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A Case of Hepatocellular Carcinoma Diagnosed with Resistant Hypoglycemia

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Abstract

Background: There are many causes of the etiology of hypoglycemia. Hypoglycemia is very rare in individuals without diabetes. Although it can accompany islet cell malignancies such as insulinoma, it is much less common in solid organ tumors such as hepatocellular carcinoma as a component of paraneoplastic syndrome. **Case Presentation:** We present a 58-year-old male patient with no additional disease, who was examined for resistant hypoglycemia and was diagnosed as having hepatocellular carcinoma radiologically for the first time. Insulin level measured when serum glucose was 44 mg/dl: 0.4 μU/mL, c-peptide level: 0.355 ng/mL detected. Viral serology was found to be positive for HbsAg. In dynamic magnetic resonance imaging, showing continuity in segments 6 - 7 and 8 in the right lobe, and also partially towards 5, heterogeneous hyperintense in T2 A's, diffusion-limiting, heterogeneous contrast enhancement in postcontrast series, cystic-necrotic in the center. The alpha-fetoprotein level was 60,500 ng/mL. **Conclusion:** Paraneoplastic hypoglycemia due to underlying malignancies should be considered in patients presenting with hypoglycemia.

Keywords

Hepatocellular Carcinoma, Resistant Hypoglycemia

1. Introduction

There are many causes of the etiology of hypoglycemia. It is often seen as a side effect of the treatment of diabetes. The most common cause of hypoglycemia is sulfonylurea or exogenous insulin usage as a treatment of diabetes. However, organ failure, sepsis, alcoholism, and gastric bypass are also common etiologies. Hypoglycemia is very rare in individuals without diabetes. Although it can ac-

company islet cell malignancies such as insulinoma, it is much less common in solid organ tumors such as hepatocellular carcinoma as a component of paraneoplastic syndrome. It constitutes approximately half paraneoplastic hypoglycemia due to non-islet cell tumors, whereas HCC constitutes only one-fourth of hypoglycemia. Islet tumors of the pancreas cause hypoglycemia with excessive insulin production. Extra pancreatic (non-islet) tumors have hypoglycemia with concurrent low insulin levels. Proposed mechanisms for hypoglycemia of extrapancreatic tumors include increased and preferential glucose utilization by tumors, failure of glycogenolysis, and decreased gluconeogenesis [1]. Hepatocellular cancer (HCC) is the most common primary tumor of the liver and accounts for 80% - 90% of primary liver cancers. Diagnosis of HCC is a difficult case, generally; serum markers, one or more imaging modalities, and histological confirmation are required. Delays in diagnosis can occur because of the absence of pathognomonic symptoms for HCC and the large functional reserve of the liver. The paraneoplastic syndrome can be observed especially in HCC cases with large diameters and high alpha-fetoprotein (AFP) values and it has been associated with poor prognosis [2] [3]. It has been reported that hypoglycemia occurs in approximately 4% - 27% of patients with a diagnosis of HCC. HCC usually presents with complaints of right upper quadrant pain, distention, icterus, and weight loss. Hypoglycemia is a rare clinical presentation [4]. Non-islet cell tumor hypoglycemia (NICTH) presents as recurrent or constant hypoglycaemic episodes and mostly affects elderly patients with advanced tumors [5]. Occasionally, these hypoglycaemic episodes can predate the diagnosis of the underlying tumor [6]. A 58-year-old male patient diagnosed as having hepatocellular carcinoma with resistant hypoglycemia was reported in this paper. Written informed consent was obtained from the patient participating in this study.

2. Case Presentation

A 58-year-old male patient was admitted to the psychiatry clinic with the prediagnoses of dissociative disorder and conversion disorder due to headache, dizziness, and disorganized behavior for 2 months. It was discovered that the patient had hypoglycemia in the follow-ups. Due to persistent hypoglycemia despitedextrose infusion, further investigations were conducted. He had no previous history of systemic disease and no history of drug use. Upon physical examination, his general condition was moderate, conscious, oriented, and cooperative. His blood pressure was 140/90 mmHg, heart rate was 85/minute and body temperature was 36.2˚C. The liver was palpated 4 cm below the right rib. In laboratory examinations, complete urinalysis was normal. In the complete blood count, white blood cell count was 6.910/mm^3, hemoglobin 14.6 g/dL, and platelet count was 251.000/mm^3. Alanine aminotransferase: 83 U/L (N: 0 - 40 U/L) Calcium: 8.3 mg/dL, albumin was 4.74 g/dL. Serum electrolytes were normal. Prothrombin time and activated partial thromboplastin time were normal. C-reactive protein was 10 mg/dL, sedimentation was 19 mm/hour. Fingertip

glucose was 29 mg/dL. Insulin, c-peptide, cortisol, and serum glucose were studied at the time of hypoglycemia. Insulin level measured when serum glucose was 44 mg/dl: 0.4 μU/mL (N: 1.9 - 23 μU/mL), c-peptide level: 0.355 ng/mL (N: 1.1 - 4.4 ng/mL), cortisol: 12.2 ug/dL detected (Table 1). An Adrenocorticotropic hormone (ACTH) stimulation test was performed to rule out the diagnosis of adrenal insufficiency. Any cortisol level was found to be >18 ug/dL. Adrenal insufficiency was ruled out.

Considering that the patient may have paraneoplastic hypoglycemia, thorax and abdomen imaging were performed for solid tumors. Thorax computed tomography was unremarkable. In dynamic magnetic resonance imaging, the liver was approximately 132 × 124 × 120 mm in size in its widest part, showing continuity in segments 6 - 7 and 8 in the right lobe, and also partially towards 5, heterogeneous hyperintense in T2 A's, diffusion-limiting, heterogeneous contrast enhancement in postcontrast series, cystic-necrotic in the center (Figure 1). A

Table 1. Patient's laboratory values.

White blood cell	6.910/mm^3	Alanine aminotransferase	83 U/L
Hemoglobin	14.6 g/dL	Calcium	8.3 mg/dL
Thrombocyte	251.000/mm^3	Albumin	4.74 gr/dL
C reactive protein	10 mg/dL	Sedimentation rate	19 mm/saat
Glucose	44 mg/dL	Cortisol	12.2 ug/dL
İnsulin	0.4 μU/mL	C-peptide	0.355 ng/mL
HbsAg*	Positive (3762 S/Co)	Alpha-fetoprotein	60,500 ng/mL

*HbsAg: hepatitis B surface antigen.

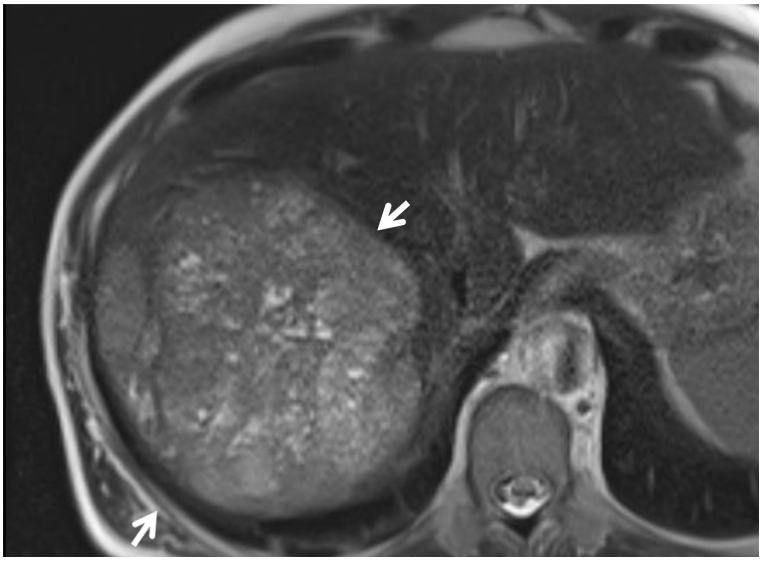

Figure 1. The mass lesion in the liver compatible with HCC.

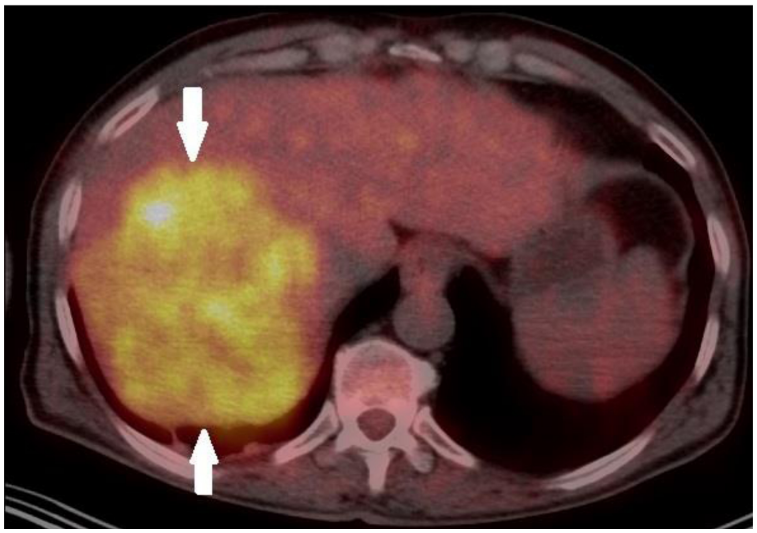

Figure 2. A hypermetabolic lesion with heterogeneous increased FDG uptake was observed in the liver.

space-occupying lesion image with components was observed. The pancreas is of normal size and normal localization; its internal structure is smooth and its outer contours are lobulated. A positron emission tomography (PET/CT) with fluorine-18-fluorodeoxyglucose (18-FDG) was performed. A hypermetabolic lesion with heterogeneous increased FDG uptake was observed in the liver (**Figure 2**). The alpha-fetoprotein level was 60,500 ng/mL (N: 0 - 5.8 ng/mL). Biopsy was not performed on the patient since the patient's current imaging methods and high AFP level were compatible with HCC. Viral serology was found to be positive for HbsAg. HBV DNA was 2556 IU/mL and entecavir 1 mg/day was started. IGF-II measurement was attempted, but the assay is not available in Turkey. The patient required treatment with dextrose in continuous infusion to achieve normal blood glucose and to remain symptom-free. The patient was started on 2 × 20 mg methylprednisolone treatment. Then, the dose was gradually reduced and steroid treatment was implemented at the physiological dose. It was accepted as inoperable by the surgical oncology council. The patient underwent transarterial chemoembolization. Octreotide was given to the patient whose hypoglycemia attacks continued after transarterial chemoembolization. There was no improvement in blood sugars with octreotide treatment either. The patient underwent chemoembolization with antineoplastic drug together with lipiodol, twice in total, by preserving the hepatic artery branches feeding the normal liver parenchyma. In control films, it was observed that the vascularization of the mass decreased significantly and intra-mass stagnation developed. No complications were observed after the procedures. Lastly, 400 mg/day sorafenib treatment was started in the patient with resistant hypoglycemia. The patient is still receiving sorafenib and physiological doses of prednisolone. Dextrose infusion is given to achieve normal blood sugar. Response to treatment will be evaluated 2 months later by control PET-CT and whether there is a decrease in hypoglycemia attacks.

3. Discussion

High glucose use in patients with decreased gluconeogenesis plays an important role in the pathophysiology of hypoglycemia in non-islet cell malignancies such as HCC. This type of NICTH (type A) is observed in late-stage HCC when the tumoral burden is high and hepatic destruction is extensive [7]. In such cases, insulin and C-peptide levels are found to be low [8]. While glucose level was low in our case, insulin and C-peptide levels measured were significantly low. Another cause of paraneoplastic hypoglycemia is increased glucose utilization due to stimulation of insulin receptors and excessive production of tumoral insulin-like growth factor-2 (IGF-2). In type B NICTH, there is increased tumor secretion of incompletely processed IGF-2 (pro-IGF-2), which is poorly metabolized due to defective hepatocytes in cirrhosis. This defective pro-IGF-2 is smaller, crosses the capillary membranes easier, and stimulates more insulin receptors throughout the body than normal IGF-2. This occurs early in liver disease and is characterized by overwhelming tissue glucose uptake and severe, persistent hypoglycemia [9] [10]. In our patient, clinically due to persistent hypoglycemia, it was thought to be Type B in the foreground. However, high tumor burden, low insulin, and c-peptide levels were observed to be compatible with Type-A.

About 90% of patients with HCC have cirrhosis, usually due to chronic alcohol use and chronic viral hepatitis B and C. HCC may occur before cirrhosis develops in some cases of chronic hepatitis B [11]. The emergence of hepatocellular carcinoma before the development of cirrhosis in our patient is another important feature of the case. Treatment options such as frequent nutrition, parenteral dextrose infusion, corticosteroids, glucagon, and growth hormone are used successfully in the treatment of hypoglycemia [12]. Dietary advice regarding frequent intake of complex carbohydrates is beneficial. Steroids are the most used drug to treat HCC-associated hypoglycemia. The therapeutic effect is based on hepatic gluconeogenesis stimulation and peripheral glucose intake inhibition. Furthermore, steroids can reduce "big" IGF-2 levels, whether it is through a reduction of production or promoting a maturation process of pro-IGF-2 and normal complex formation [13]. The beneficial effects of corticosteroids are reversible when treatment is withdrawn or when the dose declines below a critical threshold [5]. The combination of corticosteroids and GH has also been proposed as a palliative treatment option [14]. GH stimulates hepatic gluconeogenesis and glycogenolysis as well as the production of IGF-binding protein-3 and acid-labile subunit [15]. Somatostatin analogs such as octreotide generally do not restore blood glucose levels to normal in non-islet cell tumor hypoglycemia. In our patient, blood glucose levels did not return to normal after octreotide treatment. We administered parenteral dextrose infusion and corticosteroid treatment to the patient. Thus, we prevented complications that may arise from hypoglycemia in the period until the initiation of the underlying HCC treatment. The main treatment for hypoglycemia due to paraneoplastic syndrome is to treat the underlying malignancy and appropriate surgical resection is the most effec-

tive treatment option. Chemotherapy, embolization, and radiotherapy are other treatment methods [16]. Since our patient was considered inoperable, transarterial chemoembolization was performed and sorafenib treatment was started. Consequently, paraneoplastic hypoglycemia due to underlying malignancies should be considered in patients presenting with hypoglycemia.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Bergman, P.J. (2001) Paraneoplastic Syndromes. In: Withrow, S.J., MacEwen, E.G., Eds., *Small Animal Clinical Oncology*, 3rd Edition, Saunders, Philadelphia, 35-53.

[2] Luo, J.C., Hwang, S.J., Wu, J.C., Lai, C.R., Li, C.P., Chang, F.Y., *et al.* (2002) Clinical Characteristics and Prognosis of Hepatocellular Patients with Paraneoplastic Syndromes. *Hepatogastroenterology*, **49**, 1315-1319.

[3] Saigal, S., Nandeesh, H.P., Malhotra, V. and Sarin, S.K. (1998) A Case of Hepatocellular Carcinoma Associated with Trouble Some Hypoglycemia: Management by Cytoreduction Using Percutaneous Ethanol Injection. *American Journal of Gastroenterology*, **93**, 1380-1381. https://doi.org/10.1111/j.1572-0241.1998.427_h.x

[4] Tangkijvanich, P., Thong-Ngam, D. and Kullavanijaya, P. (2000) Fibrolamellar Hepatocellular Carcinoma in a Thai Man Who Presented with Hypoglycemia: Case Report and Review of the Literature. *Journal of the Medical Association of Thailand*, **83**, 809-816.

[5] Teale, J.D. and Wark, G. (2004) The Effectiveness of Different Treatment Options for Non-Islet Cell Tumorhypoglycemia. *Clinical Endocrinology*, **60**, 457-460. https://doi.org/10.1111/j.1365-2265.2004.01989.x

[6] Nayar, M.K., Lombard, M.G., Furlong, N.J., McNulty, S.J., Hardy, K.J. and Vora, J. (2006) Diagnosis and Management of Non-islet Cell Tumorhypoglycemia: Case Series and Review of the Literature. *Endocrinologist*, **16**, 227-230. https://doi.org/10.1097/01.ten.0000226008.02412.0b

[7] Forde, J.J., Ewelukwa, O., Brar, T. and Cabrera, R. (2017) Intractable Fasting Hypoglycemia as a Manifestation of Hepatocellular Carcinoma. *Case Reports in Hepatology*, **2017**, Article ID: 7465025. https://doi.org/10.1155/2017/7465025

[8] Fukuda, I., Hizuka, N., Ishikawa, Y., Yasumoto, K., Murakami, Y., Sata, A., Morita, J., Kurimoto, M., Okubo, Y. and Takano, K. (2006) Clinical Features of Insulin-Like Growth Factor-II Producing Non-Islet-Cell Tumor Hypoglycemia. *Growth Hormone & IGF Research*, **16**, 211-216. https://doi.org/10.1016/j.ghir.2006.05.003

[9] Nikeghbalian, S., Bananzadeh, A. and Yarmohammadi, H. (2006) Hypoglycemia, the First Presenting Sign of Hepatocellularcarcinoma. *Saudi Medical Journal*, **27**, 387-388.

[10] Yeung, R.T. (1997) Hypoglycemia in Hepatocellularcarcinoma: A Review. *Hong Kong Medical Journal*, **3**, 297-301.

[11] Tang, A., Hallouch, O., Chernyak, V., Kamaya, A. and Sirlin, C.B. (2018) Epidemiology of Hepatocellular Carcinoma: Target Population Forsurveillance and Diagnosis. *Abdominal Radiology*, **43**, 13-25. https://doi.org/10.1007/s00261-017-1209-1

[12] Hoff, A.O. and Vassilopoulou-Sellin, R. (1998) The Role of Glucagon Administra-

tion in the Diagnosis and Treatment of Patients with Tumor Hypoglycemia. *Cancer*, **82**, 1585-1592.

[13] Thipaporn, T., Bubpha, P. and Varaphon, V. (2005) Hepatocellular Carcinoma with Persistent Hypoglycemia: Successful Treatment with Corticosteroid and Frequent High Carbohydrate Intake. *Journal of the Medical Association of Thailand*, **88**, 1941-1946.

[14] Gullo, D., Sciacca, L., Parrinello, G., Tomaselli, L. and Vigneri, R. (1999) Treatment of Hemangiopericytoma-Induced Hypoglycemia with Growth Hormone and Corticosteroids. *The Journal of Clinical Endocrinology & Metabolism*, **84**, 1758-1759. https://doi.org/10.1210/jcem.84.5.5677-1

[15] Baxter, R.C., Holman, S.R., Corbould, A., Stranks, S., Ho, P.J. and Braund, W. (1995) Regulation of the Insulin-Like Growth Factorsand Their Binding Proteins by Glucocorticoid and Growthhormone in Non-islet Cell Tumor Hypoglycemia. *The Journal of Clinical Endocrinology & Metabolism*, **80**, 2700-2708. https://doi.org/10.1210/jcem.80.9.7545698

[16] Kalebi, A.Y., Hale, M.J., Wong, M.L., Hoffman, T. and Murray, J. (2009) Surgically Cured Hypoglycemia Secondary to Pleural Solitary Fibrous Tumor: Case Report and Update Review on the Doege Potter Syndrome. *Journal of Cardiothoracic Surgery*, **4**, 45.