Secondary Polycythemia and Non-Islet Cell Tumor-induced Hypoglycemia in Advanced Hepatocellular Carcinoma: A Case Report

Maria Satya Paramitha[1], Dekta Filantropi Esa[1], Ni Made Hustrini[2]*, Nadia Ayu Mulansari[3], Irsan Hasan[4], Agnes Stephanie Harahap[5]

[1]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Division of Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[5]Department of Anatomical Pathology, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

****Corresponding Authors:***
Ni Made Hustrini, MD. Division of Nephrology and Hypertension, Depthe artment of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: madekum99@gmail.com.

ABSTRACT

Continuously holding its position as the sixth most common cause of cancer and the third leading cause of cancer death, globally, Hepatocellular Carcinoma (HCC) remains as a healthcare priority. Production of various substances may result into systemic or metabolic complications, often known as paraneoplastic phenomena of HCC.

A 56-year-old male with history of untreated chronic hepatitis B arrived with generalized weakness and intermittent headache in the last two days prior to admission. Laboratory findings demonstrated elevated hemoglobin (20.5 g/dl), alpha-fetoprotein (29,845 ng/dl), and d-Dimer (2,120 ng/ml) levels. Hypoglycemia (44 mg/dl) was documented with normal basal insulin level, confirming non-islet cell tumor hypoglycemia. Abdominal multiphasic CT-scan demonstrated a large solid lesion involving the whole right liver lobe, hyper-enhanced at arterial phase and wash-out pattern at venous and delayed phases, with portal vein thrombosis; thus, confirming HCC BCLC C. Further examinations revealed hypercellularity from bone marrow biopsy with the absence of JAK2 mutation. He underwent serial phlebotomy and received 80 mg acetylsalicylic acid orally, as well as cytoreductive agent to reduce the risk of thrombosis. Despite applications of different interventions, control of hypoglycemia could not be achieved without parenteral administration of high dextrose load. He was planned to receive oral multikinase inhibitor, however, he passed away due to severe hospital-acquired pneumonia.

Paraneoplastic phenomena are common in HCC. Increased risk of blood hyper-viscosity and thrombosis attributed to polycythemia, as well as medical emergency resulting from hypoglycemia showed that both conditions should not be overlooked since they may worsen the patient's prognosis.

Keywords: *Hepatocellular Carcinoma, Secondary Polycythemia, Secondary Erythrocytosis, Non-Islet Cell Tumor-Induced Hypoglycemia.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common liver-related malignancy worldwide, including in the Southeast Asia region. Aside from continuously increasing annual incidence, HCC also maintains its position as the sixth most common malignancy and the third most common cause of cancer-related death globally.[1,2] In the last two decades, the increased global healthcare burden due to HCC has been mainly affected by a higher incidence rate of HCC-related risk factors, for instance, chronic hepatitis B, chronic hepatitis C, or non-alcoholic steatohepatitis. Additionally, many HCC patients only came to seek medical assistance after clinical manifestations had occurred, in which most of them had already been in advanced stages with small opportunities to perform potentially curative therapies.[3] In Indonesia itself, the incidence rate of HCC is estimated to be as high as 10.4 cases per 100,000 person-years.[1]

One of the events that can result in worsening clinical progression of HCC patients is paraneoplastic phenomena. Paraneoplastic complications may occur in the form of systemic and metabolic events as a direct or indirect effect of the release of abnormal substances by tumor cells to extracellular organs through the bloodstream.[4] Aside from being widely known as oncologic emergencies, previous studies demonstrated paraneoplastic phenomena as a clinically and statistically significant independent predictor of worse prognosis in HCC patients with 36 days of average survival. The most common paraneoplastic phenomena in HCC patients are polycythemia or erythrocytosis, hypoglycemia, hypercholesterolemia, and hypercalcemia.[4,5] The case that will be discussed in this report will highlight the importance of early detection of paraneoplastic phenomena in HCC patients, particularly polycythemia and recurrent hypoglycemia, as well as their implications on the care plan of the patients.

CASE ILLUSTRATION

A 56-year-old male arrived with the chief complaint of worsened generalized weakness in the last two days before hospital admission. The patient reported recurrent headaches with a Visual Analogue Scale (VAS) of 3-4 without any sign of central involvement. Significant weight loss (approximately 10 kg) was reported in the last three months, accompanied by an enlarged mass in the right upper quadrant of the abdomen and chronic pain (VAS 4-5). Past medical history of untreated chronic hepatitis B infection in the last four years before hospital admission. He also had a family history of his older brother with liver cancer, as well as smoking habits and alcohol consumption for more than two decades.

Clinical examination demonstrated normal vital signs and a stable hemodynamic state. His functional status score was 2 according to the Eastern Cooperative Oncology Group (ECOG) classification. Abdominal examination revealed an immobile, hard, and irregular hepatomegaly with dilation of collateral veins. Splenomegaly was identified at Schaffner 2. There was also pain upon palpation of the right hypochondriac region. Skin examination demonstrated multiple plethoras on both of his upper extremities without any pain upon palpation. Pitting edema was observed on both of his lower extremities.

Laboratory examinations showed a significant increase in hemoglobin (20.5 g/dl) and hematocrit (65.8%) levels. We found hypoalbuminemia (2.6 mg/dl), increased levels of total bilirubin (2.41 mg/dl) and direct bilirubin (1.44 mg/dl), as well as increased d-Dimer level (2,120 ng/ml). A peripheral blood smear examination indicated polycythemia with thrombocytopenia. Hypoglycemia of 46 mg/dl was noticed, and he was immediately resuscitated with intravenous dextrose infusion. Further examination showed a normal basal insulin level (20 mIU/ml). His serology results showed reactive hepatitis B surface antigen (HBsAg), non-reactive hepatitis B e-antigen (HBeAg), reactive anti-hepatitis B e-antigen (anti-HBe), together with a high quantitative HBV DNA level of $4.72x10^4$ IU/ml. Serum alpha-fetoprotein (AFP) level was significantly increased (29,845 ng/ml).

Multiphasic upper abdominal Computed Tomography (CT) scan demonstrated a large-sized lesion, involving almost the whole portion of the right liver lobe with a hypervascularity appearance on arterial phase and wash-out appearance on venous and delayed phases.

Additionally, there were multiple satellite nodules on the second, seventh, and eighth segments of the liver (**Figure 1**). The radiographic findings also showed a right portal vein tumoral thrombus (**Figure 1(d), 1(e)**). Another tumoral thrombus was also seen on the inferior vena cava, located as high as the inter-diaphragm until the right atrium (**Figure 1(a)**). Bilateral pleural effusions and multiple lung nodules were also detected from the CT scan.

The patient was then diagnosed with HCC Barcelona Clinic Liver Cancer (BCLC) stage C. A bone marrow biopsy examination was performed and confirmed the presence of polycythemia with hypercellularity of bone marrow (**Figure 2(a), 2(b)**). From the biopsy findings, increased megakaryocytes with normal morphology were also observed (**Figure 2(c)**). From reticulin staining, there was no increased reticulin fibers from the findings (**Figure 2(d)**). No presence of somatic mutation of the Janus Kinase 2 (JAK-2) gene.

The main focus of the initial treatment was to manage the oncological emergencies,

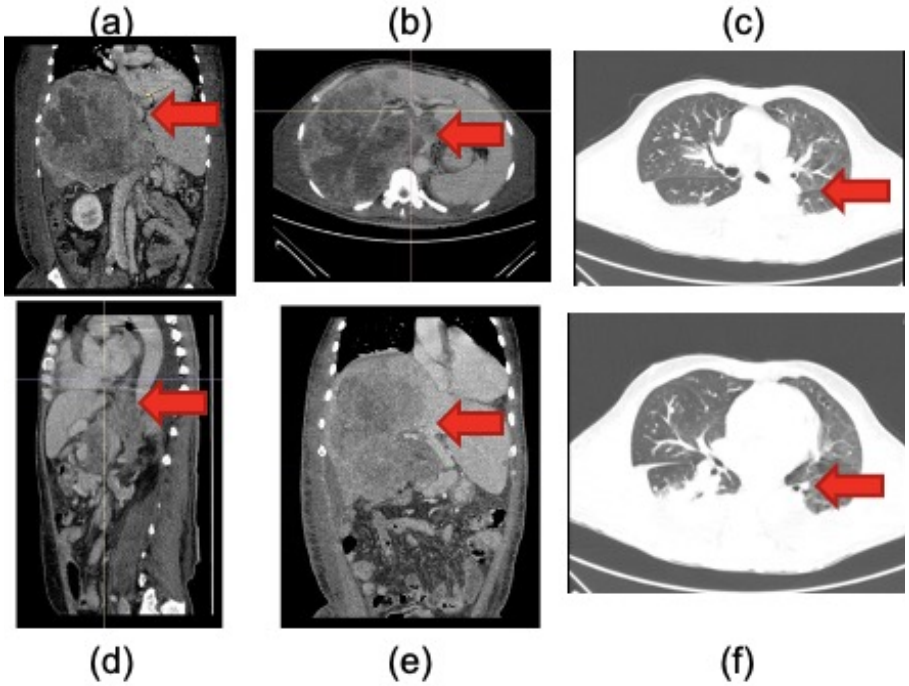

Figure 1. Radiographic findings from upper abdominal multiphasic CT-scan demonstrated a large hepatic lesion [(a), (b)] with the involvement of portal vein [(d), (e)] and extrahepatic manifestation [(c), (f)].

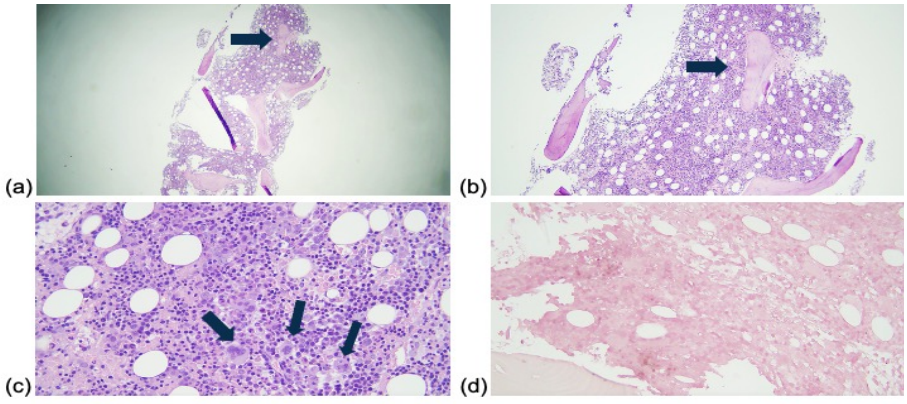

Figure 2. Histopathological examination with hematoxylin-eosin staining showed bone marrow hypercellularity ((a) and (b)) and increased megakaryocytes with normal morphology (c). No appearance of increased reticulin fibers was observed from reticulin staining (d).

i.e., polycythemia with the evidence of metastatic thrombosis in addition to recurrent hypoglycemia. We performed serial phlebotomy (twice a week), together with adequate hydration, initial administration of 50 ml of dextrose 40% intravenously, and maintained with dextrose 10% to a target level of at least 70 mg/dl of random blood glucose. Despite having received additional complex carbohydrates in his diet, hypoglycemic episodes still recurred; thus, parenteral administration of dextrose was continued until the end of his hospitalization. The patient also received cytoreductive agents in the form of hydroxyurea, as well as antiplatelet therapy (80 mg of acetylsalicylic acid daily per oral). **Figure 3** shows the clinical response after serial phlebotomy and oral cytoreduction treatment. Due to the advanced stage of the disease and the poor clinical condition of the patient, he was not a candidate for surgical therapy. However, the administration of oral multi-kinase inhibitors as one of the available systemic therapies for HCC in Indonesia was considered along with nucleoside and nucleotide analog as antiviral therapy. Unfortunately, both plans were never been implemented because the patient passed away due to severe hospital-acquired pneumonia.

DISCUSSION

Polycythemia and hypoglycemia are two paraneoplastic phenomena that can be found in HCC patients. Erythrocytosis or polycythemia cases are more uncommonly found in HCC patients compared to recurrent hypoglycemia. Nevertheless, previous studies in the African population found that the incidence of polycythemia in HCC patients ranged from 1% to 15.6%. In these studies, however, several confounding factors were noticed, such as the geographical locations of the subjects, where almost all of them were located in areas with an altitude of 1,750 meters above sea level. Another important confounding factor was a prominent delay in diagnosing HCC. Consequently, there might be some subjects who demonstrated normal or low hemoglobin levels attributed to anemia of chronic disease, while actually, they might exhibit polycythemia manifestation before the diagnosis of HCC.[4,6] An epidemiological study involving 792 HCC patients in China demonstrated that the prevalence of polycythemia was approximately 2%-5%.[7] On the other hand, the incidence of paraneoplastic hypoglycemia in HCC patients is more frequently found, with the incidence reaching as high as 24% in South America and 40% in Hong Kong.[4,8] More data from more recent epidemiological studies found that the prevalence of polycythemia was 3.9% in 457 HCC patients,[9] while the incidence of persistent hypoglycemia was 28.9% in 232 HCC patients.[10] A systematic review also pointed out that the estimated blood glucose level of HCC patients when they were first diagnosed was 30.8±12.2 mg/dl. This study also found that early manifestations related to hypoglycemia in these patients were significant dizziness (44.4%), nausea and/or abdominal pain (22.2%), and weight loss (27.8%).[11] All those findings were in line with the clinical manifestation and laboratory findings of our patient in this report.

Polycythemia or erythrocytosis is a paraneoplastic syndrome in HCC which can be attributed to increased production of erythropoietin by tumor cells. Generally, polycythemia can be classified into absolute and

	April 5th, 2022	April 6th, 2022	April 7th, 2022	April 9th, 2022	April 11th, 2022	April 13th, 2022
Hb	20.5	19.7	18.8	18.5	19	19.5
Ht	65.8	63.1	65	31	59.9	62.6
Platelets	234,000	213,000	182,000	148,000	142,000	130,000

Figure 3. Follow-up of laboratory examinations after serial phlebotomy and administration of cytoreductive agent had been conducted.

relative polycythemia. Absolute polycythemia consists of primary polycythemia (e.g., polycythemia vera), tumor-related secondary polycythemia (e.g., HCC, renal tumors), and hypoxia-related polycythemia (e.g., polycythemia found in patients with chronic obstructive pulmonary disease). Meanwhile, relative polycythemia occurs due to any conditions that may cause depleted plasma volume or body fluid volume, such as dehydration.[12,13] In the pathophysiology of HCC, synthesis and secretion of abnormal erythropoietin by tumor cells occurred by involving modified or naïve erythropoietin.[4] Another proposed mechanism of HCC-related polycythemia is a reduction of alpha-ketoglutarate and propyldehydroxilase levels in the tumor cells. As a result, there will also be a disruption in the signal transduction pathway of Hypoxia-inducible Factor-1-alpha (HIF-1-alpha), which leads to excessive production of erythropoietin. When erythropoietin binds to its receptors, a cascade of JAK-2 signal transduction pathways will be activated. Consequently, proliferation, stabilization, and differentiation of red blood cells will arise.[12,14]

In this case report, diagnosis of secondary polycythemia related to HCC BCLC stage C was considered due to the presence of increased hemoglobin level higher than 18.5 g/dl, accompanied by myeloproliferative appearance from peripheral blood smear examination and bone marrow hypercellularity from histopathological findings without any evidence of JAK2 exon 12 mutation. The clinical and laboratory findings in our patient were in line with the presence of secondary polycythemia, which might be attributed to higher synthesis and secretion of abnormal erythropoietin by a large number of tumor cells, indicated by large tumor volume and high serum AFP level. Relative polycythemia due to blood hyper-viscosity, either associated with increased red blood mass or malignancy-related hypercoagulability, was initially considered as an underlying mechanism in our patient. However, despite being adequately hydrated, the patient only demonstrated a good clinical response after serial phlebotomy and oral cytoreduction treatment; thus, diminishing the possibility of relative polycythemia condition.

In this patient, serial phlebotomy and administration of cytoreductive agents were conducted to treat secondary polycythemia. A population-based study performed on subjects with high-risk secondary polycythemia in South Korea exhibited the benefits of serial phlebotomy with a 2-week interval at most to significantly lower hematocrit level and thrombosis events.[15] Another study by Podoltsev, et al. in 2018 showed that more frequent serial phlebotomy accompanied by a higher proportion of days covered with hydroxyurea significantly improved the survival rate of patients with polycythemia vera and high risk of thrombosis.[16] Regardless, it is undeniable that peripheral blood tap also needs to be drawn periodically to monitor the therapeutic effect of recurrent phlebotomy; thus, at the same time, escalating the risk of iron deficiency which may also increase the blood viscosity. When 500 ml of blood is drawn, it is estimated that serum iron level could decrease 200-250 mg and serum ferritin level could decrease up to 44%.[12]

In our patient, initially, improvement of clinical symptoms and laboratory findings related to polycythemia had been observed. To minimize the risk of thrombotic events, our therapeutic aim is to maintain the hematocrit levels at a maximum of 45%. However, the hematocrit levels tended to increase again, even after the addition of cytoreductive agents. A retrospective study conducted by Mao, et al. showed a similar experience, in which phlebotomized patients had higher hemoglobin and hematocrit levels in comparison to the patients who did not undergo serial phlebotomy. The study also did not find any significant difference between the prevalence of arterial, venous, or total thrombosis before and after serial phlebotomy in secondary polycythemia cases.[17] In contrast, a case report by Fuqua, et al. demonstrated successful use of serial therapeutic phlebotomy in severe secondary polycythemia due to chronic lung disease. It is important to note, though, that the authors also successfully treated the main etiology of secondary polycythemia in the patient, which is chronic hypoxia, by administering adequate supplemental oxygen to the tissue.[18] In our assessment, secondary polycythemia condition

in our patient was strongly associated with HCC, therefore, the mainstay treatment is by administering a systemic therapy for advanced HCC, which had not been able to be implemented. Taken together, although there is still a paucity of high-quality evidence for evaluating the risk and benefit of routine phlebotomy in secondary polycythemia, clinicians should be aware that a definitive therapy for the underlying diseases still needs to be performed despite good initial clinical response after routine phlebotomy and administration of the cytoreductive agent.

In patients with a high risk of thrombosis, including our patient in this report, the administration of low-dose acetylsalicylic acid (ASA) (80-100 mg daily) with or without cytoreductive agents (e.g., hydroxyurea) is still recommended.[13,19] The anti-thrombotic properties of ASA itself are mainly attributed to impaired platelet activation due to the inhibition of thromboxane A_2 and acetylation of COX-1.[20] Another promising mechanism of ASA in HCC is the anti-tumor effect by decreasing the expression of collagen prolyl 4-hydroxylase A subunit 2, controlling glucose uptake through the NF-kB/GLUT1 axis, suppression of hepatocyte growth factor-induced invasion of HCC cells, and ASA-mediated immune-metabolic response through the modulation of the peroxisome proliferator-activated receptor delta-AMPK-peroxisome proliferator-activated receptor gamma coactivator 1-alpha axis.[21] A pooled analysis of two national-based cohort studies confirmed these theories by showing that increasing the cumulative mean dose of ASA can reduce the risk of HCC.[22] Nonetheless, one case report in a patient with HCC BCLC B and secondary polycythemia highlighted the fact that life-threatening cardiovascular complications may still develop despite routine administration of low-dose ASA.[12]

Although many benefits have been proven to be yielded from administering ASA, the possible risk of bleeding may require further anticipation. Around 0.4% to 20% of patients with advanced and invasive HCC have been shown to exhibit gastrointestinal metastasis. Additionally, 10% of cancer-related deaths in HCC were due to gastrointestinal bleeding.[23] Due to its anti-platelet activity, administration of ASA, even with low-dose, has been associated with an elevated risk of bleeding, especially in combination with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), clopidogrel, and Selective Serotonin Re-uptake Inhibitors (SSRIs).[24] Regardless, a recent meta-analysis by Wang, et al. demonstrated that utilization of ASA did not increase the risk of bleeding in patients with HCC (OR 1.19). In contrast, their subgroup analysis also demonstrated a risk reduction of liver cancer after administration of ASA by as high as 47%.[25] In line with the findings of Wang, et al., our patient in this case report also did not exhibit any clinical manifestation of gastrointestinal tract bleeding throughout his course of treatment with ASA. Our case was in line with studies favoring the use of ASA, in which, no new onset of thrombosis was observed throughout his hospitalization.

As has been explained in this case, another dilemma that can be encountered in the management of secondary polycythemia is the use of cytoreductive in the presence of severe infection. A previous database study by Polverelli, et al. demonstrated a slightly higher number of infectious complications in myelofibrosis patients who received cytoreductive therapy (78%) compared to the control group.[26] Conflicting evidence, however, emerged from a study comparing ruxolitinib and standard therapy, which included hydroxyurea, in patients with polycythemia vera. This study showed a lower rate of infections in groups treated with hydroxyurea (36.9%), in comparison to groups treated with ruxolitinib (41.8%).[27] A possible reason behind this is that the administration of a cytoreductive agent does not necessarily cause immune suppression. As a cytoreductive agent, hydroxyurea displays its cytostatic effect through the inhibition of ribonucleoside diphosphate reductase, which catalyzes the conversion of ribonucleotides to deoxyribonucleotides; thus, arresting the cell cycles between G1 and S phases or in early S phase. This step, nonetheless, does not significantly affect the T-lymphocyte's immunological functionality. Instead, increased T-helper type 1 and type 2 cytokine production was found upon treatment with hydroxyurea.[28]

Based on the onset, etiology, and

pathophysiology, persistent hypoglycemia in HCC can be grouped into two types. Type A hypoglycemia is mild-to-moderate hypoglycemia, which is usually observed in advanced HCC, particularly in a large-sized progressive tumor. Enlarged tumor cells, exceeding the normal size of the liver, will diminish the capability of liver cells to perform gluconeogenesis and glycogenolysis optimally, while at the same time, the requirement of glucose will also be increased as tumor size is getting larger, contributing to higher direct consumption of glucose by tumor cells. Meanwhile, type B hypoglycemia, which is usually found in 5%-13% of HCC patients, tends to have the more severe manifestation of hypoglycemia in the early phase of malignancy. The mechanism of type B hypoglycemia is thought to be associated with the production of partially processed Insulin Growth Factor/ IGF-2 molecules. In this case report, the patient was thought to exhibit manifestation of type A hypoglycemia due to the most recent radiographic examinations, which showed an extension of liver mass with hardly observed normal remnants of liver parenchyma, indicating enlarged progressive mass.[11] Our patient also exhibited recurrent hypoglycemia without any increase in basal insulin level. Normal basal insulin level, along with the absence of any radiographic findings showing an islet cell tumor, further confirmed the diagnosis of non-islet cell tumor hypoglycemia in our patient.

Aside from excessive glucose utilization by tumor cells, secretion of partially processed molecules, such as IGF-2, can also disturb glucose metabolism, resulting in persistent HCC-related hypoglycemia.[29-31] A report on one HCC patient with the presence of liver cirrhosis due to alcoholic liver disease and persistent hypoglycemia showed a high IGF-2 level until almost twofold of its normal limit. In HCC, higher IGF-2 is strongly affected by higher pro-IGF-2, which was caused by the reduced ability of pro-IGF-2 to bind with Insulin-like Growth Factor Binding Protein (IGFBP)-3. This cascade of events will stimulate insulin receptors continuously, leading to suppression of free fatty acids release, as well as inhibition of gluconeogenesis, glycogenolysis, and ketogenesis of the liver. Therefore, hypoglycemia events will be more severe in HCC patients.[31]

In this report, we also highlighted an example of an advanced HCC case with a less than favorable prognosis, which can be predicted since the initial hospital admission of the patient. Even without the presence of tumor-related complications, a higher BCLC stage has been identified as a significant risk factor for a higher mortality rate in an Indonesian cohort retrospective study.[32] Previous evidence in 196 subjects also pointed out that HCC BCLC C patients who did not receive any systemic therapy only had short median survival (56 days) with the most common cause of death being tumor-related progression (50%) and secondary infection (21.7%).[33] In our patient, systemic therapy became the best therapeutic option due to the presence of vascular invasion, i.e., portal vein thrombosis, and extrahepatic spread.[34] Following the previous findings from Jasirwan, et al.[32] and Hasan, et al.[33], our patient was also presented with BCLC stage C upon admission and eventually passed away due to secondary pulmonary infection before he was able to get any systemic therapy. Both studies above also demonstrated the fact that hepatitis B was still the most common etiology of HCC (63.1%-69.4%) in Indonesia.[32,33] History of untreated hepatitis B, which led to lack of surveillance and follow-up, was the most prominent contributing factor to diagnostic delay in our patient.

The presence of paraneoplastic polycythemia may also worsen the prognosis of our patient. Miao, et al. and Ke, et al. revealed that a worse prognosis in HCC patients with polycythemia was significantly associated with larger tumor size, higher AFP levels, and mutations of genes that have a role in oxidative phosphorylation of mitochondria. This study also showed that erythropoietin has a direct role in tumor progression through signal transduction JAK/ STAT pathway.[14,35] Aside from those things, difficulty in treating polycythemia also becomes a problem behind poorer prognosis of the patients. Another case report exhibited evidence that a combination of phlebotomy, trans-arterial chemoembolization, and administration of low-dose aspirin did not decrease the risk of

cardiovascular-related mortality in HCC BCLC stage B patients.[12] Another study by Evers, et al. in 2014 also highlighted the possibility of utilizing therapeutic erythrocytapheresis as a treatment option for secondary polycythemia. Evers, et al. demonstrated that in comparison to phlebotomy, the group treated with erythrocytapheresis had a more significant decrease in red blood cell volume and needed longer intervals between procedures.[36]

Concurrently, the poorer prognosis of HCC patients with recurrent hypoglycemia has been strongly associated with hypoglycemia-related emergencies and a lack of good clinical response toward conventional hypoglycemia treatment. In patients with severe persistent hypoglycemia, administration of intravenous glucose and/or carbohydrate intake as high as 1,500 grams daily often did not show adequate results in maintaining blood glucose levels. Further available evidence also showed that administration of steroids, glucagon, and growth hormones did not have any significant therapeutic impact on HCC-related persistent hypoglycemia. Until now, the best definitive therapeutic option for HCC-related hypoglycemia is cytoreductive options, such as surgery, radiotherapy, and/or systemic therapy.[28,29]

CONCLUSION

Polycythemia and persistent hypoglycemia are paraneoplastic phenomena that can be found in HCC patients. Elevated risk of blood hyperviscosity and polycythemia-related thrombosis, as well as medical emergencies attributed to autonomic and neuroglycopenic manifestations of hypoglycemia, highlight the importance of close monitoring and prompt treatment of both conditions. Aside from escalated tumor burden, both phenomena occur more often in patients with advanced HCC; thus, limiting the availability of therapeutic options, in particular the curative strategies. As a result, lower survival of these patients may also be observed. This case also emphasized the importance of performing a national surveillance program appropriately for early detection of HCC in high-risk patients, particularly patients with chronic hepatitis B. Continuously increasing incidence of hepatitis B in Indonesia, which may also be untreated or underdiagnosed, has been proven to be a significant risk factor in HCC-related morbidity and mortality. Therefore, early diagnosis and prompt treatment of hepatitis B are also strongly recommended as preventive strategies for HCC and its complications.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
2. Wu J. The changing epidemiology of hepatocellular carcinoma in Asia versus the United States and Europe. Advances in Modern Oncology Research. 2017;3(S1):51-8.
3. Hasan I, Loho IM, Setiawan PB, et al. Konsensus terapi sistemik karsinoma sel hati di Indonesia. Perhimpunan Peneliti Hati Indonesia. 2021.
4. Kew MC. Paraneoplastic phenomena in patients with hepatocellular carcinoma. Journal of Liver Research, Disorders, and Therapy. 2016;2(1):9-12.
5. Luo JC, Hwang SJ, Wu JC, et al. Clinical characteristics and progress of hepatocellular carcinoma with the paraneoplastic syndrome. Hepatogastroenterology. 2002;49(47):1315–19.
6. Jacobson RJ, Lowenthal MN, Kew MC. Erythrocytosis in patients with hepatocellular carcinoma. S Afr J Med. 1978;53(17):658– 60.
7. Hwang SJ, Lee SD, Wu JC. Clinical evaluation of erythrocytosis in patients with hepatocellular carcinoma. Zhonghua Yi Xue Za Thi. 1994;53(5):262–69.
8. Shapiro ET, Bell GI, Polonsky KS, et al. Tumor hypoglycemia: Relationship to high molecular weight insulin-like growth factor. J Clin Invest. 1990;85(5):1672–79.
9. Chang PE, Ong WC, Lui HF, et al. Epidemiology and prognosis of paraneoplastic syndromes in hepatocellular carcinoma. ISRN Oncology. 2013;684026. [DOI: 10.1155/2013/684026]
10. Zheng XJ, Yan HH, Gan B, et al. Incidence and risk factors for hypoglycemia in patients with hepatocellular carcinoma. Research Square. 2021. [DOI: 10.21203/rs.3.re-905429/v1]
11. Yu X, Liang X, Chen Y, et al. Hepatocellular carcinoma with worsened hypoglycemia after transarterial chemoembolization: A case report and systematic review. Int J Clin Exp Pathol. 2021;13(12):3167-73.
12. Setiawan PB, Maimunah U, Siagian N. Secondary polycythemia in hepatocellular carcinoma: Treat or no treat. Indones J Gastroenterol, Hepatol, and Dig Endosc. 2020;21(1):64-7.
13. Vannucchi AM, Barbui T, Cervantes F, et al. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines

for diagnosis, treatment, and follow-up. Ann of Oncol. 2015;26(Suppl5):v85-v99. [DOI: 10.1093/annoncmdv203]
14. Miao S, Wang SM, Cheng X, et al. Erythropoietin promoted the proliferation of hepatocellular carcinoma through hypoxia-induced translocation of its specific receptor. Cancer Cell Int. 2017;17:119. DOI: 10.1186/s12935-017-0494-7.
15. Lee HJ, Shin KH, Song D, et al. Optimal phlebotomy interval to change hematocrit levels in patients with polycythemia. Korean J Blood Transfus. 2016;27(3):220-8. [DOI: 10.17945/kjbt.2016.27.3.220]
16. Podoltsev NA, Zhu M, Zeidan AM, et al. The impact of phlebotomy and hydroxyurea on survival and risk of thrombosis among older patients with polycythemia vera. Blood Advances. 2018;2(20):2681-90.
17. Mao C, Olszewski AJ, Egan PC, et al. Evaluating the incidence of cardiovascular and thrombotic events in secondary polycythemia. Blood. 2019;134(Suppl1):3511. [DOI: 10.1182/blood-2019-122943]
18. Fuqua J, Reece J, Sofka S. Successful use of phlebotomy to treat severe secondary polycythemia due to chronic lung disease. Hematology Reports. 2021;13:8961. [DOI: 10.4081/hr.2021.8961]
19. Chirardi A, Carobbio A, Masciulli A, et al. Incidence of solid tumors in polycythemia vera treated with phlebotomy with or without hydroxyurea: ECLAP follow-up data. Blood Cancer Journal. 2018;8:5. [DOI: 10.1038/s41408-017-0038-3]
20. Undas A, Brummel-Ziedins KE, Mann KG. Antithrombotic properties of aspirin and resistance to aspirin: Beyond strictly antiplatelet actions. Blood. 2007.109:2285-92. [DOI: 10.1182/blood-2006-01-010645]
21. Qiu X, Gao F, Wang K, et al. Aspirin in hepatocellular carcinoma: Is it an out-of-date or promising treatment? iLiver1. 2022:55-64. [DOI: 10.1016/j.iliver.2022.03.003]
22. Simon TG, Ma Y, Ludvigsson JF, et al. Association between aspirin use and risk of hepatocellular carcinoma. JAMA Oncology. 2018;4(12):1683-90. [DOI: 10.1001/jamaoncol.2018.4154]
23. Hot S, Yesiltas M, Gokcek B, et al. Massive and life-threatening upper gastrointestinal bleeding due to invasive hepatocellular carcinoma: A case report. Int J Surg Case Rep. 2016;26:69-72. [DOI: 10.1016/j.ijcsr.2016.06.045]
24. García Rodríguez LA, Martín-Pérez M, Hennekens CH, et al. Bleeding risk with long-term low-dose aspirin: A systematic review of observational studies. PLoS One. 2016;11(8):e0160046. [DOI: 10.1371/journal.pone.0160046]
25. Wang Y, Wang M, Liu C, et al. Aspirin use and the risk of hepatocellular carcinoma: A meta-analysis. J Clin Gastroenterol. 2022;56(7):p.293-e302.
26. Polverelli N, Breccia M, Benevolo G, et al. Risk factors for infections in myelofibrosis: Role of disease status and treatment. A multicenter study of 507 patients. Am J Hematol. 2017;92:37-41. [DOI: 10.1002/ajh.24572]
27. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372(5):426-35. [DOI: 10.1056/NEJMoa1409002]
28. Lova L, Groff A, Ravot E, et al. Hydroxyurea exerts a cytostatic but not immunosuppressive effect on T lymphocytes. AIDS. 2005;19:137-44.
29. Regino CA, Lopez-Montoya V, Lopez-Urbano F, et al. Paraneoplastic hypoglycemia in hepatocarcinoma: Case report and literature review. Cureus. 2020;12(12):e12013. [DOI: 10.7759/cureus.12013]
30. Tsai CY, Chou SC, Liu HT, et al. Persistent hypoglycemia as an early, atypical presentation of hepatocellular carcinoma: A case report and systematic review of the literature. Oncology Letters. 2014;8:1810-4. [DOI: 10.3892/ol.2014.2365]
31. Rana P, Kim B. A unique case of IGF-2-induced hypoglycemia associated with hepatocellular carcinoma. Case Rep Endocrinol. 2019;4601484. [DOI: 10.1155/2019/4601484]
32. Jasirwan COM, Hasan I, Sulaiman AS, et al. Risk factors of mortality in the patients with hepatocellular carcinoma: A multicenter study in Indonesia. Curr Probl Cancer. 2019. [DOI: 10.1016/j.currproblcancer.2019.05.003]
33. Hasan I, Lutfie L, Rinaldi I, et al. Comparison between Neutrophil-Lymphocyte Ratio and Systemic Immune-Inflammation Index as predictors of one-year survival in patients with untreated advanced hepatocellular carcinoma. J Gastrointest Cancer. 2021. [DOI: 10.1007/s12029-021-00796-7]
34. Hasan I, Loho IM, editors. Konsensus nasional penatalaksanaan karsinoma sel hati. Perhimpunan Peneliti Hati Indonesia. 2017. ISBN 978-602-18991-7-5.
35. Ke S, Chen S, Dong Z, et al. Erythrocytosis in hepatocellular carcinoma portends a poor prognosis by respiratory dysfunction secondary to mitochondrial DNA mutations. Hepatology. 2017;65(1):134-51. [DOI: 10.1002/hep.28889]
36. Evers D, Kerkhoffs JL, Egmond LV, et al. The efficiency of therapeutic erythrocyte apheresis compared to phlebotomy: A mathematical tool for predicting response in hereditary hemochromatosis, polycythemia vera, and secondary erythrocytosis. J Clin Apheresis. 2014;29:133-8. [DOI: 10.1002/jca.21303]