Carcinoembryonic Antigen in Patients with Cervical Carcinoma

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The determination of carcinoembryonic antigen (CEA) in serum has been of much interest currently concomitant with the search for an immunologic diagnosis test. In this study, serum CEA values from 68 patients with histologically proved cervical carcinoma were determined by radioimmunoassay before or/and at two intervals after radiotherapy. Fourteen patients of 68 had CEA values over 10 ng per milliliter before treatment. The incidence of positive CEA values was higher in the advanced stages of disease. Three patients of five with CEA levels greater than 10 ng per milliliter before treatment showed a drop of CEA levels to below 10 ng per milliliter seven weeks after treatment whereas two patients showed no change in CEA values at the end of radiotherapy. Two patients with palliative therapy showed no change in CEA values. The CEA test seems to be of little value for the early diagnosis and the evaluation of therapy in patients with cervical carcinoma but appears to be interesting for the surveillance of patients who have shown a drop of CEA level after therapy.

Carcinoembryonic antigen (CEA) is a tumor-associated antigen found by Gold and Freedman in 1965 within the tissue extracts from adenocarcinoma of the colon and in fetal colonic mucosa but absent in extracts of normal adult colon. Subsequent studies by Gold and Freedman (1965) showed CEA to be present in other malignant tumors of the gastrointestinal tract.

Moore and associates (1971) have similarly reported on the high incidence of elevated CEA values in patients with gastrointestinal malignancies. Purification, chemical characterization and localization of the antigen to the cell surface of the gastrointestinal epithelium were reported (Gold et al., 1968). A radioimmunoassay for plasma CEA determination was developed by Thomson and associates (1969).

The specificity of this antigen to malignancies of the digestive tract exclusively has come under considerable question in the past several years. Reynoso and associates (1972) have reported positive CEA values in patients with different cancers. A significant number of patients with squamous-cell carcinoma of the cervix and vulva were found to have elevated plasma levels of CEA (DiSaia et al., 1975). Other reports (Kupchik and Zamcheck, 1972; Moore et al., 1972) have established that positive CEA values are found in approximately 50% of patients with alcoholic liver disease.
addition, Rule and associates (1972) showed that 33% of patients studied with inflammatory bowel disease also had positive plasma CEA values.

Thus, it is now evident that CEA or a substance that has an immunologic reaction similar to that of CEA is found in a variety of tumor tissues as well as in the blood of a number of these patients. Moreover, small amounts of CEA can be found in normal tissue (Dyce et al., 1974).

The purpose of this study is to determine the incidence of positive CEA in cervical carcinoma and the usefulness of CEA test in the follow-up of cervical carcinoma after radiotherapy.

MATERIALS AND METHODS

The patients were seen first in the gynecology department, where they were histologically confirmed for primary tumor and sent subsequently to the Radiation Therapy Clinic at Yonsei Cancer Center for radiotherapy. Sixty-two patients with primary invasive carcinoma of the cervix ranging from stage I through stage IV were included in this study. Six additional patients with carcinoma in situ of the cervix were also included. Treatment was given according to the type of disease, its extent and general condition of the patient. A serum sample for CEA determination was obtained from each patient before treatment and/or during the early treatment period (2 weeks) and at the end of treatment (7 weeks). Serum samples collected were stored in a deep freezer (Kelvinator, series 500, U.S.A.) until used.

Serum CEA values were determined with the radioimmunoassay kit developed by CEA Co. (France). Four main steps were involved in the assay procedure. Serum, without extraction and dialysis, was preincubated with antibody to CEA for 24 hours at 20–25°C and subsequently antigen labeled with ^125I was added to the mixture and incubated for 24 hours. Free and bound CEA were separated by means of a second antibody fixed on cellulose (immunosorbent) which required 4 hours incubation with stirring at room temperature. The solid phase corresponding to the bound fraction was then centrifuged and washed. The radioactivity was measured with a well type γ-counter (Nuclear Chicago, U.S.A.) In the absence of an international standard, there is no reference value. Therefore the results obtained with the standard used in this study may differ from results obtained with other standards. In this study a positive CEA value was considered as being greater than 10 ng of CEA per milliliter.

RESULTS

Individual CEA values observed before treatment in the 68 patients with carcinoma of the cervix are presented in Table 1. The cases are separated according to the degree of spreading, with the use of the classification of the International Federation of Gynecology and Obstet-

<table>
<thead>
<tr>
<th>Table 1. Carcinoma of Cervix</th>
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<tbody>
<tr>
<td>No. of patient</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Invasive</td>
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<tr>
<td>Stage I</td>
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<td>Stage II</td>
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<tr>
<td>Stage III</td>
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<tr>
<td>Stage IV</td>
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<tr>
<td>Total</td>
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Carcinoembryonic Antigen in Patients with Cervical Carcinoma

<table>
<thead>
<tr>
<th>Cervical carcinoma</th>
<th>Ca in situ</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (ng/mL)</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>500</td>
</tr>
</tbody>
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Table 2. Individual values of serum CEA (nanogram per milliliter) obtained before treatment in all patients with carcinoma of cervix.

Among the 68 patients studied, 14 (20.1%) had elevated CEA levels over 10 ng per ml and 54 (79.9%) had levels below 10 ng per ml (Table 1, 2).

Six patients with carcinoma in situ of the cervix were found to have a negative CEA value (Table 1, 2). The distribution of positive CEA values in the 62 patients with invasive carcinoma of the cervix was such that the incidence of positive CEA values appeared to increase as the stage advanced. The percentage of patients with positive values was increased from 11.1% in stage I to 33.3% in stage II. Only one patient who was in stage IV was evaluated and noted to have a negative CEA. Since the number of patient was only one, no correlation concerning disease process can be made.

CEA levels were additionally determined at two and seven weeks after the starting of the radiotherapy in seven patients with CEA values over 10 ng per milliliter before treatment. Seven patients were divided into two groups according to the type of treatment. Group I consisted of 5 patients, who had an invasive squamous cell carcinoma (three stage II and two stage III) and had radical radiotherapy. Three patients who had high initial levels of CEA showed levels under 10 ng per ml at the end of treatment whereas two others showed no decrease in CEA levels (Fig. 1). At the present time, no correlation between evolution of CEA levels and clinical status can be drawn. Group 2 consisted of 2 patients with advanced dissemination of cancer. Two patients with stage II and stage III cervical carcinoma (one invasive epidermoid Ca and one squamous Ca) underwent palliative radiotherapy. Fig. 2 shows that in these patients no significant changes in CEA levels were observed at the end of therapy.

DISCUSSION

The incidence of over-all cervical carcinoma with CEA positive values reported here is lower than that observed in the previous studies (Barrelet and Mach, 1975: DiSaia, et al., 1975). About 20% of the 68 patients in the present study had CEA values over the arbitrary positive limit of 10 ng per ml while others reported as positive more than 50% of the patients with cervical carcinoma. If one takes into account that most patients with cervical carcinoma had relatively low CEA values when already clinically symptomatic and that several nonmalignant conditions and even heavy smoking can give rise to elevated CEA.
values, one should conclude that the CEA test is of little use for the early diagnosis of gynecologic carcinoma. It certainly should not be considered as a screening test for this type of cancer. The previous findings also suggest that negative tests may be obtained in subjects with early cancerous lesions, while positive tests do not always indicate the presence of malignant growth (Shuster et al., 1974; Fuks et al., 1975; Gold et al., 1975). Gold et al. (1973) reported 81 patients with nonspecific gastrointestinal complaints and positive CEA assays, but no evidence of digestive system cancer by the usual diagnostic procedures. Of these 37 were later found, during a surveillance period of two years in which repeated radiologic and endoscopic investigations were performed, to have gastrointestinal cancers. Thus CEA determinations of selected groups of individuals may be of predictive diagnostic value.

The patients with more advanced disease appear to have higher CEA values (Table 2) and higher incidence of positive CEA (Table 1, 2). The changes in CEA levels during the course of radiotherapy are not clear. Three patients of 5 showed a drop to below 10 ng per ml. The persistence of an elevated CEA even after a good clinical response to radiotherapy, already observed by Khoo and Mackay (1975), is difficult to explain. It might be due to a residual nonproliferating tumor or to the release of CEA by cancer cells undergoing postactinic necrosis. These patients could be followed for a longer period of time to determine whether the CEA level will drop progressively with the slow destruction of the tumor or if persistant elevated CEA indicates the presence of residual tumoral tissue which
might subsequently cause a relapse of the disease. At the present time, it might be fair to say that application of the CEA assay for cervical carcinoma is only for the surveillance of patients who have shown a drop of CEA levels after therapy.

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