Non-islet cell tumor hypoglycemia as an initial presentation of hepatocellular carcinoma coupled with end-stage liver cirrhosis: A case report and review of literature

Bo Yu, Rana Douli, Jose Amaya Suarez, Victor Perez Gutierrez, Mohammad Aldiabat, Maria Khan

BACKGROUND
Non-islet cell tumor hypoglycemia (NICTH) is a rare cause of persistent hypoglycemia seen in patients with hepatocellular carcinoma (HCC). It is likely to be underdiagnosed especially in the patients with poor hepatic function and malnutrition. Herein, we report a rare case of NICTH as the initial presentation of HCC in a patient with chronic hypoglycemia due to end-stage liver cirrhosis.

CASE SUMMARY
A 62-year-old male with chronic fasting hypoglycemia secondary to end-stage hepatitis C-related cirrhosis, presented with altered mental status and dizziness. He was found to have severe hypoglycemia refractory to glucose supplements. Imaging studies and biopsy discovered well differentiated HCC without metastasis. Further evaluation showed low insulin, C-peptide and beta-hydroxybutyrate along with a high insulin-like growth factor-2/insulin-like growth factor ratio, consistent with the diagnosis of NICTH. As patient was not a candidate for surgical resection or chemotherapy, he was started on prednisolone with some improvements in the glucose homeostasis, but soon decompensated after a superimposed hospital acquired pneumonia.

CONCLUSION
NICTH can occur as the sole initial presentation of HCC and is often difficult to correct without tumor removal. Clinicians should maintain high clinical suspicion for early recognition of paraneoplastic NICTH in patients at risk for HCC, even those with chronic fasting hypoglycemia in the setting of severe hepatic failure and malnutrition.

Key words: Non-islet cell tumor hypoglycemia; Hepatocellular carcinoma; Liver cirrhosis; Insulin-like growth factor-2; Paraneoplastic syndrome; Case report
INTRODUCTION

Non-islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic complication associated with malignancies of both epithelial and mesenchymal origin. One of the most common epithelial tumors is hepatocellular carcinoma (HCC)\(^1\). Hypoglycemia is induced either by tumor consumption of glucose (type A) or overproduction of incompletely processed insulin-like growth factor-2 (IGF-2) (type B), while levels of insulin, C-peptide, pro-insulin, and beta-hydroxybutyrate are suppressed\(^3\). NICTH occurs in 4% to 27% of patients with HCC\(^4\). However, the actual prevalence might be underestimated due to limited availability of testing for IGF-2. In addition, the etiologies of hypoglycemia in HCC patients are often multifactorial. Many patients might have developed tolerance to chronic fasting hypoglycemia due to long-term poor hepatic function and nutritional status at the time of discovery of HCC. Here we report a case of persistent NICTH as the initial presentation in a patient with newly diagnosed HCC overlapped with end-stage liver cirrhosis.

CASE PRESENTATION

Chief complaints
A 62-year-old Hispanic male with long-standing hepatitis C-related cirrhosis was brought to the emergency room on December 7, 2019 due to 2 episodes of altered mental status and non-vertiginous dizziness witnessed by his family. He also reported an unintentional 1-kg weight loss over the past 1 mo.

History of present illness
There was no history of loss of consciousness, falls, or head trauma. He was first found to have hepatitis C infection with concurrent liver cirrhosis and portal hypertension in 2015. Viral load became undetectable after the completion of antiviral therapy but the patient lost follow-up ever since July 2018. Child-Pugh score during the last outpatient visit was 8 (class B). AFP was within the normal limit. No signs of malignancy were found on liver ultrasound.

Physical examination upon admission
On physical exam, he was all the time conscious and had full ability to communicate. Vital signs were within normal limits. Rest of the physical exam was significant for cachectic appearance, jaundice, and bilateral lower extremity edema up to the knee.

Laboratory examination, imaging studies and diagnostic reasoning
In the emergency room, his blood glucose was detected to be 26 mg/dL. He denied poor oral intake or history of diabetes, alcohol abuse or illicit drug use. Of note, his blood glucose level tended to be on the lower side (75-85 mg/dL) seen in the records.
of several outpatient visits before he lost follow-up. The blood glucose level was corrected by two immediate intravenous 50% dextrose pushes, but dropped again down to 10 mg/dL in 2 h for which continuous 10% dextrose infusion was started and the patient was instructed to consume frequent carbohydrate-rich snacks. However, recurrent hypoglycemic attacks still occurred since admission that required multiple IV 50% dextrose and glucagon pushes.

Laboratory evaluation of hypoglycemia showed undetectable insulin [< 0.4 µU/mL (2.6-24.9 µU/mL)], low C-peptide [0.2 ng/mL (1.1-4.4 ng/mL)], lower normal pro-insulin [1.3 pmol/L (0-10.0 pmol/L)], and undetectable beta-hydroxybutyrate [< 0.1 mg/dL (0.2-2.8 mg/dL)], excluding the possibility of insulinoma. Sulfonfyurea screen test was negative. Adrenal insufficiency was also unlikely due to a high serum cortisol concentration. His hepatic function deteriorated [INR 2.8; albumin 2.9 g/dL (3.5-5.2 g/dL); total bilirubin 3.76 mg/dL (0.2-1.2 mg/dL); aspartate transaminase 145 U/L (< 40 U/L); alanine transaminase 93 U/L (< 41 U/L); alkaline phosphatase 263 U/L (40-130 U/L)]. Hepatic encephalopathy was also suspected due to high ammonia level [101 µmol/L (16-60 µmol/L)]. Child-Pugh score was calculated to be 11 (class C). AFP level was found to be elevated [108 ng/mL (< 8.3 ng/mL)]. Computed tomography of the abdomen with contrast showed cirrhosis and there was a centrally necrotic mass in the left hepatic lobe, measuring 6.7 cm × 6.5 cm (Figure 1). Three-phase liver computed tomography scan demonstrated suboptimal arterial phase enhancement due to the timing of the contrast with washout on delayed phase of the study. A subsequent biopsy confirmed the diagnosis of well differentiated HCC. No metastasis was found on bone scan. Therefore, NICTH was suspected. To establish the diagnosis, serum insulin-like growth factor-1 (IGF-1), IGF-2, and insulin-like growth factor-binding protein 3, the major binding protein for IGF-2 were measured. IGF-1 was suppressed [14 ng/mL (49-214 ng/mL)], IGF-2 was lower normal [303 ng/mL (300-960 ng/mL)], insulin-like growth factor-binding protein 3 was slightly decreased [2.2 µg/mL (2.6-4.8 µg/mL)], and the IGF-2/IGF-1 ratio was 21.6 (> 10), consistent with the diagnosis of NICTH.

**FINAL DIAGNOSIS**

NICTH (type B); well differentiated HCC, Barcelona Clinic Liver Cancer Stage D; decompensated liver cirrhosis, Child-Pugh Class C.

**TREATMENT**

The patient was not a candidate of transplant, surgical resection, or palliative chemotherapy due to the baseline poor hepatic function. He was started on oral prednisolone with a dose titrated up to 60 mg daily. There were less hypoglycemic episodes and the patient showed improvements in the severity of hypoglycemia. However, he still required on and off glucose supplements to maintain glucose homeostasis. While waiting for the trial of trans-arterial chemoembolization and radiotherapy, he developed hospital-acquired pneumonia. And concurrently his plasma glucose dropped and became difficult to correct again (Figure 2).

**OUTCOME AND FOLLOW-UP**

The patient opted for inpatient hospice care and died of septic shock on day 19 of hospitalization.

**DISCUSSION**

NICTH is a rare complication seen in patients with HCC. In the present case, the patient had advanced cirrhosis without regular follow up for a year, so it’s unclear when the HCC first developed. Interestingly, acute hypoglycemic encephalopathy occurred as the sole initial clinical symptom prior to the diagnosis of HCC. Different from a few previously reported cases, our patient had a very poor hepatic function and nutritional status which could both contribute to his hypoglycemia to some extent.
He might have developed chronic hypoglycemia with diminished awareness during the past year since there were no signs of sympathetic activation. This might obscure other underlying causes of hypoglycemia if patient was not assessed thoroughly. However, his glucose level fluctuated drastically and was very difficult to correct. Further investigation for NICTH is merited given high risk of malignancy.

Two types of NICTH (type A and B) are seen in HCC patients. Type A often occurs at the terminal stage of disease when there is an increased glucose consumption by the tumor on top of a progressive reduction in glucose supply due to hepatic failure on the residual liver tissue and in part due to malnutrition. The tumor mass is usually rapid growing and poorly differentiated, associated with severe anorexia, muscle wasting and weight loss. But hypoglycemia is often mild and relatively easier to correct.

Type B, less common than type A, is related to an overproduction of IGF-2 and its precursors by the tumor. It often occurs at the earlier course of the disease and is thought to be a paraneoplastic syndrome. The severity of hypoglycemia is predominant and is often difficult to control. Glucose utilization by the tumor might also contribute to the hypoglycemia but is not a significant pathway. The excess of IGF-2 Messenger RNA overwhelms the enzyme transforming pro-IGF-2 to mature IGF-2, thus producing various sizes of incompletely processed and unprocessed pro-IGF-2, the so called “big IGF-2”.

Normally most of serum IGF-2 is transported in the form of a 150 kDa ternary complex together with insulin-like growth factor-binding protein 3 and acid-labile sub-unit. But the “big IGF-2” mainly forms a 50 kDa binary complex with only insulin-like growth factor-binding protein 3. These binary complexes have a higher biological activity and can readily cross the capillary membrane to interact with insulin receptors in the liver, adipose tissue, and skeletal muscle due to their smaller size, leading to more glucose uptake and inhibition of gluconeogenesis. By interacting with the IGF-1 receptors in the hypothalamus, the excess of pro-IGF-2 and IGF-2 inhibits the secretion of growth hormone, which in turn suppresses the production of IGF-1, insulin-like growth factor-binding protein 3, and acid-labile sub-unit. Therefore, more amount of free IGF-2 might gain access to the target tissue.
As to our patient, IGF-2 was inappropriately normal for the extremely low IGF-1 level. An IGF-2/IGF-1 ratio greater than 10 has been proposed to be enough to confirm the diagnosis of NICTH\(^{22,23,24}\). IGF-2 might be falsely normal in our patient because the sample was collected after the first dose of prednisolone was administered, which was able to inhibit the production of IGF-2\(^{25}\). In addition, serum IGF-2 levels in NICTH are often not elevated partially because most “big IGF-2” are not measured by common commercially available assay\(^{26,27}\). It has also been found by a few case reports that the levels of serum IGF-2 were decreased or normal in contrast to an increased pro-IGF-2 in NICTH\(^{25,26}\). Pro-IGF-2 was not measured in this patient because the test was not available in our setting. Although we are not able to entirely exclude the possibility of excessive glucose consumption by the tumor, the tumor mass was not extensive, only occupying part of the left lobe, and the level of AFP was not significantly elevated, indicating mild biological activities. The hepatic failure was more likely due to his advanced cirrhosis rather than the tumor. Therefore, we believe that our case fits more into type B rather than type A NICTH.

Priority of management of NICTH is still tumor resection. In inoperable patients, several treatment options of local tumor cytoreduction are recommended, including percutaneous ethanol injection and trans-arterial chemoembolization\(^{28,29}\). Systemic chemotherapy, such as Sorafenib or FOLFIRI (oxaliplatin and 5-fluorouracil/leucovorin), has also been showed to be effective\(^{30}\). In addition, emerging drugs that directly inhibit the IGF signals (PI3K-AKT-TOR or RAF-MEK-ERK) are under investigation\(^{31}\). In case that the primary malignancy cannot be treated, palliative medical management can be chosen. Glucocorticoid together with frequent high carbohydrate meals and IV glucose infusions is an ideal option to achieve long-term prevention of hypoglycemia. Glucocorticoid, on one hand, stimulates hepatic gluconeogenesis and inhibits peripheral glucose uptake; on the other hand, can reduce the level of “big IGF-2” either by decreasing tumor production or by promoting the maturation of pro-IGF-2 and the formation of normal ternary complexes\(^{22,23,24}\). Other than glucocorticoid, glucagon, growth hormone, and octreotide infusion are also recommended, but their effects are transient and limited\(^{25,32-34}\). Our patient initially showed responses to high-dose prednisolone, but it failed to last for a long time mainly because of a poor hepatic reserve from cirrhosis. And the concurrent sepsis and pneumonia further destroyed patient’s ability to maintain the euglycemic status.

**CONCLUSION**

In conclusion, paraneoplastic NICTH should be considered in the evaluation of refractory hypoinsulinemic hypoglycemia in patients with risk factors of HCC, even in the setting of chronic fasting hypoglycemia induced by severe hepatic failure and malnutrition. NICTH can occur as the only initial presentation of HCC. Oral corticosteroids and frequent high carbohydrate meals are often recommended but the outcome is unfavorable in general if tumor removal is not possible.

**REFERENCES**

1. Marks V, Teale JD. Tumours producing hypoglycaemia. *Diabetes Metab Rev* 1991; 7: 79-91 [PMID: 1665409 DOI: 10.1002/dmr.56160070202]

2. Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumor hypoglycemia: a clinical review. *J Clin Endocrinol Metab* 2014; 99: 713-722 [PMID: 24423303 DOI: 10.1210/jc.2013-3382]

3. Ishida S, Noda M, Kuzuya N, Kubo F, Yamada S, Yamazaki T, Itozaki O, Hizuka N, Kanazawa Y. Big insulin-like growth factor II-producing hepatocellular carcinoma associated with hypoglycemia. *Intern Med* 1995; 34: 1201-1206 [PMID: 8979635 DOI: 10.2169/internalmedicine.34.1201]

4. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74-108 [PMID: 15761078 DOI: 10.3322/canjclin.55.2.74]

5. Lau CI, Wang HC, Hsu WC. Hypoglycemic encephalopathy as the initial presentation of hepatic tumor: a case report. *Neurologist* 2010; 16: 206-207 [PMID: 20445433 DOI: 10.1097/NRL.0b013e3181a6ec5f]

6. Jha V, Borpujari P. Hypoglycaemia presenting as sole manifestation of hepatocellular carcinoma. *Med J Armed Forces India* 2012; 68: 75-77 [PMID: 24669040 DOI: 10.1016/S0377-1237(11)60113-5]

7. Tsai CY, Chou SC, Liu HT, Lin JD, Lin YC. Persistent hypoglycemia as an early, atypical presentation of hepatocellular carcinoma: A case report and systematic review of the literature. *Oncol Lett* 2014; 8: 1810-1814 [PMID: 25202415 DOI: 10.3892/ol.2014.2365]

8. Sharma M, Reddy DN, Kiat TC. Refractory Hypoglycemia Presenting as First Manifestation of Advanced Hepatocellular Carcinoma. *ACG Case Rep J* 2014; 2: 50-52 [PMID: 26157905 DOI: 10.14309/crj.2014.82]

9. Zhou S, Jiang L, Sun M. Recurrent hypoglycemic coma as the initial and single clinical manifestation of advanced hepatocellular carcinoma. *J Gastrointest Cancer* 2015; 46: 64-67 [PMID: 25407746 DOI: ]
Yu B et al. NICTH as an initial presentation of HCC

10.1007/s12029-014-9670-3

McFadzean AJ, Yeung RT. Further observations on hypoglycaemia in hepatocellular carcinoma. Am J Med 1969; 47: 220-235 [PMID: 4209111 DOI: 10.1016/0002-9345(69)90148-3]

Yeung RT. Hypoglycemia in hepatocellular carcinoma: a review. Hong Kong Med J 1997; 3: 297-301 [PMID: 11847375]

Sorlini M, Benini F, Cravarezza P, Romaneli G. Hypoglycemia, an atypical early sign of hepatocellular carcinoma. J Gastrointest Cancer 2010; 41: 209-211 [PMID: 20204540 DOI: 10.1007/s12029-010-9137-0]

Daughaday WH, Emanuele MA, Brooks MH, Barbato AL, Kapadia M, Rotwein P. Synthesis and secretion of insulin-like growth factor II by a leiomyosarcoma with associated hyperglycemia. N Engl J Med 1988; 319: 1434-1440 [PMID: 3185562 DOI: 10.1056/NEJM1988123132202]

Iseman RC, Carson RE, Orloff DG, Cochran SS, Perdue JF, Teichler MM, Lanau F, Roberts CT Jr, Shapiro J, Roth J. Glucose utilization in a patient with hepatoma and hypoglycemia. Assessment by a positron emission tomography. J Clin Invest 1989; 85: 1958-1963 [PMID: 1318326 DOI: 10.1172/JCI115803]

Daughaday WH, Kapadia M. Significance of abnormal serum binding of insulin-like growth factor II in the development of hypoglycaemia in patients with non-islet-cell tumors. Proc Natl Acad Sci USA 1989; 86: 6778-6782 [PMID: 2771956 DOI: 10.1073/pnas.86.17.6778]

Teale JD, Marks V. Inappropriately elevated plasma insulin-like growth factor II in relation to suppressed insulin-like growth factor I in the diagnosis of non-islet cell tumour hypoglycaemia. Clin Endocrinol (Oxf) 1990; 33: 87-98 [PMID: 2205424 DOI: 10.1111/j.1365-2265.1990.tb00469.x]

Frohman LA, Downs TR, Chornycynski P. Regulation of growth hormone secretion. Front Neuroendocrinol 1992; 13: 344-405 [PMID: 1369911]

Dynekvy V, Rother KI, Whitford I, Qureshi K, Galiveetti S, Szulc AL, Danoff A, Breen TL, Kaviani N, Shanik MH, Leroith D, Vigneri R, Koch CA, Roth J. Tumors, IGF-2, and hypoglycemia: insights from the clinic, the laboratory, and the historical archive. Endocr Rev 2013; 34: 798-826 [PMID: 23671155 DOI: 10.1210/er.2012-0033]

Rana P, Kim B. A Unique Case of IGF-2 Induced Hypoglycaemia Associated with Hepatocellular Carcinoma. Case Rep Endocrinol 2019; 2019: 4601484 [PMID: 31737377 DOI: 10.1155/2019/4601484]

Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seasholtz ER, Service FJ, Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94: 709-728 [PMID: 19088155 DOI: 10.1212/jc.0b013e3181c84d9f]

Garla V, Sonani H, Palabindala V, Gomez-Sanchez C, Subauste J, Lien LF. Non-islet Cell Hypoglycemia: Case Series and Review of the Literature. Front Endocrinol (Lausanne) 2019; 10: 316 [PMID: 31156561 DOI: 10.3389/fendo.2019.00316]

Teale JD, Marks V. Glucocorticoid therapy suppresses abnormal secretion of big IGF-II by non-islet cell tumors inducing hypoglycaemia (NICTH). Clin Endocrinol (Oxf) 1998; 49: 491-498 [PMID: 9876347 DOI: 10.1046/j.1365-2265.1998.00564.x]

Yonei Y, Tanaka M, Ozawa Y, Miyazaki K, Tsukada N, Inada S, Inagaki Y, Miyamoto K, Suzuki O, Okawa H. Primary hepatocellular carcinoma with severe hypoglycaemia: involvement of insulin-like growth factors. Liver 1992; 12: 90-93 [PMID: 1320177 DOI: 10.1111/j.1600-0677.1992.tb00563.x]

Forde JJ, Ewelukwa O, Brar T, Cabrera R. Intractable Fasting Hypoglycemia as a Manifestation of Hepatocellular Carcinoma. Case Reports Hepatol 2017; 2017: 7465025 [PMID: 28783493 DOI: 10.1155/2017/7465025]

Zapf J, Futo E, Peter M, Froesch ER. Can “big” insulin-like growth factor II in serum of tumor patients account for the development of extrapancreatic hypoglycaemia? J Clin Invest 1992; 90: 2574-2584 [PMID: 1281841 DOI: 10.1172/JCI116152]

van den Berg SAA, Krol CG. Pro-IGF2-induced hypoglycaemia associated with hepatocellular carcinoma. Endocrinol Diabetes Metab Case Rep 2017; 2017 (PMID: 28561530 DOI: 17-0094)

Saigal S, Nandeshp 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: 1380-1381 [PMID: 9707076 DOI: 10.1111/j.1572-0241.1998.427_h.x]

Whitsett M, Lindenmeyer CC, Shaw CM, Civan JM, Fenkel JM. Transarterial chemoembolization for palliation of paraneoplastic hypoglycemia in a patient with advanced hepatocellular carcinoma. J Vasc Interv Radiol 2013; 24: 1918-1920 [PMID: 24267531 DOI: 10.1016/j.jvir.2013.07.002]

Huang JS, Chang PH. Refractory hypoglycaemia controlled by systemic chemotherapy with advanced hepatocellular carcinoma: A case report. Oncol Lett 2016; 11: 898-900 [PMID: 26873032 DOI: 10.3892/ol.2015.3915]

Gualberto A, Pollak M. Emerging role of insulin-like growth factor receptor inhibitors in oncology: early clinical trial results and future directions. Oncogene 2009; 28: 3009-3021 [PMID: 19581933 DOI: 10.1038/onc.2009.172]

Baxter RC, Holman SR, Corobud 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 tumour hypoglycaemia. J Clin Endocrinol Metab 1995; 80: 2700-2708 [PMID: 7545639 DOI: 10.1210/jeccm.80.9.7545639]

Thipaporn T, Bubpha P, Varaphon V. Hepatocellular carcinoma with persistent hypoglycemia: successful treatment with corticosterone and frequent high carbohydrate intake. J Med Assoc Thai 2005; 88: 1941-1946 [PMID: 16518997]

de Groot JW, Rikhof B, van Doorn J, Bilo HJ, Alleman MA, Honkoop AH, van der Graaf WT. Non-islet cell tumour-induced hypoglycaemia: a review of the literature including two new cases. Endocr Relat Cancer 2007; 14: 979-993 [PMID: 18045950 DOI: 10.1677/ERC-07-0161]

Wing JR, Panz VR, Joffe BI, Kalk WJ, Sefeld HC, Zapf J, Kew MC. Hypoglycemia in hepatocellular carcinoma: failure of short-term growth hormone administration to reduce enhanced glucose requirements. Metabolism 1991; 40: 508-512 [PMID: 1850816 DOI: 10.1002/0495190232-1]

Hoff AO, Vassilopoulou-Sellin R. The role of glucagon administration in the diagnosis and treatment of patients with tumor hypoglycemia. Cancer 1998; 82: 1585-1592 [PMID: 9554538]
