Plasmablastic Lymphomas With *MYC/IgH* Rearrangement

Report of Three Cases and Review of the Literature

Agata M. Bogusz, MD, PhD, Adam C. Seegmiller, MD, PhD, Rolando Garcia, MS, CLSp(CG), Ping Shang, MS, Raheela Ashfaq, MD, and Weina Chen, MD, PhD

Key Words: Plasmablastic lymphoma; *MYC* rearrangement; t(8;14); HIV/AIDS-related lymphomas

DOI: 10.1309/AJCPFUR1BK0UODTS

Abstract

We report detailed clinicopathologic features of 3 cases of plasmablastic lymphoma (PBL) with MYC/IgH *rearrangement, representing one third of PBL cases diagnosed at our institution. This study brings the total number of reported cases in the literature to 6. All patients were HIV+ with very low CD4 counts at diagnosis. The involved locations were mediastinum, anus, and bone marrow. Tumors exhibited predominantly immunoblastic/plasmablastic morphologic features and had a plasma cell–like immunophenotype. Bright CD38 expression by flow cytometry had a tendency to be more common in these cases compared with PBL without* MYC *rearrangement. All cases were positive for Epstein-Barr virus–encoded RNA but lacked human herpesvirus-8 latent nuclear antigen. The 2 patients with follow-up died within 3 months. These findings show that PBL is often associated with* MYC/IgH *rearrangements and that this finding may portend an aggressive clinical course, suggesting that cytogenetic studies should be routinely applied in cases of PBL.*

Plasmablastic lymphoma (PBL) is a rare aggressive B-cell lymphoma characterized by a diffuse proliferation of large neoplastic cells with predominant immunoblastic/plasmablastic morphologic features and a plasma cell–like immunophenotype.[1,2] This entity was first described in the oral cavity of HIV+ patients in 1997[3] and subsequently in extraoral locations.[4] It can also be seen in HIV– immunocompromised patients following solid organ transplantation or steroid therapy.[2,4,5] This lymphoma is now considered a separate diagnostic entity, distinct from diffuse large B-cell lymphoma, not otherwise specified, in the 2008 World Health Organization (WHO) classification of lymphoid neoplasms.[2]

Although the clinical and pathologic features of this lymphoma are well characterized,[4-8] its molecular pathogenesis remains poorly understood, partly owing to its rarity. It has been suggested that aberration of the genes involved in cell cycle regulation may contribute to PBL oncogenesis. Indeed, hypermethylation of the *p16* gene has been reported,[9] and *MYC* up-regulation by translocation between the *MYC* gene and immunoglobulin heavy chain gene (*MYC/IgH*) was reported recently in 3 separate case reports.[10-12]

The *MYC* gene (8q24) rearrangement with immunoglobulin heavy chain [t(8;14)] or light chain genes [t(2;8) or t(8;22)] is characteristic of Burkitt lymphoma.[13] However, this rearrangement can also be observed in other high-grade B-cell lymphomas,[14-17] many of which may belong to the newly proposed category of "B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma" in the 2008 WHO classification of lymphoid neoplasms.[18]

In this report, we describe a detailed clinicopathologic profile of 3 cases of PBL with *MYC/IgH* rearrangement, the

largest reported series to date, which accounts for one third of the PBL cases diagnosed at our institution. Our data suggest that PBL is frequently associated with deregulation of *MYC* and, therefore, conventional cytogenetics and/or fluorescence in situ hybridization (FISH) studies should be routinely applied to characterize the genetic features of this rare neoplasm.

Materials and Methods

Search of the files of the University of Texas Southwestern Medical Center (Dallas) pathology and clinical flow cytometry database yielded 16 cases of PBL diagnosed from 2004 to 2008. Of these, 9 had sufficient material to be examined for *MYC*/*IgH* rearrangements by conventional karyotypic or FISH studies. Three cases were positive for *MYC* rearrangement and are described in detail in this report, whereas 6 cases without *MYC* rearrangement are briefly described for comparison.

The diagnosis of PBL was based on the criteria described by the WHO classification of lymphoid neoplasms.[2] Routine H&E-stained sections were prepared from formalin-fixed and/or B5-fixed paraffin blocks. Bone marrow (BM) trephine biopsy specimens were fixed in B-5 or Zenker solution, washed, decalcified, and processed. BM aspirate smears were prepared and stained with Wright-Giemsa stain. Immunohistochemical analysis was performed by previously described methods[19] using a broad panel of antibodies, including CD3 (clone 2GVS), CD30 (Ber-H2), CD79a (JCB117), bcl-2 (124), Ki-67 (30-9), and anaplastic lymphoma kinase (ALK-1) (DAKO, Carpinteria, CA); CD10 (56C6), CD38 (SPC32), CD138 (MI15), and human herpesvirus (HHV)-8–latent nuclear antigen (LNA; 13B10) (Novocastra, Newcastle upon Tyne, England); PAX-5 (24) and bcl-6 (GL19E/A8) (Ventana, Tucson, AZ); CD20 (L26, Signet Laboratories, Dedham, MA); CD44 (156-3C11, Lab Vision, Fremont, CA); CD56 (BC56C04, Biocare, Concord, CA); IRF-4 (MUM-1, Santa Cruz Biotechnology, Santa Cruz, CA); and T-cell leukemia (TCL)-1 (4042, Cell Signaling Technology, Danvers, MA).

A case was scored as positive if immunostaining was obtained in more than 25% of the neoplastic cells. Focal or patchy expression was defined as positive staining in 10% to 25% of cells. In situ hybridization analysis for EBV-encoded small RNA (EBER) was performed using a Novocastra in situ hybridization kit according to the manufacturer's instructions.

All cases were immunophenotyped using 4-color FACSCalibur flow cytometry instruments with CellQuest software (Becton Dickinson, San Jose, CA) and analyzed using cluster analysis with Paint-a-Gate Software (Becton Dickinson). The cell preparation and data analysis were performed as previously described.[20]

Conventional chromosome analysis was performed by the standard cytogenetics protocols for neoplastic studies. FISH analysis was performed on cell suspensions or paraffin blocks using a commercially available tricolor dual-fusion FISH probe set for *MYC*/*IGH* rearrangement [t(8;14)] with chromosome 8 centromeric probe as an internal control (Vysis, Downers Grove, IL), using a dual-color break-apart rearrangement probe (Vysis) for *bcl*-6 (3q27) and using a SpectrumOrange probe (Vysis) for *p53* (17p13) deletion. FISH analysis for *bcl*-6 and *p53* and molecular studies for *IgH* and T-cell receptor (TCR)-γ chain gene rearrangements by polymerase chain reaction, using the methods as previously described,[21] were performed only on case 1.

Results

Clinical Findings

The clinical manifestations and laboratory data are summarized in **Table 1**. The cases with *MYC* rearrangement included 1 man and 2 women, with a median age of

Table 1
Clinical Features of 9 Cases of Plasmablastic Lymphoma at Diagnosis

Case No./ Sex/Age (y)	*MYC*	Tissue Sampled/ Other Lesions	Duration of HIV Before Diagnosis	CD4/Viral Load*	Therapy	Outcome
1/F/31	+	Mediastinal mass	28 mo	21/>750,000	EPOCH, ×4; HAART	DOD, 3 mo
2/M/40	+	Anal mass; BM	3 y	48/<400	HAART	NA
3/F/35	+	BM	15 y	35/425	CHOP, ×3; RT, ×1; HAART	DOD, 3 mo
4/M/44	–	Mandibular mass	26 y	204/53,100	EPOCH, ×6	Alive, 5 mo
5/F/44	–	Mediastinal and lung masses	NA	NA	CHOP, ×1; ProMACE-CytaBOM, ×1	DOD, 2 mo
6/M/42	–	Submandibular LN; BM	14 y	145/36,250	HyperCVAD, ×1; HAART	Alive, 1 mo
7/M/42	–	Cutaneous masses	16 y	395/493,000	CHOP, ×2; HyperCVAD, ×2; ESHAP, ×1; RT; HAART	Alive, 9 mo
8/M/56	–	Oral cavity mass	New diagnosis	484/NA	EPOCH, ×3	Alive, 5 mo
9/M/59	–	Cervical mass; BM	NA	NA	None	DOD, 2 wk

BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DOD, died of disease; EPOCH, cyclophosphamide, doxorubicin, etoposide, prednisone, and vincristine; ESHAP, etoposide, cytarabine, cisplatin, and methylprednisolone; HAART, highly active antiretroviral therapy; HyperCVAD, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with cycles of high-dose methotrexate and cytarabine; NA, not available; ProMACE-CytaBOM, cyclophosphamide, doxorubicin, etoposide, and prednisone–cytarabine, bleomycin, vincristine, methotrexate, and leucovorin; RT, radiation therapy.
* CD4 count given as cells/mm^3; viral load, copies/mL.

DOI: 10.1309/AJCPFUR1BK0UODTS

35 years (range, 31-40 years). All patients were HIV+; the time from diagnosis ranged from 28 months to 15 years. At diagnosis, all patients had markedly decreased CD4 counts (median, 35 cells/mm^3), but variable viral loads, despite the fact that all had received highly active antiretroviral therapy (HAART). Patients 1 and 3 had opportunistic infections. None of the patients had a history of a plasma cell neoplasm. Tumors involved extraoral locations, including mediastinum, anus, and bone marrow. Patients were treated variably with HAART alone or HAART plus chemotherapy. Two patients had clinical follow-up; both died of disease within 3 months.

In 6 PBL cases without *MYC* rearrangement, the median CD4 count at diagnosis was 300 cells/mm^3 (range, 145-484 cells/mm^3), higher than that in cases with *MYC* rearrangement (P = .034; t test). These patients tended to have a longer median survival. Four patients were alive at 1 to 9 months and then were lost to follow-up. The other 2 patients died at 2 weeks and 2 months.

Morphologic Features

The 3 cases showed similar morphologic features, consisting of a diffuse proliferation of predominantly large lymphoid cells with immunoblastic or plasmablastic features **Image 1**. The neoplastic cells had round nuclei, smooth nuclear and cytoplasmic contours, moderately clumped chromatin, a single prominent nucleolus or multiple small nucleoli, variably eccentrically located nuclei, and moderate basophilic cytoplasm. The proliferative activity was high with frequent mitotic figures. A distinct "starry sky" pattern with abundant apoptotic bodies and tingible body macrophages was readily appreciable in cases 1 and 2, whereas this pattern was less distinct on the bone marrow sections in case 3. Neoplastic cells with morphologic features of small, mature plasma cells were largely absent. The bone marrow aspirate from case 3 exhibited lymphoma cells with overall cytomorphologic features similar to those seen in the tissue sections and with deeply basophilic, variably vacuolated cytoplasm.

The morphologic features in 6 cases without *MYC* rearrangement were essentially similar to cases with *MYC* rearrangement.

Immunohistochemical Analysis and In Situ Hybridization

Table 2 provides a summary of the immunohistochemical staining and viral studies. All tested *MYC*-rearranged cases were positive for MUM-1, CD38, CD44, CD79a (focal), and CD10, and negative for CD3, CD20, CD30, bcl-2, bcl-6, CD56, PAX-5, and ALK **Image 2**. CD138 was present in 1 of 3 cases, p53 in 2 of 3 (focal), and TCL-1 in 1 of 3 cases. The proliferative index, determined by Ki-67 staining, was 70% or more in all cases. All cases were positive for EBER but negative for HHV-8-LNA.

Table 2 also provides a summary of the immunophenotypic results determined by flow cytometry. All *MYC*-rearranged cases were positive for CD45 and exhibited bright CD38 but were negative for CD3, CD5, CD19, CD20, CD23, FMC-7, and CD30 **Image 3**. The mean fluorescence intensity of CD38 averaged 4,595, which had a tendency to

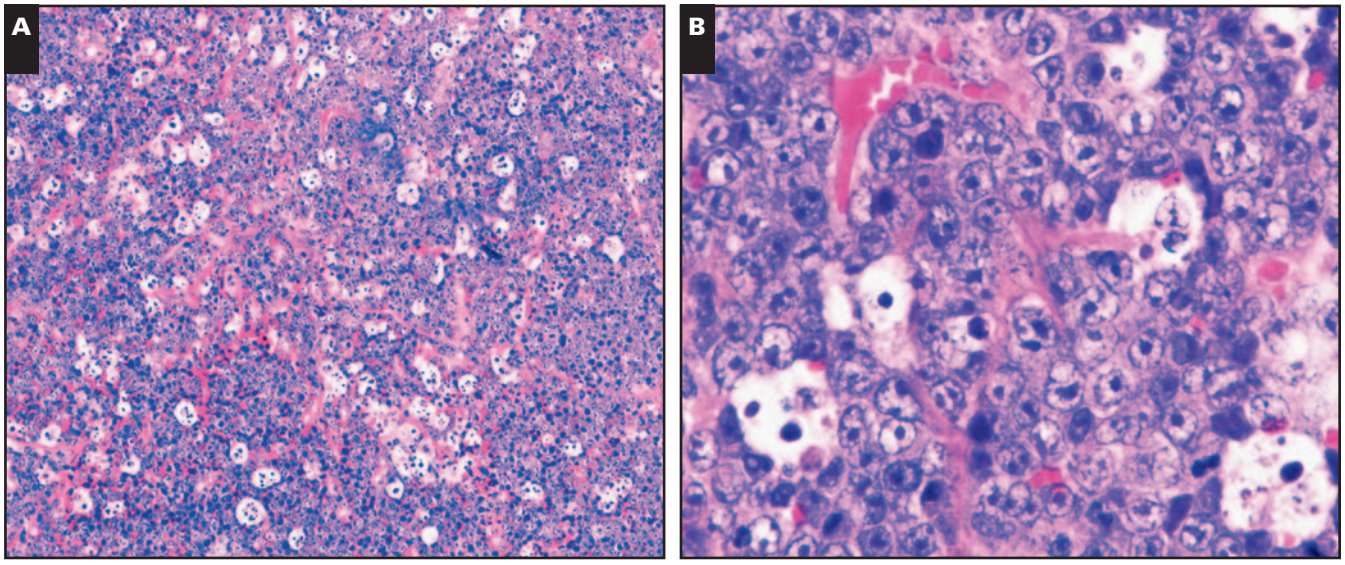

Image 1 (Case 1) Histomorphologic features of plasmablastic lymphoma with t(8;14). **A**, Diffuse infiltrate of large lymphoma cells with a starry-sky pattern of tingible body macrophages (H&E, ×200). **B**, Tumor cells have features of immunoblasts, ie, round nuclei, vesicular chromatin, and frequently prominent central nucleoli (H&E, ×500).

DOI: 10.1309/AJCPFUR1BK0UODTS

Table 2
Summary of 9 Cases of Plasmablastic Lymphoma Immunophenotypes by Immunohistochemical and Flow Cytometric Results and Viral Profiles*

	MYC+		MYC–	
Antibody	**IHC**	**FC**	**IHC**	**FC**
CD3	0/2 (0)	0/3 (0)	0/6 (0)	0/5 (0)
CD4	0/2 (0)	1/3 (33)	1/5 (20)	2/4 (50)
CD5	ND	0/3 (0)	ND	0/5 (0)
CD10	2/2 (100)	0/3 (0)	2/5 (40)	2/5 (40)
CD19	ND	0/3 (0)	ND	0/5 (0)
CD20	0/2 (0)	0/3 (0)	1/6 (17)	0/5 (0)
CD23	ND	0/3 (0)	ND	0/4 (0)
CD30	0/2 (0)	0/2 (0)	1/6 (17)	1/4 (25)
CD38	2/2 (100)	4,595 ± 202†	2/5 (40)	1,983 ± 1,459†
CD44	2/2 (100)	ND	6/6 (100)	ND
CD56	0/2 (0)	0/1 (0)	0/5 (0)	ND
CD79a	3/3 (100; focal)	ND	ND	ND
CD138	1/3 (33)	ND	4/5 (80)	ND
PAX-5	0/3 (0)	ND	0/6 (0)	ND
bcl-2	0/2 (0)	ND	0/5 (0)	ND
bcl-6	0/2 (0)	ND	0/5 (0)	ND
MUM-1	2/2 (100)	ND	6/6 (100)	ND
TCL-1	1/3 (33)	ND	0/6 (0)	ND
Ki-67 (%)	70-100‡	ND	60-100‡	ND
FMC-7	ND	0/3 (0)	ND	0/4 (0)
p53	2/3 (67; focal)	ND	1/5 (20)	ND
ALK	0/2 (100)	ND	ND	ND
sIg	ND	0/3 (0)	ND	1/5 (20)
icIg	ND	0/3 (0)	ND	3/5 (60)
EBER	3/3 (100)	ND	5/6 (83)	ND
HHV-8-LNA	0/3 (0)	ND	1/6 (17)	ND

ALK, anaplastic large cell lymphoma kinase; EBER, Epstein-Barr virus–encoded RNA; FC, flow cytometry; HHV-8-LNA, human herpesvirus-8–latent nuclear antigen; icIg, intracellular immunoglobulin; IHC, immunohistochemical analysis; ND, not done; sIg, surface immunoglobulin; TCL-1, T-cell leukemia-1.
* Data are given as number positive/total (percentage) unless otherwise indicated.
† Mean fluorescence intensity ± standard error (SEM); $P = .08$ for MYC+ vs MYC–.
‡ Estimated percentage of neoplastic nuclei stained.

be higher than in cases of PBL without *MYC* rearrangement (range, 87-6,187; mean, 1,983; $P = .08$; *t* test). CD4 was positive only in case 2. Unlike in immunohistochemical testing, all cases were negative for CD10 by flow cytometry. This may be due to different antibody clones used in immunohistochemical analysis and flow cytometry (clones 56C6 and W8E7, respectively).

The immunophenotypic features and viral profiles in 6 PBL cases without *MYC* rearrangement were essentially similar to those in cases with *MYC* rearrangement.

Conventional Cytogenetic and FISH Analyses

Of 9 patients with PBL who had conventional karyotypic and/or FISH analysis, 3 (33%) had *MYC* rearrangement. **Table 3** details these findings. Two patients had complete karyotypes showing an *MYC* rearrangement, t(8;14)(q24.1;q32) or der(8)t(8;14)(q24.1;q32). These results were confirmed by FISH for t(8;14) in all patients **Image 4** and **Image 5**. This was accompanied by additional complex abnormalities in 2 patients. In case 1, the *MYC* rearrangement [t(8;14)] was detected by FISH only.

Of 6 PBL cases lacking *MYC* rearrangements by FISH, only 2 cases had informative karyotypes. One case had a normal karyotype, and the other had complex abnormalities.

Other Molecular Cytogenetic and Molecular Studies

FISH analysis for bcl-6 and p53 was performed only on case 1 and showed no evidence for *bcl*-6 rearrangement or *p53* deletion. *TCR* and *IgH* rearrangement studies performed only in case 1 were positive for *TCR* gene rearrangement and indeterminate for *IgH* rearrangement.

Discussion

We report 3 cases of PBL with *MYC*/*IgH* rearrangement in HIV+ patients. Although all cases demonstrated morphologic and immunophenotypic similarities to those previously described PBL cases without specification of *MYC* rearrangement status[3-8] and to our 6 cases without *MYC* rearrangement, this subgroup of PBL seems to occur in severely immunosuppressed people and have a more aggressive clinical course. This study brings to 6 the total number of reported cases of PBL with *MYC* rearrangement.

PBL with *MYC* rearrangement has morphologic features of typical PBL with immunoblastic/plasmablastic cytologic features with generally round, centrally to eccentrically located nuclei, prominent single central to multiple smaller nucleoli, and moderate amounts of variably vacuolated cytoplasm. All cases show evidence of EBV infection with uniform expression of EBER but lack immunoreactivity for HHV-8-LNA, in agreement with the previously reported findings.[4-8] Although PBL with *MYC* rearrangement shows immunophenotypic features of plasmacytic differentiation (expression of CD38 and/or CD138) with absent or weak expression of B-cell markers (CD19, CD20, CD79a, and PAX-5), frequent immunophenotypic aberrations were noted. These included the abnormal phenotype CD10+/bcl-6–/MUM-1+ in cases 1 and 2, CD138–/CD38^{bright}+ in cases 1 and 3, and CD4 expression in case 2. This similar immunophenotypic aberration was also observed in a small subset of 6 PBL cases without *MYC* rearrangement. CD4 expression was also reported in a subset of PBL cases in recent studies[6,9] in which 1 case had a rearranged TCR-γ gene. One of our cases (case 1) also had a positive TCR-γ gene rearrangement but lacked CD4 expression.

The important finding in this study is the presence of *MYC* rearrangement in 3 cases of PBL, representing one third of the PBL cases diagnosed at our institution. This rearrangement has also been reported recently in 3 separate case reports.[10-12] Although the actual prevalence of *MYC* rearrangement is

DOI: 10.1309/AJCPFUR1BK0UODTS

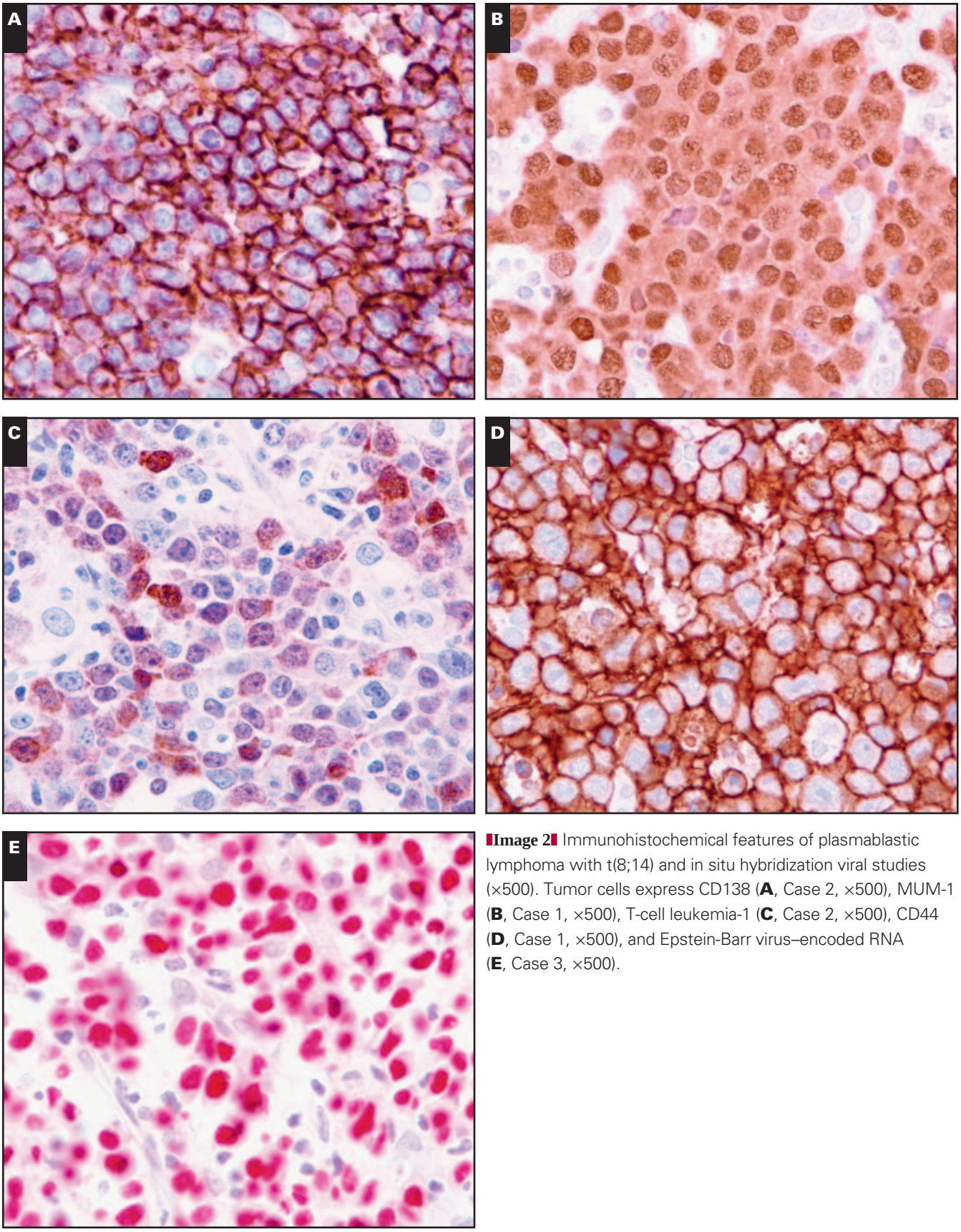

Image 2 Immunohistochemical features of plasmablastic lymphoma with t(8;14) and in situ hybridization viral studies (×500). Tumor cells express CD138 (**A**, Case 2, ×500), MUM-1 (**B**, Case 1, ×500), T-cell leukemia-1 (**C**, Case 2, ×500), CD44 (**D**, Case 1, ×500), and Epstein-Barr virus–encoded RNA (**E**, Case 3, ×500).

DOI: 10.1309/AJCPFUR1BK0UODTS

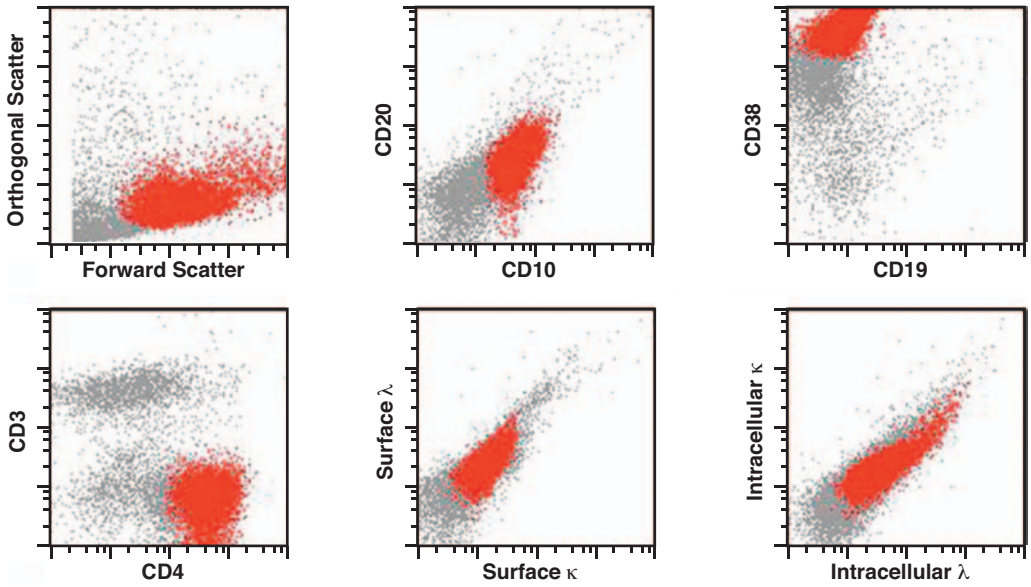

Image 3 (Case 2) Flow cytometric analysis of plasmablastic lymphoma with t(8;14). Neoplastic cells express CD4 and CD38 (bright), and lack CD3, CD10, CD19, CD20, and surface and intracellular light chain expression. Red, neoplastic cells.

Table 3
Cytogenetic Results of 9 Cases of Plasmablastic Lymphoma

Case No.	Karyotype	FISH t(8;14)
1	Unsuccessful (lack of dividing cells)	+
2	47,XY,add(6)(p23),+7,add(8)(p23),t(8;14)(q24.1;q32),der(13)t(13;15)(p12;q13),der(21)t(1;21)(q12;q22) [13 cells]/46,XY [7 cells]	+
3	48~49,XX,del(1)(p34.1p36.3),add(2)(p11.2),add(2)(q31),der(8)t(8;8)(p23;q11.2),der(8)t(8;14)(q24.1;q32),add(9)(p22),der(12)t(1;12)(q21;p13)ins(12;?)(p13;?)add(12)(q24.1),add(13)(p11.2),add(14)(q32),der(14)add(14)(p11.2),t(8;14)(q24.1;q32),–15,–15,add(16)(q22),add(17)(p11.2),add(21)(q22),+3~4 mar [cp4 cells]/46,XX [16 cells]	+
4	ND	–
5	46,XY	–
6	ND	–
7	ND	–
8	Unsuccessful (lack of dividing cells)	–
9	47,XY,+X,del(5)(q13q31),–6,+11,add(11)(q23)x2,psu dic(14;14)(p11.2;p11.2)ins(14;?)(p11.2;?),–17,–20,add(20)(p13),i(21)(q10),+der(?)t(?;6)(?;p21.1),+psu dic(?;17)(?;p11.2)t(?;6)(?;p21.1) [9 cells]/47~48,XY,+X,del(5)(q13q35),–6,add(11)(q23)x2,psu dic(13;13)(p11.2;p11.2),psu dic(14;14)(p11.2;p11.2),–17,psu dic(18;13)(p11.32;p11.2),–20,i(21)(q10),+der(?)t(?;6)(?;p21.1),+psu dic(?;17)(?;p11.2)t(?;6)(?;p21.1) [cp 2 cells]/46~49,XY,+X,–Y,del(4)(q25q31.1),–6,ins(6;?)(p21.1;?),del(7)(q32q36),add(9)(q34),der(17)t(1;17)(q12;p11.2),add(18)(q23),–20,i(21)(q10),+der(?)t(?;6)(?;p21.1),+der(?)t(?;6)(?;p21.1) [cp 6 cells]/46,XY [3 cells]	–

FISH, fluorescence in situ hybridization; ND, not done.

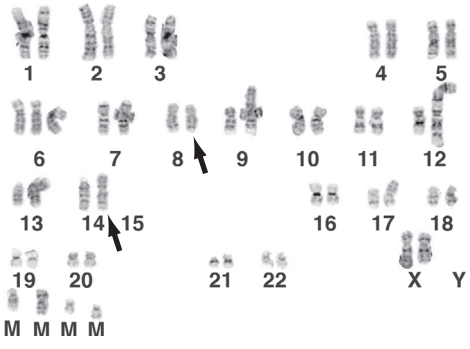

Image 4 Conventional cytogenetic analysis performed on G-banded metaphases demonstrates der(8)t(8;14)(q24.1;q32) and der(14)add(14)(p11.2)t(8;14)(q24.1;q32). Arrows indicate abnormal chromosomes. M, marker chromosome.

unknown, our studies suggest that *MYC* aberration is not uncommon. Routine cytogenetic and/or FISH studies in PBL will help to further evaluate the prevalence of *MYC* aberrations and to further delineate the genetic features of this disease. Identification of the *MYC* rearrangement in PBL adds to the growing list of *MYC* aberrations linked to the pathogenesis of hematolymphoid malignancy.

The clinicopathologic features of the 3 previously reported cases are similar to those described in our 3 patients **Table 4**. A combined analysis of the 6 reported cases demonstrates that *MYC*-rearranged PBL mainly affects adults (age range, 31-49 years) with a male predominance (M/F, 4:2). Patients usually have low CD4 count at the time of diagnosis (range, 21-200 cells/mm^3; median, 48 cells/mm^3)

DOI: 10.1309/AJCPFUR1BK0UODTS

and short survival (range, 3-14 months; median, 3 months). Of note, the 1 patient with longer survival (14 months) described by Dawson et al[12] received combined radiation and chemotherapy followed by autologous stem cell transplantation. These findings are in contrast with those of all patients with PBL (with unknown *MYC* status) who have relatively higher CD4 counts at diagnosis (median, 178 cells/mm^3) and a longer median survival (about 1 year).[4,8] This is also true in 6 PBL cases without *MYC* rearrangement at our institution. Although the affected regions are not confined to the oral cavity (involving bone marrow, lung, and mediastinum in 4 cases), the overall morphologic and immunophenotypic features and association with EBV infection are similar to those being reported in general PBL without specification of *MYC* status.

It is interesting that all 4 cases with informative *MYC* status demonstrated an *MYC* rearrangement with *IgH* [(t(8;14)]. Among 4 cases with karyotypic results, *MYC* rearrangement was the sole cytogenetic abnormality in 1 patient and part of a complex karyotype in the other 3 patients. Regardless of this apparent karyotypic difference, they all had dismal clinical outcomes, suggesting that *MYC* aberrations may have an important role in the pathogenesis of at least a subset of PBL cases. Overexpression of *MYC* could drive cell proliferation and affect other diverse cellular processes such apoptosis,[22] which may account for the rapid proliferation and very aggressive clinical course in this group of PBL patients with *MYC* rearrangement. Identification of *MYC* deregulation may, in the future, lead to more targeted therapies that alter the dismal nature of this disease.

Previous studies have suggested that the distinct immunophenotype of CD10+/bcl-6+/bcl-2– and CD38+/CD44–/TCL-1+ could predict the presence of *MYC* rearrangement in the vast majority of high-grade B-cell lymphomas and Burkitt lymphomas.[14-17,23] However, none of our 3 *MYC*-rearranged PBL cases had this immunophenotype, suggesting that these markers are perhaps less likely to predict *MYC* rearrangement in terminally differentiated B-lineage lymphomas. It is interesting that all 3 cases had bright expression of CD38 by flow cytometry, compared with PBL cases without *MYC* rearrangement, similar to what is seen in other high-grade B-cell lymphomas.[24] These results suggest that bright CD38 expression may predict the presence of *MYC* rearrangement.

Besides *MYC* aberrations, other genetic aberrations have been explored in a limited number of studies, partially owing to disease rarity, and are summarized in **Table 5**. PBL seems to have frequent loss of cyclin-dependent kinase

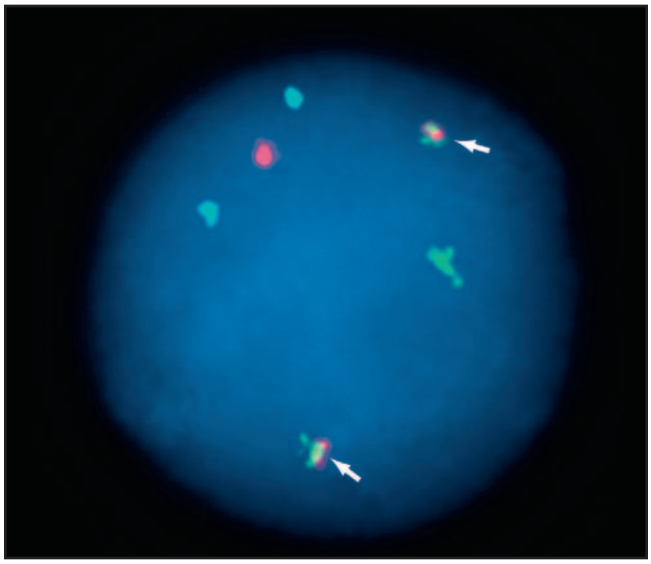

Image 5 Fluorescence in situ hybridization study performed on interphase cells using probes to the *MYC* (red signal) and *IGH* (green signal) loci and chromosome 8 centromere (blue signal) demonstrates that the neoplastic cells contain a reciprocal translocation between the *MYC* and *IGH* loci (yellow signals, arrows).

Table 4
Clinical and Pathologic Features of the Three Reported Cases of Plasmablastic Lymphoma With *MYC* Rearrangement

Reference	Age (y)/Sex/ HIV Status	Location	Immunophenotype	CD4/ Viral Load*	EBER/ HHV-8	Karyotype/ FISH *MYC* R	Treatment	Outcome
Hassan et al,[10] 2007	49/M/+	Jaw	CD45w+/CD138+/MUM-1+/ CD20–/CD79a–/bcl-6–/ 90-95% Ki-67	NA	+/NA	NA/t(8;?)†	NA	NA
Dawson et al,[12] 2007	36/M/+	Gingiva	CD45+/CD138+/CD10–/ CD20–/CD79aw+/high Ki-67	192/33,200	NA/–	t(8;14)/+	HAART, CHOP, RT, ASCT	DOD, 14 mo
Chuah et al,[11] 2008	49/M/+	Lung; BM	CD10+/CD138+/MUM-1+/ CD20–/CD79a focal+/90% Ki-67	200/NA	+/–	t(8;14), t(20;22)/+	NA	NA

ASCT, autologous stem cell transplantation; BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DOD, died of disease; EBER, Epstein-Barr virus–encoded RNA; HAART, highly active antiretroviral therapy; HHV-8, human herpesvirus-8; NA, not available; R, rearrangement; RT, radiation therapy; w, weak.
* CD4 count given as cells/mm^3; viral load, copies/mL.
† *MYC* rearrangement was detected by fluorescence in situ hybridization using the *MYC* break-apart probe with an unknown partner gene.

DOI: 10.1309/AJCPFUR1BK0UODTS

Table 5
Summary of Immunohistochemical and Molecular Genetic Studies in the Pathogenesis of Plasmablastic Lymphomas*

Tests	Positive Results	
	From the Literature	Present Study
bcl-6 mutation	1/12 (by molecular study)[25]	0/1 (by FISH)
bcl-2 rearrangement	0/3[3]	ND
p53 overexpression by IHC	8/8[6]	3/8 (38%; focal)
IgV_H hypermutation	5/11[10,25]	ND
p16 hypermethylation	1[9]	ND
Loss of p16 by IHC	8/8[6]	ND
Loss of o27 by IHC	2/4[6]	ND
MYC rearrangement	3[10-12]	3/9 (33%)

IHC, immunohistochemical analysis; FISH, fluorescence in situ hybridization; ND, not done.
* Data are given as positive cases/tested cases.

inhibitors and p53 expression or aberration, whereas *bcl*-6 mutation or *bcl*-2 rearrangement is uncommon. Notably, 3 of 8 cases showed focal expression of p53. This suggests the presence of a *p53* mutation because wild-type p53 is usually undetectable by immunohistochemical analysis. One of these cases (case 1) showed no evidence for *p53* deletion or *bcl*-6 rearrangement by FISH.

The differential diagnosis of PBL includes plasmablastic plasma cell myeloma, immunoblastic large B-cell lymphoma, Burkitt lymphoma with plasmacytoid differentiation, primary effusion lymphoma, and ALK+ large B-cell lymphoma. The distinction between PBL and plasmablastic plasma cell myeloma frequently depends on clinical correlation because these 2 entities have nearly identical immunophenotypic profiles.[6] Typically, the presence of serum paraprotein and/or lytic bone lesions in older patients would favor plasma cell myeloma, whereas the presence of EBV-infected tumor cells in HIV+ patients is more strongly associated with PBL.[6,7] The presence of an *MYC* rearrangement does not aid in differentiating PBL from plasma cell myeloma because *MYC* rearrangements are present in 15% of plasma cell myelomas.[26] Distinction of PBL from the other aforementioned morphologic mimics could be achieved by strong expression of CD20 and CD79a in immunoblastic large B-cell lymphoma and Burkitt lymphoma with plasmacytoid differentiation, ALK expression or/and *ALK* rearrangement in ALK+ large B-cell lymphoma, and, finally, HHV-8 immunoreactivity in primary effusion lymphoma.

We describe 3 cases of PBL with *MYC*/*IgH* rearrangement in HIV+ patients, representing one third of PBL cases diagnosed at our institution. Although these neoplasms are similar to other cases of PBL with regard to morphologic features, immunophenotype, and viral profile, *MYC* rearrangements seem to portend a more aggressive clinical course. These findings suggest that conventional karyotyping and/or FISH analysis should be routinely applied to identify this group of high-risk patients.

From the Department of Pathology, Division of Hematopathology, the University of Texas Southwestern Medical Center at Dallas.

Address reprint requests to Dr Chen: Dept of Pathology, UT Southwestern Medical Center at Dallas, Dallas, TX 75390-9072.

References

1. Carbone A. AIDS-related non-Hodgkin's lymphomas: from pathology and molecular pathogenesis to treatment. *Hum Pathol*. 2002;33:392-404.
2. Stein H, Harris NL, Campo E. Plasmablastic lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008:256-257.
3. Delecluse HJ, Anagnostopoulos I, Dallenbach F, et al. Plasmablastic lymphomas of the oral cavity: a new entity associated with the human immunodeficiency virus infection. *Blood*. 1997;89:1413-1420.
4. Rafaniello Raviele P, Pruneri G, Maiorano E. Plasmablastic lymphoma: a review. *Oral Dis*. 2009;15:38-45.
5. Colomo L, Loong F, Rives S, et al. Diffuse large B-cell lymphomas with plasmablastic differentiation represent a heterogeneous group of disease entities. *Am J Surg Pathol*. 2004;28:736-747.
6. Vega F, Chang CC, Medeiros LJ, et al. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. *Mod Pathol*. 2005;18:806-815.
7. Dong HY, Scadden DT, de Leval L, et al. Plasmablastic lymphoma in HIV-positive patients: an aggressive Epstein-Barr virus–associated extramedullary plasmacytic neoplasm. *Am J Surg Pathol*. 2005;29:1633-1641.
8. Castillo J, Pantanowitz L, Dezube BJ. HIV-associated plasmablastic lymphoma: lessons learned from 112 published cases. *Am J Hematol*. 2008;83:804-809.
9. Arbiser JL, Mann KP, Losken EM, et al. Presence of p16 hypermethylation and Epstein-Barr virus infection in transplant-associated hematolymphoid neoplasm of the skin. *J Am Acad Dermatol*. 2006;55:794-798.
10. Hassan A, Kreisel F, Gardner L, et al. 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.
11. Chuah KL, Ng SB, Poon L, et al. Plasmablastic lymphoma affecting the lung and bone marrow with CD10 expression and t(8;14)(q24;q32) translocation [published online ahead of print May 28, 2008]. *Int J Surg Pathol*. 2009;17:163-166.
12. Dawson MA, Schwarer AP, McLean C, et al. 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-e12. doi:10.3324/haematol.10933.
13. Leoncini L, Raphael M, Stein H, et al. Burkitt lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008:262-264; vol 2.
14. Cogliatti SB, Novak U, Henz S, et al. Diagnosis of Burkitt lymphoma in due time: a practical approach. *Br J Haematol*. 2006;134:294-301.

15. Haralambieva E, Boerma EJ, van Imhoff GW, et al. Clinical, immunophenotypic, and genetic analysis of adult lymphomas with morphologic features of Burkitt lymphoma. *Am J Surg Pathol*. 2005;29:1086-1094.
16. McClure RF, Remstein ED, Macon WR, et al. Adult B-cell lymphomas with Burkitt-like morphology are phenotypically and genotypically heterogeneous with aggressive clinical behavior. *Am J Surg Pathol*. 2005;29:1652-1660.
17. Rodig SJ, Vergilio JA, Shahsafaei A, et al. Characteristic expression patterns of TCL1, CD38, and CD44 identify aggressive lymphomas harboring a MYC translocation. *Am J Surg Pathol*. 2008;32:113-122.
18. Kluin PM, Harris NL, Stein H, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008:265-266.
19. Xu Y, McKenna RW, Doolittle JE, et al. The t(14;18) in diffuse large B-cell lymphoma: correlation with germinal center–associated markers and clinical features. *Appl Immunohistochem Mol Morphol*. 2005;13:116-123.
20. Chen W, Asplund SL, McKenna RW, et al. Characterization of incidentally identified minute clonal B-lymphocyte populations in peripheral blood and bone marrow. *Am J Clin Pathol*. 2004;122:588-595.
21. van Dongen JJ, Langerak AW, Bruggemann M, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. *Leukemia*. 2003;17:2257-2317.
22. Boxer LM, Dang CV. Translocations involving *c-myc* and *c-myc* function. *Oncogene*. 2001;20:5595-5610.
23. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting—Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17:3835-3849.
24. Maleki A, Seegmiller AC, Uddin N, et al. Bright CD38 expression is an indicator of MYC rearrangement. *Leuk Lymphoma*. 2009;50:1054-1057.
25. Gaidano G, Cerri M, Capello D, et al. Molecular histogenesis of plasmablastic lymphoma of the oral cavity. *Br J Haematol*. 2002;119:622-628.
26. Avet-Loiseau H, Gerson F, Magrangeas F, et al. Rearrangements of the *c-myc* oncogene are present in 15% of primary human multiple myeloma tumors. *Blood*. 2001;98:3082-3086.

DOI: 10.1309/AJCPFUR1BK0UODTS