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ORIGINAL ARTICLE

Clinical and pathological aspects of human immunodeficiency virus-associated plasmablastic lymphoma: analysis of 24 cases

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Abstract Plasmablastic lymphoma (PBL) is a rare AIDS-related malignancy with a poor prognosis. Little is known about this entity, and no standard treatment regimen has been defined. To establish an adequate treatment strategy, we investigated 24 cases of PBL arising in human immunodeficiency virus-positive individuals. Most of the patients were in the AIDS stage, with a median CD4 count of 67.5/μL. Lymph nodes (58 %), gastrointestinal tract (42 %), bone marrow (39 %), oral cavity (38 %), and CNS (18 %) were the most commonly involved sites. Histology findings for the following were positive at varying rates, as follows: CD10 (56 %); CD30 (39 %); CD38 (87 %); MUM-1 (91 %); CD138 (79 %); EBER (91 %); and LMP-1 (18 %). There was a marked increase in patients in 2011–12, and the cases found in that period appeared to be more aggressive, showing a higher rate of advanced-stage PBL. Fourteen cases were treated with CHOP, while the others were treated with more intensive regimens, including bortezomib and hematopoietic stem cell transplantation. The overall median survival time was 15 months. A CD4 count of >100/μL at diagnosis and attaining complete remission in the first-line chemotherapy were associated with better outcomes ($P = 0.027$ and 0.0016, respectively). Host immune status and chemosensitivity are associated with improved prognosis in PBL.

Keywords Plasmablastic lymphoma · Acquired immunodeficiency syndrome · Human immunodeficiency virus · CD4 · Combination antiretroviral therapy · Epstein–Barr virus

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Introduction

Plasmablastic lymphoma (PBL) is a rare subtype of non-Hodgkin lymphoma (NHL) [1]. It has unique pathological and clinical features, such as the absence of CD20 expression, Epstein–Barr virus (EBV) positivity, characteristic oropharyngeal lesions, an aggressive clinical course, and a close association with human immunodeficiency virus (HIV) infection. As one of the acquired immunodeficiency syndrome (AIDS)-related NHL, PBL case series have been reported since the 1990s. It is well known that the nature of this malignancy, i.e., rapid disease progression, aggressive invasion into extranodal sites, and frequent relapse even after attaining remission makes its prognosis extremely poor [1–9].

The development of combination antiretroviral therapy (cART) has decreased the incidence and improved the prognosis of AIDS-related NHL, including PBL in western countries [10–12]. However, the epidemiology of HIV infection and incidence of AIDS-related NHL are somewhat different in Japan from those in western countries. The number of HIV-1-infected individuals and AIDS patients with multiple opportunistic diseases has been increasing continuously, and is disproportionately conspicuous from that in other industrialized countries, and AIDS-related NHL is now one of the most difficult, life-threatening complications in our country [13]. Our previous data suggested that the composition of AIDS-related NHL subtypes has markedly changed between the pre-cART era (1987–1997) and cART era (1997–2012). The percentage of diffuse large B-cell lymphoma (DLBCL) almost halved, whereas that of Burkitt lymphoma (BL) increased from 7 to 31 % and plasmablastic lymphoma (PBL) increased from none to 10 % [14]. The percentage of PBL in Japan is now markedly higher than that previously reported in other countries, <2–2.6 % [5, 15].

There have been several case series or reviews to date [1–9], yet little is known about PBL. Thus, for the establishment of an appropriate treatment strategy for HIV-positive PBL, we conducted a multi-institutional retrospective study in Japan, focusing on the analyses of clinical and pathological factors affecting the prognosis of this malignancy.

Materials and methods

Patients

The clinical and pathological data of HIV-positive PBL cases, diagnosed histologically between 1999 and 2012, were investigated retrospectively. Patients were recruited from 8 hospitals in Japan: Tokyo Metropolitan Komagome Hospital; National Center for Global Health and Medicine Hospital; the Institute of Medical Science, The University of Tokyo; Nagoya Medical Center Hospital; Osaka Medical Center Hospital; Osaka City General Hospital; University of Fukui Hospital; and Kawasaki Medical School Hospital. This study was approved by the Institutional Review Boards in all the above hospitals.

All cases were pathologically diagnosed as PBL under a central review by five pathologists (YO, TH, MM, YK, and HK) according to the diagnostic flow chart for AIDS-related lymphoma [14], i.e., CD20-negative, Kaposi sarcoma-associated herpesvirus (KSHV)-encoded latency-associated nuclear antigen 1 (LANA-1)-negative large neoplastic cells with typical plasmablastic differentiation, expressing CD38, CD138, and EBV-encoded small RNAs (EBERs).

Clinical data

Clinical data included age, sex, route of HIV transmission, history of AIDS, receipt of cART, and performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale, CD4-positive cell count (CD4 count) at the PBL diagnosis, CD4 count at the lowest (nadir CD4 count), a history of or co-existing opportunistic infections, plasma HIV-RNA level, lactate dehydrogenase (LDH) level, soluble interleukin-2 receptor (sIL-2R) level, EBV antibody levels (Viral Capsid Antigen-IgG, IgM: VCA-IgG, IgM, EBV antibody to Nuclear Antigen: EBNA), EBV-DNA level in peripheral blood mononuclear cells (EBV-DNA level), clinical stage, location of lymph node lesions, number and site of extra-lymph node lesions, age-adjusted International Prognostic Index (aa-IPI) score, chemotherapeutic regimen, receipt of radiation therapy, the initial response to chemotherapy, the final outcome, progression-free survival (PFS), overall survival (OS), and cause of death.

Complete remission (CR) was defined as the disappearance of all clinical evidence of disease at the completion of the first induction therapy. The presence of residual disease, but with ≥50 % decrease in the sum of the product of the greatest diameter was defined as a partial response (PR). When the tumor showed ≥50 % increase or new lesions appeared, it was regarded as progressive disease (PD). Otherwise, it was defined as stable disease (SD) [16].

Pathological analysis

Pathological data included the immunohistochemical expression of CD79a, CD10, CD20, CD38, CD138, MUM1, CD56, CD30, immunoglobulin light chain lambda, kappa, BCL-2, and BCL-6, and the MIB-1(Ki67) index. The presence of EBV in tumor cells was evaluated by the

in situ hybridization of EBERs [17]. The latency of EBV in tumor cells was evaluated by immunohistochemical analyses of latent membrane protein-1 (LMP1) and EBV nuclear antigen (EBNA2).

MYC rearrangements were investigated using fluorescent in situ hybridization on paraffin sections, as described previously [18].

Statistical analysis

Analyses of the significance of differences were performed using the Fisher's exact test for a bivariate tabular analysis and the Student's *t* test or Mann–Whitney *U* test for comparisons of two independent groups of sampled data.

The Kaplan–Meier method and log-rank test were used for the univariate survival analyses. Furthermore, univariate and multivariate Cox regression analyses were performed to evaluate prognostic factors. *P* values of <0.05 were regarded as significant. Data analyses were performed using the statistical software JMP® 10 (SAS Institute Inc., Cary, NC, USA).

Results

Patient backgrounds

Twenty-four patients from eight institutions were included in this study (Table 1).

Patient backgrounds and clinical characteristics are summarized in Table 2.

All patients were male and the median age at the PBL diagnosis was 44 years (range 24–59 years). The median CD4 count at the PBL diagnosis and nadir CD4 count before the diagnosis were 67.5/μL (range 1–520/μL) and 36/μL (range 1–394/μL), respectively, suggesting that many patients showed an advanced stage of HIV infection. Seven patients (29 %) were receiving cART at the PBL diagnosis, but plasma HIV-RNA levels were only undetectable in two cases (less than 1000 copies/mL in six cases). The median plasma HIV-RNA level at the PBL diagnosis was 122,500 copies/mL (range, from undetectable to 1,120,000 copies/mL). All the cases were started with cART by day 1 of the chemotherapy against PBL. All the cases were EBV seropositive. Plasma EBV-DNA levels were measured in 14 cases and ten patients (71 %) had more than 1000 copies/10^6 WBC.

Clinical findings

PBL was detected in the lymph nodes in 14 cases (58 %). The cervical, thoracic, peritoneal, and inguinal lymph nodes were involved in 10 (42 %), 7 (29 %), 6 (25 %), and 4 (17 %) patients, respectively. Extranodal involvements were observed in all patients. In ten cases (42 %), extranodal lesions were the only involved sites. The gastrointestinal (GI) tract (10 cases, 42 %), bone marrow (BM, 9 cases, 39 %), oral cavity (9 cases, 38 %), central nervous system (CNS, 4 cases, 18 %), lungs (3 cases, 13 %), maxillary sinus (2 cases, 8 %), and pleural effusion (2 cases, 8 %) were the commonly affected extranodal sites. The external genitals, liver, and chest wall were also affected in one case each. No patient showed leukemic changes at the PBL diagnosis.

Fifty-four percent of cases were in Ann-Arbor stage IV at the diagnosis. Patients in stage IV had significantly lower CD4 counts (median 32/μL, range 6–181/μL) than those in the other stages (median 174/μL, range 1–520/μL, $P = 0.017$).

The Ann-Arbor stage was significantly lower in cases with oral involvement ($P = 0.010$, Fisher's exact test). The performance status was poor (PS = 2–4, according to the ECOG criteria) in 46 % and aa-IPI was poor (aa-IPI = 2 or 3) in 54 % of patients. B symptoms were found in 43 % of cases.

Pathological findings

Immunohistochemistry findings are shown in Table 3.

Plasma cell markers, such as CD38, CD138, and MUM1, were generally positive in most cases; 88, 79, and 91 %, respectively. CD79a (57 %) and CD10 (56 %) were less frequently positive. CD56, BCL-2, and BCL-6 positivities were relatively low (14, 31, and 7 %, respectively). There were several cases with CD30 positivity (7 out of 18 cases, 39 %). The positivity of EBER was 91 %, whereas LMP-1 was positive in 18 % of cases. *MYC* abnormalities were detected in 63 % (5 out of 8 cases) and MIB1 expression was high in 79 % of cases.

Treatments and outcomes

Information on treatments and prognoses is listed in Table 2.

Fourteen patients received chemotherapy alone, 8 chemotherapy and radiation, and 1 chemotherapy + radiation + surgery. One patient received only best supportive care.

Approximately 2.13 [average, (range 1–6)] chemoregimens were performed per one PBL case. As a first-line regimen, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was selected for 61 % of patients. EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), HyperCVAD/High-dose MTX/Ara-C (cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, and cytarabine), CODOX-M/IVAC

Table 1 Clinical features of 24 PBL cases in this study

	year	Age /Sex	Prior AIDS diagnosis	cART at PBL diagnosis	CD4 count (/μL) at diagnosis	CD4 count (/μL) Nadir	Plasma HIV-RNA (copies /mL)	Plasma EBV-DNA (copies /10*6WBC)	Lymph node lesion	Extra lymphatic lesion Oral	CNS	BM	others	Ann-Arbor stage	ECOG PS	LDH (IU/L)	sIL-2R (U/ml)	aa-IPI	Chemotherapy regimen 1st line:	2nd line:	3rd line:	4th line:	5th line:	Response to the initial regimen	Survival (months)	Outcome
1	1999	47 /M	-	-	394	394	74000	N.A	C,T, I	+	-	-	-	3 A	1	261	N.A.	2	CDE					CR	167.5	alive
2	2002	51 /M	-	+	68	N.A.	670000	3000	C	+	-	-	sinus	2 B	3	185	3993	1	EPOCH＋RT	DHAP				PD	4.3	DOD
3	2003	52 /M	+	-	1	1	110000	2000	T	+	-	-	sinus	3 B	2	277	875	2		(Best supportive care)				-	2.8	DOD
4	2004	40 /M	-	+	104	104	1100000	N.A	C, I	+	-	-	-	3 A	0	204	1311	1	EPOCH					CR	105.2	alive
5	2005	32 /M	+	+	50	20	130	200000	T	-	-	N.T.	adrenal gland, kidney, liver, pleural effusion, ascites, stomach, duodenum	4 B	3	6708	1582	3	EPOCH					PR	lost f/u	DOD
6	2006	35 /M	-	+	498	276	<40	N.A	-	-	-	-	anus	1 A	1	1185	1757	1	CHOP					CR	27.5	alive
7	2006	32 /M	+	+	10	40	290	160000	C	+	N.A.	-	-	2 A	3	428	1340	2	CHOP					CR	5.3	DOI (BKV cystitis)
8	2007	48 /M	+	+	26	26	340000	N.A	-	-	-	-	stomach, lung	4 B	1	296	1281	1	EPOCH					CR	66.6	alive
9	2009	51 /M	+	+	520	162	<40	N.A	-	+	-	-	-	1 B	2	216	N.A	1	CHOP＋RT	ESHAP	ICE	MEAM＋SCT		CR	105.5	alive
10	2010	33 /M	-	+	174	29	680000	<200	-	-	-	-	rectum	1 A	2	281	659	1	CODOX-M /IVAC					CR	7.4	DOI (IPA)
11	2010	39 /M	-	+	143	143	8400	N.A	-	+	-	-	sinus	2 A	0	149	364	0	CHOP					CR	26.9	alive
12	2011	40 /M	-	−	40	40	160000	<200	C	-	+	-	-	4 A	1	348	1480	1	CHOP	ESHAP	ICE	MEAM＋SCT		PD	14.8	DOD
13	2011	43 /M	-	+	6	N.A.	4100	5000	-	-	-	-	sinus, bone,	4 A	1	210	7320	1	CHOP	ESHAP	ICE	VTD-PACE	BD	PR	13.3	DOD
14	2011	59 /M	-	+	67	67	135000	150	C, T, P, I	-	-	-	lung, spine, spleen, bone	4 B	2	1161	15000	3	CHOP	HDMA	CODOX-M	BD		PR	7.5	DOD
15	2011	52 /M	-	+	7	7	220000	N.A	P	-	-	-	stomach	4 B	1	121	5500	2	CHOP	ESHAP	BD			PD	17.7	alive
16	2011	39 /M	+	−	181	250	700000	<20	C, T, P	-	+	+	-	4 B	1	1522	1890	2	CHOP	CODOX-M /IVAC				PR	0.3	DOD
17	2011	24 /M	-	−	208	208	48000	N.A	-	-	-	-	stomach, rectum	2 A	1	282	1897	1	CHOP	DeVIC	VP-16 (SCH)	CPT-11	ESHAP BD	PR	15.3	DOD
18	2012	47 /M	+	−	80	16	210000	2000	-	-	-	+	bone, jejunum, lung, external gonad	4 B	4	999	5140	3	CHOP					SD	3.2	DOD
19	2012	53 /M	+	+	7	7	1120000	6700	C, T, P, I	+	-	+	spleen, lung	4 B	1	300	5080	2	HyperCVAD /HDMA	HLH2004				PR	4.5	DOI (EB-VAHS, sepsis)
20	2012	39 /M	-	+	32	32	817000	17000	P	-	+	-	-	4 B	2	395	2030	3	CHOP	HyperCVAD /HDMA	ESHAP	HyperCVAD /HDMA		PR	8.3	DOD
21	2012	59 /M	+	+	126	4	170	130000	-	-	-	+	pleural effusion	4 B	2	2647	383	2	CHOP					PR	11.6	alive
22	2012	36 /M	+	+	30	13	360	N.A	C, T, P	-	-	+	-	4 B	1	341	7540	2	CHOP					PD	1.3	DOD
23	2012	45 /M	+	+	27	27	373350	410000	-	-	-	+	duodenum	4 B	4	1876	8660	3	CODOX-M /IVAC					CR	12	alive
24	2012	55 /M	-	-	276	276	26000	N.A	C	+	-	-	-	2 A	0	214	645	1	HyperCVAD /HDMA	CHOP				CR	9.9	alive

BD bortezomib and dexamethasone, *C* cervical, *CDE* cyclophosphamide, doxorubicin, and etoposide, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CODOX-M* cyclophosphamide, vincristine, doxorubicin, and methotrexate, *CPT-11* irinotecan, *CR* complete remission, *DeVIC* dexamethasone, etoposide, ifosfamide, and carboplatin, *DHAP* dexamethasone, high-dose cytarabine, and cisplatin, *DOD* died of disease, *DOI* died of infection, *EPOCH* etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, *ESHAP* etoposide, prednisone, cytarabine, and cisplatin, *HDMA* High-dose methotrexate and cytarabine, *HyperCVAD* cyclophosphamide, doxorubicin, vincristine, and prednisone, *I* inguinal, *ICE* ifosfamide, carboplatin, and etoposide, *IVAC* ifosfamide, etoposide, and high-dose cytarabine, *MEAM* ranimustine, etoposide, cytarabine, and melphalan, *N.A.* Data not available, *N.T.* not tested, *P* peritoneal, *PD* progressive disease, *PR* partial remission, *SCH* stem cell harvest, *SCT* stem cell transplantation, *SD* stable disease, *T* thoracic, *VP-16* etoposide, *VTD-PACE* bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide

Table 2 Patients' backgrounds and clinical characteristics

Age, years, median, (range)	44 (24–59)
Men, n, (%)	24 (100 %)
Prior AIDS diagnosis, *n*, (%)	3 (13 %)
CD4 + cell count,/mL median, [range]	
At PBL diagnosis	67.5 (1–520)
At the lowest	36 (1–394)
Plasma HIV-RNA ($n = 24$), *n* (%)	
Copies/mL, median, [range]	122,500 (ud-1,120,000)
Cases with <1000 copies/mL	6 (25 %)
Cases with ≧1000 copies/mL	18 (75 %)
Plasma EBV-DNA ($n = 14$), *n* (%)	
Cases with <1000 copies/10^6 cells	4 (29 %)
Cases with ≧1000 copies/10^6 cells	10 (71 %)
Location of the lymphoma ($n = 24$)	
Nodal	14 (58 %)
Cervical	10 (42 %)
Thoracic	7 (29 %)
Abdominal	6 (25 %)
Inguinal	4 (17 %)
Extranodal	24 (100 %)
Gastrointestinal tract	10 (42 %)
Bone marrow	9 (39 %)*
Oral cavity	9 (38 %)
Central nervous system	4 (18 %)*
Lung	3 (8 %)
Nasal cavity/sinus	2 (8 %)
Pleural effusion	2 (8 %)
Ann-Arbor stage ($n = 24$), *n* (%)	
I	3 (13 %)
II	5 (21 %)
III	3 (13 %)
IV	13 (54 %)
ECOG PS ($n = 24$), *n* (%)	
0–1	13 (54 %)
2–4	11 (46 %)
Age-adjusted IPI ($n = 24$), *n* (%)	
0	1 (4 %)
1	10 (42 %)
2	8 (33 %)
3	5 (21 %)
Cases with B symptoms ($n = 24$), *n* (%)	10 (43 %)
Location of the lymphoma ($n = 24$), *n* (%)	
Nodal	14 (58 %)
Cervical	10 (42 %)
Thoracic	7 (29 %)
Abdominal	6 (25 %)
Inguinal	4 (17 %)
Extranodal	24 (100 %)
Gastrointestinal tract	10 (42 %)
Bone marrow	9 (39 %)*
Oral cavity	9 (38 %)

Table 2 continued

Central nervous system	4 (18 %)*
Lung	3 (13 %)
Nasal cavity/sinus	2 (8 %)
Pleural effusion	2 (8 %)
Treatment ($n = 24$), *n* (%)	
Chemotherapy alone	14 (59 %)
Chemotherapy + radiation	8 (33 %)
Chemotherapy + radiation + surgery	1 (4 %)
Best supportive care	1 (4 %)
First-line chemotherapy regimen ($n = 23$), *n* (%)	
CHOP	14 (61 %)
EPOCH	4 (17 %)
HyperCVAD + high-dose MTX/Ara-C	2 (9 %)
CODOX-M + IVAC	2 (9 %)
CDE	1 (4 %)
Response to the first chemotherapy regimen ($n = 23$), *n* (%)	
CR	10 (44 %)
PR	8 (35 %)
SD	1 (4 %)
PD	3 (13 %)
Clinical outcome ($n = 24$), *n* (%)	
Alive	10 (42 %)
Dead	14 (58 %)

* Out of 23 cases examined

CDE cyclophosphamide, doxorubicin, and etoposide, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CODOX-M* cyclophosphamide, vincristine, doxorubicin, and methotrexate, *CR* complete remission, *EPOCH* etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, *HDMA* high-dose methotrexate and cytarabine, *HyperCVAD* cyclophosphamide, doxorubicin, vincristine, and prednisone, *IVAC* ifosfamide, etoposide, and high-dose cytarabine, *PD* progressive disease, *PR* partial remission, *SD* stable disease, *ud* undetectable

(cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, and high-dose cytarabine), and CDE (cyclophosphamide, doxorubicin, and etoposide) were used for 17, 9, 9, and 4 %, respectively. CR to the first regimen was obtained in 44 % of patients ($n = 10$), while 35 % ($n = 8$) had PR, 4 % ($n = 1$) with SD, and 13 % ($n = 3$) with PD.

Autologous stem cell transplantation (ASCT) was performed on two refractory cases. One patient was cured after transplantation (case 9) and one died of the disease (case 12). The survivor (case 9) had a high CD4 count (520/μL) and well-controlled HIV-RNA levels (below the detection level) at the PBL diagnosis. In contrast, case 12 had a low CD4 count (40/μL) and high HIV-RNA levels (160,000 copies/mL) at the PBL diagnosis.

Bortezomib was administered to four patients as a third- or fourth-line regimen. In three patients, it was combined with dexamethasone alone, and in the remaining, patient was part of VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide). Efficacy was transient in most cases, and all, except for one later died of the disease.

Prognosis

A Kaplan–Meier analysis for the whole group revealed that median progression-free survival (PFS) was 13 months (Fig. 1a) and median overall survival (OS) was 15 months (Fig. 1b). Fourteen patients died, nine patients are still alive, and one patient was lost to the follow-up. Of the 14 patients who died, the cause of death was the progression of PBL in 11 cases (one with leukemic changes), and 3 died of critical infection (one with *Escherichia coli* septicemia, one with invasive pulmonary aspergillosis, and one with BK virus cystitis) (Table 1).

We analyzed prognostic factors in patient backgrounds and treatments. A CD4-positive cell count ≥100/μL at the diagnosis and better ECOG-PS (0 or 1) correlated with a better outcome ($P = 0.027$ and $P = 0.045$, respectively) (Fig. 2a, b). Cases with low aa-IPI (0 or 1) had a slightly better prognosis ($P = 0.084$, Fig. 2c). The clinical stage (Stage I, II vs. III, IV) and EBV-DNA level at the PBL diagnosis did not affect the prognosis ($P = 0.52$, and $P = 0.31$, respectively). The presence of oral lesions at the PBL diagnosis was associated with

a lower Ann-Arbor stage ($P = 0.010$), but was not a significant prognostic factor of survival ($P = 0.52$). The response to the first-line regimen affected the prognosis; patients obtaining CR had a longer survival time than those who did not ($P = 0.0016$, Fig. 2d). Notably, the CR rate after the first-line chemotherapy was higher in the group with a higher CD4 count (≥100/μL) ($P = 0.019$, Fisher's exact test). Univariate Cox regression analysis yielded CD4 count more than 100/mL [HR 0.251, 95 % CI (0.055, 0.841), $P = 0.024$], normal serum LDH level [HR 0.285, 95 % CI (0.044, 1.072), $P = 0.065$], and response to the first-line chemotherapy [HR 0.225, 95 % CI (0.050, 0.748), $P = 0.014$], as major prognostic factors for survival. Multivariate Cox regression analysis showed that those parameters were not significant. i.e., CD4 count ($P = 0.137$), serum LDH level ($P = 0.077$), and response to the first-line chemotherapy ($P = 0.067$). Moreover, we performed stepwise selection for those three factors, and found that response to the first-line chemotherapy was the only significant factor (Table 4).

Comparison of cases before and after 2011

Since there was an abrupt increase in 2011 and 2012, we made a comparison between the two groups, namely, patients diagnosed in 1999–2010 ($n = 11$) and patients diagnosed in 2011–12 ($n = 13$) (Table 5). The latter group included a significantly higher rate of stage IV cases (85 %) than the former group (18 %, $P = 0.0031$, Fisher's exact test). Of note, the former group more frequently had oral lesions (64 vs. 18 %, $P = 0.032$, Fisher's exact test) and had no involvements in the bone marrow or central nervous system.

Serum sIL-2R levels at the PBL diagnosis were higher in the latter group (range 364–3993 U/mL, median 1311 U/mL) than in the former group (range 383–15000 U/mL, median 5080 U/mL, $P = 0.016$, Mann–Whitney U test).

The CD4 count was slightly lower in the latter (83.6 ± 87.8/μL) than in the former group (180.7 ± 195.9/μL, $P = 0.12$, Student's t test). In reference to the response rate to the first-line chemotherapy, the CR rate was significantly higher in the former group (73 vs. 18 %, $P = 0.011$, Fisher's exact test), although there was no significant difference in the survival curve analysis or the final outcomes. There were no significant differences between the two groups in the context of other clinical or histological features; however, LMP-1 positivity was exclusively observed in the former group.

Discussion

PBL was first reported by Delecluse et al. in 1997 [1]. Clinically, its predominance in HIV-positive individuals and its characteristic oral tumors, and pathologically, plasma cell marker VS38c positivity instead of CD20 or CD45, were highlighted. Its histological appearance was similar in most cases: large neoplastic cells with either a single prominent centrally located nucleolus or several peripherally located nucleoli. They proposed to designate this entity as plasmablastic lymphoma in reference to its blastoid morphology and immunophenotypic features. It was originally classified as a variant of diffuse large B-cell lymphoma (DLBCL), and was subsequently recognized as a distinct entity among mature B-cell neoplasms [19]. Approximately 250 cases of PBL have been reported so far [2–4, 6, 20–29], and it is now well known that extranodal involvements other than the oral cavity occur, that MYC rearrangements or other cytogenetic abnormalities may affect prognoses, and the development of cART has somewhat improved prognoses.

In this study, most cases were at the AIDS stage and cART had not yet been or had just been started at the time of the PBL diagnosis. As our previous study shows, the median CD4 count at the lymphoma diagnosis was lower in PBL cases than in patients with HIV-related BL or HL [14, 30]. This suggests a difference in the immunological background between PBL and other HIV-associated lymphoma subtypes.

The positive rate of plasma cell markers (CD38 and CD138), frequency of MYC gene abnormalities, and high MIB-1 index were almost concordant with the previous findings [2, 4, 6, 7]. CD20 and HHV-8 LANA were negative in all cases, as defined in our diagnostic criteria [14]. No particular immunohistochemical phenotypes were detected in oral, CNS, or BM lesions. Almost 40 % of the cases were CD30-positive. This is of particular importance, because the anti-CD30 monoclonal antibody, brentuximab vedotin, was recently launched as salvage therapy for anaplastic large cell lymphoma or HL [31]. It has been used for HIV-negative PBL or AIDS-related DLBCL, achieving certain responses [32, 33]. CD30 expression in PBL has not been well described in the previous case series, but will be worth focusing on because refractory cases to the conventional chemotherapy may benefit from this agent. Most cases in our study harbored EBER-positive tumors, but the LMP-1 positivity rate was lower than that in other studies (20 vs. 38–64 %) [13–15]. There were three LMP-1-positive cases (cases 3, 9, 10), and they shared only one common factor; they were all diagnosed before 2011.

The location of lymphoma lesions was different from that in the previous studies [2–4]. All cases had extranodal lesions, with a higher rate of GI tract involvement than previously reported. This may be due to the easier access to endoscopes and Positron Emission Tomography (PET) in Japan. Most GI lesions of our cases were detected in

Table 3 Immunohistochemical features of 24 PBL cases

Markers	Cases positive	Cases examined	Percentage
CD3	1	24	4
CD5	0	8	0
CD10	10	18	56
CD15	0	3	0
CD20	0	24	0
CD30	7	18	39
CD56	1	7	14
CD38	14	16	88
CD79a	12	21	57
MUM1	10	11	91
CD138	19	24	79
cIgM	0	2	0
Lambda	4	8	50
Kappa	1	8	13
EMA	0	2	0
EBER	20	22	91
LMP1	3	17	18
EBNA2	1	8	13
HHV8 LANA	0	20	0
BCL-2	4	13	31
BCL-6	1	14	7
MIB1 index >90 %	11	14	79
MYC abnormality	5	8	63

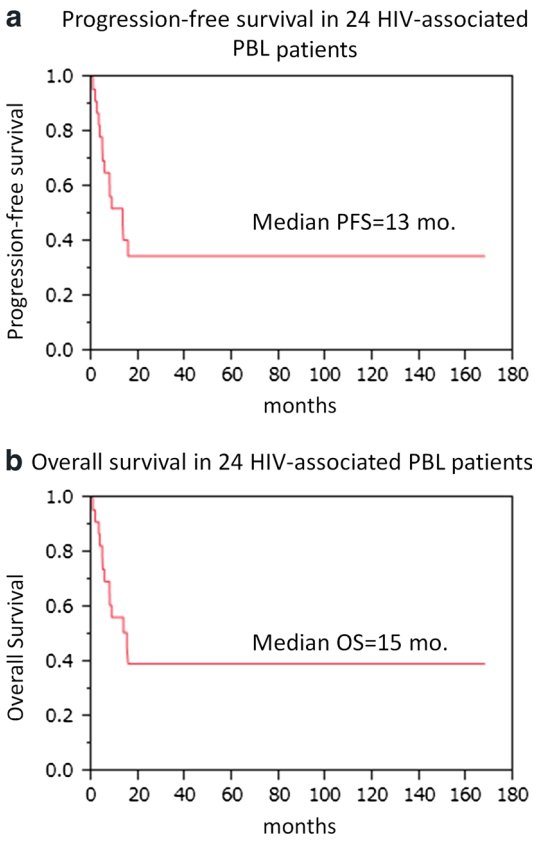

Fig. 1 Survival curves showing progression-free survival (**a**) and overall survival (**b**) in 24 HIV-associated PBL patients

routine endoscopy or PET without any GI symptoms. The rate of GI involvement may have been underestimated and further investigations may change the clinical picture of PBL. Our study was concordant with recent case series, showing that the rate of advanced cases is higher, while the frequency of oral involvement is lower than those in older series. These findings suggest changes in the clinical features of PBL.

There was a drastic increase in PBL cases between 2011 and 2012. The reason is not clear, but at least we can say that there is no bias in case selection or collection process, because this study stems from the retrospective multicenter investigations on whole cases of ARL diagnosed between 1987 and 2012. All the cases were re-diagnosed under reviews by both pathologists and clinicians, sometimes with additional immunostaining if needed. One possible speculation is that the HIV viral proteins, such as gp120 or p17, might play a role in lymphomagenesis. Those molecules are reported to accumulate even under cART, in the absence of any detectable HIV replication in plasma or lymph nodes [34]. Recent changes in cART regimens may develop certain mutations in those proteins, whose accumulation can cause enhancement of B-cell clonogenicity and proliferation. The marked increase in PBL cases between 2011 and 2012 prompted us to compare the clinical features of these two groups (cases diagnosed in 1999–2010 and 2011–12). The characteristic features of cases in the 1999–2010 group were: (1) a high frequency of oral cavity lesions, (2) the absence of BM & CNS invasion, and (3) a high CR rate with the first-line chemotherapy. On the other hand, cases in the 2011–12 group had: (1) a lower CD4 count at the PBL diagnosis, (2) the absence of LMP-1-positive cases, (3) a higher Ann-Arbor stage, (4) a higher sIL-2R level, and (5) chemoresistance. The prognosis cannot be properly evaluated, because of the difference in chemotherapeutic regimens between the two groups, but recent cases have more aggressive biological features. We need longer follow-ups on these cases.

The current guidelines favor intensive chemotherapy regimens as the first-line treatment for PBL. HyperCVAD/highdose and MTX/Ara-C, CODOX-M/IVAC, or EPOCH are recommended [35]. In our study, CHOP was the most commonly used regimen as the first-line chemotherapy. The initial response rate to CHOP was high (85 %); however, many patients subsequently died of recurrent PBL. On the other hand, regimens more intensive than CHOP appeared to cause more severe immunosuppression,

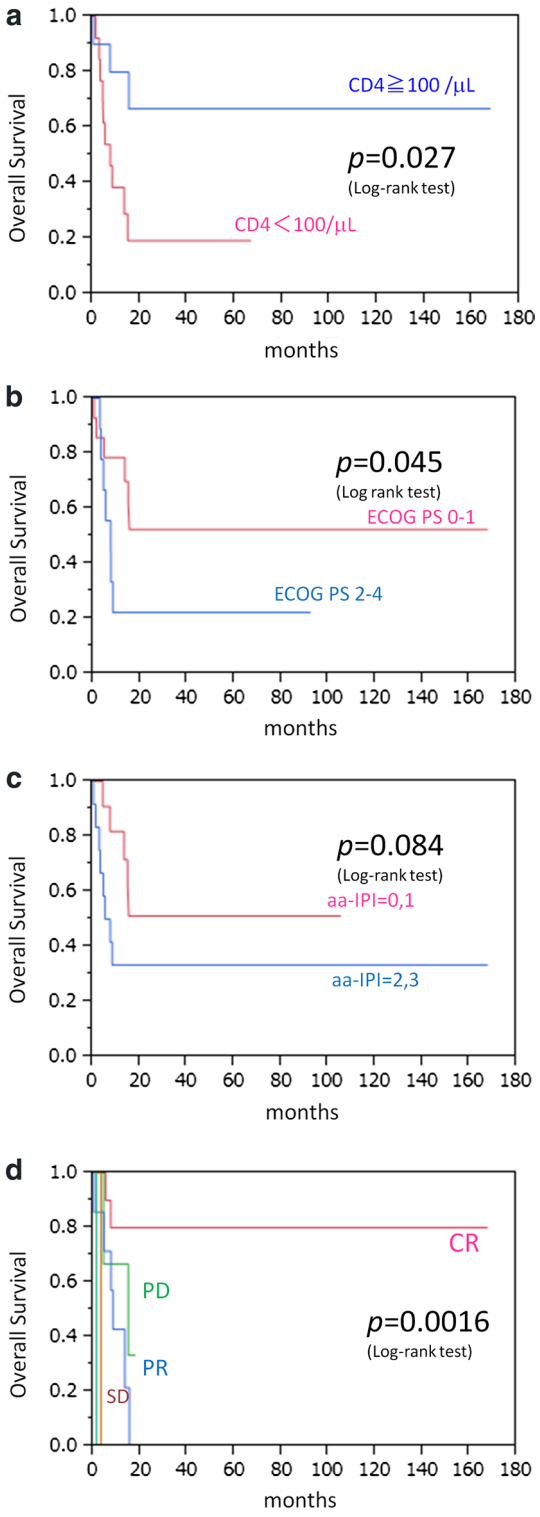

Fig. 2 Overall survival curves in HIV-associated PBL patients according to the variables. **a** Overall survival in 24 HIV-associated PBL patients according to the CD4 count at the PBL diagnosis; Cases with a CD4 count higher than 100/μL had significantly better overall survival rates. **b** Overall survival in 24 HIV-associated PBL patients according to the ECOG PS at the PBL diagnosis; cases with a better ECOG PS had significantly better overall survival rates. **c** Overall survival in 24 HIV-associated PBL patients according to the age-adjusted International Prognostic Index (aa-IPI) at the PBL diagnosis; Cases with a better aa-IPI appeared to have slightly better overall survival rates. **d** Overall survival in 23 HIV-associated PBL patients according to responses to the first-line chemotherapy; Patients who attained complete remission had significantly better overall survival rates

leading to serious infections. As a result, this study showed no significant difference between CHOP and more intensive regimens in terms of survival benefit.

Bortezomib has been used in several PBL case reports. Its effects were sometimes dramatic, but transient, followed by severe infection or tumor relapse [26–33]. Our results were almost concordant. When we consider resistance against bortezomib, front-line combination therapy may be a reasonable strategy. For example, a combination regimen of bortezomib and dose-adjusted EPOCH had certain effects in the treatment of PBL cases [29]. ASCT may be an option for AIDS-related NHL in the cART era [35, 36]. It is important to note that the recommendations described above are based on small case series or case reports [3, 4, 37], and there is no consensus on the treatment regimen for PBL, because of its rarity and paucity of large clinical trials. With the development of cART, the incidence of PBL will decrease even further. Therefore, the results of every case series need to be carefully interpreted.

The most significant result in this study is that a higher CD4 count (≥100/μL) at the PBL diagnosis and obtaining CR with the first-line regimen are favorable prognostic factors. The CR rate was closely associated with a higher CD4 count, emphasizing the importance of the immune status as a prognostic factor. This may be supported by the findings that immunosuppression was identified as an unfavorable prognostic factor in HIV-negative PBL [38]. Patients with a low CD4 count developed EBV-associated complications, such as CAEBV (case 14) or EBV-associated hemophagocytic syndrome (case 19), as critical complications. The relationship between EBV and the PBL prognosis was inconclusive in our study, because of its small size, and detailed analyses on EBV dynamics were incomplete. However, EBV-DNA levels are relevant to the clinical course of PBL [39] and bortezomib is a potent inducer of EBV lytic infections [40, 41], suggesting the importance of EBV in the pathogenesis and treatment of PBL. The nature of PBL may be on one hand the rapid growing tumor driven by potent proliferation signals, such as MYC, and, on the other hand, an opportunistic infection by the oncogenic virus, EBV. Therefore, host immunity and EBV dynamics need to be evaluated in future PBL studies.

In conclusion, we conducted a multi-institutional, retrospective study on PBL in Japan. We confirmed that PBL was associated with a low CD4 count and, despite intensive chemotherapy and improvements in the cART regimen, its

Table 4 Univariate and multivariate analyses of the prognostic factors in PBL cases survival

Parameters	Cases	Univariate cox regression				Multivariate cox regression			
		Hazard ratio	*P* value	Lower 95 % CI	Upper 95 % CI	Hazard ratio	*P* value	Lower 95 % CI	Upper 95 % CI
Patient background at the time of PBL diagnosis									
Calendar year									
1999–2010	11 (46 %)	0.430	0.153	0.114	1.355				
2011–2012	13 (54 %)	1							
Age									
<45 years old	12 (50 %)	1.638	0.382	0.544	5.437				
45≥ years old	12 (50 %)	1							
AIDS state									
−	13 (54 %)	0.509	0.238	0.167	1.601				
+	11 (46 %)	1							
cART									
+	17 (71 %)	0.580	0.353	0.193	1.925				
−	7 (29 %)	1							
CD4 count									
≥100/mL	10 (42 %)	0.251	0.024	0.055	0.841	0.379	0.137	0.080	1.339
<100/mL	14 (58 %)	1							
HIV-RNA									
<100,000 copies/mL	11 (46 %)	0.418	0.133	0.113	1.295				
≥100,000 copies/mL	13 (54 %)	1							
EBV-DNA									
<2000 copies/10^6WBCs	7 (47 %)	1.980	0.267	0.585	7.011				
≥2000 copies/10^6WBCs	8 (53 %)	1							
Clinical characteristics									
Oral lesion									
−	15 (63 %)	1.476	0.509	0.478	5.470				
+	9 (37 %)	1							
CNS invasion									
−	20 (87 %)	0.349	0.157	0.101	1.598				
+	3 (13 %)	1							
BM invasion									
−	17 (74 %)	0.305	0.087	0.086	1.208				
+	6 (26 %)	1							
Ann-Arbor Stage									
I–III	11 (46 %)	1.925	0.250	0.633	6.467				
IV	13 (54 %)	1							
B symptoms									
Absent	10 (42 %)	0.496	0.217	0.148	1.506				
Present	14 (58 %)	1							
ECOG-PS									
0, 1	13 (54 %)	0.396	0.116	0.119	1.264				
2, 3, 4	11 (46 %)	1							
LDH									
Normal	7 (29 %)	0.285	0.065	0.044	1.072	0.294	0.077	0.044	1.127

Table 4 continued

Parameters	Cases	Univariate cox regression				Multivariate cox regression			
		Hazard ratio	*P* value	Lower 95 % CI	Upper 95 % CI	Hazard ratio	*P* value	Lower 95 % CI	Upper 95 % CI
Abnormal	17 (71 %)	1							
sIL-2R									
<3442 U/mL	14 (64 %)	0.483	0.207	0.157	1.528				
≥3442 U/mL	8 (36 %)	1							
age-adjusted IPI									
0, 1	11 (48 %)	0.413	0.137	0.119	1.329				
2, 3	12 (52 %)	1							
first-line chemotherapy regimen									
CHOP	14 (58 %)	1.348	0.614	0.438	4.986				
Other than CHOP	10 (42 %)	1							
Response to the first-line chemotherapy									
CR	11 (46 %)	0.225	0.014	0.050	0.748	0.311	0.067	0.067	1.081
Non-CR	13 (54 %)	1				0.225*	0.014*	0.050*	0.748*

BM bone marrow, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CNS* central nervus system, *CR* complete remission, *IPI* international prognostic index, *PS* performance status, *sIL-2R* serum soluble interleukin-2 receptor

* Multivariate cox regression with stepwise selection

Table 5 Comparison between cases diagnosed in 1999–2010 and in 2011–12

	Cases diagnosed in 1999–2010 ($n = 11$)	Cases diagnosed in 2011–2012 ($n = 13$)	*P* value	
Age (year), mean (median, range)	42 (40, 32–52)	45 (45, 24–59)	0.26	(MW)
CD4 count at the PBL diagnosis (/mL),				
Mean	180.7 ± 195.9	83.6 ± 87.8	0.12	(ST)
Median, range	104, 1–520	40, 6–276	0.33	(MW)
Oral cavity involvement (%)	64	18	**0.032**	(FE)
Bone marrow involvement (%)	0	23	**0.019**	(FE)
CNS involvement (%)	0	46	0.23	(FE)
ECOG PS 2–4 (%)	55	31	0.41	(FE)
Age-adjusted—IPI 2–3 (%)	40	69	0.22	(FE)
Stage IV at the PBL diagnosis (%)	18	85	**0.0031**	(FE)
Serum sIL-2R level (U/ml)	1462	4812	**0.016**	(MW)
Mean median, range	1311, 364–3993	5080, 383–15000		
Serum LDH level (IU/L)	926	801	0.22	(MW)
Mean median, range	277, 149–6708	341, 121–2647		
CHOP as the first-line chemotherapy (%)	14	77	0.17	(FE)
CR to the first-line chemotherapy (%)	73	18	**0.011**	(FE)
Final survival rate (%)	55	31	0.41	(FE)

FE Fisher's exact test, *MW* Mann−Whitney *U* test, *ST* Student's *t* test

prognosis is still poor. Our study found that gastrointestinal involvement in PBL was more frequent than previously estimated, suggesting the need for vigilant investigations. It is notable that the clinical behavior of PBL in recent cases is more aggressive than before. Furthermore, and most importantly, a higher CD4 count at the PBL diagnosis and attaining CR to the first-line regimen chemotherapy were favorable prognostic factors. We always need to pay attention to the immune statuses of PBL patients receiving chemotherapy or ASCT. Further evaluations on chemotherapeutic intensity, new molecular targets, such as CD30, and host immunity against PBL itself or EBV need to be

continued to establish appropriate treatment strategies for PBL.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest. A summary of relevant information will be published with the manuscript.

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