Successful Control of Intractable Hypoglycemia Using Radiopharmaceutical Therapy with Strontium-89 in a Case with Malignant Insulinoma and Bone Metastases

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This report describes the case of a 57-year-old woman with liver and bone metastases from malignant insulinoma, who was afflicted with severe hypoglycemia. Treatment of the liver metastases using octreotide, diazoxide and transarterial embolization failed to raise her blood glucose level and she required constant glucose infusion (about 1000 kcal/day) and oral feeding (about 2200 kcal/day) to avoid a hypoglycemic attack. Subsequently, 110 MBq (2.0 MBq/kg) of strontium-89 were administered by intravenous injection. Three weeks after the strontium-89 injection, we could reduce the dose of constant glucose infusion while maintaining a euglycemic status. Six weeks after the injection, the constant glucose infusion was discontinued. Although strontium-89 therapy is indicated for patients with multiple painful bone metastases, it was also useful as a means of inhibiting tumor activity and controlling hypoglycemia in this case. To our knowledge, this is the first report to provide evidence that strontium-89 can be useful in controlling intractable hypoglycemia in patients with malignant insulinoma with bone metastases.

Key words: strontium-89 – malignant insulinoma – bone metastases

INTRODUCTION

Insulinomas are rare tumors that arise from the pancreatic islet cells that produce insulin. Approximately 5–10% of the insulinomas are cancerous (1). It is often difficult to control inappropriate insulin secretion and hypoglycemia in patients with a malignant insulinoma. Although surgery is indicated for symptomatic or malignant insulinoma, only medical therapy is suggested for unresectable patients (2). Some cases suffer from intractable hypoglycemia as a result of the limited efficacy of medical therapy. We report here on the case of a 57-year-old woman with a malignant insulinoma and bone metastases in whom intractable hypoglycemia was successfully controlled by using radiopharmaceutical therapy with strontium (Sr)-89.

CASE REPORT

In March 2002, a 57-year-old woman experienced frequent hypoglycemic attacks and was diagnosed as having an insulinoma of the pancreas tail at a previous hospital. She
underwent surgery including a distal pancreatectomy and splenectomy at the previous hospital. The maximum diameter of the surgically removed tumor was 10 cm. The histopathological findings revealed a pancreas islet cell carcinoma. The tumor had directly invaded the spleen and protruded into the splenic vein and pancreatic duct. The surgical resection stump was negative.

In February 2005, multiple liver metastases were detected and the patient was referred to our hospital. Then, she received a partial hepatectomy for multiple liver metastases in our hospital. The histopathological findings of resected specimen showed a low-grade endocrine cell carcinoma. The immunohistochemical staining showed positive for chromogranin A and synaptophysin, but it showed negative for insulin. In July 2006, she underwent a second partial hepatectomy for recurrent multiple liver metastases. Histopathological examination of the liver metastases showed similar findings to the first liver segmental resection.

In December 2008, multiple liver metastases and multiple bone metastases including lumbar vertebrae and iliac bone were detected. In March 2009, she started zoledronic acid hydrate treatment for the bone metastases, but it was discontinued because of severe jaw pain suggesting the possibility of mandibular osteonecrosis. In November 2009, the patient experienced a hypoglycemic attack again. The patient was hospitalized to control her serum glucose level. The laboratory data obtained at admission are shown in Table 1. Regarding the serum hormonal level, the insulin level was slightly elevated but the glucagon level was not elevated. The level of neuron-specific enolase was slightly elevated. The patient underwent short-acting somatostatin analogs for 14 days to control the serum glucose level due to their anti-proliferation effect. After having confirmed that there was no worsening of the hypoglycemia symptoms, we changed her treatment to a long-acting somatostatin analog (Sandostatin-LAR; Novartis Pharmaceuticals). However, hypoglycemia occurred frequently (Fig. 1) even after the initiation of octreotide therapy. The patient refused to continue the octreotide therapy because her hypoglycemic attacks had not improved. The hypoglycemia persisted after the discontinuation of octreotide. Next, diazoxide was administered with no effect but with the side effects of significant edema and weight gain. We decided to undertake transarterial embolization (TAE) to necrotize the liver metastases and

### Table 1. Laboratory data upon the first admission after the experience of a hypoglycemic attack

<table>
<thead>
<tr>
<th>Category</th>
<th>Actual level</th>
<th>Normal level</th>
<th>Tumor markers</th>
<th>Actual level</th>
<th>Normal level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocyte</td>
<td>10 200</td>
<td>(3900–6300)</td>
<td>CEA (ng/ml)</td>
<td>2.5</td>
<td>(&lt;5)</td>
</tr>
<tr>
<td>Leukocyte (per mm³)</td>
<td>11.9</td>
<td>(11.3–14.9)</td>
<td>CA19–9 (U/ml)</td>
<td>12</td>
<td>(&lt;37)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>39 × 10⁴</td>
<td>(12.5–37.5 × 10⁴)</td>
<td>NSE (ng/ml)</td>
<td>18.5 (H)</td>
<td>(&lt;15)</td>
</tr>
<tr>
<td>Platelet (per mm³)</td>
<td>13.6</td>
<td>(12.5–37.5 × 10⁴)</td>
<td>ProGRP (pg/ml)</td>
<td>37.7</td>
<td>(&lt;46)</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td>Hormones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>8.0</td>
<td>(6.3–8.3)</td>
<td>Insulin (mIU/ml)</td>
<td>12.9 (H)</td>
<td>(1.84–12.2)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.6 (L)</td>
<td>(3.7–5.2)</td>
<td>Gastrin (pg/ml)</td>
<td>82</td>
<td>(&lt;200)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.6</td>
<td>(0.3–1.2)</td>
<td>Glucagon (pg/ml)</td>
<td>120</td>
<td>(50–150)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>70</td>
<td>(69–104)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>14</td>
<td>(8–22)</td>
<td>pH</td>
<td>6.0</td>
<td>(4.6–7.5)</td>
</tr>
<tr>
<td>Creatine (mg/dl)</td>
<td>138</td>
<td>(138–146)</td>
<td>Protein (—)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>4.2</td>
<td>(3.6–4.9)</td>
<td>Sugar (—)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>104</td>
<td>(99–109)</td>
<td>Blood (—)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride (mEq/l)</td>
<td>9.0</td>
<td>(8.7–10.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>64</td>
<td>(42–132)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase (IU/l)</td>
<td>440 (H)</td>
<td>(115–359)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP (IU/l)</td>
<td>16</td>
<td>(13–33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>9</td>
<td>(6–27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>174</td>
<td>(119–229)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH (IU/l)</td>
<td>25</td>
<td>(10–47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ-GTP (IU/l)</td>
<td></td>
<td></td>
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</tbody>
</table>

BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltransferase; APTT, activated partial thromboplastin time; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NSE, neuron-specific enolase; Pro-GRP, pro-gastrin-releasing peptide; (H), high; (L), low.
prevent the hypoglycemia. TAE was performed on the 20th hospital day. We succeeded in necrotizing the metastases, as shown in Fig.2. However the hypoglycemia persisted, and then the patient required constant glucose infusions and oral feeding to avoid a hypoglycemic attack (Fig. 1). As shown in Fig. 3A and B, bone scintigraphy revealed a worsening of the bone metastases, compared with images obtained 1 year previously.

89Sr is a novel radiopharmaceutical agent used for the palliation of bone pain from multiple osseous metastases (3). The patient suffered from slight lumbago as a result of the bone metastases, so we attempted to use 89Sr to alleviate her pain and to control her hypoglycemia. In the computed tomography (Fig. 4), the bone metastases showed osteoplastic findings that suggested high sensitivity to 89Sr (4). A 110-MBq dose (2 MBq per kg) of 89Sr was administered by intravenous injection on the 37th hospital day (Fig. 1). One week after the injection, the serum level of alkaline phosphatase was normalized. We were able to confirm the accumulation of 89Sr in metastatic foci that corresponded to bone scintigraphy by using gamma camera (Fig. 3C). Three weeks after the 89Sr injection, we were able to reduce the dose of constant glucose infusion while maintaining a euglycemic status. Six weeks after the injection, she stopped constant glucose infusion and the bone pain was relieved (Fig. 1). The patient was discharged on the 83rd hospital day. Two months after the 89Sr injection, she was hospitalized again for 3 weeks because of a transient liver dysfunction due to a hepatitis C virus infection. Liver dysfunction was improved using conservative treatment. In December 2010, no progression of bone metastases was seen on bone scintigraphy, and the hypoglycemic control was consistently good. The patient received a second 89Sr treatment 1 year after the first 89Sr treatment because of the recurrence of bone pain. After the 89Sr treatment, the bone pain has remained improved until the time of writing. Local

Figure 1. Clinical course. Three weeks after the strontium-89 injection, the patient was weaned from the constant glucose infusion while successfully maintaining euglycemia and lower circulating insulin levels. About 6 weeks after the injection, the constant glucose infusion was completely stopped, even though the previous treatment had failed.

Figure 2. Liver metastases were observed using enhanced computed tomography (A and B, arrow). The liver metastases did not exhibit remarkable hypervascular staining in computed tomography before transarterial embolization (A, arrow), but successful necrotization was achieved using transarterial embolization, as shown in this enhanced computed tomographic imaging 1 week after the treatment (B, arrow). However, the treatment failed to increase the patient’s blood glucose level.
recurrences of the liver metastases were detected 18 months after TAE (May 2011). Although we proposed additional treatment by TAE or with anticancer agents, the patient refused any additional cancer treatment. At that time, the neuron-specific enolase level was normal (12.1 ng/ml). As of June 2011, the patient continued to be followed up as an outpatient, but she has not received any further treatment for hypoglycemia.

**DISCUSSION**

Although most patients with malignant insulinoma have lymph node or liver metastasis, there are very few reports in which malignant insulinoma metastasized to a bone (5–7). The prognosis of these patients is relatively poor with a median survival period of ~2 years (8,9).

Glycemic control is a key aspect of managing malignant insulinomas. Mild symptoms can sometimes be controlled by diet (10). Some reports have shown good control of blood glucose levels using a somatostatin analog (11–13). Somatostatin analogs such as octreotide may be helpful for the control of insulin release, but they can also suppress counter-regulatory hormones such as growth hormones, glucagon, and catecholamines (10). In this situation, somatostatin analogs can lead to the worsening of hypoglycemia (14). However, octreotide had neither a good nor a bad influence on the hypoglycemia in the patient. Diazaoxide, an anti-hypertensive agent known to increase the blood sugar level, inhibits the release of insulin in pancreatic beta cells by opening ATP-sensitive potassium channels (15,16). Its side effects include edema, weight gain, renal impairment, and hirsutism (10). Although our patient exhibited edema and weight gain, her hypoglycemia did not improve (Fig. 1). Some authors reported that selective TAE for liver metastases may have the greatest benefit, next to diazoxide (17–22). However, in the present patient, TAE was not effective for glycemic control because unregulated secretion of insulin was mainly caused by the bone metastases.

Concerning other treatment options, De Jong et al. (23) reported that radiolabeled somatostatin analogs, such as [(90)Y-DOTA, Tyr(3)] octreotide and [(177)Lu-DOTA, Tyr(3)] octreotide, are promising treatment modalities for patients with neuroendocrine tumors. However, these radionuclide therapies are not available in Japan. Antiproliferative agents such as streptozotocin, sunitinib, and everolimus are also good treatment options (24–26). However, these agents are not covered by the national health insurance in Japan.

\(^{89}\)Sr decays by beta emission, with a maximum beta energy of 1.46 MeV, an average soft-tissue penetration of 2.4 mm, and a half-life of 50.6 days. After administration, \(^{89}\)Sr is taken up into the mineral matrix of the bone and is selectively concentrated in areas of osteoblastic activity in disease-affected bone, with a biological behavior resembling that of calcium (27). The biodistribution of \(^{89}\)Sr parallels technetium bone-scanning agents (28,29). Pain relief is often obtained 14–21 days after injection (30). Thrombocytopenia and neutropenia are the most common toxic effects, but these effects are generally mild and reversible. Because \(^{89}\)Sr is eliminated mainly via the kidneys, patients are advised to carefully dispose of urine for the first 10 days after administration (27).

The biological mechanism by which \(^{89}\)Sr mediates pain palliation remains unclear. In some basic studies, two possible mechanisms of pain palliation by \(^{89}\)Sr have been proposed (31). One of these mechanisms is a direct radiotoxic effect on the cancer cells caused by the beta-ray emission.
from $^{89}$Sr. The second mechanism is an indirect action through prostaglandin E2 (PGE2) and interleukin-6 (IL-6) produced by cells in response to $^{89}$Sr. PGE2 and IL-6 are known as potent biochemical modifiers of bone turnover. In the patient, the mechanism of improved hypoglycemia was thought to be a direct radiotoxic effect of $^{89}$Sr on the cancer cells. The tumoricidal effect of $^{89}$Sr on metastatic bone tumors has been reported previously. Dafermou et al. (32) reported that $^{89}$Sr therapy resulted in the scintigraphic regression of bone metastases in patients with painful bone metastases from prostate cancer. In addition, Porter et al. (33) reported the reduction of tumor markers, including prostate specific antigen and alkaline phosphatase in the $^{89}$Sr therapy of painful bone metastases from prostate cancer. Suzawa et al. (34) reported a case of the complete regression of multiple painful bone metastases from hepatocellular carcinoma after the administration of $^{89}$Sr. 

In our case, although obvious regression of bone metastases was not detected by the subsequent computed tomography image (Fig. 4), the alkaline phosphatase level decreased (Fig. 1). Because bone scintigraphy was not useful for strict response evaluation, we did not perform it immediately after the strontium-89 injection in this case. Successful pain relief was achieved. Although the intractable hypoglycemia was resistant to all other treatments, it was improved by $^{89}$Sr therapy. Though $^{89}$Sr therapy is generally indicated for patients with multiple painful bone metastases, in this case, it was also useful as a means of arresting tumor growth and inhibiting tumor activity. To our knowledge, this report is the first to provide evidence that $^{89}$Sr can be useful in controlling intractable hypoglycemia in malignant insulinoma with bone metastases.

CONCLUSION
We experienced a case of malignant insulinoma and bone metastases in which intractable hypoglycemia was successfully controlled by using radiopharmaceutical therapy with $^{89}$Sr.

Conflict of interest statement
Dr Chigusa Morizane received lecture fee from Novartis Pharma Co., Ltd.

References


