Combined Liver-Lung-Kidney Transplant in a Patient with Cystic Fibrosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient:	**Male, 23-year-old (7 months at the diagnosis)**
Final Diagnosis:	**Cystic fibrosis**
Symptoms:	**Cough**
Medication:	**—**
Clinical Procedure:	**Transplantation**
Specialty:	**Pulmonology**

Objective: Unusual clinical course

Background: Individuals with cystic fibrosis (CF) constituted approximately 10% of organ transplants in 2019, with the majority of transplants consisting of bilateral lung transplant. Multiorgan transplantation in individuals with cystic fibrosis (CF) is rare, and usually involves the liver and lung combined. Since kidney disease is not a common sequela of CF, the need for renal transplant in individuals who have not previously undergone lung transplant is uncommon.

Case Report: We report a case of successful liver-lung-kidney transplant in a 23-year-old man with CF-related liver and lung disease, who developed renal failure due to IgA nephropathy. He required renal replacement therapy during the months before transplantation. After discussions among the liver, lung, and renal transplant teams, the patient was listed for multiorgan transplantation. An appropriate single donor for all organs was identified, and the patient underwent transplantation. The patient required extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) perioperatively, with total operative time of 23 h and 1 min. Postoperative course was notable for hemothorax and medication-induced acute tubular necrosis, which resolved without the need for renal replacement therapy. Liver and lung graft function was normal at 6 months, and renal function was minimally reduced.

Conclusions: Triple organ transplantation in CF is a viable option for individuals with multiorgan failure who may otherwise not qualify for single/dual organ transplantation. Use of ECMO and CRRT can be necessary during the long operative procedure. Optimal immunosuppression protocols for this group of patients has not yet been established, and ethical concerns regarding multiorgan transplantation exist.

Keywords: Cystic Fibrosis • Multiple Organ Failure • Renal Insufficiency, Chronic

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Background

Cystic fibrosis (CF) is a genetic disease affecting approximately 30 000 individuals in the United States and over 80 000 worldwide [1,2]. Individuals with CF constituted approximately 10% of organ transplants in 2019, with the majority of transplants consisting of bilateral lung transplants (based on Organ Procurement and Transplantation data available at https: optn.transplant. hrsa.gov/data/view-data-repors/national-data/#, published 2017. Accessed November 1, 2018). CF is the most common autosomal recessive disease affecting the White population [3,4]. The underlying pathophysiology of the disease is related to the abnormal function of the CF transmembrane conductance regulator (CFTR), an anion transport channel present in the apical membrane of epithelial cells [3,5]. The disease leads to multiorgan manifestations, but primarily affects the respiratory and digestive tracts; up to 40% of adults with CF develop diabetes due to the involvement of pancreatic endocrine cells. The majority of individuals with CF develop chronic lung infections and progressive loss of lung function, which leads to the need for lung transplantation or death. Improved treatments over the past several decades have led to gradually increased life expectancy, with a median survival of 47 years in 2018 [6,7]; however, lung transplantation continues to be a lifesaving procedure for patients with advanced lung disease.

While morbidity and mortality rates in CF are usually associated with pulmonary complications and end-stage lung disease, liver disease occurs in 40% of patients and is a frequent independent prognostic factor, cited as the second leading cause of death among these patients [8]. The majority of affected patients are asymptomatic, with mild hepatic function abnormalities; cirrhosis develops in 5% to 10% of patients, and liver transplantation is required in 2% to 5% of patients for hepatic failure and complications related to portal hypertension [9].

Combined liver-lung transplantation is performed when individuals with advanced lung disease requiring lung transplantation also have decompensated liver failure [10]. As of November, 2020, there have been 144 liver-lung transplants conducted in the United States, and the majority were performed in patients with CF [11]. Since CF does not directly injure the kidney, end-stage kidney disease is relatively rare [12]. Therefore, renal transplantation is uncommon in patients with CF, with most cases occurring only in patients who have kidney failure from calcineurin-inhibitor nephrotoxicity following prior lung transplantation [6]. To date, only 2 cases of combined liver-lung-kidney transplants are reported on the Organ Procurement and Transplantation Network Registry, 1 case in 2018 and 1 case in 2019, and both were in individuals with CF who were over the age of 35 years. One of these cases has been published and is described as a combined liver-lung transplant followed by a delayed kidney transplant [13]. To the best of our knowledge, the present case is the first published report of a simultaneous liver-lung-kidney transplant in a patient with CF.

There is limited description of appropriate pretransplant evaluation of patients requiring multiorgan transplants, with no standardization of selection criteria, although the typical approach is independent evaluation of each organ [14]. Candidacy for multiorgan transplantation in CF is usually determined with criteria for lung transplantation, with subsequent organ transplant candidacy based on the severity of disease in other organs [15]. We describe the evaluation process and transplant outcomes for a patient who underwent liver-lung-kidney transplantation.

Case Report

This case report was deemed exempt from Institutional Review Board (IRB) review by the Columbia University IRB. The patient, a 23-year-old man, was diagnosed with CF at the age of 7 months because of pneumonia and failure to thrive (genetic mutations: 3120+1G-A/3120+1G-A). At the age of 9 years, he was noted to have cirrhosis with splenomegaly and portal hypertension. An endoscopic examination did not reveal varices, and liver biopsy results demonstrated nodular regenerative hyperplasia. At the age of 17 years, he presented with hematemesis and worsening thrombocytopenia; endoscopic examination demonstrated grade II/III non-bleeding esophageal varices, and imaging revealed a splenic size of 27 cm, for which he underwent splenic artery embolization. At age 20 years, he underwent esophageal banding at 3 sites for stage II-III esophageal varices. A transjugular biopsy sample of the liver at age 22 revealed a transhepatic gradient of 30 mmHg, with pathology results demonstrating stage III-IV biliary cirrhosis with focal intrahepatic cholangitis and mild nodular regenerative hyperplasia. Subsequent surveillance endoscopic examinations showed minimal (grade I) non-bleeding esophageal varices and grade II gastroesophageal varices at the gastroesophageal junction. He continued to have worsening thrombocytopenia and poor hepatic synthetic function. Serial magnetic resonance imaging scans of the liver showed only a 1.0-cm Liver Imaging Reporting and Data System grade III lesion, which was stable over time. Serologic evaluation for other causes of liver disease were negative.

The patient's clinical course was notable for increasing frequency of pulmonary infections due to multidrug-resistant *Pseudomonas aeruginosa*, necessitating frequent hospitalizations for treatment with intravenous antibiotics, including aminoglycosides. His pulmonary disease continued to progress, and he was referred for lung transplant evaluation at age 21. At the time of referral for lung transplantation, forced expiratory

volume in 1 s (FEV1) was 1.62 L (30% predicted); forced vital capacity (FVC) was 2.78 L (44% predicted), and FEV1/FVC was 0.58. The patient's body mass index was 23.6 kg/m^2. He did not require supplemental oxygen and was not yet activated for transplantation after completion of evaluation. He was referred to the liver transplant service as part of the lung transplant evaluation.

The patient was subsequently noted on several occasions to have acute kidney injury and hematuria associated with respiratory infections. A renal biopsy result demonstrated diffuse mesangial proliferative and focal sclerosing glomerulonephritis with focal crescentic features, consistent with IgA nephropathy and mild diabetic glomerulosclerosis. Immunosuppressive therapy for IgA nephropathy was deferred owing to his recurrent pulmonary infections. The patient's kidney failure progressed, and he started hemodialysis at age 23 years. He was referred for evaluation for renal transplantation; however, it was determined that the severity of his lung disease placed him at high-perioperative risk, and he was initially denied.

As the patient's lung disease progressed, activation for lung transplantation was deemed appropriate. However, given the severity of cirrhosis and reduced hepatic function, the patient was felt to be a high risk for bilateral lung transplantation alone, without simultaneous liver transplantation. The renal transplant team agreed to accept him as a candidate for renal transplantation, only if he had been approved for liver and lung transplantation; he was not approved for isolated kidney transplant alone. A series of interdisciplinary meetings were held with members of the liver, lung, and renal transplant medical and surgical teams and the transplant anesthesiology team. At the time of consideration, although 2 cases were listed on the United Network for Organ Sharing registry, review of the literature revealed no reported cases of liver-lung-kidney transplantation. Combined transplantation of all 3 organs was deemed to be the safest approach for this patient, and he was listed for liver-lung-kidney transplantation. At the time of listing, the patient's lung allocation score was 92.0937 (scale 0-100), creatinine clearance was 11.7 mL/min, and his model for end-stage liver disease was 22 (range 6-40). The preoperative bubble echocardiogram revealed normal-sized cardiac chambers, with pulmonary artery systolic pressure of 33 mg Hg and no intrapulmonary shunt. During an admission for submassive hemoptysis and acute-on-chronic respiratory failure, an appropriate organ donor was identified; donor age was 26 years. Multiorgan transplantation occurred after 28 days on the active list. Left-internal jugular and left femoral vein extracorporeal oxygenation (ECMO) was initiated percutaneously in the operating room, with a 25 French catheter in the femoral vein and a 20 French catheter in the left-internal jugular vein (sweep 0.8, flow 3.34, RPM 2545, SvO2 76, membrane gradient 20) (CardioHelp Circuit, Maquet, Germany) due

to the advanced lung disease and expected prolonged operating time. The patient first underwent lung transplantation; the cold ischemic time was 3 h and 24 min for the right lung and 5 h and 50 min for the left lung. Following lung transplantation, the patient underwent liver transplantation; the cold ischemic time was 9 h and 30 min. Next, he underwent renal transplantation; the cold ischemic time was 16 h 35 min. The patient's chest was left open throughout the liver and kidney transplants, and he remained on ECMO throughout all 3 transplants. Intraoperative CRRT was run off of the ECMO circuit throughout the 3 transplant surgeries, with dialysis flow of 2 L/h, blood flow of 300 mL/min. In total, the surgical time was 23 h and 1 min.

An intraoperative echocardiogram immediately following transplantation of the lung showed intact airway anastomosis, normal left ventricular function, and no evident pulmonary vein thrombi [16]. The postoperative course was notable for mild intermittent pressor requirements for 3 days; the patient remained on CRRT for 24 h. He was treated with intravenous meropenem, based on methicillin-sensitive *Staph aureus* and *Pseudomonas aeruginosa* in his most recent sputum cultures, as well as inhaled amphotericin. His immunosuppressive regimen was based on the usual regimen for lung transplantation (the organ most prone to rejection) and consisted of basiliximab 20 mg×2, mycophenolate mofetil 1 g twice daily, solumedrol 125 mg every 8 h for 24 h, and then 0.5 mg/kg daily thereafter; tacrolimus was held pending recovery of renal function and then held indefinitely due to a possible episode of posterior reversible encephalopathy syndrome. He remained intubated, utilizing assist-control ventilation (respiratory rate 10/min, PEEP 10 cm H$_2$O, FiO$_2$ 0.6, initially). The liver Doppler ultrasound on postoperative day 1 was normal. He developed a hemothorax on postoperative day 1 and returned to the operating room for washout of the pleural space, with resolution of bleeding. ECMO was continued through postoperative day 4, and he was extubated on postoperative day 5. The patient's liver function normalized by postoperative day 10, and creatinine nadired at 1.52 mg/dL on postoperative day 10. The transient elevation in white blood cell count to 55 000 cells/mL^3, with purulent secretions noted on bronchoscopy, led to the initiation of intravenous polymyxin for multidrug-resistant *Pseudomonas aeruginosa*, which was discontinued after 4 days, when the creatinine level rose to 3.28 mg/dL. A biopsy of the kidney allograft revealed diffuse degenerative and regenerative changes consistent with acute tubular injury, which we believed was likely due to drug toxicity. The patient was discharged home on postoperative day 37, with gradually improving renal function. He required readmission 2 months following transplantation for *E. coli* and *Klebsiella* bacteremia, likely due to urosepsis, and completed a 14-day course of ertapenem. At the 9-month follow-up, the graft function of the liver and lug was normal, and the estimated glomerular

filtration rate was stable at 62 mL/min. His immunosuppressive regimen consists of prednisone 10 mg daily, cyclosporine 350 mg twice daily (goal trough 250-350 mg), and mycophenolate mofetil 500 mg twice daily.

Discussion

We report the case of a 23-year-old man with CF who underwent successful multiorgan transplantation with liver, lung, and kidney from a single deceased donor. While liver-lung transplantation is the most common multiorgan transplant performed in patients with CF, this is only the third recorded liver-lung-kidney transplant performed in the United States, and to the best of our knowledge, the first published report.

Renal failure in patients with CF without a previous transplant is rare [17]. In our patient, a kidney biopsy result showed advanced IgA nephropathy, which was possibly related to his underlying liver disease [18]. He developed progressively worsening kidney failure, necessitating the institution of hemodialysis. Given his multiorgan disease, single-organ or even double-organ transplantation posed significant potential risk for poor outcomes. Once activated, the patient's wait time was only 28 days, likely owing to the fact that his lung allocation score of 92.0937 reflected underlying kidney disease.

Patients with end-stage lung, liver, and kidney disease who meet criteria for each individual organ transplant are appropriate candidates for combined liver, lung, and kidney transplantation. Our case demonstrates that combined lung-liver-kidney transplantation can be performed safely, even in patients who require ECMO and/or CRRT during surgery. While there are no standard selection criteria for potential recipients of multiple organs, the advantages of multiorgan transplantation in our patient are multifold and include improved survival, single surgery with a single waitlist period, and possible immunologic benefit. There are data suggesting a combined organ effect, with lower rejection rates, for both combined lung-liver and liver-kidney transplants [12,19]. It is unknown whether this immunologic benefit will be seen in liver-lung-kidney transplantation as well. Although there are no data on immunosuppression management in this population, use of regimens for the organ with the highest rate of rejection, in this case the lung, appears to be appropriate.

Studies examining outcomes following multiorgan transplants are generally in small cohorts, and report lower to similar 5-year and 10-year survival compared with single organ transplants, with postoperative bleeding and sepsis cited as common complications, likely due to prolonged bypass time [15,19]. Ethical concerns regarding the use of 3 organs for a relatively high-risk procedure have been raised and merit further discussion. For example, individuals listed for multiorgan transplantation can receive priority for their nonprimary organ over other individuals with a higher need for that organ, although outcomes for such transplants have not been well characterized. In the case of our patient, a triple-organ transplant for a single patient potentially jeopardized health outcomes for other patients awaiting transplantation of those organs.

Conclusions

Liver-lung-kidney transplantation is a viable option for patients with multiorgan failure and requires close collaboration between the medical and surgical teams. Successful outcomes can be achieved, even with the perioperative use of CRRT and ECMO.

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