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Case Report

Metastatic Insulinoma Managed With Continuous Glucose Monitoring in a Young Female Patient

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Abstract

Insulinomas are rare neuroendocrine neoplasms and causes of hypoglycemia. They present with neuroglycopenic symptoms, including confusion and seizures. Suspected diagnosis must be confirmed through bloodwork and imaging. The majority of insulinomas are benign and cured surgically; less than 10% of insulinomas are malignant. Malignant insulinomas present a unique and rare challenge in managing persistent hypoglycemia and tumor burden. We present a case of a young woman who presented with Whipple triad and high-grade masses in her pancreas, liver, and distant lymph node metastases on imaging. Insulinoma was diagnosed. Hypoglycemia was managed with continuous dextrose infusion, diazoxide, and lanreotide. She was discharged on medical management and a continuous glucose monitor. Her metastatic disease is being treated with a capecitabine and temozolomide (CAPTEM) regimen showing 30% reduction in tumor burden. In conjunction with the National Institutes of Health, she is undergoing evaluation with numerous neuroendocrine tumor surgeons for cytoreductive surgery.

Key Words: insulinoma, hypoglycemia, CGM, CAPTEM, neuroendocrine tumor

Introduction

Insulinomas, which are rare neuroendocrine neoplasms, secrete excess insulin and are usually diagnosed in the fifth decade of life. They are a rare cause of hypoglycemia occurring in 1 to 4 people per million per year, with 99% originating in the pancreas. Over 90% of insulinomas are localized to the pancreas and are benign. Less frequently they may be metastatic, defining these tumors as malignant. Benign or indolent insulinomas can have a 94.5% to 100% 5-year survival rate; metastatic disease has 24% to 66.8% 5-year survival rate. Insulinomas are diagnosed by a 72-hour or shorter fast, with evidence of inappropriate insulin secretion in the setting of hypoglycemia. The tumors are localized and characterized by imaging and biopsy. Management includes treatment of refractory hypoglycemia along with tumor resection. Additional therapies may include hormonal treatment, chemotherapy, and radiation [1, 2].

Case Presentation

A 28-year-old woman with history of migraines and exercise-induced asthma reported symptoms of increased hunger, diaphoresis, and morning "shakes" for 6 weeks prior to presenting to an outside institution for altered behavior. Her family noted her nonsensical speech and inappropriate behavior in public for several weeks prior to admission. On admission, she was found to have a point-of-care glucose level of 41 mg/dL (2.28 mmol/L) (normal reference range, 60-100 mg/dL; 3.33-5.55 mmol/L). There was no history of diabetes, or use of glucose lowering agents. She responded to 50% dextrose, with mental status improvement, but then developed refractory hypoglycemia. Brain imaging (including computed tomography [CT] head without contrast, CT angiography of the head and neck, and CT brain perfusion) did not reveal any abnormalities. Blood work told a different story (Table 1).

Diagnostic Assessment

A 72-hour fast was initiated. Nine hours into the fast, with a point-of-care blood glucose of 55 mg/dL (3.05 mmol/L), she developed hypoglycemic symptoms. Blood work drawn at this time was consistent with inappropriately excessive insulin release (Table 2).

The 9-hour fast, along with Whipple triad, led to a strong suspicion for an insulinoma. A CT with and without contrast of her abdomen and pelvis showed a hypo-enhancing mass within the pancreatic neck, and pancreatic tail mass. The mass was encasing and narrowing the splenic artery and occluding the splenic vein. Numerous hypo-enhancing lesions within the liver were noted, along with abdominal and mediastinal lymphadenopathy.

She was transferred to our institution for further evaluation and treatment of presumed metastatic insulinoma. Endoscopic ultrasound with biopsy of the pancreatic mass confirmed a high-grade pancreatic neuroendocrine tumor. Ultrasound-guided biopsy of the liver masses revealed well-differentiated neuroendocrine tumors consistent with metastases from pancreatic primary. The tissue stained negative for CK 7, MUC 1, and CK 20 and positive for CK19, CD56, synaptophysin, chromogranin,

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Table 1. Initial blood work on presentation to the emergency room of an outside institution

Lab	Patient value	Reference range
Thyroid stimulating hormone	0.58 μU/mL (0.58 mU/L)	0.35-4.94 μU/mL (0.35-4.94 mU/L)
Free T4	1.0 ng/dL (12.9 pmol/L)	0.7-1.5 ng/dL (9.03-19.35 pmol/L)
Cortisol	28 μg/dL (772.8 nmol/L)	3.7-19.4 μg/dL (102.12-535.44 nmol/L)
Glucose (serum)	38 mg/dL (2.11 mmol/L)	65-100 mg/dL (3.61-5.55 mmol/L)
BUN	6 mg/dL (2.142 mmol/L)	8-23 mg/dL (2.856-8.211 mmol/L)
Creatinine	0.82 mg/dL (72.488 μmol/L)	0.5-1.00 mg/dL (44.2-88.4 μmol/L)
AST	45 U/L	0-50 U/L
ALT	59 U/L	0-50 U/L
Alkaline phosphatase	209 U/L	0-120 U/L
Ammonia	40.56 μg/dL (24 μmol/L)	0-59.15 μg/dL (0-35 μmol/L)
C-peptide	3.7 ng/mL (1.221 nmol/L)	1.1-4.4 ng/mL (0.363-1.452 nmol/L)
Total insulin	15 μU/mL (15 mU/L)	0-17 μU/mL (0-17 mU/L)
Free insulin	12 μU/mL (12 mU/L)	0-17 μU/mL (0-17 mU/L)
Serum sulfonylurea analysis	Negative	N/A

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; T4, thyroxine.

Table 2. Results 9 hours after initiation of the fast

Lab	Patient value	Reference range
Glucose (serum)	56 mg/dL (3.108 mmol/L)	65-100 mg/dL (3.61-5.55 mmol/L)
C-peptide	3.4 ng/mL (1.122 nmol/L)	1.1-4.4 ng/mL (0.363-1.452 nmol/L)
Pro-insulin	24 μU/mL (143.8 pmol/L)	0-1.67 μU/mL (0-10 pmol/L)
Total insulin	28 μU/mL (28 mU/L)	0-17 μU/mL (0-17 mU/L)
Free insulin	26 μU/mL (26 mU/L)	0-17 μU/mL (0-17 mU/L)
Beta-hydroxybutyrate	4.2 mg/dL (0.403 mmol/L)	0.2-2.8 mg/dL (0.019-0.269 mmol/L)

and CDX2. Additionally, 10% to 15% of tumor cells were Ki-67 positive.

A follow-up 68-Ga-tetraazacyclododecane-tetraacetic acid Tyr3-octreotate (DOTATATE) scan (Fig. 1) revealed tracer activity in the pancreatic neck and tail, innumerable liver metastases, and lymph nodes in the chest and abdomen confirming the diagnosis of metastatic insulinoma.

She was discharged with continuous glucose monitor (CGM), oncology referral, and on 10% dextrose (D10). As an outpatient, she initiated diazoxide at 3.5 mg/kg/dose every 8 hours for persistent symptomatic hypoglycemia. Days after diazoxide initiation, hypoglycemia stabilized, and D10 was discontinued.

Oncology work-up included comprehensive genetic testing, which did not reveal any specific mutations in *BRCA1*, *BRCA2*, *MEN1*, *RET*, *SDH* family, or *VHL* among others.

She underwent a fluorodeoxyglucose positron emission tomography evaluation for a possible trial treatment with peptide receptor radionuclide therapy (PRRT). Imaging confirmed a significant tumor proportion to be fluorodeoxyglucose-avid. However, she opted for chemotherapy treatment with capecitabine 1500 mg twice daily days 1 to 14 and temozolomide 400 mg daily days 10 to 14 with 2 weeks off (CAPTEM regimen).

Treatment

Ten weeks after presentation, she initiated simultaneous monthly lanreotide 120 mg, and CAPTEM.

Two weeks after initiating lanreotide and CAPTEM, she discontinued diazoxide and has had no further hypoglycemia.

Capecitabine and temozolomide doses were reduced to 1000 mg twice daily and 300 mg daily respectively due to treatment induced diarrhea.

After the third cycle, surveillance CT (Fig. 2) showed interval improvement of metastases in the liver and lymph nodes.

After the sixth cycle, surveillance magnetic resonance imaging showed unchanged extent of disease from prior CT.

Outcome and Follow-Up

In conjunction with the National Institutes of Health, she has been referred to surgery for possible debulking in the setting of her response to CAPTEM. Her surgical consults to date note risk outweighs benefit of surgery, and no plans for surgical intervention are made at this time.

Discussion

Malignant insulinomas present 2 major obstacles: refractory hypoglycemia and metastatic disease limiting the curative role of surgery.

We present a rare case of a malignant insulinoma with unique management including chemotherapy, 2-month course of diazoxide, lanreotide, and CGM.

The gold standard for diagnosing insulinomas is a 72-hour fast with sensitivity of 99%. Diagnostic criteria for an

insulinoma during a 72-hour fast includes blood glucose level less than 55 mg/dL with simultaneous insulin level 3 μU/mL (3 mU/L) (normal reference range, 0-17 μU/mL; 0-17 mU/L) or greater. Alternatively, C-peptide level 0.606 ng/mL (0.2 nmol/L) (normal reference range, 1.1-4.4 ng/mL; 0.363-1.452 nmol/L) or greater and pro-insulin level 0.83 μU/mL (5 pmol/L) (normal reference range, 0-1.67 μU/mL; 0-10 pmol/L) or greater during an episode of hypoglycemia may be alternate indicators of an insulinoma [1].

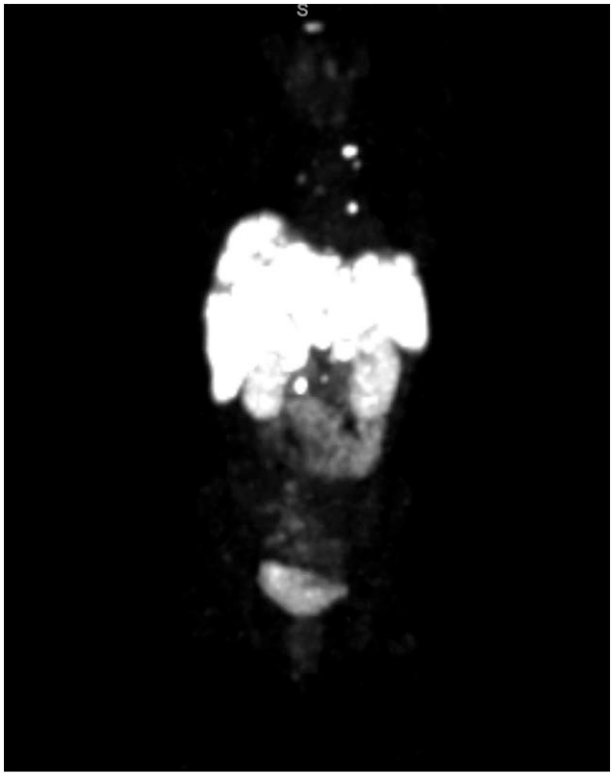

Figure 1. DOTATATE scan with innumerable enhancements in the liver; illuminated mediastinal and intra-abdominal lymph nodes.

Hypoglycemia poses danger for all insulinomas; however, availability of CGMs in the outpatient setting allows for close monitoring and medication titration for hypoglycemia treatment. In fact, a prospective and case-control study argues for use of CGM as a diagnostic tool in outpatient insulinoma screening to help cut costs of the inpatient 72-hour fast [3]. Yuan et al used CGM for several days before and after treatment of pancreatic insulinoma with endoscopic ultrasound-guided ethanol injection [4]. Nakajima et al also noted use of a CGM in a patient with postprandial hypoglycemia and monitoring blood glucose before and after insulinoma treatment [5]. Other case studies describe timely treatment of asymptomatic hypoglycemia or prevention of hypoglycemic episodes with use of CGM [6, 7]. However, most published cases are limited to several weeks of CGM use until definitive treatment was provided. A case of a 70-year-old individual with an unresectable insulinoma highlights similar benefits of a CGM as found in our patient, but given the difference in age and activity level, CGM in our patient has opened further benefits of live monitoring of glucose levels [8]. Our patient was dependent on the CGM for months to self-titrate D10 and diazoxide dosing, until the stabilizing effect of somatostatin and chemotherapy agents took place. This allowed her to minimize the side effects of diazoxide while effectively mitigating hypoglycemia episodes prior to their occurrence, thus avoiding recurrent emergency department visits. The CGM also now allows her to pursue a physically taxing job

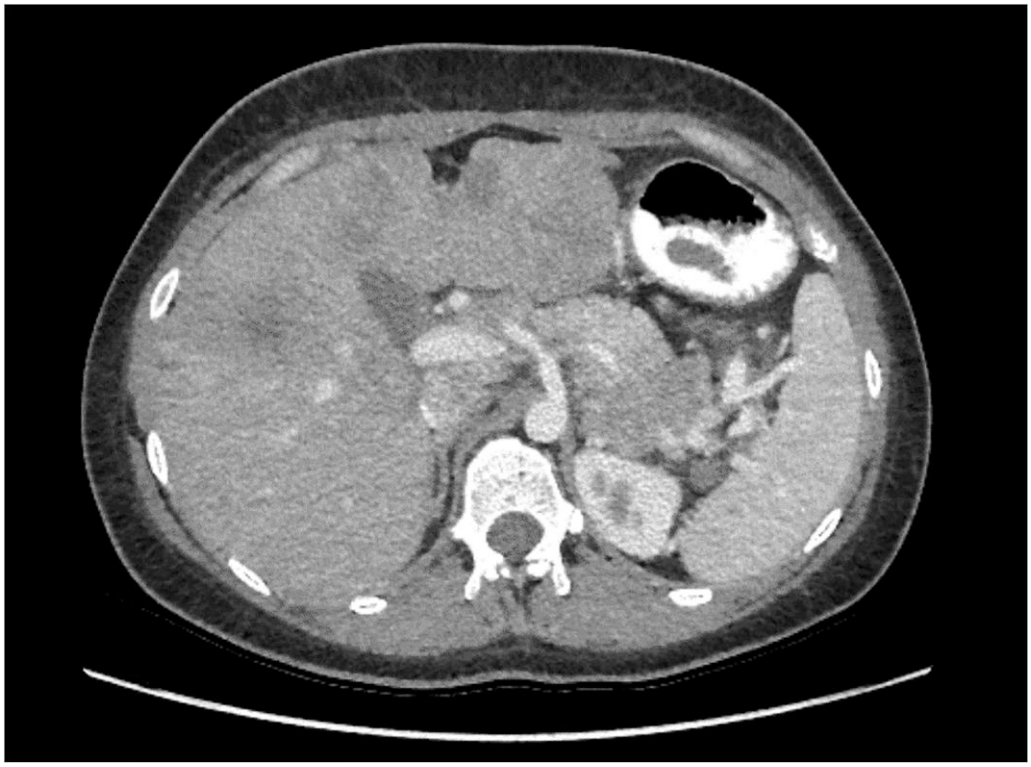

Figure 2. CT abdomen and pelvis with contrast with reported size reduction in liver metastases (a few are highlighted by white arrows) with evidence of tumor necrosis after the third CAPTEM cycle.

as an emergency department nurse without compromising her or her patient's safety. Finally, while her malignant insulinoma remains unresectable and her treatment continues to evolve, long-term use of the CGM allows her to monitor her response to treatment and monitor signs of progression more effectively than serial imaging. This highlights a potential role for long-term use of CGM in diagnosis and monitoring of hypoglycemia in young patients with nonresectable insulinomas without compromising their personal and work lives. Alternative hypoglycemia treatments may include intravenous and enteral nutrition to maintain euglycemia. Medical treatment with diazoxide, everolimus, somatostatin analogs, verapamil, and prednisone may also be used.

Diazoxide, a nondiuretic benzothiadiazine derivative, blocks the sulfonylurea receptor-1 subunit of the potassium-ATP channel on pancreatic beta cell. Increase in potassium permeability and hyperpolarization of beta cells inhibits insulin release [1, 9-11].

Somatostatin analogues relieve hypoglycemia by inhibiting insulin release from the pancreas and reduce blood glucose by inhibiting counter-regulatory glucagon response to hypoglycemia [1, 2, 10]. They may also reduce the tumor size of an insulinomas [2].

Everolimus, mTOR pathway inhibitor, controls symptomatic hypoglycemia by inhibiting insulin release and increasing insulin resistance [1, 12].

Calcium channel blockers, like verapamil, have shown efficacy in controlling hypoglycemia in nonoperative insulinomas. Calcium channel blockers are believed to prevent insulin release from B-cells by acting on the cell membrane electrical activity [13]. Interestingly, verapamil was also found to have some beta-islet cell protective properties and reducing B-cell apoptosis in type 1 diabetes mellitus resulting in better glucose control [14].

Additionally, there are published case reports using prednisone for management of unresectable insulinomas. In one case, a patient with insulinoma that was not identified on imaging or laparotomy tried verapamil monotherapy, verapamil and diazoxide combination therapy, along with a somatostatin analogue. Symptoms were not relieved until she initiated low-dose prednisone (5 mg daily eventually reduced to 2.5 mg daily). She continues this regimen 7 years later without any visible insulinoma lesions. Glucocorticoids relieve hypoglycemia by increasing insulin resistance and gluconeogenesis [15].

Malignant insulinoma is defined by the presence of metastases. Malignant insulinomas most commonly metastasize to the liver and lymph nodes. Malignant/metastatic disease is treated with chemotherapy and partial resection or other destruction of metastatic lesions. Prior studies found that partial resection reducing tumor burden of malignant insulinomas increased life expectancy from 26 months to 72 months [1, 2, 16].

Chemotherapy, particularly CAPTEM (capecitabine and temozolomide protocol) has been used in the treatment of neuroendocrine neoplasms, including metastatic insulinomas. Temozolomide is a second-generation alkylating agent that methylates DNA and induces cell apoptosis. Temozolomide reportedly has synergistic action with capecitabine which depletes one of the DNA repair enzymes. Data comparing CAPTEM to other regimens including temozolomide or other chemotherapy protocols altogether is limited. Side effects include gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal pain, leukopenia, and thrombocytopenia. There are no clear guidelines for duration of treatment [16-18]. Chatzellis et al reported 27 patients who were maintained on CAPTEM for over 12 months and 19 out of 27 had favorable responses without significant toxicities [19].

PRRT has shown efficacy in the realm of neuroendocrine tumor treatment. Lutetium 177-[177Lu]-oxodotreotide (Lutathera®) is one such treatment. The peptide component (in this case a somatostatin analog) allows for targeted cytotoxic radionuclide delivery to somatostatin-expressing cells. It has shown improvement of progression-free survival, overall survival, and quality of life in patients with well-differentiated neuroendocrine tumors [20, 21]. In the future, this may prove to be a reliable treatment for insulinomas.

This case showcases obstacles associated with presentation of metastatic insulinoma. There is a lack of consensus and guidelines in the treatment of malignant insulinomas from managing persistent hypoglycemia to tumor burden. This case explores the use of numerous modalities, including CGM, somatostatin analogues, CAPTEM, PRRT in malignant insulinoma treatment in a young patient with metastatic insulinoma.

Learning Points

- Continuous glucose monitors allow us to not only monitor and manage hyperglycemia in diabetes mellitus, but also to diagnose and monitor hypoglycemia episodes in insulinomas.
- Unresectable insulinomas require multimodal management to help manage symptoms of hypoglycemia and tumor burden.
- Surgical debulking in unresectable insulinomas may further prove to help with symptom control and management of hypoglycemia.

Contributors

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. de Herder WW, Hofland J. Insulinoma. In: Feingold KR, Anawalt B, Blackman MR, eds. *Endotext* [Internet]. MDText.com, Inc.; 2023 [updated 2023 Apr 4].
2. Okabayashi T, Shima Y, Sumiyoshi T, *et al*. Diagnosis and management of insulinoma. *World J Gastroenterol*. 2013;19(6):829-837.
3. Ma J, Huang X, Zhao J, *et al*. CGM for insulinoma screening: a prospective and observational case-control study. *Endocr Relat Cancer*. 2021;28(5):291-300.
4. Yuan T, Liu S, Zhu C, *et al*. Continuous glucose monitoring in patients with insulinoma treated by endoscopic ultrasound-guided ethanol injection. *Pancreas*. 2021;50(2):183-188.
5. Nakajima R, Idesawa H, Sato D, *et al*. Continuous glucose monitoring in a patient with insulinoma presenting with unawareness of postprandial hypoglycemia. *Endocrinol Diabetes Metab Case Rep*. 2023;2023(3): 23-0056.
6. Lyerla RC, Bajaj A, Shrestha RT. Use of a continuous glucose monitor for preoperative monitoring and treatment of hypoglycemia in a case of pancreatic neuroendocrine tumor. *AACE Clin Case Rep*. 2019;5(4):e255-e258.
7. Koceva A, Krajnc M. Insulinoma unmasked: a continuous glucose monitoring-fueled journey. *Curr Oncol*. 2024;31(9):5452-5461.
8. Sawyer AM, Schade DS. Use of a continuous glucose monitor in the management of inoperable metastatic insulinoma: a case report. *Endocr Pract*. 2008;14(7):880-883.
9. Warren AM, Topliss DJ, Hamblin PS. Successful medical management of insulinoma with diazoxide for 27 years. *Endocrinol Diabetes Metab Case Rep*. 2020;2020:20-0132.
10. Chen X, Feng L, Yao H, Yang L, Qin Y. Efficacy and safety of diazoxide for treating hyperinsulinemic hypoglycemia: a systematic review and meta-analysis. *PLoS One*. 2021;16(2):e0246463.
11. Newman-Lindsay S, Lakshminrusimha S, Sankaran D. Diazoxide for neonatal hyperinsulinemic hypoglycemia and pulmonary hypertension. *Children (Basel)*. 2023;10(1):5
12. Alexandraki KI, Kaltsas GA, Grozinsky-Glasberg S. Emerging therapies for advanced insulinomas and glucagonomas. *Endocr Relat Cancer*. 2023;30(9):e230020.
13. Ulbrecht JS, Schmeltz R, Aarons JH, Greene DA. Insulinoma in a 94-year-old woman: long-term therapy with verapamil. *Diabetes Care*. 1986;9(2):186-188.
14. Arefanian H, Koti L, Sindhu S, Ahmad R, Al Madhoun A, Al-Mulla F. Verapamil chronicles: advances from cardiovascular to pancreatic β-cell protection. *Front Pharmacol*. 2023;14:1322148.
15. Spiro AJ, Shakir MKM, Hoang TD. Successful long-term medical management of unresectable insulinomas. *Case Rep Oncol*. 2020;13(2):948-954.
16. Veltroni A, Cosaro E, Spada F, *et al*. Clinico-pathological features, treatments and survival of malignant insulinomas: a multicenter study. *Eur J Endocrinol*. 2020;182(4):439-446.
17. Chauhan A, Farooqui Z, Murray LA, *et al*. Capecitabine and temozolomide in neuroendocrine tumor of unknown primary. *J Oncol*. 2018;2018:3519247.
18. Fine RL, Gulati AP, Tsushima D, *et al*. Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors. *J Clin Oncol*. 2014;32(3):179. doi:10.1200/jco.2014.32.3_suppl.179
19. Chatzellis E, Angelousi A, Daskalakis K, *et al*. Activity and safety of standard and prolonged capecitabine/temozolomide administration in patients with advanced neuroendocrine neoplasms. *Neuroendocrinology*. 2019;109(4):333-345.
20. Deshayes E, Assenat E, Meignant L, Bardiès M, Santoro L, Gourgou S. A prospective, randomized, phase II study to assess the schemas of retreatment with Lutathera® in patients with new progression of an intestinal, well-differentiated neuroendocrine tumor (ReLUTH). *BMC Cancer*. 2022;22(1): 1346.
21. Hennrich U, Kopka K. Lutathera®: the first FDA- and EMA-approved radiopharmaceutical for peptide receptor radionuclide therapy. *Pharmaceuticals (Basel)*. 2019;12(3):114.