

Peripheral B-Cell Neoplasms

Pathogenesis • morphology • immunophenotype • clinical behavior

CLL/SLL Follicular lymphoma DLBCL Burkitt lymphoma Mantle cell lymphoma

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

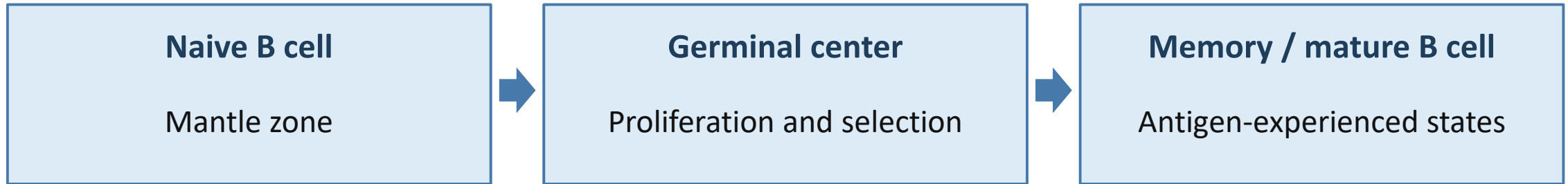
Relate tumor biology to B-cell maturation and lymphoid tissue architecture.

Identify morphologic and immunophenotypic hallmarks of five major neoplasms.

Explain oncogenic consequences of BCL2, BCL6, MYC, and cyclin D1 alterations.

Integrate growth tempo, site of disease, and transformation with diagnosis.

Normal B-cell differentiation provides the diagnostic framework



Different neoplasms preserve features of B-cell developmental stages; Lineage markers alone do not establish a specific diagnosis.

Schematic

Clinical tempo is a first diagnostic clue

CLL/SLL and follicular lymphoma commonly show indolent clinical courses.

Mantle cell lymphoma is often disseminated and typically more aggressive than indolent lymphomas.

DLBCL usually enlarges rapidly; Burkitt lymphoma is among the fastest-growing human tumors.

An indolent lymphoma can acquire new lesions and transform into a high-grade neoplasm.

Five disease entities: A first-pass map

Entity	Growth / architecture	Defining molecular association
CLL/SLL	Small-cell, diffuse; proliferation centers	13q14 deletion / BCL2 overexpression
Follicular lymphoma	Nodular / follicular	IGH–BCL2, t(14;18)
DLBCL	Diffuse large B cells	BCL6 / BCL2 / MYC lesions; heterogeneous
Burkitt lymphoma	Intermediate cells; very rapid growth	Immunoglobulin–MYC rearrangement
Mantle cell lymphoma	Small to medium cells; mantle / diffuse	IGH–CCND1, t(11;14)

A diagnosis requires concordant evidence

Growth pattern and cytology establish the morphologic differential.

Immunophenotyping confirms mature B-cell lineage and narrows lineage subtype.

Characteristic genetic lesions strengthen diagnosis and inform tumor biology.

Anatomic distribution and clinical history reveal important exceptions and transformations.

CLL/SLL: Two manifestations of one neoplasm

Chronic lymphocytic leukemia and small lymphocytic lymphoma share the same cellular disease.

The leukemia designation reflects sufficient circulating clonal lymphocytes.

Predominantly tissue-based presentation with less blood lymphocytosis is termed SLL.

CLL is a common adult leukemia in Western populations.

CLL and SLL differ in distribution, not core biology

CLL

Persistent circulating small lymphocytes are prominent.

Peripheral blood smear often reveals fragile lymphocytes / smudge cells.

Marrow, nodes, spleen, and liver may also be infiltrated.

SLL

Lymphadenopathy and tissue involvement may dominate.

Peripheral blood lymphocytosis may be below the leukemia threshold.

Tissue morphology and marker profile match CLL.

CLL/SLL cytology: Predominance of small mature lymphocytes



Recognize the pattern

Condensed chromatin

Scant cytoplasm

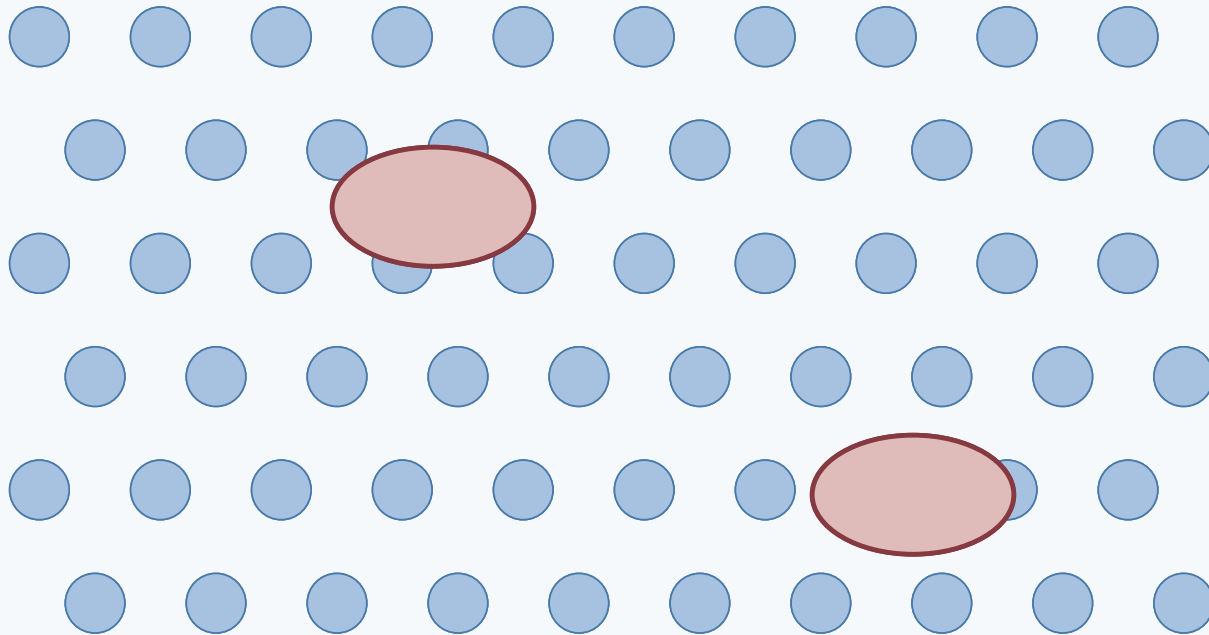
Small round or slightly irregular
nuclei

Smudge cells in blood smears

Cell diagrams are schematic—not photomicrographs

CLL/SLL: Diffuse nodal effacement with proliferation centers

Simplified nodal architecture



Diffuse small cells

Most of the node is replaced.

Proliferation centers

Loose larger-cell aggregates with mitoses.

Diagnostic context

Characteristic for CLL/SLL in this setting.

Schematic nodal architecture; Not a histologic section.

CLL/SLL: Proliferation centers reflect local growth

Most neoplastic lymphocytes are small and relatively inactive in tissue.

Scattered larger activated cells form pale aggregates termed proliferation centers.

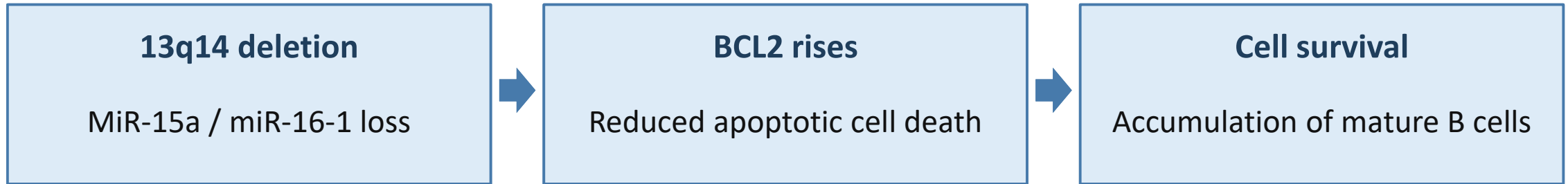
Proliferation centers concentrate mitotically active tumor cells.

Microenvironment-derived signals help sustain neoplastic cell growth.

CLL/SLL immunophenotype: The diagnostic combination

Marker	Usual pattern	Interpretive value
CD19; CD20	B-lineage; CD20 present	Supports mature B-cell neoplasm
CD5	Positive	Aberrant coexpression with B lineage
CD23	Positive	Favors CLL/SLL over typical mantle cell lymphoma
Surface IgM ± IgD	Relatively dim	Characteristic weak surface immunoglobulin
BCL2	Strong	Supports apoptosis resistance

13q14 loss provides a route to apoptosis resistance



BCL2 overexpression favors prolonged survival; It is not simply a marker of increased mitotic rate.

Schematic

CLL/SLL: Additional recurrent genetic lesions

Common cytogenetic findings include deletions of 11q and 17p and trisomy 12.

Deletion of 17p may involve TP53 and is associated with worse outcome.

NOTCH1 gain-of-function mutations are associated with less favorable prognosis.

Mutations affecting RNA splicing are also documented.

IGHV somatic hypermutation stratifies biologic behavior

Hypermutated IGH genes

Suggest antigen-experienced / post–germinal center history.

Associated with comparatively more favorable clinical behavior.

Unmutated IGH genes

May reflect naive B-cell derivation.

Associated with more aggressive clinical behavior in the source.

CLL/SLL infiltrates multiple hematolymphoid organs

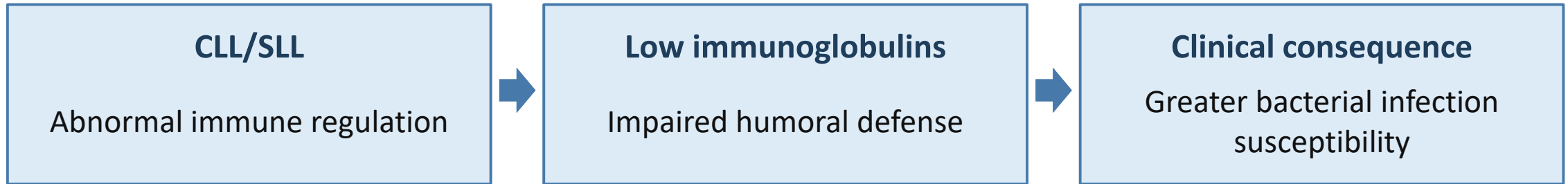
Peripheral blood involvement varies from modest to marked lymphocytosis.

Marrow involvement is common and may contribute to cytopenias.

Splenic and hepatic infiltration can accompany lymphadenopathy.

Liver involvement may be visible as periportal lymphocytic infiltrates.

CLL-associated hypogammaglobulinemia produces infection risk



Immunodeficiency is clinically important even when the lymphoma burden appears indolent.

Schematic

CLL/SLL can cause autoimmune cytopenias

Autoantibodies produced by nonneoplastic B cells can damage circulating blood cells.

Autoimmune hemolytic anemia and immune thrombocytopenia are recognized complications.

Anemia may therefore reflect immune destruction, marrow replacement, or both.

A peripheral smear and appropriate laboratory correlation are essential.

CLL/SLL: Clinical heterogeneity is substantial

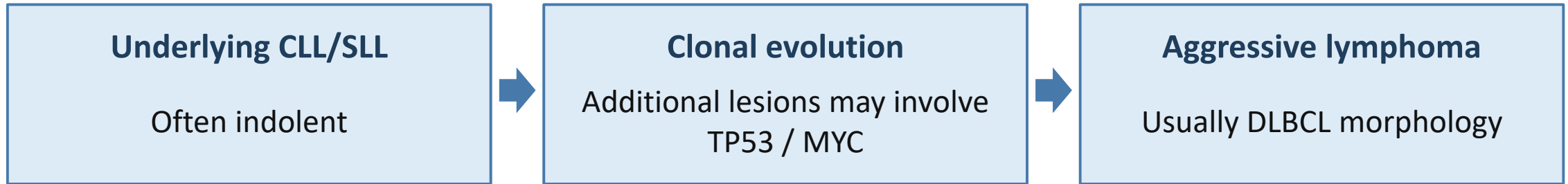
Many patients have minimal symptoms at presentation.

Fatigue, weight loss, lymphadenopathy, and hepatosplenomegaly may develop.

Some patients remain stable for long periods while others progress rapidly.

Clinical stage and selected molecular features correlate with prognosis.

Richter transformation changes the disease tempo



A newly rapidly enlarging nodal or splenic mass should prompt assessment for Richter transformation.

Schematic

CLL/SLL: Therapeutically relevant biology

BCL2 inhibitors target the survival program common in CLL/SLL.

BTK inhibitors interfere with B-cell receptor–associated survival signaling.

Anti-CD20 antibodies target the surface B-cell antigen.

Specific regimen selection is evolving and lies beyond the morphologic diagnosis.

Follicular lymphoma: A germinal center B-cell neoplasm

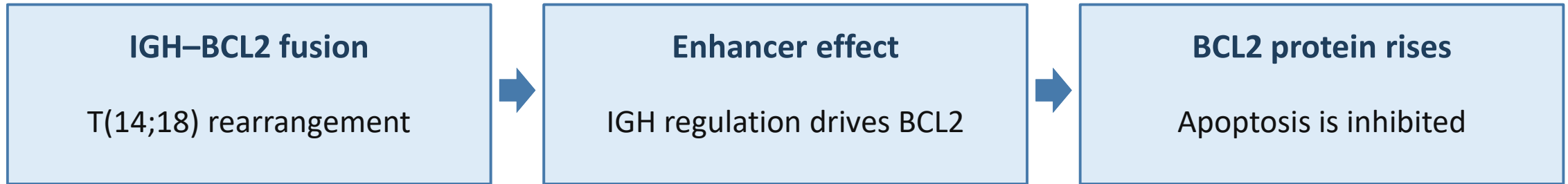
An important indolent non-Hodgkin lymphoma, generally presenting in middle age.

The tumor commonly shows nodular / follicular nodal growth.

Neoplastic cells resemble germinal center centrocytes and centroblasts.

The neoplasm commonly expresses BCL2 despite its germinal center phenotype.

T(14;18) connects immunoglobulin regulation to BCL2



The translocation favors persistence of germinal center-derived cells that would normally be deleted by apoptosis.

Schematic

Normal vs neoplastic germinal center: BCL2 is the discriminator

Reactive germinal center

Germinal center B cells are usually BCL2-negative.

Apoptosis helps eliminate cells failing selection.

Mantle zone B cells retain BCL2 expression.

Follicular lymphoma

Neoplastic follicle cells usually express BCL2.

Reduced apoptosis permits persistence of altered cells.

The pattern is interpreted alongside follicular architecture.

Histone-modifying enzymes contribute to FL pathogenesis

KMT2D encodes a histone-modifying enzyme and is frequently mutated.

EZH2 encodes a different chromatin-modifying enzyme and may carry activating lesions.

Abnormal epigenetic programs complement BCL2-driven survival.

The source links EZH2-mutated tumors to sensitivity to EZH2 inhibition.

Follicular lymphoma depends on its microenvironment

Neoplastic follicles contain a follicular dendritic-cell network.

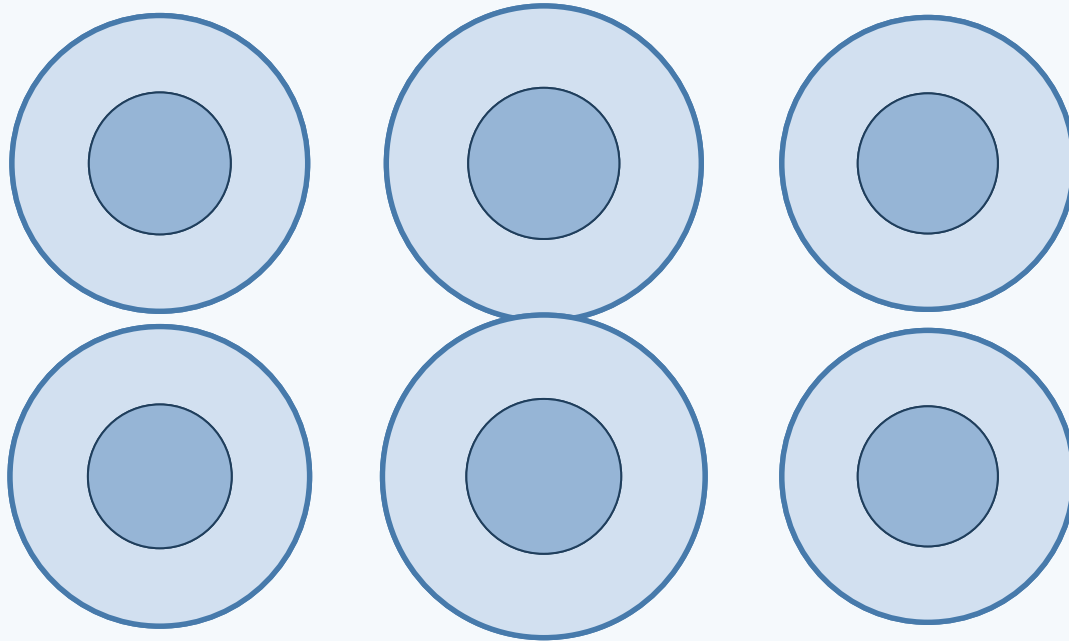
Macrophages and reactive T cells coexist with lymphoma B cells.

Gene-expression features of surrounding stromal cells relate to outcome.

This illustrates that clinical behavior is not determined solely by tumor-cell mutations.

Follicular lymphoma: Repeated neoplastic follicles

Simplified nodal architecture



Nodular pattern

Follicles replace the nodal architecture.

Mixed cytology

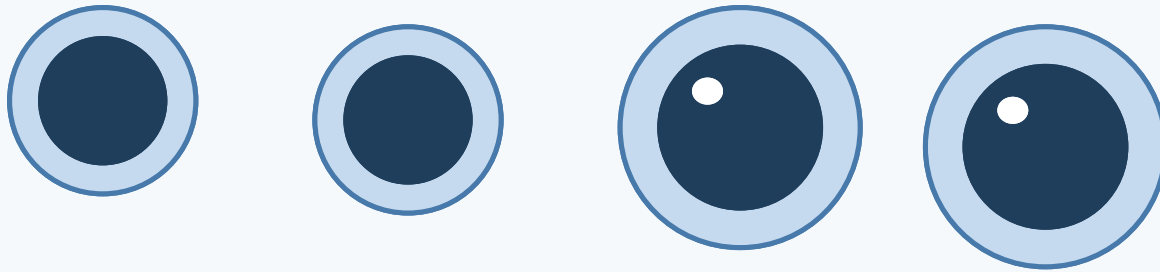
Centrocytes with variable centroblasts.

Diagnostic principle

Morphology needs IHC corroboration.

Schematic lymph node; Do not interpret as actual H&E.

Follicular lymphoma: Centrocytes and centroblasts



Recognize the pattern

Centrocytes: Irregular cleaved nuclei

Centroblasts: Larger cells with nucleoli

Proportions vary among tumors

Both populations contribute to grading considerations

Cell diagrams are schematic—not photomicrographs

FL commonly infiltrates marrow paratrabecularly

Bone marrow involvement is frequent description.

Neoplastic lymphoid aggregates preferentially track along bony trabeculae.

Spleen white-pulp nodules and hepatic portal triads may also be involved.

Anatomic patterns support—but never independently prove—the diagnosis.

Follicular lymphoma: Germinal center marker profile

Feature	Expected profile	Why it matters
CD19 / CD20	Positive	Mature B-cell lineage
CD10 / BCL6	Positive	Germinal center differentiation
CD5	Negative	Distinguishes from typical CLL/SLL and MCL
BCL2	Often positive in follicles	Distinguishes most FL from reactive germinal centers

Follicular lymphoma versus reactive follicular hyperplasia

Reactive germinal centers typically lack BCL2 in center B cells.

Lymphoma follicles commonly contain BCL2-positive neoplastic cells.

Distribution and cytologic uniformity add evidence beyond BCL2 staining.

Interpret immunostaining by cellular compartment rather than global tissue positivity.

FL: The typical clinical presentation is widespread lymphadenopathy

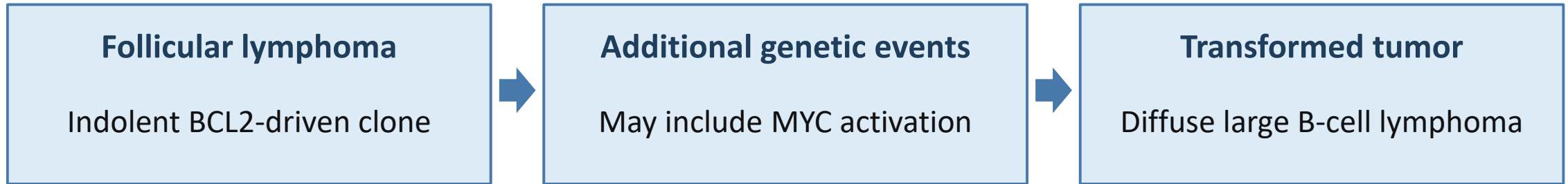
Painless generalized adenopathy is characteristic.

Extranodal sites including gut, central nervous system, and testis are less common.

The natural history is often relapsing and remitting.

Indolent clinical tempo does not exclude extensive marrow or splenic involvement.

Histologic transformation: FL may evolve into DLBCL



Accelerated enlargement or new aggressive clinical findings warrant reassessment of histology.

Schematic

FL clinical biology guides therapeutic concepts

Anti-CD20 therapy exploits retained B-cell lineage antigen expression.

EZH2 inhibition is biologically relevant to tumors with activating EZH2 mutations.

Choice and intensity of treatment depend on clinical circumstances.

High-grade transformation requires a different clinicopathologic approach.

DLBCL: A common aggressive mature B-cell lymphoma

Diffuse large B-cell lymphoma is the most common non-Hodgkin lymphoma.

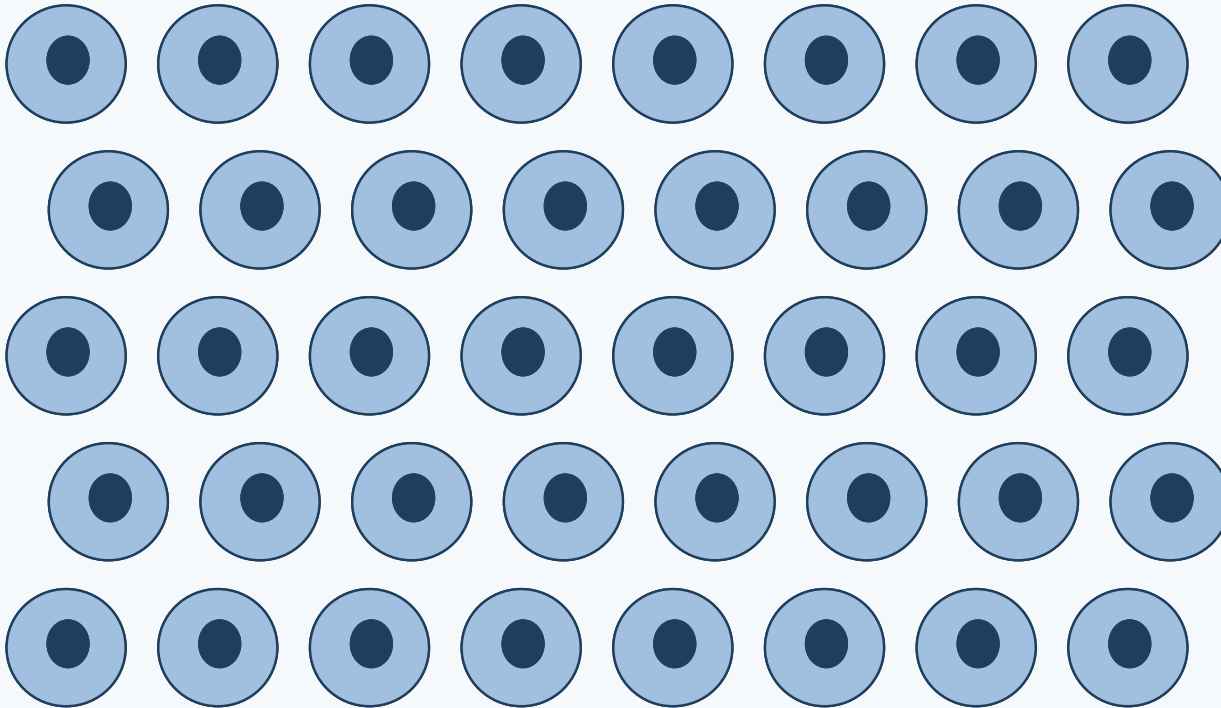
It affects adults frequently but also occurs in younger patients.

It typically presents with a rapidly enlarging mass.

DLBCL is a heterogeneous family of tumors, not a single molecular lesion.

DLBCL: Diffuse effacement by large lymphoid cells

Simplified nodal architecture



Diffuse growth

Native architecture is replaced.

Large tumor cells

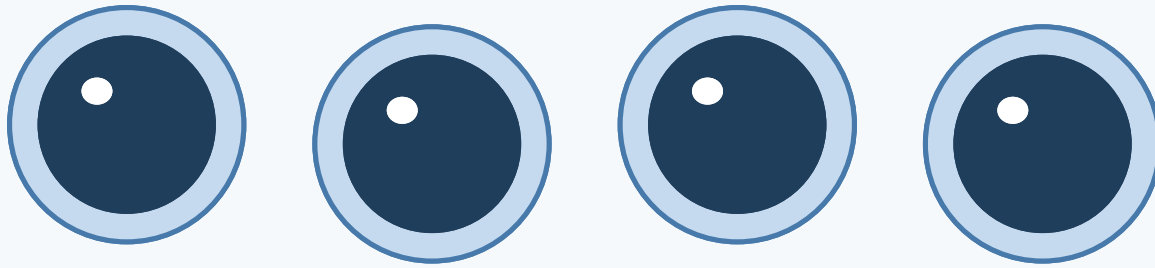
Size greatly exceeds a small lymphocyte.

Cytologic diversity

Nuclear shape and nucleoli vary.

Schematic; Actual tumor morphology requires an authentic slide.

DLBCL cell morphology: Large nuclei and active nucleoli



Recognize the pattern

Large lymphoid cell size

Vesicular / open nuclear
chromatin

Prominent nucleoli

Variable cytoplasm and nuclear
contour

Cell diagrams are schematic—not photomicrographs

BCL6 controls the germinal center transcriptional state

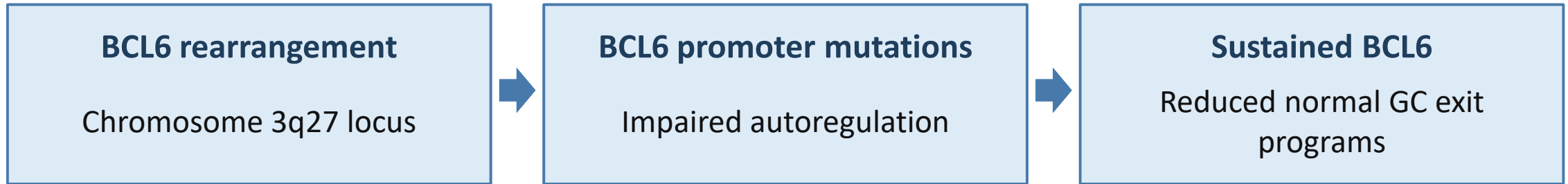
BCL6 is a transcriptional repressor needed in normal germinal center development.

It restrains programs promoting growth arrest, apoptosis, and differentiation.

Persistent inappropriate BCL6 expression can favor neoplastic survival and expansion.

Several DLBCL molecular lesions converge on BCL6 dysregulation.

BCL6 dysregulation can arise by more than one route



Rearrangements and promoter lesions are distinct routes to abnormal BCL6 activity.

Aberrant somatic hypermutation may target oncogenes

Germinal center DNA-modifying processes can inadvertently affect non-Ig genes.

The source describes BCL6 promoter mutations as a prominent example.

Similar acquired changes may involve MYC and other oncogenes.

Off-target mutation helps explain the genetic diversity of DLBCL.

BCL2-associated DLBCL represents another survival route

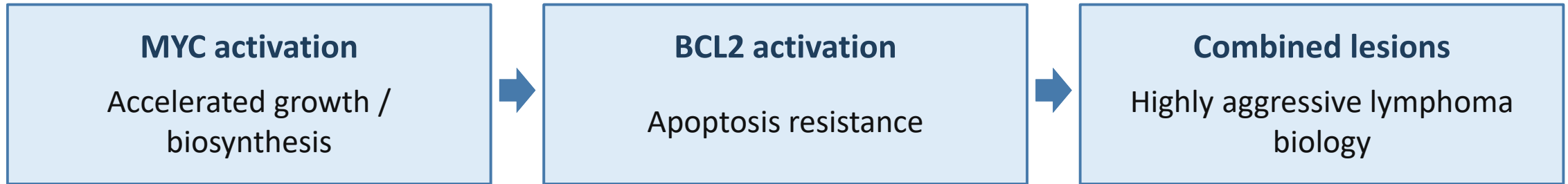
A subset contains t(14;18), causing BCL2 overexpression.

Some cases may arise through transformation of follicular lymphoma.

BCL2 and BCL6 rearrangements can occur in different molecular contexts.

An antiapoptotic phenotype alone does not establish a follicular lymphoma origin.

MYC plus BCL2 couples growth with survival



This combination is distinct from protein coexpression alone; Genetic rearrangements must be established by molecular testing.

Schematic

DLBCL has multiple genetic backgrounds

BCL6, BCL2, and MYC rearrangements account for some—not all—tumors.

The text also implicates CD79B, MYD88, EZH2, NOTCH1, and NOTCH2 alterations.

Different combinations of abnormalities underlie molecular subgroups.

Do not equate a morphologic DLBCL diagnosis with one uniform genotype.

DLBCL: Immunophenotype and Key diagnostic consideration: S

Marker / testing	Textbook expectation	Caveat
CD19, CD20	Expressed by most cases	Confirms mature B-cell lineage
CD10, BCL6	Variable	May reflect germinal-center phenotype
Surface immunoglobulin	Often present	Expression may vary
MYC and BCL2 protein	High in some cases	Protein coexpression ≠ proven gene rearrangement

DLBCL: The mass can arise at almost any site

Most cases present as rapidly growing nodal or extranodal masses.

Waldeyer ring, gastrointestinal tract, skin, bone, and brain are possible sites.

Liver and splenic tumors may form large destructive masses.

Marrow disease is less conspicuous early than in several indolent B-cell lymphomas.

Splenic involvement: Indolent lymphoma versus DLBCL

Indolent B-cell lymphoma

Often expands multiple white-pulp nodules.

May produce generalized splenic enlargement.

DLBCL

Can produce a solitary dominant destructive splenic mass.

Aggressive growth may efface normal architecture.

Immunodeficiency-associated DLBCL: EBV is important

Some large B-cell proliferations occur with impaired T-cell surveillance.

Advanced HIV infection and organ or stem-cell transplantation are contexts in the text.

Tumor B cells are often Epstein–Barr virus-associated.

Restoration of immune surveillance can lead to regression in selected settings.

Primary effusion lymphoma: Fluid-space disease

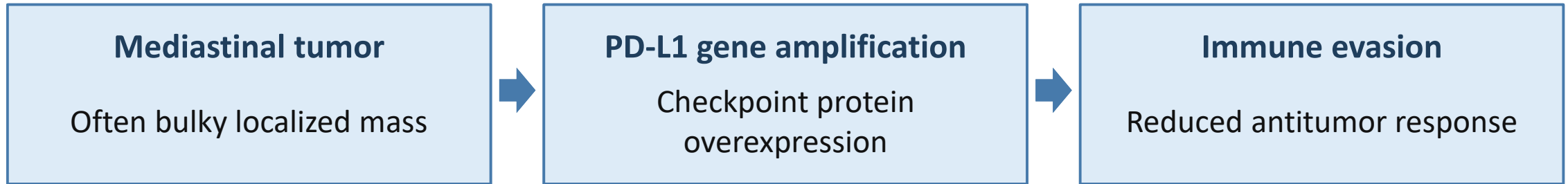
May present as malignant pleural or ascitic effusion rather than a solid mass.

Classically associated with severe immune compromise but also seen in older adults.

Tumor cells can lack conventional surface B- and T-cell markers.

HHV8 infection and clonal immunoglobulin gene rearrangement identify its lineage.

Primary mediastinal large B-cell lymphoma: Immune escape



Mass effect may cause superior vena cava obstruction and swelling of face or neck.

Schematic

Intravascular large B-cell lymphoma: A deceptive presentation

Tumor cells preferentially proliferate inside small vessels.

A conventional enlarged nodal mass may be absent.

Neurologic symptoms may result from cerebral small-vessel involvement.

Skin biopsy can reveal the diagnosis when the entity is suspected.

Large B-cell lymphoma with MYC and BCL2 rearrangements

Combined oncogenic drivers create rapid proliferation and enhanced survival.

May arise de novo or evolve from follicular lymphoma.

Genetic documentation matters: Rearranged genes are distinct from IHC protein positivity.

The source describes these lesions as exceptionally aggressive.

DLBCL: Clinically relevant treatment principles

Untreated DLBCL has an aggressive natural history.

Combination immunochemotherapy can cure a substantial subset of patients.

Anti-CD20 therapy targets the surface B-cell antigen.

CD19-targeted CAR-T cells provide an option in relapsed/refractory disease.

Burkitt lymphoma: One histology, three epidemiologic settings

Endemic, sporadic, and immunodeficiency-associated cases share characteristic morphology.

An immunoglobulin–MYC rearrangement is a central feature of classic Burkitt lymphoma.

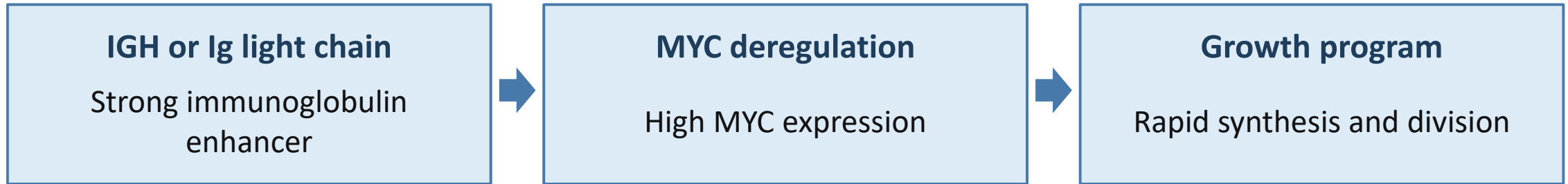
Clinical distribution and EBV association differ by setting.

The tumor exhibits extraordinarily rapid proliferative behavior.

Burkitt lymphoma: Clinical settings

Setting	Typical distribution	EBV association in source
Endemic	Often jaw; can involve abdominal viscera	Essentially all cases
Sporadic	Often ileocecal / peritoneal mass	Minority of cases
HIV-associated	Aggressive lymphoma in immune compromise	Subset of cases

Immunoglobulin–MYC rearrangement drives Burkitt lymphoma



MYC is a transcriptional regulator of biosynthesis, cellular metabolism, and proliferation.

Schematic

Canonical Burkitt lymphoma rearrangements

Translocation	Partner genes	Consequence
t(8;14)	MYC / IGH	Most common immunoglobulin enhancer juxtaposition
t(2;8)	IGK / MYC	Alternative immunoglobulin light-chain partner
t(8;22)	MYC / IGL	Alternative immunoglobulin light-chain partner

AID links germinal-center biology to MYC rearrangements

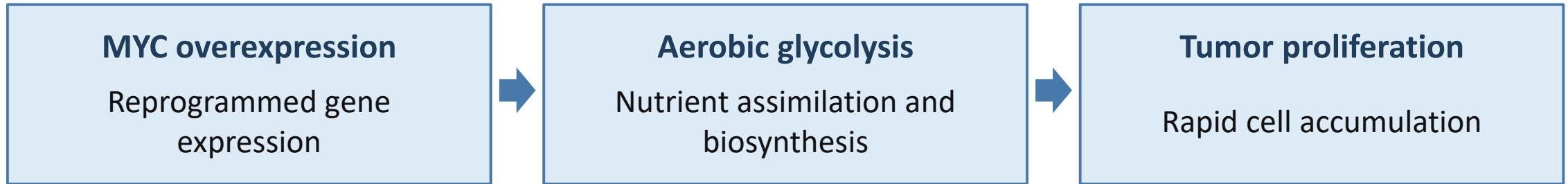
Activation-induced cytidine deaminase participates in class switching and somatic hypermutation.

DNA breaks created during normal antibody diversification can be misrepaired.

The source implicates AID in MYC–immunoglobulin translocations.

Breakpoint patterns vary between endemic and sporadic Burkitt lymphoma.

MYC promotes biosynthesis through Warburg-type metabolism



Enhanced synthesis of nucleotides, lipids, and proteins supports the extraordinary growth rate.

Schematic

TCF3 signaling cooperates with MYC

Many tumors harbor lesions increasing TCF3 transcription-factor activity.

The source describes TCF3 as a regulator of germinal center gene expression.

Its downstream program includes genes promoting cell-cycle progression.

Burkitt biology therefore cannot be explained by MYC deregulation alone.

EBV association differs among Burkitt settings

EBV is present in essentially all endemic cases in the source.

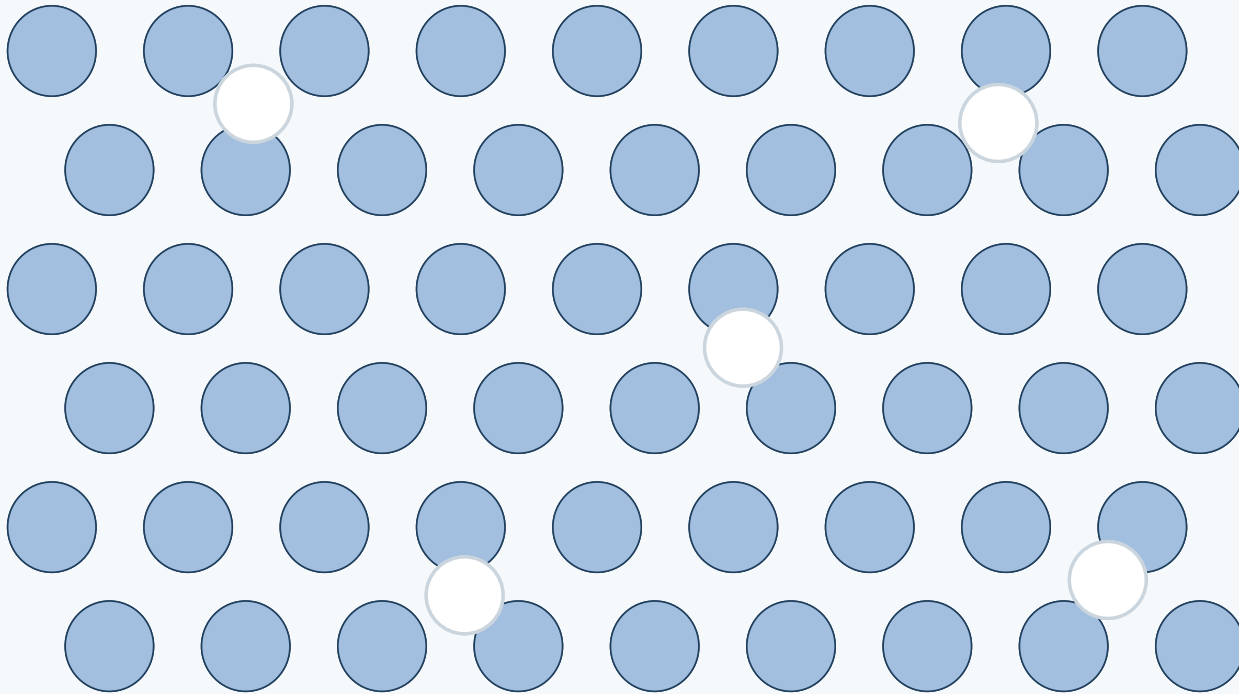
A smaller fraction of sporadic and HIV-associated tumors harbor EBV.

Clonally uniform viral genomes suggest infection precedes malignant expansion.

The specific causal contribution of EBV remains incompletely resolved.

Burkitt lymphoma: Macrophages create a “starry sky”

Simplified nodal architecture



Monomorphic tumor

Intermediate-sized lymphoid cells.

Numerous apoptotic bodies

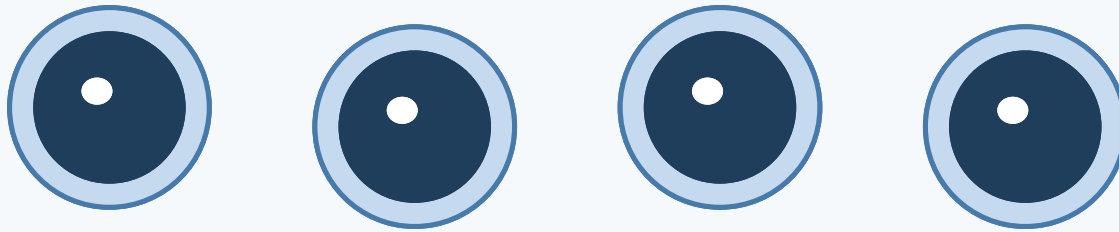
High cellular turnover.

Pale macrophages

Phagocytosis produces starry-sky spaces.

Conceptual architecture only; The starry-sky pattern is not exclusive to Burkitt lymphoma.

Burkitt lymphoma: Intermediate cells with intense turnover



Recognize the pattern

Intermediate-sized, relatively monotonous cells

Coarse chromatin and multiple nucleoli

Cytoplasmic vacuoles may be seen in aspirates

High mitotic and apoptotic activity

Cell diagrams are schematic—not photomicrographs

Starry-sky morphology reflects cellular death and clearance

Numerous tumor cells undergo apoptosis in this rapidly proliferating neoplasm.

Benign tingible-body macrophages ingest apoptotic debris.

Pale macrophage cytoplasm interrupts the dense basophilic tumor field.

The resulting “starry sky” is a pattern, not a standalone diagnosis.

Burkitt lymphoma: Immunophenotypic profile

Marker	Usual pattern	Interpretive value
CD19 / CD20	Positive	Mature B-cell differentiation
CD10 / BCL6	Positive	Germinal center phenotype
Surface IgM	Positive	Surface immunoglobulin expression
BCL2	Typically negative	Consistent with abundant apoptotic cells

Burkitt presentation depends on epidemiologic context

Endemic presentation

Often a jaw / mandibular mass.

May involve kidneys, ovaries, or adrenal glands.

Predominantly children or young adults.

Sporadic presentation

Ileocecal and peritoneal masses are characteristic.

May present with abdominal symptoms.

Also predominantly younger patients.

Burkitt lymphoma: Aggressive but potentially curable

The natural growth rate is extremely high.

Intensive multidrug chemotherapy can be highly effective.

Most children and young adults in the text can be cured.

Outcome is more guarded in older adults.

Mantle cell lymphoma: Usually a naive B-cell phenotype

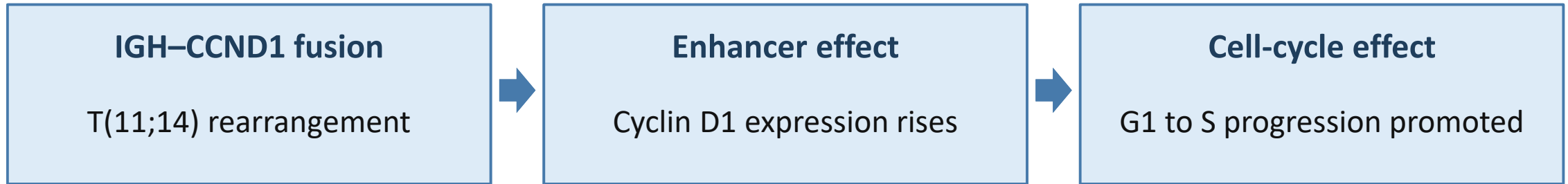
Tumor cells resemble B lymphocytes normally surrounding germinal centers.

Often presents in the fifth or sixth decade with male predominance.

Dissemination is frequent and may include extranodal gastrointestinal sites.

The common genetic hallmark is IGH–CCND1 rearrangement.

T(11;14) causes cyclin D1 overexpression



Cyclin D1 is a cell-cycle regulator; Its dysregulation promotes inappropriate proliferation.

Schematic

Cyclin D1 connects the genotype to the cell cycle

Cyclin D1 promotes transition from G1 into S phase.

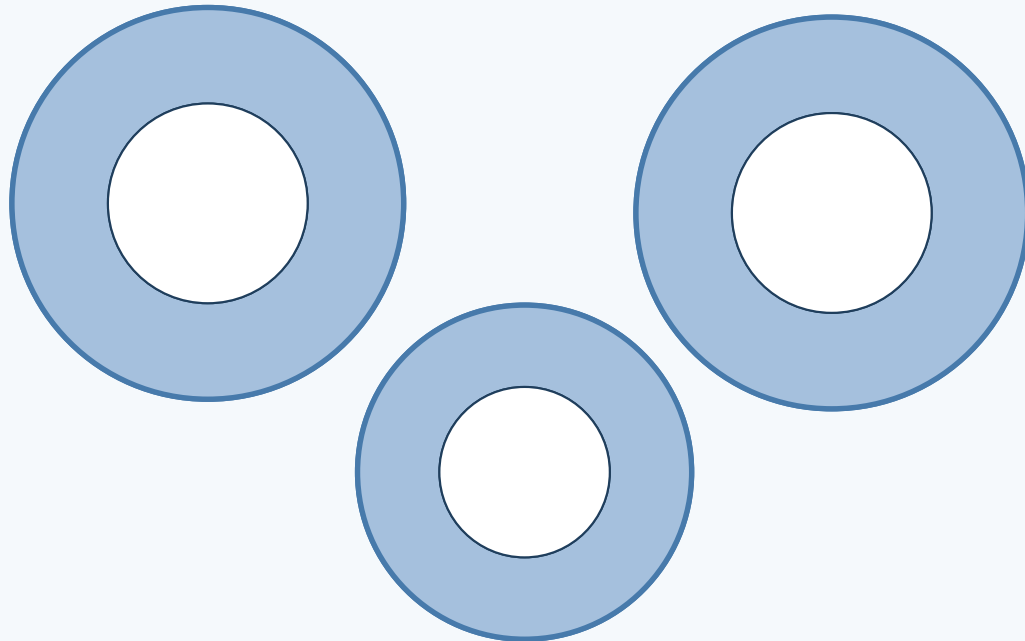
IGH–CCND1 rearrangement induces inappropriate cyclin D1 overexpression.

The lesion therefore enhances cell-cycle entry rather than primarily blocking apoptosis.

Cyclin D1 IHC is a high-value diagnostic adjunct in an appropriate B-cell phenotype.

Mantle cell lymphoma: Expanded mantle zones or diffuse growth

Simplified nodal architecture



Mantle-zone pattern

Tumor surrounds small residual germinal centers.

Diffuse pattern

Architecture may become completely effaced.

Characteristic clue

Lacks CLL/SLL proliferation centers.

Schematic; Actual tissue section not provided.

Mantle cell lymphoma: Relatively uniform irregular small cells



Recognize the pattern

Small cells, sometimes clefted nuclei

Condensed chromatin

Inconspicuous nucleoli

No typical centroblast-rich follicles

Cell diagrams are schematic—not photomicrographs

Mantle cell lymphoma: B-cell markers plus cyclin D1

Marker	Typical profile	Differential utility
CD19 / CD20	Positive	Confirms mature B-cell lineage
Surface IgM / IgD	Usually appreciable	Often stronger than in CLL/SLL
CD5	Usually positive	Shared with CLL/SLL
CD23	Usually negative	Contrasts with typical CLL/SLL
Cyclin D1	Strong overexpression	Supports IGH–CCND1 biology

CLL/SLL versus mantle cell lymphoma: CD5 is not enough

CLL/SLL

CD5+, CD23+ usually.

Surface immunoglobulin often weak.

Pseudofollicular proliferation centers may be present.

Mantle cell lymphoma

CD5+, CD23– typically.

Cyclin D1 strongly expressed.

Mantle-zone growth or uniform small-cell infiltrate.

Mantle cell lymphoma: Gastrointestinal dissemination

Gut involvement can be prominent and sometimes produces multiple mucosal polyps.

The pattern is termed lymphomatoid polyposis.

Marrow, spleen, and liver are other common extranodal sites.

Systemic spread is therefore common even when the diagnosis is made in a lymph node.

The blastoid variant is a diagnostic and prognostic challenge

Some tumors show larger cells with open chromatin and brisk mitotic activity.

Such blastoid cases may resemble lymphoblastic leukemia/lymphoma morphologically.

B-lineage markers and cyclin D1 help establish the correct differentiation state.

Blastoid morphology correlates with less favorable clinical behavior.

MCL: Clinical behavior and prognostic modifiers

Painless lymphadenopathy is a common initial finding.

Splenic and intestinal involvement can produce organ-related symptoms.

The disease is typically moderately aggressive with variable survival.

Blastoid morphology, high proliferation, and TP53 lesions are adverse.

Genetic driver comparison across the five neoplasms

Neoplasm	Selected molecular driver	Biological effect
CLL/SLL	miR-15a/16-1 loss; BCL2 expression	Enhanced survival
Follicular lymphoma	IGH–BCL2; epigenetic regulators	Antiapoptotic survival / chromatin change
DLBCL	BCL6, BCL2, MYC; diverse pathways	Variable survival / differentiation / growth
Burkitt lymphoma	Immunoglobulin–MYC	Accelerated metabolism and proliferation
Mantle cell lymphoma	IGH–CCND1 (cyclin D1)	G1–S cell-cycle progression

Comparative immunophenotype: Interpret the full panel

Disease	CD5	CD23	CD10 / BCL6	Cyclin D1 / BCL2
CLL/SLL	+	+	Usually –	BCL2 high
Follicular	–	Not defining	CD10+, BCL6+	BCL2 in neoplastic follicles
DLBCL	Variable	Variable	Variable	May express BCL2
Burkitt	Usually –	Not defining	CD10+, BCL6+	Usually BCL2–
Mantle cell	Usually +	Usually –	Usually –	Cyclin D1 high

Architectural recognition across mature B-cell neoplasms

CLL/SLL

Small diffuse cells
± pale centers

Follicular

Repetitive nodules

DLBCL

Large diffuse cells

Burkitt

Diffuse + starry sky

Mantle cell

Expanded mantle zones

These labels are schematic diagnostic abstractions—not substitutes for examining H&E sections.

Clinical tempo directs the differential diagnosis

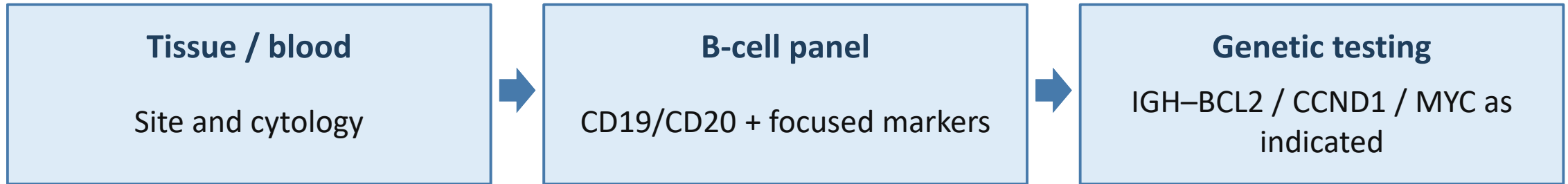
Slow, waxing-and-waning adenopathy suggests an indolent lymphoma but is not definitive.

Rapidly enlarging masses support aggressive entities such as DLBCL or Burkitt.

New rapid growth in known CLL or follicular lymphoma raises concern for transformation.

Morphology, markers, and genetics must resolve the clinical impression.

A practical workup: From architecture to molecular interpretation



The most informative test set is dictated by the morphologic differential, not a single positive marker.

Schematic

Diagnostic pitfall: One marker rarely defines a disease

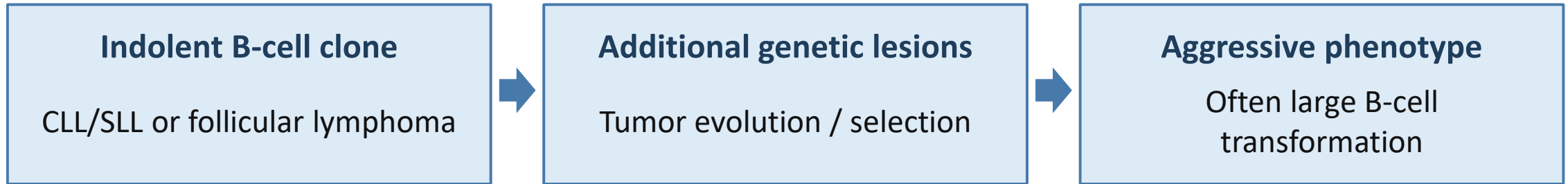
CD5 is shared by CLL/SLL and most mantle cell lymphomas.

CD10 and BCL6 are seen in both follicular and Burkitt lymphomas and some DLBCLs.

BCL2 IHC expression is not equivalent to a BCL2 gene rearrangement.

MYC and BCL2 protein coexpression is not synonymous with rearrangements of both genes.

Indolent lymphomas can evolve through clonal progression



Abrupt clinical change creates a new biopsy question: Has the histology transformed?

Application 1: Small lymphocytes with CD5 and CD23

Hypothetical case: Blood lymphocytosis with mature small lymphocytes.

Flow cytometry: CD19+, CD5+, CD23+, relatively dim surface Ig.

Question: Which lymphoma is favored, and what blood-film artifact may be seen?

Interpretation: CLL/SLL; Smudge cells may be present.

Application 2: BCL2-positive follicles

Hypothetical case: Persistent painless generalized lymphadenopathy.

Biopsy: Nodular population of centrocytes and centroblasts.

Immunophenotype: CD10+, BCL6+, BCL2+ within the follicles.

Interpretation: Follicular lymphoma; Correlate with IGH–BCL2 rearrangement.

Application 3: Rapidly progressive extranodal B-cell mass

Hypothetical case: A rapidly enlarging extranodal destructive mass.

Biopsy: Diffuse sheets of large lymphocytes with prominent nucleoli.

Immunophenotype establishes a mature B-cell neoplasm.

Interpretation: DLBCL is a major consideration; Molecular characterization follows.

Application 4: Starry sky with a MYC lesion

Hypothetical case: Young patient with an ileocecal mass.

Biopsy: Monomorphic intermediate cells and many tingible-body macrophages.

Profile: CD10+, BCL6+, BCL2–; MYC–immunoglobulin rearrangement.

Interpretation: Classic Burkitt lymphoma.

Application 5: CD5-positive lymphoma with cyclin D1

Hypothetical case: Generalized adenopathy with intestinal polyposis.

Biopsy: Relatively uniform small lymphocytes with irregular nuclei.

Markers: CD20+, CD5+, usually CD23–, cyclin D1 high.

Interpretation: Mantle cell lymphoma with gastrointestinal involvement.

Final diagnostic discriminators

CLL/SLL: CD5+CD23+, weak surface immunoglobulin, proliferation centers.

Follicular: Follicular growth, CD10/BCL6+, abnormal follicular BCL2 expression.

DLBCL: Diffuse large B cells and genetically heterogeneous aggressive disease.

Burkitt: MYC rearrangement, germinal-center phenotype, extreme turnover.

Mantle cell: CD5+, cyclin D1+, t(11;14), frequent extranodal spread.

Primary reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).

Chapter 13: Diseases of White Blood Cells, Lymph Nodes, Spleen, and Thymus.

Section: Peripheral B-Cell Neoplasms.

Morphologic schematics in this lecture are instructional drawings, not photomicrographs.