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CASE REPORT | LIVER

Refractory Hypoglycemia Presenting as First Manifestation of Advanced Hepatocellular Carcinoma

Mithun Sharma, MD[1,3], Duvurru Nageshwar Reddy, MBBS, MD, DM[2], and Tan Chee Kiat, MBBS, FRCP, FAMS[3]

[1]*Department of Hepatology, Asian Institute of Gastroenterology, Hyderabad, Andhra Pradesh, India*
[2]*Department of Gastroenterology, Asian Institute of Gastroenterology, Hyderabad, Andhra Pradesh, India*
[3]*Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore*

Abstract

Hypoglycemia is a well-established paraneoplastic manifestation of hepatocellular carcinoma (HCC). However, hypoglycemia presenting as the primary presentation of HCC is extremely rare. Most cases are resistant to glucose infusion and may lead to severe complications such as hypoglycemic seizures. We present a patient who had hypoglycemia as first manifestation of HCC and was managed conservatively.

Introduction

Hypoglycemia is a known paraneoplastic manifestation of hepatocellular carcinoma (HCC) with a prevalence of 4–27%.[1,2] However, hypoglycemia presenting as the initial manifestation of HCC is extremely rare. Management of such hypoglycemic episodes is more difficult given many patients are unaware of their hypoglycemia.

Case Report

A 59-year-old man was referred to the hospital by his local physician due to non-vertiginous dizziness that started on the same day. He gave a history of progressive abdominal distention and bloating for 1 month and passage of tea colored urine for 1 week. He had lost 9 kg of weight in the last 6 months. His oral intake during this period had only marginally decreased. Past medical history included hypertension treated with enalapril and a small intracerebral hemorrhage 5 years ago with no residual neurological deficit. On physical examination, he was lethargic and cachectic (BMI 18.15 kg/m^2) with scleral icterus and signs of dehydration. Examination of his abdomen revealed a large, irregular, hard hepatic mass extending 4 cm below the right costal margin. No splenomegaly or other stigmata of chronic liver disease was noted. A bruit was heard over the hepatic mass. His cardiovascular and respiratory system findings were within normal limits.

Laboratory tests revealed hypoglycemia as documented by a very low serum glucose 1.2 mmol/L, serum-C peptide 0.70 µIU/mL, serum insulin 0.70 µIU/mL, and serum creatinine 75 µmol/L. He was immediately resuscitated with intravenous dextrose infusion and his mental status improved to baseline with adequate increase in blood glucose. Subsequent investigations showed serum α-fetoprotein 763 µG/L, insulin-like growth factor 1 (IGF1) 10.09 µg/L, and IGF2 330 ng/mL. The underlying etiology for hepatocellular carcinoma (HCC) was hepatitis B e-antigen (HBeAg)-negative chronic hepatitis B infection with a viral load of 3.14 log IU/mL, for which he was started on entecavir. Laboratory parameters are shown in Table 1.

Computed tomography (CT) revealed multiple hepatic lesions, with the largest measuring 15.9 x 13.4 x 17.3 cm in the right lobe of the liver. The lesions showed heterogeneous arterial enhancement with portal/delayed phase

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Correspondence: Mithun Sharma, Asian Institute of Gastroenterology and Hepatology, 6-3-661, Somajigudda Red Rose Cafe Lane, Hyderabad, Andhra Pradesh, 500082, India (drmithunsharma@gmail.com).

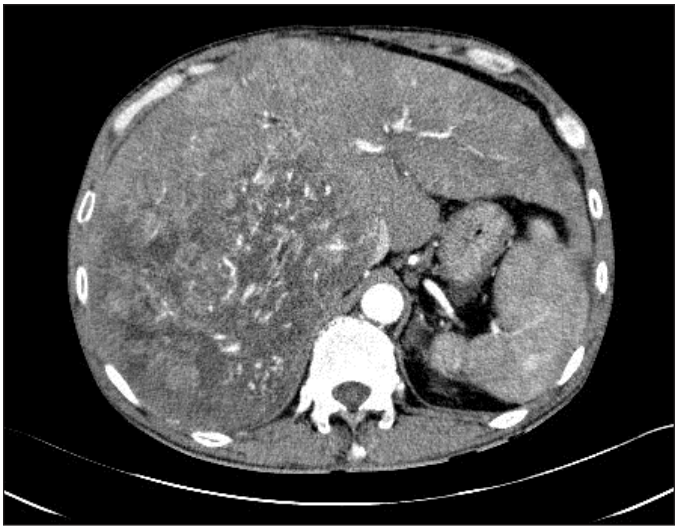

Figure 1. Triphasic contrast-enhanced CT showing large HCC.

washout, consistent with multifocal multicentric HCC. The right portal vein was thrombosed and multiple pulmonary metastases were present. The liver, however, appeared to be non-cirrhotic (Figure 1).

The patient was initially treated with continuous 10% dextrose infusion, but remained persistently hypoglycemic. His hypoglycemic episodes usually occurred in the early morning, and surprisingly, he had very few symptoms of hypoglycemia. In view of his continuing hypoglycemic episodes, he was treated with frequent high complex carbohydrate meals. Oral prednisolone 40 mg once daily was started on day 5 of hospitalization. Following that, there were no further hypoglycemic episodes and he was discharged home. The patient was able to maintain his euglycemic state with the above regimen for the next 3 months. However, he developed cholestatic jaundice due to the compression effect of the tumor and sepsis secondary to cholangitis. Despite all conservative efforts, he succumbed to sepsis and died.

Table 1. Patient Laboratory Values and Normal Values

Laboratory Parameter	Patient Value	Normal Values
Serum bilirubin, mmol/L	110	3–24
AST, U/L	233	15–33
ALT, U/L	29	7–36
ALP, U/L	95	32–103
Albumin, g/L	35	37–52
Total calcium, mmol/L	2.66	2.10–2.60
Prothrombin time, sec	15.8	9.2–11.2
Hemoglobin, g/dL	11.8	14–16
HbsAg	Positive	Negative
Anti-Hbs	Negative	Negative
HbeAg	Negative	Negative
Anti-Hbe	Positive	Negative
HBV DNA, IU/mL	3.14	Not detectable
Serum cortisol, nmol/L	328	140–700
Serum cholesterol, mmol/L	10.6	<5.20
Ionic calcium, mmol/L	1.12	1.18–1.37
Parathyroid hormone, pmol/L	1.19	0.9–6.2
IGF2, ng/mL	300	288–736
Serum insulin, μIU/mL	0.70	1–30
C peptide, μIU/L	0.70	0.1–3.2
Glucagon, pg/ml	300	<100
Serum AFP, μg/L	763	<7.1

AFP = alpha fetoprotein; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; IGF2 = insulin growth factor.

Discussion

Two types of hypoglycemia are seen in HCC patients. Type A hypoglycemia occurs with rapidly growing tumors in markedly emaciated patients with significant muscle wasting. This is usually seen in the late stage of the disease, and the mechanism is attributed to the inability of the liver, largely replaced by a tumor, to satisfy glucose demands of the tumor and other tissues. These patients have suppressed insulin and c-peptide levels and increased glucagon, which is due to hypoglycemia-induced counter-regulatory mechanisms. Type B hypoglycemia, which represents only 5–13% of paraneoplastic hypoglycemia in HCC, manifests as severe hypoglycemia early in the course of the malignancy. It results from defective processing of the precursor to IGF2 (pro IGF2) by the hepatocytes. IGF2 circulates as smaller particles, which transfer more easily through capillary membranes and have more access to IGF1, IGF2, and insulin receptors, thereby causing increased glucose uptake.[3–5] Our case was possibly due to type A hypoglycemia, as the tumor was extensive and has almost replaced the liver parenchyma. The ratio of IGF2/IGF1 was greater than 10, which, along with low insulin and normal c-peptide, supported the fact that the hypoglycemia was non-islet cell tumor related. Non-islet cell hypoglycemia due to other causes such as multiple myeloma, colorectal malignancy, and lymphoma were ruled out.

Most of these patients are managed with intravenous glucose infusions. However, the majority of them do not respond and require a second modality to treat hypoglycemia. There are reports of management with cytoreduction following ethanol injection.[6] Transarterial chemoembolisation (TACE) has shown to improve 6-month survival in subjects of HCC and has been used in patients with HCC-induced hypoglycemia.[7] Use of frequent high-carbohydrate diet with corticosteroids has also been reported. Tharavanij et al reported long-term maintenance with dexamethasone 2 mg per day to maintain euglycemia in a patient with persistent hypoglycemic attacks despite prednisolone 40 mg per day.[8]

Steroids counter hypoglycemia by stimulating gluconeogenesis. In such hypoglycemia patients, IGF2 is found mainly as a binary complex with IGF-binding protein rather than forming the normal ternary complex with IGF binding protein 3 (IGFBP3) and acid labile subunit. Prednisiolone has been shown to accentuate IGFBP3 binding to acid labile subunit, thereby decreasing pro IGF2 levels.[9]

We kept our patient euglycemic on a combination of prednisolone 40 mg per day and 3–4 hourly frequent high-carbohydrate feeds. Cytoreduction was not considered due to the advanced stage of HCC, and the general condition of the patient made him an unsuitable candidate for surgery. Cytoreductive surgery has been studied in 26 patients with advanced HCC and has been shown to improve mortality and increase the median survival to 10 months. However, in-hospital procedure mortality is approximately 7.1%.[10] Other possible treatment options include continuous glucagon infusion and supra-physiological dose of growth hormone.[11,12]

HCC patients with paraneoplastic manifestations have decreased survival independent of tumor size and stage.[13] The diagnosis of HCC with paraneoplastic manifestation must be considered in a patient with chronic liver disease who presents with refractory hypoglycemia. The use of frequent, high complex carbohydrate meals and oral steroids are options for management of this condition.

Disclosures

Author contributions: M. Sharma collected the data, wrote the manuscript, and is the article guarantor. DN Reddy and TC Kiat edited the article.

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