Primary Cauda Equina Lymphoma Treated With High-Dose Methotrexate

—Case Report—

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Abstract

A 69-year-old man presented with a very rare case of primary central nervous system lymphoma originating in the cauda equina manifesting as progressive paraparesis. The patient underwent a biopsy, and was treated with intravenous high-dose (3.5 g/m²) methotrexate chemotherapy and local irradiation. Histological study revealed large B cell type lymphoma. Follow-up magnetic resonance imaging showed complete remission of the lesion, but the patient died of pneumonia at 18 months after the initial onset without tumor recurrence, so the efficacy of this strategy remains unknown.

Key words: spinal lymphoma, cauda equina, high-dose methotrexate, prognosis

Introduction

Primary spinal intramedullary lymphoma is a very rare entity, first reported in 1976,9) with only one case of cauda equina origin reported in 1983,18) although the incidence of primary central nervous system lymphoma (PCNSL) is increasing (0.4/100000). The therapeutic management has not been established because of the rarity of this disease. In recent years, intravenous injection of high-dose methotrexate (MTX) has mainly been performed as a chemotherapy for PCNSL, especially for brain lymphoma, leading to favorable outcome with mean survival time of over 39.3 months in Japan.11) Here we present a case of primary cauda equina lymphoma treated with high-dose MTX and local irradiation.

Case Report

A 69-year-old male was admitted to our hospital with progressive paraparesis, hypesthesia, and ischuria persisting for one week. Deep tendon reflexes were hypoactive in the bilateral lower extremities, and paresis with hypesthesia was mainly apparent on the left. The patient had a history of vertebral body fracture of L1 concomitant with lumbar pain 8 months previously. Magnetic resonance (MR) imaging showed angular deformity of L1, indicating vertebral fracture, which had compressed the conus and spinal cord with intracordal high intensity on the T₂-weighted image above the T11 level (Fig. 1A). A well-enhanced lesion was recognized in the conus medullaris and cauda equina (Fig. 1B–D). The presumptive diagnosis was myelitis or intramedullary tumor, such as lymphoma and glioma.

Laminectomy was performed from T12 to L1, revealing enlarged reddish-gray cauda equina with invasion into the adjacent nerve rootlets involving a small region of the distal conus medullaris (Fig. 2). Intraoperative pathological diagnosis revealed malignant lymphoma, so only the tumorous cauda equina was resected and no further surgical procedure was undertaken. Immunohistological examination of the sample showed proliferation of large round cells with basophilic nuclei stained positively for CD20 (Fig. 3). Bone marrow aspiration and whole body computed tomography with contrast medium demonstrated no apparent abnormality in the extra-central nervous system region. Systemic bone scintigraphy only revealed...
the old vertebral fracture, so that the definitive diagnosis was diffuse large B cell lymphoma of cauda equina origin. Human immunodeficiency virus test was negative and there was no history of immunodeficiency.

Based on the diagnosis, chemotherapy using intravenous high-dose MTX (3.5 g/m²), according to the protocol of Osaka University in Japan, was selected. The protocol includes 3 cycles of MTX injection; one injection on the first day of 2-week periods with high-volume hydration. Following the last cycle of chemotherapy, adjuvant local radiotherapy was administered to the lumbar lesion with a total radiation dose of 30 Gy per 15 fractions. MR imaging, performed immediately after all treatments were finished, showed complete remission of the lesion. Intramedullary hyperintensity on T₂-weighted MR imaging and enhancement on T₁-weighted MR imaging with gadolinium had disappeared (Fig. 4). The patient’s symptoms gradually improved except for continuous left leg pain.

Three months after treatment, the patient was still in complete remission under pain management and started training to walk, then was transferred to another hospital for rehabilitation. Radiographical remission was sustained for over a year. However, he died of pneumonia at 18 months after the initial onset.

Discussion

Spinal intramedullary lymphoma as primary spinal cord disease is uncommon, and accounts for only about 1% of PCNSL. Spinal lesion is more commonly associated with other systemic lymphoma.

Only 21 cases of primary spinal intramedullary lymphoma have been reported including our case (Table 1). Review of all cases of primary spinal malignant lymphoma revealed that the patients were aged 24–77 years (mean 51.4 years), with 10 males and 11 females. The location was cervical in 8 cases, thoracic in 2, lumbar and conus in 3, cauda equina in 2, and multiple in 6. Epidural spinal involvement occurs in about 5% of patients with systemic lymphoma.

Cauda equina lymphoma is exceedingly rare with only one case of primary cauda equina lymphoma in a 68-year-old woman with chronic onset of symptoms and appearance of multiple gray-white nerve roots enlarged at surgery. Radiotherapy was performed in the lumbar region. Although there was no improvement of paralysis and bowel-bladder function, no metastasis was recognized 3 months after treatment. This case is similar to our present patient in that both involved multiple nerve rootlets and the histological diagnosis of B-lymphocyte origin. Although the interpretation of histological appearances described in the literature is difficult because of varied nomenclature, B cell, T cell, and low grade of no definite type accounted for 17, 3, and 1 cases, respectively, of primary spinal malignant lymphoma.

The possibility of immunodeficiency was recognized in 4 patients, including one with positive serum human T-lymphotropic virus type I antibody titer after renal transplantation, one with systemic lupus erythematosus with a preceding history of a lupus-erythematosus-like disorder given 20 mg of prednisone daily and tapered off gradually for 6 months, one after thymectomy, and one with herpes zoster infection simultaneous with the onset of neurological symptoms. Our patient had a history of vertebral compression fracture adjacent to the tumor, but the relationship between the fracture and occurrence of malignant tumor is unclear.

There is no optimal established strategy for either pri-
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Location</th>
<th>Examination</th>
<th>Histology</th>
<th>Chemotherapy</th>
<th>Irradiation</th>
<th>Survival</th>
<th>Immuno-deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbst et al. (1976)</td>
<td>51</td>
<td>M</td>
<td>conus</td>
<td>myelography</td>
<td>B cell</td>
<td>MTX i.t. 12 mg/m² × 12</td>
<td>LC (7800 rads)</td>
<td>48 mos</td>
<td>alive</td>
</tr>
<tr>
<td>Bruni et al. (1977)</td>
<td>53</td>
<td>M</td>
<td>C1–T1</td>
<td>myelography</td>
<td>B cell</td>
<td>none</td>
<td>none</td>
<td>9 mos</td>
<td>dead</td>
</tr>
<tr>
<td>Mitsumoto et al. (1980)</td>
<td>63</td>
<td>F</td>
<td>lumbar</td>
<td>myelography</td>
<td>B cell</td>
<td>none</td>
<td>WNA (4000 rads)</td>
<td>5 mos</td>
<td>dead</td>
</tr>
<tr>
<td>Slager et al. (1982)</td>
<td>45</td>
<td>F</td>
<td>C1–C5</td>
<td>myelography</td>
<td>B cell</td>
<td>none</td>
<td>8 mos</td>
<td>dead</td>
<td>none</td>
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<tr>
<td>Hautzer et al. (1983)</td>
<td>26</td>
<td>F</td>
<td>T6–L2</td>
<td>myelography</td>
<td>B cell</td>
<td>none</td>
<td>10 mos</td>
<td>dead</td>
<td>thymectomy</td>
</tr>
<tr>
<td>Mauney and Sciotto (1983)</td>
<td>68</td>
<td>F</td>
<td>cauda equina</td>
<td>myelography</td>
<td>B cell</td>
<td>none</td>
<td>LC (4500 rads)</td>
<td>3 mos</td>
<td>alive</td>
</tr>
<tr>
<td>Ilami et al. (1986)</td>
<td>24</td>
<td>F</td>
<td>T4–T6</td>
<td>MR imaging</td>
<td>T cell</td>
<td>none</td>
<td>WNA (40.5 Gy)</td>
<td>18 mos</td>
<td>alive</td>
</tr>
<tr>
<td>Kamata et al. (1986)</td>
<td>55</td>
<td>M</td>
<td>cervical–conus</td>
<td>myelography</td>
<td>B cell</td>
<td>none</td>
<td>not in detail</td>
<td>5 yrs</td>
<td>dead</td>
</tr>
<tr>
<td>Landan et al. (1987)</td>
<td>37</td>
<td>F</td>
<td>cervical–conus</td>
<td>myelography</td>
<td>B cell</td>
<td>none</td>
<td>42 mos</td>
<td>dead</td>
<td>none</td>
</tr>
<tr>
<td>Bluemke and Wang (1990)</td>
<td>61</td>
<td>M</td>
<td>C1–C4</td>
<td>MR imaging</td>
<td>B cell</td>
<td>none</td>
<td>not in detail</td>
<td>7 mos</td>
<td>dead</td>
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<td>Slowik et al. (1990)</td>
<td>49</td>
<td>F</td>
<td>C3–C6</td>
<td>myelography</td>
<td>low grade</td>
<td>VCP × 2 + BACOP × 2</td>
<td>LC (40 Gy)</td>
<td>25 mos</td>
<td>alive</td>
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<tr>
<td>Miyazaki et al. (1991)</td>
<td>68</td>
<td>F</td>
<td>conus</td>
<td>MR imaging</td>
<td>B cell</td>
<td>VEPA</td>
<td>LC (36 Gy)</td>
<td>20 mos</td>
<td>dead</td>
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<tr>
<td>Nakao et al. (1994)</td>
<td>48</td>
<td>M</td>
<td>T1–T4</td>
<td>MR imaging</td>
<td>B cell</td>
<td>VEPA</td>
<td>LC (16 Gy) + WSP (30 Gy)</td>
<td>15 mos</td>
<td>dead</td>
</tr>
<tr>
<td>McDonald et al. (1995)</td>
<td>46</td>
<td>M</td>
<td>C2–C6</td>
<td>MR imaging</td>
<td>T cell</td>
<td>none</td>
<td>WNA (31.5 Gy) + LC (14.8 Gy)</td>
<td>30 mos</td>
<td>dead</td>
</tr>
<tr>
<td>Urasaki et al. (1996)</td>
<td>52</td>
<td>F</td>
<td>T9-cauda equina</td>
<td>MR imaging</td>
<td>T cell</td>
<td>none</td>
<td>WSP (750 cGy)</td>
<td>27 mos</td>
<td>dead</td>
</tr>
<tr>
<td>Caruso et al. (1998)</td>
<td>77</td>
<td>M</td>
<td>C4-C5, T5-T6</td>
<td>MR imaging</td>
<td>B cell</td>
<td>not in detail (after recurrence)</td>
<td>none</td>
<td>5 yrs</td>
<td>alive</td>
</tr>
<tr>
<td>Hori et al. (1999)</td>
<td>51</td>
<td>M</td>
<td>brain–conus</td>
<td>MR imaging</td>
<td>B cell</td>
<td>MTX 1.35 g + vincristine + procarbazine × 3, MTX i.t. × 3</td>
<td>none</td>
<td>22 mos</td>
<td>alive</td>
</tr>
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<td>Bekar et al. (2001)</td>
<td>41</td>
<td>M</td>
<td>C2–C4</td>
<td>MR imaging</td>
<td>B cell</td>
<td>VEPA × 6</td>
<td>LC (4500 cGy)</td>
<td>12 mos</td>
<td>alive</td>
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<tr>
<td>Herrlinger et al. (2002)</td>
<td>36</td>
<td>F</td>
<td>C2–C3</td>
<td>MR imaging</td>
<td>B cell</td>
<td>high-dose cytarabine (i.v., i.t.) →MTX (1 g/m²) + CHOP</td>
<td>LC (45 Gy)</td>
<td>15 mos</td>
<td>dead</td>
</tr>
<tr>
<td>Machiya et al. (2007)</td>
<td>60</td>
<td>F</td>
<td>C2–C7</td>
<td>MR imaging</td>
<td>B cell</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Present case</td>
<td>69</td>
<td>M</td>
<td>cauda equina</td>
<td>MR imaging</td>
<td>B cell</td>
<td>high-dose MTX (3.5 g/m² × 3)</td>
<td>LC (30 Gy)</td>
<td>18 mos</td>
<td>dead</td>
</tr>
</tbody>
</table>

BACOP: combined chemotherapy with bleomycin, Adriamycin-doxorubicin, cyclophosphamide, Oncovin-vincristine, and prednisone; CHOP: combined chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone; F: female; i.t.: intrathecal; i.v.: intravenous; LC: local; M: male; MR: magnetic resonance; MTX: methotrexate; NM: not mentioned; SLE: systemic lupus erythematosus; VCP: combined chemotherapy with vincristine, CCNU, and prednisolone; VEPA: combined chemotherapy with vincristine, prednisolone, doxorubicin, and cyclophosphamide; WNA: whole neuraxis; WSP: whole spinal.
mary spinal intramedullary lymphoma or primary brain lymphoma. Of the total of 21 cases, 14 patients underwent irradiation, 6 did not undergo irradiation, and one treatment is not mentioned. Of all patients who underwent radiotherapy, 3 patients received whole neuraxis radiotherapy for brain metastasis[20] or prophylaxis.[13,19] Local radiotherapy and whole spinal irradiation were given in 8 and 1 patients, respectively. Two were unknown in detail. The overall survival rate at 5 years is 42.3% for those who received greater than 50 Gy to the whole brain and spinal cord, but 12.8% for those receiving less than 50 Gy.[20] However, this study was reported in 1986. In recent years, combined chemotherapy has reduced the total amount of radiation and avoided the unfavorable side effects.

Conventional chemotherapy has been gradually applied subsequent to radiotherapy, but cannot achieve abundant therapeutic effects. Eight patients underwent chemotherapy on at first admission and 11 did not. One patient underwent only laminectomy at the first admission, and underwent chemotherapy after recurrence. The chemotherapy consisted of VEPA (vincristine, doxorubicin, prednisolone, and cyclophosphamide) in 3 patients,[2,21,23] VCP (vincristine, CCNU, and prednisolone) + BACOP (bleomycin, Adriamycin-doxorubicin, cyclophosphamide, Oncovin-vincristine, and prednisone) in one,[20] intravenous normal-dose MTX injection + CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) following intravenous and intrathecal high-dose cytarabine in one,[10] intravenous and intrathecal normal-dose MTX + vincristine + procarbazine in one,[12] and intrathecal MTX in one.[9] Of these 8 patients, 7 underwent combined radiotherapy, but one patient did not because of bone marrow suppression.[12] The treatment protocol was not described in one report.[17] We used 3 cycles of high-dose MTX and subsequent local irradiation. Recently, better long-term outcome in patients with cranial PCNSL treated with irradiation following high-dose MTX has been reported. Median overall survival time was 55.4 months and complete remission was achieved in 52%. In this study, the maximum number of injection cycles allowed was 8 cycles every 2 weeks using 8 g/m² MTX until complete response which showed disappearance of tumor, and the median number of cycles to achieve complete response was 6.[1,7] Mean survival time was 39.3 months in another series,[11] so high-dose MTX might attain better prognosis in spinal lymphomas. However, our patient died at 18 months after onset, so the benefit of this strategy is still unknown although he was of advanced age.

In all cases of combined therapy except one [alive at 48 months], survival time remains insufficient compared to conventional methods. In this study, median overall survival time of spinal lymphomas was 27 months (95% confidence interval 10 to 42 months), and mean survival time was 29.5 ± 5.26 months. A log-rank test revealed no significant relationship between survival time and the strategy of treatment. At this point, spinal lymphomas cannot attain better prognosis than cranial lymphomas.[14] Also, the loading dose of high volume infusion on the heart and kidney, aiming to salvage folic acid, could be a risk in aged patients with existing comorbidities. We need more experience with therapeutic cases to achieve better prognosis by methods adapted for the age or background of individual patients.

References

19) McDonald AC, Nicoll JA, Ramlng R: Intramedullary non-


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