Tumor Markers Carbohydrate Antigens CA 19-9 and CA-50 and Carcinoembryonic Antigen in Pancreatic Cancer and Benign Diseases of the Pancreatobiliary Tract

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ABSTRACT

Sera from patients with diseases in the pancreas, gallbladder, and bile duct were analyzed for the tumor markers CA 19-9, CA-50, and carcinoembryonic antigen. In particular CA 19-9 and CA-50 appear to be valuable in differentiating malignant from benign disease in these organs. Our sample of 72 patients with pancreatic cancer also indicates that CA 19-9 and CA-50 complement each other in 21% of the cases. They are also shown to be reliable for monitoring disease: following radical surgery for pancreatic cancer low levels of CA 19-9 and CA-50 were noted, while progressive rises of these tumor markers were related to disease progression.

INTRODUCTION

The incidence of pancreatic cancer, e.g., adenocarcinoma of the pancreas, seems to be increasing. In Sweden, about 1250 cases are registered every year. The results of treatment have not improved much in recent decades. After radical surgery the 5-year survival is only 5%. Very early diagnosis is commonly believed to be important for a better prognosis. The diagnostic possibilities have been strengthened in the last years (1, 2). About 70% of pancreatic tumors are localized to the caput. For these, reliable diagnosis is obtained by percutaneous transhepatic gall duct cannulation or by cannulation of papilla Vateri. For other pancreatic tumors a diagnosis is more difficult to establish, and the time of diagnosis is later. The diagnostic methods used for the latter group are computed tomography, endoscopic cholangiopancreatography, and nuclear magnetic resonance.

It is important to try new methods in order to diagnose pancreatic cancer as early as possible. In this study we demonstrate the use of 3 tumor markers: CA 19-9; CA-50; and CEA. The antigen is similar to the Lewis-a determinant with an N-acetylenuraminic acid substituted 3' position of the terminal nonreducing galactose residue. CA-50 was first described by Lindholm et al. (7) in 1983. One monoclonal antibody to CA-50 binds to the same antigen as the CA 19-9 antibody but also to the compound lacking the fucose residue, e.g., to the substance from Lewis negative (Le a–b–) individuals (8). CEA, a well-documented tumor marker (9), is associated with colon carcinoma but also with other cancers of the gastrointestinal tract such as pancreatic cancer (10). The antigen is a glycoprotein (11).

Sera from patients with pancreatic cancer were analyzed for CA 19-9, CA-50, and CEA. The results were compared with values of sera from patients with gallbladder carcinoma, cancer of the bile duct, a number of defined benign diseases in the pancreatoiliary tract, and sera from healthy blood donors.

MATERIALS AND METHODS

Patients. There were 76 patients with adenocarcinoma of the pancreas (72 patients with or without metastasis and 4 cured after radical surgery), 20 patients with gallbladder carcinoma, and 7 patients with bile duct cancer. Patients with benign diseases were 11 with chronic pancreatitis, 7 with cirrhosis of the liver, 7 with sclerotic cholangitis, and 6 patients with stones in the gallbladder (Table 1). 45 healthy persons provided control sera.

Tumor Marker Determinations. Radioimmunoassay for CEA was performed with reagents from Hoffmann-La Roche (Basel, Switzerland) or from Pharmacia (Uppsala, Sweden). A commonly used border value is ≥5 μg/liter. Radioimmunoassay for CA 19-9 was performed with reagents from International CIS (Cedex, France). A mouse Mab of the IgG1 class was used (12). The border value was set at 37 IE/liter by International CIS. Time-resolved immunofluorometry for CA 50 was performed with DELFIA kits from Stena Diagnostics (Gothenburg, Sweden). The Mab was of IgM class. The border value was set at 14 kU/liter by Stena Diagnostics.

RESULTS

CA 19-9 and CA-50 values in malignant diseases were compared with values in benign diseases of the corresponding organs pancreas, gallbladder, and bile duct (Fig. 1). CA 19-9 and CA-50 appear to differentiate malignant from benign diseases in these organs, provided the cutoff values are set higher than those recommended by the reagent producers. CEA determinations were less discriminating between malignant and benign disease.

The summarized results of CA 19-9, CA-50, and CEA serum determinations are shown in Table 1. The 72 patients with pancreatic cancer tended to have very high values for CA 19-9 and CA-50 (see also Fig. 1, top); 82% had CA 19-9 values over 120 IE/liter and 81% had CA-50 values over 100 kU/liter. CEA values were often elevated but only 25% reached levels above 25 μg/liter. The patients with gallbladder carcinoma also tended to have very high values: 89% were elevated for CA 19-9 and 83% were elevated for CA-50 above 120 IE/liter and 100 kU/liter, respectively. CA 19-9 and CA-50 levels were all very high for the 6 patients with cancer of the bile duct. From healthy blood donors 45 samples were analyzed for CEA, 45 samples were analyzed for CA 19-9, and 17 samples for CA-50. Of these samples no values for CEA or CA 19-9 were elevated; 2 slightly elevated values (19 and 24 kU/liter) were seen for CA-50 (not shown).

Initial tumor marker levels and changes in them were studied. Five patients with progressive pancreatic cancer after radical surgery were shown (Fig. 2). The levels for CA 19-9 and CA-50 decreased in direct relation to surgery and rose again as the disease progressed. For one of the patients CA 19-9 and CA-50 were elevated 9 months before any clinical symptoms or
computed tomography examinations showed signs of progressive disease (patient V). CEA levels for this patient did not rise distinctly when the disease progressed. CA 19-9, CA-50, and CEA levels for patients with no evidence of disease after radical surgery for pancreatic cancer are also shown (Fig. 3). Four patients with pancreatic cancer were cured. During the follow-up 2 to 10 years after surgery, slightly elevated values of CA-50 and CEA were seen in one patient; all other values were normal.

We analyzed whether determinations of both CA 19-9 and CA-50 had an additive effect in the diagnosis of pancreatic or gallbladder cancer or cancer of the bile duct (Fig. 4). With our cutoff levels, 18 patients had elevation of one of these markers only. Thus, 8 of the 72 patients with pancreatic cancer had CA-50 levels over 100 kU/liter but CA 19-9 levels less than 120 IE/liter. Seven of the patients with pancreatic cancer had CA 19-9 levels over 120 IE/liter but CA-50 levels less than 100 kU/liter. Of the patients with gallbladder carcinoma one patient had a CA-50 value over 100 kU/liter and a CA 19-9 value of 88 IE/liter, and 2 patients had CA 19-9 levels over 120 IE/liter but CA-50 levels less than 100 kU/liter. The correlation coefficient for CA 19-9 related to CA-50 was 0.81. We also analyzed whether CEA gave any additional information compared to CA 19-9 and CA-50 values (not shown in Fig. 4). Of the patients with pancreatic cancer 4 had CEA values over 25 /ig/liter but CA-50 values less than 100 kU/liter and 5 patients had CEA values over 25 /ig/liter but CA 19-9 values less than 120 IE/liter. Of these patients with elevated CEA values 2 had both CA 19-9 and CA-50 values below our suggested cutoff levels. Thus, a certain additional value of CEA could be seen but it should be noted that all together only a fourth of the patients with pancreatic cancer reached CEA values over 25 /ig/liter. In our small sample of patients with gallbladder carcinoma or cancer of the bile duct, CEA did not give any additional information. The correlation coefficients for CEA against CA 19-9 and CA-50 were 0.28 and 0.19, respectively.

**DISCUSSION**

Serum contents of CA 19-9 and CA-50 were usually very high in pancreatic cancer. These markers are therefore valuable in the diagnosis of pancreatic cancer. CEA in sera from patients with many nonmalignant diseases had levels in the interval of 5 to 25 /ig/liter. We found levels higher than recommended border values in some of the patients with benign disease as well as in some of healthy blood donors. This finding indicates that the recommended and commonly used cutoff values for the present markers are not ideally chosen to show optimal specificity for malignancy. The choice of 25 /ig/liter for CEA will in this material diminish the problem of false-positive reactions in benign disease, but at the same time reduce the true-positive findings in pancreatic cancer to about 25%. In gallbladder carcinoma the sensitivity is reduced to less than 50% and also leaves all the patients with bile duct carcinoma without positive findings. To select a value of >25 /ig/liter for CEA would mean a too poor sensitivity for malignancy. Thus CEA serum determinations appear to be of less value for these diseases. This conclusion agrees with the results of del Favero et al. (3) who determined the CEA and CA 19-9 levels in 29 patients with pancreatic cancer. The results of Table 1 suggest that cutoff levels of 120 IE/liter for CA 19-9 and 100 kU/liter for CA-50 assist in differentiating between malignant and benign diseases of the pancreas, the gallbladder, and the bile duct. No false-positive findings were then seen in benign disease. With CA 19-9 the sensitivity for pancreatic cancer was 82% and with CA 50 the sensitivity for pancreatic cancer was 81%. With sensitivity rates of 83 to 100% the same markers seem to be of value also for gallbladder carcinoma and cancer of the bile duct although studies with larger patient groups are needed for these diseases. Safi et al. (5) have also investigated CA 19-9 and pancreatic cancer. With a sample of 48 patients with pancreatic carcinoma, a sensitivity of 77% was found with a cutoff level used of 120 IE/liter; 66 patients with chronic pancreatitis and 36 patients with acute pancreatitis were included in their material. Using 37 IE/liter as the borderline a sensitivity for pancreatic cancer of 92% and a specificity of 85% were seen. In our material we did not reach such a high specificity if the lower cutoff level at 37 IE/liter was used. Haglund et al. (13) used an immunoradiometric assay to determine serum CA-50. He found that 71% of 95 patients with pancreatic cancer had serum values elevated above normal values. In comparison to benign diseases in the pancreatobiliary tract, however, the sensitivity for malignancy was 45% if a cutoff level at 250 kU/liter was used to reduce the number of false-positive findings among the benign diseases. Our sample of patients with benign diseases is not as large as theirs but...
As demonstrated by an immunoperoxidase method by Haglund et al. (16) CA-50 and CA 19-9 have similar staining patterns in pancreatic carcinoma. The CA-50 positive but CA 19-9 negative specimens stained negatively for Lewis-a and Lewis-b blood group substances or were positive for Lewis-b but negative for Lewis-a. This supports the finding that the CA-50 Mab recognizes a different carbohydrate structure. However, Haglund et al. (16) could not show any correlation between the histological expression and the serum levels of the antigens. Furthermore some specimens stained positive for CA 19-9 and negative CA-50, which was also true for the serum determinations in Haglund’s and our material. An explanation for this has not been found.

Our sample of pancreatic cancer indicates that CA 19-9 and CA-50 are valuable for monitoring malignant disease of the ductum of sialylated Lewis-a. DELFIA may be a better discriminating assay for CA-50. It appears diagnostically valuable to analyze both CA 19-9 and CA-50 since they proved to have additive effects. This may be because the CA 19-9 and the CA-50 Mabs recognize different epitopes (14–16). We have not had samples to analyze whether the patients positive for CA-50 but not for CA 19-9 are Lewis negative but that could be one explanation. The CA-50 and the CA 19-9 Mabs react with sialosylfucosyllactotetraose (8), corresponding to sialylated blood group antigen Lewis-a. The CA-50 Mab also reacts with at least one other carbohydrate structure, the sialosyllactotetraose, which lacks the fucose molecule.
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N.E.D. PANCREATIC CANCER

Fig. 3. Levels of CA 19-9, CA-50, and CEA, for patients with no evidence of disease (N.E.D.) after radical surgery for pancreatic cancer. Time 0 is the time of surgery. Maximum levels shown are 120 IE/liter for CA 19-9, 100 kU/liter for CA-50, and 25 µg/liter for CEA.

pancreatobiliary tract. The few patients who recovered after radical surgery had persistently low marker levels, while continual increases of CA 19-9 and CA-50 values were related to progression. Attempts to immunolocalize minor tumor deposits that may exist after surgery are in progress.

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