

Primary CNS lymphoma

Pathogenesis • morphology • diagnostic reasoning

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Learning outcomes

- Define primary CNS lymphoma and distinguish secondary CNS lymphoma.
- Explain the host-related EBV and PD-L1 immune-evasion contexts.
- Recognize the characteristic distribution, histology and CD20 phenotype.
- Integrate morphology, lineage and anatomic context in diagnosis.

The entity is an extranodal lymphoid neoplasm

- Primary CNS lymphoma is a lymphoma arising within the CNS compartment.
- The designation “primary” distinguishes it from spread of a lymphoma originating outside the CNS.
- The predominant histologic type is diffuse large B-cell lymphoma (DLBCL).
- Brain parenchyma is a major site; Ocular involvement may accompany CNS disease.

Why this tumor is not a glioma

Primary CNS lymphoma

- Malignancy of lymphoid (usually B-cell) lineage
- Infiltrates brain parenchyma
- Typically expresses B-cell antigens

Diffuse glioma

- Glial lineage rather than lymphoid lineage
- May infiltrate brain parenchyma
- Classification depends on glial and molecular features

The word “primary” is an anatomic statement

Primary CNS lymphoma

- Initial tumor arises in CNS compartment
- Extracranial involvement is rare and generally late
- Can affect brain and eye

Secondary CNS lymphoma

- Systemic lymphoma precedes or accompanies CNS involvement
- Usually involves meninges or CSF rather than brain parenchyma
- May yield lymphoma cells on CSF cytology

Relative frequency: Uncommon, clinically consequential

2%

Of extranodal lymphomas

1%

Of intracranial tumors

These are Robbins 11e textbook frequencies; Denominators are different.

Two host contexts frame the disease

Immunosuppressed host

- AIDS and post-transplant immunosuppression are classic settings
- Primary CNS lymphoma is a prominent CNS neoplasm in this population
- Tumor B cells are usually EBV infected

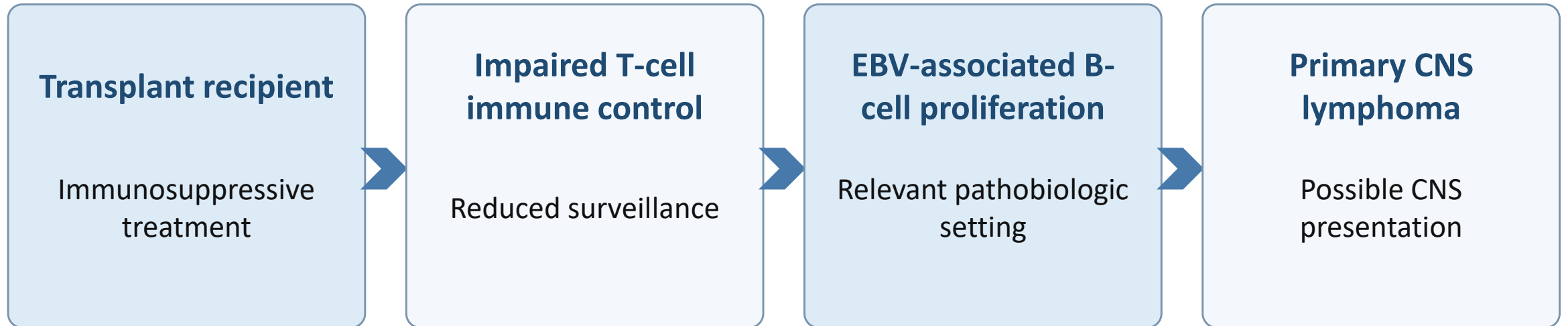
Host without known immunosuppression

- Occurs over a wide adult age range
- Frequency increases after age 60
- PDL1 amplification/overexpression is described in many tumors

AIDS is an established high-risk setting

- Primary CNS lymphoma as the most common CNS neoplasm in immunosuppressed individuals.
- Advanced HIV-associated immunodeficiency is a major example.
- Many AIDS-associated lesions as EBV-positive B-cell tumors.
- Effective antiretroviral therapy has reduced secondary neurologic effects of HIV.

Post-transplant immunosuppression



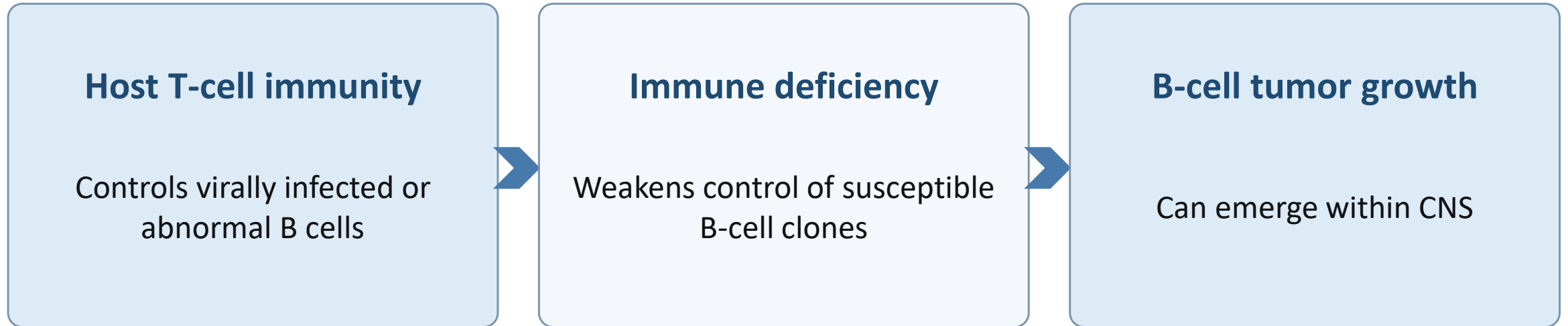
Older age matters without immunosuppression

- The age range in non-immunosuppressed patients is relatively broad.
- Disease frequency rises after 60 years of age.
- Age is epidemiologic context—not a stand-alone diagnostic criterion.
- The characteristic pathology remains that of an aggressive B-cell lymphoma.

Host context changes mechanistic expectations

Characteristic	Immunosuppressed	Not immunosuppressed
Risk setting	AIDS or transplant therapy	Frequency increases after age 60
Commonly emphasized mechanism	Latent EBV infection in B cells	PDL1 amplification/overexpression in many tumors
Morphologic clue	Necrosis often prominent	No specific necrosis rule stated

T-cell surveillance is central to the story

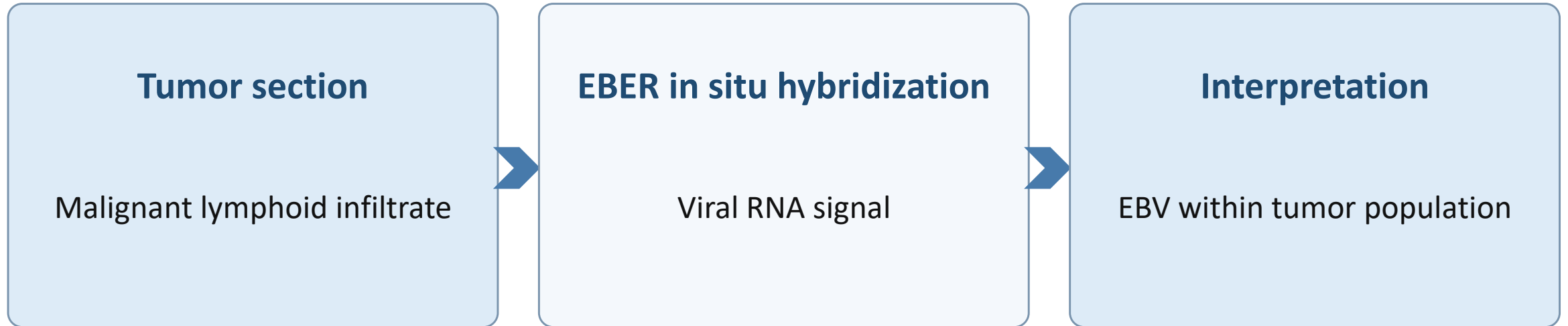


Conceptual synthesis immunodeficiency-associated DLBCL.

EBV latency in malignant B cells

- In immunosuppression-associated primary CNS lymphoma, malignant B cells are usually latently infected by Epstein–Barr virus.
- The virus is a biologic association of the malignant B-cell population, not a histologic stain itself.
- The textbook supports EBER in situ hybridization as the tissue assay for detecting EBV.
- The strength of the EBV association depends on host context.

EBV detection is a tissue-level observation



What a positive EBER signal supports

- EBERs are small RNAs encoded by the Epstein–Barr virus genome.
- EBER in situ hybridization identifies viral RNA within cells.
- Detection in the malignant population supports an EBV-associated lymphoma context.
- EBER detection must be interpreted together with cell morphology and lineage.

Do not equate all CNS lymphomas with EBV

- EBV especially strongly to immunosuppressed hosts.
- A CNS lymphoma in an immunocompetent patient need not follow that EBV-associated pattern.
- The immunocompetent setting has a separate PD-L1 immune-evasion association.
- A universal “EBER-positive” expectation would misrepresent the textbook.

DLBCL provides the cellular identity

- Most primary CNS lymphomas are diffuse large B-cell lymphomas.
- DLBCL is a mature B-cell malignancy.
- “Diffuse” describes a non-follicular tissue growth pattern; “large B-cell” describes cell size and lineage.
- Primary CNS presentation does not make the cells a glial neoplasm.

DLBCL cytology: Large atypical lymphoid cells

- Typical cells are several times larger than resting small lymphocytes.
- Nuclei can be round or oval, sometimes irregular.
- Open/vesicular chromatin and prominent nucleoli are common.
- Cytologic variation within DLBCL is substantial.

DLBCL cytology: Nucleoli and cytoplasm

Nuclear details

- Vesicular chromatin
- One prominent central or several peripheral nucleoli
- Occasionally irregular or lobated forms

Cytoplasm and growth

- Moderately abundant cytoplasm; Pale or basophilic
- Diffuse sheets of malignant cells
- Microscopic phenotype requires B-cell marker confirmation

The B-cell phenotype has diagnostic value

- The primary CNS lymphoma excerpt explicitly identifies CD20 expression.
- The general DLBCL section also describes CD19/CD20 positivity.
- CD10 and BCL6 can vary among systemic DLBCLs.
- CD20 provides lineage support, but must be interpreted in a tissue context.

CD20 is a lineage marker, not an anatomic marker

What CD20 addresses

- Is the malignant population B-cell lineage?
- Does lymphoma belong in the diagnostic frame?
- Does the immunophenotype support a B-cell neoplasm?

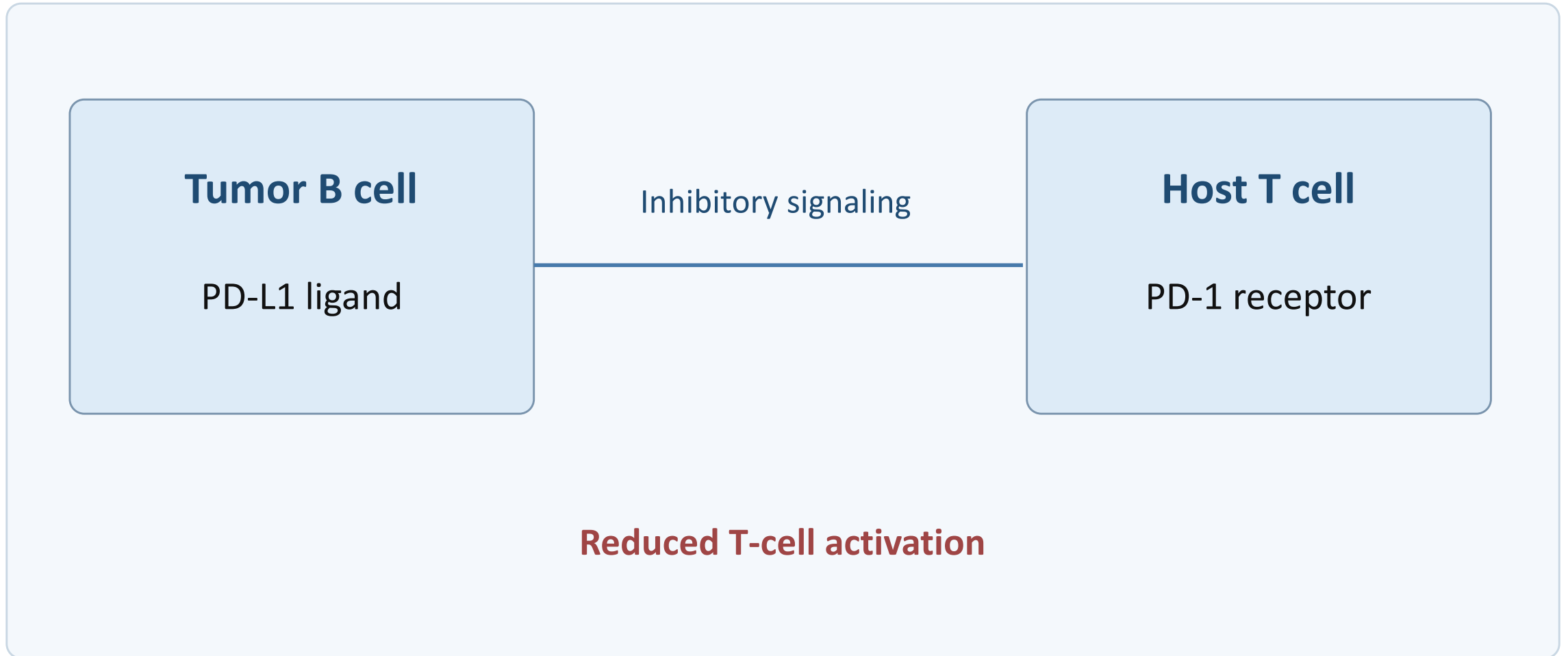
What CD20 cannot answer alone

- Whether CNS involvement is primary or secondary
- Whether tumor B cells harbor EBV
- Whether a lesion is multifocal or periventricular

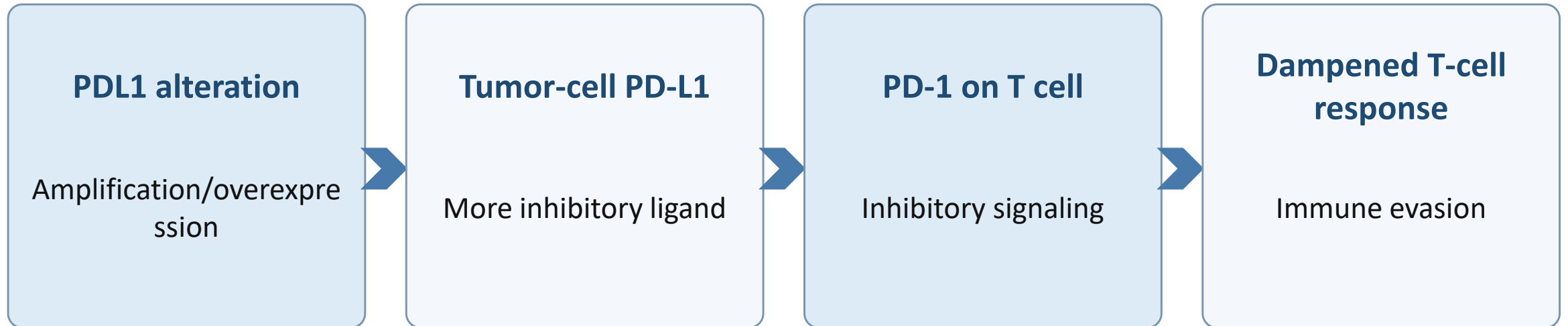
PDL1 amplification is a different route

- Amplification and overexpression of the PDL1 gene in many primary CNS large B-cell lymphomas without immunosuppression.
- The encoded protein PD-L1 acts as an immune checkpoint ligand.
- Increased checkpoint signaling suppresses anti-tumor T-cell responses.
- This mechanism is distinct from EBV latency in immunodeficiency.

PD-1–PD-L1 checkpoint signaling



How PD-L1 overexpression favors escape



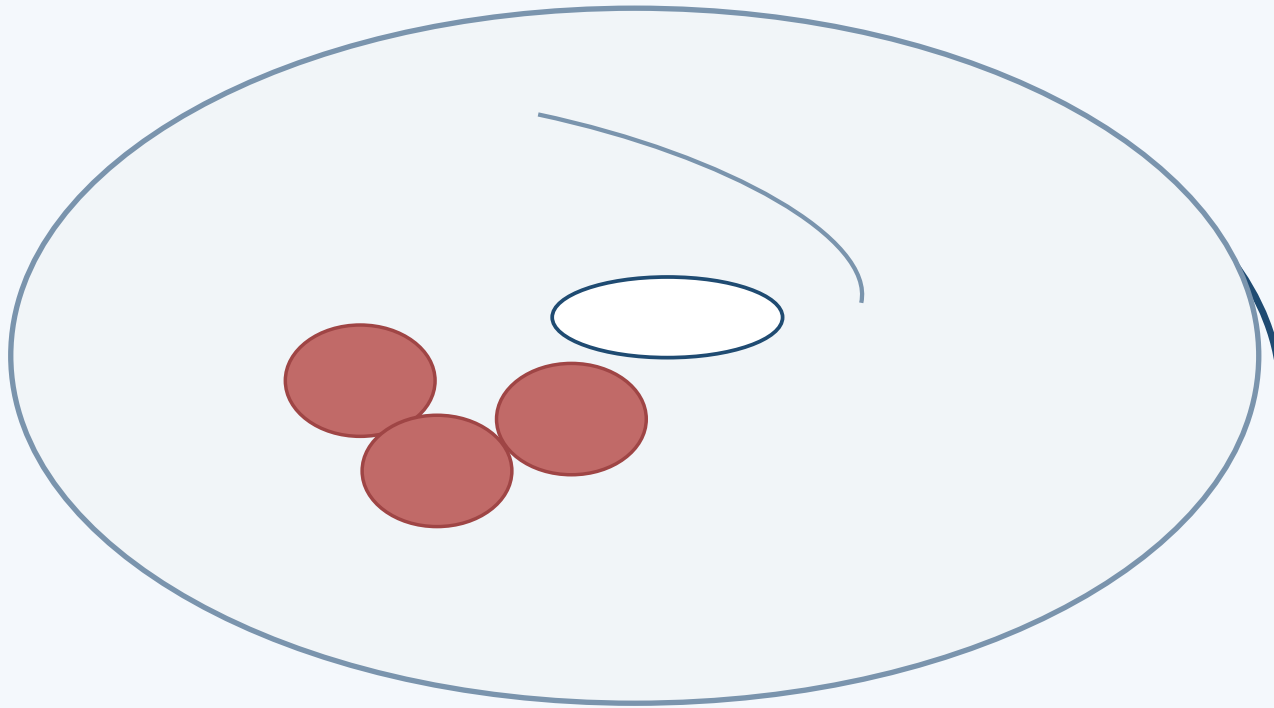
Checkpoint blockade is an investigational context

- Immune-checkpoint inhibition is designed to interrupt PD-1/PD-L1 mediated T-cell suppression.
- The Robbins primary CNS lymphoma section reports ongoing trials of checkpoint inhibitors.
- It does not provide response rates, approved regimens or outcomes for those trials.
- No efficacy estimate is asserted on this slide.

Two biologic settings—do not collapse them

Dimension	EBV-associated context	PD-L1 context
Host emphasis	Immunosuppression	Without immunosuppression
Key finding	Latent EBV infection	PDL1 gene amplification/overexpression
Relevant detection	EBER in situ hybridization	PD-L1 pathway analysis (conceptual)
Textbook distinction	Association is usually present	Described in many tumors

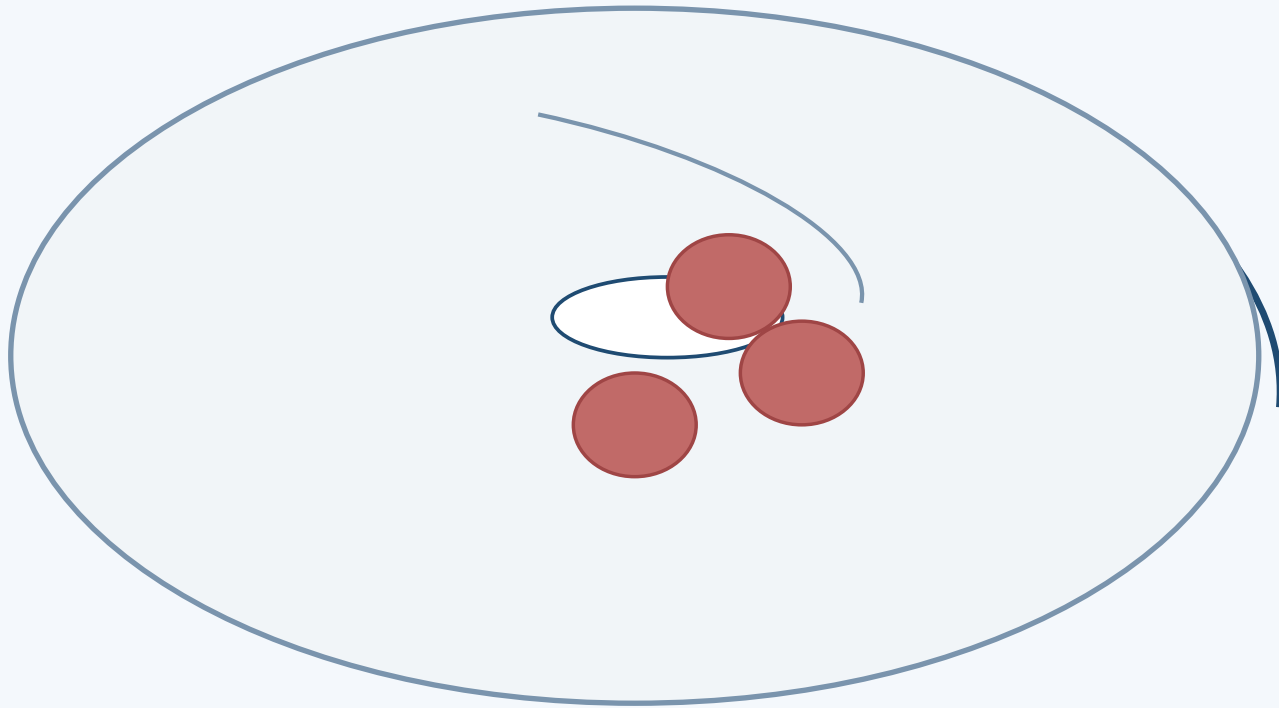
Macroscopic location: Deep subcortical brain



Simplified anatomy

- Masses often occupy deep subcortical tissue.
- A solitary or multifocal pattern is possible.
- Diagram is schematic.

Periventricular spread is common



Simplified anatomy

- Lesions can border ventricular spaces.
- Periventricular extension is common.
- Diagram is schematic.

One mass or multiple masses

Single lesion

- A solitary CNS lymphoma mass is possible
- Can still infiltrate the surrounding parenchyma
- Macroscopy alone does not determine lineage

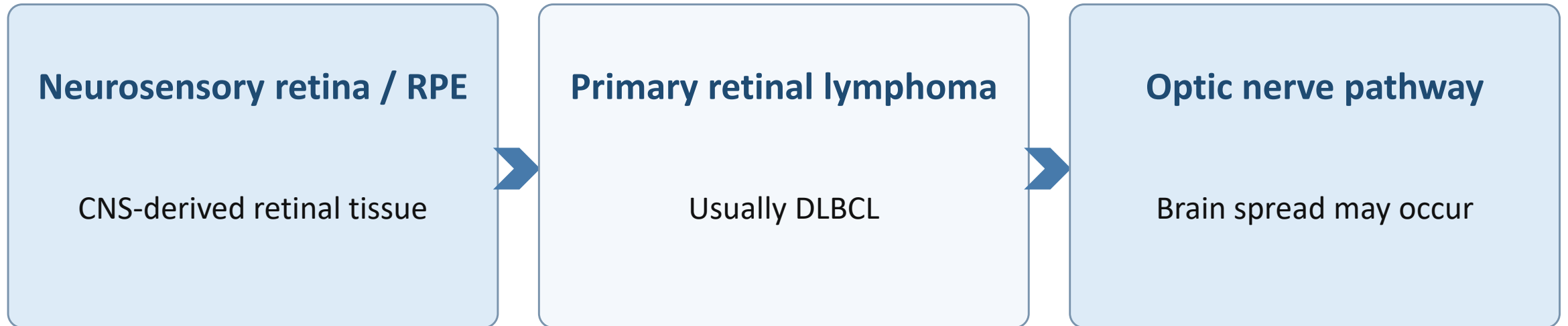
Multiple lesions

- Multiple masses are frequent
- Multifocality is compatible with primary origin
- Distribution does not by itself demonstrate systemic disease

Ocular involvement belongs to CNS lymphoma biology

- Primary brain lymphoma may also involve the eye.
- The retina has tissue layers derived developmentally from the brain.
- Primary retinal lymphoma as predominantly DLBCL.
- Ocular disease does not automatically establish lymphoma outside the CNS category.

Primary retinal lymphoma: The eye–brain link



Vitreous aspiration can establish retinal disease

- Primary retinal lymphoma may mimic uveitis clinically.
- Robbins specifies demonstration of lymphoma cells in vitreous aspirates for diagnosis.
- Ocular sampling evaluates an intraocular population; It is not identical to CSF cytology.
- Interpret ocular involvement in the context of the CNS lymphoma distribution.

Extracranial disease is unusual in primary CNS lymphoma

- Lymph-node or bone-marrow involvement outside the CNS is rare.
- When it occurs, it as a late complication.
- The “primary” designation requires attention to the initial distribution.
- This differs from a systemic lymphoma extending into CNS structures.

The site of secondary CNS involvement differs

Primary CNS lymphoma

- Typically affects brain parenchyma
- Often deep/periventricular and sometimes multifocal
- May affect the eye

Secondary CNS lymphoma

- Systemic lymphoma may involve the CNS
- Meningeal and CSF compartments are characteristic
- Parenchymal brain involvement is relatively rare

CSF cytology can reveal secondary lymphoma



Map the CNS compartments before assigning origin

Brain parenchyma

Usual primary CNS pattern

Eye / retina

Can participate in CNS lymphoma

Meninges + CSF

Common secondary CNS route

Lymph nodes / marrow

Rare and late in primary CNS lymphoma

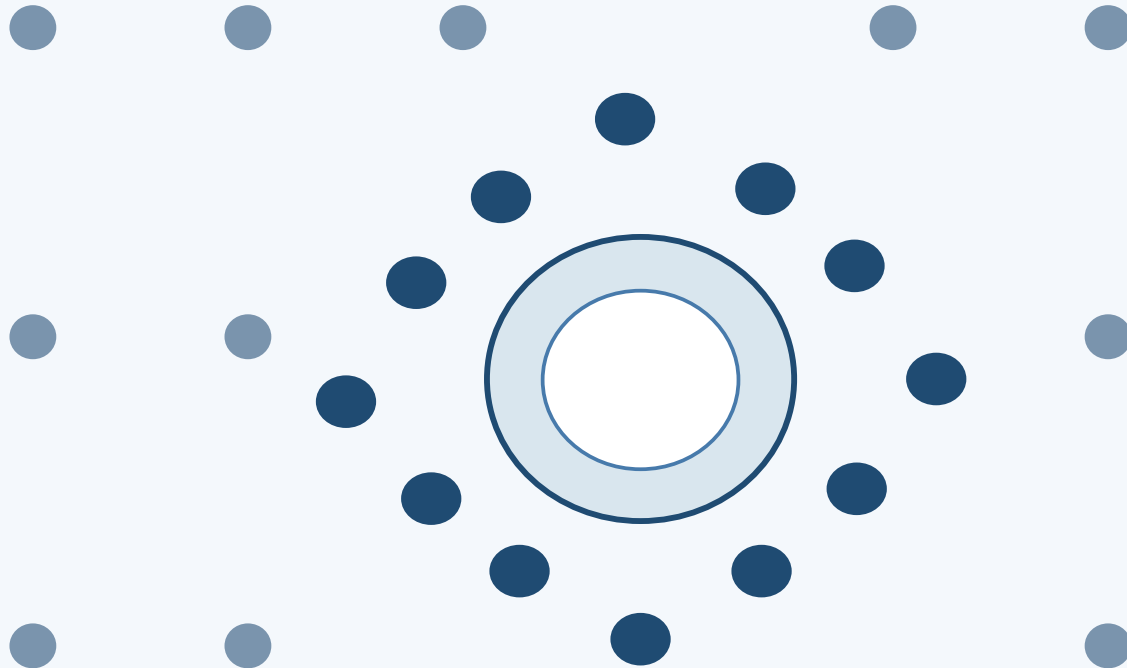
Gross appearance: Soft gray-white masses

- A soft consistency and gray-white appearance.
- The disease can form one or more masses.
- Masses often occupy deep subcortical parenchyma.
- Their superficial color does not establish a specific lymphoma subtype.

Tumor invades the brain rather than merely compressing it

- Malignant lymphoid cells infiltrate the surrounding brain parenchyma.
- This microscopic infiltration is a defining relationship to host tissue.
- The tumor can coexist with a grossly visible mass.
- Anatomic infiltration should be conveyed in both low-power and high-power interpretation.

Perivascular accumulation is characteristic



Schematic

Dark ovals: Malignant B cells

Central pale area: Vessel lumen

Tumor cells cluster around vessel and infiltrate surrounding parenchyma.

Interpreting perivascular lymphoma on a section

- Identify the vessel lumen and its wall first.
- Determine whether malignant lymphoid cells accumulate around the vessel.
- Assess adjacent parenchyma for diffuse infiltration by the same cells.
- Link the pattern to CD20 expression and cytologic malignancy.

Angiocentric distribution $\neq$ intravascular growth

Primary CNS lymphoma

- Malignant cells infiltrate brain tissue
- Perivascular accumulation is common
- Tumor cells are described outside vessel walls

Intravascular large B-cell lymphoma

- Preferential proliferation within small venules
- May produce neurologic symptoms due to brain vessels
- Often does not form conventional tissue masses

A high proliferative index supports aggressiveness

- High proliferative indices in primary CNS lymphoma.
- A proliferation-associated stain assesses cell cycling, not B-cell lineage.
- No numeric Ki-67 threshold is provided in the primary CNS lymphoma section.
- The finding complements—but cannot substitute for—morphology.

Necrosis has a host-related pattern

With immunosuppression

- Necrosis is often prominent
- EBV is usually detectable in malignant B cells
- EBER in situ hybridization is explicitly described

Without immunosuppression

- PD-L1 pathway alterations
- A distinct necrosis percentage or threshold is not given
- Necrosis alone cannot assign the biologic context

Gross and microscopic observations connect

Level	Observation	Interpretive relevance
Gross	Soft gray-white mass(es)	Macroscopic neoplasm
Distribution	Deep subcortical/periventricular	Characteristic CNS topography
Histology	Infiltrative/perivascular lymphoid cells	Parenchymal growth pattern
Immunophenotype	CD20 positive B cells	Lymphoid lineage
Host context	EBER in immunosuppression	EBV-associated biology

Three distinct tissue questions

H&E morphology

Are atypical lymphoid cells present?



CD20 immunophenotype

Is there B-cell lineage support?



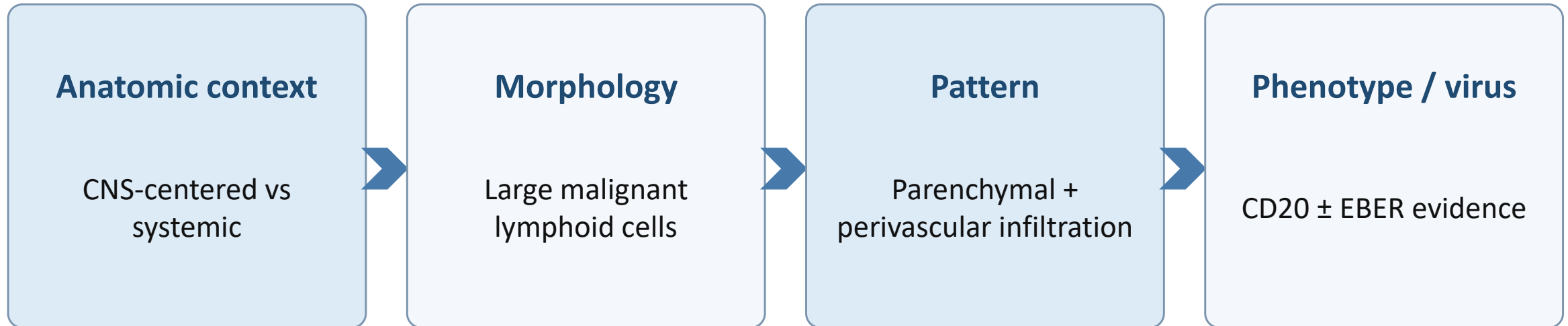
EBER in situ hybridization

Is EBV detectable in tumor cells?

Do not confuse diagnostic and biologic tests

Observation	What it tests	What it does not establish
CD20	B-cell lineage	Primary rather than secondary origin
EBER ISH	Latent EBV in examined cells	Every possible EBV-negative PCNSL excluded
Proliferation marker	Cell-cycle activity	Specific lineage
PD-L1 pathway	Immune evasion biology	Tissue-of-origin on its own

The diagnostic synthesis needs four axes



Differential diagnosis: Diffuse glioma

CNS lymphoma

- Malignant lymphoid-cell morphology
- CD20 supports B-cell origin
- Characteristic perivascular tumor accumulation

Diffuse glioma

- Glial neoplastic lineage
- Molecular and histologic glial classification
- Infiltration may be present, but lineage differs

Differential diagnosis: Metastasis

Primary CNS lymphoma

- Primary lymphoid neoplasm in CNS
- B-cell lineage is expected
- Systemic spread is rare and generally late

Metastatic tumor

- Originates outside CNS
- Carcinomas comprise the commonest metastases
- CNS involvement follows dissemination from primary elsewhere

Differential diagnosis: Meningioma

Primary CNS lymphoma

- Usually intraparenchymal, often deep
- Infiltrative malignant lymphoid cells
- CD20 B-cell phenotype

Meningioma

- Usually attached to dura
- Arises from meningotheial/arachnoid cells
- Often compresses brain rather than diffusely infiltrating it

The highest-impact differential is secondary lymphoma

Dimension	Primary CNS lymphoma	Secondary CNS lymphoma
Initial disease	Within CNS	Elsewhere in body
Typical CNS site	Parenchyma (often deep)	Meninges/CSF
Eye	May be involved	Not the defining distinction
Systemic spread	Rare, late	Present by definition of systemic origin
CSF cells	Not specified as required	May establish involvement

Clinical effects depend on site as well as cell type

- That location strongly modifies outcomes for any CNS mass.
- Brain infiltration can disrupt neurologic function even without extracranial spread.
- Deep/periventricular involvement places tumor within functionally important tissue.
- Do not infer a particular symptom complex without patient-specific evidence.

Biologic behavior is aggressive

- Most primary CNS lymphomas are DLBCL.
- The textbook characterizes them as aggressive tumors.
- Outcomes are generally worse than comparable histologic lymphomas at non-CNS sites.
- The excerpt does not quantify survival or specify a therapeutic regimen.

Why systemic DLBCL data cannot simply be transferred

What Robbins establishes

- Shared DLBCL histologic identity
- CD20-positive B-cell malignant population
- Aggressive biology at both sites

What differs in CNS

- CNS anatomic compartment and tissue interaction
- Often different host/immune context
- Textbook states poorer outcomes at CNS site

Application case: Immunosuppressed host

Hypothetical teaching scenario

An immunosuppressed adult has several deep cerebral masses. A biopsy shows a CD20-positive infiltrative large B-cell lymphoma with prominent necrosis.

Which additional tissue assay is especially informative in this setting?

Case reasoning: Immunosuppression and EBV

EBER in situ hybridization

- Immunosuppressed PCNSL with latent EBV infection.
- Prominent necrosis is a compatible host-associated morphologic feature.
- EBER positivity in tumor cells supports EBV-associated pathobiology.

Application case: Ocular involvement

Hypothetical teaching scenario

An older adult has ocular inflammation clinically resembling uveitis. Vitreous sampling reveals malignant large B lymphocytes.

What CNS association should enter the anatomic interpretation?

Case reasoning: Retina and CNS

Primary retinal lymphoma may accompany or spread to brain lymphoma.

- Primary retinal lymphoma as usually DLBCL.
- It can mimic uveitis and is evaluated with vitreous aspirates.
- Brain spread via the optic nerve is recognized in the retinal lymphoma section.

Application case: Systemic lymphoma

Hypothetical teaching scenario

A patient already has systemic B-cell lymphoma. Malignant lymphoid cells are identified in cerebrospinal fluid; No parenchymal tumor is demonstrated.

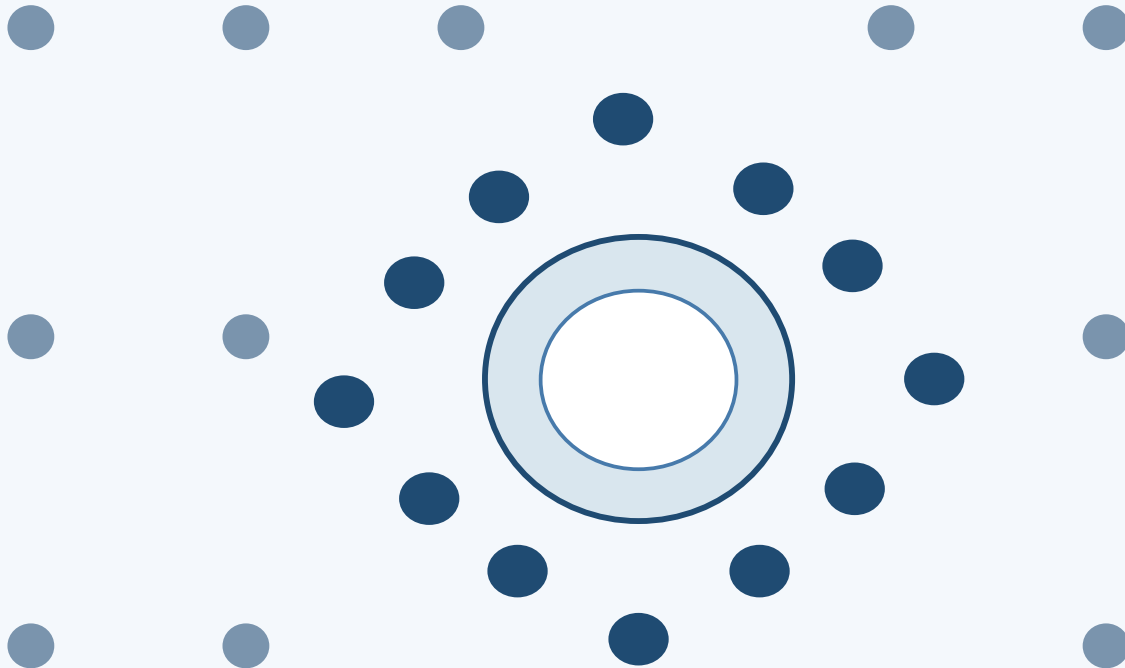
Does this presentation favor primary or secondary CNS involvement?

Case reasoning: Secondary involvement

Secondary CNS lymphoma

- The lymphoma originated outside the CNS.
- CNS extension from systemic lymphoma commonly involves meninges or CSF.
- CSF malignant cells can establish CNS involvement in that setting.

Morphology exercise: Locate the tumor cells



Schematic

Identify the vessel,
tumor-cell distribution,
and supporting
immunophenotype.

Morphology exercise: Interpret the pattern

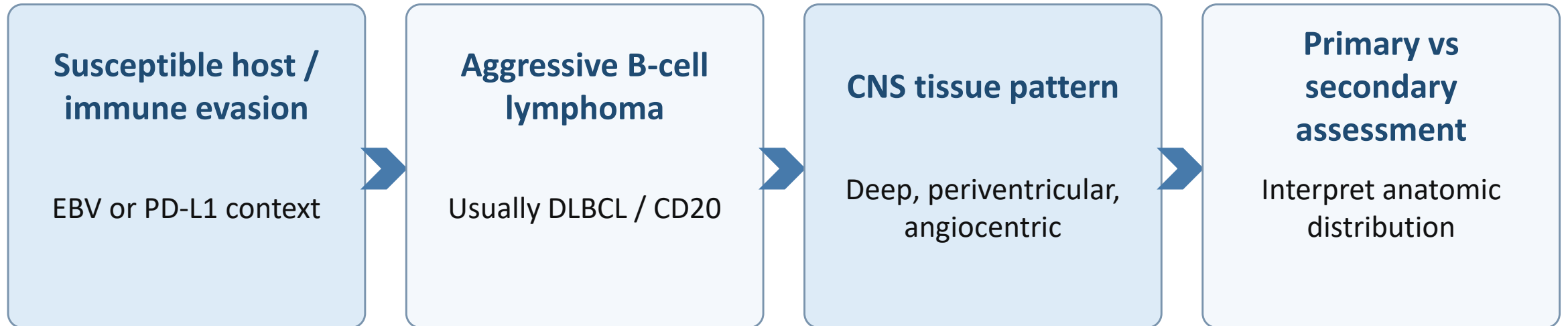
Perivascular accumulation within an infiltrative B-cell lymphoma

- Cells concentrate around the blood vessel rather than only inside its lumen.
- The pattern supports the PCNSL morphologic constellation.
- CD20 confirmation is needed to establish the B-cell phenotype.

Five features to retain

Axis	Primary CNS lymphoma
Identity	Usually DLBCL
Host	Immunosuppression; Or older adults without it
Distribution	Deep subcortical, often multifocal/periventricular
Histology	Parenchymal infiltration with perivascular accumulation
Phenotype/virus	CD20; EBER commonly detectable in immunosuppressed hosts

Integrating mechanism, phenotype and anatomy



Source-specific boundaries of this lecture

- Textbook focus: Host, lineage, gross/microscopic morphology and CNS distribution.
- Mechanistic context drawn from the same Robbins edition (Chapters 6, 7 and 13).
- Eye–brain relationship drawn from the same edition (Chapter 29).
- Current clinical guidelines, drug protocols and molecular taxonomies were not independently reviewed for this deck.

Primary references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Ch. 28, p. 1182 — Primary CNS Lymphoma.
- Robbins, Cotran & Kumar. 11th ed. Ch. 13, pp. 546–547 — Diffuse Large B-Cell Lymphoma.
- Robbins, Cotran & Kumar. 11th ed. Chs. 6–7 — PD-1/PD-L1 and tumor immune evasion.
- Robbins, Cotran & Kumar. 11th ed. Ch. 29, p. 1207 — Retinal Lymphoma.