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Case Report

Primary gingival diffuse large B-cell lymphoma: a case report and a review of the literature

Kei-Ji Sugimoto[1], Asami Shimada[1], Hiroko Sakurai[2], Mutsumi Wakabayashi[1], Hidenori Imai[1], Yasunobu Sekiguchi[1], Noriko Nakamura[3], Tomohiro Sawada[3], Hiroshi Izumi[4], Yasunori Ota[5], Norio Komatsu[2], Masaaki Noguchi[1]

[1]Department of Hematology, Juntendo University Urayasu Hospital, Urayasu, Japan; [2]Department of Hematology, Juntendo University School of Medicine, Tokyo, Japan; [3]Department of Clinical Laboratory, Juntendo University Urayasu Hospital, Urayasu, Japan; [4]Department of Pathology, Juntendo University Urayasu Hospital, Urayasu, Japan; [5]Department of Pathology, Research Hospital, The Institute of Medical Science, The University of Tokyo, Japan

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Abstract: The patient was a 73-year-old male who came to our hospital with a chief complaint of pain and swelling of the left side of his jaw. Computed tomography revealed a mass in his left gingiva but no bone destruction. No lesions were observed at any other sites, and an incisional biopsy was performed on the gingival mass on the left side. Histologically, the mass was a diffuse large B-cell lymphoma (DLBCL), and it was CD20-positive, and CD5-negative, CD10-negative, surface immunoglobulin-negative, and Epstein-Barr virus-encoded RNA (EBER)-negative. A serum Human immunodeficiency virus (HIV)-antibody test was negative. A complete remission was achieved after 6 courses of systemic combination chemotherapy, and the complete remission has been maintained for approximately 3 years. According to the literature, primary gingival DLBCL have a high Ki-67-positive rate and many of the cases are stage I and international prognostic index low-risk. However, HIV patients have a high EBER-positive rate and a high risk of developing a CD20-negative, CD138-positive plasmablastic lymphoma, and they have a poor prognosis. By contrast, limited-stage primary gingival lymphomas whose data can be used have been rare in human immunodeficiency virus-negative patients, and only 12 cases, including our own, have ever been reported. Many of the patients have been around 65 years of age, and all of the cases have been CD20-positive, CD138-negative DLBCLs, and the CD5-negative, Epstein-Barr virus-positive rate has been low, with most cases having been non-germinal-center B-cell-like. The prognosis for relapse-free survival has been favorable.

Keywords: Diffuse large B-cell lymphoma, plasmablastic lymphoma, CD20, gingiva, human immunodeficiency virus

Introduction

Primary oral lymphomas are said to account for less than 5% of oral malignant tumors and for about 1% of lymphomas as a whole [1]. Plasmablastic lymphoma (PBL) is cited as a type of lymphoma that often occurs in the mouth. PBL is a rare tumor and is most common in Human immunodeficiency virus (HIV)-positive males, but it is also seen in immunocompromised states and the elderly. Limited-stage primary non-tonsillar oral diffuse large B-cell lymphoma (DLBCL) is rare in non-HIV patients, and there have been reports of only 12 cases, including our own. Even though they have a high Ki-67-positive rate and many are the non-germinal center B-cell-like (non-GCB) type, because many of them are international prognostic index (IPI) low-risk and stage I cases, the prognosis is good [2]. Below we report a case of limited-stage primary gingival DLBCL in a non-HIV patient together with a review of the literature.

Case report

The patient was a 73-year-old male who came to our hospital with a chief complaint of pain and swelling of the left side of his jaw. He had a past history of surgery for prostate cancer at 63

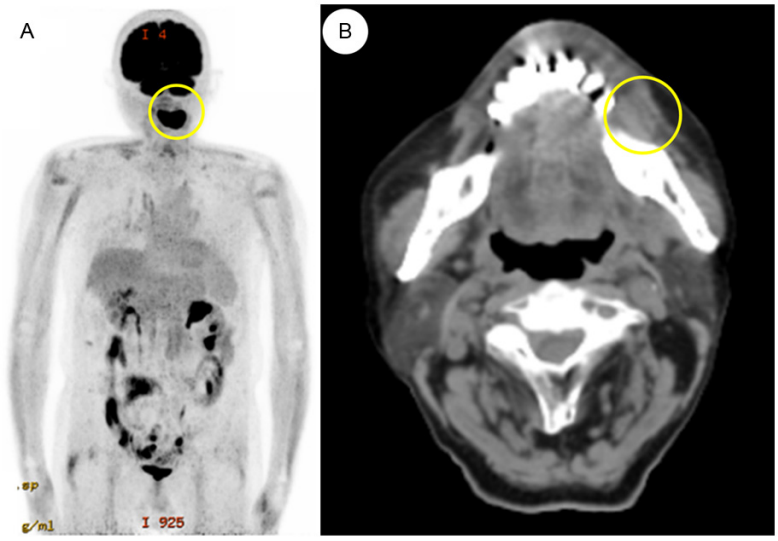

Figure 1. ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) and cervical CT images. The lesion is shown within the yellow circle. A: FDG-PET shows a soft-tissue shadow extending buccally and lingually from the left mandibular to the left alveolar region that has taken up FDG (SUVmax, 22.0). B: The CT image (non-contrast) of the neck shows no evidence of osteolytic change or cortical destruction.

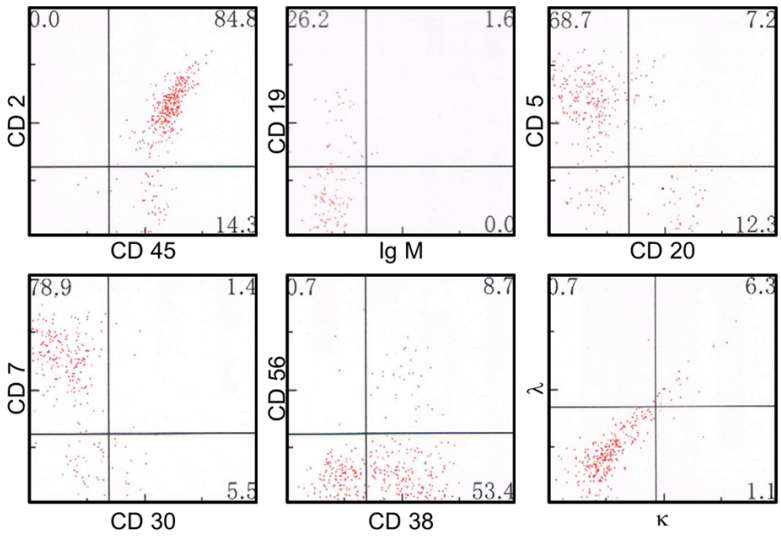

Figure 2. Flow cytometry testing of the gingival lymphoma cells. Approximately 80% are T cells and 20% B cells. Because the B cells do not express immunoglobulin light chain k or λ, and are IgM-negative, CD19-positive, CD20-positive, CD38-positive large cells, it was concluded to be a B-cell lymphoma.

years of age that was treated surgically, stent placement for acute myocardial infarction at 71 years of age, and esophageal varices at 72 years of age.

The history of the present illness revealed that the patient first noticed left lower jaw pain and swelling in December 2010, and when his symptoms became severer, he was examined by a local physician. Necrosis was observed in the left lower front-tooth to premolar area, and a biopsy was performed in that area. Diffuse growth of lymphocytoid tumor cells that exhibited atypia was observed. A malignant lymphoma was suspected, and in February 2011 the patient was referred to our department and examined. An incisional biopsy was performed in the left lower gingiva area.

At the time of the initial examination the patient's body height was 163 cm, body weight 61 kg, and body temperature 36.5°C. Mild anemia was observed, and ulceration and necrosis of the left gingiva were noted. Four left lower teeth were missing (left lower 3-6), and no superficial lymph nodes were palpable. There was no hepatosplenomegaly.

Laboratory tests at the time of the initial examination revealed mild anemia, but were otherwise unremarkable.^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) showed a 1.5 cm x 1.5 cm soft-tissue shadow extending buccally and lingually from the left mandibular to left alveolar region that exhibited FDG uptake (standard uptake value [SUV] max, 22.0), but no osteolytic change or cortical destruction was observed (**Figure 1**). Diagnostic imaging did not show any particular abnormalities at any other sites.

Flow cytometry (FCM) showed a large B-cell tumor that was CD38-positive, CD19-positive, CD20-positive, with no surface immunoglobulin light chain expression (**Figure 2**).

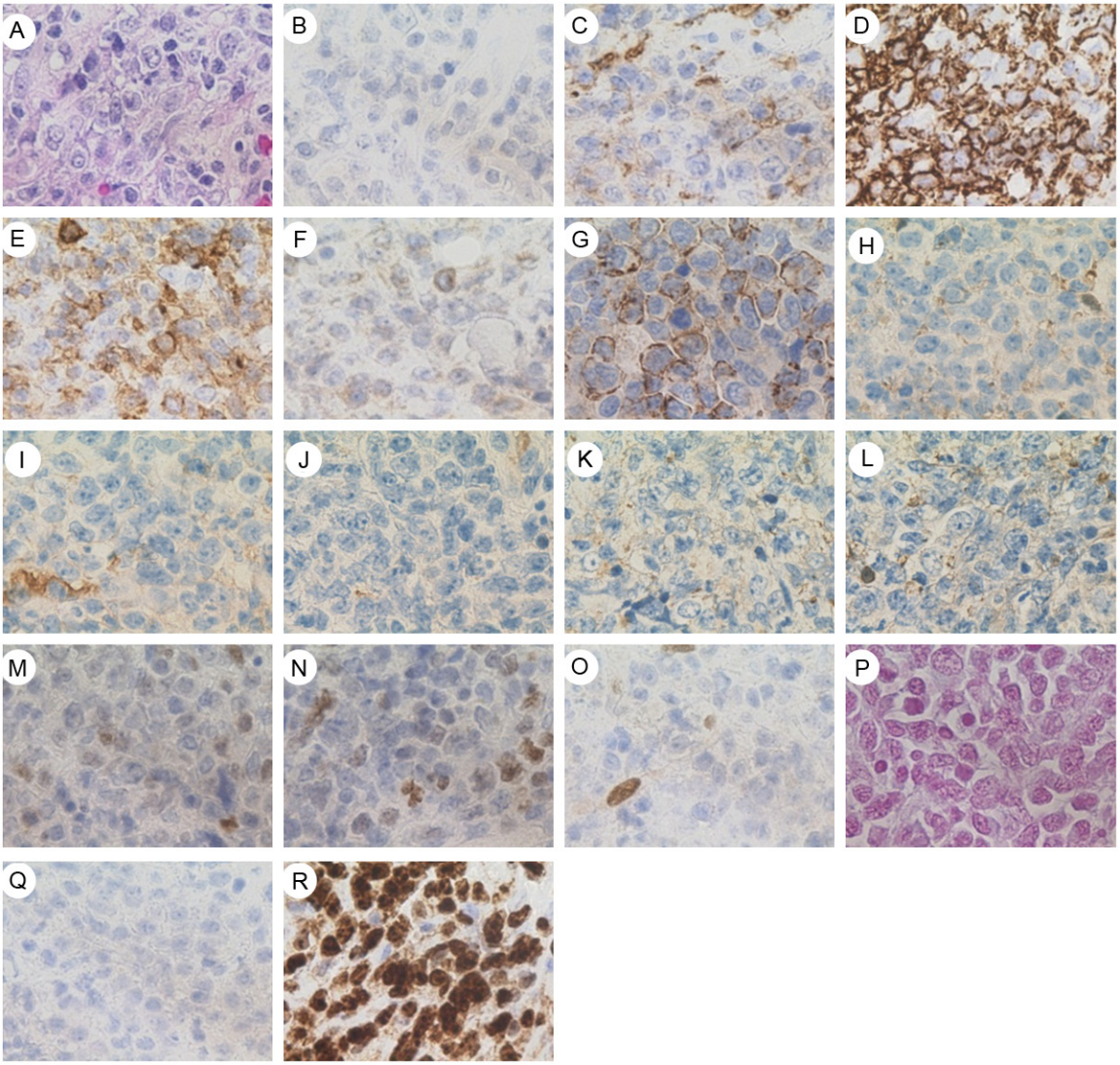

Figure 3. Immunohistological staining of the gingival lymphoma (x600). A: Hematoxylin eosin (HE) stain. Diffuse growth of intermediate-to-large atypical lymphocytes was observed beneath the mucosal epithelium. B: CD5-negative, C: CD10-negative, D: CD20-positive, E: CD30-positive, F: Weakly CD79a-positive, G: CD138-negative, H: IgG-negative, I: IgA-negative, J: IgM-negative, K: Kappa-negative, L: Lambda-negative, M: Partly BCL6-positive, N: Partly MUM1-positive, O: Cyclin D1-negative, P: Epstein-Barr virus-encoded small RNA (EBER) in situ hybridization-negative, Q: LMP1-negative, R: High Ki-67 labeling index rate.

Histopathological examination revealed diffuse growth of intermediate-size to large atypical lymphocytes beneath the mucosal epithelium (**Figure 3**). There was no follicle formation, but there was necrosis and bacterial infection in the surface portion. Immunohistochemically the cells stained positive for CD20, CD79a, and CD30 and negative for CD5, CD10, IgG, IgA, IgM, κ, λ, B-cell lymphoma 2 (BCL2), cyclin D1, latent membrane protein 1 (LMP1), and Epstein-Barr virus-encoded RNA (EBER). The Ki-67 labeling index was more than 90%.

The diagnosis was DLBCL, stage IE, and IPI low-risk, and Rituximab combined with THP-COP (tetrahydropyranyl-adriamycin, cyclophosphamide, vincristine, and prednisolone) therapy was started. The symptoms decreased after the first course, and a complete remission was confirmed by FDG-PET/CT after 6 cycles had been performed. The complete remission has been maintained even after approximately 3 years has passed since the onset of symptoms.

Discussion

There have also been many reports of oral lymphomas by dentists and oral surgeons in the past, but there have been hardly any reports

Table 1. Clinical findings of primary gingival diffuse large B-cell lymphoma in non-HIV patients

Case	Sex/Age (years)	LDH*	CS	IPI	Tumor size (cm)	Treatment	Outcome (months)	References
1	F/57	-	IE	L	2.5	RT	ANED, 79	[2]
2	F/65	+	IE	LI	3.5	R-CHOP + RT	ANED, 13	[2]
3	F/68	-	IE	LI	3.5	CHOP + RT	ANED, 22	[2]
4	M/60	-	IE	L	2	R-CHOP + RT	ANED, 16	[2]
5	F/68	+	IE	LI	>5	NA	NA	[2]
6	M/62	-	IE	LI	2, multiple	R-CHOP	ANED, 19	[2]
7	M/76	-	IE	L	4	R-THP-COP + RT	ANED, 33	[2]
8	F/72	-	IE	L	3	NA	NA	[2]
9	F/62	+	IE	LI	1.5	CHOP + RT	ANED, 177	[2]
10	F/77	-	IIE	L	3.5	Partial resection + CHOP	ANED, 31	[2]
11	M/57	-	IIE	L	3	R-CHOP	ANED, 52	[2]
12	M/73	-	IE	L	2	R-THP-COP	ANED, 36	present

Abbreviations: ANED, alive with no evidence of disease; CHOP, cyclophosphamide, adriamycin, vincristine, prednisolone; CS, clinical stage; F, female; M, male; IPI, international prognostic index; L, low risk; LDH, serum lactate dehydrogenase; LI, low-intermediate risk; NA, not available; R, rituximab; RT, radiation therapy; THP, THP-doxorubicin; *, >upper limit of normal.

Table 2. Immunohistochemical findings of primary gingival diffuse large B-cell lymphoma in non-HIV patients

Case	EBER	CD3	CD5	CD10	CD20	CD138	BCL6	MUM1	Ki-67 labeling index (%)	Immunophenotype	Reference
1	-	-	-	-	+	-	-	+	85	Non-GCB	[2]
2	+	-	-	-	+	-	-	+	75	Non-GCB	[2]
3	-	-	-	-	+	-	-	+	60	Non-GCB	[2]
4	-	-	-	-	+	-	+	+	90	Non-GCB	[2]
5	-	-	-	+	+	-	+	-	80	GCB	[2]
6	+	-	-	-	+	-	+	+	70	Non-GCB	[2]
7	-	-	-	-	+	-	+	+	80	Non-GCB	[2]
8	-	-	-	+	+	-	+	+	50	GCB	[2]
9	-	-	-	-	+	-	+	+	65	Non-GCB	[2]
10	-	-	-	-	+	-	+	+	80	Non-GCB	[2]
11	-	-	-	-	+	-	-	+	90	Non-GCB	[2]
12	-	-	-	-	+	-	+	+	90	Non-GCB	present

Abbreviations: EBER, Epstein-Barr virus-encoded small RNA; GCB, germinal center B-cell like.

regarding the pathological types or phenotypes of the lymphomas. As many as 100 cases of primary oral lymphomas in non-HIV patients have been reported, and the majority of them have been DLBCLs. Among the cases for which the data have been relatively complete are the cases in the report by Sato et al. [2], and when our own case is included, it brings to 12 the number of cases of primary oral limited-stage DLBCLs that have been reported in non-HIV patients (**Table 1**). The median age of the patients was 65 years (57 to 77 years), and females accounted for 64% of the total. Many of the cases had serum lactate dehydrogenase (LDH) values within the normal range, were Stage I, and were IPI low-risk. The size of many of the tumors was around 3 cm (2 cm to more than 5 cm), and many of them had ulcerated. Our own case can be described as relatively typical. Many of the cases have been treated by radiation therapy in addition to a cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-like regimen, and the results have been few cases of relapse and a very good outcome. Our own patient was treated with a Rituximab-CHOP-like regimen alone, and his course has been favorable.

As shown in **Table 2**, a study of the immunophenotypes of the limited-stage oral primary DLBCLs in the 12 non-HIV cases showed that only 2 cases (approximately 17%) were Epstein-

Table 3. Clinical data of primary gingival plasmablastic lymphoma

Case	Sex/Age (yeays)	HIV	CS	IPI	Tumor size (cm)	Treatment	Outcome (months)	References
1	M/37	+	IBE	NA	NA	PC	DOD, 11	[4]
2	M/33	+	IAE	NA	NA	RT	LFU	[4]
3	F/75	-	IAE	NA	NA	RT	DOC, 3	[4]
4	M/41	+	IAE	NA	NA	PC + RT	DOC, 6	[4]
5	M/42	+	IAE	NA	NA	PC + RT	DOD, 5	[4]
6	M/55	+	IAE	NA	NA	PC	Alive, 18	[4]
7	M/27	+	IAE	NA	NA	PC	NA	[4]
8	M/39	+	IAE	NA	NA	RT	Alive, 8	[4]
9	M/63	-	IAE*	LI*	NA	NA	NA	[5]
10	M/66	-	IAE	LI	2	PC + RT	DOD, 8	[6]
11	M/30	+	IAE*	L*	3 x 2	NA	LFU	[7]
12	M/49	+	I or II	NA	NA	NA	NA	[8]
13	M/49	+	I or II	NA	NA	NA	NA	[8]
14	F/23	+	I or II	NA	NA	NA	NA	[8]
15	M/41	+	I or II	NA	NA	NA	NA	[8]
16	M/40	+	I or II	NA	NA	NA	NA	[8]
17	M/41	+	I or II	NA	NA	NA	NA	[8]
18	M/42	+	I or II	NA	NA	NA	NA	[8]
19	M/29	+	I or II	NA	NA	NA	NA	[8]
20	F/30	+	I or II	NA	NA	NA	NA	[8]
21	M/36	+	IAE	L	NA	PC + ASCT, HAART	Dead, 14	[9]
22	M/49	+	IA	L	5.5 x 3.3	NA	NA	[10]

Abbreviations: ASCT, autologous stem cell transplantation; CS, clinical stage; DOC, dead of unrelated causes; DOD, dead of disease; F, female; HAART, highly active antiretroviral therapy; IPI, international prognostic index; L, low risk; LFU, lost to follow up; LI, low intermediate risk; M, male; NA, not available; PC, polychemotherapy; RT, radiation therapy; *probably.

Barr virus (EBV)-positive, a relatively low incidence. There have been no CD5-positive DLBCLs. After excluding 2 CD10-positive cases, 10 cases (approximately 83%) were non-GCB lymphomas. Moreover, the Ki-67 labeling index was high, around 70%, in many of the cases, and it is very interesting that the outcome has been favorable in many of the limited-stage cases. In contrast to the HIV cases, all of the non-HIV cases were CD20-positive and CD138-negative, and they appeared to be the findings of an ordinary DLBCL rather than of a PBL.

PBL is a DLBCL subtype with a characteristic immunohistochemical phenotype that was first reported in 1997. The 22 cases with relatively complete data are listed in **Table 3**. PBL has usually been more common in HIV-positive patients, but it is also seen in other immunocompromised conditions and the elderly. The prognosis is poor in spite of Stage I, IPI low- to low-intermediate risk patients. The PBL phenotypes shown in **Table 4** are plasma cell phenotypes, and CD138, VS38c, and MUM1 were positive, while CD20 and CD45 were negative or at most weakly positive. A few were CD79a-positive. Half were positive for immunoglobulin IgG and for one of the light chains (κ, λ). Epstein-Barr virus nuclear antigen 2 (EBNA2) and LMP1 were negative, but a high proportion, 60-75%, were EBER-positive. The Ki-67-positive rate was high. Comparisons between primary gingival DLBCL and PBL patient group are summarized in **Table 5**. They have in common the fact that many cases have been Stage I and IPI low-risk. However, the PBL patients have been younger, more have been male; more have had a poor outcome, been CD20-negative or weakly positive, and EBER-positive; they have had a higher Ki-67 labeling index, and more have been CD138-positive.

According to a review by Sarode [3], gingival cases accounted for 28 (43%), i.e., close to half of the 65 oral cases. HIV-positive patients accounted for 59 (92%) of the 64 cases that

Table 4. Immunohistochemical findings of primary gingival plasmablastic lymphoma

Case	EBER	EBNA-2	LMP-1	CD20	CD45	CD79a	CD138	VS38c	k	λ	IgG	Ki-67*	References
1	+	-	-	+/-	-	+/-	NA	+	-	-	-	NA	[4]
2	+	-	-	-	+/-	+/-	NA	+	-	-	-	NA	[4]
3	NA	NA	NA	-	-	NA	NA	+	-	+	-	NA	[4]
4	-	-	-	-	-	+/-	NA	+	-	+	+	NA	[4]
5	+	-	+/-	-	-	+/-	NA	+	-	-	-	NA	[4]
6	-	-	-	+/-	+/-	+	NA	+	+	-	+	NA	[4]
7	-	-	-	-	-	+/-	NA	+	-	-	+	NA	[4]
8	+	-	+/-	-	+/-	+/-	NA	+	-	+	+	NA	[4]
9	+	-	-	NA	NA	NT	+	NA	NA	NA	+	>85%	[5]
10	-	NA	NA	-	+/-	+	++	NA	NA	NA	NA	90%	[6]
11	-	NA	NA	-	-	NT	+	NA	-	+	NA	NA	[7]
12	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
13	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
14	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
15	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
16	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
17	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
18	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
19	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
20	+	NA	NA	+/-	NA	+/-	NA	+	+**	+**	NA	NA	[8]
21	NA	NA	-	-	+	+/-	+	NA	+	-	NA	High	[9]
22	+	NA	-	-	+/-	-	++	NA	NA	NA	NA	90-95%	[10]

Abbreviations: EBER, EBV-encoded small RNAs 1 and 2; EBNA-2, EBV nuclear antigen 2; LMP-1, latent membrane protein 1; NA, not available; +, positive; -, negative; +/-, weakly positive; *, percentage of cells positive in a given tumor, **, positive for either kappa or lambda.

Table 5. Comparison between primary gingival diffuse large B-cell lymphoma and plasmablastic lymphoma patient group

	DLBCL	PBL	Present case
Age (median)	65	41	73
Sex (M)	4/11 (36%)	19/22 (86%)	+
CS (I or II)	9/11 (82%)	13/13 (100%)	+
IPI (L)	6/11 (55%)	4/5 (80%)	+
OS (months)	49.1/9	9.1/8	12
HIV (+)	0/11 (0%)	19/22 (86%)	-
EBER (+)	2/11 (18%)	15/20 (75%)	-
CD20 (+)	11/11 (100%)	0/21 (0%)	+
k (+)	NA	2/10 (10%)	-
λ (+)	NA	4/10 (40%)	-
CD38 or VS38c (+)	1/1 (100%)	16/16 (100%)	+
Ki-67* (>85%)	3/11 (27%)	4/4 (100%)	+
CD138 (+)	0/11 (0%)	5/5 (100%)	-

Abbreviations: CS, clinical stage; DLBCL, diffuse large B-cell lymphoma; EBER, Epstein-Barr virus-encoded small RNA; IPI, International Prognostic Index; M, male; L, low risk; OS, overall survival; PBL, plasmablastic lymphoma; *, percentage of cells positive in a given tumor; The denominator indicates the evaluable number of cases.

had been tested for HIV, and 46 (71%) of the 65 cases were EBV-positive. The outcome data showed that 10 out of 40 patients had survived after a mean follow-up period of 24.87 months, 23 had died after a mean follow-up period of 10.07 months, and 7 had been lost to follow-up.

To summarize, many primary gingival malignant lymphomas are Stage I and IPI low-risk. In many HIV-positive patients the lymphoma is an EBER-positive, CD138-positive, CD38-posivtive, but CD20-negative, and CD45-negative PBL, and the prognosis is poor. On the other hand, there have been reports of 12 cases, including our own, of non-HIV primary gingival

DLBCL cases, in which even the outcome and phenotype have been reported in detail. Although many have been non-GCB and had a high Ki-67-positive rate, they have been EBER-negative and CD5-negative, and, perhaps because rituximab was used in their treatment, they have survived without relapse, and the outcome has been favorable. The case we have reported here can be described as a typical case. It will be necessary to accumulate additional cases in the future and investigate the outcome and phenotype in greater detail.

Disclosure of conflict of interest

The author(s) indicated no potential conflicts of interest.

Address correspondence to: Dr. Kei-Ji Sugimoto, Department of Hematology, Juntendo University Urayasu Hospital, 2-1-1 Tomioka, Urayasu 279-0021, Japan. Tel: +81-47-353-3111; Fax: +81-47-381-5054; E-mail: keijis@juntendo.ac.jp

References

[1] Epstein JB, Epstein JD, Le ND and Gorsky M. Characteristics of oral and paraoral malignant lymphoma: a population-based review of 361 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001; 92: 519-525.

[2] Sato Y, Onishi N, Morito T, Takata K, Mizobuchi K, Nagatsuka H, Ichimura K, Tanaka T, Tamura M and Yoshino T. Patients with localized primary non-tonsillar oral diffuse large B-cell lymphoma exhibit favorable prognosis despite a non-germinal center B-cell-like phenotype. Cancer Sci 2009; 100: 42-46.

[3] Sarode SC, Zarkar GA, Desai RS, Sabane VS and Kulkarni MA. Plasmablastic lymphoma of the oral cavity in an HIV-positive patient: a case report and review of literature. Int J Oral Maxillofac Surg 2009; 38: 993-999.

[4] Delecluse HJ, Anagnostopoulos I, Dallenbach F, Hummel M, Marafioti T, Schneider U, Huhn D, Schmidt-Westhausen A, Reichart PA, Gross U and Stein H. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. Blood 1997; 89: 1413-1420.

[5] Tzankov A, Brunhuber T, Gschwendtner A and Brunner A. Incidental oral plasmablastic lymphoma with aberrant expression of CD4 in an elderly HIV-negative patient: how a gingival polyp can cause confusion. Histopathology 2005; 46: 348-350.

[6] Lee OJ, Kim KW and Lee GK. Epstein-Barr virus and human immunodeficiency virus-negative oral plasmablastic lymphoma. J Oral Pathol Med 2006; 35: 382-384.

[7] Desai RS, Vanaki SS, Puranik RS, Giraddi G and Pujari RV. Plasmablastic lymphoma presenting as a gingival growth in a previously undiagnosed HIV-positive patient: a case report. J Oral Maxillofac Surg 2007; 65: 1358-1361.

[8] Ferrazzo KL, Mesquita RA, Aburad AT, Nunes FD and de Sousa SO. EBV detection in HIV-related oral plasmablastic lymphoma. Oral Dis 2007; 13: 564-569.

[9] Dawson MA, Schwarer AP, McLean C, Oei P, Campbell LJ, Wright E, Shortt J and Street AM. AIDS-related plasmablastic lymphoma of the oral cavity associated with an IGH/MYC translocation--treatment with autologous stem-cell transplantation in a patient with severe haemophilia-A. Haematologica 2007; 92: e11-2.

[10] Hassan A, Kreisel F, Gardner L, Lewis JS and El-Mofty SK. Plasmablastic lymphoma of head and neck: report of two new cases and correlation with c-myc and IgVH gene mutation status. Head Neck Pathol 2007; 1: 150-155.