INSULINOMAS are tumors that secrete insulin and cause hypoglycemia [1]. Approximately 80-90% of insulinomas occur as a single mass and can be treated via surgical resection; however, in cases of unclear localization, the presence of metastasis, advanced patient age, or other conditions that make surgery difficult, medical therapy is preferred [2]. Octreotide is a somatostatin analog that affects the somatostatin receptors (SSTRs), with a strong affinity for SSTR2 and SSTR5 isoforms. This drug has been shown to inhibit the secretion of gastrointestinal hormones from the tumor as well as the growth of tumor cells [3]. Octreotide is sometimes used to prevent hypoglycemia caused by insulinomas; however, this drug can induce hyperglycemia as a side effect because it suppresses both insulin and glucagon secretion. There are 2 ways to administer this drug; daily subcutaneous injection of octreotide or monthly intramuscular injection of octreotide LAR, a slow-release formulation of octreotide. The half-life of octreotide is approximately 1.8 hours, whereas the effect of octreotide long-acting repeatable (LAR) persists for over a month. We report herein on a case of a woman with malignant insulinoma who showed uncontrolled hypoglycemia and postprandial hyperglycemia when treated with octreotide but achieved good glycemic control after octreotide treatment was replaced with octreotide LAR.
Case Report

A 73-year-old woman had undergone partial gastrectomy for gastric cancer at the age of 63. During the gastrectomy, a tumor was incidentally found on the pancreas and was subsequently resected. Pathological examination of this tumor revealed positive staining for chromogranin A, grimeius, and neuron-specific enolase suggestive of a pancreatic endocrine tumor. Three years after the operation, a liver metastasis of the pancreatic cancer was identified for the first time, and the patient underwent transarterial embolization (TAE). Thereafter, she underwent repeated TAE, radiofrequency (RF) ablation, and a partial resection of the liver because of recurrent metastases. At the time of her second partial liver resection, a pathological examination revealed that the metastatic pancreatic cancer was secreting proinsulin (Fig. 1a) and insulin (Fig. 1b). Based on these results, we reexamined the original pancreatic tumor sample and found that it was also positive for proinsulin (Fig. 1c) and insulin (Fig. 1d) but negative for somatostatin. Therefore the patient was diagnosed as having malignant insulinoma. When the patient was 72 years old, a metastatic pancreatic cancer in the liver that was positive for SSTR2 expression was identified (Fig. 1g), and daily injections of 100 μg of octreotide were started to suppress the growth of the tumor cells. Although the standard regimen for octreotide includes multiple injections per day, this patient received only one injection per day because of her impaired cognitive function, which made multiple injections difficult. No hypoglycemic attack was observed at that time. Approximately one year later, a positron-emission tomography (PET) examination showed the presence of metastases in the first thoracic vertebra and in the liver (Fig. 2), and the patient was admitted to the general surgery department of our hospital for radiation therapy and the relief of the pain caused by the bony metastasis. Although she had never been diagnosed as having diabetes or received any treatment for it before, she repeatedly presented with hypoglycemia early in the morning and hypergly-

Fig. 1 Pathological examination of the original pancreatic tumor and the resected liver metastases. a,b: Immunohistochemical staining of a metastatic lesion in the liver for proinsulin (a) (×40) and insulin (b) (×40). c,d: Immunohistochemical staining of the original pancreatic tumor for proinsulin (c) (×40) and insulin (d) (×20). e,f: Immunohistochemical staining of the normal pancreatic tissue (control) for proinsulin (e) (×20) and insulin (f) (×20). g: Immunohistochemical staining of a metastatic lesion in the liver for SSTR2 (×20). h: Immunohistochemical staining of a metastatic lesion in the liver for gastrin (×20). These staining procedures were performed using the following antibodies: proinsulin (1:200, 778620; Abcam plc, Cambridge, UK), insulin (diluted, N1542; Dako Japan, Tokyo, Japan), SSTR2 (1:1000, polyclonal; Gramsh Laboratories, Schwabhausen, Germany), and gastrin (1:1000, A0568; Dako Japan, Tokyo, Japan).
Octreotide LAR improved glycemic control

The patient’s son was expected to administer octreotide injections after discharge. Therefore, considering her son’s convenience, the patient received 1 octreotide injection in the evening during the admission period. When the injection was given at 4 PM, we observed hypoglycemia before breakfast and hyperglycemia after dinner, and the patient’s blood glucose levels at 3 AM were very low. When the injection was given at 11 AM as a trial, hyperglycemia was observed not after dinner, but after lunch. When no injection was given, we observed hypoglycemia (but not hyperglycemia) several times during the day (Fig. 4). These effects could be explained by assuming that the serum concentration of octreotide was higher than that required after injection, causing oversuppression of insulin and hyperglycemia, and conversely it was lower than that required for efficient suppression of insulin in the morning, resulting in fasting hypoglycemia. Based on this assumption, we changed the daily injection of octreotide to a monthly injection of octreotide LAR (10 mg), expecting that its concentration would be more stable all day long than that of a daily octreotide injection. The new treatment resulted in stable blood glucose levels within the normal range and the patient no longer suffered from hypoglycemia early in the morning (Fig. 5 and 6). One week after the initiation of octreotide LAR treatment, the early morning insulin level was 4.0 µU/mL and the plasma glucose level was 80 mg/dL.

Table 1 The results of laboratory examinations at the time of referral

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free plasma glucose (FPG) (mg/dL)</td>
<td>51</td>
</tr>
<tr>
<td>HbA1c (NGSP) (%)</td>
<td>5.2</td>
</tr>
<tr>
<td>Immunoreactive insulin (IRI) (µU/mL)</td>
<td>8.8</td>
</tr>
<tr>
<td>C-peptide immunoreactivity (CPR) (ng/mL)</td>
<td>1.3</td>
</tr>
<tr>
<td>Proinsulin (PI) (pmol/L)</td>
<td>68</td>
</tr>
<tr>
<td>PI/IRI (%)</td>
<td>111.3</td>
</tr>
<tr>
<td>Glucagon (pg/mL)</td>
<td>108</td>
</tr>
<tr>
<td>Cortisol (µg/dL)</td>
<td>18.7</td>
</tr>
<tr>
<td>Insulin antibody (%)</td>
<td>&lt;0.4</td>
</tr>
<tr>
<td>Fajans’ index (IRI/BS)</td>
<td>0.17</td>
</tr>
<tr>
<td>Grunt’s index (FBS/IRI)</td>
<td>5.80</td>
</tr>
<tr>
<td>Gastrin (pg/mL)</td>
<td>1200</td>
</tr>
</tbody>
</table>

Fig. 2 Positron emission tomography (PET) examination showed metastases in the first thoracic vertebra and the liver.

cemia after dinner during the course of hospitalization. To stabilize the blood glucose levels, she was referred to our department.

At the time of referral, the patient’s body height and weight were 143 cm and 38.8 kg, respectively, and her body mass index was 18.9 kg/m². The results of laboratory examinations are listed in Table 1. The day before examination, octreotide injections were discontinued to allow elimination of the drug effect. The Fajans index value was 0.17 and the proportion of proinsulin to insulin was relatively high. Serum glucagon and cortisol levels were within normal limits. On another day, the gastrin level was 1200 pg/mL (normal range, 37–172 pg/mL). Because of the extremely high gastrin level and the positive staining for gastrin in the metastatic pancreatic cancer in the liver (Fig. 1h), a gastrinoma was suspected; however, an upper gastrointestinal endoscopy revealed no indication of gastric or duodenal ulcers, which are often associated with a gastrinoma [4]. The original pancreas tumor was also stained and found to be positive for gastrin, after similar findings were noted for the metastatic cancer in the liver. The patient was not taking an oral proton pump inhibitor (PPI) or an H2 blocker at the time of the gastrin level measurement, and an upper gastrointestinal endoscopy was performed.

Mean preprandial, postprandial, and before-sleep blood glucose levels during the period when the patient received daily injections of octreotide (100 µg) are shown in Fig. 3. Because of her cognitive impairment, the patient’s son was expected to administer octreotide injections after discharge. Therefore, considering her son’s convenience, the patient received 1 octreotide injection in the evening during the admission period. When the injection was given at 4 PM, we observed hypoglycemia before breakfast and hyperglycemia after dinner, and the patient’s blood glucose levels at 3 AM were very low. When the injection was given at 11 AM as a trial, hyperglycemia was observed not after dinner, but after lunch. When no injection was given, we observed hypoglycemia (but not hyperglycemia) several times during the day (Fig. 4). These effects could be explained by assuming that the serum concentration of octreotide was higher than that required after injection, causing oversuppression of insulin and hyperglycemia, and conversely it was lower than that required for efficient suppression of insulin in the morning, resulting in fasting hypoglycemia. Based on this assumption, we changed the daily injection of octreotide to a monthly injection of octreotide LAR (10 mg), expecting that its concentration would be more stable all day long than that in the case of a daily octreotide injection. The new treatment resulted in stable blood glucose levels within the normal range and the patient no longer suffered from hypoglycemia early in the morning (Fig. 5 and 6). One week after the initiation of octreotide LAR treatment, the early morning insulin level was 4.0 µU/mL and the plasma glucose level was 80 mg/dL.
Fig. 3  Mean and standard deviation of blood glucose levels after the daily injection of 100 μg of octreotide, as measured over 11 consecutive days (except day 4) during hospitalization. The results of day 4 are shown in Fig. 4.

Fig. 4  Blood glucose levels on a day when octreotide was not injected. An oral dose of 10 g of glucose was administered in response to the hypoglycemic episodes (9:50 and 21:20).
Fig. 5  Blood glucose levels on the last day of octreotide injection, when hyperglycemia occurred, and on the first day of octreotide LAR injection, when no hyperglycemia was noted.

Fig. 6  Mean and standard deviation of blood glucose levels after the monthly injection of 10 mg of octreotide LAR, as measured over 21 consecutive days during hospitalization.
Discussion

Insulinomas are tumors that often cause hypoglycemia by secreting insulin, over 90% of which present with fasting hypoglycemia as observed in this patient [5]. The incidence of insulinoma is estimated to be four cases per 1 million person-years [6]. Approximately 80–90% of insulinomas are solitary and can be treated by surgical resection. Approximately 10–14% are malignant, and 7% develop metastases [7, 8]. The major metastatic sites are the lymph nodes (50%) and the liver (70%). In general, liver metastases are present in approximately 5% of all insulinomas. In the present case the tumor was malignant and had developed metastases; therefore there was no indication for surgical resection of the primary lesion and medical treatment with octreotide was chosen.

Since octreotide binds with high affinity to both SSTR2 and SSTR5 [9, 10], daily injections of octreotide at 100 μg were initiated in this case after confirming the expression of SSTR2 in the tumor through pathological examination. Approximately 50% of insulinomas express SSTR2 [10, 11], and in the case of malignant insulinomas, there were several reports stating different results; some reported that all of them presented SSTR2 [10], while another reported that not all of them did [12]. The presence of SSTR2 may have been one reason why octreotide LAR was very effective in controlling blood glucose levels in this patient. Our data indicate that it is important to confirm SSTRs expression at an early stage for the treatment of insulinoma, if possible.

About the method of administration, the standard dose of octreotide injection is 100 μg or 150 μg daily, and it can be increased up to 300 μg if the effect is insufficient. Although the usual regimen for octreotide includes multiple injections in a day, it was not possible in the present case because of patient’s impaired cognitive function. As mentioned above, unstable blood concentration of the drug due to a shortage of the frequency of injection could have been one of the reasons for the large variation in blood glucose levels. Multiple injections of a lower dose of octreotide might have been more effective. Regarding the favorable change after the replacement of octreotide with octreotide LAR, the improvement probably occurred because the blood concentration of octreotide LAR was more appropriate and stable, compared with during octreotide treatment, allowing the insulin level to decrease to an appropriate range, thereby enabling the stabilization of the blood glucose level after the initiation of octreotide LAR treatment. In addition, octreotide LAR might have had a suppressive effect on gastrointestinal motility.

The possibility of postgastrectomy syndrome should also be considered when blood glucose levels become unstable after a gastrectomy. In the present case, the gastric carcinoma was 1.0 cm long and was located in the posterior wall of the greater curvature. The resection included the removal of an approximate 3-cm margin of normal tissue. The gastric wall was sutured organoaxially with no intestinal anastomosis, leaving a sufficiently large inner cavity within the remaining stomach and preserving the major vessels and the vagal nerve. Because of the absence of postgastrectomy syndrome during a 9-year follow-up period, we concluded that the future occurrence of postgastrectomy syndrome was unlikely, although it remains possible. The physiological levels of glucagon-like peptide-1 might be of some help in evaluating the effects of postgastrectomy syndrome.

In determining the diagnosis of insulinoma, Fajans’ index or Grunt’s index is often used to evaluate the excessive secretion of insulin, and an insulinoma is strongly suspected when its value is more than 0.3 or less than 2.5, respectively [13, 14]. Additionally, Service’s diagnostic criteria for insulinoma has been used recently; fasting serum insulin, ≥6 μU/mL; C peptide, ≥0.6 mg/mL (0.6nmol/L); and proinsulin, ≥5 pmol/L [15, 16]. In this patient, although neither Fajans’ and Grunt’s index values met the criteria, the patient met Service’s diagnostic criteria for insulinoma. This might have been due to the low activity of insulin which caused a relatively higher blood glucose level than estimated. The proinsulin-insulin ratio was relatively high (>1.0), as shown in Table 1, and it is conceivable that the absolute activity of insulin may have been relatively low because of the reduced secretion of mature insulin and the increased secretion of proinsulin, which has a relatively lower immunoreactivity [17]. Therefore index values which require fasting blood glucose (FBS) levels for their formula, like Fajans’ and Grunt’s indices, did not meet the criteria.

A similar argument can be made for gastrin. The patient did not have any typical symptoms of gastrinoma, such as gastrointestinal tract ulcers, hematemesis, melena, severe watery diarrhea, or steatorrhea, although her serum gastrin levels were very high without taking a PPI or an H2 blocker. Although the exact reasons
remain unknown, the gastrin activity level might have been relatively low because of the presence of a prohormone or similar product, as in the case of insulin.

In general, insulin and gastrin are rarely secreted from the same tumor simultaneously as we observed in this patient, although the combination of insulinoma and gastrinoma in 1 individual has been reported in multiple endocrine neoplasia type 1 cases which account for approximately 6 to 8% of all insulinomas [5, 18, 19].

In conclusion, we report herein on the case of a woman with octreotide-treated malignant insulinoma who experienced drug-induced glycemic fluctuations. After replacing a daily injection of octreotide with a monthly injection of 10 mg octreotide LAR, the blood glucose levels became stable. Our findings indicated that octreotide LAR could be useful for the long-term treatment of unresectable insulinomas and improve the patient’s quality of life.

References