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REVIEW ARTICLE: CLINICAL AND LABORATORY ASPECT OF HEPATOMA

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ABSTRACT
Hepatoma (hepatocellular carcinoma) is liver cancer derived from hepatocyte. Incidence hepatoma was 5,6 from all the cancer which affect human. Mortality and incidence hepatoma are 500.000 until 1 million case each year. Risk factor of hepatoma are hepatitis B virus (HBV) ,hepatitis C virus (HCV), liver cirrhosis, aflatoxin,obesity,diabetes mellitus,and alcohol. Pathogenesis of hepatoma derived from risk factor and progress to chronic phase.Infection caused by HBV and HCV will be cause inflammation and produces free radical,cytokine,and chemokine resulting in damage of DNA cell, cell proliferation, fibrosis, and angiogenesis. Clinical manifestation of hepatoma are jaundice, hepatic encephalopathy, oedema anasarca, ascites, and varises. Diagnosis of hepatoma was established from anamnesa, physical examination , tumor marker e.q Alpha-1 Fetoprotein (AFP) Lens Culinaris Agglutinin-Reactive AFP (AFP-L3) Des-g-carboxy prothrombin, Alpha-l-fucosidase (AFU), Glypican-3 (GPC3), Squamous cell carcinoma antigen (SCCA), Golgi protein 73, Hepatocyte growth factor (HGF), Transforming growth factor-beta 1 (TGF-b1), Vascular endothelial growth factor (VEGF), and Serum proteomics also biopsy.
Keyword: *Hepatoma,HBV.HCV,Tumor marker*

ABSTRAK
Hepatoma (karsinoma hepatoseluler) adalah kanker hati yang berasal dari hepatosit. Insiden hepatoma adalah 5,6 dari semua kanker yang menyerang manusia. Angka kematian dan kejadian hepatoma adalah 500.000 sampai 1 juta kasus setiap tahunnya. Faktor risiko hepatoma adalah virus hepatitis B (HBV), virus hepatitis C (HCV), sirosis hati, aflatoksin, obesitas, diabetes melitus, dan alkohol. Patogenesis hepatoma berasal dari faktor risiko dan berkembang menjadi fase kronis, infeksi yang disebabkan oleh HBV dan HCV akan menyebabkan inflamasi dan menghasilkan radikal bebas, sitokin, dan kemokin yang mengakibatkan kerusakan DNA sel, proliferasi sel, fibrosis, dan angiogenesis. Manifestasi klinis hepatoma adalah ikterus, ensefalopati hepatik, oedema anasarca, asites, dan varises. Diagnosis hepatoma ditegakkan dari anamnesis, pemeriksaan fisik, penanda tumor seperti Alpha-1 Fetoprotein (AFP) Lens Culinaris Agglutinin-Reactive AFP (AFP-L3) Des-g-carboxy prothrombin, Alpha-l-fucosidase (AFU), Glypican-3 (GPC3), Squamous cell carcinoma antigen (SCCA), Golgi protein 73, Hepatocyte growth factor (HGF), Transforming growth factor-beta 1 (TGF-b1), Vascular endothelial growth factor (VEGF), dan Proteomik serum serta biopsi.
Kata kunci: Hepatoma, HBV.HCV, Penanda tumor

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INTRODUCTION

Hepatoma or hepatocellular carcinoma is a primary liver malignant tumor that originates from hepatocyte cells. Hepatoma usually develops from chronic liver disease mainly caused by viral hepatitis. Hepatoma happen in 5.6% of all human cancer cases and third among gastrointestinal system cancers after colorectal cancer and gastric cancer[1].

The incidence of hepatoma is nearly 500,000 to 1,000,000 cases annually. The incidence of the disease continues to increase from less than 5 new cases per 100,000 population to more than 100 cases per 100,000 population in Southeast Asia and Sub- Saharan Africa. The incidence of hepatoma cases in developed countries correlates well with HCV infection [1,2].

Hepatoma is rarely found at a young age, except in areas where HBV infection is endemic and perinatal transmission of HBV is common. Generally, in areas with a high incidence of hepatoma, patients are 10-20 years younger than in areas with a low incidence of hepatoma. This can be explained by the fact that in areas with a high incidence of hepatoma, HBV infection is transmitted during the perinatal period or childhood and hepatoma occurs after two decades. Hepatoma cases are more common in males than females. This remains unexplained but may be due to the greater susceptibility of men to the onset of tumors or because men are more exposed to hepatoma risk factors such as viral hepatitis or alcohol. The life expectancy of hepatoma patients is very poor with an average life expectancy of 6 to 20 months. This shows the importance of proper diagnosis and treatment for patients[1-3]. Hepatoma has several risk factors, especially viral hepatitis infection. Some of the risk factors for hepatoma are: hepatitis B virus, hepatitis C virus, liver cirrhosis, aflatoxin, obesity, diabetes mellitus, and alcohol[3].

Pathogenesis

The mechanism of hepatoma occurs through several processes starting from normal cells to the preneoplastic stage and finally to cancer. The *phenotypic* characteristics of cancer cells are the ability to continue to grow, insensitivity to signals that inhibit cell development, inhibit apoptosis, replicate, prolong angiogenesis, invasion into tissues, metastasis and inhibition of the immune system[3,4].

The pathogenesis of hepatoma starts with risk factors and progresses to chronic phase, dysplasia, then early phase

hepatoma and advanced hepatoma. Infection by HBV and HCV can cause inflammation that produces free radicals, cytokines and chemokines resulting in cell DNA damage, cell proliferation, fibrosis and angiogenesis. There is overexpression of proinflammatory cytokines such as TNF-α, INF-γ, and IL-1 in chronic hepatitis infection. These cytokines can increase the concentration of *nitric oxide* (NO) in hepatocytes causing damage to cell DNA and gene mutations such as TP53 mutation[5]. One pathway of hepatoma pathogenesis is chronic infection with hepatitis B virus.

This infection is accomplished through three mechanisms. The first mechanism is through incorporation of viral DNA into the *host* genome which induces chromosomal instability. The second mechanism is a genetic mutation that results in the HBV genome entering specific sites in the *host* and activating endogenous genes such as *retinoic acid receptor* (RAR). Another mechanism is through cell proliferation by the expression of viral proteins, especially the HBV X (HBx) protein, which can lead to overexpression of the virus and cell structures. Some studies suggest HBx may be associated with the process of malignant changes that occur in hepatoma. HBx can coactivate the transcription process of cell and viral genes which then forms an imbalance between cell proliferation and cell apoptosis. Factors that can activate cell proliferation and transcription due to HBx activation are interleukin 8 (IL-8), *tumor necrosis factor* (TNF), *transforming growth factor* (TGF-β1), and *epidermal growth factor receptor* (EGFR). HBx also activates signaling in the Ras/Raf/MAPK pathway causing activation of several oncogenes in the cell cytoplasm. One study mentioned HBx can activate the *Wnt/β catenin* pathway that joins the Wnt-1 protooncogene protein causing cell phosphorylation.

Another mechanism of Wnt activation in hepatoma through decreased expression of *E-cadherin* and *β-catenin* in the cytoplasm and/or nucleus leads to increased activation of *β-catenin* and cell phosphorylation. Another alternative pathway that can cause hepatoma is that HBx can bind to p53 and inactivate p53 then mediate cell apoptosis. Overexpression of angiogenic factors such as *vascular endothelial growth factor* (VEGF) can be induced by HBx and may contribute to tumor cell formation in hepatoma[4,5]. Another risk factor that can lead to hepatoma is hepatitis C virus infection. However, in hepatitis C virus infection, hepatoma occurs

indirectly because the HCV virus is an RNA virus that cannot combine with the *host* genome, so in HCV virus infection, hepatoma usually occurs after *cirrhosis (HCV-induced cirrhosis*). HCV core protein induces the occurrence of *Reactive Oxygen Species* (ROS). ROS interact with tumor suppressor proteins to inhibit apoptosis and trigger the cell cycle. HCV core proteins also activate the Raf1/MAPK, Wnt/β-catenin, TNF-α receptor, NF-kb pathways and inhibit the TGF-β pathway resulting in phosphorylation of cells and cell mutations that support hepatoma[5].

Stage Of Hepatoma

Hepatoma like any other tumor has staging to determine the prognosis of the disease. Prognosis and treatment depend on liver dysfunction, tumor stage, and the general state of (BCLC), French Classification, and Karnofsky Classification. Another classification for hepatoma is the TNM classification. This classification looks at the size and number of nodules, vascular invasion, and lobe involvement. Liver function is not looked at in this classification although it is an important factor in determining prognosis[2,6].

Diagnosis

Clinical Examination

Hepatoma is usually asymptomatic and diagnosed at an advanced stage. Clinical manifestations are associated with the extent of liver involvement. Cirrhotic patients have low tolerance to tumor cell infiltration and show nonspecific symptoms such as jaundice hepatic the patient. There are various classifications for staging hepatoma. Some classifications for staging hepatoma are Okuda's staging, Barcelona Clinic Liver Cancer Classification encephalopathy and anasarka edema. Portal hypertension symptoms of ascites and variceal bleeding indicate invasion of the hepatoma into portal structures[7].

Other symptoms associated with malignancy and tumor growth include malaise, anorexia, pain in the right upper quadrant of the abdomen and on physical examination, abdominal masses and vascular *bruits* are found. Extrahepatic manifestations of hepatoma are related to the extent of metastasis of the tumor and paraneoplastic phenomena. Advanced hepatoma can metastasize to all organs via hematologic or lymphatic pathways. Most metastases occur to the bones, lungs and abdominal viscera[2,7].

Laboratory Examination

Laboratory examinations that can support the diagnosis are hematological examination, clinical chemistry examination, and tumor markers. Hematological examination of hepatoma patients usually shows hemostasis by increasing the amount of sialic acid in the fibrinogen molecule that reacts with an enzyme in thrombin, causing an increase in the enzyme *sialyl transferase*, an enzyme present in fibrinogen that is present in the fetus and can arise due to the influence of tumor cells. Dysfibrinogenemia leads to abnormal production of polymerized fibrin and causes prolongation of thrombin time as well as PT and PTT[8,9]. Clinical chemistry in hepatoma is non-specific but important to determine the patient's cirrhotic status and the stage of the hepatoma.

Liver function tests such as aminotransferases,phosphatase, gamma transpeptidase, bilirubin, and albumin. *Aspartate aminotransferase* (AST) or *serum glutamyl oxalo acetate transaminase* (SGOT) and *alanine aminotransferase* (ALT) or *serum glutamyl pyruvate transaminase* (SGPT) are elevated but not very high. AST is usually more elevated than ALT. Normochromic anemia caused by chronic disease. Hepatoma rarely causes obstructive jaundice but can cause damage to hepatocytes and lead to progressive liver failure. Hemostasis is impaired in hepatoma due to dysfibrinogenemia, a disorder of ALT. Alkaline phosphatase is elevated less than 2 to 3 times the upper normal limit. *Gamma glutamyl transpeptidase* (GGT) is elevated. Bilirubin is used to determine the stage of hepatoma and may be elevated in advanced cirrhosis. Albumin levels decrease due to liver damage[8]. Currently, there are various tumor markers in the diagnosis of hepatoma, especially for early diagnosis and monitoring tumor progressivity, therapy response, and tumor recurrence[10].

Tumor Marker in hepatoma shows in table 1.

Table 1. Tumor Markers in hepatoma[11].

Seromarker HCC
Alpha-fetoprotein (AFP)
Lens culinaris agglutinin reactive(AFP-L3)
Des-g-carboxy prothrombin (DCP)
α-l-fucosidase
Glypican-3
Squamous cell carcinoma antigen (SCCA)
Golgi protein 73 (GP73)
Hepatocyte growth factor (HGF)
Transforming growth factor-beta 1 (TGF-β1)
Vascular endothelial growth factor (VEGF)
Serum proteomics

Differential Diagnosis

Based on the type of cell of origin, liver tumors can be divided into benign and malignant. Both benign and malignant liver tumors can be further divided into epithelial tumors and mesenchymal tumors. Hepatoma is an epithelial malignant liver tumor that can be differentiated with[12]:

a. fibroamellar carcinoma
b. hepatoblastoma
c. cholangiocarcinoma
d. cystadenocarcinoma

Management Therapy

Hepatoma is usually diagnosed at an advanced stage when the patient is symptomatic and liver function is impaired. However, there are now many diagnostic tests that can detect hepatoma at an earlier stage. Many hepatoma therapies also extend the life expectancy of patients. Some therapies for hepatoma include[12]:

a. Tumor resection
b. Liver Transplant
c. Ablation
d. Transarterial embolization or chemoembolization

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