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)

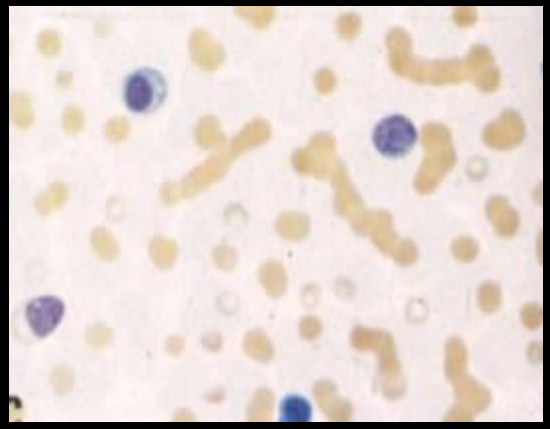
Etiology

- 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

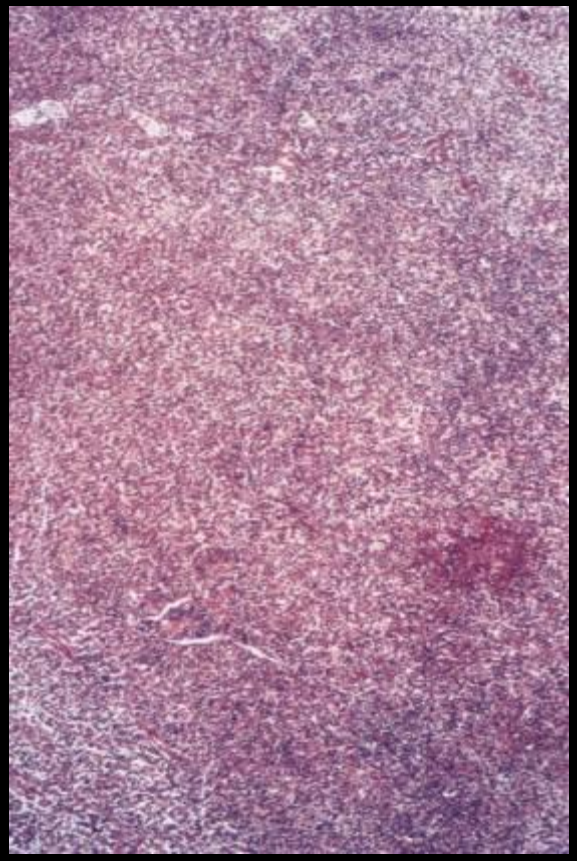


Morphology

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

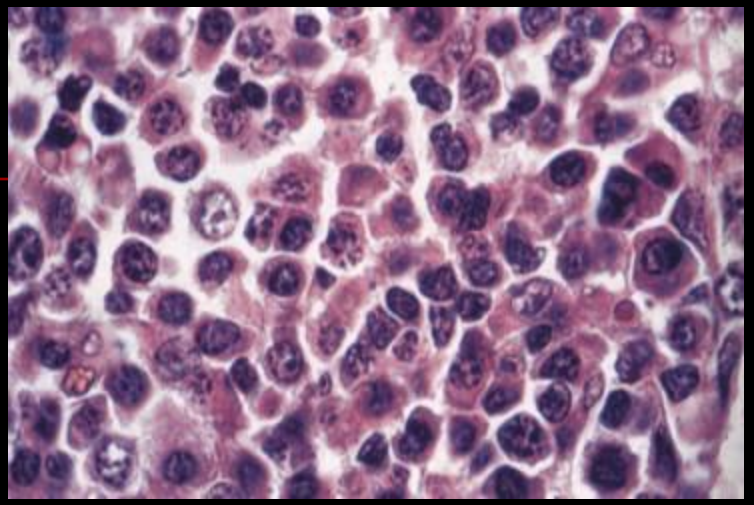
Morphology in LNs

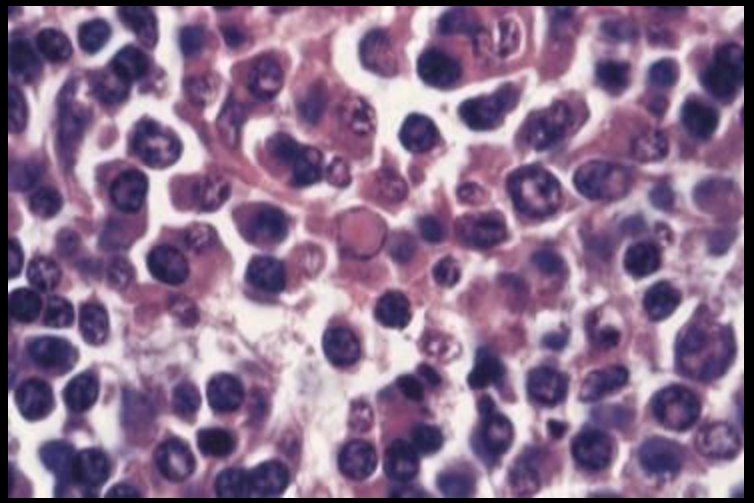
- Growth pattern
  - diffuse
  - may be interfollicular with sparing of sinuses
- No pseudofollicles



Morphology in LNs

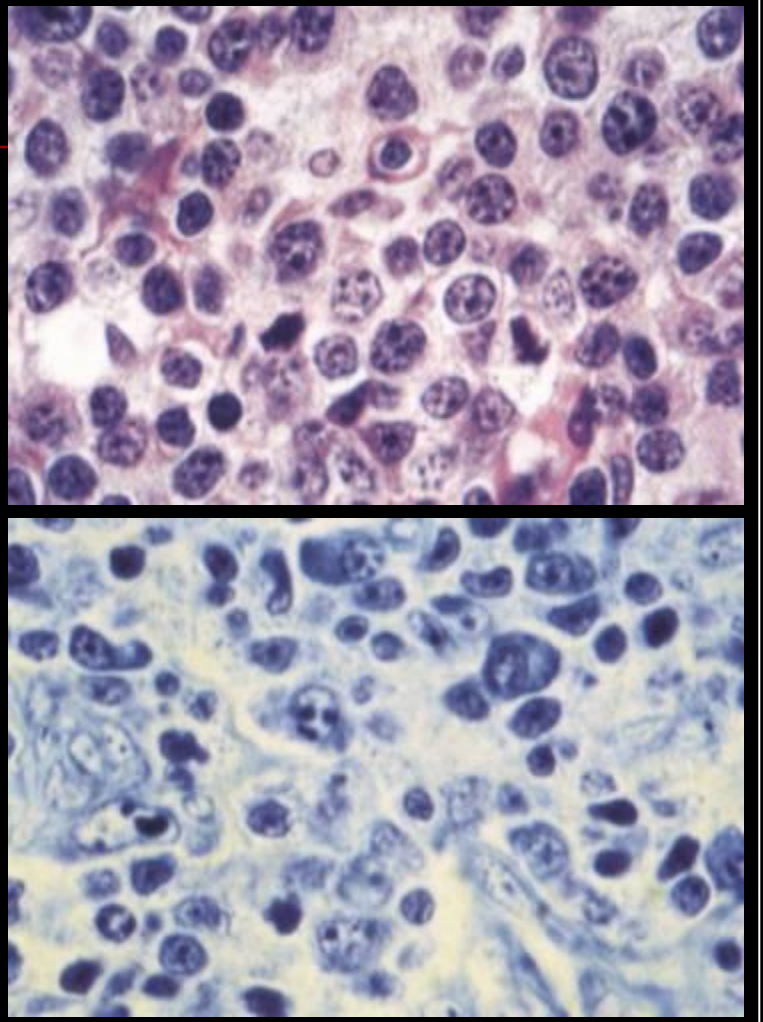
- Neoplastic cells
  - small lymphocytes
  - plasmacytoid lymphocytes
  - plasma cells +/- Dutcher bodies





Morphology in LNs

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



Immunophenotype

- sIg and cIg 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 sxs
  - 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

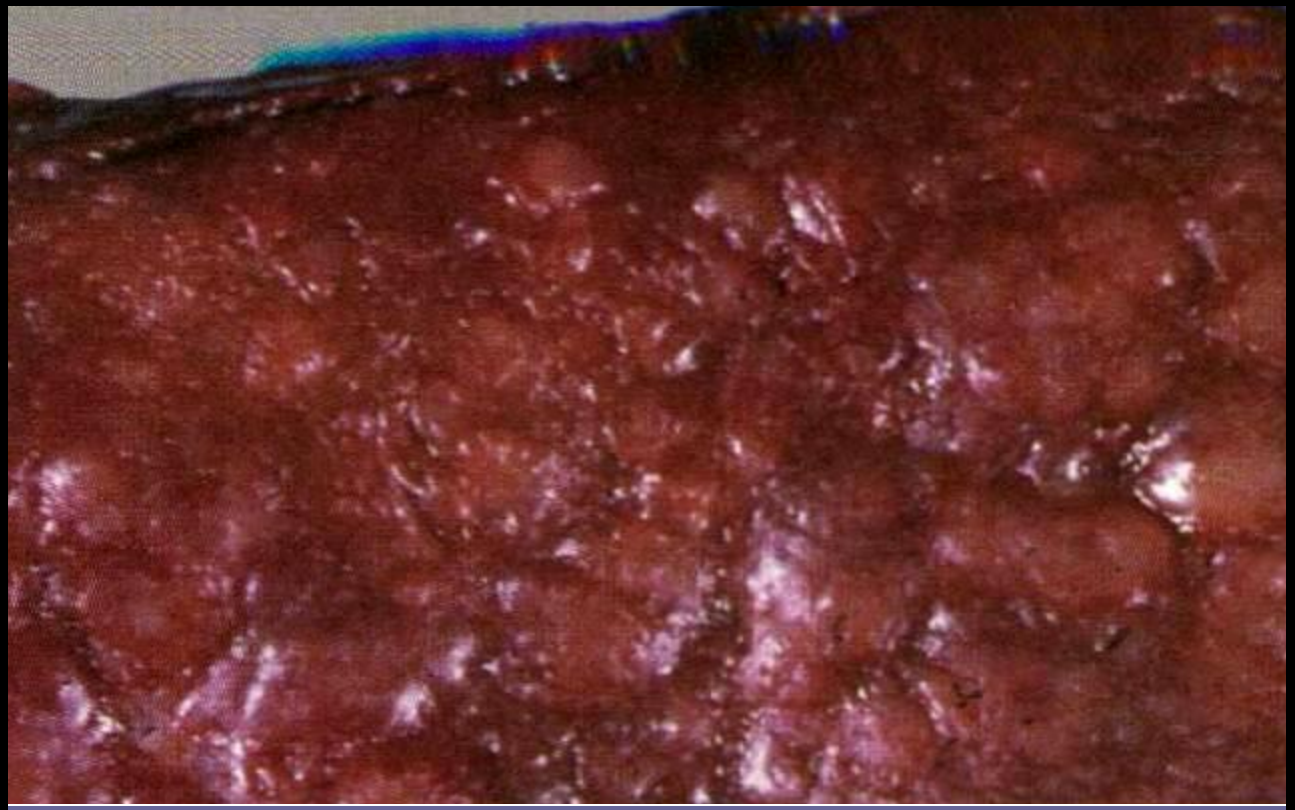
- Splenomegaly
- Autoimmune thrombocytopenia or anemia
- PB villous lymphocytes, variable
- BM, usually positive
- Peripheral lymphadenopathy, uncommon
- Extranodal infiltration, extremely uncommon
- Small monoclonal serum protein, 1/3 of cases
- Marked hyperviscosity and hypergammaglobulinemia, uncommon

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

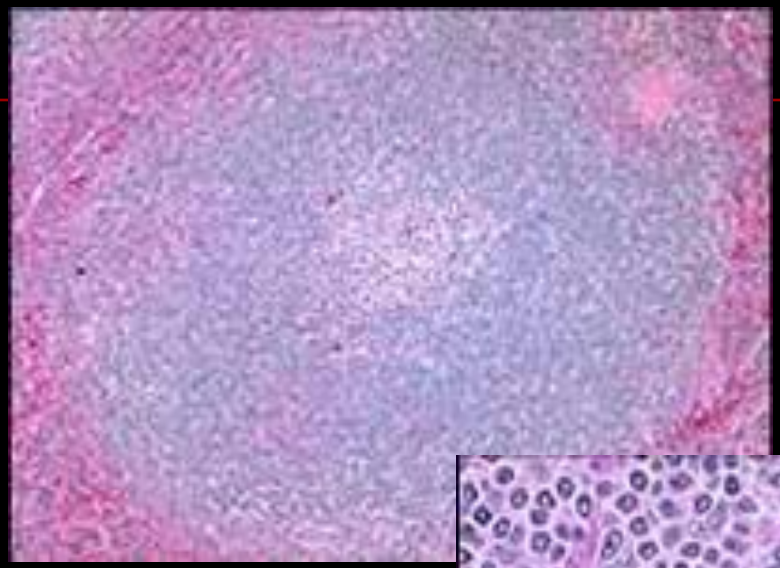
SMZL: Morphology

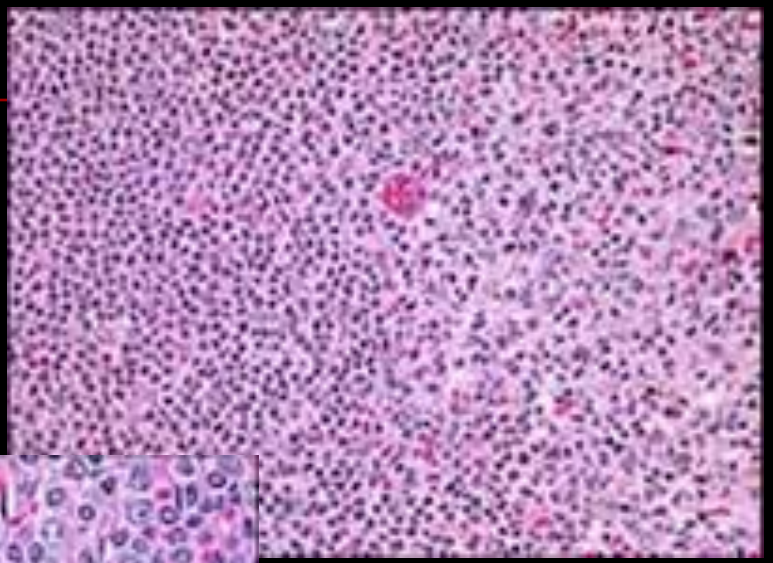
- Epithelial histiocytes: may be present in the lymphoid aggregates
- Plasmacytic differentiation: may occur. Rarely, clusters of plasma cells may be present in the centers of the white pulp follicles

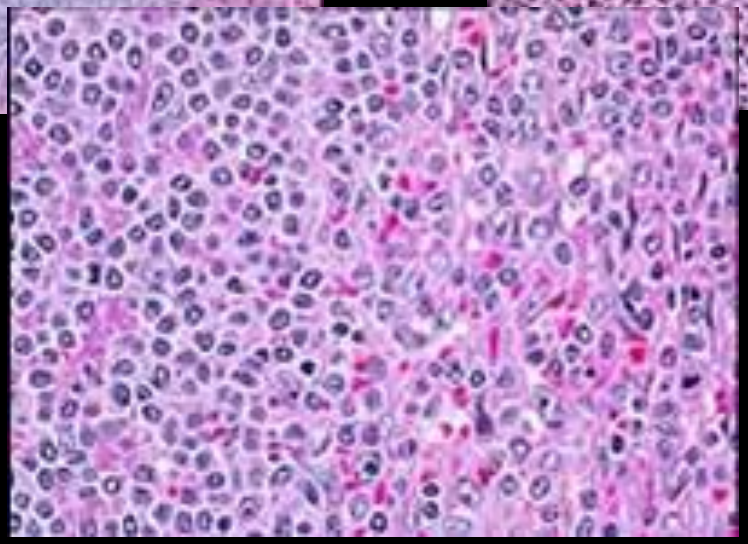


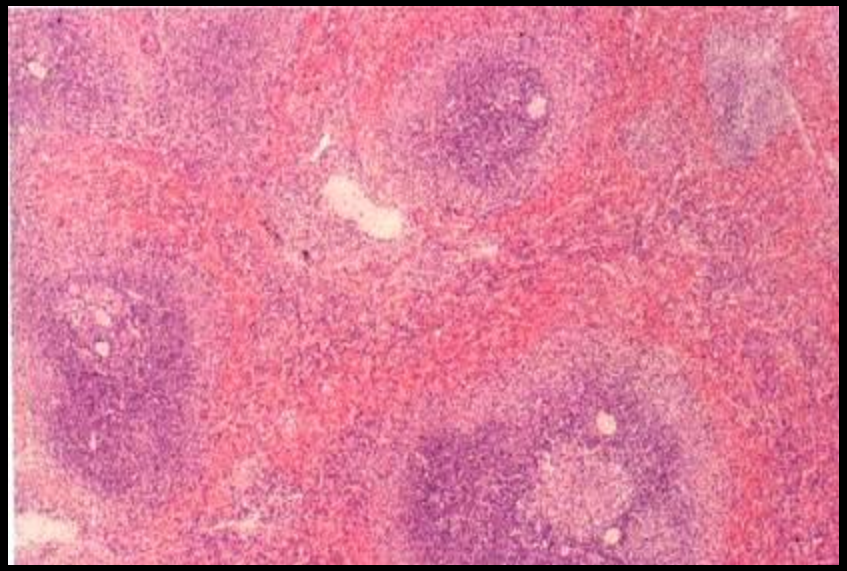
Spleen: white pulp expansion with red pulp infiltration

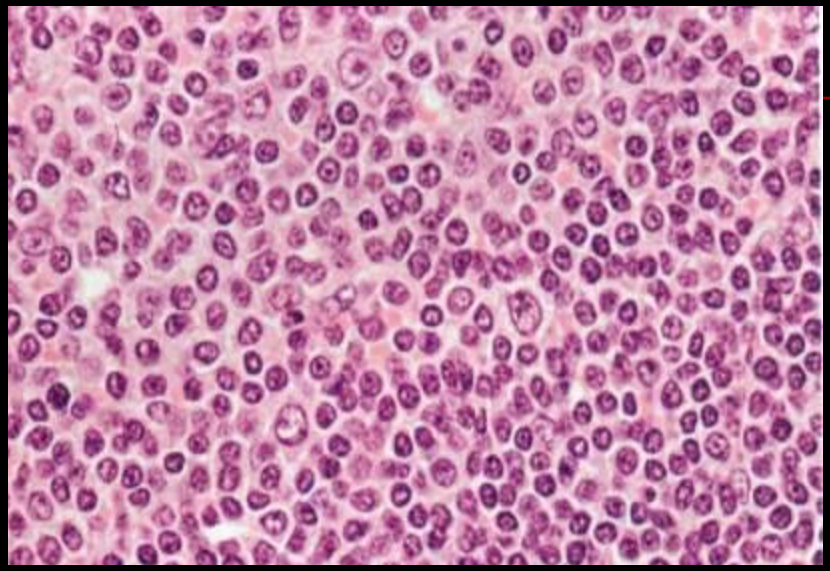
Splenic Marginal Zone Lymphoma





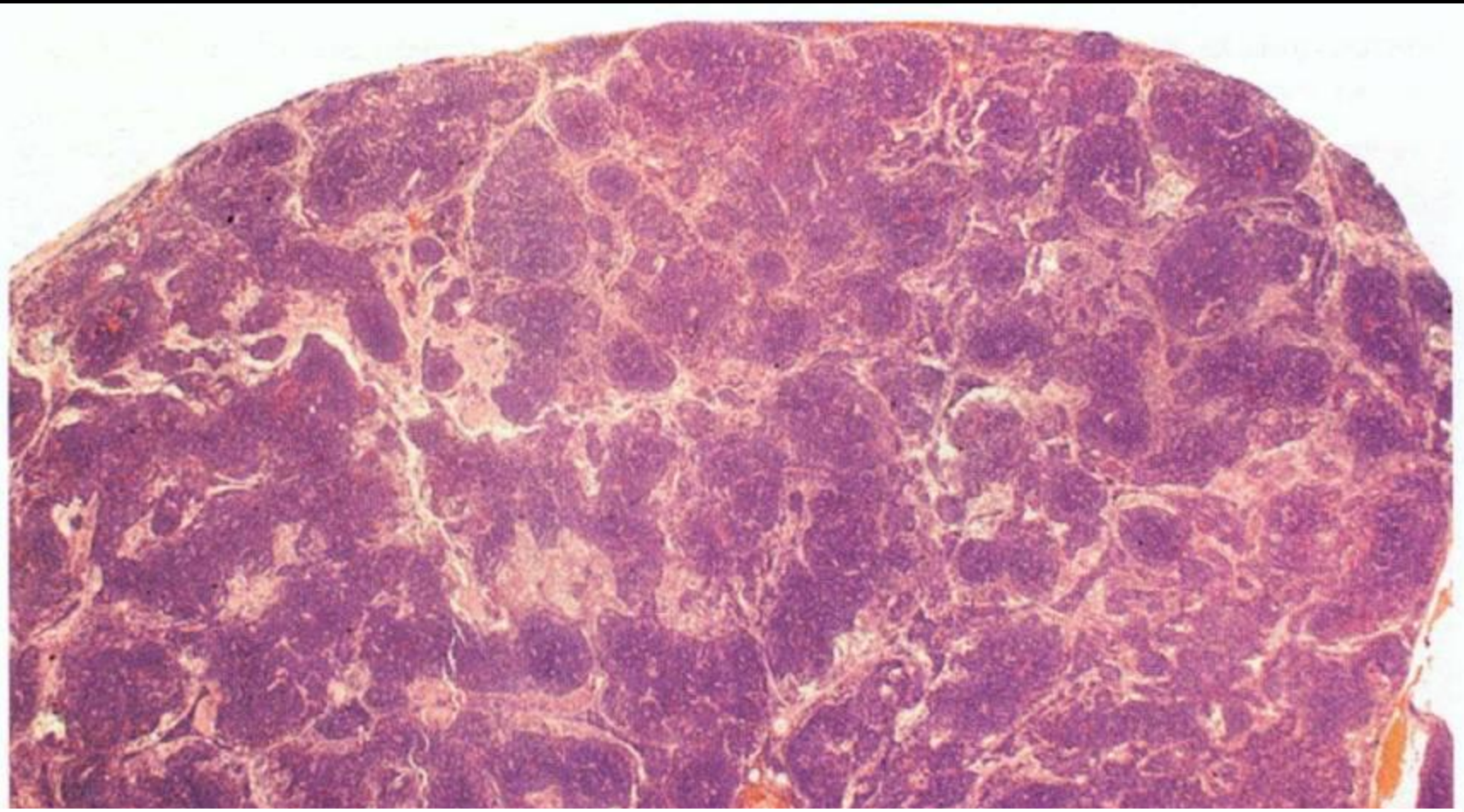


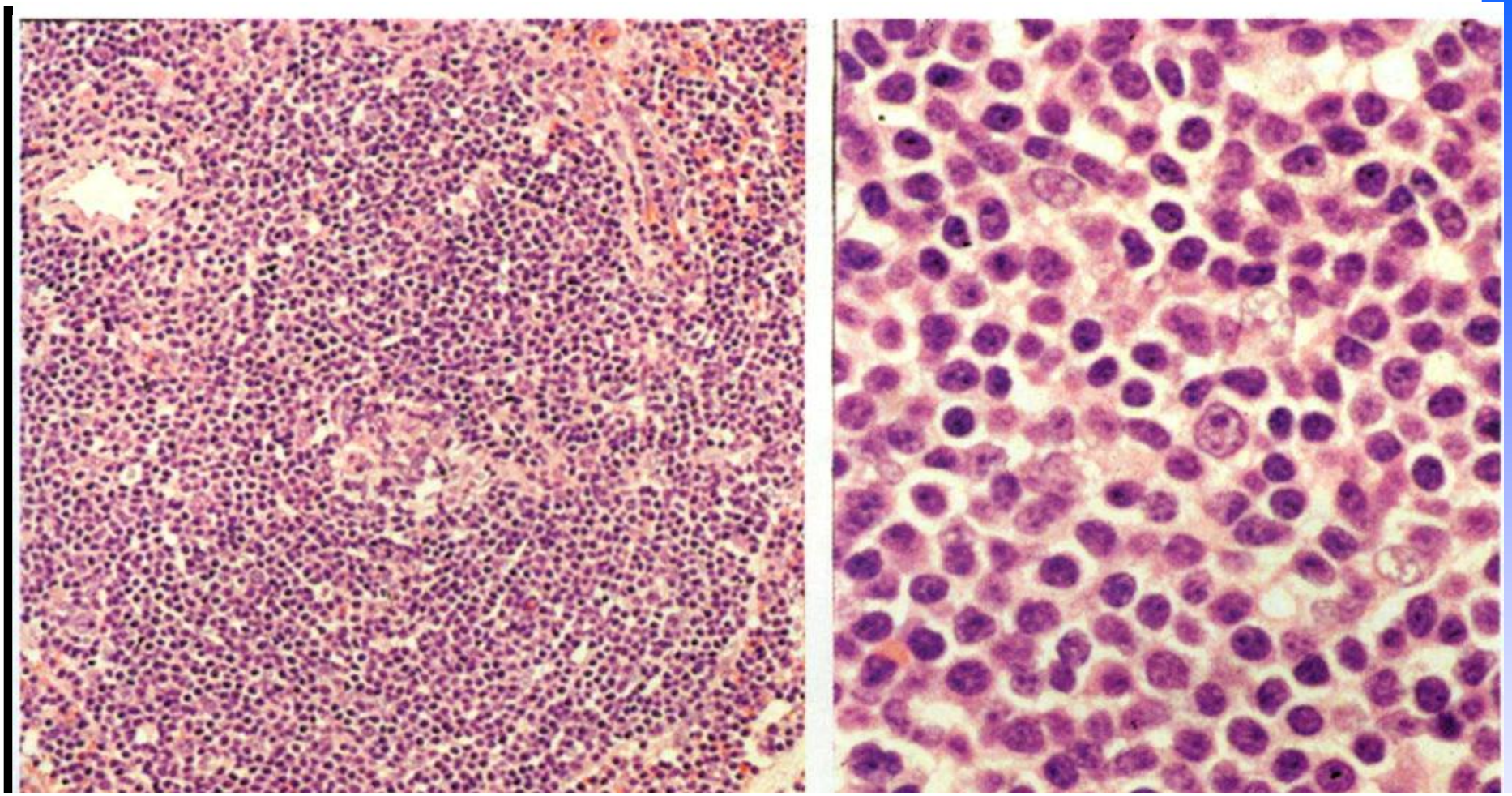




SMZL: Morphology-Hilar LN

- 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.

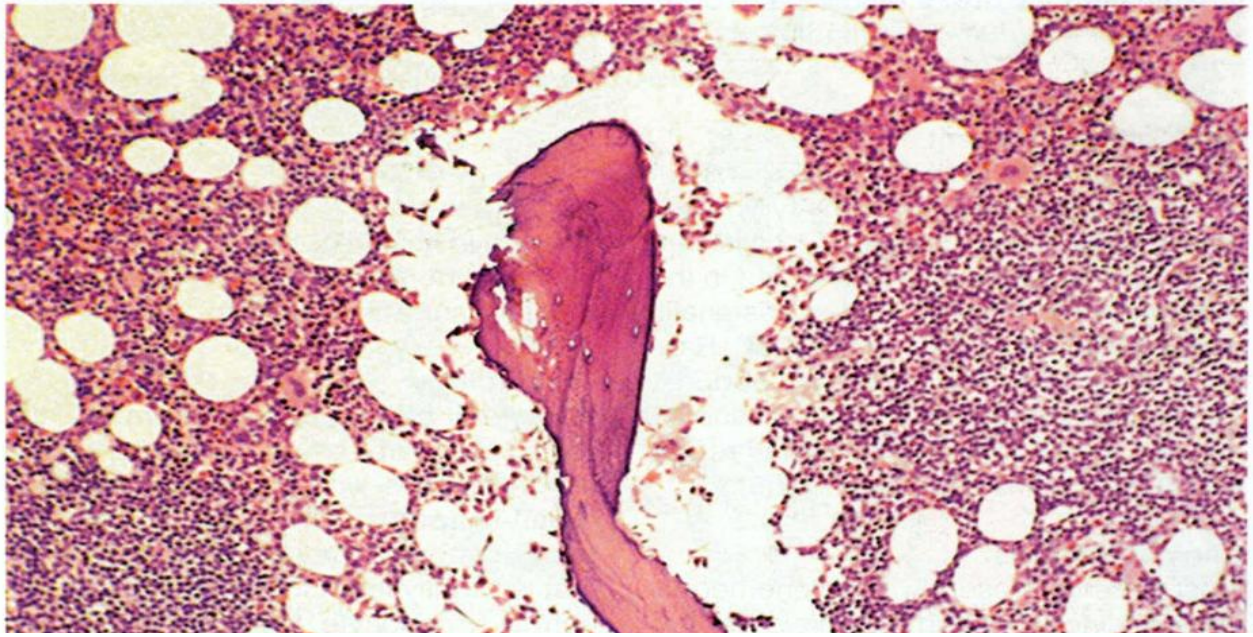




SMZL, splenic hilar lymph node

SMZL: Morphology-BM

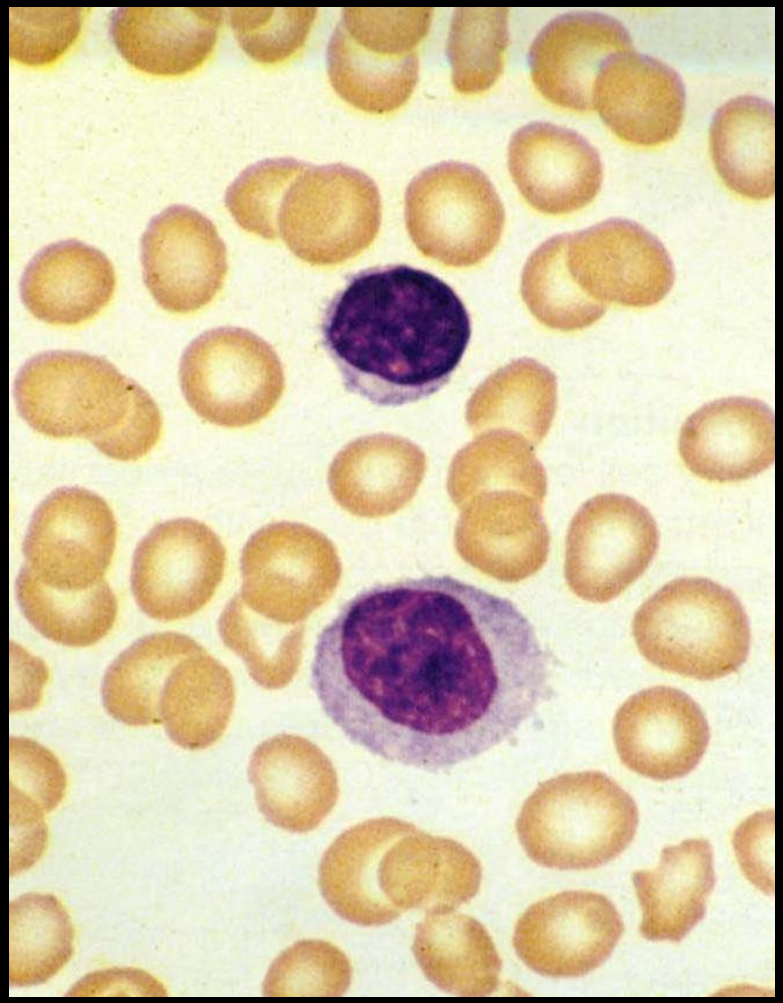
- Nodular interstitial infiltrate, cytologically similar to that in the lymph nodes.
- Occasionally neoplastic cells surround reactive follicles, but this is not a consistent finding
- Intrasinusoidal lymphoma cells are characteristic



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

SMZL: Morphology-DDX

- 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