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Case Report

Securing diagnostic accuracy in HIV-cryptococcus co-infection: the power of clinical microbiology

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ABSTRACT

Cryptococcal meningitis is a life-threatening opportunistic fungal infection in patients with advanced HIV infection. Early diagnosis is essential to reduce morbidity and mortality. Conventional microbiological techniques remain valuable, particularly in resource-limited settings. A 40-year-old male with a three-year history of HIV infection and irregular antiretroviral therapy presented with a two-week history of progressively worsening headache, low-grade fever, nausea, vomiting, photophobia, blurred vision, and altered sensorium. Cerebrospinal fluid (CSF) examination revealed markedly elevated opening pressure, lymphocytic pleocytosis, elevated protein, and reduced glucose. India ink examination demonstrated encapsulated, budding yeast cells. Gram staining revealed round, budding yeast cells, while fungal culture on Sabouraud dextrose agar yielded creamy, mucoid colonies. The isolate was urease-positive, and bacterial cultures were negative. Based on the clinical presentation and conventional microbiological findings, a diagnosis of cryptococcal meningitis was established. The patient received induction therapy with liposomal amphotericin B and flucytosine, followed by planned consolidation therapy with fluconazole. This case highlights the importance of considering cryptococcal meningitis in HIV-positive patients presenting with subacute headache and fever. A systematic approach combining clinical assessment, CSF examination, India ink staining, fungal culture, and urease testing can facilitate diagnosis in routine microbiology laboratories, particularly where advanced diagnostic facilities are unavailable.

Keywords: Cryptococcal meningitis, HIV, *Cryptococcus* spp., India ink, Fungal culture, Opportunistic infection

INTRODUCTION

Cryptococcal meningitis is a severe, life-threatening infection of the central nervous system (CNS) caused by encapsulated basidiomycetous yeast belonging to the *Cryptococcus* species complex. Historically recognized as a defining opportunistic infection of the HIV/AIDS pandemic, it remains responsible for approximately 19% of all AIDS-related deaths globally, accounting for roughly 112,000 to 181,000 fatalities annually, predominantly across Sub-Saharan Africa.[1,2] While individuals with advanced immunosuppression (specifically those with CD4 counts below 100 cells/mm³) bear the highest burden, advancements in clinical mycology have highlighted a rising incidence of cryptococcosis among non-HIV populations, including solid organ transplant recipients, individuals receiving immunomodulatory therapies, and even seemingly immunocompetent hosts.[3]

Cryptococcal meningitis in HIV-infected individuals present in an acute-to-chronic spectrum, often lacking classic meningeal signs due to impaired host immunity. Patients typically exhibit non-specific symptoms like headache and fever. This diagnostic ambiguity complicates differentiation from other chronic encephalopathies, leading to frequent diagnostic delays.[4,5]

We report a case of cryptococcal meningitis in a 40-year-old patient to evaluate the diagnostic utility of constitutional fever and immunocompromised status as primary indicators prompting urgent microbiological

screening for *Cryptococcus* and to assess their impact on time-to-diagnosis and patient outcomes.

CASE REPORT

A 40-year-old male, driver by profession, presented to a tertiary-care hospital with a 2-week history of progressively worsening headache, low-grade fever since 1 week, nausea, 1-2 episodes of non-bilious vomiting for past 2-3 days and increasing lethargy and generalized weakness since 1 week. The headache was diffuse, persistent and was worse in the morning. Over the past 5 days, he developed photophobia, blurred vision, and occasional confusion. The patient was diagnosed with HIV infection 3 years ago during evaluation for recurrent oral candidiasis and weight loss. His initial CD4 count was 280 cells/µL. He was started on antiretroviral therapy (ART) but had been irregular with treatment for approximately last 8 months because of poor adherence. Six months ago, his CD4 count was 92 cells/µL and his HIV viral load was elevated. He has not received any treatment for cryptococcal infection previously. There was no history of tuberculosis or previous central nervous system infection. There was no history of recent head trauma, neurosurgery or malignancy. The patient was also HBsAg positive and had a history of chronic alcohol consumption.

On examination, the patient had pallor, but no icterus and no cyanosis. Heart rate, respiratory rate and blood pressure were normal. On oral examination, the oral mucosa

revealed tongue covered with creamy white patches. Respiratory examination revealed multiple small bilateral pulmonary nodular opacities, with no pleural effusion or significant hilar lymphadenopathy.

On admission, patient was initially started on Inj. Monocef 1 gm BD, Inj. Pan40 OD, Inj. Ondem 4mg BD, Inj. Thiamine 200 mg OD and Inj. Atropine 1CC SOS, Inj. Metronidazole 500 mg BD and IV fluids. Blood samples were sent for investigations, which revealed haemoglobin as 7.4 g/dL. RBC, WBC, DLC and platelet count were within the normal range. Peripheral smear examination revealed normocytic normochromic RBCs with few microcytes and pencil cells and mild anisocytosis.

CSF examination was also ordered by collecting CSF by lumbar puncture, which revealed opening pressure as markedly elevated and appearance as clear, WBC count 80 cells/µL, predominantly lymphocytes; proteins raised and glucose levels were reduced.

CT brain revealed multiple ill-defined hypodense lesions in the subcortical regions of the bilateral cerebral hemispheres, with the largest measuring 8×6 mm in the right parietal region. No midline shift was noted. MRI brain was advised for further evaluation.

Direct microscopy examination of CSF by India ink preparation demonstrated round yeast cells surrounded by prominent clear halo, raising suspicion of cryptococcal infection (Figure 1). Gram staining of the CSF smear demonstrated round, budding yeast cells (Figure 2). ZN staining was also done which was negative for *M. tuberculosis.* Bacterial cultures were negative.

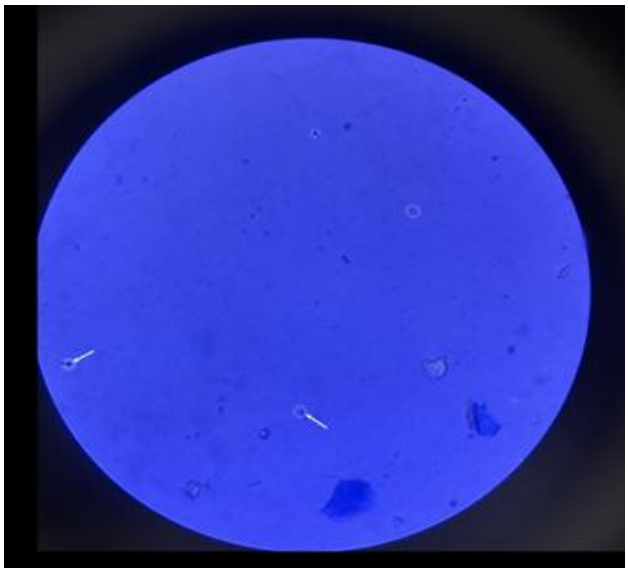


Figure 1: India ink preparation of CSF showing encapsulated budding yeast cells with clear halos.

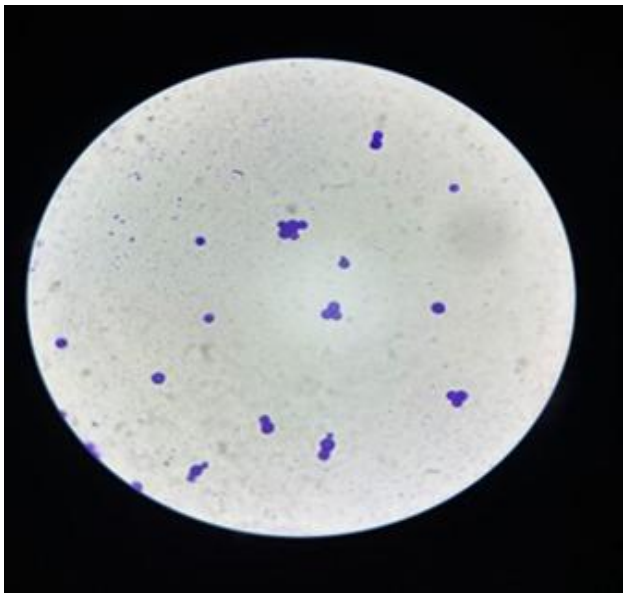


Figure 2: Gram-stained smear showing Gram-positive budding yeast cells.

The specimen was cultured on Sabouraud Dextrose agar (SDA) and incubated at 25ºC and 37ºC for 2 to 5 days. Cream-colored and smooth colonies were observed after 24 hrs later becoming highly mucoid, moist, and runny due to capsule production (Figure 3).

Urease production was seen (Figure 4). Based on the correlation of the CSF India ink findings with the cultural

and phenotypic characteristics, the isolate was identified as *Cryptococcus neoformans.* A final diagnosis of Cryptococcal meningitis with late state HIV infection was given.

The patient was started on liposomal amphotericin B 3-4 mg/kg IV OD for 14 days and flucytosine 25 mg/kg orally QID daily (total 100 mg/kg/day) as induction therapy. Following completion of amphotericin B therapy, a neurologic consultation was done, and oral fluconazole 800 mg OD for 8 weeks was prescribed as consolidation phase. Repeat CSF examination was also advised to assess the response to treatment. Antiretroviral therapy (ART) was planned to be continued after completion of the advised fluconazole course.



Figure 3: SDA culture showing creamy-white, smooth, mucoid colonies of *Cryptococcus* spp.

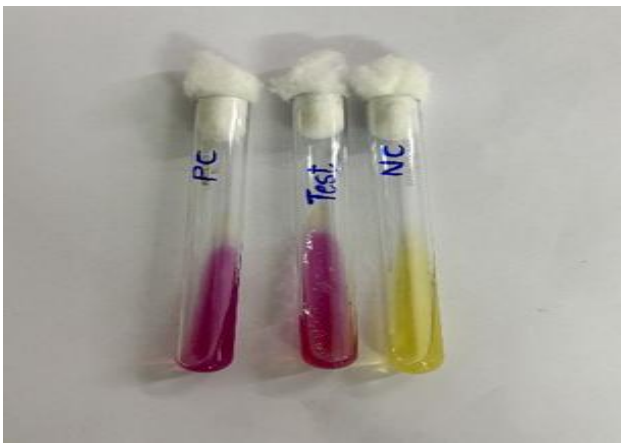


Figure 4: Positive urease test showing pink colour development.

DISCUSSION

The association between human immunodeficiency virus (HIV) infection and cryptococcosis represents an important clinical manifestation of advanced immunosuppression. Cryptococcosis is a major opportunistic fungal infection in individuals with HIV, predominantly caused by *Cryptococcus neoformans*. Approximately 90% of HIV-associated cryptococcal infections occur in patients with CD4+ T-lymphocyte counts below 100 cells/mm³. The increased susceptibility is primarily attributed to progressive depletion of CD4+ T lymphocytes, impaired cell-mediated immunity, defective Th1-mediated responses and reduced macrophage activation, which collectively compromise host defence against the organism.[6] The major virulence determinants of *Cryptococcus* include its polysaccharide capsule, melanin production, urease and phospholipase enzymes, which facilitate immune evasion, survival and dissemination within the host. Clinically, the disease may manifest as pulmonary cryptococcosis, cryptococcal meningitis or disseminated infection involving multiple organ systems. Following inhalational acquisition, the fungus may disseminate haematogenously from the lungs to various organs, particularly the central nervous system, resulting in cryptococcal meningitis or meningoencephalitis[7]. In patients with advanced HIV infection, the clinical presentation is frequently subacute, with persistent headache, fever, vomiting and altered sensorium. Classical meningeal signs may be absent because of impaired inflammatory responses. Diagnosis relies on cryptococcal antigen detection in serum and cerebrospinal fluid, direct microscopy and fungal culture. India ink staining may demonstrate characteristic encapsulated budding yeast cells; however, its limited sensitivity necessitates complementary antigen testing and culture.[8] Cryptococcal antigen screening among individuals with advanced HIV disease is an important preventive strategy, particularly in those with CD4 counts below 100 cells/mm³. Another important consideration in the management of HIV-associated cryptococcal meningitis is the timing of antiretroviral therapy initiation. Early ART initiation may precipitate cryptococcal immune reconstitution inflammatory syndrome (IRIS), which can result in neurological deterioration and increased mortality. Therefore, ART initiation is generally deferred for 4-6 weeks after commencing antifungal treatment in patients with confirmed cryptococcal meningitis. Despite advances in diagnostic techniques and antifungal therapy, HIV-associated cryptococcosis continues to pose a significant clinical challenge, emphasising the importance of early recognition, appropriate antifungal management and comprehensive HIV care.[6]

Cryptococcal meningitis remains an important opportunistic infection in people living with HIV, particularly in those with advanced immunosuppression. The illness may have a subacute course and present with nonspecific symptoms.[9] Previous Indian studies have reported headache and fever as common presenting symptoms of HIV-associated cryptococcalmeningitis.[10] The presentation in our case was similar with headache and fever as the main presenting symptoms.

In this case, the diagnosis was supported by conventional microbiological methods. India ink examination of CSF

suggested cryptococcal infection, which was further supported by fungal culture, Gram staining and urease testing. Similar laboratory methods have been described in previous reports of cryptococcal meningitis. These methods can be useful in routine laboratories where advanced diagnostic facilities may not be available.[11]

Based on the India ink findings, culture characteristics, Gram staining and urease test, the isolate was identified as *Cryptococcus neoformans*.

Most cases of cryptococcal meningitis in HIV-infected individuals are thought to result from the reactivation of previously acquired latent infection. In the present case, the possibility of latent infection followed by reactivation cannot be excluded. The patient though a driver also works in fields, has a low socioeconomic background, may have increased the likelihood of environmental exposure to *Cryptococcus* through contaminated soil, dust and other environmental sources. Such exposure may have occurred several years before the onset of clinical manifestations, with subsequent reactivation in the setting of HIV-associated immunosuppression.[9]

Management of cryptococcal meningitis requires appropriate antifungal therapy and subsequent clinical and microbiological monitoring. In this case, amphotericin B was administered for 14 days, followed by planned fluconazole therapy and repeat CSF examination. ART was planned after completion of the advised fluconazole course.

This case emphasizes the importance of considering cryptococcal meningitis in HIV-positive patients with subacute symptoms and of correlating clinical findings with microbiological results. The use of simple conventional methods such as India ink examination, fungal culture, Gram staining and urease testing can help in establishing the diagnosis in routine microbiology practice.[11]

CONCLUSION

Diagnosing cryptococcal meningitis should be a top priority whenever an HIV-positive individual develops a subacute headache and fever. This case highlights that classic mycological modalities-specifically direct cerebrospinal fluid (CSF) microscopy via India ink preparation, Gram staining for characteristic encapsulated yeast morphology, isolation on fungal culture, and biochemical confirmation via urease activity-provide definitive diagnostic evidence for the *Cryptococcus neoformans*. In resource-limited settings lacking access to advanced molecular assays or point-of-care antigen testing, a systematic, conventional microbiological workflow remains indispensable for ensuring early detection and timely therapeutic intervention.

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