Diagnostic Utility of Molecular and Flow Cytometric Findings in T-cell Large Granular Lymphocytic Leukemia

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Disclosures

- Nothing to disclose

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Background

- T-cell large granular lymphocytic leukemia (T-LGLL)
  - Rare chronic lymphoproliferative disorder of mature cytotoxic T-cells
  - 2-3% of mature small lymphocytic leukemias
  - Underlying etiology is unknown
  - Difficult to distinguish from reactive conditions
  - Diagnosis requires integration of morphologic, immunophenotypic, molecular, and clinicopathologic findings

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Background

- 2017 World Health Organization (WHO) definition:

  "Heterogeneous disorder characterized by a persistent (>6 months) increase in the number of peripheral blood large granular lymphocytes (LGLs)…without a clearly identified cause"

(Swerdlow et al, 2017)

Background

- Jaffe et al definition:

Table 31-1 Major and Minor Diagnostic Criteria for T-Cell Large Granular Lymphocytic Leukemia and Chronic Lymphoproliferative Disorder of NK Cells

	T-Cell Large Granular Lymphocytic Leukemia

Major criteria	• Flow-cytometric immunophenotyping revealing >50% of the total peripheral blood or bone marrow surface CD3-positive T cells to have two or more of the following*:
	  • CD8 positive (may be dim)
	  • Uniform expression of CD16 or CD57 (>75% of cells positive)
	  • Loss of CD5 expression (partial or complete)
	  • Uniform expression of one or more of the KIRs CD158a, CD158b, and CD158e†
	• Intrasinusoidal bone marrow or splenic infiltration by cytotoxic lymphocytes positive for one CD8 and one or more of the cytotoxic markers TIA-1, granzyme B, granzyme M, or perforin†
	• T-cell clonality by flow-cytometric analysis of TCR Vbeta expression or molecular genetic analysis of T-cell–receptor gene rearrangements
	• *STAT-3* gene mutation in exons 20 or 21

Minor criteria	• Peripheral blood granular lymphocytes (morphology) or CD8-positive T cells (flow cytometry) either >2 × 10^9/L or >80% of total lymphocytes • Unexplained persistence of cell population for longer than 6 months • Positive rheumatoid factor, ANA, or polyclonal hypergammaglobulinemia • Unexplained neutropenia (<1.8 × 10^9/L) and/or anemia (<10 g/dL) • Peripheral blood absolute NK-cell count <0.1 × 10^9/L or <5% of total lymphocytes • *STAT-5B* gene mutation in exons encoding the SH2 domain.

(Jaffe et al, 2017)

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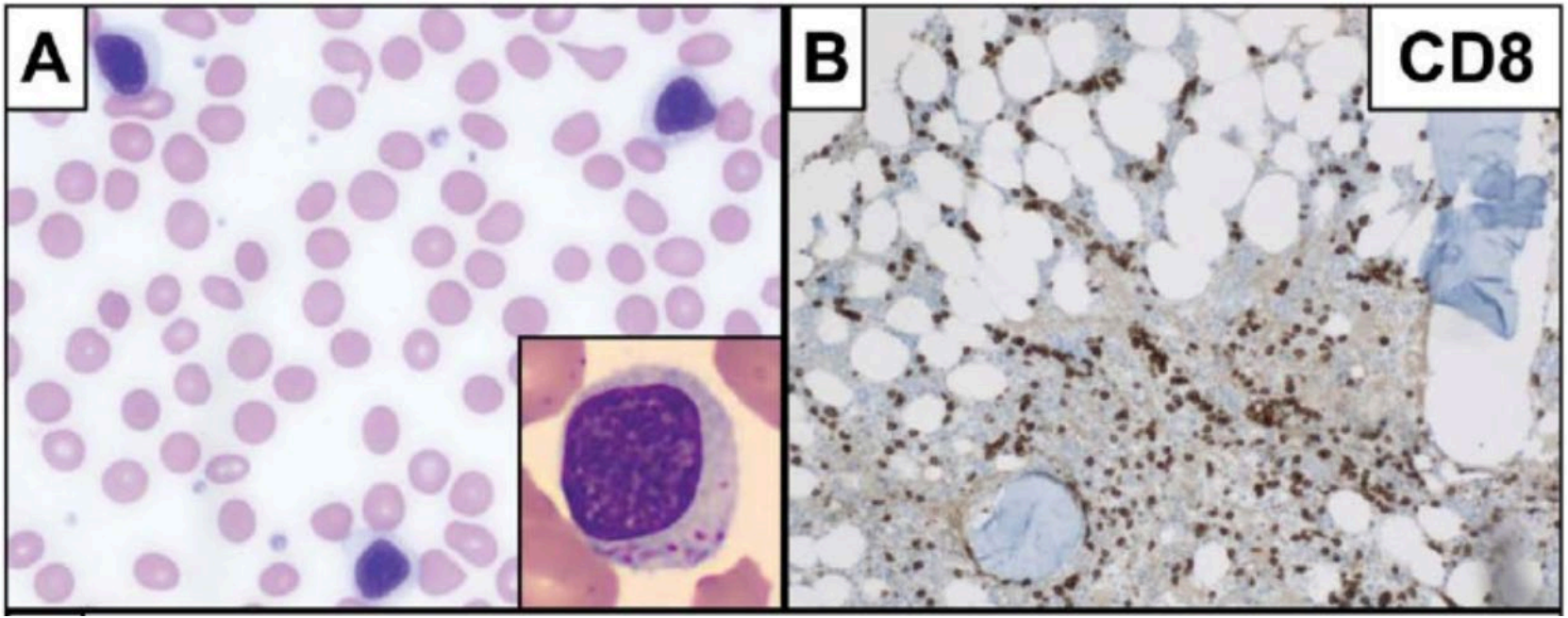
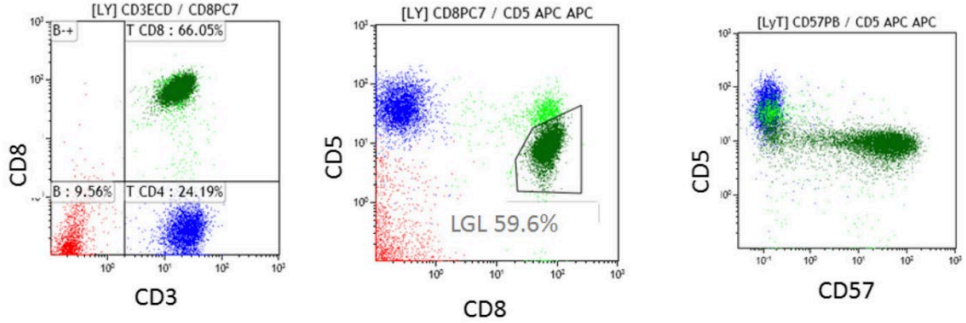
Morphology

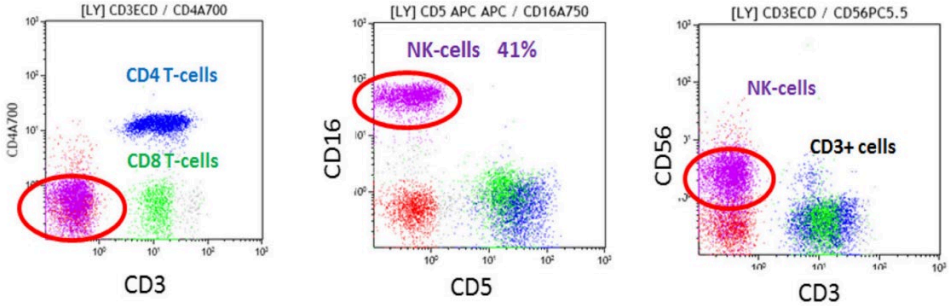


(Raess et al, 2017)

Immunophenotype

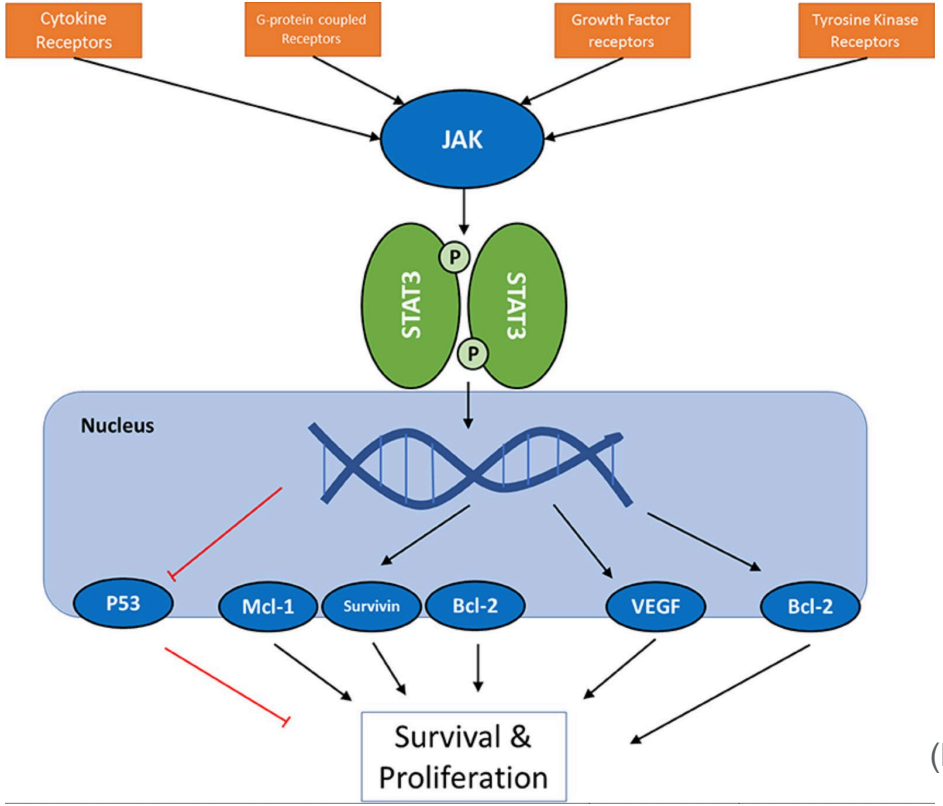


Natural killer cell subtype



(Moignet et al, 2018)

Genetics



(Bousoik et al, 2018)

Significance

- Multiple points of clinical follow-up
- Extensive and costly laboratory analysis
- Requires continued access to healthcare system
- Broad differential diagnosis
- Delays in treatment

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Research Question

- How do we improve the diagnostic criteria for T-LGLL?

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Methods

- Retrospective review
  - Cases with clinical or hematopathologic suspicion for T-LGLL at OHSU
  - Reviewed:
    - Flow cytometry
    - Next-generation sequencing
    - T-cell receptor gene rearrangement (TCR)
    - Antigen aberrancy
    - Demographic and laboratory data

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Results

Table 1. Clinicopathologic characteristics of patients with clinical or hematopathologic suspicion for T-LGLL

Parameter	T-LGLL	Suspicious for T-LGLL	CLPD-NK	Suspicious for CLPD-NK	Indeterminate	Negative
Number of patients	26	10	2	4	17	86
Sex (M/F)	18/8	7/3	2/0	4/0	11/6	52/34
Median age (IQR)	64 (27-89)	71 (51-78)	42.5 (37-48)	61 (46-67)	66 (21-82)	60.5 (1-91)
Hematologic manifestations % (n)						
Anemia (Hb < 11 g/dL)	42% (11)	0% (0)	50% (1)	25% (1)	6% (1)	35% (30)
Thrombocytopenia (platelets <150 x 10^9/L)	30% (8)	20% (2)	100% (2)	50% (2)	35% (6)	51% (44)
Neutropenia (ANC <1.5 x 10^9/L)	39% (7)*	38% (3)*	100% (2)	0% (0)*	23% (3)*	39% (27)*
Severe neutropenia (ANC <0.5 x 10^9/L)	22% (4)*	13% (1)*	50% (1)	0% (0)*	0% (0)*	9% (6)*
Lymphocytosis (ALC >2.9 x 10^9/L)	50% (9)*	50% (4)*	0% (0)	33% (1)*	15% (2)*	26% (18)*

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Results-Molecular Data

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STAT5B mutations	1/21	0/2	0/2	0/1	1/8	1/38
Other mutations	11/21 *TET2* (3), *MPL* (2), *KRAS* (2), *ASXL1* (2), *PTPN11* (2), *PAX5* (2), others (17)	2/2 *DNMT3A* (2)	2/2 *TET2* (2), others (4)	1/1 other (3)	5/8 *TET2* (2), *DNMT3A* (2), *ATM* (2), *NOTCH1* (2), *ABL1* (2), others (19)	33/38 *TET2* (8), *DNMT3A* (5), *IDH1* (5) *TP53* (4), *SRSF2* (4) others (54)
TCR monoclonality	24/24	10/10	1/1	1/2	11/11	20/30

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Conclusion

- Need better diagnostic testing
- Most commonly observed abnormalities:
  - Monoclonal TCR gene rearrangements
  - Immunophenotypic aberrancy
- *STAT3/STAT5B* mutations occurred at similar frequencies in those with T-LGLL and those without
- Research is ongoing

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Thank You!

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