

Large Granular Lymphocytic Leukemia

Disease biology • Morphology • Diagnostic integration • Clinicopathologic relevance

A mature cytotoxic lymphocyte neoplasm

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Learning outcomes

- Recognize the cytologic and tissue features of LGL leukemia.
- Explain STAT3 activation and the paradox of severe cytopenias with limited infiltration.
- Distinguish T-cell and NK-cell disease using immunophenotype and lineage-aware testing.
- Integrate neutropenia, anemia, rheumatologic disease, and relevant mimics.

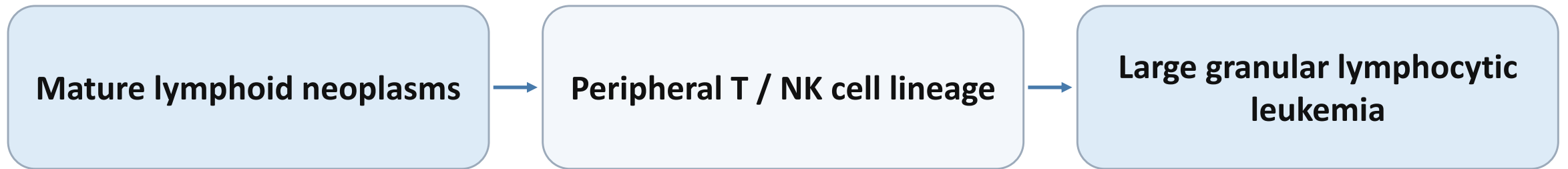
A low-grade leukemia with major clinical consequences

Clonal cytotoxic Lymphocytes

Three defining features

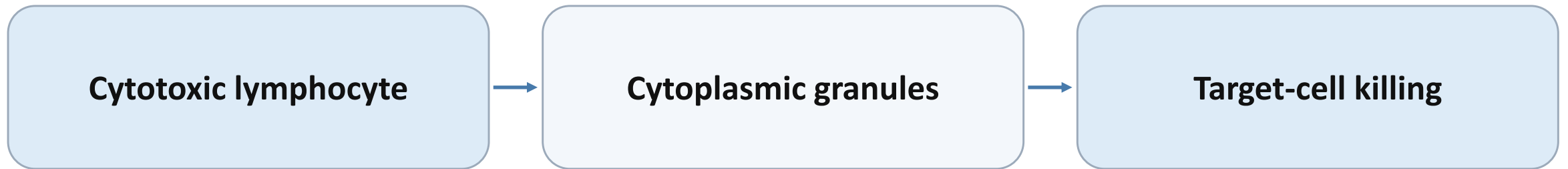
- An adult-predominant mature lymphoid proliferation
- T-cell and NK-cell lineages are recognized
- Cytopenias and autoimmunity may be prominent

Where this disease fits



In contrast to rapidly growing lymphoid tumors, a relatively low burden of infiltrating cells can coexist with clinically important cytopenia.

Normal large granular lymphocytes have a cytotoxic role



“Large granular lymphocyte” describes morphology; Benign activated cytotoxic lymphocytes may also appear granular.

Reactive expansion is not automatically leukemia

Reactive granular lymphocytes

Expansion may follow immune stimulation

Often polyclonal and transient

Interpret in its clinical context

LGL leukemia

Sustained cytotoxic-cell population

Often demonstrable clonal restriction

Link clone to symptoms and cytopenia

Two major lineages

T-cell LGL leukemia

Derived from mature T cells

Surface CD3 positive

Often has lymphocytosis and splenomegaly

NK-cell LGL leukemia

Derived from NK cells

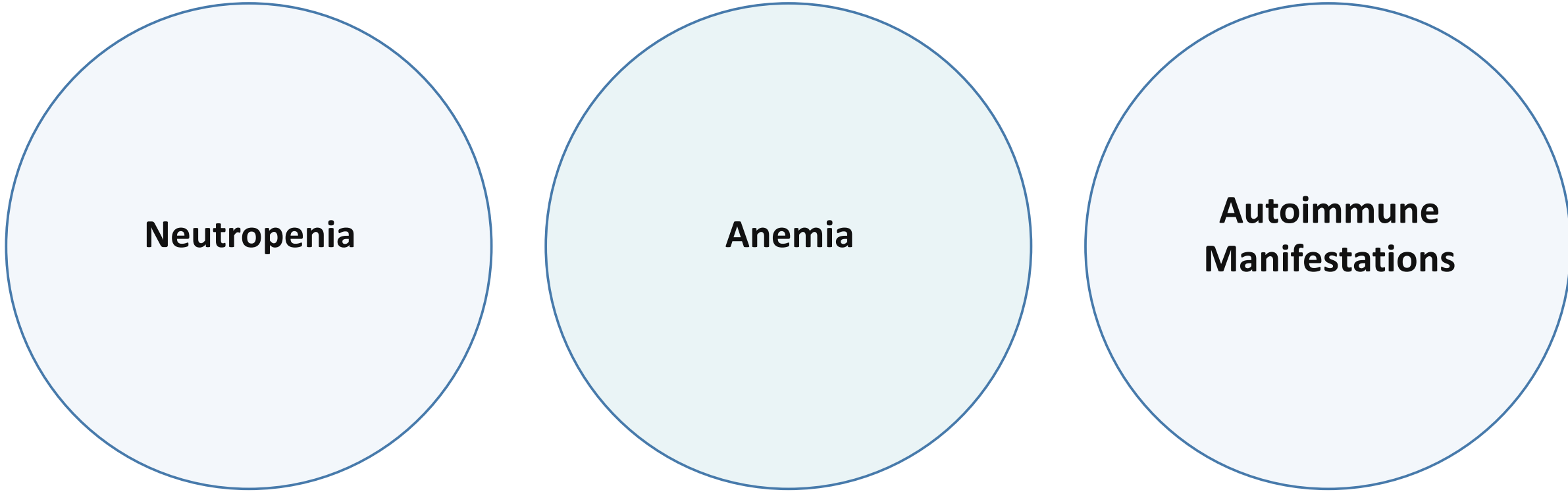
Surface CD3 negative

Can have minimal lymphocytosis or splenic enlargement

Typical age and clinical tempo

- Both recognized forms occur mainly in adults.
- The textbook characterizes the overall proliferation as uncommon.
- Clinical presentation ranges from subtle detection to symptomatic cytopenias.

The presenting phenotype can be recognized clinically



The diagram consists of three light blue circles arranged horizontally. Each circle contains a clinical term in bold black text. The first circle on the left is labeled 'Neutropenia', the middle circle is labeled 'Anemia', and the third circle on the right is labeled 'Autoimmune Manifestations'.

Neutropenia

Anemia

**Autoimmune
Manifestations**

Typical T-cell presentation

- Mild-to-moderate lymphocytosis is common.
- Splenomegaly is a characteristic associated finding.
- The dominant clinical threat may still be neutropenia or anemia.

NK-cell disease can be difficult to detect clinically

- Peripheral lymphocyte count may show little or no elevation.
- Splenomegaly may be minimal or absent.
- A normal or only mildly elevated lymphocyte count does not eliminate suspicion.

Findings that are present versus commonly absent

Commonly encountered

Neutropenia / anemia

Granular cells on smear

Splenomegaly in T-cell disease

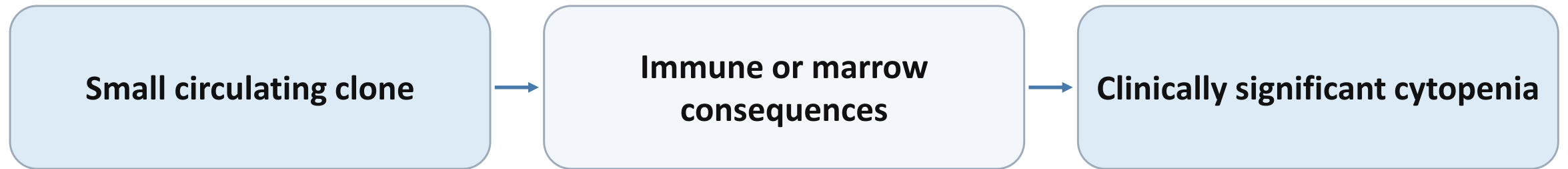
Often absent

Large lymph nodes

Clinically obvious liver enlargement

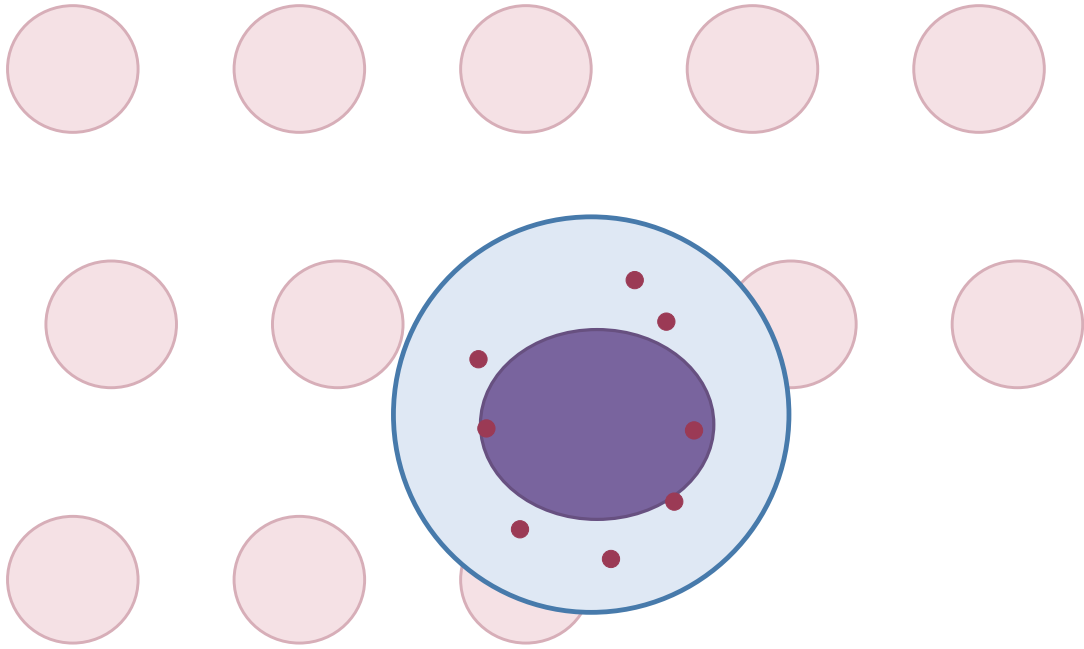
Marked mass-forming disease

Why an indolent neoplasm may present abruptly



A small neoplastic infiltrate does not reliably predict the severity of peripheral blood abnormalities.

Classic peripheral blood appearance



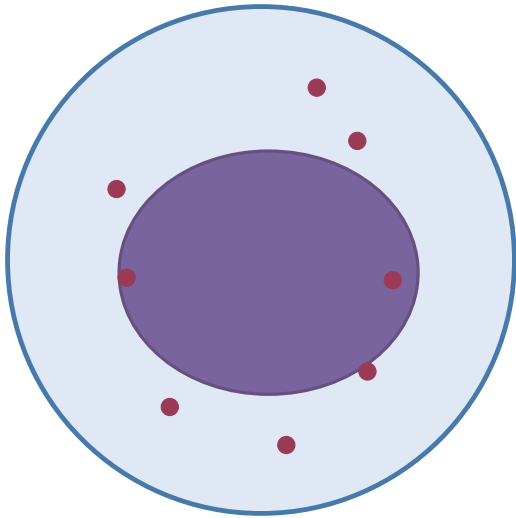
Large, mature-appearing lymphocyte

Pale blue cytoplasm

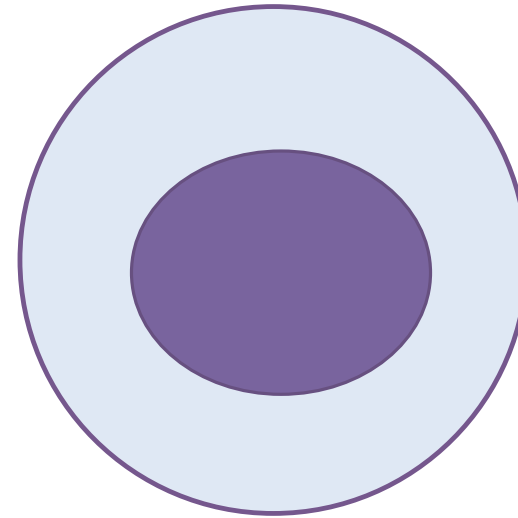
Coarse azurophilic granules

Original schematic — not a diagnostic blood smear

Granules are helpful—but not diagnostic



Granular cytotoxic lymphocyte



Simplified lymphocyte without granules

Schematic comparison; Morphology alone cannot establish lineage or clonality

How to describe the neoplastic cell

- A relatively large, mature-appearing lymphocyte.
- Abundant pale-blue cytoplasm.
- A small number of coarse azurophilic cytoplasmic granules.
- Peripheral blood smear provides the clearest morphologic view.

What the granules signify

- Azurophilic granules are a conspicuous cytotoxic-cell feature.
- Their presence supports the LGL morphology.
- The smear alone cannot classify the cell as T versus NK or prove neoplasia.

Blood, marrow, spleen, and liver show different patterns

Peripheral blood

Often conspicuous cytoplasmic granules

Bone marrow

Sparse interstitial cells may be overlooked

Spleen

May be enlarged; Subtle infiltrate

Liver

Sparse infiltrate; Hepatomegaly often absent

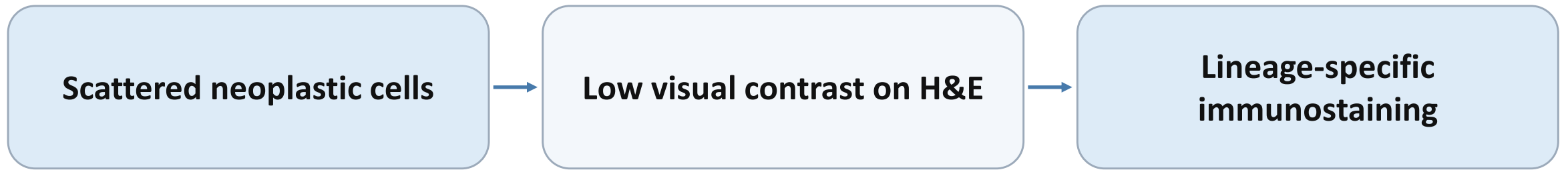
Marrow disease may be deceptively subtle

Sparse interstitial Infiltrates

The diagnostic paradox

- The infiltrate can be difficult to appreciate on routine morphology.
- Immunohistochemistry increases visibility of the neoplastic population.
- Cytopenia severity may exceed the apparent infiltrative burden.

Why immunohistochemistry can reveal marrow disease



This schematic explains detection strategy; It is not a histologic specimen.

Surface CD3 is the essential lineage fork

T-cell disease

Surface CD3 positive

T-cell markers support lineage

May be tested for TCR clonality

NK-cell disease

Surface CD3 negative

NK markers such as CD56 support lineage

TCR rearrangement is not the appropriate NK clone test

Typical expanded T- versus NK-phenotypes

T-LGLL

CD3+; Often CD8+

CD57 often positive

TCR clonality assessment

NK-LGLL

Surface CD3–; Often CD16+

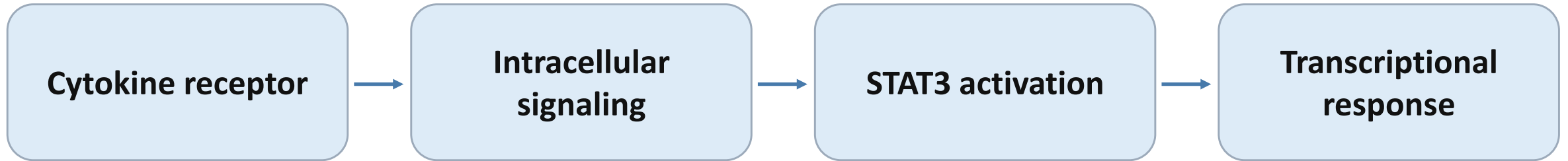
CD56 may be expressed

NK repertoire / KIR restriction can support clonality

Avoid single-marker diagnosis

- CD3 determines T-lineage in the standard setting; CD56 alone is not sufficient.
- CD8, CD16, CD56, and CD57 patterns have exceptions.
- A coherent cytotoxic phenotype must be integrated with morphology and clinical context.

Physiologic placement of STAT3 downstream of cytokines

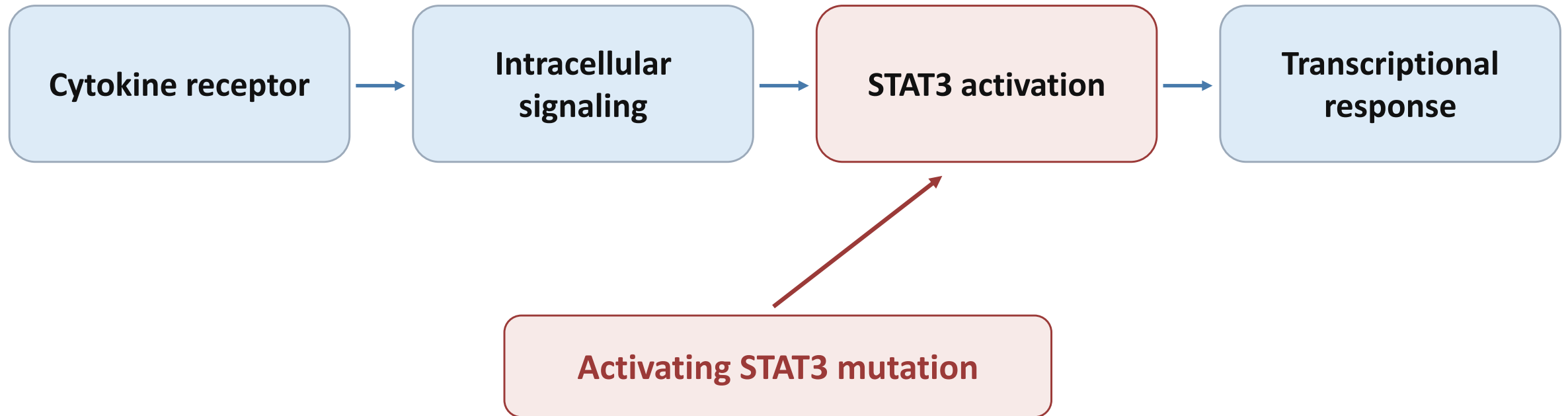


STAT3 functions downstream of cytokine receptors in normal cell signaling.

STAT3 mutations are recurrent but not universal

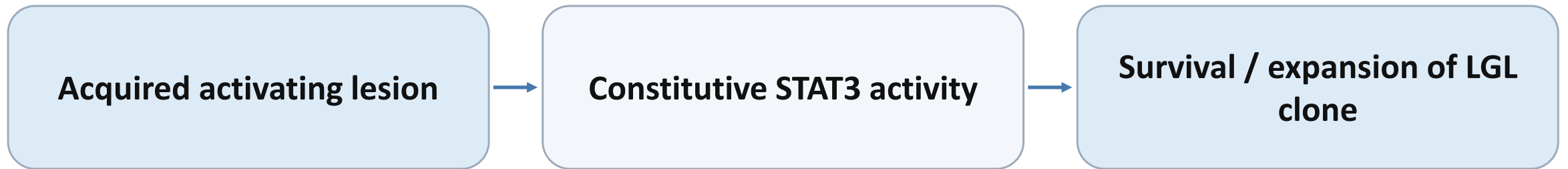
- Acquired STAT3 mutations in approximately 30%–40% of cases.
- The mutations occur in both T-cell and NK-cell forms.
- STAT3 is a transcription factor functioning downstream of cytokine receptors.

Mutant STAT3 can escape cytokine dependence



Mutant signaling can persist without ordinary cytokine-dependent control.

How persistent signaling supports cell expansion



The proposed biological link is supported by recurrent activating lesions; It does not establish the mechanism of each cytopenia.

A negative STAT3 result does not exclude LGL leukemia

- Most cases do not carry a detectable STAT3 mutation estimate.
- Molecular findings support—but do not replace—morphology, phenotype, and clonality.
- Classifying disease solely by STAT3 mutation status would miss many cases.

Why molecular evidence must be interpreted cautiously

- STAT3 mutation is an acquired supportive lesion, not a universally present marker.
- Demonstrating clonality does not by itself establish that a clone causes the cytopenia.
- The patient's clinical and hematologic context remains essential.

Cytopenias dominate the clinical picture

**Neutrophils
Reduced**

**Erythrocytes
Reduced**

**Cytopenia-related
Symptoms**

Neutropenia is a defining clinical problem

- Neutropenia is frequently more consequential than lymphocytosis.
- Reduced mature neutrophils can predispose to bacterial infection.
- Possible arrest of granulocyte progenitor maturation.

One marrow correlate of neutropenia



Maturation arrest is a possible observation, not a universal biopsy finding.

Anemia is part of the core disease phenotype

- Anemia is one of the dominant hematologic abnormalities.
- Fatigue and reduced exercise tolerance may follow diminished oxygen-carrying capacity.
- Cell counts alone do not explain the underlying mechanism of every case.

Pure red cell aplasia is an uncommon association

- Pure red cell aplasia may occasionally occur.
- The clinical consequence is profound erythroid underproduction.
- The marrow finding is distinct from simple replacement by numerous leukemic cells.

Cytopenia severity need not follow tumor burden

Anatomic finding

Sparse marrow infiltration

Only limited space occupied by tumor

No clear mass effect

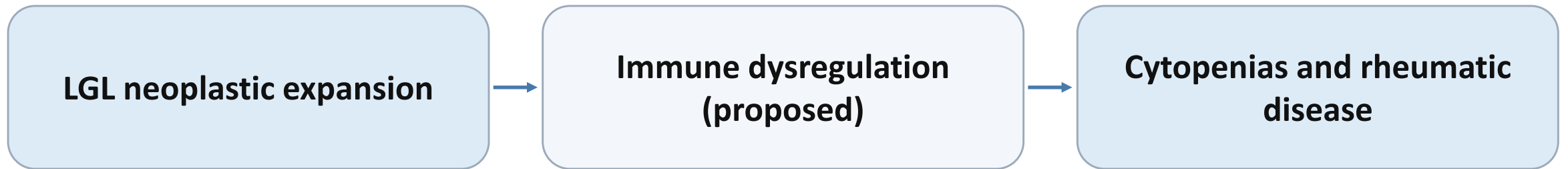
Functional outcome

Potentially marked neutropenia

Anemia and sometimes pure red cell aplasia

Clinically important hematologic disease

Autoimmune mechanisms are plausible, not fully established



Robbins explicitly describes the mechanistic basis as uncertain.

Rheumatologic disease is enriched

- Patients have an increased incidence of rheumatologic disorders.
- The clinical association raises suspicion of immune dysregulation.
- Association does not prove a single causal pathway in each patient.

Felty syndrome is defined by a clinical triad

**Rheumatoid
Arthritis**

Splenomegaly

Neutropenia

Felty syndrome and LGL leukemia can overlap

- Some patients presenting with Felty syndrome have underlying LGL leukemia.
- The same triad may motivate hematologic evaluation.
- Neither rheumatoid arthritis nor splenomegaly alone proves a clonal LGL disorder.

T-cell and NK-cell presentation patterns

T-cell predominant pattern

May reveal clear lymphocytosis

Splenomegaly relatively characteristic

Generally indolent

NK-cell predominant pattern

May have little lymphocytosis

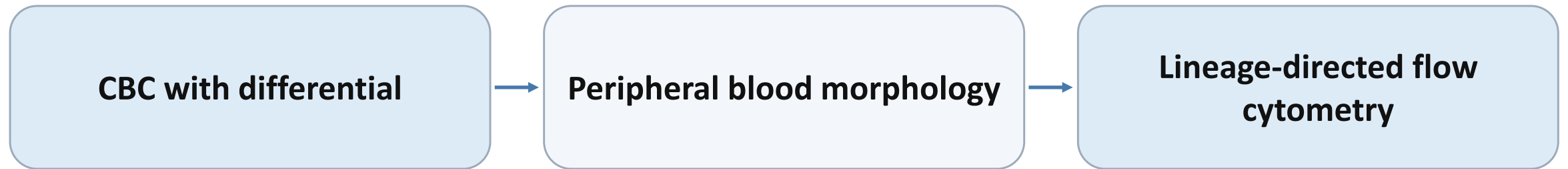
Splenomegaly may be subtle

Course varies; Must separate aggressive NK leukemia

When to suspect LGL leukemia clinically

- Persistent unexplained neutropenia, with or without anemia.
- Rheumatoid arthritis / splenomegaly plus cytopenias.
- Granular lymphocytes noted on peripheral smear.
- An atypical or persistent cytotoxic lymphocyte population.

Initial evaluation begins with blood findings



Clinical context determines whether further clonality and marrow studies are needed.

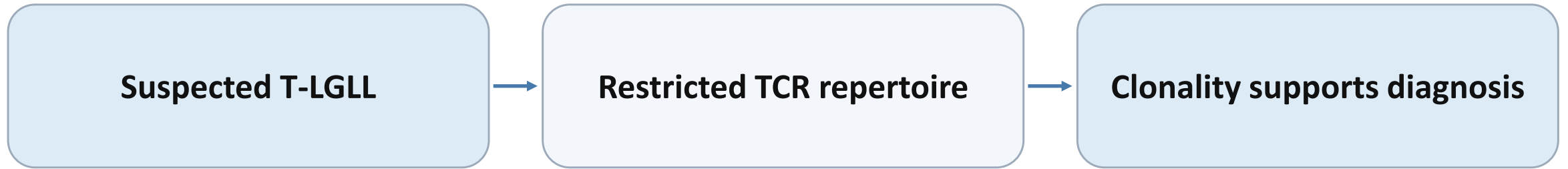
Peripheral blood smear: Interpret with restraint

- Check for granular cytoplasm and mature lymphoid appearance.
- Estimate whether granular lymphocytes are increased.
- Recognize that morphology is suggestive rather than specific.

Flow cytometry characterizes the lineage

- Determine surface CD3 status to separate T and NK patterns.
- Use cytotoxic T/NK marker combinations rather than an isolated positive result.
- Look for a relatively uniform, aberrant or restricted cell population.

Demonstrating a T-cell clone



T-cell receptor gene rearrangement or repertoire-based assays provide evidence of a persistent clone.

NK-cell clonality requires different logic



NK cells do not use T-cell receptor rearrangement as a clonality readout.

A STAT3 mutation is an adjunct, not a shortcut

- A mutation strengthens the evidence for an acquired LGL population.
- A negative molecular panel does not rule out disease.
- Somatic findings must be considered alongside immunophenotype, persistence, and clinical effects.

When marrow examination adds value

- Unexplained or complex cytopenias despite peripheral blood testing.
- A need to evaluate alternative marrow pathology.
- Suspicion of sparse LGL infiltrates that require immunostaining.

An integrated diagnostic approach

Clinical trigger



Blood assessment



Lineage characterization



Evidence of clone



Integrated conclusion

Unexplained cytopenias ± autoimmune disease

CBC, morphology of LGLs

T- vs NK-cell flow cytometry

TCR clonality or NK-associated evidence

Clinical + phenotype + clonality; Exclude mimics

Reactive LGL expansion: The major mimic

Reactive proliferation

Often follows an inflammatory or infectious trigger

Potentially mixed and polyclonal

May resolve as stimulus subsides

LGL leukemia

Persistent clinical and hematologic pattern

Evidence of a restricted cytotoxic population

Continued cytopenias or disease-associated findings

Do not assume all neutropenia is leukemic

- Drug-related, infectious, autoimmune, and other marrow causes may coexist.
- A small incidental clone may not explain all hematologic abnormalities.
- Assigning causation requires clinicopathologic correlation and appropriate exclusions.

Distinguish NK-LGLL from aggressive NK-cell leukemia

NK-LGLL

Usually persistent/indolent clinical course

Mature NK phenotype and clone evidence

Evaluate chronic cytopenias / NK cells

Aggressive NK-cell leukemia

Acute, fulminant systemic presentation

Systemic organ involvement and atypia

Urgent distinction due to severe behavior

Distinguish LGL leukemia from extranodal NK/T lymphoma

LGL leukemia

Usually circulating LGLs / cytopenias

Sparse marrow / organ infiltration

STAT3 alterations in subset

Extranodal NK/T lymphoma

Often destructive extranodal mass

Angiocentric destructive infiltrate

Classically strongly EBV-associated

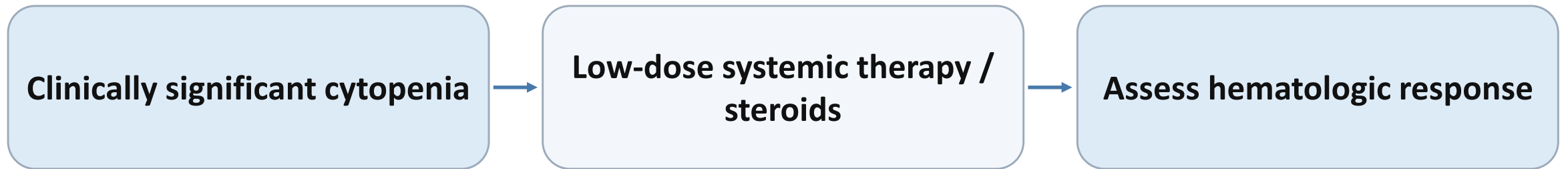
WHO-HAEM5 clarifies NK-cell nomenclature

- WHO 5th edition uses “NK-large granular lymphocytic leukemia.”
- This replaces the older designation “chronic lymphoproliferative disorder of NK cells.”
- Aggressive NK-cell leukemia remains a separate, clinically different entity.

Prognosis is tied to hematologic consequences

- The clinical course is variable rather than universally aggressive.
- Severity of neutropenia and anemia is a major determinant of morbidity.
- The response of cytopenias to treatment influences the clinical course.

Therapeutic logic



Response to low-dose chemotherapy or steroids; This slide does not prescribe a regimen.

Monitoring priorities follow the dominant problem

- Track neutrophil count and clinically relevant infections.
- Assess hemoglobin and symptoms related to anemia.
- Follow the clinical course and tolerance/response to any chosen treatment.

Case 1 — neutropenia with rheumatoid arthritis

Clinical vignette

An older adult with rheumatoid arthritis has persistent neutropenia and a palpable spleen. The peripheral blood smear shows several mature lymphocytes with coarse azurophilic granules.

What further evidence is needed before calling this LGL leukemia?

Case 1 — diagnostic reasoning

- The Felty triad is present, but it is not by itself a leukemia diagnosis.
- Flow cytometry should establish the cytotoxic lineage and phenotype.
- TCR clonality or other appropriate clonality assessment supports an LGL neoplasm.
- Exclude competing causes of neutropenia.

Case 2 — subtle NK-cell proliferation

Clinical vignette

An adult is evaluated for persistent anemia and neutropenia. The absolute lymphocyte count is not strikingly elevated. Flow cytometry identifies a uniform surface CD3-negative NK-cell population.

Which additional distinction and tests matter most?

Case 2 — diagnostic reasoning

- Minimal lymphocytosis does not exclude NK-LGLL.
- Assess whether the NK population is restricted or otherwise clonal.
- Distinguish chronic NK-LGLL from aggressive NK-cell leukemia using clinical tempo and systemic findings.

Apply the phenotype: T or NK?

Clinical vignette

A persistent granular lymphocyte population is surface CD3-positive, often CD8-positive, and appears restricted by a TCR-based clonality assay. The patient has chronic neutropenia.

Which large granular lymphocytic leukemia lineage is favored?

Answer — lineage and evidentiary limits

- Surface CD3 positivity supports T-cell lineage.
- TCR clonality provides supportive evidence of a T-cell neoplasm.
- The entire diagnostic picture must remain compatible with LGL leukemia rather than an incidental T-cell clone.

Five high-yield clinicopathologic principles

- Cytotoxic T- and NK-lineage disease has similar granular morphology.
- STAT3 activating mutations occur in a substantial minority, not all cases.
- Marrow infiltrates may be sparse even when cytopenias are important.
- Neutropenia, anemia, and rheumatologic associations dominate clinical reasoning.
- Lineage, clonality, and context—not granules alone—establish diagnosis.

Core reference

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Elsevier; 2026. Chapter 13, p. 552.

This deck is organized around the “Large Granular Lymphocytic Leukemia” section and nearby T-/NK-neoplasm context.

The original chapter PDF was not available; The supplied Markdown extraction was reviewed for the topic passage.

Classification and diagnostic context

Alaggio R, et al. The 5th edition of the WHO Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022;36:1720–1748.

Calabretto G, et al. LGL Clonal Expansion and Unexplained Cytopenia: Two Clues Don't Make an Evidence. *Cancers*. 2022;14:5236.

T-large granular lymphocytic leukemia. *Blood Research*. 2023;58(Suppl 1):S52–S57.

The fifth edition of the WHO classification of mature T-cell, NK-cell and stroma-derived neoplasms. *J Clin Pathol*. 2025;78:217 ff.