Localization of carcinoembryonic antigen in mature intracranial teratomas

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Carcinoembryonic antigen (CEA) in serum and cerebrospinal fluid (CSF) was measured in four patients with intracranial teratoma. The CEA levels were elevated in the CSF of two patients, but were within normal limits in the serum of all four. After surgical removal of the teratomas, which were verified as mature teratomas, CEA was localized by an immunohistochemical method. Positive reactions both to anti-CEA serum and to another anti-CEA serum absorbed with nonspecific cross-reacting antigen were seen in glandular structures, with or without goblet cells, and in some portions of stratified squamous epithelium. It is concluded that CEA, detected in CSF, may originate in mature teratomas, and CEA-positive structures (especially glandular) may differentiate into gastrointestinal tract structures. An examination of serum and CSF levels of CEA may offer additional clues to the diagnosis of intracranial germ-cell tumors.

KEY WORDS • intracranial teratoma • carcinoembryonic antigen • tumor marker

ALPHA-FETOPROTEIN (AFP) and human chorionic gonadotropin (HCG) are well known biochemical markers of intracranial germ-cell tumors. Carcinoembryonic antigen (CEA) has also been measured, and is frequently elevated in patients with malignant intracranial tumors, but its correlation with the histopathology of intracranial germ-cell tumors has not been clarified.

Mature teratomas contain endodermal tissues, which may exhibit a gut-like differentiation and produce CEA. If this is true, CEA may be a useful tumor marker, like AFP and HCG. Therefore, the localization of CEA may provide a clue to the histogenesis and differentiation of intracranial germ-cell tumors. We have identified the tissue localization of CEA in four cases of mature pineal teratomas using immunohistochemical technique. In two of these cases, high cerebrospinal fluid (CSF) levels of CEA were observed.

Clinical Material and Methods

Four cases of mature teratomas surgically removed from the pineal region were included in this study. The clinical features of the four cases are summarized in Table 1. Serum and CSF levels of AFP, HCG, and CEA were measured in all cases.

Surgical specimens were fixed in 10% formalin and embedded in paraffin. Several sections were cut in areas pathologically diagnosed as mature teratomas, and stained with hematoxylin and eosin. These sections were examined immunohistochemically by a peroxidase-antiperoxidase (PAP) method. Sections were de-waxed and treated with 3% hydrogen peroxide to block the endogenous peroxidase activity. The sections were then washed in phosphate-buffered saline (PBS) with a pH of 7.4, and treated with normal swine serum for 50 minutes. Sections were again washed with PBS, and then incubated overnight at 4°C with rabbit anti-CEA serum (dilution 1/200) and with another anti-CEA serum absorbed with nonspecific cross-reacting antigen (dilution 1/200). The sections were rinsed in PBS and incubated with swine anti-rabbit immunoglobulin G for 20 minutes. After washing with PBS, the sections were incubated with PAP complex for 20 minutes. After a further washing, the enzyme reaction was developed with DAB-hydrogen peroxide solution (20 mg of 3,3’-diaminobenzidine-4HCl in 100 ml of 0.05 M Tris-HCl buffer, pH 7.6, containing 0.005% hydrogen per-
TABLE 1

Clinical features of four cases of pineal teratoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Symptoms &amp; Signs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>M</td>
<td>headache, nausea, vomiting, upward gaze palsy</td>
<td>irradiation: 5200 rads. total removal</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>M</td>
<td>gait &amp; speech disturbance, upward gaze palsy</td>
<td>total removal</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>M</td>
<td>diplopia, rt hemiweakness, upward gaze palsy</td>
<td>total removal</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>M</td>
<td>headache, diplopia, disturbance of consciousness, upward gaze palsy</td>
<td>total removal; 2 yrs later, recurrence in 4th ventricle was totally removed</td>
</tr>
</tbody>
</table>

Results

In the four cases with mature teratoma, the AFP values in serum and CSF did not exceed 1.0 ng/ml, and the HCG concentrations were no higher than 6.6 mIU/ml. Serum levels of CEA were within normal limits, but CSF levels of CEA were elevated in two patients before tumor removal and decreased to within normal limits in one of the two after the operation (Table 2). In the other case, CEA was not measured postoperatively. (The normal range of the serum CEA level is less than 2.5 ng/ml, measured by the one-step "sandwich" method, and that of the CSF level is less than 0.5 ng/ml.

Histological examination revealed mature teratomas with three germinal elements in all cases. In Case 1, cell clusters with atypia were seen in a few areas. In all cases, immunohistochemical examination showed positive reactions both to the rabbit anti-CEA serum and to another anti-CEA serum absorbed with nonspecific cross-reacting antigen. In Case 1, reaction products were seen in the luminal surface and in the cytoplasm of the cylindrical cells, which formed a lumen (Fig. 1A). Tumor cells with atypia were negative for CEA, AFP, and HCG. In Case 2, some portions of stratified squamous cells and a layer of cuboidal cells (which formed a small lumen) showed positive reactions. In Case 3, positive reactions were obtained in stratified squamous epithelium (Fig. 1C). The distribution of reaction products was different in some portions: squamous cells were diffusely stained, and in another area staining in the cytoplasm was scattered. In Case 4, staining revealed a luminal surface of the cylindrical epithelium with goblet cells, cytoplasm near the lumen, and its exudate in the lumen (Fig. 1D). Stratified squamous epithelium was also stained in some areas.

In summary, positive reactions to anti-CEA serum were seen in the cytoplasm and/or luminal surface of cylindrical epithelial cells, which formed glandular structures with or without goblet cells, and in some portions of the stratified squamous epithelium. Positive reactions to anti-CEA serum absorbed with nonspecific cross-reacting antigen were observed in the same portions of the tissue as with anti-CEA serum, and the intensity of the reactions was almost the same as with anti-CEA serum.

Discussion

The presence of a tumor marker in mature teratomas has not been reported previously, although some authors have stated that CEA, as well as AFP and HCG, should be measured in patients with intracranial germ-cell tumors. The present study suggests that the CEA detected in CSF might have originated in mature teratomas. Positive reactions to anti-CEA serum absorbed with nonspecific cross-reacting antigen were observed in our study. Several CEA-related antigens are known (Table 3). This suggests, therefore, that CEA or CEA-related antigens other than nonspecific cross-reacting antigens may be produced in mature teratomas, and a high CSF level of CEA may be obtained when those biochemical markers exude into the CSF.
FIG. 1. Immunohistochemical studies of tumor sections prepared with hematoxylin counterstain. A: Case 1. A positive reaction to anti-carcinoembryonic antigen (CEA) serum is visible in a layer of cylindrical cells. $\times 140$. B: Case 1. Negative-staining control section adjacent to A. $\times 140$. C: Case 3. A positive reaction to anti-CEA serum is shown in stratified squamous epithelium. $\times 70$. D: Case 4. A luminal surface of cylindrical epithelium with goblet cells and its exudate are stained, using anti-CEA serum. $\times 70$. E: Positive-staining control specimen of an adenocarcinoma of the colon. $\times 70$.

In 1965, CEA was demonstrated in extracts of colon cancers.\(^5\) In addition, CEA appeared to be present in gastrointestinal,\(^6\) lung,\(^7\) breast,\(^8\) and gynecological cancers\(^9\) and in normal human colon mucosa.\(^10\) Recently, the presence of CEA-related antigens has been demonstrated in normal organs, such as the lungs, spleen, liver, and stomach.\(^11\) Mature teratoma appears to contain precursor elements which may differentiate into lung, spleen, liver, and stomach, and these structures may react to non-absorbed anti-CEA serum. Although cross-reactions cannot be completely excluded by using anti-CEA serum absorbed with nonspecific cross-reacting antibodies, our results suggest that CEA-positive structures (especially glandular) may differentiate into gastrointestinal tract structures. We have also reported a case of intracranial endodermal sinus tumor with immature teratoid differentiation in which CEA was demonstrated in a gland-like structure, which was considered to be representative of gut-like differentiation.\(^12\) Stratified squamous cells were stained in some areas, but whether these elements exhibit an endodermal differentiation or not remains to be resolved.

Both AFP and HCG are known as biochemical markers of intracranial germ-cell tumors; they have been demonstrated in endodermal sinus tumors and choriocarcinomas, respectively.\(^2,8\) Suzuki\(^16\) suggested that CEA positivity of serum and CSF may be more frequent in pineal tumors (two of 12 patients) than in...
other brain tumors. High CSF levels of CEA were obtained in a case of intracranial endodermal sinus tumor. Serum levels of CEA may be elevated in cases of testicular teratomas with malignant transformation or gut-like differentiation. In cases of mature intracranial teratomas, it is postulated that CSF levels of CEA may be elevated or within normal limits, and serum levels of CEA may be within the normal range in nearly all cases. Negative AFP and high CEA levels in the CSF of a patient with suspicion of intracranial germ-cell tumor indicate that the tumor may be a mature teratoma with or without malignant transformation. Conversely, CSF positivity for both antigens would be suggestive of an endodermal sinus tumor which contains an element with mature or immature teratoid differentiation, as in our previously reported case. A cystic teratoma can be easily diagnosed by computerized tomography, but a solid teratoma may be difficult to differentiate from other tumors which do not produce biochemical markers. An examination of serum and CSF levels of CEA may be a diagnostic key to intracranial germ-cell tumors.

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