بسم الله الرحمن الرحیم

Practical Immunohistochemical Approach to T-Cell & NK-Cell Lymphoproliferative Disorders

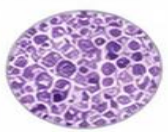
Master Algorithm – Nodal T-Cell Lymphomas

1 EVALUATE ARCHITECTURE

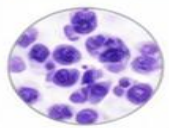
Paracortical

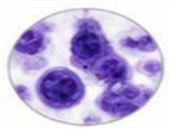
Diffuse

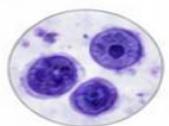
Sinusoidal

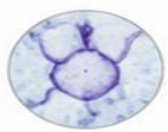

Polymorphous

2 ASSESS CYTOLOGY


Small/medium atypical cells


Pleomorphic large cells

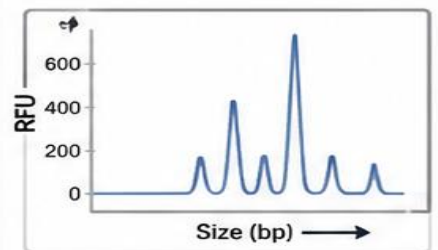

Hallmark cells


Clear cells

3 APPLY TARGETED IMMUNOHISTOCHEMISTRY

PHENOTYPE	MARKERS
TFH phenotype	PD-1 ICOS CXCL13
ALCL	CD30 ALK
Cytotoxic phenotype	TIA-1 Granzyme B
EBV-associated	EBER

4 MOLECULAR TESTING



TCR GENE REARRANGEMENT

Assess clonality to distinguish neoplastic vs reactive T-cell proliferation.

Architecture narrows the differential before immunostains do.

Immune System (T-cell~focused): Innate vs Adaptive

INNATE / INNATE–LIKE
(rapid, less specific)

NK cell (NOT a T cell, but T-cell mimicker)

- CD56+ (bright or dim)
- CD16 ±
- Surface CD3 -
- cytoplasmic CD3ε can be in NK/T lymphoma
- TCRαβ ~ / TCRγδ ~
- Cytotoxic molecules: TIA-1+, GzmB+, Prf+

ADAPTIVE
(antigen-specific, memory)

αβ T cell (~95%)

Conventional T cells

- CCRαβ+:
- TCR αβδ+ (βF1+)
- Subsets:
  - CD4 helper (CD4+)
  - CD8 cytotoxic, CD3+ (TIA-1/GzmB/Prf+),
  - Treg (FOXP3+, CD25+, (CD127low,
  - TFH (PD-1, ICOS, CXCL13, BCL6+)
  - Th2 (GATA3); **Th17** (RORγt)

γδ T cell (1~5%)

γδ T cell (~1-5%)

- CD3+
- TCRγδ−
- often CD4− /CD8− (or CD8+)
- often cytotoxic markers +CD56

Practical Approach to Leukemic T-Cell Disorders

- **Peripheral blood morphology often provides the first diagnostic clue.**
- **Important Integrative Clues**
  - Clinical presentation
  - CBC findings
  - Flow cytometry
  - Viral studies
  - Organ involvement

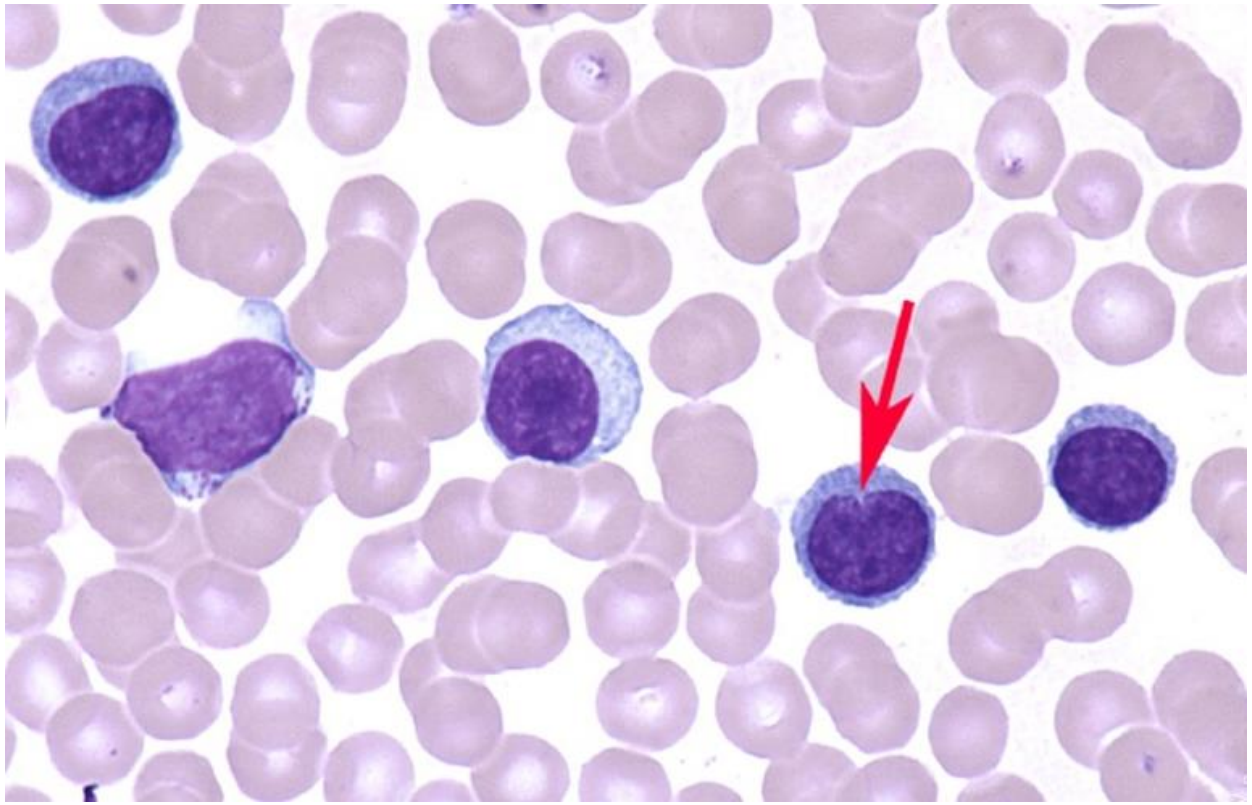
Clinical Presentation-Based Approach

Clinical Scenario	**Think About**
Massive lymphocytosis + splenomegaly	T-PLL
Hypercalcemia + skin lesions	ATLL
Erythroderma	Sézary syndrome
Neutropenia + RA	T-LGL
Fulminant EBV illness	Aggressive NK

Morphology-Based Approach

Morphology	**Differential**
Prolymphocyte	T-PLL
Flower cell	ATLL
Cerebriform cell	Sézary
Large granular lymphocyte	T-LGL
CD56+ atypical cell	Aggressive NK

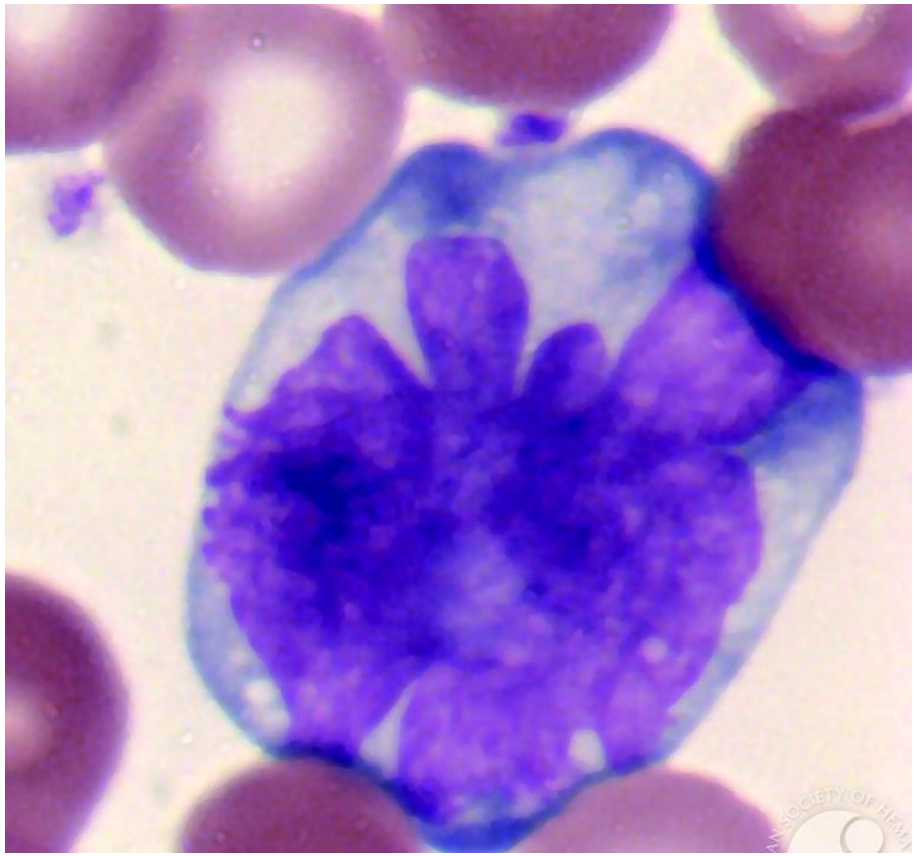
- **T-PLL Prolymphocyte**
  - Medium-sized mature lymphoid cell
  - Moderately condensed chromatin
  - Single prominent nucleolus
  - Pale basophilic cytoplasm
  - Cytoplasmic blebs may be present



•**The most important morphologic clue is a prominent nucleolus in a mature-appearing lymphoid cell.**

Suggested Report
“Circulating atypical lymphoid cells with medium-sized lymphoid cells, prominent nucleoli and occasional cytoplasmic blebs are identified. Correlation with flow cytometry is recommended.”

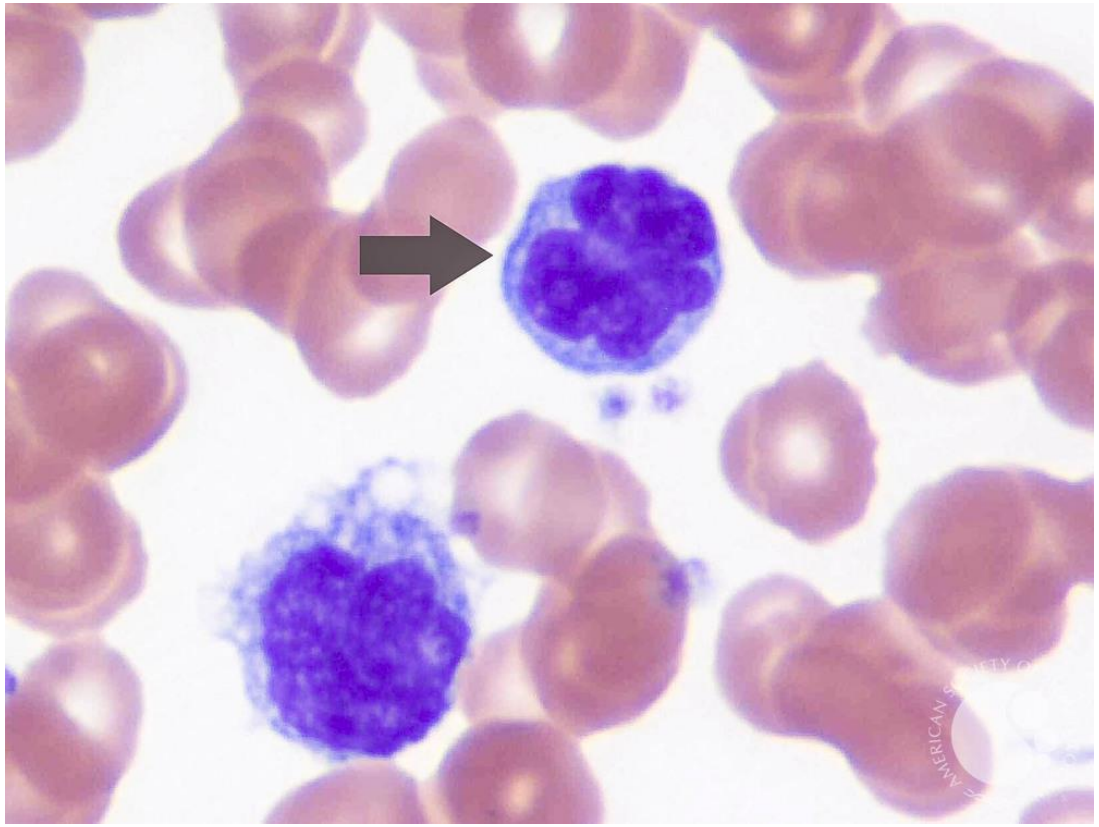
- ATLL Flower Cells
  - Medium to large atypical lymphoid cells
  - Deeply convoluted, multilobated nuclei
  - Irregular nuclear contours
  - Coarse chromatin
  - Small or inconspicuous nucleoli
  - Moderate pale cytoplasm



Flower cells: atypical lymphoid cells with deeply convoluted, multilobated ("flower-like") nuclei and coarse chromatin.

Suggested Report
"Atypical lymphoid cells with flower-cell morphology are present. Correlation with clinical findings, HTLV-1 status, and flow cytometry is recommended."

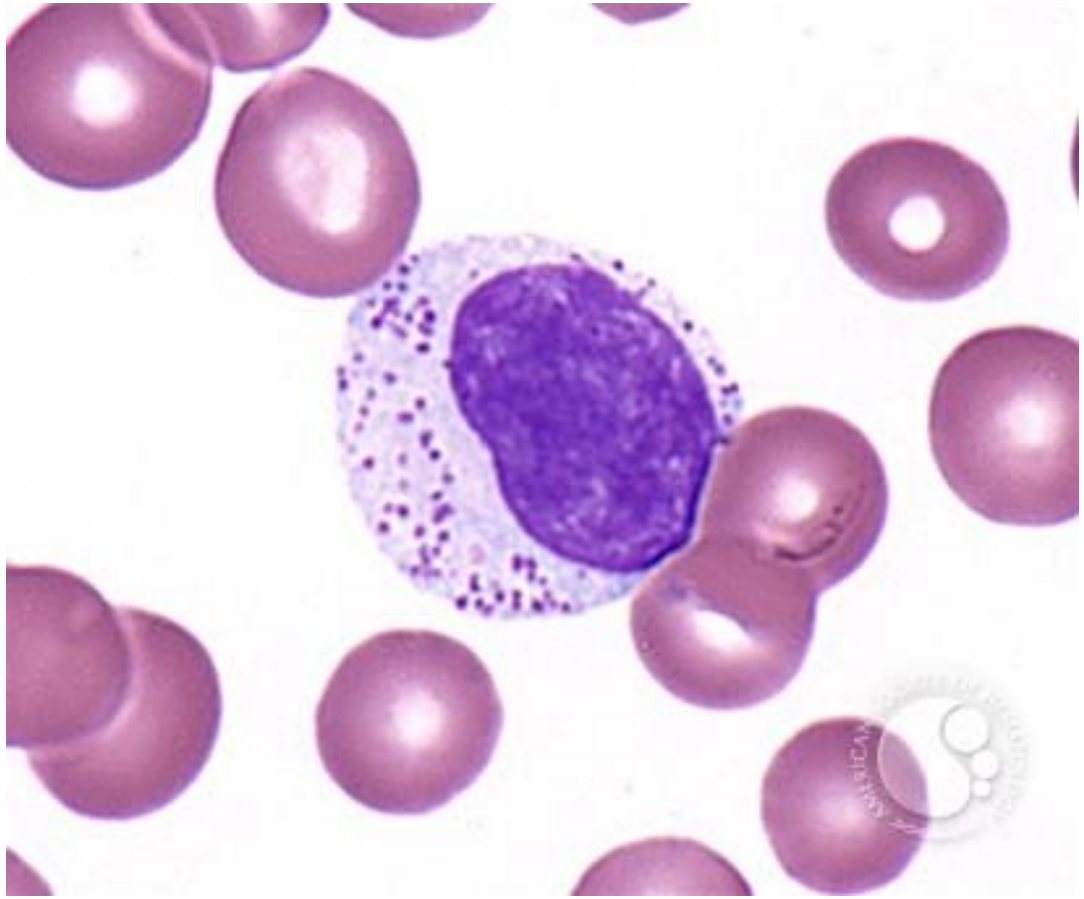
- **Sézary Cells**
  - Small to medium atypical lymphocytes
  - Cerebriform ("brain-like") nucleus
  - Superficial nuclear convolutions
  - Hyperchromatic chromatin
  - Scant cytoplasm
- Sézary cells are the neoplastic cells, whereas Sézary syndrome is the leukemic form of cutaneous T-cell lymphoma characterized by erythroderma, lymphadenopathy, and circulating Sézary cells.



- **Sézary cells may be seen in mycosis fungoides and other cutaneous T-cell lymphomas. The diagnosis of Sézary syndrome requires clinicopathologic correlation and cannot be established by morphology alone.**

Suggested Report
"Circulating atypical lymphocytes with cerebriform nuclear contours are identified. Correlation with clinical findings and flow cytometry is recommended "

- **T-LGL Cells**
  - Large granular lymphocytes
  - Abundant pale cytoplasm
  - Fine azurophilic granules
  - Round to slightly irregular nuclei
  - Mature chromatin
  - Inconspicuous nucleoli



Not every large granular lymphocyte population is leukemia. Persistent lymphocytosis, clonality, and an appropriate clinical setting are required for the diagnosis of T-LGL leukemia.

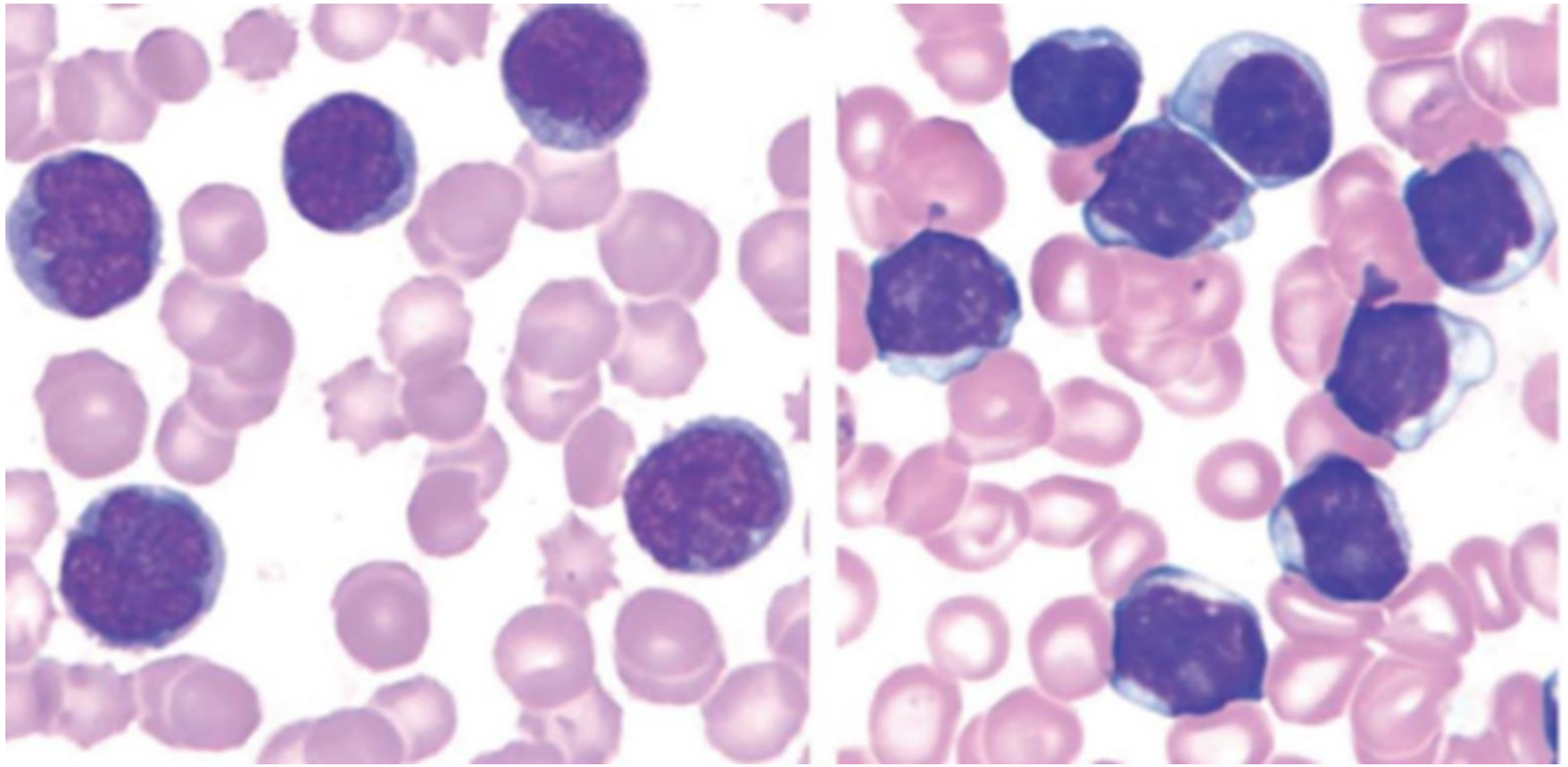
Suggested Report
"Increased large granular lymphocytes are identified. If Persistent: Correlation with flow cytometry is recommended to exclude a clonal LGL proliferation."

T-Cell Prolymphocytic Leukemia (T-PLL)

- **Clinical Features**
  - Older adult
  - Marked lymphocytosis
  - Hepatosplenomegaly
  - Skin involvement
  - Aggressive course
- **Morphologic Clues**
  - Medium-sized prolymphocytes
  - Prominent nucleoli
  - Cytoplasmic blebs
- **Typical Immunophenotype**
  - CD2+
  - CD3+
  - CD5+
  - CD7+
  - TCL1+

Diffuse marrow infiltration by mature T-cells strongly suggests T-PLL.

T-Cell Prolymphocytic Leukemia (T-PLL)



Medium-sized mature T lymphocytes with condensed chromatin and a single prominent nucleolus (prolymphocyte).

T-Cell Prolymphocytic Leukemia (T-PLL)

- T-PLL typically shows a mature post-thymic T-cell phenotype: CD2+, CD3+, CD5+, strong CD7+, usually CD4+, often TCL1+, with frequent CD4+/CD8+ co-expression.

🔘 Retention of strong CD7 expression is a major clue.

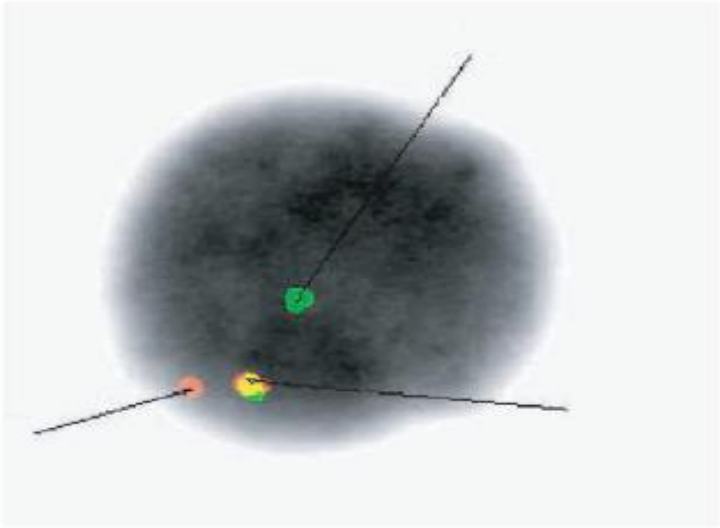
🔘 CD4+/CD8+ co-expression should immediately raise suspicion for T-PLL.

Think T-PLL when you see a mature lymphoid cell with a conspicuous nucleolus and cytoplasmic blebs in a patient with marked lymphocytosis and splenomegaly

T-Cell Prolymphocytic Leukemia (T-PLL)

- The most frequent chromosome abnormality in T-PLL involves inversion of chromosome14, seen in 80% of patients and described as inv(14)(q11q32)>>>>>activation of TCL1 oncoprotein

Fluorescence *in situ* hybridization analysis confirmed the rearrangement of *TCL1* gene

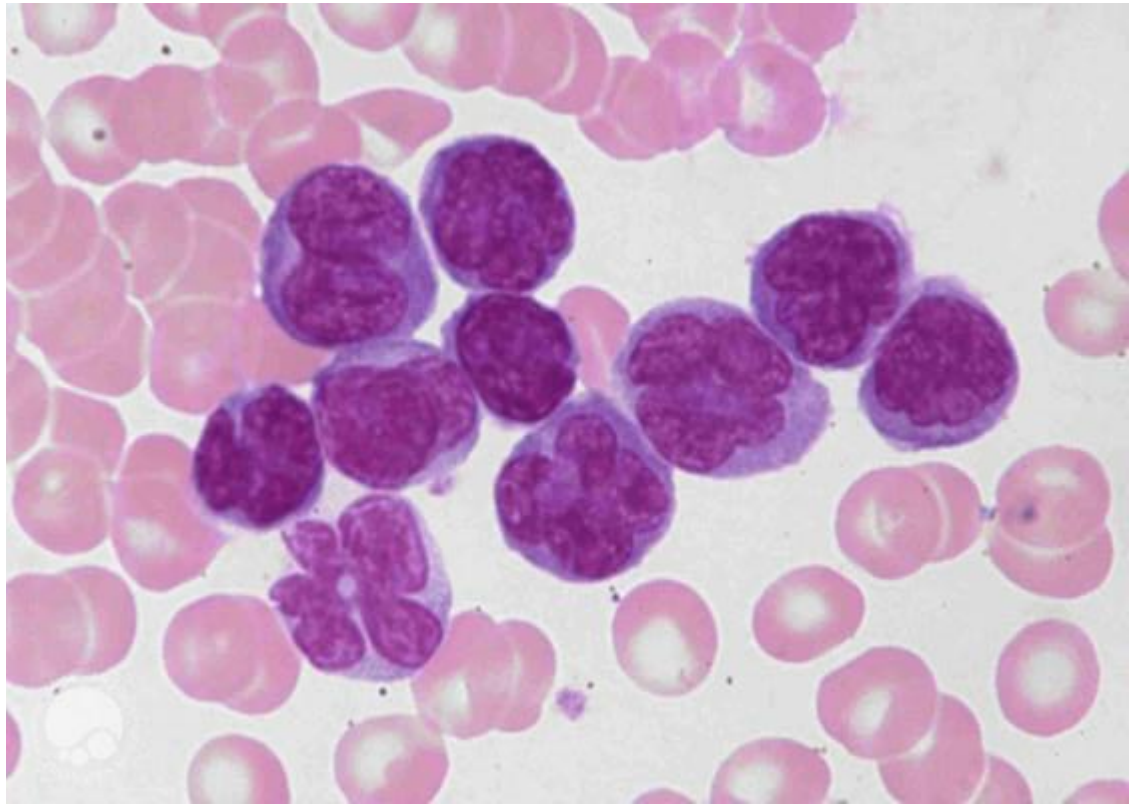


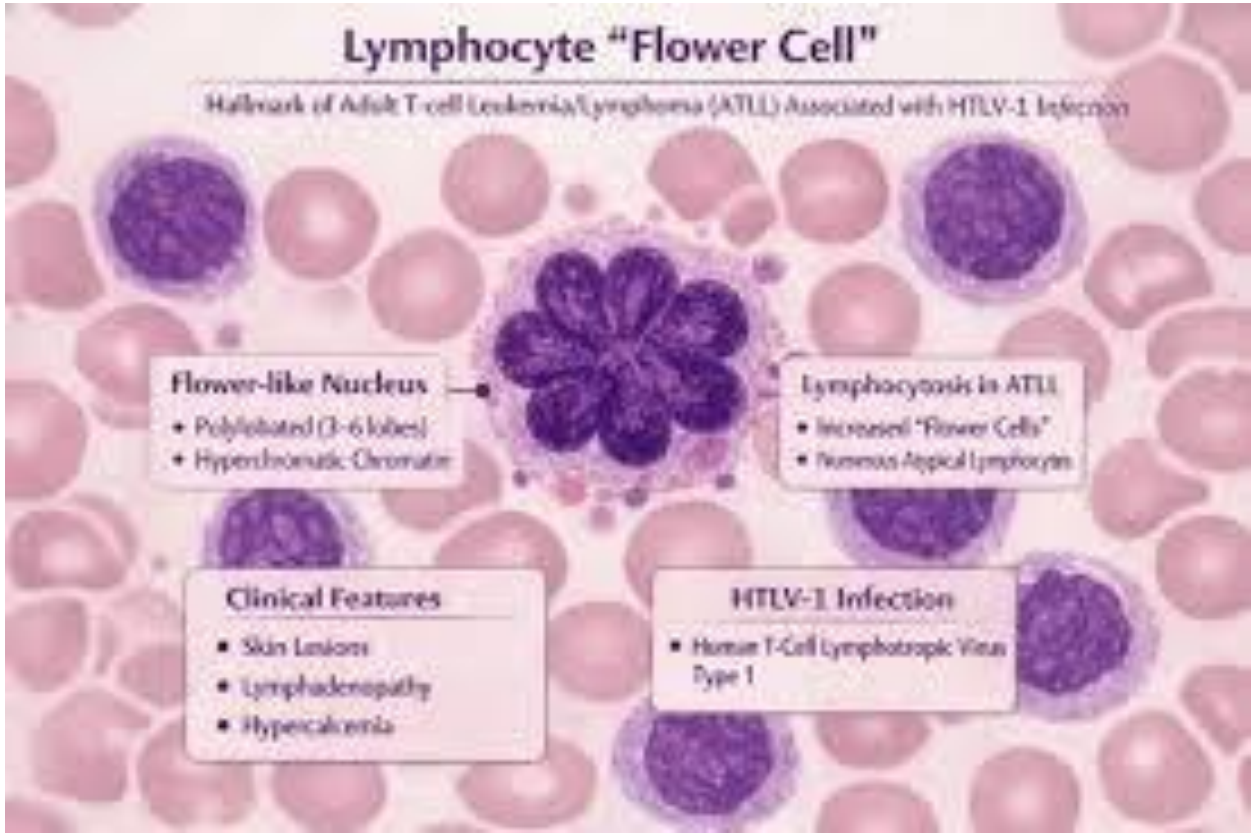
Adult T-Cell Leukemia/Lymphoma (ATLL)

- **Key Association**
  - HTLV-1 infection
- **Clinical Features**
  - Generalized lymphadenopathy
  - Hypercalcemia
  - Skin lesions
  - Leukemic presentation
- **Morphologic Clue**
  - **“Flower cells”**
- **Typical Immunophenotype**
  - CD3+
  - CD4+
  - CD25+
  - Frequent CD7 loss

Geographic and epidemiologic context is critical in ATLL diagnosis.

Adult T-Cell Leukemia/Lymphoma (ATLL)





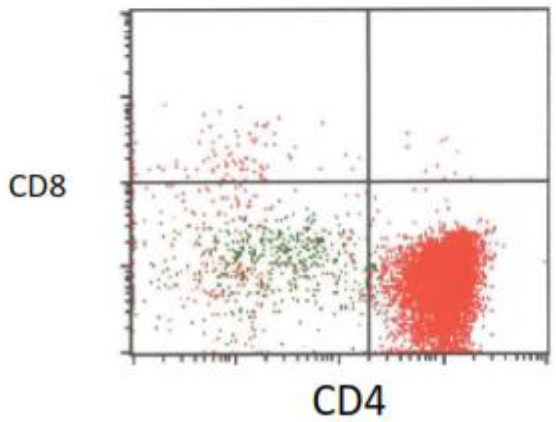
Feature	Smoldering ATL (chronic)	Chronic ATL	Acute ATL	Lymphomatous ATL (lymphoma type)
HTLV-1 association	Positive	Positive	Positive	Positive
Lymphocytosis (peripheral blood)	No	Mildly increased ($>4 \times 10^9$/L)	Markedly increased (usually $>20–30 \times 10^9$/L)	No (variable)
Immunophenotype (typical)	CD3+, CD4+, CD25+, CCR4+, CD7 variable/−, CD2 variable	CD3+, CD4+, CD25+, CCR4+, CD7 variable/−, CD2 variable	CD3+, CD4+, CD25+, CCR4+, CD7 variable/−, CD2 variable	CD3+, CD4+, CD25+, CCR4+, CD7 variable/−, CD2 variable
T-cell receptor (TCR) PCR	Sometimes monoclonal (often oligoclonal)	Monoclonal	Monoclonal	Monoclonal
Serum LDH	Not elevated	Normal or mildly elevated	Elevated	Elevated
Serum calcium	Normal	Normal	Often elevated (hypercalcemia)	Variable (may be elevated)
Skin lesions	Erythematous rash (common)	Rash, papules (common)	Variable, >50%	Variable, >50%
Lymphadenopathy	Absent	Mild	Usually present	Usually present
Hepatosplenomegaly	Absent	Mild	Usually present	Often present
Bone marrow involvement	Absent	Absent or minimal	May be present	Absent or minimal
Hemophagocytic syndrome (HSM)	Absent	Mild (rare)	Often present	Often present
Prognosis (median survival)	>2 years	Approximately 2 years	<1 year (6–9 months)	<1 year (6–9 months)
Morphology (peripheral blood)	• Small lymphocytes • Minimal atypia • Occasional "flower cells" (may be absent)	• Mild atypia • "Flower cells" (multilobated nuclei) sometimes seen	• Marked atypia • Pleomorphic • "Flower cells" common • Sometimes blast-like forms	• Marked atypia • Pleomorphic • "Flower cells" common • Sometimes blast-like forms
Clinical presentation	• Incidental finding • Skin rash • No organomegaly • Asymptomatic	• Skin rash • Mild lymphadenopathy • Mild organomegaly • No hypercalcemia • No HSM (usually)	• High fever • Generalized lymphadenopathy • Hepatosplenomegaly • Hypercalcemia • HSM • Rapid progression	• Prominent lymphadenopathy • Tumor masses • Extranodal involvement • Hypercalcemia variable • HSM often
WHO/ICC category	Smoldering ATL (Indolent)	Chronic ATL	Acute ATL	ATL – Lymphoma type

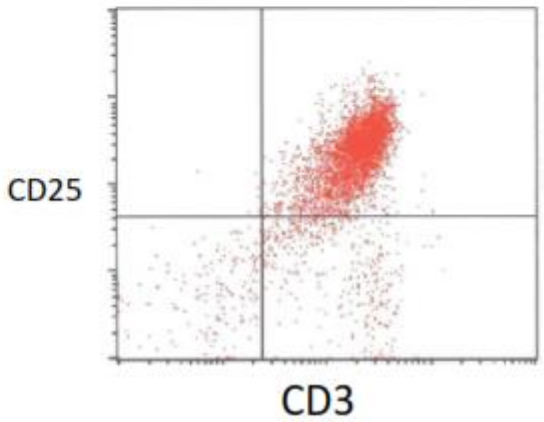
Abbreviations: ATL = Adult T-cell leukemia/lymphoma; HTLV-1 = Human T-lymphotropic virus type 1; LDH = Lactate dehydrogenase; HSM = Hemophagocytic syndrome; PCR = Polymerase chain reaction; TCR = T-cell receptor.

Key Points

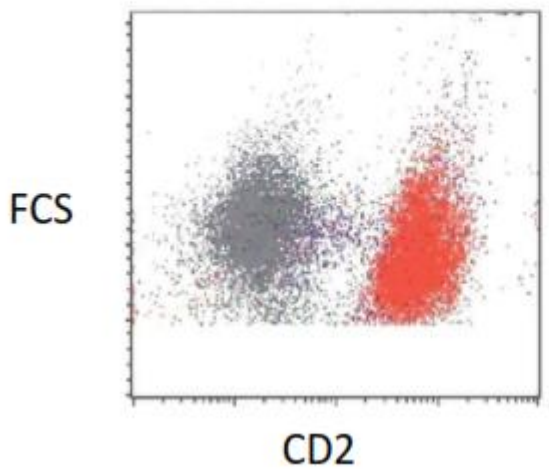
- All forms are HTLV-1 associated.
- "Flower cells" (multilobated nuclei) are characteristic but may be absent in smoldering ATL.
- Hypercalcemia, high LDH, and HSM are poor prognostic indicators.
- Diagnosis requires integration of clinical, morphologic, immunophenotypic, and molecular findings.

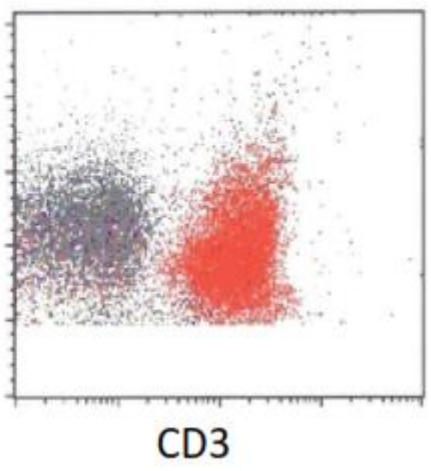
Adult T-cell leukaemia/lymphoma

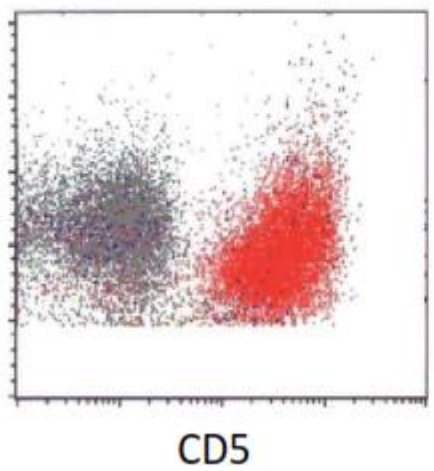


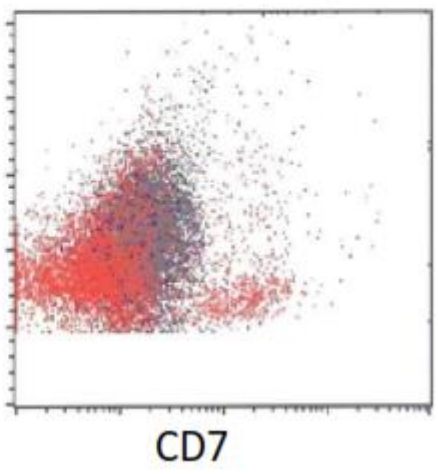


flow cytometry of the bone marrow. Leukemia cells show CD4 subset restriction and typical CD25 expression, Of all pan-T antigens, only CD7 is absent.









Sézary Syndrome

- **Classic Triad**
  - Erythroderma
  - Lymphadenopathy
  - Circulating Sézary cells
- **Morphologic Clue**
  - Cerebriform nuclei

- **Typical Immunophenotype**
- Absolute Sézary cell count ≥1000/μL

OR

- Expanded CD4+ T-cell population with CD4/CD8 ratio ≥10

OR

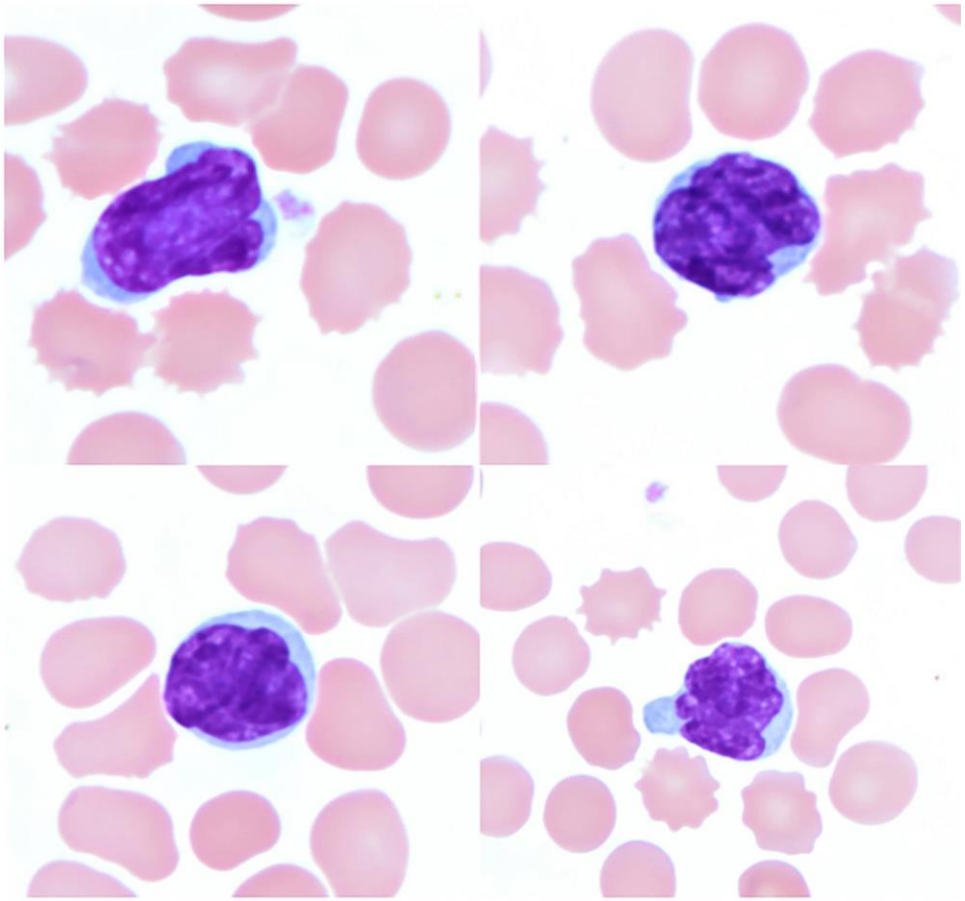
- Aberrant T-cell phenotype with loss of CD7 and/or CD26

Mycosis Fungoides vs Sézary Syndrome

Feature	MF	Sézary Syndrome
Cell of origin	Skin-resident effector memory T cell	Central memory recirculating T cell
Blood involvement	Minimal/late	Prominent
Lymph node involvement	Variable	Common
Clinical presentation	Patch/Plaque/Tumor	Erythroderma
Circulating tumor cells	Rare	Numerous
CD7 loss	Variable	Common
CD26 loss	Variable	Common

MF is thought to arise from skin-resident effector memory T cells, whereas Sézary syndrome originates from central memory T cells with the ability to recirculate between skin, blood, and lymph nodes.

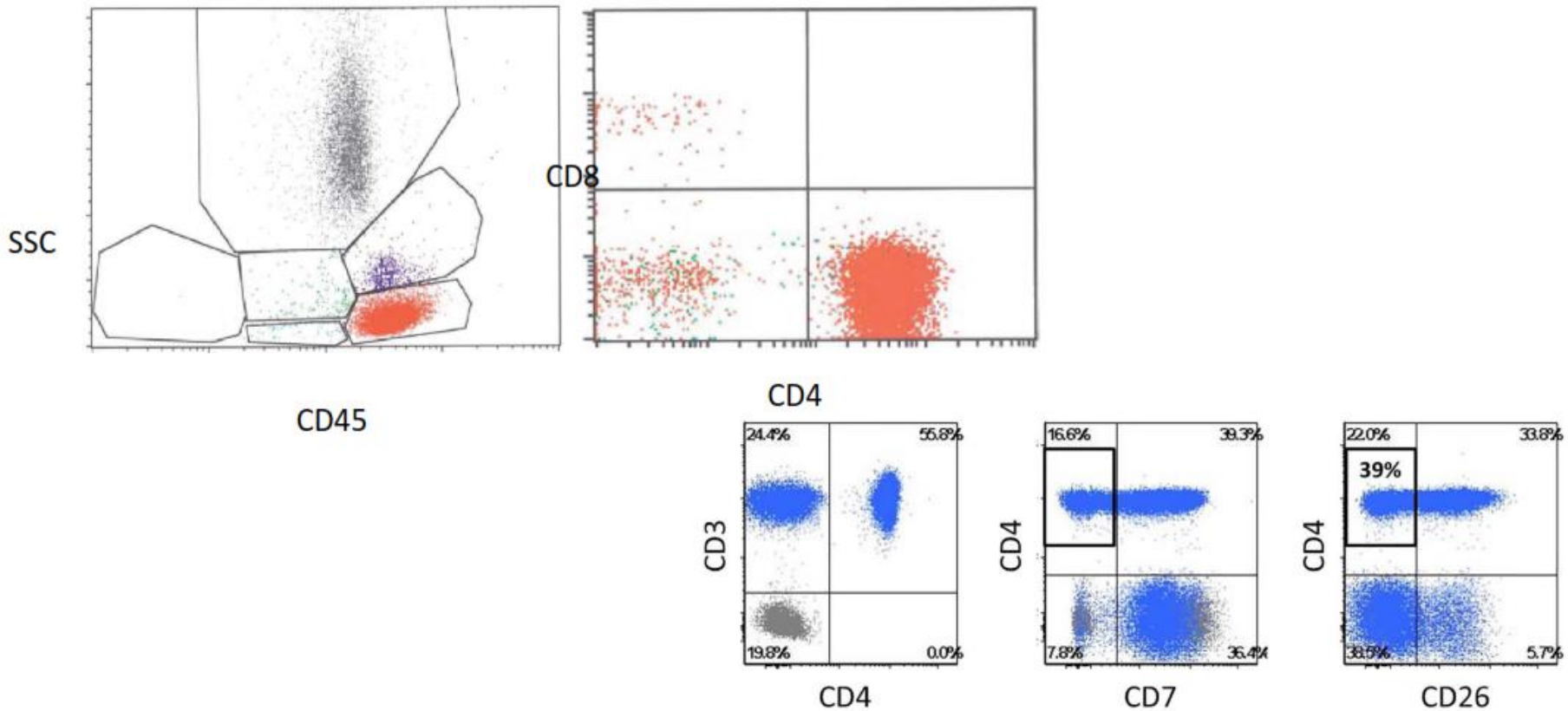
Sézary Syndrome



- **Diagnosis of Sézary syndrome requires erythroderma plus evidence of blood involvement.**
- **Sézary cells alone are insufficient for diagnosis.**

- **Erythroderma**
  - Diffuse, confluent erythema involving most of the body surface
  - Typically >80% of the skin surface
  - Characteristic clinical feature of Sézary syndrome
  - **Erythroderma refers to generalized confluent skin redness, not merely multiple widespread erythematous lesions.**

Flow cytometry shows lymphocyte with predominance of CD4+ cells.



Flow cytometry analysis of peripheral blood lymphocytes shows

CD4+/CD7— (> 30%) or

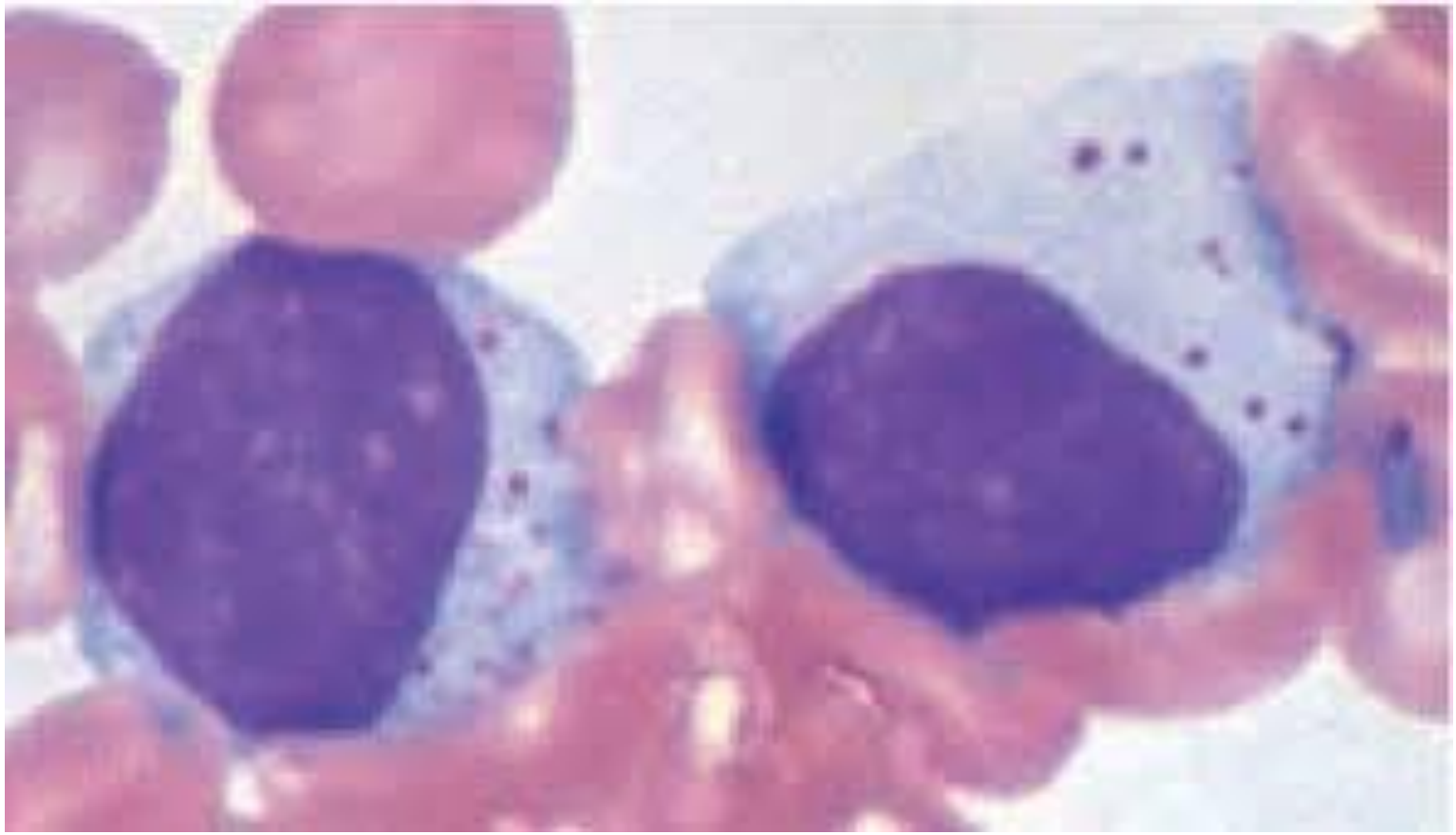
CD4+/CD26— (> 40%) T-cell population

T-Large Granular Lymphocytic Leukemia (T-LGL)

- **Clinical Features**
  - Chronic lymphocytosis
  - Neutropenia
  - Autoimmune disease association
  - Indolent clinical course
- **Morphologic Clue**
  - **Large granular lymphocytes with azurophilic granules**
  - **Typical Immunophenotype**
  - CD3+
  - CD8+
  - CD57+
  - TIA1+

Persistent cytotoxic large granular lymphocytosis should raise suspicion for T-LGL.

T-Large Granular Lymphocytic Leukemia (T-LGL)



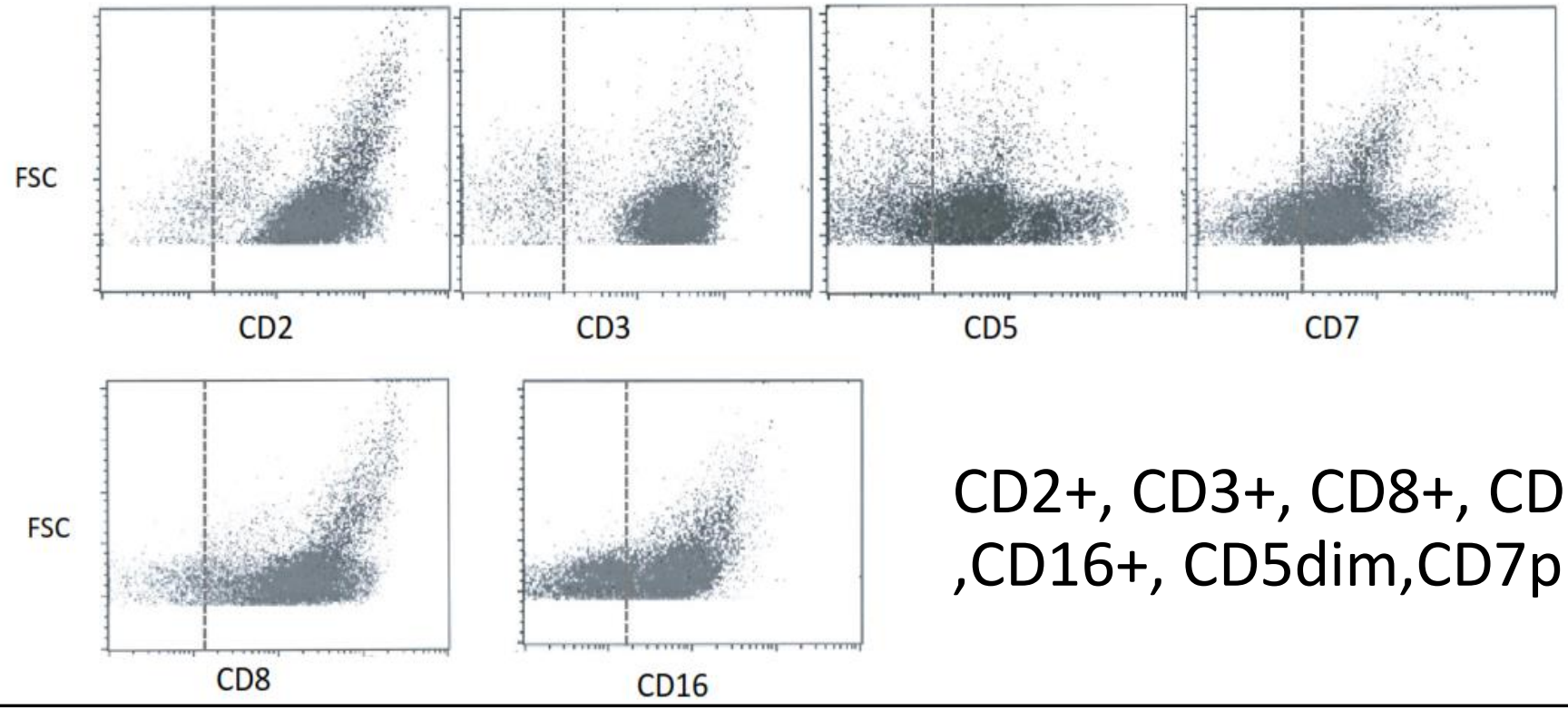
T-Large Granular Lymphocytic Leukemia (T-LGL)

Feature	Reactive LGL Expansion	T-LGL Leukemia
Duration	Transient	Persistent (>6 months)
Clonality	Polyclonal	Clonal
Cytopenias	Usually absent	Common
RA association	Uncommon	Common
STAT3 mutation	Absent	May be present

- **Persistent clonal cytotoxic T-cell proliferation with characteristic clinical features is more important than the absolute LGL count alone.**

🕮 **LGL count >2 × 10^9/L is no longer mandatory.**
Diagnosis may be established with:
•Lower LGL counts
•Typical phenotype
•Demonstrated clonality
•Compatible clinical findings

Flow Cytometric Clues Suggesting T-LGL



CD2+, CD3+, CD8+, CD57+ ,CD16+, CD5dim,CD7preserved.

CD5 downregulation in a CD8+/CD16+ cytotoxic T-cell population is a classic flow cytometric clue to T-LGL leukemia.

KIR EXPRESSION IN T-LGL LEUKEMIA

What is KIR?

- Killer-cell Immunoglobulin-like Receptor (KIR)
- Expressed on NK cells and subsets of cytotoxic T cells
- Regulates cytotoxic activity

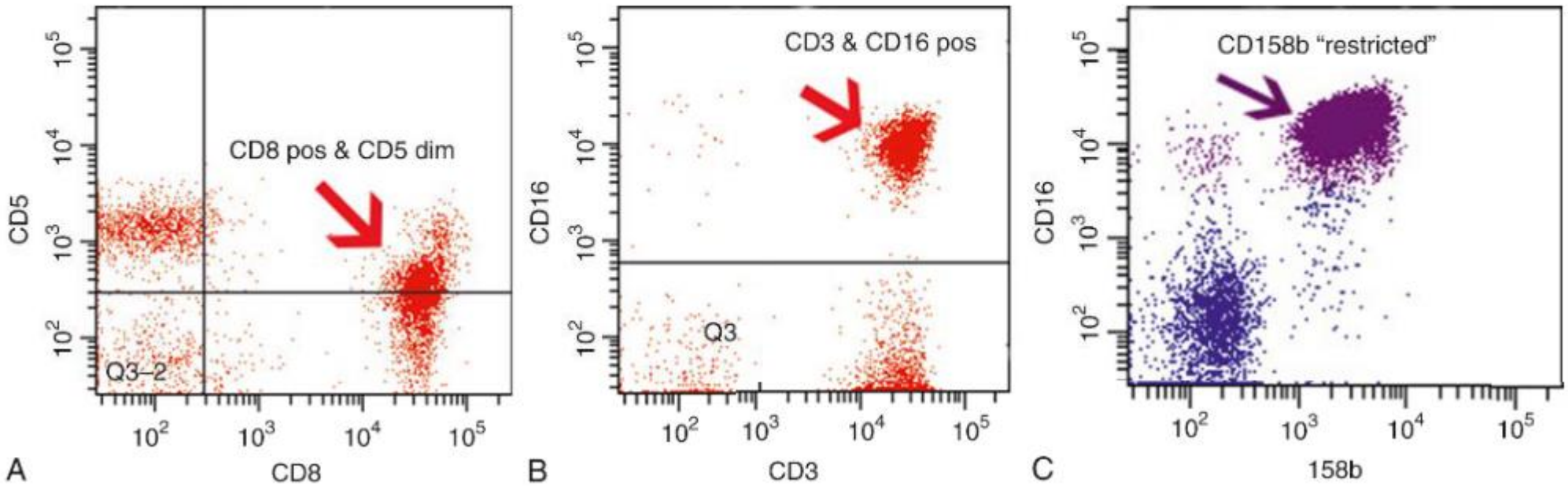
Why is KIR Important?

- Normal/reactive T-cell populations show heterogeneous KIR expression
- Neoplastic T-LGL cells often show restricted KIR expression

- Common KIR Markers
  - CD158a
  - CD158b
  - CD158e

- Diagnostic Significance
  - Restricted KIR expression strongly supports clonality
    Analogous to light-chain restriction (κ/λ) in B-cell neoplasms
- Restricted KIR expression is one of the strongest flow cytometric clues supporting a clonal T-LGL proliferation.

Flow cytometric immunophenotyping in T-LGL.
A, Flow cytometry in a T-LGL case reveals the CD3 positive T cells with co-expression of CD16. B, These T cells are CD8 positive and have slightly diminished expression of CD5. C, uniformly express the CD158b isoform; CD158a and CD158e were not expressed (not shown). **This pattern of KIR expression is loosely analogous to restricted immunoglobulin light chain expression by B-cells and is strongly correlated with clonality in LGL**



AGGRESSIVE NK-CELL LEUKEMIA

Clinical Features

- Young to middle-aged adults
- Fulminant clinical course
- Fever
- Hepatosplenomegaly
- Cytopenias
- Multiorgan failure
- Common Association
  - Epstein-Barr virus (EBV)
- Practical Pearl:
  - Aggressive NK-cell leukemia is one of the most aggressive mature lymphoid neoplasms.
  - Surface CD3 is one of the most useful markers for separating T-cell from NK-cell neoplasms

AGGRESSIVE NK-CELL LEUKEMIA:

- Morphology
  - Medium to large atypical lymphoid cells
  - Irregular nuclei
  - Cytoplasmic azurophilic granules
- Immunophenotype
  - CD2+
  - CD56+
  - Cytoplasmic CD3ε+
  - Surface CD3−
  - EBER+
  - TIA1+
  - Granzyme B+

Practical Pearl:
CD56-positive cytotoxic leukemia with EBER positivity strongly favors aggressive NK-cell leukemia.

Bone Marrow Patterns in T/NK-Cell Neoplasms

Pattern	Suggestive Entities
Diffuse infiltration	T-PLL
Intrasinusoidal infiltration	HSTCL, T-LGL leukemia, Aggressive NK-cell leukemia
Subtle interstitial cytotoxic cells	Aggressive NK
Mixed inflammatory infiltrate	AITL

Important Principle

Bone marrow involvement patterns may be highly diagnostically informative.

🧫 Intrasinusoidal marrow infiltration is a major hematopathology clue.

PRACTICAL ROLE OF FLOW CYTOMETRY

- **Major Utilities**
  - Detect aberrant antigen expression
  - Evaluate CD4/CD8 restriction
  - Identify NK phenotype
  - Detect loss of pan-T-cell markers
  - Support clonality assessment
- **Commonly Useful In:**
  - T-PLL
  - Sézary syndrome
  - T-LGL
  - Leukemic T-cell proliferations
- **Important Limitation**
  - Reactive conditions may also show aberrancies.

CLONALITY IN LEUKEMIC T-CELL DISORDERS

- Methods
  - TCR gene rearrangement studies
  - Flow cytometric restriction
  - Molecular testing
- Important Concept
  - Clonality supports lymphoma but does not prove lymphoma.
  - Lack of clonality argues against lymphoma but does not exclude lymphoma.
  - Clonality is evidence of neoplasia, but neoplasia can exist without demonstrable clonality

Practical Pearl:

Clonality must always be interpreted with morphology and clinical findings.

THE CYTOTOXIC PATTERN

- Characteristic Features
  - Tissue destruction
  - Apoptosis
  - Necrosis
  - Angioinvasion
  - Cytotoxic granules

- Angiocentricity:
  Tumor cells surround vessels.
- Angiodestruction:
  Tumor cells damage vessel walls.
- Consequences
  - Ischemia
  - Necrosis
  - Tissue destruction
- Practical Pearl:
  - Angioinvasion plus necrosis should immediately raise concern for ENKTL.

Cytotoxic T-Cell Phenotype

- **Key Cytotoxic Markers:**
  - TIA1 (T-cell intracellular antigen 1)
  - Granzyme B
  - Perforin
- **Diagnostic Utility:** Directly supports the identification of **cytotoxic T-cell** or **NK-cell differentiation**.
- Helps distinguish these active functional phenotypes from helper or regulatory T-cell subsets.

Cytotoxic markers indicate cellular function rather than pointing to a specific, unique disease entity.”

Cytotoxic T/NK-Cell Disorders

Finding	Suggestive Entity
Angioinvasion + necrosis	ENKTL
Intrasinusoidal BM infiltration	HSTCL
Granular lymphocytes	T-LGL
CD56+ leukemic process	Aggressive NK

Extranodal NK/T-Cell Lymphoma (ENKTL)

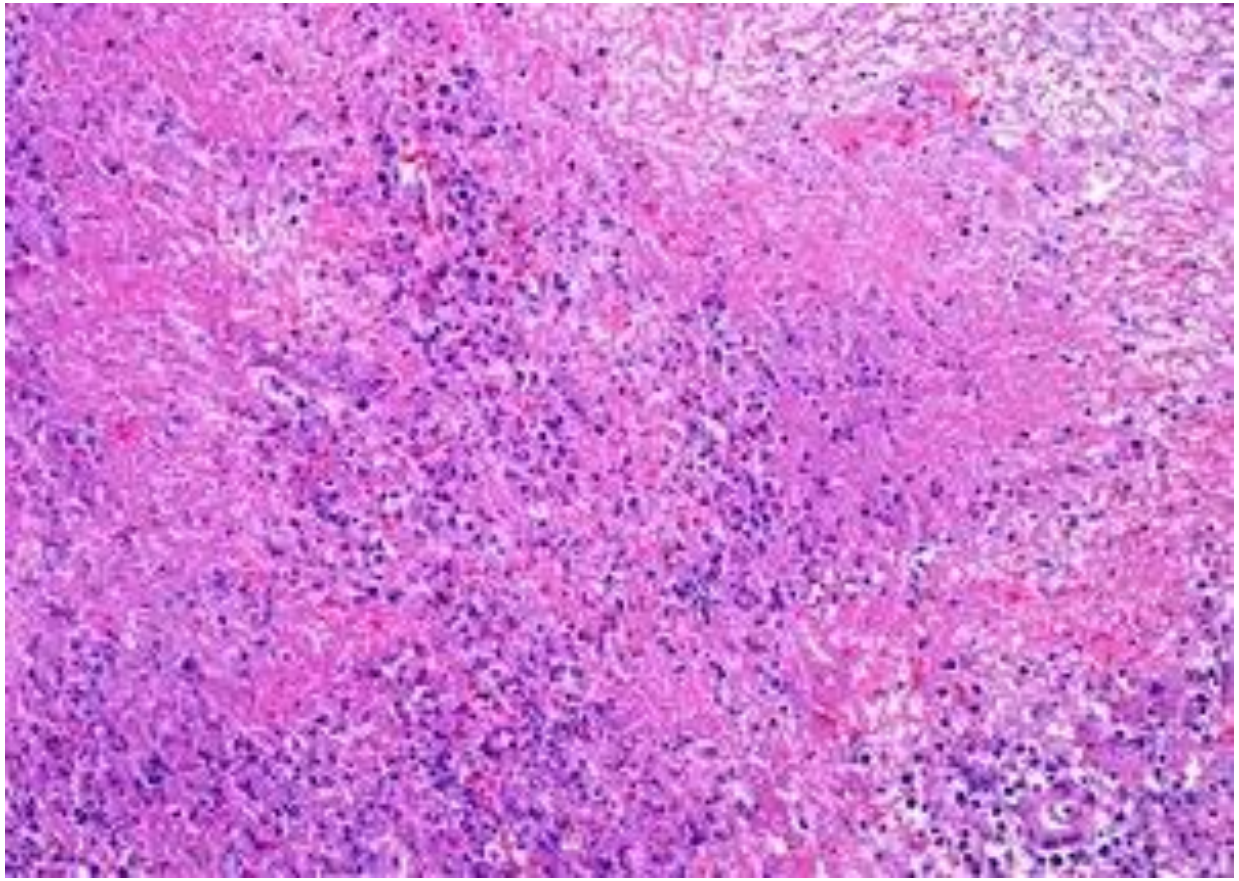
- **Morphological Hallmarks:**
  - Angiocentric growth
  - Angiodestruction
  - Extensive necrosis
  - Mixed inflammatory background
- **Important Diagnostic Pitfalls**
  - Necrosis may obscure:
    - Tumor cells
    - Immunostaining quality
    - Architecture
- **Important Differential Diagnoses**
  - Granulomatous inflammation
  - Fungal infections
  - Vasculitis
  - Reactive EBV proliferations

Extranodal NK/T-Cell Lymphoma (ENKTL)

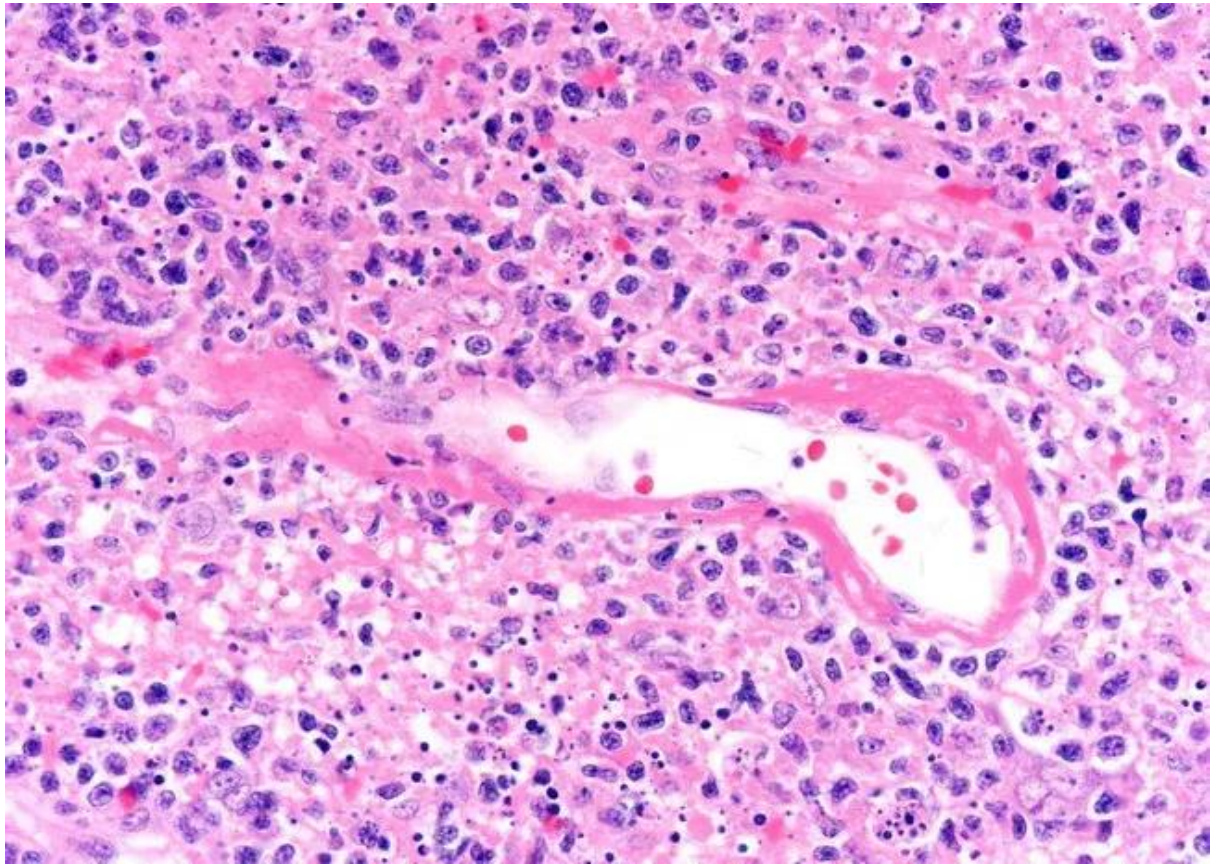
- **Phenotype:**
  - Cytotoxic profile (consistent with NK/T-cell lineage).
- **Typical Immunophenotype Surface/Cytoplasmic Markers:**
  - CD3 epsilon positive (cytoplasmic)
  - CD56 positive
  - Positive for cytotoxic markers (e.g., TIA1, Granzyme B)
- **Critical Diagnostic Marker:**
  - **EBER** (EBV-encoded small RNA) is **strongly positive**

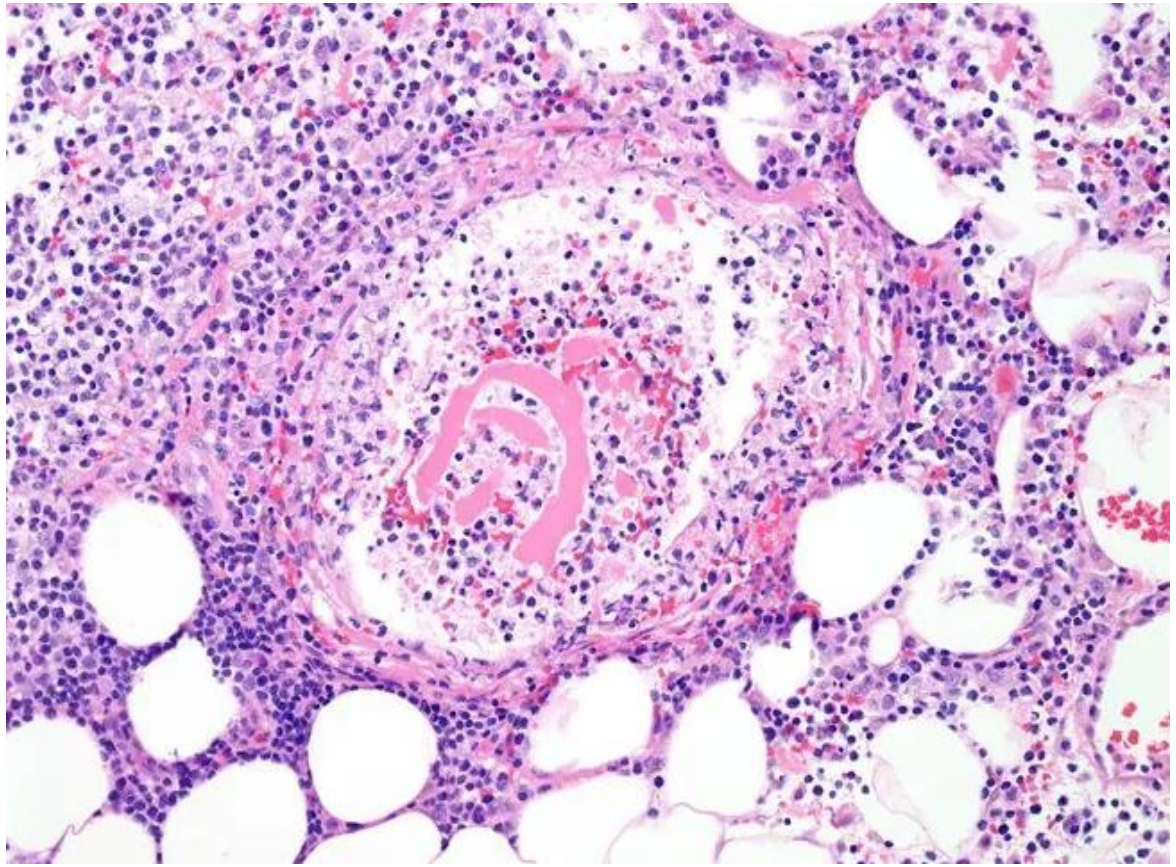
“The diagnosis hinges on the characteristic angiocentric growth pattern and the demonstration of Epstein-Barr virus (EBV) via EBER positivity.”

Extranodal NK/T-Cell Lymphoma (ENKTL)



Extranodal NK/T-Cell Lymphoma (ENKTL)





Common Immunophenotype of Extranodal NK/T-cell Lymphoma

Marker	Typical Result
CD2	Positive
Surface CD3	Negative
Cytoplasmic CD3ε	Positive
CD56	Usually positive
Cytotoxic markers TIA-1 / Granzyme B / Perforin	Positive
EBER	Positive
CD5	Usually negative
CD7	Variable
TCRαβ / βF1	Negative
TCRγδ	Negative
CD4 / CD8	Usually negative or variable
Ki-67	Often high

EBER Interpretation in T-Cell Proliferations

- **Reactive Processes:**
  - Present in reactive immunoblasts.
- **Neoplastic Entities:**
  - **Extranodal NK/T-Cell Lymphoma**
  - **EBV-Positive Diffuse Large B-Cell Lymphoma (DLBCL)**
- **Microenvironmental Patterns:**
  - Commonly seen in the background B-cells of **TFH (Follicular Helper T-cell) Lymphomas**.

- **Important:** EBER positivity is not pathognomonic for a single entity.
- It must be interpreted based on the specific cell population that is positive.

Interpretation relies entirely on cellular identity and staining distribution; do not assume EBER status alone defines the malignancy.

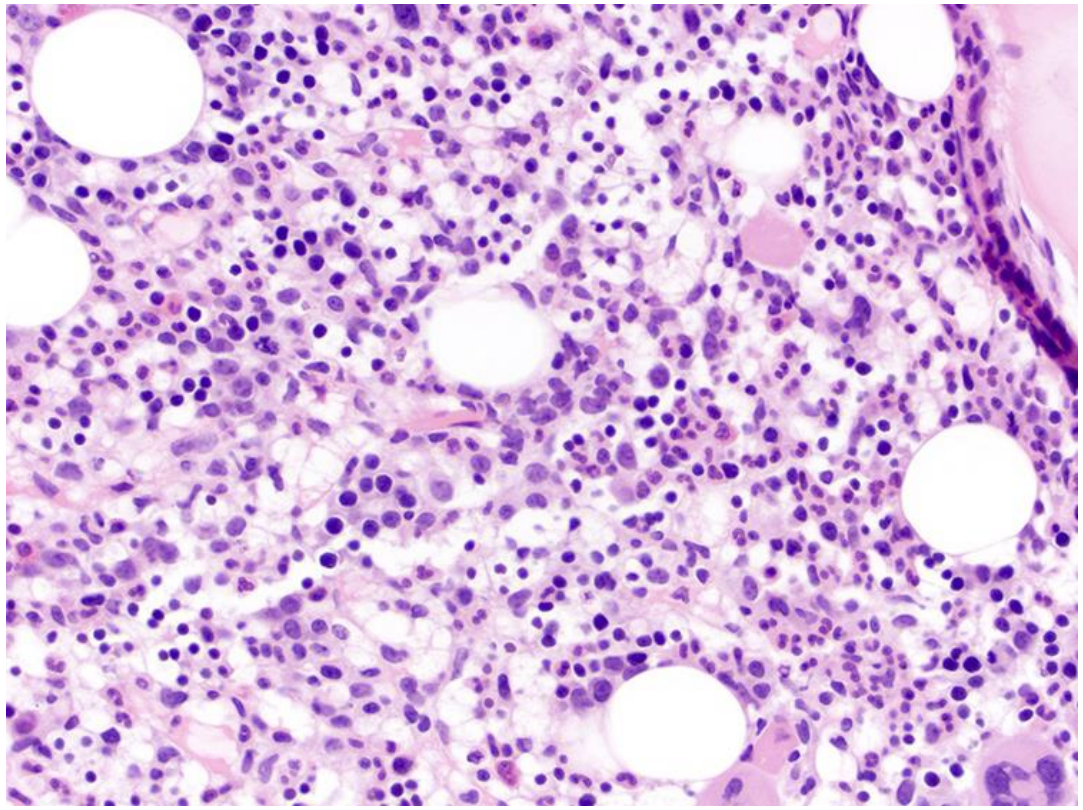
Hepatosplenic T-Cell Lymphoma (HSTCL)

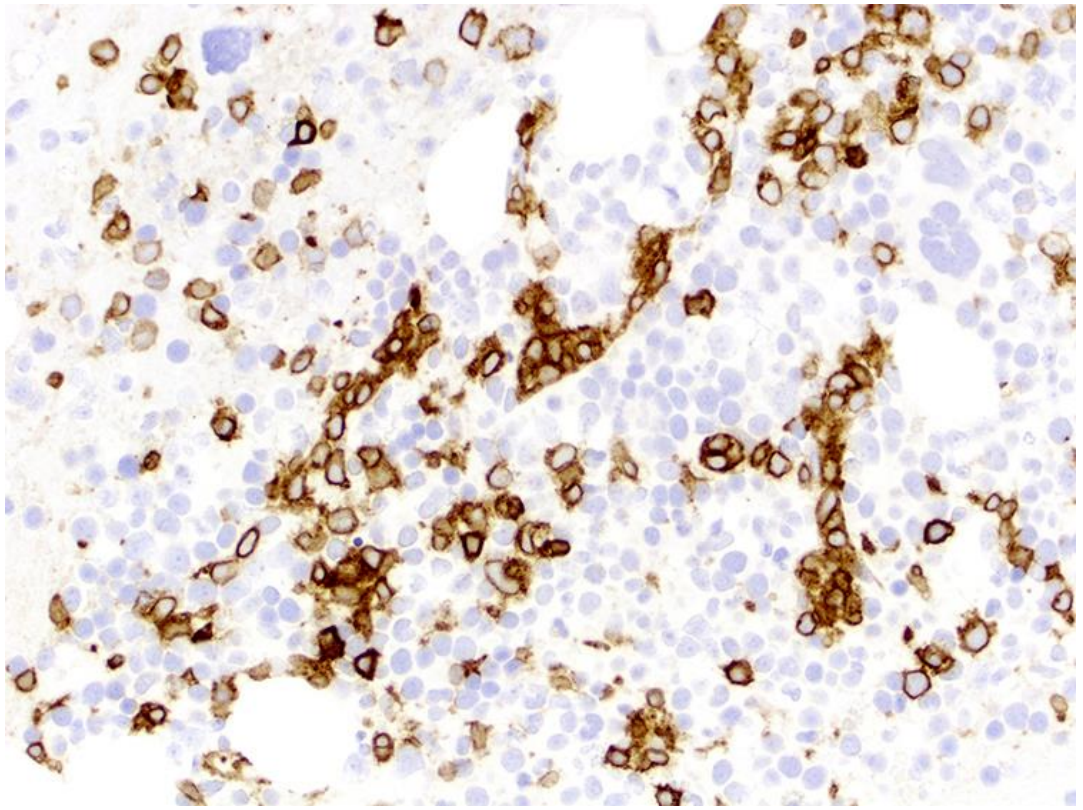
- **Clinical Features**
  - Young males
  - Chronic Immunosuppression
  - Hepatosplenomegaly
  - Cytopenias
  - Minimal lymphadenopathy
- **Characteristic Findings**
  - Sinusoidal infiltration
  - Bone marrow involvement
  - γδ T-cell phenotype common

- **Typical Immunophenotype**
  - CD3+
  - CD56+
  - TIA1+
  - Usually CD4− / CD8−

Intrasinusoidal infiltration is a major clue to HSTCL.

Hepatosplenic T-Cell Lymphoma (HSTCL)





PRACTICAL APPROACH TO INTESTINAL T-CELL LYMPHOMAS

- Key Questions
  - History of celiac disease?
  - Monomorphic or pleomorphic?
  - Epitheliotropism present?
  - CD8/CD56 status?
  - Cytotoxic phenotype present?

PRACTICAL APPROACH TO INTESTINAL T-CELL LYMPHOMAS

- Major Differential Diagnoses
  - EATL
  - MEITL
  - Intestinal TCL-NOS
  - Indolent GI T-cell LPD
- Practical Pearl:
  Clinical context and morphology are often more informative than immunophenotype alone.

MONOMORPHIC EPITHELIOTROPIC INTESTINAL T-CELL LYMPHOMA (MEITL)

- Key Morphologic Features
  - Monomorphic medium-sized cells
  - Marked epitheliotropism
  - Uniform cytology
  - Minimal inflammatory background
- Characteristic Pattern
  - Neoplastic lymphocytes infiltrate intestinal epithelium.
- Practical Pearl:
  - Monomorphic cells plus prominent epitheliotropism should immediately suggest MEITL.

MEITL IMMUNOPHENOTYPE

- Typical Profile
  - CD3+
  - CD8+
  - CD56+
  - TIA1+
  - Granzyme B+
- Usually Negative
  - CD30
  - TFH markers

- Clinical Feature
  - Usually NOT associated with celiac disease.
- Practical Pearl:
  - CD8-positive, CD56-positive cytotoxic intestinal lymphoma strongly favors MEITL.

ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA (EATL)

- Clinical Features
  - Strong association with celiac disease
  - Malabsorption
  - Weight loss
  - Abdominal pain
  - Intestinal perforation
- Morphology
  - Pleomorphic large cells
  - Inflammatory background
  - Tissue destruction
  - Necrosis

Practical Pearl:
EATL is the prototypical celiac-associated intestinal T-cell lymphoma.

EATL IMMUNOPHENOTYPE

- Typical Profile
  - CD3+
  - CD7+
  - Cytotoxic markers positive
- Variable
  - CD8
  - CD56
  - Often Positive
  - CD30

Practical Pearl:
CD30 positivity in an intestinal T-cell lymphoma favors EATL over MEITL.

EATL vs MEITL

Feature	EATL	MEITL
Cell of origin	Cytotoxic T-cell	Cytotoxic T-cell
Association with celiac disease	Strong	Usually absent
Clinical setting	Long-standing celiac disease	Sporadic
Morphology	Pleomorphic large cells	Monomorphic medium-sized cells
Inflammatory background	Prominent	Minimal
Necrosis	Common	Less prominent
Epitheliotropism	Present, variable	Marked
CD8	Variable	Positive
CD56	Usually negative	Positive
CD30	Often positive	Usually negative
Cytotoxic markers	Positive	Positive
Typical clue	Celiac disease + pleomorphic cells	Monomorphic cells + CD8+CD56+

REFRACTORY CELIAC DISEASE TYPE II (RCD-II)

- Key Concept
  - Premalignant precursor lesion of EATL.
- Morphology
  - Villous atrophy
  - Crypt hyperplasia
  - Increased IELs
  - No destructive mass lesion
- Immunophenotype
  - Surface CD3 loss
  - CD8 loss
  - Aberrant IEL population

Practical Pearl:
RCD-II is characterized by abnormal IELs without overt lymphoma.

RCD-II VS EATL

Feature	RCD-II	EATL
Mass lesion	Absent	Common
Cytologic atypia	Mild	Marked
Necrosis	Absent	Common
Tissue destruction	Minimal	Prominent
CD30	Usually negative	Often positive
Clinical significance	Precursor lesion	Overt lymphoma

Practical Pearl:
Transformation from RCD-II to EATL is accompanied by morphologic and immunophenotypic evolution

INDOLENT T-CELL LYMPHOPROLIFERATIVE DISORDER OF THE GI TRACT

- Clinical Features
  - Chronic symptoms
  - Persistent disease
  - Slow progression
- Morphology
  - Small mature lymphocytes
  - Minimal atypia
  - Non-destructive infiltrate
- Important Differential
  - Aggressive intestinal T-cell lymphoma
- Practical Pearl:
  - Do not overdiagnose indolent GI T-cell LPD as aggressive lymphoma.

PRACTICAL ALGORITHM: INTESTINAL T-CELL LYMPHOMAS

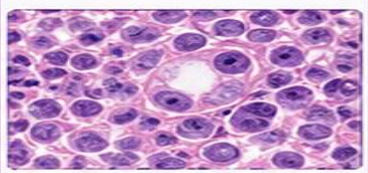
INTESTINAL T-CELL LESION

HISTORY OF CELIAC DISEASE?

- **YES**
- **NO / UNKNOWN**

PLEOMORPHIC LARGE CELLS → EATL

Enteropathy-Associated T-cell Lymphoma

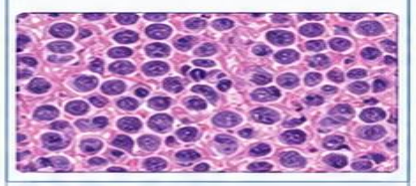


Key Features

- Large pleomorphic cells
- High-grade
- Associated with celiac disease (type I)
- Often CD8+, CD56+, cytotoxic+

MONOMORPHIC CELLS → MEITL

Monomorphic Epitheliotropic Intestinal T-cell Lymphoma

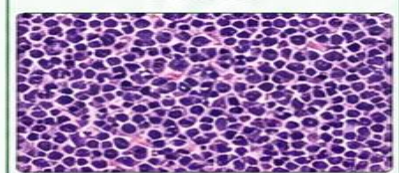


Key Features

- Medium-sized monomorphic cells
- Epitheliotropic
- Not associated with celiac disease
- Often CD8+, CD56−/+, cytotoxic+

SMALL MATURE CELLS → INDOLENT GI T-CELL LPD

Indolent Gastrointestinal T-cell Lymphoproliferative Disorder



Key Features

- Small mature lymphocytes
- Indolent behavior
- Nay be associated with celiac disease
- Usually CD8−/+, CD56−, cytotoxic+

EVALUATE IMMUNOPHENOTYPE

CD8

Usually positive in EATL and MEITL

- Supports cytotoxic T-cell origin

CD56

Frequently positive in EATL

- Associated with aggressive behavior

CD30

Variable expression (especially in EATL)

- May occasionally be positive in MEITL

Cytotoxic markers (TIA-1, Granzyme B, Perforin)

- Usually positive in EATL and MEITL

Celiac Disease Association

Strong: EATL > Indolent LPD
None: MEITL

Clinical Behavior

EATL: Aggressive
MEITL: Intermediate
Indolent LPD: Indolent

Pearl

Epitheliotropism + monomorphic cells in a patient without celiac disease → Think MEITL

TAKE-HOME MESSAGE

Morphology + Clinical Context (Celiac Disease) + Immunophenotype
= Accurate Classification of Intestinal T-cell Lymphomas

EATL: Enteropathy-Associated T-cell Lymphoma *MEITL: Monomorphic Epitheliotropic Intestinal T-cell Lymphoma* *LPD: Lymphoproliferative Disorder*

Major Diagnostic Pitfalls in T-Cell Pathology

Pitfall	Why Dangerous
CD30 positivity	Reactive immunoblasts
PD1 positivity	Reactive TFH cells
CD7 loss	May be reactive
EBER positivity	Background B-cells
Molecular clonality	May occur in reactive states

Core Principle

No isolated finding should override morphology and architecture.

🕸 T-cell pathology is one of the most context-dependent areas in hematopathology..

Practical Sign-Out Language

- **Avoid Overcalling**
- ❌ “Diagnostic of AITL”
- ✅ “Findings support nodal TFH lymphoma.”

- ❌ “Rules out lymphoma”
- ✅ “No definitive evidence of lymphoma identified.”

- ❌ “Consistent with ALCL”
- ✅ “Morphology and immunophenotype support ALCL.”

- **Expert hematopathology language reflects diagnostic confidence appropriately.**

Practical Reporting Principles in T-Cell Lymphomas

- **Key Reporting Goals**
  - Communicate diagnostic confidence clearly
  - Avoid overinterpretation
  - Correlate morphology with immunophenotype
  - Acknowledge limitations when necessary

- **Expert Reporting Style**
- Use:
  - “Supports”
  - “Favors”
  - “Consistent with”
- “In the appropriate clinicopathologic context”
- Avoid:
  - “Diagnostic of” when evidence is incomplete
  - “Rules out” when sensitivity is limited

Good hematopathology reporting is precise, cautious, and clinically useful.

FEATURE	T-PLL	ATLL	MF-SS	LGLL	HSTCL
Lymphocytosis	Marked (usually >100 × 10^9/L)	Marked	Mild to moderate	Mild (usually <15 × 10^9/L)	No*
Peripheral blood morphology	Prolymphocytic (most common), small lymphocytic, cerebriform	Pleomorphic nuclei, multilobated ("flower cell")	Cerebriform nuclei	Large azurophilic granules (cytoplasmic)	Intermediate-large size
Pattern in bone marrow	**Diffuse** (common), interstitial, nodular	Patchy, sparse (rarely diffuse)	**Uncommon in bone marrow**; small focal or interstitial, eosinophilia	Interstitial (small clusters), **intrasinusoidal**	**Intrasinusoidal**, interstitial
HSMegaly	Common	Variable	Rare*	Common	Common
LAP	Variable	Common	Common	Rare	Rare
Skin	Variable (dermal infiltrates)	Common	Common	—	—

★ * Rare: Organomegaly (MF-SS) is rare; Peripheral blood involvement (HSTCL) is typically absent.

FEATURE	T-PLL	ATLL	MF-SS	LGLL	HSTCL
Immunophenotype	$CD4^+/CD8^-$ (common); $CD4^+/CD8^+$, $CD4^-/CD8^+$	$CD4^+/CD8^-$	$CD4^+/CD8^-$	$CD4^-/CD8^+$ (common); $CD4^+/CD8^-$, $CD4^+/CD8^+$	$CD4^-/CD8^-$
	TCRαβ	TCRαβ	TCRαβ	TCRαβ	TCRγδ (common); TCRαβ (rare)
	$CD5^+$, $CD7^+$	$CD5^+$, usually $CD7^-$	$CD5^+$, usually $CD7^-$	CD7 variable	$CD5^-$, CD7 variable
	$CD26^+$	$CD26^-$, $CD25^{++}$	$CD26^-$	$CD26^-$	$CD26^-$
	NK marker negative, cytotoxic markers negative, $TCL1^+$	Cytotoxic markers negative	Cytotoxic markers negative	$CD57^+$, cytotoxic markers positive, $CD56^{+/-}$	$CD16^+$, $CD56^+$, TIA^+, perforin negative
Clinical course	Aggressive	Usually aggressive	Chronic	Indolent	Aggressive
Viral etiology	—	HTLV-1	—	—	—
Genetics	Rearrangements at 14q11.1 (*TCL1*, *TCL1B*)	Clonal integration of HTLV-1	Complex karyotypes, no unique	No unique abnormalities	iso7q, trisomy 8

Key Take-Home Messages
Major Principles

- T-cell lymphoma diagnosis is integrative
- Architecture is critically important
- No single marker is diagnostic
- Broad morphologic overlap exists with reactive conditions
- Pattern recognition is essential
- TFH lymphomas are microenvironment-rich neoplasms
- PTCL-NOS is a diagnosis of exclusion

🛑 Always interpret immunostains in morphologic and clinical context.

thank you