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FATAL CRYPTOCOCCAL MENINGITIS IN A NON-HIV PATIENT: A CASE REPORT

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ABSTRACT

Cryptococcal infections are fungal infections most commonly seen in immunocompromised patients. *Cryptococcus neoformans* is a saprophyte usually found in soil contaminated with pigeon droppings. Suspicion to diagnose begins with clinical symptoms that can be non-specific such as fevers and headaches. We present a case of *Cryptococcus meningitis (CM)* in a patient with cardiopulmonary arrest. A 55 year old male patient came with history of headache with fever since last 3 months. He also had neck rigidity for last 3 months. The patient was admitted as a case of Cryptococcal meningitis based on clinical laboratory and radiological features. Investigations were done to rule out other immune system disorders. He was treated with Amphotericine B (IV) and Fluconazole orally for 2 weeks. Culture of CSF was done which showed *Cryptococcus neoformans*. As a conclusion, *Cryptococcus* might affect non-HIV patients regardless to their immune system.

**Keywords: Crptococcal infection, Cardiopulmonary Arrest, *Cryptococcus neoformans*,
Cryptococcal meningitis**

INTRODUCTION

Cryptococcus neoformans is an opportunistic infection seen in immunocompromised patients and is the fourth most common infection in AIDS patients. It is an encapsulated fungal organism that can affect the central nervous system (CNS) with pulmonary manifestations usually being the first presenting signs [1]. Infections are a major cause of hospitalization and death in immunocompromised patients, representing 20.9% [2] and 3.6% [3] of all death causes among renal transplant recipients and Systemic Lupus Erythematosus (SLE) patients, respectively. Though most are due to bacterial infections, invasive fungal infection prevalence is increasing in these populations [2].

Cryptococcosis is mostly caused by two encapsulated yeasts, *Cryptococcus neoformans* and *Cryptococcus gattii*. It is a life-threatening infection occurring mainly in patients with impaired cellular immunity with >1,000,000 cases estimated each year worldwide [4]. Sub-Saharan Africa has the highest incidence and mortality attributed to cryptococcal meningoencephalitis (CM) with more than 600,000 deaths reported each year among HIV/AIDS patients [5]. CM has an important long-term impact on mortality and disability. In the meantime, fluconazole

preemptive treatment, early diagnosis, and improved access to timely effective combined antifungal therapy should be implemented to prevent death and other long-term consequences of CM [6]. In addition, early detection of impairments and access to rehabilitation services will improve quality of life in CM survivors. By contrast, in developed countries, the overall incidence of cryptococcosis in HIV/AIDS patients has been decreasing due to the improved access to antiretroviral therapy. In these regions, the burden of the disease appears to be increasing in non HIV-immunocompromised populations [7]. In countries where the incidence of HIV remains high, investigating CM is paramount whenever the CD4 count drops below $100/\text{mm}^3$. However, cryptococcosis does not necessarily come to mind in an apparently immunocompetent individual. Depending on the site of invasion of the pathogen, a disseminated cryptococcal infection can be manifested in various clinical forms that include meningoencephalitis, pulmonary disease, skin disease, osteomyelitis, peritonitis, or comorbidities [8-13].

The importance of rapid and accurate diagnosis of cryptococcosis is emphasized.

CASE REPORT

A 55 year old male with a medical history of Diabetes mellitus, chronic obstructive pulmonary disease and use of steroid in last 5 yrs.

The patient came to the hospital with severe headache with fever last 3 months and neck rigidity also present and 2-3 kg wt loss over a 3 to 6 weeks period. He described an inability to stand without collapsing prior to admission. He also reported contact with a large pigeon population in the area.

Oral temperature was 37⁰C, heart rate 86, blood pressure 120/76, respiratory rate 20 and oxygen saturation of 96% on room air. He displayed completely normal neurologic functioning and was alert and oriented.

Initial laboratory results included a Erythrocyte 2.07x10⁶/μl, Leukocyte 13.78x10³/μl, Hb 6.5 gm/dl, Serum Creatinine 1.09mg/dl, S. Potassium 2.05mmol/L and S. Urea 53 mg/dl, Glucose (random) 134mg/dl. Normal renal and Liver function. There was no suspicious tumor marker and no HIV, Hepatitis B, Hepatitis C and Syphilis as well. The patient underwent a head Computed Tomography (CT) which showed a heterogeneous density of the cerebellum and a subsequent MRI of the brain, which confirmed. Multiple ring-

enhancing lesions of the inferior cerebellum with four discrete lesions (**Figure 1**).

Patient suffered by severe sepsis included signed decreased urination, low platelet count (70,000/mm³) and breathing problem. Body temperature 21⁰C, heart rate 60, respiratory rate 16, High sensitive C-Reactive Protein 10 mg/ml, Procalcitonin (PCT) 5ng/ml and C-Reactive protein was 110 mg/L respectively. The patient was empirically started on treatment for sepsis with in appropriate antibiotics included intravenously Ceftriaxone 2 gm and Azithromycin 500mg intravenously per day.

On day 3, patient CSF was analysed for sugar and protein levels. The CSF sugar was 0.08mg/dl and protein was 243.8mg/dl respectively. Patient was evaluated clinically; patient CSF sample was obtained by Lumbar Puncture in the microbiology Laboratory. Wet mount, Gram staining and India ink preparation revealed 4-7μm, round budding yeast with capsule (**Figure 2**) and 6-8 lymphocytes per high power field. CSF was cultured by standard method [14]. Creamy white, mucoid colonies were grown on sabouraud dextrose agar (SDA) medium (**Figure 3**). The identification of *Cryptococcus neoformans* was done by growth at 37⁰C and urease production. Treatment for cryptococcosis was initiated

with Liposomal Amphotericin B 350 mg intravenously daily and Flucytosine (100mg/kg/day, QDS). Head CTs were done every 2-3 days to assess brain edema and mass effect to determine if it would be safe to undertake a lumbar puncture.

On day 15 of admission, repeat LP was performed by CSF analysis confirmed Cryptococcal Antigen with a titer of 1:32 and a positive culture.

On day 20, the values of repeat LP and CALAS titer was 1:32 and again a positive culture. Treatment for cryptococcosis was

Fluconazole (1200 mg daily) + Flucytosine (100 mg/kg/day, QDS) and Amphotericine B (1.0 mg/kg/day). High sensitivity C-Reactive Protein level was high, it indicates that acute inflammation of the arteries of the heart, which can mean the high risk of heart attack. An aging population, sepsis is more common in seniors and weakened immune system. The outcome was fatal after 30th day of treatment with sepsis with shock with cardiopulmonary arrest after few hours the patient had expired.

Figure 1: Multiple ring-enhancing lesions of the inferior cerebellum with four discrete lesions

Figure 2: India ink preparation showing encapsulated budding yeast cells of *C. neoformans*

Figure 3: Creamy color colonies of *C. neoformans* on Sabouraud's dextrose agar

DISCUSSION

C. neoformans is the most common cause of fungal meningitis in HIV and non-HIV individuals [15]. It is thought to be acquired through inhaling soil contaminated with bird droppings. Two species, transmitted by inhalation, are the principal human pathogens: *C. neoformans* and *Cryptococcus*

gattii [16]. *Cryptococcus neoformans* var. *neoformans* is an opportunistic fungal pathogen that causes cryptococcal meningitis, which is mostly in HIV-infected and immunocompromised/ immunocompetent patients [17]. The incidence of meningitis increase is attributed to an enlarging population of high risk

immunosuppressed patients, which is due in part to more successful pharmacological immunosuppression and chemotherapies and the frequent use of antibacterial and antiviral therapies. In addition seemingly immuno-competent individuals can acquire this CNS infection with fungi such as *Cryptococcus neoformans* being the commonest [18]. Sub-Saharan Africa is experiencing an increasing prevalence of diabetes [19].

Kiertiburanakul *et al.*, 2006, [20] showed that conditions associated with Cryptococcal infection in non-HIV individual included immunosuppressive drug treatment (41%), systemic lupus erythematosus (16%), malignancies (16%), and diabetes mellitus (14%) [20]. Although relatively uncommon, our case has shown diabetes mellitus remains an important cause for *C. neoformans* meningitis. *Cryptococcus neoformans* infection then spreads to other organs by the circulatory system, mainly to the brain and meninges. Less frequently, other organs such as bones, joints and skin can be involved. In Non-HIV patients, the disease may occur if they have underlying immunosuppressive conditions such as Cushing's syndrome, sarcoidosis, haematological malignancies (Leukemia or Lymphomas) receipt of TNF inhibitors, or organ transplant [21]. Our patient had diabetic state during presentation

with CNS cryptococcal infection and secondary bacterial sepsis. He had not recovered and repeat the CSF CALAS and culture at 2 weeks and 4 weeks were positive. IDSA 2010 guidelines recommended 2 weeks of combination of amphotericin (0.7–1mg/kg/day) and flucytosine (100 mg/kg/day) for most cases of cryptococcal meningitis but also suggested at least 4–6 weeks of same combination for induction therapy in non-HIV infected, nontransplant hosts and at least 6 weeks for those with cerebral cryptococcomas [18]. Although the evidence of Cryptococcal infection in non HIV patients are still less. Data suggests presence of significant variation in clinical presentation and prognosis between HIV and non-HIV non organ transplant patient. In this study, 50% of apparently non-immunocompromised develop *Cryptococcus* meningitis, 40% pulmonary manifestations, 24% blood stream infections, and 5% bone and soft tissue infection. Same study suggests that 1-year mortality is: 26% in HIV patients, and 24% in organ transplant, while it was 35% in non-HIV, non-organ transplant patients, mostly due to delay in diagnoses [15].

This is bound to increase the occurrence of cryptococcal meningitis in non HIV non transplant patients, who are predominantly

diabetic patients. Of note is that low levels of adequate glucose control are achieved in diabetic patients who are on any form of treatment [22, 23].

Some factors associated with increased mortality such as advanced age (over 60 yr) and chronic or organ failure [24]. India ink staining sensitivity and specificity are 70.5% and 100% respectively [18]. A previous study observed CALAS (Serum Cryptococcal Latex Agglutination) titres are 87% sensitive for HIV negative patients and 95% sensitive for Cryptococcal meningitis patient [25].

CONCLUSION

Cryptococcal meningitis should be considered in the differential diagnosis for all individuals, including Non-HIV patients, presenting with chronic headache and fever. A non-HIV patient requires a longer duration of combination therapy.

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Declaration of Patient consent:

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient/s has given his consent for his clinical information to be reported in the journal. The patient/s understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of Interest:

There are no conflicts of interest.

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