Pulmonary Hypertensive Changes Secondary to COVID-19 Pneumonia in a Chronically SARS-CoV-2-Infected Bilateral Lung Explant

Joseph M. Rohr, MD, PhD1, Heather Strah, MD2, David Berkheim, MD3, Aleem Siddique, MBBS3, Stanley J. Radio, MD1, and Benjamin J. Swanson, MD, PhD1

Abstract
COVID-19, the syndrome caused by the novel coronavirus SARS-CoV-2, has spread throughout the world, causing the death of at least three million people. For the over 81 million who have recovered, however, the long-term effects are only beginning to manifest. We performed a bilateral lung transplant on a 31-year-old male patient for chronic hypoxic respiratory failure, severe pulmonary hypertension and radiographically identified pulmonary fibrosis five months after an acute COVID-19 infection. The explant demonstrated moderate pulmonary vascular remodeling with intimal thickening and medial hypertrophy throughout, consistent with pulmonary hypertension. The parenchyma demonstrated an organizing lung injury in the proliferative phase, with severe fibrosis, histiocytic proliferation, type II pneumocyte hyperplasia, and alveolar loss consistent with known COVID-19 pneumonia complications.

This report highlights a novel histologic finding in severe, chronic COVID-19. Although the findings in acute COVID-19 pneumonia have been well-examined at autopsy, the chronic course of this complex disease is not yet understood. The case presented herein suggests that COVID-induced pulmonary hypertension may become more common as more patients survive severe SARS-CoV-2-related pneumonia. Pulmonologists and pulmonary pathologists should be aware of this possible association and look for the clinical, radiographic, and histologic criteria in the appropriate clinical setting.

Keywords
COVID-19, pneumonia, pulmonary hypertension, lung transplant

Introduction
Vaccination for SARS-CoV-2 has significantly reduced the risk of severe disease from acute infection. Despite the thorough histologic examinations performed on decedents’ tissues performed through the world, there is a paucity of histological data on those who do not develop severe disease, likely driven by a combination of variable post-infection sequelae and unclear benefit of histopathologic characterization for these patients. This is particularly relevant because of so-called “breakthrough” cases despite adequate vaccine protection, as well as the severe worldwide dearth of vaccine.

Here, a patient developed severe COVID-19 pneumonia, eventually requiring transplantation.

Case Report
The patient is a 31-year-old male resident of the rural Midwestern United States with a past medical history significant only for Grade 3 obesity who was diagnosed with COVID-19 by two distinct RT-PCR assays under emergency use authorization. He had not received COVID-19 vaccination and initially felt well enough to perform physically rigorous work. Over the next few days, he worsened, requiring hospital admission for metabolic encephalopathy and hypoxic respiratory failure for which he received dexamethasone, remdesivir, and convalescent plasma. His chest CT demonstrated typical findings of acute COVID-19 pneumonia. His condition deteriorated such that he required mechanical ventilation and prone positioning for hypoxia. His course was complicated by acute kidney injury, septic shock, deep venous thrombosis

1Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, USA
2Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Omaha, NE, USA
3Division of Cardiothoracic Surgery, Department of Surgery, University of Nebraska Medical Center, Omaha, NE, USA

Corresponding Author:
Joseph M. Rohr, Department of Pathology and Microbiology, University of Nebraska Medical Center, 983135 Nebraska Medical Center, Omaha, NE 68198-3135, USA.
Email: joseph.rohr@unmc.edu
The patient was successfully transplanted, and fully weaned from mechanical ventilation on post-operative day 5. He is currently doing well and progressing through pulmonary rehabilitation similarly to non-COVID transplant recipients.

**Discussion**

The novel coronavirus SARS-CoV-2, the causative agent in COVID-19, irrevocably altered human interactions from its discovery in Wuhan, China in late 2019 and its subsequent distribution throughout the globe. The pandemic has infected over 224 million people worldwide and is tied to over 4.6 million deaths at the time of writing.6 Though numerous primary care and autopsy reports have highlighted the systemic physiological changes focused on the lungs caused by acute and fatal COVID-19 cases,2-5 as the pandemic continues, the long-term histologic sequelae in patients become more apparent. “Long COVID,” a group of physical, physiological, and psychological symptoms that follow SARS-CoV-2 infection for an extended period,7 is a related concept, but this patient’s rapid and prolonged deterioration does not fit with the use of this term.

We report here a patient with chronic respiratory failure secondary to COVID-19 who received a bilateral lung transplant for post-COVID respiratory failure. He developed marked pulmonary hypertension in the months leading up to his transplantation. His explant demonstrated pulmonary hypertensive changes in addition to end-stage fibrosis and chronic-phase diffuse alveolar damage / organizing pneumonia. The oblitative changes that are identified in this explant are consistent with what we and others have previously described at autopsy in fatal acute and subacute COVID-19 pneumonia.3-5 We also report probable histoplasmosis, a likely incidental finding that is common in our geographic area. Of note, a recent report of COVID pneumonia requiring lung transplantation demonstrated a granuloma containing Candida.8 This patient did not receive any treatment for his Histoplasma but receives prophylaxis post-transplant due to his now immuno-compromised status.

In two case series describing lung transplantation for COVID-19 pneumonia, pulmonary hypertension was a common finding.9,10 Other groups as well have found a possible association between pulmonary hypertension and COVID,11 including on autopsy specimens.12 To our knowledge, this case report is unique in demonstrating pictorially the histologic changes of pulmonary hypertension in a patient on maximal pre-transplant prostaglandin therapy, as well as the longest reported ventilatory requirement (128 days). Further work is needed to describe the prevalence of pulmonary hypertension and the associated pathologic changes in patients who develop chronic symptoms after COVID-19. Given the large number of people who
Figure 1. Representative lung explant. A: The lung parenchyma demonstrates the organizing phase of diffuse alveolar damage (DAD), with prominent fibrosis (H&E, ×200). B: Type II pneumocyte hyperplasia and collapsed alveoli with interspersed histiocytes are easily identified (H&E, ×400).

Figure 2. Representative vascular changes in lung explant. A-B: Scattered arterioles demonstrated moderate intimal thickening (A: H&E, B: Movat pentachrome; ×200). C-D: Scattered arteries had moderate medial hyperplasia (C: H&E, B: Movat pentachrome; ×200).
have been infected with the virus, this could have enormous clinical relevance to patients and the medical community. Interestingly, the patient’s first positive COVID screen was three months prior to his negative test during transplant evaluation. However, a nasopharyngeal rapid test performed shortly prior to transplant had a Ct value of 43 cycles, a detectable but low level of virus. Although we cannot necessarily exclude reinfection, a high Ct value in ultrasensitive assays is thought to represent remaining viral nucleic acid but not transmissible virus and can persist for months after primary infection.13 His repeat test the next day was negative.

In contrast to other cases of COVID-related lung transplant in the literature,9,10 in which the majority of the patients demonstrated severe pulmonary adhesions, the patient reported here did not have any adhesions. The significance of this finding is unclear.

As this is a single case, there are some limitations. We cannot know what the patient’s baseline pulmonary function was prior to infection because he had never been tested. He was obese, but had never presented for any significant medical workup, including pulmonary or cardiac, prior to his hospitalization. We also cannot generalize our findings to all infected individuals without more specimens.

**Conclusion**

This case report contributes to the growing body of evidence supporting the development of pulmonary hypertension in patients with chronic COVID-19 pneumonia. As the post-COVID population will only increase, pulmonologists and pulmonary pathologists should be aware of the possibility of COVID-induced pulmonary arteriolar remodeling and consider clinical, radiologic, and perhaps histologic correlation when the situation arises.

**Author Contributions**

Conception and design of study: BJS, SJR, JMR. Medical management and surgical performance: HS, DB, AS. Pathologic performance: JMR, SJR, BJS. Drafting of manuscript: JMR. All authors edited and approved the final version of the manuscript.

**Declaration of Conflicting Interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Swanson serves on the scientific advisory board of Cogen Biosciences and owns stock in the company.

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**Ethical Approval**

At our institution, single case studies with participant approval do not require IRB oversight.
Informed Consent
The patient gave informed consent for this study.

Trial Registration
N/A

ORCID iD
Joseph M. Rohr https://orcid.org/0000-0002-9710-6471

References
1. Moline H, Whitaker M, Deng L, et al. Effectiveness of COVID-19 Vaccines in Preventing Hospitalization Among Adults Aged ≥65 Years — COVID-NET, 13 States, February–April 2021. Vol. 70. 2021:1088-1093. Morbidity and Mortality Weekly Report. August 13, 2021.
2. Greenhalgh T, Knight M, A’Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. Aug 11 2020;370(m3026). doi:10.1136/bmj.m3026
3. Alshomrani A, Rohr J, Carda M, et al. A Sticky Issue: Thrombotic Phenomena Amidst Autopsy Findings in Fatal Cases of COVID-19. Video and abstract, United States and Canadian Academy of Pathology Annual Meeting (virtual meeting), March 2021.
4. Elsoukkary SS, Mostyka M, Dillard A, et al. Autopsy findings in 32 patients with COVID-19: a single-institution experience. Pathobiology. 2021;88(1):56-68. doi:10.1159/000511325
5. Satturwar S, Fowkes M, Farver C, et al. Postmortem findings associated With SARS-CoV-2: systematic review and meta-analysis. Am J Surg Pathol. May 1 2021;45(5):587-603. doi:10.1097/PAS.0000000000001650
6. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. May 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1
7. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. Nat Med. Apr 2021;27(4):626-631. doi:10.1038/s41591-021-01292-y
8. Aesif SW, Bribriseco AC, Yadav R, et al. Pulmonary pathology of COVID-19 following 8 weeks to 4 months of severe disease: a report of three cases, including One With bilateral lung transplantation. Am J Clin Pathol. Mar 15 2021;155(4):506-514. doi:10.1093/ajcp/aqaa264
9. Bharat A, Querrey M, Markov NS, et al. Lung transplantation for patients with severe COVID-19. Sci Transl Med. Dec 16 2020;12(574). doi:10.1126/scitranslmed.abe4282
10. Bharat A, Machuca TN, Querrey M, et al. Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries. Lancet Respir Med. Mar 31 2021;9(5):487–497. doi:10.1016/S2213-2600(21)00077-1
11. Lee JD, Burger CD, Delossantos GB, et al. A survey-based estimate of COVID-19 incidence and outcomes among patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension and impact on the process of care. Ann Am Thorac Soc. Dec 2020;17(12):1576-1582. doi:10.1513/AnnalsATS.202005-521OC
12. Suzuki YJ, Nikolaenko SI, Shults NV, Gychka SG. COVID-19 patients may become predisposed to pulmonary arterial hypertension. Med Hypotheses. Feb 2021;147:110483. doi:10.1016/j.mehy.2021.110483
13. Plebani M. Persistent viral RNA shedding in COVID-19: caution, not fear. EBioMedicine. Feb 2021;64:103234. doi:10.1016/j.ebiom.2021.103234