Insulin and Somatostatin Releasing Islet Cell Tumor Caused Hypoglycemia


Abstract

We report a hypoglycemic case with normal insulin levels, which was caused by an islet cell tumor that was releasing insulin and somatostatin. A fasting test suggested the over secretion of insulin. Moreover, this hypoglycemia was enhanced by the inhibitory effect of somatostatin on the secretion of insulin counter-regulatory hormones, such as glucagon, in addition to the autonomous secretion of insulin from the tumor. In cases of hypoglycemia with apparently normal insulin levels, the measurement of somatostatin and various provocative tests are recommended. Arterial stimulation venous sampling (ASVS) was useful to detect the location of this functioning islet cell tumor. (Internal Medicine 40: 324-330, 2001)

Key words: insulinoma, somatostatinoma, fasting test, oral glucose tolerance test (OGTT), arterial stimulation venous sampling (ASVS)

Introduction

The effects of tumoral insulin are enhanced by tumoral somatostatin under pathological conditions. An insulinoma is the most common cause of hypoglycemia resulting from hyperinsulinism. However, there have been some reports which discuss the presence of normal insulin levels together with clinical symptoms strongly suggestive of insulinomas (1–3). Pancreatic islet cell tumors often produce more than one hormone, and elevated levels of more than one peptide can be found in the plasma of patients. The predominant hormones produced by the tumor define the clinical syndrome. Pancreatic somatostatinoma is a very rare islet cell tumor. Usually the symptom is mild diabetes mellitus due to the inhibitory action of somatostatin for endocrine functions (4). The secreted somatostatin from the tumor inhibits the secretion of pancreatic glucagon, but cannot inhibit tumoral insulin release (5). It is possible that the hypoglycemia of tumoral insulin is enhanced by somatostatin, if an islet cell tumor secretes both insulin and somatostatin. Here, we present a case of an islet cell tumor that released insulin and somatostatin. This tumor caused hypoglycemia with an apparently normal insulin level. In addition, we found 6 similar cases of pancreatic somatostatinoma in a literature review, all of which recurred hypoglycemic attacks (6–10).

Case Report

A 43-year-old man had been referred to Shinshu University Hospital for the evaluation of his hypoglycemic attacks that occurred with normal plasma insulin levels. He suffered from delirium periodically when hungry, and he also experienced general fatigue and diarrhea for 6 months before admission. On the occasion of an attack in another hospital, the patient's plasma glucose level was 20 mg/dl, which was improved by glucose injection. This episode suggested the presence of insulinoma. However, plasma levels of insulin and C-peptide immunoreactivity (CPR) were within normal limits and no tumors were found. This patient had never been prescribed insulin, sulfonylureas, or other medications. There was no family history of multiple endocrine neoplasia (MEN).

On admission, the patient's height and weight were 169 cm and 58 kg, respectively. The patient had normal blood pressure. His pulmonary, cardiac, abdominal, and neurological examination were unremarkable. In addition, no pituitary, thyroid, parathyroidal, adrenal, or carcinoid tumors were present. The patient did not show mucosal neuromas. Laboratory studies revealed normal blood cell counts and biochemical values. Blood sugar was 73 mg/dl. Serum calcium (Ca) was 9.2 mg/dl (normal value, 8.6–10.1 mg/dl). Among the various hormones
measured, only the plasma somatostatin level showed a high value of 59 pg/ml (normal value, 1–12 pg/ml). Regarding other hormones related to plasma glucose regulation, insulin 6.6 μU/ml (normal value, 5–25 μU/ml), CPR 1.8 ng/ml (normal value, 1.5–3.6 ng/ml), and glucagon 107 pg/ml (normal value 23–197 pg/ml) were within the normal ranges. Plasma gastrin 33 pg/ml (normal value 37–172 pg/ml) decreased mildly with hypochlorhydria, in which basal acid output was 1.2 mEq/h (normal value, 3.0–10.0 mEq/h) and maximal acid output was 6.1 mEq/h (normal value, 7.7–15.0 mEq/h), respectively. Plasma levels of secretin, pancreatic polypeptide (PP) and vasoactive intestinal peptide (VIP) were within normal limits. Plasma levels of pituitary hormones, thyroid hormones, and adrenal hormones were within normal limits. Plasma and 24-hour urinary excretions of both catecholamines and 5-hydroxyindoleacetic acid (5-HIAA) were normal. Tests for insulin antibody and insulin receptor antibody were negative.

Various provocative tests were performed to clarify the characteristics of this unusual hypoglycemia. A 18-hour fasting test revealed a marked decrease of plasma glucose with normal levels of insulin and CPR at the endpoint. Despite the normal plasma insulin level, the evaluations of CPR/glucose ratio (3) and “amended” insulin/glucose ratio [insulin×100/(glucose–30)] by Turner et al (1) showed over-secretion of insulin. Moreover, we measured the plasma levels of proinsulin before and after the 18-hour fasting test (5, 11). Even in the basal condition, proinsulin was elevated. At the endpoint, we observed a more increased level of proinsulin than the basal condition. After the 18-hour fasting test, the proinsulin/insulin ratio also showed abnormal proinsulin secretion. In this study, insulin-like growth factor (IGF)-1, IGF-2, and IGF-binding protein (IGFBP)-3 were within normal limits (Table 1).

The patient showed an increased level of plasma somatostatin. We used a 75 g oral glucose tolerance test (OGTT) to confirm the presence of the somatostatinoma, as glucose causes the release of somatostatin within 120 minutes in patients with somatostatinomas (4). The OGTT showed an increase of plasma somatostatin in accordance with an increase of insulin. In contrast, plasma levels of glucagon decreased with increases in somatostatin. At the end of the OGTT, glucagon recovered to the basal level with the decreasing secretion of somatostatin (Fig. 1).

Systemic imaging tests were performed to detect the source of the over-secretion of hormones. Abdominal ultrasonography and MRI scan showed a small mass (10 mm in diameter) involving the pancreatic body partially protruding from the pancreas. This image was enhanced with contrast medium (Fig. 2). Metastatic lesions of the liver and lymph nodes were not found. Because neither an abdominal angiography nor simple venous samplings determined the location of the tumor, we used arterial stimulation venous sampling (ASVS) with selective intraarterial injection of an insulin secretagogue to confirm the position of the tumor (12). Calcium gluconate (0.02 mEq calcium/kg) was used as a releasing stimulant. With hepatic venous sampling, an injection to the proximal site of the splenic artery resulted in a 3.5-fold rise of insulin (Fig. 3). This site corresponded to the tumor’s position as observed on the abdominal imaging studies. Consequently, a solid tumor (10 mm in diameter) of the pancreatic body was surgically removed. On the cut surface, it appeared gray and focally hemorrhaged. Histologically the tumor was incompletely encapsulated but well demarcated from the surrounding normal pancreatic tissue. The architectural pattern of the tumor was solid and medullary with fine fibrovascular stroma. It was composed of medium-sized monotonous cells having round to ovoid nuclei with single distinct nucleoli. Mitotic figures were less than 3 per 10 high power fields and cellular atypia was moderate. No amyloid deposition was identified (Fig. 4A and B). Immunohistochemically, almost all of these tumor cells showed granular cytoplasmic coexpression of insulin and somatostatin of various intensities (Fig. 4C–E).

A decline in plasma levels of somatostatin and proinsulin

Table 1. Results of the 18-Hour Fasting Test

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before</th>
<th>End point</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose</td>
<td>62 mg/dl</td>
<td>32 mg/dl</td>
<td>60–110 mg/dl</td>
</tr>
<tr>
<td>Insulin</td>
<td>4.7 μU/ml</td>
<td>6.3 μU/ml</td>
<td>5–25 μU/ml</td>
</tr>
<tr>
<td>CPR</td>
<td>1.9 mg/ml</td>
<td>2.2 mg/ml</td>
<td>1.5–3.6 mg/ml</td>
</tr>
<tr>
<td>Insulin/Glucose</td>
<td>0.08</td>
<td>0.20</td>
<td>less than 0.30</td>
</tr>
<tr>
<td>CPR/Glucose</td>
<td>0.03</td>
<td>0.07</td>
<td>less than 0.03</td>
</tr>
<tr>
<td>“Amended” Ratio</td>
<td>15</td>
<td>315</td>
<td>less than 30</td>
</tr>
<tr>
<td>Proinsulin</td>
<td>19.8 pmol/l</td>
<td>27.9 pmol/l</td>
<td>6.4–9.4 pmol/l</td>
</tr>
<tr>
<td>Proinsulin/Insulin</td>
<td>0.59</td>
<td>0.62</td>
<td>less than 0.25</td>
</tr>
<tr>
<td>IGF-1</td>
<td>254 ng/ml</td>
<td>309 ng/ml</td>
<td>106–398 ng/ml</td>
</tr>
<tr>
<td>IGF-2</td>
<td>480 ng/ml</td>
<td>470 ng/ml</td>
<td>374–804 ng/ml</td>
</tr>
<tr>
<td>IGFBP-3</td>
<td>2.54 μU/ml</td>
<td>2.91 μU/ml</td>
<td>2.17–4.05 μU/ml</td>
</tr>
</tbody>
</table>

Note: “Amended” ratio = [insulin×100/(glucose–30)] as reported by Turner et al (1).

Insulin 1 μU/ml is 7.175 pmol/l; the insulin component includes proinsulin. Proinsulin/Insulin ratio is less than 0.25 in normal subjects (11).
Figure 1. These panels show the responses of plasma somatostatin, glucagon, insulin and glucose in the pre- (open symbols) and postoperative OGTT (closed symbols, 14 days after the operation), respectively. (A) Before the operation, the basal levels of somatostatin (△) were 24 pg/ml, which was above the normal range (1–12 pg/ml). Plasma somatostatin increased to its peak (60 pg/ml) by glucose stimulation. After the operation, plasma levels of somatostatin (△) were within normal ranges (less than 10 pg/ml). There was no response of somatostatin. (B) Before the operation, plasma glucagon (○) decreased in inverse proportion to the increase of somatostatin. As the secretion of somatostatin decreased, glucagon recovered to the basal level at the end of the preoperative OGTT. After the operation, plasma levels of glucagon (●) were almost constant. (C) Before the operation, insulin secretion (□) was inhibited as an increase of somatostatin, but some insulin secretion (7.9–9.8 μU/ml) was maintained after the peak of somatostatin. After the operation, insulin secretion (■) from normal pancreatic tissue increased (peak level; 26.5 μU/ml). (D) The basal and peak levels of plasma glucose (○) in the preoperative OGTT were 41 mg/dl and 146 mg/dl, respectively. Although the secretion of insulin increased, the response of glucose (●) shifted upward with the increased basal (90 mg/dl) and peak (171 mg/dl) levels after the operation.

was noted following the removal of the tumor. The plasma levels of insulin, glucagon, and gastrin were normal before and after the operation. At 14 days after the operation, hormonal assay showed no abnormal values in plasma levels of fasting plasma glucose (90 mg/dl), insulin (3.4 μU/ml), CPR (0.8 ng/ml), proinsulin (2.2 pmol/l), somatostatin (7.6 pg/ml), glucagon (55 pg/ml) and gastrin (65 pg/ml). The insulin/glucose ratio (0.04), CPR/glucose ratio (0.01), “amended” insulin/glucose ratio (5.7), and proinsulin/insulin ratio (0.09) were all within normal limits. A postoperative OGTT showed that the response of glucose shifted upward and that the response of insulin increased. However, there were either very slight or no responses of both somatostatin and glucagon (Fig. 1). After the operation, the hypoglycemic attacks disappeared.

Discussion

A major problem of this patient was hypoglycemic attacks, although he had normal insulin levels. The clinical symptoms were strongly suggestive of an insulinoma. To clarify the mechanism of this unusual hypoglycemia, extensive studies were performed. Initially, the over-secretion of insulin was recognized despite the presence of normal insulin levels. An 18-hour fasting test showed an elevation of CPR/glucose ratio and
Figure 2. Abdominal ultrasonography (A), horizontal (B) and sagittal sections (C) of abdominal MRI scan showed a small mass (arrows), 10 mm in diameter, involving the pancreatic body and partially protruding from the pancreas. The MRI images (B and C) were enhanced with contrast medium.

Figure 2. Abdominal ultrasonography (A), horizontal (B) and sagittal sections (C) of abdominal MRI scan showed a small mass (arrows), 10 mm in diameter, involving the pancreatic body and partially protruding from the pancreas. The MRI images (B and C) were enhanced with contrast medium.
Figure 3. Insulin response following the rapid injection of calcium gluconate (0.02 mEq calcium/kg) into the gastroduodenal (GDA ◊), the superior mesenteric (SMA ◊), the proximal site (PSA ●) and the distal site (DSA ○) of splenic arteries. With hepatic venous sampling, the 3.5-fold rise (from 7.6 μU/ml to 26.3 μU/ml) in insulin levels in response to the Ca injection to the proximal site of the splenic artery (PSA ●) definitely showed an islet tumor in the pancreatic body. This finding agreed with the position of the tumor as detected by the abdominal imaging studies.

"amended" insulin/glucose ratio [insulin×100/(glucose−30)], which are evidences of over-secretion of insulin (1–3). Moreover, the elevation of both the plasma levels of proinsulin and the proinsulin/insulin ratio under fasting conditions were suggestive of insulinoma (5, 11). These findings suggested that the hypoglycemia reported here was caused in part by insulin over-secretion (Table 1).

Over-secretion of somatostatin by an islet cell tumor could inhibit the secretion of other insulin counter-regulatory hormones, including glucagon, which is the primary defender against hypoglycemia (13). A preoperative OGTT showed an increase of plasma somatostatin in accordance with an increase of insulin. In contrast, plasma levels of glucagon decreased in inverse proportion to the increase of somatostatin. As the secretion of somatostatin decreased, glucagon recovered to the basal level at the end of the preoperative OGTT. Furthermore, such responses disappeared on the postoperative OGTT (Fig. 1A, B). These results suggest that the increase of plasma somatostatin observed at the preoperative OGTT were caused by the islet cell tumor. Taking into account the immunostaining results, this islet tumor released both insulin and somatostatin.

We observed that the oversecretion of somatostatin from the islet cell tumor inhibited the secretion of glucagon from normal pancreatic tissue on the preoperative OGTT. Insulin secretion was also inhibited as an increase of somatostatin. However, some insulin secretion (7.9–9.8 μU/ml) was maintained after the peak of somatostatin (Fig. 1C). As somatostatin cannot inhibit the secretion of insulin from insulinomas (5), tumoral insulin release might continue even in concomitance with hypersomatostatinemia. It is possible that the hypoglycemia of tumoral insulin is enhanced by the inhibitory action of somatostatin for other insulin counter-regulatory hormones. Because the plasma level of glucose increased in spite of an increase of insulin secretion from normal pancreatic tissue on the postoperative OGTT (Fig. 1C, D).

Since the first report in 1977, about 40 cases of pancreatic somatostatinomas have been reported. Somatostatin inhibits diverse endocrine functions, which causes mild diabetes mel-
Figure 4. Histologically the islet cell tumor is well circumscribed (A, HE stain, x200) and shows a solid growth pattern and occasional mitotic figures (B, HE stain, x400). Immunohistochemically insulin (C, x400) and somatostatin (D, x400) are positive. They coexpressed granularly in the cytoplasms of the tumor cells (E, labeled red with antiinsulin antibody and brown with antisomatostatin antibody).

Insulin-Somatostatin Releasing Tumor

litus, cholelithiasis, steatorrhea, indigestion, and hypochlorhydria (4). However, 6 cases of pancreatic somatostatinoma with hypoglycemic symptoms have been reported (Table 2). With the exception of one case (case 1), all showed normal levels of plasma insulin. Two cases (case 3 and case 6) revealed immunohistochemically insulin-negative tumors. However, many islet cell tumors have been reported as immunohistochemically negative or weakly positive for secreting hormones in comparison with normal tissue. This is partly explained by the combined defects in the storage and biosynthesis of hormones in the tumor cells. Even in the cases with the tumors that were weakly immunohistochemically positive for secreting hormones, several hormone genes were overexpressed (14). Moreover, the somatostatinomas were immunohistochemically positive for somatostatin as well as for other peptides, especially insulin, which was positive in 33% of the cases (15). This may be related to the fact that islet B cells and D cells arise from a common precursor in the mammalian pancreas (16). These findings suggest that both somatostatin and insulin could be released in all cases shown in Table 2. Therefore, the same mechanism may account for the hypoglycemia of all cases listed in Table 2 including that of the presenting case.

In general, islet cell tumors are small or occult tumors (less than 20 mm in size) that are not revealed on imaging studies. We attempted ASVS as a method to determine the location of such a tumor. After a rapid calcium injection at a proximal site of the splenic artery, plasma insulin levels increased for about 30–60 seconds and continued for 60 seconds. These results agreed with those of a previous report (12). The response described here is not in normal subjects but only in patients with insulinomas (17). A positive calcium stimulation test provided not only strong evidence of a functioning islet cell tumor but also confirmation of the tumor position, as detected by imaging tests.

Most cases of islet cell tumors are nonfamilial and sporadic, but some patients with somatostatinomas (about 50%) and insulinomas (less than 10%) are associated with MEN (15). However, the case discussed here might not be classified as
MEN type 1, because over 90% of MEN type 1 patients can be diagnosed by the concomitant occurrence of hyperparathyroidism by this age (18). The patient of the present study has been doing well 1 year after the operation and shows no endocrine symptoms. Careful clinical follow-up will be necessary due to the possible recurrence of an islet cell tumor and the occurrence of MEN.

**References**


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**Table 2. Hypoglycemic Cases of Pancreatic Somatostatinoma**

<table>
<thead>
<tr>
<th>Case (Age/Sex)</th>
<th>Plasma level of Insulin (μU/ml)</th>
<th>Somatostatin (μg/ml)</th>
<th>Tissue immunostaining</th>
<th>Authors (References)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (33/F)</td>
<td>25–35</td>
<td>4,600–11,500 pg/ml</td>
<td>+</td>
<td>Wright et al (6)</td>
</tr>
<tr>
<td>2 (45/F)</td>
<td>13</td>
<td>Not done</td>
<td>+</td>
<td>Yano et al (7)</td>
</tr>
<tr>
<td>3 (54/M)</td>
<td>41.9</td>
<td>5,200 pg/ml</td>
<td>–</td>
<td>Pipeleers et al (8)</td>
</tr>
<tr>
<td>4 (47/M)</td>
<td>23.5</td>
<td>544 pg/ml</td>
<td>+</td>
<td>Arihiro et al (9)</td>
</tr>
<tr>
<td>5 (64/F)</td>
<td>&lt;17</td>
<td>Not done</td>
<td>+</td>
<td>Presenting case</td>
</tr>
<tr>
<td>6 (66/M)</td>
<td>Unknown</td>
<td>245 pg/ml</td>
<td>–</td>
<td>Presenting case</td>
</tr>
<tr>
<td>7 (43/M)</td>
<td>6.6</td>
<td>59 pg/ml</td>
<td>++</td>
<td>Presenting case</td>
</tr>
</tbody>
</table>

Table 2 shows all reported cases of hypoglycemic pancreatic somatostatinoma. PP: pancreatic polypeptide. In case 6, insulin levels were appropriate for the plasma glucose. * In case 1, plasma insulin levels were consistently moderate, but there was an inappropriate hyperinsulinemia. † After a 17-hour fasting test in case 2, an hypoglycemic attack developed with plasma levels of glucose at 43 mg/dl, insulin 12 μU/ml, and CPR 1.2 ng/ml. The evaluations of insulin/glucose ratio, CPR/glucose ratio, and "amended" insulin/glucose ratio were 0.28, 0.03, and 92.3, respectively. These results showed over-secretion of insulin. Plasma insulin levels 1,745 pg/ml, 978 pg/ml, normal values (800–1,800 pg/ml) are transformed into 41.9 μU/ml, 23.5 μU/ml, and normal values (19.2–43.2 μU/ml), respectively, as insulin 1 U is 0.04167 mg in cases 3 and 4. The insulin levels in cases 3 and 4 were within normal limits. Immunostaining was not done in case 3. However, tumoral tissue contained a level of insulin that was 140-fold lower than that of normal pancreatic tissue and a level of somatostatin that was 1,200-fold higher than that of normal pancreatic tissue. In case 4, immunostaining revealed tissue that was weakly positively for insulin and somatostatin. However, tumoral tissue contained 100-fold lower insulin levels and 9-fold higher somatostatin levels than normal pancreatic tissue. * In case 5, the evaluations of insulin/glucose ratio and "amended" insulin/glucose ratio were 0.88 and 1,400, respectively. These results showed over-secretion of insulin.