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Chronic Pancreatitis and Primary Sclerosing Cholangitis—First Report of Intrahepatic Autologous Islet Transplantation

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Abstract

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Background—We are reporting first successful intrahepatic autologous islet transplantation after total pancreatectomy in a patient with chronic pancreatitis and primary sclerosing cholangitis.

Methods—Total pancreatectomy and subsequent islet autotransplantation were performed in a 16-year-old boy with intractable pain due to chronic pancreatitis in the setting of ulcerative colitis and primary sclerosing cholangitis (PSC). Liver biopsy revealed PSC with focal bridging fibrosis. The pancreas was surgically removed and digested, and islets were isolated, highly purified, and infused intraportally.

Results—Over 18-month follow-up, the patient did not show progression of chronic liver disease or signs of portal hypertension. Magnetic resonance cholangiopancreatography revealed no new changes, and liver biopsy did not show progression of the periportal fibrosis. Pain medication was weaned over 12 months at which time glycemic control was excellent without exogenous insulin supplementation. HbA1c was 5.9. Fifteen months after the procedure, stimulation with a mixed meal led to a fourfold increase of serum C-peptide and an eightfold increase of insulin level.

Conclusion—Pancreatic autologous islets can be successfully transplanted into a liver affected by PSC without compromising hepatic or graft function. Durability of the procedure may be limited in the future by the natural course of the liver injury caused by PSC.

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammation that slowly progresses to biliary cirrhosis. PSC has a close association with inflammatory bowel disease (IBD) as well as autoimmune pancreatitis.¹ Autologous islet transplantation has been developed to preserve beta cell mass and insulin secretory capacity in patients who would otherwise suffer severe postpancreatectomy endocrine deficiency. The liver is currently considered the optimal site for islet grafts. Islets infused into the portal vein initially create micro or macro embolization and thrombosis.² Clinically, islet infusion is often followed by a transient increase of the liver enzymes, usually without long-term liver dysfunction. Hepatic parenchymal disease such as steatohepatitis has been considered a relative contraindication to intraportal islet infusion.³ However, it is not known whether there are certain instances in which intrahepatic islet autotransplantation may be considered despite the presence of liver disease. Here, we present a patient affected by PSC and IBD who developed recurrent and intractable abdominal pain associated with chronic pancreatitis. He underwent total pancreatectomy with successful pancreatic islet autotransplantation, and 18 months after the procedure, he remains insulin free with stable liver function and without progression of his liver disease.

Case Presentation

A 16-year-old male was referred with acute abdominal pain, elevated pancreatic enzymes, and abnormal LFTs. Magnetic resonance cholangiopancreatography (MRCP) revealed multifocal stenosis with post-stenotic dilatation of the intra- and extrahepatic biliary ducts. The pancreatic duct was mildly dilated with a hypointense signal in the body of the pancreas suspicious for chronic pancreatitis. A liver biopsy demonstrated signs consistent with PSC with focal bridging fibrosis. He was diagnosed with ulcerative colitis by endoscopy. The serum IgG was elevated, but IgG4 subclass were normal. Genetic testing for mutations in

CFTR, PRSS1, and SPINK1 was negative. He subsequently had frequent hospitalizations for recurrent abdominal pain, vomiting, dehydration, and significant weight loss. He underwent an ERCP, which demonstrated mild changes of chronic pancreatitis, and an irregular main pancreatic duct with slightly dilated side branches was noted. A pancreatic sphincterotomy was performed as a therapeutic trial. He was started on 40 mg prednisone daily for 6 weeks, and a follow-up MRCP with secretin injection showed no improvement in his pancreatic duct narrowing. Prednisone was tapered and he continued his regimen of mesalamine, ursodiol, pancreatic enzyme replacement therapy, and proton pump inhibitor. His pain was poorly controlled. A celiac nerve block provided only temporary relief, as did a pancreatic stent on two occasions. Over the following 2.5 years from his initial diagnosis, the abdominal pain became severe and unremitting, and his nutritional status significantly deteriorated despite receiving parenteral nutrition. It was always clear that his abdominal pain was unrelated to ulcerative colitis flares or PSC complications. In addition, there was no further pancreatic parenchymal target amenable to stenting, decompression, or focal resection. At this point, total pancreatectomy was considered the last remaining surgical option for pain relief. Islet isolation from the surgically removed pancreas and subsequent islet autotransplantation were considered in order to prevent postsurgical diabetes. The patient and parents were presented with the option of total pancreatectomy either with or without autologous islet transplantation and elected to proceed with autologous islet transplantation.

Preoperative Evaluation

In order to assess liver and portal vein current status as a potential islet engraftment site, transjugular liver biopsy with hepatic venogram and manometry was performed. CVP was 3–5 mmHg, free hepatic vein pressure was 6 mmHg, and wedged hepatic (portal) pressure was 14 mmHg. Therefore, his hepatic venous pressure gradient (HPVG) was 8 mmHg, which was slightly lower than the conventionally defined cutoff for portal hypertension (HPVG>10 mmHg). Liver biopsy confirmed PSC with focal bridging fibrosis (stage 3), which was essentially similar to the histologic staging at his diagnosis.

Prior to surgery, patient was normoglycemic. HgA1c was 5.2 mg%, and non-fasting C-peptide was 1.42 pmol/mL (normal range 0.3–2.35).

Total Pancreatectomy

At operation, the pancreas was atrophic, firm, and nodular. The pancreas was transected over the portal vein, and then, the body and tail were removed from the abdomen and placed on the back table in cold University of Wisconsin (UW) solution. Pancreatic duct cannulation (14 G) was performed allowing for digesting enzyme infusion during islet isolation (Fig. 1). The splenic artery and vein were taken with the specimen; and the spleen was preserved via the short gastric blood vessels according to the Warshaw method. Next, the duodenum with the head of the pancreas was resected and similarly preserved in UW. Both pancreatic segments were transported to the cGMP cellular isolation laboratory on ice. The gastrointestinal tract was reconstructed with Roux-en-Y hepaticojejunostomy and gastrojejunostomy in antecolic orientation. A jejunostomy was placed for postoperative

feeding. The patient remained in the operating room intubated with open abdomen awaiting islet infusion.

Pancreatic Islet Isolation

Islet isolation was performed using a modified Ricordi method based on the Consortium of Islet Transplantation (CIT) protocols.⁴ Briefly, the digestion solution containing Liberase MTF C/T GMP Grade (2,208 Wünsch units of collagenase and 103,500 units of thermolysin in final 350 mL Hanks' balance salt solution with heparin 10 IU/mL) was injected into pancreatic duct via a previously placed angiocatheter. Next, the organ was cut into over 20 pieces and transferred into the chamber applying manual shaking for mechanical and enzymatic digestion. The time of digestion was 12 min. Sixty out of 69-g pancreas was digested. Fifteen milliliters of pancreatic tissue volume was collected, so islet purification was implemented to reduce acinar content and volume of the final preparation. The islets were purified with a continuous gradient using CIT Purification Density Gradients (CIT Purification Solution, Optiprep, and Gradient Stock with densities of 1.113 to 1.060) and COBE 2991. Purified islets were washed and transferred to CIT Wash Media. Final islet product in the high purity fraction contained 170,764 islet equivalent (IEQ) (Fig. 2) and 1.5 mL settled tissue volume. The low purity portion of the final islet product contained 63,476 IEQ in 9 mL settled tissue volume. In both portions of final product, islet viability was over 94 %, and endotoxin was below 5 EU/kg. Gram stains were negative meeting criteria for clinical transplantation. Final bacterial and fungal cultures were negative.

Islet Transplantation

Next, the high purity islet fraction containing over 170 kilo islet equivalent (kIEQ) was suspended in 250 mL of CIT Transplant Media containing human albumin and 2,000 U of heparin and placed in a transplant bag for infusion. The less purified islet fraction was prepared separately in the same fashion. Upon availability of the islets, a 14-G angiocatheter was inserted into the portal vein under direct vision. Baseline portal pressure was transduced and measured at 19 mmHg. The decision was made to infuse the high purity islet fraction first. After the infusion, the portal pressure did not change; however, it was still borderline high, so we decided to abort infusion of the low purity fraction. It contained relatively low number of islets in large amount of tissue (9 mL), so additional infusion would substantially increase risk for portal vein thrombosis and liver dysfunction with minimal potential metabolic benefit.

Postoperative Course

For glucose control, the patient was maintained on an insulin drip for 2 days postoperatively at a rate of 0.5–2 units/h to maintain goal glucose of 80–120 mg/dL. He was then switched to subcutaneous long- and short-acting insulin with glargine and aspart. For thromboembolic prophylaxis, he was given subcutaneous heparin for 6 days and then transitioned to enoxaparin. The patient gradually recovered from surgery without major complications and was discharged home 35 days post-surgery on 1–3 U of short-acting sliding scale insulin only, tube feeds, still requiring oral pain medications in addition to the fentanyl patch, but with vastly improved subjective pain control than prior to operation.

Follow-up

While liver function tests fluctuated over his 15-month follow-up time, physical exam and ultrasound showed no signs of progression of chronic liver disease or signs of portal hypertension. The portal vein continued to have normal flow per Doppler ultrasound. Nine months after operation, a follow-up MRCP revealed no changes in the intrahepatic biliary system compared to the initial study. He underwent a liver biopsy that once again demonstrated evidence of PSC but now with less portal and periportal fibrosis (stage 2). He was maintained on oral vancomycin as an immunomodulator for PSC and IBD, along with pancreatic enzyme oral replacement therapy. During follow-up, the patient presented with recurrent emesis and epigastric pain. An upper endoscopy was diagnostic for autoimmune gastritis that required a temporary course of total parenteral nutrition (TPN) and enteral tube feeds (Peptamen). The gastritis was eventually controlled with oral budesonide. His abdominal pain was relieved by periodic oral tramadol, which was weaned off completely around 12 months after the procedure. Currently, his glucose control is excellent, with HbA1c of 5.9 and no requirement of exogenous insulin supplementation. Prior to that, he required only 6–10 units of NPH insulin with his tube feeds or 10–20 units of the same insulin while on TPN titrated allowing keeping HgA1c between 5.3 and 6.6 mg% (Fig. 3). At the same time, serum non-fasting C-peptide level oscillated in the physiologic range of 0.2–1.8 pmol/mL. Fifteen months after the procedure, stimulation with a meal led to a fourfold increase of serum C-peptide and an eightfold increase of serum insulin level in mixed meal tolerance test (MMTT) and he is still maintained off insulin (Fig. 4).

Discussion

The liver was suggested as an optimal site for islet transplantation for the first time by Paul Lacy 40 years ago based on experiments in a rodent model.⁵ Robust and immediate blood supply to islets infused intraportally is the main advantage of the liver as a transplant site. Clinical experience confirmed Lacy's observations.⁶ The first case report of successful intrahepatic islet autotransplantation in humans was published in 1980s.⁷ Subsequently, in 1990s, the first report of insulin independence in a diabetic patient after allogeneic islet infusion into the portal vein established the liver as the site of choice for islet transplantation in clinical practice.⁸ Currently, more than 500 islet autotransplants and more than 600 patients with sequential islet allograft infused intraportally have been reported.⁶ The results of the islet transplantation have been encouraging, with many patients maintaining near-normal glycemic control for extended periods, becoming insulin free or maintaining partial islet graft function.⁶ Liver function has not been compromised in a chronic or permanent fashion after islet transplant in long-term follow-up.⁶ However, our entire clinical experience is based on patients with essentially normal liver function and normal histology prior to islet transplant. Therefore, it remains to be established whether islet infusion into a liver compromised by chronic inflammation and subsequent portal hypertension adversely affects liver or islet graft function. To our knowledge, ours is the first reported instance of islet autotransplantation into a liver affected by PBC in a patient with chronic pancreatitis and IBD. Because the liver was affected by PSC with focal bridging fibrosis and borderline portal hypertension, we considered alternative sites for islet infusion. However, there are no well-documented long-term clinical outcomes for any other transplant sites other than the

liver. Omentum or peritoneum has been used as a secondary site for autoislet infusion in situations when portal pressure rises over the safety limit of 22 mmHg. However, the efficacy of such practice has never been assessed clinically. Similarly, the spleen has been described as an alternative site, but only in experimental animals.⁹ Although the spleen may be spared during total pancreatectomy, we were concerned about the risk of splenic infarction and the lack of human data using this site. There are several single reports of other alternative sites such as bone marrow, anterior eye chamber, small bowel pouch, vascular pouch, and subserosa or submucosa of the stomach, but all of these are purely experimental.^{10–13} Despite encouraging reports about intramuscular islet infusion, this approach has failed clinically despite success in animals due to abscess formation at the site of the injection likely promoted by local pancreatic enzyme activation and tissue necrosis.¹⁴ In recommending the liver as the target site for this patient, we considered the potential for PSC progression to biliary cirrhosis, which might eventually require liver replacement and loss of the islet graft. We reasoned that subsequent simultaneous liver and pancreas or islet transplantation would be possible at that point, and the patient would meanwhile have had the benefit of relatively stable glucose control due to the initial islet autograft, which may last for many years in healthy livers.⁶ In order to minimize risk for portal vein thrombosis and intrahepatic inflammation, we decided to maximize islet purification and to limit the amount of acinar tissue as well as the final tissue volume. We were able to obtain a relatively large number (170 kIEQ) of high-quality islets in a relatively small volume of tissue (1.5 mL). The portal pressure was not affected by the islet infusion, which remained constant at 19 mmHg before and after the procedure. We decided not to infuse remaining low purity prep due to its larger tissue volume, which we felt substantially increased the risk of both portal vein thrombosis and subsequent liver and islet dysfunction and portal hypertension. A high load of relatively unpurified acinar tissue could enhance the intrahepatic/intraportal inflammatory response compromising the function of the infused islets. We also did not infuse remaining tissue into the greater omentum or mesentery because of the patient's limited visceral fat and the unproven metabolic advantage of these alternative sites. Over 18 months of follow-up, our patient has experienced substantial improvement in quality of life from both the total pancreatectomy and the islet autotransplantation. Currently, his chronic abdominal pain is virtually resolved, and he no longer requires daily pain medication. The overall inflammatory activity of his IBD and PSC has not worsened. His postoperative liver function tests fluctuated, but physical examination and ultrasound showed no signs of progression of chronic liver disease or portal hypertension. One year postoperatively, liver biopsy showed less advanced fibrosis (periportal stage 2) compared to focal bridging fibrosis (stage 3) preoperatively, a finding likely representing a sampling error. Our patient's metabolic control has been excellent. Serum C-peptide has remained within the normal range. He requires long-acting insulin supplementation only during exacerbations of inflammatory disease when steroid therapy and metabolic demand increase insulin requirements. Mixed meal tolerance test 18 months after autotransplantation revealed strong metabolic beta cell reserve—it showed a fourfold increase in C-peptide and an eightfold increase in insulin in response to a meal. Even though he has required occasional small doses of insulin, he has not experienced hypoglycemic events as his islet graft exhibits its well-recognized protective role. This case has important implications for teenagers who tend to be more noncompliant with medication regimens.

Currently, his HgbA1c has been maintained at physiologic levels below 6 mg%. The metabolic outcome in our patient was comparable with results of islet autograft into healthy livers. Pancreatic islet isolation remains a sophisticated and expensive procedure performed in only a handful of highly specialized GMP facilities. Islet isolation from pancreata damaged by chronic inflammation is especially challenging. Even in the most experienced centers, islet yield depends mostly on the degree of the organ damage. The more advanced the state of inflammation and organ destruction due to pancreatitis, the lower the chance for sufficient islet yield and clinical outcomes of autotransplantation.¹⁵ Overall, only about one third of patients remain insulin free after autotransplantation, another third show good metabolic control but require modest insulin supplementation, and the remaining patients are insulin dependent with poor glucose control.⁶ Our patient received 3.5 kIEQ/kg body weight. Based on the reported results, only 27 % of patients become insulin free when they received 2.5–5 kIEQ/kg rising to 63% with greater than 5 kIEQ, whereas if fewer than 2.5 kIEQ are infused, the odds for insulin-independence decrease to 7 %.

Conclusions

Autologous pancreatic islets were safely infused into a liver compromised by PSC without deterioration of hepatic function or portal hypertension, providing the benefit of stable glucose control in a patient suffering from autoimmune chronic pancreatitis. In this setting, we recommend that islets are highly purified in order to limit the volume of the preparation and the amount of acinar tissue infused. While the results in short-to-medium term follow-up have been excellent, the long-term durability of this approach, particularly with respect to the natural course of the liver injury caused by PSC, remains to be determined.

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Abbreviations

PSC	Primary sclerosing cholangitis
IBD	Inflammatory bowel disease
kIEQ	Kilo islet equivalent
LFT	Liver function test
MRCP	Magnetic resonance cholangiopancreatography
CVP	Central venous pressure
CIT	Consortium of Islet Transplantation
cGMP	Current good manufacture practice

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Fig. 1.
Surgically resected pancreas (body and tail). Pancreatic duct was cannulated for collagenase infusion during the islet isolation

Fig. 2.
Isolated islets, view under the light microscope. Islet stained with Dithizone in *red* and acinar tissue unstained in *yellow* (magnification $\times 30$)

Fig. 3. Glucose control after islet autotransplantation. **a** Patient exhibited excellent glucose control: HgA1c oscillated below 6.6. Twelve months after the transplant, he stopped requiring exogenous insulin and dropped HgA1c to 6 mg%. **b** Random serum C-peptide has remained in physiologic range (0.35–1.8 pmol/mL) after the procedure

Fig. 4. Glucose control based on MMTT—15-month follow-up. Patient remained insulin free. Stimulation with mixed meal led to robust, over fourfold increase in serum C-peptide secretion (**a**) and eightfold serum insulin secretion (**b**)