Human herpesvirus-8 (HHV-8) DNA sequences have been reported to be strictly associated not only with various forms of Kaposi's sarcoma but also with an unusual subgroup of acquired immunodeficiency syndrome (AIDS)-related B-cell lymphomas. A possible relation of this putative virus also with multicentric Castleman’s disease (MCD) has been recently suggested. We used polymerase chain reaction to look for the presence of HHV-8 sequences in a well characterized series of benign, atypical, and malignant lymphoid tissues from 45 Hodgkin’s disease and 43 non-Hodgkin’s lymphoma (NHL) cases, as well as from 5 MCD, 15 angioimmunoblastic lymphadenopathy (AILD), and 23 benign lymphadenopathy cases. Among the 38 AIDS-related lymphoid lesions, only 1 NHL and 1 persistent generalized lymphadenopathy (PGL) case were positive. Furthermore, among the 92 non-AIDS-related lymphoproliferative disorders, HHV-8 sequences were detected in 3 classic AILD cases and in 4 reactive lymphadenopathies. Six of 9 HHV-8 positive lymphoid lesions (1 NHL, 1 PGL, 1 AILD, and 3 reactive lymphadenopathy cases) were also positive for Epstein-Barr viral sequences. The four human immunodeficiency virus (HIV) negative lymphadenopathies positive for HHV-8 sequences showed an almost identical histology, characterized by a predominantly follicular lesion, with giant germinal center hyperplasia, and increased vascularity, resembling HIV-related lymphadenopathy and MCD. Our results, while providing the first evidence of the presence of HHV-8 sequences in AILD cases, suggest a possible association of these herpesviral sequences with a distinct histologic type of non-neoplastic lymphadenopathy, not associated with other common herpes infections.

Novel unique and specific DNA sequences were first identified in Kaposi’s sarcoma (KS) tissues from patients with acquired immunodeficiency syndrome (AIDS). The reported sequences of the apparently KS-specific DNA segments showed partial similarity to two capsid-protein coding genes of known γ-herpesviruses, namely Epstein-Barr virus (EBV) and herpesvirus Saimiri (HVS). The presence of these sequences suggested in favor of the existence of a new human herpesvirus called KS virus (KSHV) or human herpesvirus-8 (HHV-8).

 clear cells (PBMCs) of KS patients with and without AIDS notably in CD19+ B-cell fraction.

In the attempt to investigate the possible occurrence of HHV-8 in proliferative lesions other than KS, we judged it appropriate to use PCR to look for HHV-8 sequences in a large and well characterized series of benign, atypical, and malignant lymphoid disorders both in immunocompetent and in HIV positive subjects.

Materials and Methods

Patient samples. We retrospectively analyzed pathologic tissues obtained from a group of 131 benign and malignant lymphoid lesions including 45 Hodgkin’s disease (HD) (42 non-AIDS- and 3 AIDS-related), 43 non-Hodgkin’s lymphoma (NHL) (10 non-AIDS- and 33 AIDS-related), 20 HIV negative atypical lymphoproliferative disorder, and 23 benign lymphadenopathy (21 non-AIDS- and 2 AIDS-related) cases (Table I). The distribution of HD cases according to subtype was as follows: 23 mixed cellularity, 11 nodular sclerosis.
5 lymphocyte prevalence (diffuse), and 6 lymphocyte depletion. The non–AIDS-related NHL cases were six of B- and four of T-cell origin. Cellular pellets from three pleural and one peritoneal effusion from four of these six HIV negative patients with B-NHL were also available for molecular studies. The AIDS-related NHL cases were all of B-cell origin and also included 20 cases of primary cerebral lymphoma. The atypical lymphoproliferative disorders included 15 angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), and 5 MCD cases. The series of 23 benign lymphadenopathies consisted of 12 cases with a predominantly follicular lesion, including 5 cases with florid germinal center hyperplasia and 7 cases of Castleman’s disease of localized, hyalin-vascular type; 6 cases with a predominantly paracortical lesion (2 of which with serologically confirmed EBV induced infectious mononucleosis); 2 cases of persistent generalized lymphadenopathy (PGL); 2 cases with histologic features consistent with cat scratch disease; and 1 case of serologically confirmed toxoplasmosis. Representative portions of each tissue specimen were routinely fixed in buffered formalin and embedded in paraffin; sections were stained with hematoxylin and eosin.

**Immunohistochemistry.** Monoclonal antibodies, including L26 (cluster of differentiation-CD20; DAKO Glostrup, Denmark) and 4KB5 (CD45 RA, DAKO) for B cells; polyclonal CD3 (CD3, nodular sclerosis) and monoclonal UCHL1 (CD45 RO, DAKO) for T cells; polyclonal factor VIII-related antigen (DAKO) for endothelial cells; monoclonal KPI (CD68, DAKO) for macrophages; and monoclonal CD21 (DAKO) for follicular dendritic cells, were obtained commercially and used for standard immunohistochemical examination (avidin biotin method). Staining with the lectin Ulex europaeus lectin agglutinin I (UEA-1; Vector, Burlingame, CA) was also performed.

**Polymerase chain reaction (PCR) analysis.** DNA was extracted from cellular pellets from pleural and peritoneal effusions with a modification of the technique described by Enrietto et al.12 Crude extracts were prepared from single 5 μm formalin-fixed and paraffin-embedded tissue sections, as we previously reported.13 Aliquots of 5 μl were submitted to PCR using a pair of specific primers, derived from the HHV-8 sequences (K5330,50), amplifying a fragment of 233 base pairs (bp) as described.1,11 Each 100 μl reaction contains 30 pmol of each primer, 2.5 U of Taq polymerase, 200 μmol/L each of deoxynucleotide triphosphate, 10 mmol/L Tris-HCl, 1.5 mmol/L MgCl2, and 50 mmol/L KCl (pH 8.3). PCR conditions were as follows: 94°C for 1 minute followed by 45 cycles of 94°C for 30 seconds, 58°C for 1 minute, and 72°C for 90 seconds. Reactions were terminated by a 7-minute extension at 72°C. For each PCR test the positive controls were represented by the crude extracts obtained from 10 HHV-8 positive AIDS- and non–AIDS-KS biopsies. All standard recommended procedures were performed in order to avoid false positive results.14 PCR analysis was invariably performed on tissue sections derived from different paraffin blocks for each patient. Negative controls, consisting of all reagents except sample DNA, were also present during the crude extract preparation and equalled or exceeded the number of the assayed samples. Primers for the DQα gene were used as a positive amplification control.15 The PCR products were analyzed on 1.5% ethidium bromide-stained agarose gel, which allowed the direct visualization of the predicted 233 bp band. In order to confirm the viral origin of the amplified DNA template, one-fifth of the PCR product was subjected to electrophoresis on a 1.5% agarose gel blotted on Zeta-Probe GT Membrane (Bio-Rad Laboratories, Hercules, CA) and hybridized with an internal oligonucleotide probe specific for HHV-8,16 labeled with γ-32 P-ATP (Amersham-USB, Cleveland, OH).17 To exclude amplification of other types of herpes virus, virus preparations of EBV, herpes simplex virus 1 and 2 (HSV1, 2), cytomegalovirus (CMV), and human herpesvirus 6 (HHV-6) were examined by PCR, using the same HHV-8 primers, but no PCR products were obtained with any of these virus strains.

Specific DNA sequences of HIV gag/pol genes were searched by PCR as described.13 B-cell clonality was investigated by PCR according to the procedure described by Trainor et al.15 The PCR procedure we used for EBV detection and subtype characterization has been previously described by Borisch et al.18

**Sequence of PCR products.** The HHV-8 PCR products were subjected to direct sequence analysis by “cycling sequencing,” a modification of the classic dideoxy chain termination technique.19,20 Briefly, DNA bands were cut from a 1% low-melting agarose gel and further purified by a commercial kit (PCR Preps DNA Purification System; Promega). The cycle sequencing reaction was performed in a total volume of 8 μL containing 50 mmol/L KCl; 50 mmol/L Tris-HCl, pH 8.3; 2.5 mmol/L MgCl2; 10 μmol/L each of dATP, dTTP, and dCTP; 20 μmol/L 7-deaza-dGTP; 0.4 pmol 32P-labeled primer; 0.2 U of Taq polymerase; 100 fmol of purified PCR products; and 60 μmol/L ddGTP, 400 μmol/L ddATP, 600 μmol/L ddTTP, or 200 μmol/L ddCTP. The DNA was amplified in 20 cycles of 1 minute at 95°C, 1 minute at 55°C, and 1 minute at 72°C. The reactions were stopped with 4 μL of 95% formamide, 20 mmol/L EDTA, 0.05% bromophenol blue, and 0.02% xylene cyanol. The sequence products were analyzed on a 7 mol/L urea, 6% polyacrylamide sequencing gel. The two strands and two independent PCR products were sequenced to exclude mismatches due to polymerase mistakes.

**RESULTS**

The amplification of DQα gene was positive in all samples, suggesting the absence of major PCR inhibitors in crude

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**Table 1. Screening for HHV-8 Sequences by PCR in Lymphoproliferative Disorders in Non-AIDS and AIDS Patients**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases</th>
<th>No. Positive for HHV-8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-AIDS patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mixed cellularity</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>nodular sclerosis</td>
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<td>0</td>
</tr>
<tr>
<td>lymphocyte prevalence</td>
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<td>0</td>
</tr>
<tr>
<td>lymphocyte depletion</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td><strong>Non-Hodgkin’s lymphoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B cell</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>T cell</td>
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<td>0</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Atypical lymphoproliferative disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicentric Castleman’s disease</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Angioimmunoblastic lymphadenopathy</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>20</td>
<td>3</td>
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<tr>
<td><strong>Benign lymphadenopathies</strong></td>
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<td></td>
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<tr>
<td>Florid germinal center hyperplasia</td>
<td>5</td>
<td>4</td>
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<tr>
<td>Castleman’s disease (localized, hyalin-vascular type)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Paracortical lesion</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Cat scratch disease</td>
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<tr>
<td>Toxoplasmosis</td>
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<td>0</td>
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<tr>
<td><strong>Subtotal</strong></td>
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<td>4</td>
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<tr>
<td><strong>AIDS patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s disease (mixed cellularity)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Persistent generalized lymphadenopathy</td>
<td>2</td>
<td>1</td>
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<tr>
<td><strong>All patients</strong></td>
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<td></td>
</tr>
</tbody>
</table>
HHV-8 IN AILD AND BENIGN LYMPHADENOPATHIES

To further characterize the relative amounts of HHV-8 DNA present, we amplified serial dilutions of the crude extracts from both the HHV-8 positive formalin-fixed lymph node samples and the formalin-fixed KS biopsies used as controls. The load of HHV-8 DNA resulted in roughly similar results in both the AIDS-related (1 PGL and 1 NHL) and the non–AIDS-related (3 AILD and 4 reactive lymphadenopathy cases) lymphoid lesions as well as in the 10 KS biopsies examined (data not shown).

Moreover, PCR products from all 9 HHV-8 positive samples were sequenced (Fig 2) and compared with the prototypic sequence originally derived from a genomic library made from a Kaposi’s sarcoma lesion. PCR products from three reactive lymphadenopathies (cases 6, 10, and 16) showed five base-pair substitutions (at positions 46, 47, 69, 146, and 153). Base-pair changes at positions 46 and 47 code for a proline-to-isoleucine substitution and a base-pair change at position 146 codes for an aspartate-to-glycine substitution, as compared with the prototypic sequence. The remaining base-pair changes do not involve amino acid substitutions. PCR products from one reactive lymphadenopathy (case 14), from the three AILD (cases 25, 27, 28), from the PGL (case 21), and from the AIDS-related NHL (case 24) samples revealed three base-pair substitutions (at positions 47, 100, and 153). The base-pair change at position 47 codes for a proline-to-leucine substitution, while the other two base changes are isocoding alterations from the prototypic coding sequence. The high degree of sequence conservation among PCR products suggests that the sequences obtained by PCR from our four reactive lymphadenopathy cases, three AILD, one PGL, and one AIDS-related NHL case correspond to the same putative agent previously identified in Kaposi’s sarcoma.

Histologically, the three AILD cases positive for HHV-8 sequences showed classic features, including complete effacement of the lymph node architecture, abundance of small arborizing vessels, and a polymorphous infiltrate, in strict adherence to the original criteria of Frizzera et al for the diagnosis of AILD. In two cases the predominant cell population was represented by CD3 positive peripheral T cells, with very few B cells in a scattered pattern, but with particularly abundant plasma cells. In one case the portion of CD20 positive B cells was particularly elevated, forming the 35% of the mononuclear component.

It should be noted that careful examination of the four positive cases of reactive lymphadenopathy showed identical histologic features. In details, follicles of different shape and dimensions occupied the whole cross-sectional area of each lymph node, pushing residual sinuses at the periphery. The majority of follicles appeared hyperplastic with giant germinal centers, surrounded by markedly attenuated mantle zones, often partially lost. Adjacent germinal centers tended to coalesce one with another, acquiring bizarre, “geographic” shapes (Figs 3A and 4A). Tangible body macrophages were numerous within germinal centers, giving them a “starry sky” appearance (Fig 4A and B). In addition, small involuted follicles were also present, constituting approximately 30% to 40% of the follicular population. They were

extracts from tissue biopsy specimens. Crude extracts from all the 131 benign, atypical, and malignant lymphoid lesions shown in Table 1 were analyzed for the presence of HHV-8 (KS330233) sequences by PCR. Among the 38 AIDS-related lymphoid lesions, agarose-gel electrophoresis of the PCR products and subsequent Southern blot hybridization revealed the presence of the specific viral 233 bp fragment in one of the 2 PGL and in 1 of the 33 B-NHL cases, while the 3 HD were negative. Unfortunately, clinical records were not available, so we could not assess if the clinical features of the positive B-NHL patient were similar to those reported by Cesarman et al. Neither the 52 HIV negative lymphoma specimens (10 NHL and 42 HD), nor the 5 non–AIDS-related MCD showed an amplified product, even after hybridization with an internal oligonucleotide probe (Table 1). In particular, the lymphomatous effusions from four HIV negative B-NHL patients did not harbor HHV-8 sequences. Of interest, 3 lymph node biopsies of 15 HIV negative cases with confirmed clinical and histologic diagnosis of AILD and, unexpectedly, 4 of 21 benign non–AIDS-related lymphadenopathies were clearly positive for HHV-8 sequences (Fig 1). In these HHV-8 positive specimens no HIV-1 provirus DNA was detected by PCR. Moreover, we could not document B-cell clonality in any of the 4 HHV-8 positive reactive lymphadenopathies by PCR, thus confirming the benign nature of the lymphoid hyperplasia in these cases.
mainly composed of CD21-positive dendritic reticulum cells and residual large lymphoid cells, frequently devoid of a rim of mantle lymphocytes. Numerous small blood vessels were invariably present in interfollicular areas and particularly abundant in one case (Fig 3B). Focal collections of cells exhibiting abundant, pale cytoplasm and oval, indented nuclei with small nucleoli were clearly recognizable; such cells were not accompanied by hepatosplenomegaly. Fever or constitutional symptoms were absent, while no laboratory abnormalities indicative of viral or other infections and inflammation were documented. Serology for common herpes viruses like EBV, CMV, HSV 1 and 2 and for common hepatitis viruses was consistently negative. Seronegativity for HIV infection was repeatedly confirmed at 6-month intervals by ELISA, for at least 2 years. The patients did not have a history of KS at the time of lymph node enlargement and have not developed KS, after a 4 to 6 year follow-up. In two patients marked thrombocytopenia was present at the time of lymph node enlargement: in one patient thrombocytopenia persisted and the diagnosis of idiopathic thrombocytopenic purpura was finally made; in the other patient the platelet count became normal in 2 months, without therapy.

Our series of non-AIDS-related benign lymphadenopathies included a further case with similar histologic features but negative for HHV-8. Of interest, these herpesviral sequences were absent in all the other 16 benign lymph node biopsies examined, which showed significantly different histologic features, including 7 cases of Castleman’s disease of localized type, 6 cases with predominantly paracortical lesions typically seen in viral infections, 2 cases with histologic features consistent with cat scratch disease, and 1 case of serologically confirmed toxoplasmosis.

EBV sequences were identified in 6 of the 9 HHV-8 positive cases, in particular in both the AIDS-related lesions (1 NHL and 1 PGL), in 1 of 3 AILD, and in 3 of 4 benign lymphadenopathy cases. EBV subtype characterization could be performed only in three cases. It showed B type in one case.
benign lymphadenopathy and in the NHL case, while a mixture of A and B types was present in the PGL case (data not shown).

DISCUSSION

In a recent study, Cesarman et al. investigated the presence of HHV-8 sequences in a series of AIDS- and non-AIDS-related lymphoid lesions, which included only malignant lymphomas, mainly NHLs. Out of 193 cases examined, they could identify these sequences only in an unusual subgroup of 8 HIV positive body-cavity-based lymphomas, characteristically showing pleural, pericardial, or peritoneal lymphomatous effusions, two of which also showed a history of KS. Our study confirmed the infrequent occurrence of these herpesviral sequences not only in NHLs, AIDS-related or not, but also in a large series of HD cases, representative of all histologic subtypes. In fact, only one AIDS-related NHL, typed histologically as diffuse large B-cell lymphoma, was positive for HHV-8. The pleural and peritoneal lymphomatous effusions obtained from four HIV negative B-cell NHL patients were negative, confirming the apparent restriction of the presence of HHV-8 sequences to lymphomatous effusions occurring in the rare body-cavity-based B-NHL of HIV positive patients.
The detection of these herpesviral sequences in pathologic lymph node tissues from three patients with classic clinical and histologic diagnosis of AILD is the first evidence of this novel herpesvirus in this rare type of atypical lymphoproliferative disorder. Although the cause of AILD is unknown and is likely to vary in different subjects, a common feature is excessive immune activity, and much speculation has centered on the possibility that a viral infection could directly or indirectly trigger this disorder. In particular, human herpesviruses like EBV20,21 and HHV-6,13 have been found to be associated with AILD. Thus, it is not totally unexpected that these new herpesviral sequences, belonging to the family of lymphotropic γ-herpesviruses, are found at least in some cases of the disease. However, it is not possible to rule out that HHV-8 sequences detected in these cases represent mere passengers in AILD lesions, resulting either from reactivation or primary infection induced by the immunosuppression.

On the other hand, the disease etiologically related to the presence of HHV-8 sequences, namely KS, is itself characterized by chronic immune activation and release of inflammatory cytokines, so that common immune dysfunctions underlying both disorders may be hypothesized.22 Furthermore, at least nine well-documented cases of KS have been reported in patients with AILD,22 and vascular hyperplasia is characteristically observed in both pathologic lesions. The other atypical lymphoproliferative disorder known to be associated with an increased risk of developing KS is the multicentric giant lymph node hyperplasia,23 now commonly defined as MCD.24 Rather unexpectedly, the five cases of HIV negative MCD available for this study were also negative for the presence of HHV-8 sequences. The small number of cases examined, all collected at the early stage of the disease, might explain the discrepancy with the results reported by Soulier et al,9 who found 7 positive out of 17 HIV negative MCD cases examined.

The most unexpected finding is, however, the identification of these herpesviral sequences in four of five cases of HIV negative reactive lymphadenopathies, all showing the same histologic features, characterized by florid germinal center hyperplasia (giant follicles) associated with various degrees of condensation and regression of germinal centers (follicular involution), in the presence of increased vascularity and of "monocytoid B cell" hyperplasia. The above described lymphoid lesion harboring these sequences is predominantly a follicular lesion, which rarely occurs in the course of herpes infections.25 In fact, in EBV-induced infectious mononucleosis, as well as in other lymphadenitis caused by cytomegalovirus or herpes simplex virus, the prototypical histologic lesion is predominantly a diffuse paracortical expansion, with an abundance of immunoblasts and high endothelial venules, usually with small germinal centers.25 The six reactive lymphadenopathies with a predominantly paracortical lesion in our series were all negative for HHV-8 sequences. Similarly, HHV-8 sequences were absent in all seven cases of hyaline vascular, localized type CD, showing a typical follicular lesion, which significantly differs from the giant germinal center hyperplasia.25

The histologic features of florid germinal center hyperplasia invariably recognized in the four HHV-8 positive and HIV negative benign lymphadenopathies may be observed in a spectrum of other clinical conditions, like autoimmune disorders (especially rheumatoid arthritis, and Sjögren’s syndrome), MCD and HIV infection.25 In fact, one of two AIDS-related cases of PGL included in our study was positive for the same herpesviral sequences. Similarly, Chang et al found HHV-8 sequences in 3 of 12 benign HIV lymph nodes. In addition, vascular hyperplasia is also a common feature of all the HHV-8 positive lesions identified so far, including KS, MCD, AILD, and the above described benign lymphadenopathies. In other words, the histologic features recognized in these HHV-8 positive cases of reactive lymphadenopathy represent a defined pattern of response of the lymph node, possibly induced by a wide range of antigenic stimuli. HHV-8 should now be considered in the differential diagnosis of the possible causes for such a response. We are aware of the fact that the assessment of a causal link between these four cases of reactive lymphadenopathies and HHV-8 infection would require viral isolation and also serologic confirmation. However, the identification of these herpesviral sequences in four of five cases of apparently benign lymphadenopathies with shared typical histologic features, suggests that this distinct histologic pattern of lymphoid response induced by HHV-8 is likely to reflect the original pathogenic potential of this herpesvirus in HIV negative subjects. It is worth mentioning that Soulier et al9 reported the presence of HHV-8 in one reactive axillary lymph node, with pathologic evidence of follicular hyperplasia, from a clinically asymptomatic HIV negative subject, which seems similar to our cases. These cases may thus reveal the possible clinico-pathologic entity, benign in nature, which might occur during the primary HHV-8 infection in normal subjects; similarly, infectious mononucleosis represents the most common clinical manifestation of EBV infection in the general population.

The possibility still remains that HHV-8 may exhibit an indirect transforming ability in conjunction with other factors, like EBV, as it has been proposed for the unusual subgroup of AIDS-related body-cavity-based lymphomas.8 The only one AIDS-related HHV-8 positive NHL patient in our series harbored EBV sequences, but we could also document the coinfection with both herpesviruses in five nonmalignant lymphoid lesions. These data clearly indicate that the presence of EBV together with HHV-8 is not necessarily associated with the full neoplastic phenotype.

Finally, it also should be noted that all four patients with HHV-8 positive lymphadenopathies are from the areas of Italy with the highest incidence of classic KS (3 from the Po valley and 1 from Sicily).26 Therefore, the possibility is also raised that the unexpectedly higher frequency of HHV-8 sequences in our series of reactive lymphadenopathies is due, at least in part, to the different geographic distribution of the putative KS-associated virus and to its possibly higher frequency in the Italian population.

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Human herpesvirus-8 DNA sequences in human immunodeficiency virus- negative angioimmunoblastic lymphadenopathy and benign lymphadenopathy with giant germinal center hyperplasia and increased vascularity

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