 as she thought she was withdrawing from benzodiazepines and heroin and was subsequently sent to the Emergency Department that day.

In the ED, the patient was ill appearing and drowsy with slight tachycardia and mild hypotension but afebrile. She was not noted to have nuchal rigidity at that time however later complained of severe headache and neck pain. Lumbar puncture was performed in the ED on Day 0 and the patient was started on empiric vancomycin and ceftriaxone for possible meningitis and UTI. CSF analysis revealed 725 nucleated cells (76% lymphocytes), elevated protein (170 mg/dL) and low glucose (<20 mg/dL). Opening pressure was not initially obtained in the ED however repeat LP on Day 1 had an OP of 37 cm H₂O. CBC was unremarkable with a normal differential. HIV Ag/Ab test and RNA PCR were non-reactive/not detected, and her HCV RNA PCR was 193,572 IU/mL. Blood cultures were no growth and transthoracic echo did not reveal any vegetations or valvular abnormalities. CSF Viral PCR studies including HSV, Enterovirus, CMV, EBV were negative, however CSF Cryptococcal Ag returned positive with titer 1:160 on Day 2. Serum Cryptococcal Ag was negative and absolute CD4 was 535 cells/uL. CSF cultures ultimately grew <1+ *Cryptococcus neoformans*; no susceptibility

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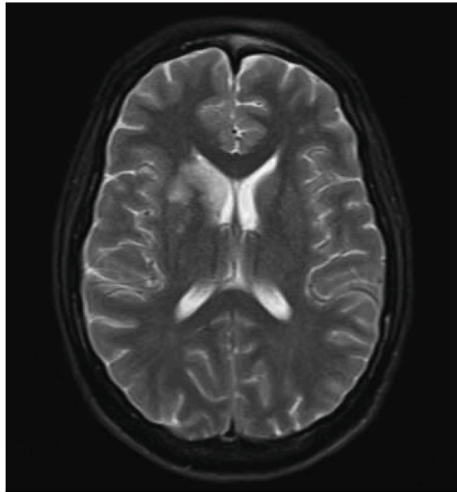
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testing was performed.

While CT head without contrast on admission (Day 0) was unremarkable, MRI brain with and without contrast on Day 1 revealed T2/FLAIR hyperintensities in the right basal ganglia with increased diffusion signal reflecting subacute infarcts as well as several enhancing foci in the bilateral basal ganglia in the lenticulostriate artery distribution both concerning for cryptococcomas and cryptococcal vasculitis.



The patient was started on intravenous liposomal amphotericin B 4mg/kg/day and oral flucytosine 25mg/kg every 6 hours on Day 2 with plan for 6 weeks of induction therapy given findings on MRI brain followed by 8 weeks of oral fluconazole 800mg daily consolidation and maintenance. Therapeutic drug monitoring for flucytosine was not obtained. Serial LPs were performed until opening pressures normalized on Day 12. Addiction medicine was also consulted and the patient was initiated on buprenorphine-naloxone for opioid use disorder on Day 5.

On further discussion, the patient reported daily IV heroin use and intermittently smoked cocaine and methamphetamine, most recently a week prior to admission, but had not nasally inhaled substances for at least 5 years. She did have a pet blue headed pionus parrot that she did not keep in a cage and was free in the home that had died 2 months prior to presentation.

3. Discussion

To our knowledge, this is the seventh case reported in the *recent* literature of cryptococcal meningitis in otherwise immunocompetent persons who inject drugs. Prior case reports were from the 1990s. It remains unclear why or how disseminated cryptococcal disease occurs in this patient population.

As noted in the two prior case series on this phenomenon [1,2], opioids including heroin and fentanyl and methamphetamines can impact immune function. Animal models have indicated immunomodulatory effects of methamphetamines on antigen processing with increased dissemination of cryptococcus from the lungs to the brain [3]. Short- and long-term use of opioids, particularly morphine and fentanyl,

have been shown in animal and human models to alter T-lymphocyte activity among others [4], but there is a paucity of controlled clinical studies examining the relevance of these findings [5].

For our patient, we suspect that she developed cryptococcal meningitis due to a combination of potential immunosuppression from injecting heroin and smoking methamphetamine in addition to inhaling a high inoculum related to having a bird living free in the home. It should be noted that all the cases in the recent literature occurred on the East Coast (West Virginia and North Carolina).

While causal inferences cannot be made from a case report, our patient does add to the number of cryptococcal CNS infections among otherwise immunocompetent patients with IDU and suggests there may be an association that should be investigated further in basic science labs and prospective cohort studies. Given the rise of IDU in the United States, this may be an emerging and under-recognized infectious entity.

We suggest that cryptococcal CNS disease should be in the differential for patients with IDU who present with symptoms of meningitis. Infarcts on brain imaging in immunocompetent persons with IDU and fever should also invoke consideration of this disease process [6–8], especially if the patient has negative blood cultures or echocardiography making embolic phenomenon less likely. Furthermore, Addiction medicine consultation and/or initiation of medication for opioid use disorder should be considered, especially as some patients may require prolonged IV antifungal therapy that may not be able to be completed in the home setting. Abundant research shows these interventions improve post-discharge overdose-related mortality.

Conflict of interest

There are none.

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