Serum CEA Levels in Gastrointestinal Diseases

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Serum CEA titers in patients with benign gastrointestinal disease and gastric carcinoma were measured using the CEA-Roche Kit.

CEA levels in all the patients with benign disease were under 5.0 ng/ml, therefore, a CEA titer under 5.0 ng/ml was thought to be "normal" in measurements by the Roche-Kit.

High serum CEA titers were seen in patients with "advanced" gastric cancer, especially in patients with hepatic metastasis.

Differences in serum CEA titers of gastric cancer patients were assumed to be caused by differentiation of cancer cells or by CEA producibility of tumor tissue.

(Key Words: CEA (Carcinoembryonic antigen), Gastric Carcinoma, Intestinal Metaplasia, Differentiation of Cancer Cells)

MATERIALS AND METHODS

I Patients with benign disease (Controls)
Serum CEA levels in 54 patients with gastric ulcers or gastritis, aged 18 to 72 years, were measured. All of them were diagnosed by radiology and endoscopy. None had any abnormalities in blood counts, hematochemical examinations or urinalysis.

II Patients with gastric cancer
Serum CEA levels in 54 patients with gastric ulcers or gastritis, aged 18 to 72 years, were measured. All of them were diagnosed by radiology and endoscopy. None had any abnormalities in blood counts, hematochemical examinations or urinalysis.

One of the four was treated with Mitomycin C and Futraful, and is living now. A clinical estimate of the extent of the tumor using "The general rules for gastric cancer study in surgery and pathology" *(see Tables 1 and 2) was performed by the operating surgeon during surgery and by the pathologist during the autopsy. The surgeon's clinical evaluation of the extent of

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*This was edited in the Japanese Research Society for Gastric Cancer. It contains the most useful rules for estimating the extent of gastric cancer in Japan.
the tumor was confirmed by pathological studies of cleared specimens for lymph node involvement and histological studies of possible metastasis. According to "The general rules for gastric cancer study in surgery and pathology", the clinical estimate of the extent of gastric cancer was obtained from liver-scintigrams, abdominal angiograms and cytology of ascites in the three inoperable patients who were not explored by autopsy.

Table 1. Stage of gastric cancer (macroscopic)
The stage is decided by the degree of metastasis of tumor to the peritoneum, liver and lymph node and/or by the degree of tumor invasion into the Tunica serosa, macroscopically during surgery.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Metastasis to Peritoneum</th>
<th>Metastasis to Liver</th>
<th>Metastasis to Lymph node</th>
<th>Invasion into Tunica serosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>P₀</td>
<td>H₀</td>
<td>N (−)</td>
<td>S₀</td>
</tr>
<tr>
<td>II</td>
<td>P₀</td>
<td>H₀</td>
<td>N₁ (+)</td>
<td>S₁</td>
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<tr>
<td>III</td>
<td>P₀</td>
<td>H₀</td>
<td>N₃ (+)</td>
<td>S₂</td>
</tr>
<tr>
<td>IV</td>
<td>more than P₁</td>
<td>more than H₁</td>
<td>N₄ (+)</td>
<td>S₃</td>
</tr>
</tbody>
</table>

Table 2. Stage of gastric cancer (histological)
The stage is decided by the degree of metastasis of tumor to the peritoneum, liver and lymph node and/or by the mode of tumor invasion into the Tunica serosa, histologically.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Metastasis to Peritoneum</th>
<th>Metastasis to Liver</th>
<th>Metastasis to Lymph node</th>
<th>Invasion into Tunica serosa</th>
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</thead>
<tbody>
<tr>
<td>I</td>
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<td>n(−)</td>
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<td>III</td>
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<td>more than P₁</td>
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<td>n₄ (+)</td>
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</tr>
</tbody>
</table>

Samples of 5 ml of blood were drawn into tubes which contained disodium ethylenediamine tetracetic acid (EDTA) as an anticoagulant.

The samples were centrifuged and frozen until the analysis was performed. CEA levels in these samples were measured using the CEA-Roche Kit (indirect method).

RESULTS

I Serum CEA levels in 47 out of 54 patients with benign diseases were less than 2.5 ng/ml and those of the other seven patients were between 2.6—5.0 ng/ml.

II Serum CEA levels in gastric cancer patients are shown in Table 3, in accordance with the stage of cancer extension. The serum CEA level of only one out of 21 "early" cancer patients was between 5.1—10.0 ng/ml while those of the other 20 patients were under 2.5 ng/ml. In Table 3, closed circles show patients with "advanced" cancer and the three patients shown in
parentheses consist of two inoperable patients without autopsy and one living patient with chemotherapy. Eight out of 13 patients with stage IV gastric cancer showed serum CEA titers of more than 10.1 ng/ml.

III Serum CEA levels, in accordance with the histological differentiation of the cancer, are shown in Table 4. Histologically, adenocarcinoma was differentiated into three groups: "papillary", "tubular" and "poorly differentiated", although they are collectively shown as "Adeno Ca" in table 4.

Only three "Adeno Ca" patients (one of 15 "Adeno Ca" patients in A, one "Adeno Ca" patient in B and one "Adeno Ca" patient in C) had "poorly differentiated" adenocarcinoma and the other 33 "Adeno Ca" patients had more than "moderately" differentiated adenocarcinoma. In Table 4, "Signet Ring" indicated patients with signet ring cell carcinoma. Six patients had "poorly differentiated" adenocarcinoma among eight patients whose serum CEA levels were more than 10.1 ng/ml, and five of these six patients had liver metastasis. In patients with stage IV cancer, all those with serum CEA titers of less than 5.0 ng/ml had signet ring cell carcinoma.

Table 3. Serum CEA levels in accordance with the stage of gastric cancer. Eight of 13 patients with stage IV gastric cancer showed a serum CEA level of more than 10.1 ng/ml.

<table>
<thead>
<tr>
<th>CEA LEVELS in SERUM (ng/ml)</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tbody>
<tr>
<td>25.1</td>
<td></td>
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<td>C</td>
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<tr>
<td>25.0</td>
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<tr>
<td>10.1</td>
<td>Adeno Ca. 5</td>
<td>Adeno Ca. 1</td>
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<tr>
<td>10.0</td>
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<tr>
<td>5.1</td>
<td>Adeno Ca. 2</td>
<td>Adeno Ca. 1</td>
<td>Adeno Ca. 1</td>
<td>Adeno Ca. 1</td>
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<td>5.0</td>
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</tr>
<tr>
<td>2.6</td>
<td>Signet Ring 2</td>
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<td></td>
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</tr>
<tr>
<td>2.5</td>
<td>Adeno Ca. 4</td>
<td>Adeno Ca. 5</td>
<td>Adeno Ca. 2</td>
<td>Adeno Ca. 2</td>
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<tr>
<td>0</td>
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</tbody>
</table>

STAGE of GASTRIC CANCER
Table 4. Serum CEA levels in accordance with differentiation of the gastric cancer cells. Serum CEA levels in patients with hepatic metastasis were higher than 10.1 ng/ml.

![Graph showing serum CEA levels in accordance with stage of gastric cancer]

DISCUSSION

Since 1965, when Gold and his colleagues reported that CEA (carcinoembryonic antigen) existed in the tissue of colorectal cancer (2), CEA has been determined in the tissue of various gastrointestinal cancers or in the serum, pleural effusion fluid, and ascites of cancer patients (4, 6, 9). Today it is considered that CEA is not a “tumor specific antigen” in human colonic carcinoma, but periodical follow-up of serum CEA titers is beneficial in examining therapeutic effectiveness after surgical treatment and/or chemotherapy (12).

There have been many reports about the serum CEA titer in gastric carcinoma patients and the results can be summarized as follows:

1) Papillary, tubular adenocarcinoma and mucinous adenocarcinoma tissue contain a larger amount of CEA than poorly differentiated adenocarcinoma.
2) The further the gastric cancer extends, the higher the serum CEA level becomes. An excessively high serum CEA level is often seen in patients with hepatic metastasis (3, 7, 11, 13).
In our examination, result II) was the same as in 2) above.

On the basis of the following three opinions: 1) carcinoma with a striated border, differentiated carcinoma, originates in epithelium of the intestinal type, and the others, undifferentiated carcinoma, in the ordinary mucosa (8); 2) CEA exists in the tissue of intestinal type gastric carcinoma, not in the tissue of gastric type gastric carcinoma (1); and 3) papillary and tubular adenocarcinoma has a tendency to metastasize to the liver, while poorly differentiated mucinous adenocarcinoma tends to lead to peritonitis carcinomatosa (10); it can be assumed that differentiated adenocarcinoma, which can produce CEA, originates in the gastric mucosa with intestinal metaplasia and has a tendency to metastasize to the liver and that undifferentiated adenocarcinoma, which can not produce much CEA, originates in the ordinal gastric mucosa and expands by infiltration but does not tend to metastasize to the liver. These assumptions, described above, agreed with our result that the difference in serum CEA titer of patients with stage IV gastric cancer was assumed to be caused by the differentiation of their cancer cells.

High serum CEA titers are frequently seen in gastric and colorectal cancer patients with hepatic metastasis. This is thought to be caused by CEA production in the increased tumor tissue, not by CEA production in the liver tissue which borders on the metastasized tumor, because of the conclusions that CEA titers were under 25 ng/ml in all patients with hepatoma (13) and that "chromatographed fractions of normal bowel and liver showed no significant optical density" in the study to detect serum CEA (5).

CONCLUSIONS

1) Serum CEA levels in all patients with benign diseases were under 5.0 ng/ml; Therefore, CEA titers under 5.0 ng/ml were thought to be "normal" in measuring serum CEA by the Roche kit.
2) High serum CEA titers were seen in patients with "advanced" gastric cancer, especially in patients with hepatic metastasis.
3) The difference in serum CEA titers of gastric cancer patients was assumed to be caused by differentiation of cancer cells or by the CEA production capacity of tumor tissue.

ACKNOWLEDGEMENT

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REFERENCES

5) Krupey J, Gold P, Freedman SO: Physicochemical studies of the carcinoembryonic
10) Sano R: Surgical Pathology of Gastric Cancer, 1st edition. Igaku Shoin (Japan) 1974, p 112—192