Meningitis Due to Cryptococcus gattii in an Immunocompetent Patient

RAJESH T PATIL1, JYOTI SANGWAN2, DEEPAK JUYAL3, SUMIT LATHWAL4

ABSTRACT

The incidence of cryptococcal infection is high in developing countries such as India. Cryptococcus gattii, formerly known as Cryptococcus neoformans var gattii, is an encapsulated yeast that causes disease in both immunocompetent and immunocompromised individuals. The organism enters via respiratory tract and causes a spectrum of illness ranging from asymptomatic infection to severe illness, including pneumonia and disseminated infection involving multiple sites, including the central nervous system, eyes and skin. Cryptococcal meningitis is generally considered as rare in immunocompetent patients; therefore, specific treatment is not implemented until the organism is identified or a cryptococcal antigen is detected. We describe the case of a 30-years-old man without prior medical history who presented with meningitis and was treated successfully. This case illustrates the importance of considering infectious causes such as C. gattii in the differential diagnosis of meningitis, regardless of the patient’s immune status.

CASE REPORT

A 30-years-old male, driver by occupation, was admitted to a neurology department with chief complaints of high-grade fever, intermittent, moderately severe headache lasting for 30 days associated with multiple episodes of vomiting. He had no history of seizures, ear discharge or earache, nor any focal neurological deficit, head trauma, weight loss, chronic cough, drug abuse including steroids, blood transfusion, or high-risk behavior. He did not have any history of cutaneous or respiratory manifestations neither he had any history of tuberculosis, diabetes, malignancy or any other such chronic illness.

On examination, the patient was febrile (39°C) and conscious, alert, oriented to time, place and person. Higher motor functions were intact and speech was normal. Signs of meningeal irritation (nuchal rigidity and Kernig’s sign) and bilateral papilloedema was present. Examination of other systems revealed no obvious abnormality. Laboratory investigations revealed Haemoglobin of 11 mg/dl, total leukocyte count (13,000/mm cu.) with 78% lymphocytes. Serum electrolytes, renal function tests, and liver function tests were within normal limits. A Cerebrospinal Fluid (CSF) examination revealed 210 cells/mm³, predominantly lymphocytes, with protein 92 mg/dl and glucose 22 mg/dl (corresponding blood glucose was 136 mg/dl). A Computerized Tomography (CT) scan of the head and a Chest X-ray were both normal. The CSF specimen was received in laboratory for microbiological investigations such as staining, culture and sensitivity. Macroscopically, the CSF was clear and without coagulum. On microscopy, Gram stain showed round budding yeast cells varying in size [Table/Fig-1a]. There were no acid fast bacilli on Ziehl-Neelsen (ZN) stain. India ink preparation showed characteristic round budding yeast cells varying in size [Table/Fig-1b]; a bacterial culture was sterile. The CSF Cryptococcal Latex Agglutination Test (CALAS, Meridian Diagnostics, Cincinnati, Ohio) for Cryptococcal Antigen (CRAG) was positive, with a titer of 1:1024. Serum was also tested for CRAG and was positive. A presumptive diagnosis of cryptococcal meningitis was given to the clinicians and patient was promptly put on Amphotericin B and Flucytosine. Subsequently, culture on Sabouraud’s dextrose agar yielded smooth colonies of yeast after five days of incubation at 37°C, with no growth at 30°C. With a battery of tests and biochemical reactions performed [Table/Fig-2], the isolate was characterized as C. gattii. Serotyping of the organism was not possible at this point. The anti-fungal susceptibility testing of the isolate was performed by using microbroth dilution technique and results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines [1]. The Minimum Inhibitory Concentration (MIC) values for fluconazole, Amphotericin B (Amp B), and voriconazole were ≤ 1 μg/ml, 0.50 μg/ml, and ≤ 0.12 μg/ml respectively. Also E-Test (AB Biodisk, Sweden) was used for Amphotericin B, which showed MIC of 0.38 μg/ml.

The patient was tested for HIV antibodies and found to be non-reactive for HIV1 and HIV2. His immunoglobulin levels (IgG, IgA, IgM) were normal and CD4 cell counts were 696 cells/mm³, thus ruling out any immune deficiency.

Treatment was started with combination of Amp B (1 mg/kg/day) and Flucytosine (100 mg/kg/day) as an intravenous infusion along with intravenous fluids and mannitol. A therapeutic CSF tap was also performed to lower intra-cranial pressure. Complete blood counts, serum electrolytes and renal functions were monitored on daily basis for the drug toxicity. Amp B and flucytosine were

Key words: Amphotericin, Cryptococcus gattii, Immunocompromised, Meningitis

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[Table/Fig-2] Biochemical tests used for identification

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Growth on Niger seed agar</td>
<td>Mucoid, brownish black colonies after 48 hours of incubation [Table/Fig-3a]</td>
</tr>
<tr>
<td>Urease production</td>
<td>Positive within 4 hours</td>
</tr>
<tr>
<td>Growth on L-canavanine glycin e bromothymol blue (CGB)</td>
<td>Present. CGB media became cobalt-blue in colour after 48 hours of incubation [Table/Fig-3b]</td>
</tr>
</tbody>
</table>

[Table/Fig-1a]: Gram staining picture showing gram positive round budding yeast cells (magnification x40)

[Table/Fig-1b]: India ink preparation showing round budding yeast cells with distinct halos (magnification x40)

[Table/Fig-3a]: Gram-positive colonies on L-canavanine glycine bromothymol blue (CGB) agar at 35°C after 48 hours of incubation (magnification x40)

[Table/Fig-3b]: Gram-positive colonies on L-canavanine glycine bromothymol blue (CGB) agar at 35°C after 48 hours of incubation (magnification x40)

[Table/Fig-4a]: Growth on Niger seed agar (magnification x40)

[Table/Fig-4b]: Growth on L-canavanine glycin e bromothymol blue (CGB) agar (magnification x40)
continued for 2 weeks; after which a repeat CSF analysis showed no yeast in Gram stain and India ink wet mount. Also CRAG levels have fallen to 1: 256. Thereafter, patient was put on oral fluconazole (800 mg/day) for 8 weeks. On subsequent follow up patient improved considerably, with complete resolution of symptoms.

Current practices of anti-cryptococcal therapy in India for immunocompetent patients generally include Amp B alone or with flucytosine (5-fluorocytosine), and sometimes followed by fluconazole [7]. In immunocompetent patients, initial therapy should be Amphotericin B (0.7-1 mg/kg per day) alone or in combination with fluconazole (100 mg/kg per day in four divided doses). Amphotericin B can be administered alone for six to ten weeks or in conjunction with flucytosine for two weeks, followed by fluconazole for a minimum of ten weeks [8].

Patient in this case was started on combination therapy with Amp B and Fluconazole as soon as the provisional diagnosis was provided on the basis of Gram stain, India ink and CRAG. With early diagnosis, cryptococcal infections, including CNS and disseminated infections, are usually amenable to therapy. In patients with no demonstrable immunosuppression, Amphotericin B therapy, with or without fluconazole, is effective in controlling or terminating infection in 70% - 75% of patients [8]. There had been few cases where lack of timely diagnosis and delayed treatment has resulted in patient death [5]. Therefore, irrespective of the immune status of the patient, the outcome can be severe unless the disease is diagnosed early in the course of illness.

CONCLUSION

Cryptococcosis is a life-threatening infection caused by two main species, Cryptococcus neoformans and Cryptococcus gattii. Despite appropriate antifungal therapy, mortality from cryptococcal meningitis, the most severe form of cryptococcosis, remains high. Early diagnosis, targeted screening and prompt management have been proposed to reduce meningitis related deaths.

REFERENCES


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