

## Cryptococcal Meningitis in an Immunocompetent Patient

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**Abstract:** The incidence of cryptococcal meningitis is increasing due to underlying human immunodeficiency virus (HIV) infection. *Cryptococcus neoformans*, the causative agent, has two varieties - var *neoformans*, which is usually seen in immunodeficient and var *gattii*, in immunocompetent individuals. Whether the patient is immunocompromised or immunocompetent, the outcome of the disease can be severe unless the disease is diagnosed early in the course of illness. In this case report, *Cryptococcus neoformans* var *neoformans* is the cause of meningitis in a young immunocompetent female. This report highlights the importance of thorough microbiological work-up for early diagnosis of the disease.

**Keywords:** *Cryptococcus neoformans*, Immunocompetent, Meningitis

### INTRODUCTION

*Cryptococcus neoformans* is an encapsulated fungus that has become of increasing medical importance, due to rapid increase in the immunocompromised human populations. The predisposing conditions include HIV infection, diabetes, immunosuppressive therapy after solid organ transplantation, hematological malignancies etc [1]. Cryptococcal meningitis rarely occurs in apparently immunocompetent individuals. The diagnosis is often delayed because of non-specific symptoms. We hereby report a case of cryptococcal meningitis in an immunocompetent adolescent female. The symptomatology, diagnosis and treatment of the disease are discussed.

### CASE REPORT

A 17-year-old female student, resident of a village in Bareilly, Uttar Pradesh, presented to the medical emergency with complaints of headache for 20 days and altered sensorium for 1 day. Headache was present throughout the day with increasing severity for 20 days. Patient had altered sensorium for which she was taken to the hospital. The patient had past history of tubercular meningitis 3 years back for which she was treated with anti-tubercular drugs for 9 months. She got improved after treatment and was apparently well when recent symptoms developed. She had no history of diabetes, hypertension, chronic cough, malignancy etc.

On examination, vital signs were stable and patient was afebrile. Patient was conscious but disoriented. Higher mental functions could not be

assessed. Neck rigidity was present. Pupillary response was bilaterally sluggish. Plantars were bilaterally extensor and all deep tendon reflexes were diminished. There were no focal neurological deficits or palsy of cranial nerves. A sensory and motor system examination could not be performed but patient could move all four limbs. Examination of cardiac, respiratory, gastrointestinal and genitourinary system revealed no abnormality.

Chest X ray and electrocardiogram (ECG) were normal. NCCT scan of head revealed bilateral third, fourth and lateral ventricular dilation suggestive of communicating hydrocephalus.

The patient was tested as non-reactive for HIV antibodies. CD4 count and immunoglobulin level were within normal limits. Her blood and urine cultures were sterile and sputum culture did not yield any significant pathogen. Laboratory investigations revealed raised total leukocyte count (12,000/mm<sup>3</sup>) with 85% neutrophils and 15% lymphocytes. Serum electrolytes, renal function tests and liver function tests were within normal limits.

Cerebrospinal fluid (CSF) was received in the Microbiology laboratory and processed as per standard operating procedures. On gross examination, CSF was clear and without coagulum. No microorganisms were detected on Gram and Ziehl-Neelsen (Z-N) stains. On India ink preparation, round budding yeast cells ranging from 5-20 µm in size with distinct halos were seen (Fig. 1). Bacterial culture was sterile. Cryptococcal latex

agglutination test was positive. On Sabouraud's dextrose agar (SDA), smooth white colonies of yeast were obtained after three days of incubation at 37°C. The urease test of this isolate was positive. Sub-culture was performed on Niger seed agar and after 72 hours of incubation at 28° C, chocolate brown colonies suggestive of *Cryptococcus neoformans* were obtained (Fig. 2). The identity of the isolate was confirmed with the Microscan Walkaway yeast identification system to be *Cryptococcus neoformans*.

CSF examination revealed 50 white blood cells per mm<sup>3</sup>, all lymphocytes with protein of 165 mg/dl and

glucose of 22 mg/dl. Mycobacterium tuberculosis complex and non-tuberculous mycobacterium were not detected in CSF by polymerase chain reaction (PCR).

Treatment was started with Amphotericin B at 0.75 mg/kg per day as an intravenous infusion along with intravenous fluids and mannitol. Serum electrolytes and renal functions were monitored on a daily basis. After five days of treatment, the patient developed aspiration pneumonia, after which she was put on ventilatory support. The condition of the patient deteriorated and later expired after one month due to respiratory failure.



Fig. 1: India Ink Preparation showing budding yeast cell in CSF sample



Fig. 2: Niger Seed Agar (Upper half: Brown colonies of *Cryptococcus neoformans*, Lower half: White colonies of *Candida albicans*)

## DISCUSSION

Cryptococcal meningitis is an opportunistic infection which is relatively rare in immunocompetent individuals therefore, specific treatment is not implemented until a definitive diagnosis of cryptococcal meningitis is available. Delay in diagnosis as well as in institution of effective therapy is responsible for fatal disease outcome. In immunocompetent hosts, 70-80% of cryptococcal infections are caused by *Cryptococcus*

*var. gattii* whereas *Cryptococcus var. neoformans* is rarely implicated [2]. The patient in this case report was immunocompetent and developed meningitis due to *Cryptococcus neoformans var. neoformans*.

The onset of disease is insidious with a subacute or chronic course in 'non-AIDS' patients. Symptoms of meningitis may begin months-to-years before clinical diagnosis. Our patient had subacute

presentation with a history of headache over duration of 20 days. The radiological findings of CNS are normal in HIV positive cryptococcal meningitis patients whereas in case of HIV negative patients, hydrocephalus, cerebral infarct, edema etc. can be seen in CT/MRI of brain. However, none of these findings are pathognomonic for cryptococcal meningitis [3]. Of these findings, hydrocephaly is more frequently seen in HIV negatives compared to HIV positives. In this patient, CT scan revealed bilateral third, fourth and lateral ventricular dilation suggestive of communicating hydrocephalus.

The mortality of cryptococcal infected non-HIV patients can vary from 0 to 47% [4]. Alteration in mental status is among one of the poor prognostic factors reported by Dismukes, Diamond and Bennett, and Saag [5-7]. As the patient in this case report also presented late in the disease with altered mental status, this might be responsible for the fatal course. Other poor prognostic factors are (i) steroid usage which could not be withdrawn or with a daily required use of >20 mg prednisolone, (ii) lymphoreticular malignancy, (iii) cryptococcus growth from sites other than CSF, (iv) elevated CSF pressure >20 cmH<sub>2</sub>O, (v) hypoglycorrhachia (abnormally low CSF glucose level) before treatment (CSF glucose < 40 mg/dl), (vi) CSF cell count < 20/mm<sup>3</sup> before treatment, (vii) negative cryptococcal latex agglutination test, (viii) cryptococcal latex agglutination test titre >1 : 10000, (xi) CSF cryptococcal latex agglutination test titre >1 : 8 after full course of treatment, (x) positive India ink stain after 4 weeks of treatment, and (xi) hypoglycorrhachia after 4 weeks of treatment.

In India, treatment of cryptococcal meningitis is done with amphotericin B alone or with flucytosine (5-fluorocytosine) as induction therapy followed by fluconazole maintenance therapy [8]. Due to its unavailability and high cost, flucytosine is not used in our setup. Despite all the measures taken, such as intravenous infusion of amphotericin B, mannitol and intravenous fluids along with ventilator support, our patient could not survive and died of respiratory failure. She might have survived if an early diagnosis could be made before the development of CNS complications.

## CONCLUSION

*Cryptococcus* causes meningitis mostly in the immunocompetent patients. In this case, the patient presented with complications of cryptococcal meningitis, despite being immunocompetent and died even after getting appropriate clinical treatment. Therefore, both clinical suspicion and thorough microbiological work up are necessary for timely diagnosis and treatment of cryptococcal infection, thus reducing the morbidity and mortality associated with the disease.

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