CASE REPORT

Disseminated Cryptococcosis in an Immunocompetent Toddler

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Received: May 13, 2016; Initial review: August 11, 2016; Accepted: December 22, 2016.

Background: Immunodeficient children are more prone for invasive cryptococcal infections. **Case characteristics:** A 2-year-old boy with disseminated cryptococcosis was evaluated for underlying immunodeficiency without success. **Intervention/outcome:** Child was managed successfully. **Message:** Immunocompetent children with disseminated cryptococcosis can present diagnostic or therapeutic challenge in resource-limited settings.

Keywords: *Cryptococcus, Immunodeficiency, Lymphocyte proliferation defect*.

Cryptococcosis is an uncommonly recognized and often fatal disease in children [1]. Following invasion of respiratory tract, the organism may become quiescent in immunocompetent host, until an immune defect appears. Here we present an apparently immunocompetent child with disseminated cryptococcal infection, who was managed successfully with antifungal treatment.

CASE REPORT

A 2-year-old 11.5 kg boy, presented with intermittent high-grade fever and cough for 2 months and irritability for 15 days, despite having received multiple antibiotics and four drug anti-tubercular therapy for one month (due to prolonged illness). Hospitalization for pneumonia at 6 months of age was the only significant past history. There was no history of any direct contact with pets/birds or other risk factors. He was well-nourished (height 85 cm, head-circumference 48.4 cm) with generalized lymphadenopathy and massive hepatosplenomegaly (Liver 10 cm, spleen 3 cm below costal margin). Diffuse crepitations were heard over chest. There were no clinical features of meningeal irritation. Hematological investigations revealed white-blood-cell count 39100/µL ($N_{57}L_{23}E_{16}$), hemoglobin 6.3 g/dl (iron deficiency anemia) and ESR 113mm/1st hour. C-reactive protein was 107 mg/l. Chest *X*-ray (***Web Fig*. 1a**) showed military pattern with generalized lymphadenopathy. Abdomino-thoracic computed tomogram (CT) suggested hyperdense nodular areas in lungs and spleen (***Web Fig***. **1b**). Investigations for malaria, typhoid and tuberculosis were non-contributory. Treatment with Meropenem and Teicoplanin was empirically started, on which child showed no improvement. Microscopic analysis of bone marrow aspirate and bronchoalveolar lavage were inconclusive, with negative staining for acid-fast bacilli. After 5 days of blood incubation in Sabouraud-dextrose-agar, *Cryptococcus neoformans* was grown. CSF examination revealed 98 cells (100% lymphocytes), 75 mg/dl protein and positive cryptococcal antigen test with encapsulated yeast cells. MRI brain suggested prominent gyri and sulci. Later, Cryptococcus was also identified in bronchoalveolar lavage fluid analysis and bone-marrow biopsy. Stool examination was negative. Antifungal agents (Amphotericin-B and Flucytosine) were started, as per standard guidelines [2]. In view of the disseminated nature of disease, he was evaluated for underlying immunodeficiency. HIV ELISA was negative. Immunological investigations suggested high IgE (1565.68 IU/mL), with mildly elevated immunoglobulin G and A. Lymphocyte subset analysis showed normal CD19, CD3, CD4, CD8 and CD56 positive cells. Chronic granulomatous disease was also ruled out by nitroblue-tetrazolium (NBT) dye test. T lymphocyte proliferation after stimulation with PHA was significantly less for the patient sample when compared with the control (17% *vs.* 86%). Targeted sequencing, done for STAT1, STAT3, CARD9, IFNGR1 and IFNGR2 genes in view of the invasive fungal disease, were normal. Whole exome sequencing was not performed.

After starting antifungal therapy, fever decreased in five days with reduction in cough, irritability, hepatosplenomegaly, lymphadenopathy and resolution of chest infiltrates in 2 weeks. CSF cleared after 6 weeks of intravenous antifungals. Child has been neurodevelopmentally well without any recurrence.

DISCUSSION

There are two varieties of *Cryptococcus neoformans* with different virulence: *var neoformans* consisting of serotype A and D, which cause disease in immunodeficient patients and *var gatti* consisting of serotype B and C, which have the potential to affect normal hosts. In the present case, we were unable to identify the serotype.

The organism can lead to disseminated disease in persons with severe cell-mediated immunodeficiency. In humans, cryptococci may survive because of a polysaccharide capsule (CPS) that allows them to evade phagocytotosis [3]. Disseminated cryptococcal infection is uncommon in patients with intact immune system and almost always occurs in HIV-infected patients [4]. The other risk factors include: corticosteroid use, lymphomas, solid organ transplant recipient, sarcoidosis and patients with immune-suppressive disease or receiving such drugs. Clinical presentation of disseminated cryptococcosis is variable. CNS involvement is the most common manifestation of disseminated disease [5]. Classic meningeal signs, such as nuchal rigidity, are absent in 75% of cases [6]. Our case presented with fever and irritability although meningeal signs were absent. Lung is the second most commonly affected organ, which was involved in present case [3].

A recent study demonstrated that *C. neoformans* can cause an allergic bronchopulmonary mycosis characterized by production of Th2 cytokines, elevated levels of serum IgE, recruitment of eosinophils and alternative activation of macrophages [7]. Another study suggested that CPS-induced IL-10 production was an important mechanism in the CPS-mediated suppression of lymphocyte proliferation [8]. Recently there have been some reports about invasive cryptococcosis in immunocompetent patients. Goldman described an adult male with pulmonary and CNS lesions due to C. gattii [9]. Bothra and colleagues identified the fungus in a 5-year immunocompetent child [10]. In our case, we detected elevated IgE levels with reduced T-cell proliferation, which may be secondary to cryptococcal infection *per se* rather than primary cause, as the child was previously well and our investigations did not yield any cause.

As per the Infectious Diseases Society of America guidelines for management of Cryptococcal disease [2], non-HIV, non-transplant patients should be treated with dual therapy (Amphotericin B and Flucytosine during induction phase (up to 4 weeks after CSF clearance) followed by Fluconazole in consolidation and maintenance phase. Our patient required longer duration of intravenous antifungals in view of prolonged CSF clearance.

To conclude, one should apply a cautious approach towards diagnosis and treatment of unusual organisms such as cryptococcosis due to changing resistance pattern and host-predilection. This becomes more challenging in immunocompetent individuals; that too with limited resources.

Acknowledgements: Dr Manisha Madkaikar, NIIH, Mumbai for T lymphocyte proliferation assay and Prof. Hidenori Ohnishi, Gifu University, Japan for the molecular work-up.
Contributors: NG: collected the clinical details and managed the case; NR: helped in immunological work-up; AS, DG: supervised case management. All were involved in drafting the manuscript.
Funding: None; Competing *interest*: None stated.

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