A 51-year-old man was admitted with hyperglycemia and a duodenal tumor. Although his glycemic control was poor, basal C-peptide levels were not suppressed. Further examination revealed a mass measuring 7.8 cm in diameter in the third portion of the duodenum. Duodenectomy revealed a slow-growing sessile tumor located near Treitz’s ligament. The immunohistochemical profile of sections of the specimen revealed the presence of somatostatin. The patient’s serum somatostatin was elevated to 300 pg/ml preoperatively, but was reduced to 10 pg/ml postoperatively. Glycemic control also normalized after the operation.

Key words: duodenal somatostatinoma, endocrine tumor, somatostatin, insulin, diabetes mellitus

Introduction

Somatostatin is recognized as a brain-gut hormone, and is known to suppress numerous hormones, including insulin, glucagon, and gastrin. Somatostatinoma is an extremely rare endocrine neoplasm, producing somatostatin and arising mostly in the pancreas or the duodenum. Duodenal somatostatinoma is particularly rare, accounting for only 2% of all gastrointestinal endocrine tumors (1). Most of the duodenal somatostatinomas are reported in the second part of the duodenum, particularly in the ampulla and the peri-ampullary area. Few cases have revealed somatostatinomas in the third or fourth part of the duodenum (2). The clinical features are somewhat different between pancreatic somatostatinomas and duodenal somatostatinomas. The manifestations of duodenal somatostatinoma are local symptoms, such as abdominal pain, jaundice and cholelithiasis, but cases are often asymptomatic. Pancreatic somatostatinoma usually presents with the clinical triad of diabetes mellitus, cholelithiasis and steatorrhea, known as the “somatostatinoma syndrome” (3). The glucose intolerance accompanying somatostatinoma is mainly induced by the suppression of insulin due to the oversecretion of somatostatin. Here, we report a duodenal somatostatinoma in the third portion of the duodenum with hyperglycemia, apparently not due to the suppressive effect of somatostatin.

Case Report

A 51-year-old man was admitted to the hospital with hyperglycemia. The patient had experienced abdominal pain and gastrointestinal endoscopy had revealed a duodenal tumor 2 months previously. On admission, the abdominal pain had resolved and no diarrhea, jaundice, anemia or weight loss were observed. There was no family history of multiple endocrine neoplasia (MEN). Laboratory studies revealed glucose intolerance, with a fasting plasma glucose of 224 mg/dl following the subcutaneous injection of insulin (Lispro 4 units) at the previous meal, and a hemoglobin A1c of 10.0% (Table 1). The secretory response to glucagon was not suppressed, as the basal level of C-peptide was slightly elevated to 3.04 ng/ml in the glucagon loading test. Diurnal glucose values were unstable, varying between 70 mg/dl and 310 mg/dl with insulin therapy. The upper gastrointestinal series showed a submucosal tumor measuring 7.8 cm in diameter in the third portion of the duodenum, with relatively smooth superficial features (Fig. 1). The mass occupied almost the whole duct in the third portion of the duodenum. Biopsy revealed no malignancy. Computed tomography of the abdomen also detected the mass measuring 27×80 mm, which was enhanced by contrast medium (Fig. 2). No metastasis to the liver, lymph nodes or other sites, and no ascites were observed. A duodenectomy was performed, which revealed a slow-growing, sessile tumor located near Treitz’s ligament. The tumor measured 60×40×25 mm and did not in-

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vade the serosal layer. However, the mesenteric lymph nodes were swollen, measuring 10 mm. Sections of the specimen showed neoplastic cell proliferation with a vague acinar to ribbon-like pattern (Fig. 3A). The “psammoma body”, the pathological feature of a somatostatinoma, was not observed. The immunohistochemical profile revealed the presence of somatostatin (Fig. 3B). However immunoperoxidase stains for glucagon, gastrin and insulin were negative. After the diagnosis of somatostatinoma, we measured endocrinological parameters before and after the operation. The serum somatostatin was elevated to 300 pg/ml preoperatively, but was reduced to 10 pg/ml postoperatively (Table 2). There was no feature of von Recklinghausen’s disease.

The patient had an uneventful recovery after the tumor resection. No recurrence or metastasis were revealed on subsequent computed tomography. Glycemic control also was normalized and has been stable for one year. The 75 g OGTT showed a normal pattern after the operation.

### Discussion

Somatostatinoma is a very rare endocrine tumor, with only about 180 cases reported (4). The first cases of somatostatinoma were reported by Larsson et al in 1977 (5). Kaneko et al reported the first case of a duodenal somatostatinoma in 1979 (6). Somatostatin is recognized as a brain-gut hormone, secreted by the hypothalamus, cerebrum, limbic system, spinal cord, vagus nerve, autonomic nervous system, D cells in Langerhans’s islets of the pancreas, antrum of the stomach, duodenum and small intestine. Somatostatin suppress various hormones, including insulin, growth hormone (GH), glucagon, thyroid stimulating hormone (TSH), pancreatic polypeptide (PP), secretin, gastric inhibitory polypeptide (GIP) and cholecystokinin-pancreozymin (CCK-PZ). Hypersomatostatinemia caused by the neoplasm of the cells producing somatostatin occurs particularly in the D cells of the pancreas or digestive tract. The pancreas is the most common site of somatostatinomas, representing 68% of all tumors. Other sites of somatostatinomas include the duodenum (19%), the papilla of Vater (3%), and the small intestine (3%). Among duodenal somatostatinomas, most cases are located in the descending part of the duodenum, whereas few cases, including the present case, are found in the third or fourth portion. Tanaka et al reported that 63% of duodenal somatostatinomas originate in the ampulla and peri-ampullary area. Only one case has been reported in the fourth part, and no case in the third portion (2). Immunoreactive somatostatin cells are widely distributed in the digestive tract, but are particularly dense in the antrum of the stomach and the duodenum (7). The occurrence of
duodenal somatostatinomas in the ampulla and periampullary region may relate to the distribution of D cells secreting somatostatin, but the details are unknown.

The clinical features associated with pancreatic somatostatinomas and duodenal somatostatinomas are somewhat different. Pancreatic somatostatinomas usually present with diabetes mellitus, cholelithiasis and steatorrhea, also known as the “somatostatinoma syndrome” (3). Duodenal somatostatinomas produce local symptoms, such as jaundice, abdominal pain and gastrointestinal bleeding, or are asymptomatic. The present patient complained of abdominal pain and had glucose intolerance. The abdominal pain was probably caused by the local effect of the tumor mass. However, the mechanism of the glucose intolerance was unclear in our case. The glucose intolerance in somatostatinoma generally results from the suppression of insulin secretion by over-secretion of somatostatin. In our case, the serum concentration of somatostatin was elevated, whereas the basal level of C-peptide was not suppressed. This result might mean that the insulin resistance existed preoperatively. Some factor inducing the insulin resistance, such as tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), might be produced from the tumor mass. Reports of glucose intolerance with somatostatinoma are inconsistent. Some reports show that the somatostatinoma induced serious hyperglycemia with ketoacidosis (8), while others report hypoglycemia (9). Other reports show that the serum insulin level with somatostatinoma is within the normal range (10). The degree of the glucose intolerance might also be re-

### Table 2. Hormone and Biochemistry Studies before and after the Operation

<table>
<thead>
<tr>
<th></th>
<th>Pre-operation</th>
<th>Post-operation (30 days after)</th>
<th>(normal range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin</td>
<td>300 pg/ml</td>
<td>10 pg/ml</td>
<td>(1.0〜12 pg/ml)</td>
</tr>
<tr>
<td>Glucagon</td>
<td>53 pg/ml</td>
<td>81 pg/ml</td>
<td>(40〜180 pg/ml)</td>
</tr>
<tr>
<td>Gastrin</td>
<td>180 pg/ml</td>
<td>380 pg/ml</td>
<td>(&lt;200 pg/ml)</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>33 pg/ml</td>
<td>38 pg/ml</td>
<td>(15〜86 pg/ml)</td>
</tr>
<tr>
<td>ACTH</td>
<td>8.2 pg/ml</td>
<td>33.9 pg/ml</td>
<td>(9〜52 pg/ml)</td>
</tr>
<tr>
<td>GH</td>
<td>1.64 ng/ml</td>
<td>2.36 ng/ml</td>
<td>(&lt;0.42 pg/ml)</td>
</tr>
<tr>
<td>Cortisol (not measured)</td>
<td></td>
<td>8.0 (\mu)g/dl</td>
<td>(4.0〜18.3 (\mu)g/dl)</td>
</tr>
<tr>
<td>Insulin</td>
<td>29.7 (\mu)U/ml*</td>
<td>5.9 (\mu)U/ml</td>
<td>(1.8〜11.3 (\mu)U/ml)</td>
</tr>
<tr>
<td>FPG (on the test day)</td>
<td>161 mg/dl*</td>
<td>85 mg/dl</td>
<td>(1.8〜11.3 (\mu)U/ml)</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>11.81*</td>
<td>1.24</td>
<td>(4.3〜5.8%)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>10.0%</td>
<td>4.9%**</td>
<td>(4.3〜5.8%)</td>
</tr>
<tr>
<td>Glucagon loading test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-peptide (basal)</td>
<td>3.06 ng/ml</td>
<td>1.61 ng/ml**</td>
<td>(0.94〜2.80 ng/ml)</td>
</tr>
<tr>
<td>(6 min)</td>
<td>9.28 ng/ml</td>
<td>6.40 ng/ml**</td>
<td></td>
</tr>
</tbody>
</table>

*under insulin therapy, **the data after 90 days of the operation.
lated to the balance of the secretion of insulin and counter-regulatory hormones. Glucose intolerance is more often associated with duodenal somatostatinoma than with pancreatic somatostatinoma. About 50% of extrapancreatic somatostatinomas are concomitant with von Recklinghausen’s disease. The tumor often produces other hormones, such as insulin, gastrin, calcitonin, ACTH, vasoactive intestinal peptide (VIP), and pancreatic polypeptide (PP). Psammoma bodies are observed pathologically in more than 50% of the extrapancreatic somatostatinomas (11). One of the characteristics of our case was that there were few features of duodenal somatostatinoma.

Duodenal somatostatinomas are generally smaller (mean size, 2–3 cm) than pancreatic somatostatinomas (mean size, 5–6 cm) (11). Most duodenal somatostatinomas are present in the ampulla. On the other hand, the somatostatinoma syndrome, which is usually observed in pancreatic somatostatinoma, might not appear until the tumor mass increases. Regarding metastasis, approximately 30% of duodenal and 70% of pancreatic somatostatinomas were found to be characterized by lymph node or hepatic metastases in an earlier review (12). The metastasis of the somatostatinoma appeared to depend on the tumor size. Duodenal somatostatinomas might be relatively earlier detected than pancreatic somatostatinomas. In the present case, the tumor size was large (6.0 cm) and there was metastasis to the lymph nodes. It was difficult to detect clinical symptoms because the tumor located in the third portion of the duodenum would not produce any local symptoms until the tumor mass increased. The duodenal somatostatinomas are malignant by nature, and the risk of metastasis significantly increases with tumors larger than 2.0 cm (2). This case needs to be followed carefully regarding metastasis and recurrence.

The index for metastasis and recurrence has not been clearly established. The somatostatin concentration is seldom useful for the follow-up care of patients with somatostatinoma, as it is generally elevated, but has no relation to the tumor size, invasion or metastasis (12–14). Recently, a modified analogue of octreotide, labeled with indium 111, was shown to detect localized primary and metastatic somatostatinoma tumors (15). The somatostatin analogue may improve diagnosis and treatment.

Though the prognosis of somatostatinoma had been previously proposed to be poor, some reports of a malignant duodenal somatostatinoma revealed a relatively long survival (16). The duodenal somatostatinomas with distant metastases may have a low malignant potential, providing an improved prognosis.

References