Introduction to Lymph Node Pathology

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Normal lymph node
Reactive patterns

• Follicular hyperplasia discussed
• Sinus hyperplasia
• Paracortical hyperplasia
Reactive Lymphoid Hyperplasia
Follicular Pattern

- Numerous enlarged, oddly shaped follicles
- Prominent germinal centers
- Tingible body macrophages
- Nonhomogenous lymphoid population
- Frequent mitoses
- Polyclonal surface immunoglobulins
- Germinal centers negative for bcl-2
Common Lymphomas

- Diffuse large B cell lymphoma, NOS
- Follicular lymphoma
- Small lymphocytic lymphoma
- Peripheral T cell lymphoma, NOS
- Classical Hodgkin lymphoma
Diffuse Large B-Cell Lymphoma
DLBCL: Definition

- Diffuse proliferation of large neoplastic B lymphoid cells
- Nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte
DLBCL: Epidemiology

- 30-40% of adult non-Hodgkin lymphomas in western countries; higher proportion in developing countries
- Broad age range (median: 7th decade) including children
- Slightly more common in man
- Increasing incidence, independent of HIV
DLBCL: Morphology

- Typically replaces the normal architecture in a diffuse pattern
- LN involvement may be complete, partial, interfollicular, or, less commonly sinusoidal
- The perinodal soft tissue is often infiltrated; broad or fine bands of sclerosis may be observed
Diffuse Large Cell Lymphoma
Morphologic Variants
Centroblastic

- Medium to large cells with oval to round, vesicular nuclei with fine chromatin and 2-4 nucleoli. The cytoplasm is generally scanty.
- May have a monomorphic or polymorphic appearance.
- Cells may be multilobated. Centroblasts may be admixed with some immunoblasts.
DLBCL, Centroblastic variant
Morphologic Variants

Immunoblastic

- Immunoblasts > 90%, with a single centrally located nucleolus and an appreciable amount of basophilic cytoplasm
- Centroblasts <10%
- Plasmacytoid differentiation may be present
- Clinical and/or immunophenotypic findings may be essential in differentiating from extra-medullary involvement by a plasmablastic variant of plasma cell myeloma
DLBCL, Immunoblastic variant
Diffuse Large B-Cell Lymphoma

Centroblastic

Immunoblastic
DLBCL: Immunophenotype

- Express pan-B markers (CD19, CD20, CD22, and CD79a), but may lack one or more
- Surface/cyto Ig (IgM > IgG > IgA): 50-75%. Cyto Ig is often seen in cases with plasmacytic differentiation
- CD30: vast majority of anaplastic LBCL and occasional non-anaplastic cases
- CD5+ in 10% and CD10+ 25-50%. CD5+ DLBCL are negative for cyclin D1 (vs blastoid MCL). CD5+ DLBCL may arise de novo rather than as progression of SLL/CLL
**DLBCL: Immunophenotype**

- BCL2+ in 30-50%
- BCL6+ in a very high proportion of cases
- P53 expression, usually associated with *TP53* mutations, in a minority of cases
- Plasma cell-associated markers such as syndecan (CD 138) in a minority of cases
- Ki-67+ is usually high (>40%) and may be greater than 90%
DLBCL: Genetics

- Most cases have rearranged Ig H and L chain genes and show somatic mutations in the variable regions
- t(14:18) occurs in 20-30%
- Up to 30% show abnormalities of the 3q27 involving BCL6
- MYC rearrangement is uncommon
- Many cases exhibit complex cytogenetic abnormalities
- EBV+ is more common in cases associated with immunodeficiency
DNA microarrays identified two major molecular categories with gene expression patterns suggestive of different stages of B-cell development.

One type had an expression profile characteristic of germinal center B-cells, whereas the other type had a profile similar to that of in vitro activated peripheral blood B-cells.
Follicular Lymphoma
Follicular Lymphoma, Definition

- Neoplasm of follicular centre B cells, with at least a partially follicular pattern. The lymphoma cells consist of two types: centrocytes (cleaved follicle centre B cells), and centroblasts (non-cleaved follicle centre B cells)
- Predominantly adults
- 70% of low grade lymphomas
- Most patients have widespread disease at diagnosis (bone marrow involvement in 40-50%)
- Patients are usually asymptomatic at diagnosis, except for lymph node enlargement
Follicular Lymphoma, Morphology

- Follicular architecture
- Neoplastic follicles are: poorly defined and closely packed, no mantle zone, no polarization, no tingible-body macrophages
Follicular Lymphoma
Follicular Lymphoma

Centrocytes

Centroblasts
Follicular Lymphoma, Grading

- Grade 1: 0-5 centroblasts / hpf
- Grade 2: 6-15 centroblasts / hpf
- Grade 3: > 15 centroblasts / hpf
  - 3a: Some centrocytes present
  - 3b: Solid sheets of centroblasts
Follicular Lymphoma in Bone Marrow

Paratrabecular pattern
Follicular Lymphoma, Grade 3
Follicular Lymphoma, Grade 3
Follicular Lymphoma, Immunophenotype

- Surface Ig +
- Express B-cell antigens: CD19, CD20, CD22, CD79a
- CD 10 +
- BCL-2 + (can help distinguishing from reactive follicles; however, grade 3 and cutaneous type may be negative)
- BCL 6 +
BCL2 Staining
Use in distinguishing reactive follicular hyperplasia from follicular lymphoma
Follicular Lymphoma, Grade 3

Bcl2
CD10

Follicular Lymphoma, Grade 3
Follicular Lymphoma, Pattern

- Follicular: > 75% follicular
- Follicular and diffuse: 25-75% follicular
- Minimally follicular: < 25% follicular
Follicular Lymphoma, Genetics

- $t(14;18)$ (q32;q21)
- BCL 2 rearrangement, present in 70-95% of cases
- Confers a survival advantage on B cells; failure to switch off BCL 2 during blast transformation may contribute to development of lymphoma by preventing apoptosis
Follicular Lymphoma, Prognosis

- Grades 1 and 2: indolent
- Grade 3: aggressive; treatment as for DLBCL, 25-33% of cases progress to DLBCL
Small Lymphocytic Lymphoma
SLL/CLL: epidemiology

- CLL: comprises 90% of chronic lymphoid leukemias in USA and Europe.
- SLL: 6.7% of non-Hodgkin’s lymphoma.
- Majority of patients >50 y/o (median 65).
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 $> 5 \times 10^3/ul$
- Healthy pts with a B cell clone, PB monoclonal B cell count $< 5 \times 10^3/ul$ -> monoclonal B cell lymphocytosis (3.5% of pts $> 40$ y/o)
- SLL: restricted to non-leukemic cases (PB monoclonal B cell count $< 5 \times 10^9/l$) -> This talk is limited to SLL
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
Small Lymphocytic Lymphoma

Pseudo-follicle
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.
Small Lymphocytic Lymphoma
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 abnormalities 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 abnormalities 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 Bcl-1 gene rearrangement have been reported. These cases may have been leukemic MCL and misdiagnosed as CLL.
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%. Overall median survival is 7 yrs.
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.
Peripheral T-cell Lymphoma, unspecified
Peripheral T-Cell Lymphoma, NOS

- T-cell lymphomas that don’t meet the criteria for the more specific types
- About 50% of the T-cell lymphomas
- Mostly adults, but may occur in children
- Usually nodal, but may be extranodal
- Usually advanced stage at diagnosis
Peripheral T-Cell Lymphoma Unspecified

- Patients present with lymphadenopathy
- Constitutional symptoms often present
- Paraneoplastic features: eosinophilia, pruritus, hemophagocytic syndrome
- Aggressive clinical course
  - Patients respond poorly to treatment
  - Relapses are frequent
  - Overall 5 year survival 20-30%
Peripheral T-Cell Lymphoma Unspecified

- Diffuse infiltration with effacement of lymph node architecture
- Broad cytologic spectrum: usually predominance of medium-sized or large cells with irregular nuclei
- Clear cells and Reed-Sternberg-like cells
- High endothelial venules increased
- Polymorphous inflammatory background
Peripheral T-Cell Lymphoma
Unspecified

- T-zone variant
  - Interfollicular growth pattern with preserved or even hyperplastic follicles
  - Tumor cells predominantly small or medium-sized without nuclear pleomorphism
- Lymphoepithelial variant (Lennert lymphoma)
  - Diffuse or interfollicular
  - Numerous small clusters of epitheliod histiocytes
Peripheral T-Cell Lymphoma
Unspecified
Peripheral T-Cell Lymphoma
Unspecified

**Immunophenotype**
- T-cell associated antigens (CD3, CD5, CD7)
- Often show loss of normal antigen expression
- Most nodal cases are CD4+, CD8-
- CD30 may be positive, but not cytotoxic granule associated proteins
- Some cases may express CD56, usually extranodal with cytotoxic T-cell phenotype

**Genetics**
- TCR genes clonally rearranged in most cases
Classical Hodgkin lymphoma
Classical Hodgkin lymphoma

- 95% of Hodgkin lymphomas
- Bimodal age distribution
- EBV has been postulated to play a role
Sites of involvement

- Cervical lymph nodes
- 60% have mediastinal involvement
- Bone marrow involvement rare (5%) – stage IV disease
Hodgkin Lymphoma
Malignant Cell Variants

Mononuclear Hodgkin Cell

Lacunar cells seen in nodular sclerosis Hodgkin lymphoma
Hodgkin Lymphoma

Diagnostic Reed-Sternberg cell
Reed-Sternberg cell
RS cells
Mummified RS cell
Defining characteristics

- RS cells in the appropriate cellular background
Immunophenotype

CD45- , CD15+ , CD30+

The neoplastic cells are usually not CD20 positive

The background lymphocytes are T cells (CD20 negative)
RS cells and CD15
CD15

Neutrophil

RS Cell

RS Cell
CD30
EBV

- The prevalence of EBV in RS cells varies according to the histological subtype:
  - Highest in mixed cellularity (75%)
  - Lowest in nodular sclerosis (10-40%)
EBV-encoded Latent Membrane Protein 1 (LMP 1)
Hodgkin Lymphoma
Nodular Sclerosis Type
Nodular Sclerosis
Lacunar cells
RS and lacunar cells
Nodular Sclerosis

- Most common type
- The only type of HL without a male predominance
Mixed Cellularity HL

- More frequent in patients with HIV infection and in developing countries
- A bimodal age distribution is not seen
Mixed cellularity
Mixed cellularity
Lymphocyte rich classical Hodgkin lymphoma

- Nodular (common)
- Diffuse
Nodular lymphocyte rich HD
LRHD and CD20
Lymphocytde depleted HD
Lymphocyte depleted HD
Classical Hodgkin: Prognosis

- Prognosis is now based on the clinical stage rather than the histological subtype.