Unusual presentation of cryptococcal meningoencephalitis in a patient with renal transplant

Mohammed A. Yassin, *MBBS, MD,*
Fahmi Y. Khan, *MBBS, CABM,*
Ahmed A. Al-Ani, *CABM, MRCP(UK).*

The diagnosis of cryptococcal meningoencephalitis can be difficult because of the subacute onset of symptoms and nonspecific presentation. Our patient presented with non-specific symptoms and cerebellar signs, which are unusual; thus, a high index of suspicious is needed to diagnose cryptococcal meningoencephalitis. In general, the disease should be suspected in any immunocompromised patient with fever, headache, and signs or symptoms referable to the CNS. The objective in presenting this case is to highlight that rare diseases or presentations should be kept in mind and should not be neglected as it is treatable.

A 28-year-old Indian male patient, admitted with a 7-day history of fever and jaundice. Three years ago, he had renal transplantation and is under immunosuppressive medications. His medical history was unremarkable. On examination; the patient was ill, conscious, oriented; febrile; jaundiced; no signs of meningeal irritation; the chest and cardiovascular system were normal; in the abdomen there was right iliac fossae scar with the transplanted kidney in situ. No signs of hepatic encephalopathy. Initial investigations; white blood cell (WBC) 10000/uL; hemoglobin (HB) 15.1 g/dL; platelet 429000/uL; cytomegalovirus serology was negative. Hepatitis B surface antigen was negative and hepatitis C antibody screening negative. Total protein 50 gm/L, albumin 25gm/L, total bilirubin 120 umol/L (normal range [NR] 3.5-24 umol/L), alkaline phosphatase 290 U/L (NR 40-129), alanine aminotransferase 210 U/L (NR 0-40), aspartate aminotransferase 237 U/L (NR 0-37), gamma-glutamyl transferase 965 U/L, direct bilirubin 146 umol/L, antimitochondrial antibody, anti nuclear antibody negative, and antismooth muscle antibody were negative, prothrombin time 14.6 sec, international normalized ratio 1.1, partial prothrombin time 31.4 sec, cyclosporine 188, cholesterol 6.48 mmol/L (desirable range <5.17), triglycerides 2.81mmol/L, EEG showed normal tracing. On the third day of hospitalization, he developed cerebellar signs in the form of limb ataxia and nystagmus. Urgent CT head and MRI were carried out and showed normal study. Lumbar puncture revealed elevated CSF pressure, lymphocytic pleocytosis, elevated protein level (98g/l, NR 20-40), remarkably decreased glucose level, and presence of cryptococcal antigen. India ink staining and culture of CSF identified *Cryptococcus neoformans*. It was sensitive to amphotericin B and fluconazole. The patient was given liposomal amphotericin B and flucytosine. On the following days, the patient improved dramatically, and he was discharged on the following medications; cyclosporine 100 mg twice daily, prednisolone 10 mg per os daily, imuran 50 mg per os daily, and omeprazole 20 mg per os daily.

Cryptococcal meningitis is a life-threatening infection caused by a fungus called *Cryptococcus neoformans*. Most people have been exposed to this organism, which is found in soil contaminated by bird droppings, but it usually does not cause disease in healthy people. Most people with cryptococcal meningitis have immune systems that are damaged by disease, such as AIDS, or suppressed by drugs. *Cryptococcus neoformans* produces infection following inhalation through the respiratory tract. The organism disseminates hematogenously and has a propensity to localize to the central nervous system. Patients without AIDS usually have symptoms for a longer time, up to several months, prior to diagnosis. Most patients (70-90%) present with signs and symptoms of subacute meningitis or meningoencephalitis.[1] Headache, fever, lethargy, coma, personality changes, and memory loss typically develop over a 2-4 week period. However, there is tremendous variability in the clinical presentation. Patients may present with severe headache for only a few days, intermittent headache for months, or without a headache. The presence of a headache may improve the prognosis by facilitating earlier diagnosis and treatment.[2] The diagnosis of cryptococcal meningoencephalitis can be difficult because of the subacute onset of symptoms and nonspecific presentation. To establish the diagnosis, the patient should have lumbar puncture, with measurement of opening pressure, and careful examination of CSF with India ink should suggest the diagnosis in most cases. Culture will almost always establish the diagnosis.

Examination of the spinal fluid with India ink will show the typical encapsulated yeast forms in approximately 75% of patients with AIDS and 50% of those not infected with HIV.[2,3] Assaying for the cryptococcal polysaccharide antigen in the CSF is an important adjunct to the diagnosis of meningoencephalitis to guard against false positive India ink readings. False positive tests can result from rare infections due to the fungus *Trichosporon beigelii* or the bacterial genera *Stomatococcus* or *Capnocytophaga*.[4,5] Radiologic imaging of the brain (with a CT scan or MRI) prior to a lumbar puncture is important in a patient with focal neurologic signs or symptoms or with papilledema. Imaging tests may also be useful in detecting hydrocephalus, which may require placement of a ventricular shunt.

Untreated, cryptococcal meningoencephalitis is uniformly fatal. Combination therapy with amphotericin B and flucytosine again appears to be the preferred

induction regimen. Amphotericin B and flucytosine should be continued until the CSF cultures become negative. Fluconazole (400 mg/day per os) may then be instituted. Liposomal preparations of amphotericin B have been used in limited numbers of patients with cryptococcal meningoencephalitis. Their use is reserved to patients who either develop toxicity to conventional amphotericin B or who present with baseline renal insufficiency. The most important prognostic factor for a patient with cryptococcosis is the underlying illness. Patients with underlying malignancies or AIDS have a much poorer prognosis than those with no apparent risk factor. In one study of patients with cryptococcal meningoencephalitis, patients with malignancy had a shorter median survival rate than those with AIDS (2 versus 9 months).[6] Thus, cryptococcal meningoencephalitis should be suspected in any immunocompromised patient with fever, headache, and signs or symptoms referable to the CNS. *Cryptococcus neoformans* should also be considered in immunocompetent individuals presenting with subacute to chronic meningitis.

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From the Department of Medicine, Hamad General Hospital, Doha, Qatar. Address correspondence and reprint requests to: Dr. Mohammed A. Yassin, Specialist, Department of Medicine, Hamad General Hospital, PO Box 3050, Doha, Qatar. Fax. +(974) 4392273. E-mail: yassin160@yahoo.co.uk

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