Cryptococcal Meningitis -------- Case Report and Review of Literature

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Cryptococcus neoformans is a saprophytic encapsulated yeast with a worldwide distribution in soil contaminated usually with avian excreta, mostly from pigeons(1). Infection is acquired by inhalation of the organism and could be asymptomatic and limited to the lungs, especially in the immunocompetent host.(2) Haematogenous dissemination, especially to the meninges, and fatal outcome occurs in patients with other disorders, particularly malignancy, diabetes mellitus, treatment with corticosteroids and infection with human immunodeficiency virus.(3) Although there is a marked increase in the incidence of cryptococcosis around the world, due to its association with AIDS, reports concerning this infection from our region are rare.(4,5,6)

Here we report a case of C. neoformans meningitis and present an update on the pertinent literature, especially in relation to non AIDS versus AIDS patients.

Case Report

A 65 years old Asian female presented in the medical emergency unit of Ammar Medical complex with a week old history of fever, severe headache, productive cough, mental changes and increasing drowsiness. Her previous medical history revealed hospitalization for right hypochondrial pain and a positive hepatitis B profile almost a year back. Her physical examination was unremarkable except for a tender abdomen. Neurological examination revealed the patient to be disoriented in time, place and person but responsive to verbal orders. Chest X-Ray was normal. Haemogram showed an elevated ESR (55mm).

Renal and liver function tests were normal. The electrolytes showed levels slightly below normal and blood sugar levels were elevated. ELISA test for HBsAg, Anti HCV and HIV 1 and 2 were negative. Urinalysis showed abnormality in sugar (4+). Blood and urine cultures were negative.

Initial diagnosis of diabetes mellitus and chronic liver disease was made and the patient put on appropriate medications.

Due to gradual deterioration in patient’s condition, lumbar puncture was done and subsequently repeated at intervals (Table 1). Lumbar puncture yielded pale, hazy fluid with the following values: WBC’s 960 cells/cmm (60% neutrophils, 40% Lymphocytes); RBC’s 280 cells/cmm. Glucose level was lower than normal (24 mg/dl) whereas the proteins were markedly raised (254 mg/dl).

Direct examination of CSF revealed the presence of numerous oval budding cells of variable sizes, surrounded by a refractive mucinous capsule. India ink preparation confirmed the diagnosis. Culture was put up on glucose medium which revealed creamy, tan colored, mucoid colonies after 3 days of incubation, both at 25°C and 37°C. The patient was started on 5- flucytosine immediately after the results of India Ink preparation were received. Repeat lumbar punctures were performed to relieve CSF pressure and for investigation purposes. Her blood sugar was stabilized. Meanwhile, adverse effects to anti-fungal agents began to appear as evidenced by abnormal liver function tests. Repeat metabolic profiles showed low levels of sodium and potassium. Arterial blood gases revealed PO2 of 48.6 (lower than normal) PCO2 (normal) and pH of 7.505 & B.E. of 3.5. After two days the PO2 was 73,
PCO₂ (normal) and pH 7.576 and B.E. of 9.6. Six hours later the patient expired.

**Table 1**

<table>
<thead>
<tr>
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<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
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<tbody>
<tr>
<td>Gram Stain</td>
<td>+</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Acid fast</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>India Ink</td>
<td>Encapsulate Yeast Cells++</td>
<td>Encapsulated Yeast Cells++</td>
<td>Encapsulated Yeast Cells++</td>
<td>NS</td>
</tr>
<tr>
<td>WBC</td>
<td>960/cmm</td>
<td>150/cmm</td>
<td>85/cmm</td>
<td>32/cmm</td>
</tr>
<tr>
<td>PMN (%)</td>
<td>60%</td>
<td>8%</td>
<td>5%</td>
<td>0%</td>
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<tr>
<td>Lymphocytes (%)</td>
<td>40%</td>
<td>92%</td>
<td>95%</td>
<td>100%</td>
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( NS = not significant )

**Discussion**

The menace of cryptococcosis has assumed global proportions over the years, becoming a highly recognizable, major opportunistic pathogen with deadly consequences. (1) It has become a major cause of infectious morbidity and mortality in patients receiving immunosuppressive chemotherapy for cancer or organ transplantation or in immunodeficient patients, such as individuals with AIDS (7). Recently literature describes cases of cryptococcal meningitis in non-immunosuppressed individuals as well (8, 9, 10). Older patients with diabetes mellitus or pulmonary disease are also at increased risk of infection with environmentally acquired opportunistic Cryptococcus, manifesting simply as confusion (11,12,13,14).

Cryptococcus neoformans is a cosmopolitan zoopathogenic fungal organism and it is one of the most prevalent lethal mycotic agents, being found in bird droppings, in the soil, and on vegetables or fruits (2).

This encapsulated yeast was first described in 1894 in a paper by pathologist named Busse, who isolated the yeast from the tibia of a 31 year old woman (15). Since the initial reports, researchers identified the diverse spectrum of host responses to cryptococcal infections. The responses range from a harmless colonization of the airways to meningitis or disseminated disease. Of the 19 species that comprise the genus Cryptococcus, human disease is associated only with Cryptococcus neoformans. Host response to cryptococcal infection includes both cellular and humoral components. A successful response includes an increase in helper T cell activity, skin test conversion and a reduction in the number of viable organisms in the tissue. In addition, anti-cryptococcal antibodies and soluble anti-cryptococcal factors and described (16,17).

Although Cryptococcus neoformans enters the body via the lungs, the CNS is the main site of infection in hosts whether they are immunocompetent or immunosuppressed (15,18,19,20). Following pulmonary infection, cryptococci disseminate widely and may cause infection in any organ. The organs most often involved include the CNS, bone, prostate, eye, and skin. Cryptococcal CNS infections usually involve both the brain and the meninges causing diffuse disease. Presentation may be indolent and non-specific, with symptoms including fever, headache, nausea and vomiting (21). Rigidity in the neck, photophobia, cough and altered mental status, including personality changes are also observed (15,21). Or, it may cause an asymptomatic pulmonary infection followed by the development of meningitis in these patients (2, 16, 23).

Since the mid-1980’s most cryptococcal disease occurred in patients with AIDS. Today approximately 7 - 15% of the patients with AIDS develop cryptococcal infection (2,16,19,23).

Although the percentage is considerably higher in certain parts of the world like Sub-Saharan Africa and Zimbabwe, the decline in percentage reflects the development of more effective anti-retroviral therapy and prophylactic regimens designed to prevent fungal infections (19).
Differences in the incidence of some signs and symptoms have been noted between non AIDS and AIDS patients; headache (87% vs. 81%); fever (60% vs. 88%); mental status changes (52% vs. 19%); meningeval signs (50% vs. 31%); photophobia (33% vs. 19%); and seizures (15% vs. 08%) (16, 19). Since 10% of both non-AIDS and AIDS patient are asymptomatic, it is recommended that the CSF be examined keeping this diagnosis in mind also.

Reaching a definitive diagnosis in patients with cryptococcal meningitis could be delayed, as the clinical presentation and routine haematological, biochemical and CSF results may overlap with a variety of non-infectious and infectious diseases, especially those prevalent in our part of the world, like tuberculosis and brucellosis, making the differential diagnosis perplexing to the unaware. Such non-specific clinical findings often lead to mis-diagnosis, as mentioned by Liu et al.(15) As antibody and skin tests are unreliable, a definitive diagnosis requires isolation of C. neoformans from serum or sterile body fluids such as CSF.

In conclusion, although cryptococcal infection has been rarely reported from our region, all the factors for its existence are available in this part of the world. Thus the differential diagnosis of cryptococcal meningitis should be pursued when investigating febrile patients with signs and symptoms of CNS.

References