Small B-cell (Histologically Low Grade) Lymphoma

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Frequency of Lymphoid Neoplasms

- B-cell neoplasms: 88%
  - Diffuse large B-cell lymphoma: 31%
  - Follicular lymphoma: 22%
  - MALT lymphoma: 8%
  - CLL/SLL: 7%
  - Mantle cell lymphoma: 6%
  - Mediastinal large B-cell lymphoma: 2%
  - Nodal marginal zone lymphoma: 2%
  - Burkitt/Burkitt-like lymphoma: 3%
  - Lymphoplasmacytic lymphoma: 1%
  - Splenic marginal zone lymphoma: <1%
- T-cell neoplasms: 12%
  - Peripheral T-cell NOS: 4%
  - Anaplastic large cell lymphoma: 2%
  - Precursor T-LBL: 2%
  - Nasal NK/T-cell lymphoma: 1%
  - Angioimmunoblastic T-cell lymphoma: 1%
  - Enteropathy-type T-cell lymphoma: <1%
  - Adult T-cell lymphoma/leukemia: <1%

WHO Classification of B-cell Neoplasms 2008

- Mature B-cell neoplasms
  - - B-cell CLL/SLL
  - - B-cell prolymphocytic leukemia
  - - Splenic marginal zone B-cell lymphoma +/- villous lymphocytes
  - - Hairy cell leukemia
  - - Lymphoplasmacytic lymphoma
  - - Heavy chain disease
  - - Plasma cell myeloma
  - - Solitary plasmacytoma of bone
  - - Extramedullary plasmacytoma
  - - Mucosa-associated lymphoid tissue lymphoma
  - - Intravascular large B-cell lymphoma
  - - ANLL with B-cell phenotype
  - - Diffuse large B-cell lymphoma, NOS
  - - 1 lymph node involvement of cutaneous T-cell lymphoma - primary cutaneous CTCL
  - - Diffuse large B-cell lymphoma with chronic inflammation
  - - Lymphomatoid papulosis
  - - Primary cutaneous diffuse large B-cell lymphoma not otherwise specified
  - - Primary cutaneous angiocentric lymphoma
  - - Primary cutaneous CD30 positive lymphoproliferative disorder
  - - Cutaneous diffuse large B-cell lymphoma, unspecified
  - - Primary cutaneous marginal zone B-cell lymphoma
  - - Primary cutaneous follicle center cell lymphoma
  - - Diffuse large B-cell lymphoma associated with HHV8- Castleman disease
  - - Primary cutaneous follicle center cell lymphoma, not otherwise specified
  - - Primary cutaneous follicle center cell lymphoma, follicle center type

"WHO: Histologically Low Grade B-Cell Lymphomas"

- B-CLL / SLL – minority are clinically aggressive
- Prolymphocytic – clinically aggressive
- Mantle cell lymphoma – clinically aggressive

Small B-Cell Lymphomas: Overall Survival

- Small Lymphocytic (CLL)
- Mantle Cell

Armitage et al, 1997
Histologically Low Grade B-Cell Lymphomas: Differential Diagnosis

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  - Plasma cell myeloma
  - Solitary plasmacytoma of bone
  - Extramedullary plasmacytoma
  - Extramedullary marginal zone B-cell lymphoma (MALT type)
  - Nodal marginal zone B-cell lymphoma
  - Follicular lymphoma
  - Primary cutaneous follicular lymphoma
  - Mantle cell lymphoma

B-cell Small Lymphocytic Lymphoma (CLL)

- Morphology
  - Small lymphocytes
  - Proliferation centres

- Immunology
  - Surface IgM weak
  - CD19, 20, 79a
  - CD5
  - CD23
  - CD10, CycD1

- Genetics
  - t(11;14) or t(14;18) in 25%
  - trisomy 12
  - > 50 % have somatic mutations

- Clinical
  - Usually leukaemic
  - Insidious

B-Cell CLL/SLL: Pseudofollicular Pattern
Small Lymphocytic Lymphoma (CLL)

- Small lymphocytic lymphoma
- Tissue variant of CLL
- Lymphoplasmacytoid lymphoma
- Older patients, male predominance
- Paraprotein with associated symptoms
- Overlap with Waldenstrom’s

CD5 in lymphoma

- 80% T cell lymphomas
- >95% SLL (CLL-like) NHL (strong)
- >90% mantle cell lymphoma (weak)
- Minority of DLBCL
- Other B-cell NHLs negative

SLL (CLL): Richter’s Transformation

Differential diagnosis: IHC

- **SLL vs B-LB**
  - TdT<sup>neg</sup> CD5<sup>pos</sup> CD23<sup>pos</sup>
- **SLL vs MCL**
  - CD23<sup>pos</sup> cyclin-D1<sup>neg</sup> Ki-67 low
- **SLL vs FL**
  - CD5<sup>pos</sup> CD23<sup>neg</sup> BCL-6<sup>pos</sup> (proliferation centres)

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Follicular Lymphoma: definition

Lymphoma of follicle centre B-cells (centrocytes/cleaved FCC and centroblasts/noncleaved FCC) which has at least a partially follicular growth pattern

Follicular Hyperplasia

- Zonation (polarity)
- Tingible body macrophages

Follicular hyperplasia vs Follicular Lymphoma

- Well-defined mantle
- Heterogeneous cytology
- Homogeneous cytology

Follicular Lymphoma

- Morphology:
  - Germinal centre cells
  - CBs & CCs
  - Follicular
- Immunology:
  - Surface Ig
  - CD19, 20, 22, 79a
  - BCL-2
  - Bcl-6
  - CD10 +/-
  - Bcl-6
- Genetics:
  - t(14;18)
  - BCL-2 rearranged
- Clinical:
  - Adults; indolent

Follicular hyperplasia vs Follicular Lymphoma

- Indistinct mantle
- Zonation (polarity)
- Tingible body macrophages
Follicular Hyperplasia

- Small centrocytes (small cleaved)
- Large centroblasts (large non-cleaved)
- Follicular dendritic cells
- Tingible body macrophages

Case 17

- 59 årig kvinde
- Værgtab 10 kg indenfor 1 år
- Gennem 1 måned hastig voksende lymfeknude på hals
- 3 cm stor tumor basis linguæ - biopteret

Case 17 - diagnoseforslag

**Diagnoser:**
- Mantlecell lymfom – 7
  - "blastoid" - 1
  - DLBCL & high grade B – 3
  - Ekstraossæst plasmacytom - 3

**Diff. diagnose:**
- MCL, (evt. blastoid)
- PTL
- BL
- MCL
- DLBCL
- Maltom
- FL
- B-CLL / SLL
- HL
- Carcinoma
- Grey zone lymphoma

Case 17: CD20
Case 17: CD5

CD5 in lymphoma

- 80% T cell lymphomas
- >95% SLL (CLL-like) NHL (strong)
- >90% mantle cell lymphoma (weak)
- Minority of DLBCL
- Other B-cell NHLs negative

SLL

CD5

Basic stains: CD5

- Modulates T & B cell signalling
- Pan-T cell marker
  - >95% thymocytes
  - 100% post-thymic T-cells
  - ↑ expression with maturity
- Minor population normal B-cells:
  - ca. 10% peripheral B-cells
  - ↑ in autoimmunity
- Lymphomas:
  - >50% T-cell neoplasms
  - B-cell NHL
    - B-CLL/SLL (80%)
    - Mantle cell NHL (80%)
    - 10% DLBCL

Case 17: CD5

CD5

Case 17: Ki-67

Basic stains: Cyclin D1

- cyclin family
  - control of cell cycle
- normal proliferating cells, e.g. basal epidermal cells positive
- variable clone sensitivity
- Bcl-1 gene product at 11q13
- upregulated in cells with t(11;14)
- >90% MCLs positive (nuclear)
- 15% myelomas positive (nuclear)
Case 17: Cyclin-D1

• CD23<sup>−</sup>
• Cyclin-D1<sup>+</sup>
• SOX11<sup>+</sup>

Paraffin FISH:
• split at 11q13 (BCL-1; CCND1)
• Compatible with t(11;14)

Case 17: supplementary

• CD23<sup>−</sup>
• Cyclin-D1<sup>+</sup>
• SOX11<sup>+</sup>

Paraffin FISH:
• split at 11q13 (BCL-1; CCND1)
• Compatible with t(11;14)

Abnormal: 1Y 1G 1O

Case 17: Diagnosis

Mantle cell lymphoma

Morphology
• small-medium lymphocytes
• irregular angled nuclei
• nodular or mantle-zone or diffuse

Clinical
• adults (elderly males)
• LN, liver, spleen, Waldeyer’s ring
• frequent spread to blood and bone marrow
• may be extra-nodal
• lymphomatoid polyposis
• aggressive
• median survival 3-4 yrs

Mantle Cell Lymphoma 1

Morphology
- small-medium lymphocytes
- irregular angled nuclei
- blastoid variant
- nodular or mantle-zone or diffuse

Clinical
- adults (elderly males)
- LN, liver, spleen, Waldeyer’s ring
- frequent spread to blood and bone marrow
- may be extra-nodal
- lymphomatoid polyposis
- aggressive
- median survival 3-4 yrs

Immunology
- surface Ig +
- CD5 +
- CD10, 19, 20, 22, 79a +
- cyclin D1 +
- CD10/blastoid -
- CD23 -

Genetics
- t(11;14)
- BCL-1 rearranged

Mantle Cell Lymphoma 2

Immunology
- surface Ig +
- CD5 +
- CD19, 20, 22, 79a +
- cyclin D1 +
- CD10/blastoid -
- CD23 -

Genetics
- t(11;14)
- BCL-1 rearranged

Mantle Cell Lymphoma
Mantle Cell Lymphoma

Mantle Cell Lymphoma: Blastoid Variant

Mantle Cell Lymphoma: Blastoid Variant

Ki-67

Mantle Cell Lymphoma: Lymphomatous Polyposis

MCL vs B-LB

- Favours MCL:
  - coexpression of CD5 and B-cell Ag
  - TdT -
  - CyclinD1\textsuperscript{pos}
  - SOX11\textsuperscript{pos}
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- Marginal Zone NHL
  - MALT
    - Extranodal sites: gastric, skin, ocular, lung, breast, thyroid
    - May have history of
      - Autoimmunity
      - Helicobacter pylori
    - Indolent
      - Local treatment
      - Antibiotics
    - Transformation
  - Nodal marginal zone
  - Primary splenic (villus lymphocytes)

MALT Lymphoma: Primary Sites

20% - 50% of extranodal NHL

- GI only: 42%
  - Stomach: 33%
    - Helicobacter pylori
  - Intestine: 9%
- Head/neck: 11%
- Skin: 10%
- Orbit: 10%
- Chlamydia psittaci
- Lung: 10%
- Thyroid: 4%
- Breast: 3%
- Multiple MALT: 11% (78% GI)

Marginal Zone Lymphoma (MALToma)

Morphology
- small centrocyte-like
- monocytoid B cells
- plasma cells

Immunology
- surface Ig +
- CD19, 20, 22, 79a +
- CD5, 10, 23 -

Genetics
- t(11;18)
- trisomy 3

Clinical
- extranodal & nodal
- indolent
- autoimmune disease
- gastritis: H. pylori
- trisomy 3

Normal MALT: Peyer’s Patch

Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type: definition

- extranodal lymphoma
- heterogeneous small B cells including in varying proportions
  - marginal zone (centrocyte-like) cells
  - monocytoid cells
  - small lymphocytes
  - scattered immunoblast- and centroblast-like cells
- plasma cell differentiation in 40% of the cases
- infiltrate in the marginal zone of reactive B-cell follicles and extends into the interfollicular region.
Gastric MALT Lymphoma

- Basic immunoarchitecture
- CD79a positive lymphoma cells surround reactive follicles

Gastric MALT Lymphoma: MZ B cells

Gastric MALT Lymphoma: Lymphoepithelial lesions
Gastic MALT lymphoma
- neoplastic B cells form lymphoepithelial lesions
- a marginal zone distribution is often seen when MALT lymphoma spreads to lymph nodes

MALT lymphoma: Follicular colonization

Marginal zone/MALT type lymphoma: Grading
- MALTOMA – use only for histologically low-grade lesion (mostly small cells)
- †† scattered large cells - still good prognosis (no need to grade as for FL)
- Areas of diffuse large B-cell lymphoma - diagnose separately (similar to FL with DLBCL)
  - Marginal zone B-cell lymphoma of MALT type
  - Diffuse large B-cell lymphoma (estimate proportion of each)
  - Not: “high-grade MALT lymphoma”

Marginal zone/MALT lymphoma: Immunophenotype
- Immunoglobulin + (M>G>A; D-): clg 40%
- B-cell antigens + (CD20, CD79a, CD19, CD22)
- CD 23 +/-, CD43 +/-
- CD5-, CD10-, Cyclin D1-
Marginal zone/MALT lymphoma: Genetics

- Cytogenetics
  - Trisomy 3: 60%
  - t(11;18)(q21;q21): 40%
  - do not respond to H. pylori eradication
  - t(1;14): rare

Gastric MALT Lymphoma: Treatment

- H. Pylori infection in 50-100%
- Eradication of HP: regression in 50-90% of positive cases
- t(11;18) do not respond
- Differential diagnosis gastritis vs MALTOM
  - Decide diagnosis before treating with HP therapy

MALT lymphoma: Differential diagnosis

- Reactive lymphoid infiltrate
  - e.g. follicular gastritis, thyroiditis, lymphoepithelial saladenitis, follicular conjunctivitis
  - Extrafolicular proliferation of marginal zone B cells
  - Epithelial infiltration in stomach
- Look for
  - Ig light chain restriction (surface, cytoplasmic)
  - Consider PCR clonality studies
- Other small B-cell lymphomas
  - Lymphoplasmacytic
    - Distinguish on clinical features
  - FL, MCL, CLL: immunophenotype usually diagnostic

MALT vs Reactive

- Favours MALT:
  - diffuse sheets CD20+ B-cells
  - lymphoepithelial lesions
  - cytological atypia
  - Dutcher bodies
  - CD43+ B-cells

MALT vs B-Cell Lymphoma

- MALT vs MCL
  - CD5 - CyclinD1 -
- MALT vs FL
  - CD10 -
  - CD5 -
  - Bcl-6 -

Marginal Zone B-cell Lymphoma: Lymph node Involvement
Splenic Marginal Zone Lymphoma vs Other B-Cell Lymphoma

- marginal zone component
- outer zone with blasts
- no mantle zone
  - CD10 -
  - CD5 -
  - CD43 -
  - CyclinD1