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Case Report

Extremely Severe Hypoglycemia in a Patient Who Experienced Spontaneous Rupture of a Hepatocellular Carcinoma

Honda A[1], Masada T[2], Morita M[3], Kono F[4], Imashuku S[5]*

[1]Department of Internal Medicine, Uji-Tokushukai Medical Center, Uji, Kyoto, Japan
[2]Department of Radiology, Uji-Tokushukai Medical Center, Uji, Kyoto, Japan
[3]Department of Internal Medicine 1, Shimane University Faculty of Medicine, Izumo, Shimane, Japan
[4]Division of Diagnostic Pathology, Uji-Tokushukai Medical Center, Uji, Kyoto, Japan
[5]Department of Laboratory Medicine, Uji-Tokushukai Medical Center, Uji, Kyoto, Japan

***Corresponding author:** Shinsaku Imashuku, Department of Laboratory Medicine, Uji-Tokushukai Medical Center, Uji, Kyoto, 611-0041, Japan

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Abstract

An 85-year-old woman was brought to the emergency room because of shock and coma. She was found to have extreme hypoglycemia (blood glucose <10 mg/dL), associated with the spontaneous rupture of an end-stage Hepatocellular Carcinoma (HCC). Because the patient had declined any treatment for her HCC during the preceding year, no specific treatment was instituted for the ruptured HCC. Intravenous infusion of high-glucose fluid normalized her blood glucose concentration within 4 hours, but she died further 6 hours later. At autopsy, neither insulinoma nor a malignancy other than the HCC was identified. Her liver weighed 1,290 g and was filled with tumor masses. The HCC cells were negative for insulin-like growth factor 2 expression on immunohistochemistry, indicating that the extreme hypoglycemia was not a "Non-Islet Cell Tumor Hypoglycemia (NICHT)".

Keywords: Hypoglycemia; Hepatocellular carcinoma; Rupture; Insulin growth factor 2

Introduction

The development of severe hypoglycemia (defined as a circulating glucose concentration of <40 mg/dL) in critically ill patients is common [1], and may be caused, for example, by gram negative bacterial shock [2] or cardiogenic shock [3]. In addition, hypoglycemia is a paraneoplastic feature of Hepatocellular Carcinoma (HCC), along with erythrocytosis, hypercalcemia, diarrhea, and dermatitis [4,5]. Two types of HCC-associated hypoglycemia are defined: type A, mild hypoglycemia, which develops at the end stage of the tumor pathology; and type B, severe hypoglycemia, caused by large amounts of Insulin-Like Growth Factor 2 (IGF2) being released by HCC cells, a phenomenon that is termed Non-Islet Cell Tumor Hypoglycemia (NICTH) [6,7]. To date, several cases of HCC-associated NICTH have been reported [6-13]. The spontaneous rupture of HCCs is not infrequent and is a life-threatening condition that requires acute intervention, such as trans-arterial embolization for hemostasis and partial liver resection [14-16]. However, hypoglycemia has rarely been reported in patients who experience spontaneous rupture of an HCC [17]. Here, we report the case of an elderly patient who had extreme hypoglycemia (blood glucose <10 mg/dL) that was associated with the spontaneous rupture of an end-stage HCC.

Case Presentation

An 85-year-old non-diabetic woman was brought to the emergency room of our hospital in a state of shock and coma. She was not anemic, but her vital signs were: Japan Coma Scale 100, Glasgow Coma Scale E1V2M4, heart rate 63 /min, and respiratory rate 14 / min; her blood pressure and oxygen saturation were unmeasurable. In addition, she was found to be extremely hypoglycemic (blood glucose <10 mg/dL; in fact, repeated tests showed concentrations of only 1.0 mg/dL), as well as having hepatic and renal dysfunction (Table 1). She had been diagnosed with hepatitis B and C-negative HCC one year earlier, but no history of alcohol consumption was available. She and her family had declined any treatment and made no further visits to the clinic. According to her family, the patient had been unable to eat food for nearly a week prior to her hospitalization. Computed tomography performed in the emergency room revealed massive tumor nodules in both lobes of the liver and rupture of the HCC in the left lobe (Figure 1). After cardiopulmonary arrest, the patient's circulation returned spontaneously, and intravenous glucose administration, including the rapid infusion of 40 mL of 50 % glucose, followed by continuous infusion (20 mL/hour) of 10 %

Table 1: Laboratory data on admission.

Complete blood count		Total protein; g/dL (6.6-8.1)	7.2
WBC; /μL (3,300-8,600)	11,100	Albumin; g/dL (4.1-5.1)	2.5
RBC; x10^6/μL (3.86-4.92)	5.11	**Renal function**	
Hb; g/dL (11.6-14.8)	15.5	BUN: mg/dL (8.0-20.0)	94.3
PLTc; ×10^3/μL (158-348)	94	Creatinine; mg/dL (0.46-0.79)	4.36
Glucose-related indices		Uric acid; mg/dL (2.6–5.5)	24.2
Blood glucose; mg/dL (73-109)	1.0	eGFR; (>60)	9
HbA1C; % (<6.2)	4.9	**Inflammation-related indices**	
Liver-related indices		CRP; mg/dL (<0.14)	5.57
AST; U/L (13-30)	681	Procalcitonin; ng/mL (<0.05)	0.72
ALT; U/L (7-23)	101	**Blood gas analysis**	
LDH; U/L (124-222)	1,256	pH; (7.35-7.45)	7.32
ChE; U/L (100-240)	145	BE; mEq/L (-3-+3)	-0.9
Gamma-GTP; U/L (9-32)	231	Glucose; mg/dL (70-110)	1.0
Total bilirubin; mg/dL (0.4-1.5)	3.62	Lactate; mg/dL (5-15)	61

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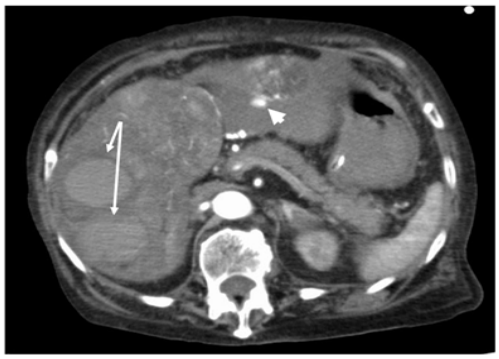

Figure 1: Contrast-enhanced computed tomography revealed widespread Hepatocellular Carcinoma (HCC) in both lobes of the liver and a rupture of the tumor in the left lobe. Arrows indicate intrahepatic hematomas and the arrowhead indicates extra hepatic hemorrhage.

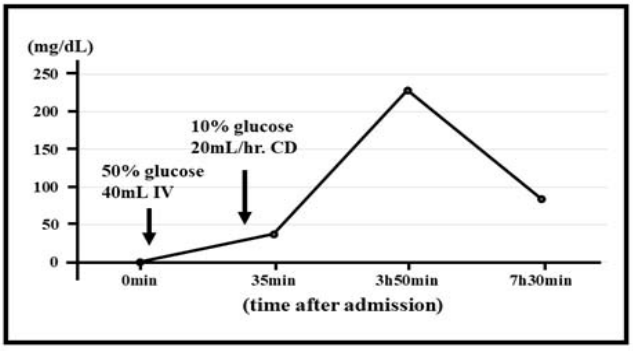

Figure 2: Clinical course of the patient's hypoglycemia after admission. IV: Intravenous Infusion; CD: Continuous Infusion.

glucose, returned her blood glucose concentration to normal within 4 hours, but this decreased thereafter, and she died 10 hours after admission (Figure 2).

At autopsy, neither insulinoma nor a gastrointestinal stromal tumor was found. Her liver weighed 1,290 g, showed cirrhosis, and was filled with moderately differentiated HCC tumor masses, one of which had ruptured (Figure 3). We also determined whether the HCC had been producing excessive amounts of IGF2 by immunohistochemical staining as previously described [9,11]. Formalin-fixed, paraffin-embedded HCC tissue was sectioned and immunostained using an anti-IGF2 antibody (anti-rabbit polyclonal antibody; Merck, Kenilworth, NJ, USA), but no expression was found (data not shown).

Discussion

Rupture of an HCC creates a life-threatening condition that requires acute intervention [14-16]; however, the present patient, who was in the terminal stage of the disease, could not be treated aggressively, because her family did not give their permission. The cause of the underlying hepatic cirrhosis in the patient was unknown. We considered several possible causes of her extremely severe hypoglycemia: Spontaneous rupture of the HCC [17] and a combination of type A and type B hypoglycemia [5-12]. We were unable to assay serum IGF2 or undertake western blot analysis pre-

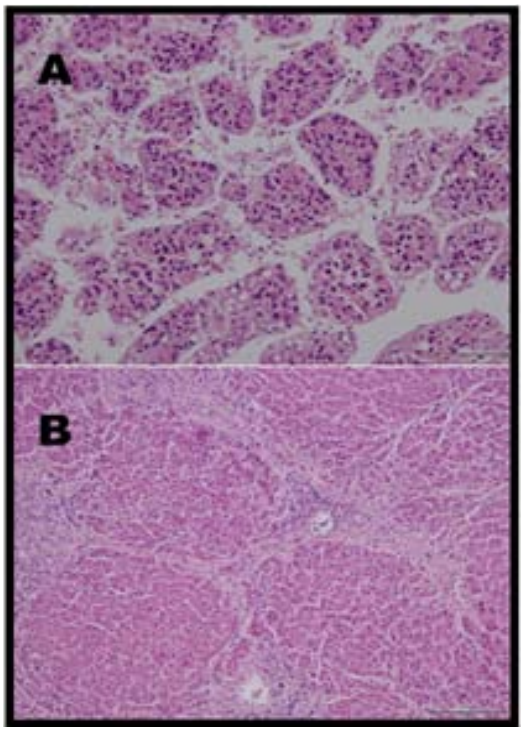

Figure 3: Histology of the patient's liver, showing Hepatocellular carcinoma and cirrhosis. A) Original magnification, ×200 and B) Original magnification, ×100. Immunostaining for insulin-like growth factor 2 was negative in both samples (data not shown).

mortem for the diagnosis of NICTH, but we immunostained liver tissue obtained at autopsy for IGF2, but the results were negative, implying that the severe hypoglycemia in this case was not HCC-related NICTH. In addition, NICTH caused by other tumors was ruled out. Because the patient did not survive for long, detailed studies of hormone, catecholamine, and cytokine concentrations could not be performed to further investigate the cause(s) of the severe hypoglycemia.

We could not find any previous reports of HCC-related extreme hypoglycemia (blood glucose concentration <10 mg/dL) in the literature. In previous reports of HCC-associated NICTH, the blood glucose concentrations of the patients were 20–38 mg/dL [5-9,12,13]. Type A hypoglycemia is generally characterized as being mild [6,7]. For the present case, we hypothesized that the causes of the extremely severe hypoglycemia were shock induced by the rupture of the HCC; impaired glucose metabolism in the liver, associated with the loss of functional hepatocytes; consumption of glucose by the HCC; and poor nutrition, especially the lack of food intake during the week preceding hospitalization. However, we do not have specific evidence for effects of shock-related factors on the patient's glucose metabolism. After admission, her hypoglycemia was rapidly improved by therapy, but the outcome was poor. Finally, the lack of significant anemia, despite the rupture of the HCC, might be explained by HCC-related erythrocytosis [4].

Conclusion

Spontaneous rupture of an HCC may induce severe hypoglycemia through a mechanism not involving NICTH.

Acknowledgements

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Ethical Approval

This study was performed in accordance with the Declaration of Helsinki.

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