

Von Hippel-Lindau disease

A hereditary multisystem tumor-predisposition syndrome

Molecular pathogenesis • CNS morphology • renal and adrenal associations

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Learning objectives

- Connect germline VHL inactivation to hypoxia-inducible-factor signaling.
- Recognize the characteristic cystic and microscopic architecture of hemangioblastoma.
- Relate CNS, retinal, renal, adrenal and visceral manifestations to the same syndrome.
- Apply lesion morphology and family context in short clinicopathologic cases.

A multisystem syndrome—not an isolated brain tumor

CNS

Cerebellar and other CNS hemangioblastoma

Retina

Retinal hemangioblastoma

Kidney

Cysts and clear cell RCC

Adrenal

Pheochromocytoma

Viscera

Pancreatic and hepatic cysts

The phenotype crosses anatomical specialties

- Neurosurgical: CNS hemangioblastoma; Ophthalmic: Retinal hemangioblastoma.
- Renal: Cysts and clear cell renal cell carcinoma.
- Endocrine: Pheochromocytoma; Abdominal: Pancreatic and hepatic cysts.
- One organ lesion should prompt consideration of the wider phenotype.

Population frequency and clinical recognition

- A disease frequency of approximately 1 in 30,000–40,000 individuals.
- A single lesion does not establish hereditary VHL disease; Assess the constellation of manifestations.
- Family history may aid recognition because the predisposition is autosomal dominant.
- Symptoms vary with which organ develops a clinically important lesion.

Autosomal dominant predisposition

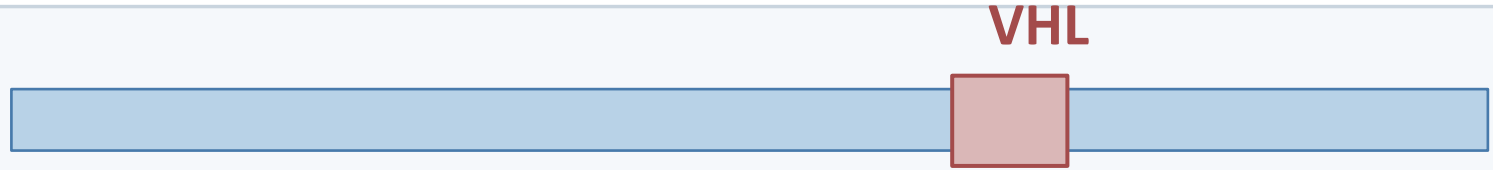
- A germline pathogenic VHL alteration can be transmitted in an autosomal dominant fashion.
- The inherited genotype creates susceptibility to tumor formation in multiple organs.
- Subsequent alterations at the cellular level permit individual lesions to emerge.
- Familial inheritance and tumor-specific genetic events operate at different levels.

The organ–lesion matrix

Site	Manifestation	Pathologic category
Cerebellum / CNS	hemangioblastoma	vascular neoplasm.
Retina	hemangioblastoma	vascular neoplasm.
Kidney	cysts / renal cell carcinoma	cystic and malignant epithelial lesions.
Adrenal medulla	pheochromocytoma	catecholamine-producing neuroendocrine tumor.
Pancreas / liver	cysts	visceral non-CNS component.

VHL is a tumor-suppressor gene

Chromosome 3p25.3



- VHL encodes an element of the ubiquitin ligase machinery.
- The gene is a tumor suppressor, rather than a growth-factor gene.
- Inactivation deregulates HIF protein turnover.

The distinction between gene and protein

- VHL denotes the gene at 3p25.3; VHL protein acts in the oxygen-response machinery.
- The protein acts with other complex members to target defined substrates for degradation.
- A loss-of-function mutation affects a cellular control system, not simply an anatomic organ.
- Accurate terminology avoids conflating the inherited syndrome with individual tumors.

Hereditary versus sporadic VHL inactivation

Hereditary disease

Germline VHL predisposition

Multiple organs may be at risk

Family context matters

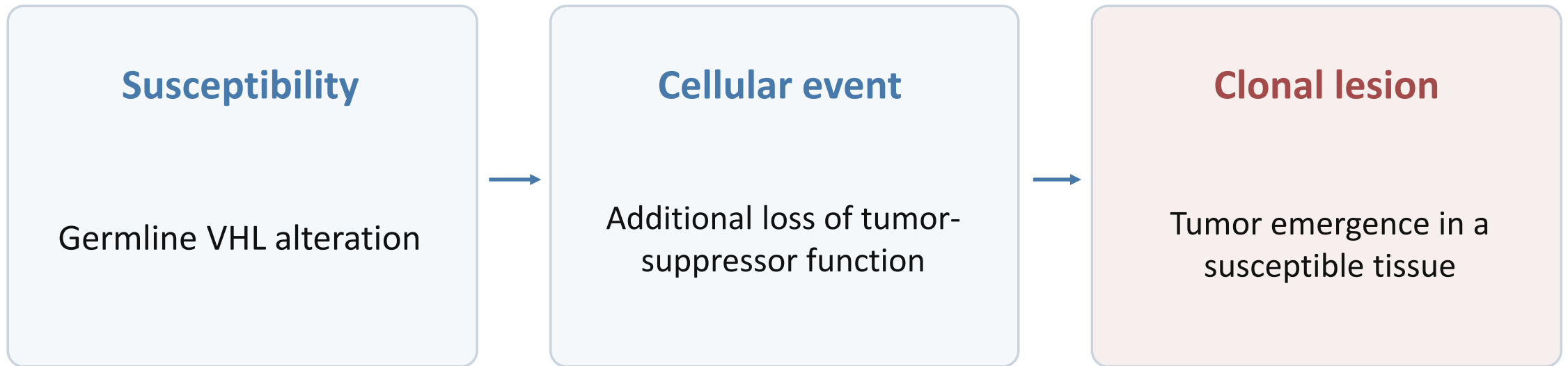
Sporadic tumor

Acquired VHL alteration in tumor

Localized clonal alteration

Tumor change alone not syndromic proof

Tumor-suppressor logic in a susceptible cell



General tumor-suppressor framework; Not a molecular diagnostic criterion

The normal role of the VHL complex

- VHL participates in a ubiquitin ligase that identifies hydroxylated HIF- α for degradation.
- Ubiquitin tagging directs the substrate toward proteasomal destruction.
- Under adequate oxygen, this pathway restrains unnecessary hypoxia-response signaling.
- VHL is therefore a negative regulator of the HIF transcriptional program.

Oxygen availability determines HIF fate

Normoxia + VHL intact

HIF- α hydroxylation → degradation

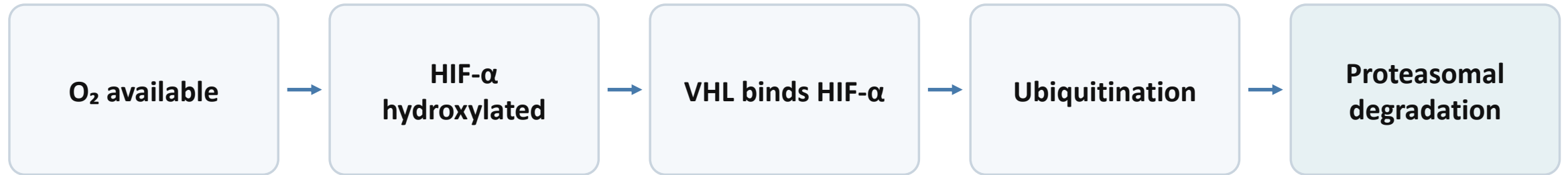
Hypoxia + VHL intact

HIF- α stabilization → target genes

Normoxia + VHL absent

HIF- α stabilization → inappropriate signaling

Normoxia: Controlled HIF degradation



Physiologic feedback: Signal is suppressed in normoxia.

Hypoxia: HIF is stabilized adaptively



Physiologic adaptation: The pathway responds to genuinely low oxygen.

VHL loss creates “pseudohypoxia”



Pseudohypoxic signaling: The response persists despite adequate oxygen.

Three oxygen-response states compared

Normoxia + VHL intact

HIF- α hydroxylation → degradation

Hypoxia + VHL intact

HIF- α stabilization → target genes

Normoxia + VHL absent

HIF- α stabilization → inappropriate signaling

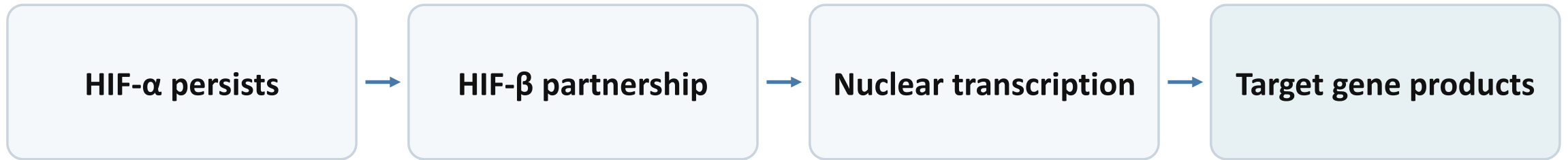
Prolyl hydroxylation is the oxygen-sensitive step

- HIF prolyl hydroxylase requires oxygen to modify HIF- α .
- VHL recognition follows this molecular modification rather than detecting O₂ directly.
- When hydroxylation fails, HIF- α is no longer efficiently targeted by the VHL complex.
- This explains how both hypoxia and VHL loss converge on HIF stabilization.

Ubiquitination links recognition to destruction

- Ubiquitin chains are covalently attached to recognized protein substrates.
- The proteasome degrades tagged HIF- α , limiting its nuclear signaling.
- Defective VHL uncouples substrate recognition from destruction.
- The molecular defect acts upstream of growth-factor production.

HIF acts in the nucleus as a transcription factor



The transcriptional program alters angiogenesis, proliferation and metabolism.

HIF target genes have different biological outputs

VEGF

Angiogenesis

Erythropoietin

Erythropoiesis

PDGF / IGF-1

Growth signaling

GLUT1 / glycolysis

Metabolic adaptation

VEGF explains prominent tumor vascularity

- VHL pathway disruption increases HIF-driven VEGF expression.
- VEGF promotes a dense capillary network and excessive vessel growth.
- Hemangioblastomas are exceptionally vascular tumors.
- The mechanism provides a direct link between genotype and microscopic architecture.

Erythropoietin links tumor signaling to blood counts

- HIF-dependent erythropoietin expression can increase red-cell production.
- Polycythemia in about 10% of patients with hemangioblastoma.
- An elevated hematocrit can therefore be paraneoplastic rather than an independent marrow disease.
- Polycythemia is possible, not required, for a hemangioblastoma diagnosis.

Growth signaling contributes alongside angiogenesis

VEGF

Angiogenesis

Erythropoietin

Erythropoiesis

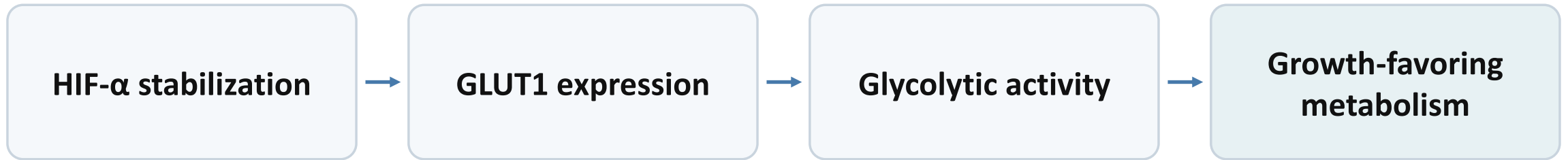
PDGF / IGF-1

Growth signaling

GLUT1 / glycolysis

Metabolic adaptation

HIF signaling reshapes cellular metabolism



This is a regulatory mechanism; No fabricated quantitative flux is shown.

From VHL loss to recognizable morphology

- VHL dysfunction → HIF stabilization → VEGF and growth-program expression.
- VEGF-related angiogenesis → numerous thin-walled vessels in hemangioblastoma.
- Growth and metabolic signaling → support expansion of the neoplastic stromal component.
- The microscopic pattern expresses a molecular pathway in tissue form.

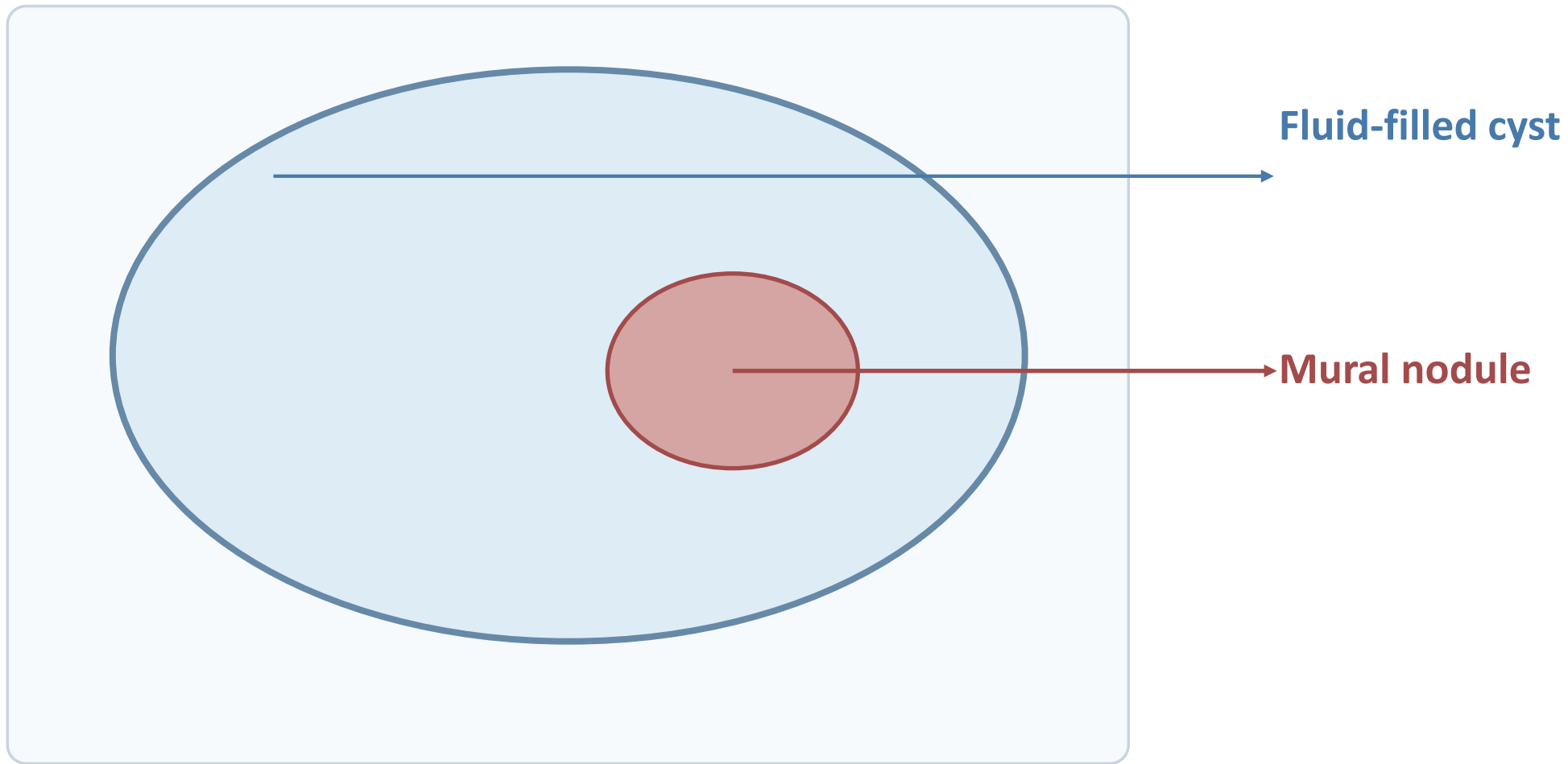
Hemangioblastoma: The characteristic CNS tumor

- Hemangioblastoma is a highly vascular neoplasm associated with VHL disease.
- It commonly affects the cerebellum and retina but can occur elsewhere within the CNS.
- Its tissue architecture combines many vessels with neoplastic stromal cells.
- The lesion is not simply a blood-vessel malformation.

Where hemangioblastomas arise

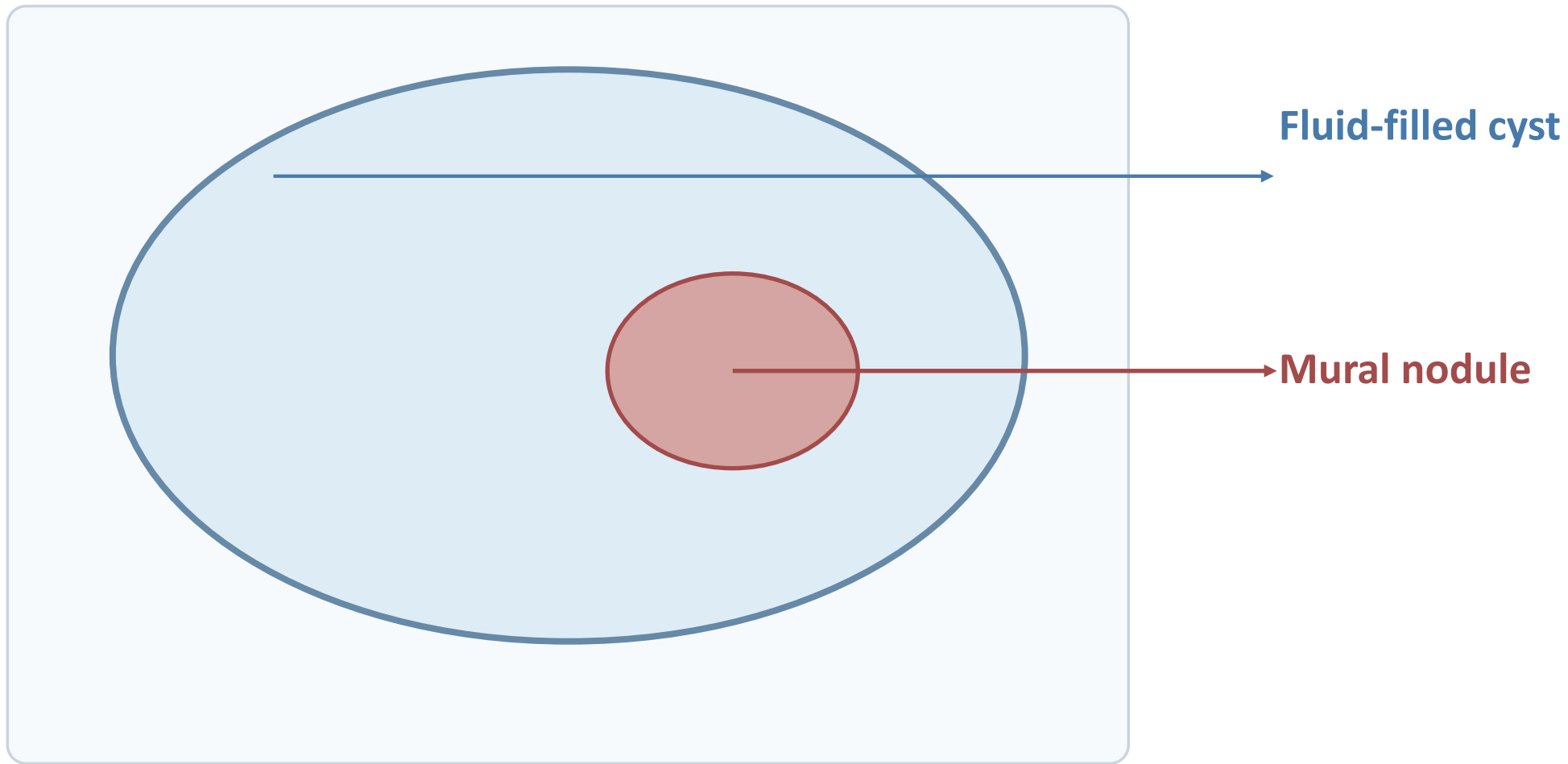
- The cerebellum and retina as common locations.
- Other CNS sites can also be involved.
- A posterior fossa lesion may produce substantial morbidity through local compression.
- Anatomic location matters even when cellular malignancy is not the central issue.

Gross pattern: A cyst with a mural nodule



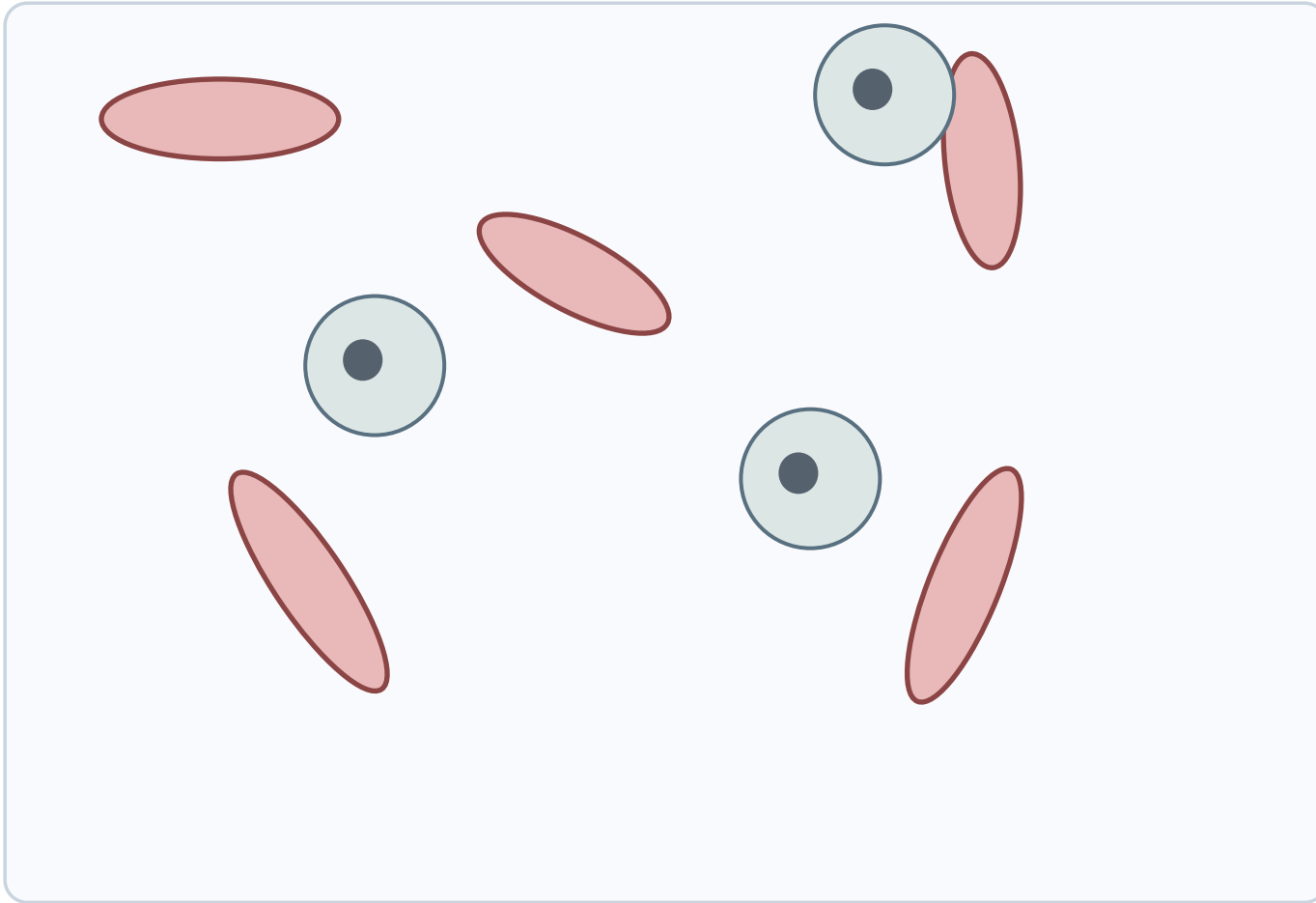
Native schematic • not a clinical image

The mural nodule is the tissue to characterize



Native schematic • not a clinical image

Microscopy: A capillary-rich neoplasm



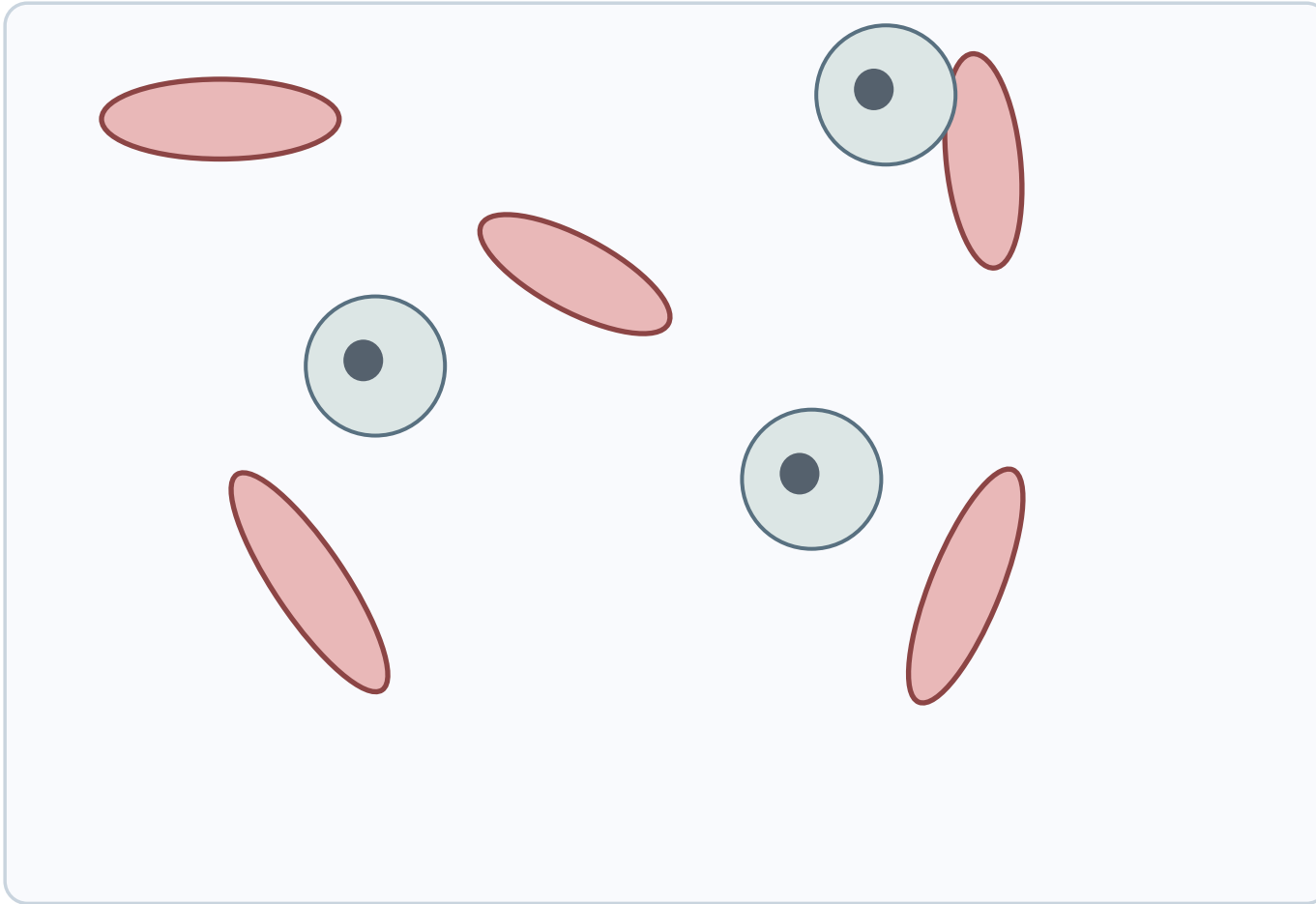
Schematic cellular fields

Pink narrow ovals = capillary lumina

Pale larger circles = stromal cells

Not a histology image; Spatial abstraction only

Stromal cells are the neoplastic component



Schematic cellular fields

Pink narrow ovals = capillary lumina

Pale larger circles = stromal cells

Not a histology image; Spatial abstraction only

Why hemangioblastoma stromal cells appear vacuolated

- The tumor stromal cells contain abundant intracellular lipid.
- Lipid-rich cytoplasm produces a characteristic vacuolated or clear appearance.
- Clear cytoplasm alone is nonspecific across different tumor types.
- Architecture and marker pattern help resolve the differential.

Inhibin is a useful diagnostic marker

Stromal tumor cells

Inhibin (diagnostically useful)

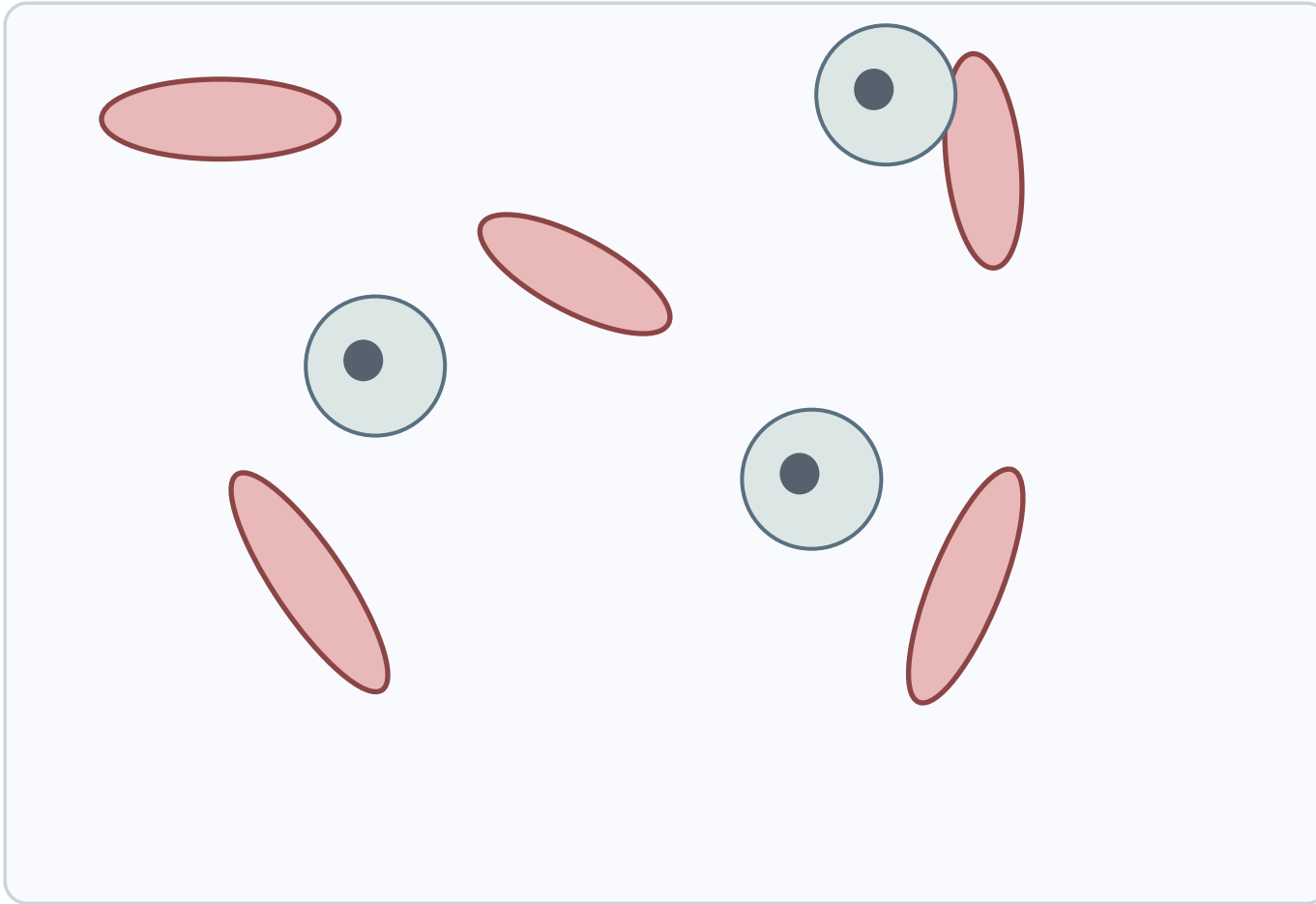
Stromal tumor cells

VEGF expression

Stromal tumor cells

Erythropoietin expression

Vessels and stromal cells perform different roles



Schematic cellular fields

Pink narrow ovals = capillary lumina

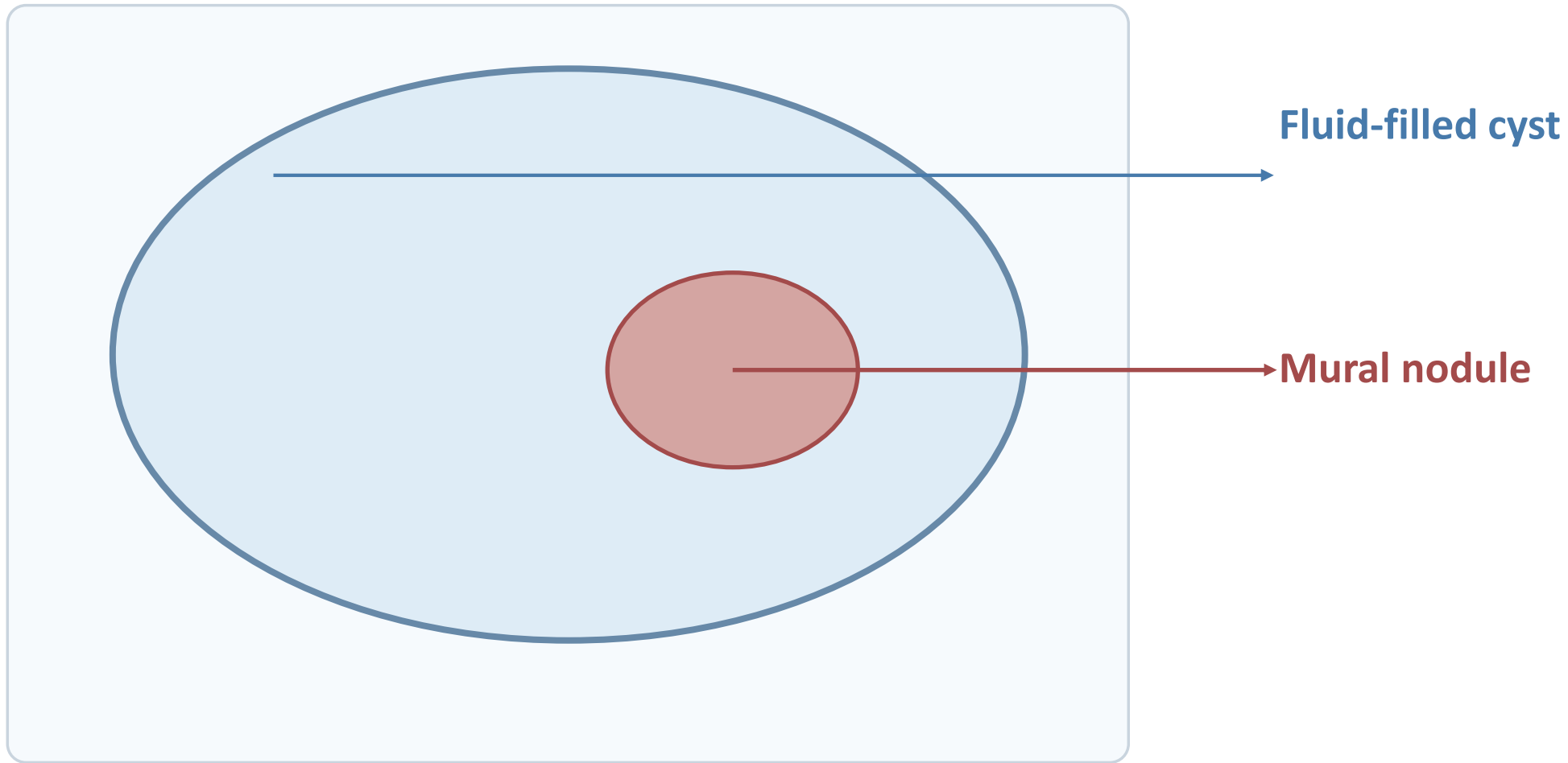
Pale larger circles = stromal cells

Not a histology image; Spatial abstraction only

A clinical correlate: Tumor-associated polycythemia

- Erythropoietin synthesis by hemangioblastoma stromal cells may increase erythropoiesis.
- Polycythemia is observed in a minority, not in all affected patients.
- Mechanism: Tumor-derived EPO → bone marrow red-cell production → elevated red-cell mass.
- This shows that a CNS tumor can cause systemic hematologic effects.

Why a low-grade-appearing mass can cause serious harm



Native schematic • not a clinical image

Retinal hemangioblastoma broadens the phenotype

- Retinal vascular lesions are among the common sites described in VHL disease.
- Their detection ties an ophthalmic manifestation to a systemic genetic disorder.
- Retinal and cerebellar lesions are anatomically different expressions of the same predisposition.
- Laser therapy for retinal hemangioblastomas as an organ-directed approach.

Therapy is directed at clinically significant lesions

Cerebellar hemangioblastoma

Can produce posterior fossa mass effect

Robbins: Resection for symptomatic tumor

Anatomically targeted treatment

Retinal hemangioblastoma

Involves retinal vasculature

Robbins: Laser-directed therapy

Anatomically targeted treatment

Renal involvement includes cysts and carcinomas

- VHL syndrome can produce both renal cysts and renal cell carcinomas.
- Cystic disease does not equate automatically with carcinoma.
- Renal tumors often arise bilaterally and at multiple sites in hereditary cases.
- Renal morphology must distinguish simple cystic involvement from epithelial malignancy.

The hereditary renal cancer pattern

Hereditary/VHL setting

Bilateral or multifocal lesions

Renal cysts may coexist

Inherited predisposition

Typical sporadic setting

Often solitary, unilateral

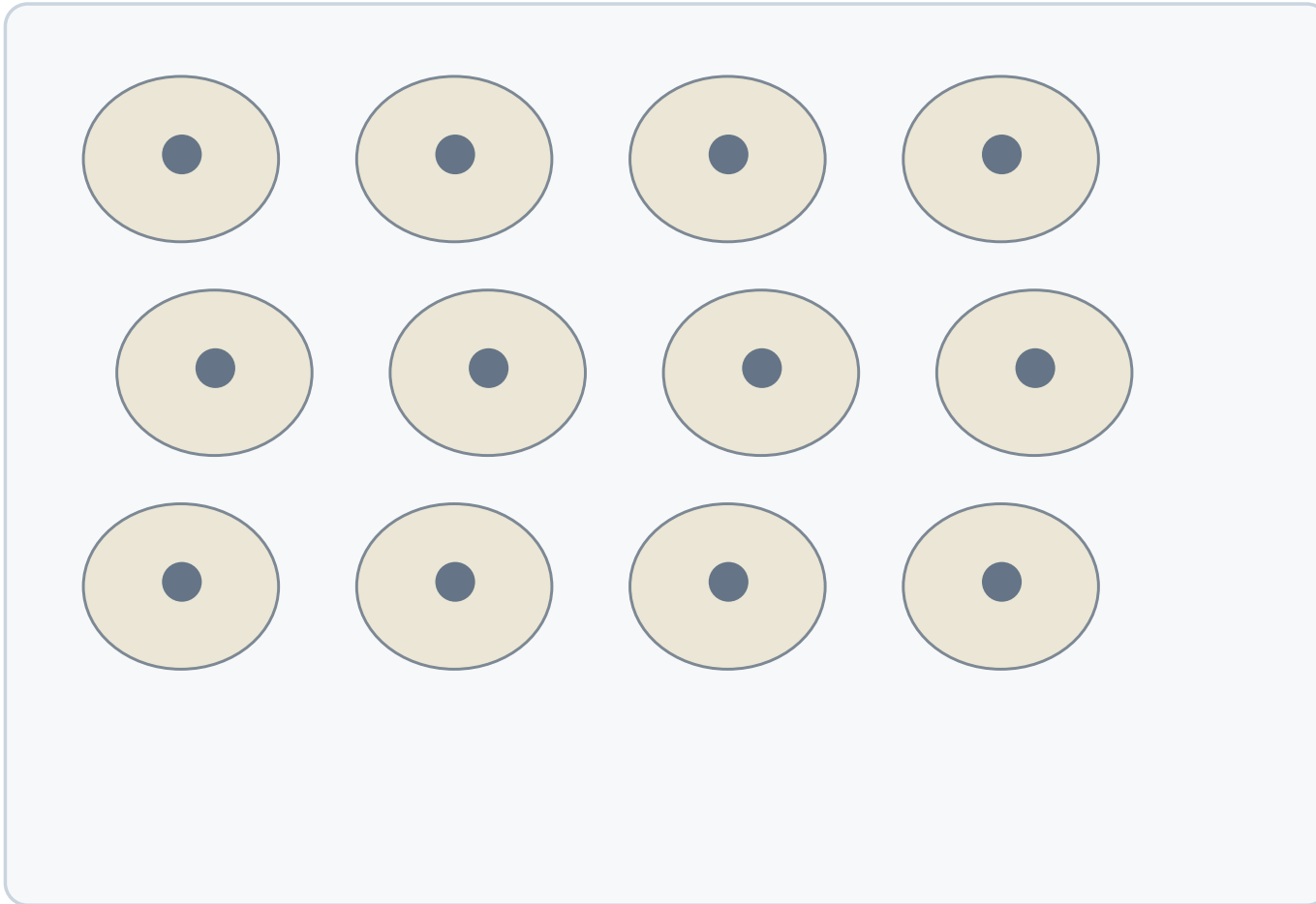
No necessary syndromic cystic pattern

Somatic evolution

Renal cell carcinoma: Gross features

- Clear cell RCC often appears as a sharply demarcated, bright yellow-gray-white mass.
- Intracellular lipid accumulation contributes to the yellow color.
- Hemorrhage and necrosis commonly create heterogeneous cut surfaces.
- This gross pattern is for clear cell RCC generally, not uniquely for VHL.

Renal cell carcinoma: Microscopic growth patterns



Editable architecture schematic
—not a stained specimen

→ **Nests of pale cells**

What makes renal carcinoma cells appear “clear”?

- Lipids and glycogen accumulate in the cytoplasm of clear cell RCC cells.
- The resulting pale appearance is a biochemical feature, not absence of cytoplasm.
- A delicate vascular network often complements this clear-cell architecture.
- The appearance differs in context from lipid-rich stromal cells of hemangioblastoma.

VHL loss is central in sporadic clear cell RCC

- Chromosome 3p loss affecting the VHL locus in the great majority of clear cell RCCs.
- The second allele may be disrupted by mutation or epigenetic silencing.
- Consequent HIF stabilization enhances angiogenesis and growth signals.
- Syndromic and sporadic tumors converge mechanistically despite different clinical contexts.

Clear cell and papillary renal carcinomas differ

Clear cell RCC

VHL/3p pathway commonly altered

Nests and clear cytoplasm

Delicate branching vasculature

Papillary RCC

MET-related pathway in hereditary form

Papillary/tubulopapillary architecture

Papillary cores; Foam cells may occur

Renal carcinoma may present indirectly

- Hematuria may be intermittent or microscopic.
- Pain, palpable mass and hematuria together are uncommon as a classic triad.
- Some tumors are detected on imaging performed for unrelated reasons.
- Systemic symptoms can obscure the renal site of origin.

Adrenal involvement: Pheochromocytoma

- Pheochromocytoma is a neoplasm of adrenal medullary chromaffin cells.
- The cells produce catecholamines and may induce paroxysmal or sustained hypertension.
- VHL is one of several hereditary syndromes associated with pheochromocytoma.
- The endocrine phenotype complements CNS and renal tumor predisposition.

Pheochromocytoma and the HIF pathway

VHL-associated

VHL loss-of-function

Pseudohypoxia / HIF stabilization

May coexist with RCC/HB

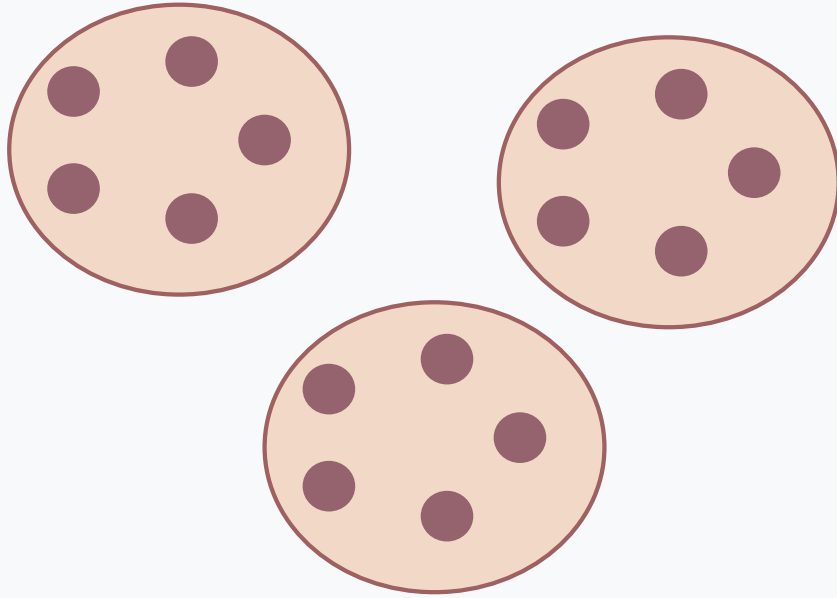
MEN2-associated

RET oncogene activation

Growth-factor receptor pathway

Associated with medullary thyroid cancer

Pheochromocytoma has a nested architecture



Zellballen nests

Chief-cell groups

Surrounding sustentacular cells

Intervening rich vasculature

Native schematic; Not a micrograph

Pheochromocytoma: Marker compartmentalization

Chief cells

Chromogranin / synaptophysin

Sustentacular cells

S-100

Architecture

Zellballen nests

Catecholamine release determines symptoms

- Catecholamine excess can cause hypertension and tachycardia.
- Paroxysms may include palpitations, headache, sweating and tremor.
- Symptoms reflect hormone secretion rather than direct mass effect alone.
- A familial syndrome can thus be recognized through an endocrine crisis phenotype.

The biochemical diagnostic principle

Biochemical evidence

Plasma or urinary metanephrines

Documents catecholamine excess

Pheochromocytoma-oriented test

Syndrome evaluation

Consider associated organ lesions

Inherited context and VHL status

Not a substitute for tumor evaluation

Visceral cystic lesions are part of the spectrum

- VHL-associated cysts may involve the pancreas, liver and kidneys.
- Congenital pancreatic cysts in this syndrome.
- Cysts coexist with neoplastic manifestations but are not equivalent to malignancy.
- A multiorgan cystic pattern can be a clue when interpreted with characteristic tumors.

Cyst and neoplasm are different categories

Cystic hemangioblastoma

Solid vascular mural nodule

Cerebellum / CNS

Associated with a neoplasm

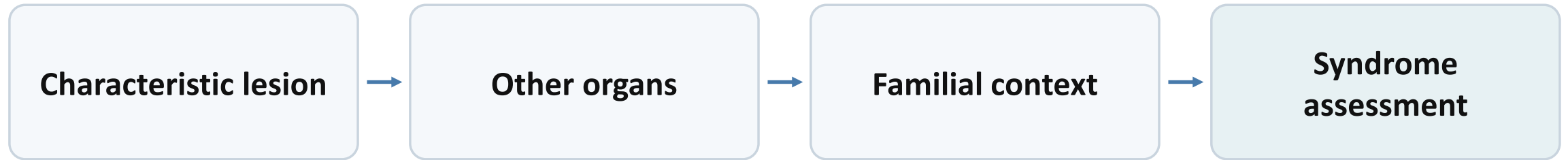
Visceral organ cyst

May be a non-neoplastic cyst

Kidney, pancreas, liver

Must be classified by site and lining

A pattern-based approach to possible VHL disease



Genotype–phenotype interpretation requires care

Hereditary disease

Germline VHL predisposition

Multiple organs may be at risk

Family context matters

Sporadic tumor

Acquired VHL alteration in tumor

Localized clonal alteration

Tumor change alone not syndromic proof

Case 1: Cystic posterior fossa mass

A patient presents with a cerebellar cystic lesion containing a small solid mural nodule.

Histology shows prominent thin-walled capillaries and lipid-rich vacuolated stromal cells.

Question: What is the most likely lesion, and what wider phenotype deserves consideration?

Case 1: Morphology identifies the lesion

The cyst-plus-mural-nodule pattern and vascular stromal-cell histology support hemangioblastoma.

Consider VHL disease when this tumor is placed in a broader patient or family context.

Additional concern: Retinal lesions, renal neoplasia, pheochromocytoma and visceral cysts.

Do not diagnose inherited VHL solely from one morphologically typical tumor.

Case 2: Multiple renal masses

A patient has bilateral renal masses and several renal cysts.

A resected mass shows clear polygonal cells arranged in nests with delicate vessels.

Question: Which carcinoma subtype fits, and what syndrome-level association is relevant?

Case 2: Apply renal and genetic morphology

Clear cytoplasm, nested growth and thin branching vessels support clear cell RCC.

Bilateral multifocal tumors with renal cysts raise suspicion for hereditary predisposition including VHL.

The same VHL pathway also occurs in sporadic clear cell RCC.

Molecular alteration in a renal tumor and inherited syndrome diagnosis are not interchangeable.

Case 3: Endocrine lesion in multisystem disease

A patient with a family history of VHL disease develops episodic hypertension and palpitations.

An adrenal medullary tumor shows Zellballen nests of chromaffin cells.

Question: Identify the tumor and explain how it fits the VHL phenotype.

Case 3: Distinguish the endocrine component

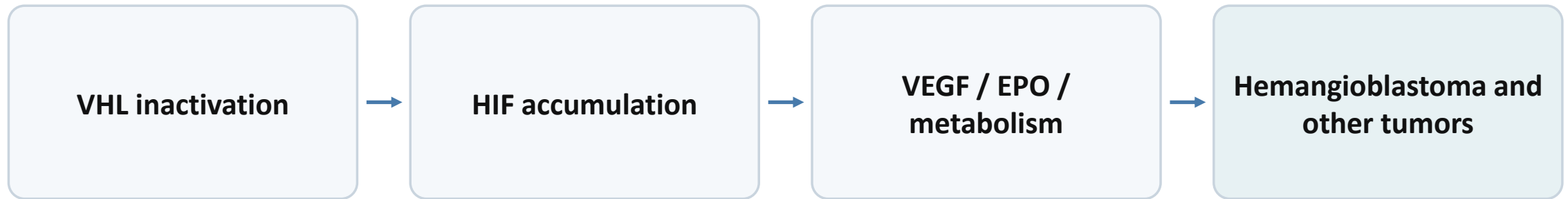
The adrenal lesion is a pheochromocytoma; Catecholamine production explains symptoms.

VHL loss may favor HIF stabilization and pseudohypoxic biology.

Evaluate the lesion in the context of other VHL-associated manifestations.

It is a distinct neoplasm from hemangioblastoma despite the shared syndrome.

Integrated pathology synthesis



From inherited predisposition to gene regulation, tissue morphology and multisystem clinical disease.

Four diagnostic distinctions worth retaining

- VHL syndrome ≠ any sporadic tumor with a VHL mutation.
- Hemangioblastoma stromal cell ≠ the endothelial lining of its capillaries.
- Cystic hemangioblastoma ≠ pancreatic or renal congenital cyst.
- Inhibin in hemangioblastoma ≠ the neuroendocrine marker profile of pheochromocytoma.

Summary: Mechanism, morphology, phenotype

- Molecular: VHL tumor-suppressor dysfunction stabilizes HIF under inappropriate oxygen conditions.
- CNS: Hemangioblastoma often forms a mural nodule and cyst, with capillaries plus vacuolated stromal cells.
- Systemic: Renal clear cell carcinoma, pheochromocytoma and pancreatic/hepatic/renal cysts are important associations.
- Clinical reasoning: Integrate family context, organ distribution and lesion-specific morphology.

Source material and image limitations

PRIMARY TEXTBOOK

Robbins, Cotran & Kumar: Pathologic Basis of Disease

CORE SOURCE

Chapter 28: Von Hippel-Lindau Disease

RELATED SOURCE SECTIONS

Chapter 7: VHL–HIF signaling • Chapter 20: Renal cell carcinoma • Chapter 24: Pheochromocytoma