Clinical and pathological differences between human immunodeficiency virus-positive and human immunodeficiency virus-negative patients with plasmablastic lymphoma

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Abstract
Plasmablastic lymphoma (PBL) is a distinct variant of diffuse large B-cell lymphoma initially described in HIV-positive patients. Several studies have reported the occurrence of PBL in HIV-negative patients, but comparative data are lacking. The goal of this study was to compare the characteristics of HIV-positive and HIV-negative patients with PBL. A MEDLINE search was undertaken through August 2009 for cases of PBL in HIV-positive and HIV-negative patients. Cases were identified and clinicopathological data were gathered. \( \chi^2 \) was used to compare categorical and \( t \)-test to compare continuous variables between groups. Calculated Kaplan–Meier survival estimates were compared using the log-rank test. Cox proportional-hazard regression was used for multivariate analysis. From 228 identified cases of PBL, 157 were HIV-positive and 71 HIV-negative. HIV-positive patients were younger, and more likely to be men, present with oral involvement, respond to chemotherapy, and express CD20, CD56, and EBV-encoded RNA than HIV-negative patients. In univariate analysis, age \( \geq 60 \), advanced stage, bone marrow involvement, no chemotherapy, Ki-67 expression \( \geq 80\% \), and HIV-negative status were associated with worse overall survival. In multivariate analysis, advanced stage and no chemotherapy were independent adverse prognostic factors. In conclusion, HIV-positive and HIV-negative patients with PBL have different clinicopathological characteristics, including a better response to chemotherapy and longer survival in HIV-positive patients.

Keywords: HIV, AIDS, plasmablastic lymphoma, HAART, chemotherapy

Introduction
Plasmablastic lymphoma (PBL) is a distinct variant of diffuse large B-cell lymphoma (DLBCL). This rare entity was initially described in 1997 by Delecluse and colleagues [1]. In this seminal report, 16 cases were described with morphological features of DLBCL but with a lack of CD20 and CD45 expression. These cases showed a plasmacytic differentiation based on the expression of VS38c and cytoplasmic immunoglobulin (Ig). Their B-cell lineage was demonstrated through the presence of Ig gene rearrangements. Fifteen of these patients (94%) were infected with the human immunodeficiency virus (HIV), and they all presented with involvement of the oral cavity. Epstein–Barr virus (EBV)-encoded RNA (EBER) was expressed in nine patients (60%). Since 1997, many cases of PBL have been reported in the English and non-English literature [2–11]. Several cases have been reported in patients without HIV infection [3,10,12,13], and several more have reported the occurrence of PBL in extraoral sites [5,10,14,15]. Cases of HIV-negative PBL have been described in the post-transplant setting [12] or arising from previously existing lymphoproliferative disorders [16]. Recent reviews have shown that PBL...
is not only a diagnostic challenge, given its morphology and absence of CD20 staining, but a therapeutic challenge as well. Although this malignancy may have an initial good response to therapy, it is typically hallmarked by a high relapse rate, resistance to intensive therapies, and short survival [17,18].

To date, there have been no studies evaluating the differences between HIV-positive and HIV-negative patients with PBL. We hypothesize that the clinical and pathological characteristics of PBL in these two groups may be different. Hence, in this study, we compared the clinical and pathological characteristics of HIV-positive and HIV-negative patients with PBL.

**Methods**

**Search design and case selection**

An extensive literature search using PubMed/MEDLINE from January 1997 through August 2009 was undertaken for articles in all languages reporting cases with a histological and/or pathological diagnosis of PBL in HIV-positive or HIV-negative individuals. The search key was (‘lymphoma, large-cell, immunoblastic’[MeSH Terms] OR (‘lymphoma’[All Fields] AND ‘large-cell’[All Fields] AND ‘immunoblastic’[All Fields]) OR (immunoblastic large-cell lymphoma’[All Fields] OR (‘plasmablastic’[All Fields] AND ‘lymphoma’[All Fields])) OR plasmablastic lymphoma’[All Fields]). The reference lists of each retrieved article were scrutinized for additional reports. Pediatric and adult cases of PBL were selected based on the initial diagnosis provided by the authors of each publication. Cases with an unknown HIV status or cases already reported in other articles were excluded. Due to controversy on the potential role of human herpesvirus-8 (HHV-8) [19,20], these cases and those reported as HHV-8- or Castleman disease-associated plasmablastic microlymphoma were excluded. Editorials, reviews without additional cases, and non-published abstracts were excluded.

**Data gathering**

Data were gathered according to the following parameters: (1) clinical data included country of report, age at presentation, gender, HIV status, performance status, lactate dehydrogenase (LDH) level, Ann Arbor clinical stage, site of involvement, including bone marrow, presence of B symptoms, frontline therapy, response to therapy, outcome, and overall survival in months; (2) pathological data included expression of CD45, B-cell markers (i.e. CD20 and CD79a), T-cell markers (i.e. CD3, CD4, CD8, and CD56), Ki-67, and EBER. We attempted to contact approximately 40% of the authors to clarify the HIV status and other data pertinent to the reported patients, if needed, with a response rate of 30%.

**Statistical analyses**

Overall survival was defined as the time between diagnosis and death or last follow-up. Cases were separated into two groups, HIV-positive and HIV-negative. The $\chi^2$ test was used to compare categorical clinicopathological variables between groups and the $t$-test was used to compare continuous variables between groups. Survival curves were estimated using the Kaplan–Meier method for incomplete observations and compared using the log-rank test. The Cox proportional-hazard regression test was used for multivariate analysis. $p$-Values of less than 0.05 were considered statistically significant. Calculations and survival graphs were obtained using MedCalc statistical software (Mariakerke, Belgium).

**Results**

**Search results**

The initial search rendered 374 articles. After review of abstracts and full-text articles, 83 articles were deemed suitable for our study; 80 articles were in English, one article was in Spanish [21], one in French [22], and one in Polish [23]. These articles included 248 cases from which 20 had an unknown HIV status. From the 228 cases that were included in our study, 157 were HIV-positive and 71 were HIV-negative.

**Clinicopathological characteristics**

The comparative analysis of the clinical and pathological characteristics between 157 HIV-positive and 71 HIV-negative patients can be seen in Tables I and II, respectively. Statistically significant differences between HIV-positive and HIV-negative patients with PBL were observed in age, gender, rate of oral involvement, response to therapy, and expression of CD20, CD56, and EBER. There were no differences in stage distribution, rate of bone marrow involvement, presence of B symptoms, therapy received, and CD4, CD45, CD79a, BCL-2, or Ki-67 expression.

**Survival analysis**

Survival data were available in 138 patients with PBL, 87 HIV-positive patients and 51 HIV-negative patients. The median overall survival (OS) for the entire group was 12 months, with an estimated
5-year OS of 21% [Figure 1(A)]. In the univariate analysis, age \( \geq 60 \) years, advanced stage, bone marrow involvement, no chemotherapy, and HIV-negative status were associated with worse OS (Table III). HIV-negative patients \((n = 51)\) had a median OS of 9 months, versus 14 months in HIV-positive patients \((n = 87)\) \((p = 0.03; \text{Figure 1(B)})\). As expected, the use of chemotherapy showed significant improvement in survival in both HIV-negative \((14 \text{ vs. } 3 \text{ months}; \ p < 0.001)\) and HIV-positive patients \((16 \text{ vs. } 4 \text{ months}; \ p = 0.04)\) (data not shown). In the multivariate analysis, advanced stage at presentation and no chemotherapy were independent adverse factors for OS in patients with PBL (Table III).

**Discussion**

PBL is a recently described aggressive variant of DLBCL initially reported in the HIV-infected population [24]. However, in recent years, several cases have been described in HIV-negative individuals [3,10,12–15]. Nonetheless, PBL is a rare malignancy. Therefore, large informative studies of this entity are not currently available. Hence, our effort on gathering data from previously published small series and case reports in patients with and without HIV infection is an attempt to improve the current understanding of this unusual malignancy, as there have been no previously published studies comparing the characteristics of HIV-positive and HIV-negative patients with PBL.

Based on the results of this study, PBL arising in HIV-positive and HIV-negative individuals has distinct clinical and pathological differences. Among the most notable clinical differences, we found that HIV-positive PBL patients are younger, include a higher proportion of male cases, have more common oral involvement, and have a better response to chemotherapy than their HIV-negative counterparts. The former two factors, we believe, are due to the closely related historical epidemiology of HIV infection, which has more frequently affected younger men.

The predilection for HIV-associated PBL to present in the oral cavity may be due to the high incidence of chronic premalignant oral lesions in

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**Table I. Clinical characteristics of 157 HIV-positive and 71 HIV-negative patients with plasmablastic lymphoma.**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>HIV-positive</th>
<th>HIV-negative</th>
<th>(p)-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong> (n = 228)</td>
<td>228 (100%)</td>
<td>157 (69%)</td>
<td>71 (31%)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Age</strong> (n = 223)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older than 60 years</td>
<td>35 (16%)</td>
<td>2 (1%)</td>
<td>33 (47%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>60 years or younger</td>
<td>188 (84%)</td>
<td>151 (99%)</td>
<td>37 (53%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Mean age (range)</strong></td>
<td>45 (1–90)</td>
<td>39 (3–65)</td>
<td>58 (1–90)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong> (n = 228)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>172 (75%)</td>
<td>128 (82%)</td>
<td>44 (62%)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Female</td>
<td>56 (25%)</td>
<td>29 (18%)</td>
<td>27 (38%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong> (n = 174)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>56 (32%)</td>
<td>42 (37%)</td>
<td>14 (23%)</td>
<td>0.3760*</td>
</tr>
<tr>
<td>II</td>
<td>23 (13%)</td>
<td>13 (12%)</td>
<td>10 (16%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10 (6%)</td>
<td>1 (1%)</td>
<td>9 (15%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>85 (49%)</td>
<td>57 (50%)</td>
<td>28 (46%)</td>
<td></td>
</tr>
<tr>
<td><strong>Site of involvement</strong> (n = 213)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>98 (46%)</td>
<td>88 (58%)</td>
<td>10 (16%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Extraoral</td>
<td>115 (54%)</td>
<td>64 (42%)</td>
<td>51 (84%)</td>
<td></td>
</tr>
<tr>
<td><strong>Bone marrow</strong> (n = 83)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Involved</td>
<td>25 (30%)</td>
<td>17 (30%)</td>
<td>8 (30%)</td>
<td>0.8511</td>
</tr>
<tr>
<td>Not involved</td>
<td>58 (70%)</td>
<td>39 (70%)</td>
<td>19 (70%)</td>
<td></td>
</tr>
<tr>
<td><strong>B symptoms</strong> (n = 69)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Present</td>
<td>28 (41%)</td>
<td>15 (33%)</td>
<td>13 (54%)</td>
<td>0.1553</td>
</tr>
<tr>
<td>Absent</td>
<td>41 (59%)</td>
<td>30 (67%)</td>
<td>11 (46%)</td>
<td></td>
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<tr>
<td><strong>Therapy</strong> (n = 120)</td>
<td></td>
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</tr>
<tr>
<td>Chemotherapy</td>
<td>94 (78%)</td>
<td>59 (77%)</td>
<td>35 (81%)</td>
<td>0.7059</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>26 (22%)</td>
<td>18 (23%)</td>
<td>8 (19%)</td>
<td></td>
</tr>
<tr>
<td><strong>Response to therapy</strong> (n = 78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>38 (49%)</td>
<td>23 (55%)</td>
<td>15 (42%)</td>
<td>0.0208*</td>
</tr>
<tr>
<td>Partial response</td>
<td>16 (21%)</td>
<td>11 (26%)</td>
<td>5 (14%)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>6 (8%)</td>
<td>0 (0%)</td>
<td>6 (16%)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19 (23%)</td>
<td>8 (19%)</td>
<td>10 (28%)</td>
<td></td>
</tr>
</tbody>
</table>

*\(p\)-Value for trend.

HIV, human immunodeficiency virus.
patients with HIV. Furthermore, patients with HIV have increased rates of EBV, HHV-8, and human papillomavirus (HPV) in the oral cavity [25–27]; however, further research is needed to understand the relationship between these viruses and the pathogenesis of PBL.

The better response to chemotherapy seen in HIV-positive patients could be partially explained by the use of highly active antiretroviral therapy (HAART). That is, HIV-positive patients with aggressive B-cell lymphomas are frequently accompanied by a depressed CD4+ cell count and its associated weakened immune system. These deficiencies can improve in response to HAART, and therefore may result in better survival through improved immunosurveillance [28,29]. Moreover, the immune defects in HIV-negative patients with other immunosuppressive predisposing factors (e.g. post-transplant or chronic autoimmune states) may be less likely to correct with therapy.
With regard to differences in their pathological characteristics, HIV-positive individuals have a significantly higher expression of CD20, CD56, and EBER. Although the prognostic role of the immunohistochemical expression of CD20 has not been formally investigated in DLBCL, the loss of CD20 has been associated with plasmacytic differentiation, and conveys a worse prognosis [30]. Our study found a higher proportion of CD20-positive PBL in HIV-positive patients. This finding suggests that further research is needed to evaluate the prognostic value of CD20 and the potential therapeutic role of rituximab in CD20-positive PBL. Although it is possible that some of these patients were DLBCL cases misdiagnosed as CD20-positive PBL, these data are thought-provoking, as the differences of CD20 expression between HIV-positive and HIV-negative patients with PBL allow one to postulate that HIV-positive PBL could arise from a B-cell at earlier stages of plasmacytic differentiation, compared with HIV-negative PBL.

The expression of CD56 in DLBCL is rare, and has been associated with a germinal center-like phenotype [31,32]. However, the cell of origin of PBL almost invariably shows a post-germinal center-like phenotype, making the significance of this finding unclear. In a previous study, more than half of PBL cases showed expression of CD56 [11], although there was not an association between CD56 expression and prognosis in PBL. There are no clear explanations for the difference in CD56 expression in HIV-positive and HIV-negative patients with PBL. This is a novel finding that deserves further research.

Finally, the expression of EBER is more frequently seen in HIV-positive PBL. HIV infection creates a permissive environment for chronic EBV infection, with a subsequent latency that predisposes the EBV-transformed B-cells to become malignant. In fact, a type 3 EBV latency pattern has been associated with the development of both acquired immunodeficiency syndrome (AIDS)-associated lymphomas and post-transplant lymphoproliferative disorders [33]. Likely, there is a connection between HIV-induced immunosuppression and the development of EBV-associated PBL. Furthermore, strengthening this argument is that some but not all of the HIV-negative PBL cases are associated with other types of immunosuppression, such as chronic steroid use or post-transplant states.

When evaluating for survival, HIV-positive patients with PBL had a better survival than HIV-negative patients with PBL. This correlates with a better response rate to chemotherapy seen in HIV-positive PBL patients, which may be associated with the administration of HAART and restoration of immune surveillance. However, other factors could also have affected negatively the survival of HIV-negative patients, such as multiorgan failure, engraftment rejection in post-transplant patients, or infectious complications due to immunosuppression. HIV-negative patients with PBL in this study were older, and therefore may have had a higher likelihood of poor organ reserve and possibly worse organ performance status at diagnosis, making them poorer candidates for consideration of chemotherapy. Although HIV-positive patients can have infectious complications, and the potential interactions between HAART and chemotherapy can be cumbersome and difficult to manage, the supportive therapy for HIV-positive patients could potentially have a stronger impact than for HIV-negative patients.

In the univariate analysis, age $\geq 60$ years, advanced stage, bone marrow involvement, no chemotherapy, and expression of Ki-67 at $>80\%$ were also identified as adverse prognostic indicators for OS in all patients with PBL. Most of these factors have previously been reported as adverse prognostic indicators in other aggressive lymphomas; hence, their association with poor OS in PBL patients is not surprising. In the multivariate analysis, advanced
stage and no chemotherapy were independent adverse prognostic factors for OS. Advanced stage has previously been reported as an adverse factor in HIV-positive patients with PBL [34]. Our study also shows that there was an improvement in survival in patients who received chemotherapy, regardless of their HIV status. Given the aggressive nature of this lymphoid malignancy in both HIV-positive and HIV-negative patients, this is not surprising.

Among the major limitations of our study is its retrospective nature, which could have introduced a selection bias, since case reports tend to emphasize great responses or poor clinical courses. However, several larger case series have also been included, somewhat balancing out this potential bias. Additionally, the authors acknowledge the potential pitfalls of reviewing previously published data on PBL, given that the criteria for its pathological diagnosis continue evolving and may not have been entirely well defined over the past several years. However, a recent publication addressed minimal criteria for the pathological diagnosis of PBL, irrespective of HIV or EBV status, in countries with limited resources [35].

Conclusions

Plasmablastic lymphoma is a rare variant of DLBCL, but is increasingly being described in HIV-positive as well as HIV-negative patients. Our study identified several clinicopathological differences between HIV-positive and HIV-negative patients, including age, sex, oral involvement, response to chemotherapy, and CD20, CD56, and EBER expression. The survival of HIV-negative patients with PBL appears shorter than for HIV-positive patients. Better treatments are needed for this aggressive B-cell malignancy.

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