The history of lymphoma classification, the WHO 2008, and beyond!!!

A journey from morphology to a multidisciplinary view

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Heterogeneity of Lymphoid Neoplasms
Lymphoma Pathogenesis
*Integrating genetic and microenvironment interactions*

- Genetic susceptibility
- Somatic Genetic Alterations
- Microenvironment Interactions
Relevance of a Precise Diagnosis

- Epidemiological characterization
- Distinctive pathogenesis
- Clinical manifestations and evolution of the disease
- Different therapeutic strategies (from wait and see to very aggressive or specific target therapies)
- Neoplasms potentially curable
- Therapeutic regimens with iatrogenic risk
Malignant Lymphomas as Disease Entities

- Non-overlapping (mutually exclusive)
- Stratified according to cell lineage
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 Dr S Swerdlow
Lymphoma Entities, Basic Discoveries, and Classifications

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

Entities & Discoveries
- HD
- FL
- Burkitt
- MM
- Sarcoma
- Sternberg
- Waldemström’s Macroglobulinemia
- Lymphosarcoma
- Reticulum Cell Sarcoma

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”

National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin’s Lymphomas

Summary and Description of a Working Formulation for Clinical Usage

The Non-Hodgkin’s Lymphoma Pathologic Classification Project

1982

Morphological Perspective

Functional Perspective

Lukes, USA

Lennert/Kiel

Malignant Lymphomas

Other Than Hodgkin’s Disease

Histology, Cytology, Ultrastructure, Immunology

K. Lennert

In collaboration with N. Mohr, H. Stein, E. Kaestler, H.K. Müller-Hermelink

Springer-Verlag Berlin Heidelberg New York
WHO Classification: Hematologic Neoplasms

• “REAL” Classification (ILSG, 1994)
  – List of Clinicopathologic Entities
  – Cell lineage and Differentiation
  – Integration of Morphological, Immunological, Genetic, Molecular and Clinical Information

• NHL Classification Project (1999)
  – University of Nebraska
  – Pathologists and Clinicians of 9 Centers around the world

• WHO Classification (2001/2008)
  – The first true international consensus
  – European Association for Haemathopathology Society of Hematopathology,
  – Clinical Advisory Committee
  – > 100 Authors
## Agreement Between Referral and Final Diagnosis

<table>
<thead>
<tr>
<th>Referral Diagnosis</th>
<th>Final Pathology Category</th>
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<tbody>
<tr>
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<td>Indolent N=304</td>
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<tr>
<td>Indolent*</td>
<td>296 (97%)</td>
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<tr>
<td>Follicular, any grade</td>
<td>1 (0.3%)</td>
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<tr>
<td>Diffuse large B-cell</td>
<td>1 (0.3%)</td>
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<tr>
<td>Mantle cell</td>
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<td>Highly Aggressive</td>
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<td>Other Cancer</td>
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</table>

* CLL/SLL, FL1-2, NMZL

LaCasce A et al J Clin Oncol 2008
Lymphomas as Malignant Counterparts of Specific Stages of Lymphocyte Maturation

WHO Classification - 2008 and beyond

- Diagnostic criteria
  - Morphology
  - Phenotype
  - Clinical Criteria
  - Molecular
  - Infectious agents
- Early steps in lymphoid neoplasms
- Categories with overlapping features between entities
- Introducing Precision Medicine
Follicular lymphoma
## Expert Pathologist Agreement With the Consensus Diagnosis

<table>
<thead>
<tr>
<th>Consensus Diagnosis</th>
<th>Dx 1 (%)</th>
<th>Dx 2 (%)</th>
<th>Dx2 (%) + Phenotype</th>
<th>Dx 3 (%)</th>
<th>Clinical Data</th>
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*NHL project, Blood 1997; 89: 3909-3918*
“Phenotype an numbers as diagnostic criteria”

**Chronic Lymphocytic Leukemia**

- Current definitions (> $5 \times 10^9$/L monoclonal lymphocytes with the CLL phenotype)

- SLL is the same disease but restricted to tissues of non-leukemic (< $5 \times 10^9$/L) patients without cytopenias

*WHO 2008*
Gene expression profiling and mutation analysis has helped to clarify the interrelationship among nodal T-cell lymphomas of TFH origin.
Gene expression profiling allowed reclassification of 14% of PTCL, NOS as AITL

Gene expression signatures of PTCL; Iqbal et al. *Blood* 2014
Clinical criteria in diagnosis

**DLBCL Topographic site**

- **Primary mediastinal**
- **Intravascular**
- **Primary CNS**
- **Primary cutaneous DLBCL, leg type**
Children and young adults
- Striking male predominance
- Nodal presentation, head and neck

- Grade 3, blastic
- No diffuse areas
- High proliferation rate

- Lack of t(14;18)

- Excellent prognosis
- Local therapy / Watch & wait recommended

“Large B-cell lymphoma with IRF4 rearrangement”

- New provisional entity segregated from other pediatric FL
- Waldeyer’s ring, head and neck nodal, bowel presentation
- Most commonly in children/young adults
- Follicular and diffuse areas with grade 3
- Germinal center phenotype (CD10/BCL6)
- BCL2 expression but no t(14;18)
- Strong IRF4 expression and IRF4 translocation
- Cases without the genetic alteration may be detected
- Treatment is often required

Molecular Definition of entities

ALK + and ALK – ALCL are Different Entities

• Acceptance (reluctantly) 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.
Lymphoma entities related to Infectious agents

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

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

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 MCL**
  - progress to overt FL

Jegalian AG et al Blood 2011
Mamessier E et al Haematologica 2014; 99: 802–810
Indolent T-cell Lymphoproliferative diseases of low malignant potential

Multiple mucosal polyps
Can affect entire GI Tract

Most common in:
- small intestine
- colon

Less often:
- stomach
- oral mucosa

Perry et al., Blood 2013, Indolent T-LPD of the GI Tract
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
Human Genome Project
Towards a personalized medicine
Diagnostic value of somatic mutations in mature small B-cell lymphoid neoplasms

Hairy Cell Leukemia

- BRAF V600E
- HCL-v
- HCLc IGHV4-34

79-100% HCL
- 4% Plasma cell myeloma
- 3% NHL (Other BRAF mut)

Waldenstrom M/LPL

- MAP2K1
- MYD88 L265P

50% HCLv
- 50% HCLc IGHV4-34
- 0% HCL BRAFmut

90% WM
- 29% DLBCL-ABC
- 6% MZL
- 3% CLL

Somatic Mutations and CNA in CLL and MBL (Whole genome/exome sequencing)

Puente X et al. Nature 2015
## Recurrently Mutated Pathways in Lymphoid Neoplasms

<table>
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<tr>
<th>Pathway</th>
<th>U-CLL</th>
<th>M-CLL</th>
<th>MCL</th>
<th>FL GCB</th>
<th>ABC</th>
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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
Clinical Advisory Meeting, March 31-April 1, 2014