CASE REPORT

# Hepatocellular Carcinoma with Chronic Hepatitis B and Non-Islet Cell Tumor Hypoglycemia: A Case Report

**Angela Kimberly Tjahjadi[1], Imelda Maria Loho[2], Ummi Maimunah[3,4*]**

[1]Internal Medicine Specialist Study Program, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[2]Division of Gastroenterology and Hepatology, Dharmais National Cancer Center Hospital, Jakarta, Indonesia

[3]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[4]Indonesian Association of Internal Medicine

**ABSTRACT**

Non-islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome manifestation associated with hepatocellular carcinoma (HCC). This report details a case of a 20-year-old woman with HCC linked to untreated chronic hepatitis B. The patient presented with refractory hypoglycemia that was suspected to be NICTH. She also exhibited decreased consciousness with an initial blood glucose reading of 31 mg/dL. After the administration of intravenous dextrose solution, the patient's consciousness improved, yet intermittent hypoglycemic episodes persisted due to insufficient oral intake. The laboratory findings revealed low levels of insulin and C-peptide. The management of the patient included a continuous infusion of 5% dextrose solution, administration of corticosteroids, and adherence to a high-calorie complex carbohydrate diet. Despite presenting with significant right upper abdominal discomfort and weight loss, the patient was diagnosed with HCC at stage B, according to the Barcelona Clinic Liver Cancer (BCLC) Staging System. The stage was determined based on the presence of extensive multifocal lesions, which rendered surgical resection and transarterial chemoembolization (TACE) non-viable. Consequently, palliative treatment using lenvatinib and antiviral therapy with tenofovir were initiated. NICTH involves an increased insulin-like growth factor 2 (IGF-2) precursor processing by tumor cells, leading to heightened peripheral glucose utilization and persistent hypoglycemia. Although tumor resection is the most effective treatment for NICTH, it was not feasible in this case. This report emphasizes the importance of considering NICTH in the differential diagnosis of refractory hypoglycemia for non-diabetic patients. It also underscores the need for parenteral nutrition and corticosteroid therapy to maintain euglycemia.

**Keywords:** Chronic hepatitis B; hepatocellular carcinoma (HCC); refractory hypoglycemia; non-islet cell tumor hypoglycemia (NICTH); well-being

**Correspondence:** Ummi Maimunah
E-mail: ummi.maimunah@fk.unair.ac.id

**Highlights:**

1. This case report details a rare clinical presentation of non-islet cell tumor hypoglycemia (NICTH) associated with hepatocellular carcinoma (HCC) and chronic hepatitis B in a young patient, adding to the limited documented cases of this paraneoplastic syndrome.
2. The report provides a thorough clinical description, extensive diagnostic workup, and comprehensive management strategies, offering valuable insights into the complexities and challenges in diagnosing and treating NICTH in HCC patients.
3. This case emphasizes the critical need for early detection and intervention in HCC, particularly in non-cirrhotic patients with chronic hepatitis B, and highlights the importance of considering paraneoplastic syndromes in the differential diagnosis of refractory hypoglycemia in non-diabetic patients.

*Article history*: •Received 23 January 2024 •Revised 17 March 2024 •Accepted 5 April 2024 •Published 31 August 2024

## INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) has increased worldwide, reaching 906,000 new cases in 2020. This increase has made the disease rank as the sixth most common cancer around the world (Bray et al., 2018; Maharani et al., 2020; Putri et al., 2022). According to the Cancer Indonesia 2020 Country Profile, the incidence of HCC was 5.3% in 2018–2020, while the mortality rate reached 12.3% (Muljono, 2017; World Health Organization, 2020).

Until now, HCC are often diagnosed late and already at an advanced stage, resulting in more limited treatment alternatives, poor prognosis, and low survival rates. Among Asian populations where hepatitis B is endemic,

Available at https://e-journal.unair.ac.id/CIMRJ ; DOI: 10.20473/cimrj.v5i2.52406

the increased risk and faster onset of HCC is related to vertical hepatitis B infection (Kew, 2014; McGlynn et al., 2021; Azzahra et al., 2023). One of the very rare symptoms of paraneoplastic syndrome in HCC is non-islet cell tumor hypoglycemia (NICTH). It is characterized by a massive tumor burden and increased production of insulin-like growth factor 2 (IGF-2). The occurrence of refractory hypoglycemia in non-diabetic patients as a complication of HCC highlights the importance of considering paraneoplastic syndromes as a differential diagnosis. This case report aimed to present a rare clinical manifestation of NICTH as a paraneoplastic syndrome in HCC related to perinatally transmitted hepatitis B infection.

## CASE REPORT

A 20-year-old woman presented to the emergency room of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, with worsened generalized weakness, cold sweat, blurred vision, and confusion. Prior to admission at the emergency room, the patient was referred from Syarifah Ambami Rato Ebu Regional General Hospital, Bangkalan, Indonesia. The patient had been suffering from recurrent hypoglycemia, hepatocellular carcinoma (HCC), and chronic Hepatitis B for two months. The patient arrived at the emergency room in a state of unconsciousness due to hypoglycemia, with a blood glucose level of 31 mg/dL. After the administration of a 40% glucose (D40) intravenous injection, the patient's blood glucose was maintained with a continuous infusion of a 10% dextrose solution (D10), resulting in a blood glucose reading of 92 mg/dL. The patient initially complained of a palpable mass in the upper right abdomen, which had been causing discomfort for two months. The lump was not painful at first but became painful because it rapidly enlarged. The patient experienced rapid bloating and anorexia, resulting in a weight loss of 7 kg within the last two months.

According to the examination of the patient, a previous history of jaundice was denied. Additional risk factors, including needle use, tattooing, promiscuity, alcohol consumption, blood transfusions, and smoking, were also denied. The patient's family members initially denied a history of jaundice or hepatitis. However, it was later discovered that their screening results were reactive for hepatitis B surface antigen (HBsAg).

Upon physical examination, it was observed that the patient was malnourished, as indicated by a body mass index (BMI) of 17.9 kg/m2. An examination of the abdomen revealed a palpable mass in the right hypochondriac and epigastric regions, measuring approximately 5 x 4 x 3 cm. The mass was hard, with a smooth surface, and fixed, accompanied by hepatomegaly extending 4 cm below the right costal arch.

The initial laboratory examination showed the following results: a hemoglobin level of 10.3 g/dL, a hematocrit concentration of 31.1%, a mean corpuscular volume (MCV) level of 68.4 fL, a mean corpuscular hemoglobin (MCH) level of 22.6 pg, a mean corpuscular hemoglobin concentration (MCHC) of at 33.1 g/dL, and a reticulocyte count of 0.6%. The examination also revealed that the leukocyte count was 12,510 cells/µL, with the eosinophil count at 1.2%, the basophil count at 0.5%, the neutrophil count at 63.9%, the lymphocyte count at 29.4%, and the monocyte count at 5.0%. The platelet count was found to be 755 x 109/L.

The patient's peripheral blood smear revealed hypochromic microcytic anemia and leukocytosis. The blood glucose reading was 40 mg/dL, and the hemoglobin A1c (HbA1c) level was 3.4%. Additionally, the blood smear revealed the following results: a serum iron level of 35.0 mcg/dL, a total iron binding capacity (TIBC) of 273 mg/dL, a transferrin saturation of 12.82%, a blood urea nitrogen (BUN) level of 3.0 mg/dL, and a serum creatinine level of 0.4 mg/dL. The electrolyte levels were measured as follows: sodium at 139 mmol/L, potassium at 3.6 mmol/L, and chloride at 103 mmol/L.

The results of the liver function tests exhibited an aspartate aminotransferase (AST) level of 311 U/L, an alanine transaminase (ALT) level of 31 U/L, a total

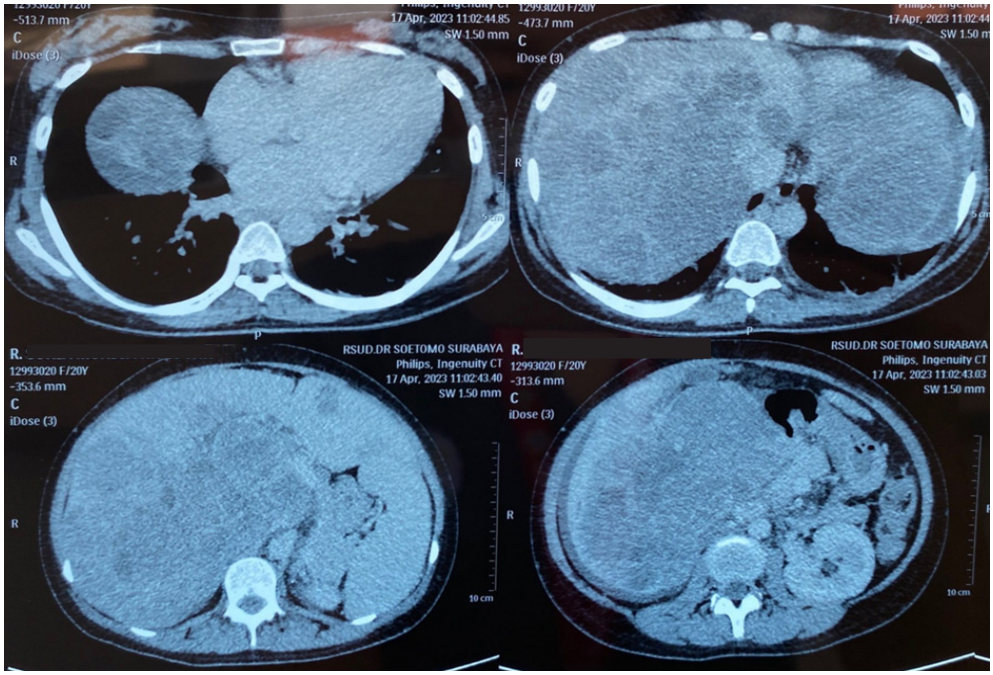


Figure 1. Results of the patient's abdominal computed tomography scan

bilirubin level of 0.7 mg/dL, and a direct bilirubin level of 0.3 mg/dL. In addition, the levels of amylase and lipase were measured to be 44 U/L and 103 U/L, respectively.

The coagulation profile revealed a prothrombin time of 11.9 seconds, an international normalized ratio (INR) of 1.04, and an activated partial thromboplastine time (APTT) of 28.3 seconds. The measured albumin level was found to be 3.81 g/dL. The hepatitis B markers were reactive for hepatitis B surface antigen (HBsAg) and total antibody to the hepatitis B core antigen (total anti-HBc), but non-reactive for hepatitis B e-antigen (HBeAg). The level of hepatitis B virus deoxyribonucleic acid (HBV DNA) was determined to be 20 (log 1.3). The alpha-fetoprotein (AFP) level was greater than 1,000 ng/mL, while the serum cortisol was 291.6 mcg/dL.

A comprehensive evaluation of the refractory hypoglycemia revealed significantly suppressed serum insulin concentrations (<0.2 mU/L; normal range: 3–25 mU/L). No sulphonylurea derivatives or C-peptide (<0.01 pmol/L; normal range: 350–700 pmol/L) were detected. Unfortunately, tests for examining insulin antibodies, pheochromocytoma screening, and insulin-like growth factors 1 and 2 (IGF-1 and IGF-2) were not available at our hospital. As a result, the suspected diagnoses included hypoglycemia due to tumor consumption or paraneoplastic hypoglycemia caused by "big" IGF-2 production. The patient required continuous dextrose intravenous infusion to maintain normal blood glucose levels and remain symptom-free.

A three-phase contrast-enhanced computed tomography (CT) scan of the patient's abdomen revealed hepatomegaly with enhancing solid masses in both the right and left lobes of the liver (Figure 1). The largest mass, measuring approximately 6.97 x 5.8 x 6.4 cm, was located in segment VIII of the right lobe and appeared to be a hepatoma. The mass demonstrated early wash-in during the arterial phase (68 HU), early wash-out during the venous phase (46 HU), and delayed phase (48 HU). No visible thrombus was observed in the portal vein, and there were no signs of ascites or para-aortic lymphadenopathy (approximately 1.1 cm).

The assessment of the patient revealed that she had hepatocellular carcinoma (HCC) classified as stage B according to the Barcelona Clinic Liver Cancer (BCLC) Staging System, non-islet cell tumor hypoglycemia (NICTH), chronic hepatitis B, anemia of chronic disease, and cancer pain. Furthermore, the patient was assessed to have a Child-Turcotte-Pugh (CTP) score that corresponds to class B. The Eastern Cooperative Oncology Group (ECOG) Performance Status assessment indicated that the patient was in grade 2. A blood glucose evaluation was carried out every hour until the levels were stabilized above 100 mg/dL, after which it was evaluated periodically. We recommended a high-calorie and high-protein diet, with a daily intake of 2,100 kcal. This diet particularly consisted of complex carbohydrates, such as a slice of whole wheat bread or a teaspoon of honey every two hours. The medications administered included 1,000 mL of 5% dextrose infusion every 24 hours, 300 mg qd tenofovir disoproxil fumarate (TDF), 10 mg tid intravenous metoclopramide, 30 mg bid intravenous lansoprazole, 100 mg qd hydrocortisone, 500 mg tid intravenous paracetamol, 10 mg tid codeine, and 100 mg qd spironolactone.

The patient underwent consultation with the Department of Interventional Radiology regarding the consideration of receiving transarterial chemotherapy embolization (TACE). However, absolute contraindications for TACE were found: tumor extending to both liver lobes and tumor size above 50% of the total liver mass. The administration of systemic targeted therapy with lenvatinib or sorafenib was planned. Before the initiation of tyrosine kinase inhibitor therapy, the patient underwent endoscopic examination for a pretreatment evaluation of erosive gastritis. The patient was discharged from the hospital after her blood glucose levels were stabilized using a dextrose infusion, 5 mg q8h prednisone, and a frequent feeding schedule. During the outpatient visits, moderate ascites was found. As a result, the patient was prescribed additional therapy, comprising per oral administration of 100 mg qd spironolactone and 40 mg qd furosemide. However, three weeks later, the patient's condition had deteriorated with a Child-Turcotte-Pugh (CTP) score of 8, indicating a classification of class B. In addition, the Eastern Cooperative Oncology Group (ECOG) Performance Status assessment revealed that the patient had a performance status of 1–2. Therefore, the patient did not qualify for tyrosine kinase inhibitor therapy. The patient was admitted for supportive palliative therapy with the aim of improving her quality of life. Nevertheless, the patient succumbed to her illnesses as a result of respiratory arrest after experiencing another episode of hypoglycemia at home.

## DISCUSSION

Refractory hypoglycemia linked to paraneoplastic syndrome, namely non-islet cell tumor hypoglycemia (NICTH), is a rare complication of hepatocellular carcinoma (HCC). Hypoglycemia is a medical emergency characterized by the presence of Whipple's triad, which includes symptoms and/or signs consistent with hypoglycemia, serum blood sugar levels below 55 mg/dL as measured using a venous blood sample, and the resolution of symptoms and signs after an increase in serum blood sugar levels. The symptoms and signs of hypoglycemia are divided into two categories: autonomic (such as palpitations, tremors, anxiety, pallor, hunger, diaphoresis, and paresthesia) and neuroglycopenic (such as delirium, amnesia, blurred vision, diplopia, dysarthria, seizures, and decreased consciousness) (Martens & Tits, 2014; Alwi et al., 2019; Melmed et al., 2019; Sabatine, 2020). The patient reported in this paper was found to have neuroglycopenic and autonomic symptoms of hypoglycemia. The patient's initial blood glucose level was recorded at 37 mg/dL. Following the injection of 40% dextrose solution, the patient's consciousness began to improve, and her blood glucose reading was monitored periodically.

NICTH is prevalent among patients with epithelial tumors (45%) and mesenchymal tumors (42%), particularly in HCC patients (20%). Approximately 50% of patients with NICTH exhibit hypoglycemia as the first manifestation of the disease. However, the remaining half of the patients experience hypoglycemia, which frequently occurred long after the diagnosis of the neoplasm was established (Thiruchelvam et al., 2015; Garla et al., 2019; Rojbi et al., 2021). The pathophysiology of NICTH in HCC is often associated with abnormalities in the maturation process of insulin-like growth factor 2 (IGF-2). Insulin-like growth factors 1 and 2 (IGF-1 and IGF-2) are able to reduce the levels of glucose in the blood. However, under physiological conditions, both protein hormones are retained intravascularly because they are almost entirely bound to the IGF binding protein 3 (IGFBP-3). In normal people, it is estimated that as much as 20% of IGF-2 exists

in the form of binary complexes, whereas the remaining 80% is present as the more stable ternary complexes. Meanwhile, in patients with NICTH, there is an increase in total and large IGF-2 production. This leads to an increase in the concentration of free IGF-2 in a binary form with a higher bioavailability to cross the endothelial wall more easily. As a result, persistent hypoglycemia occurs more often in patients with NICTH (Wong, 2015; Behringer-Massera et al., 2017; Albayrak et al., 2022).

The patient in this case report was diagnosed with refractory hypoglycemia, which was suspected to be a non-islet cell tumor hypoglycemia. The diagnosis was established based on the massive size of the HCC epithelial tumor, high IGF-II production, decreased glycogen reserves, suboptimal gluconeogenesis, and hepatocyte glycogenolysis. Additionally, the diagnosis was supported by a C-peptide level measuring below 0.01 nmol/L and an insulin level under 0.2 uIU/L during an episode of hypoglycemia. Unfortunately, the assessment of the IGF-2 to IGF-1 ratio and the autoimmune insulin antibody was not possible due to limited resources. The IGF-2/IGF-1 ratio is helpful in cases where the levels of IGF-2 are within the normal range. A ratio greater than 10:1 is virtually conclusive in terms of diagnosis (Jannin et al., 2019; Rojbi et al., 2021; Ariana et al., 2024). Very low levels of serum C-peptide and insulin rule out the differential diagnosis of endogenous hyperinsulinism, including cases resulting from insulinoma and the usage of exogenous insulin or insulin secretagogues. The patient's morning serum cortisol levels were within normal limits, indicating that the possibility of adrenal insufficiency could be ruled out (Alharbi, 2014; Sharma et al., 2015). No signs of acute liver failure, decompensated cirrhosis, or severe infections were present in this patient. Yet, individuals who are undernourished and have insufficient subcutaneous fat may be at a higher risk of experiencing hypoglycemia compared to those with normal nutritional status.

If the tumor size can still be resected, a surgical intervention is proven to be the most effective first-line therapy for NICTH. Generally, the symptoms of hypoglycemia will not recur after a complete or incomplete tumor resection (Huang & Chang, 2016; Kitada et al., 2016; Rojbi et al., 2021). The administration of corticosteroids, such as dexamethasone, hydrocortisone, prednisolone, and methylprednisolone, at a dose of 1–1.5 mg/kg bw per day (equivalent to 30–60 mg of prednisone) is proven to be able to maintain euglycemia. These medications have the ability to suppress IGF-2 secretion and reduce tissue sensitivity to insulin, resulting in the reduction of glucose utilization by peripheral tissues and the stimulation of gluconeogenesis in the liver and kidneys (Sharma et al., 2015; Regino et al., 2020; Sandooja et al., 2020; Haeri et al., 2021). Hydrocortisone (with a half-life of 8–12 hours) or methylprednisolone (with a half-life of 12–36 hours) are glucocorticoids that are recommended due to their short duration of action (Samuel et al., 2017). Providing enteral nutrition via a nasogastric tube (NGT) or parenteral route, both partial and total, is mandatory when oral intake is inadequate (Bodnar et al., 2014; Regino et al., 2020; Albayrak et al., 2022).

Initially, we planned to insert a nasogastric tube or central venous access to provide additional parenteral nutrition if the patient continued to have difficulty with oral intake. However, the patient's oral intake gradually increased as her consciousness improved. The patient was then educated to consume a complex carbohydrate diet every two hours while also receiving 1,000 cc of 5% dextrose intravenous infusion per 24 hours. Intravenous injection of hydrocortisone at a dose of 100 mg was also given per 24 hours (Sharma et al., 2015). However, considering the risk of hepatitis B relapse or flare, steroids were only administered temporarily during the inpatient treatment for four days. The patient did not receive any glucagon or recombinant growth hormone injections due to the unavailability of these treatments at our center. The patient's blood glucose levels were finally stabilized within the range of 60-80 mg/dL, with no episodes of severe hypoglycemia.

This paper presents a detailed and comprehensive case report on a rare and complex condition known as non-islet cell tumor hypoglycemia (NICTH) that is associated with hepatocellular carcinoma (HCC) and chronic hepatitis B. The strength of this case report lies in its thorough clinical descriptions, extensive diagnostic workup, and management strategies, providing valuable insights into the challenges and decision-making processes in treating similar cases. However, a significant limitation in this study is the absence of advanced diagnostic tests, such as the measurement of insulin-like growth factor 2 (IGF-2), which could have definitively confirmed the diagnosis of NICTH. Additionally, the lack of long-term follow-up data limited the assessment of the full impact of the treatment strategies employed. The reliance on palliative care without the possibility of surgical intervention due to the advanced stage of the disease also underscores the critical need for early detection and intervention.

## SUMMARY

This case report underscores the complexity and rarity of non-islet cell tumor hypoglycemia (NICTH) associated with hepatocellular carcinoma (HCC) in a young patient with chronic hepatitis B. Despite the comprehensive diagnostic and therapeutic efforts, including the administration of corticosteroids and continuous dextrose infusion, the advanced stage of HCC and the extensive tumor burden precluded curative surgical interventions. The case highlights the critical need for early detection and intervention in HCC to prevent its progression to advanced stages where treatment options become severely limited. Furthermore, it reiterates the importance of taking paraneoplastic syndromes, such as NICTH, into consideration when determining the differential diagnosis of refractory hypoglycemia in non-diabetic patients. This report adds valuable insights into the management challenges and clinical decision-making processes for such complex cases, advocating for heightened awareness and multidisciplinary approaches in similar future scenarios.

## ACKNOWLEDGEMENT

We would like to express our sincere gratitude to the patient and her family for allowing us to publish this case, thereby contributing to the broader medical community's knowledge, particularly in Indonesia. We hope that this invaluable contribution will lead to improved care and better outcomes for patients with similar illnesses.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## PATIENT CONSENT FOR PUBLICATION

Before submitting this case report, we obtained informed consent from the patient's mother for the purpose of publication. We maintain strict confidentiality concerning the patient's identity and personal information.

## FUNDING DISCLOSURE

The authors received no external funding from any institutions.

## AUTHOR CONTRIBUTION

AKT contributed to the conception and design, analysis and interpretation of the data, drafting of the article, final approval of the article, provision of the patient, and collection and assembly of data. IML and UMH contributed to the conception and design, critical revision of the article for important intellectual content, final approval of the article, and administrative, technical, or logistic support.

## REFERENCES

Albayrak B, Duman MB, Ayvaz E (2022). A case of hepatocellular carcinoma diagnosed with resistant hypoglycemia. Open Journal of Gastroenterology 12(08): 179–185. doi: 10.4236/ojgas.2022.128018.

Alharbi MS (2014). A 94-year-old man with recurrent hypoglycemia caused by non-islet cell tumor hypoglycemia (NICTH). International Journal of Health Sciences 8(4): 430–433. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25780362.

Alwi I, Salim S, Hidayat R, Kurniawan J, Tahapary D (2019). Penatalaksanaan di bidang ilmu penyakit dalam panduan praktik klinis. PIP Interna, Jakarta, 4th ed. Retrieved from https://library.stikesmus.ac.id/index.php?p=show_detail&id=356&keywords=.

Ariana AM, Permadi GA, Susanto H (2024). Approach to refractory hypoglycaemia in a patient with hepatocellular carcinoma: A case study and literature review. Journal of Agromedicine and Medical Sciences 10(1): 5–11. doi: 10.19184/ams.v10i1.45924.

Azzahra S, Kholili U, Setiawati R, Maimunah U (2023). Profile of patients of hepatocellular carcinoma in the Internal Medicine Inpatient Room at Dr. Soetomo General Academic Hospital. Current Internal Medicine Research and Practice Surabaya Journal 4(1): 1–5. doi: 10.20473/cimrj.v4i1.42287.

Behringer-Massera S, Brutsaert EF, Epstein EJ (2017). Refractory hypoglycemia from paraneoplastic insulin-like growth factor 2 secretion in a patient with hepatocellular carcinoma. AACE Clinical Case Reports 3(4): 364–366. doi: 10.4158/EP171744.CR.

Bodnar TW, Acevedo MJ, Pietropaolo M (2014). Management of non-islet-cell tumor hypoglycemia: A clinical review. The Journal of Clinical Endocrinology & Metabolism 99(3): 713–722. doi: 10.1210/jc.2013-3382.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 68(6): 394–424. doi: 10.3322/caac.21492.

Garla V, Sonani H, Palabindala V, Gomez-Sanchez C, Subauste J, et al. (2019). Non-islet cell hypoglycemia: Case series and review of the literature. Frontiers in Endocrinology 10. doi: 10.3389/fendo.2019.00316.

Haeri NS, Mahmud H, Korytkowski MT (2021). Paraneoplastic hypoglycemia leading to insulin independence in a patient with type 1 diabetes. AACE Clinical Case Reports 7(6): 376–378. doi: 10.1016/j.aace.2021.05.006.

Huang JS, Chang PH (2016). Refractory hypoglycemia controlled by systemic chemotherapy with advanced hepatocellular carcinoma: A case report. Oncology Letters 11(1): 898–900. doi: 10.3892/ol.2015.3915.

Jannin A, Espiard S, Benomar K, do Cao C, Mycinski B, et al. (2019). Non-islet-cell tumour hypoglycaemia (NICTH): About a series of 6 cases. Annales d'Endocrinologie 80(1): 21–25. doi: 10.1016/j.ando.2018.01.005.

Kew M (2014). Hepatocellular carcinoma: Epidemiology and risk factors. Journal of Hepatocellular Carcinoma 115. doi: 10.2147/JHC.S44381.

Kitada M, Yasuda S, Takahashi N, Okazaki S, Ishibashi K, et al. (2016). Non-islet cell tumor hypoglycemia caused by intrathoracic solitary fibrous tumor: A case report. Journal of Cardiothoracic Surgery 11(1): 49. doi: 10.1186/s13019-016-0463-6.

Maharani I, Koesmarsono N, Laraswati B (2020). Relation between the increase of alpha fetoprotein serum level and the size of hepatocellular carcinoma in multi slice computed tomography examination. Indian Journal of Forensic Medicine & Toxicology 14(2): 2353–2357. doi: 10.37506/ijfmt.v14i2.3380.

Martens P, Tits J (2014). Approach to the patient with spontaneous hypoglycemia. European Journal of Internal Medicine 25(5): 415–421. doi: 10.1016/j.ejim.2014.02.011.

McGlynn KA, Petrick JL, El-Serag HB (2021). Epidemiology of hepatocellular carcinoma. Hepatology 73(S1): 4–13. doi: 10.1002/hep.31288.

Melmed S, Koenig R, Rosen CJ, Auchus RJ, Goldfine AB (2019). Williams textbook of endocrinology. Elsevier, Philadelphia, 14th ed. Retrieved from https://books.google.co.id/books/about/Williams_Textbook_of_Endocrinology_E_Boo.html?id=j-u9DwAAQBAJ&redir_esc=y.

Muljono DH (2017). Epidemiology of hepatitis B and C in Republic of Indonesia. Euroasian Journal of Hepato-Gastroenterology 7(1): 55–59. doi: 10.5005/jp-journals-l0018-1212.

Putri DRI, Maimunah U, Retnowati E (2022). Serum AFP (alpha fetoprotein) levels profile of hepatocellular ccrcinoma patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Majalah Biomorfologi 32(1): 6. doi: 10.20473/mbiom.v32i1.2022.6-12.

Regino CA, López-Montoya V, López-Urbano F, Alvarez JC, Roman-Gonzalez A (2020). Paraneoplastic hypoglycemia in hepatocarcinoma: Case report and literature review. Cureus 12(12): e12013. doi: 10.7759/cureus.12013.

Rojbi I, Ben Elhaj W, Mchirgui N, Jrad M, Ben Nacef I, et al. (2021). Non-islet-cell tumor hypoglycemia as first manifestation of an advanced hepatocellular carcinoma. Clinical Case Reports 9(10): e05012. doi: 10.1002/ccr3.5012.

Sabatine MS (Ed.) (2020). Pocket medicine: The Massachusetts General Hospital handbook of internal medicine. Wolters Kluwer, 7th ed. Retrieved from https://internalmedicine.lwwhealthlibrary.com/book.aspx?bookid=2726.

Samuel S, Nguyen T, Choi HA (2017). Pharmacologic characteristics of corticosteroids. Journal of Neurocritical Care 10(2): 53–59. doi: 10.18700/jnc.170035.

Sandooja R, Moorman JM, Kumar MP, Detoya K (2020). Critical low catastrophe: A case report of treatment-refractory hypoglycemia following overdose of long-acting insulin. Case Reports in Endocrinology 2020: 1–5. doi: 10.1155/2020/8856022.

Sharma M, Reddy DN, Kiat TC (2015). Refractory hypoglycemia presenting as first manifestation of advanced hepatocellular carcinoma. ACG Case Reports Journal 2(1): 50–52. doi: 10.14309/crj.2014.82.

Thiruchelvam N, Kistangari G, Listinsky C, Daw H, Kumar V (2015). Life-threatening hypoglycemia resulting from a nonislet cell tumor. The Journal of Community and Supportive Oncology 13(8): 296–297. doi: 10.12788/jcso.0163.

Wong WK (2015). Non-islet cell tumour hypoglycaemia (NICTH) in malignant mesothelioma: Case report. The Malaysian Journal of Medical Sciences : MJMS 22(4): 81–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26715913.

World Health Organization (2020). Cancer Indonesia 2020 country profile. Retrieved from https://www.who.int/publications/m/item/cancer-idn-2020.