Pathology of the indolent B-cell lymphomas

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Small B-cell lymphomas

- NAIVE -B LYMPHOCYTE
- FL
- LPL
- MZL
- MCL
- CLL

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

- **CLL**: Median: 10 years
- **FL**: Median: 9 years
- **MCL**: Median: 3-5 years
Lymphoid Cell Circulation and Lymphoid Tissue Compartment

Key elements in Small B-cell lymphomas

CLL  LPL  MCL  FL  MZL
Transformation in Small B-Cell Lymphomas

Microenvironment

Primary Genetic Events → Small B-cell neoplasms → Transforming Genetic Events → DLBC

Genetic alterations
Chronic lymphocytic leukaemia

- Presence of $\geq 5 \times 10^9$/L monoclonal lymphocytes with the CLL phenotype

- SLL is the same disease but restricted to tissues without evidence of leukemic involvement
Disease progression in CLL

Clonal B-cell selection and expansion

MBL  CLL  Progressed Refractory CLL

DLBCL: diffuse large B-cell lymphoma; MBL: monoclonal B-cell lymphocytosis
Chronic lymphocytic leukaemia
Clinical impact of molecular and genetic subtypes

Consecutive series of 308 patients with previously untreated CLL

**del(17p)/TP53 mutations significantly reduce time to chemotherapy-refractory disease**

- **TP53 mutation**
  - Median 6.3 months
  - Median 72.7 months

- **del(17p)**
  - Median 21.4 months
  - Median 66.3 months

**p<0.001**
**p=0.002**

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Follicular Lymphoma

- Usually follicles of similar size/shape but some variation may occur
- Cytologically monotonous with cleaved nuclei and no tingible body macrophages
- Polarization of normal follicles absent
### WHO classification: Grading in FL

<table>
<thead>
<tr>
<th>Grade</th>
<th>Centroblasts/high power field</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤5</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>6–15</td>
<td>–</td>
</tr>
<tr>
<td>3A</td>
<td>&gt;15</td>
<td>Centroblasts with intermingled centrocytes</td>
</tr>
<tr>
<td>3B</td>
<td>&gt;15</td>
<td>Pure sheets of blasts</td>
</tr>
</tbody>
</table>

**Grade 1**

**Grade 2**

**Grade 3a**

**Grade 3b**

WHO: World Health Organization
Diffuse component in FL
Follicular Lymphoma: A single disease? *FL subtypes*

- Follicular lymphoma, pediatric type
- Primary duodenal follicular lymphoma
- Primary cutaneous follicular centre lymphoma
- Diffuse variant of follicular lymphoma
- Follicular lymphoma negative for the t(14;18)

*Xerri L et al Virchows Arch. 2016;468:127-39
Quintanilla-Martinez L et al Virchows Arch. 2016;468:141-57*
Different subtypes of t(14;18) negative FL

- **FL with conventional morphology**¹
  - 30% BCL2 protein positive
  - Lower GC expression signature (CD10 negative)
  - Higher proliferation
  - No clinical impact

- **Diffuse variant of FL**²
  - Large nodal tumors in inguinal region
  - Localized disease
  - CD10, BCL2, BCL6, CD23 positive
  - Del 1p36

¹ Leich et al. Blood 2009;114:826-34
² Katzeberger T et al Blood 2009;113:1053-61
Extra Nodal MZL: Morphology
Extra Nodal MZL: Etiological Factors

Chronic Inflammatory Response

- Stomach: H pylori
- Ocular: Chlamydia Psittaci
- Salivary Gland: Sjogren’s
- Thyroid: Hashimoto’s
- Skin: Borrelia
- Other: ?
- HCV?

Genetic and environmental background

- Polymorphisms
- Thymic MZL: Asians
Nodal Marginal Zone Lymphoma

NMZL resembles extranodal or splenic MZL but is only localized in lymph nodes

Adults median age 60, M=F

Need to rule out extranodal site

Hepatitis C virus?

Tri 3, 18, 7
Mutations in KLF2, NOTCH2, PTPRD

50-60% have 5 year survival
Lymphoplasmacytic Lymphoma

- **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

- **BTK**
  - Patients treated with Ibrutininb
  - Mutations before clinical progression

- **Useful information in the differential diagnosis of LPL**
- **Need to be interpreted in the global context of the disease**

Mantle Cell Lymphoma

- Complete Response: 25% (6-50%)
- Duration of CR: 1.5 yrs (0.5-2.5 yrs)
- Median Survival: 3-4 years

ICH/CCND1

Cyclin D1

ICH/CCND1

14 der(14) 11 der(11)
Mantle cell lymphoma
CCND1-negative variant

Classic MCL

CCND1 neg MCL  Cyclin D1  Sox11

CCND2 trans 55%

Mozos et al Haematologica 2009
Salaverria et al Blood 2013
Mantle cell lymphoma
Indolent Variants

- Clinical concept with different pathological conditions
  - In situ MC neoplasia, Mantle zone pattern, low proliferation index (SOX11+ or SO11-)
  - Leukemic non-nodal subtype of MCL
    - Non-nodal leukemic (splenomegaly) disease
    - SOX11-negative
    - Hypermutated IGHV
    - Simple karyotypes
    - May transform into blastoid MCL (TP53 mut)

Molecular Pathogenesis and Clinical Subtypes of MCL

- Sox11-
  - Non-nodal, leukemic and splenic MCL
  - TLR2
  - Blastoid MCL

- Sox11+
  - Classic MCL
  - Blastoid MCL
  - ATM, NOTCH1/2, WHSC1, MLL2, MEF2B

- “In situ” MCL lesion
- Genetically stable

- Pre B-Cell
- t(11;14)
- Cyclin D1 Neg
- Naïve B-cell

- Hyperrmutated IG
  - Unmutated/Minimally Mutated IG

Fernandez V et al Cancer Res 2010

Genomic Instability, Proliferation, and cell survival
Small B-cell Lymphomas

- A heterogeneous group of lymphoid neoplasms with different clinico-pathological characteristics
- Increasing recognition of early or “in situ” lesions (Multi-step pathogenesis in NHL)
- Specific variants in each disease with particular clinical and pathologic characteristics