

# 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

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### ABSTRACT

**Objectives:** Current knowledge of the pulmonary pathology of coronavirus disease 2019 (COVID-19) is based largely on postmortem studies. In most, the interval between disease onset and death is relatively short (<1 month). Information regarding lung pathology in patients who survive for longer periods is scant. We describe the pathology in three patients with severe COVID-19 who underwent antemortem examination of lung tissue at least 8 weeks after initial diagnosis.

**Methods:** We conducted a retrospective case series.

**Results:** The first patient developed acute respiratory failure and was started on extracorporeal membrane oxygenation (ECMO) on day 21, with subsequent hemothorax. Debridement (day 38) showed extensive lung infarction with diffuse alveolar damage and *Candida* overgrowth. The second patient developed acute respiratory failure requiring mechanical ventilation that did not improve despite ECMO. Surgical lung biopsy on day 74 showed diffuse interstitial fibrosis with focal microscopic honeycomb change. The third patient also required ECMO and underwent bilateral lung transplantation on day 126. The explanted lungs showed diffuse interstitial fibrosis with focal microscopic honeycomb change.

**Conclusions:** This series provides histologic confirmation that complications of COVID-19 after 8 weeks to 4 months of severe disease include lung infarction and diffuse interstitial fibrosis.

### Key Points

- Information regarding late complications of coronavirus disease 2019 (COVID-19) is scant, and antemortem data regarding the pulmonary pathology of long-term disease are lacking.
- Case 3 of this series represents the second comprehensive report of the pulmonary pathology in a patient undergoing lung transplantation for prolonged COVID-19–related hospitalization.
- Diffuse interstitial fibrosis with early microscopic honeycomb change can develop following recovery from COVID-19 and prolonged hospitalization.

In a time without precedent to living memory, the ongoing and evolving coronavirus disease 2019 (COVID-19) pandemic has affected millions worldwide. Our current understanding of COVID-19 pathology is based almost entirely on autopsies (both complete and partial) and postmortem biopsies performed on patients dying after a few days to a few weeks of severe disease.<sup>1–25</sup> In one series, the interval between onset of illness and death ranged from 1 to 32 days.<sup>25</sup> In another, the range was 1 to 58 days (median, 21 days).<sup>23</sup> A series of 30 “minimally invasive autopsies” included six patients with duration of illness listed as 63, 68, 75, 63, 71, and 82 days.<sup>6</sup> Not unexpectedly, the most striking degree of tissue damage has consistently been reported in the lungs. Like most severe viral pneumonias, the pattern of injury most often encountered on histologic review is diffuse alveolar damage (DAD), which is the expected histologic correlate to the acute respiratory distress syndrome (ARDS).<sup>26–28</sup> These findings are similar to reports from previous coronavirus-related outbreaks (ie, severe acute respiratory syndrome [SARS] and

Middle East respiratory syndrome [MERS]),<sup>29-31</sup> Fifteen percent to 30% of patients who recovered from SARS and MERS went on to develop persistent long-term lung abnormalities, including pulmonary fibrosis.<sup>30-32</sup> Similarly, the natural progression of infectious and noninfectious ARDS has long been thought to include the potential for long-term pulmonary complications, including the development of significant and irreversible pulmonary fibrosis.<sup>26-28</sup> Although this remains to be proven at a histologic level in COVID-19, if we extrapolate data from prior outbreaks of severe viral disease to the current pandemic, it seems plausible that long-term complications following recovery from COVID-19 infection will be encountered in coming months and years.

In addition to the lack of pathologic information regarding antemortem pulmonary changes associated with COVID-19, there is little information regarding pathologic findings in the lungs of patients who survived initial infection but remained severely ill for more than a few weeks. In the first such case reported, the explanted lungs of a 44-year-old woman who underwent bilateral lung transplantation on day 58 showed large zones of necrosis, DAD, and widespread thromboemboli.<sup>33</sup> Interestingly, while cultures were negative at the time of transplantation, polymerase chain reaction (PCR) testing remained positive. Two earlier preliminary reports from China documented the feasibility of lung transplantation for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR-negative patients.<sup>34,35</sup> Of the five patients reported, histologic assessments were only reported for two patients, both as “extensive pulmonary interstitial fibrosis,” with varying descriptions of thrombosis and hemorrhage. No other histologic data were provided, and the interval between disease onset and transplantation was not explicitly stated.

Here we report the antemortem pathologic findings in the lungs of three patients who survived with severe COVID-19 for intervals ranging from 8 weeks to 4 months (range, 57-126 days) followed by surgical lung biopsy/resection, autopsy, or lung transplantation.

## Cases

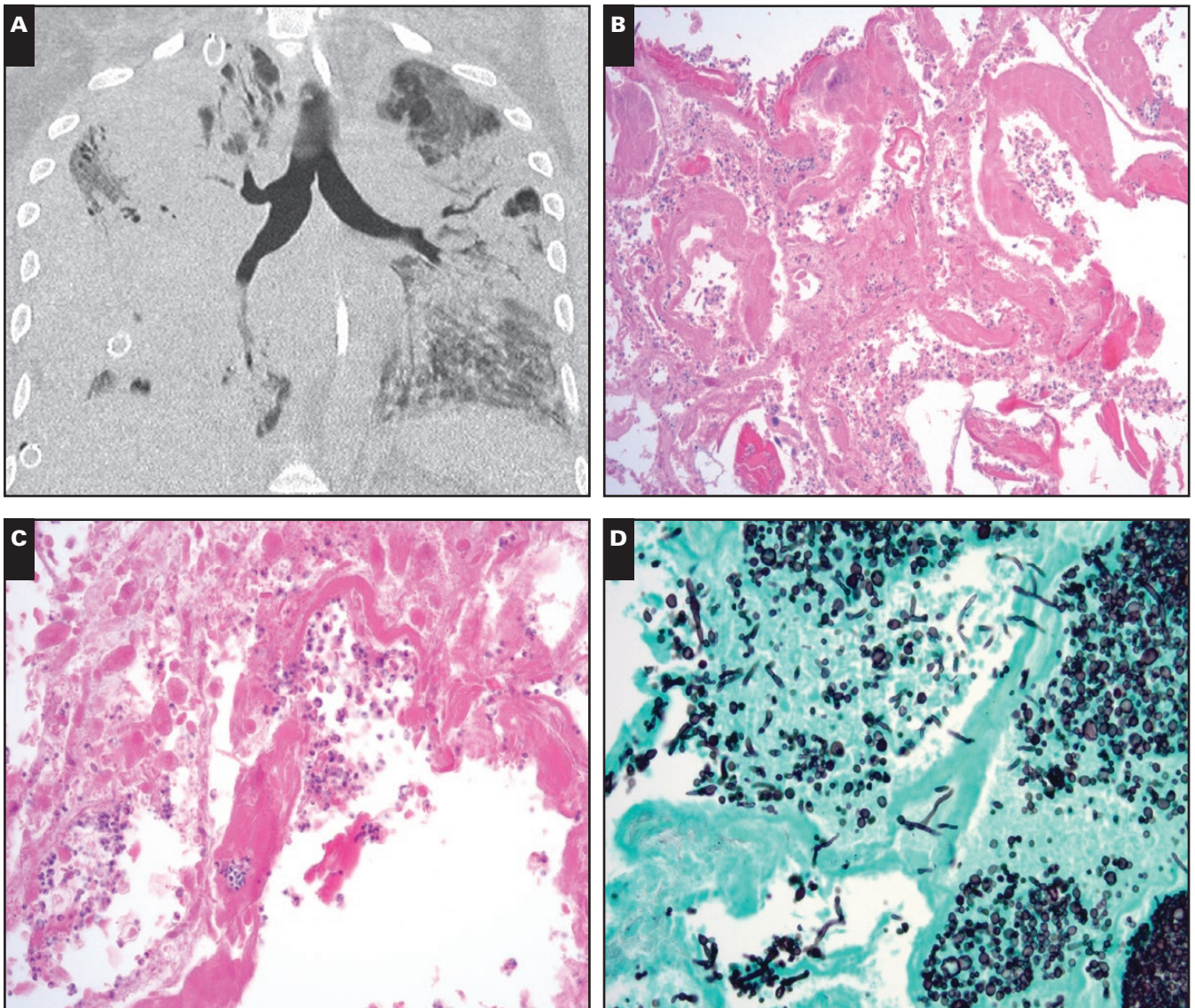
### Case 1

A 46-year-old Black man with hypertension, obesity (body mass index, 36.9 kg/m<sup>2</sup>), and chronic lymphocytic leukemia (2 years in remission) sought treatment for moderate respiratory symptoms. Reverse transcriptase (RT)-PCR for SARS-CoV-2 by nasopharyngeal swab was positive (day 1). After initial management as

an outpatient, he presented on day 10 with worsening dyspnea. Chest imaging showed bilateral multifocal peripheral consolidation. He was lymphopenic (total leukocyte count 3,700/ $\mu$ L, 13.7% lymphocytes) with elevated C-reactive protein (CRP, 19.5 mg/dL), ferritin (853.5 ng/mL), lactate dehydrogenase (401 IU/L), D-dimer (2,919 ng/mL), and fibrinogen (761 mg/dL). Despite treatment with remdesivir, convalescent plasma, and tocilizumab, he deteriorated and was intubated on day 18. Refractory hypoxia persisted despite neuromuscular blockade, airway-pressure release ventilation, and prone positioning. Given persistent hypoxemia, veno-venous extracorporeal membrane oxygenation (V-V ECMO) was started on day 21. His lungs showed worsening diffuse airspace disease and were poorly compliant on lung-protective mechanical ventilation settings. Bilateral lower extremity deep vein thromboses were treated with anticoagulation. Nasal and oropharyngeal bleeding was managed with packing. Repeat SARS-CoV-2 testing was positive on day 23. A spontaneous right pneumothorax (day 24) required chest tube placement. Right hemothorax (day 29) required chest tube placement followed by video-assisted thoracoscopic surgery on day 31 with hemothorax evacuation. The right lung surface was gelatinous and flaccid despite intraoperative ventilation. He continued to require frequent blood transfusions for persistent bleeding from the right chest. A lung parenchymal-pleural fistula (air leak) was observed, making recruitment of potentially salvageable lung impossible. Chest computed tomography (CT) on day 35 **Image 1A** showed extensive airspace consolidation in the right lung, mixed airspace and ground-glass opacities in the left lung, and a loculated right hemopneumothorax. On day 38, exploratory thoracotomy showed liquefying necrosis of the right middle lobe with retained clots in the visceral pleura. Debridement of the necrotic right middle lobe was performed with suture closure of visible small airways and right middle lobe pexy with application of BioGlue (CryoLife) to mitigate loss of ventilation from bronchopleural fistulas. A spontaneous left pneumothorax occurred subsequently, requiring chest tube insertion. The next 2 weeks saw no clinical improvement, complete dependence on V-V ECMO, and persistent bilateral air leaks. Repeat SARS-CoV-2 testing was negative on day 44. He then developed renal insufficiency requiring dialysis, as well as elevated liver enzymes and shock requiring vasopressor support. Without a realistic chance of meaningful recovery, he was transitioned to comfort care and died on day 57.

Histologic examination of the debrided right middle lung lobe confirmed extensive infarct-like necrosis of the lung. Within the necrotic lung, “ghosts” of alveolar





**Image 1** Case 1, late complications of coronavirus disease 2019. **A**, Chest computed tomography coronal reformatted image (day 35) shows extensive airspace consolidation in the right lung, especially the right middle lobe. Scattered mixed airspace and ground-glass opacities are present in the left lung with a few thin-walled cysts/cavitary lesions suggesting superinfection. **B, C**, The surgically debrided lung tissue is completely necrotic, with “ghosts” of hyaline membranes visible within the necrotic lung (H&E,  $\times 10$  and  $\times 20$ , respectively). **D**, Grocott methenamine silver stain showing numerous *Candida* organisms within the necrotic lung ( $\times 40$ ).

septa lined by hyaline membranes remained appreciable **Image 1B** and **Image 1C**. A few blood vessels (mainly small arteries) within the necrotic areas contained thrombi. Grocott methenamine silver staining highlighted extensive colonization of necrotic lung by budding yeast with pseudohyphae **Image 1D**. Culture of the lung tissue confirmed *Candida albicans*. Subsequent autopsy showed findings identical to the original lung specimen. While largely obscured by the extensive infarction-related necrosis, overall the pattern of lung injury was compatible with diffuse alveolar damage in the acute stage. No significant fibrosis was observed.

## Case 2

A 57-year-old obese Hispanic woman with distant myocardial infarction presented with 3 days of dyspnea, cough, hypoxia, and fever (101.4°F). RT-PCR for SARS-CoV-2 by nasopharyngeal swab was positive (day 1). CRP was 169 mg/dL, creatinine was 0.76 mg/dL, and total leukocyte count was 8,000/ $\mu$ L. Chest x-ray showed bilateral airspace opacities. On day 4, she was started on hydroxychloroquine. Mechanical ventilation was started on day 6. At this time, she developed septic shock attributed to a urinary tract infection (*Proteus* spp). Over the next 4 days, she was paralyzed and prone. Convalescent plasma was administered

on day 10. Despite these measures, her respiratory status continued to worsen. On day 12, she was transferred to a regional ECMO center, arriving prone on 100% fraction of inspired oxygen and positive end-expiratory pressure of 14 cm H<sub>2</sub>O. Supine O<sub>2</sub> saturation was 80% with a Murray score of 3.8. Chest x-ray showed extensive bilateral airspace opacities. Percutaneous V-V ECMO was initiated upon arrival. Oxygen saturation improved to 98% with 4.5 L/min of flow. A course of remdesivir was started. On day 18, a second dose of convalescent plasma was administered and cytokine filter treatment performed. *Enterococcus faecalis* septic shock on day 20 necessitated change of ECMO circuit, including cannulas. Spontaneous bilateral hemothoraces occurred subsequently, requiring chest tube drainage on day 25. Repeat SARS-CoV-2 testing on day 38 was negative. Her respiratory status, inflammatory markers, and radiographic picture never improved. Chest CT (day 40) showed marked bilateral consolidation and moderate bilateral pleural effusions. Repeat CT on day 59 showed findings suspicious for evolving fibrotic lung disease with superimposed diffuse consolidation **Image 2A**. On day 74 (after 63 days of ECMO), surgical lung biopsy was performed. Shortly thereafter, the patient experienced acute deterioration in respiratory status. The goals of care were switched to comfort, and she died on day 74.

Histologic sections of the surgical lung biopsy specimen showed diffuse, somewhat mild, and relatively uniform interstitial expansion **Image 2B**, a pattern vaguely reminiscent of nonspecific interstitial pneumonia (NSIP). Focal microscopic honeycomb change was also present **Image 2C**. Foci of superimposed organizing acute lung injury, patchy interstitial lymphocytic infiltrates, and mild chronic pleuritis with fibrinous exudates were also present. The superimposed organizing acute lung injury appeared compatible with organizing DAD; however, Movat pentachrome stains demonstrated the majority of the interstitial fibrosis to be more mature collagen-type **Image 2D**. Definitive hyaline membranes, Masson bodies, or fibroblastic foci were not appreciated. No capillaritis/vasculitis or thromboembolic changes were observed.

### Case 3

A 57-year-old man with coronary artery disease and hypertension was diagnosed by nasopharyngeal swab elsewhere with COVID-19 and subsequently developed progressively worsening hypoxic respiratory failure due to ARDS despite treatment with plaquenil, azithromycin, solumedrol, tocilizumab, and an interleukin 1 receptor blocker (anakinra). He required mechanical ventilation on day 14. His hospital course was complicated by atrial fibrillation with rapid ventricular response and high D-dimer. He was initially placed on apixaban and

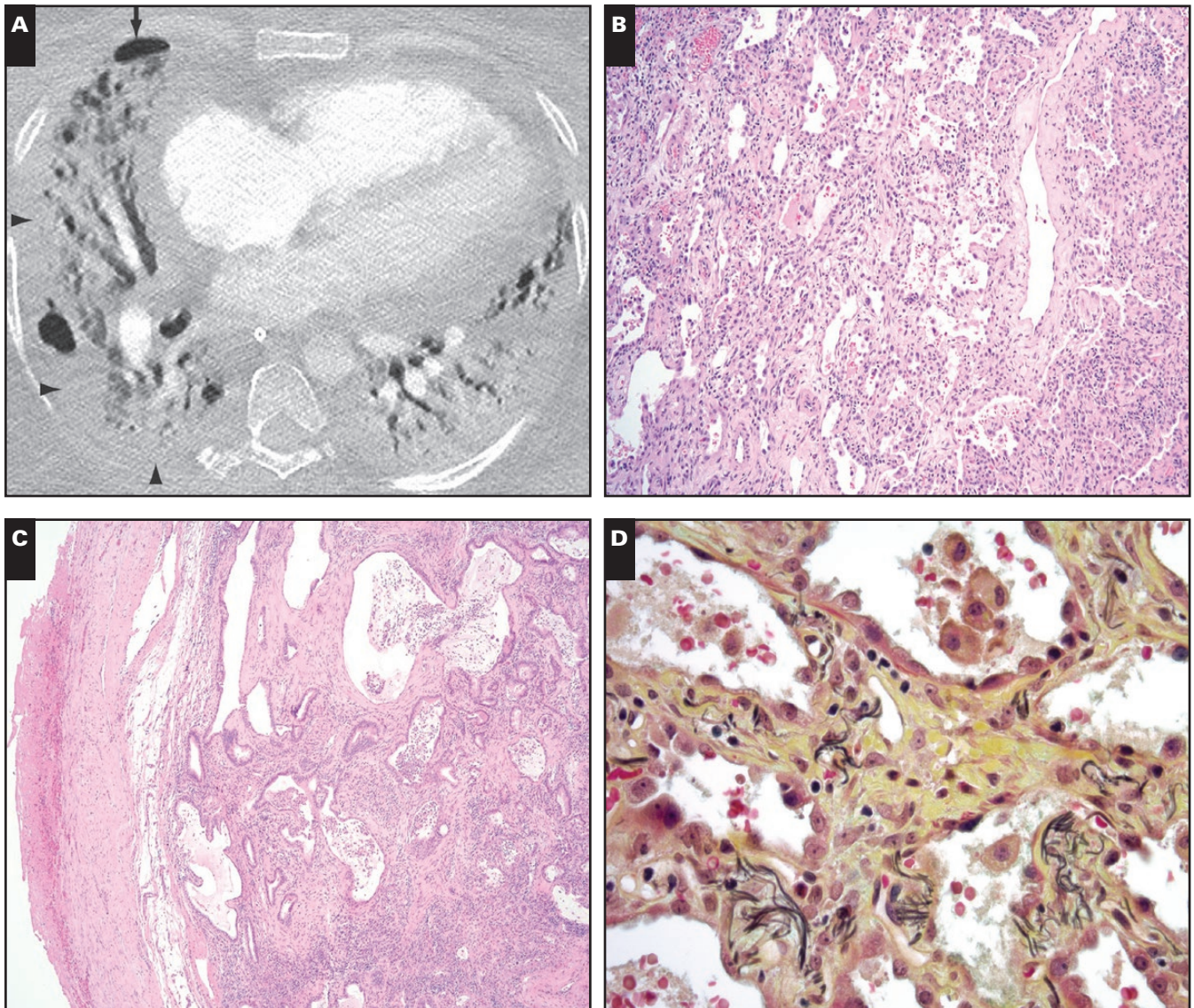
then switched to tissue plasminogen activator to prevent thromboembolism. Despite use of inhaled nitric oxide and proning, his oxygenation did not improve. Tracheostomy was performed on day 13 of mechanical ventilation. His course was further complicated by bacteremia (*Escherichia coli* and methicillin-sensitive *Staphylococcus aureus*). On day 54, he was placed on V-V ECMO due to worsening pulmonary parameters. Subsequent complications included pneumomediastinum, pneumothorax, and lower gastrointestinal bleed. Chest CT on day 59 revealed diffuse bilateral consolidation, a large right pneumothorax in the setting of a pleural drain, and findings suggesting bronchopleural fistula **Image 3A**. Following multiple negative RT-PCR tests for SARS-CoV-2, he was transferred to our institution for consideration of lung transplantation (day 74). Chest x-ray at admission revealed low lung volumes with diffuse mixed bilateral interstitial and airspace opacities, a small right pneumothorax, and bilateral pleural effusions. He underwent thorough pretransplant evaluation, including bronchoalveolar lavage, to exclude persistent viral infection. Chest radiograph on day 122 demonstrated low lung volumes with complete opacification of both hemithoraces. On day 126, he underwent bilateral sequential lung transplantation. Two and a half months following lung transplantation (day 202, approximately 7 months after his initial diagnosis), he remains hospitalized, requiring mechanical ventilation in the intensive care unit.

Histopathologic examination of the explanted lungs revealed mild diffuse interstitial chronic inflammation with diffuse, relatively uniform-appearing interstitial expansion **Image 3B**. This pattern again vaguely resembled NSIP. Peribronchiolar metaplasia was also present but not extensive **Image 3C**. This was accompanied by numerous hemosiderin-laden and foamy macrophages within the airspaces **Image 3D** and **Image 3E**. Foci of microscopic honeycomb change were also present (not shown). There was no evidence of acute lung injury or capillaritis/vasculitis. A single small vessel demonstrated some intimal fibroplasia, but no definitive evidence of a thromboembolic event was seen. Fibroblast foci were not observed, and a Movat pentachrome stain revealed most of the interstitial expansion to be composed of collagen-type fibrosis.

### Discussion

This report offers an early glimpse into the longer-term pathologic aftermath of severe COVID-19 managed with prolonged mechanical ventilation and ECMO, summarized in **Table 1**. To our knowledge, case 3 of this



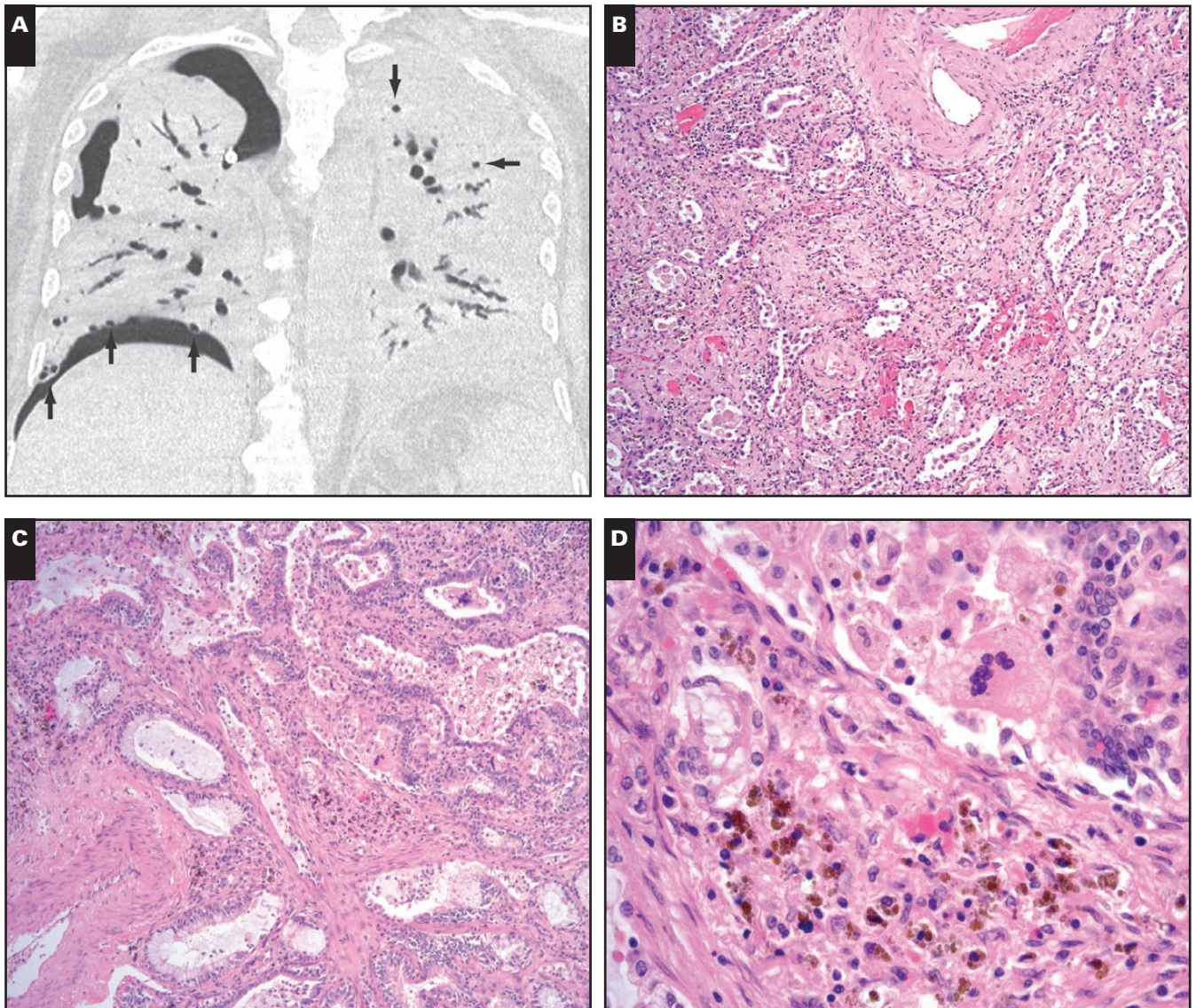


**Image 2** Case 2, late complications of coronavirus disease 2019. **A**, Axial chest computed tomography on day 59 showing diffusely consolidated lungs with air bronchograms as well as dilated bronchi with undulating contours suggesting traction bronchiectasis likely related to underlying fibrosis. A few small peripheral cystic changes are also noted, possibly representing early honeycombing. Right hydro-pneumothorax (arrow) and left pleural effusion (arrowheads) are also seen. **B**, Diffuse, uniform interstitial expansion with associated pneumocyte hyperplasia (H&E,  $\times 10$ ). **C**, Focal microscopic honeycomb change (H&E,  $\times 4$ ). **D**, Movat pentachrome stain ( $\times 40$ ).

series represents only the second detailed description of the pulmonary pathology in a patient undergoing lung transplantation for prolonged COVID-19–related hospitalization and the longest follow-up of successful lung transplantation in this setting (the patient is alive on day 202; day 79 after transplantation). The main pathologic finding is that diffuse interstitial fibrosis with early microscopic honeycomb change can develop within this time frame. Persistence of DAD beyond 8 weeks with massive unilateral lung necrosis and extensive colonization by *Candida* is also hitherto unreported in COVID-19.

Potential limitations to this study include the possibility of preexisting pulmonary fibrosis or predisposing conditions (ie, lung-toxic chemotherapy in case 1) that may have predated COVID-19–related hospitalization but contributed to the fibrosis seen on resection. For case 1, chest CT on admission showed typical imaging features of COVID-19 pneumonia with no findings to suggest underlying fibrotic interstitial lung disease ([Supplemental Image 1A](#); all supplemental materials can be found at *American Journal of Clinical Pathology* online). For case 2, initial portable chest radiograph showed airspace





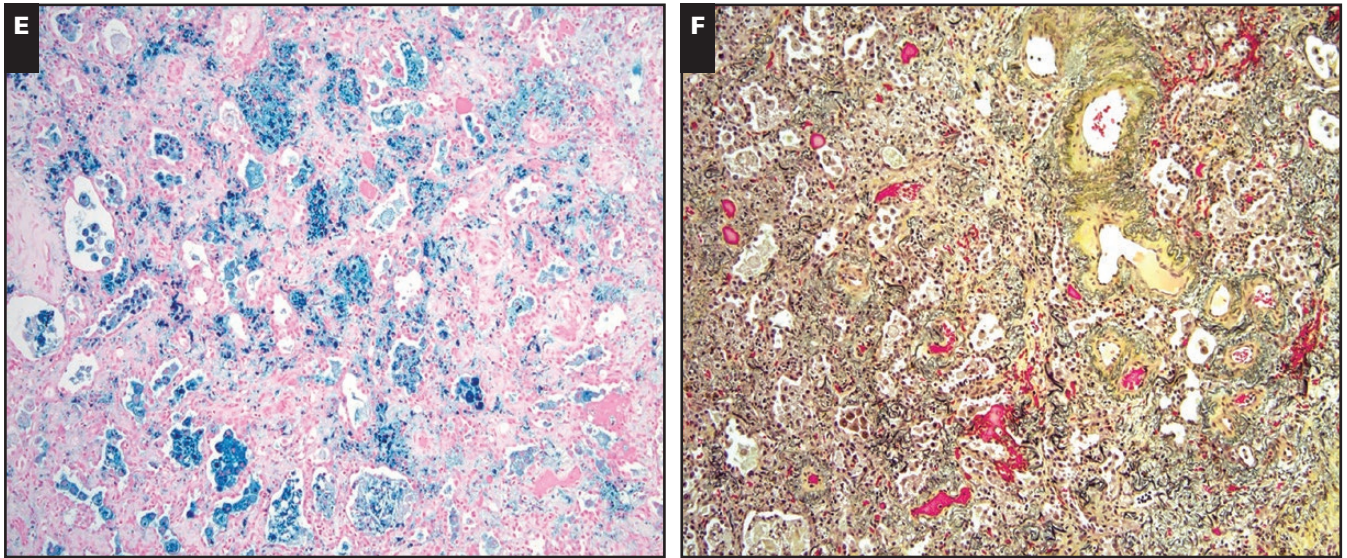
**Image 3** Case, 3, late complications of coronavirus disease 2019. **A**, Chest computed tomography coronal reformatted image (day 75) shows homogeneous diffuse bilateral consolidation with volume loss, traction bronchiectasis, and a few peripheral cystic changes likely representing early honeycombing (arrows). The findings are suggestive of an acute process superimposed on underlying fibrotic lung disease. A large right pneumothorax is seen despite the presence of a pleural drainage catheter. A few of the subpleural cystic changes communicate with the pleura, suggesting a bronchopleural fistula. **B**, Diffuse, uniform, and somewhat cellular interstitial expansion (H&E,  $\times 10$ ). **C**, Focal peribronchiolar metaplasia (H&E,  $\times 10$ ). **D**, Filling of the airspaces by pigmented and foamy macrophages (H&E,  $\times 40$ ).

opacities in both lungs, worse in the periphery and lung bases ([Supplemental Image 1B](#)), with a subsequent radiograph obtained post-ECMO placement demonstrating worsening bilateral extensive airspace opacities with air-bronchograms, most likely related to diffuse alveolar damage ([Supplemental Image 1C](#)). Unfortunately, preadmission imaging was not available to document normal lungs, and no chest CT was performed at the time of admission, precluding a confident assertion that all findings on chest x-ray were from COVID-19 pneumonia

and not preexisting background fibrosis. Case 3 unfortunately had DAD on admission.

All three patients underwent prolonged ECMO runs. Although DAD can occur in patients with COVID-19 who have never been ventilated, it is possible that ventilator-associated injury occurs in COVID-19-damaged lung despite lung-protective strategies facilitated by ECMO support. This is especially probable in nonparalyzed, spontaneously breathing patients who are asynchronous with the ventilator (so-called patient self-inflicted





**Image 3** (cont) **E**, Iron (Prussian blue) stain ( $\times 10$ ). **F**, Movat pentachrome stain ( $\times 10$ ).

lung injury) and can manifest as spontaneous pneumothorax. With regard to the possibility of the observed fibrosis being a sequela of the ECMO itself, there are little data available to examine this issue due to inherent confounding in clinical situations. The issue is more one of association than of causality. The pulmonary insult that caused ARDS requiring ECMO, followed by the lungs' subsequent healing, is what most likely caused the fibrosis, not the ECMO itself. Lindén et al<sup>36</sup> observed that for treatment of severe ARDS, the protracted parenchymal CT imaging abnormalities seen in conventional ventilator-treated ARDS were not present in patients treated with ECMO. The authors go on to suggest that ECMO therapy itself may in fact protect the pulmonary parenchyma from so-called ventilator-associated damage. It should be noted, however, that histologic evidence of thrombosis and evidence of organizing DAD have been reported in patients with prolonged ECMO therapy; having acknowledged this, current protocols aim to mitigate this risk to the greatest extent possible. That being the case, the largest series on the subject was consistently definitive in the authors' ability to classify the patterns of fibrosis seen in patients who received prolonged ECMO therapy as most likely being organizing DAD in nature.<sup>37</sup>

In the current series, the patterns of fibrosis seen in cases 2 and 3 largely defied definitive classification. The diffuse and homogeneous interstitial changes were more reminiscent of a fibrotic NSIP pattern and not convincingly organizing DAD. While focal microscopic honeycomb change was seen, the patchwork pattern of fibrosis seen in cases of usual interstitial pneumonia was not observed. The composition of the airspace macrophages

observed in case 3 was also unique in that there appeared to be evidence of prior alveolar hemorrhage in the form of hemosiderin-laden macrophages. We could not find evidence of vasculitis or capillaritis. At the same time, there appeared to be postobstructive changes given the presence of foamy-appearing macrophages, although there was little evidence of an organizing pneumonia. Postobstructive changes are commonly seen in the setting of organizing pneumonia, which has been inconsistently reported in patients with COVID-19 infections. Certain severe viral pneumonias, such as cytomegalovirus, are known to cause a necrotizing bronchiolitis that conceptually could result in some pulmonary hemorrhage without evidence of vascular inflammation. No such necrotizing pneumonia was observed in any of the patients reported herein.

Currently, there is no definitive histologic evidence to suggest that the symptoms experienced by what the lay literature has labeled COVID-19 "long haulers" are due to the development of subclinical pulmonary fibrosis.<sup>38,39</sup> However, the histologic findings in this report confirm that the development of interstitial fibrosis in the lungs is a real possibility in patients who survive their initial acute COVID-19 infections.

The mechanisms by which COVID-19 infection results in pulmonary fibrosis remain to be elucidated, although curiously, the mechanisms may be independent of the virus's ability to induce acute lung injury.<sup>40,41</sup> As a family, coronaviruses have been demonstrated to induce, within infected cells, a significant degree of endoplasmic reticulum stress, which has been linked to the development of pulmonary fibrosis, independent of acute lung injury.<sup>41</sup> Endoplasmic

**Table 1**  
**Timeline of Major Events in Three Patients With Severe COVID-19<sup>a</sup>**

Event	Case 1 (46 y/M)	Case 2 (57 y/F)	Case 3 (57 y/M)
Test for COVID-19 positive	Day 1	Day 1	Day 1
ECMO	Day 21	Day 12	Day 54
Mechanical ventilation	Day 14	Day 5	Day 15
Pathology	Lung debridement on day 38, 5 weeks after positive test; autopsy on day 57	Open lung biopsy on day 74, 10 weeks after positive test	Bilateral lung transplantation on day 126, 4 months after positive test
Last follow-up or death	Died on day 57, 8 weeks after positive test	Died on day 74, 10 weeks after positive test	Alive, 7 months after positive test

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

<sup>a</sup>Day 1 in this table is the day of the first positive severe acute respiratory syndrome coronavirus 2 test.

reticulum stress has long been known to be a consequence of cellular redox imbalances. Replication of coronaviruses has been demonstrated to be dependent on the precise redox status of infected cells.<sup>40</sup> It remains to be determined if the redox state of an individual cell or organ will play a significant role in mitigating the effects of COVID-19 infection.

Regardless, based on the findings presented herein, it appears that the development of varying degrees of pulmonary fibrosis can be a sequela of COVID-19 infection and will be an important avenue for future clinical research. Based on the pathologic appearance, it is plausible that the fibrosis may represent the residuum of prior organizing DAD. Although the pathogenesis of these findings is likely complex and multifactorial, our pathologic findings support observations from the radiology literature that diffuse interstitial fibrosis can occur later in the course of severe COVID-19 treated with aggressive life-supporting therapies.<sup>42</sup>

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