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# Prognosis in primary effusion lymphoma is associated with the number of body cavities involved

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**Abstract**

**Primary effusion lymphoma (PEL) is a rare lymphoma associated with Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV8), and characterized by a malignant body cavity effusion without solid organ or nodal involvement. Prognostic factors in patients with PEL have not been systematically studied. We conducted a literature search for patients with HHV8-positive PEL to identify potential prognostic factors for survival. Our search identified 147 patients, among which 104 patients were HHV8-positive. The median overall survival was 9 months. The median age was 57 years with a male predominance (6:1). Pathologically, 33% of the patients expressed CD20 and 69% expressed CD30. Patients with PEL with > 1 body cavity involved had a median overall survival (OS) of 4 months compared with 18 months in patients with only one cavity involved ($p = 0.003$). Additionally, in patients with one involved body cavity, pericardial involvement was associated with a longer median OS than pleural followed by peritoneal involvement (40, 27 and 5 months, respectively; $p = 0.04$). In conclusion, our study suggests that the number and location of body cavities involved are prognostic in patients with PEL.**

**Keywords:** Primary effusion lymphoma, PEL, prognostic factors, prognosis, HHV8, KSHV

## Introduction

Primary effusion lymphoma (PEL), previously known as body cavity lymphoma or body cavity-based lymphoma, is a rare subtype of non-Hodgkin lymphoma (NHL) mostly associated with human immunodeficiency virus (HIV) infection. In 1995, Cesarman *et al.* isolated DNA sequences of Kaposi sarcoma-associated herpesvirus, also known as human herpesvirus 8 (HHV8), in eight cases of B-cell lymphoma occurring exclusively in the body cavities of HIV-infected individuals, establishing the importance of HHV8 in the pathogenesis of PEL [1].

PEL is estimated to constitute fewer than 5% of all acquired immunodeficiency syndrome (AIDS)-related lymphomas (ARLs) [2], and has a specific clinical and pathologic profile [3,4]. PEL is clinically characterized as an isolated lymphomatous effusion in a body cavity without evidence of a tumor mass elsewhere [5]. It usually presents in HIV-seropositive individuals with AIDS or low CD4 + counts [5], although the disease is not limited to this population. PEL has been diagnosed in patients who are immunocompromised as a result of organ transplant, and also in otherwise immunocompetent individuals [2,6,7].

Although there have been advances in the understanding of the pathophysiology of PEL, there are areas of uncertainty with regard to staging, therapy and prognostic factors. In this study, we conducted a systematic review of the literature looking for cases of PEL to identify potential prognostic indicators for survival.

## Methods

Since its initial description in 1995, the spectrum of PEL has evolved. Hence, it is likely that some of the early cases of PEL were PEL-like, plasmablastic or other lymphomas. With the advent of the World Health Organization (WHO) classification in 2001, PEL was better understood. Hence, we selected cases after the year 2000 to more likely include cases that would fit modern criteria. A literature search using PubMed from January 2000 through June 2011 was undertaken, looking for case reports and series of pathologically proven PEL regardless of HIV status. The search key was "primary effusion lymphoma." The reference list of each selected article was scrutinized for additional reports. Our minimal inclusion criteria were age > 18 years, presence of a lymphomatous effusion without solid mass or lymphadenopathy, and evidence of HHV8 in tumor cells or effusion by immunohistochemistry or molecular studies. Editorials, reviews without additional cases and non-published abstracts were not included.

Clinical data included country of report, age at presentation, sex, HIV status by enzyme-linked immunosorbent assay (ELISA) or Western blot studies, HHV8 and Epstein–Barr virus (EBV) status by serology studies, body cavity involved, frontline therapy, response, outcome, overall survival (OS)

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in months and cause of death. Pathological data included expression of CD45, CD20, CD79a, CD3, CD30, CD56, CD38, CD138, MUM1/IRF4, HHV8 latency-associated nuclear antigen-1 (LANA-1) and EBV latent membrane protein-1 (LMP-1). Molecular data included immunoglobulin (Ig) gene rearrangement, T-cell receptor (TCR) gene rearrangement, and detection of HHV8 by polymerase chain reaction (PCR), EBV-encoded RNA (EBER) by *in situ* hybridization (ISH) and EBV by PCR. Attempts were made to contact authors to complete data.

Overall survival was defined as the time elapsed between date of diagnosis and date of death or last follow-up. Clinicopathological data are presented using descriptive statistics. For the univariate analyses, survival curves were estimated using the Kaplan–Meier method for incomplete observations and compared using the log-rank test. *p*-Values of less than 0.05 were considered statistically significant. All calculations and graphs were obtained using the statistical software MedCalc (Mariakerke, Belgium).

## Results

From a total of 1126 articles, 146 were selected for further review. After excluding PEL-like lymphomas, PEL with tumors outside of body cavities and PEL cases without report of HHV8 expression by the tumor cells, 96 articles were included in our study, accounting for a total of 147 patients, of which 43 were excluded because they were HHV8-negative. Finally, 104 cases of HHV8-positive PEL were included. The median age was 57 years (range 27–96 years; normal distribution) with a male predominance of 6:1. According to the region of diagnosis, 59 cases (57%) were from Europe, 30 (29%) from Asia and 15 (14%) from America. Selected clinical and pathological characteristics are shown in Tables I and II, respectively.

Eighty-six patients received therapy, among which 41 (48%) received cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or CHOP-like regimens, 11 (13%) infusional cyclophosphamide, doxorubicin and etoposide (CDE), eight (9%) interferon and cidofovir, five (6%) cyclophosphamide, vincristine and prednisone (CVP), three (3%) infusional etoposide, cyclophosphamide, doxorubicin, vincristine and prednisone (EPOCH) and 18 (21%) received other regimens. Response and final outcome data are presented in Table I. The median OS for the group was 9 months [Figure 1(A)]. Patients obtaining a complete response (CR) with chemotherapy had a longer OS than patients who had a partial response (PR) or did not respond to treatment [42, 5.5 and 4 months, respectively; $p < 0.0001$; Figure 1(B)].

In the univariate analysis (Table III), patients with only one body cavity involved had a median OS of 18 months vs. 4 months in patients with > 1 cavity involved [$p = 0.003$; Figure 2(A)]. When evaluating the number of body cavities involved by region of report, > 1 body cavity had a significantly worse prognosis in American and Asian patients ($p = 0.03$ and $p = 0.04$, respectively), and a trend toward significance in European patients ($p = 0.13$). When evaluating patients with only one cavity involved, patients with pericardial involvement had a longer median OS than patients with pleural or peritoneal involvement [40, 27 and 5 months, respectively; $p = 0.04$; Figure 2(B)].

Table I. Clinical characteristics in 104 cases of HHV8-positive PEL.

| Characteristic | Number (%) |
|---|---|
| Age ($n = 104$) | |
| Age > 60 | 49 (45%) |
| Age < 60 | 55 (55%) |
| Sex ($n = 104$) | |
| Male | 89 (86%) |
| Female | 15 (14%) |
| HIV status ($n = 104$) | |
| Positive | 56 (54%) |
| Negative | 48 (46%) |
| EBV status ($n = 44$) | |
| Positive | 24 (55%) |
| Negative | 20 (45%) |
| No. of cavities involved ($n = 104$) | |
| One | 71 (68%) |
| Two or more | 33 (32%) |
| Therapy received ($n = 101$) | |
| Chemotherapy | 86 (85%) |
| No chemotherapy | 15 (15%) |
| Response to therapy ($n = 83$) | |
| Complete | 34 (41%) |
| Partial | 16 (19%) |
| No response | 33 (40%) |
| Outcome ($n = 99$) | |
| Dead | 69 (70%) |
| Alive | 30 (30%) |

HHV8, human herpesvirus 8; PEL, primary effusion lymphoma; HIV, human immunodeficiency virus; EBV, Epstein–Barr virus.

## Discussion

Primary effusion lymphoma is included in the WHO classification as a distinct entity more commonly seen in HIV-positive individuals, and has been classically associated with HHV8 infection [5]. HHV8 has been linked to PEL since 1995 [1]. HHV8 is a gamma-herpesvirus with the ability to replicate in lymphoblastoid cells [8,9]. There is evidence that HHV8 establishes latency in infected cells through expression of LANA-1, which recruits the viral genome to the host during mitosis [10,11]. In addition, LANA-1 inhibits apoptosis by binding p53 and tumor suppressor retinoblastoma protein [12,13]. LANA-1 has been found to promote the cell cycle by

Table II. Pathological characteristics of HHV8-positive PEL.

| Characteristic | Number (%) |
|---|---|
| CD45 expression ($n = 43$) | |
| Positive | 38 (72%) |
| Negative | 5 (28%) |
| CD20 expression ($n = 76$) | |
| Positive | 25 (33%) |
| Negative | 51 (67%) |
| CD3 expression ($n = 58$) | |
| Positive | 5 (9%) |
| Negative | 53 (91%) |
| CD30 expression ($n = 54$) | |
| Positive | 37 (69%) |
| Negative | 17 (31%) |
| CD38/CD138/MUM1 expression ($n = 51$) | |
| Positive | 47 (92%) |
| Negative | 4 (8%) |
| EBV expression ($n = 70$) | |
| Positive | 42 (60%) |
| Negative | 28 (40%) |

HHV8, human herpesvirus 8; PEL, primary effusion lymphoma; EBV, Epstein–Barr virus.

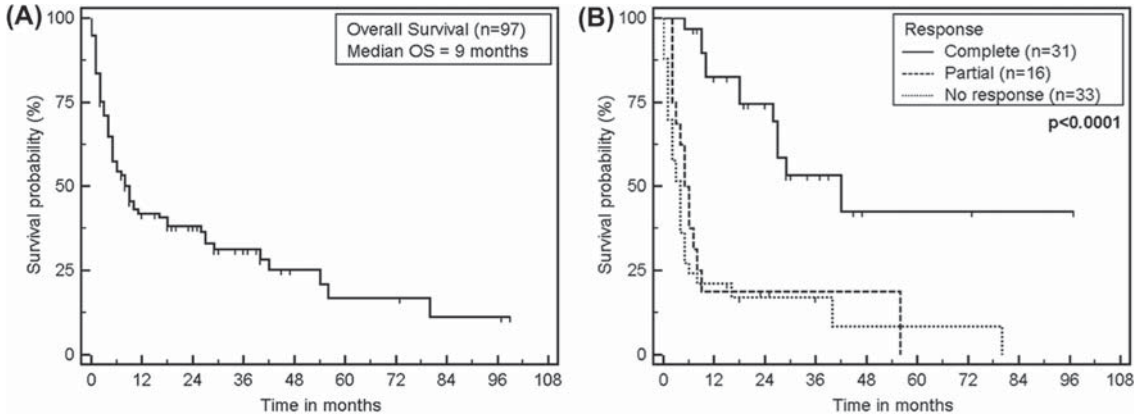


Figure 1. Kaplan–Meier overall survival estimates in patients with PEL (A) for the whole group and (B) according to response to therapy.



inhibiting glycogen synthase kinase 3β (GSK-3β) [14]. A distinct protein called LANA-2, another p53 inhibitor, has also been associated with PEL [15]. Interleukin-6 (IL-6) production and IL-6 receptor expression are highly up-regulated in PEL cells infected with HHV8, which may be responsible for cell survival and B-cell stimulation [16]. Additionally, HHV8 produces a series of viral proteins directed at protecting lymphoma survival such as viral IL-6 (vIL-6), viral FLICE inhibitory protein (vFLIP) and viral cyclin (vCyclin). HHV8 vIL-6 can be detected at high concentrations in PEL effusions. vIL-6 induces vascular endothelial growth factor, contributing to increased vascular permeability and facilitating the formation of PEL effusions [17]. vFLIP, in turn, deregulates the nuclear factor-kappa B pathway, which is a key regulator of genes associated with cell proliferation and survival [18]. vCyclin is a homolog of human cyclin D, which controls the cell cycle by activating cyclin-dependent kinases (CDKs). vCyclin, however, is resistant to the activity of CDK inhibitors [19]. The improved understanding of the biology of HHV8-associated lymphomagenesis provides an opportunity for the development of targeted therapies.

The data on prognostic factors in patients with PEL are scant. Only one previous multicenter retrospective study evaluated this issue in 28 patients with HIV-associated PEL, and reported poor performance status and absence of highly active antiretroviral therapy before PEL diagnosis as adverse prognostic factors [20]. Based on the present study including 104 patients with PEL, $>1$ body cavity involved was an adverse prognostic factor for OS. To our knowledge, this finding has not been previously evaluated or reported and could serve as a simple method for staging PEL. The standard Ann Arbor staging classification is of limited utility since PEL, by definition, presents with stage IV disease due to the diffuse involvement of an extranodal site. Therefore, a specific staging system for PEL, such as one based on the number of body cavities involved, which may correlate with prognosis, may be of value. Additional studies should evaluate this possibility.

Of additional interest is the better prognosis seen in patients with pericardial involvement compared with patients with pleural and peritoneal involvement by PEL. To explain this finding, one could hypothesize that, based on the size and volume of the body cavity, pericardial involvement is associated with a smaller burden than pleural involvement, while peritoneal involvement would reflect a larger burden of disease. However, based on the retrospective and heterogeneous nature of our study, these findings should be considered rather preliminary.

The response to chemotherapy and survival of patients with PEL remain poor. The CR rate to chemotherapy and median OS time seen in our study are consistent with previous reports [20]. However, the group of patients obtaining a CR to chemotherapy had a longer median OS time than patients in PR or who had progressive disease (PD). The most recent response criteria for aggressive lymphomas advocate the use of positron emission tomography in conjunction with computed tomography (PET/CT) scans [21]. However, the majority of cases in the present study (69%) were reported before 2007; hence, the response assessment was likely done on the basis of CT scans alone. Assuming that a good portion of the patients considered being in CR with CT scans would have been in PR based on PET/CT scans, then the patients in true CR would have probably experienced an even longer survival. Additional studies should focus on the need for standardization of response assessment in PEL.

Future efforts should be directed toward improving our current therapies. Our study showed that 33% of cases of PEL expressed CD20 and 69% expressed CD30, which is similar to previous reports [22]. These findings entail specific therapeutic implications. CD20-positive PEL should be treated with rituximab (Rituxan®; Genentech, South San Francisco, CA), given the potential benefit seen in a few case reports of CD20-positive PEL [23–25]. Brentuximab vedotin (Adcetris®; Seattle Genetics, Bothell, WA), an anti-CD30 antibody–drug conjugate, could be of value for PEL expressing CD30. In a

Table III. Prognostic factor analysis in HHV8-positive PEL.

| | Univariate analysis | |
|---|---|---|
| Variable | HR (95% CI) | *p*-Value |
| Age $>60$ years | 0.89 (0.55–1.43) | 0.61 |
| Male sex | 0.83 (0.41–1.71) | 0.84 |
| $>1$ cavity involved | 2.00 (1.16–3.45) | 0.003 |
| CD20 expression | 0.78 (0.42–1.48) | 0.46 |
| CD30 expression | 1.32 (0.62–2.79) | 0.48 |
| HIV + status | 0.81 (0.49–1.34) | 0.39 |
| EBV + tumor cells | 1.24 (0.63–2.43) | 0.52 |

HHV8, human herpesvirus 8; PEL, primary effusion lymphoma; EBV, Epstein–Barr virus; HR, hazard ratio; CI, confidence interval.

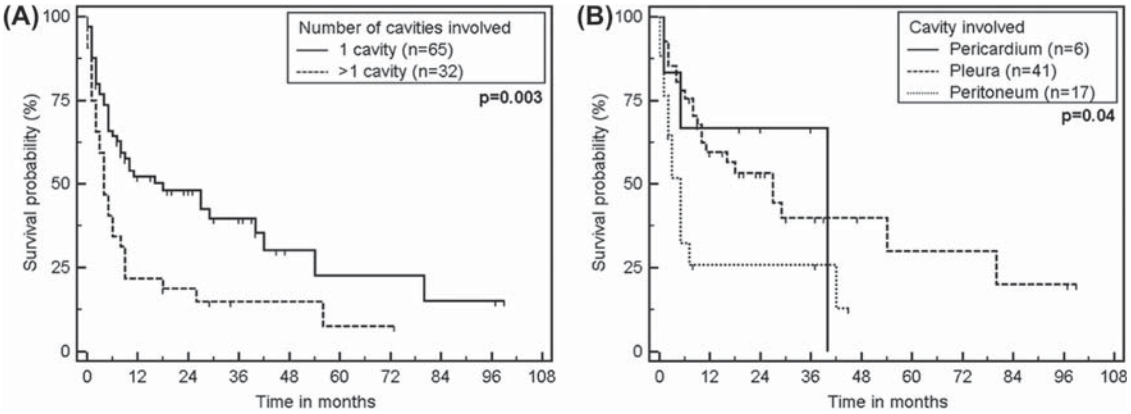


Figure 2. Kaplan–Meier overall survival estimates in patients with PEL according to (A) number of body cavities involved and (B) location of body cavity involvement in patients with only one cavity involved.

recent report, brentuximab vedotin was shown to be effective at inducing apoptosis and cell death while reducing cell proliferation in CD30-positive PEL cells [26]. Additionally, brentuximab vedotin extended the survival of mice exposed to PEL cells. The proteasome inhibitor bortezomib (Velcade®; Millennium Pharmaceuticals, Cambridge, MA) has also shown preclinical activity in PEL cell lines [27–29] and clinical activity in at least one case report [25]. Finally, hematopoietic stem cell transplant could also be of value in PEL; however, current case reports have shown conflicting results [30,31].

The present study carries inherent weaknesses associated with the quality of the published case reports and series, limiting the quality of our study. First, data on important prognostic factors in aggressive lymphomas such as lactate dehydrogenase levels and performance status were seldom reported ($<10\%$ of the cases reviewed). Second, there was heterogeneity in the therapeutic approaches, as some patients were treated with drainage, chemotherapy, immunotherapy and/or antibiotics, likely a reflection of the lack of a standard of care in PEL. Third, the response criteria for PEL have not been fully defined, and we based our response analysis on the response stated by the authors of each publication. Finally, there were limitations regarding the characteristics of the cases analyzed. As an example, the high proportion of cases of HIV-negative or EBV-negative PEL in our study may not reflect the actual rates of the general population. Despite our shortcomings, our study shows that the number of body cavities involved could be used as a simple prognostic and/or staging method.

## Conclusion

The survival of patients with PEL remains poor, advocating for an improvement in our current therapies. Survival appears longer in patients with PEL who present with only one body cavity involved. Additionally, the location of the effusions may also be associated with survival.

***Potential conflict of interest:*** Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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