Clinical presentation of anaplastic large-cell lymphoma in the central nervous system

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Abstract. The majority of primary central nervous system (CNS) lymphomas are diffuse large B-cell lymphomas (DLBCLs) and anaplastic large-cell lymphoma (ALCL) is a type of T-cell tumor that is rare in the CNS. The aim of this study was to elucidate the clinical presentation and standard therapy of ALCLs by investigating reported cases. Additionally, a case of anaplastic lymphoma kinase (ALK)-positive ALCL in a 20-year-old man who exhibited no recurrence for >5 years following high-dose methotrexate (HD-MTX) treatment was described. Twenty-six immunocompetent patients with ALCL of the CNS that were previously reported and 1 case of ALCL of the CNS treated at our hospital were investigated. Overall survival (OS) was analyzed in relation to survival factors such as age, ALK status and the treatment regimen. The male:female ratio of the patients was 19:8. Of the 27 patients, 13 (48.1%) were ALK-positive, 9 (33.3%) were ALK-negative and the ALK status was not determined in the remaining 5 patients (18.5%). ALK-positive ALCL occurred at a younger age (median age, 17 years) and exhibited a favorable course (5-year OS, 75.0%), whereas ALK-negative ALCL presented at an older age (median age, 65 years) and resulted in fatal outcomes (5-year OS, <12.5%). Similar to the findings for systemic ALCL, ALK positivity, age <40 years and chemotherapy are associated with long-term survival for ALCL of the CNS. Chemoradiotherapy including methotrexate is recommended for ALCL and the possibility of treatment with chemotherapy alone for ALK-positive ALCL is currently under consideration.

Introduction

Primary central nervous system (CNS) lymphoma (PCNSL) is the second most common malignant brain tumor, accounting for ~2.9% of the primary brain tumors in Japan (1). Age, performance status (PS), lactate dehydrogenase (LDH) serum levels, cerebrospinal fluid protein concentrations and the involvement of deep structures of the brain are independent predictors of survival (2). The 2-year overall survival (OS) rate varies from 24 to 85% in proportion to the prognostic score based on the aforementioned risk factors (2). Although the majority of PCNSLs are diffuse large B-cell lymphomas (DLBCLs), primary T-cell lymphoma of the CNS accounts for only 2-8.5% of PCNSLs (3,4). However, the survival of patients with primary T-cell lymphoma is similar to that of patients with B-cell PCNSL (5).

Anaplastic large-cell lymphoma (ALCL) is an uncommon type of T-cell lymphoma first reported by Stein et al (6). It is characterized by large pleomorphic CD30 (Ki-1)-expressing lymphoid blasts containing horseshoe-shaped nuclei (7). Currently, the fourth edition of the WHO classification of Tumors of Haematopoietic Lymphoid Tissues, published in 2008, divides systemic ALCLs into two entities: anaplastic lymphoma kinase (ALK)-positive and ALK-negative (8). In total, 60-85% of systemic ALCLs are ALK-positive lymphomas that exhibit the characteristic t(2;5) (p23;q35) translocation that produces the ALK protein (7). This type is associated with a younger age of onset and a more favorable prognosis (9-11). Patients with ALK-positive ALCL are usually younger and have a better prognosis compared to those with ALK-negative ALCL. The 5-year OS rates are 80 and 40% in ALK-positive and -negative patients, respectively (7).

Although ALCL frequently involves lymph nodes and occasionally involves extranodal sites, such as the skin, soft
tissues, bone, bone marrow, liver, lungs and gastrointestinal tract, it rarely occurs in the CNS (9,12) and ALCL of the CNS is limited to case reports. A few case reviews suggested that although ALK positivity and younger age appear to be favorable prognostic factors, this disease is generally much more aggressive compared to systemic ALCL or PCNSL (13,14). However, the precise prognosis and standard treatment have not yet been determined due to the small number of reported cases.

In this study, we reviewed previously published cases of ALCL and discussed the therapeutic management of ALCL of the CNS. We also report a case study of a patient with ALK-positive brain ALCL who underwent successful treatment with high-dose methotrexate (HD-MTX) alone and has not exhibited recurrence for >5 years.

Materials and methods

A search was conducted using PubMed for published studies in English on cases of immunocompetent patients with ALCL of the brain. The keywords used were ‘anaplastic large-cell lymphoma’, ‘ALK’ and ‘primary central nervous system lymphoma’. Information regarding age, gender, location, ALK positivity, treatment and clinical course were collected from each study.

In addition to the 13 cases reviewed by George et al (13), an additional 13 reported cases (12-33) were selected and a total of 27 cases were summarized, including those of the present study (Table I). The survival time of 2 patients (cases 10 and 22) was not described, 13 patients had succumbed to the disease and 12 patients exhibited no evidence of disease at the time the studies were published.

The OS for 25 patients was calculated by the Kaplan-Meier survival method. Statistical analyses were performed using JMP software version 9 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. Details of the 27 reported cases are provided in Table II. The male:female ratio was 19:8. The median age of the patients was 20 years (range, 4.0-82).

Of the 27 patients, 13 (48.1%) were ALK-positive, 9 (33.3%) were ALK-negative and the ALK status was not determined in the remaining 5 patients (18.5%). Twenty-four patients expressed T-cell antigens and 3 patients had null-cell tumors (cases 1, 16 and 23). There was a difference in the age distribution between the ALK-positive and -negative groups. The ALK-positive tumors occurred in patients aged <40 years. Moreover, 10 out of the 13 ALK-positive patients (76.9%) were aged ≤20 years and the median age of these 13 patients was 17 years (range, 4.0-39 years). Conversely, ALK-negative tumors occurred in older patients. Out of the 9 ALK-negative patients, 8 (88.9%) were >40 years of age and the median age of these 9 patients was 65 years (range, 22-82 years). No ALK-negative patient was <20 years of age.

A single lesion was observed in 13 (48.1%) and multiple lesions in 12 patients (44.4%), including 1 case of leptomeningeal metastasis (case 10).

The postoperative treatment was chemoradiotherapy for 14 (51.9%), chemotherapy alone for 3 (11.1%), radiotherapy alone for 6 (22.2%) and supportive care alone for 4 patients (14.8%). In total, 17 patients (63.0%) received some form of chemotherapy. The chemotherapy regimens of these 17 patients were as follows: MTX-based agents for 8 (47.1%), cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP)-based agents for 4 (23.5%), both MTX- and CHOP-based agents for 3 (17.6%), other agents for 1 (5.9%) and unknown for 1 patient (5.9%).

Clinical courses and OS. The patients aged <40 years (n=17) exhibited a longer OS compared to those aged >40 years (n=8) and the median OS of the groups was not reached (NR) and 2.5 months, respectively (P<0.01, log-rank test; Fig. 1A), which demonstrated younger age as a good prognostic factor. The median OS of patients aged ≤20 (n=13) and >20 (n=12) years was NR and 3.5 months, respectively (P=0.089).

In total, 10 out of the 13 ALK-positive patients (76.9%) exhibited no evidence of disease at the time of case report publication. At least 4 out of the 13 ALK-positive patients (30.7%), including our patient, exhibited no evidence of disease for >5 years after the initial diagnosis, whereas 6 out of the 9 ALK-negative patients (66.7%) succumbed to the disease within 4 months after diagnosis. The median OS of each group was NR and 2 months, respectively (P<0.01; Fig. 1B). ALK was significantly correlated with the prognosis, with a 5-year OS of 75.0 and <12.5% in patients with ALK-positive (n=12) and -negative ALCL (n=8), respectively.

There was no difference in the OS patients with a single lesion (n=12) and those with multiple lesions (n=11; P=0.36; Fig. IC).

Chemotherapy improved patient survival, as the median OS with (n=10) or without (n=15) chemotherapy was NR and 2.5 months, respectively (P=0.01; Fig. 1D). Chemoradiotherapy tended to improve OS compared to radiotherapy alone (P=0.08); however, there was no difference in OS between patients who had received chemoradiotherapy and those who had received chemotherapy alone (P=0.73, Fig. 1E). Three patients treated with chemotherapy alone had no evidence of disease until the time when their cases were reported and 2 patients them exhibited no recurrence for >5 years.

Case presentation. We have treated 90 cases of histologically proven PCNSL from 2000 to the present at our department, including 88 cases of DBCL and 2 cases of T-cell lymphoma, including 1 ALCL. A 20-year-old immunocompetent man with no other significant medical history was hospitalized with generalized seizures. He did not have any neurological deficits and physical examination on admission revealed no abnormal findings. Complete blood counts and serum chemistries, including LDH and soluble interleukin-2 receptor levels, were normal. Magnetic resonance imaging (MRI) with gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) revealed a well-enhanced mass lesion in the left frontal lobe (Fig. 2A), with a surrounding high-intensity lesion on T2-weighted images, indicating significant edema. Whole-body CT scans with contrast medium revealed no abnormality. Based on the suspicion of high-grade glioma, awake brain surgery and gross total removal of the tumor were performed. No residual tumor was identified on postoperative MRI with Gd-DTPA. Pathological findings revealed the proliferation of large, atypical lymphocytes containing...
| No. | ALK | Age | Gender | Location | Marker | Lesion | RT | CT regimens | Survival | Authors (Ref.) |
|-----|-----|-----|--------|----------|--------|--------|----|-------------|----------|----------------|
| 1   | +   | 4.5 | F      | Multifocal brain, brain stem, spinal cord, intra-axial and meningeal | Null-cell | M      | +  | CHOP       | NED at 6.1 years | Havlioglu et al (15) |
| 2   | +   | 10  | F      | Parietal hole abutting against falx | T-cell | S     | +  | CHOP-MTX   | Dead at 6 months from CT | Buxton et al (16) |
| 3   | +   | 13  | M      | Frontal, parietal | T-cell | M     | -  | -          | Dead shortly after CT | Abdulkader et al (12) |
| 4   | +   | 29  | M      | Frontotemporal (traversing) | T-cell | M     | +  | MTX        | NED at 13 months | Ponzoni et al (17) |
| 5   | +   | 17  | M      | Parietal dura | T-cell | M     | +  | MTX        | NED at 4.8 years | Georg et al (13) |
| 6   | +   | 18  | F      | Frontotemporal eroding skull | T-cell | M     | -  | -          | Dead at 1 month | Ozkaynak et al (23) |
| 7   | +   | 17  | M      | Dura cerebellum, temporal, 4 additional lesions | T-cell | M     | +  | MTX        | NED at 15 months | Ponzoni et al (17) |
| 8   | +   | 39  | M      | Occipital | T-cell | S     | +  | MTX        | NED at 9 months | Cooper et al (18) |
| 9   | +   | 12  | F      | Dura cerebellum, temporal, 4 additional lesions | T-cell | M     | -  | -          | Dead at 11 days | Karkat et al (20) |
| 10  | -   | 20  | M      | Region of the sylvian fissure | T-cell | M     | +  | MTX        | NED at 18 months | Vivekanandan et al (22) |
| 11  | -   | 38  | M      | Frontal | T-cell | M     | +  | MTX        | NED at 5 years | Carmichael (23) |
| 12  | -   | 22  | M      | Dura cerebellum, temporal, 4 additional lesions | T-cell | M     | +  | MTX        | NED at 15 months | Ponzoni et al (17) |
| 13  | -   | 46  | F      | Pariotemporal, 2 additional supramarual, dura | T-cell | M     | +  | MTX        | NED at 9 months | Cooper et al (18) |
| 14  | -   | 59  | M      | Frontotemporal, dura, brain | T-cell | M     | +  | MTX        | NED at 5 years | Ponzoni et al (17) |
| 15  | -   | 65  | F      | Frontotemporal, dura, brain | T-cell | S     | +  | CHOP       | NED at 15 months | Cooper et al (18) |
| 16  | -   | 66  | M      | Frontotemporal, dura, brain | T-cell | M     | +  | MTX        | NED at 5 years | Ponzoni et al (17) |
| 17  | -   | 79  | M      | Posterior fossa attaching to the tentorium | T-cell | M     | +  | MTX        | NED at 5 years | Ponzoni et al (17) |
| 18  | -   | 82  | M      | Bilateral hemisphere mimicking lymphomatosis cerebri | T-cell | M     | +  | MTX        | Dead at 3 weeks | Paulus et al (25) |
| 19  | -   | 75  | M      | Bilateral hemisphere mimicking lymphomatosis cerebri | T-cell | M     | +  | MTX        | Dead at 6 weeks | Ponzoni et al (17) |
| 20  | -   | Unknown | F  | Occipital |Null-cell | S     | +  | MTX        | NED when 2 courses of CT | Colen et al (29) |
| 21  | -   | Unknown | F  | Parietal | T-cell | S     | +  | MTX        | Dead at 24 months | Bergmann and Eidel (30) |
| 22  | -   | Unknown | F  | Parietooccipital | T-cell | S     | +  | MTX        | Dead at 3 months | Feldges et al (31) |
| 23  | -   | Unknown | F  | Parietooccipital | T-cell | S     | +  | MTX        | Dead at 3 months | Goldhammer et al (32) |
| 24  | -   | Unknown | F  | Parietooccipital | T-cell | S     | +  | MTX        | NED at 98 months | Abla et al (34) |
| 25  | -   | Unknown | F  | Parietooccipital | T-cell | M     | +  | MTX        | Dead at 8 months | Abla et al (34) |
| 26  | -   | Unknown | F  | Parietooccipital | T-cell | M     | +  | MTX        | Dead at 8 months | Abla et al (34) |

ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; RT, radiotherapy; CT, chemotherapy; M, male; F, female; M, multiple lesions; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisolone; NED, no evidence of disease; S, single lesion; MTX, methotrexate; LMM, leptomeningeal metastases.
scattered horseshoe-shaped nuclei on hematoxylin and eosin (H&E)-stained slides (Fig. 2C). Immunohistochemistry revealed that the tumor cells were positive for CD3 and ALK-1 (Fig. 2D), but negative for CD20. This patient was finally diagnosed with ALK-1-positive ALCL. Bone marrow examination findings were normal. Treatment was immediately initiated with intravenous HD-MTX (3.5 g/m²). The patient completed 3 courses of HD-MTX, one every 2 weeks. Cerebral MRI and systemic positron emission tomography with fluorodeoxyglucose (FDG-PET) revealed no abnormal findings and radiotherapy was not performed. He had regular MRI examinations every 3 months until 3 years after the diagnosis and every 6 months thereafter. There has been no recurrence of the disease for 5 years (Fig. 2B) and the patient has exhibited no neurological deficits.

**Discussion**

We demonstrated that ALK-positive ALCL in the CNS presents at a younger age, has a good prognosis and is sensitive to chemoradiotherapy in the analysis of reported cases.

Shenkier et al (5) reported a retrospective analysis of patients with T-cell PCNSL diagnosed between 1983 and 2003 at 12 institutions in 7 countries. In that report, among 25 cases of T-cell PCNSL in which the pathology report was reviewed, 3 cases (12%) exhibited the characteristics of ALCL. Thus, ALCL is a rare disease of the brain, for which the literature

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Table II. Summary of ALK lymphoma of reported cases.

| Variable          | Total | ALK-positive | ALK-negative |
|-------------------|-------|--------------|--------------|
| No.               | 27    | 13           | 9            |
| Median age (range)| 20.0 (4.0-82.0) | 17.0 (4.0-39.0) | 65.0 (22.0-82.0) |
| Gender (M:F)      | 19:8  | 10:3         | 6:3          |
| Lesions           |       |              |              |
| Single            | 13    | 6            | 5            |
| Multiple          | 12    | 7            | 4            |
| Unknown           | 2     | 0            | 0            |
| Initial therapy   |       |              |              |
| RT alone          | 6     | 1            | 4            |
| RT+CT             | 14    | 10           | 1            |
| CT alone          | 3     | 2            | 0            |
| None              | 4     | 0            | 4            |
| CT regimens       |       |              |              |
| MTX-based         | 8     | 5            | 1            |
| CHOP-based        | 4     | 4            | 0            |
| MTX+CHOP-based    | 3     | 3            | 0            |
| Others            | 1     | 0            | 0            |
| Unknown           | 1     | 0            | 0            |

ALK, anaplastic lymphoma kinase; M, male; F, female; RT, radiotherapy; CT, chemotherapy; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisolone; MTX, methotrexate.
is limited to case reports. We collected twice as many cases as the largest reviews (13) and although our review was based on incomplete data from the literature, our findings may be of value in understanding this rare disease.

In general, ALCL of the CNS has been recognized to be significantly more aggressive compared to systemic ALCL or PCNSL (13,14). However, our data demonstrate that ALK-positive ALCL has a good prognosis, similar to systemic ALCL (10,11). Only 3 ALK-positive patients were reported to have succumbed to the disease. Tuberculosis or other infectious diseases of the CNS were suspected in these 3 patients (cases 2, 3 and 8) at the initial presentation and they were treated with antituberculosis medications or antibiotics. Delayed diagnosis may result in a worse outcome compared to that observed in other ALK-positive patients. PCNSL is rare in adolescence (34) and the radiological findings of primary ALCL in the CNS often mimic those of infectious or immunological disease. However, an early diagnosis and the timely initiation of the appropriate treatment is critical.

There is no standard treatment for primary ALCL of the CNS. Our findings demonstrate the importance of chemoradiotherapy for ALCL. Of the 17 patients treated with chemotherapy, 11 received MTX-based agents. Moreover, 9 of these 11 patients exhibited no evidence of tumor at the time of case report publication, although 2 patients died shortly after treatment. As it is known that the standard chemotherapy regimen for PCNSL is MTX and that CHOP has not been proven to be effective against PCNSL (35,36), MTX-based regimens are recommended for ALCL of the CNS. Our patient was treated with 3 courses of HD-MTX alone and he has exhibited no recurrence for >5 years. Abla et al (21) reported 10 pediatric cases of PCNSL, including 2 ALCLs treated with chemotherapy alone and the majority of the children achieved long-term remissions. Radiotherapy may decrease cognitive function and it is possible that ALK-positive patients, particularly younger patients, may need to start treatment with chemotherapy alone.

Our review also demonstrated that ALK-negative ALCL exhibits a poor prognosis and is very often fatal. The majority of ALK-negative patients were treated with radiotherapy or supportive care, due to their older age or poor PS. As ALK-negative ALCL tends to occur in older individuals, similar to PCNSL and DLBCL, chemoradiotherapy including HD-MTX should be initiated earlier.

In conclusion, our findings indicate that the prognosis of ALCL of the CNS is correlated with ALK positivity and patient age of <40 years. Chemoradiotherapy with MTX is recommended as the standard treatment for ALCL. However, additional multicenter studies including large numbers of cases are required.

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