Small B-cell lymphoma
WHO Classification 2016 update

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Small B-cell lymphomas

- Small cell size
- Low proliferation
- “Homing” growth patterns
- Immunomodulation by microenvironment
- Indolent clinical behavior
Heterogeneity of Small B-cell Lymphomas

Median: 10 years

Median: 9 years

Median: 3 years

CLL

FL

MCL

CLL

FL

MCL
Updating WHO classification
What's new in small B-cell lymphomas?

- Definitions, diagnostic criteria and terminology
- New defined entities and variants
- Provisional entities
- Relevance and clinical impact of NGS
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- Maintain current definitions ($\geq 5 \times 10^9/\text{L}$ monoclonal lymphocytes with the CLL phenotype)

- Extramedullary tissue involvement allow for lower number of atypical lymphocytes

- SLL is the same disease but restricted to tissues of non-leukemic ($< 5 \times 10^9/\text{L}$) patients without cytopenias
Monoclonal B-cell Lymphocytosis
Definitions and Subtypes

- Monoclonal B-cells < 5x 10⁹/L
- no lymphadenopathy, organomegaly, other extramedullary involvement, or any other feature of a B-lymphoproliferative disorder
- More than 3 months

CLL-like (70%)
- Atypical CLL* (15%) (CD20/IG bright, CD23-neg)
- Non-CLL* (15%)
  * Cytogenetic studies are recommended

Low-count MBL
- Low lymphocyte and B cell counts (usually < 0.5x 10⁹/L)
- Different IGHV/No stereotyped BCR
- Very low risk of progression (if any)
- No indication to monitor even if detected incidentally

Clinical MBL
- High lymphocyte and B cell counts (≥ 0.5x 10⁹/L)
- Lymphocytosis
- High risk cytogenetic alterations (5-9%)
- Annual progression requiring treatment 1-2%
- Clinical monitoring

Dagklis et al Blood 2009
Karube et al Sem Cancer Biol 2014
**Histological Progression in CLL**

*Clinical significance of proliferation centers*

- **Heterogeneous terminology:**
  - Accelerated CLL
  - Proliferation center-rich-CLL
  - Histologically Aggressive CLL

- **CLL with expanded proliferation centers**
  - Expanded / confluent proliferation centers
  - High proliferation (Ki67 >30%)
  - Del(11q) 25%, del(17p) 16%, t(14q) 31%

- **Histological criteria not standardized**

- **Survival intermediate between CLL and Richter transformation**

Gine E et al Haematologica 2010; 95:1526-33
Ciccone M et al Leukemia 2012 26:499-508
Falchi L et al Blood 2014; 123; 2783-90
Somatic Mutations and CNA in CLL and MBL (Whole genome/exome sequencing)
Clinical Impact of Somatic Mutations and Copy Number Alterations in CLL

Puente X et al Nature 2015
Lymphoplasmacytic Lymphoma

- Broader spectrum of cytological and architectural patterns
  - Diffuse architecture
  - Follicular colonization
  - Monotonous lymphoid population, minor “plasmacytic” morphology

- Polymorphic composition most probably other entities

- Recognition of anomalous phenotypes
  - CD10 + (3-16%), CD5+ (17%) IgD+, IgM

- IgM MGUS carries *MYD88* mutations in 47-87% 
  - Precursor of LPL/WM.

- Gamma heavy chain disease lacks *MYD88* L265P and is not considered LPL

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Somatic Mutations in Waldenstrom Macroglobulinemia /LPL

- **MYD88 L265P**
  - 95% WM/LPL
  - 29% DLBCL-ABC
  - 6% MZL
  - 3% CLL

- **CXCR4**
  - 25-35% WM/LPL
  - Associated with MYD88
  - More active disease
  - Less lymphadenopathy
  - More resistant disease to new drugs

- Usefulness in the differential diagnosis of LPL
- Other entities with plasmacytic differentiation are negative (e.g., gamma heavy chain disease).
- Need to be interpreted in the global context of the disease

References:
Early steps in Follicular Lymphoma

“In Situ” and early involvement lesions

- **t(14;18) in peripheral blood**
  - Detection require sensitive methods
  - Most do not progress but some evidences of FL precursor related with higher levels of these cells

- **“in situ” follicular “neoplasia”**
  - Incidental finding
  - Low incidence of progression (<5%)
  - Need to exclude systemic lymphoma
  - Associated with other lymphomas

- **Partial involvement by FL**
  - 50% progress to overt FL
  - Usually low stages (I/II)

*Mamessier E et al Haematologica 2014; 99: 802–810*
Follicular lymphoma grading

- Maintain current grading system 1-2, 3a and 3b

- Some cases do not fit well in classical definitions
  - Low morphological grade with high proliferation
  - FL « pediatric type »
  - FL with blastoid morphology

- FL grade 3B
  - Relation to GC-type DLBCL
  - Low frequency of t(14;18)
  - High IRF4 expression in some cases (3A/B, elderly, nodal, CD10 negative, high Ki67)

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4 Karube K et al Blood. 2007;109:3076-9
Different subtypes of t(14;18) negative FL

- **FL with conventional morphology**
  - 30% BCL2 protein positive
  - Lower GC expression signature (CD10 negative)
  - Higher proliferation
  - No clinical impact

- **Diffuse variant of FL**
  - Large nodal tumors in inguinal region
  - Localized disease
  - CD10, BCL2, BCL6, CD23 positive
  - Del 1p36

- **Primary extranodal FL** (e.g. cutaneous)

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1. Leich et al. Blood 2009;114:826-34
Pediatric Type Follicular Lymphoma

- 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

Louissaint A Jr et al Blood. 2012, 120:2395-404
Pediatric Type Follicular Lymphoma

Quintanilla-Martinez L et al Virchows Arch 2016
Pediatric Type Follicular Lymphoma

Quintanilla-Martinez L et al Virchows Arch 2016
Pediatric Type Follicular Lymphoma

Quintanilla-Martinez L et al Virchows Arch 2016
### Genetic alterations in Pediatric Type Follicular Lymphoma

<table>
<thead>
<tr>
<th>Genes</th>
<th>PTFL (n=42) (%)</th>
<th>t(14;18)-neg FL (%)</th>
<th>tt(14;18)-pos FL* (%)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>TNFRSF14</td>
<td>51</td>
<td>36</td>
<td>18-46</td>
<td>Ns</td>
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<tr>
<td>KMT2D</td>
<td>16</td>
<td>36</td>
<td>67-82</td>
<td>Ns</td>
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<tr>
<td>CREBBP</td>
<td>3</td>
<td>45</td>
<td>33-64</td>
<td>0.001</td>
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<tr>
<td>FOXO1</td>
<td>5</td>
<td>27</td>
<td>-</td>
<td>Ns</td>
</tr>
<tr>
<td>GNA13</td>
<td>11</td>
<td>0</td>
<td>-</td>
<td>Ns</td>
</tr>
<tr>
<td>EZH2</td>
<td>0</td>
<td>18</td>
<td>7-20</td>
<td>0.0049</td>
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</tbody>
</table>

Note: tt(14;18)-pos FL* indicates the presence of a specific translocation.

*Schmidt J et al Blood 2016*

**Genes**

<table>
<thead>
<tr>
<th>Genes</th>
<th>PTFL (n=24)</th>
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<tbody>
<tr>
<td>MAP2K1</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>MAPK1</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>RRAS</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

*Louissaint A et al Blood 2016*
New provisional entity segregated from other pediatric FL

Waldeyer’s ring, head and neck nodal, bowel presentation

Most commonly in children/young adults

Follicular, follicular & diffuse, or purely diffuse

Germinal center phenotype (CD10/BCL6)

BCL2 expression but no t(14;18)

BCL6 is expressed and frequently rearranged

Strong IRF4 expression and IRF4 translocation

Cases without the genetic alteration may be detected, but usually have IG rearranged

Treatment is often required

“Large B-cell lymphoma with IRF4 rearrangement”

“Large B-cell lymphoma with IRF4 rearrangement”

Quintanilla-Martinez L et al Virchows Arch 2016
**IG/IRF4 translocation-positive cases have a good prognosis**

Overall Survival vs. Overall Survival adjusted to age

- **IG/IRF4+**
  - (n=19, D=2)

- **IRF4-**
  - (n=324, D=114)

- **IG/IRF4+**
  - (n=19, D=2)

- **IRF4- <=60**
  - (n=178, D=34)

- **IRF4- >60**
  - (n=146, D=80)

*Salaverria et al Blood 2011*
Mantle cell lymphoma

**CCND1-negative variant**

**Classic MCL**

**CCND1 neg MCL**

**MCL**

**MCL CCND1-**

**SOX11**

**CCND1**

**SOX11**

**CCND2 trans 55%**

**CCND2 BAP**

**MCL CCND1- SOX11**

**Mozos et al Haematologica 2009**

**Salaverria et al Blood 2013**
MCL with Indolent Clinical Behavior

- Early stages of the disease
  - “In situ” Lesions and Mantle zone pattern
  - Low proliferation fraction
  - Early stage disease

- A distinctive variant of the disease?
Mantle cell lymphoma

*Indolent Variants*

* Clinical concept with different pathological conditions

- Low proliferation
- In situ MC neoplasia
- Mantle Zone MCL

- Incidental finding
- Low progression rate
- Associated with other lymphomas
- Frequent disseminated disease
- Better outcome in some studies

### Conventional MCL

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Pathology</th>
<th>Genetic</th>
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</thead>
<tbody>
<tr>
<td>Generalized Lymphadenopathy</td>
<td>Classic/Blastoid</td>
<td></td>
</tr>
<tr>
<td>Extranodal</td>
<td>CD5 positive</td>
<td></td>
</tr>
<tr>
<td>Leukemic expression</td>
<td>CD200 negative</td>
<td></td>
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<tr>
<td>ECOG &gt; 2 / High MIPI</td>
<td>IGHV unmutated</td>
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<tr>
<td>Need of treatment</td>
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</tr>
</tbody>
</table>

### Indolent “Leukemic non-nodal subtype MCL”

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Pathology</th>
<th>Genetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemic expression</td>
<td>Small cell</td>
<td></td>
</tr>
<tr>
<td>Non-nodal</td>
<td>CD5 negative (50%)</td>
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</tr>
<tr>
<td>Splenomegaly</td>
<td>CD200 positive</td>
<td></td>
</tr>
<tr>
<td>ECOG &lt; 2 / low MIPI</td>
<td>IGHV mutated</td>
<td></td>
</tr>
<tr>
<td>Delay Chemotherapy</td>
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</table>

Indolent Leukemic non-nodal subtype MCL

Indolent Conventional

LGALS3BP CSNK1E SOX11
KIAA1909 FARP1 PON2 CNN3 DBN1
HDGFRP3 CDK2AP1 HMGB3 SETMAR CNR1 RNGTT

iMCL cMCL

Cyclin D1 SOX11

Proposed model of molecular pathogenesis in MCL

Swerdlow et al. Blood 2016;127:2375-2390
Updating WHO classification
What’s new in B-cell lymphomas?

- Refinement of definitions, diagnostic criteria and terminology
  - MBL variants, LPL, Follicular and Mantle cell neoplasias

- Inclusion of new defined entities and variants
  - FL t(14;18) negative, MCL variants

- Provisional entities: Updates and open questions
  - FL Pediatric type, IRF4 + LBCL,

- Relevance and clinical impact of NGS
Clinical Advisory Meeting, March 31-April 1, 2014