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CASE REPORT

Pancreatic insulinoma combined with glucagon positive cell: A case report

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Abstract

We present a 70-year-old man who was referred for surgery with uncontrollable hypoglycemia. Ultrasonography and abdominal contrast computed tomography revealed a hypervascular tumor of 1 cm in diameter in the pancreatic tail. With a diagnosis of insulinoma, we performed a distal pancreatectomy. The patient showed a good postoperative course without any complications. The patient's early morning fasting hypoglycemia disappeared. The respective levels of C-peptide and insulin dropped from 14.9 ng/mL and 4860 μIU/mL preoperatively to 5.3 ng/mL and 553 μIU/mL after surgery. A histopathological examination demonstrated that the tumor was a pancreatic neuroendocrine tumor, grade 1. Immunostaining was negative for insulin and positive for CD56, chromogranin A, synaptophysin and glucagon. These findings suggested that the tumor was clinically an insulinoma but histopathologically a glucagonoma. Among all insulinoma cases reported between 1985 and 2010, only 5 cases were associated with independent glucagonoma. In this report, we characterize and discuss this rare type of insulinoma by describing the case we experienced in detail.

Key words: Hypoglycemia; Insulinoma; Pancreas; Neuroendocrine tumor; Glucagon

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INTRODUCTION

Gastrointestinal and pancreatic neuroendocrine tumors (PNETs) comprise a group of rare neoplasms arising from the neuroendocrine system of the gut. The annual incidence is estimated at 1-4 in 100 000, showing a trend toward a higher incidence over recent decades[1-5]. Advancing diagnostic techniques have enabled the early detection of both functional and nonfunctional PNETs in recent years and, as a result, these tumors are more likely to be cured by radical operation. Most of these tumors are sporadic and completely cured by enucleation, but cases of high-grade malignancy, those accompanied by independent tumor(s) that secrete other hormone(s) and those with multiple tumors require careful attention.

CASE REPORT

The case was a 70-year-old man diagnosed with diabetes mellitus 15 years prior to the current presentation who

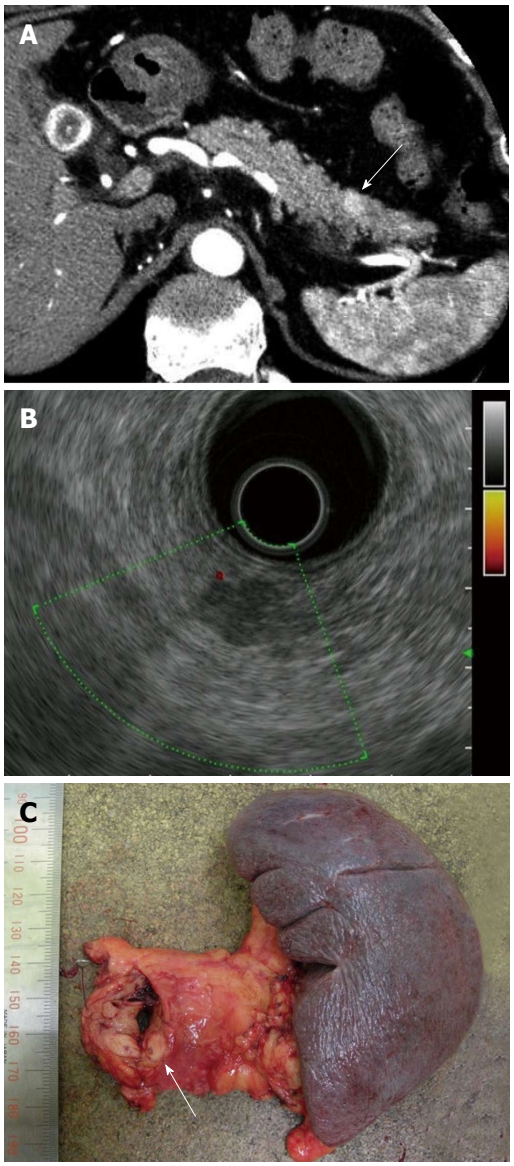

Figure 1 Removal of tumor. A: Enhanced abdominal computed tomography showed a tumor of 1 centimeter in diameter in the tail of the pancreas which was highly contrasted in the arterial phase (arrow); B: Endoscopic ultrasonography identified a uniformly hypoechoic tumor which measured 11 mm × 6 mm with a smooth surface in the tail of the pancreas; C: The resected specimen obtained from distal pancreatectomy and splenectomy included a solid whitish nodule (arrow).

was started on insulin self-injections in 2011. In 2012 he was placed under observation by the hospital due to worsening nephropathy. Two months ago, he presented with overhydration and started dialysis; he developed fasting hypoglycemia that did not improve after discontinuing the insulin injections. Careful examinations suggested that he had an insulinoma in the tail of the pancreas. He was given diazoxide and referred for surgery. The examinations on admission showed the following results: level of consciousness, lucid; blood pressure, 136/91 mmHg; pulse, 82 bpm; temperature, 36.6 ℃; overall status, stable. The patient had renal anemia and hypoalbuminemia (Table 1). The renal function test results and fasting blood glucose level before starting dialysis are shown in Table 1.

Table 1 Blood test findings on admission

Albumin, g/dL	3.0 (3.9-4.9)
Total bilirubin, mg/dL	0.3 (0.2-1.0)
Aspartate aminotransferase, IU/L	7 (10-40)
Alanine aminotransferase, IU/L	7 (5-45)
Blood urea nitrogen, mg/dL	54 (7.2-20.0)
Creatinine, mg/dL	8.2 (0.5-1.1)
Sodium, mmol/L	131 (136-145)
Potassium, mmol/L	4.1 (3.6-4.8)
Chlorine, mmol/L	101 (99-109)
White blood cell, μL	8000 (3100-9500)
Hemoglobin, g/dL	9.9 (13.5-16.9)
Platelet /μL	23.6×10^4 (15.1-34.9)
Fasting blood sugar, mg/dL	290 (70-109)
Hemoglobin A1c	7.6% (4.3%-5.8%)
Insulin, μIU/mL	4860 (1.8-12.2)
C-peptide, ng/mL	14.87 (0.61-2.09)
Binding rate of anti-insulin antibodies	76.2% (< 0.4%)
Carcinoembryonic, ng/mL	7.8 (< 5.0)
Pancreatic cancer-associated antigen-2, U/mL	190 (< 150)

Renal function test results and fasting blood glucose level before starting dialysis. Values in parentheses are normal ranges in our institution. All data were collected during the fasting state.

The blood levels of insulin and C-peptide were remarkably high, and those of carcinoembryonic antigen and duke pancreatic monoclonal antigen type 2 were slightly high. The levels of thyroid hormone and pituitary hormone were normal. The binding rate of anti-insulin antibodies was high, and we therefore could not deny insulin autoimmune syndrome.

Abdominal contrast computed tomography revealed a tumor 1 cm in diameter in the tail of the pancreas that was highly contrasted in the arterial phase (Figure 1A). The main pancreatic duct was not expanded, and the tumor was a suspected islet tumor. Endoscopic ultrasonography identified a uniformly hypoechoic tumor in the tail of the pancreas that measured 11 mm × 6 mm and had a smooth surface. Doppler ultrasonography demonstrated blood flow in the marginal regions of the tumor (Figure 1B). No other tumors were observed in the pancreas. We performed a distal pancreatectomy because intraoperative ultrasonography (IOUS) revealed that the tumor was close to the main pancreatic duct, making enucleation difficult. A cross-section of the surgical specimen showed a solid whitish nodule (Figure 1C). The tumor was preoperatively suspected as an insulinoma, but immunostaining showed that the main lesion was negative for insulin and positive for glucagon (Figure 2A and B). Additionally, the tumor was positive for CD56, chromogranin A and synaptophysin and negative for somatostatin. With an MIB-1 index of 1.6% and mild venous invasion, the tumor was identified as an NET, grade 1 (G1). At the slightly tail side of the main lesion, one hyperplastic nodule 3 mm in diameter was observed. Immunostaining demonstrated that the microadenoma was positive for insulin and glucagon (Figure 2C and D). After surgery, the blood levels of insulin and C-peptide significantly decreased, but the binding rates of anti-insulin antibodies were unchanged (Table 2). The patient resumed insulin self-injections and

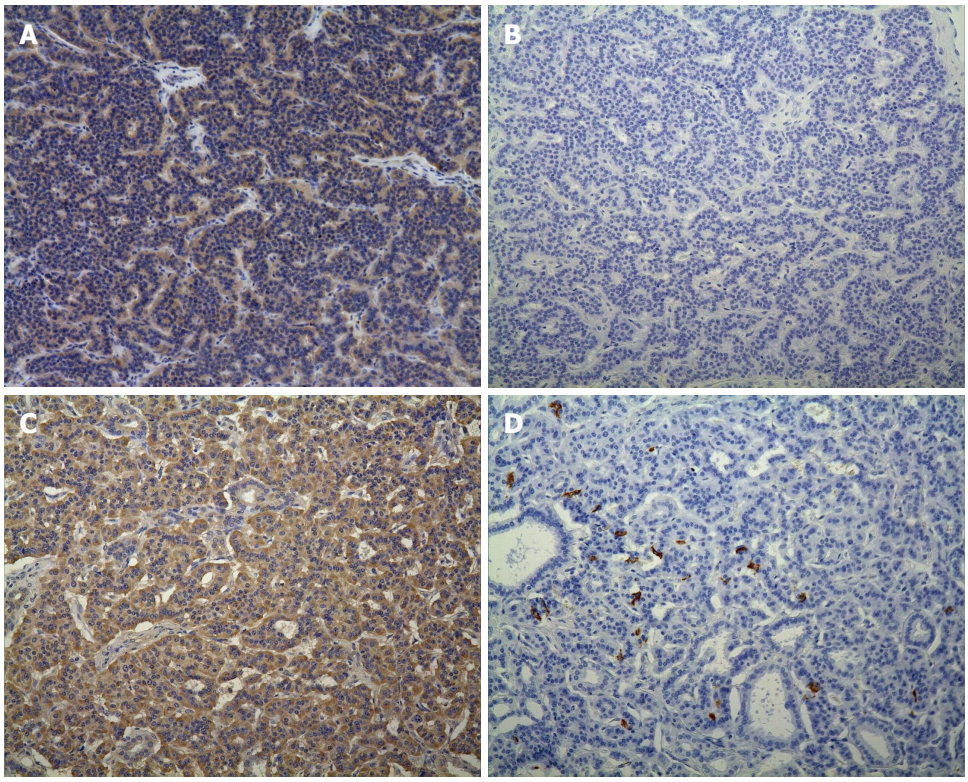

Figure 2 Immunostaining histological findings for the main lesion and the microadenoma (× 100). A: The main lesion revealed positive for glucagon; B: The main lesion revealed negative for insulin; C: The microadenoma revealed most positive for glucagon; D: The microadenoma revealed weakly positive for insulin.

Table 2 Changes of three parameters around distal pancreatectomy

	Before the operation	After the operation (POD 14)
Serum insulin level (1.8-12.2 μIU/mL)	4860	553
Serum C-peptide level (0.61-2.09 ng/mL)	14.87	5.28
Binding rate of anti-insulin antibodies (< 0.4%)	76.2	70.3

Values in parentheses are normal ranges in our institution. POD: Postoperative day.

achieved good glycemic control without taking diazoxide. He was discharged without complications on postoperative day 14.

DISCUSSION

Neuroendocrine tumors (NETs) originate from the pancreas or gastrointestinal tract and are histologically divided into NET G1, NET G2 and neuroendocrine carcinoma, including small cell type, large cell type, and mixed adenoneuroendocrine carcinoma, according to the World Health Organization classification[6]. Our case was ultimately diagnosed as an NET G1. Endocrinologically, functional tumors account for 41%-48%, and most are insulinomas[7,8]. The symptoms of insulinoma generally include hypoglycemia resulting in neuroglycopenic symptoms and hyperadrenalism because of a vicarious increase in adrenalin[9]. While blood examinations are useful for identifying insulinoma, imaging studies are helpful for localizing tumors. In recent years, surgeons have had to guess the locations of some microscopic tumors by observing the hormones flowing back to the hepatic vein after an intraarterial injection of calcium and then resecting the tumors under IOUS[10,11]. Most insulinomas are sporadic and completely cured by enucleation. After surgical therapy, patients with insulinomas generally have excellent long-term survival. A large patient cohort from the Mayo Clinic in Rochester demonstrated that cure was achieved in 98% of patients after surgical resection[12,13]. However, some cases, including high-grade malignant tumors with a poor expected prognosis, those accompanied by independent tumor(s) that secrete other hormone(s) and patients with multiple insulinomas, require careful attention[14]. Specifically, the percentage of patients with concomitant insulinoma and glucagonoma among all insulinoma cases reported in Japan between 1991 and 2000 was 1.7% (6/358)[15]. Many were mixed tumors, which can produce more than one type of hormone. Mixed endocrine pancreatic tumors producing several peptide hormones have also been reported in the West[16,17]. However, our patient had 2 independent lesions, and it is therefore highly likely that we could not achieve good glycemic control only by simple enucleation of the main lesion. To our knowledge, only 6 cases including our case, which had both insulinoma and glucagonoma, have been reported since 1985 in Japan (Table 3)[18-22]. There were no particular correlations with age or gender among the 6 patients, and in all cases, only the insulinoma was responsible for their chief complaints.

Table 3 Reports of coexistent cases of pancreatic insulinoma and glucagonoma in Japan

Case	Age (yr)	Gender	Chief compliant	Definitive diagnostic procedure	Preoperative diagnosis	Operative procedure	Postoperative diagnosis
1[18]	24	M	Consciousness disturbance	ASVS + AG	Six insulinoma at pancreatic tail	DP	Five insulinomas and two glucagonomas
2[19]	73	F	Consciousness disturbance	ASVS	One insulinoma at the region of GDA perfusion	enucleation	One insulinoma and one glucagonoma
3[20]	21	M	Consciousness disturbance	ASVS	One insulinoma at the region of SpA perfusion	1st enucleation, 2nd DP	One insulinoma and one glucagonoma
4[21]	60	F	Consciousness disturbance	AG	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma
5[22]	59	F	Consciousness disturbance	CT	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma
6 (our case)	70	M	Fasting hypoglycemia	CT + EUS	One insulinoma at pancreatic tail	DP	One insulinoma and one glucagonoma

ASVS: Arterial stimulation and venous sampling; AG: Angiography; CT: Computed tomography; EUS: Endoscopic ultrasound; GDA: Gastroduodenal artery; SpA: Splenic artery; DP: Distal pancreatectomy; M: Male; F: Female.

Glucagonoma was postoperatively diagnosed in most cases by examining additional tumors that were perioperatively identified by IOUS and resected. In 1 case (Case 3), the surgeons postoperatively identified an enucleated tumor as a glucagonoma and performed further surgery to improve persisting hypoglycemia; the patient later underwent distal pancreatectomy. Some PNETs secrete multiple hormones or are accompanied by independent hormone-positive cells that secrete other hormone(s). In this case, a small hyperplasic nodule secreting insulin incidentally coexisted with a glucagonoma. Some have reported that pancreatic islet cell hyperplasia could cause hyperinsulinemic hypoglycemia[23-27]. It is not necessarily easy to clinically and preoperatively diagnose such rare cases, even with advancing localization techniques. Careful attention is thus required to identify possible multiple lesions and monitor patients for the postoperative recurrence of tumors secreting the same or other hormone(s).

In this report, we characterized and discussed a rare insulinoma case that was preoperatively diagnosed as pancreatic insulinoma and postoperatively shown to be accompanied by glucagon-positive cells.

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