Case Report

A Case of Disseminated Cryptococcal Infection and Concurrent Lung Tuberculosis in a Patient under Steroid Therapy for Interstitial Pneumonia

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Both disseminated cryptococcal infection and tuberculosis occur in hosts with impaired cell-mediated immunity, but there have been few reports about the concurrent infections in patients without human immunodeficiency virus infection. A 64-year-old man, who had been taking corticosteroids for interstitial pneumonia, was diagnosed with disseminated cryptococcal infection. While the patient was receiving anticytotoxic treatment, pulmonary tuberculosis also emerged. The patient developed acute exacerbation of interstitial pneumonia and passed away. Based on the patient’s clinical course, serial computed tomography images, and autopsy results, we believe that the preceding several months of corticosteroid treatment might have contributed to these coinfections in the lungs already vulnerable due to underlying fibrosis.

1. Introduction

Disseminated cryptococcal infection and tuberculosis are both known to occur in immunocompromised hosts, such as patients with human immunodeficiency virus (HIV) infection and diabetes mellitus and patients taking immuno-suppressants [1]. However, there are a limited number of reports regarding Cryptococcus neoformans and Mycobacterium tuberculosis coinfection [2–13] (Table 1). Here, we report a case of disseminated cryptococcal infection and concurrent pulmonary tuberculosis in a patient under prolonged corticosteroid treatment who experienced fatal acute exacerbation of previously diagnosed interstitial pneumonia.

2. Case Presentation

In April 2012, a 64-year-old man previously diagnosed with interstitial pneumonia presented to a local hospital, complaining of increasing dyspnea over the preceding 3 months. Because exacerbation of his interstitial pneumonia was considered, the patient was hospitalized and 60 mg/day oral prednisolone (PSL) was administered. As his dyspnea improved, the PSL dose was tapered by 5 mg every 4 weeks following discharge.

On September 2, almost three months after discharge, the patient suddenly developed a fever around 38°C and felt intermittent pain in his left lower leg. At that time, he was taking 25 mg of PSL daily. Although he developed steroid diabetes, his HbA1c levels were controlled within the normal range. When he presented to the emergency room of our hospital, his left lower leg had a localized reddish appearance and was slightly edematous without snowball crepitation. Although his consciousness was slightly impaired (Glasgow Coma Scale; E4V4M6), a cerebrospinal fluid (CSF) test without India ink staining was normal. Blood culture
Table 1: Reported cases of concurrent cryptococcosis and tuberculosis in patients without HIV infection.

| Age/sex | Race | Region | Underlying disease | Pathological lesions (Cryptococcus/tuberculosis) | Treatment (Cryptococcus/tuberculosis) | Outcome | References |
|---------|------|--------|--------------------|-----------------------------------------------|-------------------------------------|---------|------------|
| 1 61M   | NA   | United States | NA | CSF/lung | AMPH-B/INH, SM | Recovered | [2] |
| 2 69M   | Caucasian | United States | NA | Both were detected in the same nodule in the lung | KCZ/INH, RFP | NA | [3] |
| 3 51M   | NA | Spain | Chronic epididymitis | Both were detected in CSF at almost the same time | AMPH-B, 5-FC/EB, INH, RFP, PZA | NA | [4] |
| 4 61F   | Caucasian | NA | Waldenstrom's macroglobulinemia | CSE, blood/cerebral tissue | NA/EB, INH, RFP, SM | Lost to follow-up | [5] |
| 5 34F   | Asian | Saudi Arabia | NA | L4-5 vertebral abscess/right axillary lymph node | FLGZ/EB, INH, RFP, PZA | Recovered | [6] |
| 6 25F   | Asian | Italy | NA | Both were detected in CSF from the same sample | FLGZ, L-AMB/EB, INH, RFP, PZA, SM | NA | [7] |
| 7 62 (on average) | NA | Taiwan | * | Mediastinal lymph nodes and CSE/right upper lung lobe | AMPH-B, 5-FC/EB, INH, RFP, PZA | Two patients died due to either of the two primary infections | [8] |
| 8 18F   | Asian | Canada | NA | Both were detected in a large endobronchial mass | AMPH-B, LTCZ/NA | Lost to follow-up | [9] |
| 9 65M   | Asian | NA | NA | Both were detected in a large endobronchial mass | AMPH-B, INH, RFP, PZA | Discharged with neurological impairment | [10] |
| 10 58F  | Asian | Taiwan | NA | Left upper and right lower lung lobe/neck lymph node | FLGZ/NA | NA | [11] |
| 11 45F  | NA | Turkey | SLE | Both were detected in CSF at almost the same time | AMPH-B, FLGZ, L-AMB/EB, INH, RFP, PZA | Died due to aspiration pneumonia | [12] |
| 12 65F  | Asian | Japan | Diabetes | CSF/left upper lung lobe | AMPH-B, FLGZ, INH, RFP, PZA | Died due to hepatocellular carcinoma | [13] |
| 13 56M  | Asian | Japan | Diabetes, liver cirrhosis | Lung (revealed in autopsy)/lung, CSE | NA/INH, RFP, PZA, LVFX | Died due to respiratory and heart failure | [13] |
| 14 83F  | Asian | Japan | Rheumatoid arthritis, diabetes | Lung (revealed in autopsy)/lung, CSE | No treatment/EB, INH, RFP, PZA | Died due to respiratory failure | [13] |
| 15 64M  | Asian | Japan | Interstitial pneumonia | Skin, CSF, lungs, pleural membranes, prostate gland/right lower lung lobe, and right pleural effusion | FLGZ, 5-FC, L-AMB, VRCZ/INH, LVFX, AMK | Died due to respiratory failure | Present case |

NA: not available, SLE: systemic lupus erythematosus, CSF: cerebrospinal fluid, L4-5: the 4th and 5th lumbar vertebrae, AMPH-B: amphotericin B, INH: isoniazid, SM: streptomycin, KCZ: ketoconazole, RFP: rifampicin, 5-FC: 5-fluorocytosine, EB: ethambutol, FLGZ: fluconazole, L-AMB: liposomal amphotericin B, PZA: pyrazinamide, IT CZ: itraconazole, VRCZ: voriconazole, LVFX: levofloxacin, and AMK: amikacin.

*The article describes a study involving 12 non-HIV patients with coinfection of Cryptococcus and tuberculosis. Among the 12 patients, six had underlying diseases such as diabetes and eight had concurrent infections of the two pathogens in lungs, CSF, and other organs.
tests turned out to be negative. He was hospitalized with a diagnosis of acute bacterial cellulitis.

After admission, the patient received intravenous meropenem. His fever subsided and his mental status returned to normal within days. On day 23 after admission, his leg was no longer swollen or reddish, but the localized pain had not completely disappeared. In order to rule out malignancy and collagen vascular diseases, a skin biopsy of his left ankle was done, and it revealed *Cryptococcus neoformans* infection. We performed a second lumbar puncture, and India ink staining of the CSF also revealed *Cryptococcus* (Table 2). Since a latex agglutination test showed that both his serum and sputum were also positive for *Cryptococcus* antigen, we diagnosed the patient with disseminated cryptococcal infection.

A chest computed tomography (CT) scan taken on day 20 showed that a consolidation in the right upper lung lobe had increased from approximately 25 mm to approximately 40 mm in size (Figures 1(b) and 1(c)); this observation was considered to be asymptomatic focal pneumonitis due to *C. neoformans*. On October 4 (day 30), we initiated antifungal treatment with 250 mg/day (3.6 mg/kg/day) of intravenous liposomal amphotericin B (L-AMB) and 7,000 mg/day (100 mg/kg/day) of oral 5-fluorocytosine (5-FC). After 2 weeks of antifungal treatment, a follow-up CSF culture was negative, suggesting that the treatment was effective. Leukocytosis and serum CRP levels gradually decreased, and his leg pain disappeared. No meningeal signs were observed throughout the treatment course.

Nevertheless, the patient developed acute kidney failure and watery diarrhea possibly due to the L-AMB and 5-FC treatments, respectively. On day 50, we discontinued L-AMB and 5-FC and started the patient on 400 mg/day of oral fluconazole (FLCZ). When we confirmed that the side effects had abated, we added L-AMB again (Figure 2). Despite 4 weeks of cryptococcosis induction therapy, a CT scan on day 71 showed bilateral pleural effusions and further growth of the consolidation in the right upper lung lobe. However, based on repeated negative CSF culture results, we continued maintenance antifungal treatment using FLCZ.

On November 20 (day 77), the patient had a fever over 40°C and severe oxygen desaturation. A CT scan revealed diffuse ground-glass opacities in both lungs, which suggested acute exacerbation of interstitial pneumonia (Figure 1(d)). We started pulse intravenous steroid therapy with methylprednisolone (mPSL) 1,000 mg/day for three days, followed by intravenous PSL 1 mg/kg/day. However, this only halted...
Table 2: Major test results of CSF, blood, and sputum.

(a)

|                | Day 1 | Day 30 | Day 49 | Day 70 |
|----------------|-------|--------|--------|--------|
| Pressure (cmH₂O) | 13    | 5      | 6      | 10     |
| Cell numbers/µL (total) | 7     | 12     | 9      | 3      |
| (mono)          | 5     | 12     | 9      | 3      |
| (poly)          | 2     | 0      | 0      | 0      |
| CSF Cryptococcal antigen | N/A  | N/A  | >512  | 256   |
| India ink stain | N/A   | N/A   | Positive | N/A  |
| Cryptococcal culture | N/A | N/A | N/A | N/A |

(b)

|                | Day 23 | Day 30 | Day 38 | Day 72 | Day 78 | Day 91 |
|----------------|--------|--------|--------|--------|--------|--------|
| Blood QFT      | Negative |        |        |        |        | Undeterminable |
| Cryptococcal antigen | >512 |      |        |        |        | >512 |
| CMV antigenemia | Negative | Negative |        |        |        | Negative |
| Acid-fast staining | Negative |              |        |        | Positive (I+) | Negative |
| TB culture      | Negative |              |        |        | Positive | Negative |
| TB PCR          | Negative |              |        |        | Positive* | Negative |
| Cryptococcal antigen | Positive |        |        |        |        |        |

Bold parts: the results became positive while the patient was alive.

* Positive: the test results turned out to be positive after the patient died.

** Positive: the test result turned out to be positive on day 78.

QFT: QuantiFERON TB-2G test; NA: not available.

Figure 2: Clinical course. PSL: prednisolone, mPSL: methylprednisolone, L-AMB: liposomal amphotericin B, 5-FC: 5-fluorocytosine, FLCZ: fluconazole, VRCZ: voriconazole, DRPM: doripenem, PIPC/TAZ: piperacillin/tazobactam, INH: isoniazid, LVFX: levofloxacin, AMK: amikacin, BT: body temperature, KL-6: sialylated carbohydrate antigen KL-6, and CRP: C-reactive protein.

3. Discussion

We present a case of disseminated cryptococcal infection in a non-HIV patient who had received systemic corticosteroids (750 mg/every other day) intravenously. After 2 weeks of antituberculous treatment, acid-fast staining tests of his sputum were negative. However, his respiratory failure did not improve, and multiple organ failure developed gradually. He passed away on the 104th day of admission, and his body was autopsied.

The autopsy results were as follows. The lungs had developed significant fibrosis with honeycombing, particularly in the lower lobes. There were areas with diffuse alveolar damage characterized by dense infiltration of inflammatory cells and hyaline membranes. These findings were consistent with the clinical diagnosis of exacerbation of interstitial pneumonia. Cryptococcus was found mainly in the pleural membranes as well as in several lung lobes and the prostate gland; however, it was undetectable in the skin or CSF. M. tuberculosis was histologically observable as a caseous necrosis in the right upper lung lobe, where CT scans had revealed a 4 cm size consolidation (Figure 1(c), arrowheads). Furthermore, a slight amount of cytomegalovirus (CMV) was detectable throughout the bilateral lungs and seminal vesicles.

Because the patient had no known factors for immunosuppression other than prolonged steroid treatment, serum levels of autoantibodies against interferon-γ (IFN-γ) and granulocyte macrophage colony-stimulating factor (GM-CSF) were measured. Neither anti-IFN-γ nor anti-GM-CSF antibodies were detected in the serum.

The exacerbation, and the patient did not improve. On day 78, sputum PCR tests on both day 72 and day 78 turned out to be positive for M. tuberculosis (Table 2). Since the patient had respiratory failure and had difficulty taking oral medication consistently, we decided to treat him with isoniazid (300 mg/day), amikacin (250 mg/day), and levofloxacin (750 mg/every other day) intravenously. After 2 weeks of antituberculous treatment, acid-fast staining tests of his sputum were negative. However, his respiratory failure did not improve, and multiple organ failure developed gradually. He passed away on the 104th day of admission, and his body was autopsied.

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3. Discussion

We present a case of disseminated cryptococcal infection in a non-HIV patient who had received systemic corticosteroids
for several months prior to admission. Consolidation in the right upper lung lobe, which was first considered to be a primary focus of cryptococcal infection, grew in spite of antifungal treatment and was revealed to be tuberculosis during pathological examination. Although combination therapies targeting both cryptococcosis and tuberculosis seemed effective, the patient developed fatal multiple organ failure following acute exacerbation of interstitial pneumonia. The present case indicates that multiple pathogens should be considered for opportunistic infections in patients undergoing prolonged steroid therapy.

Serial changes in the CT appearance and laboratory tests as well as the autopsy findings indicated that this patient might have developed pulmonary infection within only three months due to three different pathogens: *C. neoformans*, *M. tuberculosis*, and CMV. Since tuberculosis screening by acid-fast staining of his sputum and interferon-γ releasing assay results were not definitive until day 78 (Table 2), development of tuberculosis was considered unlikely. However, CT images on the day of admission (Figure 1(a)) showed small nodules with centrilobular distribution in the right upper lung lobe, where the consolidation developed later in the disease course. Retrospectively, the small nodules on the CT images could have represented early radiological signs of tuberculosis. In addition, CMV pneumonia, which was not treated in the disease course, might have contributed to the fatal acute exacerbation of interstitial pneumonia. An intensive examination such as bronchoscopy could have detected *M. tuberculosis* and CMV at an earlier stage.

Although cryptococcosis and tuberculosis are both known to occur in immunocompromised hosts, there have been limited reports regarding concurrent cryptococcosis and tuberculosis infections [2–13]. Huang et al. and Kakeya et al. reported 8 and 3 cases of concurrent infection of *C. neoformans* and *M. tuberculosis*, respectively [8,13]. However, as explained by the authors in the former report, the diagnoses of the two pathogens did not always accurately account for disease pathogenesis: for example, they diagnosed cryptococcosis by only elevated cryptococcal antigen titer in clinical specimens. As summarized in Table 1, more than half of the reported cases had no underlying disease [2, 3, 6–11], which suggests that concurrent development of cryptococcosis and tuberculosis is rare but possible even in immunocompetent, non-HIV patients.

The present case also involved steroid-induced diabetes, which might have contributed to the development of the infection. We considered that, in addition to the prolonged corticosteroid treatment for interstitial pneumonia, there might have been a host factor that increased susceptibility to infection. It has been reported that neutralizing anti-IFN-γ autoantibodies are detectable in a large number of non-HIV Asian adults with multiple opportunistic infections [13], but none were detected in our patient. During the disease course, the patient’s serum immunoglobulin G (IgG) levels decreased from 1,268 to 583 mg/dL, while his CD4 level remained at 458/μL (day 30). Impaired humoral immunity, which might be associated with prolonged administration of systemic corticosteroids, could have been responsible for multiple opportunistic infections in our patient.

In this case, the tuberculosis diagnosis was delayed because a newly developed lung consolidation was presumed to be focal pneumonitis due to *C. neoformans* infection. Moreover, the CMV infection was not diagnosed during his lifetime since CMV antigenemia tests were repeatedly negative (Table 2). We usually consider multiple abnormal shadows within lungs to have the same etiology. However, pulmonary cryptococcal infections and pulmonary tuberculosis are known to produce a variety of patterns of CT findings, such as consolidations, small nodules, and pleural effusion, especially in an immunocompromised host [14, 15]. The present case suggests that prolonged steroid therapy could be associated with multiple opportunistic infections caused by different organisms, notably in patients with underlying lung disease.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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