Successful treatment of mixed yolk sac tumor and mature teratoma in the spinal cord: case report

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Primary spinal germ cell tumors are rare, and spinal nongerminomatous germ cell tumors represent an even rarer subset for which no standard therapy has been established. The authors report the case of a 24-year-old woman with multifocal primary spinal germ cell tumors scattered from T-12 to L-5 that consisted of yolk sac tumor and mature teratoma. After diagnostic partial resection, the patient was treated with 30 Gy of craniospinal irradiation and 30 Gy of local spinal irradiation, followed by 8 courses of chemotherapy based on ifosfamide, cisplatin, and etoposide (ICE). Salvage surgery was also performed for residual mature teratoma components after the third course of ICE chemotherapy. Chemotherapy was continued after the operation, but ifosfamide was entirely eliminated from the ICE regimen because severe myelosuppression was observed after previous courses. The patient remains recurrence free as of more than 5 years after the completion of chemotherapy. This case suggests that this treatment strategy is an effective option for primary spinal yolk sac tumor.

https://thejns.org/doi/abs/10.3171/2016.8.SPINE16465

KEY WORDS germ cell tumor; spinal cord; yolk sac tumor; teratoma; radiotherapy; chemotherapy; oncology

Central nervous system (CNS) germ cell tumor is a rare pathology that accounts for approximately 2%–3% of CNS tumors in Japan and 0.3%–0.6% in Western countries. Most CNS germ cell tumors occur in the suprasellar or pineal region, followed by the basal ganglia, and germ cell tumors originating in the spinal cord are extremely rare. While a standard therapeutic strategy for intracranial germ cell tumor has been evaluated to some extent, recommended treatment regimens for primary spinal germ cell tumor are less developed due to the rarity of this entity. In particular, primary spinal nongerminomatous germ cell tumor (NGGCT) has been reported in only a small number of cases, including 2 cases of spinal yolk sac tumor that had poor outcomes despite intensive chemoradiotherapy. Effective treatment protocols against spinal NGGCT thus need to be developed. Here, we present a case of spinal mixed germ cell tumor comprising yolk sac tumor and mature teratoma. Successful treatment was achieved using whole-craniospinal irradiation and local spinal irradiation followed by ifosfamide, cisplatin, and etoposide (ICE) chemotherapy, based on a protocol widely used in Japan for the subset of intracranial germ cell tumors categorized as having a poor prognosis.

Case Report
History and Examination
A 24-year-old woman who had noticed back pain after physical exercise a month earlier presented with progressive numbness and weakness of the lower extremities. She

ABBREVIATIONS AFP = alpha-fetoprotein; BEP = bleomycin, etoposide, and cisplatin; CE = carboplatin and etoposide; CNS = central nervous system; ICE = ifosfamide, cisplatin, and etoposide; JPBTSG = Japanese Pediatric Brain Tumor Study Group; NGGCT = nongerminomatous germ cell tumor; OS = overall survival rate; PE = cisplatin and etoposide; PVB = cisplatin, vinblastine, and bleomycin; STGC = syncytiotrophoblastic giant cell.

SUBMITTED April 26, 2016. ACCEPTED August 31, 2016.
INCLUDE WHEN CITING Published online December 2, 2016; DOI: 10.3171/2016.8.SPINE16465.
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could not walk but could still move her right leg. Neurological examination revealed severe paraparesis of the lower limbs (paralysis of the left lower leg and severe weakness of the right lower leg), sensory disturbance below T-10, and bladder-bowel dysfunction. Both knee-jerk and Achilles tendon reflexes were deteriorated.

Magnetic resonance imaging (MRI) of the spinal cord demonstrated mass lesions 30 mm in diameter at T-10 and L2–3, as well as several smaller lesions between T-12 and L-5 (Fig. 1). Cranial MRI revealed no lesions in the brain. Imaging with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed elevated maximum standardized uptake values (SUV\textsubscript{max}) of 3.2 at the T-10 lesion and 4.2 at the L2–3 lesion.

Operation and Pathological Findings

Because the T-10 lesion was suspected of being responsible for the progressive paraparesis, emergent decompressive laminectomy of T9–10 and partial resection of the tumor located at T-10 were performed. Although decompressive laminectomy was performed, the patient’s symptoms progressed further, and her lower legs were completely paralyzed during the postoperative period. Histopathological examination indicated a yolk sac tumor (Fig. 2), and blood tests showed elevated levels of alphafetoprotein (AFP) (2182 ng/ml) and normal levels of beta-human chorionic gonadotropin (β-HCG).

**FIG. 1.** Gadolinium-enhanced T1-weighted (A–C, E, and F) and T2-weighted (D) MR images showing spinal germ cell tumors. Mass lesions (arrowheads) approximately 30 mm in diameter can be seen at T-10 (A, sagittal image; B, axial image) and L2–3 (A and C [axial image]). The sagittal T2-weighted image (D) shows peritumoral edema within the spinal cord. The sagittal images in panels E and F show several smaller lesions (arrows) between T-12 and L-5.

**FIG. 2.** Surgical specimens of yolk sac tumor obtained at the T-10 level. A and B: H & E staining reveals primitive-appearing cells in a reticular-microcystic pattern. C and D: Immunohistochemical staining reveals the presence of SALL4 (C) and AFP (D). Bar = 500 μm (A), 50 μm (B and D), and 100 μm (C).
Postoperative Course

Because a standard chemoradiotherapy regimen is lacking for spinal germ cell tumors, the patient was treated with a slight modification of the protocol proposed by the Japanese Pediatric Brain Tumor Study Group (JPBTSG) for intracranial NGGCT with poor prognosis. Briefly, the patient received 30 Gy of whole-craniospinal irradiation delivered in 17 fractions, followed by local boost irradiation at the spinal lesions consisting of 30 Gy delivered in 17 fractions. Eight cycles of ICE chemotherapy were then administered. All radiotherapy was conducted prior to chemotherapy, because the tumors were growing rapidly and radiotherapy was thought to be more reliable than chemotherapy for the immediate control of tumor masses. The ICE chemotherapy regimen comprised 900 mg/m² of ifosfamide (Days 1–5), 20 mg/m² of cisplatin (Days 1–5), and 60 mg/m² of etoposide (Days 1–5). Due to severe myelosuppression appearing during the course of chemotherapy, dose reduction was conducted following the method described by Sawamura et al.; a reduced dose of etoposide and ifosfamide was administered for the second and third courses, and ifosfamide was therefore not used during the fourth to eighth courses.

The patient’s serum AFP level rapidly decreased to less than 100 ng/ml toward the end of radiotherapy, and it fell further to within the normal range after the first cycle of ICE chemotherapy, which was carried out right after the radiotherapy. In accordance with the decrease in serum AFP level, spinal MRI demonstrated marked shrinkage of the enhanced lesions, but remnant tumor was suspected at L-2 (Fig. 3A) after the third course of ICE chemotherapy. Salvage surgery was therefore performed. One nerve root was found to be completely involved with the remnant tumor, and both the residual tumor and the nerve root were totally removed (Fig. 3B). The histopathological diagnosis of this remnant was mature teratoma, with no evidence of residual yolk sac tumor (Fig. 3C), suggesting that the chemoradiotherapy had successfully eradicated the yolk sac tumor component.

Five courses of adjuvant chemotherapy, consisting of cisplatin and a 75%–100% dose of etoposide, were administered after the salvage surgery; the chemotherapy was completed 18 months after the initial operation. MRI (Fig. 3D) and measurement of AFP levels (3 ng/ml) showed no evidence of recurrence at more than 5 years after completion of chemotherapy. The patient still has the severe paraplegia of the lower limbs, sensory disturbance below T-10, and bladder-bowel dysfunction that were present before treatment, but she is otherwise healthy and did not incur any additional deficit due to the nerve root resection.

Discussion

Here, we have described a case we encountered of primary malignant spinal germ cell tumor, which is extremely rare. The patient was successfully treated with whole-craniospinal and local irradiation followed by ICE chemotherapy and salvage surgery. Our experience and review of the literature suggest that this treatment strategy might be effective for malignant spinal germ cell tumor, although further evaluation of the treatment protocol is warranted.

Primary Spinal Germ Cell Tumors

Primary spinal germ cell tumors are rare. To date, including our case of mixed germ cell tumor, 38 cases of primary spinal germ cell tumor have been reported—in-
cluding 27 cases of pure germinoma (71%), 5 cases of germinoma with syncytiotrophoblastic giant cells (STGCS) (13%), 3 cases of mixed germ cell tumor (8%), 2 cases of yolk sac tumor (5%), and 1 case of embryonal carcinoma (3%).

The proportion of NGGCTs among primary spinal germ cell tumors appears slightly lower than that among intracranial germ cell tumors. Among these 38 cases, 25 (66%) involved Japanese patients and 19 (50%) involved male patients. Whereas intracranial germ cell tumors seem more frequent in males, the sex ratio appears about equal for primary spinal germ cell tumors. The mean age at diagnosis of primary spinal germ cell tumors is 25 years (range 1.4–45 years). Primary spinal germ cell tumors occur most frequently in the thoracic spinal cord and least frequently in the cervical region. Of the 38 patients, 6 (16%) were reported to experience recurrence; those recurrences involved germinoma in 2 cases, germinoma with STGC in 1 case, yolk sac tumor in 2 cases, and embryonal carcinoma in 1 case. The recurrence rate of primary spinal NGGCT (3 of 6, 50%) is significantly higher than that of primary spinal germinoma (3 of 32, 9.4%; Fisher’s exact test, p < 0.05).

**Radiotherapy**

Excluding 1 case of germinoma with STGC in which the postoperative treatment was unclear, 36 primary tumors were treated with radiotherapy. Local-field radiotherapy was performed in most cases (34 of 36, 94%), with 15 patients (41%) receiving whole-spine irradiation and 10 of these 15 patients also treated with whole-brain irradiation. Among the 19 patients with germinoma with or without STGC who did not receive whole-spine irradiation, 3 patients (16%) suffered recurrence. CNS dissemination was evident in 2 of these 3 cases. In contrast, no recurrence was seen in the 12 patients with germinoma who received whole-spine irradiation. The 3 patients who suffered recurrence had not been treated with systemic chemotherapy, suggesting that treatment with local radiation alone is insufficient to control even germinoma.

**Chemotherapy**

Among the 37 cases of primary tumors whose postoperative treatment was reported, chemotherapy was performed in 20 (54%). This chemotherapy consisted of CE (carboplatin and etoposide) in 7 cases, ICE in 6 cases, BEP (bleomycin, etoposide, and cisplatin) in 3 cases, PE (cisplatin and etoposide) in 2 cases, PVB (cisplatin, vindesine, and bleomycin) in 2 cases, and methotrexate and etoposide in 1 case. (In 1 case, the patient was treated with both CE and ICE.) The patients with NGGCT were treated with various chemotherapeutic regimens (Table 1). Among the patients with primary spinal germinoma, 2 of the 17 cases treated without chemotherapy had tumor recurrence, whereas only 1 of the 14 patients treated with chemotherapy showed recurrence. CE chemotherapy was used for 6 cases of germinoma, and all 6 patients reportedly remained free of recurrence, although CE chemotherapy used for 1 NGGCT case was not effective. All 6 patients treated with ICE chemotherapy likewise showed no recurrence over a reported follow-up of 22–88 months. These 6 cases treated with ICE chemotherapy

### TABLE 1. Summary of cases of primary spinal NGGCT reported in the literature

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age, Sex</th>
<th>Pathology</th>
<th>Tumor Location</th>
<th>Surgery</th>
<th>Treatment</th>
<th>Chemotherapy</th>
<th>Radiation (Gy)</th>
<th>OS (mos)†</th>
<th>Recurrence Status</th>
<th>Local</th>
<th>CSI</th>
<th>CSF</th>
<th>Recurrence</th>
<th>Response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurisaka et al., 1998</td>
<td>17 mos, F</td>
<td>YST</td>
<td>T2–7</td>
<td>STR</td>
<td>0</td>
<td>25 PVB × 2 cycles</td>
<td>CR</td>
<td>7</td>
<td>Local</td>
<td>Dead</td>
<td>Alive</td>
<td>None</td>
<td>Alive</td>
<td>Dead</td>
</tr>
<tr>
<td>Kan et al., 2006</td>
<td>25 yrs, F</td>
<td>YST</td>
<td>L1–3</td>
<td>STR</td>
<td>0</td>
<td>40 PE × 4 cycles</td>
<td>CR</td>
<td>22</td>
<td>None</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
</tr>
<tr>
<td>Takahasi et al., 2006</td>
<td>20 mos, M</td>
<td>YST</td>
<td>L1–2</td>
<td>STR</td>
<td>0</td>
<td>ICE × 2 cycles, ICE</td>
<td>CR</td>
<td>22</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
</tr>
<tr>
<td>Biswas et al., 2009</td>
<td>28 yrs, M</td>
<td>EC</td>
<td>L2–4</td>
<td>GTR</td>
<td>0</td>
<td>ICE × 2 cycles, ICE</td>
<td>CR</td>
<td>11</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Yamamoto et al., 2013</td>
<td>42 yrs, F</td>
<td>MX2</td>
<td>L1–3</td>
<td>STR</td>
<td>24</td>
<td>ICE × 2 cycles, ICE</td>
<td>CR</td>
<td>11</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Present case</td>
<td>24 yrs, F</td>
<td>MX3</td>
<td>T-10, L2–3, T12–L5</td>
<td>Bx &amp; salvage††</td>
<td>30</td>
<td>ICE × 8 cycles</td>
<td>CR</td>
<td>88</td>
<td>None</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Bx = biopsy; CR = complete remission; SI = craniospinal irradiation; GC = germinoma; GTG = gross-total resection; CE = carboplatin, vincristine, and etoposide; BEP = bleomycin, etoposide, and cisplatin; PVB = cisplatin, vindesine, and bleomycin; PE = cisplatin and etoposide; PVB = cisplatin, vindesine, and bleomycin; PVB = cisplatin, vindesine, and bleomycin; PVB = cisplatin, vindesine, and bleomycin; PVB = cisplatin, vindesine, and bleomycin; PVB = cisplatin, vindesine, and bleomycin.

† Indicates overall survival as of this writing.
‡ After 4 cycles of PE chemotherapy and radiotherapy, 4 additional cycles of consolidation chemotherapy were performed with carboplatin, vincristine, and etoposide.
§ Local recurrence with dissemination and/or metastasis was suspected.
¶ Patient was treated with 20 Gy of local radiotherapy after tumor recurrence.
** Postoperatively, 2 cycles of CE chemotherapy were administered. Since tumor progression was observed after CE chemotherapy, the treatment protocol was altered and 4 cycles of ICE chemotherapy and irradiation were administered.
†† The yolk sac component of MX3 showed a complete response, but since the mature teratoma component did not respond to chemoradiotherapy, salvage surgery was performed.
include 2 pure germinomas, 1 germinoma with STGC, and 3 mixed germ cell tumors (germinoma + choriocarcinoma, germinoma + immature teratoma, and yolk sac tumor + mature teratoma). Such findings suggest that ICE chemotherapy may be effective against primary spinal germ cell tumors, including NGGCT.

Primary Spinal NGGCT

Primary spinal NGGCT is extremely rare, and only 6 cases have been reported, including the present case. The 6 cases include 2 yolk sac tumors, 1 embryonal carcinoma, 2 mixed germ cell tumors, and 1 embryonal carcinoma. Use of neoadjuvant chemotherapy and radiotherapy combined with ICE chemotherapy, and none showed any recurrence during follow-up (range of overall survival 22–88 months). In contrast, the 3 other patients with spinal NGGCT (2 yolk sac tumors and 1 embryonal carcinoma) were treated with chemotherapy (PVB, PE, or BEP) with or without local irradiation, and all showed recurrence and died within 22 months (mean overall survival 13 months). These small case series suggest that whole-craniospinal irradiation and local spinal irradiation combined with ICE chemotherapy as we performed represents a promising treatment protocol for primary spinal NGGCT.

Although the number of reported cases of spinal germ cell tumor is quite limited, the results of clinical studies of intracranial germ cell tumor suggest a recommended protocol for the treatment of patients with malignant germ cell tumors. Studies of intensive chemotherapy for malignant intracranial germ cell tumor have shown that NGGCT is highly responsive to chemotherapy and demonstrate a 5-year overall survival rate (OS) of nearly 60%–75% for patients treated with chemotherapy without irradiation at initial therapy (most of the patients were subsequently treated with radiotherapy); nevertheless, chemotherapy alone results in a higher relapse rate than chemotherapy combined with radiotherapy, indicating that irradiation should be included in treatment regimens. Bromberg et al. reviewed the recent literature for intracranial germ cell tumor and reported that radiotherapy combined with platinum-based chemotherapy was effective and should represent the current standard for intracranial NGGCT. Neoadjuvant chemoradiotherapy is also an effective strategy, as Kochi et al. treated 11 patients with NGGCT using neoadjuvant chemotherapy with platinum-based agents (CE, PE, or ICE) and radiotherapy and reported that the 5-year progression-free survival rate and 5-year OS were both 90.9%. Taking these results together, application of combined radiation and ICE chemotherapy for spinal germ cell tumor appears reasonable. Of note, spinal NGGCT requires treatment with whole-spine irradiation, which often causes severe myelosuppression and would thus make the subsequent intensive chemotherapy more difficult. The protocol for intracranial NGGCT may therefore require some modifications to achieve the optimal regimen for spinal NGGCT. In this regard, whether irradiation should be performed before or after several courses of chemotherapy is a matter for discussion. We decided to use radiotherapy prior to chemotherapy in the present case, as this therapy is more reliable for controlling rapidly growing tumors. Due to the severe myelosuppression that resulted, we were obliged to reduce the dose of ICE chemotherapy, and ifosfamide was entirely eliminated after the third course of ICE chemotherapy. Initial irradiation thus carries a risk of requiring a reduction in the strength of subsequent chemotherapy. The timing of radiation may therefore warrant further evaluation.

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

Author Contributions
Conception and design: Mukasa, Yanagisawa, K Saito. Acquisition of data: Mukasa, Yanagisawa, K Saito, Tanaka, Takai, Shibahara, Ikegami, Nakao, Takeshita. Analysis and interpretation of data: Mukasa, Yanagisawa, K Saito, Tanaka, Takai, Shibahara, Takeshita, Matsutani. Drafting the article: Yanagisawa, K Saito, Shibahara. Critically revising the article: Mukasa, Yanagisawa, K Saito, Tanaka, Takai, Shibahara, Takeshita, Matsutani, N Saito. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mukasa. Administrative/technical/material support: Takai, Shibahara, Ikegami, Nakao, Takeshita, Matsutani, N Saito. Study supervision: Matsutani, N Saito. Involved in patient’s treatment: Mukasa, K Saito, Tanaka, Shibahara. Involved in patient’s surgical treatment: Mukasa, Takai, Ikegami, Nakao, Takeshita.

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