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Diagnostic Usefulness of Carbohydrate Antigen-125 in Cancerous and Noncancerous Peritoneal Effusions

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Kemer, T., Ormen, M., Kuralay, F., Pehlivan, M., Unsal, B. and Tankurt, E. *Diagnostic Usefulness of Carbohydrate Antigen-125 in Cancerous and Noncancerous Peritoneal Effusions*. Tohoku J. Exp. Med., 2005, **205** (1), 11-18 —— Carbohydrate antigen-125 (CA-125) is a tumor marker that has been used for differential diagnosis of peritoneal malignancies. The aim of the present study was to evaluate the diagnostic usefulness of simultaneous quantification of CA-125 in peritoneal fluid and serum for abdominal cancer cases and noncancer diseases. Noncancer disease group included cirrhotic patients (n = 28) and spontaneous bacterial peritonitis (SBP) patients (n = 11). Abdominal cancer group was composed of histologically diagnosed various malignancies (n = 10), such as gastric cancer. CA-125 levels were quantified by chemiluminescent enzyme immunoassay. Diagnostic usefulness tests and receiver operating characteristics (ROC) curve analysis were performed for the levels of peritoneal fluid CA-125 (pCA-125) and serum CA-125 (sCA-125), and the ratio of pCA-125 to sCA-125 (p/sCA-125). The sCA-125 levels were significantly higher in noncancer patients than those in the cancer patients, while the pCA-125 levels showed no significant difference between the two groups. Notably, the p/sCA-125 ratio was significantly lower in the noncancer patients than that in the cancer patients. Area under the ROC curve was 0.267 for sCA-125, 0.542 for pCA-125 and 0.831 for p/sCA-125. The accepted cutoff values were the combination of values that gave the greatest diagnostic sensitivity plus specificity. Either sCA-125 or pCA-125 value gave lower diagnostic accuracy, whereas p/sCA-125 value demonstrated a significantly higher diagnostic accuracy (sensitivity-specificity pairs: 0.40-0.33 for sCA-125, 0.60-0.54 for pCA-125, and 0.80-0.72 for p/sCA-125, respectively). Hence, determination of p/sCA-125 improves the biochemical discrimination of abdominal cancerous cases from noncancerous diseases. ———— carbohydrate antigen-125(CA-125); cirrhosis; spontaneous bacterial peritonitis; cancer; peritoneal effusion

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Peritoneal effusion presents a challenging diagnostic problem which remains unsolved even after clinical and laboratory evaluation. The differential diagnosis is diverse, but most common causes include abdominal cancers, cirrhosis and peritonitis. Studies on peritoneal fluid yield a definitive or presumptive diagnosis in about 95% of cases (Molina et al. 1991, 1998).

The availability of a rapid and formal proof of malignancy by using less invasive procedures is a constant goal in the diagnosis of cancer-originated effusions. In this respect, cytological examination is the most commonly used diagnostic procedure in the differential diagnosis of peritoneal effusions (PE), although the sensitivity of this method in malignancy compared with more invasive procedures is only about 60% (Molina et al. 1985).

Several studies have tried to increase the sensitivity of the cytological examination by using the determination of lactate dehydrogenase (LDH) and its isoenzymes, C-reactive protein (CRP), neutrophil count, total protein content, tumor associated antigens or expression of different cellular antigens (Jacobs and Bast 1989; Hoefs 1990; Chi et al. 1996). The evaluation of body fluids is more simple than the analysis of cellular parameters, especially tumor associated antigens, which are released by the tumour cells to the effused fluid, and could be of significance in the diagnostic differentiation of the cancerous from the noncancerous origin of effusions (Ricolleau et al. 1984; Mezger et al. 1998).

Despite the combination of the peritoneal fluid cytological studies and the peritoneal biopsy, the diagnosis could not be obtained in many cases. To increase the sensitivity of the peritoneal fluid study, several tumor markers have been analysed (Sarı 2001; Kiluk et al. 2002; Sedlaczek et al. 2002; Sehouli et al. 2003; Uenishi et al. 2003). Besides, the development of a peritoneal malignancy is frequently associated with high blood levels of tumor markers such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen-125 (CA-125), carbohydrate antigen-19.9 (CA-19.9), carbohydrate antigen-15.3 (CA-15.3) and ferritin. Among them, CA-125 is the most commonly studied and used, with an accuracy in peritoneal fluid greater than that of other tumor markers. However, in almost all series on CA-125 in peritoneal fluid, high false-positive results have been reported (Shen-Gunther and Mannel 2002; Miralles et al. 2003).

The aim of the present study was to determine the usefulness of simultaneous quantification of CA-125 in peritoneal fluid (pCA-125) and in serum (sCA-125) for differentiating cancer and noncancer cases. This study was designed and carried out to determine CA-125 in various cancers, including gastric, ovarian and colon cancers, non-Hodgkin lymphoma, and a neuroendocrine tumor, and to compare sCA-125, pCA-125 and the ratio of pCA-125 to sCA-125 (p/sCA-125) in these cases with those in noncancerous conditions, cirrhosis and spontaneous bacterial peritonitis (SBP).

Materials and Methods

Patients

This study was undertaken in the Clinics of Gastroenterology at Dokuz Eylul University Hospital and Ataturk State Hospital and Department of Biochemistry of Dokuz Eylul University, Medical Faculty. Peritoneal effusions of 49 patients were collected by simple needle aspiration or tube drainage. In all cases, a standard clinical protocol was followed and routine laboratory tests for each fluid were performed (total protein, albumin, glucose, LDH, cholesterol, triglyceride, neutrophil count, cytological examination). Portions of all samples were also sent to microbiology laboratory for cultures.

Noncancer group (n = 39) included cirrhotic patients with PE (n = 28) and SBP cases with PE (n = 11). Cancer group (n = 10) included histologically diagnosed abdominal malignancies: six gastric cancer, one ovarian cancer, one colon cancer, one non-Hodgkin lymphoma and one neuroendocrine tumor. Peritoneal effusion was present in all cases. Ages of the patients as mean ± S.D. were 53.75 ± 2.36 in cirrhosis, 59.18 ± 3.51 in SBP and 52.2 ± 5.08 in cancer group.

The etiology of cirrhosis in these patients was alcoholic liver disease (n = 11), viral hepatitis B or C (n = 11); primary biliary cirrhosis (PBS) (n = 1), Budd Chiari Syndrome (n = 2), and idiopathic cirrhosis (n = 3). The serum-peritoneal fluid albumin gradient was higher than

1.1 g/100 ml, confirming portal hypertension related PE and excluding etiologies such as malignancy or tuberculosis of cirrhotic patients.

Diagnosis of SBP was based on the following criteria: Peritoneal fluid polymorphonuclear (PMN) cell count > 250/mm^3 and a compatible clinical picture (abdominal pain and/or fever and/or unexplained encephalopathy). The etiology of 11 patients of SBP included alcoholic cirrhosis (n = 3), viral hepatitis B or C (n = 4), PBS (n = 1), and idiopathic SBP (n = 3). The possibility of secondary peritonitis was excluded in all patients.

At the time of paracentesis, none of the patients were on antibiotic prophylaxis and the following data were collected: age, gender, ethiology of cirrhosis, Child-Pugh score, history of SBP, and history of variceal hemorrhage. The severity of the liver disease in SBP and cirrhosis was characterized as Child-Pugh class C based on serum bilirubin, albumin, prothrombin time (PT), and on the degree of PE and encephalopathy (Pugh et al. 1973).

This study was approved by the Ethical Committee for Clinical Research of Dokuz Eylul University School of Medicine.

Laboratory tests

Peritoneal fluid obtained at paracentesis and simultaneously obtained blood samples were determined for white blood cell, PMN and lymphocyte count, LDH, alanine aminotransferase (ALT), aspartate aminotransferase (AST) activities, total protein, albumin, CRP, CA-125 concentrations. Peritoneal fluid samples were cultured. Blood samples were also analysed for total and direct bilirubin concentrations, alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) activities, erythrocyte sedimentation rate (ESR), fibrinogen, prothrombin time (PT), INR (International Normalized ratio for PT), activated partial tromboplastin time (APTT). Biochemical parameters were analysed using Roche Diagnostics kits on Hitachi 714 analyzer. Coagulation parameters were analysed by Amelung-Amax 190 plus. Peritoneal fluid cultures were performed using conventional culture methods (Agar, Eosin-Methylene Blue and Lowenstein Jensen media).

Peritoneal fluid samples were centrifuged at 2000 rpm for 10' to remove cellular components. Supernatants were stored at −70°C until the performance of the CA-125 assays. CA-125 levels were quantified by chemiluminescent enzyme immunoassay using Elecsys 2010 automated analyzer (Roche Diagnostics, Germany). The intra- and interassay coefficients of variations were 4.2% and 7.5%, respectively. The curve included standard values between 10 and 540 U/ml.

According to cutoff levels for sCA-125, pCA-125 and p/sCA-125, patients in each group were classified as true positive (TP), false positive (FP), true negative (TN), and false negative (FN). The term "positive" referred to histologically proven cancer while negative referred to noncancer conditions. Sensitivity (S) was defined as TP/(TP+FN), specificity (s) as TN/(TN+FP). Receiver-operating characterics (ROC) curves were obtained by plotting S vs 1−s for different possible cutoff values for sCA-125, pCA-125 and p/s CA125 levels.

Statistics

Comparisons of the groups were made by using Mann Whitney's U-test and Pearson correlation coefficient by SPSS 10.0 (SPSS Inc., Chicago, IL, USA). P values < 0.05 were considered as significant. To characterize the diagnostic accuracy for sCA-125, pCA-125 and p/sCA125, we calculated the S and s; then created the ROC curves of the parameters (Zweig and Camphell 1993). Computing for ROC analysis was also done by SPSS 10.0 program.

Results

Levels of sCA-125 and pC-125 in cancer and noncancer groups (mean ± S.E.M) are shown in Table 1. Both CA-125 values were highest in SBP group. sCA-125 levels in cirrhosis and SBP were significantly higher than those in the cancer group (p = 0.031 and p = 0.029, respectively). In contrast, there were no significant difference in the pCA-125 levels between the groups. On the other hand, p/sCA-125 levels in cancer group were significantly higher than those in noncancer groups, cirrhosis (p = 0.001) and SBP (p = 0.029). When we evaluated the correlation analysis between the parameters, there was a significant positive correlation between sCA-125 and pCA-125, and significant negative correlation between sCA-125 and p/sCA-125 (p = 0.000, r = 0.604; p = 0.011, r = –0.360, respectively).

Either sCA-125 or pCA-125 levels gave low accuracy, whereas p/sCA-125 demonstrated a significantly higher diagnostic accuracy. For sCA-125, when cutoff value was accepted as 281.5 U/ml, the sensitivity was 0.40 and the specificity was 0.33. For pCA-125 when cutoff value

TABLE 1. *CA 125 (U/ml) and CRP (mg/liter) levels in serum and peritoneal fluid in patients with cirrhosis, SBP and abdominal cancer*

Group	*n*	sCA-125	pCA-125	p/sCA-125	sCRP	pCRP
Cirrhosis	28	630.1 ± 382 [c]	634.5 ± 106.4	1.64 ± 0.31 [a]	72.28 ± 27.22	6.21 ± 0.8 [e]
SBP	11	888.1 ± 332 [d]	810.6 ± 169.3	2.65 ± 1.09 [b]	89.18 ± 30.93	4.91 ± 0.76 [f]
Cancer	10	273.8 ± 92.2	802.4 ± 210.6	5.42 ± 1.59	46.40 ± 16.66	43.9 ± 24.07

[a] $p = 0.001$; p/sCA-125 levels in cirrhosis are significantly higher than the cancer group.
[b] $p = 0.029$; p/sCA-125 levels in SBP are significantly higher than the cancer group.
[c] $p = 0.031$; sCA-125 levels in cirrhosis are significantly higher than the cancer group.
[d] $p = 0.029$; sCA-125 levels in SBP are significantly higher than the cancer group.
[e] $p = 0.028$; pCRP levels in cirrhosis are significantly lower than the cancer group.
[f] $p = 0.018$; pCRP levels in SBP are significantly lower than the cancer group.
Data are presented as mean ± S.E.M.

was accepted as 463 U/ml, the sensitivity was 0.60 and the specificity was 0.54. For p/sCA-125 when cutoff value was accepted as 1.94, the sensitivity was 0.80 and the specificity was 0.72.

The diagnostic accuracy evaluation, by ROC curve analysis is presented in Fig 1. Area under the curve was 0.267 for sCA-125, 0.542 for pCA-125 and 0.831 for p/sCA-125. When the areas of ROC curve were compared, significant differences were observed between sCA-125 and pCA-125 ($p < 0.005$) and between p/sCA-125 and sCA-125 ($p < 0.001$) or pCA-125 ($p < 0.0001$).

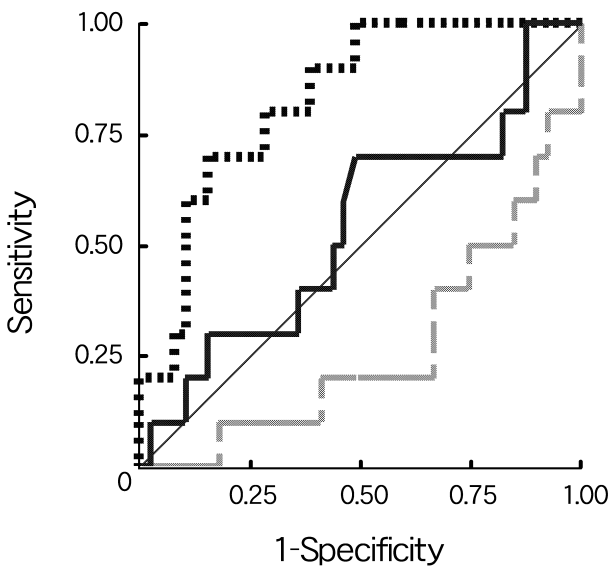

Fig. 1. ROC curves for pCA-125, sCA-125 and p/sCA-125. The curves are useful in discriminating abdominal cancer group from noncancer group.
——, Reference line; ▪▪▪▪, p/sCA-125; – – –, sCA-125; ▬▬, pCA-125.

Peritoneal fluid CRP (pCRP) but not serum CRP (sCRP) levels in cancer group were significantly higher than the noncancer group ($p = 0.028$ for cirrhosis; $p = 0.018$ for SBP) (Table 1). No difference was found in sCRP and pCRP levels between SBP and cirrhosis groups.

Of the conventional parameters used for evaluating the patients with PE, PT ($p = 0.022$), serum total protein ($p = 0.011$), serum total ($p = 0.008$) and direct bilirubin ($p = 0.023$) levels in malignancy group were significantly lower than both noncancer groups, while peritoneal fluid LDH levels were significantly elevated ($p = 0.005$) (Table 2).

DISCUSSION

Determination of tumor markers in serum and peritoneal fluid has been proposed as a nonaggressive way of discrimination of PE. CA-125 is a large glycoprotein of about 220 kDa. However, the specificity of sCA-125 is low, as its elevation has been reported in various noncancerous and cancerous diseases, such as endometriosis, pelvic inflammatory disease, ovarian hyperstimulation syndrome, and carcinomas of endometrium, pancreas, colorectum, breast, lung, and liver (Halila et al. 1986; Jager et al. 1987; Ozasa et al. 1987; Haglund et al. 1991; Haglund and Kuusela 1999; Krasnicki 2001). The source

TABLE 2. *Laboratory tests in serum (*), plasma (**) and peritoneal fluid (***) of cancer and noncancer groups*

	Noncancer Group		Cancer Group
	Cirrhosis $n = 28$	SBP $n = 11$	$n = 10$
ESR (mm/h)	50.17 ± 6.18	45.09 ± 10.30	36.5 ± 8.09
AST (IU/liter)*	57.57 ± 5.33	92.27 ± 19.47	57.2 ± 20.99
ALT (IU/liter)*	31.60 ± 3.58	50.72 ± 8.71	38.10 ± 11.56
GGT (IU/liter)*	102.1 ± 21.58	86.63 ± 27.19	159.30 ± 75.57
LDH (IU/liter)*	344.18 ± 32.87	448.45 ± 69.92	405.70 ± 113.18
ALP (IU/liter) *	136.89 ± 10.50	164.36 ± 40.93	261.70 ± 101.34
T. Protein (g/100 ml)*	6.36 ± 0.16	6.09 ± 0.29	5.46[a] ± 0.29
Albumin (g/100 ml)*	2.68 ± 0.11	2.60 ± 0.11	2.84 ± 0.20
T. Bil (mg/100 ml)*	2.32 ± 0.36	5.10 ± 1.08	1.27[b] ± 0.43
D. Bil (mg/100 ml)*	0.89 ± 0.17	2.43 ± 0.62	0.57[a] ± 0.04
PT (sec)**	16.29 ± 0.87	15.44 ± 3.02	12.6[a] ± 1.4
APTT (sec)**	21.59 ± 3.46	25.59 ± 6.39	20.11 ± 8.44
INR**	1.36 ± 0.10	1.53 ± 0.20	1.01 ± 0.18
Fibrinogen (g/liter)**	1.96 ± 0.32	2.11 ± 0.50	3.14 ± 0.32
LDH (IU/liter)***	102.89 ± 31.48	117.63 ± 36.67	289.90[b] ± 85.81
Protein (g/100 ml)***	1.26 ± 0.14	1.26 ± 0.27	1.93 ± 0.41
Albumin (g/100 ml)***	0.58 ± 0.09	0.60 ± 0.16	1.04 ± 0.09

[a]$p < 0.05$, [b]$p < 0.05$ significantly different from noncancer groups.
Data are presented as mean ± 1 S.E.M.

of CA-125 in these patients were reported as celomic epithelium, including the mesothelial cells lining the peritoneum, the pericardium and the pleura, which are derivated from the same embriyonic origin.

Chronic liver disease, particularly liver cirrhosis, is one of the most common disorders associated with increased levels of sCA-125. The strong association between peritoneal fluid formation and elevated sCA-125 levels in cirrhosis led to the suggestion that CA-125 in serum could be used as a marker to detect PE in these patients (Molina et al. 1991; Collazas et al. 1992; Zuckerman et al. 1999; Sarı et al. 2001; Devarbhavi et al. 2002). These data led us to test the diagnostic usefulness of serum and peritoneal fluid CA-125 as a discriminator of abdominal cancerous diseases from cirrhosis and SBP.

Molina et al. (1991) showed that the concentrations of sCA-125 were similar in cirrhosis and hepatocellular cancer patients, but were higher in SBP patients. Interestingly, it has been shown that sCA-125 is more sensitive than physical examination in detecting a small to moderate amount of peritoneal fluid collection (Collazos et al. 1992). Devarbhavi et al. (2002) also reported that sCA-125 might be useful for differential diagnosis of cirrhosis and hepatocellular carcinoma. The release of this antigen in liver cirrhosis is not dependent on the hepatic disorder, and elevated serum CA-125 levels can indicate peritoneal involvement. In fact, sCA-125 level increased in a diversity of noncanceros and cancerous conditions and the common factor in all of them was serosal involvement (Miralles et al. 2003), suggesting that sCA-125 is not a marker specific for malignancy. Increased levels of sCA-125 in patients with chronic liver disease may be due to impaired metabolism of this tumor marker in the liver, even in the absence of peritoneal fluid (Topalak et al.

2002; Sevinc et al. 2003). The present study reveals that sCA-125 is higher both in SBP and cirrhosis than cancerous cases. We found that cirrhotic patients had three fold higher sCA-125 than abdominal cancer cases. Our findings support the study of Haglund and Kuusela (1999), reporting more than a three-fold increase in sCA-125 of cirrhotic patients compared to abdominal cancers.

It has been suggested (Zeimet et al. 1996; Sanusi et al. 2001; Fujimura et al. 2002) that CA-125 might be synthesized by the peritoneal epithelium in response to mechanical stress caused by the presence of PE, and then passed from the peritoneal cavity to serum through the peritoneum. This hypothesis of the peritoneal fluid-serum exchange is supported by the significantly higher level of pCA-125 found in the PE of cancer, when compared with its corresponding serum level. The reason of low serum levels in cancer patients may be explained by the presence of large fibrotic damage in peritoneal cavity which might alter the permeability. The elevated pCA-125 levels and positive correlation between sCA-125 and pCA-125 in noncancer group may be a sign of contribution of peritoneally derived CA-125 to circulating CA-125. This finding may also support the notion that CA-125 is of mesothelial rather than tumoral origin. This is consistent with the findings in previous studies (Bergmann et al. 1987; Zeimet et al. 1996; Epiney et al. 2000; Sjoval et al. 2002; Miralles et al. 2003; Uenishi et al. 2003).

On the other hand, peritoneal fluid LDH levels were significantly higher ($p < 0.05$, Table 2) in the cancer group than the noncancer group, which might be due to a deficiency in peritoneal circulation which could reffect the impairment of lymphatic obstruction and increased anaerobic glycolysis in cancer. Additionally, decreased levels in serum total protein levels in malignancy group may indicate increased catabolic processes**,** while increased PT and serum bilirubin levels in noncancer group are the expected laboratory findings of cirrhosis. An acute phase reactant, pCRP was significantly higher in cancer group than the noncancer group. Low levels of pCRP in cirrhosis and SBP can be explained by the decreased opsonic activity (Zahedi and Mortensen 1986).

In this study, the ratio of p/sCA-125 was found to be diagnostically more useful in differentiating peritoneal effusions in cancer patients from noncancer ones. This ratio was at least two fold higher in cancer cases than cirrhosis or SBP. Additionally, when we evaluated the ROC plot, the area under the curve was greatest for p/sCA-125 (0.831), pointing out that p/sCA-125 had higher diagnostic accuracy than sCA-125 (0.267) and pCA-125 (0.542). High p/sCA-125 ratio in the cancer group supports the peritoneal production of the CA-125 rather than passive diffusion from serum.

We show that high p/sCA-125 ratio is closely related to the presence of abdominal malignancies with PE. These findings are consistent with the study of Topalak et al. (2002) and Sjöval et al. (2002) in non-ovarian abdominal cancers with PE. Hence, in addition to the levels of sCA-125 and pCA-125, we recommend to measure the ratio of peritoneal fluid to serum CA-125 in differential diagnosis of PE of cancer origins from PE of noncancer origins.

The lack of diagnostic sensitivity for sCA-125 is confirmed in our study. sCA-125 gave the lowest diagnostic sensitivity plus specificity pairs (0.40, 0.33), while pCA-125 had better results (0.60, 0.54) and p/sCA-125 gave the best results (0.80, 0.72). To improve diagnostic utility of tumor markers is important to avoid false-positive results which may expose patients to unnecessary, invasive techniques. In conclusion, determination of p/sCA-125 improves the biochemical discrimination of PE with malignant origins from that of cirrhosis or SBP.

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