A Case of Mixed Germ Cell Tumor in the Intramedullary Spinal-cord

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A 28-year-old man was hospitalized with advancing paraplegia. Under the diagnosis of Guillain-Barre syndrome, steroid pulse therapy was administered and plasmapheresis was performed. However, the paraplegia gradually progressed. Subsequently, a spinal cord tumor was revealed by magnetic resonance imaging (MRI). The pathological diagnosis, obtained by open biopsy, confirmed a mixed germ cell tumor in the spinal cord. Multiple lung and lymph nodes metastases were also detected upon computed tomography, along with increased serum alpha-fetoprotein (33.9 ng/mL) and human chorionic gonadotropin (182.5 mIU/mL) levels. Consequently, he received chemotherapy comprising three courses of BEP (bleomycin, etoposide, and cisplatin) as first-line therapy, followed by four courses of TGN (paclitaxel, gemcitabine, and nedaplatin) as second-line treatment. As a result, the spinal cord lesion area was significantly decreased and the alpha-fetoprotein and human chorionic gonadotropin levels were normalized. Four years after chemotherapy, MRI revealed pituitary gland and pineal organ recurrence of the germ cell tumor and additional TGN chemotherapy was performed.

Key words: Mixed germ cell tumor, TGN chemotherapy, Extragonadal germ cell tumor

INTRODUCTION

Primary central nervous system germ cell tumors (GCTs) commonly occur in the pineal gland or in the suprasellar region, including the thalamus, basal ganglions, and cerebral ventricles [1]. However, primary spinal cord GCTs are uncommon, and there have, to our knowledge, been only 3 previous reports of primary spinal cord mixed GCTs with several histological types of cells [2–4]. We experienced a case of primary spinal cord mixed GCT in which long-term survival could be achieved by TGN therapy following BEP therapy. This case is presented herein.

CASE REPORT

The patient, a 28-year-old man, visited his local medical doctor in March 2007 with chief complaints of sensory disturbance of the lower limbs and progressive leg paralysis. The patient's condition was diagnosed as Guillain-Barre syndrome and he was treated with plasmapheresis and steroid pulse therapy; however, the symptoms were aggravated. In December 2007, sensory disturbance of the upper limbs also developed. In March 2008, the patient was transferred to our hospital for further examination and treatment.

The physical findings on admission indicated that the patient had clear consciousness, muscle weakness of the lower limbs (decreased to MMT0), and absent patellar tendon reflexes and ankle jerks of the lower limbs. Thermal hypoalgesia at the Th4–Th8 levels and thermal anesthesia/analgesia from the Th9 level downwards were found. No symptoms of intracranial hypertension, such as headache, queasiness, or vomiting, were noted.

Magnetic resonance imaging (MRI) on admission revealed a mass at the C5–C6 level showing iso- to high-signal intensities and low- to high-signal intensities on T1- and T2-weighted images, respectively, along with an area from Th4 to the cauda equina with a mass showing low- to high-signal intensities on both T1- and T2-weighted images. Both lesions were slightly contrast-enhanced [Fig. 1-a, b, c]. Head MRI revealed no lesions. Computed tomography (CT) showed no retroperitoneal or mediastinal lesions other than the spinal cord lesions. On ultrasound examination of the testicles, no tumor lesions were found.

In March 2008, to make a diagnosis, open biopsy was performed on the lower thoracic spinal cord (Th10, Th11); however, only necrotic scar tissue was noted, not leading to any specific diagnosis. Therefore, another open biopsy was performed on the upper thoracic spinal cord (Th4–Th5) in April 2008.

This time, the histopathological findings showed perivascular undifferentiated cells with a large nucleus, an obvious nucleolus, and a bright endoplasmic reticulum; a subset of the cells stained positive for AFP, indicating embryonal carcinoma [Fig. 2-a, b]. Tumor cells similar to multinucleated syncytiotrophoblasts with eosinophilic cytoplasm were also found and showed positive hCG staining, indicating choriocarcinoma [Fig. 2-c, d]. Furthermore, spindle-shaped mesenchymal stem cells were found, suggesting the presence of immature teratoma [Fig. 2-e]. According to the above results, a diagnosis of mixed GCTs (embryonal carcinoma, choriocarcinoma, and immature teratoma) was established.

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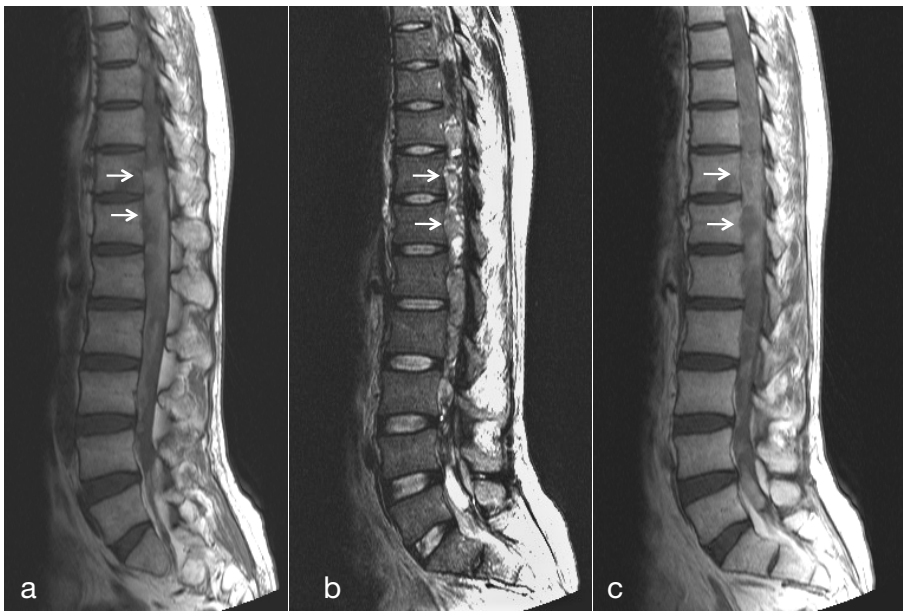

Fig. 1 Initial magnetic resonance imaging (MRI) findings. (a) Sagittal view of a T1-weighted sagittal image showing low-signal intensity with high-signal intensity spots at the Th4-cauda equina. (b) Sagittal view of a T2-weighted image showing an intramedullary tumor presenting with heterogeneous intensity at the Th4-cauda equina. (c) Gadolinium-enhanced T1-weighted sagittal image showing homogeneous enhancement of the mass at the Th4-cauda equina. Arrows in a, b, and c indicate the main tumor lesion at Th10–12.

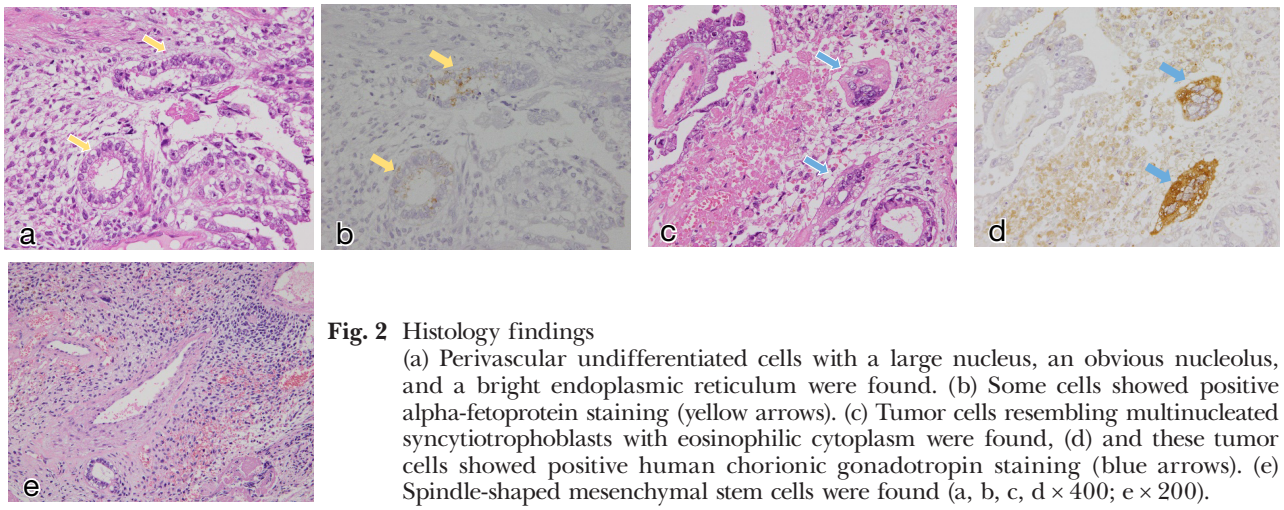

Fig. 2 Histology findings
(a) Perivascular undifferentiated cells with a large nucleus, an obvious nucleolus, and a bright endoplasmic reticulum were found. (b) Some cells showed positive alpha-fetoprotein staining (yellow arrows). (c) Tumor cells resembling multinucleated syncytiotrophoblasts with eosinophilic cytoplasm were found, (d) and these tumor cells showed positive human chorionic gonadotropin staining (blue arrows). (e) Spindle-shaped mesenchymal stem cells were found (a, b, c, d × 400; e × 200).

On postoperative day 10, the tumor marker levels were increased, as follows: lactate dehydrogenase, 576 IU/L; alpha-fetoprotein (AFP), 33.9 ng/mL; and human chorionic gonadotropin (hCG), 182.5 mIU/mL. No abnormal findings were apparent in other blood or biochemical tests.

After the establishment of the diagnosis, CT was performed to confirm the disease status, revealing multiple metastases to the bilateral lung fields and to the left renal hilar and para-aortic lymph nodes. In May 2008, BEP therapy (cisplatin 20 mg/m^2 on days 1 to 5, etoposide 100 mg/m^2 on days 1 to 5, and bleomycin 30 mg/m^2 on days 2, 9, and 16) was started. During the 1st course of BEP therapy, grade 4 febrile neutropenia (according to the Common Terminology Criteria for Adverse Events Version 4.0) occurred and led to sepsis, necessitating intensive care management. However, MRI after the 1st course of therapy revealed that the tumors had diminished in size, and decreased tumor marker levels were noted; thus, 2 more courses of BEP therapy were performed. At the completion of the 3rd course of BEP therapy, the AFP and hCG levels were within the normal ranges [Fig. 3] and CT no longer showed any metastases in the lungs and lymph nodes. The cervical spinal cord lesion and lumbar spinal cord lesion downwards were resolved, while the thoracic spinal cord lesion remained [Fig. 4].

It is recommended that patients who experience an incomplete response to 1st-line therapy (three courses of BEP therapy) be treated with 2nd-line therapy. However, there is currently no established 2nd-line chemotherapy for mixed GCTs. As BEP therapy caused grade 4 febrile neutropenia and a great deal of mental stress due to adverse reactions, the 2nd-line chemotherapy regimen needed to induce fewer adverse reactions. Therefore, TGN therapy (paclitaxel 210 mg/m^2 on

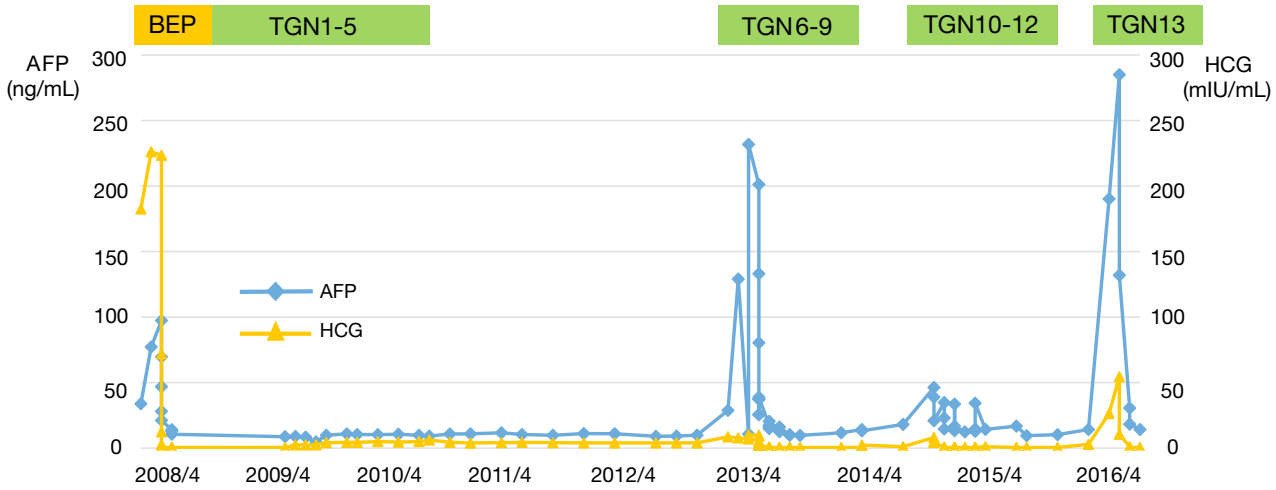

Fig. 3 Changes in the serum AFP and HCG levels during BEP and TGN chemotherapy. AFP: alpha-fetoprotein, HCG: human chorionic gonadotropin.

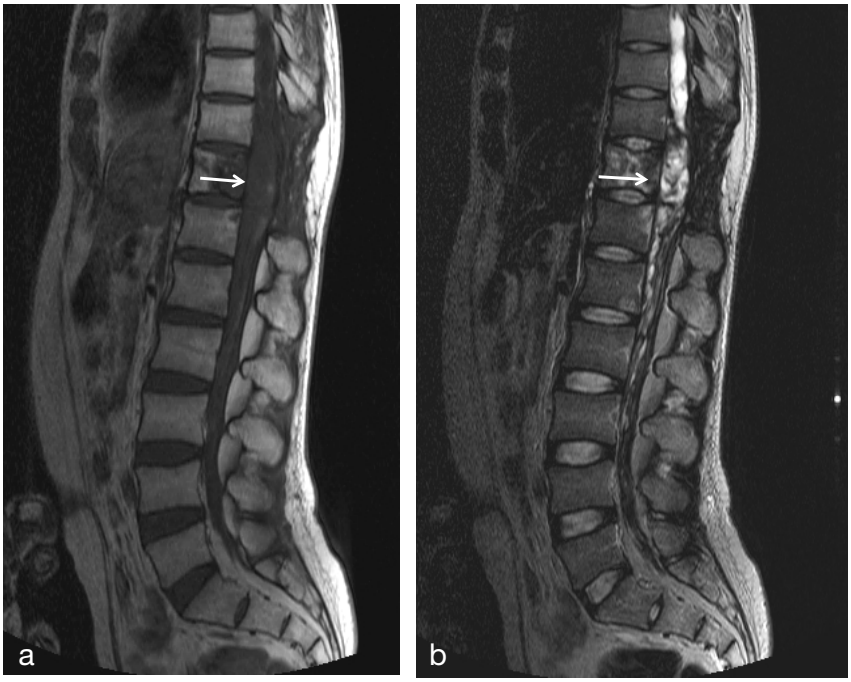

Fig. 4 Post-chemotherapy magnetic resonance imaging (MRI) findings. Sagittal view of (a) T1-weighted and (b) T2-weighted images. MRI revealed a remaining tumor presenting as a heterogeneous signal intensity at the Th11 level (arrows).

day 1; gemcitabine 1000 mg/m^2 on days 1, 8, and 15; and nedaplatin 100 mg/m^2 on day 1) was started in October 2008, and 5 courses of this therapy were performed. During TGN therapy, no grade 4 adverse reactions occurred. After the 5 courses of chemotherapy were performed, the sensory disturbance of the upper limbs was alleviated; however, the sensory disturbance of the lower limbs and leg paralysis remained. MRI no longer showed an upper thoracic spinal cord lesion, but still showed a lower thoracic spinal cord lesion around Th11. Radiotherapy and excision surgery for the residual tumors were considered, but were not performed since the patient and his family rejected further treatment.

The subsequent course was uneventful, with no metastases or changes in the lower thoracic spinal cord mass; however, symptoms of strabismus developed in March 2013. MRI revealed the development of new masses in the pituitary and pineal glands, along with hydrocephalus associated with aqueductal stenosis due to these masses. The AFP and hCG levels increased to 238.1 ng/mL and 10.2 mIU/mL, respectively; the masses were determined to be metastatic tumors. Ventricular drainage was performed for the hydronephrosis, alleviating the symptoms of strabismus. TGN therapy was restarted in April 2013 and 4 courses (9 courses in total) were completed. In July 2013, the AFP and hCG levels decreased to 10.0 ng/mL and 0.5 mIU/mL, respectively, which were within the normal ranges. In September 2014, the AFP (46.3 ng/mL) and hCG (8.1 mIU/mL) levels increased again; consequently, 4 more courses of TGN therapy were performed.

There appeared to be no tumor-diminishing effect on the masses of the pineal and pituitary glands. However, the AFP and hCG reverted to levels within normal range and the patient's condition was thus managed conservatively by regular follow-ups. In March 2016, AFP and hCG levels increased again. The patient is currently receiving TGN therapy, as this therapy was effective in the previous treatment rounds.

DISCUSSION

Extragonadal GCTs are uncommon, accounting for approximately 2–5% of all GCTs. These tumors develop mostly within the central line of the body, and no testicular or ovarian tumor lesions are apparent in patients with extragonadal GCTs. The most common types of extragonadal GCTs are mediastinal and retroperitoneal GCTs, and intracranial GCTs of the pineal gland and the suprasellar region may also occur [1]. According to differences in the responsiveness to treatment and treatment methods, extragonadal GCTs can be classified into germinomas (known as seminomas for primary testicular GCTs) and nongerminomatous GCTs (NGGCTs). On the other hand, extragonadal GCTs of the spinal cord are extremely rare. As compiled by Wu *et al.* [5], 28 cases of primary spinal cord germinomas have been reported in previous studies. However, there have been only 3 previous case reports of primary spinal cord mixed GCTs with several histological types of cells, as diagnosed in our patient [2–4].

Most GCTs are reportedly visualized as iso- to high-signal and high-signal intensities on T1- and T2-weighted MRI, respectively, and as a slightly contrast-enhanced lesion upon gadolinium-diethylenetriamine pentaacetic acid enhancement [6–8]. However, it is accepted that there are currently no characteristic findings of GCTs, and spinal cord GCTs show findings similar to those of spinal astrocytoma [9]. Therefore, tumor resection or biopsy is necessary to establish the diagnosis of a GCT. Meanwhile, teratomas are visualized as heterogeneous intensities due to the presence of fat, calcification, cysts, or hemorrhage, and this is considered effective in establishing its diagnosis [2]. In the present patient, both the T1- and T2-weighted MRI images showed tumors with low- to high-signal intensities. Thus, it was inferred retrospectively that the tumors were partly composed of teratomas rather than comprising a single histological type of teratoma. For this reason, it was difficult to establish the diagnosis of GCT in this patient based on only the MRI findings.

For the treatment of primary central nervous system NGGCTs, Nakamura *et al.* [10] recommended the concomitant use of tumor resection, chemotherapy, and radiotherapy. As for the prognosis of NGGCTs, Aoyama *et al.* [11] and Ogawa *et al.* [12] reported that the 5-year survival rates ranged 45–50%; however, Kim *et al.* [13] reported that a satisfactory 10-year survival rate of 74.6% was achieved by the concomitant use of surgery, radiotherapy, and chemotherapy. As mentioned above, there have been 3 previous case reports of primary spinal cord NGGCTs [2–4]. These 3 patients were treated in accordance with the treatment methods for primary central nervous system NGGCTs; 2 patients received chemotherapy and radiotherapy after tumorectomy and had no recurrence at approximately 1 year of follow-up [2, 3], while 1 patient received chemotherapy after tumorectomy and achieved complete remission, but experienced recurrence of a spinal cord tumor 3 months later, resulting in death from metastasis or myelitis [4]. Our patient received only chemotherapy since the patient did not provide consent to undergo other therapies; hence, radiotherapy or excision of the residual tumors was not performed. Of the 3 previous patients with primary spinal cord NGGCTs, 1 patient with tumor recurrence received no radiotherapy following chemotherapy, while the other 2 patients received both therapies. In these 2 patients, the duration of follow-up was short and it was thus uncertain whether the radiotherapy, in combination with chemotherapy, was effective; however, we consider performing radiotherapy following chemotherapy to be essential. Nonetheless, there is no definite opinion on radiotherapy for primary spinal cord GCTs, including whether radiation should be performed to the whole spinal cord or spinal cord lesions, or to the whole brain as well as to the spinal cord [8]. In addition, adverse reactions such as cognitive disorders and disturbed endocrine functions may occur due to radiation to the whole brain or whole spinal cord [14]; accordingly, radiation to these areas must always be performed with caution.

Other than the three courses of BEP or four courses of EP (cisplatin, etoposide) commonly administered for testicular and ovarian tumors, cisplatin-based chemotherapy, such as ICE therapy [10], is also administered as the 1st-line chemotherapy for primary central nervous system GCTs, with demonstrated effectiveness. It is recommended that patients who do not experience a durable complete response to 1st-line therapy or those who experience a recurrence be treated with 2nd-line chemotherapy. However, there is currently no established 2nd-line chemotherapy regimen or appropriate number of courses. For testicular GCTs, VIP (etoposide, ifosfamide, and cisplatin) and TIP (paclitaxel, ifosfamide, and cisplatin) therapies have been shown to be effective [15–17] and are commonly used. Although TGN therapy (paclitaxel, gemcitabine, and nedaplatin), which was administered to our patient, has not been established as 2nd-line chemotherapy, Shiraishi *et al.* [18] reported that 2–11 cycles of TGN therapy was effective in certain cases, achieving a partial response rate of 47% and long-term survival in some patients. Importantly, with TGN therapy, the incidences and severity of adverse reactions are expected to be reduced since no cisplatin is used, and the mental stress of the patient is also expected to be reduced since repeated daily administration of anticancer agents is not required. Thus, TGN therapy, considered to be one of the 2nd-line chemotherapy treatment options, was selected for our patient and could continuously be performed over the long term.

In summary, we experienced a rare case of primary spinal cord mixed GCTs, in which long-term survival could be achieved by TGN therapy following BEP therapy. Despite TGN therapy not having been established as 2nd-line chemotherapy, this therapy was considered an appropriate treatment option based on the patient's condition.

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