A Case of a Giant Glucagonoma with Parathyroid Hormone-related Peptide Secretion Showing an Inconsistent Postsurgical Endocrine Status

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Abstract

A 53-year-old woman was admitted because of a giant pancreatic tumor. Hypercalcemia and a high serum parathyroid hormone-related peptide (PTHrP) level were observed. A hypoglycemic attack occurred during pancreatectomy, and the surgical specimen revealed a PTHrP-secreting glucagonoma. Liver metastases developed 1 and 5.5 years later, and bone metastases appeared 6 years after surgery. Her serum PTHrP concentrations remained normal after surgery, despite re-elevation of the serum glucagon concentration after recurrence. The clinical course of this case illustrates the process of development of neuroendocrine tumors secreting two or more hormones.

Key words: glucagonoma, PTHrP

(Intern Med 50: 1689-1694, 2011)
(DOI: 10.2169/internalmedicine.50.5357)

Introduction

Glucagonomas are rare, accounting for only 5% of all pancreatic neuroendocrine tumors. In Japan, approximately 50% of glucagonomas are malignant, and they are associated with multiple endocrine neoplasia type 1 (MEN 1) in approximately 4% of cases (1). These tumors present with various clinical findings, such as skin eruptions, decreased glucose tolerance, and hypo-aminoacidemia.

Parathyroid hormone-related peptide (PTHrP) was discovered in 1987 as the tumor product responsible for humoral hypercalcemia of malignancy (2). Parathyroid hormone (PTH) and PTHrP show significant sequence homology within the first 13 amino acid residues. PTHrP binds to PTH receptor-1 with the same affinity as PTH; consequently, PTHrP secretion leads to hypercalcemia and hypophosphatemia. PTHrP secretion is occasionally detected in various malignant tumors, such as lung cancer and renal cell cancer. However, there have been only a few reports of PTHrP-secreting pancreatic neuroendocrine tumors (3-16), and even fewer reports of PTHrP-secreting glucagonomas (14).

The present case had a giant pancreatic tumor with hypercalcemia, hypophosphatemia, and a normal glucose level. A hypoglycemic attack was observed during and after surgery, and the histopathological examination showed a PTHrP-secreting glucagonoma. After surgical resection, the patient developed distant metastases with re-elevation of the serum glucagon level, while the PTHrP level was continuously normal. This is a very rare case of a pancreatic neuroendocrine tumor showing inconsistent endocrine features after surgery.
Table 1. Blood Analysis and Urinalysis on Admission

<table>
<thead>
<tr>
<th>Blood</th>
<th>Total bilirubin 0.4 mg/dL</th>
<th>CEA 1.3 ng/mL (0-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 3600 /µL</td>
<td>Direct bilirubin 0.0 mg/dL</td>
<td>CA19-9 10.0 U/mL (0-37)</td>
</tr>
<tr>
<td>Neutrophil 54.0 %</td>
<td>Aspartate aminotransferase 11 IU/L</td>
<td>PTH-intact &lt;8.0 pg/mL (10-65)</td>
</tr>
<tr>
<td>Eosinophil 3.0 %</td>
<td>Alanine aminotransferase 13 IU/L</td>
<td>PTHrP-Intact 2.8 pmol/L (0-1.1)</td>
</tr>
<tr>
<td>Basophil 1.0 %</td>
<td>Lactic dehydrogenase 92 IU/L</td>
<td>Aldosterone 34.9 pg/mL (30-160)</td>
</tr>
<tr>
<td>Monocyte 9.0 %</td>
<td>Alkaline phosphatase 137 IU/L</td>
<td>Guicagon 4000 pg/mL (40-180)*</td>
</tr>
<tr>
<td>Lymphocyte 33.0 %</td>
<td>γ-glutamyl transpeptidase 39 IU/L</td>
<td>Insulin 12.6 µU/mL (1.1-17)*</td>
</tr>
<tr>
<td>Red blood cell 319x10^12 /µL</td>
<td>Cholinesterase 305 IU/L</td>
<td>Gastrin 34.6 pg/mL (30-150)*</td>
</tr>
<tr>
<td>Hb 9.2 g/dL</td>
<td>Amylase 53 IU/L</td>
<td>VIP 5 pg/mL (&lt;100)*</td>
</tr>
<tr>
<td>Hematocrit 28.7 %</td>
<td>Lipase 13 IU/L</td>
<td></td>
</tr>
<tr>
<td>MCV 90.0 fl</td>
<td>C-reactive protein 0.26 mg/dL</td>
<td></td>
</tr>
<tr>
<td>MCHC 32.1 g/dL</td>
<td>Blood urea nitrogen 10 mg/dL</td>
<td>pH 6.0</td>
</tr>
<tr>
<td>Platelet 14.3x10^4 /µL</td>
<td>Creatinine 0.4 mg/dL</td>
<td>Protein (-)</td>
</tr>
<tr>
<td>Prothrombin time 91.9 %</td>
<td>Uric acid 5.1 mg/dL</td>
<td>Sugar (-)</td>
</tr>
<tr>
<td>Total protein 5.7 g/dL</td>
<td>Sodium 141 mEq/L</td>
<td>Occult Blood (-)</td>
</tr>
<tr>
<td>Albumin 3.6 g/dL</td>
<td>Potassium 2.8 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Triglyceride 87 mg/dL</td>
<td>Chloride 111 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol 118 mg/dL</td>
<td>Calcium 3.07 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Fasting blood sugar 97 mg/dL</td>
<td>Phosphorus 0.65 mmol/L</td>
<td></td>
</tr>
<tr>
<td>HbA1c 4.8 %</td>
<td>Hepatitis B virus, surface antigen (-)</td>
<td>Arterial blood gas</td>
</tr>
</tbody>
</table>

*: normal
*Stored serum
CA19-9; Carbohydrate antigen 19-9
CEA; Carcinoembryonic antigen
HCO3-; bicarbonate
MCH; mean corpuscular hemoglobin
MCHC; mean corpuscular hemoglobin concentration
MCV; mean corpuscular volume
PaCO2; partial pressure of arterial carbon dioxide
PaO2; partial pressure of arterial oxygen
PTH; parathyroid hormone
PTHrP; parathyroid hormone-related peptide
VIP; vasoactive intestinal peptide

Case Report

A 53-year-old woman who had been aware of discomfort in the left lateral abdomen for more than 6 months underwent abdominal ultrasonography in February 2003. Because a large mass was detected in the left hypochondrium, she was admitted to our hospital for further medical examinations. She showed no other physical manifestations, including skin eruptions or neurological signs.

On admission, blood analysis showed normocytic anemia, hypokalemia, hypercalcemia, and hypophosphatemia, while urinalysis showed hypercalciuria and hyperphosphaturia. Blood gas analysis revealed metabolic alkalosis. In addition, a decrease in the serum PTH level and an increase in the PTHrP level were observed. The PTHrP appeared to have directly caused the hypercalcemia, and the hypokalemia seemed to be related to metabolic alkalosis due to the PTHrP. Hepatic and renal functions, as well as the serum glucose level, were all normal (Table 1). There was no hypo-aminoacidemia.

Abdominal contrast-enhanced computed tomography showed a solid, poorly-demarcated, high-density, hypervasular mass of 14 cm in diameter with internal necrosis involving the pancreatic body and tail (Fig. 1). Abdominal angiography showed a tumor stain with the left gastric and splenic arteries as major feeding vessels (Fig. 2). The splenic vein was not visualized on portography, strongly suggesting intravenous tumor invasion. Magnetic resonance cholangiopancreatography showed discontinuity of the main pancreatic duct in the head of the pancreas caused by the tumor. Neither pancreatic duct dilatation nor cystic lesions were observed.

Upper gastrointestinal endoscopy showed an elevated lesion in the anterior wall of the gastric angle, suggesting a giant submucosal tumor or compression by an extragastric mass. Endoscopic ultrasonography revealed a large solid tumor in contact with the pancreatic body and tail. Although the identification of the primary organ was difficult due to the large size, the relatively preserved gastric wall structure
Most likely. Normal fasting blood glucose and HbA1c levels, despite its large size, a pancreatic neuroendocrine tumor was vascular and showed no distant or lymph node metastasis development. The tumor was highly suspected. Since the tumor was hypervascular, lymph node swelling was not observed.

Suggested an extragastric tumor, such as a pancreatic tumor. Lymph node swelling was not observed.

Given these examination findings, a malignant pancreatic tumor was highly suspected. Since the tumor was hypervascular and showed no distant or lymph node metastasis development, a pancreatic neuroendocrine tumor was most likely. Normal fasting blood glucose and HbA1c levels, hypercalcemia, and a high PTHrP level suggested that the tumor was a PTHrP-secreting neuroendocrine tumor. After normalization of the serum calcium level with infusion of electrolytes and fluid, distal pancreatectomy was performed (Fig. 3). The tumor showed lobulated growth, and its border with the surrounding organs was relatively clear macroscopically. The spleen, left adrenal gland, and mesentery were also resected due to tumor invasion. Continuous hypoglycemia observed during and after the operation indicated that the tumor caused abnormal glucose metabolism.

Histopathological examination showed tumor cells in a ribbon-like or trabecular pattern, containing mainly round nuclei and eosinophilic granules (Fig. 4a). In addition, dense small cells with a high nucleus/cytoplasm ratio and an increase in mitotic figures were observed, suggesting a malignant tumor. Immunostaining was positive for chromogranin, glucagon, and PTHrP (Fig. 4b). Interestingly, the glucagon- and PTHrP-positive cells formed tumor nests separately, and each type of cell was distributed in a different manner within the nests. The glucagon level in preoperatively stored serum was markedly elevated (4,000 pg/mL). All together, the final diagnosis was a malignant glucagonoma with PTHrP secretion. There were no findings suggesting MEN 1 on blood analysis and imaging techniques including the pituitary gland and parathyroid. In addition, the patient had no family history of endocrine or malignant diseases.

One month after the operation, the blood glucose level became stable, and the glucagon, PTH, and PTHrP levels were normalized. The hypercalcemia also improved. In April 2004 (1 year after the initial operation), a solitary liver metastasis of 30 mm in size developed in the right lobe, without an increase in the serum glucagon level. This was successfully resected with right hepatic lobectomy. The histopathological features appeared to be those of a neuroendocrine tumor, but immunostaining was negative for both glucagon and PTHrP. In September 2008 (5.5 years after the initial operation), serum glucagon was again markedly increased, with the emergence of multiple liver metastases, which were treated with transcatheter arterial chemoembolization and radiofrequency ablation. Both in February 2009 and April 2010 (6 and 7 years after the initial operation), bone metastases appeared in the lumbar spine and sacrum and were treated with radiotherapy. The serum glucagon level has

Figure 1. Abdominal contrast-enhanced CT (a: arterial phase, b: equilibrium phase). There is a solid, poorly demarcated, high-density, hypervascular mass of 14 cm in diameter with internal necrosis involving the pancreatic body and tail. CT: computed tomography

Figure 2. Abdominal angiography (a: celiac angiography, b: portography). There is a tumor stain with the left gastric and splenic arteries as major feeding vessels. The splenic vein is not visualized on portography, which strongly suggests intravenous tumor invasion.
been continuously high after emergence of multiple liver metastases, while the serum PTHrP and calcium levels have been normal during the disease course after the initial operation (Fig. 5).

Figure 3. Surgically resected specimen. The tumor shows lobulated growth, and its border with the surrounding organs is relatively clear macroscopically. The spleen, left adrenal gland, and mesentery were also resected due to tumor invasion.

Figure 4. Histopathological findings. a. Hematoxylin and Eosin staining: Tumor cells show a ribbon-like or trabecular structure and contain round nuclei and eosinophilic granules, suggesting a neuroendocrine tumor. There are dense small cells with a high nucleus/cytoplasm ratio and an increase in mitotic figures, suggesting a malignant tumor. b. Immunohistochemical analysis using specific antibodies (b-1. glucagon, b-2. PTHrP): Chromogranin, glucagon, and PTHrP are positive, consistent with a diagnosis of glucagonoma with PTHrP secretion. The glucagon- and PTHrP-positive cells form tumor nests separately, and each cell type is distributed in a different manner within the nests. PTHrP: parathyroid hormone-related peptide

Discussion

A case of a pancreatic neuroendocrine tumor that exhibited an interesting and inconsistent endocrine status during the patient’s clinical course was presented. Although endocrinological and immunohistochemical examinations revealed a PTHrP-secreting glucagonoma, the serum glucagon and PTHrP levels did not parallel the tumor status.

Glucagonomas are rare, accounting for only 5% of all pancreatic neuroendocrine tumors. In Japan, approximately 50% of glucagonomas are malignant (1), and it has been reported that 60-80% of glucagonomas \( \geq 5 \) cm in size are malignant, with distant metastases (17). Although glucagonomas could show various clinical signs and symptoms, the mean tumor diameter at the time of diagnosis is \( \geq 5 \) cm because of a poor correlation between tumor size and symptoms (17). Overall, 54% of tumors are symptomatic, and the preoperative diagnosis is made correctly in only half of cases (18). In fact, the present case could not be correctly diagnosed as a glucagonoma prior to resection, which gave rise to a hypoglycemic attack during and after surgery. Al-
Although the curative resection rate of glucagonoma is low, the survival rate in patients with glucagonoma is relatively high, with a 5-year survival of 64.3% (18). Hence, according to the treatment strategy proposed by the National Cancer Institute of the United States (19), even tumors with distant metastases should be resected when possible, and for unresectable tumors, radiofrequency ablation or cryosurgical ablation, transcatheter arterial chemoembolization, systemic chemotherapy, and somatostatin analogue therapy should be considered.

The present case achieved more than 7 years survival after the initial operation, despite recurrence with liver and bone metastases. The serum glucagon levels have been continuously high except for the period after the initial operation until emergence of multiple liver metastases. Interestingly, the serum glucagon level was still low when the solitary liver metastasis, which exhibited negative immunostaining for glucagon, developed. Thus, although the serum glucagon level can be used as a tumor marker for not only diagnosis but also follow-up to indicate treatment effectiveness and disease progression (21), small recurrent regions of neuroendocrine tumors may not secrete the hormone. In addition, a high serum glucagon level may indicate the existence of a large number of tumor cells, even though imaging technology cannot detect obvious recurrence. Hence, patients in the postoperative stage of neuroendocrine tumors with high hormone levels should be followed carefully so as not to miss the emergence of significant recurrence.

In the present case, despite the markedly elevated serum glucagon level, no clear glucose intolerance was noted preoperatively. A hypoglycemic attack during and after surgery, which has been reported in some case presentations of glucagonoma patients in Japan, was the sole manifestation suggesting an abnormal glucose metabolism. Excessive glucagon produced by a glucagonoma is involved in glycogenolysis and gluconeogenesis in the liver, and it also stimulates beta cells, promoting insulin secretion. Furthermore, the involvement of biologically inactive glucagon precursors or down-regulation of the action of glucagon in the liver has also been reported (20). Therefore, the blood glucagon concentration is not always proportional to the degree of glucose tolerance, which is expected to vary considerably among glucagonomas (20).

PTHrP is a single-chain peptide, and its amino terminal domain has considerable similarity to PTH (22). If PTHrP is produced in excess, it exerts an endocrine effect by interacting with the classical bone and kidney PTH-receptor leading to the humoral hypercalcemia of malignancy (23). In general, the serum PTHrP level is normalized by resecting the tumor secreting it, and it increases again at recurrence. Therefore, the serum PTHrP level is considered to be a useful tumor marker for such tumors (24). It has been reported that it can also be used to indicate treatment effectiveness and disease progression in patients with hypercalcemia associated with islet cell carcinoma (22). In addition, Papazachariou et al (12) reported that all cases of 13 patients who had pancreatic neuroendocrine tumors with hypercalcemia due to a high PTHrP level showed marked decreases in serum PTHrP and calcium levels after pancreatectomy. Srijajaskanthan et al (16) reported 5 case series of PTHrP-secreting pancreatic neuroendocrine tumors in which the serum calcium level could also be controlled using treatments other than surgery, such as chemotherapy, hepatic embolization, and somatostatin analogue therapy.

A pancreatic neuroendocrine tumor secreting multiple hormones is not uncommon, as Lam and Lo (25) reported that immunohistochemical staining showed evidence of multi-hormone production in 18% of pancreatic neuroendo-
crine tumor cases. In the present case, after the initial resection, serum PTHrP and calcium levels remained normal, despite repeated episodes of recurrence with elevation of the serum glucagon level. There are hypotheses that may explain the dissociation of the hormone status in this case. First, there had originally been two distinct tumors, which secreted either PTHrP or glucagon in the pancreas, and only a tumor secreting glucagon recurred. Second, tumor cells secreting one hormone gained the function of secreting another hormone with progression, and then lost the PTHrP-secreting function at recurrence. In fact, Wynick et al (26) reported that 6.8% of pancreatic endocrine tumors had elevated concentrations of other hormones over a median of 19 months. Finally, a large number of tumor cells may be needed to increase the serum PTHrP concentration. To the best of our knowledge, there has been only one report of a PTHrP-secreting glucagonoma (14). In this previous case, serum glucagon, PTHrP, and calcium levels decreased after tumor resection. Interestingly, however, after the emergence of a large local recurrence, serum glucagon remained normal, while PTHrP and calcium levels increased again, which is opposite to what happened in the present case.

A rare case of a giant glucagonoma with PTHrP secretion showing an inconsistent postsurgical endocrine status was reported. Although a neuroendocrine tumor secreting two or more hormones simultaneously is not uncommon, the clinical course and endocrine features have not yet been fully evaluated. Hence, in the future, the natural history of these tumors may be elucidated in more detail, and there will be more effective therapeutics and follow-up methods for such patients.

The authors state that they have no Conflict of Interest (COI).

References


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