Noninsulinoma Pancreatogenous Hypoglycemia Syndrome: A Rare Case of Adult-onset Nesidioblastosis

Motoyoshi TSUJINO, Toru SUGIYAMA, Kenji NISHIDA, Yukari TAKADA*, Kijuro TAKANISHI**, Mitugu ISHIZAWA*** and Yukio HIRATA****

Abstract

The most common cause of hyperinsulinemic hypoglycemia in adults is insulinoma. Nesidioblastosis is a rare, but well-recognized disorder of persistent hyperinsulinemic hypoglycemia in infancy, but adult-onset nesidioblastosis associated with hyperinsulinemic hypoglycemia, termed noninsulinoma pancreatogenous hypoglycemic syndrome (NIPHS), has been reported. Here, we describe an extremely rare case of NIPHS in an elderly man. A 78-year-old man was admitted to our hospital due to hypoglycemic coma. During the previous 3 months, he noticed excessive sweating at midafternoon. His low fasting plasma glucose level (27 mg/dl) and high immunoreactive insulin level (11.1 TypeOneU/mL) were consistent with the possible presence of insulinoma. Localizing studies including computed tomography of the abdomen and celiac arteriography were negative, but selective arterial calcium infusion (SACI) test suggested the presence of insulinoma in the body and tail of the pancreas. Surgical exploration by palpation and intraoperative ultrasonography failed to detect any mass in the pancreas, and 60% distal pancreatectomy was performed. Postoperatively, his hypoglycemic episodes completely disappeared. Histological examination of the resected pancreas revealed diffuse islet cell hyperplasia consistent with a pathological diagnosis of nesidioblastosis. Thus, our case is a very rare case of NIPHS in an elderly man. A selective arterial calcium injection (SACI) test was proven to be a useful diagnostic tool for localization of the pancreatic lesion.

Introduction

Nesidioblastosis is a rare disorder of infancy characterized by persistent hypoglycemia induced by insulin hypersecretion from diffuse β-cell hyperplasia in the pancreas (1). In the hereditary form of hyperinsulinemic hypoglycemia of infancy, mutations in β-cell sulfonylurea receptor (SUR1) gene or inwardly rectifying potassium channel (Kir6.2) gene, have been identified in some cases (2, 3). In adults however, the most common cause of hyperinsulinemic hypoglycemia is insulinoma (4). Neuroglycopenic episodes in the food-deprived state are a typical clinical feature of patients with insulinoma. Selective arterial calcium injection (SACI) is currently recognized as a diagnostic localization test for insulinoma (5). Nesidioblastosis in adults is extremely rare, mostly diagnosed during adolescent to midlife period (6). The clinical characteristics of adult-onset nesidioblastosis are represented by postprandial hyperinsulinemic hypoglycemia, negative 72-hour fasts, negative preoperative localization studies for insulinoma, but positive SACI tests (6, 7), which is currently recognized as a noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS). We report herein a very rare case of an elderly man with NIPHS who had postprandial hypoglycemia with negative imaging studies for insulinoma but positive SACI test, was found to have nesidioblastosis after partial pancreatectomy.

Case Report

A 78-year-old man was brought to the emergency room of Tokyo Metropolitan Fuchu Hospital because of impaired consciousness five hours after eating lunch. He was found to have low plasma glucose (27 mg/dl), and recovered from unconsciousness after intravenous administration of 50% glucose. In the previous 3 months, he had noticed a discomfort feeling with excessive sweating during midafternoon. He had...
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partial gastrectomy (Billroth I) due to gastric cancer nine years previously, although he did not complain of post-prandial discomfort feeling after surgery. Physical examination revealed no abnormal findings and normal vital signs.

Endocrine examination excluded hypopituitarism and adrenal insufficiency as a cause of his hypoglycemia, and anti-insulin antibody was negative. During hospitalization, he had profound hypoglycemia (20–41 mg/dl), which necessitated continuous intravenous infusion of glucose (16 g/h). Blood sampling during hypoglycemic episodes revealed inappropriate high immunoreactive insulin (IRI) levels (11.1–6.4 μU/ml) in the presence of low plasma glucose levels (38–41 mg/ml), respectively (Fajans’ index: 0.29–0.16). Plasma C-peptide was relatively high (5.4 ng/ml) at the lowest plasma glucose (38 mg/ml). Oral glucose tolerance testing (OGTT) was performed under the continuous intravenous infusion of glucose (16 g/h); a remarkable increment of IRI, with a peak value (137.2 μU/ml) after 30 minutes, accompanied by a gradual decrement of plasma glucose, reaching a trough value (26 mg/dl) after 120 minutes (Fig. 1A). Neither dynamic CT scanning nor dynamic MRI revealed any mass lesions in the pancreas.

To exclude the possibility of an occult insulinoma, selective arterial calcium injection (SACI) test was performed for its localization in the pancreas (5). After injection of calcium gluconate (0.05 mg/kg body weight) into the splenic, superior mesenteric, and gastroduodenal arteries, blood samples were collected from the right hepatic vein every 30 seconds for 120 seconds; an increment in plasma IRI levels greater than 2-fold over the prestimulation levels was considered to be positive for the localization of insulinoma.

SACI into the splenic distribution caused about 13-fold (IRI) and 5-fold (C-peptide) increments. In contrast, no significant increments in IRI or C-peptide were induced after SACI into the gastroduodenal or superior mesenteric arteries, respectively (Fig. 2).

Under the presumptive diagnosis of insulinoma localized in the body and/or tail of the pancreas from the results of SACI test, surgical exploration was performed. Careful palpation and intraoperative ultrasonography of the pancreas failed to detect any mass lesions. Finally, a distal 60% pancreatectomy was performed. The resected body and tail of the pancreas grossly appeared normal. Serial section of the specimen at the 5 mm-interval revealed uniformly normal parenchyma without any evidence of tumor.

Postoperative course was uneventful, and the patient started to take regular diet 10 days after surgery. His plasma glucose levels remained between 82–185 mg/dl without glucose infusion. OGTT performed 3 weeks after surgery showed a normal IRI response (56.2 μU/ml at 30 minutes) without a significant drop in the glucose level (112 mg/dl at 120 minutes) (Fig. 1B). The patient no longer experienced hypoglycemic episodes thereafter. He is currently free from either hypoglycemia or hyperglycemia.

Histopathological and immunohistochemical study of the resected pancreatic tissue revealed that dysplastic islets were randomly scattered which increased in size and number (Fig. 3A). The contour and size of the islets were markedly variable; some islets were budding from the pancreatic duct epithelium, so-called “ductuloinsular complexes” (Fig. 3B). These findings were consistent with a pathological diagnosis of nesidioblastosis (1). Immunohistochemical study was performed by streptavidin-peroxidase complex method using antibodies against insulin, glucagon, and somatostatin (final dilution 1 : 500). Immunohistochemical analysis revealed an increased number of insulin-secreting β-cells (Fig. 4A), but a decreased number of glucagon-secreting α-cells (Fig. 4B) and somatostatin-secreting δ-cells (Fig. 4C).
Nesidioblastosis is a rare, but well-recognized disease in persistent hyperinsulinemic hypoglycemia of infancy (PHHI). Mutations of SUR1 and Kir6.2 genes encoding the subunits of the pancreatic ATP-sensitive potassium channel responsible for glucose-induced insulin secretion, have been reported in some hereditary form of PHHI (2, 3). However, adult-onset nesidioblastosis associated with hyperinsulinemic hypoglycemia, currently recognized as NIPHS (6, 7), is a very rare entity, representing only 0.5–5% of cases of organic hyperinsulinemia (8); since the first reported series of adult-onset nesidioblastosis by Harness et al in 1981 (9), only 71 cases have been reported to date.

Discussion

Nesidioblastosis is a rare, but well-recognized disease in persistent hyperinsulinemic hypoglycemia of infancy (PHHI). Mutations of SUR1 and Kir6.2 genes encoding the subunits of the pancreatic ATP-sensitive potassium channel responsible for glucose-induced insulin secretion, have been reported in some hereditary form of PHHI (2, 3). However, adult-onset nesidioblastosis associated with hyperinsulinemic hypoglycemia, currently recognized as NIPHS (6, 7), is a very rare entity, representing only 0.5–5% of cases of organic hyperinsulinemia (8); since the first reported series of adult-onset nesidioblastosis by Harness et al in 1981 (9), only 71 cases have been reported to date.

Since the SACI test is recommended as a reliable diagnostic tool for the localization of insulinoma (5), the positive responses following SACI into the splenic artery in the present case, strongly suggested the presence of insulinoma in the tail and/or body of the pancreas. However, insulinoma was not detected during surgical exploration, thus distal 60% pancreatectomy was chosen based on the results of SACI test; the morphological feature of the resected pancreas was consistent with the diagnosis of nesidioblastosis. This is different from the surgical management of neonates with diffuse nesidioblastosis requiring subtotal (95%) pancreatectomy (10).

The present patient had frequent hypoglycemic episodes mostly in the midafternoon, but not in the morning fast. It
should be noted our patient had partial gastrectomy, although postprandial hypoglycemia following gastrectomy usually occurs 1.5 to 3 hours after food digestion (11). However, gastrectomy-related postprandial hypoglycemia is sometimes severe enough to cause loss of consciousness as a neuroglycopenic symptom (12). Thus the coexistence of a past history of gastrectomy in the present case may have partly aggravated the postprandial hyperinsulinemic hypoglycemia.

Some argue against the contribution of nesidioblastosis for the development of hypoglycemia in adults (13, 14). Nevertheless, the postoperative improvement of hyperinsulinemic hypoglycemia after OGTT as well as the disappearance of hypoglycemic episodes in the present case strongly supports the pivotal contribution of nesidioblastosis in the pathogenesis of hypoglycemia.

Recently, Service et al first reported a novel syndrome of five cases (6) and an additional five cases (7) with postprandial hyperinsulinemic hypoglycemia in adults, and termed it NIPHS. The criteria for the diagnosis of NIPHS include: 1) postprandial neuroglycopenia, 2) negative 72-h fasts, 3) negative perioperative imaging studies for insulinoma, 4) positive SACI test, and 5) the presence of islet hypertrophy and/or nesidioblastosis (7). Despite the lack of 72-h fasts due to the continuous glucose infusion for the sustained hypoglycemia, the present case well fits the criteria (4 out of 5) for the diagnosis of NIPHS. It is noteworthy that none of the original five cases reported by Mayo Clinic group had mutations in either SUR1 or Kir6.2 genes (6). Although genetic analysis of either SUR1 or Kir6.2 genes was not performed in our case, the clinical features of our case are quite similar to those of ten cases of NIPHS as originally reported by the Mayo Clinic group (6, 7).

There have been only 8 elderly cases including ours with NIPHS thus far reported in the literature (6, 15–18) (Table 1). Except for two cases medically treated with either octreotide or diazoxide, 6 cases were successfully free of hypoglycemic symptoms after partial pancreatectomy as was our case. Thus surgical treatment with pancreatectomy is the recommended therapeutic method even in even elderly patients with NIPHS. Although the extent of pancreatectomy remains open to discussion, SACI test could be a useful diagnostic tool not only for localization of the pancreatic lesion, but also for the decision making as to the portion and the extent of pancreatectomy. However, it is necessary to continue

Figure 4. Immunohistochemistry of the resected pancreas. Immunostaining for (A) insulin, (B) glucagon, and (C) somatostatin, respectively (×400).
a thorough and long-term follow-up for its possible recurrence.

References


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