“Aggressive” B-cell Lymphomas

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“Aggressive” B-cell Lymphomas
WHO 4th Edition

- Diffuse large B-cell lymphomas
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (BCL-U)
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (Gray-zone lymphoma)
- Classical Hodgkin lymphoma
- Lymphocyte-Predominant Hodgkin lymphoma
WHO 4th Ed
Diffuse Large B-cell Lymphomas

- Diffuse large B-cell lymphoma, not otherwise specified
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatisis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive DLBCL
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman Disease

No major changes
Diffuse large B-cell lymphoma, not otherwise specified

WHO 4th Ed
- Variants (optional)
  - Morphologic variants (CB, IB, anaplastic)
  - Immunophenotypic (CD5+, GCB, non-GCB)
  - Genetic (GCB/ABC)
- Subtypes (required)
  - T cell/histiocyte rich large B-cell lymphoma
  - Primary CNS DLBCL
  - Primary cutaneous DLBCL ("leg type")
  - EBV+ DLBCL of the elderly

Update
- Variants (optional)
  - Morphologic (CB, IB, anaplastic, "blastoid")
    - Not in the "diagnosis" line
- Subtypes (required)
  - GCB/ABC (genetic or immunophenotypic)
  - T cell/histiocyte rich large B-cell lymphoma
    - Relationship to NLPHL?
  - Primary CNS DLBCL*
  - Primary cutaneous DLBCL ("leg type")*
  - EBV+ DLBCL NOS
    - Distinction from EBV+ mucocutaneous ulcer
- Prognostic factors
  - Immunophenotypic: MYC/BCL2 IHC
  - Genetic: MYC, BCL2, BCL6 rearrangements (single)

*These are usually ABC/non-GCB; both topographic and COO information are important
DLBCL: Clinical Advisory Committee

- Classification should have a greater emphasis on the importance of cell of origin (COO)
  - COO is important for prognosis now and will be necessary for treatment selection in the NEAR future
    - Many clinical trials are enrolling based on COO
  - IHC algorithms should be used and the algorithm should be stated in the report
    - Terminology (GCB, ABC, non-GCB) will depend on the IHC algorithm used
    - Move to mRNA gene expression-based platforms as soon as they are available

- Clinical subtypes (CNS, leg-type) are typically non-GCB/ABC type
  - Clinical subtypes are important and take precedence over COO
  - COO should be stated if known
WHO update: Burkitt Lymphoma

• MYC- Burkitt lymphoma
  - Rare, but accepted
  - *ID3 mutation often present*
  - **11q aberrations may be seen**

• New variant: “Burkitt-like lymphoma with 11q aberrations”


Double Hit Lymphomas (DHL)
Clinical Advisory Committee

• Consensus that DHL is defined as translocation of *MYC* and *BCL2* or *BCL6*
  - Cases may have DLBCL or BCL-U morphology
  - FISH for *BCL2* and *MYC* in all cases of DLBCL and BCL-U is preferred by clinicians when it will impact therapy
    ▪ May not be practical as a universal recommendation
    ▪ Two step approach based on IHC for MYC, BCL2, Ki67 or some other algorithm that works locally

• Controversy re where DHL should be classified (DLBCL or BCL-U)
  - Clinicians prefer a new category for both DLBCL and BCL-U with DH
  - Does genetics trump morphology?
Double-Hit Lymphomas: Morphology

- Morphologic spectrum (WHO 2008)
  - B-cell lymphoma intermediate between BL and DLBCL (60-67%)
  - Diffuse large B-cell lymphoma (31-35%)
  - Lymphoblastic lymphoma (2%)
  - Follicular lymphoma (2%)
- Progressed/transformed follicular lymphoma (25-35%)
- DLBCL morphology predicts better outcome
  - OS 3 yr vs 4m (p<.00001)*

*Johnson et al Blood 2009; Snuderl et al AJSP 2010; Cook et al AJSP 2014
DLBCL with MYC and BCL2 Co-expression (IHC)

• IHC for MYC (cutoff 40%) and BCL2 (cutoff 40%)
• 20-30% of DLBCL are MYC+ BCL2+ by IHC (“double expressing”)
  - Some but not all have MYC/BCL2R
• Worse prognosis than non double-expressing cases
• Not as bad as genetic “double hit”

Johnson N et al., JCO 2012; Green TM et al., JCO 2012; Valera A et al. Haematologica 2013; Cook et al. AJSP 2014
DHL and BCL-U: WHO Update, Current Thinking

• WHO 4\textsuperscript{th} ed:
  ∘ B-cell lymphoma, unclassifiable, intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma (BCL-U)
    ▪ Morphologically resembling BL but that don’t “fit” (morphology, immunophenotype, genetics [DH])
    ▪ Includes but not limited to DH cases; does not include DLBCL-DH

• WHO 4\textsuperscript{th} ed Update:
  ∘ High-grade B-cell lymphomas, NOS
    ▪ High-grade B-cell lymphoma with \textit{MYC} and \textit{BCL2} or \textit{BCL6} rearrangements (“double hit”)
      ∘ Specify whether DLBCL or BCL-U morphology
      ∘ If FISH or CG pending, sign out as “B-cell lymphoma with high-grade features, pending genetic studies”
      ∘ FL or LBL with DH are not included in this category
    ▪ High-grade B-cell lymphoma, NOS
      ∘ Cases with BCL-U morphology or other high-grade features and no DH
CHL-DLBCL Gray-Zone Lymphoma

- **Who 4th ed:**
  - B-cell lymphoma, intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma (Gray-zone lymphoma)
    - Discussed primarily as a mediastinal tumor
    - Chapter acknowledged that non-mediastinal cases can occur, but their features were not described in detail

- **Update**
  - Studies have shown some clinical (age) and genetic differences between mediastinal and non-mediastinal cases, but similar survival
  - No name change, but two subtypes now distinguished: mediastinal and non-mediastinal

Eberle Mod Pathol 2011;24:1586
Nodular Lymphocyte Predominant Hodgkin Lymphoma: Issues

- Variant patterns in NLPHL*
  - B-cell-rich nodular/serpiginous (Fan)
  - T-cell-rich nodular/diffuse, internodular LP cells

- Diffuse areas/progression in NLPHL vs THRLBCL

NLPHL – Immunoarchitectural patterns

T-cell-rich nodular

Extranodular LP cells

THRLBCL-like

NLPHL: Patterns (GHSG 413 cases*)

- **Typical**: 75%
  - B-cell-rich nodules

- **Variant**: 25%
  - Extranodular LP cells: 6.5%
  - T-cell-rich nodules: 5%
  - THRLBCL-like: 3.6%
  - Typical with a minor variant component: 10%

- **Variant patterns associated with**
  - High stage (p=0.0012),
  - IPS score (p=0.0005),
  - Early relapse (p=0.0009)
  - Not worse OS (p=0.1751)

*Hartmann et al Blood 2013; also Boudova et al Blood 2003*
“Diffuse” NLPHL vs. THRLBCL

• Distinction between diffuse areas of NLPHL and THRLBCL may be impossible
  - Some make a diagnosis of relapsed NLPHL with a diffuse pattern
  - Others make a diagnosis of progression to THRLBCL

• WHO 2008
  - Diagnosis of THRLBCL should be restricted to primary/de novo cases
  - Occurrence or relapse of NLPHL with a partially or entirely diffuse pattern should be called either diffuse LPHL or “NLPHL, THRLBCL-like”
  - Careful search for focal NLPHL important in de novo cases of THRLBCL
    ▪ One nodule of NLPHL rules out THRLBCL
Borderline between NLPHL and THRLBCL

• Genetic features
  - Genetic similarities
    ▪ Rearranged, mutated *IGH* genes with ongoing mutations (GCB)
    ▪ Partial gain of 4q, rare in lymphomas
    ▪ GEP in THRLBCL intermediate between NLPHL and CHL; or indistinguishable from NLPHL and NLPHL-THRLBCL*
  - Genetic Differences
    ▪ Number of genomic imbalances greater in NLPHL (10.8 vs 4.7)**
    ▪ 42 genes distinguish NLPHL from THRLBCL*

• Clinical features
  - NLPHL with diffuse areas/progression tend to be higher stage, earlier relapse
  - Outcome still not as aggressive as de novo THRLBCL***

• Conclusion
  - NLPHL and THRLBCL have genetic similarities and differences; relationship still unclear
  - Diffuse areas/progression in NLPHL has clinical prognostic importance and needs to be reported

*Brune J. Exp. Med. 2008; Hartmann Plos1; 2013; **Franke Blood 2001
***Hartmann et al Blood 2013; also Boudova et al Blood 2003
NLPHL and THRLBCL
Clinical Advisory Committee

- **NLPHL vs TCHRLBCL**
  - Distinction is clinically important

- **NLPHL with histological progression should not be classified as THRLBCL**
  - Diffuse areas in the background of NLPHL do not equate to TCHRLBCL

A. Zelenetz summary 4/2/14
NLPHL and THRLBCL WHO update

• NLPHL Pattern should be described at diagnosis, particularly cases with variant patterns
  - Clinical implications will be discussed

• In patients with prior or concurrent NLPHL who have site(s) biopsied that would fulfill criteria for THRLBCL:
  - “THRLBCL-like transformation of NLPHL should be used, rather than just histologic progression of NLPHL”
  - Compromise decision, still under discussion
WHO 4th ED Update
Plasma Cell Neoplasms

- Includes non-IgM MGUS only (IgM with LPL/WM)
- IMWG genetic testing recommendations included (2009)*
- New provisional category: “PC neoplasm with associated paraneoplastic syndrome”
  - TEMPI (telangiectasias, elevated erythropoietin/erythrocytosis, monoclonal gammopathy (IgG MGUS), perinephric fluid collections, intrapulmonary shunting)**
  - Dramatic responses to bortezomib

Leukemia 2009; 23:2210
Other Categories

• Large B-cell lymphoma with \( IRF4 \) rearrangement
  - New provisional entity; may have a follicular component

• Plasmablastic lymphoma
  - \( MYC \) rearrangements common
  - Overlap with plasma cell neoplasms

• Large B-cell lymphoma associated with multicentric Castleman’s disease
  - Now “HHV8-associated lymphoproliferative disorders” including
    ▪ MCD (rare progression to DLBCL)
    ▪ Germinotrophic lymphoproliferative disorder
    ▪ Primary effusion lymphoma (PEL)
      - Includes “extracavitary” PEL (vs “solid” PEL)

• Classical Hodgkin lymphoma – no major changes
WHO Update Summary

• Emphasis on COO classification of DLBCL
  - Retain anatomic variants, but give COO when available (CNS, leg, etc)

• Change in nomenclature and definition of “BCL-U”
  - Retain morphologic description (DBLCL vs BCL-U) for DH cases

• Importance of pattern in NLPHEL
  - Change in terminology for cases that relapse with a diffuse pattern being discussed
I’ll be happy to answer any questions....

Dan Harris, ABC news, Kandahar (Oct 2001)
DLBCL with \textit{IG/IRF4} Translocation

- DLBCL +/- Grade 3B FL > 3B FL
- Distinct entity within both DLBCL (most) and FL3B (some)
- Younger patients, Waldeyer’s ring
  - Require treatment but good prognosis

Salaverria; Liu
Unsupervised Clustering of NLPHL vs Other B-Cell Lymphomas
Expression of B-Cell Program by NLPHL vs Other B Cell Lymphomas
NLPHL and THRLBCL
Gene Expression Profiling-1

- Microdissected cells from NLPHL, CHL, THRLBCL, DLBCL, BL, FL (unsupervised clustering)
  - NLPHL formed a distinct cluster
  - Closer to CHL and THRLBL than DLBCL, BL, FL
  - 42 genes distinguished NLPHL from THRLBCL

- Comparison with naïve, memory, GCB and plasma cells (principal component analysis)
  - NLPHL cells intermediate between GCB and memory B cells ("late" GCB cells)

- Expression of B-cell program genes
  - Decreased compared to normal GCB cells
  - Decreased compared to FL, BL, DLBCL
  - Increased compared to THRLBCL, CHL

- Conclusion:
  - NLPHL and THRLBCL may be a spectrum of the same disease

Microdissected NLPHL, NLPHL-THRLBCL-like, THRLBCL cells
- No clustering; all distinct from GCB cells
- No consistent differentially expressed genes

IHC of microenvironment (NLPHL THRLBCL-like +THRLBCL vs NLPHL)
- Fewer CD4+ T cells
- Fewer rosetting MUM1+ PD1+ T cells
- More CD168+ macrophages
- No difference in CD8+ T cells

Conclusion:
- NLPHL and THRLBCL may be a spectrum of the same disease

Hartmann et al. Plos1, 2013
NLPHL and THRLBCL Genetics

- Both: *IGH* genes clonally rearranged, mutated, ongoing mutations, functional
- NLPHL
  - *BCL6* rearrangements: *IGH* (20%); other genes (48%)
  - CGH:
    - Recurrent genomic imbalances (average 10.8 per case)
    - Gains: 1, 2q, 3, 4q, 5q, 6, 8q, 11q, 12q, X; loss: 17 (36.8% to 68.4% of cases)
- THRLBCL
  - *BCL6* rearrangements uncommon
  - CGH:
    - Genomic imbalances (average of 4.7 per case)
    - Gains (Xq, 4q13q28, Xp21p11, 18q21); loss (17p)

Franke et al. Blood 2001