Case Report

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Disseminated Cryptococcal Infection in Apparently Immunocompetent Child: a Case Report

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Abstract

Cryptococcal infection is the third most common fungal infection which commonly affects immune-compromised hosts but is increasingly recognized in immunocompetent hosts also. Here, we report disseminated cryptococcosis in an apparently immunocompetent child presenting with high-grade fever, headache and altered sensorium for one month. He had pallor, lymphadenopathy, skin lesions, decreased vision, sixth and seventh cranial nerve palsy, and hepatosplenomegaly. Cerebrospinal fluid analysis report, contrast-enhanced Computed Tomography of brain, and bone-marrow aspiration were normal. The diagnosis was confirmed on bone marrow biopsy. Early diagnosis and timely management of this disease would be life-saving for many children.

Keywords: Cryptococcosis; Eosinophilia; Meningitis

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Informed consent was obtained from the patient's parents for the publication.

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Cryptococcosis is the third most common invasive fungal infection after candidiasis and aspergillosis. Cryptococcus infection is principally caused by two species namely *Cryptococcus neoformans and Cryptococcus gattii. C. neoformans* is capsulated yeast that is found worldwide but commonly found in temperate climates predominantly in soil contaminated with pigeon's droppings. It may also be found on rotting wood, fruits, and vegetables and may be carried by cockroaches [1]. Cryptococcal infection is commonly suspected in immunodeficient children presenting with meningitis. However, this condition is rarely considered in a child with apparently good immune status. In this case report, we report systemic cryptococcal infection in an apparently immune-competent child presenting with clinical features of meningitis, hepatosplenomegaly, skin eruptions, and bicytopenia with eosinophilia.

CASE

A five-year-old, developmentally normal boy from Sarlahi, Nepal presented with high-grade fever and headache for one month. He had progressive pallor for which he received blood transfusion once. He had swelling of the body with abdominal distension for one week and bleeding from the nose once. He became more sleepy and irritable for the last few days. He did not have any history of significant illness in the past. Physical examination revealed a drowsy child with Glassgow Coma Scale - 12/15, M5V4E3, periorbital puffiness, moderate pallor and bilateral pitting pedal edema. He had bilateral multiple, discrete, non-tender axillary lymphadenopathy measuring 1 cm and cervical lymph nodes measuring 1.5 × 2 cm. His abdomen was distended with flank full, and palpable liver with 14 cm span. Spleen was palpable 10 cm below the left lower costal margin. Neck stiffness was present. He also had lower motor neuron type of seventh cranial nerve palsy and bilateral sixth cranial nerve palsy. During his hospital stay, he developed blindness and superficial cutaneous lesion over the scalp and forehead which were necrotic initially and healed with scarring. Differential diagnoses such as disseminated tuberculosis, acquired immunodeficiency syndrome (AIDS), parasitic infection, lymphoma/ leukemia, and hemophagocytic lymphohistiocytosis were considered.

Laboratory investigations showed hemoglobin 7.6 gm/L, platelets 45,000 cells/L, leucocytes 11,300 cells/L (N36, L30, M6, E28) with absolute eosinophil count of 3,164/L, and ESR 13 mm at 1 hr. Serum biochemistry, and renal and liver function tests were normal. Blood culture was negative and cerebrospinal fluid (CSF) analysis for cytology and biochemistry was normal. Serology for human immunodeficiency virus (HIV), RK-39 antigen, malarial parasites smears, Mantoux intradermal skin test, chest radiograph, gastric aspirates and gene-Xpert for acid-fast bacilli were negative. Since skin lesions had healed, skin biopsy from the lesion was not taken. Contrast-enhanced computed tomography scan of the head was normal. Bone-marrow aspiration showed a hypocellular marrow. The bone marrow biopsy showed multiple granulomas with large macrophages showing intracellular clear, refractile capsulated yeast-like structures with budding **(Fig. 1).** The size appeared to be larger than red blood cells and lymphocytes and these structures were positive on staining with Periodic Acid Schiff (PAS) **(Fig. 2).** The hematopoietic elements were reduced. A retrospective examination of PAS stained bone marrow aspiration showed presence of these fungal elements within histiocytes in the aspiration smears also. Before the diagnosis could be confirmed, the patient had refractory seizure and succumbed to death.

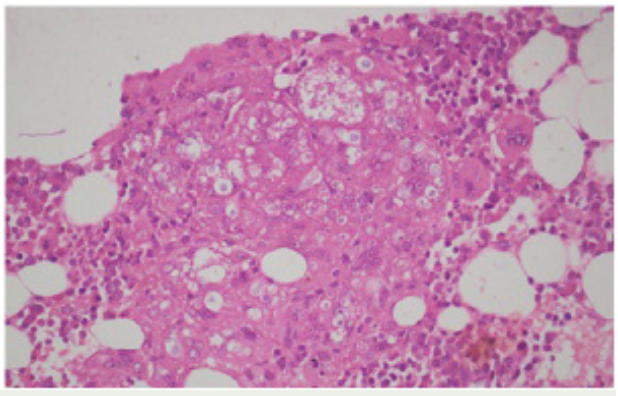

Figure 1: Bone marrow biopsy showing a granuloma with presence of refractile bodies with budding within the macrophages. (H and E x400)

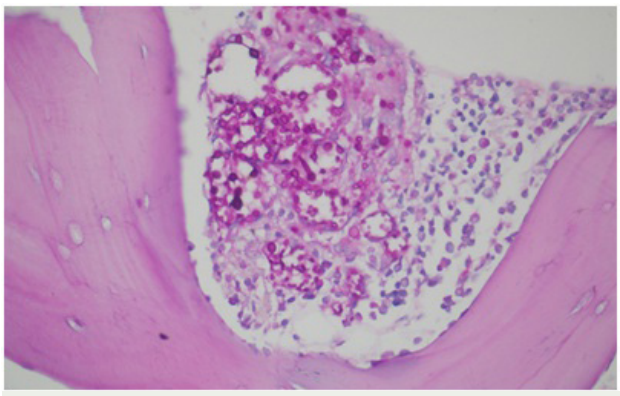

Figure 2: Periodic Acid Schiff (PAS) stain on bone marrow biopsy highlights the presence of the budding yeasts of cryptococcosis. (PAS x400)

DISCUSSION

Clinical clues, in this case, were signs of meningeal irritation with normal CSF report, prolonged fever with hepatosplenomegaly, bicytopenia with eosinophilia and skin lesions. Disease secondary to *C. neoformans* primarily occurs in immunocompromised individuals, especially in those with defects in cellular immunity. Apart from HIV infection, drugs, especially immunosuppressive, hematologic malignancy, solid-organ transplantation, chronic organ failure, and rheumatologic disorders can also predispose individuals to this infection [2]. We failed to suspect cryptococcal infection in this child as he was apparently immunocompetent. A previous study reported that the rate of cryptococcal infection could be as high as up to 30% in patients with AIDS compared to 1% in immunocompetent children [3, 4]. However, various other studies from China found that the majority (60 - 75%) of pediatric patients with cryptococcosis were immunocompetent [5 - 7]. Though our patient was not investigated for primary immunodeficiency as he was a well-thriving child without any history of significant infection in the past, we presumed the child was immunocompetent. However, in a clinical presentation like this, individual needs evaluation for primary immunodeficiency. In a retrospective study from Hongkong done on 46 immunocompetent and immunocompromised adults, apparently immunocompetent patients presented more commonly with meningitis when compared to non-HIV-infected patients with predisposing factors [8]. Also, severe neurological complications like hydrocephalus and seizure are more common in immunocompromised patients [9]. Immunocompetent patients usually have a longer duration of symptoms, typical meningeal signs, and neuroimaging findings [4]. The CSF profile in patients with cryptococcal meningitis may reveal a mild lymphocytosis and elevated protein but is often normal [1]. As CSF was normal in our patient, the neurological signs were mistakenly ignored. Latex agglutination test for cryptococcal antigen in serum and cerebrospinal fluid has high sensitivity (> 90%) so titers above 1:4 in body fluids highly suggest infection [3, 10]. In our case too, latex agglutination test for cryptococcal antigen should have been sent, especially in the background of CNS involvement with normal CSF and CT findings. This would have helped to clinch the diagnosis earlier. Lungs and the central nervous system are the most commonly involved organs followed by skin and reticuloendothelial systems involvement [9]. Cutaneous disease involvement is a sign of disseminated cryptococcosis and is rarely due to local inoculation [1]. Poojary et al. showed that cutaneous cryptococcosis may develop 2 to 8 months before systemic signs of infection, and therefore this period could provide an opportunity for confirmation of disease and treatment before fatal complications occur [11]. In a case series of disseminated cryptococcosis in immunocompetent children reported from Beijing, China between January 1996 and December 2015, 24 cases (42.3%) out of fifty-two children were found to have eosinophilia [9]. The presence of eosinophilia was reported in our patient too. With anti-fungal drugs treatment the level of eosinophils and IgE decreased quickly. Definite diagnosis is made by isolation of the fungus by culture or its demonstration in the histologic sections of infected tissue. The condition is defined as disseminated cryptococcosis if the fungal culture is positive from at least two different sites or a positive blood culture [14]. In this case, although the organism was not cultured, there was CNS bone marrow involvement and cutaneous lesions indicating disseminated infection. Early detection and treatment of disseminated cryptococcosis reduces morbidity and improves outcomes. Treatment consists of four weeks of induction therapy with intravenous amphotericin B/ liposomal amphotericin and oral flucytosine followed by 8 weeks of consolidation phase with oral fluconazole and 6 to 12 months of maintenance phase with oral fluconazole [15]. We believe that this case report would be helpful in saving the lives of children with similar conditions in the future.

CONCLUSION

Disseminated cryptococcosis can manifest as prolonged fever with hepatosplenomegaly, cytopenia and eosinophilia. Cryptococcal infection can occur in apparently immunocompetent individuals. Skin lesions are an important clue for disseminate infection. CSF might be normal in cryptococcal infection so a latex agglutination test for cryptococcal antigen in CSF would be helpful for confirmation of diagnosis early. High index of suspicion of this condition, appropriate investigation and timely management can save life and long-term morbidity.

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