Comprehensive Assessment and Classification of High-Grade B-cell Lymphomas

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KEYWORDS

• Diffuse large B-cell lymphoma • Burkitt lymphoma • Cell of origin • MYC

ABSTRACT

High-grade B-cell lymphomas (HGBCLs) are a heterogeneous group of neoplasms that include subsets of diffuse large B-cell lymphoma, Burkitt lymphoma, and lymphomas with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma. Morphologically indistinguishable HGBCLs may demonstrate variable clinical courses and responses to therapy. The morphologic evaluation and classification of these neoplasms must be followed by further genetic and immunophenotypic work-up. These additional diagnostic modalities lead to a comprehensive stratification of HGBCL that determines the prognosis and optimal therapy. This article reviews the well-established and emerging biomarkers that are most relevant to the clinical management of HGBCL.

Key Features

- Determination of cell of origin (COO), GCB vs ABC, is essential in all cases of diffuse large B-cell lymphoma (DLBCL) because it predicts prognosis and may guide treatment.
- Double-hit lymphomas (DHLs) demonstrate aggressive clinical behavior, and evaluation for *MYC*, *BCL2*, and *BCL6* rearrangements by fluorescence in situ hybridization (FISH) should be considered for all cases of high-grade B-cell lymphoma (HGBCL).
- Using proliferative index or MYC expression by immunohistochemistry (IHC) as a surrogate for FISH testing misses a subset of cases with rearrangement.
- MYC and BCL2 expression by IHC has shown prognostic value in DLBCL but currently is not clinically actionable.
- Evaluation for *IGH-IRF4* rearrangement should be considered in cases of DLBCL or high-grade follicular lymphoma (FL) in young patients.
- Evaluation for aberrations of chromosome 11q and *ID3* mutation should be considered for Burkitt lymphomas (BLs) that lack *IGH-MYC*.

OVERVIEW

HGBCL encompasses a broad group of B-cell neoplasms that are histologically characterized by proliferation of intermediate to large B-cells. The morphology-based diagnostic entities in this group include DLBCL, BL, and the more recently described B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL

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(BCLU). BCLU is a provisional category in the World Health Organization (WHO) 2008 lymphoma classification, and as the name implies, it was created to identify tumors that have overlapping morphologic and immunophenotypic features between DLBCL and BL (**Fig. 1**A, B).[1] Insight into the molecular pathogenesis of HGBCLs in recent years has provided biomarkers that can be integrated in the diagnostic work-up to predict the clinical course and response to various therapies. This article focuses on highlighting the ancillary diagnostic studies that are currently the standard of care for evaluation of HGBCL. Morphologic and site-specific subclasses of DLBCL (including T-cell/histiocyte-rich large B-cell lymphoma, primary effusion lymphoma,

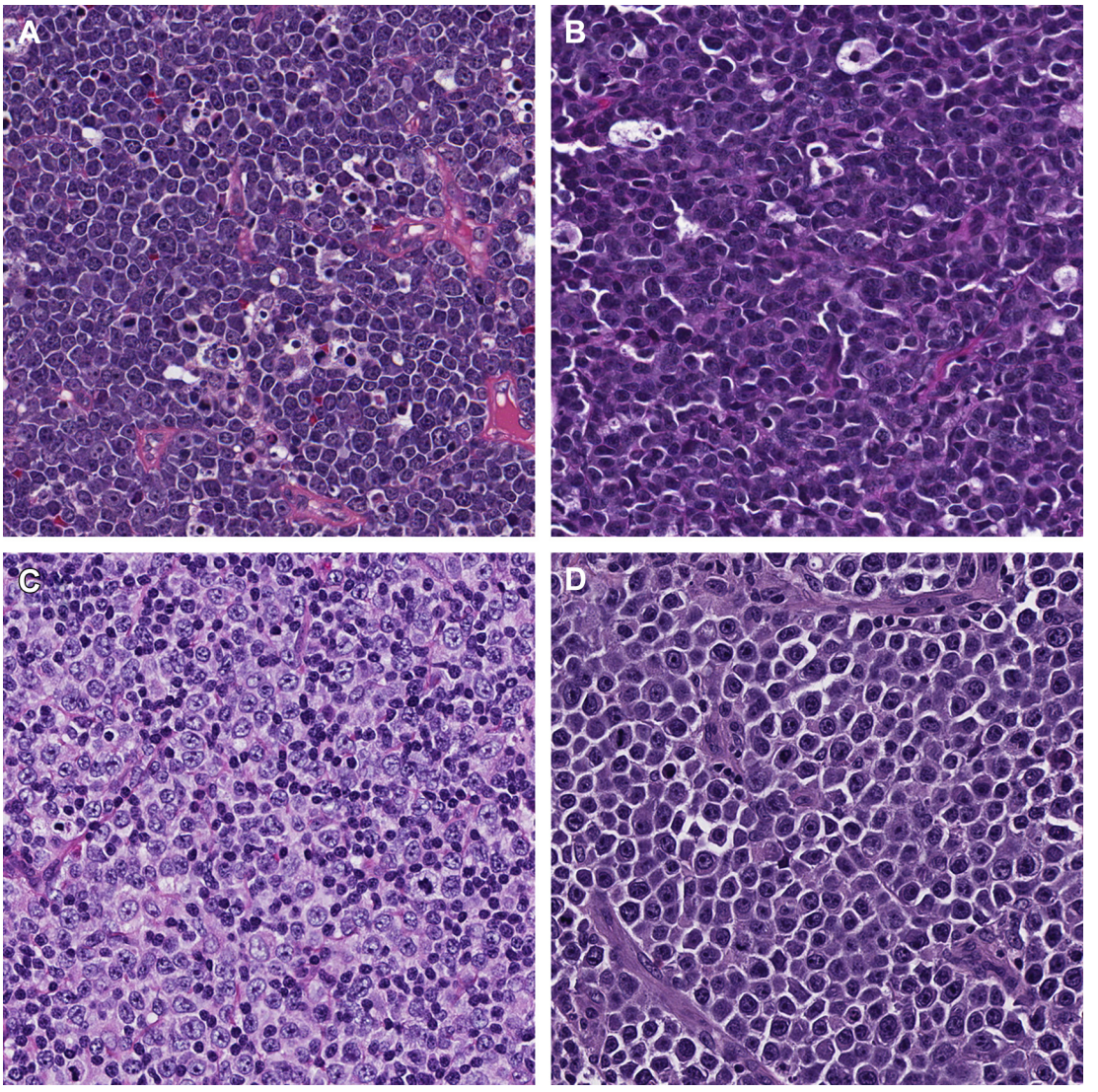

Fig. 1. Morphologic features of HGBCLs. (*A*) BL, characterized by sheets of intermediate-sized lymphocytes with round, fairly monotonous nuclei and multiple indistinct nucleoli. A starry-sky background is present, with numerous apoptotic bodies and mitotic figures. (*B*) BCLU. This tumor exhibits a starry-sky background, with somewhat more nuclear pleomorphism than is present in prototypical BL. This example had rearrangements of both *MYC* and *IGH-BCL2*. (*C*) DLBCL, with centroblastic morphology. The large B cells have ovoid nuclei and multiple small nucleoli, reminiscent of cells in the dark zone of the germinal center. (*D*) DLBCL, with immunoblastic morphology. Greater than 90% of the lymphoma cells exhibit prominent central nucleoli or features suggestive of plasmacytic differentiation, such as eccentric nuclei and amphophilic cytoplasm. All images ×400, hematoxylin-eosin stain.