

Opportunistic Fungal Infection Associated With COVID-19

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We report 2 cases of severe coronavirus disease 2019 requiring prolonged hospitalization complicated by the late onset of opportunistic fungal infections, histoplasmosis, and cryptococcosis.

Keywords. COVID-19; *Cryptococcus*; *Histoplasma*; pulmonary infection.

Invasive fungal infection (IFI) has been increasingly recognized as a severe, late sequel of coronavirus disease 2019 (COVID-19). Invasive pulmonary aspergillosis (IPA) is a well-known complication of severe influenza, with rates in patients with postinfluenza pneumonia approaching those seen in patients with myeloid neoplasms, graft vs host disease, and lung transplants [1, 2]. While the pathogenesis remains under investigation, prolonged critical illness, immune dysregulation, mechanical ventilation, and glucocorticoid therapy have been posited as risk factors [3–5]. We report here 2 cases of pulmonary mycoses as a late complication of severe COVID-19 with associated cytokine and lymphocyte subset profiles in 2 patients without preexisting immune-compromising conditions on admission.

PATIENT 1

A 78-year-old man with a history of hypertension and chronic obstructive pulmonary disease maintained on umeclidinium/vilanterol without home oxygen requirement was admitted with 5 days of myalgia, dyspnea, fever, diarrhea, and headache. On presentation, he was hypoxic with an oxygen saturation of 88% on ambient air and rapidly developed an increased oxygen requirement. He was admitted to the intensive care unit, where he was placed on BIPAP. A nasopharyngeal swab for SARS-CoV-2 nucleic acid was positive, and remdesivir, 200 mg intravenously (IV) once then 100 mg daily for 4 days, and methylprednisolone,

40 mg IV every 12 hours, were administered. He was enrolled in a randomized, blinded, placebo-controlled study of DAS181 (1:1 inhaled recombinant sialidase vs placebo—NCT03808922) and received study medication for 10 days, on hospital days 2–12. Following database lock, subject allocation was unblinded, and receipt of active drug was confirmed.

The patient remained critically ill for 16 days with a gradual decrease in oxygen requirement, transitioning sequentially from BIPAP to high-flow nasal cannula to standard nasal cannula, and was then transferred to the medical stepdown unit. After 4 days, he developed recrudescence fever with rapidly progressive respiratory insufficiency, requiring intubation and mechanical ventilation. Bronchoscopy with bronchoalveolar lavage, performed 36 hours after readmission to the intensive care unit, showed growth of *Cryptococcus neoformans*, while serum cryptococcal antigen was not detected. Due to clinical instability and the absence of focal neurologic findings, a lumbar puncture was not obtained. Testing for HIV infection via fourth-generation Ab/Ag assay performed before admission was negative. Treatment with liposomal amphotericin B 3 mg/kg for 6 days was changed to isavuconazole following development of acute kidney injury requiring continuous renal replacement therapy.

The patient continued to deteriorate, with an increasing oxygen requirement and hypotension requiring vasopressors. He developed ventilator-associated pneumonia due to multidrug-resistant *Enterobacter cloacae* and *Alcaligenes* spp. requiring treatment with ceftazidime/avibactam. Despite maximal medical therapy, he had continued clinical progression. Care was withdrawn at the family's request, and he died on hospital day 39.

PATIENT 2

A 62-year-old woman with a history of diet-controlled diabetes mellitus, gastroesophageal reflux disease, and asthma was admitted with 3 days of dyspnea, nausea, emesis, and diarrhea. Before admission, she had received oral treatment with levofloxacin and azithromycin without improvement. Chest radiograph at presentation showed extensive bilateral ground glass opacities with oxygen saturation on ambient air of 83%.

SARS-CoV-2 nucleic acid testing of the nasopharynx was positive, and remdesivir, 200 mg IV once then 100 mg IV daily for 4 days, and dexamethasone, 6 mg IV daily, were started. She had a rapid increase in oxygen requirement and was transferred to the intensive care unit, where computed tomography angiography of the chest demonstrated occlusion of the right pulmonary artery. Therapeutic anticoagulation with enoxaparin as well as inhaled nitric oxide, tocilizumab (8 mg/kg), and prone positioning were initiated.

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Over the next 2 weeks, she had ongoing daily fever between 102°F and 104°F. Multiple cultures of blood and urine were negative, while lower respiratory tract cultures obtained via bronchoscopy showed growth of *Candida* spp. Her fever persisted despite empiric therapy with vancomycin and cefepime. On hospital day 26, serum cryptococcal antigen and urinary *Histoplasma* antigen (MiraVista Diagnostics, Indianapolis, IN, USA) were not detected. However, *Histoplasma capsulatum* complement fixation titers were positive at >1:64 (yeast phase) and 1:16 (mycelial phase), and M-band was detected by immunodiffusion (Quest Diagnostics, San Juan Capistrano, CA, USA). After receipt of these results on hospital day 33, treatment with liposomal amphotericin B 3 mg/kg per day was initiated. After 13 days of liposomal amphotericin, therapy was changed to intravenous isavuconazole. She was subsequently discharged and transferred to the inpatient rehabilitation service on hospital day 89, after which she was discharged; she has slowly returned to baseline functional status.

DISCUSSION

These 2 cases are examples of pulmonary mycoses developing as late sequelae of severe COVID-19 among 195 COVID-19 patients who admitted to the intensive care unit during this time. While invasive pulmonary aspergillosis has been widely recognized as a late complication [6], the cases of cryptococcosis and histoplasmosis reported with COVID-19 thus far have been associated with either preexisting infection or coincident immunocompromising disease [7–12]. Of interest, neither patient had evidence of extrapulmonary disease.

Both patients presented in June/July 2020 and had a number of potential risks for systemic fungal infection, including prolonged mechanical ventilation, lymphopenia, high-dose glucocorticoid therapy, broad-spectrum antibiotics, tocilizumab (Patient 2), and immune dysregulation associated with critical illness. While host–pathogen interactions and immune dysregulation play a key role in the pathogenesis of COVID-19, the precise interactions remain incompletely understood at this time [13–16]. Lymphocyte subset populations via flow cytometry and cytokine profiles (quantitative multiplex bead platform, ARUP Laboratories, Salt Lake City, UT, USA) were obtained during the course of these patients' hospitalizations and are provided in Supplementary Appendix A for further reference. Data for patient 1 are listed in Supplementary Table 1, while data for patient 2 are listed in Supplementary Table 2.

Both patients received isavuconazole rather than fluconazole and itraconazole, respectively, as recommended by the Infectious Diseases Society of America guidelines. Isavuconazole has in vitro activity against both organisms and has demonstrated effectiveness in cases of invasive fungal infection due to *Cryptococcus* and *Histoplasma* [17].

Although Patient 1 was enrolled in a blinded clinical trial of an inhaled recombinant sialidase (DAS181) inhibitor, the proposed mechanism seems unlikely to have influenced the development of pulmonary cryptococcosis. DAS181 is a recombinant fusion protein with a sialidase catalytic domain and a respiratory epithelium anchoring domain; the sialidase domain is capable of transiently cleaving $\alpha(2,3)$ - and $\alpha(2,6)$ -linked sialic acid receptors [18]. As *Cryptococcus* does not utilize sialic acid in the process of binding or endocytosis [19] and no cases of pulmonary cryptococcosis have been reported in the use of DAS181 in >900 subjects to date, the use of DAS181 appears unlikely to be a contributing factor, although a relationship cannot be excluded.

Given our experience, we believe that, in the proper clinical context, clinicians should consider pulmonary fungal infections such as cryptococcosis or histoplasmosis in progressive or recrudescing respiratory failure in patients with severe COVID-19.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. The authors concluded that this report does not include information requiring informed consent for publication. This was reviewed with the chairman of the institutional review board, who agreed with this conclusion.

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