

Lymphoplasmacytic lymphoma

Mature B-cell neoplasia • Morphology • IgM-related clinical pathology

Biology

Diagnostic morphology

Clinicopathologic effects

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Learning outcomes

By the end of this lecture, learners should be able to:

- Identify the lymphoid and plasma-cell components of the neoplasm.
- Explain MYD88-associated survival signaling and the IgM phenotype.
- Connect marrow infiltration and IgM effects to clinical manifestations.
- Distinguish key mimics and apply an integrated diagnostic approach.

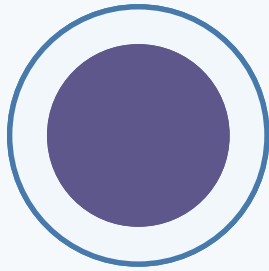
An indolent neoplasm of mature B cells

Lymphoplasmacytic lymphoma combines lymphoid proliferation with terminal plasma-cell differentiation.

- Arises predominantly in older adults.
- The marrow is usually involved at presentation.
- A monoclonal immunoglobulin, most often IgM, is commonly secreted.

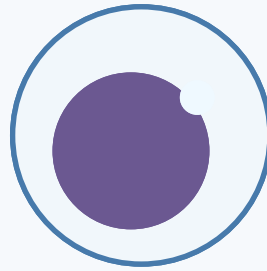
The lineage spectrum explains the name

A single neoplasm spans small lymphocytes, plasmacytoid lymphocytes, and plasma cells.



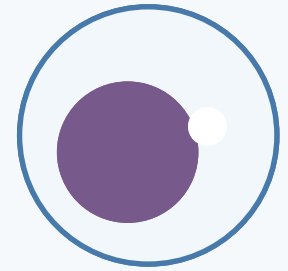
Small B lymphocyte

Limited cytoplasm; Lymphoid phenotype



Plasmacytoid lymphocyte

Intermediate differentiation



Plasma cell

Secretory immunoglobulin phenotype

Schematic cell profiles — not a histologic specimen.

The same tumor shows lymphoid cells, intermediate plasmacytoid cells and secretory plasma cells.

Lymphoma and secretory disorder coexist

Two simultaneous sources of disease burden

Tissue infiltration

Tumor-cell infiltration produces marrow dysfunction and organ enlargement.

IgM-mediated effects

Secreted IgM can alter blood flow, red-cell survival, coagulation, and cold-dependent protein behavior. Symptoms from the paraprotein need not parallel visible tissue enlargement.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Why it belongs among B-cell neoplasms

The lymphoid population expresses B-cell markers and surface immunoglobulin.

- Plasma-cell differentiation occurs within the same neoplastic process.
- This differs from a proliferation made almost entirely of plasma cells.
- Lineage, morphology, and immunoglobulin concordance must be interpreted together.

LPL and Waldenström macroglobulinemia

Pathologic entity and clinical syndrome are related but not identical concepts.

LPL: Tumor identity

LPL is the underlying B-cell lymphoid neoplasm.

Waldenström: IgM-associated presentation

Waldenström macroglobulinemia describes the IgM-associated clinicopathologic presentation. An IgM monoclonal protein alone is not sufficient to classify any B-cell neoplasm as LPL.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

The age profile shapes the clinical question

Usual presentation in the sixth or seventh decade of life.

- A new monoclonal IgM in an older adult merits clinicopathologic correlation.
- Fatigue, anemia, and organ enlargement can be the initial clues.
- The age range supports suspicion, but is not a diagnostic criterion.

Presentations are not uniform

Symptoms can arise from tumor infiltration, secreted IgM, or both.

Cellular disease

Constitutional symptoms:
Weakness, fatigue, weight
loss.

Molecular / IgM effect

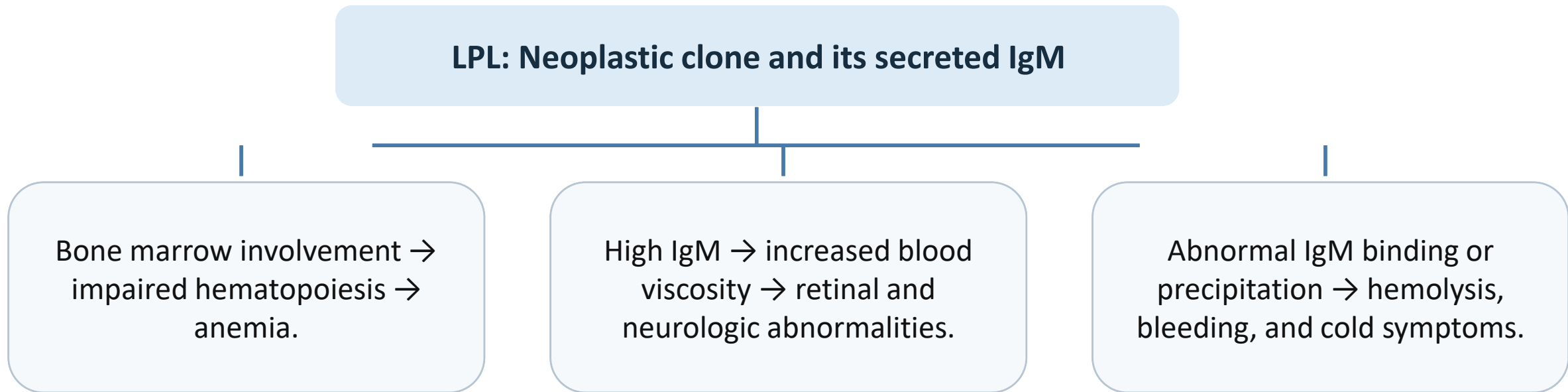
Tissue involvement: Anemia,
lymphadenopathy,
splenomegaly, hepatomegaly.

Clinical interpretation

IgM complications: Visual,
neurologic, bleeding, cold-
related abnormalities.

The clinicopathologic causal map

Distinguish the cellular burden from the serum-protein burden.



Conceptual causal pathways; Arrows indicate interpretation, not measured patient-specific effects.

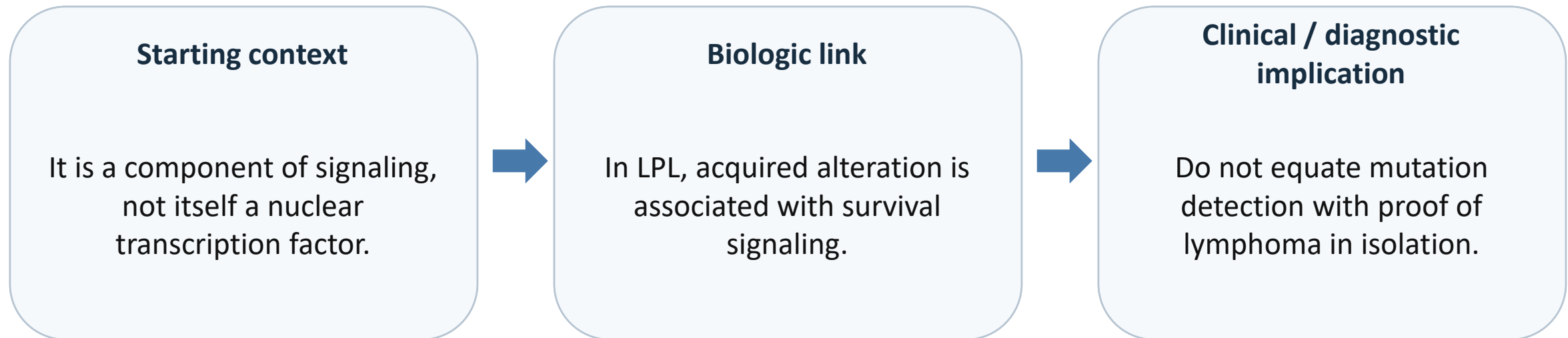
MYD88 is a central molecular association

Acquired MYD88 mutations in virtually all LPL cases.

- MYD88 encodes a signaling adaptor protein.
- Its mutation is linked to pathways supporting lymphoma-cell growth and survival.
- Molecular findings are supportive and must be interpreted with the tissue phenotype.

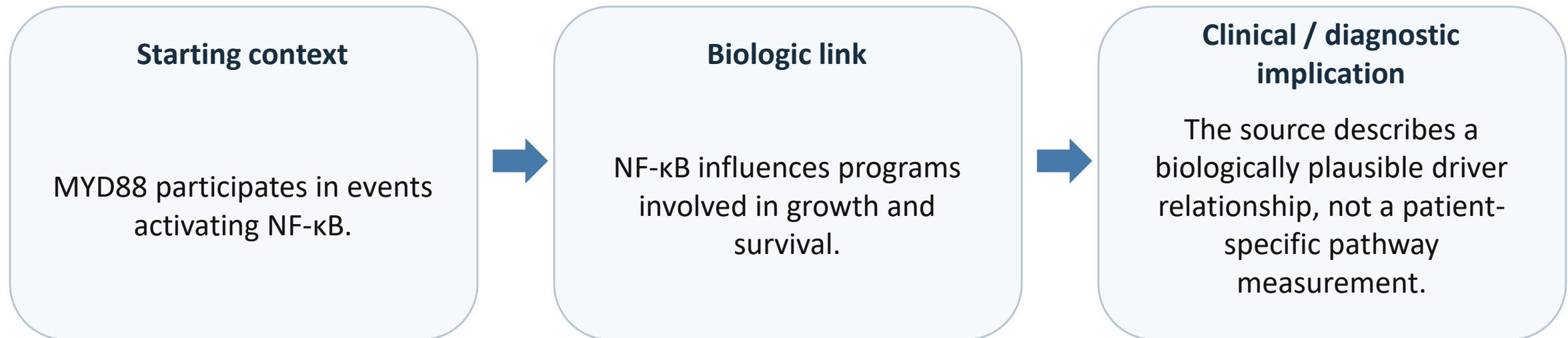
What an adaptor protein contributes

MYD88 relays upstream receptor-associated signals toward intracellular transcriptional responses.



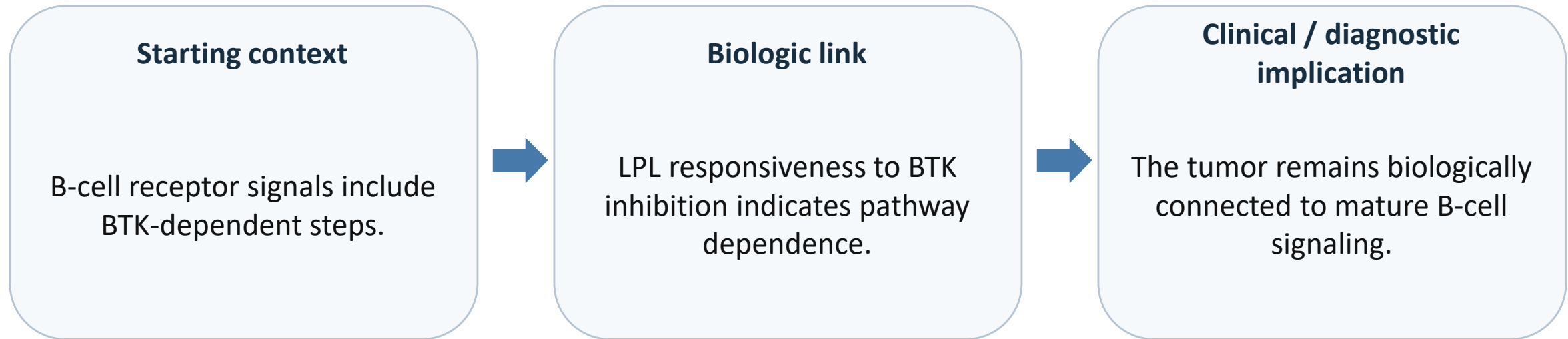
NF-κB links signaling to cell survival

Activated signaling converges on a transcriptional response that may favor the tumor clone.



B-cell receptor signaling remains relevant

Bruton tyrosine kinase (BTK) is a functional therapeutic vulnerability.



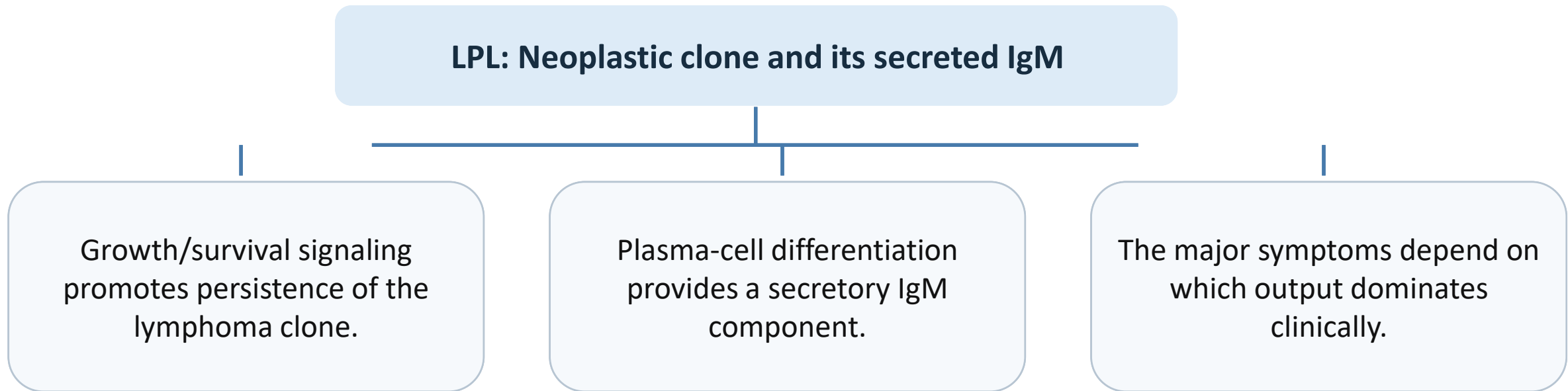
Molecular support is not a substitute for morphology

High MYD88 association does not eliminate the differential diagnosis.

- Other B-cell neoplasms may show plasmacytic differentiation.
- MYD88 alterations can overlap across low-grade B-cell disorders.
- Interpret molecular results alongside cellular composition, immunophenotype, and clinical findings.

Two related pathogenic outputs

Cell-survival mechanisms and immunoglobulin secretion produce different consequences.



Conceptual causal pathways; Arrows indicate interpretation, not measured patient-specific effects.

A mechanistic explanation for targeted therapy

Treatment vulnerabilities reflect identifiable biologic compartments.

Cellular disease

Anti-CD20 targets the B-cell surface-marker-bearing population.

Molecular / IgM effect

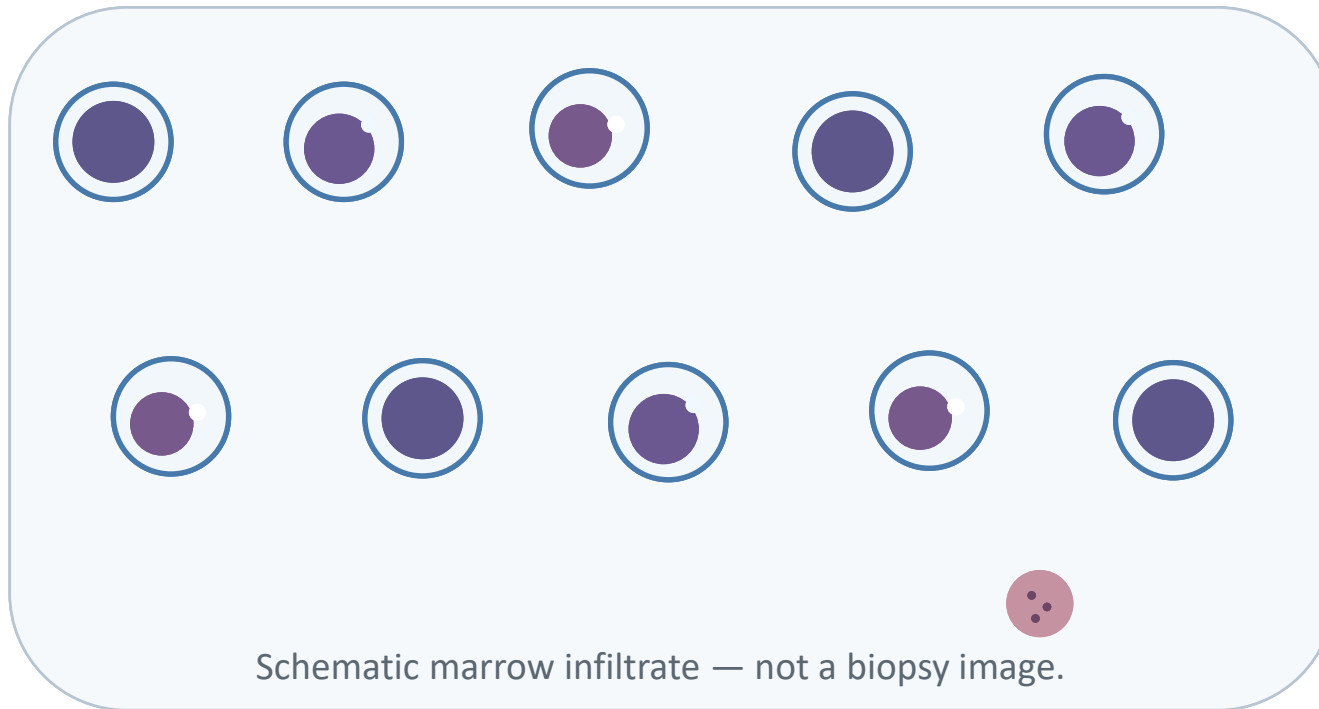
BTK inhibitors disrupt a signaling dependency.

Clinical interpretation

Plasmapheresis removes circulating IgM but does not directly eradicate tissue lymphoma.

Bone marrow is the diagnostic tissue focus

The typical infiltrate contains three morphologic cell populations.

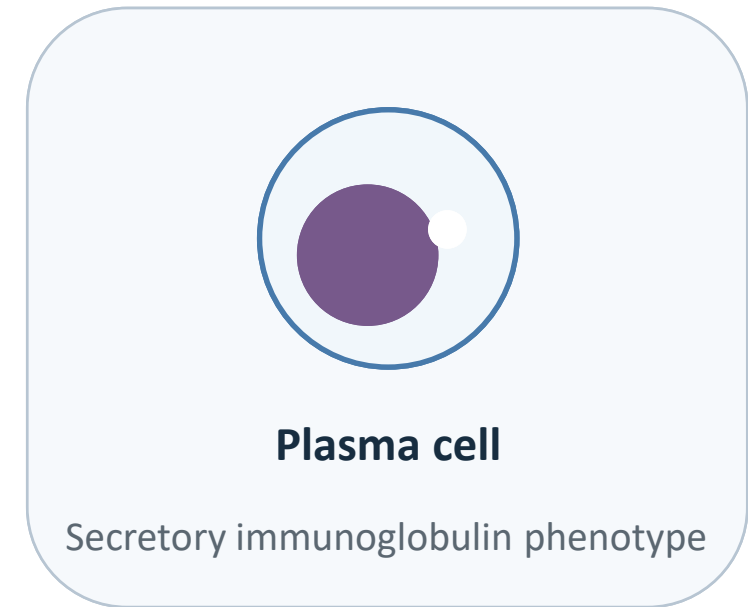
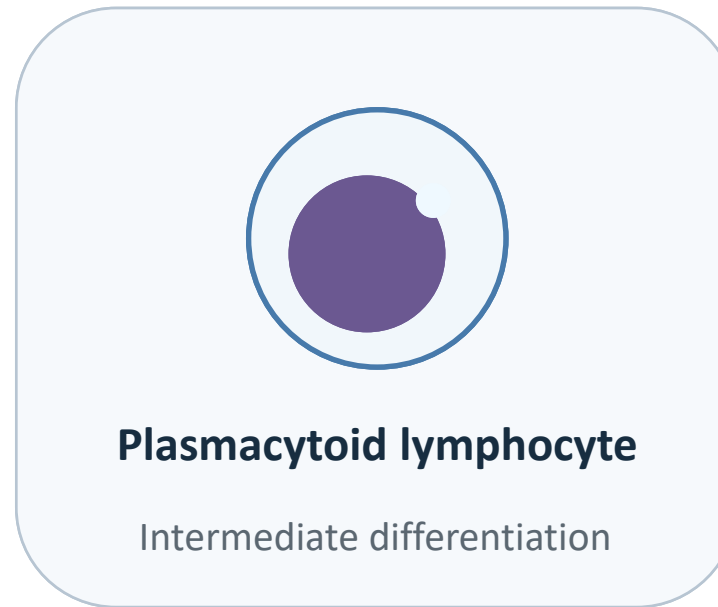


What to recognize

- Small lymphocytes.
- Plasmacytoid lymphocytes.
- Mature plasma cells, in varying proportions.

Small lymphocytes establish the B-cell component

Cells with a small lymphoid appearance coexist with secretory elements.

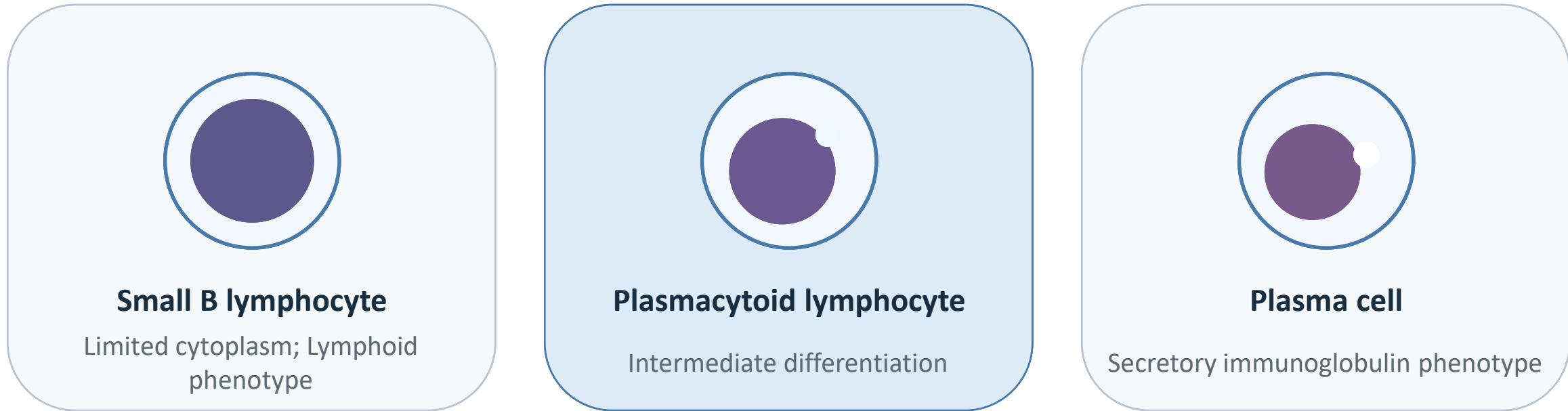


Schematic cell profiles — not a histologic specimen.

The small-cell compartment is part of the neoplastic infiltrate.

Plasmacytoid lymphocytes mark differentiation

The intermediate population is central to morphologic recognition.

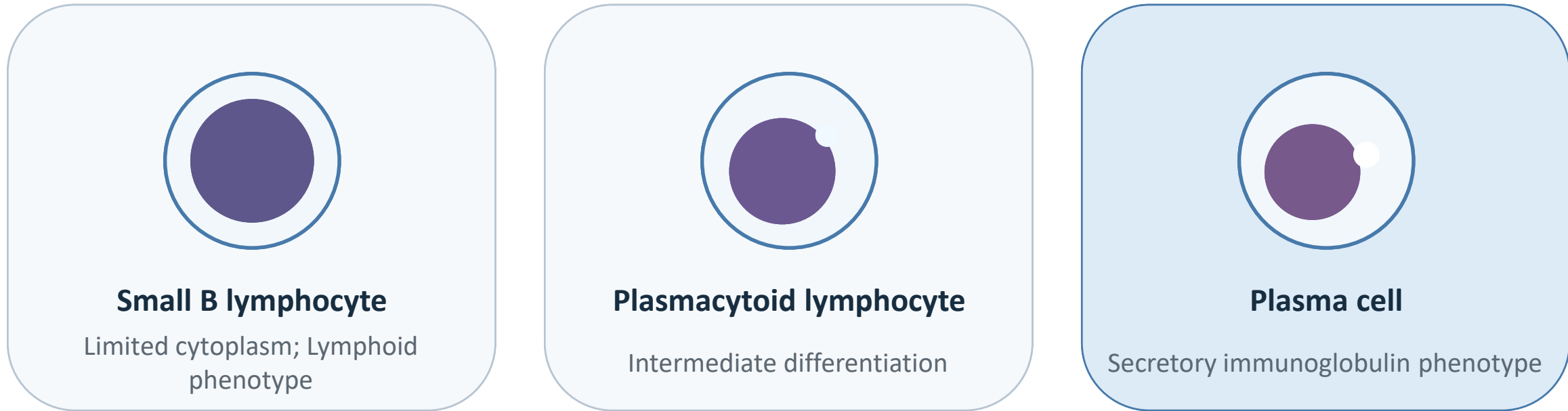


Schematic cell profiles — not a histologic specimen.

The infiltrate is not restricted to two disconnected cell types.

Plasma cells explain the secreted paraprotein

Terminally differentiated cells provide the immunoglobulin secretory component.

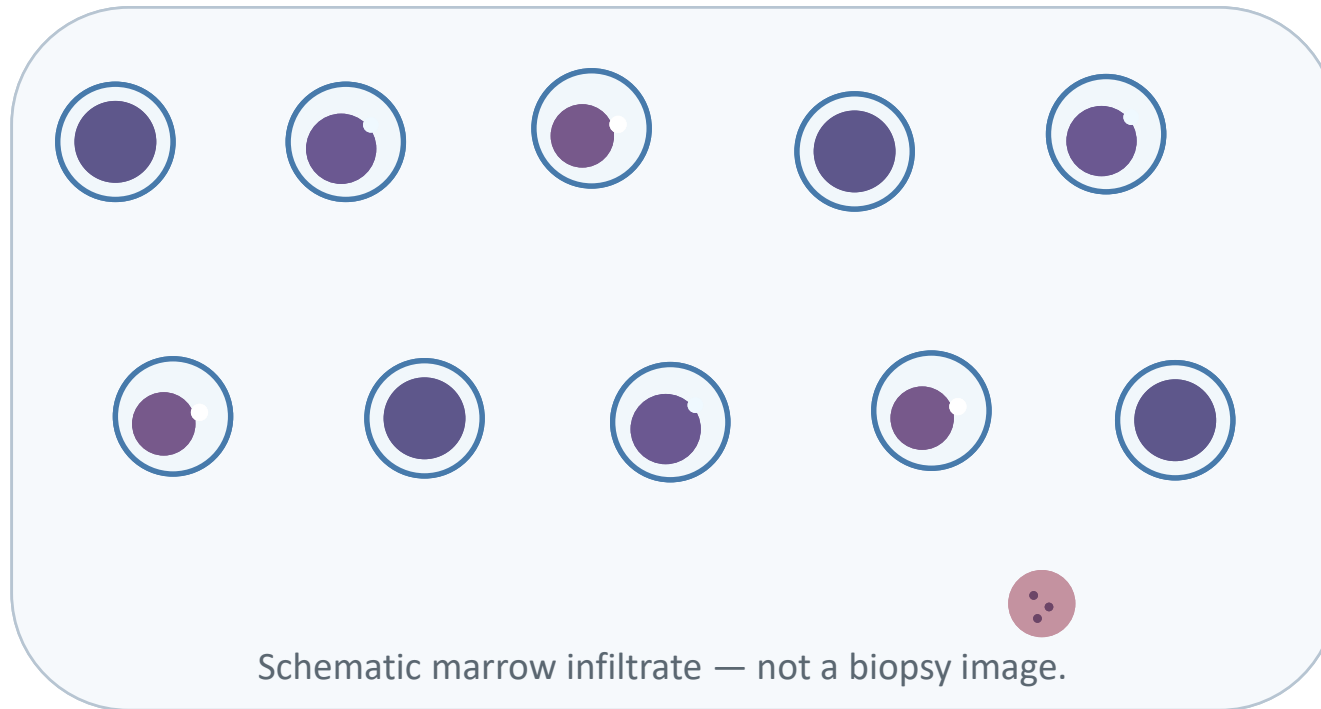


Schematic cell profiles — not a histologic specimen.

The secreted immunoglobulin matches that displayed by the lymphoid cells.

Mast cells are an important accompanying clue

Marrow infiltration is often associated with mast-cell hyperplasia.



What to recognize

- The mast cells are an accompanying population, not the defining malignant cell type.
- Identify them separately from lymphocytes and plasma cells.
- This is supportive morphology, not a standalone diagnostic test.

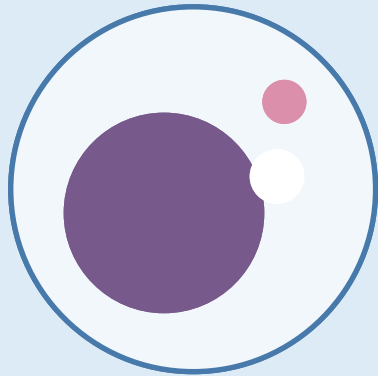
A subset of larger lymphoid cells may occur

Some tumors include larger cells with distinctive nuclear changes.

- More vesicular chromatin may be present.
- Nucleoli can become prominent.
- A small large-cell component is not, by itself, proof of transformation.

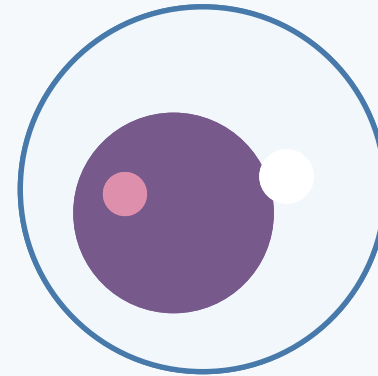
Russell bodies: Cytoplasmic immunoglobulin

Accumulated immunoglobulin may form PAS-positive cytoplasmic inclusions.



Russell body

Immunoglobulin
accumulation in cytoplasm



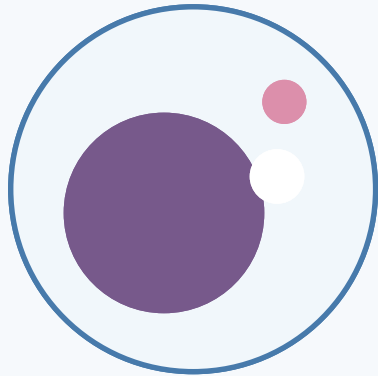
Dutcher body

Immunoglobulin
accumulation in the
nuclear profile

Schematic subcellular locations; Not diagnostic photomicrographs.

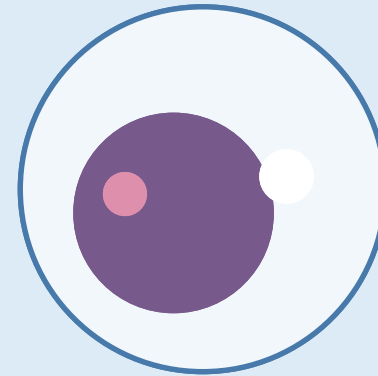
Dutcher bodies: Nuclear pseudoinclusions

Immunoglobulin-containing inclusions can appear within the nuclear profile.



Russell body

Immunoglobulin
accumulation in cytoplasm



Dutcher body

Immunoglobulin
accumulation in the
nuclear profile

Schematic subcellular locations; Not diagnostic photomicrographs.

Morphology is a composite pattern

The diagnostic impression arises from several findings taken together.

Mixed small lymphoid and plasma-cell differentiation.

Associated mast-cell hyperplasia.

Occasional Russell or Dutcher bodies.

Possible larger lymphoid cells with more open chromatin.

Systemic dissemination may be present

Lymph nodes, spleen, and liver are often involved at diagnosis.

Bone marrow

Mixed cellular infiltrate

Lymph nodes

Lymphadenopathy

Spleen

Splenomegaly

Liver

Hepatomegaly

Nervous-system infiltration is uncommon

Progressive disease can involve neural structures.

Direct infiltration

Nerve roots and meninges can be infiltrated.

Hyperviscosity physiology

Brain involvement is described as rarer. Distinguish direct infiltration from hyperviscosity-related neurologic symptoms.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

The immunophenotype has two compartments

Lineage markers and secretory behavior must be assigned to the correct cells.

Lymphoid compartment

Lymphoid cells: CD20 and surface immunoglobulin.

Plasma-cell compartment

Plasma cells: Secretion of concordant immunoglobulin, generally IgM. Concordance is more informative than an isolated immunostain.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

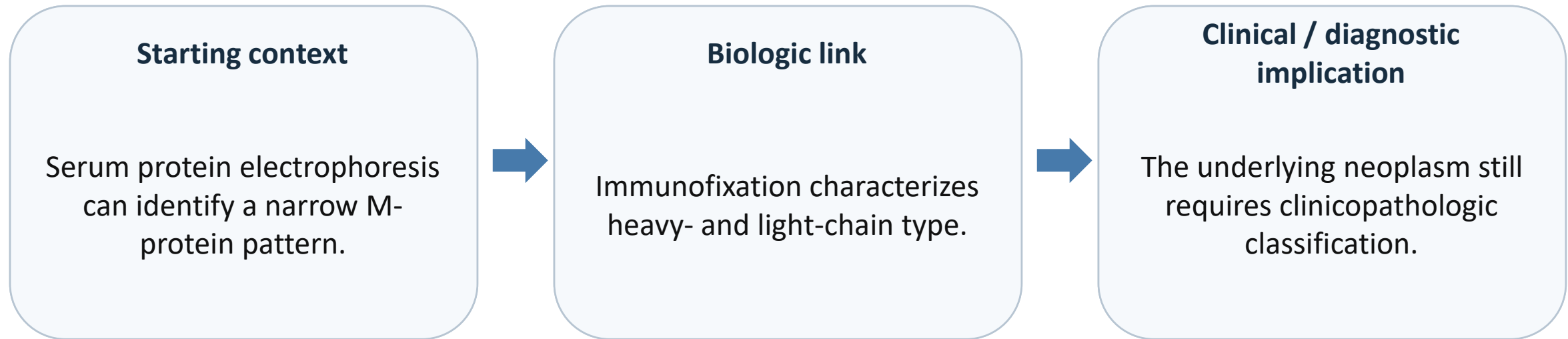
Monoclonal IgM is a biologic readout

An IgM paraprotein reflects the tumor's secretory differentiation.

- It gives a measurable serum feature of the clone.
- High IgM can produce clinical pathology independently of bulk infiltration.
- Neither IgM concentration nor a single protein study replaces marrow assessment.

What a serum M component means

A restricted immunoglobulin band suggests monoclonal protein production.



An integrated work-up has distinct questions

Avoid using one test to answer every diagnostic question.

- 1 Marrow: Which cell populations and infiltration pattern are present?
- 2 Immunophenotype: Is there a B-cell and concordant secretory component?
- 3 Serum studies: Is monoclonal IgM present and clinically consequential?
- 4 Molecular data: Does MYD88 support the integrated diagnosis?

Why IgM alone is insufficient

An IgM paraprotein can accompany more than one B-cell or plasma-cell process.

- The protein identifies a secretory phenotype, not a unique histologic entity.
- A mixed lymphoid–plasma-cell marrow infiltrate is essential context.
- Molecular and lineage evidence helps resolve competing diagnoses.

CLL/SLL: Overlap and distinction

Both diseases can contain small mature B cells, but the dominant patterns differ.

CLL/SLL: Small-cell program

CLL/SLL often has proliferation centers and a characteristic small-cell infiltrate.

LPL: Mixed lymphoplasmacytic program

LPL has conspicuous plasma-cell differentiation and often high IgM. The presence of plasmacytic cells alone is not exclusive to LPL.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Marginal zone lymphoma: A key mimic

Plasmacytic differentiation can occur in marginal zone lymphoma.

MZL: Diverse anatomic settings

MZL can arise in nodes, spleen, or extranodal tissues.

LPL: Marrow-based mixed infiltrate

Clinical distribution and marrow architecture contribute to interpretation. MYD88 supports LPL in context but does not resolve every overlapping case.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Multiple myeloma: Plasma-cell dominance

The major clinical complications provide a useful contrast.

Myeloma: Plasma-cell disease

Myeloma characteristically produces lytic bone destruction.

LPL: Lymphoid + plasma-cell disease

Light-chain-related kidney injury and amyloidosis are prominent concerns in myeloma. Bone destruction is absent and free-light-chain complications are relatively rare in LPL.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Monoclonal gammopathy is not synonymous with lymphoma

A serum monoclonal protein may occur without a symptomatic lymphoid malignancy.

Monoclonal protein finding

MGUS is defined by asymptomatic monoclonal gammopathy.

Demonstrable lymphoid neoplasm

LPL requires evidence of a compatible lymphoid neoplasm. Clinical findings and marrow morphology separate protein detection from tumor diagnosis.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Differential diagnosis: Discriminating evidence

No single feature should be used as an isolated rule.

01

Mixed marrow cellularity and concordant IgM favor LPL.

02

Proliferation centers suggest CLL/SLL in the appropriate setting.

03

Lytic skeletal disease and light-chain nephrotoxicity suggest myeloma.

04

Marginal zone lymphoma remains an important overlap diagnosis.

A common interpretive trap

A MYD88 result cannot replace a morphologic diagnosis.

- A positive mutation finding supports a compatible LPL phenotype.
- A negative result should prompt reassessment rather than automatic exclusion.
- Correlate clone, serum protein, architecture, and clinical presentation.

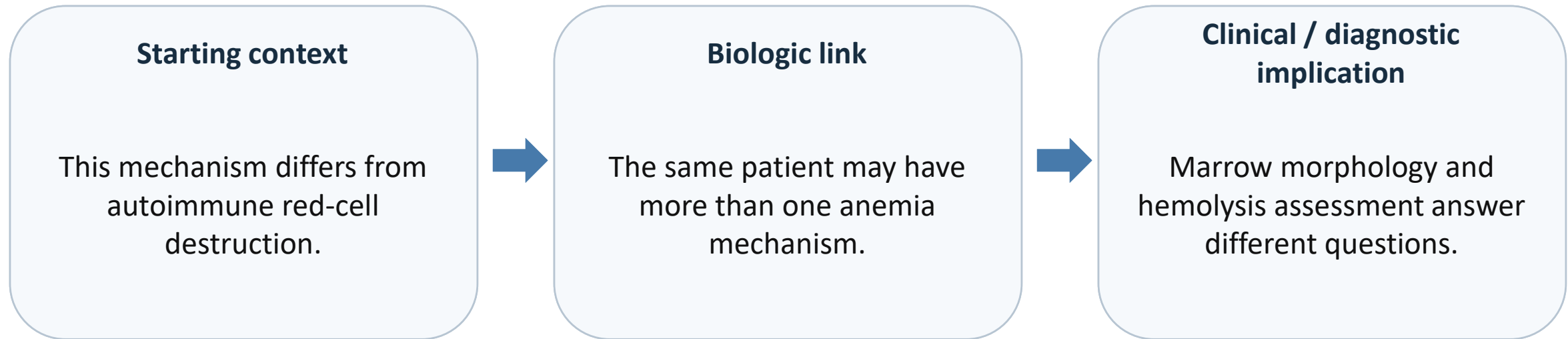
Constitutional symptoms are common

Weakness, fatigue, and weight loss may dominate the first consultation.

- They are nonspecific symptoms of systemic disease.
- Evaluate blood counts and evidence of marrow involvement.
- Do not assume every symptom results directly from high IgM.

Anemia: A direct marrow consequence

Replacement of functional marrow by neoplastic cells contributes to anemia.



Organ enlargement reflects tissue involvement

About half of patients have lymphadenopathy, hepatomegaly, or splenomegaly.

Bone marrow

Mixed cellular infiltrate

Lymph nodes

Lymphadenopathy

Spleen

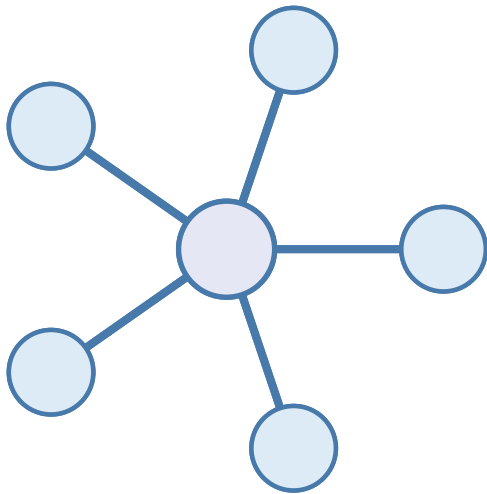
Splenomegaly

Liver

Hepatomegaly

The physical properties of IgM matter

At high concentration, this large immunoglobulin increases blood viscosity.



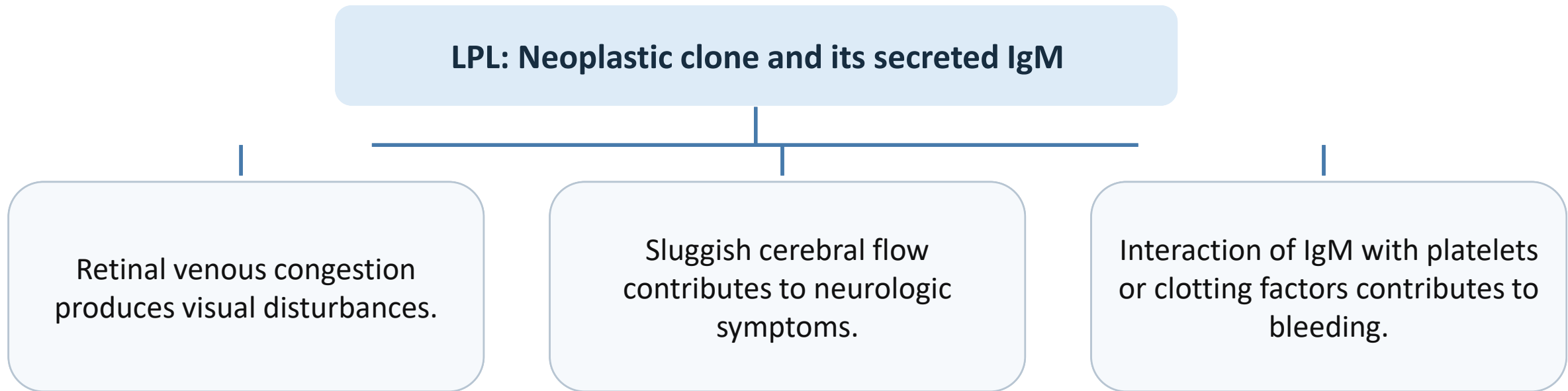
Conceptual high-molecular-size IgM

Schematic — not a molecular structural model.

- IgM is predominantly confined to the intravascular space.
- High concentrations reduce efficient flow in the microcirculation.
- The resulting syndrome is clinically termed hyperviscosity.

Hyperviscosity is a circulation problem

Viscous blood impairs tissue perfusion and vascular function.



Conceptual causal pathways; Arrows indicate interpretation, not measured patient-specific effects.

Ocular signs are particularly informative

The retina gives a direct view of venous flow disturbance.

- Tortuous, distended retinal veins indicate venous congestion.
- Retinal hemorrhages and exudates may contribute to reduced vision.
- Visual symptoms in a high-IgM patient require urgent clinical assessment.

Neurologic manifestations of hyperviscosity

Reduced efficient blood flow can impair nervous-system function.

Flow-related dysfunction

Headache and dizziness may occur early.

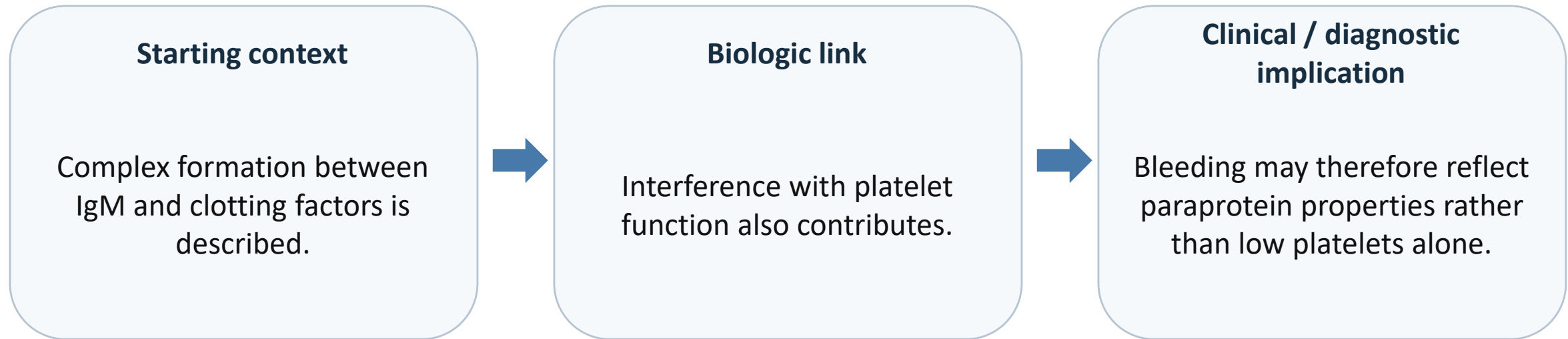
Direct tissue infiltration

Deafness and stupor represent more severe reported manifestations. Mechanism differs from rare direct lymphoma infiltration of nerves or CNS.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Bleeding can occur despite abundant IgM

High IgM interferes with normal hemostatic function.



Cryoglobulinemia: Precipitation in the cold

Some secreted IgM precipitates as temperature falls.

Cooler conditions

This is a physicochemical property of the immunoglobulin.

IgM-specific interaction

Cold precipitation can disturb peripheral perfusion.

Clinical consequence: Raynaud phenomenon and cold urticaria are described symptoms.

Raynaud phenomenon illustrates cold sensitivity

The clinical clue is peripheral vascular reactivity associated with cold.

- Cold-exposed acral regions can develop episodic symptoms.
- Precipitating IgM is a different process from the rise in whole-blood viscosity.
- Link symptoms to the IgM mechanism demonstrated in the individual patient.

Cold urticaria is a distinct clinical clue

Cold-related skin symptoms can accompany IgM cryoprecipitation.

- Cold exposure precedes the characteristic urticarial reaction.
- Cryoglobulin-related effects are not interchangeable with cold agglutinin hemolysis.
- A single IgM-producing clone can produce diverse clinical effects.

Cold agglutinins can cause hemolysis

IgM autoantibodies bind erythrocytes more avidly below 37°C.

Cooler conditions

Autoimmune hemolysis in about 10% of patients.

IgM-specific interaction

This is a red-cell immune mechanism, not marrow replacement.

Clinical consequence: The diagnosis depends on hemolysis evaluation in the clinical setting.

Two cold-dependent mechanisms are not identical

The same ambient trigger does not imply the same molecular event.

Cold precipitation

Cryoglobulinemia: IgM precipitates when cooled.

Red-cell binding

Cold agglutinin hemolysis: IgM binds red cells in cooler conditions. Different target phenomena lead to different organ manifestations.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Separate the major IgM syndromes

Mechanism-specific recognition is more useful than memorizing an isolated symptom list.

01	Hyperviscosity → retinal and neurologic symptoms.
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02	Hemostatic interference → abnormal bleeding.
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03	Cryoprecipitation → Raynaud phenomenon or cold urticaria.
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04	Cold agglutinins → autoimmune hemolysis.
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Neurologic symptoms require two explanations

A neurologic problem may reflect circulation or direct lymphomatous infiltration.

High-IgM circulation effect

Hyperviscosity is associated with sluggish blood flow.

Anatomic infiltration

Progression can involve nerve roots and meninges; Brain involvement is rarer. Context, examination, and relevant investigations distinguish these mechanisms.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Treating the clone and removing IgM are different

Two therapeutic goals act on different compartments.

Control the lymphoma

Disease-directed therapy seeks to control lymphoma growth.

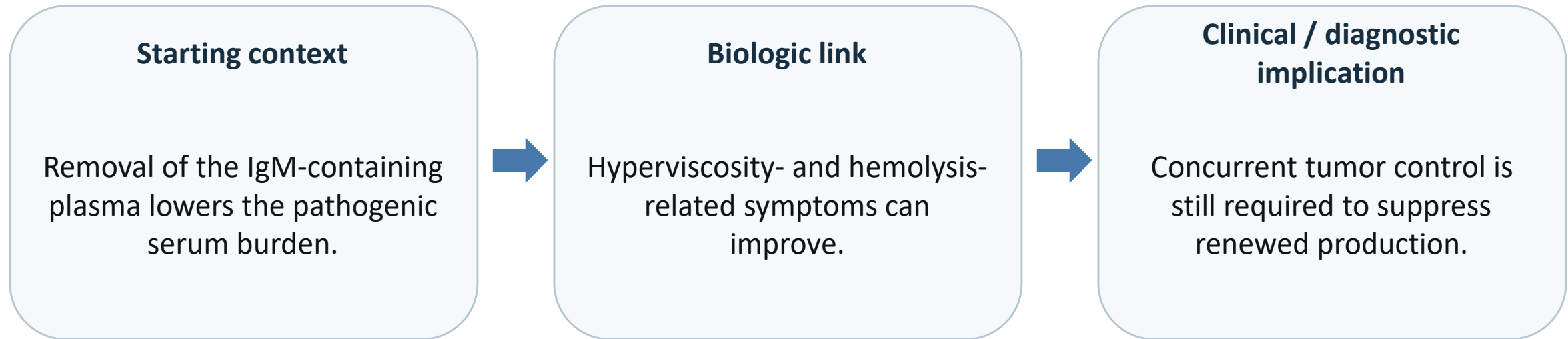
Reduce circulating IgM

Plasmapheresis reduces the circulating IgM burden. Serum-protein removal alone does not eliminate IgM-producing neoplastic cells.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

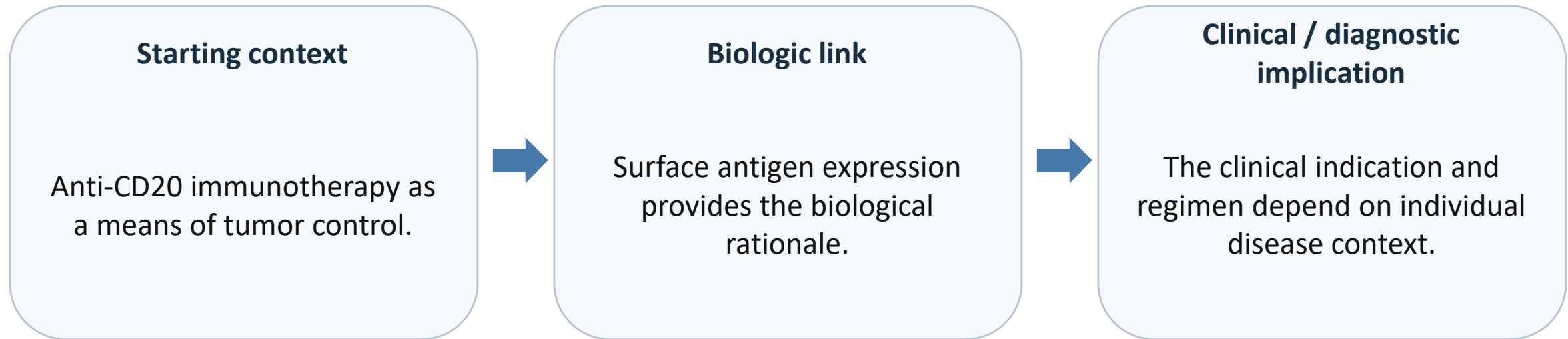
Why plasmapheresis provides rapid relief

Most IgM remains intravascular, making physical removal biologically useful.



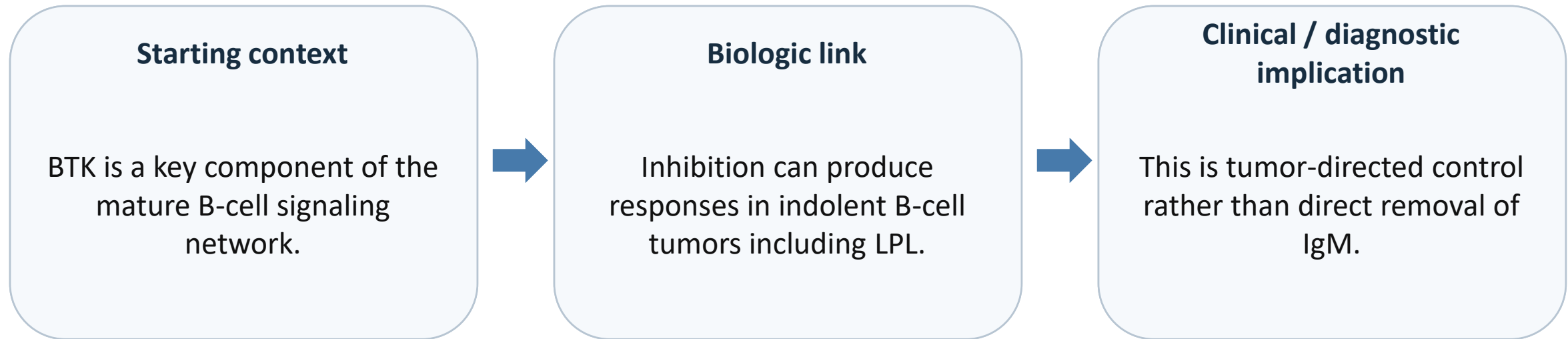
Anti-CD20 treatment targets B cells

The neoplastic lymphoid compartment expresses the CD20 surface antigen.



BTK inhibitors target signaling dependence

The response to BTK inhibition supports a B-cell-receptor signaling vulnerability.



Indolence does not mean absence of risk

LPL is generally a slow-growing disease but may remain clinically consequential.

- Symptoms can arise from IgM even without marked tumor growth.
- Transformation to large-cell lymphoma is uncommon, but recognized.
- Median survival greater than 10 years with recent therapies.

Longitudinal assessment must follow both axes

An integrated follow-up asks about cells and circulating protein.

Cellular disease status

Reassess anemia, organ involvement, and systemic symptoms.

IgM clinical effects

Evaluate IgM-related visual, neurologic, bleeding, and cold manifestations. Interpret changes in paraprotein alongside the clinical picture.

Interpret the two components together; Neither alone is equivalent to a complete diagnosis.

Case 1: Visual symptoms and bleeding

A 68-year-old has fatigue, episodic blurred vision, mucosal bleeding, and serum monoclonal IgM.

- Which pathophysiologic process explains the visual and bleeding findings?
- What additional clinical clue would help identify the circulating protein effect?
- Why might a therapy directed at the plasma compartment be considered?

Case 1: Hyperviscosity explains the pattern

High circulating IgM links retina, nervous system, and hemostasis.

- Retinal venous distention supports an IgM-related flow disturbance.
- Platelet/clotting-factor interference explains bleeding.
- Plasmapheresis targets intravascular IgM, whereas lymphoma therapy controls production.

Case 2: Marrow mixed-cell infiltrate

A marrow biopsy shows small lymphocytes, plasmacytoid cells, plasma cells, and increased mast cells.

- Which lymphoid neoplasm fits this morphologic pattern?
- What B-cell marker is expected on the lymphoid component?
- Which molecular pathway is strongly associated with the diagnosis?

Case 2: Morphology and phenotype converge

A mixed lymphoplasmacytic neoplasm favors LPL in the appropriate context.

- CD20 marks the B-cell component.
- The plasma-cell compartment usually secretes concordant IgM.
- MYD88-associated NF- κ B signaling provides molecular support.

Case 3: Distinguish LPL from myeloma

An older adult has a monoclonal protein and marrow abnormality; Imaging shows multiple lytic bone lesions.

- Which disease is more consistent with the skeletal finding?
- What complication from free light chains would further support that alternative?
- Why should the serum protein alone not settle the classification?

Case 3: Bone destruction shifts the differential

The described skeletal pattern is characteristic of multiple myeloma, not usual LPL.

- Myeloma is associated with osteolysis and light-chain nephrotoxicity.
- Robbins explicitly contrasts LPL with the absence of bone destruction.
- Classify the marrow process, rather than equating all monoclonal proteins with LPL.

Integrated morphologic summary

Recognize LPL as a composite cellular and molecular phenotype.

Bone marrow: Small lymphocytes +
plasmacytoid lymphocytes + plasma cells.

Associated mast cells; Occasional Russell and
Dutcher bodies.

Lymphoid CD20/surface Ig; Plasma-cell
secretion of concordant IgM.

MYD88-associated signaling often supports the
diagnosis.

Integrated clinical summary

The major clinical effects arise through two separable pathways.

Cellular disease: Anemia, lymphadenopathy, and hepatosplenomegaly.

IgM: Hyperviscosity, bleeding, cryoglobulinemia, and cold agglutinin hemolysis.

Plasmapheresis relieves selected IgM effects; Lymphoma therapy addresses the clone.

The course is typically indolent; Large-cell transformation is uncommon.

Principal references

Primary pathology source and supplementary diagnostic context

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 13, pp. 555–556.

Brunner A, et al. In-depth molecular analysis of lymphomas with lymphoplasmacytic differentiation. Ann Hematol. 2024;103:553–563.

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