

# Human Immunodeficiency Virus Related Non-Hodgkin's Lymphoma

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**Abstract:** Human immunodeficiency virus infection is related with an increased risk of hematological malignancy principally, non-Hodgkin lymphoma. Most non-Hodgkin lymphomas are acquired immunodeficiency syndrome defining and constitute greater than 50% of all acquired immunodeficiency syndrome defining cancers. The main pathogenesis mechanisms are immunodeficiency, chronic antigenic stimulation, and the ability to infect cancer cells causing direct carcinogenesis. Human immunodeficiency virus related non-Hodgkin lymphomas are heterogeneous in immunophenotyping and molecular features; and choice of drug treatments is similar with sporadic types. The main objective is to assess the epidemiology, pathogenesis, and morphology of human immunodeficiency virus related non-Hodgkin lymphoma. The searching strategy was done by searching relevant original and review articles from [www.biosemanticjane.org](http://www.biosemanticjane.org), Google scholar, Google, and PubMed sites using keywords like; Acquired immunodeficiency syndrome, Human immunodeficiency virus, and non-Hodgkin lymphoma. In conclusion, human immunodeficiency virus infected people continue to have elevated risk of non-Hodgkin lymphoma. Diffuse large B-cell lymphomas are the most common and severe subtype. The pathogenesis of this type of lymphoma is associated with chromosomal abnormalities that deregulate the expression of various oncogenes by different viral particles and cytokines. However, the role of these viral particles and cytokines on pathogenesis is not clearly stated, so further study could be required.

**Keywords:** acquired immunodeficiency syndrome, Burkitt lymphoma, diffuse large B-cell lymphoma, human immunodeficiency virus, non-Hodgkin lymphoma, plasmablastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma

## Introduction

Human immunodeficiency virus (HIV) infection is associated with an increased risk of hematological malignancy. Lymphoid neoplasms, particularly non-Hodgkin lymphoma, are the main hematologic malignancies that occur more frequently in connection with HIV infection non-Hodgkin lymphoma (NHL).<sup>1</sup> Lymphomas are neoplastic lesions of the lymphoid system. According to World Health Organization (WHO) grouping, HIV associated lymphomas are assembled into three categories; i) Lymphoma occurring in immunocompetent patients includes; Burkitt lymphomas (BL), diffuse large B-cell lymphomas (DLBCL), mucosa associated lymphoid tissue (MALT) lymphomas, Peripheral T-cell lymphoma (PTCL), and Hodgkin lymphoma (HL), ii) Lymphoma occurring more specifically in HIV positive patients as primary effusion lymphoma (PEL) and plasmablastic lymphoma (PBL) and human hepatitis B virus positive diffuse large B cell lymphoma, not otherwise specified, and iii) Lymphoma occurring in patients with other forms of immunosuppression as polymorphic B-cell lymphoma (PTLD-like), and constitutes about 5% of all HIV lymphomas.<sup>2,3</sup>

HIV-infected patients' risk of developing NHL has decreased thanks to the effectiveness and widespread use of highly active anti-retroviral medication (HAART).<sup>4,5</sup> However, HIV-infected people in the HAART era still remain to have elevated risk of NHL relative to the general population, and this risk varies substantially by subtype.<sup>6</sup> Before the invention of HAART, an individual with HIV had a risk of developing acquired immunodeficiency syndrome (AIDS)-related NHL that was 60–200 times greater than that of the general population.<sup>3</sup> In patients with HIV infection, the incidence of AIDS-defining NHL subtypes reduced to 6–15 times over the HAART era.<sup>7,8</sup>

NHL make up more than half of all AIDS-defining cancers, and it is the leading cause of cancer-related death in people with HIV.<sup>9</sup> Known virus-mediators of oncogenesis, such as Epstein-Barr virus (EBV), which was found in 30–50% of cases overall and nearly 100% of primary central nervous system lymphomas (PCNS), are more frequently linked to AIDS-associated NHL cases.<sup>10</sup>

The majority of NHLs are the defining NHL subtypes for AIDS; this may be because immunosuppression and EBV infections have such a significant impact.<sup>6</sup> The most common AIDS related NHLs are DLBCL, BL, and PCNSL. They constitute about 90% of HIV related NHL,<sup>3</sup> and rare entities include PEL and PBL. Less frequently occurring subtypes of non-AIDS-defining lymphomas include follicular lymphoma (FL), peripheral T-cell lymphoma, and anaplastic large cell lymphoma (ALCL).<sup>6</sup> HIV related NHL usually display several features like; aggressive clinical course, frequent extranodal presentation, and poor outcome compared to the general population with NHL.<sup>11</sup> The significance of this review is, because HIV infection is continued to be a relevant health problems around the world, investigations of its complications are essential for proper patient management. Particularly, hematological malignancies including NHLs are the current most important issue. So this review is important to address the general characteristics, epidemiology and possible pathogenesis of HIV related NHL, particularly AIDS related NHL, because it is the most common lymphoma types frequently encountered in HIV positive patients.

The main objective of this review is to assess the epidemiology, pathogenesis, morphology, treatment prognosis, and immunophenotype of HIV related NHL. To review this seminar I searched relevant original articles, books, and review articles from [www.biosemanticjane.org](http://www.biosemanticjane.org), Google scholar, Google, and PubMed sites using HIV and AIDS related NHL, DLBCL, PBL, PCNSL, BL, and PEL key words.

## HIV Related Non-Hodgkin Lymphoma General Pathogenesis of HIV Related NHL

HIV-positive patients' neoplasms develop conceptually in a manner similar to patients who have had solid organ transplants, who are using long-term immunosuppressive medications, and who have severe cell-mediated immune deficiencies. The main pathogenesis mechanisms that have been hypothesized for HIV related lymphomagenesis are immunodeficiency, chronic antigenic stimulation, and the ability to infect cancer cells initiating direct carcinogenesis.<sup>12</sup>

Progressive loss of cluster of differentiation 4 (CD4) T cells during HIV infection period leads to immunodeficiency. In HIV infection both host and viral factors play a significant role in CD4 T cell loss.<sup>13</sup> CD4 T cell can be lost by i) Direct cell massacre due to infection; ii) Apoptosis brought by viral proteins like the Env, Tat, negative regulatory factor; iii) Cell death due to extreme activation of immune cells-activation induced cell death; and iv) Bystander apoptosis of neighboring uninfected cells.<sup>14</sup> From those factors, bystander apoptosis is the principal cause of CD4 T cell loss. Envelope (Env) glycoprotein is a main trigger in HIV induced bystander apoptosis cell death.<sup>14</sup> Env glycoprotein is organized on the surface of the virus and virus-infected cells as a hetero-trimer and interacts with bystander cells that express CD4 and chemokine receptor type 4/5 (CXCR4/CCR5), causing syncytia to form or hemifusion (partial mixing of the outer lipid membranes without complete fusion). Each monomer is made up of a glycoprotein 41 transmembrane unit, which facilitates the fusion of the viral and cellular membranes, and a receptor-binding gp120 unit. As a result, uninfected CD4 T cells die as a bystander.<sup>15</sup> During syncytial formation, phosphorylation of p53 precedes Bax upregulation, which leads to subsequent release of cytochrome c and caspase activation.<sup>16</sup> The interaction between Env glycoprotein and uninfected bystander cells are influenced by Co-receptor expression on CD4 T cells, illness stage, virus tropism, env glycoprotein phenotype, immunological activation, and treatments targeting the viral envelope.<sup>14</sup>

Bystander T cells are also killed by macrophages through the Fas (CD95) and TNFR1 (tumor necrosis factor receptor 1) pathways. Via interactions between TRAIL (TNF Related Apoptosis Inducing Ligand) and DR5 (Death Receptor) in a major histocompatibility complex and Fas-Fas ligand on the surface of activated macrophages, tumor necrosis factor (TNF) can promote apoptosis in bystander T cells.<sup>13</sup>

Polyclonal antibody synthesis has been linked to immune dysregulation, including B cell dysfunction, dendritic cell dysfunction, hypergammaglobulinemia, and weakly inducible pathogen-specific antibody responses. HIV viral particles directly interacting with one another, such as glycoprotein 120 (GP120), have been shown to affect B cell activity and

immunoglobulin (Ig) class switching. The expression of CD39 and CD73, which are crucial for the B cell-mediated inhibition of T cell activities and the start of the immunoglobulin class switch, was lowered in HIV infections. Due to a defective IgG isotype switch brought on by HIV infection, this causes a delayed and diminished IgG response.<sup>17</sup> In general, both immunodeficiency and immune dysfunctions seem to subsidize to the growth of AIDS related NHL through the loss of T-cell mediated control of over proliferation B cells and EBV infection.

Chronic immune activation as an outcome of direct stimulation of B cells by HIV,<sup>13</sup> CD40 ligand induced B cell activation,<sup>18</sup> and complement proteins bound to HIV virions can relate with CD21 on B cells. Nef protein stimulates polyclonal activation indirectly by inducing proinflammatory cytokine produced by macrophages,<sup>19</sup> overproduction of B-cell-stimulatory molecules,<sup>13</sup> outflow of gut microbes in peripheral circulation,<sup>20</sup> and stimulation of toll-like receptor (TLR) pathways all play a role on the pathogenesis of HIV related NHL.<sup>13</sup>

Interleukin (IL)-6, IL-10, interferon gamma induced protein 10 (IP-10), neopterin, tumor necrosis factor (TNF), and chemokine (C-X-C motif) ligand 13 are B-cell-stimulatory cytokines and biomarkers (CXCL13).<sup>21</sup> Individuals with HIV who develop NHL and pre-NHL have higher levels of the soluble cytokine receptors (sCD30, sCD27), immunoglobulin free light chains (FLC), C-reactive protein (CRP), sCD23, and sCD44.<sup>21,22</sup> Several cytokines and biomarkers play a direct or indirect role in the pathogenesis of NHL associated with HIV. For instance, class-switched and somatically hypermutated antibodies can be produced when HIV-positive patients have greater percentages of CD27-B cells.<sup>19</sup>

Th17 cells which originate on mucosal surfaces that keep intestinal barrier integrity are depleted by HIV infections. This leads to microbial particle translocation in the blood that causes systemic immune initiation in chronic HIV infection.<sup>20</sup> For a long period recognition of pathogens by Toll-Like receptors (TLRs) that modify adaptive immune reply results in making of inflammatory cytokines making this pathway important for immune activation.<sup>13,23</sup> Immune activation results in the expression of activation-induced cytidine deaminase (AICDA), a deoxyribonucleic acid (DNA) editing enzyme required for the occurrence of somatic hypermutation (SHM) and immunoglobulin gene (Ig) class-switch recombination (CSR), as well as cMYC/IgH recombination and DNA rearrangements in B-cell lymphoma.<sup>21</sup> AICDA can also cause DNA double-strand breaks, which result in extensive genomic instability, not just in (Ig) genes but also in other locations.<sup>2</sup> Conversely, immunological stimulation results in the overexpression of CXCR4 and CCR5 on cells, which raises CD4 T cells' sensitivity to HIV Env-mediated death.<sup>24</sup>

Lymphomagenesis is also influenced by the direct impacts of viral particles. P17 protein has the capacity to activate the key intracellular signaling pathways known as extracellular signal-regulated kinase 1/2 (ERK1/2). Moreover, it functions as a viral cytokine on pre-activated human T cells, encouraging cell growth, the production of pro-inflammatory cytokines, and HIV-1 replication after attaching to a cellular receptor. This creates an environment that is conducive for HIV-1 infection and replication.<sup>25</sup>

HIV gp120 has the ability to persuade interleukin secretion and AICDA expression.<sup>26</sup> HIV Tat expression in lymphoid tissue of transgenic mice was seen to induce the production of lymphoma-associated cytokines, such as interleukin-6 (IL-6) and IL-10, leading to the development of B-cell lymphoma.<sup>2</sup> CD40L, which is expressed on the surface of activated T cells, can be incorporated into HIV virions and can stimulate B cells to secrete different types of interleukins as well as induce AICDA expression on the surface of B cells. AICDA positive B cells express CD71, interleukin-6 (IL-6), IL-8, IL-10, granulocyte macrophage colony stimulating factor (GM-CSF) and CD10, which are B-cell activator markers.<sup>2,18</sup> In addition, the interaction between CD4-positive virions and major histocompatibility complex (MHC) class II molecules as well as CD80, which is found in dendritic cells, and CD28, which is found in T cells, can activate B cells that represent additional pathogenetic mechanism for HIV related NHL.<sup>19</sup> Neoplastic lymphocytes are attached to HIV-infected endothelium cells in AIDS-related lymphomas. The extravasation of malignant cells into the tissues is sped up when neoplastic cells are responsive to the growth factors supplied by endothelial cells.<sup>27</sup>

## Clinical Trial and Treatment Choice for HIV Related NHL

In addition to HAART HIV related NHL both autologous and allogeneic hematopoietic cell transplant largely suggested. According to AIDS Malignancy Consortium 071 trial and Blood and Marrow Transplant Clinical Network 0803 trial

patients sensitive for chemotherapy- relapsed/persistent HRL and age greater than 15 years old are eligible for hematopoietic cell transplant.<sup>28</sup> A research entitled “Remission of HIV-related naïve and high-risk Burkitt’s lymphoma treated by autologous stem cell transplantation plus cART” suggests that the use of intensive non-myeloablative chemotherapy with transplantation, joint with antiretroviral therapy, in HIV-related naïve and high-risk Burkitt’s lymphoma was accepted and safe.<sup>28,29</sup>

## AIDS Related Diffuse Large B-Cell Lymphoma

AIDS related DLBCL is an aggressive type of NHL and usually develops from the B-cells in the lymphatic system.<sup>30</sup> DLBCL can present either PCNSL or systemic (non-PCNSL). Systemic DLBCL is the most common subtype. Centroblastic variant and immunoplastic variant are the different variants of DLBCL based on cellular morphology. The immunoblastic variant is further characterized plasmacytoid features with down-regulation of mature B cell markers and up-regulation of plasma cell markers.<sup>31,32</sup>

Based on cellular origin and expression of a set of genes algorithm, DLBCL was split into gene expression profiles of germinal center B cells (GCB) and activated B cells (ABC). However, some cases do not meet the predefined criteria they grouped under unclassified. This type of classification was found to have prognostic implications and to identify new drugs with selective activity in GCB-like and ABC-like DLBCL.<sup>33</sup>

A study which was done in German by Baptista et al in 2018 showed that there were few associations between clinical features and cell origin subtypes. The ABC-like subtype was significantly associated worse prognosis in HIV-positive patients. It was observed that GCB-like DLBCL cases were higher than ABC-like cases (64% vs 19%) and the unclassified were 17%.<sup>33</sup> However, a study conducted in Japan by Ota et al in 2014 showed that non-germinal center type DLBCL were higher than germinal center DLBCL, which were 76% and 24%, respectively.<sup>34</sup>

Risk of AIDS-related DLBCL patients are more likely to be presented with different clinical disease manifestation and they are more likely diagnosed at advanced stage.<sup>3</sup> A population based outcome analysis of DLBCL in people living with HIV infection and competent individuals in Italy by Conconi et al in 2018, showed that DLBCL patients are more likely positive for hepatitis B virus (61% vs 4%) and hepatitis C virus (25% vs 13%) infections.<sup>35</sup>

## Epidemiology

It is the most prevalent type of NHL and it accounts for approximately 45% and 50% of all AIDS related lymphoma and NHL, respectively. Around 30–40% of the cases are EBV associated.<sup>3</sup> It is more prevalent among young age groups and male individuals.<sup>36</sup>

## Pathogenesis

The primary risk factor for developing DLBCL associated with AIDS is immunosuppression. Persistent HIV viremia, low CD4+ cell count, and the duration of immune function impairment brought on by low CD4+ cell count all seem to be significant.<sup>37</sup>

EBV-induced pathogenesis, which is caused by immunosuppression, is one possible mechanism that can compel the differential marker expression by HIV status. The immunoblastic variation of DLBCL, which typically arises in the more immunosuppressed host compared to the centroblastic variant of DLBCL, is highly implicated in lymphomagenesis due to specifically decreased T-cell immunity against EBV. The pleiotropic effects of EBV-encoded latent membrane proteins 1 and 2 (LMP1 & 2) are manifested by activating the anti-apoptotic B-cell lymphoma 2 (BCL-2) protein and increasing the expression of CD23 and CD40, which are involved in B-cell activation and proliferation.<sup>12</sup> The mammalian target of rapamycin (mTORC1) gene is stimulated through latent membrane protein 2A (LMP2A) mediators, which may lead to genetic alteration.<sup>38</sup> The mammalian target of rapamycin (mTORC1), through its downstream effectors 4E-binding protein 1 and 70 ribosomal S6 protein-kinase, is in charge of controlling cell cycle proliferation (70S6K). Protein synthesis induced by mTORC1 may promote polyclonal proliferation and then monoclonal proliferation when there is significant immunosuppression and prolonged HIV antigen stimulation, playing an important role in lymphogenesis.<sup>39</sup> In 30–60% of HIV-associated DLBCL, EBV is found in neoplastic lymphoma cells; this prevalence is substantially greater in the immunoblastic variety of DLBCL (80–100%).<sup>40</sup>

In contrast, overexpression of the tumor suppressor gene p53 is caused by mistakes in immunoglobulin (Ig) gene class-switch recombination (CSR) and somatic hypermutation (SHM) in B cell lymphoma cells. c-MYC overexpression, BCL2 activation, and somatic hypermutation involving PIM1, PAX5, and RhoH/TTF have all been identified in about 50% of HIV-related DLBCL patients as additional pathogenic factors.<sup>41</sup> In HIV-infected patients, persistent and excessive c-MYC expression has been linked to worse survival. Since the c-MYC gene controls cell development, proliferation, and death, aberrant expression of this gene may result in the deregulation of several genes.<sup>42</sup> In contrast to their HIV-unrelated counterparts, GCB-like HIV-related DLBCL exhibit defective B-cell receptor (BCR) signaling and ABC-like enrichment in MYC targets, the ARF pathway, and cell cycle components.<sup>33,43</sup>

A comparative study in California by Chao et al in 2015 showed that over-expression of PKC- $\beta$ 2, MUM1, and CD44, and silencing of CDKN1B (gene that encodes p27) than HIV-unrelated DLBCL.<sup>44</sup> In DLBCL unrelated to HIV, P27 is a marker of non-proliferating cells. Moreover, a 2017 study in this area by Browne et al demonstrated that both p70S6K-paired epitopes tested had significant levels of positivity, with 48% of Ser235/236 and 86% of Ser240/244.<sup>39</sup>

In addition to increased hyperproliferation, c-Myc rearrangements, decreased CD4+ and FOXP3+ T cells, and increased activated cytotoxic cells, AIDS-related DLBCL also exhibited enhanced hyperproliferation. Moreover, AIDS-related DLBCL demonstrated increased blood vessel density, higher numbers of cytotoxic cells expressing LMP1 and/or p24, and higher levels of angiogenesis than random DLBCL.<sup>45</sup>

## Morphology and Immunophenotype

The morphological prospects of HIV-related DLBCL are typically characterized by a diffuse infiltration of large lymphoid cells with immunoblastic, centroblastic, and anaplastic cytology (big tumor cells with anaplastic nuclei). Immunoblasts are made of a single, conspicuous nucleolus. Neoplastic cells exhibit CD19, CD20, CD79a, and pax5 positivity,<sup>3</sup> and GCB-like cases exhibited CD10 expression more frequently than ABC-like cases, but not BCL6.<sup>33</sup>

## Treatment

AIDS related DLBCLs are more resistant and have a poor outcome when compared to sporadic DLBCL. Dysregulation of MUM1 and c-MYC has been connected with more treatment resilient activated B-cell subtypes.<sup>44</sup> However, some documented cases demonstrate that DLBCL had regressed with HIV treatment alone. This type of case shows that HAART can help HIV-infected people rebuild their immune systems and can establish an anti-tumor impact, which causes the lymphoma to regress.<sup>27</sup> EPOCH (etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin + rituximab) plus rituximab is the recommended course of treatment.<sup>27</sup> Despite frequent high-risk characteristics, the 2-year OS of HIV-DLBCL patients have reached 75% in the recent combined antiretroviral therapy (cART) period. Results of EPOCH therapy are comparable to those of individuals with a comparable age adjusted international prognostic index (aIPI) who is HIV-negative.<sup>46</sup>

## AIDS Related Plasmablastic Lymphoma

PBL is a relatively uncommon subtype of NHL that has recently been identified as a diffuse immunoblastic lymphoma with diffuse proliferation of giant neoplastic cells, the majority of which are B-immunoblasts that resemble plasma cells. The principal areas of involvement are the gastrointestinal and oral cavities.<sup>47</sup> The brain, testicles, cutaneous nodules, mediastinum, lungs, liver, bone marrow, gingiva, and nasal cavity are further rare extra-oral PBL locations.<sup>48</sup>

## Epidemiology

PBL accounts for around 3–12% of all AIDS related lymphomas.<sup>10</sup> It is predominant in HIV-positive individuals and highly associated with oral cases (80%) and extra oral cases (30–50%).<sup>47</sup> PBL tends to occur when CD4+ count is less than 200/ $\mu$ L and it is an early symptom of HIV infection in around 5% of HIV-PBL patients.<sup>48</sup>

## Pathogenesis

The pathogenesis of PBL is likely related to HIV and/or EBV-encoded RNA infection. Genetic abnormalities, such as BCL-6 mutation, BCL-2 rearrangements, and P53 mutation, were frequently associated with EBV infection. The current



study has shown that recurring rearrangements involving MYC, a well-known oncogene with the immunoglobulin gene, are possible lymphopathogenesis factors in PBL.<sup>49</sup> EBV encoding small RNA (EBER) has been shown in 74% of HIV-related PBL cases.<sup>50</sup> Its pathologic role would be the protection against apoptosis of B lymphocyte through amplification of MYC oncogene expression.<sup>49</sup> However, EBV is only identified in 17% of PBL patients without HIV infection, indicating that EBV is not the only causal factor for the pathogenesis of HIV associated PCNSL.<sup>51</sup>

Gp120 and p17, two HIV viral proteins, may directly influence the growth of lymphomas. These compounds are known to accumulate in plasma or lymph nodes of HIV patients through triggering B-cell activation, and this accumulation has been shown to increase B-cell clonogenicity and proliferation. It has been demonstrated that, via upregulating AICDA, HIV gp120 activates B cells and causes class switch recombination. Several HIV P17 matrix protein variations have been demonstrated to cause B cells to undergo malignant transformation by actively promoting B-cell growth factors.<sup>47,49</sup>

## Morphology and Immunophenotype

It is assumed that NHL came from terminally differentiated, post-germinal center B cells that were probably transitioning from immunoblast to plasma and characterized by massive, round to oval, monomorphic proliferations of cells with eosinophilic cytoplasm and distorted nuclei. The tumor cells resemble immunoblasts in terms of shape and immunophenotype, and their Ki67 proliferation index is frequently higher than 90%. PBL tumor cells usually display plasma cell markers like MUM-1, VS38c, and CD38 and occasionally express the broad B cell marker CD79a. Neither the B cell marker CD20 nor the common leukocyte antigen CD45 are expressed by them.<sup>47</sup>

## Treatment

Despite the availability of intense treatment, the median overall survival only lasts 14 to 15 months. Poor prognostic factors include age greater than 60 years old, MYC/IgH gene rearrangement, being male, and being at an advanced stage at diagnosis.<sup>48,52</sup> Modified CODOX-M/IVAC chemotherapy consisting of cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, alternated with ifosfamide, etoposide, and high-dose cytarabine is the recommended treatment. EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) or 2–4 are also preferable for the therapy.<sup>53</sup> Fit individuals may be considered for intensification with autologous bone marrow transplantation (ABMT).<sup>54</sup>

## AIDS Related Primary Central Nervous System Lymphoma

PCNSL is defined as an extra nodular form of NHL which is limited to the brain, spinal cord, or eyes. It is a type of DLBCL with immunoblastic subtype. PCNSL can present as either monofocal or multifocal in any site in the central nervous system. The brainstem, basal ganglia, cerebellum, and cerebral hemispheres are the areas where it is most frequently found. Compared to HIV negative people, HIV positive patients have lower performance status, high levels of lactic dehydrogenase (LDH), and shorter overall survival.<sup>3</sup> The majority of individuals with HIV who develop PCNSLs are more immunocompromised with a median CD4 count of  $30 \times 10^6/L$ .<sup>55</sup>

## Epidemiology

AIDS associated PCNSL accounts for up to 15% of AIDS patients compared with 1% in the general populations.<sup>53</sup> Before the development of HAART, people with AIDS had a 3,600–5,000 times increased risk for developing central nervous system lymphoma. Since the introduction of HAART its incidence has decreased, due to the improvement of the immune status of the patients. HIV associated PCNSL are almost all EBV related, and more frequently seen in age groups between 20 and 60 years compared with greater than 60 years old in non-HIV related PCNSL.<sup>56</sup>

## Pathogenesis

The most likely cause of lymphomagenesis is poor immune control of EBV, which promotes the production of oncogenic proteins and causes lymphocyte proliferation to increase, with apoptosis occurring later. LMP 1 and 2, EBV nuclear antigen, and short EBV-encoded nuclear RNA (EBERs), which have oncogenic properties and cause apoptosis loss, let the EBV contribute to the malignant transformation of infected cells. This allows for additional proliferation. EBV does

not multiply in central nervous system (CNS) tissue, although infected T cells are likely more prevalent there since the host immune system has lost immunologic control over them.<sup>55,57</sup>

One of the potential pathways of HIV lymphomagenesis, PCNSL, has been shown to have a close relationship with cell adhesion molecules. The CNS may become the homing site for a clone of malignant systemic lymphocytes that express a particular adhesion. Interleukin 8 production and lymphocyte function associated antigen 1 (LFA-1, CD11a/CD18) expression were found to be higher in HIV-infected lymphoid cell lines than in HIV-uninfected lymphoid cell lines in an EBV positive lymphoblastoid cell line (LCLs) study from HIV-infected and HIV-uninfected individuals. Interleukin-8 expression brought on by HIV-positive individuals may have caused a clone of cancer cells to express CD18, which led to an adhesion between CD18 and CD54 and CNS involvement by homing mechanism.<sup>58</sup>

## Morphology and Immunophenotype

Around 95% of PCNSL are predominantly of B-cell origin.<sup>55</sup> This is characterized by immunoblasts with plasmacytoid features. These cells express plasma cell differentiation related markers like CD138 with 60–80% B cell lymphocyte-6 (BCL6), which is the marker of a germinal center B cell,<sup>59</sup> and downregulation of mature B cells markers, such as CD20 and CD45.<sup>12</sup> On histology, the tumor cells have pre-vascular distribution and are often similar to centroblasts. The tumor cells can be presented with macrophages, small reactive lymphocytes, and reactive astrocytes.<sup>1</sup>

There have been a small number of cases documented that suggest PCNSL also has T cell origins. Because CD4 positive cells are depleted as a result of HIV infections, it is challenging to discover CD4 positive T cells lymphoma in HIV patients. On investigation, atypical T cells positive for CD2, CD4, and cCD3 with reduced expression of CD3, CD5, and CD7 were found in a 64-year-old HIV-positive lady who had lethargy and left-sided weakness. The T cell receptor locus' molecular study revealed that clonal T cell receptor gene rearrangement was present.<sup>1</sup>

## Treatment

Nowadays, systemic chemotherapy in conjunction with HAART is used to treat immunocompetent patients. Most HIV-positive individuals have received high dose methotrexate (MTX) and high dose cytarabine chemotherapy regimens.<sup>10</sup> The use of HAART raises CD4 T cells and extends survival to more than 18 months. In a retrospective analysis by Biggar et al, 29% of patients with HIV-associated CNS lymphoma survived more than 24 months.<sup>60</sup>

## AIDS Related Burkitt Lymphoma

BL is a lymphatic system cancer that develops from a germinal-center B cell. It is extremely aggressive, malignant, and expanding quickly.<sup>61</sup> Three clinical variations of BL are recognized by the World Health Organization (WHO) classification: sporadic, endemic, and immunodeficiency-related. Patients with HIV infection are more likely to get BL associated to immunodeficiency. There was no difference in BL risk between the AIDS and HIV alone periods.<sup>6</sup> demonstrates both severe HIV infection with a CD4 cell level of 48 cells/mm<sup>3</sup> and reasonably maintained CD4 numbers.<sup>62</sup>

Most patients report with advanced illness encompassing numerous extranodal locations in addition to peripheral lymphadenopathy. Similar to random BL, AIDS-associated BL frequently manifests in the gastrointestinal tract, bone marrow, and brain, and frequently involves lymph nodes. There have also been reports of unilateral and bilateral orbital tumors causing noticeable facial abnormalities.<sup>62</sup> Acute renal failure secondary to hydronephrosis, tumor lysis syndrome, due to the hasty cell turnover,<sup>40</sup> and intussusceptions (obstruction of the intestine) are the most common clinical presentation.<sup>63</sup> In terms of stage, extra-nodal involvement, and histology, patients with HIV-BL match the general BL population.<sup>64</sup>

## Epidemiology

BL is the second commonest subtype next to DLBCL and covers 25–40% of HIV-associated NHL.<sup>64</sup> Most common in adults, the incidence rate is 6 per 1,000 AIDS cases. Around 30–45% of cases are associated with EBV infections.<sup>65</sup>

## Pathogenesis

As BL is rarely linked to cases of other types of immunosuppression, HIV may be more of a factor in the etiology of BL than previously thought. Ig gene CSR and/or SHM mistakes are the cause of BL pathogenesis. The translocation of the c-MYC gene results in the juxtaposition of the gene with the Ig heavy chain (IgH) locus on chromosome 14 or the Ig light chain loci on chromosomes 2 or 22, which causes an uncontrolled increase of c-MYC production. C-myc and Ig heavy chain (IgH) locus are involved in the most prevalent translocation, t(8;14).<sup>66</sup>

Moreover, cyclin-dependent kinases and mutations in the phosphatidylinositol 3-kinase pathway caused by HIV-induced persistent antigenic stimulation of B-cells result in overexpression of the c-MYC protein gene, which causes fast cell proliferation.<sup>10</sup> RBL2 (Rb2/p130), a wild type tumor suppressor gene, is abnormally overexpressed in HIV-1-related BL. According to studies, interactions between Rb2/p130 and the HIV-1 Tat protein may have an impact on how well it functions. There may be a route by which HIV-1 proteins work in concert with MYC activation to cause the development of BL.<sup>67,68</sup> It has been demonstrated that latent EBV promotes genomic instability in BL cells.<sup>67</sup>

## Morphology and Immunophenotype

Monomorphic small–medium round lymphocytes with a basophilic cytoplasm and vacuoles make up basophilic lymphocytes (BL). Nearly all tumor cells express the lymphocyte, which also displays B-cell markers including IgM, CD19, CD20, CD22, and CD79b, CD79a, germinal center markers like CD10 and BCL-6, and the proliferation marker Ki67.<sup>62</sup> The majority of patients have high lactate dehydrogenase levels (LDH) and advanced stage upon diagnosis, and they are negative for bcl-2 and TdT.<sup>40</sup>

## Treatment

A viable treatment option for HIV-infected patients with BL is AIDS Malignancy Consortium 048 (AMC 048) combined with Rituximab and combination chemotherapy. AMC 048 was able to aggressively treat HIV-infected patients with BL and achieve high rates of long-term disease remission thanks to a modified intensive chemotherapy regimen that included cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine as well as rituximab. Because it contains high doses of the blood–brain barrier-crossing medications methotrexate and cytarabine, the modified AMC 048 version of CODOX-M/IVAC-R may be more beneficial for patients who have CNS disease or are at high risk for CNS relapse (such as those with bone marrow, testicular, or multiple extranodal sites).<sup>64</sup> There is a lack of information on patients' prognoses for HIV-BL. An international analysis of 249 patients with HIV-BL treated from 2008 to 2019 showed that the 3-year progression-free survival (PFS) and overall survival (OS) were 61–67% and 66–71%, respectively, with a median follow-up of 4.5 years.<sup>69</sup>

## AIDS Related Primary Effusion Lymphoma

PEL is an uncommon kind of NHL that is typically found in HIV-positive, critically immunocompromised people. It typically manifests as a lymphomatous effusion in serous bodily cavities and is connected to HHV-8 and EBV infection. The morphology of a rare solid extra-cavity version can be confused with other aggressive lymphoma forms.<sup>70</sup>

## Epidemiology

Up to 5% of HIV positive people have this extremely uncommon NHL, compared to 0.3% of HIV negative patients.<sup>40,71</sup> PEL is more common in people with advanced immunodeficiency, a CD4 count of fewer than 150 cells/mL, and a history of prior AIDS-defining diseases.<sup>40</sup>

## Pathogenesis

The pathogenesis of PEL is almost universally linked to prior HHV-8 associated transforming proteins like viral latency associated nuclear antigen 1 and 2 (LANA1 and 2), V-cyclin, vFLIP, and vIL6 which provide proliferative and anti-apoptotic signals.<sup>3</sup> Latency associated nuclear antigen (LANA) is able to antagonize p53 and retinoblastoma protein



(pRb) function, and activate MYC.<sup>12</sup> In addition, the combination of immunodeficiency and EBV have been proposed as co-factors causing PEL.<sup>3</sup>

## Morphology and Immunophenotype

Extra-cavity PEL manifests as solid masses that, with a few exceptions, have the same morphology, immunophenotype, and gene expression patterns as classic PEL. Large round to irregular eccentric nuclei with prominent single nucleoli are prominent in the tumor cells, which also feature an abundance of highly basophilic and occasionally vacuolated cytoplasm.<sup>11</sup>

The PEL originates from the post germinal-center and usually lacks expression of most B-cell associated antigens including immunoglobulins. The most expressed antigens are CD30, MUM1, CD45, CD79a, p53, and CD138. The B-cell origin of PEL can be confirmed by the presence of clonal immunoglobulin gene rearrangements. Solid variant express CD20, CD79a, and T cell antigens C3 and CD7. Abnormal laboratory findings are also common, like anemia, elevated lactate dehydrogenase (LDH) levels, and hypo albuminemia due to development of nephrotic syndrome. The presence of HHV-8 infection in PEL supports the differential diagnosis from plasmablastic lymphoma, because these two entities have overlapping morphologic and immunophenotypic features.<sup>67,70</sup>

## Treatment

For the management of PEL, there is no set standard of care. The most often utilized therapy has been concurrent HAART and CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone), as it has been in the majority of patients with AIDS-associated lymphomas. However, it is commonly resistant to chemotherapy with a short median persistence of less than 6 months. In HIV positive individuals with PEL, starting HAART has been demonstrated to be a crucial element of effective therapy regimens.<sup>70</sup> A better prognosis is anticipated with more rigorous chemotherapy, such as dose-adjusted EPOCH (DA-EPOCH; etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) and CDE (cyclophosphamide, doxorubicin, etoposide).<sup>72</sup>

## Conclusion

HIV infected people continue to have elevated risk of NHL, even this risk varies substantially by subtype. The primary cause is due to immunodeficiency, this is why oncogenic viral infections like EBV are more associated. The most common AIDS related NHL are DLBCL, BL, PCNSL, PBL, and PEL. From these, DLBCL is the most severe and common type, while PBL and PEL are rare. Various B-cell biomarkers and cytokines were elevated in pre-NHL and NHL in HIV-positive individuals. The pathogenesis is associated with chromosomal abnormalities that deregulate the expression of various oncogenes by viral particles and cytokines in different ways. However, the role of these viral particles and cytokines on pathogenesis is not clearly stated, so further study should be conducted to know the specific role of those viral particles and cytokines. Because NHL are worse in HIV positive patients, special concerns like early screening, diagnosis, and treatment should be taken to prevent further complications.

## Abbreviations

ABC, Activated B Cell; AICDA, Activation-Induced Cytidine Deaminase; AIDS, Acquired Immunodeficiency Syndrome; BCL, B Cell Lymphoma; CD, Cluster of Differentiation; CNS, Central Nervous System; CSR, Class-Switch Recombination; DLBCL, Diffuse Large B-Cell Lymphoma; DNA, Deoxyribonucleic Acid; EBV, Epstein-Barr Virus; GCB, Germinal Center B Cell; Gp120, Glycoprotein 120; HAART, Highly Active Anti-Retroviral Therapy; HHV-8, Human Herpes Virus-8; HIV, Human Immunodeficiency Virus; HL, Hodgkin Lymphoma; Ig, Immunoglobulin; LMP, Latent Membrane Protein; NHL Non Hodgkin Lymphoma; Nef, Negative Regulatory Factor, PBL Plasmablastic Lymphoma; PCNSL, Primary Central Nervous System Lymphoma; SHM, Somatic Hypermutation.

## Disclosure

The authors report no conflicts of interest in this work.

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