INTERNAL MEDICINE

CASE REPORT

Three Cases of Concurrent Infection with *Mycobacterium tuberculosis* and *Cryptococcus neoformans*

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Abstract

Impaired cellular-mediated immunity is a known risk factor for both tuberculosis and cryptococcosis. However, pulmonary cryptococcosis associated with pulmonary tuberculosis is rare. We herein describe three cases of concurrent infection with *Mycobacterium tuberculosis* and *Cryptococcus neoformans*. All patients had underlying diseases; all three had uncontrolled diabetes mellitus, and other underlying diseases were liver cirrhosis, malignancy, and rheumatoid arthritis requiring long-term steroid use. We also review other relevant reports.

Key words: pulmonary cryptococcosis, pulmonary tuberculosis, co-infection

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Introduction

Impaired cellular-mediated immunity is a known risk factor for both tuberculosis and cryptococcosis. However, only a handful of cases of pulmonary cryptococcosis associated with pulmonary tuberculosis have been reported (1-5). We herein report three cases of tuberculosis and cryptococcosis co-infection in patients treated at Nagasaki University Hospital and also carry out a review of other relevant reports.

Case Reports

Case 1

A 65-year-old woman with type II diabetes that had remained untreated for an extended duration was admitted to a local hospital with appetite loss, general fatigue of seven days' duration, and severe dyspnea of two days' duration. Chest radiography revealed a left pneumothorax, small bilateral granular shadows, and consolidation with a cavity in the left upper field. We immediately performed drainage of the thoracic cavity. Nodular shadows with cavities and diffuse small opacities were seen on thoracic computed tomography (CT) (Fig. 1). She was transferred to our hospital the next day. She did not have a past history of any evident exposure to tuberculosis.

Her physical state on examination revealed malnutrition. Her body temperature was 38.0°C, her blood pressure was 122/64 mmHg, her heart rate was 92/min, and she had mild pretibial pitting edema. Moist rales were heard in both lung fields, but no heart murmur was audible. The patient's abdominal examination was normal, and the neurological examination revealed no nuchal rigidity, cranial nerve deficit, or papilledema. Her tendon reflexes were normal without any pathological reflexes.

Laboratory studies showed severe inflammation: her white blood cell (WBC) count was 6,000/μL with a neutrophil

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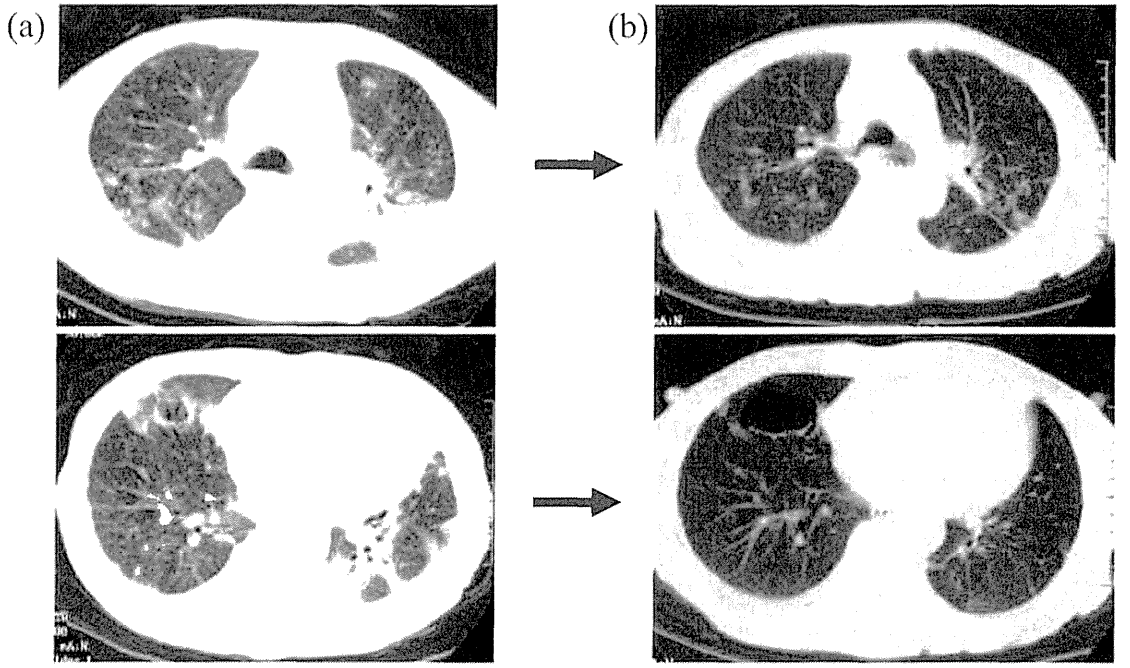

Figure 1. Thoracic CT images of case one. (a) on admission and (b) on day 120 after admission.

count of 96%, and her C-reactive protein level (CRP) was 30.35 mg/dL. Her erythrocyte sedimentation rate (ESR) was 86 mm/h. Blood chemistry data revealed a low protein level (5.2 g/dL), a low albumin level (2.5 g/dL), and a low cholinesterase level (72 IU/L; normal range 200-450 IU/L), suggesting nutritional deficiency. Fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) levels were 387 mg/dL and 13.6%, respectively, suggesting poorly controlled diabetes mellitus. The QuantiFERON test (QFT) and human immunodeficiency virus (HIV) screening test were not performed. A blood gas analysis showed a PaO_2 of 63.5 mmHg and a $PaCO_2$ of 49.4 mmHg under 6 L/min O_2 through a mask.

Acid-fast staining of her sputum revealed a few beaded bacilli (Gaffky 7). Polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* was positive. She was diagnosed with pulmonary tuberculosis, and antituberculosis chemotherapy was initiated, consisting of isoniazid (INH) 400 mg/day, rifampicin (RFP) 450 mg/day, pyrazinamide (PZA) 1.2 g/day, and streptomycin (SM) 0.75 g every day for two weeks, then three times a week thereafter. *M. tuberculosis* was not detected in her bone marrow, urine, or blood. Although her chest radiography findings improved and her sputum culture became *M. tuberculosis*-negative, a low-grade fever and headache persisted. Therefore, meropenem was concurrently administered under a tentative diagnosis of double-bacterial infection. One month after the start of administration, inflammatory response was improved (CRP: 1.85 mg/dL). With respect to the secondary pneumothorax, the trocar catheter was removed.

Approximately 50 days after admission, she exhibited a low-grade fever of between 37 and 37.8°C. Her serum cryptococcal antigen titer was positive at 1:32 (Serodirect® 'Eiken' Cryptococcus, Eiken Co., Tokyo, Japan). She complained of a headache, but no nuchal rigidity was observed. Lumbar puncture was performed, and cerebrospinal fluid (CSF) cryptococcal antigen was positive at a titer of 1:8. However, the total nucleated cell count was not increased, and *Cryptococcus neoformans* was not isolated.

Thereafter, a thoracic CT revealed a new shadow in the right S1a region, and a bronchoscopy was performed; however, no pathogenic bacteria were detected. On day 90 after admission, the patient's fever returned, and her level of consciousness deteriorated. A neurological examination revealed nuchal rigidity.

A second lumbar puncture was performed to rule out meningitis, and her CSF cryptococcal antigen was positive at a titer of 1:512. Examination of her CSF showed a total nucleated cell count of 250/3 per mm^3 with 80% mononuclear cells. An India ink mount of CSF revealed a few encapsulated yeast cells, which was suggestive of *C. neoformans*. Therefore, we diagnosed pulmonary tuberculosis co-infection with cryptococcal meningoencephalitis.

The patient was started on combination therapy with amphotericin B deoxycholate (AMPH-B) (0.1 mg/kg/day during the first day of therapy, 0.5 mg/kg/day from the second day, and continuation with 1.0 mg/kg/day) and fluconazole (FLCZ) (400 mg/day). Thereafter, her consciousness level transiently improved, and pyretolysis was observed. Approximately two months later, the number of cells in her CSF had normalized. As a result, the antifungal agents were therefore discontinued (Fig. 2).

However, on day 100 after admission, aspiration pneumonia, pyelonephritis, *Pseudomonas aeruginosa*-related sepsis,

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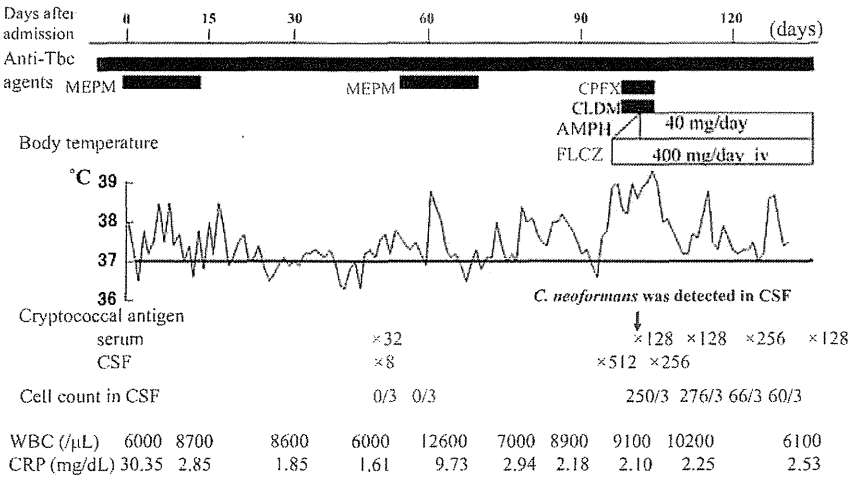

Figure 2. Clinical course of case 1. Tbc: tuberculosis, MEPM: meropenem, CPFX: ciprofloxacin, CLDM: clindamycin, AMPH: amphotericin, FLCZ: fluconazole, iv: intravenous, CSF: cerebrospinal fluid, WBC: white blood cell, CRP: C-reactive protein

pneumonia, and herpes zoster developed. On day 175 after admission, fever, deterioration of respiratory condition, and kidney/liver dysfunction appeared. On day 180 after admission, the patient died of respiratory failure due to aspiration pneumonia, although she had been provided with mechanical ventilation for a few days. An autopsy did not detect any *C. neoformans* in the lungs or other organs.

Case 2

Case 2 was a 56-year-old man with a 10-year history of hypertension, type II diabetes, and liver cirrhosis (hepatitis C). Although he had no respiratory symptoms, multiple nodular opacities were found in both upper lung fields on a routine follow-up chest radiograph. Because a serum cryptococcal antigen test was positive at a titer of 1:4, he was transferred to our hospital. He did not have a past history of tuberculosis, but his mother had died of pulmonary tuberculosis.

On admission, no abnormal breath sounds were detected and no heart murmur was audible. An abdominal examination detected hepatomegaly with an irregular surface that elastic-hard on palpation. The neurological examination results were not remarkable. No nuchal rigidity was observed. His body temperature was 35.6°C.

The patient's laboratory studies showed a WBC count of 7,900/μL with a neutrophil count of 85%, a red blood cell (RBC) count of 376×10^4/μL, and a blood platelet count of 8.6×10^4/μL. His CRP level was 0.48 mg/dL, and ESR was 65 mm/h. Blood chemistry data revealed a low protein level (6.2 g/dL), a low albumin level (2.8 g/dL), and a prothrombin time international normalized ratio (PT-INR) of 1.10. The patient was positive for hepatitis C virus antibody. His FBS and HbA1c levels were 174 mg/dL and 9.6%, respectively, suggesting poorly controlled diabetes mellitus. Protein induced by vitamin K absence (PIVKA) level was 315 mAU/mL. A blood gas analysis showed a PaO_2 of 77.3 mmHg and a $PaCO_2$ of 37.7 mmHg in room air. As a subset of lymphocytes, the ratio of CD4 to CD8 cells was 0.78 on admission. An HIV test was not conducted at that time; however, a tuberculin reaction test showed strong positivity. QFT testing was not performed.

A chest CT scan indicated the presence of multiple nodular shadows; some shadows showed cavitary lesions, and some opacities were located adjacent to the pleura (Fig. 3a).

A cryptococcal serum antigen test was positive (1:4), and *C. neoformans* was cultured from his sputum. Furthermore, acid-fast staining of his sputum revealed a few beaded bacilli (Gaffky 3). The PCR for *M. tuberculosis* was positive, but the CSF culture was negative for *C. neoformans* and mycobacteria. The cryptococcal antigen was negative in the CSF. Based on these findings, antituberculosis chemotherapy was initiated.

After starting antituberculosis chemotherapy, the patient developed an allergic reaction to INH, and a drug lymphocyte stimulation test was positive against INH. Therefore, administration of INH was started using the hyposensitization method. INH at 450 mg/day, RFP at 450 mg/day, SM at 750 mg twice per week, and levofloxacin at 600 mg/day were continuously administered. *M. tuberculosis* was undetectable from sputum approximately one month after the start of treatment. The patient's blood sugar control improved after treatment was switched to insulin injection (FBS: 80 mg/dL, HbA1c: 5.1%).

We selected antituberculosis chemotherapy to avoid an interaction between antituberculosis agents and azole antifungal agents. After antituberculosis chemotherapy, the administration of antifungal agents was scheduled. As a subset of lymphocytes, the ratio of CD4 to CD8 cells was 3.85 at four months after admission, suggesting a Th1-dominant immunoreaction (Fig. 4). A thoracic CT scan showed improvement nine months after admission (Fig. 3b). His cryptococcal serum antigen titer became negative at nine months after

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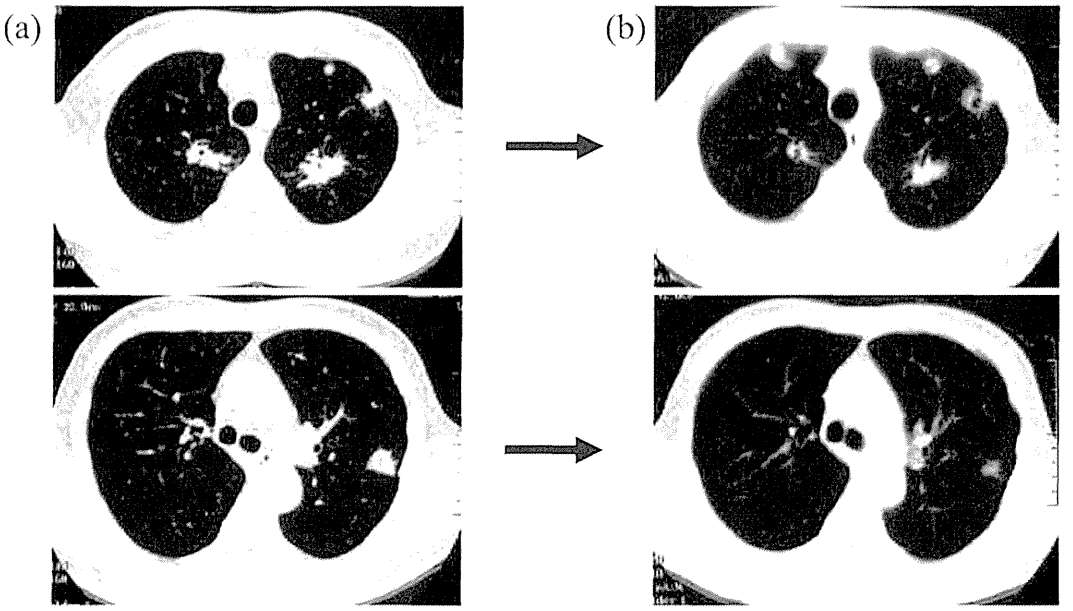

Figure 3. Thoracic CT images of case 2. (a) on admission and (b) nine months after admission.

admission.

After one year, the patient developed hepatocellular carcinoma (HCC) and visited our hospital again. The cryptococcal antigen was not detected at re-admission, and no new pulmonary shadows were present. He died of HCC one year after re-admission.

Case 3

An 83-year-old woman with rheumatoid arthritis had been treated with prednisolone (PSL, 5 mg/day) for several years in another hospital. She did not have a past history of evident exposure to tuberculosis, and prophylactic antimycobacterial agents were not administered.

After an increase of the PSL daily dose to 40 mg to address worsening of arthralgia, a chest radiograph revealed a cavitary lesion in the right upper lobe, and diffuse small granular shadows were observed in both lungs (Fig. 5). Acid-fast staining of her sputum showed bacilli (Gaffky 3), and the PCR analyses for *M. tuberculosis* were positive in samples of CSF, urine, and stool. Miliary tuberculosis was confirmed. Because of anemia due to digestive tract bleeding, her unconscious state, and other aspects of her general condition, she was transferred to our hospital.

On arrival, she was in a comatose state [Japan Coma Scale (JCS) III-300 or Glasgow Coma Scale score of three]. Coarse crackles were heard in both lung fields, and systolic heart murmurs were audible. An abdominal examination indicated moderate ascites. A neurological examination revealed paralysis of both lower limbs. Nuchal rigidity was not observed. Left inguinal region/lymph node swelling was noted. Her body temperature was 36.1°C.

Laboratory studies showed a WBC count of 8,800/μL with a neutrophil count of 89%, an RBC count of 416×10^4/μL, a hemoglobin level of 12.4 g/dL, and a blood platelet count of 2.9×10^4/μL. Her CRP level was 25.9 mg/dL, and ESR was 78 mm/h. Blood chemistry data revealed a low protein level (5.3 g/dL), a low albumin level (1.6 g/dL), and a PT-INR of 1.0. FBS and HbA1c were 173 mg/dL and 6.6%, respectively. Serum cryptococcal antigen testing was negative. QFT and HIV testing were not performed. A blood gas analysis showed a PaO_2 of 114.5 mmHg and a $PaCO_2$ of 40.9 mmHg at O_2 5 L/min through a mask. Antituberculosis agents (INH 300 mg/day, RFP 450 mg/day, ethambutol 500 mg/day, and PZA 1,200 mg/day) were immediately started.

She exhibited disseminated intravascular coagulation (DIC) on admission. Platelet transfusion, gabexate mesilate (FOY®), and human antithrombin III concentrate were also started. Transfusions of 400 mL RBCs were performed three times because of her anemia. Corticosteroid treatment was stopped for three days beginning on admission. After admission, she experienced nausea, vomiting, fatigue, dizziness, and headache. For her suspected withdrawal syndrome and nephrotic syndrome (protein urea 5.6 g/day), steroid pulse therapy (500 mg/day for three days) was also performed; subsequently, PSL was tapered (30 mg/day to 5 mg/day). Her DIC improved, and her consciousness level temporarily recovered (JCS II-20 or Glasgow Coma Scale score of five). Transiently, blood sugar control became more favorable immediately after the start of insulin injections (blood sugar: 100-200 mg/dL).

Although antituberculosis agents were administered immediately, the antimycobacterial drugs were not effective. In addition, concurrent herpes zoster and bacterial pneumonia infection occurred. Acyclovir and meropenem were additionally administered; however, the patient died of respiratory failure and heart failure (Fig. 6).

C. neoformans was cultured in lung aspiration fluid during autopsy.

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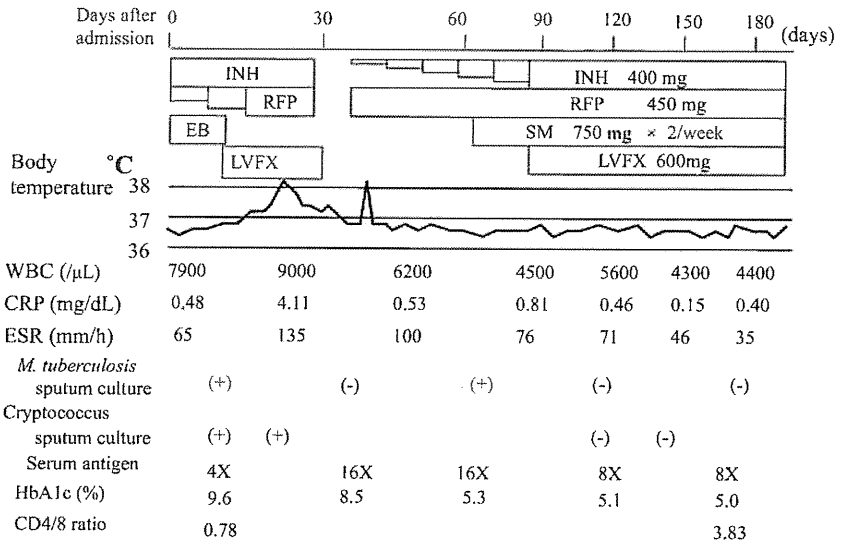

Figure 4. Clinical course of Case 2. INH: isoniazid, RFP: rifampicin, EB: ethambutol, SM: streptomycin, LVFX: levofloxacin, WBC: white blood cell, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, HbA1c: glycated hemoglobin

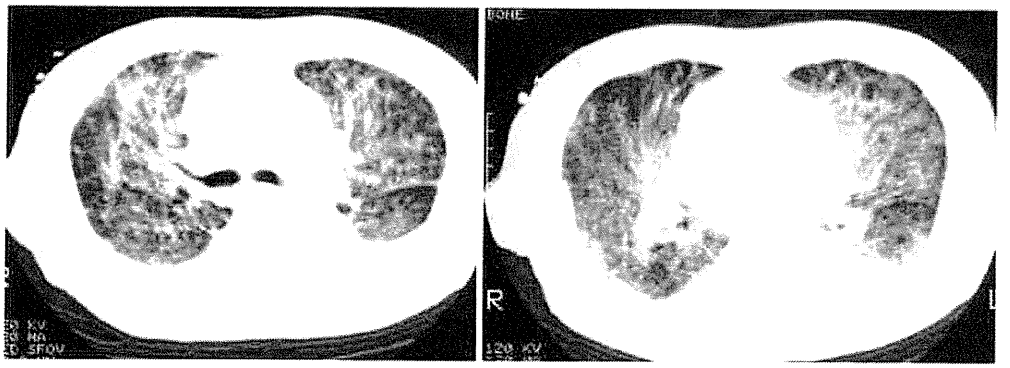

Figure 5. Thoracic CT image of case 3 on admission.

Discussion

Cases of cryptococcosis and tuberculosis co-infection are rare, even in the current HIV/acquired immunodeficiency syndrome (AIDS)-endemic era. Over the previous two decades, only a few cases of co-infection have been reported in the English literature (6-12). Between 1993 and 2006, cryptococcosis and tuberculosis co-infection was reported at one university hospital in Taiwan. That report described 23 patients with co-infection, representing 5.4% of cryptococcosis and 0.6% of tuberculosis cases. Among them, 12 patients (52%) were not infected with HIV (13). During a 35-year period in our hospital and affiliated hospitals, pulmonary cryptococcosis has been diagnosed in 151 patients. Of these, only three patients had cryptococcosis and tuberculosis co-infection (1.99%) (unpublished data).

Important underlying diseases that are common to patients with pulmonary tuberculosis and those with pulmonary cryptococcosis include immunodeficiency syndromes such as AIDS, kidney diseases, blood diseases, and cancer. In addition, the proportion of such patients who are receiving corticosteroid treatment or immunosuppressive agents is high. Diabetes mellitus is also an important underlying disease in patients with pulmonary tuberculosis and cryptococcosis.

Most studies of innate cellular immunity in patients with diabetes show decreased function (chemotaxis, phagocytosis, or killing) of polymorphonuclear cells and monocytes/macrophages, compared to controls (14). In our three patients, especially cases 1 and 2, blood sugar control was poor in the presence of other underlying diseases.

C. neoformans and *M. tuberculosis* infections are believed to be acquired through inhalation of aerosolized particles from the environment. Primary pulmonary tuberculosis is thought to be a latent infection in many cases. Pulmonary tuberculosis in elderly patients may be etiologically associated with reactivation of a latent pulmonary infection. However, the mechanism of cryptococcosis onset is still unclear. Several possibilities have been considered, including primary progression, reactivation, and reinfection (15). Persistent *C.*

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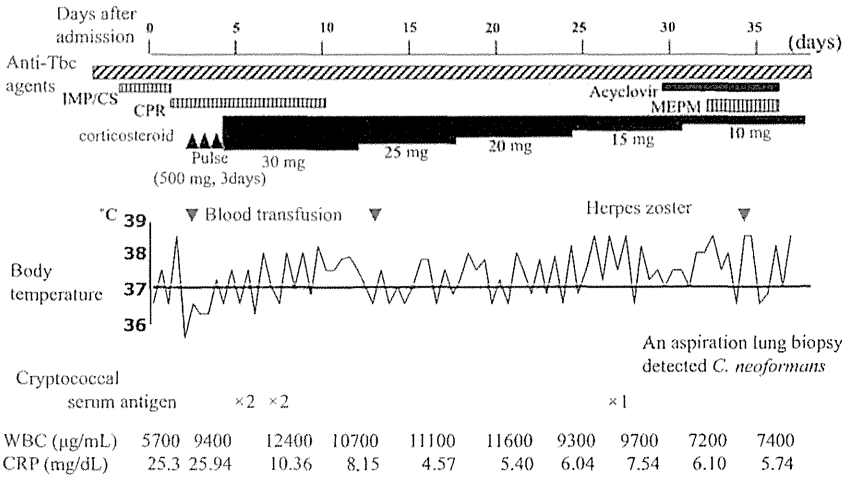

Figure 6. Clinical course of case 3. Tbc: tuberculosis, IPM/CS: imipenem/cilastatin, CPR: cefpirome, MEPM: meropenem, WBC: white blood cell, CRP: C-reactive protein

neoformans pulmonary infection is associated with intracellular parasitism (16). Moreover, recent studies support the idea that cryptococcosis onset is due to reactivation (17-19). Clinical studies have reported that patients with cryptococcosis may have developed their disease after a latent infection period of a few months to a few years (20). The finding of cryptococcal infection in two patients after ventriculoperitoneal shunting suggested reactivation of a pre-existing infection (21). These cases suggest the possibility of reactivation, as has been reported for tuberculosis.

T-cell-mediated immunity is an important defense against both mycobacterial and cryptococcal infections. It is well known that corticosteroids impair a variety of T-cell functions and inhibit the secretion of inflammatory cytokines, including interleukin (IL)-2, IL-6, IL-8, tumor necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (22). The immunosuppressed state of case three, which was related to an increased dose of corticosteroid, may have played a central role in the development of cryptococcosis complicated by pulmonary tuberculosis.

An extremely low $CD4^+$ count (<50 cells/mm^3) is thought to be a risk factor in HIV-infected patients for the development of cryptococcosis and tuberculosis co-infection (13). However, little is known about additional risk factors for the development of co-infection in patients without HIV infection. Tuberculosis infection causes alterations in cellular immunity and is recognized as a predisposing factor for developing cryptococcosis (4, 23). Furthermore, cryptococcosis inhibits the production of TNF-α and predisposes patients to tuberculosis reactivation or infection (24, 25). Altered host immunity may explain why cryptococcosis and tuberculosis developed in these patients without HIV infection.

We did not perform HIV testing in our patients. On reflection, we should have considered doing so, even if they had evident underlying diseases and risk factors (e.g., steroid administration) that impair innate immunity and T-cell mediated immunity. HIV testing may have explained why they had mycobacterial and cryptococcal co-infection.

However, cases of cryptococcosis and tuberculosis co-infection are rare in actual clinical practice, This may be because they are rare, they may be overlooked and go undiagnosed, or cryptococcus may spontaneously resolve as in case 2.

It is known that pulmonary cryptococcosis can improve without treatment in some patients. In case 2, no antifungal agent was administered as initial therapy, due to the risk of an interaction between RFP and azole antifungal agents: RFP decreases the blood concentration and half-life of azole antifungal agents (26). Rifabutin is another option for the treatment of tuberculosis; however, the patient's clinical condition improved, making additional treatment unnecessary.

It has been reported that a central nervous system (CNS) dissemination of cryptococcal infection (cerebrospinal meningitis) develops in 14% of nonimmunosuppressed patients (27). CNS dissemination can be fatal, and it is recommended that antifungal therapy should be started immediately. In case 1, cerebrospinal meningitis developed concurrently, and AMPH-B and FLCZ were combined with antitubercular agents. The use of combination treatment with antifungal agents is controversial. Some in vitro data indicate that this combination of AMPH-B plus FLCZ may be antagonistic (28, 29); however, favorable outcomes have been described when these antifungals have been administered together, and some animal studies of the combination have shown an additive effect (30). It has been reported that combination therapy is more effective than FLCZ monotherapy (31, 32).

Treatment guidelines recommend the use of induction therapy with AMPH-B and flucytosine for cryptococcal meningitis (33). However, such treatment has not been shown to reduce mortality compared with AMPH-B alone. Recently, the results of a randomized, three-group, open-label trial of induction therapy for cryptococcal meningitis in patients with HIV infection were reported. According to

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this report, AMPH-B plus flucytosine, in comparison to AMPH-B alone, was associated with improved survival among patients with cryptococcal meningitis. Furthermore, a survival benefit for AMPH-B plus FLCZ was not found (34). On reflection, AMPH-B plus flucytosine would have been a better option for case one. However, we treated this patient before the Infectious Disease Society of America guidelines were issued and the clinical trial results were reported.

There are some commonalities in chest radiography findings in the two infectious diseases; therefore, it can be difficult to distinguish between them. The CT findings of pulmonary cryptococcosis in many cases include isolation of an area immediately below the pleura or multiple nodular shadows. Cavity formations can also be observed. However, findings vary among patients, and there is no disease-specific finding; in practice, it is often difficult to differentiate this disorder from pulmonary tuberculosis and lung cancer. In addition, these diseases sometimes show extensive consolidation, which is affected by the patient's immune state, further complicating physicians from making a definitive diagnosis. Furthermore, co-infection with cryptococcosis and tuberculosis can be difficult to distinguish clinically from cryptococcosis or tuberculosis mono-infection. Serum cryptococcal antigen test, PCR for *M. tuberculosis*, and QFT should be considered for immunocompromised patients with abnormal pulmonary shadows.

Among developed countries, Japan has a relatively high incidence of tuberculosis. The incidence of tuberculosis had been decreasing annually since the end of World War II but now shows signs of leveling off. Recent data indicate that the proportion of tuberculosis cases that occur in patients aged 65 or older has increased 1.6-fold, from 36.8% in 1987 to 59.1% in 2010; in particular, the proportion in those aged 80 or older has increased 3.8-fold, from 7.9% in 1987 to 29.7% in 2010 (35). This tendency may be associated with the phenomenon of an aging population and an increase in the number of patients with underlying diseases. In such settings, pulmonary tuberculosis remains one of the most important infectious diseases in Japan. In the future, we might encounter more cases of pulmonary tuberculosis complicated by cryptococcosis.

Author's disclosure of potential Conflicts of Interest (COI).
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INTERNAL MEDICINE

ORIGINAL ARTICLE

Importance of Functional Assessment in the Management of Community-acquired and Healthcare-associated Pneumonia

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Abstract

Objective In Japan, the number of elderly people who have difficulties performing the activities of daily living (ADLs) is increasing. The objective of this study was to assess the relationship between ADL and the clinical characteristics of pneumonia.

Methods We conducted a retrospective study of 219 adult patients hospitalized due to pneumonia [151 patients with community-acquired pneumonia (CAP) and 68 patients with healthcare-associated pneumonia (HCAP)]. CAP, HCAP, and all the patients were stratified into two groups using a modified version of the Katz index of five ADLs as follows: independent in all ADLs or dependent in one to three ADLs (CAP-A, HCAP-A, and All-A groups) and dependent in four or five ADLs (CAP-B, HCAP-B, and All-B groups). Disease severity, microbiological findings, and mortality were compared between the groups.

Results As the ability to perform ADLs declined, A-DROP scores (the CAP severity measurement index) increased significantly in CAP (CAP-A: 1.1±1.1, CAP-B: 2.6±1.1), HCAP (HCAP-A: 2.0±1.0, HCAP-B: 2.8±1.0), and all patients (All-A: 1.3±1.1, All-B: 2.8±1.0). Thirty-day mortality was higher in the CAP-B (23.1%) and All-B (19.2%) groups than in the CAP-A (0.7%) and All-A (1.8%) groups, respectively. A multivariate Cox proportional hazards analysis showed an ADL score ≥ four to be a significant predictor of 30-day mortality in CAP patients [hazard ratio (HR), 19.057; 95% confidence interval (CI), 1.930-188.130] and in all patients (HR, 8.180; 95% CI, 1.998-33.494).

Conclusion A functional assessment using a modified version of the Katz index is useful for the management of CAP and HCAP patients.

Key words: activities of daily living, respiratory tract infections, frail elderly, mortality, healthcare

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Introduction

In Japan and other developed countries, the number of elderly people who have difficulties and require supports in their activities of daily living (ADLs) is growing (1, 2). To manage patients with pneumonia who have frequent or chronic contact with the healthcare system and are found to be at risk of having drug-resistant pathogens with high mortality, healthcare-associated pneumonia (HCAP) that requires broad-spectrum antimicrobial drugs was included as a category of pneumonia according to the 2005 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines (3).

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However, the HCAP population is heterogeneous and overlaps with that of community-acquired pneumonia (CAP) in the elderly (4-6). Additionally, physical functional status is not included in the HCAP definition, even though it is a crucial predictor of drug-resistant pathogens and patient outcome (4, 7, 8).

El Solh et al. previously analyzed 88 patients with culture-positive, severe nursing home-acquired pneumonia (NHAP) and reported that the degree of ADL decline was one of the important predictors of drug-resistant pathogens (9). In addition, Lim et al. evaluated 437 patients with NHAP and CAP in the UK and found that NHAP patients had greater mortality related to poor functional status (10).

It is conceivable that ADLs are an important factor in the management of elderly patients with pneumonia. Nevertheless, few studies have evaluated the relationship between ADLs and the clinical characteristics of CAP and HCAP in Japan. The objective of this study was to evaluate differences in the clinical characteristics of pneumonia among patients classified by stratification of ADL before admission and to determine how ADL is related to clinical outcome in CAP and HCAP patients.

Materials and Methods

Study design, subjects, and definitions

We conducted a retrospective study of 219 patients with pneumonia who were hospitalized at Nijigaoka Hospital (a 150-bed community hospital in Nagasaki, Japan) between July 2009 and March 2012.

All patients were divided into CAP and HCAP groups based on the 2005 ATS/IDSA guidelines. Briefly, a patient with HCAP was defined as any patient with pneumonia who satisfied one of the following criteria: (1) hospitalization for two or more days in the preceding 90 days, (2) residence in a nursing home or extended care facility, (3) home infusion therapy (including antibiotics), (4) chronic dialysis within 30 days, or (5) home wound care (3). Long-term care facilities (LTCFs) included nursing homes, homes with more medical services, chronic-care hospitals, and psychiatric hospitals.

The ADL dependency of all hospitalized patients was routinely evaluated by nurses according to a uniform format used in Nijigaoka Hospital. ADL decline was defined as the need for personal assistance in performing one or more ADLs. The physical functional status was measured using a simplified and modified version of the Katz index of five ADLs: bathing, dressing, moving from a bed to a chair, using a toilet, and eating (11). CAP patients, HCAP patients, and all patients were divided into two groups according to their level of dependence on assistance to perform ADLs before admission as follows: patients with pneumonia who were independent in all ADLs or dependent in one to three ADLs (CAP-A, HCAP-A, and All-A groups) and those who were dependent in four or five ADLs (CAP-B, HCAP-B, and All-B groups).

We compared the baseline characteristics, identified pathogens, and clinical outcomes between the groups. The study was approved by the institutional review board of Nijigaoka Hospital. Informed consent was not required because the study was retrospective and the data were obtained within the context of normal daily practice. Pneumonia was defined as the appearance of a new infiltrate on chest images that was accompanied by clinical symptoms, such as cough, sputum and fever, or inflammatory reactions (e.g., leukocytosis, leukopenia, or increased C-reactive protein levels) on laboratory tests. Patients who were diagnosed with hospital-acquired pneumonia (HAP), lung cancer-associated obstructive pneumonia, interstitial pneumonia, organizing pneumonia, or eosinophilic pneumonia were excluded. Probable aspiration was defined as aspiration witnessed, confirmed by the water-drinking test on hospital admission, or strongly suspected based on the patient's clinical course (12). The outcome measures were 30-day mortality and initial treatment failure. Initial treatment failure was defined as death during initial treatment or change of therapeutic agents from initial agents to others due to clinical ineffectiveness (e.g., lack of response or worsening of fever pattern, respiratory condition, and/or radiographic findings). Therapy was deemed inappropriate if the identified pathogens were resistant to the initially prescribed antibiotics based on in vitro susceptibility testing or if the initially administered antibiotics were not recommended for treatment of the identified pathogens according to the Japanese CAP and HAP guidelines (13, 14).

Severity evaluation

Pneumonia severity was evaluated using the predictive rule of a five-point scoring system for CAP: the A-DROP [age, dehydration, respiratory failure, orientation disturbances, and low blood pressure (BP)], which was proposed by the Japanese Respiratory Society (13). These are basically modified versions of the CURB-65 (13, 15, 16).

Microbiological evaluation

Pathogens in samples obtained from sputum, blood, or other body fluids were investigated using standard microbiological procedures. The results of blood cultures were accepted as an etiological diagnosis if no other source could be identified for the positive culture. Sputum samples were cultured in a quantitative manner, and positive bacterial culture results for sputum were documented from medical records. Serologic methods using single sera were used to detect immunoglobulin (Ig)M antibodies against *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. Rapid immunochromatographic assays were used to detect the influenza virus antigen in nasopharyngeal swabs, *Streptococcus pneumoniae* in urine and *Legionella pneumophila* serogroup 1 antigen in urine. These examinations were ordered by attending physicians as needed for each patient. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas* species, *Acinetobacter* species, and extended-spectrum beta-

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Table 1. Baseline Characteristics of Patients with Pneumonia

	CAP (n = 151)		p value	HCAP (n = 68)		p value	All patients (n = 219)		p value
	CAP-A n = 138	CAP-B n = 13		HCAP-A n = 29	HCAP-B n = 39		All-A n = 167	All-B n = 52	
Age (years)	67.6 ± 18.9	88.0 ± 8.3	<0.001	79.8 ± 9.7	82.7 ± 12.5	0.076	69.7 ± 18.2	84.0 ± 11.7	<0.001
Sex (male / female)	77/61 (55.8)	5/8 (38.5)	0.257	17/12 (58.6)	15/24 (38.5)	0.141	94/73 (56.3)	20/32 (38.5)	0.027
Tube feeding	0 (0.0)	1 (7.7)	0.086	0 (0.0)	6 (15.4)	0.034	0 (0.0)	7 (13.5)	<0.001
Antibiotic use within 90 days	0 (0.0)	0 (0.0)	-	10 (34.5)	5 (12.8)	0.042	10 (6.0)	5 (9.6)	0.357
Use of gastric acid-suppressants[a]	40 (29.0)	5 (38.5)	0.530	19 (65.5)	20 (51.3)	0.323	59 (35.3)	25 (48.1)	0.105
Probable aspiration	10 (7.2)	6 (46.2)	0.005	9 (31.0)	25 (64.1)	0.014	19 (11.4)	31 (59.6)	<0.001
Comorbidities									
Cerebrovascular disease	11 (8.0)	5 (38.5)	0.005	5 (17.2)	16 (41.0)	0.040	16 (9.6)	21 (40.4)	<0.001
Chronic pulmonary disease	42 (30.4)	3 (23.1)	0.756	15 (51.7)	5 (12.8)	0.001	57 (34.1)	8 (15.4)	0.009
Congestive heart failure	14 (10.1)	4 (30.8)	0.051	2 (6.9)	7 (17.9)	0.282	16 (9.6)	11 (21.2)	0.050
Chronic renal dysfunction	4 (2.9)	1 (7.7)	0.367	2 (6.9)	8 (20.5)	0.171	6 (3.6)	9 (17.3)	0.002
Chronic liver disease	7 (5.1)	2 (15.4)	0.174	3 (10.3)	2 (5.1)	0.644	10 (6.0)	4 (7.7)	0.746
Diabetes mellitus	22 (15.9)	2 (15.4)	1.000	4 (13.8)	10 (25.6)	0.364	26 (15.6)	12 (23.1)	0.215
Gastrectomy	5 (3.6)	0 (0.0)	1.000	3 (10.3)	2 (5.1)	0.644	8 (4.8)	2 (3.8)	1.000
Malignancy	6 (4.3)	2 (15.4)	0.143	5 (17.2)	3 (7.7)	0.272	11 (6.6)	5 (9.6)	0.541
Immunosuppression[b]	9 (6.5)	0 (0.0)	1.000	0 (0.0)	6 (15.4)	0.034	9 (5.4)	6 (11.5)	0.204

Values are expressed as mean ± standard deviation or the number (%).

CAP: community-acquired pneumonia, HCAP: healthcare-associated pneumonia

[a] Gastric acid-suppressants included histamine H_2-receptor blockers or proton pump inhibitors.

[b] Immunosuppression was defined as administration of corticosteroids (5 mg/day or more) or other immunosuppressive agents.

lactamase (ESBL) producing *Enterobacteriaceae* were considered as multidrug-resistant (MDR) pathogens (3, 17).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, and differences between groups were statistically analyzed by Student's *t*-tests when variables were normally distributed and Mann-Whitney U tests when variables were not normally distributed. Fisher's exact tests were used to compare categorical data between the groups. Survival rates within 30 days were estimated using the Kaplan-Meier method and compared between the groups with log-rank tests. We conducted univariate and multivariate analyses using a Cox proportional hazards model. Variables with p values <0.2 in univariate analysis were selected and adjusted by forward stepwise selection in multivariate analysis to identify the predictors of 30-day mortality. The data were analyzed using SPSS 16.0J for Windows (SPSS Inc., Chicago, USA), and p values of 0.05 were considered statistically significant.

Results

Patient characteristics

The characteristics of the 219 patients enrolled in the study are presented in Table 1. The mean age was significantly higher in the CAP-B and All-B groups than in CAP-A and All-A groups. All patients who received tube feeding were included in the reduced ADL group. As inactivity advanced, the proportion of aspiration pneumonia increased. About 40% of CAP-B and HCAP-B patients had cerebrovascular disease as a comorbidity. Immunosuppression was significantly higher in the HCAP-B group compared to the HCAP-A group. Conversely, the incidence of chronic lung disease was lower in the HCAP-B and All-B groups than in the HCAP-A and All-A groups. Chronic renal dysfunction was higher in the All-B group compared to the All-A group.

Regarding ADL dependency, a total of 75.5% of CAP patients and 27.9% of HCAP patients were independent in all ADLs. Conversely, 7.3% of CAP and 44.1% of HCAP patients needed support in all five ADLs.

HCAP-A patients were previously administered antibiotics within 90 days more frequently than HCAP-B patients. Gastric acid-suppressants were similarly prescribed between the groups.

Symptoms, clinical, laboratory, and radiographic findings

Cough was the most common symptom in CAP patients (CAP-A group: 80.4%, CAP-B group: 61.5%, p=0.150), with a lower frequency in HCAP patients with declined ADL (HCAP-A group: 69.0%, HCAP-B group: 43.6%, p= 0.050). In contrast, the percentage of disoriented patients significantly increased along with ADL decline in CAP (6.5% in CAP-A group, 53.8% in CAP-B group, p<0.001) and HCAP patients (10.3% in HCAP-A group, 56.4% in HCAP-B group, p<0.001).

Table 2 shows the physical findings and laboratory data of the study subjects. Hypoxia was observed in 53.8% of the CAP-B group but only 23.9% of the CAP-A group. More than 60% of HCAP patients had hypoxia, which was similar for the HCAP-A and B groups. The frequency of low BP was higher in the HCAP-B group compared to the HCAP-A group.

The laboratory data indicated that serum albumin decreased with worsening physical function in CAP and

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Table 2. Physical Examinations and Laboratory Findings of the Patients

	CAP (n = 151)		p value	HCAP (n = 68)		p value	All patients (n = 219)		p value
	CAP-A n = 138	CAP-B n = 13		HCAP-A n = 29	HCAP-B n = 39		All-A n = 167	All-B n = 52	
Clinical parameters									
Temperature (°C)	38.4 ± 1.0	37.9 ± 1.1	0.201	38.2 ± 0.8	38.3 ± 0.7	0.610	38.3 ± 1.0	38.2 ± 0.9	0.458
Pulse rate (/min)	88.5 ± 16.6	78.3 ± 15.3	0.035	85.4 ± 18.7	89.4 ± 18.4	0.378	87.9 ± 16.9	86.6 ± 18.2	0.636
Systolic BP ≤ 90 mmHg	1 (0.7)	0 (0.0)	1.000	1 (3.4)	9 (23.1)	0.036	2 (1.2)	9 (17.3)	<0.001
SpO_2 ≤ 90%	33 (23.9)	7 (53.8)	0.042	18 (62.1)	25 (64.1)	1.000	51 (30.5)	32 (61.5)	<0.001
Laboratory data									
White blood cell (/μL)	10,891.3 ± 5,301.4	10,092.3 ± 3,929.7	0.779	12,073.4 ± 5,111.8	11,723.1 ± 5,422.0	0.788	11,096.6 ± 5,273.0	11,315.4 ± 5,103.3	0.609
Red blood cell ($\times 10^4$/μL)	402.2 ± 53.1	387.5 ± 45.8	0.336	378.6 ± 43.2	369.8 ± 61.7	0.204	398.1 ± 52.2	374.2 ± 58.2	0.006
Platelets ($\times 10^4$/μL)	21.6 ± 8.0	24.1 ± 6.3	0.162	21.2 ± 9.9	20.6 ± 9.4	0.968	21.5 ± 8.3	21.5 ± 8.8	0.987
Total protein (g/dL)[a]	6.9 ± 0.6	6.6 ± 0.7	0.135	6.5 ± 0.8	6.3 ± 0.7	0.055	6.8 ± 0.7	6.3 ± 0.7	<0.001
Albumin (g/dL)[a]	3.6 ± 0.6	3.0 ± 0.4	0.002	3.1 ± 0.6	2.8 ± 0.5	0.037	3.5 ± 0.6	2.8 ± 0.5	<0.001
BUN (mg/dL)	16.2 ± 8.5	23.3 ± 6.9	<0.001	20.3 ± 10.4	27.3 ± 25.5	0.611	16.9 ± 9.0	26.3 ± 22.3	<0.001
Creatinine (mg/dL)	0.9 ± 0.4	1.0 ± 0.4	0.399	0.9 ± 0.4	1.1 ± 0.6	0.802	0.9 ± 0.4	1.0 ± 0.6	0.396
Na (mEq/L)	136.6 ± 3.9	132.1 ± 7.4	0.013	137.7 ± 4.6	136.4 ± 6.1	0.329	136.8 ± 4.0	135.3 ± 6.6	0.188
K (mEq/L)	3.9 ± 0.5	4.4 ± 0.9	0.053	4.0 ± 0.6	4.2 ± 1.0	0.424	3.9 ± 0.5	4.3 ± 1.0	0.024
Cl (mEq/L)	99.3 ± 4.4	94.5 ± 8.4	0.035	100.6 ± 4.7	100.5 ± 6.1	0.937	99.5 ± 4.5	99.0 ± 7.2	0.843
CRP (mg/dL)	12.0 ± 9.3	9.1 ± 5.8	0.427	9.7 ± 8.6	10.5 ± 8.7	0.522	11.6 ± 9.2	10.2 ± 8.1	0.457

Values are expressed as mean ± standard deviation or the number (%).

CAP: community-acquired pneumonia, HCAP: healthcare-associated pneumonia, BP: blood pressure, SpO_2: pulse oximetric oxygen saturation, BUN: blood urea nitrogen, CRP: C-reactive protein

[a] Serum total protein and albumin were measured in 79.5% and 82.2% of all patients, respectively.

HCAP patients. High levels of blood urea nitrogen (BUN) and hyponatremia were observed in the CAP-B group compared to the CAP-A group. A significant difference in potassium levels was seen between All-A and All-B patients.

Radiography demonstrated that the incidence of bilateral involvement was similar between the groups in CAP (CAP-A group: 31.9%, CAP-B group: 30.8%, p=1.000), HCAP (HCAP-A group: 51.7%, HCAP-B group: 56.4%, p=0.807), and all patients (All-A group: 35.3%, All-B group: 50.0%, p=0.073). Pleural effusion tended to occur more frequently in ADL-declined groups in CAP (CAP-A group: 26.1%, CAP-B group: 53.8%, p=0.051), HCAP (HCAP-A group: 27.6%, HCAP-B group: 46.2%, p=0.138), and all patients (All-A group: 26.3%, All-B group: 48.1%, p=0.006).

Distribution of identified pathogens

Streptococcus pneumoniae was the most frequently isolated pathogen in all patients, and the isolation rate was similar between the CAP (20.5%) and HCAP groups (23.5%). *Mycoplasma pneumoniae* was the second most commonly detected pathogen in the CAP (12.6%) and HCAP (14.7%) groups.

The microbes identified in each group are shown in Table 3. MRSA was significantly more frequently identified in the All-B group (13.5%) compared to the All-A group (3.0%). An inter-group comparison indicated no significant differences between the groups in terms of the numbers of identified pathogens.

Among patients with identified pathogens, MDR pathogens were identified more frequently in the All-B group (36.0%, nine of 25 patients) than the All-A group (13.4%, nine of 67 patients) (p=0.035).

Disease severity, antibiotic treatment, and clinical outcome

Pneumonia severity and the clinical outcomes are presented in Table 4. As physical function diminished, the A-DROP score increased, with statistically significant differences between groups. The 30-day mortality was higher in the CAP-B and All-B groups compared to the CAP-A and All-A groups. A similar was observed in the comparison of the HCAP-A and B groups, although the difference was not significant.

Initial treatment failure occurred more frequently in the CAP-B group than in the CAP-A group, and the duration of antibiotic therapy and length of hospital stay were much longer in the CAP-B and All-B groups than in CAP-A and All-A groups.

No significant differences were seen between the groups in terms of overall antimicrobial therapy by monotherapy in CAP patients (CAP-A group: 55.8% and CAP-B group: 69.2%, p=0.396) or in HCAP patients (HCAP-A group: 58.6% and HCAP-B group: 71.8%, p=0.305). A total of 67.3% of patients in the All-B group received monotherapy with beta-lactams. In particular, carbapenem was administered to 13.5% of patients in All-B and only 3.6% of the All-A group (p=0.015). Conversely, combination therapy with beta-lactams plus tetracyclines was administered to 17.4% of patients in the All-A group and 3.8% of patients in the All-B group (p=0.012).

In the All-A group, 11 of 67 patients with at least one identified pathogen received inappropriate therapy. Initial treatment failure occurred in five of 56 patients (8.9%) who received appropriate therapy, while four of 11 patients (36.4%) in the All-A group received inappropriate therapy (p=0.034). In the All-B group, nine of 25 patients with iden-

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Table 3. Pathogens Identified in Patients with Pneumonia

	CAP (n = 151)		p value	HCAP (n = 68)		p value	All patients (n = 219)		p value
	CAP-A n = 138	CAP-B n = 13		HCAP-A n = 29	HCAP-B n = 39		All-A n = 167	All-B n = 52	
Gram-positive pathogens									
Streptococcus pneumoniae	30 (21.7)	1 (7.7)	0.306	6 (20.7)	10 (25.6)	0.775	36 (21.6)	11 (21.2)	1.000
Staphylococcus aureus	8 (5.8)	1 (7.7)	0.566	3 (10.3)	7 (17.9)	0.498	11 (6.6)	8 (15.4)	0.085
MSSA	5 (3.6)	0 (0.0)	1.000	1 (3.4)	1 (2.6)	1.000	6 (3.6)	1 (1.9)	1.000
MRSA	3 (2.2)	1 (7.7)	0.305	2 (6.9)	6 (15.4)	0.451	5 (3.0)	7 (13.5)	0.009
Gram-negative pathogens									
Haemophilus Influenzae	11 (8.0)	0 (0.0)	0.600	2 (6.9)	1 (2.6)	0.571	13 (7.8)	1 (1.9)	0.196
Klebsiella pneumoniae	2 (1.4)	0 (0.0)	1.000	2 (6.9)	4 (10.3)	1.000	4 (2.4)	4 (7.7)	0.093
Pseudomonas aeruginosa	1 (0.7)	1 (7.7)	0.165	1 (3.4)	2 (5.1)	1.000	2 (1.2)	3 (5.8)	0.088
Escherichia coli	1 (0.7)	0 (0.0)	1.000	0 (0.0)	2 (5.1)	0.504	1 (0.6)	2 (3.8)	0.141
Acinetobacter baumannii	0 (0.0)	0 (0.0)	-	2 (6.9)	0 (0.0)	0.178	2 (1.2)	0 (0.0)	1.000
Moraxella catarrhalis	1 (0.7)	0 (0.0)	1.000	0 (0)	0 (0)	-	1 (0.6)	0 (0.0)	1.000
Other gram negative pathogens	1 (0.7)	0 (0.0)	1.000	0 (0.0)	1 (2.6)	1.000	1 (0.6)	1 (1.9)	0.419
MDR pathogens	5 (3.6)	2 (15.4)	0.112	4 (13.8)	7 (17.9)	0.747	9 (5.4)	9 (17.3)	0.016
Atypical pathogens									
Mycoplasma pneumoniae	17 (12.3)	2 (15.4)	0.669	6 (20.7)	4 (10.3)	0.305	23 (13.8)	6 (11.5)	0.817
Chlamydophila pneumoniae	1 (0.7)	1 (7.7)	0.165	1 (3.4)	0 (0.0)	0.426	2 (1.2)	1 (1.9)	0.558
Legionella pneumophila	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0)	-	0 (0.0)	0 (0.0)	-
Influenza virus	2 (1.4)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	-	2 (1.2)	0 (0.0)	1.000
The number of identified pathogens									
At least one	52 (37.7)	5 (38.5)	1.000	15 (51.7)	20 (51.3)	1.000	67 (40.1)	25 (48.1)	0.337
Single	32 (23.2)	4 (30.8)	0.510	9 (31.0)	13 (33.3)	1.000	41 (24.6)	17 (32.7)	0.281
Double	16 (11.6)	1 (7.7)	1.000	4 (13.8)	3 (7.7)	0.449	20 (12.0)	4 (7.7)	0.458
Triple	4 (2.9)	0 (0.0)	1.000	2 (6.9)	4 (10.3)	1.000	6 (3.6)	4 (7.7)	0.253

Values are expressed as the number (%).

CAP: community-acquired pneumonia, HCAP: healthcare-associated pneumonia, MSSA: methicillin-susceptible *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus*, MDR: multidrug-resistant

Table 4. Disease Severity according to the A-DROP Scoring System, and Clinical Outcomes

	CAP (n = 151)		p value	HCAP (n = 68)		p value	All patients (n = 219)		p value
	CAP-A n = 138	CAP-B n = 13		HCAP-A n = 29	HCAP-B n = 39		All-A n = 167	All-B n = 52	
Severity evaluation									
A-DROP score	1.1 ± 1.1	2.6 ± 1.1	<0.001	2.0 ± 1.0	2.8 ± 1.0	0.002	1.3 ± 1.1	2.8 ± 1.0	<0.001
Outcome									
Initial treatment failure	8 (5.8)	5 (38.5)	0.002	5 (17.2)	4 (10.3)	0.481	13 (7.8)	9 (17.3)	0.063
30-day mortality	1 (0.7)	3 (23.1)	0.002	2 (6.9)	7 (17.9)	0.282	3 (1.8)	10 (19.2)	<0.001
Duration of intravenous antibiotics (days)	6.6 ± 3.5	10.0 ± 5.7	0.013	6.5 ± 2.7	8.6 ± 4.3	0.064	6.6 ± 3.3	8.9 ± 4.7	0.001
Hospitalization (days)	14.7 ± 19.5	21.8 ± 16.9	0.008	20.5 ± 18.0	29.8 ± 24.0	0.061	15.7 ± 19.3	27.8 ± 22.5	<0.001

Values are expressed as mean ± standard deviation or the number (%).

CAP: community-acquired pneumonia, HCAP: healthcare-associated pneumonia, A-DROP: age, dehydration, respiratory failure, orientation disturbances and low blood pressure

tified pathogens received inappropriate therapy. The frequencies of initial treatment failure were similar in patients with appropriate therapy (two of 16 patients, 12.5%) and those with inappropriate therapy (one of nine patients, 11.1%) (p= 1.000) in the All-B group.

Survival analysis and independent prognostic factors in CAP and HCAP patients

Kaplan-Meier curves showed that survival rates in the CAP-B and All-B groups were significantly lower than those in the CAP-A and All-A groups (Figure a, c). These trends were similar for the HCAP group (Figure b), although the difference was not significant.

Table 5 shows the results of the univariate and multivariate analyses of prognostic factors for 30-day mortality in patients with CAP and HCAP. On multivariate analysis, the independent predictors of 30-day mortality were ADL score ≥ four in CAP patients, malignancy, systolic BP ≤90 mmHg, and creatinine in HCAP patients and malignancy, ADL score ≥ four, and oxygen saturation (SpO_2) ≤90% in all patients.

Discussion

The present study demonstrates the differences in baseline characteristics, identified pathogens, disease severity, and clinical outcome among patients with pneumonia divided according to their ability to perform ADLs.

In our study, A-DROP scores and the 30-day mortality

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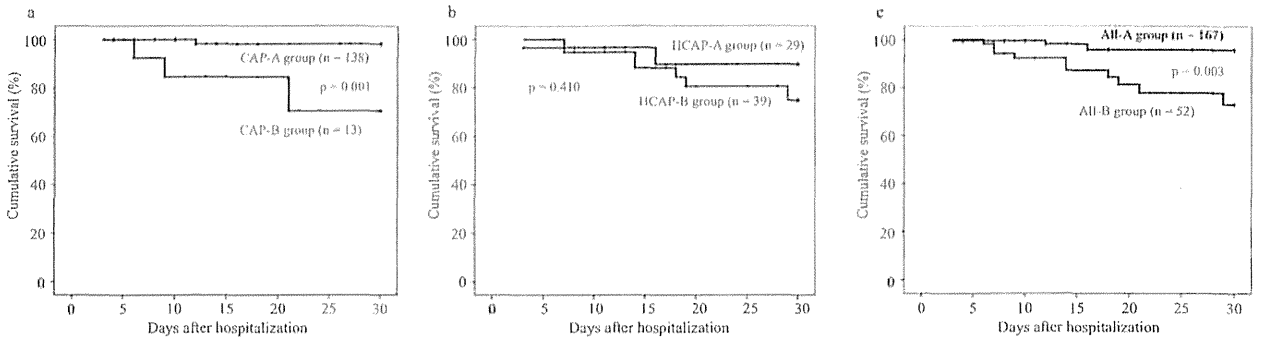

Figure. Kaplan-Meier survival analysis of patients with pneumonia according to activities of daily living (ADLs) in community-acquired pneumonia (CAP) patients (a), healthcare-associated pneumonia (HCAP) patients (b), and all CAP and HCAP patients (c). The survival rates of the CAP-B and All-B groups were significantly lower than those in CAP-A and All-A groups, respectively. The prognosis in HCAP-B patients tended to be worse compared to HCAP-A patients, although the difference was not significant.

Table 5. Univariate and Multivariate Analysis of Prognostic Factors for 30-day Mortality in Patients with Community-acquired and Healthcare-associated Pneumonia

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
CAP						
ADL score ≥ 4	19.057	1.930-188.130	0.012	19.057	1.930-188.130	0.012
Temperature (°C)	0.088	0.011-0.692	0.021			
Altered mental status	14.871	1.475-149.908	0.022			
K (mEq/L)	4.414	1.339-14.548	0.015			
Initial treatment failure	18.487	1.869-182.871	0.013			
HCAP						
Systolic BP ≤ 90 mmHg	3.159	0.789–12.648	0.104	7.762	1.567-38.450	0.012
Chronic renal dysfunction	4.315	1.152–16.159	0.030			
Malignancy	5.264	1.299-21.340	0.020	8.739	1.558-49.004	0.014
Immunosuppression	4.541	1.133–18.195	0.033			
BUN (mg/dL)	1.019	1.000–1.039	0.048			
Creatinine (mg/dL)	4.400	1.627–11.898	0.004	5.107	1.800-14.491	0.002
All patients						
ADL score ≥ 4	6.001	1.620–22.231	0.007	8.180	1.988-33.494	0.003
Congestive heart failure	3.216	1.049–9.866	0.041			
Chronic renal dysfunction	4.283	1.310–14.001	0.016			
Malignancy	6.411	1.964–20.932	0.002	13.370	3.291-54.313	<0.001
Systolic BP ≤ 90 mmHg	4.161	1.139–15.197	0.031			
SpO_2 ≤ 90%	4.774	1.034–22.040	0.045	7.464	1.422-39.185	0.018
BUN (mg/dL)	1.026	1.008–1.043	0.004			
Creatinine (mg/dL)	2.522	1.250–5.086	0.010			
K (mEq/L)	2.170	1.304–3.610	0.003			
Initial treatment failure	3.537	1.144–10.943	0.028			

HR: hazard ratio, CI: confidence interval, CAP: community-acquired pneumonia, HCAP: healthcare-associated pneumonia, ADL: activity of daily living, BP: blood pressure, BUN: blood urea nitrogen, SpO_2: pulse oximetric oxygen saturation

rate tended to be higher in patients with diminished ADL. A multivariate analysis indicated that ADL decline was an independent predictor of 30-day mortality in CAP patients and all patients. A previous report identified ADL dependency as an independent risk factor for both in-hospital and post-discharge mortality (18). Our results support those of a previous study in which functional status was the main determinant of outcome in elderly patients with pneumonia (7). Additionally, previous reports have indicated that performance status (PS) evaluation is useful for predicting the outcome of patients with pneumonia (19, 20). Therefore, PS is one of the criteria of nursing and healthcare-associated pneumonia (NHCAP), which was newly categorized in the 2011 Japanese Respiratory Society guidelines (6, 21). Although PS could not be documented from the medical records in the present study, our results, which focus on ADL dependency, correspond with the concept of NHCAP which includes patients with diminished PS in addition to HCAP patients.

We did not detect a significant difference between the 30-day mortalities of HCAP-A (6.9%) and HCAP-B (17.9%) patients, and ADL decline was not identified as an inde-

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pendent risk factor for 30-day mortality in HCAP patients. Therefore, we should consider other factors when predicting prognosis in HCAP patients, a group that mainly includes patients with diminished ADL.

We found that malignancy was an important predictor of 30-day mortality in HCAP and all patients. A recent study reported that it was an independent risk factor for in-hospital mortality in HCAP patients (22). The number of outpatients undergoing cancer therapy is increasing as a result of dramatic advances in cancer treatment and care (23). Therefore, we should recognize malignancy as a risk factor for mortality in patients with pneumonia, excluding those with HAP.

Previous studies reported that serum albumin was an independent prognostic factor in CAP, NHAP, and HAP patients (19, 20). In the present study, the low serum albumin levels observed in the diminished ADL group could be indicative of malnutrition, which is probably related to the high frequency of tube feeding in these patients. However, we could not adequately assess it as a prognostic factor because serum albumin was not measured in 17.8% of the patients. Aspiration pneumonia, defined by the presence of risk factors for aspiration and chest computed tomography (CT) findings, is also an independent risk factor for 30-day mortality among CAP and HCAP patients (24). However, we could not apply a strict definition for aspiration pneumonia in this study because CT was not performed in all patients.

In the All-B group, the mortality rate within 30 days (19.2%) tended to be higher than the proportion of patients in whom primary treatment failed (17.3%). Primary antibiotic therapy was successful in seven of 10 patients who subsequently died, with the ultimate poor outcome in these patients attributed to the development of secondary complications or exacerbation of comorbidities. Therefore, the systemic management of these complications and preventing the onset of pneumonia, such as by prophylaxis against aspiration or vaccination, are as essential as treatment with appropriate antibiotics in patients with diminished ADL.

The identities of the causative pathogens are also important when considering pathophysiology in patients with pneumonia. Lopez et al. previously described that MDR pathogens are implicated in a variable percentage of HCAP patients and do not seem to be the unique or direct cause of their increased mortality (25). In the present study, the rate of MRSA isolation was significantly higher in All-B patients. However, MRSA was not identified from the sputum of any of the All-B patients who died within 30 days of admission (except from fecal culture in one of the patients who died). This indicates that the high 30-day mortality of the All-B patients was not directly associated with the increased frequency of MRSA isolation from sputum.

Because our study was retrospective, there are some limitations associated with it that should be considered. First, microbiological evaluations were not uniformly and sufficiently performed, particularly with respect to anaerobic pathogens that are an important cause of aspiration pneumonia. However, because about 60% of patients in the All-B group were suspected to have developed aspiration pneumonia, treatment to cover anaerobic pathogens should be prescribed for patients with decreased ADL. Second, previous studies indicated that the sensitivity of IgM antibodies against *Mycoplasma pneumoniae* was 33.3% (26). Therefore, our diagnosis using IgM against *Mycoplasma pneumoniae* might be insufficient. Third, two of 12 patients with MRSA isolation in this study ultimately required treatment with anti-MRSA drugs, but we were not able to assess whether empirical broad-spectrum antibiotic therapy with anti-MRSA drugs could improve the outcome of patients with ADL decline. Additionally, the frequency of HCAP (31.1%) was lower than that of CAP (68.9%) in the present study. Because the proportion of HCAP or NHCAP compared to CAP is very diverse and varies according to the geographic region and medical environment, some of our results might not apply to other institutions (12, 21, 22).

In conclusion, our findings revealed that ADL dependency correlates with high mortality and that subgrouping based on ADL score is useful for predicting the outcome in CAP and all CAP and HCAP patients. Furthermore, patients with decreased ADL have several disadvantages, including multiple comorbidities and malnutrition (hypoalbuminemia). Because they are predisposed to a poor outcome, appropriate antibiotic usage and systemic management, including prophylaxis, are required for adult patients with diminished ADL.

Functional assessment using the modified version of the Katz index is simple, useful, and important for predicting outcome and managing CAP and HCAP patients.

The authors state that they have no Conflict of Interest (COI).

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INTERNAL MEDICINE

□ CASE REPORT □

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

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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-

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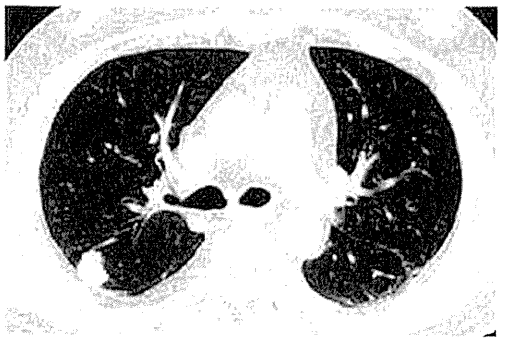

Figure 1. Thoracic computed tomography (CT) image obtained on admission showing a solitary well-defined, pleural-based nodule in the right S2 region. No pleural effusion or cavitation were observed.

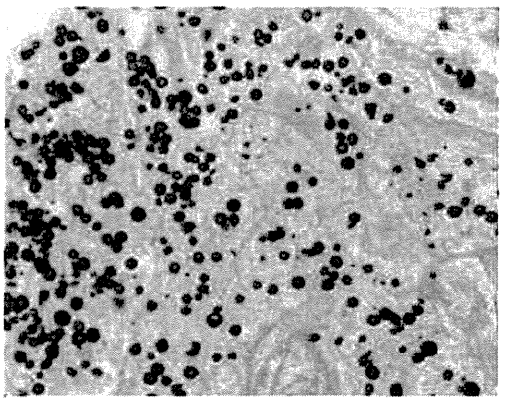

Figure 2. A histopathological examination of a lung biopsy specimen. Gomori's methenamine-silver stain showing encapsulated yeast forms that resemble *Cr. neoformans* (Magnification, ×400).

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 resembled *Cr. neoformans* (Fig. 2). Although the patient had no headaches or nuchal rigidity, lumbar puncture

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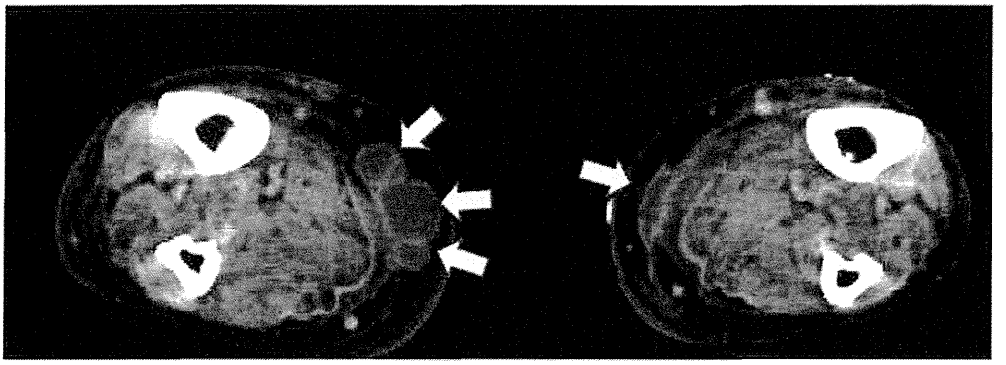

Figure 3. T1-weighted magnetic resonance image showing a well-demarcated collection of fluid in the soft tissue of both lower legs (arrows), suggesting a subcutaneous abscess.

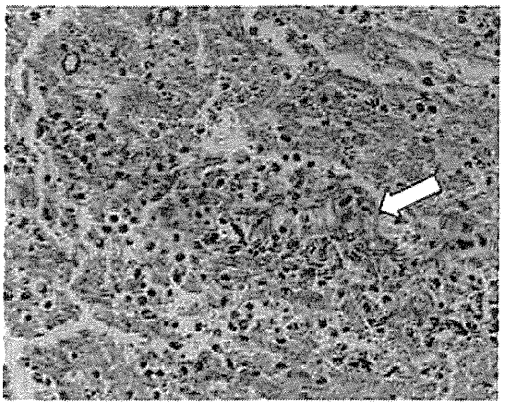

Figure 4. A histopathological examination of the needle aspirate of a lower extremity abscess. Periodic acid-Schiff stain showing yeast and hyphal forms (arrow) of the fungus (Magnification, ×400).

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

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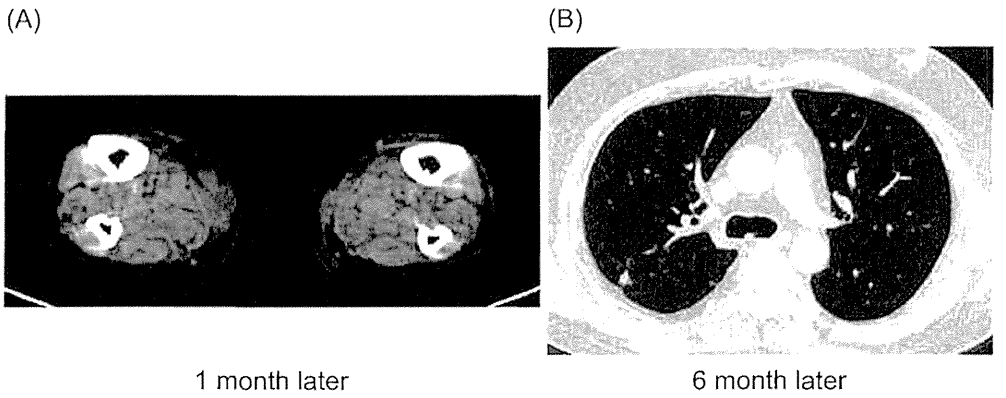

Figure 5. Antifungal therapy reduced the size of the patient's leg skin abscesses and lung nodule. (A) A leg CT image obtained one month after the initiation of antifungal therapy showing a reduction in the size of the skin abscesses. (B) A thoracic CT image obtained six months after the start of antifungal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