


CASE REPORT

Early COVID-19 infection after lung transplantation

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COVID-19, the clinical syndrome caused by the novel coronavirus, SARS-CoV-2, continues to rapidly spread, leading to significant stressors on global healthcare infrastructure. The manifestations of COVID-19 in solid organ transplant recipients are only beginning to be understood with cases reported to date in transplant recipients on chronic immunosuppression. Herein, we report the first case of COVID-19 in a lung transplant recipient in the immediate posttransplant period, and we describe the epidemiologic challenges in identifying the source of infection in this unique situation.

KEYWORDS

coronavirus, COVID-19, lung transplant

1 | CASE REPORT

The emergence of the novel coronavirus, SARS-CoV-2, and its associated clinical syndrome, COVID-19, resulted in the largest global pandemic since the 1918 influenza. While widespread in the general population, to date, there are few reports of COVID-19 in solid organ transplant (SOT) recipients.¹⁻⁵ Herein, we report a case of COVID-19 infection in the early postoperative period following lung transplantation (LT).

A 68 year-old white female with idiopathic pulmonary fibrosis, gastroesophageal reflux disease, hyperlipidemia, and psoriasis was listed for bilateral LT with a lung allocation score of 31.8784. At admission for transplant, the patient reported feeling well without symptoms of acute respiratory infection. Vital signs included

temperature, 37.1°C; heart rate, 78 beats per minute; blood pressure, 124/83 mm Hg; and oxygen saturation, 94% on 3 L/min oxygen.

The donor, a 30 year-old female with a history of hypertension and inflammatory bowel disease treated with a tumor necrosis factor inhibitor presented to the hospital with severe headache, confusion, and vomiting. There was no history of fever or respiratory symptoms. She was intubated, and head CT revealed a large intracerebral hemorrhage. Due to poor neurologic prognosis, her family elected to pursue organ donation following cardiac death. Chest CT demonstrated "focal areas of consolidation in the bilateral dependent lower lobes with adjacent tree-in-bud opacities most consistent with pneumonia, possibly secondary to aspiration" (Figure 1A). Bronchoscopic examination identified erythematous mucosa of the trachea and main carina with purulent secretions in all lobes. Bronchoalveolar lavage (BAL) culture resulted in normal upper respiratory flora. No viral testing was performed, and no confirmed COVID-19 cases had been reported in the county of the donor hospital. p_aO_2 on the last challenge arterial blood gas prior to procurement was 482 mm Hg.

Abbreviations: AKI, acute kidney injury; BAL, bronchoalveolar lavage; CDC, Centers for Disease Control and Prevention; HCW, healthcare worker; LT, lung transplant; MMF, mycophenolate mofetil; NPS, nasopharyngeal swab; OPO, organ procurement organization; POD, postoperative day; PPE, personal protective equipment; SOT, solid organ transplant.

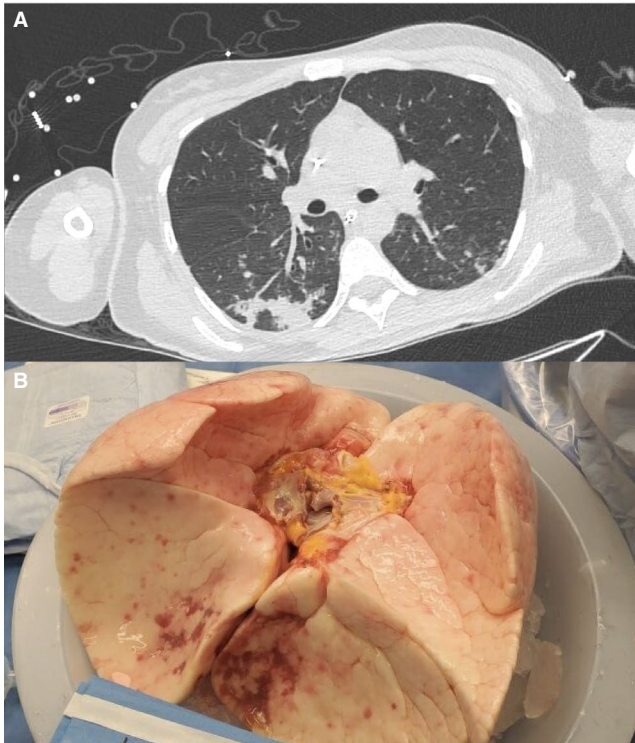


FIGURE 1 Donor lungs. A, Axial view of the donor chest CT scan demonstrating areas of focal consolidation and tree-in-bud opacities. B, Donor lungs following procurement [Color figure can be viewed at wileyonlinelibrary.com]

Sixty hours after hospital admission, the donor was taken to the operating room for organ procurement following cardiac death. A repeat bronchoscopic examination revealed minimal airway secretions. Having met programmatic parameters for quality, the lungs were procured and prepared for transport (Figure 1B).

The recipient underwent bilateral sequential LT via thoracosternotomy with 86 minutes of cardiopulmonary bypass. The intraoperative course was without incident. Ischemic times for the right and left allografts were 246 and 335 minutes, respectively. Induction immunosuppression included intraoperative corticosteroids and basiliximab with a second basiliximab dose on postoperative day (POD) 4. Maintenance immunosuppression with mycophenolate

mofetil (MMF) and corticosteroids was started immediately postoperatively, and tacrolimus, started on POD3, was titrated to a goal trough of 10–12 ng/mL. Four days of empiric antibiotics were administered per protocol and discontinued once intraoperative donor and recipient cultures finalized negative.

The patient was liberated from mechanical ventilation on POD1. She developed worsening hypoxemia with extensive pulmonary edema on chest radiography, consistent with grade 3 primary graft dysfunction (Figure 2), and was reintubated on POD2. On POD6, she became diaphoretic and febrile (39°C) with onset of atrial fibrillation/flutter. Vancomycin and cefepime were started, but all cultures remained negative. Bronchoscopy on POD8 revealed airway inflammatory changes and purulent secretions. BAL bacterial and fungal cultures and multiplex respiratory viral panel were negative. Inflammatory markers were markedly elevated (Table 1). Given concern for infection, MMF was decreased to 500 mg every 12 hours, and SARS-CoV-2 RT-PCR testing via nasopharyngeal swab (NPS) was obtained on POD9, returning positive 35 hours later. She was placed in droplet and contact precautions and transferred to a designated COVID-19 ward.

The patient's condition deteriorated with worsening oxygenation and hemodynamic instability requiring escalating doses of vasopressors. She developed acute kidney injury (AKI) requiring renal replacement therapy and atrial arrhythmias recurred, requiring amiodarone and cardioversion. Treatment with chloroquine and azithromycin was initiated on POD11. Remdesivir was contraindicated due to severe AKI; tocilizumab was considered, but not administered due to an unclear risk to benefit ratio in this recently transplanted patient. Prone positioning was considered although never implemented due to improving oxygenation with lung protective ventilation (Figure 2). Following an initial period of vasopressor escalation, hemodynamics stabilized. On POD14, chloroquine was discontinued due to QTc prolongation and new data indicating lack of benefit.⁶ MMF was discontinued, and the tacrolimus trough goal was decreased to 8 ng/mL.

Repeat SARS-CoV-2 RT-PCR testing via NPS on POD12 and POD14 was negative. The patient was transferred back to the cardiothoracic intensive care unit on POD28 and underwent tracheostomy on POD30. MMF was reinstated on POD34 at 500 mg every 12 hours. As of POD57, she has been liberated from mechanical

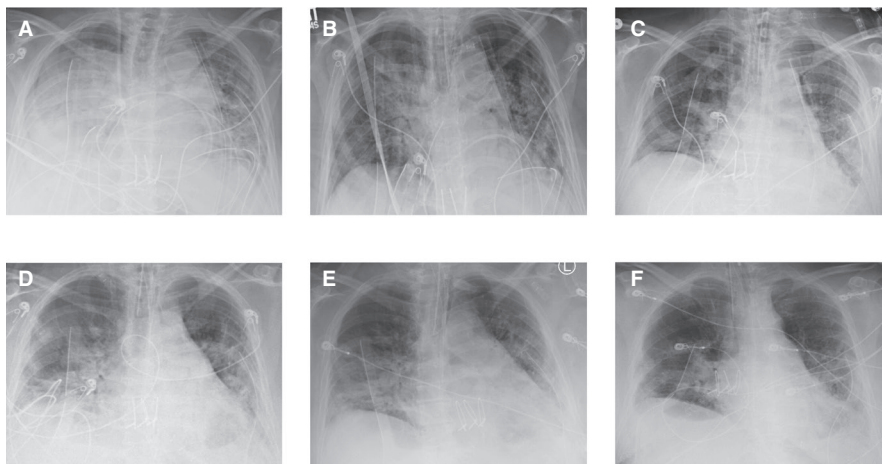


FIGURE 2 Posttransplant evolution of chest radiographs. Serial posttransplant chest radiographs representing (A) PGD on POD1, (B) postintubation for PGD on POD2, (C) POD6, (D) at time of COVID-19 diagnosis on POD9, (E) 1 day after initiation of chloroquine and azithromycin on POD12, and (F) POD17

TABLE 1 Laboratory values obtained at baseline (before transplant or immediately posttransplant) and peak or nadir of values during COVID-19 infection

	Baseline	COVID-19	Reference range
White blood cell count (K/ μ L)	7.51	22.51	3.99-11.19
Granulocytes (K/ μ L)	5.43	21.72	1.64-7.28
Lymphocytes (K/ μ L)	1.39	0.23	1.16-3.51
Eosinophils (K/ μ L)	0.48	0.00	0.22-0.87
Lactate (mmol/L)	0.7	1.75	0.5-1.60
Lactate dehydrogenase (U/L)	nd	271	100-190
C-reactive protein (mg/L)	194.15	311.03	<10
Erythrocyte sedimentation rate (mm/h)	nd	50	<30
Ferritin (ng/mL)	nd	593.9	10-291
Fibrinogen (mg/dL)	212	713	220-410
D-dimer (mcg/mL)	nd	2.85	<0.5
Procalcitonin (ng/mL)	nd	1.37	\leq 0.5
Interleukin-6 (pg/mL)	nd	93.9	<6
Interleukin-2 receptor/soluble CD25 (pg/mL)	nd	2977	\leq 1033
Quantitative IgG (mg/dL)	nd	283	600-1560
Quantitative IgM (mg/dL)	nd	43	30-360
Quantitative IgA (mg/dL)	nd	111	90-410
Serum creatinine (mg/dL)	0.71	4.62	0.5-1.2
Aspartate transaminase (U/L)	43	34	14-40
Alanine transaminase (U/L)	24	23	9-48

Note: Preoperative laboratory values were within normal limits, but markers of inflammation increased with the onset of fever and diagnosis of COVID-19.

ventilation and no longer requires supplemental oxygen. There has been no further hemodynamic instability or arrhythmia. She remains dependent on intermittent hemodialysis and is deconditioned, but is improving with physical therapy.

In an attempt to determine the source of our patient's COVID-19 infection, previously collected specimens were retrospectively analyzed by RT-PCR. These included a preoperative oral saline rinse and BAL collected from her native lung prior to explant as part of a clinical research study, and the BAL collected on POD8. All samples were negative for SARS-CoV-2 RNA. Histopathologic analysis of the explanted lungs revealed usual interstitial pneumonia without evidence of diffuse alveolar damage or evidence of viral cytopathic effect. Unfortunately, no donor respiratory samples were available for testing.

An exposure investigation and contact tracing was initiated the day the SARS-CoV-2 RT-PCR returned positive per hospital policy. A list of employees with potential contact with the patient since admission was generated through a query of the electronic medical record and examination of staffing rosters provided by unit/department managers. Each employee was interviewed by Employee Health Services to determine level of risk exposure per Centers for Disease

Control and Prevention (CDC) guidance. Anyone with medium- or high-level risk exposure was excluded from work for 14 days; employees with low-level risk exposure were allowed to work with daily symptom and temperature monitoring. Hospital policy strictly prohibited any symptomatic healthcare worker (HCW) from coming to work. Additionally, HCWs were prohibited from work if any household member had a positive or pending SARS-CoV-2 test.

A total of 140 HCWs were included in the investigation. One HCW tested positive for SARS-CoV-2 4 days after the patient tested positive, and a second HCW tested positive on POD19. The first HCW reported mild gastrointestinal symptoms that began one day before she cared for the patient on POD8, but this HCW never developed fever or respiratory symptoms. The second HCW, a patient care associate, cared for the patient for 4 hours on POD4 before developing symptoms on POD17. This HCW was considered a low-risk exposure as she wore a facemask with eye protection during her time with the patient.

The first confirmed case of COVID-19 was diagnosed in Ohio 2 days before the transplant, and the first case in the county was diagnosed on POD3. At the time of transplant, testing in Ohio was available through the Ohio Department of Health for inpatients meeting strict case definition criteria or via send out testing to a commercial lab. On-site testing for inpatients became available on POD8 with limited capacity. Our institution increased lab capacity and performed all outpatient and inpatient testing on-site starting POD15. At the time of this investigation, symptomatic HCWs and household contacts were prioritized for testing, but there was insufficient capacity to test asymptomatic individuals.

Hospital infection prevention and isolation policies have been instituted and updated per CDC guidance. HCWs underwent extensive education regarding the importance of hand hygiene, proper use of personal protective equipment (PPE), social distancing, and monitoring patients and themselves for signs and symptoms of SARS-CoV-2. Additional interventions to reduce transmission, including restriction of visitors, mandatory employee temperature and symptom monitoring, and universal masking of all persons were introduced in concordance with CDC recommendations. Exposure investigations are conducted for all patients and employees who test positive for SARS-CoV-2.

2 | DISCUSSION

The COVID-19 pandemic presents a complex challenge in the field of SOT. The rapid spread and high infectivity of SARS-CoV-2 have important implications, not only for transplant recipients, but also for organ donors and teams involved in organ recoveries and transplantation. To date, few cases of COVID-19 in SOT recipients have been published.¹⁻⁵ Most of these cases occurred in kidney,^{2,3} heart,¹ or lung⁵ transplant recipients 13 months to greater than 20 years from transplant, with one case occurring in the perioperative period of liver transplantation.⁴ To our knowledge, ours is the first report of COVID-19 in a LT recipient during the acute posttransplant period.

Diagnosis of COVID-19 in the postoperative setting was complicated by several confounding factors, including the recent transplant surgery, initiation of new medications, primary graft dysfunction, and the possibility of different sources of infection (recipient-derived, donor-imported, or de novo nosocomial infection). We were fortunate to have pretransplant specimens collected from the recipient as part of an ongoing clinical biorepository, which allowed us to retrospectively analyze for SARS-CoV-2 infection at the time of admission. With both upper and lower airway specimens negative for SARS-CoV-2 RNA, the presumed source was donor-imported infection or nosocomial transmission.

Blood-derived transmission of COVID-19 has not yet been demonstrated, although SARS-CoV-2 viral RNA has been detected in the blood of some patients.⁷ In organ donation in the setting of COVID-19, the lungs are felt to be the organ most likely to transmit COVID-19 from donor to recipient, although transmission through other solid organs may be possible. The recipients of other organs (liver, kidney) from our patient's donor appear to be doing well without signs of COVID-19 infection (Jefferson Jones, CDC, personal communication).

At the time of our patient's diagnosis, COVID-19 hospital case prevalence was low, and there were no COVID-19 patients on the unit. The patient's spouse, at bedside daily following the transplant, was and remains asymptomatic. Out of 140 HCWs with exposure to our patient from time of admission, 2 tested positive for COVID-19. One HCW exhibited only mild gastrointestinal symptoms the day before assuming care of the patient on POD8, 2 days after the onset of fever in our patient and the day before the patient's positive SARS-CoV-2 test. The other HCW was asymptomatic for 13 days following her interactions with the patient. In the weeks following our patient's diagnosis, other HCWs on the unit reported symptoms concerning for COVID-19, but none tested positive for SARS-CoV-2. Therefore, it remains possible that an asymptomatic carrier was the source of a nosocomial transmission. Given limitations in testing at the time and the lack of available donor specimens to test, this question remains unanswered.

At the time of our patient's transplant neither the patient nor the donor were tested for COVID-19, although over the following week, some United States organ procurement organizations (OPOs) and transplant centers began to test potential donors and recipients, dependent upon testing availability. As testing and PPE supply chains improve, recommendations regarding COVID-19 continue to evolve. The International Society of Heart and Lung Transplantation's recently updated guidance document⁸ provides recommendations for cardiothoracic transplantation during COVID-19. Briefly, donors should be tested for SARS-CoV-2 with NPS and/or oropharyngeal swabs, sputum/tracheal aspirate, or BAL, although BAL performed solely for COVID-19 testing should be avoided given risks of aerosolization. Donors with exposure to confirmed or probable COVID-19 individuals should be excluded from donation for 14 days after exposure, and all donors positive for COVID-19 or with symptoms consistent with COVID-19 should be declined. For lung donors, a chest CT to evaluate for signs of viral pneumonitis should be obtained. Recipients should be screened for COVID-19 exposure and symptoms and undergo

rapid testing with NPS and/or oropharyngeal swab for SARS-CoV-2 upon admission for transplant. Appropriate PPE, based on CDC recommendations, should be utilized by HCWs, with local procurement recommended, if possible.

At our institution, we elected to continue LT during the COVID-19 pandemic, limiting the procedure to those waitlist candidates at highest need for transplant. Despite increasing numbers of COVID-19 patients in the hospital, we have had no further COVID-19 infections in LT recipients. The decision to transplant or not, though, cannot be universally applied, and factors such as local COVID-19 prevalence, available hospital resources, and transplant program-specific variables must be taken into account.

We have described the epidemiological and treatment challenges faced with COVID-19 infection in the early postoperative period following LT. The lack of pretransplant COVID-19 testing in our patient and the donor make identification of the infection source difficult. We feel the case presented here supports the importance of donor and recipient COVID-19 testing in the setting of a spreading pandemic.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. NAM is a consultant for Abbott, Medtronic, SynCardia, and Carmat.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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