A Case of Mediastinal and Pulmonary Cryptococcosis in a 3-Year-Old Immunocompetent Girl

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=Abstract=

Cryptococcosis is an infrequently recognized infection in children, particularly those who are immunocompetent. The disease is mainly caused by *Cryptococcus neoformans*, a fungal pathogen that primarily affects the central nervous system (CNS) and lungs. Most reports of children with cryptococcosis are of the CNS or disseminated infections among immunocompromised patients. This report is a case of a 3-year-old immunocompetent girl who presented with intermittent fever and cough; a large mass was found in the right infrahilar area on chest X-ray. Chest computed tomography revealed large conglomerated mediastinal lymph nodes caused by *C. neoformans*, which was confirmed by the polymerase chain reaction as well as a histological evaluation. The patient improved after a prolonged period of antifungal therapy. This is the only known report of mediastinal and pulmonary cryptococcosis in an immunocompetent child. **[Pediatr Allergy Respir Dis(Korea) 2011;21:350-355]**

Key Words : Mediastinum, Cryptococcosis, *Cryptococcus neoformans*

Introduction

Cryptococcosis is caused by *Cryptococcus neoformans*, an important fungal pathogen that primarily affects the central nervous system (CNS) and lungs.[1)] This fungus most commonly infects immunocompromised hosts, particularly patients with human immunodeficiency virus (HIV) infection.[2)] Cryptococcal infection occurs less frequently in immunocompetent hosts and is much less common in children than in adults. The majority of reported cases in children are of a CNS infection or disseminated cryptococcosis with underlying immunodeficiency.[3)] In this report, a 3-year-old immunocompetent girl is described. She presented with an intermittent fever and cough and a large mass in the right infrahilar area on chest X-ray. Chest computed tomography (CT) revealed large conglomerated mediastinal lymph nodes caused by *C. neoformans*, which was confirmed by the polymerase chain reaction (PCR) and histological features.

Case Report

A 3-year-old girl, previously in good health, was admitted with a 1 month history of a productive cough and intermittent fever. A chest X-ray revealed a large mass in the right perihilar area (Fig. 1), and she was

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referred to our institution. Her medical history was unremarkable, and developmental status was normal. None of the family members had a history of pulmonary tuberculosis. The patient did not have a history of contact with birds such as pigeons. A review of systems showed an otherwise normal child except for the fever, productive cough, and anorexia. The child appeared acutely ill; however, vital signs were stable, chest auscultation showed no abnormal findings, and other physical examinations were normal except for palpation of a lymph node at the right supraclavicular area.

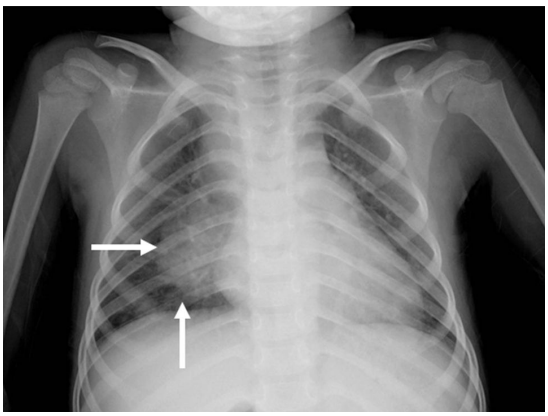

Fig. 1. Chest radiograph showing mediastinal widening and mass-like opacity (arrows) in the right lower lung field.

A chest CT was performed at the referring hospital and revealed large conglomerated mediastinal lymph nodes with a nodule that had a cavitation measuring 13 mm in diameter in the right lower lobe (Fig. 2). These findings suggested pulmonary tuberculosis, so we performed a tuberculin skin test, acid-fast bacilli fluorescent smear of sputum, *Mycobacterium* culture, and complex PCR. No specific laboratory findings supported the diagnosis of tuberculosis. An excisional biopsy of the right supraclavicular lymph node was performed, and a lymph node of about 1.5×1.5×1 cm^3 was excised. The results of the biopsy showed granulomatous inflammation and a number of yeast cells within phagocytic cells that had a mucicarmine positive capsule, which was consistent with *C. neoformans* (Fig. 3).

Laboratory findings included a white blood cell count of 20,690 cells/mm^3 with 71% polymorphonuclear leukocytes. The blood and urine cultures showed

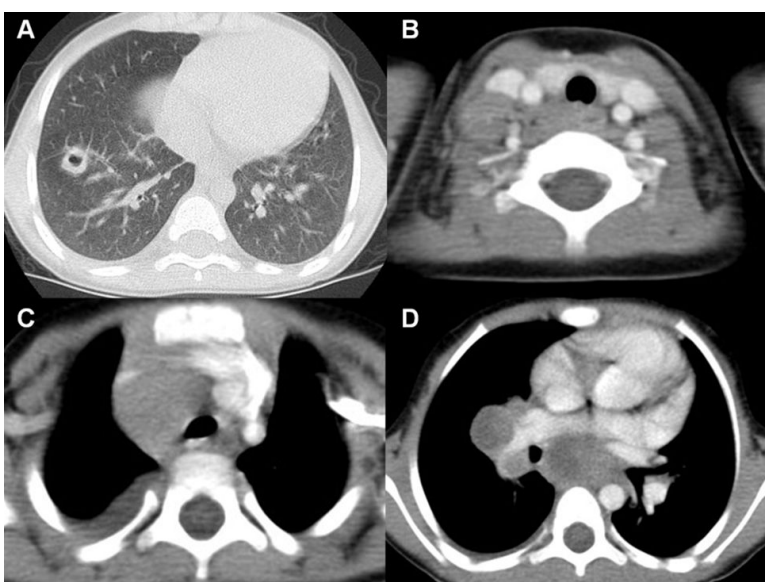

Fig. 2. Chest computed tomography scan demonstrating a cavitary lesion in the right lower lobe (A) with lymph node enlargement in the right lower neck (B), mediastinum (C), and hilum (D).

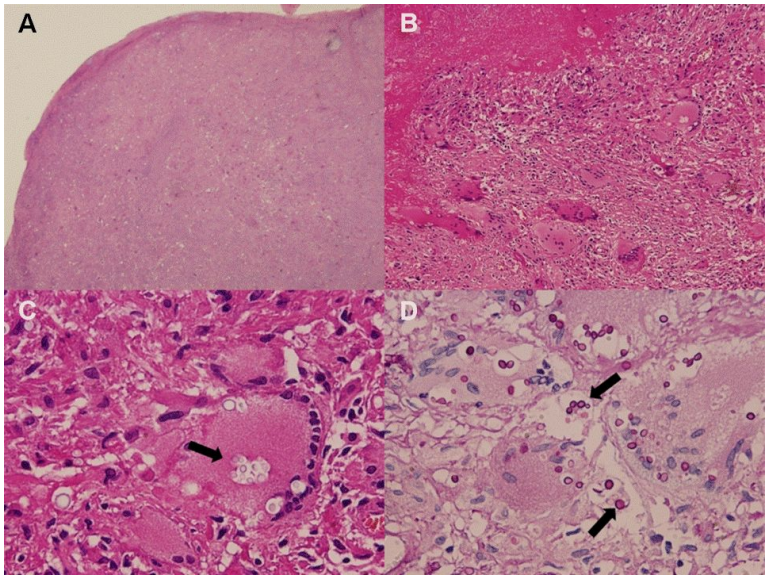

Fig. 3. Histopathology of the neck lymph node is consistent with *Cryptococcus neoformans*. Necrotizing granulomatous inflammation (A, H&E, ×10; B, H&E, ×100). Mucicarmine-positive yeasts of variable sizes (arrow) (C, H&E, ×400). Yeasts with a thickened capsule on periodic acid-Schiff stain (arrows) (D, ×400).

no growth of any organisms. A lumbar puncture was performed to assess whether the fungus had spread to the CNS. The results of a cerebrospinal fluid (CSF) cryptococcal antigen test were negative, as were the results of a CSF culture. The serum cryptococcal antigen test result was also negative. The patient was evaluated for underlying immune deficiencies, but all findings were normal including the results of HIV testing. A blood flow cytometric T-cell subtype analysis revealed normal CD4 (40.1%) and CD8 (17.5%) subsets, and the total immunoglobulin (Ig) A, IgG, IgM, and IgE levels were all within the normal range. We also evaluated for chronic granulomatous disease, and the result was negative.

Antifungal therapy with intravenous amphotericin B was started on the day that the cryptococcosis was diagnosed. However, after 2 weeks of administering amphotericin B, the fever spiked again and a repeat chest X-ray did not show a significant reduction in the mass identified initially. The mass eventually required dissection and an excision biopsy to rule out malignancy. The mediastinal lymph nodes were excised, the subcarinal, right paratracheal and interlobar lymph nodes were enlarged, and the white, hard, well-capsulated lymph nodes adhered to surrounding organs including the trachea. A histological examination revealed the same features as the former node biopsy. The diagnosis of *C. neoformans* was confirmed by PCR amplification of the specimens obtained. Treatment was changed to liposomal amphotericin B instead of amphotericin B because of hypokalemia and hypotension, and flucytosine was added to the liposomal amphotericin B while planning the mediastinal lymph node dissection. The fever remitted, and an improvement in the subjective symptoms including coughing was observed promptly thereafter. The patient received an additional 2 week course of therapy with liposomal amphotericin B plus flucytosine, and now she is on fluconazole therapy for 8 months. The follow-up chest CT revealed a reduction in the mass, and her clinical course continues to improve.

Discussion

Cryptococcosis is a systemic fungal infection found mainly in adult patients and is uncommon in children.[4] It is common opportunistic infection of immunocompromised individuals such as patients with cellular immune deficiencies including HIV infection, hematologic malignancies, and organ transplants.[4] In a study of 52 patients with disseminated cryptococcosis, only three had no underlying disease, and the most common underlying condition was an HIV infection.[5]

A cryptococcal infection is caused by the encapsulated yeast-like organisms *C. neoformans* and *C. gattii*, and they cause infection in immunocompromised patients and immunocompetent hosts, respectively.[4] *C. neoformans* is predominantly found in soil contaminated with pigeon excreta and decaying wood, and it commonly causes CNS disease through hematogenous dissemination.[6] Pulmonary cryptococcosis, the second most common type of infection, is acquired by inhaling infectious particles.[4] Occasional sites of infection also include the skin, bone, liver, spleen, adrenals, prostate, kidneys, and lymph nodes.[3,4] Some studies have been conducted on non-immunocompromised adults with pulmonary cryptococcosis,[7,8] and some cases of cryptococcal meningitis have been reported in immunocompetent children.[9,10] However, cryptococcal mediastinal lymphadenopathy, as reported here, is very rarely recognized in immunocompetent hosts. A case of massive mediastinal lymphadenopathy in an immunocompetent pregnant woman with isolated pulmonary cryptococcosis was reported;[11] this patient had a primary pulmonary focus with lymphogenous involvement of the hilar lymph nodes. A case with "mediastinal cryptococcoma" was reported in 1978 in a 24-year-old Zambian man with a very large mass in the mediastinum, which was initially thought to be a lymphoma.[12] The patient died during bronchoscopy, and the autopsy confirmed the cryptococcosis diagnosis. Two cases of immunocompetent children with primary abdominal lymphonodular cryptococcosis caused by *C. neoformans* have been described in China.[13] However, the case reported here is the first mediastinal presentation of cryptococcosis in an immunocompetent child. A pulmonary nodule with a cavitation was present in this patient and was also considered cryptococcosis, although cryptococcal invasion was not confirmed. But the main lesion was in the mediastinum where *C. neoformans* was confirmed.

The most common symptoms of cryptococcosis with a CNS infection are fever, headache, nausea, vomiting, and often altered mental status.[4] The most frequent symptoms of pulmonary cryptococcosis include cough and fever, but it can often be asymptomatic and diagnosed incidentally on chest X-ray.[8] In one study, six of 13 cases of pulmonary cryptococcosis were asymptomatic.[14] Disseminated disease is rare but often fatal in children.

The radiological findings of crypococcosis are influenced by the underlying immune status of the patient.[1,15] Solitary or multiple isolated pulmonary nodules are found more often in immunocompetent individuals, but lymphadenopathy is rarely found on radiology or CT studies of pulmonary cryptococcosis.[15] CT findings in immunocompetent patients with pulmonary cryptococcosis have been reported, and nine of 10 patients had pulmonary nodules.[16] Isolated pulmonary or CNS nodules are often mistaken for tuberculosis or cancer. In particular, intrathoracic lymphadenopathy is frequently mistaken as lymphoma at diagnosis.[17] In the patient reported here, multiple enlarged mediastinal lymph nodes initially suggested a lymphoma, due to their large size and unusual presence.

A microscopic evaluation and histopathology as well as detecting the capsular antigens are necessary to confirm the diagnosis, because the clinical symptoms and X-ray findings are nonspecific.[4] Sputum is the most readily obtained sample; however, its sensitivity for diagnosing pulmonary cryptococcosis is limited because of the potential for airway colonization by *C. neoformans*.[1,15] Therefore an invasive procedure such as a biopsy or needle aspiration may be

required for a definitive diagnosis.[2,7,15] Histopathology may reveal specific features, such as granulomatous inflammation, intracellular yeast within histiocytes, and multinucleated giant cells using acid-fast, Gomori methamine silver, and mucicarmine stains.[1] In the context of a negative culture, an immunohistochemical approach is useful with a specific monoclonal antibody that can identify the main cryptococcal capsular polysaccharide antigen. These tests are easily performed and take only 1 day, whereas a culture requires 7 to 8 days.[1]

The medical literature on pediatric cryptococcosis is limited to case reports and small series, and no clinical trials have been performed. Therefore, treatment recommendations are based on the extrapolation of findings from studies performed in adults. The treatment options for cryptococcosis differ depending on the underlying immune status of the host, disease severity, and the site of infection.[18] The need for treatment in all immunocompetent patients remains controversial. It is widely thought that spontaneous resolution of pulmonary cryptococcosis in immunocompetent hosts is the usual course; however, dissemination can occur.[18] Therefore, the mild form of treatment for isolated pulmonary cryptococcosis tends to be conservative, and antifungal therapy is generally limited to progressive disease. Fluconazole has been recommended to treat isolated pulmonary cryptococcosis in immunocompetent hosts.[18,19] "The Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America" recommends 6 to 12 months use of fluconazole for cryptococcal pneumonia in children.[20] Amphotericin B plus flucytosine followed by fluconazole is recommended for a CNS infection and disseminated disease in children. Children generally tolerate amphotericin B better than adults, and a dose of 1 mg/kg per day is commonly used. Because there are no large prospective randomized studies of the specific sites of infection for non-meningeal non-pulmonary cryptococcosis, the treatment depends on disease severity, therapy response, and immune status of the host. Treatment regimens for non-meningeal non-pulmonary cryptococcal infection are similar to those for CNS and disseminated infection even in cases in which the clinical symptoms are limited to the site of infection, usually as a result of dissemination. Similar to the case presented here, patients with prolonged symptoms and slow resolution of X-ray findings may require treatment regimens similar to disseminated cases.

한 글 요 약

3세 면역정상 여아에서 발견된 종격동과 폐를 침범한 Cryptococcosis 1례

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Cryptococcosis는 소아에서 드문 질환으로 주로 면역억제된 환자에서 전신에 파급되어 치명적인 중추신경계의 감염을 일으키는 질병이다. 그러나 면역이 정상인 환자에게도 발생할 수 있으며 중추신경계 이외에 폐나 다른 장기에도 침범을 보이기도 하지만 이는 매우 드물다. 특히 소아에서의 cryptococcosis는 지금까지 보고된 예도 대부분 면역억제가 있는 환아에서 보인 전신성 감염이거나 뇌수막염에 대한 것이었다. 평소 건강했던 3세 여아가 한달 간의 기침과 발열 주소로 내원하여 흉부 컴퓨터 촬영상 우측 종격동 종괴와 폐결절을 보였으며, 임파선 절제 및 생검을 시행하였고 병리학적 소견 및 중합효소연쇄반응을 통해 *Cryptococcus neoformans*이 진단되었다. 저자들은 면역 기능이 정상인 3세 여아에서 발견된 종격동과 폐를 침범한 cryptococcosis 1례를 경험하였기에 보고하는 바이다.

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