

CASE REPORT

COVID-19-Associated Pulmonary Aspergillosis: A Case Report from the COVID-19 Surveillance Program

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Abstract

A 72-year-old male was brought to the hospital following a motorcycle crash and was admitted for multiple trauma management. His initial course of hospitalization was complicated by mild hypoxemia and altered mental status. Respiratory workup and imaging were consistent with SARS-CoV-2 pneumonia. He completed a five-day course of remdesivir and a ten-day course of dexamethasone. Twenty days later, he developed a low-grade fever. His chest computerized tomography (CT) showed gas and fluid containing parenchymal collection in the anteromedial right middle lobe measuring up to 4.8 cm, most consistent with a pulmonary abscess. Antimicrobial treatment was started.

The patient became hypoxic and was intubated and mechanically ventilated. Bronchoalveolar lavage fluid was positive for galactomannan assay, a diagnostic marker for possible aspergillosis. A repeat chest CT showed a cavitary lesion with a positive air crescent sign, a common CT finding of invasive pulmonary aspergillosis. The patient was diagnosed with COVID-19-associated pulmonary aspergillosis and was started on antifungal treatment. He improved clinically and was successfully extubated.

Introduction

Bacterial and fungal superinfections are common complications of viral pneumonia. The incidence varies between hospitals. One prospective study reported that 22% of the hospitalized COVID-19 patients experienced superinfections during their hospital stay. The median time from their admission to superinfection was 19 days.[1] The SARS-CoV-2 virus may affect the length of stay and prognosis. The combination of severe respiratory infections caused by SARS-CoV-2 or influenza, with or without a severely weakened immune system and vascular invasion of the airways, is thought to compromise the mucosal clearing mechanism and weaken its ability to protect the lungs.[2] This may increase the severity of the respiratory infection, prolong the duration of hospitalization, and worsen the overall outcome. The following report summarizes a case of COVID-19-associated pulmonary aspergillosis (CAPA); IRB #20.0225.

Case report

A 72-year-old male with a history of essential hypertension, hyperlipidemia, and gout was brought to the emergency department following a motorcycle crash. Radiologic reports determined no skull, chest, or pelvic fractures. However, upon admission, he was found to have multiple long bone fractures in his upper and lower extremities. Chest X-ray was negative for pneumonia upon admission. He had a temperature of 96.7 °F, a heart rate of 86 beats/minute, a respiratory rate of 18 breaths/minute, blood pressure of 103/56 mmHg, and an O₂ saturation of 95% on 2 L of supplemental oxygen. A nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR) swab was positive for SARS-CoV-2. His initial arterial blood gases showed pH 7.33, pCO₂ 37.5 mmHg, pO₂ 325 mmHg, bicarbonate 20 mmol/L, and a base deficit of -3.5 nmol/L while receiving an FiO₂ of 100%.

On day 4 of hospitalization, he developed a low-grade fever of 101.3 °F, along with a new mildly altered mental status. The patient denied shortness of breath and

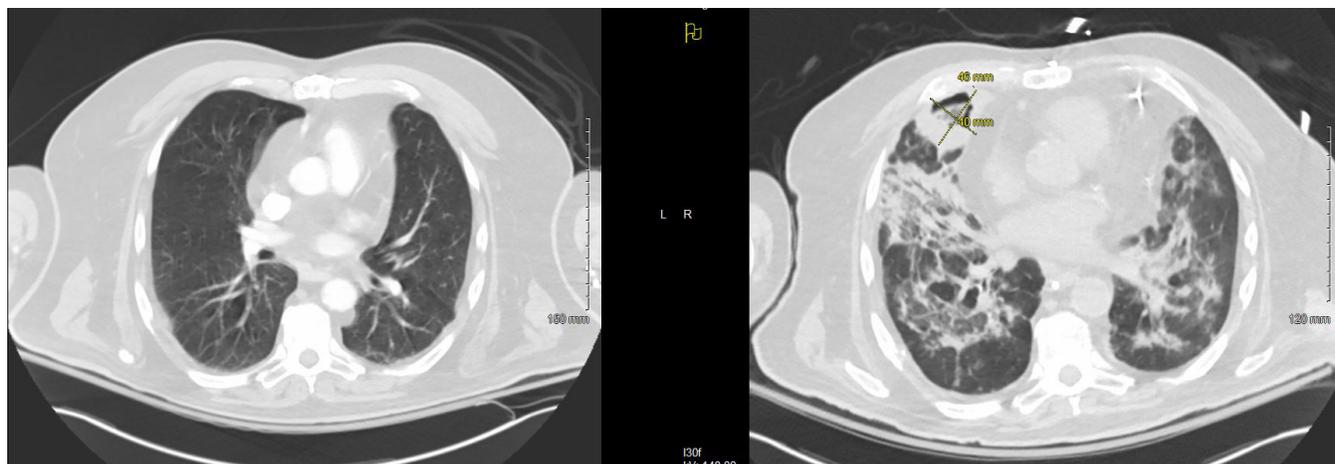


Figure 1. Chest computed tomography of a patient with COVID-19-associated pulmonary aspergillosis with worsening pulmonary infiltrates between admission (left) and hospital day 29 (right).

chest tightness but developed labored breathing with increased oxygen requirements. Although his mental status continued to decline over the following two days, it was thought to be due to hypoxemia. He was admitted to the intensive care unit (ICU) and started treatment with 200 mg remdesivir, followed by a four-day course of 100 mg remdesivir along with 6 mg of dexamethasone daily for a total of 10 days. The patient completed his anti-COVID-19 regimen and was weaned to high-flow O₂ via an oxygen mask.

A repeat chest X-ray showed bibasilar infiltrates. His hospital course was complicated by a persistent fever, which in turn increased the suspicion of hospital-acquired pneumonia.

On day 29 of hospitalization, the patient had a chest computed tomography (CT), which showed an air-fluid collection in his right middle lobe measuring 4.8 cm, consistent with a lung abscess (**Figure 1**). The patient was started on vancomycin and piperacillin-tazobactam. Serum galactomannan assay was negative, while bronchoalveolar lavage (BAL) galactomannan was positive. His serum (1,3)- β -D-glucan was <31 pg/mL (<80 pg/mL). He was started on 6 mg/kg voriconazole every 12 hours to cover invasive pulmonary aspergillosis (IPA). After nine days of voriconazole use, his liver enzymes increased. Aspartate aminotransferase increased to 124 U/L, alanine aminotransferase increased to 40 U/L, and alkaline phosphatase increased to 407 U/L. The voriconazole dose was decreased to 4 mg/kg every 12 hours, and the transaminases were monitored. After 32 days of voriconazole, the patient was switched to 200 mg posaconazole every 8 hours to minimize the risk of hepatic toxicity. Despite the patient's clinical improvement, the liver enzymes continued to trend upward, and clinical judgment dictated that the risk of continuing an-

tifungal medication outweighed the expected benefits. Therefore, the posaconazole was stopped after a total antifungal treatment of 35 days. Outpatient follow-up was recommended to reassess the need for antifungal medications.

Discussion

Secondary respiratory infections in patients with COVID-19 are significant complications to recognize, especially in critically ill patients admitted to the ICU. Factors complicating the study of CAPA include the novelty of the COVID-19 pandemic, the rapidly evolving number of new cases, and the lack of standardized protocols for the diagnosis and management of cases.

Bronchoscopy is an aerosol-generating procedure, so its use is limited in COVID-19 patients.[3] As a result, the bronchial fluid galactomannan assay and (1,3)- β -D-glucan cannot be performed for some patients despite the high suspicion of CAPA.

CAPA is a complication following SARS-CoV-2 in critically ill patients with acute respiratory distress syndrome (ARDS); incidence rates of coinfection vary between 8 and 33%.[4] In a study from the United Kingdom National Mycology Reference Laboratory, among 719 critically ill patients, the incidence of probable/proven cases of CAPA was 5% and of possible cases of CAPA was 15%.[4]

Aspergillus is a common mold, over 40 species of which can infect humans. *Aspergillus* is ubiquitous both indoors and outdoors, and its spores can easily reach the host's alveoli.[5] For those who are immunosuppressed, breathing in *Aspergillus* conidia—a type of spore produced at the tip of specialized fungal

hyphae—can cause an infection in the lungs or sinuses, spreading to other parts of the body.[5] The invasive nature of this pathogen is propagated when the conidia reach the host's alveoli, germinate inside the respiratory tract, and activate neutrophil recruitment. In turn, there is a massive influx of inflammatory cytokines, including tumor necrosis factor- α (TNF- α). Immunocompetent hosts can clear these conidia and prevent invasion of the alveoli.[5, 6]

The use of dexamethasone is a cornerstone of the treatment of hypoxic respiratory failure in critically ill patients with COVID-19 pneumonia, but corticosteroid use may increase the risk of developing IPA.[7–9] A retrospective database review of 412 patients with IPA in the ICU, excluding transplant, cancer, AIDS, and neutropenic patients, found that 77% ($n=315$) of the patients received high-dose corticosteroid therapy, such as dexamethasone, during their hospital stay.[7] Among 108 intubated patients with COVID-19 in the ICU, 30 (28%) were diagnosed with probable CAPA between a median of 4 days (range 2–8 days) following intubation to a median of 14 days (range 11–22 days) from the first day of COVID-19 symptoms.[8] The only factor associated with CAPA was prolonged steroid use at a dosage higher than or equivalent to prednisone 16 mg/day for at least 15 days. Furthermore, in a systematic review performed in Basel, Switzerland, 85 patients with CAPA in 22 studies were identified.[9] None of the cases had immunosuppression due to organ transplant or neutropenia, although 39 out of 85 patients received corticosteroids as a part of the COVID-19 treatment.

The benefit of dexamethasone treatment to patients with SARS-CoV-2 infection is believed to be due to the anti-inflammatory effect of dexamethasone during the cytokine storm and ARDS.[10, 11] However, dexamethasone also compromises the function of alveolar macrophages, providing a greater opportunity for *Aspergillus* conidia to germinate, resulting in an increased

risk of developing CAPA.

The respiratory epithelial structural damage in patients with ARDS following SARS-CoV-2 infection may also contribute to the increased risk of developing CAPA.[12] Respiratory viral infections damage the lung epithelium by disrupting tight junctions among epithelial cells.[13] Moreover, viral infections hamper ciliary clearance by respiratory epithelium.[14] Together, these factors enable *Aspergillus* conidia to proliferate and invade lung tissue while avoiding clearance.

Early diagnosis and treatment of CAPA are crucial to predict and improve patient outcomes.[8] Bartoletti et al. found that a diagnosis of CAPA was associated with increased 30-day mortality from ICU admission, even after adjusting for renal replacement therapy, and Sequential Organ Failure Assessment score at ICU admission.[8] The same study assessed mortality outcomes of CAPA patients who underwent antifungal treatment. A total of 53% ($n=16$) underwent antifungal treatment, of whom 81% ($n=13$) underwent treatment with voriconazole. Among patients with probable CAPA, those treated with voriconazole trended towards a lower mortality.[15] These results demonstrate the need for treatment of CAPA when clinically suspected.

Conclusion

CAPA is a major complication of SARS-CoV-2 pneumonia. It worsens the course of the disease, increases the risk of mortality, increases the severity of the infection, and prolongs the duration of hospitalization.[4, 8] The use of dexamethasone and alveolar structural damage caused by SARS-CoV-2 infection both play a role in facilitating the invasion of the pulmonary tissue and vessels by *Aspergillus*. [11, 12] Therefore, early diagnosis is critical for improved patient outcomes. Further studies are required to establish a standardized algorithm for early diagnosis and management of cases of CAPA.

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