Case Report 2

A 94-year-old man with recurrent hypoglycemia caused by non-islet cell tumor hypoglycemia (NICTH)

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Abstract:

Non-islet cell tumor hypoglycemia (NICTH) is a rare but serious paraneoplastic syndrome in which a tumor secretes the high molecular weight form of IGF-II, causing hypoglycemia and requiring early diagnosis and management. Here, I report a rare case of NICTH caused by fibrosarcoma in a 94-year-old male with recurrent hypoglycemia.This case report describes the clinical presentation and diagnostic and management issues involved in a case of NICTH that was diagnosed at a tertiary care institute.

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Introduction

Hypoglycemia can be caused by several tumors, including islet and non-islet cell tumors (NICTH). [1] NICTH is a rare and serious type of tumor that secretes a high-molecular weight form of IGF-II that stimulates insulin receptors and increases glucose utilization, causing hypoglycemia. NICTH occurs more commonly in patients with mesenchymal tumors, fibromas, carcinoid, myelomas, lymphomas, hepatocellular, and colorectal carcinoma table 1. [2]

Table 1. Tumors that reportedly cause NICTH

Carcinomas	Other tumors (mesenchymal and nonmesenchymal)
Adrenal cortex Bile duct Breast Cervix Colon Esophagus Larynx Lung Ovary Pancreas Prostate Stomach	Carcinoid tumor Fibrosarcoma, fibroma 50% Fibrous tumor of the pleura Hemangiopericytoma Hepatoma Hypernephroma Lymphoma Leiomyosarcoma Liposarcoma Meningioma Mesothelioma Multiple myeloma Neurilemmoma Neurofibroma Neurofibrosarcoma Pheochromocytoma Wilms' tumor

The true incidence of NICTH is unknown, and in many cases, particularly in metastatic disease, it can go unrecognized.

Although hypoglycemia is common, NICTH is considered to bea rare cause of the condition. In addition, NICTH is accompanied by serious complications, which is why I chose to report this case, as well as to remind clinicians of this cause of hypoglycemia.

Case

In 2012, a 94-year-old male with no risk factors for hypoglycemia was admitted to the emergency department with serum glucose of 1.6 mmol/l and a history of weight loss and recurrent episodes of autonomic and neuropsychiatric symptoms of hypoglycemia, which occurred regularly, particularly in the mornings. For the past 6 months, eating breakfast relieved these episodes. The patient's body mass index (21.2 Kg/m^2), vital signs, clinical examination andinvestigation were normal. Adrenal disease was excluded, and hissulphonylurea derivatives and insulin antibodies were negative. The patient had diminished C peptide, (pro-) insulin, insulin-like growth factor 1 (IGF-I) and IGF binding protein 3 levels; the total IGF-II level was within the normal range, and the molar ratio between the total IGF-II and IGF-I levels was 17.7 (a high ratio). The serum pro-IGF-IIE ('big'-IGF-II) levels were markedly elevated. An IGF-II secreting tumor was suspected. Computed tomography of the abdomen and pelvis with contrast (figure 1) revealed a large heterogeneous pelvic tumor mass, without metastasis.

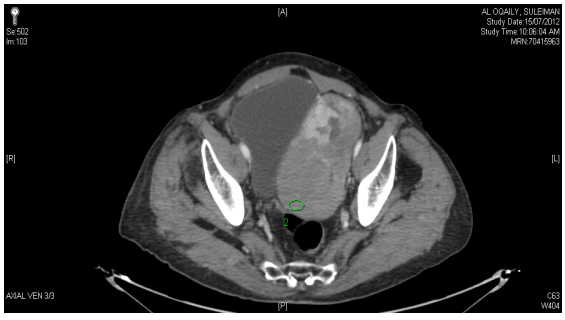


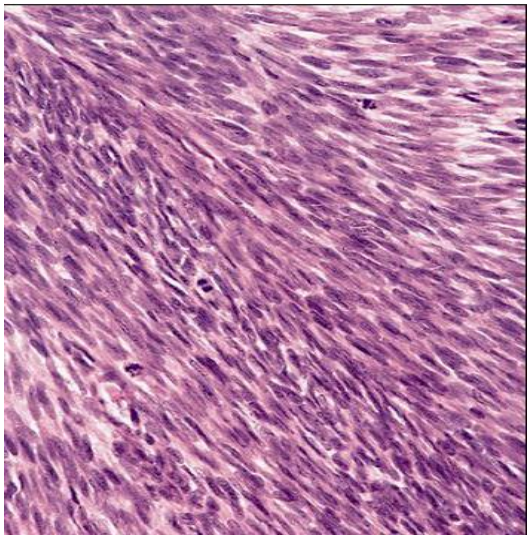
Figure 1. A large heterogeneous pelvic tumor mass measuring 4x6 cm in size, with bladder wall mass effect.

The patient was initially managed by intravenous glucose administration; then, he underwent laparotomy, with resection of the tumor. There were no complications.

Histopathology (figure 2) revealed homogenous spindle shaped cells, with little pleomorphism and some mitosis, which was suggestive offibrosarcoma. In situ hybridization

revealed high levels and increased expression of IGF-II.

A.



B.

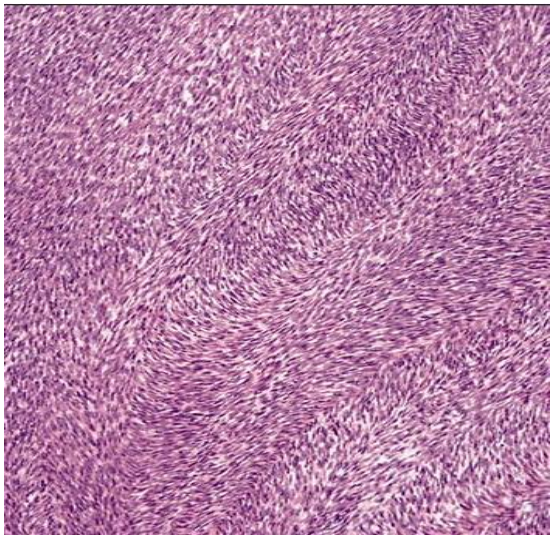


Figure 2. High (A) and low (B) power photomicrographs (10×, H&E stain) showing homogenous spindle shaped cells, with little pleomorphism and some mitosis.

The patient's postoperative biochemical IGF, glucose, insulin,C peptide, and proinsulin levels returned to normal, and he experienced no further hypoglycemic episodes.

Discussion

NICTH is rare, and it is the second most common cause of tumor-related hypoglycemia, following insulinoma. [4] NICTH was first described in 1929 in a patient with hepatocellular carcinoma. [5] Mesenchymal tumors of non-pancreatic origins are the most common tumorsassociated with hypoglycemia (cancer 1979). [6] Fibrosarcoma, which was discovered in our patient, is a tumor of mesenchymal cell origin and consists of malignant fibroblasts. [6] No single pathogenetic mechanism can explain all cases of NICTH. However, the major cause of NICTH appears to be increased glucose utilization (particularly in the skeletal muscle) and inhibition of glucose releasefrom the liver, which is caused by tumoral secretion of incompletely processed insulin-like growth factor (IGF)-II, (termed "big" IGF-II) [7] acting through the insulin receptor, or, rarely, IGF-I.Big IGF-II also suppresses glucagon and growth hormone release. [7] The net result is continued glucose utilization by skeletal muscle and inhibition of glucose release, glycogenolysis, and gluconeogenesis in the liver. [7] Our case is one of only 290 cases of NICTH that have been reported in the English language medical literature in the past 25 years. [2] NICTH usually presents in the fifth to sixth decade of life andgenerally occurs between meals or in the morning, [4] with a mean duration of symptoms from weeks to months. Our 94-year-old patient is the oldest reported case, and he presented with a mean duration of symptoms of 6 months. Hypoglycemia can be a presenting symptom of a tumor, or it can present later during the course of the disease. In our patient, the symptom of hypoglycemia led to the discovery of the tumor. In NICTH, the serum levels of insulin, C-peptide, and IGF1 are usually decreased or undetectable; however, the circulating level of total IGF2 may be increased, decreased, or normal, with an IGF-II:IGF-I ratio of 10 or more. When a tumor is not previously known or readily apparent,imaging of the chest, abdomen, and pelvis are helpful in the diagnosis. Initially,

regular carbohydrate snacks can prevent hypoglycemia, which is also the case for intravenous dextrose; glucagon can be used in an emergency. The most effective long-term management of NICTH is to reduce the tumor size by surgery, radiotherapy, or chemotherapy. Alternative treatment options for patient for whom the underlying malignancy cannot be treated include human recombinant growth hormone, glucocorticoids and continuous glucagon infusion. [8] Octreotide and diazoxide do not play a role in NICTH. [2] Preoperatively, our patient was treated with increased caloric intake through iv dextrose and then underwent surgical resection of the tumor; he responded well, and he did not require any other interventions. However, close follow-up is required to manage these patients.

Conclusion

NICTH is rare and should be considered in patients who present with recurrent hypoglycemia associated with a mesenchymal tumor and low serum insulin and IGF1 levels, with or without a high level of IGF II. Surgical resection is curative. Glucocorticoid therapy and other conservative measures may be useful when the tumor is inoperable or in cases of recurrence

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