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Short Communication

A Case of *Legionella pneumophila* Pneumonia Followed by Invasive Aspergillosis

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SUMMARY: We report a rare case of *Legionella pneumophila* pneumonia followed by invasive aspergillosis (IA). Legionellosis was ameliorated by the administration of ciprofloxacin, erythromycin, and corticosteroid as adjunctive therapy. Although intravenous administration of the corticosteroid was effective at reducing severe inflammation due to legionellosis, IA occurred at 12 days after admission. Combination therapy with micafungin and voriconazole was effective in this case; however, it remains necessary to exercise caution when making decisions regarding indications for corticosteroid use and observation in the treatment of severe pneumonia patients.

A 56-year-old man with mild alcoholic liver injury complaining of fever and shortness of breath was admitted to a local hospital. Chest roentgenogram and computed tomography (CT) revealed massive consolidation of the entire left lung. The patient was diagnosed with *Legionella pneumophila* pneumonia based on a positive *Legionella* urinary antigen test and was referred to our hospital for further treatment.

The patient was a construction worker and had visited a hot spring 10 days prior to hospital admission; there was no significant past history of immunosuppressive diseases.

Vital signs of the patient on admission were as follows: body temperature, 39.1°C; heart rate, 153 beats/min and regular rhythm; respiratory rate, 60 breaths/min; and blood pressure, 163/110 mmHg. Arterial blood gas analysis during 12 L/min oxygen inhalation was characterized as follows: pH 7.385; PaO_2, 70.3 torr; $PaCO_2$, 24.6 torr; and HCO_3^-, 14.4 mmol/L. The PaO_2/FiO_2 ratio was 70.

On physical examination, consciousness was slightly altered (Glasgow coma scale: E4V4M6), and left respiratory sounds were moderately diminished by auscultation. No abnormality was identified by neurological examination. Laboratory findings on admission are shown in Table 1. Following bronchoalveolar lavage (BAL) performed on the day after admission, *L. pneumophila* serogroup 1 was isolated by BAL fluid (BALF) culture. The findings indicated severe *L. pneumophila* pneumonia with respiratory failure, multiple organ damage (including the liver and kidneys), disseminated intravascular coagulation (DIC), and rhabdomyolysis. X-ray films, including CT on admission, revealed massive infiltration of the entire left lung with no abnormalities in the right lung or mediastinum (Figure 1).

The patient was admitted to the intensive care unit (ICU) and was placed on a ventilator with intubation. Both intravenous ciprofloxacin (CPFX) at a dose of 600 mg/day and erythromycin (EM) at 500 mg/day were administered for legionellosis. Hydrocortisone (240 mg/day) was also administered intravenously. After 7 days of treatment, the patient's body temperature declined to between 37 and 37.5°C, oxygenation improved moderately (PaO_2/FiO_2 ratio was 194), and the levels of C-reactive protein (CRP) and serum creatinine decreased to 6.86 and 3.6 mg/dl, respectively. Chest X-ray film showed reduced infiltration of the left lung. Hydrocortisone treatment was discontinued on day 7. CPFX and EM were discontinued on days 34 and 10, respectively.

On day 8, *Aspergillus fumigatus* was isolated via bronchial

Table 1. Laboratory findings on admission

Leukocyte	$3.1 \times 10^3/\mu l$	BUN	91 mg/dl
Nt	96%	Cr	5.9 mg/dl
Hemoglobin	15.1 g/dl	UA	12.3 mg/dl
PLT	$7.4 \times 10^4/\mu l$	T-Bil	2.5 mg/dl
		D-Bil	1.8 mg/dl
		ALP	194 IU/L
PT (INR)	1.23	γ-GTP	153 IU/L
APTT	36.9 sec	AST	119 IU/L
Fib	984 mg/dl	ALT	219 IU/L
FDP	19.1 μg/ml	LDH	1,746 IU/L
D-dimer	9.2 μg/ml	CK	669 IU/L
		CK-MM	99%
		Myoglobin	160 ng/ml
		CRP	63.3 mg/dl

Nt, neutrophil; PLT, platelet; PT (INR), prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; Fib, fibrinogen; FDP, fibrin degradation product; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; T-Bil, total bilirubin; D-Bil, direct bilirubin; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CRP, C-reactive protein.

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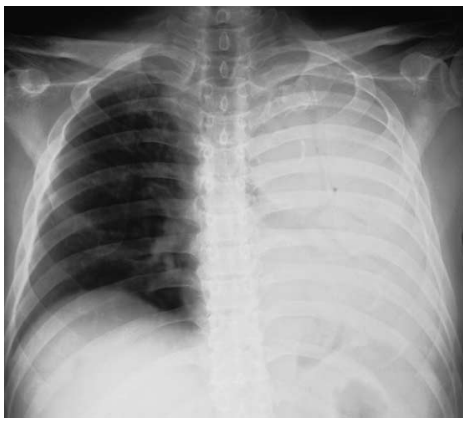

Fig. 1. Chest roentgenogram on admission shows infiltration of entire left lung.

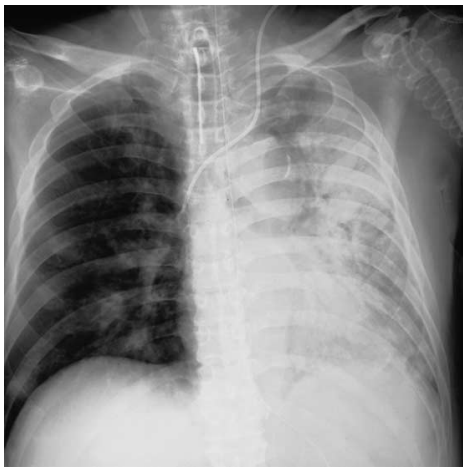

Fig. 2. Chest roentgenogram on day 12 shows multiple nodular shadows in the right lung and improvement of consolidation in the left lung.

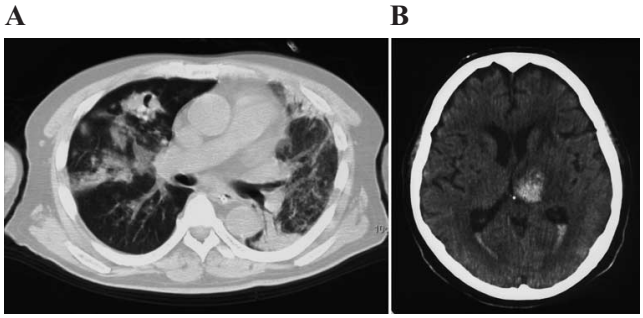

Fig. 3. (A) Chest CT on day 19 shows multiple patchy consolidations with one cavity lesion resembling an air crescent sign. (B) Brain CT on day 19 shows a high-density area surrounded by a low-density area in the left thalamus.

aspiration, although there were no significant changes seen on the chest X-ray. On day 12, multiple nodular shadows were recognized on the X-ray of the right lung (Figure 2), and the patient's leukocyte count and CRP level increased to 13,000/ μl and 14.35 mg/dl, respectively. Due to suspected invasive pulmonary aspergillosis (IPA), we initiated the administration of 150 mg/day of micafungin (MCFG). Despite these antimicrobial and antifungal therapies, the patient's body temperature increased to 38.5°C and right hemiparesis appeared on day 19. Brain, chest, and abdominal CT scans were performed, and multiple patchy consolidations with one cavity lesion resembling an air crescent sign were visible by chest CT (Figure 3A). A high-density area surrounded by a low-density area in the left thalamus was recognized by brain CT (Figure 3B). The β-D-glucan titer and results of an *Aspergillus* antigen test (ELISA) were 87.7 pg/ml and 1.101, respectively. Gomori's methenamine silver-nitrate stain indicated hyphae of filamentous fungi in the BAL fluid, and *A. fumigatus* was isolated from the BALF culture. These findings indicated the presence of invasive pulmonary and central nervous system aspergillosis.

The dose of MCFG was then increased to 300 mg/day and concomitant voriconazole (VRCZ) (400 mg/day) was administered. Although the general condition of the patient had gradually improved after the administration of antifungal drugs, liver dysfunction occurred on day 24. Since the concentration of VRCZ in the serum was elevated to 6.34 μg/ml, the dose of VRCZ dose was reduced to 100 mg/day. The liver dysfunction was reversed after the dose reduction of VRCZ, and the concentration of VRCZ fell to 0.05 μg/ml. We then increased the dose of VRCZ to 200 mg/day and achieved clinical improvement without liver dysfunction. Intubation was discontinued, as was treatment with MCFG and VRCZ on days 80, 34, and 90, respectively. Chest and brain CT images obtained on day 80 showed apparent improvement. On day 102, the patient was discharged from the hospital and no recurrence of pneumonia or aspergillosis has occurred to date. The minimum inhibitory concentrations (MICs) of the antifungal agents, with the exception of those of MCFG, against the isolated *A. fumigatus* were determined by the microdilution method according to the methods of the Clinical Laboratory Standards Institute, M38-A (1). Susceptibility to MCFG was measured by a method previously reported (2). The MICs of VRCZ, posaconazole, fluconazole, itraconazole, MCFG, and amphotericin B were 0.125, 0.03, 64, 0.125, 1.0, and 0.25 μg/ml, respectively.

L. pneumophila counts severe causative agents of community-acquired pneumonia (CAP), accounting for 3.9% of cases, and this pathogen is the third most commonly isolated in patients aged 40 - 54 years in Japan (3). The mortality among patients admitted to the ICU with severe CAP, including legionellosis, remains extremely high (22 to 54%) (4). Elevation of pulmonary and circulatory cytokines in severe CAP cases is considered to be associated with higher mortality and a poor outcome (5).

Corticosteroids suppress inflammatory reactions and prevent the migration of inflammatory cells from the circulatory system to tissues by inhibiting the synthesis of chemokines and cytokines (6). The use of corticosteroids has been demonstrated to be effective in patients with catecholamine-dependent septic shock and late acute respiratory distress syndrome (6,7). A recent study has also shown that adjunctive corticosteroid therapy improves clinical outcome in patients with severe CAP (8). We therefore selected a dose of 240 mg/day of continuous intravenous hydrocortisone for 7 days upon the patient's admission. In our case, corticosteroid treatment was effective at reducing severe inflammation due to legionellosis, however, invasive aspergillosis (IA) occurred 5 days after the discontinuation of corticosteroid treatment.

IA usually occurs in immunocompromised hosts such as patients with prolonged neutropenia, and mortality is extremely high (9). The use of corticosteroids for more than 3 weeks is considered a predisposing host factor of IA (10). Dual infection with *L. pneumophila* and *A. fumigatus* has rarely been reported and corticosteroid administration is also

considered a major risk factor, based on two previous reports (11,12). The steroid administration protocol in these reports was 40 mg/day of prednisolone for 3 weeks and 100 mg/day of prednisolone for 1 month. In our case, hydrocortisone treatment corresponding to 60 mg of prednisolone per day had been administered from days 1 to 7, i.e., for a relatively shorter duration than that reported in the literature. However, the status of the illness was extremely severe due to the preceding *Legionella* infection, and the ensuring infirmity may have influenced the immune status of the patient. Furthermore, since the patient was a construction worker by trade, it is possible that *A. fumigatus* derived from the soil might have colonized the patient's respiratory tract prior to the onset of legionellosis, and may have caused the IPA. These findings indicate that corticosteroid usage in cases of severe pneumonia might be a risk factor associated with IA, especially in patients with potentially heavy exposure to *Aspergillus* spp.

VRCZ is the first-line drug for the treatment of IPA, and combination use of antifungals is not routinely recommended according to the latest guidelines of the Infectious Diseases Society of America (13). However, there is a case report indicating the effectiveness of the combined use of caspofungin, an antifungal in the same class with MCFG, and VRCZ for the treatment of IA involving the cerebrum (14); a synergic interaction has also been reported in vitro and in animal studies (15,16). In our case, we administered MCFG alone, followed by an increased dose of MCFG concomitant with VRCZ therapy in order to maximize efficacy. This approach led to a full recovery in 3 months. Since both the drug MIC data and the VRCZ concentrations in the serum were favorable, it remains unclear whether increasing the dose of MCFG and/or the addition of VRCZ influenced the good outcome of this case. Further clinical studies will be necessary to determine the effectiveness of the combination use of antifugal agents for the treatment of IA.

In conclusion, we reported a case of severe *L. pneumophila* pneumonia followed by aspergillosis, which was successfully treated by the administration of CPFX, EM, MCFG, and VRCZ. Even the short-term use of corticosteroids in severely ill patients due to a preceding near-fatal infection such as legionellosis is considered to be a cause of IA. Adherence to accurate indications for corticosteroid use and careful observation of all patients receiving corticosteroid treatment remain important.

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