A Case of Disseminated Cryptococcosis in an Immunocompetent Adult

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정상 면역 성인에서 발생한 파종성 크립토콕쿠스증 1례

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*Cryptococcus neoformans*는 비둘기 배설물이나 비둘기 배설물로 오염된 토양에서 흔히 발견되는 효모양 진균으로 호흡기를 통해 신체 내부로 침입하여 폐에 병변을 일으키고 혈액을 따라 전신으로 파급되어 주로 중추신경계를 침범하며 그외 골격계, 임파조직, 전립선, 피부 등을 침범한다. 크립토코쿠스증은 면역저하 환자, 특히 세포면역이 저하된 환자에서 발생하나 정상 면역 환자에서도 발생할 수 있고, 국내에서도 정상 면역 환자에서 고립성 폐 크립토콕쿠스증 또는 피부 크립토콕쿠스증에 대한 보고들이 있었다. 그러나 정상 면역 성인에서 림프절, 피부, 폐 및 중추신경계를 침범하는 파종성 크립토콕쿠스증은 아직 국내에서 보고된 바 없다. 저자들은 발열과 림프절 종대를 주소로 내원한 정상적인 면역상태의 젊은 남자에서 피부, 폐 및 중추신경계를 침범한 파종성 크립토콕쿠스증을 림프절 및 피부 조직생검과 조직배양으로 진단하였고, 2주간 amphotericin B와 flucytosine을 정맥투여하고 8주간 fluconazole을 경구투여 후 2년간 재발하지 않고 추적관찰 중인 증례를 경험하였기에 보고하는 바이다.

Key Words : Cryptococcosis, Disseminated, Immunocompetent

INTRODUCTION

Cryptococcus neoformans is a ubiquitous yeast with a worldwide distribution and usually causes opportunistic infections in immunocompromised hosts. Cryptococcus usually enters through the respiratory route and hematogenous dissemination occurs from the lungs, most commonly to the meninges. Cryptococcosis is frequently encountered in patients with compromised cell-mediated immunity, especially those with HIV infection. However, cryptococcal disease can occur in immunocompetent persons (1). There are several reports about isolated pulmonomary cryptococcosis or cutaneous cryptococcosis in immunocompetent host (2-4). However, disseminated cryptococcosis involving multiple lymph nodes, skin, lung, and CNS in adults without underlying predisposing factors hasn't been reported in Korea so far. Here, we report a case of disseminated cryptococcosis in an immunocompetent adult patient.

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CASE REPORT

A 26-year-old man was admitted to the hospital because of persistent fever and cervical lymphadenopathy. The patient was well until two weeks earlier, when fever and myalgia developed. He had been treated with cephradine and dexamethasone (5 mg/day) empirically at a private clinic for five days. However, fever persisted and cervical lymphadenopathy devel-

oped, so that he was referred to our hospital.

He had no history of smoking or heavy alcohol use. He denied any intravenous drug use. He had no history of blood transfusion or previous surgery. The patient denied any recent travel and exposures to animals. He had no family history of tuberculosis.

On admission, body temperature was 38.6℃, blood pressure was 100/50 mmHg, pulse rats was 100/minute, and respiration rate was 20/minute. Several tender enlarged lymph nodes (measuring approximately 0.8×0.8×0.5 cm) in the left supraclavicular area and posterior neck triangle were palpated. The liver edge was palpated 1 cm below the right costal margin. The other findings on physical examination were unremarkable.

Laboratory findings showed white blood cell count of 18,000/mm^3 (neutrophils 80%, lymphocyte 11%), hemoglobin of 13.9 g/dL, and platelet count of 427,000/mm^3. The erythrocyte sedimentation rate was 65 mm/h, and C-reactive protein was 16.84 mg/dL. The blood chemistry was as follows : AST 60 IU/L, ALT 86 IU/L, alkaline phosphatase 357 IU/L, γ-GTP 144 IU/L, total protein 6.5 g/dL, albumin 3.2 g/dL, total bilirubin 0.4 mg/dL, LDH 357 IU/L. Renal profiles, electrolytes, and urinalysis were normal. Cerebrospinal fluid (CSF) profiles were normal. Chest X-ray on admission showed no abnormalities. Treatment with intravenous ciprofloxacin was started empirically. Further evaluations on cervical lymphadenopathy and hepatomegaly included neck and abdominal computed tomography (CT) scans. The neck CT scan showed multiple enlargend lymph nodes with some central necrosis in the left posterior triangle and supraclavicular area (Figure 1). The abdominal CT scan showed mild hepatomegaly with intra-abdominal lymphadenopathy in the porta hepatis, portocaval space, and near the hepatoduodenal ligament, which encased hepatic artery and vein (Figure 2). Blood and urine cultures yielded no organism.

On the 4th hospital day, several erythematous papules appeared over his back and extremities (Figure 3). A follow-up chest X-ray showed newly developed miliary pulmonary infiltrates and mediastinal widening. The chest CT scan revealed tiny nodules scattered in both lung fields and multiple lymphadenopathy in paratracheal, perivascular, and subcarinal areas (Figure 4). In order to exclude miliary tuberculosis, bronchoscopy was performed, but no endobronchial lesion was found. No organism was isolated on bronchoalveloar lavage. Biopsy of cevical lymph nodes, and skin papule was done on the 6th hospital day. The pathologic results showed granuloma with multinucleated giant cells and

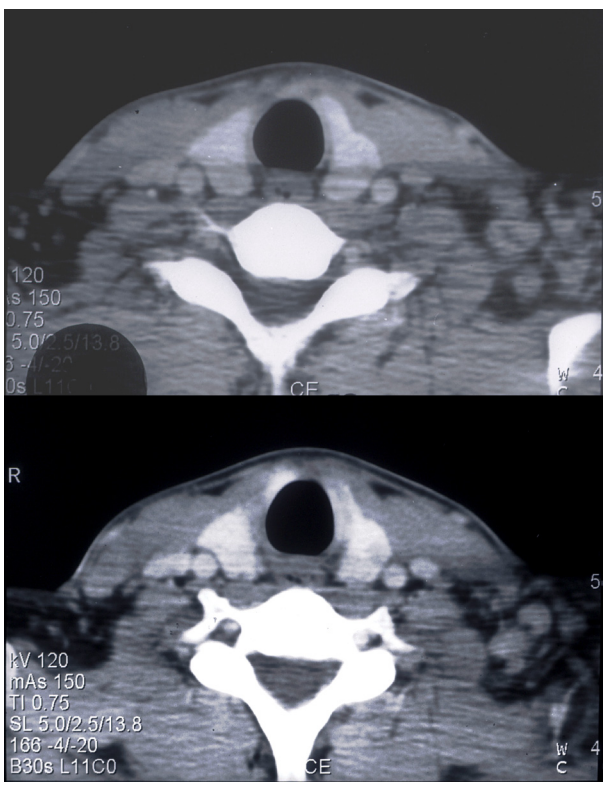

Figure 1. The neck CT scan showed multiple, enlarged lymph nodes with some central necrosis in the left posterior triangle and supraclavicular area.

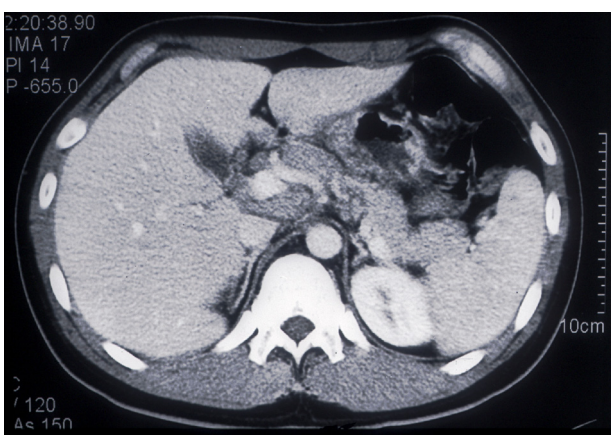

Figure 2. The abdomen CT scan showed hepatomegaly with multiple intra-abdominal lymphadenopathy in porta hepatis, portocarval space, and near the hepatoduodenal ligament. Proper hepatic artery and vein were encased with enlarged lymph nodes.

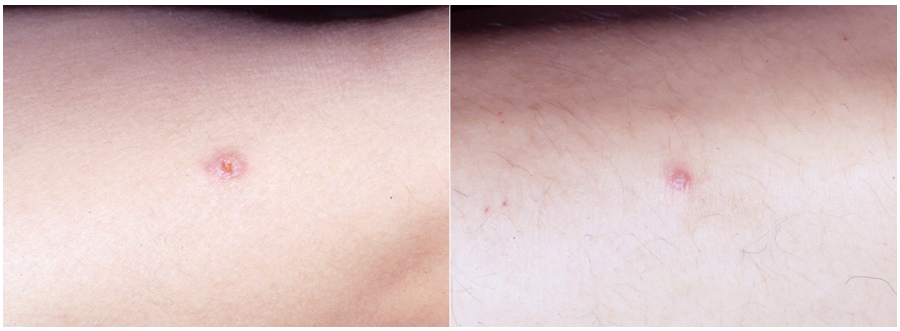

Figure 3. Erythematous papules developed on the back and both extremities (4th hospital day).

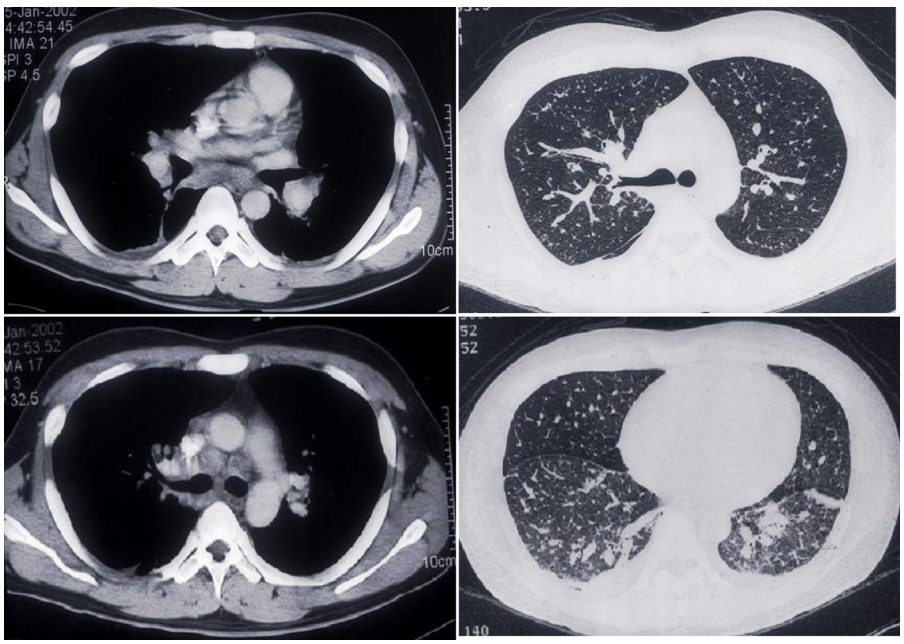

Figure 4. The chest CT scan showed multiple small nodules scattered in random distribution in both lower lung fields and prominent lymphadenopathy in both paratracheal, perivascular and subcarinal areas.

multiple *Cryptococcus*-like yeasts in both cervical lymph node and skin on periodic acid-Schiff stain (Figure 5A-5C). Latex agglutination test for serum cryptococcal antigen was negative, but tissue culture of cervical lymph nodes grew *Cryptococcus neoformans*. We started systemic amphotericin B (0.6 mg/kg) plus flucytosine on the 10th hospital day, and fever subsided after 2 days of antifungal therapy.

On the 13th hospital day, in spite of antifungal treatment, he developed slurred speech without focal neurologic deficit. Brain MRI findings were negative and CSF findings were as follows: opening pressure of 14.5 cmH_2O, white blood cells of 32/mm^3 (lymphocyte 98%), protein 34 mg/dL, and sugar 75 mg/dL. No organism was seen on Gram stain, Ziehl-Neelsen stain, and India ink preparation of the CSF. PCR for *M. tuberculosis* and latex agglutination test for cryptococcal antigen in CSF were all negative. He became stable with continuing systemic amphotericin B plus flucytosine therapy.

We evaluated the immune status of the patient. The ELISA for HIV antibody was negative on two consecutive tests (interval of 6 weeks). Serum immunoglobulin G, A, M and E were in normal ranges. Total peripheral blood lymphocyte count was 1,478/mm^3 and the ratio of CD4 to CD8 cell count was 1.2.

He received systemic amphotericin B (0.6 mg/kg) with flucytosine for 2 weeks, and additional oral fluconazole (400 mg) for 8 weeks. There was no evidence

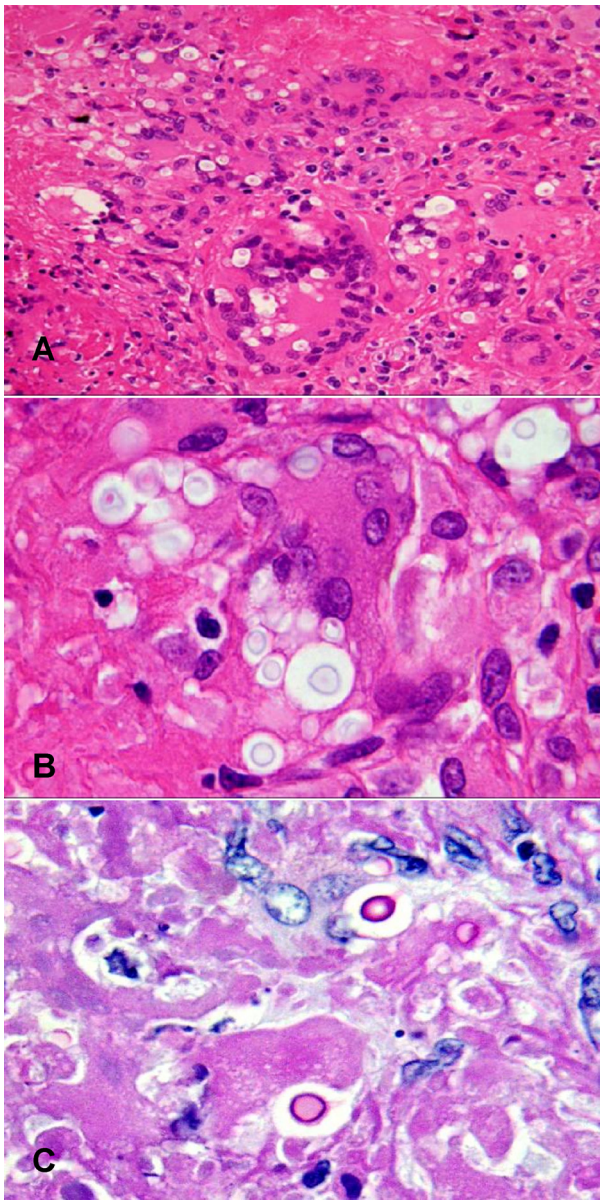

Figure 5. Histologic findings of cervical lymph nodes(A) Chronic granulomas with central necrosis, and multinucleated giant cells, and several encapsulated yeast, not stained with hematoxylin and eosin (HE stain, ×400). (B) Several yeasts surrounded by capsule not stained with HE (HE stain, × 1,000). (C) Chronic granuloma and several yeasts with capsule stained (PAS stain, ×1,000).

of recurrence disease for 2 years.

DISCUSSION

Cryptococcosis is a systemic infection caused by *Cryptococcus neoformans*, which is an ubiquitous yeast with a worldwide distribution. Defects in cell-mediated immunity and HIV infection constitute the major predisposing conditions for disseminated cryptococcal infection (5). Other risk factors for cryptococcal disease include, lympho-reticular malignancy, corticosteroid treatment, sarcoidosis, diabetes mellitus, hepatic cirrhosis and transplantation, which is the second most common risk factor (6, 7). Although attack rate is much higher among immunocompromised persons, cryptococcal disease, even life-threatening infection, can occur in apparently normal individuals (8).

There are two varieties of *Cryptococcus neoformans*; *C. neoformans* var *neoformans* including serotype A and D, and *C. neoformans* var *gatti* including serotype B and C. *C. neoformans* var *neoformans* accounts for most cases of human disease throughout the world and more often affects patients with acquired immunodeficiency syndrome or who were otherwise immunocompromised. In contrast, *C. neoformans* var *gatti* is found mostly in subtropical or tropical areas, largely in Australia and mainly causes disease in immunocompetent host (9-11). Infections caused by *C. neoformans* var *gatti* tend to be associated with cerebral or pulmonary mass lesions and high serum and CSF cryptococcal antigen titers. Despite lower mortality rate, neurologic sequelae are more common after CNS infection caused by *C. neoformans* var *gatti* (11). In our case, no further identification of *C. neoformans* strains was performed, so that we could not clearly document which variety caused the disseminated infection. However, considering that isolation of *C. neoformans* var *gatti* has not been reported before pre-AIDS era and until now in Korea and that geographic distribution of *C. neoformans* var *gatti* is largely confined to tropical and subtropical areas, we thought that *C. neoformans* var *neoformans* might have been the causative agent, although the patient was immunocompetent.

The respiratory tree is the route of entry for *C. neoformans*, so that cryptococcus initially causes pulmonary infection, and then is disseminated to the CNS and every other organs in the body. In a recent review of cryptococcosis in HIV-negative patients, 36% of patients had only pulmonary involvement, 51% had CNS disease, and the rest had other or multiple site involvement (12). In HIV-positive patients, more CNS and extrapulmonary involvement developed (8, 13). Symptoms of pulmonary infection ranged from asymp-

tomatic colonization to life-threatening pneumonia. The most common radiologic finding is single or multiple pulmonary nodules in apparently normal hosts but mass-like infiltrates, hilar lymphadenopathy, pleural effusion, and cavitaiton can occur (2, 6, 8). Most patients with cryptococcal meningitis present with signs and symptoms of subacute meningitis or meningoencephalitis, such as headaches, fever, lethargy, coma or memory loss over 2 to 4 weeks. However, acute manifestations can also occur, more commonly in immunocompromised patients (6, 8, 12, 13). Skin involvement can manifest almost any type of human skin lesions, which are also prominent clues to dissemination even though these skin lesions develop in only 5-10% of patients with cryptococcosis (2, 6). Cervical lymphadenopathy is a rare manifestation of cryptococcosis (6, 8) and only a few cases have been presented in the literatures (14).

There are some reports about isolated pulmonomary or cutaneous crypotococcosis in immunocompetent host (2-4). So far, disseminated cryptococcosis involving multiple lymph nodes, skin, lung, and CNS in adults without underlying predisposing factors has not been reported in Korea.

Isolation of the organism by culture is the definitive diagnosis of cryptococcosis but a negative culture does not exclude this disease. The diagnosis can be made by India ink examination and histopathology of tissue specimen. *C. neoformans* are clearly demarcated by Methenamine siliver or PAS stain and then distinguished from other yeast-like fungi as well as from artifacts by Mayer's mucicarmine stain that stains only the crypotococcal capsule rose red (3, 6, 8). The most commonly used serologic test is the detection for *C. neoformans* capsular antigen using the latex agglutination test or ELISA. Whereas latex agglutination detects antigen in CSF or serum in more than 90% of patients with crypotcoccal meninigitis, serum antigen tests are less often positive in extraneural cryptococcosis (6, 8, 10).

And serum crypotococcal antigen testing is far less reliable for non-HIV infected patients than for HIV-positive patients. Only 56% and 86% of HIV-negative patients with pulmonary and CNS disease are positive for serum cryptococcal antigen respectively, whereas, among HIV-positive patients, almost all with cryptococcosis have positive serum cryptococcal antigen (12, 13). However, false-negative results are rare in case of dissemiated crytpococcosis. These false-negative results may be caused by low titers, early infection, presence of immune complexes, prozone effect of high titers, or poorly encapsulated strains with low production of polysaccharides (8). In this case, diagnosis was definitely proven by the tissue culture of cervical lymph node and histopathologic findings even though results of serum and CSF cryptococcal antigen were negative. The experience of negative cryptococcal antigen in disseminated cryptococcosis indicates the importance of cultural investigation in case of any suspected case of cryptococcosis.

The choice of treatment for disease caused by *C. neoformans* depends on both the anatomic sites of involvement and the host's immune status (15). Several reports recommend careful observation for isolated pulmonary disease in immunocompetent host. However, administration of fluconazole is often effective as primary treatment for uncomplicated disease. Long-term chronic suppression with fluconazole for HIV-negative patients probably should be limited to patients with disorders associated with significant ongoing immunosupression and evidence of persistent disease (2, 14, 15). For those with non-CNS isolated crypotococcemia, a positive serum cryptococcal antigen titer >1 : 8 or urinary tract or cutaneous disease, recommended treatment is oral fluconazole therapy for 3-6 months and careful assessment of the CNS is required to rule out occult meningitis. But, patients with more severe disease, treatment with amphotericin B (0.5-1 mg/kg/d) may be necessary for 6-10 weeks.

Immunocompetent patients with CNS disease can be treated with amphotericin B (0.7-1 mg/kg/d) plus flucytosine (100 mg/kg/d) for 6-10 weeks or alternatively with amphotericin B (0.7-1 mg/kg/d) plus flucytosine (100 mg/kg/d) for 2 weeks, followed by fluconazole (400 mg/day) for 8-10 weeks. Fluconazole consolidation therapy may be continued for as long as 6-12 months, depending on the clinical status of the patient. HIV-negative, immunocompromised hosts should be treated in the same fashion as those with CNS disease, regardless of the site of involvement (12, 15). In this case, the patient was successfully treated with 2 weeks

of systemic amphotericin B plus flucytosine and additional 8 weeks of oral fluconazole. Without long-term fluconazole consolidation therapy, he had no evidence of relapse for 2 years.

Because cryptococcosis is a relatively rare disease in individuals without impaired immunity and rarely manifested by lymphadenopathy, most physicians do not consider disseminated cryptococcosis as a diffenential diagnosis when patients present with cervical lymphedenopathy and fever. However, our expererience showed that not only meningitis and pulmonary involvement but also persient fever and cervical lymphadenopathy can be the first manifestations of cryptocccosis, and widely disseminated cryptococcosis could occur even in an immunocompetent host. We wish our experience would help another patients and physicians in the similar situations.

ABSTRACT

Disseminated cryptococcosis is a systemic infection that occurs most commonly in immunocompromised patients, especially those with human immunodeficiency virus (HIV) infection. Although the attack rate is much higher among immunocompromised patients, cryptococcal disease does occur in persons without any apparent predisposing conditions. A previously healthy 26-year-old man was admitted to the hospital because of persistent fever and cervical lymphadenopathy. Despite empirical antibiotic therapy, he developed cutaneous erythematous papules, generalized lymphadenopathy, miliary pulmonary infiltration, and meningitis successively soon after admission. Biopsy of the skin and the cervical lymph node revealed chronic granuloma with cryptococcal organisms and tissue culture of lymph node confirmed cryptococcal infection. He was treated with intravenous amphotericin B plus flucytosine for 2 weeks, and then with fluconazole for 2 months. After the therapy, there was no evidence of recurrence for 2 years.

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