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CASE REPORT

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Preoperative detection of functional somatostatin receptors in a patient with an insulinoma

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Key Clinical Message

Octreotide is used in patients with insulinomas to treat hypoglycemia, and somatostatin receptor (SSTR) 2 expression is important for its efficacy. We report a case of insulinoma in a 50-year-old woman that responded to an octreotide test, showed accumulation in somatostatin scintigraphy, and was positive for SSTR2A on immunostaining.

KEYWORDS

Insulinoma, octreotide test, somatostatin receptor, somatostatin scintigraphy

1 | INTRODUCTION

Insulinomas are rare pancreatic tumors that occur in 1–4 people per million in the general population.[1] Insulinomas are the most common cause of endogenous hyperinsulinemic hypoglycemia. Although surgical removal is the main treatment for insulinomas, medical treatment is required in patients who are not surgical candidates and patients who present with symptomatic hypoglycemia before surgery. Somatostatin inhibits the secretion of insulin and glucagon in the pancreas. Somatostatin receptors have five isoforms (SSTR1-5). Octreotide is an analog of somatostatin and binds mainly to SSTR2 and SSTR5.[2]

In pancreatic neuroendocrine tumors other than insulinomas, SSTR-2 is expressed in more than 90% of cases and octreotide is effective. On the contrary, insulinomas have a low expression level of SSTR, and octreotide is effective in only about half of the cases.[3] Conversely, when octreotide is administered to SSTR2-negative insulinomas, it has been reported that there is a risk of hypoglycemia due to suppression of glucagon secretion.[4] Therefore, in preoperative and inoperable cases of insulinoma, prediction of SSTR2 expression may be useful in the administration of somatostatin analogs.

We herein report a case of insulinoma in which a preoperative octreotide test and somatostatin scintigraphy indicated SSTR2 expression.

2 | CASE REPORT

A 50-year-old woman was transferred to the emergency department of another hospital with impaired consciousness. On evaluation, fingerstick glucose was 33 mg/dL. After administration of glucose, her impaired consciousness improved. She was admitted for further evaluation of hypoglycemia, but no specific diagnosis was made, and sugar intake was recommended. Thereafter, she

continued to have hypoglycemic symptoms such as dizziness, diaphoresis, and fatigue. Her weight increased by approximately 10 kg in 3 months, and she therefore sought evaluation in another hospital.

Her blood glucose level was 63 mg/dL, and serum immunoreactive insulin (IRI) was 35.8 μIU/mL. She was referred to our department for further evaluation and treatment of hyperinsulinemic hypoglycemia. She was not taking any medications other than losartan. She had no family history of endocrine disorders. On physical examination, her height was 153 cm, her weight was 67.7 kg, and her body mass index was 28.9 kg/m^2. Laboratory tests showed mildly abnormal liver function. A blood test after 18 hours of fasting revealed a blood glucose level of 44 mg/dL, IRI of 47.5 μIU/mL, Turner index of 339 (normal ≤200), Taminato index of 2492 (normal <280), Fajans index of 1.08 (normal ≤0.3), Grunt index of 0.93 (normal ≥2.5), C-peptide level of 5.1 ng/mL, cortisol level of 19.4 μg/dL, and GH level of 1.34 ng/mL. Abdominal computed tomography (CT) with contrast showed a 9 mm nodule in the pancreatic tail. Abdominal magnetic resonance imaging (MRI) showed a nodule with a low signal on a T1-weighted image and a mildly high signal on a diffusion-weighted image in the pancreatic tail.

Somatostatin scintigraphy showed a mild uptake in the pancreatic tail (Figure 1). Endoscopic ultrasound (EUS) showed a hypoechoic 9 mm nodule in the pancreatic tail, and endoscopic ultrasonography-guided fine needle biopsy (EUS-FNB) was performed. Pathological analysis revealed homogeneous proliferation of cells with round nuclei, positive immunostaining for chromogranin A and synaptophysin, and a Ki-67 index of 0.2%. Based on these results, a diagnosis of insulinoma was made. An octreotide test was performed before surgery to evaluate the efficacy of octreotide for hypoglycemia. The octreotide test showed elevated blood glucose and decreased IRI and C-peptide at 120 min values (Figure 2). Thereafter, IRI and C-peptide values increased, but no hypoglycemia was observed.

Traditional distal pancreatectomy with splenectomy was performed and her hypoglycemic symptoms resolved. Postoperative blood tests revealed a blood glucose level of 108 mg/dL, IRI of 7.9 μIU/mL, and C-peptide level of 1.82 ng/mL. Pathological findings showed a proliferation of tumor cells with round nuclei in gyriform patterns. Immunocytochemistry showed strong positive staining for SSTR2A and positive staining for CD56, synaptophysin, chromogranin A, and insulin. Immunostaining for gastrin, glucagon, and SSTR5 was negative (Figure 3). The mitotic count was less than 2 cells/10 high power field, and the Ki-67 index level was below 1%.

3 | DISCUSSION

The present case of insulinoma showed a response to an octreotide test, accumulation in somatostatin scintigraphy, and positive immunostaining for SSTR2. The somatostatin analog octreotide has been shown to be effective

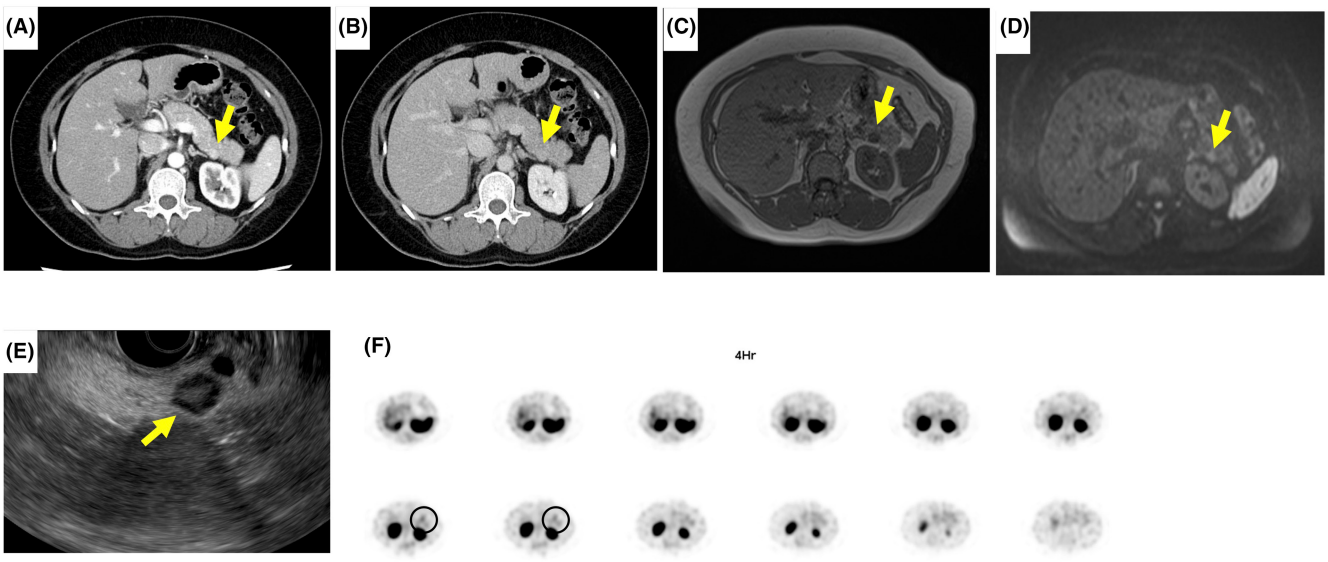

FIGURE 1 Imaging findings. Abdominal computed tomography (CT) with contrast showed an enhanced 9 mm nodule in the pancreatic tail on early image (arrow). (A) The lesion was isodense on delayed image (arrow). (B) Abdominal magnetic resonance imaging (MRI) revealed a nodule with a low signal on a T1-weighted image (arrow) (C) and a mildly high signal on a diffusion-weighted image (arrow) (D). Endoscopic ultrasound (EUS) showed a hypoechoic area (arrow). (E) Somatostatin scintigraphy showed mild uptake in the pancreatic tail (circle). (F).

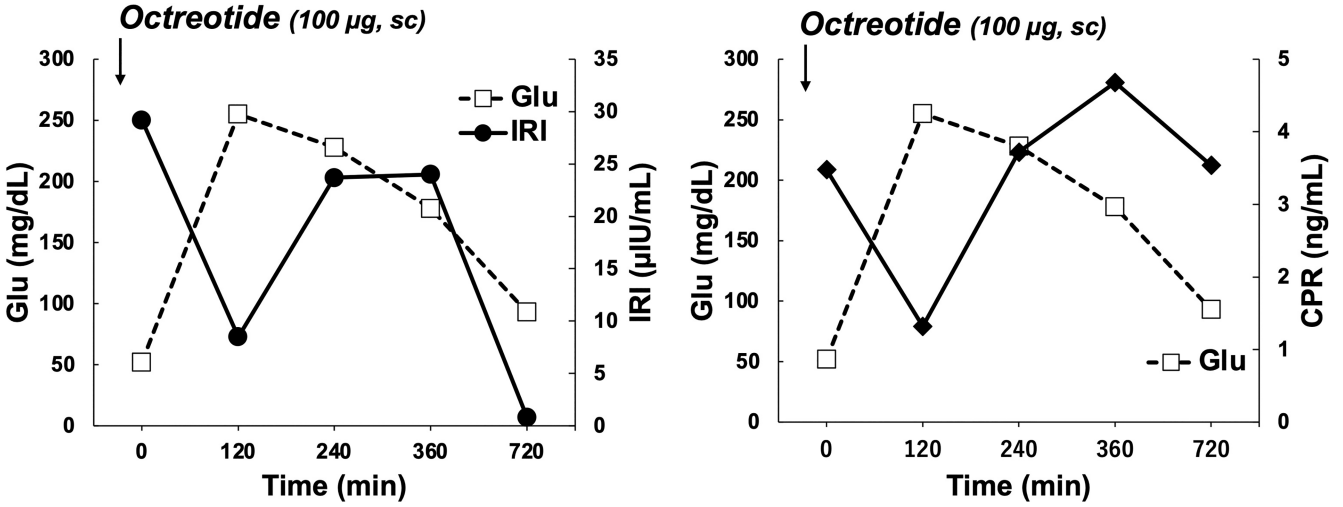

FIGURE 2 Plasma glucose, serum insulin, and C-peptide (CPR) levels during the octreotide test. The glucose level at 720 min is low due to hemolysis.

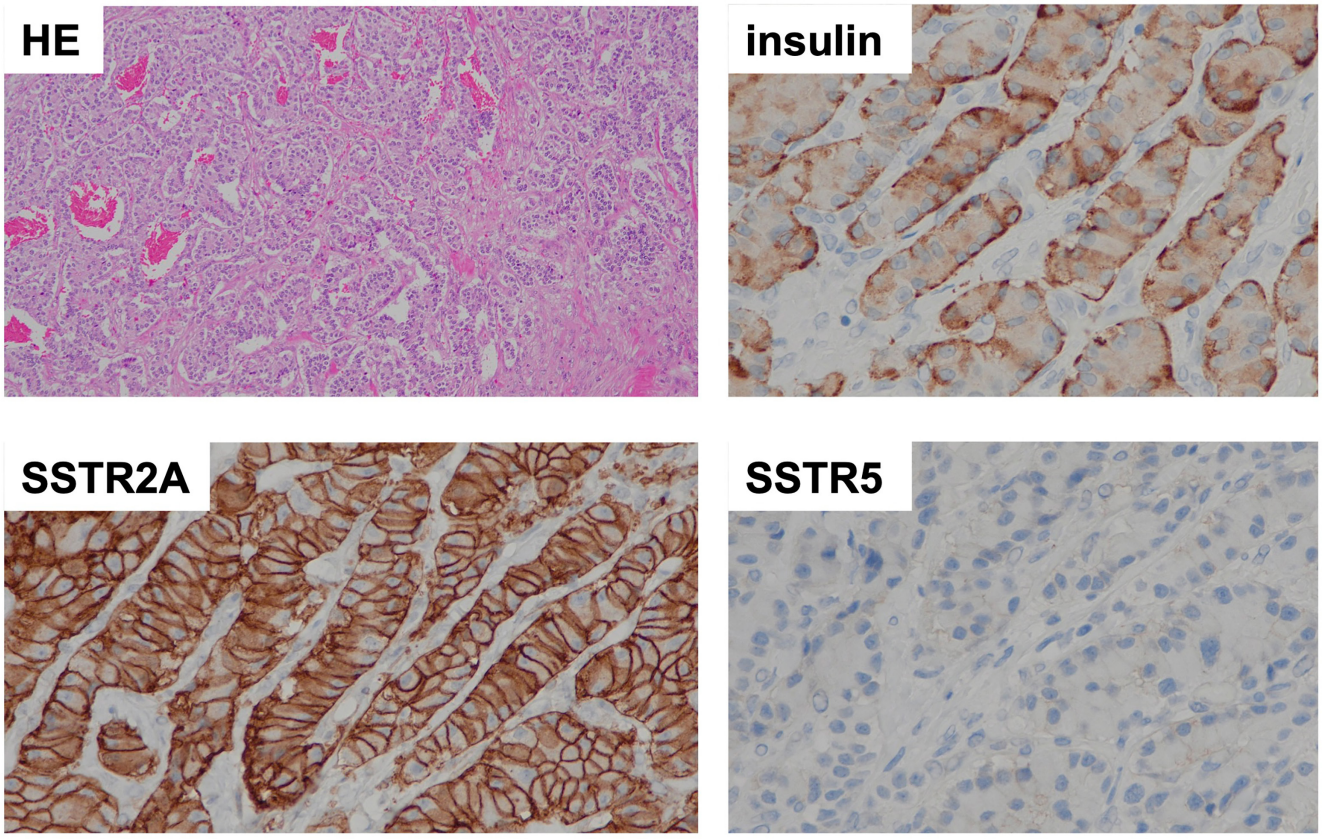

FIGURE 3 Microscopic examination of the resected pancreatic tumor. Hematoxylin and eosin staining section of the tumor (magnification, x100). Immunohistochemical staining for insulin, somatostatin receptor 2A, and somatostatin receptor 5 (magnification, x400).

for the control of hypoglycemia in some patients with insulinomas. The response to octreotide has been reported to depend mainly on SSTR2 expression in the tumor. SSTR2 is expressed in approximately 70% of insulinomas.[5] In insulinomas with SSTR2 expression, octreotide might be effective for preoperative hypoglycemic

treatment and for patients who are unable to undergo surgery. SSTR2 agonists inhibit not only the secretion of insulin but also the secretion of counter-regulatory hormones such as glucagon and growth hormone.[6,7] In insulinomas without SSTR2 expression, octreotide can aggravate hypoglycemia due to suppression of the secretion of glucagon and growth hormone.[4] Therefore, prediction of SSTR2 expression is crucial before administration of octreotide.

In patients with in insulinomas, the results of an octreotide test and somatostatin scintigraphy have been shown to be associated with SSTR2 expression. Vezzosi reported that six of eight patients with insulinomas who were responsive to an octreotide test had expression of SSTR2. Three of four insulinomas with uptake in somatostatin scintigraphy expressed SSTR2. All patients with positive SSTR2 immunostaining were responsive to octreotide.[8] Nakamura reported that five patients with a positive response in the octreotide test showed positive results of immunocytochemistry for SSTR2 expression.[9]

An octreotide test might be useful for predicting SSTR2 expression in insulinomas, but one problem is that the definition of a response in the octreotide test is inconsistent. Vezzosi reported that a blood glucose level of >100 mg/dL within 6 h after administration of octreotide was a responsive result. Nakamura defined a positive result as a blood glucose level of >54 mg/dL and an insulin level of <3 μIU/mL within 8 h after administration. The present case met both criteria and was responsive to octreotide. Another problem is that the low sensitivity of somatostatin scintigraphy can lead to false-negative results in SSTR2-positive insulinomas. The sensitivity of somatostatin scintigraphy has been reported to be approximately 50%.[10] Although somatostatin scintigraphy uptake suggests the expression of SSTR2 in the tumor, it should be noted that no uptake cannot always rule out the expression of SSTR2.

In conclusion, an octreotide test and somatostatin scintigraphy might be useful for predicting the expression of SSTR2 in insulinomas. Since insulinomas expressing SSTR2 benefit from octreotide treatment, an octreotide test may assist in the selection of treatment options for preoperative and inoperable patients.

AUTHOR CONTRIBUTIONS

Kohei Oguni: Writing – original draft. **Shinnosuke Fukushima:** Writing – review and editing. **Yukichika Yamamoto:** Writing – review and editing. **Kou Hasegawa:** Writing – review and editing. **Hideharu Hagiya:** Writing – review and editing. **Naoko Inoshita:** Resources. **Fumio Otsuka:** Supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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