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Clinical profile of disseminated cryptococcal infection-a case series

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ABSTRACT

Objective: To study disseminated cryptococcal infection in a tertiary care hospital in Southern India. **Methods:** The clinical profile of 12 disseminated cryptococcosis patients with the age group of 28-52 years was retrospectively analyzed. **Results:** 7(58.3%) presented with fever < 30 days and 3(25%) > 30 days whereas 2(16.7%) did not have fever. All the 12(100%) had headache, 2(16.7%) had altered sensorium, one (8%) seizure. 5(41.7%) had diarrhea and vomiting. 6(50%) had oral candidiasis, and anemia. 9(75%) had elevated erythrocyte sedimentation rate (ESR). 6(50%) had neck stiffness. Cerebrospinal fluid (CSF) pressure was elevated in all 12(100%) patients. Blood culture positive for *Cryptococcus neoformans(C. neoformans)* in 11(91.7%) and CSF culture positive in all 12 (100%), one (8%) had urine culture positive. India ink preparation was positive in 10(83.3%). CD4 count was less than 50/microl in 4 (33.3%), between 50-100 in 6(50%) and 2(16.7%) in the range of 100-200. 6(50%) were treated with parenteral amphotericin B (0.7 mg/kg/d) during intensive phase followed by oral fluconazole 400 mg/d for 8 weeks then maintenance oral fluconazole 200 mg/d. 5(41.6%) were treated with fluconazole alone. 8(66.7%) improved and 4(33.3%) patients died. Among those who succumbed to the illness, 2(16.7%) received amphotericin and fluconazole, 2(16.7%) patients received fluconazole alone. **Conclusions:** Disseminated cryptococcosis can cause considerable mortality in HIV patients and immunocompromised non-HIV individuals. At times, its presentation closely mimics that of Tuberculosis. Early diagnosis and appropriate treatment should be started as early as possible.

1. Introduction

Cryptococcosis is the infection caused by *Cryptococcus neoformans* (*C. neoformans*). The organism enters into the human body through lungs and spreads to the central nervous system. Other organs involved apart from lungs and brain are skin, prostate, medullary cavity of bone and rarely liver. It has wider spectrum of manifestation from an asymptomatic pulmonary lesion to a fatal disseminated cryptococcosis. It gets reactivated with immunosuppression. Disseminated cryptococcosis is mainly the disease of the immunocompromised patients with impaired cell mediated immunity. Predisposing factors are advanced HIV (AIDS), lymphoma, prolonged use of corticosteroids, solid organ transplant recipients, those on immunosuppressive drugs. Serious life threatening infections caused by *C. neoformans* is steadily increasing since the onset of AIDS and frequent usage of immunosuppressive agents. Higher incidence of cryptococcal infection is seen among patients living with AIDS in Africa and South East Asia. The objective of this study is to evaluate the clinical profile, risk factors, laboratory data, and correlation with low CD4 count, management and outcome of the patients suffering from disseminated cryptococcosis in a tertiary care hospital.

2. Materials and methods

Retrospective analysis of 12 cases of disseminated cryptococcosis were carried out. The study was done in a tertiary care hospital from January 2006 to April 2010, which is a referral centre in Southern India. All the twelve cases were HIV positive, with no other associated risk factors like diabetes, cirrhosis, chronic steroid intake, and other concomitant illnesses. Cryptococcal infections limited to single system were excluded. Disseminated cryptococcosis was defined as the disease that involved more than one system diagnosed by positive culture from two different

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Information collected from patients' records with special emphasis on clinical presentation, symptomatology, and organ system involvement, laboratory data including CD4 count, management and outcome of the patients.

Diagnosis of disseminated cryptococcosis was made by isolating the fungus from cerebrospinal fluid(CSF) and blood culture, urine culture and India ink preparation. The samples were also cultured on Sabourauds dextrose agars and fungal colonies identified. The growth of the yeast was identified by rapid urease test and melanin production on inoculating it on caffeic acid media.

3. Results

Of the 12 patients of disseminated cryptococcosis, 7 were males (58.3%), 5 were females (41.7%) with the age group ranging from 28-52 years. 7(58.3%) patients were less than 40 years of age and 5(41.6%) were between 40-60 years of age. 7(58.3%) patients presented with fever less than 30 d and 3(25.0%) and fever more than 30 d whereas 2(16.7%) patients did not have fever. All the 12(100.0%) patients presented with headache and only 2(16.7%) had altered sensorium, one (8.0%) had generalized tonic clonic seizure. 5(41.7%) patients had gastrointestinal disturbances in the form of diarrhea and vomiting. 6(50.0%) patients each had oral candidiasis, and anemia with haemoglobin less than 10 g%. 9(75.0%) had elevated erythrocyte sedimentation rate (ESR) more than 50 mm at the end of 1 hour, None had thrombocytopenia. 6(50.0%) had marked neck stiffness. CSF pressure was elevated in all 12(100.0%) patients with pressure ranging from 220-330 mm of CSF.

Blood culture BACTEC was positive for *C. neoformans* in 11(91.7%) patients and CSF culture was positive in all 12(100.0%) patients, one (8.0%) patient had urine culture positive. India ink preparation was positive in 10(83.3%) patients. CD4 count was less than 50/microl in 4(33.3%) patients, between 50 and 100 in 6(50.0%) patients and 2(16.7%) patients had in the range of 100-200. Two (16.7%) patients were on antiretroviral therapy (ART) since 2 months and 3(25.0%) patients were on antituberculosis therapy (ATT) outside for the presentation as chronic meningitis. 6(50.0%) patients were treated with parenteral amphotericin B (0.7 mg/kg/d) for 2 weeks during intensive phase followed by oral fluconazole 400 mg/d for 8 weeks then maintenance oral fluconazole 200 mg/d. 5(41.6%) patients were treated with fluconazole alone due to financial constraints. 8(66.7%) patients improved and 4(33.3%) patients died. Among the patients who succumbed to the illness, 2(16.7%) received amphotericin and fluconazole, 2(16.7%) patients received fluconazole alone.

4. Discussion

C. neoformans is an encapsulated basidiomycete yeast like fungus with a predilection for the respiratory and nervous system of humans and animals with two varieties, *C. neoformans* var neoformans which is responsible for 98% of all cryptococcal infection in patients with AIDS and *C. neoformans* var gatti[1,2]. Incidence of cryptococcal infection is higher among patients with AIDS in Africa and Southeast Asia than in the US, whereas it appears less frequently in Europe. *Cryptococcus* most commonly initiates as a primary pulmonary infection. Approximately 5%-10% of HIV infected patients develop cryptococcal meningitis as an AIDS defining illness and in about 40% it may be the initial manifestation[3]. More than 50% of patients with disseminated disease are immunocompromised. Melanin positive *cryptococci* are pathogenic while melanin negative strains were nonpathogenic with few exceptions[4]. A clinical study from western India reported cryptococcal meningitis in 67.4% of patients of HIV infection[3]. Disseminated disease is uncommon in cryptococcosis but when present is mostly seen in HIV infected patients[5]. The systemic infection of *Cryptococcus* is essentially hematogenous from the primary pulmonary focus. Similar to tuberculosis spread to the brain results in leptomeningitis.

Disseminated cryptococcosis in HIV patients can be an AIDS defining illness and can also present as disseminated cutaneous lesions[6]. There are some reports of rare manifestations of disseminated cryptococcosis in AIDS patients presenting as multifocal choroiditis[7], cholecystitis[8], co-infection with disseminated histoplasmosis[9]. Among HIV negative patients with disseminated disease, Cirrhosis was the most frequent predisposing condition and was associated with grave prognosis[10]. There are reports of disseminated cryptococcosis in HIV negative patients presenting as extensive subcutaneous nodules in renal transplant patients[11], and patients with nephritic syndrome[12]. It can also present as intracranial granuloma[13], necrotizing fasciitis[14] or with multiple osseous involvement[15]. Disseminated cryptococcosis closely mimicks disseminated TB and lymphoreticular malignancy[16].

In our study, all patients were immunocompromised due to HIV infection; the commonest presentation was headache prompting CSF analysis and CSF fungal cultures in all 12(100.0%) patients which were positive. Microscopic examination with India ink stain being more sensitive indicator of CNS infection in cryptococcosis was positive in 10(83.3%) patients. *Cryptococcal polysaccharide* antigen testing was not carried out in any patients due to economic concerns. There was no correlation with low CD4 count and dissemination since only 3(25.0%) patients had CD4 count less than 50.

Treatment with amphotericin B plus fluconazole versus fluconazole alone did not alter the mortality, although the

study involved only a small group. Among 2(16.7%) patients who were on ART one patient died of severe disseminated cryptococcal infection, had very low CD4 count of 14, probably due to systemic inflammatory response syndrome. Two patients presented with altered sensorium and elevated CSF pressure also succumbed to the illness.

Disseminated cryptococcosis can cause considerable mortality in HIV patients and immunocompromised non-HIV individuals. At times, its presentation closely mimics that of tuberculosis. Early diagnosis and appropriate treatment should be started as early as possible.

Conflict of interest statement

We declare that we have no conflict of interest.

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