

# Elevation of CA 125 and CA 19-9 in patients with end-stage liver disease

Ashish Singhal<sup>1</sup>, Elaine Lander<sup>1</sup>, Andreas Karachristos<sup>1</sup>, Ellen Daly<sup>1</sup>, Phyllis Dowling<sup>1</sup>, Vishal Patel<sup>2</sup>, Manoj Maloo<sup>1</sup>, Ashokkumar Jain<sup>1</sup>

<sup>1</sup>Division of Abdominal Organ Transplantation, Department of Surgery, Temple University Hospital, Philadelphia, PA - USA

<sup>2</sup>Division of Hepatology, Department of Medicine, Temple University Hospital, Philadelphia, PA - USA

## ABSTRACT

**Background:** The serum tumor markers CA 19-9 and CA 125 are the serologic markers used for the monitoring of biliopancreatic and ovarian cancer, respectively. They are reported to be elevated in a variety of nonneoplastic clinical situations, including end-stage liver disease (ESLD). However, their prevalence and degree of elevation in patients with ESLD remained unclear.

**Aim:** To examine the prevalence and degree of elevation of CA 19-9 and CA 125 in patients with ESLD and to determine their association with severity of liver disease.

**Methods:** Retrospective analysis of 161 patients with ESLD that were evaluated for liver transplantation at our institution between March 2009 and December 2010. The mean age was  $55.15 \pm 8.75$  years and 107 (66.4%) of the patients were men. Serum CA 19-9 and CA 125 levels were determined during evaluation of their candidacy for liver transplantation.

**Results:** Eighty-three (51.5%) patients had elevated CA 125 and 44 (53%) of them had a serum concentration >5 times the upper limit of normal (ULN). Elevated CA 125 was associated with alcoholic liver disease, high Model for End-Stage Liver Disease (MELD) score, and presence of ascites. Similarly, 37 (23%) patients had elevated CA 19-9 and 8 (21.6%) of them had a serum concentration >5 times ULN. Elevation of CA 19-9 was associated with high MELD score.

**Conclusions:** CA 125 and CA 19-9 concentrations were elevated in 51.5% and 23% of patients with ESLD, respectively. Although the definite etiology remained unclear, their elevation was associated with the pathological conditions associated with advanced liver disease. Further studies are needed to clarify the underlying mechanism(s) responsible for their increased levels.

**Key words:** Liver, Tumor, Markers, CA 125, CA 19-9, MELD

Received: May 20, 2011; Accepted: August 30, 2011

## INTRODUCTION

Serum tumor markers are widely used for the screening and follow-up of various malignancies. However, these markers are elevated in a variety of nonneoplastic diseases including end-stage liver disease (ESLD), thus decreasing their usefulness in patients affected by these diseases (1, 2). Moreover, the causes for their association with liver diseases vary.

Cancer antigen 125 (CA 125) is a high-molecular-weight glycoprotein produced by epithelial ovarian tumor and mesothelial cells (3). It has been used in monitoring the course of epithelial ovarian cancer (4, 5). However, the CA 125 levels were found to be increased in patients with chronic liver disease (6-9). Similarly, CA 19-9, a glycoprotein with structural homology to Lewis blood group antigen, is a marker for biliopancreatic malignancy (10, 11). Elevation of CA 19-9 has been described in

nonmalignant chronic pulmonary diseases (12) and ESLD (13, 14). However, the exact prevalence and degree of elevation of these markers have not been studied in patients with chronic liver disease.

The aims of this study were 1) to examine the prevalence and degree of increase in serum levels of non-liver-specific tumor markers (CA 19-9 and CA 125) in patients with ESLD, and 2) to determine the correlation between their degree of elevation, etiology, and severity of liver disease.

## MATERIALS AND METHODS

This is a retrospective study involving 161 patients with ESLD who underwent an evaluation for liver transplantation between March 2009 and December 2010 at our institution. The institutional review board approved the study.

We measured the serum levels of CA 19-9 and CA 125 in all patients at the time of their evaluation for liver transplantation. The CA 19-9 and CA 125 assays were performed by a 2-step immunoenzymatic method based on the "sandwich" principle using the Access Immunoassay Systems (Beckman Coulter Inc., CA, USA). The normal ranges for CA 125 and CA 19-9 at our laboratory were 0-35 IU/mL and 0-60 IU/mL, respectively.

We also examined the following data: patients' age and sex, etiology of cirrhosis, variables of the Model for End-Stage Liver Disease (MELD) score (serum bilirubin, prothrombin time, and serum creatinine), and serum alpha fetoprotein levels. All patients underwent contrast-enhanced computed tomography (CECT)/magnetic resonance imaging (MRI) of the abdomen and pelvis to screen for malignancy. None of the patients had any radiological evidence of biliopancreatic or ovarian malignancy.

### Statistical analyses

The results were expressed as mean ± standard deviation (SD) unless otherwise specified. Comparisons were made using the chi-square test for categorical variables. The unpaired t-test was used to compare the means. SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA) statistical software was used for analysis and differences were considered significant when  $p < 0.05$ .

## RESULTS

The baseline characteristics of the patients are given in Table I. The mean age was  $55.1 \pm 8.7$  years (median: 55, range: 22-77) and 107 (66.4%) patients were male. Chronic hepatitis C virus (HCV) infection was the commonest cause of ESLD involving 96 (59.6%) patients, followed by alcohol-related cirrhosis in 32 (19.9%) patients. Hepatocellular carcinoma (HCC) was detected in 45 (28%) patients at the time of evaluation. The mean MELD score was  $15.2 \pm 8.5$  (median: 13; range: 6-40). Sixty-eight (42.2%) patients had a history of smoking. Twenty-seven (16.8%) patients from the present cohort underwent liver transplant during the study period and no biliopancreatic or ovarian malignancies were detected at the time of transplant.

### CA 125

The CA 125 level was increased in 83 (51.5%) patients, 55 (66.3%) of whom were males. The mean serum level was  $182.7 \pm 306.6$  IU/mL (median: 41; range: 5-1887). Forty-four (27.3%) patients had serum levels 5 times above the upper limit of normal (ULN) levels ( $>175$  IU/mL). Elevation of the CA 125 level was correlated with the

severity of liver disease (MELD score) and the presence of ascites. The mean serum level of CA 125 in patients with MELD scores  $\leq 15$  and  $>15$  were  $125.3 \pm 221.5$  IU/mL and  $272.5 \pm 400.7$  IU/mL, respectively ( $p < 0.05$ ) (Tab. II). Similarly, the mean serum levels in patients with and without ascites were  $218.3 \pm 293.9$  IU/mL and  $104.7 \pm 308.6$  IU/mL, respectively ( $p < 0.05$ ). Elevated CA 125 was also related to alcohol-related liver disease. The mean serum levels in patients with alcohol-related liver disease vs non-alcoholic liver disease were  $347.2 \pm 390.2$  IU/mL and  $134.1 \pm 262.8$  IU/mL, respectively ( $p < 0.05$ ).

### CA 19-9

Elevated CA 19-9 levels were detected in 37 (23%) patients, 26 (70.3%) of whom were males. The mean serum level was  $83.2 \pm 194.4$  IU/mL (median: 34; range: 1-1490). Eight (5%) patients had serum levels 5 times above ULN levels ( $>300$  IU/mL). Elevated CA 19-9 levels were significantly higher in patients with severe liver disease (MELD score). The mean serum levels in patients with MELD scores  $\leq 15$  and  $>15$  were  $46.4 \pm 63.5$  IU/mL and  $140.5 \pm 303.1$  IU/mL, respectively ( $p < 0.05$ ) (Tab. III).

## DISCUSSION

It is interesting to report our experience of elevated CA 125 and CA 19-9 in patients with chronic liver disease but without any extrahepatic malignant disease, or any other chronic diseases that may explain their elevated serum levels. Our findings indicate that CA 125 was more

TABLE I - BASELINE PATIENT CHARACTERISTICS

Patient characteristics	n (%)
Age (years)	$55.1 \pm 8.7$
Males	107 (66.4)
Smoking	68 (42.2)
Etiology of liver disease	
HCV	96 (59.6)
EtOH	32 (19.9)
Others	33 (20.5)
Presence of HCC	45 (28)
Presence of ascites	99 (61.5)
MELD score	$15.2 \pm 8.5$
CA 125 (IU/mL)	$182.7 \pm 306.6$
CA 19-9 (IU/mL)	$83.2 \pm 194.4$

Age, MELD score, CA 125, and CA 19-9 are presented as mean ± SD. HCV, hepatitis C virus; EtOH, ethanol; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease

commonly altered in patients with liver disease compared with CA 19-9 (51.5% vs 23%).

CA 125 is a high-molecular-weight glycoprotein produced by epithelial ovarian tumors and by mesothelial cells and is used in monitoring the course of epithelial ovarian cancer (3-5). Interestingly, 66.3% of our patients with elevated CA 125 were males. In concordance with observations of earlier studies, our findings indicate that the elevation of serum CA 125 concentration was associated with severe liver disease as measured by the MELD score, alcohol-related cirrhosis, and ascites (15-17). Bergmann et al (15) studied 47 patients with ovarian cancer, 21 with hepatoma, and 40 with cirrhosis; they found elevated CA 125 levels in all 3 groups but particularly in those with ascites. Several other studies found a correlation between the CA 125 level and the severity of liver disease and the presence of ascites (16, 17). It is known that the coelomic

epithelium of the embryo and its derivatives, such as the mesothelial lining of the peritoneal cavity, can secrete CA 125. The mechanical stress associated with abdominal distension stimulates CA 125 secretion through mesothelial cell proliferation (6). In a study by Deschênes et al (17) it was found on immunohistological staining that peritoneal mesothelial cells secrete CA 125. These findings suggest that the stimulus for secretion of CA 125 is abdominal distension rather than a particular attribute of ascites per se. This idea is supported by reports of increased CA 125 secretion associated with other instances of mesothelial cell proliferation, such as mesothelioma (18, 19). Moreover, serum CA 125 levels were elevated to a greater extent in patients with peritoneal fluid than in those with pleural or pericardial fluid and this difference was attributed to the larger surface area of the peritoneum or to the amount of fluid in the peritoneum (3). On the other

**TABLE II - CA 125 SERUM LEVEL STRATIFICATION WITH PATIENT CHARACTERISTICS**

Patient characteristics	Serum concentration IU/mL		
	<35 n = 78	>35 n = 83	>175* n = 44
Age (mean ± SD)	55.4 ± 8.8	54.9 ± 8.7	52.5 ± 9.0
Males, n (%)	52 (66.6)	55 (66.2)	28 (63.6)
Smoking, n (%)	37 (47.4)	32 (38.5)	17 (38.6)
Etiology of liver disease, n (%)			
HCV	50 (64.1)	46 (55.4)	20 (45.5)
EtOH	9 (11.5)	23 (27.7)	15 (34.1)
Others	19 (24.4)	14 (16.9)	9 (20.5)
Presence of ascites, n (%)	31 (39.7)	68 (81.9)	36 (81.8)
MELD score (mean ± SD)	11.9 ± 5.4	18.3 ± 9.7	19.7 ± 10.2

\*Serum level 5 times above the upper limit of normal levels

HCV, hepatitis C virus; EtOH, ethanol; MELD, Model for End-Stage Liver Disease

**TABLE III - CA 19-9 SERUM LEVEL STRATIFICATION WITH PATIENT CHARACTERISTICS**

Patient characteristics	Serum concentration IU/mL		
	<60 n = 124	>60 n = 37	>300* n = 8
Age (mean ± SD)	56.0 ± 8.4	52.2 ± 9.1	58.4 ± 6.2
Males, n (%)	81 (65.3)	26 (70.3)	4 (50)
Smoking, n (%)	53 (42.7)	15 (40.5)	3 (37.5)
Etiology of liver disease, n (%)			
HCV	75 (60.5)	21 (56.8)	5 (62.5)
EtOH	25 (20.2)	7 (18.9)	1 (12.5)
Others	24 (19.3)	9 (24.3)	2 (25)
Presence of ascites, n (%)	74 (59.7)	25 (67.6)	2 (25)
MELD score (mean ± SD)	13.8 ± 6.7	19.9 ± 11.8	26.3 ± 10.6

\*Serum level 5 times above the upper limit of normal levels

HCV, hepatitis C virus; EtOH, ethanol; MELD, Model for End-Stage Liver Disease

hand, Sari et al (20) described high serum and ascitic CA 125 levels in patients with ascites owing to various etiologies but without a relationship with the amount of ascites. The presence of other factors was hypothesized including an antigen synthesized by both peritoneal cells and malignant ovarian cells or a cross-reaction between ovarian cancer antigen and an undefined ascitic protein (15). According to Collazos et al (7) CA 125 elevations could also be related to failure of the liver to metabolize the antigen. Perhaps, this may be the reason as several studies reported that CA 125 levels return to normal range after large volume paracentesis (16), peritoneovenous shunt (21), and liver transplantation (17).

The present study demonstrates an elevated serum levels of CA 19-9 in 23% of patients with ESLD. CA 19-9 is a marker for biliopancreatic malignancy; it can increase in patients affected with nonmalignant respiratory diseases including idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis, diffuse panbronchiolitis, bronchiectasis or collagen-disease-associated pulmonary fibrosis. The increase in serum CA 19-9 levels in these conditions reflects progression of chronic pulmonary disease to lung fibrosis, in the absence of malignancy (12, 14). Elevation of CA 19-9 in chronic pulmonary diseases may also be helpful in understanding the significant increase in serum CA 19-9 in patients with chronic liver disease. Normal biliary epithelial cells secrete mucins carrying the epitope of CA 19-9. In fact, immunohistochemical studies have demonstrated that CA 19-9 immunoreactivity is present in the cell membranes of biliary canaliculi and ductules in patients with chronic hepatitis and cirrhosis (22). Increased serum CA 19-9 may be secondary to necroinflammatory processes, small bile duct alterations, the presence of regenerative nodules, and collagen hyperproduction, all of which are typical features of progression of chronic hepatitis to cirrhosis. Thus, CA 19-9 serum levels increase in close correlation with the grade of liver inflammation and this can explain the correlations between CA 19-9 levels and advanced liver disease (23). Recently, Bertino et al (24) reported that the increase in CA 19-9 is significantly higher in patients with HCV infection, and thus related to the viral etiology.

Based on the most recent literature, we propose that this may be due to fibrogenic properties of HCV, but further research is needed to assess the specific role of HCV in CA 19-9 synthesis. Further investigations may clarify the potential role of CA 19-9 as an indirect marker of hepatic fibrosis, in addition to being a neoplastic marker.

## CONCLUSIONS

In the setting of ESLD, serum levels of CA 125 and CA 19-9 are frequently elevated. The increase in CA 125 and CA 19-9 in these patients is apparently not related to malignant disease, even in those with serum levels more than 5 times of ULN levels. Although the definite etiology remained unclear, the elevation of CA 125 and CA 19-9 in ESLD patients was associated with the pathological conditions associated with advanced liver disease. Further studies are needed to clarify the underlying mechanism(s) responsible for their increased levels.

**Financial Interest:** None.

**Conflict of Interest Statement:** None.

**Meeting Presentation:** This data was presented at the 17<sup>th</sup> Annual International Congress of the International Liver Transplantation Society, June 22-25, 2011, Valencia, Spain.

Address for correspondence:  
Ashokkumar Jain, MD, FACS  
Division of Abdominal Organ Transplantation,  
Department of Surgery  
Temple University Hospital  
3401 North Broad Street  
Parkinson Pavilion, 6<sup>th</sup> Floor, Suite C640  
Philadelphia, PA 19140, USA  
e-mail: ashokkumar.jain@tuhs.temple.edu

## REFERENCES

1. Sturgeon C. Practice guidelines for tumor marker use in the clinic. *Clin Chem* 2002; 48: 1151-9.
2. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006; 24: 5313-27.
3. Sevinc A, Camci C, Turk HM, Buyukberber S. How to interpret serum CA125 levels in patients with serosal involvement? A clinical dilemma. *Oncology* 2003; 65: 1-6.
4. Canney PA, Moore M, Wilkinson PM, James RD. Ovarian cancer antigen CA 125: a prospective clinical assessment of its role as a tumor marker. *Br J Cancer* 1984; 50: 765-9.
5. NIH Consensus Development Panel on Ovarian Cancer.

- Ovarian cancer: screening, treatment, and follow-up. *JAMA* 1995; 273: 491-7.
6. Molina R, Filella X, Bruix J, et al. Cancer antigen CA 125 in serum and ascitic fluid of patients with liver diseases. *Clin Chem* 1991; 37: 1379-83.
  7. Collazos J, Genolla J, Ruibal A. CA 125 serum levels in patients with non-neoplastic liver disease. A clinical and laboratory study. *Scand J Clin Lab Invest* 1992; 52: 201-6.
  8. Kadayifci A, Simsek H, Savas MC, Toppare M. Serum tumor markers in chronic liver disease. *Neoplasma* 1996; 43: 17-21.
  9. DiBaise JK, Donovan JP. Markedly elevated CA125 in hepatic cirrhosis: two case illustrations and review of the literature. *J Clin Gastroenterol* 1999; 28:159-61.
  10. Lamerz R. Role of tumour markers, cytogenetics. *Ann Oncol* 1999; 10 (Suppl 4): 145-9.
  11. Okusaka T, Yamada T, Maekawa M. Serum tumor markers for pancreatic cancer: the dawn of new era? *J Pancreas* 2006; 7: 332-6.
  12. Kodama T, Satoh H, Ishikawa H, et al. Serum levels of CA19-9 in patients with nonmalignant respiratory diseases. *J Clin Lab Anal* 2007; 21: 103-6.
  13. Mathurin P, Cadranet JF, Bouraya D, et al. Marked increase in serum CA 19-9 level in patients with alcoholic cirrhosis: report of four cases. *Eur J Gastroenterol Hepatol* 1996; 8: 1129-31.
  14. Ventrucchi M, Pozzato P, Cipolla A, et al. Persistent elevation of serum CA 19-9 with no evidence of malignant disease. *Dig Liver Dis* 2009; 41: 357-63.
  15. Bergmann JF, Bidart JM, George M, Beaugrand M, Levy VG, Bohuon C. Elevation of CA 125 in patients with benign and malignant ascites. *Cancer* 1987; 59: 213-7.
  16. Zuckerman E, Lanir A, Sabo E, et al. Cancer antigen 125: a sensitive marker of ascites in patients with liver cirrhosis. *Am J Gastroenterol* 1999; 94: 1613-8.
  17. Deschênes M, Michel RP, Alpert E, Barkun JS, Metrakos P, Tchervenkov J. Elevation of CA-125 level is due to abdominal distension in liver transplantation candidates. *Transplantation* 2001; 72: 1519-22.
  18. Almudevar Berbero E, Garcia-Rostan Perez GM, Garcia Bragado F, Jimenez C. Prognostic value of high serum levels of CA 125 in malignant secretory peritoneal mesotheliomas affecting young women. A case report with differential diagnosis and review of the literature. *Histopathology* 1997; 31: 267-73.
  19. Ordóñez NG. Role of immunohistochemistry in distinguishing epithelial peritoneal mesotheliomas from peritoneal and ovarian serous carcinomas. *Am J Surg Pathol* 1998; 22: 1203-14.
  20. Sari R, Yildirim B, Sevinc A, Hilmioglu F. Re. Zuckerman et al. Sensitivity of CA-125 in patients with liver cirrhosis in the presence of ascites. *Am J Gastroenterol* 2001; 96: 253-4.
  21. Leggio L, Abenavoli L, D'Angelo C, et al. Marked decrease of serum Ca 125 levels after Denver shunt placement in a patient with cirrhosis and refractory ascites. *Dig Dis Sci* 2006; 51: 1644-6.
  22. Kitagawa Y, Iwai M, Muramatsu A, et al. Immunohistochemical localization of CEA, CA19-9 and DU-PAN-2 in hepatitis C virus-infected liver tissues. *Histopathology* 2002; 40: 472-9.
  23. Schoniger-Ekele M, Muller C. The combined elevation of tumor markers CA 19-9 and CA 125 in liver disease patients is highly specific for severe liver fibrosis. *Dig Dis Sci* 2006; 51: 338-45.
  24. Bertino G, Ardiri AM, Calvagno GS, Boemi PM. In chronic viral hepatitis without malignancy, abnormal serum carbohydrate 19-9 antigen levels are associated with liver disease severity and are related to different viral aetiology. *Dig Liver Dis* 2010; 42: 458-9.

Copyright of International Journal of Biological Markers is the property of Wichtig Editore and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.