Immunohistochemistry

A cost effective approach to lymphoma diagnosis

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University of Southern California

Disclosures; CRT – has consulting arrangements with for Philips, Agilent, PerkinElmer, Optra
1. Lymphoma VS Anaplastic tumor

2. Reactive VS Malignant

3. Sub-classification, B VS T, HL VS Non-HL & specific types, CD1, ALK etc

4. Prognostic markers & predictive markers Inc PDL1

5. Micrometastases in nodes and marrow
ANAPLASTIC TUMOUR discussed elsewhere

IHC stains

Carcinoma??
Lymphoma??
Melanoma??
Sarcoma??
### Basic screening panel

- **Carcinoma**: Keratin
- **Sarcoma**: Vimentin, CD 45, S100
- **Lymphoma**: CD 45
- **Melanoma**: S100

**Notes**: CRT. USC.
The Different Types of NHL and HL

Fetus

Post-natal life

Thymus / T cells

Bursa / marrow / B cells

Lymphocyte differentiation
* gene rearrangement
* diversification
* tolerance

Immune response in peripheral lymphoid tissues

Multiple morphologies
Beginning with Hodgkin in 1832 there have been numerous classifications of lymphoma.
THE FIRST "LYMPHOMA"

ON SOME MORBID APPEARANCES OF THE ABSORBENT GLANDS AND SPLEEN.

BY DR. HODGKIN.

PRESENTED BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

The morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.

7 AUTOPSY CASES

No microscopy

Thomas Hodgkin

1825-1837

Inspector of the Dead
Curator of the Museum,
Guys Hospital, London.
60 years later – the microscope makes its mark.

**Sternberg Reed Cells**

**Sternberg, C. (1898)**  
Über eine eigenartige unter dem Bilde der Pseudoleukamik verlaufende Tuberculose des lymphatischen Apparates.  
_Ztchr Heilk_, **19**, 21-90

**Reed, D. (1902)**  
*On the pathological changes in Hodgkin's disease, with especial reference to its relation to tuberculosis.*  
Johns Hopkins Hospital Reports 10, 133-196
With advent of microscopy - many other ‘lymphomas’ were described – based upon morphology.

By 1950 more than 50 different lymphomas had been described; and almost as many different classifications.

Giant Lymph Follicle Hyperplasia - 1927
For 100+ years Pattern Recognition

Panel 7 pathologists - ‘experts’.
Reviewed 105 follicular lymphomas

**Diagnosis - small cell**
consensus 39 cases,  range 24 - 65 among the 7

**Diagnosis - mixed cell**
consensus 40 cases;  all 7 unanimous in only ONE

In 37% of cases both small & large cell were diagnosed by different members of the 7.

Diagnosis by Pattern Recognition

vol 29, 2061, 1996.

Accuracy versus consensus Dx.

Average panelist  71 %
Best panelist      81 %
Image Analysis*   89 %

*Using a continuous class approach, based upon SD cell/nuclear size, & measurements of high and low frequency diversity
Then from 1960-1990 we had the struggle to change classification basis from morphology alone --

Rappaport – histiocytic / lymphocytic

The beginning of the WHO consensus process

Bob Collins, Karl Lennert, Bob Lukes
To Immune based

To Immune based
Lymphoid neoplasms related to normal Lymphoid Development

Stem cell

precursor

precursor

Phenotype

Morphology

CD2 CD3 CD4 CD5 CD8

Fetus

Post-natal life

Thymus / T cells

Lymph node

spleen

respiratory

gastrointestinal

Bursa / marrow / B cells

B lymphocyte

differentiation

* gene rearrangement

* diversification

* tolerance

Transformation / amplification

Transformation / amplification

Cell mediated immunity

* sets T cells

Humoral immunity

* antibodies

Plasma cells

Igs

Immune response in peripheral lymphoid tissues

CD10 CD19 CD20 CD79

follicle

6 main groups
72 + types

Precursor Lymphoid Neoplasms
Mature B-Cell Neoplasms
Mature T-Cell & NK-Cell Neoplasms
Hodgkin lymphoma (Hodgkin disease)
Immunodeficiency-associated lymphoproliferative disorders
Histiocytic and Dendritic Cell Neoplasms
Relative incidence of ML

Seer data (HL vs NHL) & NHL Classification project, Blood 89:3909

THE POINT-- 3 common types - rest uncommon (ADULTS).
## Who classification 2008 – main types

<table>
<thead>
<tr>
<th>Precursor</th>
<th>B types</th>
<th>T types</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B lymphoblastic leukemia / lymphoma</td>
<td>T lymphoblastic leukemia / lymphoma</td>
</tr>
<tr>
<td>Mature</td>
<td>B-Cell</td>
<td>T &amp; NK Cell</td>
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<td></td>
<td>CLL</td>
<td>NK cell</td>
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<td>Hairy cell</td>
<td>Adult T cell</td>
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<td>Lymphoplasma</td>
<td>Enteropathy Ass</td>
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<tr>
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<td>Myeloma</td>
<td>M Fungoides</td>
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<tr>
<td></td>
<td>MALTOMA</td>
<td>Sezary Syn</td>
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<tr>
<td></td>
<td>Follicular</td>
<td>Peripheral T</td>
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<td></td>
<td>Mantle</td>
<td>Anaplastic Large</td>
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<tr>
<td></td>
<td>Diffuse</td>
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<td></td>
<td>Burkitt</td>
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<td>Hodgkin</td>
<td>Nodular LP</td>
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<td></td>
<td>Classic</td>
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<td>Nod sclerosis</td>
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<td></td>
<td>Mixed cell</td>
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<td>Immdeficiency-assoc</td>
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<tr>
<td>Histiocytic and Dendritic</td>
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</table>
the basis Who classification 2008

Morphology
- Small v large cell
- Hodgkin v NHL
- Follicular v diffuse
- + fine criteria

Phenotype
- IHC B v T
- 80+ antibodies

molecular

Translocations
- Gene rearrangements

6 main groups
- 72 + types
## Expert agreement with consensus

<table>
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<tr>
<th>Diagnosis</th>
<th>Histology only</th>
<th>+ IHC</th>
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<tr>
<td>Follicular - (by grade)</td>
<td>93 (60)</td>
<td>94 (61)</td>
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<td>MALT / marginal z</td>
<td>84</td>
<td>86</td>
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<tr>
<td>small lymph / CLL</td>
<td>84</td>
<td>87</td>
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<tr>
<td>lymphoplasmacytoid</td>
<td>53</td>
<td>56</td>
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<td>Burkitt (like)</td>
<td>47</td>
<td>53</td>
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<tr>
<td>mantle</td>
<td>77</td>
<td>87</td>
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<tr>
<td>diff Large B</td>
<td>73</td>
<td>87</td>
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<tr>
<td>precursor T</td>
<td>52</td>
<td>89</td>
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<tr>
<td>peripheral T</td>
<td>45</td>
<td>86</td>
</tr>
<tr>
<td>anaplastic large T/null</td>
<td>46</td>
<td>85</td>
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</tbody>
</table>
This assumes your IHC lab is based on science, NOT witchcraft -

Then lymphoma diagnosis is a more than just a magic trick ---
Assuming that most of these key leucocyte markers are validated in your lab.
The WHO Classification of Lymphomas: Cost-effective Immunohistochemistry Using a Deductive Reasoning “Decision Tree” Approach

Part II: Diffuse Patterns of Proliferation in Lymph Nodes

Clive R. Taylor, MA, MD, DPhil

(Appl Immunohistochem Mol Morphol 2009;17:470–482)
Diagnosis of lymphoma

4 decisions

* Reactive (‘benign’) vs malignant
* Lymphoma (leukemia) vs metastasis
* Hodgkin vs Non-Hodgkin
* Sub-type, classification, B/T etc

4 methods

Morphology – gold standard

Phenotype – flow
  IHC
Gene RX – Ig / TCR
Genotype – t(8;14), t(14;18)
Lymphoma

Morphology - - - abnormal architecture?

- Diffuse
- Follicular

Single cell type

Mixture cell types

A dendrogram or ‘decision tree’
Robb Smith, Taylor
“Lymph Node Biopsy” 1980

‘gold’ standard

IHC molecular
Architecture

Diffuse
- 'normal'
- reactive

Abnormal
- single cell type
  - B
  - T
- mixed cell types
  - HL
  - B
  - T

Follicular
- 'normal'
- reactive

Abnormal
- other
- HL
- B
- T

Taylor CR
AIMM 2009
Immunohistochemistry (flow cytometry)

B or T

B - red
T - brown

Morphology
Phenotype
Architecture

Diffuse

- ‘normal’ reactive
- Abnormal

Follicular

- Abnormal
  - HL
    - Hodgkin lymphoma
      - Lymphocyte Predominant
        - Nodular Sclerosis
  - B
    - FCC lymphoma
      - Burkitt L
      - Mantle cell L
      - Marginal zone L
      - Small lymphocytic L
  - T
    - Lympho-blastic
    - Other
Reactive Follicle

Pan B +

Variable T cells
CD3+, CD5+ : usually few
In mantle

Morphology

Marginal Zone:
small lymphocytes
Pan B +
SIgM +

Mantle Zone:
small lymphocytes
Pan B +
SIgD+, SIgM +

Reactive/germinal center:
larger cells
Pale zone – centrocytes
Dark Zone – centroblasts

Lymphocytes
Pan B+
CD10+
BCL6+
MUM1+/-
Ki67++
BCL2 neg

Dendritic cells
CD21+
CD35+

Histiocytes
CD68+
CD163+

Phenotype
<table>
<thead>
<tr>
<th></th>
<th>H&amp;E</th>
<th>BCL2</th>
<th>BCL6</th>
<th>CD10</th>
<th>Ki-67</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary (Resting) Follicles</strong></td>
<td>![Image]</td>
<td>![Image]</td>
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<td>![Image]</td>
</tr>
<tr>
<td><strong>Follicular Lymphoma, Grade 1</strong></td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

R. Miller 2003 – Propath.
Bcl-2 - the protein product
Inhibits apoptosis

Reactive Follicles – negative

Neoplastic Follicles – positive

T(14;18)
FCC lymphoma

18 bcl-2

14 H chain

Bcl-2 +++

Inhibits apoptosis

Immune stimulation

t 14;18

B

FCC t 14;18

Burkitt t 8;14

mec

Bcl-2

V D J sw C

error error

USC
Goldfish - Tubbs 2001
Reactive Follicle ‘center’

Neoplastic Follicle FCC lymphoma

Shows ‘red’ FCC cells do not express BCL2

Bcl6 Red

Bcl2 brown

Shows ‘red’ FCC cells express BCL2
CD10 REACTIVE

CD 10   FCC Lymphoma

CD10
Helpful with
loss polarity
and
extra-follicular
Diffuse areas
**Summary - Follicular pattern**

**Differential**

**Reactive hyperplasia**

<table>
<thead>
<tr>
<th>B cell lymphoma</th>
<th>FCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt</td>
<td></td>
</tr>
<tr>
<td>Mantle cell</td>
<td></td>
</tr>
<tr>
<td>Nodal Marginal</td>
<td></td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td></td>
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</table>

**Hodgkin lymphoma**

<table>
<thead>
<tr>
<th>LP</th>
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</thead>
<tbody>
<tr>
<td>NS (classic)</td>
</tr>
<tr>
<td>T lymphoblastic lymphoma</td>
</tr>
</tbody>
</table>

**IHC**

**Molecular**

**‘gold’ standard**

- Follicular
- B cell
- FCC
- HL LP
- other

**T**
### Role of IHC

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<thead>
<tr>
<th></th>
<th>Nod LP</th>
<th>FCC</th>
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<tbody>
<tr>
<td><strong>CD45</strong></td>
<td>+ RS</td>
<td>+</td>
</tr>
<tr>
<td><strong>CD20</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>CD79a</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>bcl6</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pax5</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>EMA</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>bcl2</strong></td>
<td>+/-</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>CD3</strong></td>
<td>(++++)</td>
<td>(+/-)</td>
</tr>
<tr>
<td><strong>K/L clonal</strong></td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

+ mantle and marginal – under diffuse

**Follicular**

- CD19, CD20
- Pax5, CD79a
- CD10, bcl 6, (bcl 2)
- cyclinD1, K, L
- CD23
- (cd5, cd43)
- PD-1

**Hodgkin’s Lymphoma (HL)**

- LP

**Follicular Center Cell (FCC)**

- + RS

**Nodular Lymphocyte Predominance (Nod LP)**

- +
<table>
<thead>
<tr>
<th>FOLLICULAR</th>
<th>Lymphoma markers</th>
<th>‘follicles’</th>
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</thead>
<tbody>
<tr>
<td><strong>Reactive hyperplasia</strong></td>
<td>‘B’</td>
<td>reactive*</td>
</tr>
<tr>
<td><strong>B cell lymphoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCC</td>
<td>‘B’ CD10, BCL6</td>
<td>BCL2+</td>
</tr>
<tr>
<td>Burkitt</td>
<td>‘B’ CD10, BCL6,-/+43</td>
<td></td>
</tr>
<tr>
<td>Mantle cell</td>
<td>‘B’ Cyclin D1,CD5,43</td>
<td>reactive*</td>
</tr>
<tr>
<td>Marginal ‘Nodal’</td>
<td>‘B’ 21, -/+43</td>
<td>reactive*</td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td>‘B’ CD23, 5, 43</td>
<td>‘pseudo-’</td>
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<tr>
<td><strong>Hodgkin lymphoma</strong></td>
<td></td>
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</tr>
<tr>
<td>LP</td>
<td>‘B’ EMA</td>
<td>reactive*</td>
</tr>
<tr>
<td>NS (classic)</td>
<td>- CD15, 30</td>
<td>reactive*</td>
</tr>
<tr>
<td>T lymphoblastic L</td>
<td>T CDc3,7,4+8,Tdt</td>
<td></td>
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</table>
Architecture

Diffuse

- ‘normal’ reactive
- 70% of all Lymphomas fit here

Abnormal

- single cell type
  - B
  - T

Follicular

- ‘normal’ reactive

Abnormal

- mixed cell types
  - HL
  - B
  - T

- other
  - HL
  - B
  - T

Taylor CR
AIMM 2009

70% of all Lymphomas fit here
diffuse

Single Cell type

CD19, CD20, CD79a, Pax5, CD10, bcl 6, MUM1, Bcl 2, cyclinD1, K,L, CD56

Small cell

V

large cell

CD3, CD5, CD43, CD4, CD8, CD7, CD56

B

T
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CD 1</th>
<th>CD 10</th>
<th>CD 21</th>
<th>CD 23</th>
<th>CD 5</th>
<th>CD 43</th>
<th>bcl6</th>
<th>Other*</th>
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<tr>
<td>B (B cell)</td>
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<tr>
<td>SL lymph/CLL</td>
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<td>+</td>
<td>+</td>
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<td>cd11c</td>
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<td>L’pcytoid</td>
<td>+</td>
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<td>CIg,cd38</td>
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<tr>
<td>FCC</td>
<td>+</td>
<td>+</td>
<td>(+/-)</td>
<td>-/+</td>
<td></td>
<td>+</td>
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<td>(bcl2)</td>
</tr>
<tr>
<td>mantle</td>
<td>+</td>
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<td></td>
<td>+</td>
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<td>D1</td>
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<tr>
<td>marginal</td>
<td>+</td>
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<td>[+/-]</td>
<td>-/+</td>
<td></td>
<td></td>
<td></td>
<td>OCT,BOB</td>
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<tr>
<td>Diff large cell</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>-/+</td>
<td>+/-</td>
<td>+/-MUM1</td>
<td>cd38</td>
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<tr>
<td>Burkitt</td>
<td>+</td>
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</table>

*CD19, 20, 22, 79a, Pax5 [ ] FDC network

Post or non GC case –

CD 20 Poorer Prognosis?

Bcl 6

MUM 1

Myc/BCL2 both positive also indicates poor prognosis Threshold >40% myc+
Germinal Center GC - and Post GC - DLBCL

GC = CD10+, or BCL6+ and MUM-

The 5-years overall survivals

<table>
<thead>
<tr>
<th></th>
<th>GCB (64 cases)</th>
<th>Non-GC (88 cases)</th>
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<tbody>
<tr>
<td>GCB (42 cases)</td>
<td>76% (p &lt; .001)</td>
<td>36%</td>
</tr>
</tbody>
</table>

Chang et al 2004

DLBCL..Also….Bcl2+ and survivin + = poorer prognosis
CYCLIN D1 / PRAD1: MANTLE CELL.

T 11;14, translocates BCL-1

MCL 90% +

Other ML -: rare immcytoma; marginal ML

Nuclear stain; requires AR ++*
Bcl-1

Mantle cell

Bcl-2

Follicular center cell

Seen in ‘mature’ B lymphomas’ but break at early B stage ‘cancer stem cell’
Bcl-1  - t(14;11) – mantle cell – B lymphoma

Break points cluster around cpg sites (red)

Bcl-2  - t(14;18) – follicular center cell – B lymphoma

Tsai et al

Translocation events common in ML Because of gene rearrangement
Lymphomas - remarkable fit between ‘old morphologic types
And IHC and molecular classification

<table>
<thead>
<tr>
<th>t (14;18)</th>
<th>t (11;14)</th>
<th>t (2;5)</th>
<th>t(11;18)</th>
<th>t(9;14)</th>
<th>t (8;14)</th>
<th>t (3;14)/n 12+</th>
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<tr>
<td>FCC</td>
<td>mantle</td>
<td>ALCL</td>
<td>marginal(malt)</td>
<td>lymphoplasma</td>
<td>burkitt</td>
<td>diff large cell</td>
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<tr>
<td>bcl-2</td>
<td>bcl-1;cycD1</td>
<td>npm/alk</td>
<td>API2/MALT1</td>
<td>pax5</td>
<td>myc</td>
<td>bcl-6</td>
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12+ CLL
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<th>4</th>
<th>8</th>
<th>5</th>
<th>7</th>
<th>25</th>
<th>30</th>
<th>56</th>
<th>other</th>
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<td>B</td>
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<td>NK</td>
<td>+</td>
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<tr>
<td>M fungoides</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
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<tr>
<td>Peripheral</td>
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<td>-/+</td>
<td>-/+</td>
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<tr>
<td>Anaplastic</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoblastic*</td>
<td>+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
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</tbody>
</table>

*+CD99,34  
# cytoplasmic CD3 only

CRT 2017
## Expert agreement with consensus

<table>
<thead>
<tr>
<th></th>
<th>Histology</th>
<th>+ IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular - (by grade)</td>
<td>93 (60)</td>
<td>94 (61)</td>
</tr>
<tr>
<td>MALT / marginal z</td>
<td>84</td>
<td>86</td>
</tr>
<tr>
<td>small lymph / CLL</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>lymphoplasmatoid</td>
<td>53</td>
<td>56</td>
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<tr>
<td>Burkitt (like)</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>mantle</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td>diff Large B</td>
<td>73</td>
<td>87</td>
</tr>
<tr>
<td>precursor T</td>
<td>52</td>
<td>89</td>
</tr>
<tr>
<td>peripheral T</td>
<td>45</td>
<td>86</td>
</tr>
<tr>
<td>anaplastic large T/null</td>
<td>46</td>
<td>85</td>
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</table>
Diffuse

Mixed

Histio + Dendritic

B

CD19, CD20, CD79a, CD10, BCL6, MUM 1 Cyclin D1, K,L CD23 (CD5,CD43)

T

CD3, CD5, CD43 CD4, CD8, CD7, CD25, CD56 [CD30] [ALK]

Hodgkin L

(CD45) (EMA) CD30, CD15 BLA36, Fascin MUM1 Pax5 CD40 LMP
<table>
<thead>
<tr>
<th></th>
<th>R-S cells</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical MC LR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- LP: Lymphocytes
- Classical MC LR: Classical Monocyte/Leukocyte
- NS: Neutrophils
- LD: Lymphocytes

- R-S cells: +++
- Fib bands: +
Classic HL
diffuse

CD 30

CD 15

PAX5

vs

ALCL +

vs

HL LP+

ALK1

EMA
Markers useful for subclass HL and other lymphomas

**HD -- LP**

- **Ig Genes:** rrgmt
- **Somatic mutations**
- **Bcl-2**
- **Bcl-6**
- **CD45 / LCA**
- **J Chain**
- **Ig :K > L**
- **No CD30**
- **+ B cell Markers**

**HD classical CD 15, CD30**

**HD -- NS: MC**

- **Ig Genes:** incomplete $V_H$ rrgmt
- **c-myc**
- **c-ras**
- **EBV ~ 40%**
- **CD15**
- **CD30**

**Pre-B CELL**

**HDLP - CD 20, CD45**

Taylor CR
Human Path 36, 1-4, 2005.

Hodgkin’s disease is a non-hodgkin lymphoma
<table>
<thead>
<tr>
<th></th>
<th>CHL</th>
<th>V</th>
<th>ALCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>90+%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>T ags</td>
<td>0-30%</td>
<td>20-80%</td>
<td></td>
</tr>
<tr>
<td>B ags</td>
<td>10-60%</td>
<td>0-30%</td>
<td></td>
</tr>
<tr>
<td>CD15</td>
<td>90%</td>
<td></td>
<td>0-25%</td>
</tr>
<tr>
<td>CD45</td>
<td>10%</td>
<td></td>
<td>30-90%</td>
</tr>
<tr>
<td>EMA</td>
<td>10-20%</td>
<td></td>
<td>30-60%</td>
</tr>
<tr>
<td>Pax5</td>
<td>90-95%</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>ALK</td>
<td>-</td>
<td></td>
<td>80-90%*</td>
</tr>
<tr>
<td>Clusterin</td>
<td>-</td>
<td></td>
<td>80%</td>
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</table>

*not cutaneous ALCL*
Table I. Referral diagnosis of 61 TC/HRBCL cases.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of cases</th>
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<tbody>
<tr>
<td>\textbf{Classic Hodgkin’s disease}</td>
<td>20</td>
</tr>
<tr>
<td>cHL, lymphocyte – predominant</td>
<td>12</td>
</tr>
<tr>
<td>cHL, mixed cellularity</td>
<td>7</td>
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<tr>
<td>cHL, nodular sclerosis</td>
<td>1</td>
</tr>
<tr>
<td>\textbf{Nodular, lymphocyte – predominant HL}</td>
<td>5</td>
</tr>
<tr>
<td>\textbf{Non-Hodgkin’s lymphoma}</td>
<td>25</td>
</tr>
<tr>
<td>\textbf{TCRBCL}</td>
<td>11</td>
</tr>
<tr>
<td>Diffuse mixed B cell lymphoma</td>
<td>8</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Diffuse large B cell lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoproliferative disorder</td>
<td>7</td>
</tr>
<tr>
<td>Malignant lymphoma NOS vs. HL</td>
<td>4</td>
</tr>
</tbody>
</table>

CD20, CD79a, CD15, Fascin, EMA
<table>
<thead>
<tr>
<th>PANEL</th>
<th>Nod LP RS cell</th>
<th>Classic RS cell</th>
<th>LRBcell Large cell</th>
<th>ALCL Large cell</th>
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</thead>
<tbody>
<tr>
<td>cd45</td>
<td>+</td>
<td></td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td>cd30</td>
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<td>+</td>
</tr>
<tr>
<td>cd15</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cd20,79a</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MUM1</td>
<td></td>
<td>+</td>
<td>-/+</td>
<td></td>
</tr>
<tr>
<td>Bcl6</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pax5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>OCT2</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>+/-</td>
<td>+</td>
<td>-/+</td>
<td>+/-</td>
</tr>
<tr>
<td>lymphocytes</td>
<td>many B+T</td>
<td>Vary B+T</td>
<td>Many B</td>
<td>few</td>
</tr>
</tbody>
</table>
Added to which is the PD-1 PD L-1 story, which now is becoming important for lymphomas
-----With all of the challenges of scoring etc.

**PD-L1 Expression in Primary CHL**

1. 87% (33 of 38 cases) of primary CHL show PD-L1 expression by the Reed-Sternberg cells

*Chen BJ et al., Clin Cancer Res., 2013*
Nivolumab in Relapsed/Refractory CHL

1. PD-L1/2 locus integrity
   - Red = PD-L1
   - Green = PD-L2
   - Yellow = Red + Green
   - Cyan = Centromere

2. PD-L1/2 Protein Expression
   - PD-L1 (brown)
   - PAX-5 (red)
   - PD-L2 (brown)
   - pSTAT3 (red)
The Nature of Reed Sternberg Cells

The Nature of Reed-Sternberg Cells and Other Malignant "Reticulum" Cells

Clive R. Taylor
Gibson Laboratories, Radcliffe Infirmary, Oxford

Summary

Immunoperoxidase methods have been applied to formalin-paraffin sections of more than 100 lymphoreticular neoplasms. Intracellular immunoglobulin components have been identified in plasma-cell neoplasms, and also in the "malignant reticulum cells" of some cases of reticulosarcoma and Hodgkin's disease. Some of the preliminary morphological correlations are presented, and the significance of these findings is briefly considered. Finally, a tentative scheme is offered, relating some of the different histological types of lymphoreticular neoplasm to the various morphological forms assumed by the lymphocyte during its cell cycle.

Introduction

Many of the problems of diagnosis and classification of lymphoreticular neoplasms stem from the lack of a clear understanding of the basic cell types from which these neoplasms originate. In particular, there is the problem of those neoplasms which are traditionally believed to be derived from the "reticulum cell"—principally Hodgkin's disease and the "reticulum cell sarcoma" group (the histiocytic and stem-cell lymphomas of the American literature).

Immunoglobulin has been identified within Reed-Sternberg cells and within the cells of some cases of reticulum-cell sarcoma by the application of a peroxidase-labelled antibody method to formalin-fixed paraffin-embedded tissue. I have confirmed and consolidated these observations in cases of Hodgkin's disease, reticulum-cell sarcoma, and follicular lymphoma. This evidence supports the suggestion that at least some so-called "malignant reticulum cells"
Molecular Biology of Hodgkin’s Lymphoma –
Thomas et al – Lancet Oncology 5, 11, 2004


Relevant personal bibliography