Aggressive B-cell Lymphomas
*Updated WHO classification*

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Diffuse Large B-cell Lymphoma  
A Heterogeneous Category

- Subtypes with differing:
  - histology and phenotype
  - genetic alterations
  - response to treatment

Histology and Phenotype

Diffuse Large B-cell lymphoma in the 2016 WHO classification

Diffuse large B-cell lymphoma, not otherwise specified (NOS)
  Germinal center B-cell type
  Activated B-cell type

T-cell/histiocyte-rich large B-cell lymphoma

DLBCL, topographic site related

DLBCL, EBV-related

LBCL Terminal B-cell differentiation

Gene Expression Profiling Identifies two Molecular Subtypes of DLBCL

ABC and GCB DLBCL have significantly different survival rates following R-CHOP

Lenz et al., NEJM, 2008
Molecular Subtypes of DLBCL Have Different Molecular Pathogenesis

Roschewski M et al Nat. Rev Clin Oncol 2014; 11:12-23
Translating GEP Signatures to Clinics
Is it Possible?

- Limitation to translate complex signatures into restricted immunophenotypic panels
- Need alternative techniques to apply GEP in routinely processed tissues
2016-WHO Classification of Lymphoid Neoplasms

- The revised classification will require the identification of germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes of DLBCL.

- With gene expression profiling (GEP) still not a routine clinical test, the use of immunohistochemistry (IHC) algorithms will be considered acceptable.

- Newer methods [of GEP] based on quantification of RNA transcripts extracted from formalin-fixed paraffin-embedded tissues …. may represent a promising alternative to the current IHC-based algorithms.

Swerdlow SH et al Blood. 2016;127(20):2375-2390
Relationship between THRLBCL and NLPHEL

- Tumor cells in NLPHEL and THRLBCL have similar GEP
- More complex karyotypes in THRLBCL than in NLPHEL
- Gains of 2p16.1 and losses of 2p11.2 and 9p11.2 recurring aberrations in THRLBCL and NLPHEL.
- Similar expression of REL protein
- NLPHEL can show a THRLBCL-like transformation

Histological variants with B-cell depletion:

- Advanced disease (29.5% vs 14.6%, P = .0012)
- Higher relapse rate (18.1% vs 6.5% at 5 years, P = .0009).
- Independent prognostic factor (odds ratio = 2.955)

Similar lymphomas may be less common but can occur in younger individuals.
- Usually more pleomorphic and R-S-like cells
- Better outcome

NOS added to emphasize it is a diagnosis for cases that do not fulfill the criteria for a more specific type of EBV+ large B-cell lymphoma
- Lymphomatoid granulomatosis
- DLBCL associated with chronic inflammation

Nicolae A et al. Blood 2015;126:863-872
EBV+ Mucocutaneous Ulcer

- Immunosuppressed patients (Age, iatrogenous)
- Atypical large cells, Hodgkin-like features
- Polymorphic background
- EBV+, latency II, large and small B-lymphocytes
- CD20, PAX5, CD30, CD15+
- Localized
- Indolent course, occasional spontaneous regression

Jaffe ES, 2016 WHO monograph
HHV8-positive DLBCL, NOS

- Associated with MCD, but not always
- Immunosuppressed patients (HIV+), but not always
- Immunoblast/Plasmablast morphology
- HHV8+, EBV-, IgM, lambda
- Spleen, lymph nodes
Aggressive lymphomas with *MYC* genetic and protein alterations

- **ALK+ Large Cell Lymphoma**
- **Plasmablastic Lymphoma**
- **Burkitt Lymphoma**
- **ABC DLBCL**
- **GCB DLBCL**
- **Double hit lymphoma**

*MYC* genetic and protein alterations include:

- der(14)
- der(8)
- 8

Diagram showing genetic alterations and protein expression.
Molecular Pathogenesis of Burkitt Lymphoma

Campo E. Nat Genet 2012
Burkitt-like lymphoma with 11q aberrations

Salaverria I et al Blood 2014; 123: 1187–1198

chr11

MYC BAP

-11q23.3-q25
Burkitt-like lymphoma with 11q aberrations

- Frequent nodal presentation (15/18)
- Cytological pleomorphism
- Occasional follicular pattern
- More complex karyotypes and absence of 1q gain
- Clinical course seems to be similar to BL
- Only a limited number of cases have been reported
- Very similar cases have also been reported in the post-transplant setting
MYC / BCL2 Genetic vs Protein Double Hit
Do they have the same clinical significance?

\[ \text{t}(8;14) \quad \text{t}(14;18) \quad = ? \]

Johnson NA et al J Clin Oncol 2012
“Double Hit” Aggressive Lymphomas

Definition
• MYC and BCL2/BCL6 rearrangements

Exclude:
  FL (2%)
  Transformed FL or MCL with MYC-R
  Lymphoblastic lymphoma (TdT+)

Morphology
• DLBCL morphology (15%-70%)
• BCLU (35-75%)
• Blastoid

Phenotype
• GC phenotype, BCL2 +
• MYC/BCL6-R, less CD10 and BCL2+
• High proliferation
Not all “Double Hit” lymphomas are created equal

Modulators of the prognostic impact

Translocation partner
- IG
- Non-IG
- MYC

DH partner
- IG
- BCL2
- BCL6

DH-non IG
DH-
DH-IG

Swedlow S Hematology 2014; Copie-Bergman C et al Blood 2015
Substitute BCLU category with:

High grade B-cell lymphoma

- High-grade B-cell lymphomas with *MYC* and *BCL2* or *BCL6* rearrangements (*double-hit*)
  Specify whether DLBCL, blastoid or BCLU morphology
  Cases with previous FL are to be designated “HGBL-DH transformed from follicular lymphoma”

- High-grade B-cell lymphoma, NOS
  Cases with BCLU or blastoid morphology but no DH is found
  DLBCL with high proliferation are not included
Burkit and DLBCL Mutational profile in BCL-U Double-hit, and DLBCL with MYC translocations

- Mut BL: \textit{ID3, TCF3, CCND3, MYC}
- Mut DLBCL-GC: \textit{BCL2, EZH2, CREBB, MEF2B, SGK1}

\textit{Momose S et al Leukemia 2015}
Open and unresolved questions

- No consensus on specific guidelines for FISH studies in Aggressive B-cell lymphomas
  - From “All cases” to a “Selection” based on different criteria
    - Blastoid or BCLU morphology
    - GC-DLBCL
    - High proliferation (60%) , Strong BCL2 (50%), and high MYC expression (>40%)
  - Caveat MYC-R in low Ki67, and low MYC expression
  - Some FISH probes may not capture all rearrangements (Muñoz-Marmol Histopathology 2013)

- Controversies on Clinical Impact of DH-HGBL
  - Not all DH-HGBCL have a dismal prognosis.
  - Modulators of biological evolution in these cases not yet clearly understood
  - No consensus on clinical management but standard RCHOP seems insufficient
Summary

• **DLBCL, NOS**
  – Distinction of **GCB vs ABC/non-GC type required** (IHC algorithms acceptable)

• Close relationship of THRLBCL and diffuse forms of NLPHL

• **DLBCL related to Infectious agents**
  – EBV+ DLBCL, NOS replaces the previous term “of the elderly”
  – HHV8+, DLBCL, NOS

• **High Grade B-cell lymphomas**, new category
  – **HGBL-DH**: defined by cytogenetic findings, different morphology
  – **HGBL, NOS**: BCLu or blastoid morphology, no DH
  – Still open questions both on biological and clinical aspects of this category
Diffuse Large B-cell lymphoma, NOS

*Morphologic and Phenotypic Variants*


Target biomarker

CD30
Gene Expression Profiling Identifies two Molecular Subtypes of DLBCL
Molecular Subtypes of DLBCL

Wright G et al PNAS 2003

### DLBCL Molecular Subtypes Have Different Oncogenic Mechanisms That May Be Targets of New Therapies

**Table 1 | Oncogenic mechanisms and potential targets in DLBCL subtypes**

<table>
<thead>
<tr>
<th>DLBCL subtype</th>
<th>Cell of origin</th>
<th>Oncogenic mechanisms</th>
<th>Potential targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCB</td>
<td>Germinal centre B-cell</td>
<td><em>BCL2</em> translocation**&lt;br&gt;<em>EZH2</em> mutations‡&lt;br&gt;<em>PTEN</em> deletions§&lt;br&gt;Loss of <em>PTEN</em> expression</td>
<td><em>BCL6</em>&lt;br&gt;<em>EZH2</em>&lt;br&gt;PI3K/Akt</td>
</tr>
<tr>
<td>ABC</td>
<td>Post-germinal centre B-cell</td>
<td><em>NF-κB</em> activation|</td>
<td></td>
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</tbody>
</table>
CARD11 mutations<br>*MYD88* mutations<br>*CD79B* mutations<br>A20 deletions | *BCR*<br>CBM complex<br>IRAK-4<br>JAK–STAT |
| PMBL          | Post-thymic B-cell | *NF-κB* activation\|
9p24 amplification\|
*REL* amplification<br>*JAK2* mutations<br>*CIITA* translocations# | JAK–STAT<br>PD-1# |

*Roschewski M et al Nat. Rev Clin Oncol 2014; 11:12-23*
B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL and BL (BCLU)

Categories
- Morphologically intermediate between DLBCL and BL
- Burkitt with atypical features (BCL2+)
- “Double hit lymphomas” (inconsistency with DLBCL or blastoid morphology)

Exclude
- Transformed FL or MCL with MYC rearrangements
- Burkitt lymphomas without MYC rearrangements

**MYC Rearrangements in DLBCL**

- No major differences in clinical and morphological presentations
- Similar distribution in GCB and non-GCB DLBCL
- Frequent translocations to non-\( IGH \) genes

MYC-Rearrangements are frequently (70-98%) associated with other genetic alterations

- BCL2-R  60-70%
- BCL6-R  6%
- Triple hit  15-20%
- Complex karyotypes

Yoon 2008; Klapper 2008; Savage 2009; Obermann 2009; Barrans 2010, Valera 2013
Myc Protein Overexpression is more frequent than Genetic Alterations in DLBCL

Myc FISH R  5-15%
Myc IHC+  29-64%
Myc-R Myc-high  70-90%
Myc-nonR Myc-high  30-40%

Cytologic spectrum of HGBL, with MYC and BCL2 and/or BCL6 rearrangements
Not all “Double Hit” lymphomas have been created equal

Modulators of the prognostic impact

Morphology matters: BCLU vs DLBCL

BCL2 and MYC protein expression matters

Profile of Somatic Mutations in Burkitt Lymphoma

- **ID3**: 38-68%
- **TCF3**: 10-30%
- **CCND3**: 38%
- **MYC**: 70%
- **TP53**: 50-60%

Morphological spectrum of EBV+ DLBCL, NOS