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
ANTIGEN PATHOPHYSIOLOGY

Precursor B cell lymphoblasts

VDJ gene rearrangement

Naïve B cell (sIgM+/sIgD+; CD5+)

Mantle cell

Follicular blast

Centroblast

Centrocyte

Marginal zone

Plasma cell

Immunoblast

Plasmacytoid lymphocyte
Precursor B cell lymphoblasts

VDJ gene rearrangement

Naïve B cell (sIgM+/sIgD+; CD5+)

Mantle cell lymphoma

Mantle cell

Follicular blast

Burkitt lymphoma

Centroblast

Follicular lymphoma

Centrocyte

Immunoblast

Marginal zone lymphomas

Marginal zone

Plasmacytoid immunoblast

Plasma cell myeloma

Plasma cell

Lymphoplasmacytic lymphoma

Precursor B-ALL

B-CLL/SLL

LBCL

Pre-B ALL

Marginal zone lymphomas

Plasma cell myeloma

Lymphoplasmacytic lymphoma

ANTIGEN

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
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
• 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
• 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 > $5 \times 10^9$/l.
- **Dx** can be done with < $5 \times 10^9$/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. Occasionally is interfollicular.
  – The predominant cell is a small lymphocyte with clumped chromatin, round nucleus, occasionally a nucleolus.
  – Mitotic activity usually very low.
Pseudo-follicles and paraimmunoblasts
(Diffuse) Small Lymphocytic Lymphoma
Small Lymphocytic Lymphoma

Paraimmunoblasts
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%. Increasing numbers correlate with more aggressive disease, p53 abnormalities and trisomy 12.
  – With increased prolymphocytes-> (CLL/PLL) defined by prolymphocytes 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 slg, 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 $>100 \times 10^9$/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
  - slgM (+/- 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