Central Nervous System Primitive Neuroectodermal Tumor of Spinal Cord Developing 20 Years After Curative Treatment of Pineal Tumor

—Case Report—

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Abstract
A 65-year-old male who had previously received curative treatment for a pineal tumor presented with an extremely rare case of primary central nervous system (CNS) primitive neuroectodermal tumor (PNET) of the spinal cord manifesting as progressive tetraparesis. Although the histology was not verified, highly radiosensitive tumor was suspected because of the benign clinical course for over 20 years after only radiation therapy. Magnetic resonance imaging demonstrated an intramedullary tumor extending from C5 to T1. He underwent partial resection and histological examination revealed blue tumor with undifferentiated small round cells. Immunohistochemically, c-kit was negative but CD99 was strongly and diffusely positive. Therefore, rearrangement of the Ewing sarcoma gene was examined to determine the presence of peripheral type of PNET. The results were negative and systemic workup revealed no other disease. These findings led to the diagnosis of primary intramedullary CNS PNET of the spinal cord, and suggested that the spinal cord tumor occurred independently of the prior pineal disease. The residual tumor was controlled by postoperative local radiation therapy.

Key words: spinal cord, intramedullary primitive neuroectodermal tumor, CD99, genetic study

Introduction
Primitive neuroectodermal tumor (PNET) in the spinal canal is an extremely rare disease with only 30 cases reported. Spinal PNETs consist of two histological subtypes: a central type (central nervous system [CNS] PNET)17) developing within the spinal cord and a peripheral type (pPNET)20) occurring mainly in the cauda equina. These two subtypes have very similar histology and clinical course with dismal prognosis, but are genetically different and independent. Approximately 20 cases of pPNET have been reported and specific chromosomal translocations have been ascribed to genetic mechanisms. Only 12 cases of CNS PNET have been reported1,2,4,5,7,11,12,13,15,16,18,19) and the genetic pathway is still unclear. A definite distinction between the two is critical for future molecular targeting therapy. We report a case of primary intramedullary CNS PNET in an elderly patient who had received curative treatment for a pineal tumor 20 years previously.

Case Report
A 65-year-old male was admitted to our hospital because of headache caused by a pineal tumor and obstructive hydrocephalus 20 years previously. Computed tomography (CT) showed a circumscribed and slightly hyperdense tumor measuring 25 mm in diameter with central calcification. The values of tumor markers, including human chorionic gonadotropin, alpha-fetoprotein, and carcinoembryonic antigen, were all within normal limits, so pure germinoma was suspected, and ventriculoperitoneal shunting and radiation therapy were conducted without histological confirmation. The radiation therapy consisted of whole brain irradiation of 13 Gy and local irradiation of 40 Gy, for a total of 53 Gy. Spinal irradiation was not performed.

Six months before the present admission, he noticed progressive tetraparesis that was marked in the upper limbs (hand grip: right, immeasurable; left, 5 kg). Ambulation was unsteady because of decreased positional sensation. Deep tendon reflexes in the lower limbs were hyperactive. Sphincter function was preserved. Magnetic resonance (MR) imaging revealed an intramedullary tumor extending from C5 to T1, which was well enhanced after gadolinium administration (Fig. 1). CT and MR imag-
Fig. 1 Preoperative T₁-weighted magnetic resonance images with gadolinium enhancement showing a solid and almost homogeneously enhanced tumor located between C5 and T1 (A: sagittal section), and eccentric to the right at the upper part (B, C: axial sections).

Fig. 2 Photomicrographs of tumor specimens showing diffusely proliferated small round cells with hyperchromatic nuclei and occasional endothelial proliferation (A: hematoxylin and eosin stain, original magnification ×100), occasional mitoses (arrow) but not rosette formation (B: hematoxylin and eosin stain, original magnification ×200), and tumor cells positive for chromogranin A in the cytoplasm (C: original magnification ×200) and CD99 (MIC2) in the cytoplasmic membrane (D: original magnification ×200).

Fig. 3 Sagittal (A, B) and axial (C, D) T₁-weighted magnetic resonance images with gadolinium enhancement showing the residual tumor (arrows) immediately after surgery (A, C), and partial shrinkage 3 months after radiation therapy (B, D).

Partial resection of the tumor was performed under suspicion of ependymoma, astrocytoma, or delayed intramedullary metastasis of the pineal germinoma. After laminotomy, the dural sac was opened. The dura mater was not involved and the surface of the spinal cord was intact. A dark red and vascular-rich tumor was disclosed immediately after midline myelotomy. No gliotic plane was found between the tumor and the normal spinal cord, which made tumor dissection difficult and finally impossible on the ventrolateral side. The ventral portion of the middle third of the tumor remained. The laminae were reconstructed in an open-door manner using ceramic spinous spacers.

Histological examination revealed so-called blue tumor at low magnification and diffuse proliferation of small round cells with hyperchromatic nuclei and a high nucleus/cytoplasm ratio at high magnification. Occasional endothelial proliferation, necrosis, and mitosis were present, but no rosette formation or definite structural pattern (Fig. 2A, B). The tumor cells were immunoreactive for neurofilament, neuron-specific enolase, chromogranin A, synaptophysin, CD56 (NCAM), and CD99 (MIC2) (Fig. 2C, D), but negative for glial fibrillary acidic protein, vimentin, epithelial membrane antigen, S-100 protein, cytokeratin, lymphocyte common antigen, and c-kit. MIB-1 labeling index was approximately 15%. Intense membranous staining for CD99 was observed, so the expression of the chimeric genes of EWS/FLI1 and EWS/ERG was examined by polymerase chain reaction to differentiate the tumor from Ewing sarcoma (EWS) and pPNET, but no amplification of the target genes was detected (data not shown). The final diagnosis was primary intramedullary CNS PNET of the spinal cord.

The patient was wheelchair-bound immediately after the operation, but became ambulant with a cane 4 months later, with occasional urinary incontinence. Local radiation therapy was performed with a single shots of 2 Gy...
over 22 days (44 Gy in total). Chemotherapy was not employed. The residual tumor diminished in volume (Fig. 3) and he was transferred to another hospital 6 months after the surgery.

**Discussion**

CNS PNET is defined as a new tumor entity of embryonal tumors in the latest edition of the World Health Organization classification (2007).\(^{17}\) Prefixing CNS to PNET enabled the grouping of supratentorial PNET with tumors of similar morphology in the brainstem and the spinal cord, and the distinction from pPNET, which is derived from the peripheral nervous system, bone, and soft tissues, and has a different genetic background. pPNET is now considered to be the same tumor as EWS but with different grade of differentiation, so these two tumors are grouped as the Ewing family of tumors (EWS/pPNET). In the neurosurgical field, EWS/pPNETs occasionally occur in the meninges of the cranial vault, epidural space of the spinal canal, and cauda equina.\(^{8,13}\)

CD99 is a 30 or 32 kDa cell surface glycoprotein derived from the MIC2 gene. This molecule was initially isolated as an EWS antigen and so expression was considered pathognomonic for EWS/pPNET. Subsequently, many cases were diagnosed as pPNETs solely on the basis of CD99 expression. More recently, CD99 expression was confirmed in normal ependymal cells and various histological types of neuroepithelial tumors, including ependymoma (~100%), astrocytoma, oligodendroglioma, CNS PNET (including the former supratentorial PNET) (~40%), choroid plexus papilloma, and pituitary adenoma.\(^{3,9}\) Therefore, more definite evidence is required to establish the correct diagnosis.\(^{17,20}\) EWS/pPNETs share common and characteristic chromosome changes with t(11;22)(q24;q12) in 85% and t(21;22)(q22;q12) in 10–15% of cases, generating chimeric genes of EWS/FLI1 and EWS/ERG, respectively.\(^{20}\) In the present case, the possibility of pPNET was negated by molecular analysis, despite the high CD99 expression, and marked neuronal differentiation and intramedullary location also supported the diagnosis of CNS PNET.\(^{17,20}\)

We believe that the spinal cord tumor developed independently of the prior intracranial disease in the present case. However, if the former is a metastasis of the latter, we have to consider the possibility that the prior pineal tumor was a pineal parenchymal tumor or a PNET. Because the patient remained in complete remission for over 20 years, pineoblastoma and PNET were most unlikely. Indeed, less malignant tumors, such as pineocytoma and pineal parenchymal tumor with intermediate differentiation (PPTID), occasionally respond to radiation therapy. However, no pineocytomas have been shown to metastasize, and the 5-year survival of patients with PPTID ranges from 39% to 74% in a series of strictly classified tumors.\(^{10}\) These findings suggest that these two tumor entities are also unlikely to be the primary tumors.

A review of literature revealed only 30 cases reported as primary spinal PNETs.\(^{11,13,19}\) Because of the confusion in classification and scarce clinical data for individual cases, the distinction between CNS PNET and pPNET has not always been made. Recently, attempted division of reported cases found 12 cases of CNS PNET and 17 cases of pPNET.\(^{13}\) In addition, reviews of the literature found 7 and 11 cases of intramedullary CNS PNET.\(^{11,16}\) We re-examined individual clinical data, CD99 expression, and genetic studies for these cases, and recognized 12 cases as definite primary intramedullary CNS PNETs (Table 1). The present case is the 13th known case and the first to be evaluated by both immunohistochemistry and molecular

**Table 1** Summary of reported cases of histologically verified intramedullary central nervous system primitive neuroectodermal tumor

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author (Year)</th>
<th>Age (yrs)/Sex</th>
<th>Level</th>
<th>Location</th>
<th>CD99 immunohistochemistry</th>
<th>Genetic analysis</th>
<th>Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jaksche et al. (1988)(^{12})</td>
<td>15/F</td>
<td>thoracolumbar</td>
<td>intra-, extramedullary</td>
<td>ND</td>
<td>ND</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Freyer et al. (1989)(^{7})</td>
<td>7/M</td>
<td>thoracolumbar</td>
<td>intramedullary</td>
<td>ND</td>
<td>ND</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Ogasawara et al. (1992)(^{18})</td>
<td>16/F</td>
<td>lumbar</td>
<td>intramedullary</td>
<td>ND</td>
<td>ND</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>Kwon et al. (1996)(^{15})</td>
<td>3 mos/F</td>
<td>thoracolumbar</td>
<td>intramedullary</td>
<td>ND</td>
<td>ND</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Deme et al. (1997)(^{9})</td>
<td>22/F</td>
<td>thoracolumbar</td>
<td>intramedullary</td>
<td>ND</td>
<td>ND</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>Mawrin et al. (2002)(^{16})</td>
<td>69/M</td>
<td>thoracic</td>
<td>intra-, extramedullary</td>
<td>ND</td>
<td>ND</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Albrecht et al. (2003)(^{1})</td>
<td>29/F</td>
<td>thoracic</td>
<td>intramedullary</td>
<td>ND</td>
<td>negative</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>Chen et al. (2005)(^{19})</td>
<td>18/F</td>
<td>cervicothoracic</td>
<td>intramedullary</td>
<td>ND</td>
<td>negative</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>De Tomassi et al. (2006)(^{10})</td>
<td>38/M</td>
<td>thoracic</td>
<td>intra-, extramedullary</td>
<td>ND</td>
<td>ND</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>Jain et al. (2006)(^{11})</td>
<td>54/F</td>
<td>cervical</td>
<td>intra-, extramedullary</td>
<td>negative</td>
<td>ND</td>
<td>alive as of this writing</td>
</tr>
<tr>
<td>11</td>
<td>Kampman et al. (2006)(^{13})</td>
<td>3/M</td>
<td>cervical</td>
<td>intramedullary</td>
<td>negative</td>
<td>ND</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>Otero-Rodriguez et al. (2009)(^{19})</td>
<td>17 mos/M</td>
<td>thoracic</td>
<td>intramedullary</td>
<td>ND</td>
<td>ND</td>
<td>alive with progression</td>
</tr>
<tr>
<td>13</td>
<td>Present case</td>
<td>65/M</td>
<td>cervicothoracic</td>
<td>intramedullary</td>
<td>positive</td>
<td>negative</td>
<td>alive at 18</td>
</tr>
</tbody>
</table>

ND: not done.
analysis.

The imaging characteristics of CNS PNET remain unclear, although MR imaging findings seem to be similar to those of common ependymomas or astrocytomas. The optimal and standard therapeutic approach has not yet been established. Although maximal tumor resection followed by whole-neuraxis irradiation and chemotherapy has been recommended, as performed for medulloblastoma, survival is not prolonged even in such a setting. The imaging characteristics and optimal management of spinal CNS PNET have yet to be determined.

Acknowledgments

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