**SMALL B-CELL LYMPHOMAS**

**Follicular Lymphoma (FL)**

- **B-cell neoplasm composed of follicular center (germinal center) B cells**
- **Second most common lymphoma (after DLBCL) in western countries, affects primarily middle aged to older adults**
- Primarily a lymph node disease, but also occurs in extranodal sites (see variant types below)
- Slow growing with wide spread disease at presentation, mostly high stage, usually asymptomatic

**Morphology:** Follicular growth pattern in majority cases, diffuse pattern in rare cases

**Five key morphologic features** of neoplastic follicles: uniform size, back-to-back, attenuated or loss of mantle zone, no tingible body macrophages, no polarization

**Cytology:** Two types of neoplastic cells are present in variable proportions: centrocytes (small cleaved cells) and centroblasts (large noncleaved cells)

**Grading:** Based on the number of centroblasts + number of mitosis in 40X field

- **Low grade:** grade 1 and 2 (<15 centroblasts per high power field)
- **High grade (two types):** grade 3a (>15 centroblasts per high power field but centrocytes are also present), grade 3b (all cells are centroblasts, no or very few centrocytes)

**Blood and bone marrow:** Blood involvement uncommon

**Bone marrow involvement common (40-70%),** with characteristic paratrabecular location

**Phenotype:** CD19+, CD20+, CD22+, BCL2++, CD10+, BCL6+, clonal kappa or lambda

**BCL2:** positive in nearly all low grade FL and in about 70% high grade FL

- **Expression of BCL-2** (by immunohistochemistry) in follicular B cells confirms lymphoma
- **Ki-67 index:** useful for grading and generally correlates with grade. However, cases of low grade FL with high Ki-67 are present

**Genetics:** Hallmark of FL: t(14;18)(q32;q21) involving BCL2 and IGH genes, present in nearly all low grade FL, but absent in about 30% high grade FL

**Function of BCL2:** A pro-survival, anti-apoptotic protein that is downregulated in normal germinal center and overexpressed in follicular lymphoma. The protein regulates cell survival and cell death with other BCL2 family proteins (pro-survival proteins, pro-death proteins, BH3 proteins)

**Prognosis:** Low grade FL has a median survival >12 years.

**Treatment:** Low grade: observe or single agent. High grade: combination chemotherapy

**Variants:**

- **In situ follicular lymphoma:** Only some follicles are neoplastic (reactive follicles coexist), precursor of full blown FL
- **Duodenal follicular lymphoma:** Restricted to duodenal mucosa, usually low grade, rarely spreads out of intestine, very indolent
- **Testicular follicular lymphoma:** Restricted to testicle, do not spread
- **Primary cutaneous follicular lymphoma:** Involves upper body, mostly head and neck, may lack follicular pattern, CD10 and BCL-2 often negative, indolent without distant spread (discussed in more detail in lesson 11)
- **Pediatric type follicular lymphoma:** Primarily in children, sporadic in adult, isolated peripheral lymphadenopathy, irregularly-shaped, reactive-appearing follicles with tingible body macrophages, intermediate-sized “blastoid” type cells predominant, lack of t(14;18)
Large B-cell lymphoma (diffuse or follicular) with IRF4: typically affects Waldeyer’s ring, FL grade 3B or DLBCL morphology, MUM-1/IRF4 positive by immunohistochemistry, IFR4-IGH rearrangement, no t(14;18)

Diffuse follicular lymphoma with deletion 1p36: typically affects inguinal region, local disease, usually do not spread, predominantly diffuse histologic pattern, 1p36 deletion, no t(14;18)

Types of follicular lymphoma

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Grade</th>
<th>BCL-2 expression</th>
<th>BCL-2 translocation</th>
<th>CD10</th>
<th>Genomic</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic FL</td>
<td>Follicular</td>
<td>Low or high</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Duodenal FL</td>
<td>Follicular</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Testicular FL</td>
<td>Follicular</td>
<td>High</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>t(14;18)</td>
</tr>
<tr>
<td>Cutaneous FL</td>
<td>Follicular or diffuse</td>
<td>Low or high</td>
<td>No</td>
<td>No</td>
<td>Usually No</td>
<td>None</td>
</tr>
<tr>
<td>Pediatric FL</td>
<td>Follicular, reactive-like</td>
<td>High (medium size, blastoid)</td>
<td>No or weak+</td>
<td>No</td>
<td>Yes</td>
<td>1p36 del frequent</td>
</tr>
<tr>
<td>FL with IRF4</td>
<td>Follicular and/or diffuse</td>
<td>High</td>
<td>2/3 +</td>
<td>No</td>
<td>2/3 +</td>
<td>IRF4-IGH</td>
</tr>
<tr>
<td>FL with 1p36</td>
<td>Diffuse</td>
<td>Low or high</td>
<td>No or weak</td>
<td>No</td>
<td>Yes</td>
<td>1p36 del</td>
</tr>
</tbody>
</table>

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

An indolent CD5+ B-cell leukemia/lymphoma typically affects blood, bone marrow, and lymph nodes

**CLL:** ≥ 5000x10⁶/L monoclonal lymphocytes in blood

**MBL:** < 5000x10⁶/L monoclonal lymphocytes classified as monoclonal B-lymphocytosis

**SLL:** Lymph node or tissue involvement of neoplastic cells indistinguishable from CLL cells

Most common leukemia in adults >60 years, male to female ratio 2:1

Primarily affects Whites and Blacks, uncommon in Asians

Lymphadenopathy (SLL) (65%), splenomegaly (40%), hepatomegaly (25%)

MBL is considered as precursor of CLL which may or may not progress to CLL

Clinically asymptomatic or weakness, fatigue, weight loss, fever, chills. Mild to severe hemolytic anemia in 10-15% cases (caused by autoantibodies produced by CLL)

**Morbidity:** Blood: monomorphic small mature lymphocytes with small round nuclei, mature clump chromatin (“soccer ball pattern”), and scant to nearly invisible cytoplasm, smudge cells common

**Bone marrow:** various patterns of involvement: nodular, interstitial, diffuse, mixed

**Small lymphocytic lymphoma (SLL):** Lymph node or extranodal tissue involvement.

Completely effaced nodal architecture, diffuse infiltrate of small mature lymphocytes, variable numbers of pale nodules (proliferation centers composed of prolymphocytes)

**Prolymphocytic transformation: in CLL:** if prolymphocytes >55% of neoplastic lymphocytes in blood

**In SLL:** if proliferation centers are coalescent and diffuse
Phenotype: monoclonal kappa or lambda, express all B-cell markers (usually low intensity), CD5+, CD23+, LEF1+ (most specific)

Genetics and Prognosis: FISH markers: deletion 17p (worst), deletion 11q (worse), trisomy 12 (neutral), deletion 13q (better)

Immunoglobulin gene hypermutation: unmutated (worse), mutated (better)

Flow markers: Worse prognosis: ZAP70+, CD38+, CD49d+
Better prognosis: ZAP70-, CD38-, CD49d-

Treatment and Survival: Overall survival >10 years. Symptomatic or positive deletion 17p require treatment. Typically treated with rituximab or other single agents. Immune modulatory medication for hemolytic anemia

Transformation: Large cell transformation (Richter’s transformation): aggressive course
Prolymphocytic transformation: outcome intermediate between CLL and Richter’s

Mantle Cell Lymphoma (MCL)

An aggressive B-cell lymphoma with small to medium sized neoplastic lymphocytes driven by cyclin D1 or other members of cyclin D family
Usually high stage disease (III and VI) at presentation
Middle to older aged men most common, male predominance (male to female ratio >2:1)
Lymph node involvement most common, other sites include spleen, GI, Waldeyer’s ring, lung, pleura, bone marrow (>50% cases), blood involvement uncommon (see below)

Morphology: Three morphologic patterns: mantle zone, nodular, diffuse (represents disease course)

Cell morphology: Common type: Small to medium sized nuclei, nuclear irregularity (in contrast to SLL), disperse chromatin, inconspicuous nucleoli. Mitotic figures always present, histiocytes usually present, transformed large cells absent
Blastoid variant: Larger nuclei, more dispersed chromatin resembling blasts, clinically more aggressive
Pleomorphic variant: Cells are more pleomorphic, clinically more aggressive

Phenotype: Pan B-cell markers+ (CD19, CD20, CD22, CD79a, Pax-5), CD5+, CD23- (in contrast to SLL), CD10-, >95% cyclin D1+, remaining cases cyclin D2+ or cyclin D3+. Sox11+ in nearly all cases (useful for diagnosis in cyclin D1- cases)

Genetics: t(11;14)(q13;q32) involving IGH and CCND1 gene (cyclin D1) in >95% cases. Remaining cases have CCND2 or CCND3 translocation

Prognosis: Aggressive course with median survival 3-5 years. Adverse prognostic factors: high mitosis, high Ki-67, 17p deletion or TP53 mutation, blastoid or pleomorphic morphology

Variants: Mantle cell leukemia: Blood (and marrow, spleen) involvement without nodal disease. Cells often resemble prolymphocytes (with a small nucleolus). t(11;14)+ and cyclin D1+, SOX-11-. More indolent than nodal type
In situ mantle cell neoplasm: Cyclin D1+ cells in mantle zone in hyperplastic appearing follicles. Mantle zone is not expanded. Often CD5-. Majority have stable disease, small numbers progress to mantle cell lymphoma

Intestinal mantle cell lymphoma: Presented with numerous “polyps” in intestine (aka lymphomatoid polyposis). More indolent if lymph node involvement is absent

Lymphoplasmacytic Lymphoma (LPL)

A mature B-cell neoplasm with small lymphocytes, lymphoplasmacytic cells, and plasma cells
Vast majority involves bone marrow with or without nodal involvement. Rare cases involve lymph node only. Blood involvement uncommon
Associated with IgM paraprotein (Waldenstrom macroglobulinemia), hyperviscosity (30%), cryoglobulinemia (20%)

Nearly all cases have **MYD88** mutation

**Morphology:** **Bone marrow:** nodular, interstitial, and/or diffuse pattern. Variable proportion of clonal small lymphocytes and clonal plasma cells, but both are always present

**Lymph node:** Interfollicular pattern or diffuse pattern. Mixture of small lymphocytes, lymphoplasmacytic cells, plasma cells. Scattered immunoblasts may be present

**Phenotype:** **Lymphoid component:** Pan B-cell antigens+ (CD19, CD20, CD22, CD79a, Pax-5), CD5-, CD10-. monoclonal kappa+ or lambda+

**Plasma cell component:** CD138+, monoclonal kappa+ or lambda+

Lymphocytes and plasma cells have same light chain expression (arising from same clone)

**Genetics:** **MYD88** L265P mutation >90% cases. **CXCR4** mutation in ~30%

**Differential:** Nodal marginal zone lymphoma with plasma cell differentiation (usually **MYD88**-)

**Prognosis:** Indolent, median survival 5-10 years. **MYD88**+ is a target for ibrutinib, **CXCR4**+ incurs resistance

**IgM MGUS:** precursor of LPL. Bone marrow involvement <10%, serum IgM <3 g/DL, asymptomatic, no end-organ damage

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**Marginal Zone Lymphoma**

Three large categories of marginal zone lymphoma: nodal marginal zone lymphoma, extranodal marginal zone lymphoma (MALT), splenic marginal zone lymphoma. These lymphomas are considered as distinct entities and are not related

**Nodal marginal zone lymphoma**

Involving lymph node without extranodal or splenic disease

Uncommon, 1-2% of all lymphoid neoplasm

Older adults most common, but can involve young adults and children

Increased incidence in women with autoimmune diseases

Usually involves peripheral lymph nodes

**Morphology:** **Cytologic morphology:** Marginal zone cells have slightly enlarged, round nuclei; chromatin is more open than small mature lymphocytes; increased pale cytoplasm ("monocytoid"). A few transformed large cells are always present (in contrast to mantle cell lymphoma)

**Histologic pattern:**

**Nodular pattern (most cases):** Marginal zone cells proliferate and expand in marginal zone, often surrounds residual mantle zone and germinal centers. Follicular colonization may be present

**Diffuse pattern:** Diffuse infiltration, no visible residual follicles by morphology. Remnants of follicular dendritic cells may be present (CD21 immunostain)

**Plasma cell differentiation:** Monoclonal plasma cells. Need to distinguish from lymphoplasmacytic lymphoma

**Phenotype:** Monoclonal kappa or lambda, all B-cell markers+ (CD19, CD20, CD22, CD79a, Pax-5). Aberrant expression of CD43 in up to 50% cases. CD5 and CD10 negative

**Variant:** **Pediatric nodal marginal zone lymphoma:** Morphology mimic progressive transformation of germinal center

**Genetics:** No specific genetic abnormalities

**Prognosis:** Good. 5-year survival rate 70%
**Splenic marginal zone lymphoma**

B-cell lymphoma originates from splenic white pulp, with frequent infiltration of red pulp, blood, and bone marrow. No peripheral lymphadenopathy

Uncommon, 1-2% of B-cell neoplasm, affect older adults

Splenomegaly, often massive when symptomatic. Autoimmune thrombocytopenia may occur

**Morphology: Spleen:** Expansion of marginal zone of while pulp, with or without intact mantle zone and germinal centers. Lymphoma cells are small to medium in size, with mature nuclei and abundant pale cytoplasm. Invariably involves red pulp with sinusaloidal pattern

**Blood:** Frequent, but percentage of circulating lymphoma cells are often low. Cells have “polar hair” morphology (in contrast to hairy cell leukemia)

**Bone marrow:** Frequent involved. Often subtle with sinusoid pattern. CD20 immunostain is helpful to reveal lymphoma

**Differential diagnosis:** Hairy cell leukemia, hairy cell leukemia variant, splenic red pulp small cell lymphoma (all have cytoplasmic projections)

**Phenotype:** Monoclonal kappa or lambda, all B-cell markers+ (CD19, CD20, CD22, CD79a, Pax-5), IgD+, CD5 and CD10 negative

**Genetics:** Deletion of 7q in 30%

**Prognosis:** Good. Indolent course. Splenectomy serves as both diagnostic and therapeutic purposes. Usually treated with single agent Rituximab or with combination chemotherapy

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**Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)**

A group of lymphoma involving only extranodal sites, associated with epithelial cells prone to reactive lymphoid response (lung, stomach, skin, salivary, lacrimal, thyroid)

Often associated with chronic inflammatory disorders of the involved organs

Clinical and pathologic features are different in different locations

Overall more frequent than nodal and splenic MZL, comprising of 7-8% of all B-cell neoplasms

Affects middle aged to older adults

<table>
<thead>
<tr>
<th>MALT Lymphomas</th>
<th>Associated Condition</th>
<th>Degree of linkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>H. pylori</td>
<td>Strong</td>
</tr>
<tr>
<td>Ocular</td>
<td>Chlamydia psittaci</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Borrelia burgdorferi</td>
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<tr>
<td>Salivary</td>
<td>Sjogren syndrome</td>
<td>Strong</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Hashimoto thyroiditis</td>
<td>Strong</td>
</tr>
<tr>
<td>Alpha heavy chain</td>
<td>Campylobacter</td>
<td>?</td>
</tr>
</tbody>
</table>

**Morphology:** Small sized lymphocytes, with round, slightly cleaved, or monocytoid nuclei. Usually have increased pale cytoplasm

**Gastric:** Aggregates of lymphocytes involve lamina propria. Lymphoma cells infiltrate gastric glands (lymphoepithelial lesion)

**Lung:** Nodules or confluence sheets of lymphocytes, surrounding remnant germinal centers

**Skin:** Involves dersmis, may be patchy or diffuse (more details in lesson 11)

**Salivary glands:** Lymphoma cells surround remnant epithelial islands and infiltrate into islands. Remnant or hyperplastic reactive germinal centers often present

**Thyroid:** Sheets of lymphoma cells in background of sclerosis. Remnant or hyperplastic reactive germinal centers often present

**Lacrimal gland:** Patchy or sheets of lymphoma cells under conjunctiva

**Phenotype:** Monoclonal kappa or lambda, all B-cell markers+ (CD19, CD20, CD22, CD79a, Pax-5), CD5 and CD10 negative, CD43+ in subset (useful for diagnosis), plasma cell differentiation often present (useful for proof of clonality)
**Genetics:** t(11;18)(q21;q21) involving \textit{MALT1-API2} in \~40% gastric and lung MALT, in \~10% ocular and salivary MALT

**Prognosis:** Indolent, slow growing. \textit{H.pylori} associated gastric MALT responds to antibiotics. Others treated by single agent therapy such as rituximab or combination chemotherapy