Case Report

Hepatocellular Carcinoma with Persistent Hypoglycemia: Successful Treatment with Corticosteroid and Frequent High Carbohydrate Intake

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The authors report a 36-year old man, who had hepatocellular carcinoma with lung metastasis and presented with coma from hypoglycemia. Serum insulin and c-peptide level were suppressed. Serum cortisol level was appropriately increased during the event. He needed glucose at least 3.65 mg/kg/min intravenously to maintain euglycemia. Cytoreduction of the tumor was not possible due to advanced stage disease. The patient had several episodes of morning hypoglycemia, despite having oral prednisolone 40 mg/day. However, glucose requirement was decreased after steroid usage.

Normoglycemia was accomplished by adjunctive frequent high carbohydrate meal. Prednisolone was replaced to a lower dosage dexamethasone (2 mg/day). He did not have recurrent hypoglycemia as long as he had a midnight snack. Articles regarding hypoglycemia in HCC were extensively reviewed.

Keywords: *Hepatocellular carcinoma, Hypoglycemia, Corticosteroid, Carbohydrate*

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Hypoglycemia in non-islet cell tumor has been well described since 1980[1]. Among these tumors, there are mesenchymal, adrenocortical, gastrointestinal tumor and lymphoma. Hepatocellular carcinoma (HCC) is the second most common cause. Paraneoplastic manifestation of hypoglycemia is common in a large abdominal mass. The patients were usually older than 30 years. The absence of inappropriate circulating insulin is a hallmark of these tumors. Ectopic insulin secretion is extremely rare[2].

The prevalence of hypoglycemia in HCC ranged from 4 to 27%[3]. Refractory hypoglycemia is troublesome. The authors reported a Thai-male patient with HCC and recurrent episodes of severe hypoglycemia. He was treated with steroid and frequent high carbohydrate meals. Treatment modality was reviewed.

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Case Report

A 36-year old man presented with epigastric pain, abdominal discomfort and weight loss of 3 kilograms in 2 months. He had been an alcoholic and smoked for 20 years. He denied blood transfusion and illicit drug. He had chronic hepatitis B viral infection for 1 year with no treatment. Physical examination revealed hepatomegaly with nodular surface and hard consistency. Liver span was 14 cm. Abdominal bruit was negative. He was anicteric with no chronic liver disese stigmata or ascites. Complete blood count was normal. Liver function test showed total bilirubin 0.85 mg/dl, direct bilirubin 0.4 mg/dl, AST 127 U/L, ALT 100 U/L, ALP 429 U/L (normal range 50-136), albumin 3.6 gm/dl, globulin 4.4 gm/dl. Prothrombin time was normal. Serum alpha-fetoprotein was 81,045 ng/ml (normal 0-15). HBsAg and HBeAg were positive. CT scan of the upper abdomen showed hepatomegaly, multiple low-density mass almost entire liver with sparing segment 7, left portal vein occlusion and main portal vein partial

occlusion. There were no ascites, paraaortic lymphadenopathy nor splenomegaly. Chest X-ray revealed bilateral multiple pulmonary nodules.

The patient was diagnosed with hepatocellular carcinoma based upon huge liver mass and elevated serum alpha-fetoprotein level. Liver biopsy was not done. He was palliatively treated due to extensive stage of malignancy. He was doing well until 1 month after diagnosis, when he was found unconscious in the morning. His vital signs were normal. Neurological examination showed semicoma with no localizing signs. Initial plasma glucose was 26 mg/dl. After glucose infusion, he regained consciousness. His liver function test was stable. There was no azotemia. Serum cortisol level (electrochemiluminescence immunoassay) during hypoglycemia was appropriate (562.5 nmol/L). Serum insulin and c-peptide level (chemiluminometric assay) were suppressed (2.6 IU/ml and 1.8 ng/ml respectively). He needed at least 3.65 mg/kg/min of glucose infusion to maintain normoglycemia, especially during the night. Cytoreduction therapy was not done due to advanced tumor stage. Although the patient was treated with prednisolone 40 mg/day, he still had intermittent mild hypoglycemia at night and in the early morning. The authors solved this problem by having him take a midnight snack and frequent high carbohydrate meals during the day (every 4 hours). However, two weeks after the hospital discharge, he was admitted comatose in the early morning because he did not wake up to have a snack that night. The authors decided to change prednisolone to dexamethasone 2 mg/day expecting its long half-life effect. He has not had a hypoglycemic attack until now (1 month) as long as he had a meal at midnight.

Discussion

HCC is one of the most common neoplasms worldwide. It is often diagnosed in the background of chronic liver disease such as cirrhosis. There is strong association with chronic hepatitis B virus, chronic hepatitis C virus and alcoholic cirrhosis. In most cases, HCC occurs in cirrhotic patients. A significant percentage of HBV-related HCCs occur in the absence of cirrhosis, suggesting a specific role for HBV in the development of HCC. HBV integrates into the host genome in almost all patients with chronic hepatitis. Viral integration almost invariably precedes the development of HCC. With better surveillance strategies, most HCCs will be identified during the asymptomatic stage. However, other patients have presented with advanced HCC. The clinical manifestations of advanced HCC are protean including decompensated cirrhosis, tumoral symptoms, acute abdominal catastrophe, cholestasis, fever of unclear etiology, paraneoplastic phenomena, and metastasis.

Liver biopsy for histopathology remains the accurate method to diagnose HCC. However, the risk for tumor seeding was about 3.4% to 5.1%[4,5]. Criteria for diagnosis of HCC in this patient are one imaging study with hypervascularization and high serum alpha-fetoprotein level of more than 400 ng/ml

Paraneoplastic syndrome of HCC is not uncommon. In a Nigerian patient series[6], there was 24.6% hypercholesterolemia, 27.7% hypoglycemia, 10% hypercalcemia and only 1% erythrocytosis. Other manifestations indicating poor prognostic factors, besides Child-Pugh's score C, were ineligibility for active treatment, serum alpha-fetoprotein level > 10,000 ng/ml and main portal vein thrombosis. Median survival in HCC with paraneoplastic manifestation was 36 days. Erythrocytosis tended to have longer survival than hypoglycemia and hypercalcemia.

Two types of hypoglycemia in HCC have been described by Mc Fadzean AJS[7]. Type A is a poorly differentiated tumor with mild to moderate severity of hypoglycemia that occurs in the late stage of the disease. The less common type B tumor is a well-differentiated slow growing tumor in which severe hypoglycemia occurs in early stages of the disease. In the present patient, severe hypoglycemia occurred in the late stage of the disease.

The cause of hypoglycemia in HCC is either from impaired gluconeogenesis due to decompensated liver (glucose underproduction) or high big insulin-like growth factor II (IGF-II) level produced by tumors. Big IGF-II is from a defect in processing pro IGF-II to 7.5 kDa IGF-II (normal IGF). Normally 75% of IGFs are formed in ternary complexes. This complex compounds of IGF, IGFBP-3, and acid labile α-subunit. Big IGFII-IGFBP-3 complex cannot bind with acid labile α-subunit. As a result, smaller complex facilitates transport across the capillary membrane and increases access to target tissues. Big IGF-II binds IGF-I receptor and inhibits pituitary GH secretion. It leads to decreased growth hormone (GH) and insulin like growth factor binding protein-3 level (IGFBP-3)[8]. Diagnosis of hypoglycemia from this mechanism is proved by demonstration of suppressed 7.5 kD IGF-II and elevated big IGF-II in serum whereas total IGF-II maybe within normal range[9].

The presented patient did not have signs of liver decompensation. He needed glucose 3.65 mg/kg/

Table 1. Patient characteristics, management of hypoglycemia and results of treatment

Ref.	Patient characteristics	Tumor management	Hypoglycemic treatment	Results of hypoglycemic events and mortality
3	24 years old female HCC	Percutanous ehtanol injection		Less hypoglycemic attack and decreased glucose requirement
8	74 years old female mesenchymal tumor	NA	-GH + octreotide +bendrofluazide	-not improved
			-GH+prednosolone30mg/d +bendrofluazide	-no hypoglycemia-death 9 months after hypoglycemia
9	22 years old male HCC	-TOCE -Systemic chemotherapy	-prednisolone 50 mg/day	-Not improved
			-glucagon	-transient improved
			-enteral tube feeding	-Could not tolerate -Death in 3 months after HCC diagnosis
13	6 cases of HCC	NA	-Low dose GH infusion	-not improved
			-High dose GH infusion	-no significant decrease in glucose requirement
14	36 years old female HCC	NA	-prednisolone alone	-morning hypoglycemia
			-prednisolone + GH	-no hypoglycemia -death 6 months after HCC diagnosis
15	4 non-islet cell tumor patients (HCC, colon, meningeal sarcoma, hemangiopericytoma)		-glucagon stimulation test and glucagon infusion	Less hypoglycemia in cases with increased plasma glucose after glucagon stimulation test
16	4 African HCC patients aged 24-50 year old	NA	Somatostatin analogue intravenous infusion	Ineffective
18	1 HCC patient	Tumor resection		Improved
19	64 years old male HCC patient	Intrahepatic Adriamycin	-GH 2 units sc OD	-decrease hypoglycemic attack
			-Octreotide	-no hypoglycemia -death 26 months after diagnosis
20	38 years old male neurofibrosarcoma	NA	-GH 0.1 mg/kg IM bid	-transient improved
			- glucagon infusion 0.31mg/hr	-no hypoglycemia

Abbreviation; NA= not available, HCC=Hepatocellular carcinoma, TOCE=transhepatic oily chemoembolization

min, exceeding normal glucose production rate, to maintain euglycemia. This is suggesting glucose overutilization was the cause of hypoglycemia. The insulin and C-peptide level were suppressed. Unfortunately, the IGF-II or big IGF-II level could not be measured since it would be the most probable mechanism. Richard C. Eastman, et al demonstrated circulating big IGF-II is partial insulin agonist. Positron emission tomography showed predominantly increase in skeletal muscle glucose uptake and suppression of hepatic glucose production in hypoglycemic hepatoma patient[10].

Treatment of hypoglycemic HCC patients is sometimes problematic. The optimal treatment is tumor removal. Partial hepatectomy should be considered in patients without cirrhosis or in those with mild liver disease. The best outcomes are observed in patients with unicentric disease, no vascular invasion, tumors smaller than 5 cm, and relatively inactive liver disease. Orthotopic liver transplantation (OLT) is the treatment of choice in patients with advanced stage of cirrhosis. Inoperable cases can be treated with cytoreduction using percutaneous ethanol injection[3](PEI), radiofrequency ablation therapy (RFA)[11] or intrahepatic adriamycin[8,9]. PEI is a widely accepted modality of therapy for small, localized HCC. The suitable lesion is a tumor less than 3 cm.in size and fewer than 3 nodules. RFA is a new therapeutic method in the management of HCC. The tumor size for this procedure also should not be larger than 3 cm. TOCE is an alternative procedure for patients with a large, inoperable tumor. Contraindication in this procedure is portal vein thrombosis, Child class C. The presented patient had tumor progression beyond this stage of treatment. Systemic therapy for advanced HCC are cytotoxic therapy, immunotherapy, hormonal therapy, and gene therapy. Most systemic therapy have not shown favourable outcomes at the present time.

Frequent high carbohydrate meal is the simplest way to resolve hypoglycemia although sometimes it may not overcome glucose overutilization. Steroid is one of the therapeutic options with dose titration up to 1 mg/kg/day. It counteracts hypoglycemia by stimulating gluconeogenesis. Prednisolone accentuates IGFBP-3 binding with acid-labile subunit to form a ternary complex, thus free pro-IGF-II level is decreased[12].

Supra-physiologic dosage of GH administration can reduce glucose requirement[13]. It could be used as an adjuctive treatment[14]. One report demonstrated a patient with mesenchymal tumor who was able to normalize plasma glucose by combination of GH and prednisolone treatment[8].

Glucagon is one of the insulin counter-regulatory hormones. Its action on hepatic glucose output in chronic liver disease patient decreases. Continuous glucagon infusion might be beneficial in hypoglycemia treatment of a non-islet cell tumor. Glucagon stimulation test may be also useful to predict treatment responsiveness[15].

Two reports using somatostatin analogue in patients with hepatocellular carcinoma[16] and mesenchymal tumor[17] were unsuccessful in treating hypoglycemia.Review of treatment modalities is shown in Table 1.

The presented patient was euglycemia after treatment with frequent high carbohydrate meal and corticosteroid.

In conclusion, steroid combined with frequent high carbohydrate meal is an effective and inexpensive way in palliative treatment of hypoglycemia from advanced stage HCC.

References

1. Kahn CR. The riddle of tumour hypoglycaemia revisited. Clin Endocronol Metab 1980; 9: 335-60.
2. Comi RJ, Gorden P. Hypoglycemia. In: Becker KL, editor. Principles and practice of endocrinology and metabolism. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001: 1469-77.
3. Saigal S, Nandeesh HP, Malhotra V, Sarin SK. A case of hepatocellular carcinoma associated with troublesome hypoglycemia: management by cytoreduction using percutaneous ethanol injection. Am J Gastroenterol 1998; 93: 1380-1.
4. Torzilli G, Minagawa M, Takayama T, Inoue K, Hui AM, Kubota K, et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. Hepatology 1999; 30: 889-93.
5. Kim SH, Lim HK, Lee WJ, Cho JM, Jang HJ. Needle-tract implantation in hepatocellular carcinoma: frequency and CT findings after biopsy with a 19.5-gauge automated biopsy gun. Abdom Imaging 2000; 25: 246-50.
6. Nduduba DA, Ojo OS, Adetiloye VA, Rotimi O, Durosinmi MA, Uchegbu LO. The incidence and characteristics of some paraneoplastic syndromes of hepatocellular carcinoma in Nigerian patients. Eur J Gastroenterol Hepatol 1999; 11: 1401-4.
7. McFadzean AJ, Yeung RT. Further observation on hypoglycemia in hepatocellular carcinoma. Am J Med 1969; 47: 220-35.
8. Perros P, Simpson J, Innes JA, Teale DJ, McKnight JA. Non-islet cell tumor-associated hypoglycemia:

^{111}In-octreotide imaging and efficacy of octreotide, growth hormone and glucocorticosteroids. Clin Endocrinol (Oxf) 1996; 44: 727-31.
9. Tietge UJ, Schofl C, Ocran KW, Wagner S, Boker KH, Brabant G, et al. Hepatoma with severe non-islet cell tumor hypoglycemia. Am J Gastroenterol 1998; 93: 997-1000.
10. 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: 1958-63.
11. McGahan JP, Browning PD, Brock JM, Tesluk H. Hepatic ablation using radiofrequency electrocautery. Invest Radiol 1990; 25: 267.
12. Baxter RC, Holman SR, Corbould A, Stranks S, Ho PJ, Braund W. Regulation of the insulin-like growth factors and their binding proteins by glucocorticoid and growth hormone in nonislet cell tumor hypoglycemia. J Clin Endocrinol Metab 1995; 80: 2700-8.
13. Wing JR, Panz VR, Joffe BI, Kalk WJ, Seftel HC, Zapf J, et al. Hypoglycemia in hepatocellular carcinoma: failure of short-term growth hormone administration to reduce enhanced glucose requirements. Metabolism 1991; 40: 508-12.
14. van Wijngaarden P, Janssen JA, de Man RA. Hepatocellular carcinoma complicated by non-islet cell tumor hypoglycemia. Ned Tijdschr Geneeskd 2002; 146: 859-62.
15. Hoff AO, Vassilopoulou-Sellin R. The role of glucagons administration in the diagnosis and treatment of patients with tumor hypoglycemia. Cancer 1998; 82: 1585-9.
16. Joffe BI, Kew MC, Panz VR, Kalk WJ, Shires R, Wing J, et al. Evaluation of the synthetic somatostatin analogue SMS 201-995 in patients with hypoglycaemia associated with hepatocellular carcinoma. Br J Cancer 1988; 58: 91-2.
17. Perros P, Simpson J, Innes JA, Teale JD, McKnight JA. Non-islet cell tumour-associated hypoglycemia: ^{111}In-octreotide imaging and efficacy of octreotide, growth hormone and glucocorticosteroids. Clin Endocrinol 1996; 44: 727-31.
18. Kitazawa T, Nakamura S, Sano Y, Hishiki S, Sakaguchi S, Maeda M, et al. Successful resection of giant hepatocellular carcinoma with hypoglycemic attack. Nippon Geka Gakkai Zasshi 1984; 85: 1591-6.
19. Hunter SJ, Daughaday WH, Callender ME, McKnight JA, McIlrath EM, Teale JD, et al. A case of hepatoma associated with hypoglycaemia and overproduction of IGF-II (E-21): beneficial effects of treatment with growth hormone and intrahepatic adriamycin. Clin Endocrinol 1994; 41: 397-401.
20. Samaan NA, Pham FK, Sellin RV, Femandez JF, Benjamin RS. Successful treatment of hypoglycemia using glucagon in a patient with an extrapancreatic tumor. Ann Intern Med 1990; 113: 404-6.

ภาวะน้ำตาลต่ำในผู้ป่วยมะเร็งตับชนิดปฐมภูมิซึ่งประสบความสำเร็จในการรักษาด้วยคอร์ติโคสเตียรอยด์และการรับประทานอาหารคาร์โบไฮเดรตขนาดสูงและบ่อย

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รายงานผู้ป่วยชายอายุ 36 ปี ได้รับการวินิจฉัยโรคมะเร็งตับชนิดปฐมภูมิ ซึ่งแพร่กระจายไปปอด มาโรงพยาบาลด้วยอาการหมดสติจากภาวะน้ำตาลในเลือดต่ำ ในขณะนั้นระดับอินซูลิน และซีเปปไทด์ต่ำ ระดับคอร์ติซอลในเลือดสูงขึ้นอย่างเหมาะสม ผู้ป่วยได้รับการรักษาด้วยน้ำตาลกลูโคสทางหลอดเลือดดำอย่างน้อย 3.65 มิลลิกรัมต่อกิโลกรัมต่อนาที เพื่อให้ระดับน้ำตาลในเลือดอยู่ในเกณฑ์ปกติ การรักษาเพื่อลดขนาดก้อนเนื้องอกไม่สามารถทำได้เนื่องจากระยะของโรคเป็นระยะสุดท้าย ผู้ป่วยยังมีอาการน้ำตาลในเลือดต่ำช่วงเช้าหลายครั้ง แม้ได้รับเพรดนิโซโลน 40 มิลลิกรัมต่อวัน อย่างไรก็ตามความต้องการน้ำตาลกลูโคสลดลงหลังได้รับการรักษาด้วยสเตียรอยด์ในที่สุดระดับน้ำตาลในเลือดสามารถอยู่ในเกณฑ์ปกติได้ด้วยการรับประทานอาหารประเภทคาร์โบไฮเดรตขนาดสูงและบ่อย เพรดนิโซโลนได้ถูกเปลี่ยนเป็นเด็กซาเมทาโซน 2 มิลลิกรัมต่อวัน หลังจากนั้นผู้ป่วยไม่มีอาการน้ำตาลในเลือดต่ำอีกตราบเท่าที่สามารถรับประทานอาหารว่างช่วงเที่ยงคืน

รายงานผู้ป่วยฉบับนี้ได้มีการทบทวนวรรณกรรมเรื่องภาวะน้ำตาลในเลือดต่ำในผู้ป่วยมะเร็งตับชนิดปฐมภูมิในตอนท้าย