An update on high grade B-cell lymphoma

Milind M Velankar

John Kennedy Sydney Sir Philip

Girish Venkataraman

Abstract

The new WHO 2017 revised fourth edition details updates on several large B-cell entities, the most important including separation of cases of large B-cell lymphomas with the so called "double-hit" or "triple-hit" phenotype that harbor rearrangements of *MYC* in conjunction with rearrangements of *BCL2* and/or *BCL6*. In addition, the knowledge of several EBV-driven B-cell lymphoproliferations has led to the firm establishment of the entity called EBV+ diffuse large B-cell lymphoma, not otherwise specified which can mimic several other Hodgkin-like lymphoproliferations including classical Hodgkin lymphoma and T-cell/histiocyte rich large B-cell lymphoma. Certain other newer provisional entities with unique molecular alterations including *Burkitt-like lymphoma with 11q aberration* which do not harbor *MYC* alterations occurring mostly in the paediatric population as well as *large B-cell lymphoma with IRF4 rearrangement* are also discussed in this review although these may not necessarily exhibit aggressive clinical behavior.

Keywords aggressive; B-cell; classification; lymphoma; WHO

Introduction

In the past decade, we have gained a much better understanding of the biology of B-cell lymphomas paralleling rapid strides made in sophisticated molecular methods. Much of this review will focus largely on B-cell lymphomas with high-grade features and the rationale for some of the large B-cell entities listed in the WHO 2017 revised 4th edition with discussion of the underlying literature detailing the change of terminology from the WHO 2008 schema.[1] Specifically, site-specific entities such as primary mediastinal (thymic) large B-cell lymphomas, primary CNS large B-cell lymphomas and B-cell lymphoma, unclassifiable with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (so called "gray-zone lymphoma") will be not be covered.

High grade B-cell lymphoma (WHO 2017)

A landmark gene expression profiling (GEP) study in early 2000 established the existence of unique genetics subsets of diffuse large B-cell lymphoma (DLBCL), germinal center B-cell (GCB) and a non-germinal center/activated B-cell (non-GC/ABC) subgroups.[2] The GCB subgroup was associated with better outcome compared to the non-GCB subgroup. Since these original studies, molecular studies noted the existence of cases with molecular features intermediate between DLBCL and Burkitt lymphoma.[3] A subsequent study noted worse outcome of cases *MYC*-rearrangement negative-DLBCL with Burkitt-like cytomorphology using conventional DLBCL treatment regimens.[4] Recognizing that this subgroup of LBCLs may benefit from more aggressive therapy, the 2008 WHO classification schema recognized two major categories of LBCLs, namely DLBCL, nos and BCL unclassifiable with features intermediate between DLBCL and Burkitt lymphoma (BCLU).[5] Since then, a large scale study DLBCLs examining *MYC* translocation in DLBCLs noted that 3 cases in this series showed concurrent *IGH/BCL2* translocation and *MYC*-translocated DLBCLs followed an aggressive clinical course with poor response to conventional treatment regimens for DLBCL, nos.[6] Several other studies have corroborated this adverse outcome of *MYC*-rearranged large B-cell lymphomas. However, molecular profiling within the BCLU subset demonstrated marked heterogeneity in mutational spectrum and hence there was a need to separate out subclasses within the BCLU category. As a result, the new WHO category of '**HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements**' was proposed[1] to capture cases with "double-hit" or "triple hit" biology more objectively and separate them from the generic BCLU category proposed in the WHO 2008.

High grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements

Large B-cell lymphomas harboring *MYC, BCL2* and/or *BCL6* translocations are included in this new WHO 2017 diagnostic category.{Swerdlow, 2017 #12120} However, follicular lymphoma or lymphoblastic lymphoma[7] harboring these genetic abnormalities are excluded.[1] These aggressive lymphomas may arise as de novo disease, or less frequently, as transformation in prior low-grade lymphomas most commonly follicular lymphomas. The category comprises 4–8% of all DLBCLs. The clinical course in these patients is uniformly aggressive and these patients often are treated upfront with more intensive regimens such as EPOCH-R as opposed to CHOP-R for typical DLBCLs.

Morphology and immunohistochemistry: cases in this category may exhibit morphology compatible with either typical DLBCL, DLBCL/BL or exhibit blastoid cytomorphology.[8] Areas of necrosis and numerous mitoses may be seen frequently. Most cases exhibit centroblastic cytomorphology although cases harboring *BCL6* translocation often are described to exhibit immunoblastic cytomorphology.[9](Figure 1)

A comprehensive immunohistochemical panel for all aggressive large cell lymphomas is necessary to document B-cell lineage (CD20, PAX5) and to identify cell of origin (CD10, BCL6 and Mum 1 and additional LMO2 and/or HGAL in some instances).[10] Nearly 75–90% of DHL/THL cases are positive for CD10 and BCL6 while about 20% express concomitant Mum1. Given the prognostic relevance of accurate COO subtyping, several other IHC based classifiers were proposed to improve the diagnostic accuracy over the Hans classifier including the Choi, Tally,

Milind M Velankar *MD, Department of Pathology, Loyola University Medical Center, Maywood, IL, USA. Conflicts of interest: none declared.*

John Kennedy Sydney Sir Philip *MD, Department of Pathology, Section of Hematopathology, University of Chicago Medical Center, Chicago, IL, USA. Conflicts of interest: none declared.*

Girish Venkataraman *MD, Department of Pathology, Section of Hematopathology, University of Chicago Medical Center, Chicago, IL, USA. Conflicts of interest: none declared.*

Please cite this article in press as: Velankar MM, et al., An update on high grade B-cell lymphoma, Diagnostic Histopathology (2018), https://doi.org/10.1016/j.mpdhp.2018.05.010

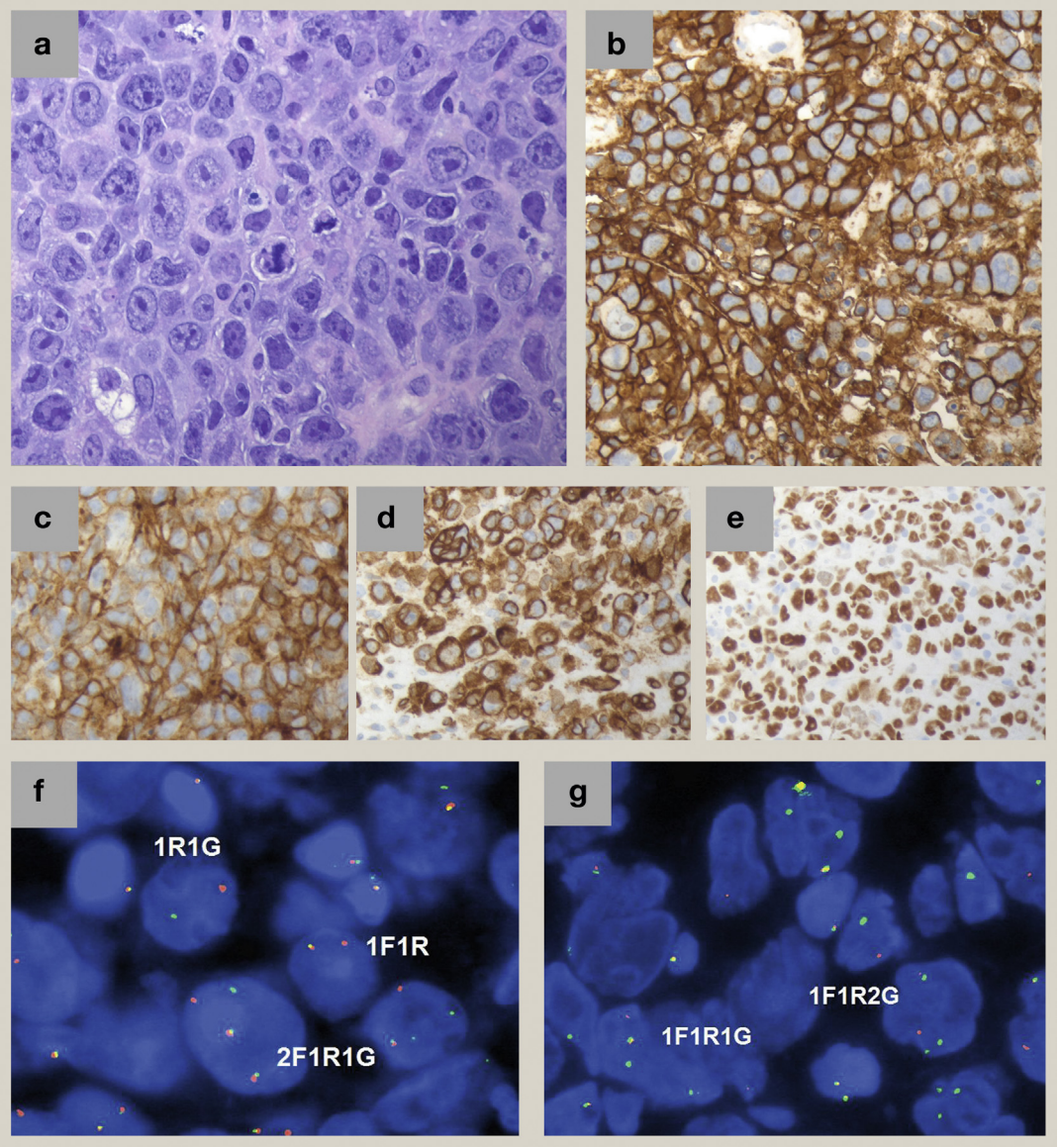

Figure 1 High grade B-cell lymphoma with *MYC* and *BCL6* rearrangement ("double-hit" lymphoma). (**a**). Large sheets of pleomorphic lymphoma cells with predominant immunoblastic cytomorphology. The lymphoma cells express strong CD20 (**b**), CD10 (**c**), BCL2 (**d**) with nearly 100% MYC expression (**e**) by immunohistochemistry. FISH studies with dual color break-apart probes for *MYC* (**f**) and *BCL6* (**g**) demonstrate *MYC* breaks and *BCL6* breaks consistent with rearrangements of *MYC* and *BCL6* loci (image courtesy Dr. Carrie Fitzpatrick, division of cytogenetics, University of Chicago).

Colomo, Muris, Visco algorithms.[11] These algorithms included additional GC-specific (GCET1, HGAL/GCET2, LMO2) as well as non-GC specific markers such as (FOXP1, BCL2) however, a poor concordance was found among these immunohistochemistry based classifiers[12,13] and the latter study noted the superiority of GEP in the GC vs. non-GC subtyping and outcome prediction. This led to the development of small-scale commercial panels such as the Lymph2Cx assays is available for paraffin tissue molecular subtyping of COO.[14] although some studies (including the RICOVER-60 trial of German High-Grade Non-Hodgkin's Lymphoma Study Group) did not see any prognostic significance to Lymph2Cx-based COO subtyping.[15,16]

MYC and BCL2 immunostaining: several studies have corroborated the adverse biology of cases that are "double expressor (DE)" for both these proteins regardless of any underlying genetic alterations.[17] In one study, DLBCLs with co-expression of MYC and BCL2 using cut offs of >40% and >70% respectively were associated with low complete response rate, shorter overall and progression-free survival.[15,17] Although several other cut points have been used in different study cohorts (ranging from 30 to 70% for both), currently the WHO recommends cutoffs of >40% for MYC and >50% for Bcl-2 by immunohistochemistry.[8] Co-expression of MYC and BCL2 protein is often associated with activated B-cell phenotype and these cases had similar adverse outcome as GCB DE-DLBCLs.[18] MYC protein can be expressed regardless of the *MYC* translation status due to presence of mechanisms other than *MYC* translocation that can lead to MYC protein expression, however, higher percentage of MYC protein expression (>80%) correlates with *MYC* translocation.[19] In

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