HEPATOCELLULAR CARCINOMA (HCC) AND DIAGNOSTIC SIGNIFICANCE OF α-FETOPROTEIN (AFP)

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Background: Alpha-fetoprotein (α-fetoprotein, AFP) is a Glycoprotein, belonging to the intriguing class of onco-development protein**.** Generally designated as tumour marker, AFP is recognized as an important blood component, having specific diagnostic utilities Elevation of its level up to pathological range in adults correlate with the appearance of several malignant and chronic conditions, such as hepatocellular carcinoma (HCC) and chronic liver disease, respectively**. Methods:** To evaluate the diagnostic significance of AFP in HCC, a study was carried out for a period of two years (Jan 2004 to Dec 2005) A brief history of Patients was taken with clinical symptoms and signs and initial diagnosis. Patients admitted in wards or visiting OPDs with diagnosis or suspicions of HCC and additional conditions of Chronic Liver disease (CLDs), hepatitis C (HCV) and hepatitis B viral (HBV) infections, were selected and classified according to gender. When confirmed, their HCC status was evaluated and classified according to clinical condition. **Results:** In 1012 adults including, males 762 (75.3%) and females 250 (24.7%) patients suspected of or diagnosed with HCC and presence of HBV and HCV infections. Out of 480 males, who depicted elevated AFP levels, 39 (8.13%) were diagnosed with HCC. Similarly, 7 (5.34%) females out of 131 with elevated levels of AFP were diagnosed with HCC. Mean elevated AFP levels in all HCC patients were, 421±59 μg/ml (range 157–4019 μg/ml) in males and 163±32 μg/ml (range 101–2341 μg/ml) in females. In males, the overall estimated mean AFP elevated values were analysed to be 514 μg/ml (range 67–4019±59 μg/ml,), whereas in females it was 396±42 μg/ml (range 21–2341 μg/ml). It was also noted that 43 (8.96%) males and 7 (5.34%) female patients, exhibited elevated levels of AFP, however, found negative for HCV and HBV infections. **Conclusion**: It is concluded that AFP is a significant markers for Hepatocellular carcinoma, helpful in assessing problems in management of HCC and monitoring treatment regiments. In addition, AFP is also an indicator of HCC risks mostly in patients with cirrhosis and HCV/HBV infections

Keywords: AFP, Hepatocellular carcinoma HCC, Hepatitis infections HCV, HBV

INTRODUCTION

Alpha-fetoprotein (α-fetoprotein, AFP) is a large serum glycoprotein, belonging to the intriguing class of onco-development protein.[1] Generally designated as tumour marker, it is recognised as an important blood component, having specific diagnostic utility after it was shown that the change in its serum concentration during pregnancy is the sign of numerous embryonic disorders such as spina bifida.[1–4] Likewise, elevation of its level up to pathological range in adults correlates with the appearance of several malignant and chronic conditions, such as hepatocellular carcinoma (HCC) and chronic liver disease, respectively.[1,2,5–8] Most importantly, even after three decades of research and scientific studies regarding AFP usefulness as a significant marker for HCC, GCT and foetal abnormalities, substantiation of its sensitivity and specificity[9–12], in addition to investigation of structure-function relationship and isoforms[1,13], the research is still in progress to suggest more functional activities of AFP, receptor interaction, regulatory mechanism, and a possible input of all aspects in clinical application and diagnoses[1,2,13]. Due to the imperative significance of AFP as a tumour maker in HCC, the present study was undertaken in a selected group of patients suffering from Hepatic clinical conditions to evaluate AFP levels in patients suspected of hepatocellular carcinoma and to establish a possible correlation with occurrence, cause and extent of the disease.

MATERIALS AND METHOD

The study covered the period of Jan 2004 to Dec 2005 and includes only adults (age range 23–60 years). A brief history of Patients was taken with clinical symptoms and signs and initial diagnosis. Patients admitted in wards or visiting OPDs with diagnosis or suspicions of HCC and additional

conditions of Chronic Liver disease (CLDs), hepatitis C (HCV) and hepatitis B viral (HBV) infections, were selected and classified according to gender. When confirmed, their HCC status was evaluated and classified according to clinical condition.

For collection of samples 5 ml blood was collected in clot activated tubes. Serum was separated and stored at -20 ºC until a1nalysed.

All AFP analysis was performed in duplicates by Automated ELISA technique and ECL technology with two -point calibration and controls with definite cut-off values on Roche Cobas Core and Elecsys 2010, 1010 (Roche Diagnostics, Basil) automated immuno-analyser.

Data was statistically compared using student's *t*-tests. AFP Values >20 µg/ml (NV: <10 µg/ml) in smokers and >10 µg/ml (NV: <5 µg/ml) in non-smokers were considered significant. Data of patients are also presented in the form of percentage occurrence for clarity.

RESULTS

The results are summarized in Tables 1, 2. In brief, AFP analysis was carried out in 1012 patients, males 762 (75.3%) and females 250 (24.7%).

Out of 762 males, 480 (63%) showed elevated levels of AFP, whereas out of 250 females, 131 (52.4%) showed elevated levels of AFP. The highest abnormal value detected was 4019 µg/ml and the elevated values are in the range of 21 to 4019 µg/ml. The normal cut-off value for adults is less than 5.0 µg/ml. It is interesting to note that a large number of patients, both males and females with elevated levels of AFP are basically diagnosed with HCV or HBV infections. However, out of 480 males, who depicted elevated AFP levels, only 39 (8.13%) were diagnosed with or suspected of HCC. Similarly, 7 (5.34%) females out of 131 with elevated levels of AFP were diagnosed with HCC. Mean elevated AFP levels in all HCC patients were 421±59 µg/ml (range 157–4019 µg/ml) in males and 163±32 µg/ml (range 101–2341 µg/ml) in females. Further classifications are presented in Table-2. The patients with normal AFP were mostly diagnosed with chronic liver diseases of unspecified origin, amoebic liver abscess and hepatitis A or E infections. In males, the overall estimated mean AFP elevated values were analysed to be 514±59 µg/ml (range 67–4019 µg/ml), whereas in females it was 396±42 µg/ml (range 21–2341 µg/ml). It was also noted that 43 (8.96%) males and 7 (5.34%) female patients, exhibited elevated levels of AFP, however, found negative for HCV and HBV infections.

Table-1: Details of males and females patients assessed for AFP and various clinical conditions.

AFP values	Group	No.	Conditions	%	AFP results
Males		762	---	75.3	---
Elevated		480	---	63.0	67–4019 µg/ml (514±59)
	I	226	HCV	47.1	
	II	211	HBV	44.0	
	III	43	No-infection	8.96	
Normal		282	---	37.0	---
	I	102	CLD	36.2	
	II	98	Liver Abscess	34.8	
	III	82	Hepatitis A/E	29.1	
Females		250	---	24.7	---
Elevated		131	---	52.4	21–2341 µg/ml (396 ± 42)
	I	61	HCV	46.6	
	II	62	HBV	48.1	
	III	7	No infection	5.34	
Normal		119	---	47.6	
	I	35	CLD	29.4	
	II	44	Liver Abscess	37.0	
	III	40	Hepatitis A/E	33.6	

CLD= Chronic liver disease, HVB, HCV= hepatitis C and B virus infections.

Table-2: Distributions of HCC patients with respect to AFP values and clinical conditions

Gender	No.	Conditions	%*	AFP results
Males	39	HCC	8.13	157–4019 µg/ml (421±59)
I	20	HBV	51.3	121–4019 µg/ml (291±41)
II	12	HCV	30.8	286–3118 µg/ml (301±34)
III	7	No-infection	17.9	157–2446 µg/ml (276±30)
Females	7	HCC	5.34	101–2341 µg/ml (163±32)
I	4	HBV	57.1	100–2119 µg/ml (259±36)
II	2	HCV	28.6	98–2446 µg/ml (201±26)
III	1	No-infection	14.3	101–1926 µg/ml (129±29)

*Percentage relative to those patients with elevated AFP values

DISCUSSION

It is well documented that AFP estimation remains a useful test for clinicians, oncologists and physicians involved in the management of patients with foetal defects (spina bifida), hepatic malignancies (HCC, hepatoma, Hepatoblastoma, Hb), hepatic infections (HCV, HBV) and cancers of pancreas and germ cell.[2,9,10,14] Blood AFP level is also used in monitoring response to therapy.[14] It has been determined that AFP is specific marker of embryonal carcinoma.[2,15,16] Likewise, tumour of testicular or ovarian localisation and

retroperitoneal tumours of embryonic origin can equally be diagnosed by AFP.[15] A constant rise and persistence in AFP level is observed in malignancies, mainly germ cell[16,17], paediatric Hb[16,18], HCC and in rare case of GIT tumors[18].

An AFP test is generally recommended for differential diagnosis as well as monitoring of surgery and chemotherapy in GCT, Hb and HCC.[16] Another clinical utility of AFP, which is becoming more and more common, is its utilisation for surveillance of HCC in patients with chronic viral hepatitis (HCV, HBV) or risk factor of liver cirrhosis.[6,8–11] In our study we have noted several consistencies related to reported data for HCC and AFP. Elevated levels of AFP was noted in patients with HCC and also in patients with no sign of HCC, diagnosed with HCV and HBV infections. It is also interesting to note that there are several patients with elevated levels of AFP were devoid of any hepatitis infections. Upon investigations, they were found to be diagnosed with multiple complications, such as germ cell tumours, colorectal metastasis, chronic jaundice, alcoholism, strong long-term medications etc. The patients with normal AFP levels were found to be suffering from CLD, amoebic liver abscesses and hepatitis A/E.

In present study we have included adults only however, HCC is also reported to be manifest in children. Paediatric b is a distinct type of cancer, differentiated from HCC by the presence of hepatoblast like cells similar to embryonal liver parenchymal cells.[16] In Hepatoblastoma (Hb), the specificity of AFP is 90%[16], which means that, Paediatric Hb is sero-positive for AFP in almost all cases with AFP level greater than 1000 ηg/ml. In HCC, however, its specificity is up to 70–80%, probably due to AFP production in poorly differentiated tumours.[2] However, a vast majority of basic as well as clinical studies strongly suggests that AFP is one of the best diagnostic entities for HCC of both cirrhotic and non-cirrhotic origin.[6,8–11,19–21]

It is also described that AFP in GCT provides marked specificity to differentiate embryonal cancer and yolk sac tumour from seminoma, dysgerminoma and stromal cell tumors.[2,16,22] Local tumour invasion, in case of pancreatoblastoma, cause a rise in AFP level, as reported by a recent study.[23] Chemotherapy induces 95% fall in AFP level and depict the progress of treatment. Another recently reported study indicates the importance of AFP in diagnosing a uterine corpus cancer as hepatoid adenocarcinoma of endometrium.[12]

CONCLUSION

In conclusion AFP is a significant marker for Hepatocellular Carcinoma (HCC). It is also helpful in assessing problems in management of HCC and monitoring treatment regiments. Related studies also suggest that AFP is also useful in evaluating malignancies in germ cells and pancreas. Most importantly, AFP is an indicator of HCC risks mostly in patients with cirrhosis and HCV/HBV infections.

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