Adult T-cell Leukemia/Lymphoma
Definition

• Peripheral T-cell neoplasm

• Most often composed of highly pleomorphic lymphoid cells

• Usually widely disseminated

• Caused by the human T-cell leukemia virus type 1 (HTLV-1)
Epidemiology

- Endemic in
  - Japan
  - Caribbean basin
  - Central Africa

- Disease distribution closely linked to prevalence of HTLV-1 in the population
Epidemiology

- Long latency

- Affected individuals are exposed to the virus very early in life

- Virus transmission
  - Breast milk
  - Blood
  - Blood products
Epidemiology

• Incidence of 2.5% among HTLV-1 carriers in Japan

• Sporadic cases found in USA and elsewhere in the world

• Adults (median age 55 years)

• M:F = 1.5:1
Sites of Involvement

- Widespread LN and PB involvement (most common presentation)

- Number of circulating neoplastic cells does not correlate with degree of BM involvement
  - Circulating cells may be recruited from other organs like skin
Sites of Involvement

- Systemic disease with involvement of
  - Spleen
  - Skin (most common extralymphatic site of involvement; >50%)
  - Lung
  - GI
  - CNS
Sites of Involvement
Adult T Cell Leukemia/Lymphoma
Clinical Variants

- Acute
- Lymphomatous
- Chronic
- Smoldering
Clinical Features

• Acute variant
  – Most common
  – Leukemic phase
  – Markedly elevated WBC
  – Skin rash
  – Generalized lymphadenopathy
  – Hypercalcemia, with or without
    lytic bone lesions
Clinical Features

• Acute variant
  – Systemic disease
    • Hepatosplenomegaly
    • Constitutional symptoms
    • Elevated LDH
  – Eosinophilia
  – T-cell immunodeficiency (PCP; Strongyloidiasis)
Clinical Features

• Lymphomatous variant
  – Prominent lymphadenopathy without PB involvement
  – Advanced stage disease
  – Hypercalcemia is less often seen
Clinical Features

• Chronic variant
  – Skin lesions (exfoliative rash)
  – May have absolute lymphocytosis (but atypical lymphocytes are not numerous in PB)
  – No hypercalcemia
  – Progression to acute variant in 25% of cases, but after a long duration
Clinical Features

- **Smoldering variant**
  - Normal WBC with <3-5% neoplastic cells
  - Skin or pulmonary lesions are frequent
  - No hypercalcemia
  - Progression to acute variant in 25% of cases, but after a long duration
### Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>ACUTE</th>
<th>LYMPHOMATOUS</th>
<th>CHRONIC</th>
<th>SMOLDERING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukemic phase</strong></td>
<td>+</td>
<td>-</td>
<td>ATLL cells &gt;10%</td>
<td>ATLL cells &lt;3-5%</td>
</tr>
<tr>
<td><strong>WBC</strong></td>
<td>↑↑↑↑</td>
<td>↑</td>
<td>Normal</td>
<td>-</td>
</tr>
<tr>
<td><strong>LN</strong></td>
<td>+</td>
<td>+</td>
<td>Mild</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hypercaldemia</strong></td>
<td>Common</td>
<td>Uncommon</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hepatosplenomeg</strong></td>
<td>+</td>
<td>+</td>
<td>Slight</td>
<td>-</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>↑</td>
<td>↑</td>
<td>Slight ↑</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Skin rash</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>+</td>
<td>+</td>
<td>&lt; 2 yrs</td>
<td>&gt; 2 yrs</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>2 wks to &gt;1 yr</td>
<td>2 wks to &gt;1 yr</td>
<td>&lt; 2 yrs</td>
<td>&gt; 2 yrs</td>
</tr>
</tbody>
</table>
Etiology

• HTLV-1 is causally linked to ATLL

• p40 tax viral protein leads to transcriptional activation of many genes in the infected lymphocytes

• HTLV-1 infection alone is not sufficient for neoplastic transformation. Additional genetic alterations may result in development of a malignancy
Morphology

- Acute and lymphomatous variants
  - Large to medium-sized cells
  - Pronounced nuclear pleomorphism
  - Coarsely clumped chromatin
  - Prominent nucleoli
Morphology

• Acute and lymphomatous variants
  – Rare cases may have small atypical lymphocytes with nuclear pleomorphism
  – Clinical course is unrelated to cell size
**Morphology**

- **PB**
  - Polylobated cells ("flower cells")
  - Deeply basophilic cytoplasm
  - Small proportion of blast-like cells

- **BM**
  - Patchy infiltrates
  - Osteoclastic activity may be prominent (even in absence of infiltrate of neoplastic cells)
Adult T-Cell Leukemia/Lymphoma
Adult T Cell Leukemia/Lymphoma
Morphology

- Acute and lymphomatous variants
  - Skin
    - Epidermal infiltration with Pautrier-like microabscesses
Morphology

- Chronic and smoldering variants
  - Small cells
  - Minimal cytological atypia
  - Skin
    - Sparse dermal infiltrate
    - hyperkeratosis
Morphology

- **Lymph node**
  - Some cases may show a leukemic pattern of involvement (malignant cells in preserved or dilated sinuses)
Early and smoldering variants may show Hodgkin lymphoma-like LN histology

- Paracortical areas expanded with a diffuse infiltrate

- Small to medium-sized lymphocytes with mild nuclear irregularities, indistinct nucleoli, scant cytoplasm

- Interspersed RS-like cells and giant cells with lobulated nuclei (EBV and CD15/30 positive)

- Progresses to overt ATLL within months
ATCLL: Immunophenotype

- Positive for
  - CD2/3/5/25

- Usually negative for
  - CD7

- Most cases are CD4+/CD8-

- Large transformed cells
  - May be CD30+
  - But negative for ALK / TIA-1 / granzyme B
Genetics

• Consistent TCR beta rearrangement

• Clonally integrated HTLV-1 found in all cases

• Possible loss of putative tumor suppressor gene on 6q (6q15-21)

• Alteration of p16 and p53
Postulated Cell of Origin

• Peripheral CD4+ T cells in various stages of activation
Prognosis

• Prognostic factors
  – Clinical subtype
  – Age
  – Performance status
  – Serum Ca
  – Serum LDH
Prognosis

• Survival
  – Acute and lymphomatous variants
    • 2 wks to > 1 year
    • Causes of death
      – Infectious complications
        » PCP
        » Cryptococcus meningitis
        » Disseminated herpes zoster
      – Hypercalcemia
  – Chronic and smoldering variants
    • longer survival
    • Can transform into an acute phase (aggressive)