Immunodeficient patients are at an increased risk for developing lymphoproliferative disorders/lymphomas (LPDs). The WHO recognizes four categories of immunodeficiency-associated LPDs (ID-LPDs) that are defined by the clinical setting in which they arise: (1) lymphoproliferative diseases associated with primary immune disorders, (2) lymphomas associated with HIV infection, (3) post-transplant lymphoproliferative disorders and (4) other iatrogenic ID-LPDs. These lesions are highly heterogeneous, largely due to the various underlying causes of the different immunodeficiencies; however, they share several features, including frequent involvement of extranodal sites, diffuse aggressive histology, B cell lineage, associated herpesvirus infection, and rapid clinical progression. In some instances these lesions may regress if the patient’s immune status can be restored. However, the development of secondary genetic structural alterations in oncogenes and tumor suppressor genes, not all of which have been defined, can result in transformation to a neoplastic process that is no longer responsive to immune-modulation. Thus, in spite of aggressive therapeutic intervention due either to the inability to re-establish normal immune function or due to neoplastic transformation, these lesions may progress leading to the patient’s demise. The morphologic diagnosis of LPDs is often difficult. In some instances the lesions are clearly neoplastic, however, other lesions are difficult to classify due to their polymorphic appearance. Thus, accurate diagnosis and treatment of ID-LPDs often requires careful evaluation of the morphology, immunophenotype, genotype, viral status, and clinical history (including evaluation of family history).

For today’s Society of Hematopathology session, two of the four ID-LPD categories recognized by the WHO have been selected for discussion: lymphomas / lymphoproliferative disorders associated with HIV infection, including those related to Kaposi sarcoma herpesvirus (KSHV/HHV-8) infection, and lymphoproliferative
diseases associated with primary immune disorders, as represented by autoimmune lymphoproliferative syndrome (ALPS).

**Lymphoproliferative Diseases Associated with Primary Immune Disorders**

The lymphoproliferative diseases associated with primary immune disorders (PID) arise as a consequence of an underlying primary immunodeficiency or immunoregulatory disorder. These lesions are highly heterogeneous with more than 60 recognized PIDs, each of which is associated with an underlying defect. The most common types of PID associated with ID-LPDs are ataxia telangiectasia, Wiskott-Aldrich syndrome, common variable immunodeficiency (CVID), severe combined immunodeficiency, X-linked lymphoproliferative disorder, hyper-IgM syndrome, and autoimmune lymphoproliferative syndrome (ALPS). The majority of ID-LPDs associated with PID, except for CVID, present in children and/or adolescents. The cause, clinical and pathologic manifestations, and prognosis are related to the underlying immune defect; however, the majority of these lesions are associated with Epstein Barr virus (EBV) infection.(2)

**Autoimmune lymphoproliferative syndrome (ALPS):**

Initially known as familial chronic non-malignant lymphadenopathy and splenomegaly, including pseudomononucleosis, pseudolymphoma, and the Canale-Smith syndrome, ALPS is one of the best-characterized PIDs .(3) This is partially because in the early 1990s it was recognized that the clinical manifestations exhibited by the ALPS patients closely resembled those of two related strains of mice with lymphoproliferative phenotypes, specifically the lpr (lymphoproliferation) and gld (generalized lymphoproliferative disease) mice strains. (4) Subsequently, it was found that the genetic defect in the lpr mouse strain was a loss of function mutation in a “death receptor” gene; while in humans, it was an inherited mutation in the FAS gene.(5, 6) Although most ALPS patients have an inherited germline mutation in the FAS gene, somatic FAS mutations are the second most common genetic cause of ALPS. In addition, mutations in several other genes in the apoptosis pathway, including FAS ligand, caspase 8, caspase 10 and neuroblastoma RAS (NRAS) have been indentified in patients with ALPS and related
disorders. However, in approximately 10-30% of patients, the genetic defects have yet to be identified. See Figure 1.

Figure 1: ALPS mutations and Classification

ALPS is characterized clinically as chronic (>6 months) lymphadenopathy and/or splenomegaly, autoimmune cytopenias, polyclonal hypergammaglobulinemia, and increased numbers of double negative (CD4-/CD8-) αβ T cells (DN T cells). Morphologically, the lymph nodes from ALPS patients show marked paracortical hyperplasia, expanded by CD45RO negative, CD45RA positive, CD57 positive, TIA1 positive, CD56 negative DN T cells, associated with increased lymphoid cell proliferation and decreased apoptosis. In addition, there is often follicular hyperplasia or evidence of progressive transformation of the germinal centers. The spleens from ALPS patients show expansion of both the white and red pulp by the DN T cells. In addition, in vitro studies have shown decreased lymphocyte apoptosis.

At the 2009 NIH International Workshop, the 1999 diagnostic criteria for ALPS were revised; these revised criteria are listed in Table 1. For a definitive diagnosis of ALPS, a patient has to have both required criteria and one of the primary accessory criteria, while a probable diagnosis of ALPS is made when that patient has both required criteria and any one of the secondary accessory
criteria. However, it is felt that patients with a probable ALPS diagnosis should be treated and followed like those with a definitive ALPS diagnosis.

**Table 1. Revised diagnostic criteria for ALPS**

<table>
<thead>
<tr>
<th>Required</th>
<th>Accessory</th>
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<tbody>
<tr>
<td>1. Chronic (&gt; 6 months), nonmalignant, noninfectious lymphadenopathy or splenomegaly or both</td>
<td>1. Defective lymphocyte apoptosis (in 2 separate assays)</td>
</tr>
<tr>
<td>2. Elevated CD3⁺TCRαβ⁻CD4⁻CD8⁻ DNT cells (1.5% of total lymphocytes or 2.5% of CD3⁺ lymphocytes) in the setting of normal or elevated lymphocyte counts</td>
<td>2. Somatic or germline pathogenic mutation in <em>FAS</em>, <em>FASLG</em>, or <em>CASP10</em></td>
</tr>
</tbody>
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**Secondary**

1. Elevated plasma sFASL levels (>200 pg/mL) OR elevated plasma interleukin-10 levels (>20 pg/mL) OR elevated serum or plasma vitamin B₁₂ levels (> 1500 ng/L) OR elevated plasma interleukin-18 levels >500 pg/mL |
2. Typical immunohistological findings as reviewed by an experienced hematopathologist |
3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated immunoglobulin G levels (polyclonal hypergammaglobulinemia) |
4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity |

In addition, the classification of ALPS and ALPS-related disorders were revised at this same workshop (Table 2). In light of the differences in their disease manifestations, patients with mutations in caspase-8 (*CASP8*) (previously classified as ALPS type IIb) and *NRAS* (previously diagnosed as APLS type IV) are now classified as separate entities: CEDS (caspase 8 deficiency state) and RALD (RAS-associated autoimmune leukoproliferative disease), respectively. (3, 10)

**Table 2. Revised classification of ALPS**

<table>
<thead>
<tr>
<th>Previous nomenclature</th>
<th>Revised nomenclature</th>
<th>Gene</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ALPS type 0</td>
<td>ALPS-FAS</td>
<td><em>FAS</em></td>
<td>Patients fulfill ALPS diagnostic criteria and have germline homozygous mutations in <em>FAS</em>.</td>
</tr>
<tr>
<td>ALPS type Ia</td>
<td>ALPS-FAS</td>
<td><em>FAS</em></td>
<td>Patients fulfill ALPS diagnostic criteria and have germline heterozygous mutations in <em>FAS</em>.</td>
</tr>
<tr>
<td>ALPS type Im</td>
<td>ALPS-sFAS</td>
<td><em>FAS</em></td>
<td>Patients fulfill ALPS diagnostic criteria and have somatic mutations in <em>FAS</em>.</td>
</tr>
<tr>
<td>ALPS type Ib</td>
<td>ALPS-FASLG</td>
<td><em>FASLG</em></td>
<td>Patients fulfill ALPS diagnostic criteria and have germline mutations in FAS ligand.</td>
</tr>
<tr>
<td>ALPS type IIa</td>
<td>ALPS-CASP10</td>
<td><em>CASP10</em></td>
<td>Patients fulfill ALPS diagnostic criteria and have germline mutations in caspase 10.</td>
</tr>
<tr>
<td>ALPS type III</td>
<td>ALPS-U</td>
<td>Unknown</td>
<td>Patients meet ALPS diagnostic criteria; however, genetic defect is undetermined (no FAS, FASL, or CASP10 defect).</td>
</tr>
</tbody>
</table>
Although the origin of the DN T cells is not clear, recent studies have found significant sharing of CDR3 sequences from selected Vβ-Jβ transcripts between DN T cells and CD8+ T cells, suggesting a clonal relationship. In addition, overexpression of eomesodermin (Eomes), a member of the T-box transcription factor family, which plays an important role in effector cell function and memory cell fitness of CD8+ T cells, has been identified in the T cells of lpr/lpr mice and ALPS patients, particularly in the DN T cells of ALPS patients, suggesting a role for this transcription factor in the pathogenesis of this immune deficiency. In addition, there has been a suggestion that sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) represents a forme fruste of ALPS as increased numbers of DN T cells are present in these specimens.

Presenting clinical features of patients with ALPS include chronic lymphadenopathy and/or splenomegaly for >6 months, pallor, and bruising. The median age at presentation is young (usually under 5 years of age). The patients’ symptoms are usually worse in their youth and improve with age. Patients usually have autoimmune cytopenia(s), particularly hemolytic anemia and thrombocytopenia, although some will also have autoimmune neutropenia. Other autoimmune manifestations such as Guillain-Barre syndrome, glomerulonephritis, uveitis, etc., can be seen. Increased numbers of circulating DN T cells can be identified. In addition, the patients may have elevated levels of IL10 and FasL in the blood. The differential diagnosis of ALPS includes lymphoma, hereditary spherocytosis, Evans Syndrome, Rosai-Dorfman disease, CVID, Wiskott-Aldrich syndrome, and interleukin -2 receptor α chain deficiency. Treatment includes steroids, mycophenolate mofetil, chemotherapy, sirolimus, and other immunosuppressive drugs. Rituximab may also be used, however, with caution as it can result in hypogammaglobulinemia and neutropenia. Splenectomy should be
avoided, as splenectomized patients can develop fatal opportunistic infections or pneumococcal sepsis. (7, 9, 14, 15)

Between 3 – 10% of ALPS patients develop lymphoma. ALPS patients are at an increased risk of developing both non-Hodgkin (14x) and Hodgkin (50x) lymphoma. Lymphomas occurring in ALPS patients include diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma, follicular lymphoma, T-cell/histiocyte rich large B cell lymphoma, marginal zone lymphoma, classical Hodgkin lymphoma, nodular lymphocyte predominant Hodgkin lymphoma, and rarely T cell lymphoma. These lesions can occur in either lymph nodes or in extranodal sites and may or may not be EBV positive. ALPS-related lymphoma can develop at any age, but in a cohort of patients followed at the NIH the median age at diagnosis was 17 years (6-60 years). Thus, an important aspect of the “treatment” of ALPS is careful clinical surveillance for the development of lymphoma. (16-18)

**Lymphomas/Lymphoproliferative Disorders Associated with HIV Infection**

These lesions are heterogeneous but are composed primarily of aggressive B cell proliferations, and in contrast to many of the other ID-LPDs, most are neoplastic in appearance. Although in the strict definition of the WHO classification, these lesions are confined to lymphomas, there are “grey” lesions that not necessarily neoplastic, but may behave in an aggressive fashion, for example KSHV/HHV-8 associated multicentric Castleman disease which will be included in this discussion. These lesions can be subcategorized as (1) those also occurring in immunocompetent patients, (2) those occurring more specifically in HIV-positive patients, and (3) those occurring in other immunodeficiency states. Those occurring more specifically in HIV-positive patients are often associated with infection by KSHV/HHV-8.(19)

**Lesions also occurring in immunocompetent patients:**

These lesions consist primarily Burkitt lymphoma (30% of HIV-associated lymphomas) and diffuse large B cell lymphoma (~40%), however, this category also
includes classical Hodgkin lymphoma, MALT lymphoma, peripheral T cell lymphoma, and natural killer cell lymphoma. (19, 20) Overall the incidence of non-Hodgkin lymphoma is ~70x and Hodgkin lymphoma is ~10x greater in HIV/AIDS patients than in the general population. (21) Although the incidence of non-Hodgkin lymphoma and Hodgkin lymphoma are overall decreasing in the HIV positive patient population, non-Hodgkin lymphoma during the period of 1996-2006 accounted for the majority of AIDS defining cancer events. (22)

**Classical Hodgkin Lymphoma:** Although not considered an AIDS defining illness, HIV positive individuals are at increased risk for the development of classical Hodgkin lymphoma and the disease is more aggressive. Classical Hodgkin lymphoma accounts for approximately 7% of HIV-associated lymphomas with most cases classified as mixed cellularity (54%) and smaller numbers classified as either nodular sclerosis (37%) or lymphocyte depleted (7%). (23) Most patients present with lymph node involvement, however some individuals present with disease in the bone marrow or in extra-nodal sites; in addition, most patients present with stage III or IV disease and have B symptoms.(23, 24)

Morphologically, the lesions are similar to those seen in HIV-negative patients. Immunophenotypically, the Reed-Sternberg cells are CD45-negative and CD15- and CD30-positive. However, the associated microenvironment is often characterized by a T cell population that contains a relatively large number of CD8 cells, resulting in an inversion in the CD4/CD8 ratio. Furthermore, the Reed-Sternberg cells virtually always are EBV-positive (24, 25) Although HIV positive patients have more aggressive disease than their immunocompetent counterparts, the institution of HAART with chemotherapy has improved survival from 45% at 2 years to 62% in one study.(26) Interestingly, however, the use of HAART has probably also increased the relative incidence of Hodgkin lymphoma in HIV positive patients, as the incidence of the disease appears to be highest, except for the lymphocyte depletion subtype, in individuals with an intermediate (225-249 CD4 cells/ul) CD4 count. (23)
**Burkitt Lymphoma:** Like Hodgkin lymphoma, Burkitt lymphoma 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 >250/ul. The incidence of Burkitt lymphoma drops significantly in patients with a CD4 count less than 50/ul. Morphologically, the lesions may resemble Burkitt lymphoma occurring in HIV negative patients. However, many cases exhibit plasmacytoid features with relatively abundant cytoplasm and eccentric nuclei; these plasmacytoid Burkitt lymphoma cases are more often (50-70%) EBV-positive. As in immunocompetent patients, the lesions are B cell antigen positive, CD10 and BCL6 positive, but lack expression of BCL2; nearly all of the cells are Ki67 positive, indicating a very high proliferation rate. The lesions characteristically contain a MYC rearrangement.

**Diffuse large B cell lymphoma:** This type of lymphoma, like in immunocompetent (IC) patients, is the most common type of lymphoma in HIV-positive individuals. The majority of these cases are composed of centroblasts often admixed with a small but variable number of immunoblasts; a smaller number of cases are composed predominately of immunoblasts. The lesions composed predominately of immunoblasts are frequently EBV positive, while the incidence of EBV is lower in the cases with centroblastic features.

HIV- DLBCLs are characterized by clonal rearrangements of the immunoglobulin genes; most cases also show evidence of immunoglobulin gene somatic hypermutations (SHM). Gene rearrangements involving oncogenes and tumor suppressor genes are relatively rare, but those involving MYC and BCL6 appear to be the most frequent. However, many cases have mutations in the non-coding, regulatory region of the BCL6 gene; aberrant SHM involving proto-oncogenes PIM1, PAX5, RhoH/TTF, and/or c-MYC are also seen in approximately 50% of systemic HIV-associated DLBCLs.

Recent studies, based on gene expression profiling (GEP) using array comparative genomic hybridization (CGH), have found that HIV-associated DLBCLs may be separated into germinal center (GC) and non-GC types, using previously defined GEP classifiers. These studies have also found that HIV-associated
lymphomas exhibit variable genetic complexity, but also exhibit some specific genetic characteristics, including frequent deletions in “fragile” sites, such as 3q14.3 and 16q23.1 (WWOX), the latter of which is a tumor suppressor gene. These fragile site deletions are short interstitial deletions, in contrast to IC-DLBCLs, where usually the entire gene is lost. In addition, HIV-DLBCLs tend to contain alterations in MYC targets, FAS pathway, and cell cycle genes and fewer alterations in BCR and T cell receptor signaling genes, than DLBCLs arising in immunocompetent patients, suggesting a difference in their pathogenesis. Of note, the EBV positive HIV DLBCL cases have fewer copy number changes, compared to the EBV negative cases. (34, 35)

Diffuse large B cell lymphomas (DLBCLs) in immunocompetent patients have also been divided into GC and non-GC types, based on gene expression profiling (GEP) (36) and surrogate immunophenotypic markers. (37) Although by using the Hans, et al, classification scheme, DLBCLs in HIV negative patients consist of approximately equal numbers of GC and non-GC DLBCLs, HIV-associated DLBCLs are more frequently of GC origin. Furthermore, while in immunocompetent patients GC versus non-GC origin correlates with prognosis, similar studies in HIV positive patients do not clearly show that histogenetic classification of DLBCLs is clinically relevant. (38-40) In addition, it also appears that many phenotypic markers, such as BCL2, p53, FOXP1, and BLIMP1, which are associated with prognosis in HIV negative patients with DLBCL, are not predictive of disease aggressiveness or outcome in HIV positive patients. However, CD4 count does seem to predict outcome (39, 41, 42)

HIV-LPDs Occurring More Specifically in HIV-Positive Patients:
These lesions include the majority of HIV-associated lymphoproliferative lesions and lymphomas that are KSHV/HHV-8 related, including primary effusion lymphoma (PEL), extra-cavitary PEL (EC-PEL), large B cell lymphoma arising in HHV8-associated multicentric Castleman disease (LBL-MCD) and MCD. In addition, plasmablastic lymphomas, which are EBV positive and tend to occur in the oral cavity, are also included in this category.
**Primary effusion lymphoma and extra-cavitary primary effusion lymphoma:** In 1994, using representational differential analysis (RDA), Chang, et al, identified a fragment of DNA which was found to be from a virus, KSHV/HHV-8, that was etiologically related to the development of Kaposi sarcoma.(43) Shortly thereafter, Cesarman, et al. identified the virus in a unique type of HIV-associated lymphoma, occurring primarily as an effusion, the so-called body cavity based lymphomas. These KSHV/HHV-8 positive lymphomas, although containing a clonal immunoglobulin gene rearrangement, typically lack expression of lineage specific antigens, and are composed of large, anaplastic, pleomorphic, Reed-Sternberg-like appearing neoplastic cells. (44, 45)

KSHV/HHV-8 is a human herpesvirus, closely related to herpesvirus saimiri, that encodes >90 opening reading frames (ORFs). KSHV/HHV-8, in contrast to many of the other human herpesviruses, has “pirated” a large number of genes from its host, i.e. humans. Many of these KSHV/HHV-8 encoded human homologue genes are important in the pathogenesis of KSHV/HHV-8 related diseases. Some of the more important genes involved in the pathogenesis of PEL/EC-PEL include viral Fas-associated death domain [FADD] interleukin-1b-converting enzyme [FLICE] inhibitory protein (v-FLIP) which is crucial for PEL cell survival, viral interleukin 6 (vIL6) which is important in signal transduction via the JAK-STAT pathway, viral cyclin (v-cyclin) which promotes proliferation and over-rides cell cycle controls, and latent nuclear antigen 1 (LANA) which tethers the viral genome to the human chromosome and possesses a variety of oncogenic functions including the ability to bind to p53.(46-49) See Table 3.
PEL and EC-PEL, which are relatively rare (<5% of HIV associated lymphomas), usually occur in homosexual men with a previous AIDS diagnosis and a low CD4 count, although they have been diagnosed in other patient populations, including elderly individuals and transplant recipients. These lesions contain KSHV/HHV-8 and, in most instances, are also EBV positive. Immunophenotypically, they lack T and B cell associated antigens, express activation associated antigens such as CD30, and are positive for LANA (KSHV/HHV-8) and EBER (EBV; in situ hybridization); a minority of the cells are vIL6 positive as well. They also often express antigens of terminal B cell differentiation, such as CD138, MUM1/IFR4, and BLIMP1/PRDM1 and lack expression of germinal center markers, such as BCL6 and CD10. Interestingly, they lack expression for OCT2, a transcription factor involved in immunoglobulin gene transcription. The immunoglobulin genes are clonally rearranged and contain SHM that are not on-going; they do not, however, characteristically contain structural alterations in oncogenes or tumor suppressor genes. Gene expression profiling shows that the lesions exhibit a “plasmablastic”
profile, a profile that is intermediate between DLBCL and plasma cells. (45, 50-52) (33, 44, 49, 53, 54) Gene expression profiling comparing EBV positive and EBV negative PELs have found differences in a significant number of genes, including several in the MAP-kinase pathway, suggesting that there are differences in the pathogenesis of EBV positive and EBV negative PELs. (55)

**Multicentric Castleman disease and KSHV/HHV-8 Positive Large B-Cell Lymphoma Associated with Multicentric Castleman Disease:** Both these lesions are composed of KSHV/HHV-8 infected B cells, which have the morphologic features of plasmablasts, cells that are intermediate between plasma cells and immunoblasts. In MCD, these cells are seen predominately in the mantle cell zones. In KSHV/HHV-8 positive large B-cell lymphoma associated with multicentric Castleman disease (LBL-MCD), these cells are in variably sized collections (“microlymphomas”) or form confluent sheets of cells obliterating the normal architecture. These KSHV/HHV-8 infected cells express monotypic cytoplasmic immunoglobulin of the IgM lambda isotype, lack or only weakly express B cell associated antigens, are usually negative or only weakly positive for CD30, are negative for CD138, and express IRF4/MUM1 and BLIMP1/PRDM1. Furthermore, they are positive for OCT2, a transcription factor important in immunoglobulin transcription. A proportion of the KSHV/HHV-8 positive cells express the memory B cell antigen, CD27 and a large number of cells are vIL6 positive. PCR analysis of LBL-MCD shows that only a proportion of the neoplastic cases are monoclonal at the DNA level. The immunoglobulin genes, in contrast to PEL/EC-PELs, do not show evidence of SHM, suggesting they have not traversed through the germinal center reaction. Also, in contrast to PEL/EC-PELs, the malignant cells in LBL-MCD, as well as the plasmablasts in MCD, are EBV negative. (49, 56-60)

Pathogenetically, vIL6, which exhibits many of the biologic activities of human (hu) IL6, is important in the development of both MCD and its neoplastic counterpart, LCL-MCD. Viral interleukin 6 is important in “driving” the KSHV/HHV-8 infected B cells to plasmablasts. As in PEL/EC-PELs, vIL6 can bind to IL6 receptors on the B cells, resulting in activation of the JAK-STAT pathway, as well as
induction of huIL6 production, thereby driving cell growth. In addition, vIL6 promotes angiogenesis (47, 48, 56, 57, 59) Furthermore, when vIL6 is constitutively expressed in mice, the mice develop symptoms resembling MCD. (61) In patients with MCD, serum levels of vIL6 and huIL6 correlate with symptoms, as do plasma levels of KSHV/HHV-8. Thus, MCD may also be referred to as interleukin 6 (either viral or human) syndrome.(49, 62-65)

Patients with HIV-MCD often present with fever and lymphadenopathy with or without splenomegaly or hepatomegaly; many may also have respiratory symptoms or peripheral edema. The patients often have severe cytopenias and an elevated serum C-reactive protein. Most patients, in the post-HAART era, have a CD4 >200/ul (median 230/ul) at presentation.(66, 67) The incidence of HIV-associated MCD is increasing (from 2.8 between 1997-2001 to 8.3/10000 patient years during 2002-2007), with the highest risk, based on multivariate analysis, in HIV patients with a nadir CD4 count of >200/ul who are older with no history of previous HAART therapy. (68) The risk of developing lymphoma, including LCL-MCD, in HIV positive patients with MCD is about 15x than that of the general HIV positive patient population. Approximately 15-25% of MCD patients develop lymphoma and in that group, the survival is poor(57, 66, 69)

**Plasmablastic lymphoma:** These lesions classically occur in the oral cavity, but may also arise in other mucosal sites. They are positive for EBV by in situ hybridization for EBV-encoded RNA (EBER), but are usually negative for the EBV latent membrane protein (LMP1) by immunohistochemistry. They express cytoplasmic immunoglobulins, CD38, CD138, and IRF4/MUM1 and are usually negative or only weakly express CD45, CD20, and PAX5. They have a high proliferation rate and are aggressive. There also appears to be a high association with \textit{MYC} translocation (70-72)

Although these lesions occur primarily in HIV positive patients, they also can arise in HIV negative individuals. However, the HIV positive patients tend to be younger (median age 39 vs. 58), are more often male (82% vs. 62%), and have lesions tending to arise more frequently in the oral cavity (58% vs 16%), which are
more often EBV positive (80% vs. 45%). HIV positive patients also appear to have a better response to therapy (80% vs. 56% CR or PR). In addition, there is some suggestion that lesions that arise in the oral cavity have different biologic behavior than those that arise in other sites. (73, 74)

**Lymphomas occurring in other immunodeficient states:** This category includes the *polymorphic lymphoid proliferations resembling post-transplant associated lymphoproliferative disorders*. (19) These lesions are morphologically, genetically and phenotypically similar to polymorphic PTLDs seen in transplant recipients. These lesions are rare and only limited follow-up information is available. (75)
REFERENCES


