

Perspective

# Classification of B-Cell Lymphomas and Immunodeficiency-Related Lymphoproliferations: What's New?

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**Abstract:** New insights from genomic studies have had an impact on the definition and the diagnosis of several lymphoid tumors including follicular B-cell lymphomas, aggressive diffuse large B-cell lymphomas, and lymphoproliferations associated with acquired and posttransplant immunodeficiencies. Follicular lymphoma (FL) includes tumors whose behavior varies widely from indolent/early lesions to aggressive/transformed lymphomas. Although some large B-cell lymphomas can be subclassified as specific entities, the majority lack the characteristics necessary for subclassification and, thus, are termed diffuse large B-cell lymphoma, NOS. There have been, however, some changes in the classification of specific subtypes of large B-cell lymphoma as well as the addition of new entities, a few of which are highlighted in this article. The immunodeficiency-related lymphoproliferative disorders are currently divided into four major categories based on the clinical setting in which they arose: primary immune deficiency, post-transplant, HIV infection, and iatrogenic immunosuppression. In the two upcoming classifications systems for hematolymphoid neoplasms, International Consensus Classification (ICC) and WHO-HAEM-5, there is a divergence in the approach to categorize these lesions. Furthermore, whereas the WHO-HAEM-5 confirms the ability to classify a spectrum of EBV+ lesions as EBV+ DLBCL, NOS, the ICC has separated out lesions that are composed of a heterogenous cellular infiltrate into a new separate category, “EBV-positive polymorphic B cell lymphoproliferative disorder, NOS”. Both WHO-HAEM-5 and ICC recognize a number of KSHV/HHV8-associated lymphoid lesions and acknowledge that there is significant overlap among the different lesions. In the future, translation of these innovations in general practice requires further validation.

**Keywords:** WHO classification; B-cell lymphomas; follicular lymphomas; diffuse large B-cell lymphomas; immunodeficiency-related lymphoproliferations; viral-associated lymphoproliferations



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## 1. Introduction

The World Health Organization (WHO) “*Classification of Tumours of Haematopoietic and Lymphoid Tissues*” was published in 2001 and subsequently updated in 2008 and 2017. It recognized individual disease entities based on morphologic and immune phenotypic features, clinical presentation, and genomics [1–3]. The WHO classification was validated across the world by hematologists and oncologists and was accepted with a broad consensus by pathologists, geneticists, and translational research scientists [4,5].

In the last five years, new insights from genomic studies have had an impact on the definition of several lymphoid tumors. More recently, the criteria for diagnosis of most entities have been extensively refined in a proposal by the International Consensus Classification (ICC) as well as by the upcoming World Health Organization publication, *Classification of Tumours of Haematopoietic and Lymphoid Tissues, 5th Edition* (WHO) [6,7]. Some categories, which were previously considered “provisional”, have been recognized as “definite” entities, whereas other categories have undergone major revision [6]. Novel potential subtypes

have been proposed for some entities; for example, the distinction of Epstein–Barr virus (EBV)-positive and EBV-negative subtypes has been suggested for Burkitt lymphoma (BL) instead of the three traditional epidemiologic variants. Importantly, as highlighted in this article, the development of the understanding of lymphoid proliferations associated with acquired immune disorders justified significant updates in the WHO classification [7,8].

This article reports on major revisions in the criteria and definition of follicular B-cell lymphomas (FL), aggressive diffuse large B-cell lymphomas (DLBCL), and lymphoproliferation associated with acquired immunodeficiencies. Table 1 shows the most significant changes made in B-cell lymphomas and lymphoid proliferations for the next WHO classification [6,7] compared with the 2017 WHO classification [3]. This table includes those B-cell lymphomas and lymphoid proliferations discussed in this “Perspectives” article.

**Table 1.** WHO Classification of Haematolymphoid Tumours, 5th edition: B-cell lymphoid proliferations and lymphomas\*.

WHO Classification, 5th Edition	WHO Classification, Revised 4th Edition
<b>Follicular lymphoma</b>	
In situ follicular B-cell neoplasm	In situ follicular neoplasia
Follicular lymphoma	(Same)
Pediatric-type follicular lymphoma	(Same)
Duodenal-type follicular lymphoma	(Same)
<b>Cutaneous follicle center lymphoma</b>	
Primary cutaneous follicle center lymphoma	(Same)
<b>Transformations of indolent B-cell lymphomas</b>	
Transformations of indolent B-cell lymphomas	Not previously included
<b>Large B-cell lymphomas</b>	
Diffuse large B-cell lymphoma, NOS	(Same)
T-cell/histiocyte-rich large B-cell lymphoma	(Same)
Diffuse large B-cell lymphoma/high grade B-cell lymphoma with MYC and BCL2 rearrangements	High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements
ALK-positive large B-cell lymphoma	(Same)
Large B-cell lymphoma with IRF4 rearrangement	(Same)
High-grade B-cell lymphoma with 11q aberrations	Burkitt-like lymphoma with 11q aberration
Lymphomatoid granulomatosis	(Same)
EBV-positive diffuse large B-cell lymphoma	EBV-positive diffuse large B-cell lymphoma, NOS
Diffuse large B-cell lymphoma associated with chronic inflammation	(Same)
Fibrin-associated large B-cell lymphoma	Not previously included (previously considered a subtype of diffuse large B-cell lymphoma associated with chronic inflammation)
Fluid overload-associated large B-cell lymphoma	Not previously included
Plasmablastic lymphoma	(Same)
Primary large B-cell lymphoma of immune-privileged sites	Not previously included, encompassing primary diffuse large B-cell lymphoma of the CNS in revised 4th edition (plus primary large B-cell lymphoma of the vitreoretina and primary large B-cell lymphoma of the testis)
Primary cutaneous diffuse large B-cell lymphoma, leg type	(Same)
Intravascular large B-cell lymphoma	(Same)
Primary mediastinal large B-cell lymphoma	(Same)
Mediastinal grey zone lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma
High-grade B-cell lymphoma, NOS	(Same)
<b>Burkitt lymphoma</b>	
Burkitt lymphoma	(Same)

Table 1. Cont.

WHO Classification, 5th Edition	WHO Classification, Revised 4th Edition
<b><i>KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas</i></b>	
Primary effusion lymphoma	(Same)
KSHV/HHV8-positive diffuse large B-cell lymphoma	HHV8-positive diffuse large B-cell lymphoma, NOS
KSHV/HHV8-positive germinotropic lymphoproliferative disorder	HHV8-positive germinotropic lymphoproliferative disorder
<b><i>Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation</i></b>	
Hyperplasias arising in immune deficiency/dysregulation	Not previously included, encompassing non-destructive post-transplant lymphoproliferative disorders, among others
Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation	Not previously included, encompassing polymorphic posttransplant lymphoproliferative disorders, other iatrogenic immunodeficiency-associated lymphoproliferative disorders, among others
EBV-positive mucocutaneous ulcer	(Same)
Lymphomas arising in immune deficiency/dysregulation	Not previously included, encompassing monomorphic posttransplant lymphoproliferative disorders, classic Hodgkin lymphoma posttransplant lymphoproliferative disorders, lymphomas associated with HIV infection, among others

\* Modified and adapted from refs. [6,7].

## 2. Follicular Lymphomas

In this section, we discuss on the evolution of the definition of FL. FL includes tumors derived from follicle center B cells whose behaviors vary widely from indolent to aggressive. FL tumor cells commonly express BCL2, BCL6, and CD10 and carry t(14;18) that involves the *BCL2* gene [9].

### 2.1. Incipient/Early Lesions of Follicular Lymphoma

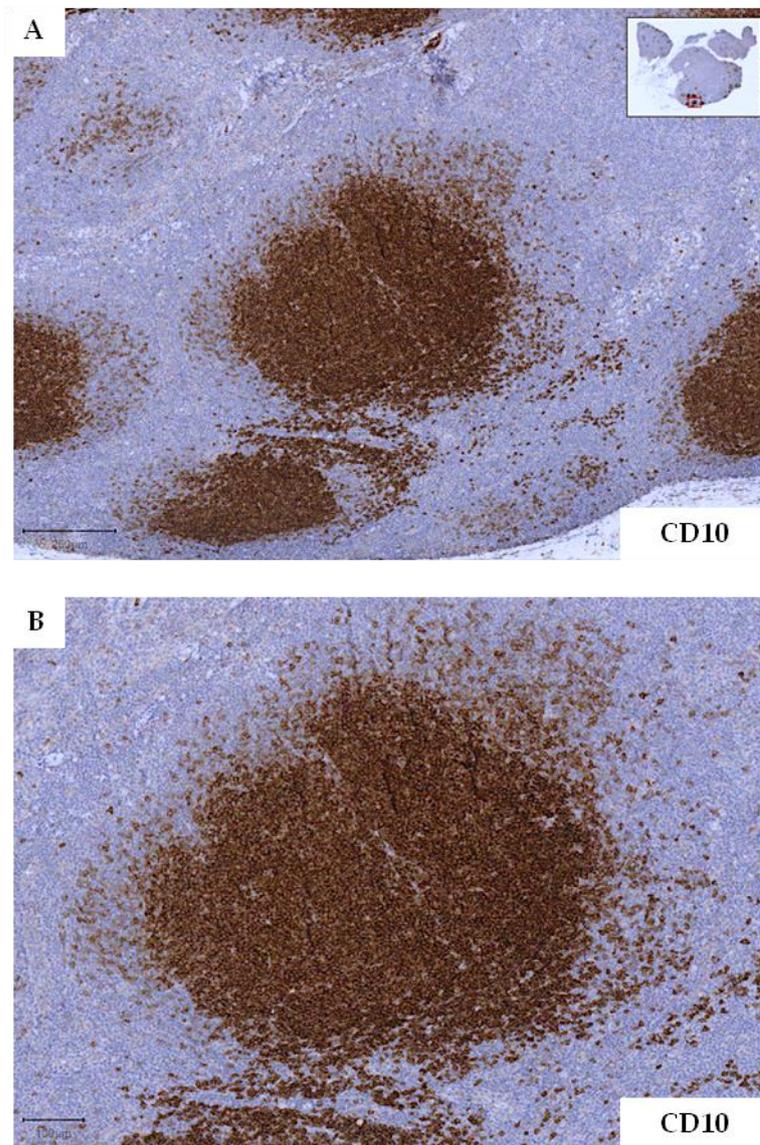
Non-neoplastic B cells that carry t(14;18), referred to as FL-like B-cells, are found in about 70% of healthy individuals over the age of 50 [9–11]. Circulating FL-like B cells can be found by sensitive PCR testing of peripheral blood lymphocytes. The histological counterpart of this early lesion, termed in situ follicular neoplasm (ISFN, WHO; in situ follicular neoplasia, ICC), can be seen as an incidental finding (2–3%) in routine lymph node biopsies but rarely develop into frank FL (Figure 1). Early lesions carry *BCL2* translocation and may show mutations in *CREBBP*, *EZH2*, and *TNFRSF14*. Mutations in *KMT2D* appear to be a later event and are associated with increased risk of progression [9,12,13].

Duodenal-type FL is another early form of FL in which the BCL2-positive cells expand within the intestinal lymphoid tissue. It has a relatively low incidence of progression to frank FL [6,9].

### 2.2. Follicular Lymphoma

Follicular lymphoma (FL) is a B-cell lymphoma that morphologically and phenotypically mimics reactive lymphoid follicles. The genetic alterations include *JH/BCL2* rearrangement, t(14;18), and somatic mutations of immunoglobulin V<sub>H</sub> genes [9]. Most patients present with advanced stage disease, (IIIA–IV A), and with indolent disease [9].

Forms of BCL2-negative FL have been recognized. BCL2-negative FL are both clinically and pathologically heterogeneous [14]. A distinctive subgroup, termed “BCL2-R negative, CD23-positive follicle center lymphoma” [6] includes those cases presenting often with inguinal disease that tend to be at a low stage. These CD23-positive cases, though negative for *BCL2* rearrangement, still carry some of the genetic alterations of BCL2-positive FL with frequent mutations in *CREBBP* [14] and have a high frequency of STAT6 mutations [6].



**Figure 1.** Incipient/early follicular lymphoma. **(A)** At low magnification some lymphoid follicles are occupied by neoplastic cells strongly expressing CD10 staining. **(B)** At higher magnification, neoplastic cells are irregularly present at the border of the neoplastic follicle. (Immunohistochemical staining; 10× **(A)**; 20× **(B)** original magnification).

### 2.3. Lymphomas with a Follicular Pattern Occurring Preferentially in Pediatric and Young Adults

B-cell lymphomas of follicle cell derivation occurring in young patients include pediatric-type FL, large B-cell lymphoma with IRF4 rearrangement, and testicular FL [9,15]. Large B-cell lymphoma with IRF4 rearrangement is discussed in the large B-cell lymphoma section (see Section 5).

Pediatric-type FL is nodal, usually involves head and neck and presents as stage I. Young patients are frequently male (M/F: 10/1). Tumor cells express CD10 and BCL6 but not BCL2 and MUM1. Genetic alterations that are observed in pediatric-type FL include mutations in *TNFRSF14*, *MAP2K1*, and *MAPK* genes and loss of 1p36.

Testicular lymphoma usually presents as stage I with a good outcome. Tumor cells express CD10 and BCL6 but not BCL2 and MUM1. Genetic alterations include occasional BCL6 breaks.

### 3. Cutaneous Follicle Center Lymphoma

Primary cutaneous FL is negative for *BCL2* rearrangement and negative for CD10 expression. Genetic alterations that are observed include 1p36 deletions and mutations in *TNFSR14* and high-level amplifications at 2p16.1 (*REL* gene). Primary cutaneous FL is an indolent disease, with a 95% disease-specific five-year survival rate [6,9,16]. It usually presents at low stage and is solitary, localized or (less often) multifocal. Molecular studies support its segregation from other follicular lymphomas and help predict extracutaneous dissemination [6].

### 4. Transformation of Indolent B-Cell Lymphomas

Forms of histologic transformation of FL include DLBCL, high-grade B-cell lymphoma with double hit, classical Hodgkin lymphoma (CHL), and histiocytic sarcoma. Some cases of high-grade B-cell lymphoma, though TdT-positive, may carry both *MYC* and *BCL2* rearrangement and are considered a variant of double-hit lymphoma [17]. Transformation to CHL and histiocytic sarcoma indicates the plasticity of the hematopoietic system (reviewed in ref. [18]).

### 5. Large B-Cell Lymphomas

Table 1 lists the major subtypes of large B-cell lymphomas of WHO classification for the revised fourth edition and fifth edition [5,6].

This category is composed of a wide spectrum of lymphoid neoplasms composed of medium to large lymphoid cells with a mature B-cell phenotype, which exhibit a variety of morphologic, immunophenotypic, and molecular genetic features. Whereas some of these lesions can be subclassified as specific entities, the majority lack characteristics necessary for subclassification and, thus, are termed *diffuse large B-cell lymphoma, NOS*. Although significant progress has been made in evaluating the molecular composition of diffuse large cell lymphoma, NOS, [19] the data are still felt to be insufficiently mature and insufficiently evaluated in the clinical arena to be employed in a definitive subclassification schema for these lesions. Thus, with additional data it is likely that many of the cases in this category will be subclassified into clinically relevant categories in the future [6,7]. There have been, however, some changes in the classification of specific subtypes of large B-cell lymphoma as well as the addition of new entities, a few of which are highlighted below.

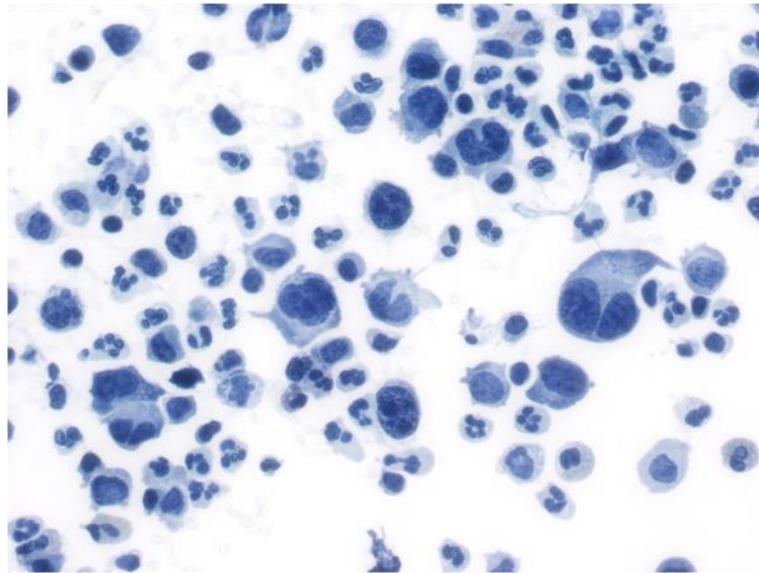
#### 5.1. Large B-Cell Lymphoma with *IRF4* Rearrangement

*IRF4* large B-cell lymphoma is extranodal and usually involves tonsil/Waldeyer's ring in which the pattern may be follicular or diffuse. Males and females are equally affected. Tumor cells co-express MUM1, BCL6, and often CD10. Genetic alterations that are observed in *IRF4* large B-cell lymphoma include frequent *IRF4* breaks.

#### 5.2. Fluid Overload-Associated Large B-Cell Lymphoma (WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 5th Edition; WHO-HAEM5)/HHV8 and EBV-Negative Primary Effusion-Based Lymphoma (International Consensus Classification; ICC)

Effusion-based lymphoma was mentioned, under the term HHV-8 negative primary effusion lymphoma, in the differential diagnosis of primary effusion lymphoma in the WHO-HAEM fourth edition, revised (WHO-HAEM4R), but was not included as a distinct subtype [20]. In the upcoming WHO-HAEM5 classification these lesions are recognized as a distinct subtype of DLBCL, "*fluid overload-associated large B cell lymphomas*", whereas in the ICC they are a provisional entity called "*HHV8 and EBV negative primary effusion-based lymphoma*" [6,7]. Both classifications recognize these as lesions arising in the setting of fluid overload, often due to an underlying medical condition such as cardiac, renal, or liver failure, without a preceding or concurrent tumor mass. There also appears to be a relationship with hepatitis C virus infection. These lesions are composed of cells that are usually morphologically reminiscent of the neoplastic cells in PEL (Figure 2). However, in contrast to PEL, the neoplastic cells are KSHV/HHV8 negative and express

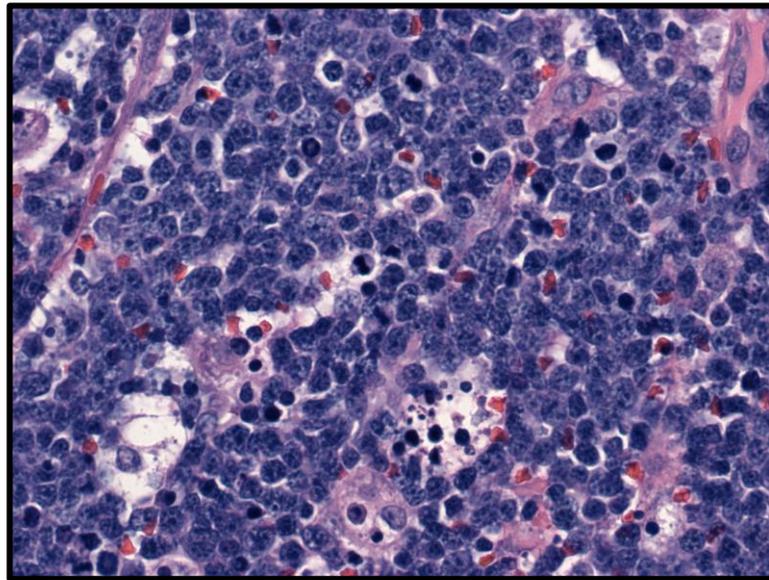
B-cell antigens such as CD20, lack expression of CD138, and occasionally contain a *MYC* rearrangement. Furthermore, the patients with this type of large cell lymphoma are usually older HIV-negative individuals who are often of Asian descent [6,7,21]. In the WHO-HAEM5, lesions that are EBV-positive are included in this category and account for a small proportion of the cases, whereas in the ICC, EBV positivity is an exclusion criterium [6,7]. Both classifications recognize that these effusion-based lymphomas are associated with a relatively good prognosis compared with PEL and pyrothorax-associated lymphoma and can in some instances be cured by drainage alone. A few patients (~15%) will subsequently develop a solid tumor mass; however, this usually occurs years after the development of the effusion-based lymphoma [6,7,20–23].



**Figure 2.** Cytospin from a cardiac failure patient with a fluid overload-associated large B-cell lymphoma. The patient underwent thoracentesis, the cardiac issues were treated but they did not receive treatment for the lymphoma. One year later the patient has no evidence of disease. Notice the pleomorphic large cells, which resemble PEL cells, admixed with a number of small mixed inflammatory cells (Papanicolaou stain, 60× original magnification).

### 5.3. High-Grade B-Cell Lymphoma with 11q Aberration (WHO-HAEM5)/Large B-Cell Lymphoma with 11q Aberration (ICC)

Burkitt-like lymphoma with 11q aberration was a provisional entity in WHO-HEAM4R that displayed clinical and pathologic features similar to Burkitt lymphoma (Figure 3) but lacked an *MYC* rearrangement [24]. Instead, these morphologically high-grade lymphomas contain cytogenetic alterations involving chromosome 11q characterized by proximal interstitial gains and telomeric losses. It is now known that these neoplasms are more variable than initially recognized and exhibit a gene expression profile that more closely resembles DLBCL than Burkitt lymphoma. For example, genomic alterations in the ID3–TCF3 complex, a molecular hallmark of Burkitt lymphoma, are only rarely, if ever, seen in these lymphomas [25,26]. Thus, these lesions have been renamed as high-grade B-cell lymphoma with 11q aberration (WHO-HEAM5)/large B-cell lymphoma with 11q aberration (ICC; provisional) [6,7].

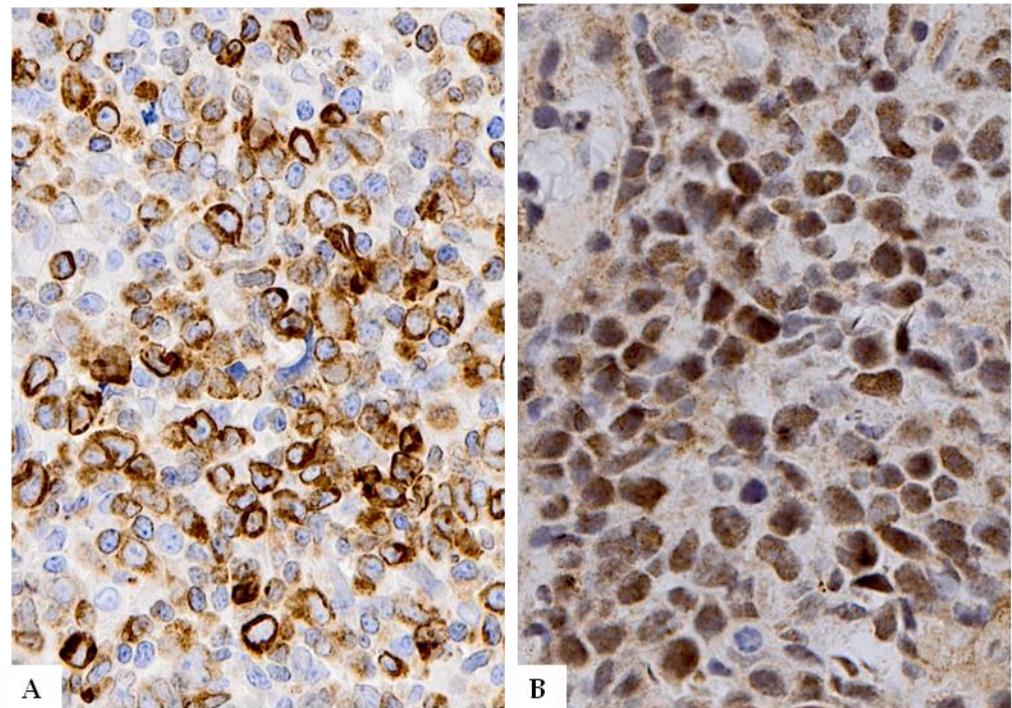


**Figure 3.** High-grade B-cell lymphoma with 11q aberration/large B-cell lymphoma with 11q aberration often shows morphologic features similar to Burkitt lymphoma, as seen here. However, these lesions are genetically different from Burkitt lymphoma, containing proximal interstitial gains and telomeric losses in the q arm of chromosome 11, while lacking *MYC* rearrangements and genomic alterations in the *ID3-TCF3* complex (hematoxylin and eosin stain, 60× original magnification).

#### 5.4. Double-Hit Lymphoma

The subcategory of “high grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements” encompassing the “double/triple hit lymphomas” no longer exists in either the ICC or WHO-HAEM5 classifications. Studies since the publication of WHO-HAEM4R have shown that the high-grade lymphomas with *MYC* and *BCL2* rearrangements, which are of germinal center origin, are a relatively distinct group of lymphomas based on genetics. These cases, usually composed of large, intermediate, or blastoid appearing cells, are classified in the two systems with slightly different nomenclature. In the WHO-HAEM5 these lesions are called “diffuse large B cell lymphoma/high grade B cell lymphoma with *MYC* and *BCL2* rearrangements” (DLBCL/HGBL *MYC/BCL2*) (Figure 4), whereas the ICC has named these lesions “high grade B cell lymphoma with *MYC* and *BCL2* rearrangements with or without *BCL6* rearrangement” (HGBL-DH-*BCL2*) [6,7,27–29].

In contrast, the cases with only *MYC* and *BCL6* rearrangements and no *BCL2* rearrangement are categorized differently in the two classifications. Cases with *MYC* and *BCL6* rearrangements, compared with those with *MYC* and *BCL2* rearrangements, appear to be more genetically diverse based on gene expression and mutational profiles and often show a non-germinal center phenotype [27–29]. These cases in WHO-HEAM5 are classified as either *diffuse large cell lymphoma, NOS*, or *high-grade B-cell lymphoma, NOS, based on morphology* [7]. Although the ICC recognizes that the cases they designate as “high grade B cell lymphoma with *MYC* and *BCL6* rearrangements” (HGBCL-DH-*BCL6*) do not exhibit as distinct biology as the *MYC* and *BCL2* rearranged cases, they retain these lesions in a separate, but provisional, category as there are reports of poor outcome associated with this genetic composition [6,27,29,30].

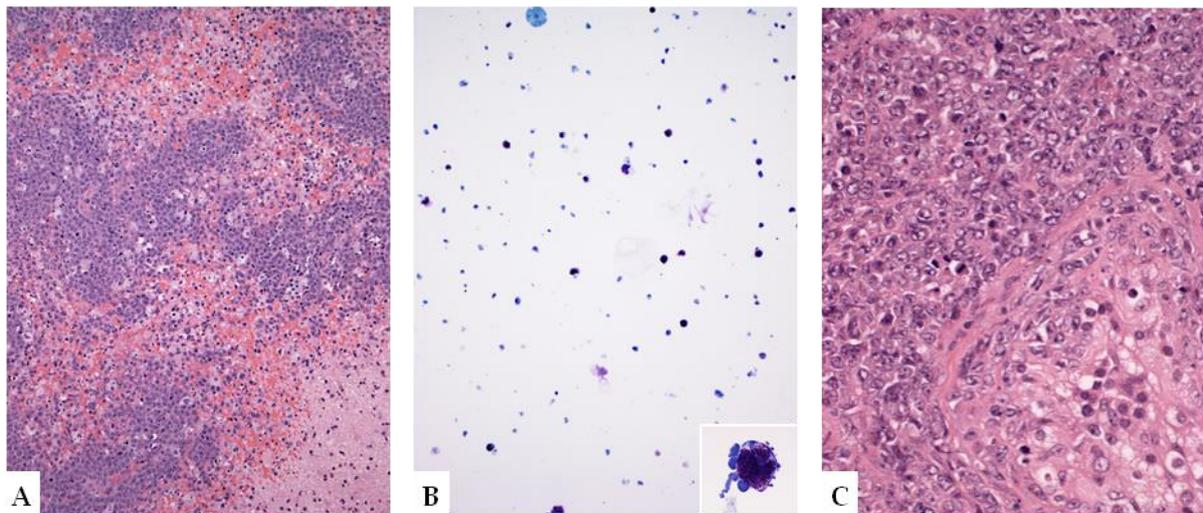


**Figure 4.** Diffuse large B-cell lymphoma/high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangement. The Figure shows *MYC* (A) and *BCL2* (B) protein expression linked to *MYC* and *BCL2* rearrangement; 40× original magnification.

It should be noted that amplifications/copy number variants of *MYC*, *BCL2*, and/or *BCL6* genes do not substitute for rearrangements [31]. However, the impact of an *MYC* rearrangement with a gene other than an immunoglobulin gene, on biology and clinical behavior is not clear [32–34]. As such, cases with *MYC* rearrangements with either an immunoglobulin or a non-immunoglobulin gene partner are included in the DLBCL/HGBL *MYC*/CL2, HGBL-DH-*BCL2*, and HGBL-DH-*BCL6* categories. In addition, TdT expression, which is seen in a small number of cases, does not exclude the diagnosis of any of these high-grade B-cell lymphomas [17].

#### 5.5. Large B-Cell Lymphomas (LBCL) of Immune-Privileged Sites

This new category of aggressive B-cell lymphomas (WHO-HAEM5) encompasses large cell lymphomas that occur primarily in the central nervous system (PCNSL), vitreoretinal compartment (VRL), and testes (Figure 5), all of which are immune sanctuaries created by the structure of their unique anatomic sites [7]. These lymphomas exhibit similar morphologic, immunophenotypic, and genetic features including concordant *MYD88* and *CD79B* mutations and a number of genetic imbalances such as gains in 18q21 (*BCL2*, *MALT1*) and 9p24.3 (*PDL1*) and losses in 6q21 (*PRMD1*) and 6q21 (HLA locus) [7,35–40]. These, and other alterations, contribute to a germinal center exit phenotype and down-regulation of the immune response. It is possible that this category in the future may expand to include lymphomas from other unique anatomic sites [7].



**Figure 5.** Large B-cell lymphomas (LBCL) of immune-privileged sites (WHO-HAEM5) include primary CNS lymphomas (A), primary vitreoretinal lymphoma (B), and primary testicular lymphoma (C). The vitreoretinal lymphomas are often associated with a significant amount of debris within the vitreous fluid with only scattered neoplastic cells ((A). hematoxylin and eosin stain 10× original magnification; (B). Giemsa stain 20× original magnification, inset 100× original magnification; (C). hematoxylin and eosin 10× original magnification).

#### 5.6. Mediastinal Grey Zone Lymphoma and Primary Mediastinal Large B-Cell Lymphoma

Mediastinal grey zone lymphoma (MGZL), previously designated B-cell lymphoma unclassifiable [6,41,42], exhibits overlap in pathologic, genetic, and molecular features with primary mediastinal large B-cell lymphomas (PMLBCL), a specific lymphoma of large B cells [43,44], and CHL of the nodular sclerosis subtype involving the mediastinum.

Morphologic features of PMLBCL include fine compartmentalizing fibrosis in which tumor cells with abundant clear cytoplasm and/or multilobated nuclei; large tumor cells with Hodgkin Reed–Sternberg (HRS)-like morphology may also be present [45]. The tumor cells express B-cell-associated antigens, the transcription factors BOB1, OCT2, and PU.1 [46]. Most PMLBCL cases express BCL6, MUM1/IRF4, BCL2, and CD23 and a variable proportion of cases also express CD30. CD30 expression is usually weak and is present only on a subset of the tumor cells in contrast to CHL in which most true HRS cells express CD30 with a strong intensity of staining.

The diagnosis of MGZL requires high tumor cell density and the immunophenotypic expression of at least two B-cell markers with strong intensity [47,48]. Cases with features of nodular sclerosis CHL showing variable expression of CD20 are still designated as CHL [49]. Moreover, cases with morphologic and immunophenotypic features similar to MGZL, without involvement of the mediastinum are better classified as DLBCL, NOS.

Gains of chromosome 9p23-p24 occur in up to 75% of PMLBCL cases. This cytogenetic abnormality has the weight of a diagnostic marker for PMLBCL [50].

The tumor microenvironment (TME) of MGZL is similar to that of NSCHL and contains sparse inflammatory infiltrate with eosinophils, plasma cells, histiocytes, and T cells. The TME of PMLBCL compared with that of NSCHL has a diminished background and contains eosinophils and T cells. Moreover, in the MGZL the sclerosis is variable, whereas in PMLBCL a fine compartmentalizing fibrosis is usually observed. Necrosis is more frequent in MGZL [42,51].

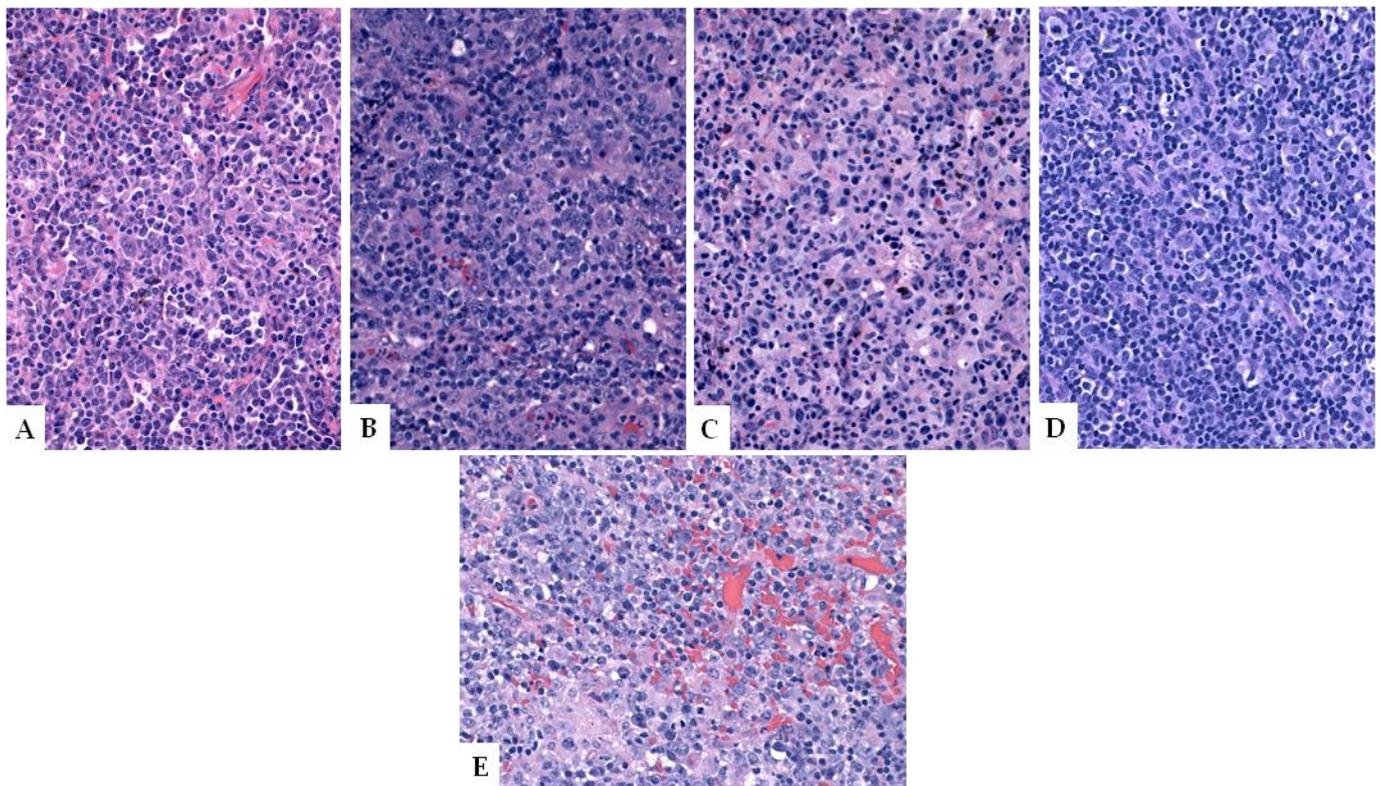
## 6. Immunodeficiency-Related Lymphoproliferative Disorders

In the 2017 WHO (HEME4R), the immunodeficiency-related lymphoproliferative disorders were divided into four major categories based on the clinical setting in which they arose. These four clinical settings included primary immune deficiency, post-transplant, HIV infection, and iatrogenic immunosuppression. This classification did not include lesions that arose in other immunodeficiency settings such as immune senescence or following chemotherapy for lymphoma [52–56].

In the two upcoming classifications systems for hematolymphoid neoplasms, there is a divergence in the approach to categorize these lesions. The International Consensus Committee (ICC) has not completely defined their classification for all previously defined immunodeficiency-related lymphoproliferations. However, due to clinical management, the ICC will maintain post-transplant lymphoproliferative disorders (PTLD) as a distinct clinicopathologic subcategory with subgroups as defined in the 2017 WHO [6,54]. Furthermore, the ICC recommends analogous subclassification of other iatrogenic lymphoproliferative disorders, such as those arising in the setting of methotrexate treatment for autoimmune disease. However, details on classification for these, the HIV-associated, and the primary immune-related disorders have not been fully delineated [6].

The WHO-HAEM5 has undertaken a new and different approach to the classification of the immunodeficiency related LPDs [7]. A significant number of reports have suggested that the morphologic, and in many instances biologic, features of lesions arising in the different immunodeficiency settings overlap [57–60]. Furthermore, studies have also shown that the spectrum of clinical settings associated with immunodeficiency is broader than previously recognized [57,58,61,62]. As such, the upcoming WHO-HAEM5 has altered the approach to these lesions by introducing a broad framework, employing a three part diagnosis with standardized structure, which recognizes (1) histopathologic features, (2) the causal associations of viral infection, and (3) the underlying cause of immune deficiency, all of which are likely to impact therapeutic decision making [7,57]. This framework also allows for documentation of additional immunodeficiency situations, such as those due to aging and specific therapies, as they are identified. This framework is sufficiently broad to include the inborn errors of immunity (IEI; nomenclature in the WHO-HAEM5; primary immune disorders 2017 WHO) and document lesions where it is not clear if the development of the lymphoid lesion is directly related to an immunodeficient state. In recognition of the wide and expanding spectrum of immunodeficiency, the WHO-HAEM5 has adopted the terminology of “lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation (IDD)” for this category [7].

In the WHO-HAEM5, the lymphoid proliferations and lymphomas associated with IDD are subclassified as hyperplasias, polymorphic lymphoproliferative lesions, EBV-positive mucocutaneous ulcers, lymphomas, and IEI-associated lymphoid proliferations and lymphoma [7]. Although some of the lesions in these categories are unique to the IDD setting, WHO-HAEM5 recognizes that many are also seen in immunocompetent individuals and that there are specific cases where the relationship to patient immune status is unclear, for example EBV-positive diffuse large B-cell lymphoma. Furthermore, the WHO-HAEM5 recognizes that each type of specific lesion can be seen in a variety of IDD settings. For example, the polymorphic lymphoproliferative lesions have been diagnosed in a number of IDD settings including post-transplant, HIV infection, iatrogenic immunosuppression, immune senescence, and post-therapy, [59–61,63,64] (Figure 6) whereas KSHV-positive primary effusion lymphomas, which are most commonly seen in HIV positive patients, are also seen in the setting of immune senescence and in post-transplant patients [65–68].



**Figure 6.** The WHO-HAEM5 recognizes that polymorphic lymphoproliferative disorders, lesions that are composed of a heterogeneous cell population, can occur in a variety of immunodeficiency settings, including (A) post-transplant, (B) iatrogenic, (C) HIV infection, (D) inborn errors of immunity, and (E) post-chemotherapy (hematoxylin and eosin, 20× original magnification).

## 7. Viral-Associated Lymphoproliferative Disorders

### 7.1. Epstein–Barr Virus Lesions (EBV)

The classification of the EBV-associated lymphoproliferative disorders is similar but different between the two classification systems. Some highlights of the differences include the classification of EBV-positive mucocutaneous ulcer (EBVMCU), which in the ICC classification is a separate entity, defined as a solitary lesion usually occurring in the oropharyngeal mucosa, gastrointestinal tract mucosa, or the skin that may be associated with iatrogenic immunosuppression [6]. In contrast, EBVMCU in WHO HAEM-5 is a separate subcategory in the “lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation” category [7]. Furthermore, whereas the WHO HAEM-5 retains the ability to classify a spectrum of EBV+ lesions, including some that are polymorphic in appearance, such as EBV+ DLBCL, NOS, [7] the ICC has separated out lesions that show altered tissue architecture and are composed of a heterogenous cellular infiltrate into a new separate category, “EBV-positive polymorphic B cell lymphoproliferative disorder, NOS”. These latter lesions can arise in individuals with or without known immunodeficiency [6].

### 7.2. Kaposi Sarcoma Herpesvirus/Human Herpesvirus 8 (KSHV/HHV8)

Both WHO-HAEM5 and ICC recognize a number of KSHV/HHV8-associated lymphoid lesions. In addition, both classifications recognize that there is significant overlap among the different lesions such that it is often difficult to clearly label a KSHV/HHV8-positive lesion as a distinct entity [6,7,65]. For example, KSHV/HHV8+, EBV+ germotrophic lymphoproliferative disorder, which classically occurs in HIV-negative older individuals and is composed of polyclonal B cells, has been identified in young HIV-positive patients and rarely has been found to be monoclonal, features that suggest extra-cavitary PEL, particularly in light of the morphologic similarities of the dually infected cells [69,70].

Partly due to the rarity of these KSHV-related lesions, it is unclear if they really represent a spectrum of lesions or separate entities with a number of cases showing non-classic features. Thus, further research is needed to better understand and classify these lesions [6,7,65,70]. Of note, the criteria for KSHV/HHV8-positive multicentric Castleman disease have been further refined in relation to the other forms of Castleman disease [7,71,72]. However, KSHV/HHV8-positive multicentric Castleman disease also shows some overlap with the other KSHV/HHV8-related lymphoid lesions [65].

## 8. Concluding Remarks

Molecular and genomic information acquired for lymphoid neoplasms since 2017 has justified the refinement of diagnostic criteria of several lymphoma entities. Some entities considered as “provisional” have been upgraded to “definite” entities and some new lymphoma entities have been proposed. The increasing recognition of lymphoid disorders and their clear inclusion in the WHO classification will result in established clinical management and consensus treatment protocols, which may lead to further improvements in outcomes.

From a diagnostic point of view, critical points still include the precise definition of grade 3 FL (3A and 3B) and the classification of aggressive B-cell lymphomas. With regard to grade 3 FL, the presence of BCL2 rearrangements and/or CD10 expression favors the diagnosis of FL 3A, whereas the absence of these favors the diagnosis of FL 3B. The classification of aggressive B-cell lymphomas is currently based on the combination of morphological and immunophenotypic features, EBER in situ hybridization, FISH analysis and B-cell clonality. In the near future, it is possible to think of a transition towards a molecular genetic classification based on the mutational profile, somatic copy number alterations, and structural variants. It is hoped that these data will ultimately lead to targeted-therapy-based treatments.

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