

HIV-associated plasmablastic lymphoma: Lessons learned from 112 published cases

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Plasmablastic lymphoma (PBL) is a distinct subtype of non-Hodgkin B-cell lymphoma, originally described with a strong predilection to the oral cavity of human immunodeficiency virus (HIV)-infected individuals. Data regarding patient age and gender, HIV status, initiation of and response to highly active antiretroviral therapy (HAART), tumor extent, pathology, treatment, and outcome were extracted from 112 cases of PBL identified in the literature. The median age at presentation was 38 years with a male predominance of 7:1, and the median CD4+ count was 178 cells/mm³. PBL presented on average 5 years after diagnosis of HIV. Common primary sites of presentation included the oral cavity, gastrointestinal tract, and lymph nodes. Most cases presented with either stage I or stage IV disease. There was a variable expression of B-cell markers in tumor cells, but plasma cell markers were expressed in all cases. EBV was detected in 74%. Chemotherapy was used to treat 55% patients and was combined with radiotherapy in 21% cases. Complete response was obtained in 66% of treated cases; the majority of these responses were seen after CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). The refractory/relapsed disease rate was 54%. Death occurred in 53% of patients, with a median overall survival of 15 months. Sex, CD4+ count, viral load, clinical stage, EBV status, primary site of involvement, and use of CHOP failed to show an association with survival. PBL is an aggressive B-cell lymphoma that presents in both oral and extra-oral sites of chronically HIV-infected immunosuppressed young men. Am. J. Hematol. 83:804–809, 2008. © 2008 Wiley-Liss, Inc.

Introduction

Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) have been associated with an increased risk for the development of lymphoproliferative disorders. Some histological types of aggressive B-cell non-Hodgkin lymphoma (NHL) are considered as AIDS-defining malignancies, namely Burkitt, Burkitt-like, and diffuse large B-cell lymphoma (DLBCL). Subtypes of DLBCL seen more commonly in HIV-infected individuals are primary CNS lymphoma (PCNSL), primary effusion lymphoma, and plasmablastic lymphoma (PBL).

PBL was formally proposed in 1997 as a new distinct subtype of DLBCL based upon morphologic, immunologic, and clinical features [1]. Delecluse et al. were the first group to describe 16 cases of a highly aggressive B-cell lymphoma with plasmacytic differentiation. These lymphomas had immunoblastic morphology and monoclonal rearrangements of the immunoglobulin (Ig) heavy chain gene, but showed absent or weak expression of CD45 and CD20 and a constant expression of the plasma cell marker VS38c, thus the plasmablastic denomination. Most (94%) of these cases were observed in HIV-positive patients, and the presence of EBV was reported in 60% of them. The primary presentation site was the oral cavity, and 69% of those cases presented with stage I disease. The average survival was 9 months, and most patients died in less than 1 year after diagnosis despite having received aggressive therapy.

In the ensuing 10 years multiple case reports [2–23] and case series [1,24–30] of PBL in HIV-infected patients have served to expand our understanding of this novel lymphoma. We present, to the best of our knowledge, the first extensive literature review of the epidemiology, clinical findings, pathology, treatment, and outcome of 112 patients with HIV-associated PBL. In addition, we sought to further elucidate some of the pathological and clinical characteristics of PBL in HIV-infected patients and to correlate these features with survival.

Results

We identified 112 published cases of PBL in HIV-positive patients from January 1st 1997 to December 31st 2007 (Table I). Articles originated worldwide including North America (USA, Canada), South America (Brazil), Europe (United Kingdom, Greece, Spain, Italy, Germany, the Netherlands), Asia (India, Thailand), and Australia.

Mean patient age at presentation was 38 years (range 7–65 years), with a male predominance of 7:1. Two patients were older than 60 years of age. The first case was a 63-year-old woman who presented with EBV-negative, stage I PBL of the skin, low CD4+ count, and low viral load [12]; no data on survival were available. The second case was a 65-year-old man diagnosed with EBV-positive, stage IV PBL of the sinuses [26]. This particular patient was still alive after 19 months of follow-up with unknown therapy. Interestingly, there were two cases reported in children. One case was a 7-year-old-boy who presented with stage I disease and an oral primary site [18]. The second pediatric case was an 11-year-old girl with an EBV-positive cutaneous PBL, without specification of stage [26]. There were no reported data on outcome or survival in these children.

Median CD4+ count at presentation was 178 cells/mm³ (range 10–498 cells/mm³), average HIV viral load was

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TABLE I. Demographics, HIV Status, and Antiretroviral Therapy of Patients with HIV-Associated PBL

	N	%
Age (<i>n</i> = 112)		
Median (years)	38	
Range (years)	7–65	
Sex (<i>n</i> = 107)		
Male	94	88
Female	13	12
CD4 count (<i>n</i> = 28)		
Median (cells/mm ³)	178	
Range (cells/mm ³)	10–498	
Duration of HIV infection (<i>n</i> = 18)		
Median (years)	5	
Range (years)	0–20	
HAART (<i>n</i> = 25)		
Before	16	64
Concurrent	6	24
After	3	12

HIV, human immunodeficiency virus; HAART, highly-active antiretroviral therapy.

TABLE II. Pathological Features of HIV-Associated PBL

	Positive/total tested cases	%
Immunophenotype (<i>n</i> = 112)		
CD45 (Leukocyte common antigen)	17/59	29
CD79a (Pan-B-cell marker)	6/42	14
CD20 (B-cell marker)	2/74	3
CD38 (Plasma cell marker)	11/11	100
VS38c (Plasma cell marker)	36/36	100
CD138 (Plasma cell marker)	37/44	84
MUM1 (Plasma cell marker)	27/27	100
CD56 (NK-cell marker)	2/8	25
EMA (Epithelial membrane antigen)	8/10	80
EBV detection (<i>n</i> = 107)		
EBV-positivity	79/107	74
Southern blotting	2/2	100
PCR	9/11	82
EBER/ISH	69/88	78
LMP-1	5/13	38
Serology	3/3	100

EBV, Epstein-Barr virus; EBER/ISH, EBV-encoded RNA in situ hybridization; PCR, polymerase chain reaction; LMP-1, latent membrane protein-1.

86,884 copies/mL (range, undetectable to more than 750,000 copies/mL), and the average duration of HIV infection prior to PBL diagnosis was 5 years (range 0–20 years). In five cases, PBL was the presenting manifestation of HIV infection. Regarding the use of highly active antiretroviral therapy (HAART), data were available for 30 patients. Twenty-five patients (83%) received HAART at some point during the treatment of their lymphoma. The response to HAART was reported in 11 cases. A good response to HAART was reported in 10 cases; in which nine patients were reported to be alive at the time of publication. Only one patient was reported to have no response to HAART, and he died of an overwhelming infection 1 month after PBL diagnosis [21].

The collective pathological features of PBL are summarized in Table II. Plasma cell markers were expressed uni-

TABLE III. Lymphoma and Therapy-Related Characteristics of Patients with HIV-Associated PBL

	N	%
Ann arbor stage (<i>n</i> = 85)		
I	49	58
II	2	2
III	0	0
IV	34	40
Primary lymphoma site (<i>n</i> = 112)		
Oral	65	58
Gastrointestinal tract	14	13
Lymph nodes	7	6
Other extranodal nonoral sites ^a	26	23
Therapy (<i>n</i> = 53)		
CHOP alone	16	30
Other chemotherapy regimens	13	25
Chemoradiotherapy (including CHOP)	11	21
Other therapies ^b	7	13
No therapy	6	11
Outcome (<i>n</i> = 55)		
Alive	26	47
Dead	29	53
Response (<i>n</i> = 35)		
CR	23	66
PR	2	6
PD	10	29

CHOP, Cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; PR, partial response; PD, progressive disease.

^a Includes nasal/paranasal, skin, anal canal, soft tissue, bone and bone marrow, gonads, CNS, and mediastinum.

^b Includes radiotherapy alone, steroids, and intrathecal methotrexate alone.

versally, whereas LCA and B-cell markers were expressed variably; CD20 was expressed in 2% of the cases and CD45 expression was identified in 29%. The proliferation index was high and ranged from 50 to 100%. EBV positivity was observed in 74% of the cases; the presence of EBV was detected by means of in situ hybridization and/or polymerase chain reaction (PCR) in more than 90% of the cases. Most of the cases (98%) presented with either stage I or stage IV disease (Table III). Oral primary sites accounted for 58% of the cases, and nonoral primary sites accounted for 42%; gastrointestinal tract, skin, and lymph nodes were the most commonly affected nonoral sites. Virtually, all cases presented with a mass-forming lesion. International Prognostic Index (IPI) or age-adjusted IPI scores were available only in five cases and did not allow for further analysis.

CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was the most commonly used therapeutic regimen (30%). Other chemotherapy regimens were used in 25% of the cases and included EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone) and CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine). Radiotherapy alone or in combination with cytotoxic chemotherapy was used in 29% of the cases. CNS prophylaxis with intrathecal methotrexate was reported in 9% of cases. Stage I patients were treated with chemotherapy in 54%, chemoradiotherapy in 27%, radiotherapy alone in 8%, and no therapy was given to 12% of the cases. Patients who presented with stage IV PBL received chemotherapy in 77% and chemoradiotherapy in 23% of the cases.

Response to therapy was reported in 35 patients, and 23 patients (66%) achieved a complete response to initial therapy. Despite this apparently good initial response, primary progressive disease was reported in 29% of cases, and the relapse rate was observed in 25% of the remaining cases. Finally, 53% of patients died, and 47% were alive with a median overall survival of 15 months from lymphoma diagnosis. Data on cause of death were available for 17 patients; the vast majority of these cases died from lymphoma (82%). Other causes of death were AIDS (12%) and sepsis (6%).

Sex, CD4+ count, viral load, use of CHOP, EBV status, primary site of involvement, and clinical stage failed to show an association with survival using log-rank tests with two-sided *P*-values (see Fig. 1).

Discussion

DLBCL is the most common type of B-cell lymphoma and accounts for 41% of the cases of NHL [31]. There are several morphologic variants of DLBCL including centroblastic, immunoblastic, anaplastic, T-cell/histiocyte rich, and PBL [31]. The spectrum of DLBCL with plasmablastic features has widened to include subtypes, such as PBL of oral mucosa type, PBL with plasmacytic differentiation, classic PEL, extracavitary/solid PEL or HHV8-associated DLBCL, and ALK-positive DLBCL [32,33]. PBL is a distinct subtype of DLBCL, that is, characterized by an immunoblastic and/or plasmablastic morphology, Ig heavy chain gene rearrangement, and consistent expression of plasma cell antigens (see Fig. 2). In our review, 100% of the published cases expressed plasma cell markers, whereas only 2% expressed CD20.

DLBCL accounts for 10–20% of pediatric lymphomas. Pediatric lymphomas differ somewhat from their adult DLBCL counterparts in that they show high expression of *c-myc*, low expression of *bcl-2*, and an increased frequency of a germinal center-like phenotype. These biological differences may bear potential therapeutic implications in pediatric lymphomas [34]. Although data on PBL in children are limited, this review did identify the occurrence of HIV-associated PBL in two young patients. Unfortunately, our study did not allow for survival analysis in this pediatric population.

It has been proposed that PBL of oral mucosa type should be renamed to simply PBL [22,23]. This review confirms that PBL is increasingly being reported in nonoral sites. The initial sparse identification of PBL in extra-oral sites could be related to the difficulty in diagnosing these unique lymphomas [35], given the absence of CD45 and B-cell expression that occurs in many of these lymphomas. The morphological differential diagnosis includes poorly differentiated carcinoma, lymphoblastic lymphoma, anaplastic plasmacytoma, plasmablastic variant of Burkitt's lymphoma, blastoid variant of mantle cell lymphoma, and undifferentiated neoplasms [30]. The most common nonoral sites include nasal and paranasal regions, gastrointestinal tract, skin and soft tissue, and lymph nodes. In our study, overall survival was not significantly associated with either primary site (oral vs. extra-oral) or EBV status suggesting that PBL pathogenesis and clinical behavior are likely unrelated to the primary site of presentation. These findings support the motion of revising the current WHO nomenclature; this would facilitate classification and further clinical and therapeutic research efforts.

EBV has been associated with a variety of B-cell lymphoproliferative disorders, such as PCNSL, endemic Burkitt lymphoma, NK/T-cell lymphoma of nasal type, and Hodgkin lymphoma. EBV also seems to be strongly associated with HIV-associated PBL; our series reports the presence of EBV in 74% of published cases. Furthermore, early clinical

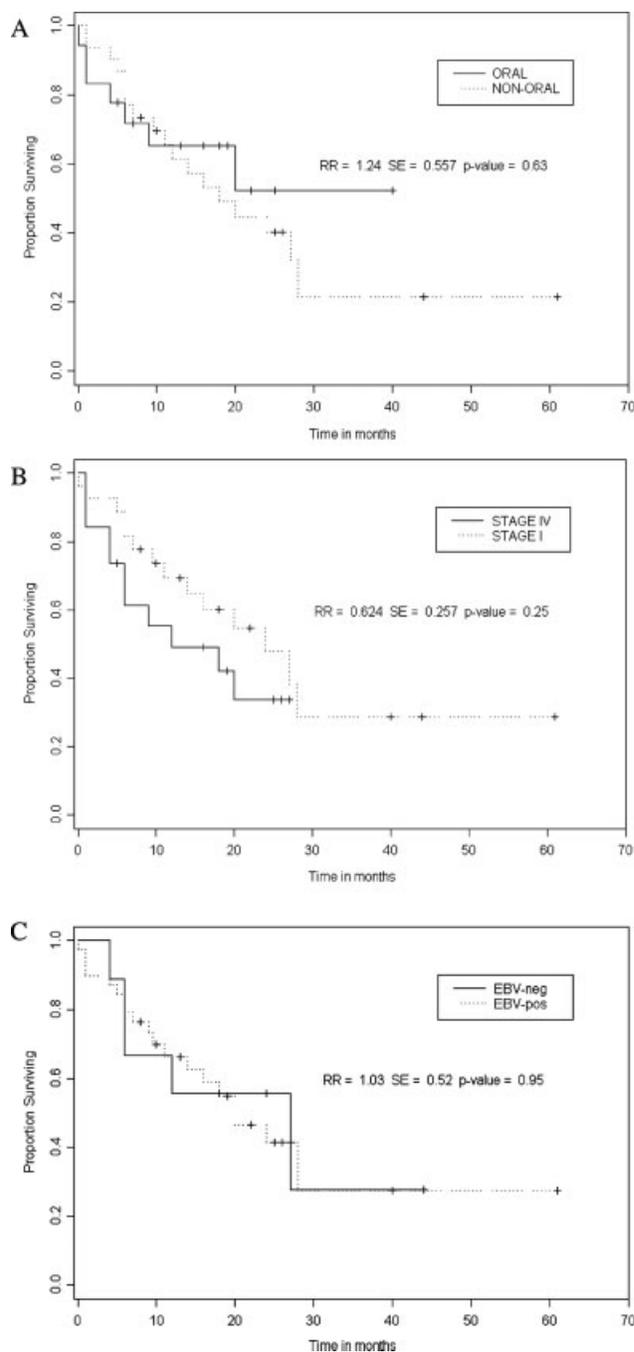


Figure 1. HIV-associated plasmablastic lymphoma Kaplan-Meier survival estimates according to (A) primary site of involvement, (B) clinical stage, and (C) EBV status.

studies showed promising results using EBV-directed therapy in patients with HIV-associated lymphomas with high-dose zidovudine, interleukin 2, and ganciclovir [36,37]. Several investigators have challenged the association between PBL and HHV8. Goedhals et al. [38] reported that only 1 out of 8 cases, that were negative by immunohistochemical analysis with HHV8 latent nuclear antigen-1, was positive for HHV8 by PCR. Similarly, Carbone et al. [39] reported a complete absence of HHV8 infection in nine cases of PBL, as documented by both immunohistochemistry and DNA-PCR studies. Extracavitary (solid) PEL (without effusion) is an HHV8-positive subtype of DLBCL with similar plasmablastic morphology, immunophenotype (i.e., frequent

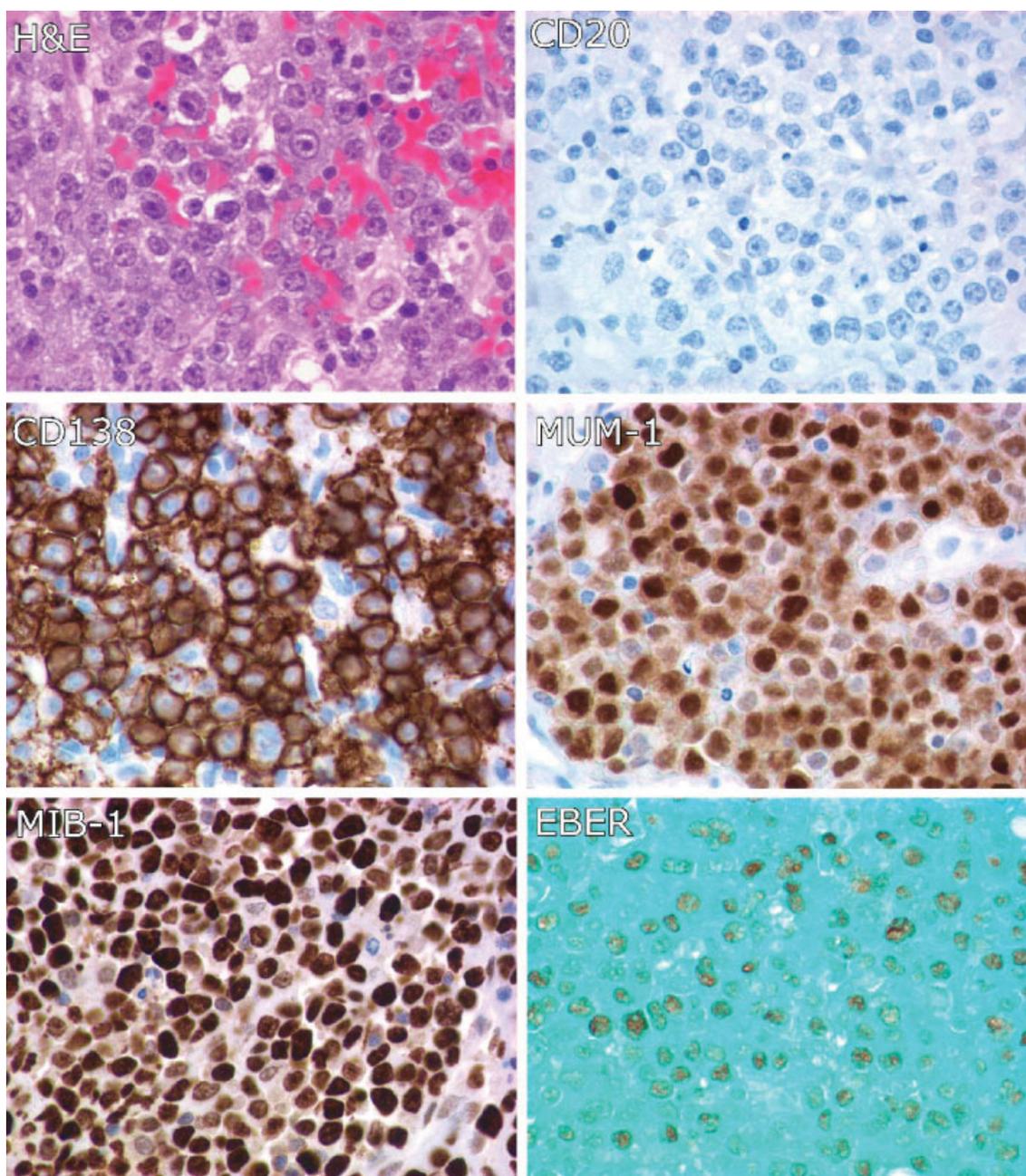


Figure 2. *Top left:* High grade lymphoma comprised of plasmablasts with prominent nucleoli (H&E stain). *Top right:* Lymphoma cells are negative for the B-cell marker CD20. *Middle left:* Lymphoma cells are immunoreactive for the plasma cell marker CD138. *Middle right:* Lymphoma cells demonstrate MUM-1 staining. *Bottom left:* Mib-1 staining shows a very high proliferation rate in tumor cells. *Bottom right:* EBER in-situ is positive in lymphoma cells. (Reproduced with permission from Pantanowitz et al. HIV & AIDS Review 2007;7:29–32). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

plasma cell marker immunoreactivity), and high proliferation index to PBL [40]. Further investigation is needed to clarify the role, if any, and diagnostic utility of HHV8 in PBL.

PBL cases have been reported both in immunocompetent individuals [24,41] and in immunosuppressed patients in the post-transplant setting [42]. Nevertheless, the vast majority of PBL cases are seen in patients with chronic HIV infection and low CD4 cell counts. HAART is of value not only to treat but also to prevent the incidence of specific lymphoma subtypes (i.e., PCNSL). The antilymphoma effect of HAART is associated with an improvement in the degree of host immunodeficiency. In this study, the use of HAART was reported in 22% of the cases and the response to HAART in 10%. Despite this fact, almost all

cases (90%) of HIV-associated PBL that responded well to HAART were still alive at the time of publication. The role of immunosuppression and HAART itself in PBL lymphomagenesis needs to be further elucidated.

The study population in this review showed a marked dichotomy with regard to clinical staging; 98% of the patients were deemed either stage I or IV. In our analysis, the overall survival of these two stages did not statistically differ. Several reasons that may account for this unexpected finding include: (1) differences in treatment between these two stages (e.g., a more aggressive and effective treatment of stage IV disease may offset its inherently worse prognosis than stage I disease), (2) inaccuracy in diagnosing or staging of PBL, (3) biological aggressiveness of lymphomas

with plasmablastic morphology [43], (4) similarities of PBL with plasma cell myeloma [44] (e.g., myeloma staging and therapy differ greatly from those of lymphoma), (5) the retrospective nature and limitations of our data, and (6) inadequate reporting of survival in the analyzed articles. Because of these shortcomings, HIV-associated PBL cases should be followed prospectively to observe the outcome of these patients in the HAART era.

CHOP was the most commonly used regimen but, given the high proliferation index of PBL and its aggressive blastoid appearance, more intensive regimens like CODOX-M/IVAC were used in some series. We speculate that the plasmacytic differentiation may have accounted for the refractoriness to treatment and the increased relapse rates. Given that plasma cells are inherently resistant to chemotherapy, agents directed toward treating multiple myeloma could potentially be of value in PBL. Although there may be no role for rituximab in CD20-negative PBL, it may have potential in those PBL cases with weak CD20 expression. Autologous stem cell transplantation (SCT) in the management of HIV-associated lymphomas has shown to be feasible and effective [45,46], but its role in HIV-associated PBL is unclear. In fact, DLBCL with plasmablastic differentiation have shown to be resistant to standard chemotherapy and even SCT [43]. As mentioned earlier, PBL can be observed as a complication of SCT. In our report, only two patients were treated with autologous SCT. One case was a 36-year-old man with hemophilia A, who acquired HIV through a blood transfusion [8]. This patient died of PBL 14 months after the diagnosis. The second case is a 36-year-old man who relapsed after CHOP regimen [30]. This patient was alive 25 months after diagnosis. There are no data on allogeneic SCT in HIV-associated PBL.

Longer survival times in patients with PBL are being reported in the literature [13,15] and the good outcome in these cases have been attributed to response to HAART, the patient's inherent immunological status, improved supportive care (i.e., antibiotic prophylaxis and growth factors), and improved delivery of chemotherapy. The average survival time for our study group was 15 months. No demographic, immunological, pathological, or lymphoma-related factors were associated with prolonged survival in HIV-associated PBL. As a result, based upon these limited retrospective data, we were unable to identify any specific predictive factors to support a novel staging system for PBL. IPI scores have shown to be a reliable prognostic tool in HIV-associated lymphomas [47]. Unfortunately, very few cases were available for analysis based on this prognostic factor. Given the limitations of our retrospectively accumulated data, prospective studies are needed to further elucidate pathogenetic mechanisms, prognostic factors, and therapeutic options for this rare but hard-to-treat HIV-associated lymphoproliferative disorder.

Conclusion

HIV-associated PBL tends to affect young men with CD4+ counts less than 200 cells/mm³. The consistent presence of plasma cell markers and frequent absence of B-cell markers are key pathologic features of this entity. The association of PBL with EBV is higher than that with HHV8. Despite a good initial response to therapy, the rate of recurrence is high, and the prognosis remains poorer than that of other DLBCL subtypes. Patient's sex, lymphoma stage, CD4+ count, viral load, EBV status, primary site of involvement seems, and use of CHOP do not appear to predict survival in HIV-associated PBL. Newer potential therapeutic approaches for PBL might include EBV-directed therapies, higher intensity therapies given its high proliferation index, and therapies borrowed from the plasma cell

myeloma field given the plasmacytic differentiation of PBL. Further basic and translational research is anticipated.

Finally, our data support the need to revise the current WHO classification and the renaming of these malignancies to include both oral and nonoral PBL as a morphologically, immunophenotypically, and clinically distinct subgroup of DLBCL.

Materials and Methods

We conducted an extensive literature search looking for case reports and case series using Pubmed/MEDLINE. The keywords "HIV," "AIDS," and "PBL" were used. Cases of plasmablastic microlymphoma, an emerging phenomenon described in HIV-infected patients often with preexistent multicentric Castleman disease, were excluded from this study. HHV8-positive PBL cases were also excluded from the analysis as great controversy in the present literature exists as to the role of this oncovirus in PBL pathogenesis [38,39,48–51]. Unpublished data and cases reported in abstract form only were also excluded.

Data were gathered and tabulated regarding the following 17 variables: country of reference, year of reference, number of cases per article, patient age and gender, CD4+ T-cell count at diagnosis, initiation of HAART with regard to the diagnosis of PBL, duration of HIV infection or AIDS diagnosis before PBL diagnosis, lymphoma immunophenotype, EBV status, primary site of lymphoma presentation, Ann Arbor clinical stage, IPI score, type of therapeutic regimen, response to therapy, final outcome, and survival time in months. Clinicopathological characteristics are reported using descriptive analysis. Survival analyses by sex, stage, CD4+ count, viral load, EBV status, primary site of involvement, and use of CHOP were performed using Kaplan-Meier survival curves and Cox proportional-hazards regression. All reported *P*-values are two-sided.

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