Int J Clin Exp Pathol 2020;13(12):3167-3173
www.ijcep.com /ISSN:1936-2625/IJCEP0122021

Original Article

Hepatocellular carcinoma with worsened hypoglycemia after transarterial chemoembolization: a case report and systematic review

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Received September 8, 2020; Accepted September 21, 2020; Epub December 1, 2020; Published December 15, 2020

Abstract: Non-islet cell tumor hypoglycemia (NICTH) is an extremely uncommon and serious complication of hepatocellular carcinoma (HCC). Here, we reported a case of a 47-year-old male patient with moderate to poorly differentiated HCC complicated by hypoglycemia that worsened after transarterial chemoembolization (TACE). The patient was admitted into The First Affiliated Hospital of Naval Medical University due to fatigue, nausea, dizziness and passage of tea colored urine. He was diagnosed with NICTH induced by HCC according to CT scanning and laboratory tests. TACE was used as the primary therapy but the hypoglycemia worsened afterward. Then the patient received a liver transplantation as a possible radical cure and hypoglycemia was resolved. We systematically review the management of hypoglycemia caused by HCC and the results show that patients undergoing treatment that mainly alleviate tumor burdens obtained a significantly higher response rate than patients undergoing therapies mainly regulating biologic functions (50.0% vs 27.3%). Cytoreductive surgery, TACE and radiotherapy which aimed to alleviate tumor burdens are effective therapies have great potential, but the risk of hypoglycemic deterioration requires particular attention when using these treatments, especially with TACE.

Keywords: Hepatocellular carcinoma, hypoglycemia, transarterial chemoembolization, case report, systemic review

Introduction

Non-islet cell tumor hypoglycemia (NICTH) is a syndrome of hypoglycemia caused by neoplasm other than an insulinoma, which is a rare complication of hepatocellular carcinoma (HCC) [1, 2]. NICTN may appear in the final stage of HCC and is associated with poor prognosis and survival [3]. Although several explicit mechanisms have been proposed to explain the hypoglycemia in HCC, including a role of overproduced insulin-like growth factor II (IGF-II) and massive tumor burden, there is currently a lack of studies exploring effective treatments or prevention [4-7].

Therefore, in this study, we report a 47-year-old male patient with moderate to poorly differentiated HCC presenting with hypoglycemia that worsened after transarterial chemoembolization. We review the literature concentrating on specific treatments for NICTH induced by HCC.

Case presentation

In November 2018, a 47-year-old male patient with chronic hepatitis B was admitted to The First Affiliated Hospital of Naval Medical University, Naval Medical University, Shanghai, China, due to fatigue, nausea, dizziness and passage of tea-colored urine for 2 weeks. The patient had been diagnosed with the chronic hepatitis B infection 30 years ago and only started to receive antiviral therapy since 2008 when he initially felt malaise and poor appetite. However, he had never undergone regular liver function examinations. No other medical history was mentioned. A physical examination suggested only slight scleral icterus.

The patient was diagnosed with HCC as the computed tomographic (CT) scanning revealed a large mass accompanied by multiple hepatic lesions, occupying roughly most of the right lobe of the cirrhotic liver, which conforms to the

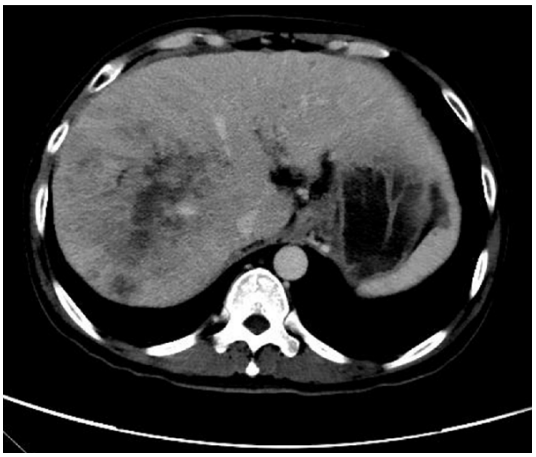

Figure 1. Computed tomography scans of the liver showed a large mass accompanied by multiple lesions in the right lobe.

characteristic of huge HCC with multiple intrahepatic metastases (**Figure 1**). His Child-Pugh's score was A and he had normal levels of total bilirubin, serum albumin, and normal prothrombin time and no manifestations of ascites or hepatic encephalopathy.

At the initial stage, the mild hypoglycemia was merely considered a transient symptom of liver dysfunction due to HCC, hence, we did not acquire any specific examinations and treatments (glucose infusion only). Though the patient appeared to be generally in good condition, hepatectomy was not considered for him due to large and multiple tumors. Transarterial chemoembolization was used as the second-choice therapy for both HCC and hypoglycemia. It was performed from the right hepatic artery using 20 mg hydroxycamptothecine + lipiodol 10 mL.

Before chemoembolization, the patient had hypoglycemia as well as increased serum levels of total bilirubin, alkaline phosphatase, aspartate aminotransferase, r-glutamyl transpeptidase and alpha-fetoprotein (**Table 1**). After chemoembolization, the level of these indicators was worsened, especially for hypoglycemia (**Table 2**). Meanwhile, the patient also had low serum levels of insulin and C-peptide, thus he was diagnosed with NICTH rather than insulinoma.

The patient was treated with continuous 20% dextrose infusion and high carbohydrate diet, but remained persistently hypoglycemic (< minimum of 1.3 mmol/L). When hypoglycemia became symptomatic, a 50% dextrose supplement was given. After two weeks of maintenance therapy for steadily worsening liver function and refractory hypoglycemia, the patient was transferred to another hospital and received a liver transplantation. Then the hypoglycemia resolved and other conditions continued to improve. Postoperative histopathology was consistent with moderately to poorly-differentiated carcinoma of the liver. The patient signed informed consent for this case report.

Systematic review

A search for relevant studies that reported HCC patients with NICTH was conducted using Medline (www.ncbi.nlm.nih.gov/pubmed), Cochrane (www.thecochranelibrary.com/view/0/index.html), EMBASE (www.elsevier.com/online-tools/embase) and ISI Web of Science (www.webofknowledge.com) in December 2018. The following search terms were used for search: hepatic carcinoma, hepatocellular carcinoma, hepatoma, liver cell carcinoma, HCC, hypoglycemia, hypoglycemic and glycopenia. In addition, the reference lists of the relevant studies were also searched. Study selection was based on an initial screen of identified titles or abstracts and a second screen of full-text articles. Two authors (Jiao Yu and Chengzhong Li) independently performed the studies screens and any disagreements were resolved by a third reviewer (Xuesong Liang). Studies were considered eligible if they met the following criteria: 1) primary HCC; 2) NICTH caused by HCC, not drug-induced hypoglycemia or other hypoglycemia; 3) published in the English language. Review articles, editorials and conference papers were not included in this systemic review. Studies that did not report the management of hypoglycemia or were lack of essential information were also excluded. Extracted from all included studies, information was recorded as follows: last name of the first author, publication year, study design; patients' general information, history, initial symptoms, laboratory findings, pathologic results, treatment regimen, effects, outcomes and other clinical information (Not fully presented in the main text, please contact authors for details). The descriptions of positive effect (NPE), only transient effect (OTE), glucose requirement decreased (GRD),

Table 1. Abnormal indicators in laboratory examination results of patient's serum pre-embolization

Indicator	Normal range	Pre-embolization level
Glucose (mmol/L)	3.5-5.5	2.7
Total bilirubin (mmol/L)	2-18	31.3
Alkaline phosphatase (IU/L)	40-150	587
Aspartate aminotransferase (IU/L)	< 64	88
R-glutamyl transpeptidase (IU/L)	< 47	480
Alpha-fetoprotein (ng/mL)	< 8.78	393.01

Table 2. Abnormal indicators in laboratory examination results of patient's serum post-embolization

Indicator	Normal range	Postembolization level
Glucose (mmol/L)	3.5-5.5	2.3
Total bilirubin (mmol/L)	2-18	81.2
Alkaline phosphatase (IU/L)	40-150	440
Aspartate aminotransferase (IU/L)	< 64	164
R-glutamyl transpeptidase (IU/L)	< 47	282
Insulin level (IU/L)	2.6-24.9	0.6
C-peptide level (μg/L)	1.1-4.4	0.31
IGF-I (ng/mL)	< 25	94-252
IGF BP-3 (μg/mL)	0.92	3.3-6.7

Note: IGF: insulin-like growth factor; IGF BP-3: insulin-like growth factor binding protein-3; The IGF-II and 'big' IGF-II levels were not measured because the tests were not available in The First Affiliated Hospital of Naval Medical University.

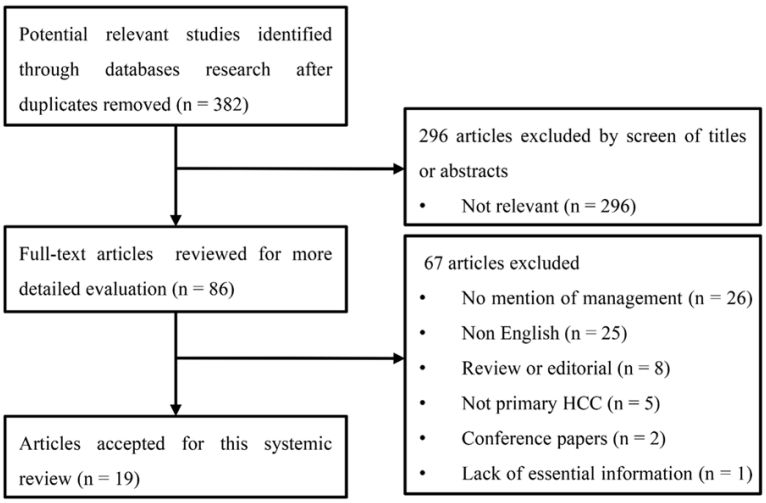

Figure 2. Flow chart of study selection.

and hypoglycemia resolved (HR) were respectively used for evaluating treatments effects based on primary sources. For groups' evaluation, response rate was defined by authors as the percent of patients with GRD or HR. **Figure 2** briefly presented the studies selection.

As shown in **Table 3**, there were 21 HCC patients with hypoglycemia (81.0% female) included for analysis, with the age of 47.0±8.0 years, fast blood glucose at diagnosis of 30.8±12.2 mg/dL and 93.8% cases were massive type of HCC [8-24] Significant dizziness, recurrent consciousness, weight loss, abdominal discomfort, and sweating were most reported initial symptoms and signs of HCC patients with hypoglycemia, with an incidence of 44.4%, 33.3%, 27.8%, 22.2% and 22.2%, respectively.

According to the treatment method the enrolled study received, the patients were divided into two groups: alleviating tumor burden group or regulating biological function group, and their total response rates were 64.28% and 26.09%, respectively, with significant different (chi square test, P = 0.037). Transarterial chemoembolization (60.0%) and glucocorticoid (28.57%) were most-applied therapies in their own groups, and their response rate were all consistent with the total response rate of groups, respectively.

Discussion

Typical cases of HCC patients with NICTH are extremely rare and the exact prevalence is not clearly known [22-24]. In our case, the initial hypoglycemic condition of the patient, appearing as nonspecific symptoms such as fatigue or dizziness and an inapparent decline in blood serum glucose levels, has not received major attention.

There are two types of hypoglycemia in HCC based on timing, etiology, and pathophysiology [4]. Type A is a mild to moderate severity hypo-

Table 3. Summary of 21 patients in 19 included studies and our report

Included studies	Age/gender	Initial symptoms and signs	HCC type	FBG (mg/dl)	Main treatments	Effects
Our report	47/M	Fatigue; nausea; dizziness; dark urine	Massive	49	Transarterial chemoembolization	NPE
Klein et al., 1959 [8]	62/F	Anorexic, weight loss; recurrent unconsciousness	Massive	30	Glucocorticoid	NPE
Schonfeld et al., 1961 [9]	27/M	Anorexia; diarrhea	Massive	46	Glucocorticoid	NPE
Wing et al., 1991 [10]	30/M			38	Growth hormone	GRD
Wing et al., 1991 [10]	27/M			36	Glucocorticoid	GRD
Yonei et al., 1992 [11]	62/M	Abdominal discomfort; weight loss	Massive	21	Systemic chemotherapy	OTE
Hunter et al., 1994 [12]	64/M	Dizziness, sweating; palpitations		34	Transarterial chemoembolization	HR
Hoff et al., 1998 [13]	34/M	Diaphoretic; tachycardic; recurrent consciousness		10	Diazoxide	NPE
Saigal et al., 1998 [14]	24/F	Recurrent unconsciousness	Massive	15	Percutaneous ethanol injection	HR
Tietge et al., 1998 [15]	22/M	Weight loss; drowsiness; dizziness; confusion	Massive	20	Systemic chemotherapy	NPE
Thipaporn et al., 2005 [16]	36/M	Abdominal discomfort; weight loss	Diffuse	26	Glucocorticoid	GRD
Nikeghbalian et al., 2006 [17]	77/M	Drowsiness; recurrent consciousness	Massive	45	Tumor completely incision	HR
Atiq et al., 2007 [18]	55/M	Dizziness	Massive	20	Transarterial chemoembolization	HR
Kampitak, 2008 [19]	16/M	Abdominal discomfort; weight loss; recurrent unconsciousness	Massive		Systemic chemotherapy	HR
Okushin et al., 2012 [20]	77/M		Massive	27	Glucocorticoid	OTE
Whitsett et al., 2013 [7]	68/F	Fatigue; jaundice; shortness of breath	Massive	61	Transarterial chemoembolization	HR
Sharma et al., 2014 [21]	59/M	Dizziness; abdominal discomfort	Massive	22	Glucocorticoid	HR
Tsai et al., 2014 [3]	42/F	Malaise, poor appetite; recurrent unconsciousness	Massive	30	Radiotherapy	GRD
Vagionas et al., 2014 [22]	51/M	Dizziness, sweating; recurrent unconsciousness	Massive	30	Transarterial chemoembolization	NPE
Huang et al., 2016 [23]	54/M	Drowsiness; dizziness; confusion; sweating	Massive	34	Systemic chemotherapy	HR
Forde et al., 2017 [24]	54/M	Dizziness, agitation; sweating		22	Glucocorticoid	OTE

Note: M: male; F: female; FBG: fasting blood glucose; NPE: no positive effect; OTE: only transient effect; GRD: glucose requirement decreased; HR: hypoglycemia resolved.

glycemia that usually occurs in terminal stages, especially in rapidly growing large tumors [4, 27, 28]. The mechanism may be that the liver is damaged and replaced by tumor, thus the impaired liver is unable to satisfy the glucose demands of the extensive tumor and regulate blood glucose levels by gluconeogenesis and glycogenolysis. Type B hypoglycemia only presents in 5-13% of NICTH with HCC, and manifests as severe hypoglycemia early in the course of the malignancy, with increases of the secretion of incompletely processed IGF-II (termed the 'big' IGF-II) from the tumor [4, 27, 28]. In our case, the patient was considered a probable type A NICTH, as the malignant neoplasm was extensive and had replaced a large proportion of the normal liver parenchyma.

At present, there are no definitive treatments for refractory hypoglycemia patients with HCC, regardless of the type they belong to [14]. The general treatments of NICTH involve immediate correction of hypoglycemia. Specific treatments aim at the underlying malignancy and palliative prevention of recurrent hypoglycemia when the tumor is not under control [22-24, 29, 30]. For the second treatment, complete surgical resection or liver transplantation remain the most effective therapeutic options and others such as cytoreductive surgery, transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), systemic chemotherapy, and radiotherapy are also possible methods [7, 14, 17, 31].

Previous studies reported that HCC-induced hypoglycemia patients may have favorable outcomes after treating by TACE [7, 12, 18]. However, TACE did not demonstrate remarkable superiority in response rate based on our pooled analysis. In our case, TACE actually aggravated the intractable hypoglycemia, causing the patient to need a liver transplantation. Based on the inference of type A hypoglycemia of the patient, we think the primary reason for the failure of TACE in treatment of hypoglycemia is the aggravated liver dysfunction and inability to regulate blood glucose levels caused by the procedure. TACE commonly induces significant death of cancer cells immediately, and it can lead to a lot of inflammation and metabolic disorder in the area, which partly induces inevitable hypohepatia. Local tissue ischemia due to embolization also intensifies the decline. These effects can be especially robust in a huge HCC and therefore largely aggravate previous systemic symptoms such as fever, malaise or rare hypoglycemia [32]. At present, TACE is still the main therapy for unresectable HCC, which has also been used in cases with HCC-induced hypoglycemia [33]. However, in our opinion, TACE's applications for huge and massive HCC with NICTH are potentially restricted by reason of the mediocre efficiency and increased risk of hypoglycemia development. There need to be more studies for further evaluation.

The major measures to control hypoglycemia is the applications of regulatory substances including glucocorticoids, glucagon, growth hormone, somatostatin analogues, tamoxifen, diazoxide or vitamin K, even though the response may be transient or unhelpful [10, 12-14, 16]. In our systematic review, we show, for the first time that treatments aimed at the malignancy are obviously more effective than palliative therapies for hypoglycemia. Therefore, we believe that palliative measures should not be advocated as main choices as long as there are any treatments for malignancy that can be used. In our sreview, we found limitations of substantial heterogeneity among included studies and the publication bias is unclear.

In conclusion, hypoglycemia due to HCC is an uncommon but possibly lethal disorder. Although there is no standardized approach in the treatment of this rare disease, specific treatments mainly alleviating tumor burden are effective therapies with great application prospect. However, it is worth noting that because the clinical circumstances may be fairly complicated, the above methods should be properly selected to avoid any negative effects. From experience of this case, we speculate that TACE may induce worsened hypoglycemia in huge HCC with NICTH. We hope HCC related hypoglycemia gets more attention from doctors and researchers.

Disclosure of conflict of interest

None.

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