Mature B-cell Neoplasms

Introduction

DEFINITION

- Clonal proliferations of B cells

  Naïve B cells -> Mature plasma cells

- Recapitulate stages of normal differentiation

EPIDEMIOLOGY

- >90% of lymphoid neoplasms worldwide; annually 4% of all cancers
- More common in developed countries
- Annual incidence
  - 15/100,000 (USA) , 1.2/100,000 (China)
- Follicular lymphoma & DLBCL (66% of NHL) are most common

EPIDEMIOLOGY

- In USA, B cell neoplasms account for >70,000 new cases per year; 6% of all cancers
- Geographic variations:
  - Follicular lymphoma (29% NHL in USA)
  - Burkitt lymphoma (equatorial Africa)
- Median age for all types: 50's and 60's, except:
  - Mediastinal LBCL: 37 years old
  - Burkitt lymphoma: 30 years old
  - Children: Burkitt lymphoma & DLBCL

EPIDEMIOLOGY

- Gender predilection: overall M>F
  - Exceptions: FL (F=58%), and mediastinal LBCL (F=66%)

- Risk factors:
  - Immune system abnormality:
    - » immunosuppression (DLBCL or BL)
    - » autoimmune disease (extranodal MZL)

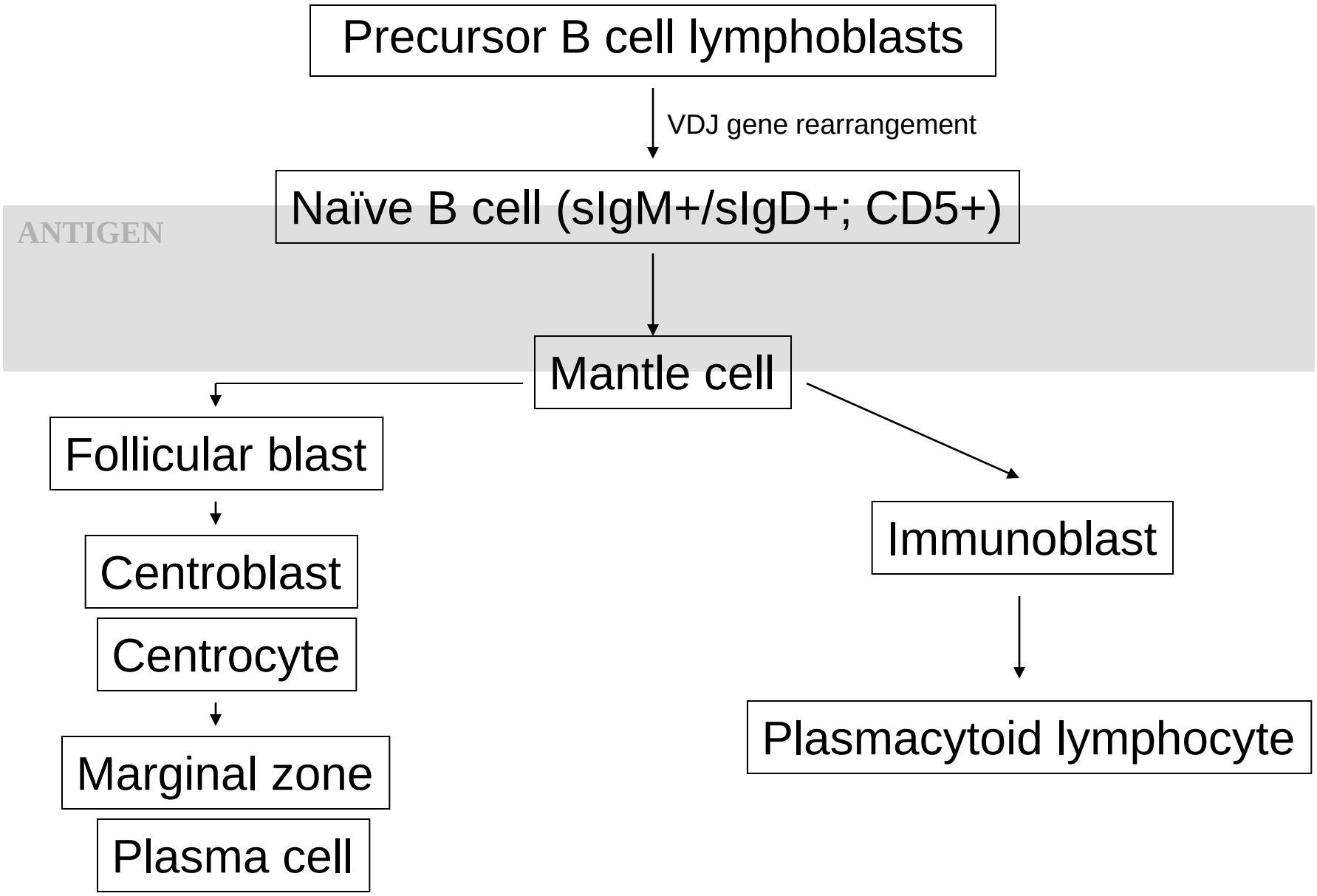
ETIOLOGY

- **Epstein-Barr virus**
  - Burkitt lymphoma:
    - Endemic (100%)
    - Sporadic & HIV-associated (40%)
  - Majority of B-cell lymphomas in iatrogenically immunosuppressed patients
- **KSHV/HHV8**
  - PEL
  - Multicentric Castleman disease-associated lymphomas in HIV patients
- **Hepatitis C virus**
  - Lymphoplasmacytic lymphoma associated with type II cryoglobulinemia
  - Some lymphomas of liver and salivary glands

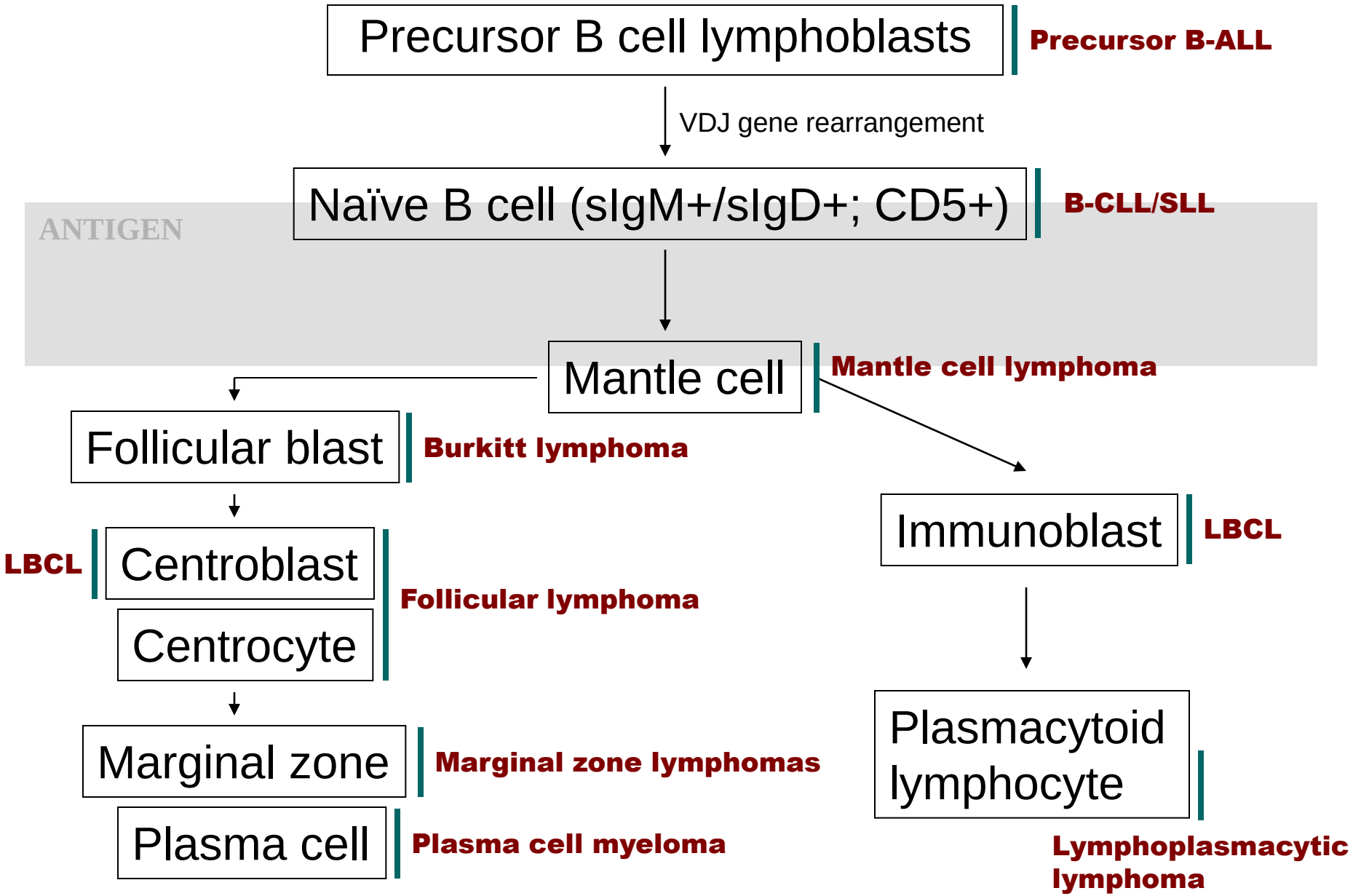
ETIOLOGY

- *Helicobacter pylori*
  - Gastric MALT
- *Borrelia burgdorferi*
  - Cutaneous extranodal MZL
- Mixed bacterial infections
  - Intestinal MALT lymphoma associated with immunoproliferative small intestinal disease (IPSID), aka. alpha heavy chain disease

PATHOPHYSIOLOGY



PATHOPHYSIOLOGY



PATHOPHYSIOLOGY

- **Germinal center:**
  - Centroblasts lack sIg ; switch off BCL2 expression
  - Centroblasts and centrocytes express BCL6 and CD10
  - Somatic mutations in immunoglobulin gene variable region
  - Ig class switch from IgM to IgG or IgA
  - BCL6 gene undergoes somatic mutation in germinal center
  - Centrocytes:
    - Express sIg being altered by somatic hypermutations (<98% homology with germline)
    - If high-affinity binding to antigen on FDC, cell is ‘rescued’
    - Interaction with surface molecules on FDC and T cells, such as CD23 and CD40 ligand causes BCL6 to be switched off and centrocytes differentiate into either memory B cells or plasma cells.
- Follicular lymphoma is caused by failure of centrocytes to undergo apoptosis because of t(14;18) that causes constitutive BCL2 expression

PATHOPHYSIOLOGY

- Memory B cells
  - Reside in follicular marginal zone
  - Round to slightly irregular nucleus with condensed chromatin and moderate amount of cytoplasm
  - sIgM+, sIgD-, pan-B antigens, CD5-, CD10-
- Plasma cells
  - Home to the bone marrow
  - Lack sIg; CD20-, CD79a+, CD138+
- Both cell types have mutated Ig gene variable region but no ongoing mutations

GENETICS

- t(11;14) in mantle cell lymphoma
- t(14;18) in follicular lymphoma
- t(8;14) in Burkitt lymphoma
- t(11;18) in MALT lymphoma

PRINCIPLES OF CLASSIFICATION

- Classification is based on utilization of all available information to define disease entities
- Morphology and immunophenotype are sufficient for diagnosis in most diseases
- In some diseases, knowledge of clinical features is essential (MZL of MALT type vs nodal or splenic MZL, and mediastinal LBL)
- In the classification, mature B cell neoplasms are listed according to their major clinical presentations:
  - Predominantly disseminated, often leukemic
  - Predominantly extranodal
  - Predominantly nodal

PREDOMINANTLY DISSEMINATED LYMPHOMA/LEUKEMIA

- Bone marrow involvement with or without peripheral blood and solid tissues
- Generally indolent
- Includes:
  - CLL
  - Lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia
  - Hairy cell leukemia
  - Splenic marginal zone lymphoma
  - Plasma cell myeloma

PRIMARY EXTRANODAL LYMPHOMAS

- Includes extranodal MZL of MALT type
- MALT lymphomas and less likely to disseminate and when they do it’s often to other extranodal sites
- Exposure to antigen may play a part in pathogenesis

PREDOMINANTLY NODAL LYMPHOMAS

- Present with disseminated disease involving LN and frequently liver, spleen, and BM
- FL and MCL comprise majority of cases
- Nodal MZL is rare and indolent
- DLBCL may present with either nodal or extranodal disease
  - Distinctive clinical subtypes:
    - » Primary mediastinal (thymic) large B cell lymphoma
    - » Primary effusion lymphoma
    - » Intravascular lymphoma
  - Distinctive morphologic subtypes:
    - » Centroblastic
    - » Immunoblastic
    - » T-cell rich
    - » Anaplastic
- Burkitt lymphoma:
  - Distinctive clinical subtypes: endemic, sporadic, immunodeficiency-associated

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

WHO CLL/SLL

- Neoplasm of monomorphic small, round B lymphocytes in blood, BM and lymph nodes, admixed with prolymphocytes and paraimmunoblasts (pseudofollicles), usually expressing CD5 and CD23.
- CLL: restricted to BM involvement, PB monoclonal B cell count > $5x10^9/l$)
- SLL: restricted to non-leukemic cases (PB monoclonal B cell count < $5x10^9/l$)
- Healthy pts with a B cell clone, PB monoclonal B cell count < $5x10^9/l$ -> monoclonal B cell lymphocytosis (3.5% of pts > 40 y/o)

Synonyms

- WF: small lymphocytic, consistent with CLL.
- REAL: B-cell chronic lymphocytic leukemia.
- FAB: B-cell chronic lymphocytic leukemia.

Epidemiology

- Comprises 90% of chronic lymphoid leukemias in USA and Europe.
- 6.7% of non-Hodgkin´s lymphoma.
- Majority of patients >50 y/o (median 65).
- M:F ratio 2:1.

Sites of involvement

- CLL: by definition, BM and PB. Monoclonal B cell count > $5x10^9$/l.
- Dx can be done with < $5x10^9$/l with the proper BM morphology and immunophenotype.
- SLL: lymph nodes, liver and spleen are typically infiltrated.
- Skin, breast and ocular adnexae may be involved.

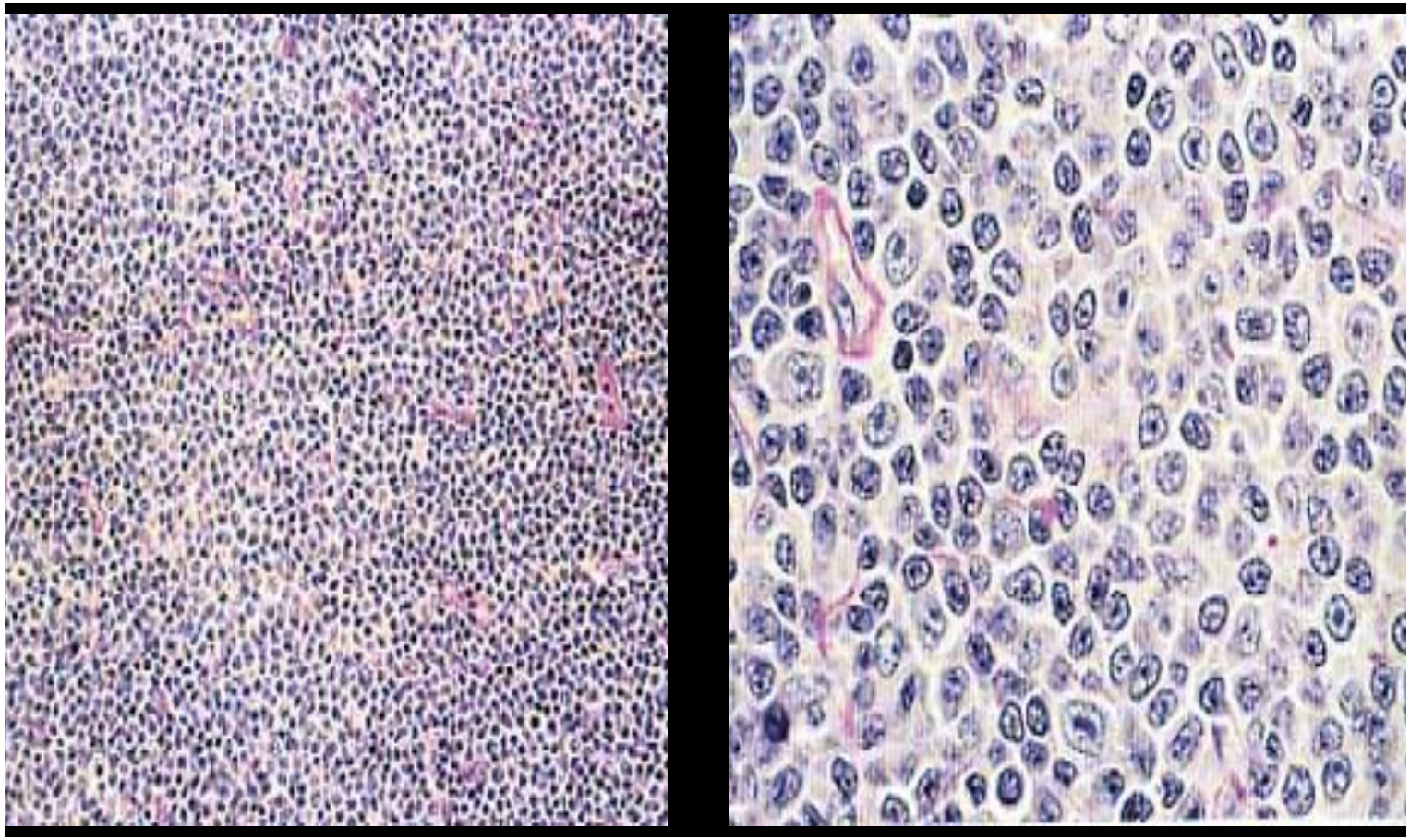
Clinical features

- Most patients asymptomatic. Some may present with fatigue, autoimmune hemolytic anaemia, infections, splenomegaly, hepatomegaly, lymphadenopathy or extranodal infiltrates.
- Small M-component in some pats.

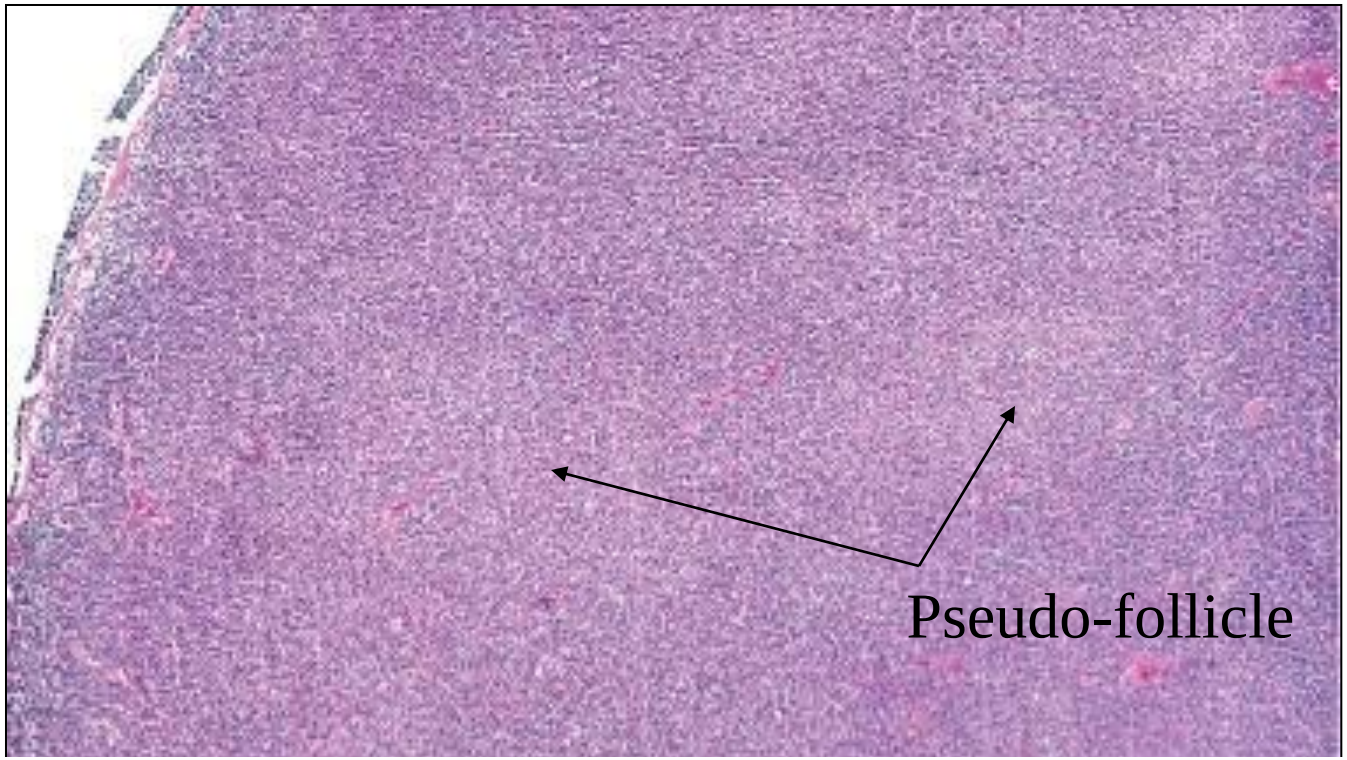
Morphology

- Lymph nodes.
  - Effacement of architecture, pseudofollicular pattern of pale areas of large cells in a dark background of small cells. Ocasionally is interfollicular.
  - The predominant cell is a small lymphocyte with clumped chromatin, round nucleus, ocassionally a nucleolus.
  - Mitotic activity usually very low.

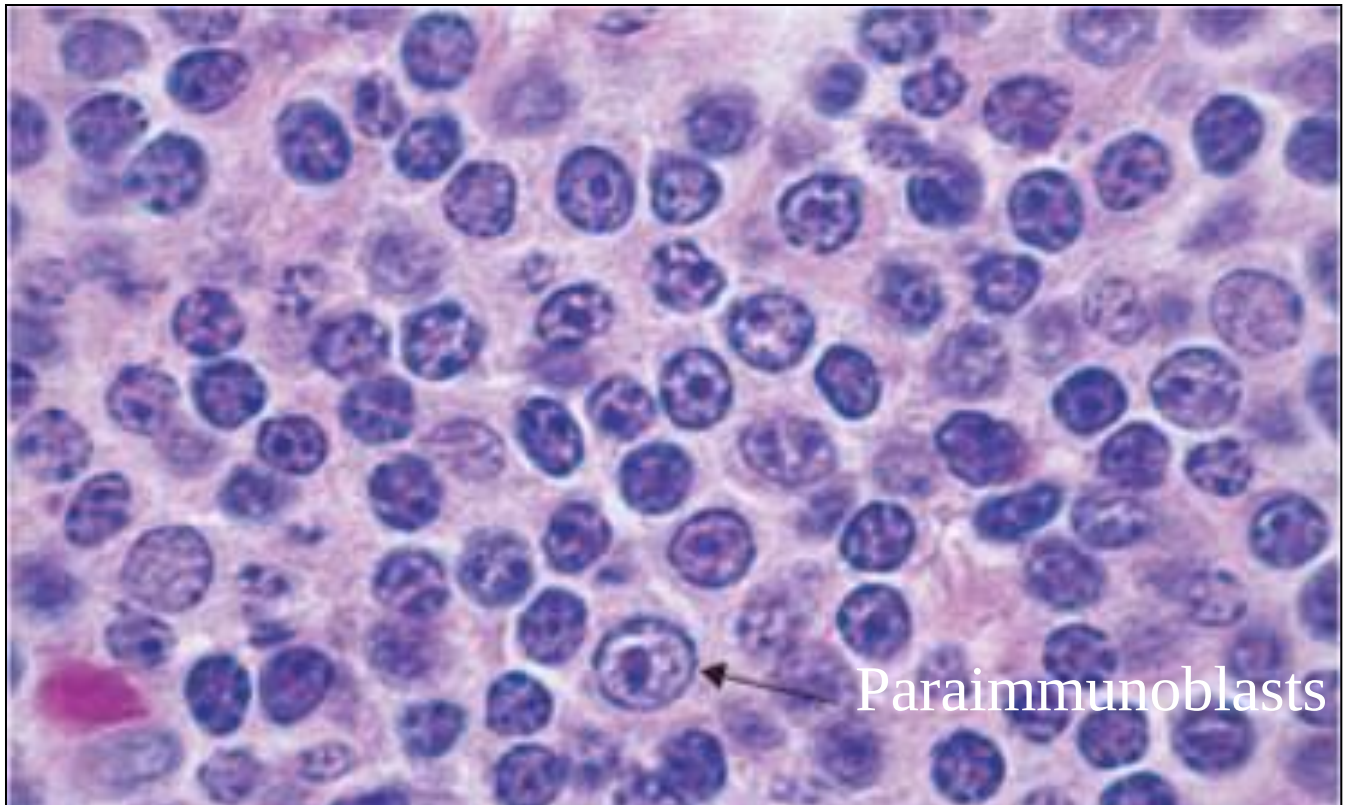
Pseudo-follicles and paraimmunoblasts



(Diffuse) Small Lymphocytic Lymphoma



Small Lymphocytic Lymphoma



Morphology

- Pseudofollicles or proliferation centers contain small, medium and large cells.
- Prolymphocytes are medium-sized with dispersed chromatin and small nucleoli.
- Paraimmunoblasts are medium to large cells with round to oval nuclei, dispersed chromatin, central eosinophilic nucleoli and slightly basophilic cytoplasm.

Morphology

- Spleen.

  - White pulp involvement predominant. Red pulp also involved.

  - Pseudofollicles less prominent.

  - Sometimes there is some nuclear irregularity mimicking MCL. Pseudofollicles, prolymphocytes and paraimmunoblasts help to rule out MCL.

  - Sometimes plasmacytoid differentiation.

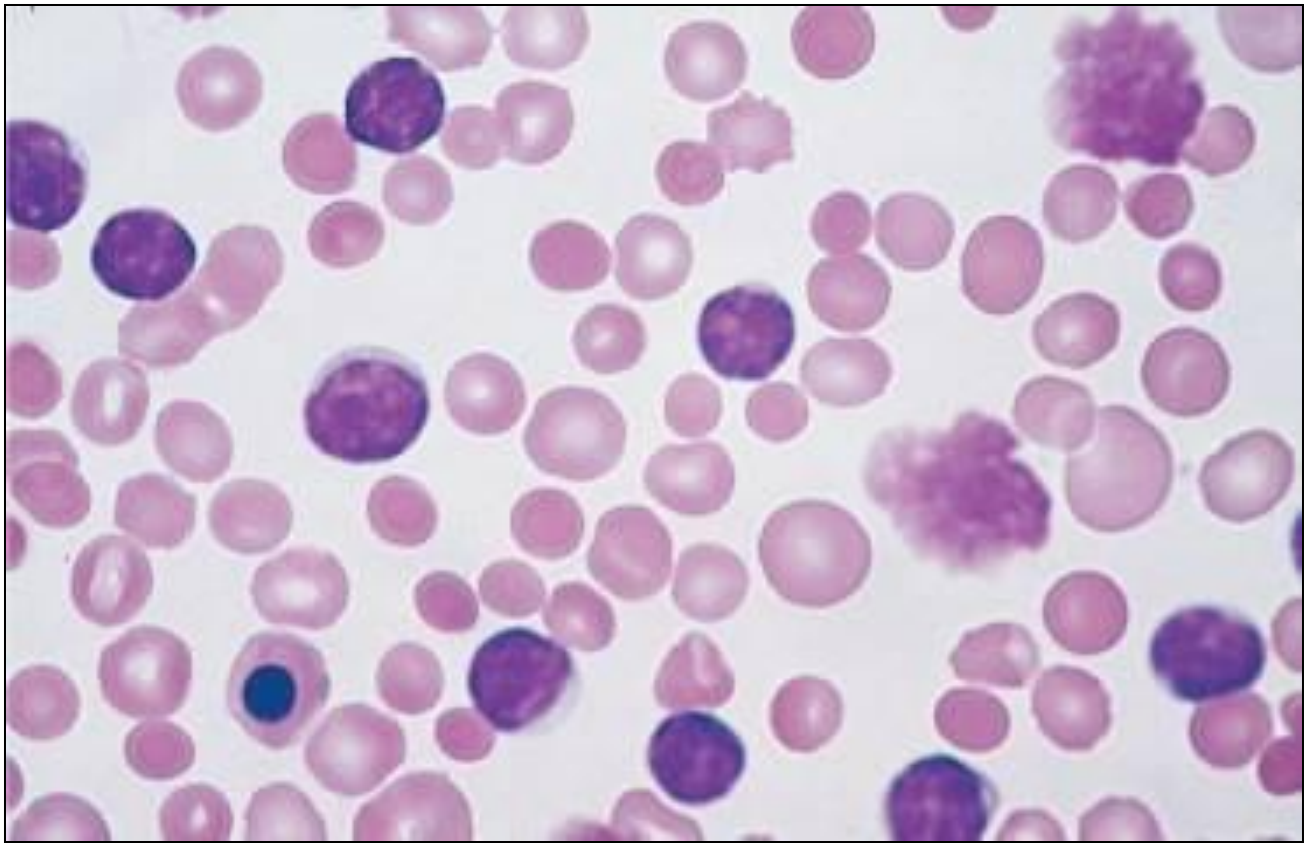
Morphology

- BM and Blood.
  - CLL cells are small lymphocytes with clumped chromatin. Cytoplasm is scanty, clear to basophilic with regular outline.
  - Smudge or basket cells are typically seen in the blood (alleviated with albumin treatment)).
  - Proportion of prolymphocytes in the smear usually < 2%. Incresing numbers correlate with more aggressive disease, p53 abnormalities and trisomy 12.
  - With increased prolymphocytes-> (CLL/PLL) defined by prolymphyctes between 10% and 55%.

Morphology

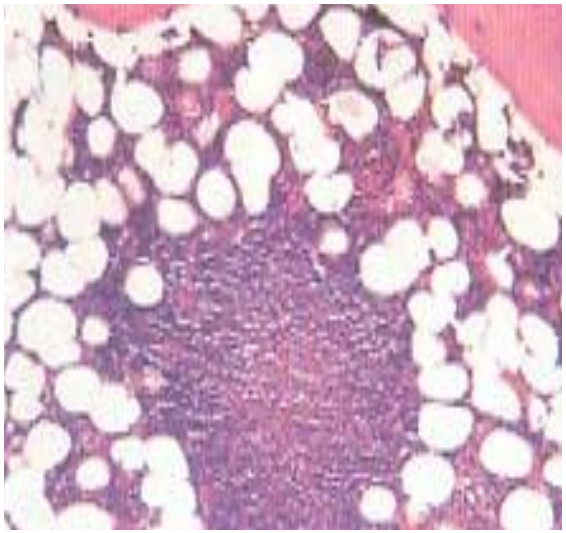
- BM involvement can be interstitial, nodular or diffuse or combinations.
- Pseudofollicles less common in BM.
- Paratrabecular aggregates not typical.
- Nodular and interstitial patterns are seen in early disease.
- Diffuse pattern associated with advanced disease and BM failure.

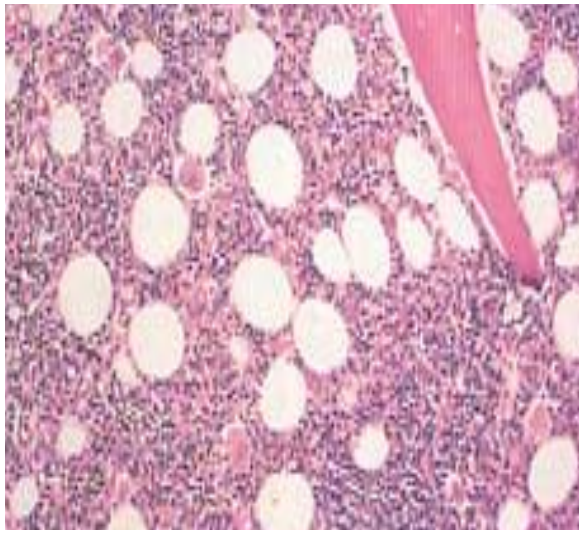
Chronic Lymphocytic Leukemia

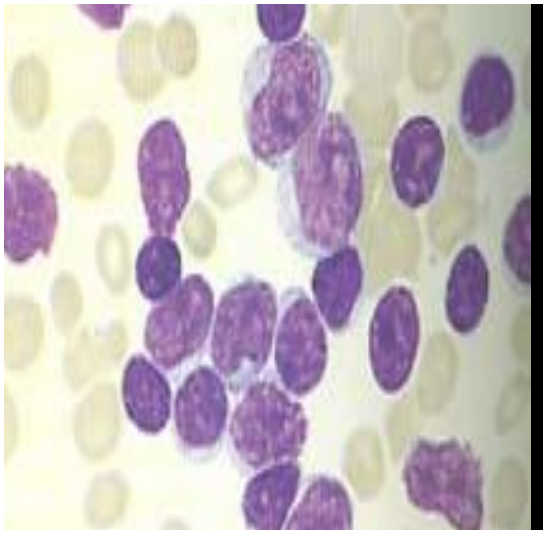


P.B.: Chronic lymphocytic leukemia

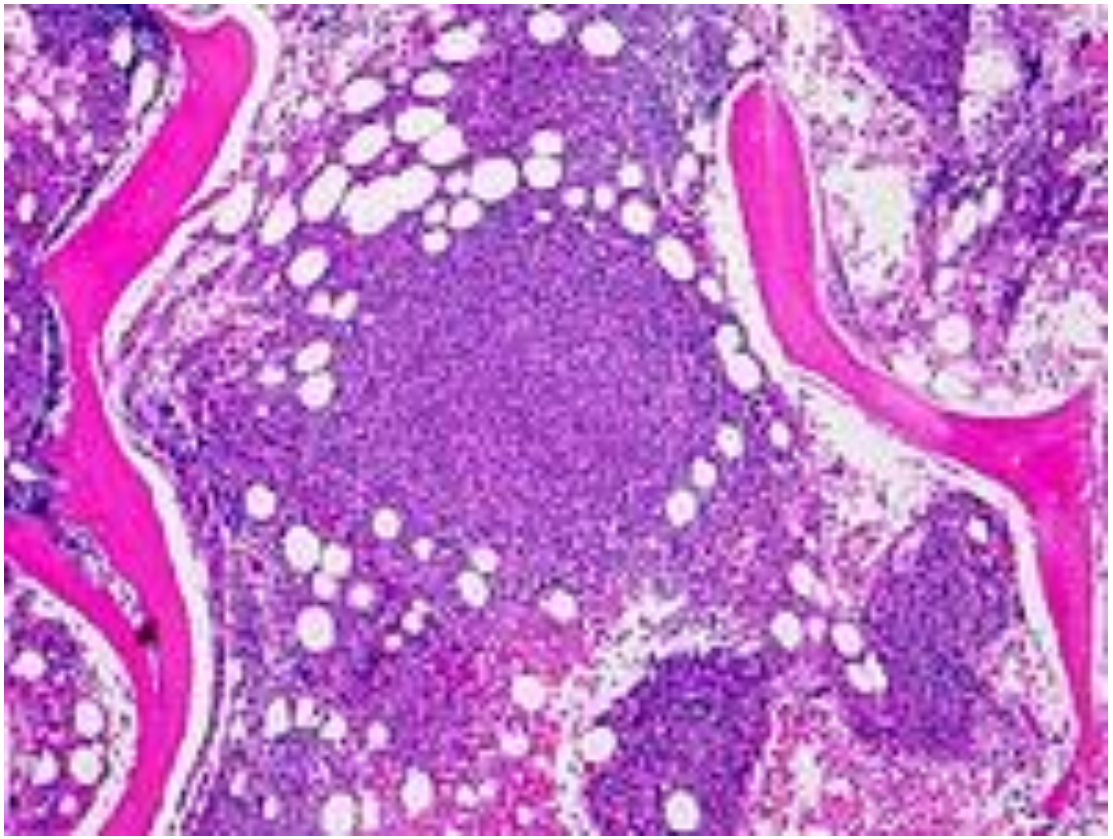
Bone marrow, PB



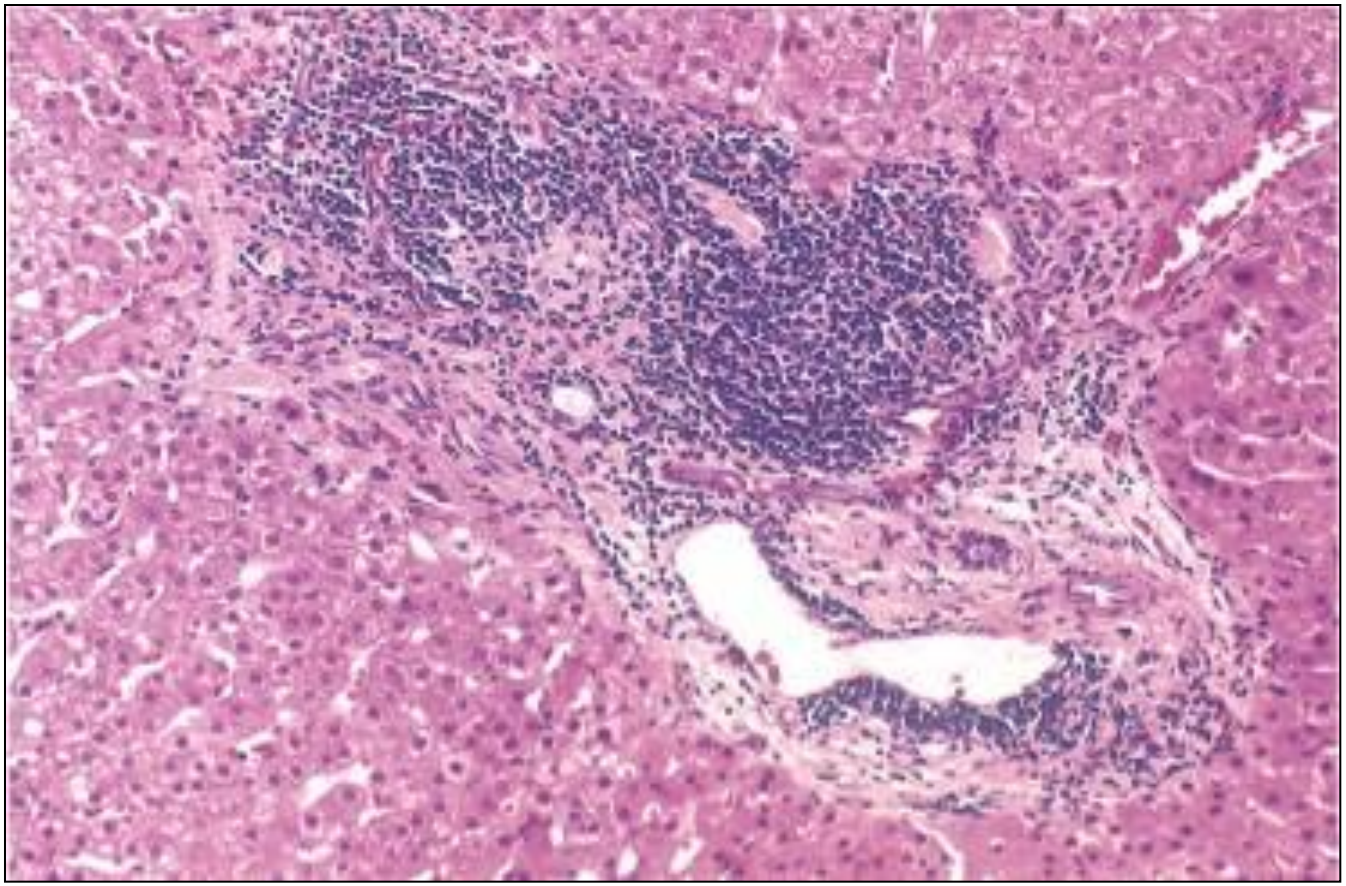




Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia in Bone Marrow



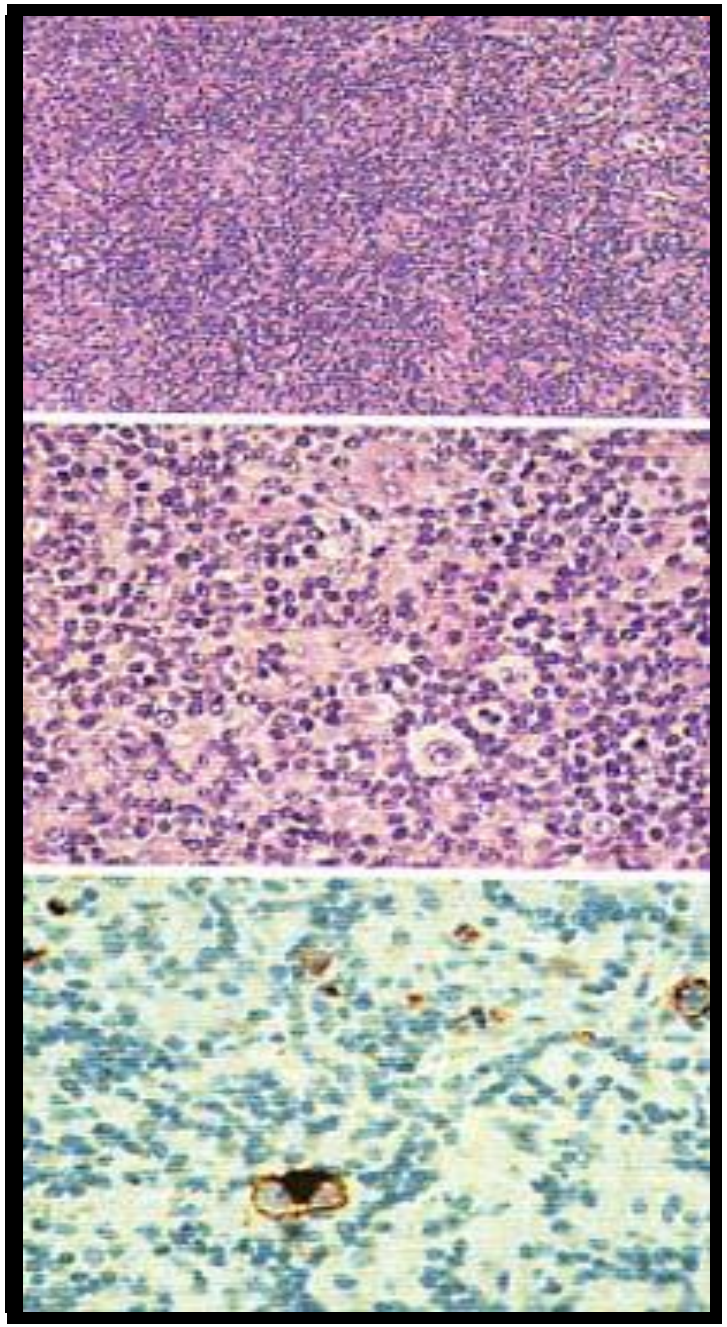
Small Lymphocytic Lymphoma in Liver



Morphology

Transformation to diffuse large B-cell lymphoma (Richter syndrome) is characterised by confluent sheets of large cells that may resemble paraimmunoblasts, but are more often centroblast- or immunoblast-like.

CLL may be associated with Hodgkin lymphoma, with scattered R-S cells and variants in a CLL background or as discrete areas of classic HL.



cHL in a pt
With CLL

RS cells (in a CLL background)

CD15

Immunophenotype

- Express weak or dim surface IgM or IgM and IgD, CD5, CD19, CD20 (weak), CD22 (weak), CD79a, CD23, CD43, CD11c (weak).
- CD10-, cyclin D1-.
- FMC7 and CD79b negative or weak.

Immunophenotype

- Cases with unmutated Ig variable region genes are reported to be CD38+ and ZAP70+.

Immunophenotype

- Cytoplasmic Ig is detectable in about 5% of the cases.
- CD5 and CD23 are useful in distinguishing from MCL. Rarely CLL is CD23-. Rarely MCL is CD23+. Perform Cyclin D1 in CD5+/CD23- cases.
- Some cases with typical CLL morphology may have a different profile (CD5- or CD23-, FMC7+ or CD11c+, or strong sIg, or CD79b+).

Genetics

- Antigen receptor genes:
  - Ig heavy and light genes are rearranged. Suggestion of 2 distinct types of CLL defined by the mutational status of the IgVH genes: 40-50% show no somatic mutations of their variable region genes (naïve cells, unmutated). 50-60% have somatic mutations consistent with derivation from post-germinal center B-cells.
  - DNA sequencing shows hypermutation if there is <98% homology with germline
  - Unmuted: poor prognosis; hypermutated: better prognosis

Genetics

- Cytogenetic abns and oncogenes:
  - About 80% of the cases have abnormal karyotypes by FISH.
  - Trisomy 12 reported in 20% of cases. Have predominantly unmutated Ig variable region genes.
  - Deletions at 13q14.3 in up to 50%. Have mutations more often (Ig variable region genes).

Genetics

- Cytogenetic abns and oncogenes:
  - Deletions at 11q22-23 are found in 20% of cases. Most often unmutated.
  - Deletions at 17p13 (p53 locus) are seen in 10% of cases, respectively. Most often unmutated.
  - t(11;14) and BCL1 gene rearrangement have been reported. These cases may have been leukemic MCL and misdiagnosed as CLL.

Postulated cell of origin

- Thought to correspond to recirculating CD5+ CD23+ IgM+ IgD+ naïve B cells., found in PB, primary follicle, and follicular mantle zone.
- Cases that show V region mutations may correspond to a subset of PB CD5+ IgM+ B cells that appear to be memory B cells.

Prognosis and predictive factors

- Clinical course is indolent, not considered to be curable with available therapy.
- Purine nucleoside analogues, such as fludarabine, may result in sustained remissions.
- 5 year OS of SLL was 51% with a FFS of 25%. Overall median survival is 7 yrs.

Prognosis and predictive factors

- Clinical staging systems (Rai 0-IV and Binet A-C) are the best predictors of survival.
- Cases of CLL/PLL and diffuse BM involvement may have a worse prognosis.

Prognosis and predictive factors

- Rapid doubling time (< 12 months) is a prediction of poor prognosis
- +12 correlates with atypical morphology and aggressive clinical course.
- Abns of 13q14 are reported associated with long survival.

Prognosis and predictive factors

- Mutations in Ig genes variable regions have a better prognosis than those with germline VH regions (median survival 7 yrs vs 3 yrs).
- CD38, ZAP70 expression appears to have worse prognosis.
- 11q22-23 deletions have extensive lymphadenopathy and poor survival.

Prognosis and predictive factors

- Transformation to high grade lymphoma (Richter syndrome) occurs in aprox. 3.5% of cases. Usually DLBCL (3%). HD (0.5%), particularly in pats treated with purine nucleotide analogues.

Prognosis and predictive factors

- Molecular genetic analysis suggests about in 50% cases the aggressive lymphoma represents transformation of the original neoplastic clone.
- In the remainder the lymphoma maybe a second, unrelated neoplasm.

Prognosis and Predictive Factors

- Variant: Mu heavy chain disease.
  - Usually associated with neoplasm resembling CLL, in which a defective mu heavy chain lacking a variable region is produced.
  - BM has characteristic vacuolated plasma cells, admixed with small, round lymphocytes.
  - Pats are adults with hepato-splenomegaly, absence of peripheral lymphadenopathy, and a slowly progressive course.

B-cell Prolymphocytic Leukemia

B-PLL

Definition

- Malignancy of B-prolymphocytes
  - Round lymphoid cells
  - Medium-sized
  - Prominent nucleoli
- Affects PB, BM, and spleen

Definition

- Prolymphocytes: >55% of PB lymphoid cells

- Exclude
  - Transformed CLL
  - CLL with increased prolymphocytes

Epidemiology

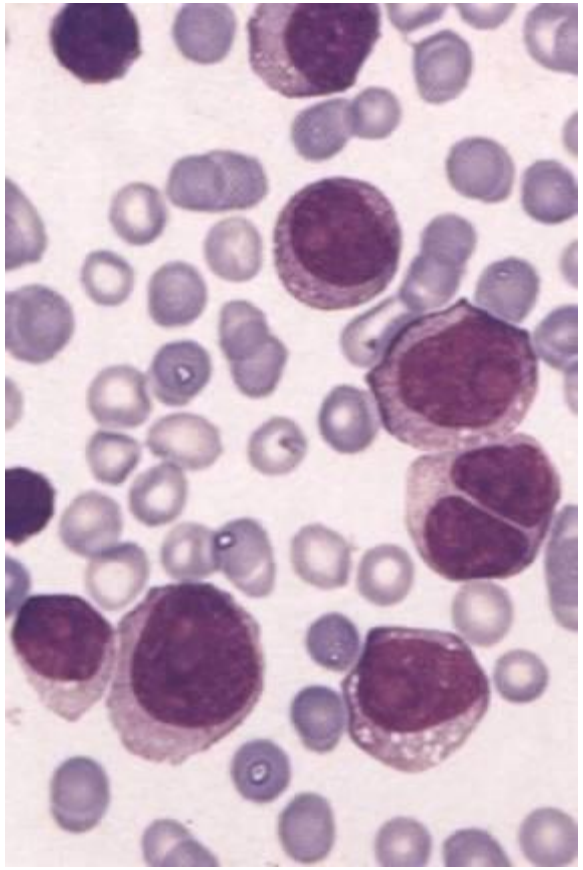
- Extremely rare (~1% of lymphocytic leukemias)
- Elderly (most >60 y/o; median 70)
- Male predominance (M:F = 1.6:1)

Clinical features

- Most patients
  - Marked splenomegaly
  - No peripheral lymphadenopathy
  - Rapidly rising lymphocyte count (usually >100 x 10^9/L)
- 50% of patients
  - Anemia
  - Thrombocytopenia
- Some patients
  - Serum M-component

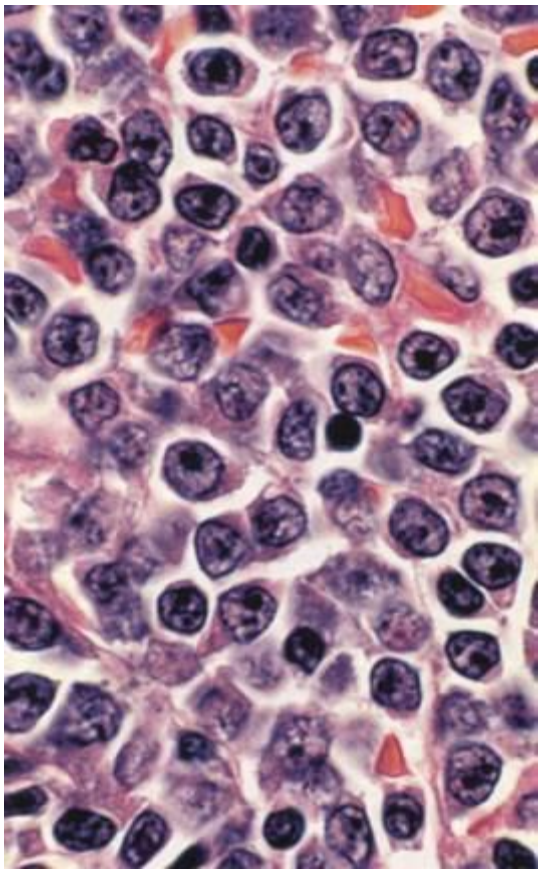
Morphology in PB and BM

- PB Prolymphocytes
  - >55% of circulating cells (usually >90%)
  - Medium-sized (2X size of a lymphocyte)
  - Round nucleus (+/- indentation)
  - Moderately condensed chromatin
  - Prominent central nucleolus
  - Small amount of faintly basophilic cytoplasm
- BM
  - Diffuse intertrabecular infiltrate



Morphology in other tissues

- Spleen
  - Extensive white and red pulp involvement
  - Morphology of prolymphocytes best seen in red pulp



Morphology in other tissues

- LN
  - Diffuse or vaguely nodular infiltrates of prolymphocytes
  - No pseudofollicles

Immunophenotype

- Strong positive for
  - sIgM (+/- IgD)
- Positive for
  - CD19/20/22/79a/79b
  - FMC7
- CD5 positive in 1/3 of cases
- Negative for CD23

Genetics

- t(11;14)(q13;q32)
  - In 20% of typical cases
  - Some might be cases of leukemic blastoid variant of MCL (misdiagnosed as PLL)
- Abnormalities of TP53 (including 17p del)
  - 53% of cases (highest in lymphoid malignancies)
  - p53 protein expression
- Deletions at 11q23 and 13q14 (by FISH)

Prognosis

- Prognosis is not dependent on: CD38, ZAP70, 17p del, or mutational status of Ig gene.
- Poor response to CLL therapy
- Short survival
- May respond to
  - CHOP
  - Fludarabine
  - Cladribine
  - Splenic irradiation
- Splenectomy
  - May improve patient's general condition
  - Does not delay disease progression