

Nodal T-follicular helper cell lymphoma

Biology, morphology, immune dysregulation, and integrated diagnosis

From normal follicular help to a complex nodal malignancy

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Learning outcomes

Explain how T-follicular helper cells support germinal-centre B-cell maturation.

Relate clonal hematopoiesis, somatic mutations, and EBV-positive B-cell proliferations.

Recognize the architectural and immunophenotypic spectrum of nodal TFH lymphoma.

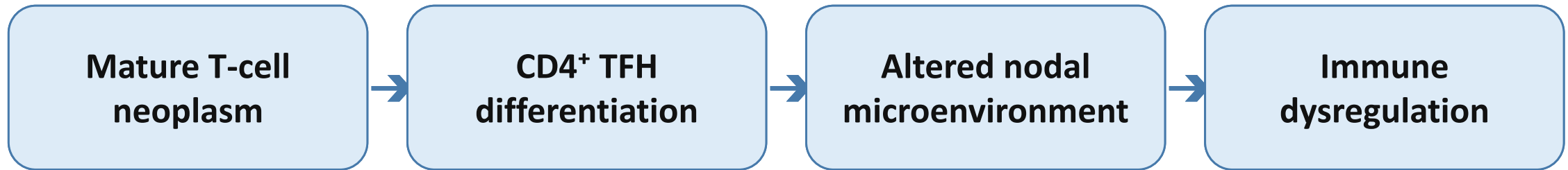
Integrate morphology, lineage, TFH phenotype, EBER, and molecular findings in differential diagnosis.

Scope

Robbins: Core disease
biology and clinicopathology

WHO-HAEM5 and pathology
reviews: Specified
supplementary detail

Disease identity in one diagnostic chain



Cell lineage, architecture, and immune phenomena belong to the same disease process.

Avoid diagnosing the lymphoma from one isolated stain or viral result.

Normal TFH cell versus malignant TFH cell

Physiological TFH cell

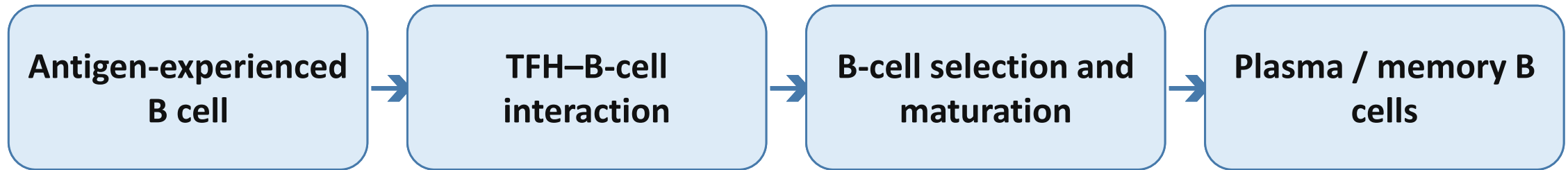
Germinal-centre localization
Support for B-cell selection and maturation
Coordinated antibody response

Nodal TFH lymphoma

Clonal expansion of TFH-phenotype T cells
Deranged B-cell support and stromal organization
Autoimmune and EBV-associated B-cell phenomena

The function of the cell of origin explains part of the clinical syndrome.

Normal germinal-centre cooperation



TFH cells support the production of high-affinity antibodies.

Abnormal TFH activity can disturb output from this response.

Where normal TFH cells operate

TFH cells home to the germinal centres of secondary lymphoid tissue.

Their main partner is the germinal-centre B cell.

TFH input influences B-cell expansion, selection, and differentiation.

Pathology link

A lymphoma derived from these cells can reshape nodal follicular architecture.

The immune phenotype preserves clues to this normal programme.

TFH homing and marker logic

CD4 helper lineage



CXCR5 expression



**Follicular
localization**



**TFH–B-cell
interaction**

CXCR5 supports follicular positioning.

BCL6, PD-1, ICOS, CXCL13, and CD10 are used to identify TFH differentiation in tissue.

Markers: Role versus interpretation

Marker	Biological / diagnostic role	Interpretive caution
CD4	Helper T-cell lineage	Not specific for TFH lymphoma
PD-1 / ICOS	TFH-associated phenotype	Reactive TFH cells also express them
CXCL13 / CXCR5	Follicular chemokine axis	Context and localization matter
CD10 / BCL6	Additional TFH differentiation clues	Not lineage-specific alone

T-cell lineage is not the same as TFH lineage

Establish T-cell identity

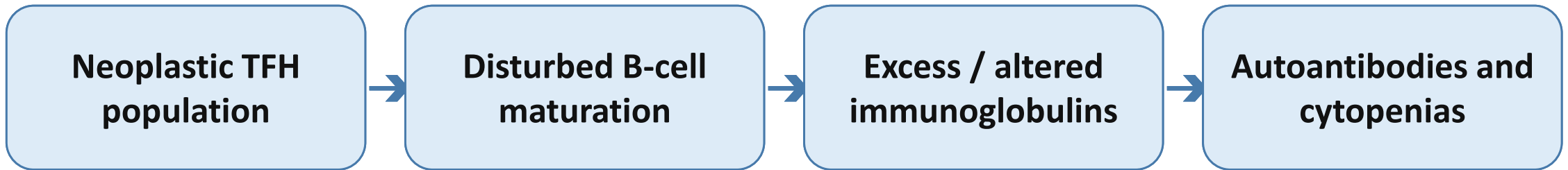
Morphology and T-lineage markers
CD3 with contextual pan-T markers
Exclude a dominant B-cell neoplasm

Establish TFH differentiation

Assess several TFH markers
Localize staining to the atypical T cells
Interpret with architecture and clinical setting

A broad TFH panel is not a replacement for demonstrating neoplastic T-cell lineage.

From TFH function to immune symptoms



Robbins explicitly links TFH dysfunction with hypergammaglobulinemia and autoimmune cytopenias.

Clinical findings help connect apparently disparate tissue and laboratory observations.

Immune dysregulation is a defining association

Hypergammaglobulinemia can accompany abnormal germinal-centre activity.

Autoantibodies may develop in the setting of altered B-cell selection.

Autoimmune cytopenias can accompany the lymphoma.

Some clinical findings arise from immune dysfunction rather than direct tissue infiltration.

Diagnostic implication

A lymphadenopathy-plus-autoimmunity presentation is compatible with this disease spectrum.

What hypergammaglobulinemia does not prove

Supportive clinical clue

Immunoglobulin excess fits TFH-driven immune disturbance.

May accompany multiple inflammatory or neoplastic states.

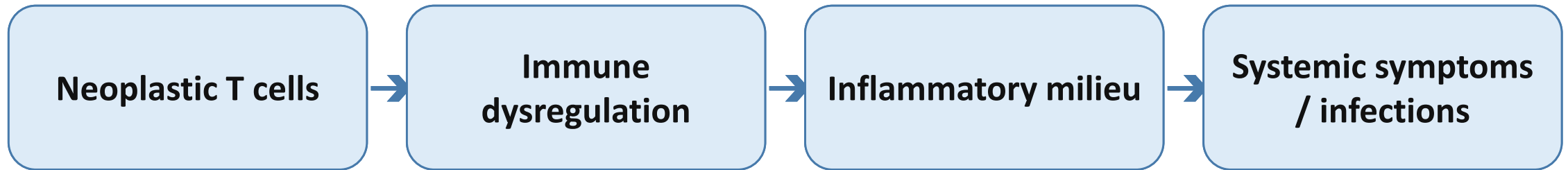
Not a diagnostic criterion alone

Does not establish the malignant cell lineage.

Does not replace node morphology and phenotyping.

Separate clinical association from tissue diagnosis.

Inflammatory symptoms have several contributors



Symptoms associated with immune abnormalities, infection, or inflammatory cytokines.

Do not attribute every symptom to a single unverified cytokine.

Presentation: Look beyond lymph-node size

Lymphadenopathy is a common presenting feature.

Immune abnormalities may dominate the clinical assessment.

Infection can complicate the presentation.

Inflammatory symptoms may coexist with the tumor burden.

Clinical integration

History, examination, laboratory patterns, and biopsy are interpreted together.

Typical age group and course

Most patients are older adults.

The natural history is variable; Not every case behaves identically.

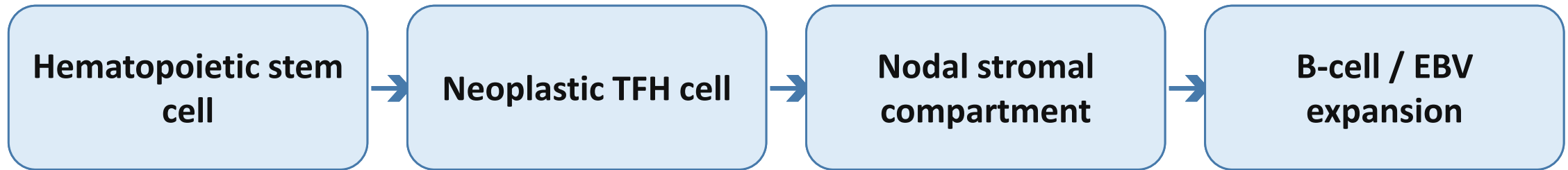
Chemotherapy responses are often transient.

That most patients die within five years of diagnosis.

Qualification

This is the textbook's broad prognostic statement, not an individualized prediction or current trial estimate.

Three linked pathogenetic compartments



Early mutations may appear across hematopoietic lineages.

Tumor-related immune disturbance and B-cell proliferations coexist within the same node.

Clonal hematopoiesis: Concept

A hematopoietic stem / progenitor clone acquires somatic mutations.

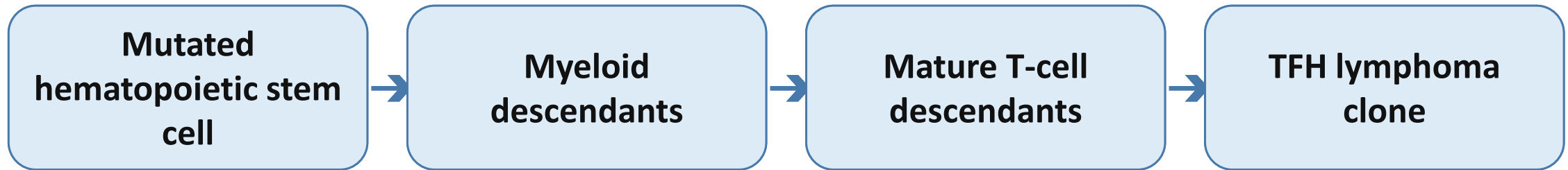
Its descendants may populate more than one blood-cell lineage.

The presence of the same alteration in separate lineages can reveal a shared ancestral clone.

Core distinction

A shared ancestral mutation does not make mature T and B tumor cells the same cell type.

Shared TET2 and DNMT3A mutations



Matching TET2 / DNMT3A mutations in tumor T cells and differentiated myeloid cells.

This supports—but does not directly prove in every patient—an early stem-cell origin.

Early and later genetic events

Event class	Examples	Interpretation
Early shared clone	TET2; DNMT3A	Can be present in hematopoietic progenitors and myeloid cells
T-cell–restricted later events	RHOA G17V; IDH2 R172	Frequently associated with evolved neoplastic TFH clone
TCR signalling lesions	CD28 / related pathway abnormalities	Additional signalling dysregulation; Heterogeneous

TET2: Mutation context matters

TET2 is frequently altered in nodal TFH lymphoma.

The same alteration can occur in clonal hematopoiesis.

TET2 positivity on tumor sequencing alone does not identify a unique disease subtype.

Paired lineage analysis can clarify whether a mutation predates transformation.

Pitfall

Do not interpret a TET2 mutation as lymphoma-specific without context.

DNMT3A: A shared ancestral signal

DNMT3A is another commonly altered gene account.

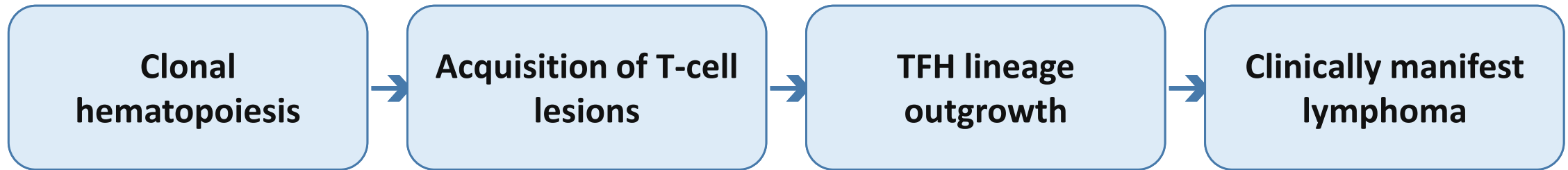
Mutant DNMT3A can be detected in tumor and myeloid descendants.

A shared mutation supports clonal ancestry across differentiated lineages.

Mechanistic significance

Genetic kinship can coexist with distinct T-cell and B-cell malignant phenotypes.

Multistep model of transformation



WHO-HAEM5 reviews describe stepwise genetics, not one sufficient mutation.

The graphic is conceptual; It does not imply a fixed sequence for each patient.

RHOA and IDH2 in the molecular landscape

RHOA G17V and IDH2 R172 are recurrent TFH-lymphoma-associated alterations in published classifications.

Unlike early shared TET2 / DNMT3A lesions, they may be concentrated in neoplastic T cells.

Mutation testing can support classification but cannot replace phenotype and morphology.

Interpretive discipline

Absence of a recurrent mutation does not exclude nodal TFH lymphoma.

Molecular clonality versus tumor identity

Shared ancestral clone

Early mutations can occur in T, myeloid, and sometimes B cells.

Explains apparent cross-lineage relatedness.

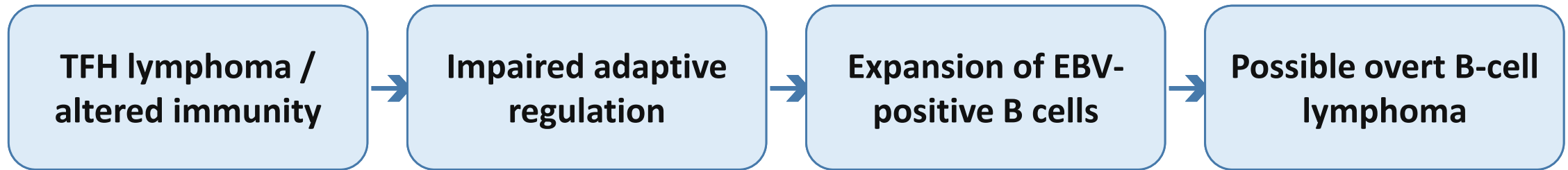
Distinct mature neoplasms

T-cell lymphoma remains a T-lineage neoplasm.

A secondary B-cell lymphoma requires separate morphologic and phenotypic classification.

Common origin is not interchangeable lineage.

Why EBV-positive B cells accumulate



Increased EBV-positive B cells and occasional secondary EBV-positive B-cell lymphoma.

The exact cause of expansion is not fully established.

EBV-associated B cells: Critical distinction

The neoplastic TFH compartment is of T-cell lineage.

EBER-positive cells in the involved node are often B-lineage immunoblasts.

The number and cytology of B cells may vary among cases.

An expanded B population should be evaluated for a separate B-cell lymphoma.

Major diagnostic trap

EBER positivity in a node does not establish an EBV-driven T-cell lymphoma.

EBV-positive immunoblasts versus overt B-cell lymphoma

Associated EBV⁺ B-cell expansion

Often part of the nodal microenvironment.

Requires attention to B-cell distribution and atypia.

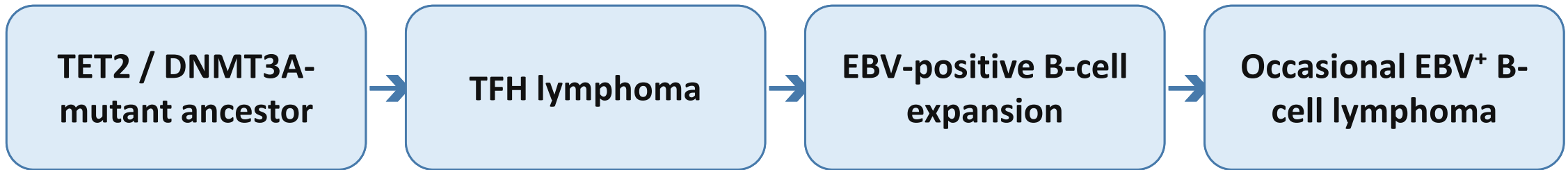
Possible secondary B-cell lymphoma

Distinct destructive B-cell population may emerge.

Apply full B-lineage workup and classification.

Do not label every EBER-positive immunoblast as a second lymphoma.

Two hematologic tumors can share early mutations



Robbins documents some paired tumors with common TET2 / DNMT3A alterations.

Shared early mutations are evidence of an ancestral clone—not proof of identical final drivers.

Nodal architecture: What to assess first

Is the normal follicular/paracortical arrangement preserved, distorted, or effaced?

Is growth follicular, vaguely nodular, interfollicular, or diffuse?

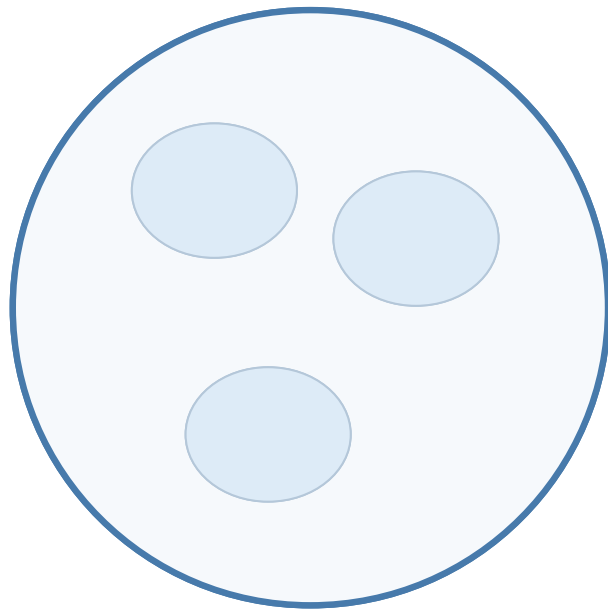
Are vessels conspicuous and is the dendritic meshwork expanded?

Where are atypical T cells positioned relative to follicles and vessels?

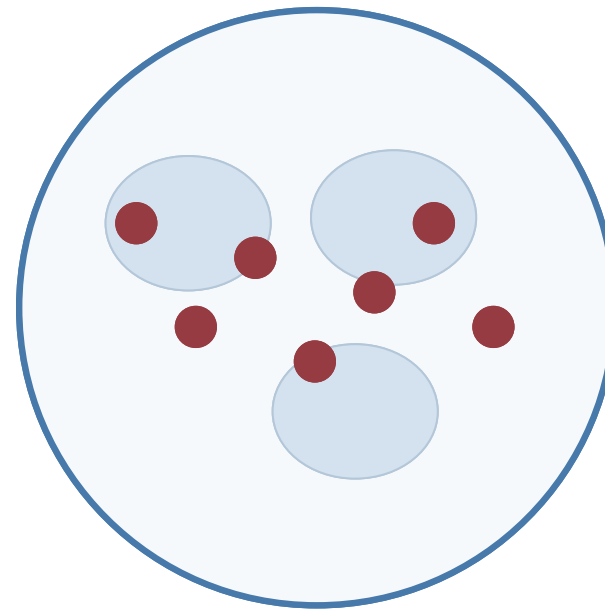
Sampling

Architectural analysis is better supported by excision than limited core tissue.

Normal versus altered nodal organization



Organized node



Altered node

Change in nodal geography reflects the interplay of tumor cells, follicles, vessels, and stroma.

Original schematic — not a histologic section

Angioimmunoblastic-type architecture

A diffuse or paracortical polymorphous infiltrate can efface the node.

Atypical T cells may be inconspicuous among reactive populations.

Branching high endothelial venules are a recognized clue.

Expanded follicular dendritic cell networks can envelop vascular structures.

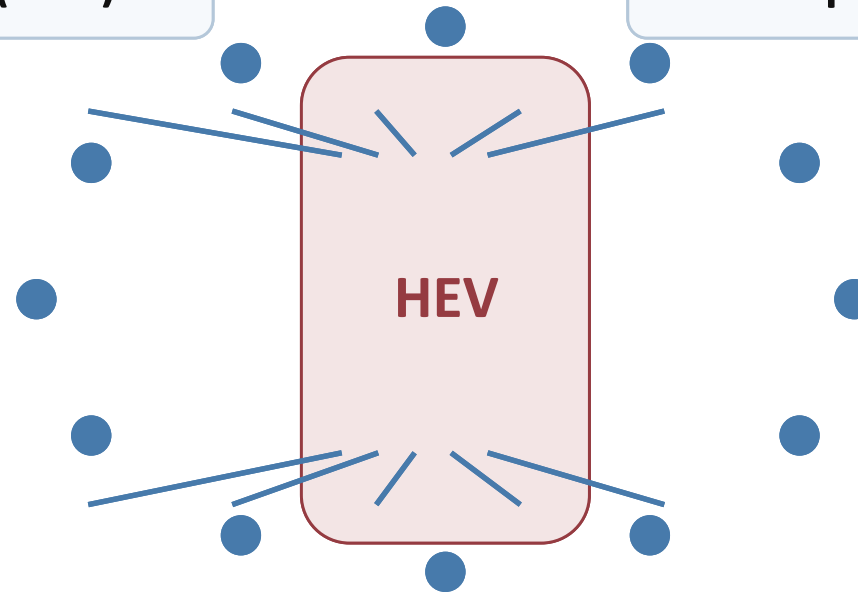
Microscopy objective

Search for the vascular–stromal pattern, not only individual tumor-cell atypia.

Vessels and dendritic-cell networks

High endothelial venule (HEV)

Expanded FDC meshwork



FDC markers (CD21 / CD23) visualize stromal networks; They are not the neoplastic T-cell markers.

Original schematic: HEV surrounded by expanded FDC network; Not a micrograph

The infiltrate may look deceptively reactive

Small and medium-sized atypical T cells may be admixed with inflammatory cells.

Reactive B cells and immunoblasts can be prominent.

The tumor compartment may be less abundant than the accompanying reactive infiltrate.

Atypia and polyclonality must be evaluated in the relevant cell lineage.

Diagnostic risk

Reactive cellular diversity does not exclude an underlying neoplastic T-cell clone.

Three WHO-HAEM5 morphologic categories

Angioimmunoblastic / follicular

Angioimmunoblastic: Vascular / FDC expansion, polymorphous infiltrate

Follicular: Tumor T cells populate nodules / follicles

Not otherwise specified

TFH phenotype with neither defining pattern
Often diffuse and variably tumor-cell-rich

These are morphologic categories inside a shared TFH-lymphoma family.

Angioimmunoblastic type: Characteristic triad

Polymorphous lymphoid and inflammatory infiltrate.

Proliferation of arborizing high endothelial venules.

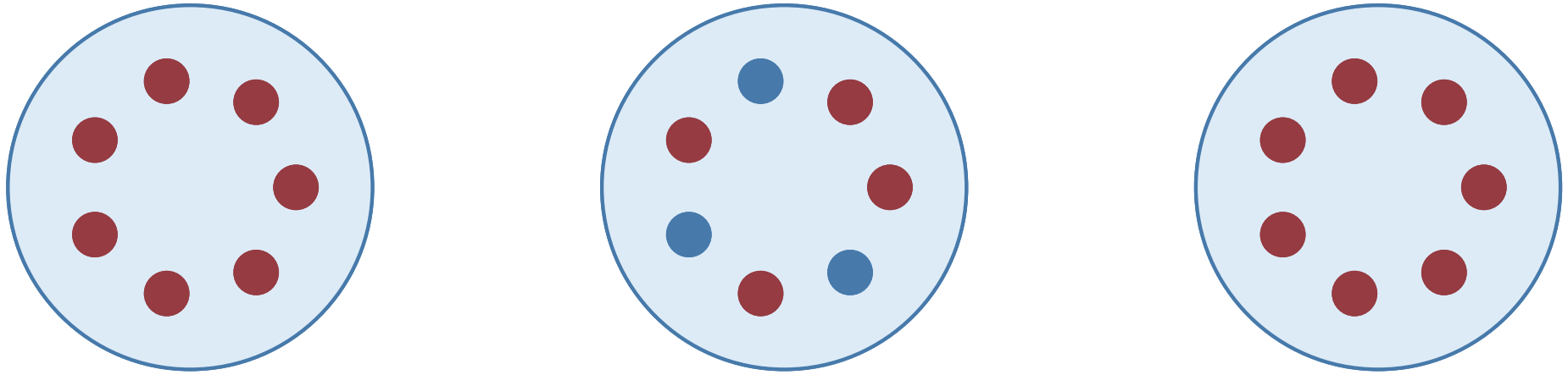
Expanded extrafollicular follicular dendritic cell meshworks.

TFH-phenotype neoplastic T cells support the integrated diagnosis.

Qualification

Features vary by pattern and tissue sample; The classic triad is not invariably conspicuous.

Follicular-type tumor distribution



Red cells: Atypical TFH-phenotype T cells clustered within follicles / nodules.

A follicular pattern can belong to a T-cell lymphoma; Establish the lineage of the cells inside the follicles.

Original schematic: TFH-phenotype tumor cells centered in nodules; Not a micrograph

Follicular type can mimic a B-cell lymphoma

Neoplastic T cells may accumulate within follicular structures.

An apparent follicular growth pattern does not establish B-cell lineage.

CD3 / CD4 and TFH-marker localization distinguish lesional T cells from resident B cells.

Native B-cell follicles can be distorted or displaced.

Practical approach

Determine which cell population actually constitutes the follicular lesion.

Nodal TFH lymphoma, NOS

TFH-phenotype nodal T-cell lymphoma without defining angioimmunoblastic or follicular architecture.

May demonstrate a diffuse population of variably atypical T cells.

Should not be confused with generic PTCL-NOS.

Classification is challenging when architecture is limited.

Case selection

Use an integrated diagnosis;
Avoid false precision in small biopsies.

Excision versus core needle sample

Excision: Strongest architecture

Follicular, interfollicular, and diffuse relationships

HEV and FDC distribution

Spatial relationships among T and B cells

Core: Often adequate for phenotype

Lineage and multi-marker immunophenotype

Some molecular / EBER information

Subtype architecture may remain indeterminate

WHO reviews advise caution when assigning morphologic subtype on limited tissue.

A practical immunohistochemistry panel

Question	Markers / methods	What is established
T or B lineage?	CD3, CD20 / PAX5	Separate abnormal T and B compartments
TFH differentiation?	PD-1, ICOS, CXCL13, CD10, BCL6	Composite TFH phenotype
Expanded FDC meshwork?	CD21 / CD23	Anatomic stromal pattern
EBV distribution?	EBER in situ hybridization	Which cells harbour EBV?

TFH phenotype requires more than a single stain

WHO-HAEM5 defines the typical phenotype using CD4 and at least two TFH markers.

Many expert reviews recommend a broad TFH panel for improved specificity.

Interpret actual tumor-cell staining rather than nearby reactive follicles.

No universal positivity threshold solves every borderline case.

WHO-HAEM5

Markers support—not substitute for—clinical, morphologic, and lineage assessment.

TFH markers have different limitations

Marker	Useful clue	Important caveat
PD-1	Often strong TFH-associated signal	Reactive TFH cells can stain
ICOS	TFH-associated co-stimulation	Not completely specific
CXCL13	Tissue TFH-associated chemokine	Distribution and technical factors matter
CD10 / BCL6	Additional TFH evidence	Also expressed in germinal-centre B cells

CD21 and CD23 interrogate architecture

They highlight follicular dendritic cell meshworks rather than neoplastic T cells.

Extrafollicular expansion and association with vessels support angioimmunoblastic morphology.

The absence of a striking meshwork on a limited sample does not exclude TFH lymphoma.

Interpretation

Keep stromal markers conceptually distinct from tumor-lineage markers.

EBER: Always assign positivity to a cell lineage

EBER demonstrates EBV-infected cells within the specimen.

Correlate stained cells with B-lineage markers and cell morphology.

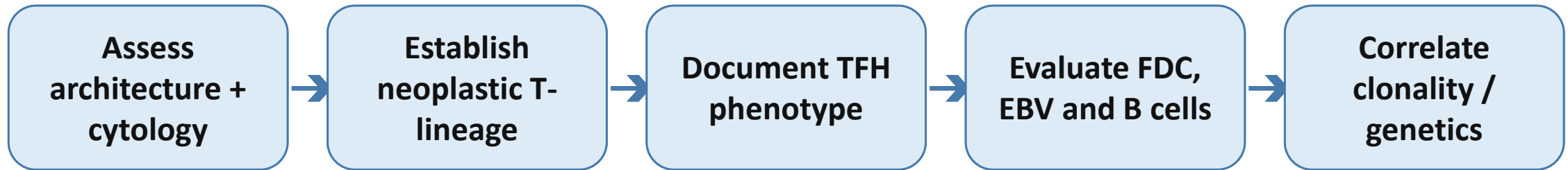
Scattered EBV-positive B cells fit the documented disease microenvironment.

Widespread EBER positivity in neoplastic T / NK cells raises a different differential.

Critical distinction

EBV detection is not the same as proving EBV is the transforming driver of the T-cell clone.

Integrated diagnostic workflow



Assign a morphologic subtype when sufficiently supported.

Maintain a broader family-level designation if sampling prevents reliable subtyping.

Clonality is an adjunct, not a shortcut

What TCR testing can contribute

Support a clonal T-cell population in equivocal cases.

Complement morphology and immunophenotype.

What it cannot establish alone

Not every T-cell clone is lymphoma.

Does not distinguish TFH subtype.

Does not identify the reactive B-cell compartment.

TCR rearrangement testing for difficult PTCL–reactive differentials.

Differential: What to discriminate

Competing diagnosis	Shared appearance	Discriminating investigation
PTCL, NOS	Nodal atypical T-cell infiltrate	Coherent TFH phenotype and architecture
Reactive hyperplasia	TFH-positive reactive follicles	Architectural preservation, cell atypia, integration
Follicular B-cell lymphoma	Follicular / nodular proliferation	Tumor-cell CD20 / PAX5 vs CD3 / TFH
Classic Hodgkin lymphoma	EBV ⁺ /CD30 ⁺ large B cells	Identify neoplastic compartment and background TFH cells

Distinguish from peripheral T-cell lymphoma, NOS

PTCL-NOS is an exclusion category for other mature T-cell neoplasms.

Its morphology may overlap with tumor-cell-rich TFH lymphoma.

Assess multiple TFH markers and nodal architecture.

Classification should be conservative when evidence of TFH derivation is marginal.

Pitfall

PD-1 or ICOS positivity alone
can be misleading.

Distinguish from florid reactive lymphadenopathy

Reactive germinal centres contain normal TFH cells expressing several relevant markers.

Malignancy requires a convincing atypical T-cell population and pattern.

Examine cytology, architecture, immunophenotype, clinical course, and clonality together.

Key question

Are the stained TFH cells the atypical lesional population or a normal immune compartment?

Distinguish from classic Hodgkin lymphoma

EBV-positive large B-cell immunoblasts may resemble Hodgkin-like cells.

TFH lymphoma can produce a prominent immunologic background.

Determine whether the defining tumor is T lineage, B lineage, or two neoplasms.

Use a proportionate B-cell / Hodgkin workup when large atypical cells are present.

Misclassification hazard

Do not let scattered CD30-positive B immunoblasts obscure the T-cell lymphoma.

Distinguish from follicular B-cell lymphoma

A follicular pattern can be created by TFH-phenotype neoplastic T cells.

Use lineage markers to identify the cells within nodules.

BCL6 and CD10 cannot assign B lineage without CD20 / PAX5 and localization.

Take-home

Follicular architecture and germinal-centre markers are not lineage-specific.

Distinguish EBV-positive nodal T/NK lymphoma

EBER-positive B immunoblasts are a recognized associated population in TFH lymphoma.

An EBV-driven T / NK neoplasm is a different diagnostic consideration.

The crucial first step is mapping EBER positivity to the malignant lineage.

Avoid an attribution error

Do not infer that tumor T cells contain EBV from an EBER-positive node.

Clinical-laboratory correlation matrix

Finding	Pathobiologic interpretation	Diagnostic weight
Generalized adenopathy	Nodal lymphomatous involvement	Prompts tissue assessment
Hypergammaglobulinemia	Deranged TFH–B-cell help	Supportive; Nonspecific
Autoimmune cytopenias	Immune-system dysregulation	Supportive; Not subtype-specific
Infection / inflammatory symptoms	Altered adaptive immunity, inflammation	Explains clinical heterogeneity

Specimen-level questions for the pathologist

What is the atypical cell?



Where is it located?



Which markers co-localize?



Is there a second B-cell clone?

These four questions prevent several common misinterpretations.

EBER, TFH stains, and FDC stains are interpreted in distinct cell compartments.

Case 1: Lymphadenopathy with immune abnormalities

An older adult presents with generalized lymphadenopathy, hypergammaglobulinemia, and autoimmune hemolytic anemia. Biopsy shows atypical CD4⁺ T cells with multiple TFH markers.

What pathogenetic connection unifies the clinical and tissue findings?

Neoplastic TFH activity deranges germinal-centre B-cell function and favors abnormal antibody production.

Interpretive answer

Case 2: EBER-positive cells in the node

A node contains atypical CD4⁺ T cells, expanded FDC meshworks, and scattered EBER-positive CD20⁺ immunoblasts.

Which compartment is most likely EBV-positive?

The associated B-cell immunoblasts. Their presence does not by itself establish EBV infection of tumor T cells.

Interpretive answer

Case 3: Shared mutation across lineages

Sequencing identifies the same TET2 mutation in sorted tumor T cells and peripheral-blood monocytes.

What does this pattern support?

An early mutated hematopoietic progenitor contributing to both mature cell lineages; It does not make monocytes malignant T cells.

Interpretive answer

Case 4: A deceptively follicular lymphoma

The lymph node contains nodules populated largely by CD3⁺ CD4⁺ PD-1⁺ CD10⁺ atypical lymphocytes; Scattered CD20⁺ B cells remain.

What is the decisive next interpretive step?

Recognize that the lesional follicular cells are T lineage; Evaluate nodal TFH lymphoma, follicular type.

Interpretive answer

Case 5: Limited core biopsy

A core shows CD4⁺ atypical T cells coexpressing several TFH markers. There is insufficient tissue to assess full nodal pattern.

Should a precise morphologic TFH subtype be imposed?

No. A family-level nodal TFH lymphoma designation may be safer when architecture is inadequate.

Interpretive answer

Case 6: A second abnormal B-cell population

Previously diagnosed TFH lymphoma is followed by an enlarged node with a destructive sheet of EBV-positive B cells.

What diagnostic possibility must be assessed separately?

A secondary EBV-positive B-cell lymphoma, rather than assuming simple reactive EBV-positive immunoblast expansion.

Interpretive answer

Diagnostic synthesis across three compartments

Compartment	Core finding	Role in final report
Neoplastic T cells	CD4 and multiple TFH-associated markers	Establish lymphomatous lineage and differentiation
Nodal stroma	Vessel / FDC pattern	Supports architecture and subtype
B-cell background	EBV-positive B cells $\pm$ overt B-cell neoplasm	Identifies associated proliferation or a second tumor

Why no single test is decisive

Morphology can be masked by a polymorphous reactive background.

TFH-associated markers also occur in benign follicular helper cells.

TET2 / DNMT3A mutations may predate the malignancy.

EBER may label associated B cells instead of the tumor clone.

Integrated diagnosis

The disease is recognized through concordance among several imperfect evidence streams.

Risk, diagnosis, and prognosis are different claims

What supports diagnosis

- Characteristic T-cell phenotype
- Appropriate nodal architecture
- Exclusion of competing lineages

What informs clinical discussion

- Immune complications and concurrent neoplasms
- Variable and often aggressive clinical course
- Response assessed with clinical context

Do not reclassify diagnostic markers as validated prognostic or predictive biomarkers.

Prognosis: Communicate uncertainty correctly

Variable outcomes with frequently transient chemotherapy responses.

The historical textbook summary reports poor overall long-term survival.

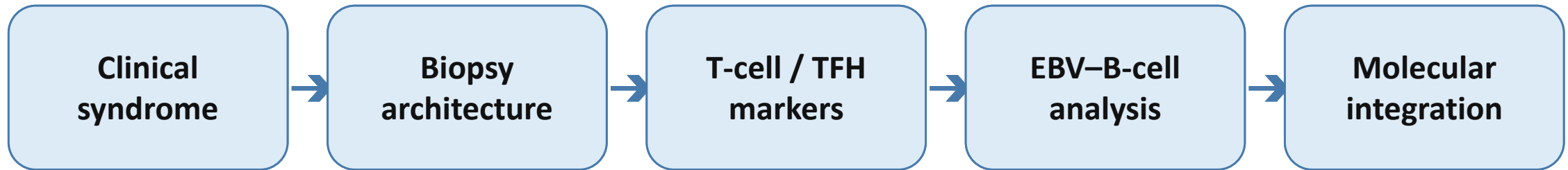
Prediction for an individual patient requires clinical staging, fitness, treatment, and broader context.

Do not extrapolate a single molecular mutation into an established individual prognosis.

Source discipline

No invented treatment effect sizes, survival curves, or patient-level forecasts.

Whole-case diagnostic model



Each layer can corroborate or challenge the preceding interpretation.

A discrepant result should trigger review, not automatic override.

Five concepts to retain

Nodal TFH lymphoma is a mature T-cell neoplasm related to germinal-centre helper function.

Immune dysregulation is integral to its biology and presentation.

TET2 / DNMT3A can connect lymphoma with clonal hematopoiesis.

EBV-positive B cells may coexist and sometimes progress to a second B-cell malignancy.

Diagnosis requires integrated T-cell phenotype, architecture, and compartment-aware interpretation.

Synthesis

Disease biology, not one stain, unifies the classification.

Selected scientific sources

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026), Chapter 13, p. 550.

WHO Classification of Haematolymphoid Tumours, 5th edition: lymphoid neoplasms framework (2022).

Marques-Piubelli ML, Amador C, Vega F. Frontiers in Oncology. 2023;13:1105651.

Alaggio R et al. Leukemia. 2022;36:1720–1748. DOI: 10.1038/s41375-022-01620-2.

Modern Pathology. 2024;37:100512. Mature T-cell, NK-cell and stroma-derived neoplasms.