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World's smallest combined en bloc liver-pancreas transplantation

Ahmed M. Elsabbagh, Jason Hawksworth, Khalid M. Khan, Nada Yazigi, Cal S. Matsumoto, and Thomas M. Fishbein

MedStar Georgetown Transplant Institute, Georgetown University Hospital, Washington, DC, USA

Abstract

We present a case of a 2-year-old child who underwent a combined en bloc liver and pancreas transplant following complications of WRS. WRS is characterized clinically through infantile insulin-dependent diabetes mellitus, neutropenia, recurrent infections, propensity for liver failure following viral infections, bone dysplasia, and developmental delay. Usually, death occurs from fulminant liver and concomitant kidney failure. Few cases with WRS are reported in the literature, mostly from consanguineous parents. To the best of our knowledge, combined en bloc liver and pancreas transplant has not been performed in small children.

Keywords

Wolcott-Rallison syndrome; en bloc liver; pancreas transplant

1 | INTRODUCTION

A 2-year-old female presented with a history of WRS associated with neonatal diabetes for which she required an insulin pump. Her height was 77 cm, and her weight was 10.4 kg. She had episodes of acute liver failure and renal insufficiency. She was born to healthy consanguineous parents following an unremarkable pregnancy and delivery. Genetic tests performed on the patient and her parents confirmed that she had WRS, homozygous for the novel frameshift mutation exon 9 of the EIF2AK3 gene, with each parent noted to be a carrier.

One week before admission, she developed fever (102°F), runny nose, and cough thought likely to be viral. Following admission, she demonstrated catastrophically elevated liver enzymes rising to aspartate transaminase >8000 units/L, INR 7.8, and bilirubin 6.5 ng/dL with decreased synthetic function. She developed encephalopathy prompting listing for liver transplant. Due to her prior neonatal diabetes, we decided to perform en bloc liver-pancreas transplantation as previously described despite the young age of the child.

2 | METHODS

2.1 | Back table

An en bloc liver/pancreas/intestine graft was procured and preserved in University of Wisconsin solution. The jejunoileum was removed, leaving the duodenum to the ligament of Treitz. The SMA was identified and ligated, and the SMV was then dissected out to the second- order branching of the SMV and then transected. The frenulum between the proximal jejunal tributaries and ileocolic tributary was opened to create a large orifice. Donor thoracic aorta was prepared as a conduit for implantation. The supraceliac aorta was transected and oversewn.

2.2 | Recipient surgery

Hepatectomy was performed in the usual piggyback fashion, and the donor thoracic aortic conduit was placed in an infrarenal position. We tunneled the conduit through the transverse mesocolon up to the area of the porta so that it could be used for inflow to the infrarenal aorta of the graft, supplying both the celiac and superior mesenteric arteries.

The en bloc liver-duodeno-pancreatic graft was transplanted (Figures 1A,B and 2A,B). A piggyback venous anastomosis was performed. The donor infrarenal aorta with CA and the SMA was used for inflow. The recipient PV was then sewn to the donor SMV. Finally, an antecolic end-to-side anastomosis was performed between transplanted duodenum and the antimesenteric side of the proximal jejunum for exocrine pancreatic and biliary drainage.

The procedure was uneventful and was completed in 5 hours and 30 minutes. Cold ischemia time was 9 hours. Warm ischemia time was 27 minutes. The native intestine was edematous due to the severity of the illness and acute portal hypertension. The abdomen was closed with an abdominal wound VAC, and a delayed primary closure was performed after 6 days.

3 | RESULTS

There were no major complications during the en bloc transplantation. Pathological examination of the native liver showed expanded portal tracts with bile ductular proliferation and early bridging fibrosis (early stage II). Hepatic parenchyma showed no significant steatosis, active hepatitis, cholestasis, necrosis, or morphologic features of a specific metabolic disorder. Postoperative duplex ultrasound showed patent vasculature.

Initial immunosuppression included induction with basiliximab (Simulect, Raritan, NJ, USA) (intraoperative and postoperative day 4) and maintenance treatment with tacrolimus (which was started on postoperative day 4 given her neutropenic status), mycophenolate mofetil (was started on post-op day 25), and low-dose steroids (0.5 mg/kg/d at time of discharge). Graft function was excellent, the INR normalized, and she was maintained on heparin to prevent clotting for 6 days. The patient remained on insulin drip for 10 days with goal blood glucose 80-140 mg/dL in order to allow the transplanted pancreas to rest.

The patient was extubated postoperatively on day 14, due to pulmonary edema and effusion, which was treated with diuretics. On postoperative day 17, all supplemental O₂ was stopped

and the patient was transferred to the regular floor. She was discharged on postoperative day 28 with normal liver function tests and serum cholesterol levels and free of insulin therapy.

Six months post-transplant, the patient was fully physically and socially rehabilitated. Liver function was normal. She remained insulin free and had a normal glycosylated hemoglobin (5.6%). Fasting C-peptide prior to and after glucagon stimulation was within normal range. Kidney function was normal. Pancreas antibodies (islet cell and insulin) were both undetectable. CT scan showed normal grafts with patent vasculature.

4 | DISCUSSION

We report here the world's smallest combined en bloc liver-pancreas transplantation, the third case of en bloc transplantation for the management of life-threatening complications of WRS. This procedure provided life-saving for a patient who presented to our hospital in acute liver failure as a result of WRS. While previous transplants were performed for this disease, they occurred in 6- and 8-year-old children, while early childhood disease has universally resulted in death.

WRS is a rare genetic disease, with a known poor prognosis. Its main clinical features include infantile-onset IDDM, neutropenia, recurrent infections, evolving bone dyscrasias, multiple epiphyseal dysplasias, renal failure, and recurrent acute liver failure secondary to stressors such as viral infection.¹⁻³ Hepatic dysfunction has been reported in 60% of patients reviewed by Ozbek et al.⁴

WRS is caused by recessive loss of function mutations in the EIF2AK3 gene.⁵ The EIF2AK3 gene encodes a protein called PERK, which plays a key role in initiating the cellular response to endoplasmic reticulum stress. Failure of proper PERK response results in accumulation of misfolded proteins, which leads to inability to respond to ER stress leading to cell damage and apoptosis.^{2,5,6} Therefore, dysfunction of the ER is central to the pathogenesis of WRS. Replacement of organs containing normal ER will not cure the syndrome but can function to prevent its fatal complications and increase patient survival.¹

En bloc transplantation is a technically challenging surgery where organs are implanted together while connected to the same-shared vasculature. In pediatric patients specifically, the small size of the graft's vessels significantly increases the technical difficulty of transplantation and the risk of vascular complications after transplantation. En bloc transplantation was established in an attempt to overcome this limitation. Moreover, the greater organ mass provided by en bloc transplantation increases the capacity of the graft to withstand episodes of rejection.⁷ Given that our team had the technical and surgical expertise to perform the procedure, an en bloc transplantation was the technique of choice. The operation of en bloc liver-pancreas transplantation stemmed from the pioneering work of Thomas E. Starzl⁸ more than four decades ago and had been employed successfully by Tzakis et al⁹ and Rivera et al¹⁰ in the two prior reported WRS cases. En bloc liver-pancreas transplantation was used also in patients with liver disease and type 1 diabetes mellitus^{11,12} and in cases of cystic fibrosis.¹³⁻¹⁵

Our patient's early post-transplant course was uneventful, except that a second surgical procedure was required to close the abdomen, as described above. However, overall, she had a quick recovery time and was discharged from the hospital after 28 days. That first patient reported by Tzakis et al⁹ had a complicated post-transplant course, including severe rejection of all transplanted organs and acute respiratory distress syndrome; her hospital stay (2 months) was longer than our patient's (less than 1 month). The second reported case by Rivera et al¹⁰ had severe infectious complications post-transplant, including septic shock from a urinary tract infection as well as a BK virus infection of the kidney.

In summary, our patient represents the third case in the literature of an en bloc multiorgan transplant to treat complications caused by WRS, and the first in such a small child. Given the known universally fatal reported outcome of this procedure, the success of this case suggests earlier consideration of combined transplantation may be advantageous. Given the frequency of episodes of ALF in this syndrome, wider awareness of the clinical opportunity for early intervention through early referral is essential.

Abbreviations:

ALF	acute liver failure
CA	celiac artery
CT	computed tomography
EIF2AK3	eukaryotic translation initiation factor 2a kinase 3
ER	endoplasmic reticulum
IDDM	insulin-dependent diabetes mellitus
PERK	pancreatic endoplasmic reticulum kinase
PV	portal vein
SMA	superior mesenteric artery
SMV	superior mesenteric vein
VAC	vacuum-assisted closure
WRS	Wolcott-Rallison syndrome

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FIGURE 1.

A, En bloc liver-pancreas graft. B, Schematic diagram of the en bloc liver-pancreas graft

FIGURE 2.

A, En bloc liver-pancreas graft after reperfusion. B, Schematic diagram of the en bloc liver-pancreas graft demonstrating vascular and enteric anastomosis