

Intermediate-Grade (Borderline) Tumors

Kaposi sarcoma • Hemangioendothelioma

Vascular tumor classification • Pathogenesis • Morphology • Clinical correlation

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Intermediate-grade vascular neoplasms

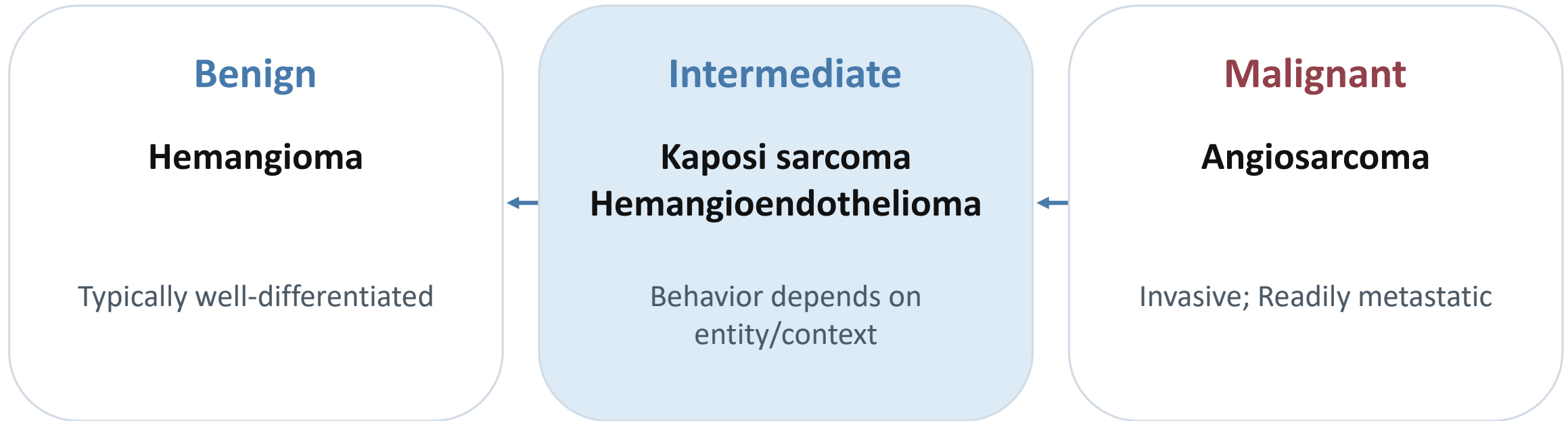
- These lesions are positioned between clearly benign vascular tumors and aggressive angiosarcoma.
- The principal Robbins examples are Kaposi sarcoma and hemangioendothelioma.
- Clinical context and morphologic stage can substantially alter their apparent behavior.

Learning outcomes

- Explain how HHV8 and altered cellular immunity cooperate in Kaposi sarcoma.
- Distinguish the four clinical forms of Kaposi sarcoma.
- Recognize patch, plaque and nodule-stage morphologic progression.
- Contrast Kaposi sarcoma, epithelioid hemangioendothelioma and their mimics.

Vascular tumor classification is a continuum

Biologic behavior (schematic continuum)



Angiosarcoma illustrates frankly malignant endothelial neoplasia.

Most entities arise from vascular endothelium

Endothelial examples	Hemangioma · Kaposi sarcoma · hemangioendothelioma · angiosarcoma
Supporting-cell example	Glomus tumor

Cell of origin and degree of malignant behavior are different classification axes.

Borderline does not mean clinically inconsequential

- Intermediate-grade lesions span persistent local disease to clinically aggressive systemic involvement.
- Both host immune status and lesional morphology inform expectations.
- The broad grade category is not a substitute for case-specific assessment.

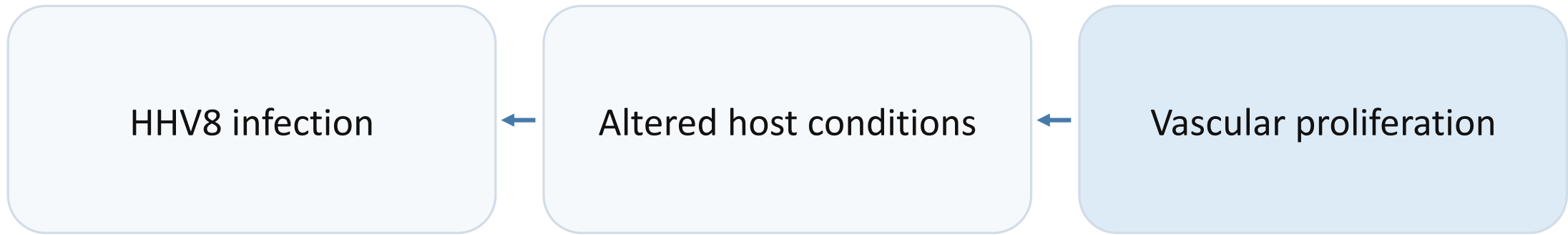
Tumor-like proliferations are an important mimic

Reactive/infectious	Bacillary angiomatosis — Bartonella species
Neoplastic	Kaposi sarcoma — HHV8-associated vascular tumor

The classification distinguishes reactive mimics from intermediate-grade neoplasia.

Kaposi sarcoma: Causal viral association

Mechanism / clinical sequence — schematic



- Kaposi sarcoma (KS) is a vascular neoplasm caused by human herpesvirus 8 (HHV8/KSHV).
- Nearly all lesions contain the virus, across the recognized clinical variants.

HHV8 infection is not equivalent to HIV infection

HHV8	Direct etiologic association with KS
HIV	Immune suppression that favors epidemic KS

KS in a person with HIV is an AIDS-defining condition in the Robbins classification.

Four clinicopathologic forms of Kaposi sarcoma

Classic

Older men; Distal skin
Usually local

Endemic African

Often HIV negative
Frequent lymph nodes

Iatrogenic

Transplant immunosuppression
Mucosal / visceral spread

Epidemic

AIDS-associated
Early dissemination

Classic KS: Characteristic host population

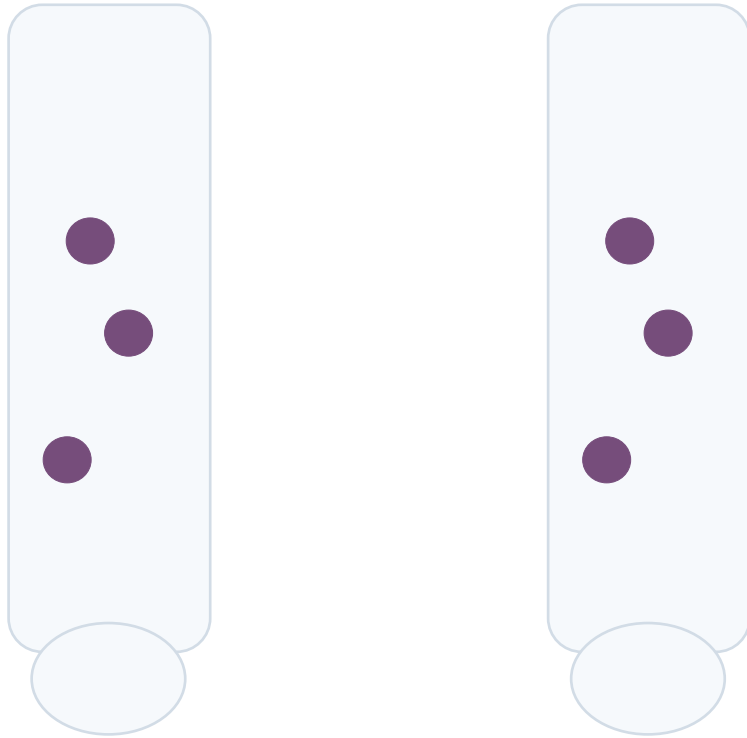
- The classic variant predominantly affects older men.
- Geographic/ancestral associations include Mediterranean and Eastern European groups.
- Classic KS does not require HIV infection.

Context

Older male; Often no HIV association
Clinical clue:
Persistent distal cutaneous vascular lesions

Classic KS: Earliest distribution

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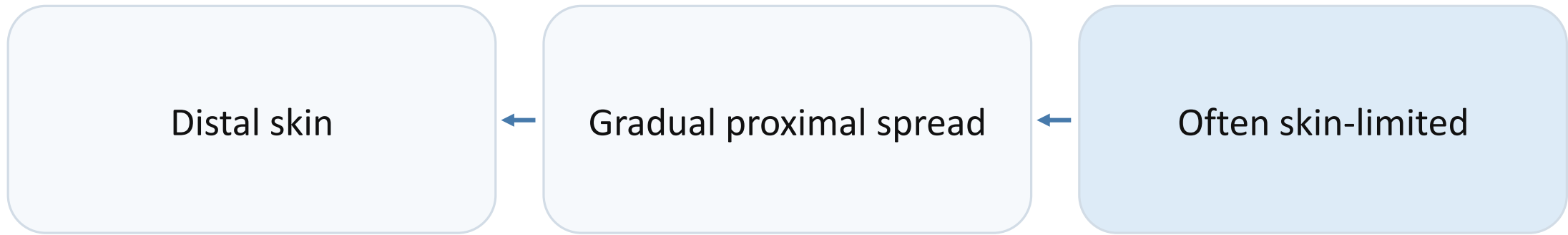


Distal lower limbs

- Multiple red-purple cutaneous plaques or nodules commonly appear on distal lower extremities.
- The lesions typically increase in number and size over time.
- Distribution can extend proximally with progression.

Classic KS: Local rather than systemic disease

Mechanism / clinical sequence — schematic



- The initial disease is often restricted to skin and subcutaneous tissue.
- Many lesions are asymptomatic despite persistence.

Classic KS: Prognosis reflects limited extent

- Local skin lesions are often amenable to surgical resection.
- An excellent prognosis for uncomplicated skin-limited classic disease.
- Clinical extent matters more than the presence of a single lesion alone.

Endemic African KS: An HIV-negative setting

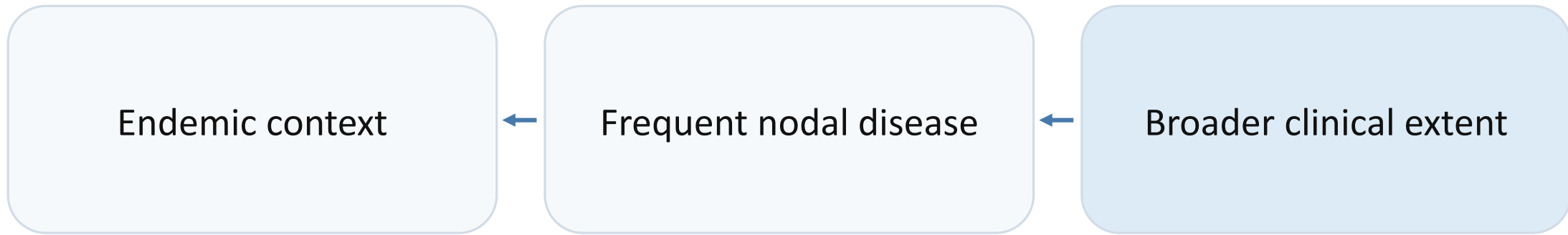
- Frequently develops in individuals who are HIV-seronegative.
- Affected individuals often younger than 40 years.
- The course ranges from indolent to aggressive, unlike a uniform phenotype.

Host

Often HIV-seronegative
Behavior: Indolent to aggressive

Endemic African KS: Nodal involvement matters

Mechanism / clinical sequence — schematic



- Lymph-node involvement is more frequent than in classic KS.
- Skin-focused examination may underestimate the anatomic extent.

Childhood endemic KS can be fulminant

- The prepubertal variant can show prominent lymph-node and visceral involvement.
- Robbins characterizes this pediatric presentation as particularly severe.
- Do not generalize the indolent behavior of classic KS to this subgroup.

Pediatric endemic disease ≠ indolent classic KS

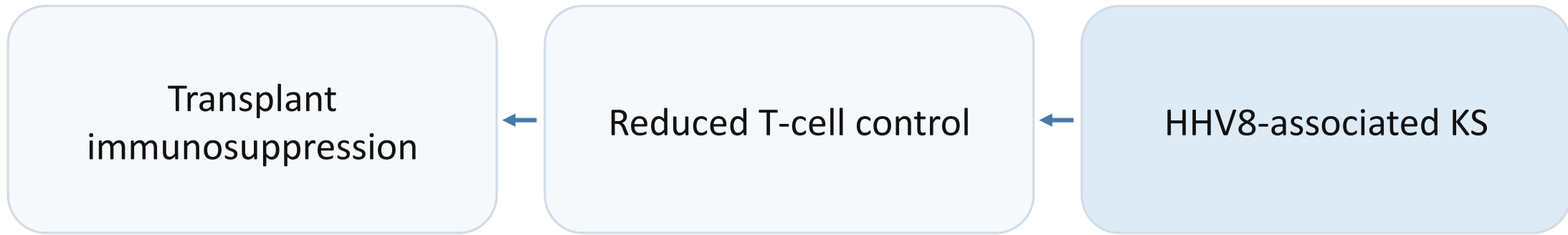
Classic versus endemic KS

Classic	Older men; Distal skin lesions; Usually indolent
Endemic African	Often younger / HIV-seronegative; Frequent nodes; Variable course

Endemic disease has a wider behavioral range and a stronger nodal tendency.

Iatrogenic KS: T-cell suppression as a cofactor

Mechanism / clinical sequence — schematic



- Solid-organ transplant recipients may develop KS during T-cell immunosuppression.
- Immune surveillance is an important restraint on HHV8-associated proliferation.

Iatrogenic KS: Visceral disease without skin lesions

- Lymph nodes, mucosa and viscera may be involved.
- The skin may be free of clinically visible lesions.
- Absence of a cutaneous plaque does not exclude transplant-associated KS.

Reducing immunosuppression introduces a trade-off

Mechanism / clinical sequence — schematic



- KS lesions may regress as T-cell immunosuppression is reduced.
- Withdrawal or reduction can threaten transplanted-organ survival.

Epidemic KS: Association with advanced HIV

- AIDS-associated (epidemic) KS is an AIDS-defining illness.
- Impaired T-cell immunity permits expansion of HHV8-associated vascular lesions.
- This is a distinct clinical setting, not a distinct causal herpesvirus.

Virologic driver

HHV8/KSHV Enabling
setting: HIV-associated
immunodeficiency

AIDS-associated KS frequently disseminates

Mechanism / clinical sequence — schematic



- Lymph-node involvement is common.
- Visceral dissemination can occur early in the clinical course.

Antiretroviral therapy changed the KS landscape

- A greater than 80% fall in AIDS-associated KS incidence after effective antiretroviral treatment became available.
- Antiretroviral treatment is generally beneficial in AIDS-associated KS.
- The incidence statement is a textbook historical comparison, not a current surveillance estimate.

Textbook historical effect, not a contemporary surveillance estimate

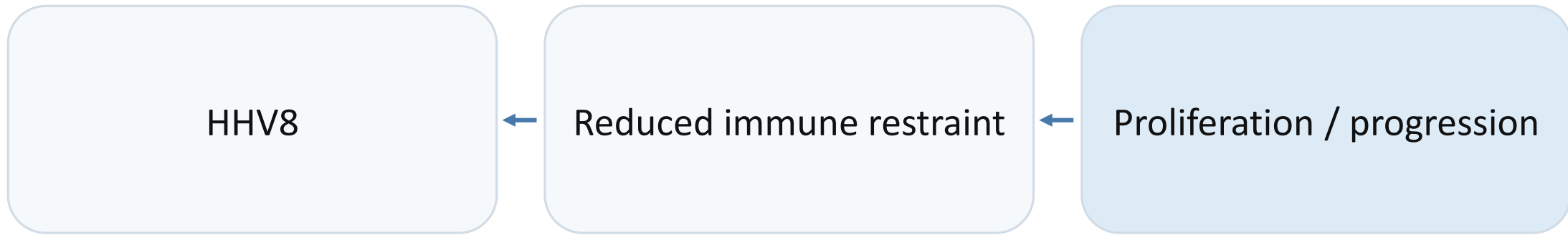
Clinical variants: Compare site and host

Classic	Skin / subcutis commonly predominate
Endemic	Nodes relatively common
Iatrogenic	Nodes, mucosa and viscera; Skin may be absent
Epidemic	Nodes and early visceral dissemination

Transplant-associated and epidemic KS may involve deep organs early.

Altered T-cell immunity is a central enabling factor

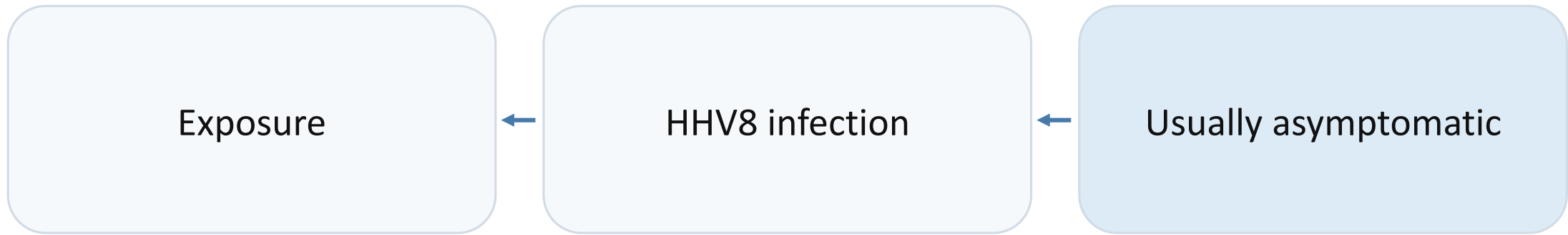
Mechanism / clinical sequence — schematic



- HHV8 infection alone does not predict clinically evident KS.
- Immune alteration can be age-related, therapy-related or HIV-associated.

HHV8 transmission: Several possible routes

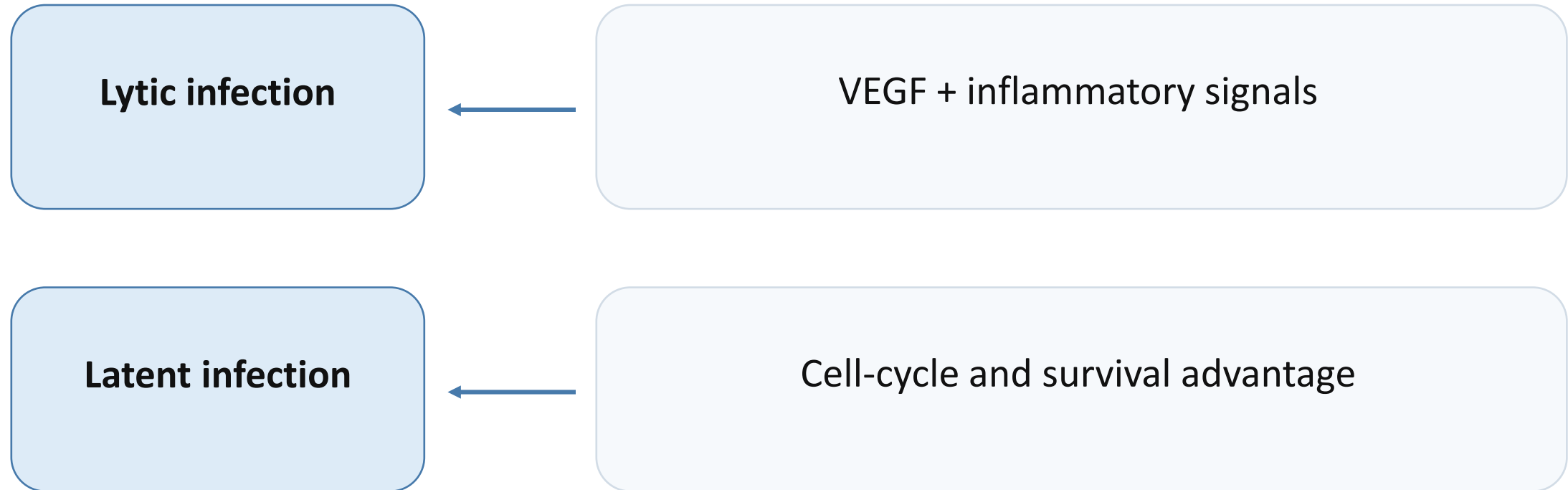
Mechanism / clinical sequence — schematic



- Sexual transmission is described in the source.
- Oral-secretory and cutaneous routes are also considered possible.

HHV8 has both lytic and latent programs

Complementary mechanisms — schematic



Latent infection changes cell-cycle control and cell survival.

Lytic viral signaling increases VEGF

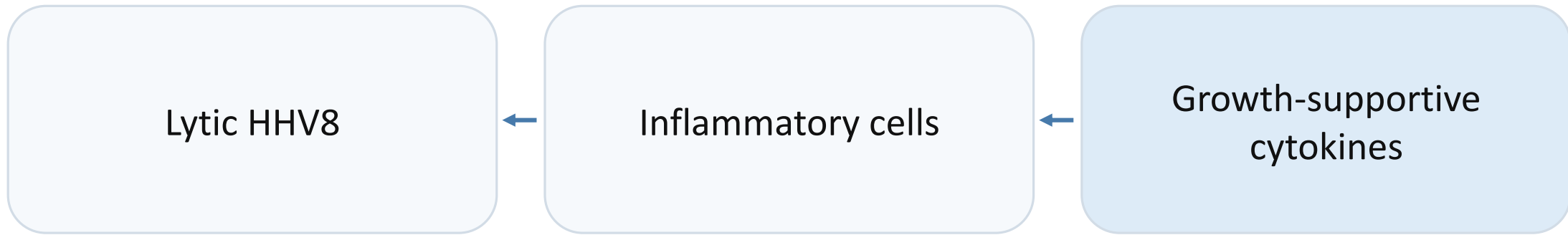
Mechanism / clinical sequence — schematic



- A virally encoded G protein promotes production of vascular endothelial growth factor (VEGF).
- VEGF stimulates endothelial proliferation.

Lytic inflammation amplifies proliferation

Mechanism / clinical sequence — schematic



- Inflammatory cells are recruited to sites of lytic viral infection.
- Their cytokines support a local proliferative environment.

Latent HHV8 perturbs cell-cycle regulation

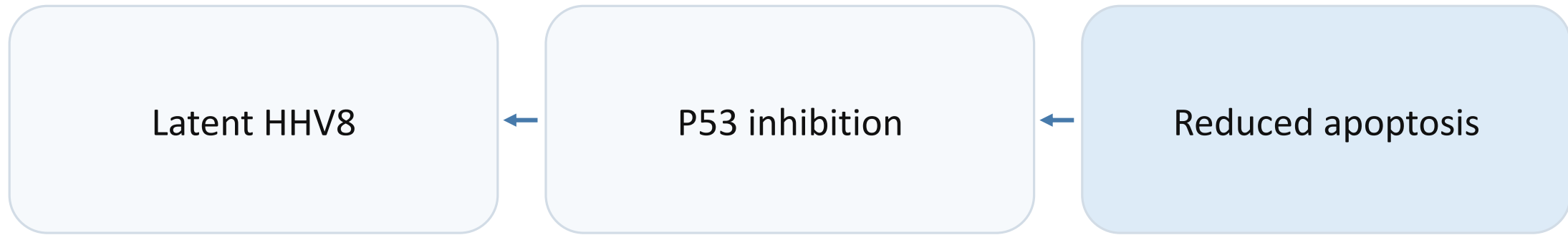
Mechanism / clinical sequence — schematic



- Latently infected cells express viral proteins that disrupt proliferation controls.
- A viral homologue of cyclin D as one mechanism.

Latent HHV8 also favors cell survival

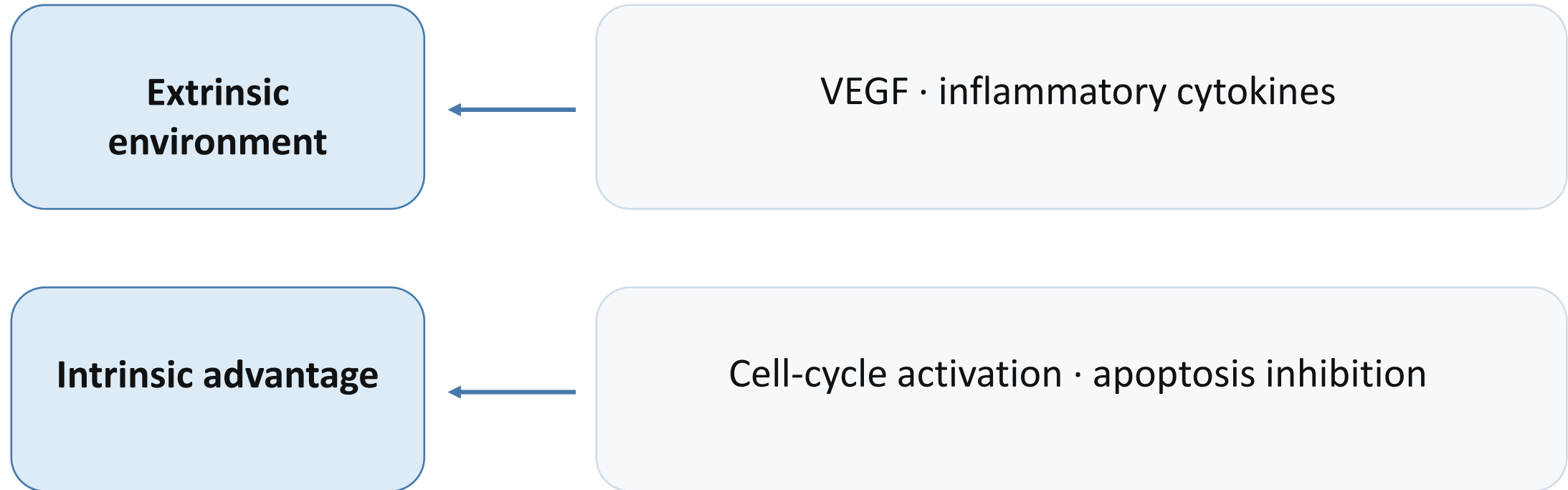
Mechanism / clinical sequence — schematic



- Viral products can inhibit the p53 pathway.
- Dampening of apoptosis favors persistence of abnormal infected cells.

Two programs converge on lesion growth

Complementary mechanisms — schematic



Together these mechanisms favor expansion of HHV8-positive vascular cells.

Infected-cell fraction expands during progression

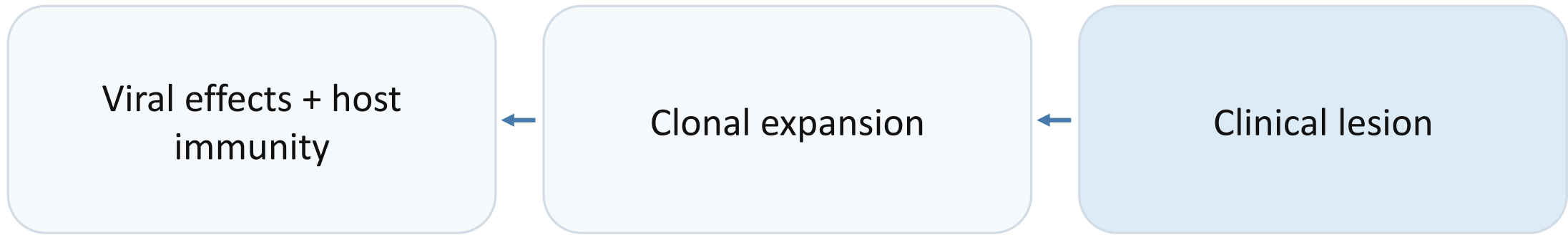
Mechanism / clinical sequence — schematic



- Early KS may contain only a minority of HHV8-infected cells.
- As lesions evolve, nearly all proliferating cells can harbor HHV8.

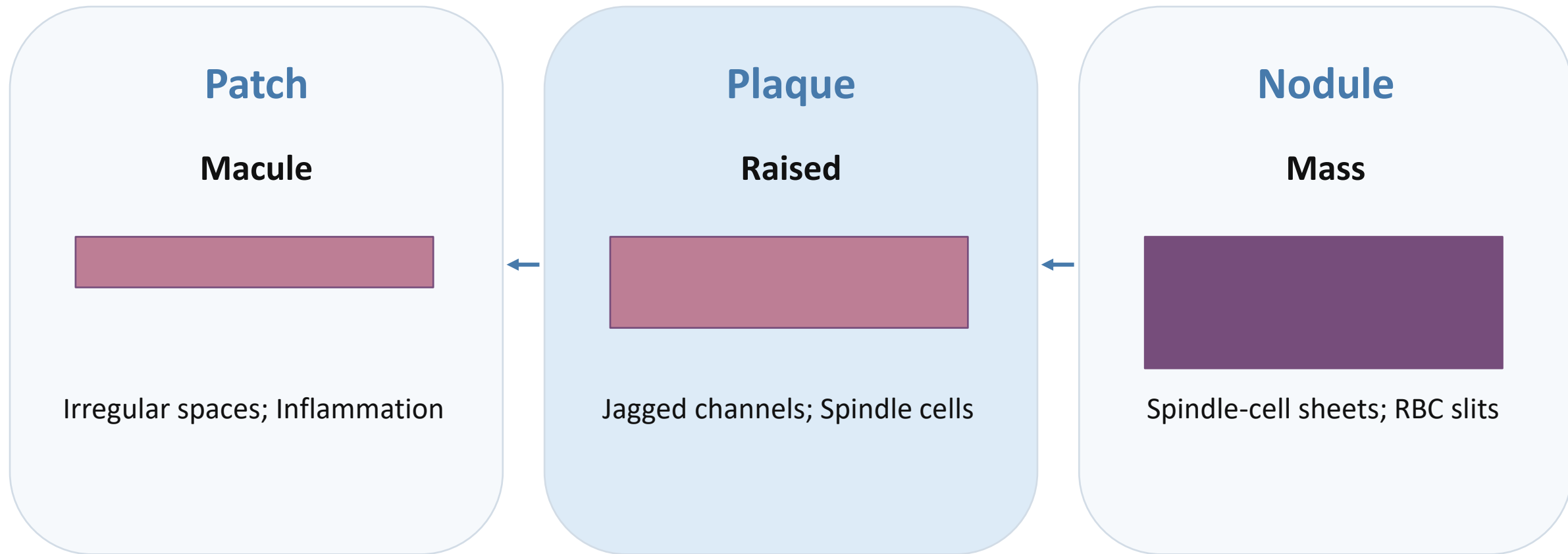
Host and tumor programs act jointly

Mechanism / clinical sequence — schematic



- HHV8 supplies proliferative and survival signals.
- Reduced T-cell control enables viral persistence and tumor expansion.

Cutaneous KS progresses through three stages



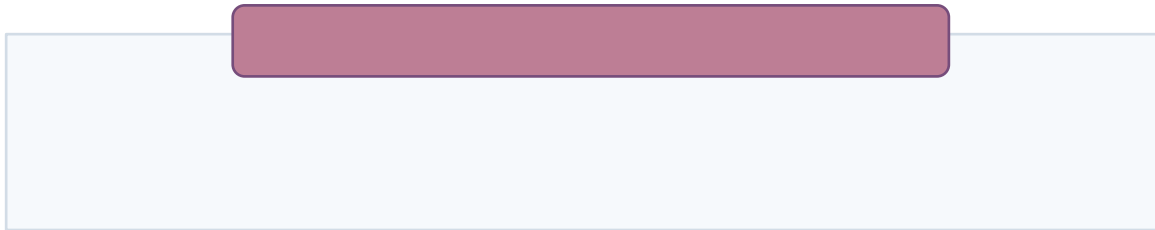
Schematic — not a photograph or histologic specimen

The sequence is characteristic but is not mandatory in every clinical variant.

Patch-stage KS: A flat red-purple lesion

Editable concept schematic — not a patient image or histologic specimen

Flat macule

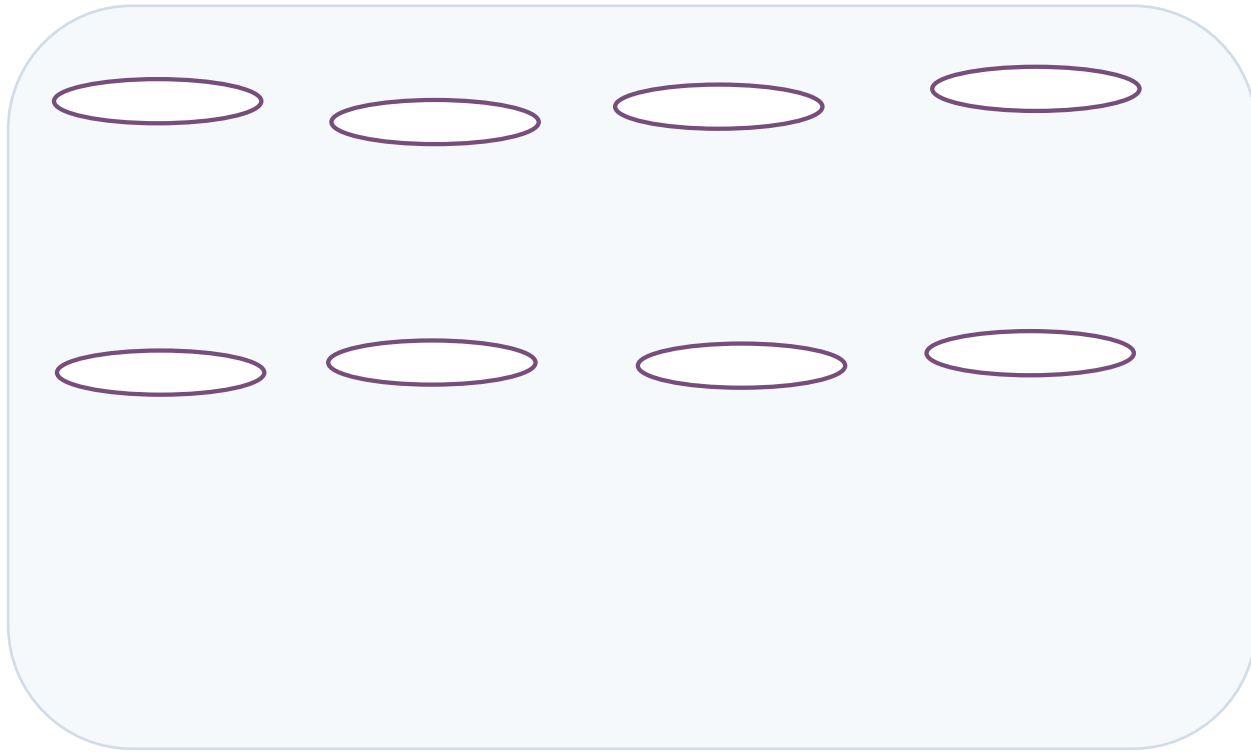


Surface elevation: Schematic

- Grossly the patch is a red-purple macule.
- The flat appearance reflects early lesional architecture.
- Clinical recognition is difficult because many benign and reactive conditions resemble this stage.

Patch-stage KS: Endothelial-lined spaces

Editable concept schematic — not a patient image or histologic specimen



Channels + inflammatory cells

- Histology demonstrates dilated, irregular endothelial-lined vascular spaces.
- Lymphocytes and plasma cells are interspersed among these channels.
- Macrophages may contain hemosiderin.

Early KS may mimic granulation tissue

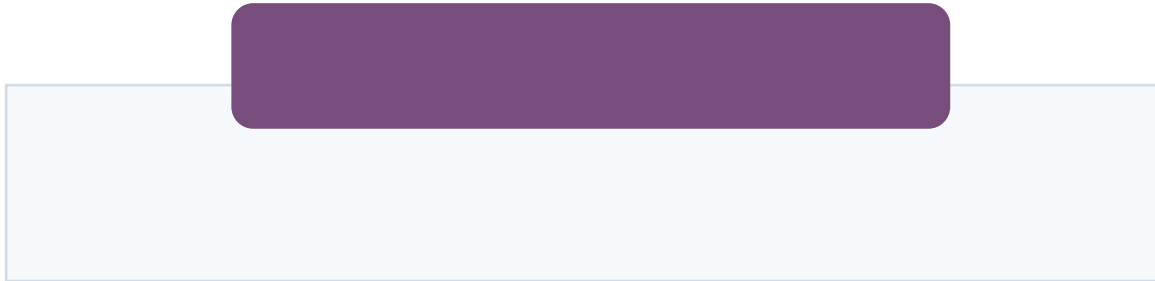
Early KS	Irregular vascular spaces + lymphocytes/plasma cells
Granulation tissue	Reactive vascular proliferation; Overlap in early KS appearance

The source specifically cautions that distinction may be difficult in early lesions.

Plaque-stage KS: Progressive elevation

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Raised plaque

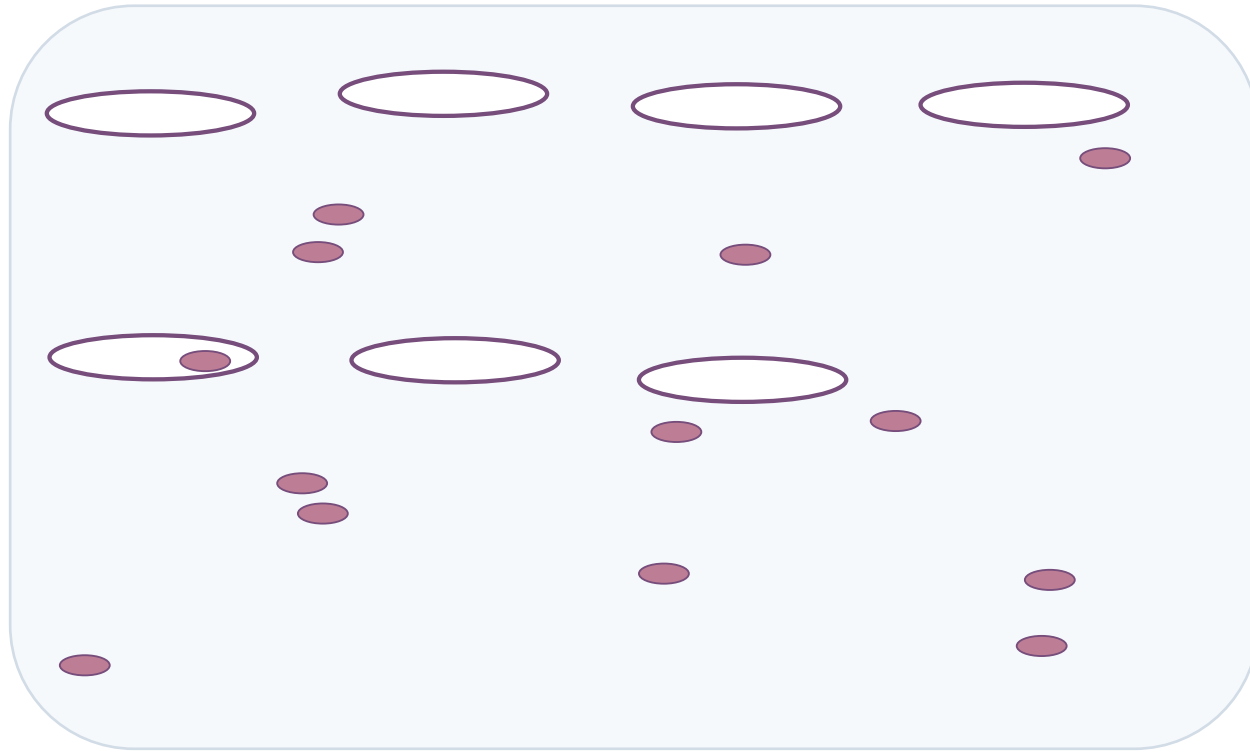


Surface elevation: Schematic

- Patches enlarge and become violaceous raised plaques.
- Dermal proliferative tissue makes the lesion more palpable.
- The histologic transition adds conspicuous spindle cells to distorted channels.

Plaque stage: Jagged vascular channels

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Jagged channels + spindle cells

- Dermal vascular channels become dilated and irregularly jagged.
- Plump spindle cells line and surround these spaces.
- Extravasated red cells and mononuclear inflammation accumulate between channels.

Nodular KS: More overt neoplasia

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Nodular mass

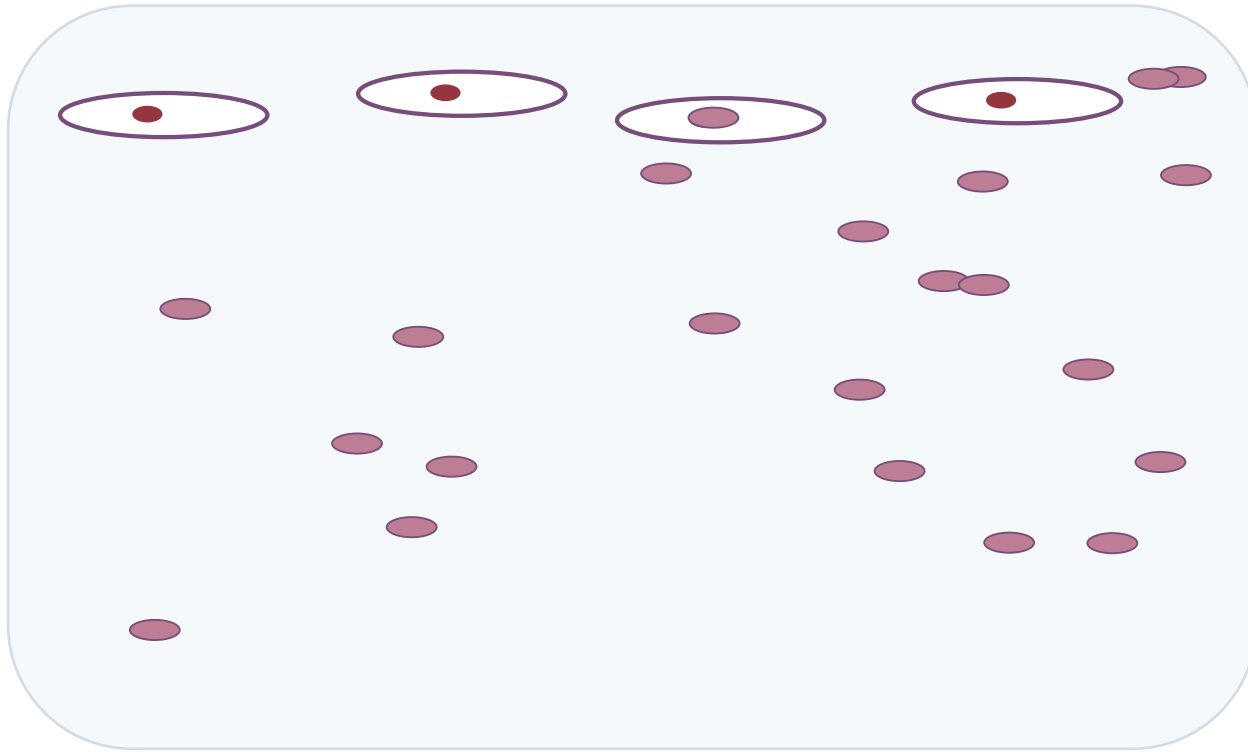


Surface elevation: Schematic

- Lesions evolve into distinct raised nodules.
- A mass of proliferating spindle cells becomes the dominant histologic component.
- Nodules can extend through dermis into subcutaneous tissue.

Nodular KS: Sheets of spindle cells

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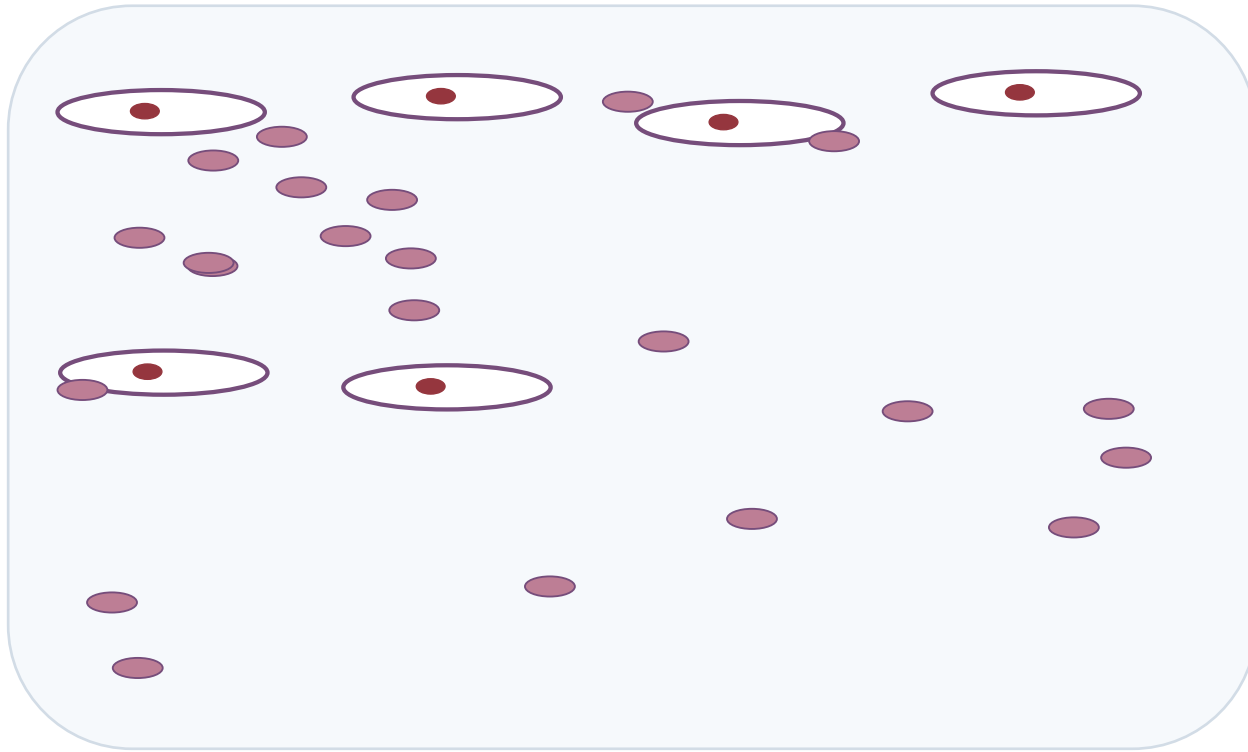


Spindle-cell sheets + small slits

- Plump spindle cells form cellular sheets.
- Small vessels and slit-like channels containing erythrocytes remain present.
- Mitoses can be common, reflecting active proliferation.

Slit-like spaces contain erythrocytes

Editable concept schematic — not a patient image or histologic specimen



Blood-containing slit-like spaces

- Small irregular slit-like spaces interrupt the spindle-cell proliferation.
- Erythrocytes within these spaces emphasize the vascular nature of the neoplasm.
- This is a hallmark of the nodular architectural pattern.

Hemorrhage and hemosiderin explain pigmentation

Mechanism / clinical sequence — schematic



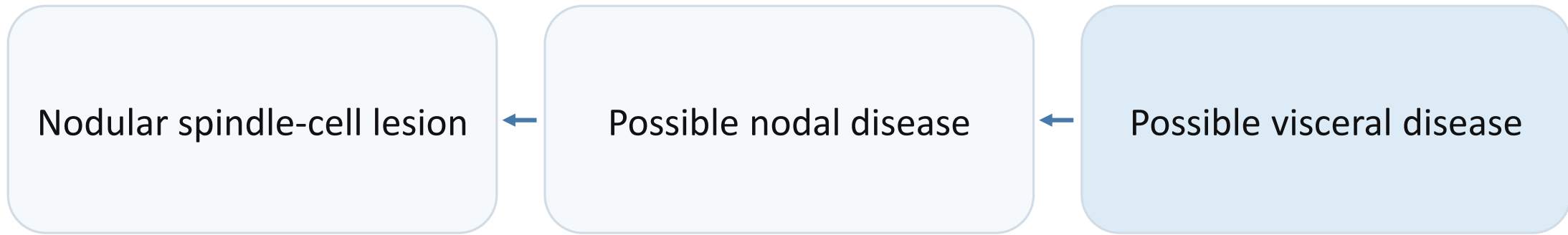
- Extravasated red cells contribute to the hemorrhagic appearance.
- Macrophages remove red-cell debris and may accumulate hemosiderin.

Eosinophilic globules in nodular KS

- Round pink cytoplasmic globules may occur within spindle-cell lesions.
- Robbins interprets these as degenerating red cells within phagolysosomes.
- The finding accompanies, rather than replaces, assessment of the overall vascular pattern.

Nodular progression may precede systemic spread

Mechanism / clinical sequence — schematic



- The nodular stage often heralds lymph-node or visceral involvement.
- This association is clinical, not proof that every nodule has disseminated.

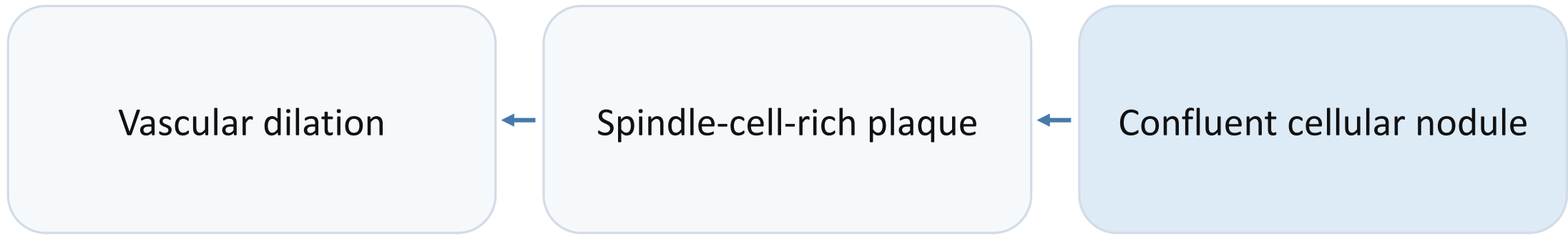
Three stages: How morphology changes

Patch	Subtle vascular spaces; Inflammatory cells
Plaque	Jagged vascular channels with plump spindle cells
Nodule	Dense spindle-cell sheets with erythrocyte-containing slits

Nodular stage becomes a dense neoplasm with slit-like spaces.

Microanatomy mirrors gross progression

Mechanism / clinical sequence — schematic



- A flat lesion is often architecturally subtle.
- Raised plaques correlate with more abundant dermal cells and channels.

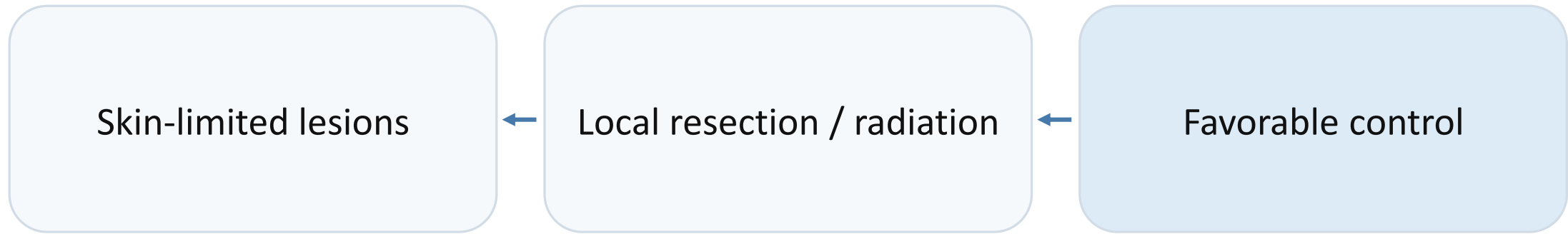
Clinical behavior depends on context and extent

Local disease	Often suitable for local measures
Disseminated disease	May need systemic and immune-directed measures

Classic, iatrogenic and epidemic settings therefore require different approaches.

Classic KS: Local treatment

Mechanism / clinical sequence — schematic



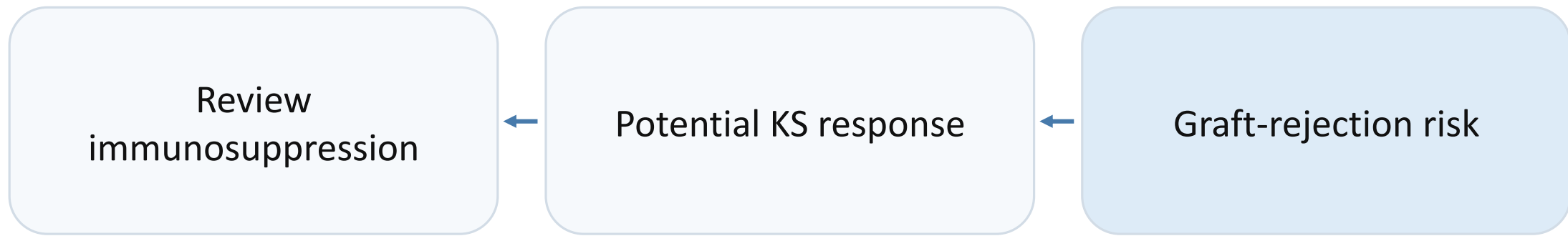
- Surgical resection is commonly adequate for limited classic cutaneous KS.
- Radiation can be used for several lesions within a restricted region.

Widespread KS often warrants systemic therapy

- The source describes chemotherapy as helpful for disseminated lesions.
- Nodal involvement changes the management context.
- Treatment choice follows disease extent rather than visible skin color alone.

Iatrogenic KS: Modify the immune environment

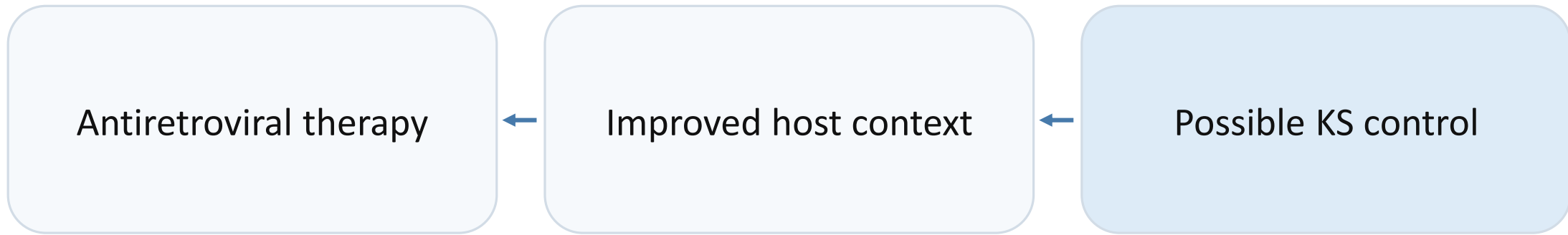
Mechanism / clinical sequence — schematic



- Reducing immunosuppression may cause KS regression.
- Local or systemic therapies may be adjuncts when necessary.

Epidemic KS: Immune restoration is important

Mechanism / clinical sequence — schematic



- Antiretroviral drugs are generally beneficial in AIDS-associated KS.
- Additional therapy may be needed depending on disease burden.

Management contrasts across clinical settings

Classic	Excision; Focal radiation when appropriate
Iatrogenic	Reduce immunosuppression if feasible; Graft risk
AIDS-associated	Antiretroviral drugs ± other therapy

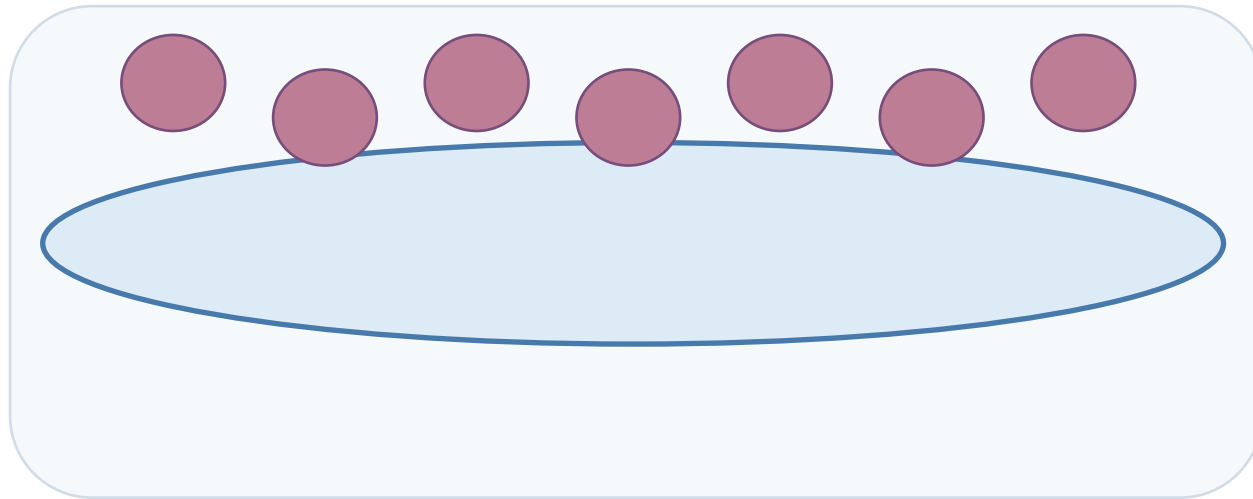
AIDS-associated disease depends strongly on antiretroviral treatment.

Hemangioendothelioma: A borderline spectrum

- Hemangioendotheliomas are vascular tumors between hemangioma and angiosarcoma in biologic behavior.
- The category is heterogeneous rather than a single uniform prognosis.
- Epithelioid hemangioendothelioma as the named example.

Epithelioid hemangioendothelioma: An adult tumor

Editable concept schematic — not a patient image or histologic specimen



Vein-associated epithelioid cells

- Epithelioid hemangioendothelioma (EHE) occurs in adults.
- Its occurrence around medium-sized and large veins.
- Its relation to veins is an anatomic clue to its vascular origin.

EHE: Epithelioid cells obscure the vascular nature

Tumor cell shape	Plump · cuboidal · epithelioid
Vascular lumina	May be difficult to identify

The name “epithelioid” describes cytomorphology, not epithelial origin.

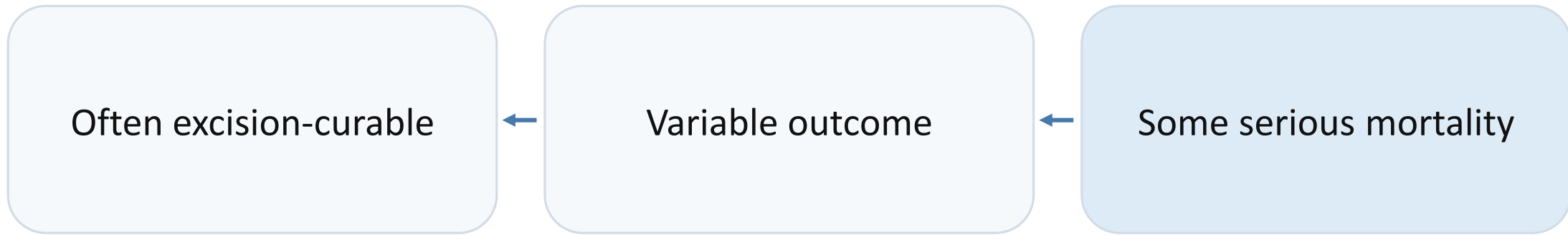
EHE: Outcome is variable

- Many EHE cases are cured by excision.
- A clinically important subset behaves aggressively.
- Approximately 25% five-year mortality; This is a textbook estimate, not individual risk prediction.

Some EHE behaves aggressively despite frequent excision cure

Why EHE remains an intermediate-grade category

Mechanism / clinical sequence — schematic



- Frequent curability by excision argues against universal high-grade malignancy.
- The reported five-year mortality argues against a uniformly benign label.

Kaposi sarcoma versus EHE

Kaposi sarcoma	HHV8-related; Patch → plaque → spindle-cell nodule
Epithelioid hemangioendothelioma	Adult tumor near veins; Cuboidal cells; Obscure channels

Shared intermediate-grade placement does not imply common etiology or appearance.

Intermediate-grade versus angiosarcoma

Intermediate-grade	Kaposi sarcoma; Hemangioendothelioma — behavior varies
Malignant	Angiosarcoma — invasive with metastatic potential

EHE and KS should not automatically inherit the same prognosis or treatment as angiosarcoma.

KS versus bacillary angiomatosis

Kaposi sarcoma	HHV8; Spindle-cell-rich vascular lesion
Bacillary angiomatosis	Bartonella; Vascular proliferation + neutrophils; Antibiotics clear infection

It is a treatable infection; KS is HHV8-associated neoplasia.

Case: Indolent distal cutaneous lesions

An older man develops multiple slowly increasing violaceous plaques on the lower legs.

Pathology interpretation

The lesions are otherwise asymptomatic and remain skin-predominant.
Most consistent Robbins clinical form: Classic Kaposi sarcoma.

Case: Systemic lesions after transplantation

A transplant recipient on T-cell suppression develops lymph-node and mucosal KS.

Pathology interpretation

There may be no characteristic cutaneous plaque.

This setting demonstrates iatrogenic KS and the graft-versus-tumor management conflict.

Case: HIV-associated disseminated KS

A patient with AIDS presents with vascular lesions and early visceral spread.

Pathology interpretation

The neoplasm is driven by HHV8, in a permissive immunodeficient host.
Antiretroviral therapy is a core treatment consideration.

Case: Epithelioid vascular tumor near a vein

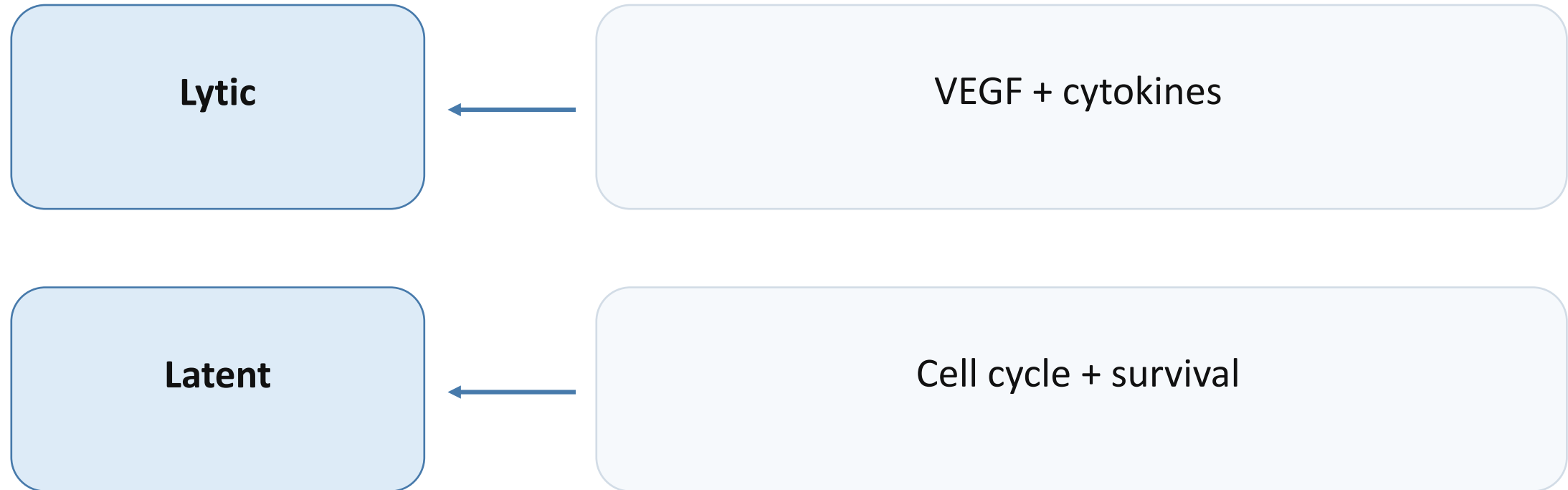
An adult has a vascular neoplasm centered near a large vein.

Pathology interpretation

Cells are plump and cuboidal; Recognizable vascular lumina are sparse.
This pattern is compatible with epithelioid hemangioendothelioma in the Robbins framework.

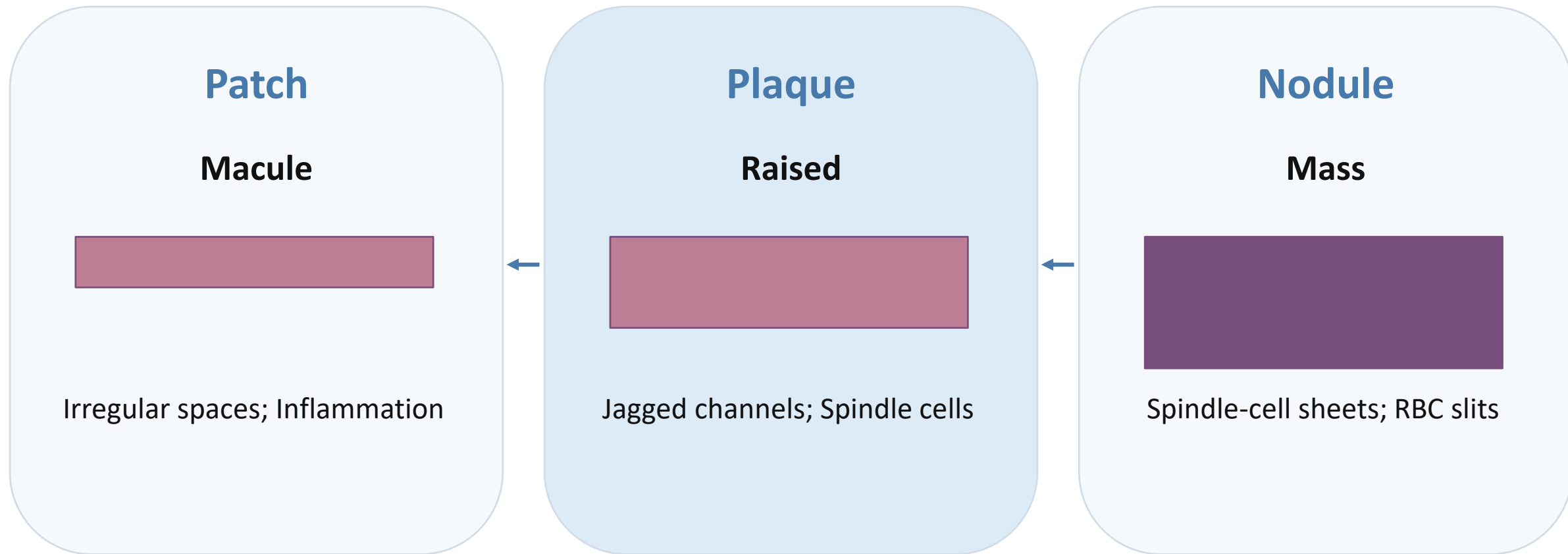
Mechanism check: Why can HHV8 drive growth?

Complementary mechanisms — schematic



Both mechanisms increase the expansion advantage of infected vascular cells.

Morphology check: Which stage is this?



Schematic — not a photograph or histologic specimen

Spindle-cell sheets with blood-containing slits: Nodule.

Integrated clinicopathologic synthesis

- Begin with the vascular-tumor classification and exclude reactive mimics.
- For KS, integrate HHV8 biology with immune setting and morphologic stage.
- For EHE, recognize epithelioid cells, venous association and variable behavior.
- Always distinguish local cutaneous disease from nodal/visceral involvement.

Principal reference and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Vascular tumors: intermediate-grade (borderline) neoplasms and immediate comparator entities.
- Course material derives from the supplied textbook extraction; no external updates or unsourced diagnostic assays have been added.
- Morphology schematics are conceptual teaching drawings, not textbook images or histology specimens.