

## A Case of Advanced Hepatocellular Carcinoma Presenting with Hypoglycemic Coma

Attila ÖNMEZ,<sup>a</sup>  
 Kürşad ÖNEÇ,<sup>a</sup>  
 Serkan TORUN,<sup>a</sup>  
 Ahmet NALBANT,<sup>b</sup>  
 Onur EŞBAH<sup>a</sup>

<sup>a</sup>Department of Internal Medicine,  
 Düzce University Medicine Faculty,  
 Düzce

<sup>b</sup>Department of Internal Medicine,  
 Sakarya University Medicine Faculty,  
 Sakarya

Received: 13.01.2018

Received in revised form: 27.02.2018

Accepted: 28.02.2018

Available online: 17.09.2018

Correspondence:

Attila ÖNMEZ  
 Düzce University Medicine Faculty,  
 Department of Internal Medicine,  
 Düzce, TURKEY  
 attilaonmez@gmail.com

**ABSTRACT** Hypoglycemia is often associated with pancreatic tumors (eg, insulinoma). However, the association of paraneoplastic hypoglycemia with non-islet cell tumors is less frequent. In a patient who has not yet been diagnosed with hepatocellular carcinoma, it is a quite rare case that the first sign is coma due to hypoglycemia. Following is a 76-year-old male patient who has no disease history except essential hypertension and chronic obstructive pulmonary disease and has no symptom caused by prior hepatic lesion or failure. Below, it is aimed to present that how the patient's hypoglycaemic episodes were controlled in the follow-up period and to present the diagnosis process of advanced hepatocellular carcinoma which was diagnosed after several application to emergency room with a severe hypoglycemic coma due to recurrent symptomatic hypoglycemia lasting few months.

**Keywords:** Hepatocellular carcinoma; hypoglycemia; non-islet cell tumor

Hypoglycemia may develop paraneoplastically and the patients with hepatocellular carcinoma (HCC) may develop hypoglycemia during the disease course.<sup>1</sup> However, it is very rare to see a patient presenting with hypoglycemia who has not yet been diagnosed with HCC. Generally, paraneoplastic syndrome develops in 43.6% of HCC patients. Hypoglycemia, however, develops in only less than 5% of HCC patients during the disease course.<sup>2,3</sup> Here we present a patient admitted to our emergency department with unconsciousness associated with severe hypoglycemia who was subsequently diagnosed with HCC as a result of the investigation on the etiology of hypoglycemia.

### CASE REPORT

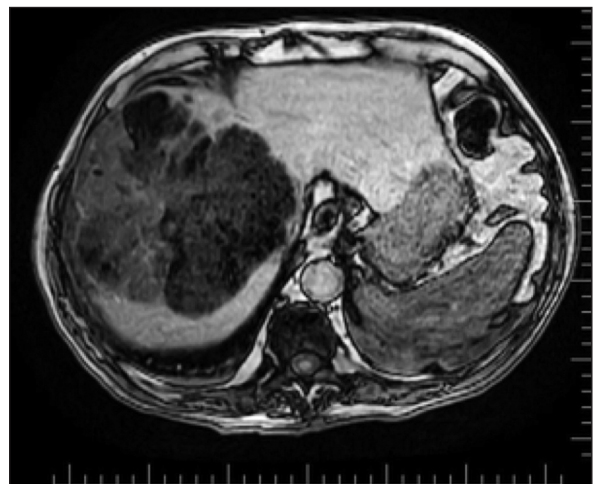
The 76-year-old male patient reported to experience occasional cold sweats, fatigue and blackouts for the last 1 month. He reported that his symptoms were relieved by eating. The patient had lost 10 kg over approximately 4 months and his past medical history revealed only hypertension and no medications other than anti-hypertensives. The patient was brought to our emergency department by ambulance due to loss of consciousness that developed in the morning hours and his blood glucose level was measured as 24 mg/dl. A 50% dextrose infusion was commenced and the patient rapidly

responded to infusion. The patient was hospitalized in our department for investigation of the etiology of hypoglycemia. His physical examination revealed no findings other than hepatosplenomegaly palpable 4 cm below the costal margins. The patient did not have diabetes or history of antidiabetic treatment and his laboratory test results were as follows: fasting blood glucose, 40 mg/dl (80-110); HbA1C, 5.1(4-6); C-peptide, 0.5  $\mu$ U/mL (0.9-6  $\mu$ U/mL); Insulin, 3  $\mu$ IU/mL (4-25  $\mu$ IU/mL); AST, 117 IU/L; ALT, 67 IU/L (<50 IU/L); ALP, 283  $\mu$ /L (7-32  $\mu$ /L); GGT, 442  $\mu$ /L(7-32  $\mu$ /L); HBsAg, negative; anti-HBs, negative; anti-HCV, negative. Abdominal ultrasound revealed a hyperechogenic solid mass of 119x112 mm with irregular borders in the right lobe of the liver. AFP level was > 363 ng/ml (normal range, 0-8 ng/ml). Upper abdominal dynamic magnetic resonance imaging (MRI) revealed a 17x12 cm lobule contoured mass with cystic necrotic areas in the right lobe of the liver, radiologically consistent with HCC, and liver biopsy was performed (Figure 1). The biopsy result was reported as HCC. The blood glucose level of the patient remained in the range of 50-70 mg/dl despite 20-50% dextrose infusion and was observed to drop below 30 mg/dl 3-4 times in a day. Since the patient continued to have intermittent hypoglycemia despite dextrose infusion, a frequent-interval high-carbohydrate diet and treatment with prednisolone 40 mg/day were initiated and dextrose infusion was tapered off. Hypoglycemia was not observed at the subsequent controls. The patient was referred to medical oncology department while on oral steroid treatment. Oral capecitabine treatment was planned for the patient who was not eligible for surgery and local treatments. Hypoglycemic episodes continued despite 40 mg/gün prednisolone in clinical follow-up. Therefore for normoglycemia 20% dextrose was added to treatment. The patient died 4 months after diagnosis without oral capecitabine treatment.

## DISCUSSION

Hypoglycemia, frequently encountered in patients with pancreatic tumors such as insulinoma, is very

infrequent in non-pancreatic cancers such as HCC. Paraneoplastic Syndromes including erythrocytosis, hypercalcemia, diarrhea, various skin findings and hypoglycemia may be seen in association with HCC and these findings are associated with a poor prognosis.<sup>4</sup> Our patient's low levels of c-peptide and insulin excluded the possibility of insulinoma and support of non-pancreatic cancer. Hypoglycemia seen during the course of HCC is generally mild to moderate and severe hypoglycemia may rarely be observed as a result of the high metabolic needs of large tumors. HCC-associated hypoglycemia is divided into two types: Type A and Type B. Type A hypoglycemia is mild to moderate. It occurs in markedly debilitated patients and is caused by the inadequacy of gluconeogenesis to maintain fasting glucose at required levels due to the increased metabolic need of rapidly growing tumors. These patients have a short survival and poor prognosis. Type B hypoglycemia is more severe and can be difficult to control. In Type B, hypoglycemia attacks accompanied with conditions ranging from severe consciousness alterations to coma can be seen. These tumors frequently secrete incompletely processed insulin-like growth factor II (IGF-II), a hormone capable of activating insulin receptors and causing hypoglycemia. Tumors secreting incompletely processed big IGF-II are characterized by an increased IGF-II to IGF-I ratio.<sup>5</sup> The glucose



**FIGURE 1:** Dynamic contrast-enhanced of the upper abdomen MR showing large HCC. HCC: Hepatocellular carcinoma.

lowering effect of IGFs is 10 times lower than that of insulin.<sup>6</sup> Although we were unable to measure IGF-II levels in our hospital and the clinical picture of our patient was more consistent with Type B hypoglycemia. Due to frequent hypoglycemia attacks despite continuous dextrose infusion, prednisolone 40 mg/day was initiated to lower IGF-2 levels.<sup>7</sup> The patient was initiated on a frequent-interval high-carbohydrate diet. Subsequent tests revealed blood sugar levels within the normal range. Rare causes of hypoglycemia should be considered in a patient who does not have diabetes or not use any antidiabetic medication.

#### **Informed Consent**

Written informed consent was obtained from patients who participated in this study.

#### **Source of Finance**

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

#### **Conflict of Interest**

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

#### **Authorship Contributions**

**Idea/Concept:** Attila Onmez, Kürşad Oneç; **Control/Supervision:** Onur Eşbah, Ahmet Nalbant; **Literature Review:** Serkan Torun; **Writing the Article:** Attila Önmez; **Critical Review:** Serkan Torun.

## REFERENCES

1. Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumor hypoglycemia: a clinical review. *J Clin Endocrinol Metab* 2014;99(3):713-22.
2. Eastman RC, Carson RE, Orloff DG, Cochran CS, Perdue JF, Rechler MM, et al. Glucose utilization in a patient with hepatoma and hypoglycemia. Assessment by a positron emission tomography. *J Clin Invest* 1992;89(6):1958-63.
3. Tietge UJ, Schöfl C, Ocran KW, Wagner S, Böker KH, Brabant G, et al. Hepatoma with severe non-islet cell tumor hypoglycemia. *Am J Gastroenterol* 1998;93(6):997-1000.
4. Luo JC, Hwang SJ, Wu JC, Lai CR, Li CP, Chang FY, et al. Clinical characteristics and prognosis of hepatocellular carcinoma patients with paraneoplastic syndromes. *Hepatogastroenterology* 2002;49(47):1315-9.
5. Gordon P, Hendricks CM, Kahn CR, Megyesi K, Roth J. Hypoglycemia associated with non-islet-cell tumor and insulin-like growth factors. *N Engl J Med* 1981;305(24):1452-5.
6. de Groot JW, Rikhof B, van Doorn J, Bilo HJ, Alleman MA, Honkoop AH, et al. Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. *Endocr Relat Cancer* 2007;14(4):979-93.
7. Thipaporn T, Bubpha P, Varaphon V. Hepatocellular carcinoma with persistent hypoglycemia: successful treatment with corticosteroid and frequent high carbohydrate intake. *J Med Assoc Thai* 2005;88(12):1941-6.