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Case Report

Chronic Pancreatitis Associated With a Variant of *CFTR* Gene Treated With Total Pancreatectomy and Autologous Islet Cell Transplantation

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ABSTRACT

Background/Objective: Total pancreatectomy is performed for pain relief in chronic pancreatitis. Concomitant autologous islet cell transplantation can be performed to improve glycemic control. We report the case of a patient with chronic pancreatitis who underwent a total pancreatectomy with autologous islet cell transplantation with increasing insulin requirements and its association with cystic fibrosis transmembrane conductance regulator (CFTR)–related disorder.
Case Report: A 40-year-old woman presented with abdominal pain and had elevated levels of serum lipase. She was treated for acute pancreatitis. In the subsequent 2 years, she had 4 additional episodes of pancreatitis and eventually developed chronic abdominal pain. She underwent total pancreatectomy for pain relief with autologous intrahepatic islet cell transplantation. She experienced repeated episodes of pneumonia and underwent screening for cystic fibrosis, which showed a 7T/7T polymorphic variant at *CFTR* intron 8. The follow-up at 8 years after procedure showed increasing hemoglobin A1c levels despite increasing insulin use with multiple hospitalizations for hyperglycemia. The patient was transitioned to continuous subcutaneous insulin infusion with improvement in hemoglobin A1c levels.
Discussion: Chronic pancreatitis can be a manifestation of an undiagnosed CFTR-related disorder, which in this case was followed by total pancreatectomy. Autologous islet cell transplantation was performed with declining postprocedural glycemic control. Interval failure of the transplanted islets is present in up to two thirds of the patients but is not affected by the presence of cystic fibrosis.
Conclusion: A gradual decline in glycemic control may be expected in patients with autologous islet cell transplantation and can be improved with the use of continuous subcutaneous insulin infusion.

Introduction

Chronic pancreatitis presents with recurrent abdominal pain, nausea, vomiting, and malabsorption. Due to the constant inflammation followed by fibrosis, exocrine and endocrine insufficiencies can occur. Often, analgesic therapy provides inadequate relief, and total pancreatectomy is undertaken for pain control.[1] A complication of chronic pancreatitis is the gradual onset of diabetes mellitus (DM), which occurs from the loss of beta cell mass or after total pancreatectomy. Due to insulin deficiency, most patients require lifelong insulin therapy. A few centers perform autologous islet cell transplantation in conjunction with pancreatectomy to prevent DM, minimize insulin requirements, and improve the quality of life. We report the case of a patient with chronic pancreatitis with a polymorphic allele variant in *CFTR* who underwent total pancreatectomy with autologous islet cell transplantation (TPIAT) followed by a gradual decline in transplanted islet cells leading to insulin dependence.

Case Report

A 40-year-old woman with a history of cholecystectomy for cholelithiasis and Graves' disease presented with recurrent episodes of severe midepigastric abdominal pain. These episodes of

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DM, diabetes mellitus; TPIAT, total pancreatectomy with autologous islet cell transplantation.

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acute pain were associated with elevated levels of serum lipase (range, 303-334 U/L [normal range, 0-160 U/L] during various episodes), and a diagnosis of pancreatitis was made. Investigations including computed tomography, magnetic resonance imaging, magnetic resonance cholangiopancreatography, esophagogastroduodenoscopy, and colonoscopy did not reveal an alternative etiology for the severe episodes of abdominal pain. Diagnostic and therapeutic endoscopic retrograde cholangiopancreatographies showed a mildly dilated common bile duct, a mean sphincter of Oddi basal pressure of 200 mm Hg (normal value, <40 mm Hg), and an ectatic pancreatic duct, which was followed by dual sphincterotomy with pancreatic duct stent placement. This did not result in relief of symptoms, and the stent was subsequently removed. Secretin-enhanced magnetic resonance cholangiopancreatography showed evidence of restrictive parenchymal disease and reduced compliance of the pancreatic duct. The patient continued to experience recurrent postprandial epigastric pain radiating to the back, nausea, and vomiting.

Because of continued episodes of acute pancreatitis and subsequent development of chronic pain, the patient underwent partial pancreatectomy consisting of a partial excision of the head of the pancreas with a distal Roux-en-Y pancreaticojejunostomy, sparing the duodenum and the bile duct. The patient continued to have recurrent postprandial epigastric pain. At the age of 42 years, she underwent total pancreatectomy and proximal duodenectomy, with a resultant choledochoduodenostomy to the distal duodenum. Before surgery, she had a normal glycemic state. Autologous islet cell harvesting and transplantation were performed during the pancreatectomy procedure. She was transplanted with 293 000 islets (5344/kg), that is, 297 080 islet equivalents (5401/kg).

Immediately after surgery, she was treated with 15 units daily of insulin glargine and correctional doses of insulin aspart. Three months after TPIAT, the HbA1c level was found to be 6.4% (46 mmol/mol) and an oral glucose tolerance test showed glucose concentrations between 85 and 158 mg/dL and a fasting C-peptide level of 0.4 ng/mL (normal range, 0.5-2.0 ng/mL) with a peak value of 3.3 ng/mL. Starting at 48 years of age, she experienced repeated episodes of severe lung infections with chronic cough and mucus production. Microbial cultures grew respiratory bacteria, including *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Burkholderia cepacia* complex, requiring broad-spectrum intravenous antibiotics. Chest imaging did not show significant bronchiectasis, and spirometry showed minimal airflow obstruction.

She reported having a half-sister who had multiple episodes of pneumonia. Due to the multiple episodes of pneumonia, a history of recurrent pancreatitis, and a family history of recurrent pneumonia, screening for cystic fibrosis (CF) was performed. Sweat chloride testing was intermediate at 42 mmol/L and 43 mmol/L (normal value, <29 mmol/L). Bidirectional sequence analysis to test for sequence variations in all coding regions, intron and exon boundaries of *PRSS1*, *SPINK1*, *CTRC*, and *CFTR*, showed a 7T/7T polymorphic variant at *CFTR* intron 8. Based on the symptoms and intermediate sweat testing, she was diagnosed with a cystic fibrosis transmembrane conductance regulator (CFTR)–related disorder.

Following TPIAT, the HbA1c value continued to increase gradually with a peak value of 10% in a span of 8 years. At 50 years of age, she had multiple hospital presentations for severe (blood glucose level of 700-800 mg/dL) hyperglycemia despite adherence to a basal-bolus insulin regimen. At 51 years of age, she was transitioned to continuous subcutaneous insulin infusion therapy, which ultimately improved the glucose time-in-range to >60% (Fig.), while requiring approximately 25 total units of insulin daily, and the HbA1c value improved to 7.2%.

Highlights

- CFTR–related disorders can be evaluated for etiology of chronic pancreatitis
- TPIAT can help maintain insulin independence postoperatively
- Risk of insulin deficiency increases with time elapsed since TPIAT
- Continuous subcutaneous insulin infusion can improve glycemic control for declining islet cell function after TPIAT

Clinical Relevance

This case report highlights the growing number of patients who have undergone total pancreatectomy with autologous islet cell transplantation (TPIAT). This article helps understand the pathophysiologic abnormalities leading to pancreatogenic diabetes and the long-term outcomes of TPIAT. It also summarizes the management of such patients after procedure.

Discussion

In the present case, chronic pancreatitis developed in the patient and she underwent total pancreatectomy for pain relief. During the procedure, autologous islet cell transplantation was performed. Genetic testing conducted on account of chronic pancreatitis and multiple episodes of pneumonia led to the diagnosis of a CFTR-related disorder. Endocrine and exocrine insufficiency occurs in patients with chronic pancreatitis because the associated progressive inflammation causes permanent structural damage to the pancreatic islets with ensuing fibrosis.[2] It is possible that proinflammatory cytokine (eg, IL-1B, TNF-a, and IFN-g) release is followed by apoptosis of beta cells initiated by CD8+ T-cells. DM in chronic pancreatitis is marked by a reduction in the beta cell mass and a relative reduction in the beta cell area.[3] The prevalence of DM 25 years from the onset of chronic pancreatitis is estimated to be 83%.[4] In chronic pancreatitis, complete loss of islet cells occurs, causing glucagon deficiency, which leads to frequent hypoglycemia. Elective distal pancreatectomy in patients with chronic pancreatitis increases the risk of the development of DM. This could be due to the heterogeneous clustering of the islets of Langerhans in the tail of the pancreas.[5] The patient in this case may not have had significant beta cell damage despite chronic pancreatitis, as supported by no insulin requirement before the pancreatectomy, but DM developed in her once resection of the pancreas was completed. However, patients in whom pancreatogenic diabetes develops are recommended to test their fasting blood glucose and HbA1c levels annually.[6] Any abnormalities may be evaluated with a 75-g oral glucose tolerance test.

Some patients with prepancreatectomy normoglycemia may be candidates for autologous islet cell transplantation. TPIAT is a strategy to preserve beta cell mass to prevent the occurrence of DM, while aiming to provide pain relief to patients with chronic pancreatitis. Patients who have had previous pancreatic surgeries or drainage procedures tend to have lower yield of islet cells, yet this procedure was completed in the patient in the present case despite distal pancreaticojejunostomy being performed.[7] The use of insulin therapy in the immediate postoperative period helps provide rest to the transplanted islet cells and avoid the stress of glucotoxicity, until they are well vascularized and oxygenated after their implantation in the liver. Exposure of such islets to hyperglycemia can induce beta cell apoptosis.

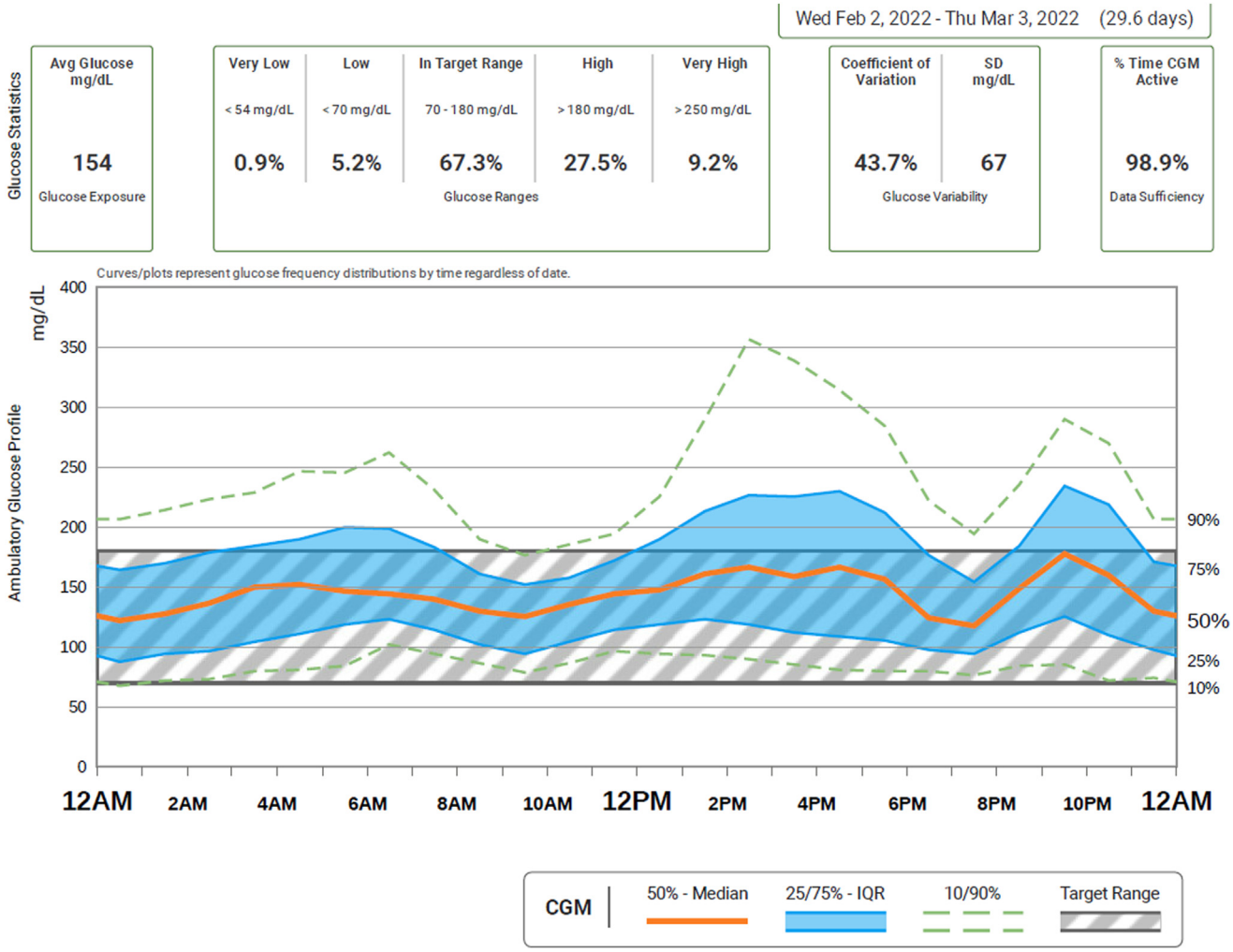

Fig. Continuous glucose monitor report showing the ambulatory glucose profile for 30 days of monitoring with time-in-range (70-180 mg/dL) at 67.3%, an average glucose level of 154 mg/dL. There continues to be 36.7% hyperglycemia which occurs postprandially and 6.1% night time hypoglycemia.

A single-center case series of 400 patients showed that 33% of patients who underwent TPIAT were found to be insulin independent at 10-years follow-up.[8] Data from the Collaborative Islet Transplant registry showed that between 1999 and 2020, 801 adult patients underwent TPIAT, whereas 113 patients underwent partial or complete pancreatectomy with autologous islet cell transplantation for chronic pancreatitis.[9] At 5 years after procedure, insulin independence was more likely in younger patients irrespective of the etiology of pancreatitis (50% of patients aged 18-35 years vs 40% of patients aged >35 years). Follow-up visits of such patients may include an assessment of serum C-peptide concentrations during either an oral glucose tolerance test or a mixed nutrient meal testing.[6]

The presence of different alleles within the poly-T tract sequences located in intron 8 of *CFTR* may lead to a decrease in the quantity of fully formed CFTR messenger RNA and levels of functional CFTR protein. CF and CFTR-related disorders are associated with chronic pancreatitis. Insulin independence and quality of life after treatment with TPIAT were similar in a study of patients without or with CF (or carriers).[10] However, patients with CF undergoing TPIAT tend to be younger due to early manifestations of the disease and might have better islet cell activity after transplantation for the same reason.

The incretin effect (ie, higher insulin response to oral than intravenous glucose) was found to be significantly reduced in patients with chronic pancreatitis and DM not requiring insulin.[11] In the same study, the insulinotropic effects of glucose-dependent insulinotropic polypeptide were lost compared with patients with chronic pancreatitis without DM but were regained after 4 weeks of strict glycemic control with insulin. Inadequate digestion of nutrients in the proximal small intestine can also diminish incretin-induced insulin release. Use of incretin receptor agonists may be a helpful strategy and remains to be evaluated in patients with chronic pancreatitis and hyperglycemia.

Our patient maintained normoglycemia after TPIAT but had declining glycemic control, as shown by a gradual increase in the HbA1c value. Despite initiation of multiple daily insulin injections, attaining good glycemic control remained a challenge and required the use of continuous subcutaneous insulin infusion. This underscores the need for patients undergoing TPIAT to be monitored frequently for islet cell failure and response to insulin therapy, possibly using a continuous glucose monitor, to better manage DM. The use of adjuvant glucose-lowering agents, such as glucagon-like peptide-1 receptor agonist, metformin, or pioglitazone, can be further studied both for efficacy and safety in this population.

Disclosure

The authors have no multiplicity of interest to disclose.

Acknowledgment

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