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Association of Portal Vein Tumor Thrombus in Hepatitis B Related Hepatocellular Carcinoma

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Abstract

Background: The highest incidence of Hepatocellular carcinoma (HCC) is in Asia, accounting for about 76% of all cases worldwide. In South East Asia, hepatitis B is the most common underlying cause. HCC exhibits intense neoangiogenic activity during its progression. In the early stages the tumor is not highly vascularized and its blood supply comes from the portal vein. However, as the tumor grows the blood supply becomes progressively arterialized. HCC have to invasion the portal venous system, which results in portal vein tumor thrombus (PVTT). Objectives: To find out the relationship of portal vein tumor thrombus (PVTT) with the hepatitis B-related hepatocellular carcinoma. Methods: This observational study was carried out in the Department of Hepatology, BSMMU from January 2012 to December 2013. The study was approved by the Ethical Institutional Review Board (IRB) of BSMMU, Dhaka. The diagnosis of HCC was confirmed by pathological examination or AFP elevation (400ng/ml) combined imaging (CT/MRI) and diagnosis of PVTT was made by non-enhanced and contrast-enhanced (10 mm slice thickness) multi-detector CT (MDCT). All CT images were evaluated by 2 trained radiologists by consensus after exclusion of hepatitis C virus infection (Anti HCV+ve) and significant alcohol intake (>20 gm. /day). All patients were HBsAg positive done by ELISA test. **Results:** A total 44 patients were included in this study. Among them, 91% were male (n=40) and 09 % were female (n=4).The mean age was 48.2 (±12.9) years with range from 23 to 80. Maximum (50%) patient's ages were belonged to 35-54 years. Urban was found 23 (52.3%). Cirrhosis was 79.5% (n=35) and no cirrhosis was found 20.5% (n=9). PVTT was found 41% (n=18) and no PVTT was found 59% (n=26). Among cirrhosis and non-cirrhosis group, PVTT was 83% (n=15) and 17% (n=03) respectively. Conclusions: From our observation we can conclude that PVTT is a significant association with HCC and PVTT increase is more in cirrhotic group. Median survival time of patients with PV invasion was 2.7 to 4 months if left untreated, whereas the median survival time of patients without PV invasion was 24.4 months if left untreated. Detection of PVTT in HCC leads to extremely poor prognosis.

Keywords: Hepatitis B virus; Portal vein tumor thrombus; Hepatocellular carcinoma.

Introduction

HCC is the sixth most common malignant tumor and the third most common cause of cancer deaths worldwide[1]. The etiological agent of HCC is known in more than 90% of cases. In South East Asia, hepatitis B is the most common underlying cause. The highest incidence of HCC is in Asia, accounting for about 76% of all cases worldwide[2]. HCC exhibits intense neo-angiogenic activity during its progression. In the early stages the tumor is not highly vascularised and its blood supply comes from the portal vein. However, as the tumor grows the blood supply becomes progressively arterialized[3]. HCC has a tendency to invade the portal venous system, which results in portal vein tumor thrombus (PVTT). Patients with both cirrhosis and hepatic carcinoma have the highest risk to develop portal vein tumor thrombosis[4].

risk to develop portal vein tumor thrombosis[4].

Based on this hypothesis, we find out the association of PVTT with the hepatitis B-related hepatocellular carcinoma

Materials and Methods

Study Population

This is a hospital based observational study of 44 HCC patients. Patients with HBsAg positive done by ELISA test and features suggestive of HCC attending at outpatient & inpatient department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from January 2012 to December 2013 is enrolled this study. Aims and objectives along with its procedure, risks and benefits of this study were explained to the patients and attendants in easily understandable local language (Bangla) and then informed written consent was taken from each participant. Prior to the commencement of the study, the research protocol was approved by the Institutional Review Board (IRB) of BSMMU.

Patients were divided into two groups. Group A (Cirrhosis-related HCC) and Group B (non-Cirrhosis with HCC). The inclusion criteria were: HCC patients were recruited prospectively. The diagnosis of HCC was confirmed by α-fetoprotein elevation (≥400 ng/ml) combined with computed tomography (CT) and/or magnetic resonance imaging (MRI) or Pathological examination (Biopsy/FNAC) [Figure 1] and diagnosis of PVTT was made by non-enhanced and contrast-enhanced (10 mm slice thickness) multi-detector CT (MDCT). All CT images were evaluated by 2 trained radiologists by consensus. Exclusion criteria were alcohol abuse (>20g/day) and infection with HCV (anti-HCV positivity).

Procedure for fine needle aspiration (FNA) from liver space occupying lesions SOL(s)

After taking informed written consent, patients laid with empty bladder. The site was painted with iodine solution and draped. Skin and deeper tissue was infiltrated with local anesthesia (2% xylocaine) at the proposed puncture site using a 23 G needle. Under real-time USG guidance and using 22 G disposable spinal needles the cavity was entered and aspirated material was collected. The prepared glass slides ware fixed with 95% ethanol and kept in Kaplan's jar after labeling. Samples were sent for cytopathological examination to the Department of Pathology, BSMMU. Dressings were applied at the needle puncture sites and patients were followed up for next 6 hours.

Statistical Analysis

All data was recorded systematically in a preformed data collection sheet and quantitative data expressed as mean ± SD. Qualitative data analyzed by chi square test and quantitative data by student's T test or Mann Whitney's U test. Differences in laboratory parameters compared using one-way ANOVA.P value of ≤0.05 was considered to be statistically significant. All statistical computations were performed by using SPSS version 20 (Statistical Package for Social Science).

Results

Demographic and laboratory characteristics

Table I includes the demographic and laboratory parameters of the subjects in the study within two groups, including gender, age, haemoglobin(Hb), platelet count(PLT), prothombin time(PT), alanine aminotransferase (ALT), aspartate aminotransferase(AST), serum bilirubin, serum albumin ,α-fetoprotein (AFP) & portal vein tumor thrombus (PVTT) .The Cirrhosis related group and the other group without Cirrhosis had statistically different laboratory results for PLT, PT, INR, ALT, AST, serum bilirubin, serum albumin ,α-fetoprotein and PVTT ($p<0.05$).

Table I: Demographic and laboratory parameters of the subjects in the study (n=44)

Groups	Cirrhosis (n=35)	No Cirrhosis (n=9)	P value
Demographic parameters			
Gender (M/F)	32/3	8/1	.614^{ns}
Age (Y) (Ç± SD)	48.2 ± 12.8	48 ± 14.1	.206^{ns}
Laboratory parameters (Ç± SD)			
Hb (g/dl)	11.37 ± 1.8	11.7 ± 1.51	.208^{ns}
PLT (10^9/L)	217.2 ± 97.6	266.6 ± 118.1	.039^{s}
PT (sec)	15.37 ± 2.2	14.18 ± 2.3	.048^{s}
INR	1.29 ± .19	1.19 ± .18	.045^{s}
ALT (U/l)	81.5 ± 53.8	53.11 ± 33.7	.038^{s}
AST (U/l)	174.9 ±166.9	37.5 ± 23.9	.012^{s}
T-Bil (µmol/l)	112.57 ± 122.98	26.56 ± 16.37	.041^{s}
ALB (g/dl)	2.9 ± 0.6	3.5 ± 0.4	.003^{s}
AFP (ng/ml)	17241.63 ± 18479	7469.5. ± 14186	.049^{s}
PVTT	15	03	.001^{s}

ns= not significant, s= significant

Distribution of the study population by age range

Table II shows distribution of the study population by age range. Maximum (50%) patients' ages were belonged to 35-55 years. The mean age was found 48.20 ±12.92 years with range from 18 to 80 years. The mean age difference was not statistically significant (P = 0.206) between two groups.

Table II: Distribution of the study population by age range (n = 44)

Age range	Frequency	Percent	Cumulative Percent
< 20	01	02.3	02.3
21 -30	05	11.4	13.7
31- 40	11	25.0	38.7
41- 50	11	25.0	63.7
51- 60	10	22.7	86.4
> 60	06	13.6	100.0
Total	44	100.0	100.0

Gender distribution of the study population

Figure 2 shows male gender was predominant 91% (40) of the study population. Male female ratio was 10:01. Male was also predominant in both groups, which were 91% (32) in cirrhosis - related HCC group and 89% (08) in non-cirrhosis with HCC group. The difference was not statistically significant (P = 0.614) between the two groups.

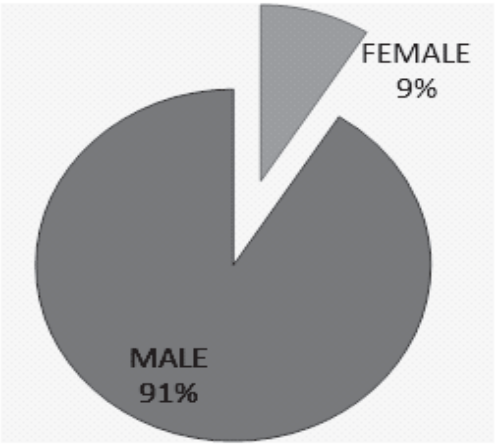

Figure 2. Gender distribution of the study population (n= 44).

Distribution of PVTT in the study population

Figure 3 shows PVTT in the study population by imaging methods (USG and CT/MRI). Among 44 patients 18(40.9%) was PVTTT and 26 (59.1%) was no PVTT. The difference was not statistically significant (P >0.5) among the two groups.

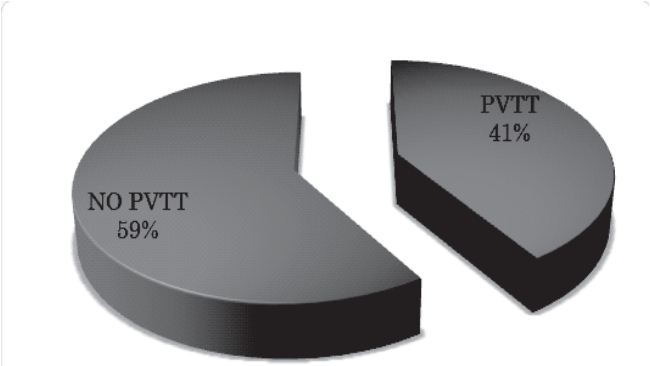

Figure 3: Distribution of PVTT in the study population (n=44)

Distribution of the PVTT according to cirrhosis status

Table III shows the PVTT in cirrhosis status. Cirrhosis was 79.5% (35) and no cirrhosis was found 20.5% (9). Among cirrhosis and non-cirrhosis group, PVTT was 83% (15) and 17% (03) respectively. The difference was statistically significant (P = 0.001) among the two groups.

Table III: Distribution of the PVTT according to cirrhosis status (n = 44).

Cirrhosis status	PVTT				
	Present (n = 18)		Absent (n=26)		
	n	%	n	%	P values*
Present	15	83	03	11.5	0.001
Absent	03	17	23	88.5	
Total	18	100	26	100	

s=significant

*Chi square test was done to measure the level of significant

Discussion

This is the study from Bangladesh in which the characteristics of HBV related HCC have been studied. HBV infection accounts for most primary HCC and treating HBV infection substantially reduces the risk of HCC development. Chronic HBV infection is recognized as the most important causal factor for HCC in humans.

The incidence of HCC increases with age. The development of HCC is uncommon before 40 years of age in western world. However, the pattern of HCC incidence by age is sometimes dependent on the geographic pattern or on etiologic factors .The age distribution of patients with HCC in the present study was similar to other studies in past. Studies from Bangladesh (M Khan *et al* & Gani ABMS *et al*), India (Sarma MP *et al*), China (Shan R *et al*) and Pakistan (Abbas Z *et al*) have shown the maximum incidence of HCC in the fifth to sixth decade[5-9]. The male preponderance is similar to our previous Bangladeshi study and other studies from India and Pakistan [5-7,9]. The population-based data show a male to female ratio of 3:1–2:1.1.22 However, high preponderance of HCC in males reported in hospital-based data could suggest a gender bias in seeking medical treatment.

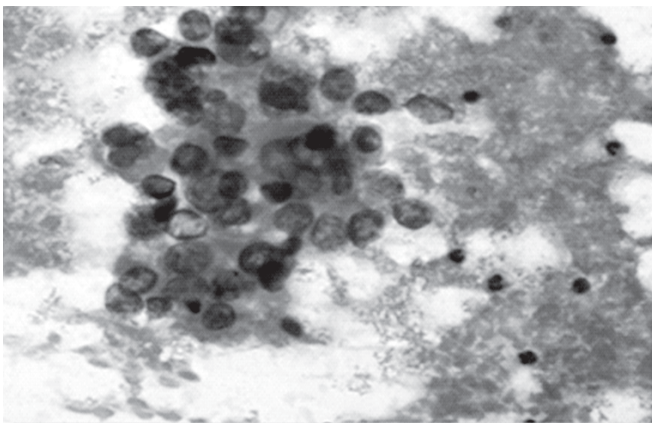

Figure 1: Cytopathic feature of Hepatocellular carcinoma (Haematoxylin and eosin stain , Courtesy: Department of Pathology, Bangabandhu Sheikh Mujib Medical University).

Underlying cirrhosis was observed in almost 79.5% of our cases. HCC is accompanied by liver cirrhosis in 70–90%[10].The cirrhosis along with HCC is reported in 70–86% of Indian autopsy studies. The clinical studies have shown 30–80% incidence of associated cirrhosis in HCC[10-11]. The present study is in conformity with the previous studies from Bangladesh[6] and India[7]. The strong association between cirrhosis and HCC is supported by the evidence of its intermediating role in the pathogenesis of HCC because of chronic viral hepatitis.The number of patients without cirrhosis (20.5%) in the present study is similar to those in Indian clinical and autopsy studies[7,12]. An increased risk was observed for HBV marker irrespective of the cirrhosis status of the HCC patients. This result confirms that HBV is the major etiological factor associated with HCC development. These findings are in agreement with biological data. HBV plays a direct role in liver cell transformation; thus, it can lead to HCC without the development of cirrhosis[13]. Like previous studies most of the lesions were multiple in cirrhotic group and single in non-cirrhotic group.

Portal vein tumor thrombus (PVTT) is a crucial factor that can worsen the prognosis of HCC because it can lead to the wide dissemination of tumors throughout the liver and cause a marked deterioration of hepatic function. Despite this marked progress in medical science, the prognosis of advanced HCC remains poor, particularly in patients with tumor thrombus in the portal vein (PV). HCC has a high frequency of PV invasion, which is reportedly observed in 11% to 42% of patients with HCC[14 -16]. PVTT was observed in almost 41 % of our cases .The present study is in similarity with the previous studies.

Conclusion

From our observation we can conclude that PVTT is a significant association with HCC and PVTT increase is more in cirrhotic group. Median survival time of patients with PV invasion was 2.7 to 4 months if left untreated, whereas the median survival time of patients without PV invasion was 24.4 months if left untreated. Detection of PVTT in HCC leads to extremely poor prognosis. Limitation of this study is its small sample size and single center. As PVTT is not infrequent, advanced treatment guideline is mandatory to increase survival.

Conflict of Interest Statement

No potential conflicts of interest are disclosed.

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