Case Report

Cryptococcal meningitis: A delineating presentation peeping toward HIV status

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ABSTRACT

Cryptococcal meningitis is an ominous presentation of the most common opportunistic fungal infection in patients affected by the Human immunodeficiency virus (HIV). *Cryptococcus neoformans* is the commonly associated species in immunocompromised patients. It is the first AIDS-defining illness in 6–10% of patients. Cryptococcosis is reported as a major opportunistic infection in India. The case of cryptococcal meningitis presented here is of a young, chronic alcoholic 28-year-old male patient with non-specific symptoms having the only significant history that he was sexually active with a woman whose husband died of unknown cause which draws attention to look for HIV status of the patient which was found to be reactive confirming it as one of the AIDS-defining illness.

Key words: AIDS-defining illness, Cryptococcal meningitis, Cryptococcosis

An encapsulated yeast *Cryptococcus* remains a major opportunistic fungal infection and the leading cause of mortality in patients affected by the Human immunodeficiency virus (HIV)/Acquired immunodeficiency disease (AIDS) [1,2] It is the most common fungal pathogen infecting the human central nervous system (CNS) [3]. Cryptococcal meningitis is the commonest presentation, whereas, infection of the lungs, skin, lymph nodes, and bones occur infrequently [4]. About 6–10% of patients with AIDS have cryptococcal meningitis as the first AIDS-defining illness [5].

Meningitis has similar clinical features whether it is due to *Cryptococcal* or other infections as a diagnosis based purely on these features is difficult; also it is imperative to check HIV status in high-risk behavior patients. Here, we present the case of Cryptococcal meningitis in a 28-year-old patient with newly diagnosed HIV who came with complaints of non-specific symptoms with the only history of high-risk behavior.

CASE REPORT

A 28-year-old male furnace worker was admitted to the emergency department complaining of nausea, several episodes of non-bilious vomiting 4–5 times/day, and generalized weakness for 15 days. He reported that he was sexually active with a woman whose husband died of an unknown cause but he did not know about her health status. He is also a chronic alcoholic.

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General examination revealed a cachexia young male with signs of anemia and was lethargic but oriented. The patient had pallor but no icterus or cyanosis. Heart rate, blood pressure, and respiratory rate were normal. He had dry skin with dermatitis and painless blisters of size 1.5–2 mm were present in a group of 3–6 around the umbilical region resembling *Herpes* and oral mucosa including tongue covered with creamy white cheese-like patches.

Both the lung sounds were clear with normal lung opacity on chest X-ray (Fig. 1). The patient was provisionally diagnosed with acute gastritis with anemia of unknown etiology and started treating symptomatically with antiemetic (Inj. Ondansetron 4 mg IM), antibiotics (Inj. Ceftriaxone 1 gm IV and Inj. Metronidazole 500 mg IV), and IV fluids. A blood sample was sent for investigations. Complete blood count revealed that the red blood cells (RBC), platelets, and white blood cells (WBC) counts were within the normal limit but differential count showed neutrophilia (90%) along with lymphopenia (8.9%). Hemoglobin was 9.8 g/dl, mean corpuscular volume (MCV) was 67 fL, mean corpuscular hemoglobin (MCH) was 20 pg, and mean corpuscular hemoglobin concentration (MCHC) was 30 g/dl. Peripheral blood smear showed a microcytic hypochromic picture of RBCs with the presence of a few pencil cells and teardrop cells. The patient was reactive for HIV with a low CD4 count, that is, 54.

On the next day morning, the patient developed absence seizures and became unconscious, irresponsive to painful stimuli with signs of meningitis. Considering the development of cerebral edema, mannitol was infused immediately and sent for computed tomography (CT) scan of the brain. The radiologist reported minimal cerebral edema on CT imaging.

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For further investigations, cerebrospinal fluid (CSF) was drawn by lumbar puncture. Microscopic examination of CSF showed 100 nucleated cells per cm with 90% polymorphs and 10% lymphocytes. The biochemical test showed a protein level of 84 mg/dl and a glucose level of 22 mg/dl. Gram stain revealed few budding yeast cells but no pus cells and no bacteria (Fig. 2a). Modified Ziehl–Neelsen (ZN) stain and cartridge-based nucleic acid amplification test (CBNAAT) result were negative for *M. tuberculosis.* Negative stain with India ink showed capsulated round budding yeast cells (Fig. 2b). The bacterial culture result was negative but the fungal culture done on Sabouraud's Dextrose Agar (SDA) had white non-mucoid colonies initially (Fig. 3a), which turns into creamy mucoid on further incubation (Fig. 3b). Negative stain done from culture gave similar findings as mentioned before. Identification of *Cryptococcus neoformans* was confirmed by growth at 37°C (Fig. 4) and the production of urease (Fig. 5).

The case was finally diagnosed as Cryptococcal meningitis with late-stage HIV. Liposomal amphotericin B (5 mg/kg OD) and fluconazole (800 mg OD) were added to the regimen. Patient was least responsive to the treatment and succumb to death on day 6.

DISCUSSION

In HIV infection, morbidity and mortality decreased significantly due to the availability of effective antiretroviral therapy, but still, it accounts for 1.5 million deaths annually [4]. Globally, the five leading infections responsible for mortality in HIV are Tuberculosis, Cryptococcosis, Hepatitis B virus, Hepatitis C virus, and Malaria [6]. The case presented here is of Cryptococcal meningitis as AIDS-defining illness.

Cryptococcal meningitis is an ominous presentation of commonest opportunistic fungal infection in patients affected by

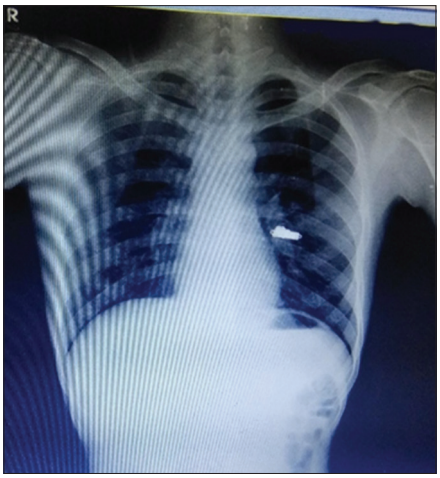

Figure 1: Chest radiograph showing normal lung opacity

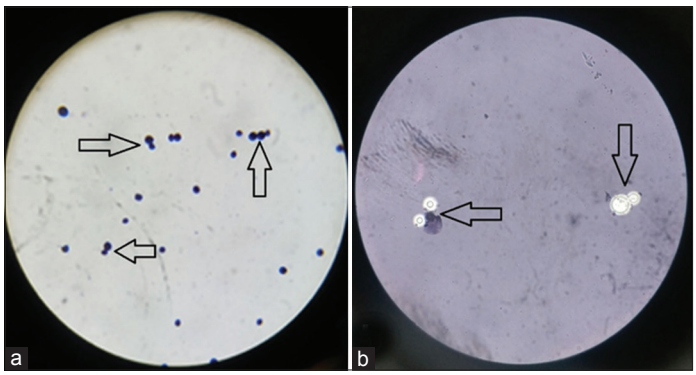

Figure 2: (a) Gram stain of CSF showed budding yeast cells without pus cells and no bacteria (×100); (b) Negative stain with India ink showed capsulated round budding yeast cells (×40)

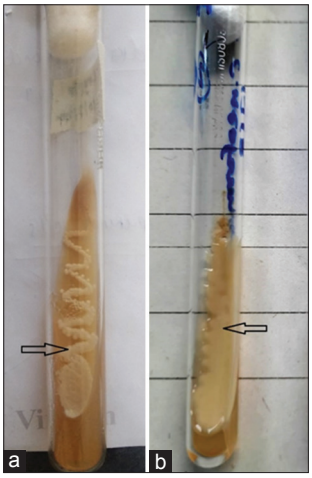

Figure 3: (a) Whitish non-mucoid colonies on SDA (b) creamy mucoid colonies on SDA after 5–6 days

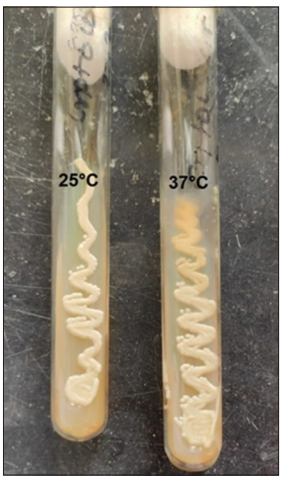

Figure 4: Growth on SDA at 25°C as well as 37°C

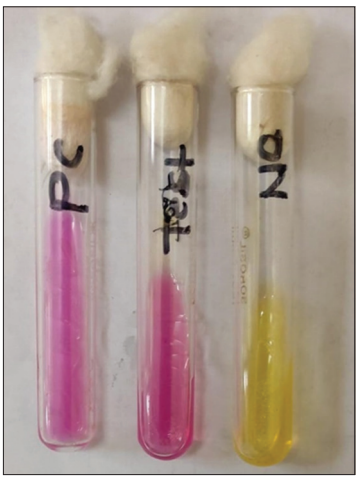

Figure 5: Urease test with positive (PC) and negative (NC) controls showed production of urease

HIV [5]. According to the U.S. Centers for Disease Control and Prevention, an estimated 220,000 cases of cryptococcal meningitis occurring worldwide each year with a case-fatality ratio of about 12% [4] and a leading cause of mortality in HIV infected patients in the developing world [2]. The two species of an invasive fungus *Cryptococcus* which is an encapsulated saprophyte commonly associated with infections in humans are *C. neoformans var neoformans* and *C. neoformans var gattii* [7,8]. The former is exclusively associated with infections in HIV/AIDS patients [5]. In this case also, the causative species is *C. neoformans*.

The worldwide distributed ubiquitous environmental fungus *C. neoformans* found in soil contaminated with pigeon droppings and has also been isolated from the heartwood of several tree species in South America and India [2]. Exposure may be common, although the exact circumstances are usually unclear [2]. Entry of encapsulated yeast or its basidiospores into the human host is through the respiratory route which may lead to an initial pulmonary infection with a propensity to localize in the basal ganglia and cortical grey matter of the CNS [2,5]. Depending on the host immune response, and the number and virulence of the organism, the infection may disseminate through hematogenous route or reactivate from latent infection at the initial site after several years when the patient becomes immunocompromised [2,7]. Most episodes of cryptococcal meningitis in HIV patients represent reactivation of latent infection [2]. Possibility of reactivation of latent infection in our patient cannot be denied as he is a furnace worker with low socio-economic status exposure to contaminated soil or other sources such as vegetables, fruits, and dairy products may occur years before.

The minority in whom cryptococcal infection disseminates typically have a defect in T cell function [2]. Current pieces of evidence suggest the mechanism by which cryptococcal cells crosses the blood–brain barrier is either by direct fungal-cell migration across the endothelium or the fungal cell carriage inside macrophages as "Trojan horse" [1]. As the cryptococcal capsule is anti-phagocytic, and the organism is an intracellular pathogen, it has the capability to vomocytosed [1,6].

Lack of complements and immunoglobulins, and the presence of selective nutritional factors in the spinal fluid which acts as a source of nitrogen such as asparagine and creatinine that may stimulate growth [5,9]. There may be extensive involvement of the brain parenchyma in addition to meningitis [2]. Focal neurological deficits occur as a complication of cryptococcal meningitis due to multiple brain infarcts, but few may be asymptomatic [5,10].

The disease caused by Cryptococcus species consists mainly of meningoencephalitis and pneumonia [1]. Low CD4 count (<100 cells/ml) may be responsible for the development of the disease. Symptoms and signs of meningoencephalitis mainly include fever, headache, visual disturbance, altered mental status, and reduced consciousness [2]. In our case, the patient had absence seizures followed by loss of consciousness with a CD4 count of 54 cells/ml.

CSF analysis usually shows low leukocytes, low glucose, and elevated protein level as seen in this case except for WBC count, but in 25–30% cases findings may be normal [7]. The success of laboratory confirmation of cryptococcal infection achieved in the present case by direct microscopy and culture of CSF. Mycological culture of CSF is considered as the gold standard diagnostic method, but it takes 48–72 h to grow on culture media [1].

In the west, cryptococcal meningitis is a problem in patients presented with late-stage HIV infection. Cryptococcosis accounts for up to 20% of AIDS-defining illnesses in Thailand and is a major opportunistic infection in India too [2]. Overall, about 6–10% of patients with AIDS have cryptococcal meningitis as the first AIDS-defining illness [5]. Mortality was higher in HIV-infected patients despite of prompt anti-fungal therapy [3]. In the presented case, cryptococcal meningitis draws the attention of the treating physician to look into HIV status and found to be reactive. Despite of adding anti-fungal to the treatment, patient succumb to death.

CONCLUSION

Timely diagnosis and prompt initiation of therapy are pivotal in limiting the complications and prolonging the life of patients. We, hereby, insist to look for HIV status in patients with a history of high-risk behavior and those presenting with AIDS-defining illness.

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