

Diagnostic Approach to Cystic Neoplasms of the Kidney



Dr. Fatima Al-Hashimi, MD, FRCPath
Salmaniya Medical Complex, Bahrain

Various hereditary, acquired and neoplastic conditions can lead to cyst formation in the kidney.

The most frequently encountered form of renal cystic lesion is the unilocular, simple, renal cortical cyst

Others can appear on imaging as solitary or multiple, complex cystic lesions, with variable likelihood of being malignant neoplasms.

Cystic lesions of the kidney

Hereditary cysts and Potential
Preneoplastic Lesions

Cystic Neoplasms

Cystic Diseases Commonly associated with Tumours

- ✎ Acquired Cystic Disease of the kidney
 - ACD-Associated RCC
 - Clear Cell Papillary RCC
- ✎ von Hippel-Lindau Syndrome
- ✎ Tuberous Sclerosis Complex
- ✎ Autosomal-Dominant Polycystic Kidney Disease
- ✎ Other cysts with or without associated Tumours

Renal Cystic Diseases Associated With Tumor Development				
Cystic Disease	Disease Incidence	Cancer Risk	Tumor Types	Potential Preneoplastic Lesions
ESRD and ACD of the kidney	ESRD > 1:3000; ACDK proportional to duration of dialysis (10 y, >90%)	Approximately 3%–7%	ACD-associated RCC; clear cell papillary RCC; usual types of RCC (papillary, clear cell, chromophobe)	Papillary adenoma; clustered microcystic lesions
von Hippel-Lindau disease	1:30–50 000	45%–60%	Clear cell RCC	Clear cell cyst (CAIX positive)
Tuberous sclerosis complex	1:10 000	2%–3%	Angiomyolipoma; clear cell RCC; oncocytoma; RCC, unclassified/TSC-related	Unknown; cysts lined by eosinophilic cells with atypia
Autosomal-dominant polycystic kidney disease	1:1000	Equivocal	Clear cell RCC; papillary RCC	Intracystic papillary epithelial proliferation
Renal cysts with atypical epithelial proliferation	Age-related; >25% at 50 y and older	Likely extremely low or nil	Coincidentally associated with RCCs	Unknown

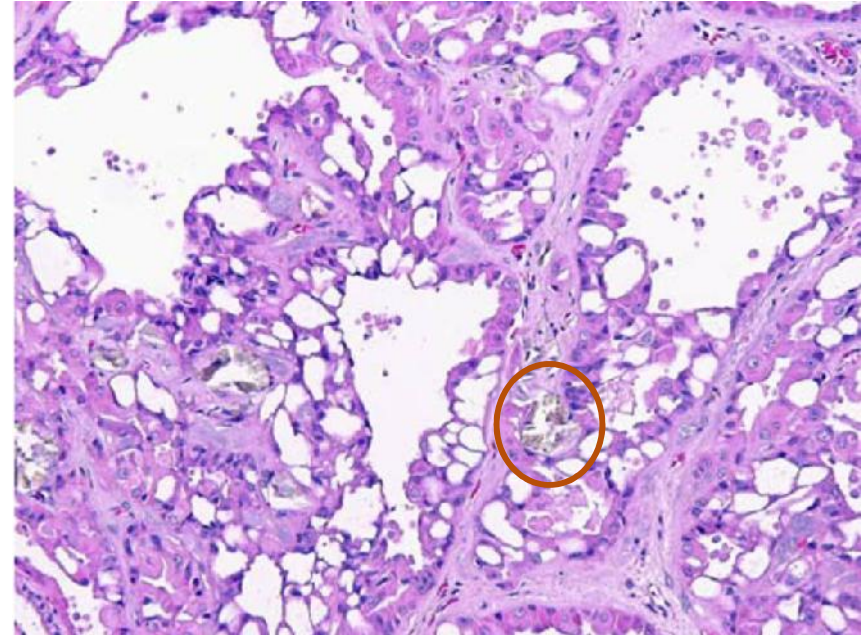
Abbreviations: ACD, acquired cystic disease; ACDK, acquired cystic disease of the kidney; CAIX, carbonic anhydrase IX; ESRD, end-stage renal disease; RCC, renal cell carcinoma; TSC, tuberous sclerosis complex.

Acquired Cystic Disease of the Kidney

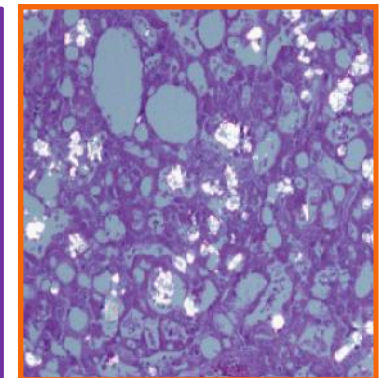
- ∞ Incidence of developing RCC in patients with ACDK is 3-7%, that represents up to 100 times greater risk than the general population
- ∞ The duration of dialysis correlates (ESRD) with the incidence of ACDK and RCC
- ∞ The tumour types seen in ESRD and ACDK encompass:
 - Three common subtypes of RCC, including: Clear Cell RCC, papillary RCC and Chromophobe RCC
 - The two other types are predominantly seen in ESRD: acquired cystic (ACD)-associated RCC and clear cell papillary RCC

ACD-associated RCC

- ☞ ACD-associated RCC is the most common subtype of RCC seen in ACDK, accounting for the dominant mass in 36% of end-stage kidneys overall and in 46% ACDK
- ☞ The tumour shows various combinations of acinar, solid alveolar, solid, microcystic and papillary architecture
- ☞ The prominent papillary architecture may lead to misinterpretation as type 2 papillary RCC
- ☞ Positive for AE1/3, CD10, RCC-Ag, and AMACR. Negative or focal for CK7.

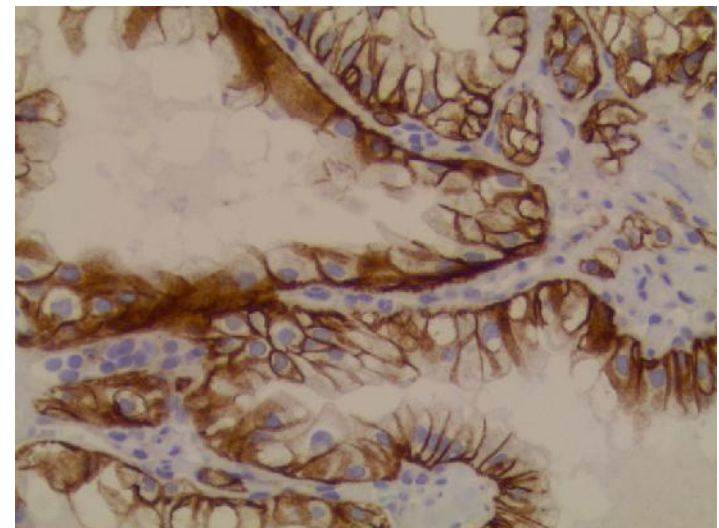
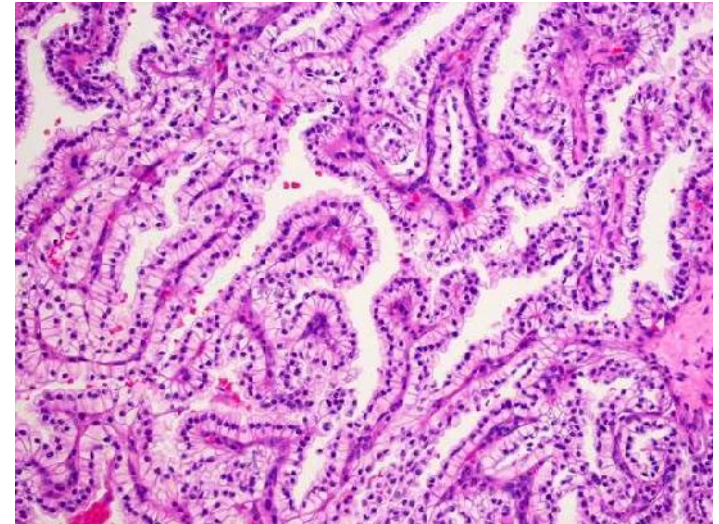


Tumour cells usually have abundant granular, eosinophilic cytoplasm and large nuclei with prominent nucleoli. Intracytoplasmic and intercellular lumina, imparting a cribriform or sievelike appearance. Exclusively have intratumoral oxalate crystals.



Clear Cell Papillary RCC

- ∞ 2nd most common subtype of RCC in ESRD
- ∞ CCP-RCC is composed of various proportions of papillary, tubular, cystic and solid or nested architectures with clear cytoplasm
- ∞ Small blunt papillae, focal branching papillae and interconnecting ribbon are common. However, extensively branching papillae are uncommon
- ∞ Low-grade (Fuhrman grade 1–2) nuclei
- ∞ Most 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
- ∞ Foamy macrophages, tumor necrosis, and vascular invasion are not a feature
- ∞ Cup shaped staining for CA-IX. CK7 positive. AMACR and CD10 negative

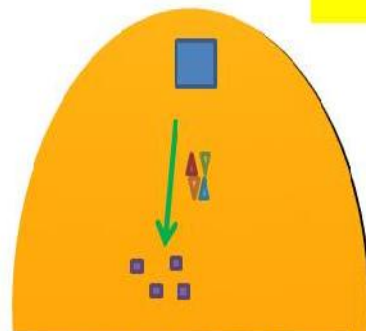


RCCs in ESRD

- ∞ The biologic behaviour of RCCs in ESRD is reported to be less aggressive than that of the RCCs in sporadic or non-ESRD settings
- ∞ The tumours, are often smaller and at lower stage. However, a few cases have behaved aggressively and metastasized
- ∞ ACD-associated RCC may have a greater potential for aggressive behavior than do other types of tumours in ESRD
- ∞ Rare cases with sarcomatoid features have been reported, and as would be expected, these cases show aggressive clinical behaviour

von Hippel-Lindau Syndrome

Von Hippel-Lindau Syndrome Defective gene: VHL



The gene product of VHL is a component of the VCB-CUL2 complex that breaks down proteins no longer needed or are damaged. One of these is HIF-2 α , which is part of the HIF protein involved in cell division among other functions. By removing HIF by degradation of HIF-2 α , excessive cell growth and division are prevented. In this way the VHL protein acts as a tumor suppressor

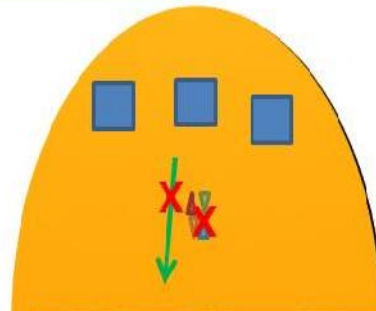
▲ E3 ubiquitin protein ligase

▲ VCB-CUL2 complex

■ HIF-2 α degradation products

■ hypoxia-inducible factor 2-alpha [HIF-2 α]

Normal Cells

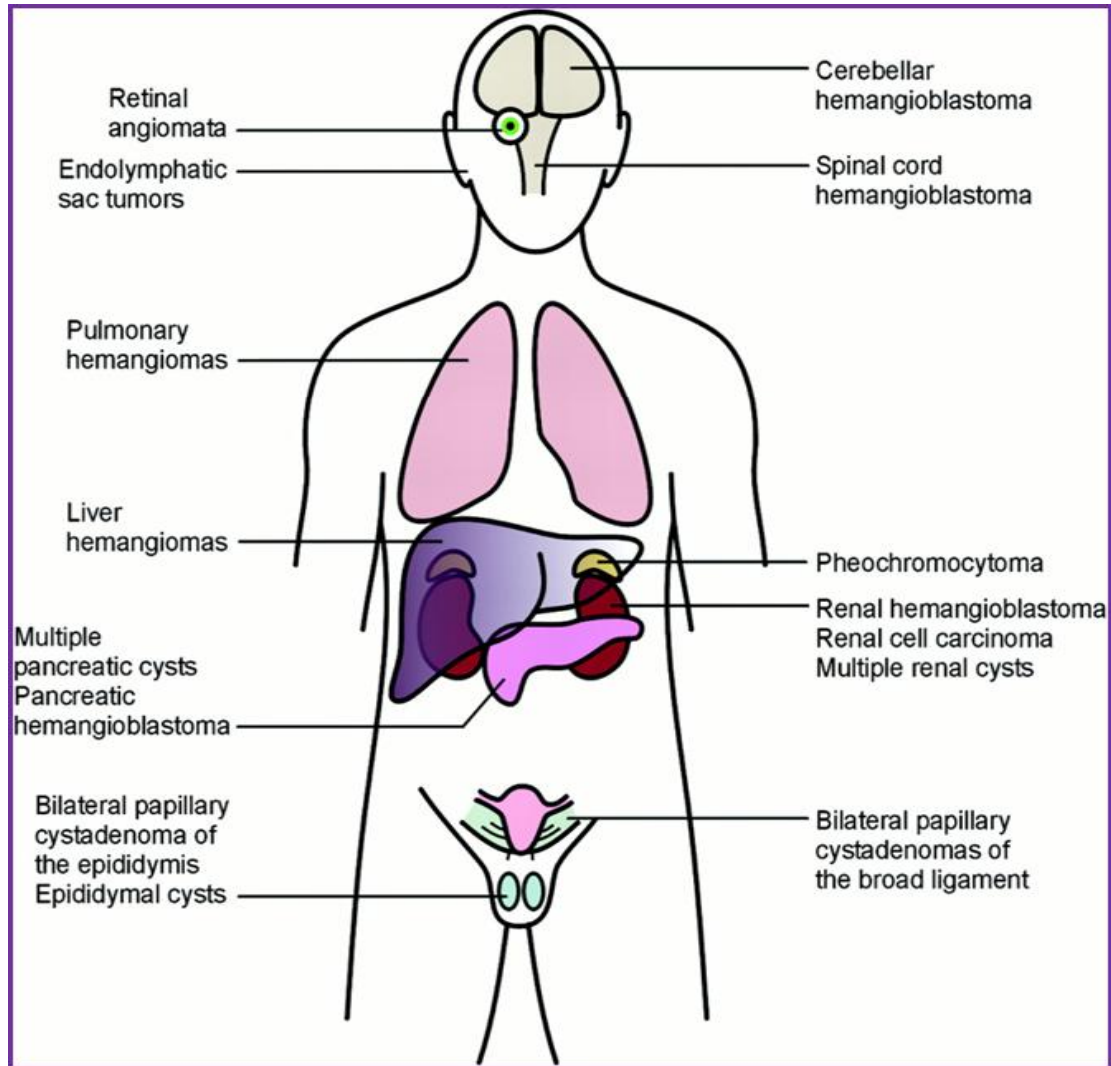


Mutation of VHL results in either lack of the protein product or an abnormal product. Hence HIF-2 α is not degraded and accumulates. This allows HIF to continue functioning with increased cell division and growth leading to tumor formation. Consequently patients have retinal angiomas, and capillary hamartomas. Systemically cerebellar hemangioblastomas occur. Benign and malignant tumors may appear in many organs.

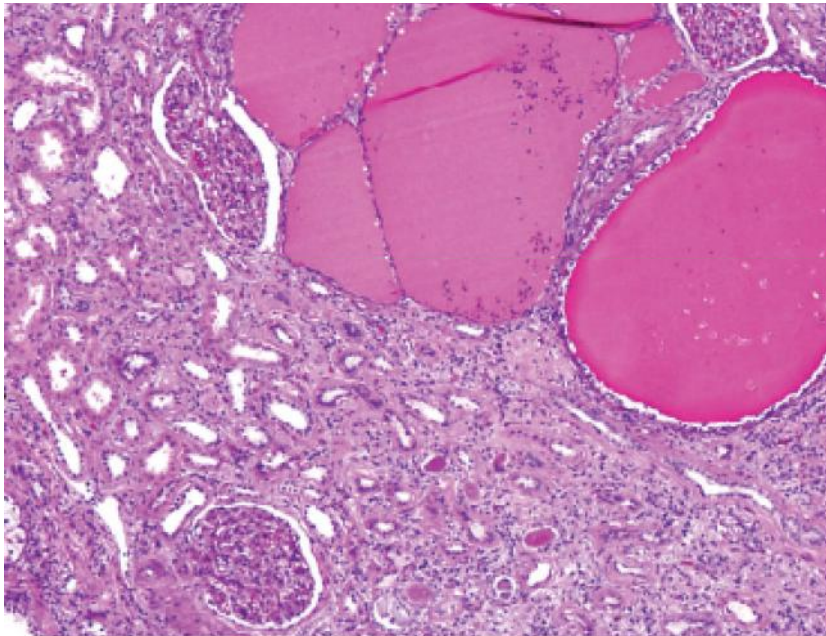
Mutated Cells

Autosomal dominant,
deletion of gene located on 3p25-26

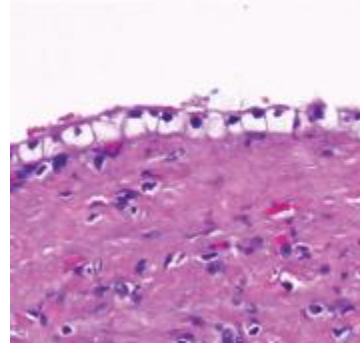
von Hippel-Lindau Syndrome



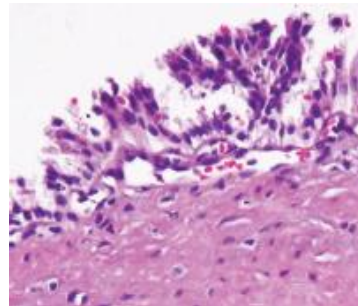
Cysts in VHL Disease



The cysts from patients with VHL disease are multiple, bilateral, and lined exclusively by clear cells.



Benign cyst, lined by a one-cell thick lining



Atypical cyst, 2-3 cells thick with focal papillary tufting

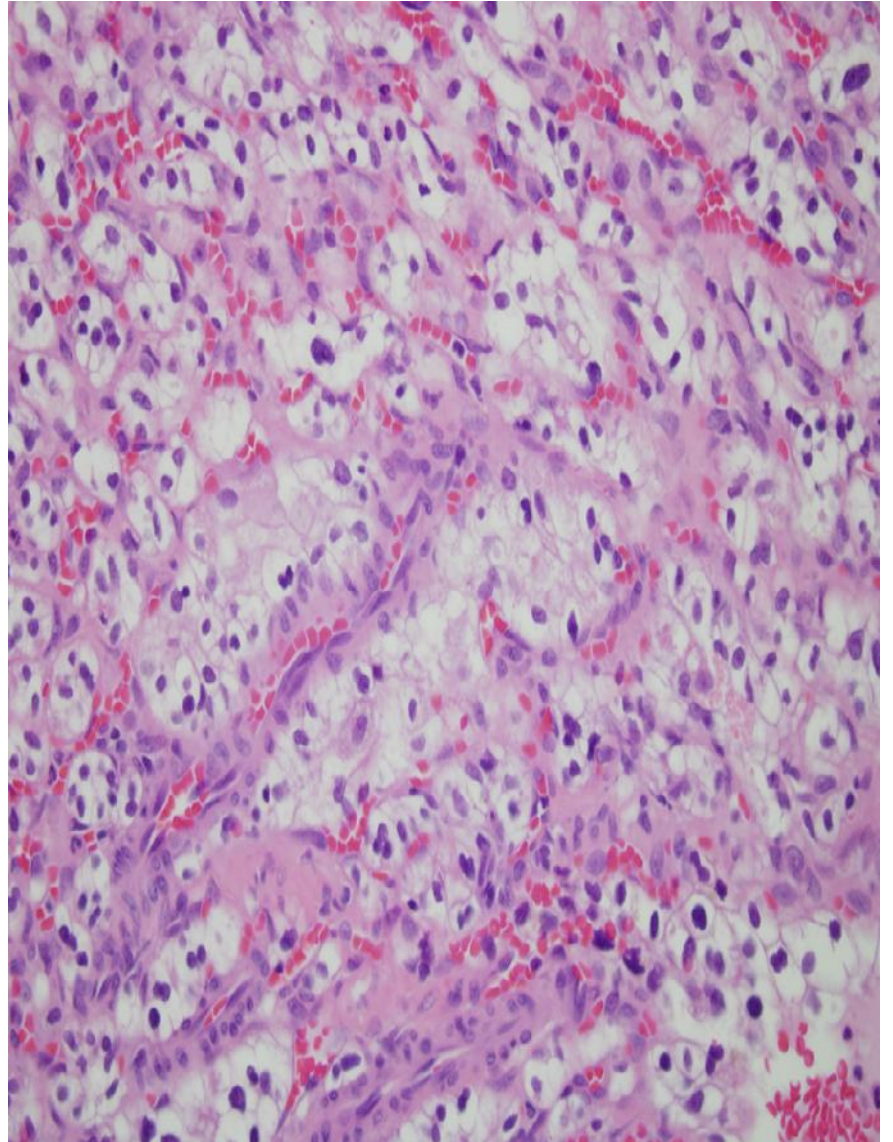
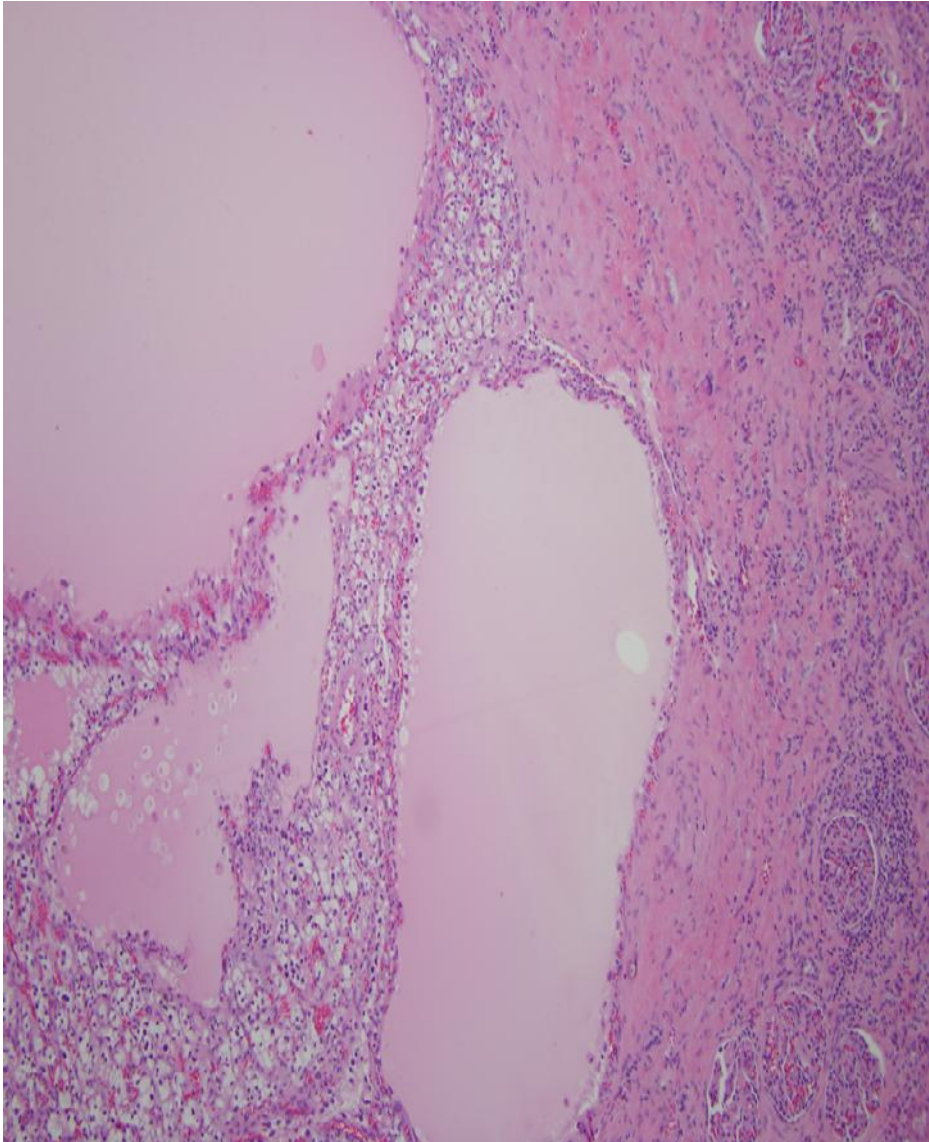
VHL-associated RCC

RCC is often multicentric and bilateral. In patients with VHL germline mutation, deletion of the second VHL allele is associated with overexpression of CAIX.

Whether histologically designated as benign or atypical, the cysts lined by clear cells, or even single renal tubular epithelial cells with the VHL gene deletion likely present precursor lesions for CCRCC

Almost all tumours in the VHL setting are clear cell RCCs of low nuclear grade (Fuhrman grade 1/2). The RCCs have often multicentric and bilateral, arising both in cysts and de novo from noncystic renal parenchyma

As RCCs continue to develop in both kidneys, clinical management relies on a delicate balance between excising tumours (>3cm) to prevent mets and preserving renal tissue



Tuberous Sclerosis Complex

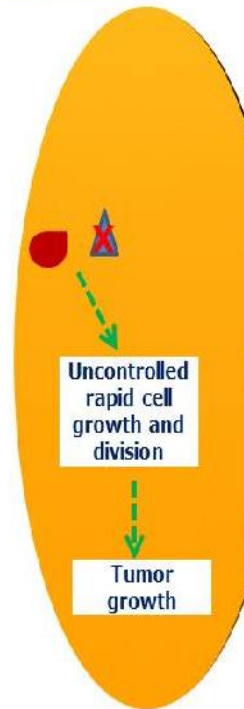
▲ Hamartin
● Tuberin

Tuberous Sclerosis 1 Defective gene: TSC1

The TSC1 gene product is a protein called hamartin. Hamartin interacts with tuberin, the TSC2 gene product. Together they help control cell growth and size. They act as tumor suppressors by controlling a wide variety of other proteins that promote rapid cell growth and division.

Rapid cell growth and division prevented; tumor suppression

Normal Cells



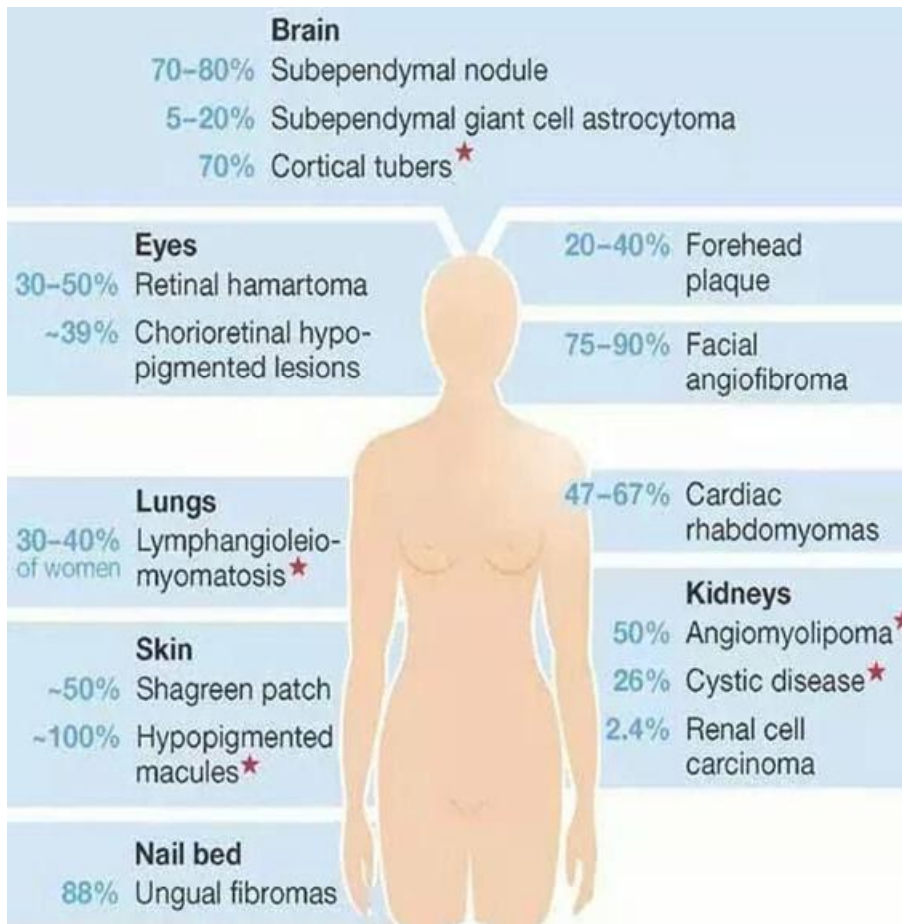
Mutated TSC1 produces a nonfunctional hamartin protein. Consequently it can no longer interact with tuberin and cells grow and divide in an uncontrolled manner. This mutation thus allows tumor growth that occurs in the form of hamartomas at numerous sites both in the eye and systemically.

Mutated Cells

Autosomal dominant, hereditary disease.

Underlying molecular alterations are inactivating mutations of TSC1 or TSC2, tumour suppressor genes on chromosome arm 9q and 16p encoding hamartin and tuberin, respectively.

Tuberous Sclerosis Complex



- ☞ Renal cysts occur in 30-40% of cases. Usually small and scattered within an otherwise unremarkable, intervening renal parenchyma
- ☞ Typical cysts of TSC are lined by granular eosinophilic cells with large nuclei; some cysts show papillary tufting or intraluminal papillary excrescences filling the cyst
- ☞ Angiomyolipomas involve 50% to 100% of patients and often bilateral and multifocal. The rare variant, epithelioid AML, is reported more frequently in TSC than in patients without TSC.

Tuberous Sclerosis Complex

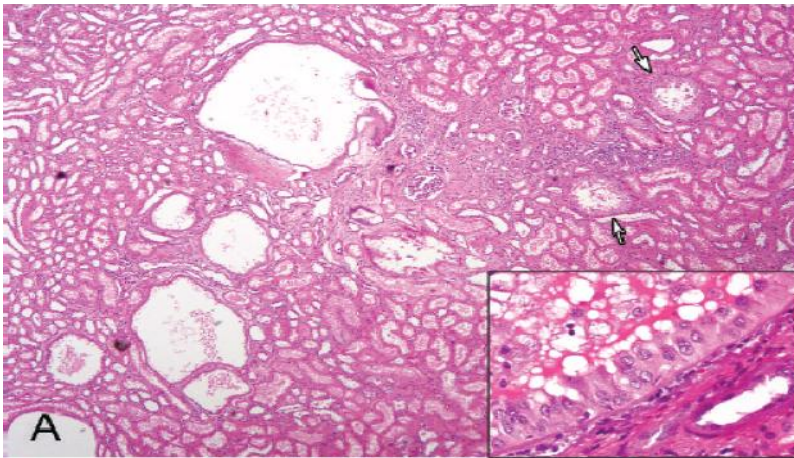
Published in final edited form as:

Am J Surg Pathol. 2014 July ; 38(7): 895–909. doi:10.1097/PAS.0000000000000237.

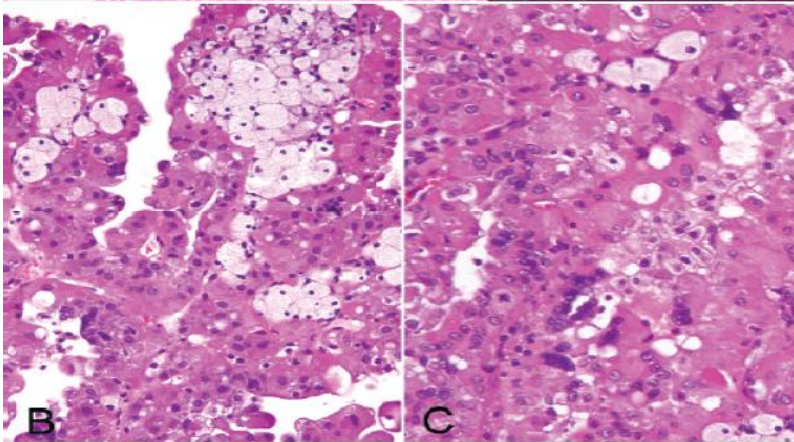
Renal Cell Carcinoma in Tuberous Sclerosis Complex

Ping Yang, M.D., Ph.D.^{*1,2}, Kristine M. Cornejo, M.D.^{*1}, Peter M. Sadow, M.D., Ph.D.¹, Liang Cheng, M.D., Ph.D.³, Mingsheng Wang, M.D.³, Yu Xiao, M.D.⁴, Zhong Jiang, M.D.⁵, Esther Oliva, M.D.¹, Sergiusz Jozwiak, M.D., Ph.D.⁶, Robert L. Nussbaum, M.D.⁷, Adam S. Feldman, M.D., MPH⁸, Elahna Paul, M.D., Ph.D.⁹, Elizabeth A. Thiele, M.D., Ph.D.⁹, Jane J. Yu, Ph.D.¹⁰, Elizabeth P. Henske, M.D.¹⁰, David J. Kwiatkowski, M.D., Ph.D.¹⁰, Robert H. Young, M.D.¹, and Chin-Lee Wu, M.D., Ph.D.^{1,8}

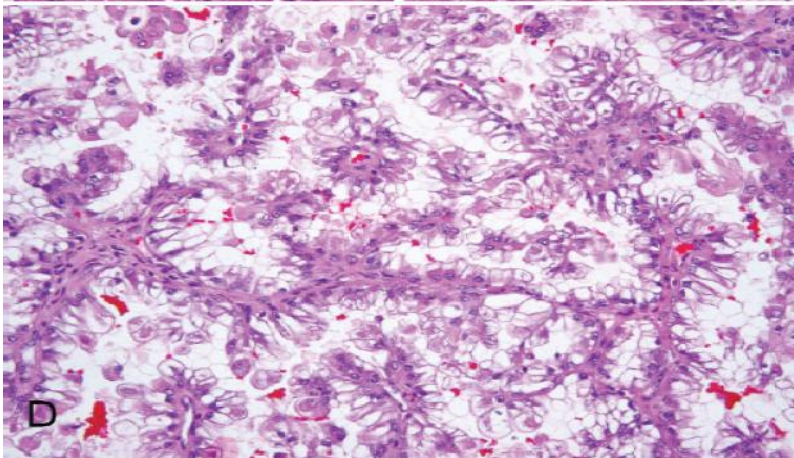
- ☀ CCRR is reported to be the most frequent type
- ☀ Other tumours include renal oncocytomas, chromophobe RCC,
- ☀ Or unclassified tumours composed of large cells with pink granular cytoplasm
- ☀ Recently, some TSC-associated RCCs mimicking translocation-associated carcinomas were described. These were negative for TFE on immunohistochemistry.



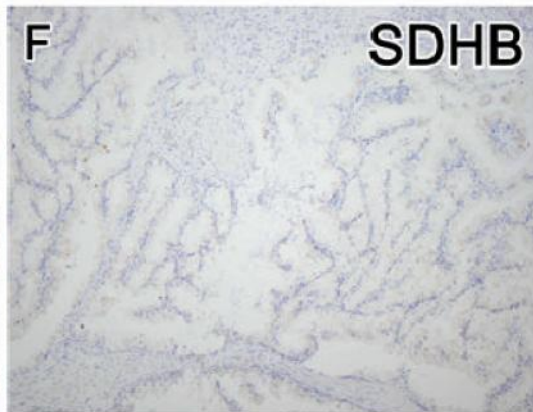
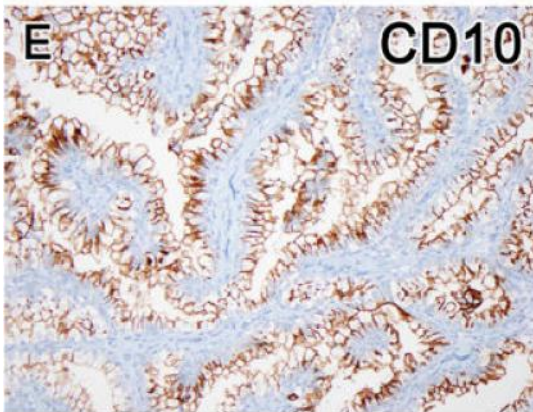
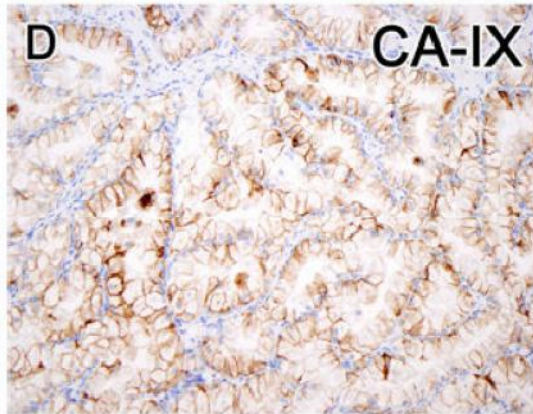
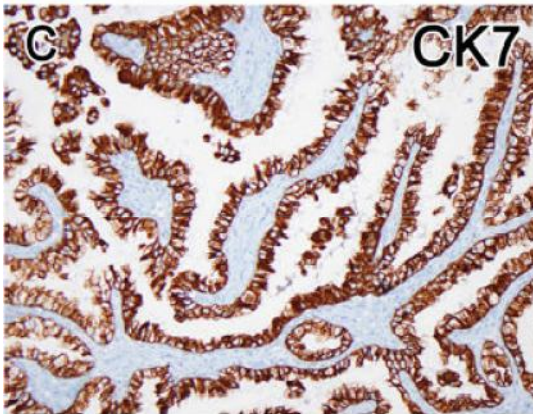
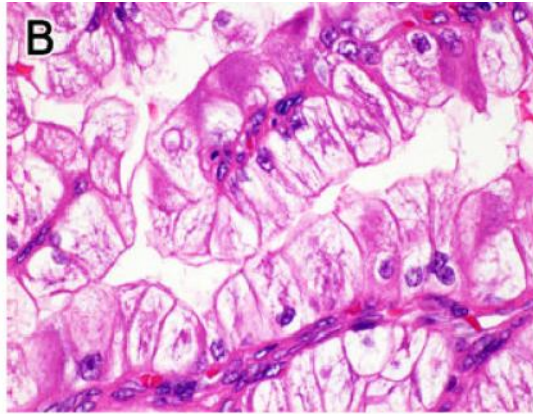
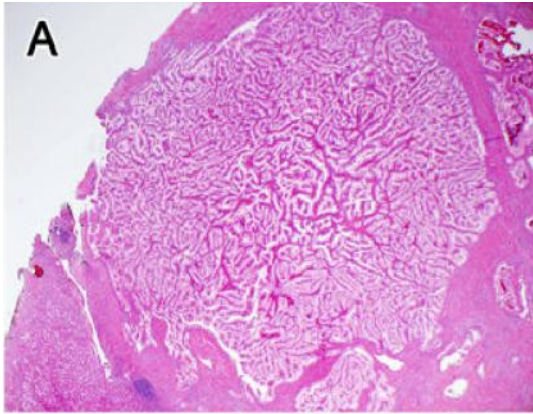
The cyst lesions in TSC can vary from scattered, occasional cysts to numerous cysts, imparting a spongelike appearance. The classic cysts in TSC are lined by granular eosinophilic cells with large nuclei



A tumor from a young patient with TSC composed of cells with abundant, eosinophilic, granular cytoplasm. The periphery of the tumor exhibits the papillary architectural pattern with prominent, foamy histiocytes filling up the fibrovascular cores.



Additional tumors resected from the same patient show prominent, papillary architecture and cells with voluminous clear cytoplasm and high nuclear grade, mimicking translocation-associated renal cell carcinoma. TFE3 and TFEB immunostains are negative in such tumors.



TSC-associated papillary RCC.

The have a nucleolar grade 2 or 3 with mostly basally located nuclei. TSC-associated PRCC show strong, diffuse labeling for CA-IX (100%), CK7 (94%), vimentin (88%), CD10 (83%), and are uniformly negative for succinate dehydrogenase subunit B (SDHB), TFE3 and AMACR.



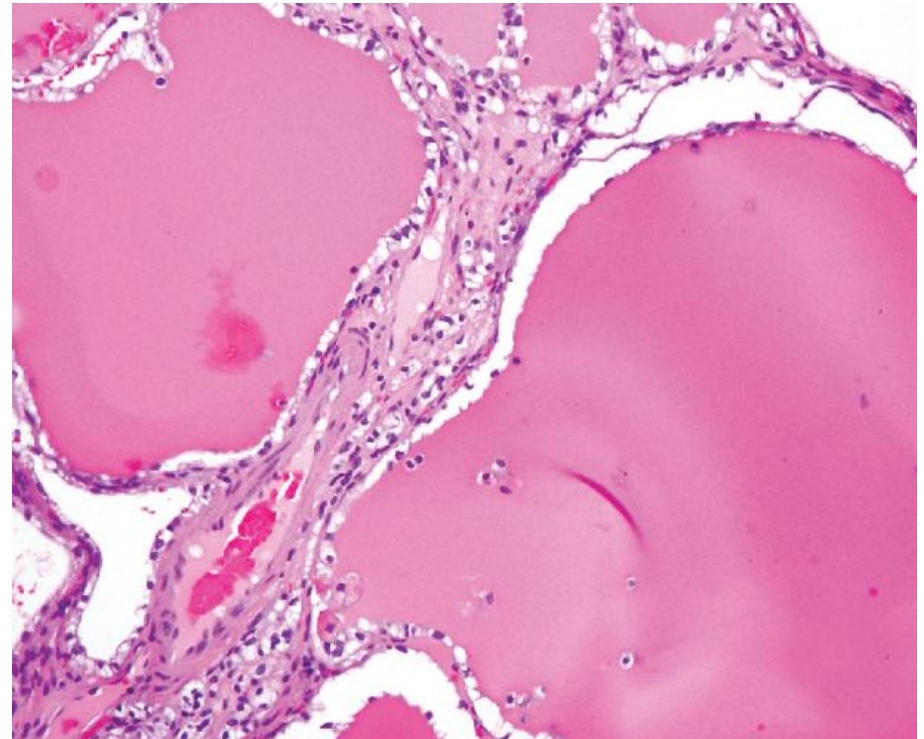
Predominantly Cystic Renal Tumours

- ✎ Multilocular Cystic RCC
- ✎ Cystic Nephroma and Mixed Epithelial and Stromal Tumour
- ✎ Clear Cell Papillary RCC
- ✎ Tubulocystic Carcinoma of the kidney
- ✎ Intrinsic Cystic Formation in Other Renal Cell Tumours of Various Subtypes
- ✎ RCC with Cystic Necrosis
- ✎ Epithelial Cysts in Mesenchymal Tumours Likely Developing from Entrapped Renal Tubules

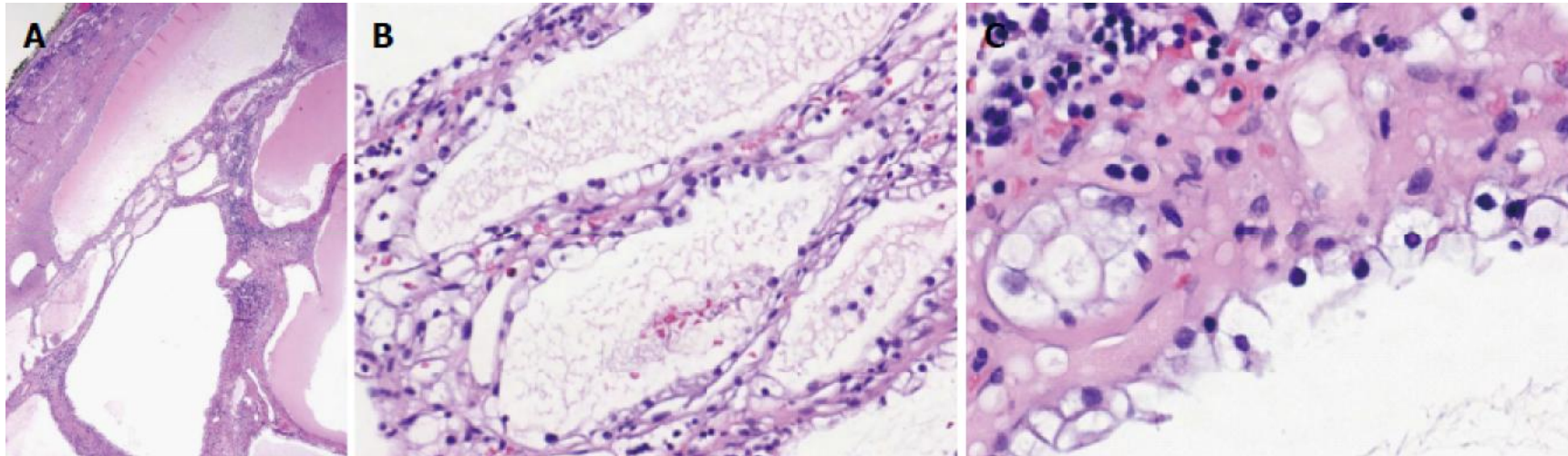
Multilocular Cystic RCC

of low malignant potential

- ☞ Multilocular cystic RCC, a renal cortical neoplasm with a distinct, multilocular gross appearance, is a variant of clear cell RCC. Solid, grossly discernable mural nodules of the tumour are incompatible with the diagnosis
- ☞ The tumour consists of numerous clear cell-lined cysts with small clusters of clear cells in the tumour septae. The tumour nuclei are small, uniform and round without prominent nucleoli
- ☞ The cystic tumor is often an incidental finding, and often presents as a unilateral, solitary lesion
- ☞ VHL mutations were identified in 25% of the cases
- ☞ The tumor cells are strongly reactive to PAX2 and CAIX, similar to typical, low-grade clear cell RCC. These findings are consistent with the concept of multilocular cystic RCC being a variant of clear cell RCCs
- ☞ In line with the minimal tumor burden present in these tumors, prognosis is excellent; there was no recurrence or metastases on mean follow-up of more than 6.5 years in a more-recent study



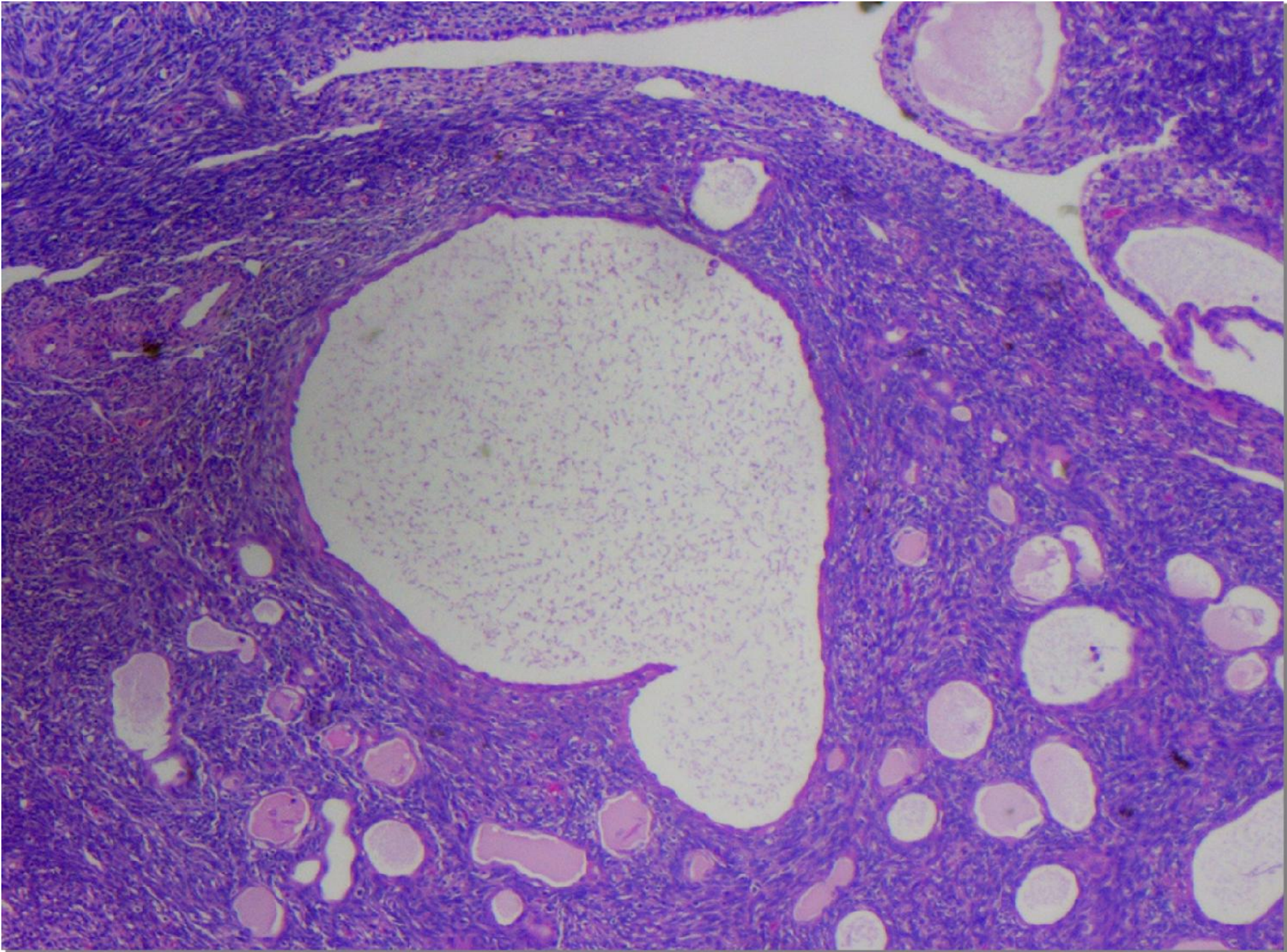
Multilocular Cystic RCC of low malignant potential



An important diagnostic feature is the presence of tumour cells in the fibrous septae similar to those lining the cysts.

Cystic nephroma and Mixed Epithelial Stromal Tumour (MEST)

- ∞ The notion is that cystic nephromas and mixed epithelial and stromal tumors represent a morphologic spectrum of the same entity
- ∞ Due to their clinical and morphological similarities, a unifying term of renal epithelial and stromal tumour (REST) was proposed
- ∞ Both tumors are typically located close to the renal hilum and pelvis
- ∞ In the adult population, both tumors show a marked female preponderance (F:M, 8:1)



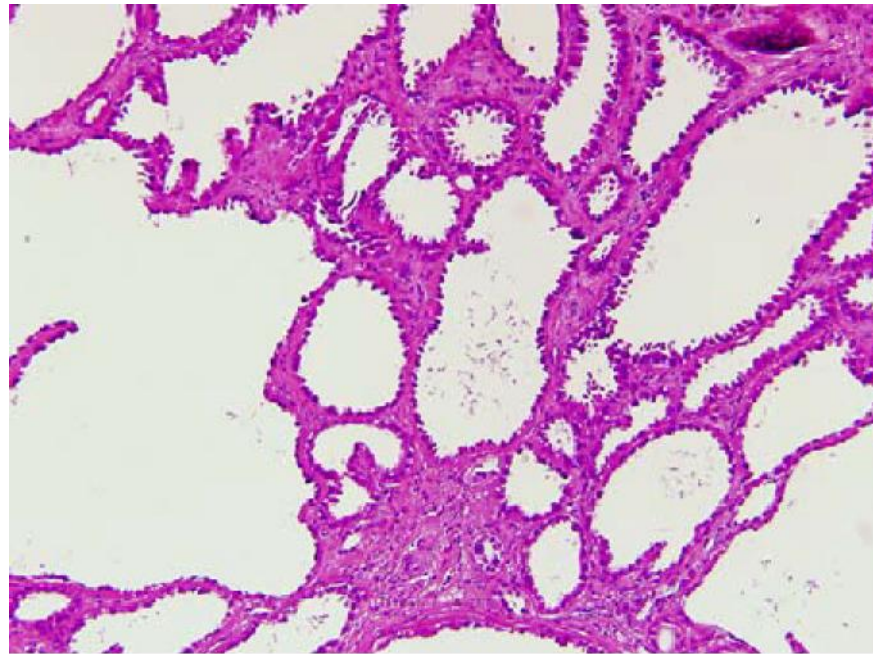
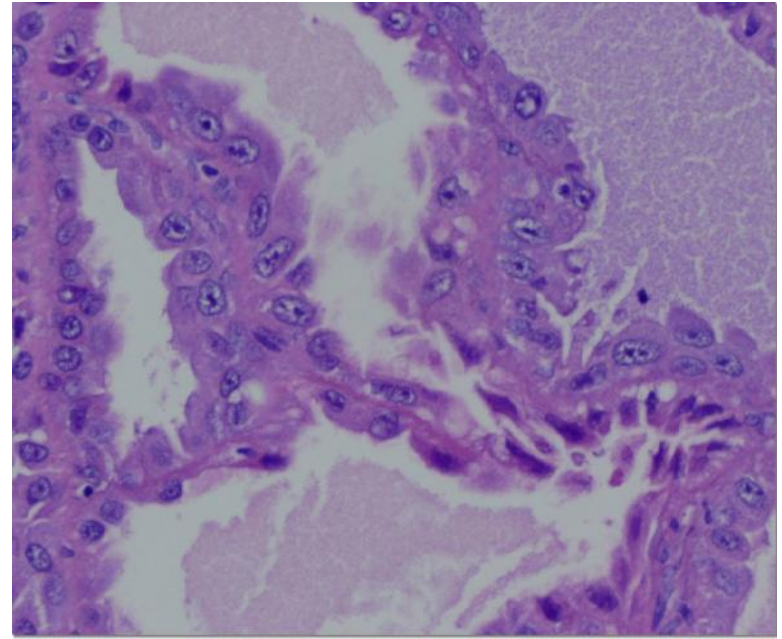
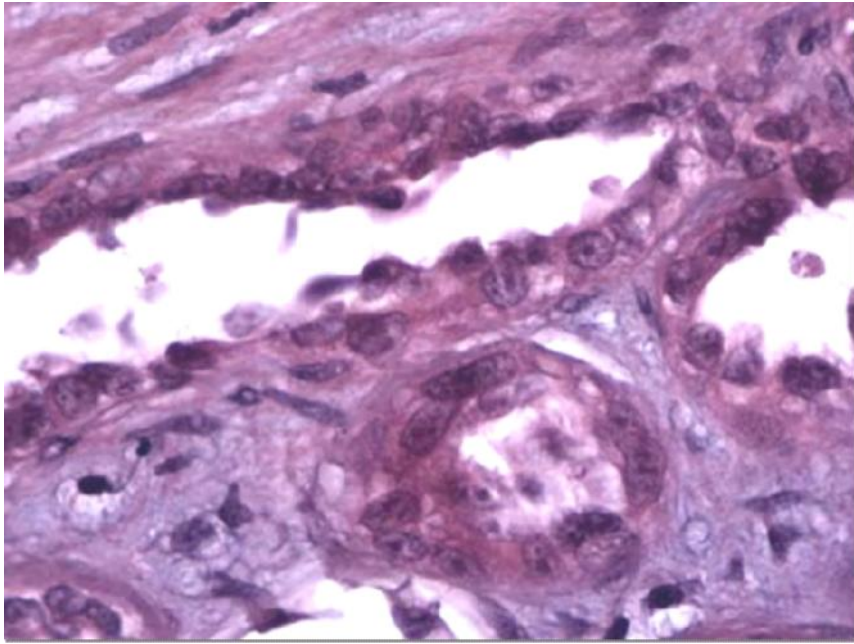
Cystic nephroma and Mixed Epithelial Stromal Tumour (MEST)

- ∞ Cystic nephroma is entirely cystic, without any solid expansile growth or mural nodules
- ∞ The mixed epithelial and stromal tumor is a multicystic or biphasic tumor with solid and cystic areas
- ∞ In the adult population, both tumors show a marked female preponderance (F:M, 8:1)
- ∞ Steroid hormones have been suggested to play a role in the genesis and evolution of these tumors

Cystic nephroma in the pediatric age group is an entity entirely distinct from the adult tumors and is considered a fully differentiated nephroblastoma (Wilms tumor)

Tubulocystic Carcinoma of the Kidney

- ∞ Well circumscribed , variable sized cystically dilated tubules, cuboidal, atypical eosinophilic/cleared cells, nucleoli, hobnail features, mucinous secretions, absent mitoses.
- ∞ Paucicellular fibrous septa
- ∞ Originally termed “low grade collecting duct carcinoma ” renamed to emphasize distinction from CDC: morphology & indolent behavior (<10% mets)
- ∞ Histogenesis: proximal convoluted tubules vs intercalated cells of collecting ducts.
- ∞ DDX: MEST both sexes, lack of hypercellular/ovarian like stroma, atypical nuclear features, prominent nucleoli
- ∞ IHC : CD10, AMACR, CK 19 & 34 E12.



Take Home Message

The presence of multiple renal cysts, both acquired and syndromic, may be associated with a variety of renal tumours.

The morphology of the cysts and associated tumour types can help predict the genetic or acquired basis of the lesions, and such potential associations should be suggested in surgical pathology reports.

Shukran!

