Lymphoid Proliferations Associated With Human Immunodeficiency Virus Infection

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Context.—Individuals who are immune deficient are at an increased risk for developing lymphoproliferative lesions and lymphomas. Human immunodeficiency virus (HIV) infection is 1 of 4 clinical settings associated with immunodeficiency recognized by the World Health Organization (WHO) in which there is an increased incidence of lymphoma and other lymphoproliferative disorders.

Objectives.—To describe the major categories of benign lymphoid proliferations, including progressive HIV-related lymphadenopathy, benign lymphoid cystic lesions, and multicentric Castleman disease, as well as the different types of HIV-related lymphomas as defined by the WHO. The characteristic morphologic, immunophenotypic, and genetic features of the different entities will be discussed in addition to some of the pathogenetic mechanisms.

Data Sources.—The WHO classification of tumors of hematopoietic and lymphoid tissues (2001 and 2008), published literature from PubMed (National Library of Medicine), published textbooks, and primary material from the authors' current and previous institutions.

Conclusions.—HIV infection represents one of the clinical settings recognized by the WHO in which immunodeficiency-related lymphoproliferative disorders may arise. Although most lymphomas that arise in patients with HIV infection are diffuse, aggressive B-cell lesions, other lesions, which are “benign” lymphoid proliferations, may also be associated with significant clinical consequences. These lymphoproliferations, like many other immunodeficiency-associated lymphoproliferative disorders, are often difficult to classify. Studies of HIV-associated lymphoid proliferations will continue to increase our understanding of both the immune system and lymphomagenesis.

count and clinical stage of disease. Furthermore, these morphologic patterns are a consequence of HIV-infection pathobiology. Florid follicular hyperplasia, the initial morphologic seen in progressive HIV-related benign lymphadenopathy, is characterized by large, irregularly shaped geographic follicles, covering up to two-thirds of the cross-sectional area of the lymph node, surrounded by an attenuated to absent mantle cell zones (Figure 1). The follicles are composed of a mixed cell population, however, centroblasts are usually the predominant cell type. The germinal centers often have a starry-sky appearance because of the relatively numerous tingible-body macrophages and mitotic figures present. In some instances, the follicles are fragmented by infiltrating small lymphocytes, a phenomenon termed follicle lysis or follicular fragmentation. Follicle lysis, in combination with effacement of the mantle cell zone, can obscure the normal lymph node architecture, which in light of the many centroblasts, can lead to confusion with malignant lymphoma. The interfollicular area of FFH lymph nodes is composed of a mixed cell population. Usually, prominent, sinusoid monocyte-B-cell hyperplasia is present; neutrophils are often also seen within the sinuses. Immunostaining shows variable disruption of the CD21 follicular dendritic cell (FDC) meshworks as well as p24 HIV viral particles present on the FDC processes. Many CD8 T cells, which are rare or absent in the germinal centers of individuals without HIV, are seen in the FFH germinal centers, sometimes in clusters in the "holes" of the CD21 FDC meshworks. The B cells in the follicles exhibit a high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. The CD4:CD8 ratio in the interfollicular area may be high proliferation rate based on Ki-67 but are negative for BCL2. 

Mixed follicular hyperplasia and follicular involution show features of both FFH and FI. However, in MX, the size of the interfollicular area is relatively larger than that in FFH, whereas the follicles and interfollicular area are more cellular than they are in FI. Furthermore, in most patients with MX and FI, the involved follicles does not exceed 50%. 

The follicles in lymph nodes classified as FI are small, atrophic, and hypocellular (Figure 2). The germinal centers consist primarily of hyalized, epithelialized, follicular dendritic cell meshworks associated with only a few germinal center B cells. Hyalized blood vessels penetrate the involuted follicles, often at right angles. Some, but not all, of the germinal centers are surrounded by mantle cell zones. Occasionally, extracellular, hyalized eosinophilic material is seen in association with the germinal centers. The interfollicular area is usually expanded, but may have a "washed-out" appearance because there are relatively few lymphocytes and relatively many histiocytes and polypycylic plasma cells. In addition, the vascular structures are often prominent and may be hyalized. Immunophenotypically, the follicle remnants consist of a few CD21 FDCs and a few B cells. In the interfollicular area, there are fewer CD3 T cells, relatively fewer CD4 T cells, with increased or normal numbers of CD8 T cells. Furthermore, the density of p24 viral particles is less than that seen in the earlier stages.

Lymphocyte depletion is characterized by a loss of germinal centers and a paucity of lymphocytes. These lymph nodes are composed predominately of medullary cords and sinoids. The interfollicular area contains primarily histiocytes, plasma cells, and a few immunoblasts with only a very few lymphocytes. Focal hyaline deposits may be seen in the sites of the degenerated follicles; in addition, subcapsular and sinusoidal fibrosis may be present. With immunostaining, virtually no FDCs are present. Most of the remaining T cells are CD8; CD4 cells are almost completely absent, whereas B cells and polytypic plasma cells are usually present. However, the number of lymphoid cells identified by immunostaining varies partially because of the degree of lymph node fibrosis. 

The progressive stages of HIV-related benign lymphadenopathy (FFH → MX → FI → lymphocyte depletion) correlate with the immune status of the patient and parallel the progressive loss of CD4 T cells, increasing viral load, and collapse of the immune system. These temporal stages are associated with progressive loss of follicles because of the destruction of the FDC meshworks. The FDC meshworks, which trap HIV in the form of immune complexes, are the major reservoir of HIV during clinical latency. With the FFH and MX patterns, there are sufficient FDCs to effectively quarantine HIV, thereby the infected patient can be maintained with a low peripheral blood viral load and a relatively high CD4 count. The atrophic or absent follicles in FI and lymphocyte depletion, due to degeneration and death of the FDCs, results in a decreased capacity to trap virus, leading to the clinical progression of HIV disease. During these stages of progressive lymphadenopathy, the immune system collapses and the patients develop opportunistic infections and die. Although the FDC meshworks are nearly destroyed after prolonged, untreated HIV infection, HAART can slowly reverse this destructive pathologic process during a period of months to several years, returning the number of FDCs to the level of that in the lymph nodes of people without HIV, even with infectious virus present. Furthermore, there may be a reversal of lymph node morphology to an earlier stage with fewer CD8 T cells in the germinal centers. The mechanism of this regeneration and reversion to a more normal state is not clear; however, genetic microarray studies comparing pre-HAART and 1-month post-HAART lymph node tissues demonstrated differences in expression in a number of genes involved in trafficking, active follicle reformation, and tissue repair. Furthermore, HAART decreases the amount of virus in the lymphoid tissue, thereby presumably, decreasing the rate of FDC destruction. In spite of these changes with HAART, the lymph node morphology is still often abnormal.

**BENIGN LYMPHOEPITHELIAL CYSTIC LESIONS**

Salivary gland enlargement associated with a significant lymphoid infiltrate was recognized early in the HIV epidemic. Because the lymphoid tissue usually exhibits morphologic and immunophenotypic features similar to those seen in FFH and the lesions often occur in association with enlarged lymph nodes, benign lymphoepithelial cystic lesions are thought to represent a manifestation of persistent, generalized lymphadenopathy. Known by several names, including benign lymphoepithelial lesion, benign lymphoepithelial cyst, cystic lymphoid hyperplasia, and HIV-related salivary gland disease, this lesion most commonly arises in the parotid gland where it is thought to occur in 3% to 6% of adults and 1% to 10% of children infected with HIV. Overall, benign lymphoepithelial cystic lesions...
Figure 1. Florid follicular hyperplasia (FFH): In FFH, the germinal centers appear large and geographic and usually show a “starry sky” pattern because of the numerous tingible-body macrophages. In some instances, evidence of follicle lysis (white arrows) is seen. The mantle cell zones are attenuated and focally absent (black arrows) (hematoxylin–eosin, original magnification ×4).

Figure 2. Follicular involution (FI): Follicular involution is characterized by small, hypocellular follicles and hyalinized follicular dendritic cells. Note the hyalinized vessel entering at a right angle (hematoxylin-eosin, original magnification ×20).

Figure 3. KSHV/HHV8-associated multicentric Castleman disease (MCD): Many plasmablasts (black arrows) are present in the mantle cell zone in this case from a patient with HIV, who died a few months following this lymph node biopsy. The plasmablasts are medium to large with relatively abundant amphophilic cytoplasm and large vesicular nuclei with one or more nucleoli (inset). The interfollicular area shows prominent vasculature (white arrows) (hematoxylin-eosin, original magnifications ×10 and ×60 [inset]).

Figure 4. Classical Hodgkin lymphoma (cHL): Morphologically, as seen in cHL in immunocompetent patients, Reed-Sternberg cells are present associated with a mixed inflammatory cell infiltrate (hematoxylin-eosin, original magnification ×20).
account for approximately 25% of enlarged salivary glands in the HIV+ patient population. Imaging reveals that the lesions are often cystic, bilateral, and multiple and are associated with lymphadenopathy. Morphologically benign lymphoepithelial cystic lesions are characterized by epithelial-lined cysts, often with squamous metaplasia, follicular hyperplasia, glandular atrophy, and in some cases, epimyoepithelial islands. In many patients, treatment with HAART results in smaller lesions or their complete resolution.

**MULTICENTRIC CASTLEMAN DISEASE**

Early in the AIDS epidemic, young, homosexual men and other people with HIV, many of whom had systemic symptoms and lymphadenopathy, had lymph node biopsies that showed features of Castleman disease. Furthermore, like HIV+ patients with MCD, many of the HIV+ patients also had or developed Kaposi sarcoma. Because of these associations, MCD lesions were examined for KSHV/HHV8 soon after its discovery. The virus was found to be present in almost all of the HIV+ and about one-half of the HIV- cases. Furthermore, most HIV+ cases showed the MCD-plasma cell–type morphology.

The HIV-related cases of MCD morphologically show features similar to the HIV+ cases or to the MX and F1 stages of HIV-related benign lymphadenopathy. However, in HIV-related MCD, the follicles may be more hyalinized, the vascular proliferation more prominent, and more plasma cells may be seen in the interfollicular area. Furthermore, the mantle-cell zone contains a variable number of cells with relatively abundant amorphophilic cytoplasm and large vesicular nuclei with one or more nucleoli, which resemble immunoblasts (Figure 3). These cells, called plasmablasts or plasmablastic cells, are the KSHV/HHV8-infected B cells, which can be identified by immunostaining for the KSHV-associated protein, latent nuclear antigen-1 (LNA-1 or LANA).

Immunophenotypically, the plasmablastic cells lack or only weakly express B-cell–associated antigens, such as CD20 and CD79a, but are positive for IRF4/MUM1, PRDM1/BLIMP1, and OCT2. The cells are negative for CD138 and CD38 and also lack evidence of infection by the Epstein-Barr virus (EBV). The plasma cells and lymphocytes in MCD lymph nodes are polytypic; however, nearly all the plasmablastic cells express cytoplasmic immunoglobulin (Ig) M. Although the KSHV/HHV8-infected plasmablastic cells are monotypic, polynemer chain reaction analysis shows that they are polyclonal B cells.

Patients with HIV and MCD often present with fever and other constitutional symptoms, lymphadenopathy, and cytopenias. At least some of these signs and symptoms are thought to be related to viral interleukin-6, produced by KSHV/HHV8-infected plasmablastic cells, as identified by immunostaining. Viral interleukin-6, which has both autocrine and paracrine effects, including inducing human interleukin-6 production, activates all known human interleukin-6 signaling pathways, thereby inducing many of the latter’s biologic activities. Furthermore, patient symptoms correlate with serum viral interleukin-6/human interleukin-6 levels and KSHV/HHV8 viral loads, whereas treatment with anti–interleukin-6 receptor antibodies decreases symptoms, further suggesting a pathogenic role for this cytokine in MCD.

The incidence of MCD in the HIV+ population has increased in the post-HAART era with the highest risk seen in older patients with HIV, with a nadir CD4 count greater than 200/μL and no prior HAART therapy. The risk of developing lymphoma for patients with HIV MCD is about 15 times higher than it is for the general HIV+ patient population. The survival of patients with HIV MCD who develop lymphoma is poor.

**LYMPHOMAS ASSOCIATED WITH HIV INFECTION**

Most HIV-related lymphomas and lymphoma-like lymphoproliferative disorders are aggressive B-cell proliferations that can be subcategorized as those occurring (1) in immunocompetent patients (most cases), (2) more specifically in HIV+ patients (approximately 5% of cases), and (3) in other immunodeficiency states (<5% of cases). Although the incidence of non-Hodgkin lymphoma in HIV+ individuals remains approximately 70 to 80 times greater than that of the general population, the epidemiology of these neoplasms has changed with the institution of HAART. Although HIV-related non-Hodgkin lymphomas now accounts for most AIDS-defining cancer events, the overall incidence of them has decreased, whereas the incidence of HIV-related CHL has increased. Furthermore, evaluation of lymphomas diagnosed between 1996 and 2000, compared with those diagnosed in 2001–2007, shows that the proportion of HIV-related diffuse large B-cell lymphomas (DLBCLs) compared with all DLBCLs, has decreased, whereas the proportion of HIV-related Burkitt lymphomas (BLs) has increased.

**Lymphomas Also Occurring in Immunocompetent Patients**

The main entities in this category of lymphomas also occurring in immunocompetent patients are BL (approximately 30% of HIV-related lymphomas), DLBCL (approximately 40%), and CHL (approximately 5%–15%). These neoplastic entities account for most of the HIV-related lymphomas, although only the first 2 entities are AIDS-defining diseases. Other types of lymphoma, including marginal zone lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, peripheral T-cell lymphoma, follicular lymphoma, natural killer cell lymphoma, and lymphoblastic leukemia/lymphoma, which occur in HIV-
Patients with HIV-related and cHL tend to have more-aggressive disease than do their immunocompetent counterparts, although the use of HAART, in addition to chemotherapy, has improved survival. However, HAART has also probably increased the incidence of HIV-related cHL. In the United States, except for the lymphocyte-depletion subtype, the incidence of cHL is highest in HIV-positive patients with an intermediate (225–249 CD4 cells/µL) CD4 count. 88,95

Burkitt Lymphoma.—Similar to cHL in the United States, BL tends to occur more frequently in patients with intermediate to high CD4 counts, with the highest crude incidence rate in patients with a CD4 count greater than 250/µL and the lowest in patients with a CD4 count less than 50/µL. 89 Morphologically many lesions occurring in HIV-positive patients resemble cases of BL occurring in HIV-negative patients (Figure 5, A). Some HIV-related BLs, however, are “plasmacytoid,” consisting of medium-sized cells with relatively abundant cytoplasm, eccentric nuclei, and central prominent nucleoli. These plasmacytoid BLs are more often EBV+ and usually express cytoplasmic immunoglobulin. Similar to BL in immunocompetent patients, HIV-related BLs are positive for pan-B-cell antigens, CD10, and BCL6, but are negative for BCL2. Nearly all cells are Ki-67+, indicating a very high proliferation rate (Figure 5, B). 2,100–102

Variations of this classic immunophenotypic profile, however, can be seen in HIV-related BL cases. 103

Almost all HIV-related BL cases contain a MYC rearrangement. Many cases also contain TP53 mutations, and some cases have mutations in RAS and/or BCL6 genes. 104–107 Recent genetic-expression profiling studies suggest that silencing of BCL2, a tumor suppressor gene, in conjunction with MYC overexpression, may be important in the development of BL. In HIV-infected patients, HIV may also contribute to the development of BL because the HIV Tat viral protein can physically interact with the BCL2/p130 gene product, potentially inhibiting its tumor-suppressor function. 108–110 In addition, studies of primarily HIV-BL cases suggest that microRNAs may be involved in the pathogenesis of at least some of the MYC and/or EBV+ BLs. 111–114 Because approximately 30% of all HIV BLs, and even more of the HIV-related BL cases showing plasmacytoid differentiation, are EBV+, microRNAs may also be important in the pathogenesis of the HIV-related BL.

Although with the advent of HAART, intensive therapy is now possible for treating HIV-related BL, an optimal treatment approach has yet to be defined. However, based on current clinical trial data, an 85% 1-year overall survival rate for patients with HIV and BL is possible. 115,116

Diffuse Large B-Cell Lymphoma.—Diffuse large B-cell lymphoma is the most common type of lymphoma in HIV+ individuals. 2,88 Most HIV-related DLBCLs are composed of centroblasts, usually admixed with a small but variable number of immunoblasts (Figure 6), and are variably EBV+, whereas fewer cases, which are usually EBV–, consist primarily of immunoblasts and are often EBV+ (Figure 7). 2 Most HIV-related DLBCLs are systemic, occurring in lymph nodes or extranodal sites, including the gastrointestinal tract and oral cavity. 96,104,105,117 However, many cases also occur primarily in the central nervous system (CNS; ie, primary CNS lymphomas; see below).

The HIV-related DLBCLs are characterized at the genetic level by clonal rearrangements of the immunoglobulin genes. Structural alterations involving oncogenes and tumor suppressor genes may occur, most frequently involving MYC and BCL6. In addition, TP53 mutations can be present and tend to occur in cases that contain MYC alterations. 104–106,118–121 Most (>90%) of the HIV-related DLBCLs contain somatic hypermutations in the immunoglobulin genes. In addition, approximately two-thirds of HIV-DLBCLs have BCL6 mutations, and about 50% of cases have aberrant somatic hypermutations in other proto-oncogenes, such as PIM1, PAX5, RhoHTTF, and MYC, all of which may contribute to the development of these neoplasms. 106,107,121,122 In addition, comparison of EBV+ and EBV– HIV-related DLBCLs shows that the EBV+ cases have fewer gene copy number changes, indicating that this virus may play a pathogenetic role in EBV+ cases. 123,124

Diffuse large B-cell lymphomas in immunocompetent patients, as determined by gene expression profiling and by immunophenotypic expression patterns, can be divided into clinically relevant groups: germinal center and activated B cellertype 3 (nongerminal center) which are composed of approximately equal numbers of cases in each category. In contrast, using the criteria of Hans et al, HIV-related DLBCLs are more frequently of germinal center origin than those arising in HIV+ individuals. 125–131 However, it is not clear whether classification of HIV DLBCLs as having germinal center or nongerminal center origins or expression
of specific markers, which are associated with disease behavior in patients with HIV, correlate with the outcome in the HIV\(^+\) patient population. Not unexpectedly, the CD4 count does predict outcome with distinct differences in survival between the HIV\(^+\) patients with less than 100 and those with more than 100 CD4\(^+\) cells/μL.\(^{125,126,132–135}\)

Although considered in the category of DLBCL, primary CNS lymphoma in HIV-infected patients is a relatively unique clinicopathologic entity. Most of these cases occur in patients who are severely immunosuppressed, with more than 90% of patients presenting with a CD4 count of less than 200/μL and approximately 60% to 70% of those patients having a CD4 of less than 50/μL.\(^{136}\) Most primary CNS lymphomas exhibit immunoblastic features. Usually the neoplastic cells are EBV\(^+\), and many express the EBV latency II gene product, latent membrane protein 1 (LMP1), suggesting that they are EBV driven.\(^{98,136–138}\) Furthermore, HIV-related, primary CNS lymphoma is aggressive with a median overall survival for those treated aggressively with both chemotherapy and whole brain radiation of only 3.4 months.\(^{136}\)

**Lymphomas Occurring More Specifically in HIV\(^+\) Patients**

The neoplasms in this category of HIV-related lymphoma are highly associated with infection by EBV, KSHV/HHV8, or both. These lesions and their associated herpesviruses include plasmablastic lymphoma, which is often EBV\(^+\); large B-cell lymphoma arising in HHV8-associated MCD, a KSHV\(^+\)/HHV8\(^+\) neoplasm; and primary effusion lymphoma (PEL)/extracavitary PEL (EC-PEL), which are usually positive for both EBV and KSHV/HHV8.\(^2\) Although these lesions preferentially occur in HIV\(^+\) individuals, they all can occasionally occur in HIV\(^-\) patients as well.

**Plasmablastic Lymphoma.**—The HIV-related plasmablastic lymphomas characteristically arise in the oral cavity (60% of cases); however, they can also occur in other mucosal sites, such as the sinonasal cavity and the gastrointestinal tract, and in nonmucosal sites, such as the skin, soft tissue, and lymph nodes.\(^{139–143}\) Plasmablastic lymphomas exhibit a spectrum of morphologic features ranging from immunoblastic to markedly plasmacytic. In general, the malignant cells are medium to large with relatively round, often eccentrically placed nuclei, each containing a single prominent nucleolus, and a moderate to abundant amount of basophilic cytoplasm. Mitotic figures and apoptotic debris are also usually seen (Figure 8). Plasmablastic lymphomas have recently been subclassified into morphologic categories—monomorphic plasmablastic lymphomas and plasmablastic lymphomas with plasma cell differentiation—which appear to preferentially occur in different patient populations and anatomic sites. Lesions that occur in patients with HIV tend to be monomorphic and to arise in the oral, nasal, and paranasal areas.\(^{139,143–144}\)

Most plasmablastic lymphomas in HIV\(^+\) patients express cytoplasmic immunoglobulin, CD38, CD138, and IRF4/MUM1 and are usually negative or only weakly positive for CD45, CD20, and PAX5. Although some cases may be CD56\(^+\), expression of this antigen should raise the possibility of a plasma-cell neoplasm warranting further workup. The plasmablastic lymphomas are frequently EBV\(^+\) by in situ hybridization but are usually LMP1\(^-\). Furthermore, consistent with the number of mitotic figures seen on the routine sections, these lymphomas have a high proliferation

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**Figure 7.** Diffuse large B-cell lymphoma (DLBCL): Some cases of HIV-associated DLBCL appear more immunoblastic. Many of these lymphomas, as in this case, are EBV\(^+\) (hematoxylin–eosin, original magnification ×60).

**Figure 8.** Plasmablastic lymphoma: This case involving the rectum and anal canal was EBV\(^+\), as are most cases in patients with HIV. The neoplastic cells are medium to large in size with relatively round, often eccentrically placed nuclei, each containing a single prominent nucleolus (hematoxylin–eosin, original magnifications ×10 and ×60 [inset]).

**Figure 9.** Primary effusion lymphoma (PEL): The neoplastic cells in PEL appear large and pleomorphic. Often, Reed-Sternberg-like cells are identified (Giemsa, original magnification ×60).
rate based on Ki-67 immunostaining.\textsuperscript{139,141–146} Plasmablastic lymphomas often have an MYC translocation or an MYC copy number gain. The MYC abnormalities appear to occur preferentially in the EBV\textsuperscript{+} monomorphic cases.\textsuperscript{144,145,147} Plasmablastic lymphomas, although they may exhibit plasmacytoid differentiation, are biologically more similar to DLBCL than they are to plasma–cell myeloma, based on array comparative genomic hybridization studies.\textsuperscript{148}

Although plasmablastic lymphomas occur primarily in patients with HIV, they can arise in HIV\textsuperscript{−} individuals. However, the patients with HIV tend to be younger males with oral cavity–based EBV\textsuperscript{−} lesions. Furthermore, the HIV\textsuperscript{−} individuals with plasmablastic lymphoma appear to have a better clinical outcome than do the patients without HIV.\textsuperscript{140,143}

**KSHV/HHV8\textsuperscript{+} Large B-Cell Lymphoma Associated With MCD.**—The neoplastic cells in KSHV/HHV8\textsuperscript{+} large B-cell lymphoma associated with MCD, as the name implies, are KSHV/HHV8-infected B cells that are morphologically similar to those seen in KSHV/HHV8-associated MCD. In large B-cell lymphoma arising in HHV8-associated MCD, the plasmablastic cells form variably sized collections, ranging from small confluent clusters, known as microlymphomas, to sheets of neoplastic cells that obliterate the normal architecture. The plasmablastic process can involve not only lymph nodes but also other sites, including the spleen, liver, gastrointestinal tract, and peripheral blood.\textsuperscript{65,68,78,149}

Immunophenotypically, the neoplastic KSHV/HHV8\textsuperscript{+} plasmablastic cells are similar to the KSHV-infected cells in MCD; specifically, the neoplastic cells lack or only weakly express B-cell antigens, are CD138\textsuperscript{−}, brightly express monotypic IgM Ig−λ, and are positive for LANA (KSHV/HHV8\textsuperscript{+}) but negative for EBER (Epstein-Barr virus-encoded RNA). In addition, many of the cells are vILE\textsuperscript{+}. PCR analysis has shown that only some of the neoplastic cases, usually those with a large number of malignant cells, are monoclonal. This neoplastic process is thought to arise from naïve B cells because the immunoglobulin genes lack somatic hypermutations.\textsuperscript{65,67,78,149}

The KSHV/HHV8\textsuperscript{+} large B-cell lymphomas associated with MCD are most frequently diagnosed in patients with HIV and KSHV/HHV8-associated MCD. The patients with HIV\textsuperscript{+} MCD have a high risk of developing lymphoma, and the survival rate for those who develop large B-cell lymphoma MCD is poor. In general, patients live less than 1 year after diagnosis of large B-cell lymphoma MCD; however, in some studies, survival is less than 1 month.\textsuperscript{65,78,149}

**Primary Effusion Lymphoma/Extracavitary Primary Effusion Lymphoma.**—In 1994, Chang et al\textsuperscript{62} identified a fragment of DNA from what is now known as KSHV/HHV8 and showed that it was etiologically related to the development of Kaposi sarcoma.\textsuperscript{150} Cesarman et al\textsuperscript{151} soon found that this virus was also present in a unique type of lymphoma occurring primarily within body cavities of patients with HIV. Further characterization of these KSHV/HHV8-related PELs, showed that they are a distinct clinicopathologic entity.\textsuperscript{151,152} A solid variant without an associated effusion, EC-PEL, has also been described.\textsuperscript{153,154}

Primary effusion lymphoma and EC-PEL are rare accounting for less than 5% of HIV-related lymphomas. They usually occur in homosexual men with a low CD4 count and a previous AIDS diagnosis but can occur in other patient populations, including elderly individuals, transplant recipients, and HIV\textsuperscript{+} individuals with CD4 counts within reference range.\textsuperscript{152,153,155,156} Primary effusion lymphoma and EC-PELs are composed of large, pleomorphic neoplastic cells that sometimes appear Reed-Sternberg-like (Figure 9). Immunophenotypically, the PEL/EC-PEL cells, in general, lack B-cell–associated and T-cell–associated antigens, although a small percentage of cases may express pan–B-cell antigens, such as CD20 and CD79a, and/or immunoglobulin, usually λ light chain. In addition, the neoplastic cells lack the germinal center markers CD10 and BCL6; express activation–associated antigens, such as CD30; and are positive for markers of terminal B-cell differentiation, such as CD138, IRF4/MUM1, and PRDM1/BLIMP1. The neoplastic cells are KSHV/HHV8\textsuperscript{+}, as detected by immunostaining for LANA, and in approximately 90% of cases, are also EBV\textsuperscript{+} based on in situ hybridization with an EBER probe.\textsuperscript{68,151–154,157}

Although the neoplastic cells usually lack B-cell antigen expression, most PELs/EC-PELs have clonally rearranged immunoglobulin genes. Furthermore, the immunoglobulin genes contain somatic hypermutations. However, the neoplastic cells characteristically do not contain structural alterations in oncogenes or tumor suppressor genes. The PELs, based on gene expression profiling, exhibit an intermediate “plasmablastic” profile between that of DLBCL and plasma cells, which is distinct from non-Hodgkin lymphomas in immunocompetent patients and from other HIV-related lymphomas.\textsuperscript{*} These findings, in conjunction with antigen expression, suggest that PELs/EC-PELs arise from terminally differentiated B cells that have gone through the germinal center reaction.

Both PEL and EC-PEL are aggressive disease processes. The median survival of patients with PEL/EC-PEL from 2 relatively large series was 3 and 6.2 months, with only a small percentage of patients surviving 1 year. In one of these studies, the absence of HAART before PEL diagnosis and a performance status greater than 2 were found to be predictive of shorter survival.\textsuperscript{153,160}

**Lymphomas Occurring in Other Immunodeficient States**

The HIV polymorphic lymphoid proliferations, which resemble the polymorphic posttransplant–associated lymphoproliferative disorders seen in solid organ transplant recipients, comprise this category of HIV-related lymphomas/lymphoma-like lymphoproliferative disorders.\textsuperscript{2} The HIV polymorphic lymphoid proliferations are extremely rare and have been diagnosed in both adults and children with HIV.\textsuperscript{89,161–163} These lesions are composed of a mixture of cells, including lymphocytes, plasmacytoid lymphocytes, plasma cells, epithelioid histiocytes, and immunoblasts, which exhibit variable degrees of cytologic atypia. Foci of coagulative necrosis can also be seen. Most lesions are EBV\textsuperscript{+},\textsuperscript{89,161–164} Many cases are monoclonal, based on genetic studies, but structural alterations in oncogenes and tumor suppressor genes are generally rare.\textsuperscript{163} Although clinical outcome information is limited, at least one patient experienced regression of their polymorphic lymphoid lesion following antiviral therapy.\textsuperscript{164}

**SUMMARY**

Human immunodeficiency virus infection represents one of the clinical settings recognized by the WHO in which immunodeficiency-related lymphoproliferative disorders

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\textsuperscript{*References 122, 151, 153, 154, 158, 159.}
may arise. Although most lymphomas that arise in patients infected with HIV are diffuse aggressive B-cell lesions, other lesions, which are ‘benign’ lymphoid proliferations, may be associated with significant clinical consequences. These latter lesions can be difficult to separate either clinically and pathologically from malignant proliferations. However, the lymphoproliferations arising in the setting of HIV, although often unique, have led to greater understanding of the immune system and lymphomagenesis.

References


I. Introduction

1. Kaposi's sarcoma

2. Multicentric Castleman's disease

3. Plasmablastic lymphoma

II. HHV-8 and Its Association with Lymphoproliferative Disorders

1. HHV-8 and Kaposi's Sarcoma

2. HHV-8 and Multicentric Castleman's Disease

3. HHV-8 and Plasmablastic Lymphoma

III. HHV-8 and Multicentric Castleman's Disease

1. HHV-8 and Kaposi's Sarcoma

2. HHV-8 and Multicentric Castleman's Disease

3. HHV-8 and Plasmablastic Lymphoma

IV. HHV-8 and Other Lymphoproliferative Disorders

1. Human Immunodeficiency Virus (HIV)-Associated Lymphomas

2. HHV-8 and Non-Hodgkin Lymphoma

V. HHV-8 and Other Pathologies

1. HHV-8 and Other Cancers

2. HHV-8 and Immunodeficiency

VI. Conclusion

References


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**CAP ’13 Abstract Program Accepting Submissions**

Abstract and case study submissions will be accepted beginning **Monday, February 4, 2013** for the College of American Pathologists (CAP) 2013 meeting. **CAP ’13 will be held October 13 through the 16th in Orlando, Florida.** Submissions for the CAP ’13 Abstract Program will be accepted through **Monday, April 1, 2013**.

Accepted submissions will appear in the October 2013 issue of the *Archives of Pathology & Laboratory Medicine*. Visit the CAP ’13 Website at www.cap.org/cap13 for a link to the abstract submission site and additional abstract program information as it becomes available.