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Case Report

Paraneoplastic Hypoglycemia Leading to Insulin Independence in a Patient With Type 1 Diabetes

Nami Safai Haeri, MD *, Hussain Mahmud, MD, Mary T. Korytkowski, MD

Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

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ABSTRACT

Objective: Non–islet cell tumor hypoglycemia (NICTH) is an uncommon paraneoplastic syndrome associated with mesenchymal neoplasms such as gastrointestinal stromal tumors (GISTs). We report the case of a patient with type 1 diabetes (T1D) and recurrent GIST who not only required discontinuation of insulin therapy but also required continuous parenteral glucose infusions to prevent hypoglycemia.
Methods: A 59-year-old woman with a 24-year history of T1D and recurrent GIST presented with frequent episodes of symptomatic hypoglycemia despite continuous reductions in her insulin therapy. Laboratory workup revealed undetectable insulin and C-peptide, low insulin-like growth factor (IGF) 1, normal IGF-2, and an elevated IGF-2:IGF-1 ratio. Medical management with prednisone alone and, later, in combination with octreotide did not reduce hypoglycemic episodes. Eventually, during hospitalization for severe hypoglycemia, she was treated and discharged with continuous intravenous dextrose infusion. She ultimately required around-the-clock glucose infusions, which helped her maintain what she believed was an acceptable quality of life during her remaining weeks.
Discussion: NICTH is characterized by excessive tumor production of IGF-2 or pro-IGF-2, leading to unrestricted glucose uptake in peripheral tissues and hypoglycemia. A diagnosis of NICTH can be made on the basis of low IGF-1 levels in the plasma with normal or elevated IGF-2. Tumor resection is the most definitive treatment for NICTH.
Conclusion: This patient with T1D presented with resistant hypoglycemia due to recurrence of an enlarging GIST. She required discontinuation of all insulin therapy and continuous dextrose infusions to maintain euglycemia.

Introduction

Hypoglycemia is a rare paraneoplastic manifestation of several non–islet cell tumors, including epithelial and mesenchymal tumors.[1] Malignancy-associated hypoglycemia is even less common in individuals with type 1 diabetes (T1D). We report the case of a woman with established T1D who required discontinuation of all exogenous insulin therapy following a recurrence of a large gastrointestinal stromal tumor (GIST). In addition to insulin discontinuation, she eventually required continuous parenteral administration of glucose to prevent hypoglycemia.

Case Report

A 59-year-old woman was diagnosed with T1D at the age of 35 years after presenting with symptoms of hyperglycemia in association with a random blood glucose value of 265 mg/dL. She was initially started on multiple daily insulin injections with transition to continuous subcutaneous insulin infusion pump therapy within 1 year of diagnosis. In 2003, she presented to her primary care physician with a complaint of abdominal pain and rectal bleeding. A diagnostic evaluation that included computed tomography (CT) abdominal imaging revealed the presence of a large (10.4 cm) right upper quadrant mass involving the right lobe of the liver. She subsequently underwent complete surgical resection of the tumor from the liver with a right colectomy.

Abbreviations: CT, computed tomography; GIST, gastrointestinal stromal tumor; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; NICTH, non–islet cell tumor hypoglycemia; T1D, type 1 diabetes.

* Address correspondence to Dr Nami Safai Haeri, Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh Medical Center, 3601 Fifth Avenue, Suite 3B, Pittsburgh, PA 15213.
E-mail address: safaihaerin@upmc.edu (N.S. Haeri).

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Table
Patient Laboratory Data

Test	Normal range	Patient values
HbA1c	4.4%-6.0 % (25-42 mmol/mol)	7.3% (56 mmol/mol)
Blood glucose	70-99 mg/dL	186 mg/dL
Insulin	<25 μIU/mL	<2 μIU/mL
C-peptide	0.8-4.0 ng/mL	<0.1 ng/mL
IGF-1	50-317 ng/mL	44 ng/mL
IGF-2	288-736 ng/mL	346 ng/mL
IGF-2:IGF-1 ratio	<3	7.86
Creatinine	0.5-1.4 mg/dL	0.6 mg/dL
Estimated GFR	>60 mL/min/1.73 m^2	65 mL/min/1.73 m^2
ACTH	9-46 pg/mL	10 pg/mL
Cortisol	2-9 μg/dL	19 μg/dL
TSH	0.3-5.0 μIU/mL	0.98 μIU/mL
Free thyroxine index	5-12	7.2

Abbreviations: ACTH = adrenocorticotropic hormone; GFR = glomerular filtration rate; HbA1c = hemoglobin A1C; IGF = insulin-like growth factor; TSH = thyroid-stimulating hormone.

Histopathologic examination confirmed the presence of GIST. Molecular sequencing revealed a *c-KIT* sequence variation. After the surgery, she received adjuvant therapy with imatinib, a tyrosine kinase inhibitor, following a CT scan that revealed a suspicious lesion in the duodenal area. Imatinib was continued for 2 years and discontinued when results of subsequent surveillance CT scans were negative for tumor persistence or recurrence. She did well until 2012 when imaging studies revealed the presence of peritoneal carcinomatosis involving the omentum, consistent with disease recurrence. Therapy with imatinib was initially resumed; however, it was changed to sunitinib and subsequently regorafenib when imaging studies demonstrated persistent disease progression. She was unable to tolerate regorafenib and was restarted on sorafenib treatment.

In 2014, she began experiencing recurrent episodes of hypoglycemia that persisted despite continuous reductions in basal insulin infusion rates. To prevent hypoglycemia, she frequently suspended insulin delivery by her pump and would instead administer multiple small bolus insulin doses whenever she noticed an increase in her fingerstick capillary blood glucose levels.

On physical examination, her body mass index was 14.96 kg/m^2 with normal vital signs. Laboratory testing that was performed during an office visit after several hours of insulin discontinuation revealed nondetectable insulin and C-peptide, low insulin-like growth factor (IGF) 1, and normal IGF-2 levels (Table). Hemoglobin A1C values ranged from 7.0% (53 mmol/mol) to 7.3% (56 mmol/mol) between 2012 and 2014. Results of thyroid, kidney, and adrenal function tests were normal. With the exception of a low albumin level (3.1 g/dL), the results of liver function studies were also normal.

To reduce the frequency of hypoglycemic events, she was administered trials of therapy with prednisone 40 mg daily, octreotide, and a combination of prednisone and octreotide, all of which were unsuccessful. She continued to experience frequent hypoglycemic events, which became difficult to manage with oral medication alone. Following repeated emergency room visits for hypoglycemia, where she was treated with 50% dextrose infusions, she was admitted to the hospital and treated with a continuous intravenous infusion of 10% dextrose. Attempts at weaning the dextrose infusion resulted in recurrent hypoglycemia. A peripherally inserted central catheter was placed, and she was discharged home with overnight dextrose infusions. All exogenous insulin therapy was discontinued. At home, she continued overnight dextrose infusions at a variable rate of 40 to 60 mg/h with dextrose 25% but eventually required infusions over 24 hours. She remained active and maintained what she believed was an acceptable quality of life, wearing a backpack to carry the dextrose solution when she was not at home for the next month. She succumbed to her disease 2 days after developing a fever with confusion.

Discussion

Non–islet cell tumor hypoglycemia (NICTH) was first reported in a patient with metastatic hepatocellular carcinoma in 1929.[2] Since then, several neoplasms have been identified as being associated with NICTH. These include tumors of the pancreas, prostate, lung, larynx, thyroid, adrenal, cervix, ovary, breast, and gastrointestinal tract.[3] GISTs are mesenchymal tumors, which arise from the interstitial cells that function as digestive tract pacemakers. The majority of GISTs are secondary to gain-of-function mutations in tyrosine kinase *KIT* receptor as observed in the patient in this report. Fewer cases have been associated with mutations in platelet-derived growth factor-α.[4,5]

The incidence of NICTH is estimated to be approximately 1 case per 1 million person-years.[1] The incidence of NICTH in people with diabetes is likely to be much lower. To our knowledge, this is the first report of malignancy-associated hypoglycemia in a patient with established T1D who was able to discontinue all exogenous insulin therapy without the development of diabetic ketoacidosis.

NICTH is characterized by an excessive tumor production of IGF-2 or pro-IGF-2 as the underlying etiology.[6,7] This leads to unrestricted glucose uptake in peripheral tissues, leading to hypoglycemia.[8] IGF-2 is a protein that is mainly produced in the liver. The structure of IGF-2 is similar to insulin, allowing cross-reactivity at the insulin receptor when present in large quantities.[8,9] IGF binding proteins (IGFBPs) are responsible for the transportation of IGFs in plasma.[8] Under normal conditions, IGF-2 binds with IGFBP-3 forming an inactive complex.[10] Abnormal processing of the gene for IGF-2 results in an increased production of pro-IGF-2, which is biologically more active than IGF-2. Pro-IGF-2 does not form a complex with IGFBP-3, which increases its ability to interact with insulin receptors. This increase in pro-IGF-2 mediates the inhibition of gluconeogenesis, glycogenolysis, and lipolysis with an associated increase in glucose disposal in peripheral tissues, all of which contribute to the development of hypoglycemia.[11]

The diagnostic evaluation of a patient who is suspicious for NICTH includes the measurement of IGF-1, IGF-2, and IGFBP-3 levels in addition to the routine hypoglycemia workup.[12] A diagnosis of NICTH can be made on the basis of low IGF-1 levels in the plasma, with normal or elevated IGF-2 serum concentrations. An abnormal IGF-2:IGF-1 ratio can be used as a complementary method for confirming the diagnosis in some patients with normal IGF-2 levels. Under normal circumstances, the IGF-2:IGF-1 ratio is approximately 3.[13] In several NICTH cases, this ratio is much higher, and a ratio of >10 is considered diagnostic for IGF-2-mediated hypoglycemia. Patients who have reduced IGFBP-3 levels such as those with chronic kidney disease or poor nutritional status may have a falsely low ratio.[4] Although IGFBP-3 was not measured in this patient, her levels were likely low due to poor nutritional status manifested by her low serum albumin and body mass index.

Tumor resection is the most definitive treatment for NICTH. Pharmacologic management with glucocorticoids, glucagon, or recombinant growth hormone can be considered in patients who are not good surgical candidates.[6] Glucocorticoids prevent hypoglycemia by inhibiting peripheral glucose uptake and stimulating hepatic gluconeogenesis and lipolysis.[14] Glucocorticoids may also suppress the tumor production of pro-IGF-2.[15] Glucagon infusions with an infusion pump have been used as a short-term therapy in some patients to ameliorate hypoglycemia in patients with NICTH.[6,16] Glucagon increases both glycogenolysis and gluconeogenesis; however, these effects are not long lasting and require

continuous infusions.[16] Recombinant growth hormone has also been used to ameliorate hypoglycemia by increasing gluconeogenesis and glycogenolysis as well as altering the production of IGF-2; however, the theoretical risk of stimulating tumor growth is present.[17] Octreotide is unlikely to be successful in managing hypoglycemia symptoms as most of these tumors generally lack somatostatin receptors.[18]

Conclusion

NICTH secondary to pro-IGF-2 should be considered as a contributor to hypoglycemia in patients with mesenchymal tumors or other malignancies. The patient in this case had intractable hypoglycemia due to the recurrence of an enlarging GIST for which she was neither a surgical candidate nor responsive to available nonsurgical therapies. Her management was complicated by the presence of T1D, necessitating ongoing insulin therapy despite intermittent hypoglycemia. Although therapeutic trials of continuous glucagon infusion or administration of human growth hormone were not conducted in part because of the rapidity of her decline, these likely would not have been successful due to her compromised nutritional status and high glucose requirements. The continuous glucose infusions allowed her to have periods of uninterrupted sleep and activity, provided her with relief from the need for constant oral ingestion of caloric foods and liquids, and allowed her to have a more satisfactory quality of life during her remaining weeks of life.

Disclosure

The authors have no multiplicity of interest to disclose.

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