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CASE ANECDOTES, COMMENTS AND OPINIONS

First lung and kidney multi-organ transplant following COVID-19 Infection

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As the world responds to the global crisis of the COVID-19 pandemic an increasing number of patients are experiencing increased morbidity as a result of multi-organ involvement. Of these, a small proportion will progress to end-stage lung disease, become dialysis dependent, or both. Herein, we describe the first reported case of a successful combined lung and kidney transplantation in a patient with COVID-19. Lung transplantation, isolated or combined with other organs, is feasible and should be considered for select patients impacted by this deadly disease.

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Broad extra-pulmonary manifestations of COVID-19 are being recognized[1]. Notably, SARS-COV-2 has selective kidney tropism, leading to acute kidney injury, found in over 40% of hospitalized patients with COVID-19 in the US[2-4]. Patients who subsequently require dialysis have a poor prognosis with a mortality rate over 75%; among patients who survive to discharge, over 30% will not recover their kidney function and require dialysis[3].

Patients who recover from severe COVID-19 may be left with end-stage multi-organ dysfunction[5]. There are no reports of kidney or multi-organ transplantation for the treatment of end-stage pulmonary and renal failure due to COVID-19. Herein, we present the first combined lung and kidney transplantation for the successful treatment of end stage pulmonary and renal failure due to COVID-19.

Case details

A 54-year-old man with no past medical history presented to the emergency department with 5 days of non-productive cough, pleuritic chest pain, and high-grade fevers. He was diagnosed with COVID-19. Within 24 hours of presentation, he required mechanical ventilation and was managed with lung protective ventilation, inhaled pulmonary vasodilators, neuromuscular blockade, and prone positioning. Subsequently, he received remdesivir, methylprednisolone, tocilizumab, and convalescent plasma. On hospital day 18, he required initiation of venovenous-extracorporeal membrane oxygenation (VV-ECMO). By hospital day 21 he developed acute kidney injury requiring continuous renal replacement therapy (CRRT).

Interval chest imaging revealed progressive and near complete bilateral airspace opacification superimposed on diffuse bronchiectasis (Figure 1). Despite aggressive supportive care, his ARDS progressed to end-stage fibrotic lung disease along with the development of corpulmonale.

He underwent extensive rehabilitation, and at the time of transplantation was neurologically intact and able to sit at the edge of bed for 20 minutes and stand with maximal assist.

The patient was taken to the operating room after suitable donor organs (lungs and kidney) were allocated from a single donor. With on-going ECMO support, the patient

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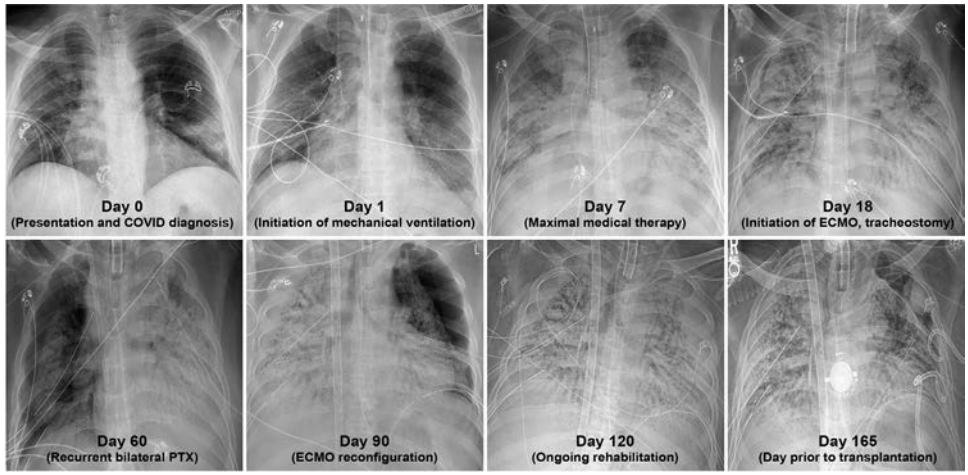

Figure 1 Serial radiographs from time of presentation and diagnosis (Day 0) to just prior to transplantation (Day 165). Imaging displays progression of disease with increasing bilateral airspace opacities, diffuse consolidation, and air bronchograms. Clinical deterioration necessitating intubation and percutaneous tracheostomy are demonstrated on Day 1 and Day 18 respectively. Maximal medical therapy included the use of lung protective ventilation, inhaled pulmonary vasodilators, neuromuscular blockade, prone positioning, remdesivir, methylprednisolone, tocilizumab, and convalescent plasma. The patient experienced recurrent pneumothoraces requiring multiple bilateral tube thoracostomies (Day 18 − 165). Initiation of veno-venous extracorporeal membrane oxygenation (VV ECMO) occurred on Day 18. The initial strategy of femoro-jugulofemoral (25 Fr femoral drainage, 19 Fr femoral return, 17 Fr internal jugular return) cannulation was later transitioned to a single dual-lumen internal jugular cannula (32 Fr Crescent®; MC3 Cardiopulmonary) to facilitate mobility and rehabilitation on Day 90. The patient remained on VV ECMO for a total of 147 days prior to transplantation.

underwent median sternotomy, cardiopulmonary bypass (CPB) and donor lungs were implanted in standard fashion. The patient was separated from CPB, without the need to re-initiate ECMO support (Supplemental Video 1). Following lung transplantation, the patient remained hemodynamically stable, and 5 hours later, was taken back to the operating room to undergo a deceased donor kidney transplant.

Post-operatively, the patient received standard triple immunosuppressive therapy with tacrolimus, methylprednisolone, and mycophenolate mofetil. Upon discharge to a rehabilitation center, he was on room air with a Cr of 0.42 mg/dL. The patient is now over 90 days post-transplant and recovering well at home. For a complete description of the clinical course, surgical procedure, and pathologic findings please refer to Supplementary Information.

Discussion

Our experience suggests that in appropriately selected candidates who have exhausted conventional therapeutic options, multi-organ transplantation is both safe and feasible. In the present case, given the patient's radiographic findings of irreversible fibrosis and lack of improvement in pulmonary function despite maximal medical therapy and the prolonged utilization of ECMO, transplantation was the only life-saving intervention available. Histopathologic assessment of the explanted lungs confirmed this clinical assessment (Figures 2-3).

This patient was a suitable candidate for multi-organ transplantation given his relatively young age and lack of significant medical comorbidities prior to COVID-19. Determining transplant candidacy included consideration of standard risk assessment such as age, ability to

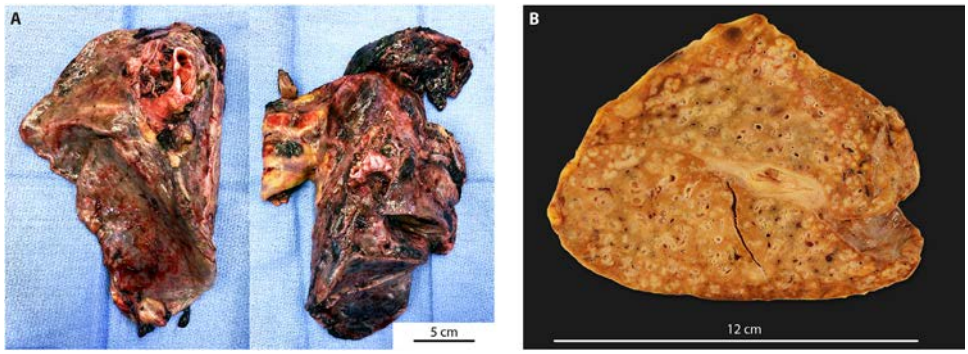

Figure 2 Gross photography of explanted native lungs. (Panel A) Right lung (screen left) and left lung (screen right). Both lungs were small with cobblestoned visceral pleura. (Panel B) Shows the lung is contracted in size with cut surface revealing complete effacement of the pale fibrous tissue and bronchiolectasis of the distal airways.

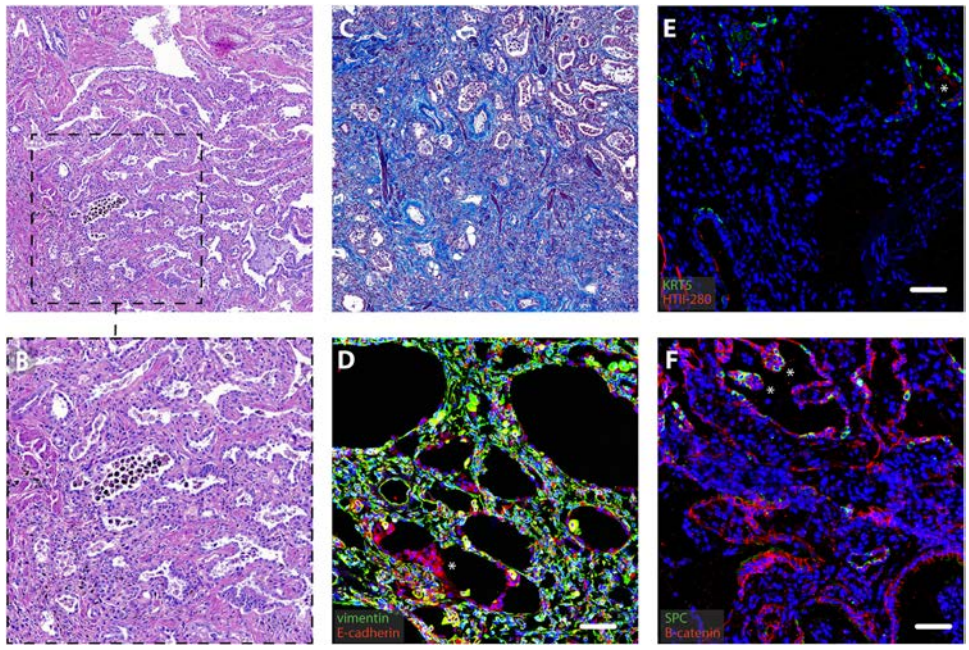

Figure 3 Pathological findings in explanted native lungs. (Panel A) Low power magnification showing complete remodeling of the lobules by predominantly fibrous widening of alveolar interstitium and preservation of bronchioles and muscular arteries. Scattered remnants of hyaline membranes are observed undergoing incorporation into the pulmonary interstitium (H&E x100). (Panel B) Higher power magnification (H&E x200). Foci of squamous or bronchiolar metaplasia along with sparse interstitial inflammation and collections of alveolar or hemosiderin-laden macrophages are also present. (Panel C) The Masson's trichrome stain highlights the abundant collagenous fibrosis of the alveolar interstitium (Trichrome x100). (Panel D) Immunohistochemistry (IHC) demonstrating massive expansion of the fibroblast population within the interstitial space as shown by increased vimentin positive cells. E-cadherin labeling of epithelial cells shows abnormal clusters of epithelial cells (asterisk). (Panel E) The distal lung alveolar space is replaced by dense chords of mesenchymal cells with areas with $KRT5^{+}$ basal cell layer and overlying ATII (type II pneumocyte) cells staining for HTII-280 (asterisk). (Panel F) B-catenin labeling demonstrating ATII hyperplasia with surfactant protein C (SPC) positive cells demonstrating dysplastic, cord-like growth into the intraluminal space (asterisk). IHC images taken at 20x. Scale bars represent 20μm. For detailed immunohistochemistry methods please refer to Supplementary Information.

participate in rehabilitation, and clinical and radiographic evidence of irreversible disease having allowed for sufficient time for recovery of organ function. In the setting of COVID-19, this case challenges previous recommendations which mandate single organ involvement for transplant candidacy.[6] Confirmation of negative SARS-COV-2 PCR to ensure recovery from COVID-19 is also a necessity when considering single or multi-organ transplantation.[7] At our institution, we perform combined lung and kidney transplantation in a staged approach. Due to the high acuity of combined end-stage pulmonary and renal dysfunction, this approach may be a suitable course for centers considering multi-organ transplantation for patients who have recovered from severe COVID-19 infection.

Conclusion

With the progression of the COVID-19 pandemic and the high incidence of acute kidney injury in the critically ill subset of infected patients, combined end-stage pulmonary and renal failure will become an increasingly common presentation.[2-4] Our successful use of combined lung and kidney transplantation should serve as cause for consideration for other centers in the treatment of multi-organ failure due to COVID-19.

Author contributors

BAG, AK, AM, JM, and YJW drafted the report. BAG, AK, JM, MK, SM, SPC, VKR, NMA, CCH, CC, ECJ, IF, AHT, JJM, TP, IAE, DZL, SLF, YS, WH, JWM, GSD, and YJW were involved in the treatment of the patient. BAG, NB, GJB, and YJW acquired, analyzed, and interpreted pathology specimens, histology and radiology images. MBM and TJD performed immunohistochemistry, acquired, and interpreted images. All authors were responsible for critical revision of the manuscript and approved the final version before submission.

Conflict of interests

The authors have no conflicts of interest related to the subject matter.

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Supplementary materials

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Importance of blood pressure control and adequate neurohormonal treatment in LVAD patients: Comment to paper by Tran T. et al.

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To the editor:—We read with great interest the recently published article "Right ventricular function and cardiopulmonary performance among patients with heart failure supported by durable mechanical circulatory support devices" from Tran T, et al.[1] The present study offers unique comprehensive data on the hemodynamics of patients supported with left ventricular assist devices (LVAD) during a protocolized step-wise cardiopulmonary exercise test. Although the clinical benefits of LVAD support are unquestionable, the improvements in peak exercise capacity are limited by the lack of adaptive capacity of current LVADs and peripheral hemodynamic parameters.[2,3]

In our opinion, the results of the study are of great relevance since pressure volume loops are the gold standard to evaluate hemodynamics and offer the opportunity to individually asses the components of cardiac function and its conditioning factors. Briefly, patients were divided in two cohorts who underwent a right heart catheterization by using either a conductance catheter placed in the right ventricle (RV) (Group 1) or a Swan Ganz catheter placed in the pulmonary artery (Group 2). The study results show a similar increase in cardiac output and LVAD flow in both cohorts during exercise, but whereas there was a non-significant increase of RV afterload in Group 1, the capillary wedge pressure was increased in Group 2 ($p < 0.001$). Therefore, the authors conclude that LVAD patients present insufficient increase in cardiac output during exercise, which might be related to the lack of RV contractile reserve and left ventricle (LV) unloading.

We would like to highlight the importance of blood pressure control and adequate neurohormonal treatment in all patients with HF, including LVAD patients, as this can significantly impact hemodynamics. The mean arterial pressure (MAP) was 88 ± 19 mm Hg in Group 1 and 91 ± 11 mm Hg in Group 2. During the exercise protocol, whereas Group 1 did not experience an increase in the MAP, Group 2 patients experienced a striking statistically significant increase in MAP up to 100 ± 15 mm Hg ($p < 0.001$). It is noteworthy that, whereas 10 patients (76%) and 5 (38%) were treated with vasodilators and betablockers respectively in Group 1, only 1 patient (8%) and 3 patients (23%) where under such treatments in Group 2.

Since LVADs are very sensitive to preload and afterload, at least a few hemodynamic results such as LVAD flow, LV unloading and even functional capacity, might be partially influenced by this high afterload. What's more, the careful management of blood pressure is of paramount importance to improve the patients' functional capacity and outcomes.[4,5] In a recent paper by our group,[6] the addition of Sacubitril/Valsartan to patients with an LVAD achieved a decrease in blood pressure, increase of LVAD flows, improvement in functional class and reduction of natriuretic peptides. Consequently, given that one of the limitations to increasing cardiac output during exercise in the study is poor LV unloading, which is directly influenced by systemic blood pressure, it would be of great interest to confirm these results in patients with adequate HF treatment and a MAP closer to 75 to 80 mm Hg.

Disclosure Statement

José González-Costello reports receiving consultancy fees from Abbott and Novartis. David Dobarro has received personal fees from Novartis. Carles Díez has no conflict of interest to disclose.

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