CASE REPORT

Disseminated cryptococcosis in an immunocompetent child

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SUMMARY

Cryptococcus is a ubiquitous fungus and is known for causing meningitis and cutaneous infections in immunocompromised individuals. Disseminated cryptococcal infection is very rare and almost always found to occur in immunocompromised individuals especially in persons infected with HIV. This is particularly attributed to its capsulated spores. But there are few reported cases in which it has been found to cause disseminated infections even in immunocompetent individuals. We report a similar case of disseminated cryptococcal infection in an immunocompetent host. Early detection and treatment of disseminated cryptococcosis is essential to reduce morbidity and for better outcome.

BACKGROUND

In an Indian setup where tuberculosis is endemic, one should also keep other differentials in mind regarding multiple enlarged lymph nodes in a child.

Although cryptococcosis involves mainly immunocompromised hosts few cases have been reported in immunocompetent individuals also.

So, on the basis of fine-needle aspiration cytology (FNAC) and culture for fungus one can easily diagnose cryptococcosis and this will help in early and fast management of the patient.

CASE PRESENTATION

A 2½-year-old girl presented to Paediatric Outpatient Department of Jawaharlal Nehru Medical College, Aligarh with her parents. She came with symptoms of high-grade fever, an abdominal lump and swelling in the right inguinal region for 1½ months. On examination, she was of normal built and nutrition with a weight of 11.1 kg, height 86 cm, weight/age 92%, height/age 95% and was alert and conscious. There was no history of chronic cough, significant weight loss, blood transfusion or any other chronic illness. Neither there was any history of seizures, abnormal behaviour, ear discharge or ear ache nor any sort of head injury in the past. There was no history of steroid or any immunosuppressant drug intake. General examination revealed mild pallor with insignificant cervical, axillary and inguinal lymphadenopathy. On systemic examination, hepatomegaly (5 cm below the costal margin) along with massive splenomegaly (16 cm below the costal margin) was present. Rest of the systemic examination (respiratory, cardiovascular and central nervous systems (CNS)) was within normal limit.

The patient was admitted with a provisional diagnosis of fever with anaemia and hepatosplenomegaly under evaluation. The possible differentials for this patient were: chronic malaria, tuberculosis, leukaemia, and parasitic infestation such as leishmaniasis. Thus patient was admitted and full work up was performed to rule out these differentials.

Routine investigations such as complete blood count revealed haemoglobin level of 6.6 g/dL, total leucocyte count 34 000 cells/mm³, with an absolute neutrophil count of 4080/mm³, lymphocytes 13 600/mm³, eosinophils 16 320/mm³ and platelets 208 000 cells/mm³. Peripheral blood smear showed moderate-to-severely hypochromic and microcytic anaemia with eosinophilia (48%) and was negative for immature cells and malarial parasites. Rest of the routine blood investigations such as urea (28 mg/day), creatinine (0.7 mg/dL), total bilirubin (0.7 mg/dL), aspartate aminotransferase (9 IU) and alanine transaminase (7 IU) were also within normal limits. Special investigations such as quantitative buffy coat test for malarial parasite was negative. Result of tests for HIV, and hepatitis B and C performed by ELISA were found to be non-reactive. Moreover, Mantoux test for tubercular infection also showed a negative result. Serum IgG antibody for leishmaniasis was negative. Other immunoglobulin levels (IgA, IgM) and complement levels were within normal range, thus ruling out any immune deficiency.

Figure 1 Chest X-ray shows fine diffuse infiltrates (miliary shadows) involving both the lung parenchyma.

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Chest X-ray showed fine diffuse infiltrates (miliary shadows) throughout involving both the lungs parenchyma (figure 1). Ultrasonography of abdomen showed hepatosplenomegaly with few subcentimetric mesenteric lymph nodes (largest 8×4 mm) and flecks in the urinary bladder (cystitis). Urine showed fungal hyphae both in routine examination as well as in a culture phial. Blood culture was positive for *Klebsiella*; however, stool culture did not show any abnormal growth. Following this antitubercular drug was started.

FNAC from one of the enlarged cervical lymph nodes was advised. Cytology smear revealed low cellularity with polymorphous population of lymphoid cells mixed with eosinophils. Additionally, background also showed many spherical structures surrounded by clear halos, suggestive of fungal infection (cryptococcosis) (figure 2A). The capsule of these yeast-like structures was highlighted on periodic acid-Schiff (PAS) staining of the smear (figure 2B). Subsequently, bone marrow aspiration and biopsy were advised and sent to the pathology department. Bone marrow aspirate was pauciparticulate; however, myeloid hyperplasia with increase in eosinophils and their precursors was clearly evident, along with few encapsulated budding fungal spores (figure 2C). Biopsy of marrow revealed adequate cellularity for age, myeloid hyperplasia with increased eosinophils and their precursors. Focal collection of histiocytes with budding fungal spores was identified. These were again highlighted on PAS (figure 2D). Serum IgG level was 2473 mg/dL (reference normal 340–1200 mg/dL) again suggesting an ongoing chronic infectious disease.

For the fungal infection, amphotericin B was started and the patient showed improvement. However, after 2–3 days, the patient developed respiratory distress, tachypnoea and pulmonary bleeding. Later the patient had cardiopulmonary arrest and died.

DISCUSSION

Cryptococcus neoformans is an encapsulated yeast, responsible for causing subacute-to-chronic infection known as cryptococcosis. Individuals with immunocompromised states, especially HIV-positive patients, facilitate the survival and dissemination of *Cryptococcus* to different parts of the body. However, disseminated cases of cryptococcosis are even documented in immunocompetent HIV-negative individuals.¹ Similarly our patient was also immunocompetent HIV-negative girl child. The most common site of infection, whether in immunocompromised or immunocompetent individuals, is the respiratory tract which is asymptomatic and resolves spontaneously.² Among the sites for disseminated form, the CNS is most commonly involved manifesting as meningoencephalitis.³ Other organs involved in order of decreasing frequency are skin, gastrointestinal tract and bone marrow, with the involvement of lymph nodes found in only few case reports.^{1 4} Philip *et al*⁵ reported a case with generalised lymphadenopathy, hepatosplenomegaly and miliary patches on chest X-ray while Supparatpinyo⁶ reported that cryptococcal lymphadenitis presents with involvement of multiple sites. Our case was quite similar to his study, as our patient was also having disseminated cryptococcosis with lymphadenopathy of multiple sites (cervical, axillary, inguinal) along with hepatosplenomegaly and involvement of bone marrow. Our patient was an immunocompetent child with negative HIV status.

For early diagnosis of disseminated cryptococcosis many differential diagnoses have to be kept in mind, such as tuberculosis, malignancies and other fungal infections mimicking *Cryptococcus* (*Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Candida*).⁷

Figure 2 (A) Low cellularity smear of cervical lymph node showing mild inflammatory infiltrate with foamy macrophages containing intracytoplasmic encapsulated spores (Pap, ×40). (B) Periodic acid-Schiff (PAS) staining of cervical lymph node smear highlighting the capsule of *Cryptococcus* (PAS, ×40). (C) Bone marrow aspirate shows myeloid and erythroid precursors along with the encapsulated spores (40×). (D) PAS stain of bone marrow biopsy highlighting the capsules of *Cryptococcus* (PAS, ×40).

In India where tuberculosis is endemic, the first differential of lymphadenopathy should be tubercular lymphadenitis which is much more common than cryptococcal lymphadenitis or both may occur together.⁸ Therefore, it is recommended to first rule out tuberculosis by performing the Mantoux test, acid-fast staining and culture of aspirated lymph node sample.

Microscopically, *C. neoformans* organisms are narrow-based budding encapsulated yeasts with an average size of 5–10 µ. It is usually associated with mild inflammation consisting of scattered lymphocytes or macrophages containing intracytoplasmic organisms.⁹ Blastomyces are broad-based budding encapsulated yeast with a larger size of 10–15 µ. The cellular pleomorphism of cryptococci, larger cell size and lack of pseudohyphae help to differentiate it from *Candida*, whereas *Cryptococcus* have a much larger size than the small round *H. capsulatum* (2–4 µ).¹⁰

Cytology of cryptococcal lymphadenitis usually reveals minimal granulomatous and inflammatory reactions,¹¹ which was also found in our case. For the confirmation of cryptococcosis, one has to perform culture for fungus. In our case culture could not be performed due to insufficient material even after repeated aspiration. It is reported that *C. neoformans* var. *neoformans* is found to be associated with immunocompromised HIV-infected patients while *Cryptococcus gattii* is associated with HIV-negative immunocompetent patients.³

Intravenous amphotericin B and oral fluconazole are the drugs of choice; however, sometimes oral flucytosine is also added.¹² In our case, intravenous amphotericin B was started and the patient was responding to it. Unfortunately the mortality in untreated cases of disseminated cryptococcosis can be as high as 80%.¹³

To conclude disseminated cryptococcosis can present without CNS involvement, in an immunocompetent, HIV-negative child. Hence, one has to be cautious that even immunocompetent individuals with multiple enlarged lymph nodes having no response to antibiotics, especially antitubercular, should undergo FNAC to rule out cryptococcal lymphadenitis, followed by confirmation with fungal culture.

Second, possibilities of cryptococcal infection should not be excluded merely on the basis of immunocompetent host if fungal spores and other features are favouring your diagnosis. By this approach, not only early diagnosis will be possible, it will also help in proper and timely management of a patient. Thus complications and dissemination of infection will be prevented, which may prove fatal if not managed timely.

Contributors All the authors have contributed equally to this case report. NS and HAA have reported this case as the consultant in-charge taking into account the differentials in mind. NS and MA have screened this case by taking the detailed history, performing complete examination and advising relevant investigations to the paediatricians.

Learning points

- ▶ Cryptococcosis usually involves immunocompromised hosts, but it can occur in immunocompetent individuals also.
- ▶ The most common manifestations of cryptococcosis are respiratory and central nervous system infections, but the disseminated form can involve any organ of the body with very rare sites such as the gastrointestinal tract, bone marrow and lymph nodes.
- ▶ Cryptococcal lymphadenitis on cytology reveals scant-to-moderate cellularity with minimal inflammation along with narrow-based budding encapsulated yeasts, which can be highlighted on periodic acid-Schiff (PAS) and mucicarmine staining.

Competing interests None declared.

Patient consent Obtained.

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