Case Series

# Cryptococcal meningitis in non-human immunodeficiency virus patients: A case series

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## ABSTRACT

Cryptococcosis is a fungal infection caused by encapsulated yeast in the genus *Cryptococcus.* It is mostly observed in immunocompromised, organ transplant, and human immunodeficiency virus (HIV) positive patients, but it is also seen in non-HIV and immunocompetent patients. The majority of the cases have been reported in patients suffering from cryptococcal meningitis in HIV/acquired immunodeficiency syndrome. In this study, we reported a case series of three cases of cryptococcal meningitis in non-HIV patients. These cases were suspected and diagnosed according to their underlying immune status and clinical presentations.

**Key words:** Amphotericin-B, Cryptococcosis, India ink preparation

Cryptococcal meningitis is an invasive fungal infection mainly caused by *Cryptococcus neoformans* and *Cryptococcus gatti* [1]. The World Health Organization estimates that approximately 223, 100 cases of cryptococcal meningitis contribute to an annual death rate of 181,000 people living with human immunodeficiency virus (HIV) [2]. These two species transmit their infections through inhalation and after getting deposited in pulmonary alveoli, they disseminate into organs and tissues, especially to the central nervous system [3]. Recent studies have shown that non-HIV and immunocompetent patients with cryptococcal meningitis suffer higher mortality rates than HIV-positive patients [4].

Here, we report a case series of three cases of cryptococcal meningitis in non-HIV patients.

## CASE SERIES

### Case 1

A 55-year-old male with a history of diabetes mellitus and on anti-tuberculosis treatment (ATT) for tuberculosis meningitis presented with complaints of high-grade fever, blurring of vision, vertical diplopia for the past 8 days and headache, vomiting, and loss of appetite for 1 month.

On local examination, he was conscious, oriented, and moving all four limbs. On laboratory investigations, his hematological panel, renal function, and liver function were found to be normal. Magnetic resonance imaging (MRI) of the brain showed partially resolved meningitis with mild hydrocephalus. Computed tomography (CT) of the brain showed persistent ventricular dilatation with no interval change. A lumbar puncture was performed, in which he had high opening pressure (300 cm $H_2O$) and 30 mL of fluid was drained every 3 days. Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis (WBC – 200 cells/cumm, lymphocytes – 85%) with raised lactate (76 mg/dL), glucose (93 mg/dL), and protein (38.2 mg/dL) with normal adenosine deaminase (ADA)-2.0 U/L**.** During therapy, despite aggressive management with insulin, his blood glucose remained on the higher side (>200 mg/dL). CSF culture was found to be negative. The patient had one episode of focal seizure followed by giddiness and he became unresponsive to treatment; hence, fungal etiology was suspected. Follow up MRI brain was performed and depicted in (Fig. 1). CSF pan fungal polymerase chain reaction (PCR), varicella-zoster virus (VZV) Deoxyribonucleic acid PCR, tuberculosis (TB) gene Xpert PCR followed by India ink preparation, and *Cryptococcus* antigen titer were sent for analysis, in that *Cryptococcus* antigen titer (1:1280) found to be positive. Thus, the patient was diagnosed with cryptococcal meningitis and he was started on injection of amphotericin B deoxycholate 50 mg IV OD and oral flucytosine 1500 Q6H. After a 1-month course of treatment, *Cryptococcus* titer value had not changed, but the patient was clinically better and follow-up CSF analysis showed WBC (200 cells/cumm, lymphocytes – 80%) and protein (277 mg/dL) levels remained the same. The patient was clinically stable after 4 weeks on

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amphotericin B and was discharged with oral flucytosine and fluconazole for 2 weeks.

## Case 2

A 68-year-old male was admitted with complaints of headache, nausea, and constipation for 5 days. He had a history of systemic hypertension, coronary artery disease, coronary artery bypass surgery, and benign prostate hyperplasia. Previously, the patient presented with complaints of headache, nausea, and increased frequency and urgency of urination for which ultrasonography abdomen was performed, which showed grade II prostatomegaly with post-void volume within the normal limits, and he was discharged with non-steroidal anti-inflammatory drugs and calcium supplements. At present, he presents with complaints of headaches mostly in the bifrontal region, with no neck pain and seizures. On examination, vitals were normal, and a lumbar puncture was performed. CSF analysis showed decreased glucose (48 mg/dL) and WBC – 100 cells/cumm (lymphocytes were predominant). CSF analysis showed probable viral etiology. Acyclovir **(**500 mg IV TID) and doxycycline (100 mg IV BD) were started empirically. CSF-herpes simplex virus, VZV-PCR, and acid-fast bacilli (AFB) CSF stain were found to be negative. MRI Brain was carried out and shown in (Fig. 2) and india ink preparation showed capsulated yeast cells resembling *C. neoformans*.

Hence, he was diagnosed with *cryptococcus* meningitis, for which he was started on conventional amphotericin B (70 mg) and oral flucytosine (1500 mg Q6H) as induction therapy. During therapy, the patient had sudden desaturation followed by loss of consciousness with excessive sweating for which he was treated with 3% normal saline and oral salt 12 g/day. He had hypomagnesemia (1.53 mEq/L), and hypokalemia (3.0 mg/dL) for which corrections were made. On the 14$^{th}$ day of treatment, CSF culture showed *C. neoformans*, then conventional amphotericin B was changed to lipid emulsion amphotericin B 400 mg IV OD along with oral flucytosine. On the 21$^{st}$ day of treatment, the *cryptococcus* antigen titer was found to be positive, and fluconazole **(**400 mg OD) was started as consolidation therapy. The patient had occasional headaches during treatment. He received a cumulative dose of conventional amphotericin B for 10 days, lipid emulsion amphotericin B for 21 days, and oral flucytosine for 23 days. Due to high CSF opening pressure, 30 mL of CSF fluid was drained

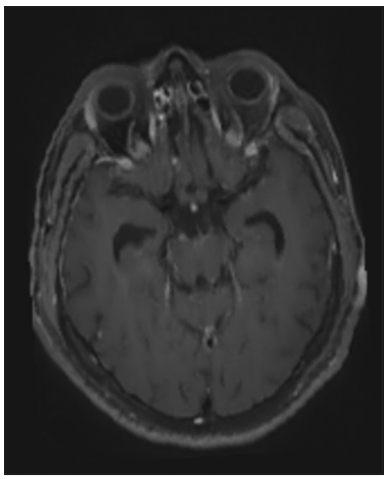

**Figure 1: Interval increase in sulcal and folial FLAIR signal changes with post contrast enhancement with diffuse involvement of the bilateral cortical sulcal and cerebellar folial regions.**

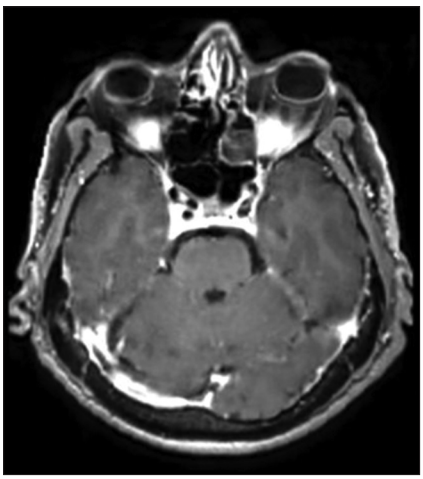

**Figure 2: Suspicious post contrast sulcal FLAIR changes are noted involving cerebellar folia and occipital regions.**

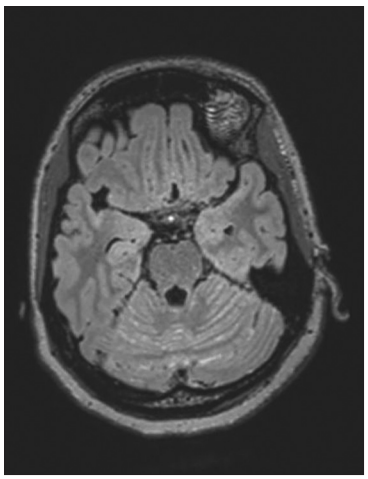

**Figure 3: Mild sulcal FLAIR hyperintensity in bilateral occipital and superior cerebellar regions with smooth leptomeningeal enhancement (Pre-treatment).**

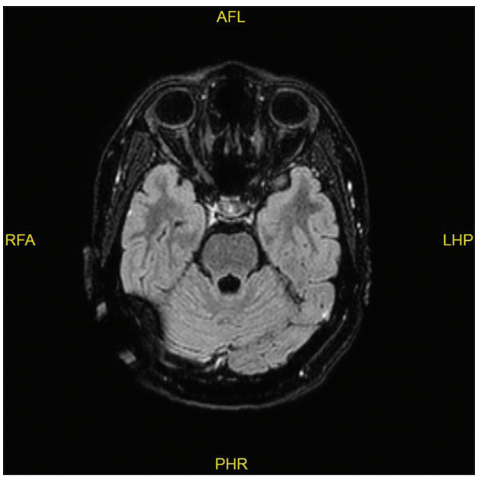


**Figure 4: Resolution of leptomeningeal enhancement - s/o treatment response (Post-treatment).**

every 3 days. On clinical resolution, he was discharged with oral fluconazole (400 mg OD**)** and flucytosine (1500 mg Q6H) for 2 more weeks. On follow-up, he was clinically stable and was advised to continue fluconazole 600 mg for 2 weeks.

### Case 3

A 29-year-old female was admitted with complaints of holo cranial, continuous, and throbbing headache associated with vomiting. The patient had a history of idiopathic thrombocytopenic purpura in remission and was on azathioprine and steroid add-on therapy for 3 years. On examination, the patient had signs of dysarthria and raised intracranial tension with no neck stiffness.

MRI brain showed leptomeningeal enhancement at the cerebellar region (Fig. 3). CSF analysis showed protein (27 mg/dL), glucose (87 mg/dL), WBC (50 cells/cumm) lymphocytes – 86%, polymorphs-14%, and ADA-1.1 U/Land CSF opening pressure of 27 cm $H_2O$. Based on probable viral etiology, acyclovir was started. VZV PCR, AFB CSF stain, and culture were found to be negative.

During therapy, the patient continued to have persistent headaches and slurring of speech, CSF analysis was repeated, and it showed glucose (75 mg/dL), protein (48 mg/dL), WBC (400 cells/cumm), polymorphs (48%) lymphocytes (52%), and lactate (25 mg/dL) with opening pressure of 60 cm $H_2O$. Hence, a lumbar drain was placed to prevent loss of vision. Further investigations were done; among them, India ink preparation revealed *C. neoformans*, and she was diagnosed with cryptococcal meningitis. The patient was treated with liposomal amphotericin B (3 mg/kg/day IV OD) and flucytosine (1500 mg Q6H) for 14 days. CT brain revealed no interval changes. On the 13$^{th}$ day of treatment, the ventriculoperitoneal (VP) shunt procedure was performed due to increased intracranial pressure. After the completion of 2 weeks of treatment, the patient showed signs of meningeal irritation in the form of rigidity, photophobia, headache, and fever spikes. CSF opening pressure continued to be elevated in the post-VP shunt. CSF analysis revealed that low sugar, high protein, and high WBC (all were lymphocytes) and high ADA. In view of persisting meningitis, underlying probable immunosuppressants, and considering the rising trend of ADA, she was empirically treated with ATT and fluconazole. MRI brain revealed an interval increase in meningitis with folial involvement and nodular enhancement, especially along basal ganglia, concerning disease progression and cryptococcomas. Hence, two more weeks of amphotericin B, fluconazole, and steroids were continued. She had no complaints of headache and no other signs of elevated intracranial pressure. The follow-up MRI brain shown in (Fig. 4) and CSF analysis showed improvement along with *cryptococcus* antigen titer, India ink preparation, and TB gene Xpert found to be negative and she was discharged with fluconazole 400 mg for 1 week.

## DISCUSSION

The vast majority of cases globally were caused by *C. neoformans* rather than *C. gatti* [5]. The common occurrence of cryptococcal meningitis was in immunocompromised, transplant, and hematological malformation patients, but there are few cases were reported in immunocompetent patients with a known history of diabetes mellitus, renal disease, hepatic disease, and glucocorticoid treatment [6]. In our study, we report three cases with a history of diabetes mellitus, the use of immunosuppressant, and one case with no known history, eventually diagnosed with cryptococcal meningitis. Kushawaha *et al*. reported that uncontrolled diabetes mellitus can cause susceptibility to infection by raising proinflammatory mediators, disrupting the immune system, and contributing to opportunistic infection [7].

Shih *et al*. conducted a systematic review at National Taiwan University Hospital among HIV-negative patients who were diagnosed with cryptococcal meningitis and presented with clinical manifestations such as fever (69.1%), headache (86.2%), vomiting (72.3%), blurred vision (34.0%), diplopia (28.7%), altered mental status (43.6%), and seizure (21.3%) [8]. This was consistent with our study, where patients had persistent headaches, fever, photophobia, and an increase in intracranial pressure among patients diagnosed with cryptococcal meningitis. In our study, CSF results showed elevated levels of WBC (predominantly lymphocytes) in all three cases and we tested a panel of viral and fungal pathogens, which was found to be negative. Out of three cases, a patient underwent a VP shunt procedure as a result of persistently high intracranial pressure. Liu *et al*. reported that persistent and uncontrollable intracranial pressure is a serious complication in patients suffering from cryptococcal meningitis and it is closely associated with the *cryptococcus* count. They reported a case with a lower *cryptococcus* count after the VP shunt procedure with an improved headache, with no change in altered mental status [9]. This was inconsistent with our study, counts were high, and intracranial pressure was found to be high, even with a VP shunt in our patient**.** In three cases, an increase in CSF opening pressure combined with leukocytosis and leptomeningeal enhancement should have raised suspicions of cryptococcal meningitis in non-HIV patients. However, due to its lower incidence rate among non-HIV patients, led to the delay in diagnosis of cryptococcal meningitis in non-HIV patients.

According to the Infectious Diseases Society of America, therapy for cryptococcal disease in non-HIV patients is conventional amphotericin B (0.7–1.0 mg/kg/day IV) and flucytosine (100 mg/kg/day orally in 4 divided doses) for at least 4 weeks as an induction therapy. If there is a neurological complication, consider extending induction therapy for a total of 6 weeks, and oral fluconazole (400 mg/day) is considered as consolidation therapy for 8 weeks. After induction and consolidation therapy, fluconazole (200 mg/day orally) should be continued as a maintenance therapy for 6–12 months [10]. Therefore, all three cases mentioned above have completed induction, consolidation, and maintenance therapy for cryptococcal infection. They were all clinically stable and their outcomes improved.

## CONCLUSION

Disseminated cryptococcal infection can affect both immunocompetent and immunocompromised individuals. In

non-HIV patients, early diagnosis can contribute to changes in the clinical course of treatment and reduce morbidity and mortality. Although India ink preparation for fungal elements turns out to be negative, cryptococcal antigen titer is required to rule out cryptococcal meningitis. Cryptococcal meningitis should also be considered in non-HIV patients presenting with sub-acute meningitis, irrespective of their immune status.

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