Subacute Aspergillosis “Fungal Balls” Complicating COVID-19

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Abstract
Severe acute respiratory syndrome coronavirus-2 infection (SARS-CoV-2), commonly known as COVID-19 (coronavirus disease-2019 [COVID-19]), began in the Wuhan District of Hubei Province, China. It is regarded as one of the worst pandemics, which has consumed both human lives and the world economy. COVID-19 infection mainly affects the lungs triggering severe hypoxemic respiratory failure, also providing a nidus for superimposed bacterial and fungal infections. We report the case of a 73-year-old male who presented with progressive dyspnea; diagnosed with SARS-CoV-2–related severe acute respiratory distress syndrome and complicated with lung cavitations growing Aspergillus sp. COVID-19, to our knowledge, has rarely been associated with subacute invasive pulmonary aspergillosis with aspergillomas. Subacute invasive pulmonary aspergillosis as a superimposed infection in patients with SARS-CoV-2 is a rare entity. By reporting this case, we would like to make the readers aware of this association.

Keywords
infection, pulmonary aspergillosis, SARS-CoV-2, COVID-19, acute respiratory distress syndrome

Introduction
Severe acute respiratory syndrome coronavirus-2 infection (SARS-CoV-2) disease (coronavirus disease-2019 [COVID-19]) has led to pandemic throughout the globe. Patients infected with COVID-19 may develop multiple superinfections, mostly bacterial and rarely fungal. Although, to our knowledge, rarely has a superinfection association of COVID-19 with subacute invasive pulmonary aspergillosis been reported.

Case Presentation
A 73-year-old male with past medical history of hypertension, diagnosed with COVID-19 infection 3 days prior to admission, presented to the emergency room with progressive worsening of shortness of breath. He endorsed 4 days of subjective fevers, chills, productive cough, generalized weakness, and decreased oral intake. On presentation to the emergency room, he was tachypneic to 35 breaths per minute with oxygen saturation of 85% on room air. He was immediately placed on a non-rebreather with improvement in oxygenation. Blood work showed elevated inflammatory markers with C-reactive protein of 25.85 mg/dL, ferritin 1847 ng/mL, and lactate dehydrogenase of 475 IU/L. Chest radiograph on day of admission showed bilateral peripheral infiltrates suggestive of COVID-19 without any signs of cavitary lesions (Figure 1). Nasopharyngeal swab polymerase chain reaction for SARS-CoV-2 tested positive. Blood and respiratory cultures were drawn.

Due to progressive respiratory distress, the patient was initially placed on high-flow nasal cannula. Subsequently, he required intubation and was transferred to the medical intensive care unit. He started on remdesivir, dexamethasone, and received convalescent plasma based on current COVID-19 recommendations. With persistent fever spikes to 102 °F, he was initiated on broad-spectrum antibiotics. Respiratory cultures obtained at time of intubation grew methicillin-resistant Staphylococcus aureus, and antibiotics were narrowed. With...
worsening P/F ratios, the patient was proned for a total of 48 hours, per hospital acute respiratory distress syndrome protocol, with significant improvement in the gas exchange.

Despite appropriate antibiotics, the patient continued to have persistently high-grade fevers and progressively higher oxygen requirements. Computed tomography scan of the chest was performed 3 weeks after admission demonstrating extensive airspace disease with bilateral peripheral ground glass pattern, along with newly formed thin-walled cavitary lesions in the right middle lobe and left upper lobe (Figure 2a and b). These cavities were occupied by fungal ball-like lesions, and subsequent respiratory cultures grew *Aspergillus flavus*, without any fungal growth in blood cultures, and aspergillus/galactomannan serum assay showed no results. The patient was then started on intravenous voriconazole for subacute invasive pulmonary aspergillosis. Due to persistence of the SARS-CoV-2 and severe acute respiratory distress syndrome complicated by pulmonary aspergillosis, the patient further underwent tracheostomy and was discharged to a subacute rehabilitation facility.

**Discussion**

Coronaviruses are a group of enveloped, nonsegmented, single-stranded RNA viruses belonging to the subgroups Coronavirinae and Torovirinae in the family of Coronaviridae. The virus was first discovered in 1960 and per their genomic structure and phylogenetic relationship, divided into 4 genera: Alphacoronavirus, Betacoronavirus, Gammacorona-virus, and Deltacoronavirus. Among the 4 subtypes, Alphacoronavirus and Betacoronavirus are known to infect humans causing respiratory and gastrointestinal symptoms, while Gammacoronavirus and Deltacoronavirus mainly affect birds.

SARS-CoV-2, also popularly known as COVID-19, belongs to the Betacoronavirus subtype. This infection typically manifests with fever (88.9%), cough (76.5%), fatigue/malaise (32.5%), and dyspnea (13.3%), as pointed out by Wan et al. The diagnosis of the COVID-19 is usually established with nasopharyngeal swab polymerase chain reaction and computed tomography scan of the chest showing a bilateral multilobular consolidation with ground glass pattern.

Superimposed bacterial and fungal infections has been well described in viral pneumonia. In the 2009 H1N1 influenza pandemic, every 1 out of 4 patients had superimposed bacterial/fungal infections. Superimposed bacterial and fungal were also described in the 2003 SARS-CoV-1 outbreak. The most common pathogens implicated during the 2003 pandemic were gram-negative bacilli and *Candida* sp. Also during prior pandemics *Aspergillus* sp have caused superimposed infection. Commonly known manifestations of *Aspergillus* sp are aspergilloma, allergic bronchopulmonary aspergillosis, invasive pulmonary aspergillosis (IPA), tracheobronchial aspergillosis, and chronic pulmonary aspergillosis.

Aspergilloma is a fungal ball that develops in preformed thick-walled cavities. Typically, patients are asymptomatic with incidentally findings of chest radiography, although can progress to hemoptysis due to vascular damage by mechanical effects of the fungus ball and fungal toxins.

Allergic bronchopulmonary aspergillosis is an allergic pulmonary disorder caused by hypersensitivity to *Aspergillus* sp antigens. Typically noted in steroid-dependent asthmatics and cystic fibrosis patients.

Invasive aspergillosis, the most severe form of pulmonary aspergillosis, is usually due to *Aspergillus* sp invading through tissue and blood vessels into the blood stream and infecting distant tissues including heart, brain, and the eyes. IPA has been implicated as superimposed infection in severe influenza pneumonias. It is a well-known complication of immunocompromised patients, especially hematological malignancies. There are very few cases of invasive aspergillosis described in conjunction with COVID-19 infection.

Tracheobronchial aspergillosis is a rare form of IPA, typically only encountered in lung and heart-lung transplant patients at the bronchial anastomotic sites.

Chronic pulmonary aspergillosis, another form of pulmonary aspergillosis, comprises chronic cavitory, subacute IPA, and chronic fibrosing. Chronic cavitory disease is usually accompanied by new cavity formation, although without invasion into surrounding lung parenchyma. Subacute IPA is more invasive than chronic cavitory pulmonary aspergillosis. Typically seen in patients with variable degrees of immunosuppression and arising from a thin-walled cavity. In disparity to aspergilloma, subacute IPA causes destruction of surrounding tissue. Chronic fibrosing is seen in conjunction with extensive fibrosis around the cavity.
Pulmonary aspergillosis typically affects structurally abnormal lungs with preexisting thick-walled well-formed cavities. They usually involve the posterior segment of the upper lobe and superior segment of the lower lobe. Pulmonary tuberculosis is one of the most common risk factors for pulmonary aspergillosis. Other common preexisting conditions linked with pulmonary aspergillosis are as follows: pulmonary sarcoidosis, bronchiectasis, and other pulmonary cavities (eg, bronchogenic cysts).

We report this case of subacute invasive pulmonary aspergillosis in a patient with SARS-CoV-2 infection, who did not have any history of pulmonary tuberculosis, sarcoidosis, or preformed cavities to predispose for aspergillus infection. Subacute IPA, to the best of our knowledge, has rarely been reported during the COVID-19 pandemic. As noticeable in the computed tomography images, the cavities were thin walled (Figure 2a and b). These cavities were not noted on prior chest radiograph on admission (Figure 1), suggesting they were caused by the underlying COVID-19 infection. As like any other bacterial or fungal infection, superimposed infection with pulmonary aspergillosis greatly increases the morbidity and mortality, especially when associated with conditions like COVID-19.

**Conclusion**

Subacute invasive pulmonary aspergillosis as a superimposed infection in patients with SARS-CoV-2 is a rare entity. By reporting this case, we would like to make the readers aware of this association.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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