INTERNAL MEDICINE

Concurrent Subcutaneous Candidal Abscesses and Pulmonary Cryptococcosis in a Patient with Diabetes Mellitus and a History of Corticosteroid Therapy

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Abstract

A 50-year-old man with a history of long-term corticosteroid treatment following adrenalectomy for Cushing's syndrome and uncontrolled diabetes mellitus was admitted for an examination of an abnormal thoracic shadow. Cryptococcal serum antigens were positive, and the histopathology of a lung biopsy showed encapsulated yeast resembling *Cryptococcus neoformans*. On admission, the serum β-D-glucan level was approximately twice the cutoff value, several nodules were observed on both legs and magnetic resonance imaging revealed subcutaneous abscesses. *Candida albicans* was identified from needle aspirates, and the patient was successfully treated with fluconazole and flucytosine. We herein report the first case of concurrent *C. albicans* skin abscesses and pulmonary cryptococcosis.

Key words: subcutaneous candidal abscess, pulmonary cryptococcosis, serum 1,3-β-D-glucan

Introduction

Cryptococcus neoformans is a ubiquitous, encapsulated, yeast-like fungus found worldwide, particularly in soils that are contaminated with pigeon droppings and decaying wood. Pulmonary cryptococcosis is caused by the inhalation of *Cr. neoformans* into the lungs, with subsequent hematogenous dissemination that may induce central nervous system infection. Although pulmonary cryptococcosis can occur in both healthy individuals and immunocompromised patients, it is frequently recognized as an opportunistic pathogen, particularly in patients with lymphohematological disorders, those

receiving steroids or immunosuppressants and those with acquired immunodeficiency syndrome (AIDS) (1, 2). Another *Cryptococcus* subspecies, *Cr. gattii* has been cultured from river red gum trees (*Eucalyptus camaldulensis*) and forest red gum trees (*Eucalyptus tereticornis*) in Australia (3, 4). In addition, an outbreak of *Cr. gattii* infection was reported in Vancouver Island, British Columbia in 1999 (5).

Candida albicans is the most common cause of candidiasis; however, there has been an increase in the isolation of non-albicans *Candida* species (i.e., *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei*) in recent years (6, 7).
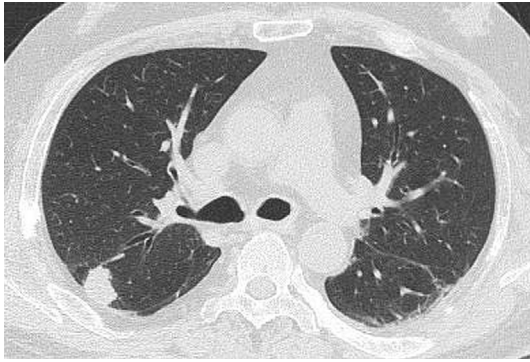
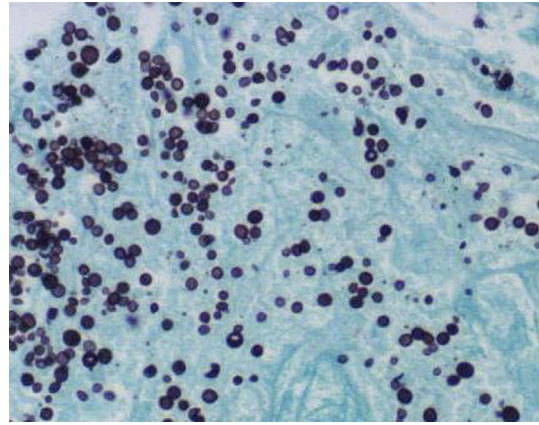The clinical manifestations of candidiasis range from local mucosal membrane infection to widespread dissemina-

Figure 1. Thoracic computed tomography (CT) image obtained on admission showing a solitary well-defined, pleural-based nodule in the right S2 region. No pleural effusion or cavitation were observed.

Figure 2. A histopathological examination of a lung biopsy specimen. Gomori's methenamine-silver stain showing encapsulated yeast forms that resemble *Cr. neoformans* (Magnification, ×400).

tion. Local overgrowth on mucous membranes (oropharyngeal involvement or vaginitis) is often observed in patients with changes in normal flora or deficiencies in cell-mediated immunity, as in AIDS. Invasive focal infections, such as pyelonephritis, endocarditis and meningitis, most often occur following hematogenous spread or in patients with anatomic abnormalities or implanted medical devices (e.g., prosthetic heart valves or central nervous system shunts). Widespread visceral dissemination occurs in patients with neutropenia when *Candida* species gain access to the bloodstream, and candidal infections can occur in various locations throughout the body; however, subcutaneous candidal abscess formation is very rare, even in immunocompromised patients. Some cases of subcutaneous candidal abscesses have been reported in patients with skin breakdown, such as that due to bacterial cellulitis or abscess formation, trauma, parenteral substance abuse, iatrogenic procedures or central venous catheter insertion (8).

This report describes the first reported instance of co-infection with *C. albicans* and *Cr. neoformans* in a patient without human immunodeficiency virus (HIV)/AIDS infection and speculates an association with diabetes mellitus and steroid therapy.

Case Report

A 50-year-old man with type II diabetes (undergoing insulin treatment), hypertension and a herniated lumbar disc was diagnosed with Cushing's syndrome. Right adrenalectomy was performed two months before the described hospital admission, and daily corticosteroid replacement therapy (40 mg/day of hydrocortisone, 0.5 mg/day of dexamethasone) was initiated. The patient had not received any antifungal or antimicrobial prophylaxis since the adrenalectomy. He was admitted to a local hospital due to lower leg palsy, suggesting exacerbation of the herniated lumbar disc. Chest radiography revealed a pulmonary nodule in the right upper field of the lung, and he was transferred to our hospital for a further examination.

On admission, a physical examination revealed full moon face, centripetal obesity and mild pretibial pitting edema. No abnormal respiratory sounds were heard in either lung field, and no heart murmurs were audible. An abdominal examination showed abdominal striae, and a neurological examination revealed no nuchal rigidity, cranial nerve deficits or papilledema. The patient's tendon reflexes were normal without pathological reflexes; however, proximal muscle weakness was observed. His body temperature was 37.0℃, his blood pressure was 140/91 mmHg and his heart rate was 90 beats/min. The results of laboratory tests were as follows: leukocyte count, 13,200/mm^3 (82% polymorphonuclear leukocytes); hemoglobin level, 8.7 g/dL; hematocrit concentration, 30.8%; serum Fe level, 42 μg/dL (suggesting iron deficiency anemia); platelet count, 645,000/mm^3; urea level, 11 mg/dL; creatinine level, 0.63 mg/dL; total protein level, 6.4 g/dL; albumin level, 3.8 g/dL; and C-reactive protein level, 0.10 mg/dL. The CD4 count was 533/μL. The fasting blood sugar level and HgbA1c concentration (Japan Diabetes Society) were 146 mg/dL and 7.7%, respectively, suggesting poorly controlled diabetes mellitus. Regarding blood gases, the PaO$_2$ and PaCO$_2$ values were 59.2 and 50.7 mmHg on room air, respectively. The cortisol level was 1.4 μg/dL, and the adrenocorticotropic hormone level was <5 pg/mL. A serum cryptococcal antigen test was positive, with a titer of 1:8 (Serodirect® "Eiken" Cryptococcus, Eiken Co., Tokyo, Japan), and the serum β-D-glucan level was 43.7 pg/mL (cutoff, <20 pg/mL; Fungitec G test, Seikagaku Kogyo, Tokyo, Japan). An HIV test was negative.

Thoracic computed tomography (CT) showed an 18-mm solitary, well-defined nodule in the right S2 region (Fig. 1). In order to examine the pulmonary nodule, a CT-guided biopsy was performed, followed by a histopathological examination of the lung biopsy specimen using Gomori's methenamine-silver stain, which showed encapsulated yeast forms that resemble *Cr. neoformans* (Fig. 2). Although the patient had no headaches or nuchal rigidity, lumbar puncture
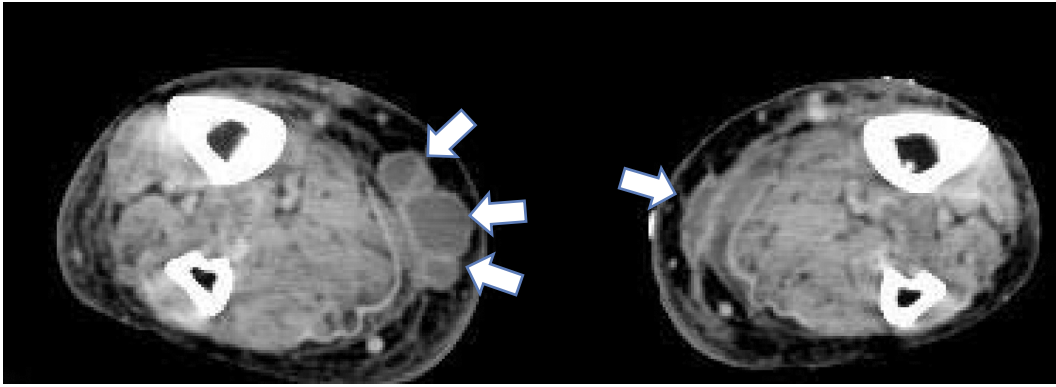
Figure 3. T1-weighted magnetic resonance image showing a well-demarcated collection of fluid in the soft tissue of both lower legs (arrows), suggesting a subcutaneous abscess.
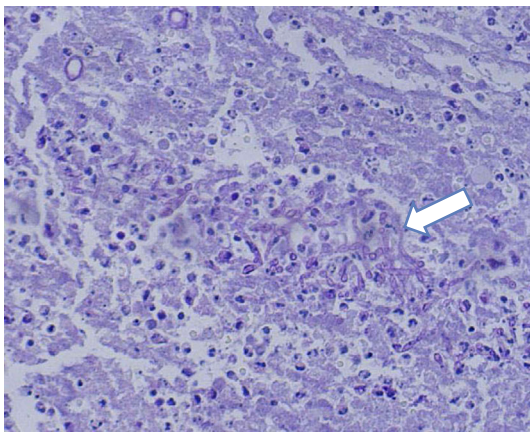
Figure 4. A histopathological examination of the needle aspirate of a lower extremity abscess. Periodic acid-Schiff stain showing yeast and hyphal forms (arrow) of the fungus (Magnification, ×400).

was performed to confirm the diagnosis of cryptococcal meningoencephalitis. However, a cerebrospinal fluid cryptococcal antigen test was negative, the total nucleated cell count was not elevated and no *Cr. neoformans* was cultured. The patient was consequently diagnosed with pulmonary cryptococcosis based on the positive cryptococcal antigen test and pulmonary histopathological findings.

The patient subsequently developed several firm subcutaneous nodules on both lower legs. The nodules each measured approximately 1.0 cm in diameter and were reddish, movable and warm. A T1-weighted magnetic resonance image revealed a rounded fluid-collection signal in the soft tissue of the legs, suggesting a subcutaneous abscess formation (Fig. 3). The image showed no evidence of osteomyelitis. Needle aspiration was performed, and a histopathological examination using periodic acid-Schiff stain showed both the yeast and hyphal forms of the fungus (Fig. 4). *C. albicans* was successfully cultured from the aspirate. No bacteria were isolated from aerobic or anaerobic cultures, and a blood culture was negative. Diabetic retinopathy, without candidal endophthalmitis, was observed. No other signs of

candidal infection (i.e., of the oral cavity, esophagus, nails or gastrointestinal tract) were observed.

The minimum inhibitory concentration (MIC) of the isolated *C. albicans* revealed that the pathogen was susceptible to all antifungals tested: voriconazole, 0.015; amphotericin B (AMPH-B), 0.125; flucytosine (5-FC), 0.25; fluconazole (FLCZ), 0.125; itraconazole, 0.03; and micafungin, 0.03 mg/mL. Therefore, the patient was treated with FLCZ (400 mg/day) and 5-FC (8 g/day) for both fungal infections, and drainage of the subcutaneous abscesses was performed.
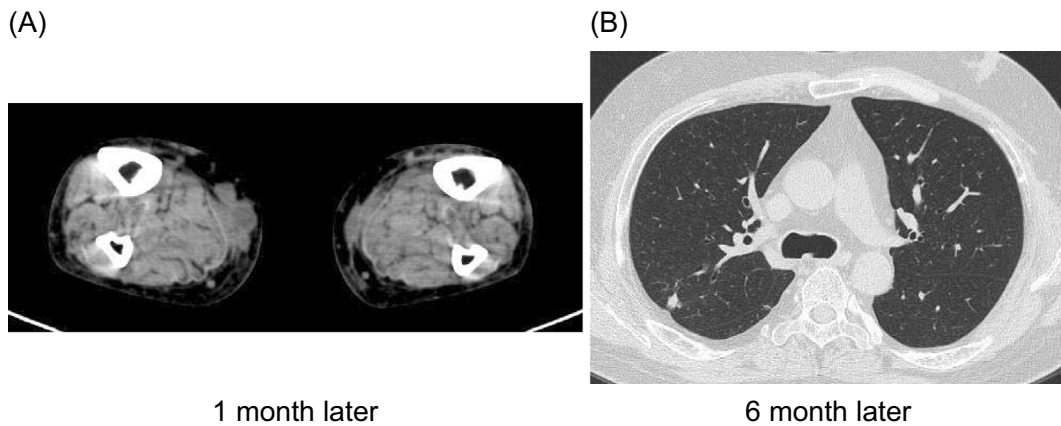
One month after the start of antifungal treatment, the size of the pulmonary cryptococcal nodule had generally decreased on thoracic CT, and the subcutaneous candidal abscesses had improved on lower extremity CT (Fig. 5A). In addition, the serum β-D-glucan level decreased to 19.6 and 27.1 ng/mL after one and three months, respectively.

Following a three-month course of FLCZ and 5-FC treatment, renal dysfunction was observed; therefore, both antifungals were stopped for a three-week period. Thereafter, only FLCZ was continued for a total of six months for treatment of pulmonary cryptococcosis according to the recommendations of the Japanese Mycology Study Group guidelines for patients with underlying disease (9). The titer of cryptococcal antigens gradually decreased over five months. After six months, the cryptococcal antigen test became negative and the pulmonary nodule reduced in size on thoracic CT (Fig. 5B).

The patient is currently receiving daily corticosteroid replacement therapy (5 mg/day of hydrocortisone and 0.5 mg/day of dexamethasone) without antifungal treatment. Periodic follow-up observations have revealed no trends towards relapse.

Discussion

Subcutaneous candidal abscesses are very rare, even in immunocompromised patients (10). However, cases of such lesions have been reported in patients with skin breakdown, such as that due to bacterial cellulitis or abscess formation, iatrogenic procedures, trauma or parenteral substance

(A)

(B)

1 month later

6 month later

Figure 5.   **Antifungal therapy reduced the size of the patient's leg skin abscesses and lung nodule. (A) A leg CT image obtained one month after the initiation of antifungal therapy showing a reduction in the size of the skin abscesses. (B) A thoracic CT image obtained six months after the start of antifungal therapy showing a 5-mm (reduced from 18 mm) nodule in the right S2 region.**

abuse (11-16).

Many risk factors for the development of candidal infection have been recognized, including immunosuppression, corticosteroid use, chemotherapy, prolonged neutropenia, broad-spectrum antibiotic use, indwelling central catheter placement, hyperalimentation, dialysis, abdominal surgery disrupting the integrity of the bowel mucosa, intravenous drug use, prosthetic intravascular implantation, severe burns and *Candida* spp. colonization (17, 18). Florescu et al. reviewed the risk factors associated with the development of subcutaneous candidal abscesses and found that these factors included indwelling central venous (CV) and intravenous catheter placement, antibiotic use, diabetes mellitus, gastrointestinal surgery, hyperalimentation, immunosuppression due to corticosteroid therapy or AIDS and *Candida* spp. colonization (19). In the present case, the patient had several of the above mentioned factors, i.e., uncontrolled diabetes mellitus and corticosteroid use, due to which, he was at risk of candidal abscess infection. Several firm subcutaneous nodules were observed on both lower legs. However, no apparent injuries or scars were noted. Lower extremity CT showed subcutaneous abscesses on both legs, suggesting that *Candida* had disseminated via the bloodstream. Sites of intravenous catheter placement and the gastrointestinal tract are major portals of entry for systemic *Candida* infection. However, the patient did not have a CV catheter for a long period. Therefore, the gastrointestinal tract may have been the portal of entry in this case.

Although cryptococcal infection can develop in individuals with normal immunity, it most commonly occurs in immunocompromised hosts. Cell-mediated immunodeficiency is an important underlying condition of cryptococcal infection. Predisposing factors include AIDS and other causes of impaired T cell-mediated immunity, e.g., transplant-related immunosuppression, hematological malignancies, corticosteroid administration and diabetes mellitus (20-23). Prolonged, high-dose corticosteroid use (i.e., 20 mg/day) is re-

ported to be an independent factor for disseminated disease (24). In the present case, uncontrolled diabetes and corticosteroid use were co-factors of pulmonary cryptococcosis and candidal skin abscess formation.

Neutrophil chemotaxis and adherence to the vascular endothelium, phagocytosis, intracellular bactericidal activity, opsonization and cell-mediated immunity are all depressed in diabetes patients with hyperglycemia (25, 26). In addition, glucose-inducible proteins promote the adhesion of *C. albicans* to buccal or vaginal epithelium, which impairs phagocytosis, giving the organism an advantage over the host (27). Glucocorticoid administration also results in neutrophilic leukocytosis accompanied by dramatic reductions in circulating eosinophils, monocytes and lymphocytes (28). In the present case, CD4 lymphopenia was observed without HIV infection. CD4 lymphopenia is thought to be related to impaired T-cell-mediated immunity, resulting in disseminated candidiasis and cryptococcosis.

Little is known about other risk factors for the development of co-infection. TNF-α and interleukin (IL)-17 may be key factors for co-infection. TNF-α is a factor for the reduction of the pathogenic burden of *C. albicans* in animals (29, 30). In contrast, cryptococcal infection is reported to inhibit TNF-α production (31). Furthermore, cryptococcal infection may exacerbate candidiasis.

IL-17 is a proinflammatory cytokine produced by a subset of CD4 T-cells, termed Th17 cells. Increased IL-17 production is associated with a reduced cryptococcal burden, suggesting that IL-17 plays a significant role in the generation of a protective anti-cryptococcal immune response. In contrast, *C. albicans* is reported to dampen the host defense by downregulating IL-17 production (32). Candidal infection may alter cellular immunity and is recognized to be a predisposing factor for developing cryptococcosis. Altered host immunity may explain why cryptococcosis and candidiasis developed in this patient without HIV infection.

During a 35-year period at Nagasaki University hospital

and its affiliates, the diagnosis of pulmonary cryptococcosis was confirmed in 151 patients. Of these patients, only the present subject exhibited pulmonary cryptococcosis and candidal skin abscess co-infection (0.66%, unpublished data).

Approximately two decades have passed since the introduction of the serum β-D-glucan assay for the clinical diagnosis of deep-seated mycosis in Japan (33). The assay is now widely accepted in Japan and other countries as an indispensable tool for managing febrile episodes in immuno-compromised hosts. In addition, its use is included in the guidelines for the diagnosis and treatment of deep-seated mycosis (9, 34, 35). The presence of β-D-glucan in the serum signifies the presence of fungal invasion; however, the results are not specific for *Candida* species (36). False-positive findings can occur for a variety of reasons, including the use of glucan-contaminated blood collection tubes, gauze and depth-type membrane filters for blood processing, as well as *in vitro* tests using various antibiotics (e.g., some cephalosporins, carbapenems and ampicillin-sulbactam) (34, 37). Therefore, a serum β-D-glucan level exceeding the cutoff value even slightly may indicate the absence of deep-seated mycoses. A high serum β-D-glucan level is associated with cryptococcal meningitis (38) and cryptococcemia (39). The present patient was diagnosed with pulmonary cryptococcosis in addition to a moderate immunosuppressive state. A lumbar puncture did not reveal cryptococcal meningoencephalitis, and no microorganisms were cultured from his blood. On admission, the serum β-D-glucan level was approximately twice the cutoff value. Therefore, we interpreted this to be a false-positive result. However, a cautious medical examination revealed that he had candidal skin abscess co-infection.

Cryptococcus was not cultured in this case; therefore, we were unable to perform antifungal susceptibility tests for *Cryptococcus* isolates. It is difficult to distinguish between *Cr. neoformans* and *Cr. gattii* infections based on the results of histopathological examinations. Nevertheless, the first case report of a patient in Japan infected with *Cr. gattii* genotype VGIIa noted that the patient had no recent history of travel to any disease endemic areas (40), suggesting that the virulent strain may have spread to regions outside North America. *Cr. gattii* is generally geographically restricted. Furthermore, among cryptococcal infections in Japan, *Cr. neoformans* (serotype A) is the most common, with a frequency exceeding 95% (41). In addition, no azole-resistant *Cr. neoformans* isolates have been detected, even in the latest reports (42).

The *C. albicans* isolated from this patient was found to be susceptible to all antifungals tested. In the updated practical guidelines for the management of candidiasis issued by the Infection Disease Society of America, treatment with FLCZ or echinocandin is recommended for candidemia in patients with neutropenia as the initial therapy (43). The administration of a combination of the lipid formulation AMPH-B (LFAmB) or AMPH-B deoxycholate with 5-FC is recommended in cases of central nervous system (CNS) candidiasis, candidal endophthalmitis, candidal infection of the cardiovascular system, endocarditis and others (43). We chose the combination of FLCZ and 5-FC as the initial antifungal therapy in the present case based on the antifungal activity against both *Cr. neoformans* and *C. albicans* infection (44, 45). On the other hand, if a non-albicans *Candida* species e.g., *C. glabrata* or *C. krusei*, had been identified, these antifungal agents would have been changed to LFAmB. However, the patient's treatment was successful, as originally prescribed.

In conclusion, we herein reported, to the best of our knowledge, the first published case of pulmonary cryptococcosis and candidal skin abscess co-infection in an immuno-compromised patient.

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