J Clin Exp Hematop
Vol. 54, No. 3, Dec. 2014

Original Article

Primary Central Nervous System Lymphoma in Miyazaki, Southwestern Japan, a Human T-Lymphotropic Virus Type-1 (HTLV-1)-Endemic Area: Clinicopathological Review of 31 Cases

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Primary central nervous system lymphoma (PCNSL) is a rare and aggressive brain tumor. The aim of this study was to clarify the prevalence of T-cell-type PCNSL (T-PCNSL) in a human T-lymphotropic virus type-1 (HTLV-1)-endemic area of Southwestern Japan. We retrospectively investigated 31 PCNSL cases diagnosed between 1996 and 2013 at the University of Miyazaki Hospital. These cases accounted for 4.4% of all nodal or extranodal malignant lymphomas. Histologically, most of these cases were diagnosed as diffuse large B-cell lymphoma, while only two cases were considered to be low-grade and high-grade B-cell lymphoma (not otherwise specified). No T-PCNSL was found in this series. In addition, Epstein-Barr virus-encoded RNAs were not detected by *in situ* hybridization in any of the cases. Overall, no T-PCNSL cases were found in 18 years in a region with a high frequency of HTLV-1 seropositivity, namely, Southwestern Japan. This suggests that PCNSL and lymphomas of other anatomical sites are biologically distinct. 〔*J Clin Exp Hematop 54(3) : 179-185, 2014*〕

Keywords: B-cell lymphoma, human T-lymphotropic virus type 1, primary central nervous system lymphoma, T-cell lymphoma

INTRODUCTION

Primary central nervous system (CNS) lymphoma (PCNSL) is defined as a lymphoma arising in the brain, spinal cord, or leptomeninges in the absence of lymphoma outside of the nervous system at the time of diagnosis. PCNSL is a rare tumor that comprises approximately 1.5% to 3% of all brain tumors and 1% of all non-Hodgkin lymphomas; however, the incidence of PCNSL has recently increased within populations of immunocompromised individuals with human immunodeficiency virus infection and in immunocompetent elderly individuals.[1] The vast majority of PCNSLs have a B-cell origin (B-PCNSL), particularly diffuse large B-cell lymphoma (DLBCL) in most Western countries, with only 2-3% of PCNSLs being derived from T cells.[2] In contrast, a higher prevalence of T-PCNSL was reported in Asia: 8-14% in Japan and 16.7% in Korea.[3] However, in our experience, the reported prevalence of 8-14% in Japan seems to be too high. Therefore, we postulated that some specific phenomenon may contribute to the high PCNSL prevalence in Japan and investigated clinical and histological findings of PCNSL at the University of Miyazaki Hospital, in a human T-lymphotropic virus type-1 (HTLV-1)-endemic area. We also investigated the association of Epstein-Barr virus (EBV) with PCNSL, which may account for the high prevalence of PCNSL in Japan.[4]

Received: May 23, 2014
Revised : July 1, 2014
Accepted: August 8, 2014
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MATERIALS AND METHODS

Patient characteristics

We searched the archives of the University of Miyazaki Hospital for newly diagnosed nodal or extranodal malignant lymphomas between 1996 and 2013, as after this time, an electronic medical chart system was introduced in our hospital, and detailed clinical information has become available. We extracted the cases of newly diagnosed PCNSL as well as

all cases of nodal or extranodal lymphoma. The following information was requested: 1) clinical status before treatment; 2) history of presence or absence of immunocompromised status including a cancer, congenital immune deficiency, acquired immune deficiency syndrome, and immunosuppressive therapy; 3) tumor location; 4) nature of adjuvant therapy (radiation and/or chemotherapy); 5) evaluation of clinical status at the end of the first treatment; and 6) outcome as of Nov. 2013. Cases were excluded if any clinical information was not available.

Histological studies

All biopsies and surgical samples were fixed in 10% buffered formalin and embedded in paraffin. Sections (4 μm) were routinely stained with hematoxylin and eosin (H&E). The histological subclassification of lymphomas was based on the revised WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues.[3] We examined the growth pattern of the lymphomas and recorded the presence of perivascular cuffing and infiltration in the vascular wall.

Immunohistochemistry and in situ *hybridization*

All of the cases were evaluated immunohistochemically. To determine whether each PCNSL was of the B- or T-cell lineage, immunohistochemical staining was performed using antibodies against CD79a (1:200, heat treatment (HT), DakoCytomation, Denmark), CD20 (1:400, DakoCytomation), and cytoplasmic CD3 (cCD3) (1:200, DakoCytomation) in all 31 cases. For a more detailed examination of B-cell-derived PCNSLs, we evaluated the immunoreactivity using antibodies against CD10 (Diluted, Nichirei Bioscience Inc., Japan), BCL2 (1:50, DakoCytomation), BCL6 (1:200, HT, Dako Cytomation), IRF4/MUM1 (1:100, HT, DakoCytomation), and CD5 (1:100, HT, DakoCytomation). To evaluate the proliferation activity of lymphoma cells in all cases, an antibody against Ki-67 (1:50, HT, DakoCytomation) was used. Ki-67 labeling index was defined as the percentage of Ki-67-positive cells among the total lymphoma cells and was evaluated in the hotspots. Immunohistochemical stains were performed on a Leica Autostainer (Bond III, Leica Biosystems, Germany) using standard methods. *In situ* hybridization (ISH) for EBV-encoded small RNAs (EBERs) was conducted on paraffin sections from all cases using the EBV Probe ISH Kit (Leica Biosystems).

Ethical issues

This study was approved by the Local Ethics Committee (2013-132), and informed consent was obtained from all patients.

RESULTS

In total, 710 cases of newly diagnosed nodal or extranodal malignant lymphomas were detected between 1996 and 2013 at the University of Miyazaki Hospital. Thirty-one cases (4.4%) of these 710 lymphomas originated in the CNS. The

Table 1. Patient Characteristics for 31 cases of primary central nervous system lymphoma (PCNSL)

Characteristics	No. of patients	%
Age		
> 60	22	71
< 60	9	29
Sex		
M	17	55
F	14	45
Tumor location		
Supratentrial space	27	87
frontal	8	26
temporal	3	10
occipital	1	3
basal ganglia	2	6
multifocal	9	29
others	4	13
Cerebellum	1	3
Pituitary	2	6
Occular	1	3
Symptoms		
Hemiplegia	8	26
Headache	5	16
Amnesia	4	13
Dysopia	4	13
Disorientation	3	10
Disturbed consciousness	3	10
Convulsion	2	6
Fatigue	1	3
Eye-pain	1	3
Immunocompromised status		
Yes	7	23
No	24	77
Therapy		
Radiation (R)	2	6
Chemotherapy (C)	13	42
R + C	14	45
Surgery + C	1	3
Non-Tx	1	3
Effect of the first therapy		
CR	9	29
PR	15	48
SD	2	6
NE	2	6
Unknown	3	10
Outcome		
Alive with disease	7	23
Alive without disease	5	16
Dead of disease	7	23
Dead of other disease	1	3
Unknown	11	35

R, radiation; C, chemotherapy; Tx, therapy; CR, complete remission; PR, partial remission; SD, stable disease; NE, not evaluable

principal clinical characteristics of the patients at the time of diagnosis are summarized in Table 1. The patients included 17 males and 14 females. There were no pediatric cases, with a median age at diagnosis of 67 years (range: 21-85 years), with 71% (22/31) being over 60 years of age. Twenty-seven cases (87%) involved the supratentorial space, including 8 cases in the frontal lobe (26%), 3 in the temporal lobe (10%), 2 in the basal ganglia (6%), and 1 in the occipital lobe (3%). Two cases involved the sellar region (6%), and 1 case (3%) originated from either the cerebellum or the ocular region. Multifocal lesions were detected in 9 cases (29%). Most of the patients experienced neurological symptoms, especially hemiparesis (26%) and headache (16%), and four patients presented with amnesia and dysopia (13%). Seven patients (23%) had a history of an immunocompromised status, including diabetes mellitus (4 cases), cancer (2 cases), and hemodialysis (1 case). The result of serologic study for HTLV-1 was negative in all patients. Thirteen patients (42%) were treated by chemotherapy alone, 14 patients (45%) by chemotherapy followed by radiation, and 2 patients received radiation alone. Additionally, one patient received chemotherapy followed by complete surgical resection, and another patient died before treatment was initiated. The effectiveness of the initial treatment was assessed by magnetic resonance imaging. The initial treatment resulted in complete remission in 9 patients (29%), partial remission in 15 patients (48%), and stable disease (SD) in two patients (6%), while 2 patients (6%) could not be evaluated. As of Nov. 2013, 7 patients (23%) survived with disease, 5 patients (16%) survived and were disease-free, and 7 patients (23%) had died of the disease. Follow-up data were unavailable in 11 patients.

Histologically, all of the cases showed a perivascular infiltrative pattern (Fig. 1A), but diffuse proliferation was also noted (Fig. 1B). Lymphoma cells infiltrated the walls of medium-sized to large vasculature (Fig. 1C). In all cases except 2, the lymphoma cells were medium-sized to large, with centroblast- or immunoblast-like nuclei (Fig. 2). In two cases, the lymphoma cells were small to medium-sized with relatively uniform round nuclei that proliferated in a perivascular infiltrative pattern (Fig. 3). Reactive gliosis, necrosis, and/or hemorrhage were observed in some cases.

Immunohistochemically, while lymphoma cells were positive for CD79a and CD20 in all cases, CD10 expression was observed in approximately 13%, BCL2 in 78%, BCL6 in 78%, and IRF4/MUM1 in 87% (Fig. 4). The histological subtypes and the results of the immunohistochemical study are listed in Table 2. Small lymphocytes of varying densities, which were present in the tumor or in the tumor periphery, may have been reactive lymphocytes, which were immunopositive for cCD3 or CD5. In contrast, the lymphoma cells were negative for cCD3 in all cases. In only one case, the lymphoma cells were positive for CD5 (Case 29), and this was one of the cases in which initial treatment resulted in SD.

According to the WHO classification system,[3] we diagnosed 29 cases as DLBCL: 23 of these (79%) were subclassified as the non-germinal center B-cell type (non-GCB) and 6 cases as the GCB type (21%). The GCB cases seemed to be associated with a better prognosis than the non-GCB ones, which is similar to findings in systemic or other organ lesions described in a previous study.[5] The Ki-67 labeling index in

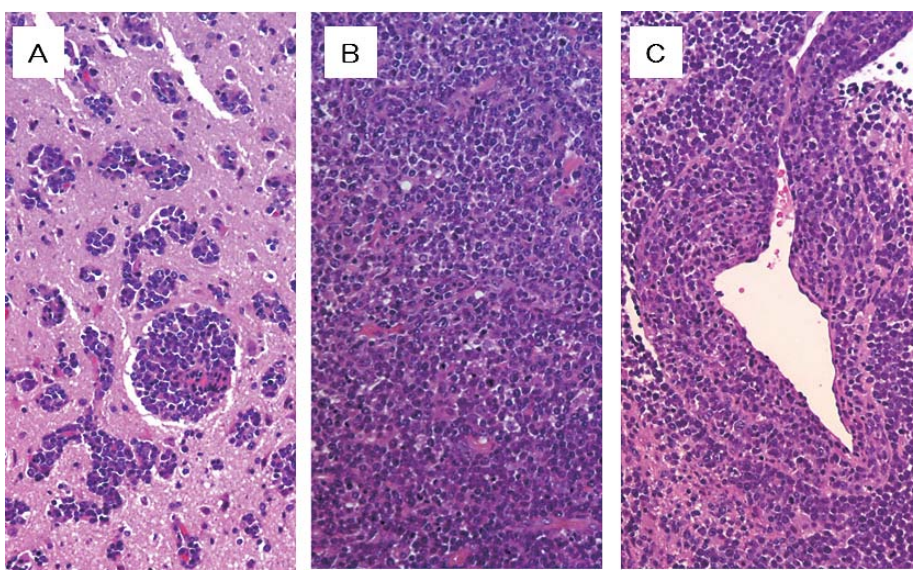

Fig. 1. Invasive pattern of lymphoma cells. Perivascular (*1A*), diffuse (*1B*), and vascular wall (*1C*). (*1A*) Case 15, and (*1B*) and (*1C*) Case 11, H&E stain, × 100.

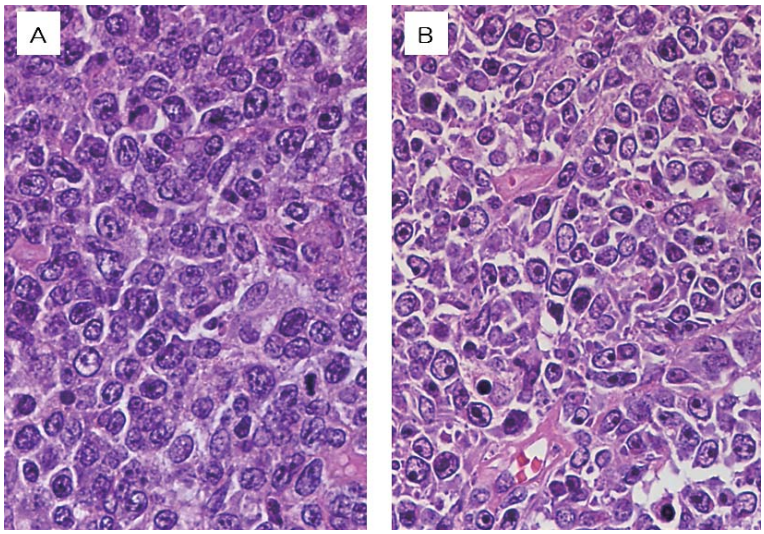

Fig. 2. High magnification of lymphoma cells. Immunoblastic (*2A*) and centroblastic (*2B*) lymphoma cells. (*2A*) Case 11 and (*2B*) Case 18, H&E stain, × 400.

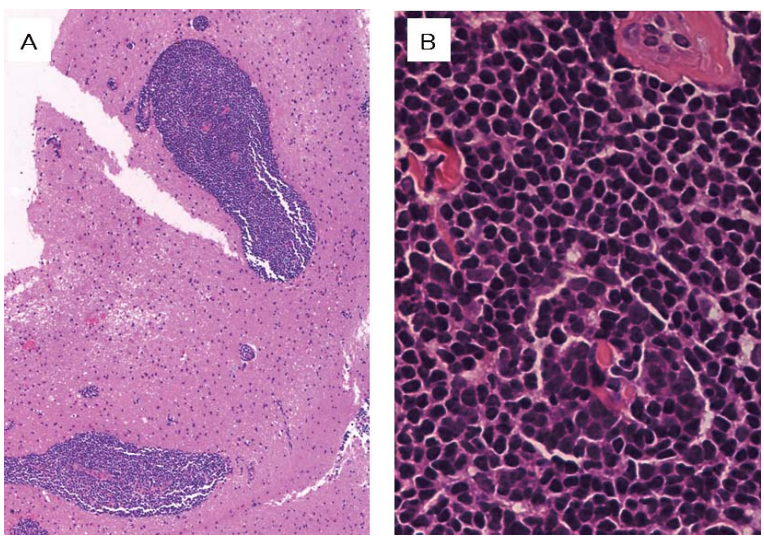

Fig. 3. Low-grade B-cell lymphoma in case 25. Perivascular infiltration of lymphoma cells (*3A*) and small lymphoma cells under high magnification (*3B*). H&E stain, (*3A*) × 100, (*3B*) × 400.

all cases was more than 70% in DLBCL. Two cases in which the lymphoma cells were small or medium in size were diagnosed as unclassifiable low-grade B-cell lymphoma with a low Ki-67 labeling index (4.3%) or unclassifiable high-grade B-cell lymphoma with a high Ki-67 labeling index (81%). No positive signal was detected with EBER-ISH in any of the cases (Table 2).

DISCUSSION

In the WHO Classification of Tumours of the CNS, PCNSL is defined as a lymphoma arising in the CNS without extra-CNS lesions present at the time of diagnosis.[6] However, in the WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues, PCNSL is listed as a subtype of DLBCL that occurs as an intracranial or intraocular lesion, excluding intravascular large B-cell lymphoma and lymphomas that arise in the dura or in the orbital region.[3] PCNSLs other than DLBCL are rare, although such cases have been reported.[7,8] In addition to B-PCNSL, the WHO Classification of Tumours of the CNS also states that T-PCNSLs constitute approximately 2-5% of all PCNSLs in Western countries and 8-14% in Japan.[6] These data of a high prevalence of T-PCNSL listed in the WHO Classification of Tumours of the CNS[6] were cited from a report by Hayabuchi *et al*. as 8.5% among 234 PCNSLs assessed using a panel of T/B-cell markers[9] and a report by Hayakawa *et al*. as 14% among 21 PCNSLs assessed by immunohistochemical techniques.[10] In other East Asian countries, the T-PCNSL prevalence was reported as 16.7% in Korea[11] and 1% in Taiwan.[12] Using the criteria described in the WHO Classification of Tumours of the Haematopoietic and

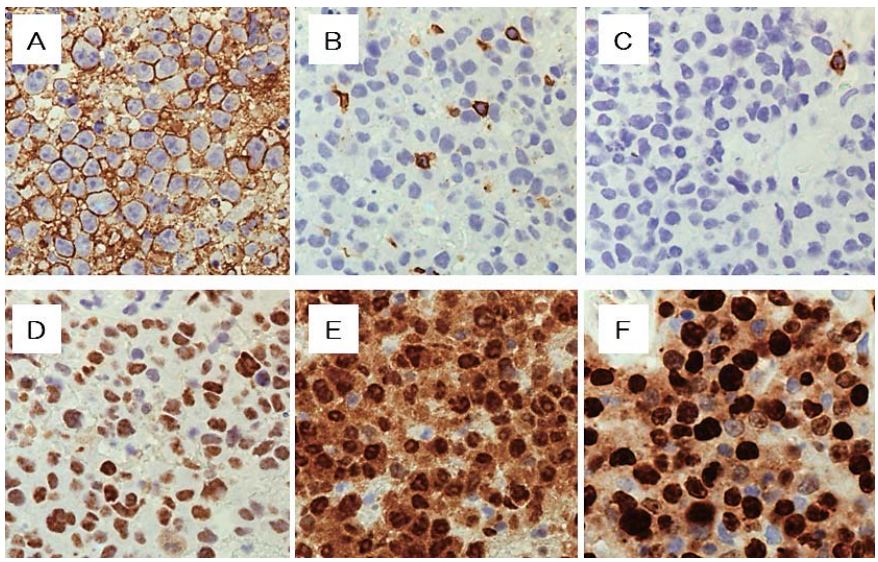

Fig. 4. The results of immunohistochemical staining in case 20. CD20 (*4A*), cCD3 (*4B*), CD10 (*4C*), BCL6 (*4D*), MUM1 (*4E*), and Ki-67 (*4F*). Lymphoma cells were positive for CD20, BCL6, and MUM1, but negative for cCD3 and CD10. Ki-67-positive index was over 80%.

Table 2. Immunohistochemistry, *in situ* hybridization for Epstein-Barr virus-encoded small RNAs (EBER-ISH) and histological subtype

Case	CD79a	CD20	cCD3	CD10	BCL2	BCL6	MUM1	CD5	EBER-ISH
1	+	+	−	−	−	−	−	ND	−
2	+	+	−	−	+	+	+	ND	−
3	+	+	−	−	+	−	+	ND	−
4	+	+	−	−	+	−	+	ND	−
5	+	+	−	−	+	+	+	ND	−
6	+	+	−	−	−	−	−	ND	−
7	+	+	−	−	+	+	−	ND	−
8	+	+	−	−	+	+	+	ND	−
9	+	+	−	+	+	+	+	ND	−
10	+	+	−	−	−	+	+	ND	−
11	+	+	−	−	+	−	+	ND	−
12	+	+	−	−	+	−	+	ND	−
13	+	+	−	+	+	+	+	ND	−
14	+	+	−	−	+	+	+	−	−
15	+	+	−	−	+	+	+	−	−
16	+	+	−	−	−	+	+	−	−
17	+	+	−	+	+	+	+	−	−
18	+	+	−	−	−	+	+	−	−
19	+	+	−	−	−	+	−	−	−
20	+	+	−	−	+	+	+	−	−
21	+	+	−	−	+	+	+	−	−
22	+	+	−	−	+	+	+	−	−
23	+	+	−	−	+	+	+	−	−
24	+	+	−	−	+	+	+	−	−
25	+	+	−	−	+	−	+	−	−
26	+	+	−	−	+	+	+	ND	−
27	+	+	−	−	+	+	+	−	−
28	+	+	−	+	−	+	+	−	−
29	+	+	−	−	+	+	+	+	−
30	+	+	−	−	+	+	+	−	−
31	+	+	−	−	+	+	+	−	−

ND, not done

Lymphoid Tissues, we diagnosed 29 cases as primary DLBCL of the CNS and the other two cases as low- and high-grade B-cell lymphoma (not otherwise specified). There were no T-PCNSL cases in this study, even though these cases were from an HTLV-1-endemic region in Southwestern Japan, where 6.6 to 12.1% of the population are seropositive for HTLV-1.[13] Shibamoto *et al*. reported that T-PCNSL in Japan decreased by 8.5% during 1985-1994, by 5.2% during 1995-1999, and by 1.7% during 2000-2004, although these authors did not discuss the reason for this.[14] Moreover, other reports described that T-PCNSLs constituted 8 or 14% of PCNSLs, which may be outdated, but no detailed examinations of the histological findings were described.[9,10] Additionally, Dulai *et al*. indicated that T-PCNSL may not be recognized unless examinations are performed to detect T-cell receptor gene rearrangements for CNS lesions composed of a polymorphous but predominant T-cell infiltrate, because of a high degree of overlap in morphologic and immunophenotypic features between T-PCNSL and reactive infiltrate.[15] Conversely, a lesion of reactive T-cell infiltrate in the CNS can be misdiagnosed as T-PCNSL unless detection of T-cell receptor gene rearrangements is performed. There have been only a few reports of adult T-cell leukemia/lymphoma (ATLL) in PCNSL,[2,16] and no T-PCNSL including ATLL was detected in the present study, which was performed in an HTLV-1-endemic area. In fact, the annual incidence of new-onset T-cell lymphoma in our hospital was approximately 35% (unpublished data), and most of these cases were ATLL. Considering these data, the current incidence of T-PCNSL in Japan might not be so high. Thus, it is necessary to ascertain the "true" incidence of T-PCNSL and the relationship between T-PCNSL and HTLV-1 in a worldwide study including Japan and other HTLV-1-endemic areas. Furthermore, in a study reviewing 47 autopsy cases of ATLL in Miyazaki Prefecture, Japan, CNS involvement developed in 4 of 35 cases examined (11.4%).[17] The relatively high reported prevalence of T-PCNSL, therefore, might be due to CNS invasion by lymphomas that originated outside of the CNS.

Histologically, all cases showed a diffuse and perivascular infiltration pattern. Regarding the relationship between blood vessels and lymphoma cells, certain morphological features are important for PCNSL diagnosis, such as "perivascular cuffs and angiocentric infiltration pattern".[1,3,9] However, these textbooks do not mention vessel wall invasion. In our study, we detected vessel wall invasion by lymphoma cells in tissue samples including large blood vessels in 88% of the cases. Perivascular lymphocytic infiltration itself is also found in non-neoplastic CNS diseases such as inflammatory diseases or demyelinating disorders. Thus, invasion of the vessel wall may be a characteristic feature of PCNSL and can be a diagnostic indicator to differentiate a lymphoma from inflammatory or demyelinating disorders.

Hans *et al*. showed that non-GCB was associated with a poor prognosis compared with GCB in systemic DLBCL.[5] In addition, Camilleri-Broet *et al*. suggested that the activated B-cell-like immunophenotype of PCNSL was also associated with a poor prognosis.[18] Thus, the GCB cases of PCNSL might have a good prognosis compared with the non-GCB cases. We were unable to evaluate the prognostic difference between GCB and non-GCB due to the small number of cases.

CD5-positive DLBCL is associated with female predominance, older age at diagnosis, higher serum lactate dehydrogenase level, and poor prognosis.[19,20] Imai *et al*. reported that 12 from 40 CNS DLBCL cases (30%) were revealed as CD5-positive and they showed poorer prognosis than the CD5-negative cases.[21] In our series, only one female case was CD5-positive from 29 DLBCLs (3%), and her age at diagnosis was 85 years old, with no data on the serum LDL level. The therapeutic effect of the initial treatment was SD in this case and alive with disease after a very short follow-up period. In another study of systemic DLBCL excluding PCNSL, Ennishi *et al*. reported that 11 from 121 cases (9%) were revealed as CD5-positive by flow cytometry, whereas only 7 (6%) cases showed positive staining for CD5 (4C7, Novocastra) immunohistochemically.[22] Ennishi *et al*. pointed out that CD5 paraffin immunohistochemistry is less sensitive and they concluded that flow cytometric analysis or frozen-section immunohistochemistry needs to be carried out for the detection of CD5 in DLBCL. We consider that the very low proportion of CD5-positive cases in this study arose from these methodological conditions.

EBV-positive DLBCL can occur among immunocompetent elderly patients over 50 years of age. In this study, there were no EBV-positive cases, although this study included 22 (71%) elderly cases aged over 60. Actually, we experienced a case of EBV-positive PCNSL that had suffered from ATLL,[23] but we excluded it from the present study because this was just a consultation case from another hospital. Oyama *et al*. hypothesized that the malignant transformation of B cells occurs because of a decrease in immune function associated with aging.[24,25] Thus, it is suggested that the incidence of EBV-positive PCNSL may be higher in a study with a larger number of cases.

In summary, we reported PCNSL diagnosed over a period of 18 years (1996-2013) at our hospital. Most of our results are in accordance with previous reports, with the exception of the two PPL cases. However, no T-PCNSL cases were found in this study, despite it being in an HTLV-1-endemic area of Japan. To determine the true prevalence of T-PCSNL, it is necessary to conduct further research, including multicenter studies.

DISCLOSURE STATEMENT

There is no conflict of interest.

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