

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

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ABSTRACT

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 Brudzinkin'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 × 10⁹/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. The patient's 4-month admission was complicated with repeated episodes of nosocomial infections needing intensive care unit admission.

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

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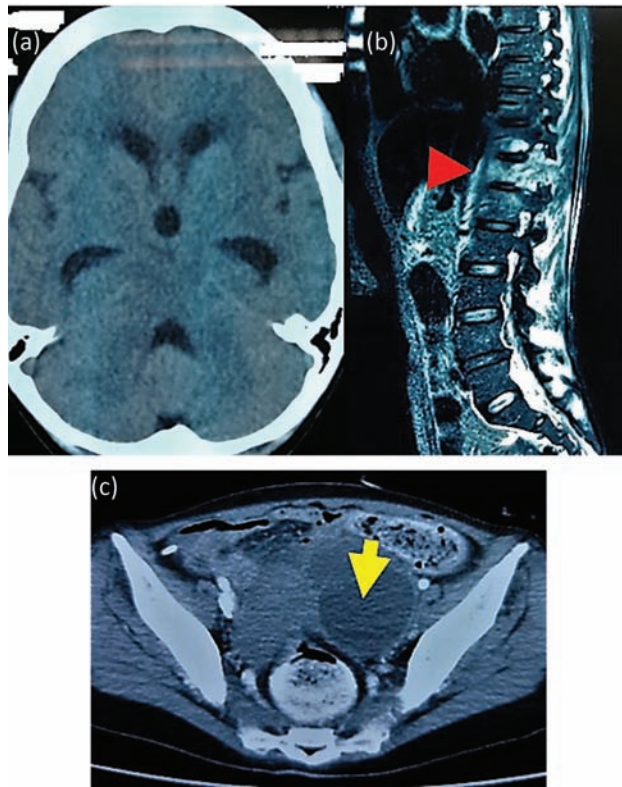


Fig 1. Computed tomography scans. (a) Communicating hydrocephalus. (b) Thoracic vertebral spine osteolytic lesion (red arrow). (c) Left adnexal mass (yellow arrow).

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 mild cognitive deficit. Her serial CD4 count was low with repeated negative HIV result.

Discussion

Cryptococcosis is a fungal infection caused by a *cryptococcus* sp. The infection usually affects HIV cases when the CD4 is less than 100 cells/ μ L although non-HIV cases are seen as well.¹ The sites involved include lung, brain and, less commonly, the bone and vertebral spine. Cases of disseminated cryptococcal infection defined by either the presence of *Cryptococcus* in the blood stream or involvement of two or more non-contiguous sites has been well described in HIV positive patient.² However disseminated cryptococcal infection is not common among the non-HIV patients especially when the female reproductive organ is involved.³

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/ μ L 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.⁴ Our case's first CD4 count was 330 cells/ μ L (11% of total lymphocytes) and the second CD4 count was 227 cells/ μ L (11% of total lymphocytes), both taken 8 months apart.

Idiopathic CD4 lymphopenia needs to be considered in HIV negative patient with cryptococcosis as identification of this rare entity may have both therapeutic and prognostic implication. A patient with idiopathic CD4 lymphopenia who had history of cryptococcosis may warrant lifelong fungal static agent to prevent relapse. However strong evidence to answer this clinical question is still lacking. Literature review showed that CD4 count is an important prognostic factor in cryptococcal infection. One study showed that the odds ratio of contracting disseminated cryptococcal infection was 23.3 among individual with reduced CD4 count.⁵ Other poor prognostic markers for cryptococcosis includes positive CSF India ink, CSF white cell count less than 20 cells/ μ L, initial CSF or serum cryptococcal antigen titre more than 1:32 and/or high opening pressure of lumbar puncture.⁶ Our patient fulfilled all the poor prognostic markers identified.

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. ■

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