

Peripheral T- and NK-Cell Neoplasms

Mature T-cell and natural killer-cell lymphoid malignancies

Morphology • immunophenotype • mechanisms • clinicopathologic reasoning

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Learning outcomes

- Distinguish mature T-cell from NK-cell neoplasms using lineage, site, and phenotype.
- Recognize the morphologic and clinical profile of PTCL-NOS.
- Explain Tfh-associated immune dysregulation, ALK signaling, and HTLV-1 oncogenesis.
- Compare cutaneous, leukemic, and extranodal presentations.

A heterogeneous mature lymphoid group

- These neoplasms resemble mature peripheral T cells or natural killer (NK) cells.
- Multiple entities are defined by distinct tissue tropism, phenotype, viral association, or molecular lesions.
- A generic diagnosis must not displace a specific entity supported by clinicopathologic evidence.

Geographic distribution

United States and Europe

- Peripheral T-cell tumors represent approximately 5%–10% of non-Hodgkin lymphomas.
- NK-cell tumors are distinctly uncommon.

East Asia

- Both T- and NK-cell neoplasms occur more frequently.
- The basis for this geographic difference is uncertain.

Cellular lineage establishes the first branch

Mature lymphoid neoplasm



T-cell lineage: CD3 / TCR



NK lineage: NK markers; Usually no surface CD3



Entity-specific morphology and clinical context

Mature T cells and NK cells

Peripheral T cells

- Rearranged T-cell receptor genes.
- Typical T-lineage antigens include CD2, CD3 and CD5.
- Helper or cytotoxic subsets may express CD4 or CD8.

Natural killer cells

- Cytotoxic innate lymphocytes; No conventional rearranged TCR.
- NK-cell neoplasms may express markers including CD56.
- Lineage interpretation uses a panel, not CD56 alone.

Mature versus precursor T-cell tumors

- “Peripheral” refers to a mature/post-thymic T-cell phenotype.
- T-lymphoblastic leukemia/lymphoma belongs to precursor lymphoid neoplasms, not this group.
- Morphology and differentiation antigens must be interpreted together.

Tissue distribution guides the differential

Generalized nodes → nodal T-cell lymphoma



Skin → MF / Sézary; Also other subtypes



Blood + cytopenias → T/NK large granular lymphocytic leukemia



Nasal destructive mass → extranodal NK/T-cell lymphoma

Nodal architecture carries diagnostic information

- Diffuse architectural effacement favors an overt infiltrative lymphoma over preserved reactive architecture.
- Pleomorphic tumor cells and a conspicuous inflammatory stroma may coexist.
- Patterns involving follicles, vessels, sinuses, or skin help prioritize defined entities.

Integrated diagnostic reasoning

Clinical syndrome / sites



Architecture and cytology



T/NK lineage and subtype markers



Viral or molecular support



Integrated disease assignment

What each modality contributes

Evidence	Interpretive question
H&E morphology	Is there an abnormal infiltrate; What architecture is altered?
Immunophenotype	Which lineage and differentiation program is represented?
TCR clonality	Is an expanded T-cell clone detectable?
Clinical / virology	Does the distribution or virus association define an entity?

T-cell clonality: Appropriate role

- Clonal T-cell receptor rearrangements can support lymphoma in difficult reactive-versus-neoplastic cases.
- TCR analysis does not identify all NK-derived tumors, which usually lack rearranged TCR genes.
- A clonal result requires interpretation alongside morphology, immunophenotype, and clinical context.

Recognizable signatures across the family

Entity	Characteristic association
PTCL-NOS	Pleomorphic nodal T-cell infiltrate; Diagnosis after exclusion
Nodal Tfh lymphoma	Tfh phenotype, immune dysregulation, clonal hematopoiesis
ALCL	CD30-rich anaplastic morphology; ALK rearrangement in subset
Adult T-cell leukemia/lymphoma	HTLV-1 associated CD4+ mature T-cell tumor
Extranodal NK/T lymphoma	EBV association, angiodestruction and necrosis

PTCL-NOS is a diagnosis of exclusion

- Many mature T-cell lymphomas cannot be assigned confidently to a defined subtype.
- These cases are designated peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).
- The category is biologically and morphologically heterogeneous; No single feature is pathognomonic.

Why “NOS” comes late, not early

Confirm malignant mature T-cell process



Assess Tfh, ALCL, cutaneous and leukemic patterns



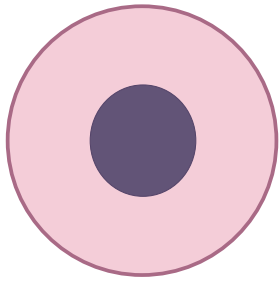
Evaluate relevant viral and tissue associations



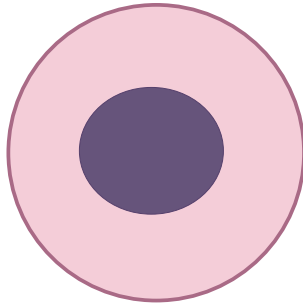
Retain PTCL-NOS when a specific entity is unsupported

PTCL-NOS: Cytologic heterogeneity

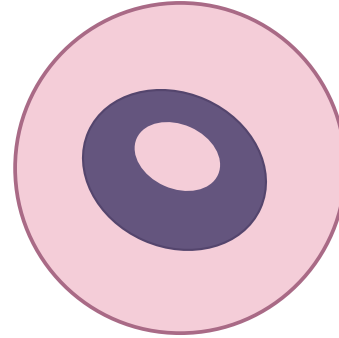
Schematic only — not a microscopic specimen



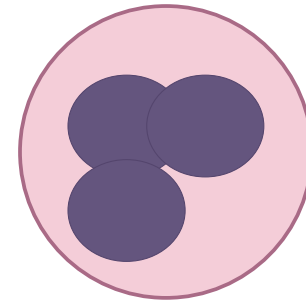
Small cell



Intermediate cell



Large pleomorphic cell



**Irregular nuclear
contour**

Size heterogeneity is characteristic but not diagnostic.

Illustrated cell shapes are schematic—not a histologic field.

PTCL-NOS effaces nodal architecture

- Lymph nodes are typically replaced by a diffuse malignant T-cell infiltrate.
- A full low-power view helps assess loss of normal follicles and sinus structures.
- The extent of architectural destruction must be reconciled with the clinical presentation.

Why the infiltrate looks mixed

- Malignant cells vary substantially in size and shape.
- Reactive eosinophils, macrophages and other inflammatory cells may be conspicuous.
- A polymorphous infiltrate should not be presumed reactive solely because many bystander cells are present.

Tumor cytokines and the reactive background

Malignant T-cell population



Tumor-derived cytokines (proposed)



Recruitment of eosinophils and macrophages



Prominent reactive inflammatory stroma

PTCL-NOS may exhibit neoangiogenesis

- Brisk formation of new vessels may accompany the infiltrate.
- Vascular proliferation can contribute to architectural distortion.
- Neither vascularity nor inflammatory background alone is specific for PTCL-NOS.

T-lineage immunophenotype in PTCL-NOS

Feature	Robbins description
Mature T-cell markers	Usually CD2, CD3 and CD5
T-cell receptor	$\alpha\beta$ or $\gamma\delta$ receptor expression
Helper / cytotoxic markers	Some tumors express CD4 or CD8
Phenotypic variation	Some tumors do not resemble a recognized normal T-cell subset

A practical marker hierarchy

Establish T lineage: CD2 / CD3 / CD5



Assess CD4 and CD8 pattern



Characterize TCR phenotype when informative



Investigate competing defined entities

CD4 and CD8 suggest functional origin

- CD4 expression is compatible with a helper T-cell differentiation program.
- CD8 expression is compatible with cytotoxic T-cell differentiation.
- Some mature T-cell tumors show aberrant or unclassifiable phenotypes.

T-cell receptors: $\alpha\beta$ versus $\gamma\delta$

- Normal mature T cells can express $\alpha\beta$ or $\gamma\delta$ T-cell receptors.
- PTCL-NOS may retain either receptor phenotype.
- A receptor category does not replace evaluation for other defined mature T-cell entities.

PTCL-NOS and a reactive lymph node

Concern for lymphoma

- Diffuse effacement with atypical pleomorphic T cells.
- An abnormal T-cell population and supportive clonality.
- Unexplained systemic lymphadenopathy.

Concern for reactivity

- Clinical or infectious trigger with reactive architecture.
- Heterogeneous activated T cells without a coherent neoplastic pattern.
- Results of ancillary tests must be interpreted in context.

Ancillary work-up when morphology is equivocal

Reassess architecture and distribution



Examine the complete lineage/subtype panel



Consider TCR gene rearrangement study



Integrate molecular and clinical evidence

Typical clinical presentation of PTCL-NOS

- Generalized lymphadenopathy is common.
- Pruritus, eosinophilia, fever and weight loss may accompany disease.
- Symptoms may reflect inflammatory cytokines as well as tumor burden.

Symptoms linked to underlying processes

Lymphoma burden

- Multiple enlarged nodal groups.
- Systemic symptoms such as fever and weight loss.

Reactive and immune effects

- Eosinophilia and pruritus.
- Macrophage/eosinophil-rich histology supports an inflammatory milieu.

PTCL-NOS: Prognosis in context

- Durable cures can occur.
- As a group, peripheral T-cell lymphomas have a worse outcome than comparably aggressive mature B-cell lymphomas.
- Prognosis must not be inferred from a single morphologic feature.

PTCL-NOS and diffuse large B-cell lymphoma

Axis	PTCL-NOS	DLBCL
Lineage	Mature T cell	Mature B cell
Microscopy	Variable pleomorphism; Often reactive admixture	Large B-cell lymphoma phenotype
Ancillary tests	T-cell markers / TCR studies	B-cell markers
Robbins prognosis	Overall less favorable	Comparator mature B-cell lymphoma

Case: Pleomorphic nodal infiltrate

A patient has generalized lymphadenopathy; Biopsy shows diffuse effacement by irregular, variably sized lymphoid cells. Eosinophils are conspicuous.

Salient evidence

- Mature T-cell antigen expression
- No defining features for another specific T-cell entity
- TCR rearrangement found on ancillary analysis

Peripheral T-cell lymphoma, NOS

A clonally expanded mature T-cell infiltrate with pleomorphism may support PTCL-NOS after exclusion of defined categories.

PTCL-NOS: Report the evidence, not a shortcut

- State architectural pattern and the degree of cytologic atypia.
- Summarize mature T-cell phenotype and any aberrancies established by the actual panel.
- Record why a more specific mature T-cell lymphoma is or is not supported.

Tfh cells normally support germinal-center B cells

- T-follicular helper (Tfh) cells home to germinal centers.
- They promote B-cell expansion and affinity maturation.
- Neoplastic distortion of this interaction underlies prominent immune abnormalities.

Nodal Tfh lymphoma links two compartments

Neoplastic Tfh cell



Disturbed germinal-center B-cell maturation



Hypergammaglobulinemia / autoantibodies



Autoimmune cytopenias and immune dysfunction

Clonal hematopoiesis is a key Tfh association

- Nodal Tfh lymphoma often coexists with clonal hematopoiesis.
- TET2 and DNMT3A mutations are found in both settings.
- Shared mutations in lymphoma and myeloid cells support origin from an early mutated hematopoietic stem cell.

Proposed shared precursor in Tfh lymphoma

Mutated hematopoietic stem cell



Myeloid descendants sharing mutations



Tfh-lineage malignant descendant



Occasionally EBV-positive B-cell neoplasm sharing mutations

Tfh-associated immune dysregulation

- Hypergammaglobulinemia may reflect distorted B-cell help.
- Autoantibody formation can produce autoimmune cytopenias.
- Immune dysfunction can also predispose to infections and EBV-positive B-cell expansions.

EBV-positive B cells in Tfh lymphoma

- Nodal Tfh lymphomas frequently contain increased EBV-positive immunoblasts.
- Occasional patients develop overt EBV-positive B-cell lymphoma.
- The associated B-cell proliferation should not be mistaken automatically for the malignant T-cell clone.

Tfh markers: Interpret as a program

Markers	Interpretation
PD-1, CXCL13, CXCR5	Tfh-associated differentiation markers
CD10, BCL6	Additional Tfh-associated markers
CD4	Common neoplastic T-cell phenotype
Follicular dendritic expansion	Supportive architectural context

Nodal Tfh lymphoma: Architecture

- Vaguely nodular or follicular-appearing T-cell aggregates may develop.
- Follicular dendritic-cell networks can expand.
- Increased vascularity and EBV-positive immunoblasts commonly occupy intervening tissue.

Nodal Tfh lymphoma: Clinical behavior

- Most affected patients are older adults and present with lymphadenopathy.
- Clinical manifestations may be driven by immune abnormalities or inflammatory cytokines.
- Chemotherapy responses are often transient; Long-term outcome is generally unfavorable.

ALK-positive ALCL has a defining kinase lesion

- ALK rearrangements at chromosome 2p23 create chimeric genes.
- The resulting fusion proteins are constitutively active tyrosine kinases.
- This molecular lesion provides a strong diagnostic marker and a potential therapeutic target.

ALK fusion drives proliferative signaling

ALK gene rearrangement



Constitutively active ALK fusion kinase



RAS and JAK/STAT signaling



Growth and survival of lymphoma cells

ALCL: Hallmark cells and growth pattern

- Large anaplastic cells have abundant cytoplasm and markedly atypical nuclei.
- Some cells display horseshoe-shaped or embryoid nuclei (hallmark cells).
- Tumor cells often cluster around venules or infiltrate lymphoid sinuses.
- The epithelial-like arrangement can mimic metastatic carcinoma.

Why ALCL can resemble carcinoma

- Large anaplastic cells sometimes infiltrate lymphoid sinuses.
- Perivenular clustering can amplify the epithelioid appearance.
- The immunophenotypic work-up is essential when morphology is misleading.

ALK immunostaining is mechanistically meaningful

- Normal lymphocytes lack ALK protein expression.
- Tumor-cell ALK staining strongly supports the presence of an ALK fusion.
- ALK staining should be interpreted together with large-cell morphology and CD30.

ALK-positive versus ALK-negative ALCL

Aspect	ALK-positive	ALK-negative
ALK alteration / stain	Rearranged / positive	Absent / negative
Typical age	Children / young adults	Usually older adults
General outcome	Relatively favorable	Substantially worse
CD30	Usually expressed	Usually expressed

CD30: A shared target, not a lineage test

- Both ALK-positive and ALK-negative ALCL usually express CD30.
- CD30 is a member of the tumor necrosis factor receptor family.
- CD30-targeted antibody–drug conjugates have antitumor activity in CD30-positive lymphomas.

ALK-positive ALCL is an outcome exception

- This subtype often occurs in younger patients and may involve soft tissues.
- Chemotherapy cure rates around 75%–80%.
- ALK inhibitors can be effective when conventional chemotherapy fails.

Case: Large atypical cells in nodal sinuses

A young adult has a soft-tissue mass; Large anaplastic cells show horseshoe-shaped nuclei and grow around venules.

Salient evidence

- Strong tumor-cell CD30 positivity
- Tumor-cell ALK expression
- Morphology raises metastatic carcinoma in the differential

ALK-positive anaplastic large-cell lymphoma

ALK expression connects the characteristic tumor morphology to an ALK rearrangement and explains targeted inhibitor activity.

Adult T-cell leukemia/lymphoma is HTLV-1 linked

- ATLL is a neoplasm of mature CD4-positive T cells.
- The disease occurs in adults infected with human T-cell leukemia virus type 1 (HTLV-1).
- All tumor cells contain clonally integrated HTLV-1 proviral material.

HTLV-1 endemic settings

Regions emphasized

- Southern Japan
- West Africa
- Caribbean basin

Clinicopathologic relevance

- Exposure history supports diagnostic suspicion.
- Infection is necessary description but transformation is uncommon.
- Geography is a clue, not evidence of malignancy.

HTLV-1 infection and prolonged latency

HTLV-1 infection



Long asymptomatic latent interval



Additional oncogenic alterations



Adult T-cell leukemia/lymphoma in a minority

Clonal provirus supports a direct viral role

- Identical proviral integration is present in the tumor-cell population.
- This observation supports expansion of an infected progenitor clone.
- The transformation process remains incompletely understood despite viral protein studies.

ATLL accumulates additional genetic lesions

- Aggressive ATLL commonly carries acquired tumor-suppressor alterations.
- TP53 and CDKN2A, as well as chromosomal copy-number changes.
- Viral infection alone does not explain why only a small fraction of carriers develop disease.

ATLL: “flower” or “cloverleaf” nuclei

- Blood and tissue tumor cells can have strikingly multilobated nuclei.
- The “flower” or “cloverleaf” description reflects irregular nuclear contours.
- Morphology is variable: Not every ATLL cell has this appearance.
- Confirm the HTLV-1-associated clinicopathologic context rather than relying on a cell silhouette.

ATLL involves blood, nodes, skin and organs

- Peripheral blood lymphocytosis may occur.
- Generalized lymphadenopathy and hepatosplenomegaly are frequent.
- Skin lesions may be conspicuous at presentation.

Hypercalcemia is a notable ATLL clue

- Hypercalcemia is among the characteristic clinical findings.
- It should raise suspicion when combined with lymphocytosis, cutaneous lesions and endemic exposure.
- The supplied Robbins passage does not specify a complete mechanism for this finding.

ATLL: Common manifestations and their correlates

Finding	Clinicopathologic interpretation
Lymphocytosis	Circulating malignant T cells
Nodal / splenic enlargement	Tumor infiltration
Skin lesions	Cutaneous involvement
Hypercalcemia	Important metabolic complication
“Flower” cells	Characteristic, variable cytology

ATLL: Aggressive and less aggressive patterns

- Most patients develop rapidly progressive disease.
- Many aggressive cases as fatal within months to approximately one year despite intensive chemotherapy.
- Less commonly, predominantly cutaneous disease can follow a more indolent course.

Why ATLL and MF are not interchangeable

Adult T-cell leukemia/lymphoma

- Associated with HTLV-1 infection.
- Often involves blood and systemic organs.
- Flower-cell morphology may be present.

Mycosis fungoides

- Cutaneous-homing mature CD4 T-cell neoplasm.
- Often remains clinically skin-limited for prolonged periods.
- Characteristic epidermal infiltration and cerebriform nuclei.

Case: Lymphocytosis with hypercalcemia

An adult from an HTLV-1 endemic region has lymphocytosis, skin lesions, generalized lymphadenopathy and hypercalcemia.

Salient evidence

- Blood smear shows markedly lobulated nuclei
- Mature CD4-positive T-cell phenotype
- Evidence of HTLV-1 infection

Adult T-cell leukemia/lymphoma

The combination of viral setting, systemic syndrome and mature T-cell tumor phenotype is characteristic.

Mycosis fungoides: Skin-homing T-cell neoplasm

- A neoplasm of CD4-positive helper T cells that preferentially localizes to the skin.
- Cutaneous lymphocyte antigen and CCR4 contribute to this tropism.
- Clinical evolution may include patch/inflammatory, plaque and tumor stages.

Mycosis fungoides: Morphology and course

- Epidermis and upper dermis may be infiltrated by atypical T cells.
- Tumor nuclei may be cerebriform because of nuclear membrane infolding.
- Clinical disease often remains skin-limited for prolonged periods despite detectable systemic circulation.

Mycosis fungoides versus Sézary syndrome

Dimension	Mycosis fungoides	Sézary syndrome
Typical skin pattern	Patches → plaques → possible tumors	Diffuse exfoliative erythroderma
Peripheral blood	Overt leukemia usually late	Characteristic leukemic involvement
Lymphadenopathy	Variable; Often later	Generalized
Course	Often prolonged / indolent	More aggressive

Large granular lymphocytic leukemia

- A tumor of cytotoxic T cells or NK cells, usually arising in adults.
- Peripheral blood cells have pale cytoplasm and coarse azurophilic granules.
- T-cell variants express surface CD3; NK-cell variants lack surface CD3 and can express CD56.

STAT3 mutations in LGL leukemia

Acquired activating STAT3 mutation



Cytokine-independent STAT3 signaling



Persistent cytotoxic lymphocyte clone



Immune dysregulation and cytopenias

LGL leukemia: Cytopenias dominate

- Neutropenia and anemia often dominate even when marrow infiltration is sparse.
- Autoimmune features and rheumatologic disorders may coexist.
- Some patients with Felty syndrome have an underlying LGL proliferation.

Extranodal NK/T lymphoma: Destructive anatomy

- Often presents as a destructive nasopharyngeal mass.
- Malignant cells surround and invade small vessels.
- Vascular damage leads to ischemia and extensive necrosis.

Angioinvasion explains tissue destruction

NK/T-cell malignant infiltrate



Invasion of small vessels



Ischemic injury



Extensive necrosis and destructive local mass

Extranodal NK/T lymphoma: EBV and lineage

- Strongly associated with Epstein–Barr virus infection.
- Identical EBV episomes in tumor cells support clonal derivation from one infected cell.
- Most cases lack surface CD3 and TCR rearrangements and express NK-cell markers.

Extranodal NK/T lymphoma: Clinical implications

- This neoplasm is more common in Asia than in the United States or Europe.
- Many tumors respond to radiotherapy but are relatively chemotherapy resistant.
- Advanced-stage disease generally has a poor outcome.

Disease-defining biologic associations

Disease	Anchor association
PTCL-NOS	No pathognomonic marker; Exclusion of defined entities
Nodal Tfh lymphoma	Tfh program; TET2/DNMT3A and clonal hematopoiesis
ALK-positive ALCL	ALK rearrangement → active kinase
Adult T-cell leukemia/lymphoma	HTLV-1 proviral infection
Extranodal NK/T lymphoma	EBV and an angioinvasive destructive pattern

Clinical syndrome as a diagnostic pointer

Presentation	Consider first
Generalized nodes + pleomorphism	PTCL-NOS; Nodal Tfh lymphoma
Nodes + immune abnormalities / autoantibodies	Nodal Tfh lymphoma
Younger patient + large CD30-positive cells	ALK-positive ALCL
HTLV-1 exposure + blood cells + hypercalcemia	Adult T-cell leukemia/lymphoma
Erythroderma with leukemic T cells	Sézary syndrome
Neutropenia + granulated lymphocytes	LGL leukemia
Destructive nasal lesion	Extranodal NK/T-cell lymphoma

A mature T/NK work-up: Avoid common pitfalls

Begin with complete biopsy and syndrome



Resolve T-cell versus NK-cell lineage



Seek entity-defining phenotype / viral association



Use clonality selectively for equivocal processes



Integrate findings; Retain NOS only if required

Integrated case: Immune dysregulation

An older adult has generalized lymphadenopathy, autoimmune cytopenia and hypergammaglobulinemia. The node has prominent vessels and follicular dendritic expansion.

Salient evidence

- Abnormal CD4 T cells express PD-1 and CXCL13
- EBV-positive reactive B immunoblasts are present
- TET2 mutation also detected in a myeloid compartment

Nodal T-follicular helper cell lymphoma

The Tfh program, immune disturbance and shared clonal hematopoiesis are mutually reinforcing.

Integrated case: Destructive nasal mass

A patient presents with an ulcerative destructive nasopharyngeal lesion. Biopsy shows an atypical lymphoid infiltrate centered on vessels with extensive necrosis.

Salient evidence

- Tumor cells express NK-associated markers
- No surface CD3 or rearranged TCR demonstrated
- EBV is present in the tumor cells

Extranodal NK/T-cell lymphoma

Vascular injury explains necrosis; EBV association and NK phenotype help resolve lineage.

Interpret common stains in the correct order

- CD3/CD2/CD5 establish a mature T-cell context when appropriately expressed.
- Tfh markers, ALK and CD30 can redirect classification toward defined entities.
- NK markers and EBV studies become particularly important in destructive extranodal lesions.
- No individual marker should overrule tissue distribution and architecture.

Why the same lineage has different clinical courses

Indolent / prolonged patterns

- Mycosis fungoides may remain skin-limited for years.
- T-cell LGL leukemia is often dominated by chronic cytopenias.

Aggressive patterns

- PTCL-NOS and nodal Tfh lymphoma frequently have adverse outcomes.
- ATLL and advanced extranodal NK/T lymphoma often behave aggressively.
- ALK-positive ALCL is an important relatively favorable exception.

Four durable diagnostic principles

- Classify the mature lymphoid lineage before assigning a subtype.
- Explain the morphology: vascular injury, reactive recruitment, or tissue homing.
- Use entity-defining viral and molecular associations only where actually present.
- Reserve PTCL-NOS for cases not meeting a more specific disease definition.