AWLP Lymphoma Course
T-cell Lymphomas

Dr Stefan Dojcinov

University Hospital of Wales
Cardiff
T-cell LYMPHOMAS

- KNOWLEDGE LAGGING BEHIND B-CELL NHL
- POOR UNDERSTANDING OF MOLECULAR PATHOGENESIS
- DEFINITION OF ENTITIES ON CLINICAL GORUNDS, MORPHOLOGY AND IMMUNOPHENOTYPE
WHO Classification

Precursor T-cell neoplasms
  Precursor T / NK lymphoblastic leukaemia/lymphoma

Peripheral T-cell neoplasms (excl. cutaneous lymphoma)
  T-cell prolymphocytic leukaemia
  Indolent large granular lymphocyte leukaemia (LGL)
  T-cell large granular lymphocyte leukaemia (TLGL)
  Aggressive NK cell leukaemia
  Adult T-cell lymphoma/leukaemia
  Extranodal NK/T cell
  Enteropathy type T-cell lymphoma
  Hepatosplenic T-cell lymphoma
  Subcutaneous panniculitis-like T-cell lymphoma
  Angioimmunoblastic T-cell lymphoma (AILD)

Peripheral T-cell lymphomas (unspecified)
  Anaplastic large cell lymphoma (ALCL) ALK1-
  Anaplastic large cell lymphoma (ALCL) ALK1+
Relative Frequencies (%) of Various Lymphoma Types (LNs)

- B-cell neoplasms
- T-cell neoplasms
- Hodgkin's lymphoma
- Lymphoma unclassifiable (NOS)

AWLP & SFMC
TCL - EPIDEMIOLOGY

• Variable incidence of different types – role of infection
  – T/NK cell lymphoma in Asian population
  – Fulminant EBV+ T-cell lymphoproliferative disorder
  – Adult T-cell leukaemia (HTLV1) (Japan, Caribbean)

• Role of immunosuppression
  – Gamma / delta TCL following
    • Immunosuppression / transplantation
Innate - Gamma/delta T-cells
- Splenic red pulp
- Intestinal epithelium
- Other epithelial sites
- CD3+/CD56+/Granzyme+

Adaptive IS – Heterogeneous
- CD4+ regulatory cells
- CD4+/CD57+/CD10+ FC helper T-cells
- CD8+ cytotoxic

NK-cell leukemia
Fulminant EBV+ T-cell LPD
Hepatosplenic T-cell lymphoma

Spectrum of nodal TCL
- Anaplastic Large Cell Lymphoma
- Angioimmunoblastic T-cell lymphoma
- Peripheral TCL NOS
### T-cell LINEAGE MARKERS

<table>
<thead>
<tr>
<th>T-cell Stage</th>
<th>CD7</th>
<th>CD2</th>
<th>CD5</th>
<th>CD3</th>
<th>CD1</th>
<th>CD8</th>
<th>CD4</th>
<th>TdT</th>
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<tr>
<td>Prothymocyte</td>
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<td>Subcapsular Thymocyte</td>
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<td>Cortical Thymocyte</td>
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<td>Medullary Thymocyte &amp; Peripheral T-Cell</td>
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**Legend:**
- **CD7, CD2, CD5, CD3, CD1, CD8, CD4, TdT** are markers specific to different stages of T-cell development.
- The length of the bars indicates the expression level of each marker in the respective cell stage.
T-cell LINEAGE MARKERS

NK/CYTOTOXIC
- CD16, CD56, CD57, TIA1, GRANZYME

GERMINAL CENTRE DERIVATION
- CD10, Bcl6
TCL - PRESENTATION PATTERNS

**Often leukemic or disseminated**
- T-cell prolymphocytic leukemia
- T-cell granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell lymphoma/leukemia (HTLV1 +)
- Hepatosplenic T-cell lymphoma

**Extranodal/Cutaneous**
- Cutaneous TCL
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma

**Mainly nodal**
- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (systemic)
Precursor T Lymphoma/Leukaemia (“ALL”) - Must Know

- Clinical: uncommon (children 15% ALLs), 90% lymphoma, 10% leukaemia
- Small / medium cell size; “primitive” chromatin
- Immunophenotype: CD10 -/+ (var), CD1a, CD2, CD3c, CD4, CD5, CD8, TdT+, Ki67 high, CD79a+/-, CD45+, PAX5-, myeloid markers
- Genotype: variable
Precursor T Lymphoma/Leukaemia ("ALL")-Diagnostic Pitfalls

- Reactive: haematogones
- AML: Myeloperoxidase+, TdT-
- B-ALL: T cell lineage markers (*CD1a, CD2, CD3c, CD4, CD5, CD8), PAX5-, PCR
- Burkitt: TdT-, CD20+, CD34-, sIgM, c-myc
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<tr>
<th>Type</th>
<th>CD20/Pax5</th>
<th>Bcl2</th>
<th>CD10</th>
<th>CD3</th>
<th>CD99</th>
<th>TdT</th>
<th>Ki67</th>
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<tr>
<td>Burkitt</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>~100%</td>
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<tr>
<td>ALL</td>
<td>85%</td>
<td>+</td>
<td>+</td>
<td>15%</td>
<td>+</td>
<td>+</td>
<td>~90%</td>
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<td>DLBCL</td>
<td>+</td>
<td>+/-</td>
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<td>20-90%</td>
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LARGE GRANULAR LYMPHOCYTE LEUKAEMIA

R1 = LYMPHOCYTES
R2 = NK-CELLS
Large Granular Lymphocyte Leukaemia
Must Know

- Clinical – association with RA
- Histology/Cytology:
  - Large Granular Lymphocytes
- Immunophenotype:
  - T-cell
  - NK cell
- Genotype: no specific changes
- Indolent clinical course - ? Lymphoma
- Rarely aggressive disease
AGGRESSIVE NK-CELL LEUKAEMIA / LYMPHOMA

CSF

PB
BM Surface staining
BM Surface staining
Aggressive NK-Leukaemia
Must Know

- Clinical – Asian population, young
  - Leukaemic picture, hepatosplenomegaly
- Histology/Cytology:
  - LGL like morphology, larger, pleomorphic
- Immunophenotype:
  - CD2+, CD3-, CD56+, granzyme+
- Genotype: no specific changes
- Counterpart of NK lymphoma of nasal type
- EBV association
- Aggressive course
ADULT T-CELL LEUKAEMIA / LYMPHOMA
Adult T-cell leukaemia/lymphoma

- Clinical – Adults; Japan; Caribbean
  - Widespread lymphadenopathy, leukaemia, hepatosplenomegaly, skin and bone involvement
- Histology/Cytology:
  - Marked pleomorphism, polylobated nuclei ("flower cells")
- Immunophenotype:
  - CD2+, CD3+, CD4+, CD7-, CD8-
- Genotype: no specific changes
- HTLV1 association / integration
- Aggressive course or smoldering variant.
ANGIOIMMUJNOBLASTIC T-CELL LYMPHOMA
Epstein-Barr Virus–Associated B-Cell Lymphoproliferative Disorders in Angioimmunoblastic T-Cell Lymphoma and Peripheral T-Cell Lymphoma, Unspecified

Andreas Zettl, MD,¹ Seung-Sok Lee, MD,¹ Thomas Rüdiger, MD,¹ Petr Starostik, MD,¹ Mirella Marino, MD,² Thomas Kirchner, MD,³ Michaela Ott, MD,¹ Hans Konrad Müller-Hermelink, MD,¹ and German Ott, MD¹
EBER (LMP1+)
Angioimmunoblastic T-cell (AIL) Must Know

- Clinical: Elderly patients;
  - Generalised lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, skin rush
- Histology:
  - Polymorphous cytology; Clear cells; Immunoblasts
  - Vascular proliferation
  - Occasional lymphoid follicles
- Immunophenotype: CD45+, CD3+-/-, CD4+, CD8-, CD10+, TIA1-, Granz-, CD21+ DCs (GC T-cells) CD20+/CD30+/CD45+/EBER+ blasts
- Genotype: no specific changes
- Association with EBV driven B-cell proliferations
AIL – Diagnostic Pitfalls

- Reactive: paracortical hyperplasia (drug reaction; viral infection)
  - T-cell and B-cell blasts
  - PCR polyclonal
  - Serology
- Classical Hodgkin
  - RS-like cells in AIL: CD45+, OCT2+, BOB1+, CD20+, CD30+
  - RS in HL: CD45-, Oct2-, Bob1-, CD20+/-, CD30+
- TCR BCL: lack of CD10+ T-cell population, lack of CD21+ DCs
- Lymphoplasmacytic lymphoma: Polymorphous cytology, B-cell phenotype
ANAPLASTIC LARGE CELL LYMPHOMA

- CD3
- CD4
- CD30
- ALK1
- EMA
- TIA1
- EMA
**Anaplastic Large Cell Lymphoma (ALCL) Must Know**

- **Clinical:** Two entities!
  - Primary Systemic (ALK1+ / ALK1-)
  - Primary Cutaneous
- **Histology:**
  - Anaplastic morphology
  - Small cell variant
- **Immunophenotype:** T/Null cell: CD45+, CD30+, CD3-/+ , CD4+, TIA1+, Granzyme+, EMA+, *ALK1+, CD15-
- **Genotype:** t(2;5)
- **Favourable prognosis of ALK1+ type**
ALCL – Diagnostic Pitfalls

- ALK1+/ALK1-: ALK1, cytogenetics
- Cutaneous CD30+ disease:
  - ALK1-, CD30+
  - Clinical features
- Classical HL:
  - CD45-, CD30+, CD15+, EMA-, CD4-
  - PCR
- ALK1+ B-cell lymphoma: IgA+, CD57+, B-cell genotype, CD138+
EXTRANODAL NK/T-CELL LYMPHOMA
Extranodal NK/T-cell lymphoma, Nasal Type – Must Know

- Clinical presentation: Adults; Asia, Mexico, Central & South America
  - Nasopharyngeal region, GI tract, other extranodal sites
- Histology:
  - Variable cytology, often small cells!
  - Necrosis
  - Angioinvasion
- Immunophenotype: CD45+, CD3+ (cytoplasmic), CD4-, CD8-, CD16, CD56+, TIA1+, Granzyme+, EBER+
- Cytogenetics: germline TCR, no specific marker
- Aggressive clinical course
Extranodal NK/T-cell lymphoma, Nasal Type – Diagnostic Pitfalls

- Wegener’s granulomatosis:
  - Negative biopsy samples with necrosis
  - Be careful about assessment of cells invading vessels
ENTERPATHY TYPE T-CELL LYMPHOMA
Enteropathy –type T-cell Lymphoma

Must Know

- Clinical: Adults with history of Coeliac disease
- Histology:
  - Ulceration
  - Very variable (small cell – anaplastic)
  - Inflammatory cells
  - Enteropathy in background
- Immunophenotype: CD3+, CD4-, CD8-/+, CD103+, CD30(var), CD56+(var), loss of CD8 in epithelium.
Enteropathy – type T-cell Lymphoma
Diagnostic Pitfalls

• Coeliac disease:
  – Clonal intraepithelial T-cell proliferation (refractory coeliac disease)

• Intestinal involvement by extranodal NK-lymphoma (EBER+)
SUBCUTANEOUS PANNICULITIS TYPE T-CELL LYMPHOMA
Subcutaneous Panniculitis-like TCL

• Clinical: Wide age range
  – Subcutaneous nodules on extremities
• Histology:
  – Rimming around fat
• Immunophenotype: CD3+, CD4-, CD8+, Granzyme+, Perforin+, TIA1+, EBER-
• Genotype: Alpha/Beta and Gamma/delta (CD56+) TCR types – association with prognosis
• Aggressive clinical course
Other TCL

• Peripheral TCL Unspecified
  – 50% of TCL
  – Variable morphology
  – Variable immunophenotype
  – Diagnosis of exclusion

• Hepatosplenic gamma/delta:
  – Gamma/delta TCR rearrangement
  – CD3+, CD56+, CD4-, CD8-, CD56+, TIA1+, Granzyme-, EBER-
Summary

• Peripheral TCL not as well understood as B-cell NHL
  – No genetic markers except ALCL

• Mostly aggressive
  – Exceptions: ALCL ALK1+; LGL

• Wide spectrum of morphology and immunophenotype

• Differential diagnosis with HL, other NHL, non haematological malignancies and reactive conditions
  – e.g. AIL, ALCL, extranodal NK.