Ectopic Pancreas and the Islet Cell Dysmaturational Syndrome*

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ABSTRACT

Two cases of ectopic pancreas are described in the setting of the islet cell dysmaturational syndrome. Microscopic and immunostaining studies revealed both lesions to be composed of primarily (80 percent to 90 percent) islet tissue with nuclear hyperchromasia and probable depletion of immunoreactive insulin in one case. Persistent hyperinsulinemic hypoglycemia required a second laparotomy with resection of ectopic pancreas in one case. Awareness of the phenomenon led to successful identification and resection of ectopic islet tissue on first surgery in a subsequent case. Ectopic pancreas is a relatively common developmental pancreatic anomaly, and knowledge of its potential contribution to life-threatening hypoglycemia may obviate the need for multiple surgeries in some cases of islet cell dysmaturational syndrome.

Introduction

Islet cell dysmaturational syndrome is a general designation for the spectrum of histopathologic changes in the pancreas that are associated with hyperinsulinemic hypoglycemia and its presentation during infancy.2 The usual pathologic finding in this setting11 has been the presence of islet cell lesions limited to the pancreas proper. Two cases are reported of ectopic pancreas in infants with hyperinsulinemic hypoglycemia and associated intrapancreatic islet cell lesions. The origin of these ectopic lesions and their possible functional activity have important therapeutic implications.

Materials and Methods

Patients

Case 1: This white female infant was the 36-week gestational age, 3.82 kilogram product of a 28-year-old Gravida 1, Para 1 O-positive mother whose pregnancy was uncomplicated, with vaginal delivery. Initial dextrose stick at 30 minutes of life was less than...
25 mg per dL. Despite oral and intravenous boluses of glucose, the infant remained persistently hypoglycemic. An initial insulin level was measured at 142.8 U per ml with a glucose level of 13.

Serum glucose control was difficult, necessitating frequent increases in dextrose load. Diazoxide was utilized without any effect. A persistent hypoglycemia remained in the face of hypertonic glucose infusions and elevated insulin levels. On the 18th day of life, a subtotal (90 to 95 percent) pancreatectomy was performed.

After surgery, persistent hypoglycemia necessitated institution of total parenteral nutrition and placement on a somatostatin protocol to increase serum glucose. Because of unstable glucose levels, the patient was returned to the operating room three months later for exploratory laparotomy and a total pancreatectomy.

The patient has done well postoperatively with gradual weaning from total parenteral nutrition and institution of oral feedings which she has tolerated well. Three years after surgeries, she has been treated with pancreatic exocrine enzyme replacement, nocturnal feedings through a gastrostomy tube, and intermittent cornstarch feedings. Fasting glucose levels are in the range of 40 to 80 mg per dL, and no insulin replacement has been needed.

Case 2: This 6-week-old white male infant was initially evaluated for hard stools and rectal bleeding; the latter was subsequently found to be due to a rectal fissure. In the hospital, blood glucoses were found to range between 19 and 40 mg per dL. Insulin levels ranged from 13.4 to 18.9 U per ml with fasting blood sugars of 25 to 27 mg per dL. The hypoglycemia was refractory to medical therapies, including intravenous glucose and somatostatin analogue (octreotide acetate). The patient was subsequently taken to surgery for 95 percent pancreatectomy 35 days after admission.

The patient has done well postoperatively. With three months of follow-up, the patient’s fasting blood sugars are in the 200 range with no insulin replacement currently required.

Tissue Studies

Pancreatic and extrapancreatic tissues were formalin-fixed and paraffin-embedded for histologic examination in both cases. They were totally submitted for hematoxylin-eosin staining in both cases at initial surgery. In case 1, subsequent resection specimens were also submitted in their entirety for histologic examination.

Representative paraffin tissue sections were processed for immunoperoxidase staining using the avidin-biotin-peroxidase technique.\(^5\) Primary antisera included rabbit antihuman neuron-specific enolase, insulin, glucagon and somatostatin.* Results were evaluated qualitatively by the absence or presence and localization of the staining to specific cell types.

Results

Case 1: Subtotal pancreatectomy (90 percent to 95 percent estimated) included a portion of uncinate process (8 mm × 4 mm × 4 mm) and pancreatic body and tail (4 cm × 8 mm × 8 mm). The total weight of submitted tissues was 1.8 gms.

Histologic and immunostaining studies of submitted tissues revealed segmental adenomatosis of islet cell tissue involving the proximal half of the body of the pancreas. Adenomatosis\(^3,4\) was defined as nodular hyperplasia of islet cell tissue occupying greater than 40 percent of the cross-sectional area of the pancreas in any given tissue section and displacing exocrine elements. In areas of the body of the pancreas, these islet cell nodules occupied up to 75 percent of the tissue cross-sectional areas. Immunostaining confirmed the presence of a normal spatial relationship\(^4\) of endocrine cells with peripheral alpha and delta cells and central beta cells. Minimal nuclear hyperchromasia was present.

Subsequent total (completion) pancreatectomy performed three months later included a remnant of pancreatic head measuring 3 cm × 2 cm × 1 cm. A separate nodular portion of tissue was identified adjacent to the portal vein and common bile duct measuring 1.5 cm × 5 mm × 5 mm, and thought to represent fleshy portal lymph nodes (figures 1A and B).

Examination of the pancreatic remnant microscopically revealed residual

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adenomatosis (at least four separate foci), again occupying up to 75 percent of the cross-sectional area of the pancreatic sections.

The portal vein nodule was composed of 50 percent benign lymph nodes and 50 percent ectopic pancreatic tissue (figure 1A). The latter tissue was composed of 80 percent islet tissue (figure 1B) with exocrine tissue seen only focally.

Immunostaining of the portal nodular islet lesion revealed the normal spatial
relationship of central beta cell mass and peripheral alpha and delta cells.

Case 2: Given the experiences with Case 1, the surgeon in this case made a thorough search for ectopic pancreatic tissue during a 95 percent pancreatectomy. A four mm nodule removed around the gallbladder and common bile duct was identified microscopically as a group of benign lymph nodes on frozen section. Another 7 mm × 10 mm nodule (figure 2A) was identified adjacent and superior to the neck of the pancreas with a separate blood supply from the superior mesenteric artery and vein, and lying anterior to the portal vein. This lesion was thought to be distinctly different in appearance from lymph nodes or pancreas, and frozen section was again obtained.

Frozen section and subsequent permanent section of the 7 mm × 10 mm nodule revealed primarily (90 percent) islet tissue with extensive nuclear hyperchromasia (figure 2B) and a few associated ductal/acinar elements (10 percent).

The 95 percent pancreatectomy itself (9.5 cm × 9 mm × 7 mm) showed only so-called nesidioblastosis1 with scattered small packets of two to six beta cells (insulin positive) scattered around small ducts or acini without more confluent lesions identified (figure 3A). No nuclear hyperchromasia was identified.

Immunostaining did confirm the normal spatial relationship of central beta cell mass and peripheral alpha and delta cells in islets of the pancreas proper. However, the extrinsic pancreatic nodule found at the neck of the gland showed depletion of immunoreactive insulin (figure 3B) with intact staining of alpha and delta cells.

Discussion

Islet cell dysmaturational syndrome2 is a term designated to include the spectrum of histopathologic lesions seen with life-threatening hyperinsulinemic hypoglycemia in infancy. The sine qua non of diagnosis in this idiopathic syndrome is not the underlying pathologic substrate, but rather inappropriately elevated plasma insulins (usually ≥10 U per ml) in the presence of simultaneously low blood glucose levels (≤50 mg per dL)2,10,11 refractory to medical therapies. The diagnostic algorithm followed to exclude other causes of hypoglycemia in arriving at this diagnosis is well-established.11 Both of the cases presented in this study meet the criteria for the islet cell dysmaturational syndrome.

The recommended therapy for the islet cell dysmaturational syndrome is a near total (90 to 95 percent) pancreatectomy in most case series2,6,8,9,10 unless a discrete adenoma can be identified and resected. The pancreas may show a variety of other pathologic lesions in this setting which are not grossly discernible including nesidioblastosis or islet cell adenomatosis as seen in our two cases. A plethora of other synonyms7 for intra-pancreatic islet cell proliferations in this setting is confusing and does not offer further insight into the management of the lesions. Whatever the terminology used, the irregular distribution of the islet lesions in the pancreas microscopically obviates the use of frozen section2,11 as a guide to resection.

Unfortunately, even with 95 percent pancreatectomy, a few patients continue to have life-threatening hypoglycemia.6 In some cases this may be ascribed to residual adenomatous tissue left in the head of the pancreatic remnant.11 However, at least one case has been discussed anecdotally in the literature of ectopic pancreatic tissue grossly thought to be lymph node from the aortic side of the pancreas, which was associated with erratic blood glucose levels on manipulation.6 Frozen section revealed ectopic pancreas with the microscopic appearance of
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Figure 2A. Ectopic pancreas in Case 2 adjacent to the neck of the pancreas. The lesion is a discrete 7 mm × 10 mm nodule (inset, upper right) composed almost entirely of islet tissue. (H&E stain, 15 × magnification). B. The lesional tissue above shows striking nuclear hyperchromasia of islet cells with rare associated ducts and acinar elements (the latter not pictured). (H&E stain, 350 × magnification).

nesidioblastoma (islet and admixed ductal tissue), this case has been hailed and discussed as a singular event.

The cases presented in this study suggest that ectopic pancreas should be carefully searched for in the islet cell dysmaturational syndrome both grossly and microscopically, via frozen section. In lieu of this approach, a liberal sampling of peripancreatic nodules for permanent section may also serve to pick up incidental pancreatic ectopias. While
Figure 3A. The pancreas in Case 2 shows nesidioblastosis (scattered packets of two to six beta cells—arrows—with or without ducts) (Hematoxylin and anti-insulin immunostain, 350 × magnification). B. The ectopic islet tissue of Case 2 shows negative immunostaining for insulin consistent with depletion of immunoreactive insulin as compared with pancreas proper in figure 3A. (Hematoxylin and anti-insulin immunostain, 350 × magnification).
thorough gross evaluation for pancreatic ectopias is advocated\(^9\) prior to subtotal pancreatic resection, large reviews\(^{10}\) of the literature (71 total cases) have shown no identification of ectopic pancreas using this approach. However, ectopic pancreas is the most common form of pancreatic maldevelopment (2); it affects one percent to two percent of the population with over 50 percent of cases identified in the region of the stomach or duodenum (often the second part), and 60 to 70 percent of cases containing islet tissue. In our cases, knowledge of this phenomenon discerned from the second laparotomy in the first patient, allowed for effective frozen section identification of ectopic pancreas on first surgery in the subsequent case.

The functional significance of these pancreatic ectopias found with the islet cell dysmaturational syndrome could be questioned; however, the high percentage of islet tissue in our cases (80 to 90 percent), the presence of nuclear pleomorphism, and the depletion of immunoreactive insulin are all supportive correlates with hypoglycemia.\(^{3,5}\)

The present study does not offer new insights into the relationship of intrinsic pancreatic pathology to the islet cell dysmaturational syndrome. It does, however, emphasize the need for a careful search for ectopic pancreas by intraoperative gross and subsequent microscopic inspection of tissues to help obviate the need for recurrent surgery. By this prospective approach, one may better define the contribution of ectopic pancreas to the islet cell dysmaturational syndrome.

Acknowledgments

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References