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CASE REPORT

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Non-islet cell tumor hypoglycemia (NICTH) associated with sarcoma, case report

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Abstract

Non-islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome caused by the secretion of high molecular weight insulin-like growth factor II (IGF-II) from tumors, particularly those of mesenchymal and epithelial origin. This case report describes a 71-year-old male with pelvic sarcoma who presented with severe hypoglycemia, with blood glucose levels dropping below 40 mg/dL and exhibiting neuroglycopenic symptoms. The diagnosis of NICTH was confirmed through biochemical analysis showing hypoinsulinemic hypoglycemia alongside low C-peptide and IGF-1 levels. Initial management with dextrose infusions and glucocorticoids proved ineffective until recombinant human growth hormone (rhGH) therapy was initiated, resulting in a decreased requirement for dextrose. Following angioembolization of the tumor, the patient's blood glucose levels stabilized sufficiently to allow for the complete cessation of dextrose administration. This case highlights the critical role of rhGH in reducing dextrose dependency and the effectiveness of angioembolization in managing NICTH when surgical options are limited.

Keywords Case report, Hypoglycemia, Non-islet cell, Recombinant growth hormone, Angioembolization

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Introduction

Hypoglycemia can result from various tumors, including both islet and non-islet cell tumors. Non-islet cell tumor hypoglycemia (NICTH) is a rare but significant complication associated with malignancies [1, 2]. It is particularly prevalent in patients with mesenchymal tumors, fibromas, carcinoid tumors, myelomas, lymphomas, as well as hepatocellular and colorectal carcinomas [2–5]. There is no single mechanism that accounts for all instances of NICTH. The predominant cause appears to be heightened glucose utilization, especially in skeletal muscle, combined with the inhibition of hepatic glucose release. This is often due to the tumoral secretion of incompletely processed insulin-like growth factor 2 (IGF-2), known as pro-IGF-2, or, less commonly, IGF-1 [6].

We report a case involving severe hypoglycemia linked to a large recurrent and non-resectable pelvic sarcoma that did not respond to standard treatments, but had partial response to rhGH and angioembolization of the tumor. This case underscores the necessity of considering IGF-2 induced hypoglycemia when diagnosing patients with hypoglycemia and pelvic sarcoma, as well as exploring different management strategies for such cases.

Case presentation

A 71-year-old man with a medical history of hypothyroidism, hypertension, and pelvic sarcoma presented to the emergency room of Shariati hospital, affiliated to Tehran University of Medical Silences, exhibiting signs of hypoglycemia, including episodes of weakness, lethargy, decreased consciousness, and seizures. His blood sugar levels were recorded below 40 mg/dL, and he experienced frequent neuroglycopenic symptoms over the past month.

In May 2022, he was diagnosed with pelvic sarcoma measuring 150 × 80 mm and subsequently underwent surgery followed by chemotherapy. The pathology report indicated a high-grade malignant fibrous histiocytoma (MFH)-like pleomorphic sarcoma with necrosis and a Ki-67 index of 50%. A positron emission tomography (PET) scan conducted in June 2022 showed no evidence of metastasis. In March 2023, he required a repeat laparotomy due to tumor recurrence (116 × 112 mm). However, the mass was deemed non-resectable. After undergoing colostomy insertion, he was discharged with recommendations for chemotherapy.

Table 1 Laboratory results on admission

Laboratory	
WBC = 10,140 per microliter	TSH = 15.2 μIU/ml (0.3–4.94)
Hb = 7 gr/dl	T4 = 6.3 μg/dl (4.87–11.72)
Plt = 223,000 per microliter	T3 = 0.70 ng/ml (0.35–1.93)
CRP = 50 mg/l (up to 6)	Ca = 7.5 mg/dl (8.5–10.5)
ESR = 90 mm/hr (up to 20)	Ph = 1.8 mg/dl (2.6–4.5)
LDH = 874 U/l	Alb = 2.5 gr/dl (3.5-5)
Cr = 1.52 mg/dl (0.6–1.3)	Plasma glucose = 40 mg/dl
Estimated GFR = 46 ml/min/1.73m2	Insulin = 0.4 μg/ml (2.6–24.9)
Na = 147 meq/l (135–145)	c-peptide = 0.6 ng/ml (1.1–4.4)
K = 3.6 meq/l (3.6–5.2)	GH = 1.5 ng/ml (Up to 3)
	IGF-I = 25.6 ng/ml (38.3-182.5)
	Cortisol = 13.5 μg/dl (4.8–19.5)
	ACTH = 64.5 pg/ml (7.2–46)

At the time of the current admission (March 2024) due to severe hypoglycemia and neuroglycopenic symptoms, the patient's vital signs were stable and within normal limits. A physical examination revealed a body mass index (BMI) of 32 kg/m² and mild bilateral edema in the lower limbs. The patient had been bedridden for the past two months due to the compressive effects of the mass on the lumbar spinal cord, which resulted in decreased strength in the lower limbs. The results of the admission tests are presented in Table 1. A blood sample was collected to measure insulin, C-peptide, cortisol, growth hormone (GH), and insulin-like growth factor 1 (IGF-1).

The patient received a 10% dextrose in water (D/W) infusion, but despite receiving high doses, he experienced hypoglycemic episodes that necessitated repeated bolus doses of 50% D/W. The patient required 600 g of glucose daily to maintain euglycemia (100–180 mg/dL). Additionally, oral prednisolone was initiated at a daily dose of 50 mg; however, there was only a moderate reduction in glucose requirements, with daily needs ranging from 450 to 500 g. Given the requirement for substantial dextrose infusion, a central venous line was placed for the patient. A nutrition consultation was conducted, and a diet high in protein and cornstarch was also initiated.

The results of lab tests were consistent with NICTH. Although we could not assess IGF-2 levels in this case (since it is not commercially available in our country), the diagnosis of NICTH was established based on the presence of hypoinsulinemic hypoglycemia, alongside low levels of C-peptide and IGF-1, in conjunction with a significant tumor burden. We did consider other potential causes of hypoglycemia, including malnutrition, sepsis, severe hepatic dysfunction, and adrenal insufficiency. However, laboratory results and the patient's lack of response to dietary adjustments made by a nutritionist, high-dose corticosteroid treatment, and a negative initial sepsis work-up indicated that these conditions were not contributing factors in this scenario. Thus, the evidence strongly supported that NICTH was the primary cause of the patient's hypoglycemia.

Recombinant human growth hormone (rhGH) therapy was initiated for the patient at a daily dosage of 0.37 mg, which was subsequently increased to 2.8 mg daily. Following the commencement and adjustment of the rhGH dosage, we observed a significant decrease in glucose requirements to between 75 and 100 g per day. Despite this improvement, complete cessation of exogenous glucose support was not yet achievable at that stage. After

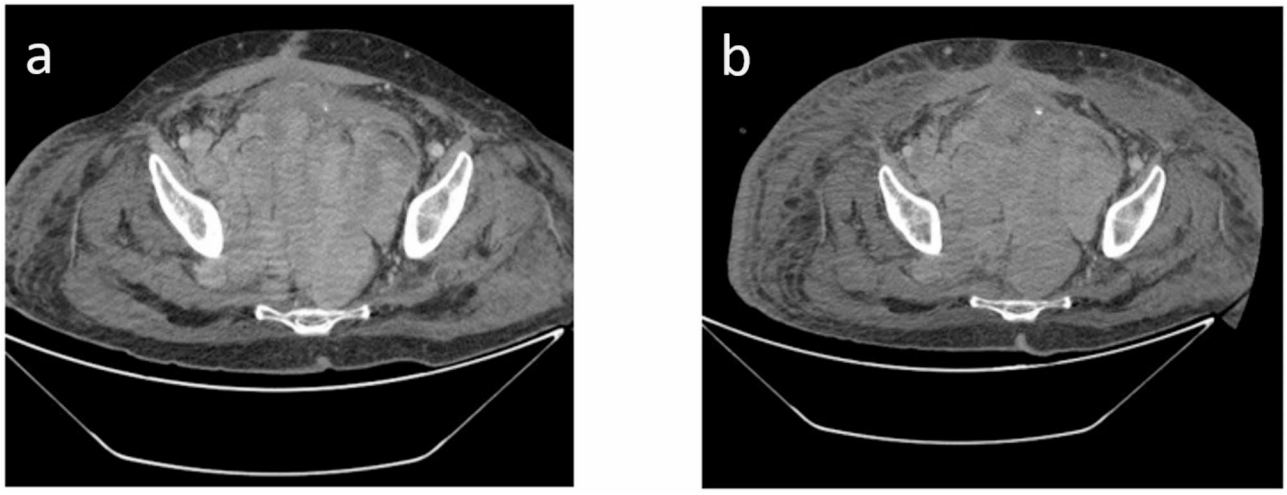

Fig. 1 The large enhancing tumor in pelvic cavity (**a**) before and (**b**) after embolization shows marked reduction of enhancement

discussions with the surgical and radiointervention teams, it was determined that the patient was qualified for angioembolization as a means of tumor devascularization. Ten days following angioembolization (Fig. 1), the patient's blood sugar levels began to rise gradually to the levels above 180 mg/dl, allowing for the decrease and cessation of dextrose/water infusion for a couple of weeks. The patient continued receiving rhGH at a daily dosage of 2.8 mg. During the hospital stay, the patient developed persistent lower limb edema that did not respond to treatment with albumin and furosemide, despite normal heart function. Subsequently, after a reduction in colostomy output accompanied by nausea and vomiting, the patient experienced aspiration pneumonia and required intubation. Blood pressure decreased, prompting a transfer to the intensive care unit (ICU), where treatment with norepinephrine and broad-spectrum antibiotics was initiated. Due to anuria and rising creatinine levels along with persistent edema, dialysis was performed, and rhGH treatment was discontinued. Unfortunately, the patient passed away two week later.

Discussion

NICTH, or non-islet cell tumor hypoglycemia, is a rare paraneoplastic syndrome first identified in the 1980s [7]. Although it can arise from various malignancies, it is predominantly linked to tumors of epithelial or mesenchymal origin [8]. As the prevalence of malignancies increases, the incidence of reported NICTH cases is also expected to rise.

Diagnosis of NICTH is challenging since IGF-2 levels may not be commercially available for testing within many countries. It can be confirmed through the presence of hypoinsulinemic hypoglycemia alongside low C-peptide levels in patients with significant tumor burden [8, 9]. Additionally, low levels of GH and IGF-1 can support the diagnosis. In instances where IGF-2 assays are accessible, results may vary according to the assay used; however, an IGF-2/IGF-1 molar ratio greater than 10 is indicative of NICTH [2]. NICTH was the most appropriate diagnosis for our case, supported by suppressed insulin and C-peptide levels, decreased IGF-1, and a significant mesenchymal tumor burden, with worsening of hypoglycemia as tumor size increased. Furthermore, other potential causes of hypoglycemia, such as malnutrition, sepsis, and adrenal insufficiency, were not indicated in this patient's scenario based on laboratory results and their lack of response to dietary adjustments made by a nutritionist, high-dose corticosteroid treatment, and a negative sepsis work-up.

Management of NICTH ideally involves the surgical removal of the tumor responsible for the condition; however, this is frequently unfeasible. Literature indicates that partial excision and localized treatments, such as radiotherapy, can effectively reduce tumor burden and alleviate symptoms [2]. In cases where surgical intervention is not possible, various therapeutic options such as chemotherapy, radiation therapy, cryoablation, radiofrequency ablation, or selective embolization have been explored. When the malignancy cannot be treated, medical therapy is essential to prevent recurrent hypoglycemia. Glucocorticoids, typically administered at doses equivalent to prednisone 30 to 60 mg per day, have shown effectiveness in managing hypoglycemia [10]. Additionally, rhGH has been utilized, with supraphysiological doses ranging from 3 to 12 mg daily reported in some cases [2]. While rhGH can be beneficial, it must be used cautiously due to risks of increasing IGF-1 levels and the potential to stimulate tumor growth. This therapy is typically reserved for palliation in end-stage cancer patients with NICTH [11–17]. Other treatments like somatostatin analogues and diazoxide have not proven effective [2, 3, 18–20].

Several cases of NICTH have been documented in the literature. One case involved a patient with unresectable pelvic sarcoma who was treated with a daily dose of 4 mg dexamethasone [21]. In another instance, two patients with benign pleural tumors and one with pleural fibrosarcoma experienced hypoglycemia; they were treated with recombinant growth hormone at doses of 6 and 8 units daily, respectively. Unfortunately, the first patient underwent debulking surgery but died from pneumonia 12 weeks later, while the second patient succumbed to respiratory failure five months after treatment [12]. Additionally, a case of poorly differentiated squamous cell carcinoma of the esophagus resulted in NICTH, which was managed with prednisone at 40 mg, leading to discharge from the hospital [22]. Another patient with a non-resectable abdominal solitary fibrous tumor experienced hypoglycemic attack but saw resolution of symptoms two weeks post-chemoradiotherapy [23]. A different case involving a uterine mass was treated with prednisone at 20 mg daily for hypoglycemia, and after surgery, the patient's symptoms resolved within three months, allowing for tapering off the medication [24]. In two further cases of hypoglycemia suggestive of NICTH, one patient diagnosed with metastatic hemangiopericytoma responded positively to a combination therapy of prednisone (30 mg daily), octreotide (100 mg daily), and recombinant growth hormone (initially 0.67 mg, increased to 1.67 mg). The second patient, diagnosed with an abdominal solitary fibrous tumor, underwent complete resection and showed improvement in hypoglycemic symptoms after six weeks [25].

In this case study, we implemented various therapeutic strategies based on current evidence due to the patient's severe hypoglycemia, which persisted despite high dextrose infusion, significant doses of prednisolone, and a diet rich in starch and complex carbohydrates. In general, growth hormone therapy is not preferred unless it is for palliative care in patients with advanced cancer experiencing NICTH. We initiated treatment with rhGH, resulting in a partial response that reduced the patient's dependence on dextrose infusion. The patient perceived this treatment as beneficial and expressed hope for a timely discharge. Nonetheless, he remained reliant on intravenous dextrose infusions. Subsequently, we attempted angioembolization, which successfully led to a temporary independence from IV dextrose for several weeks. Unfortunately, the patient later developed pneumonia and other complications, ultimately leading to his passing.

Conclusion

The primary approach to managing NICTH involves addressing the underlying malignancy. When a tumor secretes insulin-like growth factors (IGFs) or insulin, complete surgical removal can effectively resolve hypoglycemia [2, 26]. Some cases may respond to medical therapy with glucocorticoids or rhGH. In cases where the tumor is inoperable, palliative measures such as tumor debulking are typically undertaken. Treatment modalities may include chemotherapy, radiation, cryoablation, radiofrequency ablation, or selective embolization of blood vessels supplying the tumor, depending on its type, to help control the tumor and alleviate hypoglycemia [23]. Our case is notable for its exploration of multiple interventions in a challenging instance of NICTH linked to a recurrent and unresectable large sarcoma, where glucocorticoids failed to elicit a response, rhGH provided only partial relief, and angioembolization offered a relative improvement in dextrose independence as a method of tumor debulking.

Supplementary Information

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Supplementary Material 1

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Author contributions
A.JA and N.P. were responsible for drafting the main manuscript. N.P. and M.PS collaborated with N.A., A.Z., and M.K. in managing the patient care. The angioembolization procedure was carried out by O.G., M.J., and B.R. Senior oversight of the management plan was provided by M.M., A.S., and H.A. All authors reviewed and approved the final version of the manuscript.

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Data availability
The laboratory data and imaging of the patient is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Since the patient passed away, signed informed consent was obtained from the patients' wife for reporting his de-identified clinical and imaging data.

Competing interests
The authors declare no competing interests.

Consent for publication
Since the patient passed away, signed informed consent was obtained from the patients' wife for reporting his de-identified clinical and imaging data.

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