

Case Report

## Sporadic Cryptococcal Meningitis - A Rare Presentation

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Received: 16/09/2015

Revised: 30/09/2015

Accepted: 03/10/2015

### ABSTRACT

Cryptococcal meningitis has been rarely seen in patients without immunodeficiency state. Most common association has been seen with HIV positive patients. 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. In this study we report a case of seronegative cryptococcal meningitis who presented with partial seizures. Patient responded to conventional and liposomal amphotericin, along with oral fluconazole and antiepileptics. Brisk response to therapy, negative smear and cultures after a short period of antifungal therapy and the non-requirement of long term maintenance treatment are more commonly seen in cryptococcal meningitis affecting non-HIV infected patients.

**Key Words:** Cryptococcal meningitis, Amphotericin, Fluconazole, immunocompetent.

### 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. <sup>[1]</sup> 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. <sup>[2]</sup>

Recent data indicates that the incidence of cryptococcal infection is high in developing countries such as India. <sup>[3,4]</sup>

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. <sup>[1]</sup>

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. <sup>[5]</sup> We report here a rare case of *Cryptococcus neoformans* var. *grubii* as the cause of meningitis in an immunocompetent adult male.

## CASE REPORT

In this case report we present a case of 40 year old male who came with complaints of partial seizures of right upper limb. No history of loss of consciousness, aura, weakness, sensory loss, bowel and bladder incontinence, tongue bite and trauma. The post-ictal state was associated with seizures. For similar complaints he was rushed to nearby local hospital where after receiving loading dose of phenytoin he was referred to our hospital.

At the time of admission to hospital, the patient was conscious, oriented with GCS 15. There was no sign of meningeal irritation with no lateralizing neurological deficits. No evidence of papilloedema. The rest of systematic examinations were unremarkable.

His routine blood parameters showed Hb of 10.2mg/dl with TLC count of 7000Cells/Cumm and platelet count of 4,28,000mcL. His renal and liver parameters were within normal limits. His HbA1c was 7%. His CXR was normal. HIV Elisa was non-reactive. MRI brain plain and contrast was obtained which showed T1hyperintense intraparenchymal lesions involving left frontal, parietal, temporal and bilateral occipital. On contrast study it showed leptomeningeal enhancement. His repeat CSF showed 5 cells with lymphocytic predominance. Proteins were 87 mg/dl and sugar 33mg/dl. CSF ADA was 17.9 and CSF for India ink was negative.

Subsequently CSF for Cryptococcal Ag was sent for qualitative and semi-quantitative assays. It was positive with assays more than 1:8. In view of seronegative assays his T cell profile (CD4, CD8, CD3, CD45, CD4:CD8) was sent which were found out to be normal.

As there was no sign of meningeal irritation he was continued with oral fluconazole 200 mg /day and tab Eptoin 300 mg/ day in divided doses. There were

no further episodes of seizures or febrile illness. Patient recovered well and is on regular follow up.

Our patient in Feb 2014 was diagnosed with cryptococcal meningitis and had receive conventional amphotericin 25 mg/day along with steroids, antiedema and supportive line of management. He received a total of 800 mg with regular monitoring of renal parameters. Oral fluconazole 200 mg/day was started for remission phase for 2 months. Following treatment patient showed improvement in clinical as well as laboratory parameters. During treatment he developed drug induced diabetes along with renal failure which improved with treatment. There was no history of recurrent infection, skin rash, bleeding tendencies and diabetes in past.

## 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*.

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).<sup>[9]</sup> In addition, more than half of the isolates studied were derived from patients who had no known impairment of their immune systems.

Our patient had come with seizures with responded well with antiepileptic medications with no recurrence of seizures. But 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.<sup>[11]</sup> 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.<sup>[10]</sup> 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.<sup>[6]</sup> Our Patient had T1hyperintense intraparenchymal lesions involving left frontal, parietal, temporal and bilateral occipital. On contrast study it showed leptomeningeal enhancement.

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.<sup>[12]</sup> 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.<sup>[13]</sup>

Our patient had received treatment with Amphotericin B in past and had responded. As there were no signs of meningeal irritation he was treated with oral fluconazole and continued with tab Eptoin.

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.<sup>[13]</sup> Therefore, whether the patient is immunocompromised or immunocompetent, the outcome can be severe unless the disease is diagnosed early in the course of illness.

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How to cite this article: Panpalia N, Chandak P, Patil A et al. Sporadic cryptococcal meningitis- A rare presentation. *Int J Health Sci Res.* 2015; 5(11):392-395.

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