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Recurrent Hypoglycemia Triggered by Sorafenib Therapy in a Patient with Hemangiopericytoma

Si Won Lee[1], Eun Kyung Lee[1], Tak Yun[1], Young-Woong Won[1,*], Eun Jeong Ko[1], Mihong Choi[1], Sang Il Choi[1], Sun Seob Park[1], Eun Kyung Hong[2]

Departments of [1]Internal Medicine, [2]Pathology, National Cancer Center, Goyang, Korea

Targeted therapy has been proven to be one of the most effective cancer treatments. However, some endocrine disorders can occur during treatment with targeted agents. We report the case of a patient who exhibited a wax and wane pattern of hypoglycemia that was attributed to sorafenib therapy. A 32-year-old woman with metastatic hemangiopericytoma visited the emergency department in a stuporous state. Nonhyperinsulinemic hypoglycemia was diagnosed, was exacerbated shortly after sorafenib therapy, and was improved by the cessation of sorafenib with additional glucocorticoid therapy. Patients with metastatic hemangiopericytoma should be carefully monitored with particular attention to hypoglycemia when sorafenib therapy is initiated.

Keywords: Hemangiopericytoma; Hypoglycemia; Sorafenib

INTRODUCTION

Targeted therapy has been proven to be one of the most successful treatment modalities in many cancers. However, some endocrine disorders have been associated with treatment with targeted agents, including hypothyroidism (sunitinib and pazopanib), hypoglycemia (sunitinib), and hyperglycemia (everolimus) [1]. Recently, tyrosine kinase inhibitors were reported to have a potential hypoglycemic effect [2]; mean declines in blood glucose were 53 mg/dL for dasatinib, 9 mg/dL for imatinib, 12 mg/dL for sorafenib, and 14 mg/dL for sunitinib. However, the exact mechanism of this hypoglycemic effect remains unclear.

Hemangiopericytoma (HPC) is a soft tissue sarcoma derived from vascular pericytes, which are normally arranged along capillaries and venules throughout the body [3]. HPC-associated hypoglycemia is a unique paraneoplastic syndrome related to high levels of insulin-like growth factor (IGF)-II, which can be improved by the surgical reduction of tumor burden. Here, we report a patient who exhibited a wax and wane pattern of hypoglycemia that was exacerbated shortly after sorafenib therapy and was improved by the cessation of sorafenib.

CASE REPORT

A 32-year-old woman was hospitalized due to loss of consciousness in March 2010. The patient had been diagnosed with HPC after a neck mass resection in 2000. In August 2009,

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Corresponding author: Eun Kyung Lee
Department of Internal Medicine, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 410-769, Korea
Tel: +82-31-920-1743, **Fax:** +82-31-920-2798, **E-mail:** waterfol@gmail.com
*Current affiliation: Center for Clinical Trials, National Cancer Center, Goyang and Division of Hematology and Oncology, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea

she experienced a recurrent mass at the same site with multiple hepatic metastases. She underwent right hemihepatectomy and radiofrequency ablation of multiple nodules. However, multiple hepatic and pulmonary metastases progressed, and were treated with palliative chemotherapy. Unfortunately, the first- (doxorubicin alone) and second-line (a combination of etoposide, ifosfamide, and cisplatin) chemotherapies did not lead to any response. As the third-line chemotherapy, the patient was treated with oral sorafenib 400 mg twice a day.

Soon after starting sorafenib, the patient experienced repetitive hunger, palpitation, and diaphoresis during the nighttime. On the 8th day of sorafenib therapy, she lost consciousness and was transported to the emergency department. Her plasma glucose was 8 mg/dL and hemoglobin A1c level was 5.0%. The hypoglycemia and symptoms were resolved by a 10% intravenous dextrose infusion. She had never experienced hypoglycemia during the first- and second-line chemotherapy. Baseline serum glucose level before sorafenib started was 105 mg/dL. The patient had no past medical or family history of diabetes, she had not taken any medications except sorafenib, and her nutritional status was adequate. Her body mass index (BMI) on the day she visited emergency room was 22.5 kg/m^2 (height 163 cm, weight 59.8 kg), similar to her BMI at the start of sorafenib treatment, 22 kg/m^2 (height 163 cm, weight 58.5 kg). There was no change in oral intake before or during the sorafenib therapy. On average, the patient ate about 1,600 to 2,000 kcal per day. Renal function was normal and liver enzymes were mildly elevated (aspartate aminotransferase [AST] 99 IU/L, alanine aminotransferase [ALT] 46 IU/L, total bilirubin 30.8 μmol/L, prothrombin time [PT] 14.2 seconds [88%; international normalized ratio, INR 1.08]), whereas the patient's baseline values of liver enzymes had been within normal range, as follows: AST 42 IU/L, ALT 25 IU/L, total bilirubin 29.1 μmol/L, PT 14.6 seconds (80%; INR 1.16).

Because the patient experienced hypoglycemia even when the infusion rate of dextrose fluid was reduced, a prolonged fasting test was not necessary to confirm a hypoglycemic event. She had a blood glucose level of 12 mg/dL with undetectable insulin, IGF-1 3.3 nmol/L (reference range, 14.3 to 43.1) and C-peptide level 0.024 nmol/L (reference range, 0.3 to 1.3), suggesting nonhyperinsulinemic hypoglycemia.

After cessation of sorafenib, there was no recurrence of the hypoglycemic event. However, the patient had no alternatives to sorafenib as a cancer treatment. Thus, sorafenib was resumed with oral prednisolone (60 mg per day), dextrose infusion and frequent meals. After discontinuation of dextrose infusion, the patient was discharged with minimal hypoglycemia. Ten days after discharge, she discontinued sorafenib therapy due to chemotherapy-related mucositis and insufficient recovery from hypoglycemia. Following the cessation of sorafenib, she did not experience hypoglycemia, and died of disease progression after 2 months.

DISCUSSION

Sorafenib is a tyrosine kinase inhibitor that was developed as an anti-angiogenic therapeutic, and has excellent antitumor activity in renal cell carcinoma, thyroid cancer, hepatocellular cancer, and pancreatic cancer. However, the effect of sorafenib on glucose metabolism has been reported in a few cases. This report is about a patient with metastatic HPC with repetitive hypoglycemic episodes, which were triggered by sorafenib therapy and were resolved by the discontinuation of sorafenib combined with steroid therapy.

Hypoglycemia associated with a non-islet cell tumor is a rare endocrine paraneoplastic syndrome caused by the oversecretion of IGF [4]. Tumors manifesting hypoglycemia are typically of mesodermal or epithelial origin, such as several specific liver tumors including hepatocellular carcinoma, solitary fibrous tumor of liver, and HPC. The severity of hypoglycemic episodes depends on the tumor burden; most patients experienced more profound or frequent hypoglycemia as tumors grew. A single case of refractory hypoglycemia was controlled with improvement in the primary tumor, a solitary fibrous tumor, treated by sorafenib [5].

The typical biological findings of HPC-associated hypoglycemia are as follows: low glucose, low insulin, low C-peptide, low IGF-I, low IGF binding protein (IGFBP)-3; increased levels of IGFBP-2 and IGFBP-6; and slightly elevated serum IGF-II [6]. This phenomenon is mediated through IGF families, which are produced by HPC cells [7]. A high degree of homology with the insulin A and B chains [8] and similarities between IGF-I and insulin receptor structure could explain the hypoglycemic effects of IGF, the insulin-like activity of which is estimated to be 1% to 2% of that of insulin [9,10].

In this case, there were some factors that may contribute to the development of hypoglycemia: HPC-associated paraneoplastic hypoglycemia, excessive glucose consumption as tumor grows, and impaired hepatic function due to hemihepatectomy or hepatic metastasis. From the compensatory suppression of insulin/C-peptide/IGF-I level, we could infer that the resulting hypoglycemia was nonhyperinsulinemic hypoglyce-

mia. Much to our regret, we did not check the patient's IGF-II level and do not have remaining tissue or serum from the patient, making it impossible to exclude HPC-associated paraneoplastic hypoglycemia (IGF-II mediated hypoglycemia).

The mechanism of sorafenib-associated hypoglycemia remains unclear; however, the glucose-lowering effects of sunitinib have been previously documented. Billemont et al. [11] reported the time sequence of sunitinib treatment interventions and measured blood glucose concentrations/insulin concentrations in metastatic renal cell carcinoma patients. These authors suggested that the hypoglycemic effect comes from sunitinib itself rather than IGF-II [11], which could explain the mechanism behind our case as well. The frequency and severity of hypoglycemia was aggravated soon after starting sorafenib, and was improved after cessation of sorafenib, strongly suggesting sorafenib-associated hypoglycemia.

HPC-associated hypoglycemia can be treated by surgical resection in operable conditions. However, when debulking surgery is not feasible, other modalities such as glucocorticoid [12], somatostatin analog [13], tumor embolization [14], or radiotherapy [15] are considered. As an alternative therapy, Adams et al. [16] described a successful liver transplantation in a patient with diffuse liver metastasis and persistent hypoglycemia resulting from malignant HPC. In the case we report, prednisolone was also given (20 mg three times a day), because there was no clear evidence to exclude HPC-associated hypoglycemia at that time. The possibility of hypoglycemia caused by adrenal insufficiency may also be considered, since the patient improved after steroid replacement; however, an adrenal function test during steroid therapy in general reveals no significant findings, besides, there was no metastasis to the adrenal glands in this patient. Furthermore, the patient's oral intake and liver function were normal with no systemic symptoms of blood pressure change or general weakness, and an electrolyte imbalance such as hyponatremia or hyperkalemia was not found. In this aspect, it is hard to doubt that the patient had adrenal insufficiency.

In summary, HPC-associated hypoglycemia may be triggered by sorafenib therapy even in the patients who have never experienced hypoglycemia before. Therefore, when treating HPC patients with sorafenib, particular attention to hypoglycemia is warranted.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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