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Pathology of lymphoma in HIV

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Abstract

Purpose of review—Individuals with HIV infection have a greatly increased risk of developing malignancies, even when HIV infection is successfully controlled with antiretrovirals. Non-Hodgkin's lymphoma is considered an AIDS-defining entity, and this disease is currently the most common type of cancer in HIV-infected individuals in the US and Europe. Here we describe the different types of lymphomas occurring in individuals with AIDS, and the most relevant pathologic features helpful for histologic and immunohistochemical diagnosis.

Recent findings—The incidence of some AIDS-related lymphoma subtypes has changed since the introduction of combined antiretroviral therapy, and some of the diagnostic methodologies have evolved. New biomarkers of disease have been identified, which may be useful for diagnosis.

Summary—Better pathological classification strategies and deeper molecular understanding of the different lymphoma subtypes that occur in people with AIDS will begin to allow the transition to more precise diagnosis and targeted treatments.

Keywords

AIDS; lymphoma; Epstein Barr virus (EBV); Kaposi's sarcoma herpesvirus (KSHV/HHV-8); Human immunodeficiency virus (HIV)

Introduction

Non-Hodgkin lymphomas (NHL) are considered an AIDS-defining condition and currently represents the most common types of cancer in individuals with HIV infection in developed countries. Kaposi's sarcoma (KS) used to be more common than NHL, and while it remains more common in sub-Saharan Africa, KS has decreased in incidence in developed countries, so that NHL now has a higher incidence than KS in this part of the world (1, 2). One recent epidemiologic study found that NHL comprises 53% of all AIDS defining cancers (1). Furthermore, NHLs have been reported to be the most common cancer-related cause of death in HIV-infected individuals in the US (36% of deaths during 1996-2006) (1). While NHL overall has been decreasing in incidence since the introduction of combined antiretroviral therapy (cART), classical Hodgkin lymphoma (CHL) has been increasing in incidence. While in the United States CHL appears to remain much less commonly reported in HIV-infected patients than NHL (2), the Swiss Cohort Study found a standardized incidence ratio (SIR) of 35 for CHL, which was higher than that of KS (SIR=25) and NHL

(SIR=24) (3). Here we will review the pathology of AIDS-related lymphomas, including NHL and CHL, providing the most up to date nomenclature and pathologic diagnostic criteria.

The pathogenesis of NHL in the context AIDS is complex and may be related to disrupted immune surveillance, viral infection, genetic alterations, chronic antigenic stimulation, and cytokine dysregulation (4-6). In terms of viral infection, the effects of HIV may be indirect, by altering immune responses, but possible direct effects through secreted viral proteins have not been ruled out (7). What is clear is that specific lymphoma subtypes are caused by one or both herpesviruses of the gamma subfamily: Epstein Barr virus (EBV/HHV-4) and Kaposi's sarcoma herpesvirus (KSHV/HHV-8). Although it has been difficult to pinpoint the specific immunological events that lead to lymphoma, several B cell stimulatory cytokines have been found to be increased in HIV-infected people prior to a diagnosis of lymphoma, in particular IL6, IL10, CRP, sCD23, sCD27, and sCD30 (8). One recent study revealed that serum levels of the CXCL13 chemokine are increased in HIV-infected individuals before a diagnosis of lymphoma, and furthermore specific alleles of CXCL13 or its receptor CXCR5 are associated with these increased CXCL13 levels, suggesting a possible genetic predisposition (9). Assessment of the serum levels of these cytokines may be used to identify patients at highest risk for NHL, and perhaps for earlier diagnosis.

AIDS-related lymphomas are almost always of B cell origin, and some distinct lymphoma types are more common. Some of these lymphoma types can occur in both HIV uninfected and infected patients, while others preferentially develop in the context of HIV or in patients with other immunodeficiencies. The latter tend to be more frequently viral associated. HIV-related lymphomas have traditionally been classified by morphology, and/or by primary site of presentation (i.e. systemic, primary central nervous system, body cavity) (6). More recently, these lymphomas have been classified according to the WHO classification as distinct disease entities based on morphology, immunophenotype and, in some instances, molecular alterations (10, 11). The distribution of these subtypes and association with EBV, as determined on analysis of 72 cases is shown in Figure 1A.

Lymphomas subtypes occurring in HIV-infected individuals

Diffuse large B cell lymphomas (DLBCL)—These lymphomas occur in both HIV-infected and uninfected individuals, but there are some differences between these two groups. In the context of HIV, DLBCLs have been divided on the basis of cellular morphology into centroblastic and immunoblastic categories. The immunoblastic type is mostly seen in people with AIDS, and is more frequently associated with EBV infection, with reported rates approaching 90%. EBV is most commonly detected in diagnostic pathology laboratories using *in situ* hybridization for EBERs (Figure 1B), which are abundantly expressed, non-coding viral RNAs. Patients with the immunoblastic variant usually have very advanced AIDS and are significantly immunosuppressed, so the frequency of this subtype has dramatically decreased with the widespread use of cART in the US and Europe. The reason why these lymphomas occur in people with more advanced immunodeficiency is that EBV within the tumors cells expresses a number of proteins, including LMP1 and EBNA2 that are oncogenic but also immunogenic, in what has been

termed a Latency III pattern (reviewed in (12)). In contrast, cases with centroblastic morphology occur in individuals with or without AIDS, and these are further subdivided into germinal center and non-germinal center subtypes in both patient populations. However, in people with AIDS, the clinical significance of this sub-classification remains controversial and may be treatment dependent (13-15). Differences in DLBCLs occurring in HIV+ patients when compared to DLBCL occurring in immunocompetent individuals include more frequent extranodal presentation, a larger proportion of the germinal center subtype and a more common association with EBV in HIV (30% vs. <5%). One recent study of 70 AIDS-related DLBCL showed that EBV positivity was independently associated with a higher 2-year overall mortality, and recommended incorporating EBV status with IPI in prognostic categorization (16), although this association has not been found in other studies (13).

A diagnosis of DLBCL can be made from biopsies based on a loss of normal tissue architecture, with infiltration of large B-cells. B-cell origin should be confirmed by immunohistochemistry for a B-cell antigen, such as PAX5 or CD20. For classification into subtypes by cell of origin, molecular approaches such as gene expression profiling are more reliable, however since this is not always available as part of routine diagnosis, surrogate immunohistochemistry can be used, as illustrated in Figure 2 (17). In the context of a lymphoma occurring in the setting of HIV, immunohistochemistry with Ki67 is also useful to evaluate the proliferation index, which can have prognostic significance; individuals with tumors with higher proliferation appear to respond better to chemotherapy (13). In addition, while many DLBCLs can have very high proliferation rates, in some instances Ki67 may help differentiate a DLBCL from a Burkitt's lymphoma.

Primary central nervous system (CNS) lymphoma is a subtype of DLBCL that is much more common in HIV-infected individuals, and is very similar to the immunoblastic variant. Tumor cells have an immunoblastic morphology, frequent EBV infection, and it has declined in incidence with cART.

Burkitt's lymphomas (BL)—This is another lymphoma type that can be present in people with or without HIV infection. Three epidemiologic subtypes are recognized (endemic, sporadic and AIDS related). BL accounts for around 14% of AIDS-related NHL and is more commonly seen with HIV infection than with other forms of immunodeficiency such as transplant recipients (12, 18). This disease typically occurs in less immunosuppressed patients with HIV, peaking at CD4 lymphocyte counts above the laboratory cutoff for AIDS onset (200 cells/ μ L) (19). In HIV-infected patients, BL may have the typical histologic features of BL, which are characterized by cohesive sheets of malignant cells which are small to intermediate-sized and contain moderately abundant basophilic cytoplasm and round, regular nuclei possessing two to five distinct nucleoli. Classical pathologic features of BL are the presence of abundant mitotic figures, and numerous, evenly distributed tingible body macrophages with abundant clear cytoplasm that lead to a starry-sky pattern (Figure 3). However, individuals with HIV can also have BL with atypical features, such as some showing plasmacytoid differentiation and others exhibiting greater nuclear polymorphism. In the past, these cases were referred to as atypical Burkitt's or Burkitt-like lymphoma, but these categories are no longer favored, and a

separate category had been described, called B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (see below) (10).

Immunohistochemically, BL is characterized by positivity for B-cell antigens, CD10, and BCL6, and negativity or only weak positivity for BCL2. Importantly, BL is one of the fastest growing tumors in humans, which can be shown with Ki67 immunohistochemistry that will stain practically all the tumor cells.

Translocation of *MYC* into one of the immunoglobulin (Ig) loci is the molecular hallmark of BL. The most common translocation is a t(8;14), involving the *MYC* and immunoglobulin heavy chain (*IGH*) genes, but in 10% of the cases it can involve *MYC* and one of the Ig light chain genes. The method most commonly used to demonstrate this translocation in the clinical setting is fluorescent *in situ* hybridization (FISH) using a break-apart probe, which will show a split signal regardless of the translocation partner. This translocation leads to deregulated expression of *MYC*. While in rare cases this translocation cannot be demonstrated by FISH, it is likely that *MYC* is nevertheless deregulated in true BL. Mutations in the *MYC* regulatory and coding regions also occur in BL (20-24), and may also lead to abnormal expression or prolonged protein stability. If no demonstrable *MYC* translocation is identified, the histology and phenotype must be otherwise completely typical for a diagnosis of BL.

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL—The designation of B-cell lymphoma, unclassifiable (BCL-U), with features intermediate between DLBCL and BL, has been given to high grade lymphomas that do not fit cleanly into the DLBCL or BL categories (25). Previously, some of these cases were classified as atypical or Burkitt-like lymphoma. The presence of or absence of *MYC* translocations is not sufficient to place into this category otherwise typical cases of BL or DLBCL, respectively. This category is rather confined to cases with an unusual morphology or phenotype. BCL-U appears to be a heterogeneous category, but is useful for classification purposes. Some of these may belong to a separate molecular category ascribed to lymphomas with *MYC* translocations with a complex karyotype, with additional translocations in oncogenes such as BCL-6 and BCL-2. Some of these cases may correspond to those cases classified by histology as BL, but upon gene expression profiling do not have a Burkitt signature (26, 27). These cases include both EBV-positive and negative cases, but the proportion is not clear.

Classical Hodgkin's lymphoma (CHL)—While not considered an AIDS-defining malignancy, CHL is increased in incidence in HIV-infected individuals (28), and the proportion of CHL appears to have increased in patients with longer survival and better immunological status (28). This disease occurs in both HIV-infected and uninfected individuals, however there are some differences in these two patient populations. One of these differences is the association with EBV; approximately one third of CHLs are positive for EBV in immunocompetent individuals, but almost all cases are positive for EBV in HIV-infected patients. In addition, while the nodular sclerosis subtype is more common in the general population, the mixed cellularity or lymphocyte depleted forms of CHL comprise the vast majority of cases in HIV+ patients (10, 29).

Primary effusion lymphoma (PEL)—This lymphoma subtype occurs primarily, albeit not exclusively, in HIV-infected individuals. The presence of KSHV within the tumor cells is a diagnostic criterion for this disease, and the vast majority also contain EBV (10, 30, 31). Case reports have described patients presenting with a primary lymphomatous effusion that lack KSHV, but this appears to be a different disease entity, which has been called KSHV- or HHV-8-negative PEL (32-35). A recent report of two cases and review of the literature describes 48 cases of KSHV-negative PEL, with 21% being positive for EBV, and 22% for the hepatitis C virus (HCV). Remarkably, where clinical information was available, all these KSHV-negative cases occurred in HIV-negative individuals and had a median age at diagnosis of 74 years (36), highlighting that this is a disease that is different than PEL. Classical PEL is characterized, in addition to KSHV infection, by the lack of expression of B cell-associated antigens and immunoglobulins (Ig), in spite of being a lymphoma of B cell origin based on the presence of monoclonal immunoglobulin gene rearrangements. This lack of B cell antigens in a neoplastic cell of B cell origin is reminiscent of the Reed-Sternberg cells of CHL. Diagnostically, the tumors cells are large, with features that can be immunoblastic or anaplastic, but immunophenotypically are difficult to classify. They do express CD138, which is an antigen present in differentiated B cells, such as plasma cells and multiple myeloma. The presence of KSHV is most easily documented by immunohistochemistry for the KSHV nuclear antigen LANA (encoded by ORF73), which is commercially available.

PEL is a rare disease, accounting for less than 5% of all HIV-related NHLs. The most common presentation is as an effusion involving one or more of the pleural, peritoneal and pericardial spaces. However, about one third of the cases can show dissemination to extracavitary sites. In addition to classical PEL, KSHV can be found in the tumor cells of some rare cases of AIDS-related NHL with no evidence of body cavity involvement. These have been called solid or extracavitary PEL. These represent approximately 5% of all AIDS-NHLs and they typically have the morphology of immunoblastic lymphoma but like PELs, they frequently lack expression of B-cell antigens and are commonly co-infected with EBV (37).

Plasmablastic lymphoma (PBL)—This aggressive malignancy was first reported in the oral cavity of HIV-infected individuals (38), but can also occur in other sites, as well as in conjunction with other immunodeficient states (39). There may be an uneven geographic distribution since this lymphoma subtype seems to be particularly common in HIV-infected patients in India (40). The vast majority of cases in the oral cavity are EBV-infected, but in other sites, EBV can be found in around 75% of cases. The immunophenotype is that of plasma cells. There is expression of plasma cell antigens like MUM1 and CD138, but usually no expression of B-cell antigens like CD20 and CD79a. In contrast to the immunophenotype seen in PEL, there is expression of monotypic cytoplasmic immunoglobulin in the majority of cases. The stringency of the criteria used for classification of PBL has varied over time, leading some studies to use a very strict definition (including presentation in the oral cavity and presence of EBV) which has resulted in this tumor being considered extremely rare (38), to a more general definition provided by the WHO that accepts EBV-negative cases and extra-oral presentation, as long as the

morphology and immunophenotype is that of B immunoblasts or plasma cells (41). A recent report of five cases with a review of the literature identified 248 PBL cases, out of which 157 were in HIV-positive patients, 43% were outside the oral cavity and EBV was identified in 86% (42). This is a highly aggressive tumor with a median survival of around 14 months. Approximately half of the cases have been shown to have a *MYC* translocation (43). This study failed to detect rearrangements of other oncogenes altered in lymphoma (*BCL2*, *BCL6*, *MALT1*, *PAX5*), but gains in these loci were found in over a third of the cases.

Lymphoma arising in KSHV-associated multicentric Castleman's disease

(MCD)—These lymphomas mainly occur in HIV positive patients (44) and are very rare. They were initially called plasmablastic lymphomas (44). However, they are different from plasmablastic lymphomas (described above) in that they are KSHV-positive but EBV-negative. Lymphomas arising in KSHV-associated MCD are also different from PEL in that they are EBV-negative, and express IgM λ cytoplasmic immunoglobulin (while PELs do not express Ig). These lymphomas do not contain mutations in the immunoglobulin genes, are thought to arise from naïve B-cells rather than terminally differentiated B-cells as in PEL. A different entity has also been reported, called germinotropic lymphoproliferative disorder, in which germinal center B-cells are co-infected with EBV and KSHV (45).

Polymorphic B-cell lymphomas—These are rare lesions but morphologically resemble polymorphic post-transplantation lymphoproliferative disorders (PTLDs) (46).

Molecular analysis of AIDS-related lymphomas and diagnostic implications

Genetic alterations can be useful for the proper classification of different lymphoma subtypes. For example fluorescent *in situ* hybridization (FISH) is routinely used to detect *MYC*, *BCL2* and *BCL6* translocations to support a diagnosis of BL, follicular lymphoma and DLBCL, respectively. Therefore, gaining additional understanding of what defines a specific diagnostic entity can assist diagnosis. With the introduction of advanced genomic approaches we have gained much deeper understanding of cell of origin, driving genetic alterations, and pathogenetic mechanisms of many cancers, including lymphoma. During the past year a series of next generation sequencing studies have been published reporting novel alterations in BL (47-50). A notable finding was the presence of frequent genomic alterations in *TCF3* (also called E2A) or its negative regulator *ID3*. *TCF3* is a transcription factor that can activate the PI3K pathway, increasing tonic B-cell receptor signaling (47). While these studies examined mostly cases obtained from immunocompetent or not otherwise specified patients, it may be assumed that many of the same alterations will be found in BL cases occurring in people with AIDS, as this is known to be the case for major translocations that we have recognized for some time (i.e. *MYC* and *BCL6*). However, many of the newly described alterations have not been evaluated specifically in the context of AIDS yet.

Very few genomic studies have focuses exclusively on AIDS-related lymphomas in the past few years. Deffenbacher et al. evaluated 20 cases for gene expression and somatic DNA copy number changes by high-resolution array comparative genomic hybridization which reported numerous gain and losses, including some novel ones, reflecting great molecular

heterogeneity in AIDS-related lymphomas (51). A more focused study recently identified genetic alterations leading to loss of function of the tumor suppressor gene A20 in 23% of AIDS-related lymphomas (52). A20 plays a role in inhibiting NF- κ B, a transcription factor that is active and involved in cell survival of DLBCL of non-germinal center origin. The LMP1 protein encoded by EBV and expressed in a subset of AIDS DLBCLs potentially activates NF- κ B, adding a rationale for evaluating this pathway in the context of lymphomas with EBV infection. In AIDS-related lymphoma, A20 inactivation was found in 23% of cases, and there was no predilection for a specific histologic subtype. Both EBV+ and EBV- cases showed A20 inactivation, but LMP1 was usually not expressed in the EBV+ cases with A20 abnormalities, indicating that that loss of A20 function may be an alternative mechanism of NF- κ B activation in AIDS-related lymphoma cells.

Conclusion

We currently have a good understanding of how to classify the major types of lymphoma that occurs in HIV-positive individuals. Much of the information about the molecular alterations in these cases comes from genomic analysis of the same tumor types occurring in the general population, but some studies have focused specifically on the analysis of AIDS-related lymphomas. One of the most significant differences in lymphomas occurring among HIV-infected and uninfected individuals is a higher association with a oncogenic herpesviruses, namely EBV and KSHV. Many studies have focused over the past years in understanding the mechanisms of oncogenesis of these viruses, and assessment of their presence or absence can greatly help with accurate diagnosis and classification. It is not yet clear whether there are other, as yet unidentified, oncogenic infectious agents. Additional questions remain regarding the pathologic diagnosis of AIDS-related lymphomas. In particular two entities, plasmablastic lymphomas and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL, remain poorly defined with low concordance in terms of accurate diagnosis even among experienced pathologists. Some of these cases may comprise distinct clinico-pathologic categories, and it is likely that next generation sequencing and other advanced genomic tools will identify distinct molecular entities. The challenge thus far has been the limited number of patient specimens to do these analyses for rare subtypes, in particular for methods that would require fresh or frozen tissue. Nevertheless, when garnered, this information is likely to lead to a better understanding and therapies based on specific genetic alterations.

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Key points

- Individuals with HIV infection are at increased risk of lymphoma development.
- Certain lymphoma subtypes are more common in people with AIDS.
- Lymphomas in HIV-infected individuals are most frequently of B-cell origin,
- The association with EBV or KSHV is much more common in HIV than in the general population.
- Hodgkin lymphoma appears to be increasing in incidence in people with HIV.
- Few genomic studies have been conducted specifically on AIDS-related lymphomas, and much of our current understanding comes from studies in lymphomas in the general population.

Figure 1. Distribution and EBV status of AIDS related lymphomas. Tumor Characterization

A) Distribution of tumor type among 72 AIDS-related lymphoma specimens is shown.

Cases included DLBCL of the GCB (n=24) and non-GCB (n=18) subtypes, Burkitt lymphoma (n=12), plasmablastic lymphoma (n=5), BCL, U (n=4), and polymorphic lymphoproliferative disease (LPD) (n=1). Proportion of EBV positivity is shown as determined by EBV encoded RNA (EBER) in situ hybridization. B) EBV status is most commonly determined by EBER in situ hybridization. A negative case is shown on the left and a positive one is shown on the right. Original magnification: 40X.

Figure 2. Subclassification of AIDS-related DLBCL into differentiation subtypes

Cases can be sub-classified using immunohistochemistry according to the algorithm reported by Hans *et al.* as in non-AIDS related DLBCL as shown in the diagram (18). Left panel shows the histology (hematoxylin and eosin) and immunophenotype of a representative case of AIDS-related DLBCL with a GC phenotype: CD10+, BCL-6+, MUM-1-, and the right panel shows a case of AIDS-related DLBCL with a non-GC phenotype: CD10-, BCL-6-, MUM-1+. The original magnification for hematoxylin and eosin was 132X and for the immunohistochemistry pictures 66X. Adapted with permission from (13).

AIDS-related Burkitt lymphoma

Immunophenotype:

CD20/Pax5 +

CD10 +

BCL6 +

BCL2 – or weak

Ki67 >95%

Figure 3. AIDS related Burkitt's lymphoma

The left panel shows the histology (hematoxylin and eosin) of a case of Burkitt's lymphoma, with fairly monotonous medium sized cells, mitotic figures (black arrows) and a starry-sky pattern due to numerous tangible body macrophages (white arrows). Original magnification: 400X. The diagnostic immunophenotype of BL is listed.