Clinicopathologic Comparison of Plasmablastic Lymphoma in HIV-positive, Immunocompetent, and Posttransplant Patients

Single-center Series of 25 Cases and Meta-analysis of 277 Reported Cases

Julie Morscio, MSc, Daan Dierickx, MD, PhD,† Jan Nijs,* Gregor Verhoef, MD, PhD,† Emilie Bittoun,* Xanne Vanoeteren, MD,† Iwona Wlodarska, MD, PhD,‡ Xavier Sagaert, MD, PhD,*§ and Thomas Tousseyn, MD, PhD*§*

Abstract: Plasmablastic lymphoma (PBL) is a rare B-cell non-Hodgkin lymphoma often associated with Epstein-Barr virus (EBV) infection. To gain insight in this aggressive lymphoma subtype, the clinicopathologic characteristics of 25 unpublished single-center PBLs (2 in acquired immunodeficiency syndrome patients, 11 in immunocompetent individuals [IC-PBL], 12 in transplant recipients [PT-PBL]) and of 277 reported PBLs were summarized. In the reported series, PBL patients were predominantly male (77%) with a median age at diagnosis of 46 years (range, 1.2 to 87 y). The majority of the biopsies (66%) was EBV positive. Extranodal presentation was most frequent (88%, of which 35% were oral, 18% gastrointestinal, 12% cutaneous). PBL was diagnosed in acquired immunodeficiency syndrome patients (50%), immunocompetent individuals (35%), and transplant recipients (14%). These subgroups differed in age at diagnosis (median: 41, 64, 47 y, respectively), primary localization (oral, oral, cutaneous, respectively), EBV positivity (75%, 50%, 67%, respectively), CD45 expression (31%, 33%, 70%, respectively), and *C-MYC* aberrations (78%, 44%, 38%, respectively). Ann Arbor stage I, EBV positivity, CD45 expression, and lack of *C-MYC* aberrations were associated with better outcome ($P < 0.05$). Our series of IC-PBL and PT-PBL cases revealed differential expression of CD10 (0% vs. 42%, respectively), CD56 (22% vs. 42%, respectively), TP53 (67% vs. 8%, respectively), and BCL2 (88% vs. 25%, respectively). Gene expression analysis of 5 of our PT-PBLs revealed upregulation of *DNMT3B*, *PTP4A3*, and *CD320* in EBV-positive PT-PBL and suggested a role for cancer/testis antigens. The results of this retrospective study suggest different pathogenic mechanisms of PBL in different immunologic settings and a potentially important impact of EBV and CD45 on prognosis.

Key Words: posttransplantation lymphoproliferative disorder, PTLD, plasmablastic lymphoma, PBL, EBV, Epstein-Barr virus, posttransplant PBL, immunodeficiency-related lymphoproliferative disorders, clinicopathologic characteristics, retrospective study

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Plasmablastic lymphoma (PBL) is a rare B-cell non-Hodgkin lymphoma often related to Epstein-Barr virus (EBV) infection. It is defined by the World Health Organization (WHO) as a "diffuse proliferation of large neoplastic cells most of which resemble B-cell immunoblasts, but in which all tumor cells have a plasma cell immunophenotype."[1] PBL is regarded as a very aggressive lymphoma with overall survival rates between 6 and 12 months. It was originally described in the oral cavity of acquired immunodeficiency syndrome (AIDS) patients[2] and accounts for 2.6% of all AIDS-related lymphomas.[3] Over the years, PBL has also been reported in patients with other causes of immunodeficiency, for example, in the context of immunosuppressive drug therapy.[4] Because of the immunosuppressive therapy administered to prevent graft rejection, transplant recipients are at risk for the development of an often EBV-related posttransplant lymphoproliferative disorder (PTLD).[5] Diffuse large B-cell lymphoma (DLBCL) is the most common subtype but sporadically cases of PBL have been reported.[6] PBL also occurs in patients without known immunodeficiency. However, series are small and comprise elderly patients[7] in whom lymphoma development can be related to age-related immunosenescence.

From the *Translational Cell and Tissue Research Lab, Department for Imaging and Pathology; ‡Center of Human Genetics, KU Leuven; Departments of †Hematology; and §Pathology, University Hospitals, UZ Leuven, Leuven, Belgium.

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Correspondence: Thomas Tousseyn, MD, PhD, Translational Cell and Tissue Research Lab, KU Leuven, Minderbroederstraat 12, blok Q, B-3000 Leuven, Belgium (e-mail: thomas.tousseyn@uzleuven.be).

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Currently, very little is known about the molecular-genetic basis that drives PBL. One study showed that up to 47% of EBV-positive AIDS-related PBLs are marked by *C-MYC* translocations,[8] which have previously been associated with other AIDS-related lymphomas.[9,10] Array comparative genomic hybridization involving 16 PBLs demonstrated that, despite the high degree of immunophenotypical similarity between PBL and plasma cell myeloma (PCM),[11] the genomic aberration pattern of PBL is more similar to DLBCL than to PCM.[12] Currently, no published gene expression data of PBL are available.

The aim of this article is to report the clinicopathologic and molecular-genetic characteristics of PBL focusing on the differences between PBL in individuals with a different immunologic status. Therefore, a retrospective clinicopathologic analysis of 25 PBL cases available in the database of the department of Pathology at the University Hospitals KU Leuven and of 277 reported PBLs was performed. In addition, the gene expression profile of 5 EBV-positive posttransplant PBLs (PT-PBLs) was analyzed.

MATERIALS AND METHODS

Patient Selection

All available slides from patients diagnosed as PBL over the last 23 years at the Department of Pathology (University Hospitals, KU Leuven, Belgium) were reviewed independently by 2 hematopathologists (X.S., T.T.). In total 25 patients fulfilled the histopathologic criteria for PBL, as defined by the WHO. Of these, 2 cases occurred in AIDS patients (AIDS-related PBL, cases 1 and 2), 11 in immunocompetent individuals with no evidence for primary or secondary immunodeficiency (IC-PBL, cases 3 to 13), and 12 in transplant recipients (posttransplant or PT-PBL, cases 14 to 25). The PT-PBLs were part of a series of 231 PTLD biopsies (in 173 patients) diagnosed at our center as B-cell PTLD.[13] Two of the immunocompetent patients who were 50 years of age or older and had EBV-positive PBL (cases 12 and 13) were regarded as a separate category. We considered them as EBV-positive immunocompetent age-related PBL (IC/AR-PBL) similarly to EBV-positive DLBCL of the elderly, a provisional category defined by the WHO.[14]

Clinical data were obtained from medical records and correlated with histopathologic findings.

This study was approved by the Ethical Committee of the University Hospitals Leuven and was conducted according to the Declaration of Helsinki.

Immunohistochemistry

Formalin-fixed paraffin-embedded tissue sections were stained automatically (Dako, Carpinteria, CA) according to manufacturers' protocol. All antibodies were purchased from Dako unless stated otherwise and targeted MIB1, MUM1, BCL2, TP53, CD10, CD20, CD45, CD56, CD138, and ALK1. All tissues were also stained for human herpesvirus type-4 (EBV) and type-8 (HHV-8) viral proteins. On the basis of the expression of EBV latency membrane protein (LMP1) and nuclear antigen (EBNA2; Abcam, Cambridge Science Park, Boston) we defined 3 different conventional latency types of EBV infection. $LMP1^-/EBNA2^-$, $LMP1^+/EBNA2^-$, and $LMP1^+/EBNA2^+$ represent latency types I, II, and III, respectively, also referred to as restricted, intermediate, and broad latency.[15] The antibody dilutions and antigen retrieval conditions for all antibodies used are given in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/PAS/A201).

EBV-encoded RNA In Situ Hybridization

EBV-encoded RNA (EBER) in situ hybridization was performed on all our 25 PBLs for diagnosis of EBV infection as previously described.[16] In the published PBL cases, EBV positivity was determined on the basis of EBER in situ hybridization or immunohistochemical staining of EBV-encoded LMP1.

Statistical Analysis

Statistical analysis was performed using Statistica 7.0 (Statsoft) and consisted of univariate Kaplan-Meier analysis for which statistical significance was determined with the log rank and Wilcoxon test. In some of the Kaplan-Meier plots, the curves start at $<100\%$ as some patients passed away in <1 month after diagnosis of PBL. One of our PBL cases with an unusually long survival of 190 months (case 2) was omitted from all survival analyses.

χ^2 tests were performed to analyze pathologic differences in different patient groups. PBL cases were compared with 48 previously reported DLBCL cases arising in immunocompetent individuals (IC-DLBCL, $n = 15$) and transplant recipients (PT-DLBCL, $n = 33$)[16] (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/PAS/A202) regarding sex, type of graft, interval between transplantation and diagnosis of lymphoma, age at lymphoma diagnosis, localization, EBER status, and survival.

Gene Expression Profiling

Microarray gene expression profiling (GEP) data were available for 5 PT-PBLs (cases 14, 19, 21 to 23) (GEP data are available at GEO GSE38885). These cases were analyzed in the framework of a larger series of PTLDs as previously described.[16] Briefly, total RNA was extracted from 20-μm-thick sections of frozen tissue sections using the TriZol reagent (Invitrogen, Carlsbad, CA) and the RNeasy minikit (Qiagen, Venlo, The Netherlands). RNA quality and concentration were measured using a Nanodrop spectrophotometer (Nanodrop Technologies, Wilmington, DE). Cases with insufficient RNA quality were excluded; the other samples were analyzed at the Nucleomics Core (VIB, KU Leuven). Five micrograms of mRNA were biotin-labeled and hybridized onto human oligonucleotide microarrays (Affymetrix HG-U133 Plus 2.0 GeneChip; Affymetrix, High Wycombe, UK). GEP data analysis was performed using the software Array Studio V5.0 (OmicSoft Corporation). The "robust multichip average" was used as the

normalization method with the initial signal values log2-transformed. On these normalized data a general linear model (using a *t* test) was applied for inference analysis. The resulting report was filtered on the fold change and the corrected *P*-value (false discovery rate), which was obtained with the Holm-Bonferroni method. Hierarchical clustering for samples and variables (genes) was performed using a complete linkage method and a Centered Pearson correlation for the distance measurement. To define the characteristic molecular profile of EBV-positive PT-PBL, the GEP data were compared with 22 previously reported EBV-positive PT-DLBCLs (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/PAS/A202). The results of this analysis were correlated with published array comparative genomic hybridization data on PBL.[12] Supervised hierarchical clustering analysis was performed by applying our previously reported EBV gene signature (obtained by comparing EBV-positive and EBV-negative PT-DLBCLs and mainly involving innate inflammatory and immunotolerant responses) to define the EBV-related stromal responses in EBV-positive PT-PBL.[16]

Meta-analysis

We conducted a literature search on Pubmed using the search terms: "plasmablastic," "plasmablastic AND lymphoma," and "PBL." After exclusion of reviews without additional cases, unpublished abstracts, and HHV-8-related PBLs, 277 individual PBL cases were retrieved (all references are listed in Supplementary Table 3, Supplemental Digital Content 3, http://links.lww.com/PAS/A203). All cases expressed at least 1 plasma cell marker (CD138, MUM1, VS38c) and were negative or partially positive for CD20.

RESULTS

Case Reports

Detailed data of our 25 cases are shown in Tables 1 and 2. The histology and immunophenotype of PBL are shown in (Figs. 1A–E).

In our PBL series, staining results for ALK1 and HHV-8 were consistently negative in all cases tested, excluding other large B-cell lymphomas with terminal B-cell differentiation like ALK-positive large B-cell lymphoma or HHV-8-positive lymphoma related to multicentric Castleman.

PBL arose mainly extranodally with a predilection for the oral/nasal cavity (30%) and the gastrointestinal tract (15%). Overall, male individuals were predominantly affected. In transplant recipients, PBL arose most frequently after heart transplantation (42%). EBER was detected in 64% of our cases (all AIDS-related PBLs,

TABLE 1. Clinical Features of 25 Cases of PBL From our Center

Case	Immune Status	Sex	Graft	Underlying Disease	Age at Diagnosis of PBL (y)	Interval Tx-PBL (y)	Localization of PBL	Survival (mo)	Status at Last FU
1	HIV	M	—	—	66	3	LN, BM	0.8	D
2	HIV	M	—	—	40	8.4	Nasal	191	A
3	IC	F	—	—	58	—	Skin	11	D
4	IC	M	—	—	72	—	Oral	2	D
5	IC	M	—	—	56	—	Soft tissue	NA	NA
6	IC	M	—	—	43	—	LN	19.8	D
7	IC	M	—	—	34	—	LN	19.1	D
8	IC	M	—	—	68	—	LN	31	A
9	IC	M	—	—	71	—	Soft tissue	7.2	D
10	IC	M	—	—	79	—	Liver	34.6	A
11	IC	M	—	—	73	—	GI	1	A
12	IC/AR	M	—	—	73	—	Oral	15.9	A
13	IC/AR	F	—	—	78	—	Nasal	12.8	A
14*	PT	M	Heart	ICM	65	7	GI	70	D
15	PT	M	Lung	COPD	65	3.9	Urogenital	3	D
16	PT	M	Lung	Sarcoidosis	60	11.8	GI	11	D
17	PT	M	Heart	ICM	63	2.8	LN, GI	4	D
18	PT	M	Heart	DCM	76	10.3	Skin	42	D
19*	PT	M	Liver	EHBA	6	5.7	Oral	12	A
20	PT	M	Kidney	NA	53	9	Oral	60	A
21*	PT	M	HSC	X-ALD	11	0.3	LN, CNS, GI lung	53	A
22*	PT	M	HSC	MDS	41	0.4	LN	36	A
23*	PT	M	Heart	DCM	70	14.8	BM, urogenital	5	D
24†	PT	M	Heart	ICM	54	2	BM	15	D
25	PT	M	HSC	MDS	65	0.5	LN	2	A

*PBL cases that have been included in a microarray experiment.

†This case was diagnosed as PBL and not plasmablastic PCM because of the EBER positivity.

A indicates alive; BM, bone marrow; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; D, dead; DCM, dilated cardiomyopathy; EHBA, extrahepatic biliary arthresia; F, female; FU, follow-up; GI, gastrointestinal; HSC, hematopoietic stem cells; ICM, ischemic cardiomyopathy; LN, lymph node; M, male; MDS, myelodysplastic syndrome; NA, not available; Tx, transplantation; X-ALD, X-linked adrenoleucodystrophy.

TABLE 2. Immunophenotypical Features of 25 Cases of PBL From Our Center

Case	Immune Status	ALK	HHV-8	CD20 (%)	MUM1	CD138	MIB1 (%)	CD10	BCL6	CD45	CD56	TP53	BCL2	C-MYC (%)	EBER	LMP1	EBNA2	Latency
1	HIV	–	–	–	+	+	50-75	–	–	+	–	–	–	10	+	+	–	II
2	HIV	ND	ND	–	+	+	50-75	+	–	+	Partial	–	–	10	+	NR	–	
3	IC	–	–	–	+	+	25-50	–	–	–	+	30	+	75	–			
4	IC	–	–	–	Partial	+	5	–	–	–	–	–	+	–	–			
5	IC	ND	ND	–	+	+	< 1	–	–	–	–	–	+	–	–			
6	IC	–	–	–	+	+	75-100	–	–	–	–	10	+	75	–			
7	IC	–	–	–	Partial	+	25-50	–	–	+	–	25	–	5	–			
8	IC	ND	–	–	+	+	75-100	–	–	–	–	80	ND	100	–			
9	IC	ND	ND	–	Partial	+	25-50	–	–	–	–	100	+	–	–			
10	IC	–	–	–	+	Weak	75-100	–	–	ND	–	–	+	NA	–			
11	IC	–	–	–	+	+	30	–	–	ND	Partial	50	+	10	–			
12	IC/AR	–	–	–	+	+	50-75	Partial	–	–	+	5	–	25	+	–	–	I
13	IC/AR	–	–	–	+	+	25	–	–	+	–	–	–	10	+	+	–	II
14*	PT	–	–	–	Weak	+	25-50	Partial	–	–	+	–	–	–	+	–	–	I
15	PT	–	–	–	Partial	+	75-100	–	–	+	Partial	–	–	NA	+	–	–	I
16	PT	–	–	–	+	+	75-100	+	–	+	–	–	–	10	+	+	–	II
17	PT	–	–	–	Weak	+	75-100	+	–	+	–	–	–	–	+	+	–	II
18	PT	–	–	–	+	+	50-75	–	–	Partial	Partial	–	+	–	+	Partial	–	II
19*	PT	–	ND	–	+	+	75-100	+	–	+	Partial	–	–	25	+	+	–	II
20	PT	ND	ND	–	+	+	50-75	+	–	ND	+	–	+	20	+	–	–	I
21*	PT	–	ND	5	Partial	+	50-75	–	–	+	–	–	–	–	+	+	+	III
22*	PT	–	–	10	+	+	75-100	–	–	+	–	–	–	–	+	+	–	II
23*	PT	–	–	–	–	+	50-75	–	–	–	–	–	–	50	+	+	–	II
24	PT	–	–	–	+	+	50-75	–	–	Partial	–	–	–	25	+	+	–	II
25	PT	ND	ND	–	+	+	90	–	–	+	–	5	Weak	10	+	Partial	–	II

*Cases that have been included in the gene expression profiling microarray experiment.
ALK indicates anaplastic lymphoma kinase; ND, not determined; NR, not representative.

IC/AR-PBLs, and PT-PBLs and none of the IC-PBL cases). The EBV latency I, II, and III profiles were expressed in 25%, 63%, and 6%, respectively (Figs. 1F–L).

We detected differences between IC-PBL and PT-PBL regarding the expression of CD10 (0% vs. 42%, respectively, $P = 0.03$), CD45 (14% vs. 82%, respectively, $P = 0.005$), CD56 (22% vs. 42%, respectively, $P > 0.05$), TP53 (67% vs. 8%, respectively, $P = 0.005$), and BCL2 (88% vs. 25%, respectively, $P = 0.006$). C-MYC was variably expressed in IC-PBL and PT-PBL, but only in the IC-PBL series there were cases that expressed C-MYC in $\geq 75\%$ of the tumor cells (Fig. 2).

Meta-analysis

Data of the 277 reported PBL cases are summarized in Tables 3–5.

PBL occurred at all ages and was characterized by a male predominance. Half of the individuals were positive for human immunodeficiency virus (HIV), and, of the HIV-negative PBL patients, 70% were immunocompetent individuals and 28% were transplant recipients. Three reported PBLs occurred in Crohn disease patients treated with immunosuppressants[8,17,18] such as infliximab[17] and could be considered as immunomodulatory agent-related lymphoproliferative disorders.[19] The majority (66%) of the biopsies were positive for EBV. Extranodal involvement (with or without nodal localizations) was predominant (88%), comprising mainly oral, gastrointestinal and cutaneous lesions. In 3 cases, the bone (marrow) was the only site involved,[20–22] which could point to PCM rather than PBL. However, all 3 cases were EBV positive making PCM unlikely.[11]

The PBL patients were most frequently diagnosed in Ann Arbor stage IV, which was associated with the poorest outcome (Supplementary Figure S1, Supplemental Digital Content 4, http://links.lww.com/PAS/A204). The median overall survival was 8 months but varied considerably (range, 0 to 105 mo). PBL patients had a worse outcome compared with those with DLBCL following transplantation or in immunocompetent patients (Fig. 3A). Each of the PBL subgroups (AIDS-related, IC-PBL, and PT-PBL) showed a trend for worse survival compared with PT-DLBCL; however, none of the comparisons was significant (Fig. 3B). There was no significant difference in survival of HIV-positive and HIV-negative PBL patients (Supplementary Figure S2, Supplemental Digital Content 5, http://links.lww.com/PAS/A205) or between patients with AIDS-related PBL, IC-PBL, and PT-PBL (Supplementary Figure S3, Supplemental Digital Content 6, http://links.lww.com/PAS/A206). Overall, 62% (43/69) of deceased patients died of lymphoma; other causes of death were sepsis (8/69; 12%) and multiorgan failure (4/69; 6%).

CD10 (a germinal center marker) and CD56 (a natural killer cell/T-cell marker) were aberrantly expressed in 19% and 24% of PBLs, respectively. Of the cases with known CD10 and CD56 expression, 64% were double negative, 12% double positive, and 24% expressed either of the 2 proteins. Neither CD10 nor CD56 was

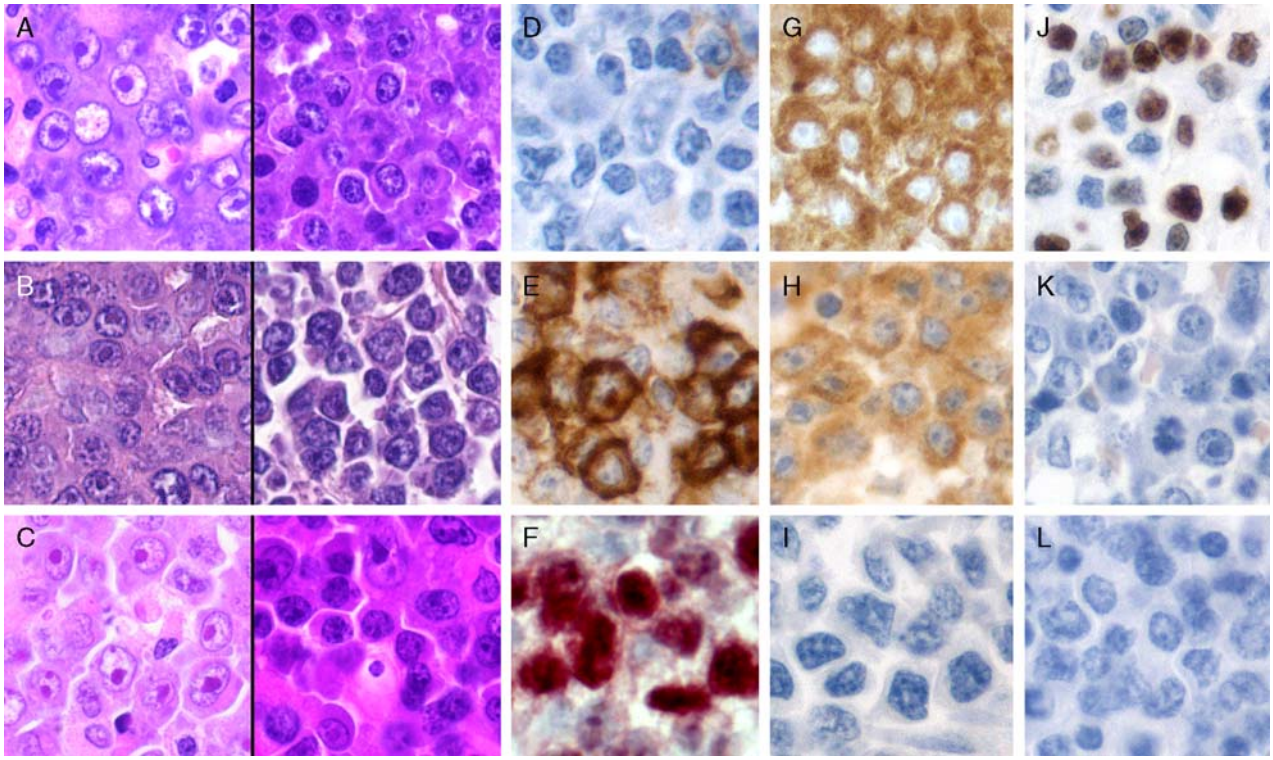

FIGURE 1. Histology and immunophenotype of PBL. PBL consists of a homogenous population of lymphoma cells with immunoblastic morphology (large vesicular nuclei and centrally located eosinophilic nucleoli; left panel in A–C) or plasmacytic morphology (relatively smaller and darker-appearing nuclei with fewer and smaller nucleoli; right panel in A–C). Both morphologic subtypes may arise in AIDS-related PBL (A), IC-PBL (B), and PT-PBL (C). PBL typically lacks CD20 (D) expression but is strongly positive for CD138 (E). EBV-positive cases are positive for EBER (F) and express 1 of 3 conventional latency types defined on the basis of the expression of LMP1 and EBNA2: latency III ($LMP1^+/EBNA2^+$ in G and J, respectively), latency II ($LMP1^+/EBNA2^-$ in H and K, respectively), and latency I ($LMP1^-/EBNA2^-$ in I and L, respectively). All images were taken with a Leica 300DC camera.

associated with survival. Taking into account the EBV status, we observed that patients with EBV-positive PBL had a significantly better outcome than patients with EBV-negative PBL (Fig. 4A). CD45 was (partially) expressed in 37% and was also associated with better outcome (Fig. 5A). The majority of PBLs had aberrations of *C-MYC* (57%), either gains (16%) or translocations (84%), associated with worse outcome (Fig. 6).

In the following subsections, the clinicopathologic characteristics of AIDS-related PBL, IC-PBL, and

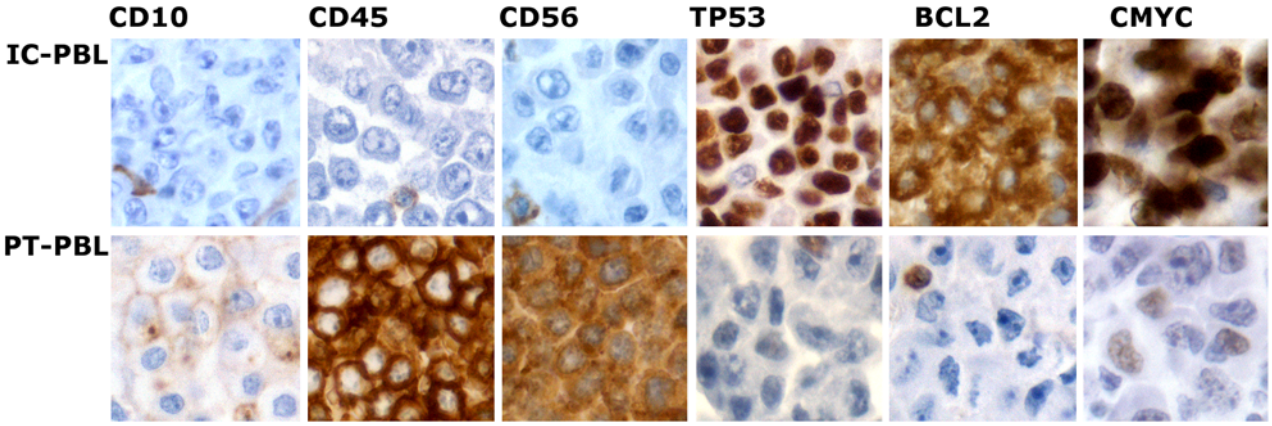

FIGURE 2. IC-PBL and PT-PBL differed in expression of CD10, CD45, CD56, TP53, BCL2, and C-MYC. All images were taken with a Leica 300DC camera.

TABLE 3. Summary of 277 Reported Cases of PBL

	Total (%)	EBV$^+$ (%)	EBV$^-$ (%)
No. cases	277	122/186 (66)	64/186 (34)
HIV$^+$	127/253 (50)	57/76 (75)	19/76 (25)
HIV$^-$	126/253 (50)	55/99 (55)	44/99 (44)
Posttransplant patients	35/126	20/30 (67)	10/30 (33)
Immuncompetent patients	88/126	34/67 (50)	33/67 (50)
< 50 y of age	21/88	6/13 (46)	7/13 (54)
≥ 50 y of age	67/88	28/54 (52)	26/54 (48)
Autoimmune	3/126	1	1
Age at onset (y)			
Median	46	45	55
Mean	47	47	51
Range	1.2-87	3-87	4-84
Male/female ratio	3.3/1	3.7/1	4.3/1
Localization			
Nodal	31	10	7
Extranodal	246	111	57
Mouth	86/246	41/111	16/57
Nose, pharynx	19	15	2
Skin	29	13	5
Gastrointestinal tract	44	14	18
Liver	4	1	3
Lung, pleura	3	3	
Brain	4	2	2
Heart, pericardium	1	1	
Eye	9	4	
Mediastinum	4	3	
Urogenital tract	7	3	2
Bone (marrow)	7	4	1
Soft tissue	16	4	3
Ann Arbor stage			
I	41	24	11
II	7	4	2
III	9	3	5
IV	57	25	26
Survival (mo)			
Median	8	10	6
Mean	14	14	10
Range	0-105	0-60	0-36
Status (dead/alive)	112/92	34/56	40/13

PT-PBL are compared. In addition, IC-PBLs and PT-PBLs are compared with previously reported IC-DLBCL and PT-DLBCLs, respectively.

AIDS-related PBL

AIDS-related PBL was most frequently associated with EBV (75%) compared with IC-PBL and PT-PBL. In accordance with the first report of PBL, the oral mucosa was affected in most cases (49%). Survival analysis confirmed a trend for better survival of EBV-positive cases (Fig. 4B) and cases expressing CD45 (Fig. 5B). *C-MYC* aberrations were more frequently observed in HIV-positive cases (78%) compared with IC-PBL (44%) and PT-PBL cases (38%) suggesting that *C-MYC* aberrations are not equally important in the pathogenesis of the 3 PBL subtypes.

PBL in Immunocompetent Patients

Although PBL was originally associated with AIDS, an increasing number of reports have described cases arising in immunocompetent individuals. As in AIDS-related PBL, the oral cavity was most frequently affected in IC-PBL. In comparison, nodal involvement was predominant (80%) in our IC-DLBCL series. Interestingly, taking into account the EBV status, it was observed that EBV-negative IC-PBL arose primarily in the gastrointestinal tract and the oral cavity, whereas EBV-positive cases (mainly comprising IC/AR-PBL) affected the nasal cavity. As IC/AR-PBL consisted of most EBV-positive IC-PBLs, the clinical (Table 4) and immunopathologic (Table 5) characteristics of these 2 PBL subgroups were similar.

The overall survival of IC-PBL patients (median 8 mo) was inferior to the overall survival of IC-DLBCL patients (median 70 mo). Positivity of EBV (Fig. 4C) or CD45 (Fig. 5C) was associated with a better outcome.

The majority of IC-PBL patients were aged 50 years or older, suggesting that age-related immunosenescence increases the susceptibility to lymphoma development. Also in our series of IC-DLBCL patients 73% were 50 years of age of older. However, the impact of the patient's age seemed to be complicated by the EBV status. Within the EBV-positive IC-PBL subgroup there was no survival difference between patients below 50 years of age (median 11 mo) and patients 50 years of age or older (median 12.5 mo). In the EBV-negative PBL group, however, survival of patients below 50 years of age was better (median 13 mo) compared with patients 50 years of age or older (median 4 mo) (not shown). These results suggest that, independently of the patient's age, mainly the EBV status of the PBL determines the outcome.

PBL in Transplant Recipients

Similarly to PBL in HIV patients, PBL in transplant recipients is associated with the immunodeficient condition of the patient. Sixty-seven percent of the PT-PBL biopsies was positive for EBV, comparable to 72% of our PT-DLBCLs. PT-PBL arose most frequently after kidney (14/47; 37%) or heart (29%) transplantation. In comparison, 18% of PT-DLBCL cases were heart transplant recipients. Intriguingly, the skin was the most commonly affected region (37%); the oral cavity was affected in only a minority of the cases (7%). In comparison, PT-DLBCL mainly affected lymph nodes (58%) and the gastrointestinal tract (24%).

Median survival of PT-PBL patients was slightly better for EBV-positive cases (Fig. 4D). CD45 was most frequently positive in PT-PBL compared with AIDS-related and IC-PBL, but because of limited data no survival analysis could be performed. Instead, all PBL cases were sorted according to EBV and CD45 status into: EBV$^+$/CD45$^+$, EBV$^+$/CD45$^-$, EBV$^-$/CD45$^+$, and EBV$^-$/CD45$^-$ (Fig. 5D). Survival analysis comparing these groups showed the best prognosis for cases positive for both CD45 and EBV or either of these. EBV$^-$/CD45$^-$ was the group with the worst prognosis.

Comparison of GEP data of PT-PBL and PT-DLBCL revealed that PT-PBLs partially positive for CD20 (n = 2) tend to cluster with PT-DLBCL rather than with CD20-negative PT-PBL (n = 3)

TABLE 4. Clinical Characteristics of 277 Reported Cases of PBL in HIV-positive, Immunocompetent, and Posttransplant Patients

	HIV			IC				PT		
	Tot	EBV$^+$	EBV$^-$	Tot	EBV$^+$	IC/AR§	EBV$^-$	Tot	EBV$^+$	EBV$^-$
Age at onset (y)										
Median	41	39	41	64	65	67	66	47	51	43
Mean	40	37	41	60	62	68	60	44	51	42
Range	3-78	3-78	19-63	2-87	24-87	50-87	8-84	1.2-73	20-73	4-72
Male/female ratio	4.5/1	4.2/1	All male	2.8/1	4.7/1	3.7/1	2.7/1	1.9/1	2.3/1	2.3/1
Graft	—	—	—	—	—	—	—			
Kidney								13	6	4
Heart								10	7	3
Lung								2	2	
Liver								2	1	1
Pancreas								1	1	
Intestines								5	1	2
HSC								2	2	
Interval AIDS/Tx-Dx (mo)										
Median	150	168	84	—	—	—	—	96	62	131
Mean	122	113	108					111	121	120
Range	0-240	0-240	72-168					2-360	2-360	3.4-314
Primary localization										
Nodal	10	1	0	14	7	7	5	5	2	2
Extranodal	117	57	19	74	27	21	28	30	20	8
Mouth	57/117	31/57	8/19	18/74	3/27	2	8/28	2/30	2/20	0/8
Nose	2	1		14	12	9	2	2	2	
Skin	13	4	4	3	2	2	1	11	7	
Gastrointestinal tract	21	10	4	15	2	1	10	3		3
Liver								4	1	3
Lung, pleura	2	2		1	1	1				
Brain	2	1	1	2	1		1			
Heart, pericardium				1	1	1				
Eye	6	3		3	1	1				
Mediastinum								2	2	
Urogenital tract	3	2		3	1	1	1	1		1
Bone (marrow)	3	1		1			1	1	1	
Soft tissue	4		1	8	2	2	1	2	2	
Ann Arbor Stage										
I	16	10	6	18	10	9	2	7	4	3
II	1	1	0	6	3	2	2	0	0	0
III	2	1	0	6	2	2	4	1	0	1
IV	20	11	6	25	8	6	14	11	6	5
Survival (mo)										
Median	10	12	6	8	11	11	6	7	9	4
Mean	16	13	9	15	17	17	10	10	11	9
Range	0-105	0-31	0-27	0-73	0-60	0-60	0-36	0-48	0-48	0-22
Status (dead/alive)	51/34	17/22	11/2	38/38	8/23	8/18	22/7	15/15	7/10	5/4

§EBV-positive immunocompetent age-related PBL.
Dx indicates diagnosis; Tx, transplantation.

(Supplementary Figure S4, Supplemental Digital Content 7, http://links.lww.com/PAS/A207).

Applying our previously published EBV gene expression signature (mainly involving innate inflammatory responses and immunotolerance) on PT-PBL and PT-DLBCL revealed clustering of PT-PBL with EBER-positive PT-DLBCL as expected (Supplementary Figure S5, Supplemental Digital Content 8, http://links.lww.com/PAS/A208).

Comparison of the gene expression profiles of 3 CD20-negative EBER-positive PT-PBL with 22 EBER-positive PT-DLBCL revealed 141 differentially expressed probes representing 137 genes (fold change 5; $P < 0.05$; false discovery rate < 0.001) (Supplementary Table 4, Supplemental Digital Content 9, http://links.lww.com/PAS/A209). Thirty-seven genes were upregulated in EBER-positive PT-PBLs, including *DNMT3B* (involved in de novo DNA methylation and expressed in multiple myeloma[23]), *PTP4A3* (potentially involved in migration of malignant plasma cells[24]), and *CD320* (involved in plasma cell differentiation,[25]). Interestingly, overexpression of these genes correlated with gain of their corresponding chromosomal location (20q11.1, 8q24.3, 19p13.2, respectively) in PBL.[12] Among the strongly upregulated genes in EBER-positive PT-PBL were also *LIN28B* and *PVT1*. *LIN28B* is involved in a positive feedback loop regulating *C-MYC* expression,[26] whereas translocations of *PVT1* have been described in B-cell malignancies harboring abnormalities at 8q24, that is, the chromosomal region comprising *C-MYC* among others.[27]

TABLE 5. Immunopathologic Characteristics of 277 Reported Cases of PBL in HIV-positive, Immunocompetent, and Posttransplant Patients

	HIV			IC				PT		
	Tot	EBV$^+$	EBV$^-$	Tot	EBV$^+$	IC/AR§	EBV$^-$	Tot	EBV$^+$	EBV$^-$
CD20	7/97	5/57	2/18	2/77	2/33	1/27	0/33	1/32	1/19	0/9
CD79a	28/62	19/39	6/14	20/56	9/23	7/18	9/29	11/16	6/10	2/2
CD138	65/69	34/35	11/12	60/69	24/29	20/23	26/30	29/33	17/20	8/9
MUM1	21/23	17/17	4/6	41/46	22/22	20/20	18/23	4/4	3/3	1/1
CD10	7/22	5/14	1/5	6/39	0/18	0/15	5/19	—	—	—
CD45	20/64	13/38	3/15	14/43	6/17	3/12	5/17	7/10	5/6	1/1
CD56	6/22	4/14	2/5	11/48	5/19	4/15	5/26	7/25	5/14	0/9
MIB1 (median %)	90	90	90	83	85	85	83	88	83	90
MYC aberrations	31/40	7/9	4/5	11/25	4/11	3/10	2/6	3/8	1/4	1/3
Translocations	29	7	4	8	4	3	2	2	1	1
Gains	2			3				1		

§EBV-positive immunocompetent age-related PBL.

We also observed that a number of cancer-related genes overexpressed in PT-PBL (*MAGEA1*, *SSX1*, *SSX4*, *CTAG1-2*) are located on the X-chromosome. B-cell markers *CD20*, *PAX5*, and *CD19* were downregulated as expected, whereas the plasma cell marker *CD138* was upregulated confirming the reliability of the GEP data.

DISCUSSION

PBL is an aggressive B-cell non-Hodgkin lymphoma that has mainly been studied in the setting of HIV infection. In this report, we investigated the clinical and pathologic characteristics of 302 cases of PBL (among which 25 were unpublished cases from our center) occurring in HIV-positive, immunocompetent, and posttransplant patients.

In the general PBL population and in the PBL subgroups the majority of the patients were male. This observation can be partly explained by the male predominance in the HIV-positive subgroup and in the cohort of transplant recipients and posttransplant lymphoma patients. However, an intriguing observation is that a number of cancer-related genes located on the X-chromosome (*MAGEA1*,[28] *SSX1* and *SSX4*,[29] and *CTAG1/2* [or *NY-ESO-1/LAGE-1*][30]) were highly upregulated in PT-PBL, which would mainly affect male individuals. These 4 genes belong to a category of tumor antigens known as cancer/testis antigens (CTAs), which are highly immunogenic proteins (almost) exclusively expressed in normal testis tissue. However, CTAs can be aberrantly expressed in different types of cancer.[31,32] Interestingly, a recent study demonstrated a high frequency of CTAs in multiple myeloma.[33] Furthermore, comparison of genes overexpressed in malignant plasmablasts versus polyclonal plasmablasts showed that 5/8 most

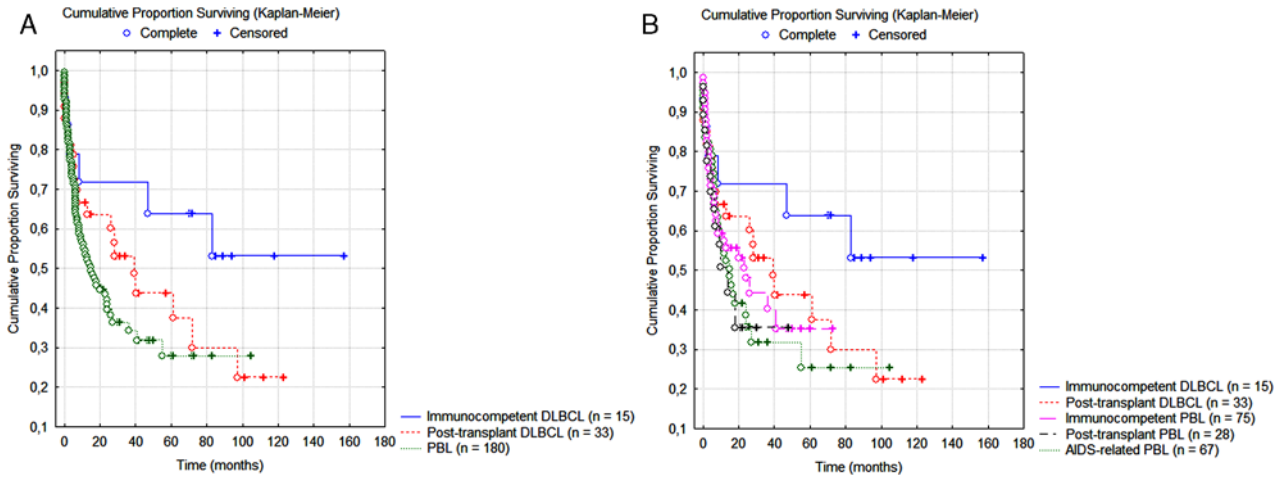

FIGURE 3. PBL patients have a worse prognosis than posttransplant and immunocompetent DLBCL patients. A, Survival analysis of DLBCL (in immunocompetent and posttransplant patients) and pooled PBL (in HIV-positive, immunocompetent, and posttransplant patients) (n = 228): IC-DLBCL versus PBL: Wilcoxon $P > 0.05$; log rank $P < 0.03$. PT-DLBCL versus PBL: Wilcoxon and log rank $P > 0.05$. PT-DLBCL versus IC-DLBCL: Wilcoxon and log rank $P > 0.05$. B, Survival analysis of DLBCL (in immunocompetent and posttransplant patients) and each of the PBL subgroups (in HIV-positive, immunocompetent, and posttransplant patients) (n = 228): none of the comparisons were statistically significant except for: IC-DLBCL versus AIDS-related PBL: Wilcoxon $P > 0.05$; log rank $P = 0.04$.

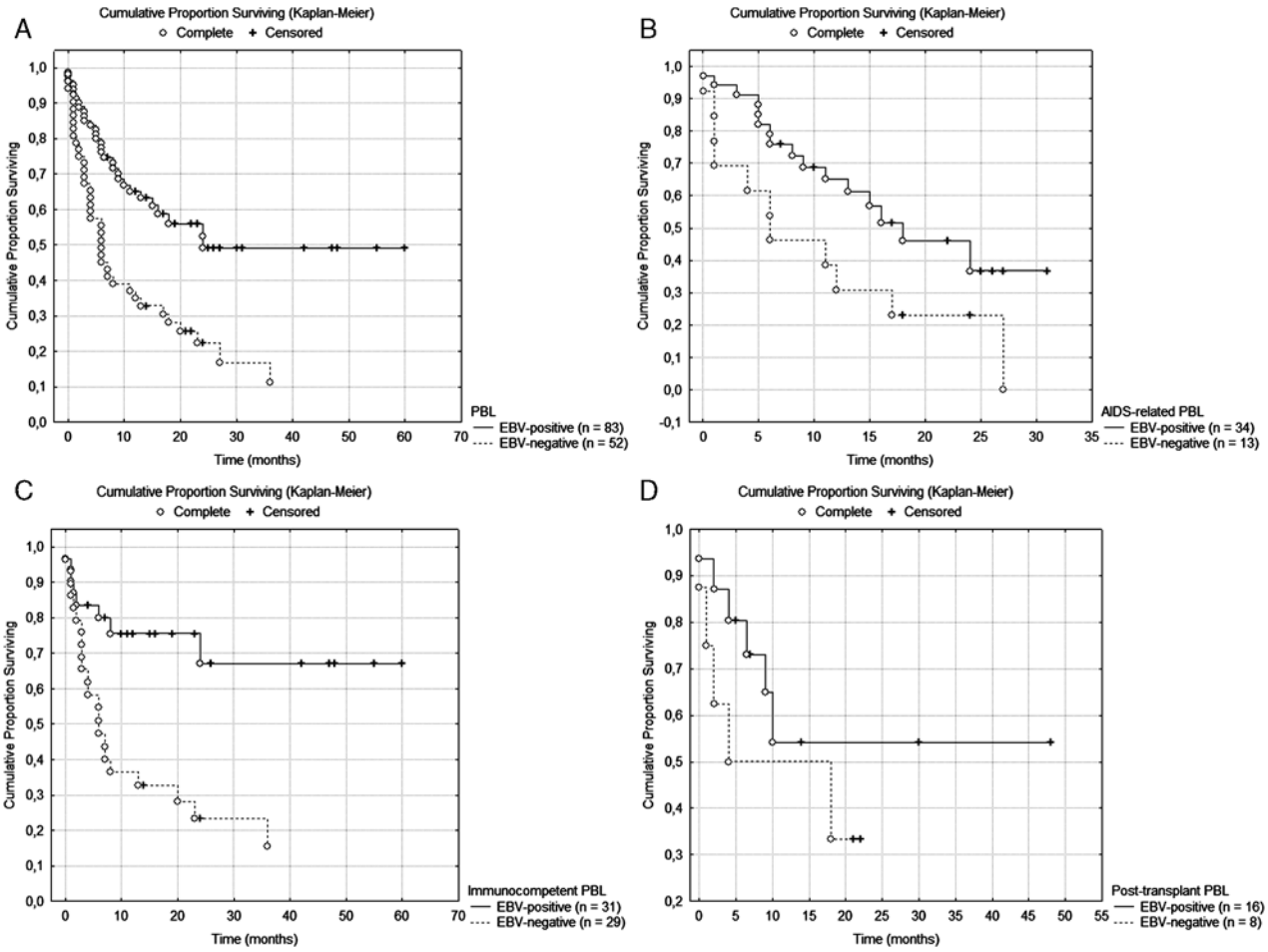

FIGURE 4. Positivity for EBV was associated with a better outcome of PBL in HIV-positive and immunocompetent patients but not posttransplant patients. A, Survival analysis of pooled PBL comparing EBV-positive and EBV-negative cases (n = 135): Wilcoxon and log rank $P < 0.0003$. B, Survival analysis of AIDS-related PBL comparing EBV-positive and EBV-negative cases (n = 47): Wilcoxon $P = 0.038$ and log rank $P = 0.05$. C, Survival analysis of IC-PBL EBV-positive and EBV-negative cases (n = 60): Wilcoxon and log rank $P < 0.007$. D, Survival analysis of PT-PBL EBV-positive and EBV-negative cases (n = 24): Wilcoxon and log rank $P > 0.05$.

relevant genes overexpressed in the malignant cells were CTAs.[34] These studies together with our GEP data indicate a potentially important role for CTAs in PBL. Our gene expression analysis also revealed a number of other genes that were upregulated in EBER-positive PT-PBL compared with EBER-positive PT-DLBCL, justifying further investigation in larger series.

The oral cavity was the primary localization of AIDS-related and IC-PBL. Peculiarly in PT-PBL patients the skin was most frequently affected, whereas EBV-positive IC-PBL (mainly IC/AR-PBL) predominantly arose in the nasal cavity. The reasons for this are unclear, but these observations suggest that PBL comprises different subentities related with the immune status of the patient.

The majority of PBLs was positive for EBV, an oncogenic HHV that is strongly associated with lymphoma in immunodeficient individuals.[35] Clustering of EBER-positive PT-PBLs with EBER-positive PT-DLBCLs in our GEP analysis suggested a role for immune responses in these PBLs, likely related to the presence of EBV or perhaps to the expression of CTAs. Overall, EBV positivity of the tumor was linked with a good prognosis, as was put forward by Zimmermann et al[36] for PT-PBL. This observation may be explained by the hypothesis that EBV-positive lymphoma cells gradually lose EBV while accumulating genetic mutations resulting in a more aggressive phenotype. In our meta-analysis, the survival difference between EBV-positive and EBV-negative cases was most outspoken in IC-PBL patients. A potential explanation could be the stronger immune system in these patients compared with HIV-positive patients or transplant recipients: EBV-positive PBL could trigger more effective immune responses than EBV-negative PBL resulting in more profound antitumor effects and eventually longer survival. Concerning PT-PBL, the influence of EBV on prognosis was less obvious potentially (partly) because of the high rate of non–PTLD-related deaths. Despite being immunocompromised, AIDS patients may represent an intermediate category, as the current highly active antiretroviral therapy results in partial restoration

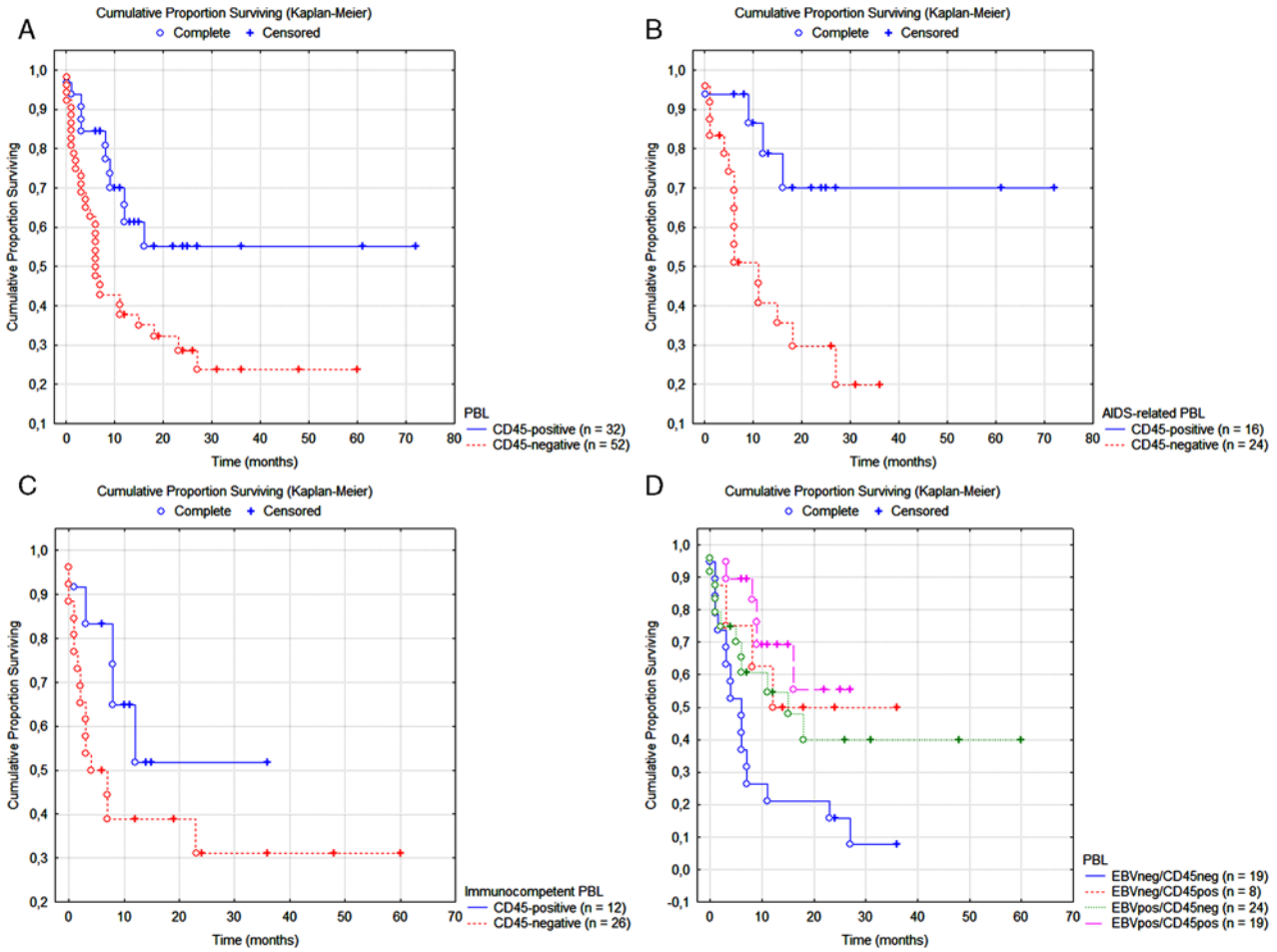

FIGURE 5. Expression of CD45 was associated with a better outcome of PBL in HIV-positive patients. A, Survival analysis of pooled PBL comparing CD45-positive and CD45-negative cases (n = 84): Wilcoxon and log rank $P < 0.005$. B, Survival analysis of AIDS-related PBL comparing CD45-positive and CD45-negative cases (n = 40): Wilcoxon and log rank $P < 0.01$. C, Survival analysis of IC-PBL comparing CD45-positive and CD45-negative cases (n = 38): Wilcoxon and log rank $P > 0.05$. D, Survival analysis of pooled PBL based on combined EBV and CD45 status (n = 70): comparisons with a significant *P*-value were: $EBV^-/CD45^-$ versus $EBV^+/CD45^-$: Wilcoxon $P > 0.05$; log rank $P = 0.05$. $EBV^-/CD45^+$: Wilcoxon $P > 0.05$; log rank $P = 0.05$. $EBV^+/CD45^+$: Wilcoxon and log rank $P < 0.02$.

of the cellular immune system enabling (partial) upregulation of cellular immune responses directed against EBV. In this study, this hypothesis is supported by the modest positive effect of EBV positivity on survival of AIDS-related PBL patients.

Although PBL was originally described in HIV patients, a considerable fraction of the cases occurred in immunocompetent individuals, the majority of whom were older than 50 years. Recently, it was suggested that PBL in immunocompetent patients over 50 years of age should be regarded as a subtype of EBV-positive lymphoma of the elderly related to immunosenescence.[37] In this analysis age seemed to be a prognostic factor only in EBV-negative IC-PBL, suggesting that age-related immunosenescence could be the cause of PBL development but that it is not necessarily associated with poor outcome. On the basis of this meta-analysis we cannot conclude whether IC/AR-PBL should be considered as a new WHO category; however, we do stress the potential prognostic importance of EBV.

In our series, the majority of EBV-positive cases expressed latency II. Because expression of LMP1 is thought to be incompatible with C-MYC signaling,[38,39] the relative rarity of latency I (in which LMP1 is not expressed) in our EBV-positive PBLs is rather unexpected. A possible explanation could be that *C-MYC* translocations play a minor role in PT-PBL. This hypothesis is illustrated by the higher frequency of *C-MYC* translocations in AIDS-related PBL compared with PT-PBL.

CD45 is a protein tyrosine phosphatase that is necessary for lymphocyte activation and development.[40] In normal B-cell development, CD45 expression is high in immature B cells and decreases during differentiation but rarely disappears.[41] Interestingly, absence of CD45 expression in multiple myeloma has been associated with terminal disease and poor prognosis.[42] In vitro, knockdown

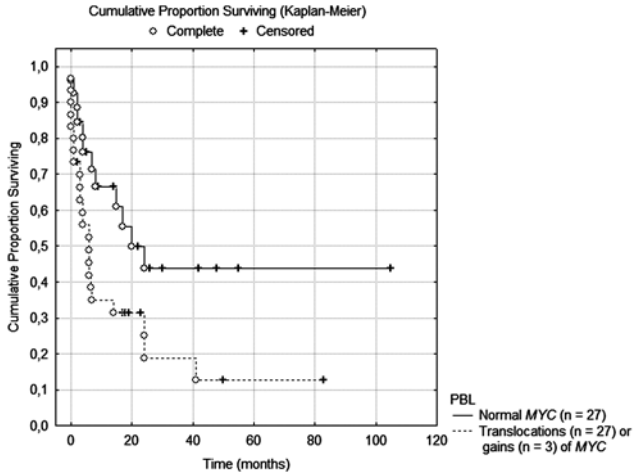

FIGURE 6. *C-MYC* aberrations (gains or translocations) were associated with a worse outcome of PBL. Survival analysis of pooled PBL comparing cases with and without *C-MYC* aberrations (n = 57): Wilcoxon and log rank $P < 0.02$.

of CD45 causes proliferation of hematopoietic stem cells,[43] and, in mouse models, a CD45 null background has been associated with aggressive lymphomas.[44] These studies together with the results of this meta-analysis support a potentially important role for CD45 in lymphomagenesis.

The observations that some PBLs partially expressed CD20 and that 2 PT-PBLs partially positive for CD20 clustered with DLBCL in the microarray indicate that there is a continuum of lymphoma phenotypes between DLBCL and PBL. Furthermore, the different primary locations and the genetic (*C-MYC* translocations) and immunophenotypic (BCL2, TP53, CD10, CD56) differences suggest that several PBL entities exist, related with the immune status of the patient. However, given the impact of EBV on the prognosis of PBL patients independently of their immune status, we suggest that in future studies PBL cases should be distinguished on the basis of the EBV status to confirm the prognostic value of EBV in larger patient populations.

The authors acknowledge the potential biases that may have influenced the conclusions of this study, namely publication bias, the retrospective nature of the study, and the lack of standardization in the definition of PBL. Nevertheless, it could be worthwhile to validate the potential prognostic value of EBV and CD45 expression in prospective studies of PBL.

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