Pancreatic insulinoma combined with glucagon positive cell: A case report

Suguru Yamashita, Nobutaka Tanaka, Michiro Takahashi, Motoki Nagai, Takatoshi Furuya, Yoshio Suzuki, Yukihiro Nomura

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. Immunohistostaining 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.

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...
A Yamashita et al. Pancreatic insulinoma combined with glucagonoma

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 fast-

ing 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 exami-
nations on admission showed the following results: level of consciousness, lucid; blood pressure, 136/91 mmHg; pulse, 82 bpm; temperature, 36.6 °C; 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.

The blood levels of insulin and C-peptide were remark-

ably high, and those of carcinoembryonic antigen and
duke pancreatic monoclonal antigen type 2 were slightly

high. The levels of thyroid hormone and pituitary hor-
mone were normal. The binding rate of anti-insulin anti-
bodies 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 intraop-
erative 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 (arrow).

Table 1  Blood test findings on admission

| Test                          | Value       | Normal Range                  |
|-------------------------------|-------------|-------------------------------|
| 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          | (7-20.0)                      |
| Creatinine (mg/dL)            | 8.2         | (0.5-1.1)                     |
| Sodium (mmol/L)               | 131         | (136-145)                     |
| Potassium (mmol/L)            | 4.1         | (3.6-4.8)                     |
| Chloride (mmol/L)             | 101         | (99-109)                      |
| White blood cells (μL)        | 8000        | (3000-9500)                   |
| 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 (μU/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.

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).
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. Our case was ultimately diagnosed as an NET G1. Endocrinologically, functional tumors account for 41%-48%, and most are insulinomas. The symptoms of insulinoma generally include hypoglycemia resulting in neuroglycopenic symptoms and hyperadrenalism because of a vicarious increase in adrenaline. 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. 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. 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. 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). 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. 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). 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 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.

---

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.
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.\(^{[21-27]}\). 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.

**REFERENCES**

1. **Quaedvlieg PF**, Visser O, Lamers CB, Janssen-Heijnen ML, Taal BC. Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients. *Ann Oncol* 2001; 12: 1295-1300 [PMID: 11697843]

2. **Modlin IM**, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; 97: 934-959 [PMID: 12569593 DOI: 10.1002/cncr.11105]

3. **Lepage C**, Bouvier AM, Philip JM, Hatem C, Vernet C, Faiivre J. Incidence and management of malignant digestive endocrine tumours in a well defined French population. *Gut* 2004; 53: 549-553 [PMID: 15016750 DOI: 10.1136/gut.2003.026401]

4. **Hemminki K**, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. *Cancer* 2001; 92: 2204-2210 [PMID: 11596039]

5. **Ehehalt F**, Saeger HD, Schmidt CM, Grützmann R. Neuroendocrine tumors of the pancreas. *Oncologist* 2009; 14: 456-467 [PMID: 19413317 DOI: 10.1634/thoeneurol.2008-0259]

6. **Rindi G**, Arnold R, Bosman FT. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumors of the digestive system. Lyon: IARC, 2010

7. **Pomianowska E**, Gladhaug IP, Grehy K, Rosok BI, Edwin B, Bergstuen DS, Mathisen O. Survival following resection of pancreatic endocrine tumors: importance of R-status and the WHO and TNM classification systems. *Scand J Gastroenterol* 2010; 45: 971-979 [PMID: 20441530 DOI: 10.3109/003655210.2013.783265]

8. **Phan GQ**, Yeo CJ, Hruban RH, Lilleeom KE, Pitt HA, Cameron JL. Surgical experience with pancreatic and periampullary neuroendocrine tumors: review of 125 patients. *J Gastrointest Surg* 1998; 2: 472-482 [PMID: 9843608 DOI: 10.1016/S1091-5840(05)00555-7]

9. **Norton JA**, Fang TD, Jensen RT. Surgery for gastrinoma and insulinoma in multiple endocrine neoplasia type 1. *J Natl Compr Canc Netw* 2006; 4: 148-153 [PMID: 16451771]

10. **Baba Y**, Hayashi S, Senokuchi T, Nakaoka M. Which indexes are appropriate among those derived from selective arterial calcium stimulation and venous sampling (ASVS) for diagnosing pancreatic insulinomas? Evaluation using receiver operating characteristic analyses. *Pancreas* 2011; 40: 308-310 [PMID: 21313108 DOI: 10.1097/MPA.0b013e3181f7a4a4]

11. **Haji S**, Nomura H, Yasuda K, Hashimoto N, Ohyanagi H. Combining the selective arterial calcium injection test and intraoperative blood glucose monitoring for multiple insulinomas: report of two cases. *Surg Today* 2000; 30: 537-540 [PMID: 10883467 DOI: 10.1007/s005950070123]

12. **Grant CS**. Insulinoma. *Best Pract Res Clin Gastroenterol* 2005; 19: 793-798 [PMID: 16253900 DOI: 10.1016/j.bpg.2005.05.008]

13. **Service FJ**, McMahon MM, O’Brien PC, Ballard DJ. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc* 1991; 66: 711-719 [PMID: 1677058]

14. **de Herder WW**, Niederle B, Scoazec JY, Pauwels S, Kloppel G, Falcoz M, Wiekeweeboom DJ, Oberg K, Eriksson B, Wiedeman B, Rindi G, Lilleeom KE, Pitt HA, De C, Tani H. Well-differentiated pancreatic tumor/carcinoma: insulinoma. *Neuroendocrinology* 2006; 84: 183-188 [PMID: 17512278 DOI: 10.1159/000089010]

15. **Tsuuki Y**, Ishii H. [Insulinoma--a statistical review of 358 cases of insulinoma reported from 1991 to 2000 in Japan]. *Nihon Rinsho* 2001; 59 Suppl 8: 121-131 [PMID: 11808217]

16. **Larsson LI**, Grimalius L, Håkanson R, Rehteld JF, Stadil F, Holst J, Angervall L, Sundler F. Mixed endocrine pancreatic

---

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

| Case | Age (yr) | Gender | Chief complaint | Definitive diagnostic procedure | Preoperative diagnosis | Operative procedure | Postoperative diagnosis |
|------|---------|--------|-----------------|---------------------------------|-----------------------|---------------------|------------------------|
| 1\(^{[24]}\) | 24 | M | Consciousness disturbance | ASVS + AG | Six insulinomas at pancreatic tail | DP | Five insulinomas and two glucagonomas |
| 2\(^{[28]}\) | 73 | F | Consciousness disturbance | ASVS | One insulinoma at the region of GDA perfusion | enucleation | One insulinoma and one glucagonoma |
| 3\(^{[22]}\) | 21 | M | Consciousness disturbance | ASVS | One insulinoma at the region of SpA perfusion | 1\(^{st}\) enucleation, 2\(^{nd}\) 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 \(\text{(our case)}\) | 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.
tumors producing several peptide hormones. *Am J Pathol* 1975; 79: 271-284 [PMID: 1675866]

17 **Larsson LI**, Schwartz T, Lundqvist G, Chance RE, Sundler F, Rehfeld JF, Grimmelius L, Fahrenkrug J, Schaffalitzky de Muckadell O, Moon N. Occurrence of human pancreatic polypeptide in pancreatic endocrine tumors. Possible implication in the watery diarrhea syndrome. *Am J Pathol* 1976; 85: 675-684 [PMID: 1998736]

18 **Larsson LI**, Osada S, Komori S, Matsu S, Tokuyama Y, Okumura N, Tanaka H, Hosono Y, Sugiyama Y, Adachi Y. A case of pancreatic insulinomas with glucagon producing tumors after enucleation for pancreatic endocrine tumor 4 years before. *Jpn J Gastroenterol Surg* 2007; 40: 634-638

19 **Larsson LI**, Egami T, Tsurusaki S, Ayame H, Nakai K. A case of small insulinoma associated by clinically silent glucagonoma. *Jpn J Gastroenterol Surg* 1995; 28: 2295-2298

20 **Noguchi Y**, Yoshii M, Tukaguti I. A case of MEN type 1 combined insulinoma and glucagonoma. *Rinsho Hoshasen* 1996; 41: 385-388

21 **Miura S**, Sasakuri M, Koga M, Noda K, Deishi M. A case of insulinoma associated by glucagonoma. *Horumon To Rinsho* 1991; 39: 152-154

22 **Kyo M**, Ichikawa Y, Nakano E. A case of metastatic renal tumor from pancreatic malignant glucagonoma combined with benign insulinoma. *Nishinichin Rinsho* 1987; 49: 235-240

23 **Webb GC**, Akbar MS, Zhao C, Swift HH, Steiner DF. Glucagon replacement via micro-osmotic pump corrects hypoglycemia and alpha-cell hyperplasia in prohormone convertase 2 knockout mice. *Diabetes* 2002; 51: 398-405 [PMID: 11812747 DOI: 10.2337/diabetes.51.2.398]

24 **Zhang X**, Gaspard JP, Mizukami Y, Li J, Graeme-Cook F, Chung DC. Overexpression of cyclin D1 in pancreatic beta-cells in vivo results in islet hyperplasia without hypoglycemia. *Diabetes* 2005; 54: 712-719 [PMID: 15734847 DOI: 10.2337/diabetes.54.3.712]

25 **Sun L**, Eklund EA, Chung WK, Wang C, Cohen J, Freeze HH. Congenital disorder of glycosylation id presenting with hyperinsulinemic hypoglycemia and islet cell hyperplasia. *J Clin Endocrinol Metab* 2005; 90: 4371-4375 [PMID: 15840742 DOI: 10.1210/jc.2005-0250]

26 **Meier JJ**, Butler AE, Galasso R, Butler PC. Hyperinsulinemic hypoglycemia after gastric bypass surgery is not accompanied by islet hyperplasia or increased beta-cell turnover. *Diabetes Care* 2006; 29: 1554-1559 [PMID: 16801578 DOI: 10.2337/dc06-0392]

27 **Escribano O**, Guillén C, Nevado C, Gómez-Hernández A, Kahn CR, Benito M. Beta-Cell hyperplasia induced by hepatic insulin resistance: role of a liver-pancreas endocrine axis through insulin receptor A isoform. *Diabetes* 2009; 58: 820-828 [PMID: 19135650 DOI: 10.2337/db08-0551]