Lymphoid Neoplasms

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### Incidence of Haematological Malignancies

**UK2001 (CRUK)**

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cancers</td>
<td>271,000</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>6,760 (2%)</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>9,280 (3%)</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>1,430 (&lt;1%)</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>3,570 (1%)</td>
</tr>
</tbody>
</table>
Overview of Lymphoma

• neoplasms of lymphoid origin, typically causing lymphadenopathy

• leukemia vs lymphoma

• lymphomas viewed as clonal expansions of lymphocyte arrested at a certain stage of development and transformed into a malignant cell

• types of non- Hodgkin’s lymphoma reflect the developmental stages of lymphocytes.

• 85% of NHL are of B cell origin
Fig. B and T cell Maturation Pathway
Types of Lymphoid neoplasms

- Precursor B- and T- cell
  (lymphoblastic leukaemia/lymphoma)

- Mature B-cell neoplasms
  (includes NHLs, chronic leukaemias, plasma cell dyscrasias)

- Mature T-cell and NK-cell neoplasms
  (includes NHLs, chronic leukaemias)

- (Hodgkin lymphoma)
B-cell development

- Stem cell
- Lymphoid precursor
- Progenitor-B
- Pre-B
- Mature naive B-cell
- Germinal center B-cell
- Memory B-cell
- Plasma cell
- CLL, MCL
- LBL, ALL
- DLBCL, FL, BL, HL
- MM
- MZL
- CLL

Bone marrow

Lymphoid tissue
The challenge of lymphoma classification

Biologically rational classification
Diseases that have distinct
• morphology
• immunophenotype
• genetic features
• clinical features

Clinically useful classification
Diseases that have distinct
• clinical features
• natural history
• prognosis
• treatment
<table>
<thead>
<tr>
<th>B-cell neoplasms</th>
<th>T- and NK-cell neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precursor B-cell neoplasm</strong></td>
<td><strong>Precursor T-cell neoplasm</strong></td>
</tr>
<tr>
<td>Precursor B-lymphoblastic leukemia/lymphoma</td>
<td>Precursor T-lymphoblastic lymphoma/leukemia</td>
</tr>
<tr>
<td>(precursor B-cell acute lymphoblastic leukemia)</td>
<td>(precursor T-cell acute lymphoblastic leukemia)</td>
</tr>
<tr>
<td><strong>Mature (peripheral) B-cell neoplasms</strong></td>
<td><strong>Mature (peripheral) T-cell neoplasms</strong></td>
</tr>
<tr>
<td>B-cell chronic lymphocytic leukemia/small lymphocytic</td>
<td>T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>lymphoma</td>
<td>T-cell granular lymphocytic leukemia</td>
</tr>
<tr>
<td>B-cell prolymphocytic leukemia</td>
<td>Aggressive NK-cell leukemia</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>Adult T-cell lymphoma/leukemia</td>
</tr>
<tr>
<td>Splenic marginal zone B-cell lymphoma (with or w/o</td>
<td>(human T-cell lymphotropic virus type I positive)</td>
</tr>
<tr>
<td>villous lymphocytes)</td>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>Enteropathy type T-cell lymphoma</td>
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<tr>
<td>Plasma cell myeloma/plasmacytoma</td>
<td>Hepatosplenic gammagammadelta T-cell lymphoma</td>
</tr>
<tr>
<td>Extranodal marginal zone B-cell lymphoma of mucosa-</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>associated lymphoid tissue type</td>
<td>Mycosis fungoides/Sezary syndrome</td>
</tr>
<tr>
<td>Nodal marginal zone B-cell lymphoma (with or w/o</td>
<td>Anaplastic large cell lymphoma, T/null-cell,</td>
</tr>
<tr>
<td>monocytoid B cells)</td>
<td>primary cutaneous type</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>Peripheral T-cell lymphoma, not otherwise characterized</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>Anaplastic large cell lymphoma, T/null-cell,</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>primary systemic type</td>
</tr>
<tr>
<td>Mediastinal large B-cell lymphoma</td>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>Anaplastic large cell lymphoma, T/null-cell,</td>
</tr>
<tr>
<td>Burkitt's lymphoma/Burkitt's cell leukemia</td>
<td>primary systemic type</td>
</tr>
</tbody>
</table>
B-Cell Lymphoma

Precursor lymphoblastic lymphoma/leukemia

Mature
- Small lymphocytic lymphoma/leukemia
- Lymphoplasmacytic lymphoma
- Marginal Zone Lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B cell
- Burkitt’s lymphoma
- Hairy cell leukemia
- Plasma cell myeloma
T-Cell Lymphoma

• **Precursor** lymphoblastic lymphoma/leukemia

**Mature**
• Peripheral T (unspecified)
• T-cell large granular lymphocytic leukaemia
• NK leukaemia
• Anaplastic large cell T/null
• Cutaneous anaplastic large cell T/null
• Mycosis Fungoides/Sezary syndrome
• Adult T-cell lymphoma/leukemia HTLV-1 +
• Enteropathy-type intestinal
• Hepatosplenic gamma delta
• Angioimmunoblastic
Non-Hodgkin lymphoma Incidence

- Diffuse large B-cell lymphoma
- Follicular NHL
- Other NHL
Pillars of “WHO/REAL” Classification

- Cell of origin
- Cell morphology
- Immunophenotyping
- Genotyping
- Clinical picture

Abandon the use of indolent – aggressive – highly aggressive
Prognostic Indicators

• **Histopathologic Type**
  Grades within subtypes e.g. follicular lymphoma
  Variants within subtypes e.g. Blastoid mantle cell

• **Biology**
  Proliferation fraction
  Oncogenes, tumor suppressor genes, MDR

• **Clinical Parameters**
  Stage and bulk of disease
  International prognostic index
## WHO Classification

<table>
<thead>
<tr>
<th>Indolent</th>
<th>Aggressive</th>
<th>Very Aggressive</th>
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</thead>
<tbody>
<tr>
<td>• CLL/SLL</td>
<td>• PLL</td>
<td>• PrecursorB-lymphoblastic lymphoma/leukemia</td>
</tr>
<tr>
<td>• Lymphoplasmacytoid/WM</td>
<td>• Plasmacytoma/multiple myeloma</td>
<td>• Burkitt’s lymphoma/B-cell acute leukemia</td>
</tr>
<tr>
<td>• HCL</td>
<td>• Mantle cell NHL</td>
<td>• Plasma cell leukemia</td>
</tr>
<tr>
<td>• Splenic marginal zone lymphoma</td>
<td>• Follicular NHL (grade III)</td>
<td></td>
</tr>
<tr>
<td>• Marginal zone lymphoma</td>
<td>• DLBCL</td>
<td></td>
</tr>
<tr>
<td>– Extranodal (MALT)</td>
<td>• High-grade B-cell lymphoma/Burkitt’s-like</td>
<td></td>
</tr>
<tr>
<td>– Nodal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Follicular NHL (grade I-II)</td>
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<td></td>
</tr>
<tr>
<td>Category</td>
<td>Survival of untreated patients</td>
<td>Curability</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Indolent</td>
<td>Years</td>
</tr>
<tr>
<td></td>
<td>Aggressive</td>
<td>Months</td>
</tr>
<tr>
<td></td>
<td>Very aggressive</td>
<td>Weeks</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>All types</td>
<td>Variable – months to years</td>
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</tbody>
</table>
Risk factors for NHL

- Immune suppression
  - Inherited immunodeficiencies
  - organ transplant (cyclosporine)
  - AIDS
  - increasing age

- DNA repair defects
  - ataxia telangiectasia
  - xeroderma pigmentosum
Risk factors for NHL

• Chronic inflammation and antigenic stimulation
  – *Helicobacter pylori* inflammation, stomach
  – *Chlamydia psittaci* inflammation, ocular adnexal tissues
  – Sjögren’s syndrome

• Viral causes
  – EBV and Burkitt’s lymphoma
  – HTLV-I and T cell leukemia-lymphoma
    Hepatitis C and SLVL
Clinical Features

• Variable
  • severity: asymptomatic to extremely ill
  • time course: evolution over weeks, months, or years

• Systemic manifestations (B symptoms)
  • fever, night sweats, weight loss, anorexia, pruritis

• Local manifestations
  lymphadenopathy, splenomegaly most common,
  any tissue potentially can be infiltrated

• Cytopenias
Clinical Features

• Extranodal primary - more common in high-grade lymphoma.

• Lymphadenopathy may fluctuate or spontaneously remit, especially in low-grade lymphomas.

• B symptoms more common in high-grade lymphomas.

• Haematogenous spread of disease, with no predictable pattern.
Other complications of lymphoma

- bone marrow failure (infiltration)
- CNS infiltration
- immune hemolysis or thrombocytopenia
  neutropenia in LGL leukaemias
- immunosuppression eg ↓ Igs (chronic LPDs),
  T cell (Hodgkin’s or post fludarabine)
- compression of structures (eg spinal cord, ureters) by bulky disease
- pleural/pericardial effusions, ascites
Types of Lymphoma

• Indolent (low grade)
  – Life expectancy in years, untreated
  – 85-90% present in Stage III or IV
  – Incurable (except ? by allogenic SCT)

• Intermediate eg Mantle cell NHL

• Aggressive (high grade)
  – Life expectancy in weeks, untreated
  – Potentially curable
Epidemiology

• Indolent lymphomas are rare in young people and increase in incidence with age.

• High grade lymphoma is less age related, and is among most common cancers affecting the young.

• Burkitt’s and lymphoblastic lymphoma are common in adolescents.

• AIDS patients develop aggressive, high grade lymphomas (Burkitt’s, Burkitt’s -like).
Diagnosis of NHL

• Excisional biopsy needed to show nodal architecture (follicular vs diffuse).

• Immunophenotyping
  - immunohistochemistry of tissue sections
  - flow cytometry (blood / BM / biopsy)

• Cytogenetics (including FISH, molecular studies)

• Ig / TCR gene rearrangement studies (clonality)
Molecular pathogenesis of B-cell lymphomas
Staging Workup

Requires

• CT scans of chest, abdomen and pelvis

• Bone marrow biopsy and aspirate

• (Lumbar puncture)
  eg AIDS lymphoma
  lymphoblastic lymphoma
  High grade lymphoma with positive marrow
Staging of lymphoma (Ann Arbor)

Stage I: absence of B symptoms
Stage II: fever, night sweats, weight loss
Stage III: extranodal
Stage IV: advanced disease
International Prognostic Index (IPI)

Patients of all ages

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Patients ≤60 years (age-adjusted)</th>
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<tbody>
<tr>
<td>Age</td>
<td>≥60 years</td>
</tr>
<tr>
<td>Performance status (PS)</td>
<td>2–4</td>
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<tr>
<td>Lactate dehydrogenase (LDH) level</td>
<td>Elevated</td>
</tr>
<tr>
<td>Extranodal involvement</td>
<td>&gt;1 site</td>
</tr>
<tr>
<td>Stage (Ann Arbor)</td>
<td>III–IV</td>
</tr>
</tbody>
</table>

Patients ≤60 years (age-adjusted)

<table>
<thead>
<tr>
<th>Risk factors</th>
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<td>PS</td>
<td>2–4</td>
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<tr>
<td>LDH</td>
<td>Elevated</td>
</tr>
<tr>
<td>Stage</td>
<td>III–IV</td>
</tr>
</tbody>
</table>
Diffuse Large B-Cell Lymphoma (DLCL): OS

P<0.001
Strategies for Improving Outcome for Aggressive NHL

• Monoclonal antibodies (MoAbs)
  – Rituximab (anti-CD20)
    • Combination with chemotherapy

• Dose intensification
  – High-dose chemotherapy/ASCT
  – Growth factor incorporation
Treatment for advanced indolent NHLs

- Deferred therapy
- Single alkylating agent
- Radiation therapy
- Combination chemotherapy
- Purine analogues

- Biological therapy
  - MoAbs
  - IFN

- Transplant
  - Autologous
  - Allogenic
# MoAbs for Lymphoid malignancies

<table>
<thead>
<tr>
<th>MoAb</th>
<th>Antigen</th>
<th>Type</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>CD20</td>
<td>Chimeric</td>
<td>B cells</td>
</tr>
<tr>
<td>epratuzumab</td>
<td>CD22</td>
<td>Humanized</td>
<td>B cells</td>
</tr>
<tr>
<td></td>
<td>CD30</td>
<td>Humanized</td>
<td>anaplastic / Hodgkin</td>
</tr>
<tr>
<td></td>
<td>CD25</td>
<td>Humanized</td>
<td>adult T-cell leukaemia</td>
</tr>
<tr>
<td>campath</td>
<td>CD52</td>
<td>Humanized</td>
<td>CLL, T-PLL</td>
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</table>
Proposed Mechanisms of Action for MoAbs

Immune

- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Complement-dependent cytotoxicity (CDC)
- Apoptosis

+/- radioactive labels (eg Iodine, Yttrium)
Immunophenotyping

- Differentiation of normal and malignant haematological populations

- Uses antibody recognition of surface / intracellular antigens

- Important for
  - diagnosis / prognostic evaluation
  - monitoring treatment response (MRD)
  - identification of suitable targets for antibody therapy

- Flow cytometry v Immunohistochemistry of tissue sections
CD20 Expression in B-Cell Malignancies

Histology

- Hairy cell
- DLBCL
- Burkitt’s lymphoma
- Marginal zone
- Follicular
- LP/Waldenström’s
- Mantle cell
- CLL/PLL
- CLL

Mean channel fluorescence
Immunophenotyping

Flow cytometry

Disadvantages (compared to immunohistochemistry)

- No visualisation of tissue architecture
- Poor yield of cells from sclerotic and some “packed” samples
- Misses rare neoplastic cells eg Hodgkins
- Sampling differences in patchy neoplastic infiltrates
Immunophenotyping

Diagnosis

• Lineage classification  myeloid v lymphoid   (B or T or NK)

• Maturation classification
Immunophenotyping

**B cell LPD**
Light chain restriction (clonality)

Aberrant pattern of antigens compared with normal subsets

**T cell LPD**
Subset restriction eg CD4 or CD8 (but need TCR gene clonality)

Aberrant pattern of antigens compared with normal subsets
### Lymphoproliferative Panel

<table>
<thead>
<tr>
<th>Tube</th>
<th>FITC</th>
<th>PE</th>
<th>PERC P/APC</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>IgG control</td>
<td>IgG control</td>
<td>IgG control</td>
</tr>
<tr>
<td>2</td>
<td>CD 7</td>
<td>CD 56</td>
<td>CD 3</td>
</tr>
<tr>
<td>3</td>
<td>CD 4</td>
<td>CD 8</td>
<td>CD 3</td>
</tr>
<tr>
<td>4</td>
<td>kappa</td>
<td>lambda</td>
<td>CD 19 APC</td>
</tr>
<tr>
<td>5</td>
<td>CD 20</td>
<td>CD 5</td>
<td>CD 19 APC</td>
</tr>
<tr>
<td>6</td>
<td>TCR gamma delta</td>
<td>CD 2</td>
<td>CD 3</td>
</tr>
<tr>
<td>7</td>
<td>CD 79b</td>
<td>CD 23</td>
<td>CD 19 APC</td>
</tr>
<tr>
<td>8</td>
<td>CD 19</td>
<td>CD 38</td>
<td>CD 45</td>
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<tr>
<td>9</td>
<td>CD 10</td>
<td>CD 19</td>
<td>CD 34</td>
</tr>
<tr>
<td>10</td>
<td>CD 103</td>
<td>CD 22</td>
<td>CD 19 APC</td>
</tr>
</tbody>
</table>
Notable Subtypes of Lymphoma
Follicular lymphoma

- most common type of “indolent” lymphoma
- usually widespread at presentation
- not curable (some exceptions)

- cell of origin: germinal center B-cell
  - centrocytes / centroblasts
  - expression of CD10
  - IgV mutations (and signs of ongoing mutations)
  - BUT maintain high BCL-2 [t(14;18)]
Mantle cell NHL

- Intermediate
- usually widespread at presentation
- 20-30% longterm survival

- cell of origin: resemble follicle mantle cells (mature naïve B cells)
  - IgV either not mutated (90% of cases) or only very few mutations
  - positive for CD5 (like CLL)
  - but lack CD23 (unlike CLL)
  - t(11;14) - overexpression of cyclin D1
Lymphoplasmacytoid/Waldenstrom’s

- Low grade
- Spleen, bone marrow, lymph nodes
- IgM paraprotein - hyperviscosity symptoms (10-30% of patients)
  - autoantibody or cryoglobulin activity
- cell of origin: may originate from B cells that have bypassed germinal centre
  - IgVH restricted, somatically mutated,
    predominantly CD27neg, IgM+IgD+
- CD10neg CD5neg
Marginal zone lymphomas

- Usually localised extranodal (30% disseminated)
- Associated with
  1) autoimmune diseases eg Sjogren’s, Hashimoto’s
  2) infections eg H Pylori - gastric MALT NHL
      Hep C - SLVL
- Can transform to DLBCL

**cell of origin**: marginal zone (memory) B cell
- IgM (absence of IgD)
- typically have mutated IgV genes with ongoing mutations

- CD10neg CD5neg
Hairy cell Leukaemia

- low grade, rare
- Splenomegaly, pancytopenia,
- “Hairy cells” in spleen red pulp, blood, bone marrow (rarely LAD)
- Long-term survival with purine analogues
- Immune dysfunction, includes vasculitis

- cell of origin: ?
  - has activation markers CD25, CD11c, CD103
  - 40% of HCL express multiple surface Ig isotypes
  - on-going somatic mutation but lacks other features of germinal centre cells
  - gene profiling - more related to memory B cells
Chronic Lymphocytic Leukaemia /SLL

• Most prevalent leukaemia (30% of all leukaemias)
• Variable clinical course
  asymptomatic for many years v aggressive
• 5-10% transform to high grade (Richter’s) - poor prognosis
• Hypogammaglobulinaemia
• Autoimmune cytopenias

• cell of origin: ?
  - 50% CLLs - unmutated IgVH genes (poor prognosis)
  - (50% CLLs - mutated IgVH genes (better prognosis)
  however both types - common gene expression signature (but different from other lymphomas /leukaemias)

  - CD5+CD23+ weak surface Ig / BCR
Diffuse large B-cell lymphoma (DLBCL)

- most common type of “aggressive” lymphoma
- usually symptomatic
- extranodal involvement is common
- curable in ~ 40%

- cell of origin:
  - immunophenotypic and genetic features of B cells and B cell subsets but often incomplete / aberrant
AIDS Lymphoma

- Aggressive lymphomas of B cell origin.
- ↑ risk in HIV+ despite HAART
- Burkitt’s, Burkitt’s-like, and DLBCL.
- Primary CNS lymphoma/ Primary Effusion lymphoma
- Hodgkins
- Treatment often limited by immunocompromised status eg rituximab benefit offset by ↑ infections.
- Prognosis improved with HAART therapy.
Adult T Cell Leukemia-Lymphoma

- Associated with HTLV-I infection.
- CD4+ CD8neg CD7neg CD25+
- Caribbean, Japan, southeastern U.S.
- Hepatosplenomegaly, leukocytosis, lymphadenopathy, skin involvement, lytic lesions of bone, hypercalcemia.
- May respond to - combination chemotherapy (CHOP) - AZT and interferon - CD25 MoAb
Large Granular Lymphocyte Leukaemia (LGL leukaemia)

• Clonal proliferation of CD8+ T cells (rarely NK cells)

• CD8+ CD4neg, positive for NK markers (CD56, CD57, CD16)

• Disease of elderly, usually indolent, modest or no lymphocytosis

• 85% have neutropenia, (other haematological cytopenias frequent)

• Associated with autoimmune disorders eg RhA (Felty’s), SLE,

• May require immunosuppression/cytotoxics eg MTX, cyclophosphamide, cyclosporin
Mycosis Fungoides / Sezary’s

- Malignancy of helper T cells (Th2 response)
- CD4+ often CD7neg (CD25neg)
- Affinity for skin.
- Can be treated with electron beam therapy, PUVA, retinoids, IFN
- Sezary’s when systemic (blood, lymph nodes)
Angio-immunoblastic T cell NHL

• 1-2% of all NHLs, subtype of peripheral T-NHL

• Previously thought to be abnormal immune response (AILD) but T cell clonality

• Median age -60’s

• B symptoms, lymphadenopathy, hepatosplenomegaly, rash, autoimmune manifestations (eg AIHA, vasculitis, arthritis), hypergammaglobulinaemia

• May respond to steroids when more indolent but usually needs chemotherapy (SCT in younger patients)
Hodgkin lymphoma

- Lymphocyte predominant
  - B cell neoplasm (CD20+) with features of germinal centre origin (rearranged Ig, somatic mutations)

- Classical Hodgkin’s
  - neoplastic cells –rearranged, mutated Ig genes
  - no or little B cell immunophenotype, gained CD30, CD15

- Reed-Sternberg cells (or RS variants) in the affected tissues

- most cells in affected lymph node are polyclonal reactive lymphoid cells, not neoplastic cells
RS cell and variants

- Classic RS cell (mixed cellularity)
- Lacunar cell (nodular sclerosis)
- Popcorn cell (lymphocyte predominance)
A possible model of pathogenesis

germinal centre

transforming event(s) EBV?

loss of apoptosis

germinal centre B cell

RS cell

cytokines

inflammatory response