

Immunoblastic Lymphoma in Persons with AIDS-Associated Kaposi's Sarcoma: a Role for Kaposi's Sarcoma-Associated Herpesvirus

Eric A. Engels, M.D., Stefania Pittaluga, M.D., Denise Whitby, Ph.D., Charles Rabkin, M.D., Yoshiyasu Aoki, M.D., Elaine S. Jaffe, M.D., James J. Goedert, M.D.

Viral Epidemiology Branch, Division of Cancer and Epidemiology and Genetics (EAE, CR, JJG) and Hematopathology Section, Laboratory of Pathology, Center for Cancer Research (SP, ESJ), National Cancer Institute, Rockville; Viral Epidemiology Section, AIDS Vaccine Program, National Cancer Institute-Frederick (DW), Frederick; and Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, Bethesda (YA), Maryland

Kaposi's sarcoma-associated herpesvirus, the viral agent of Kaposi's sarcoma, is associated with two lymphoproliferative disorders: primary effusion lymphoma and multicentric Castleman's disease. To identify other lymphoproliferative conditions linked with Kaposi's sarcoma-associated herpesvirus, we studied non-Hodgkin's lymphomas arising in individuals with AIDS-associated Kaposi's sarcoma. Formalin-fixed tissues from 24 such lymphomas were examined. As expected, two primary effusion lymphomas were Kaposi's sarcoma-associated herpesvirus-positive, with immunohistochemistry demonstrating the Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen in the nuclei of all neoplastic cells. Additionally, three of seven evaluable cases of the immunoblastic variant of diffuse large B-cell lymphoma (immunoblastic lymphoma) showed similar latency-associated nuclear antigen staining. These Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas resembled primary effusion lymphoma histologically but were not known to involve body cavities (sites included lymph nodes, soft tissues of the neck, and spleen). Notably, 5–20% of the neoplastic cells in the Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas also showed cytoplasmic staining for viral interleukin-6, a biologically active cytokine homologue found in primary effusion lymphoma. We conclude that Ka-

posi's sarcoma-associated herpesvirus is present in some immunoblastic lymphomas in persons with AIDS-associated Kaposi's sarcoma.

Mod Pathol 2003;16(5):424–429

The viral agent of Kaposi's sarcoma, Kaposi's sarcoma-associated herpesvirus (also known as human herpesvirus 8), may cause non-Hodgkin's lymphoma. Kaposi's sarcoma-associated herpesvirus is universally present in primary effusion lymphoma cells (1, 2). Histologically, primary effusion lymphoma resembles the immunoblastic variant of diffuse large B-cell lymphoma (*i.e.*, immunoblastic lymphoma) but uniquely involves serous body cavities (1). Additionally, Kaposi's sarcoma-associated herpesvirus is found in a subset of multicentric Castleman's disease cases and in plasmablastic lymphomas that can arise during multicentric Castleman's disease (3, 4). Primary effusion lymphoma and multicentric Castleman's disease occur most commonly in human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), although even in that setting they are rare (5, 6).

Kaposi's sarcoma-associated herpesvirus is less clearly involved in other non-Hodgkin's lymphoma types. In large pathology-based studies (2, 7–9), 0–22% of AIDS-associated immunoblastic lymphomas were Kaposi's sarcoma-associated herpesvirus positive by polymerase chain reaction (2, 7–9). However, these studies had very few AIDS-associated immunoblastic lymphomas, and Kaposi's sarcoma-associated herpesvirus appeared to be present at a low level in positive specimens, leaving its role uncertain. More recently, Kaposi's sarcoma-associated herpesvirus was detected by immunohistochemistry and polymerase chain reaction in additional cases of extracavitary lymphoma, de-

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VOL. 16, NO. 5, P. 424, 2003 Printed in the U.S.A.

Date of acceptance: December 7, 2002.

Address reprint requests to: Eric A. Engels, M.D., M.P.H., Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, EPS 8010, Rockville, MD 20892; fax: 301-402-0817; e-mail: engelse@exchange.nih.gov.

DOI: 10.1097/01.MP.0000056629.62148.55

scribed histologically as diffuse large B-cell lymphoma or immunoblastic lymphoma, in persons with multicentric Castleman's disease or HIV/AIDS (4, 10).

We previously used registry data to study cancers occurring in persons with AIDS-associated Kaposi's sarcoma, using the presence of Kaposi's sarcoma as a marker for Kaposi's sarcoma-associated herpesvirus infection (11). In that study, individuals with Kaposi's sarcoma had significantly increased risk for immunoblastic lymphoma (relative risk, 2.44; 95% CI, 2.00–2.96, compared with others with AIDS). The association persisted even after adjustment for possible confounding factors (adjusted relative risk, 1.58; 95% CI, 1.29–1.93) and was not present for other subtypes of non-Hodgkin's lymphoma. Our analyses thus suggested that Kaposi's sarcoma-associated herpesvirus might be etiologically important in a subset of AIDS-associated immunoblastic lymphomas. Notably, only 1 of the 151 immunoblastic lymphomas in persons with Kaposi's sarcoma arose in the pleura or peritoneum (11), implying that the link between immunoblastic lymphoma and Kaposi's sarcoma was not explained wholly by the occurrence of primary effusion lymphoma.

The phenotypic spectrum and incidence of Kaposi's sarcoma-associated herpesvirus-positive non-Hodgkin's lymphomas are not well characterized. In the present investigation, we systematically examined non-Hodgkin's lymphomas from HIV-infected individuals who also had a diagnosis of Kaposi's sarcoma. We hypothesized that because persons with AIDS-associated Kaposi's sarcoma control Kaposi's sarcoma-associated herpesvirus infection poorly, they might be especially prone to Kaposi's sarcoma-associated herpesvirus-induced non-Hodgkin's lymphoma.

METHODS

From the National Cancer Institute's AIDS Cancer Specimen Bank (1982–2001) and the pathology department of University of California, Los Angeles (1994–2001), we retrieved formalin-fixed, paraffin-embedded tumor tissue from 24 non-Hodgkin's lymphomas arising in HIV-infected persons who also had Kaposi's sarcoma at some point in their clinical course. For 14 cases, tissues were obtained at autopsy, resulting in decreased viability of tumor cells.

Immunohistochemical stains of tissue sections were performed using antibodies against CD20 (DAKO, Carpinteria, CA), CD3 (Dako), CD38 (Novocastra, Vector Laboratories, Burlingame, CA), and κ and λ immunoglobulin (Ig) light chains (DAKO). κ and λ Ig stains were scored as negative when tumor

cells appeared negative in the presence of adequate staining of background plasma cells. Unsatisfactory was defined as absence of staining caused by poor antigenic preservation or, in the case of κ and λ , nonspecific staining of the cytoplasm of tumor cells for both light chains caused by nonspecific uptake of serum proteins. This latter pattern was most commonly seen in tumor specimens obtained at autopsy.

Non-Hodgkin's lymphomas were categorized using the World Health Organization classification (12) by two hematopathologists (SP and ESJ). Because the distinction between immunoblastic and plasmablastic variants of diffuse large B-cell lymphoma is sometimes ambiguous, subclassification was based on a combination of cytological and immunophenotypic criteria. Plasmablastic lymphomas had abundant basophilic cytoplasm, eccentric nuclei, and prominent central nucleoli. The tumor cells tended to have a cohesive growth pattern and were relatively uniform in cellular appearance. Plasmablastic lymphomas were by definition CD20 negative and CD38 and cytoplasmic Ig positive. Immunoblastic lymphomas were more pleomorphic and variable in appearance but exhibited basophilic cytoplasm and large nuclei with prominent nucleoli. Immunoblastic lymphomas usually expressed CD20 and had variable expression of CD38 and Ig.

We identified Kaposi's sarcoma-associated herpesvirus-infected cells using a rat monoclonal antibody against the Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen (Advanced Biotechnologies, Columbia, MD). Additionally, we stained for viral interleukin-6, a Kaposi's sarcoma-associated herpesvirus cytokine homologue, using mouse monoclonal antibody v6m12.1.1 (13). Epstein Barr virus was detected by *in situ* hybridization with an EBER-1 RNA riboprobe.

RESULTS

Of the 24 non-Hodgkin's lymphoma cases, all but three were extranodal, with sites including brain (6 cases), lung (3 cases), liver (3 cases), pericardium (2 cases), or other (7 cases; see Table 1). As shown in Table 1, 20 cases (83%) were diffuse large B-cell lymphomas, further subclassified as immunoblastic (10 cases), centroblastic (8 cases), or plasmablastic (2 cases) variants. Other non-Hodgkin's lymphomas were classified as primary effusion lymphoma (2 cases), Burkitt's lymphoma (1 case), and aggressive B-cell non-Hodgkin's lymphoma, not otherwise subtyped (1 case). Foci of Kaposi's sarcoma were present in sections adjacent to two immunoblastic lymphomas (Cases 8 and 9), and an additional immunoblastic lymphoma was associated with both multicentric

TABLE 1. Characteristics of 24 Non-Hodgkin's Lymphomas in Individuals with AIDS-Associated Kaposi's Sarcoma

Case Number	Site	CD3	CD20	CD38	Ig Light Chain	KSHV	EBV
DLBCL, immunoblastic variant							
1	Lymph node	Positive	Positive	Weak pos	Unsatisfactory	Positive	Positive
2	Soft tissue	Negative	Negative	Weak pos	Unsatisfactory	Positive	Positive
3	Spleen	Negative	Negative	Positive	λ	Positive	Negative
4	Orbit	Unsatisfactory	Unsatisfactory	Negative	Unsatisfactory	Unsatisfactory	Negative
5	Liver	Negative	Positive	Positive	κ	Negative	Negative
6	Brain	Negative	Positive	Negative	κ	Negative	Positive
7	Brain	Negative	Positive	Negative	Unsatisfactory	Negative	Unsatisfactory
8	Lung	Negative	Negative	Positive	Unsatisfactory	Negative	Unsatisfactory
9	Lung	Negative	Unsatisfactory	Negative	Unsatisfactory	Unsatisfactory	Positive
10	Brain	Negative	Positive	Negative	Negative	Unsatisfactory	Negative
DLBCL, plasmablastic variant							
11	Lymph node	Negative	Negative	Positive	λ	Negative	Positive
12	Skin	Negative	Negative	Positive	λ	Negative	Positive
DLBCL, centroblastic variant							
13	Brain	Negative	Positive	Positive	κ	Negative	Unsatisfactory
14	Liver	Negative	Positive	Negative	κ	Negative	Positive
15	Liver	Negative	Positive	Negative	Unsatisfactory	Negative	Negative
16	Small intestine	Unsatisfactory	Unsatisfactory	Unsatisfactory	Unsatisfactory	Unsatisfactory	Negative
17	Lung	Negative	Positive	Negative	Unsatisfactory	Negative	Negative
18	Brain	Negative	Positive	Negative	Unsatisfactory	Negative	Positive
19	Nasal sinus	Negative	Negative	Negative	Negative	Negative	Positive
20	Brain	Negative	Positive	Negative	κ	Unsatisfactory	Positive
Primary effusion lymphoma							
21	Pericardium	Negative	Negative	Positive	λ	Positive	Positive
22	Pericardium	Negative	Negative	Negative	Unsatisfactory	Positive	Negative
Burkitt's lymphoma							
23	Lymph node	Negative	Positive	Weak pos	Negative	Negative	Positive
Aggressive, NHL, NOS							
24	Heart	Negative	Positive	Positive	κ	Negative	Positive

AIDS = acquired immunodeficiency syndrome; NHL = non-Hodgkin's lymphoma; NOS = not otherwise specified; Ig = immunoglobulin; KSHV = Kaposi's sarcoma-associated herpesvirus; EBV = Epstein Barr virus; weak pos = weakly positive.

Castleman's disease and Kaposi's sarcoma (Case 1, see below). Kaposi's sarcoma was not seen in sections from other lymphomas.

Immunoblastic lymphomas were composed of a proliferation of transformed lymphoid cells with prominent central nucleoli and relatively abundant amphophilic cytoplasm. Three immunoblastic lymphomas (Cases 1, 2, and 9) showed more pronounced plasmacytoid differentiation, with frequent binucleation and occasional multinucleation. Immunoblastic lymphomas generally showed greater pleomorphism and a broader range in cell size, when compared with the plasmablastic variant of diffuse large B-cell lymphoma. Both immunoblastic and plasmablastic diffuse large B-cell lymphomas were often CD38 positive, and loss of CD20 was associated with plasmablastic features and plasmacytoid differentiation. Centroblastic diffuse large B-cell lymphomas involved extranodal sites, were often associated with necrosis, and tended to be CD20 positive and CD38 negative.

Three of seven evaluable immunoblastic lymphomas were positive for Kaposi's sarcoma-associated herpesvirus, with the tumors demonstrating nuclear staining for latency-associated nuclear antigen in all neoplastic cells (Fig. 1). Similar Kaposi's sarcoma-associated herpesvirus staining was seen in both primary effusion lymphomas. All other non-Hodgkin's lymphomas were negative for Kaposi's sarcoma-as-

sociated herpesvirus. Thirteen of 21 evaluable non-Hodgkin's lymphomas (including 4 of 7 immunoblastic lymphomas) were Epstein Barr virus positive.

We now describe the three Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas in more detail (Cases 1–3, Table 1). In Case 1, a 48-year-old white male developed Kaposi's sarcoma and nodal immunoblastic lymphoma simultaneously. Immunoblastic lymphoma cells co-expressed CD20 and CD3 and were Epstein Barr virus positive. Of interest, an adjacent lymph node had Kaposi's sarcoma and showed features of multicentric Castleman's disease, with scattered Kaposi's sarcoma-associated herpesvirus-positive plasmablasts in interfollicular areas. In Case 2, lymphoma presented as a soft-tissue neck mass in a 48-year-old white homosexual male, and Kaposi's sarcoma was diagnosed 8 months later. The immunoblastic lymphoma was both CD20 and CD3 negative and Epstein Barr virus positive. In Case 3, a 41-year-old white homosexual male (also a former injection drug user) developed idiopathic thrombocytopenic purpura and splenomegaly. This occurred when his CD4 lymphocyte count was 94 cells/mm³ and 1 month after Kaposi's sarcoma diagnosis. The spleen, on removal, showed extensive infiltration of the red pulp and large areas of tumor necrosis. Only small foci of viable tumor cells were identified. The tumor cells were CD20 and CD3 negative, λ restricted, and Epstein Barr virus negative.

Additionally, 5–20% of neoplastic cells in each Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphoma demonstrated positive cytoplasmic staining for Kaposi's sarcoma-associated herpesvirus viral interleukin-6 (Fig. 1)

DISCUSSION

We describe Kaposi's sarcoma-associated herpesvirus involvement in three immunoblastic lymphomas (43% of evaluable cases) arising in individuals with AIDS-associated Kaposi's sarcoma. Although primary effusion lymphoma can present first as a solid mass or subsequently develop an extracavitary component (1), our three Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas would not be classified as primary effusion lymphomas because they were not known to involve body cavities during their course (12). Still, these cases

demonstrate features frequently found in primary effusion lymphoma and other recently described Kaposi's sarcoma-associated herpesvirus-positive non-Hodgkin's lymphomas (1, 4, 10). First, they occurred in persons who already had or subsequently developed Kaposi's sarcoma or multicentric Castleman's disease (1, 4). Second, they had an immunoblastic morphology along with an aberrant immunophenotype. Although some Kaposi's sarcoma-associated herpesvirus-associated lymphomas arising in multicentric Castleman's disease are described as "plasmablastic," the distinction between immunoblastic lymphoma, the plasmablastic variant of diffuse large B-cell lymphoma, and primary effusion lymphoma is difficult, because most cases show overlapping histological features. Plasmacytoid differentiation and nuclear pleomorphism are generally prominent in AIDS-associated immunoblastic lymphomas, and plasmacytoid differentiation is often seen in Kaposi's

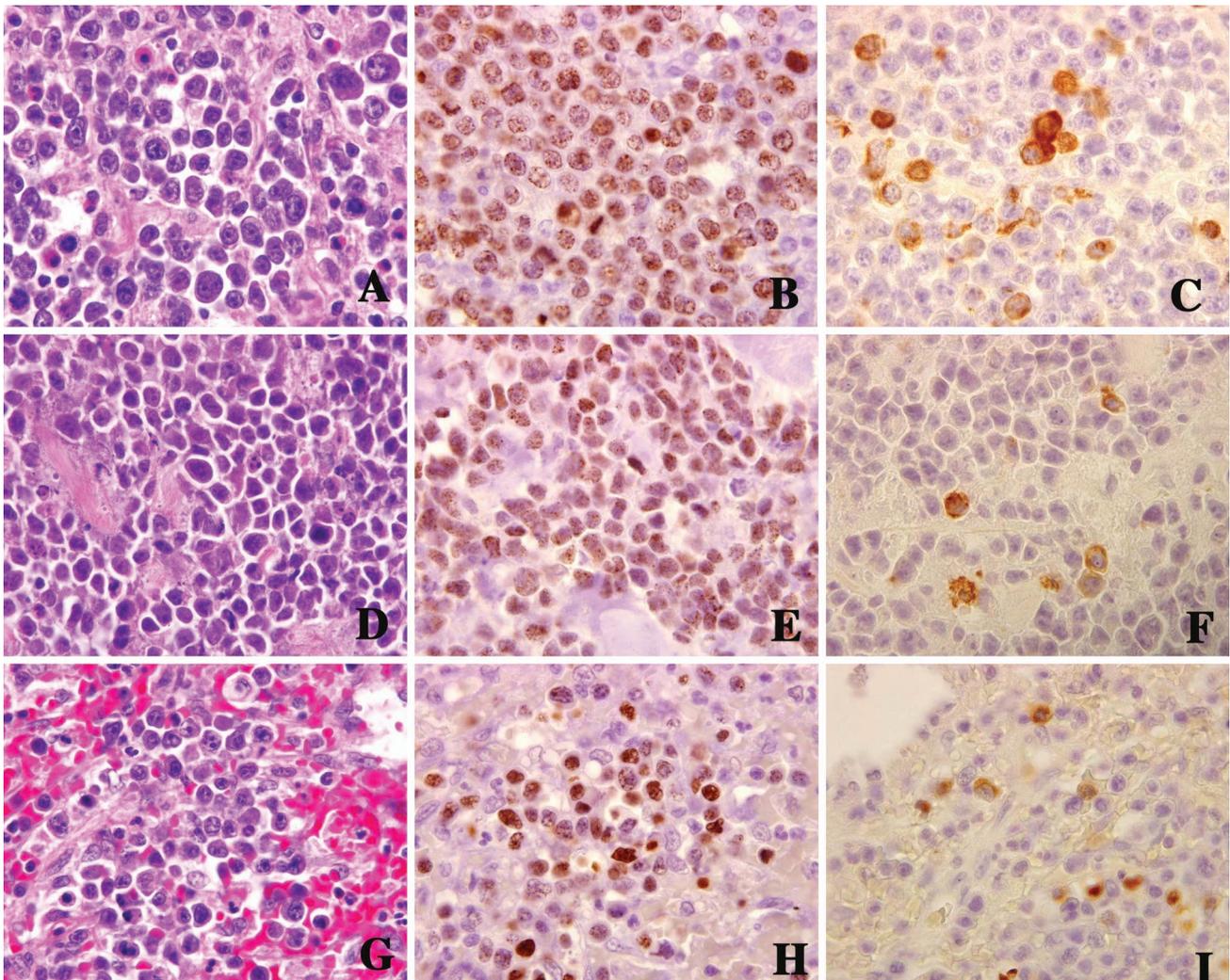


FIGURE 1. Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas. As described in the text and Table 1, sections are presented from three cases: Case 1 (A–C); Case 2 (D–F); and Case 3 (G–I). A, D, G, hematoxylin and eosin stain reveals the cytological features of neoplastic cells. B, E, H, staining with a rat monoclonal antibody for the Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen demonstrates nuclear staining in all neoplastic cells. C, F, I, staining with a mouse monoclonal antibody for Kaposi's sarcoma-associated herpesvirus viral interleukin-6 shows strong cytoplasmic staining in a minority of neoplastic cells. Original magnification in all panels, 500 \times .

sarcoma-associated herpesvirus-associated lymphoid proliferations (14). Third, two Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas were coinfecting with Epstein Barr virus, similar to the profile of primary effusion lymphoma (1). The other Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphoma showed λ restriction, like multicentric Castleman's disease-associated plasmablastic lymphoma (3), and involved the spleen, which is also sometimes seen in multicentric Castleman's disease-associated non-Hodgkin's lymphoma (3, 4). The extensive infiltration of the red pulp with large areas of tumor necrosis favored a diagnosis of immunoblastic lymphoma over multicentric Castleman's disease in this case.

Localization of Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen in the nuclei of all tumor cells of Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas provides evidence that Kaposi's sarcoma-associated herpesvirus was involved in the pathogenesis of these lymphomas. Prior systematic studies of immunoblastic lymphomas in HIV-infected persons relied exclusively on polymerase chain reaction to detect Kaposi's sarcoma-associated herpesvirus (2, 7-9). In those studies, given that Kaposi's sarcoma-associated herpesvirus was absent or present at low levels in a few cases, infection of tumor cells and infection of rare normal bystander lymphocytes could not be distinguished.

It is noteworthy that we found viral interleukin-6, a Kaposi's sarcoma-associated herpesvirus cytokine homologue, in a minority of tumor cells in each Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphoma. Viral interleukin-6, which is expressed during lytic viral replication, is also consistently detected in primary effusion lymphoma (in a minority of tumor cells) and multicentric Castleman's disease (in mantle zone plasmablasts; 15, 16). Viral interleukin-6 is secreted by primary effusion lymphoma cells and by Kaposi's sarcoma-associated herpesvirus-infected primary effusion lymphoma cell lines (13, 17). Furthermore, viral interleukin-6 receptors are present on primary effusion lymphoma cells, and viral interleukin-6 functions as an autocrine growth factor (13, 17). Therefore, intralesionally produced viral interleukin-6 could stimulate tumor cell growth in primary effusion lymphoma, multicentric Castleman's disease, and the Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas that we observed. Other Kaposi's sarcoma-associated herpesvirus gene products interact with cell-cycle control proteins, including p53, and might also play a role (18, 19).

There are two possible reasons that our study identified a higher fraction of Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas than did previous studies (2, 7-9). First,

all of our subjects demonstrated poor immune-mediated control of Kaposi's sarcoma-associated herpesvirus infection, because they all also had Kaposi's sarcoma, and this may have predisposed them to Kaposi's sarcoma-associated herpesvirus-associated immunoblastic lymphoma. Second, because we selected for study only individuals known to be infected with Kaposi's sarcoma-associated herpesvirus (*i.e.*, as manifested by Kaposi's sarcoma), the fraction of Kaposi's sarcoma-associated herpesvirus-associated immunoblastic lymphoma may have been especially high. This fraction, termed the *population attributable risk* (PAR), is calculated as follows:

$$\text{PAR} = p_{\text{KSHV}} \times (\text{RR} - 1) / [p_{\text{KSHV}} \times (\text{RR} - 1) + 1]$$

where p_{KSHV} is the prevalence of Kaposi's sarcoma-associated herpesvirus infection in the source population and RR is the relative risk for immunoblastic lymphoma associated with Kaposi's sarcoma-associated herpesvirus infection. We previously estimated this relative risk as 1.58 (11). When $p_{\text{KSHV}} = 1.00$ (*i.e.*, all subjects are infected with Kaposi's sarcoma-associated herpesvirus), the PAR is 37%, similar to what we observed for the fraction of Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas (43%). When $p_{\text{KSHV}} = 0.20$ (*i.e.*, roughly the Kaposi's sarcoma-associated herpesvirus prevalence among unselected HIV-infected persons), the PAR is only 10%. Thus, differences in the prevalence of Kaposi's sarcoma-associated herpesvirus in the source population may suffice to explain differences in the proportion of Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas in various reports.

A limitation of our study was the small number of cases for separate non-Hodgkin's lymphoma subtypes. Also, we are uncertain whether the lymphoma cases retrieved from pathology archives were fully representative of cases arising in conjunction with AIDS-associated Kaposi's sarcoma. As a result, it is difficult to generalize our findings to estimate the incidence of Kaposi's sarcoma-associated herpesvirus-associated non-Hodgkin's lymphomas. Furthermore, many specimens were obtained at autopsy, which limited the amount of available clinical data and made histologic characterization difficult. Although Kaposi's sarcoma-associated herpesvirus has been reported in non-Hodgkin's lymphomas associated with multicentric Castleman's disease (3, 4), we were unable to characterize how common it was for persons in our study to have this condition.

We conclude that Kaposi's sarcoma-associated herpesvirus is present in some immunoblastic lymphomas in persons with AIDS-associated Kaposi's sarcoma. Our immunoblastic lymphoma cases add to the spectrum of lymphomas associated with Ka-

posi's sarcoma-associated herpesvirus. Future work should characterize the incidence of Kaposi's sarcoma-associated herpesvirus-positive immunoblastic lymphomas in persons with HIV/AIDS and elucidate the role that Kaposi's sarcoma-associated herpesvirus plays in their genesis.

Acknowledgments: *The authors thank the collaborating institutions and individuals of the National Cancer Institute's AIDS Cancer Specimen Bank for providing the specimens used in this study, in particular Debra Garcia (University of California, San Francisco), who coordinated access to specimens. We also thank Steven Miles and Jonathan Said (University of California, Los Angeles) for providing additional specimens. We gratefully acknowledge the laboratory contributions of Giovanna Tosato (National Cancer Institute). Finally, we thank the National Cancer Institute Pathology Department's immunohistochemistry laboratory, particularly Leong Sonn Mann, for assistance.*

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