2008 WHO Classification of Lymphoid Neoplasms: Small B-Cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukemia, unclassifiable
  - Splenic diffuse red-pulp small B-cell lymphoma
  - Hairy cell leukemia-variant
- Nodal marginal zone lymphoma
- Lymphoplasmacytic lymphoma
  - Waldenstrom macroglobulinemia
- Mantle cell lymphoma
- Follicular lymphoma

B-cell Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- Diffuse B-cell lymphoma with morphologic features of small, mature lymphocytes admixed with prolymphocytes and paraimmunoblasts
- Arbitrary distinction between lymphoma and leukemia
- >5,000/mm³ for at least 3 months, unless patient has cytopenias or symptoms
- Low grade in Working Formulation
- 10% of non-Hodgkin’s lymphomas in biopsies; higher in Hematology clinics
Monoclonal B-Cell Lymphocytosis

- Defined as < 5 x 10^9 cells/L, with no tissue involvement
- Same phenotype as CLL
- 3-5% in general population over 50 years
- 5% progress to CLL overall; about 1% per year
- Possesses 13q deletion in 50% of cases, similar to CLL
- Has mutated Ig gene repertoire that differs from CLL

CLL/SLL: Architecture

- Effacement of architecture or, more rarely, interfollicular
- Pseudofollicular pattern (proliferation centers)
CLL/SLL: Cytology

- Small lymphocytes:
  - May be same size or slightly larger than normal lymphocytes
  - Round nuclei, mature clumped chromatin, and inconspicuous nucleoli
  - Can show some atypia or plasmacytoid features
- Prolymphocytes:
  - Slightly larger but look similar
- Paraimmunoblasts:
  - Larger cells with dispersed chromatin, and central eosinophilic nucleoli and more abundant cytoplasm
- Reed-Sternberg-like cells (very rare)
CLL/SLL: Immunophenotype and Gene Rearrangement Studies

- CD20 and other B lineage markers
- CD43, CD5, and CD23+ in 95%
- CD10, FMC-7, CD79b-
- ZAP-70, CD38+ in a subset (correlates with non-mutator)
- Clonal Ig gene rearrangements
- 40-50% of cases non-mutated (poorer prognosis and 50-60% with somatic hypermutation)
**CLL/SLL: Molecular Cytogenetics**

- **80% show clonal aberrations**
  - Deletions at 13q (50%) (good prognosis)
  - Deletions at 11q22-23 (20%) (aggressive)
  - Trisomy 12 (20%) (aggressive)
  - Deletions at 17p13 (10%) (aggressive)
  - Deletions at 6q21 (5%) (aggressive)
- **20% show normal cytogenetics**

**CLL/SLL: Progression**

- **General increase in paraimmunoblasts over time—not progression**
- **Prolymphocytoid progression occurs in about 15% (CD5 +)**
- **Progression to DLBCL occurs in about 5%**
  - Architectural effacement seen
  - Usually CD5 -
  - Usually clonal related (unmutated)
  - May be clonally unrelated, usually occurring in mutated cases
  - Poor survival (median 1 year)
- **Progression to classical HL occurs in <1% (usually EBV+, occurring in mutated cases)**
- **Paraimmunoblastic progression occurs in <1% (CD5 +)**
- **Fludarabine-related EBV + DLBCL may occur in <1%**
B-Cell Prolymphocytic Leukemia

- Neoplasm of B prolymphocytes affecting blood, bone marrow, spleen, and occasionally other tissues
- Prolymphocytes must exceed 55% of lymphoid cells in the peripheral blood
- Aggressive neoplasm
- Cases of transformed CLL excluded
- Cases with t(11;14) excluded
- Extremely rare

B-Cell PLL: Morphology

- Blood: Medium-sized cell (2x normal lymphocyte), round nucleus, with moderately condensed chromatin, prominent central nucleolus, and small amount of faintly basophilic cytoplasm
- Bone marrow: Interstitial or nodular inter trabecular infiltrate
- Spleen: Expanded white and red pulp
- Lymph node: Diffuse or vaguely nodular infiltrates without pseudofollicles
B-Cell PLL: Phenotype

- CD20 and other pan-B cell antigens
- CD43 + in majority
- CD5 + in 25%
- CD23 + in 10-20%
- ZAP-70 + in 50%

B-Cell PLL: Molecular

- Clonal Ig rearrangements
- Unmutated in 50%
- Complex karyotypes
- Deletion of 17p in 50% (associated with p53 gene mutations)
- 13q deletions in 25%
- By definition, no t(11;14)

Splenic B-Cell MZL: Histology

- Surrounds and replaces the splenic white pulp germinal centers, effaces the follicle mantle and merges with a peripheral zone of larger cells
- Infiltrates the red pulp
- Small cells dominate centrally, merging with a peripheral zone of small to medium-sized cells with more dispersed chromatin and abundant pale cytoplasm, which resemble marginal zone cells and interspersed transformed cells
- Plasmacytic differentiation may be occasionally seen
Splenic B-Cell MZL: Immunophenotype and Molecular

- CD20 and pan-B-cell antigen +
- IgM and often IgD +
- CD5, CD10, CD23, CD43, bcl-6, cyclin D1 –
- CD103 usually negative
- Clonal Ig gene rearrangements, with somatic hypermutations seen in 50%
- Loss of 7q31-32 in 40%
- Trisomy 3q in some cases

Hairy Cell Leukemia

- Neoplasm of small B lymphoid cells with oval nuclei and abundant cytoplasm with “hairy” projections in bone marrow and peripheral blood, diffusely infiltrating bone marrow and splenic red pulp
- Patients are usually middle-aged to elderly adults with median age of 55 years and 5:1 M:F ratio
- Tumor infiltrates may also occur in liver, lymph nodes, and skin
- Tumor cells are TRAP positive
- Express CD20 and other pan-B cell markers, CD103, CD25, CD123, DBA.44, annexin A1, and CD11c
- Cyclin D1 stains a subset of the cells
Hairy Cell Leukemia-Variant (HCL-v)

- B-chronic lymphoproliferative disorder that architecturally resembles classic HCL but exhibits variant hematologic and/or cytologic features
- Variant hematologic features include leukocytosis and monocytosis
- Variant cytologic features include prominent nucleoli, blastic or convoluted nuclei, or lack of hairy projections
- TRAP -, CD25 -, annexin A1 -
- Poor prognosis to HCL therapy
Splenic Diffuse Red Pulp Small B-Cell Lymphoma

- Uncommon lymphoma with a diffuse pattern of involvement of the splenic red pulp (cords and sinusoids) by small monomorphous B-lymphocytes
- Also involves bone marrow sinusoids, commonly with a villous morphology
- DBA.44 +, IgG +, IgD –
- Must exclude all other known lymphomas involving the spleen
- May be overlap with hairy cell leukemia-variant
Nodal Marginal Zone B-cell Lymphoma

- Primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by marginal zone lymphoma of extranodal or splenic type, but without evidence of extranodal or splenic disease.
- Cases with involvement of extranodal sites (1/3), Hashimoto thyroiditis or Sjögren syndrome should be considered to have nodal involvement by MALT lymphoma.
- Involves peripheral lymph nodes, and occasionally bone marrow and peripheral blood.
- About 2% of lymphomas.
- May be associated with hepatitis C.

Nodal MZBL: Histology

- Infiltration around reactive follicles and extending into interfollicular areas.
- May see follicular colonization or remnants of follicles.
- Varying numbers of centrocyte/monocytoid-like lymphoid cells, plasma cells, and scattered transformed cells.
- Plasma cells may dominate.
- May be many transformed cells, but not patternless sheets, which indicates transformation to diffuse large B-cell lymphoma.
Nodal MZBL: Phenotype and Molecular

- CD20 and other pan-B antigens +
- CD43+ in 50%; bcl-2 in 80%
- CD5, CD10, CD23, bcl-6, cyclin D1 -
- Clonal Ig rearrangements
- Not associated with translocations found in MALTomas but may have trisomy 3, 7, 18
Pediatric MZBCL

- Rare; 20:1 M:F ratio
- Usually confined to head and neck lymph nodes
- Often show PGTC
- BCL-2 in only 40%; CD43 coexpression in 70%
- Needs to be distinguished from atypical marginal zone hyperplasia found in tonsil or appendix (monotypic lambda but polyclonal)

Lymphoplasmacytic Lymphoma

- Neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells
- Usually involves bone marrow, and sometimes lymph nodes and spleen
- Usually associated with Waldenstrom macroglobulinemia (IgM monoclonal gammopathy with bone marrow involvement by LPL)
- Many cases may be associated with hepatitis C infection (particularly in Italy); some cases familial
- Rare; must be differentiated from plasmacytoid variants of extranodal or nodal marginal zone lymphoma and chronic lymphocytic leukemia

Lymphoplasmacytic Lymphoma: Histology

- Diffuse or interfollicular proliferation
- No proliferation centers
- Population of small lymphocytes, plasmacytoid lymphocytes, and plasma cells
- No monocytoid cells (think marginal zone lymphoma)
- May see Dutcher bodies
- May see scattered large transformed cells
- May see scattered mast cells, epithelioid histiocytes
- May see PAS + material, amyloid, or crystal-storing histiocytes
Lymphoplasmacytic Lymphoma: Immunophenotype and Molecular

- CD20 and other pan-B antigen +, but may be - in a subset
- Cytoplasmic Ig; usually IgM, sometimes IgG, rarely IgA
- CD10, bcl-6, CD23 –; CD5 -/+  
- CD138, CD38+/-, but may be in a subset
- t(9;14) rarely found (despite initial studies)
- No distinctive molecular markers
Lymphomas with Plasmacytic Features

- Lymphoplasmacytic
- CLL/SLL
- MALT lymphoma
- Nodal marginal zone lymphoma
- Follicular lymphoma
- DLBCL
- Plasmablastic lymphoma
Mantle Cell Lymphoma
- B-cell neoplasm composed of monomorphic small to medium-sized lymphoid cells with irregular nuclear contours
- Well-defined clinicopathological and genotypic entity
- Usually involves lymph nodes, but may be seen in spleen, bone marrow, blood, gastrointestinal tract (e.g., lymphomatous polyposis), and Waldeyer ring
- Clinical: Median survival of 3-5 years; not curable in most cases
- About 5% of non-Hodgkin lymphomas
- Indolent variant: Patients present with high WBC, splenic involvement, and less LN involvement

Mantle Cell Lymphoma: Architecture
- Mantle cell: May be restricted to inner mantle zone, narrow mantles, or, more commonly, expanded mantles, with retained germinal centers
- Follicular: Proliferation extends to obliterate central reactive germinal center
- Vaguely nodular: Hard to see pre-existent germinal centers
- Diffuse: Most common
**Mantle Cell Lymphoma: Cytology**

- Monomorphous population of small to medium-sized lymphoid cells
  - Slightly irregular nuclear contours
  - Relatively mature chromatin
  - Inconspicuous nucleoli
- No admixed larger lymphoid cells
- May see scattered epithelioid histiocytes

**Mantle Cell Lymphoma: Cytologic Variants**

- Other variants
  - Mimicking small lymphocytic lymphoma
  - Mimicking marginal zone B-cell lymphoma
- Blastic
  - Classic: Resembles lymphoblastic lymphoma; 2-3 mitoses/HPF
  - Pleomorphic: Resembles large cell lymphoma
Mantle Cell Lymphoma: Immunophenotype

- CD20 and pan-B antigen +
- Cyclin D1+ in 95%, SOX-11+ in 100%
- CD5+ in 90%; CD43+ in 80%; FMC-7 +/-
- CD10 -, Bcl-6 -, CD23 -/+ 
- IgM + IgD, with 1:1 K:L ratio
- Cases negative for cyclin D1 are usually positive for cyclin D2 or cyclin D3
- Ki-67 and p53 may be useful in identifying blastic variants
Mantle Cell Lymphoma: Molecular Genetics

- t(11;14) found in >95% of cases, translocating cyclin D1 to the immunoglobulin heavy chain gene
- Rare cases lacking t(11;14) may have translocations involving cyclin D2
- Other non-random secondary gross cytogenetic changes and/or specific gene mutations are frequently seen
  - ATM gene
  - p53 gene

### Differential Diagnosis of Small Lymphocytic Lymphoproliferations

<table>
<thead>
<tr>
<th></th>
<th>CLL/ SLL</th>
<th>Lymphoplasmacytic</th>
<th>Marg</th>
<th>Follic</th>
<th>Mantle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ig</td>
<td>98%</td>
<td>98%</td>
<td>98%</td>
<td>90%</td>
<td>98%</td>
</tr>
<tr>
<td>Heavy</td>
<td>IgM + IgD</td>
<td>IgM</td>
<td>IgM, D, A</td>
<td>IgM, G</td>
<td>IgM + IgD</td>
</tr>
<tr>
<td>K:L</td>
<td>2:1</td>
<td>2:1</td>
<td>2:1</td>
<td>2:1</td>
<td>1:1</td>
</tr>
<tr>
<td>CD20</td>
<td>99%</td>
<td>98%</td>
<td>98%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>CD43</td>
<td>98%</td>
<td>60%</td>
<td>50%</td>
<td>2%</td>
<td>80%</td>
</tr>
<tr>
<td>CD5</td>
<td>96%</td>
<td>25%</td>
<td>10%</td>
<td>1%</td>
<td>90%</td>
</tr>
<tr>
<td>CD10</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>95%</td>
<td>1%</td>
</tr>
<tr>
<td>CD23</td>
<td>90%</td>
<td>10%</td>
<td>5%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
<td>95%</td>
</tr>
</tbody>
</table>