Hodgkin’s Lymphoma
1828

Robert Carswell

“Cancer cerebriformis of the lymphatic glands and spleen”
Hodgkin’s Disease
Historical Background

1832 T. Hodgkin

“On some morbid appearances of the absorbent glands and spleen”

Reports seven cases, including the case of Carswell

1865 S. Wilks reports 15 “Cases of enlargement of the lymphatic glands and spleen

(Proposes the eponym “Hodgkin’s disease”)
1837 - T. Hodgkin fails to get post as Asst. Physician at Guy’s Hospital

Hodgkin was a Quaker and social activist - had crossed the administration

1857 - Travels to the Holy Land with Sir Moses Montefiore

1866 - Died in Jaffa during a Cholera epidemic while distributing relief to local Jewish population

Rosenfeld L. Annals Diagnostic Pathology, 4:124-133, 2000
On the Pathological Changes In Hodgkin’s Disease with Especial Reference to its Relation to Tuberculosis

D.M. Reed, JHH Reports 10: 133-199, 1902
D. Reed described features of neoplastic cells (Reed-Sternberg cells) that hold true to today -

She disputed view of Sternberg, who proposed in 1898, that Hodgkin’s was a chronic inflammatory process related to tuberculosis
Other notable insights (1902)

- “The general health of the patient before the onset of the disease is usually excellent”
- Noted early peak among children and young adults
- Noted high incidence of anergy
- Presents as painless progressive cervical adenopathy without leukemia
- Proposes that the pathological picture is sufficient for diagnosis
What ever happened to Dorothy Reed?


- Graduated in 1900, 5th in her class
- Did internship in medicine under Osler, followed by pathology fellowship
- Published a case of lymphatic leukemia, proposing an origin from the bone marrow, in addition to one other paper during her pathology fellowship
- Seeks post as an “Assistant” in pathology from Chairman Wm.Welch

Welch answered, “no women had ever held a teaching position in the school, and there would be great opposition to it.”

(She notes her predecessor as a fellow in pathology had received an appt. as Asst. Professor with no publications or research.)

“Suddenly, as I saw what I had to face in acceptance of injustice - I knew that I couldn’t take it.”
Hodgkin’s Disease vs Hodgkin’s Lymphoma

• The name “Hodgkin’s disease” was based on the uncertain status of HD, infectious or neoplastic?
  —The neoplastic nature is proven

• The cell of origin of HD was uncertain - histiocyte, reticulum cell, lymphocyte, granulocyte?
  —A B-lymphocyte origin is now proven for nearly all cases

• Therefore, the name “Hodgkin’s lymphoma” reflects our modern understanding
Hodgkin’s Lymphoma (WHO)

• Classical Hodgkin’s Lymphoma
  Nodular sclerosis (70%)
    Grade 1-2 (optional)
  Mixed cellularity (10-15%)
  Lymphocyte depleted (<5%)
  Classical Hodgkin’s lymphoma, lymphocyte-rich (5 %)
    - nodular and diffuse

• Nodular lymphocyte predominant Hodgkin’s Lymphoma
  (10-20 %)
Hodgkin’s Lymphoma is a B-cell neoplasm of GC origin

Ig gene V(D)J recombination

Somatic Mutation
Antigen Selection
Isotype switch

Plasma cell

Germinal Center

Pro B → Pre B → Naïve B

Precursor B-LL

MM

LPL

MZBCL

Memory

Classical HL

CLL

Pro B

Pre B

Naïve B

DH

JH

VH

MM

FCL
BL
DLBCL

NLPHL

NLP HL

MCL

BL

DLBCL

Classical HL

CLL

Precursor B-LL
Classical Hodgkin’s Lymphoma: Genetic Features

- Single cell PCR:
  - Ig genes rearranged, clonal, somatic mutation of VH genes
  - No Ig production – many theories
    - Crippling mutations
    - Defects in IGH transcription factors
    - Methylation/ silencing of IG genes

- Loss of the B-cell program
  - Most B-cell markers neg, except PAX-5
Nodular Sclerosis Classical Hodgkin’s Lymphoma: Clinical Features

- Frequency: ~ 75% of HL in “Western world”
- Presentation:
  - Second to Third Decades, peak incidence
  - Females > Males
  - Stage II with Mediastinal Mass
- Course:
  - Prognosis depends on stage, bulk of disease
  - Histological significance of grading less relevant with modern therapies
Aberrant T-cell ag expression in CHL
Tzankov Modern Pathol 2005; Venkataraman 2013

- Aberrant expression of CD2, CD4, CD3 was seen in 5% of CHL
- HRS cells expressing T-ag often higher grade (CHL, NS2)
- In most cases the HRS cells are genotypically B-cell (IGHR+) & lack TCR rearrangement
- PAX5 is still positive, indicative of B-cell lineage
- Misdiagnosis as Anaplastic large cell lymphoma, ALK-negative is a common pitfall
Summary of TCM expression in TCM positive cases

<table>
<thead>
<tr>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD5</th>
<th>CD2</th>
<th>CD7</th>
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</thead>
<tbody>
<tr>
<td>49</td>
<td>47</td>
<td>42</td>
<td>39</td>
<td>32</td>
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<tr>
<td>19</td>
<td>37</td>
<td>3</td>
<td>11</td>
<td>25</td>
<td>9</td>
</tr>
</tbody>
</table>
Event-free survival (EFS) by any T-cell antigen expression
Common features of Primary Mediastinal (Thymic) Large B-cell Lymphoma & Classical Hodgkin’s Lymphoma - Nodular Sclerosis

- Females > Males, 2:1 ratio
- Adolescents, young adults
- Mediastinal mass +/- Supraclavicular LN often involved
- Common cytogenetic alterations
  - Gains at 9p24 (JAK2) & 2p16 (REL)
- Similar gene expression profile with Activation of NFκB pathway
- *Thought to arise from a “thymic B-cell”*
29 yo male with mediastinal mass
• Supraclavicular LN: Classical Hodgkin’s lymphoma, Nodular Sclerosis
• 6 cycles of chemoRx with good response
• 1 month following completion of therapy, presents with new mediastinal mass
• Mediastinal Bx: DLBCL with features of primary mediastinal large B-cell lymphoma

? Two tumors or one
Single Cell Microdissection of both component shows that they are clonally related.
Mediastinal GZL represent the “missing link” between CHL-NS and PMBL

Traverse-Glehen et al AJSP 2005

- Gray zone lymphomas exhibit a morphological and immunophenotypic continuum
- MGZL cannot be readily classified as either PMBL or CHL, with frequent asynchronous histology & immunophenotype
- Clinical features similar to NS-CHL & PMBL, except for male predominance
- Composite and sequential lymphomas are a related phenomenon
MGZL

CHL-like
Morphology

Background inflammatory cells

Sheeting out of HRS like cells

B-cell program retained

Most common pattern (2/3 of cases)
Differential Diagnosis of PMBL and CHL, NS is still important as there are major treatment differences.
Continuing Questions

• Does non-mediastinal Grey zone lymphoma exist?
• Can biological studies provide insights into biology of GZL- closer to CHL or PMBL?
• How should MGZL be treated?
<table>
<thead>
<tr>
<th></th>
<th>No mediastinal disease (9)</th>
<th>Mediastinal disease (24)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – Median (range)</strong></td>
<td>55 years (24-91 years)</td>
<td>29.5 years (16-51 years)</td>
<td>0.017**</td>
</tr>
<tr>
<td><strong>Male: Female</strong></td>
<td>3:6</td>
<td>17:7</td>
<td>0.11*</td>
</tr>
<tr>
<td><strong>FISH analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2p16.1 (BCL11, REL)</td>
<td>25% (2/8)</td>
<td>36% (8/22)</td>
<td>0.68*</td>
</tr>
<tr>
<td>9p24.1 (JAK2, PDL2)</td>
<td>38% (3/8)</td>
<td>61% (14/23)</td>
<td>0.41*</td>
</tr>
<tr>
<td>16p13.13 (CIITA)</td>
<td>44% (4/9)</td>
<td>33% (7/21)</td>
<td>0.69*</td>
</tr>
<tr>
<td>8q24 (MYC)</td>
<td>17% (1/6)</td>
<td>30% (6/20)</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* Fisher’s Exact Test, ** Wilcoxon Rank Sum Test
Continuing Questions

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• How should MGZL be treated?
Epigenetic Profiling of MGZL, CHLNS & PMBL
Principal Component Analysis (PCA) of Microdissected Tumor DNA

Epigenetic profile of MGZL lies between CHL and PMBL
Does not allow assignment to either “parent entity”

Eberle et al.
Haematologica
RNA Seq performed on PMBL, NSCHL, MGZL (60 cases)
6 cases failed
Continuing Questions

- Does non-mediastinal Grey zone lymphoma exist?
- Can biological studies provide insights into biology of GZL - closer to CHL or PMBL?
- How should MGZL be treated?
  - NCI protocol initiated, using regimen successful in PMBL – DA-EPOCH R, with mediastinal radiation for those PET + at conclusion of Rx
**DA-EPOCH R therapy of Mediastinal Gray Zone Lymphoma & comparison with PMBL**

Wilson et al.  Blood 2014

24 pts with MGZL -- M:F 15:9
Median Age 33 (14-56) ; Bulky mediastinal disease in 50%
Importance of the Microenvironment in MGZL, *Blood* 2014

DC-SIGN
CD 209
PD-1 Blockade is a new therapeutic tool in the treatment of CHL, PMBL and GZL

- Amplification at 9p24.1 leads to increased expression of PD-1 ligands, PD-L1 and PD-L2 on the neoplastic cells.
- Associated with enhanced JAK-STAT signaling and expression of pSTAT3.
- PD-1 blockade with nivolumab or pembrolizumab is effective in CHL patients who have failed standard therapy.
  - Ansell et al. NEJM 2015; Armand et al. JCO 2016.
Armand et al
PD-1 Blockade with Pembrolizumab in relapsed CHL

90% experience reduction in tumor burden from baseline
Response to PD-1 Blockade in 3 patients with MGZL
Melani et al. NEJM 2017

• All three patients had relapsed after DA-EPOCH-R
• All achieved continuous metabolic CR after PEMBRO in 2 and NIVO in 1
• Rearrangement of the PD-L1 locus was shown in Case 1, and PD-L1 amplification shown in Case 2
• IHC was positive for PD-L1 expression
18 y.o. female
Mediastinal mass
Relapse after primary therapy
CR after checkpoint inhibitor Pembro
Break in PD-L1 locus
Case 1 (Red/Green)

Amplification of PD-L1 locus in Case 2
Gray Zone lymphomas (GZL)

- Most cases present in the mediastinum
- Males > Females
- Benefit from combined modality therapy
- Non mediastinal cases show clinical differences, but may show biological overlap
- Most cases are closer to CHL, but show preservation of the B-cell program
- Importance of microenvironment similar to CHL
Influences that direct the fate of the thymic B-cell are likely a combination of epigenetic, genetic and environmental factors.
Hodgkin’s Lymphoma Mixed Cellularity

- Males > Females
- Bimodal age range, pediatric and older adults
- Often Stage III, IV
- May be HIV associated
- EBV+ (75%)
- Classical RS-cells in mixed inflammatory background
- Fine trabecular sclerosis but no fibrous bands
Hodgkin’s Lymphoma Mixed Cellularity

EBER EBV in situ
Lymphocyte Depleted Hodgkin’s Lymphoma

• < 5% of HL with strict criteria
  – Many cases in older series were NHL
• Seen with increased frequency in developing countries & with HIV infection
• Often EBV-associated (75%)
• Similar to mixed cellularity, but decreased normal lymphocytes, likely a continuum with MC
• Fibrohistiocytic background – rich in histiocytes
Nodular Lymphocyte Predominant HL
Clinical Features

• **Occurrence:**
  - 5% of Hodgkin’s disease
  - Young adults (4th-5th decade), children, M>F

• **Distribution:**
  - Localized (stage I-II) >80%
  - Peripheral nodes (cervical, axillary, inguinal)
  - Sparing of mediastinum, axial LNs

• **Course:**
  - Indolent, long natural history; >95% survival
  - Late relapses more common; localized, not fatal
  - Association with or progression to LBCL (2-3%)
Progressive Transformation of Germinal Centers
Nodular Lymphocyte Predominance HL
Immunophenotype

• CD20+, CD79a+, BCL-6+, CD45+
• OCT-2+, Bob-1+ strongly expressed
• EMA +/-, IgD variable
• CD15 & CD30 usually negative
• Ig light chains usually not demonstrable
• LP (formerly L&H cells) cells rosetted by Follicular $T_{FH}$ cells
  – T: CD57+, PD-1+
OCT-2 in NLPHL
• Younger age group
  – Median age 21 (IgD+) vs. 44 years (IgD-)
• Marked male predominance
  – M:F ratio 23:1 (IgD+) vs. M:F ratio 1.5:1 (IgD-)
• Solitary mass, Stage I
• Predilection for cervical lymph nodes
  – 56% (IgD+) vs. 18.2% (IgD-)
• Associated with *Moraxella catarrhalis* in young boys
  (Hartmann et al 2015)
Variant Patterns in NLP HL
Fan et al AJSP 2003
Histological Progression in NLPHL

• Diffuse large B-cell lymphoma
  – 5% of NLPHL
  – Clonally related by Ig gene PCR

• T-cell histiocyte rich large B-cell lymphoma
  – Controversial if these cases differ from de novo T/HRLBCL
  – Common genetic aberrations in NLPHL/ T/HRLBCL
    » JUNB, DUSP2, SGK1, SOCS1 and CREBBP
  – Probably a continuous disease spectrum
  – Cases with progression are dx as TC/HRLBCL-like transformation of NLPHL (WHO 2017)

• Stage is an important prognostic feature for clinical management in NLPHL, with or without progression
Lymphocyte Rich Classical HL

- Formerly included in LPHD of Rye classification
- Background rich in lymphocytes with few RS cells
- Growth pattern: “Nodular” or “Diffuse”
- Nodular form is more common
- Diffuse form may be a variant of mixed cellularity, rich in small lymphocytes
- Tends to be low stage, older patients
- EBV association variable
Lymphocyte Rich Classical Hodgkin's, Nodular
# The many forms of Hodgkin Lymphoma

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<thead>
<tr>
<th>Nodular Sclerosis</th>
<th>MC/ LD</th>
<th>Nodular LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High socio-eco status</td>
<td>Low socio-eco status, HIV+</td>
<td>No risk factors</td>
</tr>
<tr>
<td>F&gt; M, young adults</td>
<td>M &gt; F, children or elderly</td>
<td>M&gt; F Young adult</td>
</tr>
<tr>
<td>Mediastinal, axial LNs</td>
<td>Generalized disease</td>
<td>Peripheral LN, Mesenteric</td>
</tr>
<tr>
<td>EBV negative (25% +)</td>
<td>EBV positive (75% +)</td>
<td>EBV negative (&lt;5% +)</td>
</tr>
</tbody>
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