Islet autotransplantation after left pancreatectomy for non-enucleable insulinoma

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Abstract
Insulinoma is a rare, almost always benign endocrine tumor of the pancreas, clinically characterized by hyperinsulinemic, hypoglycemic episodes. Surgical excision is the therapy of choice, which may lead to postpancreatectomy diabetes mellitus in the case of extensive pancreatic resection. We present the cases and the metabolic follow up of two patients, 81 and 73 years old, with insulinoma localized close to the main duct in the pancreatic neck. Both patients underwent an 80% left pancreatectomy, avoiding a pancreatico-enteric anastomosis. In order to prevent postpancreatectomy diabetes, the islets from the tumor-free part of the resected pancreas were isolated and injected via a right colic vein into the portal system. After a follow up of 6 and 3 years respectively, both patients remained insulin-independent without any dietary restrictions. Fasting and glucagon-stimulated C-peptide-levels and glycylated hemoglobin remained within normal range. There were no signs of recurrent insulinoma. Liver biopsy performed in one patient at 1 year after autotransplantation, showed intact, insulin-producing islets within the […]

Reference

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Islet Autotransplantation After Left Pancreatectomy for Non-Enucleable Insulinoma

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Insulinoma is a rare, almost always benign endocrine tumor of the pancreas, clinically characterized by hyperinsulinemic, hypoglycemic episodes. Surgical excision is the therapy of choice, which may lead to postpancreatectomy diabetes mellitus in the case of extensive pancreatic resection.

We present the cases and the metabolic follow up of two patients, 81 and 73 years old, with insulinoma localized close to the main duct in the pancreatic neck. Both patients underwent an 80% left pancreatectomy, avoiding a pancreatico-enteric anastomosis. In order to prevent postpancreatectomy diabetes, the islets from the tumor-free part of the resected pancreas were isolated and injected via a right colic vein into the portal system.

After a follow up of 6 and 3 years respectively, both patients remained insulin-independent without any dietary restrictions. Fasting and glucagon-stimulated C-peptide-levels and glycosylated hemoglobin remained within normal range. There were no signs of recurrent insulinoma. Liver biopsy performed in one patient at 1 year after autotransplantation, showed intact, insulin-producing islets within the portal spaces.

In conclusion, autologous islet transplantation can preserve the insulin secretory reserve after extended left pancreatectomy for the treatment of benign tumors in the pancreatic neck.

Key words: Insulinoma, islet transplantation, pancreatectomy

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Both patients were normocalcemic and had no familial history of hyperparathyroidism, neuro-endocrine tumor of the pancreas or pituitary tumor, rendering the diagnosis of MEN–1 syndrome very unlikely.

Treatment

As both patients were otherwise in good general health, surgical therapy was proposed. In spite of the potential oncological risk, the patients agreed to an eventual islet autotransplantation in case of extensive pancreatectomy. At laparotomy, the pancreas was exposed and mobilized extensively. Both tumors were shown to be localized close to the pancreatic duct by intraoperative ultrasound (Figure 1B). A left pancreatic resection (80% of the pancreas) was performed in both cases, sectioning the pancreas to the right side of the superior mesenteric vein. This option was chosen in these elderly patients in order to avoid the risk of pancreatic fistula after simple enucleation, or of pancreatico-jejunal anastomotic breakdown after a Whipple procedure. The body and tail of the pancreas was prepared by preserving the vascular supply. After clamping the splenic arteries and veins, the tumor-bearing left pancreas was resected. The warm ischemia time was shorter than 5 min. The resected pancreas was freed from the tumor with a 3-cm safety margin and was transported in University of Wisconsin preservation solution at 4 °C to our islet isolation laboratory. Islet isolation was performed by a modified automated method (7,12). Briefly, after cannulation of the pancreatic duct, the pancreata (50 g and 53 g) were distended with 250 mL of 2% collagenase solution (collagenase type P, Boehringer Mannheim, Germany) and incubated with gentle shaking in the digestion chamber at 37 °C. Samples after 14 min of digestion showed increasing amounts of free and intact islets with an unusually high ratio of islets to exocrine tissue in the first case. The second pancreas had a normal ratio of islet to exocrine tissue. The digestion was stopped after 30 and 20 min, respectively, by 7 L of 4 °C Hank’s solution. Finally, 7 mL of unpurified tissue suspension containing 415 000 islets [551 000 islet equivalents (IEQ), calculated by normalizing the islets to a standard islet of 150 μm diameter as previously described in detail (13)] for the first patient and 11 mL of tissue containing 159 000 islets (130 000 IEQ) for the second patient were obtained. Histology of the insulinoma on frozen sections showed no signs of malignancy (low mitotic activity, no tumor necrosis, no vascular or perineural invasion) and the margins of resection were free of tumor. This assessment allowed us to proceed to islet autotransplantation in both patients. Two right colic veins were prepared and an intravenous canula was inserted in each of the colic veins. After administration of 5000 U of heparin, the islet preparations were infused under control of the portal pressure measured continuously by a pressure transducer.

Figure 1: (A) Abdominal computerized tomography with intravenous contrast enhancement: 1.5-cm hyperdense nodule in the neck of the pancreas (→). (B) Intraoperative ultrasonography in Patient 2 revealing the proximity to the main pancreatic duct of the insulinoma (→).
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(Abbott, Sligo, Ireland) connected to a catheter in the second right colic vein. During the 15 min of transplantation, the portal pressure rose in the first patient to 24 mmHg and after 10 min returned to the original value of 6 mmHg, while in the second patient the pressure rose from 8 to 20 mmHg and remained at 18 mmHg.

Follow up, histological and metabolic results
At the end of the procedure, a surgical liver biopsy was performed showing, predominantly, fragments of exocrine tissue and, to a smaller extent, insulin-containing islets within small portal branches (Figure 2).

The postoperative course was simple and without any complications in both cases. Both patients were discharged from hospital 3 weeks after surgery.

As for glucose metabolism, the patients received protective, intravenous insulin-therapy during the first 2 weeks after surgery in order to avoid exhaustion of islets (14).

The first patient was able to stop insulin therapy 2 weeks after surgery. One month after the left pancreatectomy and islet autotransplantation, the first patient had a normal oral glucose tolerance test (OGTT). From the sixth postoperative month, the first patient developed impaired glucose-tolerance on the OGTT according to the criteria of the U.S. National Diabetes Data Group (Figure 3). Nevertheless, the patient has presented normal glucose profiles without dietary restrictions for 6 years, and currently has a glycosylated hemoglobin of 5.7% (normal range 4–6.4%). Fasting and glucagon stimulated C-peptide levels have remained in the normal range (Figure 4A).

The second patient required exogenous insulin-therapy for a period of 3 months, but insulin-requirements decreased gradually and the patient has not required exogenous insulin since 4 months after the procedure. Thereafter, oral glucose tolerance was slightly impaired, however, fasting and glucagon stimulated C-peptide levels were in the normal range. HbA1c remained normal without exogenous insulin (Figure 4B).

To date, both patients remain free of hypoglycemic symptoms and none of the patients shows any evidence for recurrent insulinoma on regularly performed abdominal ultrasounds. The patients received pancreatic enzyme substitution only during the first postoperative months and never present signs of pancreatic exocrine insufficiency. Patient 2 has had rising basal and decreasing stimulated C-peptide over time, but remains free of exogenous insulin therapy and maintains HbA1c within normal range (Figure 4B).

One year after initial surgery the first patient underwent an incisional hernia repair. With the agreement of the patient, a surgical liver biopsy was performed. Pancreatic islets were present in small- to medium-sized vessels within the portal spaces. They were well preserved and free of necrosis even in the central parts of the grafts. The grafted cell groups consisted of endocrine pancreas only; no exocrine tissue was detected. All cell groups adhered intimately to the endothelial cells of the portal vessel. Anti-CD-34 staining revealed the presence of microvascular-endothelial cells within the grafted islets (Figure 5).
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Figure 3: Oral glucose-tolerance tests after islet autotransplantation in Patient 1. The patient presented with normal glucose tolerance for the first 6 months, and impaired glucose-tolerance appeared after 1 year with no significant deterioration over the next 6 years.

Discussion

To our knowledge these are the first reported cases of islet autotransplantation after extensive left pancreatectomy for insulinoma. The aim of this therapeutic approach was to preserve the good quality of life of these 81- and 73-year-old active patients.

Surgical options in these two cases included enucleation of the tumor, with the risk of developing a pancreatic fistula in view of their closeness to the pancreatic duct (3,15), or Whipple pancreatoduodenectomy, with the risk of anastomotic breakdown associated with performance of a pancreatico-jejunostomy on a nonfibrotic pancreas (16). Extended left pancreatectomy avoided these risks. The addition of autologous islet transplantation allowed the preservation of an insulin secretory reserve.

In the first case, we obtained a high islet yield in spite of the low amount of tissue volume after digestion. The pancreatic tissue section surrounding the resected tumor of this patient did not show evidence for multiple insulinomas or diffuse islet hyperplasia. Thus, the high islet yield may be the result of age-related involution of the exocrine tissue rather than of islet hyperplasia.

The second patient had a lower islet yield, and insulin independence was only obtained after a period of 3 months. This may reflect a marginal islet mass transplanted requiring a longer period for recovery than in the first patient receiving a relatively high islet mass. It is remarkable that with only 130 000 islet equivalents transplanted the second patient achieved insulin-independence and has normal HbA1C 3 years post-transplant. Over time Patient 2 increased basal C-peptide secretion, but presented with a decrease in glucagon-stimulated C-peptide response. Although insulin-independence and normal HbA1C are preserved, this finding is likely conform with an exhaustion of a marginal islet mass, similar to observations in type II diabetes or experimental marginal islet mass models (17).

In these two patients, the remnant of the pancreatic head is likely to continue to produce insulin and the impact of islet-autotransplantation to the total endogenous insulin secretion and metabolic control is difficult to evaluate. However, after an 80% left pancreatectomy, the patients would have been expected to present a low glucagon-stimulated acute C-peptide response (18), and the risk of developing diabetes was high. Particularly, the first patient presented an almost normal glucagon-stimulated acute
C-peptide response, indicating preserved insulin secretory reserve. Measuring pre- and posthepatic C-peptide levels can assess the relative contribution of transplanted and native islets to the total endogenous insulin secretion (19). However, this invasive procedure was not performed in these two elderly patients.

The immunohistology of the liver biopsy performed in the first patient 1 year after the islet autotransplantation gave additional evidence that the autologous islet transplantation had increased the total islet mass.

We considered that the risk of tumor dissemination by the procedure was low because of the presence of a single tumor, intraoperative frozen sections assuring tumor-free resection margins, as well as no invasion of surrounding tissue.

In conclusion, our cases show that insulin secretory reserve can be preserved after extensive pancreatic resection for benign tumors associated with islet autotransplantation. Autologous islet transplantation may be considered more often for patients with benign tumors necessitating extensive pancreatic resection.

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