

PREDISPOSING FACTORS FOR HEPATOCELLULAR CARCINOMA IN NORTH OF PAKISTAN

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ABSTRACT

Objectives: The main objective of this study was to search for predisposing factors for Hepatocellular Carcinoma (HCC) in North of Pakistan.

Material and Method: This study was conducted in medical units of Khyber Teaching Hospital, Peshawar, from July 2007 to February 2009. A total of 100 patients were selected. The main tools for the diagnosis of HCC were ultrasound abdomen, CT scan abdomen, serum alpha-feto protein and liver biopsy.

Results: Out of one hundred, 80 patients were males, 72% patients were above the age of 60 years. HCV was present in 74% of our patents, 13 (13%) patients turned out to be HBsAg positive, in 04 patients both HCV & HBV were present, while in the rest of 09 (09%) patients no predisposing cause found. Cirrhosis was present in 80% of patients; the P-Value being 0.538. Serum AFP was raised in 72% of patients.

Conclusion: It is concluded that chronic HCV infection is the commonest cause of HCC.

Key words: Hepatocellular Carcinoma, predisposing factors for HCC.

INTRODUCTION

Hepatoma arises from hepatic parenchymal cells^{1,2}. It is the third leading cause of cancer-related deaths worldwide³. Its incidence is rising in USA, Western countries^{2,4} and developing countries due to HBV and HCV infection^{4,5}. The incidence of hepatocellular carcinoma (HCC) is predicted to continue to increase over the next 30 years⁶. Advanced cases accompanied by multicentric carcinogenesis and portal vein thrombus have a poor prognosis^{7,8,9}. Hepatitis B virus, hepatitis C virus, and chronic heavy alcohol abuse leading to cirrhosis of the liver remain the most important causes^{2,5,7}. The various risk factors for HCC include cirrhosis, HBV & HCV infection^{2,10}, alcohol, haemochromatosis, aflatoxin B, alpha-1 antiprotease deficiency, tyrosinaemia², male gender, age more than 55, Asian or Hispanic, obesity^{2,10}, diabetes mellitus⁴, hypothyroidism, low platelets^{2,10}, prolonged Prothrombin time and elevated serum transferase². Cirrhosis accounts for upto 80% of cases^{2,11,12}. The HBV genome enters the genome of the liver cells, changing the hepatocytes into malignant cells^{13,14,15}. Heavy ingestion of alcohol more

than 50 gm/day over a period of about ten years increases the risk of HCC¹⁵. Aflatoxin B1 is the most potent liver carcinogen¹⁵. Cirrhosis resulting from NAFLD has been associated with HCC^{2,4,16}.

Unexplained weight loss or unexplained fevers are warning signs of HCC in patients with cirrhosis¹⁶. The physical findings are usually those of cirrhosis liver¹⁶. Hepatic bruit or friction rub may be heard when HCC reaches to the surface of the liver^{2,17}.

Serum Alpha-fetoprotein (AFP) is elevated in upto 70% of patients with HCC^{2,11,12}. Modestly elevated upto 30ng/ml in some patients with chronic viral hepatitis and liver cirrhosis but serum level more than 500ng/ml is highly specific for HCC¹⁸. Serum Des-gamma-carboxy Prothrombin (DCP), a variant of the gamma-glutamyl transferase, is elevated in 90% of patients with HCC^{2,19}.

Though liver biopsy is goldstandard for definitive diagnosis of HCC²⁰, characteristic triphasic CT and or dual contrast MRI features and elevated serum alpha fetoprotein (more than 200ng/ml) may obviate the need for confirmatory biopsy².

Liver resection involves removal of the tumor and appropriate surrounding liver tissue. The 5 years survival after small HCC (< 5cm) resection is about 50%²⁰ to 75%², but for early HCC with well differentiated cancer containing Glisson's triad the 5-year survival is 93%²¹. Liver transplantation is the best

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option for patient with liver failure & tumors less than 5 cm²². High dose long-term interferon alpha is known to prevent recurrence and metastasis after resection^{22,23}. Transarterial chemoembolization (TACE) is currently the first choice of treatment for most of unresectable HCC^{2,7}, patients with child A or OKUDA-1 with multifocal HCC²⁴. Octreotide is found to prolong survival from 04 to 13 months in advanced HCC²⁵. The rising incidence of HCC in Pakistan and especially in N.W.F.P²⁶ requires evaluation of predisposing factors so that preventive measures can be taken in our local setup, if possible.

RESEARCH METHODOLOGY

The study was conducted in the Medical Department of Khyber Teaching Hospital, Peshawar from 25th July, 2007 to 25th February, 2009. Patients more than 13 years of age with hepatoma were included. Patients with liver tumors other than Hepatocellular carcinoma, metastatic liver disease and those patients in whom liver biopsy was not done, were excluded from the study. After detailed history and thorough physical examination, ultra-sound abdomen, serum alpha-fetoprotein and CT abdomen were performed. If these findings were suggestive, ultrasound guided true-cut biopsy was performed on all patients. When diagnosis was confirmed by histopathology, patients were investigated for the underlying causes of HCC including haemochromatosis and Wilson's disease. Those patients in whom no underlying cause was found PCR for HBV was specifically done to find out occult HBV infection. The data of different variables i.e. age, sex, number of total patients with HCC were recorded and processed. Chi-square test and P-values were retrieved wherever needed and applicable.

RESULTS

Out of one hundred patients, 80 were male and 20 were female. Age wise analysis showed that 72% patients were above the age of 60 years, the P value being 0.025 is quite significant. HCV was present in 74% of our patients, the P-value for HCV in HCC being 0.05. HBV was present in 13 (13%) patients, both HCV & HBV were present in 04 patients, while in the rest of 09 (09%) patients no predisposing cause found (Table 1). As shown in Table 3, cirrhosis was present in 80% of patients; the P-Value being 0.538. Table 4 shows the various levels of serum AFP.

Table 1: Predisposing causes of HCC in 100 patients

S. No.	Underlying causes	Number of patients
1.	HCV	74.74%
2.	HBV	13.13%
3.	HCV+HBV	4.04%
4.	No evidence of known causes	9.09%

Table 2: Presenting Features of 100 patients with HCC

S. No.	Clinical Signs	No. of patients
1.	Anorexia	100.100%
2.	Weight loss	100.100%
3.	Abdominal discomfort	100.100%
4.	Hepatomegaly	84.84%
5.	Loss of axillary hair	82.82%
6.	Ascites	82.82%
7.	Jaundice	62.62%
8.	Splenomegaly	56.56%
9.	Spider naevi	58.58%

Table 3: Features on Ultrasound & CT Abdomen

S. No.	Clinical Signs	No. of patients
1.	Anorexia	100.100%
2.	Weight loss	184.84%
3.	Abdominal discomfort	82.82%
4.	Hepatomegaly	80.80%
5.	Loss of axillary hair	56.56%
6.	Ascites	82.82%
7.	Jaundice	62.62%
8.	Splenomegaly	56.56%
9.	Spider naevi	30.30%

Table 4: Serum Alpha Fetoprotein level in HCC patients

S. No.	Level ng/ml	Number of patients
1.	<10	28.10%
2.	10-200	5.19%
3.	201-400	28.28%
4.	401-1000	14.16%
5.	1001-2000	12.12%
6.	>2000	15.15%

DISCUSSION

HCC is the most common cancer in sub-Saharan region and in South-east Asia²⁷. In Pakistan, HCC accounts for 1.55% of all malignant tumors²⁸. In the present study, 72% patients were above the age of 60 years. The male to female ratio was 4:1. These observations are correlating with other studies published locally²⁸ and from abroad²⁷, probably because of more exposure of males to risk factors².

Mean age of 53 years and male to female ratio of 6:1 has also been reported by Farooqui JI²⁶ in the same area in 2000, this reflects that probably now the involvement of the females is increasing.

Cirrhosis was present in 80% of our patients, this figure correlates well with previous studies^{2,11,12}. The present study revealed that frequency of HCV in our patients with HCC is 74%. It correlates well with figure of 67.86% published by Farooqui JI in 2000²⁶ in the same geographical area, 77.96% by Rahman AU and Murad S in 2001²⁹ in Punjab and figure of 76.7% by Nishioka et al, from Japan³⁰. But older studies showed lower figures eg 13% by Malik et al in 1995³¹, 28% by Manzoor et al in 1997²⁷ and 37.2% by Jeng et al in 1991 in Taiwan³².

Thirteen patients (13%) were positive for HBsAg in our study. These observations are closely related to figure of 14.28% as reported in the same geographical area in 2002²⁶ and figure of 16% as reported by Haydon et al³³. But older studies showed quite high frequency of HBsAg positivity eg Malik et al³¹ reported 69.6% in 1995, Manzoor et al²⁸ reported 72.73% in 1997 from Pakistan, Colombo M et al³⁴ reported 54.21% from Italy in 1989, figure of 80% was reported from Saudi Arabia in 1991³⁵ and figure of 63% was reported from Taiwan in 1990³⁶.

These observations reflect that probably the incidence of HCV is increasing throughout the world. In the previous studies the prevalence of HCV in patients with HCC was low compared to HBV^{28,31,35}. The reasons are probably three fold, firstly less familiarity with HCV in past, secondly incidence of HBV reduced due to vaccination^{2,11,35} and finally emergence of resistant strains of HCV².

Four patients (4%) were positive for both Anti HCV and HBsAg, see Table 1, almost similar percentage of 3.57% has been reported in 2001²⁹ in the same area. The reason may be co-infection or super-infection, both may play a synergistic role in the development of HCC²⁶.

Table 4 reflects that serum Alpha fetoprotein was raised in 72% of our patients, figure correlates well with exact 72% figure reported by Tariq Parwez³⁷ and 70% by Friedman LS².

CONCLUSION

The present study reveals that HCC is more common in males compared to females and HCV is the leading underlying cause followed by HBV in local population in the North of Pakistan.

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