Journal of Investigative Medicine High Impact Case Reports
Volume 10: 1–4

DOI: 10.1177/23247096211063332
journals.sagepub.com/home/hic
SAGE

COVID-19 Infection and Late Manifestation of Pulmonary Aspergillosis

Huzefa Bhopalwala, MD[1], Vinayak Mishra, MBBS[2], Tuong Vi Do, DO[3], Mythili Gudipati, MD[3], and Subramanya Shyam Ganti, MD[3]

Abstract

We present the case of a 56-year-old woman who was diagnosed with severe coronavirus disease 2019 (COVID-19) pneumonia complicated by severe acute respiratory distress syndrome who was intubated for 19 days. She recovered from COVID-19 after a month. A computed tomography (CT) scan of the chest, after a month, showed improved infiltrates with a small residual cavity within the lingula. A CT angiogram showed a more confluent density in the lingular portion on follow-up 2 months later. She developed intermittent hemoptysis after 3 months in December 2020, which persisted for almost 6 months, and CT of the chest showed the lingular nodular with resolution of the cavitation. She underwent bronchoscopy with bronchoalveolar lavage, confirming *Aspergillus fumigatus* by galactomannan assay and histology showing branching hyphae. Once she started treatment with itraconazole, her hemoptysis resolved. The follow-up CT of the chest after 2 months of treatment did not show a cavity or a nodule in the lingula. Our patient developed invasive pulmonary aspergillosis (IPA) as a sequela of severe COVID-19 infection. COVID-19-associated invasive pulmonary aspergillosis (CAPA) is an underrecognized complication that needs to be investigated on whether prophylactic treatment is required. Our case also demonstrates that the diagnosis of IPA needs to be considered months after COVID-19 infection when a superimposed fungal infection can occur after a viral infection if the patient continues to have persistent symptoms.

Keywords

invasive pulmonary aspergillosis, COVID-19, COVID-19-associated invasive pulmonary aspergillosis, superimposed fungal infection

Background

Invasive pulmonary aspergillosis (IPA) has been recognized as a severe sequela of severe coronavirus disease 2019 (COVID-19) infection.[1] Severe COVID-19 has been recognized as those who were admitted to the intensive care unit (ICU) and subsequently intubated. It also encompasses those who then developed acute respiratory distress syndrome (ARDS). COVID-19 associated invasive pulmonary aspergillosis (CAPA) is associated with an increased 30-day mortality rate of 44% in those with ARDS, which can be significantly lowered with the early introduction of appropriate antifungals.[2,3]

According to a systematic review by Chong and Neu,[4] CAPA was diagnosed within 2 weeks of initiation of invasive mechanical ventilation (IMV) with an overall hospital mortality rate of 48.4%. In our case report, IPA was diagnosed 8 months after recovery from severe COVID-19 pneumonia complicated by severe ARDS being on IMV for a total of 19 days. We identified the possibility of IPA occurring as a delayed long-term sequela of critical COVID-19 infection. We also highlight the importance of considering IPA during the long-term follow-up of a patient recovering from severe COVID-19 pneumonia presenting with hemoptysis. After appropriate treatment with an azole antifungal, her hemoptysis resolved. The global rise in CAPA and its contribution to overall morbidity and mortality have called for further research on this superinfection diagnosis, management, and perhaps prophylaxis.

[1]Appalachian Regional Healthcare/Internal Medicine Residency Program, Whitesburg, KY, USA
[2]Grant Government Medical College and Sir J.J. Group of Hospitals, Mumbai, India
[3]Appalachian Regional Healthcare/Internal Medicine Residency Program, Harlan, KY, USA

Received August 19, 2021. Revised November 4, 2021. Accepted November 10, 2021.

Corresponding Author:
Subramanya Shyam Ganti, MD, Appalachian Regional Healthcare/Internal Medicine Residency Program, 81 Ball Park Road, Harlan, KY 40831, USA.
Email: shyam.ganti@gmail.com

Case Presentation

A 56-year-old woman with a medical history of obesity, asthma, hypertension, coronary artery disease (CAD), chronic gastroesophageal reflux disease, type II diabetes, obstructive sleep apnea (OSA), vocal cord paralysis, and seizure disorder presented to the hospital in February 2021 with multiple episodes of coughing frank blood in small quantity with blood-tinged mucus that follows an uncomfortable, scratchy throat sensation which has been worsening gradually. Hemoptysis first started 3 months ago in December 2020 and was intermittent and self-resolving. She reported dyspnea after walking 1 block and climbing stairs, orthopnea, paroxysmal nocturnal dyspnea, and occasional wheezing episodes. She denied any fever, weight loss, epistaxis, or vomiting blood. She had an unremarkable physical examination with a well-healed tracheostomy scar that was present.

Of note, she had a smoking history of 1.5 pack-years but stopped smoking 17 years ago. She is on levetiracetam and lacosamide for seizure, continuous positive airway pressure for OSA, clopidogrel for CAD, and mometasone-formoterol inhaler for asthma, which was started post-COVID-19 and is noncompliant with inhaler usage. She used to be on an albuterol inhaler on an as-needed basis and had 3 acute asthma exacerbations in the last 2 years, requiring steroids as an outpatient.

She had severe COVID-19 pneumonia in August 2020 complicated by acute respiratory failure and moderate ARDS. The chest computed tomography (CT) with angiography showed diffuse ground-glass opacities bilaterally with no pulmonary embolism. Her PaO_2-FiO_2 ratio was 113 when she was subsequently intubated for mechanical ventilatory support and transferred to a higher care center level. She then developed severe ARDS complicated by shock, bilateral pulmonary emboli, subcutaneous emphysema with pneumopericardium, and metabolic acidosis. She received broad-spectrum antibiotics, tocilizumab, convalescent plasma, remdesivir, and dexamethasone along with proning.

She was intubated for a total of 19 days and then underwent tracheostomy. She was discharged to a long-term acute rehabilitation in September 2020 with tracheostomy reversal after 17 days and discharged home on anticoagulation for 3 months. The CT of the chest in October 2020 showed improved bilateral infiltrates with a residual or contracting small cavity within the lingula. In November 2020, she reported a hoarse voice and a weak voice in the evening and was referred to an ear, nose, and throat specialist.

In December 2020, the CT angiogram (Figure 1) showed a more confluent density in the lingular portion of the left lung. In February 2021, when she was hospitalized for hemoptysis, CT of the chest showed left lingular infiltrate. In April 2021, she was hospitalized, and her CT of the chest without contrast (Figure 2) showed an elongated lingular nodule in an area that previously appeared as a cavitation. A

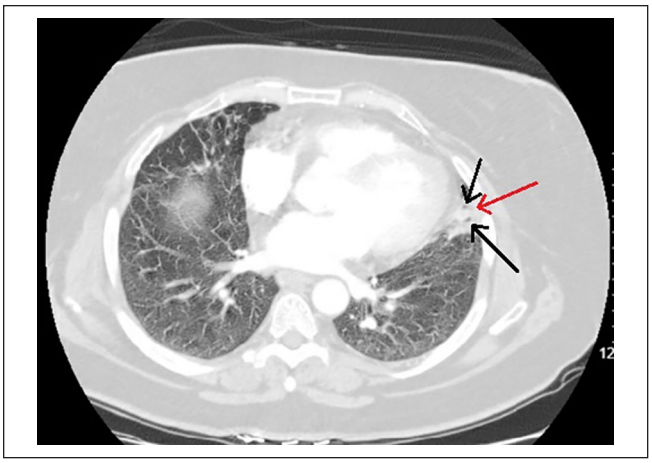

Figure 1. CT angiogram of the chest in December 2020 which showed a confluent density (red arrow) with 2 small cavitary areas (black arrows) in the lingular portion of the left lung.
Abbreviation: CT, computed tomography.

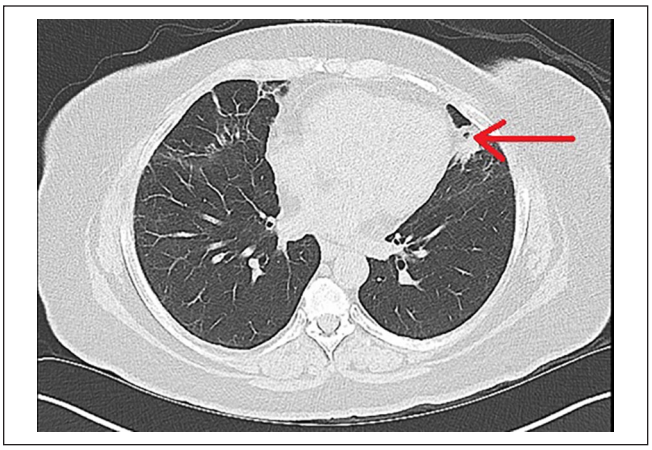

Figure 2. CT of the chest without contrast in April 2021 which showed an elongated lingular nodule (red arrow) which previously appeared as a cavitation of the left lung.
Abbreviation: CT, computed tomography.

navigational bronchoscopy with transbronchial biopsy, transbronchial brushings, and bronchoalveolar lavage (BAL) of the left upper lobe was then performed during her hospitalization. The left lingular nodule/infiltrate transbronchial biopsy revealed septated hyaline hyphae with branching, and BAL was positive for *Aspergillus* galactomannan. The BAL cell differential showed 39% neutrophils, 45% lymphocytes, 5% monocytes, 5% eosinophils, and 0% basophil. Of note, her BAL *Aspergillus* galactomannan in August 2020 was 0.062 (reference range <0.500), but in April 2021, her BAL *Aspergillus* galactomannan was 7.803. Gomori methenamine silver staining of the biopsy sample showed *Aspergillus fumigatus* fungal hyphae confirming the diagnosis of IPA.

The initial plan was to start voriconazole which was not covered by insurance, so she was started on itraconazole for

12 months. After a month and a half of oral itraconazole, her hemoptysis resolved. She then received the influenza vaccine and the first dose of the COVID-19 vaccine. After 2 months of oral itraconazole in June 2021, her chest CT did not show a nodule or cavitary lesions in the lingula (Figures 1 and 2).

Discussion

The diagnosis of CAPA has been underrecognized, with just 38 cases reported in the study by Mohamed et al[5] done on June 30, 2020. Mohamed et al[5] found that all 38 patients had COVID-19 pneumonia with ARDS requiring ventilatory support. Secondary bacterial or fungal pulmonary infections are suspected when a patient's clinical status or imaging features worsen abruptly and cannot be explained by the primary viral infection.[1,5] In the study by Wauters et al,[6] they had 9 cases of IPA that developed out of 40 ICU patients with H1N1 virus infection, where they correlated that corticosteroid use is an independent risk factor for secondary fungal infection. A fraction of patients with severe COVID-19 pneumonia requiring ICU management is also at an increased risk of secondary infections, including IPA.[7,8] This association was also observed in patients admitted to the ICU with severe H1N1 influenza.[6] The study by Wauters et al[6] was done back in 2012, establishing the association of symptoms of a viral infection not improving, leading to fungal infection as a complication. As COVID-19 is a viral infection, the possibility of superimposed fungal infection was overlooked, especially in those requiring ICU care. Corticosteroids are also a mainstay treatment for those with COVID-19. The incidence of CAPA ranges between 2.5% and 35.0% and predominantly occurred in those requiring IMV within 15 days of initiation.[4]

According to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections and the Mycoses Study Group (EORTC/MSG), specific patient factors that predispose to CAPA include severe neutropenia, allogeneic stem cell/solid organ transplant, corticosteroid therapy (0.3 mg/kg/day for $>$3 months), hematological malignancy, immunodeficiency, and treatment with T-cell/B-cell immunosuppressants.[4,9] Our patient was treated with a corticosteroid in addition to an anti-interleukin-6 receptor which could have increased her risk of developing IPA. Definitive diagnosis of CAPA requires histopathological, genetic, or microscopic evidence of invasive proliferation of *Aspergillus* species into pulmonary tissue, which is the gold standard.[1] Based on the BAL result done in August 2020 when our patient had COVID-19, the patient did not have IPA because *Aspergillus* galactomannan was negative. Imaging by chest CT showing pulmonary cavitation, nodules, or both and positive galactomannan enzyme assay provides additional evidence supporting the diagnosis of CAPA.[1,10] In April 2021, her CT of the chest showed an improving area of the previous cavitation with a nodule still present, and with BAL washing from that same area, the histology of hyphae branching along with assay positive for *A fumigatus* confirmed her diagnosis of IPA.

By using bronchoscopy, the lower respiratory tract is more accessible for sample collection. However, with the risk of respiratory droplet transmission of COVID-19, bronchoscopy was discouraged to prevent aerosolization of the virus. However, our patient had bronchoscopy when she had COVID-19 which was negative for *Aspergillus* but with CT of the chest showing cavitary lesion in lingular area. According to EORTC/MSG, they recommended bronchoscopy with BAL and lung biopsy for suspected secondary infection with negative COVID-19 test.[1] Our patient did have a second BAL done when she was negative for COVID-19, which came back positive for *Aspergillus.* In the study by Mohamed et al,[5] there were 16 cases confirmed as IPA by BAL; however, they also proposed that diagnosis can be made by endotracheal aspirate (ETA), which is not an aerosolizing procedure. Although ETA has not been validated as a diagnostic modality, Mohamed et al[5] confirmed 14 cases with IPA by ETA.

The first-line treatment for IPA is an azole antifungal of either voriconazole or isavuconazole.[1,5,11] Itraconazole is now rarely used because voriconazole and isavuconazole are more effective for the treatment of IPA. However, our patient's health insurance did not cover either of these 2 options, so she was started on oral itraconazole for at least 12 months which was what they recommended. As azoles are metabolized by cytochrome-P450 (CYP) 3A4, they cannot be used in those who may need remdesivir, which also interacts with CYP3A4.[1] Liposomal amphotericin B is used for those who are critically ill in the ICU with IPA.[11,12] As our patient was diagnosed as an inpatient but not in the ICU, she did not need treatment with amphotericin B. Amphotericin B is also used in azole restraint strains.[1] However, there is a lack of research on the efficacy of these antifungal agents in CAPA and whether or not any of these agents can be suitably used for long-term prophylaxis. In the study by Rutsaert et al,[13] they had 7 cases of IPA out of 34 COVID-19 ICU patients, and they decided to initiate prophylactic liposomal amphotericin B for those intubated with COVID-19 and had no new cases of IPA. This study prompts further research into prophylaxis after ICU admission to prevent the development of IPA.

Conclusion

We report an unusual case of IPA 8 months after treatment of severe COVID-19 pneumonia and ARDS after being on IMV. This case report provides insight into the potential late presentation of IPA as a long-term sequela of COVID-19 infection. It differs from most case reports in the literature that describe the onset of IPA within 2 weeks of starting mechanical ventilation. Therefore, the current consensus guidelines for CAPA should be extended to include the presentation of IPA a few months after recovering from severe

COVID-19 pneumonia. As the diagnosis of CAPA becomes more well known, this calls for further investigations on whether or not prophylaxis is needed for severe COVID 19 patients on IMV to prevent this complication. If prophylaxis is deemed unnecessary, further investigations are required to see whether ETA is an accurate diagnostic modality to diagnose IPA.

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.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ORCID iDs

Vinayak Mishra https://orcid.org/0000-0003-1426-0340
Tuong Vi Do https://orcid.org/0000-0003-1798-1709
Subramanya Shyam Ganti https://orcid.org/0000-0002-2042-0964

References

1. Koehler P, Bassetti M, Chakrabarti A, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis*. 2021;21(6):e149-e162.
2. Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study [published online ahead of print July 28, 2020]. *Clin Infect Dis*. doi:10.1093/cid/ciaa1065.
3. White PL, Dhillon R, Cordey A, et al. A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU [published online ahead of print August 29, 2020]. *Clin Infect Dis*. doi:10.1093/cid/ciaa1298.
4. Chong WH, Neu KP. Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. *J Hosp Infect*. 2021;113:115-129.
5. Mohamed A, Rogers TR, Talento AF. COVID-19 associated invasive pulmonary aspergillosis: diagnostic and therapeutic challenges. *J Fungi (Basel)*. 2020;6:115.
6. Wauters J, Baar I, Meersseman P, et al. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. *Intensive Care Med*. 2012;38(11):1761-1768.
7. Koehler P, Cornely OA, Böttiger BW, et al. COVID-19 associated pulmonary aspergillosis. *Mycoses*. 2020;63:528-534.
8. Alanio A, Dellière S, Fodil S, Bretagne S, Mégarbane B. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *Lancet Respir Med*. 2020;8(6):e48-e49. doi:10.1016/S2213-2600(20)30237-X.
9. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis*. 2019;71:1367-1376.
10. van Arkel ALE, Rijpstra TA, Belderbos HNA, et al. COVID-19-associated pulmonary aspergillosis. *Am J Respir Crit Care Med*. 2020;202:132-135.
11. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect*. 2018;24(suppl 1):e1-e38.
12. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63:e1-e60.
13. Rutsaert L, Steinfort N, Van Hunsel T, et al. COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care*. 2020;10(1):71.