Occurrence of metachronous pure germinomas long after treatment of a mixed germ cell tumor containing yolk sac tumor and germinoma

Case report

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The authors report a rare case involving the occurrence of metachronous pure germinomas long after treatment of a mixed germ cell tumor (GCT) categorized as having a poor prognosis. A neurohypophysial germinoma occurred 4 years and 6 months after the initial treatment of a mixed pineal GCT containing a yolk sac tumor and a germinoma. Furthermore, intramedullary germinomas occurred 21 years after the initial treatment of the mixed GCT and 15 years after the second treatment of the neurohypophysial germinoma. The neurohypophysial germinoma was not confirmed histopathologically, but the intramedullary germinoma was histopathologically diagnosed as a pure germinoma. Serum α-fetoprotein levels at the second neurohypophysial and third intramedullary occurrences of the germinomas were less than 10 ng/ml. Therefore, no yolk sac components seemed to be contained in the tumors. The second neurohypophysial and third intramedullary germinomas might be recurrences of the germinoma component of the pineal mixed GCT, which consisted of a yolk sac tumor and a germinoma. However, it seems very unlikely that only the germinoma, categorized in the good prognosis group, would be the only one to recur. Hence, it seems plausible that both the second and the third occurrences of pure germinoma were de novo metachronous GCTs arising after the pineal mixed GCT was cured. The authors’ case indicates the possibility of multicentric GCTs in the CNS.

Key Words • germ cell tumor • germinoma • multicentricity • intramedullary • metachronous • yolk sac tumor • oncology

Central nervous system GCTs are rare malignant neoplasms that typically arise from midline structures, particularly the pineal and neurohypophyseal regions. The incidence of intracranial GCTs is higher in East Asian countries than in western countries. In Japan, these tumors account for about 3% of all intracranial tumors.2 The WHO27 classifies CNS GCTs into the following 8 histological subtypes: germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, immature teratoma, teratoma with malignant transformation, and mixed GCTs. In western countries, CNS GCTs have traditionally been classified as either germinomas or nongerminomatous GCTs,5,10,16,26 but in Japan they are classified into 3 categories based on prognosis and optimal treatment: good, intermediate, or poor.15,20,22,28,29 Mixed GCTs with embryonal carcinoma, yolk sac tumor, or choriocarcinoma are assigned to the poor prognosis group.

Previous reports have described the occurrence of histologically different CNS GCTs at different sites long after total removal of CNS GCTs.2,4,8,9,12,14,31,34 Central nervous system GCTs are thus considered to have the potential to occur multicentrically at different times and with different histological types. Such tumors, that is, histologically distinct GCTs arising in different locations at different, widely separated times, have been termed metachronous GCTs,2,4,8,9,12,14,31,34 which include late metastatic recurrence from the initial tumor and de novo GCTs. However, metachronous pure germinomas have rarely been reported long after treatment of a mixed GCT, classified in the poor prognosis group. We report
Metachronous germinoma after treatment of mixed germ cell tumor

such a case here, which may support the germ cell theory that CNS GCTs originate from primordial germ cells that differentiate into all histological types.33

Case Report

Presentation and Initial Treatment. This 13-year-old boy presented with headache, vomiting, and diplopia in March 1988. Computed tomography (Fig. 1) and MRI (Fig. 2A and B) revealed a pineal region tumor with hydrocephalus. Serum AFP was markedly elevated (to 5400 ng/ml), and β-HCG was slightly elevated (to 0.70 ng/ml). The tumor was completely removed via an occipital transtentorial approach. Histopathological and immunohistochemical examinations verified a mixed GCT consisting of yolk sac tumor and germinoma components, with positive stains for AFP and PLAP (Fig. 3). After surgery, the patient was given 9 courses of EP chemotherapy (20 mg/m² cisplatin and 100 mg/m² etoposide on Days 1–5) over 2 years. An MRI study obtained in March 1990 showed no evidence of disease (Fig. 2C and D).

Second Treatment. In September 1992, the patient began complaining of polyuria and polydipsia. An MRI study obtained in November 1993 (when he was 19 years old) showed a neurohypophysial tumor without any other lesions (Fig. 4 left). Serum AFP and β-HCG levels were not elevated. In the CSF, the AFP level was less than 5 ng/ml, but the β-HCG level was slightly elevated (to 0.69 ng/ml). Cytological examination of the CSF revealed no abnormality. The patient refused a biopsy of the neurohypophysial tumor. His clinical diagnosis was neurohypophysial germinoma, and he received radiotherapy with 25.2 Gy to the entire brain and 50.4 Gy to the entire ventricle, followed by 3 courses of CARE chemotherapy (450 mg/m² carboplatin on Day 1 and 150 mg/m² etoposide on Days 1–3). Thereafter, the neurohypophysial tumor disappeared, and thus, pure germinoma without a teratoma component was the likely diagnosis (Fig. 4 right). The patient has since required hormone replacement therapy including desmopressin, hydrocortisone, and levothyroxine.

Third Treatment. In March 2009 when the patient was 34 years old, he noticed sensory disturbances of the limbs. Although brain MRI showed no evidence of disease, spinal MRI revealed intramedullary mass lesions at C3–6 and T1–2, which were isointense on T1-weighted imaging, slightly hyperintense on T2-weighted imaging, and showed mild Gd enhancement (Fig. 5). These lesions did not appear on a spinal MRI study obtained in June 2006. Serum AFP and β-HCG levels were 5 ng/ml and less than 0.1 ng/ml, respectively. The AFP level in the CSF was less than 5 ng/ml, and the β-HCG level was

Fig. 1. Left: Axial CT scan showing an isodense mass in the pineal region with calcification and hydrocephalus. Right: Axial contrast-enhanced CT scan showing a homogeneously enhancing pineal mass.

Fig. 2. Axial (A) and sagittal (B) T1-weighted MRI studies showing an isointense pineal mass with hydrocephalus. Gadolinium-enhanced MRI studies could not be obtained at the initial evaluation. Axial (C) and sagittal (D) Gd-enhanced T1-weighted MRI studies obtained 2 years after the initial surgery, showing no evidence of disease.

Fig. 3. Photomicrographs of tumor specimens obtained during the first surgery, demonstrating reactivity for AFP and PLAP. The lesion contained a yolk sac tumor and a germinoma. H & E (A and B), immunohistochemical staining for AFP (C), and immunohistochemical staining for PLAP (D). Original magnification ×100 (A, C, and D), and ×400 (B).
slightly elevated to 0.36 ng/ml. Cytological examination of the CSF revealed no abnormality. The patient underwent a surgical biopsy of the C3–6 intramedullary mass. Histopathological examination of the surgical specimen revealed a pure germinoma. Immunohistochemical staining was positive for PLAP but negative for AFP (Fig. 6). After radiation with 30.6 Gy to the entire spine and 50.4 Gy to the intramedullary tumors, the tumors disappeared. The patient received additional CARE chemotherapy, during which he suffered from severe myelosuppression and acute renal failure. He was not able to receive additional chemotherapy. Follow-up MRI in March 2011 showed disseminated tumors at the surface of the medulla oblongata. His bone marrow and renal functions had recovered at the time. He received reduced CARE chemotherapy (carboplatin 315 mg/m² on Day 1 and etoposide 105 mg/m² on Days 1–3) every 2–3 months, which has kept his condition stable.

**Discussion**

In the present case, a neurohypophysial germinoma occurred 4 years and 6 months after the initial treatment of a mixed GCT containing a yolk sac tumor and a germinoma. Furthermore, intramedullary germinomas occurred 21 years after the initial treatment of the mixed GCT and 15 years after the second treatment of the neurohypophysial germinoma. The neurohypophysial germinoma was not confirmed histopathologically, but the intramedullary germinoma was diagnosed histopathologically as a pure germinoma. Serum AFP levels at the second neurohypophysial and third intramedullary occurrence of the germinomas were less than 10 ng/ml. The tumors disappeared completely after treatment. Therefore, no yolk sac components seemed to be contained in the tumors.

According to current strategies for the treatment of CNS GCTs, neoadjuvant chemotherapy and radiation therapy without a surgical biopsy are preferred if serum AFP is markedly elevated (> 2000 ng/ml). Subsequent salvage surgery is recommended for residual tumors. Nakamura et al. reported that the germinoma component can completely disappear as a result of chemotherapy and radiotherapy, while components of teratomas or GCTs categorized in the poor prognosis group may remain. In the present case, a histopathological diagnosis of a mixed GCT, with components of a yolk sac tumor and a germinoma, was confirmed before chemotherapy and radiotherapy. A slightly elevated serum β-HCG level at the initial presentation suggested a
germinoma component. If neoadjuvant therapy had been performed, it could not be verified pathologically.

Based on the patient’s clinical presentation, MRI findings, serum tumor marker levels, and complete disappearance of the tumor after chemotherapy and radiotherapy, we concluded that the neurohypophysial tumor was a pure germinoma, without a teratoma component.

Although intramedullary GCTs are rare, primarily and metastatic or disseminated nongerminomatous GCTs have been reported. Although various types of intramedullary GCTs can occur, the majority of these are pure germinomas. While a thoracolumbar predominance is noted among primary intramedullary GCTs, metastatic or disseminated intramedullary GCTs are located in the cervical spinal cord. In the present case, 2 spinal lesions involved the cervical and thoracic regions of the spinal cord. These lesions might be metastatic or disseminated disease, or that one of the lesions was de novo disease and the other was metastatic or disseminated. However, we believe it is more likely that both the metachronous intramedullary GCTs might be de novo due to negative cytological examination of the CSF at the occurrence of the third tumor, although no de novo metachronous intramedullary GCT has been reported.

There have been some reports of second CNS GCTs arising at a different site, at a different time, and with a histological type different from that of the primary GCT. Both recurrence and multicentricity have been discussed to explain this phenomenon.

There is a possibility that some second GCTs reported as malignant transformations of germinomas into nongerminomatous GCTs might actually be recurrences of malignant components of the primary GCTs. Because the entire tumor is not examined by surgical biopsy, malignant components may not be detected. Such malignant components could then progress despite radiochemotherapy. Elevated levels of serum AFP and β-HCG are not detectable in the earliest stage of GCTs categorized in the poor prognosis groups, further hampering detection of malignant components of germinomas.

The development of a second GCT can be a recurrence of a mature teratoma after total resection without radiotherapy or chemotherapy. A pure mature teratoma is rare, and a mature teratoma is often a component of mixed GCTs, including germinoma or immature teratoma. As germinomas are invasive tumors, infiltrated germinoma tissue remains in the adjacent brain tissue after complete resection without radiochemotherapy and may become the source of a second tumor.

As far as we know, there are only 8 previous reports regarding the occurrence of metachronous CNS GCTs, which are summarized in Table 1. The clinical diagnosis of the second tumor was made without histopathological confirmation.

TABLE 1: Summary of previous reported cases of metachronous CNS GCTs

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age at Presentation (yrs), Sex</th>
<th>Site of Initial Tumor Pathology of Initial Tumor</th>
<th>Interval Btw Initial &amp; 2nd (3rd) Tumors</th>
<th>Initial (2nd) Type of Therapy</th>
<th>2nd (3rd) Tumor Site Pathology</th>
<th>2nd (3rd) Tumor Site Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsuchida et al., 1976</td>
<td>7, M</td>
<td>pineal</td>
<td>mature teratoma</td>
<td>15 yrs</td>
<td>pineal</td>
<td>mature teratoma</td>
</tr>
<tr>
<td>Kamiya et al., 1988</td>
<td>16, M</td>
<td>pineal</td>
<td>mature teratoma</td>
<td>8 mos</td>
<td>septum pellucidum</td>
<td>immature teratoma</td>
</tr>
<tr>
<td>Czirják et al., 1992</td>
<td>19, M</td>
<td>intrasellar</td>
<td>mature teratoma</td>
<td>3 yrs</td>
<td>corpus callosum</td>
<td>embryonal carcinoma</td>
</tr>
<tr>
<td>Ikeda et al., 1998</td>
<td>10, M</td>
<td>pineal</td>
<td>mature teratoma</td>
<td>8 yrs</td>
<td>hypothalamus-neurohypophysis</td>
<td>germinoma</td>
</tr>
<tr>
<td>Hirano et al., 2001</td>
<td>8, M</td>
<td>pineal</td>
<td>mature teratoma</td>
<td>10 yrs</td>
<td>corpus callosum</td>
<td>immature teratoma</td>
</tr>
<tr>
<td>Sugimoto et al., 2002</td>
<td>10, M</td>
<td>pineal</td>
<td>mature teratoma</td>
<td>8 yrs</td>
<td>hypothalamus-neurohypophysis</td>
<td>germinoma</td>
</tr>
<tr>
<td>Kamoshima et al., 2008</td>
<td>19, M</td>
<td>pineal yolk sac tumor &amp; germinoma</td>
<td>total resection, chemotherapy (whole brain irradiation, chemotherapy)</td>
<td>5 yrs</td>
<td>pineal</td>
<td>embryonal carcinoma</td>
</tr>
</tbody>
</table>

* The clinical diagnosis of the second tumor was made without histopathological confirmation.
components, categorized in the poor prognosis group. It is also noteworthy that all metachronous CNS GCTs including the present case occurred outside the field of the previous irradiation or had not received any radiotherapy.

Kamoshima et al. reported the occurrence of a metachronous mature teratoma 12 years after combined chemotherapy with localized irradiation following complete resection of a pineal germinoma. This case indicates that CNS GCTs may be multicentric in nature.

The germ cell theory, advocated by Teilum, supports the notion that CNS GCTs are multicentric. This theory proposes that CNS GCTs originate from preexisting primordial germ cells in the CNS. These primordial germ cells have the potential to differentiate into all histological types of GCTs, which are believed to account for the occurrence of de novo metachronous GCTs. Chemotherapy alone for the treatment of germinomas and nongerminomatous GCTs has proven less effective than therapies involving radiation. Optimal treatments for CNS GCTs require radiation therapy. Most tumors that recur after radiotherapy do so outside the radiation field. Late recurrence is not rare in patients with CNS germinomas. However, it is not known whether late CNS germinomas are truly recurrent tumors or de novo tumors. Central nervous system germinomas are considered curable with craniospinal irradiation. In our case, both the second and third occurrences were outside the radiation field. In a case reported by Kamoshima et al., a second tumor occurred outside the radiation field. Sugimoto et al. speculated that adjuvant chemoradiotherapy following complete removal of a mature pineal teratoma could prevent metachronous germinoma. Hence, prophylactic craniospinal irradiation for CNS GCTs might eradicate primordial germ cells and prevent development of metachronous GCTs.

In the present case, the pineal tumor was totally resected. Histopathological investigation revealed a mixed GCT containing a yolk sac tumor and a germinoma. Both the second and third occurrences of the tumors were pure germinomas located outside the radiation field. The possibility remains that these were late metastatic recurrences of only the germinoma component of the mixed GCT. However, it seems highly unlikely that the germinoma, categorized in the good prognosis group, would be the only part of the mixed GCT to recur. Accordingly, it seems plausible that both the second and third occurrences of pure germinomas in this case were de novo metachronous GCTs arising after the cured pineal mixed GCT, rather than late metastatic recurrences of the pineal mixed GCT containing a yolk sac tumor and a germinoma.

We reported here on a patient with metachronous pure germinomas (categorized in the good prognosis group) that occurred after treatment of a mixed GCT (categorized in the poor prognosis group). The present metachronous, probably de novo, GCT indicates the possibility of multicentric CNS GCTs, which may support the germ cell theory.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Manuscript submitted March 20, 2012. Accepted September 25, 2012. Please include this information when citing this paper; published online October 19, 2012; DOI: 10.3171/2012.9.PEDS12151.

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