Carcinoembryonic antigen in patients with intracranial tumors

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Carcinoembryonic antigen (CEA) in plasma, cerebrospinal fluid (CSF), and tumor cyst fluid obtained from patients with a variety of intracranial tumors was determined by radioimmunoassay. Slightly elevated levels of plasma CEA, ranging from 2.6 to 3.8 ng/ml, were noted in six (4%) of 161 patients with primary brain tumors: in three gliomas, two pineal tumors, and one acoustic neurinoma, respectively. On the other hand, 17 (37%) of 46 patients with metastatic brain tumors showed a definite elevation, and most of them had values higher than 5.0 ng/ml. Of 37 patients with primary brain tumors, only one with a pineal germinoma showed a significant elevation of CEA in CSF, whereas eight (44%) of 18 patients with metastatic brain tumors showed high values of CEA in CSF. All six patients with leptomeningeal carcinomatosis showed elevated CEA in CSF. Levels of CEA in tumor cyst fluid were determined in 17 patients with intracranial tumors, including 12 gliomas, two craniopharyngiomas, two metastatic tumors, and one meningioma; elevation of CEA in tumor fluid was noted in two craniopharyngiomas and one metastatic tumor. Sequential determination of CEA in plasma or CSF revealed that the CEA levels were well correlated with the activity of brain tumors. Consequently, the determination of CEA in plasma or CSF is valuable for the differential diagnosis between primary and metastatic brain tumors and for the management of CEA-producing tumors.

Key Words • carcinoembryonic antigen • intracranial tumor • metastatic brain tumor • leptomeningeal carcinomatosis

Since the first report of Gold and Freedman in 1965 describing carcinoembryonic antigen (CEA) extracted from colonic carcinoma as a tumor-specific antigen, numerous investigators have shown that a marked elevation of plasma CEA levels can be recorded in patients with various other types of cancer, and that a moderate increase of plasma CEA levels can also be observed in several noncancerous conditions or in apparently healthy subjects. In spite of the lack of tumor and organ specificity, CEA assay has been found useful in the management of cancer, including evaluation of treatment or detection of recurrence, as well as in screening for cancer. However, the clinical significance of CEA assay in patients with intracranial tumors has not been established, although several reports have described CEA values in a limited number of patients with intracranial tumors.

The purpose of the present paper is to evaluate the usefulness of CEA assays in plasma, cerebrospinal fluid (CSF), and tumor cyst fluid that were performed in a large number of patients with a variety of intracranial tumors.

Clinical Material and Methods

Clinical Material

A total of 285 patients were included in this study. The patients tested for CEA are shown in Table 1. Plasma CEA was determined in 253 patients with 388 assays, including 161 cases of primary brain tumor, 46 of metastatic brain tumor, and 46 of non-neoplastic disease. The 67 gliomas included 36 anaplastic gliomas, 26 astrocytomas, two oligodendrogliomas, two medulloblastomas, and one ependymoma. The 12 pineal tumors included eight germinomas, one teratoma, one embryonal carcinoma, one teratoblastoma, and one tumor histologically not verified. The six miscellaneous tumors included two hemangioblastomas, one epidermoid tumor, one choroid plexus papilloma, one reticulum cell sarcoma,
TABLE 1

Patients tested for carcinoembryonic antigen

<table>
<thead>
<tr>
<th>Disease</th>
<th>Plasma</th>
<th>CSF*</th>
<th>Cystic Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary brain tumor</td>
<td>161</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>glioma</td>
<td>67</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>pituitary adenoma</td>
<td>30</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>meningoima</td>
<td>28</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>acoustic neurinoma</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>pineal tumor</td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>craniopharyngioma</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>other</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>metastatic brain tumor</td>
<td>46</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>control</td>
<td>46</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>cerebral aneurysm</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>intracerebral hematoma</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>total cases</td>
<td>253</td>
<td>93</td>
<td>17</td>
</tr>
</tbody>
</table>

*CSF = cerebrospinal fluid.

Levels of CEA in CSF were determined with 136 assays in 93 patients, including 37 patients with primary brain tumor, 18 with metastatic brain tumor, and 38 with non-neoplastic disease. The 19 gliomas included 15 anaplastic gliomas, one astrocytoma, two medulloblastomas, and one ependymoma. The 10 pineal tumors included eight germinomas, one embryonal carcinoma, and one tumor histologically not verified. The three miscellaneous tumors included two hemangioblastomas and one choroid plexus papilloma.

Levels of CEA in tumor cyst fluid were determined in 17 cases, including 12 cases of glioma, one of meningoima, two of craniopharyngioma, and two of metastatic brain tumor. Cyst fluid was obtained at operation in 13 patients, or sampled through a silicone tube placed in the cavity resulting from the partial extirpation of tumor in four glioma patients.

Method of Assay

Samples were centrifuged at 3000 rpm for 5 minutes, and the supernatants were stored frozen at -20°C until use. Radioimmunoassay for CEA was performed by a one-step sandwich method* using a Dainabot CEA Kit. A small number of samples were assayed by Z-gel method using a Roche CEA Kit.†

*Dainabot CEA Kit manufactured by Dainabot Radioisotope Laboratory, Tokyo, Japan.
†Roche CEA Kit manufactured by Nippon Roche, Ltd., Tokyo, Japan.

Results

Carcinoembryonic Antigen in Plasma

The plasma CEA levels of normal subjects have been reported to be less than 2.5 ng/ml in the assay by the one-step sandwich method using the Dainabot CEA Kit, and less than 5.0 ng/ml in that by the Roche CEA Kit. Since the values in the assay by Dainabot Kit are about half of those in the assay by Roche Kit,* the values obtained by the Roche Kit in this study were halved to correspond to the Dainabot Kit values. Plasma CEA levels in 253 patients with or without intracranial tumors are plotted in Fig. 1.

Slightly elevated levels of plasma CEA were observed in six (4%) of 161 patients with primary brain tumors: in three (4%) of 67 gliomas, in one of 12 acoustic neurinomas, in one embryonal carcinoma, and one tumor histologically not verified. The three miscellaneous tumors included two hemangioblastomas and one choroid plexus papilloma.

On the other hand, 17 (37%) of 46 patients with metastatic brain tumors showed a definite elevation of plasma CEA level. The CEA values of the 17 patients were between 2.6 and 5.0 ng/ml in five patients, between 5.1 and 10.0 ng/ml in six, and more than 10.1 ng/ml in six (Fig. 1). The primary sites of the 17 positive patients were the lung in nine patients, the breast in one, the stomach in one, the maxillary sinus in one, the pancreas in one, the gall bladder in one, the colon in one, and unknown sites in two (Table 2).

Adenocarcinoma was the most frequent histological finding related to positive plasma CEA values; in total, seven of nine adenocarcinomas were positive. Seven among the 17 patients in whom the primary sites had not been confirmed at the time of admission were confirmed as adenocarcinomas at the time of surgery.

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![Table showing plasma carcinoembryonic antigen levels in 207 intracranial tumor patients and 46 control patients.](image)

**Fig. 1.** Plasma carcinoembryonic antigen levels in 207 intracranial tumor patients and 46 control patients.

showed elevated plasma CEA levels. In a group of control subjects, one patient with polynейritis had a CEA value of 2.6 ng/ml, and one with cerebral aneurysm, 3.1 ng/ml.

**Carcinoembryonic Antigen in Cerebrospinal Fluid**

No normal values of CEA in CSF have been described. In the present study, all of the 38 patients with non-neoplastic diseases showed CEA levels in CSF of less than 0.5 ng/ml in the assay by the one-step sandwich method using the Dainabot Kit, and the values of 34 of the 38 patients were 0 ng/ml. Therefore, an upper limit of normal CSF CEA levels by the one-step sandwich method has been proposed to be 0.5 ng/ml.

The results of CEA assay in CSF are shown in Fig. 2. Of the 37 patients with primary brain tumors, only one with pineal germinoma showing a spinal metastasis revealed a significant elevation of CEA level in CSF (16.0 ng/ml). In contrast to primary brain tumors, eight (44%) of 18 metastatic brain tumors presented high levels of CEA in CSF.

The clinical summary of the nine positive patients is shown in Table 3. Among the eight metastatic brain tumors with elevated CEA levels in CSF, six were leptomeningeal carcinomatosis and two were parenchymal metastasis. All six cases of leptomeningeal carcinomatosis assayed for CEA in CSF in this study showed elevated CEA levels. In this study, CSF cytology was performed in 12 patients with...
metastatic brain tumors. All five patients with positive tumor cells (Cases 1, 3, 4, 5, and 6; Table 3) showed positive CEA levels in CSF, and two of seven patients with negative tumor cells (Cases 2 and 8) were also positive in CSF CEA (Table 3). No significant correlation was noted between CSF CEA levels and other constituents of CSF. Three of nine patients with high CSF CEA levels (Cases 3, 7, and 9) showed normal plasma CEA levels, and the CSF CEA levels in another four patients (Cases 4, 5, 6, and 8) were higher than their plasma CEA level.

Carcinoembryonic Antigen in Tumor Cyst Fluid

The CEA levels in the tumor fluid of 12 glioma patients ranged from 0.4 to 2.5 ng/ml, with a mean value of 0.6 ± 0.6 ng/ml. A significant elevation was noted in two patients with craniopharyngioma (8.6 and 11.0 ng/ml, respectively), and in one with metastatic brain tumor from breast carcinoma (7150 ng/ml). One meningioma and one metastatic brain tumor showed values of less than 0.5 ng/ml.

Serial Carcinoembryonic Antigen Assays

Levels of CEA were determined repeatedly in some patients during or after treatment of their tumors. The results of serial CEA determinations in plasma or CSF revealed that CEA could be a useful parameter for the evaluation of treatment or detection of recurrences of CEA-producing tumors.

The following are representative patients in whom the CEA levels seemed to be well correlated with the tumor activity. Figure 3 shows serial CEA levels of a patient with brain metastasis of a small-cell carcinoma of the lung. The patient was admitted for the treatment of a huge metastatic tumor in the right parieto-occipital region. Before treatment, CEA levels in plasma and CSF were 3.0 and 36.0 ng/ml, respec-
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tively. After chemoradiotherapy, the brain tumor completely disappeared and the CEA level in CSF dropped to 0.6 ng/ml. Although the CEA level in CSF has remained normal for 4 months, the plasma CEA level is still above 2.5 ng/ml, and the patient has been receiving chemotherapy.

Figure 4 shows serial CEA levels of a patient with pineal germinoma. The patient began to complain of paraplegia and sensory impairments of the legs about 4 months after the complete remission of a pineal germinoma by initial treatments. The myelography and cytology of the CSF demonstrated spinal and leptomeningeal dissemination of the germinoma. At readmission, the CEA levels in plasma and CSF were 0.1 ng/ml and 16.0 ng/ml, respectively. After irradiation to the whole spinal axis and brain, combined with chemotherapy, the CEA levels in CSF decreased to 8.0 ng/ml, and finally to 0.1 ng/ml, and the patient has recovered well.

Discussion

Although several investigators have determined CEA levels in plasma \(^5\) or CSF \(^\) of a limited number of patients with intracranial tumors, the clinical significance of CEA determination has not been sufficiently demonstrated. The present study clearly shows that determination of CEA in plasma and CSF is very useful for the differential diagnosis between primary and metastatic brain tumors, and that CEA might be a useful parameter for the management of CEA-producing intracranial tumors.

The incidence of positive plasma CEA findings was 3% (four of 149 patients with primary brain tumors), excluding germ-cell tumors in the pineal region. This incidence was similar to that in the control group. The CEA levels of these positive cases never exceeded 5.0 ng/ml, being less than 3.8 ng/ml at most, and returned to normal values in the follow-up assays. On the other hand, 17 (37%) of 46 patients with metastatic brain tumors showed elevated plasma CEA levels, and 12 (71%) of these 17 positive cases had levels higher than 5.0 ng/ml. Similar results have been reported by Kido, et al., \(^5\) who reported that an elevation of plasma CEA levels was noted in seven (58%) of 12 metastatic brain tumors in their series, whereas all 28 primary brain tumors showed normal levels. Consequently, determination of plasma CEA levels is valuable in the differential diagnosis between primary and metastatic brain tumors, although it does not have a diagnostic value in primary brain tumors.

A high concentration of CEA in CSF can be expected when CEA-producing tumor cells are directly in contact with CSF, as in other body fluids such as urine, \(^9\) gastric juices, \(^1\) feces, \(^1\) pleural effusion, or ascites \(^7\) of patients with cancers of other organs. However, the clinical significance of the determination of CEA in CSF has been investigated less than that in plasma. \(^5\) There have been no previous reports describing normal values of CEA in CSF. Since the CEA levels in CSF of 38 patients with non-neoplastic diseases were less than 0.5 ng/ml, and most were 0 ng/ml, an upper limit of normal CEA values in CSF using the Dainabot Kit is suggested as 0.5 ng/ml. By this criterion, of 37 primary brain tumors, only one pineal germinoma showed an elevation of CEA levels in CSF, and eight (44%) of 18 metastatic brain tumors presented significantly high levels, ranging from 1.7 to 36.0 ng/ml. Therefore, the determination of CEA in CSF has a diagnostic value, again, for metastatic brain tumors.

It is worth mentioning that six of the eight metastatic brain tumors with high values of CEA in CSF were in patients with leptomeningeal carcinomatosis, and that the six represented 100% of the cases of meningeal carcinomatosis in this study. However, leptomeningeal dissemination of tumor not producing CEA does not seem to be the cause of elevation of CEA in CSF, since two medulloblastomas with leptomeningeal dissemination showed normal values of CEA in CSF in this study. The diagnosis of leptomeningeal carcinomatosis is difficult when the cytology of CSF results is negative. \(^8\) The present study revealed that the determination of CEA in CSF is more sensitive and more quantitative than CSF cytology in the diagnosis of leptomeningeal carcinomatosis.

The CEA levels in the fluids obtained from the cyst of gliomas never exceeded those in normal plasma. This finding suggests that gliomas, benign or malignant, are not CEA-producing tumors. The tumor fluid obtained from two craniopharyngiomas that had en-
dodermal origin showed a definitely high value of CEA. Thus, the determination of CEA in tumor fluids of craniopharyngiomas can be a postoperative confirmative diagnosis of this tumor, and can be useful in the management of this tumor, including evaluation of treatment or follow-up studies.

In conclusion, the frequency of metastatic brain tumors has been increasing in recent years because of the improvement of prognosis in patients with cancers of other organs, and because of employment of computerized tomography in the diagnosis of intracranial tumors. However, the differential diagnosis between primary brain tumors, especially malignant gliomas, and metastatic brain tumors is often very difficult. For the purpose of this differential diagnosis, determination of CEA in both plasma and CSF might be of great value. Furthermore, as shown in the serial study of CEA, CEA levels could be a useful parameter for the management of CEA-producing intracranial tumors, such as metastatic tumors, craniopharyngiomas, or germ-cell tumors.

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References


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