



**Review Article**

**Plasmablastic Lymphoma. A State-of-the-Art Review: Part 1- Epidemiology, Pathogenesis, Clinicopathologic Characteristics, Differential Diagnosis, Prognostic Factors, and Special Populations**

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**Abstract.** This two-part review aims to present a current and comprehensive understanding of the diagnosis and management of plasmablastic lymphoma. The first section, as presented in this paper, reviews epidemiology, etiology, clinicopathological characteristics, differential diagnosis, prognostic variables, and the impact of plasmablastic lymphoma on specific populations. Plasmablastic lymphoma (PBL) is a rare and aggressive form of lymphoma. Previous and modern studies have demonstrated a significant association between the human immunodeficiency virus (HIV) and the development of the disease. The limited occurrence of PBL contributes to a need for a more comprehensive understanding of the molecular mechanisms involved in its etiology. Consequently, the diagnostic procedure for PBL poses a significant difficulty. Among the group of CD20-negative large B-cell lymphomas, PBL can be correctly diagnosed by identifying its exact clinical characteristics, anatomical location, and morphological characteristics. PBL cells do not express CD20 or PAX5 but possess plasmacytic differentiation markers such as CD38, CD138, MUM1/IRF4, Blimp1, and XBP1. PBL must be distinguished from other B-cell malignancies that lack the CD20 marker, including primary effusion lymphoma, anaplastic lymphoma kinase-positive large B-cell lymphoma, and large B-cell lymphoma (LBCL). This condition is frequently associated with infections caused by the Epstein-Barr virus and genetic alterations involving the MYC gene. Despite advances in our comprehension of this disease, the prognosis remains dismal, resulting in a low overall survival rate, although recent reports suggest an apparent tendency towards substantial improvement.

**Keywords:** Aggressive Lymphoma; HIV; People living with HIV; Plasmablastic Lymphoma; CD20-negative large B-cell Lymphoma; CD38+; CD138+; Oral cavity lymphoma.

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**Article Highlights:**

- The 5<sup>th</sup> edition of the World Health Organization classification for hematological and lymphoid cancers recognizes plasmablastic lymphoma (PBL) as a unique subtype. This classification includes PBL as "large B-cell lymphomas".
- Fewer than 1100 cases of PBL have been reported in the medical literature.

- HIV, immunodeficiencies, persistent immunological activation, and oncogenic herpesviruses like EBV are suspected causes of this condition.
- The disease is aggressive and destructive, primarily affecting the oral cavity, as seen in its first clinical presentation. It is well known that it also affects lymph nodes and areas outside the mouth.
- A biopsy of the tissue mass or lymph nodes is necessary for diagnosis. Core needle or small needle biopsy is often limited to inaccessible areas.
- Plasmablasts, activated B cells undergoing somatic hypermutation and class-switching recombination, are believed to be the cells of origin of PBL.
- The immunophenotype often lacks CD45, CD20, and CD79a expression, but it is positive for CD38, CD138, and MUM1. Additionally, EBER and KI67 expression exceeds 80%.
- PBL is distinct from other B-cell malignancies lacking CD20 marker, such as primary effusion lymphoma, anaplastic lymphoma kinase-positive large B-cell lymphoma, and HHV8+ large B-cell lymphoma (LBCL).
- It is important to recognize that distinguishing plasmablastic myeloma from plasmablastic lymphoma can be challenging and complex.
- Historically, it has been observed that PBL has generally exhibited a less favorable prognosis, as seen by a median overall survival (OS) ranging from 8 to 15 months. Survival estimates of more recent data ranged from 32 months to 62 months.

**Definition.** According to the fifth edition of the World Health Organization Classification of Hematolymphoid Tumors (WHO-HAEM5), PBL is classified as a specific subtype within the category of "large B-cell lymphomas".<sup>3</sup> The nomenclature about PBL and other entities has undergone revision during the transition from the 4<sup>th</sup> edition of the World Health Organization Classification of Hematolymphoid Tumors (WHO-HAEM4)<sup>12</sup> to the 5<sup>th</sup> edition (WHO-HAEM5), with the aim to promote consistency. The phrase "diffuse large B-cell lymphoma" has been modified to "large B-cell lymphoma".

**History.** In the 1992 edition of "Neoplastic Hematopathology", Stein's article started and provided a comprehensive description of PBL as a novel and original concept.<sup>1</sup> In 1997, Delecluse and Stein documented the first case series of PBL. This investigation utilized consultation files from the lymphoma reference center at Benjamin Franklin Hospital in Berlin. The study consisted of a sample size of 16 participants from Germany, with 15 having been diagnosed with HIV.<sup>2</sup> The tumor demonstrates a preference for the oral cavity, particularly the gingiva or palate; additional sites, such as the bone marrow, may be

observed as a late or infrequent characteristic.

**Epidemiology.** The incidence and temporal distributions of PBL in people with either HIV-positive or HIV-negative status are not well established due to their rarity. The estimated incidence of PBL in the context of HIV-related lymphomas is approximately 2 percent.<sup>5</sup> In addition to its notable association with HIV infection, there have been recorded cases of PBL in persons with other types of immunodeficiency, including iatrogenic immunosuppression subsequent to solid organ transplantation and the geriatric population.<sup>11-17</sup> Moreover, it is crucial to recognize that PBL can also occur in patients who are HIV-negative and may be associated with preexisting lymphoproliferative or autoimmune diseases. A few cases have been documented among people with healthy immune systems.<sup>17-19</sup> PBL has been observed in people across a broad spectrum of ages, from 1 to 90 years, but there is a scarcity of reported cases of young individuals. The examination of the gender distribution of PBL cases reveals a notable predominance of males, accounting for around 75% of the overall population.<sup>19-22</sup> PBL is a rare disease with a published number of less than 1100 cases up to date. Nevertheless, there has been a recent increase in the number of reported cases in the literature. There is a possibility that the observed increase in the incidence of this disease is primarily attributable to improved diagnostic techniques and heightened awareness rather than a genuine rise in frequency. However, this information needs to be analyzed with large-scale epidemiological studies.

### Pathogenesis

*The biology of the originating cell.* Plasmablasts, which experienced the germinal center response and are currently in the process of differentiation into plasma cells, are widely recognized as the precursor cells of PBL. The essential role of the germinal center (GC) reaction is to generate B-cell clones that possess the highest affinity for a specific antigen. B-cell clones exhibit bidirectional migration between two distinct regions within the germinal center (GC), namely the "light zone" and the "dark zone". This mobility allows them to compete for antigen presentation by follicular dendritic cells while receiving survival signals from helper T cells. Acquiring somatic mutations plays a crucial role in promoting affinity development within B-cell clones.

Furthermore, B-cell clones are involved with DNA class-switching recombination, a process that leads to the production of immunoglobulin A (IgA), immunoglobulin E (IgE), or immunoglobulin G (IgG). This mechanism serves to expand the range of antibodies produced. There is a prevalent assumption that clones of autoimmune or anergic B cells undergo apoptosis. Apoptosis is expected to occur in a significant proportion

of B cells during the germinal center reaction. Various factors can induce apoptosis in the germinal center, including the B-cell receptor (BCR), T-cell growth factor beta (TGF- $\beta$ ), and Fas-mediated pathways. Both the B-cell receptor (BCR) and transforming growth factor-beta (TGF- $\beta$ ) signaling pathways induce apoptosis by interacting with proapoptotic components of the BCL-2 family. The previously mentioned signaling mechanism results in the overexpression of BH3-only proteins and the downregulation of BCL-XL, ultimately leading to mitochondrial depolarization and the initiation of intrinsic apoptosis.<sup>23-26</sup> B-cells sometimes experience programmed cell death via the FAS pathway. The FAS death induction signaling complex, which is accountable for initiating cell death, generally remains quiescent. Nevertheless, its activation occurs in the presence of an imbalance in survival signals originating from T cells and follicular dendritic cells. This activation process plays a role in the caspase-8 activation and the subsequent initiation of extrinsic apoptosis.<sup>23-26</sup> The final fate of a particular subset of B lymphocytes is to undergo differentiation into either long-lived lymphocytes or plasma cells. Without antigenic stimulation, a certain subset of lymphocytes undergoes a stochastic transformation process, generating plasma cells.<sup>23-26</sup> Signaling pathways help the first stage of plasma cell differentiation by turning off the transcription factors PAX-5 and BCL-6. This block is done by the transcription factor BLIMP-1, which is mostly found in plasma cells.

Regarding morphology, centrocytes undergo a process of transformation in which they undergo differentiation into plasmablasts before attaining maturity as plasma cells. From a phenotypic perspective, the cells display the presence of CD38, interferon regulatory factor 4/multiple myeloma 1 (IRF-4/MUM-1), and undergo a downregulation of CD20 expression while retaining CD19 expression.<sup>23-27</sup> In summary, the currently accepted assumption is that plasmablasts, activated B cells that have undergone somatic hypermutation and class-switching recombination, constitute the primary biological origin of PBL. The plasmablast undergoes a differentiation process during this phase, transforming it into a mature plasma cell. Plasmablasts are a characteristic element of reactive phenomena observed in viral infections, such as Epstein-Barr virus (EBV) and HIV.

**Etiology.** The precise etiology of PBL remains unknown, although recent studies have shed light on the importance of genetic rearrangements in the MYC gene and its correlation with EBV infection as essential pathogenic mechanisms. Furthermore, the involvement of IRF4, JAK-STAT, Notch, and RAS-RAF signaling pathways will be carefully highlighted.

*The influence of Epstein-Barr virus (EBV).* The Epstein-Barr virus is classified as a DNA virus demonstrating a preference for infecting B, T, natural killer, and epithelial cells. The prevalence of seropositivity to EBV is estimated to be around 90% among the global population. Around 80% of cases of PBL exhibit a correlation with EBV infection. Moreover, the prevalence of EBV is observed to be higher in PBL cases among individuals with human immunodeficiency virus (HIV) in comparison to those without HIV.<sup>28-29</sup> After the first infection with EBV, the virus establishes a latent state among memory B cells and maintains its presence by avoiding the host's immune system. Viral latency and persistence are promoted by creating certain viral gene products, such as the Epstein-Barr nuclear antigen (EBNA-1) and EBER. The Epstein-Barr virus (EBV) disrupts the function of proapoptotic proteins, therefore promoting the survival of host cells by activating intracellular signaling pathways such as NF- $\kappa$ B and NOTCH signaling pathways.<sup>27-29</sup> The potential outcome of an Epstein-Barr virus (EBV) infection is the acquisition of oncogenic mutations, which may subsequently trigger the transformation of B cells and ultimately contribute to the development of cancer. There is an increased incidence of B-cell lymphomas associated with Epstein-Barr virus (EBV) in populations affected by HIV infection, individuals undergoing immunosuppressive therapy, and the elderly.<sup>29</sup> Despite the utilization of combination antiretroviral therapy (cART) and the attainment of viral suppression, individuals who are infected with the human immunodeficiency virus (HIV) still experience an increased vulnerability to the occurrence of cancers associated with the Epstein-Barr virus (EBV). The phenomenon in question could potentially be ascribed to a convergence of various mechanisms, including immune evasion, prolonged inflammation characterized by a modified cytokine profile, and immunological senescence. Significantly, these characteristics continue to exist in individuals who are HIV-positive even after receiving combination antiretroviral therapy (cART) and maintaining virological suppression.<sup>29-31</sup> The immunological senescence and evasion reported in cases of Epstein-Barr virus (EBV)-positive PBL can be mostly related to the expression of programmed death ligand 1 (PD-L1) by PBL cells and tumor-associated macrophages (TAM). The primary function of this PD-L1 production is to inhibit the cellular responses directed toward tumor suppression.<sup>30</sup> The evasion of the immune system is made possible by the reduced expression of major histocompatibility complex (MHC) class II proteins in PBL infected with Epstein-Barr virus (EBV) and by the secretion of immunosuppressive agents such as interleukin 10, transforming growth factor beta (TGF- $\beta$ ), and other substances by tumor-associated macrophages (TAM) and regulatory T cells.<sup>31-32</sup>

Histological analysis is employed to confirm the existence of Epstein-Barr virus (EBV) infection in PBL, with a particular focus on detecting Epstein-Barr-encoded small RNA (EBER) through in situ hybridization (ISH) within the tumor cells. The EBV latency type I program has been associated with the occurrence of PBL. Nevertheless, it is important to acknowledge that latency types II and III have been documented in cases associated with post-transplant and HIV-related illnesses.<sup>33-34</sup>

*The role of the MYC gene.* The oncogenic transcription factor MYC is a molecular entity that plays a critical role in the development and progression of cancer. The MYC protein is known to significantly impact the regulation of key biological processes, including cell proliferation, metabolism, apoptosis, and cell differentiation. The gene expression analysis has revealed the consistent activation of MYC signaling in PBL.<sup>35</sup> Immunohistochemical labeling was utilized to evaluate the expression of MYC protein in most of the examined cases, demonstrating a notable predominance of upregulated expression. In different studies, it has been reported that MYC translocations were identified in roughly 50% of PBL cases. This discovery implies that MYC translocation does not only account for the upregulation of MYC at the protein level.<sup>35-36</sup> Approximately two-thirds of PBL cases include translocations between the MYC gene and the heavy chain immunoglobulin gene (IgH), while the remaining one-third of cases exhibit translocations with non-IgH partners. Patients with PBL who tested positive for MYC translocation displayed a significantly elevated Ki67 proliferation score. However, there is an ongoing debate questioning the influence of MYC translocation on the survival outcomes of patients diagnosed with PBL.<sup>37</sup> Around 10% of primary PBL cases demonstrate observable MYC mutations associated with translocations. The current understanding of the biological effects of these MYC mutations is still unknown. A correlation was observed between the occurrence of MYC mutations and the concurrent prevalence of MYC translocations.<sup>38</sup>

The presence of MYC mutations can be linked to the activation-induced cytidine deaminase (AID) facilitated abnormal somatic hypermutation mechanism, as demonstrated by the relocation of the MYC gene to the IgH locus in most cases.<sup>39</sup> This mechanism could explain a higher frequency of silent mutations and the predominance of subclonal MYC mutations. In addition to modifications in passenger genes, specific mutations in the MYC gene can affect important functional regions, thereby increasing the carcinogenic capacity of MYC. Prior research provided empirical support suggesting that the occurrence of MYC T58A and P57S mutations, which are frequently detected in Burkitt lymphoma, plays a role in lymphoma progression by promoting

cellular proliferation and inhibiting the proapoptotic characteristics generally associated with MYC.<sup>38-40</sup> Additionally, it is important to acknowledge that MYC's transactivation domain (TAD) undergoes ubiquitination, resulting in subsequent proteolytic degradation.<sup>40</sup> Modifications to the topologically associated domain (TAD) can impede the proteolysis mechanism, enhancing the MYC protein's stability. Approximately 50% of the MYC mutations identified in PBL were located within the transactivation domain (TAD) of exon 2. Despite the absence of a designated mutational hotspot in the study, additional functional examinations are required to definitively determine the precise role of MYC mutations in the development of PBL.<sup>41-43</sup> The observation that several cancer-promoting pathways can activate MYC in diverse cell types underscores the significance of MYC-mediated transcriptional regulation in the biology of PBL. The gene MYC assumes a pivotal function as a target gene within the JAK-STAT signaling pathway; its upregulation is facilitated by the direct contact between the activated STAT3 protein and the promoter region of the gene. Moreover, there have been reports suggesting that the activation of the RAS-RAF signaling pathway results in the enhancement of MYC production by stabilizing the MYC protein and impeding its degradation by the proteasome. MYC activation as a downstream target through NOTCH1 signaling has been documented in T-cell acute lymphoblastic leukemia/lymphoma cases.<sup>42-47</sup> The higher levels of MYC protein seen in PBL cells without MYC translocation may be because MYC is activated through various pathways that have been altered.<sup>48</sup>

*The Impact of the IRF4 gene.* The expression of IRF4 is restricted to hematopoietic systems, and it is widely recognized as a pivotal regulator of plasmacytic differentiation. Centrocytes induce plasmacytic differentiation by downregulating the expression of BCL6, a crucial regulator involved in the formation and maintenance of the germinal center. Concurrently, they upregulate the expression of transcription factors such as IRF4.<sup>49</sup> The depletion of IRF4 under specific conditions in live experiments led to the complete absence of plasma cells, thereby emphasizing the essential function of IRF4.<sup>50</sup> Additionally, it has been reported that there is a notable increase in the expression of IRF4 in several forms of lymphoid malignancies. Subsequent functional analyses have revealed that the signaling path of the IRF4 network is of paramount importance in the viability and proliferation of PCM, ABC, DLBCL, and ALCL cells.<sup>51</sup> The immunohistochemical staining results revealed a substantial increase in the expression of IRF4 in PBL samples. An underlying mechanism was identified whereby approximately 33% of primary PBL patients exhibited a unique and localized amplification of 6p25.3.<sup>52,53</sup> The reported amplification proved to

include a restricted group of genes, one of which was identified as IRF4. The molecular target IRF4 has been recognized in various lymphoma forms, including Hodgkin lymphoma, specific subtypes of T-cell lymphoma, and plasma cell myeloma (PCM). However, there is currently no data indicating the presence of recurring focal amplifications of 6p25.3. The lack of detected amplifications suggests that these genetic abnormalities may function as a unique genetic anomaly in the context of PBL. The prevalence of IRF4 mutations was seen in approximately 4% of the first PBL samples.<sup>50-54</sup>

*The role of the JAK-STAT pathway.* The JAK-STAT signaling pathway is of paramount importance in modulating cellular differentiation, proliferation, viability, and the immune response. As a result, it has been linked to the carcinogenic mechanisms associated with a wide array of cancers. Cytokines, like interleukin-6 (IL-6), engage in interactions with receptor tyrosine kinases (RTKs) that are linked to cytosolic domain proteins belonging to the Janus kinase (JAK) family, thereby initiating the JAK-STAT signaling cascade.<sup>55-56</sup> JAK transactivation occurs when JAKs become activated, resulting in the phosphorylation of tyrosine residues on receptor tyrosine kinases (RTKs). The phosphorylated residues act as binding sites for Janus kinases (JAKs), which turn on several effector proteins. In order to facilitate the regulation of gene expression, STAT proteins are recruited, undergo dimerization upon phosphorylation, and subsequently translocate to the nucleus. Mutations affecting the constituents of JAK-STAT signaling have been identified in many subtypes of T-cell lymphoma, such as T-cell large granular lymphocytic leukemia (T-LGL) and conditions involving natural killer cells. However, these mutations are rarely reported in aggressive B-cell lymphomas.<sup>57-60</sup> The presence of somatic mutations in PBL has been observed to affect many genes responsible for encoding elements of the JAK-STAT signaling pathway. This finding highlights the importance of this pathway in the disease's pathogenesis. A total of 25% of the PBL patients examined displayed STAT3 mutations.<sup>61</sup> Notably, most of these observed mutations were situated inside the SH2 domain, which plays a crucial role in dimerization and activation mechanisms. It is noteworthy that a significant link exists between mutations in the STAT3 gene and the presence of concomitant HIV infection.<sup>61</sup> The prevalence of STAT3 mutations in PBL derived from HIV-positive patients was around 50%, but the occurrence of these mutations in PBL derived from HIV-negative patients was lower than 10%.<sup>61</sup> The discrepancy observed was less pronounced in individuals with immunocompetent PBL than in those with any level of immunodeficiency. This suggests that HIV infection may have a direct impact on

the development of lymphoma, independent of its immunosuppressive effects.<sup>61</sup>

In addition to STAT3 mutations, PBL has a high frequency of mutations in other genes that code for parts of the JAK-STAT pathway. Mutations in the JAK1 gene were observed in 14% of individuals with HIV, with a significant clustering of these mutations observed at the G1097 codon.<sup>62</sup> Mutations at the G1097 codon have also been previously recorded in specific subgroups of T-cell lymphoma.<sup>62</sup> Several cases of PBL demonstrated concomitant alterations in various constituents of the JAK-STAT pathway, such as STAT3 and SOCS1/3. A considerable percentage of cases of PBL in individuals without human immunodeficiency virus (HIV) infection, specifically more than one-third, as well as a huge majority of PBL cases associated with HIV infection, specifically over sixty percent, had alterations within the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway.<sup>4,61,62</sup> In the context of PBL, it is relevant to recognize that the JAK-STAT pathway can influence not just mutations but also recurrent somatic copy-number alterations (SCNAs). The research findings indicated a high occurrence of recurring focal amplifications in the 1q21.3 area, detected in 52% of PBLs.<sup>4,61,62</sup> The change impacts the IL-6 receptor (IL-6R) gene and the MCL1 gene linked to antiapoptotic activity. The gene MCL1 is prone to direct activation by the JAK-STAT signaling pathway, whereas the IL-6R protein plays a vital role in initiating the activation of the JAK-STAT system at a higher level.<sup>62-64</sup>

*Role of NOTCH in promoting the development of PBL.* The activation of NOTCH signaling starts when ligands cut apart receptors into shorter pieces. Mammals have an overall total of four unique NOTCH receptors, specifically identified as NOTCH1, NOTCH2, NOTCH3, and NOTCH4.<sup>65</sup> The transmembrane receptor NOTCH undergoes proteolytic cleavage upon contact with specific ligands provided by neighboring cells, leading to the release of the NOTCH intracellular domain (NICD). The NICD molecule, which is unbound and not associated with any other molecules, can penetrate the cellular nucleus and performs the function of controlling the process of gene transcription.<sup>66</sup> The NOTCH pathway is a highly conserved process that regulates cellular differentiation, survival, and proliferation with the specific consequences being dependent on the cellular context. The scope of NOTCH signaling goes beyond intracellular mechanisms, embracing intercellular communication and its relevance in tumor formation, notably in enhancing interactions between tumor cells and their surrounding environment.<sup>65-67</sup> Approximately 25% of PBL cases exhibited mutations in genes responsible for encoding subunits of the NOTCH signaling system. The genes Notch1, Notch4, and SPEN,

responsible for encoding a negative regulator of the Notch signaling pathway, demonstrated the highest incidence of mutations. Except for a small group of cases, NOTCH mutations were not mostly found in either the HD or the PEST domain, as seen in T-ALL and other B-cell cancers. The primary site of most alterations has been identified as the extracellular epidermal growth factor (EGF)-like domain. Nevertheless, the functional consequences of these mutations in PBL pathogenesis have yet to be fully understood.<sup>41,68</sup> The findings of a limited-scale investigation involving individuals diagnosed with PBL revealed a consistent expression of NOTCH1, predominantly localized inside the nuclear region, as indicated by the staining pattern. The findings of this study underscore a substantial prevalence of NOTCH activation.<sup>69</sup>

*Role of the RAS-RAF pathway in promoting the development of PBL.* The RAS-RAF pathway, which regulates fundamental cellular processes such as differentiation, proliferation, apoptosis, and migration, is frequently altered in the context of cancer.<sup>70</sup> RAS proteins' activation involves several cytokines and receptor tyrosine kinases, which promote the transition of RAS proteins into their active state while being bound to GTP. The activation signal subsequently promotes the recruitment of RAF kinases to the cellular membrane, resulting in additional downstream activation. Following this, RAF kinases undergo the dimerization process and play a role in transmitting signals by interacting with MEK and ERK proteins, thus activating various transcription factors. Although the occurrence of RAS-RAF signaling mutations in aggressive lymphomas is not prevalent, it is recognized as one of the most frequently affected oncogenic pathways in the context of cancer. Somatic mutations in the RAS gene are commonly seen in primary cutaneous melanoma (PCM), with NRAS and KRAS mutations detected in around 20% of PCM cases. The abovementioned mutations, which are primarily subclonal, correlate with disease progression.<sup>71-76</sup> The frequency of recurrent NRAS mutations in PBL cases was approximately 30%, whereas KRAS mutations were detected in 10% of cases, and BRAF mutations were identified in 6% of cases. The investigators observed that a significant proportion of RAS mutations were localized at the widely recognized mutational hotspot sites G13 and Q61.<sup>41,71-75</sup> The above mutations are called gain-of-function mutations because they can keep the pathway active by making RAS more stable when it is bound to GTP.<sup>76-81</sup>

**Clinical Evaluation and Staging.** Patients suspected of having PBL should have their medical history reviewed, focusing on B symptoms, including fever, night sweats, and weight loss over 10% in the past six months. Additionally, inspect Waldeyer's ring, the integumentary

system, the hepatic region, and the splenic region, which contain lymph nodes. Further, patient performance must be assessed. A full blood count, chemical analysis with LDH determination, beta-2 microglobulin measurement, immunoglobulin profile by immunofixation, and plasma and urine kappa and lambda tests should be performed in the lab. Serological testing is required for identifying antibodies against hepatitis B and C viruses, cytomegalovirus, Epstein-Barr virus, Toxoplasma, and varicella-zoster virus, quantifying HIV loads in plasma, and analyzing CD4+ and CD8+ T-lymphocyte subpopulations. Before chemotherapy, patients' renal, hepatic, and cardiac functions must be assessed. Echocardiography is also indicated for anthracycline-based chemotherapy patients to evaluate heart function. If imaging discloses symptoms or lesions, gastrointestinal endoscopy may be recommended. Women of reproductive age must have pregnancy testing and fertility preservation counseling before treatment. According to the current guidelines, PET/CT is the recommended imaging modality for evaluating aggressive lymphoma. Further imaging with CT or MRI may be performed if there is a clinical indication. Up to 25% of PBL patients have bone marrow involvement, requiring a biopsy and aspiration. Diagnostic lumbar punctures are recommended for HIV and PBL patients due to the higher risk of CNS involvement, particularly in the meninges. Flow cytometry, cytology, and molecular tests are advised to detect leptomeningeal lymphoma in cerebrospinal fluid. The most common staging approach is Ann Arbor. The International Prognostic Index (IPI) is recommended for risk stratification. Excisional and incisional biopsies are mandatory. FNA biopsy cannot reliably diagnose lymphoma in the majority of cases. Core needle biopsy may not be effective, but it can be used in some cases. When an excisional or incisional lymph node is inaccessible, a core biopsy (preferably many biopsies) and fine-needle aspiration (FNA) biopsies are recommended. Enhancing these procedures with appropriate ancillary techniques helps differentiate diagnoses. For this scope, immunohistochemistry (IHC), flow cytometry, molecular analysis, and cytogenetic methods like karyotyping or FISH are used to detect immunoglobulin gene rearrangements and significant translocations. This comprehensive technique may offer a lot of diagnostic data. In cases where the material is undiagnostic, another biopsy is needed.<sup>5</sup>

**Clinical Features and Presentation.** As previously outlined, PBL is defined by its propensity to affect the oral cavity. Nevertheless, it is crucial to remember that a significant percentage, about 45%, of reported cases have been observed in different structures outside of the oral cavity. The anatomical locations covered in this list consist of the gastrointestinal tract, skin, soft tissue, heart,

mediastinum, retroperitoneum, liver, lungs, testes, vulva, parotid gland, breast, central nervous system (CNS), lymph nodes, bone marrow. The lymphoma exhibits a male predominance ratio of 4:1 and typically manifests at a median age of 40 years. In around 5% of cases, this disease occurs as the primary manifestation of HIV infection. The median age of diagnosis usually ranges within the approximate range of 40 years. However, it is crucial to always keep in mind that people with HIV tend to present at a younger median age of 40 years, in contrast to non-HIV patients whose median age exceeds 50 years. This finding offers evidence for the hypothesis that age-related senescence might play a role in a distinct subgroup of people who are not infected with HIV. Reported cases involving children have also been documented.<sup>8-10</sup> A significant proportion of cases are characterized by an accelerated disease progression, frequently with destructive lesions. This condition is typically accompanied by an increased concentration of lactate dehydrogenase (LDH) and the presence of B symptoms.

At the presentation, it was noted that a majority of individuals confirmed to have HIV (more than 65%), patients who received transplantation (50%), and people with apparently normal immune systems (25%) exhibited advanced disease, notably fitting into Ann Arbor stages III and IV. However, clinical differences are still observed across patients with different



**Figure 2.** A destructive lesion of a large part of the trunk and left arm from plasmablastic lymphoma (front).

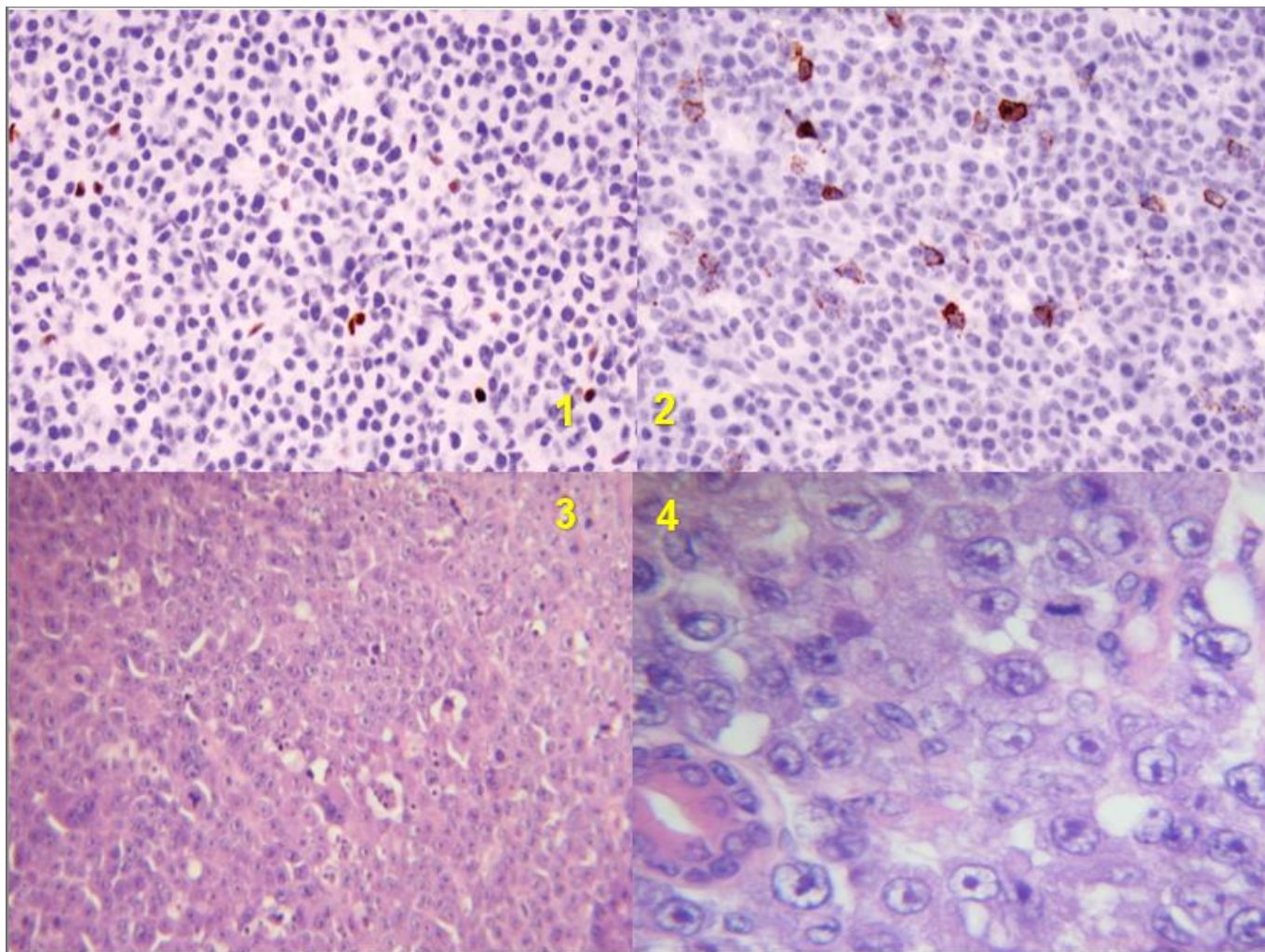


**Figure 1.** A destructive lesion of a large part of the trunk and left arm from plasmablastic lymphoma (back).



**Figure 3.** An extensive lesion caused by plasmablastic lymphoma, which affects both the integumentary system and the cranial bones.

immunological conditions. The anatomical distribution of PBL sites exhibits a higher degree of variability among persons who test negative for HIV in comparison to those who test positive for HIV. Furthermore, it is seen that bone marrow involvement and the presence of B symptoms are less commonly observed in individuals who are HIV-negative.<sup>12-13</sup> Although lymph node involvement at the time of diagnosis is very rare, it has been observed in approximately 30% of people who have had transplantation. The incidence of bone marrow



**Figure 4.** Large cells with plasmablastic morphology. 1 BCL6 negative. 2 CD20 negative. 3 Hematoxylin and eosin medium magnification. 4 Hematoxylin and eosin high magnification.

infiltration in patients with PBL has been reported to exhibit variance among individuals with HIV infection and those without HIV infection. A comprehensive examination was conducted on a large cohort of 590 patients diagnosed with PBL. The findings of this study indicate that a considerable proportion of both HIV-associated cases, up to 40%, and HIV-negative cases, up to 25%, exhibited bone marrow involvement.<sup>5</sup>

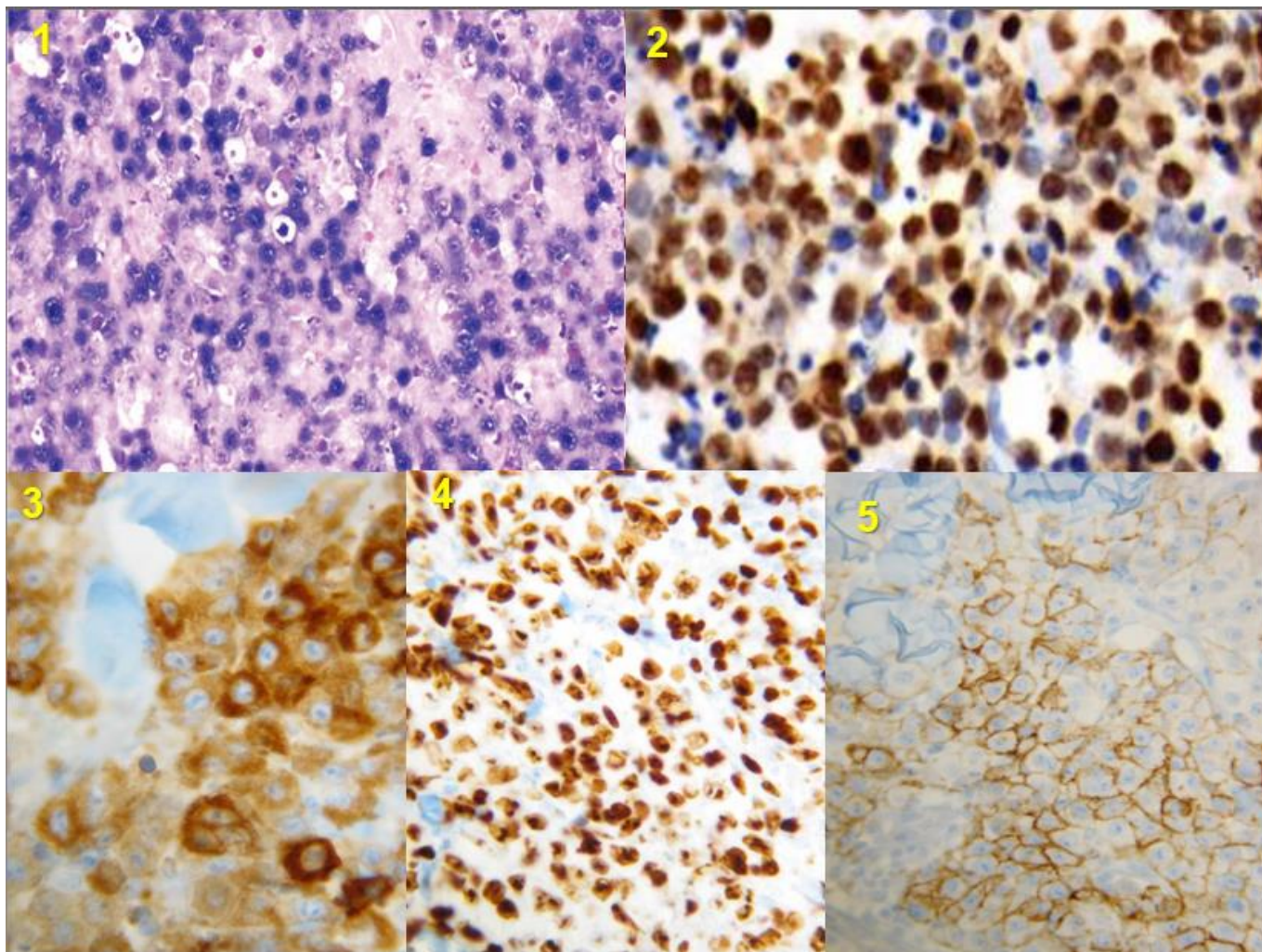
**Pathological Features.** PBL is a very aggressive malignancy characterized by large immunoblasts or giant plasma cells that express plasma cell markers but do not express B-cell markers.<sup>2-5</sup> The tumor demonstrates a diffuse growth pattern, leading to impairment of the structural integrity of both extranodal and nodal locations. The frequent observation of a "starry-sky" pattern, defined by the abundance of tingible body macrophages, is evident. The neoplastic cells exhibit features reminiscent of large immunoblasts, including a significant cytoplasmic volume and oval vesicular nuclei with prominent nucleoli. The presence of aberrant cells displaying morphological characteristics resembling larger centroblasts and/or

immunoblasts may be a distinguishing hallmark of PBL in HIV-positive individuals.

On the other hand, in those without HIV, the occurrence of plasma cell differentiation is frequently seen at extranodal sites distinct from the oral mucosa; its distinguishing features include the existence of cytoplasm with a basophilic staining pattern, the presence of para nuclear hof, and the presence of large nuclei positioned eccentrically. Necrosis, karyorrhexis, and larger mitotic figures are commonly encountered phenomena.<sup>82-83</sup>

Specifically, this disease has an immunophenotype similar to plasma cell neoplasms, as evidenced by positive markers including CD79a, IRF-4/MUM-1, BLIMP-1, CD38, and CD138. The neoplastic cells lack B-cell markers CD19, CD20, and PAX-5 expression. Nevertheless, a subset of these cells may display a little positive reaction to CD45. In specific cases, the expression of T-cell markers such as CD2 or CD4 has been seen.<sup>8</sup> The MIB-1 antibody is commonly employed in immunohistochemical investigations to detect the Ki-67 proliferation marker, which is typically shown to be expressed in malignant cells, if not universally. The





**Figure 5.** Positive stains for: 1. EBER: Epstein-Barr virus-encoded RNA. 2. MUM1/IRF4: multiple myeloma oncogene 1/inteferon regulatory factor 4. 3. EMA: epithelial membrane antigen. 4. KI-67: marker of growth fraction. 5. CD138: syndecam-1.

expression of the MYC gene is detected in approximately 50% of cases and is frequently associated with MYC translocations or amplification. EBV-encoded RNA (EBER) has been seen in around 80 percent of cases, making it the most sensitive method for identifying EBV infection in malignant cells. According to the results of a recent study, it was observed that the occurrence of Epstein-Barr virus (EBV) infection, as evidenced by the production of EBV-encoded RNA (EBER), exhibited a higher rate among HIV-positive individuals (80%), patients who acquired post-transplantation primary PBL (67%), and immunocompetent individuals (50%).<sup>83</sup> Some findings suggest a predominantly unfavorable presence of EBV LMP-1, with the typical latency pattern being type I. However, it is important to note that persons who have HIV infection and posttransplant PBL may display latency pattern type III. Based on molecular genetic testing, it has been observed that over 66% of cases present MYC rearrangements, with a lower proportion exhibiting MYC amplification. The comparative genomic hybridization analysis results indicate that PBL displays a greater genetic similarity to diffuse large B-cell lymphoma (DLBCL) compared to

multiple myeloma.<sup>84-86</sup> It is of utmost importance to remember that distinguishing between plasmablastic myeloma and lymphomas with plasmablastic features may present difficulties in correctly identifying tumor cells, hence introducing complexities to the diagnostic procedure.

**Differential Diagnosis.** Plasmablastic lymphoma (PBL), extramedullary plasma cell tumor/plasmablastic myeloma (EMPCT/PBM), primary effusion lymphoma (PEL), HHV8+ diffuse large B cell lymphoma (DLBCL) not otherwise specified, and ALK+ large B cell lymphoma (LBCL) belong to a category of lymphoproliferative neoplasms that share a common characteristic of exhibiting plasmablastic morphology. These neoplasms commonly display a tendency towards aggressive behavior and frequently correlate to a poor prognosis. Identifying each distinct entity frequently poses challenges due to the diseases' rarity and histopathologic traits overlapping with each other.

Except for cavity-based primary effusion lymphoma (PEL), which displays the presence of plasmablasts and immunoblasts within the effusion, all other neoplasms

**Table 1.** The differential diagnosis of lymphomas exhibiting plasmablastic characteristics.

	<b>DLBCL IBL</b>	<b>ALK+ DLBCL</b>	<b>DLBCL ACI</b>	<b>PBL</b>	<b>EMPCT/PBM</b>	<b>PEL</b>	<b>LBCL HHV-8+</b>
Disease distribution	Nodal	Nodal	Extranodal	<b>Extranodal</b>	Extranodal/Bone marrow	Extranodal	Nodal
HIV infection	No	No	No	<b>~70%</b>	No	Yes	Yes
Pathogenesis	unknown	ALK	EBV, IL-10, IL6	<b>EBV, HIV, IL10</b>	IL-6	HHV-8	HHV-8, MCD
Positive markers	CD20, PAX5	ALK, CD4, CD45	CD20, CD4	<b>CD138, IRF-4/MUM1, MYC</b>	CD138, cytoplasmic Ig, MYC	IRF-4/MUM-1, CD30-/+	CD20-/, CD138+/-, IgM
Negative markers	CD4, CD138	CD20, CD30, MYC	ALK	<b>CD20, PAX5, ALK</b>	CD20, PAX5, BCL6	PAX5, CD20, CD138, Ig	CD138
Proliferation rate	~80%	>90%	>90%	<b>&gt;90%</b>	>90%	>90%	>90%
Cytoplasmic immunoglobulin	Uncommon	Uncommon	Uncommon	<b>50-70%</b>	>90%	Uncommon	IgA lambda
EBV infection	No	No	Common	<b>Common</b>	No	Common	No
EBV Latency pattern	NA	NA	III	<b>I</b>	NA	I	NA
HHV-8 infection	No	No	No	<b>No</b>	No	Yes	Yes
Molecular genetics	MYC GR	t(2;17)(p23;q23)	TP53 mutations	<b>MYC GR</b>	Myeloma FISH abnormalities	Hypermutated immunoglobulins	Unmutated immunoglobulin
Bone marrow involvement	common	Rare/common	rare	<b>Rare</b>	Rare/usual	rare	rare
Serum paraprotein	rare	rare	rare	<b>20%</b>	usual	rare	rare
Prognosis	good	poor	good	<b>poor</b>	Good/poor	poor	Good/poor

PBL: plasmablastic lymphoma; LBCL: EMPCT/PCM: extramedullary plasma cell tumor/plasmablastic Myeloma. large B-cell lymphoma; HHV-8: human herpesvirus 8, LBCL: Large B-cell lymphoma; IBL: immunoblastic; ALK: anaplastic lymphoma kinase; ACI: associated with chronic inflammation; PEL: primary effusion lymphoma; EBV: Epstein Barr virus; IRF4/MUM1: interferon regulatory factor 4/multiple myeloma 1; Ig: immunoglobulin; GR: gene rearrangement; FISH: fluorescent in situ hybridization.

mentioned in this context exhibit a layout of plasmablasts and immunoblasts in a pattern of sheets. In immunophenotypic analysis, it was found that most of these tumors do not have the typical expression of mature B-cell antigens like CD19, CD20, PAX5, and CD79a. However, they demonstrate the presence of plasma cell markers, including CD138, VS38c, and MUM-1.

HHV8-positive diffuse large B-cell lymphoma (DLBCL) is a distinct entity that exhibits different levels of B-cell antigen expression and reduced expression of plasma cell antigens. EBER in situ hybridization and immunohistochemical analysis of HHV-8, LANA1, and ALK can usually be used to make a correct diagnosis. PBL is frequently distinguished by the presence of Epstein-Barr virus-encoded small RNA (EBER) positivity, human herpesvirus 8 (HHV8) negativity, and anaplastic lymphoma kinase (ALK) negativity. In contrast, PBM is distinguished by the lack of Epstein-Barr virus-encoded small RNA (EBER), human herpesvirus 8 (HHV8), and anaplastic lymphoma kinase (ALK). Both primary effusion lymphoma (PEL) and extra-cavitary PEL demonstrate frequently Epstein-Barr virus-encoded small RNA (EBER) positivity, human herpesvirus 8 (HHV8) positivity, and anaplastic lymphoma kinase (ALK) negativity. Diffuse large B-cell lymphoma (DLBCL) that is positive for human

herpesvirus 8 (HHV8) is distinguished nearly always lack of Epstein-Barr virus-encoded RNA (EBER), presence of HHV8, and absence of anaplastic lymphoma kinase (ALK) expression.<sup>5,87</sup> To summarize all of those points, ALK-positive large B-cell lymphoma (LBCL) is distinguished by the lack of Epstein-Barr virus-encoded small RNA (EBER), human herpesvirus 8 (HHV8) negativity, and the presence of anaplastic lymphoma kinase (ALK) positivity. The diagnosis of ALK+ LBCL is rather straightforward due to the specific presentation of the ALK protein, which sets it apart from the other five recognized classifications.<sup>5,87</sup> Furthermore, unlike PBL, PEL, and HHV8+ DLBCL, ALK+ LBCL does not demonstrate a preference for HIV+ or immunocompromised people. The differentiation between ALK+ LBCL and ALK+ anaplastic large cell lymphoma, as well as ALK+ non-hematopoietic malignancies, must be made thanks to the existence of ALK expression. The distinction between ALK+ LBCL and other ALK+ malignancies can be established centered on the differential expression of BOB-1 and OCT2 and the absence of CD30 expression. Distinguishing between PBL and PBM is crucial within a therapeutic context, given the significant disparities in treating these two types of neoplasms. Plasmablastic lymphoma and PBM demonstrate notable resemblances

within the domain of morphology. Based on an analysis of immunophenotypic characteristics, it is apparent that these two organisms exhibit notable similarities.<sup>86</sup> Both neoplasms demonstrate the presence of plasma cell-associated antigens, specifically MUM1, CD138, CD38, and PRDM1, but lose the expression of B-cell antigens such as CD19, CD20, and PAX-5. The rate of elevated EBER expression is greater in most cases of PBL, especially in cases where the patient is HIV positive. Conversely, EBER expression is rarely observed in cases of PBM. Cyclin D1 expression has been detected in a distinct subset of PBM. In contrast, PBL lacks the expression of cyclin D1. There have been documented cases of excessive expression of CD117 in select cases of PBM, while a lack of CD117 expression has been observed in cases of PBL. Therefore, in the context of plasmablastic morphology, detecting EBER expression may often be regarded as diagnostically meaningful for identifying plasmablastic lymphoma (PBL). In contrast, the presence of cyclin D1 or CD117 expression suggests a probable diagnosis of plasmablastic myeloma (PBM). The immunohistochemical analyses suggest that both PBL and PBM exhibit MYC gene expression. Interphase fluorescence in situ hybridization (FISH) is a more common way to find MYC translocations in PBL, especially when the translocations involve immunoglobulin genes.<sup>81-88</sup> Based on the small number of next-generation sequencing studies conducted on PBL and PBM, it can be concluded that gene mutational analysis does not appear to play a substantial role in distinguishing between these two neoplasms. Instead, differentiation is primarily achieved by considering clinical presentation and laboratory findings, particularly when markers such as EBER, cyclin D1, and CD117 exhibit negative results.<sup>81-88</sup> The probability of detecting PBL is higher in people with compromised immune systems when there is significant extramedullary involvement or lymphadenopathy present. Conversely, the likelihood of diagnosing PBM increases when the disease predominantly impacts the bone marrow or when there are signs that fulfill the CRAB criteria, including elevated levels of M protein. When a definitive distinction cannot be determined via thorough clinical and histopathologic evaluation, the designation of plasmablastic malignancy may be given, with plasmablastic lymphoma (PBL) and plasmablastic myeloma (PBM) being regarded as potential alternative diagnoses.<sup>81-88</sup> In certain cases, there can be difficulties in differentiating between HHV8+ DLBCL and PEL, especially in the context of extracavitary PEL. Human herpesvirus 8 (HHV8) and Epstein-Barr virus-encoded small RNA (EBER) are often found together in primary effusion lymphoma (PEL). However, HHV8-positive diffuse large B-cell lymphoma (DLBCL) generally does not exhibit EBER expression despite its HHV8 positivity. That said, it is important to know that some types of

primary effusion lymphoma (PEL), which are only found in people who do not have HIV, do not show expression of Epstein-Barr virus-encoded small RNA (EBER).<sup>81-88</sup> Patients diagnosed with primary effusion lymphoma (PEL) exhibit a clinical characteristic known as concurrent body cavity involvement. However, this characteristic is not observed in individuals diagnosed with human herpesvirus 8-positive diffuse large B-cell lymphoma (HHV8+ DLBCL). On the other hand, it is important to keep in mind that HHV8-positive diffuse large B-cell lymphoma (DLBCL) can arise from a lower-grade HHV8-associated lymphoproliferative disorder. Accordingly, certain signs that point to HHV8+ multicentric Castleman disease or germinotropic lymphoproliferative disease in the patient's medical history, whether from the past or the present, are used to support the diagnosis of HHV8+ DLBCL. HHV8-positive diffuse large B-cell lymphoma (DLBCL) often has different levels of pan-B-cell markers and less consistent levels of CD138 and CD38 expression within the immunophenotype. The presence of IgM and cytoplasmic k light-chain expression has been found in tumor cells. In contrast, prior studies have shown that PEL tends to demonstrate negative expression for pan-B-cell markers but positive expression for CD138 and CD38.<sup>5,81-88</sup> The PEL lymphoma cells have an impairment in the expression of both immunoglobulin heavy and light chains. The prevailing hypothesis suggests that the lymphoma cells observed in HHV8+ DLBCL exhibit the characteristics of naive B cells, specifically those that have not undergone somatic hypermutation and are in a pre-germinal center state. Further, the PEL lymphoma cells have the characteristics of B cells that have undergone terminal differentiation subsequent to the germinal center stage, and they possess somatic mutations in their immunoglobulin genes.<sup>87-88</sup> Taking advantage of molecular analysis, when available, appears to offer benefits in determining a definitive diagnosis for complex cases by determining the presence or absence of somatic mutations. Although there have been sporadic mentions in research papers regarding the presence of EBER positivity in HHV8+ DLBCL cases, it is crucial to contemplate the practical implications. The coexistence of Epstein-Barr virus-encoded small RNA (EBER) and human herpesvirus 8 latency-associated nuclear antigen 1 (HHV8 LANA1), in conjunction with plasmablastic and immunoblastic proliferation, serves as a robust indication for the diagnosis of PEL. Nevertheless, it is imperative to rule out any possibility for transformation from previous HHV8-associated lymphoproliferative disease or the existence of only nodal or splenic disease.<sup>86-89</sup>

**Prognostic Factors and Survival.** In earlier research investigations, it was reported that the median overall survival ranged from 8 to 15 months. Individuals whose

condition was not treated experienced a significantly low median overall survival (OS) that corresponds to previously reported results, surviving for an average of 1.9 months.<sup>91</sup> Presented below are a few illustrative examples. In a study of 112 HIV-positive PBL patients, the median overall survival (OS) was 15 months, and the 3-year OS rate was 25%.<sup>90</sup> In another study of 76 PBL patients with negative HIV tests, the median OS was 9 months, and the 2-year OS rate was 10%.<sup>91</sup> In a large study of 300 PBL patients, the median overall survival (OS) was 8 months. Three patient groups were compared for median overall survival (OS). HIV-positive individuals had a median OS of 10 months, while HIV-negative immunocompetent patients had 11 months. After transplantation, PBL patients had a smaller median OS of 7 months.<sup>8</sup> Another academic study of 50 HIV-positive people using cART found comparable results with a median 11-month survival length and a 24% 5-year survival rate.<sup>6</sup> An early investigation in Germany comprised 18 HIV-positive PBL patients diagnosed after 2005. The study of 30 medical centers found a median OS of 5 months.<sup>9</sup> The AIDS Malignancy Consortium abstracted data from nine locations, including 19 HIV patients who received medication after 1999. The estimated one-year survival rate was 67%.<sup>92</sup>

In recent years, there have been reports of enhanced survival rates. The Lymphoma Study Association (LYSA) examined 135 people with PBL for the study. Among these patients, 80% received chemotherapy. The study found that the median overall survival (OS) was 32 months.<sup>23</sup> The investigation conducted on 248 treated patients in the SEER database revealed a median overall survival (OS) of 47 months.<sup>24</sup> Very recently, in small-scale research including patients with PBL, the administration of bortezomib in combination with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) resulted in a median survival duration of 62 months.<sup>142</sup> Overall, several comparison studies demonstrate that HIV does not significantly affect PBL outcomes.<sup>5-10</sup>

However, several data points suggest a link between immunosuppression and worse outcomes in HIV-negative patients.<sup>93</sup> The International Prognostic Index (IPI) scoring system is widely used to classify aggressive lymphomas. PBL patients' International Predictive Index (IPI) scores are predictive, according to several retrospective investigations. However, in PBL, the International Prognostic Index (IPI) score appears to be most indicative of a poor prognosis when advanced disease stages and reduced functioning status are present.<sup>94</sup> An independent study linked age to LDH levels and unfavorable outcomes.<sup>9</sup> The prognostic consequences of Epstein-Barr virus (EBV)-related antigen expression in PBL remain unclear. Many studies have found no correlation between Epstein-Barr virus (EBV) expression and HIV-associated PBL

prognosis.<sup>5-9</sup> However, Epstein-Barr virus (EBV) has been linked to a better prognosis in immunocompetent PBL patients.<sup>94</sup> It is crucial to note that the production of EBV by malignant cells frequently affects Epstein-Barr virus (EBV) expression. Recent research has linked MYC gene rearrangements to a shorter life expectancy in PBL patients. The results showed that patients with MYC increases or translocations had significantly lower overall survival (OS) than those with normal MYC status.<sup>5-11</sup> MYC gene rearrangements were also linked to death from any cause in HIV-positive PBL patients, six times greater.<sup>5-11</sup> It is unclear if CD20 or CD45 expression levels affect PBL patients' clinical results. However, other studies have associated Ki-67 expression levels above 80% with a poor prognosis.<sup>5-11</sup> Overall survival was not significantly related to low CD4 counts in HIV-associated PBL, but lower CD4 levels were linked to shorter progression-free survival.<sup>5-11</sup>

*HIV-negative Patients with PBL.* The Moffitt Cancer Center studied nine consecutive PBL patients without HIV between 1999 and 2010.<sup>93</sup> The median age at diagnosis was 58, ranging from 46 to 67. Five of nine patients (55%) had aaIPI values greater than two. Seven of nine patients (78% of the sample) underwent CHOP. Rituximab was given to four patients. Two patients (22% of the nine-patient sample) received hyper-CVAD therapy. Seven chemotherapy patients (78% of the sample) achieved complete remission. One patient had a partial response sufficient for autologous hematopoietic cell transplantation (AHCT) consolidation, while another needed further treatment. 89% of individuals responded. After CR1, four patients (44% of the sample) with aaIPI 2 underwent AHCT. At data collection, the median overall survival (OS) was unknown.<sup>93</sup> The authors also reviewed the literature on 70 PBL patients who tested negative for HIV.<sup>93</sup> CHOP, or a comparable treatment, was given to 60% of patients. Two patients with primary refractory illnesses survived 6 and 12 months after autologous hematopoietic cell transplantation (AHCT). Overall survival (OS) was 9 months. The researchers found that advanced age, extranodal disease, and immunosuppression are risk factors for unfavorable outcomes. This single-institution study found better results than earlier ones due to the fast adoption of autologous hematopoietic cell transplantation (AHCT) in high-risk patients.<sup>92</sup>

*Differences between HIV-positive and negative PBLs.* Despite limited data on HIV-negative PBL patients, few differences have been found. HIV-negative PBL is more common in women and older adults. Regarding the clinical onset, HIV-negative PBL exhibits more extra-oral symptoms, indicating greater heterogeneity. Around 50% of HIV-negative PBL cases are linked to immunosuppression.<sup>94</sup> The literature study shows that

HIV-negative PBL patients had a worse outcome than HIV-positive patients.<sup>5-11</sup> HIV-negative PBL patients have a median survival of nine months. Interestingly, a complete remission after induction chemotherapy is the single predictor of better outcomes.<sup>93</sup> Multiple studies have shown that HIV-associated PBL patients respond better to chemotherapy than HIV-negative PBL patients. Antiretroviral therapy combination (cART) in HIV-positive people who never received cART may explain this. That treatment method improves immune surveillance and restores immunological function, contributing to the reported improvement. Patients with HIV-associated PBL who test positive for Epstein-Barr virus (EBV) have a better prognosis than those who test negative.<sup>30-33</sup> Results vary because cART reduces viral replication.<sup>30-32</sup> In addition, HIV-negative older adults often develop PBL. This group has inferior performance status and physiological reserve, making them less able to tolerate higher-dose chemotherapy.<sup>94</sup> HIV-associated PBL patients receiving cART and those not receiving cART have similar rates of opportunistic infections.<sup>31</sup> Approximately 77% of HIV-associated PBL patients who received chemotherapy, specifically the CHOP regimen or more aggressive protocols, responded.<sup>94</sup> Overall survival was poor in this trial, with a median survival period of 14 months. No evidence suggests that more intensive treatment regimens enhance survival.<sup>22,93-95</sup>

*Oral versus extra-oral plasmablastic lymphoma.* PBLs have been classified into two separate categories, respectively oral and extra-oral, as indicated in different research investigations. This classification implies that there is heterogeneity in PBL based on the particular location.<sup>96,97</sup> This issue was analyzed in a cohort of 101 cases of oral and extraoral PBL from a specific institution located in a location with a high prevalence of HIV.<sup>98</sup> The results of this study contradict the assumption that oral and extra-oral PBL should be considered distinct and unrelated entities, proposing instead that they are part of a continuum of the same disease.<sup>98</sup> These results suggest that regardless of the location and presence of HIV and EBV, PBLs displayed comparable clinicopathologic, immunophenotypic, and behavioral features. Analysis of molecular characteristics in oral and extra-oral PBL failed to identify any noticeable differences associated with the location of the tumor.<sup>98</sup> The explanation behind the increased incidence of oral manifestations of PBL in comparison to extraoral manifestations remains unknown. Nevertheless, a similar trend has been noted in instances of HIV-associated Kaposi sarcoma and Burkitt lymphoma. In conclusion, the extra-oral PBL cases demonstrated comparable attributes to their oral counterparts with regards to gender, age distribution, HIV status, morphological appearance, immunophenotypic profile, and Epstein-Barr virus-

encoded small RNA (EBER) status.<sup>99</sup>  
*CD138 negative Plasmablastic Lymphoma.* Approximately 10% of PBL cases have an unusual immunophenotypic profile, which is defined by the lack of CD138 expression. The diagnosis procedure is made much more difficult by this specific feature. When compared to CD138+ PBL, which mostly manifests as oral lesions, CD138-PBL is characterized by extraoral lesions, the most common of which is lymphadenopathy, which is then followed by gastrointestinal lesions.<sup>100-102</sup> Compared to patients who are CD138+, these patients had a reduced documented incidence of HIV and EBV infection. The MYC gene has reportedly a significant impact on disease development, especially when the Epstein-Barr virus (EBV) is present. There were no noticeable variations in survival between patients with PBL who were CD138-positive and CD138-negative.<sup>100-105</sup>

*CD 20 positive Plasmablastic Lymphoma.* The presence of CD20 expression has been detected in 10% of patients who are HIV-positive and have PBL.<sup>5-11</sup> Nevertheless, it is generally recognized that a significant proportion of PBL patients have a lack of CD20 expression, hence limiting the possible benefit of the anti-CD20 monoclonal antibody Rituximab. However, there have been recorded cases of CD20+ HIV-negative PBL.<sup>106</sup> As is well known, Rituximab has shown significant improvements in the curative treatment of diffuse large B-cell lymphoma (DLBCL) patients who are positive for CD20.<sup>106</sup> Therefore, it is recommended to include the anti-CD20 monoclonal antibody Rituximab in the treatment strategy for CD20+ PBL after doing an in-depth evaluation of the patient's histological characteristics.

*International prognostic Indices.* In a recent study, the performance of three scoring systems, namely the International Prognostic Index (IPI), Revised International Prognostic Index (R-IPI), and National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI), were examined in the context of plasmablastic lymphoma.<sup>107-110</sup> The results of this study provide evidence to endorse the utilization of the International Prognostic Index (IPI) and National Comprehensive Cancer Network (NCCN) IPI scores in PBL settings.<sup>110</sup> Nevertheless, it is imperative to have a novel prognostic tool that can effectively identify subgroups at risk of early relapse or refractory disease, as well as late relapses. The incorporation of molecular characterization and cART therapy is a promising approach to potentially achieving this outcome within the patient population.<sup>110</sup>

### **Special Population PBL**

*Pediatric cases.* Pediatric lymphoma is a rather rare

phenomenon. Lymphoma accounts for around 8% of cancers observed in the pediatric and teenage populations.<sup>111</sup> In particular, the incidence of non-Hodgkin lymphoma among pediatric cancer patients is estimated to be around 5%, while Hodgkin lymphoma is detected in approximately 3% of cases. According to currently published research, there is evidence to support the assumption that people who are younger than 14 years old display an increased likelihood of developing non-Hodgkin lymphoma.<sup>112</sup> The presence of PBL has been observed in pediatric patients with HIV infection, as well as in patients with different immunological deficiencies and immunocompetent young people, despite the higher prevalence in adult patients. The literature review resulted in the identification of a total of 35 cases.<sup>5-10</sup> According to the study, the condition was observed in individuals at a median age of ten years, with a range ranging from 0 to 17 years. Furthermore, it is significant that more than 80% of the patients had been classified into the advanced stage at their initial presentation.<sup>5</sup> In addition, it was observed that the jaw and oral cavity exhibited the highest incidence of disease presentation. Still, there have been reported cases of extranodal manifestations in various locations, such as the skin, vulva, spine, and head. The overall prognosis is typically detrimental, as seen by the scarcity of known long-term survivors. Specifically, there have been only two recorded examples of individuals who have lived for 3.5 and eight years, respectively. A total of 25 cases showed tests positive for HIV, while 10 of them were negative for HIV.<sup>10,112-118</sup>

*Limited-stage plasmablastic lymphoma (LS PBL).* Due to the limited patient population and lack of randomized studies, developing definite treatment guidelines for limited-stage plasmablastic lymphoma (LS-PBL) is difficult. Thus, guidelines largely use retroactive evidence. Due to the aggressive nature of the disease, greater chances of relapse, bad outcomes, and insufficient evidence-based outcomes for limited-stage PBL patients, intensive treatment regimens are often suggested. Various studies on LS and ES patients have indicated that intensive chemotherapy and consolidation therapy with autologous stem cell transplantation improves survival.<sup>119</sup> However, other studies have found little advantage in intense therapy. Thus, healthcare practitioners face ambiguity when suggesting treatments, especially for LS patients.<sup>119,121</sup> A recent study on LS PBL described it in detail and reported mostly positive outcomes.<sup>121</sup> The study calculated the three-year probability of progression-free survival (PFS) and overall survival (OS) at 72% (95% CI 62–83) and 79% (95% CI 69–89). HIV-positive patients had no trend toward worse progression-free survival (PFS) or overall survival (OS). Instead, HIV-positive people had better progression-free survival (PFS) and overall survival

(OS) in the multivariate analysis. When frontline treatment was considered, the multivariate regression analysis showed a statistically significant link between high levels of lactate dehydrogenase (LDH) at diagnosis and a higher risk ratio (HR) for progression-free survival (PFS). Looking to clinical characteristics like gender, age, stage, and EBV expression did not significantly affect progression-free survival (PFS) or overall survival (OS). Compared to CHOP- or EPOCH-based first-line cytotoxic treatments, aggressive first-line treatments like hyper-CVAD or modified hyper-CVAD did not improve progression-free survival (PFS) or overall survival (OS). The study found that radiation therapy (RT) consolidation improved progression-free survival (PFS) and overall survival (OS). Statistically significant ( $p < 0.05$ ) data from 108 patients showed this improvement.<sup>120</sup> It appears that PBL-LS patients have good results, especially when they receive disease-specific treatment. The multivariate regression analysis demonstrates that EPOCH-based regimens improved progression-free survival (PFS) more than CHOP-based regimens as the first therapy choice. Radiation consolidation after the first chemotherapy improved results, although the improvements were not statistically significant.<sup>121</sup>

*Post-transplant PBL (PT-PBL).* Plasmablastic lymphoma is a type of lymphoma that may occur following transplantation. Post-transplant lymphoproliferative disorder (PTLD) is a rare and aggressive tumor that mostly affects patients who have received solid organ transplants.<sup>102</sup> PT-PBL usually develops at a later stage following transplantation, with a median onset occurring at 96 months post-transplantation and a range encompassing from 2 to 360 months.<sup>5-11</sup> This condition exhibits a higher prevalence in males and in recipients of heart and kidney allografts. The clinical presentation is characterized by a predominance of skin and lymph node involvement and digestive diseases.<sup>5,10,101</sup> The characterization of PT-PBL currently needs to be improved in clarity, and available evidence is scarce regarding the clinical and genetic alterations that underlie this condition.

Although there are similarities in the genetic changes observed in HIV-related PBL and PT-PBL, there are also discernible distinctions between the two. A significant proportion, approximately 50%, of the cases examined, encompassing both EBV-positive (EBV+) and EBV-negative (EBV-) cases, had small foci characterized by plasmacytic differentiation. These observations accord with the conclusions drawn by previous researchers in this area.<sup>5-10</sup> Similar to other B-cell post-transplant lymphoproliferative disorders (PTLDs), the majority (64%) of PT-PBL exhibited germinal center transit. While the B-cell program is often suppressed in PBL, certain cases exhibit the presence of B-cell antigens. A study revealed that 27% of (PT-PBL) displayed partial

CD20 expression, a percentage that is similar to other forms of PBL (20%). More than 50% of the PT-PBL samples exhibited positivity for PAX5 and/or CD79a.<sup>122,123</sup> The expression of CD79a has been seen in 45% of PBL associated with HIV infection as well as in 68% of PT-PBL.<sup>3</sup> Additionally, PAX5 expression has been detected in 22–26% of mostly HIV-related PBL. The presence of PAX5+ was observed in a significant proportion (60%) of Epstein-Barr virus-positive (EBV+) PT-PBL. However, no disparities were observed in the functional groupings of mutations between cases that expressed B-cell antigens and those that did not.<sup>124</sup> There is a significant variation observed in the Ki-67 proliferation indices within PT-PBL, with Ki-67 labeling ranging from 25% to 100%.

The presence of PD-L1 expression, infiltration of PD1+ T cells into tumors, and elevation of immune escape genes have been documented in cases of Epstein-Barr virus-positive PBL (EBV+ PBL) and post-transplant lymphoproliferative disorder (PTLD).<sup>124-125</sup> The presence of PD-L1 expression was seen in specific subsets of EBV-positive and EBV-negative (PT-PBL). The EBV-negative PT-PBL fraction had additional alterations in immune evasion genes, namely FAS and CD58.<sup>124</sup> PT-PBL demonstrates infrequent manifestations of morphologic or immunophenotypic indications of marrow infiltration or the presence of bone (lytic) lesions on imaging, as well as myeloma-associated laboratory irregularities, such as monoclonal gammopathy and hypercalcemia. However, a small percentage of cases can manifest these alterations.<sup>123-125</sup> Moreover, several genetic abnormalities identified in PT-PBL exhibited similarities with those observed in MM. Notably, these abnormalities were detected in both EBV-positive and EBV-negative PT-PBL cases, as well as in PBL cases associated with HIV infection. The overall quantity of modifications exhibited variation in comparison to MM.<sup>67,125</sup> The prognosis of PT-PBL is determined by various factors, including age, stage of the disease, and nodal involvement. However, it has been previously documented that certain PT-PBL patients have exhibited long-term survival.<sup>98</sup> The primary objectives of post-transplant lymphoproliferative disorder (PTLD) care encompass the elimination of PTLD and the preservation of allograft function. These aims often entail conflicting treatment approaches, and often, one objective will be given priority over the other based on the individual patient's specific requirements. So, the primary strategy employed in the eradication of post-transplant lymphoproliferative disorder (PTLD) is the lowering of immunosuppression. However, it is important to note that this approach has the potential danger of graft rejection and failure. The care strategies for post-transplant lymphoproliferative disorder (PTLD) might vary across different institutions. However, a common method involves administering lymphoma-

directed drugs, which often consist of conventional chemotherapy and/or radiotherapy, to the majority of patients. A comprehensive examination of existing academic literature revealed the presence of 37 cases of PBL in individuals who had undergone organ transplantation.<sup>5-10</sup> Among these cases, it was observed that 28 (76%) were male, and the median age at which the disorder manifested was 62 years. A total of 38% of the observed cases occurred subsequent to a heart transplant, while 27% were reported following a kidney transplant.<sup>5</sup> Additionally, 14% of the cases were observed after a hematopoietic stem cell transplant, 11% after a lung transplant, 8% after a liver transplant, and 3% after a pancreas transplant. Interestingly, the lymph nodes were found to be the most frequently affected region, accounting for 30% of cases, with the skin being the second most regularly implicated site at 22%. Approximately half of the patients diagnosed with posttransplant PBL exhibit advanced clinical stages.<sup>5-10</sup>

*Spontaneous regression.* A considerable amount of empirical data exists, consisting of several reported cases and comprehensive analyses, that supports the occurrence of spontaneous regression in low-grade lymphomas, but it is infrequently observed in aggressive lymphomas.<sup>126</sup> In particular circumstances, there have been documented cases where aggressive PBL has shown spontaneous regression following the introduction of antiretroviral therapy (ART).<sup>126-132</sup> This therapy has been observed to contribute to the restoration of immune function in individuals infected with HIV and the subsequent activation of immune surveillance against the lymphoma, resulting in its regression.

Moreover, in some cases, the cessation of methotrexate treatment without the use of additional anti-neoplastic therapy could contribute to the regression of PBL.<sup>126-132</sup>

*Transformed PBL.* The evolution of indolent lymphomas into aggressive histologies is a critical phenomenon in the management of patients, requiring a modification in their treatment approach. Despite a declining trend in the general occurrence of transformation, this condition continues to pose a significant problem. It is associated with a less favorable prognosis when compared to patients who do not experience transformation.<sup>133</sup> Based on a comprehensive analysis of existing research articles, it has been reported that there are 30 cases in which PBL has originated from a preexisting hematological disorder.<sup>5</sup> Typically arising as a consequence of a transformation from chronic lymphocytic leukemia or low-grade follicular lymphoma. A total of 10 cases have been documented in which double-hit follicular lymphoma, or DLBCL, has transformed PBL among individuals who are HIV-negative.<sup>133-138</sup> In cases where a transformation is suspected, it is imperative to conduct a

biopsy in order to confirm the diagnosis and acquire tissue for genomic analysis. Because the transformation could mean either a change from the original hematological disease or the appearance of a new primary lymphoma, this is very important because it affects the prognosis and the treatment options. In order to establish the clonal link between the primary tumor and the plasmablastic neoplasm, it is possible to perform a PCR and FISH investigation targeting the immunoglobulin heavy chain and BCL2 genes.<sup>138-141</sup> When compared to clonally related T-PBL cases, cases that are genetically and immunologically different have

a better response to chemoimmunotherapy. Finally, the remaining patients must enroll in the clinical trial.<sup>138-141</sup>

**Conclusions.** This first part of the state-of-the-art review provided an overview of the epidemiology, etiology, clinicopathologic characteristics, differential diagnosis, prognostic variables, and special populations associated with plasmablastic lymphoma. In the second part of this article, our focus will be on the treatment of plasmablastic lymphoma, specifically examining both the conventional, consolidated approach and the novel therapeutic strategy.

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