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CASE REPORT

Cerebral toxoplasmosis in Malaysia: a debilitating disease, an insight from a case study

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ABSTRACT

Toxoplasmosis is an infectious disease caused by the intracellular protozoan parasite, *Toxoplasma gondii*. While the infection is typically asymptomatic in healthy individuals, it can progress to cerebral toxoplasmosis, especially in those with human immunodeficiency virus (HIV) or weakened immune systems. In this communication, we present a case of a newly diagnosed HIV infection patient who presented with neurological symptoms. The patient was later diagnosed with probable cerebral toxoplasmosis. The case depicts the severe consequences of toxoplasmosis in immunocompromised patients, highlighting the urgent need to identify those at high risk of contracting the disease and the importance of prophylactic treatment. This requires the necessity for early HIV diagnosis and close monitoring of HIV-positive patients.

Keywords: Cerebral toxoplasmosis; HIV-positive; clinical perspectives.

INTRODUCTION

Toxoplasmosis, caused by the opportunistic parasite *Toxoplasma gondii*, is among the most prevalent parasitic infections globally, affecting approximately one-third of the world's population (Dubey & Beattie, 1988). While often asymptomatic in immunocompetent individuals, this infection can lead to severe complications in the immunocompromised, typically those with HIV/AIDS (Basavaraju, 2016), organ transplant recipients (Khurana & Batra, 2016), and cancer patients undergoing chemotherapy (Brown *et al.,*1991; Ali *et al*., 2019).

In HIV-infected patients, cerebral toxoplasmosis often occurs due to the reactivation of latent infection (cysts in the brain) (Porter & Sande, 1992; Lyons *et al*., 2002) and manifesting typically with symptoms such as headache, focal neurological deficits, seizures, altered mental status, and intracranial hypertension syndromes (Skiest, 2002; Basavaraju, 2016; Vidal, 2019).

Despite its global prevalence, cases of cerebral toxoplasmosis in Malaysia have been relatively rare and underreported (Nasiru Wana *et al*., 2020). Neuroimaging using Computed Tomography scan (CT scan) and Magnetic Resonance Imaging (MRI) often facilitates early detection of cerebral toxoplasmosis, enabling prompt initiation of treatment (Benson *et al*., 2018; Senik *et al*., 2023)

In this case report, we present a case of probable cerebral toxoplasmosis in a patient with newly diagnosed HIV infection in Malaysia, highlighting the clinical presentation, diagnostic procedures, management strategies, and implications for public health awareness and surveillance. We aim to contribute to the understanding and management of cerebral toxoplasmosis in regions with limited reported occurrences.

Case presentation

A 29-year-old man with no known medical history was found unconscious at his workplace and brought to the emergency department, Hospital Al-Sultan Abdullah. Further history revealed that he had been experiencing altered sensorium and hallucination for the past 1 week before admission. On examination, his Glasgow coma scale (GCS) was 10 (E3, V1 M6), and he appeared lethargic with a pink complexion, His blood pressure was 149/85 mmHg, temperature 36.7°C, and oxygen saturation (SPO_2) of 100% at room air.

Neurological examination revealed reduced power on the left side with normal tone. with both upper and lower left limb muscle strength grade 1. The right upper and lower limb muscle grade was 4. Negative Babinski sign on the right side, equivocal on the left side. Examination of respiratory, and cardiovascular were both unremarkable. Per abdominal examination was not significant.

His routine blood test results revealed a low haemoglobin 11g/dL (reference range 13-17 g/dL), low haematocrit 35.6% (40-60%), with low MCH 17.9 pg (27-32pg) and MCV 55.8fL (83-101 fL). Blood culture was negative; however, HIV antibody was detected via 2 test platforms, electrochemiluminescence immunoassay Cobas e411 by Roche Diagnostics (GmbH, Mannheim, Germany) and particle agglutination. Cerebrospinal fluid (CSF) was obtained

to rule out infection, and they were negative for acid-fast bacilli, *Cryptococcus* and herpes simplex virus. Cultures of the CSF were also unremarkable.

CT scan done during admission revealed multiple ill-defined lesions associated with perilesional oedema and extensive mass effect onto the right lateral and third ventricles resulting in obstructive hydrocephalus and significant midline shift (Figure 1).

While he was in the ward, his GCS fluctuated ranging from 8-10 (E2 V 1 M5-6). His neurological examination remained unchanged as per the initial presentation. An MRI was performed on day 2 of admission. The ill-defined lesions on CT appear as ring enhancing lesions of varying sizes with eccentric nodules in the right basal ganglia, right frontal, right occipital and left parietal lobe. Extensive perilesional oedema is present with mass effect by the right basal ganglia lesion onto right lateral and third ventricle with uncal herniation. Significant midline shift, obstructive hydrocephalus and generalized effacement of cerebral sulci are still evident (Figure 2).

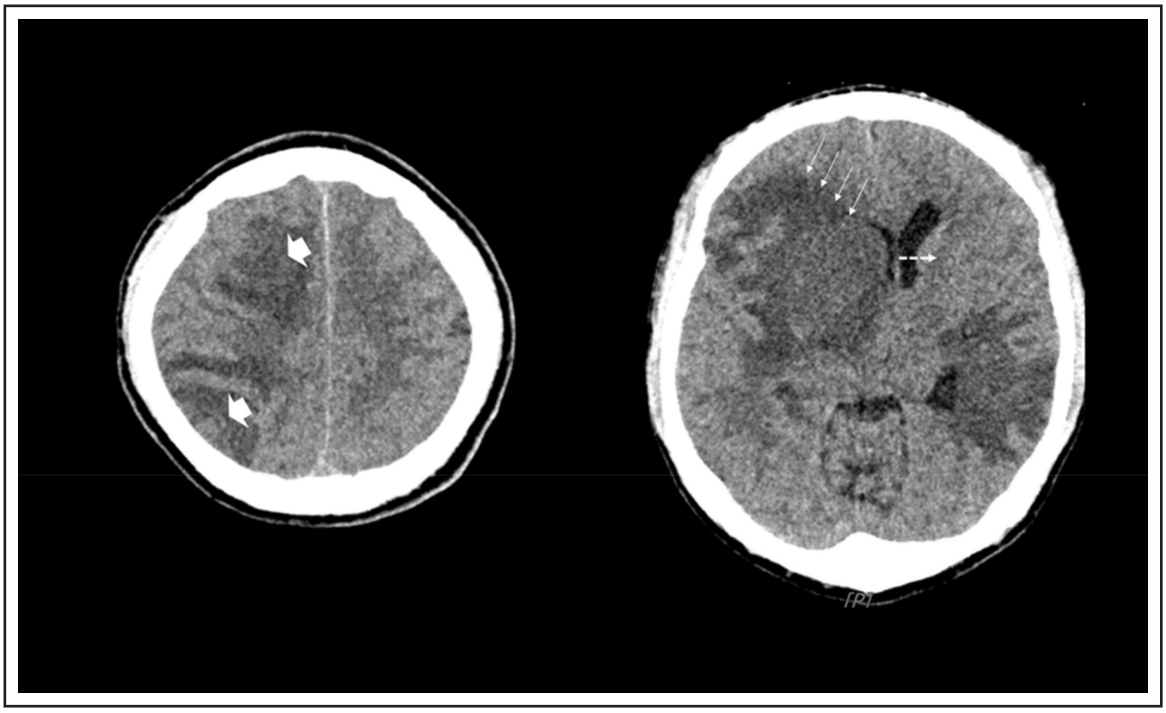

Figure 1. Axial plain CT Brain showing ill-defined lesions associated with perilesional oedema (thick arrow) and extensive mass effect (thin arrow) onto the right lateral and third ventricles resulting in obstructive hydrocephalus and significant midline shift (dashed arrow).

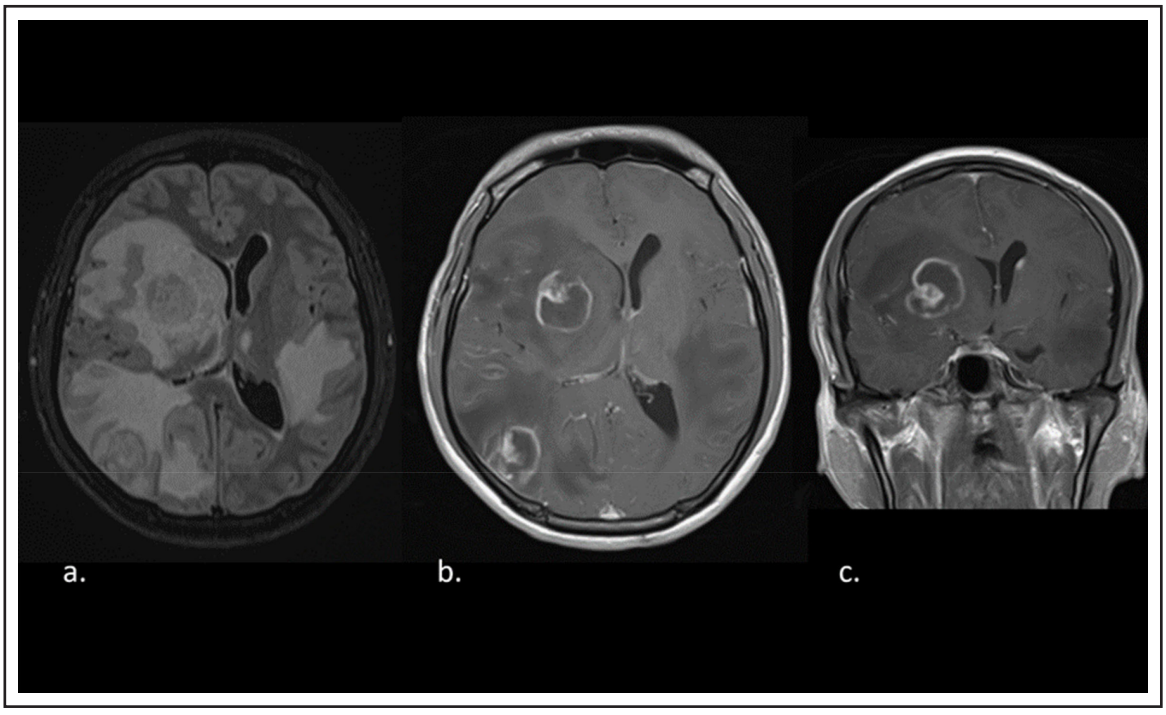

Figure 2. MRI on second day of admission. a) Axial T2 Flair image showing multiple rounded lesions with extensive perilesional oedema and mass effect to surrounding structures. b) Axial and c) Coronal T1 post contrast images showing multiple ring enhancing lesions with eccentric enhancing nodules giving the appearance of eccentric target sign.

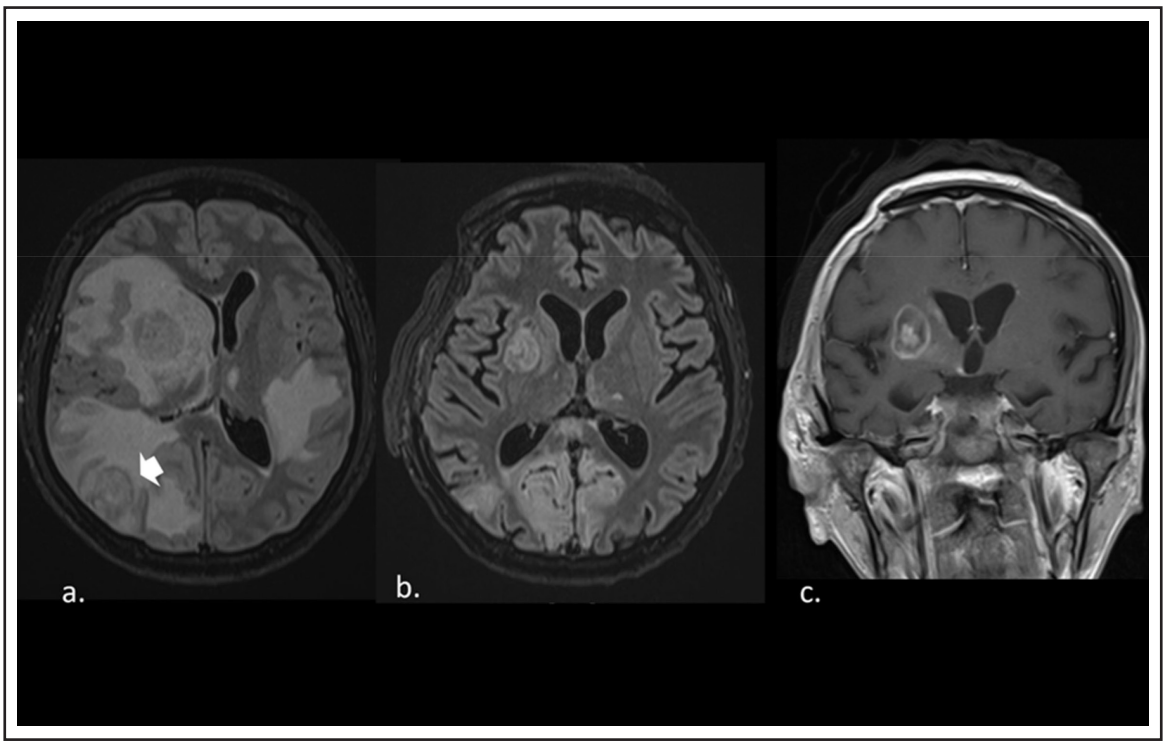

Figure 3. a) T2 Axial Flair sequence as baseline and showing the *concentric sign* (thick arrow), b) Repeat T2 Axial Flair post treatment showing evidence of craniectomy and resolved perilesional oedema and c) Coronal T1 post contrast showing reduction in size of the ring enhancing lesion.

With the findings of the MRI, and newly diagnosed HIV infection, *Toxoplasma* infection was suspected. Blood for *Toxoplasma* serology was sent and the result came back as *Toxoplasma* IgM negative with positive *Toxoplasma* IgG. The patient was then referred to neurosurgery for neurosurgical intervention. Further blood work was sent and revealed CD4 count: 16 cells/uL (2%), CD8 count: 369 cells/uL (46.9%). CD4/CD8 ratio: 0.04, HIV RNA Viral Load: 826,999 copies/mL. The patient had an external ventricular drain (EVD) inserted and decompressive craniectomy was performed given the hydrocephalus. MRI done 6 weeks post presentation showed reduction in size of the ring enhancing lesions with resolved perilesional oedema and midline shift. However the ventricles are still dilated in keeping with obstructive hydrocephalus (Figure 3).

Post-neurosurgical intervention, the patient was then referred to a rehabilitation team. At this point, the patient had poor cognitive function and required a Ryles tube for feeding along with a tracheostomy tube in place. He was fully dependent on all activities of daily living (ADLs). His journey to recovery was complicated by several issues. During his post-surgery admission, he developed a third-grade sacral sore. He also developed an adjustment disorder and was referred to the psychiatry team for further management. His vision was impaired likely due to optic nerve atrophy.

Medically, the patient was treated with a *Toxoplasma* regimen consisting of trimethoprim-sulfamethoxazole, pyrimethamine and clindamycin for 6 weeks. Subsequently, he was placed on suppressive therapy consisting of pyrimethamine plus clindamycin and folinic acid. He was also treated with Tenofovir 300 mg + Emtricitabine 200 mg + Efavirenz 600 mg for his newly diagnosed HIV infection. He underwent 5 weeks of intensive rehabilitation and was discharged home with improvement in cognitive function and managed to feed orally. At the time of writing this case report, he remained fully dependent on his caregiver. However, his rehabilitation progress was significantly impeded by his adjustment disorder and his unwillingness to participate in the rehabilitation process.

DISCUSSION

In Malaysia, there is an increasing number of cases of cerebral toxoplasmosis among immunocompromised individuals particularly in HIV/AIDS patients, including three fatal cases (Haniffah *et al*.,1996; Nissapatorn *et al*., 2003a, 2003b; Murthy, 2007; Nimir *et al*., 2013; Roslan & Hadi, 2022; Salleh *et al*., 2022; Senik *et al*., 2023) and one case in a systemic lupus erythematosus following methylprednisolone treatment (Pagalavan & Kan, 2011). Additionally, based on previous seroprevalence studies conducted among HIV patients in various settings in Malaysia from 2001 to 2016, the seroprevalence rates ranged from 21% to 63.2% (Shamilah *et al*., 2001; Nissapatorn *et al*., 2003c; Angal *et al*., 2016). Studies also demonstrated a significant difference between HIV-positive and HIV-negative participants (Shamilah *et al*., 2001; Angal *et al*., 2016). This present case further contributes to this concern by presenting a case of cerebral toxoplasmosis in a newly diagnosed HIV patient with no prior documented medical history.

Cerebral toxoplasmosis primarily manifests as *Toxoplasma* encephalitis (TE) (Vidal, 2019). In HIV patients, this disease often presents as a latent infection (characterised by IgG positive), particularly in individuals with CD4+ counts <200 cells/mm^3 (Dian *et al*., 2023) as similarly reported in this study. However, it is important to note that in some cases, the CD4 level may appear normal during the TE cases (Soleymani *et al*., 2018).

Hence a new diagnosis of HIV should prompt evaluation and testing of IgG antibody to *Toxoplasma* to detect latent infection and the patients should be counselled regarding possible sources of *Toxoplasma* infection. In *Toxoplasma* IgG positive patients who have a CD4$^+$ count of <100 cells/µL, prophylaxis should be administered against *Toxoplasma* encephalitis and the benefits has been observed in past cases (Rajapakse *et al.,* 2017). In Malaysia, the standard practice is administering daily doses of trimethoprim-sulfamethoxazole as recommended by the National antimicrobial

guideline by Ministry of health, Malaysia. This regime should be continued until patient CD4+ count reach > 200 cell cells/uL for more than 3 months.

Given its ubiquity in nature with many animals serving as reservoir hosts, humans primarily acquire this parasite through ingestion of oocysts shed by the definitive host in the feces (cats) or by consuming tissue cysts in undercooked meat. Although the possible mode of parasite acquisition in this patient was not investigated, the parasite's ability to remain dormant and reactivate for latent infection could be the factor. Additionally, the highest seroprevalence reported among healthy individuals in Malaysia was 59.7%, (Ahmad *et al*., 2014; Nasiru Wana *et al*., 2020) with Malays showing the most significant prevalence of this infection as compared to other ethnic groups (Nissapatorn *et al*., 2003a).

Probable cerebral toxoplasmosis was suspected in this patient based on neurological symptoms, serological evidence, imaging findings of characteristic lesions, and response to anti- *Toxoplasma* treatment. However, we did not perform molecular testing (such as nucleic acid amplification) to confirm laboratory-confirmed cerebral toxoplasmosis (Vidal, 2019). Imaging with contrast enhanced CT or MRI plays a role in supporting the diagnosis of neurotoxoplasmosis (Gupta *et al*.,2008; Vidal, 2019; Marcus *et al*., 2021; Senik *et al*., 2023; Zawadzki *et al*., 2023) Contrasted MRI scan increases the accuracy of diagnosis and able to aid in differentiating other CNS diseases that is associated with HIV/AIDS patient (Senik *et al*., 2023). The findings often present as multiple lesions involving the basal ganglia (as the most common site), corticomedullary junction and thalamus (Senik *et al*., 2023). The lesions are less commonly seen in the brainstem and cerebellum (Vidal, 2019).

On non-enhanced CT scan, the lesions are quite subtle and usually coupled with perilesional vasogenic oedema (Gupta *et al*., 2008; Zawadzki *et al*., 2023) Typically, the lesions appear as ring enhancing with eccentric nodule on contrasted study (Zawadzki *et al*., 2023). The lesions less commonly appear solid (Gupta *et al*., 2008; Senik *et al*., 2023) and may show haemorrhagic changes like in our case.

Presence of oedema with no obvious enhancing lesion does not completely rule out the disease (Zawadzki *et al*., 2023). MRI is the modality of choice as it has a higher sensitivity in early detection of lesions compared to contrast-enhanced CT scan. It is more precise in after a few days of onset (Zawadzki *et al*., 2023). Ring enhancing lesion with an enhancing eccentric nodule is the typical MRI appearance on post-contrast T1-weighted sequences giving the pathognomonic appearance of *eccentric target sign* (Zawadzki *et al*., 2023). This was also evident in our patient (Figure 2). On T2-weighted image, it may be depicted as a concentric target sign (Zawadzki *et al*., 2023). Concentric target sign is due to the concentric layers of hypo- and hyperintensities with central hypointensity with perilesional oedema (Vidal, 2019; Marcus *et al*., 2021; Senik *et al*., 2023; Zawadzki *et al*., 2023).

The patient in our case was treated for *Toxoplasma* encephalitis according to the recommended regime, and he responded well. One modality that can be used to assess treatment response is imaging. MRI is useful as a tool to assess treatment response (Vidal, 2019; Zawadzki *et al*., 2023) In our case, it was done approximately 6 weeks post-treatment. Response to treatment is characterized by a reduction in the size and number of the lesions as well as a reduction in perilesional oedema, as evidenced in our patient. Apart from that, change in hyper- to isointensity signal of the lesions is also associated with response to treatment.

Even though he did respond to treatment, the consequences that followed the disease were severe and impacted his life significantly. The patient was a healthy, working young man, with no medical issues before the episode. He has become fully dependent on his caregiver post-infection, with some psychological and disability issues remaining, further reducing his quality of life.

The case depicts the severe consequences of toxoplasmosis in immunocompromised patients, highlighting the urgent need to identify those at high risk of contracting the disease and the importance of prophylactic treatment. Early diagnosis of HIV and close monitoring of HIV-positive patients are essential steps in mitigating the impact of toxoplasmosis in these vulnerable individuals.

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Conflict of interest

The author declares that they have no conflict of interests.

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