# Hodgkin Lymphoma: Historical Classifications

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

- Nodular lymphocyte predominance
- Classic(al)
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte-depleted
  - Lymphocyte-rich
Classic 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
CLONAL EXPANSION
SOMATIC HYPERMUTATION

SELECTION
advantageous
mutations

DIFFERENTIATION

disadvantageous
mutations:
- nonsense mutation
- reduced affinity
- loss of reading-frame
- gain of autoreactivity

rescue from apoptosis
additional transforming events

plasma cell
memory B cell
HRS cell

apoptotic B cell
Classic 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 Classic Hodgkin Cells in Paraffin Sections: Primary Panel

- CD45 (<5% +)
- CD30 (99% +)
- CD15 (65-85% +)
- CD20 (20% +, variable)
- PAX-5 (95% +, moderate)
- CD3 (<5% +)
Phenotype of Classic Hodgkin Cells: Additional Antibodies

- BOB.1/OCT-2/CD79a (15% +)
- MUM-1 (98% +)
- Fascin (90% +)
- EBV LMP-1 (30-40% +)
- BCL-6 (40% +)
- CD138 (30% +)
- EMA (<5% +)
- Cytotoxic markers (<5% +)
- ALK (0%)
- CD43 and other T-cell markers (?1%)
Classical Hodgkin Lymphoma: Expanded Panel

- T-cell and cytotoxic markers, ALK (HL vs. ALCL)
- BOB-1, OCT-2, CD79a, MUM-1 (CHL vs. T/HRBCL or NLPHEL)
- LMP-1 (CHL vs. other, particularly in children and elderly)
Prognostic Significance of Immunohistochemical Markers in cHL

• Worse prognosis
  – CD68+ host cells
  – CD20+ H/RS cells
  – CD15- H/RS cells
  – BCL2+ H/RS cells
  – Low FOXP3 expression in H/RS cells
  – EBV+ in patients older than 60
  – EBV- in patients younger than 15
Survival & EBV in Classic HL*
Older Adults – Ages 45 to 96 Years

*J Clin Oncol 2005;23:7604-7613
GEP Predictor of Survival in Paraffin-Embedded Tissue in Advanced cHL

*J Clin Oncol 2013;31:692-700*
Nodular Sclerosis Classic Hodgkin Lymphoma: BLNI 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
Survival of NS: Grade I vs. II*

*Cancer 1994;74:708-714

Survival (%)

NS II @ 15 years = 93%
NS I @ 15 years = 87%

NS II 43 patients
NS I 211 patients
NS: Grading (GHSG) Pathologic Risk Criteria

- **Eosinophilia**
  - ~ >5% of All Cells or
  - Clusters in 5 HPF

- **Lymphocyte Depletion**
  - <33% of All Cells In Whole Section

- **Atypia**
  - >25% Bizarre & Anaplastic H/RS Cells

*High Risk = 1 or More Risk Factors*
Survival of NS: Low vs. High Risk*  
(Eosinophilia, LD, Atypia)

*Blood 2003;101:4063-4069

Probability

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 12 24 36 48 60 72 84 96 108 120

$p < 0.0001$
Survival of NS: Low vs. High Risk*  
*(Eosinophilia, LD, Atypia)

Prognostically Relevant Only in Intermediate & Advanced Stage Disease

*Blood 2003;101:4063-4069
Nodular Sclerosis Classic Hodgkin Lymphoma: Differential Diagnosis

- Carcinoma (keratin)
- Melanoma (S-100)
- Germ cell tumor (OCT4, SALL4)
- Non-Hodgkin lymphoma (CD45, CD20, CD3, PAX-5, CD30, CD15)
- Necrotizing granulomatous lymphadenitis
Gene Expression: HL & PMBL*

*Blood 2012;120:4609-4620
B-Cell Lymphoma, Unclassifiable, with Features Intermediate Between DLBCL and Classic 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 Classic 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 Classic HL: Immunophenotype

- CD30+, CD15 +/-
- CD45 +/-, CD20 +/-
- CD79a, PAX5, OCT-2 and BOB.1 +/-
- Bcl-6, CD10 -/+ 
- CD43, ALK, cytotoxic markers –
- Clonal gene rearrangements in the few cases studied
Gene Expression: NS & MC*

- **MC:** Regulated by Interferon – Inflammation
- **NS:** Extracellular Matrix Remodeling – Deposition of Fibroblasts

*Br J Cancer 2009:101:1393-1401*
Mixed Cellularity Classic 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
<table>
<thead>
<tr>
<th></th>
<th>Mixed Cellularity Hodgkin Lymphoma (MCHL) (%)</th>
<th>T-cell/Histiocyte-Rich B-Cell Lymphoma (T/HRBCL) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>CD15</td>
<td>65-85</td>
<td>1</td>
</tr>
<tr>
<td>CD45</td>
<td>&lt;5</td>
<td>98</td>
</tr>
<tr>
<td>CD20</td>
<td>20-50</td>
<td>99</td>
</tr>
<tr>
<td>EBV-LMP</td>
<td>30-40</td>
<td>1</td>
</tr>
<tr>
<td>PAX-5</td>
<td>90 (weak)</td>
<td>98 (strong)</td>
</tr>
<tr>
<td>BOB1/OCT-2CD79a</td>
<td>15/15/15</td>
<td>95/95/95/95</td>
</tr>
</tbody>
</table>
Lennert Lymphoma: Review of 98 Epithelioid Cell-Rich Lymphomas From Kiel Registry*

- B-Cell (DLBCL, T/HRBCL) 25 26%
- Hodgkin (Classic, NLP) 21 22
- AITL 16 16
- PTCL, NOS ($T_{FH}$) 9 9
- Lennert 8 8
- AITL/NOS (Borderline) 7 7
- Reactive 2 2
- ALCL, ALK– 1 1

*Histopathology 2011;58:1173-1182
## Mixed Cellularity Hodgkin Lymphoma vs. Peripheral T-Cell Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>MCHL (%)</th>
<th>PTCL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>100</td>
<td>Variable</td>
</tr>
<tr>
<td>CD15</td>
<td>85</td>
<td>&lt;5</td>
</tr>
<tr>
<td>CD45</td>
<td>&lt;5</td>
<td>98</td>
</tr>
<tr>
<td>CD3, other T</td>
<td>&lt;5</td>
<td>98</td>
</tr>
<tr>
<td>PAX-5</td>
<td>90</td>
<td>&lt;5</td>
</tr>
<tr>
<td>EBV-LMP</td>
<td>30-40</td>
<td>1</td>
</tr>
</tbody>
</table>
Lymphocyte Depletion Classic 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 B-cell lymphoma, NOS
    • CD45, CD20, CD79a, OCT-2, BOB.1, CD30, CD15, CD138
  – Anaplastic Large Cell Lymphoma
    • CD45, PAX-5, CD3, CD43, CD30, CD15, EBV-LMP, EMA, cytotoxic markers, ALK
• Sarcoma (pleomorphic)
  • CD15, CD30
<table>
<thead>
<tr>
<th></th>
<th>CHL (%)</th>
<th>ALCL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CD15</td>
<td>85</td>
<td>5-10</td>
</tr>
<tr>
<td>CD45/CD43</td>
<td>&lt;5</td>
<td>66</td>
</tr>
<tr>
<td>CD20</td>
<td>20-50</td>
<td>&lt;1</td>
</tr>
<tr>
<td>EBV-LMP</td>
<td>30-40</td>
<td>&lt;1</td>
</tr>
<tr>
<td>PAX-5</td>
<td>90 (weak)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>&lt;5</td>
<td>95</td>
</tr>
<tr>
<td>ALK</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>
Lymphocyte-Rich Classic Hodgkin Lymphoma

- Diffuse or nodular
- Diffuse histologically similar to MC with few Hodgkin cells; may be few eosinophils and plasma cells
- Nodular often histologically similar to nodular LP type
- Immunohistochemistry similar to MC, but may have higher incidence of CD79a, OCT-2, and BOB.1 expression
- 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
HL Arising in CLL*

- “Richter-Type” Transformation
  - Rare! [18/4121 Cases of CLL – 0.4% MDA]
  - [26/3887 Cases of CLL – 0.7% Mayo]
- Discrete or Intermixed
- Phenotype of Classic HL
  - CD20 +/–
- EBV+ ~90%
- Clonal Identity ~50% (Microdissection)
- Fludarabine Related
- Poor Prognosis – Median OS 0.8 Years (MDA)
  - Median OS 3.9 Years (Mayo)

Synchronous HL & NHL

- Composite or Discordant
  - CLL/SLL
  - Follicular Lymphoma
  - Mantle Cell Lymphoma
  - Marginal Zone Lymphoma
  - Large B Cell Lymphoma
- Discrete or Intermixed
- EBV+ (~50% in MZL & LBCL)
HL – Post XRT
NS + Foamy Macrophages
Histology of Relapse

• **Untreated Site***
  - Histologic Persistence 46/52 (89%)
  - Histologic Alteration 6/52 (11%)
    - NS/MC MC/NS
    - NSCP/MC NSCP/LD

• **Treated Site**
  - Histologic Persistence 25/46 (54%)
  - Histologic Alteration 21/46 (46%)
    - Unclassifiable 9/46 (20%)

*Cancer 1980;45:289-292
+Cancer 1981;48:1124-1126
HL – Recurrence in Rx Site
HL – Recurrence in Rx Site

CD30
Extranodal Hodgkin Lymphoma?

• Primary classic Hodgkin lymphoma essentially does not occur in tonsil, appendix, or extranodal sites (or mesenteric lymph nodes)

• Be extremely skeptical of case
  – More likely to be non-Hodgkin lymphoma (e.g., ALCL)
  – Or an EBV-positive lymphoproliferation (e.g. EBV+ mucocutaneous ulcer)

• Extranodal involvement may occur with contiguous or retrograde spread (e.g., lung)
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
NLPHL: 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
NLP – Variant Patterns


Pattern A
“Classical” B-cell-rich nodular

Pattern B
Serpiginous/Interconnected

CD20
NLP – Variant Patterns

Pattern C
Prominent extra-Nodular L&H cells

Pattern D
T-cell-rich nodular


CD20
NLP – Variant Patterns

Pattern E
Diffuse (TCRBCL or DLBCL-like)

Pattern F
Diffuse moth-eaten, B-cell-rich

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%)
- CD79a, OCT-2, BOB.1 + (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
LP/L & H CELLS: Immunoglobulin Expression

- **IHC:** Polytypic, monotypic (k>>l), or absent Ig proteins
- **ISH:** Absent or monotypic (k>>l), mRNA
- **SBH:** Nonclonally rearranged Ig genes
- **PCR tissue:** Nonclonally rearranged Ig genes
- **PCR cells:** Clonal or nonclonally rearranged Ig genes
- **IgD expression** identifies subset of younger patients with male predominance, in Stage I, with preferential involvement of cervical lymph nodes
NLP HL

- CD45
- CD20
- CD15
- CD30
- CD57/PD1
- MUM-1
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
• Classic Hodgkin lymphoma
  – Character of Hodgkin cells
  – Phenotype (CD30, CD15, CD45, MUM-1, CD79a, 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 (ringing of PD-1 cells may be seen in T/histiocyte-rich B-cell lymphoma on occasion
## Classic Hodgkin Lymphoma vs. Nodular Lymphocyte Predominance

<table>
<thead>
<tr>
<th></th>
<th>MCHL (%)</th>
<th>NLPHEL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>CD15</td>
<td>85</td>
<td>1</td>
</tr>
<tr>
<td>CD45</td>
<td>&lt;5</td>
<td>98</td>
</tr>
<tr>
<td>CD20</td>
<td>20-50</td>
<td>99</td>
</tr>
<tr>
<td>EBV-LMP</td>
<td>30-40</td>
<td>1</td>
</tr>
<tr>
<td>PAX-5</td>
<td>95 (moderate)</td>
<td>98 (strong)</td>
</tr>
<tr>
<td>BOB1/OCT-2/CD79a</td>
<td>15/15/15</td>
<td>95/95/95</td>
</tr>
<tr>
<td>MUM-1</td>
<td>90</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
NLP HL: 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 classic HL
B-Cell Lymphoma Arising in Association with NLPHL

- Complicates about 2-10% cases of NLPHL
- Histopath: Sheets of large B cells, particularly in internodular areas
- Immuno: B cell; rare T cell
- Molecular: Monoclonal Ig sometimes corresponding to clone in previous NLPHL
NLP Transforming to DLBCL* PFS & Survival

Actuarial Risk of Transformation:
7% & 30% @ 10 & 20 Years

62% @ 10 Years OS

52% @ 10 Years PFS

*J Clin Oncol 2010;28:793-799
“LP Cell-Rich” (Syncytial)
Conclusions

• The most recent classifications of Hodgkin lymphoma distinguish between classic 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