Hodgkin Lymphoma and
Differential Diagnosis

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Learning Objectives

• Discuss the most recent classification of Hodgkin lymphoma
• Discuss the immunohistochemical studies most useful in diagnosing Hodgkin lymphoma
• Discuss the differences between classical and nodular lymphocyte predominance Hodgkin lymphoma
• Discuss the differential diagnosis of Hodgkin lymphoma

Hodgkin Lymphoma:
Historical Classifications

<table>
<thead>
<tr>
<th>Jackson-Parker</th>
<th>Lukes</th>
<th>Rye</th>
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</thead>
<tbody>
<tr>
<td>Paragranuloma</td>
<td>Lymphocytic and histiocytic nodular or diffuse Nodular sclerosis</td>
<td>Lymphocyte predominance Nodular sclerosis</td>
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<tr>
<td>Granuloma</td>
<td>Mixed cellularity Diffuse fibrosis</td>
<td>Mixed cellularity</td>
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<tr>
<td>Sarcoma</td>
<td>Reticular</td>
<td>Lymphocyte depletion</td>
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</tbody>
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Hodgkin Lymphoma:
Modern Classification

• Nodular lymphocyte predominance
• Classical
  – Nodular sclerosis
  – Mixed cellularity
  – Lymphocyte-depleted
  – Lymphocyte-rich
Classical Hodgkin Lymphoma

- Monoclonal neoplasm of B-cells of the germinal center that have ineffective immunoglobulin receptors but have somehow escaped the normal apoptotic process that culls these cells
- Unique histology influenced by cytokine-ligand interactions
- 95% of Hodgkin lymphoma
- Male predominance with bimodal peak in young adulthood and old age
- 40% of cases associated with EBV in Western countries; higher in developing countries

Classical Hodgkin Lymphoma: Pathology

- Diagnosis established by the identification of Reed-Sternberg cells and variants in the appropriate milieu
- Reed-Sternberg cell: Multi-nucleate or multilobate large cell with each nucleus or lobe containing a prominent eosinophilic nucleolus with a modest rim of amphiphilic cytoplasm
- Hodgkin cell: Mononucleate cell with features similar to R-S cell
Phenotype of Classical Hodgkin Cells in Paraffin Sections: Primary Panel

- CD45 (<5% +)
- CD30 (98% +)
- CD15 (85% +)
- CD20 (20% + variable)
- CD3 (<5% +)
**Phenotype of Classical Hodgkin Cells: Additional Antibodies**

- MUM-1 (98% +)
- PAX-5 (90% + weak)
- Fascin (90% +)
- EBV LMP-1 (30-40% +)
- BCL-6 (40% +)
- CD138 (30% +)
- BOB.1/OCT-2/CD79a (10% +)
- EMA (<5% +)
- Cytotoxic markers (<5% +)
- ALK (0%)
Classical Hodgkin Lymphoma: Expanded Panel

- PAX-5, T-cell and cytotoxic markers, ALK (HL vs. ALCL)
- BOB-1, OCT-2 (CHL vs. T/HRBCL)
- LMP-1 (CHL vs. other, particularly in children and elderly)
- MUM-1, BOB-1, OCT-2 (CHL vs. NLPHL)

Prognostic Significance of Immunohistochemical Markers in cHL

- Worse prognosis
  - CD68+ host cells
  - CD20+ H/RS cells
  - CD15- H/RS cells
  - EBV+ in patients older than 60
  - EBV- in patients younger than 15
Nodular Sclerosis Classical Hodgkin Lymphoma: Grading

- Grade II if:
  - >25% nodules show reticular or pleomorphic lymphocyte depletion
  - >80% of the nodules show fibrohistiocytic lymphocyte depletion
  - >25% nodules contain bizarre and highly anaplastic Hodgkin cells with lymphocyte depletion

- Grade I: All other cases
Nodular Sclerosis Classical Hodgkin Lymphoma: Differential Diagnosis

- Carcinoma (keratin)
- Melanoma (S-100)
- Germ cell tumor (OCT4, keratin)
- Non-Hodgkin lymphoma (CD45, CD20, CD43, CD30, CD15)
- Necrotizing granulomatous lymphadenitis
B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL and Classical Hodgkin Lymphoma

- Lymphoma with morphologic, phenotypic, and molecular features overlapping DLBCL, particularly PMBCL and HL
- Rare; usually young adults 20-40 years, with a male predominance
- Mediastinal mass most common, often with supraclavicular LNs; may involve only lymph nodes
- May occur sequentially, usually CHL followed by DLBCL
- Usually EBV –
- Poor outcome, worse than either CHL or PMBL; usually treated as DLBCL, but still does not respond well

B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL and Classical HD: Histopathology

- Usually see confluent, sheet-like growth, often in a diffusely fibrotic stroma; may see fibrous bands
- Cells are large and pleomorphic; may resemble RS/H cells; may resemble DLBCL cells
- May see variation from field to field
- May see a cohesive or sinusoidal growth pattern focally
- Inflammatory infiltrate is often sparse
B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL and Classical HL: Immunophenotype

- CD30+, CD15 +/-
- CD45 +/-, CD20 +/-
- CD79a, PAX5, OCT-2 and BOB.1 +/-
- Bcl-6, CD10 +/-
- ALK, cytotoxic markers –
- Clonal gene rearrangements in the few cases studied
Mixed Cellularity Classical Hodgkin Lymphoma: Differential Diagnosis

- T-cell/histiocyte-rich B cell lymphoma
- Peripheral T-cell lymphoma, nos
  - *With R-S like cells*
- ALK+ anaplastic large cell lymphoma
  - *With lymphohistiocytic features*
- Reactive paracortical hyperplasia

### Mixed Cellularity Hodgkin Lymphoma vs. T-cell/Histiocyte-Rich B-Cell Lymphoma

<table>
<thead>
<tr>
<th>Marker</th>
<th>MCHL (%)</th>
<th>T/HRBCL (%)</th>
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<tbody>
<tr>
<td>CD30</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
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<td>85</td>
<td>1</td>
</tr>
<tr>
<td>CD45</td>
<td>&lt;5</td>
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<td>20-50</td>
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<tr>
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</tr>
<tr>
<td>PAX-5</td>
<td>90 (weak)</td>
<td>98 (strong)</td>
</tr>
<tr>
<td>BOB1/OCT-2</td>
<td>10/10</td>
<td>95/95</td>
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<tr>
<td></td>
<td>MCHL (%)</td>
<td>PTCL (%)</td>
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<tr>
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Mixed Cellularity Hodgkin Lymphoma vs. Peripheral T-Cell Lymphoma

CD3/PTCL

ALK/ALCL
Lymphocyte Depletion Classical Hodgkin Lymphoma

- L & C: Diffuse fibrosis and reticular types
- Elderly, HIV +, and third world countries
- Presents with abdominal nodes, spleen, liver, and bone marrow involvement
- Response to treatment typical for HL
Lymphocyte Depletion Hodgkin Lymphoma: Differential Diagnosis

- Non-Hodgkin Lymphoma
  - Diffuse large cell lymphoma, NOS
    - CD45, CD20, CD43, CD30, CD15, EBV-LMP
  - Anaplastic Large Cell Lymphoma
    - CD45, CD20, CD43, CD30, CD15, EBV-LMP, EMA, PAX-5, cytotoxic markers, ALK

- Sarcoma (pleomorphic)
  - CD15, CD30

Classical Hodgkin Lymphoma vs. Anaplastic Large Cell Lymphoma

<table>
<thead>
<tr>
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<th>ALCL (%)</th>
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Lymphocyte-Rich Classical Hodgkin Lymphoma

- Diffuse or nodular
- Diffuse histologically similar to MC with few Hodgkin cells; immunohistochemistry similar to MC
- Nodular often histologically similar to nodular LP type; immunohistochemistry similar to MC
- Associated with EBV
Lymphocyte Rich Hodgkin Lymphoma: Differential Diagnosis

- Nodular L & H lymphocyte predominance
  - CD45, CD20, CD30, CD15, CD57/PD1, MUM-1
- SLL/CLL
  - CD20, CD43, CD45, CD5, CD23, CD15, CD30, EBV-LMP-1
- Reactive paracortical hyperplasia
  - CD20, CD43, CD15, CD30, EBV-LMP-1
Nodular Lymphocyte Predominance Hodgkin Lymphoma: Clinical

- All ages, including children; M:F = 2.5:1
- Mostly Stage I; cervical, axillary, inguinal
- Lymph nodes most often involved
- Higher stages have spleen and liver
- Can arise in PTGC

NLPHEL: Architecture

- Complete or partial effacement common
- Uneffaced areas may show normal appearance, reactive follicular hyperplasia or PTGC
- Large nodules; diffuse areas may be present
- Nodules may be highlighted by epithelioid histiocytes
- Vague nodularity even in diffuse cases
NLPHL: LP/L & H cells

- Large cells with large nuclei
- Multilobated nuclear outlines
- Vesicular chromatin
- Medium-sized nucleoli
- Scanty nondescript cytoplasm
- No truly diagnostic R-S cells; mimics
### NLPHL: Host Cells
- Small lymphocytes
- Epithelioid histiocytes
- Plasma cells (between nodules)
- No eosinophils, typically

### Phenotype of LP/L&H Cells
- CD45 + (95%)
- CD30 - (10% weak +)
- CD15 - (10% +)
- CD20, PAX-5 + (95%)
- Bcl-6, bcl-2 + (95%)
- EMA +/- (70%)
- CD3, CD43, CD10, MUM-1 - (0%)

### Phenotype of Host Cells
- Nodules + for B-lineage antigens
- Numerous CD57/PD-1/bcl-6 + T cells, with ringing around L&H cells
- May see CD4 +/-CD8+ population by flow cytometry
- Numbers of T-cells increase with recurrences
Nodular Lymphocyte Predominance Hodgkin Lymphoma: Differential Diagnosis

- Progressive transformation of germinal centers
  - No effacement of architecture
  - No L&H cells; OCT-2 can be helpful
- Classical Hodgkin lymphoma
  - Character of Hodgkin cells
  - Phenotype (CD30, CD15, CD45, MUM-1, BOB.1, OCT-2)
- T-cell/histiocyte rich large B-cell lymphoma
  - Clinical history
  - No nodularity
  - No nodules of B-cells
  - No ringing of CD57/PD-1/bcl-6 + cells
Mixed Cellularity Hodgkin Lymphoma vs. Nodular Lymphocyte Predominance

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NLPHEL: Treatment and Prognosis

- **Treatment:**
  - Low stage disease: Surgical/RT/Chemo
  - High stage disease: Chemotherapy

- **Prognosis:**
  - Relapses common, independent of treatment
  - Excellent survival, independent of relapses, unless in high stage

- **Complications**
  - B cell diffuse large cell lymphoma seen in 2-10% of cases
  - PTGC may coexist or follow
  - Rare: progression to classical HL

Conclusions

- The most recent classifications of Hodgkin lymphoma distinguish between classical and lymphocyte predominance types
- There is a wide differential diagnosis of Hodgkin lymphoma
- A battery of immunohistochemical studies is most useful in distinguishing Hodgkin lymphoma from other entities