Cryptococcal Meningoencephalitis in an Immunocompetent Patient

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ABSTRACT

Cryptococcal meningitis (CM) is an uncommon opportunistic infection in immunocompetent hosts; and causes significant mortality and long-term morbidity. *Cryptococci* primarily cause disease in immunocompromised hosts, but rarely can lead to severe disease in immunocompetent individuals. A 64-year man, with no known immunosuppressive illnesses, presented in the Emergency Department with gait disturbances and lethargy for one year, which got worsened recently. After further deliberation on elevated intracranial pressure (ICP), a CT brain was performed, which showed hydrocephalus; and thus lumbar puncture (LP) was done. Fungal cultures grew *cryptococcus* neoformans. The patient was treated with anti-fungal medications. It is highly essential for emergency physicians and other clinicians to think of atypical neurological manifestations of meningitis in immunocompetent individuals.

Key Words: *Cryptococcus, Immunocompetent, Antifungal treatment, Meningitis.*

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INTRODUCTION

Cryptococcus Neoformans (CN) is not considered to be a part of microbial flora of human body. CN is known to cause serious infections in immunocompromised patients such as AIDS patients.[1] It is very rare to contract CN in an immunocompetent host. It is caused by inhalation of the etiologic agents, *CN* and *C. gattii, which are* encapsulated fungi found in the environment, bird feces, and decaying wood.[1]

It was a common thought that CN can be found only in human immunodeficiency virus (HIV)-positive patients. The second category can be non-HIV-infected immunocompromised patients; however, with widespread use of HAART therapy, the number of AIDS-related cryptococcosis cases has declined. The most common forms of immunosuppression other than HIV include glucocorticoid therapy, solid organ transplantation, cancer, particularly hematologic malignancy, sarcoidosis, hepatic failure, tyrosine kinase inhibitors, and development of anti-GM-CSF antibodies. Around 30% of cases have no apparent underlying condition.[1-3]

Literature reported mortality from CN-induced meningoencephalitis as high as 50% despite therapy.[1-3] Herein, we report a case of a 64-year male patient without any prior medical history who contracted CN-induced meningitis.

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CASE REPORT

A 64-year man presented to Emergency Department with a history of gait disturbance, worsening memory loss and intermittent urinary incontinence for the past one year. His past medical history included hypertension and stroke. The patient described worsening gait disturbances with the inability to walk without support. Lately, he was complaining of lethargy. Gait disturbances were associated with frequent episodes of fall; one of which led him to visit the Emergency Department. Gait disturbances described by the patient were limited to taking small steps. It was difficult for him to take his feet entirely off the ground. There were no associated tremors and difficulty in initiating movements. The patient also complained of gradual memory loss and urinary incontinence. The patient's primary physician suspected the possibility of limbic encephalitis initially; and planned to send paraneoplastic workup. The patient was started on five doses of pulse therapy with steroids and intravenous meropenem. However, patient's gait disturbances continued to worsen leading to the inability to walk without support. High volume lumbar puncture (LP) with suspicion of normal pressure hydrocephalus was performed before this hospital visit as computerised tomography (CT) head showed hydrocephalus. The patient's symptoms improved following high volume LP and, therefore, was planned to be referred to neurosurgery for the placement of ventriculo-peritoneal (VP) shunt. However, cerebro-spinal fluid (CSF) detailed report showed increased protein and cell counts. Therefore, repeat CSF was advised. CSF studies were repeated and samples were sent for biofilm assay, acid fast bacilli, Gene Xpert and cultures, which were negative. There

were persistently elevated proteins and cell counts (Table I). Magnetic resonance imaging (MRI) brain with contrast showed features suggestive of meningitis and ventriculitis.

Table I: CSF studies during the course of the disease.

	August 2019	October 2019	January 2020	Normal values
CSF glucose (mg/100 mL)	26	19	10	40-70
CSF chloride (meq/L)	123	124	111	122-132
CSF protein (mg/dL)	258	266	202	15-40
CSF TLC (cells/mm^3)	0.084	0.132	0.166	0-0.005
CSF Polymorphs (cells/mm^3)	15	10	35	0-5
CSF lymphocytes (cells/mm^3)	85	90	65	
CSF Red blood cells (cells/mm^3)	0.000	0.000	0.000	0-0
CSF pus cells (cells/mm^3)	Rare	Rare	Rare	0
Microorganisms	Nil	Nil	Nil	0

On general physical examination, the patient was oriented to time, place and person. Vital signs included a regular heart rate of 107 beats/minute, blood pressure of 160/91 mm Hg, respiratory rate 20 breaths/minute, and temperature of 37°C. The rest of the general examination was unremarkable. On neurological examination, there were intact cerebellar signs upon supine position. Gait was described as magnetic with difficulty turning around and full swinging of arms. His higher mental functions were normal, and cranial examination was unremarkable. There were no signs of meningeal irritation.

Differential diagnosis was divided into infective and non-infective causes. Infective causes included bacterial (pyogenic), tuberculous, syphilitic, and fungal. Non-infective causes included sarcoidosis, Behcet's disease, vasculitis, and leptomeningeal carcinomatosis.

A neurosurgery review was planned for placement of VP shunt. However, due to no significant improvement in gait, and an infective picture on CSF studies, it was deferred. Intravenous meropenem was continued to avoid superimposed bacterial infections. CSF for cryptococcal antigen came out positive; hence, long-term antifungal therapy was initiated for three months. The dose of meropenem was increased to the meningitic range. The patient became hypotensive and was shifted to special care unit. A serial complete blood count revealed a significant drop in hemoglobin. Nasogastric lavage and digital rectal examination were unremarkable. The blood pressure stabilised after blood transfusion. However, the patient continued to have fever spikes, due to which malarial parasite and ICT antigen, Dengue and Brucella serology were sent, which came out as negative. The human immunodeficiency virus (HIV) test was negative. Esophagogastroduodenoscopy was performed due to one episode of coffee ground vomiting, which revealed erosive esophagitis. The paraneoplastic panel was negative.

MRI brain with contrast was repeated to look and compare for the meningeal enhancement after adequate treatment for bacterial meningitis, to avoid superimposed infections and pulse therapy with steroids, which was an intermittent intravenous infusion of very high doses of corticosteroids, was given for the suspicion of autoimmune meningitis. During this course, the patient had variable orientation with respect to place and time even after correction of his medical issues. CT chest with intravenous contrast was done to rule out pulmonary involvement as the patient had oxygen requirement of 2 L *via* nasal prongs. He was discharged on amphotericin and fluconazole. On follow-up in the clinic, he recovered uneventfully.

DISCUSSION

It was a common thought that CN can be found in only HIV-positive patients. However, CN can occur in non-HIV patients such as transplant recipients, patients with malignancy and rheumatic disorders. Importantly, no immunodeficiency can be identified in 10-40% cases.[3,4]

Our patient had a travel history to Thailand and was denied any animal exposure. Immunocompromised patients come in with acute symptoms and mild inflammatory responses. Fungaemia is an important finding and predicts poor prognosis. It is advisable to send blood cultures. Our case report emphasises on the fact that isolated cryptococcemia is often a delayed finding; hence, a high index of suspicion is required. Once it is suspected, CSF analysis for fungal culture and cryptococcal antigen, serum *cryptococcal* antigen assay, fungal blood culture and antifungal therapies within 48 hours should be sought.

Reports suggest that host immunity plays a major role in determining the outcome of the clinical course.[2] It is crucial to deal with intracranial pressure management, which is recognised as a cornerstone of CN-induced meningitis management. Clinical manifestations and response to antifungal treatment are hugely affected by host immune status. The course of treatment in terms of regimen and duration for *cryptococcosis* in non-HIV patients is largely for 6-12 months.[2] However, most of the patients were kept on amphotericin B. The mainstay treatment is antifungals. First-line therapies were liposomal amphotericin B (AmBisome®; LAmB, 3–4 mg/kg per day IV) or amphotericin B lipid complex (*ABLC*, 5 mg/kg per day IV), followed by amphotericin B deoxycholate with flucytosine.[3]

The treatment comprises of three phases. The induction phase consists of two weeks of amphotericin B (0.7–1.0 mg/kg per day) intravenously in combination with flucytosine100 mg/kg/day as the first-line. Factors associated with poor prognosis include positive India-ink examination of the CSF, CSF white blood cell count <20/µL, initial CSF or serum cryptococcal antigen titer >1:32 and high opening pressure on LP.[4,5]

The area of interest in the last few years is the description of CN-induced meningitis in immunocompetent individuals. Few reports have described the variety of clinical presentations,

epidemiological differences, CSF findings and prognosis.[2-5] This information can help understand us the clinical course and management of CN infection.

PATIENT'S CONSENT:
Verbal consent was taken from the patient.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
SS, UJ: Drafted and edited the manuscript.

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