Immunohistochemical classification of haematolymphoid tumours

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Haematolymphoid Neoplasias: Leukaemia vs Lymphoma

CLONAL MALIGNANCIES

Bone marrow → Blood → Lymph node → Extranodal site

Leukaemia

Lymphoma

Malignant lymphoproliferative diseases

- Malignant lymphoma
- Leukaemia
  - Acute lymphoblastic leukaemia
  - Chronic lymphocytic leukaemia (CLL)
- Ca. 1600 per year in DK
- Ca. 800 000 per year in the world
Classification!

Thomas Hodgkin 1798-1866

Hodgkin’s original case: abdominal nodes

Gordon Museum, King’s College London
WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2008

- 70s – 80s: Kiel classification
  - B vs T cells: HCl
- 90s: REAL classification
- WHO (2008.....2016?)
  - "Real" disease entities
    - Clinical features
    - Morphology
    - Immunophenotype
    - Molecular genetics

Lymphoma

Hodgkin's lymphoma
- HL, LP
- HL, NS
- HL, MC
- HL, LR
- HL, LD

Non-Hodgkin's lymphoma
- B-cell
  - precursor
  - peripheral
  - ~32 subtypes
- T/NK-cell
  - precursor
  - peripheral
  - ~30 subtypes
WHO Classification: B-cell Lymphoma

WHO Classification: T-cell & NK-cell neoplasms

Lymphoma frequencies

2002 SEER database. O'Connor
What is lymphoma?

- Clonal malignancy
  - Mutational events cause cells to freeze at a single stage of normal lymphocyte differentiation
- Morphology, immunophenotype & molecular features:
  - Mirror stages of normal lymphocyte development

T and B-cell differentiation:
Stage-specific surface antigen expression

Lymphoid neoplasms:
Correlation with normal T or B-cell differentiation
What is lymphoma?

- Clonal malignancy
  - → mutational events cause cells to freeze at a single stage of normal lymphocyte differentiation
- Morphology, immunophenotype & molecular features:
  - mirror stages of normal lymphocyte development
- Resemble normal haematopoietic cells in their:
  - morphology, immunophenotype, molecular genetics

Lymphoma & Leukaemia diagnosis

- Clinical features
- Morphology
- Immunophenotype
- Molecular diagnosis

Lymphoma differential diagnosis

- Assess morphology:
  - cell size
  - architecture
- Select appropriate immune panel(s)
Enlarged lymph node

Is it malignant?

- Emphasis on lymphoma classification
- Reactive vs malignant
  - often more challenging diagnosis
- Use IHC to evaluate lymphoid tissue cytology and architecture
- Correlate immunophenotype with disease entity

International recommendations for lymphoma diagnostics

[Link 1] http://www.lymphoma.dk/index.php?id=56,0,0,1,0,0
See Lymphomadiagnostik


What are CD numbers?

- CD: "clusters of differentiation"
- Classification system for antigens (and antibodies)
- Originally for surface antigens on leucocytes
- Now includes other cells and intracellular antigens (no CD no.)
- 10 workshops since 1982
- Currently > 350 CD antigens
IHC Dogma
(also applies in diagnostic haematopathology)

- IHC complements routine staining
- Helps characterise cells and architecture
- No single antibody is disease specific
- Antibodies should be used in panels
- Interpret findings in relation to the histology

Diagnostic Applications of IHC 1

- Reactive vs malignant
- Polyclonal vs monoclonal Ig
- Follicular hyperplasia vs follicular lymphoma
- Diff. diagnosis of small cell B-cell lymphomas
  - CLL/SLL vs MALT vs FL vs Mantle cell
- Aggressive B-cell lymphomas
  - DLBCL vs BL vs BL-like / grey-zone NHL
  - DLBCL – ‘cell of origin’ – GCB vs ABC

Diagnostic Applications of IHC 2

- T-cell lymphoma vs B-cell lymphoma
- T-cell lymphoma vs T-zone hyperplasia
- Hodgkin lymphoma vs NHL
- Hodgkin lymphoma
  - NHL vs classical HL
- Lymphoblastic vs. Myeloblastic vs. Burkitt
- Undifferentiated malignant tumor
- Lymphoma prognosis
  - e.g. 80/85, AUK, c-alk
- Targeted therapy
  - e.g. CD20 / Rituximab, CD30 / Brentuximab, Alemtuzumab (anti-CD52)
Useful antigens in haematopathology

- **CD45**
  - B-cell “specific”
    - CD19
    - CD20
    - CD79α
    - Pax-5
    - OCT-2 / BOB1
  - T-cell “specific”
    - CD3
    - CD5
    - CD2
    - CD7
    - CD1a
    - CD4
    - CD8
    - PD-1 / CXCL-13 (TFH)

- Other
  - CD30
  - CD10
  - Bcl-2
  - Bcl-6
  - ALK
  - c-myc
  - CD21
  - CD23
  - CD15
  - TdT
  - Cyclin-D1
  - SOX-11
  - CD56
  - TIA-1, granzyme, perforin

- **Other**
  - EBV
    - LMP1
    - EBNA2
  - CD56
  - CD57
  - EMA
  - S100
  - CD68
  - CD163

Basic IHC panel for lymphoma diagnosis

- CD45
- CD20
- CD79α
- (PAX-5)
- kappa/lambda
- CD3
- CD5
- CD30
- CD43
- Bcl-2
- Bcl-6
- CD23 (CD21)
- Cyclin-D1
- Ki-67

Basic stains: CD45

- Membrane glycoprotein family
- Positive in all (?) haemopoietic cells
- Not expressed on non-BM-derived cells
- CD45 isoforms are more lineage specific

- In lymphomas:
  - Most NHLs positive
  - Occasionally negative in:
    - Precursor LB
    - Plasma cell neoplasia
    - Anaplastic large cell lymphoma
  - Hodgkin lymphomas:
    - LP: Popcorn cells positive
    - NRS cells in classical HL are negative

Reactive LN: CD45

HL, NC: CD45
Basic stain: Immunoglobulin

The demonstration of plasma cells and other immunoglobulin-containing cells in formalin-fixed, paraffin-embedded tissues using peroxidase-labelled antibody

C. R. Taylor and J. Burns
From the Department of Pathology, Glaxo Laboratories, Baddiley, Oxford.

- IHC-lg
  - First protocol for IHC in FFPE
  - Still one of the hardest to perform & evaluate!

Basic stains: Immunoglobulin

- B-cell specific
- Normal κ:λ ratio ca. 3:4:1
- Monotypic Ig restriction
  - Suggests clonality
  - >10:1 or < 0.2:1 = restriction
- Cytoplasmic Ig easily shown
  - In lymphomas:
    - Cy Ig:
      - lymphoplasmacytic; myeloma; MZL, DLBCL, FL
    - Surface Ig

Basic stains: Immunoglobulin

- Surface Ig
  - B-NHL clonality
  - Requires sensitive, optimised technique
  - Interpretation difficult (serum Ig)
**Basic stains: CD20**

- Many B-cell neoplasms
- Negative in:
  - early precursor B-LB
  - plasma cell neoplasms
- Negative in T-cell lymphomas
  - rare cases positive
- Hodgkins lymphoma
  - HL-LP: 90% positive
  - Other types – variably positive
    (10% - 30%; not all HRS cells)
- Predictive marker for Rituximab therapy

**Basic stains: CD79α**

- Fairly specific, sensitive B-cell marker
- Normal (wide B-cell expression):
  - pre-B cell to plasma cell
- Lymphomas:
  - majority B-cell leukaemias and lymphomas
  - 50% myelomas
  - 10%+ T-LBs positive
  - rare in mature T-cell NHL
  - Hodgkin lymphoma:
    - L&H/popcorn cells positive
    - HRS cells in classical HL ca. 20% cases positive

**Basic stains: Pax-5 (BSAP)**

- Most specific B-cell marker available
- B-cell nuclear transcription factor
- Normal – many B cells
- Lymphomas:
  - nearly all B-cell NHLs
  - Hodgkin: HRS cells and variants positive in most cases
  - plasma cell neoplasms negative
  - peripheral TCLs negative
  - some pre-T-LB positive
  - some AML positive
Usual staining pattern of B-cell neoplasms

<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>B-cell neoplasms</th>
<th>T-cell neoplasms</th>
<th>Lymphomas</th>
<th>Eosinophils</th>
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<tr>
<td>CD5</td>
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<td>+</td>
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<tr>
<td>Cyclin D1</td>
<td>-</td>
<td>+</td>
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Small cell B-cell lymphomas:
Differential Diagnosis

- Small lymphocytic NHL
- Mantle cell NHL

Small B-Cell Lymphomas: Overall Survival

Armitage et al, 1997
Basic stains: CD5

- Modulates T & B cell signalling
- Pan-T cell marker
  - 95% thymocytes
  - 100% post-thymic T-cells
  - ↑ expression with maturity
- Minor population normal B-cells:
  - ca. 15% peripheral B-cells
  - ↑ in autoimmunity
- Lymphomas:
  - 95% T-cell neoplasias
  - B-cell NHL
  - B-CLL / SLL (90%)
  - Mantle cell NHL (90%)
  - >10% DLBCL

Basic stains: Cyclin D1

- cyclin family
  - control cell cycle
- normal proliferating cells, e.g. basal epidermal cells positive
- variable clone sensitivity
- Bcl-1 gene product at 11q13
- upregulated in cells with t(11;14)
- >90% MCLs positive (nuclear)
- 15% myelomas positive (nuclear)

Basic stains: CD23

- Normal:
  - activated germinal centre cells
  - some mantle zone lymphocytes
  - some mature B cells
  - follicular dendritic reticulum cells
  - T-cells, etc.
- In lymphomas:
  - some small cell B-cell NHL
  - SLL/CLL
  - negative in MCL, pre-LB, TCLs
B-cell Small Lymphocytic Lymphoma (CLL)

Morphology
- small lymphocytes
- proliferation centres

Immunology
- surface IgM weak
- CD19, 20, 79a +
- CD5 +
- CD10, CyclD1 -

Mantle Cell Lymphoma

Morphology
- small-medium lymphocytes
- cleaved / irregular
- blastoid variant
- nodular / mantle / diffuse

Immunology
- surface Ig +
- CD19, 20, 22, 79a +
- CD5 +
- CD23 -
- Cyclin D1 +
- CD10 -

Immunophenotype: Small B-Cell Lymphomas

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<thead>
<tr>
<th></th>
<th>CD20</th>
<th>CD79A</th>
<th>CD10</th>
<th>CD23</th>
<th>CD19</th>
<th>Cyclin D1</th>
<th>TdT</th>
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<td>MZL</td>
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<td>ELB</td>
<td>+/+</td>
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</table>
**Follicular Lymphoma**

**Morphology**
- Germinal centre cells
- CBs & CCs
- Follicular

**Immunology**
- Surface Ig
- CD9, 20, 22, 79a
- BCL-2
- CD10
- Bcl-6
- CD5
- CD20

**Basic stain: bcl-2**

- Apoptosis inhibitor
- Nuclear and cytoplasmic stain
- Normal:
  - Mature B- and T-cells
  - Negative in cortical thymocytes and germinal centre cells
- In lymphoma:
  - Positive in most peripheral B-NHL and T-NHL
  - Negative in BL
  - Associated with, but not specific for t(14;18)
  - Positive in neoplastic germinal centres
  - Often negative in skin lymphoma
  - Ca 10% of follicular lymphomas re bcl-2 negative

*Original Paper*

**Lack of Bcl-2 expression in follicular lymphoma may be caused by mutations in the BCL2 gene or by absence of the t(14;18) translocation**

Maria Schuol, E. Elphine de Jong, Philip Kuus, Patricia Groenen, and Hans van Krieken
Diffuse Large B-cell Lymphoma

Morphology
- large cells
- nuclear diffuse

Immunology
- surface Ig
- cytoplasmic Ig
- CD10, 20, 22, 79a
- CD30
- CD38, CD138
- Bcl-6
- Mum1

Basic stain: Ki-67
- Nuclear protein
- Expressed in all cell cycle stages except G0
- In lymphomas:
  - "Roughly"
  - indolent / aggressive / highly aggressive NHL
  - Prognosis?
  - Characteristic pattern in HRS cells in HL

Basic stain: Bcl-6
- Nuclear protooncogene product
- Normal:
  - germinal centre cells
- In lymphomas:
  - follicular lymphoma
  - most BL
  - variable DLBCL
  - cell of origin staining in DLBCL
  - HL-LP (not classical)
  - SLL, MCL, MZL, HCL: negative
IHC for DLBCL
Add to basic panel:

- CD10
- CD138
- MUM1

Secondary stain: CD10

- >90% precursor B-LB (membrane & paranuclear stain)
- ca. 25% precursor T-LB
- Burkitt lymphoma
- Follicular lymphoma
  - Interfollicular CD10+ cells suggest lymphoma
- Some DLBCL
  - "Cell of origin" algorithm in DLBCL
  - GC B vs. ABC

Large B-cell Lymphomas
Molecular Variants

- Gene profiling identified 2 types of DLBCL
  - Germinal Centre B-cell
  - Activated B-cell
- Not applicable in routine setting

- IHC
  - surrogate molecular profiling
  - Hans ‘cell of origin’ classifier
DLBCL - the HANS Classifier: Germinal centre (GC) & Activated B cell (ABC) types

DLBCL

CD10+ GC subtype

CD10-

Bcl6+

bcl6- Non-GC (ABC) subtype

MUM1-

GC subtype

MUM1+

Non-GC (ABC) subtype

DLBCL - 'cell of origin': Competing IHC classifiers

Gray zone (bordeline) B-cell lymphomas
Immunophenotyping in Gray zone B-NHL

<table>
<thead>
<tr>
<th>CD20</th>
<th>CD3</th>
<th>BCL2</th>
<th>CD10</th>
<th>TdT</th>
<th>MYC</th>
<th>CyclinD1</th>
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<tr>
<td>↑</td>
<td>+</td>
<td>+</td>
<td>↓</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**DLBCL-like morphology**
**Bl-like immunophenotype (BCL2=neg)**
↑↑↑ proportion of double-hit B-NHL (e.g., c-myc/bcl-2 rearranged)

IHC for c-myc and bcl-2 identifies double-hit B-NHL

Hodgkins lymphoma: differential diagnosis

<table>
<thead>
<tr>
<th>CD10</th>
<th>CD1a</th>
<th>T-cell antigens</th>
<th>CD1a</th>
<th>CD30</th>
<th>CD15</th>
<th>EMA</th>
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<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**Key**

- The lymphoma cells are commonly but not always positive
- The lymphoma cells are usually but not always negative

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Immunohistochemical Double Hit Score Is a Strong Predictor of Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vinristine, and Prednisone

Hodgkin's lymphoma: Classical Hodgkin lymphoma, MC: CD30

Hodgkin's lymphoma, LP: CD20

T-cell rich B-cell lymphoma: CD20
Basic stain: CD30

- TNF-R family
- ‘Ki-1 antigen’
- Activation antigen
- Normal expression:
  - activated parafollicular immunoblasts
  - virally infected cells (EBV)
  - some clones stain plasma cells (Ber-H2)
- Pattern:
  - Membrane with dot-like Golgi

CD30 in lymphoma

- "CD30+ lymphoproliferations":
  - Py skin anaplastic large cell lymphoma
  - Systemic ALCL
  - Lymphomatoid papulosis
  - Mycosis fungoides transformation
  - Hodgkin lymphoma
    - HRS cells in classical types
    - Popcorn cells in HL-LP: 5% -15%
    - Ca. 30% of other T-cell NHL
    - Ca. 20% DLBCL
    - Target for Brentuximab

IHC for Hodgkins Lymphoma
Add to basic panel:

- PAX-5 (ALCL?)
- BCL-6, CD57, BOB-1, OCT-2 (HL, LP?)
- ALK (ALCL?)
- EBV
- (CD15)
HL vs ALCL: Immunophenotype

<table>
<thead>
<tr>
<th></th>
<th>HL ALK - pos</th>
<th>ALK - neg</th>
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</thead>
<tbody>
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<td></td>
<td>T/null - ALC</td>
<td>T/null - ALC</td>
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<tr>
<td>ALK</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EBV</td>
<td>&gt; 40%</td>
<td>-</td>
</tr>
<tr>
<td>CD30</td>
<td>+</td>
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<td>&lt; 5%</td>
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<tr>
<td>EMA</td>
<td>-</td>
<td>ca. 50%</td>
</tr>
<tr>
<td>PAX5</td>
<td>&gt; 80%</td>
<td>ca. 50%</td>
</tr>
<tr>
<td>CD20</td>
<td>ca. 25%</td>
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<tr>
<td>CD3</td>
<td>ca. 2%</td>
<td>+/-</td>
</tr>
<tr>
<td>CD45</td>
<td>-</td>
<td>ca. 50%</td>
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<tr>
<td>Granzyn/perforin</td>
<td>10 – 20%</td>
<td>ca. 90%</td>
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<tr>
<td>TCR genes</td>
<td>R (single cell)</td>
<td>G</td>
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<tr>
<td>Ig genes</td>
<td>R</td>
<td>G</td>
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</tbody>
</table>

Expression of transcription factors Pax-6, Oct-1, Oct-2 and BOB.1 in Hodgkin’s Lymphoma

Secondary stain: EBV

- Most viral antigens not relevant
- LMP1: Normal primary infection (pathology R
diagnosis G) latency and III
- HRS-cell-like morphology
- EBNA2
- Nuclear staining
- Normal primary infection (IM)
- In lymphomas:
  - Hodgkin lymphomas:
    - Classical type: 35% – 50% positive in HRS cells: LMP1+ EBNA2-
    - LMP1 (LMP positive cells negative)
  - EBV+ immunodeficiency-associated lymphomas
    - Variable (diagnostically useful) latency patterns
    - Sporadic B-NHL
    - Ca. 50% of elderly, aneuploid
  - T cell lymphomas
  - Sporadic type: 25% – 50% depending on type
    - ALCL are negative
T-cell lymphoma: immunophenotype

Complex!

Basic stain: CD3
- transmembrane molecule
- Ig superfamily
- part of T-cell receptor
- most specific T-cell marker
- pan-T cell marker
  - thymocytes: cyt. → membrane
  - most post-thymic T-cells
  - activated NK-celler

CD3 in lymphoma
- >90% peripheral TCLs
- Primitive precursor T-LB in cytoplasm
- B-cell lymphomas negative
- Hodgkins lymphoma negative
- (NK-lymfomer: cyt. expression)
IHC for PTL
Add to basic panel:

- CD1a
- CD2
- CD4
- CD7
- CD8
- CD3epsilon, TdT, CD43
- T-LB?
- CD10, CD21, CD23, PD-1
- AILD?
- CD56, CD57, perforin, granzyme B, TIA-1
- NK/NK-like?
- EBV

Secondary stain:
Anaplastic lymphoma kinase (ALK, CD246)

- Normal tissues only in CNS
- In neoplasia:
  - ALCL with t(2;5) or other translocation
  - ALK-positive prognostic factor
  - Cellular localization varies with partner gene
  - ALK-ve B-cell NHL (rare)
  - Negative in primary cutaneous ALCL

Secondary stain:
Terminal deoxynucleotidyl transferase (TdT)

- Nuclear protein involved in DNA synthesis
- Normal expression:
  - early thymocytes
  - pre-B and pre-pre-B cells
- In lymphomas:
  - stem cell leukaemias
  - most (>90%) precursor LBs
  - negative in most peripheral TCLs
  - some AMLs (up to 20%)
Secondary stain: CD1a

- T-cell marker
  - 70% cortical thymocytes
  - Peripheral T-cells negative
  - Langerhans cells / interdigitating reticulum

- In lymphomas:
  - 50% precursor T-LB
  - Langerhans cell histiocytosis
  - Peripheral TCLs are negative in paraffin

- NB! May be positive in mediaslinal biopsies from normal thymus or lymphocyte-rich thymoma

Secondary stain: CD7

- Early pan-T cell marker
  - 90% thymocytes
  - B-cells negative
  - ↑ NK cells negative

- In lymphoma:
  - nearly all T-LB +
  - many peripheral TCLs +
  - often lost in TCL
  - negative in B-NHL

Secondary stains: CD4 & CD8

- CD4
  - Thymocytes
  - T-helper cells
  - Monocytes
  - Macrophages
  - Granulocytes

Normal tonsil: CD4
Secondary stains: CD4 & CD8

- CD8
  - T-cytotoxic/suppressor cells
  - NK cells
  - Intraepithelial lymphocyte CD8+
- Most lymphomas CD4+
- γδ TCL usually CD4- CD8-
- ALCL: CD4 > CD8
- Double negs & double pos: aberrant = neoplastic?

Basic stain: CD21

- Membrane glycoprotein
- Normal:
  - Mature B cells
  - mantle zone & marginal zone B cells
  - Lost on B-cell activation
  - Follicular dendritic reticulum cells – in GCs
- C3d/EBV receptor
- In lymphomas:
  - most follicular lymphomas
  - some other B-cell NHL
  - FDC network in GC-derived tumours
    - MCL, HL, AILD

T-cell lymphoma: immunophenotype

Complex!
Nodal PTCL - immunophenotype

<table>
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<tr>
<th>PTCL NOS</th>
<th>ABL</th>
<th>ALL ALL-</th>
<th>T-R</th>
<th>MP</th>
<th>T-PLL</th>
<th>DLBCL</th>
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<td>+</td>
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Oncogenes/ Tumor Suppressor Genes Evaluation by Immunohistochemistry

- **Bcl-2**: Follicular lymphoma, (14q18)
  - marker expression not specific for translocation
- **Cyclin D1**: Mantle cell lymphoma, (11q14); myelomas (15%)
- **p53**: Progression in lymphomas, high grade lymphomas
  - 'well of origin' staining in DLBCL
- **c-myc**
  - Prognostic in DLBCL
  - Marker of "hit" lymphomas
- **ALK-1**: ALCL; NPM/ALK (t2;5)
- **CD99**: Lymphoblastic, myeloblastic

IHC for lymphoma vs other

Add to basic panel:

- panCK
- S-100
- Melan-A
IHC for lymphoid vs myeloid
Add to basic panel

- Myeloperoxidase
- CD43
- CD68
- CD163
- CD33
- (CD14, CD15, CD34, CD61, glycophorin C)

Acute myeloid leukaemia:
CD33 (paraffin section):

Myeloid sarcoma: testis
**Targeted therapy**

- **Rituximab (anti-CD20)**
  - B-cell NHL

- **Brentuximab (anti-CD30)**
  - HL
  - ALCL
  - CD30+ DLBCL

- **Alemtuzumab (anti-CD52)**
  - B-CLL
  - T-cell lymphoma