Secondary Polycythemia in Hepatocellular Carcinoma: Treat or No Treat

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ABSTRACT

A 45-year man with a chronic hepatitis B virus (HBV) infection, elevated alphafetoprotein (AFP) 628ng/dL and Abdominal CT-scan features of Hepatocellular Carcinoma was admitted with polycythemia condition (haemoglobin 20.4g/dL, haematocrit 65.4%). Elevated of erythropoietin (EPO) serum level confirmed the polycythemia was because of hepatocellular carcinoma (HCC) as a paraneoplastic syndrome. Based on diganosis criteria of HCC by Indonesian Association for the Study of the Liver 2017, the patient was diagnosed with HCC Barcelona clinic liver cancer (BCLC) B and was treated with trans arterial chemotherapy and embolization (TACE) with mixed doxorubicin. Aspirin 80mg once daily was given to patient to prevent thrombosis event. One month later after TACE, haemoglobin and haematocrite didn't improve. Then 4 months later the patient died of cardiovascular event in the last admission at district hospital.

Keywords: *hepatocellular carcinoma (HCC), polycythemia, trans arterial chemotherapy and embolization (TACE)*

ABSTRAK

Seorang pria 45 tahun dengan infeksi virus hepatitis B kronis (HBV), peningkatan alphafetoprotein (AFP) 628ng / dL dan fitur CT-scan Abdominal Hepatocellular Carcinoma dirawat dengan kondisi polisitemia (hemoglobin 20,4 g / dL, hematokrit 65,4%). Peningkatan kadar serum erythropoietin (EPO) mengkonfirmasi polisitemia yang disebabkan oleh karsinoma hepatoseluler (HCC) sebagai sindrom paraneoplastik. Berdasarkan kriteria diagnosis HCC oleh Asosiasi Indonesia untuk Studi Hati 2017, pasien didiagnosis dengan kanker hati klinik HCC Barcelona (BCLC) B dan dirawat dengan kemoterapi dan embolisasi arteri arterial (TACE) dengan doxorubicin campuran. Aspirin 80mg sekali sehari diberikan kepada pasien untuk mencegah kejadian trombosis. Satu bulan kemudian setelah TACE, hemoglobin dan hematokrit tidak membaik. Empat bulan kemudian pasien meninggal karena kejadian kardiovaskular dalam perawatan terakhir di rumah sakit kabupaten.

Kata kunci: *karsinoma hepatoseluler (HCC), polisitemia, kemoterapi dan embolisasi trans arterial (TACE)*

INTRODUCTION

Hepatocelular carcinoma (HCC) is a malignancy that arises from hepatocyte . HCC is the sixth most common cancer worldwide and the third most common cause of death from cancer. Approximately three-fourth of cases occur in Asian countries because of a high prevalence of chronic infection with HBV. HCC is undoubtedly a great health threat in Asian region[1].

Polycythemia or erythrocytosis is a well-known paraneoplastic phenomenon in patients with HCC with incidency about 3-12%, but its pathogenesis remains uncertain. Recently, it has been reported that HCC cells are responsible for the production of erythropoietin (EPO), which leads to polycythemia in HCC patients[2]. Polycythemia as well as the others paraneoplastic syndromes play a significant role in the progress of HCC and lead to poor prognosis in patient HCC especially in increasing the risk of thrombosis event due to hypervicosity in patient HCC [3,4]. The guideline of treatment of secondary polycythemia in HCC is not established yet.

CASE ILLUSTRATION

A 45-year man with history of hepatitis B admitted to our health centre due to upper right abdominal pain progresively since 4 months ago and headache intermittenly since 2 months ago. On admission laboratory analysis showed haemoglobin 20.4g/dL, haematocrit 65.4% and elevated alphafetoprotein (AFP) 628 ng/dL . The abdominal ultrasound which was taken 2 month before addmission showed HCC and the chest x-ray showed normal cardiac and pulmo. The abdomen MSCT with contrast which was also performed on admission revealing enhancing solid lession +/- 12.0x12.9x13.2 cm at segmen V.VI, VII, VIII, feeded by right a.hepatica with early wash pattern at artery phase, early wash out pattern at venous phase and delay phase without thrombus or fistula, satelite nodul at segmen II (HCC). In order to investigate a polycythemia an examination of erythropoietin (EPO) serum level was conducted revealing higher than normal 280mU/mL (4.1-19.5 mU/mL). This value confirmed the secondary polycytemia due to HCC. Trans arterial chemotherapy and embolization (TACE) with mixed doxorubicin 50mg was performed as a recommended treatment of HCC and low dose aspirin 80mg was given as a prophylaxis of thrombotic risk due to polycythemia in this case. 1 month later after TACE and during low dose aspirin treatment, the haemoglobin and haemotocrite didn't improve and 4 months later the patient died of cardiovascular event in the last admission at district hospital.

DISCUSSION

HCC is a primary cancer arising from hepatocytes in predominantly cirrhotic liver (70-90%) but it may not have cirrhosis before developing HCC, especially hep.B virus (30%). Men are generally more susceptible than women (2:1). Upper right quadrant abdominal pain and abdominal mass are common clinical manifestations of HCC. The positive of hepatitis virus marker, elevated alphafetoprotein (AFP) > 400ng/dL and HCC features by abdominal ultrasound/CT scan can confirm the diagnosis of HCC based on diagnostic criteria by the Indonesia' liver researcher association 2017. The therapy is based on the stadium that consists of size, number of nodule, performance score and Child-pugh score[5,6].

Polycthemia or erythrocytosis is a blood disorder characterised by elevated haemoglobin (Hb) more than 18.5 g/dL (man)/ 16.5 g/dL (woman) or elevated haemotocrit (Ht) more than 52% (man)/48% (woman) (Keohane). In general polycythemia is divided into two main group (1) Absolute polycythemia which includes primary polycythemia (polycythemia vera, Epo-receptor mutation,etc) and secondary polycythemia due to tumor-associated polycythemia (HCC, renal tumor, uterine myoma, etc) and hypoxia-associated polycythemia (congenital heart disease, chronic obstruction pulmonary disease, asthma,etc); (2) Relative polycythemia due to loss volume plasma, dehidration, etc. Patients are generally asymptomatic, but the symptoms they may experience are related to ischemia from hyperviscosity and thromobosis due to increased red blood mass. General symptoms may include fatigue, weakness and dyspnea and others signs and symptoms include hepatosplenomegaly, headache, vertigo and tinitus[7,8,9,10].

Patients with HCC that manifests paraneopalstic syndromes such as hypoglycemia, hypercholesterolemia and polycythemia usually has a larger tumor volume and high serum alpha-fetoprotein[11,12,13]. Hwang et al. reported 20 (2.5%) of 792 chinese HCC patients presented with polycythemia then they found that 19 patients had either bi-lobar tumor involvement or a large tumor mass (50% whole liver) confined to one lobe of the liver[12]. The pathogenesis of polycythemia in HCC is still unclear. Ke, et al, reported there is an underlying link between mitochondrial function and hypoxia inducible factor (HIF) alpha signaling, revealing a mechanism of polycythemia in HCC. Lack of alpha-ketoglutrate and prophyldehydroxilase makes HIF stable and induce over production of EPO then. EPO always binds to EPO receptor (EPOR) before transforms and activates the signaling of JAK-2 tranduction cascade that induce proliferation, stabilisation and differentiation of red blood cell. Thus, the new treatment using soluble EPO receptor to block EPO signaling [2,14,15].

The is a well defined association between polycythemia, rise in blood viscosity and the risk of thrombosis[16]. The 34 year follow-up of the framingham cohort reported an association between being in the group with the highest packed red cell volume (five groups in total) and the risk of cardiovascular mortality and morbidity was 1.6 (p = 0.0018) for women and 1.29 (p = 0.019) for men aged 35-64 years who were in this group[3]. Phlebotomy is an effective treatment modality for lowering hematocrit value in patients PV and secondary polycythemia but target hematocrit (< 45%) was not achieved after a single phlebotomy.[17,18] However, there is no study recommends routine phlebotomy for secondary polycythemia in HCC. It may becasue repeated phlebotomies could cause iron deficiency with microcytic erythrocytes that can actually increase rather than decrease blood viscosity and somehow induce erythrocytosis due to compensatory effect.[19] In healthy men, a single 500-mL whole-blood donation results in a substantial loss of heme iron (i.e., 200–250 mg) and decreases serum ferritin levels by 44%. Thus, phlebotomy without a proper monitoring of blood viscosity can potentially accentuate rather than decrease the risk of a cardiovascular or cerebrovascular accident. Recently the datas showed therapeutic erythrocytapheresis (TEA) was clearly superior to traditional phlebotomy in terms of prolonging the period between one treatment and another, independent of the type of erythrocytosis and of the treatment group. For example, for the patients undergoing only phlebotomy, the treatment time interval was 51.66 ± 29.8 days, whereas for TEA patients it was 139 ± 49.5 (p < 0.001).[20,21].

Low dose aspirin (80-100mg/day) is effective for prevention of arterial vascular events and for the primary prevention of venous thromboembolism[22]. In 2014, aspirin was demonstrated by the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) placebo-controlled randomized clinical trial, showing that low-dose aspirin can safely prevent thrombotic complications in patients with PV who have no contraindication to such treatment. Currently, hydroxyurea (HU) is recommended in PV patients who are at high risk of thrombosis, progressive disease, or in those who cannot tolerate frequent therapeutic phlebotomies. Based on results of a phase II study of The Polycythemia Vera Study Group (PVSG) trial, Hydroxyurea (HU), alone or in association with phlebotomy, was found efficacious and safe and is currently considered the first-line therapy in PV patients, but it has never been entered in controlled trials of adequate size and duration to assess its long-term safety[23,24].

The case described here demonstrates a paliative treatment such as TACE didn't improve the polycythemia in HCC BCLC B. Low-dose aspririn was required to prevent the thrombotic event as long as the hematrocrite >45%. Therapeutic phlebotomy should be considered in emergency case when the patient shows signs and symptoms of thrombosis. In the last admission at district hospital the patient had symptoms of thrombotic unfortunately phlebotomy couldn't be done because of limitation source.

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