Cryptococcal Meningoencephalitis in an Immunosuppressed Patient with Chronic Lymphocytic Leukemia

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Abstract

Cryptococcal meningoencephalitis, an invasive fungal infection caused by an encapsulated fungus *Cryptococcus neoformans* should be suspected in immune compromised individuals with defective cell-mediated immunity and patients on immunosuppressive drugs with recent development of fever, confusion and loss of consciousness. A rapid diagnosis is fundamental for decreasing morbidity and mortality from cryptococcal disease. Cerebrospinal fluid (CSF) study and simple stain like India Ink Stain can be performed for diagnosis of cryptococcal meningoencephalitis. Here, we report a case of cryptococcal meningoencephalitis in chronic lymphocytic leukemia (CLL) patient on immunosuppressive drugs diagnosed by CSF study and India ink stain which responded dramatically with antifungal agents after diagnosis.

Key-words: Cryptococcal meningoencephalitis, Chronic Lymphocytic Leukemia, Immunosuppressive drugs, Cerebrospinal fluid (CSF).

Introduction

Cryptococcosis is an infection caused by fungi that belong to the genus Cryptococcus. Two species in particular *C. neoformans* and *C. gattii* cause nearly all cryptococcal infections in human[1]. *C. neoformans* causes most cryptococcal infections in immuno-compromised patients, primarily those with defective cell-mediated immunity such as human immunodeficiency virus (HIV) infection; while C. gattii cause disease in immunocompetent and to a lesser extent in immunocompromised persons[2]. Others population known to be at risk for cryptococcal disease include solid organ and stem cell transplant recipients, patients receiving immuno-suppressive agents and patients with advanced malignancies[3]. Both species can infect any organ in the body but most often they infect the lungs or invade the central nervous system (CNS) causing life threatening meningitis[4]. Cryptococcal meningoencephalitis is invariably fatal without appropriate therapy with a case fatality rate of 35%-65% in sub-saharah Africa[5]. A rapid diagnosis coupled with timeous institution of antifungal therapy is fundamental for decreasing morbidity and mortality from cryptococcal disease. Lab diagnosis of cryptococcal meningitis includes direct visualization of cryptococci via microscopy, culture of the organism and detection of cryptococcal antigen in the CSF.

Currently the India Ink Stain is widely used for the microscopic detection of cryptococci in CSF, although culture is relatively slow, it remains as the gold standard. Antigen detection is rapid with high sensitivity (93-100%) and specificity rate (93-98%) but is not always available in low resource settings[6]. Microscopy therefore remains a rapid, cheap and reliable diagnostic method. Herein, we have reported a case of cryptococcal meningitis in a patient with CLL on immunosuppressive drugs diagnosed by CSF study and simple stain like India ink stain.

Case Report

A 70 years old hypertensive, non diabetic, male, from Dhaka reported on 26 Jan 2020. He was a diagnosed case of CLL on immunosuppressive drugs presented with 4 months history of fever and 2 months history of loss of consciousness. Fever was low grade, intermittent with night sweats and was not associated with chills and rigor. He had history of occasional vomiting, photophobia and altered behaviour for same duration. There is no history of associated convulsion or skin rash. He had no history of contact with tuberculosis (TB) patients and travelling to malaria endemic zone. After admission, he was treated with several antibiotics and anti TB drugs. On general examination, patient was unconscious, mildly anaemic; on neurological examination, Glasgow coma score (GCS) was 8/15, neck rigidity was present. All reflexes were normal except plantar which was extensor. Other systemic examination revealed no abnormality. So, the provisional diagnosis was meningoencephalitis. His relevant Laboratory reports have been tabulated in Table-I.

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Table-I: Laboratory reports of the patients

Investigation details of reported case	
Parameters/Test	**Result**
Haemoglobin (gm/dl)	11.1gm/dl
Total Red Blood Cells	$3.64x10^{12}$ /L
Haematocrit(%)	31.1%
ESR	30 mm in 1st hr
MCV	78.8 fl
MCH	30.5 pg
MCHC	35.6 gm/dl
RDW	14.9%
Total White Blood Cells	$22.6x10^{9}$ /L
Neutrophills	26%
Eosinophils	02%
Lymphocytes	70%
Platelets	$137x10^{9}$ /L
Random Blood Sugar	5.8 mm ol/L
ICT for Malaria	Negative
Urine R/E	Normal findings
Liver Function Test	
S. total bilirubin	0.48 mg/dl
S. ALT	30 Iu/l
S. AST	23 Iu/L
S. ALP	101 Iu/L
S. Protein Profile	
S. Total Protein	49 gm/L
S. Albumin	32 gm/L
S. Globulin	17 g m/L
S. A.G ratio	1.9:1
S. Urea	17 mg/dl
S. Creatinine	0.7 mg/dl

First CSF study revealed slightly reddish CSF without coagulum. Elevated protein, decreased glucose and White blood cells (WBC) count increased. Cells were lymphocytes on Leishman's stain, No microorganism were detected on Gram's stain and no acid-fast bacilli (AFB) was seen on Ziehl-Neelsen (ZN) stains. CSF Adenosine deaminase (ADA) was normal. CSF Cytology showed negative for malignant cells. MTB not detected in Gene X-part. Computerized tomography (CT) scan of brain showed normal pressure hydrocephalus. In perspective of our country, it was thought that TB meningitis. Anti TB treatment was started empirically. He initially responded to treatment. But after two weeks of therapy, his symptoms aggravated, He again developed high grade fever and neck rigidity. Repeat CSF R/E done and showed slightly reddish CSF without any visible coagulum where protein increased, sugar decreased, WBC count increased, cells were predominantly lymphocytes on leishman's stain, budding yeasts were present on Gram's stain, no AFB was seen on ZN stain. India Ink Stain shows budding yeasts surrounded by capsular hallow (Figure-2). Periodic acid–Schiff (PAS) stain showed capsulated budding yeasts (Figure-1). Fungal culture revealed white mucoid colony of cryptococcus which were urease positive. Final diagnosis was cryptococcal-meningoencephalitis.

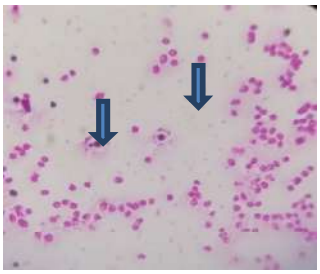

Figure-1: PAS-positive capsulated yeast

Figure-2: India Ink Stain showing budding yeasts of *C. neoformans* surrounded by capsular hallow

Treatment was started with inj liposomal Amph B in a dose of 240mg i/v OD for 2 weeks followed by oral fluconazole 800mg/day for 6 months. Patient regained consciousness after 5 days of getting treatment. During treatment another CSF study and all other investigations were done which revealed normal findings.

Dscussion

Here we presented a case of CLL patient on immunosuppressive drugs with symptoms and signs suggestive of meningoencephalitis. Final diagnosis was crypotococcal meningitis based on findings of capsulated cryptococcas on CSF gram's stain and India ink stain. Cryptocaccal meningoencephalitis is an important opportunistic fungal infection caused by variants of C. neoformans species and most affected patients have T cell dysfunction[7]. It is found in soil contaminated with avian excreta, especially pigeon droppings and in decaying wood, fruits, vegetables and dust[8]. The inhalation of small yeast forms that have been aerosolized is likely to be the main route of infection. Pulmonary infections are in most cases asymptomatic but may lead to haematogenous dissemination. Cryptococcus neoformans has a particular predilection for invasion of the CNS. Cryptococcosis of the CNS is life threatening and present as meningitis or meningoencephalitis with symptoms such as headache, increased intracranial pressure, fever, lethargy, coma, personality changes and memory loss[9]. Other sites of hematogenous dissemination include skin, bones, joints, kidneys, adrenal gland, spleen and prostate[10]. Lack of sensitive method of diagnosis causes high morbidity and mortality. Early diagnosis is essential to prevent serious complication[11]. A definitive diagnosis of crypotococcal meningoencephalitis was made by CSF culture or CSF microscopy using India ink stain. The diagnosis might further be confirmed by detection of capsular antigen using different technique such as enzyme immunoassay (EIA), latex agglutination or the lateral flow assay[12-14].

Conclusion

Diagnosis of CNS infections remains a great challenge in patients with haematological disorder since symptoms might both be masked

and be mimicked by other conditions such as metabolic disturbance or consequences from antineoplastic treatment. Thus, awareness of this complication is crucial and any suspicion of a CNS infection should lead to timely and adequate diagnosis and treatment to improve the outcome in this population.

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