Lymphoplasmacytic Lymphoma (LPL)/Waldenstrom Macroglobulinemia
Definition

- Neoplasm of
  - Small B-lymphocytes
  - Plasmacytoid lymphocytes
  - Plasma cells

- Usually involves
  - BM
  - LNs
  - spleen
Definition

- Usually lacks CD5
- Has a serum monoclonal protein with hyperviscosity or cryoglobulinemia
- Plasmacytoid variants of other lymphomas are excluded (B-CLL, MZL, FL)
Epidemiology

- Rare disease (1.5% of nodal lymphomas)
- Older adults (median age 63y/o)
- Slight male predominance (53%)
Sites of involvement

- Commonly involves
  - BM
  - LNs
  - Spleen

- May involve
  - PB
  - Extranodal sites (most previously diagnosed cases are MZL of MALT-type)
    - Lung
    - GI
    - skin
Clinical features

- In most cases, monoclonal IgM paraprotein (>3g/dl, Waldenstrom macroglobulinemia)

- M-component may result in
  - hyperviscosity (10-30% of patients) which causes
    - RBC sludging or rouleaux formation
    - reduced visual acuity
    - increased risk of CVA
  - autoimmune reactions/ cryoglobulinemia
  - neuropathies (10%)
Clinical features

- Paraprotein deposition in
  - skin
  - GI tract (causes diarrhea)

- Coagulopathy, due to binding of IgM to
  - clotting factors
  - platelets
  - fibrin
Clinical features

- Waldenstrom macroglobulinemia is NOT synonymous with LPL

- IgM paraprotein present in other diseases
  - Splenic MZL
  - B-CLL
  - Extranodal MZL of MALT type (rarely)
Etiology

- Hepatitis C virus
  - in patients with HCV, cryoglobulinemia, and LPL, decreasing viral load with interferon is a/w regression of the lymphoma
  - mechanism is unclear
    - HCV has transforming potential, or
    - LPL is antigen-driven

- Genetic susceptibility

- Occupational exposures
Morphology in BM and PB

- PB
  - if involved, WBC count is less than in CLL
- BM
  - nodular and/or diffuse lymphoid infiltrate
- Smears show a mixture of
  - small lymphocytes
  - plasmacytoid lymphocytes, and
  - plasma cells
PB: rouleaux formation
Morphology

- Should NOT have
  - pseudofollicles
  - neoplastic follicles
  - marginal zone
  - monocytoid B-cells
Morphology in LNs

- Growth pattern
  - diffuse
  - may be interfollicular with sparing of sinuses

- No pseudofollicles
Morphology in LNs

- Neoplastic cells
  - small lymphocytes
  - plasmacytoid lymphocytes
  - plasma cells +/- Dutcher bodies
Morphology in LNs

- Progression to diffuse large cell (immunoblastic) lymphoma may occur
Immunophenotype

- slg and clg positive (usually IgM)
- IgD negative
- CD19/20/22/79a positive
- CD38 positive
- CD5/10/23 negative
- CD43 is variable
Genetics

- Antigen receptor genes
  - Ig heavy and light chain genes are rearranged
  - Variable-region genes show somatic mutations
Genetics

- Cytogenetic abnormalities and oncogenes
  - in 50% patients [recent studies showed only 5%]
    - t(9;14)(p13;q32) rearrangement of PAX-5 gene (encodes B-cell-specific activator protein; important in early B-cell development)
  - 6q del [in recent studies]
Prognosis and predictive factors

- Indolent course
- Median survival of 5 years
- Asymptomatic patients NOT treated
- Not curable with available treatment
Prognosis and predictive factors

- Poorer prognosis a/w
  - advanced age
  - PB cytopenias
  - neuropathies
  - weight loss
  - transformation to diffuse large B-cell lymphoma
Gamma Heavy Chain Disease

- Results from secretion of a truncated gamma chain (lacks light-chain binding sites)
- Usually a/w a tumor resembling LPL, involving
  - LNs/ BM/ Liver/ Spleen/ PB
Gamma Heavy Chain Disease

- Adults mostly
  - Systemic sx
    - Autoimmune
      - Hemolytic anemia
      - Autoimmune thrombocytopenia
Gamma Heavy Chain Disease

- Other systemic symptoms
  - arthritis
  - lymphadenopathy
  - splenomegaly
  - hepatomegaly
  - involvement of Waldeyer’s ring
  - peripheral eosinophilia
Gamma Heavy Chain Disease

- Polymorphous proliferation of:
  - lymphocytes
  - plasma cells
  - immunoblasts
  - eosinophils

- Variable clinical course (more aggressive than that of LPL)
Splenic Marginal Zone Lymphoma
SMZL: Definition

- B-cell neoplasm
- Small lymphocytes that surround and replace the splenic white pulp germinal centers, efface the follicle mantle and merge with a peripheral (marginal) zone of larger cells including scattered transformed blasts
- Both small and larger cells infiltrate the red pulp
- Hilar lymph nodes and BM are often involved
- PB: villous lymphocytes
SMZL: Synonyms

- **Rappaport**: well-differentiated lymphocytic lymphoma
- **Kiel**: not listed
- **Lukes-Collins**: small lymphocytic lymphoma
- **Working Formulation**: small lymphocytic lymphoma
- **FAB**: splenic lymphoma with circulating villous lymphocytes (SLVL)
SMZL: Epidemiology

- Rare, <1% of lymphoid neoplasms
- May account for most cases of otherwise unclassifiable chronic lymphoid leukemias that are CD5(-)
- Most >50 y/o, F=M.
SMZL: Site of Involvement

- Spleen
- Hilar lymph nodes
- BM
- PB, often
- Liver, may be
- Peripheral lymph nodes, typically not
SMZL: Clinical Features

- Splenomegaly
- Autoimmune thrombocytopenia or anemia
- PB villous lymphocytes, variable
- BM, usually positive
- Peripheral lymphadenopathy, uncommon
- Extranodal infiltration, extremely uncommon
- Small monoclonal serum protein, 1/3 of cases
- Marked hyperviscosity and hypergammaglobulinemia, uncommon
SMZL: Morphology-Spleen

- **White pulp/central zone**: small round lymphocytes, surrounds, or, more commonly replaces reactive germinal centers with effacement of the normal follicle mantle.

- **White pulp/peripheral zone**: small to medium-sized cells with more dispersed chromatin and abundant pale cytoplasm resemble marginal zone cells and are interspersed with transformed blasts.

- **Red pulp**: always infiltrated, small nodules of larger cells and sheets of the small lymphocytes, which often invade sinuses.
SMZL: Morphology

- Epithelial histiocytes: may be present in the lymphoid aggregates
- Plasmacytic differentiation: may occur. Rarely, clusters of plasma cells may be present in the centers of the white pulp follicles
Spleen: white pulp expansion with red pulp infiltration
Splenic Marginal Zone Lymphoma
SMZL: Morphology-Hilar LN

- Sinuses are dilated
- Lymphoma surrounds and replaces germinal centers
- The two cell types (small lymphocytes and marginal zone cells) are often more intimately mixed without the formation of a distinct “marginal” zone.
SMZL, splenic hilar lymph node
Nodular interstitial infiltrate, cytologically similar to that in the lymph nodes.

Occasionally neoplastic cells surround reactive follicles, but this is not a consistent finding.

Intrasinusoidal lymphoma cells are characteristic.
SMZL, bone marrow involvement
SMZL: Morphology-PB

- When present, usually but not always, short polar villi
- Some may appear plasmacytoid
SMZL, villous lymphocytes in PB
Other small B-cell lymphoma/leukemias: CLL, HCL, MCL, FL, LPL

Nodular pattern on BM excludes HCL, but BM morphology may not be sufficient to distinguish from others

PB villous lymphocytes are helpful

Flow cytometry of PB or BM helpful

A diagnosis of exclusion in the absence of splenectomy
SMZL: Immunophenotype

- **Positive:** sIgM, sIgD, CD20, CD79a
- **Negative:** CD5, CD10, CD23, CD43, cyclin D1, CD103
SMZL: Genetics-Antigen Receptor Genes

- IgH and Ig light chain genes are rearranged
- Most cases have somatic mutation
- Intraclonal variation: ongoing mutations
SMZL: Genetics-Cytogenetics

- Allelic loss of 7q21-32: 40% of cases. Dysregulation of $CDK6$ was reported.
- No $BCL2$ rearrangement. No t(14;18).
- No $BCL1$ rearrangement. No t(11;14).
- Trisomy 3 and t(11;18), common in MALT, are uncommon in SMZL. Trisomy 3 reported in 17 cases; no t(11;18) confirmed cases.
SMZL: Postulated cell of origin

Post-germinal centre B cell of unknown differentiation stage
SMZL: Prognosis and predictive factors

- Indolent clinical course, even with BM involvement
- Poor response to chemotherapy that is typically effective in other chronic lymphoid leukemias, but typically response to splenectomy with long term survival
- Transformation to large B-cell lymphoma may occur