Plasmablastic Lymphomas With MYC/IgH Rearrangement

Report of Three Cases and Review of the Literature

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

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.
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. Routine H&E-stained sections were prepared from formalin-fixed and/or B5-fixed paraffin blocks. Bone marrow (BM) trephine biopsies were prepared. BM aspirate smears were prepared or B5-fixed paraffin blocks. Bone marrow (BM) trephine biopsies were prepared from formalin-fixed and/or B5-fixed paraffin blocks. Bone marrow (BM) trephine biopsies were prepared.

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 59 years. The clinical features of 9 cases of plasmablastic lymphoma at diagnosis are described in **Table 1**.

**Table 1**

<table>
<thead>
<tr>
<th>Case No./Sex/Age (y)</th>
<th>MYC</th>
<th>Tissue Sampled/Other Lesions</th>
<th>Duration of HIV Before Diagnosis</th>
<th>CD4/Viral Load</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/31 +</td>
<td>Mediastinal mass</td>
<td>28 mo</td>
<td>21/+750,000</td>
<td>EPOCH, x4; HAART</td>
<td>DOD, 3 mo</td>
<td></td>
</tr>
<tr>
<td>2/M/40 +</td>
<td>Anal mass; BM</td>
<td>3 y</td>
<td>48&lt;400</td>
<td>HAART</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3/F/35 +</td>
<td>BM</td>
<td>15 y</td>
<td>36/425</td>
<td>CHOP, x3; RT, x1; HAART</td>
<td>DOD, 3 mo</td>
<td></td>
</tr>
<tr>
<td>4/M/44 –</td>
<td>Mandibular mass</td>
<td>26 y</td>
<td>204/53,100</td>
<td>EPOCH, x6</td>
<td>Alive, 5 mo</td>
<td></td>
</tr>
<tr>
<td>5/F/44 –</td>
<td>Mediastinal and lung masses</td>
<td>NA</td>
<td>CHOP, x1; ProMACE-CytaBOM, x1</td>
<td>EPOCH, x3; HyperCVAD, x1; HAART</td>
<td>Alive, 1 mo</td>
<td></td>
</tr>
<tr>
<td>6/M/42 –</td>
<td>Submandibular LN; BM</td>
<td>14 y</td>
<td>145/38,250</td>
<td>HyperCVAD, x1; HAART</td>
<td>Alive, 1 mo</td>
<td></td>
</tr>
<tr>
<td>7/M/42 –</td>
<td>Cutaneous masses</td>
<td>16 y</td>
<td>395/493,000</td>
<td>CHOP, x2; HyperCVAD, x2; ESHAP, x1; RT; HAART</td>
<td>Alive, 9 mo</td>
<td></td>
</tr>
<tr>
<td>8/M/56 –</td>
<td>Oral cavity mass</td>
<td>New diagnosis</td>
<td>484/NA</td>
<td>EPOCH, x3</td>
<td>Alive, 5 mo</td>
<td></td>
</tr>
<tr>
<td>9/M/59 –</td>
<td>Cervical mass; BM</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td>DOD, 2 wk</td>
<td></td>
</tr>
</tbody>
</table>

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/mm3; viral load, copies/mL.*
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/mm³), 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/mm³ (range, 145-484 cells/mm³), 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 cytomorphic 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

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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).
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, 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. 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+/CD4−/MUM-1+ in cases 1 and 2, CD138−/CD38bright+ 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 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. Although the actual prevalence of MYC rearrangement is
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).
**Table 3**

**Cytogenetic Results of 9 Cases of Plasmablastic Lymphoma**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Karyotype</th>
<th>FISH t(8;14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unsuccessful (lack of dividing cells)</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>47,XY,add(6)(p23),+7,add(8)(p23),t(8;14)(q24.1;q32),der(13)(t13;15)(p12;q13),der(21)(t1;21)(q12;q22) [13 cells]/46,XY [7 cells]</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>48–49,XX,del(1)(p34.1),add(2)(p11.2),add(2)(q31),del(8)(p23),q11.2,del(8)(q24.1),+9(1p22),del(12)(q11.12) [13 cells]/46,XY</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>46,XY</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Unsuccessful (lack of dividing cells)</td>
<td>–</td>
</tr>
</tbody>
</table>

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

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/mm³; median, 48 cells/mm³).
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 and short survival (range, 3-14 months; median, 3 months). Of note, the 1 patient with longer survival (14 months) described by Dawson et al12 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/mm³) 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 as 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)/Sex/HIV Status</th>
<th>Location</th>
<th>Immunophenotype</th>
<th>CD4/ Viral Load*</th>
<th>EBER/ HHV-8</th>
<th>Karyotype/MYC R</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassan et al,10 2007</td>
<td>49/M/+</td>
<td>Jaw</td>
<td>CD45+/CD138+/MUM-1+/CD20–/CD79a+/bcl-6–/+CD38+/bcl-2–/CD44–/TCL-1+</td>
<td>NA</td>
<td>+/NA</td>
<td>NA(0,7)?</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dawson et al,12 2007</td>
<td>36/M/+</td>
<td>Gingiva</td>
<td>CD45+/CD138+/CD10–/CD20–/CD79aw+/high</td>
<td>192/33,200</td>
<td>NA/–</td>
<td>t(8;14)/+</td>
<td>HAART, CHOP, RT, ASCT</td>
<td>DOD,14 mo</td>
</tr>
<tr>
<td>Chuah et al,11 2008</td>
<td>49/M/+</td>
<td>Lung; BM</td>
<td>CD10+/CD138+/MUM-1+/CD20–/CD79a focal+/90% Ki-67</td>
<td>200/NA</td>
<td>+/-</td>
<td>t(8;14), t(20;22)/+</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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/mm³; viral load, copies/mL.

† MYC rearrangement was detected by fluorescence in situ hybridization using the MYC break-apart probe with an unknown partner gene.


**Table 5**

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

<table>
<thead>
<tr>
<th>Tests</th>
<th>From the Literature</th>
<th>Present Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>bcl-6 mutation</td>
<td>1/12 (by molecular study)</td>
<td>0/1 (by FISH)</td>
</tr>
<tr>
<td>bcl-2 rearrangement</td>
<td>0/3</td>
<td>ND</td>
</tr>
<tr>
<td>p53 overexpression by IHC</td>
<td>8/8</td>
<td>3/8 (38%; focal)</td>
</tr>
<tr>
<td>IgVH, hypermutation</td>
<td>5/11, 10, 25</td>
<td>ND</td>
</tr>
<tr>
<td>p16 hypermethylation</td>
<td>1/9</td>
<td>ND</td>
</tr>
<tr>
<td>Loss of p16 by IHC</td>
<td>8/8</td>
<td>ND</td>
</tr>
<tr>
<td>Loss of o27 by IHC</td>
<td>2/4</td>
<td>ND</td>
</tr>
<tr>
<td>MYC rearrangement</td>
<td>3/10-12</td>
<td>3/9 (33%)</td>
</tr>
</tbody>
</table>

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. 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. 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. 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, HIV-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.

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References


