Pancreatic Somatostatinoma Manifested as Severe Hypoglycemia

Xiaosheng He, Jianping Wang, Xiaojian Wu, Liang Kang, Ping Lan

6th Affiliated Hospital, Sun Yat-sen University, Guangzhou, Republic of China

Abstract

Somatostatinoma is a rare somatostatin-producing endocrine tumor, probably malignant. Due to its nonspecific symptoms such as vague abdominal pain, weight loss, or occult clinical features, misdiagnosis occurs. We report a case of pancreatic somatostatinoma with severe hypoglycemia. The patient had experienced severe hypoglycemic attacks for 11 months periodically. Contrast computed tomography scan revealed an isodensity mass about 2 cm in the head of the pancreas. Ultimately, a local excision was carried out as the tumor was located exactly on the surface of the pancreas. Somatostatinoma was established after immunohistochemical technique. The patient led a normal life without any complaint at 1 year follow-up.

Keywords

Pancreas – somatostatinoma – hypoglycemia.

Introduction

Somatostatinomas represent 1% to 2% of pancreatic islet cell tumors but also occur in the intestine with a prevalence of 1 in 40 million per year. Since the first description by Larsson et al in 1977 [1], about 200 cases have been reported in the world [2]. Somatostatin is known to inhibit the release of almost all gut hormones including insulin and glucagon. Due to the oversecretion of somatostatin, the clinical features comprise mild diabetes mellitus, steatorrhea, diarrhea, gallstones, and weight loss, which vary in each case. Pancreatic somatostatinomas with hypoglycemia have seldom been documented. We report on a young man with pancreatic somatostatinomas appearing as hypoglycemic, who had been previously misdiagnosed as insulinoma preoperatively in our department, even during surgery.

Received: 15.02.2008 Accepted: 22.02.2008
J Gastrointestin Liver Dis
June 2009 Vol.18 No 2, 221-224
Address for correspondence: Ping Lan, MD PhD
Sun-Yatsen University
26th Yuancun Road II
Guangzhou, Republic of China
E-mail: lpzm2008@126.com

Case report

A 22-year-old man was admitted to our hospital with periodical episodes of severe hypoglycemia for 11 months. He first presented with fatigue and sudorrhea and suffered from drowsiness when hungry, especially in the morning. These symptoms could be relieved after dining. On one attack in May 2005, the patient's plasma glucose had decreased to 3 mg/dl. He also reported a 6 kg weight gain over these months due to more food intake. On admission, physical examination showed no abnormalities. Blood testing including routine tests and plasma tumor markers were almost normal except for a lower fasting plasma glucose level of 7.02 mg/dl. The preoperative plasma hormonal determinations showed a total corticosteroid concentration of 26.40 μg/dl, adrenocorticotrophic hormone 4.91 pmol/l, total growth hormone 0.05 μg/l. Insulin autoantibody was negative and a concentration of type-1 insulin like growth factor (IGF-1) was within normal limit (207 ng/ml). C peptide immunoreactivity was detected (0.2 pmol/ml) lower than normal limit (0.26-1.32 pmol/ml) at the drowsiness attack. Gastrin, glucagon and somatostatin were not measured. The patient's plasma glucose was apparently low before admission. After being referred to our hospital, fasting blood glucose still remained low between 30 mg/dl and 120 mg/dl. The median level was 72 mg/dl even after 100 g infusion of glucose daily. Some extensive tests were performed to clarify the cause of the hypoglycemic attack. A 75 g oral glucose tolerance test (OGTT) was undertaken which showed early hypoglycemia response at 30 min and maintained a low level (Fig. 1). Although tests for insulin were normal in most conditions except a slight elevation at 2 hr and 3 hr, insulin/glucose and "amended" insulin/glucose were higher than normal value (Table I).

Abdominal CT scan in our hospital detected a contrast-enhancing isodensity nodule measuring 14 mm×22 mm protruding from the uncinate process of pancreas, which partially compressed the superior mesenteric artery and vein

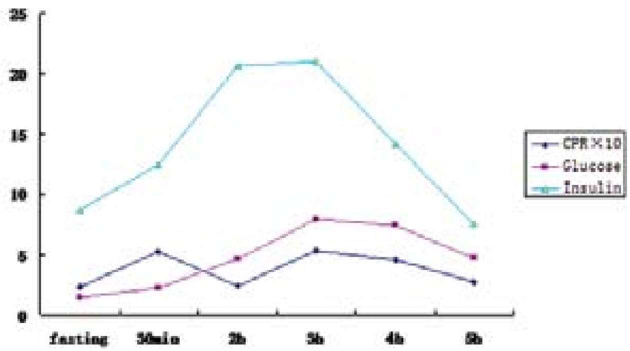

Fig 1. The relationship among CPR, glucose and insulin at prolonged OGTT. Note: 1. CPR represented C peptide immunoreactivity with pmol/ml multiplied by 10. The concentration of glucose used the unit of mmol/l, while insulin µU/ml. 2. The curve above revealed that the peak of plasma glucose was delayed and lower than normal status, suggesting the presence of autonomic tissue producing insulin. 3. CPR was relatively stable at OGTT as independent to oral glucose.

Table I. Evaluation of secretion of insulin

Insulin (µU/ml)	Glucose (mg/dl)	insulin/glucose ratio	"amended" insulin/glucose ratio
9.5	45	0.21	63.3
5	7.2	0.69	(-)
8.7	25.92	0.34	(-)

Note: 1. The normal value of insulin/glucose ratio was lower than 0.3, while "amended" insulin/glucose ratio lower than 30. 2. The value of insulin/glucose ratio and "amended" insulin/glucose ratio showed the oversecretion of insulin.

(Fig. 2). The initial ultrasonography (US) demonstrated a swollen gallbladder filled with gallstones without any lesion in the pancreas. We therefore performed an ultrasonographic visualization with the same result as we found in US. The patient refused further adjunctive examinations, such as endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA). However we still executed an exploratory laparotomy on account of the fact that the tumor was evidently present.

Surgical technique and pathological feature

A laparotomy was undertaken under general anesthesia with the patient in a supine position. No metastases in liver, greater omentum, or mesenterium were identified. The gastrocolic ligament was divided to open the omental bursa, so that the corpus of the pancreas was exposed by retracting the stomach upwards. Subsequently, a Kocher incision was performed along the right side of the duodenum to enter the retroperitoneal cavity. Dissociation of the descending and the horizontal part of the duodenum exposed the head of the pancreas for visual inspection. With its superficial location, a pancreatectomy was considered unnecessary and the patient just underwent enucleation. The operating

Fig 2. Abdominal CT scan of the patient. Note: CT scan of the abdomen confirmed a contrast-enhancing isodensity nodule about 14mm×22mm protruding in the uncinate process of pancreas, which partially compressed superior mesenteric artery and vein. No metastasis to the liver, lymph nodes or other sites in abdomen was observed.

time was 95 mins with a blood loss of 50ml. Postoperative recovery was uneventful.

There was a solid gray tumor of 30 mm in diameter with incomplete capsule which demonstrated a slow growth pattern. The relatively uniform tumor cells were medium size with find granular eosinophilic cytoplasm and a centrally located round nucleus. Mitotic figures were rare. Signs of tumor infiltrating pancreatic parenchyma were identified. Almost all the tumor cells were strongly positive for somatostatin, scatter cells positive for insulin and no tumor cells reactive with glucagon. The diagnosis of pancreatic somatostatinoma was confirmed (Fig. 3).

Discussion

Pancreatic somatostatinoma is frequently associated with "somatostatinoma syndrome", and often with metastases at the time of diagnosis. Severe hypoglycemic symptoms such as fatigue etc, lower plasma glucose level and symptom relief after food intake, which formed triad of "Whipple syndrome", were highly indicative of insulinoma and not somatostatinoma. In our case, it was difficult to distinguish from insulinoma prior to surgery because of high fasting plasma insulin and typical hypoglycemic symptoms. Although insulin levels were normal in most conditions, elevated insulin/glucose ratio, elevated "amended" insulin/glucose ratio and the delayed low peak of plasma glucose in OGTT suggested the oversecretion of insulin [3, 4]. Thus the diagnosis of insulinoma or at least autonomic hyperplasia was put in evidence clinically.

Somatostatin inhibits the secretion of insulin and other counter-regulatory hormones including glucagon and growth hormone. The inhibition of both insulin and glucagon usually give rise to mild diabetes. However, when the effect of

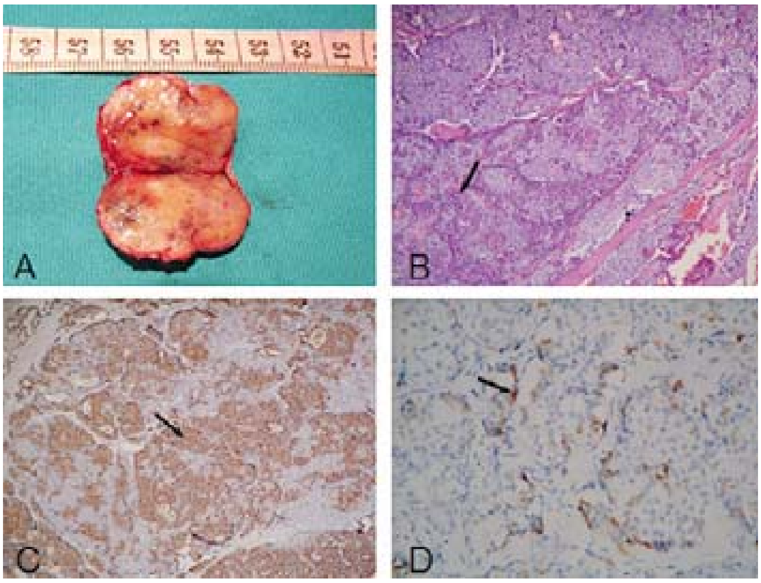

Fig 3. Pathological examination of the tumor. A. A solid, partially gray tumor of 30 mm in diameter with incomplete capsule. B.The arrow shows the tumor in the pancreas with relatively uniform tumor cells. Signs of tumor infiltrating pancreatic parenchyma were identified - C and D. Almost all tumor cells were strongly positive for somatostatin, while scatter cells were positive for insulin.

somatostatin on growth hormone and glucagon is superior to that on insulin, hypoglycemia comes out. Pancreatic somatostatinomas often produce multihormones, including glucagon, calcitonin, insulin [5-7]. On the basis of the assumption that islet B cells and D cells arise from a common precursor, somatostatinomas were immunohistochemically positive for insulin in a proportion of 33% [8, 9]. Relevant tests in our patient had discovered the oversecretion of insulin, but no test for plasma somatostatin concentration was done. Pathological results found that immunostaining for somatostatin was strongly positive, and weakly positive for insulin. Somatostatin is accepted not to inhibit the secretion of insulin by tumor so that the effect of tumoral insulin is strengthened by somatostatin inhibiting other counter-regulatory hormones [10]. In addition, due to somewhat exocrine pancreatic insufficiency, carbohydrate absorption is impaired, which can deteriorate hypoglycemia [11]. Hypoglycemia, as in our patient, emerged because of all of the above.

Identifying the exact location of somatostatinoma preoperatively is not a simple job due to its usually small size, even if the diagnosis is established. With adequate detection rates and satisfactory outcome for patients, we favor a less invasive or non-invasive imaging technique such as MRI, CT. In our case, the tumor was detected in the uncinate process of pancreas using has CT-scan, partially illustrated as "incident" as the previous cases [12]. Intraoperative ultrasound in open surgery not only has the same sensitivity as palpations by experienced surgeon, but also provides a better knowledge of the relationship between the tumor and the vessels or the pancreatic duct. When ultrasonography before surgery does not discover the tumor, we tend to use this technique.

The rarity of presence and the lack of long-term follow-up information make an optimal treatment difficult to decide. When feasible, surgical excision represents the choice of treatment to prolong survival, control the symptoms and prevent local complications [13]. Even the presence of postoperative liver or lymph node metastasis can be solved by removal. Local resection is highly effective for tumors smaller than 20 mm in diameter. Enucleation was carried out in the present case for its location, no infiltration of pancreatic duct and no metastasis to the liver or lymph nodes. Prognosis is controversial owing to the incidence of metastases at the time of diagnosis and the possible long-time survival of patients even with metastases or without any treatment. It has been reported that a patient with metastatic duodenal somatostatinoma without any treatment is still alive after 30 years [14]. A 1 year follow-up in our case showed a good prognosis. However, Shirouzu et al [15] have reported a relatively small pancreatic somatostatinoma measuring 20 mm in diameter, which produced multiple liver metastases by 6 months after operation. The average postoperative 5-year survival rate was 75.2% in 90 patients overall including 100.0% in 46 without metastases [2].

The malignancy of somatostatinoma is still being investigated.

References

1. Larsson LI, Hirsch MA, Holst JJ, et al. Pancreatic somatostatinoma. Clinical features and physiological implications. Lancet 1977; 1:

666–668.

2. Soga J, Yakuwa Y. Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. J Exp Clin Cancer Res 1999; 18: 13–22.
3. Fajans SS, Floyd JC Jr. Fasting hypoglycemia in adults. N Engl J Med 1976; 294: 766-772.
4. Hattori N, Ishihara T, Saiki Y, et al. Insulinoma with normal plasma insulin concentrations and insulin/glucose ratios during hypoglycemic episodes. Intern Med 1994; 33: 813-816.
5. Yano T, Yamamoto N, Fujimori K, Inamori S, Hayashi H, Mizumoto R. Glucagon-secreting pancreatic islet cell carcinoma, containing insulin and somatostatin, with hypoglycemic attack. Am J Gastroenterol 1982; 77: 387-391.
6. Karasawa Y, Mochizuki T, Kawa S, et al. Insulin and somatostatin releasing islet cell tumor caused hypoglycemia. Intern Med 2001; 40: 324-330.
7. Sugimoto F, Sekiya T, Saito M, et al. Calcitonin-producing pancreatic somatostatinoma: report of a case. Surg Today 1998; 28: 1279-1282.
8. Metz DC, Jensen RT. Endocrine Tumors of the Pancreas. In: *Bockus Gastroenterology*. Philadelphia: WB Saunders Co, 1995; 3002-3034.
9. Sosa-Pineda B, Chowdhury K, Torres M, Oliver G, Gruss P. The Pax4 gene is essential for differentiation of insulin-producing beta cells in the mammalian pancreas. Nature 1997; 386: 399-402.
10. Nauck M, Stockmann F, CreutzfeldtW. Evaluation of a euglycaemic clamp procedure as a diagnostic test in insulinoma patients. Eur J Clin Invest 1990; 20: 15-28.
11. Anene C, Thompson JS, Saigh J, Badakhsh S, Ecklund RE. Somatostatinoma: atypical presentation of a rare pancreatic tumor. Am J Gastroenterol 1995; 90: 819-821.
12. Tomono H, Kitamura H, Iwase M, et al. A small, incidentally detected pancreatic somatostatinoma: report of a case. Surg Today 2003; 33: 62–65.
13. Kianmanesh R, O'toole D, Sauvanet A, Ruszniewski P, Belghiti J. Surgical treatment of gastric, enteric, and pancreatic endocrine tumors Part 1. Treatment of primary endocrine tumors. J Chir (Paris) 2005; 142: 132-149.
14. Ulfberg J, Tot T, Wilander E. Thirty-year survival with an untreated malignant duodenal somatostatinoma. Endocr Pathol 1998; 9: 375-378.
15. Shirouzu K, Miyamoto Y, Shiramizu T, Morimatsu M. Somatostatinoma of the pancreas. Acta Pathol Jpn 1985; 35: 1285–1292.