The History of Lymphoma Classification and the 2017 Revision

ESMO Perceptorship on Lymphoma, Lugano 2018

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DISCLOSURE OF INTEREST

No Disclosures
Heterogeneity of Lymphoid Neoplasms
Updated 4th Edition of the WHO Classification

67 Subtypes of Mature Lymphoid Neoplasms
The Need for a Classification

- Classification is the “language” of medicine
  - Diseases must be described and defined before they can be diagnosed and treated

- Disease entities should be clearly defined and clinically distinctive

- Consensus on terminology and definitions
  - Essential for both clinical practice and research

Harris NL WHO classification
Lymphoma Classification: The History

The long & winding road

Building Consensus
(1994-2001)
The REAL Classification
The NHL Project

The Great Divide
(1975-1994)
Morphology vs Functional view

The Early Days
(<1975)
Morphology

Courtesy of S Swerdlow
Lymphoma Entities, Basic Discoveries, and Classifications


Entities & Discoveries
- HD
- FL
- Burkitt
- MM
- Sarcoma
- Sternberg
- Waldenström
- Macroglobulinemia
- Lymphosarcoma
- Reticulum Cell Sarcoma

Classifications
- American Registry
- Robb-Smith
- Gall & Mallory
- Rappaport
- Dorfman
- BLNI
- Lukes & Collins
- Kiel
- WHO

Immunology
Genetics

Effective Therapy
- Lymphocyte Transformation
- B - T cells
- Chromosomal Abnormalities
NIH Meeting in Airlie, VA (1975) of clinicians and Hematopathologists who had proposed classifications.

“No consensus”

Morphological Perspective

National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin’s Lymphomas
Summary and Description of a Working Formulation for Clinical Usage

Functional Perspective

Lukes, USA  Lennert, Kiel, Germany
The Kiel Classification: Lennert

Low grade malignant lymphoma, lymphocytic (CLL)
       agnogenic myeloid leukemia
       centrocytic
       centroblastic
       centroblastic
       non-lobular < follicular + diffuse
       diffuse

Grade 1
       lymphocytic
       Undefined
       B-type
       T-type
       non-lymphocytic
       other

Grade 2
       lymphocytic
       B-cell
       T-cell
       non-lymphocytic
       other
Kiel: Cellular Differentiation and Lymphoma Entity

Antigen

Plasma cell protective memory

memory cell reactive memory

Akute lymphatische Leukämie
Mantelzell Lymphom
Follikuläres Lymphom
Marginalzonen Lymphom
Plasmazell Myelom

Diffuses grosszelliges B-Zell Lymphom

ABC

GCB
Sir: The announcement in The Lancet of two more classifications of non-Hodgkin's lymphomas encourages me to put forward my classification of these classifications:

Well defined, high-grade oligosyllabic

Poorly differentiated, polysyllabic

<table>
<thead>
<tr>
<th>derivative</th>
</tr>
</thead>
<tbody>
<tr>
<td>neologistic</td>
</tr>
</tbody>
</table>

Unicentric

Multicentric, cycnophilic (Gk. κυκνός = swan)

Cleaved and convoluted types

<table>
<thead>
<tr>
<th>Rappaport (non-Lukes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lukes (non-Rappaport)</td>
</tr>
</tbody>
</table>

This system makes no claim to be comprehensive or even comprehensible, so there may well be scope for other classifications of classifications and ultimately, one hopes, a classification of classifications of classifications. At that point we shall need a conference in the Caribbean.

H. E. M. Kay
Building consensus for Lymphoma Classification

Precursors of the WHO Classification

“REAL” Classification (ILSG, 1994)

- List of Clinicopathologic Entities
- Cell lineage and Differentiation
- Morphological, Immunological, Genetic/Molecular and Clinical Information

PERSPECTIVE

A Revised European-American Classification of Lymphoid Neoplasms: A Proposal From the International Lymphoma Study Group


NHL Classification Project (1997)

- Panel of 5 pathologists and collaboration of pathologists and clinicians of 9 centers around the world

RAPID COMMUNICATION

A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin’s Lymphoma

By The Non-Hodgkin’s Lymphoma Classification Project
Individual evaluation of each case by experts in haematopathology
„Nohting new but Consensus…“ (on the Multihead Microscope)
WHO Classification: Hematologic Neoplasms

- **Kiel Classification (1974)**
  - Cytomorphologic definition of the entity according to the presumed cell of origin

- **REAL Classification (1994)**
  - List of clinico-pathologic entities
  - Principle of cell lineage and differentiation
  - Integration of morphologic, immunologic, genetic, molecular and clinical information

- **WHO Classification (2001)**
  - The first international consensus classification of hematologic tumors
    - SH, EAHP
    - Clinical Advisory Committee
Updated 4th Edition of the WHO Classification of ML
The Main Classification Principle of the WHO

Definition of the Entity

• Predominant cell type
  (Morphology and Immunology)

• Primary site of origin
WHO Classification Principles

Malignant Lymphomas as Disease Entities
- Non-overlapping (mutually exclusive)
- Stratified according to cell lineage
The Importance of Site in Diagnosis

DLBCL Topographic site

- Primary mediastinal
- Intravascular
- Primary CNS
- Primary cutaneous DLBCL, leg type
## Particular Genetic Traits in Distinct Subtypes and Variants

*Chapuy et al. Blood 2016*

<table>
<thead>
<tr>
<th>Genetic instability</th>
<th>DLBCL</th>
<th>PTL</th>
<th>EBV+PCNSL</th>
<th>PMBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN2A&lt;sup&gt;loss&lt;/sup&gt; bi-alleic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNAs of additional p53/cell cycle components</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CNAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genomic instability</td>
<td>All</td>
<td>ABC-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24% (43/180)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35% (19/55)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>88% (44/50)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>71% (15/21)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>0% (0/11)</td>
</tr>
<tr>
<td>19% (8/43)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26% (5/19)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77% (34/44)</td>
<td>73% (11/15)</td>
<td>0% (0/11)</td>
</tr>
<tr>
<td>multiple&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>high</td>
<td>high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>high</td>
<td></td>
<td>low</td>
</tr>
</tbody>
</table>

### Oncogenic TLR and BCR Signaling

| MYD88<sup>L265P</sup>                        |                |              |                  |               |
| NFKBI<sup>gain</sup>                         |                |              |                  |               |
| NFKBI<sup>gain</sup> and/or MYD88<sup>L265P</sup> |                |              |                  |               |
| CD79BY<sup>196mut</sup>                      |                |              |                  |               |
| Total                                         |                |              |                  |               |
| Concurrent with MYD88<sup>L265P</sup>         |                |              |                  |               |

| PD-1 Ligand Deregulation                      |                |              |                  |               |
| 9p24.1/PD-L1<sup>gain</sup> and/or PD-L2<sup>gain</sup> |                |              |                  |               |
| PD-L1 or PDL-2 translocation                 |                |              |                  |               |

- <sup>a</sup>
- <sup>b</sup>
- <sup>c</sup>
- <sup>d</sup>
- <sup>e</sup>
- <sup>f</sup>
- <sup>g</sup>
- <sup>h</sup>
- <sup>i</sup>
- <sup>j</sup>
- <sup>k</sup>
- <sup>l</sup>
- <sup>m</sup>
- <sup>n</sup>
WHO Classification - 2017 Update

- Refinement of Diagnostic criteria
  - Morphology
  - Phenotype
  - Clinical Criteria
  - Molecular
  - Infectious agents
- Early steps in lymphoid neoplasms
- Genetic Data in the Definition of Diseases
- Categories with overlapping features between entities
- Emerging Concepts of Personalized Medicine
Early Lesions of Malignant Lymphomas

Clonal Population

(Translocations, mutations)

Primary Genetic Alterations

Overt Lymphoid Neoplasia

mui

Secondary Genetic Alterations

Progression/Transformation

Microenvironment

Genetic alterations

Courtesy of Elias Campo
Early steps in Follicular and Mantle cell Lymphoma
“In Situ” and early involvement lesions

• In-situ follicular neoplasia
  – Incidental finding
  – Low incidence of progression (<5%)
  – Need to exclude systemic lymphoma

• Partial involvement by FL
  – Stages I and II
  – 50% progress to overt FL

• In-situ mantle cell neoplasia
• Mantle zone pattern of MCL
  – progress to overt MCL

Adam AJSP 2005, Carvajal-Cuenca Haematologica 2012
Jegalian Blood 2011 Mamessier Haematologica 2014

BCL2
Cyclin D1
Early Lesion

Indolent Variant/Disease
Indolent T-cell Lymphoproliferative Disorder of the GI Tract

Most common in small intestine and colon
Less often in stomach and oral mucosa

Very low proliferation rate
No destruction of the glands
No cytological atypia
CD8+

Optimal management?
Do not respond to chemorx

Perry et al. Blood 2013
Association to Infectious Agents as a Classification Principle

**EBV+ Lymphoid neoplasms**
- EBV + LBCL (previously of the elderly)
- Extranodal NK/T-cell lymphoma, nasal type
- Epstein-Barr virus (EBV) positive T-cell lymphoproliferative diseases of childhood

**HHV8+ associated lymphoid neoplasms**
- Primary effusion lymphoma
- HHV8 positive DLBCL, NOS

Clinical Relevance of Mutational Profiles in Lymphoid Neoplasms

- Diagnostic criteria to refine entities
- Identification of subsets of patients
- Prognostic and predictive significance
- Monitoring disease evolution: Dynamic evolution of mutational landscape
- Targets for therapy: Actionable mutations
## Diagnostic value of somatic mutations in mature small B-cell lymphoid neoplasms

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mutations Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hairy Cell Leukemia</td>
<td>BRAF V600E</td>
</tr>
<tr>
<td><em>HCL-v</em></td>
<td></td>
</tr>
<tr>
<td><em>HCLc IGHV4-34</em></td>
<td></td>
</tr>
<tr>
<td>Waldenström M/LPL</td>
<td>MYD88 L265P</td>
</tr>
<tr>
<td></td>
<td>79-100% HCL</td>
</tr>
<tr>
<td></td>
<td>4% Plasma cell myeloma</td>
</tr>
<tr>
<td></td>
<td>3% NHL (Other BRAF mut)</td>
</tr>
<tr>
<td></td>
<td>50% HCLv</td>
</tr>
<tr>
<td></td>
<td>50% HCLc IGHV4-34</td>
</tr>
<tr>
<td></td>
<td>0% HCL BRAFmut</td>
</tr>
<tr>
<td></td>
<td>90% WM</td>
</tr>
<tr>
<td></td>
<td>29% DLBCL-ABC</td>
</tr>
<tr>
<td></td>
<td>6% MZL</td>
</tr>
<tr>
<td></td>
<td>3% CLL</td>
</tr>
</tbody>
</table>

Molecular Definition of entities

ALK+ and ALK− - ALCL are Different Entities

Subset with DUSP22 R Comparable to ALK+

New Category: Burkitt-like Lymphoma with 11q Aberrations

- Children and young adults
- Frequently nodal presentation (15/18)
- Simple and 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

Pienkowska-Grela Med Oncol 2011
Salaverria Blood 2014
Ferreiro Haematologica 2015
Zajdel Tumour Biol 2015
Gene expression profiling allows reclassification of 14% of PTCL, NOS as AITL

Gene expression signatures of PTCL; Iqbal et al. *Blood* 2014
• Gene expression profiling and mutation analysis has helped to clarify the interrelationship among nodal T-cell lymphomas of TFH origin

- CD10
- CXCL13
- PD1
- ICOS
- BCL6
Gray Zone Lymphomas in the WHO Classification

- Recognition of biological and pathological continuum in certain entities
- Not a single criteria recognizes these categories
- Not specific entities, but working categories that need further studies
- Keep purity of well defined entities
- Challenging for clinical management. BL, HL and DLBCL protocols differ substantially
• Acceptance that, even if imperfect, IHC methods can be used for the diagnosis (Hans algorithm remains the most popular)
• Molecular methods for FFPE tissues on the horizon
Precision medicine on the Horizon in Lymphoma?

Precision medicine for DLBCL

- GCB type
  - BCL2, CREBBP, EZH2, B2M, TNFRSF14, MEF2B, KMT2D, MYC
- ABC type
  - CD79B, PIM1, PRDM1, IRF4, KMT2D, EP300, MYD88
- PMBL
  - STAT6, GNA13, SOCS1, CIITA, CD58, MFHAS1, ITPKB

Lymphopanel next-generation sequencing

Prognosis
- EZH2i
- HDACi
- BCL2i
- BTKi
- PIMi
- NF-κBi

Therapy
- JAKi
- STATi
- SINE

Lim-MS and Elenitoba-Johnson-KSJ, Clin Cancer Res 2016
The 2017 Update of the 4th Edition of the WHO Classification

- Refinement of definitions, diagnostic criteria and terminology
  - MBL variants, LPL, in situ Follicular and Mantle cell neoplasias. GI T cell lymphomas

- Come of age of Pediatric lymphomas
  - FL Pediatric type, IRF4 + LBCL

- Early and indolent lymphoproliferative disorders
  - In situ neoplasias, indolent LPD of the GI tract

- Relevance of phenotypic, genetic and molecular information for the identification of different entities
  - DLBCL GCB and ABC, Double-hit category, TFH derived T-cell lymphomas

- Relevance and clinical impact of NGS