Blood Reviews 65 (2024) 101172

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Update: The molecular spectrum of virus-associated high-grade B-cell non-Hodgkin lymphomas

H. Witte [a,b,*], A. Künstner [c,d], N. Gebauer [b,c]

[a] Department of Hematology and Oncology, Bundeswehrkrankenhaus Ulm, Oberer Eselsberg 40, 89081 Ulm, Germany
[b] Department of Hematology and Oncology, University Hospital Schleswig-Holstein (UKSH) Campus Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany
[c] University Cancer Center Schleswig-Holstein (UCCSH), Ratzeburger Allee 160, 23538 Lübeck, Germany
[d] Medical Systems Biology Group, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

ARTICLE INFO

Keywords:
HIV
EBV
KSHV
HHV8
B-cell NHL
Non-Hodgkin lymphomas
ICC
WHO-5HAEM

ABSTRACT

The vast spectrum of aggressive B-cell non-Hodgkin neoplasms (B-NHL) encompasses several infrequent entities occurring in association with viral infections, posing diagnostic challenges for practitioners. In the emerging era of precision oncology, the molecular characterization of malignancies has acquired paramount significance. The pathophysiological comprehension of specific entities and the identification of targeted therapeutic options have seen rapid development. However, owing to their rarity, not all entities have undergone exhaustive molecular characterization.

Considerable heterogeneity exists in the extant body of work, both in terms of employed methodologies and the scale of cases studied. Presently, therapeutic strategies are predominantly derived from observations in diffuse large B-cell lymphoma (DLBCL), the most prevalent subset of aggressive B-NHL. Ongoing investigations into the molecular profiles of these uncommon virus-associated entities are progressively facilitating a clearer distinction from DLBCL, ultimately paving the way towards individualized therapeutic approaches.

This review consolidates the current molecular insights into aggressive and virus-associated B-NHL, taking into consideration the recently updated 5th edition of the WHO classification of hematolymphoid tumors (WHO-5HAEM) and the International Consensus Classification (ICC). Additionally, potential therapeutically targetable susceptibilities are highlighted, offering a comprehensive overview of the present scientific landscape in the field.

1. Introduction

The spectrum of aggressive B-cell non-Hodgkin lymphomas (B-NHL) has undergone a comprehensive revision, with the latest iteration of the World Health Organization's Classification of Hemato-Lymphoid Tumors (WHO-5HAEM) now incorporating 26 entities, marking an expansion from the previous 20 entities delineated in WHO-4HAEM [1,2]. Simultaneously, the "International Consensus Classification (ICC) of Mature Lymphoid Neoplasms," a contender to WHO-5HAEM, similarly enumerates 26 entities falling within the spectrum of aggressive B-cell non-Hodgkin lymphomas [3]. Within this field, the role of viral infections in the pathogenesis of select entities has been recognized for several decades [4]. Noteworthy viruses implicated in the genesis of lymphoid diseases encompass Epstein Barr virus (EBV), human immunodeficiency virus (HIV), and human herpesvirus 8 (HHV8) or Kaposi's sarcoma associated herpes virus (KSHV) [5–7]. In recent years, there has been a substantial expansion in molecular access to the bulk of B-NHL, markedly refining our comprehension of these diseases. Lymphotropic viruses wield a direct influence on the genetic and transcriptional program of lymphoid cells, thereby exerting a pivotal impact on the development of hematologic neoplasms [8]. This review article is dedicated to elucidating the genomic characteristics of the rare aggressive and virus-associated B-NHL, drawing a clear demarcation from de novo diffuse large B-cell lymphoma (DLBCL), as the principal representative of aggressive B-NHL. Through a meticulous exploration of molecular intricacies, the scientific and clinical understanding of the nuanced landscape inherent in these lymphomas is greatly enhanced.

* Corresponding author at: Department of Hematology and Oncology, Bundeswehrkrankenhaus Ulm, Oberer Eselsberg 40, 89081 Ulm, Germany.
E-mail address: hanno.witte@uksh.de (H. Witte).

https://doi.org/10.1016/j.blre.2024.101172

Available online 20 January 2024

2. Viral biology and lymphomagenesis

2.1. Epstein Barr-virus

Epstein Barr Virus (EBV), also known as human herpes virus 4, was initially identified in Burkitt's lymphoma in 1964 [9]. Its global lifespan-prevalence exceeds 95% [10]. The virus is implicated in a diverse array of both malignant and non-malignant diseases [10]. Transmission primarily occurs through saliva, with secondary modes involving the exchange of other bodily fluids or organ transplantation [11]. Two distinct subtypes of the virus, EBV-1 and EBV-2, have been characterized [12,13]. Following primary infection, often asymptomatic, EBV persists throughout the host's lifetime. In conditions of immunosuppression, such as organ or stem cell transplantation, immunosuppressive therapy, HIV infection, or (age-related) immunosenescence, EBV may undergo reactivation [14,15]. The virus can instigate the development of malignancies through various mechanisms (Fig. 1). This can occur during viral latency (as seen in Burkitt's lymphoma), with moderate EBV viral protein expression (as observed in Hodgkin lymphoma), or during reactivation in the context of existing immunosuppression (e.g., HIV-associated lymphoma) [16]. Consequently, EBV-associated viral gene expression varies depending on the specific lymphoma subtype [10]. Numerous genes, transcripts, and proteins with regulatory functions originate from EBV DNA. Notable among these are the EBV genes *BALF4* and *BALF5*, which directly suppress apoptosis, induce the IL6/JAK/STAT signaling, and phosphatidyl-inositol-mediated signal transduction in infected human cells [17]. During the phase of viral persistence, EBV nuclear antigens (EBNA1, EBNA2, EBNA leader protein (LP), and EBNA 3 (A-C)) are produced [12]. EBNA1, crucial for genomic persistence during viral latency, prevents immune-mediated killing of infected cells, promotes proliferation and cell growth, and shields infected cells from apoptosis [18]. The dynamic interplay between EBNA2 and EBNA3 involves transcriptional activation and inhibition, respectively [19]. EBNA-LP, co-produced with EBNA2, acts as a co-activator [20]. Viral membrane proteins LMP1 and LMP2A promote proliferation of infected cells. LMP1, capable of transforming B cells in vitro, significantly contributes to malignant properties by activating the NF-κB signaling pathway, the PI3K/AKT/mTOR pathway, and the RAS/MAPK signaling pathway [21–23]. LMP2A also activates the NF-κB signaling pathway and participates in the molecular mimicry of an activated B cell receptor [24,25]. Furthermore, various non-coding RNA transcripts play regulatory roles in infected cells. These transcripts contribute to the activation of proliferation-favoring signal transduction cascades (BPLF1), inhibit apoptosis (BARTs), and regulate mechanisms masking infected cells from the immune system (BORF2, BNLF2A, BDLF3, vIL-10, BZLF2) [10,26,27].

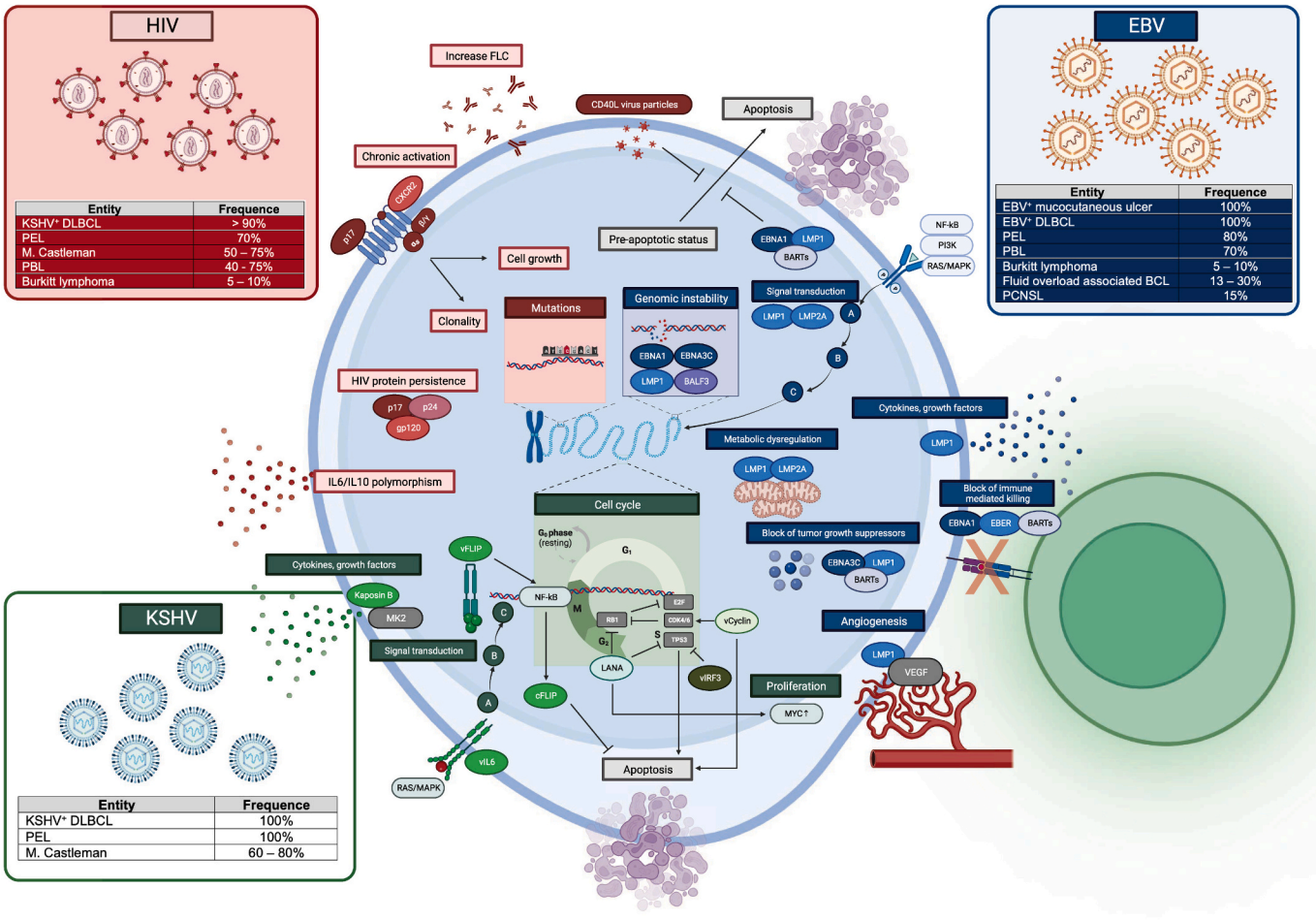

Fig. 1. The impact of lymphotropic viruses and their metabolites on the genetic programming of B-cells and the consequent development of lymphoproliferative neoplasms. Furthermore, the frequency of underlying viral infections is being elucidated for distinct subtypes of lymphomas. HIV-associated proteins perpetuate sustained cellular growth activation, induce mutagenic events, inhibit apoptosis, promote the release of free light chains, and mediate an immune response through IL-6 and IL-10 signaling pathways. EBV (Epstein-Barr virus) also inhibits apoptosis, while orchestrating the release of cytokines. This virus suppresses T-cell-mediated cytotoxicity against neoplastic B-cells. Overall, EBV induces genetic instability and promotes angiogenesis. Additionally, EBV-associated viral proteins trigger the activation of diverse signal transduction cascades. KSHV (Kaposi's sarcoma-associated herpesvirus) also promotes the release of cytokines. However, its primary impact involves complex mechanisms that influence the function of tumor suppressor genes, consequently leading to cellular growth and proliferation.

2.2. Human immunodeficiency virus (HIV)

The pathogenesis of HIV-associated lymphomas is governed by a multitude of influencing factors (Fig. 1). Immunosuppression, stemming from HIV infection or other causes, coupled with co-infection by EBV or KSHV, plays a pivotal role in the genesis of HIV-associated lymphomas. Notably, the decline in CD4+ T-lymphocytes correlates with the EBV-associated reduction in CD8+ T lymphocytes during the progression of EBV-associated non-Hodgkin lymphoma (NHL) [28]. Beyond immunosuppression, factors such as viral co-infection, CD4+ T-lymphocyte-nadir (<200/μl), heightened levels of IL-6 and IL-10, and single nucleotide polymorphisms within these interleukins are also considered predisposing factors in HIV patients for the development of B-NHL [29,30]. Moreover, elevations in serum free light chains and genetic determinants contribute to the multifactorial etiology of HIV-associated NHL [31,32]. Analogous to other lymphotropic viruses, HIV directly influences lymphomagenesis (Fig. 1). HIV viral particles, including p17, gp120, p24, and Tat, induce sustained activation of B cells [33]. The HIV-1 matrix protein p17 persists in the germinal center despite antiretroviral therapy, activating the PI3K/AKT/mTOR signaling cascade and supporting B cell growth [34]. In the presence of concurrent EBV co-infection, p17 upregulates the EBV membrane protein LMP1 [35]. Coordinated with HIV-associated CD40L virions, EBV co-infection inhibits B cells from entering apoptosis. The upregulation of CXCR2 receptors, acting as a receptor for the matrix protein p17, among other functions, further supports clonal growth of B cells [33,36].

2.3. Human herpes virus 8 (HHV8)/ Kaposi's sarcoma associated herpesvirus (KSHV)

The transmission of the virus occurs through salivary contact or sexual transmission, and the infection is characterized by a brief duration. Frequently associated with HIV infections, it actively facilitates the development of lymphatic neoplasms. The viral genome consists of double-stranded DNA, harboring approximately 100 genes that encode distinctive viral proteins, including LANA (ORF73), vIRF3 (LANA2), vIL-6, caposin B, vCYC (ORF72), and vFLIP (ORF71) [37,38]. These proteins, along with micro-RNA transcripts, exert a direct influence on the genetic program of infected B lymphocytes.

LANA is expressed in infected cells, and its detection using commercially available antibodies aids in diagnosis. This protein inhibits TP53 and RB1, thereby promoting tumor proliferation and cell growth, and enhances the activity of MYC [39–41]. The viral protein vCYC possesses the ability to inactivate BCL2, inducing apoptosis [42]. In conjunction with CDK6, vCYC forms a complex that phosphorylates *RB1*, facilitating entry into the synthesis phase (S-phase) of the cell cycle [43]. Playing a pivotal role in the proliferation of KSHV-infected lymphoma cells, vFLIP upregulates the NF-κB signaling pathway, contributing to the proliferation of lymphoma cells [44]. Kaposin B activates a kinase (MK2), resulting in the accumulation of cytokine transcripts (IL-1, IL-3, IL-4, IL-6, TNF-α) and their subsequent production, fostering an inflammatory tumor microenvironment [45]. The KSHV genome includes a gene for IL-6, which not only mediates inflammation but also directly influences lymphoma cell proliferation via the MAP kinase signaling pathway [46]. Recognized for its pathogenetic relevance in numerous B-cell neoplasms with plasma cell differentiation, IRF4 is mimicked by KSHV in the form of vIRF3. Initially, vIRF3 contributes to the plasma cell/plasmablastoid differentiation of KSHV$^+$ neoplasms by inhibiting the sumoylation of TP53 through direct binding, thereby counteracting the proapoptotic effects of vCYC (Fig. 1) [47–52].

3. EBV associated lymphoma entities

3.1. EBV$^+$ DLBCL

For an extended period, EBV$^+$ DLBCL was predominantly diagnosed in elderly and/or immunocompromised individuals [2,53–55]. While the use of EBER (EBV-encoded small RNA) in situ hybridization was a routine diagnostic tool for Hodgkin lymphoma, its application to DLBCL gained prominence only with its recognition as a distinct entity in WHO-3HAEM in 2008 [56]. Subsequent studies have unveiled the occurrence of this lymphoma in young, immunocompetent patients on rare occasions, and the nomenclature reflects its association with an underlying EBV infection, with over 80% of cells testing positive for Epstein-Barr encoding region in situ hybridization (EBER-ISH) [57,58]. Morphologically, EBV$^+$ DLBCL exhibits similarities with EBV$^+$ classical Hodgkin lymphoma and T-cell histiocyte-rich B-cell lymphoma [58,59]. However, the presence of EBV excludes the diagnosis of T-cell histiocyte-rich B-cell lymphoma [2]. Immunophenotypically, there is positivity for classical B-cell markers (CD19+, CD20+, CD22+, CD79a+, PAX5+), and the cell of origin corresponds to an activated B cell (IRF4/MUM1+, CD10-, BCL6-) [58,60,61]. Moreover, these lymphomas frequently express CD30 (> 80%), resembling Hodgkin lymphoma, and demonstrate high PD-L1 expression, indicative of their immunogenic nature [57,58,62–64].

Recent comprehensive molecular characterizations of EBV$^+$ DLBCL have highlighted the pivotal role of mutational perturbation of the IL6/JAK/STAT and NF-κB signaling pathways in its pathogenesis [65,66]. Distinct alterations in *ARID1A, KMT2A/D, ANKRD11*, or *NOTCH2* set this entity apart from classical DLBCL [65]. Molecular analyses further identify alterations associated with the NOTCH and WNT pathways, along with characteristic 6q deletions (6q21 and 6q23) impacting *A20* and *PRDM1* gene loci (Table 1) [65]. Attempts to classify EBV$^+$ DLBCL into conventional molecular clusters of DLBCL have largely failed, emphasizing its distinction within the spectrum of aggressive B-NHL [66–69]. Additional sequencing efforts have implicated mutations in *MYC, MYD88, TET2,* and *DNMT3A,* among others, further delineating the genomic landscape of this lymphoma [70,71]. Gene expression analyses preceding these investigations already indicated the significance of the IL6/JAK/STAT signaling pathway and NF-κB activation (Fig. 2) [72,73]. Moreover, for a relevant proportion of cases, it is postulated that these originate from clone-related hematopoiesis of undetermined potential (CHIP) [74].

The prognostic implications of EBV infection in DLBCL remain debated. Studies spanning both earlier and more recent periods, including the rituximab era, have linked EBV$^+$ DLBCL to an unfavorable prognosis [58,60,75,76]. However, in a sizable study comparing 80 cases of EBV$^+$ DLBCL with 76 cases of EBV- DLBCL in a propensity score matched approach, no significant differences were observed in progression-free (PFS) and overall survival (OS) between the two entities [57]. Studies with a comparable sample size came to similar results [62]. Within EBV$^+$ DLBCL, patients lacking CD30 expression appear to exhibit a less favorable prognosis [57]. In other parts of the world, the role of underlying EBV-infections on survival remains controversial. For EBV$^+$ DLBCL, a relatively high prevalence is reported in populations from South America. There exist data sets that are congruent with recent data from Europe, in which EBV-infections did not lead to significant impact on survival measures, as well as data sets in which the PFS of EBV$^+$ vs EBV$^-$DLBCL was significantly inferior [77,78]. The intricate interplay between EBV infection and the clinical outcomes of DLBCL necessitates further investigation for a comprehensive understanding of this entity's prognostic landscape.

3.2. EBV$^+$ mucocutaneous ulcer

This previously provisional entity has now attained recognition as a distinct EBV$^+$ lymphoproliferative disorder of the B-cell series in the WHO-5HAEM and is acknowledged as a definitive entity in the ICC classification [3]. EBV$^+$ mucosal ulcer predominantly presents in the oral cavity, skin, or gastrointestinal tract [79–81]. Notably, unlike other hematologic neoplasms, EBV$^+$ mucosal ulcer tends to exhibit limited systemic manifestations [82]. Males are slightly more predisposed to

Table 1
Overview of known cytogenetic aberrations and molecular alterations in aggressive B-cell NHL with viral association.

Characteristics	PCNSL	PBL	PEL	Fluid overload BCL	EBV$^+$ MC ulcer	EBV$^+$ DLBCL	Burkitt lymphoma	KSHV$^+$ DLBCL	M. Castleman
Virus-association									
- EBV	15%	70%	80%	13–30%	100%	100%	40–70%	–	–
- HIV	–	40–75%	70%	–	–	–	5–10%	>90%	50–75%
- KSHV	–	–	100%	–	–	–		100%	60–80%
Cytogenetic aberrations									
	IG::BCL6 translocations Gains on chromosome 18q21.33–23 Gains on chromosome 12 Gains on chromosome 10q23.21 6q21 deletions 6p21 deletions 8q12 deletions	t(8;14) (q24; q32)	IG heavy chain locus translocations	t(8;14) (q24;q32) t(14;18)	IG heavy chain locus translocations	6q deletions Gains on chromosome 9q24.1	t(8;14) (q24; q32) Gains on chromosome 1q Gains on chromosome 7 Gains on chromosome 12 6q deletions 13q32–34 deletions 17p deletions	–	Alterations on chromosome 7
Molecular alterations									
	MYD88, CARD11, TNFAIP3, PIM1, CDKN2A, CD79B	TP53, CARD11, MYC, STAT3, NRAS, EP300, TET2, ARID1A, PRDM1, CD44, IRF4, NTRK	FHIT, WWOX, IRAK1	PIM1, BCL2, MYD88, IRF4, BTG1/2, CREBBP, KMT2D, MEF2B	Unknown	ARID1A, KMT2A, KMT2D, NOTCH2, ANKRD11, MYD88, TET2, DNMT3A	FOXO1, GNA13, ARID1A, DNMT1, SNTB2, SMARC4A, ID3, TCF3, CCND3	Unknown	NCOA4, DNMT3A, MTCL1, PIM1, NRAS, KRAS, JAK2/3, FGFR3, BRAF, ERBB2/4, ETS1

BCL, B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr-virus; IG, Immunglobulin; KSHV, Kaposi sarcoma herpes virus; MC, mucocutaneous; PBL, plasmablastic lymphoma; PCNSL, primary lymphoma of the central nervous system; PEL, primary effusion lymphoma.

this disorder. Furthermore, the ulcer is more prevalent in older individuals or within the context of existing immunosuppression (e.g., HIV disease, autoimmune diseases, methotrexate (MTX) therapy, TNFα inhibitor therapy) [1,83]. The ulcerations consistently test positive for EBV and typically arise in areas with previous tissue damage (e.g., wounds, post-tooth extractions, chronic inflammatory bowel disease) [79,84].

Histologically, distinguishing EBV$^+$ mucosal ulcer from classical Hodgkin lymphoma or DLBCL can be challenging, given the occasional presence of Hodgkin/Reed-Sternberg-like cells (HRS-like) and B-immunoblasts beneath the ulcer [1]. In the basal portions of EBV$^+$ mucosal ulcers, a characteristic composite of EBV$^+$ T-lymphocytes is identified. Additionally, the primary extranodal intestinal or cutaneous manifestation does not align with the classical presentation of Hodgkin lymphoma [60,80]. Four histological subtypes are recognized, with the polymorphic subtype being the most prevalent [79]. In this subtype, the cell size of EBV$^+$ lymphocytes exhibits significant variation. The large cell subtype is characterized by dominant atypical and monomorphic EBV$^+$ lymphocytes. Epithelioid granulomas and an infiltration of eosinophils can be detected in this context. The Hodgkin-like subtype is distinguished by the frequent appearance of CD30+ HRS-like cells, accompanied by epithelioid granulomas and eosinophil infiltration. Lastly, the MALT-like (mucosa-associated lymphoid tissue) subtype features centrocyte-like or plasmacytic cells.

Immunoblasts express CD20, IRF4/MUM1, and CD30, while germinal center markers CD10 and BCL6 are typically negative [82].

Limited knowledge is available regarding the genomics of this disease (Fig. 2). Translocations involving the immunoglobulin heavy chain locus are frequently described. However, attempts to sequence single lymphoma-associated genes (*MYD88, EHZ2, CD79A, CD79B, CARD11*) have yielded inconclusive evidence [85].

4. HIV/EBV associated lymphoma entities

4.1. Burkitt-lymphoma

The essential features of Burkitt's lymphoma exhibit a remarkable continuity in the latest iteration of the World Health Organization's Classification of Hemato-Lymphoid Tumors (WHO-5HAEM) [2]. It remains characterized as an aggressive and highly proliferative B-cell neoplasm, with a distinctive morphology comprising medium-sized cells, round nuclei, multiple basophilic nucleoli, deeply basophilic cytoplasm, and typically numerous lipid vacuoles [86,87]. Immunophenotypically, the cells suggest an origin from the germinal center (CD10+, BCL6+, BCL2−/weak) [88–90]. The genomic hallmark is the t(8;14) (q24;q32) rearrangement between *MYC* (chr. 8q24) and the heavy chain locus of the immunoglobulin gene (chr. 14q32) (Table 1) [91]. Notably, since the seminal work of Dang et al., the *IG::MYC* rearrangement has been identified as sufficient to solely drive Burkitt lymphoma development [92]. The involvement of the transcription factor *TCF3* and its repressor *ID3* in Burkitt lymphoma pathogenesis was recognized in the previous WHO-4HAEM edition [93–97]. Alterations in these genes activate B-cell receptor signaling and are frequently observed in Burkitt lymphomas. In contrast to the WHO-4HAEM, the latest classification abandons the epidemiological and geographical categorization of Burkitt lymphoma (sporadic versus endemic and immunodeficiency-associated forms). Instead, a greater emphasis is placed on appreciating the pathogenetic implications of existing EBV

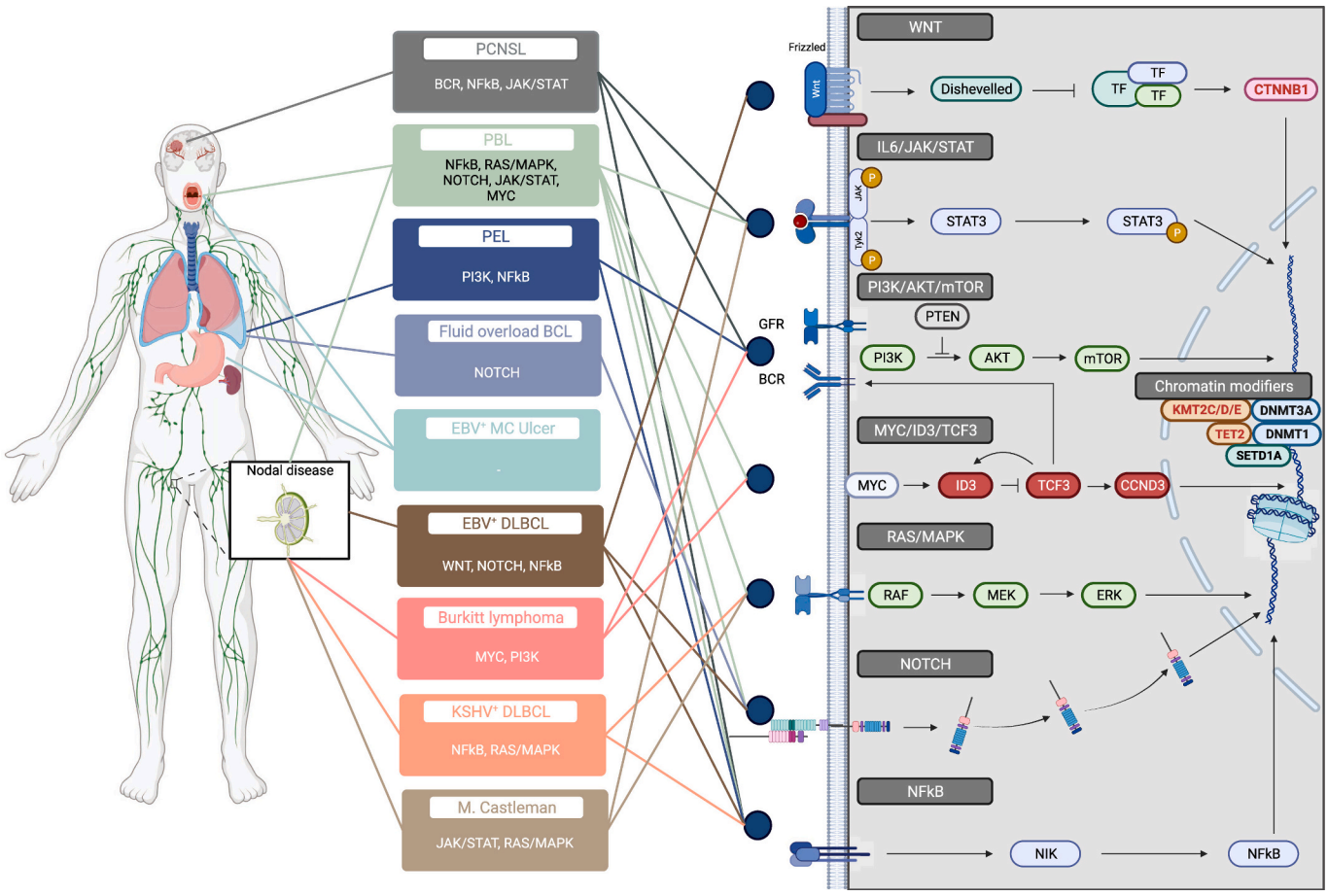

Fig. 2. The figure illustrates the typical clinical manifestations of virus-associated B-cell lymphomas, correlating them with the respective altered signaling pathways. It delineates the involvement of key signaling cascades in the proliferation and growth of these lymphomas for each individual entity.

infections [98–103]. The distinction between EBV$^+$ and EBV$^-$ Burkitt lymphomas, as introduced by the WHO-5HAEM classification, provides a valuable framework for refining the classification and deepening the pathophysiological understanding of this entity (Fig. 2). The genomic landscape of EBV$^+$ Burkitt lymphomas, in contrast to EBV$^-$ cases, reveals a lower frequency of driver mutations and alterations in *TCF1* as well as *ID3* but an overall higher tumor mutation burden [104]. However, they more frequently exhibit somatic hypermutations in non-coding sequences in direct proximity to promoter regions [104,105]. In a pivotal study, in which whole genome sequencing (WGS) was performed on 101 Burkitt's lymphomas, a distinct mutation profile of EBV$^+$ was described. Noteworthy alterations include mutations in *BCL7A, BCL6, IGLL5*, and *BACH2,* with somatic hypermutations often linked to "activation induced cytidine deaminase" (AID) [104]. The enzyme AID, responsible for alterations caused by cytosine deamination, plays a pivotal role in antibody class switching and can lead to mutations in key genes such as *FOXO1* and *GNA13* [106,107].

Gene expression profiling at the RNA level differentiates between EBV$^+$ and EBV$^-$ Burkitt lymphomas, highlighting the influence of EBV infection on pathway activation via virus-associated membrane proteins like LMP1 and LMP2, without the need for corresponding upstream gain-of-function mutations [104,105,108]. This reflects what is known from the molecular pathogenesis of Hodgkin lymphoma [109,110] and is further illustrated by the fact that *ID3, TCF3* and *CCND3* are declared to be driver genes that play a key role in the pathogenesis of Burkitt's lymphomas [95,111,112]. However, frequent mutations leading to phenotypic changes can be detected frequently in Burkitt lymphoma. At the same time, Burkitt's lymphomas formerly classified as endemic (80% EBV positivity) do not carry mutations in these genes compared to sporadic Burkitt's lymphomas [105]. An underlying EBV infection can interfere with the genomics of germinal center B cells through multiple mechanisms [113,114]. EBNA1 can directly abrogate the tumor-suppressive effects of TP53 and EBNA3C is able to directly activate CCND3. Both mechanisms block apoptosis or promote cell growth/proliferation. Accordingly, the lack of mutagenic events at the DNA level can be explained by the extraordinary virus-associated pathogenesis in these lymphomas [115,116].

Gene expression profiles also distinguish between EBV subtypes (type 1 and type 2), revealing 13 differentially expressed genes [117–119]. Particularly, the EBV-1 subtype is associated with the expression of genes involved in immunoproteasome formation, while alterations relevant to chromatin remodeling are subtype-specific [119]. The genes *SMARCA4* (EBV-2) and *ARID1A* (EBV-1) show distinct alteration patterns in EBV$^+$ Burkitt lymphomas, contributing to subtype-specific phenotypic profiles [119]. Irrespective of epidemiological or geographical circumstances, both EBV subtypes ultimately result in a loss of PTEN function. This enables dysregulated PI3K/AKT/mTOR pathway activation [119].

Intriguingly, Burkitt lymphomas associated with HIV infection, constituting up to 40% of all cases worldwide, remain a focus of investigation [120,121]. HIV$^+$ patients have a 10–20% lifetime risk of developing Burkitt's lymphoma, regardless of the effectiveness of antiretroviral therapy [122]. The pathogenetic mechanisms, albeit less understood than those of EBV infection, point to the significant role of the HIV protein Tat [123]. This protein induces aberrant overexpression of single-stranded DNA cytosine deaminase, activating the *RAG1* gene and increasing the risk for *MYC* translocations [124]. Other HIV proteins, such as gp120 and CD40-L, also contribute to Burkitt lymphoma

pathogenesis. Gp120 activates germinal center B cells and also activates single-stranded DNA cytosine deaminase, leading to more frequent immunoglobulin class switching [125]. CD40-L is associated with somatic hypermutation in germinal center B cells [126]. HIV$^+$ Burkitt lymphomas more frequently carry *DNMT1, SNTB2* and *CTCF* mutations. The genomic profile can be assigned to that of Burkitt's lymphomas formerly classified as sporadic [104,120]. Accordingly, these lymphomas can also be classified primarily according to their EBV status[104].

While therapeutic consequences are not yet evident, the insights into distinct pathogenesis between EBV$^+$ and EBV$^-$ subtypes offer promising avenues for the development of future targeted therapy approaches such as alisertib or PI3-kinase inhibitors in the era of precision oncology [127–129].

4.2. Plasmablastic lymphoma

Plasmablastic lymphoma (PBL) represents a highly aggressive entity within the spectrum of high-grade B-cell non-Hodgkin lymphomas, with an inherently unfavorable prognosis [130,131]. While to this day PBL is classified as a subtype of large B-cell lymphomas, from a pathobiological and genetic perspective PBL exhibits overlapping characteristics between DLBCL and multiple myeloma [132]. Immunophenotypically, PBL exhibits characteristic features (CD20-, IRF4/MUM1+, CD79a+/−, CD38/CD138+, PAX5-), without any markers reliably differentiating PBL from multiple myeloma [131,133]. Notably, the absence of CD20 expression is therapeutically significant [133]. CD30 is consistently expressed in a meaningful subset of patients, providing a potential therapeutic target [134]. PBL is closely associated with HIV disease, with prevalence reported in the literature ranging from 40 to 75% [131,134–136]. Additionally, a pathogenetic connection with EBV infections is evident in approximately 70% of PBL cases, and the coincidence of both viral infections is not uncommon, occurring in up to 40% of cases [134,137–140]. This aggressive lymphoma primarily manifests under conditions characterized by significant immunosuppression [138,141]. *MYC* alterations are identified in approximately half of the cases, with a predominance in EBV$^+$ PBL cases [134,142–144]. *MYC* fusions with the immunoglobulin heavy chain rather than (low level) *MYC* amplifications serve as adverse prognosticators (Table 1) [134].

Recent genomic investigations into PBL have provided valuable insights [132,145–147]. Dysregulation of the RAS/RAF/MAP kinase and IL6/JAK/STAT signaling pathways has been highlighted in targeted sequencing studies, with alterations observed in 49% and 40% of cases, respectively [147]. Distinct differences between EBV$^+$ and EBV$^-$ PBL cases were identified, particularly with higher frequency alterations in the IL6/JAK/STAT pathway in EBV$^+$ PBL. EBV$^-$ PBL exhibited a higher tumor mutational burden with frequent mutations in *TP53, CARD11,* and *MYC*. Genes influencing the epigenome or chromatin modification (*EP300, TET2, KMT2C/D, ARID1A*) were more frequently altered in EBV- PBL. Unfortunately, due to the retrospective nature of most PBL studies, the HIV status of the patients is oftentimes only known in a subet of cases. Notably, characteristic alterations seen in Burkitt's lymphoma, such as *ID3, TCF3*, and *SMARC4A*, were not detected, emphasizing distinct pathogenesis among EBV$^+$ lymphomas. In comparison to DLBCL and multiple myeloma, PBL displayed a higher frequency of alterations in *STAT3, NRAS, TP53,* and *EP300* [147]. Further studies using whole exome sequencing (WES) on exclusively HIV$^+$ PBL confirmed the significance of IL6/JAK/STAT and RAS/RAF/MAP kinase signaling pathways [146]. Additional alterations in *PRDM1* (loss of function) and CD44 (copy number alteration) genes were revealed. EBV gene expression profiling identified overexpression of lytic genes *BALF4* and *BALF5* [146]. These genes code for the viral envelope protein glycoprotein B and the catalytic subunit of DNA polymerase [10]. Genomic analyses, encompassing both HIV$^+$ and HIV$^-$ cases, showed lower frequency *STAT3* mutations in HIV$^-$ PBL [132,145]. Despite genomic heterogeneity, the overall median tumor mutational burden was surprisingly low (3.5mut/Mb in median). Involvement of NOTCH and NF-κB signaling pathways was indicated, unveiling potential therapeutic vulnerabilities (*IRF4, ERBB3, PDGFRB, NTRK*) [132,145]. Differential gene expression profiles between EBV$^+$ and EBV$^-$ PBL, identified through RNA sequencing, were found to be prognostically relevant [132]. Survival analysis suggested a less favorable prognosis for EBV$^-$ PBL compared to EBV$^+$ PBL[145].

In conclusion, PBL emerges as a genomically heterogeneous lymphoma, with key pathophysiological roles attributed to the IL6/JAK/STAT and RAS/RAF/MAP kinase signaling pathways (Fig. 2). Additionally, the NOTCH and NF-κB signal transduction cascades appear influential in the pathophysiology of this entity. The genomic analyses present numerous promising therapeutic targets for this challenging-to-treat lymphoma. A virtual approach of a molecular tumor board (MTB) uncovered the spectrum of potential therapeutic targets in a cohort of primary refractory PBL cases (e.g. enasidenib, ripretinib, erdafinib, etc.) [148]. As observed in other EBV-associated lymphoma diseases, distinct gene expression profiles between EBV$^+$ and EBV$^-$ cases indicate diverse pathogenic mechanisms between virus-associated and non-virus-associated instances.

5. KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas

In the latest edition of the World Health Organization's Classification of Hematolymphoid Tumors (WHO 5-HAEM), a spectrum is delineated, acknowledging HHV8/KSHV-associated lymphoproliferative disorders [2]. This spectrum encompasses various entities, including Castleman disease, HHV8-positive diffuse large B-cell lymphoma (HHV8$^+$ DLBCL), HHV8$^+$ germinotropic lymphoproliferative disease, and notably, primary effusion lymphoma (PEL). The latter, once regarded as a separate entity, is now categorized within this group of HHV8-associated lymphoproliferative disorders [2].

5.1. Castleman-disease

Initially described by Richard Castleman in 1956, Castleman disease remains enigmatic, characterized by its rarity, aggressiveness, and unfavorable prognosis [149,150]. Clinical manifestations range from mild symptoms to severe cytokine storms, organ failure, or sudden, dramatic fatalities. TAFRO syndrome, encompassing thrombocytopenia, anasarca, fever, reticulin fibrosis in bone marrow, and organomegaly, represents a distinctive constellation [151–153]. Pathogenetically linked to KSHV/HHV8 in 1995, the WHO-5-HAEM now distinguishes Castleman disease into unicentric, idiopathic, and multicentric KSHV/HHV8-associated forms [2,154]. Occurring in both HIV-positive and HIV-negative individuals, Castleman disease predominantly affects older individuals [150,155]. IL-6-associated inflammation plays a pivotal role in its pathogenesis. Initial therapeutic strategies focus on immunosuppressive interventions such as glucocorticoids, tocilizumab, and siltuximab [156,157].

Cytogenetically, chromosome 7 aberrations are notably frequent, primarily observed in unicentric Castleman disease cases (Table 1) [158]. Genomic characterizations, involving targeted sequencing and WES, reveal somatic alterations in *NCOA4 (L261F), DARS2, MTCL1, RABPE1,* and *DNAH11* in idiopathic multicentric Castleman disease, while unicentric disease exhibits higher associations with *PDGFRB* mutations (N666S) [159–162]. Unique to Castleman disease, mutations in *PDGFRB* and *NCOA4* emerge as specific recurrent pathogenetic events [163]. Functionally assigning detected alterations (*KRAS, NRAS, ERBB2/4, JAK2/3, FGFR3, BRAF, PIM1*) to RAS/RAF/MAP kinase and IL6/JAK/STAT signaling pathways reveals their recurrent involvement in rare aggressive B-cell neoplasms [164].

Additionally, *ETS1* mutations are present in both unicentric and idiopathic multicentric forms, while *DNMT3A* mutations exclusively characterize the idiopathic multicentric variant [163]. *ETS1* mutations frequently occur in DLBCL, Burkitt's lymphoma, and Hodgkin

lymphoma [165,166]. In contrast, *DNMT3A* alterations are known to be associated with myeloid spectrum diseases. Chromatin modifiers like *SETD1A, ASH1L,* and *KMT2E* play a genomic role exclusively in multicentric disease (Fig. 2) [160].

A singular case report notes a familial occurrence of both unicentric and idiopathic multicentric Castleman disease, revealing a germline mutation in FAS associated with both disorders. Genomic distinctions for HHV8$^+$ multicentric Castleman disease remain absent in current literature [167].

5.2. KSHV/HHV8$^+$ DLBCL

This lymphoma primarily occurs in HIV-positive patients concomitant with HHV8$^+$ multicentric Castleman disease, with sporadic cases occurring independently of Castleman disease [168]. Morphologically, the lymphoma cells exhibit a plasmablastic appearance, expressing IgM, LANA, vIL-6, and IRF4/MUM1, while being negative for EBV[169]. CD20 and CD38 may show positivity, whereas CD138 and CD79A are typically negative. The differentiation from extracavitary primary effusion lymphoma can be challenging, accordingly. The lymphoma can manifest both nodally and extranodally, occasionally presenting with a leukemic phenotype [169,170]. Marked splenomegaly is a common clinical feature [169,170].

For this particular entity, there are currently no genomic datasets publicly available or published. It is noteworthy that immunoglobulin genes are not implicated in translocations or other alterations (Table 1). Molecular insights into its pathogenesis stem from the elucidated HHV8/KSHV mechanisms. The viral protein vIL-6 induces proliferation via RAS/RAF/MAP kinases, vFLIP activates the NF-κB signaling pathway, preventing apoptosis [44,171]. The viral protein vCyclin directly stimulates the cell cycle through CDK4/6 modification [172]. Additionally, both LANA and vIRF3 directly inhibit the tumor suppressor *TP53* [51].

6. Effusion associated lymphoma entities

6.1. Primary effusion lymphoma

Primary Effusion Lymphoma (PEL) is an aggressive B-cell neoplasia obligatory associated with HHV8, presenting challenges in treatment despite immunochemotherapy [173,174]. First documented in 1989 by Knowles et al., PEL typically originates in the serous membranes (pleura, peritoneum, pericardium), primarily affecting HIV patients and leading to the development of substantial malignant effusions [174–177]. Extracavitary forms, involving lymph nodes or extralymphoid organs, are notably infrequent (approx. 20% of cases) [178]. Distinction from HHV8-negative fluid overload associated large B-cell lymphoma is crucial [2]. PEL development correlates closely with immunosuppression, notably in HIV disease or post-organ or stem cell transplantation, rendering it as an AIDS-defining disease [179]. EBV detection is common, although the absence of the EBV protein LMP1 is noteworthy [180–182]. PEL incidence is higher in males, and one-third of patients have a history or concurrent existence of Kaposi's sarcoma [183].

Phenotypically, PEL cells exhibit a post-germinal center profile, expressing CD45 while being negative for classic B-cell markers (CD19, CD20, CD79A, BCL6). Similar to PBL plasma cell markers CD38 and/or CD138 are detectable. The HHV8 protein LANA1 (ORF73) is observed in the cell nuclei, and the HHV8-encoded vFLIP protein directly activates the NF-κB signaling pathway [44,184]. Genomic insights into PEL mainly arise from cell line analyses due to limited native tumor cell availability. Early RNA-level studies underscored the close relationship between PEL and immunosenescence-associated PBL [185]. Furthermore, gene expression analyses indicated distinct signatures associated with different viral constellations (EBV+/−) [186]. Comparative genomic hybridization identified losses of tumor suppressors (*FHIT, WWOX*), and X-linked enriched targeted sequencing revealed a clustering of *IRAK1* mutations (Fig. 2) [182]. Despite sporadic case descriptions, comprehensive knowledge about the broader molecular genetic background of PEL remains limited. Existing data, primarily from panel-based and PCR/Sanger-based studies on cell lines (BC-3, JSC-1, CRO-AP2, and BC-1) and limited samples, suggests an overlap with typical lesions of other EBV-driven lymphomas [187–189]. Preclinical data hint at a significant accumulation of mutations in the ApoB mRNA-editing catalytic subunit (APOBEC) signature, linked to impaired innate immune system function in PEL and facilitating HHV8/EBV-driven lymphoma manifestation. This was interpreted in the context of the role of APOBEC in the innate immune system and the fight against viral infections, which does not function adequately in PEL and appears to allow the manifestation of HHV8/EBV-driven lymphoma disease [187]. However, a comprehensive understanding of the mutational landscape and oncogenic drivers in PEL is still lacking. Systematic investigations into established chromosomal risk markers of other B-cell neoplasms, such as *MYC, BCL2,* and *BCL6*, alongside a broader spectrum of molecular genetic or transcriptomic alterations, are warranted to unravel the intricacies of PEL pathogenesis. Given its distinctive and complex genomic landscape, HHV8-negative cases are no longer recognized as PEL. These cases must rather be categorized as fluid-overload associated large B-cell lymphoma. Beyond an equally complex karyotype, it presents with frequent mutations, CNAs, and translocations, akin to those commonly observed in aggressive ABC- and GCB-type DLBC and PBL[190].

6.2. Fluid overload associated large B-cell lymphoma

This lymphoma entity has been newly incorporated into the latest version of the World Health Organization's Classification of Hematolymphoid Tumors (WHO-5HAEM) [2]. Characterized by its exclusive manifestation in large body cavities, notably as pleural effusion, it is imperative to differentiate this entity from PEL, as no association with human herpesvirus 8 (HHV8) exists [191,192]. Pathophysiologically, a discernible link can typically be established with an underlying predisposing disease leading to relevant fluid retention, such as heart failure, chronic kidney disease, liver cirrhosis, or significant protein loss via the intestine [191,193]. Despite its association with predominantly chronic diseases, the prognosis for this entity is reported to be more favorable than for PEL, and it predominantly affects elderly patients, with a pronounced immunodeficiency not necessarily being a prerequisite [194]. EBV positivity can be detected in 13–30% of cases, occasionally accompanied by CD20 negativity [191,195]. However, in contrast to PEL that frequently lack B-cell markers, most cases are immunohistochemically positive for B-cell markers (CD20+, CD79a+, PAX5+). Most available data on this entity is derived from case reports or case series. Notably, a comprehensive work examining 11 cases, with genomic analysis performed on 8 of them through whole-genome sequencing (WGS) or targeted sequencing, distinguishes this entity genomically from PEL [190]. Immunophenotypically, it aligns with a non-germinal center B-cell (non-GCB) type. HHV8-negative effusion-based lymphoma (HHV8$^-$ EBL) commonly exhibits alterations in *PIM1, BCL2, MYD88, IRF4,* and *BTG1&2* [191,196]. Genes involved in chromatin modification, such as *CREBBP, KMT2D*, and *MEF2B*, are also implicated [196]. Larger cohort analyses are warranted to contextualize this entity within the spectrum of aggressive B-cell non-Hodgkin lymphomas. However, due to the rarity of this lymphoma and challenges associated with retrospective analysis on archival effusion material, the feasibility of assembling sufficiently large representative cohorts with adequate tissue material remains to be determined in future investigations.

7. Large B-cell lymphomas of immunoprivileged sites

In WHO-5HAEM, large B-cell lymphoma of the central nervous system (PCNSL) is classified as primary large B-cell lymphoma of immune privileged sites [2]. This lymphoma is a rare extranodal subtype that can

manifest in the cerebrum or also in the cerebrospinal fluid [2]. Histologically, perivascular infiltrates of cells of a large B-cell lymphoma can be detected. Accounting for approximately 1% of non-Hodgkin lymphomas, PCNSL typically manifests at a median age of 65 years, is often linked to pre-existing immunosuppression, and shows an association with EBV in about 15% of cases [197,198]. Numerous investigations have meticulously scrutinized the genomic and transcriptomic landscapes of PCNSL [199–202]. Frequent genetic alterations involving B-cell receptor (BCR) signaling cascades, downstream NF-KB pathways featuring *MYD88, CARD11*, and *TNFAIP3*, along with dysregulation in cell cycle regulatory genes (*PIM1, CDKN2A*), the JAK-STAT signaling pathway, frequent *CD79B* alterations and *IGH-BCL6* fusions are recurrently observed in PCNSL [199,201,203–205]. Since alterations in *CARD11* and *PIM1*, which are associated with the development of resistance to ibrutinib, occur much less frequently in EBV^+ PCNSL, the administration of BTK inhibitors may be promising here [206]. However, there also exists a rationale for effective BTK inhibition in EBV^- CNSL [207]. Moreover, PCNSL exhibits diverse mutation patterns, as defined by Alexandrov et al., encompassing SBS1, SBS2, SBS3, SBS9, and SBS18 signatures [199,208]. The application of the LymphGen algorithm by Wright et al. categorizes PCNSL into varied genomic clusters, with predominant representation in MCD and EZB subtypes, alongside less common occurrences of BN2, ST2 subtypes, and unclassified cases [68,199]. Single-cell RNA analyses unveil T-cell subset transitions towards exhaustion and the identification of a plasmablast-like program, indicative of an unfavorable prognosis within PCNSL [209].

Preliminary investigations emphasize the distinct nature of EBV^+ CNSL as a separate entity [210]. Genomic mapping stratified by EBV and HIV status reveals unique features in EBV-associated cases, with the absence of classic mutations except for IG and HLA-DRB loci [206]. EBV^+ PCNSL demonstrates a distinctive tumor microenvironment characterized by elevated macrophage levels and heightened expression of immune checkpoint genes, underscoring the potential efficacy of immunotherapeutic strategies tailored to this subtype [206]. Immunotherapeutic avenues emerge as promising prospects for EBV^+ PCNSL, capitalizing on its distinctive tumor microenvironment and lower frequencies of *CARD11* or *PIM1* alterations linked to resistance. Noteworthy, immune checkpoint inhibitors are contraindicated in post-transplant lymphoproliferative disease (PTLD) due to the high risk of graft rejection.

8. Discussion

The aggressive B-cell neoplasms adjacent to DLBCL exhibit distinct genomic characteristics [104,211]. The genomic landscape und transcriptional profile of these lymphomas is significantly influenced by viral lymphomagenesis, a fact underscored by gene expression analyses across different entities [105,132]. However, certain subtypes, such as EBV^+ mucosal ulcer, remain genomically underexplored, largely owing to their rarity [85]. The 5th edition of the WHO classification and the ICC classification have introduced substantial changes, including the reclassification of Burkitt's lymphoma and the delineation of KSHV-associated lymphomas, leading to the inclusion of $KSHV^-$ multicentric Castleman's disease and fluid overload associated large B-cell lymphoma [2,3]. The updated classifications reflect an enhanced comprehension of the genomic underpinnings of hematologic neoplasms, paving the way for targeted therapeutic interventions in the era of precision oncology. For instance, in Burkitt lymphoma, EBV has been linked to *PTEN* loss, suggesting the potential efficacy of PI3 kinase inhibitors as well as AKT inhibitors [212–215]. CD30 expression, prevalent in the majority of EBV-associated B-cell lymphomas, represents a promising therapeutic target, exemplified by brentuximab vedotin and other ADC-constructs [57,134,216]. In addition, in EBV^+ DLBCL, CD30 positivity is correlated with an unfavorable prognosis, underscoring the potential value of CD30-directed therapies [57]. Similar considerations apply to EBV^+ mucosal ulcer, where brentuximab vedotin has demonstrated promising activity, and comprehensive genomic characterization may unveil novel therapeutic avenues [217,218]. Brentuximab vedotin, due to the characteristic CD20 loss, could significantly augment chemotherapy in PBL, an entity known for its biological aggressiveness and unfavorable prognosis [50]. The extraordinary genomic heterogeneity of this disease suggests the suitability of personalized treatment strategies. Recent research examining primary refractory cases and identifying potential targeted treatment strategies emphasizes the promise of individualized approaches [148]. This translational perspective on genomic datasets holds potential to expand therapeutic options for challenging entities of virus-associated lymphoid neoplasms, often characterized by direct activation of signal transduction cascades, necessitate a transcriptomic focus due to the absence of associated DNA-level alterations.

A further therapeutic approach, which can certainly extend therapy concepts, is based on the repeatedly proven overexpression of aurora A kinases (AAK) in some aggressive lymphoma entities. Specifically, the promising activity of alisertib has been described in extent. The use of this substance in the precision oncology setting potentially expands therapeutic options [127,129,219,220].

Unique virus-induced lymphomagenesis, contributing to inflammation, has therapeutic implications, as seen in the management of Castleman disease. Therapeutic immunosuppression using the anti-IL-6 antibodies siltuximab or tocilizumab, is particularly relevant for idiopathic multicentric Castleman disease. As such anti-IL-6 antibodies seem to have less affinity to vIL-6, they are less effective in KSHV associated Castleman disease. Therefore, innovative strategies targeting virus-specific structures are being explored [221].

Preclinical efforts targeting EBV proteins (LMP1, gp350) in CAR-T cell constructs show promise, with clinical data supporting the efficacy of CD19 CAR-T cell products in EBV^+ DLBCL [222–224]. Recent approvals, such as the allogeneic CAR T-cell product tabelecleucel for EBV^+ lymphoproliferative diseases post-transplantation (PTLD), signal progress in therapeutic options [225].

There are various international collaborations, such as the 'Grupo de Studio Latinoamericano the Linfoproliferativos' (GELL), the International T-cell project or Lymphoma Epidemiology of Outcomes (LEO), which are dedicated to research efforts into the field of rare lymphomas, including virus-associated subtypes. Such scientific work groups have made a significant contribution to the constant progress in knowledge in this field of research over the past decades.

In the upcoming years, the genomic understanding of this unique spectrum of lymphoproliferative diseases will need to be further developed and refined in order to identify specific therapeutic approaches. Innovative technologies such as viewing these lymphomas at the single cell level and at the transcriptomic or genomic level in a spatial context will be helpful. The recently published WHO and ICC classifications acknowledge the existing evidence on virus-associated aggressive B-cell NHL and clearly distinguish it from DLBCL. However, thanks to improvements in anti-(retro)-viral therapy and advances in supportive treatment, the life expectancy of people with immunosuppression such as HIV infections is now virtually unlimited. Accordingly, HIV infections or equivalent conditions associated with immunosuppression must be reconsidered as an exclusion criterion for clinical trials, providing novel therapeutic options for these patients.

9. Future considerations

The delineation of genetic profiles presented here offers promising avenues for the development of innovative therapeutic modalities. Future investigations into molecular underpinnings hold substantial potential to revolutionize the prognosis of this distinct array of lymphoproliferative disorders. Advanced technologies discussed herein harbor the capacity to yield comprehensive insights into the biology of lymphomas, thereby facilitating the customization of treatment paradigms within a translational context. Notably, a recently published

prospective study has emerged, focusing on the treatment of genetic subtypes in DLBCL, demonstrating affirmative indications for the implementation of precision-based therapeutic strategies [226]. The abandonment of a "one size fits all" strategy towards tailored interventions founded upon tumor biology principles exhibits particular relevance within the pathophysiologically heterogeneous spectrum of virus-associated B-cell non-Hodgkin lymphomas.

10. Practice points

- Owing to the infrequency of occurrences and the prevailing categorization of HIV disease as an exclusionary criterion in many clinical trials, the available evidence concerning therapeutic approaches within the domain of virus-associated B-cell NHL remains notably constrained.
- The current comprehensive understanding of the pathophysiological and genomic aspects of virus associated B-cell NHL unveils auspicious avenues for novel therapeutic approaches, acknowledging the unique biological underpinnings inherent to such lymphomas.
- An initial approach may involve the future utilization of targeted therapy agents in EBV^+ B-cell NHL such as brentuximab vedotin or daratumumab with corresponding CD30 and CD38 expression, respectively.
- In the spectrum of virus-associated B-cell non-Hodgkin lymphomas, the interplay of immunological and genetic aspects appears to be of particular relevance. Immunosuppressive therapeutic modalities are employed in the management of selected entities such as Castleman disease.

11. Research agenda

- In some entities, such as EBV^+ mucocutaneous ulcer, genomic features are poorly characterized. The analysis of the genomic landscape of these entities represents a key point for an even more detailed classification in the future.
- The incorporation of pioneering molecular genetics technologies, including single-cell RNA analysis and spatially resolved transcriptomic profiling, will provide additional insights into the evolution of these diseases. These insights will play a crucial role in the development of future therapeutic paradigms.

Author contribution

Study concept: HW, NG; Data collection: HW, AK; Data analysis and creation of figures and tables: HW and AK; Initial draft of the manuscript: HW; Critical revision and approval of final version: all authors.

Declaration of competing interest

HW: Honoraria from BeiGene and Viatris as well as travel support from Janssen. NG: Consulting activities for Takeda, Roche, Janssen and AstraZeneca; lecture fees for AstraZeneca, Roche, Janssen, Stemline, FOMF and RG; travel grants from BeigGene, Janssen and Roche AK: No conflicts of interest to declare.

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