Bilateral sequential lung and simultaneous pancreas transplant:
A new approach for the recipient with cystic fibrosis

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Abstract

Cystic fibrosis (CF) is an inherited disorder that presents in childhood as a multisystem disease. Pulmonary failure and pancreatic insufficiency, including CF related diabetes (CFRD) and exocrine insufficiency, are common complications of this disease. In this report we review the first three simultaneous lung and pancreas transplantations in CF patients with diabetes.

Methods: All three CF patients presented for evaluation for lung transplantation and had pancreatic insufficiency requiring enzyme supplementation and CFRD requiring insulin. All were severely malnourished and required nutritional supplementation.

Surgical technique: In each case, the allografts were procured from a single cadaveric donor. Bilateral lung transplantation was performed first using two separate thoracic incisions. The pancreas transplant was performed with systemic venous drainage and enteric exocrine drainage.

Results: The pancreas allografts all functioned normally with normoglycemia independent of insulin. As a result of the enteric drainage of the pancreas allograft, supplemental pancreatic enzymes were no longer required. Despite several complications detailed in the manuscript, all three remain independent of supplemental oxygen, insulin and pancreatic enzyme replacement at 4, 6 and 14 months of follow-up.

Conclusion: Simultaneous lung and pancreas transplantation in patients with CF can be performed successfully and provides the advantages of normoglycemia and improves nutrition for patients requiring lung transplantation.

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Keywords: Pancreas transplantation; Lung transplantation; Cystic fibrosis related diabetes mellitus; Cystic fibrosis

Cystic fibrosis (CF) is an inherited disorder that affects epithelial chloride transport and presents in early childhood as a multisystem disease. It is an autosomal recessive disease with an incidence of 1:2500 in the Caucasian population and is the most commonly inherited condition leading to premature death. Due to improvements in pulmonary therapy, the predicted median survival for patients with CF in the year 2005 was 36.5 years [1]. As survival improves, more patients are living long enough to develop extra-pulmonary complications [2]. Despite optimized therapy however, more than 95% of affected individuals ultimately die of respiratory failure. Lung transplantation is the only available therapy that deals definitively with the end-stage pulmonary disease and has become the treatment of choice for these patients. Recently quoted survival for bilateral sequential lung transplantation in recipients with CF is 70–80% at 1-year, 55–60% at 5-year and 32–38% at 10-years [3–8].

Pancreatic failure manifesting as pancreatic exocrine insufficiency and CF related diabetes (CFRD) is a common co-morbidity in CF patients. Pancreatic islet cell transplantation at the time of lung transplantation has been previously attempted with very modest improvement in insulin requirements and no impact on exocrine insufficiency [9–12]. According to those publications, it was maintained that CF patients could not simultaneously tolerate thoracic and abdominal transplant procedures. There have already been multiple reports of simultaneous lung and liver or lung–heart and liver transplants in recipients with CF [13–17]. In addition, with the increasing frequency of hepatic transplantation for CF patients with cirrhosis and adequate pulmonary reserve [18–20], there have now been several
reports of simultaneous liver and pancreas transplants performed in recipients with CF demonstrating the unique advantage of including the pancreas allograft [21–24]. In fact, in a child with CF undergoing multivisceral transplantation for short gut secondary to meconium ileus, the authors specifically comment on the disadvantages of having performed a near total allograft pancreatectomy [25]. Glycemic control and nutritional wasting have been identified as two of the major variables predicting outcomes in the CF patient population [26–29]. The inclusion of a pancreas allograft would provide perfect sugar control independent of administered insulin. This becomes particularly relevant once the recipient is initiated on immunosuppressive therapy following lung transplantation, especially corticosteroids and calcineurin inhibitors. The enterically drained exocrine secretions will provide improved intestinal absorption and nutritional status independent of orally administered pancreatic enzymes. Based on the clear advantages a pancreas allograft offers the recipient with CF with exocrine insufficiency and CFRD, the improved technical outcomes for pancreas transplantation and the recent experience with simultaneous liver and pancreas transplantsations, the next frontier is simultaneous lung and pancreas transplantation. In this report we review our experience with the first three simultaneous bilateral sequential lung and pancreas transplantsations in CF patients with pulmonary failure and CFRD.

1. Methods

1.1. Case reports

1.1.1. Patient 1

This recipient was a 25-year-old Hispanic male with a history of CF complicated by pulmonary failure with bronchiectasis leading to recurrent episodes of pneumonia and hemoptyisis ultimately requiring embolization. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were 32% of predicted and 25% of predicted respectively (Table 1). Sputum cultures prior to transplantation grew mucoid variant of Pseudomonas aeruginosa. He also manifested CFRD requiring subcutaneous insulin and pancreatic exocrine insufficiency requiring oral pancreatic enzyme supplementation. During evaluation he was found to have normal hepatic and renal function. Prior to transplant, he was severely malnourished with a cachectic appearance; he had a prealbumin of 8 mg/dL and a body mass index (BMI) of 16.9 kg/m². A percutaneous gastrostomy tube was placed for enteral feedings. With feeds, the prealbunin increased to 14 mg/dL prior to transplantation.

1.1.2. Patient 2

This recipient was a 26-year-old Caucasian woman who presented with a history of CF complicated by end-stage pulmonary disease, CFRD of 10 years duration and pancreatic exocrine insufficiency since early childhood. FVC and FEV1 were 36% of predicted and 25% of predicted respectively (Table 1). Pretransplant bronchoalveolar lavage grew *Achromobacter xylosoxidans* and Methicillin Resistant *Staphylococcus aureus*. C-peptide was <0.5 mmol/L with an HbA1C of 10%. She had normal renal and hepatic function. She was cachectic with a BMI of 19 kg/m² and was managed with a high protein and high fat diet without a feeding tube.

1.1.3. Patient 3

The third patient was a 27-year-old Caucasian male who presented with a history of CF with end-stage pulmonary disease. FVC and FEV1 were 33% of predicted and 17% of predicted respectively (Table 1). Sputum cultures prior to transplantation grew mucoid variant of *P. aeruginosa*. He also had CFRD requiring insulin diagnosed approximately 1 year prior to transplant and pancreatic exocrine insufficiency for which he has required enzyme replacements since childhood. His c-peptide was 1.3 mmol/L and his HbA1C was 7%. His BMI was 17.7 kg/m² and he was receiving tube feeds through a percutaneous gastrostomy tube. Pretransplant prealbumin was 7 mg/dL. He too had normal liver and kidney function.

1.1.4. Surgical technique

In each case, the lung and pancreas allografts were procured from a single cadaveric donor by two separate procuring surgeons. The bilateral lung transplantation was performed first by the thoracic transplant team using two separate thoracic incisions. The first and third transplant procedures were performed without the need for cardiopulmonary bypass, but the second patient required bypass for the right lung transplant. While the lung transplantation was performed, the pancreas was prepared on the bench by the pancreas transplant surgeon. Upon completion of the thoracic portion of the operation, the recipient was returned to the supine position. The pancreas transplant was performed by a separate pancreas transplant team through a midline abdominal incision. The pancreas was positioned with the head of the organ oriented superiorly in preparation for enteric drainage and the tail pointed towards the pelvis. Systemic venous drainage was established by anastomosing the portal vein to the infrarenal Vena Cava. Arterial inflow was established by anastomosing the donor iliac Y graft to the right common iliac artery. Following graft reperfusion, enteric drainage of the exocrine secretions was established by creating a stapled anastomosis between the donor duodenum and proximal jejunum using the end-to-end anastomosis (EEA) stapler as previously described [30]. The two transplant teams agreed to adhere to the routine lung transplant immunosuppression protocol. The patients received induction immunosuppression including corticosteroids, basiliximab, mycophenolate mofetil and calcineurin inhibitors (initially intra-

### Table 1

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venous cyclosporine which was converted to oral tacrolimus once
the patient was tolerating a regular diet). Target tacrolimus levels
were 10–15 ng/mL. Steroids were tapered to 20 mg of prednisone
daily by discharge from the hospital. Rejection was treated with
pulse steroids and tapered back to baseline levels.

2. Results

All three patients had immediate pancreas allograft function
manifested by normoglycemia independent of insulin adminis-
tration and normal pancreatic exocrine function independent of
oral pancreatic enzyme replacement.

The first patient required early reexploration for small bowel
obstruction secondary to distal intestinal obstruction syndrome. He
subsequently developed a fascial dehiscence of his abdominal
wound, which was allowed to granulate and was subsequently
covered with a skin graft. He also developed a persistent wound
infection at the uppermost portion of the abdominal incision, which
required prolonged treatment with antibiotics and packing
for several months. A brief episode of acute reversible leuko-
encephalopathy manifesting as transient cortical blindness res-
ponded completely to withdrawal of calcineurin inhibitors.
Tacrolimus levels at the time were running in the target range of
10–15 ng/mL. At 14 months post-transplant, he has not required
 supplemental oxygen since the early post-operative period. His
FVC and FEV1 have improved and are currently 74 and 82% of
predicted respectively (Table 1). His nutritional status is sig-
nificantly improved with an increase in his BMI from 16.9 to 20.2.
His c-peptide is 3.1 mmol/L, HbA1C is 5.0% and his prealbumin
has increased to 23 mg/dL.

The second patient had difficulty weaning from the ventilator in
the early post-operative period. Approximately one week post-
transplant, a left allograft pneumectomy was required for pul-
monary venous thrombosis. Following removal of the infarcted
graft, the patient steadily improved. She required a tracheostomy,
but was ultimately weaned from supplemental oxygen. Her
 nutritional status has improved despite the requirement for
 supplemental enteric feeding while in the intensive care unit.
She feels well 6 months post-transplant, maintains her nutrition
with a regular diet and now has a prealbumin of 30 mg/dL. She has
gained 5 kg since discharge from the hospital and has returned to
full time work as a nurse. Her FVC and FEV1 have improved and
are currently 41% and 42% of predicted respectively (Table 1).
Her glucose control is normal with a c-peptide of 4.4 mmol/L and an
HbA1C of 4.6%.

The third patient had immediate excellent pulmonary func-
tion and was extubated within hours of transplantation. He
returned to the operating room on the fifth post-operative day for
intrapertioneal bleeding, and again three weeks post-transplant
for bronchial anastomotic dehiscence. He also developed non-
occlusive venous thrombosis of the pancreas allograft, which
required anticoagulation. This clot did not affect pancreas
allograft function. He remains free of oxygen, insulin and exo-
crine replacement therapy at 4 months post-transplant. His FVC
and FEV1 have improved and are currently 86 and 94% of
predicted respectively. His prealbumin is 49 mg/dL and his c-
peptide is 3.2 mmol/L.

3. Discussion

The original strategy for pancreas transplantation, which was
in the context of simultaneous kidney and pancreas transplan-
tation, was to include the pancreas allograft if a recipient was a
Type 1 diabetic and was already going to receive immuno-
 suppression for the renal allograft. This has been subsequently
applied to pancreas after kidney transplantation and simulta-
neous liver and pancreas transplantation. To the authors’
knowledge, this is the first report in the literature of simul-
taneous lung and pancreas transplantation, but the same rules
applied. All three patients were referred for lung transplantation
and were offered simultaneous pancreatic transplantation based
on their history of diabetes. There is a growing literature dem-
onstrating the specific advantages of an enterically drained
pancreas allograft in recipients with CF [21–24]. In most dia-
betic recipients, the goal is replacement of pancreatic endocrine
function. However, in the CF patient, an enterically drained
pancreas transplant provides the additional advantage of rees-
ablating exocrine pancreatic function. In fact, in CF patients
with pancreatic insufficiency, replacement of the exocrine pan-
creas is actually imperative and was a distinct disadvantage of
the prior simultaneous lung and islet transplant attempts [9–12].
It has been clearly demonstrated that malnutrition and CFRD
are associated with worse pulmonary function and worse out-
comes in a patient with CF [29]. In addition, there is a noticeable
improvement in the patient’s quality of life and sense of well-
being that we have appreciated in these recipients.

All three patients did very well ultimately, but there were
several complications that warrant further discussion. The
venous thrombosis and loss of the pulmonary graft in the se-
cond recipient and the bronchial dehiscence in the third recipi-
ent are unfortunate complications which are uncommon complica-
tions of lung transplantation and are well described elsewhere
[31–33]. The first patient developed DIOS. This syndrome was
originally described by Rasor and Stevenson [34], subsequently
referred to as “meconium ileus equivalent” by Jensen [35], and
ultimately renamed “Distal Intestinal Obstruction Syndrome” by
Park and Grand [36]. Intestinal obstruction is caused by impac-
tion of mucopurulent material in the distal ileum and cecum and
occurs in approximately 15.9% of the general CF population
[37]. The exact cause in this patient population is unknown, but
is believed to result from a combination of pancreatic insuf-
siciency, inspissated intestinal secretions, increased viscosity of
intestinal contents, poor intestinal motility, dehydration and
fecal stasis. An increased incidence of DIOS has been reported
following lung transplantation [38–41], likely precipitated by
the combination of high-dose narcotics, postoperative ileus,
poor oral intake and bed rest common in these patients. Several
authors have recommended a routine bowel regimen of early
enteral feeding, immediate reintroduction of pancreatic enzymes
and addition of electrolyte GI lavage solution at 50–100 mL/h at
24 h after surgery if the patient is unable to eat [39,40]. A
pretransplant bowel preparation with 2 L of polyethylene glycol
lavage solution has also been recommended [39]. N-acetylcys-
teine has also been used to reduce the incidence of DIOS in CF
patients undergoing lung transplantation [42–44]. The patients
in this cohort that underwent simultaneous lung pancreas transplantation had the additional risk factor of an abdominal operation with the resulting ileus. Following our experience with the initial patient, the subsequent two patients were initiated on oral N-acetylcysteine, early enteral feeding and electrolyte GI lavage if needed. These two patients had no obstructive symptoms. Presumably, the presence of normal pancreatic enzymes in the gastrointestinal tract following pancreas transplantation with enteric drainage may ultimately be preventive, but not in the immediate post-transplant period.

The first recipient also had a late episode of reversible leukoencephalopathy which manifested as lethargy, tremors and acute cortical blindness. This neurological complication has previously been reported in association with calcineurin inhibitor administration (either tacrolimus or cyclosporine) and occurs in 1–6% of organ transplant recipients [45]. The recipient was approximately 11 months post-transplant at the time of the neurologic event and was on maintenance immunosuppression including tacrolimus, mycophenolate mofetil and prednisone. Neuroimaging confirmed the diagnosis and cultures of blood and central spinal fluid eliminated other etiologies such as viral infections. His neurological symptoms resolved completely within several days of calcineurin inhibitor discontinuation. His maintenance immunosuppression is currently mycophenolate mofetil, sirolimus and monthly daclizumab.

The third patient developed partial venous thrombosis of the donor pancreas portal vein. This has been previously described by Ciancio et al. and was successfully diagnosed and treated with anticoagulation in 14 patients (11% of 126 transplants performed over a five year period) [46]. Our recipient was treated with a combination of aspirin and intravenous heparin, which was over a five year period [46]. Our recipient was treated with a combination of aspirin and intravenous heparin, which was over a five year period [46]. Our recipient was treated with a combination of aspirin and intravenous heparin, which was over a five year period [46]. Our recipient was treated with a combination of aspirin and intravenous heparin, which was over a five year period [46].

Despite the complicated post-operative course in all three patients, they are all at home and free of oxygen, insulin and pancreatic enzymes at 14 months, 6 months and 4 months post-transplant respectively. The post-transplant management was made significantly less complex in that the patient’s glucose control is usually very difficult in the CF lung transplant recipient but was quite straightforward with the pancreas allograft. In addition, there were no concerns regarding absorption of medications in the context of normal pancreatic exocrine function. With further experience, it is our expectation that pancreas transplantation will be routinely offered to the potential CF lung transplant recipient with CFRD and pancreatic insufficiency. In addition, we are in the process of reviewing previously successful CF lung transplant recipients with existing CFRD for pancreas after lung transplantation.

References


