Disseminated Cryptococcosis In An Immunocompetent Patient In Northeast India Caused By Serotype B - A Case Report

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ABSTRACT
Disseminated cryptococcosis is not common in immunocompetent persons. Here we report a case of disseminated cryptococcosis in an immunocompetent individual caused by Serotype B. Detailed case history with informed consent was taken followed by thorough investigation. A search was made on the Internet (Medline, ProQuest and Google) for similar findings. Cryptococcus gattii was isolated from blood, CSF and sputum in this case who presented with cough, meningitis, hemiparesis, transient loss of consciousness and sixth nerve palsy at one time.

This case of disseminated Cryptococcosis with multiple neurological symptoms caused by Serotype B in an immunocompetent individual is reported due to its rarity.

KEYWORDS: Cryptococcus gattii, Immunocompetent, disseminated, sixth nerve palsy, transient loss of consciousness, pulmonary.

INTRODUCTION
C. neoformans is an encapsulated yeast which causes infections of the central nervous system typically in immunocompromised patients. The clinical manifestations of CNS involvement of cryptococcosis are highly variable, depending not only on the patient’s risk factors, but also on the yeast variety involved [1]. There are two recognized varieties of C. neoformans: C. neoformans var. neoformans (serotypes A and D) with worldwide distribution, isolated from soil contaminated with mammalian and avian (especially pigeon) feces; and C. neoformans var. gattii. The former predominantly infects HIV-infected and other immunocompromised patients. Based on capsular differences, Serotype A has been proposed to be separated from C. neoformans var. neoformans into a new distinct variety called C. neoformans var. grubii. Cryptococcus neoformans var. gattii (serotypes B and C) arises mainly in temperate and tropical climates, is found in the soil near eucalyptus trees, and infects immunocompetent patients [2]. C. neoformans var. gattii is believed to behave more aggressively than C. neoformans var. neoformans [3]. The principal sites of cryptococcal infection are pulmonary, CNS and disseminated disease. Disseminated cryptococcosis is defined as recovery of Cryptococcus neoformans from blood, sterile body fluids or tissues other than pulmonary tissue [4].

Methods: History of the patient was taken along with informed consent of the patient followed by extensive investigations. A thorough search was also made on the Internet (Medline, ProQuest and Google) for similar articles.

CASE REPORT
A 38 years old lady hailing from Nagaland presented to the Out Patient Department of Medicine, Assam Medical College Hospital in December 2008 with transient loss of consciousness and diplopia for three days. She gave history of cough, severe headache, vomiting of one month and partial seizure for 1 week. She had fever with chill and rigor two months back and was treated empirically for malaria and typhoid fever in her hometown as outpatient and later admitted to a local hospital for investigation. She developed neck stiffness and had...
crepitation on the right chest. All routine investigations including CT scan of brain detected no abnormality and she was discharged from the hospital. She was readmitted after four weeks for severe persistent headache and vomiting. Cerebrospinal fluid (CSF) was colorless, clear, with protein 100mg/dl, sugar 45mg/dl, total count of 250cells, predominantly lymphocytes. Gram stain showed no organisms. Giemsa and PAP stain were also negative for malignant cells. CSF culture was sterile; CSF ADA was 4.5 u/l. Mountoux test was non reactive. Serology for HIV-1 and HIV-2 antibodies was negative.

Sputum for AFB was also negative in 3 consecutive samples. She was suspected to have tubercular meningitis and was put on Short Course Chemotherapy consisting of four drugs (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol). The patient did not respond to the treatment and instead her vomiting and headache became intolerable and she also developed repeated partial seizures of the left side, transient loss of consciousness and diplopia for which she was referred to Assam Medical College & Hospital and admitted.

On admission, the patient was drowsy, dehydrated without pallor, icterus or lymphadenopathy. She was febrile. Pulse rate was 100/min; blood pressure was 90/40mmHg. Auscultation of the chest revealed diminished breath sound and crepitation in the right infra axillary area. Glasgow Coma Score was12/15 and had stiffness of neck. She had right sided sixth cranial nerve palsy. Ocular fundus showed bilateral papilloedema. Sensory functions were intact and motor system showed left sided hemiparesis. She did not give any history of tuberculosis, diabetes mellitus, hypertension or any high risk behavior.

**Investigations:** Hematological investigation revealed no abnormality other than raised ESR-32mm AEFH. Test for malarial parasite was negative. Absolute CD4 count was 340 cells/µl. Repeat test for sputum AFB was also negative. Urine examination was normal. Chest X ray showed opacities in the right lobe of the lungs suggestive of pneumonitis. Computed Tomography (CT) Scan of brain showed focal well defined hypodense lesions in left occipital and right temporal regions abutting the dura. No perilesional edema was seen. Magnetic Resonance Imaging (MRI) of brain revealed, two cystic non enhancing lesion of size 1.8x 1.69cm and 1.41 x1.14cm in left post occipital and right temporal lobes. MR Spectroscopy revealed increased lactate in corresponding areas with no definite lipid peaks. GRE images report revealed a calcified lesion in right frontal lobe suggesting a granulomatous infection.

**Figure 1:** MRI showing a calcified lesion in right frontal lobe

**Figure 2:** Cryptococcus neoformans colony on Bird Seed Agar (BSA)
Based on the findings of the MRI a differential diagnosis of Neurocysticercosis (NCC) / fungal infection was made and analysis of CSF with fungal culture and ELISA for antibodies to NCC was done. Cerebrospinal fluid, blood, sputum and urine of the patient was collected for culture and sensitivity. Opening pressure during lumbar puncture was high. Biochemical analysis of the CSF showed colorless, clear fluid with no deposits, protein was 90mg/dl, sugar 40- mg/dl. Total cell count was 110cell/cumm with lymphocytes predominantly. Direct wet mount, India ink preparation and Gram stained smear of the CSF revealed large 4-7µm round budding yeast cells with thick capsules. The CSF was inoculated in duplicate into Sabauraud’s Dextrose Agar (BBL™SDA, BD,France) and SDA with chromopencinol and cycloheximide ( BBL™ Mycosel Agar, BD, France). All the plates were incubated both at room temperature (RT) and at 37°C. Culture showed exuberant growth of cream colored mucoid colonies after 24 hrs of incubation on SDA at RT while there was no growth on Mycosel agar and SDA kept at 37°C.

Direct mount of the sputum revealed few small budding yeast cells. Sample was also inoculated on to SDA and Mycosel at RT and 37°C. After 24 hrs, culture showed mixed growth of yeast like colonies at RT. Most of the colonies were moist and few were mucoid. Lacto phenol Cotton Blue staining of isolated colony showed the presence two types of yeast cells resembling Candida and Cryptococcus. Five ml of blood was inoculated into biphasic fungal culture media (HiCombi Dual Performance Fungal Kit, Himedia, India) which on subculture too yielded the growth of Cryptococcus.

**DISCUSSION**

Though there are several reports documenting *Cryptococcus neoforms* as a causative pathogen of meningitis in immunocompetent individuals [2,5,6]yet instances of disseminated infection by *C. neoforms var gattii* is rare. Our patient presented with less frequently encountered neurological and radiological findings in cryptococcal meningitis (CM) like transient loss of consciousness, hemiparesis, diplopia due to sixth cranial nerve palsy and papilloedema on fundoscopic examination. The MRI scan of the patient showed unusual findings of calcification in the frontal lobe lesion besides lesions in the left occipital and the right temporal regions all indicating possibility of granulomatous lesion in varying stages. Calcification suggested the protracted course infection in the patient. We could also isolate the organism from the sputum of the patient indicating active pulmonary infection, radiograph showed pneumonitis and she was symptomatic, which is uncommon [7].

Sixth cranial nerve palsy is the most common form of extracocular muscle palsy [8] but cryptococcal meningitis remains an uncommon cause of sixth cranial nerve palsy. Involvement of the sixth cranial nerve in cryptococcal meningitis has been reported previously in a patient of SLE [8] and in immunocompetent individual [5]. In our case it could be a false localising sign resulting from raised intracranial tension as evidenced by papilloedema. We could come across only two reports where hemi paresis [8, 9] and transient loss of consciousness [10] was the presenting complaint like ours. Neck stiffness in our patient was similar to findings elsewhere [11].

The clinical signs and symptoms of *C.neoforms* meningitis are indistinguishable from those of many other causes of meningitis. The differential diagnosis of CM includes tuberculosis, other mycoses, viral meningoencephalitis and meningeal metastasis [12]. We were also initially confused and thought of NCC based on radiological findings which is commoner in this region (Personal Communication). NCC was ruled out in our case but still the patient had to undergo initial treatment for tubercular meningitis because of the similarity of presentation and lost some time. However high degree of clinical suspicion due to non response to other antimicrobials in the patient led to opt for fungal culture and thereby early diagnosis and management which proved to be life saving. Identification of *var gattii* is essential as this variety is relatively refractory to treatment and needs prolonged or increased dose of antifungal therapy and shows long-term sequelae [12].

Also our patient did not suffer from any obvious immunosuppression. The CD4+ cell count of 340/µl could be due to idiopathic lymphocytopenia as described elsewhere [7]. Our case was unique in that the disseminated infection was caused by *C gattii* and all the unusual neurological findings were present in our patient at one point of time along with primary lesion in the lung and cryptococcemia.
We could not come across any literature reporting disseminated disease caused by *C. gattii* in immunocompetent individual. The authors would hereby like to emphasize that the differential diagnosis of fungal meningitis should be borne in mind by the clinician on encountering a case of antibiotic non-responder meningitis with or without neurological deficit as it is imperative for rapid diagnosis and timely initiation of anti fungal medication.

**ACKNOWLEDGEMENTS**

The authors are grateful to Dr Arunaloke Chakrabarti, Professor and Head, Division of Mycology at the National Advanced Research Centre for Medical Mycology at Post Graduate Institute of Medical Education and Research, Chandigarh, India for his kind permission to Serotype our isolate and Mrs. Sunita Gupta, Senior Laboratory Technologist for conducting the test.

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