Is tissue polypeptide antigen more accurate than serum CEA for diagnosing pancreatic cancer?

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SUMMARY Tissue polypeptide antigen (TPA) and carcinoembryonic antigen (CEA) were determined in the sera of 36 control subjects, 30 patients with pancreatic cancer, 35 with chronic pancreatitis and 25 with non-pancreatic digestive disease to evaluate their role in detecting pancreatic malignancy. Abnormal values of TPA and CEA were found in 28 and 19 of 30 patients with pancreatic cancer, and in four and seven of 35 patients with chronic pancreatitis, respectively. Raised titres of TPA were observed more often than equivalent serum CEA in simulated pancreatic diseases. The receiver-operating (ROC) characteristic curves showed that TPA was more discriminating than CEA in detecting pancreatic cancer. Specificity was enhanced when both titres were abnormally high and sensitivity when one titre was raised, but the diagnostic accuracy of TPA alone has not improved, which satisfactorily discriminates pancreatic cancer from chronic pancreatitis.

Carcinoembryonic antigen (serum CEA) is a glycoprotein with a molecular weight of 180 000, comprising 60% carbohydrate.¹⁻³ It exhibits an extensive heterogeneity with the carbohydrate chains, while the composition of amino acid remains remarkably constant.^{2,3} Increased serum CEA concentrations have been described in various neoplastic diseases,^{4,5} including pancreatic cancer.⁶⁻⁹ Abnormal results have also been reported, however, in inflammatory conditions such as chronic pancreatitis.^{4,6,8,10} Serum CEA has also been suggested as an indicator of tumour metastasis.^{11,12}

Tissue polypeptide antigen (TPA) is an unconjugated membrane protein without sugars, lipids, or prosthetic groups. Antibodies raised against TPA react immunologically with different proteins with molecular weights ranging from 20 000 to 45 000 and can be separated from each other.¹³⁻¹⁵ Increased TPA serum concentrations have been found not only in several neoplastic diseases but also in non-malignant pathological conditions.¹⁵⁻¹⁷ High TPA values have almost invariably been observed in pancreatic cancer^{16,18} and only occasionally in chronic pancreatitis. TPA is generally considered to be an indicator of tissue proliferation.¹³

The aim of this study was to evaluate CEA and TPA separately and in combination for their use-

fulness in detecting pancreatic cancer.

Material and methods

One hundred and twenty six subjects were studied. Thirty six were control subjects (24 men, 12 women, age range 37-66 years), all healthy members of the medical staff or blood donors. Thirty patients had pancreatic cancer of duct cell origin (21 men, nine women, age range 43-71 years), which was histologically confirmed in all cases by means of biopsy taken during operation or at necropsy.¹⁹ Staging of the disease was: T1N0M0 (three cases), T2N1M0 (six), T2N1M1 (10), and T3N1M1 (11). Thirty five patients had chronic pancreatitis (11 calcified chronic pancreatitis) (31 men, four women, age range 23-68 years); the diagnosis was made clinically and using the positive results of at least two of the following examinations: plain abdomen radiography X-ray for pancreatic calcifications, pancreatic ultrasonography, computed axial tomography and endoscopic retrograde pancreatography. The diagnosis was always histologically confirmed by means of multiple specimens taken intraoperatively. Twenty five patients were affected by pancreatic non-digestive diseases of a non-neoplastic nature (11 men, 14 women, age range 37-81 years). Diagnosis was based on the clinical picture and results of specific radiological and histological procedures: liver cirrhosis (six cases); gallstones (four); common duct stones (three); chronic gastritis (three);

Table 1 Mean serum CEA and TPA concentrations (SEM)

	No of cases	CEA ($\mu\text{g/l}$) $\bar{x}$	TPA (U/l) $\bar{x}$
Control subjects	36	1.98* (0.10)	60.7* (3.5)
Patients with:			
Pancreatic cancer	30	10.57 (3.46)	519.2 (97.2)
Chronic pancreatitis	35	2.59* (0.13)	71.6* (5.0)
Simulated pancreatic diseases	25	2.61† (0.16)	131.7* (15.9)
Total	126		
Analysis of variance:		F = 5.99 p < 0.01	F = 21.4 p < 0.01
Scheffé's method for multiple comparisons:			
*p < 0.01 (pancreatic cancer)			
†p < 0.05 (pancreatic cancer)			

Table 2 Sensitivity, specificity, and diagnostic accuracy expressed as a percentage (Youden index) of CEA and TPA for diagnosing pancreatic cancer*

	CEA	TPA	CEA and TPA†	CEA or TPA‡
Sensitivity	63.3	93.3	53.3	100
Specificity	81.7	70.0	91.7	60.0
Accuracy	45.0	63.3	45.0	60.0

*Cut off values for CEA and TPA were 3.14 $\mu\text{g/l}$ and 102.9 U/l, respectively.

†Both variables yielding abnormal results.

‡One of the two variables yielding abnormal results.

irritable colon (three); duodenal ulcer (two); benign stenosis of the papilla of Vater (two); retroperitoneal fibrosis (one); and primary biliary cirrhosis (one).

Serum CEA and TPA were determined using radioimmunoassay techniques using commercial kits (Eiken Chemical Co and Prolifigen, AB Sangtec Medical, Bromma, Sweden, respectively). The statistical evaluation of the data was done analysing variance

Fig. 1 Values of TPA and CEA in patients with pancreatic cancer related to stage of disease. Continuous lines represent upper normal limits (mean (2SD), of control subjects: 60.7 (42.2) U/l and 1.98 (1.16) $\mu\text{g/l}$ for TPA and CEA, respectively). TNM = Numbers of tumours, nodes, and metastases.

(Anova one way), Scheffé's method for multiple comparisons,²⁰ the χ^2 test, the Youden index,²¹ and receiver-operating characteristic (ROC) curves.²²

Results

Table 1 shows the mean values, standard errors, and statistical evaluation of the data. A significantly increased incidence of abnormal CEA and TPA concentrations was detected in patients with pancreatic cancer, taking the variables independently ($\chi^2 = 31.97$, $p < 0.0005$; $\chi^2 = 76.09$, $p < 0.0005$, respectively) and in combination (either or both abnormal; $\chi^2 = 64.47$, $p < 0.0005$; $\chi^2 = 41.05$, $p < 0.0005$, respectively). Fig. 1 illustrates the values of CEA and TPA in patients with pancreatic cancer according to the stage of the disease. Table 2 shows the results of the Youden index.

A significant linear correlation was noticed between serum CEA and TPA concentrations ($r = 0.3845$, $p < 0.001$). Fig. 2 shows the ROC curves of the two variables used for diagnosing pancreatic cancer.

Discussion

Published reports on the determination of TPA for diagnosing pancreatic cancer are few. Although TPA has generally been described as having a good sensitivity, its value in discriminating pancreatic cancer from chronic pancreatitis has not been established. In our study the serum TPA concentration was raised in 28 of 30 patients with pancreatic cancer, confirming the good sensitivity previously described in a preliminary study.¹⁸ Only four of 35 patients with chronic pancreatitis had raised concentrations, which

Fig. 2 Receiver-operating characteristic curves of CEA and TPA in the diagnosis of pancreatic cancer.

were only slightly above normal in two. This indicates that TPA has a satisfactory specificity. Nevertheless, abnormal values in this test were often found in inflammatory diseases of the liver or the biliary tract, thus limiting the usefulness of the determination of TPA for assessing pancreatic cancer.

Serum CEA has been extensively investigated in patients with various malignant diseases. Its sensitivity and specificity in diagnosing pancreatic cancer were not entirely satisfactory according to previous observations^{8 23 24}; only 19 of our 30 patients with pancreatic neoplasm had raised CEA values. There were seven false positive results among patients with chronic pancreatitis. Abnormal results in digestive disease simulating pancreatic diseases, however, were found less often than when TPA was used.

Considering the results of the Youden index, TPA showed the highest sensitivity (93%) and CEA the highest specificity (82%); the diagnostic accuracy was acceptable only for TPA (63%). The data were confirmed by the ROC curves: TPA was more discriminating than CEA in diagnosing pancreatic cancer for any serum value.

When patients with pancreatic cancer were divided according to the stage of the disease, no clear correlation was detected between metastasis and the serum values of either antigen. Although the highest values were observed in patients with metastatic pancreatic cancer, normal or slightly raised concentrations were also found. Thus these antigens do not provide definitive information on the stage of the tumour.

A good correlation was found between the two indexes, reflecting similar behaviour at least in part. CEA and TPA were tested in combination in an attempt to improve their diagnostic usefulness. Although an increase in specificity was obtained when both variables yielded abnormal results, and a corresponding increase in sensitivity when one variable yielded abnormal results, the overall accuracy has not improved.

In conclusion, TPA seems to be a sensitive index in diagnosing pancreatic cancer, more accurate than CEA and it satisfactorily discriminates pancreatic cancer from chronic pancreatitis, although not from non-pancreatic digestive diseases. Combining CEA with TPA does not substantially improve the results given by TPA alone.

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