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Kidney Tumors

Grading

Nuclear grading is primarily intended for **clear cell** and **papillary renal cell** carcinoma, but it can be also useful in deciding if low-grade diagnoses are appropriate for certain tumors.

WHO/ISUP grading system for clear cell and papillary renal cell carcinomas

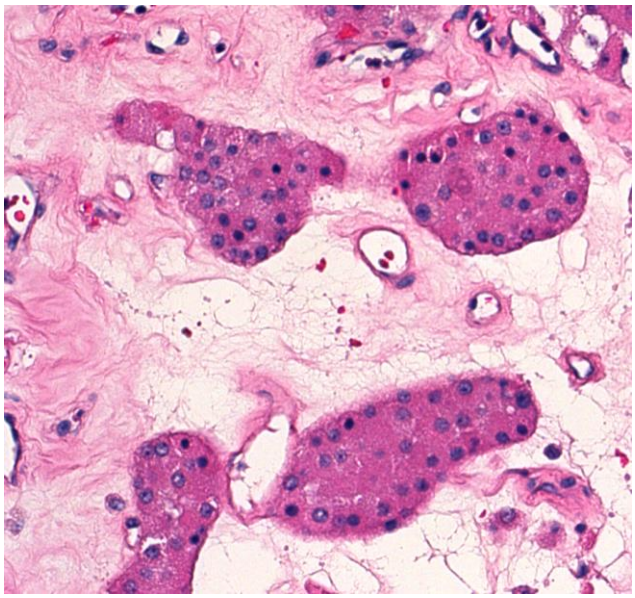
Grade	Findings
1	Nucleoli are absent or inconspicuous at 400x magnification
2	Nucleoli are conspicuous and eosinophilic at 400x and visible but not prominent at 100x
3	Nucleoli are conspicuous and eosinophilic at 100x
4	Extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or Sarcomatoid

Eosinophilic

Generally, the best stain to support renal origin is PAX8

	CK7	CK20	CD117	CA-IX	Vimentin	Cathepsin K	AMACR	SDH	FH
Oncocytoma	-	-	+	-	-	-	-	+	+
Chromophobe RCC	+	-	+	-	-	-	-	+	+
Papillary RCC	+/-	-	-	+/-	+	-	+	+	+
FH-deficient RCC	-	-		-/+		-		+	- !
SDH-deficient RCC	-	-	-	-	-	-	+/-	- !	+
Acquired Cystic disease-associated RCC	-/+	-	-		-/+	-	+	+	+
Clear Cell RCC	-		-	++	+	-	-	+	+
ESC-RCC	-	+!	-	-	+	+	-/+	+	+
Eosinophilic Vacuolated Tumor	-/+	-	+		-	+	+/-	+	+
Low-grade Oncocytic Tumor	+	-	-			-		+	+
Thyroid-like RCC	+	-/+				-	-	+	+
Angiomyolipoma, epithelioid	-	-	-	-	+	+	-	+	+

Oncocytoma



Benign and asymptomatic
Abundant eosinophilic, mitochondria-rich cytoplasm.
Round, regular nuclei throughout.

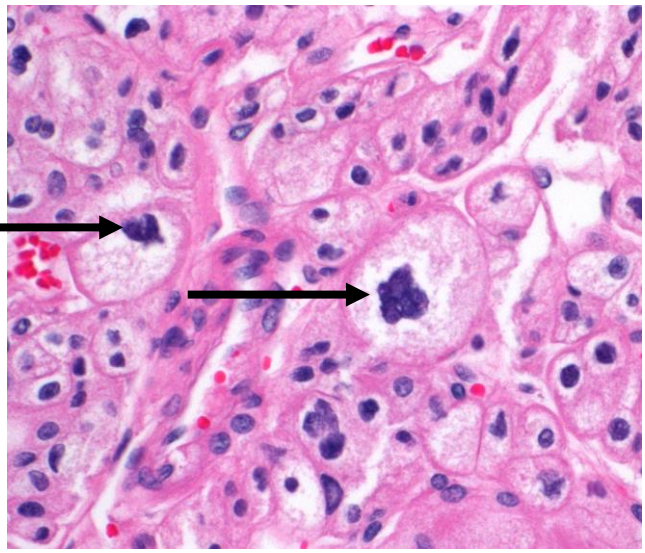
Tight nests and alveoli surrounded by myxoid or hyalinized hypocellular stroma.
Some solid areas acceptable.

Grossly: **Circumscribed**, mahogany brown. Central scar.

Allowed to invade into fat.
NOT allowed: Necrosis, Sheet-like or papillary growth, Clear or sarcomatoid cells, Lots of mitoses

Stains: Only *rare* CK7+ cells

Chromophobe Renal Cell Carcinoma



Pale, clear to eosinophilic cytoplasm
Prominent "Plant-like" cell membranes

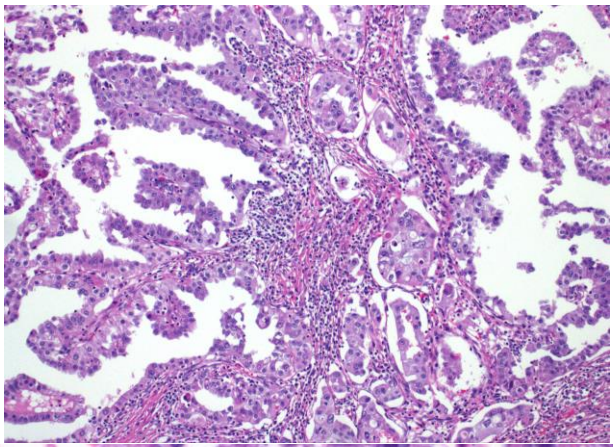
Perinuclear clearing/halos
Round to **Koilocytic nuclei** (hyperchromatic, crinkled, and/or binucleated)

Stains: CK7+ groups, Hale's colloidal iron +

Better prognosis than clear cell RCC.
Don't grade.

Chromophobe/oncocytoma hybrid tumors may be seen in Birt-Hogg-Dubé syndrome (and sporadically)

Fumarate Hydratase-deficient Renal Cell Carcinoma



Part of Hereditary Leiomyomatosis and RCC syndrome with **germline FH mutations** and **multiple leiomyomas**

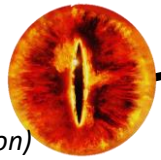
Old name: *aka "**HLRCC-associated RCC**"*

Prominent, eosinophilic, inclusion-like nucleoli with **perinucleolar clearing**

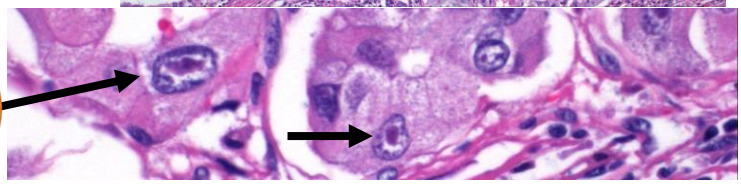
Usu. Papillary to tubular architecture

IHC: Loss of Fumarate Hydratase (FH) expression
Gain of 2-succinocysteine (2SC) staining
Usually younger patients.
Cutaneous and uterine leiomyomas.

Aggressive tumors.
Offer genetic counseling!



(Think of the eye of Sauron)



Succinate Dehydrogenase-deficient Renal Cell Carcinoma

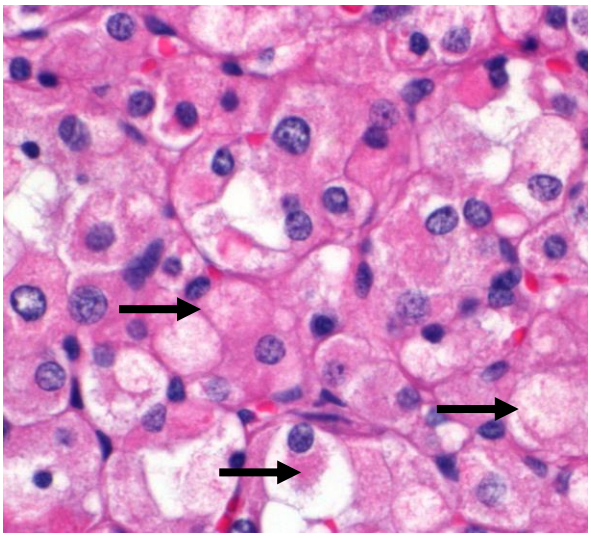
Classically, eosinophilic cytoplasm with **"flocculent" cytoplasmic inclusions** (→). Many morphologies though.

Neuroendocrine-like nuclei (round, evenly dispersed chromatin). Solid to nested architecture.

IHC: Defined by **loss of Succinate Dehydrogenase B** (SDH-B)
Majority of patients have germline SDH mutations.
Often CK negative!

Young age. **Good prognosis**. Rare.

SDH-deficient tumor syndrome: SDH-deficient RCC, paraganglioma/pheochromocytoma, SDH-deficient GISTs.
→ *Need genetic counseling!*



Acquired Cystic Disease-associated Renal Cell Carcinoma

Occurs only in patients with **End-Stage Renal Disease (ESRD) with cystic disease**

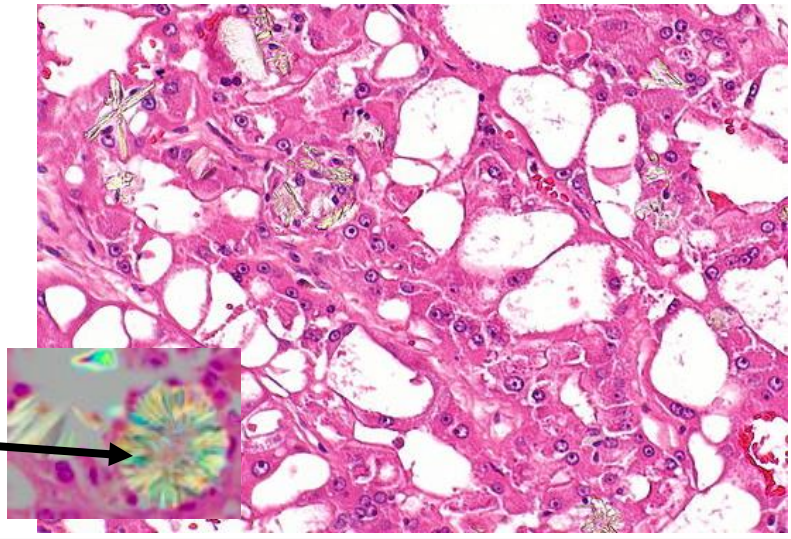
Abundant granular eosinophilic cytoplasm

Microcribriform "sieve-like" appearance due to frequent intracytoplasmic and intercellular microlumens

Large nuclei with prominent nucleoli.

Frequent oxalate crystals and calcifications (may need to polarize to see)

Usually **indolent**.



Eosinophilic Vacuolated Tumor

Emerging entity *aka "**EVT**"*

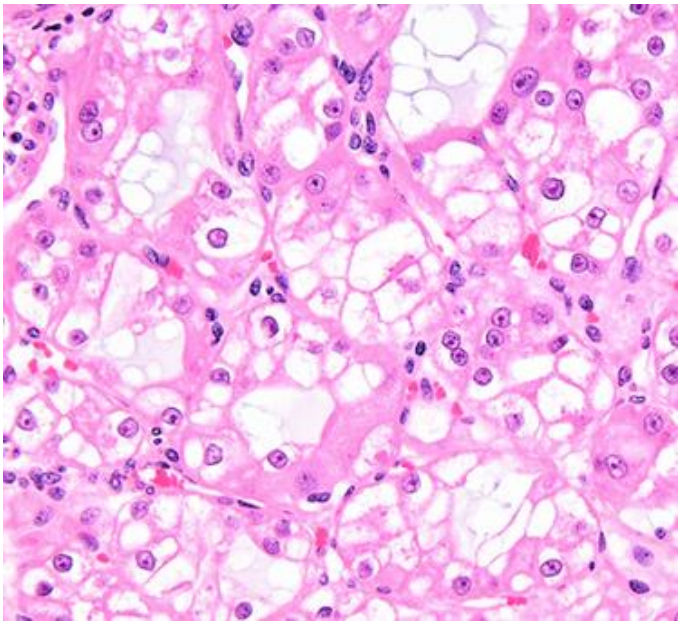
Eosinophilic cytoplasm with frequent large vacuoles.
Prominent membranes.
Round to oval nuclei with **prominent nucleoli**.

Solid to nested growth with some tubulocystic areas.

IHC: (+) PAX8, Cathepsin K, CD117, CD10.
Usually Neg: CK7 (focal/rare cells only).

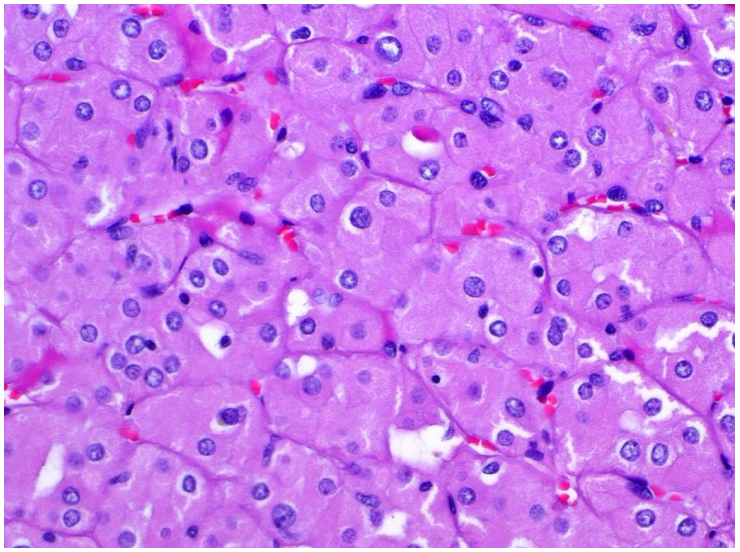
Molecular: Frequent TSC1/2 or MTOR mutations.

No aggressive cases to date (but still new)



Low-grade Oncocytic Tumor

Emerging Entity. *aka "**LOT**"*



Solid architecture.
Bland eosinophilic ("oncocytic") cells.
Low-grade round to oval nuclei.
Often delicate **perinuclear halos**.

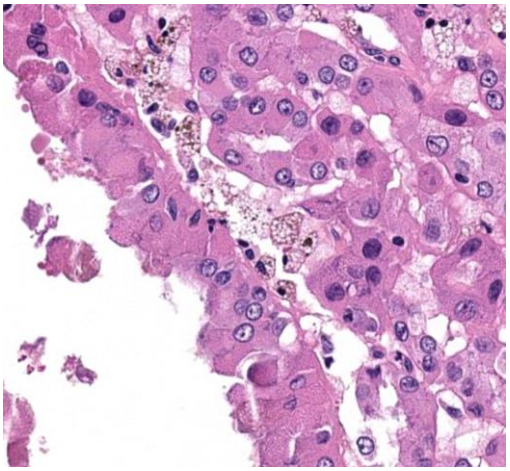
Centrally can have myxoid degeneration like oncocytomas.

IHC: CK7+ strong, diffuse; PAX8+; GATA3+
Negative CD117

No aggressive behavior to date (but new).
mTOR pathway mutations.

Eosinophilic Solid and Cystic Renal Cell Carcinoma

*aka "**ESC RCC**"*



Solid to cystic growth.
Solid areas show diffuse, compact, acinar, or nested growth.

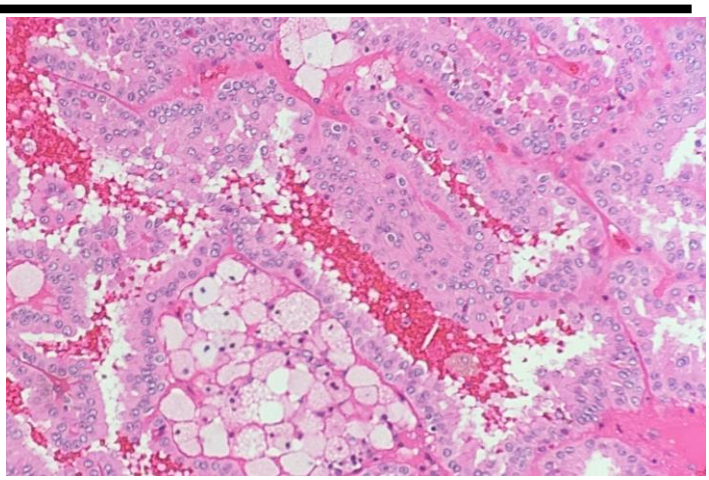
Cells have voluminous eosinophilic cytoplasm with coarse granules.
Bland, round to oval nuclei. Inconspicuous nucleoli.
Often "hobnail" arrangement in cysts.

Usually sporadic and solitary, but can be associated with TS.
Majority in **females**

IHC: CK20+ (focal or diffuse), CK7 – (or focal), PAX8+, Cathepsin K+
Molecular: TSC loss

Usually **indolent**.

Papillary Renal Cell Carcinoma



With the recognition newer entities, eosinophilic papillary RCC ("Type 2") has gone from common to a Dx of exclusion!!

Predominantly papillary architecture

If Higher nuclear grade and Prominent Nucleoli, then **consider FH-deficient RCC!!!**

Clear Cell Renal Cell Carcinoma
Although it is called "Clear Cell" RCC, some cases can have relatively eosinophilic cytoplasm. More common with higher grades. Can have "Rhabdoid" areas. Look for classic clear cell areas as a clue.

Epithelioid Angiomyolipoma
MIT family gene rearranged RCC

What if it doesn't fit into one of these diagnoses?!

If you're dealing with an eosinophilic renal neoplasm, the two most common diagnoses are oncocytoma and chromophobe RCC, so use strict criteria (and maybe a CK7) to evaluate for these DXs.

If it doesn't fit well into either of these boxes, consider the other pink kidney tumors listed above.

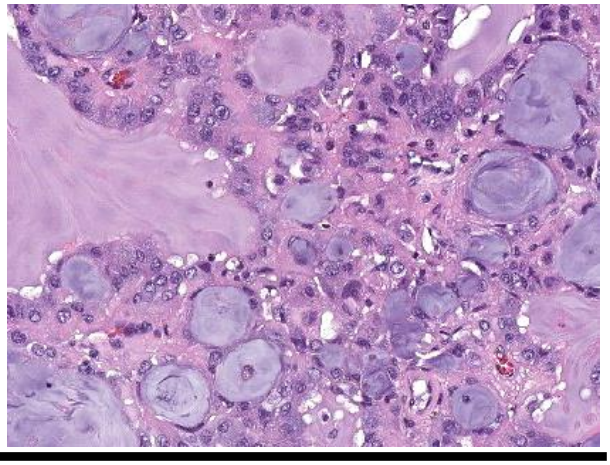
The remaining sporadic eosinophilic/oncocytic tumors with borderline features can be designated "*Oncocytic renal neoplasm of low malignant potential, NOS*" for management purposes.

What should I do with a pink kidney tumor biopsy?
Given the heterogeneity within tumors, some advocate that it's likely best to not be definitive unless it's clearly chromophobe RCC. Instead, say something like, "Oncocytic renal neoplasm, Favor ….. "

Emerging entities **(Rarer, Less well-defined, and less important for boards-studying)**

Thyroid-like Follicular Renal Cell Carcinoma

*aka "**TLFRCC**"*



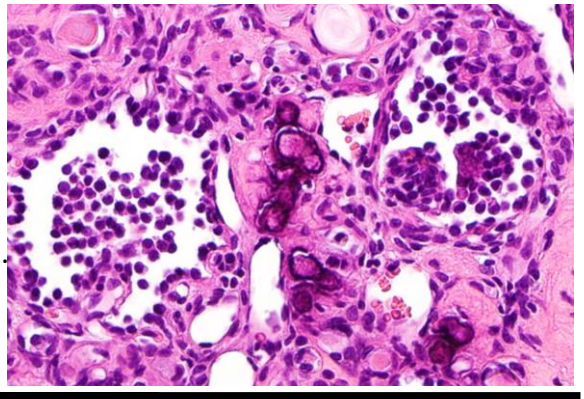
Follicular pattern: variably sized follicles, arranged back-to-back, and **filled with a colloid-like material.**

Follicles lined by a single layer of low-cuboidal epithelium with eosinophilic cytoplasm.

IHC: (+) PAX8, CK7, but TTF-1 and Thyroglobulin negative
Molecular: **EWSR1-PATZ1 fusions**

Usually behave indolently, but risk of metastasis, particularly to regional lymph nodes.

Atrophic Kidney-like Lesion

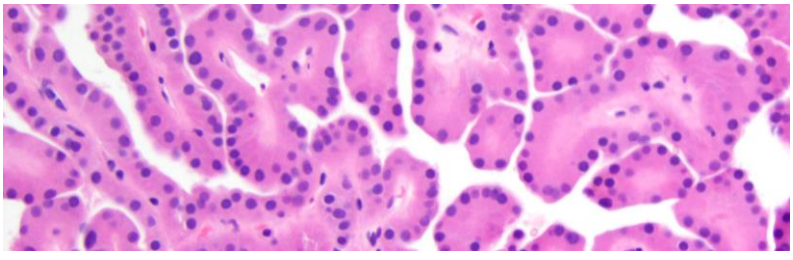


Benign, possibly reactive lesion.
Circumscribed, compact brown nodule in renal cortex

Well-developed follicular architecture: variably sized follicles with dense eosinophilic secretions and microcalcifications. Epithelial lining is flat/atrophic. Some cells detach in secretions.

IHC resembles glomerular podocytes: (+)WT-1, (-)PAX8, CK7; Negative TTF1 and Thyroglobulin.

Papillary Renal Neoplasm with Reverse Polarity



Nuclei aligned toward the apex of the cell
Thinly branching papillae. Eosinophilic cells.
IHC: **(+) GATA3**
Molecular: KRAS mutations

Clear

	CK7	CD10	CA-IX	AE1/AE3 & EMA	HMWCK	Melanocytic Markers	TFEB/TPF3
Clear Cell RCC	-/+	+	**+ (diffuse, membrane)**	+	-	-	-
Clear Cell Papillary RCC	+	-	**+ (basal cup-like)**	+	+	-	-
Chromophobe RCC	+	-	-	+	-	-	-
Multilocular Cystic renal cell neoplasm	-	+	+	+	-	-	-
MiTF translocation-associated RCC	-	+	-	- (weak to neg)	-	+/-	+
RCC with fibromyomatous stroma	+	+	+	+	+	-	-

Clear Cell Renal Cell Carcinoma

Most common Renal Cell Carcinoma in Adults

Predominantly clear cells (contains lipid and glycogen) with sharp cell borders (but gets pinker with higher grade!).

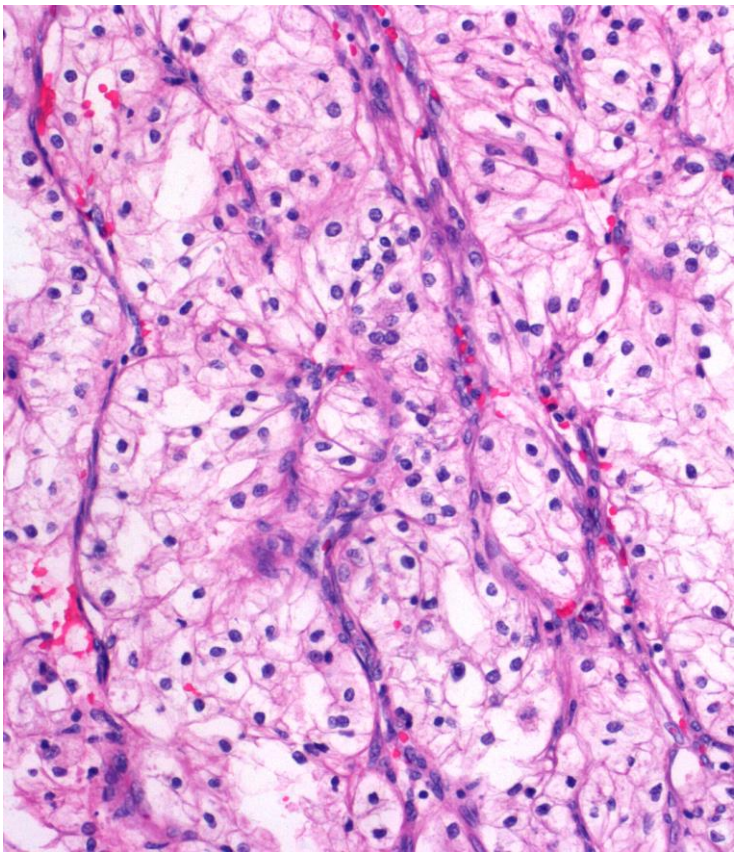
Solid, nested, tubular, or alveolar architecture with **fine arborizing vascularity** that surround essentially every nest of tumor cells.

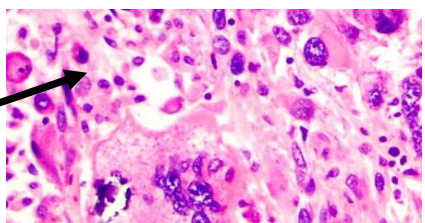
Grossly: Yellow, with frequent hemorrhage and necrosis

Molecular: Loss of short arm of chromosome 3 with inactivation of other VHL gene → **Biallelic VHL inactivation**

Metastasize hematogenously (spread through renal sinus veins→ vena cava → lung)
Famous for late Mets to odd places

Usually sporadic, but associated with von Hippel Lindau Syndrome (germline VHL mutation)→ multiple CCRCCs—Along with: Hemangioblastomas, pheochromocytoma, pancreatic serous cystadenomas, and endolymphatic sac tumor





High grade tumors often get pink, Sarcomatoid and/or Rhabdoid (grade 4)

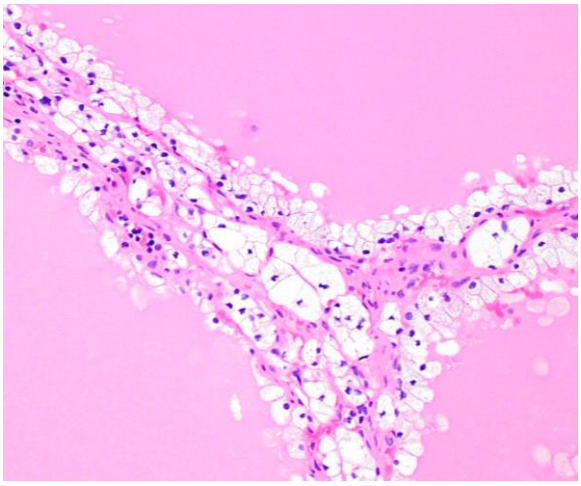
Multilocular Cystic Renal Cell Neoplasm of Low Malignant Potential

Pure cystic architecture
Cysts lined by a single layer of **low-grade clear cells** (grade 1-2 only)

Groups of low-grade clear cells are permitted within the septa, but must not be expansile nodules that alter their contour or exceed 1 mm.

Features *not* allowed: Necrosis, Vascular invasion, frequent/atypical mitoses, or Rhabdoid/Sarcomatous differentiation

NOTE: No longer called a carcinoma as act so **indolently**



Clear Cell Papillary Renal Tumor

Mixture of tubular, cystic, acinar and papillary patterns

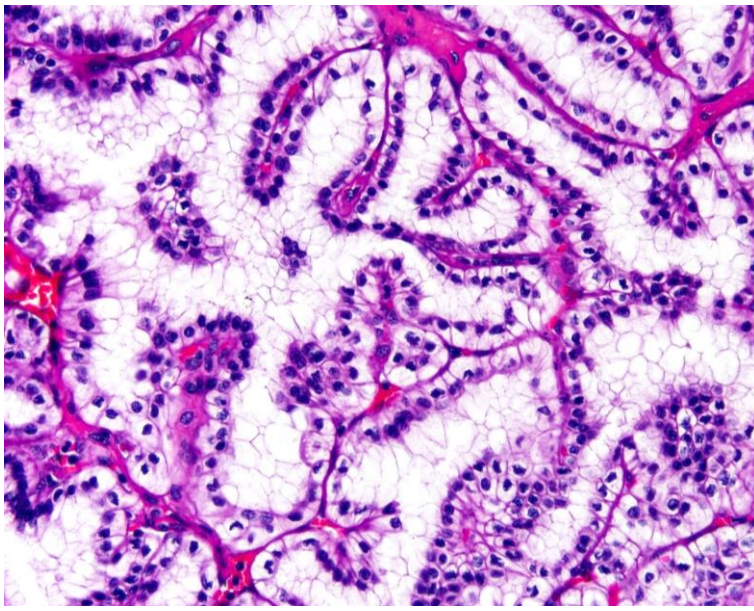
Single layer of cuboidal to columnar cells
Scant clear cytoplasm

Nuclei apical to mid-cytoplasmic orientation
("pseudoendometrial" appearance)

Low-grade (WHO 1 or 2) and Low-stage (pT1)

IHC: (+) CK7, CA-IX basolateral cup-like, GATA3,

Very **indolent** (no reported metastases!), so now called a "tumor" (was previously "carcinoma")



ELOC-mutated Renal Cell Carcinoma

Formerly TCEB1-mutated RCC

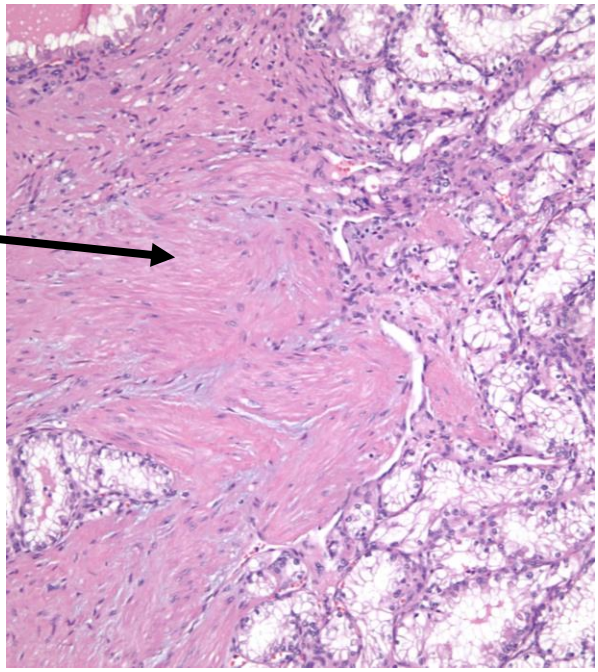
Defined by ELOC mutation

Nodular with thick **transecting fibromuscular bands**
Tubules and papillae
Voluminous clear cytoplasm with prominent cell borders

IHC: (+) CK7, CAIX (complete membrane), CD10

Usually **indolent**

Sometimes grouped with:
"Renal Cell Carcinoma with Leiomyomatous Stroma"
Less of a distinct entity, includes RCC with ELOC mutations or TSC/MTOR

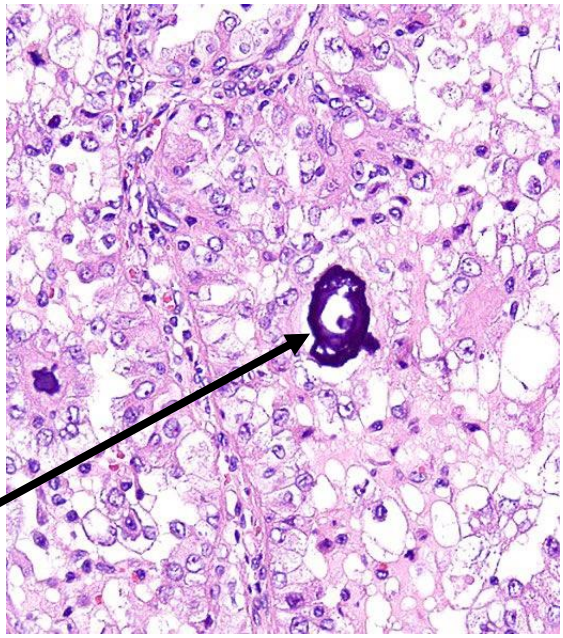


MiTF Translocation Renal Cell Carcinoma

Gene fusions in MiT family transcription factors TFE3 or TFEB
(Demonstrate with cytogenetics, FISH, or IHC)

IHC: Often *Negative* for epithelial markers (CK and EMA)
(+) PAX8, Melanocytic markers (MelanA and HMB45)
(+/-) Cathepsin K

Most often recognized in **younger patients**



TFE3-rearranged renal cell carcinoma

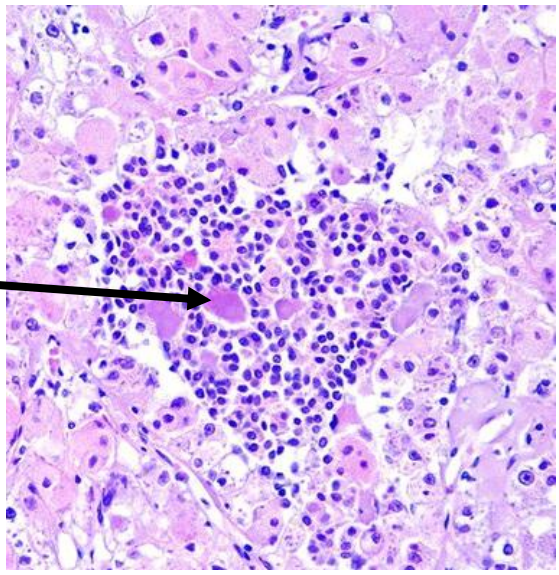
Old name: Xp11 translocation RCC

Fusion of TFE3 with one of several partners

Abundant clear (to pink) cytoplasm.
Papillary architecture with **psammoma bodies**

IHC: (+) Nuclear TFE3 staining in a clean background

Outcome similar to clear cell RCC



TFEB-altered renal cell carcinoma

Old name: t(6;11) RCC

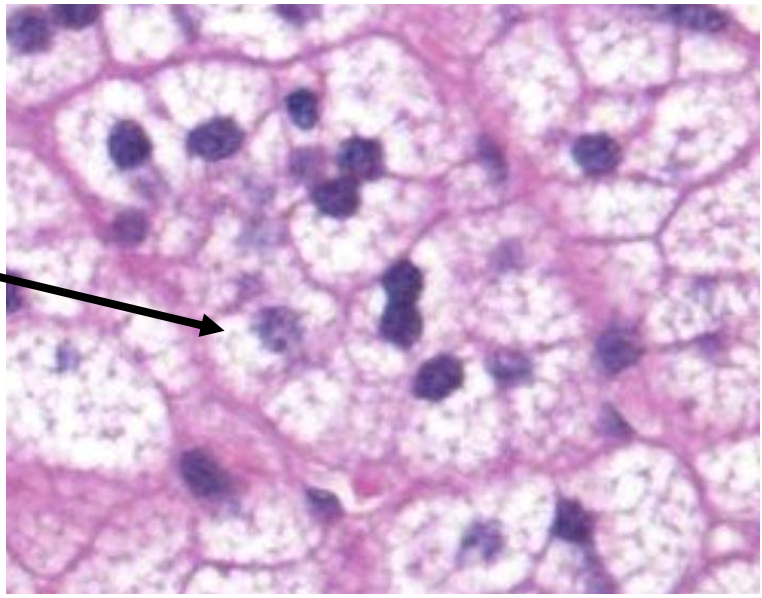
Either TFEB rearrangement or TFEB amplification

More **variable morphology**.
Sometimes larger epithelioid and smaller cells clustered around basement membrane (→)
Identify TFEB gene amplification or rearrangement by FISH
More indolent

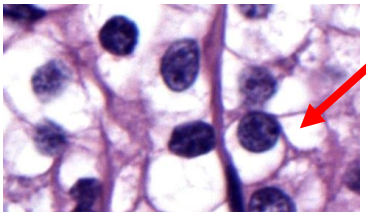
Adrenal Cortical Lesion/Tissue

Can be **developmental rest**/remnant, or inadvertent sampling on Bx, etc…
Most rests are **small** (<2 cm).
Often **incidental**, often near capsule.

Adrenal cells have lots of little vacuoles



IHC: (+) Inhibin, SF-1, Caletinin, MelanA
(-) PAX8, EMA

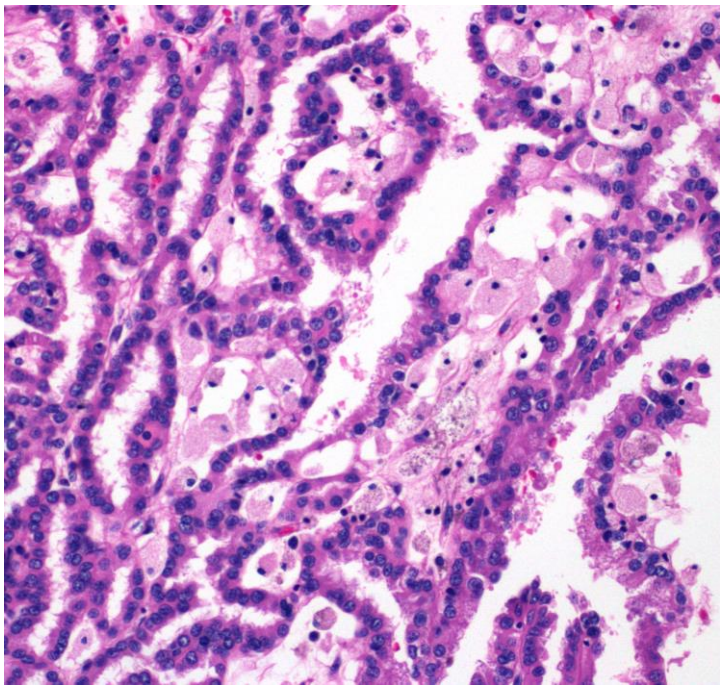


Vs.
Clear cell RCC with large clear areas

Basaloid

	CK7	CD10	CA-IX	AMCAR	WT-1	CD57
Papillary RCC	+	+ (luminal)	-/+	+	-	-
Metanephric adenoma	-	+	-	-	+	+
Wilms Tumor	-/+ (in epithelium)		-	-	+ (diffuse)	-
Mucinous Tubular and Spindle Cell RCC	+	-/+	-	+	+	-
Tubulocystic RCC	+/-	+	-/+	+	-	-

Papillary Renal Cell Carcinoma



Second-most common RCC

Papillary and tubular architecture
Cuboidal to columnar cells (often basophilic)

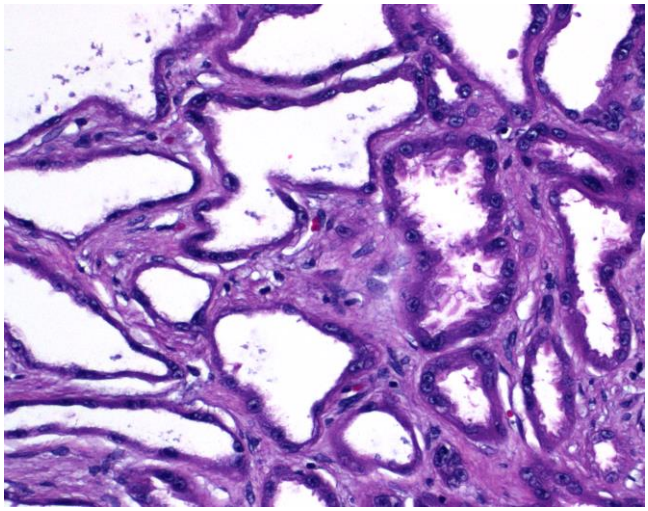
Lacking extreme heterogeneity and viral-like changes (which could suggest FH-deficient RCC)

Foamy macrophages, psammoma bodies, Grade nuclei using WHO/ISUP system.

No longer separate into Type 1 vs Type 2 (many type 2 were likely other tumors!)

Papillary Adenoma
Same thing, but < 1.5 cm, Nuclear grade 1 or 2, without a fibrous capsule. Benign

Tubulocystic Renal Cell Carcinoma



Closely packed variably sized **tubules and cysts**

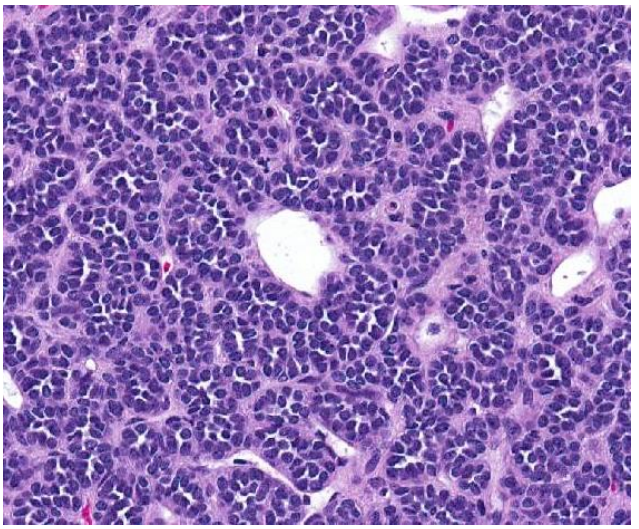
No solid component→ Grossly looks like a **sponge**

Lined by **cuboidal to flattened and hobnail cells**

High grade nuclear features with prominent round nucleoli

Good Prognosis

Metanephric Adenoma



Benign. Usually older adults.

Composed of **small, primitive tubules.**

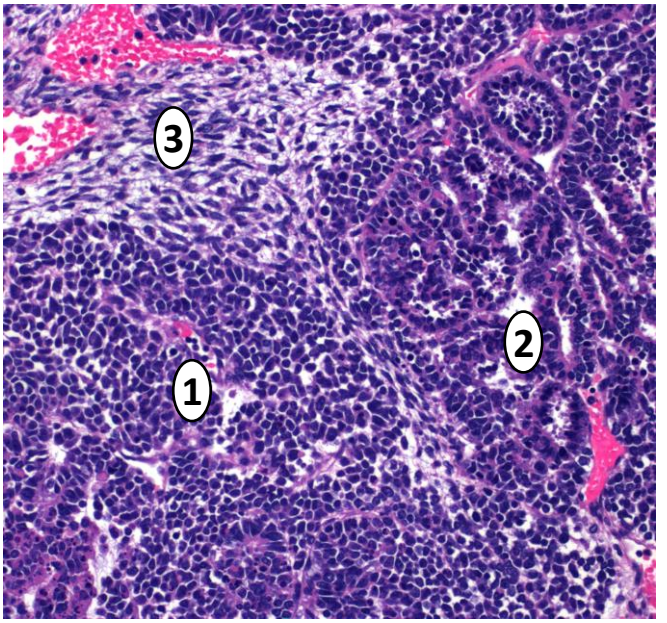
Cells have **minimal cytoplasm with uniform, small nuclei**
Minimal mitoses. Very cellular with minimal stroma.

Grossly: well-circumscribed, unencapsulated, tan nodule. Often incidental, but associated with **polycythemia** due to EPO production

IHC: **(+) WT-1**. (-) CK7
BRAF V600E mutations

Metanephric adenoma + Metanephric stromal tumor = Metanephric adenofibroma

Wilms Tumor (Nephroblastoma)



Vast majority in **Children**

Triphasic (recapitulating nephrogenesis):
1) Blastema (small, undifferentiated, overlapping cells)
2) Epithelium (Tubules, rosette-like to well-formed)
3) Stroma (Nondescript spindled cells, occasional heterologous elements)

IHC: Different components stain differently
(+) WT-1 (blastema and epithelium)
(+) Desmin, focal (blastema)
(+) CK (epithelium)

Special reporting (amount of Anaplasia, etc…)
Anaplasia = increased nuclear size (>3x size), hyperchromasia, and mitotic figures → Chemo resistant

Malignant, but often good survival if low stage. Often treat with chemo preoperatively.

Majority are non-syndromic. Subset associated with a variety of conditions including: WAGR, Denys-Drash, and Beckwith-Wiedemann

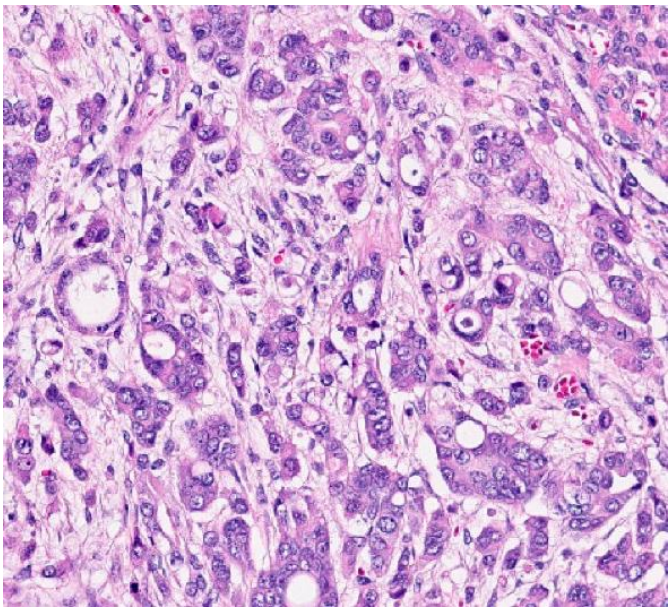
Nephrogenic rests—abnormal foci of embryonal cells (after 36 wks gestational age) that are potentially capable of *developing* into nephroblastoma.

Nephroblastomatosis—diffuse or multifocal involvement of the kidneys with nephrogenic rests

Cystic partially differentiated nephroblastoma—Multilocular exclusively cystic renal neoplasm of very young children containing nephroblastoma tissue in septae. Cured by surgery.

High-Grade

Collecting Duct Carcinoma

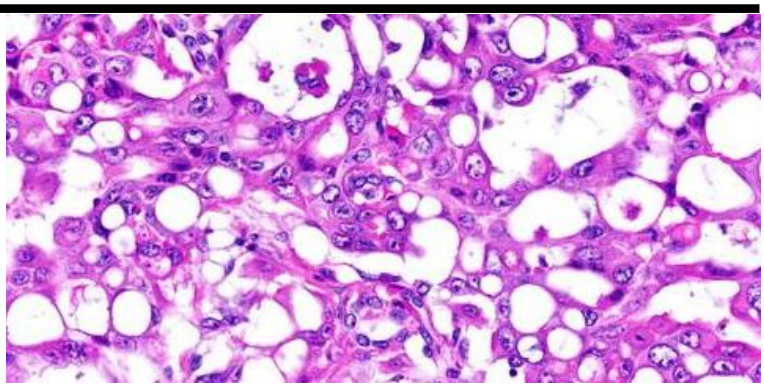


High-grade renal carcinoma arising in **medulla** of the kidney, with a **predominantly invasive tubular growth** pattern. **Rare**.

Diagnosis of exclusion. Requires:
1) No other RCC, Urothelial carcinoma, or Metastasis
2) Predominantly tubular growth
3) Involvement of medulla
4) Prominent stromal desmoplasia
5) Infiltrative growth
6) High nuclear grade

Poor Prognosis

SMARCB1-deficient Renal Medullary Carcinoma



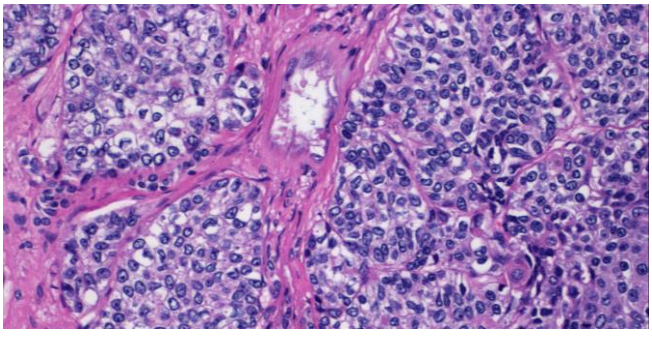
Occurs mainly in patients with **Sickle Cell Trait**

High-grade. Infiltrative. Rhabdoid and inflamed.

IHC: Loss of INI-1 (SMARCB1).
(+) PAX8, CK; (-) GATA3

Poor prognosis. Often metastatic

Urothelial carcinoma



Always consider as a possibility if doesn't fit well into one of the RCC diagnoses.

Sample and examine the renal pelvis for urothelial CIS

Stains: GATA-3 +, p63+, HMWCK+, CK7+, CK20+,
Pitfalls: PAX8+ (in upper tract!), CA-IX +

Anaplastic Lymphoma Kinase (ALK) Rearrangement-associated Renal Cell Carcinoma

Defined by ALK gene fusion → can be identified by FISH, or Sequencing → treat with ALK inhibitor.

Heterogeneous morphology!
Pediatric cases → often resemble medullary carcinoma and **associated with Sickle Cell Trait**
Keep in the DDX for any RCC with heterogenous/hard to classify morphology!
Otherwise nonspecific IHC profile (+/- PAX8, CK7, etc…)

Variable outcomes, but more often indolent.

Spindled (Adult)

(Classic) Angiomyolipoma

"AML"

Benign.

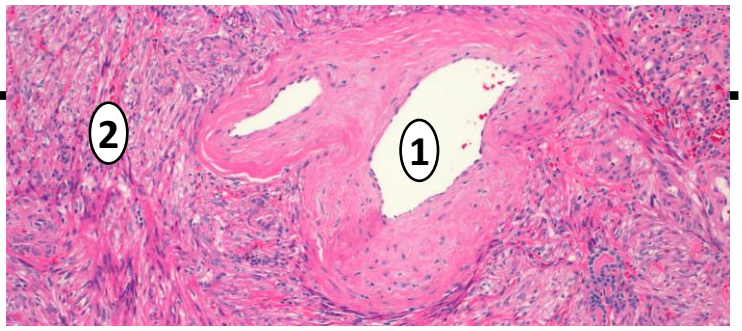
Member of "PEComa" family (Perivascular Epithelioid Cell)

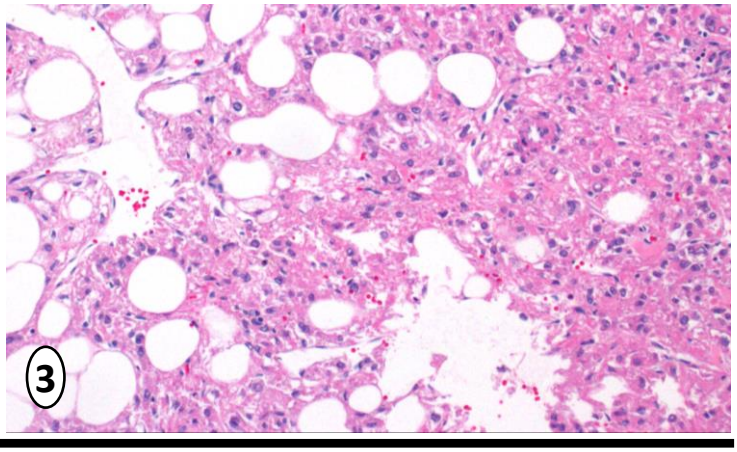
Generally 3 components (like the name):
1) Blood vessels ("Angio")
2) Smooth muscle ("Myo")—often blending with vessels. Spindled to epithelioid.
3) Fat ("Lipoma")—often seen radiographically

Stains with **Melanocytic Markers:** HMB45, MITF, (Melan A +/-); Cathepsin K+, Desmin + (in muscle)

Can have **e**pithelial **c**ysts→ "AML**EC**"

TSC1 or TSC2 inactivation mutations
Associated with Tuberous sclerosis

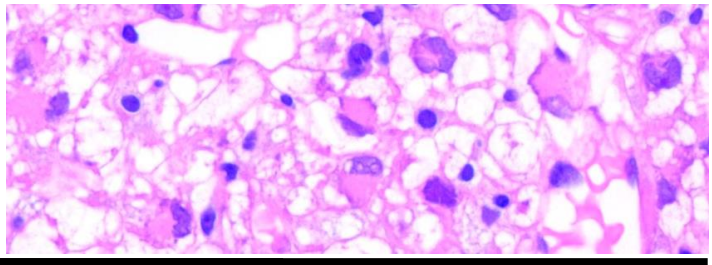




Epithelioid Angiomyolipoma

Angiomyolipoma with at least **80% epithelioid cells**.
Atypical large eosinophilic, ganglion-like, cells

Easy to confuse with carcinoma!
Can behave malignantly if lots of mitoses/necrosis



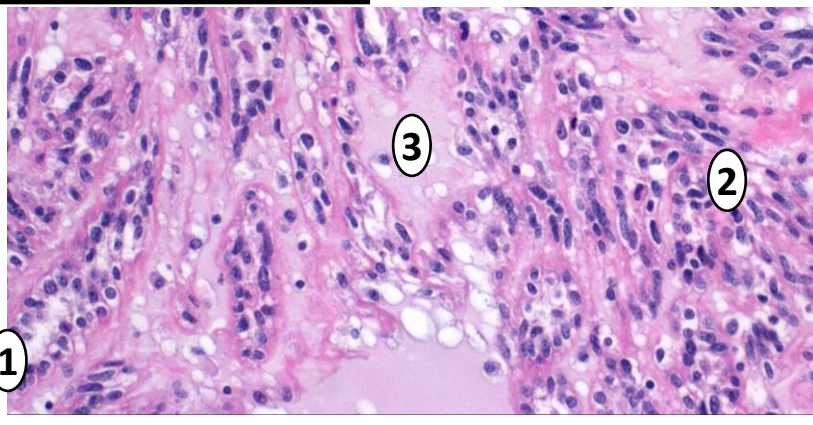
Mucinous Tubular and Spindle Cell Carcinoma

Like the name says:
1) Elongate **tubules** that blend into
2) Bland **spindle cells**, set in
3) **Mucinous stroma**

Cytologically bland with small oval nuclei.

IHC: (+) PAX8, CK7, AMACR

Usually indolent.
Can undergo high-grade transformation.



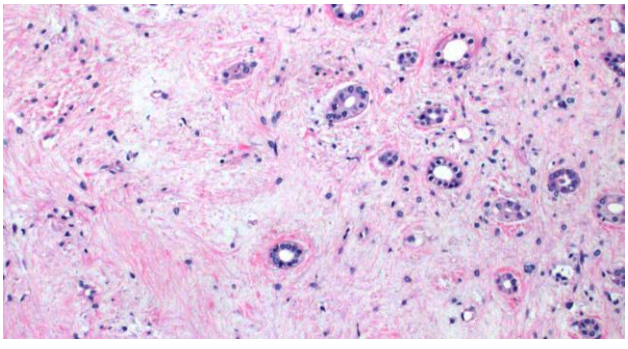
Renomedullary Interstitial Cell Tumor

Benign.

Usually incidental, **small** (<6mm), well-circumscribed

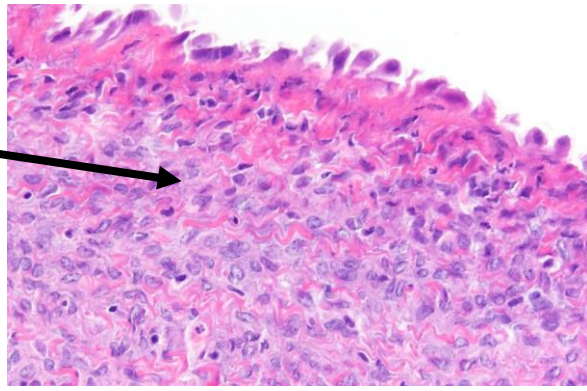
Located in **renal medulla**

Hypocellular. Composed of **bland stellate cells** set in loose to dense fibrocollagenous stroma with entrapped tubules at the periphery

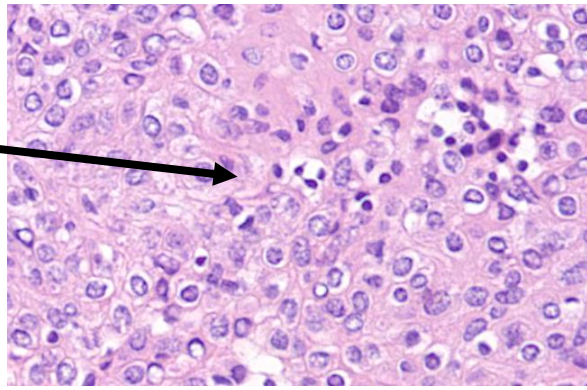


Other Spindled Tumors

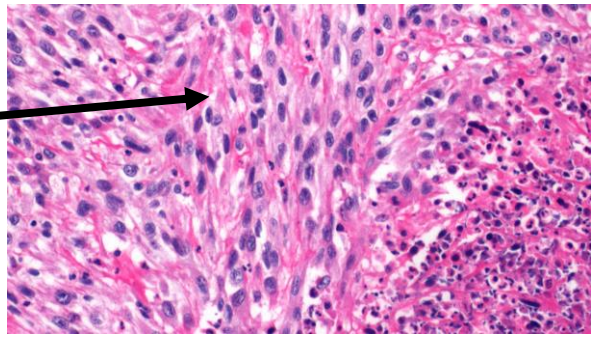
Mixed Epithelial and Stromal Tumor ("MEST")—Benign. Cystic and solid. Bland ovarian-type stroma with bland epithelial cysts (conceptually sort of like a mucinous cystic neoplasm of the pancreas, but epithelium is hobnailed and bland). Stroma stains with ER/PR.
If purely cystic→ ***cystic nephroma***



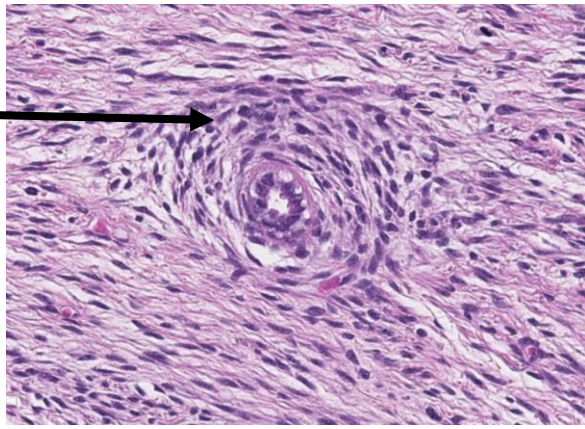
Juxtaglomerular Cell Tumor—Benign tumor that originates from smooth muscle cells in the walls of the glomerular afferent arteriole (juxtaglomerular apparatus)→ secretes renin→ Hypertension, Hyperaldosteronism, hypokalemia! Monotonous eosinophilic spindled to epithelioid cells with oval nuclei. IHC: (+) CD34, Vimentin; (-) PAX8, CK



Sarcomatoid Renal Cell Carcinoma—Renal cell carcinoma of any type exhibiting at least focal sarcomatoid/spindle cell morphology. Represents a form of high-grade transformation, not a distinct subtype of renal cell carcinoma. Requires evidence of epithelial differentiation (either conventional component or CK expression). Automatically WHO/ISUP grade 4. Poor prognosis



Metanephric stromal tumor— Spindled neoplasm with concentric peritubular growth.
BRAF V600E mutations.
Angiodysplasia and JXG hyperplasia. Benign.

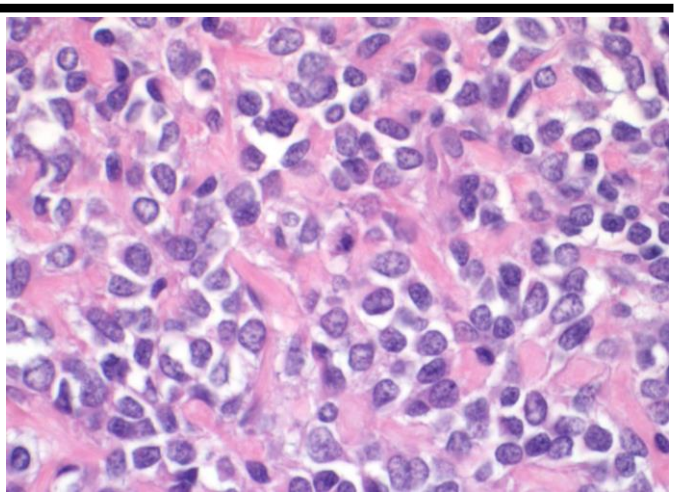


Hemangioblastoma—Similar to hemangioblastoma of the CNS.

And any other sarcoma pretty much

Spindled/Solid (Kids)

Clear Cell Sarcoma



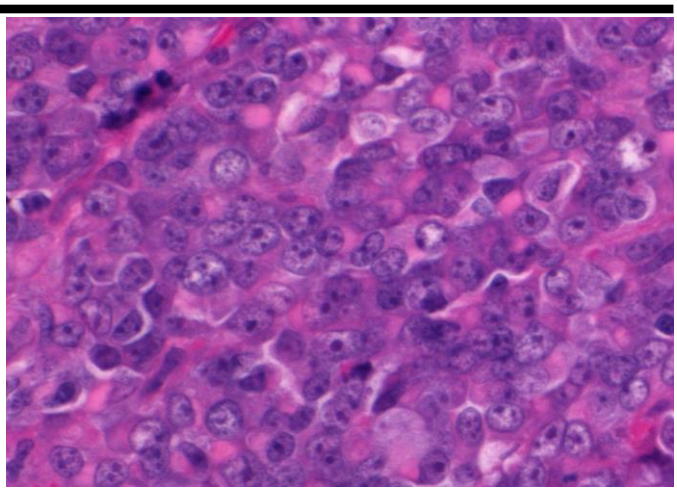
Old name "bone metastasizing renal tumor of childhood," but with modern treatment, pretty good survival.

Various patterns. Classically: nests or cords of uniform cells with clear cytoplasm and fine chromatin and a delicate vascular network

Molecular: **BCOR mutations** or **YWHAE:NUTM2 fusions**

IHC: (+) Cyclin D1, BCOR;

Rhabdoid Tumor



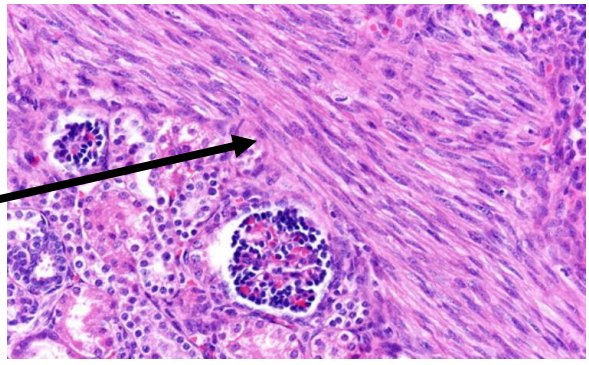
Aggressive→ dismal prognosis

Sheets and trabeculae of discohesive cells with: **Eccentric, pleomorphic nuclei** with vesicular chromatin and prominent nucleoli

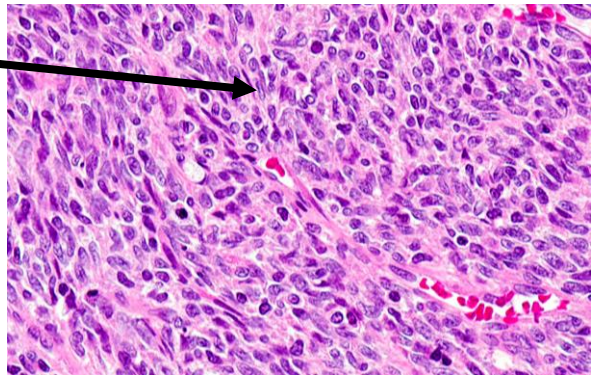
Eosinophilic cytoplasm with **pink hyaline inclusions** (looks "rhabdoid")

Stains: (+) CK+; **(-) INI-1,** Myogenin
Mutations: SWI/SNF complex **SMARCB1**

Pediatric Cystic Nephroma
Exclusively cystic neoplasm with DICER 1 mutations. Septae contain fibrous tissue and differentiated tubules.



Congenital Mesoblastic Nephroma , Classic Variant
Fibromatosis-like: intersecting bundles of bland spindled cells, infrequent mitoses. Infiltrates adjacent kidney and structures



Congenital Mesoblastic Nephroma, Cellular Variant
Recurrent ETV6-NTRK3 fusions (Same as infantile fibrosarcoma). Pushing border, dense cellularity, numerous mitoses

Ossifying Renal Tumor of Infancy
Intracalyceal tumor composed of a combination of osteoid, osteoblastic, and spindle cells. Extremely rare.

Reactive Lesions *(that mimic cancer clinically!)*

Xanthogranulomatous pyelonephritis

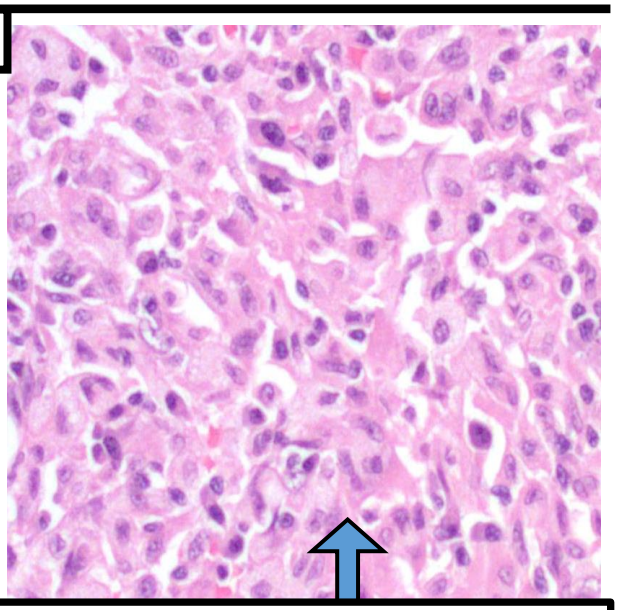
Tumefactive inflammatory process

Subacute/chronic renal pelvis/parenchymal mass-like lesion composed of **sheets of foamy histiocytes** with abundant, usually clear, cytoplasm.
Often **admixed other inflammation** (plasma cells, neutrophils, lymphocytes, giant cells).

Compared to Clear cell RCC, no nests or delicate branching vasculature.

Associated with **renal calculi**, obstruction, and **recurrent UTI's**. Most often associated with Gram-negative bacteria.

IHC: CD68+



Very similar morphologically, and possibly causally!

Malakoplakia

Mass-like lesion composed of histiocytes that can be found anywhere in the GU tract (and rarely outside the GU tract).

Aggregates of eosinophilic histiocytes, some of which contain targetoid, basophilic calcified inclusions called "**Michaelis-Gutmann bodies**" (→)
→ Can highlight with Von Kassa stain (and Fe, PAS stains too)
→ Histiocytes (+)CD68

Thought to be due to **defective macrophage lysosomal digestion of phagocytosed bacteria**.
Most often associated with Gram-negative bacteria.