**HIV-Related Lymphoproliferative Disorders**

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**INTRODUCTION**

Lymphoproliferative disorders including non-Hodgkin lymphomas (NHL) are not uncommon neoplasms in patients infected with the human immunodeficiency virus (HIV). It has been established that HIV-infected individuals are more prone to develop certain lymphoproliferative disorders and lymphomas compared to non-infected individuals. The exact mechanisms underlying these associations is yet to be established [1]. Two of the more accepted proposed mechanisms include the prolonged B-cell activation due to impaired immune function and the loss of immunoregulation of Epstein-Barr virus (EBV) and/or human Herpes virus-8 (HHV8) in HIV infection [2,3]. Different molecular pathogenetic pathways have also been studied to explore this relationship [4]. These pathways involve various types of oncogenes as well as tumor suppressor genes, i.e. inactivating mutations or deletions of the p53 tumor suppressor gene in HIV-associated Burkitt lymphoma and rearrangements in BCL-1, BCL-2, BCL-6, and MYC genes in aggressive large B-cell lymphomas. Lymphomas associated with HIV infection are often aggressive with an adverse clinical course. EBV and/or HHV8 co-infection is often seen in this group and these viruses are responsible for the pathologic disruption of cytokine networks [5]. The lymphomas associated with HIV are also heterogeneous and the incidence varies mostly depending on the anti-viral therapy status.

**Lymphomas commonly occur in HIV infected individuals**

Certain type of lymphomas have high incidence in HIV-positive patients although there is no specific association with the virus. **Burkitt lymphoma** is the most frequent lymphoma in the setting of HIV accounting for 30% of all HIV associated lymphomas [5]. It is an aggressive B-cell lymphoma with characteristic translocation involving the MYC oncogene. EBV can be positive in a portion of these cases. Although regimens such as CODOX-M/IVAC are effective in HIV seronegative patients, it remains unclear if they are equally effective in HIV-positive individuals [6]. **Diffuse large B-cell lymphoma** (DLBCL) is another type of lymphoma that is not uncommon in patients infected with HIV. The immunoblastic variant of DLBCL is often seen in these patients and show variable EBV expression [7]. It can be systemic or present as a primary central nervous system lymphoma. Multiple prospective studies showed that rituximab combined with CHOP regimen has near equal efficacy in HIV seropositive and negative patients. **Hodgkin lymphoma** (HL) also has an increased incidence in HIV infection [8]. The most common subtypes of HL in this population are mixed cellular and lymphocyte depleted with high association with EBV [5]. Most patients present at an advanced stage disease with frequent extranodal involvement and B-symptoms compared to seronegative individuals. Highly active antiretroviral therapy (HAART) has been shown to be effective in the treatment of this lymphoma when continued along with the ABVD chemotherapy regimen; however an optimum treatment regimen is yet to be established [6,9].

**Lymphomas more specifically associated with HIV infection**

**Primary Effusion Lymphoma:** Primary effusion lymphoma (PEL) is a rare large B-cell lymphoma always associated with HHV8 and frequently associated with EBV [10,11]. The lymphoma has a peculiar tropism for body cavities; however, extracavitary disease may occur [12]. A recent addition to the medical literature are lymphomas defined as “microlymphoma” which describe a possible extracavitary form of the disease confined to the lymphoid follicles without diffuse pattern [13]. PEL is a disease predominantly of HIV-infected individuals, particularly homosexual men with AIDS, and is less commonly seen in post-transplant and elderly populations [14-16]. Morphologically, PEL is a large cell lymphoma of post-germinal center B-cell with a distinct immunophenotype lacking B-cell antigens and often expressing CD30, CD38 and CD138. Simonelli and colleagues showed that immunodepletion, i.e. low CD4 count, seems to be more important in development of PEL than any other HIV-related NHL [17]. PEL has an extremely poor prognosis with no effective therapy established to the date. Few reports showed that remission was achieved with an improved survival following administration of HAART [18,19]. R-CHOP chemotherapy has also been reported to be effective in some cases [17].

**Plasmablastic lymphoma:** Plasmablastic lymphoma (PBL) is a large cell lymphoma of plasmablasts that is often seen in HIV-positive males. The most common location for HIV-related PBL is oral cavity; however it has been reported in many other sites including the nasal/paranasal tissues, lymph nodes, gastrointestinal tract, bone, soft tissue, skin, mediastinum, gonads, and central nervous system [20]. Majority of the cases are positive for EBV and lack HHV8 [21]. Similar to PEL, effective treatment is yet to be established for this rare and aggressive disease. Aggressive chemotherapy regimens including CODOX-M/IVAC are equally effective in HIV-positive individuals [6]. Effective in HIV seronegative patients, it remains unclear if they are equally effective in HIV-infected individuals compared to non-infected individuals. The exact mechanisms underlying these associations is yet to be established [1]. Two of the more accepted proposed mechanisms include the prolonged B-cell activation due to impaired immune function and the loss of immunoregulation of Epstein-Barr virus (EBV) and/or human Herpes virus-8 (HHV8) in HIV infection [2,3]. Different molecular pathogenetic pathways have also been studied to explore this relationship [4]. These pathways involve various types of oncogenes as well as tumor suppressor genes, i.e. inactivating mutations or deletions of the p53 tumor suppressor gene in HIV-associated Burkitt lymphoma and rearrangements in BCL-1, BCL-2, BCL-6, and MYC genes in aggressive large B-cell lymphomas. Lymphomas associated with HIV infection are often aggressive with an adverse clinical course. EBV and/or HHV8 co-infection is often seen in this group and these viruses are responsible for the pathologic disruption of cytokine networks [5]. The lymphomas associated with HIV are also heterogeneous and the incidence varies mostly depending on the anti-viral therapy status.
IVAC and EPOCH have been reported to be promising treatment options in recent retrospective studies [22,23].

Lymphoma arising in HHV8-associated multicentric Castleman disease

Large cell lymphoma with plasmablastic morphology in the setting of multicentric Castleman disease (MCD) is often associated with HIV infection and is near always HHV8 positive [5]. The cells express IgM with λ light chain restriction with or without B-cell and plasma cell markers, and these cells are also EBV negative. This lymphoma usually involves lymphoid organs but can be disseminated in viscera. It is a highly aggressive with no established effective standard therapy and the survival is limited to few months [24].

To conclude, HIV-infected individuals are at increased risk for the development of certain lymphoproliferative disorders compared to non-infected individuals. Some of the more common lymphoproliferative disorders encountered in these patients have been reviewed above. Many of the lymphomas encountered in these patients are associated with an aggressive clinical course, and establishing the correct diagnosis is essential to providing appropriate therapy and accurate prognostic information.

REFERENCES