Double Trouble: COVID-19 Pneumonia Concurrent With COVID-19-Associated Pulmonary Aspergillosis

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ABSTRACT

Introduction: Severe complications due to COVID-19 are a growing concern. We present a case of COVID-19 pneumonia with development of a superimposed COVID-19–associated pulmonary aspergillosis.

Case Presentation: A 52-year-old unvaccinated male with a history of asthma and sleep apnea presented with progressive dyspnea 10 days after COVID-19 diagnosis. Worsening respiratory function despite broad-spectrum antibiotics and negative cultures prompted a repeat respiratory culture that revealed *Aspergillus*; voriconazole was initiated.

Discussion: The risk of COVID-19–associated pulmonary aspergillosis is highest in patients who are immunosuppressed or who receive corticosteroids to treat COVID-19 infection. Subtle and atypical presentations can be seen; our patient had only mild leukocytosis and progressive dyspnea with a negative initial respiratory culture. COVID-19–associated pulmonary aspergillosis is associated with high morbidity and mortality; thus, prompt diagnosis and treatment may confer a survival benefit.

Conclusions: Despite the subtle presentation and variable radiographic findings in COVID-19–associated pulmonary aspergillosis, a low clinical threshold for workup is crucial to a timely diagnosis and treatment.

INTRODUCTION

Aspergillus is an opportunistic fungal pathogen that historically is known to cause potentially devastating disease in immunocompromised individuals.[1] It also has been established recently that invasive pulmonary aspergillosis (IPA) can cause illness in immunocompetent but critically ill patients with various risk factors. These include, but are not limited to, steroid use, chronic obstructive pulmonary disease, diabetes, and influenza infection.[2,3] Over the last 2 years, IPA increasingly has been reported secondary to severe COVID-19 pneumonia. This phenomenon has been termed COVID-19–associated pulmonary aspergillosis (CAPA). Diagnostic challenges and differing case definitions have made it difficult to assess the true incidence of CAPA; however, it is estimated to affect approximately 10% of mechanically ventilated COVID-19 patients.[4-6] Superinfections like CAPA may not only prolong the acute phase of COVID-19 infection but are associated with significant morbidity and mortality.[7] As the pandemic continues, awareness of rare secondary complications – particularly those that manifest with subtle and nonspecific clinical presentations – becomes exceedingly necessary.

CASE PRESENTATION

A 52-year-old unvaccinated male with a past medical history significant for asthma and uncontrolled obstructive sleep apnea presented to the emergency department (ED) in October 2021, a time when the highly infective delta variant was the dominant strain of the SARS-CoV-2 virus. He presented with worsening dyspnea 10 days after receiving a COVID-19 diagnosis from an at-home test. He also endorsed a nonproductive cough, fever, chills, and nonbloody diarrhea.

Upon initial presentation, his vitals were remarkable for arterial oxygen saturation (SaO_2) of 65% on room air; thus, he was placed on high-flow nasal cannula (HFNC) due to critical hypoxemia. A physical exam revealed scattered bilateral crackles throughout the lung space. Lab workup was significant for leuko penia (white blood cells [WBC] 1.7 K/uL). The initial lab workup was also significant for hyperglycemia (blood sugar 182 mg/dL, hemoglobin A1c 9.6%). A computed tomography (CT) pulmo-

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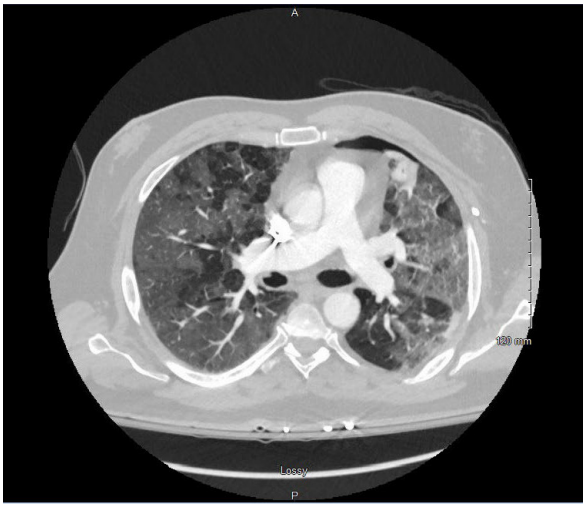
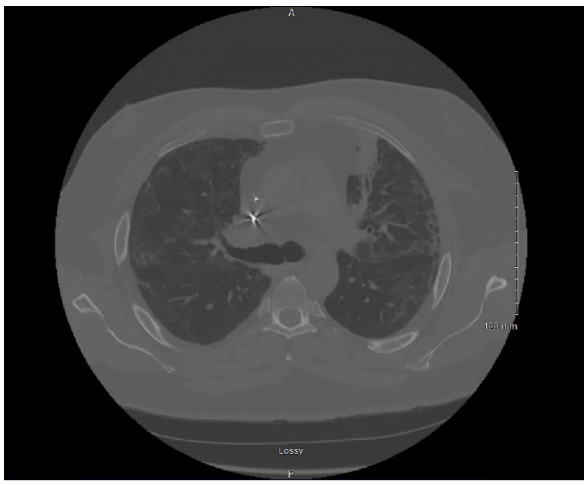
Figure 1. Repeat Chest Computed Tomography Angiography With Contrast During Initial Admission



Patient's central airways were patent with mild central airway secretions and diffuse bronchial wall thickening. There was mucous plugging in the subsegmental lower lobe. There is a presence of widespread consolidations, widespread ground glass opacities, and subpleural atelectasis in the left lower lobe.

Figure 2. Chest Computed Tomography Angiography Without Contrast 3 Months Posttreatment



At follow-up for COVID-19 pneumonia and *Aspergillus* infection, computed tomography revealed improving bilateral opacities with some areas of residual consolidation and bronchiectasis.

nary angiogram was negative, and a chest x-ray revealed multifocal, bilateral opacities. The patient was initiated on intravenous (IV) dexamethasone 10 mg twice daily and IV remdesivir 100 mg daily and later admitted to the medical intensive care unit for acute hypoxemic respiratory failure. He did not receive oral antivirals or monoclonal antibodies prior to admission. Notably, he had no prior diabetes diagnosis. Given his elevated A1c, he was started on a sliding scale insulin and glargine and followed by the diabetes care team for the remainder of his admission.

Barcitinib 4 mg daily was added to the patient's regimen for 14 days for its anti-inflammatory effects against COVID-19. Linezolid and cefepime were given as empiric antibiotic therapy due to concern for bacterial superinfection but were discontinued after receiving negative blood and sputum cultures. Days later, new leukocytosis (WBC 16.0 K/uL) and worsening dyspnea prompted a repeat standard sputum culture, which grew mold on a preliminary read. Oral voriconazole 600 mg was initiated empirically due to concern for *Aspergillus fumigatus* infection and was continued upon confirmation with a positive serum galactomannan assay.

A repeat CT pulmonary angiogram was negative for pulmonary embolus but revealed left pneumomediastinum, small right apical pneumothorax with associated subcutaneous emphysema, and bilateral ground-glass opacities (Figure 1). Despite ongoing treatment, the patient continued to require nasal cannula (NC) at rest and HFNC with minimal exertion. Nearly 2 months after admission, he was discharged home with instructions to continue voriconazole 400 mg oral twice daily, with close follow-up with pulmonology as an outpatient to monitor the medication's trough levels and assess for potential treatment side effects. He also was discharged home with new oxygen requirements of 3 L NC at rest and 6 L nasal cannula with exertion. On follow-up chart review, he completed 3 months of voriconazole, which was titrated down to 150 mg twice a day after his first follow-up appointment with pulmonology due to a supratherapeutic voriconazole level of 4.5 (reference range 0.5 – 4.0 mg/L). The trough levels became therapeutic following the dose reduction, and he did not report any side effects throughout the treatment course. Four months following discharge, he was no longer requiring supplemental oxygen and a repeat chest CT showed improving bilateral opacities with some areas of residual scarring (Figure 2).

DISCUSSION

The increasing incidence of CAPA in critically ill COVID-19 patients, in addition to regularly emerging new COVID-19 variants, makes the discussion of CAPA worthy of heightened attention. There is wide variability in the reported incidence of CAPA due to numerous factors, including differing diagnostic criteria in the first year of the pandemic, utilization of diagnostic tools with varying degrees of sensitivity and specificity, and improper diagnostic fungal workup. Furthermore, CAPA is associated with high mortality rates. One study assessed severely ill COVID-19 patients in intensive care units (ICU) across Wales and found that the mortality rate in untreated patients defined with CAPA was 57.9%.[8]

Although the risk factors for CAPA are not well elucidated, acutely ill patients in the ICU with comorbidities seem to be at higher risk. Specifically, respiratory comorbidities, such as chronic obstructive pulmonary disease and asthma, hypertension, coronary artery disease, and type 2 diabetes, frequently have been reported in patients with CAPA.[9,10,11] It also been has demonstrated that corticosteroids used to treat critically ill COVID-19 patients are independently associated with increased risk of CAPA.[12] Indeed, the patient presented in our case possessed many of these risk factors.

Similarly, the pathophysiology of CAPA remains ill-defined. It is postulated that the impaired type I and III interferon (IFN) response observed in severe COVID-19 infection contributes to the development of CAPA. Type I IFN drives the production of Type III IFN, which, in turn, causes neutrophils to fight against *Aspergillus*. Type I IFN also plays a critical role in promoting CD4+ Th1 cell activation against *Aspergillus*. Another element to the pathogenesis may lie in the depletion of alveolar macrophages in patients acutely ill with COVID-19. These cells are the front-line defense that inhaled *Aspergillus conidia* encounter.[1] Unfortunately, the treatment for hospitalized COVID-19 patients (ie, corticosteroids) is often one of the culprits in the pathogenesis of CAPA. Of their many effects, corticosteroids cause inhibition of interleukin-6, and this blockade itself is a risk factor for CAPA.[13] Nonetheless, corticosteroids remain the treatment of choice in these patients. Hence, it becomes imperative to have heightened awareness of these risk factors to remind clinicians to consider CAPA as a differential diagnosis. Early recognition and prompt initiation of treatment may confer a survival benefit in these patients.[14]

The typical clinical presentation involves either refractory fever, pleural rub, chest pain, or hemoptysis,[8] but CAPA also can present with subtler signs and symptoms as demonstrated in our case. The patient developed nonspecific symptoms, including mild leukocytosis and worsening dyspnea. Due to the potential for subtle clinical presentations, clinicians should exercise a low threshold for suspicion of CAPA. According to a 2021 task force report on CAPA, it is recommended that a diagnostic workup for CAPA be performed on all mechanically ventilated COVID-19 patients with persistently poor respiratory function and clinical deterioration with no other explanation.[15] Diagnosing CAPA poses a great challenge, as radiological findings can vary widely. Some of the findings reported in the literature include peripheral nodule, air crescent, reverse halo sign, nodular consolidation, ground-glass opacities, crazy paving pattern, pleural effusion, and pulmonary cysts.[16]

Despite nonspecific clinical and radiological signs, a reliable diagnostic tool lies in bronchoscopy and bronchoalveolar lavage, and maximum efforts should be made to perform this procedure.[15] Detecting *Aspergillus* in the sputum or endotracheal aspirate is insufficient due to the inability to distinguish normal colonization from invasion. The first line treatments are voriconazole or isavuconazole and should be initiated immediately upon diagnosis due to the high mortality associated with CAPA.[17] Voriconazole is metabolized by cytochrome P450 enzymes and, therefore, raises the potential for drug-drug interactions. Vigilant monitoring for signs of hepatotoxicity and neurotoxicity is imperative for patients undergoing voriconazole treatment with regular assessment of trough levels. Maintaining trough levels within the 2-6 mg/L range is considered therapeutic. Treatment duration is typically between 6 and 12 weeks, depending on clinical and radiologic severity. In cases where concerns regarding hepatotoxicity arise, isavuconazole is a viable alternative. Its advantages include fewer drug-drug interactions, lower toxicity, and a wider therapeutic window.

Patients in the ICU with CAPA have worse outcomes than those without CAPA. According to a European multinational observational study, patients who received systemic antifungal therapy with voriconazole or isovuconazole, had a survival rate of 52% at ICU discharge, whereas untreated patients had a survival rate of only 10%. CAPA also was found to be a significant negative prognostic factor despite adjusting for other predictors of survival, such as age and comorbidities.[18]

CONCLUSIONS

Early diagnosis and treatment are vital to preventing worse clinical outcomes; thus, it is important to have heightened awareness of the risk of developing CAPA in critically ill COVID-19 patients. Given that it may be heralded by subtle and nonspecific symptoms, as in our patient's case, a high clinical suspicion for CAPA is crucial. Mechanically ventilated patients with continued poor respiratory function and no other explanations for their clinical decline should undergo workup for CAPA; in particular, immunocompromised patients who have received a long duration of corticosteroid therapy are at increased risk. Maximum efforts to perform a bronchoscopy with bronchoalveolar lavage to diagnose CAPA is recommended due to varying clinical presentations and radiologic findings. Voriconazole therapy should be initiated immediately upon diagnosis to combat the high mortality rates in CAPA patients.

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