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NATURAL HISTORY OF HEPATOCELLULAR CARCINOMA IN CIRRHOTICS

Gastroenterology

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ABSTRACT

Background: The understanding of its natural history may influence the prognosis and choice of treatment.Most of the published literatures were retrospective studies and moreover limited number of studies available for South Indian population.. Aim:The study was conducted with the objective to study the natural history of HCC in patients with cirrhotic background. Design:descriptive study Venue:he Department of Medical Gastroenterology and Hepatology, Stanley Medical Colleg Chennai..Study population: 201 consecutive patients with cirrhosis, Period: January2008 and January 2011, All patients were followed prospectively with every 6 months ultrasound examination of the liver, clinical and laboratory evaluation, Upper abdominal computed tomography (CT) was performed in all patients with focal lesions of the liver detectable and/or with increased levels of AFP (above 200 ng/ml) or peripheral portal thrombosis during follow-up. Results:Out of 201 patients only 49 (24%) patients developed HCC, in a mean period of 30.2±6 months and range of 22-40 months. . Mean age for male was 56.4±10.6 and 48.4 ± 11 for female.Co-infected patients had 60% risk of HCC compared to 20—25% risk in those with HBV or HCV alone. No significant difference in the overall risk of HCC was observed between HBV and HCV related cirrhosis, while the annual rate of HCC development showed an opposite trend in HCV related cirrhosis compared to HBV related disease. Among the symptoms abdominal pain (79.6.7%) and weight loss (34.7%) were most commonly observed symptoms. **Conclusion**:Hepatic decompensation was seen in half the patients at first presentation with Ascites in 52.8%, jaundice in 15.9% and hepatic encephalopathy in 3.8% of patients. The median serum AFP value of 786 ng/ml (range 0.4-92625) observed in the study population. Diagnostic value of AFP >200 ng/ml was present in 27 of 49 (55.1%) patients; with normal AFP in 9 (18.3%) patient.

KEYWORDS

Cirrhosis,Hepatocellular carcinima

Background:

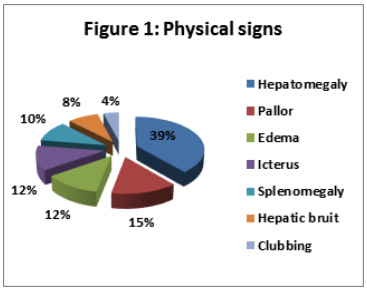
Hepatocellular carcinoma (HCC) is the third most common cause of cancer death in the world. It results in 598 000 deaths per year worldwide. [1]. From a global perspective, the two most important risk factors for HCC are chronic hepatitis B and C infection.. In India, the mean incidence of HCC in four population-based registries is 2.77% for males and 1.38% for femalesThe prevalence of HCC in India varies from 0.2% to 1.6%.. The characteristics of patients with HCC are influenced by the etiology and the status of the underlying liver disease. The understanding of its natural history may influence the prognosis and choice of treatment.Most of the published literatures were retrospective studies and moreover limited number of studies available for South Indian population. Hence we have undertaken this study to analyze the natural history of HCC, especially with regard to patients with cirrhosis: Aim: To study the natural history of HCC in patients with cirrhotic background. Materials & methods:This descriptive study was carried out in the Department of Medical Gastroenterology and Hepatology, Stanley Medical Colleg Chennai..A total of 201 consecutive patients with cirrhosis, seen in our Department between 2008 and 2011, were included in this study. All patients were followed prospectively with every 6 months ultrasound examination of the liver, clinical and laboratory evaluation, including serum alanine aminotransferase (ALT) and serum AFP levels. Serum HBV and HCV markers (hepatitis B surface antigen (HBsAg) and anti-HCV were also tested at inclusion and during follow-up in all cases, partially by retrospective analysis. Abdominal ultrasound examination was performed with a high resolution real-time instrument with standardized criteria. Upper abdominal computed tomography (CT) was performed in all patients with focal lesions of the liver detectable and/or with increased levels of AFP (above 200 ng/ml) or peripheral portal thrombosis duringfollow-up

Radiological Criteria:Two coincident imaging techniques Focal lesion >2 cm with arterial hypervascularization Combined criteria: one imaging technique associated with AFP Focal lesion >2 cm with.AFP levels I g/ml diagnosis of Hepatocellular carcinoma.Exclusion Criteria :Patients who have been diagnosed as 1.Hemangioma 2.Secondaries liver 3.Benign focal liver disorders,arterial hypervascularization Results:Baselin characteristics Two-hundred one patients who fulfilled the study criteria were included in the present study. Table 1 reveals that the mean age was 55 years with male female ratio of 5:1 .Out of 201 patients only 49 (24%) patients developed HCC, in a mean period of 30.2±6 months and range of 22-40 months. .Age distribution . Nearly half of the patients belong to the age group of 55 to 65 years. Mean age for male was 56.4±10.6 and 48.4 ± 11 for female. Overall mean age was 55.1±11. Nearly less than 10 percent of patients either belong to 40-50 years or more than 70 years of age. Clinical features at presentation Among the symptoms abdominal pain and weight loss was most commonly symptoms. (Table 3, Figure 3) More than half of the patients had anorexia and or weight loss. The features of hepatic decompensation were seen in half the patients at first presentation with Ascites in 52.8%, jaundice in 15.9% and hepatic encephalopathy in 3.8% of patients. Gastrointestinal bleed melena was present only in 1.4% patients. Hepatomegaly was seen in more than half the patients (67.8%) while in 26% of cases liver was not enlarged The enlarged liver was hard in two-third cases and was firm in consistency in the remaining one third. Clubbing, hepatic bruit and were less common. 11(22.4%) patients had a Child—Pugh stage C and 18 (36.7%) stage B and stage A 20(40.8%) cirrhosis. MELD score was 6-24 range and mean was 11. Hematological, biochemical and endoscopic profile The biochemical investigations were mildly deranged. Serum alpha fetoprotein (AFP) was diagnostic (>200 ng/ml) in 27 of 49 (55.1%) patients; with normal AFP in 9 (18.3%) patients. The median serum AFP value was 786 ng/ml (range 0.04-98422). Mean AST and ALT values were more than two time of upper limit of normal. The mean serum Bilirubin was 5.4±2. More than three fourth of cases had esophageal varices with gastric varices of 19.1%. Nearly three fourth of cases had low serum albumin level of <2.8 gm. Incidence and risk factors of HCC in HBV and in HCV associated cirrhosis Co-infected patients had 60% risk of HCC compared to 20—25% risk in those with HBV or HCV alone.

Table:1

Etiology	%
Cryptogenic	4(8.1)
HBV related	17(34.7)
HCV related	18(36.7%)
Alcohol alone	9(18.4)

HBV+HCV	1(2)
Alcohol + HCV	5(10.2)
Alcohol + HBV	3(6.1)
Alcohol + HBV + HCV	1(2)



In the anti-HCV positive patients the annual incidence of HCC raised from 2% in the first 5 year period to 4% in the third 5 year period, while decreased from 2 to 0% in the HBsAg positive group. Seventeen (34.7%) were positive for HBsAg and 18 (36.7%) were positive for anti-HCV patients developed HCC. Radiological studies Two different macroscopic patterns of HCC development were observed on the basis of US or CT findings (tumor margin, presence or absence of peri-nodular capsule : (1) tumor arising as a small, capsulated nodule, with well-defined margins and expansive growth (nodular type) and, (2) tumor presenting as a spreading mass not clearly defined, with ill-defined margins and infiltrative growth (infiltrating type). Very large tumors (>5 cm) were seen in two-third of cases. The average size of HCC was 6±4 cm. Small HCC (<2 cm lesion) was seen in only 6% of patients approximately . Single lesion was the most common presentation of HCC observed in two-third cases. Three or more lesions were seen in about one-fifth of cases. During follow-up, HCC developed as nodular type in 37 (75.5%) patients, 15(40.5%) with a single nodule and 22(59.5%) with two nodules, while in the remaining 11 (22.4%) cases the tumor developed as an aggressive and infiltrating mass. On the other hand, male sex HBsAg positivity and dual HBsAg and anti-HCV positivity were significant risk factors for development of infiltrating but not nodular HCC. Vascular invasion of either major branch of spleno-portal axis was seen in one fifth of the patients. Main trunk of portal vein or its main branches were involved in 20.8% patients. The higher risk for infiltrative/diffuse but not for nodular HCC in patients with HBV infection and with HBV/HCV coinfection. Discussion:The age distribution of patients with HCC in the present study was similar to other studies in past. Studies from India have shown the maximum incidence of HCC in the fifth to sixth decade. Our study showed that 43 percent of cases belong to 55 to 65 years of age. Only 10% belongs to 40 - 50 years age group. A very similar observation made by Saini et al HCC commonly observed in male sex. The male preponderance is similar to other studies. The population-based data show a male to female ratio of 3:1-2:1.1. In our study showed male female ration of 5:1. High preponderance of HCC in males in our study could be due to gender bias in seeking medical treatment. This could be partially explained by the fact that men are more likely to be infected with HBV andHCV due to alcohol consumption and Smoking. Hospital based data from various studies made similar .In a series of 461 Italian patients, The HBV is the most common etiologic factor in Asian countries. It accounts for up to three-fourth cases of HCC, while HCV infection may account for 10-15% of HCC cases. HBsAg positivity in our cases was 34.7% which is comparable with other Indian studies (36% to 74 %). The prevalence of anti-HCV antibody in Indian population varies from 0.3% to 1.8%. In our case series HCV positivity noted only in 36.7% of cases. However, PCR-based studies have found HCV RNA positivity in 27-33% of patients with HCC. Serological evidence of HCV infection in patients with HCC in India is 15%. Dual infection with or without alcohol was seen in 2% of patients, similar lower incidence observed in previous studies.India, despite being an intermediate endemic zone for HBV has low incidence of HCC unlike other Asian countries. This phenomenon is akin to low HCC incidence in Greenland Eskimos as compared to Alaskan Eskimos despite similar HBsAg positivity.. An earlier prospective study, the patients with unknown etiology constituted almost 20% of patients despite aggressive work up including for p53 gene mutation and dietary . A growing number of published studies have provided evidence that the natural history of chronic HBV infection differs according to the specific infecting HBV genotype and subgeno type Genotype Al is associated with HCC in young men who are usually HBeAg-negative and antiHBe-positive, have low levels of HBV DNA, and rarely have cirrhosis. Exposure to aflatoxin may be an important cofactor for the occurrence of this outcome. Genotype A2 is associated with HCC in older persons. Compared to HBV genotype D, genotype A2 is associated with a lower risk of HCC and a greater likelihood of resolution of active hepatitis, and clearance of HBV DNA and HBsAg .27 of our patients had elevated AFP values beyond diagnostic level. Others had either normal level 7 or levels were in non-diagnostic range. There are many studies available showing that, serum AFP is frequently elevated in patients with liver cirrhosis without HCC and can be normal or only moderately elevated in patients with Hepatocellular carcinoma. The median AFP level was only 786 ng/ml in the study population despite advanced HCC was noted in three-fourth cases. There are some studies which suggest that the production of AFP depends on the size or the degree of differentiation of the hepatoma cells. Even when lesions were single they were large enough in most of the cases to rule out curative resection. Another study from a tertiary care center in India showed that 56% of patients with HCC had tumor size larger than 5cm and high incidence of vascular invasion of main portal vein in 24%. More than half of the patients had a single tumor. Tumor was > 5cm in the majority(64%)ofthepatients. Moreover portal vein was thrombosed in 24% patientSummary and Conclusion:The study includes total of 49 patients, mean age was 55.1 years with male female ratio of 5:1. Mean age for male was 56.4± 10.6 and 48.4 ± 11 for femaleNearly half of the patients belong to the age group of 55 to 65 years. Two third of the patients belongs to low socio economic status. Among the symptoms abdominal pain (79.6.7%) and weight loss (34.7%) were most commonly observed symptoms. Hepatic decompensation was seen in half the patients at first presentation with Ascites in 52.8%, jaundice in 15.9% and hepatic encephalopathy in 3.8% of patients. The median serum AFP value of 786 ng/ml (range 0.4-92625) observed in the study population.

Diagnostic value of AFP >200 ng/ml was present in 27 of 49 (55.1%) patients; with normal AFP in 9. Hepatomegaly seen in more than half the patients (67.8%) while in 26% of cases liver was not enlarged 11(22.4%) patients had a Child-Pugh stage C and 18 (36.7%) stage B and stage A 20(40.8%) cirrhosis. MELD score was 6-24 range and mean was 11.Seventeen (34.7%) were positive for HBsAg and 18 (36.7%) were positive for anti-HCV patients developed HCC Age above 59 years, male sex, longer duration and more advanced stage of cirrhosis were significant risk factors for HCC in anti-HCV positive cirrhotic patients, while none of these variables were significant risk factors for HCC in HBsAg positive patients. More than three fourth of cases had esophageal varices with gastric varices of 19.1%. Nearly three fourth of cases had low serum albumin level of <2.8 gm. Very large tumors (>5 cm) were seen in two-third of cases. The average size of HCC was 6±4 cm. Small HCC (<2 cm lesion) was seen in only6%ofpatientsapproximately .

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