WHO Classification: T-Cell & NK-Cell Neoplasms

- T-lymphoblastic lymphoma/leukemia (T-LBL/ALL)
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK-cells.
- Aggressive NK-cell leukemia
- Systemic EBV+ T-cell lymphoproliferative disorder of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell lymphoma/leukemia
- Extracutaneous T-cell/NK-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30+ T-cell lymphoproliferative disorder
- Primary cutaneous gamma-delta T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK+ type
- Anaplastic large cell lymphoma, ALK- type

Case 3
- 4-årig dreng
- Tiltagende træthed gennem 1 måned
- Febril i en uge med vægttab, nattesved, hudklø
- Forstærrede lymfeknuder på halsen
- Thorax X-ray - breddeøget mediastinum
- Hals lymfeknude biopsi
Case 3 - diagnoseforslag

- Precursor LB – 7
- ALL – 4
- BL - 1
- NHL - 1

- Diff. diagnose
  - FL
  - DLBCL
  - Hodgkins lymphoma
  - Burkitt lymphoma
  - Normal thymus
  - Reactive

Case 3 - diagnosis

- Precursor, T-lymphoblastic lymphoma (leukaemia)

Case 3 - supplementary

- TdT +   CD1a +
- Obs! CD3 positiv i cytoplasm
- CD99+ CD34+

Precursor T-Cell Lymphoblastic
Lymphoma/Leukaemia

- Morphology
  - lymphoblasts
  - diffuse
  - convoluted

- Immunology
  - TdT
  - CD1a
  - CD7
  - CD3cyt
  - CD34

- Genetics
  - SCL 7 TAL-1
  - rearranged

- Clinical
  - mediastinum
  - leukaemic
  - adolescents
  - young adults
  - aggressive; curable
Peripheral T/NK-Cell Neoplasms

**Groupings**

- According to behaviour
- According to site/major presentation
- According to lineage

## Peripheral T/NK-Cell Neoplasms

### Groupings according to behaviour

- **Indolent**
  - Mycosis fungoides
  - Anaplastic large cell lymphoma, primary cutaneous
  - T-cell large granular lymphocytic (LGL) leukemia

- **Aggressive**
  - Sezary syndrome
  - T-cell prolymphocytic leukemia
  - Aggressive NK cell leukemia
  - Lymphoblastic NK cell lymphoma
  - Peripheral T-cell lymphoma (unspecified)
  - Angioimmunoblastic T-cell lymphoma
  - Adult T-cell leukemia/lymphoma
  - Anaplastic large cell lymphoma, primary systemic
  - Extramedullary NK/T-cell lymphoma, naso-type
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Enteropathy-type intestinal T-cell lymphoma
  - Hepatosplenic γδ T-cell lymphoma

### Groupings according to site/major presentation

- Predominantly leukemic/disseminated
- Predominantly nodal
- Predominantly extranodal

- Predominantly nodal

  - Peripheral T-cell lymphoma (unspecified)
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large cell lymphoma, primary systemic
Peripheral T/NK-Cell Neoplasms

**Predominantly extranodal**

**Cutaneous**
- Mycosis fungoides
- Anaplastic large cell lymphoma, primary cutaneous
- Subcutaneous panniculitis-like T-cell lymphoma

**Other extranodal sites**
- Extranodal NK/T-cell lymphoma, nasal-type
- Enteropathy-type intestinal T-cell lymphoma

**Groupings according to histogenesis / differentiation**

- Cytotoxic T-cell neoplasms
- NK-cell neoplasms
- Other T-cell phenotypes

**Cytotoxic T-Cell Neoplasms**

- T-cell large granular lymphocytic (LGL) leukemia
- Anaplastic large cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Enteropathy-type intestinal T-cell lymphoma
- Hepatosplenic γδ T-cell lymphoma (and γδ T-cell lymphomas in other sites, skin, nose, g-i tract)

**Peripheral T/NK-Cell Neoplasms**

**NK-Cell Neoplasms**

- Lymphoblastoid NK cell lymphoma
- Extranodal NK/T cell lymphoma, nasal-type
- Aggressive NK cell leukemia

**Peripheral T/NK-Cell Neoplasms**

- Difficult to subdivide based on “grouping”
- Regard as various “syndromes” defined by both the clinical features and the histological, phenotypic and genotypic characteristics
- Correct diagnosis requires team collaboration:
  - Clinic; morphology; immunophenotype; molecular genetics
  - Be familiar with spectrum of (often rare) T/NK cell related neoplasms
- Diagnosis should be confirmed in specialist centres

**Peripheral T/NK-Cell Neoplasms**

**PTL:** Hypothetical normal counterparts

**Hypothetical normal counterparts**

- Activated T-cell
- Adenosine/dehydro T-cell
- NK cell
- Cytotoxic
**WHO Classification:**

**T-Cell & NK-Cell Neoplasms**

**MATURE**
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK-cells
- Aggressive NK-cell leukemia
- Systemic EBV+ T-cell lymphoproliferative disorder of childhood
- Hairy cell leukemia
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- Anaplastic large cell lymphoma, ALK- type

**Peripheral T-Cell Lymphoma (unspecified)**
- Most frequent T-cell lymphoma in Western countries
- Any age and site, but preferentially adults and nodes
- Aggressive, often disseminated
- Morphological spectrum extremely broad
- Positive for T-cell antigens, aberrant phenotypes common, usually CD4-positive, cytotoxic molecules negative, CD30 may be expressed (large cell variants)
- TCR genes clonally rearranged (70-90%)

Exclusion diagnosis: probably not one disease

**Peripheral T-Cell Lymphoma, NOS**

Peripheral T-cell Lymphoma

Peripheral T-cell Lymphoma
Peripheral T-Cell Lymphoma, NOS

- Morphology: atypical lymphocytes, variable size, reactive background
- Immunology: CD3 +/−, CD2, 4, 5, 7, 8, 30 var, EBV −/+,
- Genetics: none specific
- Clinical: adults, aggressive, potentially curable, > Far East

Peripheral T-Cell Lymphoma

- Morphology: atypical lymphocytes, variable size, reactive background
- Immunology: CD3 +/−, CD2, 4, 5, 7, 8, 30 var, EBV −/+,
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WHO Classification: T-Cell & NK-Cell Neoplasms
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  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large cell lymphoma, ALK+ type
  - Anaplastic large cell lymphoma, ALK- type

Angioimmunoblastic T-Cell Lymphoma
- Adults, lymphadenopathy, hepato-splenomegaly, skin rashes, fever, hypergammaglobulinemia, hemolytic anemia
- Small to medium sized atypical T-lymphocytes, clear cells, eosinophils, plasma cells, arborizing vessels, regressed B-cell follicles, extensive FDC meshwork
- EBV+ (B-lymphocytes), TCR R, Ig R (10%), trisomy 3 and 5, additional X chromosome
- Transformation to large cell lymphoma of T or B-cell type in 10%

Nodal PTCL - Immunophenotype

- T-cell immunophenotype of the neoplastic cells is PTCL involving the lymph nodes

- Table showing expression of various markers:
  - CD2, CD3, CD4, CD5, CD7, CD8, CD30, EBV
  - Expression levels indicated by + or −

PTL: Lennert’s Lymphoma

- Angioimmunoblastic T-Cell Lymphoma
  - Adults, lymphadenopathy, hepato-splenomegaly, skin rashes, fever, hypergammaglobulinemia, hemolytic anemia
  - Small to medium sized atypical T-lymphocytes, clear cells, eosinophils, plasma cells, arborizing vessels, regressed B-cell follicles, extensive FDC meshwork
  - EBV+ (B-lymphocytes), TCR R, Ig R (10%), trisomy 3 and 5, additional X chromosome
  - Transformation to large cell lymphoma of T or B-cell type in 10%

- Table showing expression of various markers:
  - CD2, CD3, CD4, CD5, CD7, CD8, CD30, EBV
  - Expression levels indicated by + or −
Angioimmunoblastic T-Cell Lymphoma

Morphology
- architecture effaced
- arborising vessels
- mixed infiltrate

Immunology
- CD23 dend. retic. +
- EBV +/-

Genetics
- none specific

Clinical
- adults
- systemic disease
- fever, weight loss, skin rash
- poly. hypergammaglobulin.
- aggressive
- transformation to high grade NHL

Case 14
- 41-årig mand
- Træthed tiltagende gennem nogle uger
- Febril i en uge
- Lungeinfilt Rat
- Lille forstærret lymfeknude i aksil 1 måned, obs. metastase – biopsi
**Case 14 - diagnoseforslag**

- T/0-ALCL – 6
  - Exclude carcinoma/sarcoma/melanoma
- Carcinoma – 5
- B-alc - 1
- Reactive – 1

**Diff. diagnose**
- Carcinoma / MM
- Germinal cell tumour
- PTL / ALCL
- B-ALC
- HL,LR / NLPHL
- Intravascular B-cell
- Sinus neoplasias

**Case 14 - supplementary**

- Tumour cells are:
  - CD30 +  EMA +  Granzyme B +  CD43 + CD4 +
  - ALK -

- Obs! ALC is often:
  - CD45 negative
  - Negative for pan T-markers (e.g. CD3)
  - May be cytokeratin positive!

**Case 14 - diagnosis**

- Anaplastic large cell lymphoma, ALK negative

**Anaplastic Large Cell Lymphoma**

**Clinical variants**
- Primary systemic
- Primary cutaneous

**Histological variants**
- Common type
- Small cell type
- Lymphohistiocytic type

**Genetic variants**
- Positive or negative for ALK t(2;5) or variant translocations
T-ALC: CD30

T-ALC: Sinus Involvement
Anaplastic Large Cell Lymphoma

**Morphology**
- anaplastic, bizarre RS-like
- cohesive cells
- intrasinus spread

**Immunology**
- T or null phenotype
- CD30 +
- EMA +/-
- ALK +/-

**Genetics**
- fusion of ALK and NPM gene

**Clinical**
- ALK form better prognosis
- systemic form aggressive
- primary skin indolent

---

**T-ALC: Histological Variants**

<table>
<thead>
<tr>
<th>Variant</th>
<th>HL</th>
<th>ALK - pos</th>
<th>ALK - neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NK/T-cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoblastic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angioimmunoblastic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelioid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophilic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophilic-rich</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HL vs ALC: Immunophenotype & Genotype**

<table>
<thead>
<tr>
<th></th>
<th>ALK-pos</th>
<th>ALK-neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>EBV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD30</td>
<td>&gt; 40 %</td>
<td>&lt; 5 %</td>
</tr>
<tr>
<td>CD40</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD45</td>
<td>&gt; 80 %</td>
<td>&lt; 2 %</td>
</tr>
<tr>
<td>EMA</td>
<td>ca. 50 %</td>
<td>ca. 50 %</td>
</tr>
<tr>
<td>PAX5</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD20</td>
<td>ca. 25 %</td>
<td>-</td>
</tr>
<tr>
<td>CD45</td>
<td>ca. 50 %</td>
<td>ca. 50 %</td>
</tr>
<tr>
<td>CD43</td>
<td>most</td>
<td>most</td>
</tr>
<tr>
<td>TCR genes</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>Ig genes</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

---

**Case 2 - diagnoseforslag**
- Ekstranodal NK/T-cell lymphoma, nasal type – 8
- B-NHL - 3
- Lymphoma – 1
- Reactive? – 1
- Diff. diagnose
  - MAL/Ton
  - PT/L, AILD
  - BL
  - HHV-8, NHL
  - Carcinoma/NPC
  - Kronvik EBV
  - Wegner’s LNL

---

**Case 2 - supplementary**
- sCD3-, cCD3+, CD2+, CD5+, CD56+, TIA-1+
- EBV+
- TCR Clonality: polyclonal
Case 2 - diagnosis

- Ekstranodal NK/T-cell lymphoma, nasal type

Extranodal NK/T-cell lymphoma, nasal-type

*Synonyms:* polymorphic reticulosis; malignant midline granuloma; angiocentric immunoproliferative disease; angiocentric T-cell lymphoma (REAL)

- Adults, prevalent in Asia, South America
- Nasal cavity / nasopharynx
- Other extranodal sites e.g. skin, g-i tract, rarely lymph nodes or bone marrow
- Aggressive, may be complicated by a hemophagocytic syndrome
- Medium-sized cells (or small, large or anaplastic!)
- Often angiocentric and angiodestructive with necrosis
- sCD3-, cCD3+, CD2+, CD56+, TIA-1+
- EBV+, TCR germline

Extranodal NK/T-cell Lymphoma, Nasal Type

Morphology
- polymorphic lymphocytes
- vessel wall infiltration
- vessel destruction

Immunology
- CD2 +
- CD56 +
- CD3 -/+
- CD5, 7, 4, 8 +/-
- EBV +

Genetics
- none specific

Clinical
- children & adults
- > Far East
- extranodal sites
- skin, nose, palate
- variable course

Differential diagnoses
- Other NK-cell related neoplasms
- Other lymphomas with nasal involvement (DLBCL)
- Lymphomatoid granulomatosis

Case 16 - diagnoseforslag

- Enteropathy-type intestinal T-cell lymphom – 9
- DLBCL - 1
- Reactive/cøliaki - 1

- Diff. diagnose
  - Maltoma
  - T-ALCL
  - HL
  - DLBCL
  - PTLD
  - Kimuras

Case 16 - diagnosis

- Enteropati-type intestinal T-cell lymphom
**Enteropathy-type intestinal T-cell Lymphoma**

- **Morphology**
  - Small or large lymphocytes

- **Immunology**
  - CD3, 7 +
  - CD8 +/-
  - CD103 +
  - CD30 -/+ 

- **Genetics**
  - None specific

- **Clinical**
  - Adults
  - Coeliac disease +/-
  - Aggressive

**Peripheral T/NK Cell Neoplasms: WHO**

- T-cell prolymphocytic leukemia
- T-cell (LGL) leukemia
- Aggressive NK cell leukemia
- Lymphoblastoid NK cell lymphoma (provisional)
- Adult T-cell leukemia/lymphoma
- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, primary systemic
- Anaplastic large cell lymphoma, primary cutaneous
- Mycosis fungoides/Sezary syndrome
- Subcutaneous panniculitis-like T-cell lymphoma
- Extramedullary T-cell lymphoma, nasal-type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic γδ T-cell lymphoma

**Lymphoblastoid NK cell lymphoma**

- Young adults, not restricted to Orientals
- Multiple sites, including almost always the skin. Often disseminated with bone marrow infiltrates. Rarely blood involvement. Aggressive
- Diffuse, monomorphic, single-file, medium-sized, blastoid
- sCD3-, cCD3+, CD56+, CD4 ±, TIA-1+, TdT ±, CD34 ±
- EBV-, TCR germline
- Distinguish from AML (CD33, MPO); T-ALL (TCR genes)

**Lymphomatoid granulomatosis**

- Synonyms: polymorphic reticulosis; angiocentric immunoproliferative lesion
- Adults, often associated with immunodeficiency
- Lungs, other extranodal sites, e.g. skin, kidney, brain
- Angiocentric and angiodestructive infiltrates, consisting of EBV-positive large B-lymphocytes admixed with plasma cells, histiocytes and small T-lymphocytes
- A T-cell rich large B-cell lymphoma

**Aggressive NK Leukemia**

- Rare, young adults, Orientals
- Constitutional symptoms, blood and bone marrow involvement, hepatosplenomegaly, hemophagocytic syndrome, multiorgan failure
- Morphology, phenotype and genotype similar to extranodal NK/T-cell lymphoma
- sCD3-, cCD3+, CD2+, CD56+, TIA-1+, EBV+, TCR germline
- Possibly a leukemic counterpart of extranodal NK/T-cell lymphoma
- Distinguish from indolent NK-cell lymphoproliferative disorder

**Aggressive NK Leukemia**

- Rare, young adults, Orientals
- Constitutional symptoms, blood and bone marrow involvement, hepatosplenomegaly, hemophagocytic syndrome, multiorgan failure
- Morphology, phenotype and genotype similar to extranodal NK/T-cell lymphoma
- sCD3-, cCD3+, CD2+, CD56+, TIA-1+, EBV+, TCR germline
- Possibly a leukemic counterpart of extranodal NK/T-cell lymphoma
Aggressive NK Leukemia

- Differential diagnoses
  - Indolent NK-cell lymphoproliferative disorder
  - T-cell prolymphocytic leukemia
  - T-cell LGL leukemia
  - ATLL

Peripheral T-Cell Lymphoma (unspecified)

- Most frequent T-cell lymphoma in Western countries
- Any age and site, but preferentially adults and nodes
- Aggressive, often disseminated
- Morphological spectrum extremely broad
- Positive for T-cell antigens
  - aberrant phenotypes common
  - usually CD4-positive, cytotoxic molecules negative
  - CD30 may be expressed (large cell variants)
- TCR genes clonally rearranged (70-90%)

Exclusion diagnosis; probably not one disease