Tissue Polypeptide Specific Antigen as a Marker used to Determine the Liver Diseases

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ABSTRACT

Background

Tissue polypeptide specific antigen and its specific M3 epitope are increased in malignant as well as in some benign diseases. The level of tissue polypeptide specific antigen in serum is related mostly to proliferation capacity rather than tumor mass and cell necrosis.

Objective

The aim of this study was to evaluate the levels of tissue polypeptide specific antigen and other tumor markers in patients with liver cirrhosis, chronic active hepatitis and hepatoma to determine if tissue polypeptide specific antigen is important to other tumor markers in hepatoma patients.

Methods

Ninty-seven patients and 30 controls were included in the study. The patients were divided into three subgroups as cirrhosis, hepatoma and chronic active hepatitis. The levels of tissue polypeptide specific antigen, carcinoembryonic antigen, CA19.9, alpha-fetoprotein and transaminases were determined in all patients.

Results

Tissue polypeptide specific antigen levels were significantly higher in all patients than in the control group ($p<0.005$) According to Kruskal-Wallis test with regard to subgroups, the differences in mean values of tissue polypeptide specific antigen and alpha-fetoprotein were significant ($p<0.0001$ for both). There was a low correlation between tissue polypeptide specific antigen and alpha-fetoprotein in the cirrhotic and hepatoma groups, but these were significantly correlated in the chronic active hepatitis group. The correlation coefficient between tissue polypeptide specific antigen and transaminases in all patients was low.

Conclusions

Tissue polypeptide specific antigen is efficient for determining primary hepatoma patients and also that this marker is specific for proliferation of cells.

KEY WORDS

liver diseases, marker, tissue polypeptide specific antigen

INTRODUCTION

Tissue polypeptide antigen (TPA) is a heterogeneous combination of molecules of molecular weight between 20-45 kDa. It was first defined as a tumor associated antigen in 1957 by Bjorklund. Immunologically TPA is defined as an aggregate of nonepidermal cytokines 8, 18, 19.[1,2] Tissue polypeptite Specific Antigen (TPS) was characterized by the development of a monoclonal antibody against subgroups of TPA. Further studies have proved the similarity between M3 epitope of TPA and the second part of cytokine 18.[1]

TPA is most frequently elevated in malignant tissues (gynecological, prostate, GIS, lung, etc). Serum TPA levels not only reflect tumor mass but also tumor activity[1,4,5.8] and are related with proliferation more than necrosis. Furthermore, elevated TPA levels can also be detected in some benign events such as liver failure, renal failure, gestation, generalized infection, and diabetes mellitus (DM).[9]

In this study, we measured the levels of TPS and other Gastrointestinal stromal tumor markers in chronic active hepatitis (CAH), liver cirrhosis (S) and hepatoma (HCC) patients. Our aim was to evaluate the possible high levels of TPS in non neoplastic liver diseases and HCC to determine if it is superior to other tumor markers in the HCC subgroup.

METHODS

This was a retrosecptive case control study for which the sample was purposively selected as per availability. This study consisted of 97 patients (66 male; 31 female) and 30 healthy controls. The study was conducted during the period of December 2009 to July 2010 from several hospitals. Mean age of the patients was 50.70 +/- 13.35 years (range 15- 71 years). Fifty-one were group S, 27 group HCC and 19 group CAH. Among all patient groups, the etiologic agent was hepatitis B virus in 58 cases, hepatitis C virus in 21 cases and alcohol in 12 cases. In six cases no etiologic agent was found and and these were classified as cryptogenic. The patients with extrahepatic cancer were excluded from the study.

For the diagnosis of the diseases, clinical findings, biochemical values and histological evaluation were used. Fasting blood samples (5cc) were collected and centrifuged then stored at -20°C until studied. Serum TPA in patients and in healthy controls was determined by a noncompetetive sandwich immunoassay method by means of immulite DPC kit. For this kit the lowest standard was 6 U/L and the highest standard was 2400 U/L. The results were given in U/L (unit/liter). Furthermore, the serum levels of other tumor markers such as Alpha Fetoprotein, Cancer Antigen 19.9, and Carcinoembryonic Antigen were measured and compared with serum levels of TPA. Statistical Package of Social Science version 10.0 for windows was used. Correlation analysis test and Kruskal Wallis test were used for this purpose.

RESULTS

The mean values of TPA for all patient subgroups are reported in Table 1.

Table 1. Mean values of tissue polypeptide specific antigen (TPS)

TPS	No	Mean Value (U/L)	SD
Cirrhosis	51	243.26	152.34
CAH	29	397.71	340.30
HCC	17	2592.57	2220.69
Total	97	725.30	1304.18
Control	30	49.05	30.76

The TPS levels were highest in the HCC group. Compared with the controls, TPS levels were significantly higher in all subgroups of patients ($p< 0.005$).

The mean values of AFP, CA19.9 and CEA in patient subgroups are given in Table 2.

Table 2. Mean values of AFP, CEA, CA19-9

AFP			
	No	Mean value	SD
Cirrhosis	51	6.16	11.38
CAH	29	9.0	4.66
HCC	17	281.57	48.45
CEA			
	No	Mean value	SD
Cirrhosis	51	2.95	2.22
CAH	29	1.85	1.32
HCC	17	11.82	17.04
CA19-9			
	No	Mean value	SD
Cirrhosis	51	20.35	27.01
CAH	29	28.75	27.88
HCC	17	46.87	57.79

Since the variables were not homogeneous, the Kruskal Wallis test was used in lieu of the Levene test. According to Kruskal Wallis test with regard to subgroups, the differences in mean values of CEA and CA 19.9 were insignificant (p: 0.136, x^2: 3.985; p: 0.433, x^2: 1.676, respectively). However, the differences in mean values of AFP and TPS were significant (p: 0.0001, x^2: 16.910; p: 0.0001, x^2: 17.028, respectively).

There was a low correlation between TPA and AFP in the cirrhosis and HCC groups, but this association was highly correlated in CAH patients (Table 3).

Table 3. Pearson correlation between TPS and AFP in liver diseases.

	TPS/AFP
Cirrhosis	0.198
CAH	0.931
HCC	0.042

Mean values of serum transaminases in the patients and controls are shown in Table 4.

Table 4. Serum Transaminase levels.

ALT	No	Mean values	SD
Cirrhosis	51	38.2	32.8
CAH	29	248	274
HCC	17	69.57	50.97
Control	30	21.80	7.8
AST	**No**	**Mean values**	**SD**
Cirrhosis	51	57.7	49.7
CAH	29	179.7	229.7
HCC	17	167.14	48.42
Control	30	28.40	6.5

A striking increase in serum transaminases, similar to that seen in TPA levels, was noted in HCC patients. There was a low correlation coefficient between serum TPA and transaminase levels in all patient subgroups (Table 5).

Table 5. Correlation coefficient between TPS and transaminases.

ALT/TPS	P:0.296
AST/TPS	P: 0.093

DISCUSSION

In recent years some studies have been performed to evaluate the relationship between liver diseases and serum TPS levels.[10,12-14] In one study, the value of AFP, ferritin and TPA in diagnosing primary HCC in liver cirrhosis patients was evaluated and it was reported that AFP is a more accurate marker for HCC in cirrhotic patients compared with ferritin and TPA.[13]

In another study in which the levels of CEA, TPA and CA 19.9 in liver diseases were compared, all three markers were found to be sensitive in liver diseases, but the increase rates varied. The increase in TPA was highest, whereas it was lowest for CEA. CEA is said to be more sensitive for colorectal cancers. It was also suggested in this study that there was a significant relation between high TPA and high AST-ALT levels.[12]

Leandro et al. studied serum TPA levels for recognizing HCC in cirrhotic patients and suggested that there was a different pattern in HCC patients.[14] In addition, there is also some studies that show the correlation between TPA and transaminase levels, as markers of hepatocyte lysis.[13,14,15] Lai and colleagues studied cytokine expression in healthy cases and patients with liver diseases and HCC and suggested that the cytokines found in the liver are valuable for understanding the cellular origin of neoplasms and the pathogenesis of liver diseases.[16] Moraglio et al. evaluated the levels of TPS in 49 patients with cirrhosis, CAH and acute hepatitis and found high levels of TPA in 10 of 11 cirrhotic patients (90.9%).[10] Of these, two were HCC and they had the highest levels. In the CAH group this ratio was 32.1%. The levels of TPA in the acute hepatitis group was higher than in CAH patients.

Tumor markers in particular CA 19.9 and Alpha-fetoprotein (AFP), have aided detection of pancreatic and hepatocellular carcinoma, respectively. In addition to the association of the CA 19.9 epitope with pancreatic neoplasia, this marker has also been found in the sera of patients with tumors arising at a variety of sites. The antigen has been found in 40 to 80% of carcinomas from gall bladder, stomach, pancreas and colon.[3] Other studies demonstrate that CA 19.9 may be helpful in diagnosing pulmonary sequestration and in urothelial cancer, especially in low-grade cancer because its urinary level is high and it is more sensitive than urinary cytology.[17]

Contrary to the results of other studies, a very low correlation was determined between TPS and transaminases; the correlation test between AFP and TPA was also insignificant. In the present study, we investigated the levels of TPA and other tumor markers in CAH, cirrhotic and HCC patients and a control group. We found higher values in the HCC group than in CAH. The highest values were obtained in primary HCC group, probably due to the production of TPA mostly from malignant epithelial tissues. AFP was significantly high in the HCC group but no correlation was obtained. This may be due to the low number of cases. As a result, it was shown that TPA levels increase in liver diseases and can be used as a marker for diagnosing HCC. The insignificant correlation between TPA and transaminases may suggest indirectly that TPA is specific for cell proliferation. This finding is supported by the highest levels of TPS in HCC patients in whom hepatic proliferation is most prominent.

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