Case Report

A fatal case of meningitis caused by *Cryptococcus neoformans* var. *grubii* in an immunocompetent male

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Abstract

The incidence of cryptococcal infection is high in developing countries such as India. Cryptococcal meningitis is considered rare in immunocompetent patients and is mainly a disease of immunocompromised patients. Prognosis in immunocompetent patients is generally considered good. We report a fatal case of cryptococcal meningitis in an immunocompetent male caused by *Cryptococcus neoformans* var. *grubii*. 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.

Key words: *Cryptococcus neoformans*; meningitis; immunocompetent patient

J Infect Dev Ctries 2011; 5(1):071-074.

(Received 07 June 2010 – Accepted 09 October 2010)

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Introduction

The incidence of cryptococcal meningitis has increased in recent years, both in human immunodeficiency virus (HIV) positive and negative patients. Among all fungi causing meningitis, *Cryptococcus neoformans* remains the most common [1]. The two encapsulated yeast species *Cryptococcus neoformans* (serotype A *i.e.*, *C. neoformans* var. *grubii* and serotype D, *i.e.*, *C. neoformans* var. *neoformans*) and *C. gattii* (serotypes B and C), the causative agents of cryptococcosis, can cause life-threatening infections of the central nervous system, such as meningoencephalitis [2].

Recent data indicates that the incidence of cryptococcal infection is high in developing countries such as India (3, 4). Cryptococcal meningitis is generally considered rare in immunocompetent patients; therefore, specific treatment is not implemented until the organism is identified or a cryptococcal antigen is detected [1].

Amphotericin B, fluconazole, and amphotericin B in combination with flucytosine have been used in the treatment of cryptococcal meningitis with and without coexisting HIV infection, with significant improvements in the management of cryptococcal meningitis [5].

We report here a rare case of *Cryptococcus neoformans* var. *grubii* as the cause of meningitis in an immunocompetent adult male.

Case report

A 48-year-old male resident of a suburban area in Uttar Pradesh, India, who was a farmer by occupation, was admitted to the neurology department with chief complaints of high-grade fever, intermittent, moderately severe headache lasting 25 days associated with multiple episodes of vomiting, and altered sensorium for four days. 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. No

history of tuberculosis, diabetes, malignancy or any other such chronic illness was present. Finally, there was no history of exposure to avian excreta.

On examination, the patient was febrile and unconscious, with a Glasgow coma scale of $E_1M_5V_1$. Neck rigidity and Kernig's sign were positive. Pupillary response was bilaterally sluggish, plantars were bilaterally extensor, and all deep tendon reflexes were diminished. A sensory and motor system examination could not be performed. Examination of other systems revealed no obvious abnormality. Laboratory investigations revealed raised total leukocyte count (13,000/mm cu.) with 86% neutrophils. Serum electrolytes, renal function tests, and liver function tests were within normal limits. A cerebrospinal fluid (CSF) examination revealed 80 cells, predominantly lymphocytes, with protein of 54.7 mg/dl and glucose of 28 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 the mycology section, Department of Microbiology, Chhatrapati Shahuji Maharaj Medical University (CSMMU) and processed. Upon examination, the CSF was clear and without coagulum. With microscopy, occasional mononuclear cells were seen. There were no microorganisms on Gram and Ziehl-Neelsen (Z-N) stains. India ink preparation showed characteristic predominant round budding yeast cells ranging from 5-20 μm in size with distinct halos; a bacterial culture was sterile. The CSF cryptococcal latex agglutination test (CALAS, Meridian Diagnostics, Cincinnati, Ohio) was positive, with a titer of 1:16. A culture was performed on Sabouraud's dextrose agar (SDA), which yielded smooth colonies of yeast after five days of incubation at 37°C. The urease test of this isolate was positive. The isolate was subcultured on canavanine glycine bromothymol blue (CGB) to differentiate *C. neoformans* from *C. gatti*. After five days of incubation at 25°C, the CGB media showed no change in color. Thus the isolate was characterized as *C. neoformans.* A serotype differentiation of the isolate was conducted using a creatinine dextrose bromothymol blue thymine (CDBT) medium. On CDBT medium, after five days of incubation at 28°C, pale colonies with no apparent color effect on the medium were obtained, thereby confirming the isolate to be *C. neoformans* var. *grubii* (serotype A). The identity of the isolate was also confirmed with the Vitek 2 yeast identification system (identification profile no. 4102144253133530; identification probability, 99% [bioMerieux Inc., Hazelwood, USA]). The antifungal susceptibility of the isolate was determined using the AST-YS01 Vitek 2 card (bioMerieux). The minimum inhibitory concentration (MIC) values for flucytosine, fluconazole, Amphotericin B (Amp B), and voriconazole were ≤ 1 μg/ml, 2 μg/ml, 2 μg/ml, and ≤ 0.12 μg/ml respectively.

The patient was tested for HIV antibodies and found to be non-reactive. His immunoglobulin levels (IgG, IgA, IgM), complement levels, CD3 and CD4 cell counts were found to be within normal limits, thus ruling out any immune deficiency.

Treatment was started with Amp B at 1 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 two days of treatment, the patient developed aspiration pneumonia, after which he was put on ventilatory support. The condition of the patient deteriorated and he expired on the third day due to respiratory failure.

Discussion

Most cases of cryptococcal meningitis occur in patients with conditions that weaken their immune system, such as acquired immunodeficiency syndrome (AIDS). Cryptococcal meningitis has also been sporadically reported in HIV-negative patients caused by organ transplant and chemotherapy related immunosuppression, reticuloendothelial malignancies, corticosteroid therapy and sarcoidosis [5,6]. Occasionally, no obvious underlying cause can be detected [7,8].

Immunocompetent hosts are rarely reported to be infected with *C.* var. *grubii*, whereas *C.* var. *gattii* is usually implicated, accounting for 70-80% of cryptococcal infections in such hosts [6]. The patient in this case report was also immunocompetent and developed meningitis due to *C. neoformans* var. *grubii*. A study of the molecular epidemiology of the human pathogenic fungus *C. neoformans* in India has shown that most Indian isolates are *C. neoformans* var. *grubii* (serotype A), few are *C. neoformans* var. *gattii* (serotype B), and very few are *C. neoformans* var. *neoformans* (serotype D) [9]. In addition, more than half of the isolates studied

were derived from patients who had no known impairment of their immune systems.

Despite all the measures taken, our patient could not survive and died of respiratory failure. Despite the availability of newer antifungal agents such as fluconazole, cryptococcal disease in HIV-negative hosts continues to be associated with substantial morbidity and mortality [10]. Mortality rates can vary from 0 to 47% in non-HIV-infected patients. Moreover, in tropical countries it can vary from 0 to 38% where a low percentage of patients have underlying diseases [11]. Several factors are associated with mortality in the overall population and among specific groups of patients with central nervous system (CNS), pulmonary, or other sites of cryptococcosis. These include age over 60 years and the presence of significant underlying disease, especially organ failure syndromes and hematologic malignancy. [10]. In our patient, no underlying disease was found.

Because the signs and symptoms are similar in both diseases, cryptococcal meningitis presents late in the course of disease and has a shorter duration of symptoms in AIDS patients. In contrast, in non-AIDS patients, the onset is insidious with a chronic course. Symptoms of meningitis may begin months to years before clinical diagnosis. CT findings may also be normal in 50% of the cases [6]. Our patient had subacute presentation with a history of headaches over a duration of 25 days. The CT scan was also normal in our patient.

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 [12]. Flucytosine is not routinely used in India because of its unavailability and high cost.

In immunocompetent patients, initial therapy should be Amphotericin B (0.7-1 mg/kg per day) alone or in combination with flucytosine (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 [13].

Our patient was treated with Amphotericin B alone, but died due to respiratory failure. 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 flucytosine, is effective in controlling or terminating infection in 70 - 75% of patients [13]. The patient in this case report might have survived if he had been diagnosed with cryptococcal meningitis early in the course of disease. Therefore, whether the patient is immunocompromised or immunocompetent, the outcome can be severe unless the disease is diagnosed early in the course of illness.

Acknowledgements

The authors wish to acknowledge Dr. Rungmei S.K. Marak, assistant professor, Department of Microbiology, SGPGIMS, Lucknow, India for her kind support in the case report. We would also like to thank Dr. Bandana Mehrotra, director, RML Pathology, Nirala Nagar, Lucknow, India for her kind support in performing the sensitivity testing of the organism.

References

1. Satpute MG, Telang NV, Litake GM, Niphadkar KB, Joshi SG (2006) Prevalence of Cryptococcal Meningitis at a Tertiary care centre in Western India (1996–2005). J Med Microbiol 55: 1301-1302.
2. Voelz K, Lammas DA, May RC (2009) Cytokine Signaling Regulates the Outcome of Intracellular Macrophage Parasitism by *Cryptococcus neoformans*. Infect Immun 77: 3450–3457.
3. Chakrabarti A, Sharma A, Sood A, Grover R, Sakhuja V, Prabhakar S, Varma S (2000) Changing scenario of cryptococcosis in a tertiary care hospital in North India. Indian J Med Res 112: 56.
4. Khanna N, Chandramuki A, Desai A, Ravi V (1996) Cryptococcal infection of Central Nervous System: An analysis of predisposing factors, laboratotory finding and outcome in patients from South India in special reference to HIV infection. J Med Mirobiol 45: 376-379.
5. Pandit L, Agrawal A, Shenoy S, Kamath G (2006) Cryptococcal Meningitis and Pulmonary cryptococossis in a non-HIV Infected Patient. Eur J Gen Med 3: 80-82.
6. Viviani MA, Tortorano AM, Ajello L (2003) Cryptococcus. In: Clinical mycology, 1st edition. Anaissie EJ, McGinnis MR, Pfaller MA. Elsevier Science USA. 240-559.
7. Madan M, Ranjitham M, Chandrasekharan S, Sudhakar (1999) Cryptococcal meningitis in immunocompetent individuals. J Assoc Physicians India 47: 933-934.
8. Prasad KN, Agarwal J, Nag V, Verma AK, Dixit AK, Ayyagari A (2003) Cryptococcal infection in patients with clinically diagnosed meningitis in a tertiary care center. Neurol India 51: 364-366.
9. Jain N, Wickes BL, Keller SM, Fu J, Casadevall A, Jain P, Ragan MA, Banerjee U, Fries BC (2005) Molecular Epidemiology of Clinical *Cryptococcus neoformans* Strains from India. J Clin Microbiol 43: 5733–5742.
10. Pappas PG, Perfect JR, Cloud GA, Larsen RA, Pankey GA, Lancaster DJ, Henderson H, Kauffman CA, Haas DW, Saccente M, Hamill RJ, Holloway MS, Warren RM, Dismukes WE (2001) Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis 33: 690–699.

11. Shih CC, Chen YC, Chang SC, Luh KT, Hsieh WC (2000) Cryptococcal meningitis in non-HIV-infected patients. Q J Med 93: 245–251.
12. Datta K, Jain N, Sethi S, Rattan A, Casadevall A and Banerjee U (2003) Fluconazole and itraconazole susceptibility of clinical isolates of *Cryptococcus neoformans* at a tertiary care centre in India: a need for care. J Antimicrob Chemother 52: 683–686.
13. King JW, DeWitt, ML. Cryptococcosis. Available: http://emedicine.medscape.com/article/215354-overview Accessed 12 July 2010.

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Conflict of interests: No conflict of interests is declared.