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Case report

Non-islet cell tumor hypoglycemia in a patient with uterine carcinosarcoma

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1. Introduction

Non-islet cell tumor hypoglycemia (NICTH) is a rare phenomenon in which profound hypoglycemia is mediated by excess tumor production of insulin-like growth factor-2 (IGF-2) (Dynkevich et al., 2013). This paraneoplastic syndrome has classically been observed in patients with either mesenchymal or epithelial tumors (Dynkevich et al., 2013; Bodnar et al., 2014). Complete surgical resection is often curative; however, depending on the extent of disease, complete resection may not be possible. In these cases, partial resection of the tumor versus medical management can be offered (Dynkevich et al., 2013; Bodnar et al., 2014; Garla et al., 2019).

Uterine carcinosarcoma is an aggressive tumor that is both epithelial and mesenchymal in origin (Gorai et al., 1997; Cantrell et al., 2015). To our knowledge there have been only three published case reports detailing the diagnosis and management of NICTH in patients with carcinosarcoma of the uterus and ovary, respectively (Honma et al., 2015; Martínez-Montoro et al., 2021; Kojima et al., 2013). In these cases, the patients received primarily medical management for their hypoglycemia. In this report, we describe the case of a patient who was found to have NICTH in the setting of recurrent uterine cancer who failed multiple forms of medical management and ultimately underwent surgical debulking with partial resection of her tumor with resolution of her hypoglycemia.

2. Case

The patient is a 69-year-old woman who initially presented for evaluation of postmenopausal bleeding with subsequent endometrial biopsy showing FIGO grade 2 endometrial cancer. She was then referred to our tertiary care center for further management. In August 2019, she underwent robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node mapping with right pelvic sentinel lymph node biopsy and left pelvic complete lymphadenectomy. Final surgical pathology revealed stage 1A, grade 2 endometroid adenocarcinoma of the endometrium without myometrial invasion or lymphovascular space invasion. All lymph nodes were negative. Tumor testing revealed a microsatellite stable phenotype with intact mismatch repair proteins. The patient was dispositioned to close surveillance.

In April 2021, the patient presented to the emergency department after experiencing several falls in the setting of progressive weakness. She was noted to be hypoglycemic with a blood glucose of 46 mg/dL. She received multiple doses of dextrose in the emergency department but remained persistently hypoglycemic and required admission for further evaluation and management with a dextrose drip. Additional labs obtained during this admission are shown in Table 1. Computed tomography (CT) of the abdomen and pelvis revealed peritoneal carcinomatosis with a 14 × 9.3 × 15 cm centrally necrotic mesenteric/omental implant in the left hemiabdomen that was exerting mass effect on multiple small loops of bowel with associated swelling of the mesentery. Subsequent biopsy performed by interventional radiology

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Table 1
Selected Laboratory Values Collected Preoperatively.

	Preoperative	Reference Values
Glucose	40 mg/dL	70–179 mg/dL
Insulin	<0.5 mU/L	2.6–37.6 mU/L
C-peptide	<0.1 ng/mL	1.1–4.4 ng/mL
Beta-hydroxybutyrate	0.01 mmol/L	0.02–0.27 mmol/L
IGF-1	17 ng/mL	34–194 ng/mL
IGF-2	378 ng/mL	333–967 ng/mL

confirmed recurrent endometrial adenocarcinoma.

The patient remained hypoglycemic despite management with corticosteroids. Under the management of endocrinology, glucagon and D10 infusions were required to maintain euglycemia. Lab evaluation showed low levels of insulin, c-peptide, and beta-hydroxybutyrate in the setting of plasma blood glucose of 40 (Table 1). Due to concern for tumor-induced hypoglycemia, she received one cycle of carboplatin and paclitaxel-based chemotherapy. An IGF-2/IGF-1 ratio was elevated at 22.2, confirming the diagnosis of non-islet cell tumor hypoglycemia (NICTH) mediated by tumor production of unprocessed IGF-2.

Three weeks after chemotherapy, she continued to have refractory hypoglycemia requiring continuous infusions of glucagon and D10. The patient failed multiple types of medical management, and in discussion with endocrinology, the decision was made to proceed with surgical debulking of her recurrent tumor given that this appeared to be the only remaining option to treat her hypoglycemia. The patient underwent surgical exploration and en bloc resection of her large central abdominal tumor with blood supply from the omentum and mesentery with infracolic omentectomy, small bowel resection, and ileal to ascending colon reanastomosis. Residual diffuse carcinomatosis and 4-centimeter tumor invading the left pelvic sidewall, iliac vessels, and rectosigmoid colon were deemed unresectable. Her postoperative course was complicated by a small pelvic abscess and superficial wound separation which were managed with IV antibiotics, interventional radiology drain placement, and wet to dry dressing changes.

Despite the unresected tumor burden, the patient's blood glucose improved immediately postoperatively. Her glucagon drip was discontinued on postoperative day zero, and her dextrose drip was titrated down to maintain a goal blood glucose level of greater than 70 mg/dL and was discontinued on postoperative day two.

Regarding her NICTH, the patient remained euglycemic with diet control and close monitoring throughout her entire postoperative hospital course. Nutrition was consulted to optimize caloric intake, and her appetite improved throughout her admission. Final pathology returned as multifocal carcinosarcoma with associated peritoneal and omental nodules (Fig. 1). There was evidence of lymphovascular invasion as well as tumor invasion into the small bowel muscularis propria. Notably, pathology from the patient's original surgery that was performed at an outside institution was reviewed, and no sarcomatous elements were identified in the submitted sections from that specimen. The patient desired to receive further treatment with chemotherapy closer to family who lived in a neighboring state, and a referral was made to a Gynecologic Oncologist within close proximity to this location.

3. Discussion

Insulin-like growth factor-2 (IGF-2) is a peptide synthesized by the liver that mediates cell metabolism and growth (Dynkevich et al., 2013; Bodnar et al., 2014; Garla et al., 2019). Aberrant tumor production of unprocessed IGF-2, also known as "big" IGF-2 due to the increased molecular weight compared to mature IGF-2, has been implicated in the pathophysiology of NICTH. IGF-2 exerts similar effects as insulin and therefore promotes glucose uptake into skeletal muscle while decreasing glucose production via inhibition of gluconeogenesis, glycogenolysis, and ketogenesis (Dynkevich et al., 2013; Bodnar et al., 2014; Garla et al., 2019; Zapf et al., 1992; de Groot et al., 2007). In the absence of other

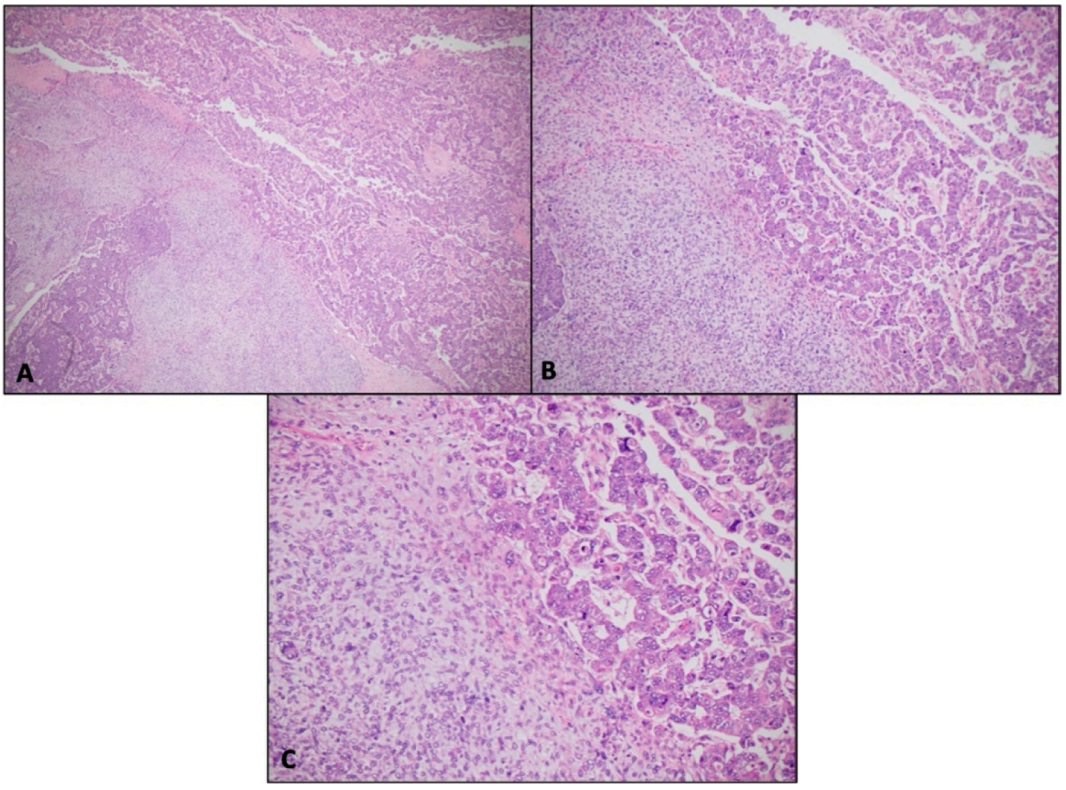

Fig. 1. A. Biphasic high grade malignant neoplasm with epithelial and sarcomatous differentiation consistent with carcinosarcoma. **B.** The tumor demonstrates a high-grade adenocarcinoma with marked nuclear pleomorphsim and numerous mitotic figures intermixed with a high-grade spindle cell proliferation consistent with sarcomatous differentiation. **C.** High power view demonstrating the biphasic growth of carcinosarcoma.

etiologies of hypoglycemia in a patient with a known tumor, IGF-1 and IGF-2 are valuable laboratory markers that can aid in diagnosis. There is no commercially available assay to measure "big" IGF-2, and therefore an IGF-2/IGF-1 ratio that is greater than 10:1 (normal 3:1) is considered diagnostic of NICTH (Bodnar et al., 2014). Additional laboratory findings may include low insulin and c-peptide levels (Bodnar et al., 2014; Garla et al., 2019). Our patient's preoperative laboratory values are notable for low insulin and c-peptide values and an elevated IGF-2/IGF-1 ratio of 22.2 (Table 1).

First-line treatment in patients with NICTH is surgical resection of the offending tumor. Complete surgical resection often leads to resolution of the associated hypoglycemia. (Dynkevich et al., 2013; Bodnar et al., 2014; Teale and Wark, 2004). Depending on the extent of tumor involvement, complete resection may not be possible. In the case of unresectable disease burden, there is no clear standard of care for management; however, there are case reports describing resolution of hypoglycemia in cases of subtotal resection (Bodnar et al., 2014). In our patient, imaging findings suggested an unresectable burden of disease. Given the limited role of surgical debulking in unresectable recurrent endometrial cancer, our patient was initially managed without surgery.

In patients who are not candidates for initial surgical intervention, primary medical management can be pursued. While there is a paucity of data surrounding the various proposed treatments of NICTH, the most well-studied of these include glucocorticoids. Glucocorticoids improve hypoglycemia in patients with NICTH by increasing hepatic gluconeogenesis, inhibiting peripheral uptake of glucose, and decreasing the amount of "big" IGF-2 in circulation while increasing the amount of mature IGF-2. Alternatively, recombinant human growth hormone (hGH) has also been shown to ameliorate hypoglycemia; however, unlike glucocorticoids, this agent acts to increase both "big" IGF-2 and mature IGF-2 (Teale and Marks, 1998). In all patients who are pursuing medical management, providers should encourage increased caloric intake. If patients are unable to tolerate oral intake, enteral or parenteral feeding can be considered short-term to optimize nutritional status (Dynkevich et al., 2013; Bodnar et al., 2014). Additionally, treating the primary tumor using either chemotherapy or radiation has been employed with inconsistent success (Dynkevich et al., 2013; Bodnar et al., 2014). Because our patient's hypoglycemia was refractory to medical management, the decision was made to proceed with surgical intervention. Despite undergoing a partial surgical resection, our patient's hypoglycemia resolved postoperatively.

4. Conclusion

In patients with known epithelial or mesenchymal tumors, consideration must be given to NICTH as a possible culprit in the setting of new-onset hypoglycemia. NICTH is a rare cause of hypoglycemia in patients with carcinosarcoma with only three other cases reported in the literature. The diagnosis is made with an IGF-2/IGF-1 greater than 10:1. Complete resection can often cure hypoglycemia; however, our case highlights that partial resection should be considered as this may provide some improvement in the hypoglycemia.

CRediT authorship contribution statement

Miller P. Singleton: Conceptualization, Writing – original draft, Writing – review & editing. **Sirisha Thambuluru:** Writing – original draft, Writing – review & editing. **Teresa Samulski:** Writing – original draft, Writing – review & editing. **Sarah E. Paraghamian:** Conceptualization, Writing – original draft, Writing – review & editing. **Leslie H. Clark:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Informed consent was obtained from the patient for publication of this case report. A copy of the consent is available for the Editor of this journal upon request.

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