Case Report

Cryptococcus gattii infection causing fulminant intracranial hypertension

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Cryptococcus neoformans variety gattii (C. gattii) causes infection in predominantly immunocompetent individuals. The majority of cases present with headache due to meningitis and its natural history normally follows an indolent course. We report a fatal case of fulminant cryptococcaemia culminating in severe intracranial hypertension due to C. gattii. Such cases of fulminant disease are rare and highlight a number of important therapeutic and diagnostic considerations. We discuss the atypical nature of this patient’s illness, the major complications of C. gattii meningitis and the role of computed tomography (CT) in preventing serious sequelae from lumbar puncture. The management of intracranial hypertension (ICH) in critically ill patients is also reviewed.

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Cryptococcus neoformans variety gattii (C. gattii) causes infection in predominantly immunocompetent individuals and often presents with headache due to indolent meningitis. In contrast to infection caused by Cryptococcus neoformans (C. neoformans), C. gattii invokes a greater inflammatory response but carries a better overall prognosis.1 We report a fatal case of fulminant cryptococcaemia culminating in severe intracranial hypertension (ICH) due to C. gattii. Such cases of fulminant disease are rare and highlight a number of important diagnostic and therapeutic considerations in patients presenting with non-specific findings.

Case history

A 57-yr-old man presented to hospital with a 5 day history of headache and a non-productive cough. He had no other systemic symptoms and was treated at his local hospital with amoxicillin–clavulane for a presumed lower respiratory tract infection. He was a diet-controlled diabetic and had no other significant co-morbidities or occupational hazards of note. Three days later, his condition deteriorated, with an increase in respiratory rate and a fluctuating level of consciousness. He was transferred to a tertiary referral centre where he was found to be cardiovascually stable with a respiratory rate of 24 bpm and oxygen saturations of 100% on an FiO2 of 0.5. Respiratory examination was unremarkable. Neurological examination revealed mild photophobia with no meningism. Glasgow coma scale (GCS) was 13/15 (motor 5, verbal 4, and eyes 4), and tone and reflexes in all four limbs were normal. There were no deficits on cranial nerve examination, and fundoscopy was normal.

Laboratory tests at this time revealed normal haematology and biochemistry except for a white cell count (WCC) of 19×10⁹ litre⁻¹ (neutrophils 16.5, lymphocytes 1.1, and monocytes 1.4×10⁹ litre⁻¹), serum sodium 126 mmol litre⁻¹, and troponin-I 3.00 µg litre⁻¹. C-reactive protein was 1.2 mg litre⁻¹ and erythrocyte sedimentation rate 5 mm h⁻¹. Electrocardiogram was normal. Further investigations included a chest X-ray (CXR) and computed tomography (CT) head scan. The CXR revealed widespread abnormalities throughout both lung fields of a principally nodular pattern. There was some confluent opacification in the right lower lobe. A contrast-enhanced head CT showed no evidence of intracranial haemorrhage, space-occupying lesion, or distension of ventricles. There was a suggestion of minor leptomeningeal enhancement in the region of the left vertex.

One hour after the scan, a neurologist reviewed both the patient and the radiology and concluded that there was sufficient evidence to support a diagnosis of meningitis and
that there was no contraindication to lumbar puncture (LP). Ceftriaxone, azithromycin, and acyclovir were commenced as empirical therapy. A decision was taken to perform the LP in the controlled environment of the intensive care unit due to the patient’s combative behaviour.

Three hours after the neurological review, soon after arriving in the intensive care unit, the patient’s GCS decreased to 10 (motor 4, verbal 3, and eyes 3). There was now a small discrepancy between pupillary size and reaction to light was noted as sluggish. He was rapidly sedated and the trachea intubated immediately after which a LP was performed. This revealed an opening pressure of 30 cm H₂O. Examination of turbid cerebrospinal fluid (CSF) showed $9 \times 10^6$ litre⁻¹ WCC (100% mononuclear cells) and numerous cryptococci on India Ink staining. CSF glucose was 1.7 mmol litre⁻¹ (serum glucose 10.9 mmol litre⁻¹) and protein 1.18 g litre⁻¹ with a cryptococcal antigen titre of 1:4096 (delayed result available). Anti-fungal therapy with amphotericin B was added to his antimicrobial regime after consultation with a microbiologist.

Less than 90 min after the LP, it was noted that both pupils were dilated and unreactive to light. Although sedated, the patient was not initiating spontaneous respirations and there was no cough reflex to deep suctioning. A further CT head was performed which showed significant changes from the initial study. There was now progressive generalized oedema with hydrocephalus, areas of loss of grey/white differentiation, and an effaced subarachnoid space and basal cisterns with significant mass effect in the posterior fossa (Fig. 1). Subsequent testing confirmed brain death.

**Discussion**

The case describes a diabetic man presenting with respiratory symptoms and altered level of consciousness. Three hours after admission, after a normal CT head, a LP was planned to exclude central nervous system infection. Six hours after admission, after a decrease in GCS from 13 to 10, this was performed and revealed numerous cryptococci on India Ink staining. CSF glucose was 1.7 mmol litre⁻¹ (serum glucose 10.9 mmol litre⁻¹) and protein 1.18 g litre⁻¹ with a cryptococcal antigen titre of 1:4096 (delayed result available). Anti-fungal therapy with amphotericin B was added to his antimicrobial regime after consultation with a microbiologist.

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_Australia, have established that C. gattii has a specific ecological association with eucalyptus trees._ However, the occurrence of C. gattii infection of a distinct genetic type in areas that lack the eucalyptus tree suggests additional environmental associations of this fungus.

In contrast to _C. neoformans_, C. gattii almost exclusively infects immunocompetent hosts and its natural history follows a more indolent course. In a population-based study of 133 cases of cryptococcal disease, all patients infected with C. gattii were immunocompetent and the mean number of days to presentation was 46 for C. gattii (compared with 17 for _C. neoformans_). A similar pattern is documented elsewhere. The rarity of cases of C. gattii in immunocompromised patients remains unexplained. Compared with _C. neoformans_, meningitis is more common with _C. gattii_ infection and in the majority of cases presents with headache. Outcomes also differ, as mortality from _C. gattii_ infection is significantly less than from _C. neoformans_ infection. A poor outcome from _C. gattii_ meningitis is associated with males, a history of convulsions before treatment and a maximum systolic blood pressure of >150 mm Hg. The fulminant nature of the meningitis in our case did not follow the typical subacute course and such a case has not been reported previously.

One of the most important complications of cryptococcal meningitis is the development of ICH.
Immunocompromised patients have a >50% chance of developing ICH and it is even more common in immunocompetent hosts. A review of 20 cases of immunocompetent patients with cryptococcal meningitis revealed a mean opening CSF pressure of 32.2 cm H2O.1 The causes of this raised opening pressure are poorly understood, but cryptococci are thought to cause outflow obstruction by mechanically blocking passage of CSF across arachnoid villi. In addition, aggregates of cryptococcal polysaccharide capsules accumulate in arachnoid villi and subarachnoid spaces potentially worsening blocking of CSF outflow.8 d-mannitol is released and together with capsular polysaccharides, these macromolecules cover the brain. This may decrease brain parenchymal compliance further exacerbating ICH.9 What causes such rapid evolution of ICH in cryptococcal meningitis as occurred in our patient is unknown.

The presence of ICH potentially makes diagnostic LP hazardous because of the risk of brainstem herniation. Performing a cranial CT scan and fundoscopy before LP, however, does not necessarily rule out serious sequelae from this procedure. Numerous authors have reported brainstem herniation immediately after LP in paediatric cases of meningitis, despite a recent CT scan failing to detect significantly raised intracranial pressure (ICP).10 11 Similar cases have more recently been published in adult patients.12 13 The inability of a CT scan to detect raised ICP in cases of meningitis has further been demonstrated using pressure measurements via a ventriculostomy at the time of cerebral imaging.14 Fundoscopy may also fail to identify raised ICP since papilloedema requires many hours or days to develop and is rarely seen with acute rises in pressure. Thus, clinical examination and reassuring radiology do not necessarily guarantee safety of LP.

Despite the concerns of safety, LP remains an important diagnostic procedure in disseminated cryptococcosis since yields from cultures of CSF are greater than from blood.15 Furthermore, India Ink staining of CSF is valuable in establishing a rapid diagnosis, thus, therefore, allowing commencement of appropriate medication.

Prompt recognition and management of ICH in cryptococcal meningitis is an important factor in reducing the morbidity and mortality from this disease, but in the acute setting, it is unclear what measures can be instituted to prevent adverse neurological complications. Treatment options are numerous, but mannitol and acetazolamide have not been demonstrated to influence outcome.7 The role of steroids is controversial. Symptomatic relief is reported,16 however, the Infectious Disease Society of America Guidelines do not currently recommend their use due to lack of established benefit. The same guidelines suggest: after marked cerebral oedema, hydrocephalus, or a space-occupying lesion have been excluded by brain imaging, patients with an opening CSF pressure >25 cm H2O should have a daily LP to achieve a closing pressure of <20 cm H2O or <50% of initial opening pressure.17 However, following these guidelines in the setting of severe ICH may put the patient in danger of brainstem herniation for the reasons already mentioned. In conscious patients, absence of changes in neurology may be reassuring that ICH has not developed between procedures, but detailed neurological assessment is more difficult in the sedated, ventilated patient, and one is largely left to rely on clinical signs and radiological assessment.

To our knowledge, there have been no previously reported cases of cryptococcaemia caused by C. gattii following such a fulminant course. Our case highlights a number of critical management issues. It is impossible to predict whether it was the LP, the natural history of the disease, or a combination of both that directly led to the patient’s demise. His declining GCS may have been indicative of a fulminant meningitic process not typical of C. gattii; however, the close association between the timing of LP and clinical brainstem herniation suggest the LP was a significant precipitant.

The case reinforces the potential danger of performing LPs even after a reassuring CT head, especially in diseases such as cryptococcal meningitis where ICH is common. The need for minimal time to be spent between performing the CT scan and LP is also highlighted in order to minimize disease progression between these two investigations. If neurological deterioration occurs before LP, a repeat CT scan should be considered.

The case also serves as a reminder to include cryptococcal disease in the differential diagnosis of patients presenting with similar symptoms, even in the immunocompetent host. Lastly, requesting India Ink staining of blood and CSF specimens is essential in ensuring a rapid diagnosis and commencement of appropriate therapy. Given the fulminant nature of our patient’s condition, however, it is unlikely that any measure would have altered the adverse outcome.

References