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Autologous Islet Transplantation After Total Pancreatectomy in a Patient Recovered from SARS-CoV-2: A Case Report

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Manuscript Preparation E
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Patient: Female, 51-year-old
Final Diagnosis: Idiopathic chronic pancreatitis
Symptoms: Poor pain control
Medication: —
Clinical Procedure: TPAIT
Specialty: Endocrinology and Metabolic

Objective: Unknown etiology

Background: SARS-CoV-2 infection or COVID-19 disease has been linked to the onset of diabetes and metabolic dysregulation because it has been suggested that viral entry proteins, specifically ACE2 and TMPRSS2, are expressed in the exocrine cells and ductal epithelium of the pancreas. Because of the unknown effect this can have on islet function, there can be doubt that patients with previous SARS-CoV-2 infections are good candidates for autologous islet transplantation after total pancreatectomy (TPAIT).





Case Report: A patient with a history of chronic pancreatitis and previous non-surgical interventions was presented as a viable candidate for TPAIT at our institution. Approximately 1 month later, the patient contracted a SARS-CoV-2 infection, resulting in a mild case of COVID-19. The infection resolved without the need for hospitalization. At the time of this occurrence, COVID-19 was primarily considered a respiratory ailment, and little was known of the potential association between metabolic dysfunction and SARS-CoV-2. Islet isolation and surgery proceeded in a textbook manner with no surgical complications. The patient was weaned off exogenous insulin within 3 months after transplantation.

Conclusions: Favorable outcomes after surgery included pain reduction, islet function, and improved quality of life for the patient in the first 6 months after the procedure. These successful results demonstrate that SARS-CoV-2 infection did not prevent the patient from achieving good glucose regulation after auto-islet transplantation. This outcome suggests that, at least in this instance of mild infection, there were no long-lasting negative COVID-19-associated effects on the transplanted islets that might impact islet function.

Keywords: Islets of Langerhans Transplantation • Pancreatectomy • Pancreatitis, Chronic • SARS-CoV-2

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Background

Total pancreatectomy (TP) is the final therapeutic option to alleviate intractable pain associated with chronic pancreatitis (CP) or recurrent acute pancreatitis that remains unresolved after less invasive procedures fail to bring relief [1]. Excision of the pancreatic organ results in type 3c or surgically induced diabetes unless it is combined with autologous islet transplantation (AIT), in which insulin-producing beta cells isolated from the pancreas are returned to the patient's liver, with a mitigating effect on diabetes. Type 3c diabetes is often regarded as "brittle" or difficult to control [2]. Alternatively, after TP with AIT (TPAIT), about 2 in 3 patients either become insulin independent or require relatively small doses of insulin to maintain glycemic control [3]. Since 2008, most patients undergoing TP for CP have undergone TPAIT rather than TP alone [4]. TPAIT offers a lower mortality rate for the patient, shorter time in the hospital, improved quality of life, and lower adjusted cost than TP alone [4] in addition to the metabolic advantages offered by the islet transplantation itself [3]. Establishing metabolic control after islet transplantation provides health benefits to recipients who would otherwise experience insulin-dependent diabetes after TP or from the association with the progression of the CP itself.

There is a growing recognition of a connection between SARS-CoV-2 and pancreatic dysfunction [5,6], with some evidence showing that the virus can physiologically alter insulin-producing beta cells, resulting in impaired ex vivo function [7]. It is not yet known whether pathological damage to endocrine cells occurs, is transient, or would potentially have a deleterious effect on islet function after clinical islet transplantation. This case report represents a first look at a patient undergoing TPAIT with a medical history including a prior infection of SARS-CoV-2 that was resolved at the time of surgery.

Case Report

At the time of pancreatectomy, the patient was a 51-year-old woman with a history of idiopathic chronic pancreatitis and possible sphincter of Oddi dysfunction. Interventions, including endoscopic retrograde cholangiopancreatography, stenting, and sphincteroplasty, dated back several years. There was a resulting pancreatic duct stricture, exocrine insufficiency requiring exogenous pancreatic enzymes, and episodes of acute pancreatitis, which at times required hospital admission. Treatment included chronic narcotic use but with poor control of pain. As a consequence, the patient could no longer work and had a reduction in overall quality of life. She had surgical evaluation for partial pancreatectomy or Puestow procedure, but owing to the uncertainty of the etiology of her pancreatitis and non-dilated duct (documented at 2-5 mm), these were not thought to be curative for this patient. The patient's symptoms, laboratory results, and



Figure 1. Computed tomography picture of the abdomen with an arrow pointing to the pancreas. Scan indicates pancreatic atrophy without ductal dilation or major calcifications.

clinical status were somewhat out of proportion to her imaging findings (Figure 1), but she had pancreatic atrophy on computed tomography along with inflammatory changes during acute pancreatitis episodes. These refractory symptoms prompted evaluation for TPAIT by her surgeon and gastroenterologist. An endocrinologist performed a metabolic assessment 4 months before surgery, including a mixed meal tolerance test (MMTT).

The MMTT involves taking baseline glucose, insulin, proinsulin, and C-peptide levels, the oral administration of a protein, fat, and carbohydrate drink, and testing laboratory values again at 30-min intervals for 2 h. Our patient had C-peptide levels of 4.2, 1.6, 5.3, and 5.1 ng/mL. Results of C-peptide >4 ng/mL are predictive of successful islet isolation of at least 2500 islet equivalents per kilogram (IEQ/kg) [8]. She had an appropriate rise in insulin to oral intake as well, which also corresponds to successful isolation and transplantation.

During the evaluation period for TPAIT, 3 months before surgery and before COVID-19 vaccines were available in the United States, the patient tested positive for SARS-CoV-2. Family members also tested positive for SARS-CoV-2 at this time. The patient felt fatigued and unwell but recovered at home without medications or supplemental oxygen and was not hospitalized for SARS-CoV-2. After recovery from SARS-CoV-2 infection, a cardiac evaluation was completed with an exercise stress test and routine laboratory work, which showed a normal fasting glucose of 87 mg/dL. A SARS-CoV-2 antibody test was positive, proving a previous exposure.

Surgical Technique

The TP was undertaken by laparotomy. The extirpative phase included dissection off the retroperitoneum, with care to

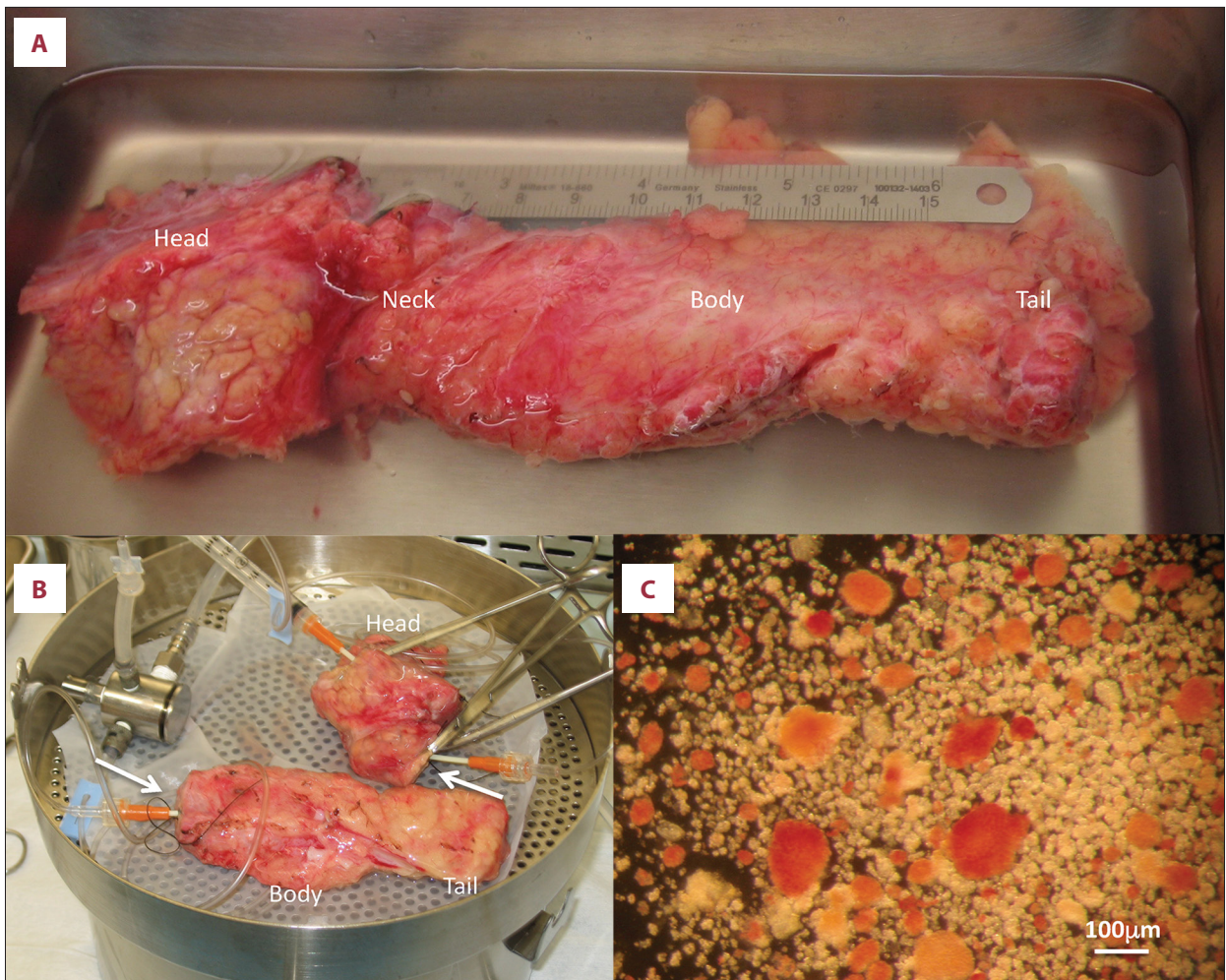


Figure 2. Excised pancreas during isolation and resulting islets. (A) Excised chronic pancreatitis pancreas cleaned of extraneous fat and tissue. The head, neck, body, and tail are labeled. (B) The pancreas head and body bisected at the neck with 14G catheters secured in the pancreatic ducts during perfusion with collagenase using a Rajotte controlled-temperature recirculation device. The head, body, and tail are labeled. Arrows are pointing to the bisected planes of the neck. (C) Sample of final islet cell mass of 30 to 40% purity. Islets are stained red with dithizone. Acinar tissue does not take up dithizone and is pale in color. Scale bar=100 μm.

isolate and preserve the splenic artery, gastroduodenal artery, and splenic vein. In the final steps, the gastroduodenal artery was serially ligated and sharply divided, and then the splenic artery was ligated proximally and sharply divided. The splenic vein was stapled to the left of the inferior mesenteric vein, and the specimen was immediately removed. The splenic artery was flushed antegrade on the back table with cold lactated ringers solution and retrograde through the splenic vein until it flushed clear. It was packaged and delivered immediately to the isolation laboratory. The warm ischemia time was 3 min. During islet isolation, the reconstructive phase of the surgery proceeded, including placement of a portal vein catheter via the splenic vein stump for infusion, hepaticojejunostomy, and retrocolic gastrojejunostomy. Following isolation, the patient was infused with 5675 IEQ/kg islets. The estimated

blood loss for the procedure was 50 mL. The length of the entire procedure was 519 min. The start of case to flushing of pancreas was approximately 210 min, and during the processing phase, the reconstruction was performed and the cannula was placed into the portal vein for infusion. Since processing of islet cells was done on site, the patient remained in the operating room for the entire time, which was around 180 min. The infusion time for islets was 43 min.

Islet Isolation and Infusion

The pancreas with the attached duodenum and spleen were transported to the islet isolation facility inside the hospital with 22 min cold ischemia time. The pancreas measured $18 \times 4.5 \times 2$ cm³ and weighed 107.8 g. The organ was visibly

inspected, and it was found that the fat deposition was average, there was no edema, the texture was firm (normal for CP pancreata), and it was well flushed with ringer's lactate solution in the operating room via the splenic artery. The pancreas was prepared by removing the duodenum and spleen (Figure 2A), cleaned of remaining fat (11.0 g), and bisected at the neck. Catheters (14G) were inserted into the pancreatic duct in the head and body and sutured in place (Figure 2B). Islet isolation was based on a previously published approach used in our laboratory [9,10]. Collagenase NB 1 GMP grade (15 PZ U/g) combined with neutral protease NB GMP grade (1.5 DMC U/g) was perfused through the pancreas for 15 min at 28°C in a Rajotte recirculation device (Figure 2B). At this point, the head and body/tail sections had inflated and taken on a glossy sheen associated with successful infusion, before deflating slightly. The pancreas was then placed in a Ricordi chamber with 7 marbles and manually disrupted by shaking. Tissue was collected from the temperature-controlled chamber for 33 min (10 min of warm collection followed by 23 min of cold collection). After collection, 30.8 g (out of initial 107.8 g, or 28.6%) of tissue remained undigested in the chamber; only 10% of the remaining tissue was determined to be non-fibrotic pancreatic parenchyma, the remainder being ductal system fragments, blood vessels, and fibrotic pancreatic parenchyma. A total of 20 mL of tissue was collected after digestion, then islets were separated on a discontinuous polysucrose gradient using a COBE cell separator, resulting in a more concentrated (purer) islet mass in a pellet volume of 7.2 mL. The purity of islets infused back to the patient was 30% to 40% (Figure 2C), and viability was >90%, based on representative samples. Islets were counted using IEQ, defined as a hypothetical islet of 150 µm in diameter [11]. The total number of islets returned to the patient was 401 775 IEQ, equaling 5675 IEQ/kg. The endotoxin level of the cell product was 0.34 U/kg, the Gram stain was negative, and follow-up microbiology showed no contamination at 30 days after surgery.

Postoperative Care

The patient was transferred to the Intensive Care Unit on an insulin drip and D5 ½ NS for strict blood glucose management. Our protocol continues this therapy until postoperative day 3, when long-acting insulin (Lantus) and sliding-scale insulin are started and the drip is discontinued. Nutrition can be initiated with liquids at this time, and D5 fluids are continued until reliable oral intake. In our patient's case, delayed gastric emptying occurred and required a post-anastomotic nasogastric feeding tube for nutrition. C-peptide levels were checked daily and goal glucose levels were less restrictive than at postoperative days 1 to 3. The patient was discharged upon becoming clinically stable and returned home with a glucometer, basal and sliding-scale insulin, and instructions for monitoring blood glucose levels. The delayed gastric emptying resolved after

discharge, with complete oral intake by 4 to 5 weeks after surgery and normal-consistency food by 8 weeks, at which time the patient had restarted pancreas enzyme supplementation.

Islet Function and Pain Resolution

In the immediate hospital postoperative period, the patient's pain was managed well with a patient-controlled analgesia pump. This was transitioned to oral medication with sips of water when oral intake was tolerated. The patient subjectively felt that the preoperative back pain had resolved and the postsurgical pain felt different in location and quality. As an outpatient, she had almost complete pain resolution. The patient's pain physician titrated the oxycodone dose down over the course of 2 months to 20 mg a day from an initial dose of 9 mg long-acting oxycodone twice daily, with breakthrough 10 mg oxycodone/acetaminophen every 6 h. At 6 months after surgery, she is on 5 mg hydrocodone every 12 h with a plan to cease this over the next few months.

Small amounts of long-acting insulin were maintained in the recovery period for islet cell support. At 3 months after islet transplantation, the patient came off exogenous insulin completely. The hemoglobin A1c level at 8 weeks after surgery was 5.9%, with an average glucose of 123 mg/dL, and fasting C-peptide 0.52 ng/mL. At 6 months, the hemoglobin A1c level was 5.8%, non-fasting blood glucose was 96 mg/dL, and C-peptide was 1.33 ng/mL, while the patient was still remaining off exogenous insulin.

Discussion

In this patient, mild SARS-CoV-2 infection did not appear to impact islet function following islet auto-transplant after pancreatectomy. Islets were isolated successfully in a volume predictive of metabolic control after TPAIT. Transplantation of >5000 IEQ/kg is strongly associated with insulin independence in recipients [10,12,13]. Approximately 4 weeks after surgery, the patient was taking 4 units of long-acting insulin (Lantus) per day, which was discontinued after 3 months. Typically, patients, including those who become insulin independent, receive insulin for a period of time (up to 3 months, depending on the transplantation center) after TPAIT to support islet engraftment without over-taxing their function [14].

The patient did not test positive for SARS-CoV-2 until approximately 1 month after undergoing a pre-procedure MMTT. At that time, relatively little was known about metabolic dysfunction potentially associated with SARS-CoV-2, which was primarily thought to be a disease of the respiratory system, and so there was no cause to consider a follow-up metabolic test to determine functional capacity of the islets after the infection

had run its course. Immediate preoperative laboratory tests showed a normal fasting blood glucose of 87 mg/dL, which did not prompt further testing after SARS-CoV-2 infection.

In the early stage after TPAIT, the patient's recovery was good. The patient remained in the hospital 15 days after surgery before returning home. The length of stay was related to delayed gastric emptying and oral intolerance. There was a subsequent admission to the hospital once for a nasojejunal feeding tube replacement while she was still receiving distal feeds for delayed gastric emptying. This is a fairly common occurrence after TP with or without islet transplantation. It should be noted here that the eventual likely consequences of CP progression are exocrine insufficiency and diabetes because viable endocrine and exocrine tissue is replaced with fibrosis. When it becomes necessary to relieve the pain of CP with the excision of the pancreas, both conditions are assured. Exogenous digestive enzymes can assist with digestion, while AIT can mitigate the severity of diabetes or even result in exogenous insulin independence.

Our experience with TPAIT during the pandemic era (beginning in March 2020) consists of isolating islets for 17 patients who underwent TPAIT at Allegheny General Hospital (Pittsburgh, PA), the Cleveland Clinic (Cleveland, OH), and the University of Pittsburgh Medical Center (Pittsburgh, PA). Our data show that there are no significant statistical differences between key outcome parameters of islet isolation/transplantation, IEQ, and IEQ/kg between the patient and pandemic era patients and a cohort consisting of the 17 previous patients (standard *t* test calculated on graphpad.com, $P=0.2955$ and $P=0.0728$, respectively). Other than the patient in this case study, to the best of our knowledge, no patients in this analysis had contracted COVID-19 prior to TPAIT. The patient in this study received 401 775 IEQ and 5675 IEQ/kg.

Now that vaccines for COVID-19 are readily available in the US, several hospital groups are requiring prospective surgical patients to be vaccinated; however, vaccination remains voluntary at this time for patients in the health systems in which we are affiliated. Recognizing the detrimental effects of patients being unable to receive a full range of health care to meet their needs during the pandemic, which can either be due to hospitals temporarily suspending elective surgeries as

they prepare for an influx of COVID-19 patients or through patients being unwilling to risk exposure in medical settings, we continue to support TPAIT for suitable patients without delay whenever possible, when there is not an active SARS-CoV-2 infection. It is well known that as CP progressively destroys the endocrine pancreas, fewer islets can be rescued at the time of surgery, resulting in a lower islet mass for transplantation and a less likely chance of insulin independence. Vaccinations are a primary tool that has helped return many sectors of society to near normalcy and should be strongly encouraged for prospective candidates for TPAIT. It allows a comfort level to patients to reengage in their medical treatments. COVID-19 testing should be mandatory for the safety of all involved with the procedure, which is placed on hold until any detected infection is resolved. After resolution (as defined by best guidance at the time), MMTT and cardiac testing should be retaken if they had already occurred; however, except in the case of significant changes since the prior testing, TPAIT should proceed after the delay. If scores are low, but the patient otherwise remains a good candidate for TPAIT, another MMTT should be considered after a period of several months to see if there is a rebound of islet function. Because the effect of SARS-CoV-2 on human islets already under attack by ongoing severe CP is not known and the potential consequences of delays in treatment are well understood, we continue to recommend TPAIT for all suitable patients with as little delay as medically possible.

Conclusions

In light of recent research that has associated even mild cases of SARS-CoV-2 with pancreatitis [5], new onset diabetes, and demonstrated changes (at least *ex vivo*) to the islets, resulting in a less efficient stimulated glucose response [7], we thought that it was important to demonstrate in a clinical setting that prior SARS-CoV-2 infection did not necessarily disqualify patients as candidates for TPAIT.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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