Idiopathic CD4 lymphopenia in a case of disseminated cryptococcosis with brain, vertebral spine and reproductive organ involvement

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Cryptococcosis is an opportunistic fungal infection commonly seen in HIV cases. We present a case of disseminated cryptococcosis with multiple non-continuous infective foci in a non-HIV, non-transplant case.

KEYWORDS: Cryptococcosis, meningitis, isolated CD4 lymphopenia, HIV, non-HIV

Case presentation
A 48-year-old lady presented with headache, neck pain, fever and lethargy for 3 weeks with worsening symptoms a week prior to admission. The headache was throbbing in nature, worse in recumbent position and upon coughing. The symptoms were debilitating, hindering her work as a school teacher. Medical history was remarkable for uterine fibroid which was treated with myomectomy in 2016. She denied any high-risk behaviour, no recent travelling, no pet at home and no sick contact. Systemic review was unremarkable.

Initial assessment revealed full Glasgow coma scale and orientation; both pupils were 3 mm and reactive to light; neck was stiff with positive Kernig’s and Brudzinski’s signs; vital signs included blood pressure of 155/80 mmHg, heart rate at 74 beats/min and afebrile and O2 saturation was 97% under room air; and the nervous system assessment was intact without focal deficits.

Investigations showed leukocytosis (19.3 x10^9/L) with predominant neutrophils (76%), elevated C-reactive protein (57.5 mg/L) and erythrocyte sedimentation rate (56 mm/H). Her renal and liver function was within normal limit. Computed tomography (CT) of brain with contrast showed bilateral hemisphere meningeal enhancement. A diagnostic lumbar puncture was performed.

Diagnosis
Provisional diagnosis of infective meningitis was given, both ceftriaxone and acyclovir were initiated as empirical treatment. The possibility of tuberculosis (TB) meningitis and cryptococcal meningitis were considered in view of subacute presentation.

Initial management and prognosis
Cerebrospinal fluid (CSF) analysis showed raised protein (2.66 g/L), reduced CSF glucose (0.11 mmol/L) and raised cell count (10 cells/microL) with negative Gram stain. Opening pressure was 48 cm H2O. India ink staining revealed encapsulated fungi with positive cryptococcal antigen titre of 1:2560. The CSF culture grew Cryptococcus neoformans. CSF for TB workup which includes Ziehl-Neelson stain, culture and sensitivity, and polymerase chain reaction was all negative. An impression of cryptococcal meningitis was made. She was commenced on intravenous (IV) amphotericin B and IV flucytosine as per local protocol.

Blood culture subsequently came back as positive for C neoformans hence prompted arrangement for CT thorax, abdomen and pelvis (TAP).

Case progression and outcome
At first week of admission, the patient’s condition deteriorated with worsening headache, double vision and confusion. Examination revealed bilateral abducens nerve palsy with papilloedema. A repeated brain CT showed communicating hydrocephalus (Fig 1a). A repeated lumbar puncture showed an opening pressure of 55 cm H2O. Throughout admission the patient needed regular lumbar puncture to relieve her raised intracranial pressure. An extraventricular drainage was inserted and later converted to a ventriculoperitoneal shunt for persistent symptomatic raised intracranial hypertension. She completed a total of 2.9 g of IV amphotericin.

CT TAP showed a left adnexal mass of mixed density. There was also osteolytic lesion seen at the T12 vertebral body on the same imaging (Fig 1b and c). A biopsy of the spine lesion and excision of the left adnexal mass were performed. Both histopathological examination of the specimens came back positive for C neoformans. No malignancy features were seen in the biopsies.

After a comprehensive multidisciplinary discussion between neurology, infectious disease, orthopedic and gynaecology team, a decision was made not to pursue further with operative intervention for the spine and adnexal mass. A repeated laparotomy for total abdominal hysterectomy with salpingo-oophorectomy was judged to be difficult given the findings of multiple fibrinous adhesions seen during the first surgical
operation. The vertebral infective foci were not able to be excised as it was felt that operative intervention may cause the infection to disseminate. Thus, the patient was placed on lifelong maintenance of fluconazole to keep the infection dormant. Six months after discharge, she made remarkable recovery with negative HIV result. Our case had disseminated cryptococcal infection with brain, vertebral spines and reproductive organ involvement with repeatedly negative HIV result. Another possibility would be a primary malignancy with metastasis and secondary immunosuppression predisposing to cryptococcal infection. However, biopsies pointed towards infection rather than malignancy. A detailed review of case history showed neither immunosuppressant medication usage nor features of connective tissue disorders. The immunoglobulin levels came back as normal however the CD4 count was persistently low.

This case highlighted a rare and important predisposition for cryptococcal infection. Idiopathic CD4 lymphopenia is defined as a CD4 count of less than 300 cells/μL or less than 20% of all lymphocytes for two readings at least 6 weeks apart in the absence of HIV infection or other secondary causes. Our case’s first CD4 count was 330 cells/μL (11% of total lymphocytes) and the second CD4 count was 227 cells/μL (11% of total lymphocytes), both taken 8 months apart.

Cryptococcal infection is an opportunistic fungal infection commonly seen in HIV cases but also encountered among non-HIV cases. Idiopathic CD4 lymphopenia is a rare and important predisposing risk for non-HIV cryptococcosis. Idiopathic CD4 lymphopenia has possible therapeutic and prognostic implication in the management of non-HIV cryptococcal infection.

**Key learning points**

- Cryptococcosis is an opportunistic fungal infection commonly seen in HIV cases but also encountered among non-HIV cases.
- Idiopathic CD4 lymphopenia is a rare and important predisposing risk for non-HIV cryptococcosis.
- Idiopathic CD4 lymphopenia has possible therapeutic and prognostic implication in the management of non-HIV cryptococcal infection.

**Acknowledgement**

The authors would like to thank the director general of Malaysia Ministry of Health and Dr Santhi Datuk Puvanarajah, head of neurology department of Kuala Lumpur Hospital for their permission and blessing to publish this case.

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