CASE REPORT

Concurrent insulinoma and impaired glucose tolerance suspected as owing to obesity

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SUMMARY

An obese 68-year-old woman was admitted for examination of fasting hypoglycaemia. A prolonged 18 h fast reduced her plasma glucose without suppressing insulin secretion, while plasma β -hydroxybutyrate levels were suppressed. Despite the prolonged fast, the glucose response to glucagon was increased by 25 mg/dL (1.39 mM) glucose, which is compatible with insulinoma. A 75 g oral glucose tolerance test (75 g OGTT) showed impaired glucose tolerance. An abdominal CT scan revealed a mass lesion in the uncinate process of the pancreas, a finding consistent with the results of angiography and selective artery calcium injection test. The patient then underwent a pancreaticoduodenectomy; the pancreatic mass was histologically diagnosed as benign insulinoma. After surgery, a prolonged 24 h fast caused no hypoglycaemia and the glucose tolerance capacity in 75 g OGTT improved. Eight months after surgery, the patient's body weight had reduced by 10 kg. This is therefore a case of concurrent insulinoma and impaired glucose tolerance.

BACKGROUND

There are several diseases that cause hypoglycaemia, although it is rare in patients without diabetes mellitus. Insulinoma is the most common type of functional primitive neuroendocrine tumour (PNET), comprising 20.9% of all PNETs, with an incidence in the general population of only four cases per million a year.^{1–3} Insulinoma can cause fasting hypoglycaemia due to inappropriate insulin secretion. A first clue that insulinoma could be the cause of hypoglycaemia in this case was the presence of Whipple's triad, signs and symptoms of hypoglycaemia with low plasma glucose (PG) concentration and the resolution of these symptoms after the glucose concentration was raised.¹ Most cases of insulinoma are benign and curable by surgical resection^{4,5}; it is therefore important to rule out the possibility of insulinoma in differential diagnosis of hypoglycaemia with respect to occurrence and curability.

We report a case of insulinoma with impaired glucose tolerance. In this case, a prolonged fasting test was helpful not only for diagnosis of the insulinoma but also for postoperative evaluation of any curative effect. The concurrence of insulinoma with glucose intolerance has been reported, however, we were not aware of this condition until we saw this case. Considering that the 75 g oral glucose tolerance test (75 g OGTT) is rarely performed in patients with insulinomas, failure to notice the

concurrence of glucose intolerance and insulinoma might be common.

CASE PRESENTATION

A 68-year-old woman had annual health examinations over a 10-year period. Between the ages of 40 and 50 years, her body weight gradually increased from 60 to 70 kg, but then remained unchanged (72 kg). At 65 years of age, her fasting PG levels were approximately 60 mg/dL (3.3 mM), and at 68 years, her fasting PG concentration dropped to 35 mg/dL (1.94 mM), with an occasional feeling of confusion especially before meals. These hypoglycaemic episodes with symptoms of confusion and dysphoria improved after eating snacks. In September, the patient's fasting glucose and insulin levels were 43 mg/dL (2.3 mM) and 17.5 μ U/mL, respectively. At testing, she had felt a slight headache. In October 2014, she was admitted to our hospital for examination and treatment for hypoglycaemia.

The patient had no family history of diabetes mellitus. Her height, weight and body mass index were 152 cm, 74 kg and 32 kg/m², respectively. Her resting blood pressure was 113/68 mm Hg. There were no abnormal findings in the thoracoabdominal region or any abnormal neurogenic signs. Laboratory data are presented in table 1. Urinalysis, haematology and biochemistry revealed no abnormalities, but the patient's glycated haemoglobin (HbA1c) level was relatively low at 4.80% (29.0 mmol/mol) (table 1).

INVESTIGATIONS

At the first visit to our hospital, we strongly suspected that this patient's hypoglycaemia was due to insulinoma, because her insulin levels were very high in spite of her hypoglycaemia. We performed a CT scan and 8 h fasting test at the same time because (1) the patient had to drive later by herself for 1 hr; (2) she was busy and could not at the time be admitted to hospital for examination and (3) if she did not eat lunch, she felt hypoglycaemic symptoms. At the same time as performing the CT scan, the patient had fasted for 8 h. She felt a slight headache and drowsiness. Despite a low PG level (50 mg/dL (2.78 mM), her plasma levels of insulin, C peptide immunoreactivity (CPR) and proinsulin were relatively raised (25.7 (1.84–12.2) μ U/mL, 3.29 (0.61–2.09) ng/mL and 62.3 (<5.0) pmol/L, respectively). In insulinoma, insulin (pmol/L) to C peptide (pmol/L) molar ratio is $\leq$ 1.⁶ The insulin to CPR ratio was lower (0.164) because plasma proinsulin levels were high due to abnormal

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Table 1 Laboratory data on admission

Urinalysis	Haematology	Biochemistry	Metabolism	Hormone
Protein	WCC 6390 (3300–7900)/ μ L	AST 18 (7–35) IU/mL	Glucose 97 (70–110) mg/dL	GH 0.45 (<3.61) ng/mL
Glucose	RBC 470 (369–507) $\times 10^4$ / μ L	ALT 15 (7–40) IU/mL	HbA1c 4.8 (4.6–6.2)%	IGF-I 88 (37–150) ng/mL
Haem	Hb 14.1 (11.3–15.4) g/dL	ALP 126 (125–225) IU/mL	Glycoalbumin 10.00 (12.4–16.3)%	PRL 4.05 (6.12–30.54) ng/mL
	Ht 42.7 (34.0–46.3)%	γ GTP 34 (<70) IU/mL	Insulin antibody <0.4 (<0.4) U/mL	TSH 1.4 (0.35–4.94) μ U/mL
	Plt 22.7 (15.5–35.0) $\times 10^4$ / μ L	Creatinine 0.64 (0.40–0.80) mg/dL		FT3 2.92 (1.71–3.71) pg/mL
		BUN 12.7 (8.0–20.0) mg/dL		FT4 1.04 (0.70–1.48) ng/mL
		Na 141 (135–147) mEq/L	Total cholesterol 135 (130–220) mg/dL	ACTH 13.4 (7.2–63.3) pg/mL
		K 4.3 (3.5–4.8) mEq/L	TG 89 (50–150) mg/dL	Cortisol 14.3 (6.2–19.4) μ g/dL
		Cl 105 (97–108) mEq/L	HDL-c 47 (40–75) mg/dL	PTH-I 30 (10–65) pg/mL
		Ca 9.6 (8.5–10.5) mEq/L		
		Pi 3.8 (2.6–4.5) mEq/L	UA 5.1 (2.5–6.9) mg/dL	

Normal values shown in parentheses.

ACTH, adrenocorticotrophic hormone; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FT3, free triiodothyronine; FT4, free thyroxine; γ GTP, γ -glutamyl transpeptidase; GH, growth hormone; HbA1c, glycated haemoglobin; Hb, haemoglobin; HDL-c, high-density lipoprotein cholesterol; Ht, haematocrit; IGF-I, insulin-like growth factor 1; RBC red blood cell; Plt, platelet count; PRL, prolactin; PTH-I, parathyroid hormone 1; TG, triglyceride; TSH, thyroid-stimulating hormone; UA, uric acid; WCC, white cell count.

proinsulin processing in insulinomas.⁷ These fulfil the diagnostic criteria of endogenous hyperinsulinaemia (plasma insulin concentrations of at least 3 μ U/mL (18 pmol/L), plasma C peptide concentrations of at least 0.6 ng/mL (0.2 nmol/L) and plasma proinsulin concentrations of at least 5.0 pmol/L when the fasting PG concentrations are below 55 mg/dL (3.0 mmol/L)).¹ A CT scan of the abdomen with contrast revealed a 1 cm diameter mass lesion in the uncinate process of the pancreas (figure 1).

To establish the diagnosis of insulinoma, we performed a 72 h prolonged fast test. After 18 h of fasting, the patient's PG level was low at 46 mg/dL despite the insulin and CPR levels being higher (11.8 (1.84–12.2) μ U/mL and 2.94 (0.61–2.09) ng/dL, respectively). As compatible with cases of insulinomas (<1.0), insulin to CPR ratio was much lower (0.08). Unfortunately, we failed to measure proinsulin levels, however, the 'amended Insulin-Glucose ratio', also called Turner index ((IRI (μ U/mL) $\times 100$)/(PG (mg/dL)-30)=73.8), fulfilled the criteria (insulinoma >20).^{8–9} Moreover, plasma ketone bodies and non-esterified free fatty acids (NEFA) were remarkably suppressed (acetoacetate 9 (<55) μ mol/L, β -hydroxybutyrate (β -OHB) 14 (<85) μ mol/L, total ketone bodies 23 (<130) μ mol/L and NEFA 390 (140–850) μ Eq/L) due to higher plasma insulin levels. At that time, the patient felt a slight headache and

blurred vision, so we stopped the fasting test. A 1 mg glucagon injection test administered intravenously was also performed. The PG levels increased above 25 mg/dL (1.39 mM) from baseline with transient but remarkable increases in plasma insulin and CPR levels, compatible with a pattern of insulinoma (figure 2). After assessing these results, the patient was diagnosed with insulinoma.¹

The patient was obese in the Japanese context. We were afraid that she might become diabetic due to decreased insulin secretion after the resection of her pancreas. To estimate the patient's glycaemic levels before surgery, we performed a 75 g OGTT, which indicated impaired glucose tolerance (PG levels: 106 (5.89), 184 (10.22), 189 (10.5), 194 (10.78) and 174 (9.67) mg/dL (mM) at 0, 30, 60, 90 and 120 min, respectively), according to the Japan Diabetes Society criteria¹⁰ (figure 3). Raised homeostasis model assessment ratio (HOMA-R) (2.60) indicated the concurrence of insulin resistance. The insulin response to glucose in the 75 g OGTT was delayed and persistent despite decreasing PG levels. Finally, to determine localisation of the insulinoma, arteriography and a selective arterial calcium injection (SACI) test were performed. In Japan, SACI tests have been shown to be highly accurate in the preoperative localisation of insulinomas, and have frequently been shown to be superior to non-invasive localisation techniques.^{2–11} Some papers reported that SACI tests had the highest accuracy (84%) for localising insulinomas to regions of the pancreas compared with MRI (25%), CT (32%) and ultrasonography (14%).¹² Consistent with the results of the abdominal CT scan, both the arteriography and SACI test revealed that insulinoma tumours were localised mainly in the region of the inferior pancreaticoduodenal artery (figure 4 and table 2). According to our surgeon's suggestion that it would be necessary to exclude the metastasis of insulinomas and the possibilities of multiple small insulinomas, we performed an oesophagogastroduodenoscopy and a colonoscopy, and found no remarkable change. Endoscopic ultrasound (EUS) also plays an important role in the diagnosis of neuroendocrine tumours especially in the pancreatic head.^{2–13} In a previous report, the sensitivity of endoscopic ultrasonography for detection of lesions in the pancreatic head, body and tail, was 92.6%, 78.9% and 40.0%, respectively.¹⁴ However, we unfortunately did not perform EUS. After surgery, we checked the histological examination of resected small intestine and found no tumours.

Figure 1 Horizontal sections of an enhanced CT scan of the pancreas. A hypervascular mass (10 mm in diameter) was observed in the uncinate process of the pancreas (arrow).

Figure 2 Glucagon loading test before and after surgery. After a prolonged fasting test, 1 mg glucagon was intravenously injected before (open square) or after surgery (closed square). PG, insulin and CPR was measured at the indicated time (CPR, C peptide immunoreactivity; IRI, immunoreactive insulin; PG, plasma glucose).

DIFFERENTIAL DIAGNOSIS

To establish the cause of hypoglycaemia, insulin autoimmune syndrome and adrenal insufficiency were ruled out; the anti-insulin antibody result was negative (<0.4 U/mL) (table 1). No abnormal results of the pituitary and adrenal hormones were observed (table 1). The patient had taken no medications that could cause hypoglycaemia.

TREATMENT

In January 2015, the patient underwent pancreaticoduodenectomy and, as expected from the results of the preoperative examinations, a 1 cm solitary mass lesion was observed at the uncinate of the pancreas. Histological examination of the resected tumour showed monotonous sheets of round tumour cells, which is consistent with a diagnosis of insulinoma. Further

Figure 3 To compare insulin sensitivity and secretory capacity before (open square) and after (closed square) surgery, 75 g oral glucose tolerance tests were performed. Plasma glucose (PG), insulin and C peptide immunoreactivity (CPR) were measured at the indicated time.

Figure 4 Inferior pancreaticoduodenal angiogram demonstrating the insulinoma tumour (arrow).

evidence of insulinoma came from the immunohistochemistry results, which revealed positive immunostaining for insulin and for the neuroendocrine cell markers (synaptophysin and chromogranin A), and negative for glucagon and somatostatin in the tumour cells. Metastasis of lymph nodes was not observed. The histopathological type of the tumour, its Ki-67 or mindbomb homologue 1 (MIB-1) proliferation index, size and location, as well as the age of the patient, seem to be the most important factors affecting prognosis and survival.¹⁵ The MIB-1 index was <1%,¹⁵ indicating that the insulinoma tumours in this case were benign.

OUTCOME AND FOLLOW-UP

Postoperatively, the patient felt no symptoms of hypoglycaemia. In a 24 h fast test, her PG was normal at 90 mg/dL (5 mM), and the plasma insulin and CPR levels were suppressed (4.3 µU/mL and 1.47 ng/mL, respectively). The plasma ketone bodies increased (β-OHB 982 µmol/L, acetoacetate 373 µmol/L and total ketone bodies 1335 µmol/L), presumably to compensate

for the suppressed insulin and CPR. The glucagon test showed much lower insulin secretory capacity compared to that before surgery (figure 2). Two months following surgery, the patient's body weight was successfully reduced from 70 to 65 kg. A 75 g OGTT indicated that the glucose clearance capacity had improved remarkably (figure 3). As with insulin sensitivity, HOMA-R improved (2.60 and 1.60 before and after surgery, respectively). Similarly, as with insulin secretory capacity, the insulinogenic index also improved (0.63 and 1.59 before and after surgery) (figure 3). Consistent with these findings, the delayed and sustained pattern of insulin secretion disappeared (figure 3). Eight months following surgery, her body weight was successfully reduced to 61.3 kg without hypoglycaemic symptoms. Her fasting PG was 112 mg/dL, CPR was 5.6 ng/mL, HbA1c was 5.6% and 1,5-anhydroglucitol was as low as 9.7 (normal range: 12.4–28.8) µg/mL.

DISCUSSION

In this case, the 75 g OGTT preoperatively showed impaired glucose tolerance. The patient's HbA1c and fasting PG levels had reciprocally changed over a 10-year period. To date, there have been only a few reported cases of insulinoma with glucose intolerance.^{16–17} A Japanese study of 443 cases of insulinoma reported only one also having diabetes.^{18–19} However, 75 g OGTT is rarely performed in patients with insulinomas. Moreover, some reports contended that insulin resistance was found in insulinoma due to the defect in peripheral glucose utilisation.^{20–21} Some reported that human insulinomas in vitro show distinct defects in insulin secretion.²² Therefore, the concurrent insulinoma and impaired glucose tolerance might not be as rare as once thought.

The HbA1c level of the patient in our study had gradually increased over 5 years, although the PG levels had decreased. Eating snacks between meals due to hypoglycaemia might have caused the gain in body weight and worsened her glycaemic control. In fact, postoperatively, by giving up snacks between meals, her body weight reduced by 10 kg and, consequently, her HOMA-R and insulinogenic index both improved. Thus, her weight gain through overeating as a result of hypoglycaemia may have contributed to the development of insulin resistance and impaired glucose tolerance.

In conclusion, we report a case of insulinoma with impaired glucose tolerance. A decrease in both pancreatic β-cell function and insulin sensitivity was observed. In the present case, diet, exercise therapy and body weight reduction will be of further benefit in protecting the patient from developing type 2 diabetes mellitus.

Table 2 Selective arterial calcium injection test

Time (sec)	0	30	60	90	120	Gradient (at 60 s/at 0 s)
Insulin (µU/mL)						
Splenic artery	111.9	118.3	124.1	108.3	86.4	1.11
Gastroduodenal artery	17.4	46.1	66.9	64	54.2	3.84
Proper hepatic artery	90.3	57	54.8	43.1	45.2	0.61
Inferior pancreaticoduodenal artery	23.5	624	817.4	859.7	765.9	34.78
Proinsulin (pmol/L)						
Splenic artery	117	ND	172	ND	ND	1.47
Gastroduodenal artery	102	ND	150	ND	ND	1.47
Proper hepatic artery	104	ND	93.2	ND	ND	0.9
Inferior pancreaticoduodenal artery	82.4	ND	311	ND	ND	3.77

ND, not determined.

Learning points

- ▶ This is a case of concurrent insulinoma and impaired glucose tolerance.
- ▶ A prolonged fasting test is beneficial for the diagnosis of insulinoma.
- ▶ A selective calcium loading test is also beneficial to determine the localisation of insulinoma.

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REFERENCES

- 1 Cryer PE, Axelrod L, Grossman AB, *et al.* Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009;94:709–28.
- 2 Grant CS. Insulinoma. *Best Pract Res Clin Gastroenterol* 2005;19:783–98.
- 3 Öberg K, Barbro E. "Endocrine tumours of the pancreas." *Best Pract Res Clin Gastroenterol* 2005;19:753–81.
- 4 Placzkowski KA, Vella A, Thompson GB, *et al.* Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. *J Clin Endocrinol Metab* 2009;94:1069–73.
- 5 Ito T, Igarashi H, Nakamura K, *et al.* Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. *J Gastroenterol* 2015;50:58–64.
- 6 van Bon AC, Benhadi N, Endert E, *et al.* Evaluation of endocrine tests. D: the prolonged fasting test for insulinoma. *Neth J Med* 2009;67:274–8.
- 7 Wiesli P, Perren A, Saremaslani P, *et al.* Abnormalities of proinsulin processing in functioning insulinomas: clinical implications. *Clin Endocrinol (Oxf)* 2004;61:424–30.
- 8 Nauck MA, Meier JJ. Diagnostic accuracy of an "amended" insulin-glucose ratio for the biochemical diagnosis of insulinomas. *Ann Intern Med* 2012;157:767–75.
- 9 Turner RC, Oakley NW, Nabarro JD. Control of basal insulin secretion, with special reference to the diagnosis of insulinomas. *Br Med J* 1971;2:132–5.
- 10 Seino Y, Nanjo K, Tajima N, *et al.* Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Invest* 2010;1:212–28.
- 11 Doppman JL, Chang R, Fraker DL, *et al.* Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. *Ann Intern Med* 1995;123:269–73.
- 12 Guettier JM, Kam A, Chang R, *et al.* Localization of insulinomas to regions of the pancreas by intraarterial calcium stimulation: the NIH experience. *J Clin Endocrinol Metab* 2009;94:1074–80.
- 13 McLean A. Endoscopic ultrasound in the detection of pancreatic islet cell tumours. *Cancer Imaging* 2004;4:84–91.
- 14 Sotoudehmanesh R, Hedayat A, Shirazian N, *et al.* Endoscopic ultrasonography (EUS) in the localization of insulinoma. *Endocrine* 2007;31:238–41.
- 15 Franchi G, Manzoni MF. Cytological Ki-67 in pancreatic endocrine tumors: a new "must"? *Gland Surg* 2014;3:219–21.
- 16 Grunberger G. Insulin resistance in a case of coexisting insulinoma and type 2 diabetes. *Acta Diabetologica* 1993;30:243–50.
- 17 Iida K, Ohara T, Hino Y, *et al.* Glucose-responsive insulinoma in a patient with postprandial hypoglycemia in the morning. *Intern Med* 2010;49:2123–7.
- 18 Ishii H, Ito T, Moriya S, *et al.* Insulinoma—a statistical review of 443 cases in Japan. *Nihon Rinsho* 1993;51:199–206. (In Japanese)
- 19 Kamocki ZK, Wodyńska NA, Pryczynicz A. Co-existence of insulinoma and diabetes: a case report. *Oncol Lett* 2014;8:1697–700.
- 20 Skirha J, Sindelka G, Haas T, *et al.* Comparison of insulin sensitivity in patients with insulinoma and obese Type 2 diabetes mellitus. *Horm Metab Res* 1996;28:595–8.
- 21 McGee GS, Kulaylat MM, Abumrad NN. Defective glucose utilization in patients with functioning beta-cell tumors persists after tumor excision. *Ann Surg* 1987;206:449–57.
- 22 Henquin JC, Nenquin M, Guiot Y, *et al.* Human insulinomas show distinct patterns of insulin secretion in vitro. *Diabetes* 2015;64:3543–53.

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