

# HIV-Associated Hodgkin Lymphoma

## A Clinicopathologic and Immunophenotypic Study of 45 Cases

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### Abstract

We retrospectively analyzed 45 cases of HIV-associated Hodgkin lymphoma (HIV-HL). HIV-HL generally is a disease of young white men (mean age, 40.1 years) who acquired HIV infection by homosexual or bisexual behavior (68%), intravenous drug use (24%), and/or blood transfusion (8%). The mean interval between the diagnosis of HIV and HIV-HL was 5.2 years. Morphologic classification of nodal biopsy specimens (2001 World Health Organization criteria) included 15 mixed cellularity Hodgkin lymphomas (MCHLs), 14 nodular sclerosis Hodgkin lymphomas (NSHLs), 9 lymphocyte depleted Hodgkin lymphomas (LDHLs), and 7 classic Hodgkin lymphomas, type not further categorized. The Hodgkin-Reed-Sternberg (HRS) cells expressed positive immunoreactivity with fascin (30/30 [100%]), CD30 (35/37 [95%]), CD15 (32/36 [89%]), bcl-X<sub>L</sub> (25/31 [81%]), bcl-2 (15/29 [52%]), CD20 (4/34 [12%]), bcl-6 (3/28 [11%]), and Epstein-Barr virus latent membrane protein-1 (32/33 [97%]) and were nonreactive for CD138/syndecan-1. CD4 and CD8 immunostaining showed an inverted CD4/CD8 ratio (<1/20) in all cases. At diagnosis, most patients (n = 27) had high-stage disease (IV<sub>E</sub>) associated with an aggressive course (16% 5-year survival). LDHL behaved more aggressively than MCHL and NSHL (15% vs 40%, 5-year survival, respectively), as did disease with a sarcomatoid pattern (11% 5-year survival). Chemotherapy and radiotherapy proved efficacious in a minority of these patients.

The association of Hodgkin lymphoma (HL) and AIDS is recognized. As early as 1984,<sup>1-5</sup> after only 3 years of AIDS recognition by the Centers for Disease Control and Prevention (CDC), HIV-associated HL (HIV-HL) was reported in patients with AIDS. Since the mid-1980s, many cases of HIV-HL have been reported, most as single case reports.<sup>6-27</sup> Many of these cases have shown atypical clinical features,<sup>7-9,12,15,16,19,20,22,26</sup> unfavorable histopathologic features,<sup>1,7-10,16-23,25-27</sup> high tumor stage,<sup>1,7-10,16-23,25-27</sup> extranodal disease at diagnosis,<sup>7,8,14,16,19,22-24,26</sup> and aggressive clinical course.<sup>8,12,17,22,26</sup> Several studies have shown an apparent increase in the relative risk for developing HIV-HL in the AIDS population compared with age- and sex-matched control subjects without HIV infection,<sup>28-30</sup> although these results were not observed by other investigators.<sup>31-35</sup> HIV-HL seems to occur with an increased frequency in patients with AIDS irrespective of the method of HIV acquisition (homosexual contact, intravenous drug abuse, HIV-infected people with hemophilia, and in women by heterosexual contact), although the frequency perhaps is higher in people who abuse intravenous drugs.<sup>7-9,19,22,23,26,29,30,36</sup>

However, HIV-HL is not a neoplasm that is currently considered by the CDC to be an AIDS-defining illness,<sup>11,37</sup> although Kaposi sarcoma (KS), diffuse aggressive B-cell lymphoma, and invasive cervical carcinoma<sup>11</sup> are considered AIDS defining. It is interesting that each of the neoplasms cited is associated with a potentially tumorigenic virus: human herpesvirus 8 (HHV-8/KSHV), Epstein-Barr virus (EBV), and human papilloma virus, respectively. These findings probably reflect the depleted CD4 counts and relative cellular immunodeficiency of these patients.

The distinctive clinical, morphologic, and epidemiologic features of HIV-HL have not been assessed thoroughly in a

single, comprehensive study applying the recently published 2001 World Health Organization (WHO) diagnostic criteria,<sup>38</sup> in addition to using epidemiologic features, stage, treatment efficacy, and clinical outcomes, focusing on the pathologic diagnosis as it relates to contemporary immunoperoxidase staining.

## Materials and Methods

The records of 58 patients with tumors diagnosed as HIV-HL between 1984 and 2000 were retrieved from the files of the AIDS Registry of the Armed Forces Institute of Pathology, Washington, DC. HIV-HL cases were defined as those affecting patients with serologically documented HIV infection and clinically reduced CD4/CD8 ratios. Thirteen cases were excluded from further consideration owing to inadequate clinical history and follow-up, a lack of H&E-stained sections, or insufficient material for immunohistochemical analysis. The remaining 45 cases form the basis for this analysis. Twenty-six cases were obtained from civilian sources, including university medical centers and foreign contributors, 15 cases from Veterans Administration medical centers, and 4 cases from military hospitals.

Materials within the Institute's files were supplemented by a review of the patient demographics (sex, age); symptoms and physical findings and duration at diagnosis (for HIV and HL); laboratory test results; and medical and surgical history. In addition, we reviewed radiographic, surgical pathology, and operative reports and obtained follow-up information from oncology data services by written questionnaires or direct communication with the treating physician(s) or the patient. Follow-up data, available for all patients, included information regarding tumor location, clinical and surgical staging (according to the "Cotswolds meeting modification" of the Ann Arbor staging system for staging the HIV-HL cases; **Table 1**<sup>39,40</sup>), presence of recurrent disease, treatment

modalities used, and the current patient status. This clinical study was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and the Department of Defense Directive 3216.2 relating to human subjects in research.

H&E-stained slides from all cases were reviewed, and HIV-HL cases were classified according to the recently published 2001 WHO criteria,<sup>38,41</sup> including morphologic and immunophenotypic findings. A morphologic diagnosis of HL was made when classic Hodgkin-Reed-Sternberg (HRS) cells and variants were found in a variably cellular background diathesis of plasma cells, eosinophils, and neutrophils. Additional histologic features were documented: tumor cell syncytial formation, nodularity, capsular thickening, stromal fibrosis, sclerotic banding, epithelioid histiocytes with granuloma formation, necrosis, depleted lymphocytic background, extracapsular extension of tumor, and sarcomatoid changes (fibroplasia, myofibroblastic proliferation, spindled stromal cell background).

*Nodular sclerosis HL* (NSHL) was defined by a nodular growth pattern, birefringent collagen banding, lacunar and mummified variant HRS cells, and a thickened fibrotic capsule. Owing to the frequently observed "lymphocyte depleted" and fibrotic nature of many HIV-HL cases, no attempt to further classify cases of NSHL into grade 1 or grade 2 was attempted.

*Mixed cellularity HL* (MCHL) was defined as cases not demonstrating the changes of NSHL. These cases have classic HRS cells in a mixed cellular background consisting of variable eosinophils, neutrophils, histiocytes, and plasma cells. Increased epithelioid histiocytes and granulomas might be associated with this type of HL.

Several patterns of lymphocyte depleted HL (LDHL) are described in the 2001 WHO classification. This type has a relative predominance of HRS cells to the background lymphocytes. Pleomorphic HRS cells might yield a "sarcomatous" appearance, while a diffuse fibrosis with proliferation of fibroblasts is another pattern seen. We evaluated these morphologically difficult cases at a multiheaded microscope to obtain a consensus diagnosis.

Immunophenotypic analysis was performed in all cases with suitable material by a standardized avidin-biotin complex method using 4- $\mu$ m-thick, formalin-fixed, paraffin-embedded sections. However, not all cases contained the requisite number of unstained sections for the complete 16-antibody immunostaining panel. **Table 2** gives the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on 1 representative block for each tumor. When required, proteolytic antigen retrieval was performed by predigestion for 15 minutes with 0.4% pepsin (Sigma Chemical, St Louis,

**Table 1**  
Modified Ann Arbor Staging System<sup>\*39,40</sup>

Stage	Criteria
I	Single lymph node region or lymphoid structure (spleen, thymus, Waldeyer ring) involved
II	Two or more lymph nodes affected on the same side as the diaphragm (mediastinum is a single site; hilar lymph nodes are lateralized)
III	Lymph nodes or structures affected on both sides of the diaphragm
IV <sub>E</sub>	Involvement of extranodal site(s) beyond those designated E

\* The number of anatomic sites is indicated by a suffix (eg, II3). Abbreviations used in the classification system are as follows: A, no symptoms; B, fever, drenching sweats, or weight loss; X, bulky disease (>1/3 widening of the mediastinum at T5-6, or maximum nodal mass >10 cm); E, involvement of a single extranodal site or contiguous or proximal to known nodal site of disease; CS, clinical stage; PS, pathologic stage.

**Table 2**  
**Immunohistochemical Antibody Panel**

Antibody	Primary Antibody	Company	Dilution	Cellular Conditioning
CD30	MM	DakoCytomation, Carpinteria, CA	1:100	Pepsin
CD15	MM	DakoCytomation	1:100	Pepsin
Fascin	MM	Cell Marque, Austin, TX	1:20	Steam
bcl-2	MM	DakoCytomation	1:100	Steam
CD20 (L26)	MM	DakoCytomation	1:200	None
CD45RB (leukocyte common antigen)	MM	DakoCytomation	1:200	None
bcl-X <sub>L</sub>	MM	Zymed, San Francisco, CA	1:5,000	Steam
EBV latent membrane protein	MM	DakoCytomation	1:50	Pepsin
CD3	RP	DakoCytomation	1:500	Protease
bcl-6	MM	DakoCytomation	1:40	Steam
CD4	MM	Novocastra, Burlingame, CA	1:40	Steam
CD8	MM	DakoCytomation	1:100	Steam
Epithelial membrane antigen	MM	DakoCytomation	1:100	None
Anaplastic lymphoma kinase-1 (ALK-1)	MM	DakoCytomation	1:100	Steam
p24	MM	DakoCytomation	1:50	Steam
CD138 (syndecan-1)	MM	Santa Cruz Biotechnology, Santa Cruz, CA	1:500	Steam

EBV, Epstein-Barr virus; MM, mouse monoclonal; RP, rabbit polyclonal.

MO) in a 0.1% hydrochloric acid buffer, pH 2.0, at 37°C. Heat-induced epitope retrieval was performed, as required, by using formalin-fixed, paraffin-embedded tissue samples treated with a 1-mmol/L concentration of EDTA buffer solution, pH 8.0, and heated for 20 minutes in a steamer. Following this, the sections were permitted to cool at room temperature in the EDTA buffer solution for 20 minutes before the procedure was continued. Standard positive control samples were used throughout; serum was used as the negative control sample.

Polymerase chain reaction (PCR) for HHV-8 was performed in 10 cases. DNA was extracted from formalin-fixed, paraffin-embedded sections for PCR assay performance as described previously.<sup>42,43</sup> Real-time PCR was used, and samples were amplified for 45 cycles. Appropriate HHV-8 primer sets were used with known positive and negative control tissue samples. Epstein-Barr virus–encoded RNA in situ hybridization was performed in 6 cases by using a previously described method.<sup>44</sup> Chromogenic positivity was determined; appropriate controls were used.

Outcome comparisons for the different morphologic patterns and types of HIV-HL were plotted on Kaplan-Meier survival curves. Statistical analysis was not done owing to insufficient numbers of cases in each category.

A review of HIV-HL in the English literature was based on a MEDLINE search from 1966 to 2003. Owing to the large number of single case reports, often from the same institution reporting larger series, and reports from the same institution over several years, we refined our review to the most recent reports with at least a few patients in a series and analyzed those results in conjunction with the present study. Isolated case reports of unusual locations for the HIV-HL were included for specific features of interest.

## Results

### Clinical

Most patients were men (n = 44); only 1 was a woman. Most patients were white (32 [71%]), although African American patients constituted 29% (n = 13) of the

**Table 3**  
**Patient Demographics in 45 Cases of HIV-Associated Hodgkin Lymphoma\***

Characteristic	Result
Sex	
Men	44 (98)
Women	1 (2)
Race	
White	32 (71)
African American	13 (29)
Age at HIV diagnosis (y)	
Range	20-56
Mean	32.5
Median	31.0
Mode of HIV transmission	
Homosexual	23 (51)
Intravenous drug abuse	8 (18)
Blood transfusion	3 (7)
Unknown	11 (24)
Age at Hodgkin diagnosis (y)	
Range	21-75
Mean	40.1
Median	39.0
Mode	27
Interval between HIV and Hodgkin diagnoses (y)	
Range	0-15
Mean	5.2
Median	5.0
Duration of symptoms related to Hodgkin lymphoma (mo)	
Range	1-24
Mean	5.7
History of Kaposi sarcoma	
Yes	3 (7)
No	29 (64)
Unknown	13 (29)

\* Data are given as number (percentage) unless otherwise indicated.

group (including the sole woman). HIV infection was acquired by homosexual or bisexual contact, intravenous drug abuse, or blood product transfusion. In 11 cases, the mode of HIV acquisition was not supplied. The age of HIV acquisition ranged from 20 to 56 years (mean, 32.5 years), while the age of HL development ranged from 21 to 75 years (mean, 40.1 years). The interval between HIV infection and HL development ranged up to 15 years (mean, 5.2 years). Patients experienced symptoms related to HL (lymphadenopathy, mass, difficulty breathing, integumentary manifestations, fever, drenching sweats, night sweating, and weight loss) for 1 to 24 months (mean, 5.7 months). While other opportunistic infections were identified, only 3 patients had documented KS, although a history of KS was not supplied for 13 patients (29%).

### Laboratory Diagnostic Studies

The clinical CD4 count at the time of HIV-HL development, as determined by flow cytometry, ranged from fewer than 10 to 500 cells per microliter ( $10\text{-}500 \times 10^6/\text{L}$ ; mean,  $154/\mu\text{L}$  [ $154 \times 10^6/\text{L}$ ]). Of the 45 patients, 38 (84%) had a CD4 cell count of less than  $200/\mu\text{L}$  ( $200 \times 10^6/\text{L}$ ) at the time of the HIV-HL diagnosis.

### Pathologic Features

#### Macroscopic

At diagnosis, the majority of patients had cervical lymphadenopathy (22 [44%]) (Table 4), although extranodal sites constituted 22% of cases ( $n = 11$ ), followed in decreasing order of frequency by axillary, inguinal, intra-abdominal, and mediastinal lymph nodes. The majority of cases developed in “peripheral” rather than “central” lymph nodes. The lymph nodes ranged in size from 0.8 to 6.0 cm in greatest dimension (mean, 2.9 cm).

#### Stage

At diagnosis, the majority of patients had pathologic stage IV (extranodal) disease, followed by stage II disease

**Table 4**  
Macroscopic Features in 50 Sites of Involvement

Feature	No. (%) <sup>*</sup>
Anatomic location	
Cervical lymph node	22 (44)
Extranodal	11 (22)
Axillary lymph node	9 (18)
Inguinal lymph node	5 (10)
Intra-abdominal lymph node	2 (4)
Mediastinal lymph node	1 (2)
Maximum dimension (cm)	
Range	0.8-6.0
Mean	2.9

\* Unless otherwise indicated.

(Table 5). Only a few patients had stage I and stage III disease; only 36% of the patients ( $n = 16$ ) had stage I through stage III disease. Clinical staging data also were available for many patients ( $n = 26$ ; Table 5). At diagnosis, most patients had clinical stage A ( $n = 12$ ) or stage C ( $n = 10$ ) disease. Of the patients, 27 (60%) experienced B symptoms, including fever, profound night sweats, weight loss, and anorexia associated with the development of HIV-HL.

#### Microscopic

The HIV-HL cases were classified histopathologically according to the 2001 WHO criteria, resulting in a nearly even split between MCHL and NSHL (Table 5), followed by LDHL and classic HL, not further categorized. These well-recognized patterns are not illustrated, but instead features considered unique to HIV-HL are emphasized. Extracapsular tumor extension was observed in 15 cases (33%), while 16 (36%) showed zones of parenchymal necrosis (Table 6). Skin (Image 1) and lung (Image 2) involvement were the most common locations for extranodal disease, sites infrequently affected in non-HIV-HL. A sarcomatoid stromal pattern was present in 11 cases (24%) (Image 3) and was developed to a sufficient degree to be part of LDHL, sarcomatoid type in 6 cases; 29 cases (64%; representing NSHL, MCHL, and LDHL types) showed depletion of the background small lymphocytes but were otherwise classifiable, with classic HRS cells (Image 4A). Eosinophils were present in 32 cases (71%). Noncaseating granulomas and/or increased epithelioid histiocytes were observed in 9 cases (20%). Only 3 cases displayed tumor cell syncytia. Plasma cells were increased in 40 cases (89%; background plasmacytosis).

For many cases, the precise 2001 WHO classification of HIV-HL was difficult owing to the presence of nonspecific, obscuring features, including stromal fibrosis, relative lymphocyte depletion, and an associated spindle, sarcomatoid stromal cell response.

### Immunophenotypic Findings

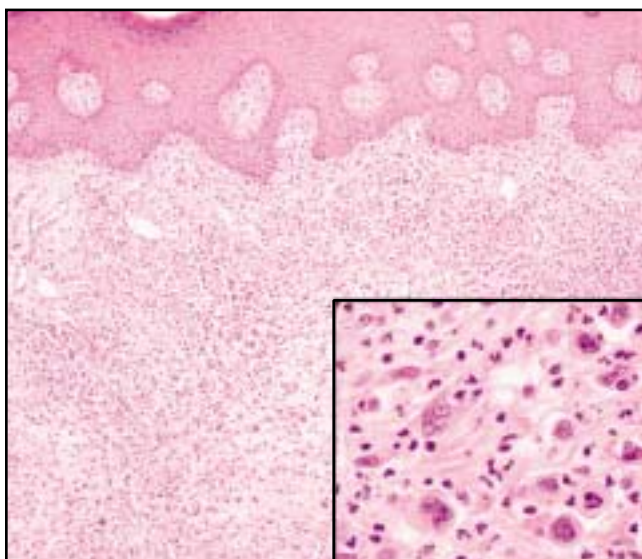
Cases of HIV-HL showed typical immunophenotypes in which the HRS cells displayed immunoreactivity for CD15 (LeuM1) and CD30 (Ki-1) with absent staining for CD45RB (leukocyte common antigen) (Table 7). Of 34 cases tested, 4 (12%) displayed immunoreactivity in the HRS cells for the B-cell marker CD20. The HRS cells were immunoreactive for latent membrane protein (LMP) in 32 (97%) of 33 cases tested, signifying EBV infection. The HRS cells were immunoreactive for fascin (Image 3B) and bcl- $X_L$  (25/31) (Image 4C) but nonreactive for CD138 (syndecan-1) (Image 4D), CD3, epithelial membrane antigen, and anaplastic lymphoma kinase-1. Of 29 cases tested, 15 (52%) were reactive for bcl-2, while only 3 (11%) of 28 were reactive for bcl-6. The malignant cells were nonreactive with the HIV-specific

**Table 5**  
**Stage and Clinical Classification in 45 Cases of HIV-Associated Hodgkin Lymphoma**

	No. (%)
Pathologic stage*	
I	2 (4)
II	11 (24)
III	3 (7)
IV	27 (60)
Unknown	2 (4)
Clinical stage	
A0	7 (16)
A1	1 (2)
A3	4 (9)
B2	1 (2)
B3	3 (7)
C0	5 (11)
C2	1 (2)
C3	4 (9)
Unknown	19 (42)
WHO 2001 Hodgkin lymphoma classification	
Mixed cellularity	15 (33)
Nodular sclerosis	14 (31)
Lymphocyte depleted	9 (20)
Classic	7 (16)

WHO, World Health Organization.  
 \* See Table 1 for an explanation of the stages.

p24 antigen, but p24 was expressed on follicular dendritic cells (n = 5) associated with a reactive follicular hyperplasia **Image 4B**. The CD4/CD8 ratio was inverted substantially in immunohistochemical studies, reflecting markedly decreased numbers of CD4+ T lymphocytes in 26 cases tested **Image 5**. The κ and λ immunoglobulin light chain staining high-lighted polytypic plasmacytosis in all 34 cases tested.



**Image 1** Extranodal Hodgkin lymphoma in the skin (H&E, ×75) with Hodgkin–Reed–Sternberg cells (inset, H&E, ×300).

**Table 6**  
**Morphologic Features in 45 Cases of HIV-Associated Hodgkin Lymphoma**

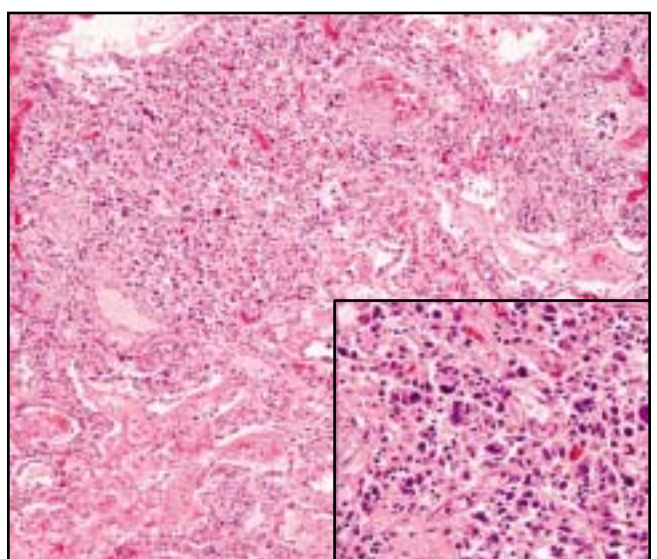
Feature	No. (%)
Extracapsular extension	
Present	15 (33)
Absent	30 (67)
Sarcomatoid growth	
Present	11 (24)
Absent	34 (76)
Depleted morphologic features	
Present	29 (64)
Absent	16 (36)
Tissue eosinophils	
Present	32 (71)
Absent	13 (29)
Granulomas	
Present	9 (20)
Absent	36 (80)
Necrosis	
Present	16 (36)
Absent	29 (64)
Syncytia	
Present	3 (7)
Absent	42 (93)
Plasma cells	
Increased	40 (89)
Decreased	5 (11)

**PCR and In Situ Hybridization Studies**

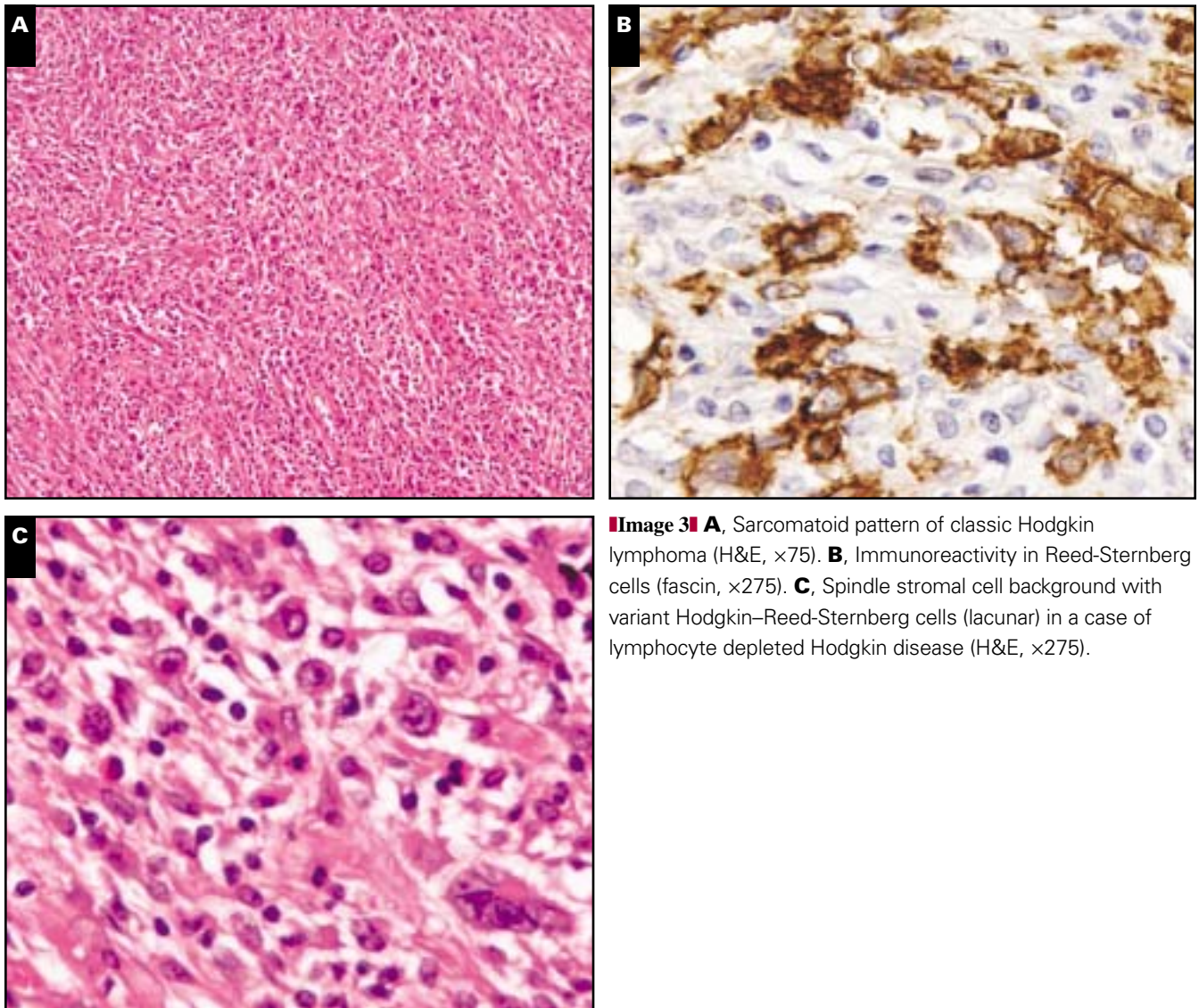
PCR testing failed to disclose any HHV-8 genomic material, while 5 of 6 cases were positive for EBV-specific messenger RNA expression.

**Treatment and Clinical Outcome**

Three patients were lost to treatment follow-up and were excluded from the treatment and clinical outcome results



**Image 2** Extranodal Hodgkin lymphoma in the lung of an HIV-positive patient. Inset, high power with mummified Reed-Sternberg variants (H&E, ×30; inset, H&E, ×150).



**Image 3** **A**, Sarcomatoid pattern of classic Hodgkin lymphoma (H&E, x75). **B**, Immunoreactivity in Reed-Sternberg cells (fascin, x275). **C**, Spindle stromal cell background with variant Hodgkin-Reed-Sternberg cells (lacunar) in a case of lymphocyte depleted Hodgkin disease (H&E, x275).

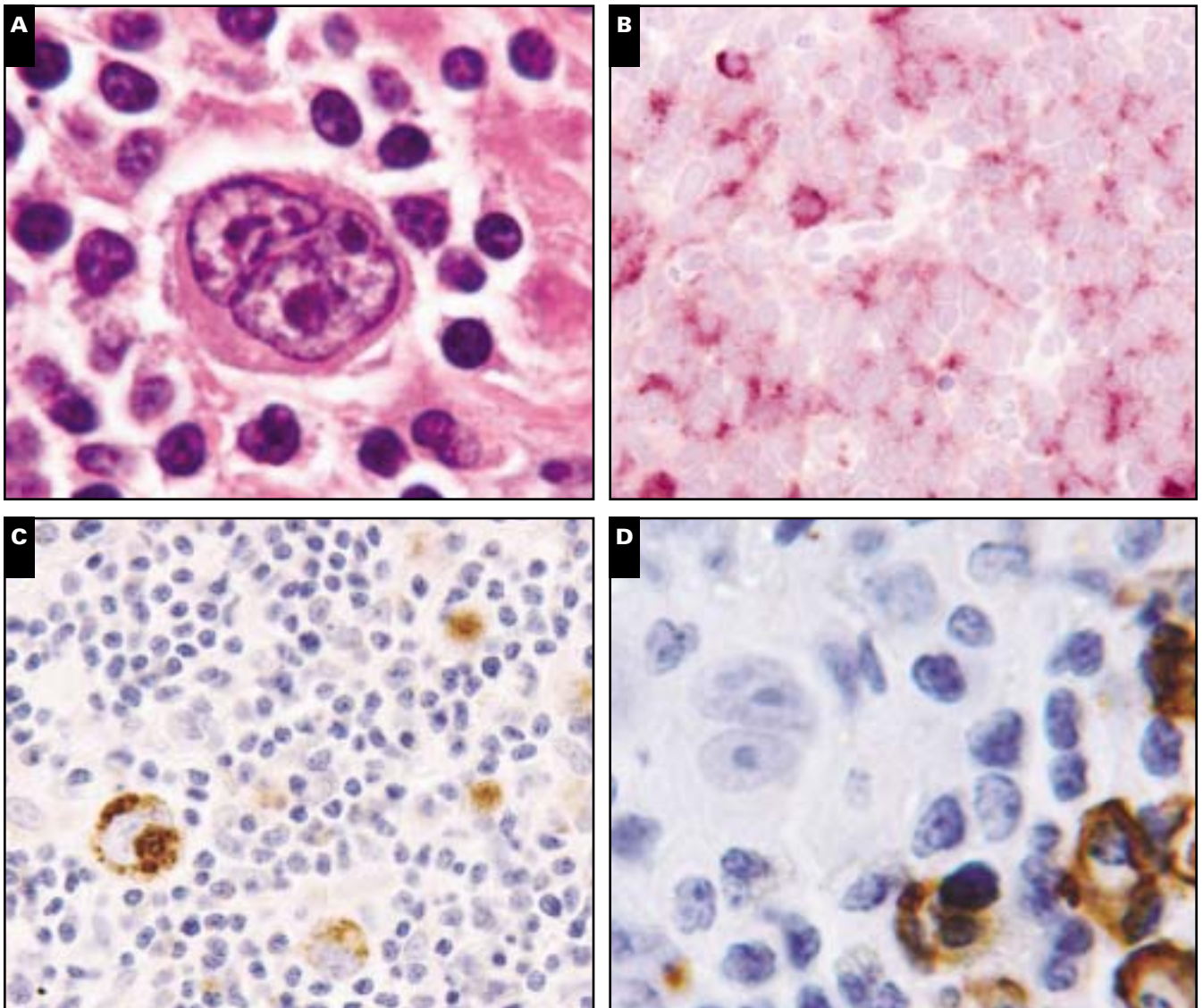
section. The majority of patients (n = 26) received anti-lymphoma chemotherapy only, while 4 patients received combined chemotherapy and radiotherapy. The remaining 12 patients received no specific postbiopsy therapy **Table 8**. In general, chemotherapy provided a prolonged disease-free survival compared with no additional therapy: chemotherapy only: 1-year survival, 77%; 3-year survival, 50%; 5-year survival, 38%; and no therapy, all 12 patients died within 1 year.

Of 42 patients, 27 (64%) died of HL and had clinicopathologic evidence of progressive high-stage disease at the time of death. The causes of death were predominantly infectious (85%; n = 23), including sepsis, pneumonia, and fungal infections. Multisystem organ failure with disseminated Hodgkin disease was a cause of death in the remaining 4 patients. Only 3 patients died of other unrelated causes without evidence of lymphoma. Twelve patients were alive at last follow-up without clinical evidence of lymphoma. It

can be inferred that these 12 and the preceding 3 patients were “cured” of their lymphoma because the mean follow-up was more than 5 years.

When separated by HL histologic subtype, the MCHL had overall better 1- and 5-year survival rates (71% and 36%, respectively) compared with other types, although only slightly: NSHL (60% and 30%, respectively), LDHL (25% and 13%, respectively), and classic (25% and 13%, respectively) **Figure 1**. In addition, the sarcomatoid type had a worse prognosis (22% and 11%, respectively) compared with nonsarcomatoid types (62% and 31%, respectively) **Figure 2**. There was no appreciable difference in overall outcome when a “depleted pattern” of background lymphocytes (1-year survival, 64%; 5-year survival, 27%) was compared with a non-depleted pattern (1-year survival, 69%; 5-year survival, 38%).

Patients with stage I, II, or III (nodal disease only) combined (because they had similar overall survival rates separately)



**Image 4** **A**, A classic Hodgkin–Reed–Sternberg (HRS) cell in a background of lymphocytes (H&E,  $\times 800$ ). **B**, Reactivity in the dendritic reticulum cells within germinal centers (p24,  $\times 300$ ). **C**, Reactivity in Reed–Sternberg cells (bcl- $X_L$ ,  $\times 300$ ). **D**, The background plasma cells are highlighted but HRS cells are nonreactive (CD138 [syndecan-1],  $\times 600$ ).

had relatively good overall survival (1-year survival, 69%; 5-year survival, 46%) compared with patients with stage IV disease (1-year survival, 44%; 5-year survival, 16%), a finding similar to stage-based survival for patients with non-HIV HL **Figure 3**. As expected, there was an association of certain types of HIV-HL with stage at initial diagnosis and specific histologic features **Table 9**. LDHL and classic HL and sarcomatoid patterns tended to manifest at higher stages.

## Discussion and Conclusions

HL is not a neoplasm that is considered by the CDC to be an AIDS-defining illness,<sup>11,37</sup> although KS, diffuse aggressive B-cell lymphoma, and invasive cervical carcinoma<sup>11</sup> are

considered AIDS defining. It is interesting that each of these neoplasms is associated with a potentially tumorigenic virus: HHV-8/KSHV, EBV, and human papillomavirus, respectively. Nearly all cases tested (32/33 [97%]) in this clinical series showed HRS cell reactivity for LMP-1, confirming EBV association with this tumor. In fact, EBV LMP-1 positivity has been well established in HIV-HL and might be lymphomagenic in this setting.<sup>45,46</sup> The absence of HHV-8 and the presence of EBV genetic material shown by PCR and in situ hybridization studies, in this series and in the literature,<sup>11,42,45,46</sup> demonstrate the viral etiologic associations of this disease. These findings probably reflect the depleted CD4 cell counts and relative cellular immunodeficiency of these patients. This study underscores the important association between HL

**Table 7**  
**Immunohistochemical Findings in 45 Cases of HIV-Associated Hodgkin Lymphoma**

Antibody	No. Positive/No. Tested (%)
CD30	35/37 (95)
CD15	32/36 (89)
Fascin	30/30 (100)
bcl-2	15/29 (52)
CD20	4/34 (12)
CD45RB	0/37 (0)
bcl-6	3/28 (11)
bcl-X <sub>L</sub>	25/31 (81)
EBV latent membrane protein	32/33 (97)
CD138 (syndecan-1)	0/26 (0)
CD3*	0/31 (0)
CD4 (decreased)	26/26 (100)
CD8 (increased)	26/26 (100)
Epithelial membrane antigen	0/22 (0)
Anaplastic lymphoma kinase-1	0/21 (0)
p24	5/29 (17)

EBV, Epstein-Barr virus.

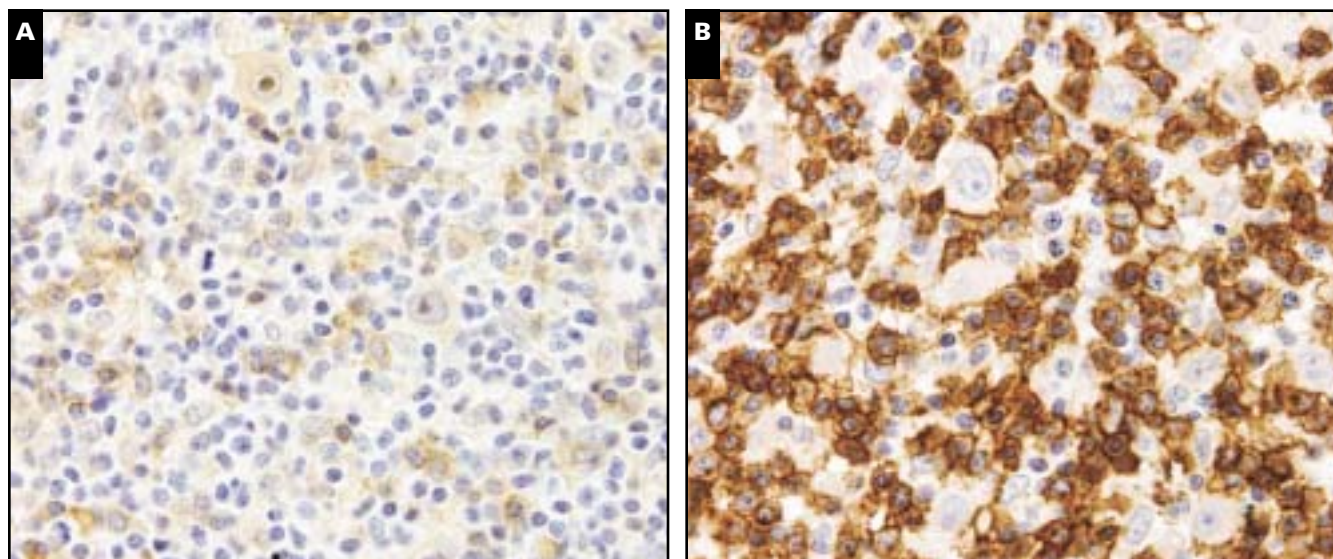
\* This result is interpreted for the Hodgkin-Reed-Sternberg cells only.

and AIDS, defining a number of the more important clinicopathologic and morphologic features of this lymphoma.

Epidemiologically, almost all patients in this clinical series were men, and approximately half of them had acquired HIV through sexual contact. This finding differs from other reports that suggest an increase in HIV-infected patients who are intravenous drug abusers. Perhaps this is a demographic difference between patients in the United States and those from Europe. Most patients were infected with HIV during the fourth decade and developed HL within the same decade, usually an average of 5 years from the date of HIV diagnosis. This substantial interval between the diagnosis of

HIV and HIV-HL corresponds to a relatively late stage of HIV infection with the clinical manifestations of AIDS, coupled with a notably low CD4 cell count by flow cytometry (mean, 154/ $\mu$ L [ $154 \times 10^6$ /L]). At diagnosis, most patients had lymphadenopathy, usually cervical, with lymph nodes measuring a mean of 3 cm. Interestingly, HIV-HL seems to involve peripheral lymph nodes more frequently than central lymph nodes. Furthermore, the majority of patients had pathologic stage IV (extranodal) disease at diagnosis. Whereas the treatment parameters could not be assessed completely at a tertiary referral center, chemotherapy was the preferred treatment for the lymphoma, although many patients (27/42 [64%]) died of disease a mean of 1.1 years after diagnosis, usually secondary to a complicating infection.

The morphologic classification of HIV-HL might be somewhat difficult. Almost two thirds of cases demonstrate depletion of the background lymphocytes corresponding to a low clinical CD4 cell count, further corroborated by an inverted CD4/CD8 ratio shown by immunoperoxidase staining. Interestingly, the inversion of the CD4/CD8 ratio seemed to be a better predictor of HIV infection in HIV-HL than was p24 immunoreactivity, which was present in only 5 (17%) of 29 cases tested in this clinical study. Prominent stromal sclerosis or spindle cell proliferation, tumor necrosis, increased histiocytes or granulomas, and polytypic plasmacytosis often are noted, in addition to extracapsular and/or extranodal extension. About 25% of cases had a sarcomatoid pattern composed of a spindled myofibroblastic proliferation. Since most of the patients with a depleted background and sarcomatoid pattern also had high-stage disease, we do not know whether the relative lymphocyte depletion and



**Image 5** Reversed CD4 (**A**) to CD8 (**B**) ratio in background lymphocytes in HIV-related Hodgkin lymphoma (**A**, CD4,  $\times 300$ ; **B**, CD8,  $\times 300$ ).

**Table 8**  
Patient Treatment and Outcome in 45 Cases of HIV-Associated Hodgkin Lymphoma\*

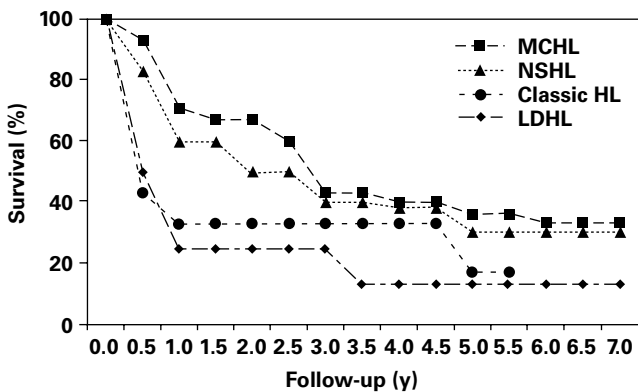
	No. of Cases	No Evidence of Disease		With Disease
		Alive	Died	Died
Overall outcome	42 (2.7)	12 (5.9)	3 (3.9)	27 (1.1)
Treatment <sup>†</sup>				
Chemotherapy only	26 (3.7)	10 (6.4)	2 (4.7)	14 (1.7)
Chemotherapy and radiation therapy	4 (3.1)	2 (2.6)	1 (2.1)	1 (3.6)
No additional therapy	12 (0.2)	0	0	12 (0.2)
Hodgkin lymphoma subtype				
Mixed cellularity	15 (4.0)	5 (7.6)	3 (3.9)	7 (1.4)
Nodular sclerosis <sup>†</sup>	12 (2.4)	4 (4.0)	0	8 (1.7)
Lymphocyte depleted <sup>†</sup>	8 (1.8)	1 (9.8)	0	7 (0.7)
Classic	7 (1.2)	2 (3.2)	0	5 (0.3)
Tumor stage				
I <sup>†</sup>	1 (2.9)	0	0	1 (2.9)
II	11 (3.8)	5 (5.7)	1 (3.5)	5 (1.9)
III	3 (4.4)	2 (6.4)	0	1 (0.6)
IV	27 (2.0)	5 (5.8)	2 (4.1)	20 (0.8)

\* Data are given as number of patients (mean years of follow-up).

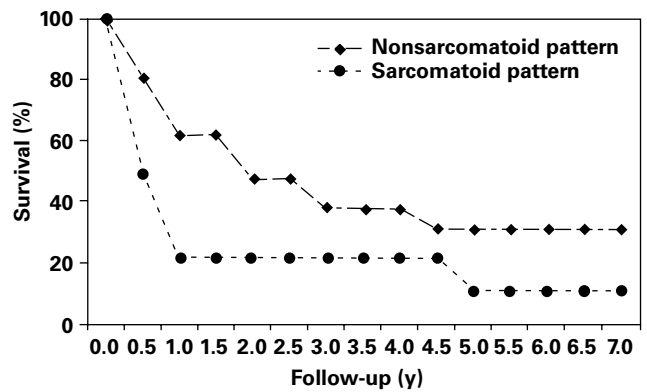
<sup>†</sup> Three patients were lost to follow-up; therefore, the numbers do not equal those of the stage and histologic type given elsewhere.

sarcomatoid growth independently predict a more aggressive disease course and poor patient outcome. Further analysis of a greater number of patients would be needed to more fully elucidate the nature of these parameters. Despite these morphologic difficulties, almost two thirds of the 45 HL cases could be classified by the 2001 WHO criteria<sup>38</sup> as MCHL (15 [33%]) or NSHL (14 [31%]), with the remaining cases considered LDHL (9 [20%]) or classic HL, not further classifiable (7 [16%]). These latter cases represented extra-nodal sites of involvement (stage IV<sub>E</sub> disease), in which a single biopsy does not always permit accurate categorization by the 2001 WHO criteria.

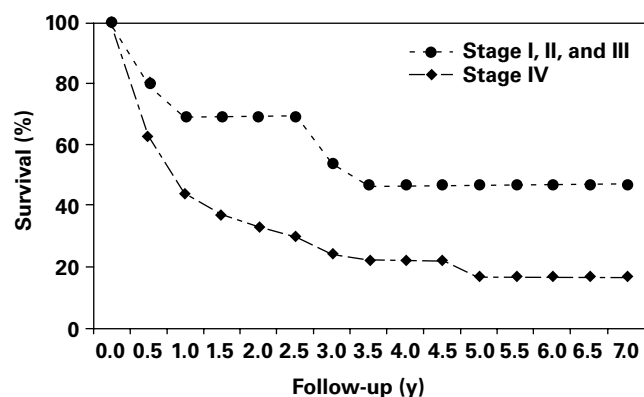
The HRS cells in HIV-HL typed characteristically: immunoreactive with CD15 and CD30 and nonreactive with CD45RB. They typically expressed fascin, bcl-X<sub>L</sub>, bcl-2, and EBV LMP-1. None of the cases were immunoreactive for CD138/syndecan-1, in sharp contrast with findings in other studies,<sup>37,47</sup> although we confirmed the predominantly bcl-6–negative phenotype of the neoplastic HRS cells reported by these same authors. As a control set, we found the neoplastic HRS cells to be negative for CD138/syndecan-1 in 50 of 52 non-HIV classic HL cases. However, all 14 nodular lymphocyte predominance Hodgkin lymphoma cases were positive in the HRS cells.



**Figure 1** Outcome by Hodgkin type in 45 cases of HIV-associated Hodgkin lymphoma. Classic HL, classic Hodgkin lymphoma, not otherwise specified; HL, Hodgkin lymphoma; LDHL, lymphocyte depleted HL; MCHL, mixed cellularity HL; NSHL, nodular sclerosis HL.



**Figure 2** Outcome by sarcomatoid pattern in 45 cases of HIV-associated Hodgkin lymphoma.



**Figure 3** Outcome by stage in 45 cases of HIV-associated Hodgkin lymphoma.

**Table 9**  
Morphologic Pattern vs Hodgkin Lymphoma Stage\*

WHO Type or Pattern	No. of Cases	Stage I-III	Stage IV
Mixed cellularity	15	8 (53)	7 (47)
Nodular sclerosis	12	6 (50)	6 (50)
Lymphocyte depleted	8	2 (25)	6 (75)
Classic	7	0 (0)	7 (100)
Sarcomatoid pattern	9	2 (22)	7 (78)

WHO, World Health Organization.

\* Data are given as number (percentage). Only patients with clinical follow-up for staging are included in the table.

Syndecan-1 (CD138) is an 85- to 92-kd, type I integral membrane proteoglycan that contains chondroitin sulfate and heparin sulfate groups and is an extracellular matrix receptor that permits epithelial organization.<sup>48,49</sup> The significance of the lack of staining for CD138/syndecan-1 with respect to the postulated post-germinal center derivation of HRS cells in HIV-HL is not clear,<sup>37,47</sup> especially since other authors have postulated a germinal center cell or a post-germinal center memory cell as the origin for the HRS cell of non-HIV classic HL.<sup>50-52</sup> Furthermore, by using a control set of 60 additional non-HIV-HL cases (46 classic HL and 14 nodular lymphocyte predominance HL), we were unable to identify any CD138/syndecan-1-positive HRS cells. Therefore, we posit that the HRS cells of HIV-HL are derived from B cells equivalent to those of non-HIV-HL based on the immunophenotypic data presented herein. Despite this support, we believe it would be prudent to confirm this postulation by additional immunoperoxidase studies or genotypic studies on microdissected HRS cells to evaluate for somatic mutations of the immunoglobulin heavy chain variable region, which will adequately determine the true immunophenotype, genotypic status, and stage of B-cell maturation of the HRS cells in HIV-HL.

bcl-X<sub>L</sub> is a protein belonging to the bcl-2 family of proteins involved in the regulation of cellular apoptosis.

bcl-X<sub>L</sub> (25/31 [81%] of cases) and bcl-2 (15/29 [52%]) reactivity in the HRS cells suggests that an antiapoptotic pathway of cellular protein expression is present, effectively immortalizing neoplastic HRS cells.<sup>53,54</sup>

Finally, fascin, an actin-binding and actin-bundling protein expressed by follicular dendritic cells in the setting of reactive follicular hyperplasia,<sup>53,55-57</sup> was expressed by the neoplastic HRS cells in all HIV-HL cases. The significance of this overwhelming reactivity is not clear. Even though it has been hypothesized that a small subset of HL cases contain HRS cells that might be derived from follicular dendritic cells,<sup>56</sup> we believe the vast majority are derived from neoplastic B-cell clones, as described earlier. This finding remains to be further elucidated by additional studies.

In this clinical series, HL seemed to develop predominantly in HIV-infected men in the later stages of AIDS, especially when the CD4 cell counts were low. At diagnosis, patients tended to have high-stage disease and an increased frequency of depleted and sarcomatoid morphologic features, which tended to yield an overall poor clinical outcome. The immunophenotype of HIV-HL, specifically the HRS cells, is similar to that of the morphologic variants of HL in patients without HIV infection, although the finding of nonreactivity with CD138/syndecan-1 is unique and requires further confirmation.

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