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CRITICAL REVIEW OF INVESTIGATIONS W.S.R HEPATOCELULAR CARCINOMA

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ABSTRACT

Hepatocellular Carcinoma is the most common type of liver cancer and constitutes 90% of cancers of liver globally. It is the 5th common cause of cancers effecting human, common in men than in women. There are multiple factors involved in the etiology of HCC, all of which may have direct or indirect impact on patient characteristics. Despite the advancement in science causative agent can often be unidentified. The clinical understanding of Hepatocellular carcinoma requires a review of disease proper with the available investigations. As there are still many gaps in current understanding of HCC, need of the hour are further efforts to elucidate the diverse mechanisms involved in the etiopathogenesis of Hepatocelular Carcinoma. Hence the present study is aimed at better understanding of laboratory parameters of Hepatocellular carcinoma for precise diagnosis and prognosis of the disease in early stage so that the patient is benefited with appropriate measures.

KEYWORDS: Hepatocellular Carcinoma, Haemoglobin, Platelet, LFT, Serum Biomarkers, Imaging, Biopsy.

DISCUSSION

Laboratory findings yield nonspecific results like Anemia, markedly elevated Serum Alkaline Phosphatase as found in Cirrhosis, and high serum Alpha-Foeto Protein (AFP). Elevated AFP level is quite specific; very high serum AFP (Above 500ng/ml) are observed in 70-80% cases of HCC but lacks sensitivity since AFP is also found elevated in yolk sac tumor, Cirrhosis, Chronic Hepatitis, Massive liver necrosis and normal Pregnancy. Ultrasound of the liver has been reported to be or sensitive than elevated AFP level. An abnormal type of Prothrombin, Des-gamacarboxy prothrombin, is also elevated and correlates well with AFP levels.

HAEMOGRAM

Haemoglobin

The major function of erythrocytes is to deliver oxygen to the tissues. To do this, a sufficient concentration of hemoglobin in the red blood cells is necessary for efficient oxygen delivery to occur. When the hemoglobin concentration falls below normal values the patient is classified as anemic.

Anemia is a common complication in several types of cancer including Hepatocellular Carcinoma (HCC). The prognostic potential of hemoglobin (Hb) levels has not yet been investigated in HCC patients. Low Hb levels (≤ 13 g/dl) were associated with higher mortality. Low Hb levels were associated with mortality independently from the tumor stage, age, gender. Anemia should be considered as a risk factor for mortality in HCC patients.[1]

Platelet Count

Thrombocytosis has been reported long ago to be associated with many tumor types and its presence even suggests the diagnosis of cancer in the absence of irondeficiency anemia and benign inflammatory disease It can also be associated with primary liver malignancy Liver and liver tumors can synthesize thrombopoietin, a major factor in platelet production and HCCs could thus induce the paraneoplastic thrombocytosis that has been reported. Conversely, platelets have been reported to interact with cancer cells and be involved in their growth enhancement and antiplatelet therapy can antagonize experimental tumor growth. Specifically with regard to HCC, platelets are known to produce multiple HCC growth stimulants, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), serotonin, and fibroblast growth factor (FGF) and its receptors. Each of these has been shown to be involved in human HCC and to be a potential target in experimental HCC therapeutics. They are also involved in hepatitis B-associated liver inflammation, and

antiplatelet therapy can inhibit experimental HCC in a Hepatitis B mouse model. Although Non cirrhotic HCC patients have been reported to have less thrombocytopenia than cirrhotic HCC patients, Thrombocytosis seems to be uncommon, with few reports Thus, even in the absence of Thrombocytosis, platelets in the normal range or their Platelet-derived HCC growth factors might be rational targets for future therapies.[2]

LIVER FUNCTION TEST

Assessment of Liver Function

An initial assessment of hepatic function involves liver function testing including measurement of Serum levels of Bilirubin, Asparate aminotransferase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), measurement of Prothorombin time (PT) expressed as international normalized ratio (INR), Albumin, and Platelet count (surrogate for portal hypertension). Other recommended tests include complete blood count and tests of Kidney function (Blood Urea Nitrogen [BUN] and Creatinine), which are established prognostic markers in patients with liver disease.

The Child - Pugh classification has been traditionally used for the assessment of hepatic functional reserve in patients with cirrhosis. The Child - Pugh score is an empirical score that incorporates laboratory measurements (ie., Serum Albumin, Bilirubin, PT) as well as more subjective clinical assessments of Encephalopathy and Ascites.

An important additional assessment of liver function not included in the Child - Pugh score is an evolution of signs of clinically significant portal hypertension. (ie., Esophagogastric varices, Spleenomegaly, Abdominal collaterals, Thrombocytopenia). Evidence of portal hypertension mat also be evident on CT/MRI. Measurement of hepatic venous pressure gradient is an evolving tool for the assessment of portal hypertension. Esophageal varices may be evaluated using Esophagogastroduodenoscopy (EGD) or contrast - enhanced cross - sectional imaging.

Model for End - Stage Liver Disease (MELD) is another system for the evaluation of hepatic reserve. It is derived using three laboratory values (Serum Bilirubin, Creatinine and INR).[4]

Consideration in the evaluation of abnormal LFT'S in Hepatocellular Carcinoma

If the elevation of Serum Bilirubin with other liver tests abnormalities, then evaluate the patients by those with a primary Hepatocellular process and those with intra or extrahepatic

cholestasis. Enzyme tests like Alanine aminotransferase (ALT), and Alkaline phosphate (ALP) are helpful in differentiating between a Hepatocellular process and Cholestatic process, a critical step in determining what additional workup is indicated. Patients with a Hepatocellular process generally have disproportionate rise in Aminotransferases compared to the Alkaline phophatase and viceversa in patients with a Cholestatic process. Conjugated and Unconjugated bilirubin elevated in almost equally proportions in Hepatocellular, where as in obstructive there is prominent increase of Conjugated Bilirubin compared to Unconjugated. It is very useful to determine Serum Albumin and Prothrombin time in liver disorders. Serum Albumin is normal in acute viral Hepatitis and Choledolithiasis, but Serum Albumin is decreased in chronic process such as cirrhosis or cancer. An elevated Prothrombin Time indicates either Vitamin K deficiency due to prolonged jaundice and malabsorption of vitamin K or significant Hepatocellular dysfunction. The failure of the Pothrombin Time to correct with parental administration of vitamin k indicates severe Hepatocellular injury, may also observe in Hepatocellular Carcinoma.[3]

SGOT (AST) & SGPT(ALT) levels and ratio in Hepatocellular disorders

The level of raise of these enzymes and ration between these two enzymes may give important clues in diagnosis of liver diseases. In acute Viral Hepatitis values in the range of 400-4000 u/l. The higher peak Amino transfererase values are found in patients with acute ischemic or toxic liver injury where it is usually above 500U/L and crossing 10,000 U/L. In chronic hepatitis there is mild to moderate rise of Aminotranferase and value usually in the range of 50 to 200 IU/L. Aminotransferase are often normal to mild rise in patients with Cirrhosis. The degree of Aminotransferase elevation can occasionally help in differentiating between Hepatocellular and Cholestatic processes. While ALT and AST Values less than 8 times upper normal limit may be seen either Hepatocellular or Cholestatic liver disease, values 25 times upper normal limit or higher are seen primarily in acute Hepatocellular disease not in Cholestatic disease. Observation of values may help in the evaluation of LFTs. But there is significant overlap between AST/ALT ratios in different conditions. Hence this ratio can’t be relied on exclusively when making diagnosis. The ratios can be less than 1, more than 1 and even more than 2. The concentration of ALT(SGPT) is more in cytoplasm of liver cells compare to AST(SGOT), so in acute liver disease like viral, toxic, cholestatic, alcoholic hepatitis and in chronic active hepatitis because of inflammation, injury, more amount of ALT is leaked in to circulation compared to AST. In these liver diseases the ratio is < 1. In chronic liver disease, liver cirrhosis because if destruction and necrosis of liver

cells, AST present in mitochondria (mitochondria consist of highest number of AST) of liver cells released into blood circulation resulting into reversal of ratio i.e > 1. In acute hepatitis reversal of ratio from <1 to >1 indicates Fulminant Hepatitis or Fulminant hepatic failure. In the chronic alcoholic liver disease the ratio is further elevated and becomes >2. The elevated AST/ALT ratio in advanced alcoholic liver disease results in part from the depletion of vitamin B6 (pyridoxine) in chronic alcoholics. ALT and AST both use pyridoxine as a coenzyme, but the synthesis of ALT is more strongly inhibited by pyridoxine deficiency than it is the synthesis of AST. Alcohol also causes mitochondrial injury, which releases the mitochondrial isoenzyme of AST resulting further evaluation of ratio even > 4. Wilson's disease also can cause the ratio to exceed 4 and similar such altered ratio found even in Hyperthyroidism. If LFT pattern suggestive of viral hepatitis then the clinician may go for appropriate testing for acute viral hepatitis which includes a hepatitis A IgM antibody, a hepatitis B surface antigen, Anti-HBs (Antibody to hepatitis B surface antigen), HBeAg (Hepatitis B enveloped antigen) Anti-HBe (Antibody to HBeAG), HBV-DNA (Hepatitis B virus DNA) and hepatitis C viral RNA test. Depending on circumstances studies for hepatitis D, E, Epstein-Barr virus(EBV)and cytomegalovirus (CMV) may be indicated. If clinician suspects Wilson disease, autoimmune disease then may ask for ceruloplasmin, ANA(Antinuclear antibody) respectively.[3]

LFT's role in Liver cirrhosis

Liver function tests play very little role in liver cirrhosis. Here Billirubin and enzymes are may be normal range even in severe cirrhosis. The proteins level especially albumin is decreased because synthetic function of liver is affected in liver cirrhosis and there is reversal of A:G ratio. Serum protein electrophoresis and immunoglobulin's level may help in the diagnosis of early and advanced liver cirrhosis. In early hepatic cirrhosis there is an increase in acute phase reactant proteins in Alpha 1 and Beta fractions of globuins. IgA levels are usually high, observed in early stage of cirrhosis the albumin. Alpha 1, globulins, Beta globulins are the subnormal levels, but there is increase of Gamma globulins. There is very high increase of serum IgA and IgG. The polyclonal gammopathy in cirrhosis is thought to result from combination of immunoregulatory abnormalities, reticuloendothelial damage, and shunting of antigens into systemic circulation, where they processed in lymph nodes leading to more vigorous response.[3]

SERUM BIOMARKERS

Although serum AEP has long been used as a marker of HCC, it is not a sensitive or specific diagnostic test for HCC. Serum AFP levels > 40 ng/mL are observed only in a small percentage of patients with HCC. In patients with chronic liver disease, an elevated AFP could be more indicative of HCC then in non - infected patients. AFP testing can be useful in conjunction with other test results to guide the management of patients for whom a diagnosis of HCC is suspected. An elevated AFP.[5]

IMAGING

HCC lesions are characterized by arterial hypervascularity, deriving most of their blood supply from the hepatic artery. This is unlike the surrounding liver, which receives its blood supply from both the portal vein and hepatic artery. Diagnostic HCC imaging involves the use of multiphasic liver protocol CT with IV contrast of multiphasic contrast - enhanced MRI. The classical imaging profile associated with an HCC lesion is characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed venous phase. LI-RADS also considers capsule appearance and threshold growth compared to previous imaging as part of diagnosis using CT or MRI imaging. Contrast - enhanced ultrasound (CEUS) is not commonly available in the United States. Through it may be used at centers of expertise as a problem - solving tool for characterization of indeterminate nodules, it is not recommended by the panel for whole - liver assessment, surveillance or staging. A meta - analyses including 22 studies with 1,721 patients with HCC showed that PET/CT may be useful for predicting prognosis, but it is associated with low sensitivity for HCC detection.

A meta - analysis including studies showed that CT and MRI are more sensitive than USG without contrast for detection of HCC, with MRI being moresensitive than CT. The use of gadoxetic acid disodium as a contrast agent is associated with good sensitivity (90%) and specificity (89%) for diagnosis of HCC.

The diagnosis of HCC can be established without biopsy confirmation if both (CCEUS and dynamic contrast enhanced MRI) studies are conclusive.[6]

BIOPSY

A diagnosis of HCC can be noninvasive in that biopsy confirmation may not be required. However, there are a few scenarios in which biopsy may be considered. First, biopsy may be considered when a lesion is suspicious for malignancy, but multiphasic CT or MRI results do

not meet imaging criteria for HCC. Second, biopsy may be done in patients who do not considered high risk for developing HCC (ie., patients who do not have cirrhosis, chronic HBV, or a previous history of HCC). Third, biopsy may be indicated in patients with conditions associated with formation of nonmalignant nodules that may be confused with HCC during imaging. These conditions include cardiac cirrhosis, congenital hepatic fibrosis, or cirrhosis due to a vascular disorder such as Budd - Chari syndrome, hereditary hemorrhagic telangiectasia, or nodular regenerative hyperplasia. Finally, biopsy may be considered in patients with elevated CA 19-9 or CEA, in order to rule out intrahepatic cholangio carcinoma. Nevertheless, the use of biopsy to diagnose HCC is limited by a number of factors including sampling error, particularly when lesions are less than 1 cm. Patients for whom a nondiagnostic biopsy result is obtained should be followed closely, and subsequent additional imaging and / or biopsy recommended if a change in nodule size is observed, a growing mass with a negative biopsy does not rule out HCC.[7]

CONCLUSION

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