

## Islet Cell Hyperplasia of the Pancreas Presenting as Hyperinsulinemic Hypoglycemia in an Adult

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### Abstract

A 72-year-old man who had suffered several episodes of syncope was diagnosed as having hyperinsulinemic hypoglycemia. Although imaging studies and percutaneous transhepatic portal venous sampling did not reveal the existence of any tumors in the pancreas, distal pancreatectomy was performed because the possibility of a small pancreatic endocrine tumor could not be completely rejected. External examination of the surgically removed pancreas did not reveal any tumors. Microscopically, the pancreas exhibited diffuse islet cell hyperplasia without nesidioblastosis. The patient remains euglycemic and has tolerated 24-hour fasting without any medication for a period of 10 months after the operation.

**Key Words:** Islet cell hyperplasia, hyperinsulinemic hypoglycemia, pancreas, adult

### INTRODUCTION

Pancreatic endocrine tumor are a well-known cause of hyperinsulinemic hypoglycemia in adults. Whereas in children, this syndrome is produced by a variety of islet cell changes, including islet cell hyperplasia, nesidioblastosis, and adenomatosis, as well as true adenoma.<sup>1</sup> However, hyperinsulinemic hypoglycemia due to islet cell changes in adults, such as islet cell hyperplasia or nesidioblastosis, is a very rarely reported condition. Furthermore, our review of the literature revealed only 30 reported cases of adults who had hyperinsulinemic hypoglycemia and yet didn't have insulinoma as proved by surgery or autopsy.<sup>2-5</sup> Islet cell hyperplasia and nesidioblastosis usually coexist in the same pancreas. The two lesions are also observed independently of each other, and only 3 cases of islet cell hyperplasia without nesidioblastosis were reported.<sup>6,7</sup>

Islet cell hyperplasia is a sporadic cause of hyperinsulinism in adults, but because of the inade-

quacies of present imaging procedures, definitive diagnosis requires exploratory surgery. Subtotal pancreatectomy is recommended for the treatment of islet cell hyperplasia.<sup>4</sup> We present a case of islet cell hyperplasia of the pancreas presenting as hyperinsulinemic hypoglycemia in an adult. The definition of this lesion and its clinical significance is discussed, and the literature is also reviewed.

### CASE REPORT

A 72-year-old man was admitted to Kyung Hee Medical Center having suffered incidences of syncope. During the previous 15 years, he had experienced three episodes of syncope while fasting. He had had a history of hypertension during the previous 15 years. There was no evidence of associated endocrine dysfunction, and family history was noncontributory. On admission, he was experiencing a fourth episode of syncope. His serum glucose level was 16 mg/dL (normal range: 76–110 mg/dL), his serum insulin level was 93.6  $\mu$ U/ml (normal range: 3–12  $\mu$ U/ml) and his plasma C-peptide level was 10.3 ng/ml (normal range: <2.8 ng/ml). After the administration of 50% dextrose, he promptly returned to a normal mental state. Results of a physical examination were almost normal.

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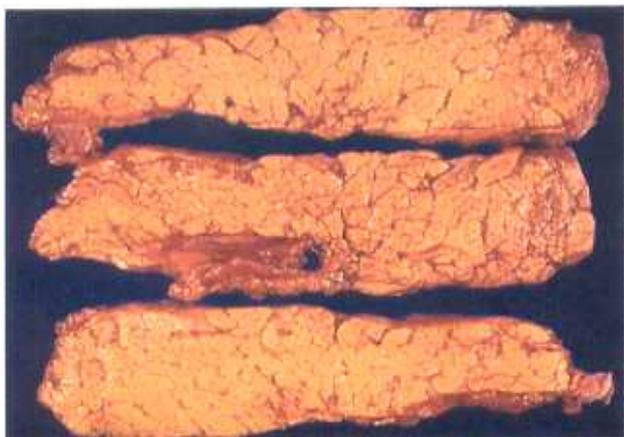


Fig. 1. Step sections of the pancreas showing a normal lobular pattern without tumor.

Although insulinoma was suspected, imaging studies (including ultrasonography, computed tomography, and magnetic resonance imaging) and celiac angiography did not reveal any abnormalities in the pancreas. Percutaneous transhepatic portal venous sampling showed elevated insulin concentrations at all sites, but without a definite increase in insulin concentration. Because the existence of a small insulinoma could not be completely excluded, exploratory laparotomy was performed. During the laparotomy, no nodular lesion was observed, and palpable and intraoperative sonography did not reveal any masses. An undetectable microendocrine tumor was suspected, and a distal 80 percent pancreatectomy was performed.

The removed pancreas, measuring  $15 \times 4.5 \times 2$  cm in dimension and 60 gm in weight, showed a normal external surface with normal color. Step sections of the pancreas at intervals of 5 mm revealed normal lobular pattern and consistency, but did not reveal any tumor (Fig. 1). The pancreatic duct was patent and of normal size.

Histologic examination revealed no tumor. There was an increase in the number of islets (Fig. 2). The size of the islets varied, they were frequently enlarged, and irregular. The islets also exhibited a great variation in shape and outline. Cytologically, the islet cells appeared normal without nuclear atypia and they had finely granular cytoplasm. The immunostaining also showed almost normal proportions of insulin-positive, glucagon-positive, and somatostatin-positive endocrine cells (Fig. 3). Evidence of nesidioblastosis such

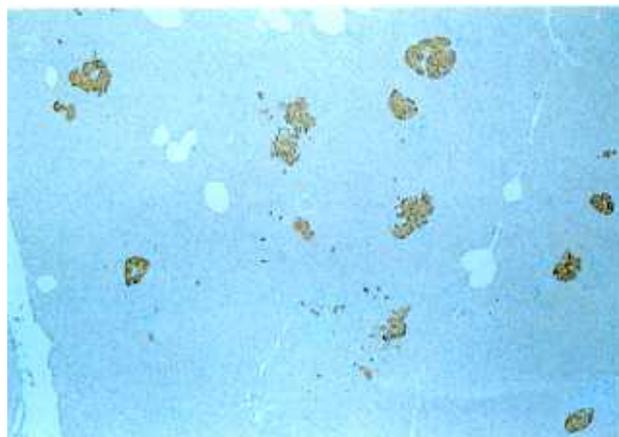


Fig. 2. Pancreas showing an increase in the number of islets with irregular configurations (ABC method, with anti-chromogranin A antibody,  $\times 40$ ).

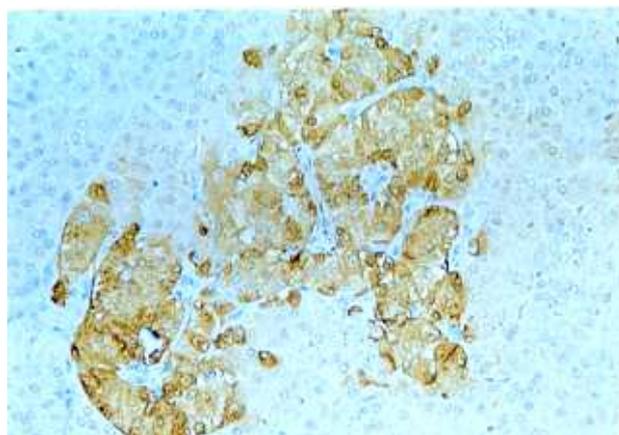


Fig. 3. Islet showing predominance of insulin-positive cells (ABC method, with anti-insulin antibody,  $\times 200$ ).

as, ductuloinisular complexes or dysplastic changes of islet cells, was not seen in any fields. There were no findings of chronic pancreatitis. The rest of the acini, vessels, and surrounding fat exhibited no significant features. We concluded that these changes could be designated as islet cell hyperplasia. Through the use of morphometry, we measured 100 islets of this lesion and an age-matched control sample. The average dimension of the islet control was  $17511.77 \mu\text{m}^2$  (range:  $3001.79 - 50643.84 \mu\text{m}^2$ ), and the average lesion of the islets was  $17695.40 \mu\text{m}^2$  (range:  $4502.69 - 57283.64 \mu\text{m}^2$ ). The difference between the average dimension of the age-matched control and this lesion was not statistically significant.

After the operation, the patient's glucose level while fasting has been stable. The patient has had no hypoglycemic symptoms for the 10 months since the operation.

## DISCUSSION

Hyperinsulinemic hypoglycemia, when not due to a tumor may be caused by islet changes and is described as nesidioblastosis or islet cell hyperplasia due to an increased number of B-cells. However, there has been considerable controversy regarding the histological diagnosis of such islet cell changes in previously reported cases.

Dahms et al. referred to islet cell hyperplasia as an increased number of normal-sized or larger islets, and diagnosed nesidioblastosis as the occurrence of small clusters of islet cells scattered without connection to Langerhans islets.<sup>8</sup> Islet cell hyperplasia is an increase in pancreatic islet mass resulting from an increase in islet absolute size or number. Microscopically, abnormally larger and apparently confluent islets accumulate in the center of the lobules leaving only narrow rims of acinar tissue at some sites. The normal distribution of the four main cell types inside the islets is retained. Nesidioblastosis is a hyperfunctional disorder of pancreatic insulin-producing cells characterized by hypertrophic B cells within enlarged or normal-appearing islets, small scattered endocrine cell clusters, and ductuloinsular complexes.<sup>1</sup>

Weinstock et al. preferred to describe the term islet cell hyperplasia as designating a diffuse proliferation of endocrine cells that may express itself with different morphologic patterns, varying from case to case. Islet cell hyperplasia therefore comprises nesidioblastosis and endocrine cell budding from ductal structures, as well as islet and islet cell hypertrophy, septal islets, islet dysplasia, and adenomatosis.<sup>9</sup> Dahms et al. wrote that the use of these different terms need not imply different diseases or pathogenetic mechanisms, since all of these terms indicate a proliferation of islet cells in not well circumscribed or encapsulated masses.<sup>8</sup> In our opinion, islet cell hyperplasia, a much less restrictive term, should be used to identify the diffused proliferation of endocrine cells with different morphologic patterns, in particular including nesidioblastosis and the variations in proportions from case to case.

A diagnosis of islet cell hyperplasia can be determined only postoperatively on the basis of histopathological findings. In our case there was no increase in volume density of the total endocrine tissue or in number of B cells compared to the age-matched control.<sup>3</sup> We estimated density differences between the lesion and normal control used by morphometry, but no difference was observed. The incidence of islet cell hyperplasia remains doubtful because the description was not based on quantitative morphometric studies.

Goudswaard et al., using quantitative histomorphological techniques comparing normal and endocrine disorders of the pancreas, have questioned whether islet cell hyperplasia is a distinct clinical syndrome.<sup>10</sup> They propose that many patients with islet cell hyperplasia actually have occult neoplasm and that the hyperplasia represents a compensatory increase in A and D cells. It would be difficult to exclude an a microadenoma of the pancreas, although there are several reasons to support our diagnosis of islet cell hyperplasia. Firstly, in most of patients with a pancreatic endocrine tumor, the tumor will be palpated at the time of surgery; secondly, in our patient, no definite increase in the insulin concentration was found by percutaneous portal venous sampling; finally, immunohistochemical staining disclosed an abundance of B cells, making it unlikely that the islet cell hyperplasia represented a compensatory growth of A and D cells in response to a pancreatic endocrine tumor.

The etiology of islet cell hyperplasia is not well understood. A genetic predisposition has been proposed by Burman et al.<sup>7</sup> Heitz et al. have concluded that such proliferations of islet tissue are consequences of a defect in islet cell stimulation or regulation, the nature of which is unclear.<sup>11</sup>

Our review of the literature reveal that there were only 30 reported cases of adults who had hyperinsulinemic hypoglycemia and who were confirmed by surgery or autopsy to have had no insulinoma. Usually in these 30 reported cases, hyperplasia with nesidioblastosis was commonly admixed. Only three cases were solely hyperplasia. The male-to-female ratio was 12 : 18. The onset of symptoms in these patients occurred in middle age (average 42.7 years, range: 23–80 years). The duration of hypoglycemic symptoms was highly variable, ranging from only days to 18 years before pancreatectomy. All patients

had pancreatectomies, ranging from 33% to 95% in extent.<sup>2-7,9</sup>

Islet cell hyperplasia causes many diagnostic and therapeutic problems when the clinician faces a patient with persistent hyperinsulinemic hypoglycemia. With a presumptive diagnosis of insulinoma, localization studies, such as a dynamic CT scan, celiac angiography, endoscopic ultrasonography, and transhepatic portal venous sampling, are undertaken. If the results are negative, and the patient is tentatively diagnosed with insulinoma, he then undergoes exploratory laparotomy. Step sectioning of the pancreas, with systemic histologic investigation, is necessary to exclude a minute insulinoma. The best treatment for this disease seems to be a resection of 80–90% of the pancreas to alleviate the hypoglycemia and prevent the subsequent development of diabetes mellitus.<sup>3,4</sup>

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