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# A fatal case report of invasive pulmonary aspergillosis and mucormycosis coinfection in an immunocompetent patient with coronavirus disease 2019 in Korea

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Systemic glucocorticoid treatment is highly recommended in critically ill coronavirus disease 2019 (COVID-19) patients. However, secondary fungal infections are of concern in such patients. Here, we describe the first case of COVID-19-associated invasive pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM) coinfection in a COVID-19 positive immunocompetent patient in Korea. A 69-year-old man was admitted to our hospital with COVID-19 pneumonia. He had no underlying comorbidities and was not taking medications. He received remdesivir, dexamethasone, and antibiotic therapy under mechanical ventilation. Although his condition improved temporarily, multiple cavities were observed on chest computed tomography, and *Aspergillus fumigatus* was cultured from tracheal aspiration culture. He was diagnosed with probable CAPA and received voriconazole therapy. However, his condition was not significantly improved despite having received voriconazole therapy for 4 weeks. After release from COVID-19 quarantine, he underwent bronchoscopy examination and was then finally diagnosed with CAPA and CAM coinfection on bronchoscopic biopsy. Antifungal treatment was changed to liposomal amphotericin B. However, his progress deteriorated, and he died 4 months after admission. This case highlights that clinical suspicion and active checkups are required to diagnose secondary fungal infections in immunocompetent COVID-19 patients who receive concurrent glucocorticoid therapy.

**Key Words:** aspergillosis; COVID-19; glucocorticoids; mucormycosis

**Case Report**

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The coronavirus disease 2019 (COVID-19) is a significant health concern worldwide. COVID-19 can cause acute respiratory distress syndrome and lead to high mortality even with proper diagnosis and treatment. Glucocorticoid therapy has been shown to reduce mortality in severely to critically ill COVID 19 patients [1]. Unfortunately, however, the widespread use of glucocorticoid therapy may be associated with opportunistic fungal infections such as COVID-19-associated invasive pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM) [2]. To our best knowledge, there have been no reports of combined fungal infections in COVID-19 patients in Korea to date. Thus, we report the first case of biopsy-proven coinfection of CAPA and CAM in an immunocompetent patient in Korea.

## CASE REPORT

This study was approved by the local Institutional Review Board of the Ulsan University Hospital (No. 2021-09-005) and abided by the principles outlined in the Declaration of Helsinki. Due to the retrospective design and the anonymization of the data, written informed consent was not obtained.

A 69-year-old man, chief engineer of the ship, was admitted to our hospital with fever, chills, dry cough, and headache. He was a 10 pack-year ex-smoker and had no comorbidities or pre-existing lung disease. He was in contact with patients with COVID-19 during a sea voyage. His reverse transcriptase-polymerase chain reaction (RT-PCR) test using a nasopharyngeal swab was positive, and he was diagnosed with COVID-19. His initial vital signs at admission demonstrated a body temperature of 36.4°C, blood pressure of 100/61 mm Hg, a heart rate of 88 beats per minute, and a respiratory rate of 20 breaths per minute. His oxygen saturation ($SpO_2$) was 90% on room air and improved to 97% with a nasal prong at 2 L/min. Laboratory results revealed a white blood cell count of 3,210 /μl, hemoglobin of 12.7 g/dl, platelets of 90,000 /μl, C-reactive protein of 8.88 mg/dl, procalcitonin of 0.41 ng/ml, ferritin of 749 ng/ml, D-dimer of 1.02 μg/ml, and lactate dehydrogenase of 335 IU/l. His initial chest radiograph showed diffuse, ill-defined increased opacity in the peripheral portion of his right upper and both lower lung zones (Figure 1A), and he was then treated with intravenous remdesivir (200 mg on day 1 and 100 mg on day 2–5), oral dexamethasone (6 mg daily), and oral moxifloxacin (400 mg daily).

On hospital day 7, he was transferred to the intensive care unit (ICU) and treated with a high-flow nasal cannula (fraction of inspired oxygen, 0.7) due to a $SpO_2$ of 88% on reservoir mask and progression of bilateral pulmonary infiltrates on his chest radiograph. The dexamethasone and moxifloxacin were switched from oral to intravenous therapy, and intravenous ceftriaxone (2 g daily) was also administered. On hospital day 10, his respiratory status deteriorated, and he was intubated; thereafter, he was positioned prone due to severe hypoxemic respiratory failure (ratio of partial pressure arterial oxygen and fraction of inspired oxygen, 70) after the application of invasive mechanical ventilation. Additionally, he received extended intravenous dexamethasone therapy (6 mg daily for 20 days and followed by 3 mg daily for 8 days). His oxygen demand and chest radiograph gradually improved, and he was extubated on hospital day 18. At this stage he showed clinical improvement; his hypoxemia improved to 98% with a high-

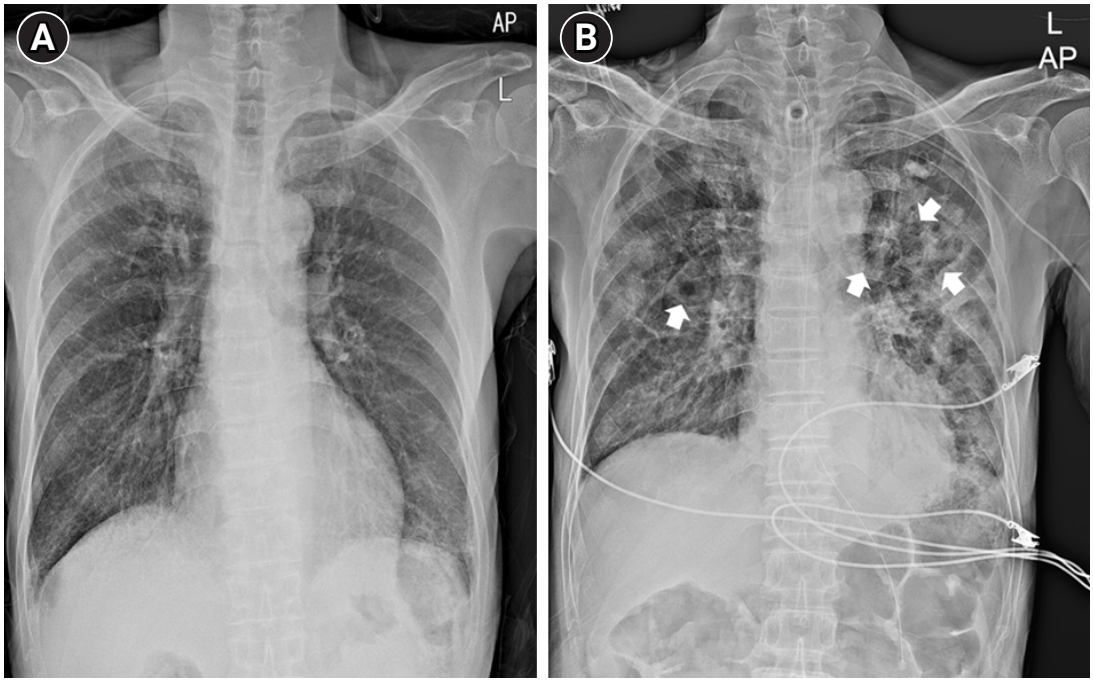


**Figure 1.** (A) Chest radiograph showing diffuse, ill-defined increased opacity in the peripheral portion of the right upper and both lower lung zones at admission. (B) Worsening of the radiograph findings showing that new bilateral patchy and ill-defined nodular consolidations and suspicious cavities (arrows) developed in both lungs. Consolidations and cavities were the most severe in the left upper to middle lung zones at time of re-intubation and tracheostomy.

flow nasal cannula (fraction of inspired oxygen, 0.35), and his chest radiograph showed significant resolution of both lower lung field infiltrations until hospital day 26. However, he was reintubated and underwent tracheostomy on hospital day 32 due to respiratory muscle fatigue, poor sputum expectoration, and an unstable hemodynamic status. On the chest radiograph, new bilateral patchy and ill-defined nodular consolidations developed in both lungs, which were most severe in the left upper to middle lung zones. Cavities were also suspected (Figure 1B). It was suspected that he had hospital-acquired pneumonia based on his clinical manifestation, and intravenous meropenem (1 g every 8 hours) and teicoplanin (6 mg/kg every 24 hours) were initiated on hospital day 32. However, transtracheal aspiration culture grew *Aspergillus fumigatus* repeatedly (on hospital days 36, 38, and 44), a galactomannan assay of tracheal aspiration was positive (5.24), and chest computed tomography (CT) showed multiple cavities with low attenuated consolidations which were surrounded by ground-glass opacity in both lungs (Figure 2). Probable CAPA was suspected; therefore, intravenous voriconazole (6 mg/kg every 12 hours daily for two doses, then 4 mg/kg every 12 hours daily) was administrated on hospital day 36 [3]. Despite 4 weeks of voriconazole therapy, his clinical condition and chest radiographic findings did not show significant improvement. On hospital day 60, bronchoscopy was performed after he was released from COVID-19 isolation following two negative RT-PCR results using both a nasopharyngeal swab and a lower respiratory specimen on sequential samples taken at least 24 hours apart. Based on bronchoscopy, white and thick mucus plugs were observed from the distal trachea via the right main to right lower lobe bronchus, suggestive of pseudomembranous tracheobronchitis (Figure 3). The galactomannan assay of the bronchoalveolar lavage was positive (4.99), and histopathology examination of the biopsy specimens demonstrated two morphological forms of fungal hyphae (broad non-septated hypha was mucormycosis and slender septated hypha was aspergillosis) involving the bronchial cartilage (Figure 4). Consequently, the diagnosis was revised to coinfection of confirmed CAPA and CAM, and the voriconazole was changed to intravenous liposomal amphotericin B (5 mg/kg daily) on hospital day 65 [4]. Considering the disease extent and the difficulty with weaning him off mechanical ventilation, he has kept on antifungal therapy without operation following consultation with a multidisciplinary team including a radiologist, pathologist, pulmonologist, and thoracic surgeon. Despite antifungal therapy, broad spectrum antibiotics, repeated bronchoscopic toileting, chest physical therapy, rehabilitation and ventilatory support, his progress deteriorated. His family was informed of treatment option, and he died of multiple organ failure including respiratory, cardiogenic, and renal failure on the 4 months after hospital admission. His hospital course and management were summarized in Figure 5.

## DISCUSSION

Aspergillosis and mucormycosis are rare, life-threatening invasive fungal infections recognized as secondary complications of COVID-19 especially among critically ill patients in the

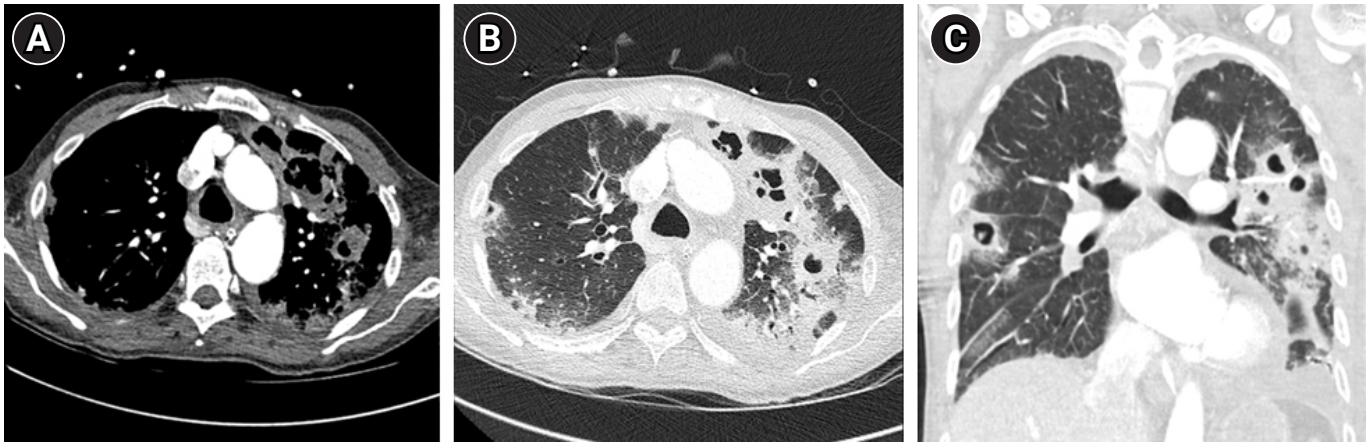


**Figure 2.** (A) Chest computed tomography (CT) showing multiple low attenuated consolidations and cavities in both lungs in the axial view of CT (mediastinal window). The cavities were surrounded by ground-glass opacity in both lungs called a "Halo sign" in transverse (B) and coronal (C) views of CT (lung window).

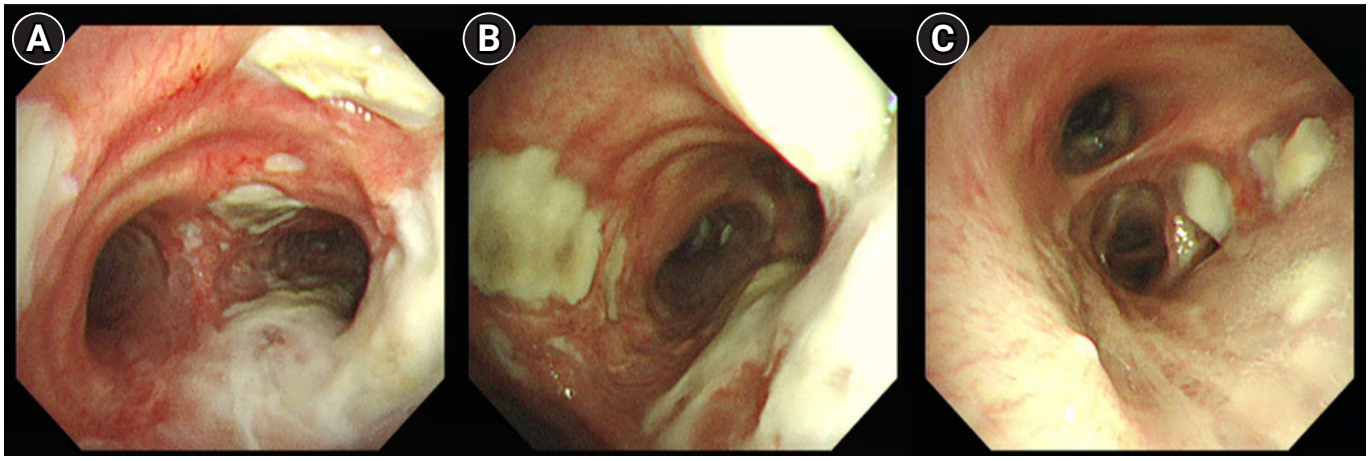


**Figure 3.** Bronchoscopic findings from the patient. Wide, raised, and cream colored thick pseudomembrane were observed from the distal trachea (A), right main bronchus (B), to the right lower lobe bronchus (C).

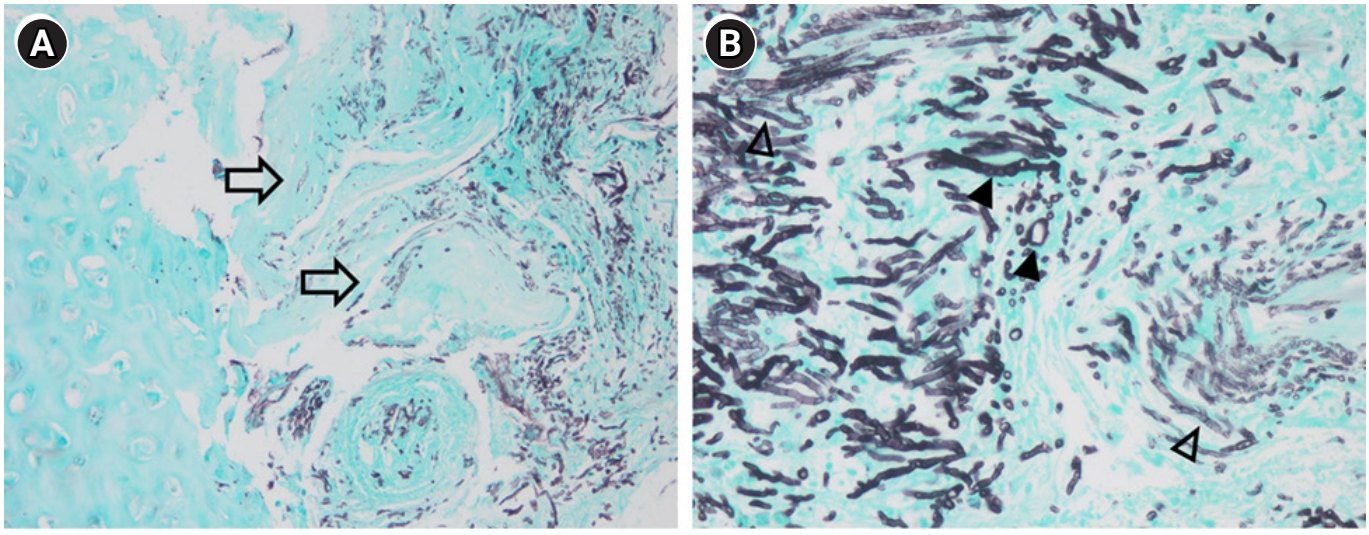


**Figure 4.** (A) Grocott methenamine silver stain of the tracheobronchial biopsy specimens. Many invasive fungal organisms were identified in the bronchial cartilage (empty arrows) with an original magnification ×200. (B) Most of the invasive component was a broad non-septate fungal organism (arrowheads), but a few fungi had more slender and septate hyphae (empty arrowheads) identified with an original magnification ×400.

ICU [2]. These fungal infections have led to high mortality in COVID-19 patients compared to COVID-19 patients without fungal infections [3,5]. The major risk factors for aspergillosis and mucormycosis include hematologic malignancies, solid organ transplantation, stem cell transplantation, uncontrolled diabetes mellitus, deferoxamine therapy, prolonged corticosteroid usage, and malnutrition [3,6]. Our patient did not have any of these risk factors or underlying diseases, nor was he taking any medications at the time of hospital admission. However, he developed a secondary fungal infection during the management of COVID-19. We hypothesize that his fungal infection was highly related to the concurrent glucocorticoid therapy for COVID-19. Although a recent case report identified a fungal infection in an immunocompetent host [7,8], this patient was the first case of biopsy-confirmed coinfection of CAPA and CAM in an immunocompetent COVID-19 patient without an underlying disease.

Diagnosis of fungal infections in COVID-19 patients remains challenging. CAM is rarer than CAPA, and both CAPA and CAM share similar risk factors, clinical presentations, and radiologic findings [9]. While a galactomannan assay using serum and bronchoalveolar lavage is a useful marker of

Transfer to intensive care unit
Extubation
Diagnosis of CAPA & start voriconazole
First bronchoscopy
Diagnosis of CAPA/CAM coinfection & start liposomal amphotericin B
Admission to general ward & isolation
Intubation
Reintubation & tracheostomy
Released from COVID-19
Second bronchoscopy
Death

| Hospital day | 1 | 7 | 10 | 18 | 21 | 29 | 32 | 36 | 42 | 46 | 49 | 52 | 57 | 60 | 65 | 68 | ▪▪▪ | 130 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dexamethasone (mg) | 6 | 6 | 6 | 6 | 3 | stop | | | | | | | | | | | ▪▪▪ | |
| Hydrocortisone (mg) | | | | | | | | 200 | 100 | 75 | stop | | | | | | ▪▪▪ | |
| Prednisolone (mg) | | | | | | | | | | | 15 | 10 | 10 | 5 | 5 | Stop | ▪▪▪ | |
| White blood cell (/ul) | 3,210 | 1,740 | 5,760 | 17,250 | 7,660 | 21,340 | 28,830 | 20,270 | 20,930 | 14,570 | 13,300 | 13,660 | 10,250 | 8,810 | 9,150 | 11,080 | ▪▪▪ | 45,090 |
| Neutrophil (%) | 66 | 82.8 | 95.3 | 97.1 | 95.8 | 94.5 | 95.3 | 97.2 | 96.4 | 94 | 89.8 | 87.8 | 84.5 | 81 | 78.6 | 81.1 | ▪▪▪ | 70 |
| Lymphocyte (%) | 24 | 13.5 | 1.2 | 0.4 | 1.4 | 2.2 | 1.1 | 0.7 | 1.4 | 2.7 | 5 | 5 | 6 | 8.1 | 8.6 | 7 | ▪▪▪ | 3 |
| C-reactive protein (mg/dl) | 8.08 | 8.56 | 2.12 | 1.57 | 12.41 | 12.6 | 21.22 | 19.43 | 5.01 | 3.32 | 5.08 | 7.19 | 7.15 | 4.31 | 7.02 | 6.93 | ▪▪▪ | 4.54 |
| Procalctionin (ng/ml) | 0.41 | 0.58 | | | 0.23 | 0.66 | | 1.42 | | | | 0.14 | | | 0.11 | | ▪▪▪ | |
| Serum glucose (mg/dl) | 117 | 82 | 199 | 147 | 83 | 116 | 117 | 266 | 108 | 146 | 111 | 95 | 102 | 107 | 128 | 182 | ▪▪▪ | 154 |
| Galactomman (serum) | | | | | | | Negative | | | | | | | | | | ▪▪▪ | |
| Galactomannan (trans-tracheal or bronchoscopic) | | | | | | | | Positive, 5.240 | | | Positive, 4.862 | | | Positive, 4.990 | | | ▪▪▪ | |

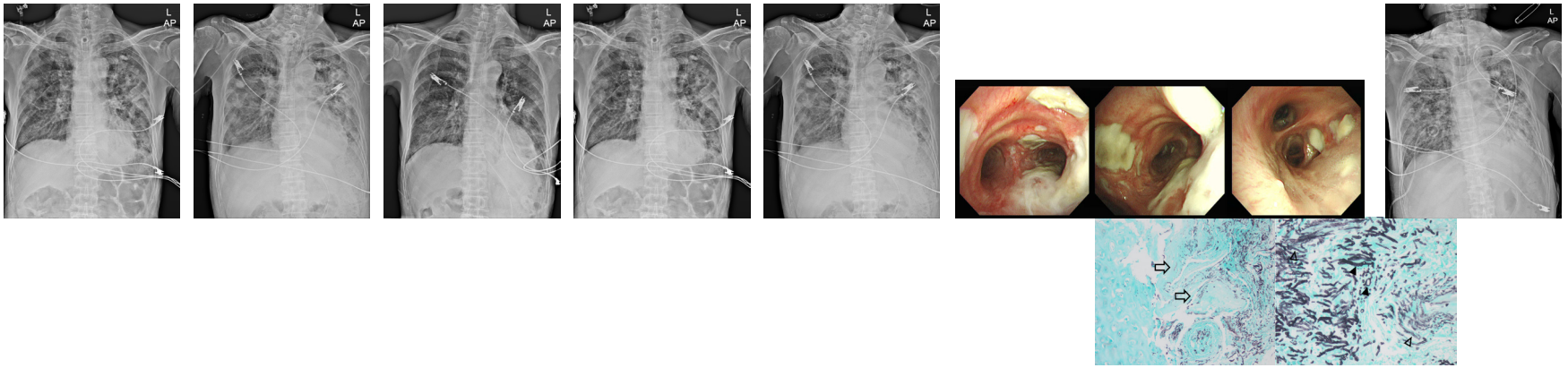

**Figure 5.** Hospital course and steroid therapy of the patient. CAPA: coronavirus disease 2019-associated invasive pulmonary aspergillosis; CAM: coronavirus disease 2019-associated mucormycosis; COVID-19: coronavirus disease 2019.

screening for CAPA [3], a routinely available fungal biomarker for CAM is lacking. Additionally, diagnostic tests such as CT, bronchoscopy with bronchoalveolar lavage, and biopsy are rarely performed due to the infectious risk of aerosols in COVID-19 patients. Therefore, delayed- or under-diagnosis of fungal infections in COVID-19 patients is relatively common and might contribute to the high mortality of fungal infections in COVID-19 patients. We initially diagnosed our patient with CAPA based on the corticosteroid usage history, transtracheal aspiration culture results, galactomannan assay results from tracheal aspiration, and the chest CT findings obtained without bronchoscopy. Thereafter, he was administered voriconazole therapy based on the guidelines for European Confederation of Medical Mycology/International Society for Human and Animal Mycology consensus criteria for research and clinical guidance [3]. However, he did not show significant clinical improvement after 4 weeks of voriconazole therapy and was finally diagnosed with CAPA and CAM coinfection at the time of release from quarantine. The isolation required for COVID-19 due to the risk of airborne transmission contributed to his delayed diagnosis. Although voriconazole was an effective treatment for aspergillosis, it did not have reliable activity against mucormycosis [4]. We thought that this might affect the bronchoscopic biopsy results of numerous mucormycosis and fewer aspergillosis cases.

Our case report highlights that a high index of suspicion and active checkups are required for the early diagnosis of fungal infections in immunocompetent critically ill COVID-19 patients who receive concurrent glucocorticoid therapy. CAPA is a common fungal infection in critically ill COVID-19 patients [10]. However, in cases where there is no clinical improvement despite the use of appropriate treatment for CAPA, CAM or CAPA and CAM coinfection should be considered. Additionally, if possible, early disposable bronchoscopic exam to obtain a bronchoalveolar lavage sample or biopsy specimens should be strongly considered for an accurate diagnosis of patients who do not respond to standard treatment.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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