Spectrum of Preneoplastic and Neoplastic Cystic Lesions of the Kidney in Adult

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- Various hereditary, acquired, and neoplastic conditions can lead to cyst formation in the kidney.
- Certain renal cystic diseases have been linked to increased risks of developing RCCs and, thus, can have preneoplastic and neoplastic lesions that coexist with benign-appearing cysts in the background.

- Several benign or malignant renal neoplasms can present as predominantly cystic lesions, and that list has been growing in the recent years.

- This review focuses on the spectrum of preneoplastic and neoplastic cystic lesions of the kidney encountered in the adult population.

The discussion is presented in 2 main categories:

- renal cystic diseases that are commonly associated with tumors.
- renal neoplasms predominantly presenting as cystic lesions.

Cystic Disease Commonly Associated with Tumors

- Acquired Cystic Disease of the Kidney
- Von Hippel–Lindau Syndrome
- Tuberous Sclerosis Complex
- Autosomal-Dominant Polycystic Kidney Disease
- Other Cysts With or Without Associated Tumors

Acquired Cystic Disease of the Kidney

- The incidence of developing RCCs in the native kidneys of patients with ACDK is approximately 3% to 7%, which represents up to 100 times greater risk than that found in the general population.

- The duration of dialysis in patients with ESRD often correlates with the incidence of ACDK and RCC

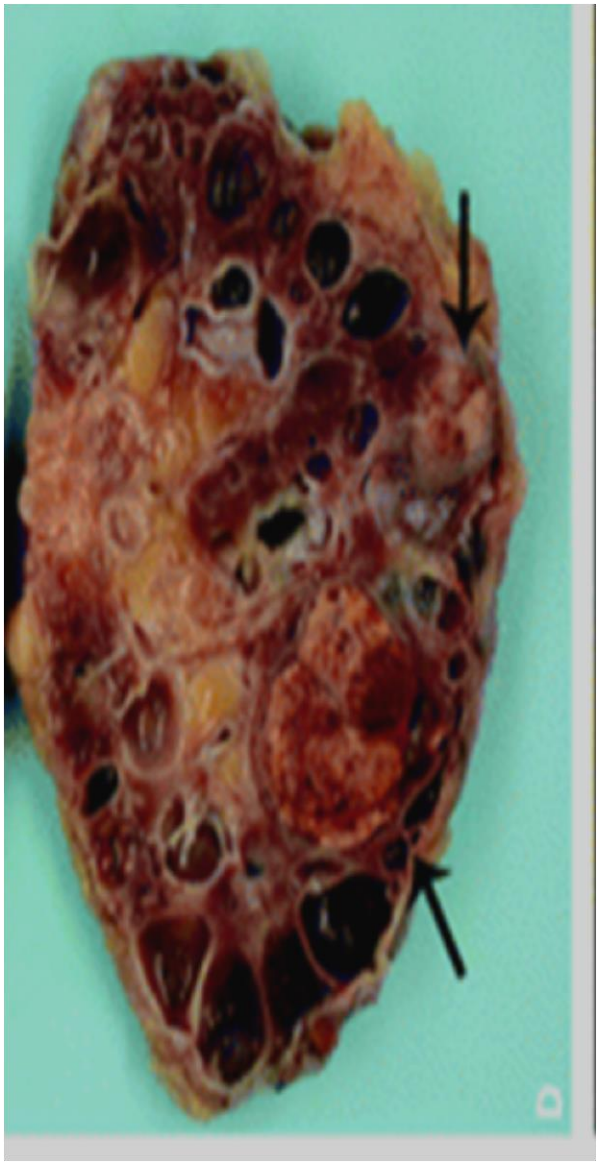
The tumor types seen in ESRD and ACDK encompass:

1) acquired cystic disease (ACD)-associated RCC (most common)
2) clear cell papillary RCC (a newly established entity).
3) papillary RCC
4) clear cell (conventional) RCC
5) chromophobe RCC.

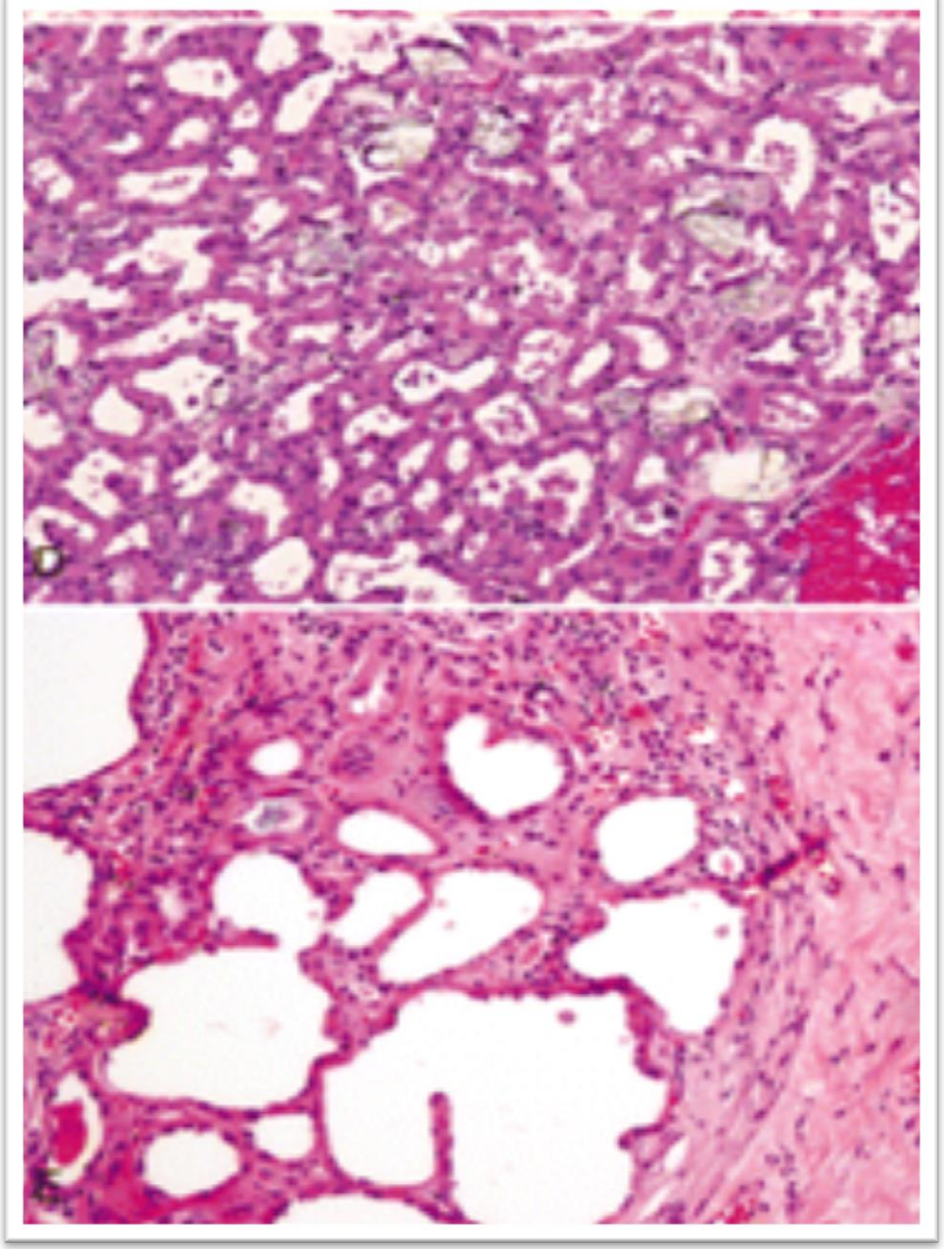
- **ACD-Associated RCC:** It is the most common subtype of RCC seen in ACDK.

  the tumors are usually multifocal and bilateral, and are identified by imaging or incidentally in nephrectomies performed on nonfunctional, small, or shrunken kidneys bearing numerous cysts.

Grossly: Most tumors are well circumscribed, often appearing to arise within cysts. Larger tumors may appear more solid, with thick, fibrous capsule and foci of necrosis and hemorrhage.

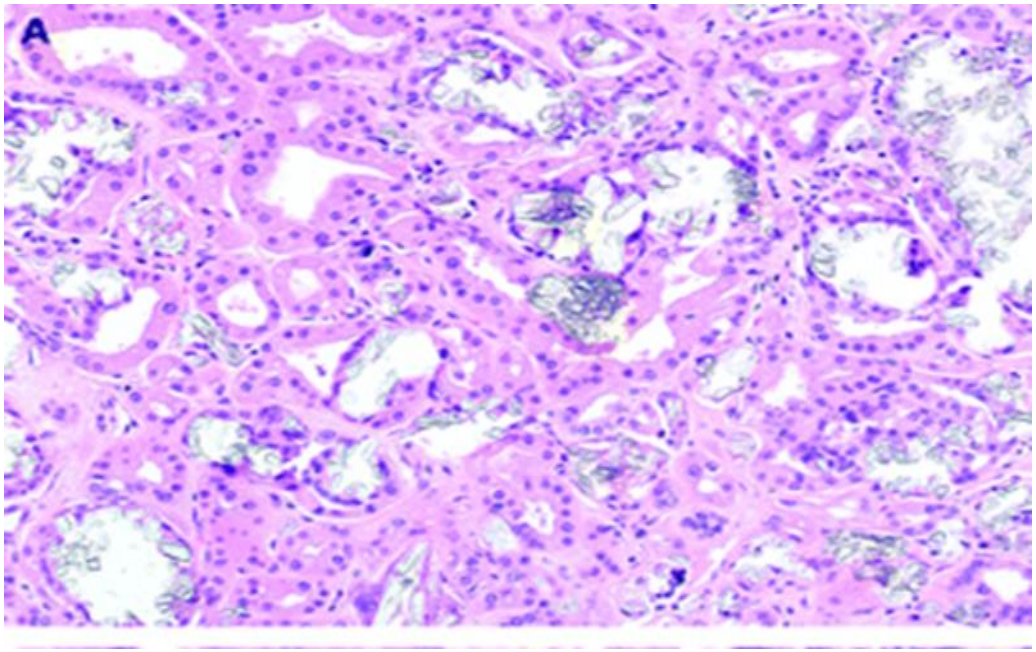


Microscopically: tumors show various combinations of acinar, solid alveolar, microcystic or macrocystic, and papillary architectural patterns. cells having abundant granular, eosinophilic cytoplasm and large nuclei with prominent nucleoli. Scattered oxalate crystals and cribriform appearance resulting from intercellular and intra-cellular lumina are characteristic findings .



- 79% show intratumoral oxalate crystals.

ACKD-associated RCC containing numerous birefringent calcium oxalate crystals.



- The prominent papillary architecture, misinterpretation as papillary RCC.

- some tumors contain variable, usually only focal, areas of clear or vacuolated cytoplasm, which requires a differential diagnostic determination with clear cell RCC.

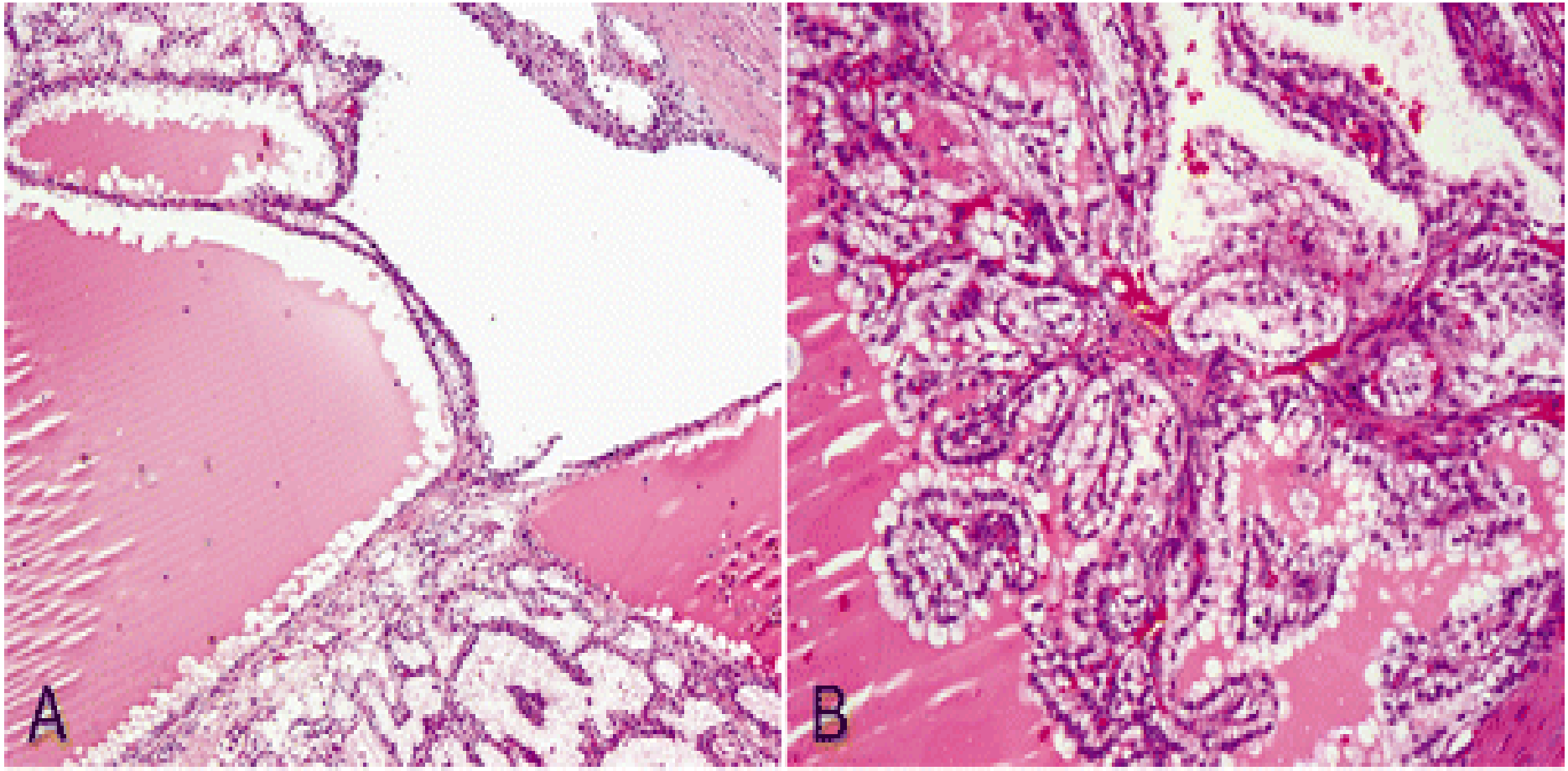
Immunohistochemistry ACD-Associated RCC:,

- diffusely positive for AMACR (α-methylacyl-coenzyme A racemase),CD10, and glutathione *S*–transferase α .
- negative or focally positive for CK7.

Genetically: showed variable combined gains of chromosomes 3, 7, 16, 17, and Y using FISH technique.

- trisomy of chromosomes 7/17 or loss of 3p, is characteristic of papillary and clear cell RCC, respectively.

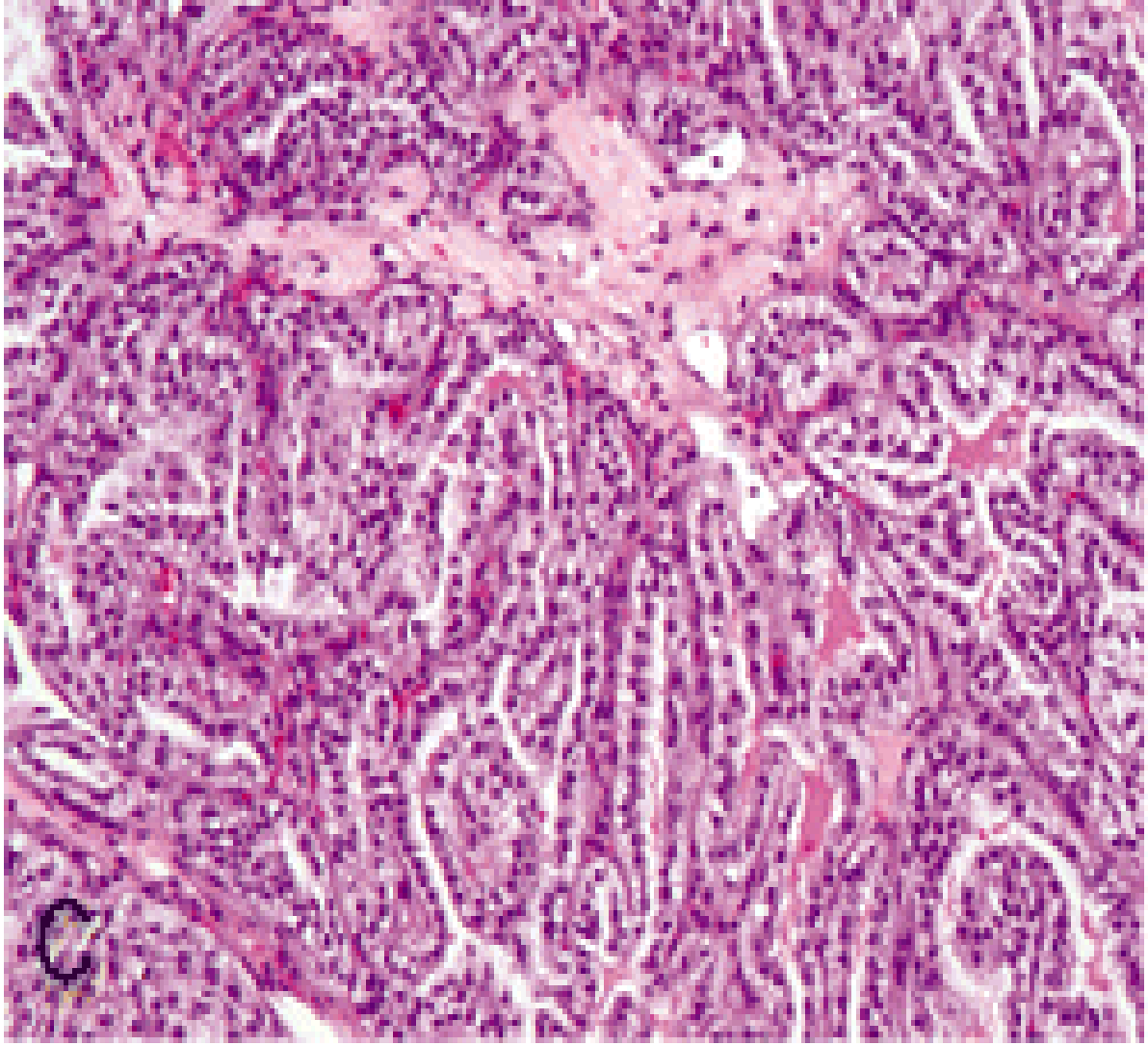
- **Clear Cell Papillary RCC:** its the second most common subtype of RCC in ESRD.
- Most of the tumors are well-circumscribed and are often variably cystic with fibrous capsule.
- Most tumors exhibit variable papillary and tubular/acinar architecture..
- Foamy macrophages, tumor necrosis, and vascular invasion are ***not*** features of these tumors.



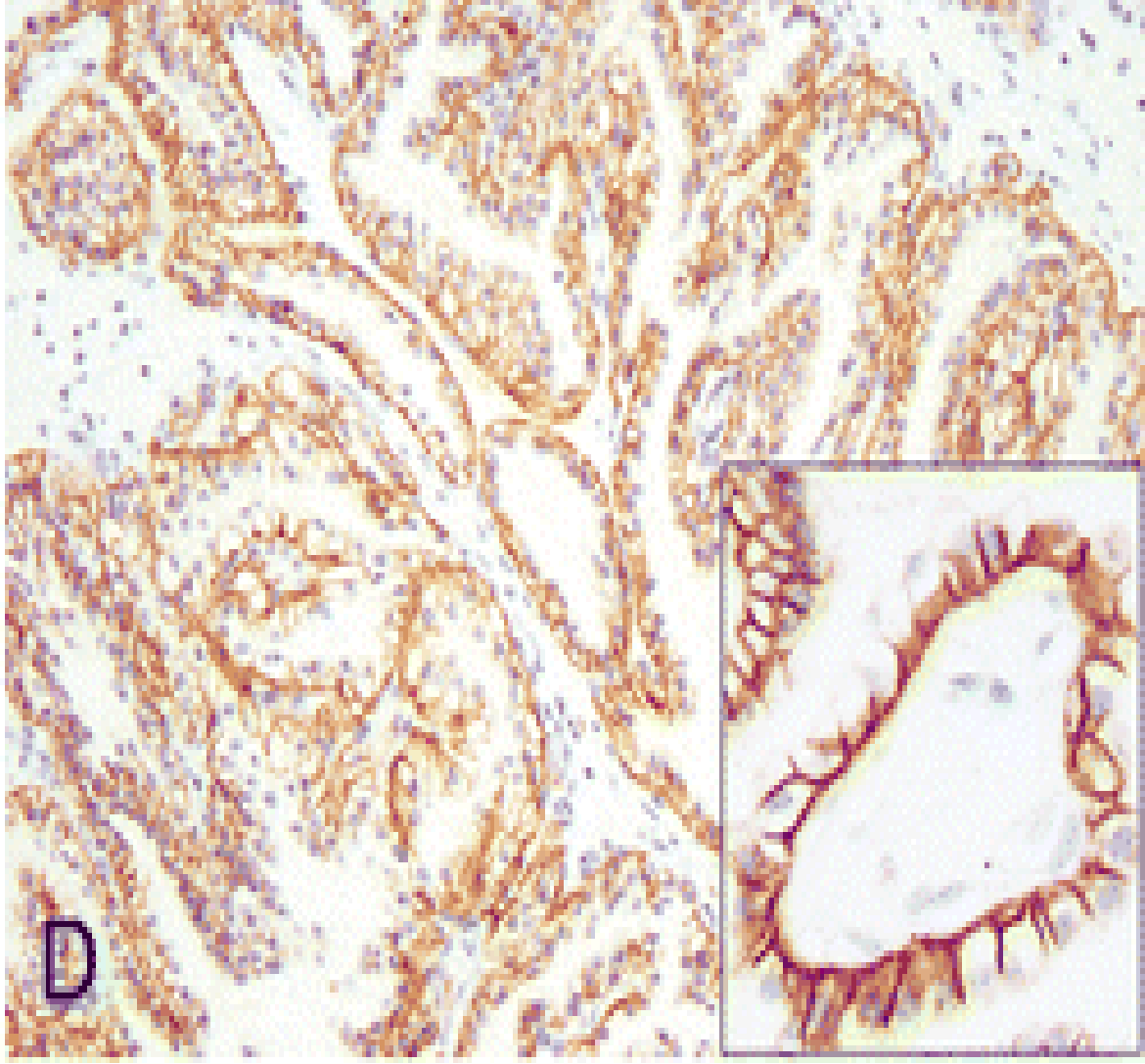
A, Clear cell papillary RCC often contains cystic areas.

B, Intracystic papillary architectural pattern is common. The tumoral cells have predominantly clear cytoplasm with low-gradenuclei. The characteristic features is the linear arrangement of the tumor nuclei away from the basal aspects of the cells, either in the middle of the cell or closer to the apex.

Clear cell papillary RCC the tumor contains tightly packed papillae and tubules, appearing solid. The linear arrangement of the nuclei away from the basement membrane is apparent



Clear cell papillary RCC Immunohistochemically stain for carbonic anhydrase IX shows a diffuse membranous distribution with **cup-shaped distribution,** and also diffusely positive for CK7



•racemase (AMACR) and CD10 staining are negative.

Prognosis:

- The biologic behavior of RCCs in ESRD is reported to be less aggressive than that of the RCCs in sporadic or non-ESRD settings; the tumors, at presentation, are often smaller and at lower stage (may be related to their incidental early detection because of close clinical follow-up and radiologic evaluations of patients with ESRD).
- ACD-associated RCC may have a greater potential for aggressive behavior than do other types.

- Rare cases with sarcomatoid features have been reported, these cases show aggressive clinical behavior.
- Papillary adenomas and dilated tubules or clustered microcystic lesions lined by the eosinophilic cells have been suggested as putative **precursors of the tumors** in the kidneys of ESRD.

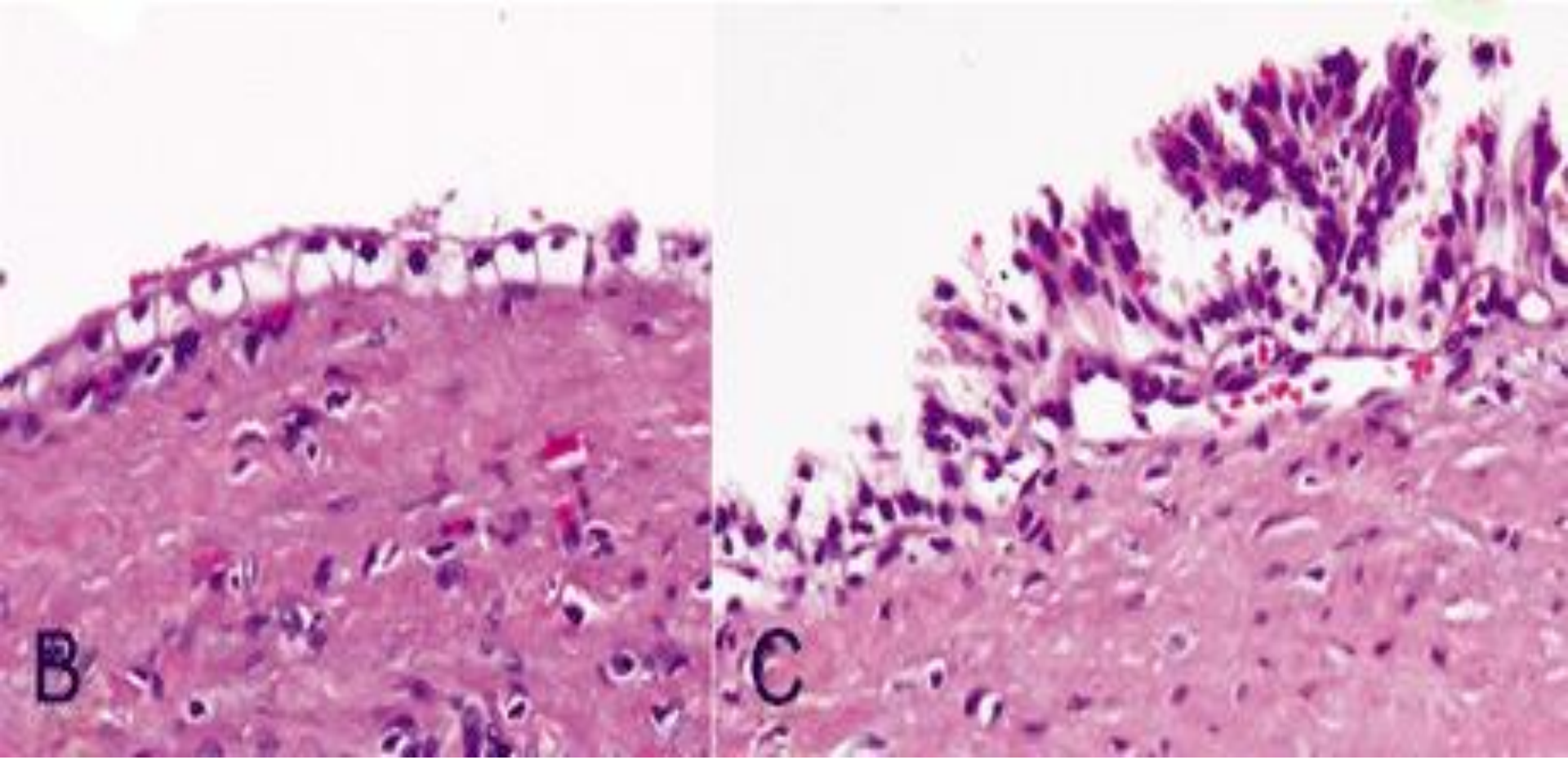
von Hippel–Lindau Syndrome

- It is an autosomal-dominant, inherited familial cancer syndrome predisposing patients to a variety of malignant and benign neoplasms, with retinal, cerebellar, and spinal hemangioblastomas, RCC, pheochro-mocytoma, and pancreatic tumors most frequent.

- Renal lesions occur in 30% to 70% of patients with VHL, (renal cysts, cystic clear cell RCCs, and solid clear cell RCCs).
- The cysts are usually multiple and bilateral, may be unilocular or multilocular, and are lined exclusively by clear cells .

Traditionally, when the epithelial lining is:

- one cell thick, the cysts ----*benign*
- the lining becomes 2 or 3 cells thick with focal papillary tufting, the cysts are called *atypical* cysts.



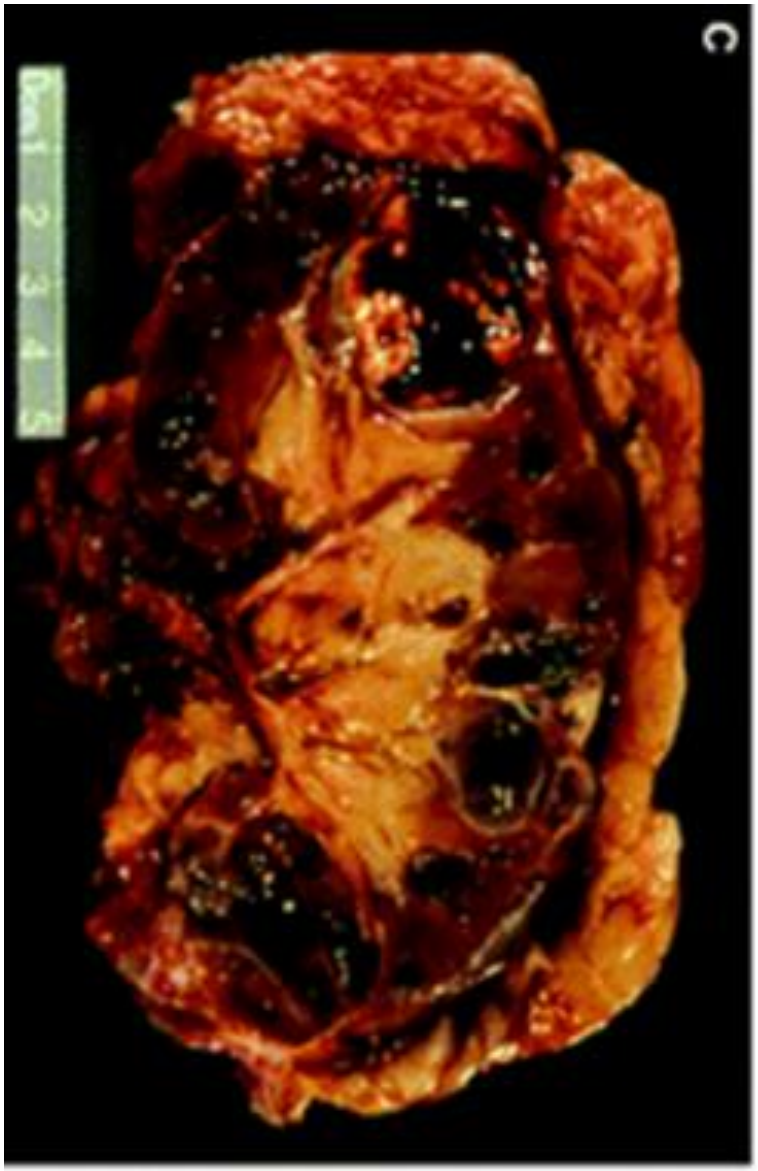
B, In the setting of VHL, the cyst is designated as *benign* when its lining is only one cell thick. C, The cyst is considered *atypical* when the lining becomes 2 or 3 cells thick or shows focal papillary tufting

- RCC are rare <20 years, but increasing frequency thereafter. 69% of patients surviving to 60 years will develop RCC.

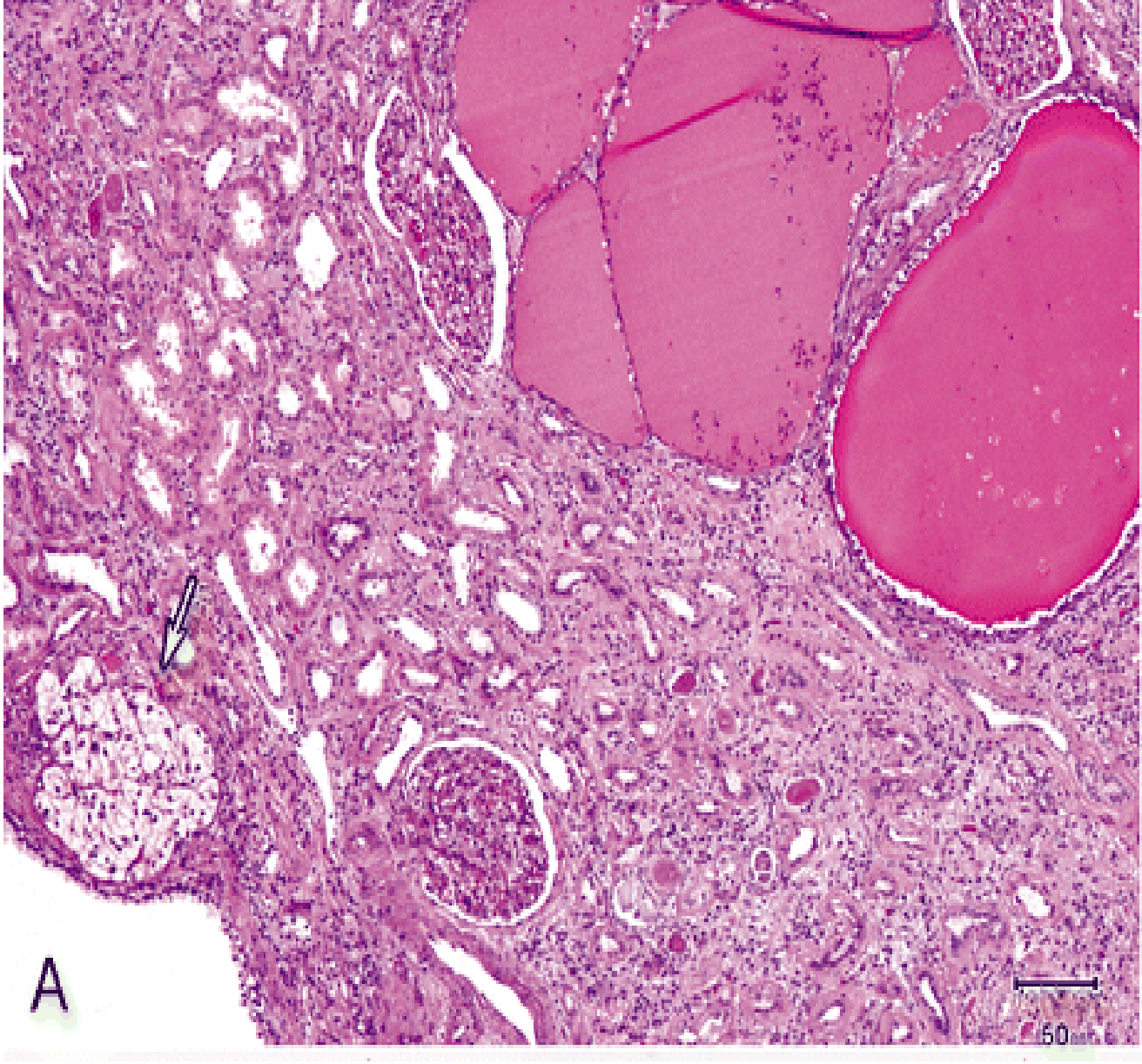
- Almost all tumors in the VHL setting are clear cell RCCs of low nuclear grade and stage.

- The RCCs are often multicentric and bilateral, arising both within cysts and de novo from noncystic renal parenchyma

von Hippel-Lindau disease showing multiple cysts and multiple cystic and solid clear cell RCCs



(VHL) disease The cysts are multiple, bilateral, and lined exclusively by clear cells. Note a cluster of clear cells (arrow) representing a microscopic clear cell RCC near a cyst.



- In patients with VHL who carry the *VHL* germline mutation, deletion of the second *VHL* allele is associated clear cell RCC.

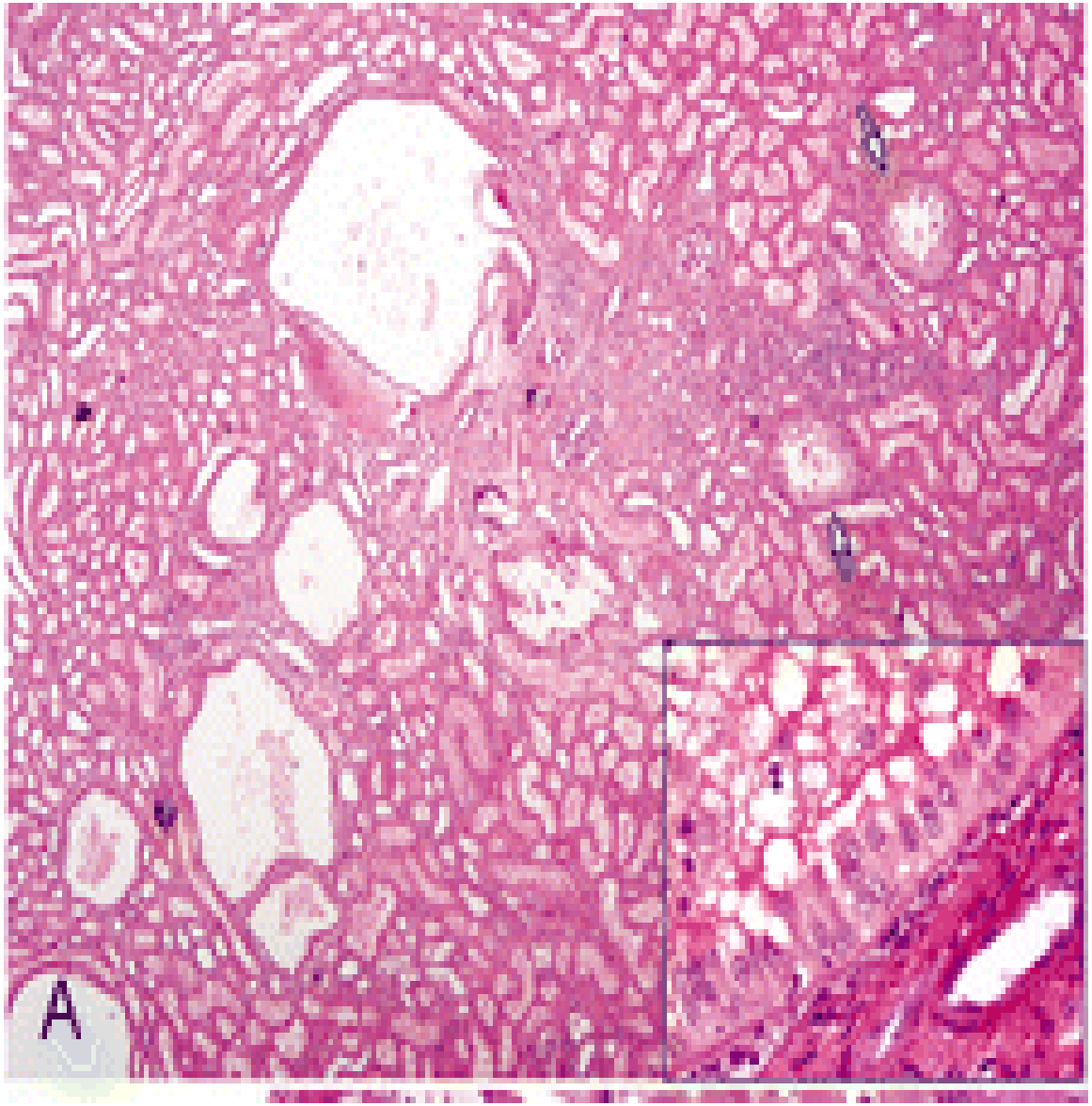
- The cysts lined by clear cells, even single renal tubular epithelial cells with the *VHL* gene deletion is a precursor lesions for clear cell RCC.

Tuberous Sclerosis Complex:

- It is an autosomal-dominant, hereditary disease involving multiple organs, such as brain, skin, heart, lungs, and kidneys.
- Up to 50% of cases have no family history and represent either new mutations or variation in disease penetrance.
- Renal involvement occurs in 50% of patients (renal cysts, angiomyolipomas, and RCCs).

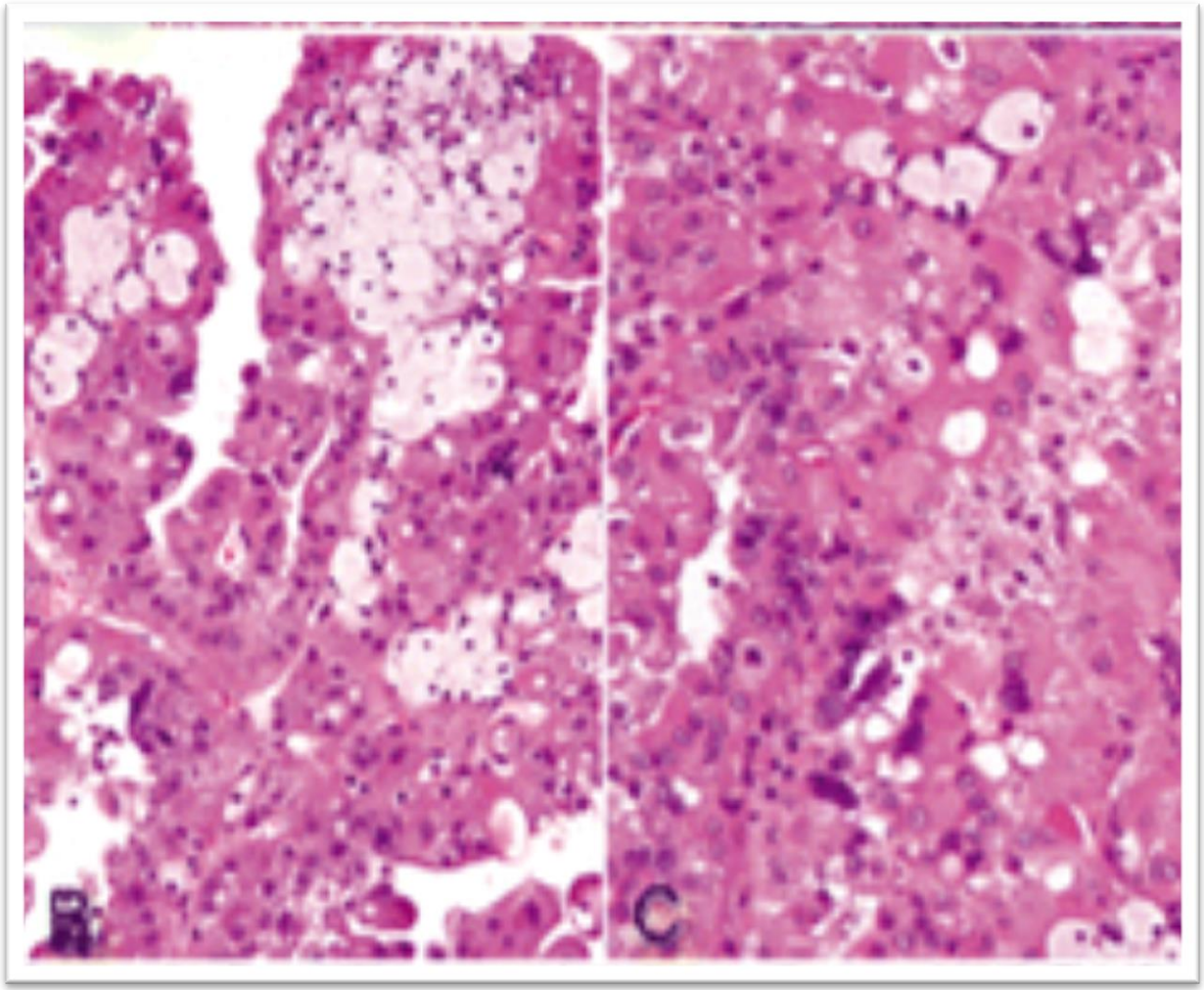
- Renal cysts occur in 30% to 40% of cases. They are usually small and scattered within otherwise unremarkable, intervening renal parenchyma or clustered within a segment to give a spongelike appearance.

TSC with scattered, small cysts, separated by otherwise unremarkable intervening renal parenchyma. The classic cysts in TSC are lined by granular eosinophilic cells with large nuclei (inset). Papillary tufting or intraluminal papillary excrescences can be seen (arrows).

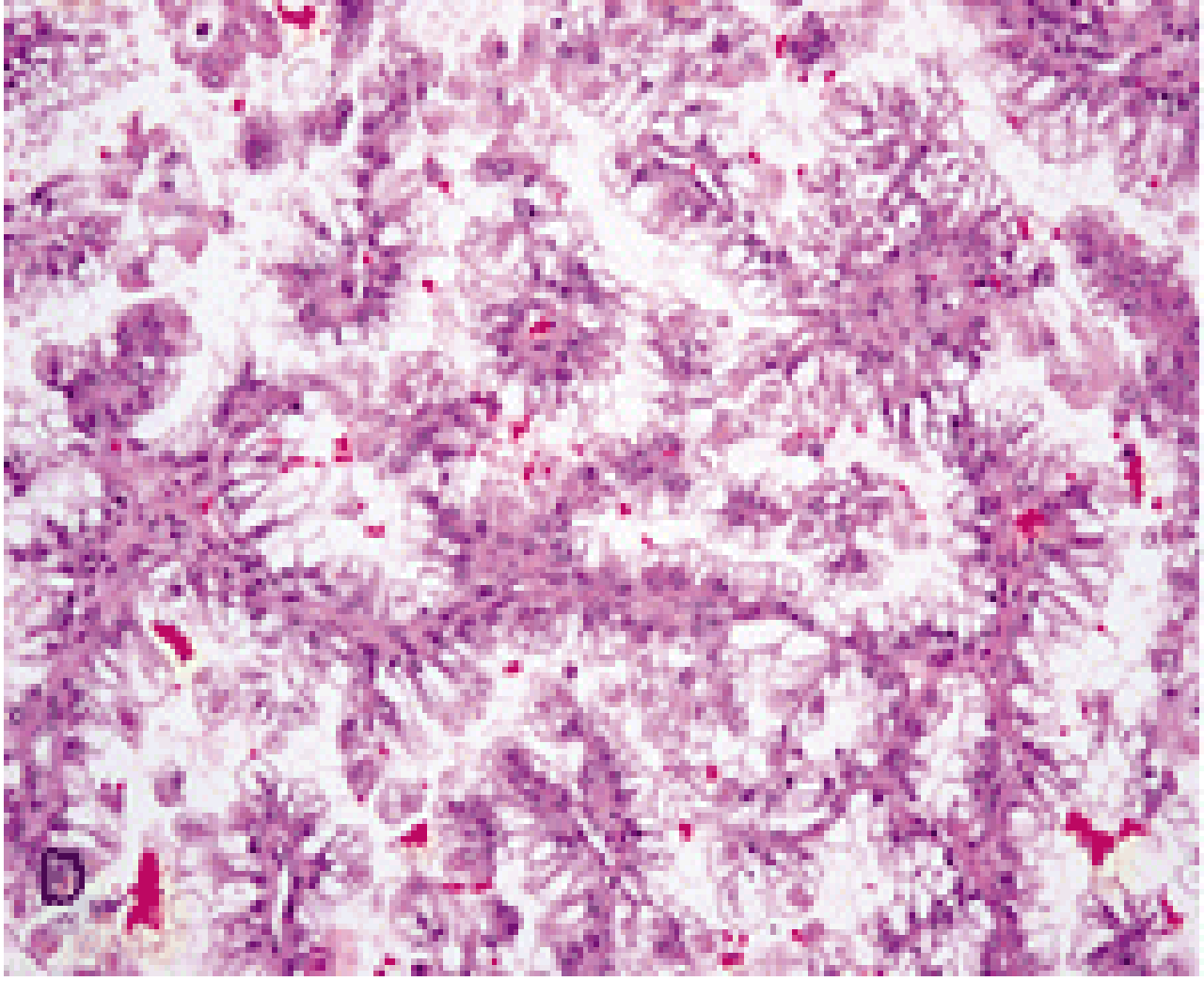


- RCCs occur in only 2% to 4% of patients with TSC.
- Clear cell RCC is reported to be the most frequent type. Several other tumors, including renal oncocytomas, chromophobe RCC have also been described.
- Also encountered tumors with sheetlike, glandular, or papillary architecture, composed of high-grade, eosinophilic, granular cells or cells with voluminous, clear cytoplasm.
- Immunohistochemically negative for TFE proteins

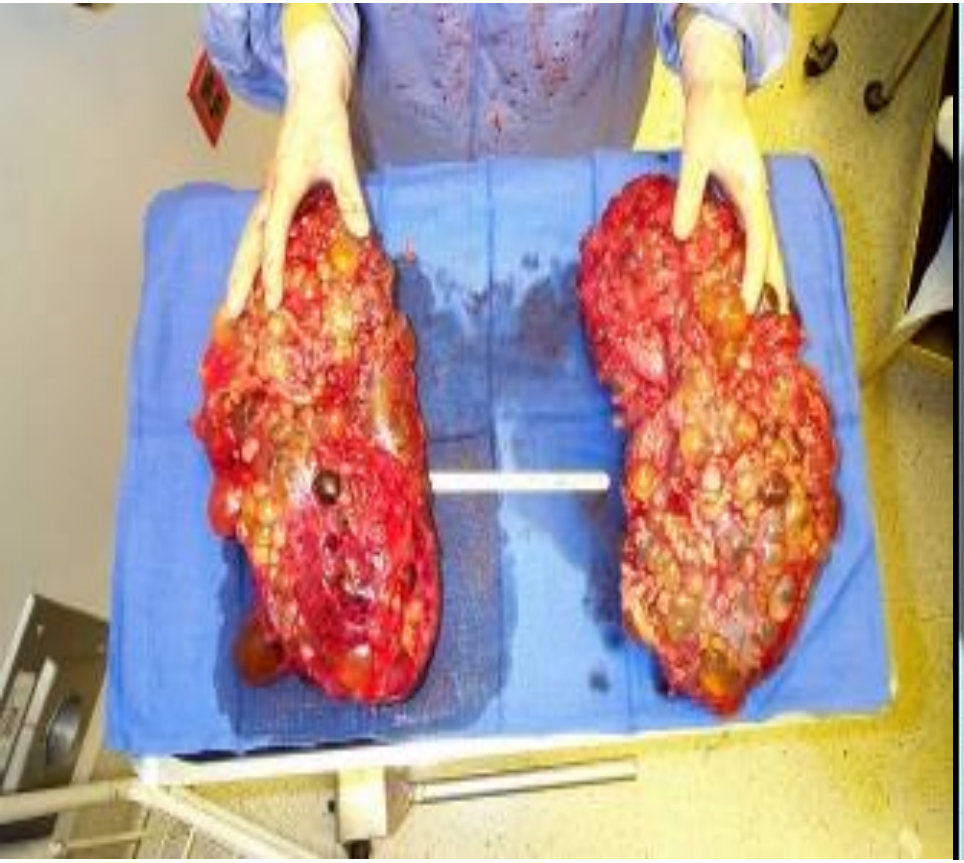
TSC is composed of cells with abundant, eosinophilic, granular cytoplasm. The tumor exhibits the papillary architectural pattern with prominent, foamy histiocytes filling up the fibrovascular cores. C, The other portion of the tumor is solid or contains tightly packed papillae. Scattered, foamy histiocytes are present

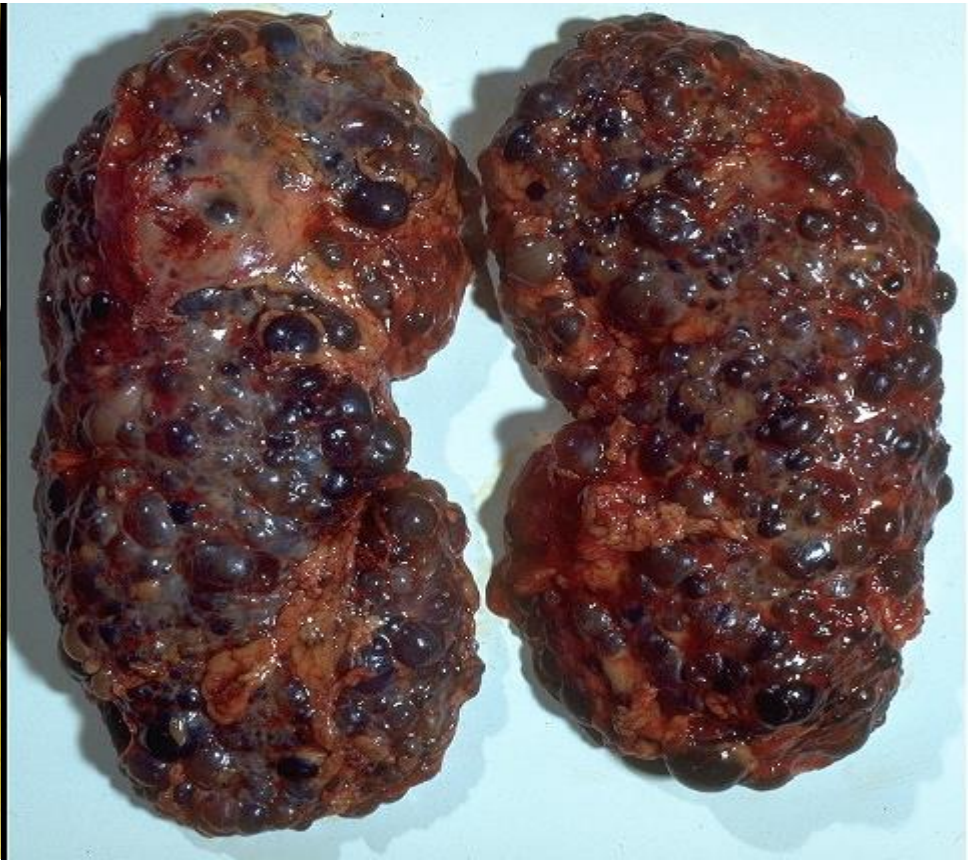


TSC tumor show prominent, papillary architecture and cells with voluminous clear cytoplasm and high nuclear grade.



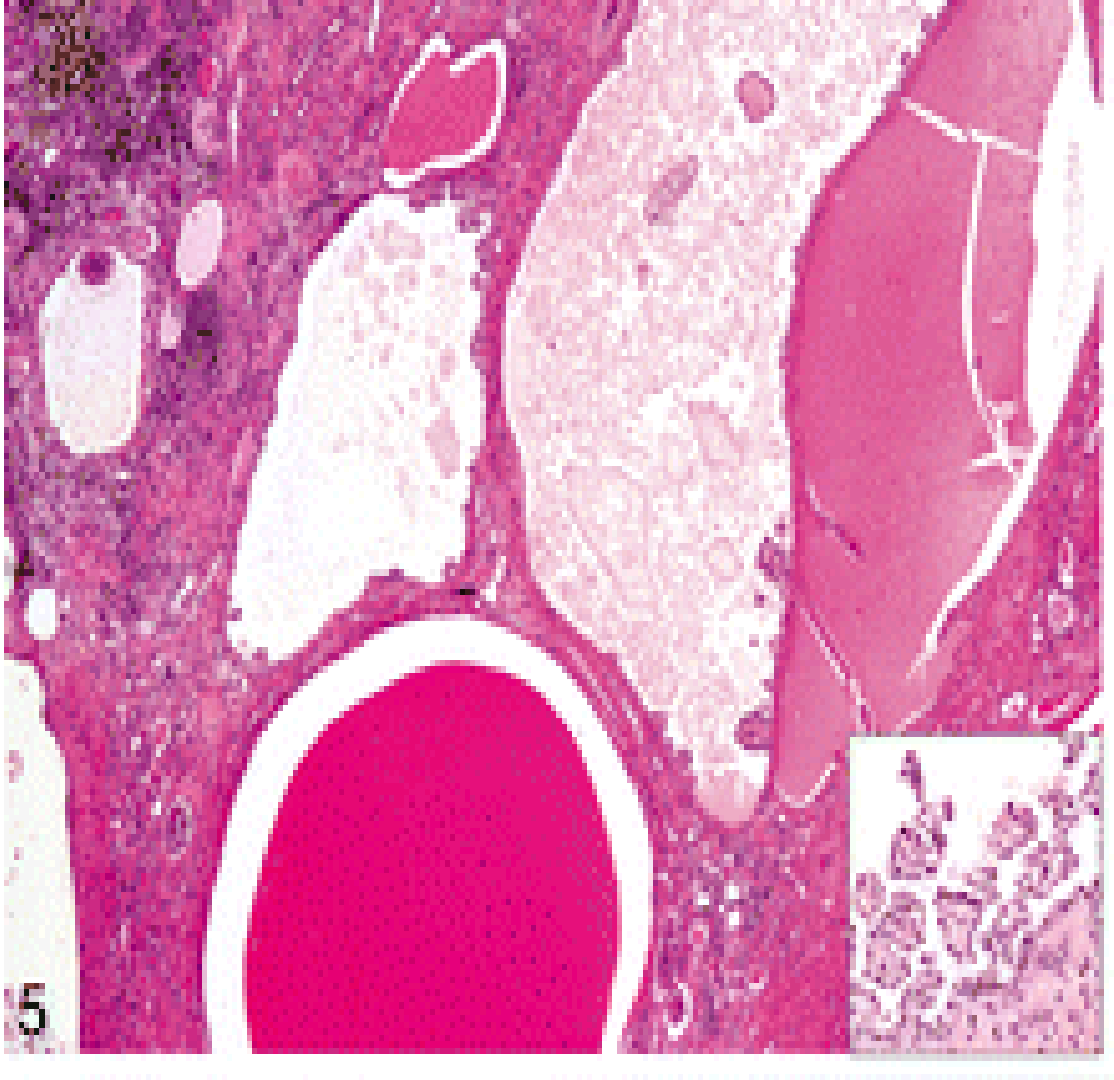
Autosomal-Dominant Polycystic Kidney Disease



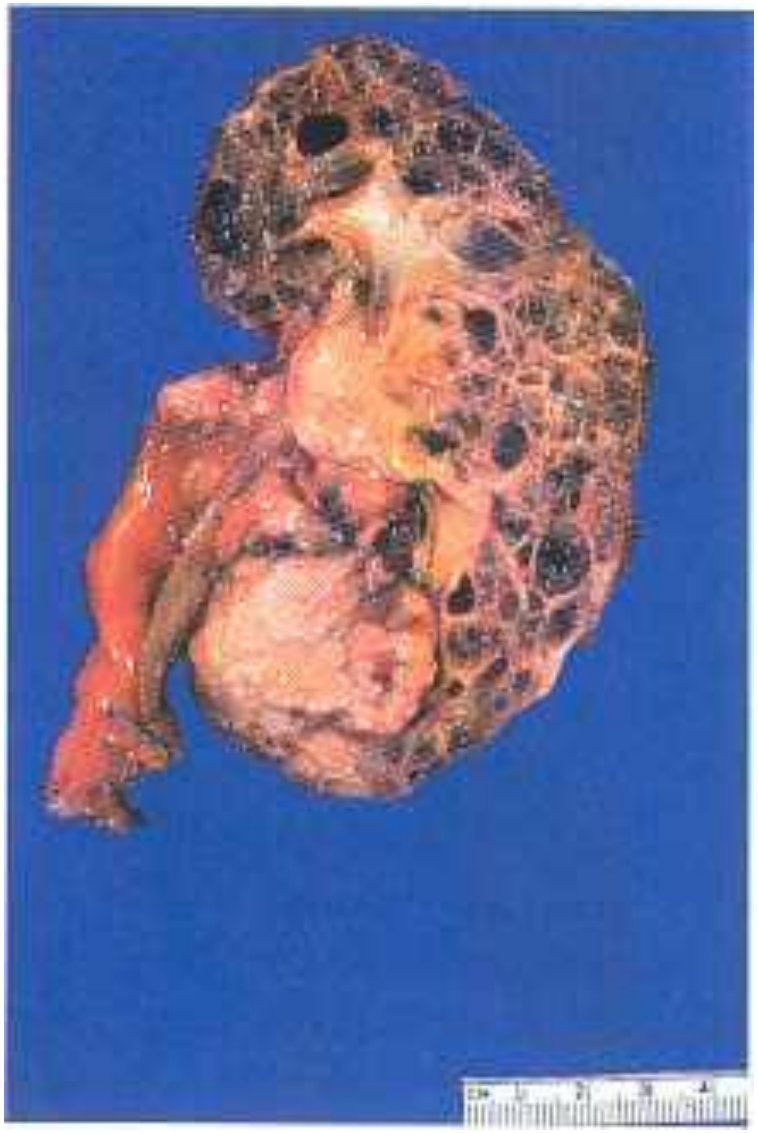


approximately 1 or 2 per 1000 live births and accounting for approximately 10% of cases requiring dialysis or renal transplantation. It has been postulated to be associated with an increased risk of RCC.

The cysts in ADPKD are innumerable, distributed evenly in the renal cortex and medulla, and vary significantly in size. intracystic papillary tuftlike proliferation, is cytologically bland and is present in about 25% of the cases . (precursor lesion for RCC)



Renal cell carcinoma developing in the ADPKD. The tumor was multicentric.

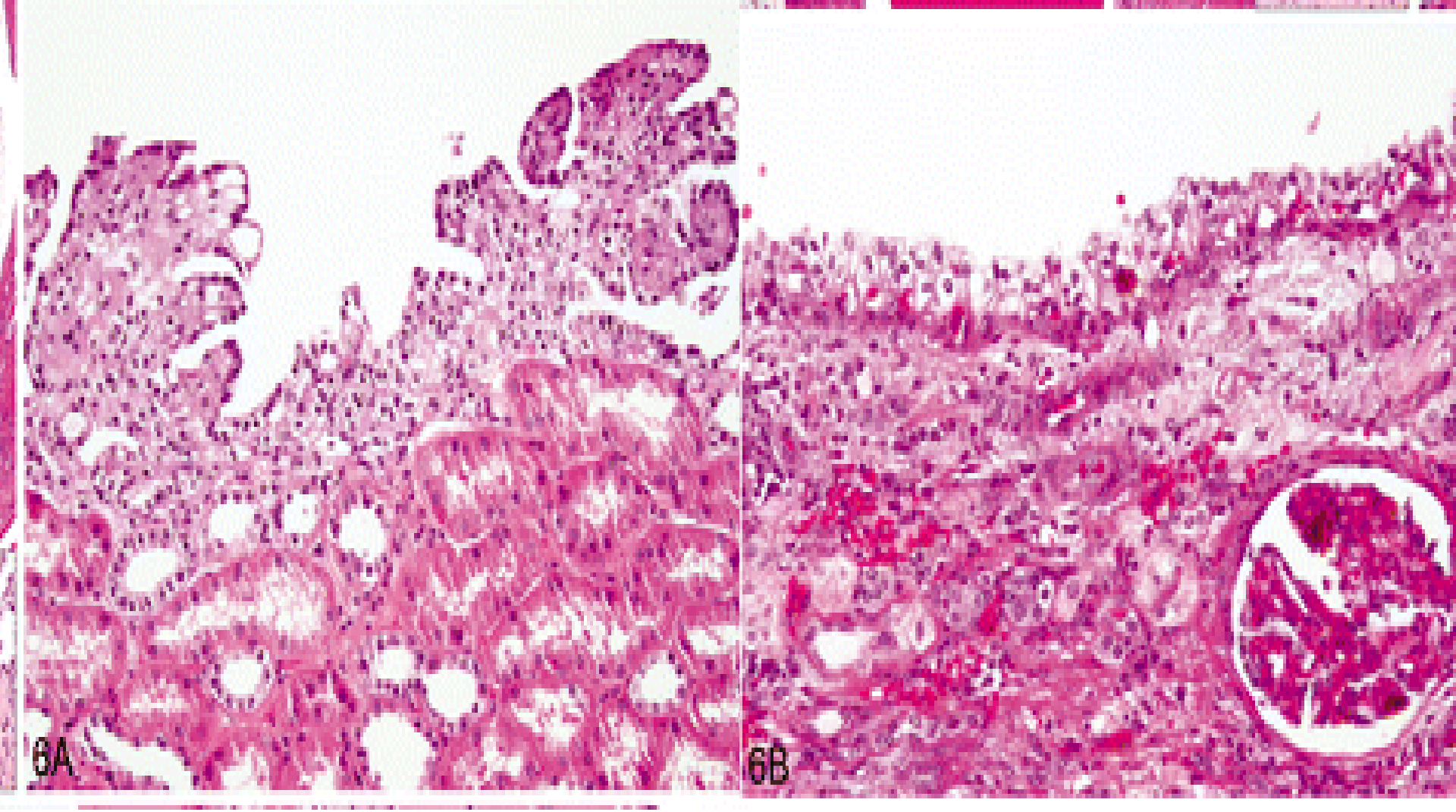


Other Cysts With or Without Associated Tumors

- **Simple cortical cysts:** constitute the most common renal cysts.
- > 27% on radiologic evaluation in individuals older than 50 years.
- The cysts are usually unilocular and oval to round with a smooth outline and lined by a single layer of flattened to cuboidal epithelium, often filled with transudate-like clear or straw-colored fluid.

- Infrequently, such cysts may be multilocular .

- The lining epithelium in some these unilocular or multilocular cysts displays papillary proliferation of cuboidal or hobnail cells with either eosinophilic or basophilic cytoplasm; in some other cysts, the lining may be composed of clear cells in single or multiple layers



The lining in some sporadic, unilocular or multilocular cysts may show focal papillary proliferation composed of cuboidal cells with eosinophilic cytoplasm. B, Some other cysts may be lined by cells with clear cytoplasm in single or multiple layers but without any mural clear cell clusters or nodules

- But, in contrast to multilocular cystic RCC, without any mural clear cell clusters or nodules. Although displaying “atypical” features, these cysts essentially behave in a benign manner.

- Positive for CK7 and CAIX and negative staining for CD10 and racemase.

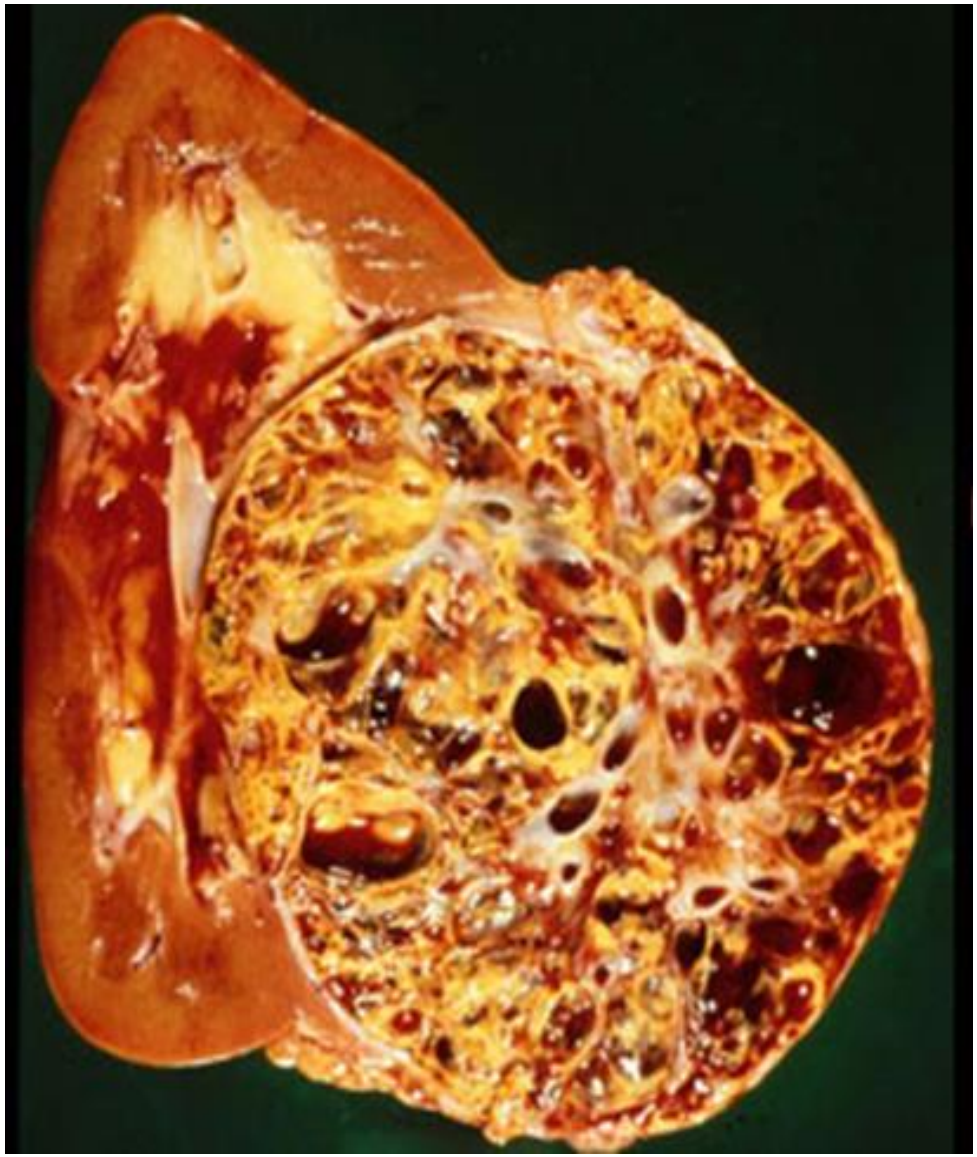
Predominantly Cystic Renal Tumors

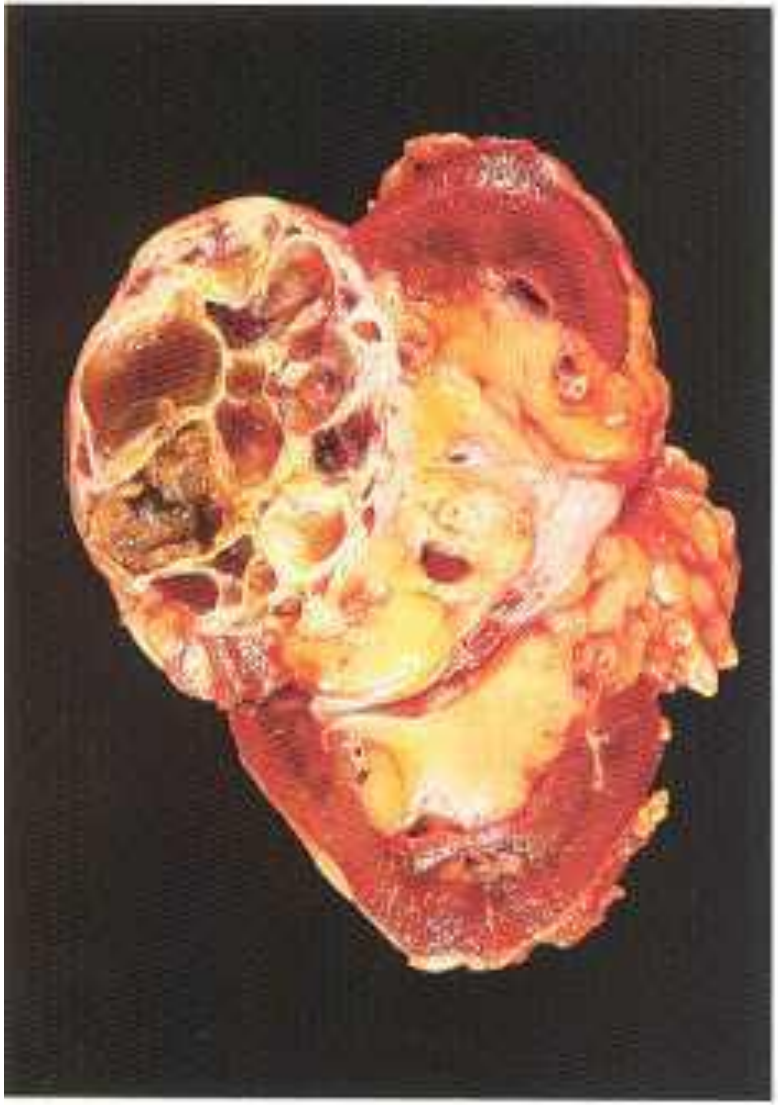
1. Multilocular Cystic RCC:

It is a variant of clear cell RCC Solid, accounts for 4% of all clear cell RCCs, middle-aged adults, F> M

Up to 90% of cases are discovered incidentally

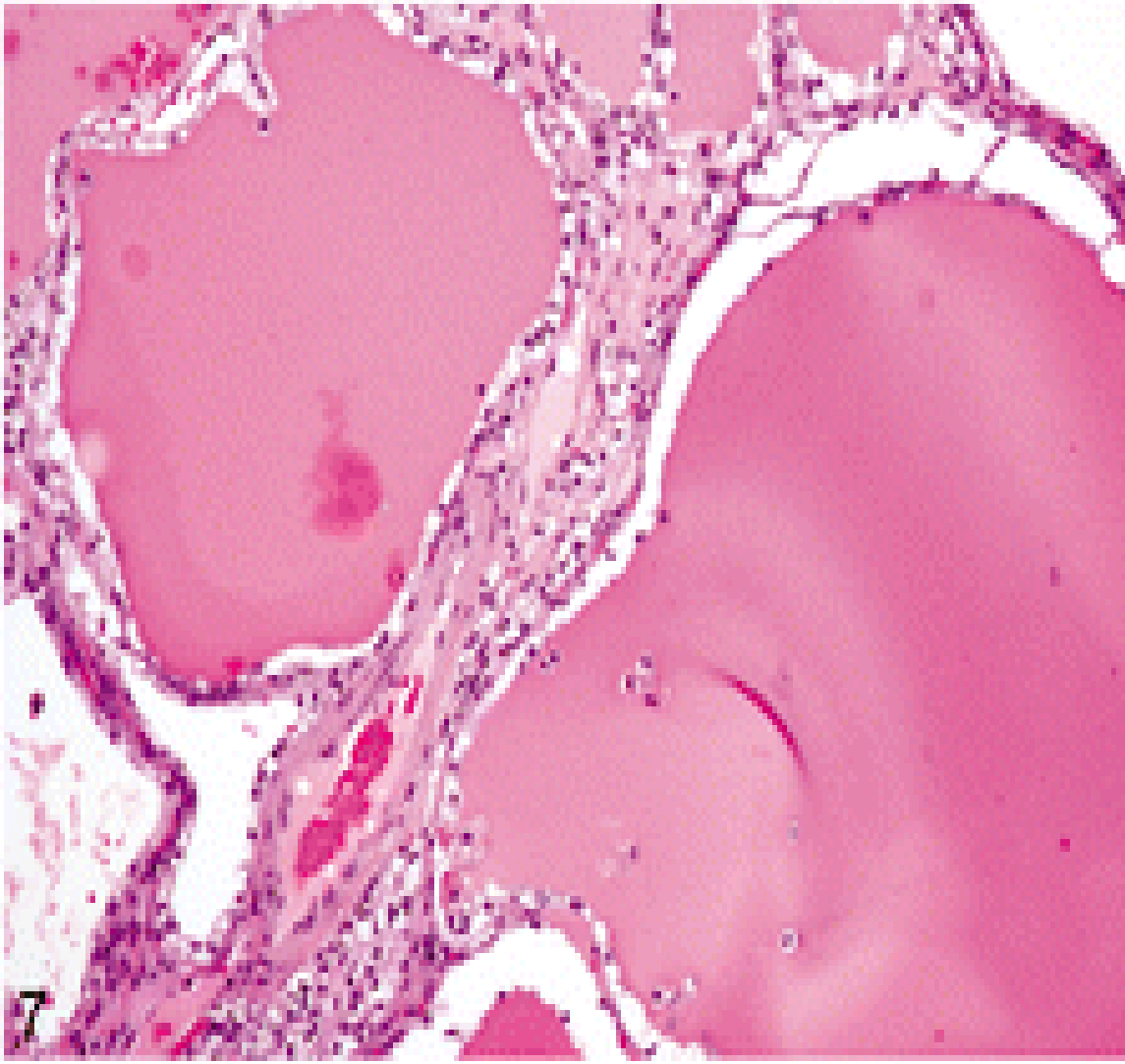
Grossly: unilateral, solitary lesion and it is renal cortical neoplasm with a distinct, multilocular.





Multilocular Cystic RCC.

Microscopically: the tumor is entirely composed of variably sized cysts that are lined by clear cells with low nuclear grade. The thin septations between cysts contain **small clusters of clear cells**. Tumors with an expansile nodular growth within the septa are not considered multilocular cystic RCC but cystic clear cell RCC.



VHL mutations were identified in 25% of tumors. strongly reactive to PAX2 and CAIX, similar to typical, low-grade clear cell RCC. (multilocular cystic RCC being a variant of clear cell RCCs)

Prognosis: is excellent (no recurrence or metastases). (*multilocular cystic renal cell neoplasms of low malignant potential)*.

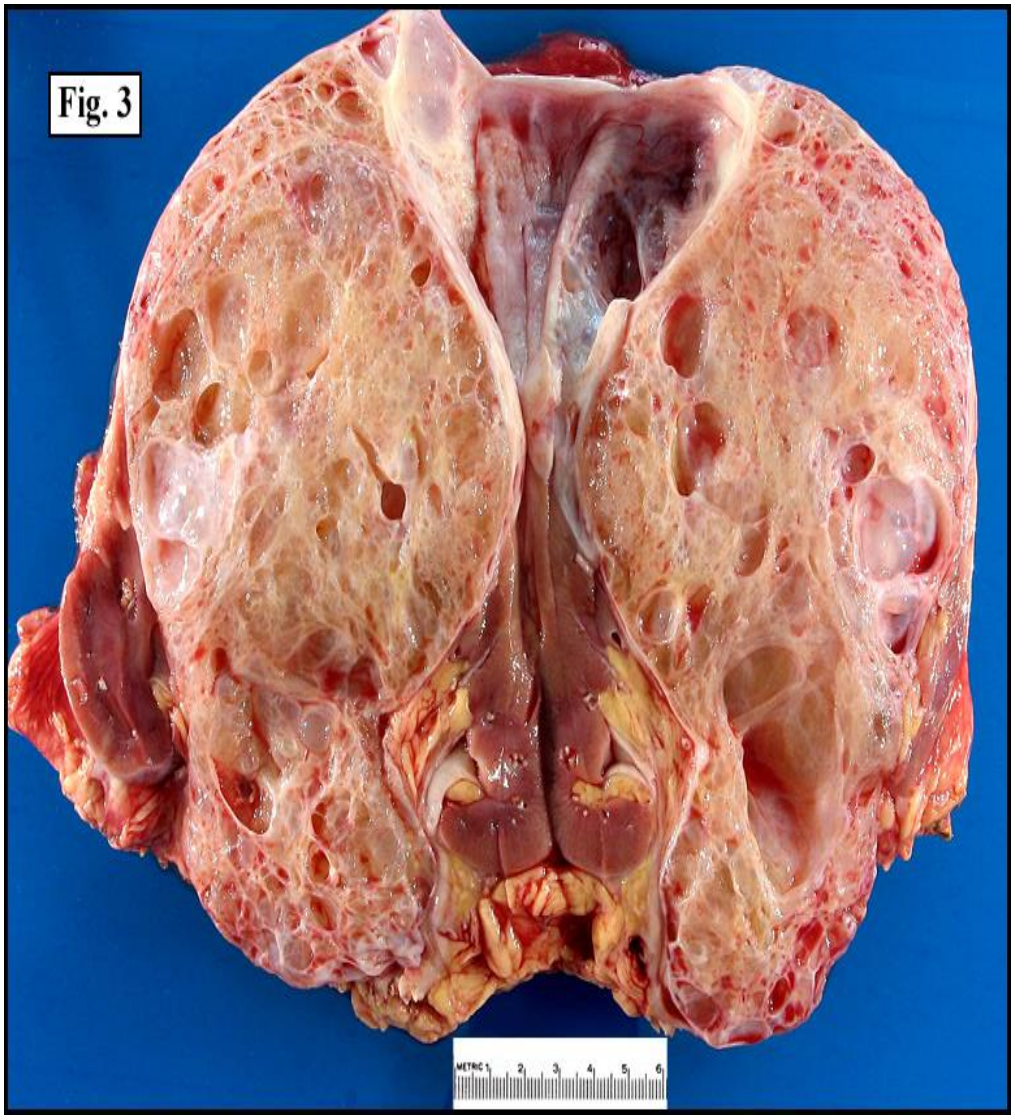
The differential diagnoses include:

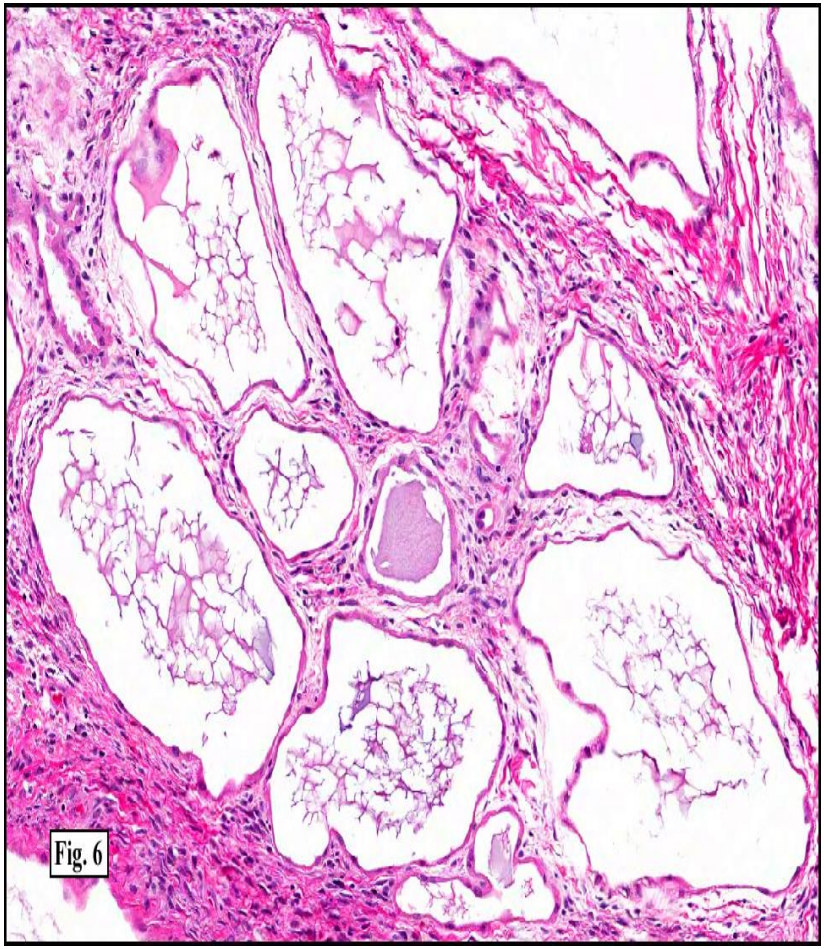
- cystic nephroma,
- benign multilocular renal cortical cysts
- clear cell papillary carcinoma with predominant cystic configuration.

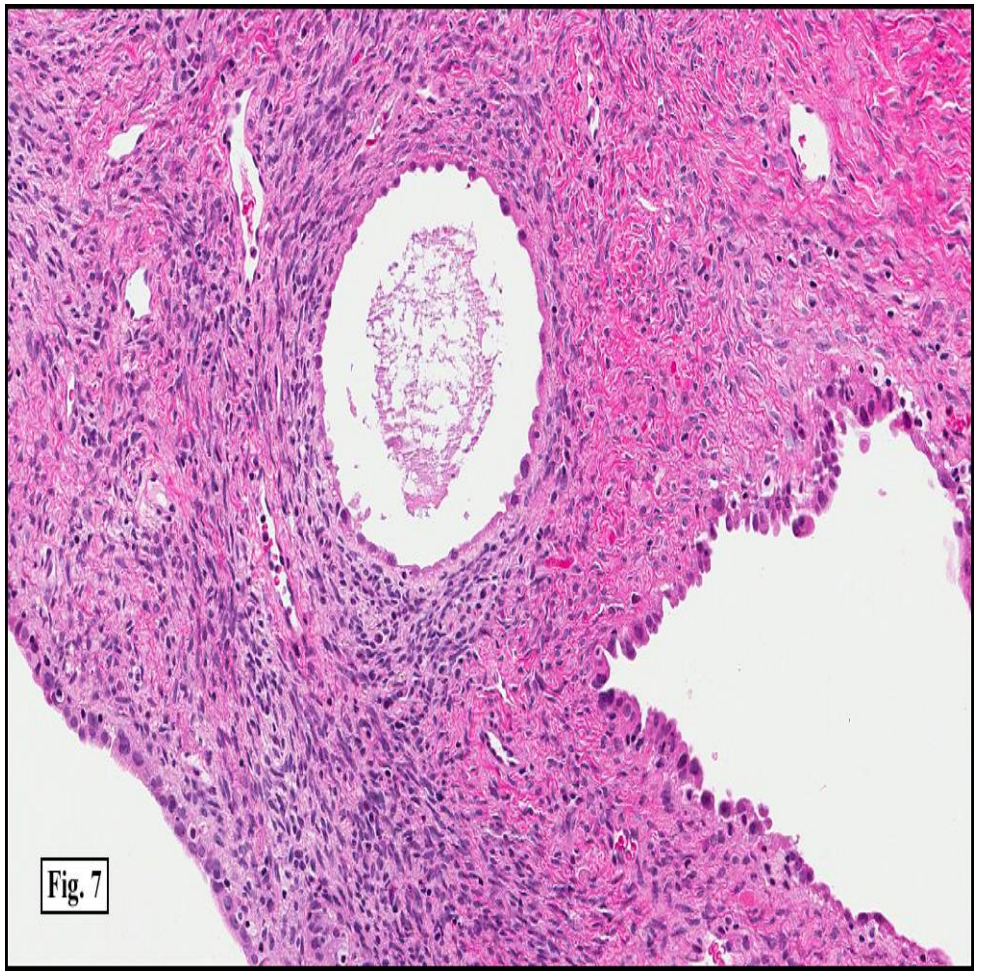
Multicystic Nephroma

It is uncommon, arises in early infancy ,but may present clinically at any age and both sex

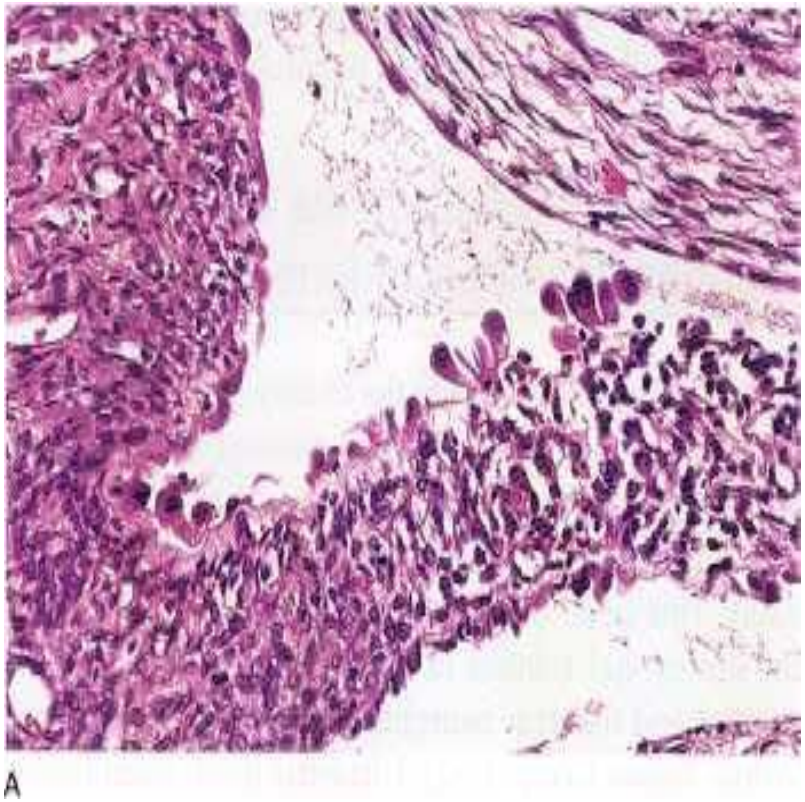
Grossly: its solitary, unilateral, sharply delineated from uninvolved renal parenchyma, cut surface multilocular cystic , the wall of the cyst thin lack papillary projections.

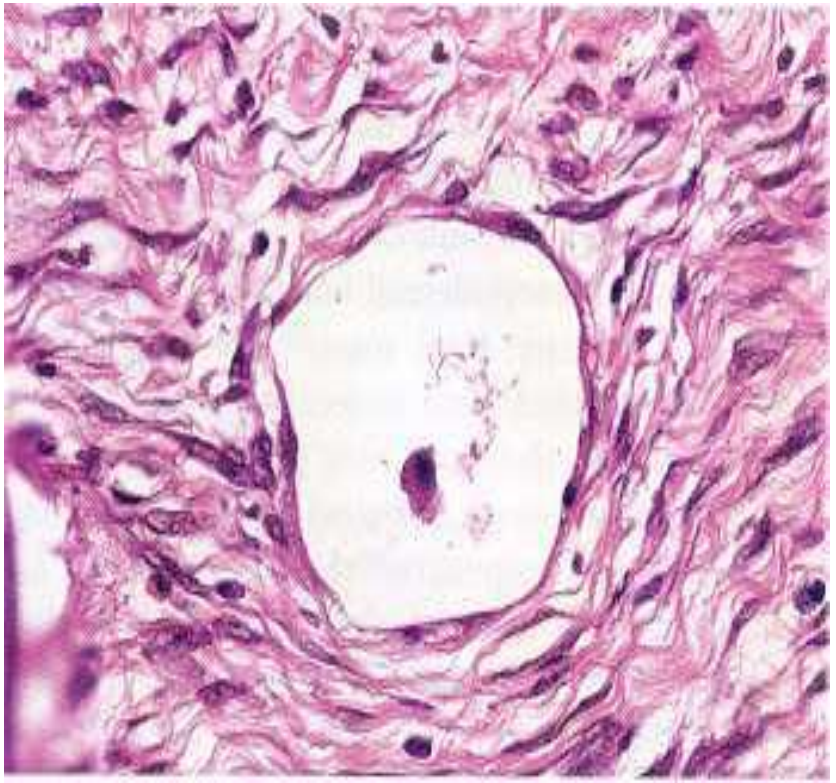






Microscopically: its showing multiple cysts lined by flattened epithelium and separated by a cellular spindle cell stroma The lining was by a single layer of flattened epithelium with eosinophilic cytoplasm simulating endothelium and bland hyperchromatic nuclei ,regions had a hobnail morphology





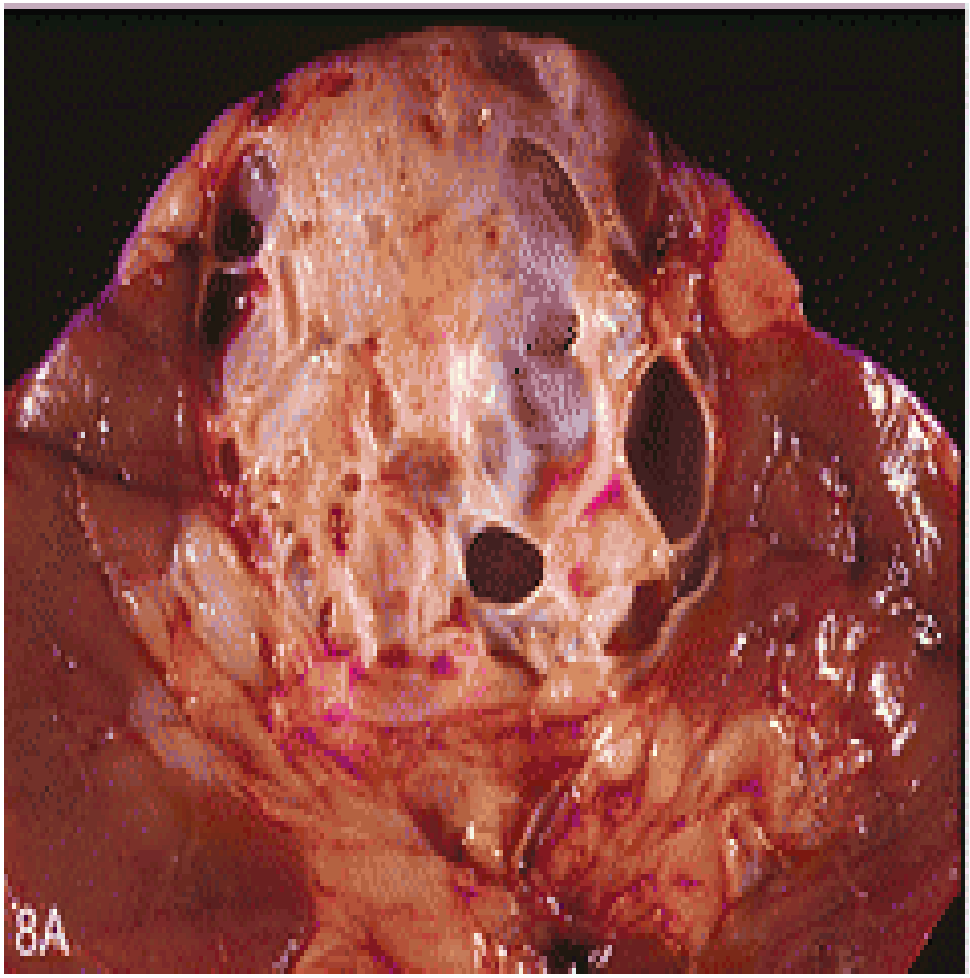
A and B, Multicystic nephroma. A, The epithelial lining of the cyst has a hobnail quality. B, In this instance the cyst lining is flat, simulating endothelium.

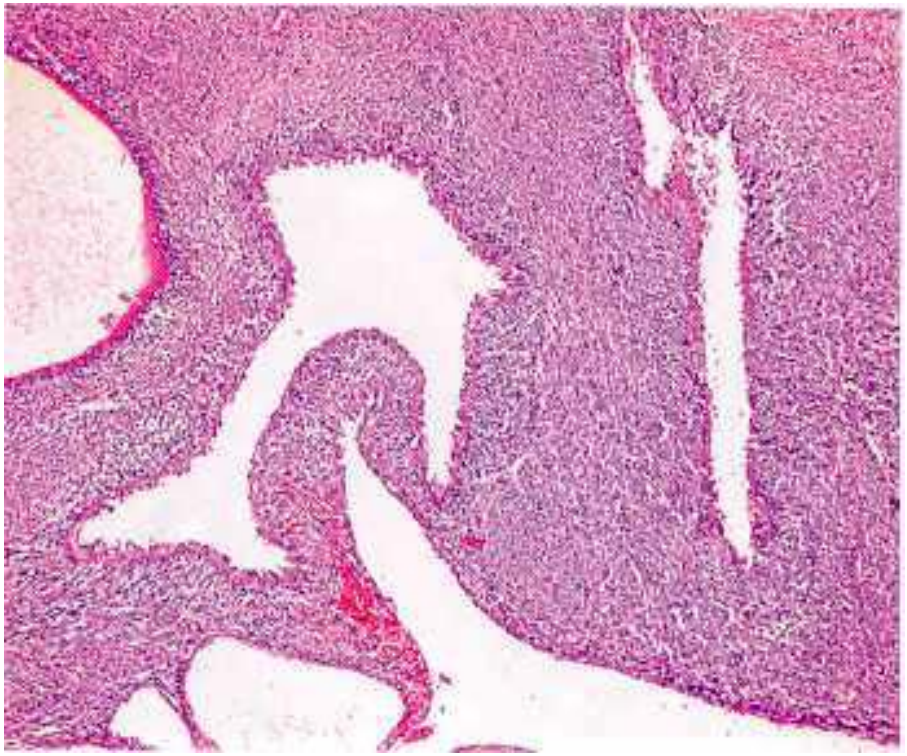
A few cases of multicystic nephroma have been reported in adult patients to contain clusters of clear cells with the appearance of renal cell carcinoma, suggesting that this entity may have a potential for malignant degeneration.

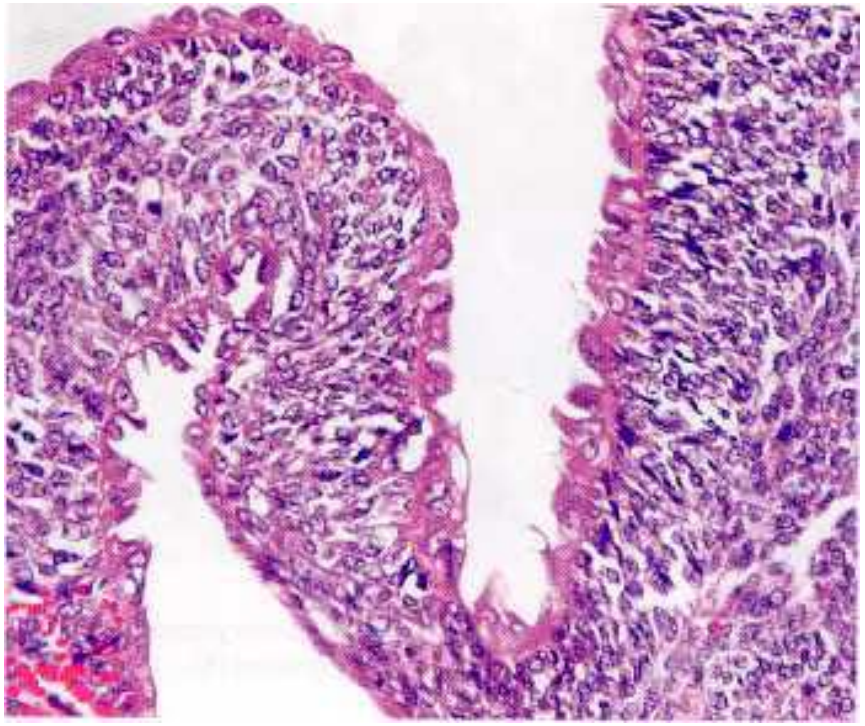
3. Mixed Epithelial and Stromal Tumor

Generally occuring in middle aged and older women

Grossly:
indistinguishable from that of multicystic nephroma







microscopically: (low and high power) spindle cell proliferation in between the individual cysts resembles ovarian stroma ,including the expression of hormone receptors and presence of structure resembling corpora albicantia.

4. Clear Cell Papillary RCC:

- Occurring in a sporadic setting, it shows similar histologic features to the tumors seen in patients with ESRD; some tumors have a prominent cystic component.

- The molecular alterations mediating the development of these tumors currently remain unknown.

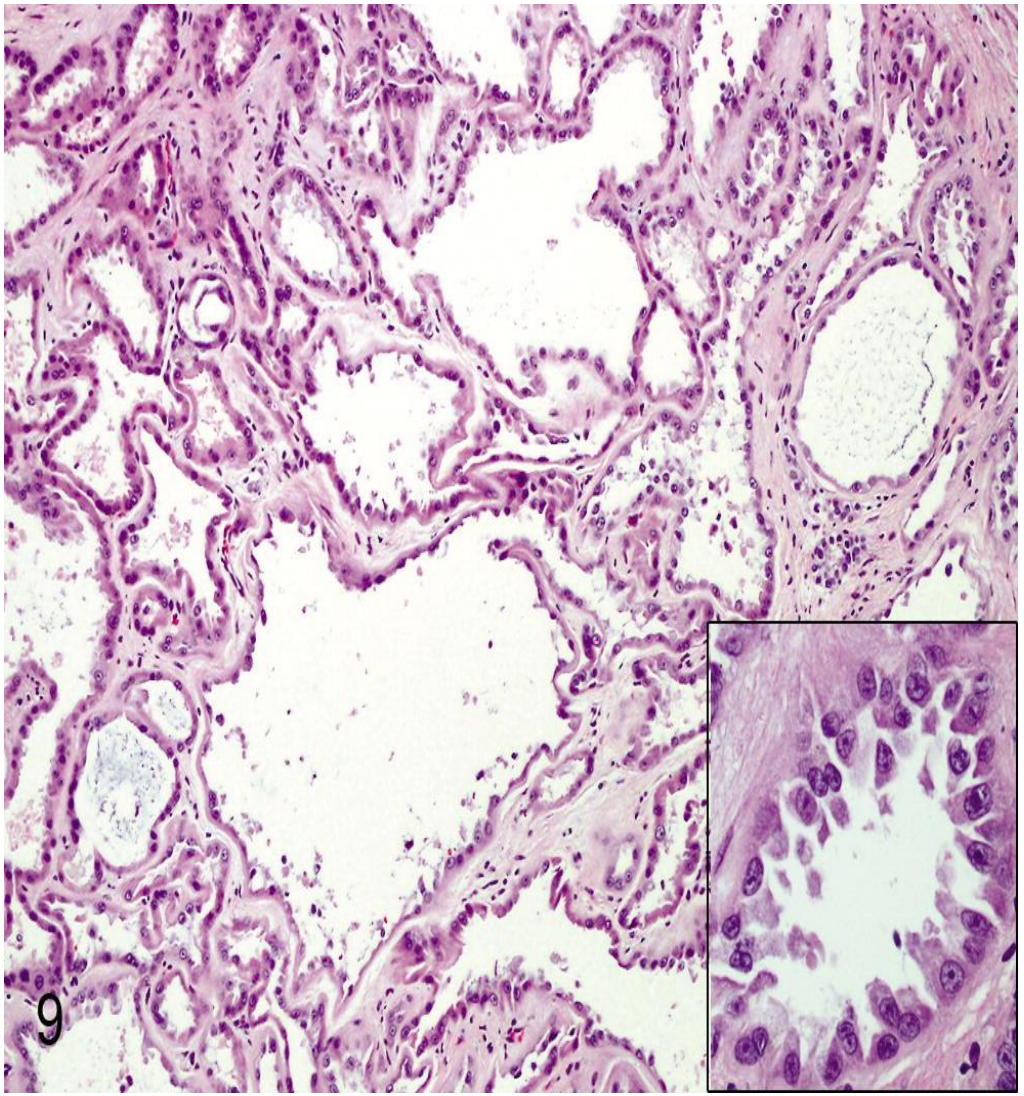
5. Tubulocystic Carcinoma of the Kidney

It is relatively uncommon, M>F.

less aggressive, 10% local recurrence or distant metastasis.

Grossly: these tumors often have spongy cut surfaces with variably sized cysts.

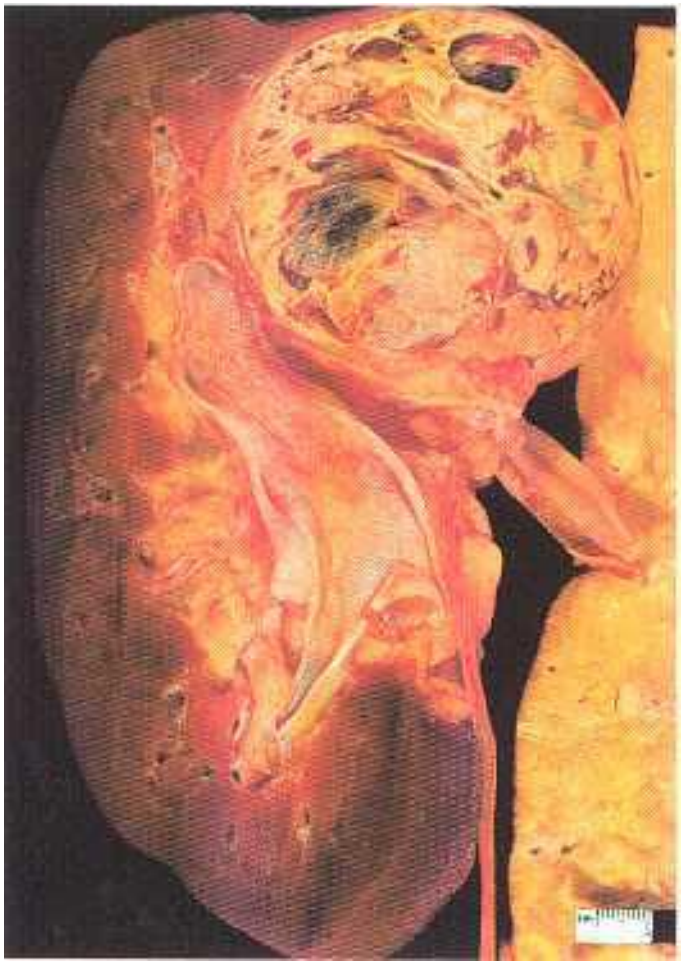
Microscopically: consists of variably sized tubules and cysts lined by a single layer of cuboidal or hobnail cells, often with abundant eosinophilic cytoplasm and large nuclei. Intervening stroma is characteristically fibrotic

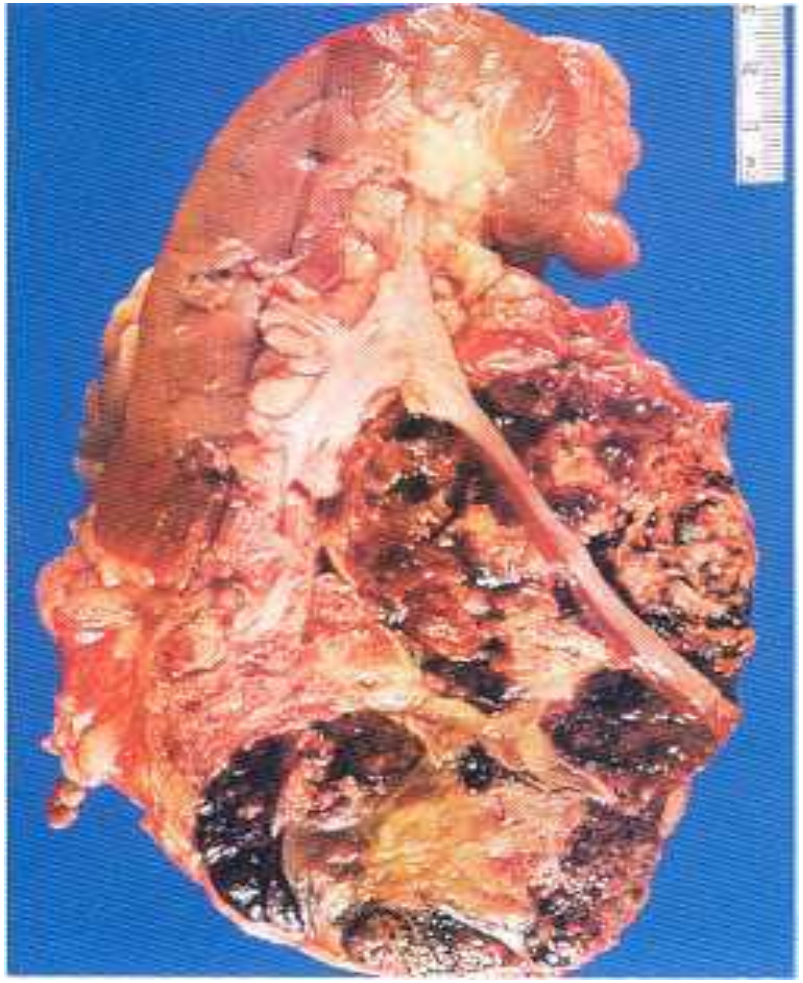


6. Intrinsic Cystic Formation in Other Renal Cell Tumors of Various Subtypes

focal to extensive cystic formation is seen in many other RCC subtypes to a varying degree.

- Clear cell RCC(especially with low nuclear grades).
- papillary RCC.
- chromophobe RCC.
- collecting duct carcinoma.
- oncocytoma
- A, thyroid-like follicular carcinoma of the kidney (rare morphologic subtype of RCC) is characterized by a follicular, partially cystic, architectural pattern mimicking metastatic thyroid carcinoma.





Gross appearances of renal cell carcinoma. Both tumors are relatively well circumscribed and variegated, with a combination of cystic, solid, and hemorrhagic areas.

7. RCC With Cystic Necrosis:

- It is a relatively common phenomenon, often associated with clear cell RCC. extensively necrotic cystic RCCs have been shown to be capable of aggressive clinical behavior.

- Extensive necrosis is not uncommon in papillary RCC. However, the extent of necrosis and cystic change in papillary RCC has no significant effect on the prognosis.

8. Epithelial Cysts in Mesenchymal Tumors

- It have been reported in primary renal synovial sarcoma and angiomyolipomas.
- These cysts have been hypothesized by some to represent entrapped, cystically dilated renal tubules in the corresponding mesenchymal tumors.

Conclusions:

- The presence of multiple renal cysts, both acquired and syndromic, can be associated with a variety of renal tumors.
- The morphology of the cysts and associated tumor types can help predict the genetic or acquired basis of the lesions, and particularly in specimens with no accompanying pertinent clinical history, such potential associations should be suggested in surgical pathology reports.


Thank you

References:

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2. Rosai and Ackerman،Surgical Pathology 10th edition volume 1 chapter 17