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Cryptococcus gattii meningitis complicated by immune reconstitution inflammatory syndrome in an apparent immunocompetent host in Malaysia

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ABSTRACT

Cryptococcosis is a systemic fungal infection caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. *Cryptococcus* causes a wide range of diseases, ranging from asymptomatic pulmonary lesions to disseminated disease involving the central nervous system, particularly meningoencephalitis. *C. gattii* infection has rarely been reported in Malaysia. We present a case of *C. gattii* meningitis with pulmonary cryptococcosis complicated by immune reconstitution inflammatory syndrome in an apparently immunocompetent person with no prior travel history.

1. Introduction

Cryptococcosis is a potentially fatal invasive fungal infection caused by *Cryptococcus*, a basidiomycetous yeast. *Cryptococcus neoformans* and *Cryptococcus gattii* are the two cryptococcal species complexes which cause the vast majority of clinical illness in humans, though other species have occasionally been associated with disease. Cryptococcal infection is acquired via inhalation followed by subsequent dissemination to the central nervous system (CNS) to cause meningitis [1]. *C. neoformans* primarily affects immunocompromised patients, whereas *C. gattii* infection occurs in people with apparent normal immune systems and those who are immunocompromised. *C. gattii*, unlike *C. neoformans*, is more likely to cause a progressive granulomatous pulmonary infection but less likely to spread to the CNS [2].

Cryptococcal meningitis is extremely difficult to treat due to the severe neurological sequelae, raised intracranial pressure, and immune reconstitution inflammatory syndrome (IRIS). IRIS associated with *C. gattii* infection has been reported infrequently. IRIS may manifest with disease deterioration or recurrence in spite of mycological evidence of effective antifungal treatment. Inability to recognize IRIS frequently leads to misdiagnosis of clinical failure and, as a result, unnecessary reinduction of antifungal treatment [1,3].

2. Case presentation

A 46-year-old man complained of headaches and difficulty walking for one month. He denied having fever, cough, head injury, or urinary or bowel incontinence. There had been no recent travel or family history of cancer. He worked as a technician for an information technology firm. He was confused when he arrived at the hospital (day 0). Physical examination revealed a blood pressure of 109/65 mmHg, a pulse rate of 95 beats per minute, and a body temperature of 37 °C. He was not tachypneic, and his oxygen saturation on room air was 99%, as measured by pulse oximetry. He showed no signs of neck stiffness or opportunistic infection. A neurological examination revealed symmetrical bilateral lower limb weakness with preserved upper extremity power and tones, reflexes, and sensation. The fundoscopic examination of both eyes was normal.

Hematological analysis revealed mild leukocytosis, with a white cell count of 13.7 $\times$ 10^3/μL, haemoglobin of 13 g/dL, and platelet count of 418 $\times$ 10^3/μL. The kidney and liver function tests were within normal range. The blood culture, antinuclear antibodies, HIV, hepatitis B, hepatitis C, and VDRL tests were all negative. The total lymphocyte count was 1051 cells/mm3. His CD4 and CD8 cell counts were 446 (normal range: 358–1279) and 296 (normal range: 268–925) cells/mm3, respectively, with a CD4/CD8 ratio of 1.51. A computed tomography (CT) scan of the brain was performed urgently, and it revealed communicating hydrocephalus with prominent ventricles. A diagnostic

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lumbar puncture was then performed, with the opening pressure measured at 40 cmH_2O. The cerebrospinal fluid (CSF) was clear and colorless, with hypoglycorrhachia (CSF glucose: 0.8 mmol/L; random blood glucose: 6.5 mmol/L) and lymphocytic pleocytosis. The CSF cell counts were 25 cells/mm3 (lymphocytes, 20 cells/mm3; neutrophils 5 cells/mm3). Gram stain and India ink demonstrated the presence of encapsulated yeast cells (Fig. 1). The latex agglutination test for *Cryptococcus* was positive, and cryptococcal antigen was present in high titer (>1:512). After 16–18 hours of incubation at 37 °C, culture of the CSF revealed growth of *Cryptococcus* and subsequently, *C. gattii* was identified using the matrix-assisted laser desorption/ionization time of flight mass spectrometry method (MALDI-TOF, Biomerieux). The CSF direct acid-fast bacilli smear, tuberculosis PCR, and mycobacterial culture were negative.

On admission, a chest radiograph revealed opacity in the right middle zone. A high-resolution CT was performed due to a high clinical suspicion of pulmonary cryptococcosis associated with *C. gattii* meningitis, which revealed a right lung nodule measuring 3.3 × 2.8 cm at the superior segment of the right lower lobe, suggestive of pulmonary cryptococcosis (Fig. 2). As a result, *C. gattii* meningitis with pulmonary cryptococcosis were diagnosed.

Following receipt of the CSF results at day +3, the patient was started on intravenous amphotericin B deoxycholate 42 mg (0.7 mg/kg) once daily, along with oral flucytosine 1.5 g (25 mg/kg) every 6 hours. Multiple lumbar punctures were performed to drain the CSF and lower intracranial pressure. After initiation of antifungal therapy, the patient's level of consciousness and lower extremity weakness improved significantly, and CSF sterilization was achieved at day +16. After one month of treatment at day +34, it was decided to replace amphotericin B with intravenous fluconazole 400 mg twice daily due to amphotericin B-associated acute kidney injury and favorable clinical response. However, he developed ataxia and his GCS gradually deteriorated until he became stuporous over the next few days. A repeat brain CT at day +37 revealed communicating hydrocephalus with no change in interval. Because of the possibility of clinical relapse and azole-resistant *C. gattii*, the CSF examination was repeated and intravenous amphotericin B was restarted at day +40. Nonetheless, the repeated CSF culture produced a negative result. At this point, antifungal susceptibility testing yielded the following MICs in μg/mL: amphotericin B, 0.75; fluconazole, 0.75; itraconazole, 0.25; voriconazole, 0.016; and flucytosine, 0.19. Magnetic resonance imaging (MRI) of the brain revealed the presence of cryptococcomas with dilated perivascular spaces, as well as minimal residual communicating hydrocephalus (Fig. 3).

The clinical diagnosis of cryptococcal-IRIS was made at day +47, and a therapeutic trial of intravenous dexamethasone 4 mg twice daily was initiated. The next day, there was a dramatic improvement, and the patient continued to improve clinically over time. Fluconazole and flucytosine were reintroduced as antifungal agents. Following that, a ventriculoperitoneal (VP) shunt was implanted at day +56 to divert CSF due to high intracranial pressure. After completing induction therapy for two months, the patient was given oral fluconazole 400 mg twice daily as consolidation therapy since day +57. He was given dexamethasone 4 mg intravenously twice a day for two weeks before being tapered to 6 mg of dexamethasone orally once a day. He was discharged from the hospital after two months. During subsequent outpatient visits, the steroid was gradually tapered off over a 6-month period, and oral fluconazole was prescribed for a 12-month period. At the time of writing, the patient was still doing well and showed no signs of disease relapse.

3. Discussion

Cryptococcosis is a fungal infection caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. Cryptococcal meningitis is a major opportunistic infection in patients with advanced HIV disease, and it is recognized as the leading cause of community-acquired meningitis in many areas with high HIV infection prevalence [4]. *C. neoformans* can infect both immunocompromised and apparently immunocompetent patients. *C. gattii*, on the other hand, has long been thought to be a pathogen of immunocompetent persons [1,2]. Early epidemiological studies suggested that *C. gattii* was restricted to tropical and subtropical regions, and the widespread distribution of *C. gattii* has been linked to eucalyptus trees [5]. Tay et al. found that *C. neoformans* was the most common *Cryptococcus* species causing cryptococcal infection in Malaysia, with 85 of the 96 (88.5%) cryptococcal isolates being *C. neoformans* and the remaining 11 isolates being *C. gattii* (11.5%) [6].

Cryptococcosis is contracted through the inhalation of infectious propagules in the air, such as spores or dried yeast cells, resulting in an initial pulmonary infection [7]. Fever, fatigue, night sweats, cough, chest pain, and weight loss are common symptoms of pulmonary cryptococcosis. *Cryptococcus* has the ability to infiltrate the CNS and cause meningoencephalitis, which is always fatal if not treated promptly [3,8]. In this case, the patient presented to the hospital one month after the onset of symptoms. The lack of fever, neck stiffness, and obvious signs of increased intracranial pressure made the diagnosis of *C. gattii* infection difficult in this case. This case also demonstrated the importance of CSF examination in the diagnosis of *C. gattii* CNS infection, as evidenced by

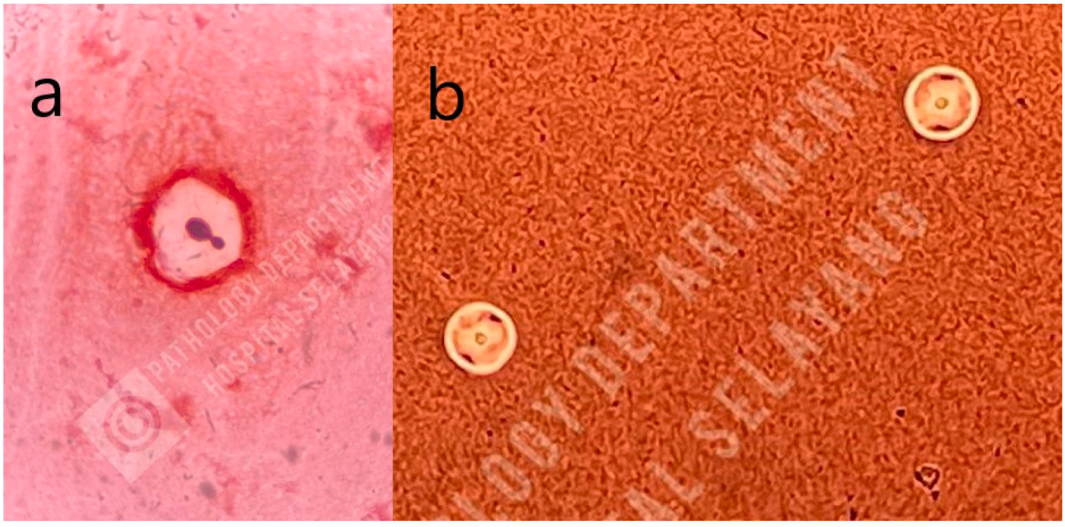

Fig. 1. Microscopic morphology of *Cryptococcus* from the CSF sample **(a)** Spherically-budded yeast cell surrounded by non-staining thick capsule on Gram stain. **(b)** Rounded yeasts surrounded by thick capsule (clear outermost layer of the organism) on India ink.

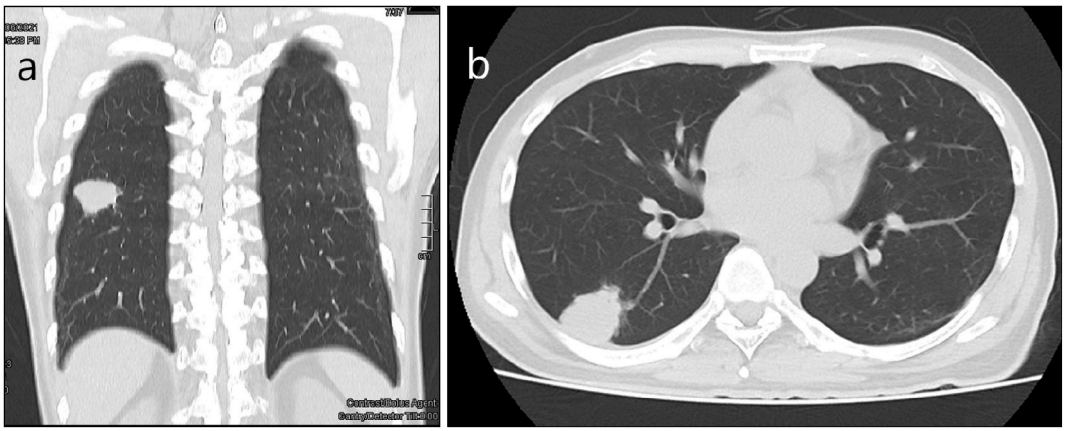

Fig. 2. High-resolution CT of the thorax **(a)** coronal view, **(b)** axial view, showing a well-defined lung nodule at the superior segment of the right lower lobe.

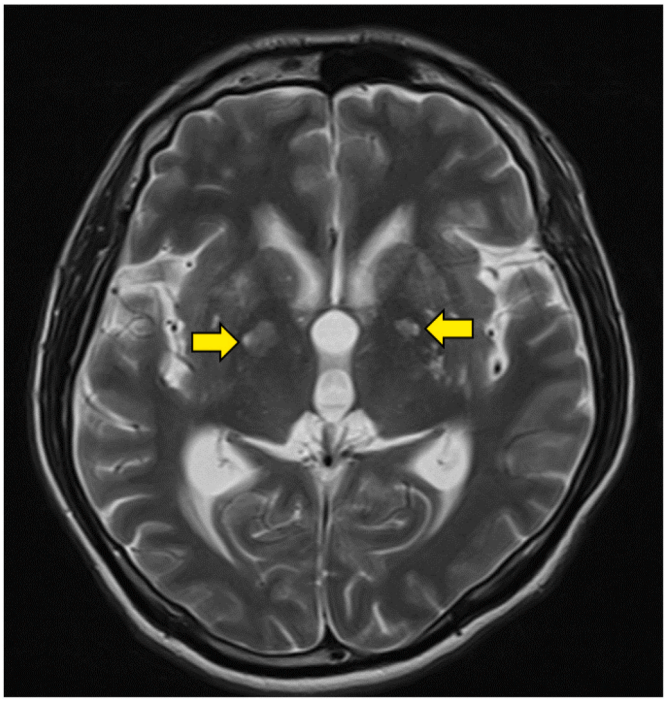

Fig. 3. MRI of the brain showing presence of cryptococcomas at bilateral basal ganglia (indicated by arrows), dilated perivascular spaces, and mild dilatation of all ventricles suggestive of communicating hydrocephalus.

increased opening pressure, positive India ink and latex agglutination, and positive CSF culture for *C. gattii*.

IRIS can develop in patients with *C. gattii* infection after an initial clinical and microbiological response. Chen et al. reported 8 cases of IRIS in an Australian cohort of 86 patients with confirmed *C. gattii* infection. Risk factors for the development of IRIS included female gender; brain involvement at presentation; concomitant brain, CSF, and lung involvement; and higher median CD4 counts. All 8 patients in the series developed IRIS after 6 weeks to 12 months of azole therapy [9]. Recognizing IRIS is critical for clinicians because it can be misdiagnosed as clinical relapse, resulting in unnecessary reinduction of antifungal therapy [3]. Our patient's neurological condition deteriorated 5 weeks after being diagnosed with *C. gattii* meningitis, and neuroimaging revealed new lesions (cryptococcomas). As a result, clinical failure was initially suspected, so amphotericin B induction therapy was restarted. The repeated CSF examination, on the other hand, revealed mycological evidence of effective antifungal therapy. Finally, IRIS was considered, and corticosteroid treatment was started immediately, which contributed to the positive outcome in this case.

O' Brien et al. described *C. gattii*-related IRIS in 3 immunocompetent children. All 3 cases were treated with high-dose corticosteroids that were gradually tapered off over 6–8 months to prevent relapse of IRIS [10]. Dexamethasone reduces *Cryptococcus*-induced meningeal inflammation by inhibiting the secretion of cryptococcal glucuronoxylomannan-induced vascular endothelial growth factor A by mononuclear cells [11]. Phillips et al. found that dexamethasone improved clinical outcomes in 3 of 4 patients with *C. gattii* CNS-IRIS. Rapid clinical improvement was observed in those cases after a median of 2 days [12]. This finding was consistent with the findings in our case, in which the patient showed significant clinical improvement the next day after receiving dexamethasone. There have been reports of thalidomide being used successfully to treat cryptococcal meningitis-associated IRIS after failure of corticosteroid therapy or to shorten the duration of steroid use [13,14].

We admitted in our case report that we were unable to rule out any potentially undiagnosed subclinical immunodeficiency such as anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies, due to the inaccessibility of the test. A previous study by Saijo et al. found that anti-GM-CSF autoantibodies may predispose otherwise immunocompetent individuals to meningoencephalitis caused by *C. gattii* but not necessarily to that caused by *C. neoformans* [15].

In conclusion, cryptococcosis caused by *C. gattii* is a rare fungal infection in Malaysia, and diagnosis can be difficult due to delayed presentation and non-specific neurological symptoms, as demonstrated in our case. Successful treatment of *C. gattii* necessitates the early initiation of antifungal therapy, aggressive management of increased intracranial pressure, and the timely recognition and treatment of cryptococcal-IRIS.

Declaration of competing interest

There are none.

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