CHRONIC LEUKEMIAS OF LYMPHOID LINEAGES

Chronic lymphocytic leukemia (CLL)
A mature B-cell neoplasm
Most common leukemia in adults >60 yr, male:female=2:1
Primarily affects Whites and Blacks, uncommon in Asians
Lymphadenopathy (SLL) (65%), splenomegaly (40%), hepatomegaly (25%)
Defined as ≥ 5000x10^6/L monoclonal lymphocytes in blood
Cases < 5000x10^6/L monoclonal lymphocytes are defined as monoclonal B-lymphocytosis (MBL)
MBL is considered as precursor of CLL which may or may not progress to CLL
Morphology: small mature lymphocytes
Lymph node or extranodal tissue involvement: Small lymphocytic lymphoma (SLL)
Phenotype: monoclonal kappa or lambda, all B-cell markers+ (usually low intensity), CD5+, CD23+, LEF-1+
Prognosis: 1. FISH: del 17p, del 11q (worse), trisomy 12 (neutral), del 13q (better)
   2. IGH hypermutation: unmutated (worse), mutated (better)
   3. Flow markers: ZAP70+, CD38+, CD49d+ (worse), ZAP70-, CD38-, CD49d- (better)
Symptomatic or positive del 17p require treatment. Overall survival >10 yr
Transformation: Diffuse large B-cell lymphoma (Richter’s transformation): aggressive
   Prolymphocytic transformation: outcome intermediate between CLL and Richter’s

B-cell prolymphocytic leukemia (B-PL)
A mature B-cell neoplasm
Affects older male, present with very high white count
Predominantly prolymphocytes in blood
Usually prominent splenomegaly without lymphadenopathy
Morphology: Large round nuclei, mature chromatin, single large nucleolus, increased blue agranular cytoplasm
Phenotype: Express high intensity of B-cell markers and monoclonal kappa or lambda, CD5+ in cases transformed from CLL, CD5- in de novo cases
Prognosis: More aggressive clinical course than typical CLL

Mantle cell leukemia
Leukemic form of mantle cell lymphoma
Morphology: Medium sized, round nucleus, with a single, small but prominent nucleolus.
Morphology similar to B-prolymphocytic leukemia (prolymphocytes)
t(11;14) positive by FISH
Prognosis: more indolent than mantle cell lymphoma
(Additional description in Lesson 6)

Hairy cell leukemia
A mature B-cell neoplasm
More common in male, median age 50 years old, may affect younger adults
Insidious onset with neutropenia, massive splenomegaly, no lymphadenopathy

**Morphology:**

**Cytomorphology:** Small round nuclei with mature chromatin, increased lightly basophilic cytoplasm with delicate projection (“hairy”), often <5% blood involvement (difficult to find on blood smear)

**Bone marrow:** Aggregates of leukemic cells most commonly located at paratrabecular location, “fried egg” morphology, associated with fibrosis

**Spleen:** Involving red pulp, sparing white pulp, “blood lakes” common

**Phenotype:** Express all B-cell markers, monoclonal kappa or lambda, and CD11c+ (bright), CD25+, CD103+, CD123+, TRAP+, BRAF+, annexin A1+

**Genetics:** 100% BRAF V600E mutated

**Prognosis:** indolent behavior, good prognosis

**Differential Diagnosis:** Other splenic B-cell lymphoma/leukemia:
- Hairy cell leukemia variant (CD11c+, CD25-, CD103+, CD123+)
- Splenic marginal zone lymphoma (CD11c+, CD25-, CD103-, CD123-)
- Splenic diffuse red pulp small B-cell lymphoma (CD11c-, CD25-, CD103-, CD123-)

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**T-prolymphocytic leukemia (T-PLL)**

Mature T-cell neoplasm, a rare disease, affect middle aged and older adults
Blood with high white count, 100% bone marrow involvement, frequent lymph node, spleen involvement

**Morphology:** Cytomorphology: mature small lymphocyte or prolymphocytes or in between, cytoplasmic “knobbing”

**Phenotype:** Express pan T-cell markers, CD4+/CD8- or CD4+/CD8+, all TCL-1+

**Genetics:** Clonal T-cell receptor gene rearrangement. Inversion (14)(q11q32) in 80% cases, t(14;14)(q11;q32) in 10% cases, involving translocations TRA-TCL1A or TRA-TCL1B. t(X;14)(q28;q11) in rare cases, involving translocation TRA-MTCP1

**Prognosis:** Poor

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**T-cell large granular lymphocytic leukemia (T-LGL)**

A mature T-cell neoplasm, persistent increase (>6 months) of peripheral LGL (>2000x10^6/L)
Affects middle aged and elderly adults, equally affects male and female
Indolent presentation, often present with neutropenia
Frequently associated with autoimmune disorders (rheumatoid arthritis, etc)
Can be difficult to differentiate from reactive LGL hyperplasia (which is far more common)

**Morphology:** Mature lymphocytes with small to medium-sized nuclei, mature chromatin, usually without nucleoli, increased pale blue cytoplasm, variable numbers of purple-red cytoplasmic granules

**Phenotype:** Pan T-cell markers+ (may have loss of CD5 or CD7), CD8+ (most frequent) or CD4+ (less frequent), CD16+, CD57+, cytotoxic markers+

**Genetics:** STAT3 mutation ~35%, STAT5B mutation ~5%

**Prognosis:** Indolent

**NK cell type LGL:**
NK cell counterpart known as **Chronic lymphoproliferative disorder of NK cells (CLPD-NK)**, very similar to T-LGL except for NK-cell phenotype (sCD3-, CD56+)
**Adult T-cell leukemia/lymphoma (ATLL)**

A mature T-cell neoplasm, caused by HTLV1 virus
Most commonly presents with blood, lymph node, and skin involvement
Endemic in Caribbean, Japan, part of central Africa

**Morphology:** Variable sized, highly pleomorphic lymphocytes with convoluted and lobated nuclei and scant to moderate cytoplasm (“flower cells”)

**Phenotype:** Pan T-cell antigens+ (frequent loss of CD7), CD25+, CD4+, CD8-

**Genetics:** No consistent genetic finding, TCR rearranged

**Prognosis:** Poor
(Additional description in Lesson 10)

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**Sezary syndrome (SS)**

T-cell neoplasm closed related to Mycosis Fungoides, with lymphoma cells involving blood (usually >1000/uL) and generalized erythroderma and lymphadenopathy
Rare disease, <5% of T-cell cutaneous neoplasm
Presented with *Triad* of erythroderma, generalized lymphadenopathy, Sezary cells in blood.
Other features include pruritus, alopecia, estropion, palmar or plantar hyperkeratosis, onychodystrophy

**Morphology:** Sezary cells: medium to large sized lymphocytes with highly convoluted nuclear contour (“cerebriform cells”)

**Phenotype:** Pan T-cell antigens+ (frequent loss of CD7 and CD26), CD4+, CD8-, PD-1+

**Prognosis:** Poor
(Additional description in Lesson 10)