

Extranodal NK-/T-cell lymphoma

An Epstein–Barr virus-associated, highly aggressive extranodal lymphoma

Clinicopathologic emphasis: nasal destruction, angiodestruction, and lineage assignment

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Recognize the principal extranodal sites and characteristic destructive presentation.
- Explain EBV association, angiodestruction, and ischemic necrosis.
- Interpret NK-/T-cell markers, EBER studies, and TCR findings.
- Construct a tissue-based differential diagnosis and link pathology to clinical behavior.

Defining the disease

Defining category

- A mature NK- or cytotoxic T-cell malignancy arising characteristically at extranodal sites.

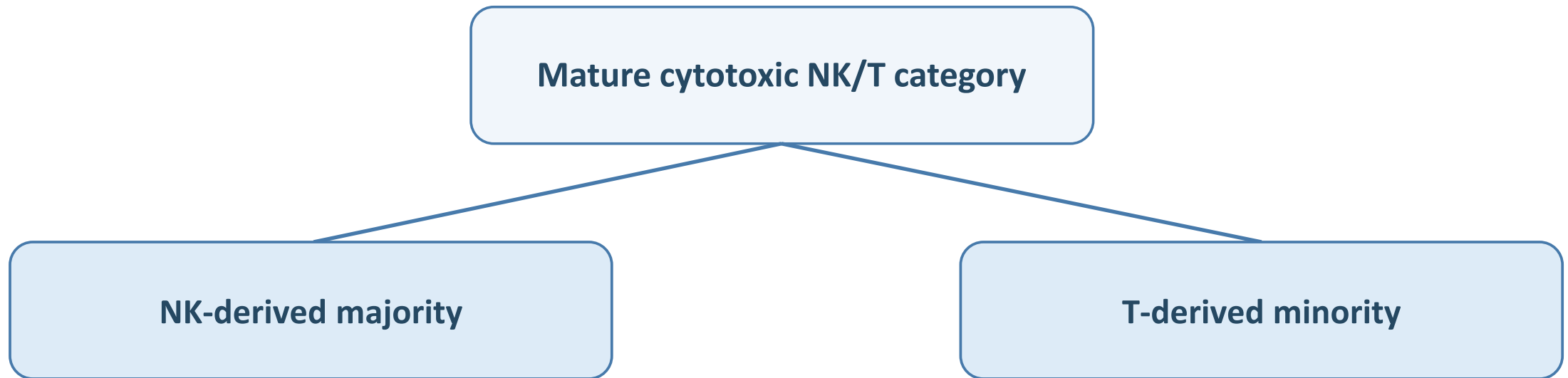
Characteristic expression

- The usual lesion is a destructive mass centered on the upper aerodigestive tract.

- Most cases have an NK-cell lineage, but a minority show a cytotoxic T-cell phenotype.

Why “NK-/T-cell” rather than “NK-cell”?

NK-lineage tumors predominate and commonly lack T-cell receptor (TCR) rearrangements.



- A subset genuinely belongs to the cytotoxic T-cell lineage and may have rearranged TCR genes.
- Morphology, viral studies, and phenotyping must be interpreted together.

The nasal presentation is a tissue-destructive process

The nasopharyngeal region is the most frequent presenting site.



- The lesion may erode local tissue through vascular invasion and ischemic necrosis.
- A destructive mass is a clinicopathologic clue—not itself a diagnostic criterion.

Opening clinical problem

- Illustrative scenario: An adult has a persistent destructive nasopharyngeal lesion.
- A superficial biopsy shows prominent necrotic debris and scattered atypical lymphoid cells.
- Diagnostic task: Decide what viable tissue, stains, and lineage studies are needed.

Which finding would most directly connect the clinical lesion to the tumor mechanism?

Geographic pattern

- Uncommon in the United States and Europe.
- Accounts for as many as 3% of non-Hodgkin lymphomas in Asia,.
- The distribution is a population-level observation, not a patient-level diagnostic test.

Anatomic predilection

Typical primary site

- Most often presents as a nasopharyngeal mass.

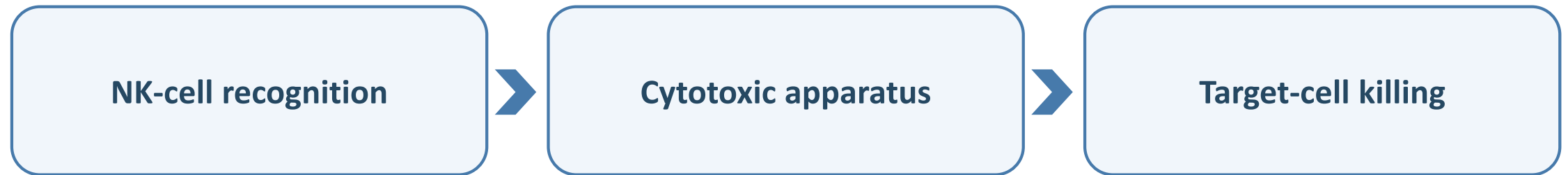
Additional extranodal sites

- Skin and testis are less common primary presentations.

- An extranodal distribution should direct sampling toward involved tissue rather than lymph nodes alone.

Normal NK cells: Useful biologic context

NK cells participate in innate immune surveillance of infected or stressed cells.



- Their cytotoxic apparatus contains granules capable of killing target cells.
- The tumor retains aspects of cytotoxic-cell differentiation, explaining the diagnostic value of granule-associated proteins.

NK cells and cytotoxic T cells are not synonymous

NK lineage

- Normal NK cells lack surface CD3 and generally lack rearranged TCR genes.

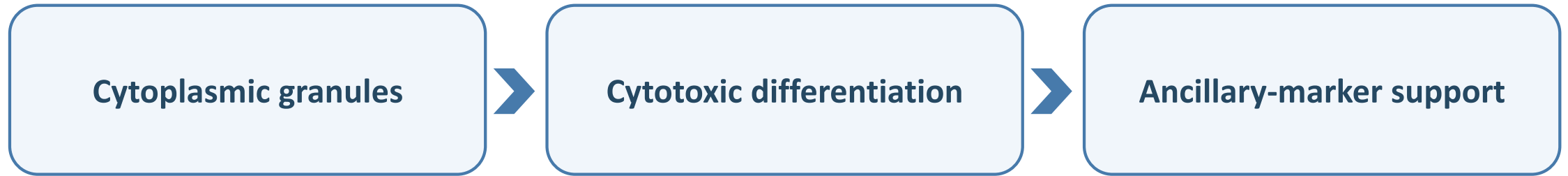
Cytotoxic T lineage

- Cytotoxic T cells use a clonotypic TCR/CD3 complex.

- Lymphoma typing therefore requires a lineage interpretation, not only a cytotoxic marker.

What cytoplasmic azurophilic granules signal

Granules are an expected feature of normal cytotoxic lymphocytes.



- Large azurophilic granules in touch preparations of tumor cells.
- Granule morphology supports cytotoxic differentiation but is not disease-specific.

EBV is central to disease association

Tumor tissue

EBV detection

Lineage phenotype

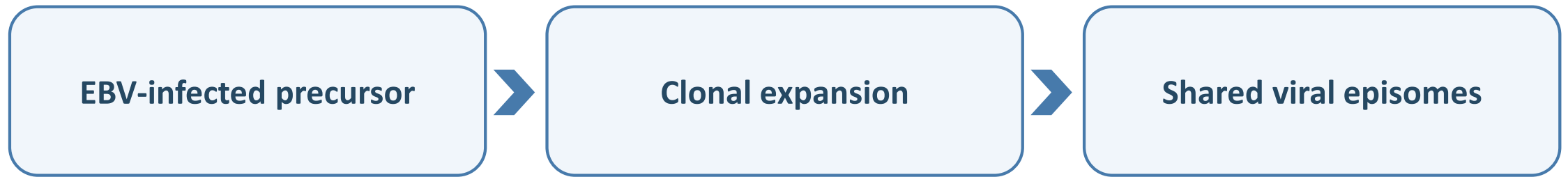
Morphologic context

Extranodal NK-/T-cell lymphoma is highly associated with Epstein–Barr virus infection. • EBV positivity should be demonstrated in tumor cells rather than inferred from patient serology.

- The association is central to current diagnostic frameworks.

EBV episomes establish a clonal relationship

Identical EBV episomes in tumor cells within an individual patient.



- Identical episomes are evidence of expansion from one EBV-infected precursor.
- This supports tumor clonality; It does not specify the complete sequence of oncogenic events.

An unresolved biological question: EBV entry

Observed finding

- The classic B-cell EBV receptor CD21 is not expressed by these tumor cells.

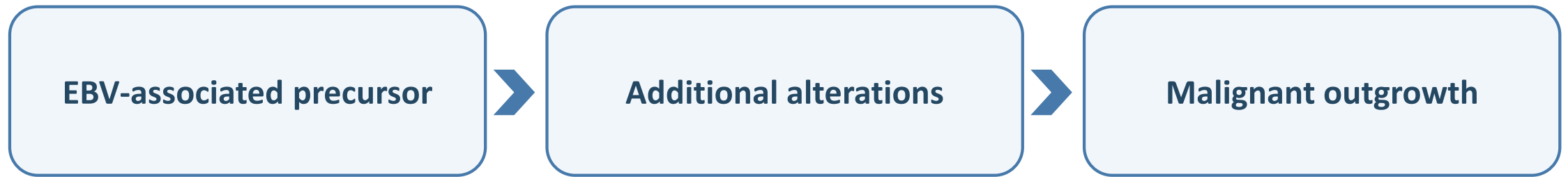
Unresolved inference

- The route by which EBV enters the NK-/T-lineage precursor remains uncertain.

- Do not replace this uncertainty with a speculative entry pathway.

Association is not a complete mechanism

Strong EBV association and clonality support a critical relationship to tumor development.



- Host-cell mutations and disordered signaling are also reported.
- A single universal sequence from infection to malignancy is not established section.

No unique diagnostic chromosomal abnormality

- Complex chromosomal aberrations are often present.
- Robbins does not identify any one specific, defining aberration.
- A molecular result must be interpreted with morphology, viral status, and phenotype.

Recurring molecular categories

JAK/STAT

Epigenetic regulation

TP53

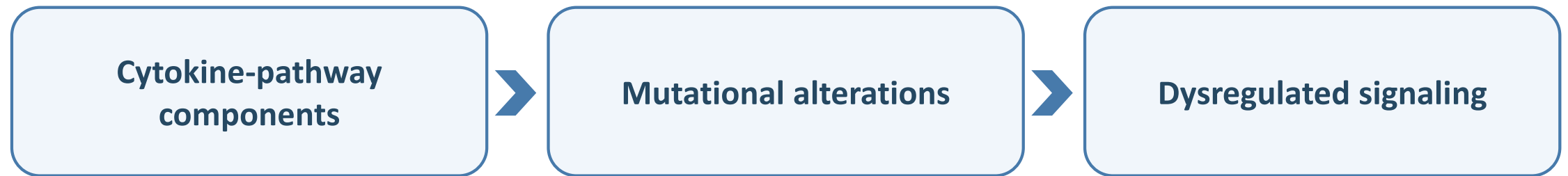
Genomic complexity

Reported alterations involve JAK/STAT signaling components. • Other affected genes encode epigenetic regulators.

- TP53 is also recurrently mutated in reported cases.

JAK/STAT: Signaling dysregulation

JAK/STAT proteins transduce cytokine-dependent growth and survival signals.



- Recurrent mutations affecting components of this pathway.
- A detected mutation alone cannot substitute for diagnostic tissue findings.

Epigenetic regulators: A separate alteration class

General role

- Epigenetic control influences gene expression without changing the DNA sequence.

Disease observation

- Mutations in regulatory components have been reported in this tumor.

- The textbook does not specify a unique epigenetic mutation for routine diagnosis.

TP53 is one reported genetic target

TP53 is involved in cellular responses to genomic injury and stress.



- Recurrent TP53 mutations among reported tumors.
- Presence or absence of a TP53 variant does not by itself establish the entity.

Integrating virus and host-cell alterations

Disease biology

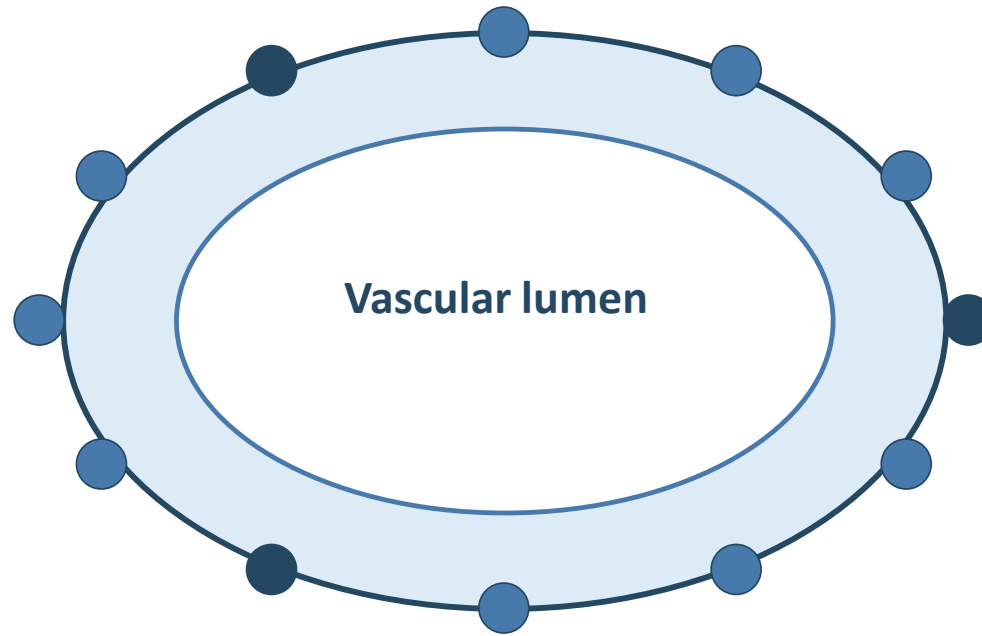
- EBV-associated clonal neoplasia coexists with heterogeneous host genomic lesions.

Diagnostic implication

- These observations explain why a single mutation is not a universal diagnostic hallmark.

- The definitive diagnosis remains an integrated clinicopathologic classification.

Angiocentric growth

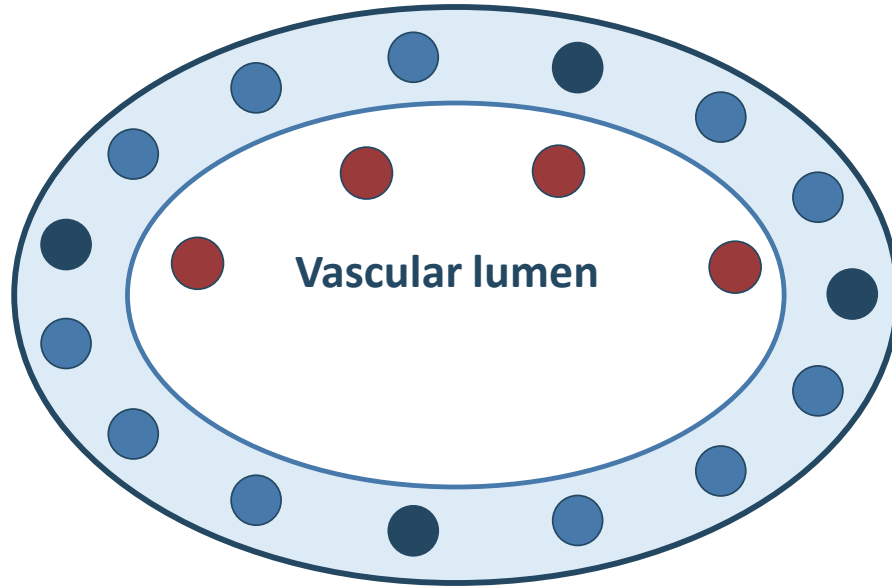


Neoplastic lymphoid cells

Schematic — not a histologic specimen

- Neoplastic cells typically accumulate around small vessels.
- Perivascular localization is an architectural clue in tissue sections.
- The degree of demonstrable vascular involvement can depend on available viable tissue.

Angiodestruction: Invasion of vessel walls



Neoplastic lymphoid cells

Schematic — not a histologic specimen

- Tumor cells may infiltrate and destroy small-vessel walls.
- This is more specific mechanistically than simple perivascular inflammation.
- Angiodestruction helps account for the striking destructive phenotype.

Why the tumor produces ischemic necrosis

Small-vessel infiltration and damage impair local perfusion.



- Ischemic injury results in necrosis of adjacent tissue.
- Necrosis may dominate the biopsy and obscure the neoplastic infiltrate.

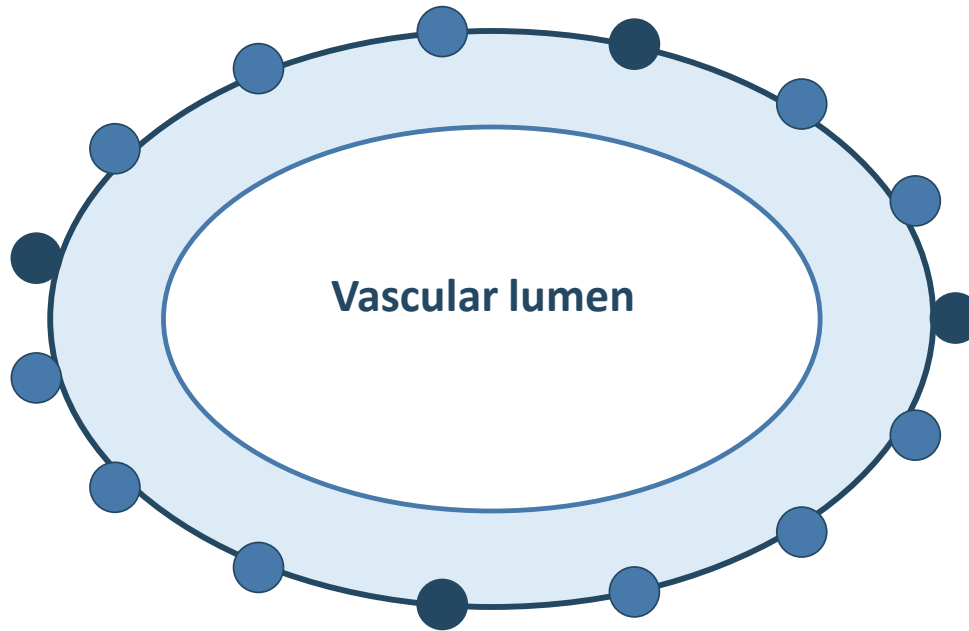
Linking the nasal mass to histologic damage

A destructive nasopharyngeal mass is the principal clinical pattern.



- Vessel-centered tumor infiltration produces focal vascular injury.
- Associated necrosis helps explain local mucosal destruction.

Schematic field interpretation



Neoplastic lymphoid cells

Schematic — not a histologic specimen

- At scanning magnification:
Identify viable tissue,
necrosis, and vessels.
- At higher magnification:
Assess the relationship of
atypical cells to vessel walls.
- Use immunophenotypic and
EBV studies to determine
whether the infiltrate is
lymphoma.

Touch preparation: Cytoplasmic granules

Observed cytology

- Large azurophilic granules in tumor-cell cytoplasm.

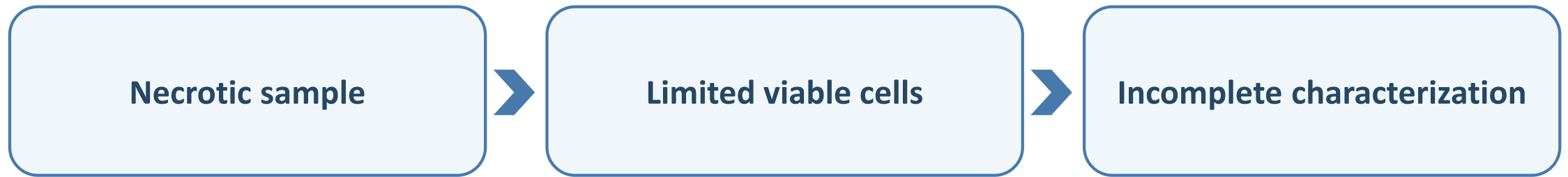
Diagnostic limitation

- This recapitulates a structural feature of cytotoxic NK cells.

- The finding supports recognition, but cannot independently identify the lymphoma.

Necrosis is a sampling problem

A specimen containing mostly necrotic tissue may contain few interpretable tumor cells.



- An adequate diagnosis requires representative viable tissue.
- Sampling and repeat biopsy decisions belong to the treating pathology–clinical team.

Cytologic heterogeneity

What varies

- Neoplastic cells may range from small to large and show irregular nuclear contours.

What remains essential

- Background inflammation and necrosis may complicate recognition.

- Cell size alone does not classify the tumor.

Inflammatory background can mislead

Potential mimic

- A mixed inflammatory infiltrate can coexist with neoplastic cells.

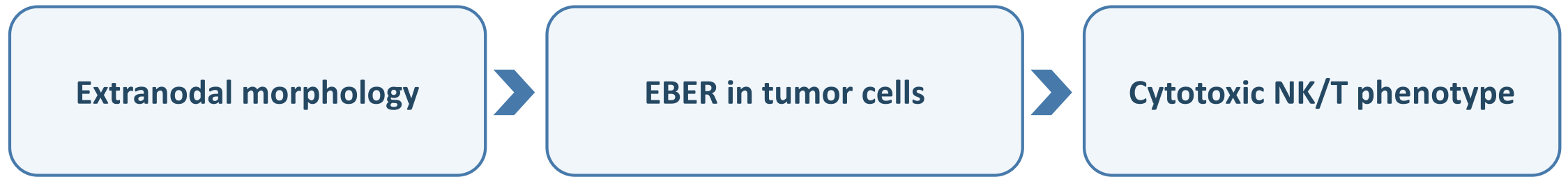
Discriminating evidence

- Prominent necrosis may prompt an infectious or inflammatory differential.

- Convergent morphology and viral/lineage studies are more reliable than appearance alone.

Three diagnostic anchors

Extranodal malignant cytotoxic lymphoid infiltrate.



- EBV detected in neoplastic cells by EBER in situ hybridization.
- Compatible NK-cell or cytotoxic T-cell phenotype.

What EBER in situ hybridization contributes

Useful evidence

- EBER probes detect EBV-associated small RNAs in affected tissue.

Potential pitfall

- The critical readout is nuclear signal within neoplastic lymphoid cells.

- An EBV-positive background cell population must not be confused with EBV-positive tumor.

Current classification: EBV in the tumor

Extranodal infiltrate

NK/cytotoxic T phenotype

EBER in most tumor cells

Integrated diagnosis

WHO-HAEM5 expects most neoplastic cells to be EBER-positive as an essential criterion. • EBER positivity should be interpreted together with cell morphology and phenotype.

- A convincing EBER-negative candidate requires re-examination of the diagnosis.

CD56: Supportive NK-associated marker

Value	Limitation
• CD56 commonly marks the neoplastic population.	• CD56 is not absolutely specific for NK-cell lineage.

- A compatible lymphoma can show atypical marker expression; Use a panel, not one stain.

Surface CD3 and cytoplasmic CD3ε differ

Surface CD3 / TCR

- Typical NK cells are negative for surface CD3/TCR expression.

Cytoplasmic CD3ε

- Paraffin-section staining for cytoplasmic CD3ε may be positive in this lymphoma.

- Thus “CD3-negative” should not be equated with all CD3 immunohistochemistry being negative.

Cytotoxic differentiation markers

TIA1

Granzyme B

Perforin

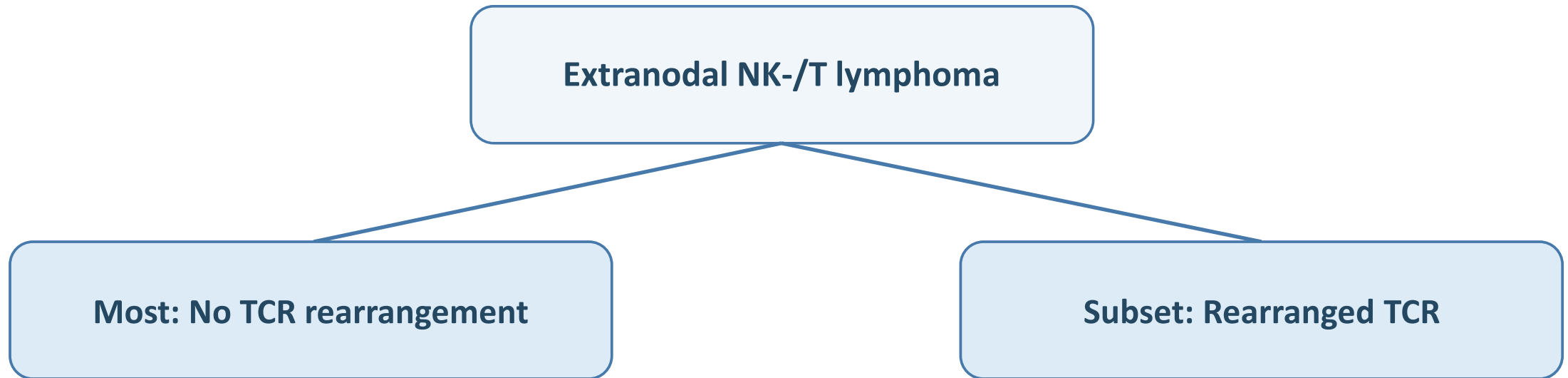
Interpret in context

TIA1, granzyme B, and perforin provide evidence of cytotoxic differentiation. • The expected panel is interpreted alongside CD2, CD56, CD3ε, and EBER.

- Cytotoxic-marker positivity alone is shared by other lymphoid lesions.

T-cell receptor gene rearrangement

Most cases lack detectable TCR gene rearrangements.



- This supports the usual NK-cell derivation.
- A subset has genuine T lineage; Absence of rearrangement is not an absolute diagnostic requirement.

Lineage classification requires a panel

Test domain	Typical NK-lineage interpretation
Surface CD3/TCR	Usually absent
Cytoplasmic CD3ε	May be positive
CD56	Commonly positive
TCR gene rearrangement	Usually absent

- Surface versus cytoplasmic antigen localization matters.
- CD56 and cytotoxic markers support but do not uniquely determine NK lineage.

Important immunophenotypic exceptions

Nonclassic result

- Some tumors lack CD56 despite compatible cytotoxic and EBV findings.

Diagnostic response

- CD30 or T-cell antigen expression can vary.

- An unexpected single stain result should trigger a broader integrated review—not automatic exclusion.

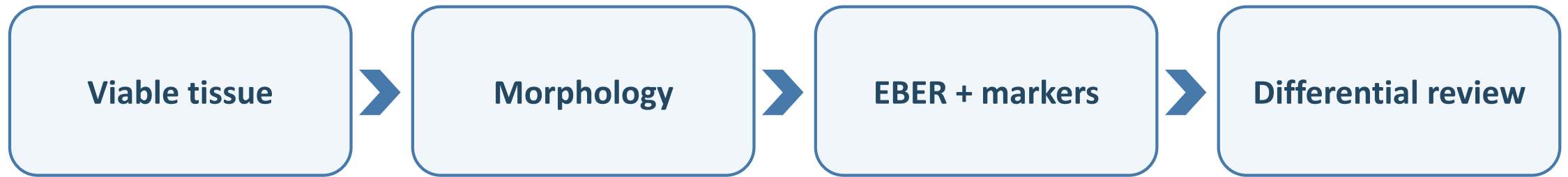
Integrating a core diagnostic panel

Question	Illustrative tests
Lymphoid/cytotoxic phenotype	CD3ε, CD2, TIA1, granzyme B
NK-associated differentiation	CD56, surface CD3/TCR if available
EBV within tumor	EBER in situ hybridization
Alternative lineage	CD20, ALK and others as indicated

- Confirm hematolymphoid nature and exclude obvious lineage mimics.
- Establish cytotoxic NK/T phenotype using CD3ε, CD2, CD56, and granule markers.

Tissue-to-diagnosis workflow

Begin with an adequate biopsy of viable lesional tissue.



- Identify the angiodestructive infiltrate and accompanying necrosis.
- Establish EBV association and NK-/cytotoxic T-cell phenotype.
- Exclude clinically and morphologically plausible mimics.

Pitfall: A sample dominated by dead tissue

Failure mechanism

- Extensive necrosis can produce nondiagnostic or falsely reassuring biopsies.

Practical remedy

- Search for the viable neoplastic edge and vessel-associated infiltrate.

- Lack of sufficient tissue is a specimen limitation—not proof against lymphoma.

Mimic: Invasive infection

Shared feature

- Destructive nasal lesions and necrosis are not lymphoma-specific.

Distinguishing approach

- Microbiologic and fungal assessment depends on clinical findings and tissue morphology.

- Do not attribute necrosis to lymphoma before excluding credible infection.

Mimic: Granulomatosis with polyangiitis

Overlapping phenotype

- Inflammatory vasculitis can also damage vessels and destroy sinonasal tissue.

Distinguishing observation

- A neoplastic cytotoxic lymphoid population with EBER positivity redirects the diagnosis.

- The pathology report should explain why a reactive vasculitic process is unlikely.

Mimic: EBV-positive B-cell proliferation

EBV-positive B cells

- EBV positivity by itself does not establish NK-/T-cell lymphoma.

NK-/T-cell lymphoma

- Evaluate whether EBV signal localizes to the atypical cytotoxic cells.

- B-cell marker expression and architectural context distinguish an EBV-associated B-cell process.

Mimic: Anaplastic large-cell lymphoma

ALK-positive ALCL

- Large atypical lymphoid cells and CD30 expression can create morphologic overlap.

Extranodal NK-/T lymphoma

- ALK-positive ALCL is characterized by ALK rearrangement/protein expression.

- EBER and the full phenotype are necessary to classify an ambiguous case.

Mimic: Aggressive NK-cell leukemia

Predominant disease pattern

- Both disorders involve NK-cell differentiation and may be clinically aggressive.

Key distinction

- A leukemic systemic presentation differs from a dominant destructive extranodal mass.

- Blood, marrow, and tissue distribution are integral to the differential.

Mimic: Indolent NK-cell proliferation of the gut

Indolent NK-cell GI proliferation

- WHO-HAEM5 separates an indolent gastrointestinal NK-cell proliferation from aggressive extranodal NK-/T-cell lymphoma.

Extranodal NK-/T lymphoma

- The indolent gastrointestinal entity is EBV-negative.

- Clinical behavior, anatomic pattern, tissue architecture, and EBER guide separation.

EBV-positive nodal T-/NK-cell lymphoma is distinct

Primary nodal pattern

- WHO-HAEM5 recognizes a separate EBV-positive nodal T-/NK-cell lymphoma.

Primary extranodal pattern

- A chiefly nodal pattern should not automatically be called nasal-type extranodal disease.

- Anatomic presentation and classification context remain important.

Define disease extent before treatment decisions

Site of origin and extranodal extension affect clinical planning.



- Clinical staging integrates imaging and tissue findings.
- A histologic diagnosis does not independently determine the distribution of disease.

Biology helps explain treatment behavior

Local response

- Extensive local infiltration and necrosis make disease control challenging.

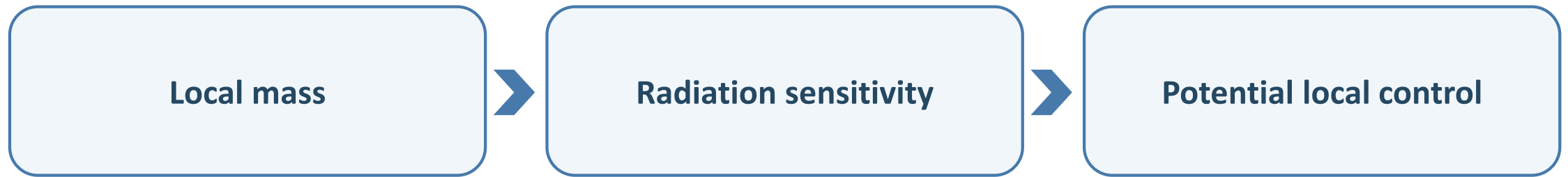
Systemic disease challenge

- Favorable response to radiation therapy.

- The same text describes relative resistance to conventional chemotherapy.

Radiation sensitivity of localized disease

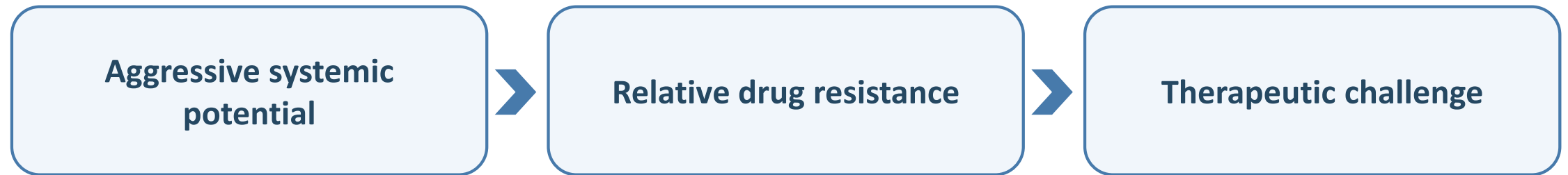
The tumor commonly responds well to radiation.



- The observation is most relevant for treatment planning in localized presentation.
- The exact regimen is outside the scope of this pathology lecture.

Relative chemotherapy resistance

Robbins characterizes the disease as relatively resistant to chemotherapy.



- This observation limits extrapolation from common B-cell lymphoma treatment approaches.
- Advanced disease requires specialist multimodality assessment.

Advanced disease has poor prognosis

Pathology signal

- Prognosis is generally poor when disease is advanced.

Prognostic implication

- Disease distribution and response to treatment are clinically relevant.

- Do not quote survival estimates without a population, regimen, and study source.

Allogeneic stem-cell transplantation

Potential role

- Allogeneic hematopoietic stem-cell transplantation as a potential option in advanced disease.

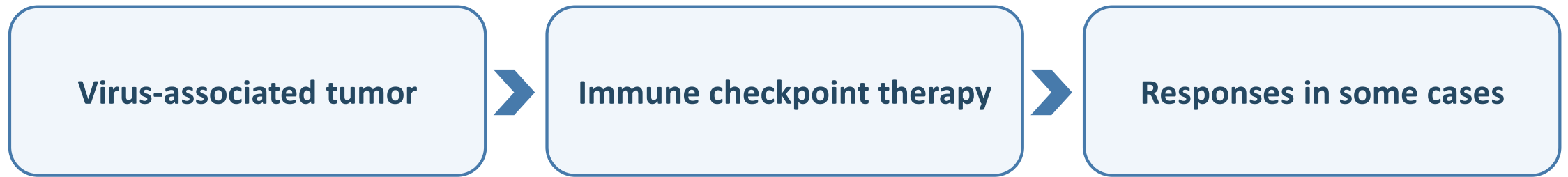
Important qualification

- This is a selected-patient strategy rather than a universal treatment.

- A pathology lecture should not imply definitive benefit for every clinical setting.

Immune-checkpoint blockade

Observed responses to checkpoint inhibitors in this virus-associated lymphoma.



- The observation is biologically compatible with immune interactions in a virus-driven malignancy.
- Responses are not an assurance of durable benefit for an individual patient.

Immune-treatment toxicity matters

Therapeutic interest

- Potential harms include immune-mediated disease.

Important risk

- Severe inflammatory toxicity, including cytokine-related syndromes, may occur.

- Therapeutic possibilities should not be presented separately from treatment risk.

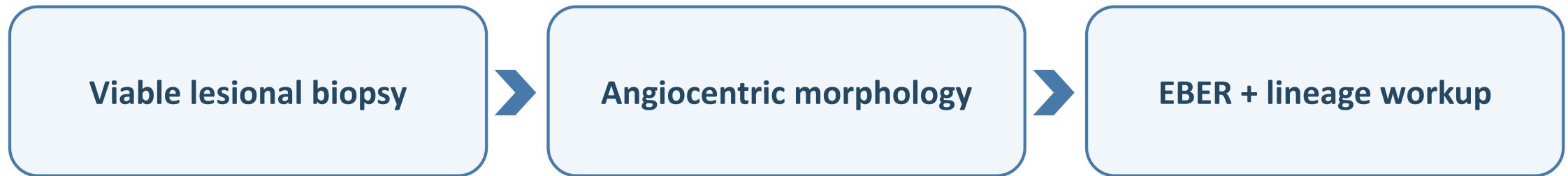
Case application: The necrotic nasal biopsy

- Illustrative case: The first sample contains necrosis and a scant atypical lymphoid population.
- The lesion remains clinically destructive despite an initially limited specimen.
- Which two actions best improve the pathologic evaluation?

Propose a sampling strategy and the first decisive ancillary test.

Case interpretation: Obtain interpretable cells

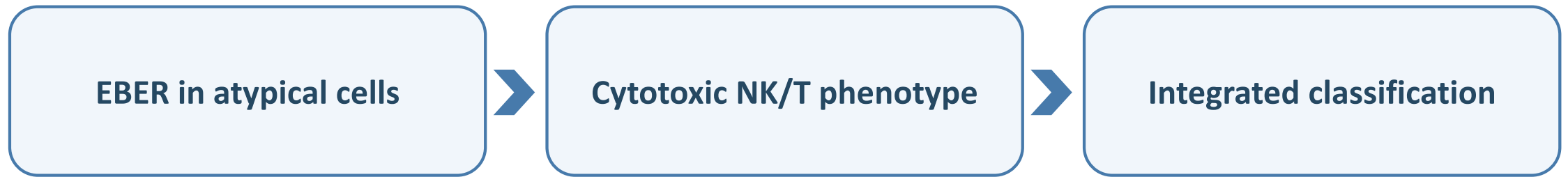
Prioritize representative viable tissue, especially at the edge of necrosis.



- Examine the relationship between neoplastic cells and vessels.
- Avoid overcalling either lymphoma or inflammation from necrosis alone.

Case interpretation: Assign EBV and lineage

EBER-positive atypical cells support an EBV-associated malignant population.



- A compatible cytotoxic NK/T marker profile supports extranodal NK-/T-cell lymphoma.
- Clinical distribution and competing diagnoses complete the interpretation.

Diagnostic synthesis

Morphology

Nasal tissue destruction + angiocentric/angiodestructive lymphoma is a strong morphologic pattern.

EBV

EBER within tumor cells is central, combined with NK/cytotoxic T immunophenotype.

Lineage

Most cases are NK-lineage; Molecular heterogeneity precludes a single defining host-gene test.

Clinical course

Clinical extent matters because advanced disease is aggressive and challenging to treat.

Sources and scientific scope

- Primary: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed., ch. 13, p. 552.
- Diagnostic supplement: WHO-HAEM5 T/NK classification review (J Clin Pathol, 2025).
- Diagnostic supplement: 2022 ICC extranodal T/NK lymphoma review (Virchows Arch, 2023).
- Morphologic supplement: ENKTCL review (Front Oncol, 2023).