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【 CASE REPORT 】

The Effect of Everolimus on Refractory Hypoglycemia in a Patient with Inoperable Metastatic Insulinoma Evaluated by Continuous Glucose Monitoring

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Abstract:

An 84-year-old Japanese woman with metastatic insulinoma suffered from frequent hypoglycemic events. Continuous glucose monitoring (CGM) confirmed severe and frequent symptomatic/asymptomatic hypoglycemia. After the initiation of everolimus treatment, the hypoglycemic events were rapidly eliminated. CGM revealed that her blood glucose levels were maintained without hypoglycemia throughout the day. Furthermore, everolimus reduced the duration of time above the upper limit (>180 mg/dL) along with the standard deviation and mean amplitude of glycemic excursions. This case shows the potential effects of everolimus on hypoglycemia and glycemic control in a patient with inoperable metastatic insulinoma evaluated by CGM.

Key words: everolimus, hypoglycemia, continuous glucose monitoring

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Introduction

Inhibitors for mammalian target of rapamycin (mTOR) have been used as anti-rejection agents for post-transplantation and anti-cancer therapies. Everolimus, an oral mTOR inhibitor, has been increasingly frequently used as one of a new class of agents for the treatment of pancreatic neuroendocrine tumors (panNETs) (1). In phase 2 and 3 trials, hyperglycemia has been recognized as a frequent adverse event of everolimus (1, 2), leading this drug to be used against hypoglycemia in the management of patients with insulinoma. Indeed, recent reports have indicated that everolimus rapidly enables the normalization of plasma glucose under conditions of refractory hypoglycemia in patients with unresectable insulinoma (3-7). However, there have been no reports showing the effects of everolimus on inappropriate blood glucose fluctuation measured using continuous glucose monitoring (CGM).

We herein report a Japanese woman with inoperable metastatic insulinoma who developed severe hypoglycemia unresponsive to octreotide. Everolimus was administered, resulting in the rapid improvement of her hypoglycemia. We evaluated her glucose level fluctuation using CGM before and after administrating everolimus.

Case Report

In 2008, a 76-year-old Japanese woman received a physical checkup. Ultrasonography occasionally revealed an abnormal lesion in her pancreas, so she received a detailed examination at a hospital. Computed tomography (CT) revealed a 30-mm-diameter mass in the pancreas. Based on the results of a biopsy of the mass, she was diagnosed with

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Table 1. Laboratory Data on Admission.

Complete blood count		HDL cholesterol	58 mg/dL
WBC	5,400 /μL	LDL cholesterol	104 mg/dL
RBC	325×10⁴ /μL	Fe	19 μg/dL
Hb	9.1 g/dL	TIBC	384 μg/dL
Hematocrit	29.7 %	Ferritin	11 ng/mL
Reticulocyte	2.0 %	Vitamin B_{12}	>1,500 pg/mL
Plt	28.2×10⁴ /μL	Folic acid	11.2 ng/mL
Coagulation		Glucose-related	
PT	103 %	Fasting plasma glucose	31 mg/dL
		HbA1c	4.4 %
Biochemistry		Glycoalbumin	15.3 %
T-Bil	0.4 mg/dL	Insulin	16.9 μU/mL
Alb	3.3 g/dL	Insulin antibody	(-)
AST	39 IU/L	C-peptide	1.36 ng/mL
ALT	33 IU/L	Fajans index	0.55 (normal range <0.3)
LDH	270 IU/L	Turner index	1,690 (normal range <50)
γ-GTP	54 IU/L		
ChE	256 IU/L	Endocrinology	
ALP	163 IU/L	GH	1.15 ng/mL
CK	82 IU/L	Insulin-like growth factor-1	83 ng/mL
Amylase	76 IU/L	ACTH	14.64 pg/mL
BUN	17 mg/dL	Cortisol	9.2 μg/dL
Cre	0.62 mg/dL	TSH	0.76 μIU/mL
eGFR	67.8 mL/min	Free T4	0.82 ng/dL
UA	4.7 mg/dL	LH	30.0 mIU/mL
Na	146 mEq/L	FSH	195.2 mIU/mL
K	3.9 mEq/L	Prolactin	9.6 ng/mL
Cl	110 mEq/L	Intact PTH	48 pg/mL
Ca	9.3 mg/dL		
Total cholesterol	177 mg/dL	Hepatitis virus-related	
Triglyceride	118 mg/dL	HBs antigen	(-)
		HCV antibody	(-)

panNET and underwent subtotal stomach-preserving pancreaticoduodenectomy. At that time, her blood glucose levels did not show hypoglycemia (Supplementary material 1). In 2010, abdominal CT revealed a hepatic tumor that was gradually increasing in size. Therefore, she received a biopsy and transcatheter arterial chemoembolization (TACE) for this tumor in January 2014. The pathologic results from the tissue biopsy showed that the cells of the hepatic tumor were similar to those from the panNET in 2008, and somatostatin receptor 2 staining was positive in this tumor. Based on these pathological results, the patient started to receive 10 mg of long-acting octreotide every 4 weeks in February 2014. However, multiple liver metastases developed, despite the absence of symptoms.

In May 2016, at 84 years of age, she was admitted to a local neurosurgery hospital due to several incidents leading to a loss of consciousness. Although magnetic resonance imaging revealed no abnormalities in her brain, her blood glucose levels ranged from 20 to 50 mg/dL during admission. She was therefore admitted to our hospital for the further evaluation of her hypoglycemia at the end of May.

On admission, her height, body weight, and body mass index were 147.4 cm, 38.2 kg, and 17.6 kg/m^2, respectively. There were no abdominal findings in the chest or abdomen except for the operation scar at her midline abdomen. The findings on a neurological examination were normal. Laboratory data identified iron-deficiency anemia and slightly increased transaminases (Table 1). A fasting blood sample revealed a low plasma glucose level of 31 mg/dL, and an elevated serum insulin level of 16.9 μU/mL. Adrenal insufficiency, hypopituitarism, insulin autoimmune syndrome, and ingestion of alcohol or hypoglycemic agents were excluded as the cause of her hypoglycemia based on the laboratory and endocrine data and her medical history. Regarding the hepatic function, the Child-Pugh score was class A. In addition, the hepatic reserve capacity was normal, as evaluated by ^{99m}Tc-GSA scintigraphy. Taken together, these data indicated that she did not have severe hepatic dysfunction. We therefore excluded the possibility that a decrease in glycogen storage in the liver might have caused the hypoglycemia.

Abdominal CT revealed multiple metastatic tumors ranging in size from 13 to 45 mm only in the liver (S2, S4, S6 and S8) (Fig. 1A). An immunohistochemical re-examination

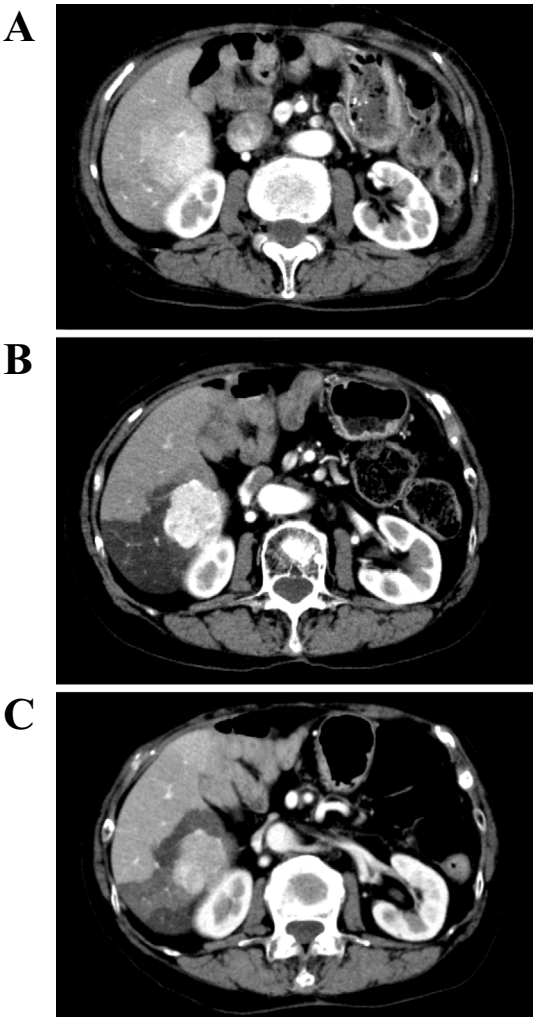

Figure 1. Abdominal computed tomography imaging of the liver: (A) before (Day 0), (B) three months after (Day 98), and (C) six months after (Day 189) the administration of everolimus. The maximum diameter of the S6 tumor was 45 mm on day 0 (A), 39 mm on day 98 (B), and 39 mm on day189 (C).

for chromogranin A, synaptophysin, and insulin revealed positive results for panNET using the surgical specimen obtained in 2008. Since the mitotic count was <1 per 10 high-power fields and the Ki-67 labelling index was 5.3%, the tumor was classified as a neuroendocrine tumor grade 2 (NET G2). The diagnosis of metastatic insulinoma was made based on hyperinsulinemic hypoglycemia and confirmed by a histopathological examination. She was found to have frequent hypoglycemic events even under the administration of octreotide via injection, frequent oral glucose administration, and nocturnal glucose infusion. Furthermore, CGM using a CGMS® System Gold™ (Medtronic MiniMed, Northridge, USA) device confirmed not only the severity and frequency of hypoglycemia but also the existence of asymptomatic hypoglycemia (Fig. 2A, Table 2 and Supplementary material 2).

Everolimus was added to octreotide at the beginning of July to help reduce the incidence of hypoglycemic events. After the initiation of everolimus at 10 mg/day, hypoglycemic events were rapidly eliminated, enabling her to discontinue nocturnal glucose infusion after three days. CGM revealed that her blood glucose levels were maintained above 70 mg/dL throughout the day (Fig. 2B, Table 2 and Supplementary material 3). Furthermore, everolimus reduced the duration of the time above the upper limit (>180 mg/dL), duration below the lower limit (<70 mg/dL), along with the standard deviation and mean amplitude of glycemic excursions (MAGEs) (Table 2). In addition, the hyperinsulinemic hypoglycemia improved after the administration of everolimus. Her plasma glucose and serum insulin levels were 115 mg/dL and 14.6 μU/mL, respectively. Even after 6 months of everolimus administration, her blood glucose levels were maintained above 70 mg/dL (Supplementary material 4). CT showed that the tumor suppression status, in accordance with RECIST CRITERIA, was "stable disease" after three and six months of everolimus (Fig. 1B and C).

Discussion

This report describes the effects of everolimus on glycemic control and hypoglycemia in a patient with inoperable metastatic insulinoma evaluated by CGM. The present findings highlight two clinical points. First, the incidence of hypoglycemia disappeared after the administration of everolimus. Second, everolimus was effective not only in normalizing refractory hypoglycemia but also in improving glucose fluctuations.

Everolimus reportedly normalizes refractory hypoglycemia in patients with unresectable insulinoma (3-7). In those previous reports, the efficacy of this agent on hypoglycemia was evaluated by measuring the capillary/laboratory glucose levels or analyzing the symptom-free hypoglycemia survival. We evaluated the hypoglycemic status, including the asymptomatic events, more precisely using CGM in the present case. The CGM data revealed that the proportion of time spent below 70 mg/dL was 0% after the addition of everolimus treatment (Table 2), clearly suggesting the impact of everolimus on resolving hypoglycemia-associated clinical issues.

Previous reports have shown that CGM in patients with insulinoma was useful for monitoring the response to surgical or medical therapy (8, 9). One report described three patients with insulinoma. These CGM data revealed that both diazoxide and octreotide reduced hypoglycemia and that surgical excision eliminated hypoglycemia in these patients (8). Regarding metastatic insulinoma, another report described the use of CGM in the management of a patient with inoperable metastatic insulinoma. In that case, treatment with diazoxide showed limited efficacy in preventing hypoglycemia (9). Since our data indicated that hypoglycemia disappeared after the administration of everolimus, the drug is expected to be useful for achieving glycemic control in patients with metastatic insulinoma. Furthermore, although the tumor suppression status in accordance with the RECIST CRITERIA was "stable disease", hyperinsulinemic hypogly-

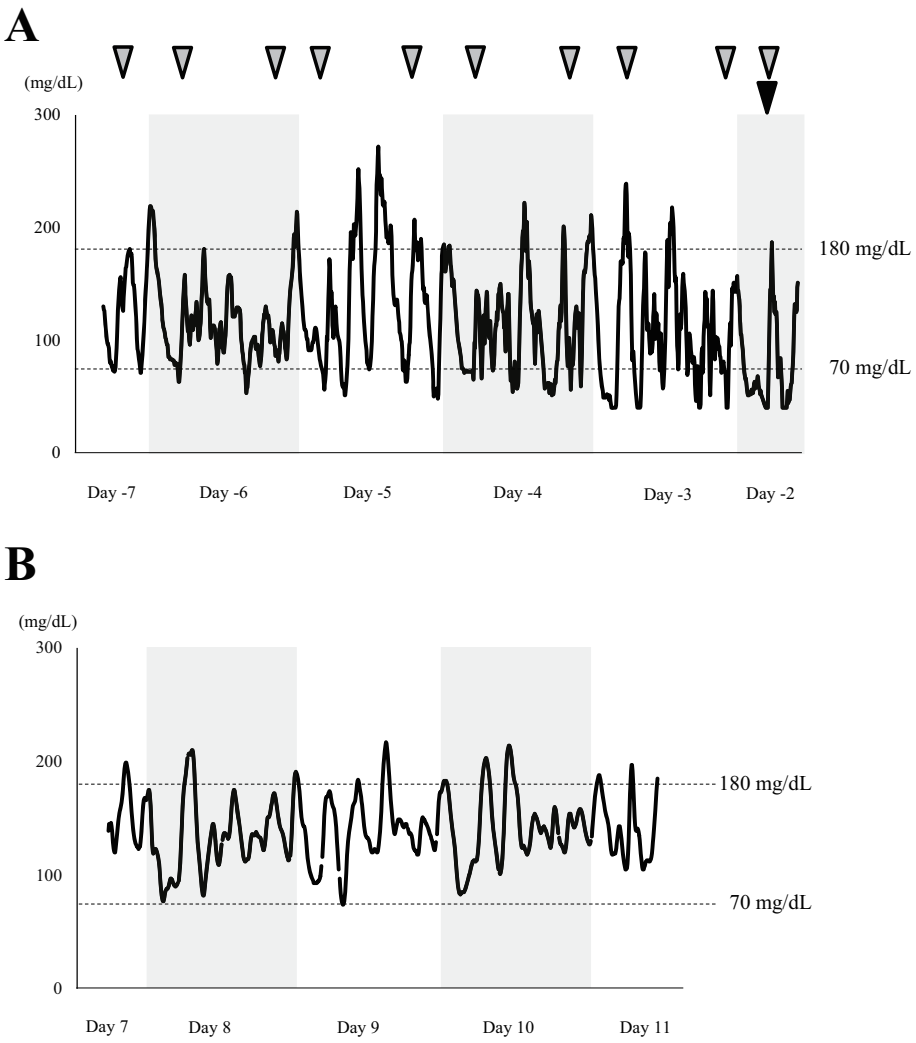

Figure 2. **Variations in the patient's 24-h glucose levels measured by continuous glucose monitoring (A) before (from Day -7 to Day -2) and (B) (from Day 7 to Day 11) after the administration of everolimus. During admission, meal times were approximately 8:00 (breakfast), 12:00 (lunch), and 18:00 (dinner). ▼: 50% glucose 20 mL i.v., ▽: supplementary food.**

Table 2. **The Parameters of Glycemic Variability before (from Day -7 to Day -2) and after (from Day 7 to Day 11) Everolimus Treatment Measured by CGM.**

	Before	After
Average (mg/dL)	114.9	140.2
Minimum (mg/dL)	40.0	74.0
Maximum (mg/dL)	272.0	217.0
SD (mg/dL)	46.2	29.8
MAGE (mg/dL)	119.7	77.6
Duration above high limit (>180 mg/dL) (%)	10.7	8.0
Duration within limits (70-180 mg/dL) (%)	73.3	92.0
Duration below low limit (<70 mg/dL) (%)	16.0	0.0

SD: standard deviation, MAGE: mean amplitude of glycemic excursion

cemia improved after the administration of everolimus. These results suggested that the mechanism of improved hypoglycemia may involve the effect of everolimus on reducing the insulin secretion rather than suppressing the tumor, as described in a previous report (10).

Another interesting finding is that the addition of everolimus improved both the standard deviation and MAGE, the indicators of glucose fluctuation (Table 1). Improvement of glucose fluctuations implies a reduction in the severity and frequency of both hypoglycemic and hyperglycemic events. We speculate that the amelioration of glucose fluctuations via everolimus in our patient may have been due to reductions in counter-regulated hyperglycemic hormones by the prevention of hypoglycemia and the discontinuation of glucose infusions or additive food intake to maintain glucose levels.

In summary, CGM before and after administering everolimus allowed us to confirm that everolimus successfully eliminated hypoglycemia and stabilized glucose fluctuation in a patient with inoperable metastatic insulinoma. Clinical trials to investigate the effect of everolimus on refractory hypoglycemia should be conducted.

The authors state that they have no Conflict of Interest (COI).

References

1. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med **364**: 514-523, 2011.
2. Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol **28**: 69-76, 2010.
3. Kulke MH, Bergsland EK, Yao JC. Glycemic control in patients with insulinoma treated with everolimus. N Engl J Med **360**: 195-197, 2009.
4. Ong GS, Henley DE, Hurley D, Turner JH, Claringbold PG, Fegan PG. Therapies for the medical management of persistent hypoglycaemia in two cases of inoperable malignant insulinoma. Eur J Endocrinol **162**: 1001-1008, 2010.
5. Fiebrich HB, Siemerink EJ, Brouwers AH, et al. Everolimus induces rapid plasma glucose normalization in insulinoma patients by effects on tumor as well as normal tissues. Oncologist **16**: 783-787, 2011.
6. Thomas N, Brooke A, Besser G. Long-term maintenance of normoglycaemia using everolimus in a patient with disseminated insulinoma and severe hypoglycaemia. Clin Endocrinol (Oxf) **78**: 799-800, 2013.
7. Bernard V, Lombard-Bohas C, Taquet MC, et al. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycaemia. Eur J Endocrinol **168**: 665-674, 2013.
8. Munir A, Choudhary P, Harrison B, Heller S, Newell-Price J. Continuous glucose monitoring in patients with insulinoma. Clin Endocrinol (Oxf) **68**: 912-918, 2008.
9. Sawyer AM, Schade DS. Use of a continuous glucose monitor in the management of inoperable metastatic insulinoma: a case report. Endocr Pract **14**: 880-883, 2008.
10. Asayama M, Yamada-Murano T, Hara H, Ooki A, Kurosumi M, Yamaguchi K. Everolimus dramatically improves glycemic control in unresectable metastatic insulinoma: a case report. Jpn J Clin Oncol **44**: 186-190, 2014.

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