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HIV-Negative Plasmablastic Lymphoma: Not in the Mouth

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Abstract

Plasmablastic lymphoma (PBL) is an aggressive variant of non-Hodgkin lymphoma initially reported in the oral cavity of HIV-positive individuals. Since its original description, several cases have been reported in patients who do not have HIV infection. However, despite its recognition as a distinct subtype of diffuse large B-cell lymphoma several years ago, comprehensive reviews of this entity are lacking. A MEDLINE search through June 2010 was performed to identify cases with a pathologic diagnosis of HIV-negative PBL based on morphology and minimal immunohistochemical criteria. Our study included a total of 76 cases. The median age was 57 years (range, 1 to 90 years) with a male-to-female ratio of 1.7. Seventy-four percent of cases did not have an apparent association with immunosuppression, 18% had a concurrent lymphoproliferative or autoimmune disorder and 9% developed PBL after solid organ transplantation. Oral involvement was observed in 21%, advanced stage in 60%, Epstein-Barr virus–encoded RNA expression was positive in 45% and Ki-67 expression of greater than or equal to 80% in 61% of the cases. Chemotherapy was documented in 43 patients, from which 43% received the cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)–like regimens. The median and the 2-year overall survival for the whole group were 9 months and 10%, respectively. Patients who had HIV-negative PBL have distinct clinicopathological characteristics, such as short overall survival and lower rates of oral involvement and Epstein-Barr virus–encoded RNA expression than the previously reported in HIV-positive patients.

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Introduction

Plasmablastic lymphoma (PBL) is an aggressive variant of diffuse large B-cell lymphoma (DLBCL) initially reported in the oral cavity of individuals infected with HIV.¹ The cell of origin (COO) is thought to be an activated, postgerminal center B-lymphocyte that has acquired a plasma cell phenotype²; hence, it expresses a plasmacytic differentiation marker (CD138, CD38 or MUM1), does not express CD20 and has variable expression of the leukocyte common antigen (CD45). Because of this distinct profile, PBL represents a diagnostic challenge and a high degree of suspicion is required for its identification. Furthermore, the clinical course of PBL is aggressive

and despite the use of intensive chemotherapeutic regimens, it has a short median overall survival (OS) reported to be only 15 months.³

With improved awareness of this entity and increased understanding of its biology by clinicians and pathologists, PBL was subsequently identified in patients who do not have HIV infection. These cases have frequently been in patients who have had an underlying immunosuppressive state such as solid organ transplantation⁴ and lymphoproliferative or autoimmune disorders.^{5,6} However, in other cases, no immunodeficiency state was identified.^{7,8} Given the rarity of HIV-negative PBL as well as its relatively recent identification and evolving status, current data on this entity are largely retrospective and rely on small case series and case reports.⁴⁻³³

The main objectives of this study are to describe the clinicopathological characteristics of HIV-negative patients who have a pathologic diagnosis of PBL, and to identify potential prognostic factors in this aggressive B-cell malignancy.

Methods

Search Design and Case Selection

Using PubMed/MEDLINE, we searched for articles in all languages reporting cases with a pathologic diagnosis of PBL in HIV-

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negative individuals from January 1, 1997, to June 30, 2010. Pediatric and adult cases of PBL were selected based on the initial diagnosis provided by the authors of each publication. The minimal criteria for inclusion were a plasmablastic morphology, lack of CD20 expression, and positive expression of at least one marker of plasmacytic differentiation (CD138, CD38, VS38c, and/or MUM1). The reference lists from each retrieved article were scrutinized in an effort to find additional reports. Cases already reported in other articles were excluded. Because of current controversy, PBL associated with human herpesvirus-8 (HHV-8) or Castleman's disease-associated plasmablastic microlymphoma were excluded. Editorials, review papers without additional cases, and nonpublished abstracts were not included.

Data Gathering

Data were gathered according to the following parameters: Clinical data included age at presentation, gender, performance status, lactate dehydrogenase (LDH) levels, Ann Arbor clinical stage, site of involvement (including bone marrow), presence of B symptoms, front-line therapy, response to therapy, outcome, and OS in months. Pathologic data included expression of CD45, B-cell markers (ie, CD20 and CD79a), T-cell markers (ie, CD3, CD4, CD8, and CD56), Ki-67, and Epstein-Barr virus (EBV)-encoded RNA (EBER). We attempted to contact approximately 40% of the authors to clarify the HIV status and other data pertinent to the reported patients. We had a response rate of 30%.

Statistical Analyses

OS was defined as the time between diagnosis and death or last follow-up examination. Clinicopathological data are presented using descriptive statistics. Survival curves were estimated using the Kaplan-Meier method for incomplete observations and compared using the log-rank test. *P* values of less than .05 were considered statistically significant. Calculations and survival graphs were obtained using MedCalc statistical software, version 11.3.3.0 (Mariakerke, Belgium).

Results

Search Results

Our initial search rendered 138 articles. After reviewing titles and abstracts, 108 articles were deemed not eligible because they were reviews, editorials, or laboratory experiments; 30 articles were selected, from which 29 articles were in English and one was in Polish.¹¹ Data from 76 individual cases that met our minimal inclusion criteria were finally collected and analyzed.

Clinical Characteristics

The main characteristics of HIV-negative PBL are shown in Table 1. The median age at presentation was 57 years (range, 1 to 90 years). The male-to-female ratio was 1.7:1 (48 male and 28 female cases). Among the clinical characteristics, advanced clinical stage (III or IV) was observed in 60% of the cases, and the majority (89%) presented with extranodal involvement; 11% of the patients presented with only nodal involvement. Of 66 patients who had extranodal involvement, oral cavity involvement was reported in 14 (21%), gastrointestinal in 13 (20%), soft tissue in 11 (17%), and bone marrow involvement in 10 (15%). B symptoms were present in 50% of the

Table 1 Clinical Characteristics of 76 Patients Who Have HIV-Negative Plasmablastic Lymphoma

Characteristic	Number	Total	Percentage
Age ≥ 60 years	37	75	49%
Male gender	48	76	63%
Clinical stage 3 or 4	40	67	60%
Exclusively nodal involvement	8	74	11%
Extranodal involvement	66	74	89%
Oral cavity	14	66	21%
Gastrointestinal tract	13	66	20%
Soft tissue	11	66	17%
Bone marrow	10	66	15%
Skin	8	66	12%
Sinuses	8	66	12%
Other*	25	66	38%
Presence of B symptoms	14	28	50%
Received any therapy	50	76	67%
Chemotherapy	44	50	88%
CHOP or CHOP-like	19	44	43%
More intensive than CHOP**	11	44	25%
Less intensive than CHOP***	5	44	11%
Not specified	9	44	20%
Radiation therapy alone	4	50	8%
Surgery	2	50	4%

*Includes lung (n = 5), liver (n = 4), spleen (n = 4), kidney (n = 3), adrenals (n = 3), CNS (n = 3), pancreas (n = 1), prostate (n = 1) and heart (n = 1).

**Includes HyperCVAD (n = 3), PromaceCytabom (n = 3), CODOX/M-IVAC (n = 2), COPP-BLAM (n = 1), CEOP-IMVP (n = 1) and BMF90 (n = 1).

***Includes VAD (n = 1), rituximab alone (n = 1), cyclophosphamide alone (n = 1), bortezomib alone (n = 1) and steroids (n = 1).

patients. LDH levels and Eastern Cooperative Oncology Group (ECOG) performance status (PS) were seldom reported (less than 10% of the patients). Therapy was reported in 53 patients, from which 18 (34%) received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or CHOP-like regimens. Response to chemotherapy was available in 36 patients, with an overall response rate of 66%. Sixteen patients achieved a complete response (44%) and 8 achieved a partial response (22%). Only one patient underwent autologous hematopoietic stem cell transplantation.⁸ At the time of each report, outcome was reported in 60 patients, from which 20 (33%) were still alive and 40 (67%) had died. Lymphoma progression was considered the cause of death in 63% of patients. With regard to predisposing factors, 74% of the cases were reported immunocompetent, 11% presented in the setting of solid organ transplant, and 16% had other preexisting conditions such as chronic lymphocytic leukemia,⁶ rheumatoid arthritis,⁵ small-cell lung cancer,⁵ Crohn's disease,⁷ and ulcerative colitis.⁸

Pathologic Characteristics

The main pathologic characteristics of HIV-negative PBL are shown in Table 2. Based on our minimal inclusion criteria, none of the cases expressed CD20. All of our cases expressed at least one

Table 2 Pathologic Characteristics of 76 Patients Who Have HIV-Negative Plasmablastic Lymphoma

Marker	Number Positive	Number Tested	Percentage
CD45	9	27	33%
CD20	0	76	0%
CD38/VS38c	23	23	100%
CD138	40	45	89%
MUM-1	20	22	91%
CD79a	10	37	27%
EMA	7	12	58%
BCL-2	2	9	22%
Ki67 ≥ 80%	14	23	61%
EBV LMP-1	6	21	29%
EBER	19	42	45%
Ig gene rearrangement	16	16	100%

EMA = epithelial membrane antigen; EBV = Epstein Barr virus; LMP-1 = latent membrane protein-1; EBER = EBV-encoded RNA; Ig = immunoglobulin.

marker of plasmacytic differentiation; CD38 was positive in 100%, CD138 was positive in 87%, and MUM1 in 89% of the tested patients. CD45 was positive in 33% (9/27), CD79a in 27% (10/37), BCL-2 in 22% (2/9), and EMA in 58% (7/12) of the patients. EBV latent membrane protein 1 (LMP-1) was positive in 29% (6/21), and Ki67 at more than 80% was observed in 61% (14/23) of the patients. EBER was positive in 45% (19/42) and immunoglobulin heavy chain gene rearrangements were observed in 100% (16/16) of the cases. Cytogenetic abnormalities were reported in three patients; one case had complex cytogenetics: t(X;1), t(2,10), inv(9), t(12;15), del(16), der(22)³²; one case presented with t(9;11) and del(16)³²; and one case presented with t(11;14).¹⁰

Survival Analysis

Survival data were available in 56 patients who had HIV-negative PBL. The median OS for the group was 9 months (Figure 1A). In the univariate analysis, age of 60 years or older; male gender; oral involvement; extranodal involvement; bone marrow involvement; presence of B symptoms; clinical stage; and expression of CD45, EBV LMP-1, Ki67 of 80% or greater, and EBER were not associated with OS (Table 3). In patients who received chemotherapy, obtaining a complete response (CR) was associated with a better OS ($P = .001$; Figure 1B). Survival analyses based on LDH levels and ECOG PS were not attempted because of the small numbers.

Discussion

PBL is a rare lymphoma in patients who do not have obvious immunosuppression. Most of the available data associates the occurrence of PBL with HIV infection. In fact, in the initial report by Delecluse et al, 15 of the 16 patients (94%) who had PBL reported were infected with HIV.¹ However, PBL has also been reported in patients who do not have HIV infection.² For this review, we have identified a total of 76 cases of HIV-negative PBL. This is, to the extent of our knowledge, the first systematic review on this topic.

With regards to the clinical characteristics of patients who have HIV-negative PBL, the median age at presentation was 57 years with a slight male predominance. Historically, HIV-associated PBL affects mainly men at a younger age (median age, 38 years).³ We believe this difference is a reflection of the epidemiology of HIV infection. HIV-negative PBL shows a striking predilection to involve extranodal sites; 89% of the cases reported at least one extranodal site of involvement with the most common sites being the oral cavity, the gastrointestinal tract, soft tissue, and the bone marrow. However, there was not a marked predilection for oral cavity involvement (21%) as is observed in HIV-positive patients. In the initial report by Delecluse et al, 100% of the patients had involvement of the oral cavity, and in a more recent review of 112 patients who had HIV-associated PBL,³ the oral cavity was involved in 58% of the cases. In that report, the gastrointestinal tract was also the second most common site of extranodal involvement. Approximately 75% of the patients included in this review did not have an underlying immunosuppressive state, although extensive workups to identify immunodeficiencies were not reported in several cases.

Clinical data on pediatric patients who have PBL is limited. Our review included four pediatric patients. Kim et al only reported two male patients.⁵ The first patient is an 8-year-old boy without apparent immunosuppression who presented with an oral lesion; he was treated with a nonspecified chemotherapeutic regimen and was alive 36 months after diagnosis. The second patient was a 13-year-old boy with history of juvenile rheumatoid arthritis; he presented with systemic involvement and, despite receiving chemoradiotherapy, died of disease 7 months later. Hernandez et al reported a 14-month-old girl with a history of small bowel and liver transplantation who developed systemic PBL in the graft and other organs; she received rituximab but died 24 hours later due to multiorgan failure.¹³ Finally, Gogia et al reported a 2-year-old girl without apparent immunosuppression with a PBL oral lesion; she started therapy with the BFM90 regimen but died after her second cycle due to an *Acinetobacter* infection.¹²

With regards to pathology, all the cases included in this review had a plasmablastic morphology with a negative expression of CD20 but positive expression of at least one plasmacytic marker such as CD38, CD138, or MUM1. This profile was chosen based on a study on the minimum diagnostic criteria for PBL in countries with limited resources.³⁴ A recent study has shown that PBL can be reliably identified by using a combination of PAX5, CD20, PRDM1/BLIMP1, and XBP1s³⁵; unfortunately, the limited data provided in the studies included in this review precluded the inclusion of these criteria. CD38 expression was positive in 100% of the patients evaluated, CD138 was positive in 89% and MUM1 in 91%. Sixty-one percent of the patients had a Ki67 expression of 80% or more (13 positive of 24 tested), which is a reflection of the degree of proliferation inherent to this aggressive DLBCL variant. EBER was positive in 45% of the patients (19 positive of 42 tested) whereas EBV LMP-1 was positive in 29% (6 positive of 21 tested). The association of HIV-negative PBL and EBV infection seems weaker than for HIV-positive patients, which has historically been reported at a rate of approximately 75%.³ Not surprisingly, 100% of the tested patients showed the presence of immunoglobulin gene rearrangements (16 positive of 16 tested), confirming the B-cell lineage of PBL.

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Figure 1 Kaplan-Meier Survival Estimates on 76 Patients Who Have HIV-Negative Plasmablastic Lymphoma for the Whole Group (A), and According to Response to Chemotherapy (B)

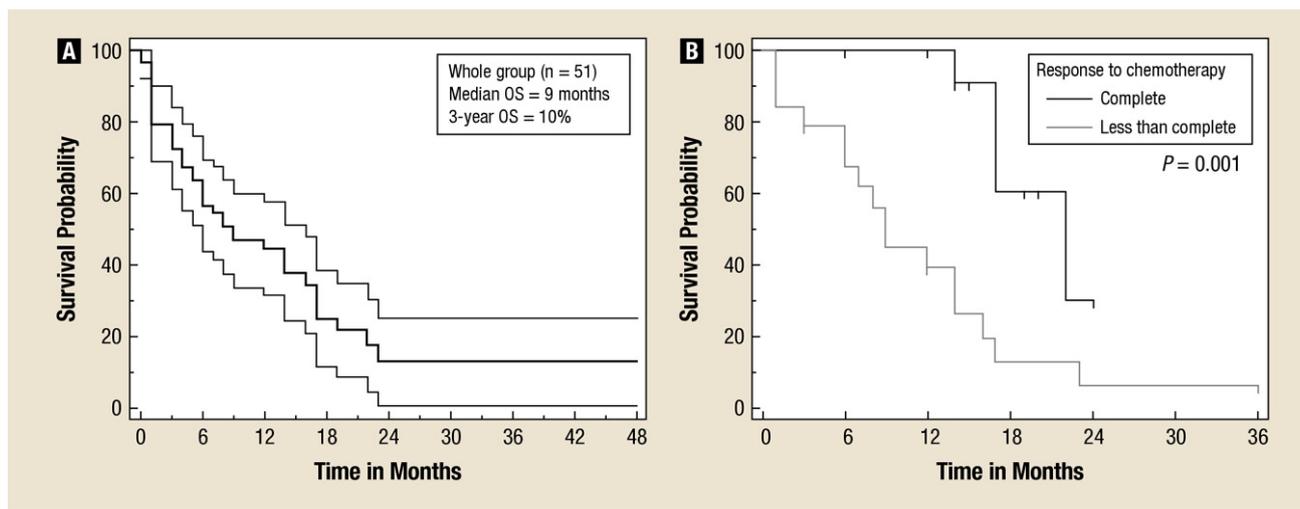


Table 3 Univariate Survival Analysis in 76 Patients Who Have HIV-Negative Plasmablastic Lymphoma

Variable	HR (95% CI)	P Value
Age ≥ 60 years	1.1 (0.6-2.1)	0.65
Male gender	0.6 (0.3-1.1)	0.07
Clinical stage 3 or 4	1.2 (0.7-2.3)	0.52
Exclusive nodal involvement	0.8 (0.2-2.5)	0.61
Oral cavity involvement	0.5 (0.2-1.1)	0.12
Bone marrow involvement	1.5 (0.6-3.6)	0.36
Advanced clinical stage	1.2 (0.6-2.3)	0.52
Presence of B symptoms	0.7 (0.3-2.0)	0.49
CD45 expression	1.0 (0.4-2.7)	0.99
Ki67 expression ≥ 80%	2.6 (0.8-9.1)	0.11
EBV LMP-1 expression	1.1 (0.1-8.8)	0.94
EBER expression	1.4 (0.6-3.5)	0.39
Complete response	0.2 (0.09-0.5)	0.001

HR = hazard ratio; CI = confidence interval; EBV = Epstein Barr virus; LMP-1 = latent membrane protein-1; EBER = EBV-encoded RNA.

Using immunohistochemistry, PBL is almost indistinguishable from plasmablastic myeloma.³⁶ However, using genomic profiling, PBL appears to be closer to DLBCL than plasma cell myeloma.³⁷ Hence, the COO in PBL is thought to be the plasmablast, a blastic proliferating nongerminal center (NGC) lymphocyte with plasmacytic differentiation.²

Our review shows that almost two-thirds of the patients who have HIV-negative PBL received some type of therapy, with chemotherapy being used in 84% of the treated cases. The most commonly used chemotherapy treatment were CHOP-like regimens, used in approximately 40% of the patients who received chemotherapy. More intensive regimens other than CHOP were used in 25% of the patients.

Bortezomib (Velcade, Millennium Pharmaceuticals, Cambridge, MA) is a proteasome inhibitor approved by the United States Food and Drug Administration for the treatment of multiple myeloma and mantle cell lymphoma; hence, there could be a potential benefit on using bortezomib in patients who have lymphomas with plasmacytic differentiation. However, there is limited clinical evidence supporting the use of bortezomib in patients who have DLBCL with a NGC profile,³⁸ in which the COO seems to be the immunoblast. In our review, one patient received bortezomib in combination with dexamethasone; however, that patient died 1 month after the initial diagnosis.³² A literature search rendered one HIV-positive PBL case treated with single-agent bortezomib; this patient responded to bortezomib but he died of infectious complications 1 month after his diagnosis.³⁹ However, clinical data with the use of bortezomib in DLBCL continues to accumulate, and there are at least two studies evaluating bortezomib in combination with chemoimmunotherapy in newly diagnosed patients with NGC variants of DLBCL^{40,41} or AIDS-related lymphomas.⁴² Although data from these studies could be of value for patients who have PBL, formal studies of this combination treatment would need to be done to determine its efficacy in patients with PBL.

Rituximab (Rituxan, Genentech, South San Francisco, CA), a monoclonal antibody directed at the CD20 antigen on malignant and normal B cells, would not be expected to be effective in PBL given this entity is CD20-negative lymphoma. Despite this, one patient who had HIV-negative PBL received rituximab as part of a protocol for posttransplant lymphoproliferative disorders.¹³ The use of rituximab cannot currently be considered a standard of care for patients who have PBL.

Based on our univariate survival analysis, obtaining a CR with chemotherapy was the only prognostic factor associated with OS. These results are in concordance with a recent study of 71 patients who had HIV-associated PBL that was treated with chemotherapy⁴³ for whom achieving a response with chemotherapy was also associated with a better OS. This is not surprising giving the aggressive nature of PBL. Male gender and Ki67 expression of 80% or more showed statistical trends toward a significant association with worse OS. However, it is likely that

our study was underpowered to reliably identify additional prognostic factors because of the small numbers. Also, a multivariate analysis was not possible because of the small numbers.

Despite our efforts to gather comprehensive data, the quality of our review depends on the quality of the reported studies and therefore carries inherent limitations. First, case reports tend to emphasize on either great responses or very poor clinical courses, introducing potential selection bias. Second, not all the preselected data categories were available in each study, rendering our analyses potentially underpowered. Finally, the minimum criteria selected for the inclusion of the cases have not been prospectively validated. We attempted to minimize these deficiencies by contacting the authors of each study to complete clinicopathological data with an overall response of 12%.

Conclusion

PBL is an aggressive DLBCL variant that is observed more frequently in HIV-infected individuals. However, during the past several years, many cases have emerged in patients who do not have HIV infection. The majority of these patients do not seem to have an underlying condition of immunosuppression. HIV-negative PBL has a striking predilection for extranodal sites of involvement and does not seem to be as highly associated with EBV infection as in HIV-positive patients. HIV-negative PBL patients derive the most survival benefit by obtaining a CR when treated with chemotherapy. Because of the small number of patients, the findings of our study should be taken with caution.

Disclosures

The authors have no conflict of interest to disclose.

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