



Diabetes mellitus as a risk factor for cryptococcal meningitis in immunocompetent

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ABSTRACT

Cryptococcal meningoencephalitis (CM) is one of the major causes of mortality and morbidity in immunocompromised patients estimating 650,000 deaths each year. Across the globe, CM has been occasionally seen in apparently immunocompetent patients who otherwise don't have established risk factors. The clinical presentation of CM in immunocompetent hosts is subtle and often results in complications including persistent neurological deficits and death. We present a case of Cryptococcal neoformans meningitis in a diabetic female with no other identified risk factors. Although her clinical presentation was atypical, her clinical course was uncomplicated. The pathophysiology in immunocompetent hosts appears somewhat different, so is the clinical presentation. Since there are no separate evidence-based treatment recommendations, it is challenging to treat this group of patients. There seems to be a need for further studies for management in CM for HIV negative, non-transplant immunocompetent patients.

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Case

A 61 years old female with a past medical history of diabetes mellitus and hypertension presented to a tertiary level hospital in Kathmandu, Nepal with three days of fever and two days of altered mental status associated with vomiting for the same duration and three months of new-onset headache. Her family members had noticed increasing irritability and subtle personality changes for more than three months. The patient had documents from an outside facility per which she was treated for bacterial meningitis for the same symptoms very recently, but she continued to deteriorate. She was a retired schoolteacher and didn't have exposure to avian dropping or farming. She was a non-smoker all her life, never consumed alcohol, and didn't use intravenous drugs.

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None of her parents, siblings, or children had symptoms suggestive of genetic immunodeficiencies.

On examination, she was disoriented, but obeying commands, vitals were within normal limits, in the emergency room, Glasgow Coma Scale (GCS) was 14/15, motor strength was 4/5 in upper and lower extremities bilaterally, deep tendon reflexes were 3+, and neck rigidity was noted. MRI of the brain was done which was notable for T2 white matter hyperintensity of presumed vascular origin and mild atrophic changes without evidence of melanosis. Labs were notable for sodium of 101 mmol/L, leukocytosis of 14,000/uL, and otherwise normal. Cerebrospinal fluid (CSF) analysis revealed WBC of 5/mm³, Total protein of 75 mg/dL, and glucose of 73 mg/dL. India ink stain was positive for the fungal capsule which was suggestive of Cryptococcal meningitis (Table 1). Lumbar puncture opening pressure was measured more than 25 mmHg that prompted the physician to test for fungal infection, and the microbiologist was requested to look for Cryptococcus. HIV 1/2 ELISA test was non-reactive, Hepatitis A IgM, HBsAg, Hepatitis C IgM were negative, and serum quantiferon was also negative. HBA1C was 9 mmol/mol.

She was admitted to the intensive care unit and was started on intravenous liposomal Amphotericin B. Flucytosine is not available

Table 1
CSF: Cerebrospinal Fluid.

CSF	Day 1	Day 2	Day 5	Day 7	Day 15
Opening pressure mmHg	>25	>25	<20	<20	<20
Appearance	Clear	Clear	Clear	Clear	Clear
Cell count/mm ³	5	3	4	3	5
Glucose mg/dL	53	80	5	6	24
Protein mg/dL	75	61	4	5	33
Indian Ink Stain	Positive	Positive	Positive	Positive	Negative

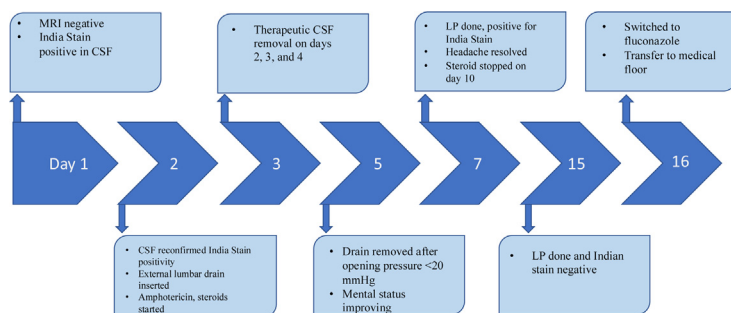


Picture 1. Indian Ink Stain Stain.

in Nepal and thus could not be used. She was also started on intravenous dexamethasone 4 mg every 6 h. An external lumbar drain was inserted with daily removal of approximately 20 mL of CSF. On the fifth day, the pressure was less than 20 mmHg and the drain was removed. Marked improvement in mental status was noted on day 5 with complete resolution of headache on day 7. Indian Ink Stain was positive on days 1, 2, 5, and 7 (Picture 1). The patient continued to improve on therapy and the India ink stain on the 15th day was negative. She received Amphotericin B for 14 days in the intensive care unit and was transferred to the medical floor on oral fluconazole 800 mg per day. The dexamethasone was tapered and was stopped on day 10. She was eventually discharged home with 8 weeks of oral fluconazole with weekly liver enzymes monitoring (See attached timeline in Table 2). She continued to show improvement with no side effects from fluconazole at 4 weeks follow up.

Fungal culture grew *Cryptococcus neoformans*. Cryptococcal Antigen tests in CSF or serum were not able to be performed due to

Table 2
Timeline of the events.



CSF: Cerebrospinal fluid, MRI: Magnetic Resonance Imaging, LP: Lumbar Puncture.

financial constraints which is not uncommon in resource-limited low- and middle-income countries.

Discussion

Annually one million patients with HIV infection are affected by central nervous system Cryptococcal infection which results in 650,000 deaths [1]. *Cryptococcus neoformans* is pathogenic encapsulated yeast which can cause a spectrum of disease ranging from symptomatic pulmonary colonization to fatal disseminated disease [2]. Acquired Immuno Deficiency Syndrome (AIDS) and solid organ transplant recipients are known to be at risk for CM. Other less established risk factors are glucocorticoid therapy, hematologic malignancy, congenital immunodeficiency syndromes, and organ failure [3].

A multicenter study done in the United States of America (USA) with cryptococcosis in people without HIV concluded that the central nervous system was affected the more than lungs, skin, or bloodstream. This study didn't recognize diabetes mellitus as a risk factor in sub-group analysis, though 30% of the sample were labeled as no underlying condition. Headache and altered mental status were the most common presenting symptoms [3]. Few studies have attempted to recognize diabetes mellitus as a risk factor for Cryptococcal infection who were not immunocompromised otherwise, but those studies were done with a small sample size though the lengths of the studies were long. The smaller sample size is likely because of the rarity of the CM in immunocompetent individuals. Headache, altered mental status, and fever were the most common symptoms in two of the studies, and fever and shortness of breath was the most common presentation in the other study [4–6]. A recent retrospective study in the USA identified diabetes mellitus as a major co-morbidity in immunocompetent and solid organ transplant patients [7]. To date, diabetes mellitus has not been established as an independent risk factor CM but there are case reports that describe CM in patients with diabetes.

Cryptococcus has the propensity to infect the nervous system [2]. Cryptococcal central nervous system (CNS) disease in non-HIV, non-transplant patients tends to have more serious outcomes in terms of morbidity and mortality. The possible explanation is

because of subacute presentation, delayed diagnosis, sequelae of overwhelming host immune response, and unique pathophysiology [8]. One study showed that solid organ transplant recipients also have a serious course and increased mortality compared to HIV positive counterparts [7]. In diabetics, hyperglycemia impairs the cell-mediated immunity, but paradoxically inflammatory cytokines are chronically elevated as a result such that there could be an exaggerated response to cryptococcus infection which can lead to increased mortality [2,9,10]. There are reported cases in which patients died because of the overwhelming immune response [11,12] or had significant morbidity [13]. Therefore implication of anti-inflammatory measures like steroids to control the overwhelming immune response in diabetic patients with CM may have an adjunctive role in the management [8]. With the increasing global prevalence of diabetes [14], and emerging sporadic cases of CM in immunocompetent and a proper study to see the correlation between DM, and CM is necessary.

The approach to CM treatment in immunocompetent hosts is based on studies that were conducted decades ago with people living with HIV and there are no evidence-based guidelines for CM treatment in immunocompetent hosts. The current recommendation is to treat with at least 2 weeks of Amphotericin B plus Flucytosine combination, and consolidation with fluconazole for 8–10 weeks. Repeat CSF culture to confirm sterilization is recommended before starting the consolidation phase [15]. In resource-limited, the low-income country such as Nepal, the unavailability of Flucytosine can lead to increased mortality and morbidity [16,17].

Since CM in immunocompetent and immunocompromised seems to be different in presentation and outcome there seems to be need for studies on immunocompetent patients considering the toxicity of the medicines used and possible adjunct steroids therapy to tackle immune response. In our case despite the atypical presentation CM was diagnosed because of high index of suspicion. The out of hospital treatment failure for bacterial meningitis raised the suspicion for CM. The favorable outcome is possibly because of the use of steroid in adjunction to Amphotericin-B.

Conclusion

Although Cryptococcal meningitis is mostly seen in immunocompromised hosts, it has been occasionally seen in immunocompetent individuals. There is growing evidence that DM may be a risk factor for CM and CM should be considered in diabetic patients with new-onset persistent headache or mental status change. CM in immunocompetent seems to have different pathophysiology and clinical presentation, more on studies on immunocompetent patients that might suggest adjunct therapy like steroids for host immune response seems necessary.

Consent

Verbal Consent.

Authors contribution

Roshan Acharya: Draft, literature review.

Kishor Khanal, Prabhaw Upadhyaya: Direct patient care, Literature Review.

Smita Kafle: Draft, Literature Review.

Vipul Savaliya: Proof reading.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgment

None.

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