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Case Report

Tumor-Induced Hypoglycemia: An Unusual Case Report and Review of Literature

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ABSTRACT

Objective: To describe a rare case of pheochromocytoma presenting with hypoglycemia.
Methods: We describe a rare case of pheochromocytoma presenting with a hypoglycemic seizure. Our article includes our differentials, work up, and management.
Results: Our patient had non–islet-cell tumor hypoglycemia that was non-insulin mediated, as noted by low insulin levels. His hypoglycemia was likely multifactorial and mediated by different mechanisms. We describe the rare case and review the causes of tumor-induced hypoglycemia.
Conclusion: Pheochromocytomas can rarely present with hypoglycemia and are associated with a poor prognosis.

Introduction

Tumor-induced hypoglycemia (TIH) is a rare clinical entity that may occur in patients with different kinds of tumors and is mediated by different mechanisms. We report an unusual case of a malignant pheochromocytoma presenting with severe refractory hypoglycemia and discuss the different mechanisms that may explain this rare presentation.

Case Report

Presentation

A 33-year-old man with no known past medical history was brought to the emergency department after having a witnessed seizure. His family described a sudden onset of diaphoresis and tremulousness, followed by loss of consciousness and tonic-clonic seizures. He was found to have hypoglycemia with plasma glucose level <20 mg/dL on presentation and was treated with intravenous dextrose. The patient reported several episodes of diaphoresis and tremors over the past few months that were relieved by eating, an 18-kg unintentional weight loss, nausea, and increasing abdominal distention. He had no access to insulin or hypoglycemic agents. The family history was significant for hypertension and end-stage renal disease in his father but not for diabetes mellitus or cancer. The patient admitted occasional alcohol use but denied cigarette smoking or illicit drug use. On physical exam, he had visible cachexia. His blood pressure was 172/92 mm Hg, his heart rate was 114 beats/min, and his body mass index was 19.5 kg/m^2. His cardiac and respiratory exams were otherwise normal. An abdominal exam revealed epigastric tenderness with a palpable mass in the left upper quadrant and hepatomegaly. There was no skin hyperpigmentation or focal neurologic deficits.

Investigation

The patient had persistent symptomatic hypoglycemia requiring multiple 50% dextrose infusions. He was admitted for intractable hypoglycemia. Laboratory examination revealed normal kidney function, elevated alkaline phosphatase, and mild transaminitis (Table 1). Abdominal computed tomography revealed a 12.6 × 12.1 × 13.2-cm centrally necrotic mass (Fig. 1) in close apposition to the stomach, with innumerable liver metastases and retroperitoneal lymphadenopathy (Fig. 2). The primary diagnosis was TIH. Bloodwork was obtained when the plasma glucose level was 31 mg/dL and revealed insulin level of <0.3 μIU/mL, C-peptide level of 1 ng/dL (normal, 0.8-3.1 ng/dL), insulin-like growth factor 1 level of

Abbreviations: IGF-2, insulin-like growth factor 2; TIH, tumor-induced hypoglycemia.

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Table 1
General Laboratory Examination

Test	Value	Normal Range
Creatinine	0.3	approximately 0.7-1.3 mg/dL
Glomerular filtration rate	>60	100-130 mL/min/1.73 m^2
Alkaline phosphatase	375	40-120 U/L
Alanine transaminase	108	7-55 U/L
Aspartate transaminase	185	8-48 U/L
Albumin	3.3	3.5-5 g/dL
Hemoglobin	13.4	13.5-17.5 g/dL

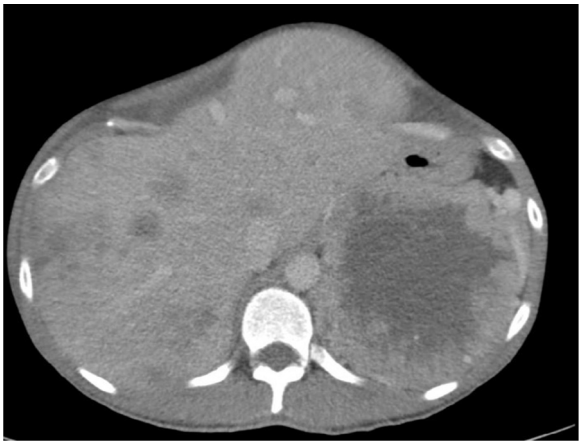

Fig. 1. Large necrotic mass measuring 12.6 × 12.1 × 13.2 cm.

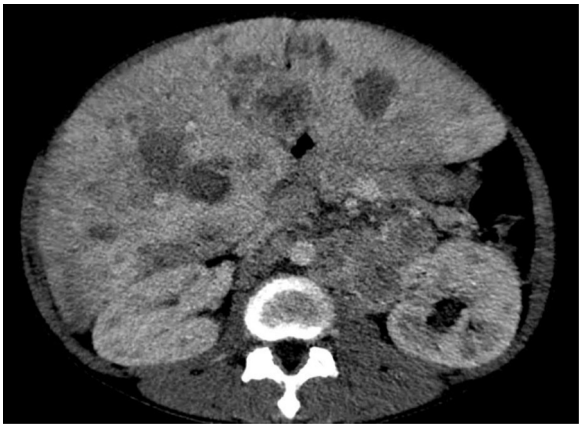

Fig. 2. Enlarged liver with multiple metastatic masses.

38 ng/dL (normal, 88-246 ng/dL), insulin-like growth factor 2 (IGF-2) level of 461 ng/dL (normal, 333-967 ng/dL) with an IGF-2: insulin-like growth factor 1 ratio of 12:1 (normal, <13:1), β-hydroxy butyrate level of 0.8 mg/dL (normal, 0.3-2.81 mg/dL), cortisol level of 21 μg/dL, and negative sulfonylurea (Table 2). The results were suggestive of non–insulin-mediated hypoglycemia, excluding the possibility of malignant insulinoma or ectopic insulin-producing tumor. He did not have adrenal insufficiency as the cortisol level was appropriately elevated in response to hypoglycemia. As there was a concern that this may be secondary to a malignancy arising from the gastrointestinal tract, namely a gastrointestinal stromal tumor or other neuroendocrine tumor, an upper endoscopy was done for further evaluation. The endoscopy showed normal upper gastrointestinal mucosa but with an evidence of external compression of both the stomach and duodenum.

Table 2
Hypoglycemia Laboratory Examination

Test	Value	Normal Range
Serum glucose	31	70-140 mg/dL
Insulin level	<0.3	2.6-24.9 μIU/mL
C-peptide	<0.1	0.8-3.1 ng/dL
Insulin-like growth factor 1	38	88-246 ng/dL
Insulin-like growth factor 2	461	333-967 ng/dL
β-hydroxybutyrate	0.8	0.3-2.81 mg/dL
Random cortisol	21	5-25 μg/dL
Sulfonylurea screen	Negative	Negative

Ultrasound-guided biopsy of the liver metastasis was performed and was consistent with malignant paraganglioma or extra-adrenal pheochromocytoma. These findings were surprising as the patient presented with hypoglycemia. Subsequent biochemical testing revealed elevated plasma metanephrine of 81 pg/mL (normal, 0-62 pg/mL), plasma normetanephrine of 7660 pg/mL (normal, 0-145 pg/mL), and 24-hour urine normetanephrine of 92 346 μg (normal, 82-500 μg), all consistent with the pathologic diagnosis.

Treatment, Outcome, and Follow-up

The patient continued to have persistent hypoglycemia. He required treatment with ten percent dextrose infusions, frequent meals, and periodic glucocorticoids. For his functioning paraganglioma, he was initially treated with prazosin. Propranolol was subsequently added to control tachycardia. He was also started on chemotherapy but was then lost to follow-up.

Discussion

Glucose is an obligate fuel for the brain under physiologic conditions. Plasma glucose levels are kept within a relatively narrow range by a complex system of neural, hormonal, and cellular controls. Hypoglycemia in nondiabetic patients is rare. Clinical hypoglycemia is a plasma glucose concentration low enough to cause neuroglycopenic and/or autonomic signs and symptoms and it is usually <55 mg/dL. It should be confirmed by the documentation of Whipple's triad, which consists of hypoglycemic signs and symptoms, a low plasma glucose concentration, and the resolution of those symptoms or signs after raising the glucose level.

The initial evaluation of hypoglycemia should include a detailed history to determine the nature and timing of symptoms if it is fasting or postprandial or both. Further information should include underlying illness, social history, and medications used by the patient or other family members. The biochemical workup must be obtained at the time of hypoglycemia before treatment. It should include plasma glucose, insulin, C-peptide, β-hydroxybutyrate, cortisol, sulfonylurea, and meglitinide levels to determine the cause of hypoglycemia. Suppressed β-hydroxybutyrate suggests hypoglycemia that is mediated by insulin or insulin action. TIH is a rare clinical entity that commonly occurs as a result of endogenous insulin hypersecretion (eutopic insulin production). It is usually associated with the rare pancreatic islet β-cell tumor or insulinoma. However, TIH can also occur in various kinds of tumors as non–islet-cell tumor hypoglycemia through insulin and non–insulin-dependent mechanisms (Table 3).[1]

Insulin-secreting tumors are generally rare. The reported incidence of insulinoma is 0.4/100 000 person-years.[2] The hypoglycemia is secondary to the uncontrolled secretion of insulin by the tumor. The diagnosis of insulin-mediated hypoglycemia from insulinoma requires documented hypoglycemia along with the evidence of endogenous insulin production, which includes

Table 3
Mechanisms for Tumor-Induced Hypoglycemia

Insulin-dependent mechanisms, insulin-secreting tumors:
• Islet cell tumors (eg, insulinomas)
• Non-islet cell tumors/ectopic insulin production (eg, bronchial carcinoids, gastrointestinal stromal tumor)
Non–insulin-dependent mechanisms:
• Tumors that secrete insulin-like growth factor 2 "IGF-omas" (eg, leiomyosarcomas, fibrosarcomas, adrenal carcinomas)
• Tumors that can produce antibodies to insulin or insulin receptors (tumor autoimmune hypoglycemia) (eg, multiple myeloma, chronic myelogenous leukemia, Hodgkin's disease)
• Massive tumor burden
• Tumor infiltration of the liver
• Adrenal gland tumor destruction
• Pituitary gland tumor destruction

elevated plasma insulin, proinsulin, and C-peptide levels at the time of hypoglycemia. The β-hydroxybutyrate level is typically low and insulin antibody is absent. Ectopic production of insulin from non–islet-cell tumors has also been reported.[1,3,4] These include bronchial carcinoid tumors, cervical carcinomas, as well as gastrointestinal stromal tumor. Our patient's blood work at the time of hypoglycemia pointed toward a non–insulin-dependent mechanism.

On the other hand, in cases where there is no excessive insulin secretion, tumors can release chemicals that promote hypoglycemia. The production of IGF-2 or its precursor, insulin-like growth factor 1, glucagon-like peptide 1, and somatostatin have been implicated in causing TIH.[5-7] IGF-2 producing tumors have been termed "IGF-2-omas"[8] and usually are large mesenchymal tumors. Retroperitoneal fibrosarcoma is the classic prototype. The main mechanism is the overexpression of the *IGF-2* gene. However, in patients with non–islet-cell tumor hypoglycemia due to IGF-2, incompletely processed nonglycosylated precursors of IGF-2 are released. These molecules are heterogeneous in size and are referred as big IGF-2. Big IGF-2 have a reduced affinity from forming a tertiary complex with an acid-labile subunit; hence, more pro-IGF-2 is available for binding to insulin receptors, promoting fasting hypoglycemia from an insulin-like activity.[1] In a retrospective study of 78 patients with IGF-2 non–islet-cell tumor hypoglycemia, the most commonly recognized tumors were hepatocellular and gastric carcinomas.[9] Interestingly, most of those tumors were >10 cm and treatment aimed to relieve the hypoglycemia and underlying tumor. Glucocorticoid therapy was shown to improve hypoglycemia in those patients.[9] Another pathogenic entity that can cause TIH is tumor autoimmune hypoglycemia, which is characterized by the presence of elevated insulin levels and anti-insulin antibodies or anti–insulin receptor antibodies.[10,11] Several tumors have been associated with this entity including multiple myeloma, chronic myelomonocytic leukemia, and Hodgkin's disease.[10,11]

The presence of a massive tumor burden causing rapid consumption of glucose can also be a cause of hypoglycemia in some cases.[12,13] The infiltration and replacement of liver parenchyma with tumor masses or metastases can cause hypoglycemia by interfering with gluconeogenesis and ketogenesis.[12-14] It can also result in the failure of compensatory glycogenolysis, especially in the setting of a poorly nourished patient with depleted glycogen stores.[12-14] The treatment is usually aimed at the underlying malignancy, which is often difficult, given the extent of disease. Lastly, tumor infiltration and the destruction of the pituitary or adrenals can result in hypoglycemia through hypopituitarism and adrenal insufficiency.[15]

Pheochromocytomas or functioning paragangliomas are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and sympathetic ganglia. They are rare tumors with an estimated incidence of 0.8/100 000 person-years.[16] Most are sporadic; however, some occur as a part of familial syndromes. The classic triad of symptoms in those patients includes episodic headaches, diaphoresis, and tachycardia.[17] The catecholamine excess causes insulin resistance, impaired fasting glucose levels, and diabetes.[18,19] Glucose metabolism abnormalities usually resolve after surgical removal of those tumors. Acute, transient hypoglycemia is sometimes reported after tumor resection.[18,19]

It is extremely unusual for patients with pheochromocytoma or paraganglioma to present with hypoglycemia, making cases like ours very rare. A workup revealed non–insulin-mediated hypoglycemia, as evidenced by the low insulin and C-peptide levels. Our patient's hypoglycemia was likely multifactorial. The presence of a massive tumor burden caused rapid consumption of glucose. The extensive metastatic liver disease and virtual replacement of the liver parenchyma with metastases interfered with both gluconeogenesis and ketogenesis that further contributed to his hypoglycemia. The lower than expected β-hydroxybutyrate level might have indicated substrate deficiency, as he had severe cachexia, and that probably contributed to the hypoglycemia as well. Lastly, although the IGF-2 level was normal, the possibility of IGF-2-mediated hypoglycemia could not be excluded as it is mainly secreted as a prohormone that is not detectable with the currently available assays.

Given that hypoglycemia in patients with pheochromocytoma is a rare entity, there are only 3 case reports in the literature. The authors of first report described a fatal case of pheochromocytoma that presented with intractable hypoglycemia with elevated levels of IGF-2 as the most likely cause of hypoglycemia.[20] In the second report, the authors proposed that direct tumor consumption was the cause of hypoglycemia based on F-2-fluorodeoxy-D- glucose positron emission tomography imaging of the tumor.[18] The authors of the third report suggested that direct eutopic islet cell response to the pheochromocytoma with high and inappropriate levels of insulin was the underlying cause of the hypoglycemia.[19]

Conclusion

Pheochromocytoma presenting with hypoglycemia is a very rare occurrence and in this case reflected an extremely malignant tumor with dismal prognosis. This case demonstrates the importance of recognizing that pheochromocytomas can be associated with hypoglycemia and understanding the different mechanisms that can account for this phenomenon.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. de Groot JW, Rikhof B, van Doorn J, et al. Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. *Endocr Relat Cancer*. 2007;14(4):979–993.
2. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma–incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clinic Proc*. 1991;66:711–719.
3. Kiang DT, Bauer GE, Kennedy BJ. Immunoassayable insulin in carcinoma of the cervix associated with hypoglycemia. *Cancer*. 1973;31:801–805.
4. Ishikura K, Takamura T, Takeshita Y, et al. Cushing's syndrome and big IGF-II associated hypoglycaemia in a patient with adrenocortical carcinoma. *BMJ Case Rep*. 2010;2010. https://doi.org/10.1136/bcr.07.2009.2100.
5. Dynkevich Y, Rother KI, Whitford I, et al. Tumors, IGF-2, and hypoglycemia: insights from the clinic, the laboratory and the historical archive. *Endocr Rev*. 2013;34(6):798–826.

6. Fukuda I, Hizuka N, Ishikawa Y, et al. Clinical features of insulin-like growth factor-II producing non-islet-cell tumor hypo- glycemia. *Growth Horm IGF Res*. 2006;16(4):211–216.
7. Basu A, Service FJ, Yu L, Heser D, Ferries LM, Eisenbarth G. Insulin autoimmunity and hypoglycemia in seven white patients. *Endocr Pract*. 2005;11(2):97–103.
8. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. *Medicine*. 2009;88(3):141–153.
9. Phuphanich S, Jacobs L, Poulos JE, Vesely DL. Case report: hypoglycemia secondary to a meningioma. *Am J Med Sci*. 1995;309(6):317–321.
10. Sorlini M, Benini F, Cravarezza P, Romanelli G. Hypoglycemia, an atypical early sign of hepatocellular carcinoma. *J Gastrointest Cancer*. 2010;41(3):209–211.
11. Lau CI, Wang HC, Hsu WC. Hypoglycemic encephalopathy as the initial presentation of hepatic tumor: a case report. *Neurologist*. 2010;16(3):206–207.
12. Vieweg WV, Reitz RE, Weinstein RL. Addison's disease secondary to metastatic carcinoma: an example of adrenocortical and adrenomedullary insufficiency. *Cancer*. 1973;31(5):1240–1243.
13. Beard CM, Sheps SG, Kurland LT, et al. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc*. 1983;58(12):802–804.
14. Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. *Medicine*. 1991;70(1):46–66.
15. La Batide-Alanore A, Chatellier G, Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensive patients. *J Hypertens*. 2003;21(9):1703–1707.
16. Wiesner TD, Blüher M, Windgassen M, Paschke R. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. *J Clin Endocrinol Metab*. 2003;88(8):3632–3636.
17. Macfarlase D, Leese G. Hypoglycaemia, pheochromocytoma and features of acromegaly: a unifying diagnosis? *QJM*. 2011;104(11):983–986.
18. Amir Habra M, Núñez R, Chuang H, et al. Fatal hypoglycemia in malignant pheochromocytoma: direct glucose consumption as suggested by 18F-2-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography imaging. *Endocrine*. 2010;37:209–212.
19. Frankton S, Baithun S, Husain E, Davis K, Grossman AB. Pheochromocytoma crisis presenting with profound hypoglycemia and subsequent hypertension. *Hormones*. 2009;8(1):65–70.
20. Martínez Garcia M, Trincado Aznar P, Lopez Alaminos ME, et al. Persistent hypoglycemia due to an IGF-II-secreting malignant pheochromocytoma: a case report and literature review. *Clin Case Rep*. 2020;8(12):2433–2435.