Intracranial growing teratoma syndrome mimicking tumor relapse: a diagnostic dilemma

Clinical article

Doo-Sik Kong, M.D., Ph.D., Do-Hyun Nam, M.D., Ph.D., Jung-il Lee, M.D., Ph.D., Kwan Park, M.D., Ph.D., Jong Hyun Kim, M.D., Ph.D., and Hyung Jin Shin, M.D., Ph.D.

Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University, School of Medicine, Seoul, Korea

Object. It is important to differentiate growing teratoma syndrome (GTS) from tumor recurrence in the setting of an enlarging residual mass present after treatment of intracranial germ cell tumors (GCTs). The aim of this study was to determine the incidence of intracranial GTS and present its clinical manifestations in detail.

Methods. The authors performed a retrospective cohort study of 52 consecutive patients with newly diagnosed intracranial GCTs who presented between January 2000 and December 2006. The records were screened to identify a study cohort in which all patients had regrowing tumor mass despite normalization of tumor markers during or after treatment of GCTs.

Results. In 6 (11.5%) of 52 patients the pathological diagnosis was GTS. The median patient age at diagnosis was 14.5 years (range 2 months–17 years), and the primary tumors included 4 mixed GCTs and 2 immature teratomas. After second-look surgery, histological testing revealed the lesions to be mature teratoma in all patients. Three of 6 patients subsequently underwent radiation therapy and 1 patient received additional chemotherapy for spinal seeding.

Conclusions. In enlarging residual masses after treatment of intracranial GCTs, GTS should be kept in mind in the differential diagnosis of tumor recurrence especially if there is a radiographic mismatch with serum marker test results. If technically feasible, second-look surgery may be necessary for an accurate diagnosis.

(DOI: 10.3171/2009.1.PEDS0857)

KEY WORDS • intracranial • germ cell tumor • teratoma

Intracranial GCTs are a heterogeneous group of lesions that arise in patients of all ages. These lesions comprise ~ 4–9% of all primary intracranial neoplasms in patients in the Far East and < 1% in the West. The early diagnosis of intracranial GCT is necessary because each disease entity requires different management despite a lack of large prospective studies on GCTs. Craniospinal radiotherapy alone is rarely curative in nongerminomatous GCTs, but outcomes in patients with radiation-treated germinomas have been known to be excellent. Therefore, adjuvant or preirradiation chemotherapy can increase the likelihood of complete remission in cases of nongerminomatous GCTs. For assessment of treatment response, monitoring tumor markers prior to each treatment cycle is mandatory.

An enlarging mass encountered during or after chemotherapy and/or radiation therapy for a GCT can usually be regarded as evidence of tumor recurrence or treatment failure. An increase in tumor markers despite chemotherapy requires the immediate initiation of salvage chemotherapy. In contrast, the presence of an unequivocally enlarging tumor mass despite a concomitant decline in tumor markers suggests a diagnosis of GTS. Logothetis et al. first described this apparent contradiction between radiological findings and tumor markers in 1982. To date, only a few reports have demonstrated GCTs in the CNS. In patients with regrowth and normalization of tumor markers, complete resection is an acceptable therapeutic option if technically feasible.

Because the therapeutic strategy entirely depends on whether the lesion is a recurrent tumor or GTS, it is very important to clearly differentiate the two. We therefore

Abbreviations used in this paper: AFP = alpha fetoprotein; GCT = germ cell tumor; GTS = growing teratoma syndrome.
Intracranial growing teratoma syndrome

used a database registry of 52 consecutive patients with newly diagnosed intracranial GCTs to attempt to elucidate the clinical manifestations of intracranial GTS.

**Methods**

We searched the database registry at our institution to identify patients with newly diagnosed intracranial GCTs who had previously undergone multimodal treatment at the Samsung Medical Center in Seoul between January 2000 and December 2006; 52 consecutive patients were confirmed. The lesions in these patients included 36 germinomas, 5 immature teratomas, and 11 mixed GCTs. Thirty-eight patients (73.1%) were male and 14 (26.9%) were female, with an overall median age at presentation of 13.6 years (2 months–23 years). Treatments administered after diagnosis were entirely in accordance with the Korean Intracranial Germ Cell Tumor Protocol, using carboplatin, etoposide (VP-16), cytoxan, and bleomycin.

All patients included in the study had: 1) normalization of previously elevated serum tumor markers (AFP and/or human chorionic gonadotropin); 2) an increase in tumor size during or after chemotherapy; and 3) the absence of any nongerminomatous GCT component (other than a mature teratoma) at resection.

Information on treatment response was obtained by reviewing radiological data and clinical medical records. Intracranial GCT regrowth was identified on serial MR images obtained at a regular follow-up intervals of 1 or 2 months.

**Results**

Clinical Features of GTS

Six of 52 patients were identified as having GTS. The clinical features of these 6 patients are summarized in Table 1. The median patient age at diagnosis was 14.5 years (range 2 months–17 years). Five patients had pineal tumors and 1 patient had tumors in the posterior fossa. The median serum AFP marker level at initial diagnosis was 86.6 ng/ml (range 5.7–2663 ng/ml). Four biopsies and 2 subtotal resections were performed in these patients, and the primary tumors included 4 mixed GCTs and 2 immature teratomas. A review of the initial pathological findings revealed that all patients had teratomatous elements in primary tumor specimens. Growing teratoma syndrome did not develop in any patient with a pure germinoma but did develop in 6 (37.5%) of 16 patients with mixed GCTs or immature teratomas. After initial biopsy sampling or resection, all 6 patients received systemic chemotherapy for a median of 4 cycles (range 3–4 cycles). The median time from initial diagnosis to second-look surgery was 4.5 months (range 4–11 months). During systemic chemotherapy before second-look surgery, the mean AFP level was reduced to 1 ng/ml (range 0–9 ng/ml). Follow-up MR images obtained during this time, however, demonstrated enlarging tumor accompanying a characteristic cystic change despite the reduction in serum markers (Fig. 1). On imaging, the lesions in all cases were heterogeneous, multilocular, and showed irregular enhancement.

**Second-Look Intraoperative Findings**

To identify whether an enlarging residual mass was consistent with GTS or tumor recurrence, second-look resection was performed in all patients. Most tumors contained large cystic components and were deficient or lacking in tumor vascularity. Most lesions had well-defined margins and gross-total resection was subsequently performed in all patients. On histopathological analysis, specimens were characterized by the presence of mature teratoma elements with no viable tumor (Fig. 2). The cysts were filled with clear liquid, and 4 of 6 tumors contained foci of mature cartilage. No mitotic activity and no immature elements including those of yolk sac tumors, germinomas, or choriocarcinomas were observed.

Treatment Outcomes in GTS

After clinicopathological diagnosis of GTS, 3 patients received no further treatment after complete resection at second-look surgery. To avoid recurrence, 2 patients underwent additional radiation therapy despite complete resection, and the remaining patient received adjuvant salvage chemotherapy and radiotherapy to treat spinal seeding. At a median follow-up of 16.5 months after second-look surgery (range 6–46 months), 5 patients were alive without local recurrence or distant metastasis and 1 patient had spinal seeding (Table 2).

**Discussion**

The prognosis of GCT is highly dependent on histological subtype. Although germinomas carry an excellent prognosis—most authors have reported 5-year progression-free survival rates of > 90%—nongerminomatous GCTs have a worse prognosis. In nongerminomatous GCTs, a single treatment modality alone is rarely curative, and relapse usually occurs within 18 months. According to recent trends, future therapeutic trials for nongerminomatous GCT will probably include more aggressive chemotherapeutic regimens and lower craniospinal radiotherapy consolidation doses. However, more intense chemotherapies can lead to a variety of complications including GTS, which, although rare, is a notable complication of chemotherapy for intracranial GCTs.

---

**TABLE 1: Patient characteristics at initial diagnosis***

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Lesion Type</th>
<th>Initial Op</th>
<th>Initial Tumor Markers (ng/ml)</th>
<th>Serial Tumor Marker (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14, F</td>
<td>MGCT biopsy</td>
<td>CEA 7.8</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11, M</td>
<td>IT STR</td>
<td>AFP 10.0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15, M</td>
<td>IT biopsy</td>
<td>AFP 19.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 mos, F</td>
<td>MGCT STR</td>
<td>AFP 153.9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>15, M</td>
<td>MGCT biopsy</td>
<td>AFP 366</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>17, M</td>
<td>MGCT biopsy</td>
<td>AFP 2663</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

* CEA = chorioembryonic antigen; GTR = gross-total resection; IT = immature teratoma; MGCT = mixed germ cell tumor; STR = subtotal resection; YST = yolk sac tumor.
Growing teratoma syndrome is defined as an increase in tumor size during or after chemotherapy for a GCT and is composed of only mature teratoma on histopathological testing. No further treatment apart from complete resection may be required for GTS because complete resection is generally accepted to be curative for this lesion. Growing teratoma syndrome tumors should be completely removed if technically feasible. In the present study, 2 patients underwent additional radiotherapy after second-look surgery because we did not entirely exclude the likelihood of tumor recurrence or leptomeningeal seeding. Craniospinal irradiation (5700/3000 cGy) was administered in these 2 patients for lesions with suspicious enhancement on imaging. Differentiation of GTS from tumor relapse is critical in clinical practice because tumor recurrence usually requires adjuvant salvage chemotherapy even after resection.
Growing teratoma syndrome has often been reported in nonseminomatous extracranial GCTs.1,3,6,7,12,21 The European Germ Cell Cancer Consensus Group reported that histological findings in subsequent surgery for residual masses after first-line chemotherapy revealed mature teratoma in ~ 30% of patients.21 To date, 2 hypotheses have been proposed to explain the pathogenesis of GTS.3 One postulates that GTS is the result of malignant cell differentiation into mature teratoma by chemotherapy, while the other postulates the selective destruction of components other than mature teratoma. The differentiation theory is based on the observation that malignant tumor cells can be induced to differentiate into well-developed cells by chemotherapy, especially in teratomas.7,13 The clonal selection theory may be the more reasonable, however, because most primary nongerminomatous GCTs include a mature teratoma component.3

Contrary to our expectation, GTS may be a common phenomenon in the treatment of nongerminomatous GCT. During the First and Second International CNS Germ Cell Tumor Studies in 126 patients4,10,57 and 64.7% of patients showed a complete response after 2 and 4 cycles of chemotherapy, respectively. Interestingly, after reviewing patient data in these studies, Weiner et al.24 noted that 10 (7.9%) of the 126 patients underwent delayed resection for residual radiological abnormalities despite declining or completely normalized serum markers. As a result, some of these lesions were found to be mature teratomas or necrotic/scar tissue on the second-look surgery. Although no mention was made of GTS in their study, some of the lesions treated with second-look surgery were probably the result of GTS. In the present study, GTS was frequently found during treatment of CNS GCTs. Moreover, if the GTS criteria were strictly applied, 6 (37.5%) of 16 patients with nongerminomatous GCTs eventually showed an increased tumor size despite decreasing or normalized serum tumor markers. The reasons for the higher incidence of GTS among our patients than in the literature cannot yet be accurately explained. However, it is possible that a number of GTS cases reported in previous studies might have been mistaken for simple tumor recurrence.

Conclusions

When there is radiographic mismatch with serum marker levels, GTS should be considered in the differential diagnosis of tumor relapse. Second-look surgery played an integral and important role in the management of GTS (Fig. 3) in our patients, and therefore, frequent surveillance with a regular MR imaging follow-up should be required in CNS GCTs during and after chemotherapy is completed.

Disclosure

This work was supported by a grant from the Ministry of Health and Welfare and the National Cancer Control Planning Board at the National Cancer Center in Korea (Study No. 7-2005-1216).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Interval Btw 1st &amp; 2nd Op (mos)</th>
<th>Lesion Type at 2nd Op</th>
<th>Subsequent Tx</th>
<th>Length of FU (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>MT</td>
<td>RT</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>MT</td>
<td>RT</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>MT</td>
<td>none</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>MT</td>
<td>none</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>MT</td>
<td>chemo &amp; RT</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>MT</td>
<td>none</td>
<td>6</td>
</tr>
</tbody>
</table>

* The second surgery in all patients was gross-total resection. Abbreviations: chemo = chemotherapy; FU = follow-up; MT = mature teratoma; RT = radiotherapy.

![Fig. 3. Flow chart of the treatment algorithm for mixed GCT or immature teratoma.](image)
References