

Cryptococcal Meningitis in an Immunocompetent Individual in a Tertiary Care Hospital: A Case Report

Amrit Kahlon¹, Guneet Kaur², Jaskaran Singh³

ABSTRACT

Introduction: Cryptococcal meningitis is a life-threatening fungal infection caused by *Cryptococcus neoformans*. *Cryptococcus neoformans* is an encapsulated yeast and an obligate aerobe that can survive in both plants and animals. It has a tropism for cerebrospinal fluid, most patients suffer from meningitis or meningoencephalitis. Symptoms of cryptococcal meningitis are non-specific: Namely headache, fever, nausea, or altered mental state and behavior. Meningitis caused by *Cryptococcus neoformans* is most commonly thought of as an opportunistic infection affecting immunocompromised patients, classically patients suffering from HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome). Rarely, this infection can also be seen in immunocompetent individuals.

Case report: We present a case of cryptococcal meningitis in a 63-year-old healthy male who presented to the emergency department with a fever and altered sensorium. He underwent a lumbar puncture consistent with cryptococcal infection, and he was initiated on the appropriate induction antifungal therapy. His workup revealed no known underlying condition leading to immune compromise.

Conclusion: This case emphasizes the need for clinicians to remain vigilant and consider cryptococcal meningitis in immunocompetent individuals even in the absence of classic risk factors.

Keywords: Cryptococcal Meningitis, Immunocompromised, Cryptococcal Neoformans

INTRODUCTION

Cryptococcus neoformans is an encapsulated yeast and an obligate aerobe that can survive both in animals and plants. It belongs to the fungal class basidiomycetes. The fungus *C. neoformans* is found in pigeon roosts and soils that are contaminated with their droppings and in other environmental reservoirs which are not yet fully defined.^{1,2} *C. neoformans* causes life-threatening infections in immunocompromised hosts, typically in patients with human immunodeficiency virus (HIV) infection. Other patient groups at risk are patients with rheumatic diseases, liver disease, hematopoietic diseases, organ transplant recipients, and cancer as well as those receiving immunosuppressive therapies.^{1,2} The most common infection is meningoencephalitis, i.e., involvement of the central nervous system.³ The mode of infection of *C. neoformans* is through the respiratory route via inhalation. It enters the body in the form of haploid yeasts or basidiospores and is settled in the lung parenchyma. These spores then reach the extra-pulmonary tissues, most commonly the central nervous system, i.e. brain and the cerebrospinal fluid (CSF)

via hematogenous spread. This extra-pulmonary spread to the CNS leads to cryptococcal meningitis (commonly known as meningoencephalitis).¹ According to the studies, almost one million new cases of cryptococcal meningitis are reported across the world yearly.⁵ Despite the aggressive anti-fungal therapy, the in-hospital mortality from *C. neoformans*-mediated meningoencephalitis is estimated to be near 50%.⁶ Cryptococcal meningitis is primarily considered an opportunistic infection because it is more prevalent in immunocompromised individuals. However, although rare, the disease can also occur in immunocompetent individuals. This case report presents a patient with no history of immune compromise who contracted the infection with Cryptococcal antigen and developed cryptococcal meningitis.¹ Therefore, this study was undertaken to identify the uncommon and rare sources of infection of cryptococcus.

CASE REPORT

A 63-year-old male presented to the emergency room with a history of continuous fever for 4 days documented to be 102 degrees F, improved with an antipyretic, and altered sensorium for 2 days. However, he denied any headache, neck stiffness, sensory and memory loss, changes in vision, nausea, and vomiting. The patient did not obtain any local treatment before coming to the hospital and he denied any history of hypertension, diabetes mellitus, or any other chronic illness in the past. His occupational history revealed that he was a farmer and belonged to the lower socio-economic strata as per the Kuppuswamy scale of evaluation. He could not remember any recent exposure to birds, cattle, and horses. He also denied a recent history of any illness, intravenous drug use, use of local medications, or travel to any endemic area.

In the emergency department, the patient was febrile to 104°F; meanwhile, the vitals were within normal limits. His examination was remarkable for agitated behavior and disorientation to time, place, and person was noticed. The meningeal signs that are kernig's sign and brudzinski's sign

¹Medical Officer, Department of Oncology, ²Senior resident, Department of Medicine, ³Medical Officer, Department of Medicine, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India

Corresponding author: Amrit Kahlon, H. No-4066, Sector 68, Mohali, Punjab, India

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CSF Parameters	Test Values	Normal Values
Neutrophils	2	Nil
Lymphocytes	326	<5/mm ³
Glucose	32	50-80 mg/dL
Protein	84	15-45 mg/dL
Negative staining (Modified India ink stain)	Capsule which appears like refractile clear space halo surrounding the round budding yeast cells	Negative
Gram Stain	Gram positive round budding yeast.	No organism
Culture (chocolate agar and Sabouraud Dextrose Agar)	Growth of <i>Cryptococcus neoformans</i> sp. (whitish mucoid colonies seen within 2-3 days.)	Negative
Cryptococcal antigen (Latex agglutination)	Positive	Negative

Table-1:

were positive. A complete neurological examination could not be performed due to his agitation, but on examination of cranial nerves II, VIII, X, and XII, no relay was noticed, and the patient had spontaneous movement of all extremities.

Laboratory studies revealed a normal basic metabolic panel, Complete blood count: white cell count 12.9/mm³; neutrophils 60 %; lymphocytes 37 %; monocytes 1 %; eosinophils 2 %; red blood cells 4.8/mm³; hemoglobin 12.5 g/dL; platelets 145/mm³ and a negative urine drug screen and blood alcohol level. A non-contrast computed tomography image of the head revealed normal findings and was inconclusive for acute bleeding or mass effect. A lumbar puncture was then performed, and CSF was analyzed for cytology, biochemistry, India ink stain, gram stain, and bacterial as well as fungal culture and serological examination. The results of the CSF analysis are shown in Table 1. Other routine investigations such as Renal Function Test (RFT), Liver Function Test (LFT), electrolytes, and urine complete examination were done which came out to be within normal limits. HIV, hepatitis B, and hepatitis C virus antibodies were checked using ELISA and were non-reactive.

Treatment

Initially, before the CSF analysis, the patient was started on empiric antimicrobial therapy, but the patient showed no improvement. The confirmation of *C. neoformans* in the CSF culture prompted us to discontinue the empiric antimicrobial therapy and initiate anti-fungal therapy (liposomal amphotericin B and flucytosine). The patient was started on Liposomal amphotericin B intravenously (1 mg/kg/day) and flucytosine orally (100mg/day) for 2 weeks followed by Fluconazole (500mg/day) for 8 weeks. His condition slowly improved. On his follow-up visit after 4 weeks, his mental and functional status improved remarkably.

DISCUSSION

Cryptococcal meningitis is an invasive cryptococcal disease caused by *C. neoformans*.^{7,8} The incidence of cryptococcal meningitis each year is approximately one million with a mortality rate being close to 50%.⁵ *C. neoformans* is distributed all over the world and it opportunistically infects immunosuppressed individuals causing central nervous system infection (meningitis or meningoencephalitis) in human immunodeficiency virus (HIV) patients.^{7,9,10} Other

than HIV/AIDS, it also causes opportunistic infections in other immunocompromised conditions such as malignancy, liver cirrhosis, systemic lupus erythematosus, tuberculosis, bone marrow, or solid organ transplant patients, and patients on chronic glucocorticoid use.¹¹ In an immunocompetent individual, *C. neoformans* is a rare cause of CNS infection.¹² Since the patient described in this case did not have any of the above immunosuppressive conditions and was infected with *C. neoformans*, the following discussion will focus on the pathogenesis, diagnosis, and management of *C. neoformans*. *Cryptococcus neoformans* is a rare cause of meningitis in immunocompetent individuals.⁷ Although the exact mechanism of disease contraction by the immunocompetent hosts is unclear, it is thought to be due to exposure to high levels of the organism, exposure to a more pathogenic strain, or undetectable or slight immune deficit in the host.¹⁵ Although the well-known causes causing immunosuppression are HIV/AIDS, malignancy, and autoimmune diseases; one must keep in mind certain conditions such as alcoholism, cirrhosis, and diabetes mellitus which predispose the host to opportunistic infections.¹⁶

According to a multicenter case study, cryptococcal meningitis in HIV-negative patients with other predisposing risk factors such as steroid use, organ transplant, malignancies, etc. presents with headache (73%), altered mental status (42%), and constitutional symptoms [fever, malaise, night sweats, and weight loss; (68%)]. However, in about 30% of the patients with CNS involvement, there was no significant risk factor predisposing them to the disease.¹⁷ In immunocompetent individuals, meningitis caused by *C. neoformans* is often misdiagnosed as a viral or bacterial infection, therefore, it is important to consider this as a differential. Patients with cryptococcal meningitis usually present with headaches, fever, altered mental status, lethargy, and vision changes unlike the classical symptoms of bacteria or viral meningitis such as neck stiffness, nausea, and vomiting.¹⁸

Although our patient was apparently immunocompetent but based on his lifestyle and occupational background, he was at an increased risk of contracting cryptococcal meningitis. Being a farmer, his exposure to cattle, and birds in his neighborhood, may have exposed him to the organism. On extensive questioning, we found that a house in his neighborhood was involved in bird farming which could have

been the source of infection for this patient. Hence, physicians should obtain personal and social history very meticulously.⁴ Early detection and treatment by obtaining a detailed personal and social history of the patient could significantly affect the prognosis of the disease. The case described in this case report was unusual as the immunocompetent patient was infected by *Cryptococcus neoformans*, a strain that usually affects immunocompromised individuals. The patient presented with minimal symptoms of fever and altered mental status.

Although the gold standard for the diagnosis of cryptococcal disease is a positive CSF culture, precise laboratory expertise is needed to make a diagnosis. In this case, the patient did undergo an LP and non-contrast CT scan of the head prior to LP. The lumbar puncture was backed up by CSF cytology, biochemistry, and culture. The treatment of cryptococcal meningitis involves an induction phase which consists of Liposomal Amphotericin B (0.7-1.0 mg/kg/day) + Flucytosine (100 mg/kg/day) for 2 weeks followed by a consolidation phase for 8 weeks in which Fluconazole (400-800 mg/day) is given.¹⁹ As the given patient was not deemed to be immunocompromised, he did not require a repeat LP prior to progression to consolidation.

He had a positive outcome after receiving the appropriate treatment with antifungals. The immunocompetent group usually has poor outcomes due to misdiagnosis, delay in the treatment, and an elevated immune response by the host.²⁰ This case reminds us to suspect cryptococcal as a cause of meningitis in an otherwise immunocompetent patient.

CONCLUSION

Cryptococcal meningitis is a rare type of meningitis in immunocompetent individuals. So, in patients without any obvious source of infection, a thorough history should be taken focusing on the personal and social history of the patient to explore all the possible sources of infection. These include conditions such as living in a village where there is indirect exposure to an environment with bird feces, cattle, and horses. Nevertheless, cryptococcal meningitis in a patient without any immunosuppression has a mortality rate of 12% and the diagnosis is often delayed due to the subacute nature of the disease, leading to a worse prognosis.¹⁷ Therefore, the need of the hour is to keep a wider approach amongst the physicians and considering a differential diagnosis of cryptococcal infection amongst the patients of fever and PUO, CSF examination should be routinely performed in such patients and the possibility should always be considered in a case of meningitis with lymphocytic predominance in CSF and elevated proteins and low sugar. Therefore, it is concluded that a wider approach, as well as prompt diagnosis and treatment with anti-fungal medications, could prevent mortality and morbidity.

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