

Tumor Hypoglycemia Mediated by Igf-1 Effects in Non-Beta Cell Tumor

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ABSTRACT

Summary: Introduction: Tumor hypoglycemia is an uncommon manifestation that can occur in advanced hepatocarcinoma, through various mechanisms associating tumor production of IGF - 1 and IGF-2.

Case presentation: We detail the clinical case of a woman diagnosed with hepatocarcinoma BCLC stage C Child Pugh class A with recurrent events of hypoglycemia during her clinical evolution, with biochemical studies that included glucose, insulin, C-peptide, cortisol and IGF-1. The patient presented low insulin and C-peptide levels ruling out a corresponding insulin cause to hypoglycemia. IGF-1 levels below the percentile were reported, suggestive of hypoglycemia mediated by dysregulation of the GH/IGF axis. Due to persistence of hypoglycemia events with Prednisone she is switched to dexamethasone presenting a significant clinical improvement with resolution of hypoglycemia episodes.

Conclusions: Patients with advanced hepatocarcinoma and non-insulin hypoglycemia (insulin levels and low C-peptide) should be suspected in IGF-mediated etiologies.

Although measured by IGF-2 is the most frequent, low IGF-1 levels can show an alteration of the GH/IGF axis in the tumor context. The use of glucocorticoids in this case is highlighted as it showed that there is no improvement in the hypoglycemia episodes with oral glucose supplementation or with parenteral glucose solutions

KEYWORDS: Tumor hypoglycemia

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INTRODUCTION

Hypoglycemia is a clinical phenomenon that can have various causes, including paraneoplastic ones. In particular, non-pancreatic neoplasms that secrete insulin-like peptides, such as insulin-like growth factor type 2 (IGF-2), form a rare but clinically relevant entity known as non- insulin-mediated hypoglycemia.

This syndrome has been described in association with mesenchymal tumors, hepatocellular carcinomas, gastric carcinomas, and soft tissue carcinomas. Its pathophysiology includes excessive secretion of IGF-2, which causes inhibition of hepatic gluconeogenesis and increased peripheral glucose uptake, mimicking the action of insulin (1). Timely identification of this cause is critical, as resolution of hypoglycemia critically depends on tumor control and has a direct impact on survival. In the context of hepatocellular carcinoma, the use of capecitabine in an alternative regimen

has recently been investigated.

This therapy has shown an acceptable clinical response and a favorable safety profile, especially in patients with comorbidities or in patients who no longer respond to conventional treatments. The importance lies in the low frequency of reported cases, since one of the primary objectives in these patients is treatment, which affects survival and prognosis according to the evidence.

CASE PRESENTATION

75-year-old female with hepatocellular carcinoma BCLC class C Child Pugh A, liver biopsy with histopathological report of well-differentiated hepatocarcinoma. Candidate for advanced stage to systemic therapy with sorafenib as first line treatment, due to portal hypertension data, liver resection was not performed. However, she had progression completing 4 cycles, with subsequent change to metronomic capecitabine, according to meta-analysis a grouped prevalence of disease

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control rate and overall response rate achieved with metronomic capecitabine (1) was 36% (95% CI: 32-41) in non-randomized controlled trials type studies according to the assessment by Medical Oncology.

She started with G1 hypoglycemia and ECOG 2 after one year of disease progression presenting symptoms such as drowsiness and hyporexia, so she went to the emergency room documenting hypoglycemia < 50mg/dl capillary and a basal glucose of 63 mg/d.

On admission reported hypoglycemia, mild hypokalemia, liver function tests with mild elevation of ALT and AST 154 U/l and 131 U/l respectively. With decreased

adrenocorticotrophic hormone 2.23 pg/ml (7.2-63.3), cortisol 2.5 u/l (5.27-22.45), insulin 0.4 mU/l (3-25), thyroid function tests with normal TSH 0.942 mIU/ml (0.55-4.78), T4t 11.9 mg/dl, T3t 4.56. with data of secondary adrenal insufficiency due to suspension of exogenous administration of steroids, Previous 5 months for hypoglycemia with serum glucose 28.8 mg/dl. C-peptide 0.08 ng/ml (1.1-4.4), Cortisol 3.9 ug/dl (decreased). Insulin 1 mU/l (3-25).

Serum cortisol 13.8 ug/dl without steroid administration and ACTH 9.57 pg/ml, treatment was started on that occasion with prednisone 25 mg for 7 days with dose reduction until reaching 5 mg in the fifth week.

Table 1. Laboratory test

LABORATORY TEST	OUTCOME	REFERENCE
Serum glucose	63 mg/dl	70-110 mg/dl
Serum glucose	28.8 mg/dl	70-110 mg/dl
Serum insulin	0.4 mU/l	3-25 mU/l
Serum insulin	1 mU/l	3-25 mU/l
C peptide	0.08ng/ml	1.1-4.4 ng/ml
IGF-1	<15 ng/ml	Variable by age/gender
Cortisol	2.5 µg/dl	5.27-22.45 µg/dl
Cortisol	3.9 µg/dl	5.27-22.45 µg/dl
Cortisol	13.8 µg/dl	5.27-22.45 µg/dl
ACTH	2.23 pg/ml	7.2-63.3 pg/ml
ACTH	9.57 pg/ml	7.2-63.3 pg/ml
TSH	0.942mIU/l	0.55-4.78mIU/mL
T4 Total	11.9 µg/dl	5.0-12.0 µg/dl
T3 total	4.56 µg/dl	0.8-2.0 ng/ml
AST	154U/L	<40 U/L
ALT	131 U/L	<41U/L

Liver of usual anatomical situation, with loss of its morphology, lobulated and defined borders, heterogeneous parenchyma at the expense of multiple lesions that affect diffusely predominantly the right lobe, are amorphous, poorly demarcated, heterogeneous predominantly hypodense (average of 22 HU), after administration of contrast medium

with heterogeneous nodular enhancement of up to 108 HU and central non-catching areas in relation to areas of necrosis, these lesions tend to confluence and the largest size is a Diana lesion occupying practically the entire right lobe. It loses the interface with the adjacent wall of the gallbladder.

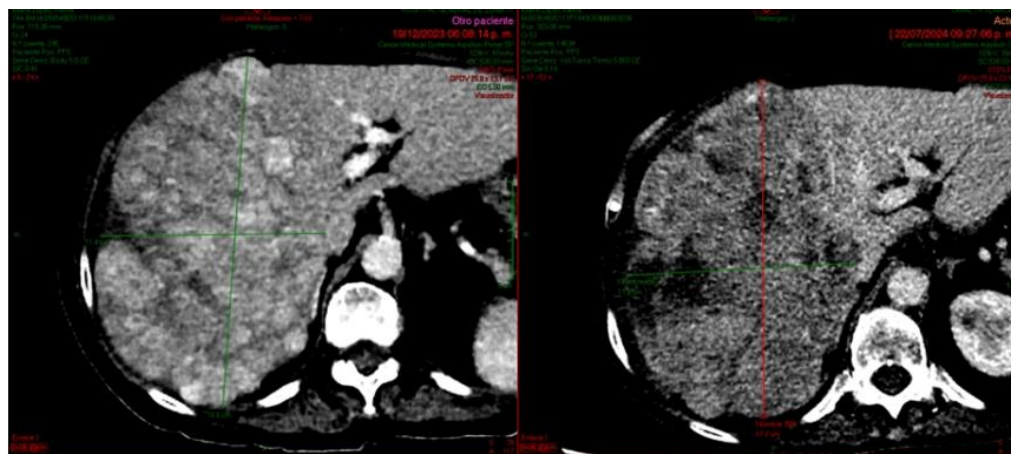


Fig 1. Abdominal CT scan.

Table 2. A RECIST 1.1 comparison of lesions in the abdomen is performed.

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There is a 12% increase in tumor burden, however, as there are new target lesions, it is considered progressive disease. The patient presented constant hypoglycemia, with frequent use of 50% glucose solution and carbohydrate-rich diet; however, according to the biochemical results and history, hypoglycemia due to non-beta cell tumor was considered as etiology.

Therefore, she was maintained on steroid treatment initially with prednisone up to 50 mg per day, later the hypoglycemia continued, deciding treatment with dexamethasone for greater glucocorticoid potency with doses of 8 mg IV every 24h where capillary glycemia ranged between 140-180 mg/dl. Due to the above, IGF-1 was requested and reported at <15, so we consider secondary to hepatocarcinoma as the origin of hypoglycemia. Due to the characteristics and stage of the disease, a steroid dose reduction was considered in conjunction with the Medical Oncology service, maintaining a dose of 2 mg

of dexamethasone in the morning orally and 1 mg of dexamethasone at night.

During the approach to hypoglycemia, the clinical characteristics of the patient should be considered, ruling out common etiologies (infectious, secondary to medication) according to clinical history, and in the second step of endogenous hyperinsulinism approach as in our case, the measurement of proinsulin, insulin, C-peptide and hydroxybutyrate as part of the protocol. With low insulin and C-peptide levels concluding IGF-1 mediated hypoglycemia.

DISCUSSION

IGF-1 is produced in liver approximately 75% and 25% in other tissues such as bones, kidneys, ovaries and even cartilage. Clinically, reduced IGF-1 levels are frequently associated with hepatocellular carcinoma. The impact of this polypeptide hormone has been studied in patients with hepatocellular

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carcinoma where it is kept inactive in surgical resection, liver transplantation or regional therapies and its elevation may indicate an increased risk of cancer progression (2). In the study by Mohamed et al, IGF-1 levels correlated with markers indicative of liver function and liver damage including AST levels, bilirubin and albumin. Concluding that lower IGF-1 levels correlated with lower overall survival but not significant in disease progression among patients with higher IGF-1 levels. Proving what was previously believed that decreased IGF-1 is a cytoprotective factor preventing oncogenesis (3)

Teale & Mar since 1998 investigated the relationship of IGF-1 and IGF-2 in hepatomas where both hormones exert potent insulin-like activity causing severe hypoglycemia. In elderly patients, whose survival period after hypoglycemia is relatively short, the use of steroids had a beneficial response in decreasing IGF-2 and increasing IGF-1 with or without the addition of glucagon to the treatment (4), since IGF-2 inhibits the secretion of insulin, growth hormone and consequently reduces IGF-1 levels (5).

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