TJC Turkish Journal of Cancer
Volume 37, No.1, 2007

The evaluation of tumor markers in acute pancreatitis

ERKAN CÜRE[1], ABDÜLKADİR BAŞTÜRK[1], MEHMET ŞAHİN[1], MEDİNE CUMHUR CÜRE[2], HASAN ŞENOL COŞKUN[3], MEHMET İŞLER[4]

Süleyman Demirel University, Medical School, Departments of [1]Internal Medicine, [2]Biochemistry, [3]Medical Oncology and [4]Gastroenterology, Isparta-Turkey

ABSTRACT

Tumor markers have been used for detecting and monitoring various malignant diseases. However, as the sensitivity and specificity of the tumor markers are not enough for detecting malignant diseases, clinical usefulness of them are limited. The aim of this study was to determine the rate of false positivity of some tumor markers in acute pancreatitis. For this aim, carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) levels were measured in acute pancreatitis. All 61 patients (37 women, 24 men) with acute pancreatitis and a total of 74 patients (39 women, 35 men) with peptic ulcus and gastritis were enrolled in to the study. All of our patients had mild acute pancreatitis, according to the Atlanta criteria. Tumor markers of patients with acute pancreatitis were examined in the first 24 hours. Serum levels of CA 19-9 in acute pancreatitis were significantly higher than the control group. In patients with acute pancreatitis, 36% of CA 19-9 levels were above the upper limit. There was no difference in CEA levels between the study groups. CA 19-9 levels could be elevated in acute pancreatitis. For this reason tumor markers should not be used for screening but they should be used for only specific indications. [Turk J Cancer 2007;37(1):11-15]

KEY WORDS:

Acute pancreatitis, carbohydrate antigen 19-9, carcinoembryonic antigen, tumor marker

INTRODUCTION

Acute pancreatitis has a relative frequency ranging from 5 to 80 cases per 100,000 population in the Western world. There are several etiological factors, the majority being gallstones- or alcohol-related (1,2). The severity of clinical presentation varies from a mild, self-limiting form to severe disease complicated by sepsis and multi-organ failure. About 25% of patients with acute pancreatitis have severe disease, with a mortality rate approaching 30-40% (3).

Tumor markers are substances developed in or induced by tumor cells and secreted into body fluids in which they can be quantified by non-invasive analyses (4). The malignant transformation of cells leads to increased concentrations of tumor markers and thus they can indicate malignant diseases. It appears, however, that other proliferative processes, i.e. inflammatory and benign transformations are also able to induce the rise of tumor marker levels (4).

There are many molecular tumor markers for diagnosing and monitoring cancer patients. Especially, quantitative assay for serum levels of tumor markers; carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9) are frequently used in daily practice because of their relative specificities and usefulness to the common cancers (5).

CA 19-9 levels often are increased in benign biliary or pancreatic conditions (6-10). Elevated CA 19-9 concentrations have been detected in about 20% of patients with benign pancreatic disease, including chronic pancreatitis

(6,11,12). It was shown that CEA was also elevated in chronic pancreatitis (13). It is known that CA 19-9 and CEA were increased in patients with acute pancreatitis (14-18).

The present case-control study was conducted at the Süleyman Demirel University in Isparta, Turkey. We aimed to investigate the rate of false positivity of some tumor markers in a benign disorder, acute pancreatitis, by detecting the levels of CA 19-9 and CEA.

MATERIALS AND METHODS

Sixty one consecutive patients with acute pancreatitis (37 women and 24 men; mean age, 49.65 ± 17.17 years) were prospectively studied on admission to the Department of Internal Medicine, Süleyman Demirel University, Medical School, Isparta, Turkey. All of our patients had mild acute pancreatitis, according to the Atlanta criteria (3). Diagnosis of acute pancreatitis was based on a history of prolonged abdominal pain and was confirmed by abdominal ultrasonography and/or contrast enhanced computed tomography (CT). All patients' serum amylase and lipase level were assayed but lipase level was not used for the diagnosis of acute pancreatitis. We examined the ranson score of patients in first hours (19). In addition, 74 patients were accepted (including 39 women and 35 men, median age 50.41 ± 15.37) as the control group, including gastritis and peptic ulcus. The control group was based on a history of prolonged abdominal pain and was confirmed by upper gastrointestinal endoscopy.

A venous blood sample was obtained on the 1st day after onset of the disease. Serum was stored at -20 °C and the assays were performed at our biochemistry laboratory. Tumor markers were examined by chemiluminescent enzyme immunoassay (Immulite 2000, DPC: Diagnostic Products Corporation, Los Angles, USA). Amylase, lipase levels and glucose, lactate dehydrogenase, aspartate transaminase (for evaluating ranson score) assays were performed with Abbott aeroset autoanalyzer by calorimetric method, in leukocyte Beckman Coulter device.

Statistical Analysis

Values are expressed as mean±SD. Parametric Independent-Samples T test, Mann-Whitney U, Chi-square test when appropriate, were used to compare the different parameters obtained between acute pancreatitis and normal healthy participants. All analyses were performed using the statistical package SPSS for Windows, and a p value less than 0.001 was considered statistically significant. The Pearson's correlation test was used for correlations.

RESULTS

Demographic and etiological data are shown in tables 1 and 2. The patients with acute pancreatitis were not different from the control group according to age and sex. Results of amylase, lipase, triglyceride (TG) and tumor markers are shown in table 3. Serum levels of CA 19-9 in the patient group were significantly higher than the control group ($p<0.001$). There was no difference in both groups according to the CEA levels. Ca 19-9 levels were similar in both genders with acute pancreatitis ($p<0.851$). When we divided the acute pancreatitis group into two according to the etiologic cause as gallstone and others (idiopathic, dysfunction of oddi sphincter, alcoholism, pregnancy, mumps, drugs and hypertriglyceridemia), CA 19-9 levels of both groups were similar ($p<0.637$). There was no significant correlation between tumor marker levels and lipase and amylase levels. Ranson score were ranged to 0-3 (respectively ranson score; patient's number: 0, 1, 2, 3; 16, 18, 10, 17). Ranson score was positively correlated with CA 19-9 level ($r=0.728$, $p<0.001$). There was no correlation between CEA and ranson score.

DISCUSSION

In this study, CA 19-9 levels were found significantly higher in patient group than the control group. CA 19-9 levels were higher than upper limits in 36% of patients with acute pancreatitis. In acute pancreatitis group, there was no difference between both genders according to the CA 19-9 levels. When etiologic causes were classified as gall stone and others, it was seen that the increment of CA

Table 1
Demographic and etiological data

	Patients (n=61)	Control group (n=74)
Age (Mean ± SD)	49.65 ± 17.17	50.41 ± 15.37
Sex (F/M)	37/24	39/35

19-9 levels were not different in various etiologic causes. It was seen that ranson scores were positively correlated with CA 19-9.

CA 19-9 is produced by adenocarcinomas of the pancreas, stomach, gall bladder, colon, ovary and lung. Serum CA 19-9 is considered the most sensitive marker for pancreatic cancer, being elevated in 75% or more of patients with pancreatic cancer (20). CA 19-9 is produced by several normal human tissues, with the highest concentrations produced by biliary and pancreatic ductal cells.

Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations (21-24). In a previous study, an elevation of CA 19-9 was detected in 5 cases of total 52 patients with benign pancreas lesion (25). Markocka-Maczka (26) suggested optimal value of 150 U/ml for CA 19-9 level for differential diagnosis of pancreas cancer and inflammatory process of pancreas. In the present study only one patient's CA 19-9 level was found as 153 U/ml.

In our study we found CA 19-9 level significantly higher in acute pancreatitis than the control group. CA 19-9 levels were above the upper limits in 22 patients. There was no pancreas or other organ cancers in our patients. From this aspect, the elevation in CA 19-9 levels in patient group rather than control group shows that without cancer etiology, CA 19-9 levels could be elevated in acute pancreatitis.

Cholestasis was present in 97.1% of patients with highly elevated CA 19-9, independent of their primary disease. 50% of patients with non-malignant diseases and increased CA 19-9 levels showed liver cirrhosis, cholecystitis, pancreatitis and/or hepatitis (27). In present study, CA 19-9 was found increased in 36% patients with acute pancreatitis.

CEA, an oncofetal glycoprotein, is expressed in normal mucosal cells and overexpressed in adenocarcinoma, especially colorectal cancer (28-30). CEA elevation also occurs with other malignancies. Non-neoplastic conditions associated with elevated CEA levels include cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, biliary obstruction, and cirrhosis. Anyway, levels exceeding 10 ng/mL are rarely due to benign disease (30).

In a previous study, CEA was found to be increased in 51% of patients with pancreatic cancer; it was also abnormal in 22% of chronic pancreatitis and 31% of extra-pancreatic diseases (31). In a previous study it was shown that CA19-9 has more sensitivity than CEA in diagnosis of acute pancreatitis (17). In a previous study, CEA levels were examined in malignant and benign disorders of pancreas and there were not any differences found (32). In the present study CEA was not found to be increased in acute pancreatitis compared to the control group.

Tumor markers are being used for screening in some clinics. Like previous studies, this study shows that tumor markers could increase in benign disorders. Using tumor markers in monitoring a patient with cancer or patients with suspicion of cancer could decrease false positive diagnoses and unnecessary examinations.

In conclusion, CA 19-9 levels could increase in acute pancreatitis at moderate ranges. This increment of CA 19-9 levels was not different in both genders and etiologic causes of acute pancreatitis. CA 19-9 levels were positively correlated with severity of acute pancreatitis. CA 19-9 levels could be increased in acute pancreatitis like many of other benign disorders. For this reason tumor markers should not be used for screening but they should be used for only specific indications.

Table 2
Etiology of pancreatitis in the study group

Etiology	Cases (%)	
Gallstones	27	(44.26%)
Idiopathic	16	(26.23%)
Sphincter of Oddi dysfunction	4	(6.56%)
Drug induced pancreatitis	4	(6.56%)
Hypertriglyceridemia	3	(4.92%)
Alcohol	5	(8.20%)
Gestational origin	1	(1.64%)
Mumps	1	(1.64%)

Table 3
Comparison of serum amylase, lipase, triglyceride and tumor markers in both groups

	Patients (n=61)	Control group (n=74)	P value
CA 19-9 (0-37 U/ml)	37.66 ± 30.37	8.58 ± 8.22	<0.001
CA 19-9 (>37 U/ml)	22 (% 36)	0	<0.001
CEA (0-3.4 ng/ml)	1.78 ± 1.13	1.83 ± 1.05	0.788
TG (40-160 mg/dl)	180.88 ± 113.45	152.82 ± 76.78	0.090
Amylase (25-100 IU/l)	624.60 ± 702.76	59.36 ± 28.83	<0.001
Lipase (0-60 U/l)	885.98 ± 842.78	31.51 ± 17.48	<0.001

CA 19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, TG: triglyceride

References

1- Steinberg SM, Gower WR Jr, Martin D, et al. Experimental pancreatitis does not produce pulmonary hypertension. Surg Gynecol Obstet 1983;157:530-3.

2- Toouli J, Brooke-Smith M, Bassi C, et al. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol 2002;17:15-39.

3- Bradley EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis. Atlanta Ga 1992;128:586-90.

4- Fiebiger W, Wiltschke C. Tumor markers. Acta Med Austriaca 2001;28:33-7.

5- Ohkura H. Clinical usefulness of circulating tumor markers. Gan To Kagaku Ryoho 2004;31:1131-4.

6- Duffy MJ. CA 19-9 as a marker for gastrointestinal cancers: a review. Ann Clin Biochem 1998;35:364-70.

7- Grem J. The prognostic importance of tumor markers in adenocarcinomas of the gastrointestinal tract. Curr Opin Oncol 1997;9:380-7.

8- Banfi G, Zerbi A, Pastori S, et al. Behavior of tumor markers CA 19-9, CA 195, CAM 43, CA 242 and TPS in the diagnosis and follow-up of pancreatic cancer. Clin Chem 1993;39:420-3.

9- Ventrucci M, Ubalducci GM, Cipolla A, et al. Serum CA 242: the search for a valid marker of pancreatic cancer. Clin Chem Lab Med 1998;36:179-84.

10- Chung MH, Gupta RK, Bilchik AJ, et al. Preoperative serum TA90-IC as an adjunct to serum CA 19-9 in the diagnosis of pancreatic malignancy: A pilot study. Curr Surg 2002;59:194-8.

11- Safi F, Beger HG, Bittner R, et al. CA 19-9 and pancreatic adenocarcinoma. Cancer 1986;57:779-83.

12- Ito T, Migita Y, Nakano I, et al. A clinical evaluation of tissue polypeptide specific antigen (TPSA) in pancreatic cancer patients. Rinsho Kenkyu 1995;72:224-8.

13- Slesak B, Harlozinska-Szmyrka A, Knast W, et al. Tissue polypeptide specific antigen (TPS), a marker for differentiation between pancreatic carcinoma and chronic pancreatitis. A comparative study with CA 19-9. Cancer 2000;89:83-8.

14- Akdogan M, Sasmaz N, Kayhan B, et al. Extraordinarily elevated CA19-9 in benign conditions: a case report and review of the literature. Tumori 2001;87:337-9.

15- Pines E, Slama JL, Holeman A, et al. Unusually high level of CA 19-9 in chronic pancreatitis Gastroenterol Clin Biol 1995;19:641-2.

16- Piantino P, Fusaro A, Randone A, et al. Increased levels of Ca 19-9, Ca 50 and Ca 125 in patients with benign diseases of the biliary tract and the pancreas. J Nucl Med Allied Sci 1990;34:97-102.

17- Changchine CS, Yung CY, Tzen KY. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9) values in patients with pancreatic cancer or pancreatitis. Changgeng Yi Xue Za Zhi 1991;14:32-8.

18- Vel'bri SK, Lilleorg AL. The immunological indices in inflammatory and tumorous diseases of the pancreas. Ter Arkh 1992;64:28-31.

19- Ranson JH, Rifkind KM, Roses DF, et al. Prognostic signs

and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 1974;139:69-81.

20- Grinbaum R, Nissan A, Beglaibter N, et al. The prognostic value of CA 19-9 in the preoperative work-up of pancreatic cancer patients. Harefuah 2006;145:793-4.

21- Steinberg WM, Gelfand R, Anderson KK, et al. Comparison of the sensitivity and specificity of the CA19-9 and carcinoembryonic antigen assays in detecting cancer of the pancreas. Gastroenterology 1986;90:343-9.

22- Steinberg W. The clinical utility of the CA19-9 tumor-associated antigen. Am J Gastroenterol 1990;85:350-5.

23- Furuya N, Kawa S, Hasebe O, et al. Comparative study of CA242 and CA19-9 in chronic pancreatitis. Br J Cancer 1996;73:372–6.

24- Malesci A, Tommasini MA, Bonato C, et al. Determination of CA19-9 antigen in serum and pancreatic juice for differential diagnosis of pancreatic adenocarcinoma from chronic pancreatitis. Gastroenterology 1987;92:61-7.

25- Cwik G, Wallner G, Skoczylas T, et al. Elevated tumor marker CA 19-9 in the differential diagnosis of pancreatic mass lesions. Ann Univ Mariae Curie Sklodowska 2004;59:213-8.

26- Markocka-Maczka K. Ca 19-9 antigen in differentiation of pancreatic inflammatory and neoplastic tumors Wiad Lek 2003;56:537-40.

27- Osswald BR, Klee FE, Wysocki S. The reliability of highly elevated CA 19-9 levels. Dis Markers 1993;11:275-8.

28- Chan DW, Beveridge RA, Muss H, et al. Use of Truquant BR radioimmunoassay for early detection of breast cancer recurrence in patients with stage II and stage III disease. J Clin Oncol 1997;15:2322-8.

29- Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. Adopted on May 17, 1996, by the American Society of Clinical Oncology. J Clin Oncol 1996;14:2843-77.

30- Fletcher RH. Carcinoembryonic antigen. Ann Intern Med 1986;104:66-73.

31- Plebani M, Fabris C, Basso D, et al. Limits of CEA and ferritin in the diagnosis of pancreatic cancer. Int J Pancreatol 1988;3:113-7.

32- Cerwenka H, Aigner R, Quehenberger F, et al. Preoperative differential diagnosis of benign and malignant pancreatic lesions--the value of pancreatic secretory trypsin inhibitor, procarboxypeptidase B, CA19-9 and CEA. Hepatogastroenterology 1997;44:1117-21.