COMMENT

# Commentary on the WHO classification of tumors of lymphoid tissues (2008): "Gray zone" lymphomas overlapping with Burkitt lymphoma or classical Hodgkin lymphoma

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**Abstract** The 2008 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues has introduced two new categories of high-grade B-cell lymphomas: entities in which features of diffuse large B-cell lymphoma (DLBCL) overlap with Burkitt lymphoma (DLBCL/BL) or classical Hodgkin lymphoma (DLBCL/HL). The DLBCL/BL category encompasses cases that resemble Burkitt lymphoma morphologically, but have one or more immunophenotypic or molecular genetic deviations that would exclude it from the BL category; conversely, some cases have immunophenotypic and/or genetic features of BL, but display cytologic variability unacceptable for BL. Many of the cases in the DLBCL/BL category contain a translocation of *MYC* as well as either *BCL2* or *BCL6* (so-called double-hit lymphomas) and have a very aggressive clinical behavior. The DLBCL/HL category encompasses lymphomas that exhibit the morphology of classical Hodgkin lymphoma but the immunophenotype of DLBCL, or vice versa. Most DLBCL/HL cases described present as mediastinal masses, but this category is not limited to mediastinal lymphomas. These new categories acknowledge the increasing recognition of cases that display mixed features of two well-established diseases. Whether the existence of such cases reflects shortcomings of our current diagnostic armamentarium or a true disease continuum in which such hybrid or intermediate neoplasms actually exist remains to be determined.

**Keywords** Burkitt · Diffuse large B-cell lymphoma · Hodgkin lymphoma · Gray zone lymphoma

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## Introduction

Classification systems represent the language of both pathology and clinical medicine and provide a critical communication medium in establishing, applying, and

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validating therapeutic protocols. The 2008 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues has refined the 2001 Classification based on new and accumulated experimental evidence. Increasingly, diagnostic criteria are based on more diverse types of information than mere morphology, such as clinical information, immunophenotype, and (particularly in the 2008 Classification), molecular genetic studies [1]. However, this ever diversifying armamentarium of tools to interrogate neoplasms has an "Achilles Heel": tumors are inherently complex and do not necessarily provide predictable answers to our broad range of studies. These complexities can stymie our attempts to force individual cases into a particular category by several ways: the tumor may lie on a true biologic continuum between two entity definitions; it may exhibit an exceptional clinical behavior, morphology, immunophenotype, or genetic finding that mimics another tumor type; it may appear to change from one tumor type to another; or it may contain subclones that appear as two discrete tumors. In recognition of the inherent complexity of aggressive B-cell lymphomas, the WHO 2008 Classification has created two new categories for tumors that appear to lie on the continuum between diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL), and between DLBCL and classical Hodgkin lymphomas (CHL). While these new categories may prove to be frustrating to clinicians who wish to treat their patients for a familiar disease with a tested therapy, they acknowledge the current reality that optimal therapy for these overlapping entities is unclear. Moreover, the creation of these diagnostic categories maintains the "purity" of existing entities (DLBCL, BL, CHL), as the inclusion of borderline cases may compromise (and has most likely already compromised) the validity of studies that use looser inclusion criteria.

### Current "state of the art" of Burkitt lymphoma

The 2008 WHO Classification continues to recognize three epidemiologic variants of BL (endemic BL, sporadic BL, and immunodeficiency-associated BL), but the previous atypical/Burkitt-like and plasmacytoid morphologic variants are no longer formally designated. Cases of BL that have features slightly deviating from the typical medium-sized monomorphous cytomorphology, such as increased nuclear irregularity, slight nuclear pleomorphism, and/or more prominent, single nucleoli (including most cases arising in adults) are classified simply as BL if they otherwise fit immunophenotypically and genetically. This change is supported by recent data showing that these morphologically "atypical" BL cases have a molecular signature similar to classic BL [2]. BL cases presenting as a

leukemia without significant lymphadenopathy (previously known as 'L3' ALL) are retained within the BL category and represent the only recognized BL variant in the 2008 WHO Classification.

The characteristic immunophenotype of BL is that of strong CD10 expression, expression of BCL6, negativity for BCL2, and a Ki67 proliferation index (PI) of near 100% (at least 90% of tumor cells) [3]. Immunohistochemistry for MYC protein is non-specific and is not useful for diagnostic purposes. The MYC rearrangement in BL usually occurs in a background of a relatively simple karyotype and should lack concomitant rearrangements of BCL2 or BCL6 [2, 4]. Two major recent gene expression profiling studies have shown that typical BL cases have a characteristic molecular signature [2, 5]. Rare cases that are otherwise characteristic for BL lack a MYC translocation; the proportion of BL cases that are MYC negative is variable in published studies, likely reflecting differing pathologic inclusion criteria. These cases bear a molecular signature similar to BL cases that have rearranged MYC, validating their classification as BL [2, 5]. Recent data suggest that BL cases lacking a MYC rearrangement may upregulate MYC expression by alternative mechanisms, possibly involving the modulation of microRNAs [6].

### B-cell lymphoma unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma

With the increasing use of detailed immunophenotyping panels and genetic studies, there has been increased recognition of cases that share many features with BL, but differ with respect to one or more findings. There has been poor reproducibility when pathologists attempt to assign such cases to BL or DBLCL categories, even when integrating ancillary laboratory results such as cytogenetics and immunophenotype [7]. The molecular profiling study of Hummel et al. also identified a group of cases displaying a molecular signature intermediate between BL and DLBCL. Moreover, some cases classified by pathologists as DLBCL bore a molecular signature of BL. These findings suggest that a true continuum between these entities may exist [2, 5]. Nevertheless, given the different therapies that are indicated, pathologists' hedging between BL and DLBCL is frustrating for clinicians and also affects the validity of clinical trials that aim to evaluate the effectiveness of therapies on discrete diagnostic entities. For these reasons, the WHO 2008 Classification established a new diagnostic category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (DLBCL/BL). These cases have morphologic, immunophenotypic, and genetic features that include aspects of both

BL and DLBCL, and thus cannot be appropriately classified into either category.

DLBCL/BL cases consist largely of cases in which the pathologist considers a diagnosis of BL, but which are excluded from the category. Cases with an immunophenotype of BL (including a PI >90%) and with "starry-sky" appearance, but with marked variation in cytomorphology that is not acceptable for BL, are classified as DLBCL/BL. Conversely, cases that have morphology that is acceptable for BL (uniform or mildly pleomorphic medium-sized cells) may be placed into the DLBCL/BL category if they do not have the typical immunophenotype of BL; while occasional BL cases may have minor immunophenotypic deviations, such as weak positivity for BCL2, strong BCL2 staining, and/or a Ki67 proliferation index of <90% are strong contraindications for a diagnosis of BL. Similarly, cases resembling BL with MYC rearrangements that are transformations of a documented prior low-grade B-cell lymphoma are classified as DLBCL/BL [8]. Rare cases resembling B-lymphoblastic leukemia/lymphoma (B-LBL) by morphology, TdT positivity, and negativity for surface immunoglobulin may bear a MYC rearrangement with or without a BCL2 rearrangement [9, 10]. It is controversial whether to diagnose these cases as B-LBL or as DLBCL/BL. However, both of these entities are treated similarly with intensive chemotherapy regimens. Importantly, B-cell lymphomas composed of large cells or those with marked cellular pleomorphism should be classified as DLBCL irrespective of their MYC status, proliferation index, or immunophenotype: indeed, up to 15% of DLBCL cases bear a MYC translocation [11, 12] and some DLBCL cases may have proliferation indices approaching 100% [13]. Although some of these cases have been shown to bear the molecular signature of BL, using current diagnostic methods they must be classified as DLBCL.

When a MYC rearrangement is present in DLBCL/BL cases, it often has atypical features, including one or more of the following: (1) rearrangement with a non-IG partner; (2) as part of a complex karyotype; (3) concurrent rearrangements of BCL2 and/or BCL6 genes (so-called double-hit or triple-hit lymphoma lymphomas). "Double-hit" lymphomas with both MYC and BCL2 rearrangements comprise a large and relatively well-characterized subset of DLBCL/BL. These cases exhibit a spectrum of morphology and a wide range of Ki67 proliferation index, but all strongly express BCL2 [14]. Rare cases of histologically low-grade follicular lymphoma that bear both MYC and BCL2 rearrangements should not be placed into this category, as these are histologically distinct [14, 15]. Rare cases of plasma cell myeloma may also bear a MYC or concurrent MYC and BCL2 rearrangements and should not be included in the DLBCL/BL category [14, 16]. Although gene expression profiling data is not available on DLBCL/

BL as a group, some "double-hit" cases with both MYC and BCL2 rearrangement have been shown to have a molecular signature similar to classic BL; other cases have a signature intermediate between BL and DLBCL [5]. Importantly, most cases of DLBCL with MYC translocation share the molecular signature of DLBCL, not BL [5].

The "double-hit" DLBCL/BL lymphomas are highly aggressive tumors that usually present with high stage of disease and appear to do poorly whether treated with intensive regimens used to treat BL or CHOP-like regimens [13, 17–19]. The aggressive nature of these tumors likely reflects their simultaneous expression of both pro-proliferative (MYC) and anti-apoptotic (BCL2) oncoproteins. The clinical behavior of other cases fulfilling criteria for DLBCL/BL (such as cases with overlapping features of BL and DBLCL but lacking a "double-hit" or even a MYC rearrangement) is unknown. It is anticipated that DLBCL/BL represents a biologically heterogeneous group that requires further genetic and clinical characterization.

## Questions and controversies

*What is the "gold standard" for a diagnosis of BL?* The two recent gene expression profiling studies validated the genetic homogeneity of typical BL cases [2, 5]. However, a substantial number of cases that would not be classified as BL (17–34%, most likely including both DLBCL/BL and DLBCL cases according to 2008 WHO Classification criteria) had a molecular signature of BL. Cases with BL molecular signature did poorly as a group when treated with CHOP-like regimens. Conversely, BL and high-proliferation DLBCL cases diagnosed by conventional criteria and treated with intensive regimens had similar outcome in one recent study [13]. Ultimately, the biologic "gold standard" of BL is that of an aggressive, but (with appropriately intensive chemotherapy) highly curable lymphoma. A prospective study is required to determine whether molecular signature, WHO classification, or a specific biologic marker (such as MYC translocation status or Ki67 proliferation index) most optimally identifies cases with this particular disease biology.

*Should a MYC rearrangement be sought on all highly proliferative B-cell neoplasms?* According to the 2008 WHO Classification, a diagnosis of BL can be made if the morphology and immunophenotype are perfect. In children, in whom classic morphology predominates, a MYC rearrangement is probably not necessary to confirm the diagnosis. Similarly, a case with overt DLBCL morphology does not require MYC investigation for classification, since DLBCL/BL would not be a diagnostic consideration (although it should be noted that MYC

rearrangement is a poor prognostic feature in DLBCL with high proliferation index, and may provide helpful prognostic information in certain clinical contexts) [13]. Accordingly, it is probably prudent to assess for a *MYC* rearrangement in all adult patients in which BL or BL/DLBCL is a diagnostic consideration based on the morphology and immunophenotype.

*When should* BCL2 *and* BCL6 *rearrangements be sought?* Because the relative incidence of DLBCL/BL appears to increase with age, while that of BL decreases, it is probably prudent to examine any adult case of putative BL for concomitant *BCL2* and *BCL6* rearrangements that would argue against a diagnosis of BL. *MYC* rearranged cases with concomitant *BCL2* or *BCL6* rearrangements would be classified as DLBCL/BL, irrespective of the other features. These "double-hit" lymphomas have a much poorer prognosis than BL, even when treated with intensive chemotherapy regimens.

*What about looking for complex karyotype and MYC rearrangement with non-IG partners?* Different centers vary in the practice of obtaining cytogenetics on lymph node samples. Comparative genomic hybridization (CGH), that shows markedly different complexity patterns in BL and DLBCL, is not routinely available. Thus, while the presence of a known complex karyotype would tend to favor a diagnosis of DLBCL/BL over BL, practical limitations such as lack of suitable material for classical cytogenetics or non-availability of CGH (especially if only paraffin material is available) impede routine performance in many laboratories. Similarly, probes to assess the rearrangement of *MYC* with non-*IG* gene loci are not widely available. Nevertheless, if performed, the knowledge that *MYC* is rearranged with a non-*IG* locus may be helpful in assigning borderline cases (such as those with minor immunophenotypic or morphologic deviations from BL) to the DLBCL/BL category.

## Primary mediastinal (thymic) large B-cell lymphoma and its borderlands with classical Hodgkin lymphoma

Primary mediastinal large B-cell lymphoma (PMBL) was the first large B-cell lymphoma entity to be delineated, by virtue of its distinctive clinical and morphological features [20, 21]. In contrast to other DLBCLs, PMBL tends to occur in younger patients, with a predilection for women, and usually presents as a localized, but often bulky anterior mediastinal mass with or without involvement of supraclavicular lymph nodes [20, 22]. Distinctive morphological features of PMBL include fine compartmentalizing sclerosis, the presence of cells with abundant clear cytoplasm and/or multilobated nuclei, and the presence of large Reed–Sternberg-like cells [23].

In the 20 years that have elapsed since the original descriptions of PMBL, further evidence has accumulated that supports the concept of a disease distinct from non-mediastinal DLBCL. The neoplastic B-cells express B-cell antigens, but often lack surface immunoglobulin (Ig), despite expression of the Ig-associated transcription factors BOB1, OCT2, and PU1 [24]. Expression of antigens related to the germinal center and post-germinal center stages of B-cell differentiation is variable, but most cases co-express BCL6 and MUM1/IRF4, often in the absence of CD10, suggesting an activated or post-geminal center phenotype [24, 25]. The majority of tumors express CD30, usually heterogeneously and with weak to moderate intensity. The frequent expression of CD23 and MAL in PMBL has been taken as evidence to suggest its cellular derivation from an immunophenotypically similar peculiar population of "asteroid" B cells normally present in the thymic medulla [26–28]. In distinction from other DLBCLs, expression of FIG1 (the product of the interleukin-4-induced gene 1) and TNF-receptor-associated factor 1 are characteristic of PMBL, especially when combined with nuclear c-REL localization [27, 29, 30]. Finally, the PMBL molecular signature differs from that of other DLBCLs [29, 31].

In practice, the diagnosis of PMBL requires the integration of the pathological and clinical presenting features. It must be stressed that the particular features listed above, albeit characteristic of PMBL, are not present in every case, and none is entirely specific. Moreover, among the different immunophenotypic markers that are differentially expressed in PMBL and other DLBCL, only CD23 and CD30 are available routinely in most diagnostic laboratories. In young patients with disease localized to the mediastinum (sometimes also involving supraclavicular nodes), histopathologic documentation of DLBCL is nearly always considered diagnostic of PMBL. In older patients, secondary mediastinal involvement by DLBCL is more common: in that setting, the characteristic features of PMBL should be demonstrated and it is preferable to restrict a PMBL diagnosis to cases that show the typical clinical and pathological features. Both entities are currently treated with anthracycline-based chemotherapy plus rituximab, and when adjusted for stage, have similar outcomes.

PMBL and nodular sclerosis CHL (NSHL) exhibit strikingly similar clinical presentations, as both diseases tend to occur as a localized mediastinal mass in young women. Moreover, in addition to some morphologic overlap (Reed–Sternberg-like cells and sclerosis), recent studies have documented many genetic and molecular similarities [29, 31]. However, importantly for diagnostic purposes, usual cases of PMBL and CHL also have several

non-overlapping distinctive pathological features. The similarities and contrasting features of PMBL and CHL are summarized in Table 1. The diagnosis of NSHL requires a nodular growth pattern, broad bands of fibrosis, and lacunar variants of Reed–Sternberg cells that have a characteristic immunophenotype (CD45−, CD30+, CD15+/−). Unlike CHL, the neoplastic cells of PMBL express CD45 and are characteristically CD15−. CD30 expression, when present, is typically weaker compared to the uniformly strong CD30 expression in CHL. Conversely, expression of B-cell associated antigens is strong and uniform in PMBL, and is usually weaker and more heterogeneous in the neoplastic cells of CHL. While Ig is not typically expressed in the neoplastic cells of either entity, Ig transcription factors such as OCT2 and BOB1 are maintained in PMBL, and may be absent in CHL. EBV may be present in CHL, but is absent in PMBL.

## B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Even after using differential diagnostic criteria, a small proportion of mediastinal large cell lymphomas cannot be classified. These cases, previously termed "gray zone lymphomas" or "large B-cell lymphomas with Hodgkin features" in the literature, represent a spectrum of tumors having characteristics of both PMBL and CHL [32–35]. In the 2008 WHO Classification, a novel category designated B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Hodgkin lymphoma (DLBCL/HL) has been created to include these neoplasms [1]. DLBCL/HL mostly encompasses lymphomas with mediastinal presentation, but also includes occasional cases with features intermediate between

**Table 1** Overlapping and contrasting features between primary mediastinal large B-cell lymphoma (PMBL) and mediastinal classical Hodgkin lymphoma, nodular sclerosis type (NSHL)

| | PMBL | NSHL |
|---|---|---|
| Clinical presentation | Common to both | |
| | •Young adults, female predominance | |
| | •Mediastinal mass involving thymus and supraclavicular nodes | |
| | •Often localized disease (stages I–II) | |
| | Involvement of other distant extranodal sites at presentation or upon recurrence | Usually no involvement of other extranodal sites |
| Morphology | Fine compartimentalizing sclerosis, diffuse pattern | Broad bands of collagen fibrosis, nodular pattern |
| | Medium to large clear cells, Reed–Sternberg-like cells can be present | Reed–Sternberg cells, lacunar cells |
| | Sheets of tumor cells, little or no inflammatory background | Scattered neoplastic cells in an inflammatory background |
| Immunophenotype | Common to both | |
| | •Absent or decreased expression of Ig and HLA | |
| | •Expression of MUM1/IRF4 | |
| CD45 | Positive | Negative |
| CD30 | Often positive, usually weak | Positive, strong |
| CD15 | Negative | Positive (85% of cases) |
| CD20 | Positive | Negative or weak |
| CD79a | Positive | Negative |
| Pax5 | Strong | Weak |
| BOB1 and OCT2 | Positive | Usually negative (one or both) |
| MAL | Usually positive | May be positive |
| EBV | Absent | May be present |
| Genetic features | Common to both [36–38] | |
| | •Gain at 2p15: REL locus | |
| | •Gain at 9p24: JAK2 locus | |
| Molecular features | Common to both | |
| | •Decreased of BCR pathway signaling and constitutive NF-kappaB activation, [29, 38, 39] | |
| | •Activation of the cytokine-JAK-STAT pathway, [40–42] | |
| | •High expression of extracellular matrix elements, overexpression of the TNF family members | |
| | •Aberrant activation of the PI3K/AKT pathway [43] | |

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