Lymphoma Update: What’s Likely to be New in the New WHO

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THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES

The 2016 revision of the World Health Organization classification of lymphoid neoplasms
Blood 127:2375; 2016

A revision of the nearly 20-year-old World Health Organization classification of the lymphoid neoplasms and the accompanying monograph is being published. It reflects a consensus among hematopathologists, geneticists, and clinicians regarding both updates to current entities as well as the addition of a limited number of new provisional entities. The revisions clarify the diagnosis and management of lesions at the very early stages of lymphomagenesis, refine the diagnostic criteria for some entities, detail the expanding genetic/molecular landscape of numerous lymphoid malignancies and their clinical consequences, and refer to investigations leading to recent targeted therapeutic strategies. Therapeutic changes are reviewed with an emphasis on the most important advances in our understanding that impact our diagnostic approach, critical interpretations, and therapeutic strategies for the lymphoid neoplasms. (Blood 2016;127:2375-2396)
Mature B-cell Lymphomas

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma & Monoclonal B-Cell Lymphocytosis

Old (2008):
- Monoclonal B-cell lymphocytosis (MBL)
  - Monoclonal B-cells in PB <5K/μL*
  - Usually with phenotype of CLL (CD20+ CD5+ CD23+)
- CLL/SLL
  - CLL phenotype cells in PB ≥5K/μL, or <5K/μL with extramedullary disease, cytopenias, or disease-related symptoms

New (2016):
- Monoclonal B-cell lymphocytosis (MBL)
  - Same as 2008, stresses “high count” MBL (≥0.5K/μL) vs. “low count” (<0.5/μL)
- CLL/SLL
  - CLL-like cells in PB >5K/μL*, or <5K/μL with EM disease

*In absence of other known LPD or autoimmune disease

Monoclonal B-cell Lymphocytosis

- “High count” MBL
  - Monoclonal B-cells 0.5-5 K/μL
  - Sig rate of CLL-like genetic mutations (5-9%)
  - 1-2% annual progression to CLL requiring therapy
- “Low count” MBL
  - Monoclonal B-cells <0.5 K/μL (usually <0.05 K/μL)
  - Does not carry CLL-like mutations
  - Very low (if any) risk of progression to CLL

Vardi et al. Blood 121:4521;2013
Rawstron et al. Cytometry B Clin Cytom 78:S19;2010
Follicular Lymphoma

Old (2008):
Follicular lymphoma, grades 1, 2, 3A, & 3B

New (2016):
Follicular lymphoma, grades 1, 2, 3A, & 3B
Follicular lymphoma, pediatric type
Large B-cell lymphoma with IRF4 rearrangement
Follicular lymphoma, duodenal type

Pediatric type follicular lymphoma

- Mostly children, but some patients up to 25 years
- Mainly nodal disease of head & neck, but tonsil and testis were next most common sites.
- In contrast to usual follicular lymphoma (which was never seen in patients <18 years), cells often had blastoid morphology, lack of BCL2 protein expression or translocation (particularly in nodal cases), and tonsillar cases expressed IRF4/MUM1
- All had low-stage (I-II) disease and achieved complete remission, even if treated only by excision (but median follow-up only 18 months)
**Large B-cell lymphoma with rearrangement of IRF4 (MUM1)**

- Salsverria et al. *Blood* 118: 139; 2011

- Shares features with pediatric type FL:
  - Often in children/young adults
  - Waldeyer's ring, head & neck common sites
- But distinguished by:
  - Large cell morphology (follicular grade 3B or DLBCL)
  - BCL2 expression but lack of t(14;18)
  - IRF4/MUM1 translocation with strong IRF4/MUM1 expression
  - Relatively aggressive, often requiring therapy

**Duodenal follicular lymphoma**


  - 63 patients all with stage I disease limited to duodenum (others excluded), median F/U 6 years
  - Median age 65 (range 32-83)
  - Most CD20+ CD10+ BCL6+ t(14;18)+
  - All low-grade disease (most grade 1)
  - With “watch & wait,” 7/24 patients showed spontaneous CR, most others had stable disease
  - Radiation led to CR in 19/19 patients
  - Only 2 untreated patient developed nodal disease
  - No patients required surgery or died of disease

**Mantle Cell Lymphoma**

**Old (2008):**

- Mantle cell lymphoma (MCL)
  - Classic
  - Blastoid (cells resemble lymphoblasts)
  - Pleomorphic (cells pleomorphic, many large)

**New (2016):**

- Mantle cell lymphoma (MCL)
  - Classic
  - Blastoid (cells resemble lymphoblasts)
  - Pleomorphic (cells pleomorphic, but many large)
  - Leukemic non-nodal → Indolent!
Leukemic non-nodal MCL


- Clinical features:
  - Typically presents in elderly patients who are asymptomatic or minimally symptomatic (e.g., due to splenomegaly); no lymph node involvement by definition
  - Follows indolent clinical course (median survival 6.6 years, vs. 2.5 years for node-based MCL)

- Pathologic features:
  - Neoplastic cells involve peripheral blood, bone marrow, & spleen in variable numbers
  - Cells typically resemble mature small lymphocytesCD5+ BCL1+ but SOX11-negative

Diffuse Large B-cell Lymphoma

Old (2008):
  - Many variants and subtypes
  - Cell of origin subtyping (GCB vs. ABC) optional
  - Testing for MYC, BCL2, & BCL6 translocations optional

New (2016):
  - Many variants and subtypes
  - Cell of origin subtyping mandatory
  - Cases with translocations of MYC and BCL2 or BCL6 assigned to new category (testing mandatory?)
  - EBV+ DLBCL of elderly renamed as EBV+ DLBCL, NOS
  - EBV+ mucocutaneous ulcer recognized as indolent

Diffuse large B-cell lymphoma subtypes
2016 WHO Classification
Double hit lymphoma

- DHL is a genotype associated with a very poor prognosis in various B-cell neoplasms
- Lymphomas with double-hit genotype:
  - Burkitt or Burkitt-like lymphoma (most common)
  - Diffuse large B-cell lymphoma (less common)
  - B-cell lymphoblastic leukemia/lymphoma (occ.)
**FISH?**

**DBLCL**

**MYC**

**BCL2**

**and/or**

**BCL6**

**IHC?**

**MYC, BCL2, & BCL6 testing in DLBCL (2016 WHO Classification)**

“All LBCL with MYC and BCL2 and/or BCL6 rearrangements will be included in a single category to be designated high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements.... A consensus has not yet been reached to provide specific guidelines as to which LBCL should have FISH studies. Some believe that all DLBCL should have genetic studies for the detection of MYC, BCL2, and BCL6 rearrangements, whereas others would limit them, for example, to cases with a GCB phenotype and/or high-grade morphology or to cases with >40% MYC+ cells.”


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**EBV+ DLBCL, NOS**

- Aggressive form of DLBCL thought to be related to age-related senescence of immune system
- Patients otherwise immunocompetent, usually >50 years
- RS-like cells often present, sometimes in polymorphous background, resembling CHL
- Variable CD30+, but usually strong CD20 & Oct2
- WHO excludes other defined EBV+ DLBCLs (PBL, PEL, LYG, DLBCL associated with CI)
- Very poor prognosis (<50% 2-year survival)

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**EBER**
EBV+ mucocutaneous ulcer

*Gratzinger et al. Leukemia & Lymphoma, 2016*

- Morphology and immunophenotype indistinguishable from polymorphous EBV+ DLBCL, NOS
- B-cell clonality tests often positive
- Presents as sharply localized ulcerative lesion of the skin, oropharynx, or GI tract, often in patients who are iatrogenically immunosuppressed
- Typically follows an indolent course, often resolving with reduction of immunosuppression alone

Burkitt Lymphoma

Old (2008):
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU, DLBCL/BL), a “gray zone” lymphoma (roughly corresponded to high-grade Burkitt-like lymphoma of 2001 WHO)

New (2016):
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration
DLBCL/BL gray zone cases all moved to new categories:
- HGBL with rearrangements MYC and BCL2 +/- BCL6
- HGBL, NOS
**Burkitt Lymphoma**

- **Typical immunophenotype:**
  - CD20 +
  - CD10 +
  - BCL6 +
  - BCL2 -

*Weak BCL2+ seen in 20% Burkitt cases, does not exclude diagnosis of typical Burkitt lymphoma*

- **Genotype:**
  - Most have translocations linking MYC to Ig genes:
    - t(8;14) → MYC-IGH
    - t(2;8) → MYC-IGL-κ
    - t(8;22) → MYC-IGL-λ

*Up to 10% of otherwise typical Burkitt lymphoma may lack MYC translocations (11q aberration?)*

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**Burkitt lymphoma with 11q aberration**

Salaverria et al. Blood 123:1187; 2014
Ferreiro et al. Haematologica 100:e275; 2015

- Resemble typical Burkitt lymphoma morphologically, immunophenotypically, and by GEP, lack MYC rearrangements, but have interstitial gains of 11q23 and losses of 11q24
- These have more cellular pleomorphism and more complex karyotypes than typical BL, seem to follow similar clinical course
- May explain rare cases of MYC negative Burkitt lymphoma

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**Burkitt Lymphoma vs. “DLBCL/BL”**

- **Acceptable for Classical Burkitt?**
  - Morphology
  - Immunophenotype

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<tr>
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<th>Burkitt Lymphoma</th>
<th>“DLBCL/BL”</th>
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<tr>
<td>Too many large cells</td>
<td>X</td>
<td>✓</td>
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<td>Double hit lymphoma by FISH?</td>
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<td>High-grade B-cell lymphoma, NOS</td>
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*Weak BCL2+ OK (seen in 20% Burkitt cases), & abnl IP can be redeemed by FISH MYC+ BCL2- BCL6-*
Double hit lymphoma

- DHL is a genotype associated with a very poor prognosis in various B-cell neoplasms
- Lymphomas with double-hit genotype:
  - Burkitt or Burkitt-like lymphoma (most common)
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T-cell Lymphomas

Nodal Peripheral T-cell lymphomas
Old (2008):
- Anaplastic large cell lymphoma (ALCL)
- Anaplastic large cell lymphoma (AITL)
- Peripheral T-cell lymphoma, NOS

New (2016):
- Anaplastic large cell lymphoma (ALCL), ALK+ and ALK-
- Nodal TCLs with TFH phenotype (umbrella category):
  - Angioimmunoblastic T-cell lymphoma (AITL)
  - Follicular T-cell lymphoma
  - Nodal PTCL with TFH phenotype
- Peripheral T-cell lymphoma, NOS

**Anaplastic large cell lymphoma**

*Attygalle et al. Histopathology 64:171; 2014
Rodriguez-Justo et al. Mod Pathol 22:753; 2009*

- Large T-cell lymphoma most common in children & young adults, in LNs +/- extranodal sites
- Has "hallmark cells" with indented, reniform, or horseshoe-shape nuclei, may have pleomorphic RS-like tumor giant cells too
- ALK+ in 75% of cases, imparts good prognosis
- ALK- cases now distinct entity related to ALK+ by GEP, with survival intermediate between ALK+ ALCL and PTCL, NOS
- ALK- ALCL also shares key morphologic & immunophenotypic features with ALK+, including hallmark cells, diffuse strong CD30+ in membrane & Golgi region, cohesive often sinusoidal growth pattern

**Angioimmunoblastic T-cell lymphoma**

*Attygalle et al. Histopathology 64:171; 2014
Rodriguez-Justo et al. Mod Pathol 22:753; 2009*

- Typically older patients, present with diffuse lymphadenopathy, hepatosplenomegaly, and B-symptoms
- Involved lymph nodes may have reactive B-cell follicles, with lymphoma occupying only interfollicular areas (pattern I)
- Neoplastic cells mainly mature small lymphs (may have clear cytoplasm), with scattered bland immunoblasts
- Arborizing proliferation of high-endothelial venules typically seen in interfollicular areas
- CD21+ FDC meshworks typically extend into interfollicular areas
- EBV+ large B-cells often present, may be RS-like

**AITL derived from TFH cells?**

- TFH cells found to have unique gene expression profile showing upregulation of PD1, CXCL13 & CD10*
  *Voss et al. Blood 104:1582, 2004
  Grogg et al. Mod Pathol 19:1191, 2006*

- Proteins encoded by these genes expressed in significant subsets of neoplastic T-cells in AITL
T-follicular helper (T\textsubscript{FH}) cells

- T-cells that provide antigen-specific help to developing B-cells in normal follicular germinal centers
- In benign lymphoid tissue, TFH cells are largely restricted to the periphery of reactive germinal centers
- Can be highlighted by stains for a variety of TFH-related markers (e.g., PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5), none of which is 100% sensitive or specific

Are any other PTCLs TFH-derived?


- Studied 146 PTCLs divided them into groups that did or did not "meet all criteria for AITL" based on 2008 WHO Classification
- Examined both groups for expression of TFH-related markers PD1, CXCL13, CD10, & BCL-6 in extrafollicular T-cells by IHC
- Stains were considered positive even if only 5% of cells stained
  - 1+: 5-15% cells positive
  - 2+: 15-40% cells positive
  - 3+: >40% positive
- All PD1+ had H&E & history reviewed for feature to suggest AITL
- Most non-AITL cases showed at least some AITL-like features
- Speculated that non-AITL may include “follicular T-cell lymphoma”

Nodal PTCLs with TFH phenotype

Attygalle et al. Histopathology 64:171; 2014

- Three entities recognized by 2016 WHO
  - Angioimmunoblastic T-cell lymphoma
  - Follicular T-cell lymphoma (follicular architecture)
  - Nodal peripheral T-cell lymphoma with TFH phenotype (all other cases)
- Shared clinical/morphologic features
  - Typically presents as nodal disease in older adults
  - EBV+ large B-cells often present, may resemble RS cells
  - Large B-cells may be clonal & transform to DLBCL
  - Even non-AITL cases often have some AITL-like features
- Shared immunophenotypic
  - Revised 2016 WHO requires expression of "at least 2 or 3" TFH-related antigens, including PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5
  - Most common: PD1 & ICOS in AITL & F-TCL, CXCL13 & BCL-6 in "NOS" group
Intestinal T-cell lymphomas

Old (2008):
- Enteropathy-associated T-cell lymphoma (EATL)
  - Type I (“classic variant”)
  - Type II (“monomorphic variant”)

New (2016):
- Enteropathy-associated T-cell lymphoma (old type I EATL type)
- Monomorphic epitheliotropic intestinal T-cell lymphoma (old type II EATL, now MEITL)