Simultaneous Radioimmunoassay for Carcinoembryonic Antigen (CEA) and Alpha-Fetoprotein (αFP) in Neoplasms of the Gastro-Intestinal Tract*

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ABSTRACT

Using a double-antibody radioimmunoassay, αFP was elevated (>40 ng per ml) in 70 percent of patients with primary liver cancer, 18 percent of patients with gastric cancer and 5 percent of patients with colorectal cancer. The elevation of αFP in metastatic gastrointestinal cancer involving the liver is determined by the site of tumor origin rather than by the liver involvement. The simultaneous measurement of CEA and αFP significantly increases the incidence of patients with a circulating marker protein in gastric cancer but not in colorectal cancer. Neoplasms of the same organ may produce different onco-fetal antigens and a single tumor may produce two onco-fetal antigens.

Introduction

A large number of circulating markers for a wide variety of neoplastic conditions have been reported. These have included immunoglobulins, hormones, isoenzymes and a number of fetal antigens. The most extensively studied of the onco-fetal antigens have been the carcino-embryonic antigen (CEA) and alpha-fetoprotein (αFP).

The initial enthusiasm regarding the possible use of circulating marker proteins for the early and definitive diagnosis of several neoplasms of different origins has been moderated by the finding that most of the markers were less specific than originally reported. The usefulness of these markers has been extended where evidence by quantitative assays indicated a possible correlation between changes in concentration of the marker and changes in tumor activity.

There is still much work to be done to demonstrate that changes in amount of marker proteins are of prognostic value in estimating effectiveness of therapy. It is obvious that having more than a single marker would increase the credibility of a laboratory test for predicting clinical
changes in neoplastic disease. The purpose of this report is to demonstrate one advantage in the use of simultaneous assays for tumor markers.

Methods

Patients

Three hundred fifty-seven patients with histologically proven gastro-intestinal cancer have had one or more measurements of serum αFP. One hundred forty-five of these patients had serum measurements of CEA as well. Patients were evaluated for extent of tumor and presence of metastases to the liver.

αFP Radioimmunoassay

The double-antibody radioimmunoassay has been described. The sensitivity of the assay was 5 ng per ml and a standard curve was constructed for every assay. More than 200 normal individuals over one year of age had levels below 30 ng per ml and less than 1 percent of 350 patients with non-hepatic, benign disease had serum levels above 40 ng per ml; therefore values above 40 ng per ml were considered significantly elevated.

CEA Radioimmunoassay

CEA was measured using the method of Lo Gerfo, et al as modified by Go and co-workers.†

Results

Serum αFP Levels in Gastrointestinal Neoplasms

In primary liver cancer where elevations of αFP were first described in the adult, 51 of 73 (70 percent) patients had levels greater than 40 ng per ml (table I). The range of these values went as high as $6 \times 10^6$ ng per ml. Of the values greater than 40 ng per ml, 69 percent were above 3,000 ng per ml and would probably have been identified as elevated by immune precipitation in agar.

Eighteen percent of patients with carcinoma of the stomach (16/91) had serum αFP levels greater than 40 ng per ml. All but two of these were below 300 ng per ml and only one was sufficiently high to be detected by common immunodiffusion techniques. Carcinoma of the large bowel had only 5 percent of patients (9/184) with elevated αFP and yet one of these was high enough for detection by double diffusion in agar. The other eight ranged between 40 and 600 ng per ml.

A group of 153 patients with acute and chronic, benign, non-hepatic gastrointestinal disease showed only two patients with minimal αFP elevation. In a larger group of 350 patients with a wide variety of non-hepatic benign disease, only one patient had serum αFP above 40 ng per ml.

Combined use of αFP and CEA Levels in Gastrointestinal Neoplasms

The 100 patients with colorectal cancer were almost evenly divided between those with evidence of liver metastasis and those with no evidence of liver involvement (table II). All three of the patients with elevated αFP were without obvious liver involvement while none of those with liver metastasis had elevated αFP. The incidence

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† The reagents were kindly supplied by Dr. Hans Hansen, Hoffman-La Roche Inc., Research Division, Nutley, NJ.
**TABLE II**

**Combined Use of αFP and CEA in Patients with Gastro-Intestinal Tract Neoplasia**

<table>
<thead>
<tr>
<th>Tumor Origin</th>
<th>Patients</th>
<th>αFP &gt;40 ng/ml</th>
<th>CEA &gt;2.5 ng/ml</th>
<th>Both Increased</th>
<th>Percent with Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>LARGE BOWEL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>53</td>
<td>0</td>
<td>45</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No liver metastasis</td>
<td>47</td>
<td>3</td>
<td>26</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>3</td>
<td>71</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>STOMACH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>20</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No liver metastasis</td>
<td>25</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>12</td>
<td>10</td>
<td>1</td>
<td>47</td>
</tr>
</tbody>
</table>

of elevated CEA was considerably higher in those patients with liver metastasis than in those without (85 percent vs 55 percent). There was no significant increase in percentage of patients with markers in colorectal cancer by using assays for both αFP and CEA.

The 45 patients with stomach cancer were also fairly evenly divided between those with and without evidence for liver metastasis. Elevation of both αFP and CEA was more frequent among those patients with liver metastasis than those without. Only one patient had elevation of both markers. The incidence of elevation for either marker individually was 27 percent for αFP and 22 percent for CEA but gave a combined total of 47 percent of patients with gastric cancer with a potential marker for disease activity.

**Discussion**

Serum αFP has been reported as a coincidental finding in isolated cases of gastro-intestinal cancer but this report gives the first figures of incidence of elevated αFP in gastric and colorectal cancer. It is essential that αFP be measured by a quantitative method as sensitive as radioimmunoassay if it is to be a useful test of tumor activity. Most of the elevations are below the level detected by less sensitive measurements and changes in level could not be appreciated by tests which operate on a dilutional titration. The finding of elevated levels of CEA in gastric cancer has been reported by many workers.

It has been shown by us that αFP is a potential marker in a significant number of patients with gastric cancer and in a small percentage of those with colorectal cancer. It does not appear that hepatic metastasis of the tumor is the cause of elevated αFP since none of the patients with colorectal cancer and elevated αFP had evidence of liver involvement and the patients with gastric cancer and elevated αFP were both with and without signs of hepatic metastasis. The data presented here favors the production of αFP being influenced by the site of tumor origin more than by hepatic involvement; gastric cancer metastatic to the liver was associated with elevated αFP while colorectal cancer metastatic to the liver was not. A study has been reported demonstrating αFP in both the primary lesion and the hepatic metastasis of a patient with gastric cancer. Synthesis of αFP has also been demonstrated in the fetal stomach and intestine in addition to fetal liver and yolk sac.
The simultaneous presence of two onco-fetal antigens has rarely been described.\textsuperscript{5,6,8} The results of this study would indicate that at least in gastric cancer it is a fairly unlikely occurrence. Of 21 patients with gastric cancer and CEA or \(\alpha\)FP elevation only one had both markers. Patients with colorectal cancer rarely have elevations of \(\alpha\)FP, two of the three that did also had elevated CEA. The simultaneous assay for both markers significantly increased the incidence of those with an elevation of one onco-fetal antigen in patients with gastric cancer but not in patients with colorectal cancer.

References


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Plan to attend the 25th Anniversary Meeting of the ASSOCIATION OF CLINICAL SCIENTISTS in Philadelphia, PA on November 8, 9 and 10, 1974

Applied Seminar on the Laboratory Diagnosis of Skeletal, Muscular and Nervous Disorders