Nesidioblastosis in an Adult with Hyperinsulinemic Hypoglycemia

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Abstract. A 50-year-old Korean man with repeated episodes of temporary loss of consciousness was diagnosed as having hyperinsulinemic hypoglycemia. Under the tentative diagnosis of insulinoma, localization procedures were carried out but no tumor was found. By percutaneous transhepatic portal venous sampling, no definite gradient in insulin concentration was found. During exploratory laparotomy no tumor was palpable in the pancreas, and intraoperative ultrasonography showed low echogenicity in the pancreatic head. Whipple's operation was performed and 70% of the proximal pancreas was removed. Histomorphometric examination of the resected specimen revealed graded hyperplasia of the islet cells. The most profuse hyperplasia was noted in the head with progressive decrease in the degree of hyperplasia to the body and tail. The patient remains euglycemic and tolerates 24 h fasting without any medication until 15 months after operation.

Key words: Nesidioblastosis, Adult, Hypoglycemia, Histomorphometry

Clinical Findings

In May 1994, a 50-year-old Korean farmer was admitted to Asan Medical Center due to repeated episodes of loss of consciousness. Seven days before the admission he suddenly lost consciousness during work in the field after feeling dizziness. He regained consciousness spontaneously within 30 min. On the next day, he lost consciousness again at dinner after mumbling and acting strangely. He was admitted to a local hospital, where he was found to have a very low blood glucose level (1.28 mmol/L; reference ranges 3.9–6.1 mmol/L). After intravenous injection of hypertonic glucose solution he promptly gained consciousness. Similar episodes occurred repeatedly during his stay in the local hospital. He was then transferred to Asan Medical Center. Several months ago he began to experience lassitude and cold sweating at night and woke up feeling dizzy. During a period
of several months he gained about 10 kg and an increased appetite. He had never smoked. He had been a social drinker but had not been drinking for the last five years. Twenty years ago pulmonary tuberculosis was treated with isoniazid, ethambutol and streptomycin for 18 months. After that, successive annual chest X-ray examination had revealed an inactive lesion in right upper lung. His family history was not in any way unusual.

On admission, his vital signs were normal and physical findings revealed nothing unusual. His height was 168 cm and his body weight was 62 kg. There were no abnormal neurological signs. After overnight fasting, his serum glucose was 2.00 mmol/L (3.9–6.1), insulin concentration was 1450 pmol/L (36–144), and C-peptide over 10 nmol/L (1.7–4.6). Other serum chemistry profiles including calcium and phosphorus were within normal range. Serum levels of thyroid hormones, anterior pituitary hormones, somatomedin-C, cortisol and testosterone were all within normal ranges. Prolonged fasting was attempted but was terminated after 17 h because the patient lost consciousness. At that time his blood glucose was 1.28 mmol/L, insulin 1686 pmol/L, and C-peptide 7.46 nmol/L.

Thereafter, he had received continuous intravenous glucose infusion at a rate of 0.46 nmol/h and remained euglycemic. Localization studies including dynamic CT scan and celiac angiography did not yield evidence of a tumor. Percutaneous transhepatic portal venous sampling showed elevated insulin concentrations at all sites but without definite step-up of insulin concentration (Fig. 1).

On the sixteenth day in the hospital, exploratory laparotomy was performed. No tumor was palpable in the pancreas even after it was completely mobilized, however, intraoperative ultrasonography showed ill-defined low echogenic area in the pancreatic head. Pancreatoduodenectomy (Whipple’s procedure) was performed and the subsequent 70% of the proximal pancreas was removed under the assumed presence of diffuse islet cell hyperplasia with a probable small tumor in the pancreatic head. Tissues from the pancreatic head, body and tail were examined in frozen section, revealing diffuse hyperplasia of dysplastic islets. Immediately after operation, the patient’s blood glucose level rose to 12.22 pmol/L with intravenous hyperalimentation. Without intervention, his blood glucose level fell within normal range five days after the operation. His convalescence was without complications. When he could resume regular meals (16 days after the operation), intravenous glucose was discontinued and the patient was held under close surveillance. He was able to tolerate overnight fasting with no major complications. After 24 h of fasting, his serum glucose level was 5.17 mmol/L, insulin concentration 136 pmol/L, and C-peptide level 0.33 nmol/L.

He had been doing well and not displaying any symptoms of hypoglycemia or exocrine pancreatic insufficiency for the 15 months since the operation. He can tolerate overnight fasting well. During the first month after surgery he lost 4 kg of body weight spontaneously; however, his body weight remained stationary after then until 15 months after the operation, at which time his overnight fasting glucose concentration was 5.12 mmol/L, insulin concentration 9.2 pmol/L, and C-peptide level 0.24 nmol/L without any medication.

Pathological Findings

The resected head and body of the pancreas which was attached to the duodenum measured 10 × 2.5 × 2 cm, and appeared normal in terms of gross anatomy. Serial section of the specimen at intervals of 0.5 cm revealed uniformly normal parenchyma with no evidence of tumor. Microscopic examination revealed that dysplastic islets had been increased in size and number and were scattered
randomly (Fig. 2). The contour and size of the islets were markedly variable. Some islets were budding from small ductules (Fig. 3). Islet cells showed dysplastic changes such as an increased nuclear-cytoplasmic ratio, hyperchromatism, coarse chromatin, and prominent nucleoli.

Immunohistochemical staining of the insulin was performed with the commercial antiserum (Dako, the Netherlands) using avidin biotin technique. In brief, tissue sections were preincubated in normal porcine serum and then anti-insulin antiserum (1:100 diluted). After washing, tissues sections were incubated with biotinylated secondary antibody. Further incubations were done in avidin biotin complex. Then they were lightly counterstained with hematoxylin and were examined under the microscope. All the islets were intensely stained with anti-insulin antibody on immunohistochemical staining (Fig. 4). Antisera to glucagon, pancreatic polypeptide, somatostatin, chromogranin and synaptophysin were also tested and all were positive at least focally.

A histomorphometric study was undertaken using the 1.5 cm interval serial sections of the pancreas. The number of the islets in each were counted at 500 high power fields and the endocrine areas were quantitated. In the head close to the duodenum, the amount of pancreatic parenchyma in the endocrine area was markedly increased (around 7%) but it declined progressively up to the resection margin near the pancreatic tail (around 2%, Fig. 5). Although density of the islets at the tail was not different from that of a normal pancreas, morphologically the islets were definitely dysplastic even in the body and tail of the pancreas.

Electron microscopic study was not undertaken. The hormone contents in the resected specimen was not measured. Molecular forms of insulin in this patient were not investigated.
Hyperinsulinemic hypoglycemia due to nesidioblastosis in adults is a very rarely reported condition and only some 20 cases have been reported in the English literature [3-5]. It can occur in any age and in either sex [3, 4], but the true incidence rates are unknown. However, asymptomatic minimal nesidioblastosis in adults is occasionally found in routine autopsy [6].

Nesidioblastosis causes many diagnostic and therapeutic problems when the clinician faces a patient with hypoglycemia. With a presumptive diagnosis of insulinoma, localization studies, such as dynamic CT scan, celiac angiography, endoscopic ultrasonography, transhepatic portal venous sampling, etc are undertaken. However, none of these methods are completely adequate and may cause diagnostic errors [7, 8]. If the results are negative, and the patient is tentatively diagnosed with insulinoma, he then undergoes exploratory laparotomy. If no tumor is found, blind distal 66-95% pancreatectomy is performed under the assumption that the patient is suffering from islet cell hyperplasia. A diagnosis of nesidioblastosis can be determined only postoperatively on the basis of histopathological findings. Some patients develop insulin deficiency postoperatively requiring permanent insulin injection or displaying exocrine pancreatic insufficiency and some suffer from persistent hypoglycemia necessitating additional resection of the pancreas or other medical treatment procedure [3-5].

In our patient, no definite step-up of the insulin concentration was found by percutaneous portal venous sampling. However, insulin concentration was elevated in every sampled site. We could not ascertain whether or not this minimal step-up of insulin concentration was due to the presence of a small insulinoma; however, the elevated insulin concentration and the low echogenicity of the pancreatic head led us to perform proximal pancreatectomy. Our assumption was verified with histomorphometric study of the resected pancreas. Hyperplastic islets were most abundant in the head of the pancreas with a decrease in number as one moved to its body and tail of the pancreas.

**Discussion**

Although diffuse and focal forms are recognized in neonatal nesidioblastosis [9], such findings have not yet been reported in adults. The graded distri-
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bution of the hyperplastic islets in the pancreas in
our patient on the one hand, and distinctly graded
diffuse nesidioblastosis on the other hand neither
been previously reported. Such patterns are clearly
very unusual, considering the even diffuse or
mere foci involvement of the pancreas in the pre-
viously reported cases [3, 4]. The exact clinical
significance is unknown, which might, however,
cause more problems in diagnosis, especially in
the localization procedure and treatment, and in
decisions as to the extent of surgery to be per-
formed. Although the postoperative follow-up
period is not long enough to assess the outcome in
our patient, based on histological findings we be-
lieve that he will not suffer from recurrent
hypoglycemia.

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