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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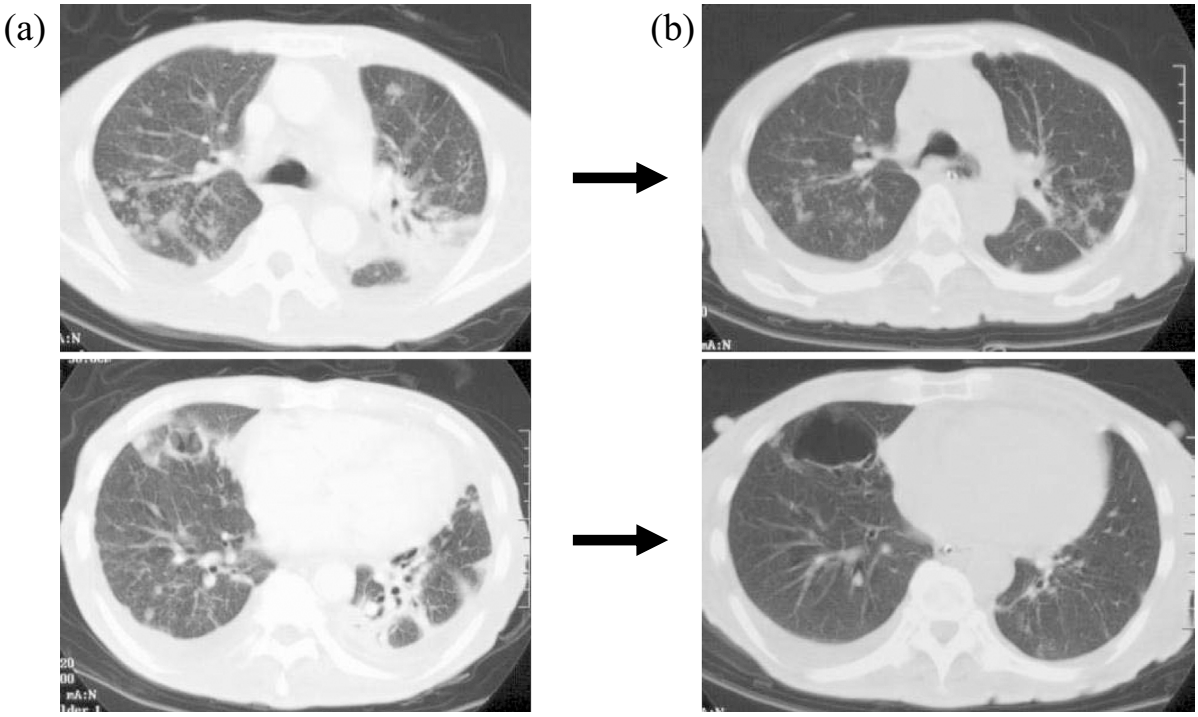

Figure 1. **Thoracic CT images of case one. (a) on admission and (b) on day 120 after admission.**

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 coinfection 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,

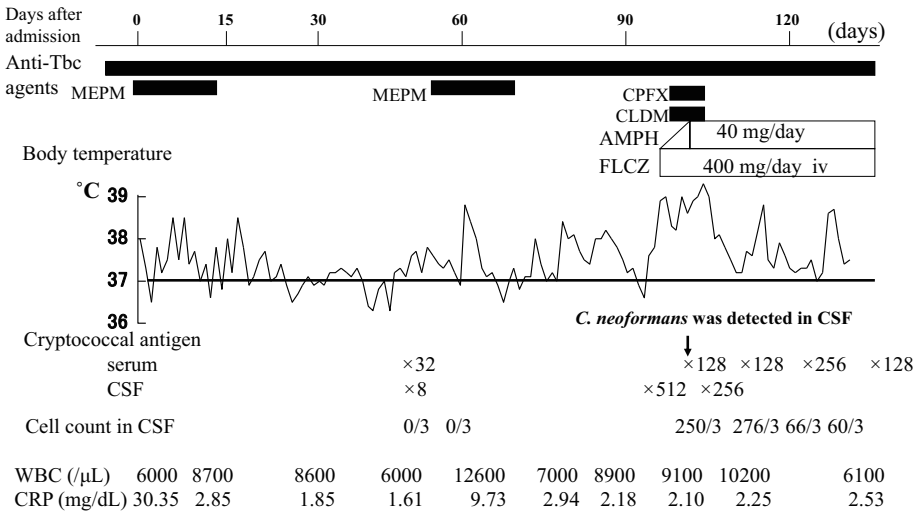

Figure 2. Clinical course of case 1. Tbc: tuberculosis, MEPM: meropenem, CPFX: ciprofloxacin, CLDM: clindamycin, AMPH: amphotericin, FLCZ: fluconazole, iv: intravenous, CSF: cerebrospinal fluid, WBC: white blood cell, CRP: C-reactive protein

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

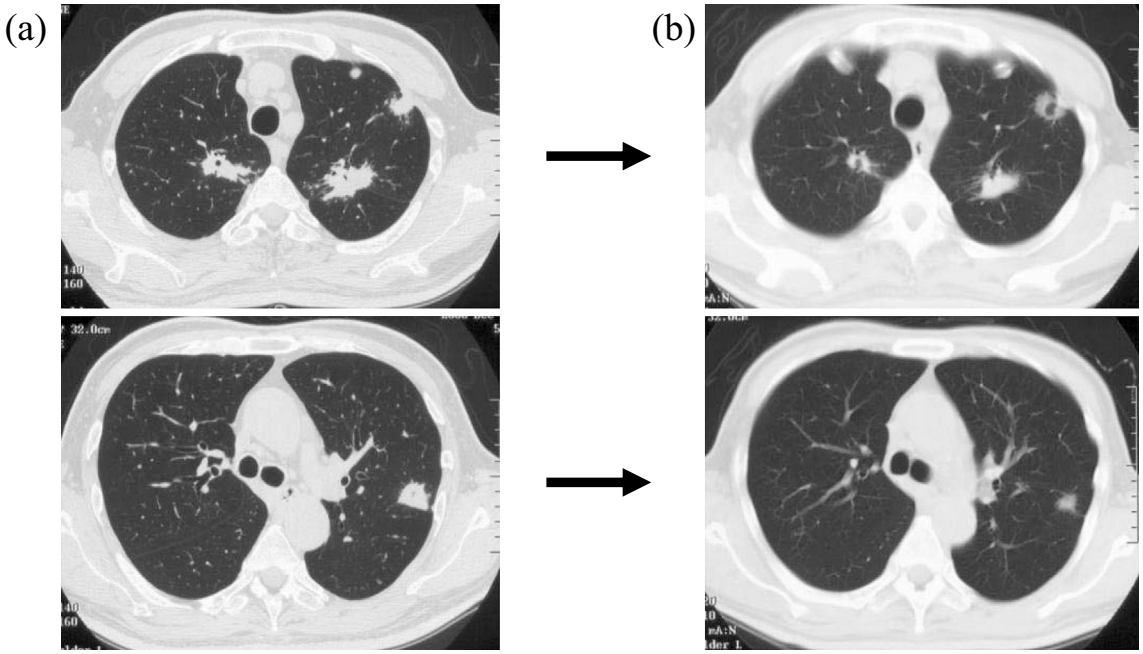

Figure 3. **Thoracic CT images of case 2. (a) on admission and (b) nine months after admission.**

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.

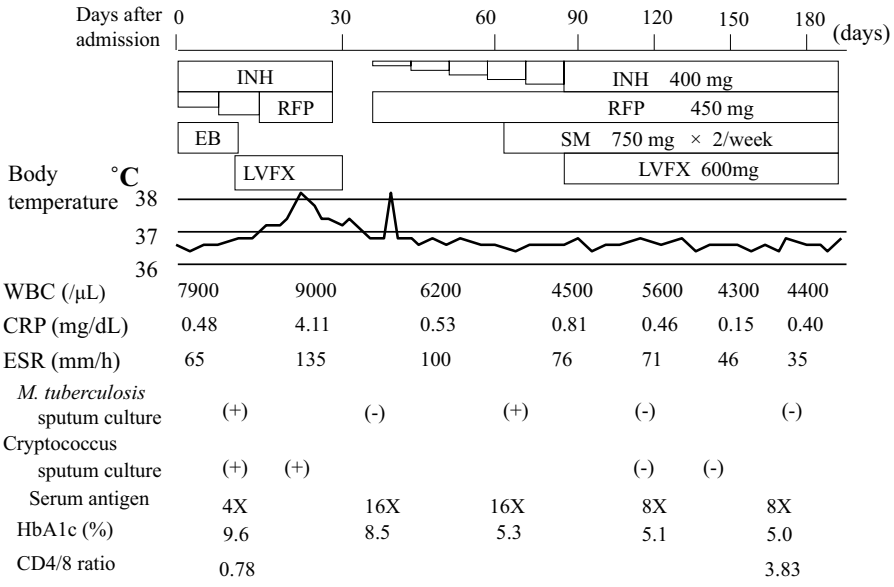

Figure 4. **Clinical course of Case 2. INH: isoniazid, RFP: rifampicin, EB: ethambutol, SM: streptomycin, LVFX: levofloxacin, WBC: white blood cell, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, HbA1c: glycated hemoglobin**

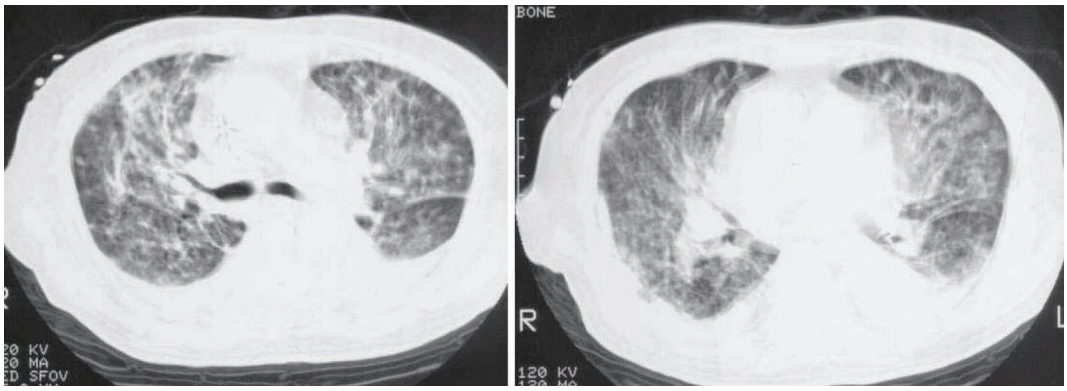

Figure 5. **Thoracic CT image of case 3 on admission.**

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.*

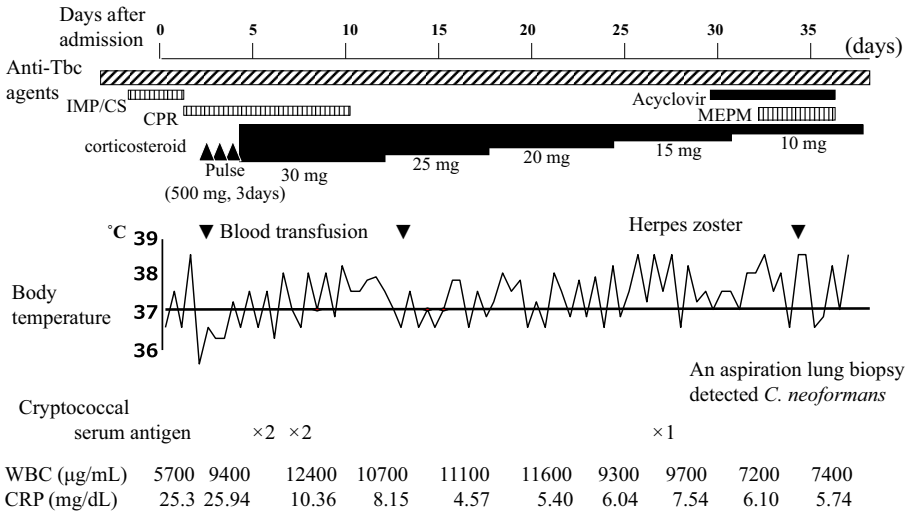

Figure 6. **Clinical course of case 3. Tbc: tuberculosis, IPM/CS: imipenem/cilastatin, CPR: cefpirome, MEPM: meropenem, WBC: white blood cell, CRP: C-reactive protein**

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

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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