Pathology of the indolent B-cell lymphomas

Elias Campo
Hospital Clinic, University of Barcelona
Small B-cell lymphomas

- 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
Transformation in Small B-Cell Lymphomas

Primary Genetic Events → Small B-cell neoplasms → DLBC

Genetic alterations

Microenvironment
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

- **MBL**
- **CLL**
- **Progressed Refractory CLL**
- **DLBCL**
- **Richter syndrome**

Clonal B-cell selection and expansion

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

Mutated $IGHV$\(^1\)

- Mutated IGHV
- Unmutated IGHV

$p<0.001$

Patients surviving (%)

Months

17p deletion
11q deletion
12q trisomy
Normal
13q deletion as sole abnormality

Patients surviving (%)

Months

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

Consecutive series of 308 patients with previously untreated CLL


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**Graphs:**

- **TP53 mutation**
  - Median 6.3 months (p<0.001)
  - Median 72.7 months

- **del(17p)**
  - Median 21.4 months (p=0.002)
  - Median 66.3 months

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**Key Points:**

- TP53 mutations significantly reduce time to chemotherapy-refractory disease.
- Median time to chemotherapy-refractory disease among patients with TP53 mutations is 6.3 months, compared to 72.7 months for patients without TP53 mutations.
- Median time to chemotherapy-refractory disease among patients with del(17p) is 21.4 months, compared to 66.3 months for patients without del(17p).
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

![Image of follicular lymphoma histology with CD20, CD3, CD10, and Bcl-2 markers]
### 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>
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<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](image1)  ![Grade 2](image2)  ![Grade 3a](image3)  ![Grade 3b](image4)

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**
  - 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

1 Leich et al. Blood 2009;114:826-34
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
Tumor Site, Etiology, and Tumor Progression in MALT Lymphomas

- Normal Cell
  - Oligoclonal Expansion
    - MALT Lymphoma
      - HP dependent
        - MALT Lymphoma
          - HP independent
            - Transformation
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

50-60% have 5 year survival
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

- Useful information 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

Mantle Cell Lymphoma

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

14 der(14) 11 der(11)

Cyclin D1

IGH/CCND1

Complete Response: 25% (6-50%)
Duration of CR: 1.5 yrs (0.5-2.5 yrs)
Median Survival: 3-4 years
Mantle cell lymphoma
CCND1-negative variant

CCND2 trans 55%

Classic MCL

CCND1 neg MCL

Cyclin D1

Sox11

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

- Hyperrmutated IG SOX11-
- Non-nodal, leukemic and splenic MCL
- Genetically stable
- "In situ" MCL lesion
- Sox11-
- Blastoid MCL
- Genomic Instability, Proliferation, and cell survival
- Classic MCL
- Sox11+ Unmutated/Minimally Mutated IG
- TP53 Inactivation
- ATM, NOTCH1/2, WHSC1, MLL2, MEF2B
- Pre B-Cell
- t(11;14)
- Cyclin D1 Neg
- Naïve B-cell

Fernandez V et al Cancer Res 2010
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