High-dose methotrexate monotherapy followed by radiation for CD30-positive, anaplastic lymphoma kinase-1–positive anaplastic large-cell lymphoma in the brain of a child

Case report

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The authors report the case of an 11-year-old immunocompetent boy with primary CNS CD30-positive anaplastic large-cell lymphoma (ALCL) that was also positive for anaplastic lymphoma kinase-1. His initial clinical manifestation was acute meningitis of unknown etiology. Findings on CT scanning were normal. Although he received empirical treatment against infection, his systemic and neurological status deteriorated. Subsequent MRI revealed newly emerged enhanced lesions and concomitant edema in the left parietal lobe. Diagnosis was confirmed following a brain biopsy and immunohistochemical staining. Three courses of systemic high-dose methotrexate (HD-MTX) treatment with 2-week intervals was started, followed by whole-brain radiation. His clinical course improved, and he has remained disease-free for more than 8 years without any additional treatment. Because ALCL originating in the brain is extremely rare and difficult to diagnose, no standard treatment has been established. This report suggests that systemic HD-MTX monotherapy can be an effective and worthwhile tailored therapeutic option for pediatric primary CNS ALCL.

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Key words • anaplastic large-cell lymphoma • anaplastic lymphoma kinase-1 • CD30 • central nervous system • methotrexate • treatment • oncology

Abbreviations used in this paper: ALCL = anaplastic large-cell lymphoma; ALK-1 = anaplastic lymphoma kinase-1; HD-MTX = high-dose methotrexate; PCNSL = primary CNS lymphoma.
and the CSF cell count gradually increased to 6000 cells/mm³ at maximum. The CSF pressure was 400 mm H₂O at that time. No malignant tumor cells were detected by CSF cytology. He was started on steroid pulse treatment (methylprednisolone 1000 mg/day for 3 days) for a total of 3 courses. Although temporary improvements in his level of consciousness and slight improvement in the severe headaches were achieved with the steroid pulse treatment, focal edema in the left parietal lobe increased as seen on serial MR images (Fig. 1B). He became lethargic again and suffered from right hemiparesis and aphasia. Thus, he was referred to the Department of Neurosurgery.

**Operation.** Because of the increased intracranial pressure in this patient, he underwent a left decompressive craniectomy 1 month after admission. On the surface of the left parietal lobe, the arachnoid was thickened and whitish. Scattered yellowish, solid-appearing, well-demarcated lesions were present on the surface of the brain. Five lesions were removed as specimens for further analysis. The next day, ventricular drainage was performed because of the progression of hydrocephalus.

**Pathological Findings.** Microscopically, we observed large tumor cells with a polymorphic appearance that had infiltrated diffusely and cohesively throughout the cortex. The nuclei of these cells were pleomorphic, and nucleoli were prominent. The cytoplasm was abundant and clear or eosinophilic (Fig. 2A). No bacteria were seen. Immunohistochemical staining showed that the tumor cells were focally positive for epithelial membrane antigen, strongly positive for leukocyte common antigen (Fig. 2B), positive for CD30 (Ki-1) in the cell membrane (Fig. 2C), positive for ALK-1 in the cytoplasm (Fig. 2D), and negative for glial fibrillary acidic protein. Tumor cells were also negative for T-cell–associated (CD3 and UCHL-1 [CD45RO]) and B-cell–associated (CD20 and CD79a) antigens. The KP-1 (CD68) antibody raised against histiocytes did not label the tumor cells. These findings were consistent with a diagnosis of ALCL of the null cell phenotype.

**Postoperative Course and Additional Treatment.** Bone marrow aspiration showed normal findings and no tumor cells. Whole-body ⁶⁷Ga-citrate scintigraphy was performed twice, but no abnormal accumulation was detected. These investigations excluded the presence of systemic lymphoma manifestation. A postoperative MR image with contrast demonstrated strongly enhanced cortical lesions concomitant with significant edema (Fig. 1C). Two weeks after the operation, the patient began 3 courses of HD-MTX monotherapy with 2-week intervals, followed by whole-brain radiation therapy in which
High-dose methotrexate therapy for anaplastic large-cell lymphoma

A total of 28.8 Gy was delivered in 16 fractions of 1.8 Gy each. During these treatments, severe brain bulging at the surgical site gradually disappeared (Fig. 1D and E). After he regained consciousness, the right hemiparesis and aphasia improved, although minimal impairment remained. His visual field was also damaged in the lower right quadrant. Over the next 2 months, he required 2 CSF shunting procedures because of shunt tube obliteration. Five months after the onset of symptoms, he underwent a cranioplasty and was discharged.

Upon follow-up after discharge from the hospital, the patient continued to have speech difficulty and visual field deficits. He has finished high school and remains in complete remission 8 years after the completion of treatment and the onset of symptoms. He is not currently receiving any other treatments.

**Discussion**

Since 1985, a novel type of lymphoma, called “ALCL,” which is characterized by frequently cohesive proliferation of large pleomorphic blasts and continuous expression of the cytokine receptor CD30 (Ki-1) on the tumor cells, has been described. Anaplastic large-cell lymphoma is an uncommon T-cell lymphoma characterized by the expression of T-cell antigens. However, null cell tumors, which frequently express genetic evidence of the T-cell lineage, are present less often. Clinically, 2 types of presentations are recognized: a systemic form and a primary cutaneous form. The systemic form of ALCL involves lymph nodes or extranodal sites, such as the bone marrow, bone, respiratory tract, skin, and gastrointestinal tract. However, CD30-positive primary CNS lymphoma (PCNSL) is rarely encountered. Currently, 2 types of the systemic form are segregated based on ALK expression, which leads to differences in clinical features and prognosis. The ALK-1–positive ALCL predominantly affects young males, and the outcome is good if appropriate treatment is given. However, unlike the favorable prognosis observed with ALK-1–positive ALCL occurring outside the CNS, most cases of CNS ALCL have a rapidly fatal course. The ALK-1–negative ALCL occurs in older patients, affects both sexes equally, and is associated with a poor outcome.

More than half of ALCL cases show the chromosomal translocation t(2;5)(2p23;5q35), which fuses the NPM1 gene (nucleophosmin [nucleolar phosphoprotein B23]) at 5q35 and the ALK gene at 2p23, which in turn leads to the expression of a novel chimeric protein. This chimeric protein contributes to mitogenic activity, which is likely to be important in the molecular pathogenesis of ALCL.

Because of the histological composition of large cells, this lesion is not always readily recognized by pathologists, particularly when it occurs in an unusual site such as the brain. Rapid clinical deterioration appears to be a characteristic of this particular subtype of lymphoma. Thus, avoiding delays in reaching an accurate diagnosis is of great importance. One month elapsed before we performed the brain biopsy, and 2 additional weeks were needed to establish an accurate diagnosis in our patient. Recognition of this disease by both pediatri-
TABLE 1: Reported cases of pediatric CNS ALCL*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>ALK-1 Positivity</th>
<th>Lesion Location</th>
<th>Chemotherapy</th>
<th>Radiation Therapy (Gy)</th>
<th>Outcome</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havlioglu et al., 1995</td>
<td>4, F</td>
<td>+</td>
<td>TL, brainstem, CC, LC, LM</td>
<td>cyclophosphamide, doxorubicin, Oncovin</td>
<td>—</td>
<td>alive</td>
<td>null cell</td>
</tr>
<tr>
<td>Buxton et al., 1998</td>
<td>10, F</td>
<td>NA</td>
<td>PL</td>
<td>HD-MTX, cyclophosphamide, daunorubicin, cytosine, vincristine</td>
<td>24, whole-brain; 12, spine</td>
<td>dead</td>
<td>T cell</td>
</tr>
<tr>
<td>Abdulkader et al., 1999</td>
<td>13, M</td>
<td>+</td>
<td>FL, PL</td>
<td>vincristine, etoposide, methotrexate, cyclophosphamide, cytarabine</td>
<td>—</td>
<td>dead</td>
<td>T cell</td>
</tr>
<tr>
<td>Karikari et al., 2007</td>
<td>4, M</td>
<td>+</td>
<td>FL, TL, pineal region, LM</td>
<td>doxorubicin, vincristine</td>
<td>25.2, whole-brain + upper cervical</td>
<td>alive</td>
<td>NA</td>
</tr>
<tr>
<td>Merlin et al., 2008</td>
<td>13, M</td>
<td>+</td>
<td>FL, LM</td>
<td>vinblastine, cyclophosphamide, Adriamycin, methotrexate, cytarabine, etoposide, ifosfamide</td>
<td>18, cerebrospinal</td>
<td>dead</td>
<td>T cell</td>
</tr>
<tr>
<td>Present case</td>
<td>11, M</td>
<td>+</td>
<td>PL, LM</td>
<td>HD-MTX</td>
<td>28.8, whole-brain</td>
<td>alive</td>
<td>null cell</td>
</tr>
</tbody>
</table>

* None of the patients received intrathecal chemotherapy. CC = cervical cord; FL = frontal lobe; LC = lumbar cord; LM = leptomeninges; NA = not applicable; PL = parietal lobe; TL = temporal lobe; + = yes.

Leptomeningeal involvement is frequently observed in primary CNS ALCL, as demonstrated in our case, and this differs from typical PCNSL.7,9,10,12–14 The relationship between the meninges and subarachnoid spaces could lead to differential diagnosis problems with either infectious diseases or metastases.13

No standard treatment for ALCL originating from the CNS has been established given the rarity of the tumor.8 Thus, further investigations to establish effective treatment modalities are needed.11 Only 6 pediatric cases of ALCL in the CNS, including our patient, have been reported in the English-language literature to date (Table 1).1,2,9,10,12 Of the pediatric cases, one may have had secondary involvement of the CNS.10 None of these cases were treated with the same chemotherapeutic drug combination. The results of the Radiation Therapy Oncology Group Study 93-10 and multicenter study analysis of 370 immunocompetent patients with PCNSL established the superiority of combined treatment (chemotherapy and radiotherapy) compared with radiotherapy alone.5,6 High-dose methotrexate is widely recognized as the single most effective chemotherapeutic agent for PCNSL.9 Patients receiving HD-MTX–based chemotherapy survive longer than those treated with other drugs, although intrathecal chemotherapy is not correlated with outcome.8 Intrathecal MTX may not be necessary for treating the subarachnoid space in patients with PCNSL when adequate intravenous doses are administered.5 Thus, we treated our patient with HD-MTX monotherapy first for disease control while avoiding the adverse effects of radiotherapy. Although a high-dose combination of anticancer drugs followed by craniospinal irradiation and/or bone marrow transplantation fails to improve survival in pediatric patients,6,12 our protocol of administering HD-MTX monotherapy to our patient with primary CNS ALCL succeeded in shrinking the lesions. Long-term follow-up over 8 years in our patient demonstrated the effectiveness of single-drug HD-MTX treatment followed by whole-brain radiation. Therefore, we propose that systemic HD-MTX monotherapy may be an effective and worthwhile chemotherapeutic option for pediatric primary CNS ALCL.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: Furuya. Acquisition of data: Furuya. Analysis and interpretation of data: Furuya, Takahashi. Drafting the article: Furuya. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Furuya. Study supervision: Nakagomi.

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