Turk J Gastroenterol 2003; 14 (3): 177-180

The use of tissue polypeptide specific antigen as a marker in liver diseases

Doku polipeptid spesifik antijeninin karaciğer hastalıklarında bir marker olarak rolü

Türkan ÇETİN, Arzu OĞUZ, Pelin ALGAN, İ. Safa YILDIRIM

SSK Ankara Education Hospital, 3. Internal Medicine Clinic, Ankara

Background/aims: *Tissue polypeptide specific antigen was first defined by Bjorklund in 1957 and is the specific M3 epitope of tissue polypeptide antigen. It is increased in malignant as well as in some benign diseases. The level of tissue polypeptide specific antigen in serum is related mostly with proliferation capacity rather than with tumor mass and cell necrosis. 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 superior to other tumor markers in hepatoma patients.* ***Methods:*** *Thirty-seven patients and 20 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 highly 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:*** *Our data suggest that tissue polypeptide specific antigen is efficient in determining primary hepatoma patients and also that this marker is specific for proliferation of cells.*

Key words: Tissue polypeptide specific antigen, liver, cirrhosis, hepatitis, hepatocellular carcinoma, diagnosis, tumor marker

Amaç: Doku polipeptid spesifik antijen ilk kez 1957'de Bjorklund tarafından tanımlanmıştır.Doku polipeptid antijeninin spesifik M3 epitopudur.Sadece malign hastalıklarda değil bazı benign olaylarda da yükselir. Doku polipeptid spesifik antijeninin serum düzeyi, tümör kitlesi ve nekrozdan çok proliferasyon kapasitesi ile ilişkilidir. Bu çalışmanın amacı, karaciğer sirozlu, kronik aktif hepatitli ve hepatomah hastalarda doku polipeptid spesifik antijen ve diğer tümör markerlarının düzeylerini belirlemek ve hepatomah hastaları belirlemede doku polipeptid spesifik antijeninin diğer tümör markerlarına üstün olup olmadığını belirlemektir. Yöntem: Çalışmaya 37 hasta ve 20 sağlıklı kontrol dahil edildi. Hastalar 3 altgruba ayrıldı.siroz, hepatoma, kronik aktif hepatit. Bütün hastalarda doku polipeptid spesifik antijenin, karsinoembriyonik antijenin, CA19-9'un, alpha-fetoproteinin ve transaminazların düzeyleri ölçüldü. ***Bulgular:*** *Bütün hasta grubunda doku polipeptid spesifik antijen değerleri kontrol grubuna göre anlamlı olarak yüksekti ($p<0.005$). Kruskal walis testine göre gruplar arasında dokupolipeptid spesifik antijeninin ve alpha-fetoproteininin ortalama değerleri arasındaki farklar anlamlı idi ($p<0.0001$). Tanılara göre doku polipeptid spesifik antijeni ve alpha-fetoproteinin arasında sirozlu ve hepatomah hastalarda zayıf korelasyon mevcutken kronik aktif hepatitli hastalarda yüksek korelasyon saptandı. Bütün hastalarda doku polipeptid spesifik antijen ve transaminazlar arasında düşük korelasyon mevcuttu.* ***Sonuçlar:*** *Bulgularımız doku polipeptid spesifik antijenin primer hepatomah hastaların tespitinde yararlı olabileceğini ve bu markerın hücre proliferasyonu için spesifik olduğunu ortaya koymuştur.*

Anahtar kelimeler: Doku polipeptid spesifik antijen, karaciğer siroz, hepatit, hepatoselular kanser, tanı, tümör işaretleyici

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). 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).

TPS is the specific M3 epitope of TPA and also known as cytokine 18. It has been used as a prognostic parameter for some neoplasms since it was isolated in the serum or urine of some cancer patients (3).

Address for correspondence: Uzm. Dr. Türkan ÇETİN
SSK Ankara Eğitim Hastanesi 3. Dahiliye Kliniği, Ankara Turkey

Manuscript received: 3.4.2003 **Accepted:** 15.7.2003

TPS is most frequently elevated in malignant tissues (gynecologic, prostate, GIS, lung, etc). Serum TPS levels not only reflect tumor mass but also tumor activity (1, 4, 5-8) and are related with proliferation more than necrosis. Furthermore, elevated TPS 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 GIS 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. In this regard, liver diseases seem to be an interesting field of application, since they consist of different combinations of two phenomena, necrosis and regeneration.

MATERIALS AND METHODS

This study consisted of 37 patients (26 male, 70.3%; 11 female, 29.7%) who admitted to our clinic between March 2001 and February 2002 and 20 healthy controls. Mean age of the patients was 50.70 +/- 13.35 years (range 15- 71 years). Twenty-one were group S, 7 group HCC and 9 group CAH. Among all patient groups, the etiologic agent was hepatitis B virus in 24 cases (64%), hepatitis C virus in 6 cases (16.2%) and alcohol in 2 cases (5.4%). In five cases no etiologic agent was found and and these were classified as cryptogenic (13.5%). The patients with extrahepatic cancer were excluded from the study.

For the diagnosis of the diseases, clinical findings, biochemical values, ultrasonography and histological evaluation were used. Fasting blood samples (5cc) were collected and centrifuged. They were stored at -20°C until studied. Serum TPS 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 AFP, CA 19-9, and CEA were measured and compared with serum levels of TPS. Correlation analysis test and Kruskal Wallis test were used for this purpose.

RESULTS

The mean values of TPS for all patient subgroups are reported in (Table 1).

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

TPS	No	Mean Values (U/L)	SD
Cirrhosis	21	243.26	152.34
CAH	9	397.71	340.30
HCC	7	2592.57	2220.69
Total	37	725.30	1304.18
Control	20	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 values**	SD
Cirrhosis	21	6.161	11.388
CAH	9	9.0	4.667
HCC	7	281.571	48.457
CEA			
	No	**Mean values**	SD
Cirrhosis	21	2.953	2.222
CAH	9	1.856	1.322
HCC	7	11.826	17.046
CA19-9			
	No	**Mean values**	SD
Cirrhosis	21	20.357	27.012
CAH	9	28.756	27.884
HCC	7	46.871	57.796

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, x2: 3.985; p: 0.433, x2: 1.676, respectively). However, the differences in mean values of AFP and TPS were significant (p: 0.0001, x2: 16.910; p: 0.0001, x2: 17.028, respectively).

There was a low correlation between TPS and AFP in the cirrhosis and HCC groups, but this as-

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

	TPS/AFP
Cirrhosis	0.198
CAH	0.931
HCC	0.042

sociation was highly correlated in CAH patients (Table 3).

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	21	38.2	32.8
CAH	9	248	274
HCC	7	69.57	50.97
Control	20	21.80	7.8
AST	**No**	**Mean values**	**SD**
Cirrhosis	21	57.7	49.7
CAH	9	179.7	229.7
HCC	7	167.14	48.42
Control	20	28.40	6.5

A striking increase in serum transaminases, similar to that seen in TPS levels, was noted in HCC patients. There was a low correlation coefficient between serum TPS 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 relation 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 TPS 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 TPS and high AST-ALT levels (12). Leandro et al. (14) studied serum TPA levels for recognizing HCC in cirrhotic patients and suggested that there was a different pattern in HCC patients. In addition, there are also some studies that show the correlation between TPS and transaminase levels, as markers of hepatocyte lysis (13, 14, 15).

Lai and colleagues (16) 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. Moraglio et al. (10) evaluated the levels of TPS in 49 patients with cirrhosis, CAH and acute hepatitis and found high levels of TPS in 10 of 11 cirrhotic patients (90.9%). Of these, two were HCC and they had the highest levels. In the CAH group this ratio was 32.1%. The levels of TPS in the acute hepatitis group was higher than in CAH patients. Contrary to the results of other studies, a very low correlation was determined between TPS and transaminases; the correlation test between AFP and TPS was also insignificant. In this study, we investigated the levels of TPS 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 TPS 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 TPS levels increase in liver diseases and can be used as a marker for diagnosing HCC. The insignificant correlation between TPS and transaminases may suggest indirectly that TPS 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.

REFERENCES

1. Rylander, Ziegler E, Bergman T. Molecular characterization of a tissue polypeptide specific antigen epitope and its relationship to human cytokeratin 18. Eur J Biochem 1996; 241: 309-14.
2. Burt AD, Stewart JA, Aitchison M. Expression of tissue polypeptide antigen (TPA) in fetal and adult liver: changes in liver diseases. J Clin Pathol 1987; 40: 719-24.

Bjorklund B. Tissue polypeptide antigen (TPA): biology biochemistry, improved assay methodology, clinical significance in cancer and other conditions and future outlook. In: Laboratory Testing for Cancer, Antibiotics, Chemotherapy. Schonfeld H, ed. Basel: Karger; 1978: 2: 16-31.

Oellerich , Burdelski M, Lautz B. Predictors of one year pretransplant survival in patients with cirrhosis. Hepatology 1991; 14: 1029-34.

5. Shabana A, Onsrud M. Tissue polypeptide specific antigen and CA 125 as serum tumor markers in ovarian carcinoma. Tumor Biol 1994; 15: 361-7.
6. Conejo JR, Benedito JE, Jimenez A. Diagnostic value of three tumor markers determined in pleural effusions. Eur J Clin Chem Clin Biochem 1996; 34: 139-42.
7. Tarle M. Serial measurements of tissue polypeptide specific antigen (TPS), PSA, PAP and CEA serotest values in treated patients with primary and metastatic prostatic cancer. Anticancer Res 1993; 13: 769-78.
8. Glimelius B, Hoffmann K, Einarsson R. Monitoring palliative chemotherapy in advanced gastrointestinal cancer using serial tissue polypeptide specific antigen (TPS) measurements. Acta Oncol 1996; 35: 141-8.
9. Tramonti G, Ferdeghini M, Donadio C. Renal function and serum concentration of five tumor markers (TATI, SCC, CYFRA21-1,TPA, TPS) in patients without evidence of neoplasia. Cancer Detect Prev 2000; 24: 86-90.
10. Moraglio D, Pagano M, Galeazzi D, et al. Tissue polypeptide specific antigen (TPS) in liver disease. Clin Chim Acta 1994; 224: 209-14.
11. Akbay A, Bozbaş A, İşgör Y. Serum dipeptidylpeptidase activity and tissue polypeptide specific antigen in patients with advanced cirrhosis: preliminary results. Clin Chim Acta 2000; 292: 181-5.
12. Putzki H, Ledwoch J, Student A, et al. Tumor markers, carcinoembryonic antigen, tissue polypeptide antigen and carbonhydrate antigen 19-9 in liver diseases. J Surg Oncol 1998; 37: 133-5.
13. Leandro G , Basso D, Fabris C, et al. Alpha-fetoprotein, tissue polypeptide antigen and ferritin in diagnosing primary hepatocellular carcinoma in patients with liver cirrhosis. J Cancer Res Clin Oncol 1989; 115: 276-8.
14. Leandro G, Zizzari S, Piccoli A, Manghisi OG. The serum polypeptide antigen in the detection of hepatocellular carcinoma in cirrhotic patients. Hepatogastroenterology 1990; 37: 449-51.
15. Collazos J, Genolla J, Ruibal A. Tissue polypeptide antigen (TPA) in chronic active hepatitis and mild liver diseases. Int J Biol Markers 1992; 7: 249-52.
16. Lai YS, Thung SN , Gerber MA. Expression of cytokeratins in normal and diseased livers and in primary liver carcinomas. Arch Pathol Lab Med 1989; 113: 134-8.