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First Report of *Cryptococcus Albidus*-Induced Disseminated Cryptococcosis in a Renal Transplant Recipient

Yeon Ah Lee, M.D., Hee Jin Kim, M.D., Tae Won Lee, M.D., Myung Jae Kim, M.D., Mu Hyoung Lee, M.D.*, Ju Hie Lee, M.D.† and Chun Gyoo Ihm, M.D.

Departments of Internal Medicine, Dermatology and Pathology†, School of Medicine, Kyung Hee University, Seoul, Korea*

Cryptococcus albidus, a non-neoformans species of the genus *Cryptococcus*, is generally regarded as a rare cause of disease. There have been only 14 previously reported cases in which this organism has been isolated as a pathogen, none of which occurred in a renal transplant recipient. A 23-year-old renal transplant recipient taking medication consisting of cyclosporine and prednisolone was admitted with a 10-day history of dry cough, fever and progressive dyspnea. The next day, his respiratory status deteriorated dramatically, and he developed acute respiratory distress syndrome (ARDS) and fulminant septic shock. On the eighth hospital day, tender macules on both his shins coalesced to form erythematous patches. *Cryptococcus albidus* was isolated by skin biopsy and tissue culture. We report here the first case of disseminated cryptococcosis caused by *C. albidus* in a renal transplant recipient who had been successfully treated with fluconazole monotherapy.

Key Words : *Cryptococcus albidus*, Fluconazole, Kidney transplantation

INTRODUCTION

Cryptococcosis is a serious opportunistic fungal infection often occurring in immunocompro mised patients[1, 2]. Despite the recognition of several species of the genus, the non-*C. neoformans* including *C. albidus* are generally regarded as non pathogenic saprophytes[3]. Infections due to other species of *Cryptococcus* are extremely rare and poorly substantiated.

There have only been 14 previously reported cases in which *Cyptococcus albidus* has been isolated as a pathogen, none of which occurred in a renal transplant recipient. To the best of our knowledge, this is the first reported case of disseminated cryptococcosis presenting cutaneous infection, septic shock, and acute respiratory distress syndrome (ARDS) caused by *C.albidus* in a renal transplant recipient. Our experience with this case is instructive since it was treated successfully with fluconazole alone despite the serious multiorgan involvement. We have reviewed and compared all known cases of infection with *C. albidus*.

CASE REPORT

A 23-year-old Asian man with chronic renal allograft dysfunction was admitted to our hospital in May 2001 with a 10-day history of fever, intermittent chills, dry cough and progressive dyspnea. He underwent renal transplantation in 1994 for end-stage renal disease of unknown cause diagnosed in 1993. He had been on a medication of cyclosporine 200 mg/day and prednisolne 5~20 mg/day. His temperature was 40℃, blood pressure 120/70 mmHg supine, pulse rate 120/min and respiratory rate 20/min. Respiratory examination revealed mildly decreased breathing sounds on the right lower chest. We also noted several erythematous tender macules measuring 0.5 cm in diameter on both shins. He had no neurological signs of meningitis. Chest radiograph obtained on admission demonstrated increased opacity on the right lower lobe. Arterial blood gas analysis on room air revealed a pH of 7.38, $PaCO_2$ 22.1 mmHg, PaO_2 49.4 mmHg, and SaO2 85.3%. A complete blood count yielded a leukocyte count of 5,600/mm (91.6% neutrophils), hemoglobin 5.6 g/dL, and platelet count

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• Correspondence to : Chun Gyoo Ihm, M.D., Department of Internal Medicine, Kyung Hee University Hospital, 1, Hoegi-dong, Dongdaemoon-gu, Seoul, 130-702, Korea Tel : 82-2-958-8200, Fax : 82-2-968-1848, E-mail : aprildaum@hanmail.net

267,000/mm^3. The renal allograft function was in acute exacerbation on chronic dysfunction; BUN 113 mg/dL, Cr 8.5 mg/dL, Na 125 mmol/L, K 6.4 mmol/L, protein 5.2 g/dL, albumin 2.9 g/dL, glucose 102 mg/dL. The patient had been treated with empirical antibiotics for the presumed diagnosis of severe community-acquired pneumonia. On the next day, his respiratory status deteriorated dramatically with a rapid development of hypotension. A repeat chest radiograph showed nearly complete opacification of both lung fields (Figure 1). The patient was intubated and placed on mechanical ventilation. Dobutamine and dopamine were administered. Urgent anti-CMV IgM, CMV PCR and anti-HIV were negative. Anti-mycoplasma antibody titer was <1:20. Acid-fast bacillus smear and methenamine silver stain of sputum yielded negative results. The initial three sputum and blood cultures were sterile. On the eighth hospital day, tender macules on both shins coalesced to form erythematous patches. Skin biopsy showed granulomatous inflammation in the dermis and numerous yeast organisms with clear thick capsules (Figure 2). The cerebrospinal fluid (CSF) exam was clear with normal glucose and slightly increased protein (95 mg/dL). The cryptococcal antigen titer was elevated in CSF at >1:256 and at >1:516 in serum. However, the microscopic examination of CSF preparations with India ink was negative for encapsulated yeasts and CSF cultures were negative. The culture of skin biopsy isolated a yeast organism, which was identified as *Cryptococcus albidus* by characteristic morphology, fermentation, and carbon assimilation tests using the API 20c AUX system (bioMérieu, Marcy-l'Etoile, France). The patient was treated intravenously with fluconazole immediately after the skin biopsy. After 10 days of fluconazole therapy, his chest radiograph and CT scan showed marked clearing with only one cavitary nodular lesion on the left upper lobe (Figure 3). Percutaneous needle aspiration was performed for the left upper pulmonary nodule. Cytologic examination of the aspirates also revealed a typical morphology of the numerous cryptococci (Figure 4). The patient was discharged on an oral regimen of fluconazole (200 mg/day). Fluconazole maintenance therapy was continued for 12 months on a long-term basis for prevention of cryptococcosis. At the time of the most recent follow-up, July 2002, his chest radiograph was stable and we detected no evidence of recurrent cryptococcal infection.

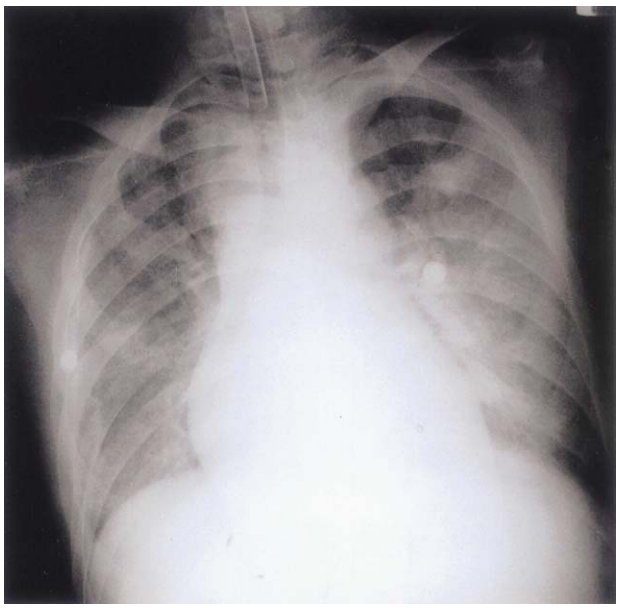

Figure 1. Chest X-ray on second hospital day, shows rapidly aggravated bilateral airspace consolidation.

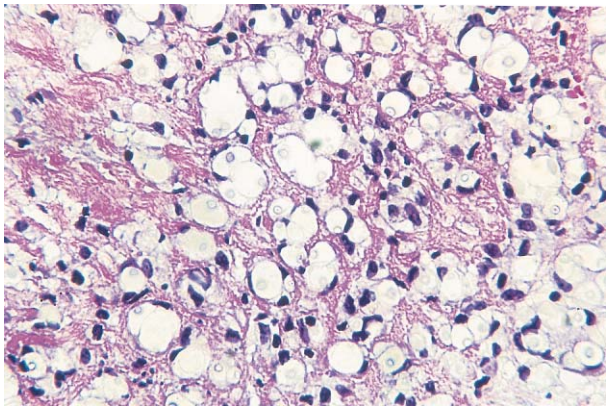

Figure 2. Skin biopsy showing numerous encapsulated yeast-like organisms surrounded by large clear spaces and inflammatory cells consisting of lymphoid cells in subcutis (H&E stain, ×400).

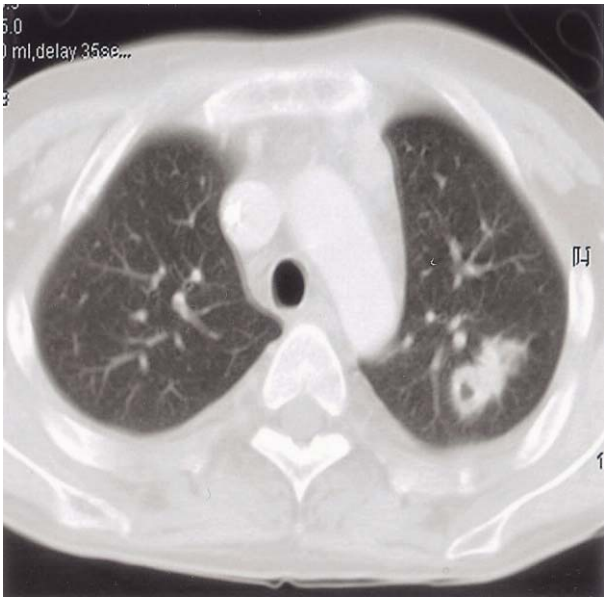

Figure 3. Chest CT showed a irregular, spiculated nodule with cavity at the apicoposterior segment of the left upper lobe.

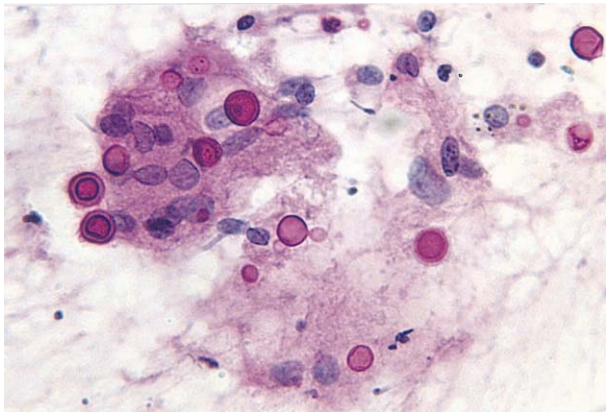

Figure 4. High power microscopic finding of fine needle aspiration specimen of the pulmonary nodule shows scattered round to ovoid cryptococcus with polysaccharide capsules and occasional budding with inflammatory cells consisting of histiocytes and a few giant cells (PAS stain, ×400).

DISCUSSION

Cryptococcosis has been the most common cause of life-threatening opportunistic fungal infection among immunocompromised patients, and its incidence ranges between 8% and 10% in HIV-infected patients and between 1% and 5% in organ transplant recipients[2].

Cryptococus albidus is traditionally considered a non- pathogenic yeast. There have been only 14 previously reported cases of systemic disease in which this opportunistic organism was isolated and implicated as a pathogen: 6 cases of meningitis, 5 cases of fungaemia, 1 case of peumonitis, 1 case of pleural infection, 1 case of direct skin infection (Table 1). However, *C.albidus* has never before been reported as a disseminated form of cryptococcocal infection nor as a pathogen in a renal transplant recipient. Septic shock is a very uncommon complication of this infection, with two cases having been reported previously, only in disseminated cryptococcosis caused by *Cryptococcus neoformans*[1]. Disseminated cryptococcosis has a mortality rate higher than 80% when associated with respiratory failure. Recent reports have highlighted diagnostic delay as a major factor contributing to its high associated mortality[4].

In this case, cryptococcal antigenic titer was considerably high in serum and CSF despite the isolation of *C.albidus*. Although *C. albidus* shares many biochemical characteristics and so\me capsular antigens with *C.neoformans,* the cryptococcal antigen latex agglutination testing has been reported to yield negative results in many cases of *C. albidus* infection[5]. The definitive diagnosis thus rests on India ink staining, fungal culture and identification by routine biochemical test to confirm the presence or absence of this organism[6, 7]. However, Miyagawa et al. have previously observed that most of the anti-*C.neoformans* IFA antibody in serum was absorbed with *C. albidus*, and vice versa[8]. *C.albidus* strains have their cell surface antigenic factors are identical to those of *C.neoformans* serotype A, with no more specific antigens in addition to the antigens shared with the latter[8].

We performed percutaneous needle aspiration of the pulmonary nodule to prove *C.albidus* to be the pathogen causing both the lung lesion as well as skin infection. However, isolation of *C.albidus* with specimen culture was not able to be performed due to a laboratory fault. We could only identify numerous cryptococcus on slides with pulmonary aspirate. Thus, there is both possibility of the coinfection of *C.neoformans* with *C.albidus* and isolated *C.albidus* infection, which cause cryptococcal antigen titers to increase. ARDS developed in this patient might be secondary to sepsis but fungal invasion into the lung tissue was identified by percutaneous needle aspiration cytology.

To date, the mainstay of treatment for systemic cryptococcosis is known to be a combination therapy of intravenous amphotericin B with or without flucytosine followed by fluconazole[9]. Immunocompromised patients, such as solid organ transplantation recipients, require more prolonged therapy. Moreover, recent evidences support the necessity for life-long maintenance therapy of fluconazole given indefinitely for secondary prophylaxis since there is more than a 50% relapse rate after an apparently successful treatment of both meningeal and extrameningeal diseases[10]. However, the administration of amphotericin B frequently results in the rapid onset of renal dysfunction, necessitating dosage reduction or discontinuation of therapy. Renal transplant recipients are particularly susceptible to the nephrotoxicity of amphotericin B since its concomitant use with cyclosprin or taclolimus can precipitate renal failure[2]. Most of the previous 14 patients with *C.albidus* infection, including 5 of the 9 survivors, were treated with amphotericin B. The patients treated with other regimens also survived, including 1 patient with oral ketoconazole, 1 patient with oral azithromycin and paromycin and 2 patients with fluconazole. There has been a report on the successful therapy of *C.albidus* septicaemia in a HIV patient with oral fluconazole monotherapy[11]. Fluconazole seems to be substitutable for amphotericin B as an initial antifungal agent for cryptococcosis. Given our success in this anecdotal case, fluconazole monotherapy warrants study in future controlled trials for the treatment of disseminated cryptococcosis by non- *neoformans* species in transplant recipients.

This case emphasizes the importance of considering unusual emerging cryptococcal as well as other fungal infections and suggests that *C.albidus* must be added to the increasing number of recently described causative agents of fungal infections in critically ill immunocompromi-sed patients such as transplant recipients.

Table 1. Feature of the 14 Known Cases of *Cryptococcus albidus* infection

Patient (Year)	age	sex	Associated Diseases	Infection Site	Duration Of Symptoms	Treatment	Outcome
1 (1965)	75	M	Psychiatric history, cerebral contusion, lung cancer on autopsy	Cerebrospinal fluid	1 month	None	Death: organism grew postmortem
2 (1968)	73	F	Polycythemia vera	Cerebrospinal fluid	5 days	None	Death: organism grew postmortem
3 (1970)	48	M	None; glioblastoma of the basal ganglia later developed	Cerebrospinal fluid	Unknown	None	Survived
4 (1970)	68	M	Cigarette smoker (50-100 pack-years) poor dentition	Lung	6 months	Amphotericin B (1.0 g)	Survived
5 (1971)	45	M	Air conditioner repair-man, exposure to pigeons	Cerebrospinal fluid	3 days	Amphotericin B (1.5 g)	Survived
6 (1971)	20	M	Psychiatric illness, neurologic illness	Cerebrospinal fluid	>20 months	None	Survived
7 (1978)	29	M	Mentally retarded, Juvenile rheumatoid arthritis, corticosteroids, alcoholic liver disease, Arteriovenous malformation of cerebellar artery	Cerebrospinal fluid	36 days after repair of arteriovenous malformation	Amphotericin B (unkown total dose)	Death 18 days into Therapy
8 (1987)	65	F	Acute myelogenous leukemia with severe neutropenia	Blood	5 days	Amphotericin B (235 mg), Flucytosine (150 mg/kg/day for 7 days)	Death 11 days into Therapy
9 (1987)	45	M	Pemphigus foliaceus, corticosteroids, cyclophosphamide	Blood	Unknown	Oral ketoconazole (unknown total dose)	Survived
10 (1989)	37	M	End-stage renal disease, hemodialysis,coinfection with mucormycosis	Pleural fluid	3 weeks	Amphotericin B (1.9 g)	Survived
11 (1993)	40	M	AIDS, complicated by pneumocyctis carinii infection,CMV retinitis	Blood	2 weeks	Oral fluconazole	Survived but died later due to recurrence
12 (1996)	47	F	AIDS, complicated by CNS toxoplasmosis, MDS	Blood	20 days	Amphotericin B and flucytosine	Death 14 days into therapy
13 (1998)	4	F	Acute lymphocytic leukemia, coinfection with pulmonary cryptosporidiosis	Blood	unknown	Oral azithromycin and paromycin	Survived
14 (1998)	70	M	Szary syndrome, methotrexate type II DM, hypertension	skin	unknown	Oral fluconazole (1.6 g)	Healed 4 weeks into therapy

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