

CLINICAL VIGNETTE

A Case of Isolated Central Nervous System Aspergillosis after COVID-19 Infection

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Case Report

A 71-year-old male was infected with COVID-19 in December 2020 and was hospitalized for 8 days with pneumonia. His comorbidities included diabetes type 2 and chronic lymphocytic leukemia (CLL). He had been taking ibrutinib for 2 years as the treatment of CLL, and it was held when he developed COVID-19. Due to COVID-19 pneumonia, he required high-flow oxygen therapy for a few days, and was treated with 5- days of remdesivir and 10-days of dexamethasone (10mg per day). He did not receive tocilizumab treatment. He significantly improved and was stable at discharge.

By one month after discharge, his prior COVID-19 symptoms had totally resolved. While awaiting recommendations from oncology regarding resuming ibrutinib, he developed sudden onset of left facial droop and slurred speech, and was readmitted to the hospital. At that time, he had no fever, chills, headache, myalgias, cough, dyspnea, or diarrhea. He denied any paranasal sinus symptoms. Repeat nasopharyngeal swab COVID-19 PCR was still positive. Both CT head and MRI brain revealed a 1.4cm ring-enhancing lesion in the right parietal white matter of posterior frontal lobe. In the emergency room, he was empirically started on vancomycin, ceftriaxone and ampicillin given concern of possible central nervous system bacterial infection. No leukocytosis was present. Blood bacterial and fungal cultures were negative. Transthoracic echocardiogram was normal. CT chest showed patchy bilateral groundglass airspace disease that was suspicious for COVID-19 infection, with mild hilar adenopathy. The CT sinus revealed mild maxillary and ethmoid sinusitis. Neurology and neurosurgery were consulted, and considered the brain lesion concerning for an infectious or neoplastic process. In the hospital, he had multiple episodes of left sided facial twitching, and levetiracetam was started given seizure concerns. On hospital day 2 he underwent right parietal craniotomy for resection of the brain mass. The pathology reported fungal hyphae with morphology consistent with *Aspergillus*. The culture of the surgical sample also isolated *Aspergillus fumigatus*. He remained on broad-spectrum antibiotics until the pathology report of aspergillus then transitioned to parenteral voriconazole. He was treated with IV voriconazole for 6 weeks, followed by oral voriconazole as long-term suppression. He was stable after surgery, and his left facial droop and dysarthria gradually improved.

Discussion

The incidence of invasive aspergillosis (IA) has increased in recent years, especially among hematopoietic stem cell recipients, solid organ transplant recipients, and patients with chronic pulmonary infections.^{1,2} Viral pneumonia also increases susceptibility to bacterial and fungal super-infections. Invasive pulmonary aspergillosis (IPA) is a well-known complication of severe influenza pneumonia. Influenza-associated pulmonary aspergillosis (IAPA) has been widely reported as a complication in many critically ill patients with acute respiratory distress syndrome (ARDS).^{3,4} Recent studies are reporting the emergence of aspergillosis in severe COVID-19 pneumonia, named COVID-19 associated aspergillosis (CAPA).⁵ The clinical course of COVID-19 shares many features with severe influenza infection. These include ARDS, lymphopenia, bilateral pulmonary infiltrates, systemic pro-inflammatory cytokine responses and sepsis leading to multiple organ failure.^{6,7} It is reasonable to suspect that patients with severe COVID-19 infection may be similarly susceptible to IPA. Patients with severe COVID-19 pneumonia and ARDS also have additional risk factors of prolonged ICU admission and use of steroids and immunomodulators. Risk factors for severe disease in COVID-19 infection are also risk factors for IPA, including underlying comorbidities like diabetes, prolonged hospitalization and use of immunosuppressives.⁸ Other risk factors described in CAPA patients include old age, lymphopenia, chronic respiratory diseases, corticosteroid therapy, antimicrobial therapy, and cytokine storm.⁹⁻¹¹

The pathophysiology of CAPA infection remains undetermined. Respiratory viruses cause direct damage to the airway epithelium, enabling *Aspergillus* to invade tissue.¹² Viral infection hampers ciliary clearance and leads to immune dysfunction or dysregulation, or both, locally or systemically.¹³ The extent of dysregulation associated with ARDS is not yet fully understood, however, some patients develop pronounced immunosuppression, facilitating bacterial and fungal super-infection. Moreover, a distinctive immune-cell event observed in patients with COVID-19 infection is decrease in T-cell populations, especially in patients with severe disease.¹⁴ Decline of lymphocyte counts can be accompanied by defective function. Severe lymphopenia has been established as a factor predicting risk of invasive fungal disease in patients with hematological malignancies.¹⁴ Immune dysregulation associated with ARDS or its treatment including tocilizumab and corticosteroids may predispose to opportunistic infections.¹⁵ Two potential mechanisms were recently proposed.¹⁶ First, the

release of danger-associated molecular patterns (DAMPs) in ARDS could promote and exacerbate the immune and inflammatory response leading to lung injury, and DAMPs have also been shown to regulate inflammation in fungal diseases. Second, IL-1 and IL-6 are involved in immune dysregulation related to the subsequent fungal infection. Early hyperactivation of IL-1 induced by COVID-19 infection may promote a permissive inflammatory environment for developing fungal infections. Moreover, IL-6 is also observed in epithelial cells following infection with *Aspergillus*, suggesting co-infection may contribute to the increased levels of this cytokine in severe COVID-19 patients.¹⁷ The use of tocilizumab, a monoclonal antibody against IL-6 receptor used as a therapeutic strategy in the immunomodulation of COVID-19 patients, was detected in high concentrations in patients with CAPA.¹⁸

In spite of the lack of precise epidemiologic data, CAPA may not be an uncommon complication in patients with COVID-19 infection given the increasing number of case reports and studies. However, cases of extra-pulmonary infection with *Aspergillus* are rarely reported. Our patients respiratory symptoms and CT chest findings were consistent with COVID-19 infection when he was diagnosed, and we believe that he had clinically recovered before the subsequent occurrence of aspergillosis. Although no sputum fungal culture or bronchoscopy was done during his two hospitalizations, we did not believe he had IPA. His sinus CT showed mild maxillary and ethmoid sinusitis, but he never had any symptoms related to sinusitis. No further evaluation such as paranasal sinus endoscopy and biopsy were performed, as aspergillus sinusitis was unlikely in our clinical evaluation. We considered that our patient likely had isolated central nervous system aspergillosis (CNS-A), though we could not rule out a temporary episode of pulmonary aspergillosis.

Except for COVID-19 infection, we presumed that the CNS-A might be related to his CLL as well as the use of ibrutinib. Ibrutinib is a small molecule drug that inhibits B-cell proliferation and survival by irreversibly binding the protein Bruton's tyrosine kinase (BTK). Blocking BTK inhibits the B-cell receptor pathway, which is often aberrantly active in B cell cancers. Ibrutinib is therefore used to treat diseases like mantle cell lymphoma, chronic lymphocytic leukemia and Waldenström's macroglobulinemia. A 2016 correspondence alerted clinicians to be aware that ibrutinib use in CLL could be associated with CNS-A.¹⁹

Usually either the lung or paranasal sinuses are typically infected prior to or concomitant with CNS-A, while isolated CNS-A cases are rarely documented in CLL patients. A 2012 meta-analysis compared cases of CNS-A at Massachusetts General Hospital (MGH) (n = 14) with globally published cases (n = 123) from 2000 to 2011.²⁰ Of the 14 cases at MGH, none had isolated CNS-A. Only one had primary discitis without antecedent pulmonary or paranasal sinus infection. Of the 123 global cases, 22.8% did not have an apparent site of extra-CNS infection. Hematogenous dissemination was confirmed from a pulmonary focus in 26.8% of cases and direct extension from

paranasal sinus infection in 27.6% of cases, but none had CLL or ibrutinib exposure. In a prospective observational cohort study of 1149 CLL patients in the United States on ibrutinib therapy, three cases with CNS-A were reported, and all were on steroids prior to developing CNS-A, within 2 months after initiating ibrutinib.¹⁹

Our patient had been on ibrutinib for 2 years before he was infected with COVID-19. During the 8-day hospitalization for his COVID-19 infection, he developed hypoxia and required high flow oxygen therapy, but was never admitted to intensive care. He received steroid treatment with dexamethasone 10mg per day for a total of 10 days. The ibrutinib had been held since he was diagnosed with COVID-19 infection. It is hard to determine the attribution of ibrutinib and COVID-19 infection to the subsequent occurrence of invasive aspergillosis in this patient. We consider chronic use of ibrutinib may have decreased his adaptive immune response to fungal infection. The damage to the airway epithelium during COVID-19 infection might be the access for invasive *Aspergillus*. Steroid treatment further destroyed the immune defense mechanisms against the fungi. Interestingly, this patient did not have a clear process of pulmonary or paranasal sinus *Aspergillus* infection. In addition, the isolated invasive infection in the brain was found after he had clinically recovered from COVID-19 infection. Therefore, we suspected that the COVID-19 infection probably initiated the invasion of *Aspergillus*, and the insufficient immune response due to his prior chronic use of ibrutinib and the later steroid treatment during COVID-19 infection contributed to the development of the CNS-A.

Our case reinforces the importance of being vigilant for invasive aspergillosis in COVID-19 infected patients. Patients with comorbidities that can compromise immune response, invasive aspergillosis including extrapulmonary infection may even occur after patients improved or recovered from COVID-19 infection. Early recognition and treatment can be lifesaving. However, the pathogenesis of invasive aspergillosis in patients with COVID-19 infection and chronic ibrutinib use requires further study.

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