Cryptococcal meningitis in an immunocompetent individual: A case report

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Abstract
Cryptococcal meningitis (CM) is mostly seen in immune-compromised patients and rarely occurs in immune-competent individuals. Immunocompetent individuals with CM present with indolent neurological disease and have better clinical outcomes after treatment. However, misdiagnosis is common and these patients may suffer from serious complications with high mortality.

KEYWORDS
cryptococcal meningitis, HIV, immunocompetent, immunocompromised, organ transplant

1 | INTRODUCTION

Cryptococcal meningitis (CM) is the most common form of adult meningitis in regions with a high prevalence of human immunodeficiency virus (HIV) infection. It is subacute meningitis, which occurs mainly in HIV and other immunodeficient conditions, particularly defective cellular immunity.1 The global prevalence rate of cryptococcal antigen positivity is 6.0% among people with a CD4 cell count of fewer than 100 cells per µl, with 278,000 cases positive for cryptococcal antigen and 223,100 incident cases of CM globally. Globally, CM takes 181,100 lives per year and is responsible for 15% of AIDS-related deaths.2 With the increasing use of anti-retroviral therapy (ART), the incidence of CM is decreasing in HIV patients; however, the incidence is in an increasing trend for organ transplant recipients and other immunocompromised cases.3

However, the occurrence of CM in immunocompetent individuals is very rare. In two retrospective studies
conducted in Nepal, all the patients with CM were immunocompromised and the majority were HIV infected. In Nepal, an immunocompetent patient presenting with features of meningitis is seldom evaluated for CM, thereby either delaying or misdiagnosing the condition; thus, the patients may suffer from serious complications including mortality.

Although some species within the Cryptococcus gattii species complex (C. deuterogattii and C. gatti) are strongly associated with apparently immunocompetent patients, their occurrence has not been reported from Nepal, and species-level identification is not possible here because of lack of resources. Moreover, in resource-limited setting, knowing whether CM is due to C. neoformans or C. gatti species complex does not change the line of treatment, rather, it increases the overall treatment expenses. What is clinically important is to aware the physicians that CM is possible in immunocompetent individuals, and they present with an indolent neurological course and have better clinical outcomes if treated timely. We herein present a case of a 59-year-old male patient who was apparently immunocompetent, yet developed CM.

2 | CASE DESCRIPTION

A 59-year-old non-diabetic normotensive male patient visited the Emergency Department of Tribhuvan University Teaching Hospital with gradual onset of altered senso-rium with sudden worsening. The patient was apparently well 7 days back when he started developing confusion and irrelevant speech. There was no history of trauma, drugs, or exposure to toxins. He had no fever, headache, shortness of breath, chest pain, nausea, vomiting, or loose stool, and the patient did not give any history of limb weakness, convulsions, vertigo, or syncope. There was no history of photophobia, neck rigidity, ear/nasal discharge, sinus pain, recent surgery, or trauma. He has no past medical, surgical, or psychiatric history and no history of similar episodes in the past. He is not on any long-term medications, and he did not take any new food, medication, traditional therapies, or supplements recently. The patient consumed alcohol and smoked for 20 years and quit both 5 years back. There was no history of change in sleep patterns, weight loss, malignancy, or exposure to toxic substances. He had no recent infectious contacts. All other family members were fine and his family history was unrevealing.

On examination, the patient was ill-looking, confused, and disoriented. He had a blood pressure of 160/100 mmHg, respiratory rate of 20 breaths per minute, oxygen saturation at room air of 95%, heart rate of 98 beats per minute, and random blood glucose of 168 mg/dl. There was no pallor, icterus, lymphadenopathy, cyanosis, or clubbing.

His pupils were equal and reactive to light and all cranial nerves were intact. Examination of the motor and the sensory system was unremarkable. Kernig’s and Brudzinski’s signs were negative. His gait was normal, and there was no nystagmus, dysmetria, or dysdiadiokinesia. There were no changes noted in fundoscopy. No cranial bruit was audible, and his cardiovascular, pulmonary, and abdominal examinations were unremarkable.

Based on these findings, tuberculous meningitis was suspected. The biochemistry and hematology panel showed a normal renal and liver function, an absence of leucocytosis with a normal differential cell count, a normal hemoglobin level of 13.2 mg/dl, and a normal platelet count of 173,000 cells/μl. Serum electrolytes, blood glucose, and urine microscopy were within normal limits. Chest X-ray and electrocardiogram revealed no abnormalities. Erythrocyte sedimentation rate and C-reactive protein were normal.

A lumbar puncture was done which showed raised opening pressure, but with clear cerebrospinal fluid (CSF). CSF examination showed 630 white blood cells/mm³ of which 20% were polymorphs and 80% were monocytes. sugar was 65 mg/dl, the protein was 2.23 g/dl, and adenosine deaminase (ADA) level was 143 U/L. Acid-fast bacteria (AFB) stain was negative; however, gram stain showed gram-positive cocci. This raised the suspicion for fungal infection and thus, Mycobacterium tuberculosis polymerase chain reaction (PCR), CSF cryptococcal polysaccharide antigen, labouraud dextrose agar (SDA) culture, and India ink staining were ordered. M. tuberculosis PCR was negative; however, cryptococcal antigen was detected in CSF, and India ink staining of CSF sample revealed yeast cells with surrounding halo (Figure 1), and SDA culture revealed growth of pasty, smooth to mucoid, and cream-colored colonies suggestive of Cryptococcus (Figure 2). Magnetic resonance imaging (MRI) of the brain was ordered, which revealed no abnormalities.

The patient was then further enquired and tested for any immunodeficiency state; however, no such clues were found. Finally, the diagnosis of CM was made the patient was treated with a 2-week course of liposomal amphotericin B along with fluconazole. After the 2 weeks course, the patient recovered well and was subsequently discharged on fluconazole 800 mg daily for 8 weeks. After completion of the 8-week therapy, he visited for follow-up was doing well and had no residual neurological features. He was then started on fluconazole 400 mg daily for 1 year.
3 | DISCUSSION

Despite a decreasing trend of CM in HIV-infected individuals thanks to ART, CM is a significant problem in organ transplant recipients and patients with defective cell-mediated immunity, with a high-mortality rate despite therapy. Hematopoietic malignancies, sarcoidosis, and autoimmune diseases such as ankylosing spondylitis, dermatomyositis, systemic lupus erythematosus, and autoimmune hepatitis have also been well associated with CM in non-HIV–infected patients.3 However, CM in previously healthy individuals is still rare,3,6-8 although recent reports about such cases are increasing,9 reported mainly in the far easts.3 The occurrence of CM in the previously healthy population is assigned to rare primary immune defects or uncommon autoimmune diseases3,8 such as idiopathic CD4+ lymphopenia (in 27% of cases), alveolar proteinosis, monogenic disorders (GATA2 mutations), and polygenetic modifiers (Fcg receptor II polymorphism).3 None of these diseases could be suspected clinically in our case.

Since 2015, various causative agents of CM have been recognized, viz. C. neoformans var. grubii, C. neoformans var. neoformans, C. gattii, C. bacillisporus, C. deuterogattii, C. tetragattii, and C. decagattii. Approximately 95% of cryptococcal infections are caused by C. neoformans var. grubii, 4% by C. neoformans var. neoformans and C. gattii, and 1% by others. C. neoformans var. grubii is found worldwide, C. neoformans var. neoformans is primarily observed in European countries and C. gattii has historically been geographically restricted to tropical and subtropical regions, such as southern California, Hawaii, Vancouver Island, and the Pacific Northwest region, Brazil, Australia, Southeast Asia, and central Africa.10,11 The species other than C. neoformans have not been isolated from Nepal so far. Although both the species have been reported in both immunocompromised and immunocompetent patients, C. neoformans affects immunocompromised individuals while C. gattii prefers immunocompetent ones.3,9 Headache and altered sensorium are the most typical symptoms that patients frequently present with, but fever, nausea, and vomiting can also be present. Diplopia, followed by reduced visual acuity due to increased CSF pressure and/or visual pathway involvement is also reported. If not treated in time, the disease can progress to confusion, seizures, reduced level of consciousness, and coma.3

Despite having a sensitivity of below 86%, India ink staining is the most commonly used diagnostic technique for CM because of its low cost and easy availability.3,12 However, when India ink staining is used without other diagnostic modalities, 1 in 11 cases can be misdiagnosed.12 The case reported in this article was first diagnosed with Lateral Flow Assay to detect the cryptococcal antigen in serum followed by confirmation by India ink staining, gram staining, and culture in SDA. Other than microbiology and

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**FIGURE 1** India ink staining of the cerebrospinal fluid sample revealed yeast cells with a surrounding halo

**FIGURE 2** Sabouraud dextrose agar showing growth pasty, smooth to mucoid, and cream-colored colonies of cryptococcus
antigen-based tests, CSF analysis can also be used to further strengthen the diagnosis. In the case of CM, CSF analysis shows an increase in mononuclear cells and protein levels with a decrease in CSF glucose level.  

Management of CM is done with three basic principles, that is, (1) use of antifungal regimens for the clearance of fungus, (2) early detection and treatment of raised intracranial pressure (ICP) and immune reconstitution inflammatory syndrome (IRIS), and (3) use of amphotericin B in liposomal form for the protection of kidney. Treatment modalities have been made different for HIV-infected cases, organ transplant cases, and non-HIV-non transplant cases. Antifungals are used in different phases namely, induction (for early fungicidal activity), consolidation, and maintenance. The regimens L-AmB 3–6 mg/kg daily or D-AmB 0.7–1.0 mg/kg daily in combination with flucytosine 100 mg/kg daily (75 mg/kg daily if the intravenous formulation is used) for 4–6 weeks were supposed to be used as induction therapy in this patient. Due to the unavailability of flucytosine in Nepal, the combination of liposomal amphotericin B and fluconazole was used for 2 weeks in this case for induction as per the indication for resource-limited settings. The patient showed significant recovery at the end of the second week of induction, and he has been prescribed fluconazole for consolidation and maintenance. Also, the patient’s ICP was monitored on follow-up as ICP can increase in the second or third week of therapy even when it is normal initially. The better prognosis, as seen at the end of induction, in this patient can be attributed to early diagnosis and the absence of any complications like raised ICP, and fungemia.

4 | CONCLUSION

Immunocompetent individuals with CM present with indolent neurological disease. Delayed diagnosis and misdiagnosis are common and patients may suffer from serious complications with high mortality. High-clinical vigilance and the use of easily available diagnostic modalities can help in early diagnosis.

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Not applicable.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

RO, SA, and GN were involved in patient care (diagnosis, treatment, and follow-up). RS performed the microbiological examination of the specimen and provided us the required images. SKY, PBS, SB, JG, and SP contributed to the collection of case information, writing of the manuscript, and manuscript revision. All authors approved the final version.

ETHICS APPROVAL

This study did not include experiments on animals or humans. The patient gave consent to use his details for this case study.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in Chief of this journal.

DATA AVAILABILITY STATEMENT

The data used in the case report are available on reasonable request.

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