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CASE REPORT

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Lung transplantation for post-COVID-19 pulmonary fibrosis

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Abstract

COVID-19 has affected over a billion people around the world, with over 2 million losing their lives (Worldometer). About 10% of patients infected with COVID-19 develop a serious illness, including respiratory failure, that require advanced life-supporting measures. Mortality among this subgroup exceeds 60%. We present a case of an otherwise healthy 34-year-old male who developed end-stage pulmonary fibrosis following COVID-19 infection. He achieved haemodynamic stability with mechanical ventilation and extracorporeal membrane oxygenation (ECMO) but did not show any sign of weaning off ECMO; however, he successfully underwent bilateral lung transplantation.

KEYWORDS

adult respiratory distress syndrome, COVID-19, extracorporeal membrane oxygenation, lung transplantation, pulmonary fibrosis

INTRODUCTION

COVID-19 has affected over a billion people around the world, with over 2 million losing their lives (Worldometer). Among the infected, 10% develop serious illnesses, including respiratory failure, that require advanced life-supporting measures such as mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO).[1] Mortality among this subgroup exceeds 60%.[2]

Elderly and those with comorbidities have a poorer outcome, yet younger age group is not spared. We present a case of an otherwise healthy 34-year-old male who developed end-stage pulmonary fibrosis following COVID-19 infection. Though he achieved haemodynamic stability with MV and ECMO, he did not show any sign of weaning off ECMO. Then, he successfully underwent bilateral lung transplantation (Ltx). Ltx is a viable option for patients developing irreversible lung damage following COVID-19 infection.

CASE REPORT

A 34-year-old otherwise healthy male was transferred to our COVID-19 critical care unit on 100% FiO_2 via a non-rebreathing mask (NRBM) and a high-frequency nasal canula for further management of bilateral pneumonia (Figure 1).

It was day 5 after having been diagnosed with COVID-19 by a positive nasopharyngeal swab for reverse transcriptase-polymerase chain reaction (RT-PCR). The patient had already been treated with hydroxychloroquine (400 mg twice on day 1 and 200 mg twice on days 2–5), Remdesivir (200 mg intravenously on day 1 and 100 mg intravenously on days 2–10), steroid (1 mg/kg methylprednisolone), anticoagulants, 4 units of convalescent plasma and intravenous injection of 400 mg tocilizumab (four doses over 96 h at an interval of 12–24 h), but without any clinical improvement.

On presentation, he exhibited severe hypoxaemia, barely managing O_2 saturation of 92% on 100% FiO_2 via NRBM. His oxygen saturation (SpO_2) used to improve in the awake-prone position, with the PaO_2/FiO_2 ratio around 150. On day 10 of his illness, however, he required MV because of worsening oxygenation. Acute respiratory distress syndrome (ARDS) strategies as per ARDSNET trial—high-positive end expiratory pressure (PEEP), high-frequency, low-tidal volume ventilation followed by prone ventilation—were attempted. These strategies also failed to maintain the desired oxygen level, and on day 11 the patient was initiated on femoro-jugular veno-venous (V-V) ECMO.

The patient was maintained on V-V ECMO with a blood flow of 3–4 L/min and sweep gas of around 8 L/min,

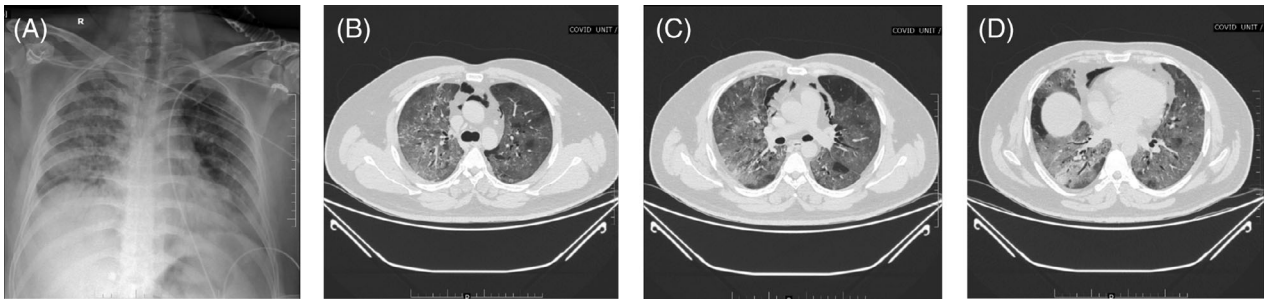

FIGURE 1 (A–D) Chest x-ray and computed tomography of the thorax done on the day the patient was tested COVID positive (27 September)

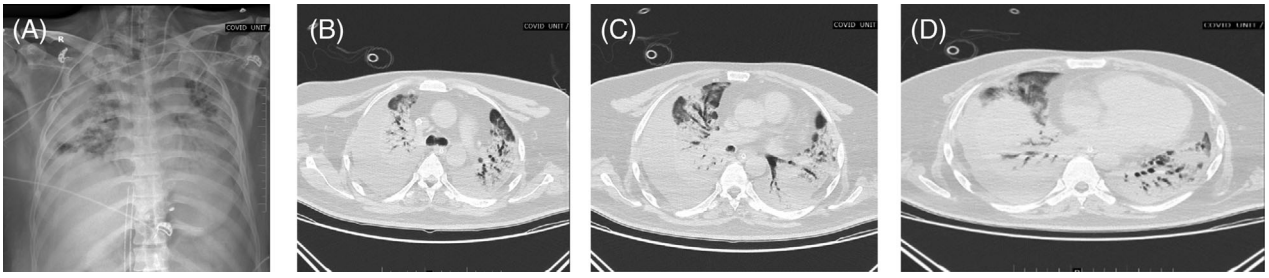

FIGURE 2 (A–D) Chest x-ray and computed tomography of the thorax after almost a month of COVID-positive report (24 October)

maintaining activated coagulation time between 200 and 250 s. The patient's SpO_2 rose to 100% immediately after ECMO initiation. The ventilation strategy was to give rest to his lungs by putting him on pressure control ventilation with 30% FiO_2 and PEEP of 8 with peak pressures not exceeding 30 cm H_2O. The patient was kept sedated and paralysed for initial 2 days and then switched to awake sedation to minimize muscle de-conditioning. The patient had no medical history of any autoimmune disease predisposing him for interstitial lung disease. Still, attempts of weaning him from ECMO remained unsuccessful on day 21, suggesting irreversible lung damage due to COVID-19.

The patient was deemed COVID-19-negative based on throat RT-PCR 23 days from the time of diagnosis and 11 days post ECMO initiation. He also showed gradual improvement in his interleukin-6 and D-dimer levels, yet remained completely dependent on ECMO.

On day 35, flexible bronchoscopy with bronchoalveolar lavage (BAL) was performed and sent for BioFire (BioFire FilmArray Respiratory Viral Panel) which grew *Acinetobacter baumannii* and *Pseudomonas aeruginosa* with genetic mutations like IMP-beta metalloproteinase, indicating carbapenem resistance. Blood cultures were also positive for *A. baumannii*. Antibiotic regimen was modified accordingly by adding polymyxin and Tigecycline(inj. polymyxin 7.5 lakh intravenously twice/day, and inj. Tigecycline 100 mg twice a day for 10 days). Incidentally, the BAL sample was negative for COVID-19 based on RT-PCR.

On day 25 of ECMO support, there were no signs of respiratory improvement and/or weaning from ECMO. Computed tomography (CT) of the chest revealed bilateral pleural effusions with loss of lung volume and extensive air space consolidation and fibrosis (Figure 2). 2D echocardiography showed normal left ventricular functions. Though on ECMO, all other organs of the patient were functioning normally and sepsis was under control, so with negative COVID-19 status, a decision for Ltx was made.

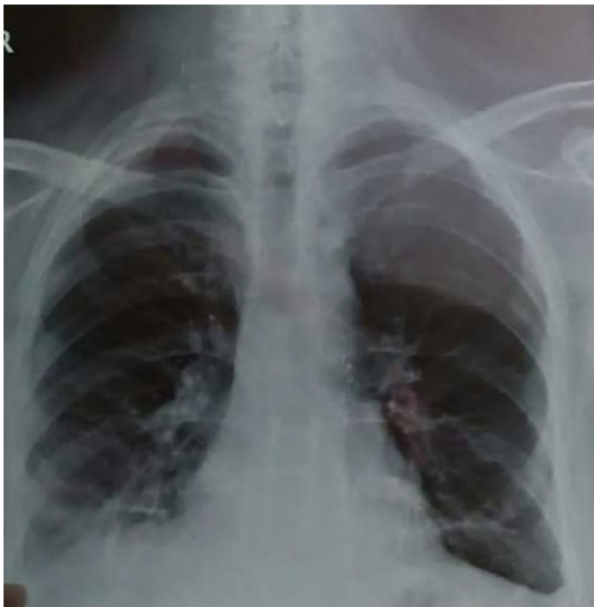

FIGURE 3 Post-transplant chest x-ray

Pros and cons of the modality, expenses, possible outcome, quality of post-transplant life and the need for life-

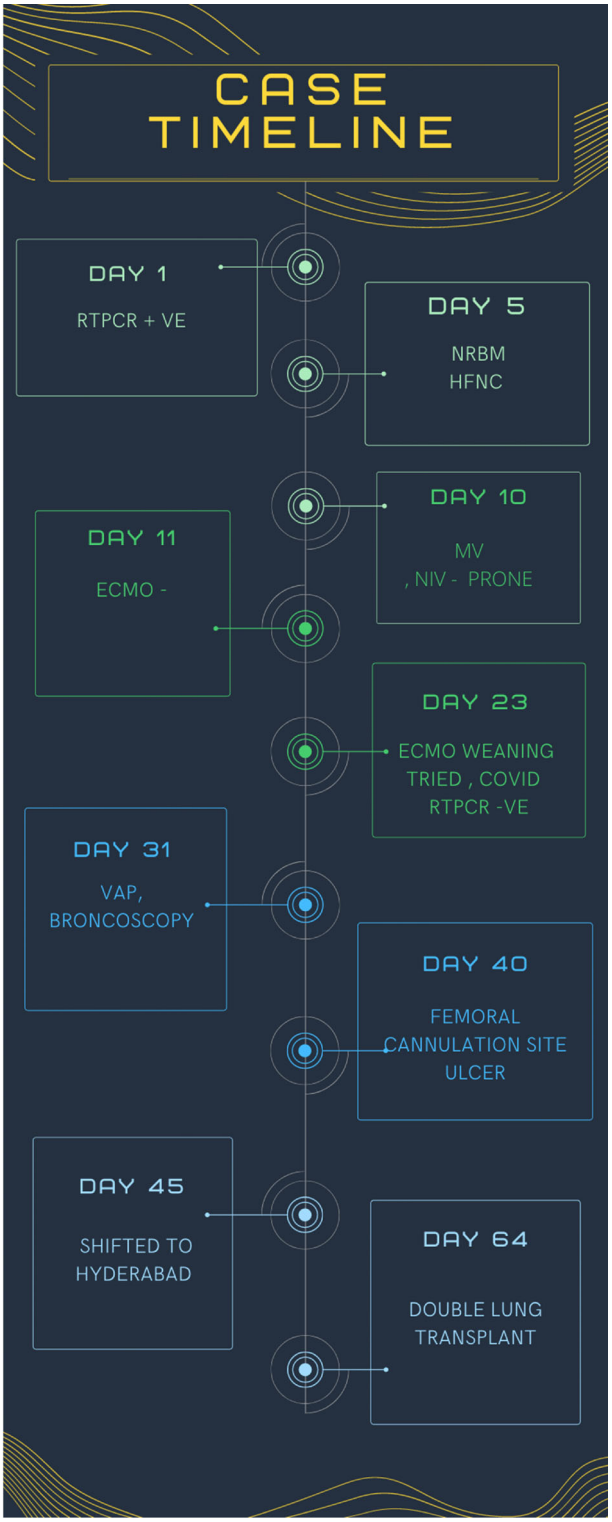

FIGURE 4 Timeline

long immunosuppression were discussed in detail with the patient's spouse, and the consent was obtained. The patient was air-lifted from Delhi to Hyderabad on day 45 of illness on same ECMO support and registered in the lung transplant list. The patient continued to be on advanced life support for another 19 days during which he underwent a tracheostomy and new circuit for ECMO along with other supportive measures.

In view of respiratory failure associated with COVID-19 and fibrotic pathology, the patient was allocated a priority position on the waiting list. On day 64, he received a double lung transplant from a blood group- and size-matched donor who had died in a road traffic accident and declared brain-dead. The donor was screened for COVID-19 by endo tracheal (ET) secretion RT-PCR after his family consented for organ donation. BAL RT-PCR done by the organ retrieval team was also negative (Figure 3).

A bilateral Ltx was carried out in a sequential manner through a clamshell incision with a pulmonary arterial catheter and trans esophageal Echocardiography (TEE) in place. After central cannulation on ECMO, hilar dissection was carried out. Inferior pulmonary ligament was released. Pneumonectomy was then performed by sequential encircling of pulmonary artery (PA) and pulmonary veins. Bronchial anastomosis was done, followed by PA anastomosis and left atrial anastomosis. His post-operative management was per protocol, and he was discharged from hospital on day 15 following lung transplantation. The patient is doing well and undergoing rigorous physical therapy on day 250 of Ltx (Figure 4).

DISCUSSION

Pharmacological therapeutic options as such as Remdesivir, steroids or tocilizumab are of limited value in severe COVID-19 pneumonia and related ARDS.[3–5] A few patients suffer irreversible lung damage, as happened with our patient, despite treatment with available antivirals and immunomodulatory agents. Supportive measures in the form of MV and ECMO allow the lungs to heal spontaneously by giving them rest.[6] The ideal process in such case would be recovery of the lung by itself—even if portions of it are destroyed—which could have better long-term results as compared to Ltx. Long-term ECMO support is also associated with several complications such as lung and blood stream infections and bleeding from random sites such as femoral cannulation site ooze; all these occurred in our patient.[7]

In severe ARDS, the 90-day mortality was significantly lowered by ECMO compared with conventional management as seen in a systemic review (CESAR and EOLIA trials).[8] ECMO is being used for four decades but it gained much significance in the last decade owing to the 2009 influenza pandemic. It is a bridge to transplantation and used to maintain oxygenation till donor lungs are available, and it is especially important in cases of severe COVID-19-associated fibrosis.[9] Use of a single-port, double-lumen catheter for V-V ECMO can also allow patients to undergo active physical therapy while awaiting Ltx.[10] No defined time frame is recommended for this waiting period on ECMO as a bridge to Ltx. Incidentally, patients on ECMO before Ltx have more peri-operative complications and mortality, though long-term survival is not affected.[9]

Ltx appears to be life-saving in cases of end-stage lungs diseases, especially if the patient is not being weaned off life-supporting modalities. This is also true for patients suffering from COVID-19 infection.[11] Ltx in COVID-19 lung infection appears to be an appropriate indication, as the mechanism of fibrosis appears to be similar to end-stage idiopathic pulmonary fibrosis as detected by SmFISH in COVID-19 lung biopsy specimen, as stated by Bharat et al. If validated, in future, the identification of $KRT17^{+}$ $KRT5^{-}$ basaloid cells or pro-fibrotic alveolar macrophages in bronchoscopic biopsies may assist in identifying patients with irreversible lung fibrosis stuck on ECMO or MV for long.[11] Transplant option may be practically useful in only a very small subset of patients, as many will have absolute and relative contraindications for this modality.[12] The criteria for patient selection and timing of Ltx need to be better defined in future.

Cypel and Keshavjee have tried to outline the criteria for Ltx in COVID-19-associated lung damage.[13] The authors suggest that young patients with a single organ failure could be considered for Ltx when sufficient time (which is not objectively defined in any study but usually 4–6 weeks as stated by a centre with large experience of COVID-19 patients)[11] has elapsed and the lung is still showing radiological and physiological signs of lung fibrosis and non-recovery. These patients should be conscious, and first-person consent should be taken; they should be able to participate in active rehabilitation while being on waiting list despite being on ECMO. They should be COVID-19 RT-PCR negative and fulfil other criteria defined for Ltx such as body mass index, absence of coronary artery disease and so forth.[14] Our patient was a young man with a single organ failure, his CT chest revealed extensive bilateral fibrosis and he could not be weaned off ECMO and MV; so it was felt he was the most suitable candidate for the procedure.

Ltx in patients on ECMO bridging for ARDS is one of the highest risk and most complex procedures, which is further complicated by COVID-19 infection damaging the vascular and pleural space. Only centres with substantial experience in ECMO bridging Ltx with access to a donor pool and low wait-list mortality should offer the procedure.[15,16]

Reports of Ltx in COVID-19 first came from China, and then from Europe and the United States. It is definitely an option of last resort with the risk of re-infection to the transplanted lung. Technical difficulties are created by COVID-19-associated damages in the native lung and native lung pneumonia posing a risk of infection to the allograft lung. High cost, presence of a robust transplant programme and availability of donor lungs are other challenges faced by potential lung transplant candidates.[11,17,18]

Our case is unique in several aspects. Ltx can be carried out successfully among patients with COVID-19-related pulmonary fibrosis even in the developing world.

This is a good example of the teamwork required between primary and tertiary care centres. This is essential for the proper utilization of the limited resources while maintaining skills and expertise in this specialized filed. Our patient is also unique in that he spent the longest time on ECMO, that is, 54 days, before transplantation with a positive outcome. Administrative support, such as managing finances, coordination between two centres and getting organs on priority from the healthcare institutions, remains the backbone for such endeavours.

Lung transplant may appear to provide survival benefit to critically ill COVID-19 patients, but its long-term benefits still remain to be studied. Whether these patients can return to productive life after the procedure still remains a question. Effects of profound muscle wasting, decubiti, malnutrition and the possibility of re-infection remain unknown.[16,17]

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Pratibha Gogia: treating pulmonologist and prepared the manuscript. Sanjay Sharma, Swapnil Khare: critical care team, collected all treatment details. Sandeep Attawar: transplant surgeon. Vivek Singh: transplant physician Contributed treatment details at KIMS, Secundrabad, Tarun Bhatnagar, Khushboo Batra: respiratory support team, helped in final editing.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this case report and accompanying images.

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