Cryptococcal meningoencephalitis in an immunocompetent host presenting with severe agitation: a case report

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: Both authors; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Background: *Cryptococcus neoformans* (*C. neoformans*) primarily infects immunocompromised patients. Several case reports have described the infection in immunocompetent patients, the vast majority presenting with mild symptoms.

Case Description: We describe the case of a 42-year-old otherwise healthy male who presented to our Southern California emergency department with acute onset of seizure, violent behavior, and altered mental status. He required heavy sedation to obtain diagnostic imaging, labs, and cerebral spinal fluid (CSF) studies. His CSF cryptococcal Ag was positive, and culture later confirmed *C. neoformans*. Although this has historically been linked to immunocompromised hosts, thorough inpatient workup and detailed history could not reveal any sources of immunosuppression. He was treated with amphotericin B and flucytosine, and discharged after a nearly 4-week hospital stay. Not only was his clinical picture abnormal for fulminant fungal meningoencephalitis, but his presentation was also highly unusual due to his severe agitation.

Conclusions: Cryptococcal meningitis should be considered in immunocompetent patients. The presentation may range from milder symptoms to severe agitation and seizures. We advocate for routine addition of fungal and viral titers in otherwise immunocompetent hosts to CSF studies, as morbidity and mortality with fungal infection is directly correlated with delay of diagnosis and treatment.

Keywords: Cryptococcal meningitis; *Cryptococcus neoformans* (*C. neoformans*); altered mental status; immunocompetent; case report

Received: 20 October 2023; Accepted: 15 December 2023; Published online: 20 February 2024.

doi: 10.21037/jeccm-23-128

View this article at: https://dx.doi.org/10.21037/jeccm-23-128

Introduction

Cryptococcus neoformans (*C. neoformans*) is an encapsulated yeast that predominantly infects immunocompromised patients, including those with acquired immunodeficiency syndrome (AIDS), hematopoietic malignancies, chronic steroid use, and solid organ transplant recipients (1). In rare cases, it can infect apparently immunocompetent hosts (2). The organism enters via the respiratory tract and causes a broad spectrum of disease, from asymptomatic infection to severe pneumonia, central nervous system meningoencephalitis, and disseminated fungemia (1,3,4). Case reports of cryptococcal meningitis in immunocompetent patients have been previously documented in the literature, but largely these patients had a mild presentation, including minimally altered mental status, trace neurological deficits, insidious headache, and even dental pain (3,5-7). Herein, we describe a case of meningoencephalitis in

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an otherwise immunocompetent 42-year-old male diagnosed in a Southern California emergency department (ED) who presented with profound altered mental status and violent behavior. We present this case in accordance with the CARE reporting checklist (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-23-128/rc).

Case presentation

A 42-year-old male with unknown past medical history presented to the ED with altered mental status. Emergency medical services (EMS) was contacted by the patient's wife who reported he had pulled his car over to the side of the road and suffered a tonic-clonic seizure. He had no prior seizure history. The initial report was that he was unresponsive with a Glasgow Coma Scale (GCS) of three and sonorous respirations. However, upon arrival at the ED the patient was combative, violent, unable to answer questions, and required six people to physically restrain him. As this event transpired during the COVID-19 pandemic and mechanical ventilators were a precious commodity, every attempt was made to avoid endotracheal intubation by using heavy chemical sedation. However, after receiving 10 mg intramuscular (IM) haloperidol, 90 mg intravenous (IV) ketamine, 50 mg IV diphenhydramine, and 2 mg IV lorazepam within a span of ten minutes, he remained agitated. He was then started on a dexmedetomidine drip, titrated up to 0.8 mcg/kg/hour and given an additional 5 mg IM midazolam. Given his continued agitated state, the decision was made to intubate him. Only after 20 mg IV etomidate, 100 mg IV rocuronium, and drips of midazolam, fentanyl, and propofol was the patient adequately quieted for imaging studies.

After the patient was sedated with high doses of the aforementioned drips, labs and computed tomography (CT) were obtained and further history was procured from the patient's wife. Prior to the onset of this seizure, he had complained for two weeks of a dull, persistent headache. He was seen at an urgent care, instructed to take acetaminophen for his discomfort, and discharged without further workup. Two days prior to his presentation at our ED, his wife reported that he was paranoid and hallucinating, claiming there were people inside the home. The day he presented to the ED, he decided to take his family for a weekend trip out of town. After reaching the downtown area he pulled the car over on the side of the road, announced that he arrived at their hotel, his right hand seized up without clonic activity, he went unresponsive, and his wife called 9-1-1. His wife only endorsed a past medical history of gastritis but vehemently denied history of seizures, recent trauma, or illicit drug use besides occasional recreational cannabis use. She reported that the night before he drank 1–2 beers to help alleviate his headache. She reported no history of heavy drinking.

The patient's initial vitals revealed only tachycardia with no fever and normal blood pressure, respiratory rate, and oxygen saturation. Initial labs revealed white blood cell count 15.6×10^3/μL with 65% neutrophils, normal hemoglobin/hematocrit, electrolytes, creatinine, creatinine kinase, and a negative troponin and human immunodeficiency virus (HIV). His ethanol level was 30 mg/dL, urine drug screen (UDS) positive for cannabinoids, and chest X-ray (CXR) and CT of the head were grossly within normal limits. A lumbar puncture was performed in the ED which revealed an opening pressure that was greater than 50 mmHg. His cerebral spinal fluid (CSF) analysis revealed a glucose of <20 mg/dL, protein 106 mg/dL, red blood cells 9 per mm^3, white blood cells 176 per mm^3 with 92% lymphocytes, 4% neutrophils and 4% monocytes. The CSF gram stain was positive for 4+ polymorphonuclear leukocytes and 3+ yeast. His CSF cryptococcal antigen was positive. He was promptly admitted to the intensive care unit (ICU) and started on 4 mg/kg IV amphotericin B liposomal augmented with flucytosine. A non-contrast magnetic resonance imaging (MRI) of the brain was done on hospital day three, which was normal.

The patient was extubated a few days later and IV antifungals were continued in a stepdown unit. CSF cultures

Highlight box

Key findings

- *Cryptococcus neoformans* (*C. neoformans*) can infect immunocompetent hosts. The presentation can include severe agitation and seizures.

What is known and what is new?

- *C. neoformans* primarily infects immunocompromised patients. This article adds to previous case reports that have described cryptococcal meningitis in immunocompetent patients. The patient described here is unique given the severity of his symptoms, primarily his agitation.

What is the implication, and what should change now?

- Cryptococcal meningitis should be considered in immunocompetent patients, and in those with severe agitation. We advocate for routine addition of fungal and viral titers in otherwise immunocompetent hosts to cerebral spinal fluid studies, as morbidity and mortality with fungal infection is directly correlated with delay of diagnosis and treatment.

confirmed the diagnosis of *C. neoformans*. Serial therapeutic lumbar punctures were done given the initial high opening pressures and continued until his opening pressure decreased. His hospital course was complicated by a course of *Clostridium* difficile colitis treated with oral vancomycin but was otherwise unremarkable. Over the next month, his clinical picture drastically improved. He routinely walked laps around the inpatient floor. The patient was evaluated by ophthalmology prior to discharge and did not exhibit any papilledema. He denied headaches, confusion, vision changes, numbness, tingling, weakness, or hallucinations. After 3 weeks of IV amphotericin B liposomal, he was transitioned to PO fluconazole and followed up with infectious disease a month later. Although he remains amnestic to the events of the day of his admission, he reports no long-term neurological deficits.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Verbal informed consent was obtained from the patient for the publication of this case report, and all attempts were made to obtain written consent. The patient consented to publication of the data included in this manuscript.

Discussion

Cryptococcosis, or invasive cryptococcal disease, is caused by either *C. neoformans* or *Cryptococcus gattii* subclasses. Classically, *C. neoformans* preferentially causes disease in immunocompromised hosts and *Cryptococcus gattii* infects the immunocompetent (4). However, case reports from all over the world reveal that exceptions do exist. Epidemiologically, *C. neoformans* has a worldwide distribution and *C. gattii* is more common in tropical, subtropical, and temperate regions including Australia, South America, Africa, USA, and Canada (1). There are reportedly 1 million new cases of cryptococcal meningitis worldwide annually with 600,000 deaths per year (8). There are an estimated 3,400 cases of cryptococcal meningitis in the US annually (2). Although the presentation is classically more dramatic in immunocompromised individuals, mortality in immunocompetent patients is high due to an initial low index of suspicion of fungal infections in this patient demographic causing delay of treatment (2,9). Patients with baseline altered mental status and increasing opening pressure have also been associated with increased mortality (10,11).

Cryptococcal meningoencephalitis is a particularly rare manifestation of cryptococcal disease in immunocompetent patients. The mechanism of contracting the disease is not well understood but is thought to be due to either particularly high organism exposure, exposure to an exceptionally pathogenic strain, or subtle immunodeficiency in the host. While HIV/AIDS, malignancy, and organ transplant are the usual underlying problems predisposing to cryptococcal infection, other risk factors such as alcoholism, diabetes mellitus, cirrhosis, and autoimmune states may cause a mildly immunocompromised state allowing for proliferation of opportunistic infections like cryptococcus (2).

In our patient, the cause of his meningoencephalitis was never conclusively identified. His HIV titers were negative, as were his herpes simplex, cytomegalovirus (CMV), and Epstein-Barr titers. IgA, IgM, and IgG counts were all within normal limits, eliminating underlying hematopoietic immunodeficiency. His blood work did not reveal any hematopoietic malignancy, he had never received a solid organ transplant, and denied IV drug abuse corroborated by his negative UDS (besides cannabinoids, to which he openly admitted). He did not routinely take steroids or any other immunosuppressants. He had no exposure to livestock or other farm animals, owned no pets, and had not traveled out of the country. He was up to date on his vaccinations, his hepatitis panel was non-reactive, and his blood sugar levels were consistently within normal limits. He had no recent surgery, no history of premature birth, and was not elderly and was otherwise in good health. His wife reported he did attempt drinking alcohol to abate his weeks-long headache but that was an infrequent practice for him. His ethanol level in our department was positive but negligible and the patient never exhibited signs of alcohol withdrawal during his hospitalization. He was incidentally found to be IgG positive for West Nile Virus, but IgM titer was negative, indicating no acute infection.

After an exhaustive history obtained by ED, general medicine, ophthalmology, neurology, neurosurgery, and infectious disease specialists, the only potential exposure our patient had to cryptococcus was that he had worked at a car wash where he was exposed to bird feces on the windshields of vehicles. *C. neoformans* has been historically linked to bird feces, particularly pigeon droppings (1,3). Studies have been conducted in isolated populations to corroborate culture and CSF findings in patients to feces from potential avian vectors such as magpies and pigeons (12,13). In the absence of other exposures or immunodeficiencies, we believe our

conclusion about his exposure to be accurate.

Moreover, the patient's particular presentation for cryptococcal meningitis in an immunocompetent patient was highly abnormal. Previous reports document that immunocompetent patients with cryptococcal meningitis overwhelmingly present with minimally altered mental status and negligible focal neurologic deficits (3,5,6,14). Our initial focused neurological exam was extremely limited by the patient's combativeness and inability to cooperate. Although he was a man of average height and weight, he exhibited superhuman strength requiring six men to physically restrain him. Whenever he was asked a question, he would howl and shriek loudly and incomprehensibly. He was so profoundly encephalopathic that he required exorbitant amounts of anxiolytics and three sedating drips at maximum doses to prevent him from fighting the ventilator. Per our review of the literature, this degree of violent behavior and combativeness in an immunocompetent patient has never been previously reported.

Treatment of cryptococcal meningitis in immunocompetent patients does not follow a standardized algorithm. Much of the treatment is based on case studies and expert opinion. Typically, IV amphotericin (0.7–1 mg/kg/day, 3–4 mg/kg/day of the liposomal formulation) is augmented with IV flucytosine initially, then as clinical picture improves patients are weaned to PO fluconazole for a course for 4 to 6 weeks (1,15). Patients will sometimes require draining of cerebrospinal fluid to facilitate resolution of elevated intracranial pressure either with temporary shunt placement or serial lumbar punctures (6,9,15). In cases of severe refractory symptoms or obstructing hydrocephalus, clinical benefit has been reported with high dose corticosteroid use, although this is not routinely indicated (16).

Our patient followed a remarkably uneventful post-treatment course. Literature suggests that post-treatment relapses are not uncommon but as of our follow up with the patient 1 year after the event, he has not had any long-term sequelae from his treatment (17). He followed up in the outpatient infectious disease clinic a month after discharge and was doing extremely well. Follow-up phone conversations with the patient have also been extremely positive. The degree of his violent behavior in his presentation also poses the question of underlying psychiatric disorder unmasked by the degree of encephalopathy, but as of our follow up he is not requiring any psychiatric or antipsychotic medication.

The patient's seemingly uneventful recovery after such a profound presentation has significant implications on future diagnosis and treatment of cryptococcal meningitis in immunocompetent patients. Many CSF studies, including cryptococcus Ag, CMV, HIV, and Epstein-Barr are not routinely ordered from the ED in immunocompetent patients. One of the major contributors to mortality in immunocompetent patients with cryptococcal meningitis is delay of diagnosis and treatment. Routinely adding these studies in the future could expedite diagnosis and minimize delays of treatment. Furthermore, we advocate for adding fungal meningitis to the routine differential of a patient with altered mental status, even if they are seemingly immunocompetent. It would have been easy to attribute this patient's initial clinical picture to a sympathomimetic or hallucinogenic toxidrome. Although it was certainly on the initial differential, we had the advantage of a reliable historian in his wife. Future physicians may not have this luxury, so we implore those to keep an open mind and a broad differential. We also posit that mitigation of cerebral edema by either temporary ventriculoperitoneal shunt placement or serial lumbar punctures early in clinical course was also advantageous in minimizing long-term sequelae of treatment. We also recognize that low fungal burden can cause false negatives in CSF analysis and cultures and recommend considering aggressive antifungal therapy in patients with subacute or insidious presentations of neurological symptoms, as this timeline is consistent with fulminant fungal pathology. It is our hope that our patient's treatment and remarkable recovery can serve as a guideline for diagnosis and treatment in future cases of cryptococcal meningitis in immunocompetent patients to mitigate long-term morbidity and mortality.

Conclusions

C. neoformans meningitis in the setting of HIV-seronegative and otherwise immunocompetent individuals is a rare phenomenon. However, delays in care associated with increased morbidity and mortality can be avoided with a high index of suspicion. Our patient's particular presentation of seizures and profoundly altered mental status with subacute onset after a week's long headache has also not yet been documented in case reports. Our treatment of the patient with aggressive antifungals and serial lumbar punctures is congruent with previously documented treatments in the literature, and he made a remarkable recovery with no long term focal neurological deficits. In the setting of insidious headache, hallucinations, focal seizures, and profoundly altered mental status, cryptococcal meningitis should be considered, even in

immunocompetent patients. The routine addition of fungal pathogens in CSF studies could aid in quicker diagnosis and treatment, leading to decreased morbidity and mortality in immunocompetent patients.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-23-128/rc

Peer Review File: Available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-23-128/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-23-128/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Verbal informed consent was obtained from the patient for the publication of this case report, and all attempts were made to obtain written consent. The patient consented to publication of the data included in this manuscript.

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doi: 10.21037/jeccm-23-128
Cite this article as: Fleming K, Agrawal S. Cryptococcal meningoencephalitis in an immunocompetent host presenting with severe agitation: a case report. J Emerg Crit Care Med 2024;8:7.