Hypereosinophilia Associated with Disseminated Cryptococcus Infection in an Immunocompetent Child: A Case Report

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ABSTRACT

Cryptococcal infection is a common opportunistic fungal infection, mostly affecting immunocompromised people, and is usually associated with HIV infection. In immunocompromised individuals, it is the world's second leading cause of death after tuberculosis. The infection rate in immunocompetent individuals is roughly 1/100,000 and is rarely documented. Disseminated cryptococcosis can affect the central nervous system (CNS), lungs, liver, and bone marrow. It is also associated with peripheral blood eosinophilia due to underlying cell-mediated immune responses. Patients with disseminated cryptococcosis exhibit different clinical presentations. Here, we describe a unique case of hypereosinophilia, marked by increased immunoglobulin levels and an absolute eosinophil count of 12.3×10^9/L. Peripheral eosinophilia is also known to be caused by two other fungal infections: Allergic bronchopulmonary aspergillosis and coccidioidomycosis. Unlike other occurrences that have been documented, the present patient was a young child and otherwise healthy.

Key Words: *Eosinophilia, Cryptococcosis, Bone marrow, Invasive fungal infection*.

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INTRODUCTION

Cryptococcosis is an opportunistic fungal infection affecting immunocompromised and immunocompetent patients and is caused by Cryptococcus neoformans or its variants.[1,2] Individuals with advanced HIV-AIDS, various T cell defects, chronic pulmonary, renal or hepatic diseases, and patients receiving immunosuppressive therapy are the main targets.[3]

It can affect any human organ system, including bone marrow, which is uncommon and rarely reported. Another unlikely finding is "eosinophilia", which appears to play a protective role in the light of preliminary research indicating an allergic reaction to the fungus. Association of cryptococcal infection with eosinophilia is rare and seldom reported in healthy individuals. Herein, we report an exceptional case of bone marrow cryptococcosis with eosinophilia in a young child.

CASE REPORT

A 5-year girl was admitted to the paediatric ICU with complaints of acute respiratory distress along with cough and abdominal distension for two weeks.

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Her mother informed that the girl had intermittent high-grade fever associated with sweats for the last two months. Past medical history revealed hospitalisation due to enteric fever nine months ago.

On examination, the patient was dehydrated and lethargic but afebrile and vitally stable apart from raised pulse rate of 180 beats/min. Mild suprasternal recessions, bilateral occasional wheezes, and crepitation on the upper-right side of the chest were found on her respiratory examination. Abdominal examination revealed a palpable liver of 3 cm below the right costal margin. It was firm and mildly tender. The spleen was also enlarged 2.5 cm below the left costal margin. Both cardiovascular and neurological examinations were unremarkable.

An extensive workup was done to reach the diagnosis, which showed an elevated total leukocyte count (TLC), chiefly showing eosinophils. Moreover, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hepatic enzymes, and immunoglobulins levels were also elevated (Table I). Radiological examination exhibited mild left-sided pleural effusion on chest X-ray. CT scan of the chest and abdomen showed diffuse ground glass haze with nodularity in bilateral lungs with mediastinal and hilar lymphadenopathy. Hepatosplenomegaly with severe ascites was also noted. Abdominal ultrasound was suggestive of hepatomegaly of 12.5 and splenomegaly of 13.8 cm. The echocardiogram showed a normal left ventricular ejection fraction but thickened pericardium.

Following the detailed history and work-up, a suspicion of haematological malignancy was raised based on the presence

of visceromegaly, lymphadenopathy, and the persistence of hypereosinophilia in the patient. Thereby, bone marrow biopsy was advised, which yielded a hypercellular aspirate. Erythropoiesis was normoblastic while myeloid cell lineage predominantly showed hyperplasia of eosinophilic precursors. Macrophage activity was relatively increased. The hallmark finding was the appearance of many small clusters of extracellular encapsulated fungal yeast forms (Figure 1). In addition, multinucleated giant cells were also demonstrated. The trephine core biopsy was also obtained which showed intact trilineage hemopoiesis. Numerous eosinophils and their precursors with multiple foci of round to oval encapsulated budding structures were seen (Figure 2). The fungi were positive for special stains i.e. periodic acid Schiff (PAS) (Figure 3) and Gomori's methenamine silver (GMS) (Figure 4), confirming the diagnosis of disseminated *Cryptococcus*. By then, blood culture and sensitivity results showed *Cryptococcus Neoformans*. The patient was managed with amphotericin B followed by fluconazole for one week and eosinophilia was resolved.

Table I: Laboratory investigations.

Haematology	
Haemoglobin	8.60 g/dl
WBC	24.2×10^9/L
Eosinophils	51% (1-4%)
AEC	12.3×10^9/L ($<0.5\times10^9$/L)
Neutrophils	38%
Lymphocytes	9%
Monocytes	2%
Platelets	102×10^9/L
ESR	70 mm/hr
Coagulation profile	
PT	12.8 sec (Control: 10 sec)
APTT	34.0 sec (Control: 25 sec)
Chemistry	
Albumin	2.39 g/dl
LDH	191 U/L
Total bilirubin	0.86 mg/dl
ALP	605 U/L
AST	11 U/L
ALT	10 U/L
Gamma GT	101 U/L
Creatinine	0.45 mg/dl
Ferritin	511 ng/ml
Fibrinogen	116 mg/dl
D-dimer	4.2 mg/l
Triglycerides	108 mg/dl
Serology	
CRP	24.5 mg/dl
MP ICT	NEGATIVE
SARS Covid antibodies	<0.6
Anti HIV 1 and 2	Non-reactive
Immunoglobulins	
IgG	2450 mg/dl (Normal: 504-1465 mg/dl)
IgA	358.6 mg/dl (Normal: 27-195 mg/dl)
IgM	193 mg/dl (Normal: 24-210 mg/dl)
IgE	348.6 mg/dl (Normal: Age 1-5 years ≤ 60)
Others	
ANA	Negative
Anti ds-DNA	Negative
Stool DR	Negative
MTB PCR	Negative
Blood C/S	C. Neoformans

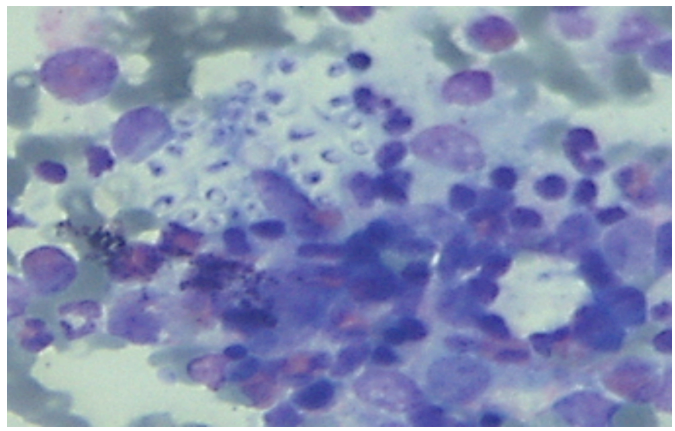

Figure 1: Bone marrow aspirate showing small clusters of extracellular encapsulated fungal yeast forms.

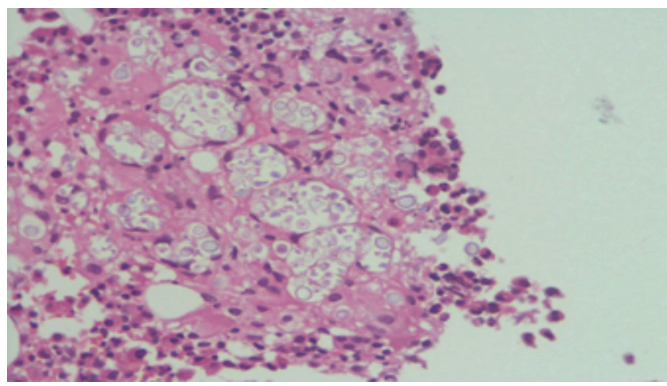

Figure 2: Trephine biopsy showing multiple foci of round to oval encapsulated budding structures.

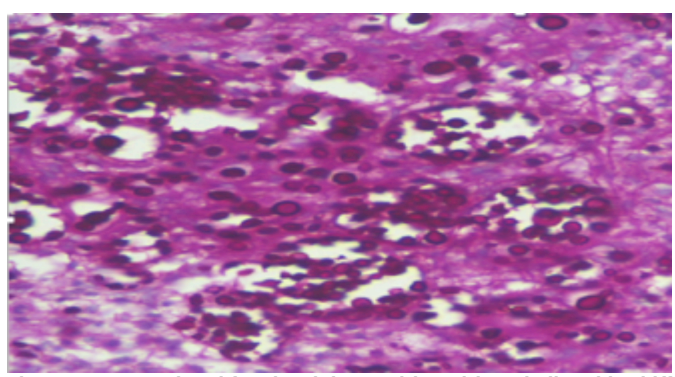

Figure 3: Encapsulated fungi staining positive with periodic acid Schiff stain.

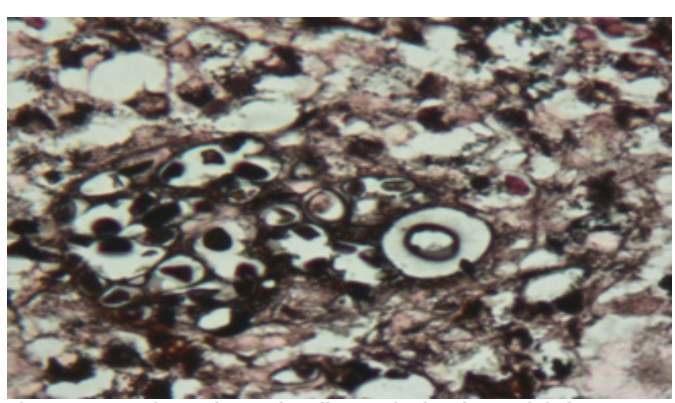

Figure 4: Gomori's methenamine silver stain showing nuclei of cryptococcus and halo surrounding them represents capsules.

DISCUSSION

We have reported a rare case of disseminated cryptococcal infection with pulmonary and bone marrow involvement in an immunocompetent child. The unique feature of this case was hypereosinophilia, with an absolute eosinophil count of 12.3 × 10^9/L with high immunoglobulins levels (Table I). Peripheral eosinophilia is commonly documented with parasitic infections, allergic disorders, vasculitides, and lymphoreticular malignancies. However, peripheral eosinophilia in fungal infection has only been reported with coccidioidomycosis and allergic bronchopulmonary aspergillosis.[4]

The underlying mechanism of eosinophilia is not fully clear yet. Some reports suggest an allergic reaction to cryptococcal infection.[3] Another possibility is that the antigens of Cryptococcus Neoformans, in the form of capsular polysaccharides and glucose mannopyranose induce the production of IgE. The binding of IgE to the mast cells causes degranulation, release of histamine and eosinophil chemotactic factors, and IL-5, which increase the differentiation of eosinophils in the bone marrow and lead to peripheral blood eosinophilia. Chen *et al.* demonstrated in the mouse model that cryptococcal infection causes an increase in the number of eosinophils, and raised serum IgE levels, which is related to type 2 helper T-cells (Th2)-mediated immune response.[5]

According to a recent retrospective study, peripheral blood eosinophilia was observed in 7 of 23 paediatric cryptococcosis patients, particularly in 5 of 11 disseminated cases, suggesting that peripheral blood eosinophilia is a more common manifestation of cryptococcal disease than is widely considered.[6] We also searched previous case reports of cryptococcosis infection with eosinophilia in adolescents and adults.[2] All of the pathogens identified were Cryptococcus Neoformans. Eosinophilia was not only identified in disseminated cases but also localised infections. No HIV-positive patients were reported. The most significant finding was that in all patients with eosinophilia, the eosinophil counts normalised with treatment, a similar finding as seen in our patient, indicating that eosinophils might play a protective role in cryptococcosis.[7]

On imaging of the present patient, we found a ground glass appearance of bilateral lungs with mediastinal lymphadenopathy on the CT chest, suggestive of Cryptococcus dissemination. There is an essential role of bone marrow examination in establishing the diagnosis of fungal infection like cryptococcosis in the presence of disseminated disease, as it can cause complete acellular bone marrow biopsy mimicking aplastic anaemia.[8] The direct examination of bone marrow biopsy has the advantage of a short turnaround time when compared to awaited cultures, as the former can reveal extra and intracellular encapsulated yeast-like organisms. In trephine biopsy, the presence of granulomas with spherical encapsulated yeasts is the hallmark finding. Special stains on trephine biopsy i.e. India ink, periodic acid Schiff and Gomori's methenamine silver are mandatory for the identification of capsule of Cryptococcus Neoformans.

Cryptococcosis can occur in non-HIV infected and immunocompetent patients. It should be included in the differential diagnosis of hypereosinophilia with no allergic or parasitic history.

In conclusion, in paediatric patients with unexplained long-term fever and chest imaging that is inconsistent with clinical symptoms and organ involvement, the differential of Cryptococcal infection should be considered. The precise mechanisms and role of eosinophil aggregation and peripheral dissemination in response to cryptococcal infection need to be elucidated by future research.

PATIENT'S CONSENT:
An informed consent was obtained from the patient's parents.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AA: Designed the concept and drafted the work along with collection, analysis, and interpretation of data.
EA, RS: Revised it critically for important intellectual content.
NR, SR: Reviewed the manuscript.
All authors approved the final version of the manuscript to be published.

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