

## Case Report

# Disseminated cryptococcosis with multiple and mediastinal lymph node enlargement and lung involvement in an immunocompetent child

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**Abstract:** Background: Disseminated cryptococcosis is less common in individuals with normal immune function. Most cases occur in HIV-infected people. Usually it affects the lungs, followed by the central nervous system (CNS), skin and bone marrow, but rarely to the lymph nodes and chest wall. Case presentation: This article reports a case of cryptococcal infection diagnosed as “lymphoma?” in a local hospital. It was characterized by chronic fever, weight loss, neck, axillary and inguinal lymph nodes enlargement, mediastinal and parabronchial lymphadenopathy, multiple nodular high-density images of both lungs, multi-serosal effusion, liver enlargement and other presentations. Conclusions: Disseminated cryptococcosis can occur in immunocompromised children without HIV infection. This case of multiple and mediastinal lymphadenopathy, easily misdiagnosed as “lymphoma”, requires high clinical suspicion and early initiation of treatment to effectively identify and treat patients.

**Keywords:** Disseminated cryptococcosis, multiple lymphadenopathy, child

## Background

Cryptococcosis is a subacute and chronic deep mycosis caused by *Cryptococcus neoformans*, which mainly invades the central nervous system and lungs, and can also invade bone marrow, skin, mucous membranes and other organs. It often occurs in people with impaired cellular immune function, such as acquired immunodeficiency syndrome, receiving steroids, cyclosporine A and other immunosuppressive agents or organ transplants, leukemia or lymphoma patients. However, there are a small number of patients without any underlying disease.

## Case presentation

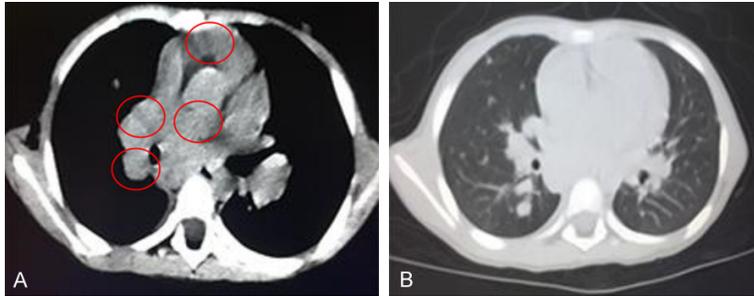
On April 2016, a 7-year-old female child, resident of Anhui Province in China presented to our department with cough for more than 40 days and recurrent fever for more than one month. She was admitted in local hospital for these symptoms but no improvement was seen. When she was presented to our hospital, she had swollen lymph nodes in addition to

fever and cough. She had no past history of tuberculosis, diabetes mellitus, malignancy chronic illness as well, and had never contact with a patient with pulmonary tuberculosis. Her family did not give any history of exposure to bird droppings.

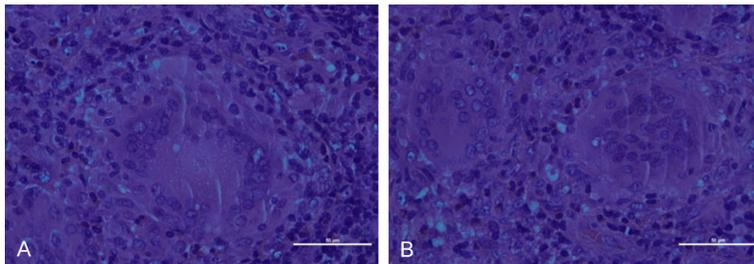
Clinical examination revealed swelling of the bilateral neck, underarm and inguinal lymph nodes, partially fused into a block, absence of tenderness. Her eyes were slightly swollen, the pharynx was congested, the tonsils were swollen, and no secretions were found. Liver was enlarged under the ribs 2 cm, but no other abnormality detected on examination of the respiratory, cardiovascular and CNS.

Laboratory investigations showed stool examination and urinalysis were normal. The erythrocyte sedimentation rate was determined as 86 mm/h, white blood cell (WBC) count as  $25,340 \times 10^6/L$  (70.4% neutrophils, 21.2% lymphocytes), the C-reactive protein (CRP) 89 mg/L, and hemoglobin as 91 g/L. Tuberculin test and widal test were both negative. The prothrombin time (PT) was 12.7 s, thrombin time

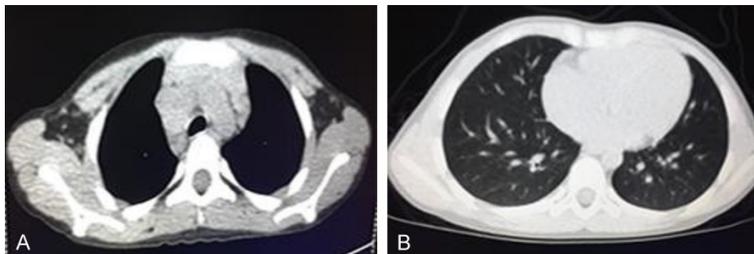
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**Figure 1.** Chest CT reveals mediastinum, bronchial lymph node enlargement, multiple nodular high-density shadows in both lungs.



**Figure 2.** Inguinal lymph node biopsy: epithelioid granulomatous lymphadenitis with central necrosis of granuloma; GMS, PAS staining showed cryptococcus, negative for acid-fast staining ( $\times 400$ ).



**Figure 3.** Chest CT obtained two months after starting treatment reveals resolution of the both lung nodules, mediastinal and parabronchial lymph node.

(TT) as 14.4 s, activated partial prothrombin time (APTT) as 36.7 s, D-Dimer as 868 ng/ml and fibrinogen (FIB) as 3.93 g/L. Other findings included *Mycoplasma pneumoniae* (MP) IgM positive (+), Blood culture (-), antinuclear antibody-granule type 1:320 (positive), antinuclear antibody-cytoplasmic type 1:100 positive (+), EBV virus (VCA)-IgG positive (+), EBV virus (VCA)-IgG positive (+), EB-DNA  $2.09 \times 10^3$  copies/ml, carcinoembryonic antigen (CEA) 0.717 ng/ml, alpha-fetoprotein (AFP)  $<0.605$  ng/ml, neuron-specific enolase, (NSE) 29.39 ng/ml, CA19-9 4.70 U/ml, ferritin 253.1 ng/ml. She was non-reactive for HIV. Investigating cellular immunity, humoral immunity did not show any evidence of immunodeficiency.

Bone marrow puncture (Jiangsu Provincial People's Hospital) suggested that the proliferation of granulocyte, erythroid and megakaryocytes was markedly active, platelet clusters were visible, toxic particles were easily seen in the cytoplasm of neutrophils, and no parasites or abnormal cells were observed. Head and chest and abdomen CT showed 1). cerebral sulcus deepened; 2). mediastinum, bronchial lymph node enlargement, multiple nodular high-density shadows in both lungs; 3). bilateral pleural effusion; 4). pelvic a little effusion (See **Figure 1**).

Inguinal lymph node biopsy showed epithelioid granulomatous lymphadenitis with central necrosis of granuloma, visible cryptococcal infection in granuloma. GMS, PAS staining can be seen in *Cryptococcus* as shown in **Figure 2**, negative for acid-fast staining. CNS involvement was excluded in cerebrospinal fluid (CSF) analysis, which was negative for *Cryptococcus* ink staining. Thus, a diagnosis of disseminated *Cryptococcus* in a HIV negative host was made.

Patient received therapy for Intravenous Amphotericin B, starting with a small dose from 0.01 mg/kg/d (2 mg/d for two days; 7 mg/d for two days; 12 mg/d for two days), gradually; increased to total dose of 14 mg/d for two weeks. Her fever, lymphadenopathy, blood, inflammatory protein and mental state improved after therapy. After discharge, the child continued to maintain Intravenous Amphotericin B 14 mg/d for 4 weeks at a local hospital, and then changed to voriconazole orally. After the outpatient follow-up, the symptoms disappeared and the lymphadenectasis ameliorated. Reexamination of chest CT, lymph node enlargement was obviously relieved (See **Figure 3**).

### Discussion and conclusions

The incidence of cryptococcal infection in children is mostly subclinical infection or occurs undetected [1]. In addition, unexplained fever and lymphadenopathy are the first symptoms, which are easily misdiagnosed as tuberculosis, sarcoidosis or malignant tumors. It has been reported that immunodeficiency, chronic wasting diseases (diabetes, sarcoidosis, leukemia, advanced cancer, AIDS and organ transplantation) and patients with pulmonary infection are susceptible to cryptococcal infection [2]. One example of misdiagnosis is that pulmonary cryptococcosis is misdiagnosed as lung cancer due to a lack of typical clinical signs and imaging [3].

In this case, the child continued to have fever for more than one month. Her lymph nodes in neck, inguinal, mediastinum and parabrachial were enlarged, and there were multiple nodular high-density shadows in two lungs. The thoracic cavity and peritoneal effusion were not effective. There is weight loss in the course of the disease, which is easily misdiagnosed as "lymphoma" in a local hospital. Morphological examination of bone marrow cells can often assist in identification, but it is often difficult to identify. Therefore, lymph node biopsy assisted identification is clearly required.

There have been many reports of cryptococcal infections in cases of negative HIV infection. Joshi et al [4] investigated 63 children aged <19 years old with cryptococcosis admitted to 42 state children's hospitals in the United States from 2003 to 2008, and found that 20.6% of children had normal immune function and 63.5% had basic diseases (including tumors, solid organ transplants, bone marrow transplants, cystic fibrosis, systemic lupus erythematosus, etc.), only 15.9% of children have HIV infection, indicating that most children with cryptococcosis in the United States occur in uninfected HIV. Yu chong et al [5] reported that only 15.7% of the 8796 cryptococcosis patients in mainland China from 1985 to 2010 were AIDS or HIV-infected.

Some literature reports that the increase in peripheral blood eosinophil count is one of the salient features of disseminated cryptococcosis. Marwaha et al [6] reported elevated peripheral blood eosinophil counts in children with

cryptococcal disease who were not infected with HIV. However, in this case, the blood samples were abnormally increased for many times, and the manifestations were mainly neutral, showing the characteristics of "sepsis".

At present, reports on childhood cryptococcosis are mostly confined to meningitis or pulmonary infection, and there are few reports of disseminated cryptococcal infection, which is also a fatal infection. Kaur et al [7] reported a case of death caused by disseminated cryptococcal infection.

In this case, at least two of the lungs, parabrachial mediastinal lymph nodes, peripheral lymph nodes are involved, accompanied by pelvic fluid, pleural effusion, so that disseminated cryptococcosis is considered. There are few reports on the clinicopathological features of cryptococcal lymphadenitis. Kawamoto et al [8] reported three patients with cryptococcal lymphadenitis, including HTLV-1 carriers and two HIV carriers, and summarized the clinical aspects of cryptococcal lymphadenitis. Pathological features: In most cases, granuloma formation, epithelioid cells and necrotic parts are common, and the diagnostic clues for cryptococcal lymphadenitis may be necrotizing granuloma formation, gelatinous formation and giant cell response. In pathological images, epithelioid granulomas with necrotic tissue may suggest cryptococcal lymphadenitis. Regarding the pathological features of lymph node examination of cryptococcal infection, the pathological manifestations of inguinal lymph nodes in this case were: epithelioid granulomatous lymphadenitis, with central necrosis of granuloma, and suspicious cryptococcal infection in granuloma. GMS, PAS special staining can be seen in *Cryptococcus*, negative for acid-fast staining.

IDSA supplemented the treatment of children in 2010 [9]. In this case, according to the guidelines issued by IDSA in 2010, the amphotericin B treatment was given for >4 weeks during the induction treatment period. After one week of systemic antifungal treatment, this child's temperature returned to normal. After the induction therapy, the clinical manifestations and laboratory indicators of the children improved significantly. We followed up through the clinic and the child did not relapse 3-6 months after completion of consolidation and maintenance treatment.

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The fine needle aspiration histological examination has a high detection rate and small trauma, which can provide a fast and accurate diagnosis method [10]. In this case, fine needle aspiration histological examination was not performed because of consideration of trauma and parental rejection and the inability to exclude "lymphoma" at the beginning of the disease. The child had swollen lymph nodes in multiple parts of the body. For the sake of safety, combined surgical consultation, with the consent of the parents, we took inguinal lymph node biopsy. However, after treatment with cryptococcal disease in this child, lymphadenectasis in the lungs, mediastinum, neck, inguinal lymph nodes ameliorated. Inflammation of the lungs and pleural effusion disappeared.

In summary, the clinical manifestations of cryptococcal infection are non-specific, this case is easily misdiagnosed as lymphoma. Lymph node biopsy combined with special staining can help to identify the diagnosis, guide the diagnosis and eventually the treatment.

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### Disclosure of conflict of interest

None.

### Abbreviations

CNS, Central nervous system; HIV, Human immunodeficiency virus; WBC, White blood cell; MP, Mycoplasma pneumoniae; EBV, Epstein-Barr virus; CSF, cerebrospinal fluid; CT, Computed tomography; GMS, Gomori's methenamine silver nitrate stain; PAS, Periodic Acid-Schiff stain; AIDS, Acquired Immune Deficiency Syndrome.

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