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Total Pancreatectomy and Islet Autotransplantation Following Treated Hepatitis C Infection

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Abstract

Hepatic parenchymal disease, including chronic viral hepatitis, has traditionally been considered a relative contraindication to islet transplantation as the islets are infused into the recipient's liver. We present a case study of a patient with treated chronic hepatitis C infection (HCV) who safely received an autologous islet transplant following total pancreatectomy with excellent clinical outcomes. The patient was a 60-year-old woman diagnosed with debilitating abdominal pain secondary to chronic pancreatitis and with preserved islet function. She had previously been treated >10 years prior to surgical evaluation with interferon monotherapy for 1 year that led to sustained virologic response, including at the time of surgical evaluation for total pancreatectomy and islet autotransplantation (TPIAT). She underwent comprehensive preoperative evaluation of the liver, including liver biopsy, which showed no significant portal inflammation or fibrosis. Following a multidisciplinary meeting and discussion of the potential risks for the patient, the decision was made to proceed with TPIAT. The patient underwent a standard total pancreatectomy, and an autologous islet dose of 6638 islet equivalents/kg body weight was infused into the liver via the portal vein. Portal vein pressure was monitored throughout the infusion with a transient peak pressure of 27 cm H_2O (basal pressure of 14 cm H_2O) and final pressure of 23 cm H_20 at 10 min post-infusion. Aside from a transient transaminitis, liver enzymes were normal at the time of hospital discharge. At greater than 1 year of follow-up, the patient has improved quality of life, with reduction in narcotic analgesia, remains insulin independent (with normal islet function), and has normal liver function. This case illustrates that islet autotransplant into the liver can be safely performed and suggests that carefully selected patients with liver disease may be eligible for TPIAT.

Keywords

islet autotransplant, chronic pancreatitis, hepatitis C infection, total pancreatectomy

Introduction

Chronic pancreatitis (CP) is a chronic inflammatory disease that is characterized by progressive fibrosis and loss of pancreatic function. These insufficiencies can lead to a variety of disease-related complications including diabetes mellitus, exocrine pancreatic insufficiency and metabolic bone disease[1]. Abdominal pain is the most common symptom affecting, up to 80% of patients with CP[2]. Management of abdominal pain comprises a combination of medical, endoscopic and surgical treatment depending on the severity, anatomy and treatment responses[3]. Unfortunately, the success rates for treatment of CP-related abdominal pain are low, particularly for patients without pancreatic duct obstruction. Total pancreatectomy with islet autotransplantation (TPIAT) is a treatment option that is available for patients with debilitating pain secondary to CP and who have preserved islet function[4]. In addition, TPIAT is considered in patients with hereditary pancreatitis and idiopathic recurrent acute pancreatitis. This procedure involves resection of the entire pancreas, isolation of the islets from the pancreas and

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infusion of the freshly isolated islets into the patient's liver via the portal vain. Since the islets are infused into the liver of the patient, patients with a history of liver disease including hepatitis infection are generally not considered to be candidates for the procedure. We report the case of a patient with treated chronic hepatitis C virus (HCV) infection who underwent TPIAT safely and had excellent clinical outcomes.

Case Presentation

A 60-year-old woman with CP since 2012 was referred for TPIAT. The patient suffered from chronic abdominal pain that limited her daily functioning and quality of life (QOL). She was diagnosed with CP based on increased lipase levels more than three times the upper limits of normal correlating with episodes of abdominal pain. Endoscopic ultrasound showed parenchymal abnormalities throughout the entire pancreas including hyperechoic strands, hyperechoic foci and lobularity. The patient underwent multiple celiac plexus blocks with temporary analgesia but loss of effect over time. The patient was referred for TPIAT. The patient underwent oral glucose tolerance testing that demonstrated preserved endocrine function. Hemoglobin A1c was normal (5.0%) at baseline, and there was a measureable fasting c-peptide level (1.2 ng/ml).

During evaluation of the patient's medical history, it was noted that the patient had a prior HCV infection originally diagnosed in 1998. A liver biopsy was performed at that time showing minimal chronic hepatitis, grade 1/4, stage 0/4, and she was treated with interferon monotherapy for 12 months.

Liver ultrasound was performed during preoperative evaluation and showed mild steatosis with normal flow in the portal vein and all hepatic vessels. A liver biopsy was repeated and showed minimal steatosis $< 2\%$ and no significant inflammation or fibrosis (grade 0/4, stage 0/4). The HCV antibody remained positive, while viral load was undetectable and liver enzymes were normal.

The patient underwent a standard total pancreatectomy with resection of the spleen and duodenum. A midline incision was performed, and the gastrocolic omentum was opened. The spleen and the tail of the pancreas were mobilized and dissected to the superior mesenteric vein. The splenic vein and artery were stapled, and the pancreas was dissected from the portal vein. When the entire pancreas was removed, it was handed over to the transplant surgeon for islet isolation. During the islet isolation process, gastrointestinal and biliary continuity was established using a roux-en-Y gastrojejunostomy and choledocho-jejunostomy. A single drain was placed in the right upper quadrant. The incision was closed partially using staplers for the skin only. The patient was kept under general anesthesia until islet isolation was completed.

The pancreas was washed sequentially in solutions of betadine (Purdue Frederick, Stamford, CT, USA), amphotericin B (X-Gen Pharmaceuticals, Horseheads, NY, USA) and cephazolin (Novaplus, Irving, TX, USA) and Hanks Balanced Salt Solution (HBSS) (Mediatech, Manassas, VA, USA). The pancreatic duct in the midbody of pancreas was cannulated with two 16 gauge angiocatheters. The spleen and duodenum were removed, and the pancreas was placed on ice in an HBSS solution and transported to the cell isolation laboratory. The pancreas was distended by infusion through the cannulated duct with a solution of Collagenase NB (minimum 2000 units) (Serva, Heidelberg, Germany) containing a neutral protease (50 dimethylcasein-units) and DNase (Genentech, Inc., South San Francisco, CA, USA). The pancreas, following perfusion, was cut into 1-inch pieces and placed in a Ricordi chamber with silicon nitride marbles for mechanical and enzymatic digestion. At the completion of the digestion phase (elapsed time: 42 min), digestion was stopped via cold dilution. The collected digestate was washed, and a final pellet volume of 19 mL (0.23 mL/kg body weight) was collected (pellet criteria must be $\leq$ 0.25 mL/kg). A total of 545,664 islet equivalents (IEq) were isolated (84% free islets, 10% purity). A stat Gram Stain did not identify organisms, and post-release testing of aerobic culture, anaerobic culture, and fungal culture all showed no growth at 14 days. Viability testing using a fluorescent microscopic method (calcein AM/ethidium homodimer stains from the Live/Dead™ kit, Life Technologies, Eugene, OR, USA) indicated 86% viability of the islet cells. A static *in vitro* glucose stimulation test was performed in which $n = 5$ hand-picked islets were incubated at 37°C for 1 h in media supplemented with either low (1.67 mM) or 10-fold higher (16.7 mM) glucose in replicates of five. Insulin released into the supernatant was measured by enzyme-linked immunosorbent assay, and a stimulation index was calculated as the proportion of insulin released at high glucose concentration divided by insulin released at low glucose concentration. A stimulation index of greater than 1.0 was considered indicative of functional islets. Testing on islets transplanted into this recipient indicated a stimulation index of 1.82.

The final islet pellet was resuspended in 600 mL of transplant media and transported on ice back to the operating room for infusion. Heparin (5000 units) was added to the islet suspension in the operating room prior to infusion. An 18 gauge angiocatheter was passed through the splenic vein stump toward the portal vein. Baseline portal pressure was measured at 14 cm H_2O. Portal pressure was measured again 5 min later and remained 14 cm H_2O. The islet suspension was then infused over 59 min. Portal pressure was measured several times during the infusion. Pressure peaked at 27 cm H_2O. At the completion of infusion, the portal pressure remained steady at 23 cm H_2O (Fig. 1). The angiocatheter was removed, and a 6-O Prolene purse string stitch was used for hemostasis. The midline incision was closed in two layers, and the patient was transferred to recovery in stable condition.

The patient was followed by endocrinology, gastroenterology and transplant surgery for post-operative care. The

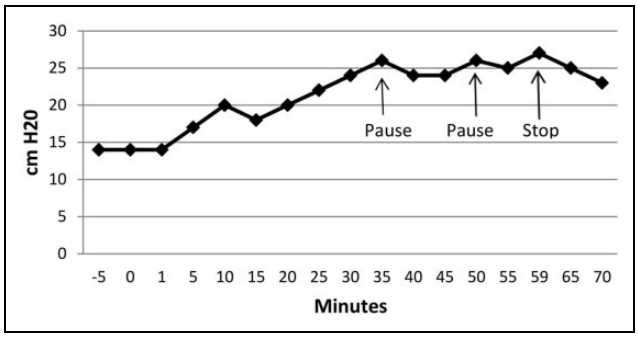

Figure 1. Portal pressure measured at baseline, throughout islet infusion and after infusion. Infusion of islets was paused briefly at both 35 and 50 min with the elevation in pressure. Infusion was restarted when the portal pressure dropped. Infusion was stopped at 59 min, and pressure was measured for 10 min post-infusion to ensure stabilization.

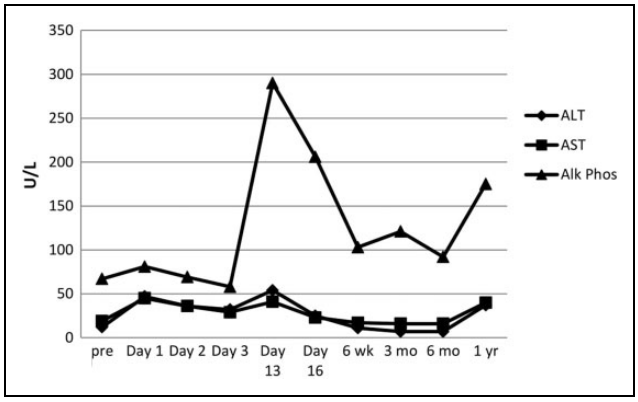

Figure 2. Liver function [AST, alanine aminotransferase (ALT) & alkaline phosphatase) levels before and after total pancreatectomy and autologous islet transplantation.

patient was given intravenous antibiotics and subcutaneous heparin (5000 units every 8 h). The patient was also maintained on an insulin drip (0.25 units/h) for 3 days post-transplant. She was then given subcutaneous insulin every 6 h as needed until discharge. Liver enzymes were monitored and shown to be elevated slightly with aspartate aminotransferase (AST) reaching 45 U/L on post-operative day (POD) 1 but returning to normal by POD 2 (Fig. 2). A liver ultrasound was performed 24 h after the procedure and showed normal flow in the portal vessels. The patient was hospitalized for 10 days following the procedure without any serious complications. At discharge, the patient was taken off of insulin and instructed to monitor her blood glucose 2–4 times daily with a goal of blood glucose < 150 mg/dL. The patient was discharged on oral pain medications and a fentanyl patch.

Follow-Up

The patient's pain improved after the procedure such that she was able to wean off the fentanyl patch completely by 6 months post-TPIAT. The patient is currently 19 months post-TPIAT and continues to take oxycodone for pain but is working on weaning her dose of this as well. The patient's daily morphine equivalent dose has reduced from 137.4 at baseline to 90 at 1 year post-TPIAT. Her pain improvement has enabled her to engage in daily exercise, thus greatly increasing her functional status compared with before the procedure. This has also contributed to a notable improvement in the patient's depression scores. Prior to surgery, the patient scored a 39 on the Beck Depression Inventory, indicating severe depression. With the assistance of regular psychotherapy and improved health-related QOL after TPIAT, her score was a 10, indicating only minimal depression.

The patient has maintained excellent glucose control and remains insulin independent at last follow-up (19 months following surgery). Her hemoglobin A1c levels have consistently remained <6.5% with a peak at 6.2% at 1 year post-

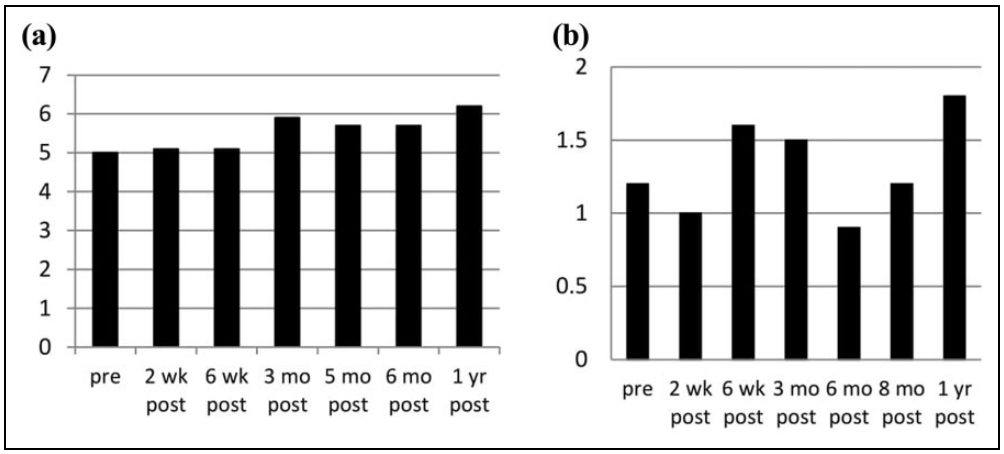

Figure 3. Islet function analysis by hemoglobin A1c (a) and c-peptide (b) levels before and after total pancreatectomy and autologous islet transplantation.

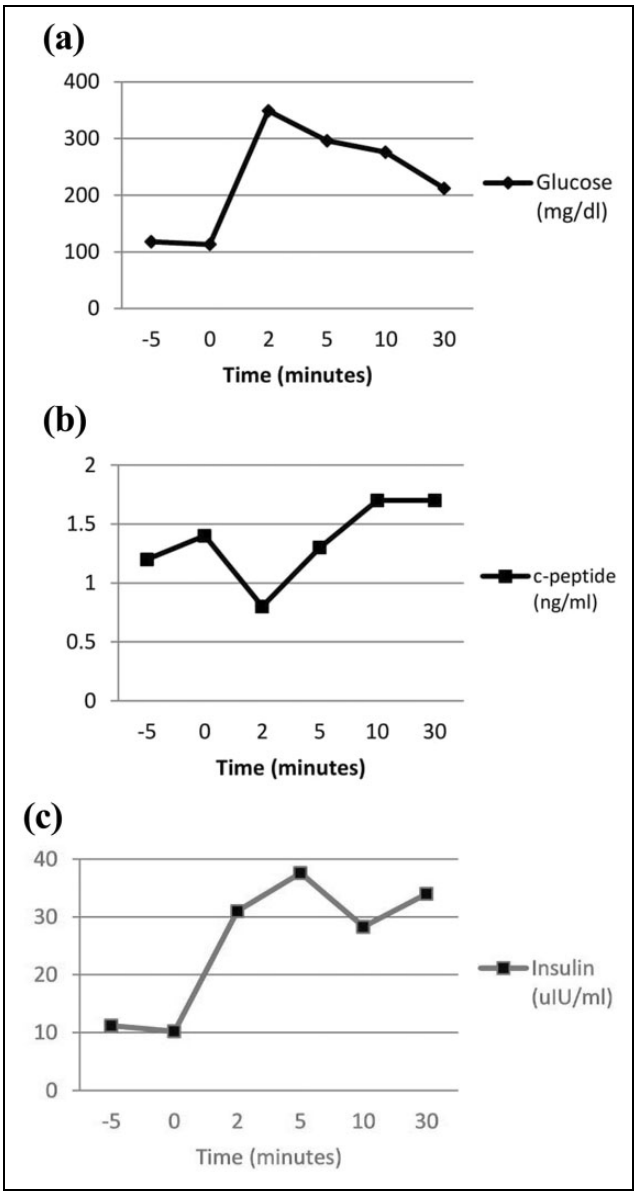

Figure 4. Glucose levels (a), c-peptide levels (b) and insulin levels (c) during a 30-min intravenous glucose tolerance test performed at 8 months post-transplant.

transplant (Fig. 3a). The patient also continues to have detectable fasting c-peptide levels (Fig. 3b). A 30 min intravenous glucose tolerance test (IVGTT) performed 8 months post-transplant showed a typical glucose curve and first-phase insulin response (Fig. 4).

Homeostasis model assessment (HOMA) of fasting glucose and insulin was used to determine beta cell function (HOMA %B) and insulin resistance (HOMA IR) at baseline and 6 months post-transplant. HOMA %B decreased from 41.1% at baseline to 29.9% 6 months post-transplant. Insulin resistance increased from 2.0 to 3.1. However, based on other measures of islet cell function, these changes do not appear to have clinical significance.

Discussion

Traditionally, clinical islet cell transplantations are performed into the liver of the recipient. This site was decided on due to the rich blood supply for enrichment of the transplanted islets as well as communication of the islets with the blood for glucose response. When evaluating patients for islet cell transplantation, therefore, any sign or history of liver damage is generally considered to be a contraindication to the procedure.

There are very few published cases of islet transplantation into patients who have suffered from liver disease. One case published in 1998 demonstrated successful allogeneic islet transplantation in a type 1 diabetic patient who had previously undergone liver transplantation for treatment of cryptogenic liver cirrhosis. Islets isolated from a donor pancreas were infused into the transplanted liver using computed tomographic-guided transhepatic catheterization. The patient was given tapered methylprednisolone, tacrolimus, azathioprine and anti-lymphocyte globulin as induction immunosuppression therapy, and they were maintained on tacrolimus. The patient had maintained the stable liver transplant for 1 year on tacrolimus prior to islet transplant. The study showed successful results for the 6-month follow-up period with no adverse effects and a reduction in exogenous insulin requirements[5]. Another case published in 1997 demonstrated successful islet autotransplantation into the liver of a patient diagnosed with cirrhosis. In this case, the patient demonstrated no portal hypertension prior to transplant and no significant or lasting increases in portal pressure during infusion of the islets. There was also no change in liver function after transplant. The patient was insulin independent throughout the 1-year follow-up period of the study[6].

In the case of our patient, despite the history of HCV infection, there were no clinical signs of liver damage when she presented for surgical evaluation. Given the severity of her CP, her poor QOL and minimal persistent liver disease, it was decided by our multidisciplinary selection committee to proceed with the TPIAT procedure.

Portal pressure was closely monitored throughout islet infusion. Some elevation was noted, and the infusion was paused twice at 35 min and 50 min. However, in both instances, the pressure reduced, the infusion was able to continue, and all of the islets were infused. Abdominal ultrasound on POD 1 showed normal flow in the main, left and right portal veins. Liver function tests (LFTs) were monitored daily throughout the patient's hospitalization. A brief elevation on POD 1 showed AST levels to be just above the normal range at 45 U/L. Alanine aminotransferase (ALT) levels remained within normal limits although they did also elevate slightly on POD 1. Both AST and ALT began decreasing on POD 2, with both values falling in the normal range. Another brief elevation was noted on POD 13 when the patient presented to the emergency department with leukocytosis. AST peaked at 41 U/L, ALT peaked at 54 U/L, and alkaline phosphatase peaked at 290 U/L. All LFTs had returned to normal when retested at 6 months post-TPIAT.

In all aspects, this patient has had excellent clinical outcomes following the TPIAT procedure. She discontinued insulin use in less than 1 month, and remained insulin independent at last follow-up (19 months post-TPIAT). In addition, there is continued c-peptide positivity, and her post-transplant IVGTT also demonstrated islet function with a typical peak and decline in the glucose curve as well as an expected response of both insulin and c-peptide (Fig. 4).

Importantly, the patient has experienced a significant improvement in QOL following TPIAT. The patient has had a 35% reduction in her total dose of narcotic analgesia, which is slightly better than the average reduction in morphine equivalents for patients who are 1 year post-TPIAT at our center (average reduction = 28%). In addition, the patient's pain score at rest improved from 4/10 at baseline to 2/10 at 1 year post-TPIAT. The patient also demonstrated a 75% improvement in her score on the Beck Depression Inventory.

In addition to the concern for complications related to transplanting islets into the liver of a patient that has had hepatic disease such as HCV, reports have been made that actually link autoimmune destruction of beta cells and development of type 1 diabetes to the interferon treatment for HCV infection as well as a link between insulin resistance and HCV infection[7,8].

This case illustrates that TPIAT can be safely performed in patients with a history of HCV. This is a particularly important consideration due to the increasing number of patients who are successfully achieving sustained virologic response following treatment with novel antiviral therapies. However, we caution that, in the absence of further studies, TPIAT should only be considered in highly selected patients with liver disease without advanced fibrosis.

Ethical Approval

This is a case study and was exempt from IRB approval.

Statement of Human and Animal Rights

This work was conducted according to Good Clinical Practice guidelines as well as the ethical standards of the latest version of the Helsinki Declaration.

Statement of Informed Consent

This is a case study, therefore informed consent is not applicable.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Disclaimer

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