Mature T-cell Leukemias

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Outline

• Overview of MTCL
• T-large granular lymphocytic leukemia
• T-prolymphocytic leukemia
• Sézary syndrome
• Adult T-cell leukemia/lymphoma
• Differential diagnosis and summary
Definition

- Clinical manifestations linked to systemic and hematologic disorders; skin manifestations may be prominent
- Post-thymic T cells (helper, cytotoxic/suppressor T cells)
- Express pan T-cell antigens CD3, CD5, CD7, CD2

*Note: Aberrant patterns of T-cell antigen expression linked to specific subtypes of MTCL*

- Lack markers of immaturity, e.g. CD34, TdT, or CD1a
- **Exception:** 30% of T-PLL can show CD4/CD8 coexpression
General Features

- Much rarer than B-CLPD
- Affect adults, wide age range
- Patients often exhibit systemic manifestations (organomegaly, skin findings, fatigue, fever)
- Key clinical and CBC “tips” to various subtypes

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Description</th>
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<tbody>
<tr>
<td>T-LGL</td>
<td>T-cell large granular lymphocytic leukemia</td>
</tr>
<tr>
<td>T-PLL</td>
<td>T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>SS</td>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>ATLL</td>
<td>Adult T-cell leukemia lymphoma</td>
</tr>
</tbody>
</table>
Key Tips: Mature T-cell Leukemias

**T-LGL**
- Cytopenias predominate
- Splenomegaly common
- Associations with RA, ARCA, PNH
- Derived from cytotoxic/suppressor T cell

**T-PLL**
- Marked leukocytosis (rapidly rising WBC)
- Marked hepatosplenomegaly
- Derived from helper T cell
Key Tips: Mature T-cell Leukemias

**SS**
- Cutaneous manifestations, erythroderma
- Blood involvement by definition in SS
- Derived from helper T cell

**ATLL**
- Endemic disease distribution (HTLV-1-associated)
- Broad spectrum of clinical manifestations
- Leukemic subtype most aggressive
- Derived from helper T cell
## Immunophenotypic Features of MTCL

<table>
<thead>
<tr>
<th>Antigens</th>
<th>T-PLL</th>
<th>T-LGL</th>
<th>ATLL</th>
<th>SS</th>
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<tbody>
<tr>
<td>CD3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ (w)</td>
</tr>
<tr>
<td>CD2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD4</td>
<td>usu +</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD7</td>
<td>+</td>
<td>var</td>
<td>-</td>
<td>usu -</td>
</tr>
<tr>
<td>CD8</td>
<td>rare</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD16</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD25</td>
<td>var</td>
<td>NA</td>
<td>+</td>
<td>var</td>
</tr>
<tr>
<td>CD56</td>
<td>-</td>
<td>usu -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD57</td>
<td>-</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
</tr>
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</table>
Features of T-LGL

Clinical:
• Variable age at presentation; usually middle-age
• Recurrent infections
• Rheumatoid arthritis/autoimmune disorders/PNH

Blood:
• Variable numbers of mature-appearing LGLs
• Cytopenias, especially neutropenia

Bone marrow:
• Variable % LGL cells; infiltrates may be subtle
• Association with acquired pure red cell aplasia, PNH
Features of T-LGL

**Morphology:**
- Mature nuclei, usually round
- Abundant cytoplasm, distinct granules

**IP:**
- Mature cytotoxic/suppressor T-cell (CD57+ , TIA-1+)

**Molecular:**
- TCR gene rearrangement

**Disease course:**
- Stable for many years; spontaneous remissions
Reactive

LGL

CD57 Spectrum

CD57 Discrete population
T-cell Large Granular Lymphocytic Leukemia (CD3+, CD8+, CD57+)
T-LGL, subtle, diffuse, patchy
Bone marrow core biopsy: T-LGL
Exemplary Case: T-LGL

Hx: 73-yr-old female w/ hx of “CLL.” 2-3 month hx of progressive fatigue, bld abnormalities. WBC 22.8, Hgb 9.9, MCV 113, Plt 207

CBC: Leukocytosis with absolute lymphocytosis

Blood: ANC 1825, ALC 19,400

IP: Increased CD8+, CD57+ T cells with reduced CD5 and CD7 expression
T-LGL, 73-year-old female

Courtesy Qian-Yun Zhang
T-Cell Large Granular Lymphocytic Leukemia

73-year-old female, bone marrow
27-year-old female, RCA and ↑ T cells
27-year-old female, RCA and ↑ T cells
T-LGL Recommendations

• Know clinical/hematologic tipoffs
• Flow cytometric immunophenotyping of blood
• Molecular confirmation of T-cell clonality (bld)
• Generous use of CD20, CD3 on BM core biopsy for unexplained cytopenias, RCA, etc.
• If T cells increased on core biopsy, add CD4, CD8, TIA-1, and EBER
T-Prolymphocytic Leukemia (T-PLL)

- Rare (2% lymphocytic leukemias)
- Middle aged to elderly patients
- Marked splenomegaly, striking leukocytosis
- Notable feature: rapidly rising WBC

**Blood:** Morphologic spectrum

**BM:** Diffuse pattern

**IP:** Majority CD4+, one third CD4+/CD8+, TCL-1 protooncogene +

**Genetic:** TCL-1 gene rearrangements
T-PLL, striking leukocytosis
T-PLL (morphologic spectrum)
T-PLL: diffuse BM effacement
Exemplary Case: T-PLL

History:  49-yr-old male with leukocytosis, hepatosplenomegaly

CBC:  WBC 900,000  Plt 47,000

Blood:  Striking mature lymphocytosis w/o distinctive nuclear features

IP:  Mature T-cell: CD2+, CD3+, CD5+, CD7+, bright CD45+, CD4/CD8 coexpression

Cytog:  inv 14(q11q32); loss of 5, 8, 10, 11, 12, 17, 18, marker chromosomes
T-PLL, CD4+, CD8+

Also CD2+, CD7+, CD5+, TdT-
T-PLL inv (14)(q11q32)
T-PLL in bone marrow
T-PLL Genetics

• TCL-1 oncoprotein dysregulation due to recurrent chromosomal rearrangements
• TCL-1 locus at 14q32.1 and T-cell receptor αδ regulatory elements at 14q11
• Most frequent cytogenetic abnormality is inv(14)(q11q32)
• Juxtaposition of TCL-1 with promoter/enhancer region of TCRαδ

Disease Course

• Variable, usually aggressive
• About 60% of patients show marked response to Campath (anti-CD52) therapy
**T-PLL Recommendations**

- Suspect T-PLL in patient with marked splenomegaly and rapidly rising WBC
- Confirm lineage and stage of maturation by flow
- Conventional karyotyping for inv(14) or other T-PLL related gene rearrangements
- Molecular assessment of T-cell clonality **not** necessary
- Mention Campath (anti-CD52) responsiveness
Generalized Erythroderma

72-yr-old male

Courtesy Dr. Beverly Nelson
SS: marked lymphocytosis
Sézary Syndrome: \(1^o\) and \(2^o\)

- \(1^o\) – erythroderma with blood involvement at presentation

- \(2^o\) – development of blood involvement in longstanding mycosis fungoides

- Skin disease predominates: two patterns
Sézary Syndrome: 1º and 2º

- Morphology: mature nuclei with subtle convolutions, variable cell size
- IP: mature T-cell (CD3, CD5, CD4); lack CD7 expression
- Defining minimal blood involvement is problematic (low #s CD4+, CD7- in normals)
Sézary syndrome
Cerebriform Sézary cell

Courtesy Dr. Beverly Nelson
Sézary cell, monocyte, normal lymph
Sézary Syndrome/Mycosis Fungoides (CD3+, CD4+, CD7-)

- FSC Height
- SSC Height
- CD3
- CD7
- CD4
- CD7

Sézary Syndrome/Mycosis Fungoides (CD3+, CD4+, CD7-)
SS: Criteria for Blood Involvement*

- Absolute Sézary cell count > 1,000
- CD4/CD8 ratio > 10
- Aberrant antigen profile (CD7-, CD26-)
- Lymphocytosis w/ positive PCR in bld, skin
- Clonal cytogenetic abnormalities in blood

*ISCL: International Society for Cutaneous Lymphoma criteria
MF/SS: subtle infiltrates in bone marrow
Exemplary Case: SS

**Hx:** 89-yr-old female with generalized itching, hypercalcemia, renal failure. WBC 21.7, Hgb 13.6, Hct 39%, MCV 96, RDW 12.7%, Plt 252

**CBC:** Leukocytosis with preservation of RBC, platelets, neutrophils

**Blood:** Marked mature lymphocytosis with subtle to prominent nuclear irregularity

**IP:** CD3+, CD4+, CD7-, CD25-

**HTLV-1 studies:** Negative

**Skin bx:** Extensive dermal infiltrate of helper T cells w/ prominent nuclear convolutions
Blood: lymphocytosis
Blood: lymphocytosis
Blood: generalized itching, lymphocytosis
Blood: generalized itching, lymphocytosis
Dermis: generalized itching
SS Recommendations

- Limitations of flow cytometric IP to identify low numbers of Sézary cells in bld
- Report percent of CD4+, CD7- T cells
- Assess for cytologic features of circulating cells (distinguish from monocytes)
- Correlate with skin findings
Adult T-cell Leukemia Lymphoma (ATLL)

- Several distinct disease types (smoldering and acute forms)
- HTLV-1 associated (RNA virus – integrates into host DNA)
- Primarily endemic disease distribution (carriers)
- Acute form: striking leukocytosis (2-4% of carriers)
Adult T-cell Leukemia Lymphoma (ATLL)

- Morphology: mature nuclei with pronounced lobations
- IP: mature T-cell (CD3, CD5, usually CD4, CD25)
- Lack CD7 expression
- Aggressive disease course (acute form)
ATLL: coarse nuclear lobations
ATLL
Differential Diagnosis: MTCL

Other T-cell neoplasms can involve blood, bone marrow at presentation

**Blood:**  T-ALL most common
Rare T-NHL such as ALCL

**BM:**  Incidence, pattern, IP varies by T-cell lymphoma subtype
Teenage male (WBC 40,000), leukemic ALCL
# BM Involvement in T-NK Lymphomas

<table>
<thead>
<tr>
<th>Lymphoma subtype</th>
<th>Incidence BM (%)</th>
<th>1st Pattern</th>
<th>IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-ALL/L</td>
<td>20-60</td>
<td>Patchy, interstitial</td>
<td>Immature T cell</td>
</tr>
<tr>
<td>SS</td>
<td>20-25</td>
<td>Patchy, interstitial</td>
<td>Mature T, often CD4+, CD7-</td>
</tr>
<tr>
<td>PTCL</td>
<td>30-75</td>
<td>Focal, non-para</td>
<td>Mature T cell</td>
</tr>
<tr>
<td>AILT</td>
<td>50-80</td>
<td>Focal, non-para</td>
<td>Mature T cell, CD10+</td>
</tr>
<tr>
<td>ALCL</td>
<td>10-20</td>
<td>Isolated individual cells</td>
<td>Mature T cell, CD30+, EMA+, ALK 1+, TIA-1+</td>
</tr>
<tr>
<td>HSTCL</td>
<td>100</td>
<td>Intravascular, intrasinusoidal</td>
<td>Mature T cell, CD3+, TIA-1+, γδ+</td>
</tr>
<tr>
<td>NK</td>
<td>&gt; 90</td>
<td>Interstitial, diffuse solid</td>
<td>True NK, cyCD3+, EBER+, TIA-1+, CD56+</td>
</tr>
</tbody>
</table>

Source: Semin Diagn Pathol 2003; 20:196-210
# Mature T-cell Leukemias

## Table: Mature T-cell Leukemias

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<tr>
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<th>T-PLL</th>
<th>T-LGL</th>
<th>ATLL (acute)</th>
<th>SS</th>
</tr>
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<tbody>
<tr>
<td><strong>WBC</strong></td>
<td>↑↑↑</td>
<td>↓ to nl</td>
<td>↑↑↑</td>
<td>var, nl to ↑↑</td>
</tr>
<tr>
<td><strong>Morph in blood</strong></td>
<td>Spectrum</td>
<td>Large granular lymphocytes-cytopenias</td>
<td>Spectrum Pronounced nuclear lobation</td>
<td>Spectrum Subtle cerebriform</td>
</tr>
<tr>
<td><strong>Usual IP</strong></td>
<td>Pan T, CD4, subset CD4/CD8 coexpress TCL-1 positivity</td>
<td>Pan T, CD8, CD57, CD16</td>
<td>Pan T, CD3&lt;sup&gt;low&lt;/sup&gt;, CD4, CD25 Absent CD7</td>
<td>Pan T, CD4, var CD25 Absent CD7, CD26</td>
</tr>
<tr>
<td><strong>Genetic features</strong></td>
<td>Inv(14)(q11q32) TCL-1 (14q32)/ TCRα/δ promoter region (14q11)</td>
<td>Not specific</td>
<td>HTLV-1-assoc. Cytog abnl common, not specific</td>
<td>Cytog abnl frequent, not specific</td>
</tr>
<tr>
<td><strong>Assoc. findings</strong></td>
<td>Hepatosplenomegaly Pleural effusions Skin lesions</td>
<td>Rheumatoid arthritis Red cell aplasia</td>
<td>Endemic Hypercalcemia Skin involvement</td>
<td>Patch, plaque epidermotropic skin disease (MF) Gen. erythroderma-SS</td>
</tr>
</tbody>
</table>

*var = variable; prom = prominent; abnl = abnormalities*
Summary: Mature T-cell Leukemias

• Integrate morphologic, immunophenotypic, and clinical findings. Most mature T-cell leukemias can be diagnosed as specific clinicopathologic entities

• Genetic testing is especially useful in T-PLL

• Consider T-LGL in patients with neutropenia (especially RA patients) or acquired red cell aplasia
Summary: Mature T-cell Leukemias

- Serologic testing for HTLV-1 is essential in ATLL
- Bone marrow involvement may be subtle in T-LGL and SS
- IHC useful in highlighting subtle infiltrates (generous use of CD3, CD20; if T’s increased, add CD4, CD8, TIA-1, EBER)