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

Ulrika Harmenberg, Britta Wahren, and Karl-Ludvig Wiechel

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.

RESULTS

Tumor Marker Determinations. Radioimmunoassay for CA 19-9 was performed with reagents from Hoffmann-La Roche (Basel, Switzerland) or from Pharmacia (Uppsala, Sweden). A commonly used border value was set at 14 kU/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.

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1 This study was supported by grants from the Swedish Cancer Society.

2 The abbreviations used are: CEA, carcinoembryonic antigen; Mab, monoclonal antibody.
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 μg/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 μg/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 μg/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 of 37 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 pancreaticobiliary 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...

Table 1  Tumor markers in patients with pancreatic cancer and organ-related diseases

<table>
<thead>
<tr>
<th></th>
<th>% of patients with CA 19-9 elevation</th>
<th>% of patients with CA-50 elevation</th>
<th>% of patients with CEA elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤17 IE/liter</td>
<td>&gt;17–≤120 IE/liter</td>
<td>&gt;120 IE/liter</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>4 100</td>
<td>50 50</td>
<td>75 25</td>
</tr>
<tr>
<td></td>
<td>49 4 18</td>
<td>20 80</td>
<td>13 65 22</td>
</tr>
<tr>
<td></td>
<td>23 4.5 4.5</td>
<td>13 83</td>
<td></td>
</tr>
<tr>
<td>Gallbladder carcinoma</td>
<td>2 100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>13 7.5 7.5</td>
<td>31 69</td>
<td>61 8 31</td>
</tr>
<tr>
<td></td>
<td>5 100</td>
<td>100</td>
<td>20 80</td>
</tr>
<tr>
<td>Bile duct cancer</td>
<td>1 100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>4 100</td>
<td>100</td>
<td>25 75</td>
</tr>
<tr>
<td></td>
<td>2 100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>11 36 64</td>
<td>36 64</td>
<td>82 18</td>
</tr>
<tr>
<td>Cirrhosis of the liver</td>
<td>7 86 14</td>
<td>14 86</td>
<td>71 29</td>
</tr>
<tr>
<td>Sclerotic cholangitis</td>
<td>7 86 14</td>
<td>43 57</td>
<td>57 43</td>
</tr>
<tr>
<td>Stone in the gallbladder</td>
<td>6 67 33</td>
<td>17 83</td>
<td>100</td>
</tr>
</tbody>
</table>

* NED, no evidence of disease.
TUMOR MARKERS IN PANCREATIC CANCER AND BENIGN DISEASES

PANCREATIC CANCER PROGRESSION

Fig. 1. CA 19-9 and CA-50 in malignant and corresponding benign disease. Border values as suggested by producers are marked in the figures (lower lines). Upper lines are border values to differentiate between malignant and benign disease suggested by us (≥120 IE/liter for CA 19-9, ≥100 kU/liter for CA-50, and ≥25 μg/liter for CEA).

Fig. 2. Levels of CA 19-9, CA-50, and CEA for patients with progressive pancreatic cancer after radical surgery. 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.

DIELFIA 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 sialylated blood group antigen Lewis-a. The CA-50 Mab also reacts with at least one other carbohydrate structure, the sialosylactotetraose, which lacks the fucose molecule of sialylated Lewis-a. 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
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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REFERENCES


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