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CASE REPORT

Recurrent Hypoglycemia in a Patient with Advanced Hepatocellular Carcinoma

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Abstract

Background: **Nonislet cell tumor hypoglycemia (NICTH) is a rare but serious complication of malignancy. Various causes of this type of hypoglycemia include excessive tumor burden resulting in destruction of the liver or adrenal glands, production of autoantibodies against insulin and tumoral production of incompletely processed IGF-2.**

Objectives: **Objective of this case report is to explore pathogenic mechanisms for hypoglycemia in hepatocellular carcinoma (HCC), and evidence-based treatment options.**

Methods: **We present a case of recurrent symptomatic hypoglycemia, despite conservative management, in a patient with extensive hepatocellular carcinoma.**

Results: **Patient developed recurrent hypoglycemia despite attempting treatment with therapies based on limited evidence available on literature review.**

Conclusion: **Management of hypoglycemia is usually challenging given patients are usually not good candidates for aggressive therapies given advanced cancer stage and/or poor general condition. Paraneoplastic hypoglycemia is usually a poor prognostic indicator. Experimental treatment options for hypoglycemia include steroids, glucagon and growth hormone.**

Keywords: Hypoglycemia, Hepatocellular, Carcinoma, Paraneoplastic

1. Introduction

Hypoglycemia is a known paraneoplastic manifestation of HCC occurring in up to ~25% of patients.[1] Management of hypoglycemia is usually challenging given these patients are usually not good candidates for aggressive therapies given advanced cancer stage and/or poor general condition (see Fig. 1).

2. Case report

A 50-year-old male presented with abdominal pain, distension, and poor appetite. He denied any nausea, vomiting and diarrhea. Patient's past medical history was significant for recent diagnosis of stage IV hepatocellular carcinoma and hepatitis B for which he was following as an outpatient with oncology and gastroenterology, respectively. He had received cycle 1 of immunotherapy with atezolizumab-bevacizumab, however it was discontinued given poor tolerance with worsening ascites, marked liver function test (LFT) elevations, vomiting, and elevated blood pressure (BP). Patient was also found to have a thrombus of portal vein and was being treated with dabigatran.

Physical examination revealed abdominal distension, however no tenderness to palpation. No palpable splenomegaly or other stigmata of chronic liver disease was noted. His cardiovascular and respiratory system findings were within normal limits.

Laboratory tests revealed low blood glucose 33 mg/dL (normal range 60−159 mg/dL), white blood cell (WBC) count 16.9 K/μL (normal range 3.7−11.1 K/μL), lactic acid 2.3 mmol/L (normal range 0.7−1.9 mmol/L), AST 1166 U/L (normal range 17−59 U/L), ALT 139 U/L (normal range 11−66 U/L), total bilirubin 4.4 mg/dL (normal range 0.2−1.3 mg/dL), albumin 2.9 g/dL (normal range 3.7−5.7 g/dL), creatinine 0.87 mg/dL (normal range <1.34 mg/dL) and normal estimated GFR >60 mL/min/1.73 m^2. Patient underwent therapeutic paracentesis with drainage of 1.5 L fluid. Ascitic fluid analysis revealed

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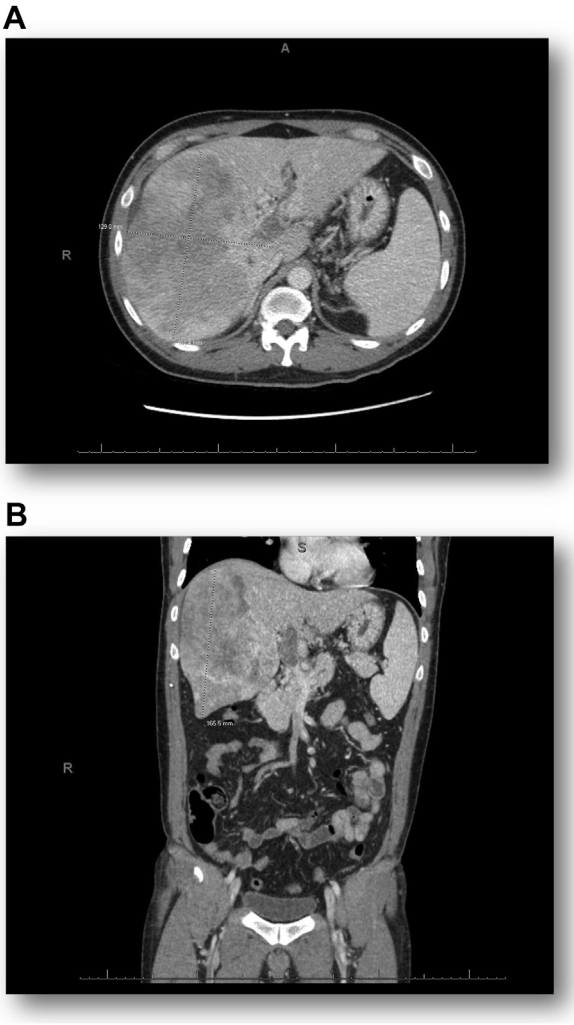

Fig. 1. (A, B) CT abdomen with contrast revealing right hepatic lobe 16 × 12 × 16 cm mass, extending into medial segment of left hepatic lobe.

WBCs 650/μL with polymorphonuclear leukocytes (PMN) of 31% not suggestive of spontaneous bacterial peritonitis, serum-to-ascites albumin gradient of 1.2 g/dL suggestive of portal hypertension. Patient was given dextrose 50% in water (D50W) 25 gm injection, 500 mL normal saline bolus. Patient was admitted to hospital and started on dextrose 5%–0.45% normal saline drip after which hypoglycemia resolved. Further blood work-up revealed serum cortisol 19.5 μg/dL (normal range 8–25 μg/dL), ACTH 30 pg/ml (normal range <46 pg/ml), insulin 0.6 μIU/mL (normal range 2–20 μIU/mL), C peptide 0.7 ng/mL (normal range 0.5–2 ng/mL), glucagon 110 pg/mL (normal range 8–57 pg/mL). CT abdomen and pelvis revealed 16.6 cm heterogeneous partially necrotic hepatic mass involving the entire right hepatic lobe, along with multiple small foci in the left hepatic lobe (Fig. 1).

Oncology was consulted who emphasized on poor prognosis given extensive liver disease. Patient was eventually discharged home with prednisolone 20 mg daily and advised to eat high carbohydrate meals every 2–4 h.

5 days after discharge, the patient was found confused at home by the family so EMS was called, and blood glucose level was extremely low at 24 mg/dL. He was given D50W 25 gm injection with return of consciousness back to baseline. Patient was brought to the emergency room (ER) for further evaluation. He reported that he had poor oral intake for a few days and has been having gradually worsening abdominal pain. While in ER, patient developed an episode of unresponsiveness when repeat blood glucose level was 27 mg/dL. He was again given D50W 25 gm and started on dextrose 5% (D5%) drip. He was readmitted to the hospital, and his blood glucose level remained stable at 80–100 mg/dL while on D5% drip. Endocrinology team was consulted and the presumptive diagnosis of hypoglycemia secondary to high tumor burden from HCC was made. Further work-up including measuring IGF-1 and IGF-2 levels was not done as it would not have significantly altered the management. Palliative team was consulted, and the patient opted for hospice and comfort measures only care. He was discharged home and again advised to maximize high sugar meals. Patient passed away peacefully at home two weeks after discharge.

3. Discussion

In patients with nonislet cell tumors, severe hypoglycemia usually occurs in epithelial, mesenchymal, or vascular cell types. Hepatocellular carcinomas are the most common[2,7] among tumors of epithelial origin and are usually large in size. Symptoms of hypoglycemia usually occur in a fasting state and include diaphoresis, lethargy, confusion and coma. Pathogenic mechanism for hypoglycemia for HCC is divided into two categories. The sheer tumor burden with high glucose demand, especially in emaciated patients, is itself responsible for hypoglycemia which appeared to be the cause in our patient based on abdomen CT findings along with low insulin and C-peptide levels. Second mechanism involves tumoral secretion of a precursor of IGF-2, known as pro-IGF 2 or "big" IGF-2 which causes increased glucose uptake (particularly in skeletal muscles) and inhibits glucose release from the liver.[2,3,5]

Acute management of hypoglycemia involves high carbohydrate drinks, intramuscular glucagon and intravenous dextrose pushes based on the patient's

mental status and severity of hypoglycemia. Patients with persistent hypoglycemia need continuous dextrose infusions. Mainstay of therapy is treatment of the underlying malignancy. Treatment options for HCC include chemotherapy, cytoreduction via surgery or radiotherapy.[1,5,11] Our patient did not tolerate chemotherapy and was not deemed to be a candidate for cytoreductive surgery. Ingestion of frequent high glucose meals decreases chances of recurrent episodes of hypoglycemia.[8] However, compliance with such meals is usually challenging given patient symptoms from the tumor itself or chemotherapy, including nausea, vomiting and poor appetite. Oral glucocorticoids have been studied and can be helpful in maintaining euglycemia.[5,6,9] Several glucocorticoids have been described in literature as a part of medical therapy, usually in doses equivalent to prednisone 30–60 mg per day. Glucocorticoids (GCs) are often used as a bridge therapy for definitive treatment. For patients with non-curable cancers, GCs have been shown to successfully decrease the need for intravenous dextrose infusions. However, GC efficacy might decrease with progression of tumor burden, requiring additional therapies.

NICTH is the second most common cause of tumor-related hypoglycemia following insulinoma.[12] The management of paraneoplastic hypoglycemia is challenging and is a poor prognostic indicator.[10] Tumor burden reduction is first line therapy but it's usually not possible to achieve in advanced stage disease. Experimental treatment options for hypoglycemia include steroids, glucagon and growth hormone.[4,5] Octreotide have been studied in multiple cases of NICTH, however usually failed to control the hypoglycemia.[13,14]

Conflict of interest

No conflict of interest.

Disclaimers

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