Insulinoma in a patient with pre-existing diabetes is extremely rare. A 74-year-old woman with type 2 diabetes mellitus who had been treated with a sulfonylurea for 6 years began experiencing frequent episodes of hypoglycemia. Endogenous hyperinsulinism was found 9 months after the sulfonylurea was discontinued, and transabdominal ultrasonography and magnetic resonance imaging identified a pancreatic tumor. Pathology examination of the resected tumor demonstrated an insulinoma. Postoperatively, the patient had no further episodes of hypoglycemia. Thereafter, she required insulin to control her hyperglycemia. Although hypoglycemic agents are the commonest cause of hypoglycemia in type 2 diabetes, insulinomas may occur in these patients. This possibility should be considered if the hypoglycemia persists despite dose adjustment or cessation of the drugs. [J Formos Med Assoc 2007;106(5):392–396]

Key Words: insulinoma, sulfonylurea compounds, hypoglycemia, type 2 diabetes mellitus

Insulinoma, a functioning neoplasm derived from the beta cells of the pancreas, is a rare tumor. The incidence in the general population is about 4 cases per million a year. The disorder usually occurs in people who are otherwise healthy. Hypoglycemia in patients with diabetes is nearly always attributable to oral hypoglycemic agents or insulin. Although insulinoma in a patient with pre-existing diabetes is extraordinarily rare, it may occur. We report such a case.

Case Report

A 74-year-old woman with rheumatoid arthritis and type 2 diabetes was admitted for evaluation of frequent hypoglycemic episodes manifested by dizziness and diaphoresis. Her diabetes had been diagnosed in 1999 and was treated with gliclazide, 160 mg/day. She had also been taking prednisolone 5 mg/day, for 3 to 4 years for her arthritis, as well as using over-the-counter topical steroids for eczema. In 2002, she experienced an initial episode of hypoglycemia, and the dose of gliclazide was reduced. However, she continued to have frequent hypoglycemic episodes, despite repeated dose reductions and finally discontinued the drug in February 2005. Two months later, her fasting plasma glucose was 33 mg/dL. She was also found to have secondary adrenal insufficiency, with plasma cortisol and adrenocorticotropic hormone (ACTH) levels of 1.35 μg/dL (normal, 5.00–20.00 μg/dL) and 1.07 pg/mL (normal, 9.00–52.00 pg/mL), for which cortisone acetate was
prescribed. Episodic hypoglycemia persisted. In November 2005, that is, approximately 9 months after discontinuation of glicazide, her fasting plasma glucose was 22 mg/dL and plasma insulin and C-peptide levels were 32.7 μIU/mL (normal, <30.0 μIU/mL) and 17.60 ng/mL (normal, 1.00–3.00 ng/mL). The insulin and C-peptide levels were measured by radioimmunoassay using a DPC GAMBYT-CR gamma counter instrument. We did not measure plasma sulfonylurea levels as we were confident the patient had indeed stopped taking glicazide. Thus, endogenous hyperinsulinism was confirmed, accounting for her hypoglycemia, and she was admitted for further management.

On admission in December 2005, her weight was 70 kg and her height was 154 cm (body mass index, 30 kg/m²). Her laboratory profile was as follows: fasting plasma glucose, 11 mg/dL; free-T4, 2.20 ng/dL (normal, 0.80–2.00 ng/dL); thyroid stimulating hormone (TSH), 2.14 μIU/mL (normal, 0.25–4.00 μIU/mL); 8AM cortisol, 9.92 μg/dL (normal, 5.00–25.00 μg/dL); ACTH, 28.30 pg/mL (normal, 9.00–52.00 pg/mL); HbA1c, 4.3% (4.2–6.4%). A test for anti-insulin antibodies was negative. Transabdominal ultrasonography (Figure 1) and magnetic resonance imaging (MRI) scan (Figure 2) showed a 2.0 × 2.2-cm well-defined soft tissue mass in the head of the pancreas. At surgery, a 2.0 × 2.0 × 2.2-cm well-circumscribed, dark-reddish tumor was successfully enucleated (Figure 3). The histopathologic diagnosis was insulinoma (Figure 4). After surgery, the patient experienced no further hypoglycemia and indeed, required insulin to treat her diabetes.

Discussion

The criteria for diagnosing insulinoma in patients with diabetes includes the following: (1) development of Whipple’s triad; (2) presence of endogenous hyperinsulinism; (3) exclusion of other causes of hypoglycemia; and (4) amelioration of hypoglycemia after resection of the tumor. When a patient with diabetes presents with hypoglycemia, the most common explanation is over treatment or inadequate food intake. Our patient, however, had hyperinsulinemic hypoglycemia even...
when completely off hypoglycemic agents. In addition to insulinoma, the differential diagnoses of hyperinsulinemic hypoglycemia include familial persistent hyperinsulinemic hypoglycemia, primary islet-cell hyperplasia, and noninsulinoma pancreatogenous hypoglycemic syndrome. Our patient’s findings clearly fulfilled the criteria for insulinoma, which was demonstrated by MRI.

Insulinoma is a rare endocrine tumor derived from pancreatic islet cells that produces excessive amounts of insulin. Such tumors are usually small, solitary, benign, well-circumscribed, and may occur anywhere in the pancreas. Patients usually present with symptoms of neuroglycopenia such as confusion, visual changes, unusual behavior and with sympathoadrenal symptoms such as palpitation, sweating and tremor. A presumptive diagnosis of insulinoma is made when there is evidence of endogenous insulin secretion that is inappropriately high for a given glucose level in a patient who is not taking an insulin secretagogue. Surgery is the only curative treatment currently available, although streptozotocin or diazoxide may be used to control the disease when the tumor cannot be completely removed. However, Arioglu et al reported a patient with a proinsulin-secreting insulinoma initially presenting with symptomatic hypoglycemia. The tumor was not resected and was treated with diazoxide. Eventually, the patient developed clinical diabetes.

In contrast to this very rare beta-cell tumor, diabetes is an exceedingly common metabolic disorder, associated with various degrees of beta-cell dysfunction. The prevalence of type 2 diabetes in adults is reported to be 4.9–9.2% in Taiwan. As mentioned above, when a patient being treated for diabetes becomes hypoglycemic, it is almost always because of the treatment, whether with oral hypoglycemic agents or insulin. It is difficult to know whether there is any pathogenetic relationship between diabetes and insulinoma. Several older reports suggested an association between insulinoma and a family history of diabetes. In a series from the Mayo Clinic, 30% of patients

Figure 4. (A) Pathology specimen demonstrating tumor cells with abundant eosinophilic cytoplasm (arrow) and bland-looking nuclei (arrowhead) arranged in a trabecular pattern (hematoxylin & eosin, 400×). On immunohistochemical staining, the tumor cells are positive for: (B) chromogranin; (C) synaptophysin; and (D) neuron-specific enolase.
Insulinoma in type 2 diabetes mellitus

with insulinoma had a family history of diabetes. Streptozotocin destroys beta cells and may thus cause diabetes. Experiments in rats demonstrate that the combination of nicotinamide and streptozotocin can induce insulinoma, although it is hard to see what bearing this would have on naturally occurring disease in humans.

The coincidence of insulinoma and diabetes is so rare that there are only a few individual case reports. Only a few well-documented cases of insulinoma associated with type 2 diabetes and one with type 1 diabetes have been published in the past 50 years. Looking at it from a different angle, the incidence of diabetes among patients with insulinoma is also quite low. Among 313 confirmed cases of insulinoma at the Mayo Clinic between 1927 and 1992, there was only one patient with pre-existing diabetes. In a similar review from Japan, of 443 cases of insulinoma between 1976 and 1990, only one patient had diabetes too. In that particular case, the insulinoma was malignant. The incidence and prevalence of insulinoma in Taiwan is unknown. However, we reviewed 23 cases of insulinoma seen at our institution between July 1984 and March 2006 and only the patient we are reporting here had diabetes.

Previous reports of the co-occurrence of these two disorders are difficult to assess because other associated diseases that might cause hypoglycemia such as renal failure or liver cirrhosis have not been mentioned. Also, earlier cases relied on less accurate diagnostic techniques than those presently available.

Our case demonstrates the current state of the art in which endogenous hyperinsulinism can be confirmed by an elevated plasma insulin and C-peptide level in the absence of a sulfonylurea and the tumor can be localized by any one of a number of imaging techniques. Sapountzi et al first reported a case with insulinoma and concomitant diabetes in which continuous glucose monitoring was an important diagnostic tool. This method, being reliable, safe and easy to perform, is worthwhile considering the possibility to detect unusual causes of hypoglycemia, including insulinoma.

Patients with adrenal insufficiency may have hypoglycemia. Our patient’s secondary adrenal insufficiency was most likely caused by the prednisolone she took for her arthritis. Suppression of the hypothalamic–pituitary axis by exogenous steroids is thought to relate to the duration of therapy, the highest dose and the total cumulative steroid dose. However, it is difficult to accurately predict the degree of adrenal suppression in any particular patient. It is reported that those who take 5 mg/day or less of prednisolone generally have an intact hypothalamic–pituitary–adrenal axis. Although our patient’s prednisolone dose was in this range, she did have suppression of the axis. Perhaps there may have been an additive effect from the topical steroids she used for a skin condition. At any rate, exogenous steroid therapy is the most likely explanation for her secondary adrenal insufficiency. There does not seem to be any connection between this condition and her insulinoma.

In conclusion, hypoglycemia in a patient with diabetes is almost invariably ascribed to the drugs used to control hyperglycemia. However, in a patient who has dramatic improvement of diabetes mellitus, particularly after withdrawal of all hypoglycemic treatment, an insulin-producing tumor should be considered.

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