Case Report

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Fatal cryptococcal meningitis in a HIV-seronegative patient with liver cirrhosis

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Introduction: A 41-year-old man with a history of alcoholic cirrhosis presented to Patan Hospital in Kathmandu, Nepal, with a severe headache.

Case presentation: Clinical examination found an isolated sixth nerve palsy of the left side with normal blood parameters and a normal brain scan. An initial cerebrospinal fluid analysis found lymphocytosis, with a significantly elevated protein level and reduced glucose. Tubercular meningitis was considered; however, the patient did not improve and a re-examination of the cerebrospinal fluid confirmed cryptococcal meningitis.

Conclusion: After diagnosis the patient was treated with amphotericin B. Despite all efforts the patient died 5 days later.

Keywords: amphotericin B; cirrhosis; cryptococcal antigen lateral flow assay; headache; meningitis.

Introduction

Cryptococcal meningitis is the most common clinical syndrome due to infection with the encapsulated yeast *Cryptococcus neoformans*. Worldwide, there are an estimated 1 million new cases of cryptococcal meningitis annually, with an overall mortality of more than 62 % (CDC, 2013). The vast majority of cases occur in HIV-infected patients; however, cases can occur in those with other causes of immunosuppression, including sarcoidosis, haematological malignancies, liver cirrhosis and immunosuppressive therapy. Rarely, disease occurs in the immunocompetent (Coagliati, 2013). As with most neurological disease, a delay in appropriate treatment is associated with a poor outcome, and timely diagnosis is a significant problem in resource-limited settings, particularly in patient groups in whom the diagnosis might not be suspected. There are limited data on the incidence and clinical outcome of cryptococcal meningitis in Nepal. This case will raise awareness of this disease in this setting and we surmise that cryptococcal meningitis should be considered as part of the differential diagnosis of chronic

headache in those with immunosuppression or other comorbidities.

Case report

A 41-year-old male, with a 7 year history of alcoholic cirrhosis, presented to the Emergency Room at Patan Hospital in Kathmandu with a 3 week history of headache and vertigo, and 3 days of vomiting. Two weeks prior to admission the patient attended his local health facility complaining of a headache and intermittent vertigo. A contrast-enhanced computerized tomography scan performed 8 days prior to admission to our hospital showed mild hydrocephalus and some brain swelling. He was referred to our centre for further evaluation. On presentation, other than headache and nausea, there were no other significant symptoms. He had stopped drinking alcohol after being diagnosed with cirrhosis of the liver 7 years previously. On physical examination there was no evidence suggesting complications of cirrhosis and the patient was alert and well oriented as to time, place and person. His vital signs were within the normal range and recorded as: temperature 98 °F, pulse 78 min⁻¹, respiratory rate 18 min⁻¹ and blood pressure 130/90 mmHg. A neurological examination revealed left sixth nerve palsy, and there

Abbreviations: ACLF, acute or chronic liver failure; CrAg LFA, cryptococcal antigen lateral flow assay; CSF, cerebrospinal fluid; IV, intravenous

were no signs of meningeal irritation. Fundoscopic examination revealed a normal bilateral optic disc.

Laboratory tests revealed a haemoglobin level of 11.3 g dl^{-1} , a white blood cell count of 4900 mm^{-3} (82 % neutrophils) and a platelet count of $206\,000 \text{ cells mm}^{-3}$. Serum glucose, renal and liver function tests were normal. Total protein and albumin were respectively 8.3 and 3.9 mmol l^{-1} . Prothrombin time was 20.6 s and INR was measured at 1.47. A lumbar puncture was performed; the opening pressure of the cerebrospinal fluid (CSF) was $31 \text{ cmH}_2\text{O}$ and CSF was collected in a controlled manner. The CSF contained $40 \text{ leukocytes mm}^{-3}$, with 38 % neutrophils and 62 % lymphocytes, and the protein and glucose levels were respectively 62 and 48 mg dl^{-1} (blood glucose level of 178 mg dl^{-1}). Gram staining of the CSF revealed a few yeast cells, while in the blood culture heavy growth of yeast cells was obtained. On further culture onto Sabouraud's dextrose agar, mucoid colonies of *C. neoformans* were obtained. Ziehl-Neelsen staining and GeneXpert MTB/RIF analysis were negative for *Mycobacterium tuberculosis* and in view of no definitive diagnosis the patient was admitted to the medical ward for further investigations. On the second day after admission, magnetic resonance imaging suggested lacunar infarction with hyperintensities in basal ganglia with calcification. The lumbar puncture was repeated on the third day and the CSF tested positive for *C. neoformans* with a cryptococcal antigen lateral flow assay (CrAg LFA; IMMY). Subsequent examination of the CSF with India ink counter-staining showed encapsulated yeasts and a CSF culture identified cream-coloured mucoid colonies consistent with the colony morphology of *C. neoformans*. Further laboratory testing found that the patient was seronegative for HIV antibodies, as well as negative for HBsAg and HCV antibodies.

The patient was started on intravenous amphotericin B (Amphotret; Gufic Bioscience) (0.8 mg kg^{-1} daily) combined with flucytosine (1750 mg three times daily). Initially the patient made good progress, with improvement in his headache. However, on the seventh day of treatment (day 10 after admission), he suffered a short seizure (approximately 5 s) and became unresponsive, with a Glasgow coma scale of 6/15. He was immediately intubated and intravenous (IV) MgSO_4 was administered, and he was transferred to the intensive care unit for close monitoring. The patient did not improve; lumbar puncture was repeated and had an opening pressure of $41 \text{ cmH}_2\text{O}$. Therapeutic CSF tapping was performed and the closing pressure was $15 \text{ cmH}_2\text{O}$. The CSF analysis revealed $250 \text{ white blood cells ml}^{-1}$ with 26 % neutrophils and 74 % lymphocytes, protein 59 mg dl^{-1} , and glucose 44 mg dl^{-1} (blood glucose level 128 mg dl^{-1}) with persistent yeast cells on Gram staining. On the same day the patient developed ventilator-associated pneumonia, which was treated with IV ceftriaxone (1 g BD daily) and vancomycin (500 mg every alternate day). However, the

patient died 2 days later due to suspected respiratory failure.

Discussion

We consider that the following sequence of events in this patient led to the development of cryptococcal meningitis. Initially, the prolonged consumption of alcohol for more than 20 years led to alcoholic cirrhosis, which was diagnosed when he had bleeding oesophageal varices. He underwent oesophageal banding with prophylactic medication. After the diagnosis the patient stopped consuming alcohol. At the time of presentation at the hospital with a headache, his liver function tests were normal, reflecting stable cirrhosis of the liver. However, even in early stage cirrhosis, the risk of opportunistic infection is high. In patients such as this the phagocytic activity of neutrophils is reduced at the site of injury (Tritto *et al.*, 2011), and they frequently have decreased complement levels, which reduces opsonizing capacity and neutrophil chemotaxis (Mabee *et al.*, 1995). This suppression of the immune system leaves the individual susceptible to infection (Hsu & Leevy, 1971; Nouri-Aria *et al.*, 1986). Indeed an infection can act as a common precipitating factor leading to acute deterioration of liver function (Tritto *et al.*, 2011) resulting in acute or chronic liver failure (ACLF). ACLF is an acute deterioration in liver function in a patient with previously stable cirrhosis, resulting in 'organ failure', which is most commonly hepatic encephalopathy or renal dysfunction (Malik *et al.*, 2009). The hallmark of the liver manifestation of ACLF is hyperbilirubinaemia and coagulopathy, but the pathophysiological basis remains unclear. Our patient developed deranged liver function during treatment with antifungal drugs (Malik *et al.*, 2009). However, due to lack of resources we found it difficult to determine whether this fluctuation in liver function was due to adverse events of the treatment or to ACLF.

In the majority of cases the gold standard for diagnosing meningitis of any aetiology is by CSF analysis, which can differ significantly between HIV-negative and -positive patients. For example, HIV-seronegative patients are known to have high cell counts with lymphocyte predominance, low glucose, elevated protein levels and a lower burden of organisms in CSF (Graybill *et al.*, 2000; Saag *et al.*, 1992). India ink staining can demonstrate encapsulated yeast in 70–90 % of the patients with HIV and in only 50 % without HIV (Perfect & Casadevall, 2002; Bicanic & Harrison, 2005). Neuroimaging is most often normal in these patients. Such CSF investigations also aid in determining the overall prognosis of disease. The poor prognostic factors for cryptococcal meningitis are: low CSF glucose, increased total protein and lactate levels, with high cell counts. In our patient a poor prognosis was reflected by a persistently high CSF pressure, a low CSF glucose level, cell counts lower than 20 cells l^{-1} , a positive India ink examination of the CSF, evidence of disseminated disease by positive antigen titres on lateral flow assay in the

blood, and an abnormal mental status with onset of seizure (Saag *et al.*, 1992).

In conclusion, cryptococcal meningitis is seldom reported from Nepal. This case was identified using a CrAg LFA test in a patient with cirrhosis of the liver. Owing to the high incidence of tuberculosis in this setting, tubercular meningitis is the most likely differential diagnosis. Therefore, we suggest that, for patients such as this individual presenting with a headache with or without fever, cryptococcal meningitis should be considered as a differential diagnosis and *C. neoformans* infection should be investigated. The CrAg LFA test and India ink preparation can be performed even in resource-poor settings. Patients with liver cirrhosis are very prone to infection; therefore, early diagnosis of *C. neoformans* followed by effective treatment could lead to a better outcome.

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