

# Pleural and Peritoneal Lymphoma Among People With AIDS in the United States

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**Objective:** To describe the occurrence and characteristics of pleural and peritoneal lymphoma in a large cohort of persons with AIDS in 11 regions in the United States.

**Methods:** We used AIDS and cancer registries to identify cases of non-Hodgkin lymphoma (NHL) among 304,439 adults with AIDS. NHLs were categorized by site codes into pleural/peritoneal lymphoma and other NHLs. Data on age, sex, HIV exposure category, histology, history of Kaposi sarcoma (KS), CD4 counts, and survival were analyzed.

**Results:** Fourteen lymphomas were identified (four within the pleura, 10 in the peritoneum) representing 0.13% (95% confidence interval [CI], 0.05–0.20) of 10,510 cases of NHL. Those with pleural/peritoneal lymphoma were similar to those with other NHLs in age (median, 43 years), race (79% white, 7% black, 14% Hispanic), and HIV transmission category (86% homosexual men), but they tended to have a higher prevalence of prior KS (29% vs. 12%;  $p = .06$ ). More cases of pleural/peritoneal lymphoma had immunoblastic histology than did other NHLs (43% vs. 22%;  $p = .06$ ). CD4 counts for pleural/peritoneal lymphomas were also higher than for other NHLs (median 203 vs. 65 cells/mm<sup>3</sup>;  $p = .05$ ), but post-NHL survival was similar (median 7.1 vs. 5.1 months, respectively;  $p = .32$ ).

**Conclusions:** Pleural and peritoneal lymphomas are a rare subtype of AIDS-associated NHL, occurring with less severe immune deficiency than for other NHLs. The increased frequency among persons with prior KS suggests a common etiology, presumably infection with KS-associated herpesvirus, as found in primary effusion lymphoma.

**Key Words:** Pleura—Peritoneum—Non-Hodgkin lymphoma—AIDS—Kaposi sarcoma—Kaposi sarcoma-associated herpesvirus (KSHV)—Primary effusion lymphoma.

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Primary effusion lymphoma (PEL) is a distinct subtype of non-Hodgkin lymphoma (NHL) previously described in patients with AIDS (1,2) and other groups, including organ-transplant recipients (3–5). PELs have a high-grade immunoblastic histology and by definition occur in serous body cavities (pleura, peritoneum, or pericardium), although a few reports have described ini-

tial presentations as isolated solid masses (2,4). PEL tumors display other distinct clinical, molecular, and virologic features, including invariable presence of Kaposi sarcoma-associated herpesvirus (KSHV), frequent presence of Epstein-Barr virus, indeterminate immunophenotype, expression of CD45 receptor, and lack of *c-myc* oncogene rearrangement (1,2).

Previous studies of PEL have been based on case series of patients attending specialized health care centers and may therefore have been susceptible to referral bias (3,6). Using population-based registry data from 11 regions of the United States, we report on the occurrence of

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pleural and peritoneal lymphomas, a surrogate for PEL, in a large cohort of adults with AIDS.

**METHODS**

We linked AIDS and cancer registries from 11 U.S. regions (New York, Massachusetts, Connecticut, New Jersey, Florida, Illinois, Seattle, San Francisco, Los Angeles, Atlanta, and San Diego) to identify NHLs arising among 304,439 adults with AIDS (age at least 15 years at AIDS onset). Linkage methods have been described elsewhere (7).

NHLs were categorized according to *International Classification of Diseases in Oncology* (2nd edition) site codes, as arising in pleura or peritoneum (codes 38.4 and 48.1–48.2) versus “other NHLs” (all other codes). Eight patients with lymphoma of the heart (code 38.0) were classified as “other NHLs” because codes did not distinguish between primary pericardial and primary cardiac lymphoma. In some analyses, we further classified other NHLs into lymph node (code 77), brain (code 71), or other/unspecified sites (remaining codes). We also classified NHLs by histology according to the Working Formulation (8), as low-grade, intermediate-grade, Burkitt, immunoblastic, and other/unspecified.

Categoric variables and continuous variables were compared across groups using the  $\chi^2$  and Wilcoxon rank sum tests, respectively. Times to NHL (after AIDS diagnosis) and death (after NHL diagnosis) were estimated with the Kaplan-Meier method and compared across groups using the log-rank test.

**RESULTS**

Of 304,439 adults with AIDS, 10,510 (3.5%) developed NHL. Fourteen NHLs arose in the pleura (4) or peritoneum (10), representing 0.13% of AIDS-associated NHLs. Sites of 10,496 other NHLs were lymph node (62%), brain (16%), or other/unspecified (21%). Patients with pleural/peritoneal lymphoma and other NHLs were similar in age, race, and HIV transmission category (Table 1).

Prior KS tended to be more common among persons with pleural/peritoneal lymphoma than with other NHL (29% vs. 12%;  $p = .06$ ). One pleural/peritoneal lymphoma case with prior KS had immunoblastic histology, whereas the histology in the remaining three cases was unspecified. Overall, 36,375 (12%) persons with AIDS had KS at or after AIDS, only 4 of whom (0.01%) also developed pleural/peritoneal lymphoma.

Compared with 293,929 people with AIDS who did not develop NHL, patients with pleural/peritoneal lymphoma were more likely to be white (79% vs. 43%;  $p = .02$ ) and homosexual men (86% vs. 52%;  $p = .02$ ). Similar differences were observed between those with other NHLs and those who did not develop NHL (65% vs. 43% were white;  $p < .0001$ ; 72% vs. 52% were homosexual men;  $p < .0001$ ). No overall differences in

**TABLE 1.** Distribution of demographic and HIV risk exposure categories among pleural/peritoneal lymphoma and other NHLs

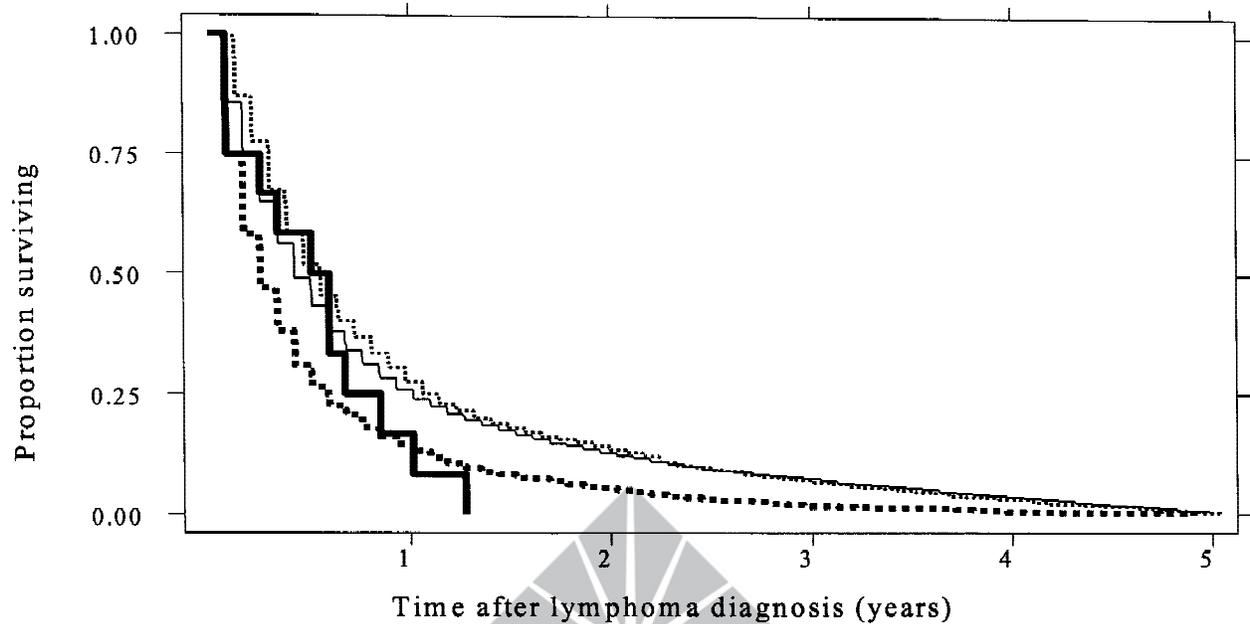
Characteristic	Pleural/peritoneal lymphoma (N = 14)	Other non-Hodgkin lymphoma (N = 10,496)	p value
Age in years, median (IQR)	43 (35–45)	39 (34–45)	.61
Race, n (%)			.72
White	11 (79)	6806 (65)	
Black	1 (7)	1682 (16)	
Hispanic	2 (14)	1893 (18)	
Other	0	115 (1)	
Gender and HIV transmission category, n (%)			.45
Homosexual male	12 (86)	7562 (72)	
Nonhomosexual male	1 (7)	2112 (20)	
Female	1 (7)	822 (8)	
Grade/histology, n (%)			.42
Low grade	0	206 (2)	
Intermediate grade	3 (21)	3359 (32)	
Burkitt	1 (7)	586 (6)	
Immunoblastic	6 (43)	2321 (22)	
Other or not specified	4 (29)	4024 (38)	
Prior KS, n (%)	4 (29)	1261 (12)	.06
CD4 count, cells/mm <sup>3</sup> , median (range)	203 (21–350)	65 (0–490)	.05
Time from AIDS to NHL in mo, median (IQR)	19 (16–25)	13 (5–25)	.42

NHL, non-Hodgkin lymphoma; KS, Kaposi sarcoma; IQR, interquartile range.

histologic types between pleural/peritoneal lymphoma and other NHLs were detected ( $p = .42$ ; Table 1). However, consistent with case reports on PEL (3–5), immunoblastic histology was observed more frequently in pleural/peritoneal lymphoma than in other NHLs (43% vs. 22%,  $p = 0.06$ ).

Eight pleural/peritoneal lymphomas (57%) were AIDS defining, compared with 4917 other NHLs (47%). The time from AIDS to NHL was similar for pleural/peritoneal lymphoma and other NHLs (median 19 vs. 13 months,  $p = 0.42$ ). CD4 lymphocyte counts in the 2 years before NHL were available for 22% of subjects. Participants with pleural/peritoneal lymphoma had higher CD4 counts than those with other NHLs (21, 147, 203, 251, and 350 cells/mm<sup>3</sup> for the 5 pleural/peritoneal lymphoma cases with values, vs. median of 65 cells/mm<sup>3</sup> for other NHLs;  $p = .05$ ).

Overall, survival after NHL diagnosis was similar for those with pleural/peritoneal lymphoma and other NHLs (median 7.1 months vs. 5.1 months;  $p = .32$ ). Survival for the first 6 months for pleural/peritoneal lymphoma was comparable with nodal or other/unspecified site NHL, but it fell rapidly thereafter (Fig. 1).



**FIG. 1.** Survival following lymphoma diagnosis, by site. *Heavy solid line*, pleural/peritoneal lymphoma; *heavy dotted line*, brain lymphoma; *light dotted line*, nodal lymphoma; *light solid line*, other/unspecified lymphoma.

## DISCUSSION

We used population-based AIDS and cancer registry data to identify AIDS-associated NHLs occurring in serous body cavity sites (pleura, peritoneum) as a surrogate for PEL. Two findings suggest that most pleural/peritoneal lymphomas correspond to PEL as described in pathologic studies (1). First, compared with other NHLs, pleural/peritoneal lymphoma was more likely to occur in those with a previous diagnosis of KS, consistent with a role for KSHV in PEL tumor cells. Second, as noted previously for PEL (1,2,9), immunoblastic histology was noted more frequently for pleural/peritoneal lymphomas than for other NHLs.

Of importance, our data suggest that pleural/peritoneal lymphoma (and, by implication, PEL) is an uncommon manifestation of AIDS, contributing only 0.13% of all AIDS lymphomas. In a smaller hospital-based series from Italy (140 AIDS-associated NHLs), four PEL cases (3%) were observed (9,10). Our study included more people with AIDS and collected data from different regions within the United States, so it may be more representative of people with AIDS. In our study, only a small proportion (0.01%) of individuals with AIDS-associated KS developed pleural/peritoneal lymphoma. People with AIDS-associated KS experience two major risk factors for PEL, namely, KSHV infection and immune suppression, but the rarity of these lympho-

mas highlights that additional factors are necessary for development of PEL, even among highly susceptible patients.

Development of PEL may require less immunosuppression than is required for other NHLs. Patients with pleural/peritoneal lymphomas had higher CD4 cell counts than patients with other NHLs (Table 1). This finding is corroborated by the somewhat better short-term survival in patients with pleural/peritoneal lymphoma than among those with brain lymphoma (Fig. 1).

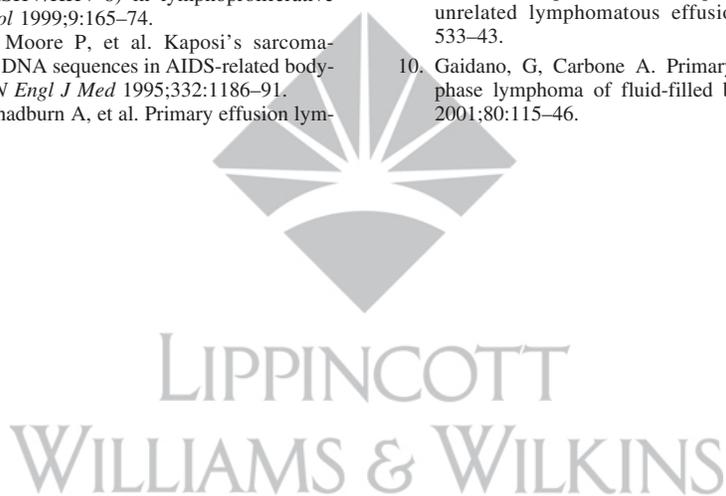
Our study's principal limitation was its reliance on registry data. Lack of a morphology code for PEL and inaccuracies in the coding of lymphoma site may have caused us to miss some cases of PEL and thereby underestimate its incidence. Registries record only the primary site, so we could not examine dissemination or involvement of other sites besides body cavities. Nonetheless, in the largest U.S. series of PEL cases, involvement of tissues outside body cavities was noted in only 19% of cases (1). Additionally, we did not include pericardial lymphomas, which may represent 13% of PELs (3). If we adjust our estimate upward on this basis of these two considerations (19% involvement outside body cavities plus 13% in pericardium), the proportion of AIDS-associated NHLs that are potentially PEL would increase only modestly to 0.2%. Conversely, however, we included one NHL as pleural/peritoneal lymphoma (e.g., a case of Burkitt lymphoma) that was not PEL.

Ideally, a study of PEL would include a review of histology and additional studies for virologic and molecular markers, which was not possible in the current study.

In summary, our data suggest that PEL is rare among individuals with AIDS in the United States, perhaps contributing as few as only 0.13% of AIDS-associated NHLs. Pleural/peritoneal lymphomas occur more commonly among patients with prior KS, supporting the role of KSHV in both these malignancies. The planned introduction in cancer registries of a morphology code for PEL should aid future epidemiologic studies.

#### REFERENCES

1. Cesarman, E, Knowles DM. The role of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in lymphoproliferative diseases. *Semin Cancer Biol* 1999;9:165-74.
2. Cesarman, E, Chang Y, Moore P, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med* 1995;332:1186-91.
3. Nador RG, Cesarman E, Chadburn A, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. *Blood* 1996;88:645-56.
4. Nador RG, Cesarman E, Knowles DM, et al. Herpes-like DNA sequences in a body-cavity-based lymphoma in an HIV-negative patient. *N Engl J Med* 1995;333:943.
5. Dotti, G, Fiocchi R, Motta T, et al. Primary effusion lymphoma after heart transplantation: a new entity associated with human herpesvirus-8. *Leukemia* 1999;13:664-70.
6. Gaidano, G, Pastore C, Gloghini A, et al. Distribution of human herpesvirus-8 sequences throughout the spectrum of AIDS-related neoplasia. *AIDS* 1996;10:941-9.
7. Goedert, JJ, Cote TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. *Lancet* 1998;351:1833-9.
8. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. *Cancer* 1982;49:2112-35.
9. Carbone, A, Gloghini A, Vaccher E, et al. Kaposi's sarcoma-associated herpesvirus DNA sequences in AIDS-related and AIDS-unrelated lymphomatous effusions. *Br J Haematol* 1996;94:533-43.
10. Gaidano, G, Carbone A. Primary effusion lymphoma: a liquid phase lymphoma of fluid-filled body cavities. *Adv Cancer Res* 2001;80:115-46.



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