Corelation of serum alpha fetoprotein and tumor size in hepatocellular carcinoma

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Abstract

Objective: To determine the correlation of elevated serum Alpha feto-protein with tumour size in hepatocellular carcinoma.

Methods: A cross-sectional analytical study was done at Jinnah Postgraduate Medical Centre, Karachi, Medical Unit-III, Ward-7 from January 2009 to June 2010. Patients enrolled in study were known cases of chronic liver disease and were complicated by development of hepatocellular carcinoma; those having metastasis in liver from any where were excluded. Demographic data such as age, gender, residence, were recorded. Detailed clinical history and examination were carried out and recorded in a preformed Performa. Complete blood count, liver function test, total protein, Albumin/Globulin (A/G) ratio, serum Albumin, HBsAg, anti HCV, alpha fetoprotein, ultrasound guided liver biopsy, ultrasound whole abdomen and/or CTscan Abdomen for size and number of tumour were also done. On the basis of alfa fetoprotein level patients were divided in to 3 groups; Group I with normal AFP (≤20IU/ml), Group II with moderately elevated AFP (20-399IU/ml), and Group III with markedly elevated AFP (≥400 iu/ml). On the basis of tumour size patients were also divided in to 3 groups; group A <3 cm, group B 3-5 cm and group C >5 cm. Correlation of serum AFP levels with tumor size was analyzed by applying Spearman's rank correlation with r-values of 0.01 being considered significant.

Results: Review of the clinical data of 98 patients male 69 (70.4%) and female were 29 (29.6%) with mean age of 53.89 ±12.511 ranging from 32 to 82 years was done. Of these there were 22 (22.4%), 25 (25.5%), 51(52%) cases in group 1, 2, 3 respectively. While in tumour size groups, 17 (17.3%) were in group A, 35 (35.7%) in group B and 46 (46.9%) in group C. There was a significant correlation of serum AFP level with tumour size in hepatocellular carcinoma. (r=0.472, 0.0001).

Conclusion: Our study suggests that serum AFP has significant correlation with the size of tumour. AFP level may serve as a useful marker for detection of Hepatocellular carcinoma and to differentiate between early and advance stage. On the basis of this proper treatment strategy can be planned.

Keywords: Hepatocellular carcinoma, Alpha feto-protein, Chronic liver disease (JPMA 62: 33; 2012).

Introduction

Hepatocellular Carcinoma (HCC or Malignant Hepatoma) is the most common primary malignancy of the liver and represents the third leading cause of cancer-related deaths worldwide.[1] Risk factors include hepatitis B and C virus infections, dietary intake of aflatoxins and drinking water contamination in the rural areas.[2] Chronic hepatitis B and C are thought to be the major causes of cirrhosis and of HCC.[3] HCC is one of the main causes of death in patients with Liver Cirrhosis (LC).[3] The annual risk to develop HCC in patients with LC is 5% (1-7%), with a published prevalence between 7.4 and 23% being found in necropsies of this group of patients. Cirrhosis is present in 80-90% of patients with this type of cancer.[4] The rise in incidence and mortality of HCC, most likely reflects the increased prevalence of hepatitis C virus (HCV) infection, and has recently been observed in industrialized countries.[3] In Pakistan its projected incidence is 8/100,000 per annum.[5]

Since the development of hepatocellular carcinoma is closely associated with chronic liver disease, particularly cirrhosis, patients with cirrhosis should be examined regularly with imaging technique like ultra sound and computer tomography, in combination with determination of serum alpha-fetoprotein (AFP).[6-8] Alpha-fetoprotein is a glycoprotein comprised of 591 amino acids with a half-life of 5-7 days. Normally produced by the foetal yolk sac, liver, and intestine, elevated levels can be associated with HCC in the appropriate clinical setting.[9] High AFP serum levels have been found in 60-70% of patients with HCC; nevertheless, there are other causes of increased levels, such as cirrhosis, lung cancer, biliary cancer, gastric cancer, pancreatic cancer, teratocarcinoma of the testis, spherocytosis and tyrosinemia.[10] Sharieff et al found alpha feto protein elevated in 76% of cases with HCC.[11]

Alpha-fetoprotein sensitivity and specificity depend on chosen cut off values; cut off value of 20 ng/ml has a sensitivity

around 60% and positive predictive value of 9 to 50%. The performance of ultrasound as a screening tool depends on experience of the examiner and technology. Its sensitivity is greater than 60% and specificity is 90.%.[12] The objective of our study was to correlate the value of alpha-fetoprotein with size of tumour determined on ultrasound and computer tomography.

Patients and Methods

This cross-sectional analytical study was conducted from January 2009 to June 2010. Specific beds were assigned in Hepatology section of medical unit 3 in the Jinnah postgraduate medical centre. Patients enrolled in the study were known cases of chronic liver disease and were complicated by development of hepatocellular carcinoma. Those having metastasis in liver from any where were excluded. Demographic data such as age, gender, residence, were recorded. Detailed clinical history and examination were carried out and recorded in preformed Performa. Complete blood count, liver function test, total protein, A/G ratio, serum Albumin, HBsAg, anti HCV, alpha fetoprotein, ultrasound guided liver biopsy, ultrasound whole abdomen and CTscan Abdomen, were done.

On the basis of alfa fetoprotein level patients were divided in to 3 groups; Group I with normal AFP (≤ 20IU/ml), Group II with moderately elevated AFP (20-399IU/ml), and Group III with markedly elevated AFP (≥ 400 iu/ml). On the basis of tumour size patients were also divided in to 3 groups; group A <3 cm, group B 3-5 cm and group C >5 cm.

Correlation of serum AFP levels with tumour size was analyzed by applying Spearman's rank correlation test. A p-value of < 0.05 was considered as significant correlation. Descriptive statistics were obtained for the variables where applicable, using SPSS version 15.

Results

We reviewed the clinical data of 98 patients male 69 (70.4%) and female 29 (29.6%) with mean age of 53.89 ±12.511 ranging from 32 to 82 years. These were histopathologically proven cases of hepatocellular carcinoma. Forty patients presented with Child-Pugh class A, 53 class B and 5 patients with class C. The mean tumor size was 5.86±3.25 cm while mean serum AFP level was 5403.28±10865.32. Of these there were 22 (22.4%), 25 (25.5%), 51(52%) cases in group 1, 2, 3 respectively. While in tumour size groups the 17 (17.3%) were in group A, 35 (35.7%) in group B and 46 (46.9%) in group C. Serum AFP level was found to have correlation with tumour size presented in Table-1. Spearman's rank correlation test revealed a relation between Serum AFP level and size of tumour (r=0.472). It was a significant correlation with p-value of < 0.0001, suggesting that, as tumour size increases the AFP levels also increase as shown in Table-2.

Table-1: Baseline characteristics of Hepatocellular carcinoma patients.

Variable		AFP Level (ng/dl)			p value
		≤ 20	21-399	≥400	
Over all	98	22	25	51	
Gender	**n (%)**				
Male,	69 (70.4)	14	19	36	0.65
Female,	29 (29.6)	8	6	15	
Age (years)	**n (%)**				
≤ 40	18 (18.4)	3	0	15	0.006
> 40	80 (81.6)	19	25	36	
Etiology	**n (%)**				
HBV	26 (26.5)	7	6	13	
HCV	47 (48)	8	13	26	
HBV+HCV	4 (4.1)	2	1	1	0.749
HBV+HDV	2 (2.04)	0	0	2	
Others	19 (19.4)	5	5	9	
Child-Pugh class	**n (%)**				
A	40 (40.8)	13	5	22	
B	53 (54.1)	9	18	26	0.078
C	5 (5.1)	0	2	3	
Tumour size (cm)	**n (%)**				
< 3	17 (17.3)	6	9	2	
3-5	35 (35.7)	7	11	17	0.001
>5	46 (49.9)	9	5	32	

Table-2: Correlation of tumour size and other variables in patients of Hepatocellular carcinoma.

Variable	Mean±SD	r	p-value
AFP (ng/ml)	5403.28±10865.32	0.472	0.0001
Age (years)	53.89±12.51	-0.335	0.001
Albumin (g/dl)	3.317±0.727	0.018	0.862
Bilirubin (mg/dl)	4.224±5.322	-0.070	0.495
Child-Pugh Score	7.173±1.65	-0.031	0.764
ALT (U/L)	108.26±298.18	-0.117	0.252

Discussion

The etiology of HCC varies world wide and HCV has replaced HBV as a major cause of HCC in Pakistan.[13] Usually men are thought to be more susceptible to HCC than women. They tend to consume more alcohol and cigarettes, and have increased iron stores. Androgenic hormones and increased genetic susceptibility have also been proposed as the contributing factors. The reason for the male predominance in previously reported studies may be due to higher prevalence of hepatitis B as the etiological factor.[14,15] In our series, males were in a larger proportion in the HCC of miscellaneous etiology (predominately HBV related HCC) than in HCV related HCC.

Patients with cirrhosis or chronic hepatitis due to either HBV or HCV require regular surveillance for HCC.[16] Some studies have demonstrated that the presence of elevated levels of AFP in patients with LC is a risk factor for the development of HCC.[17-19] thus suggesting that increased AFP

production in patients with LC might reflect, largely and abnormal or altered liver cell regeneration. Although serum AFP and ultrasonography every 6 to 12 months have been the preferred method of screening for many years, the optimal method and interval for surveillance are debated.[16-20] Elevation of the AFP level was the way HCC was diagnosed prior to the availability of sensitive abdominal imaging techniques in the late 1970"s.[21] However, it soon became apparent with the advent of ultrasonography and CT scanning that many tumors could be detected in patients without an elevated AFP. AFP is often elevated in hepatocellular carcinoma. Our study revealed 77.5% positivity in HCC cases. AFP positivity among HBV/ HCV co infected and HBV alone HCC cases is 50% and 73.07% respectively while in HCV infected HCC cases it is 82.98%.. Further, when quantitative levels of AFP were analyzed, the HCV infected group had significantly elevated levels of AFP than HBV/HCV co infected or HBV infected alone HCC cases.

The study is in disagreement with others (a) Studies on AFP levels in patients with HCC and other benign and malignant liver diseases have shown that serum AFP is greater than 400 ng/ml in 69% of patients with hepatoma.[22] These data suggest that in patients thought to have HCC on clinical grounds, AFP levels about 400 ng/ml should strongly confirm the presence of HCC by a tissue diagnosis. However, clinicians should remember that some patients with primary hepatic cancer will have normal AFP levels, and normal or moderately elevated levels should not be used to exclude the diagnosis of HCC (b) In the present study, AFP positivity is analyzed to check its co relation with the size of tumour. We found that 22.44% had AFP level of less than 20ng/ml, 25.5% had levels between 20 to 399 ng/ml and 52% had levels equal or more than 400 ng/ml. Highest AFP levels was 66408 ng/ml. Others have analyzed histopathologically confirmed HCC cases and have found that serum AFP is normal (<8.5 ng/ml) in 20%, moderately elevated (8.5-300 ng/ml) in 48%, and considerably elevated (>300 ng/ml) in 32% of cases.[23] In a north Indian study, the AFP levels were raised in 65% of the HCC cases, the highest level recorded being 580 ng/ml.[24] In another south Indian study, elevated AFP levels were observed in 47.4% of the cases.[25] Our results do not corroborate those of the Indian study.

Some clinical researchers have indicated that the simultaneous determination of supplementary markers especially glypican-3 (GPC3) along with AFP could significantly increase the sensitivity in the diagnosis of HCC,[26] which was not attempted in our study.

Conclusion

Our study suggests that serum AFP has significant correlation with the size of tumour. AFP level may serve as a useful marker for detection of Hepatocellular carcinoma and to differentiate between early and advance stage. On the basis of which proper treatment strategy can be planned.

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