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Case Report

Microbiology Section

Cryptococcal Meningitis: Challenges Faced in the Management of a Patient with Cryptococcoma

PRIYAADARSHINI URJAN MOHAN[1], ANUPMA JYOTI KINDO[2], SMH WASEEM[3]

ABSTRACT

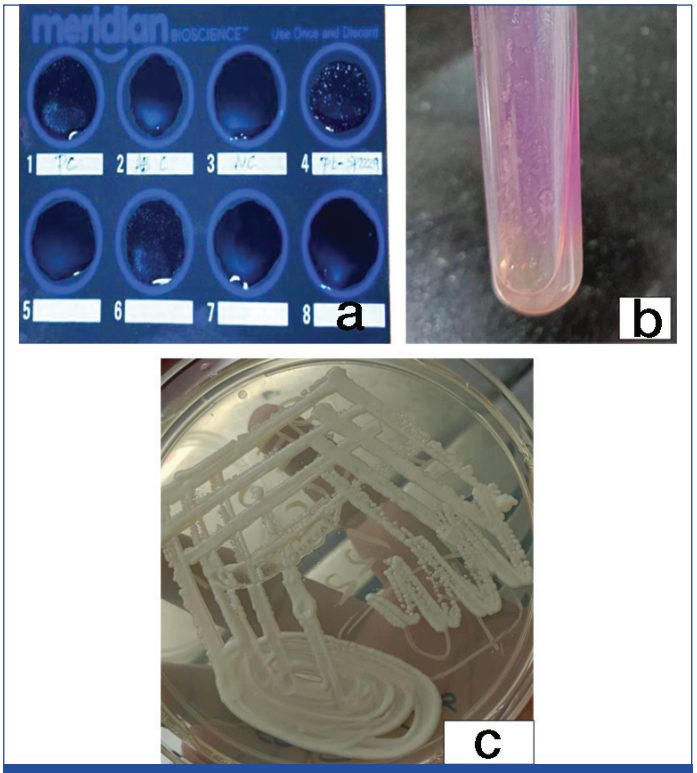
Cryptococcus is a genus of opportunistic fungal pathogens that have garnered significant attention in the medical community due to their ability to cause life-threatening infections, particularly in immunocompromised individuals. Cryptococcosis is a fungal infection that can present as an acute, subacute, or chronic infection. *Cryptococcus neoformans* are basidiomycetous encapsulated yeasts classified into five serotypes based on their capsule. The primary mode of infection is through the inhalation of basidiospores or small, poorly encapsulated yeasts. *Cryptococcus neoformans* is ubiquitous in the environment, often recovered from eucalyptus trees and bird droppings. This infection typically presents as meningoencephalitis in Human Immunodeficiency Virus (HIV) patients, while in immunocompetent individuals, the infection can be subclinical, manifesting as small granulomatous disease in the lungs without dissemination. The principal symptoms include meningitis, fever and intracranial hypertension. Additionally, altered mental status, seizures, visual changes and focal neurological deficits may arise. Diagnosis relies on the identification of encapsulated yeasts in the cerebrospinal fluid using India ink staining, which has a sensitivity of 50% in immunocompetent individuals. Biopsies of the lungs, skin, bone marrow, brain and other organs may also be conducted, offering higher sensitivity than the former method. The preferred treatment involves a combination of amphotericin B and 5-flucytosine during the induction phase to reduce the fungal load, followed by oral fluconazole in the maintenance phase. In contrast, cerebral cryptococcomas necessitate a longer treatment duration with additional antifungals. The low clinical suspicion of Cryptococcosis often leads to a delayed diagnosis of the infection. Early diagnosis and treatment are crucial for patient survival. Here, a case of Cryptococcaemia in an immunocompetent patient is reported.

Keywords: Central nervous system infection, Fungal infection, Immunocompetent

CASE REPORT

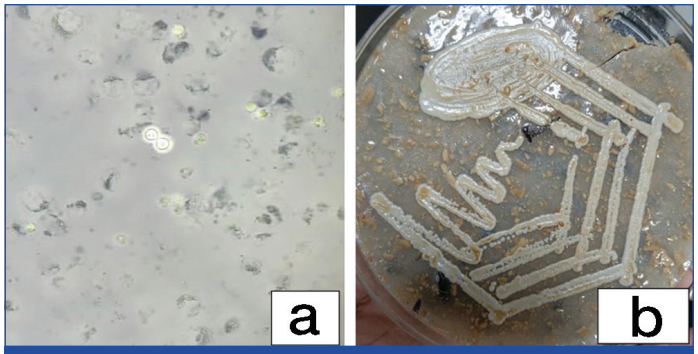
A 20-year-old male patient presented to the Emergency Department with the primary complaints of left lower limb weakness for the past two days, fever for the past day and neck pain for the past three days. He reported no history of nausea, vomiting, or blurred vision and there were no indications of gastrointestinal or other organ system infections. There was no history of surgery or trauma. Prior to this visit, he had sought treatment at other hospitals where suspected tuberculous meningitis was considered due to the prolonged nature of his symptoms, which included persistent headache, low-grade fever, left lower limb weakness and neck pain. He was empirically started on Antitubercular Treatment (ATT), including oral pyrazinamide, rifampicin and isoniazid. Despite initial treatment at other hospitals, his condition progressed, prompting advanced diagnostic evaluation due to persistent fever and meningeal signs. This led to a lumbar puncture later that same day.

The patient was admitted to the medicine ward with the above-mentioned findings. Blood parameters, such as total count and differential count, were within normal limits. The cerebrospinal fluid was sent for culture and cryptococcal antigen testing. The cryptococcal antigen test was positive using the Cryptococcal Antigen Latex Agglutination System [Table/Fig-1a], with a titer of >1:8 [1] [Table/Fig-1a] and was also confirmed by the Christensen urease slant test [Table/Fig-1b], which is a key biochemical characteristic aiding in their identification. Growth on Sabouraud Dextrose Agar (SDA) at 37°C showed creamy mucoid colonies [Table/Fig-1c]. India ink preparations revealed encapsulated fungi [Table/Fig-2a,b] [2]. [Table/Fig-2b] shows the brown pigmented colonies on Bird seed agar. Species identification was confirmed as *Cryptococcus neoformans* using BioMérieux's Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) system.



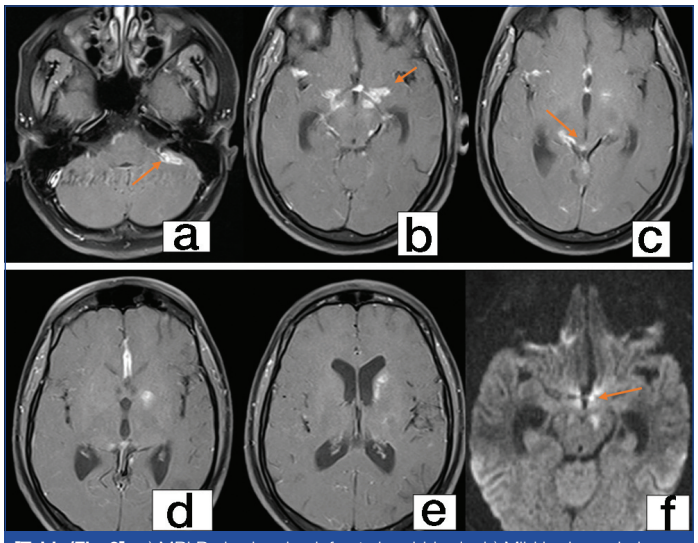
[Table/Fig-1]: a) This image depicts a positive result for the Cryptococcal antigen latex agglutination test. The agglutination reaction is evidenced by the formation of visible clumps in the reaction well, indicating the presence of Cryptococcal antigens in the sample; b) This image shows a positive result for the Christensen urease slant test, with the slope turning pink in colour; c) Sabouraud Dextrose Agar (SDA) showing white mucoid, creamy isolates of *Cryptococcus*.

The patient returned the following month with complaints of weakness in both the left lower and upper limbs, along with fever and neck pain. Plantar flexor and cerebellar signs were negative. Renal function



[Table/Fig-2]: The encapsulated *Cryptococcus* budding yeast was visualised at 40x magnification using an India ink wet mount preparation. The image shown is digitally zoomed for clarity; b) Bird seed Agar medium in which the Cryptococcal isolates had typical brownish pigmentation.

tests, liver function tests and a complete blood count were all within normal ranges. He also tested negative for HIV. Due to a high degree of suspicion, cerebrospinal fluid analysis with India ink, fungal culture and Magnetic Resonance Imaging (MRI) of the brain were performed. A repeat microscopy and cryptococcal antigen test were negative. An MRI of the brain, performed in response to the neurological complaints, revealed multiple peripherally enhancing nodules in the left gangliocapsular region, consistent with cryptococcomas. T1-weighted images [Table/Fig-3a] demonstrated hypodense cryptococcomas. Nodular leptomeningeal and perivascular enhancement within the basal cisterns, characterised by the "soap bubble sign" and indicative of meningitis caused by cryptococcal infection, was noted [Table/Fig-3b]. A cryptococcoma at the pineal site was also identified [Table/Fig-3c]. Additionally, mild hydrocephalus accompanied by a small infarct in the midbrain, likely resulting from the involvement of perforator arteries in the basal cisterns due to meningitis, was observed [Table/Fig-3d]. Axial cuts revealed a left parietal cortical lesion with perilesional oedema [Table/Fig-3e]. T2-weighted images [Table/Fig-3f] illustrated a hyperintense lesion corresponding to the same findings as [Table/Fig-3b]. As the symptoms progressed, autoimmune markers were performed to rule out autoimmune meningitis. Based on morphology on SDA, microscopy findings in India ink and culture isolate confirmation with MALDI-TOF, the diagnosis of *C. neoformans* was confirmed. The patient received induction therapy with intravenous amphotericin B (150 mg) and fluconazole (800 mg) for two weeks, followed by maintenance therapy with oral fluconazole (800 mg daily). Upon discharge, the patient was advised to continue with oral fluconazole 800 mg daily, intravenous liposomal amphotericin B 5 mg/kg/day for two weeks and oral flucytosine 100 mg/kg/day in three divided doses for two weeks.



[Table/Fig-3]: a) MRI Brain showing infarcts in mid-brain; b) Mild hydrocephalus and also showing "soap bubble appearance" a sign for meningoencephalitis due to fungal infection caused by cryptococcosis; c-e) Calcification or cryptococcoma; f) T2 weighted images showing the same findings.

Unfortunately, the patient lost to follow-up as he could not afford the ongoing therapy. Three months later, he was contacted and reported cheerfully that he had fully recovered but was still continuing his daily oral fluconazole.

DISCUSSION

Cryptococcus can cause both acute and chronic infections, primarily affecting the central nervous system. Cryptococcal meningitis is extremely common in immunocompromised individuals and is often misdiagnosed as other infectious conditions, such as tuberculous meningitis or carcinoma, since the clinical presentation is frequently non specific [2]. This diagnostic challenge is consistent with several reported cases. For example, a case report by Cardoso K and Carroll L described a patient initially diagnosed with tuberculous meningitis who, like index patient, did not respond to ATT and subsequently developed neurological symptoms leading to a cryptococcal meningitis diagnosis [3]. Similarly, Nicolas-Cruz CF et al., reported a case where the initial presentation mimicked a central nervous system tumour, highlighting the diverse clinical presentations of cryptococcosis [4].

In the present study, the patient was initially suspected of having tuberculous meningitis and was started on ATT. However, he did not improve and instead developed other CNS symptoms, such as limb weakness. In this case, the patient's clinical presentation, characterised by persistent headache, low-grade fever, disorientation and neck pain, aligns with common symptoms seen in meningitis. Considering India's significant tuberculosis burden, this constellation of symptoms initially suggested a provisional diagnosis of tuberculous meningitis. This highlights the diagnostic challenge posed by overlapping clinical features of cryptococcal meningitis and tuberculous meningitis, especially in regions with high tuberculosis prevalence. A comprehensive differential diagnosis is critical to ensure timely and accurate management, particularly in areas endemic to multiple infectious diseases.

While index case and the aforementioned reports underscore the difficulty in initial diagnosis, they also emphasise the importance of considering cryptococcosis in the differential, especially when patients are unresponsive to initial treatment for other suspected conditions. To provide a comprehensive overview, a comparison of this case with previously published reports is summarised in [Table/Fig-4] [3,4].

Parameters	Current case	Cardoso K et al., [3]	Nicolas-Cruz CF et al., [4]
Symptoms	Headache, fever, limb weakness	Headache, fever, neurological symptoms	Headache, confusion, seizures, with focal neurological deficits
Diagnosis	Misdiagnosed as tubercular meningitis	Misdiagnosed as tubercular meningitis	Mimicked CNS tumour
Treatment	ATT initially, antifungal later	ATT initially, antifungal later	Surgery and antifungal treatment
Recovery	Neurological improvement	Resolution with antifungal treatment	Stabilised with antifungal treatment

[Table/Fig-4]: Comparison of the present case history with already available previous cases [3,4].

The source of infection is the inhalation of spores, which are present in bird droppings and eucalyptus trees [5]. The spores enter the lungs and can disseminate from there. Although this patient was involved in poultry sales, the exact source of infection could not be determined. Nevertheless, the possibility of acquiring the infection from poultry droppings cannot be ruled out. This aligns with the previous report by Subramanya SH et al., regarding occupational exposure to poultry leading to cryptococcal infection [6]. However, like index case, they also faced challenges in definitively identifying the source.

The patient was not immunocompromised, which is noteworthy, as cryptococcal meningitis is more commonly associated with immunocompromised states. However, cases in immunocompetent individuals, like present case, have been documented, as seen in

the case report by Untalan AD et al., although they are less frequent [7]. As highlighted in a review by Qu J et al., it was found that 69.1% of cases occurred in immunocompetent hosts [8]. Reports of cerebral *Cryptococcus* infection in both immunocompetent and immunocompromised patients globally are depicted in [Table/Fig-5] [9-14].

Reported by	Site	Year	Key findings
Zahra LV et al., [9]	Cerebral	2004	Highlighted that Cryptococcosis mainly impacts immunocompromised individuals, with central nervous system involvement typically through haematogenous spread. Early diagnosis and antifungal therapy are crucial for better outcomes.
Capoor MR et al., [10]	Cerebral (CSF)	2007	Observed cerebral cryptococcosis predominantly caused by *Cryptococcus neoformans* var. *neoformans*, with all isolates sensitive to amphotericin B. They emphasised testing all Cerebrospinal Fluid (CSF) samples from patients with chronic meningitis.
Georgi A et al., [11]	Cerebral	2009	Reported a case of *Cryptococcus gattii* meningoencephalitis in an immunocompetent individual, highlighting diagnostic challenges due to non specific symptoms and emphasising the importance of tailored antifungal therapy and CSF management for improved outcomes.
Nath R et al., [12]	Cerebral, Skin	2016	The challenges of diagnosing cerebral cryptococcosis due its mimicry of other neurological conditions, highlighting the importance of comprehensive diagnostic methods.
Akins PT and Jian B [13]	Cerebral	2019	Cryptococcomas in HIV-negative patients, with symptoms mimicking cancer, leading to diagnostic delays.
Mani V et al., [14]	Cerebral	2023	They found that immunocompetent patients presented with meningitis more frequently but had better outcomes, including decreased mortality retrospectively.

[Table/Fig-5]: Few reports of cerebral *Cryptococcus* infection in immunocompetent and immunocompromised patients globally [9-14].

Cryptococcosis of the central nervous system is life-threatening and can present as meningitis or meningoencephalitis, with a wide range of symptoms, including headache, increased intracranial pressure, fever, lethargy, coma, personality changes and memory loss. Present case patient's presentation with limb weakness, while not uncommon, further illustrates the varied neurological manifestations. This symptom was also reported in a case series by Polk C et al., who analysed a number of patients with cryptococcal meningitis [15]. To provide a broader perspective on such presentations, [Table/Fig-5] summarises reports of cerebral cryptococcal infections in both immunocompetent and immunocompromised patients globally. The table highlights differences in clinical presentations, diagnostic challenges and treatment outcomes across these patient populations, offering valuable insights into the complexity of the disease.

Cryptococcus neoformans exhibits tropism characterised by melanin production, which is an indicator of virulence. Due to its invasive nature, the organism reaches the central nervous system by releasing various molecules, such as proteinases, mannose-binding proteins and polyol metabolites, which lead to cell destruction at the site of production [16]. Given the ambiguity in clinical presentation, the diagnosis of cryptococcosis is challenging in developing countries and is often delayed. Early isolation and accurate diagnosis are crucial for improving patient outcomes. Thus, following a diagnostic algorithm and adhering to current treatment protocols is essential for complete recovery, as demonstrated in present case patient.

CONCLUSION(S)

Cerebral cryptococcomas are challenging to diagnose and are often missed on initial evaluation due to their highly variable clinical presentation in patients. Due to the rarity of cerebral cryptococcomas and the challenges associated with their diagnosis, it is common for them to be mistaken for neoplasms; thus, a fungal aetiology must always be ruled out. Prompt treatment with amphotericin B and flucytosine, followed by long-term fluconazole, remains the mainstay of treatment in cryptococcal meningitis. Prolonged durations of induction and maintenance therapy should continue to be considered the standard of care. With the advent of newer technologies like the BIOFIRE® Meningitis/Encephalitis panel, swift diagnosis can be aided.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Microbiology, SRIHER, Porur, Chennai, Tamil Nadu, India.
2. Professor, Department of Microbiology, SRIHER, Porur, Chennai, Tamil Nadu, India.
3. Assistant Professor, Department of Microbiology, Sri Muthukumaran Medical College Hospital and Research Institute, Sikkarayapuram, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Anupama Jyoti Kindo,
No. 1, Sriramachandra Nagar, Department of Microbiology, Sri Ramachandra University, Porur, Chennai-600116, Tamil Nadu, India.
E-mail: anupamajyoti@sriramachandra.edu.in

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