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CASE REPORT

Advanced Peptide Receptor Radionuclide Therapy to Overcome Refractory Hypoglycemic Insulinoma: A Case Report and Review of the Literature

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We reported the case of a 42-year-old man with refractory hypoglycemia caused by an inoperable malignant insulinoma and multiple liver metastases. The patient initially received bi-weekly intramuscular injections of octreotide long-acting release and a daily oral dose of everolimus. Despite this treatment, hypoglycemia was only partially alleviated, and there were no changes in tumor size. As a next step, the patient underwent peptide receptor radionuclide therapy (PRRT) with lutetium-177 (177 Lu)-Dotatate as a salvage therapy. After four courses of PRRT, there was a noticeable regression of the liver masses, and the hypoglycemia resolved. In addition, the patient's quality of life significantly improved, as he no longer required antihypoglycemic medication or had to endure frequent blood sugar testing.

Key words: 177 Lu-Dotatate, case report, malignant insulinoma, mammalian target of rapamycin inhibitor, peptide receptor radionuclide therapy, refractory hypoglycemia, somatostatin analog

INTRODUCTION

Insulinoma is a type of functioning pancreatic neuroendocrine tumor (pNET) with an incidence rate of 1–4 cases per million person-years. Approximately 90% of insulinomas are reported to be benign, while malignant insulinomas are exceedingly rare, with an incidence rate ranging from 0.0 to 0.27 cases per million person-years.[1,2] The most common clinical presentation includes fasting hypoglycemia accompanied by recurrent episodes of neuroglycopenic symptoms, though some patients may only experience postprandial hypoglycemia.[3] In addition, patients with malignant insulinoma often exhibit elevated levels of insulin, proinsulin, and C-peptide.[4] Surgical intervention is the preferred treatment option; however, for patients with malignant insulinomas who are not surgical candidates, drug therapies such as octreotide, mammalian target of rapamycin (mTOR) inhibitors, and tyrosine-kinase inhibitors can help suppress tumor growth.[5] Furthermore, cytoreductive surgery and liver-directed therapies (including embolization, chemoembolization, radioembolization, and radiofrequency ablation) may be considered alternative options.

In this report, we presented a rare case of a patient initially diagnosed with malignant insulinoma and multiple hepatic metastases. Due to the patient's ineligibility for surgical resection, we administered octreotide and everolimus as first-line treatments, followed by peptide receptor radionuclide therapy (PRRT) as a second-line therapy due to the refractory nature of the disease and persisting symptoms.

CASE REPORT

A 42-year-old man was admitted to our hospital due to a 10% increase in body weight, rising from 63 kg to 69 kg, alongside persistent hunger for more than 6 months. He

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reported no medical history of systemic diseases or drug-related issues except for gastroesophageal reflux disease. Initially, he experienced intermittent palpitations and hand tremors when feeling hungry, followed by cold sweats. Over the following weeks, he developed frequent dizziness and occasional disturbances in consciousness, primarily in the mornings; however, these symptoms were alleviated after eating. Upon visiting a local clinic, he was found to have hypoglycemia, with plasma glucose measured at 47 mg/dL. His glycated hemoglobin was 4.4%, not attributable to anti-hyperglycemic agents or prolonged fasting. Key findings from his general physical examination indicated a height of 175 cm, a weight of 69 kg, and a body mass index of 22.5 kg/m^2. All other aspects of his general and systemic examinations were within normal limits. During admission, a 72-h prolonged fasting test was conducted, which revealed a rapid drop in blood sugar levels from 120 mg/dL to 30 mg/dL within 12 h. His serum insulin and C-peptide levels were 18.5 mU/L (132.7 pmol/L) and 2.63 ng/mL (0.868 nmol/L), respectively. The molar ratio of insulin to C-peptide was 0.15, suggesting a high likelihood of an insulinoma rather than excess exogenous insulin. Both ACTH and cortisol levels were within normal ranges, and the test for anti-insulin antibodies was negative.

Figure 1: Pancreas contrast magnetic resonance imaging (a) a 2.42-cm mass in the pancreatic head (white arrow), suspected adenocarcinoma of the pancreatic head. (b) Multiple nodules in both lobes of the liver, and the maximal size (white arrow) was approximately 2.7 cm

Abdominal contrast-enhanced magnetic resonance imaging (MRI) identified a mass measuring 2.42 cm in the pancreatic head [Figure 1a] and multiple nodules, the largest approximately 2.7 cm, in both liver lobes [Figure 1b]. Endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) of the pancreatic head lesion revealed isoechoic, blue elastography, and hyper-enhanced lesion [Figure 2]. Histological examination indicated the presence of tumor cells with typical features of neuroendocrine neoplasms, confirmed by positive insulinoma-associated protein 1 immunostaining [Figure 3a and b]. Furthermore, liver tumor cell biopsy was positive for chromogranin, CK, and CD56 on immunohistochemical analysis, showing a Ki-67 index of 20%, but Hep-1 staining was negative. Based on these findings, the diagnosis was pNET, G2, with multiple liver metastases. Other endocrine neoplasms were excluded, as no mass lesions were detected in the pituitary or parathyroid glands. Octreotide scintigraphy demonstrated the lesions' octreotide avidity, precluding surgical intervention due to extensive hepatic involvement.

Upon diagnosis confirmation, treatment included biweekly intramuscular injections of octreotide long-acting release (LAR) (30 mg), daily intravenous dexamethasone (4 mg), and intermittent glucagon (1 mg) as first-line therapy. Hypoglycemia persisted despite continuous intravenous dextrose infusions (up to 600 g/day). Given the risk associated with halting dextrose therapy, everolimus (10 mg/day), an mTOR inhibitor, was administered as an additional treatment. Despite combination drug therapy and optimal supportive care, frequent hypoglycemic episodes continued, necessitating inpatient care, though serum insulin and C-peptide levels decreased. No size reduction was observed in the pancreatic tumor or liver metastases, prompting PRRT as second-line therapy.

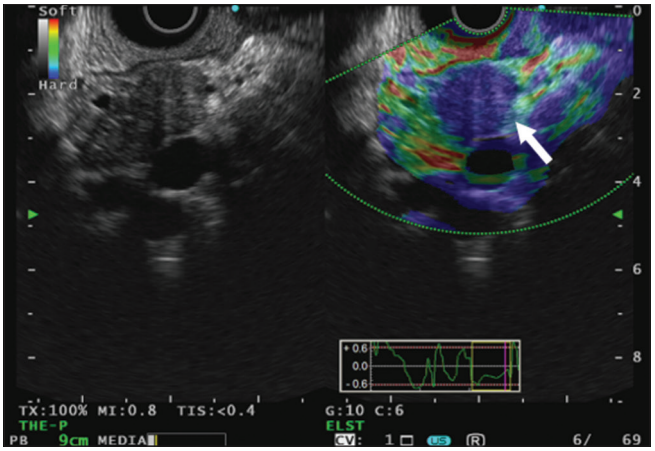

Figure 2: Endoscopic ultrasound: A hyper-enhanced lesion (white arrow) measuring 10.7mmx 19.3mm, with iso-echoic characteristics and a blue elastography pattern, at the pancreatic haed

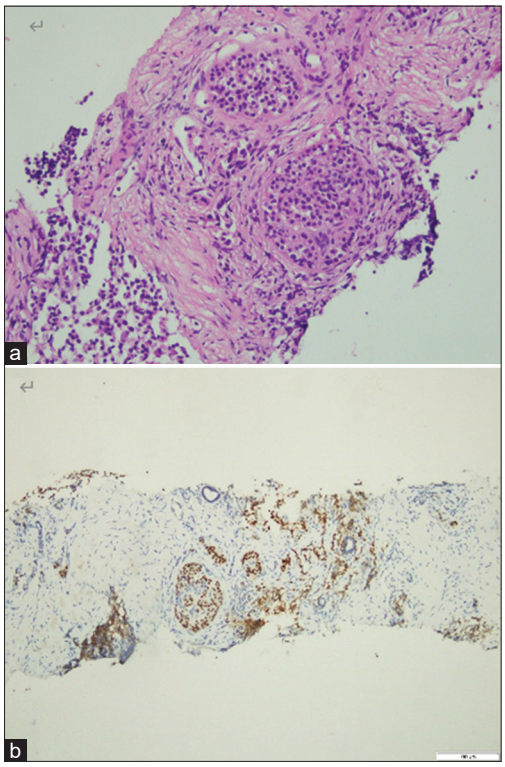

Figure 3: Histopathological and immunohistochemical findings of specimens of pancreatic head lesion (a) Individually localized neoplastic cells with neuroendocrine characteristics (×400). (b) Positive insulinoma-associated protein 1 staining (×100)

A 68Gallium labeled somatostatin analogs positron emission tomography-computed tomography (68 Ga-DOTA-SSA-PET/CT) showed liver metastases with high somatostatin receptor expression [Figure 4a], making the patient eligible for PRRT. Four treatment cycles were administered at 8-week intervals. After the third PRRT cycle, hypoglycemia improved significantly, eliminating the need for glucose supplementation and frequent blood sugar monitoring. Subsequent imaging after the fourth PRRT cycle [Figure 4b] showed a marked regression of liver metastasis compared to pre-PRRT imaging.

DISCUSSION

Malignant insulinoma occurs in approximately 10% of insulinoma cases, with primary metastases typically found in the liver.[6] The diagnosis of insulinoma is based on Whipple's triad, which consists of three criteria: symptoms of hypoglycemia, concomitant plasma glucose level of <45 mg/dL (2.2 mmol/L), and relief of symptoms upon sugar intake. The 72-h fasting test considered the gold standard for diagnosing insulinoma, reveals hypoglycemia (glucose levels <45 mg/dL) accompanied by inappropriately elevated insulin levels (>6 μU/mL or 30 pmol/L) and C-peptide concentrations

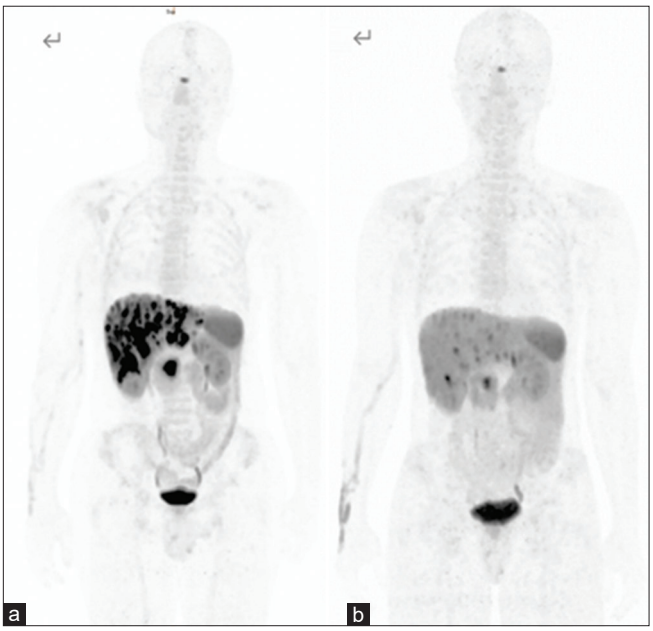

Figure 4: In the 68Gallium labeled somatostatin analogs positron emission tomography-computed tomography (68 Ga-DOTA-SSA-PET/CT) scan before peptide receptor radionuclide therapy (PRRT) (a), the hepatic metastatic lesions with intense radiotracer uptake exhibit high somatostatin receptor expression. Two months after completing four courses of PRRT, a subsequent 68 Ga-DOTA-SSA-PET/CT scan (b) showed significant tumor regression

>300 pmol/L.[7] Once a clinical diagnosis is confirmed, tumor localization can be achieved through various diagnostic methods, including ultrasound, CT scan, and MRI. If initial imaging is inconclusive, EUS with FNA may provide higher sensitivity and specificity. Additional methods, such as digital subtraction angiography and selective arterial secretagogue injection tests can also aid tumor localization. Recent advances suggest the use of imaging agents like 111 In-DOTA-exendin-4 for detecting small tumors. Tissue proof may be required to exclude other diagnoses, such as pancreatic adenocarcinoma, in certain cases.[8] Comprehensive differential diagnosis is crucial to exclude other causes of hypoglycemia.

Currently, surgery is considered the only curative treatment for insulinomas. In cases of localized and limited metastatic disease, surgical resection can be performed.[9] However, if the tumor has metastasized, medical treatment or radiation therapy may be used to alleviate symptoms or control tumor growth.[5] Several pharmacological therapies have been developed to treat insulinoma, including somatostatin receptor ligands (SRLs). First-generation SRLs, such as octreotide and lanreotide, have a high affinity for SSTR2, which is often elevated in aggressive insulinomas. Everolimus, an mTOR inhibitor, demonstrates anti-proliferative activity in metastatic NET, including malignant insulinomas.[10] In addition, sunitinib, an oral multi-targeted receptor tyrosine kinase inhibitor, exhibits

antiangiogenic and antitumor activity. These drugs can be used in the treatment of metastatic or inoperable aggressive insulinoma.

However, in our case, despite combination pharmacotherapy, the response was suboptimal. The higher standardized uptake values observed on 68Ga-DOTA-SSA-PET/CT scans indicated elevated somatostatin receptor expression, which is associated with a favorable response to PRRT, a precision treatment for NET. In the randomized phase III clinical trial (NETTER-1), focusing on inoperable advanced midgut NETs, patients receiving 177 Lu-Dotatate treatment experienced a 79% lower risk of disease progression or death compared to those receiving high-dose octreotide LAR.[11] Literature suggests that PRRT yields a better therapeutic response for pNETs compared to other types of NET. However, there are concerns about potential adverse events such as hematological, hepatic, or renal toxicity. In clinical trials, PRRT is typically administered in four courses to balance efficacy and manage potential toxicities, allowing recovery between doses while ensuring sufficient cumulative exposure to the radiopharmaceutical. Common adverse events include hematological toxicities (such as neutropenia, thrombocytopenia, and anemia), with hematological toxicity affecting about 10%–20% of patients.[12] Fortunately, in this case, none of these adverse effects were observed throughout the PRRT treatment, demonstrating a tolerable safety profile.

CONCLUSION

In summary, this case report presents a rare instance of refractory malignant insulinoma with multiple liver metastases, which remained unresponsive to initial treatment, failing to improve hypoglycemia or reduce tumor size. Consequently, the patient experienced substantial improvement following PRRT. Four courses of PRRT led to significant regression of liver metastases and resolution of hypoglycemia and eliminated the need for antihypoglycemic agents or close blood sugar monitoring. This case highlights that PRRT may serve as an effective second-line therapy, particularly when higher somatostatin receptor expression is noted on a 68Ga-DOTA-SSA-PET/CT scan. Further exploration of tailored treatment strategies is essential for optimizing outcomes in similar cases.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Tri-Service General Hospital, Taipei, Taiwan with approval number: C202315068 and date of approval: 2, June 2023.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Data availability statement

All data generated or analyzed during this study are included in the published article. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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