Hematopathology III
Lymphomas and Plasma Cell Disorders

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Hematopoietic neoplasms

**Acute**
- Lymphoid
  - Acute lymphoblastic leukemia

**Myeloid**
- Acute myeloid leukemia

**Chronic**
- Lymphoid
  - Chronic leukemias
- Plasma cell disorders
  - Lymphomas

Myeloid
- Myeloproliferative disorders

Lymphomas

**Non-Hodgkin**
- B-cell
  - Follicular lymphoma
  - Mantle cell lymphoma
  - Burkitt lymphoma
  - Diffuse large B-cell lymphoma

**Hodgkin**
Diffuse Large B-cell Lymphoma

- Constitutes about 35% of adult NHLs
- Median age: 60 years old
- Heterogeneous group of neoplasms

Diffuse Large B-cell Lymphoma
Clinical course

- Rapidly enlarging, symptomatic mass at single or multiple sites, sometimes with extranodal involvement
- Complete remission is achieved in 60-80% of patients and 50% remain free from disease for several years
- Microarray analysis shows two distinct subtypes: Germinal center B-cell (GCB) and activated B-cell (ABC)

Diffuse Large B-cell Lymphoma
GCB versus ABC

Nature. 2000 Feb 3;403(6769):503-11
Diffuse Large B-cell Lymphoma
Immunophenotypic and Cytogenetic Features

- Most express the B-cell marker CD20
- 30% of patients have t(14;18)
- 30-40% of patients have rearrangements of the BCL6 locus on chromosome 3q27
- Occasional cases have MYC translocations along with either t(14;18) or BCL6. These are called “double hit” lymphomas and have a particularly aggressive clinical course.
Lymphomas

Non-Hodgkin

Hodgkin

B-cell

T-cell

• Follicular lymphoma
• Mantle cell lymphoma
• Burkitt lymphoma
• Diffuse large B-cell lymphoma

Peripheral T-Cell Lymphoma (PTCL) NOS

• Presentation: lymphadenopathy, eosinophilia, pruritis, fever, weight loss

• Lack a specific histologic feature (waste-basket diagnostic category)

• The most important techniques to make a diagnosis are immunophenotypic (CD3+ with loss of other pan-T cell marker) and genotypic analysis
Lymphomas

Non-Hodgkin

B-cell

• Follicular lymphoma
• Mantle cell lymphoma
• Burkitt lymphoma
• Diffuse large B-cell lymphoma

T-cell

Hodgkin

Hodgkin lymphoma

• Approximately 8,000 new cases reported annually

• It has a bimodal age involvement (young adults/adolescents and older adults)

• Generally arises in single lymph node and spreads at least initially to anatomically contiguous lymphoid tissue

• Characterized by Reed-Sternberg cells

• Extranodal presentation is rare

Hodgkin Lymphoma: Classification

• Classical Hodgkin lymphoma:
  Lymphocyte rich
  Mixed cellularity
  Lymphocyte depleted
  Nodular sclerosis

• Nodular lymphocyte predominant Hodgkin lymphoma
Etiology and pathogenesis of Hodgkin lymphoma

• It is a clonal neoplastic disorder arising from B cells

• Reactive cells are most likely due to the cytokines secreted by RS cells (IL-5, IL-6, IL-13, TNF, GM-CSF)

• NF-kB activation by EBV or some other mechanism is common event in classical Hodgkin lymphoma

Hodgkin lymphoma histology

• Reed-Sternberg (RS) cells ("owl-eye")

• RS-cell variants [mononuclear variant, lacunar cells, lymphocytic & histiocytic (L&H, pop-corn) cells]

• Reactive lymphocytes, histiocytes and granulocytes

• Classical HL usually shows eosinophils

• RS cells constitute only a minor fraction (1-5%) of the total tumor mass

Histologic Classification of HL

<table>
<thead>
<tr>
<th>Classical</th>
<th>Lymphocyte rich</th>
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<th>Nodular sclerosis</th>
<th>Nodular lymphocyte predominant</th>
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<tbody>
<tr>
<td>LR</td>
<td>CD30</td>
<td>MC</td>
<td>CD15</td>
<td>NS</td>
<td>LP</td>
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Hodgkin lymphoma histology

- Lymphocyte rich subtype: Reactive small lymphocytes predominate, few mononuclear or classic Reed-Sternberg cells
- Mixed cellularity: Reed-Sternberg cells and variants on a mixed cellular background including eosinophils, plasma cells, T-lymphocytes, histiocytes
- Lymphocyte depleted type: Paucity of lymphocytes and relative abundance of Reed-Sternberg cells
- Nodular sclerosis: fibrous nodular pattern, lacunar cells
- Nodular lymphocyte predominant subtype: nodularity with predominance of mature lymphocytes and popcorn cell or L & H variant of RS cells

Histologic Classification of HL

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Nodular sclerosis Hodgkin lymphoma
Reed-Sternberg cell (Lacunar variant)

Popcorn like cells in LP-Hodgkin lymphoma

Hematopoietic neoplasms

- Acute
  - Lymphoid: Acute lymphoblastic leukemia
  - Myeloid: Acute myeloid leukemia

- Chronic
  - Lymphoid: Chronic leukemias, Lymphomas
  - Myeloid: Myeloproliferative disorders, Plasma cell disorders
Plasma cell neoplasms and related disorders

• Multiple myeloma (plasma cell myeloma)

• Monoclonal gammopathy of undetermined significance (MGUS)

• Waldenstrom’s macroglobulinemia
  A related disorder that shows high levels of IgM monoclonal protein and hyperviscosity of blood, with underlying lymphoplasmacytic lymphoma. Mutation in the MYD88 gene.

Multiple Myeloma

• The presence of monoclonal plasma cell proliferation involving bone marrow and typically skeleton at multiple sites

• Proliferation of plasma cells appears to be dependent on cytokines, especially IL-6

• Frequent cytogenetic abnormalities involving FGFR3 (fibroblast growth factor receptor 3), Cyclin D1 and Cyclin D3 genes

Diagnostic criteria for multiple myeloma

• Monoclonal protein in serum or urine IgG (60%), IgA (25%)

• Bone marrow showing clonal plasmacytosis or presence of a plasmacytoma

• Related organ damage: CRAB, i.e. hyperCalcemia, Renal insufficiency, Anemia, Bone lesions
Multiple Myeloma

![Image of a skull with bone lesions]

Multiple Myeloma

![Image of protein electrophoresis gels comparing normal serum and patient serum]

Multiple Myeloma

![Image of bone marrow biopsy showing plasma cells]
Multiple Myeloma
Clinical features

• 30,000 cases/year, median age: 70 years
• Bone resorption: hypercalcemia, fractures
• Suppression of humoral immunity leading to recurrent infections (Str. Pneumoniae, Staph. Aureus, E. coli)
• Bence-Jones proteinuria causing renal insufficiency. Light chains are toxic to tubular epithelium. Amyloidosis of the AL type.

MGUS: Monoclonal Gammopathy of Undetermined Significance

• Most common plasma cell neoplasm (3% of persons older than 50 years
• M-spike is less than 3 g/dl and patients are asymptomatic
• 1% of patients with MGUS transform to multiple myeloma per year

Thanks!

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