Duke Debates 2017

The New WHO … What’s Changing in the Classification Schema

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Friday, April 21, 2017, 3:00pm – 3:30pm
Disclaimer

• Will cover lymphomas only!
WHO 2008 vs WHO 2016
Rationale and scope of this revision

• Major advances with significant clinical and biologic implications
• A “revision” (not a “fifth edition”)
  – To maintain uniformity in the series
  – Some provisional entities are promoted to definite entities
  – New provisional entities identified
  – But no new definite entities
Main themes of the revision

• Goals
  – Identify homogeneous groups of well defined entities
  – Recognize uncommon entities requiring further clarification
• Limited alterations in classification
• Significant new information, mainly from molecular studies, related to:
  – Diagnosis
  – Prognosis
  – Therapeutic implications
Basic Classification Scheme Unchanged

- Mature B-cell neoplasms
- Mature NK-/T-cell neoplasms
- Hodgkin lymphoma
- Post-transplant lymphoproliferative disorders (PTLD)
- Histiocytic and dendritic cell neoplasms
B-cells: Provisional Entities from 2008 promoted to Definite Entities

- Monoclonal B-cell lymphocytosis
- IgM and IgA MGUS
- Monoclonal Ig deposition diseases
- Follicular lymphomas
  - In situ follicular neoplasia (no longer a “lymphoma”)
  - Duodenal type and Pediatric type FL
- In situ mantle cell neoplasia (no longer a “lymphoma”)
- DLBCL must be categorized as GCB or ABC type
- EBV+ DLBCL, NOS (no longer restricted to elderly)
- High grade B-cell lymphoma, NOS (replaces B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma)
B-cells: New Provisional Entities

• Splenic B-cell lymphoma/ leukemia, unclassifiable
  – Splenic diffuse red pulp small B-cell lymphoma
  – Hairy cell leukemia variant
• Pediatric marginal zone lymphoma
  – Marked male predominance (20:1)
  – Head and neck involvement, localized disease
• Large cell lymphoma with IRF4/MUM1 rearrangement
  – Lymphoma of children and young adults involving tonsils and Waldeyer ring.
  – Prominent follicles or diffuse
  – More aggressive than pediatric FL but good Px with Rx
• EBV+ mucocutaneous ulcer
• HHV8+ DLBCL, NOS
• Burkitt-like lymphoma with 11q aberration
T-cells: Provisional Entities from 2008 promoted to Definite Entities

• Systemic EBV+ T-cell lymphoma of childhood
• Hydroa vacciniforme-like lymphoproliferative disorder (LPD)
• Monomorphic epitheliotropic intestinal T-cell lymphoma (2008 = enteropathy associated T-cell lymphoma, type B)
• Anaplastic large cell lymphoma, ALK-
T-cells: New Provisional Entities

- Chronic LPD of NK-cells
- Indolent LPD of the GI tract
- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal T-cell lymphoma of TFH phenotype
- Breast implant associated anaplastic T-cell lymphoma
Other Additions

• Hodgkin Lymphoma
  – No changes

• PTLD
  – Florid follicular hyperplasia PTLD

• Histiocytic and Dendritic cell neoplasms
  – Erdheim-Chester disease
Diagnostic / Prognostic Refinements in Existing Conditions … CLL / SLL

- Diagnostic criterion: ≥5000 CLL cells /µL in blood required for diagnosis if tissue involvement is absent.
  - Cytopenias or disease related symptoms are NOT sufficient

- Prognosis
  - Histologic: Large / confluent proliferation centers (PC) and/or high Ki67 proliferation index (≥30%) in these ▶▶ adverse prognosis. Ciccone et al. Leukemia (2012) 26, 499–508

<table>
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<th>Univariate analysis variable</th>
<th>No. of patients</th>
<th>Median OS(se)</th>
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<td>Histology</td>
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<td>Typical</td>
<td>52</td>
<td>64 (1.6)</td>
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<td>PC-rich</td>
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<td>Ki67+ in PC</td>
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<td>&lt;30%</td>
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<tr>
<td>30%</td>
<td>14</td>
<td>4 (0.3)</td>
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- Molecular: Mutations in TP53, NOTCH1, SF3B1, BIRC1 associated with worse prognosis.
Diagnostic / Prognostic Refinements in Existing Conditions

... Monoclonal B-cell Lymphocytosis

• Must distinguish
  – Low count MBL (<500/µL): Possibly age related or due to chronic antigen stimulation
  – High count MBL (≥500/µL): A premalignant condition, genetic/ molecular features indistinguishable from Rai stage 0 CLL

• Tissue based MBL
  – CLL type monoclonal cells in small (<1.5cm) lymph nodes, without proliferation centers
  
  Haematologica. 2011 Aug;96(8):1144-52

• MBL with Non-CLL or atypical CLL phenotype
  – Many non-CLL cases related to splenic MZL
Diagnostic / Prognostic Refinements in Existing Conditions

... Follicular Lymphoma

- Mutational landscape of follicular lymphoma is well-characterized:
  - Early driver mutations in chromatin regulators: **MLL2, CREBBP**, and less commonly **EZH2**
    - enhancer of zeste homolog 2 (a histone methyl-transferase)
  - Therapeutic targets
  - Gained during transformation: **EBF1, MYD88, TNFAIP3** (regulators of NF-κB pathway).
  - Mutations in other genes at lower frequencies

Nat Genet. 2014 Feb;46(2):176-81
Diagnostic / Prognostic Refinements in Existing Conditions

... Follicular Lymphoma

• A prognostic model integrating clinical-pathological scores and mutation status of 7 genes is proposed.
  – High risk: EP300, FOX01, CREBBP, CARD11
  – Low risk: EZH2, ARID1A, MEF2B

• Needs further validation.

Lancet Oncol. 2015 Sep;16(9):1111-22.
Follicular Lymphoma

• Pediatric-type follicular lymphoma
  Louissaint A Jr et al., Blood. 2016;128:1093-100
  – Occurs mainly in children & young adults, but can rarely occur in adults
  – Localized dz
  – Large expansile follicles, often grade 3
  – BCL2 and t(14;18) negative
  – \textit{MAP2K1} mutated in 43% and \textit{TNFRSF14} in 29%
  – Excellent prognosis
**Follicular Lymphoma ...2**

- Predominantly diffuse FL with 1p36 deletion (which includes **TNFRSF14**) Katzenber et al., Blood.2009;113:1053, Siddiqi et al., Mod Pathol.2016;29:570
  - Often involves inguinal node, localized Dz
  - Grade 1-2
  - CD23 expression in lymphoma cells
  - Most lack t(14;18)
  - **TNFRSF14** is either deleted or mutated
    - NOTE: 1p36 changes (deletion or acquired uniparental disomy) seen in 65% of FL overall
  - **STAT6** mutation is frequent (82%)
  - Indolent disease with excellent prognosis
Mantle Cell Lymphoma

- Two clinicopathologic subtypes:

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<th>Classical</th>
<th>Leukemic, Non-nodal</th>
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<td>Sites of involvement</td>
<td>LN, GI tract, other extranodal</td>
<td>Blood, BM, spleen</td>
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<td>Immunohistochemistry</td>
<td>Sox11+, Cyclin D1(or D2)+</td>
<td>Sox11-, Cyclin D1 (or D2)+</td>
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<td>IgH gene</td>
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<td>Proliferation index</td>
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<td>Clinical behavior</td>
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<tr>
<td>Transformation</td>
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<td>aggressive</td>
</tr>
</tbody>
</table>

- In-situ marker progression
Mantle Cell Lymphoma …2

- **In-situ Mantle Cell Neoplasia (ISMCN)**
  - Carvajal-Cuenca et al., Haematologica. 2012 Feb;97(2):270-8
  - Less common than ISFN
  - Usually incidental finding in reactive nodes
  - Less than half have t(11;14) or Sox11 expression
  - A third are associated with other overt lymphomas
  - Very indolent behavior in most
  - Cyclin D1+ B-cells in mantle zones
    - Must distinguish from MCL with mantle zone pattern
In-situ Mantle Cell Neoplasia (ISMCN)

Mantle Cell Lymphoma

Cyclin D1

ICMCN

Cyclin D1

4X

Cyclin D1

20X

Anand Lagoo/WHO2016 lymphomas/4-2017
Diffuse Large B-cell Lymphoma

• Recommend GCB and non-GCB distinction by IHC in every case

• NGS in DLBCL: somatic mutations
  – Both subtypes: \(TP53\), immunosurveillance genes (\(B2M, CD58\)), epigenetic regulators (\(CREBBP/EP300, MLL2/3, MEF2B\)), and \(BCL6\).
  – GCB type: histone methyl transferase (\(EZH2\)), cell motility regulator (\(GNA13\))
  – Non-GCB type: activators of BCR/TLR/NF-\(\kappa\)B pathway (\(MYD88, CD79a, CARD11, TNFAIP3\))
“Double expressor” and “Double hit”

- “Double expressor” = Concomitant detection of MYC and BCL2 by IHC
- “Double (or triple) Hit” = Rearrangement of MYC and BCL2 or/and BCL6 genes
  - MYC protein is expressed in 30-50% DLBCL but MYC gene is rearranged only in 5-15%
  - Some double expressors may be Double Hit
- Double (or triple) hit lymphomas will be a category of “high grade B-cell lymphoma” (HGBL)
- Double expression will be an adverse prognostic indicator in DLBCL-NOS but will not be a separate category.
Diagnostic / Prognostic Refinements in Existing Conditions …

High Grade B-cell Lymphoma (HGBL)

• Replaces “B-cell lymphoma, unclassifiable, with features indeterminate between DLBCL and BL”

• Subdivided into
  – HGBL with MYC and BCL2 and/or BCL6 rearrangements
    • Morphology varies from BL like to DLBCL
  – HGBL NOS
    • Morphology varies from BL-like to blastoid
  – NOTE: must exclude B-lymphoblastic lymphoma or high grade FL
Burkitt Lymphoma (BL)

- Recurrent mutations in transcription factor \textit{TCF3} and the negative regulator \textit{ID3} occur in up to 70% cases of non-endemic BL.

- BL-like lymphoma with 11q aberrations
  - Morphology and phenotype like BL, but without \textit{MYC} rearrangements
  - \textit{MYC} protein expression (but lower than BL)
  - Often have 11q alterations
  - More complex cytogenetics
  - Prognosis same as BL
BL-like lymphoma with 11q aberrations

MYC negative

MYC positive

Ki67
Burkitt Lymphoma (BL)

- Recurrent mutations in transcription factor $TCF3$ and the negative regulator $ID3$ occur in up to 70% cases of non-endemic BL.

- BL-like lymphoma with 11q aberrations
  - Morphology and phenotype like BL, but without $MYC$ rearrangements
  - $MYC$ protein expression (but lower than BL)
  - Often have 11q alterations
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  - Prognosis same as BL
NK/T-cell malignancies

- Activating mutations of **JAK/STAT** pathway
  - T-LGL leukemia: mutations of **STAT3** in up to 70% and of **STAT5b** in 2-5% \(^{Rajala\ et\ al,\ Ann\ Med.\ 2014;46:114}\)
  - **STAT5b** mutated dz more aggressive
  - Hepatosplenic Lymphoma: **STAT5b** (36%) and **STAT3** (10%) \(^{Nicolae\ et\ al.,\ Leukemia\ (2014)\ 28,\ 2244–2248}\)
    - **STAT5b** mutated cases are γδ
  - Enteropathy associated lymphoma, γδ type: **STAT5b** (36%)
Enteropathy Associated Lymphoma

- Only type 1 EATL, associated with celiac disease and having a pleomorphic cell morphology, will be designated as EATL.
- The monomorphic type will be called “monomorphic epitherliotropic intestinal T cell lymphoma” (MEITL).
  - Distinct phenotype: CD+, CD56+, MATK+
  - Gains in 8q24 → overexpressed MYC
  - Many are γδ type and STAT5b mutated
  - Poor prognosis
Monomorphic Epitheliotropic Intestinal T-cell Lymphoma” (MEITL)
Indolent T-cell Lymphomas / LPD

- Indolent T-cell LPD of GI tract Hematol Oncol. Matnani et al., 2017;35:3-1
  - Rare condition primarily affecting middle aged Caucasian males
  - Clinically: chronic diarrhea (when small intestine is involved) and weight loss
  - Most involve SI, but any part of GI tract and multifocal disease possible
  - Variably dense infiltrate of small, mature, monomorphic T-cells in lamina propria and rarely deeper to muscularis mucosa
  - CD4+, CD3+, CD5+, CD7-/+ , TCRαβ, CD30-, CD56-, CD103-, PD1-
  - Monoclonal by molecular studies
  - Persistent, but localized disease for 5-10 years despite aggressive chemotherapy.
  - Less than half progress and/or disseminate.
Diagnostic / Prognostic Refinements in Existing Conditions …

**Indolent T-cell Lymphomas/ LPD ..2**

- **Primary cutaneous CD4+ small/medium T-cell LPD**
  - Alberti-Violetti et al., J Cutan Pathol. 2016;43:1121-1130
  - A proliferation of Follicular helper T-cells of undetermined malignant potential
  - Solitary nodules (80-98%) on head and neck (50-75%)
  - Non-epidermotropic, pleomorphic, nodular or diffuse dermal infiltrate, varying in depth
  - T-cells are CD3+, CD4+, CD5+, PD1+, TCRαβ+, and monoclonal in 85% cases.
  - 20%-30% of infiltrate are B-cells, including some large cells.
  - B-cells are polyclonal and EBV negative.
  - Treated with excision or radiation, with low rate of relapse or progression
Diagnostic / Prognostic Refinements in Existing Conditions …

**Indolent T-cell Lymphomas/ LPD ..3**

- Primary cutaneous acral CD8+ T-cell lymphoma  
  Kluk et al., J Cutan Pathol. 2016 Feb;43(2):125-36
  - Slowly enlarging papulonodular solitary lesion in older adults of **clonal, cytotoxic T-cells**
  - Ear(s), nose, other acral sites (eyelid, feet, hands)
  - Pathology:
    - Dermal infiltrate, monomorphous, medium sized cells
    - Irregular, **blastoid nuclei** and small nucleoli
    - Low proliferation (<10%)
  - Immunophenotype:
    - CD8+, CD3+, TIA1+, CD5+-/-, CD7-/-+, CD30-, CD56-, Granzyme B-, EBER-, **CD68+** Br J Dermatol. 2015;172:1573-80
  - Clinical course: **Indolent, localized disease**
    - Some recurrent or multifocal lesions may be progressive
• Breast implant associated ALCL (iALCL)
  – Collection of seroma fluid around saline or silicone implant, after a median of 10 years
  – CD30+, CD8+, Alk- anaplastic T-cells
    • In the seroma fluid only : in situ iALCL
    • Infiltrate surrounding tissue : infiltratative iALCL
  – Removal of implant curative for in situ disease

Laurent et al., Ann Oncol. 2016 Feb;27(2):306-14
Other T-cell Lymphomas

• PTCL-NOS:
  – Prognostic groups based on overexpression of **GATA3** (seen in 33% cases), **TBX21** and cytotoxic genes. Iqbal et al., Blood. 2014;123:2915-23
  • Possible to use IHC to identify GATA3
  • Future prognostic subgroups / therapeutic targets
Other T-cell Lymphomas

- Nodal T-cell lymphoma with T-follicular helper phenotype*
  - An umbrella category including
    - Angioimmunoblastic T-cell lymphoma
    - Follicular T-cell lymphoma
    - PTCL with T-FH phenotype
      - *Expression of at least 2 or 3 TFH antigens: PD1, CD10, BCL6, CXCL13, ICOS, SAP, CCR5
    - Recurrent mutations in TET2, IDH2, DNMT3A, RHOA, and CD28
      - Possible therapeutic targets?
Other T-cell Lymphomas ..3

• Alk- ALCL
  – Gene expression profile closer to Alk+ ALCL than PTCL-NOS
  – Activating mutations of JAK1 and/or STAT3 or translocations producing chimeras of a transcription factor (NFκB2 or NCOR2) and a tyrosine kinase (ROS1 or TYK2)
    Crescenzo et al. Cancer Cell. 2015;27:516-32
    • Activate JAK/STAT pathway
    • Targets for therapy
  – Prognostic subgroups based on genetic rearrangements of DUSP22 and TP63
    Parrilla-Castellar, Blood. 2014;124:1473-80
Summary

• WHO 2016 “revision” of lymphoma classification has
  – New molecular information for diagnostic, prognostic and therapeutic purposes
  – Promotes several provisional entities to definite entities
  – Identifies new provisional entities of B- and T-cell lymphomas
  – Suggests a conservative approach to indolent lymphoid proliferations
  – Identifies prognostic subgroups of known entities and bundles some entities bases on cell of origin