

Hairy cell leukemia

Morphology • molecular pathogenesis • clinicopathologic diagnosis

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Learning objectives

- Identify the characteristic blood, marrow, spleen and liver findings.
- Explain the BRAF mutation–MAPK pathway relationship.
- Integrate clinical presentation, morphology and immunophenotype.
- Distinguish this indolent mature B-cell tumor from neighboring entities.

A distinctive mature B-cell neoplasm

Lineage

A mature B-cell tumor in the lymphoid-neoplasm group.

Principal organs

Bone marrow and spleen are major disease sites.

Behavior

Typically indolent, often with durable treatment responses.

Molecular association

Activating BRAF mutations are highly characteristic.

A rare form of leukemia

- Accounts for approximately 2% of all leukemias.
- Uncommon relative to major mature B-cell lymphoid neoplasms.
- Despite rarity, a coherent morphologic and molecular profile permits recognition.

Typical demographic profile

Age

Median age at diagnosis: 55 years.

Sex

Male-to-female ratio approximately 5:1.

Population

Textbook reports a predominance among White patients.

Interpretation

Demographics support suspicion; They do not establish diagnosis.

HCL within mature B-cell tumors

Entity	Cell-of-origin context	Characteristic driver in Robbins
Hairy cell leukemia	Memory B cell	Activating BRAF
Follicular lymphoma	Germinal-center B cell	BCL2::IGH
Mantle cell lymphoma	Naive B cell	Cyclin D1::IGH
CLL/SLL	Naive or memory B cell	Heterogeneous genetic lesions

The characteristic clinical pattern

Physical examination

Splenomegaly, often marked; Nodes usually not prominent.

Peripheral blood

Cytopenias are common; Circulating tumor-cell numbers vary.

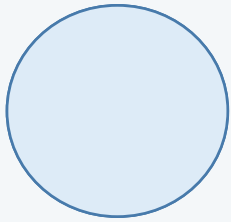
Marrow examination

Infiltration with reticulin may impair aspiration.

Natural history

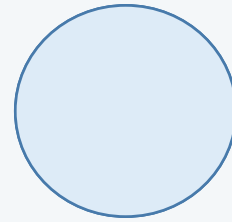
Indolent course with generally excellent outcome.

Anatomical distribution drives presentation



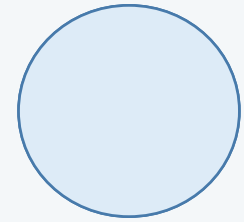
Bone marrow

Interstitial infiltration →
cytopenias



Spleen

Red-pulp expansion →
marked enlargement



Liver

Portal-triad infiltration →
sometimes hepatomegaly

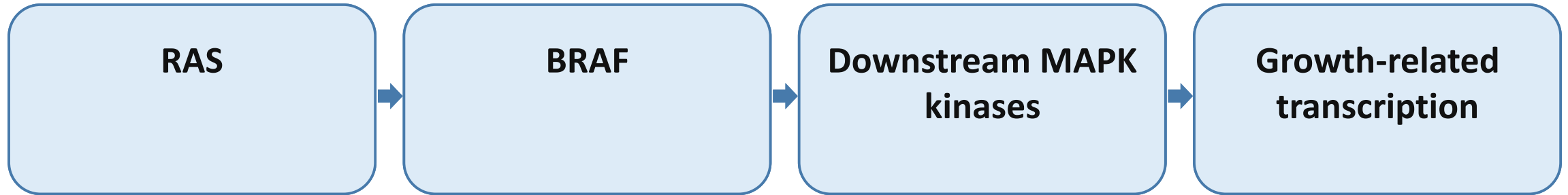
Why the disease can be overlooked

- Circulating tumor cells may be few, despite organ infiltration.
- Lymphadenopathy is uncommon rather than a dominant presentation.
- A marrow aspirate can fail even when marrow is involved.
- The spleen and marrow provide complementary diagnostic clues.

BRAF is the central molecular association

- More than 90% of cases harbor an activating point mutation in BRAF.
- BRAF encodes a serine/threonine protein kinase.
- The kinase acts just downstream of RAS in the MAPK cascade.
- This association is central to pathogenesis and therapeutic targeting.

RAS–BRAFF–MAPK signaling



- BRAF is immediately downstream of RAS,.
- Activating BRAF mutations increase signaling through downstream kinases.

The molecular change is BRAF V600E

Position

Amino-acid residue 600 in BRAF.

Substitution

Valine (V) is replaced by glutamate (E).

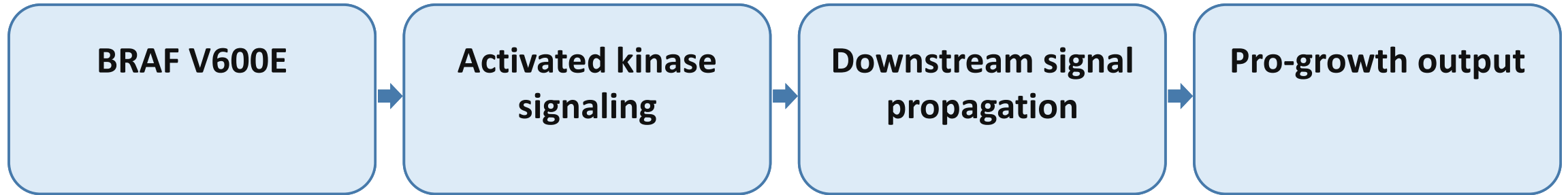
Consequence

A kinase-activating point mutation.

Specificity caveat

The same alteration also occurs in other neoplasms.

From kinase alteration to tumor behavior



- The diagram represents the molecular logic Chapter 7.
- It is not a quantitatively measured pathway activity assay.

High prevalence is not absolute universality

- The disease-specific section states BRAF mutation in more than 90% of cases.
- A negative molecular result cannot, by itself, substitute for comprehensive clinicopathologic evaluation.
- Mutation frequency and mutation identity answer different questions.

BRAF is not unique to leukemia

Hairy cell leukemia

Very strongly associated with BRAF activation.

Melanoma

BRAF activating mutations occur in a substantial subset.

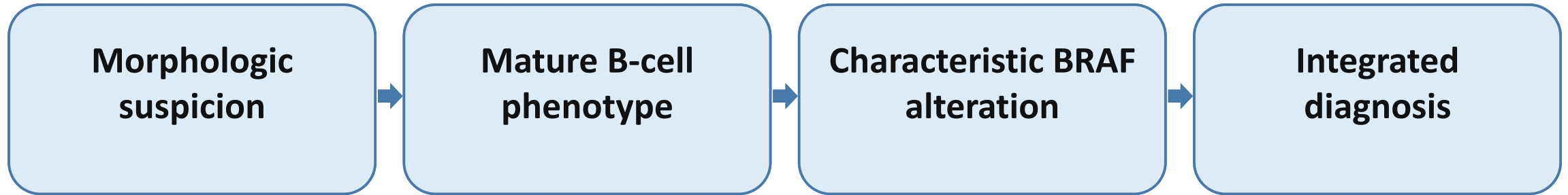
Langerhans cell histiocytosis

BRAF V600E is also identified in this neoplasm.

Diagnostic lesson

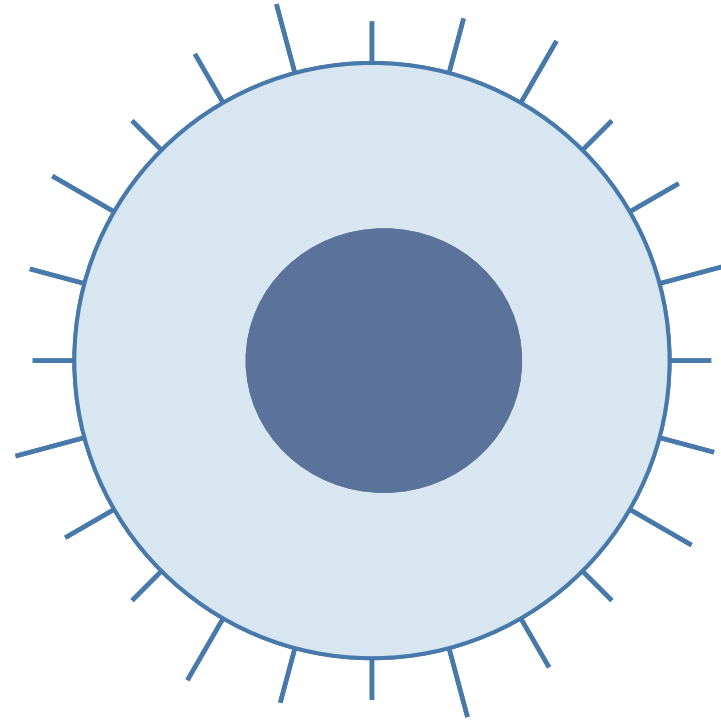
Context is required; A shared mutation does not imply a shared diagnosis.

How genotype supports pathologic classification



- Molecular findings complement rather than replace morphology.
- The source does not specify a mandatory test algorithm.

Morphologic hallmark: Surface projections



Hair-like projections are most evident with phase-contrast microscopy.

Schematic: Original vector drawing, not a photomicrograph.

Hairy projections are easiest by phase contrast

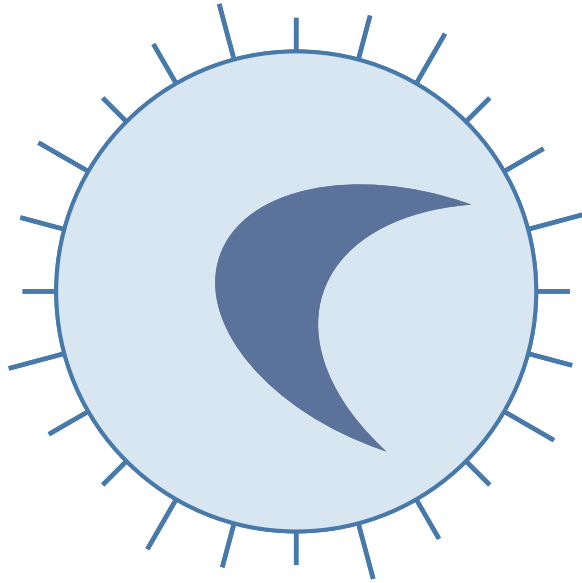
Clinical / pathologic observation

- Fine surface extensions explain the name “hairy cell.”
- Projections are most apparent by phase-contrast microscopy.

Interpretation

- Conventional stained smears may emphasize cytoplasm and nuclear contours instead.
- Avoid making diagnosis from apparent spicules alone.

Stained blood-smear appearance



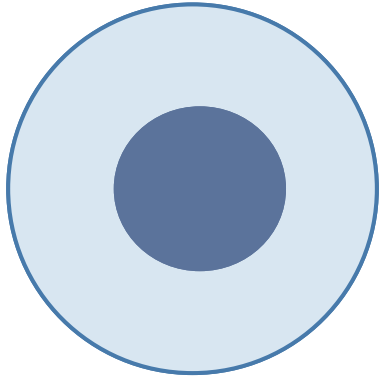
Fine surface projections

Rounded, oblong or folded nucleus

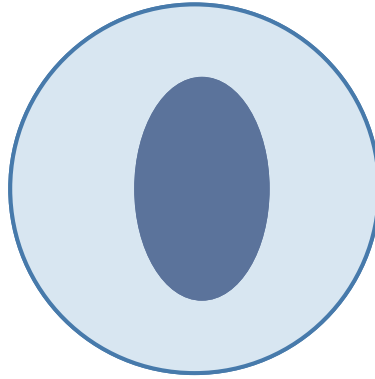
Moderate pale cytoplasm

Schematic: Original vector drawing, not a photomicrograph.

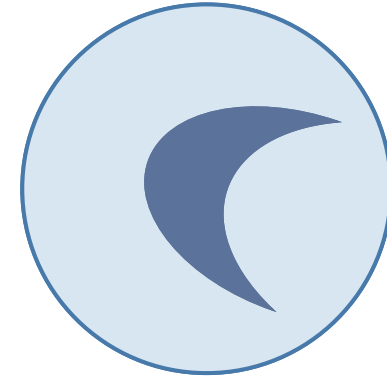
Three described nuclear contours



Round



Oblong



Reniform

Schematic: Original vector drawing, not a photomicrograph.

Cytoplasmic detail on routine smears

- Moderate amounts of pale-blue cytoplasm are typical.
- Peripheral threadlike projections or blebs may be visible.
- The source figure legend describes cytoplasm as agranular.
- Interpret cell morphology alongside lineage markers and marrow findings.

The peripheral tumor-cell count varies

Possible finding

A recognizable leukemic population is evident on smear.

Alternative finding

Only a few suspicious cells circulate.

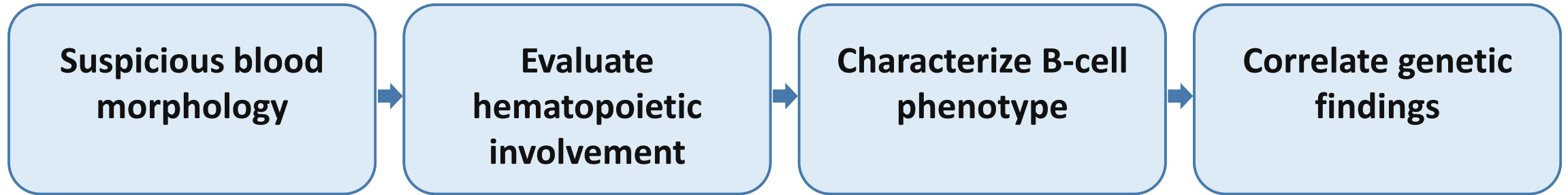
Implication

Absence of striking lymphocytosis does not exclude organ disease.

Practical correlate

Marrow and splenic involvement may dominate the presentation.

Peripheral-blood observation is not sufficient



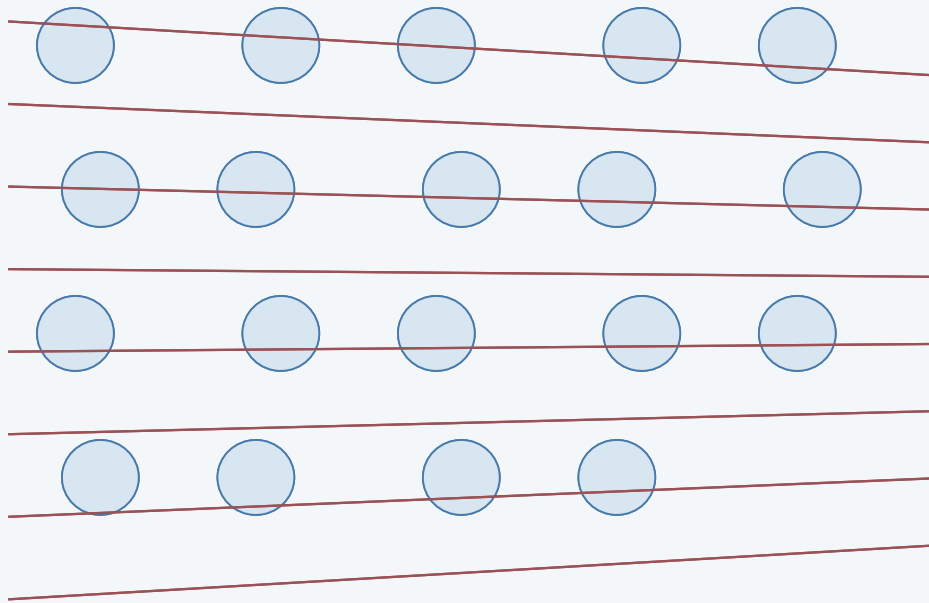
- This is a pedagogic reasoning sequence, not a prescribed clinical guideline.

Bone marrow: Interstitial infiltration

- Tumor cells infiltrate the marrow in a diffuse interstitial pattern.
- Oblong or reniform nuclei and condensed chromatin are described.
- Cytoplasm appears pale within the marrow infiltrate.
- Marrow infiltration contributes to abnormal blood counts.

Reticulin explains the dry-tap phenomenon

Marrow compartment



Sampling consequence

- Reticulin-rich matrix entraps neoplastic cells.
- Aspiration may yield a “dry tap.”
- Core biopsy reveals interstitial infiltration.

Schematic — no tissue section shown

What a dry tap means in this setting

Observation

Marrow aspiration yields little or no material.

Mechanism

Neoplastic cells lie within a reticulin-containing extracellular matrix.

Diagnostic consequence

A core biopsy may reveal infiltrates that aspiration misses.

Caution

A dry tap is not exclusive to this leukemia.

Aspirate versus trephine biopsy

Specimen	What HCL source emphasizes	Interpretive limitation
Marrow aspirate	May be inaspirable because of reticulin	Negative/empty aspirate may be noninformative
Core marrow biopsy	Shows interstitial hairy-cell infiltrate	Requires morphologic / phenotype correlation
Peripheral smear	Can reveal cells with projections	Circulating cells are variable

Marrow morphology and blood morphology agree

Blood smear

Hair-like border; Pale cytoplasm; Round to folded nucleus.

Marrow biopsy

Interstitial pale cells with oblong or reniform nuclei.

Why compare?

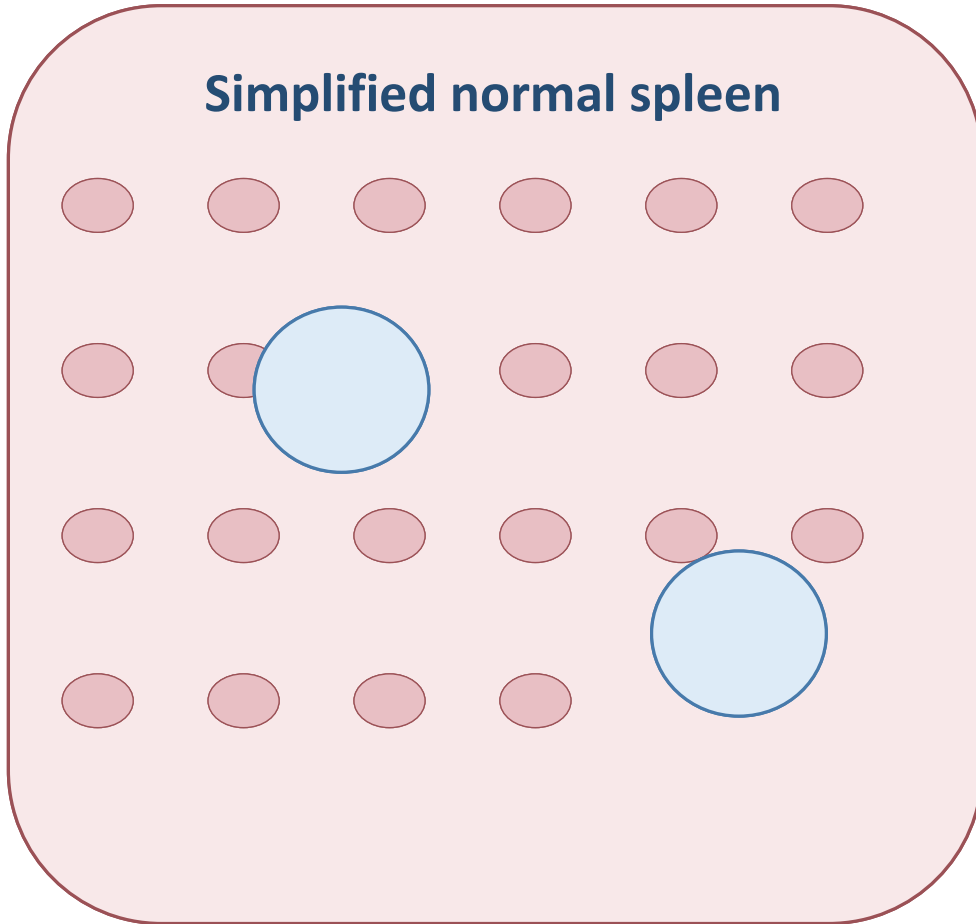
Two tissue environments change what is easiest to see.

Shared identity

Phenotype and genetics connect morphologically related populations.

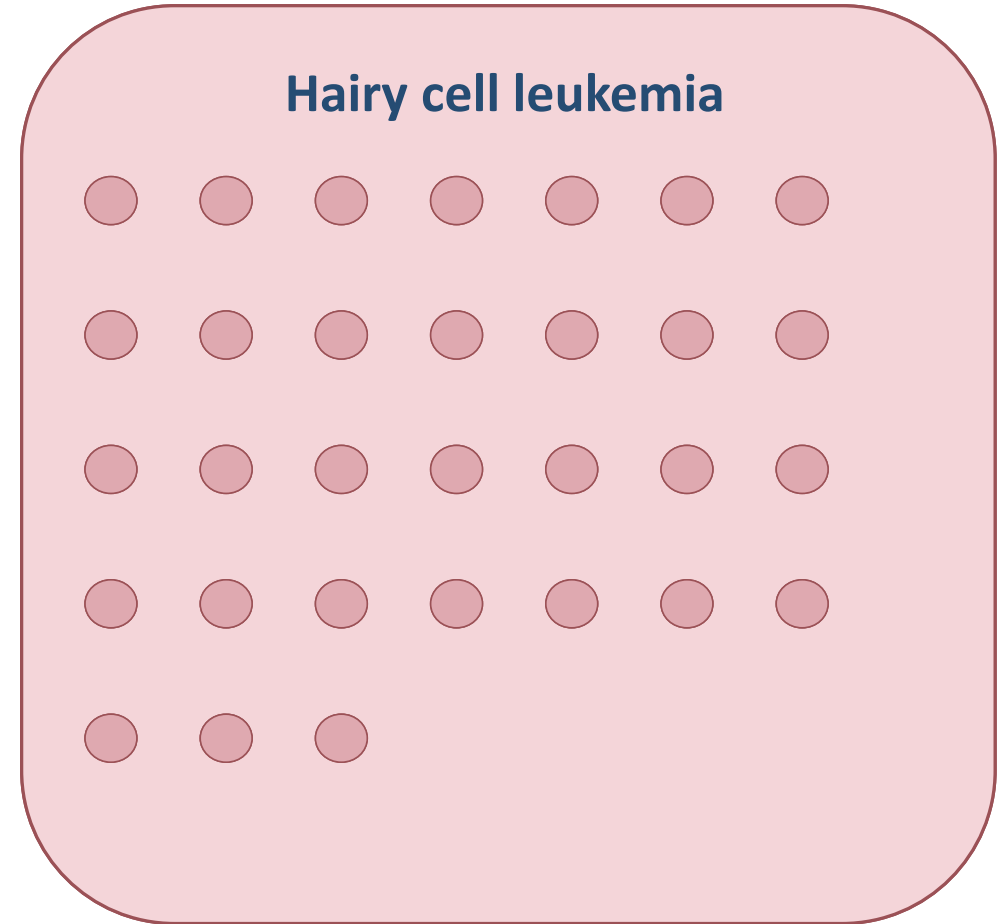
Splenic involvement centers on red pulp

Simplified normal spleen



Native schematic — not gross or histologic evidence

Hairy cell leukemia



Red-pulp expansion; White-pulp effacement

Why splenic architecture changes

- Extensive infiltration expands or replaces the red pulp.
- The normal white-pulp compartments become obliterated.
- The gross spleen may appear characteristically beefy red.
- Anatomic alteration helps explain the marked splenomegaly.

Splenomegaly may be the only examination clue

Major feature

Spleen enlargement is often substantial.

Sometimes isolated

The spleen can be the sole abnormal physical finding.

Contrast

Lymph node enlargement is uncommon.

Clinical link

The spleen may sequester circulating blood cells.

Gross splenic appearance and mechanism

Clinical / pathologic observation

- A heavy tumor burden involves splenic red pulp.
- The white-pulp architecture is progressively obscured.

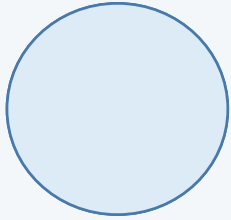
Interpretation

- A beefy-red gross appearance.
- The gross finding reflects the altered pulp distribution.

Hepatic involvement: Portal triads

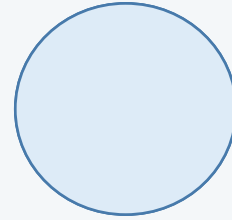
- Hepatic portal triads may be infiltrated by tumor cells.
- Hepatomegaly occurs less often than splenic enlargement.
- When present, liver enlargement is generally less pronounced.
- The liver is another component of the multisite disease pattern.

Where clinical abnormalities arise



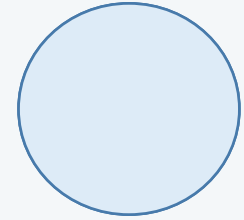
Bone marrow

Interstitial infiltration →
cytopenias



Spleen

Red-pulp expansion →
marked enlargement



Liver

Portal-triad infiltration →
sometimes hepatomegaly

Immunophenotype confirms mature B-cell identity

- Hairy cells express the pan-B-cell antigens CD19 and CD20.
- Surface immunoglobulin expression is typical.
- IgG is the most commonly described surface immunoglobulin class.
- B-lineage assignment precedes interpretation of the distinctive panel.

Distinctive immunophenotypic marker combination

B-cell identity

CD19

CD20

Surface immunoglobulin (often IgG)

Relatively distinctive markers

CD11c

CD25

CD103

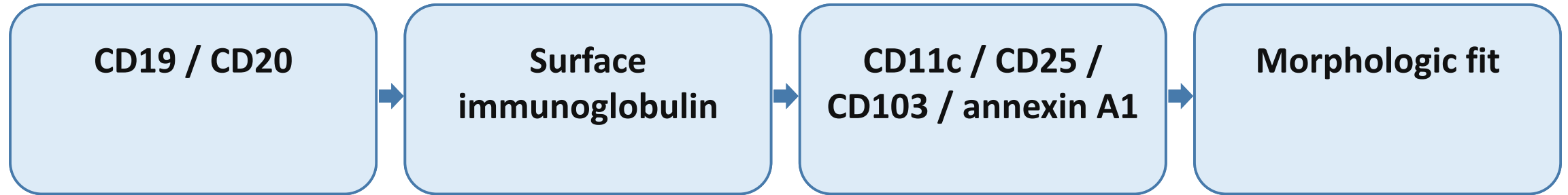
Annexin A1

Read the combined pattern with the morphologic and clinical picture.

Four relatively distinctive antigens

Marker	How Robbins uses the marker
CD11c	Part of the characteristic HCL phenotypic group
CD25	Part of the characteristic HCL phenotypic group
CD103	Part of the characteristic HCL phenotypic group
Annexin A1	Part of the characteristic HCL phenotypic group

Immunophenotyping is pattern recognition



- Neither a pan-B marker nor one isolated antigen captures the full textbook profile.

Clinical manifestation: Pancytopenia

- More than half of patients have pancytopenia account.
- Marrow infiltration impairs the blood-cell compartment.
- Splenic sequestration is an additional contributor.
- Both mechanisms must be considered together.

Two complementary routes to cytopenia



Both contributions are identified; This is not a quantitative weighting of mechanisms.

Infections may be a presenting complaint

Frequency

Approximately one-third present with infections.

Hematologic setting

Cytopenias accompany marrow/splenic disease.

Notable association

Atypical mycobacterial infections are increased.

Clinical interpretation

Infection can be a clue to the underlying hematologic disorder.

Monocytopenia and atypical mycobacteria

- Monocytopenia is commonly encountered in HCL.
- Its cause is described as uncertain.
- An association with atypical mycobacterial infection is noted.
- A possible relationship; Causality is not established.

Lymphadenopathy is relatively unusual

Clinical / pathologic observation

- Lymph node enlargement is a common lymphoma presentation.
- Some other mature B-cell tumors have prominent nodal disease.

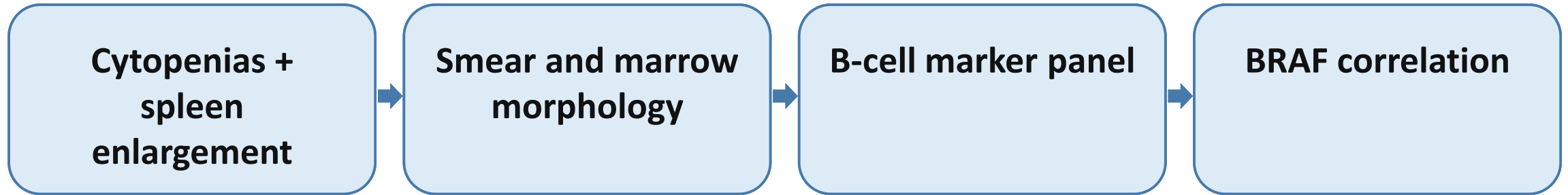
Interpretation

- In hairy cell leukemia, lymphadenopathy is rare.
- Marked splenomegaly with limited adenopathy is a stronger clue.

A compact clinicopathologic profile

Domain	Characteristic HCL feature
Clinical	Marked splenomegaly; infections; cytopenias
Blood smear	Pale cytoplasm; variable circulating cells; surface projections
Bone marrow	Interstitial infiltrate; reticulin-associated dry tap
Spleen	Red-pulp involvement, white-pulp effacement
Immunophenotype	CD19/CD20 plus CD11c/CD25/CD103/annexin A1
Molecular	BRAF V600E strongly associated

First-pass diagnostic reasoning



- This structured approach is an interpretation of the textbook features, not a formal guideline.

When circulating cells are sparse

- Do not equate a low circulating tumor burden with absent tissue involvement.
- Marrow morphology may provide the diagnostic material.
- A dry tap increases the importance of the biopsy core.
- Phenotype and genetic context help secure the integrated impression.

Differential: CLL/SLL versus HCL

Feature	Hairy cell leukemia	CLL/SLL
Dominant involvement	Marrow and spleen	Marrow and lymph nodes
Peripheral cells	Hair-like cytoplasmic edges	Small lymphocytes; smudge cells
Clinical clue	Marked spleen; nodes rare	Generalized adenopathy common
Typical phenotype	CD11c, CD25, CD103, annexin A1	CD5, CD23

Differential: Mantle cell lymphoma

Feature	Hairy cell leukemia	Mantle cell lymphoma
Dominant pattern	Spleen / marrow	Often disseminated lymphadenopathy
Driver	BRAF activation	Cyclin D1::IGH translocation
Phenotype emphasized	CD11c/CD25/CD103/annexin A1	CD5+, often CD23-
Course	Very indolent	Moderately aggressive

Differential: Follicular lymphoma

Feature	Hairy cell leukemia	Follicular lymphoma
Typical major site	Spleen and marrow	Generalized lymphadenopathy
Growth/morphology	Interstitial marrow; hairy cytoplasm	Follicles with centrocytes/centroblasts
Molecular	BRAF mutation	BCL2::IGH
Key phenotypic markers	CD11c/CD25/CD103/annexin A1	CD10 and BCL6

Differential: Marginal zone lymphoma

Shared context

Both are mature, memory B-cell–associated neoplasms.

Hairy cell leukemia

Characteristic BRAF association and hairy morphology.

Marginal zone lymphoma

A heterogeneous group of nodal, splenic and extranodal B-cell tumors.

Key distinction

Antigen-linked pathogenesis for extranodal MALT lymphoma, not HCL.

Molecular drivers distinguish related tumors

Neoplasm	Characteristic genetic association in Robbins
Hairy cell leukemia	BRAF activating point mutation
Follicular lymphoma	t(14;18) / BCL2::IGH
Mantle cell lymphoma	t(11;14) / cyclin D1::IGH
Extranodal marginal zone lymphoma	Selected translocations involving BCL10 or MALT1

Three common diagnostic pitfalls

“No leukocytosis, so not leukemia”

Circulating hairy-cell numbers are highly variable.

“No aspirate, so no marrow disease”

Reticulin can cause an uninformative dry tap.

“BRAF V600E equals HCL”

The same mutation occurs in other tumor types.

“Splenomegaly is nonspecific”

Combine splenic pattern with smear and immunophenotype.

Indolent course does not mean no morbidity

- The neoplasm is typically slowly progressive.
- Cytopenias and infections can nevertheless produce major clinical problems.
- Marrow and splenic infiltration explain much of the disease burden.
- Clinical behavior and treatment responsiveness are distinct questions.

Unusually prolonged treatment responses

- Exceptional sensitivity to relatively gentle chemotherapy.
- Remissions are often long-lasting.
- The explanation for this unusual chemosensitivity remains unclear.
- The overall outlook is generally excellent.

Late relapse does not necessarily imply resistance

Indolent onset

Response

Long remission

Late relapse



Slow course

Gentle regimen

Often prolonged

May respond again

Conceptual sequence; Timing is variable and the figure is not a survival curve.

Retreatment can remain effective

Late relapse

Recurrence often occurs after five or more years.

Repeat treatment

Many relapsing tumors respond again to the same agents.

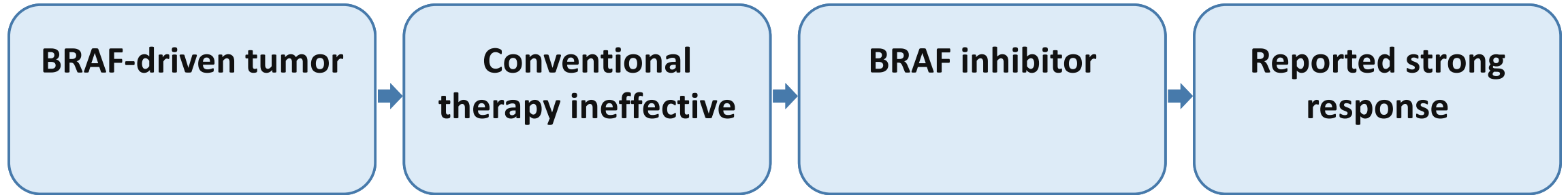
Unusual property

This pattern is uncommon among human cancers.

Interpretation

Recurrence and therapeutic failure are not synonymous in this disease.

BRAF inhibition in difficult-to-treat disease



- Excellent responses in tumors refractory to conventional chemotherapy.
- No specific agent, dose or formal treatment algorithm is supplied by this section.

Prognosis integrates biology and treatment

Biology

Generally indolent disease course.

Clinical morbidity

Complications from marrow and splenic infiltration.

Therapy

Long remissions, with frequent retreatment sensitivity.

Overall outcome

Excellent prognosis account.

Case 1: Splenomegaly with cytopenias

Hypothetical teaching scenario

A middle-aged adult has substantial splenomegaly, multiple cytopenias and little palpable lymphadenopathy.

- Which clinical pattern makes HCL worth considering?
- What blood and marrow findings would strengthen that impression?

Case 1: Pathologic interpretation

Clinical / pathologic observation

- Marked splenomegaly and pancytopenia align with common findings.
- Minimal lymphadenopathy is compatible with HCL.

Interpretation

- Look for characteristic cells in peripheral blood.
- Confirm marrow involvement and phenotypic features rather than diagnosing by examination alone.

Case 2: A marrow aspirate yields no material

Hypothetical teaching scenario

Peripheral blood shows few suspicious B cells. The marrow aspirate is unsuccessful, although cytopenias persist.

- What source-described matrix explains this event?
- Which marrow specimen remains valuable?

Case 2: Resolving the dry tap

Clinical / pathologic observation

- Reticulin-rich extracellular matrix can entrap infiltrating cells.
- Circulating neoplastic-cell numbers may be low.

Interpretation

- Evaluate the marrow core biopsy for an interstitial infiltrate.
- Use immunophenotype to correlate tissue and blood findings.

Case 3: A BRAF V600E result

Hypothetical teaching scenario

A B-cell neoplasm harbors BRAF V600E, but the clinical setting and morphology have not yet been established.

- Does this mutation alone prove hairy cell leukemia?
- Which independent observations are needed?

Case 3: Avoiding molecular overinterpretation

Clinical / pathologic observation

- BRAF mutation occurs in more than 90% of hairy cell leukemias.
- BRAF V600E also occurs in melanoma and Langerhans cell histiocytosis.

Interpretation

- Use morphology, B-cell lineage and disease distribution.
- A molecular alteration is evidence within an integrated diagnosis, not an identity label.

Synthesis: One disease, five convergent domains

Distribution

Marrow, splenic red pulp and often hepatic portal triads.

Morphology

Projections; Folded nuclei; Reticulin-rich marrow infiltrate.

Phenotype

CD19/CD20; CD11c/CD25/CD103/annexin A1.

Genetic and clinical

Activating BRAF; Cytopenias, spleen enlargement, indolence.

References and source limitations

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 13, page 549.
- Chapter 13, Table 13.6 and adjacent mature B-cell neoplasm sections support comparisons.
- Chapter 7 provides background on the RAS–BRAF–MAPK signaling cascade.
- Original textbook Figure 13.17 was unavailable; morphology diagrams are labeled schematics, not clinical images.