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Original Article

Evaluation of Tumor Markers Among Patients with Hepatitis C Infection

Shameem Bhatti[1*], Ahmed Saeed[1], Kanta Ahuja[3] Khaleeque Memon[2], Naseem Khatoon Bhatti[4],Ghulam Qasim Ujjan[1]

[1]Department of Pathology - Pir Syed Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat, Pakistan
[2]Department of Biomedical Engineering - Pir Syed Abdul Qadir Shah Jeelani Institute of Medical Sciences Gambat, Pakistan
[3]Department of Obstetrics and Gynecology - Pir Syed Abdul Qadir Shah Jeelani Institute of Medical Sciences Gambat, Pakistan
[4]Department of Chemistry - Govt Girls Degree College Gambat, Pakistan

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***Corresponding Author:**

Shameem Bhatti

Department of Pathology - Pir Syed Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat, Pakistan

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ABSTRACT

Tumor markers are biomolecules found in blood, urine and tissue of individuals and, with particularly high concentration in most cancers, therefore, their concentration has diagnostic value. These markers may be used for screening, identification (type and stage), monitoring, and predicting prognosis. Increases in tumor markers are sometimes seen in patients with chronic liver disease without hepatocellular carcinoma (HCC). **Objective:** To determine the tumor markers, present among patients with Hepatitis C infection. **Methods:** From April 2021 to March 2022, serum samples from 700 HCV patients who presented to the Department of Pathology at the Pir Syed Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat Khairpur Mirs, were used in this descriptive, cross-sectional study. Using the ACCESS-2 system, serum samples were analyzed for the presence of the specified tumor markers. **Results:** There was a significant increase in CA125 ($P = 0.03$) and AFP levels ($P = 0.03$). CA19-9, CEA, and CA15-3 levels in the blood were unremarkable ($P > 0.05$). It is too early to say if the increase in CA125 or AFP will lead to eventual carcinoma based on this study, but it deserves further exploration using a longitudinal research methodology. **Conclusion:** CA125 and AF (P were the most common tumor markers found in HCV patients. Given the association of the aforementioned indicators with hepatic cancer, HCV patients with CA125 and AFP levels over normal should be considered high-risk.

INTRODUCTION

Hepatitis C is an ailment of the liver, brought about by a viral infection (hepatitis C virus - HCV). The infection is transmitted via bodily fluids and blood in particular. Though unprotected sexual contact poses a risk, little evidence of sexual transmission is available. The condition is asymptomatic for a brief initial period, followed by vague symptoms such as low fever, yellow skin, dark urine etc. Thus, the condition is hard to notice in the initial stage, with people become aware of their ailment and attaining a diagnosis late in the infection – all the while acting as carriers and transmitting the infection forward. HCV infection has a mortality rate of 1%, with the morbidity (liver cancer and cirrhosis) rate being much higher [1,2]. More than 10 million people in Pakistan are afflicted with the condition, entailing a high morbidity and mortality. According to a comprehensive systematic review (based on literature published from 1994 to 2009), "prevalence of HCV was (4.95%± 0.53%) in the general adult population, (1.72%± 0.24%) in the pediatric population and (3.64%± 0.31%) in a young population, whereas a very high (57%± 17.7%) prevalence was observed in injecting drug users and (48.67%± 1.75%) in a multi-transfused population [3-5].Tumor markers are biomolecules found in blood, urine and tissue of individuals and, with particularly high

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concentration in most cancers, therefore, their concentration has diagnostic value [6,7]. These markers may be used for screening, identification (type and stage), monitoring, and predicting prognosis of cancer [8,9]. Patients with chronic liver illness but no hepatocellular carcinoma may see an increase in tumor markers (HCC). This could be a sign of imminent cancer and thus an opportunity to intervene quickly, avoiding a poor outcome and gaining a favorable prognosis. The goal of this study was to evaluate the levels of tumor markers in patients with Hepatitis C infection in order to identify HCV carriers who are at high risk for cancer development.

Alpha Fetoprotein (AFP): This fetal specific glycoprotein is primarily developed in the fetal liver. In normal circumstances the serum concentration of AFP falls immediately following the birth and hereafter, all production is repressed. It has been noted 7 out of every 10 HCC patients have elevated levels of AFP in the serum (attributed to secretion by the tumor). To date, serum AFP is regarded as the tumor marker that is most useful in screening HCC among suspected patients. Commonly, a serum concentration of 30 ng/mL is deemed a differentiation point or a cut-off value between normal individual and HCC patients (Sensitivity:65% and Specificity: 89%)[10].

CA 15-3: Secreted by normal cells in the breast, this murine monoclonal antibody (molecular weight: 300–450 kDa) is particularly elevated among patients with cancerous tumors (in the breast and/or elsewhere). The point of differentiation between healthy and diseased (cancerous) individuals is a concentration is 25 U/ml for CA 15-3. The marker is also known to be elevated among conditions other than hepatocellular carcinoma, such as cancer of the lungs, colon, rectum, and breast [11].

CA 19-9: The carbohydrate antigen 19-9 (CA19-9) is a known marker for illness states such as colon cancer and gastrointestinal adenocarcinoma. The point of differentiation between healthy and diseased (cancerous) is a concentration of more than 37 U/ml. In addition to hepatocellular carcinoma, the serum concentrations of this marker are also hiked among patients with cancer of the stomach, lungs, colon, and pancreas [12].

CA 125: This carbohydrate-related high molecular mass glycoprotein (molecular weight: >200 kDa) marker is a carbohydrate antigen that can be found in up to 80% of non-mucinous ovarian cancer cases. The marker is primarily a monoclonal antibody. The point of differentiation between healthy and disease (cancerous) cases is a serum concentration of an upwards of 35 U/ml. In addition to hepatocellular carcinoma, the serum concentration of CA125 is elevated among patients with cancer of the lungs, endometrium, pancreas, breast, and colon [13,14]. CEA: This antigen is an oncofetal antigen that is linked to a wide group of cell surface glycoproteins (molecular weight: 150–300 kDa) that are found on numerous cell types but have much higher concentrations in tumour patients and fetuses (normal). Smokers and nonsmokers have various points of differentiation (between normal and ill persons), namely 2.5g/l and 5.0g/l, respectively.

METHODS

This descriptive, cross-sectional study was conducted from April 2021 to March 2022 using serum samples of 700 HCV patients, presenting to the Dept. of Pathology at Pir Syed Abdul Qadir Shah Jeelani Institute of Medical Sciences, Gambat, Khairpur Mirs. The serum samples were checked for the existence of the listed tumor markers by ELISA using ACCESS-2 machine. ACCESS-2 can identify the following prominent biomarkers, among others. Since the levels (obtained via biochemical tests) of biomarkers can vary with time and between patients, the principles of best practice state that an arithmetic mean be used. Inclusion criteria was confirmed cases of HCV. Exclusion criteria was patients receiving hepatitis medication / Antiviral Therapy. Interferon-alpha (Subcutaneous Inj.) in combination oral Ribavirin & Lamivudine. Proven cases of hepatocellular carcinoma(HCC).

RESULTS

The mean age of the sample stood at 43 (SD± 3) years, with most of the sample comprising of males (59.29%), and the remaining being females (40.71%). Patients (73.14%) hailed from an urban setting while the remaining had a rural (26.86%) residence. A summary of the sociodemographic characteristics of the sample population are tabulated below. An increase in CA125 and AFP levels, was noted. Levels (in serum) of tumor marker CA15-3, CA19-9, and CEA were unremarkable.

Variables		Statistic – n (%)
Age (Years)	Up to 20	92 (13.14%)
	21 to 30	103 (14.71%)
	31 to 40	175 (25%)
	41 to 50	161 (23%)
	51 and above	94 (13.43%)
	41 to 45	75 (10.72%)
Gender	Male	415 (59.29%)
	Female	285 (40.71%)
Residence	Urban	512 (73.14%)
	Rural	188 (26.86%)
Educational Status	Educated	404 (57.71%)
	Un-Educated	296 (42.29%)

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Variables		Statistic – n (%)
CA15-3	Normal	322 (46%)
	Abnormal	378 (54%)
CA125	Normal	139 (19.9%)
	Abnormal	561 (80.1%)
CA19-9	Normal	404 (57.7%)
	Abnormal	296 (42.3%)
AFP	Normal	105 (15%)
	Abnormal	595 (85%)
CEA	Normal	301 (43%)
	Abnormal	399 (57%)

Variables		Statistic – n (%)	
CA15-3	Normal	12.93 U/mL	> 0.05
	Abnormal	44.39 U/mL	
CA125	Normal	1.35 U/mL	0.03
	Abnormal	88.51 U/mL	
CA19-9	Normal	3.82 U/mL	> 0.05
	Abnormal	67.21 U/mL	
AFP	Normal	6.99 ng/mL	0.03
	Abnormal	31.22 ng/mL	
CEA	Normal	5.6 ng/mL	> 0.05
	Abnormal	17.94 ng/mL	

DISCUSSION

A variety of markers are used for HCC and among the said markers is serum alpha-fetoprotein (AFP), which is used widely and with great effect. However, it is noted that serum AFP levels are oftentimes increased among patients with ailments of the liver other than HCC. The same conditions may also infect patients concurrently with HCV in up to 42% of the cases, putting the specificity of AFP (with regards to HCV) into doubt [15]. In this research, an 85% of the sample population had a raised AFP level. Research suggests that the hiked levels of AFP result from hepatocyte destruction (due to viral hepatitis) and consequent attempts of regeneration [16]. Recently, more alternatives have surfaced that outperform AFP in terms of specificity for HCC, [17] such as the "Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3%)" [12] and "des-c-carboxy prothrombin (DCP)" [18]. The Access-2 machine used in this research does not measure the said markers were not made a part of this research. It is noteworthy that AFP is more suited (as a diagnostic marker) to HBV, than HCV. Literature suggests that diagnostic accuracy deteriorates in cumulative samples when the proportion of HCV patients is higher than the proportion of HBV patients in the sample set [19]. Another marker that this research focused upon was CA125. Research suggests a significant correlation between CA125 and infection with hepatitis (P=0.01). CA125 is sensitive to benign and neoplastic pathologies of the liver despite not being a tissue or tumor specific antigen. However, CA125 levels are less specific to malignancy owing to the fact that the levels may increase in patients without malignant transformation. Additionally, CA125 level elevation is independent of etiology [20-22]. No significant relationship was noted between CEA levels and hepatitis which is synonymous with the existing literature [23,24]. It may thus be safe to state that patients with hepatitis may have elevated levels of CEA in the absence of a tumor / cancer. However, CEA levels may rather be more efficacious for purposes pertaining to management of the disease condition [25]. This study did have a few limitations. Firstly, it was a single center study and although the setting played host to a diverse demographic cohort, it is still a possibility that the results may not be truly generalizable to the general population. Nonetheless, care was exercised in extrapolating the study findings to other populations.

CONCLUSIONS

After careful consideration and a thorough evaluation CA125 and AFP were the prominent tumor markers detected among patients with hepatitis C. Keeping in view the co-occurrence of the said markers with hepatic carcinoma, it is advised that hepatitis C patients with CA125 and AFP levels above normal may be treated as high-risk patients.

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