THE CLINICAL SIGNIFICANCE OF CARCINOEMBRYONIC ANTIGEN IN THE PLASMA AND TUMORS OF PATIENTS WITH GYNECOLOGIC MALIGNANCIES

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Carcinoembryonic antigen is elevated in the plasma of approximately 30% of patients with endometrial adenocarcinoma, 50% of patients with ovarian carcinoma, and 60% of patients with cervical carcinoma. The incidence of elevated plasma CEA is directly related to stage of disease, and in ovarian cancer to cell type. Immunodiffusion and immunoelectrophoretic studies have indicated that CEA from ovarian and cervical cancers is similar to colonic cancer CEA. Tumor staining for CEA by the immunoperoxidase method (indicating a CEA concentration of ≥3.0 μg/g tissue) is positive in about one-half of the patients with elevated plasma CEA levels. However, there is no definite relationship between tumor and plasma antigen levels. Carcinoembryonic antigen levels characteristically return to normal within 8 weeks following complete surgical removal of tumor. In contrast, antigenemia often persists up to 4 months following curative radiation therapy. A progressive rise in plasma CEA has preceded clinical diagnosis of recurrence in about half of the patients studied. Serial plasma CEA determinations in patients whose plasma or tumors initially contain elevated amounts of antigen provides information concerning the biologic behavior of malignancy which may be of clinical significance to the patient.


Since the discovery of carcinoembryonic antigen (CEA) in patients with adenocarcinoma of the colon, much effort has been directed toward elucidation of the role of this antigen in the diagnosis and management of patients with gynecologic malignancies. With the development of a rapid and sensitive radioimmunoassay for routine laboratory use by Hansen et al.,¹ increased plasma levels of CEA have been reported in patients with a variety of gynecologic tumors.¹,²,¹¹,¹²,¹⁷,¹⁹ Likewise, immunocytochemical techniques utilizing enzyme coupled–antigen–antibody reactions have demonstrated the presence of CEA in a number of gynecologic tumors.⁶,⁷ Despite these observations, there remains a continued need to define those conditions in which CEA can be useful in patient management. The purpose of this review is to summarize the present knowledge concerning carcinoembryonic antigen in patients with cervical, endometrial, and ovarian malignancies. Those tumors in which CEA has proven most useful as a biochemical marker will be emphasized. The possible future use of this antigen as a diagnostic or staging adjunct in these neoplasms will be discussed.

CHEMICAL AND IMMUNOLOGIC PROPERTIES

Column chromatographic studies⁶ have indicated that CEA in perchloric acid extracts of squamous cell carcinoma of the cervix has a molecular size range of 370,000 daltons which is significantly larger than the molecular size (200,000 daltons) of colonic CEA. This 370,000 dalton CEA may simply represent a dimer of the CEA molecule isolated from colonic cancer, since the 370,000 dalton CEA isolated from xenografted human GW-39 colonic tumors can be reduced to a size of 200,000 daltons with enzymatic degradation. On immunodiffusion against antibody to co-
greater percent of patients with gynecologic malignancy than in either healthy volunteers, or patients with benign gynecologic disease. The incidence of elevated plasma CEA has varied both with the site and stage of disease. Plasma CEA values in patients with invasive cervical cancer are presented in Table 1. CEA is increased above normal in the plasma of 40 to 80% of patients. The incidence of elevated plasma CEA varies from 45% in patients with Stage I disease to 75% in patients with Stage IV disease (Table 2). Plasma CEA is elevated in 6 to 30% of patients with intraepithelial cervical neoplasia, and is directly related to the extent of the lesion. Carcinoembryonic antigen is increased in the plasma in 35 percent of patients with endometrial adenocarcinoma (Table 3) and is directly related both to the size of the uterus and stage of disease (Table 4). Plasma CEA is elevated in 50% of patients with ovarian cancer (Table 5) but is more related to cell type than to stage of disease. Eighty percent of patients with mucinous cystadenocarcinoma of the ovary have been reported to have an elevated plasma CEA concentration, whereas less than 10% of patients with serous ovarian neoplasms have had abnormally increased plasma CEA levels.

Plasma CEA Concentration

Using the Z-gel method of Hansen, plasma carcinoembryonic antigen has been shown to be elevated (>2.5 ng/ml) in a significantly...
Histomorphologic criteria have been of limited usefulness in predicting plasma CEA concentrations. Lymphoplasmacytic infiltration of tumor cells, and tumor necrosis have been shown to be unrelated to plasma CEA expression in both cervical and endometrial cancer. However, the presence of vascular invasion by tumor cells in the specimen has been positively correlated with plasma CEA elevation. Plasma CEA concentration has, in general, been independent of histologic differentiation in cervical cancer. However, small cell carcinoma of the cervix has been reported to contain high tissue levels of CEA. In endometrial cancer, the most undifferentiated tumors have been associated with the highest plasma CEA expression. Cell type has been related to plasma CEA concentration most clearly in ovarian cancer. van Nagell et al. reported that CEA was elevated in mucinous rather than serous ovarian cystadenocarcinomas, and Marchand et al. found that CEA levels were increased specifically in those mucinous tumors with colonic type epithelium.

Plasma CEA levels have not been directly correlated to tissue CEA concentrations in patients with gynecologic malignancies. In these tumors, plasma CEA seems more related to total tumor burden (i.e., tumor CEA concentration $\times$ tumor mass) than to tumor CEA concentration alone.

**Tumor CEA Concentration**

Carcinoembryonic antigen has been reported in perchloric acid extracts of cervical, endometrial, and ovarian cancer. Measurable quantities of CEA have been present in the tumors of about one-half of the patients with elevated plasma CEA levels. Tumor CEA concentrations have varied from 0.2 to 239 $\mu$g CEA/g tissue. The highest CEA concentration noted in any gynecologic tumor has been reported in a patient with small cell carcinoma of the cervix. Goldenberg et al., using a triple-bridge indirect peroxidase-antiperoxidase method, were able to demonstrate CEA in the tissue sections from 8 of 12 patients with carcinoma of the cervix. A positive immunoperoxidase reaction was indicative of a tissue CEA concentration of at least 3.0 $\mu$g/g tissue. Antigen was localized almost exclusively in the surface of malignant squamous cells, whereas stromal components remained unstained. van Nagell et al. measured both plasma and tissue levels of CEA in 42 patients.
with endometrial cancer. Immunoperoxidase staining was positive in only 4 of these tumors, and plasma CEA levels were unrelated to tissue CEA levels. Carcinoembryonic antigen was present in highest concentration on the surface of the cells lining endometrial glands. Carcinoembryonic antigen concentrations have been measured in the cyst fluid and stroma of ovarian neoplasms. van Nagell et al.23 have reported that CEA is present in very high concentrations in the cyst fluid of ovarian cystadenocarcinomas. Mucinous tumors reportedly contained much higher levels of CEA than did serous tumors. Carcinoembryonic antigen activity as measured in the radioimmunoassay was unrelated to blood group A substances which had previously been shown to share antigenic determinants with the CEA molecule. Elevated intracytoplasmic CEA was more directly related to cell type than to stage or histologic differentiation, since cyst fluid from benign mucinous cystadenomas also contained markedly elevated levels of CEA. Immunoperoxidase staining of mucinous and serous ovarian tumors for CEA has been performed by Marchand et al.13 These investigators reported that serous tumors contained no CEA. In contrast, mucinous cystadenocarcinomas (specifically those lined by intestinal type epithelium) almost universally contained CEA. Carcinoembryonic antigen was demonstrated in the cytoplasm of neoplastic absorptive-type cells and in the glycocalyx similar to the location of CEA noted by Gold et al.4 in colonic carcinoma. These findings were interpreted to indicate that CEA was synthesized intracellularly by the tumor cell and was then transported and incorporated into the glycocalyx. The association of CEA with a specific cell type has been further emphasized by van Nagell et al.23 These authors performed immunoperoxidase CEA staining on 79 malignant epithelial ovarian tumors and were able to demonstrate CEA only in mucinous tumors.

**Effect of Therapy on Plasma CEA Levels**

The effect of surgical treatment on plasma CEA levels in patients with gynecologic malignancies was first studied by Khoo and Mackay.10 These investigators reported that plasma CEA decreased to normal levels within 4 to 8 weeks following complete surgical excision of uterine and ovarian tumors, whereas CEA levels remained elevated in patients with incomplete surgery or persistent disease. Likewise, Barrelet and Mach1 noted a progressive decline in plasma CEA to normal levels within 7 weeks following excision of endometrial, ovarian, and cervical carcinomas. The same pattern was noted by van Nagell et al.22 following conization for cervical intraepithelial neoplasia. Plasma CEA concentration returned to normal within 8 weeks after conization except in patients with residual epithelial neoplasia of the cervix.

Plasma CEA levels have not shown consistent patterns of decline during radiation therapy of gynecologic tumors. van Nagell et al.21 noted that CEA levels often rose during radiation therapy presumably due to release into the plasma of CEA on the surface of radiation damaged tumor cells. Following completion of radiation therapy, there was a decline of plasma CEA to normal values, but this decline took much longer than that following complete tumor excision. Donaldson et al.,3 for example, noted that plasma CEA levels often did not return to normal until 4 months following completion of radiation therapy for cervical cancer.

**Carcinoembryonic Antigen as an Adjunct in Predicting Tumor Recurrence**

The efficacy of serial plasma CEA determinations in predicting tumor recurrence is presently unresolved. Khoo and Mackay10 have reported that elevated plasma CEA levels preceded the clinical diagnosis of metastases from ovarian cancer by about 2 months. In contrast, Samaan et al.18 noted that there was a good correlation between the plasma CEA level and the clinical course of ovarian epithelial cancer in only 3 of 20 patients fol-

### Table 5. Plasma CEA Values in Patients with Ovarian Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Plasma CEA ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo Gerfo (1971)</td>
<td>10</td>
<td>&lt;2.5: 6, 2.5-10: 2, ≥10: 2</td>
</tr>
<tr>
<td>Reynoso (1972)</td>
<td>5</td>
<td>&lt;2.5: 4, 2.5-10: 1*</td>
</tr>
<tr>
<td>Barrelet (1975)</td>
<td>14</td>
<td>&lt;2.5: 9, 2.5-10: 5, ≥10: 2</td>
</tr>
<tr>
<td>DiSaia (1975)</td>
<td>41</td>
<td>&lt;2.5: 23, 2.5-10: 18*</td>
</tr>
<tr>
<td>van Nagell (1975)</td>
<td>11</td>
<td>&lt;2.5: 1, 2.5-10: 10, ≥10: 0</td>
</tr>
<tr>
<td>Samaan (1976)</td>
<td>65</td>
<td>&lt;2.5: 31, 2.5-10: 29, ≥10: 5</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>146</td>
<td>&lt;2.5: 75, 2.5-10: 63, ≥10: 9</td>
</tr>
</tbody>
</table>

* These authors divided CEA values only into those <2.5 ng/ml and those ≥2.5 ng/ml.
allowed for a minimum of two years after therapy. In a study of 76 patients with invasive cervical cancer, Donaldson et al.\(^3\) reported that a progressive elevation of plasma CEA preceded the clinical diagnosis of recurrence by 1 to 4 months in over 70 percent of the cases. Likewise, van Nagell et al.\(^{21}\) noted that a persistently abnormal plasma CEA concentration following therapy for endometrial cancer was associated with tumor persistence or recurrence in over 80% of the cases.

**DISCUSSION**

Currently available data support the limited usefulness of plasma CEA as a diagnostic test in patients with gynecologic malignancy. Although the incidence of elevated plasma CEA is significantly higher in patients with gynecologic malignancies than that in normal patients or patients with benign gynecologic disease,\(^{19}\) the lack of tumor specificity of this antigen limits its diagnostic efficacy. Plasma antigenic expression is related to stage of disease and to the presence of vascular invasion by tumor cells, but is not uniformly correlated with tumor CEA concentration. Plasma CEA is generally highest in undifferentiated lesions of the cervix and endometrium, and in well differentiated mucinous tumors of the ovary. Several investigators have emphasized the importance of hepatic function relative to CEA metabolism and plasma antigen levels, but no such studies have been reported in patients with gynecologic malignancy.

Serial CEA determinations following therapy seem to be of value in predicting tumor response in certain gynecologic malignancies. Elevation of plasma CEA following the apparent surgical removal of a tumor has been associated with occult tumor persistence or recurrence in a high percent of reported cases. These follow-up CEA determinations are most indicated in patients whose tumors or plasma contain high amounts of CEA prior to therapy. Like many other biochemical tests, a single plasma CEA determination is of limited value. However, serial CEA determinations, when interpreted in relation to clinical findings, may be useful in providing information of prognostic significance to the patient.

Perhaps, the most specific use of CEA in gynecologic malignancy will be in the diagnosis and management of patients with mucinous tumors of the ovary. These tumors contain extremely high concentrations of CEA both in cyst fluid and in epithelial cells.\(^{15,20}\) One of the major problems in ovarian epithelial tumors is assessing the extent of spread of the disease. Goldenberg et al.\(^7\) have reported that primary tumors and metastases from the same patient have similar CEA staining properties. When the primary gynecologic tumor contained CEA, metastases were likewise positive for CEA content in over 90% of the cases studied. Therefore, if a mucinous cystadenocarcinoma of the ovary is noted to contain CEA, it is quite possible that CEA would be a useful biochemical marker to determine the presence of occult metastases or recurrence. Based on experimental animal models,\(^5,15\) these findings are also pertinent to the possible use of radiiodinated antibody against CEA for tumor localization. Recently, Primus et al.\(^{15}\) have reported effective localization of GW-39 human tumors in hamsters by affinity-purified antibody to carcinoembryonic antigen. The potential use of photoscan imaging using anti-CEA IgG as a diagnostic method for ovarian tumors is evident.

**REFERENCES**

8. Goldenberg, D. M.: Oncotel and other tumor-as-


