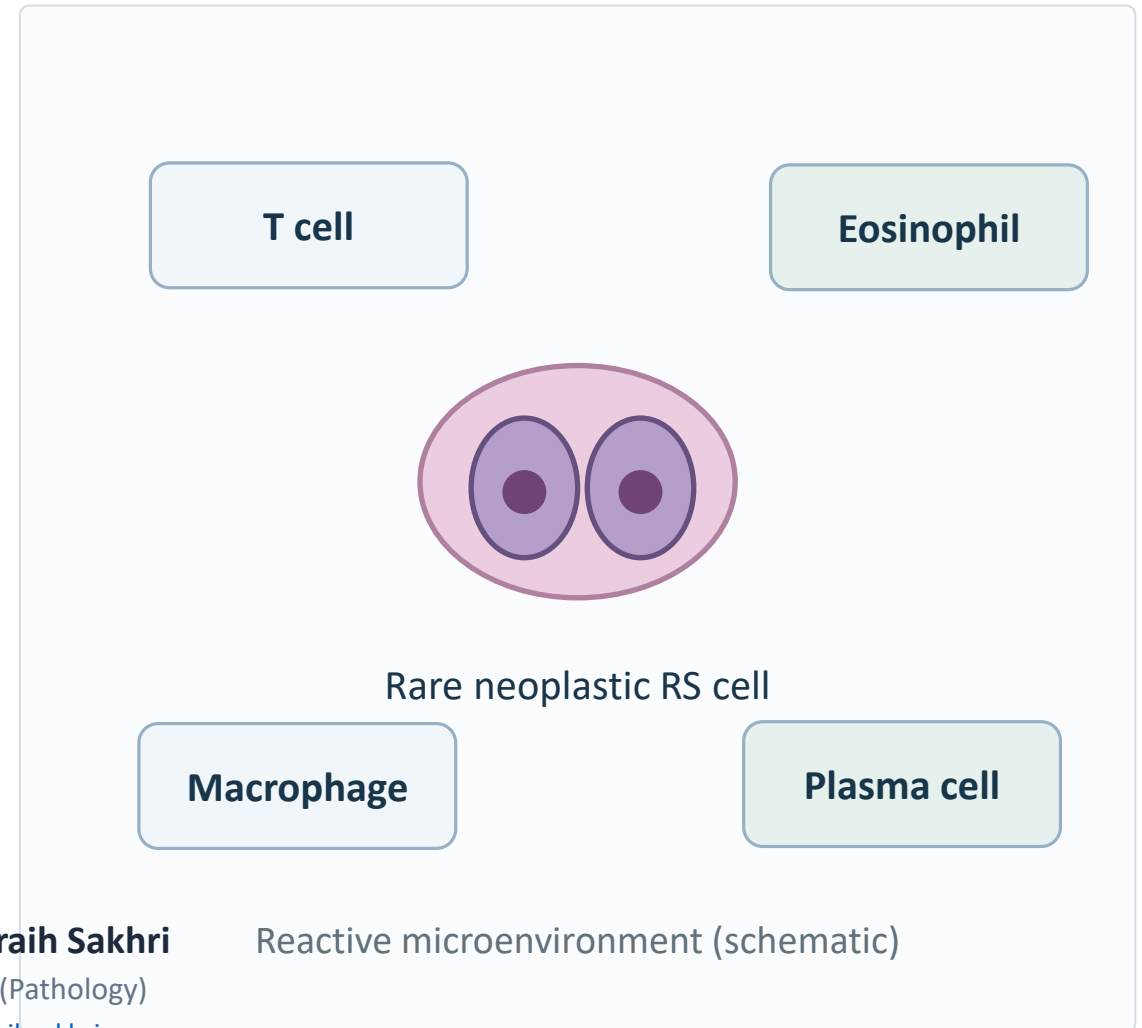


Hodgkin lymphoma: a distinctive B-cell neoplasm

- Neoplastic Reed–Sternberg (RS) cells and variants define the disease.
- Reactive lymphocytes, histiocytes, granulocytes and stromal cells dominate the tissue.
- Growth begins commonly in one nodal group and spreads to contiguous sites.



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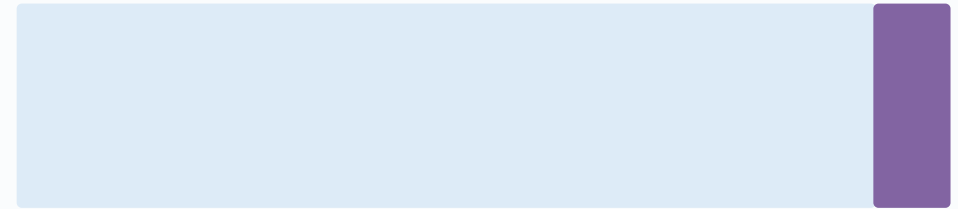
Learning objectives: Interpret the tumor and its environment

- Recognize RS cells and major morphologic variants without treating them as pathognomonic alone.
- Explain B-cell origin, NF- κ B signaling and immune escape in classic Hodgkin lymphoma.
- Differentiate classic subtypes from nodular lymphocyte-predominant disease.
- Apply morphology, immunophenotype and anatomic stage to clinicopathologic cases.

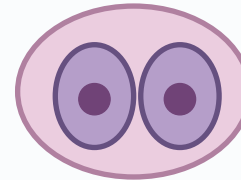
The malignant cells are numerically sparse

- Reactive cells typically contribute more than 90% of total tumor cellularity.
- Cytokines and chemokines from RS cells recruit a heterogeneous host-cell infiltrate.
- A small neoplastic population can therefore remodel an entire lymph node.

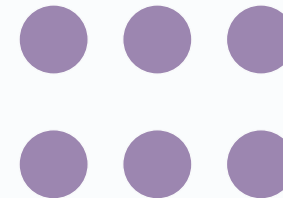
Cellular composition in classic HL



>90% reactive cellularity (textbook)



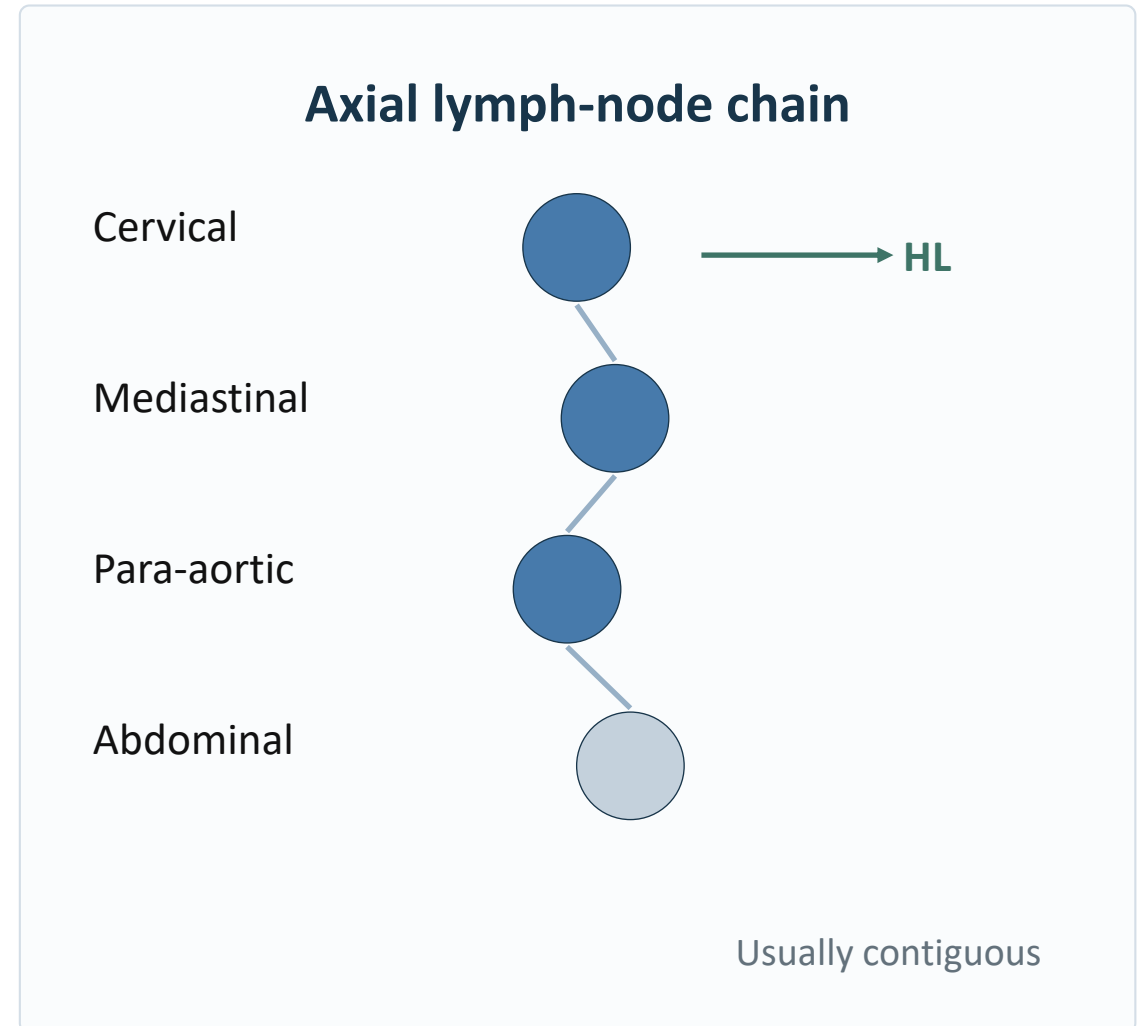
RS cells



Host inflammatory cells

Classical nodal behavior differs from most NHL

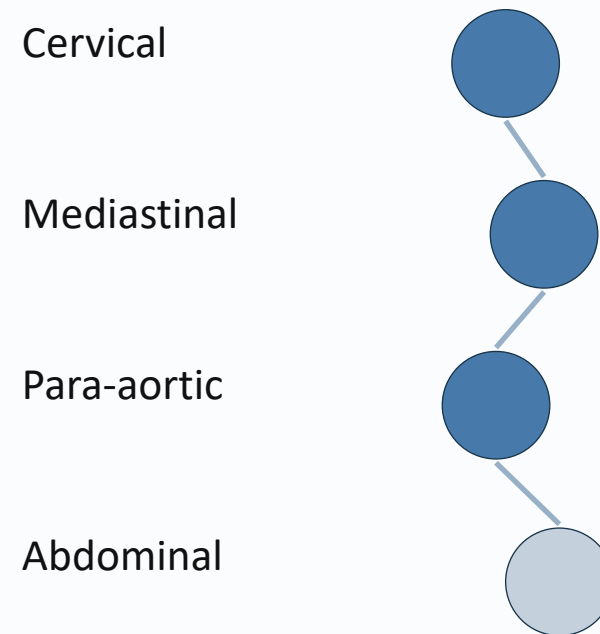
- Hodgkin lymphoma often presents in a single axial nodal group.
- Contiguous lymphatic spread is characteristic; Extranodal presentation is unusual.
- Many non-Hodgkin lymphomas show noncontiguous or extranodal disease.



Anatomic distribution guides the initial differential

- Cervical, mediastinal and para-aortic nodes are characteristic axial locations.
- Mesenteric nodal disease and Waldeyer-ring involvement are comparatively unusual.
- Pattern of distribution supports but never replaces tissue diagnosis.

Axial lymph-node chain



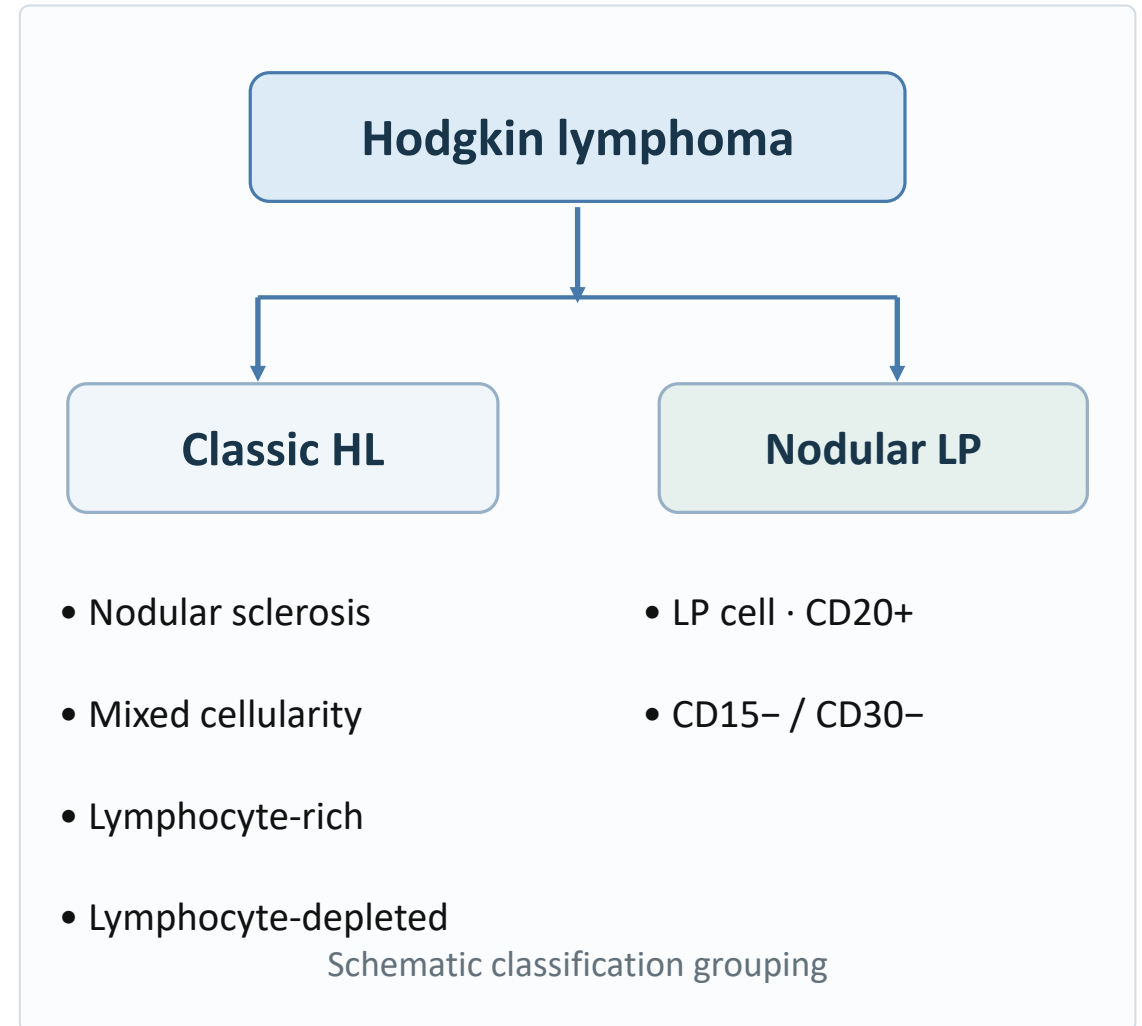
Simplified regional map; Not anatomical imaging

Epidemiologic context

- Approximately 0.7% of all newly diagnosed U.S. Cancers.
- Age at diagnosis has a bimodal distribution: Young adulthood and older than 55 years.
- Many patients are cured, making late treatment effects important.

Two biological groups—not five interchangeable subtypes

- Four variants form classic Hodgkin lymphoma (cHL) and share a characteristic RS-cell phenotype.
- Nodular lymphocyte-predominant disease retains a stronger germinal-center B-cell phenotype.
- Distinguishing these groups changes differential diagnosis and interpretation of IHC.

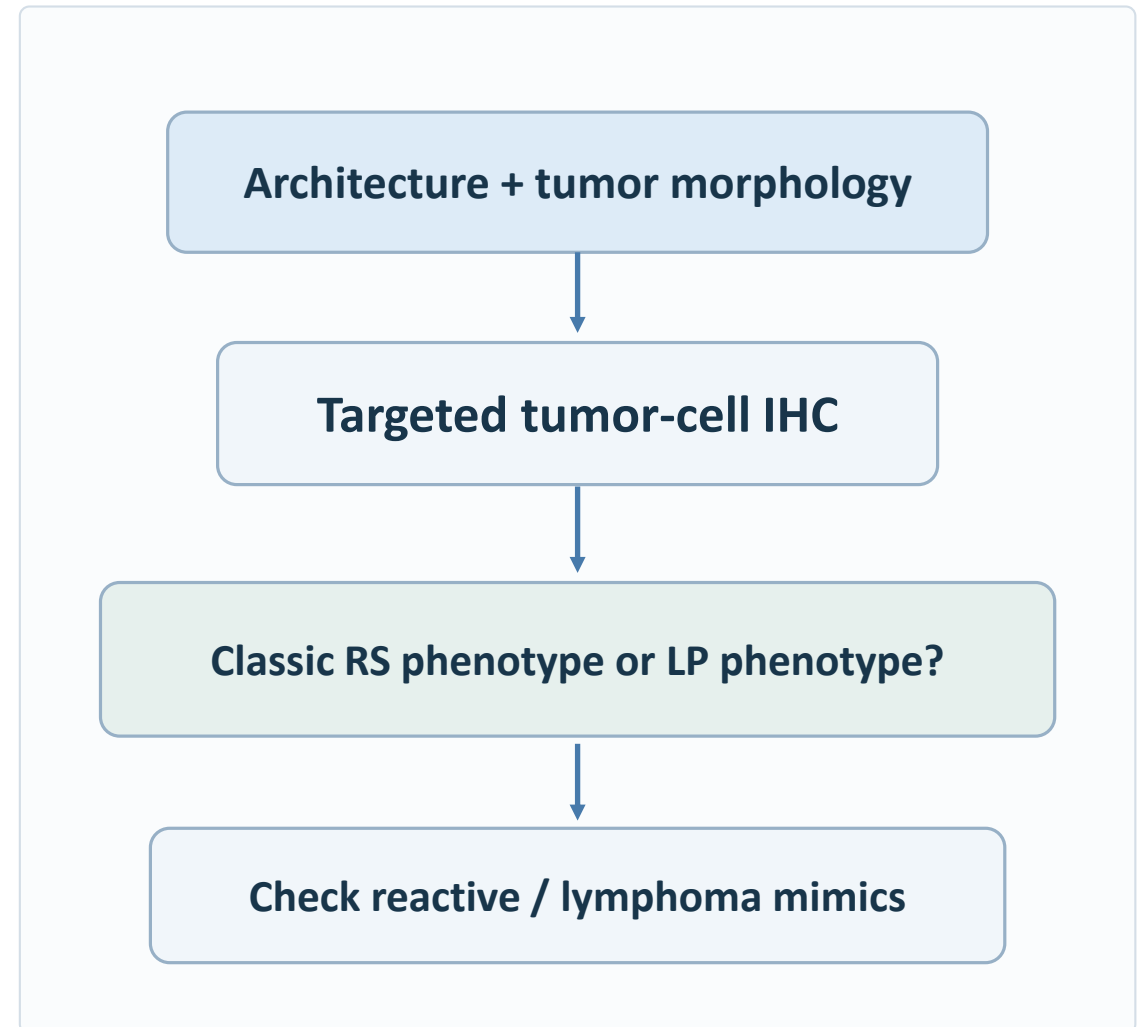


Classification terminology requires precision

- Four classic forms plus nodular lymphocyte-predominant Hodgkin lymphoma.
- The International Consensus Classification (ICC) uses “nodular lymphocyte-predominant B-cell lymphoma.”
- Do not equate the ICC name change with a transformation to diffuse large B-cell lymphoma.

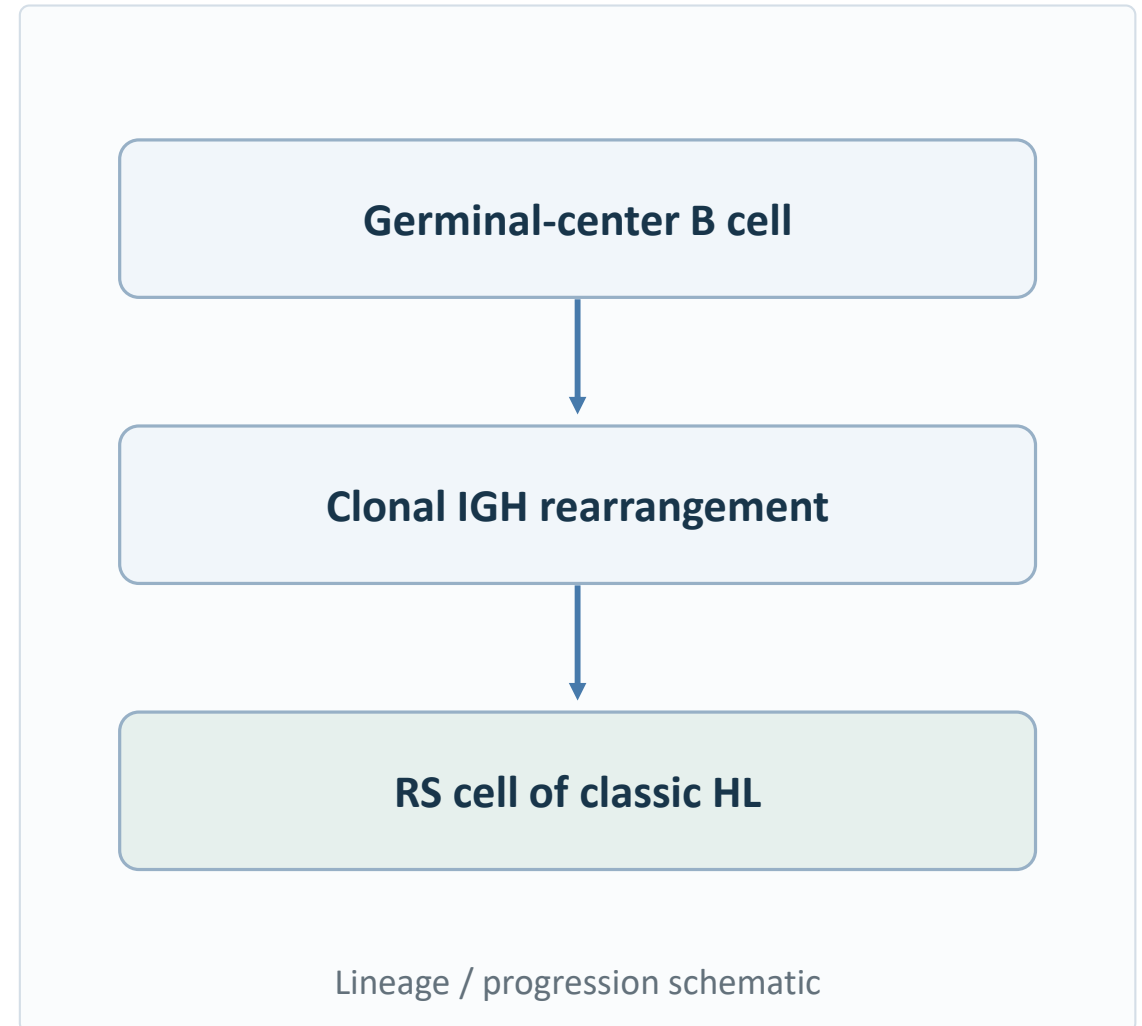
A diagnostic framework for Hodgkin lymphoma

- Architecture and cytology establish a morphologic suspicion.
- Cell-specific immunophenotype separates classic RS cells from L&H/LP cells.
- Clinical distribution, infection history and mimics complete the interpretation.



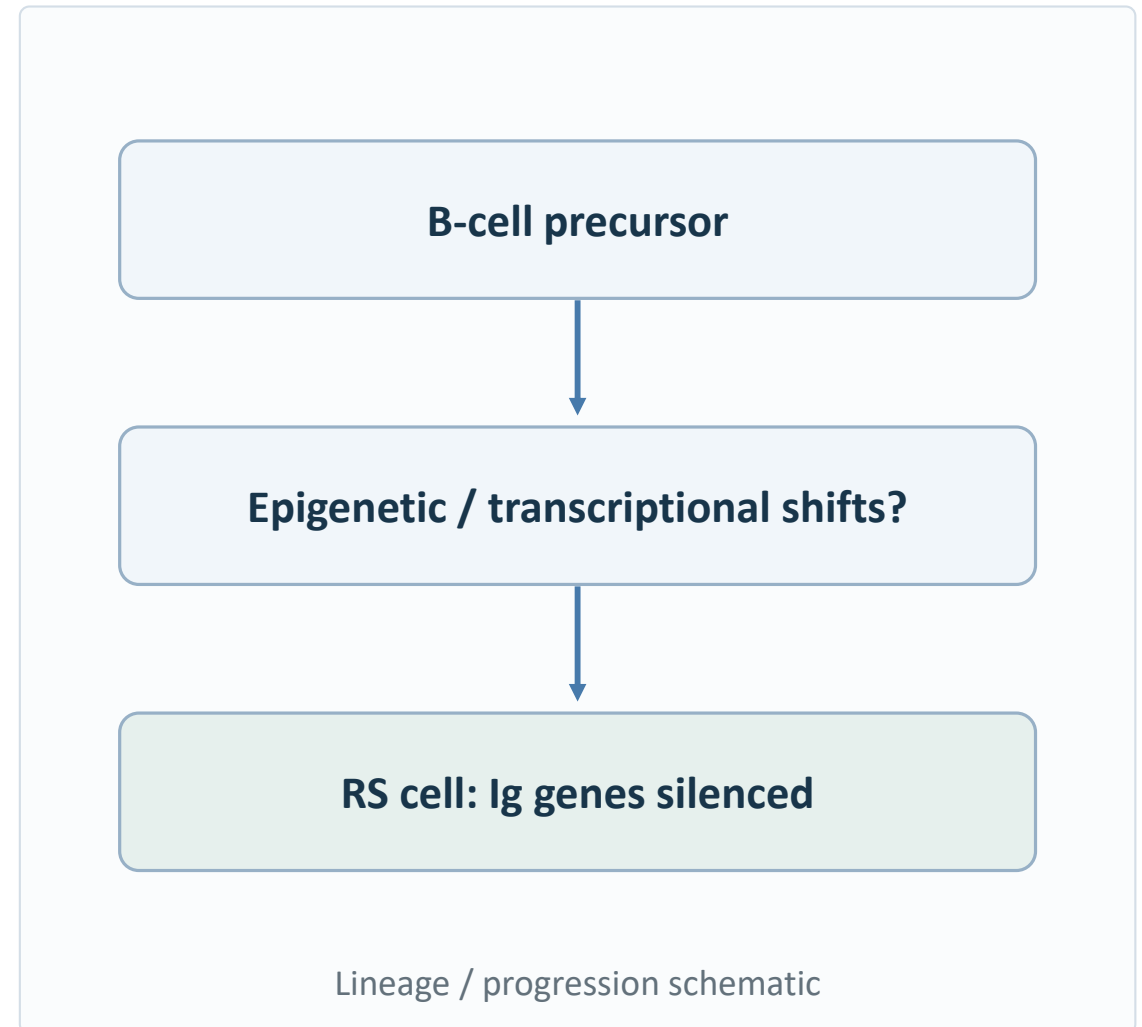
The RS cell retains evidence of B-cell ancestry

- Single-cell studies show clonal IGH rearrangements in classic RS cells.
- Somatic hypermutation places their origin in germinal-center or post-germinal-center B cells.
- The cell of origin cannot be inferred reliably from the usual cHL surface-marker pattern.



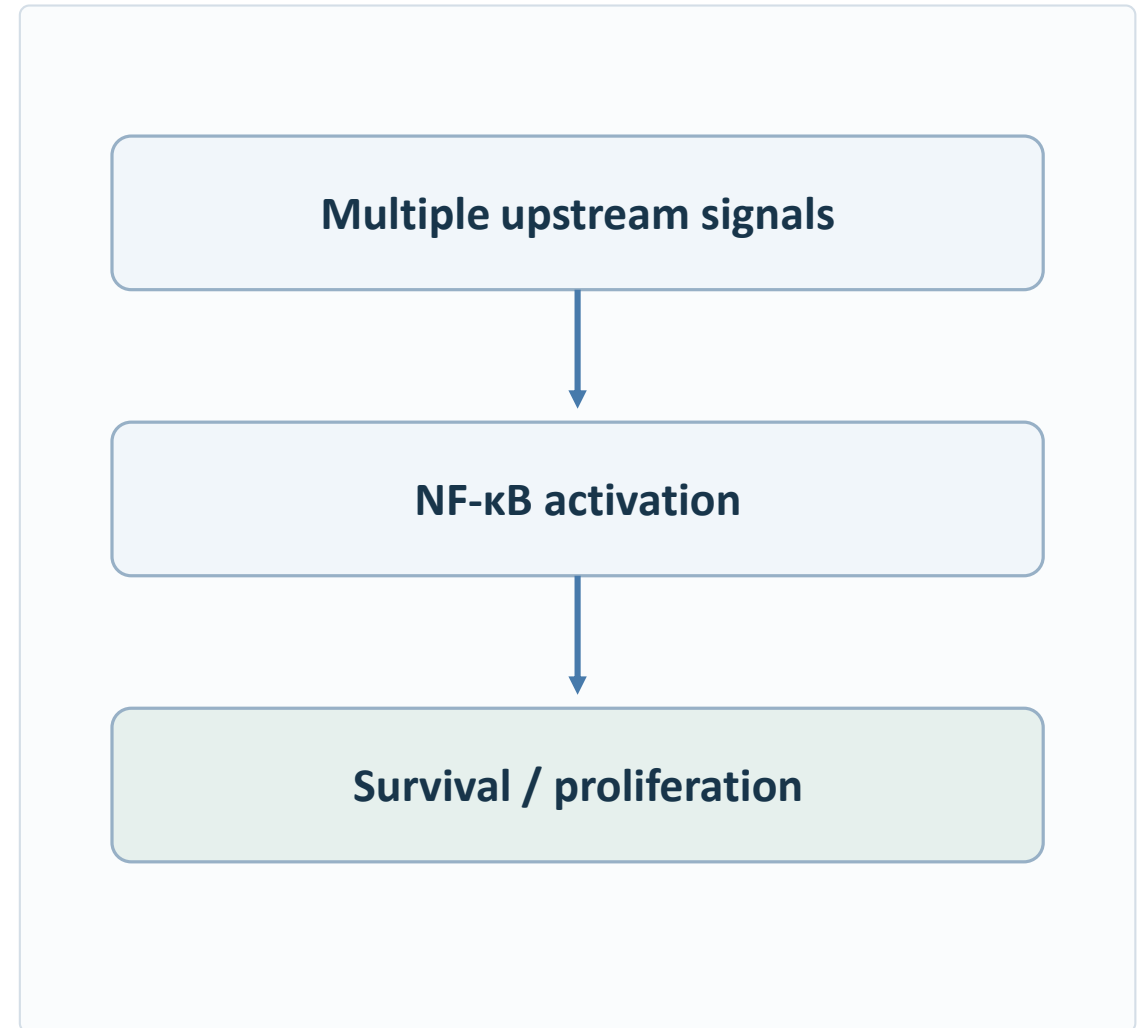
The classic RS cell suppresses its B-cell program

- Despite its B-cell origin, classic RS cells fail to express most lineage-associated genes.
- Immunoglobulin gene expression is typically absent.
- This reprogramming only tentatively to broad epigenetic changes.



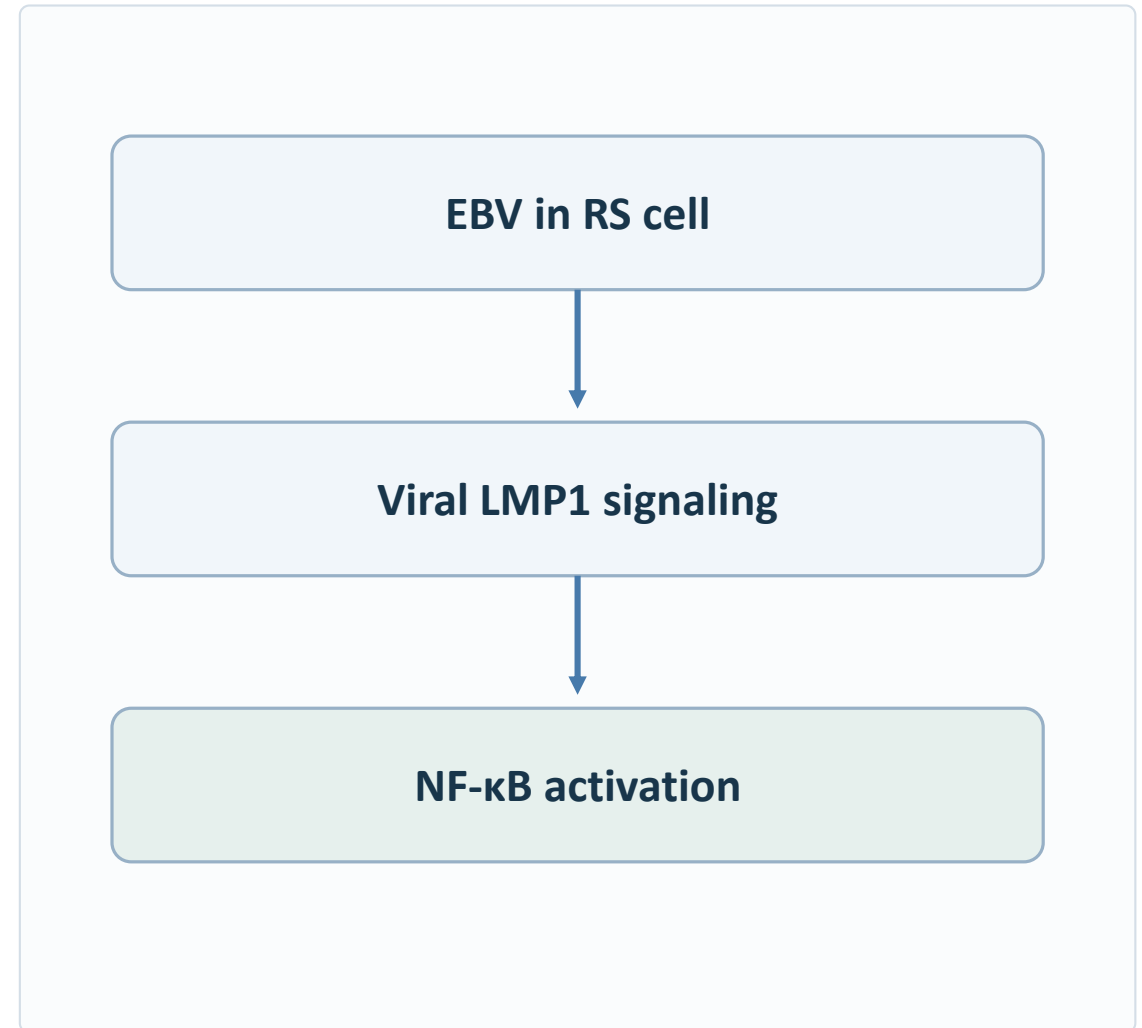
NF- κ B activation promotes tumor-cell survival

- NF- κ B is commonly activated in classic Hodgkin lymphoma.
- It induces genes supporting RS-cell growth and survival.
- Multiple molecular routes converge on the same prosurvival transcriptional program.



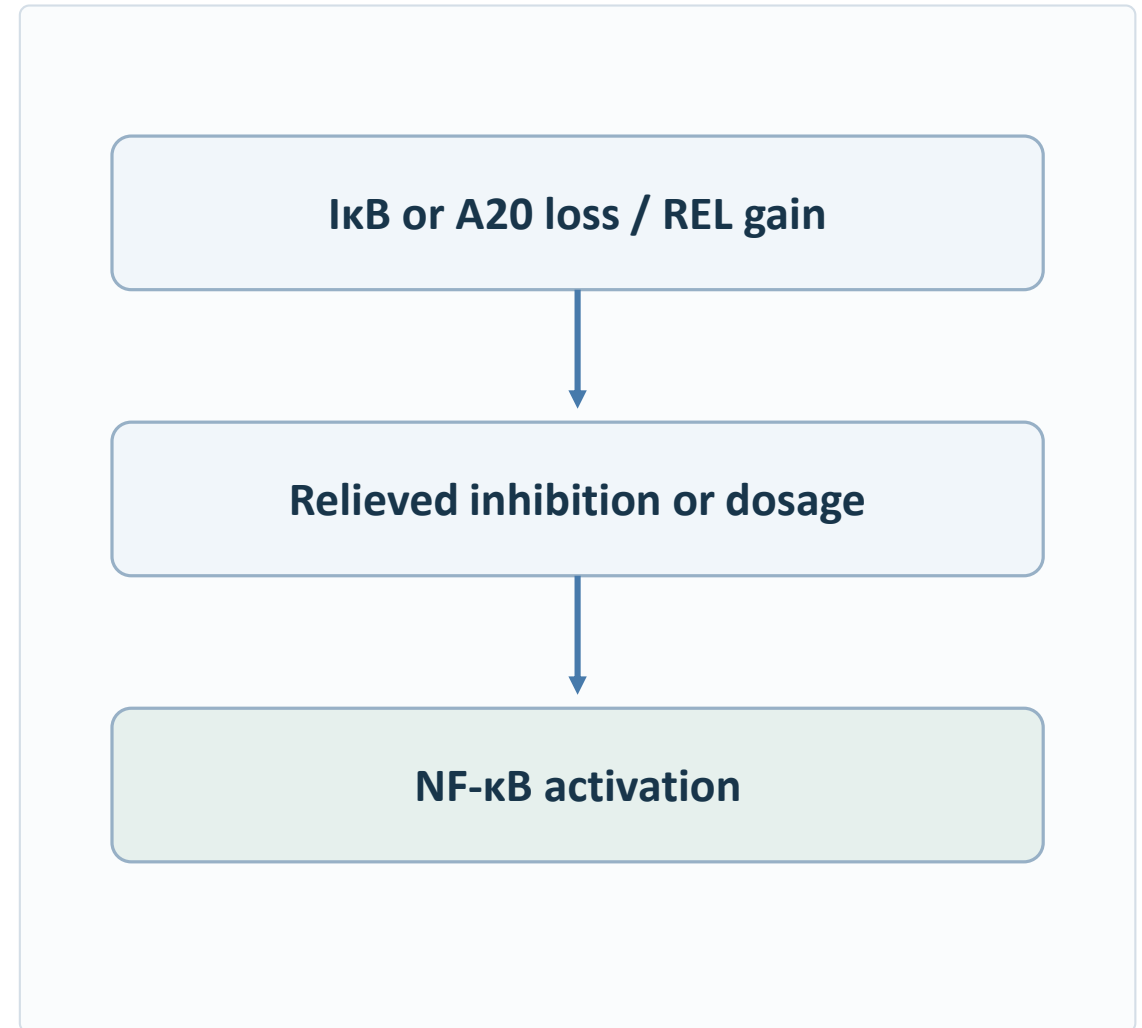
EBV can substitute for a survival signal

- A subset of classic Hodgkin lymphomas carries Epstein–Barr virus in tumor cells.
- The viral latent membrane protein LMP1 activates signaling that upregulates NF- κ B.
- EBV prevalence varies by histologic subtype; Viral association is not universal.



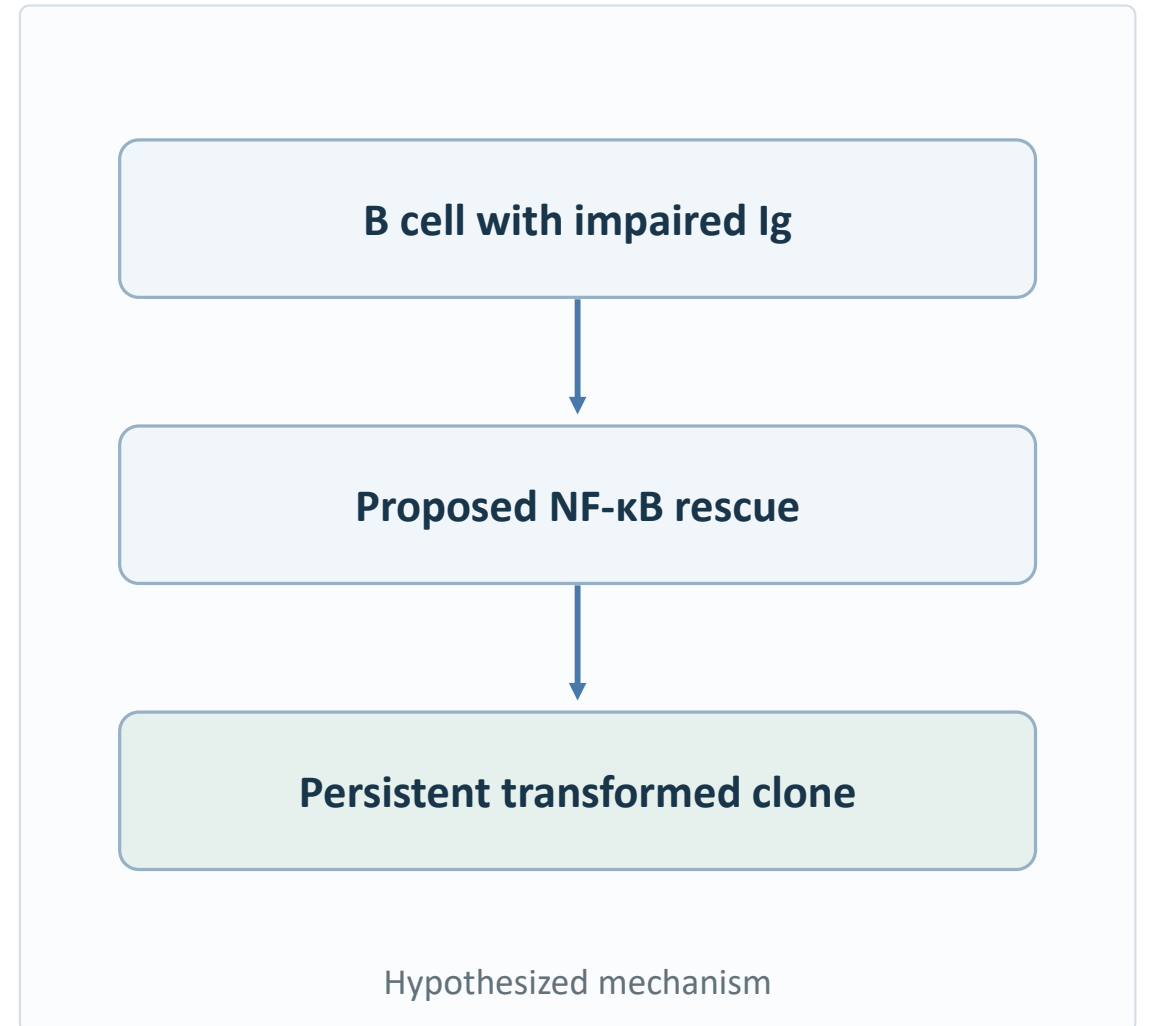
Genetic disruption can activate the same pathway

- Loss-of-function alterations affect negative NF- κ B regulators such as I κ B.
- TNFAIP3 (A20) is another cited negative regulator that may be inactivated.
- REL copy gains at chromosome 2p can augment NF- κ B output.



A proposed rescue of crippled B cells

- Some germinal-center B cells lose the ability to produce immunoglobulin.
- Such cells normally risk apoptosis after failed B-cell selection.
- NF- κ B activation may rescue these cells while additional lesions accumulate.

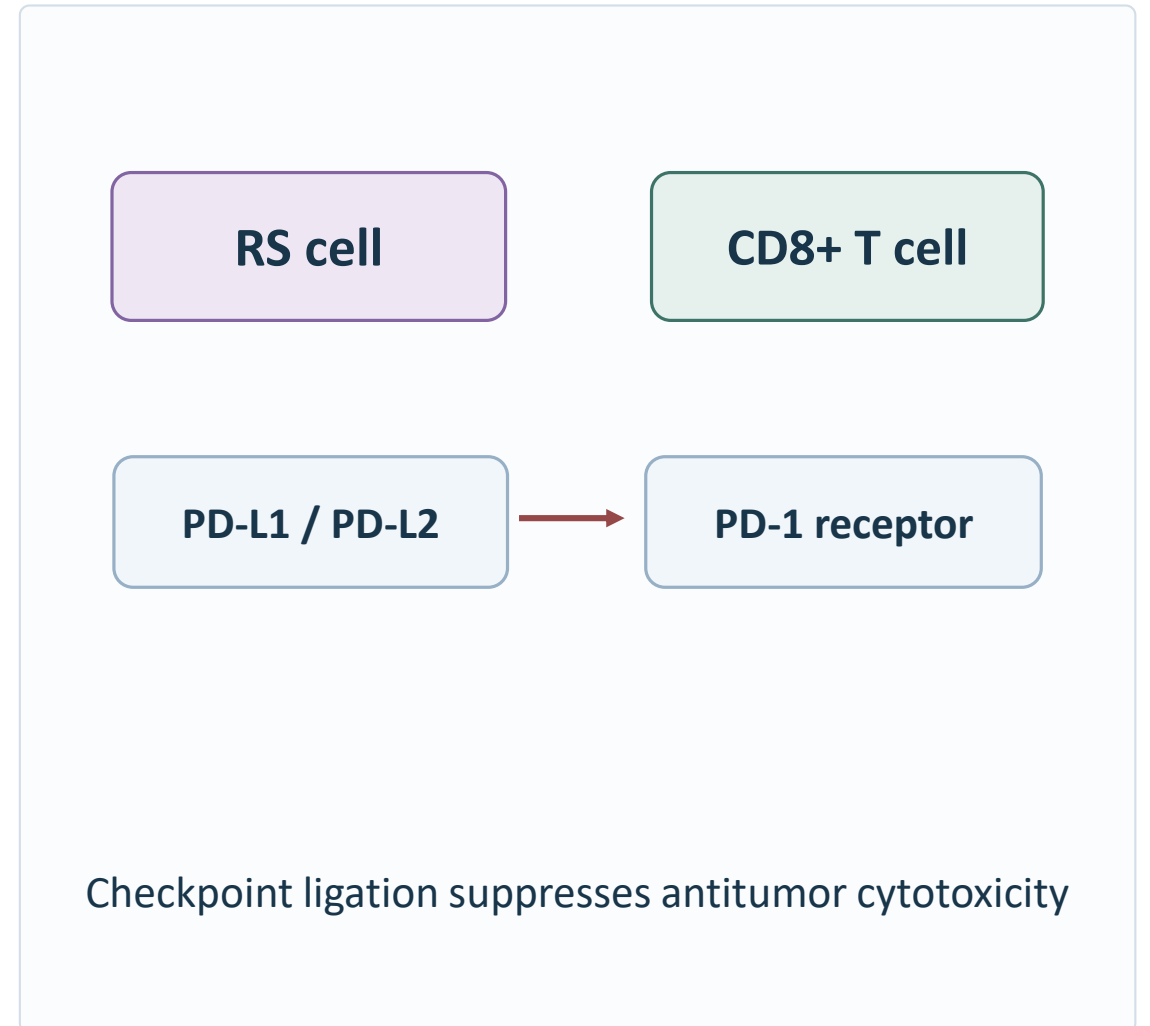


Genomic instability is an additional characteristic

- Classic RS cells are frequently aneuploid.
- Diverse clonal chromosomal aberrations coexist with abnormal transcriptional programs.
- Mechanistic pathways are heterogeneous; No single lesion accounts for every tumor.

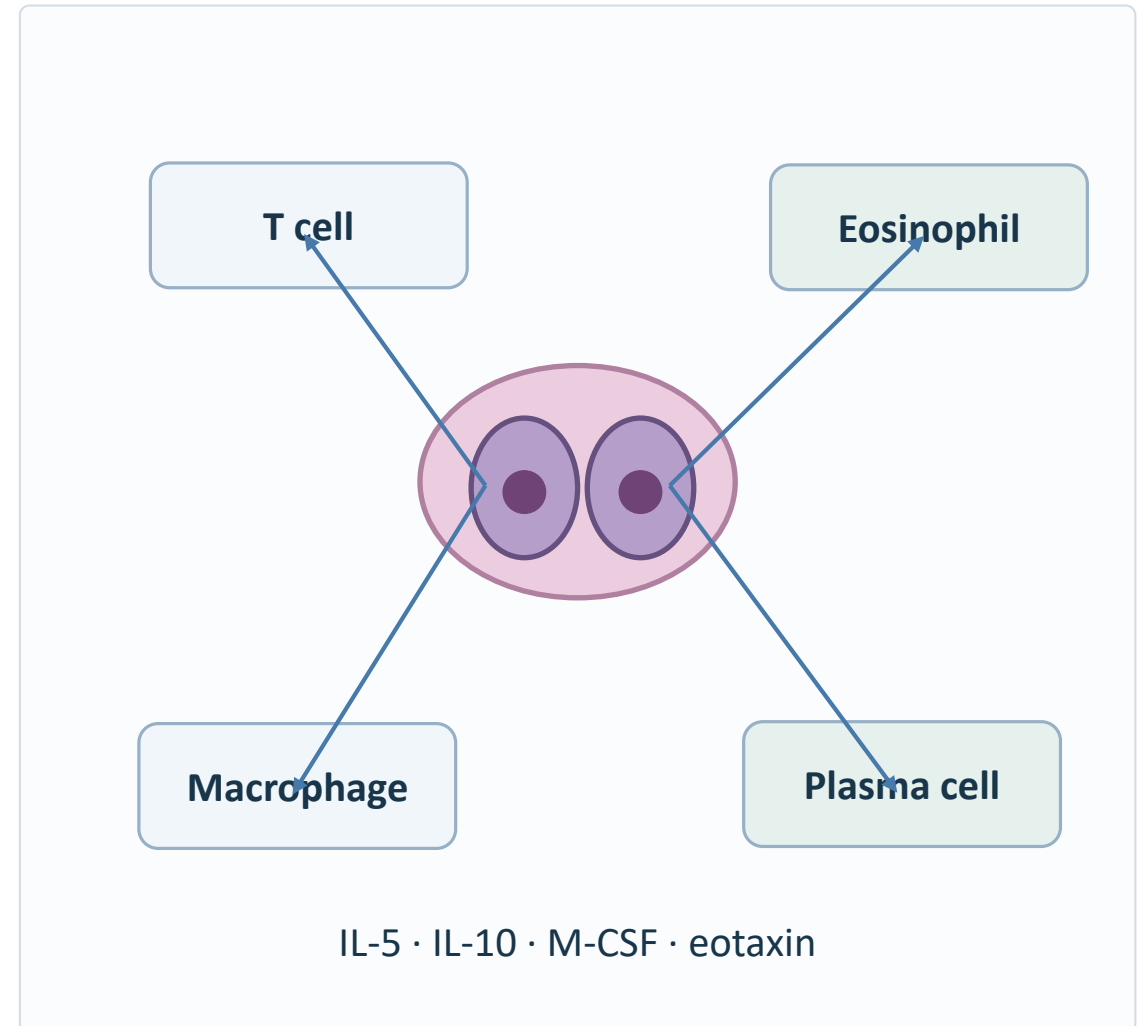
9p copy-number gain favors immune evasion

- Gains at chromosome 9p may increase the genes encoding PD-L1 and PD-L2.
- PD-L1/PD-L2 engage the inhibitory receptor PD-1 on responding T cells.
- This weakens antitumor immunity even in lymphoid tissue crowded with host cells.



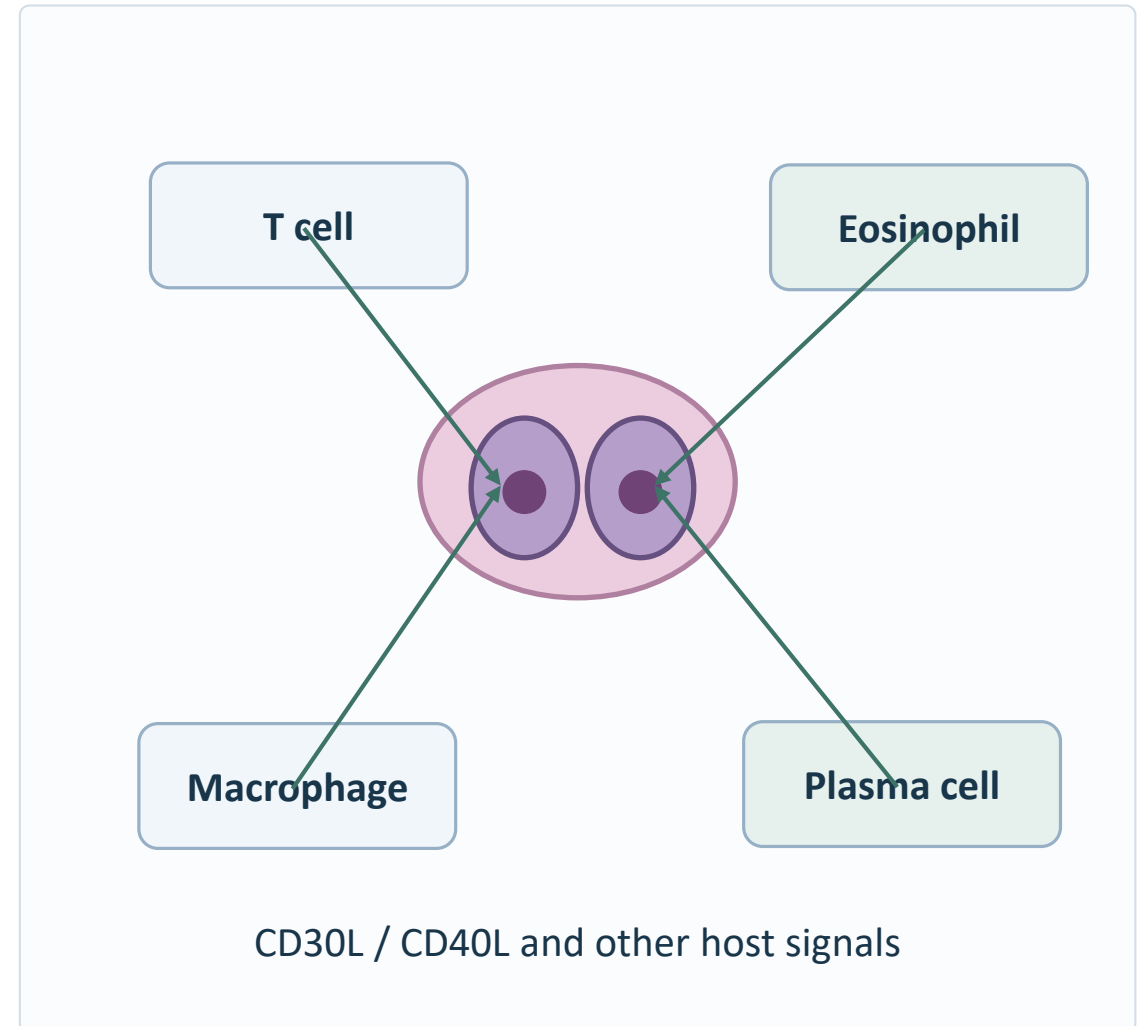
The inflammatory infiltrate is actively recruited

- RS cells release cytokines, chemokines and other soluble factors.
- Examples listed by Robbins include IL-5, IL-10, M-CSF and eotaxin.
- This recruitment shapes the polymorphous background that defines cHL histology.



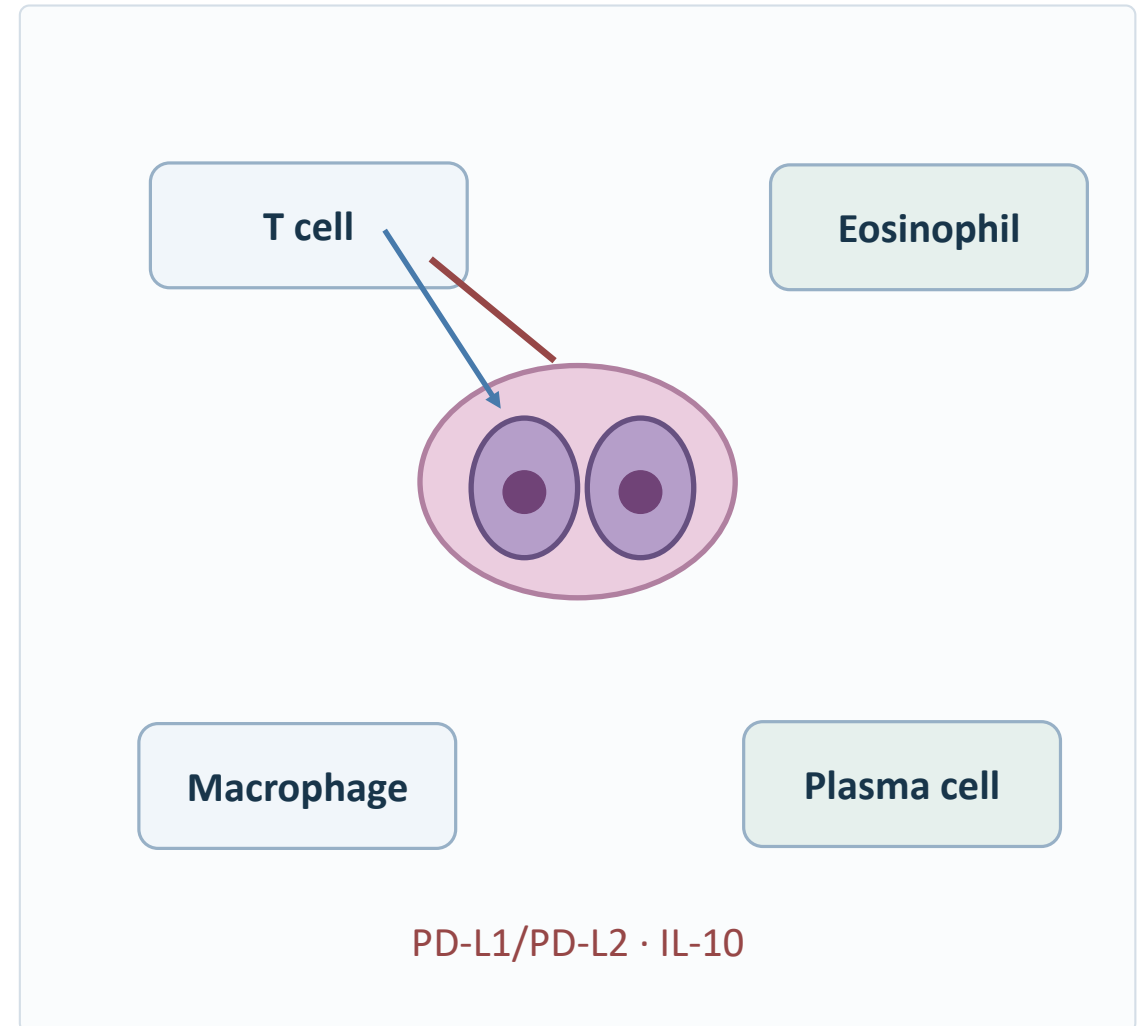
The recruited cells reciprocally sustain RS cells

- T lymphocytes and eosinophils can express ligands for tumor-cell CD30 and CD40.
- Signaling through these receptors promotes RS-cell NF- κ B activity.
- The tissue therefore functions as a reciprocal tumor–host signaling ecosystem.



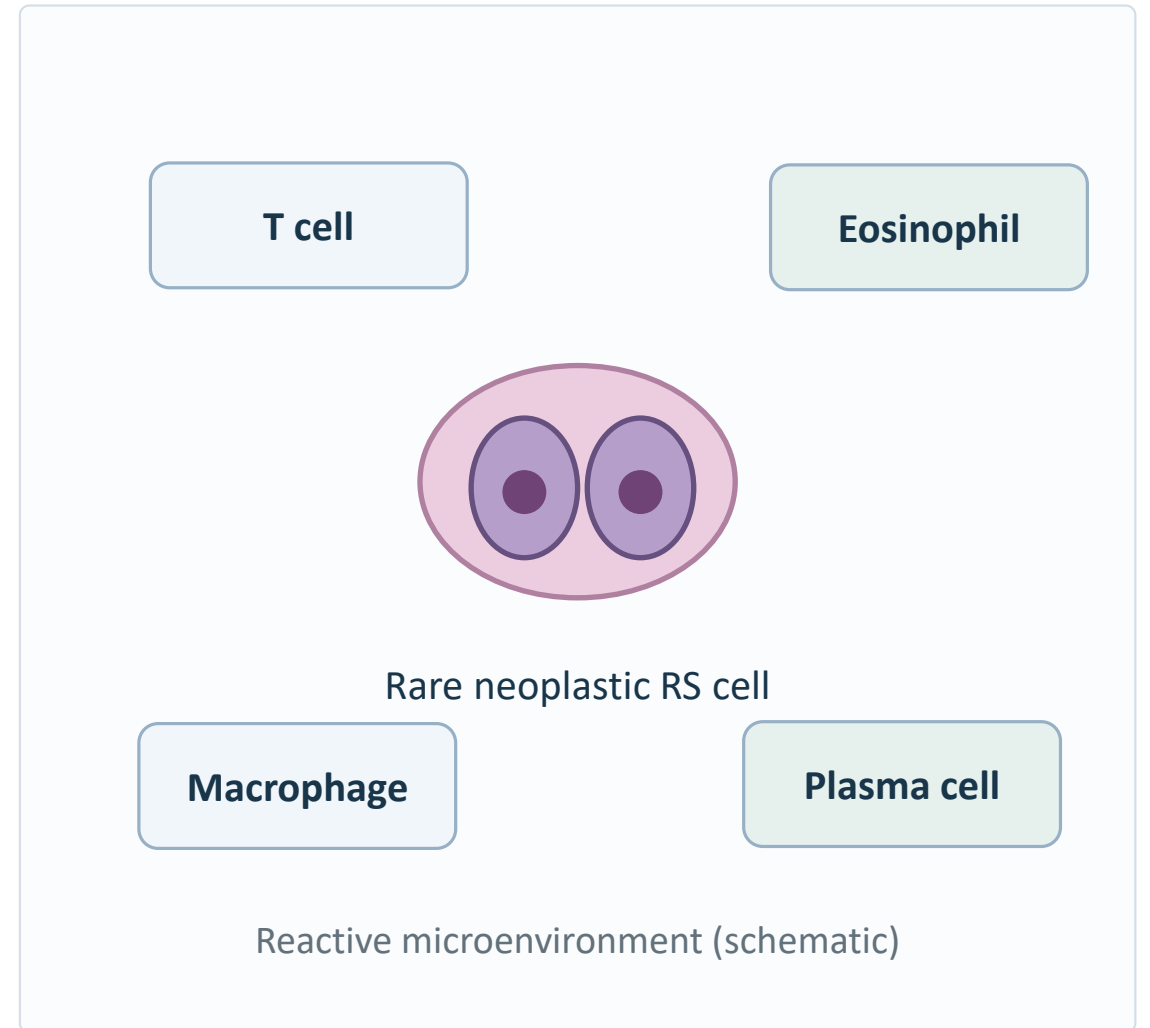
Why immune-cell abundance does not imply control

- A dense infiltrate shows that the neoplasm attracts host immune cells.
- RS-cell PD-L1/PD-L2 inhibit effective cytotoxic T-cell responses.
- Tumor-derived IL-10 can also suppress Th1-mediated immune function.



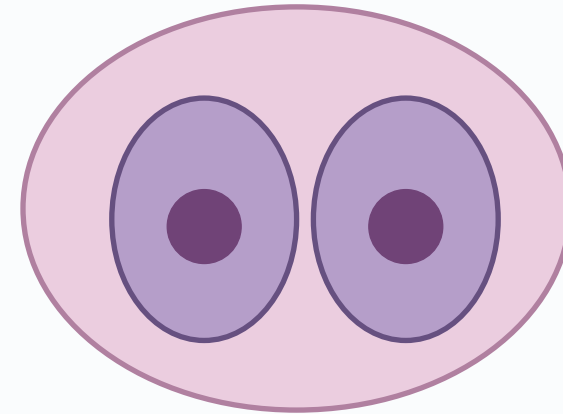
Cellular interactions explain key histology

- Recruitment produces mixed T cells, histiocytes, eosinophils and plasma cells.
- Growth signals allow rare tumor cells to persist within this abundant background.
- Immune checkpoint activity helps prevent elimination by activated T cells.



Tissue morphology: Begin with the RS-cell search

- Examine large atypical cells within their inflammatory context.
- Classic RS cells have abundant cytoplasm and multiple nuclei or nuclear lobes.
- Large inclusion-like nucleoli are conspicuous and may approximate a small lymphocyte in size.

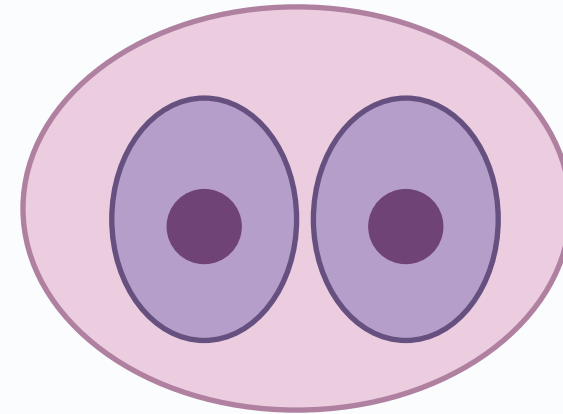


Binucleated tumor cell with conspicuous nucleoli

Schematic cell drawing—not a photomicrograph

Classic RS cell: Anatomic features of the nucleus

- Binucleation or nuclear multilobation is frequent.
- Each nucleus or lobe commonly contains a large inclusion-like nucleolus.
- The visual “owl-eye” resemblance is a teaching aid, not a stand-alone diagnosis.

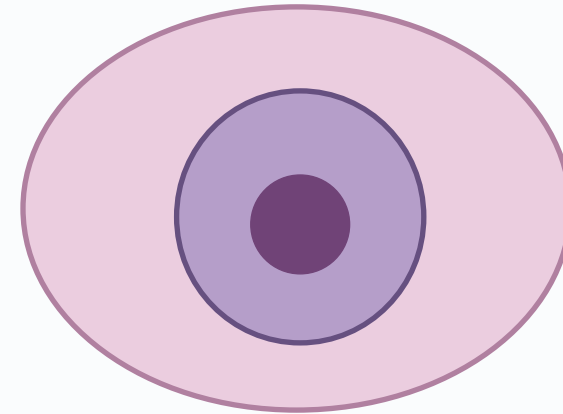


Nuclear lobes and large nucleoli

Schematic cell drawing—not a photomicrograph

The mononuclear RS-cell variant

- A single large nucleus replaces the conventional multinuclear configuration.
- The prominent inclusion-like nucleolus remains diagnostically important.
- Recognition broadens the search beyond textbook-perfect binucleated cells.

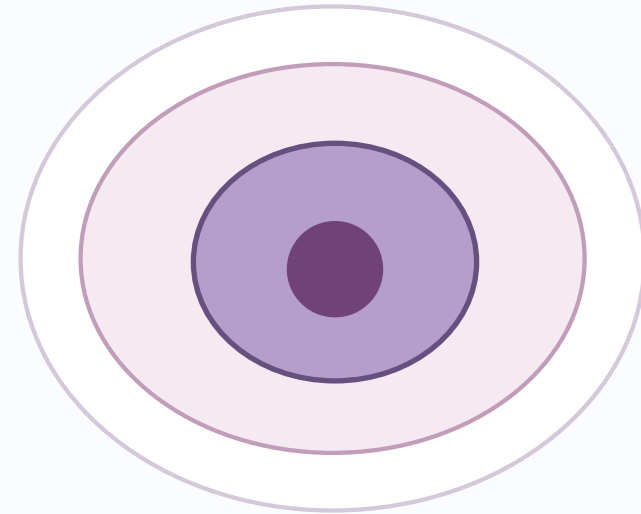


Single enlarged nucleus; Inclusion-like nucleolus

Schematic cell drawing—not a photomicrograph

Lacunar cells are a sectioning-related appearance

- These cells often have folded, delicate or multilobate nuclei.
- Pale cytoplasm may retract or fragment during preparation of tissue sections.
- The resulting empty-looking space is a lacuna, not a true physiologic compartment.

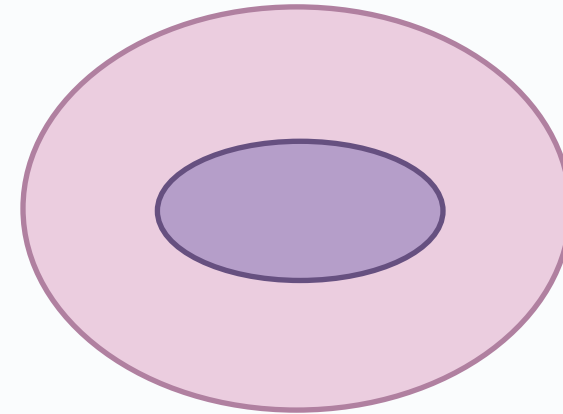


Artificial pericellular clearing after processing

Schematic cell drawing—not a photomicrograph

Mummified RS cells represent tumor-cell death

- Some RS cells undergo shrinkage with intensely condensed, pyknotic nuclei.
- This “mummification” is described in classic Hodgkin lymphoma.
- It is a recognizable morphologic variant, not a separate subtype.

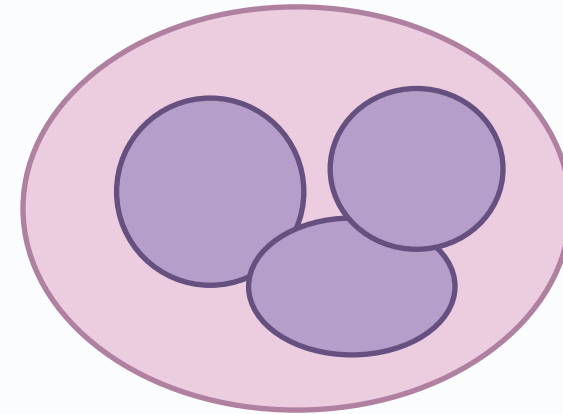


Pyknotic, shrunken tumor-cell variant

Schematic cell drawing—not a photomicrograph

LP or L&H cells have a different nuclear contour

- Nuclei are multilobulated with polypoid infoldings resembling popcorn kernels.
- Nucleoli are less conspicuous than in typical classic RS cells.
- LP cells are characteristic of nodular lymphocyte-predominant disease.

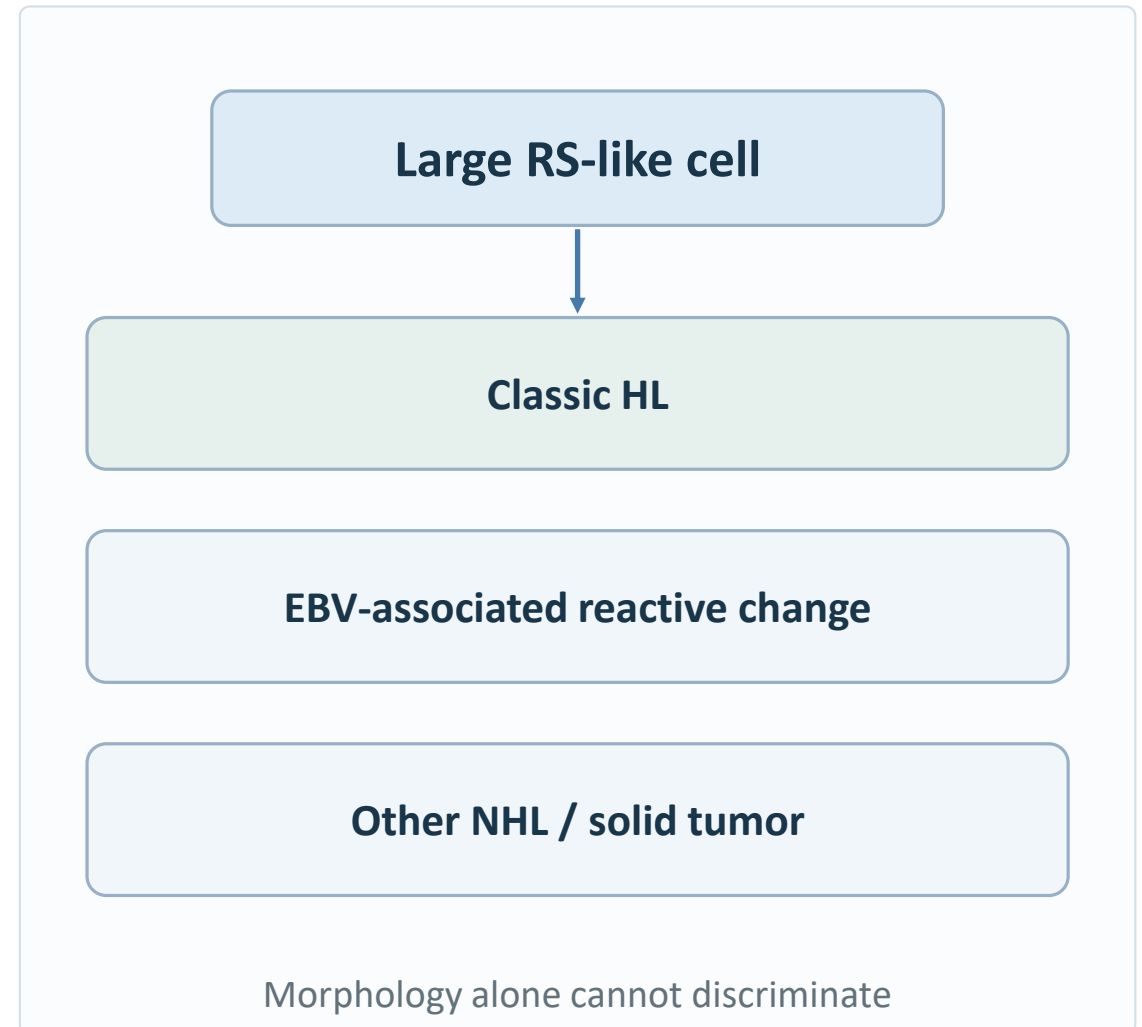


Polylobulated nucleus; Smaller nucleoli

Schematic cell drawing—not a photomicrograph

RS-like cells occur outside Hodgkin lymphoma

- Infectious mononucleosis may show atypical activated B cells resembling RS cells.
- Certain non-Hodgkin lymphomas and solid malignancies may contain RS-like cells.
- Diagnostic integration requires architectural context and immunophenotyping.



Classic immunophenotype provides confirmation

- Classic RS cells are typically positive for CD30 and CD15.
- PAX5 is expressed, reflecting residual B-cell-lineage differentiation.
- CD45, most other B-cell markers and T-cell markers are typically negative.

CD30

Positive

CD15

Positive

PAX5

Positive

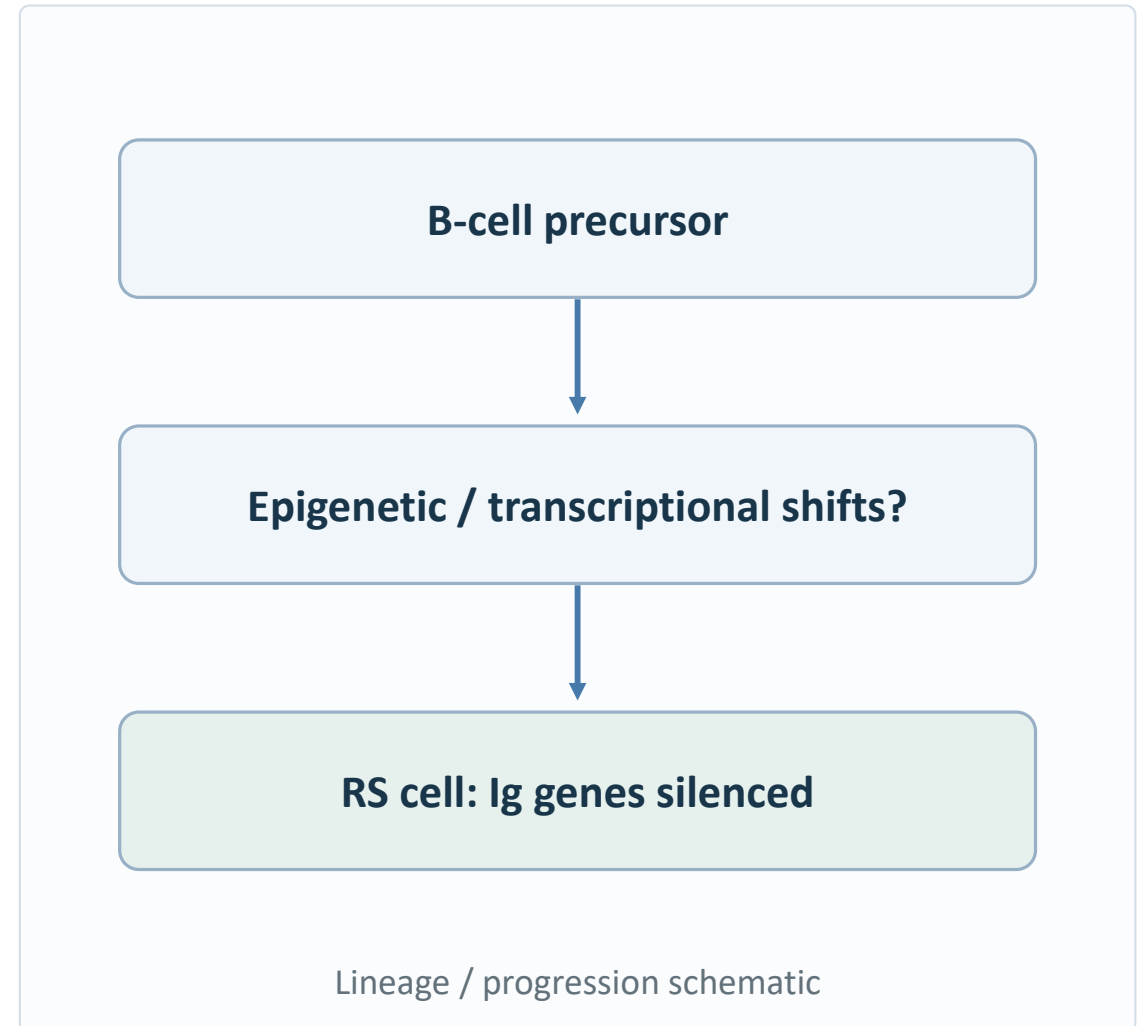
CD45

Negative

Profile is interpreted in appropriate morphology

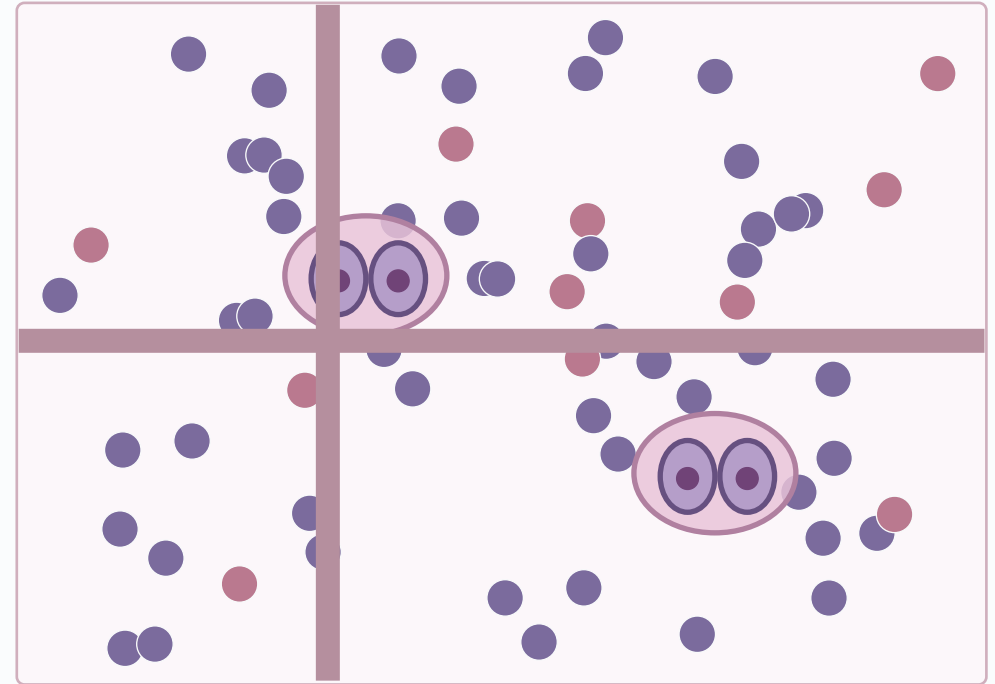
The lineage paradox: PAX5 without a B-cell program

- PAX5 expression is retained while numerous conventional B-cell markers are lost.
- Clonal IGH rearrangement establishes lineage more securely than the reduced phenotype alone.
- Morphology plus multiple markers is safer than a single-antigen diagnosis.



Nodular sclerosis: Architecture makes the diagnosis

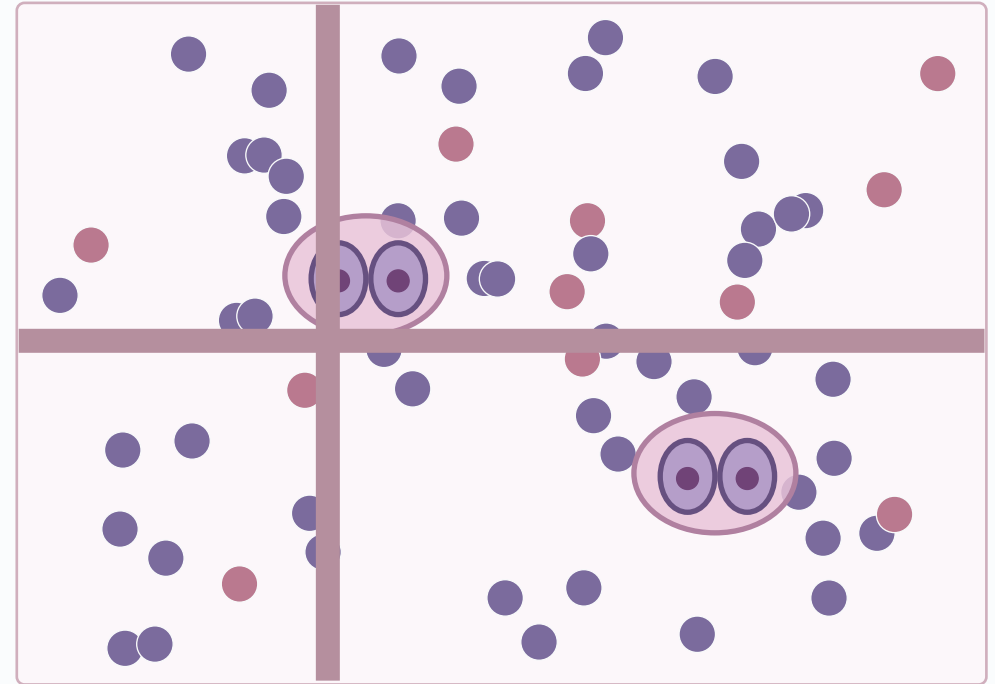
- Broad collagen bands subdivide involved lymph-node tissue into nodules.
- Lacunar variants are frequent; Diagnostic RS cells may be sparse.
- Fibrosis can be limited or extensive; The key is demonstrable nodular partitioning.



Schematic architecture — not histology

Nodular sclerosis: Tumor–host cellular mixture

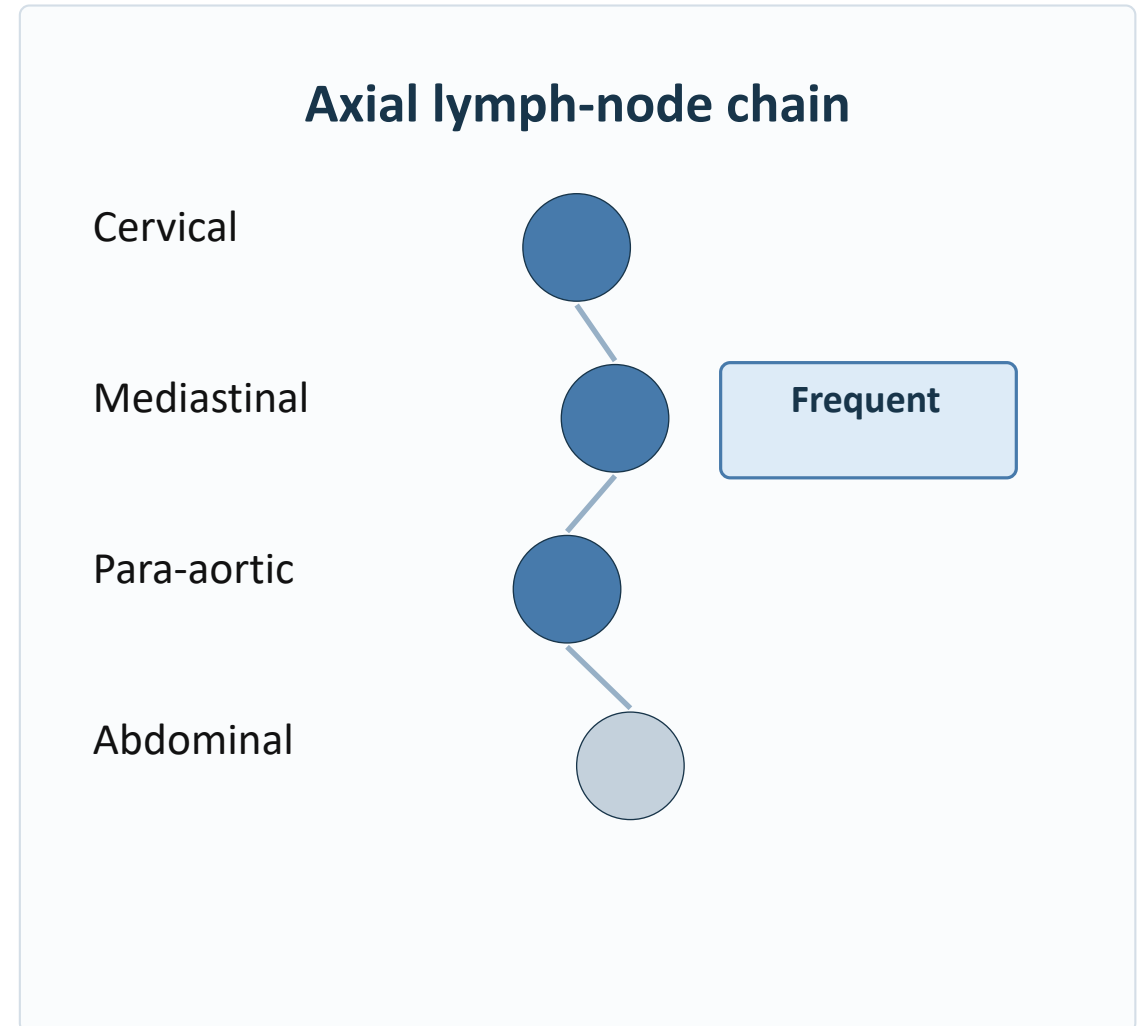
- Cell-rich nodules contain T cells, eosinophils, plasma cells and macrophages.
- Lacunar cells represent a morphologic appearance linked to processing artifact.
- CD15/CD30/PAX5 positivity supports the classic Hodgkin lineage.



Schematic architecture — not histology

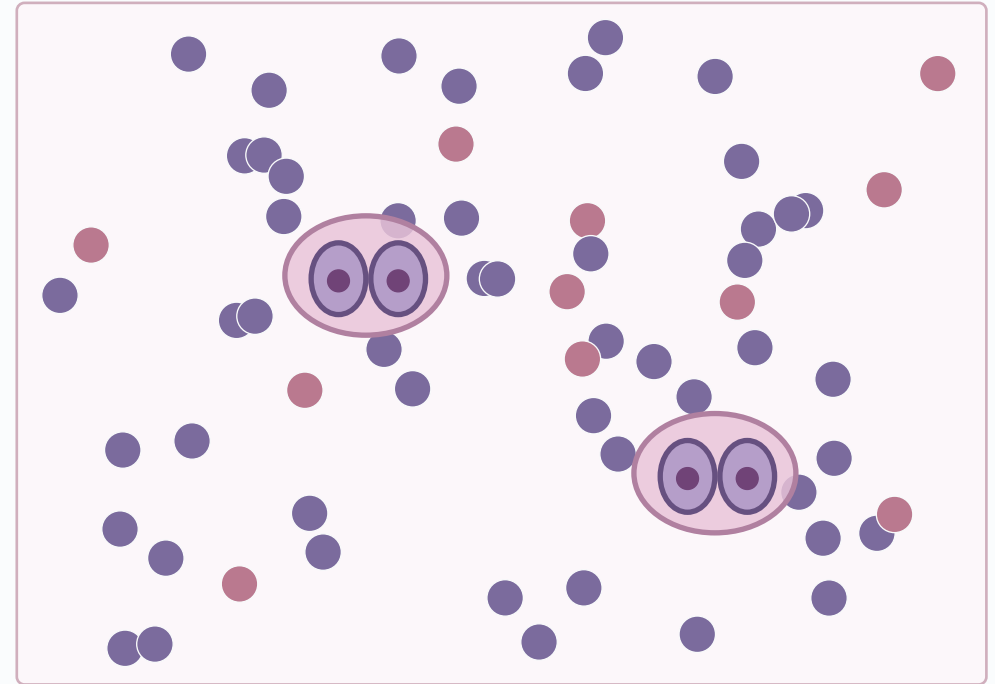
Nodular sclerosis: Epidemiology and presentation

- This is the most common classic subtype (65%–70%).
- Adolescents and young adults often present with cervical/supraclavicular or mediastinal disease.
- Sex distribution is approximately equal; EBV association is uncommon.



Mixed cellularity: Diffusely effaced lymph node

- The nodal architecture is replaced by a heterogeneous infiltrate.
- T cells, macrophages, eosinophils and plasma cells surround RS cells.
- Typical RS cells and mononuclear variants are usually readily found.



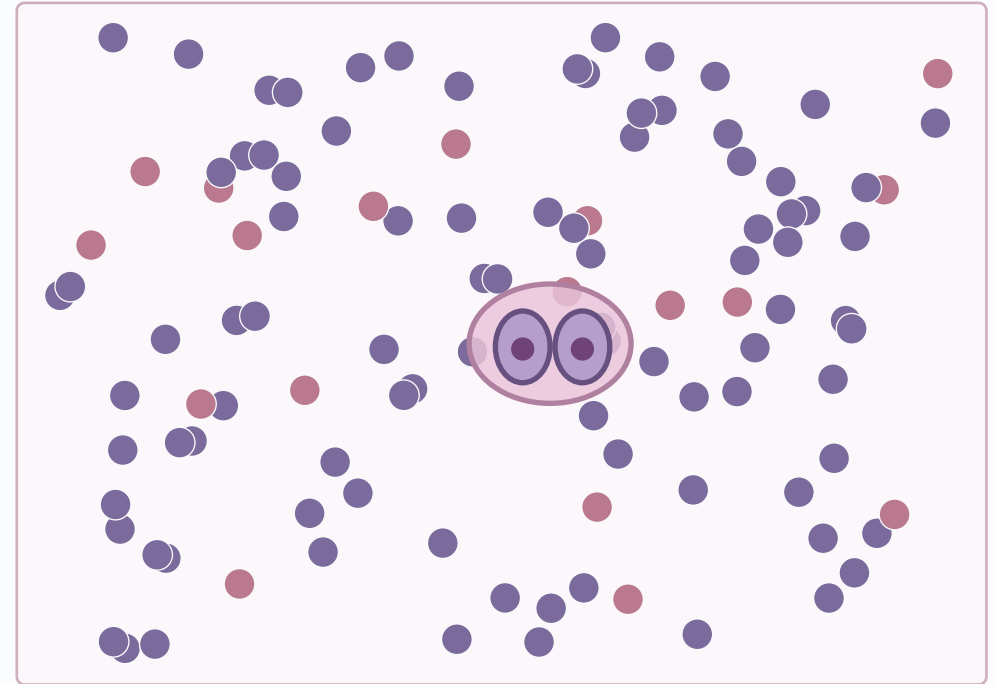
Schematic architecture — not histology

Mixed cellularity: Clinical and viral profile

- 20%–25% of all Hodgkin lymphoma cases.
- EBV is present in approximately 70% of tumors series.
- Compared with nodular sclerosis, advanced stage and B symptoms are more frequent.

Lymphocyte-rich cHL: A deceptive predominance

- Small reactive lymphocytes make up most of the infiltrate.
- The pattern is often diffuse; Some cases show vague nodules related to residual follicles.
- Conventional RS/mononuclear variants with classic IHC distinguish it from NLPHL.



Schematic architecture — not histology

Lymphocyte-rich cHL is not NLPHL

- Both may present with abundant small lymphocytes and limited overt atypia.
- Lymphocyte-rich cHL retains the CD15/CD30-positive classic phenotype.
- NLPHL instead has LP cells expressing CD20 and BCL6.

LR classic HL

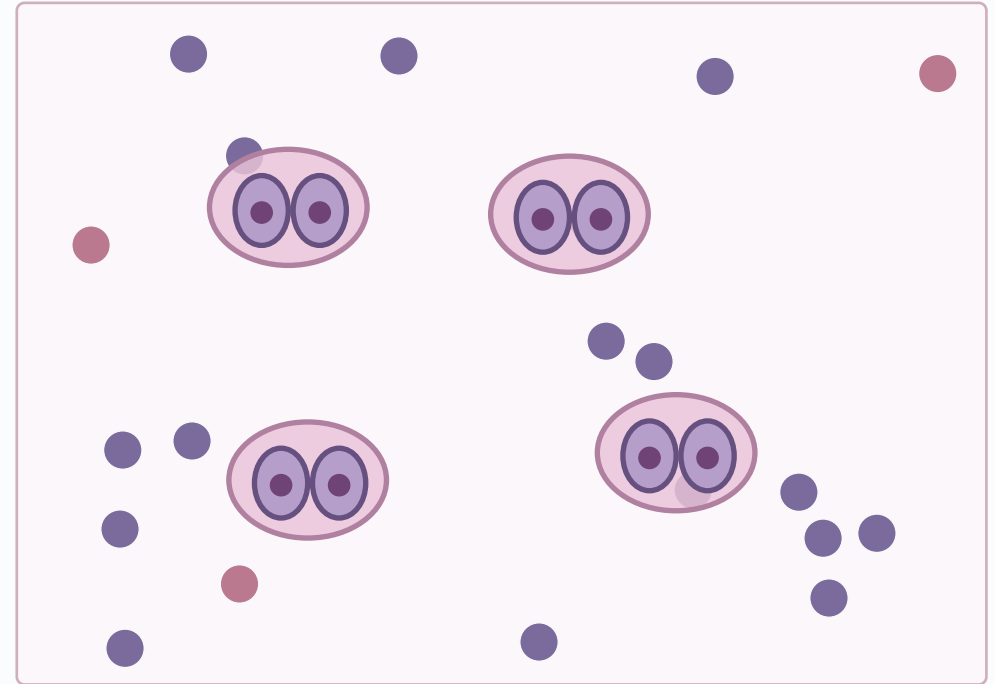
CD15+ / CD30+

Nodular LP

CD20+ / BCL6+

Lymphocyte-depleted cHL: High tumor-cell density

- There are relatively few background lymphocytes and abundant RS or pleomorphic cells.
- This is the rarest classic subtype, accounting for fewer than 5% of cases.
- Immunophenotyping is essential because many suspected cases are actually NHL.



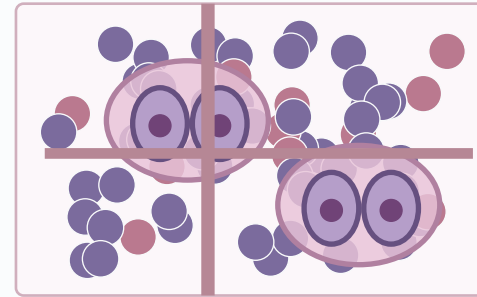
Schematic architecture — not histology

Lymphocyte-depleted cHL: Clinical context

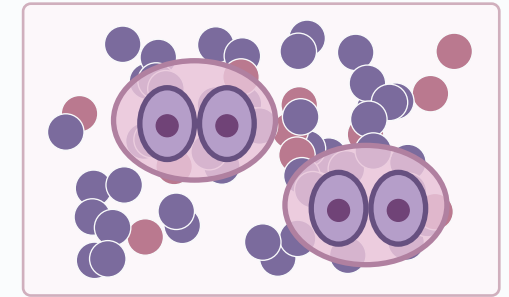
- The subtype with older adults and persons with HIV.
- EBV association is reported in more than 90% of cases.
- Advanced-stage presentation and constitutional symptoms are common.

The four classic subtypes: Distinguishing clues

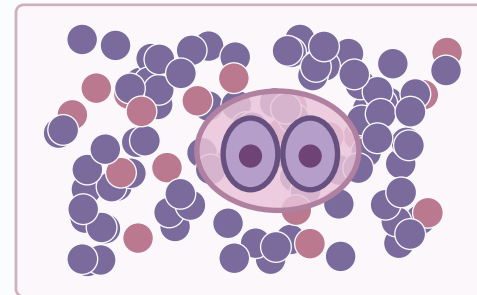
- Nodular sclerosis: Broad collagen bands and lacunar variants.
- Mixed cellularity: Diffuse polymorphous infiltrate with abundant RS cells.
- Lymphocyte-rich: Many small reactive lymphocytes and few classic RS cells.
- Lymphocyte-depleted: Relative paucity of reactive lymphocytes, many atypical RS cells.



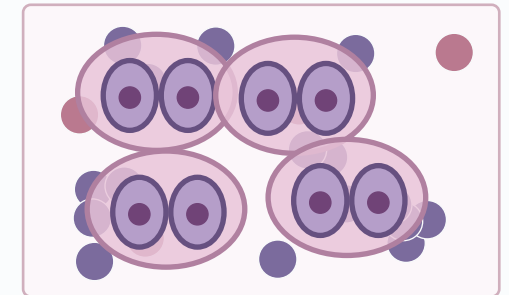
Nodular sclerosis



Mixed cellularity



Lymphocyte-rich



Lymphocyte-depleted

Classic subtypes share a diagnostic core

- CD30 and CD15 are expressed by characteristic tumor cells.
- PAX5 supports the underlying B-cell origin despite broad lineage-marker loss.
- Subtype assignment relies primarily on tissue architecture and the reactive background.

CD30

Positive

CD15

Positive

PAX5

Positive

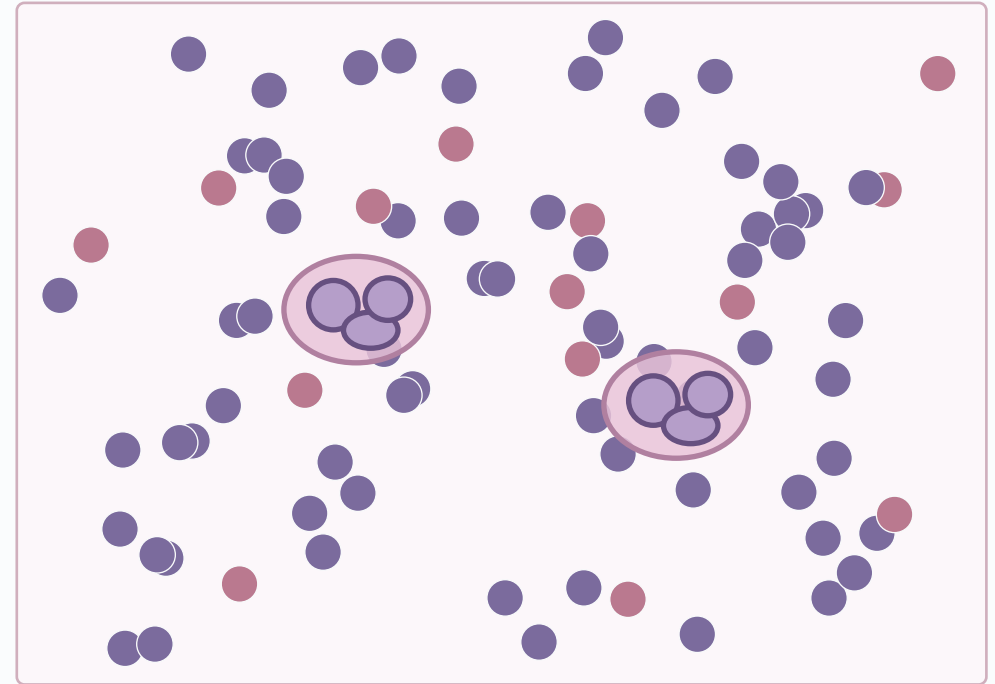
CD45

Negative

Profile is interpreted in appropriate morphology

Nodular lymphocyte predominance is biologically distinct

- This entity accounts for approximately 5% of Hodgkin lymphoma.
- Tumor-containing nodules are built around B cells and follicular dendritic cells.
- Classic RS cells are usually absent; Lymphocyte-predominant/LP cells predominate.



Schematic architecture — not histology

LP (“popcorn”) cells retain germinal-center markers

- CD20 and BCL6 are generally expressed.
- CD15 and CD30 are usually absent.
- The preserved phenotype contrasts with the profoundly attenuated B-cell program of cHL.

CD20

Positive

BCL6

Positive

CD15

Negative

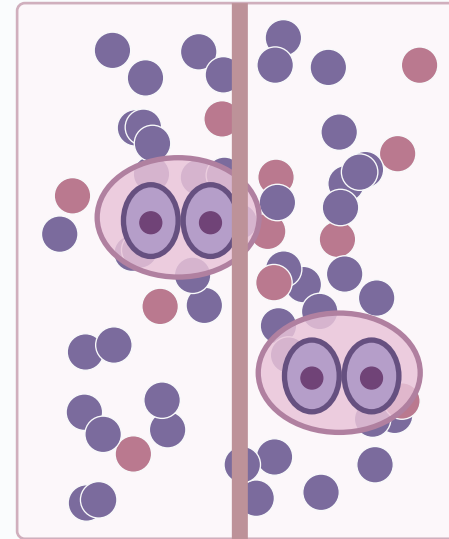
CD30

Negative

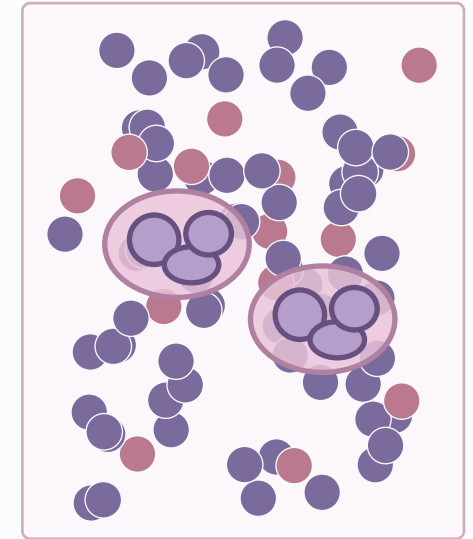
Profile is interpreted in appropriate morphology

Nodularity reflects a specific cellular architecture

- Expanded follicles contain LP cells, reactive B cells and follicular dendritic cells.
- Eosinophils and plasma cells are usually scarce.
- This microanatomy differs from collagen-banded nodules of nodular sclerosis cHL.



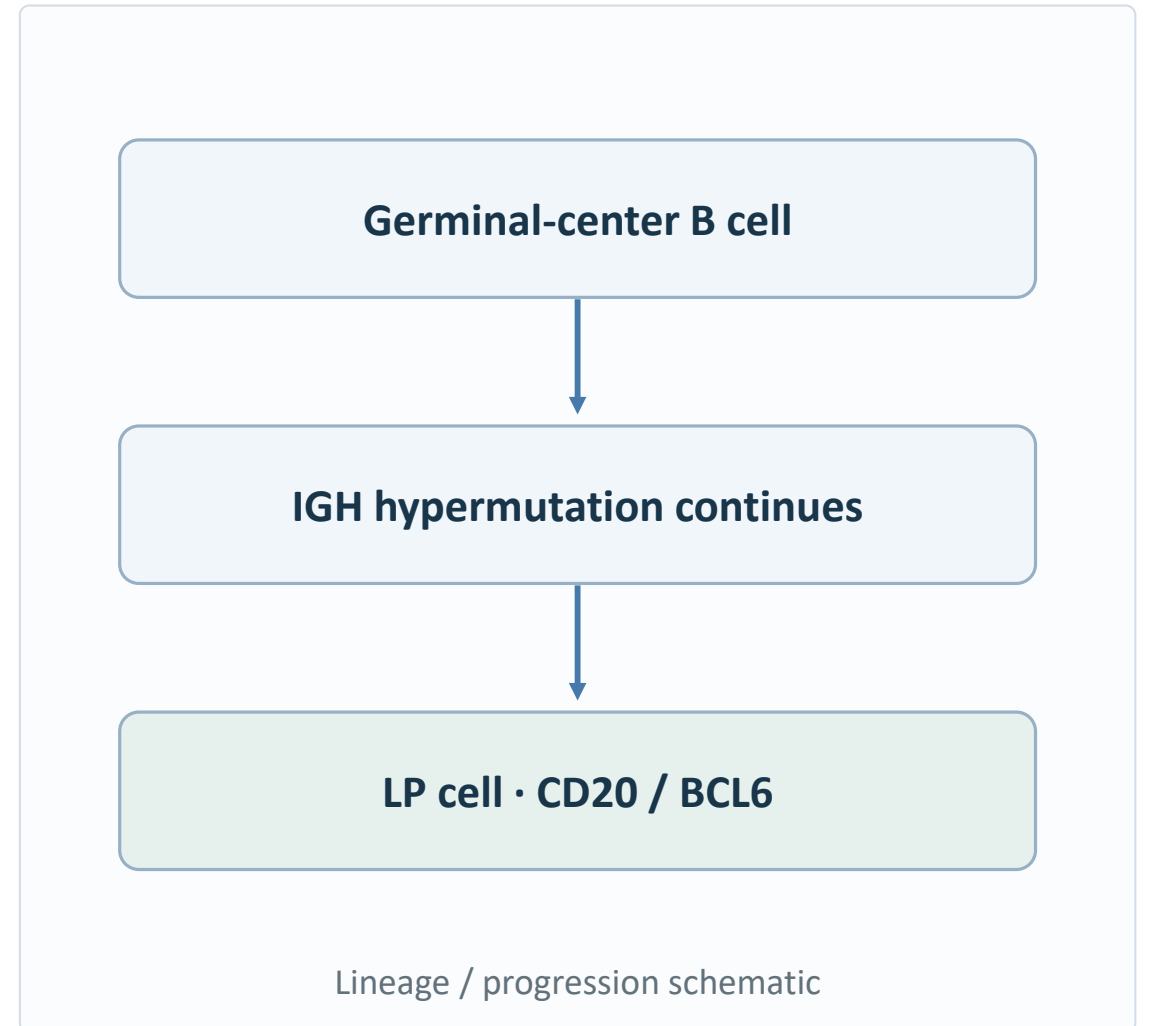
Fibrous partition



B-cell-rich nodules

LP-cell lineage is supported by IGH mutation

- Clonal IGH genes demonstrate ongoing somatic hypermutation.
- This is compatible with a transformed germinal-center B cell.
- EBV is rarely associated with the lymphocyte-predominant entity.

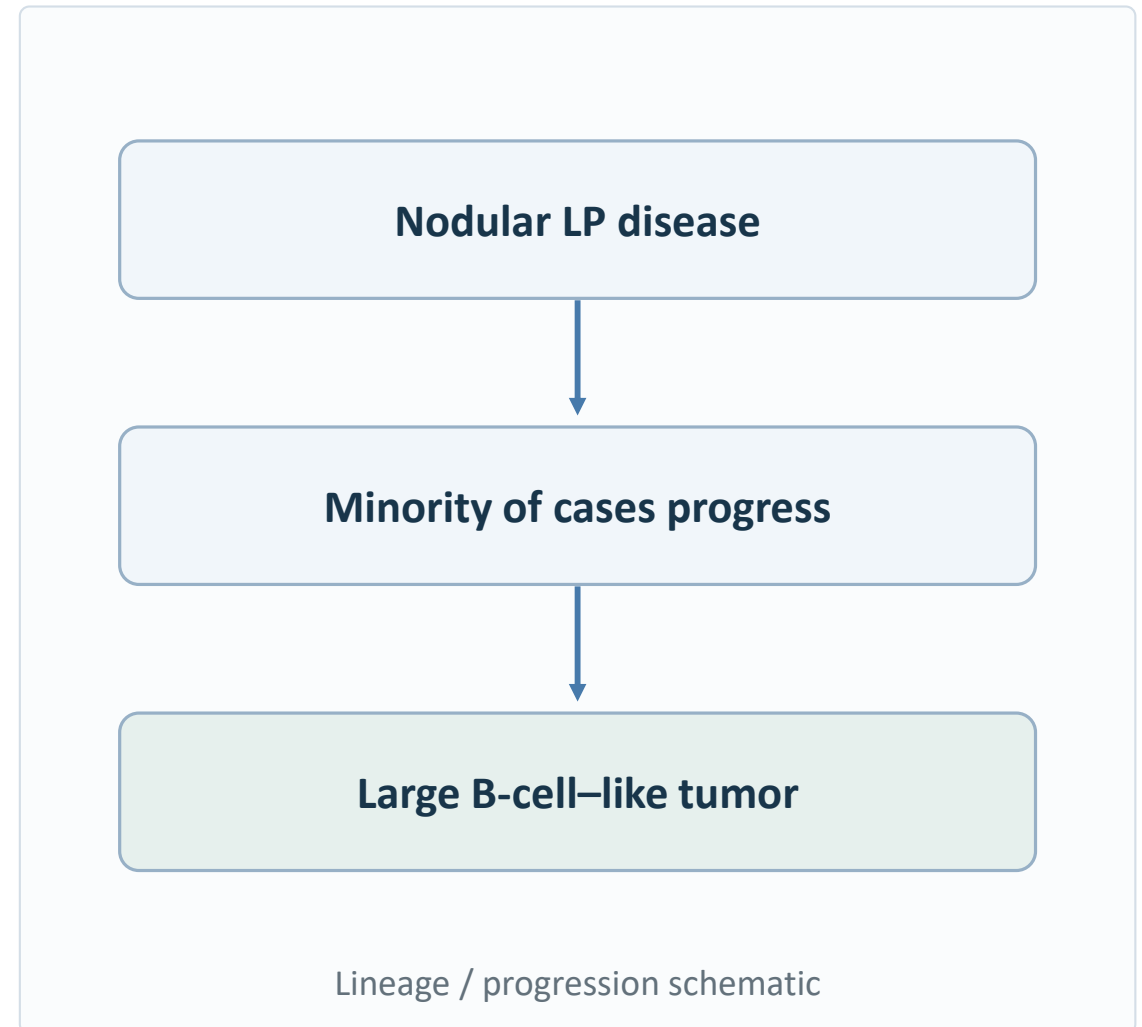


Nodular lymphocyte predominance: Clinical course

- Typically affects younger men with cervical or axillary lymphadenopathy.
- Mediastinal and bone-marrow involvement is uncommon.
- Prognosis is excellent, although recurrence may be comparatively frequent in some series.

Transformation is a separate event

- Transformation in approximately 3%–5% of cases.
- The resulting tumor may resemble diffuse large B-cell lymphoma.
- Transformation should not be assumed merely from the current ICC terminology.



Classic Hodgkin lymphoma versus NLPHL

- Classic forms: RS cells, CD15/CD30 positivity, attenuated B-cell antigen pattern.
- NLPHL: LP cells, CD20/BCL6 positivity, usually CD15/CD30 negative.
- EBV is variable among cHL subtypes but rare in NLPHL.

Classic HL

CD15+ / CD30+

Nodular LP

CD20+ / BCL6+

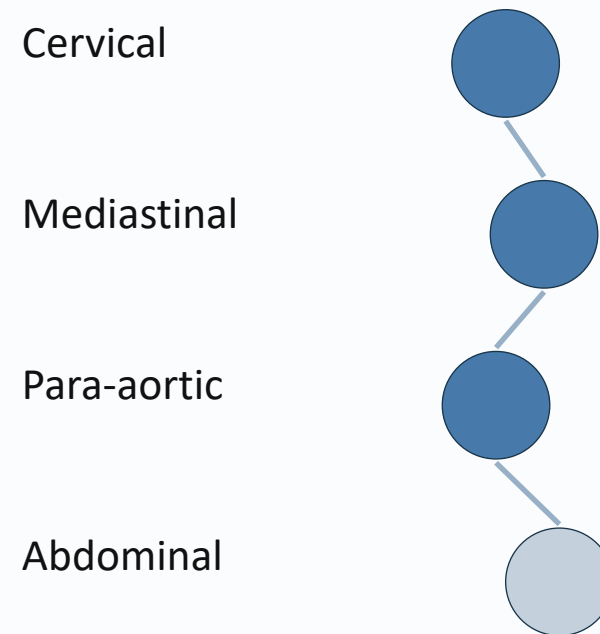
Subtype comparison: Morphology and clinical context

Entity	Key morphology	Typical context
Nodular sclerosis	Lacunar cells; Collagen bands	Young adults; Mediastinum
Mixed cellularity	Diffuse mixed background; Plentiful RS	More advanced disease
Lymphocyte-rich cHL	Reactive lymphocytes dominate	Often older adults
Lymphocyte-depleted	RS-rich; Few lymphocytes	Often advanced; HIV association
Nodular LP disease	Popcorn/LP cells; B-cell nodules	Younger men; Cervical/axillary

Painless lymphadenopathy is the usual first clue

- Affected nodes may be the only presenting abnormality.
- Localized nodular sclerosis and NLPHL are often stage I/II at recognition.
- Constitutional symptoms are more frequent with disseminated or aggressive patterns.

Axial lymph-node chain



Simplified regional map; Not anatomical imaging

B symptoms have formal staging significance

- Unexplained fever and drenching night sweats qualify as systemic symptoms.
- Unexplained weight loss exceeding 10% of normal body weight is another criterion.
- Ann Arbor staging uses A (absent) and B (present) symptom modifiers.

Fever

Unexplained

Night sweats

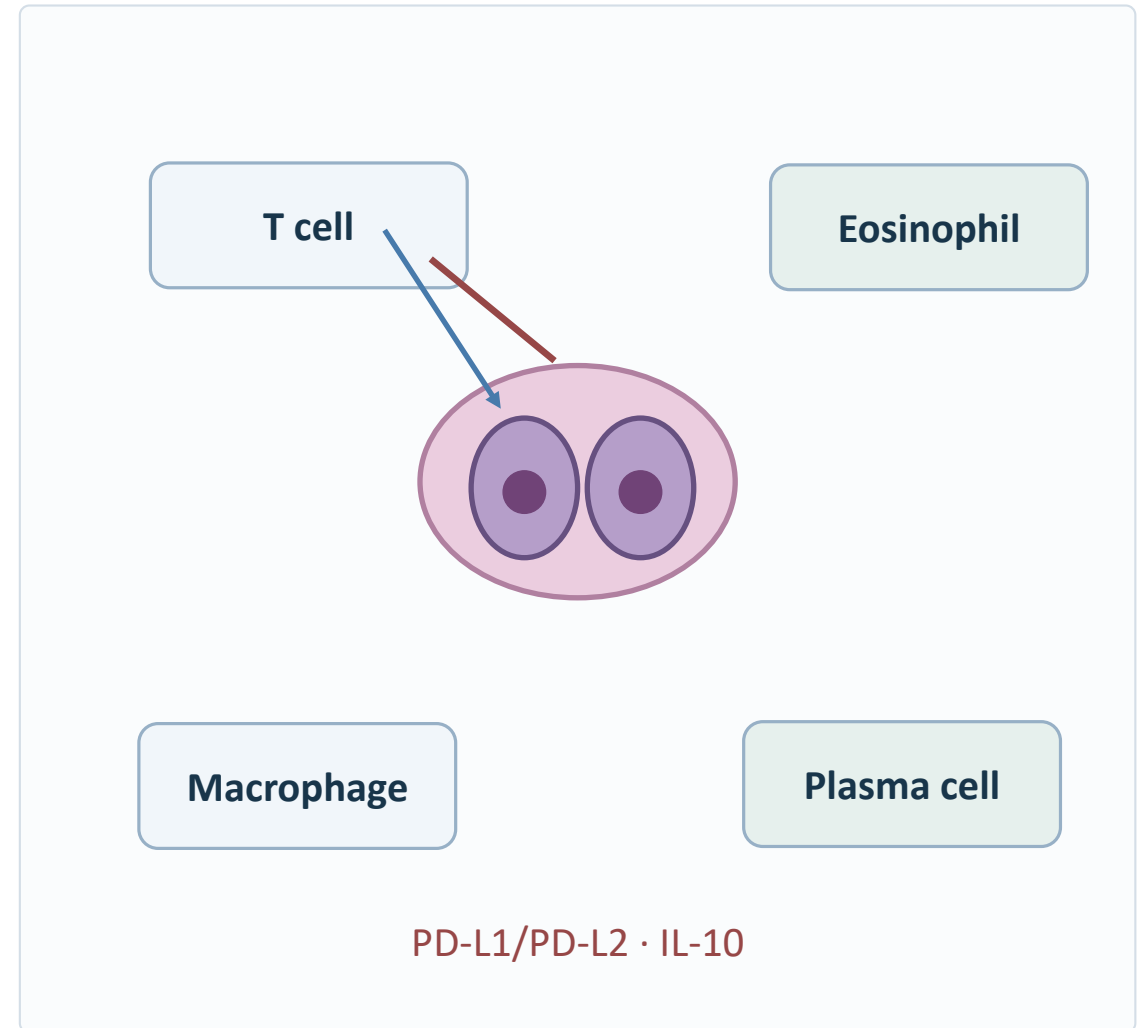
Drenching

Weight loss

>10% of normal weight

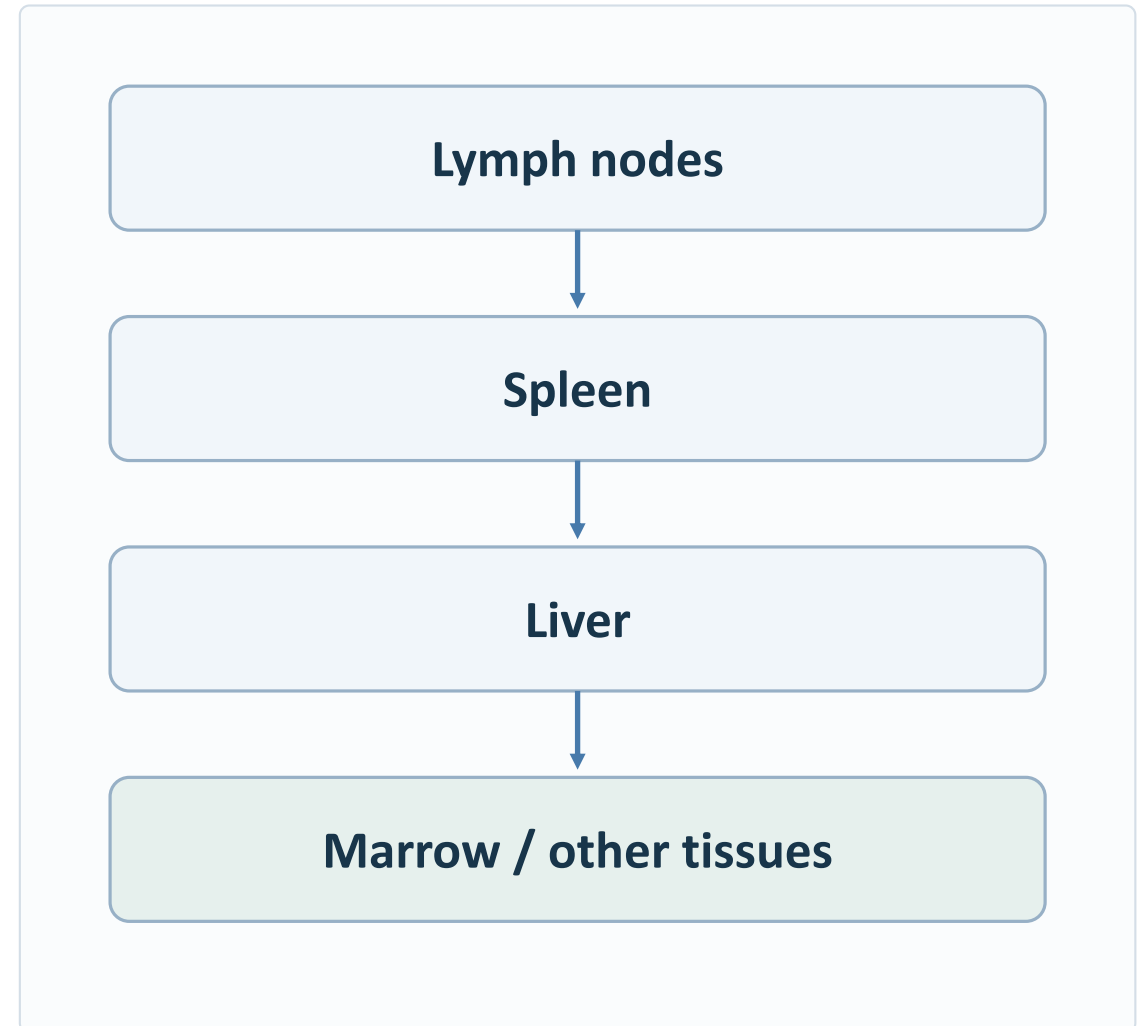
Classic Hodgkin lymphoma can impair cell immunity

- Cutaneous anergy is described in many cases of classic Hodgkin lymphoma.
- Factors including IL-10 suppress Th1-mediated immune responses.
- The phenomenon illustrates immune dysfunction despite abundant lymphoid tissue.



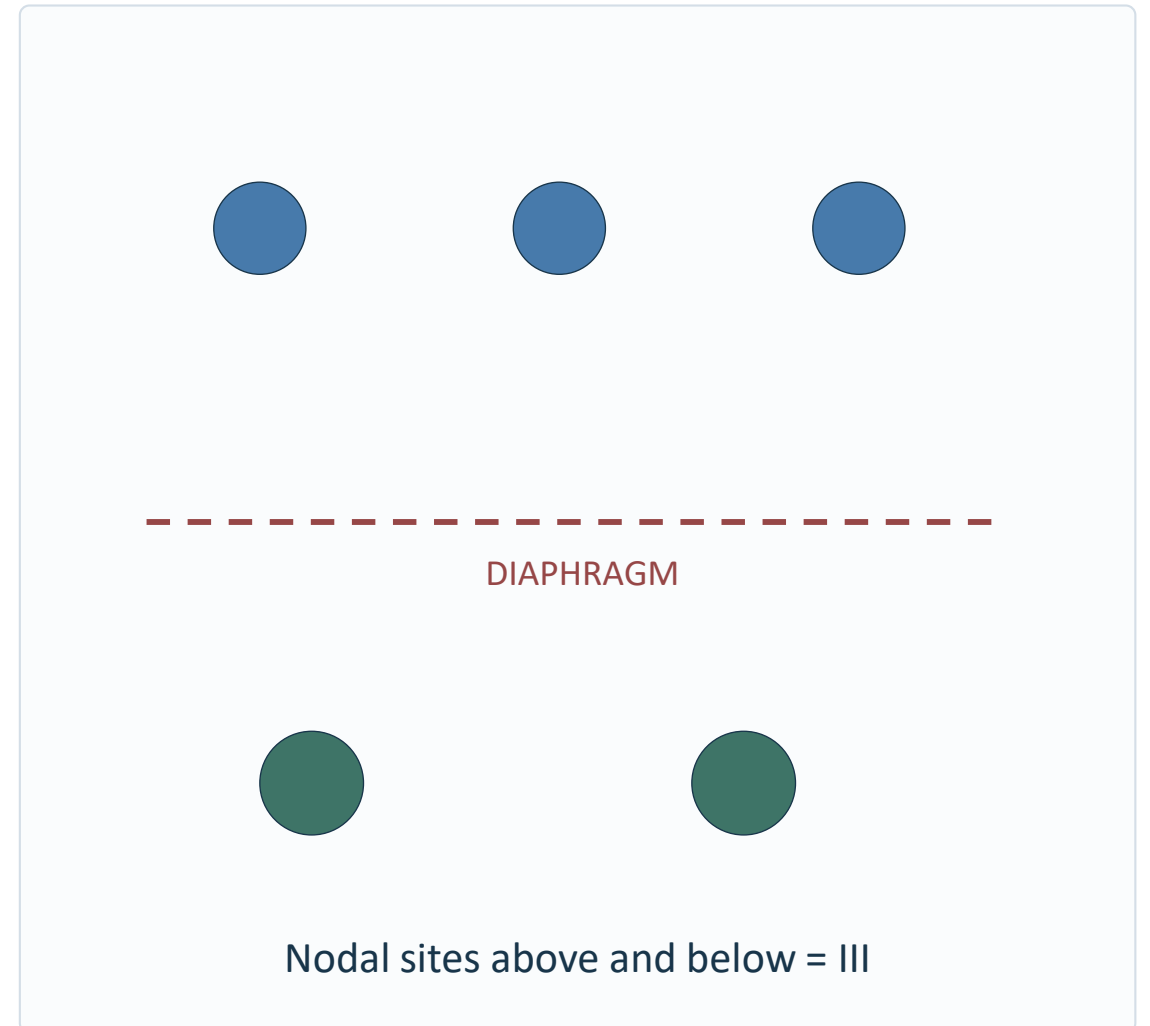
Anatomic spread often follows a recognizable order

- Lymph nodes are commonly involved first.
- Dissemination may then affect spleen, liver and eventually marrow or other organs.
- This orderly pattern is characteristic but cannot substitute for staging evaluation.



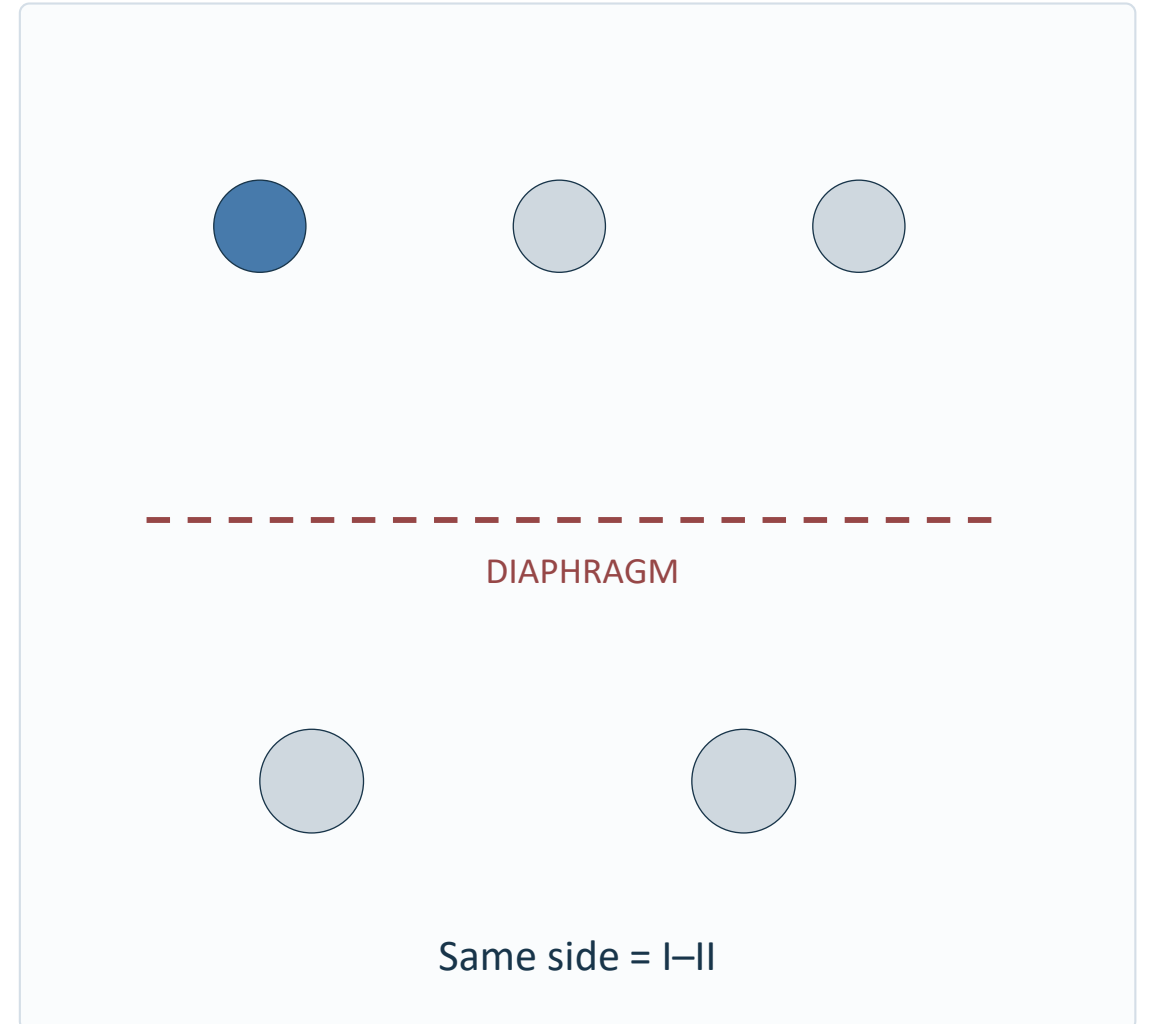
Ann Arbor staging is based on distribution

- Stage I: One lymph-node region or one isolated extralymphatic site.
- Stage II: Multiple nodal regions on one side of the diaphragm.
- Stage III: Nodal disease on both sides of the diaphragm.
- Stage IV: Diffuse extranodal organ involvement.



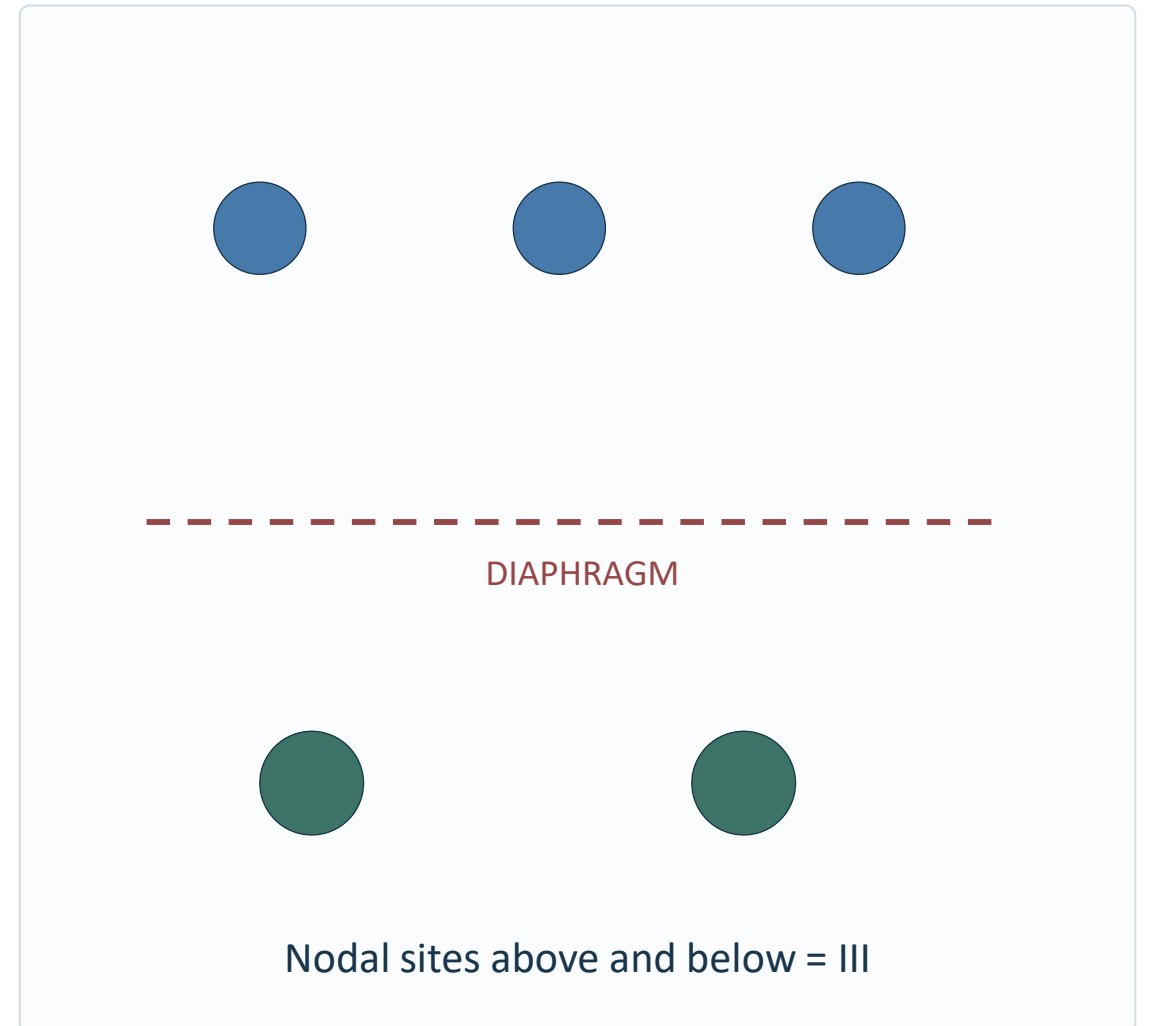
Stage I and II: Disease remains geographically limited

- Stage I refers to a single involved nodal region or isolated extralymphatic site.
- Stage II includes two or more involved nodal regions on the same side of the diaphragm.
- A localized extranodal extension may be noted with an E modifier.



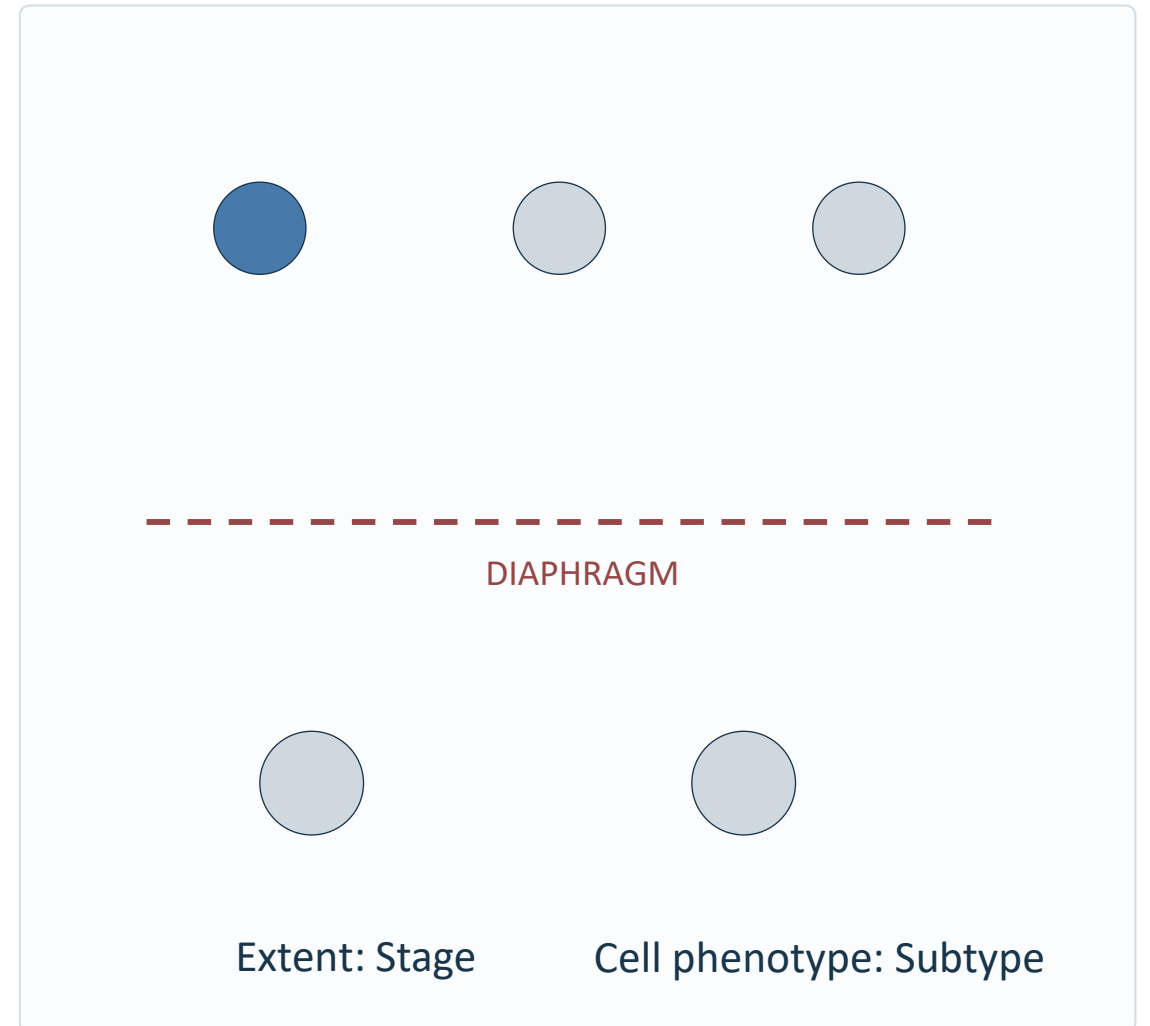
Stage III and IV: Advanced anatomic extent

- Stage III requires nodal involvement above and below the diaphragm.
- Stage IV represents diffuse extranodal organ involvement, with or without nodal disease.
- Constitutional symptom designation is assigned independently.



Histologic subtype and stage answer different questions

- Subtype describes morphology and the tumor–host cellular pattern.
- Stage measures the anatomic extent of the lymphoma.
- Tumor stage as the more important prognostic variable under contemporary treatment.

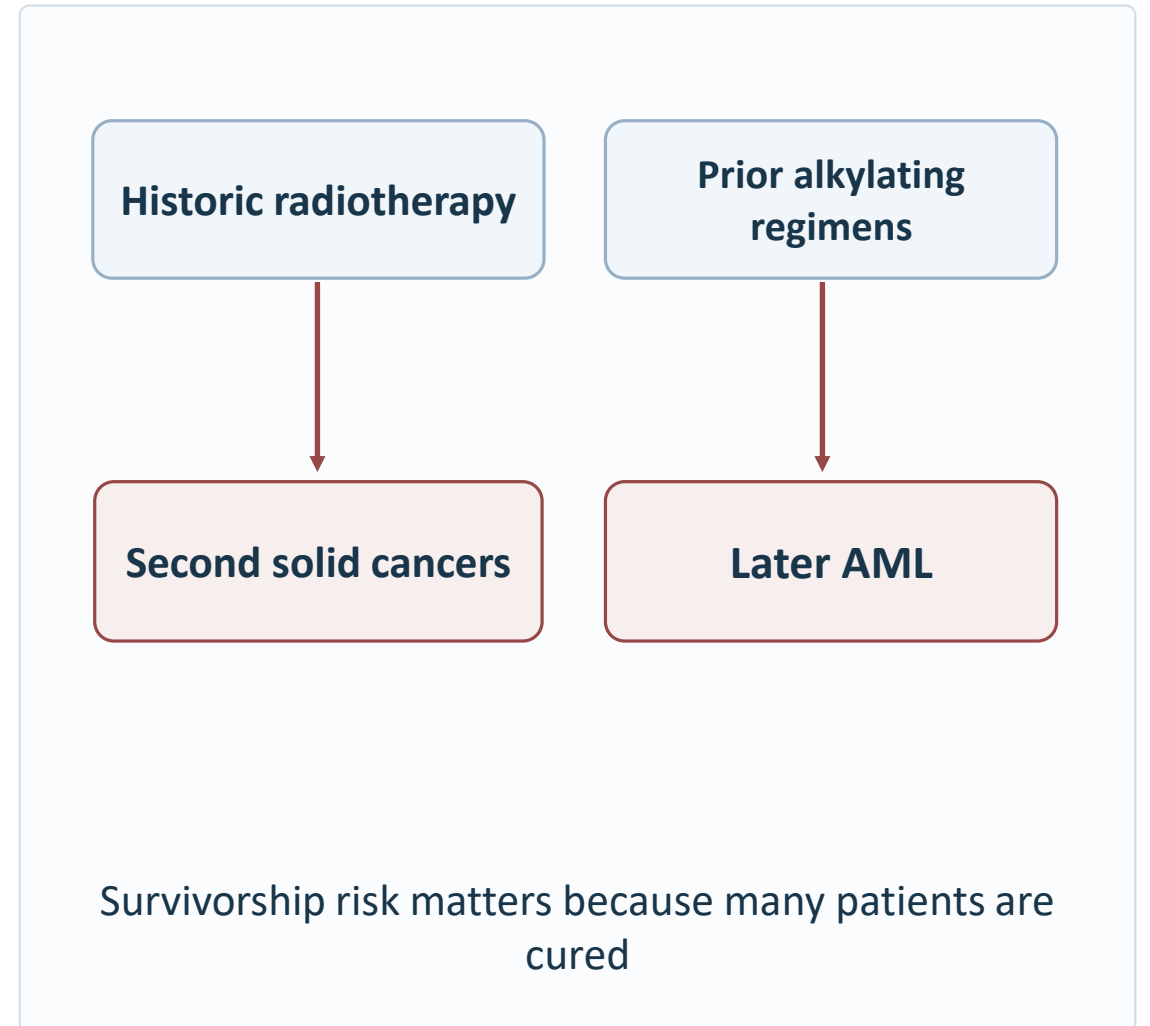


Prognostic estimates must be source-contextualized

- Cure approaching 90% for stages I and IIA.
- For stages IVA/IVB, it cites 5-year disease-free survival of 60%–70%.
- These are textbook summary estimates; Individual prognosis depends on patient and treatment context.

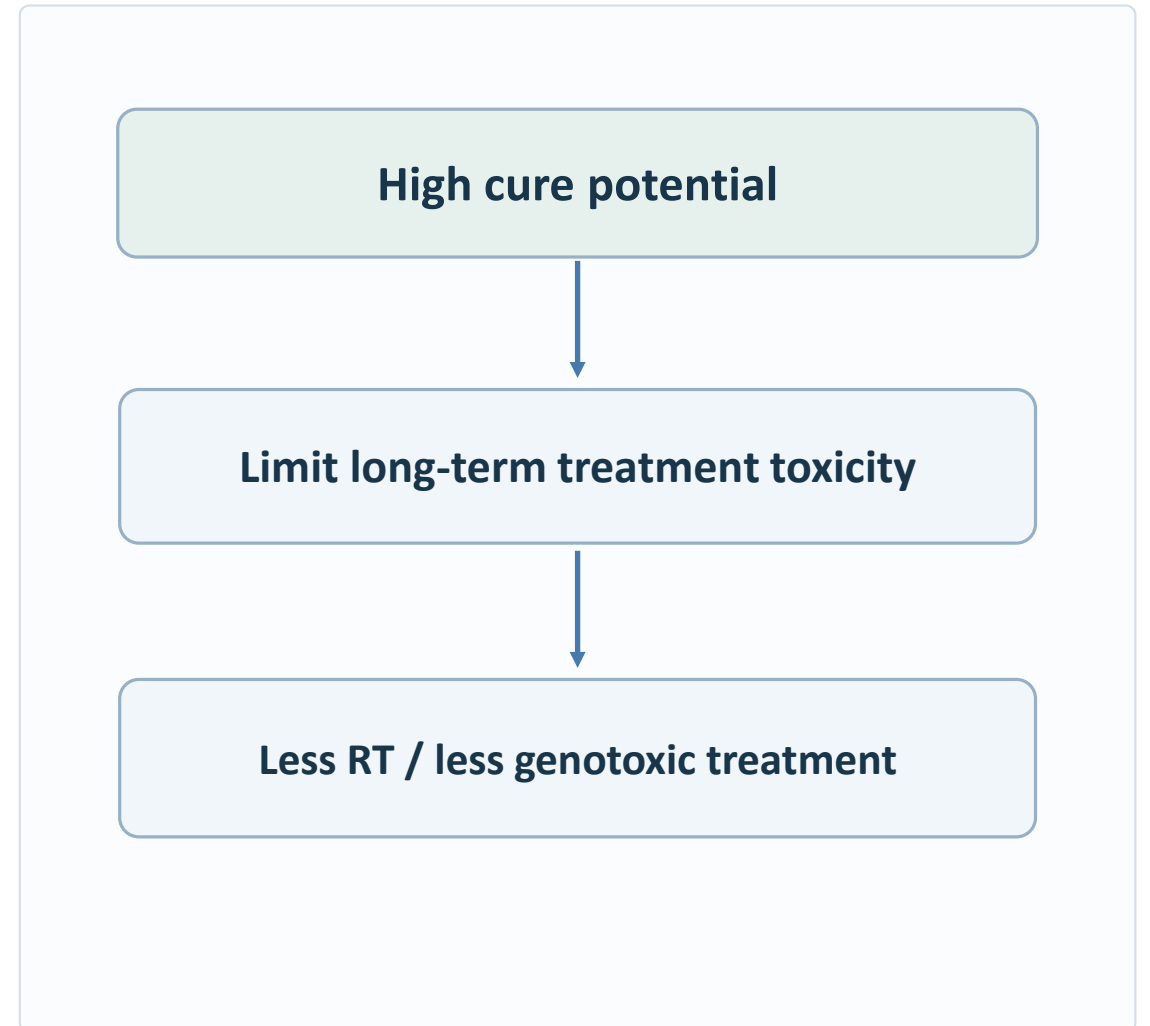
Treatment success creates late-effect responsibilities

- Hodgkin lymphoma was an early example of cure with radiotherapy or chemotherapy.
- Historical radiotherapy was associated with subsequent lung, breast and other cancers.
- Older alkylator-based chemotherapy regimens increased later AML risk.



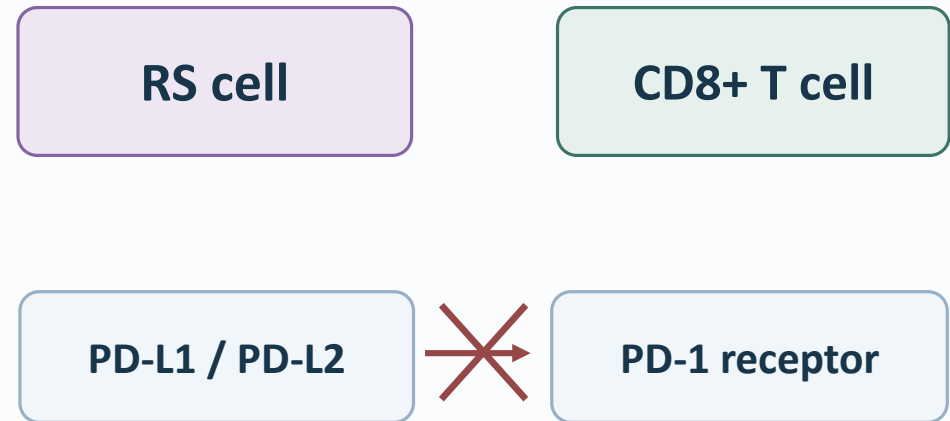
Current treatment aims to limit treatment injury

- A shift toward less extensive radiotherapy.
- Less genotoxic regimens aim to preserve disease control while reducing secondary neoplasms.
- Detailed regimen selection is outside the pathology scope of this lecture.



PD-1 blockade exploits a central tumor vulnerability

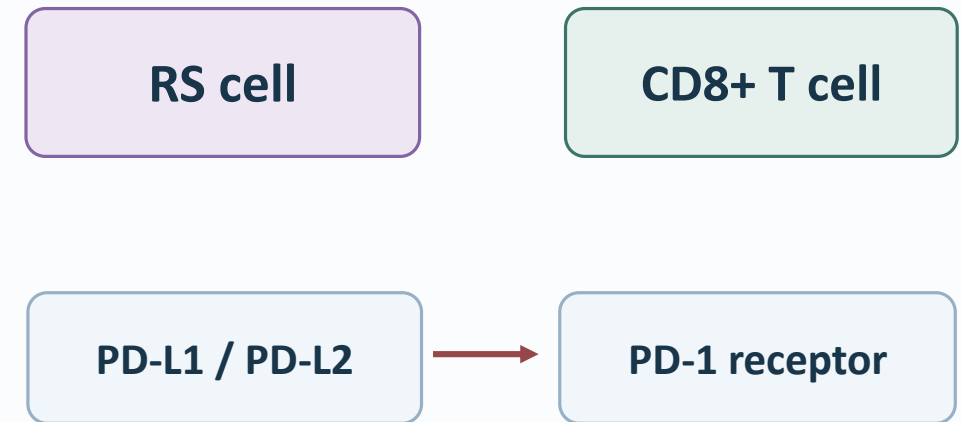
- Classic RS cells often express PD-L1 and PD-L2.
- Blocking PD-1 can reverse inhibitory signaling to cytotoxic T cells.
- High activity of checkpoint inhibitors in disease refractory to conventional therapy.



Anti-PD-1 antibody interrupts this inhibitory interaction

Checkpoint biology connects pathogenesis and therapy

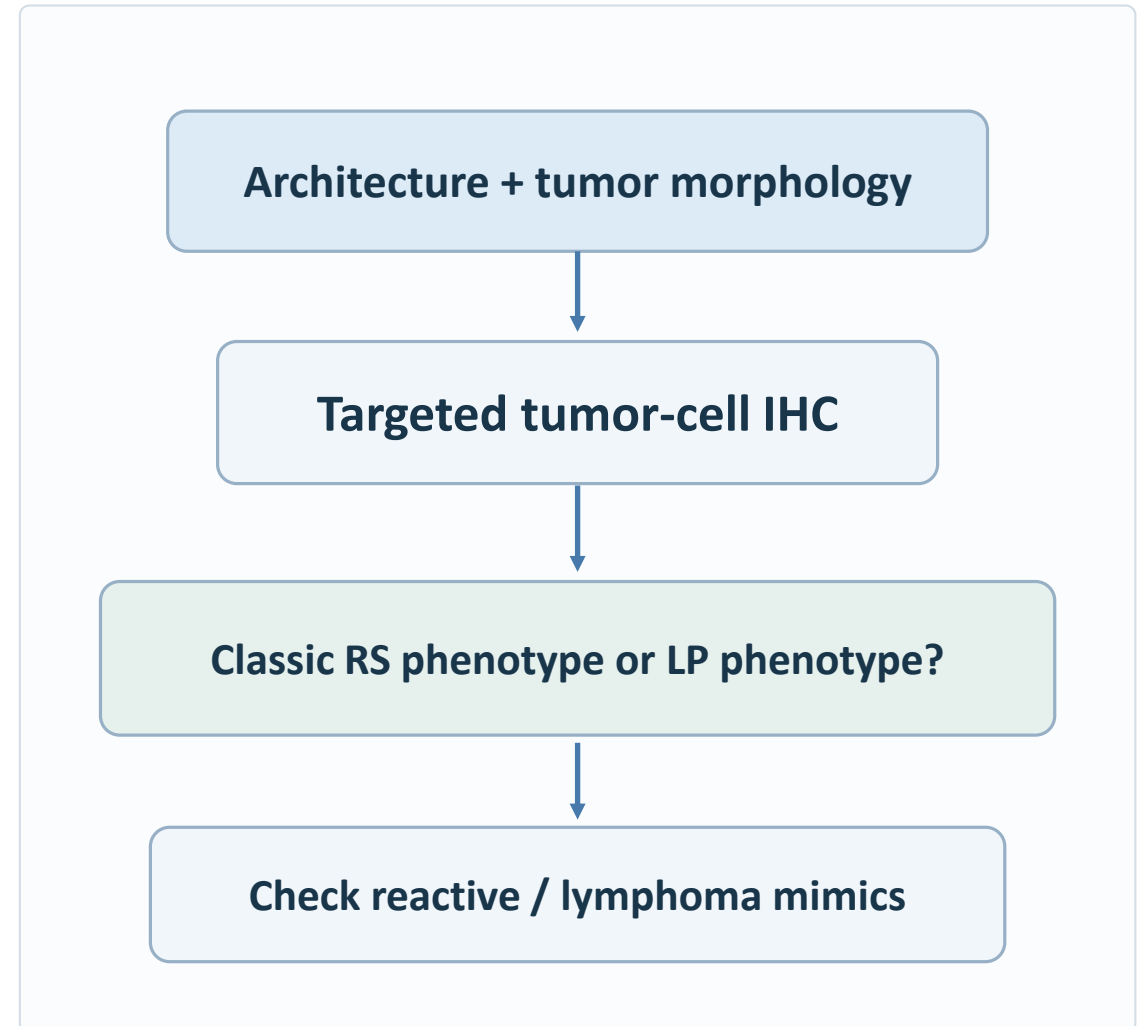
- 9p gains and related mechanisms enhance immune checkpoint ligand expression.
- The ligands permit survival in a host tissue rich in T cells.
- Checkpoint inhibitors target the immune escape mechanism rather than a morphologic subtype.



Checkpoint ligation suppresses antitumor cytotoxicity

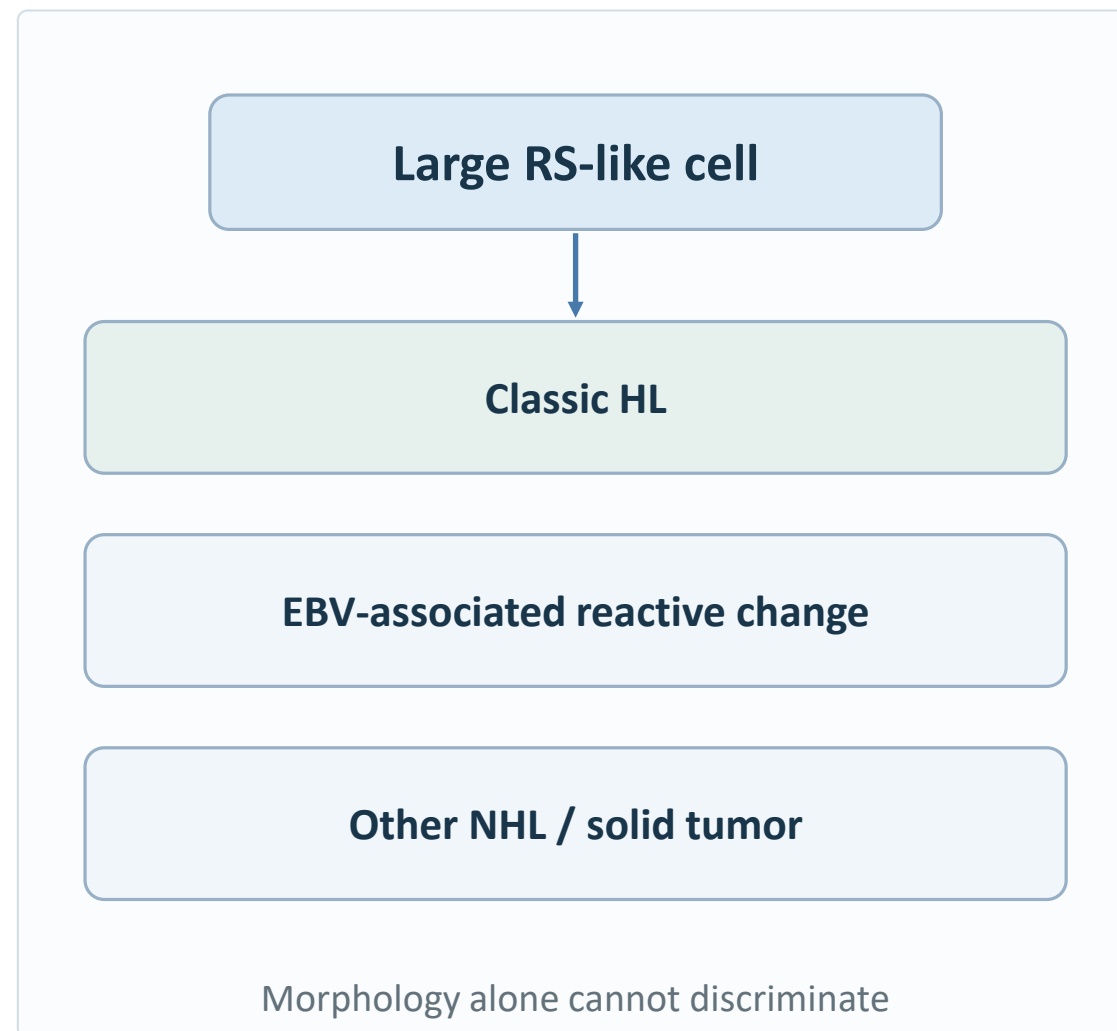
Diagnostic integration: What a biopsy must establish

- Is the architecture compatible with classic Hodgkin lymphoma or NLPHL?
- Are diagnostic tumor cells demonstrable in an appropriate host-cell background?
- Does the tumor-cell IHC profile fit the suspected entity?
- Have reactive EBV-associated and non-Hodgkin mimics been excluded?



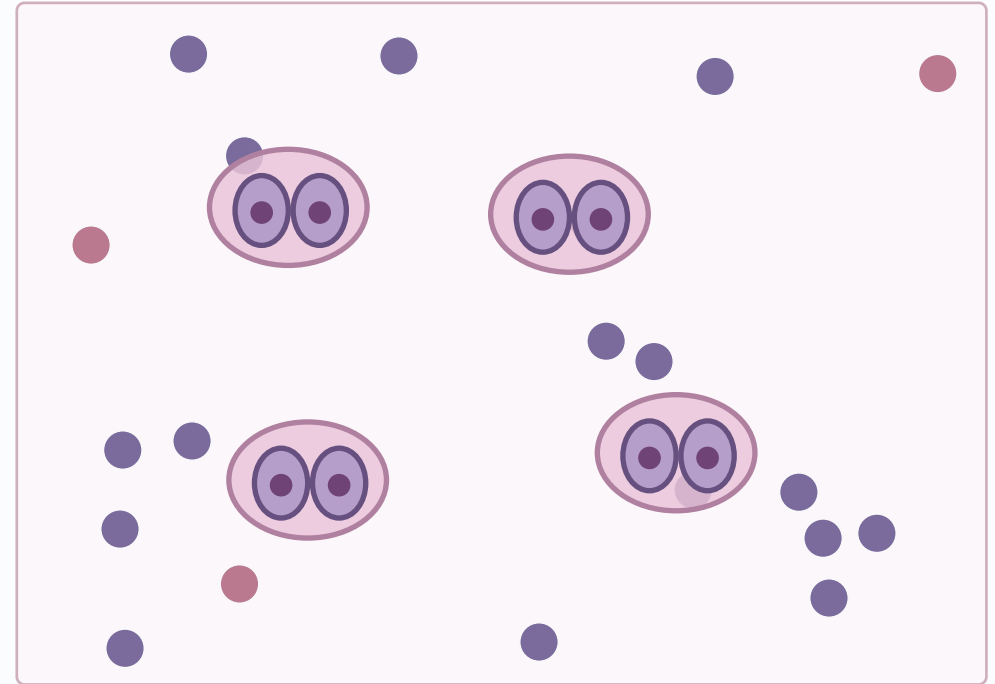
Pitfall: A striking RS-like cell is not enough

- Infectious mononucleosis can yield RS-like activated immunoblasts.
- Some other lymphomas or solid tumors can contain morphologic mimics.
- Clinical setting, architecture and multi-marker IHC prevent false classification.



Pitfall: Lymphocyte depletion can mimic NHL

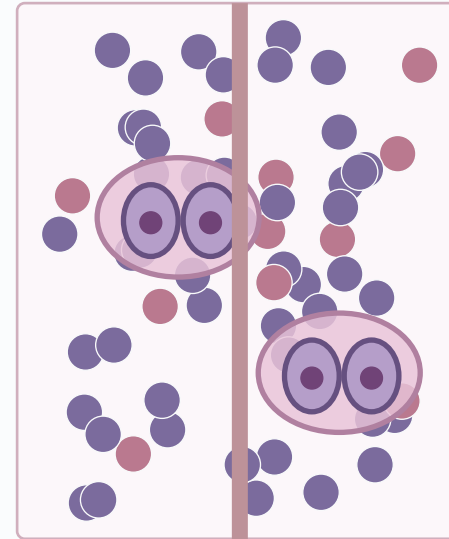
- Numerous atypical cells and scant lymphocytes reduce the usual classic background clue.
- Robbins cautions that most suspected lymphocyte-depleted examples prove to be NHL.
- Immunophenotyping is therefore not optional in this differential.



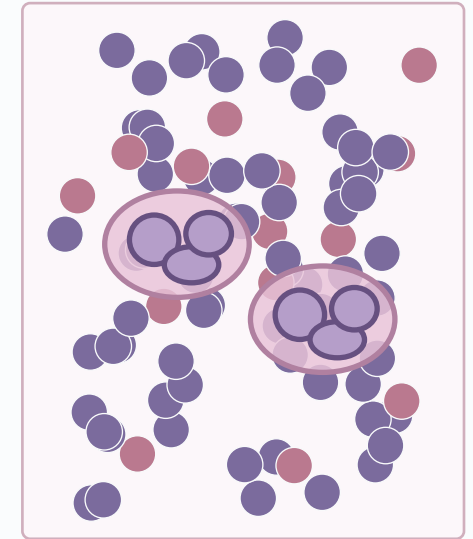
Schematic architecture — not histology

Pitfall: Collagen nodules versus B-cell nodules

- Nodular sclerosis cHL has broad fibrous septa and lacunar variants.
- NLPHL has B-cell-rich follicles with LP cells and follicular dendritic cells.
- The word “nodular” does not imply shared histogenesis or IHC profile.



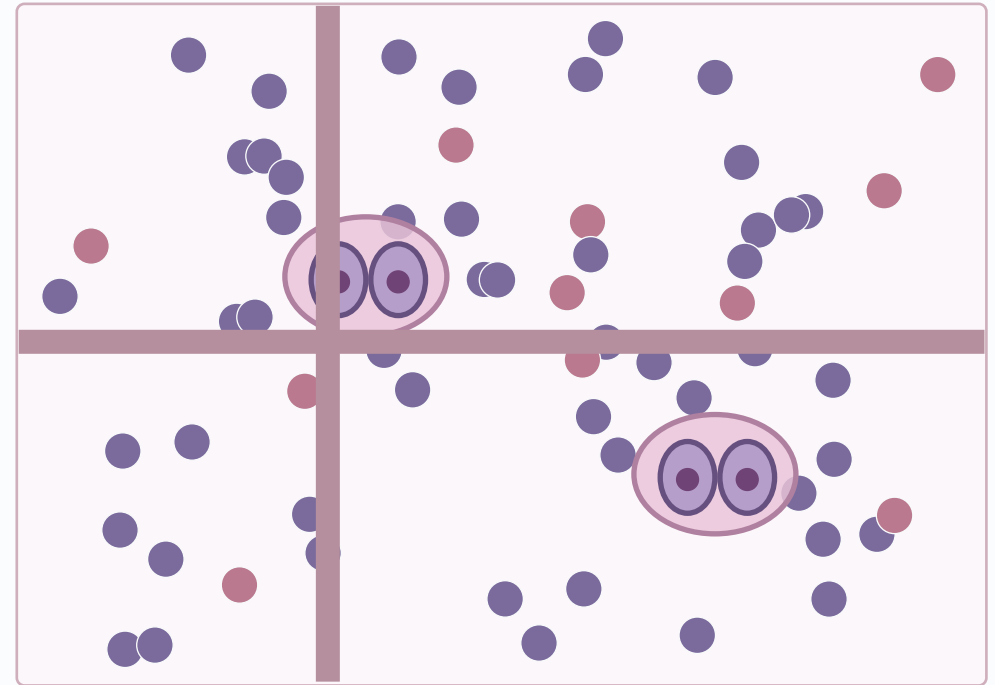
Fibrous partition



B-cell-rich nodules

Case exercise: A young adult with mediastinal nodes

- A patient has cervical and mediastinal lymphadenopathy without reported B symptoms.
- Biopsy shows collagen partitions and lacunar-appearing large atypical cells.
- Which subtype is favored, and what tumor-cell markers support it?



Schematic architecture — not histology

Case resolution: Nodular sclerosis cHL

- Broad collagen bands and lacunar variants favor nodular sclerosis.
- Classic RS-cell profile: CD30+, CD15+, PAX5+, CD45–.
- Mediastinal involvement in a young adult is a characteristic clinical association.

CD30

Positive

CD15

Positive

PAX5

Positive

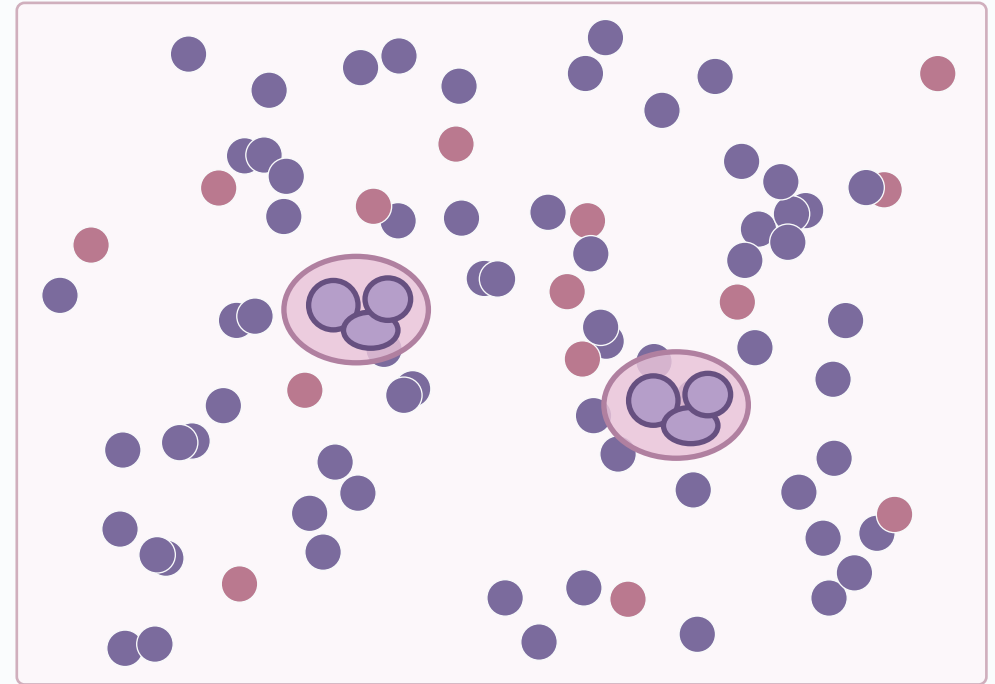
CD45

Negative

Profile is interpreted in appropriate morphology

Case exercise: A lymphocyte-rich nodular lesion

- A younger man presents with cervical lymphadenopathy.
- Nodules contain many B cells and scattered large cells with lobulated “popcorn” nuclei.
- Which tumor-cell phenotype separates this lesion from lymphocyte-rich cHL?



Schematic architecture — not histology

Case resolution: Nodular lymphocyte predominance

- LP cells express CD20 and BCL6, consistent with germinal-center B-cell differentiation.
- CD15 and CD30 are usually negative.
- The B-cell follicular microenvironment reinforces the subtype diagnosis.

CD20

Positive

BCL6

Positive

CD15

Negative

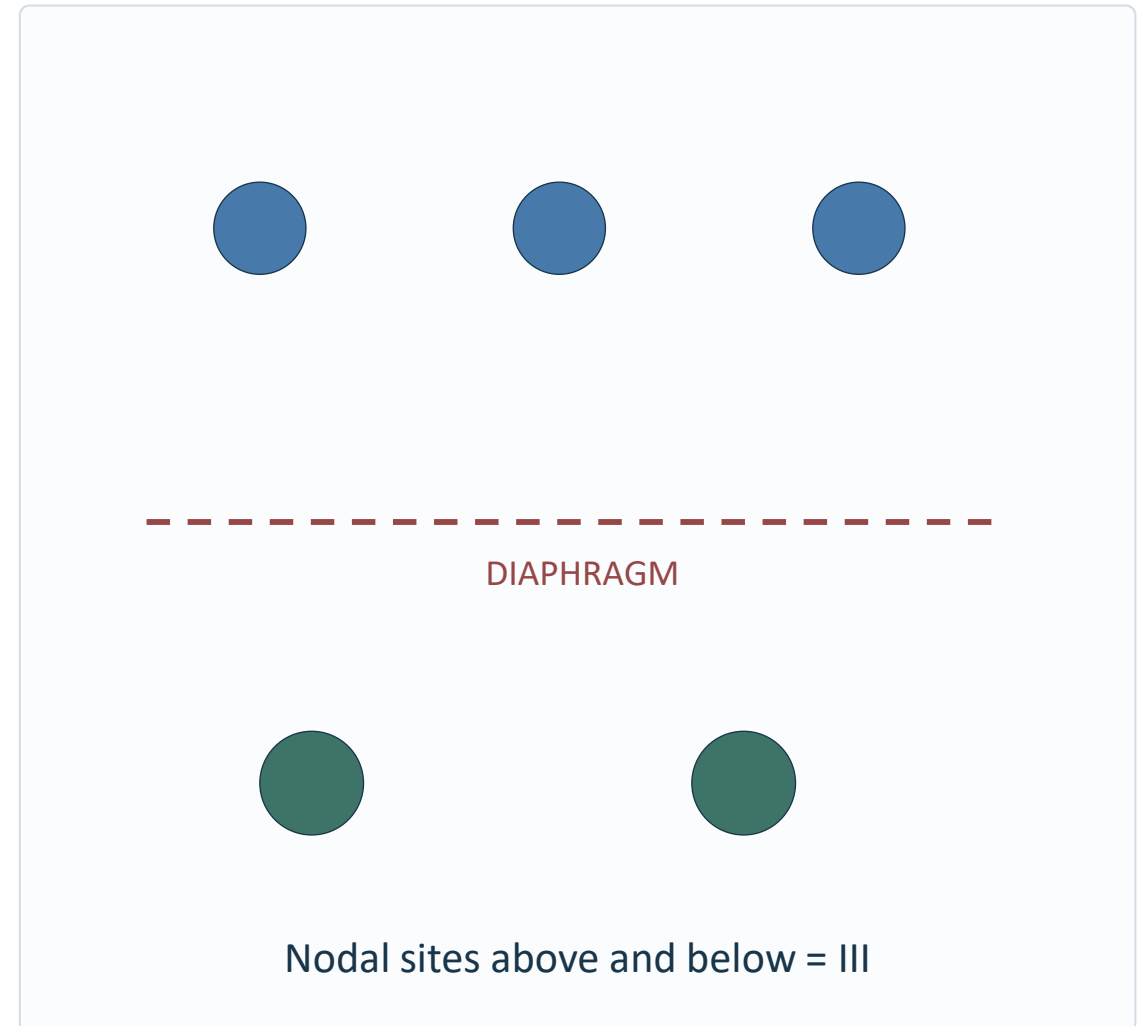
CD30

Negative

Profile is interpreted in appropriate morphology

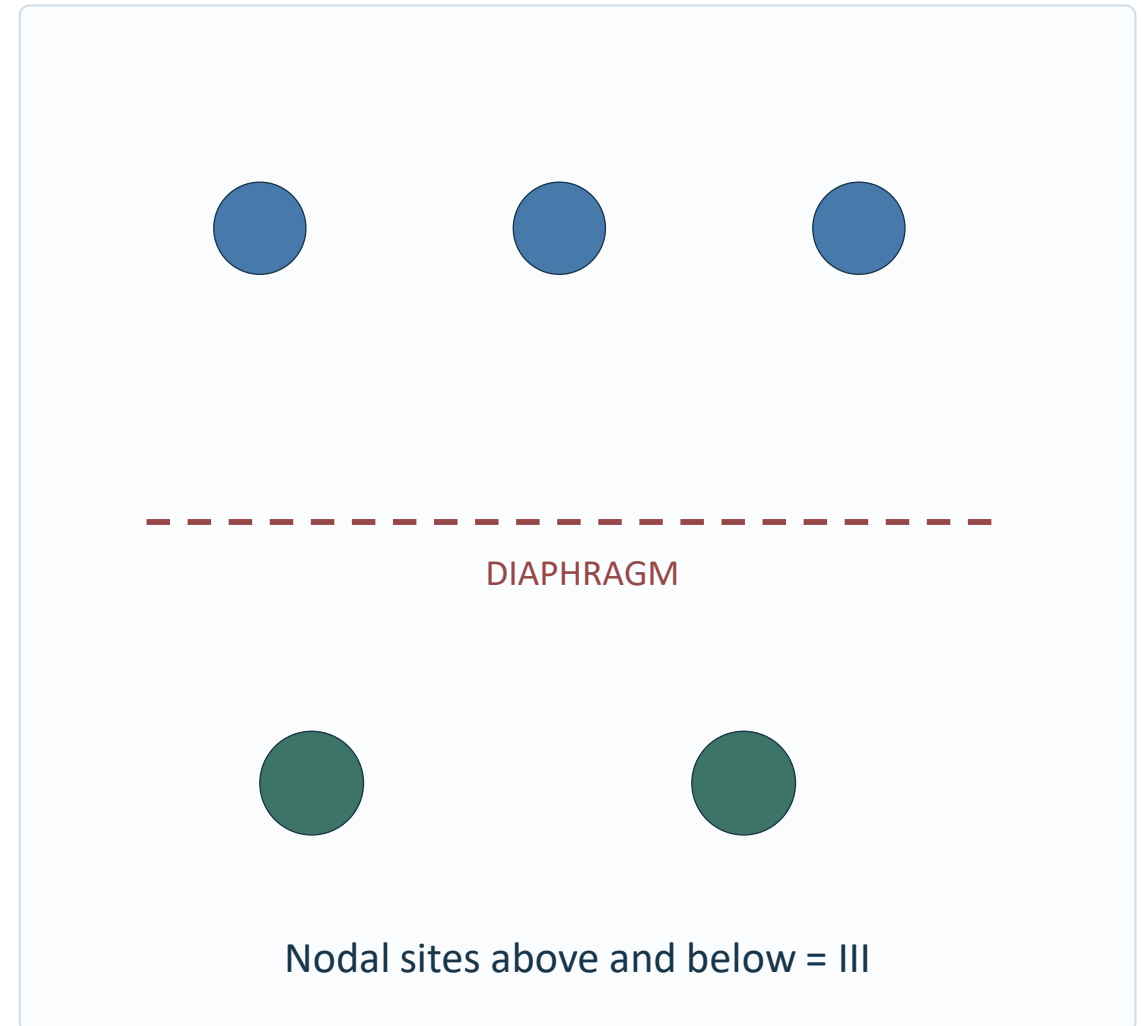
Case exercise: Disseminated disease and B symptoms

- A patient has lymph nodes on both sides of the diaphragm.
- There is drenching night sweat and unexplained weight loss greater than 10%.
- What is the minimum Ann Arbor stage and symptom modifier?



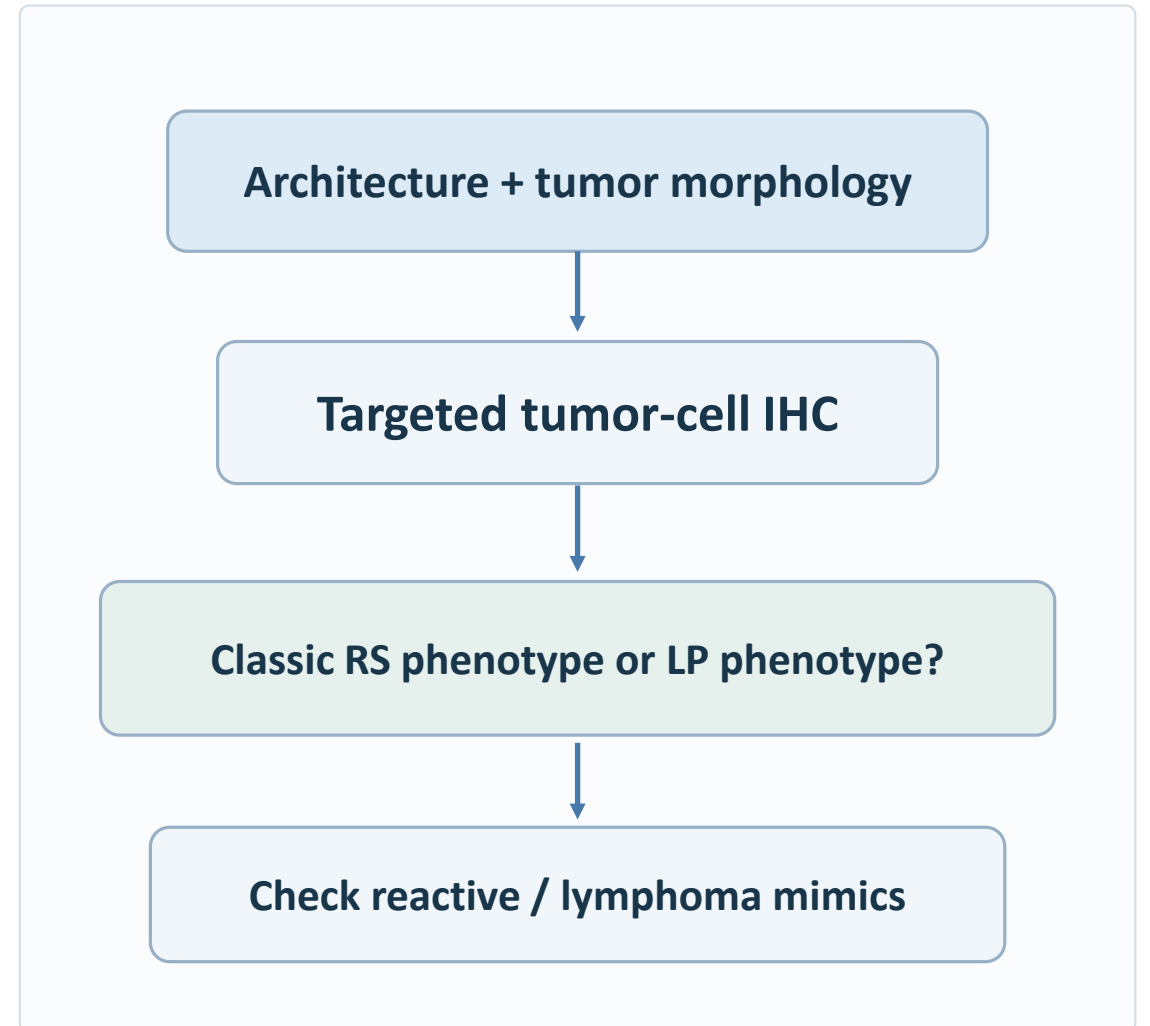
Case resolution: Ann Arbor stage IIIB

- Nodal involvement on both sides of the diaphragm meets stage III distribution.
- Qualifying constitutional symptoms confer the B modifier.
- Stage IV would require diffuse extranodal disease rather than nodal extent alone.



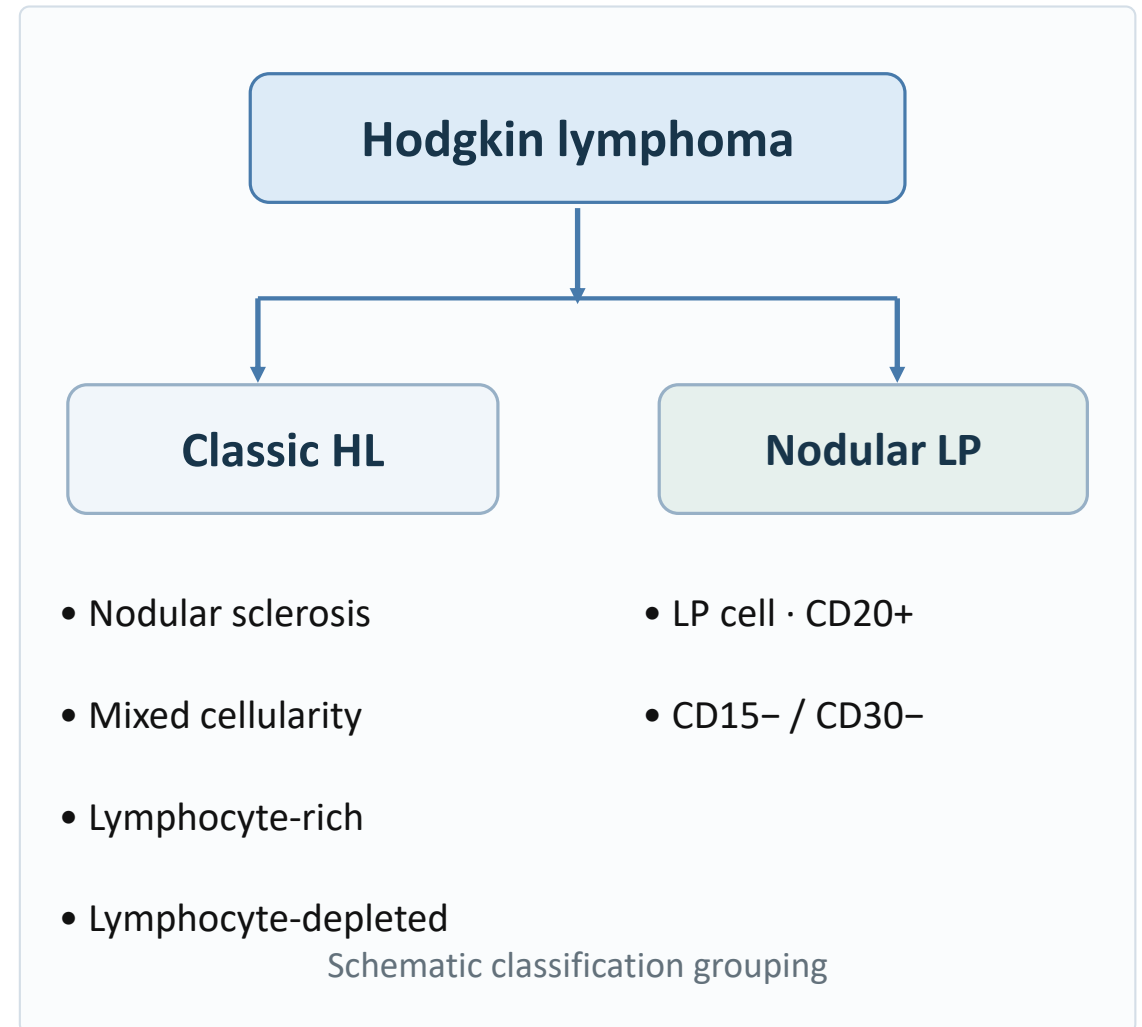
A practical morphology-to-IHC recognition pathway

- Large RS-like cells with heterogeneous inflammatory background → assess classic phenotype.
- LP cells in expanded B-cell follicles → assess germinal-center B-cell markers.
- Always reconcile any discordant stain with the tissue architecture and mimics.



Synthesis: Five distinctions to retain

- Rare RS cells can orchestrate an extensive reactive infiltrate.
- NF- κ B activation and immune-checkpoint signaling are central to cHL biology.
- Classic subtypes are architectural patterns with similar tumor-cell immunophenotypes.
- LP cells maintain CD20/BCL6 expression and differ from classic RS cells.
- Stage and B symptoms add clinically important information beyond histology.



Primary reading and diagram provenance

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Classification, pathogenesis, morphology, clinical features; Tables 13.7–13.9.
- All cellular, pathway and lymph-node drawings in this lecture are original editable schematics—not diagnostic photomicrographs.