Morphology Driven Molecular Discovery

The Story of Tuberous Sclerosis Associated Renal Neoplasia and Their Sporadic Counterparts

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Disclosure of Relevant Financial Relationships

I have no relevant financial relationships.

Lecture Outline

1. Tuberous sclerosis complex (TSC)
   - General features

2. Renal cell carcinoma (RCC) in TSC
   - Historical literature
   - Recent literature
   - Reconciling apparent inconsistencies

3. Sporadic RCC mimicking TSC-associated RCC
   - Underlying somatic changes

Tuberous Sclerosis: Historical Highlights

1835: Rayer describes facial lesions considered first report of TS

1862: von Recklinghausen describes heart tumor and brain "scleroses"

1880: Bourneville describes patient with cognitive disability, epilepsy, and "vascular eruptions" on face with cerebral "tubers" and bilateral renal masses at later autopsy

1908: Vogt describes diagnostic criteria for TS

1913: Berg credited with first stating TS was hereditary

1918: Lutembacher published first report of cystic lung disease

1942: "Tuberous sclerosis complex"

1967: Lagos/Gomez publish 71 cases (38%: no cognitive symptoms)

1979: 1st ed. Tuberous Sclerosis published by Gomez

1987: Linkage analysis- probable gene on Ch. 9

1992: Linkage analysis- probable second gene on Ch. 16 (close to PCD1)

1993: *TSC2* cloned and product named tuberin

1997: *TSC1* cloned and product named hamartin

1998: Dabora et al. *Am J Hum Genetics* provide modern criteria

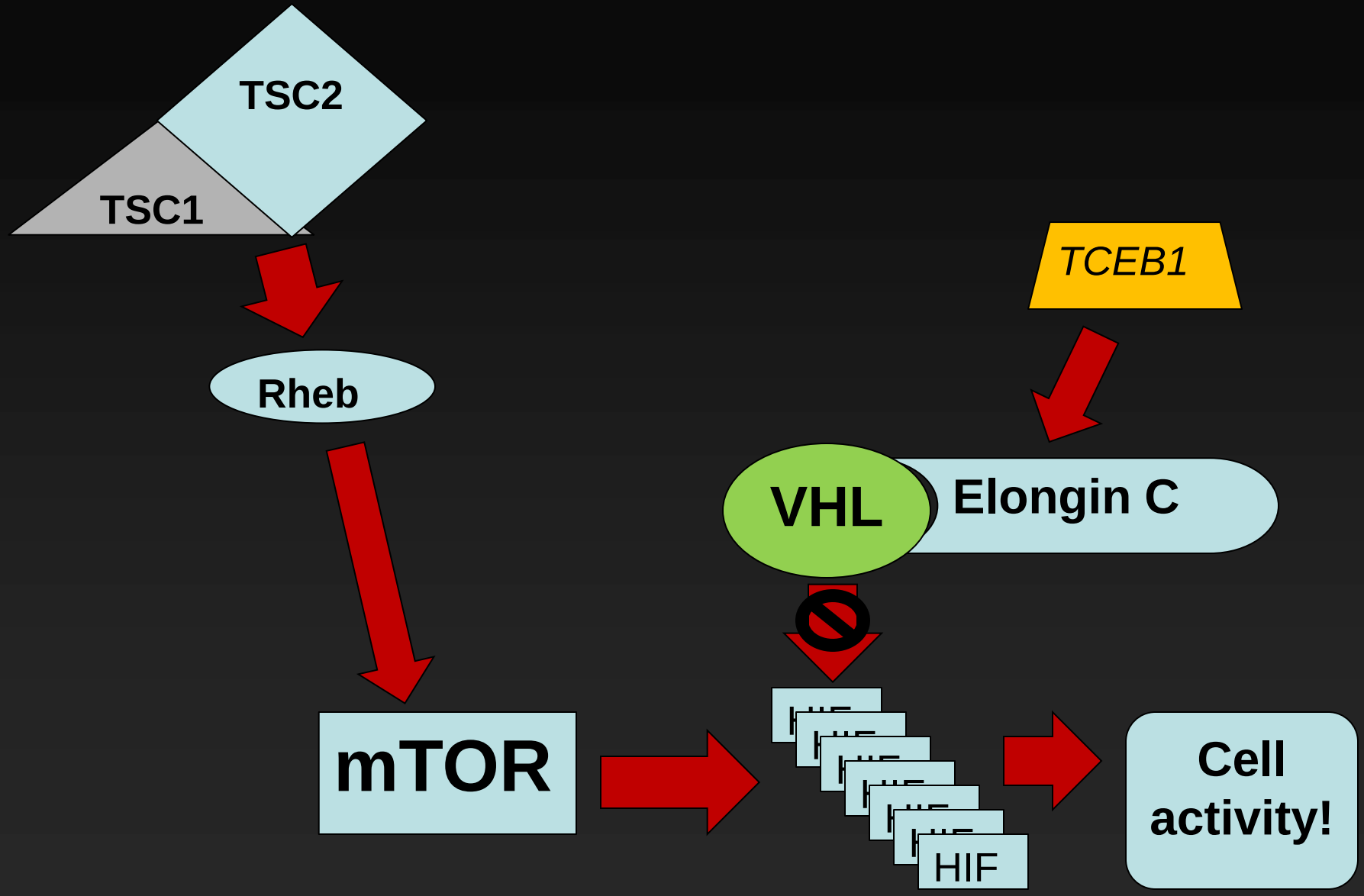
Tuberous Sclerosis Complex

- Autosomal Dominant Syndrome
  - Inactivating mutation in *TSC1* or *TSC2* genes
    - TSC1 on chromosome 9q34
      - Encodes protein hamartin
    - TSC2 on chromosome 16p13.3
      - Encodes protein tuberin
- New, spontaneous mutations common (70%)
  - No family history
- No cognitive in impairment in 30-40%

Tuberous Sclerosis: Neoplasia

- Renal Angiomyolipoma (AML)
  - Multiple, bilateral, may involve other organs
- Other renal tumors
  - Varied and inconsistent descriptions
- Other PEComa spectrum tumors
  - Lymphangioleiomyomatosis
- Cardiac rhabdomyoma
- Retinal hamartoma
- Subependymal giant cell astrocytoma (SEGA)

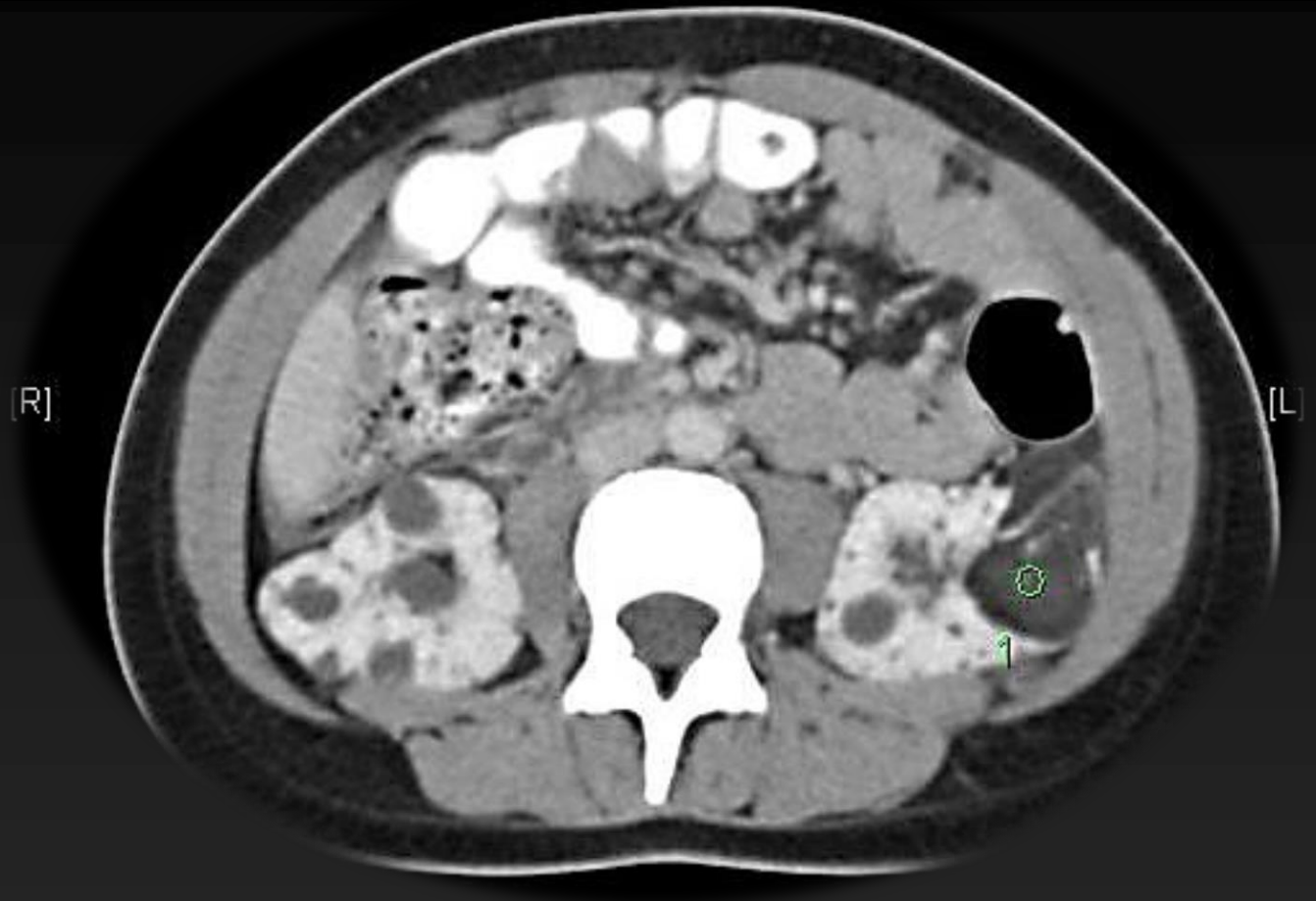
An overly simplified schematic

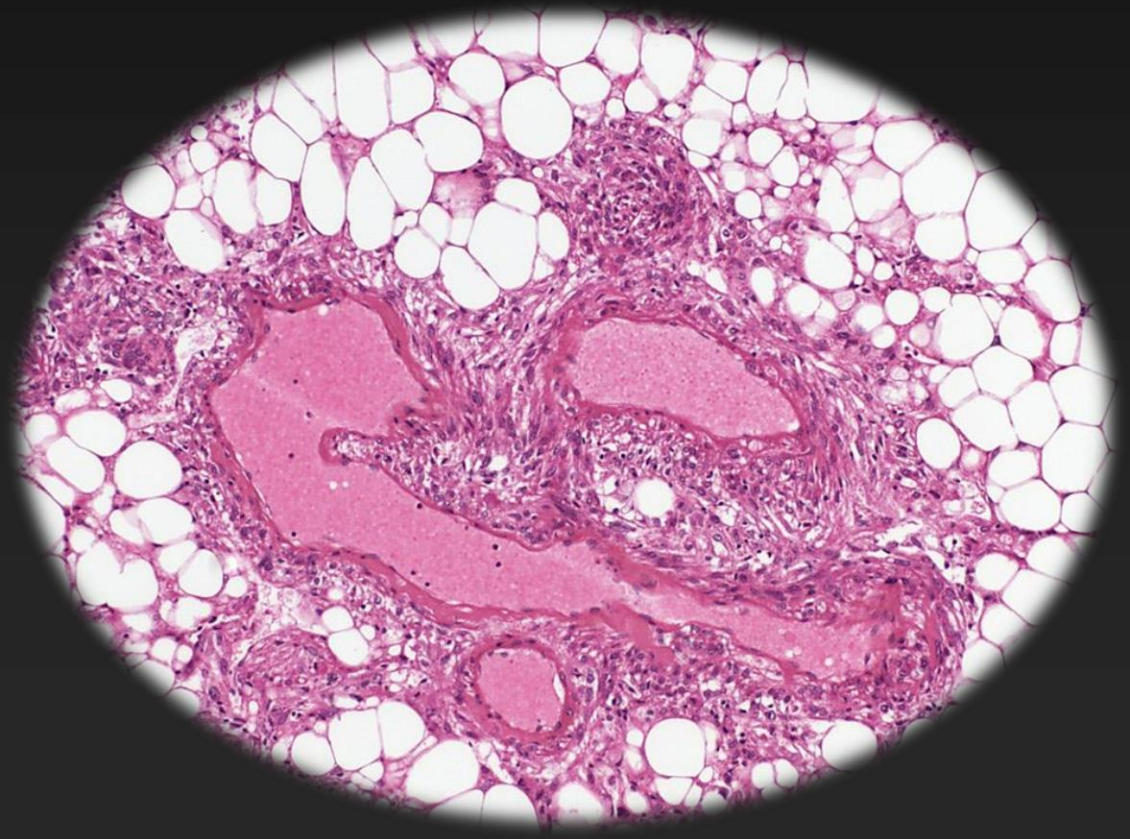


What we knew…

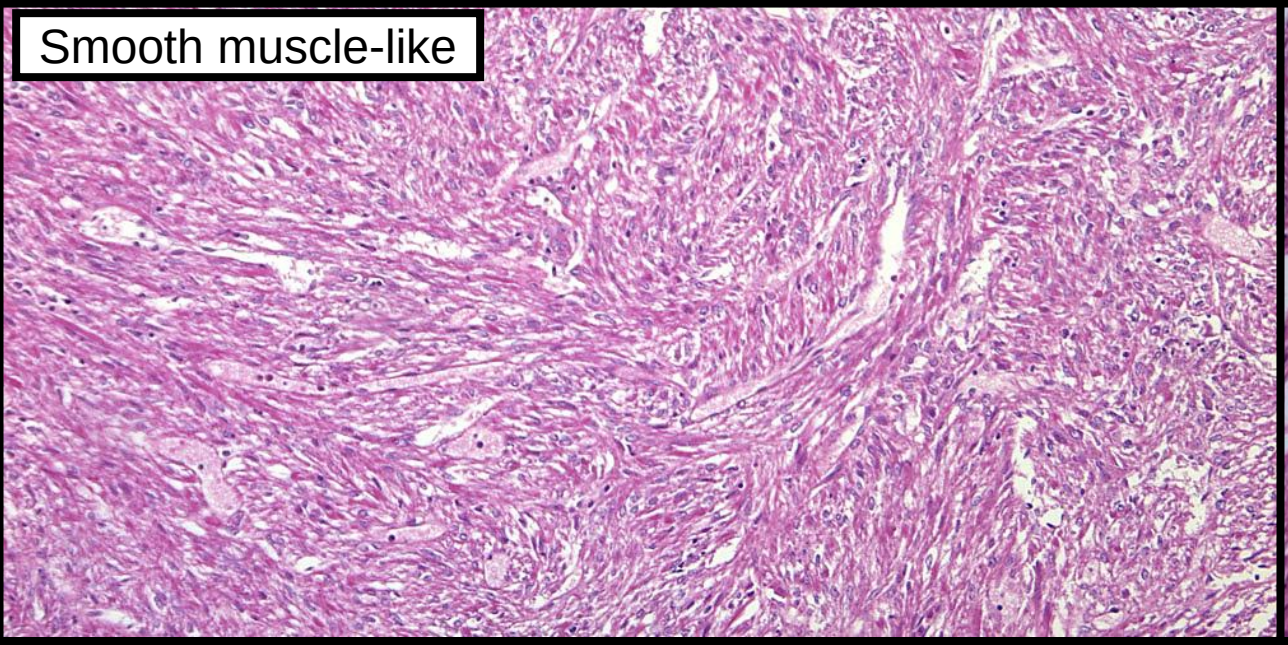
Tuberous Sclerosis
and
Renal Angiomyolipoma (PEComa)

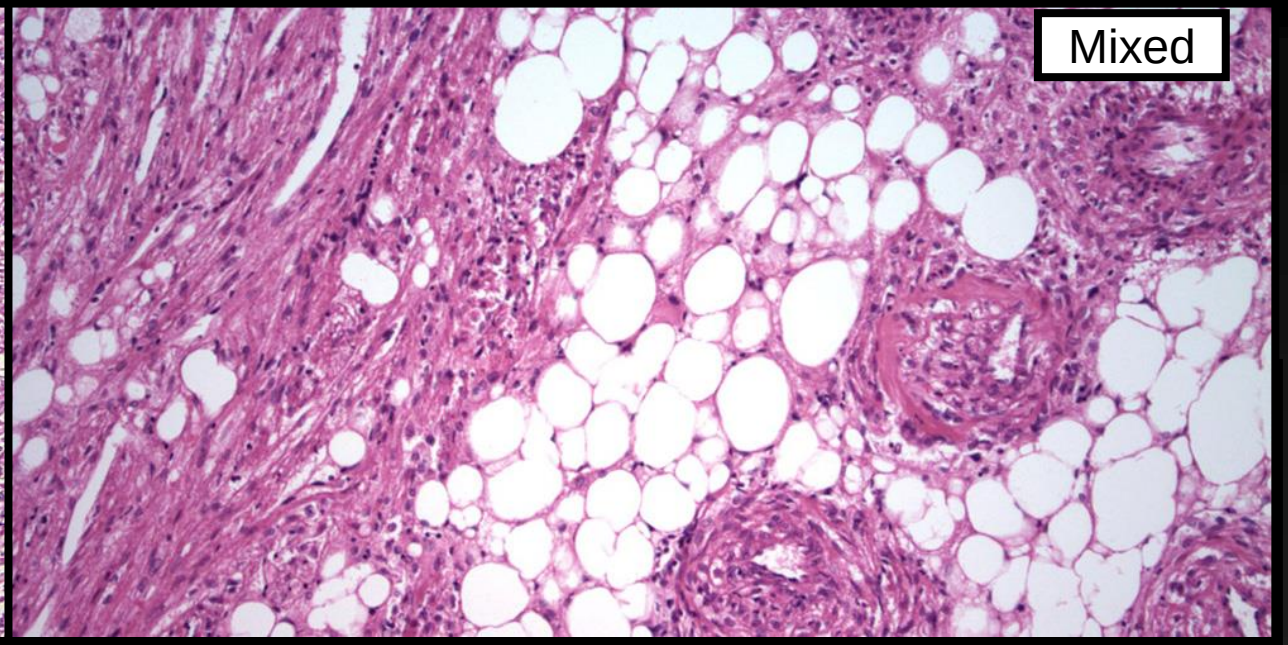
Tuberous Sclerosis: Multifocal, Bilateral AMLs

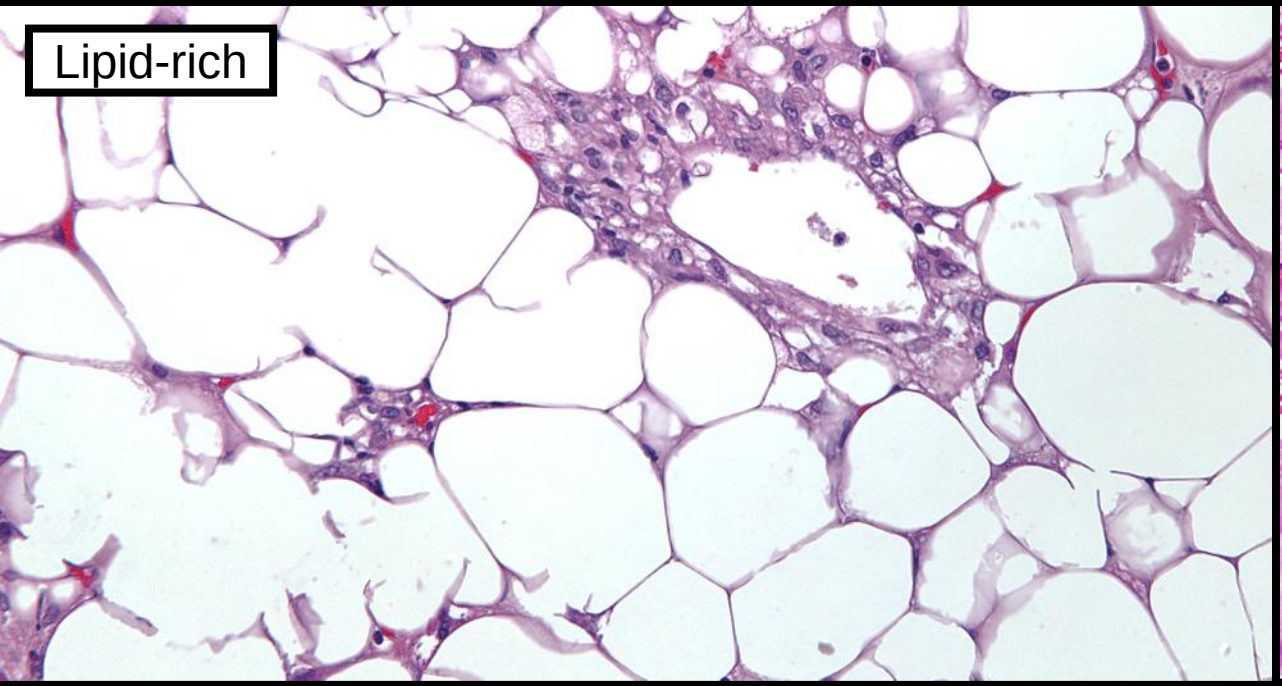


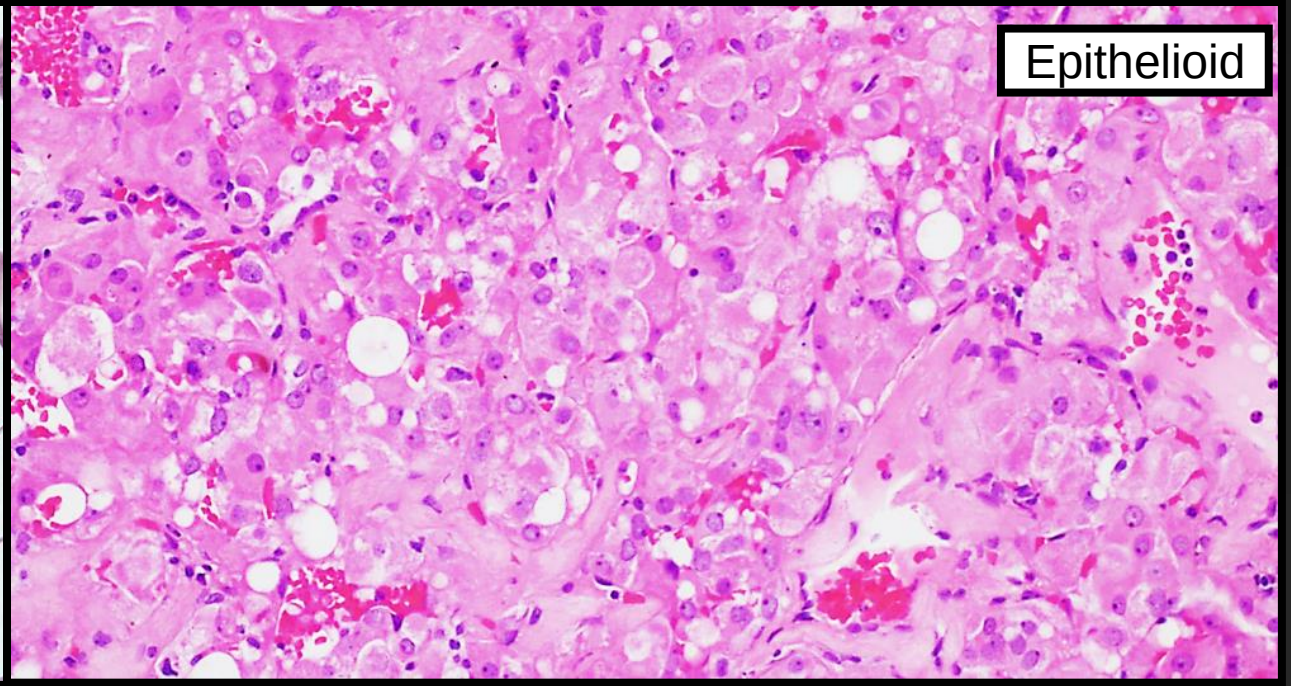


Tuberous Sclerosis Complex: AML Heterogeneity

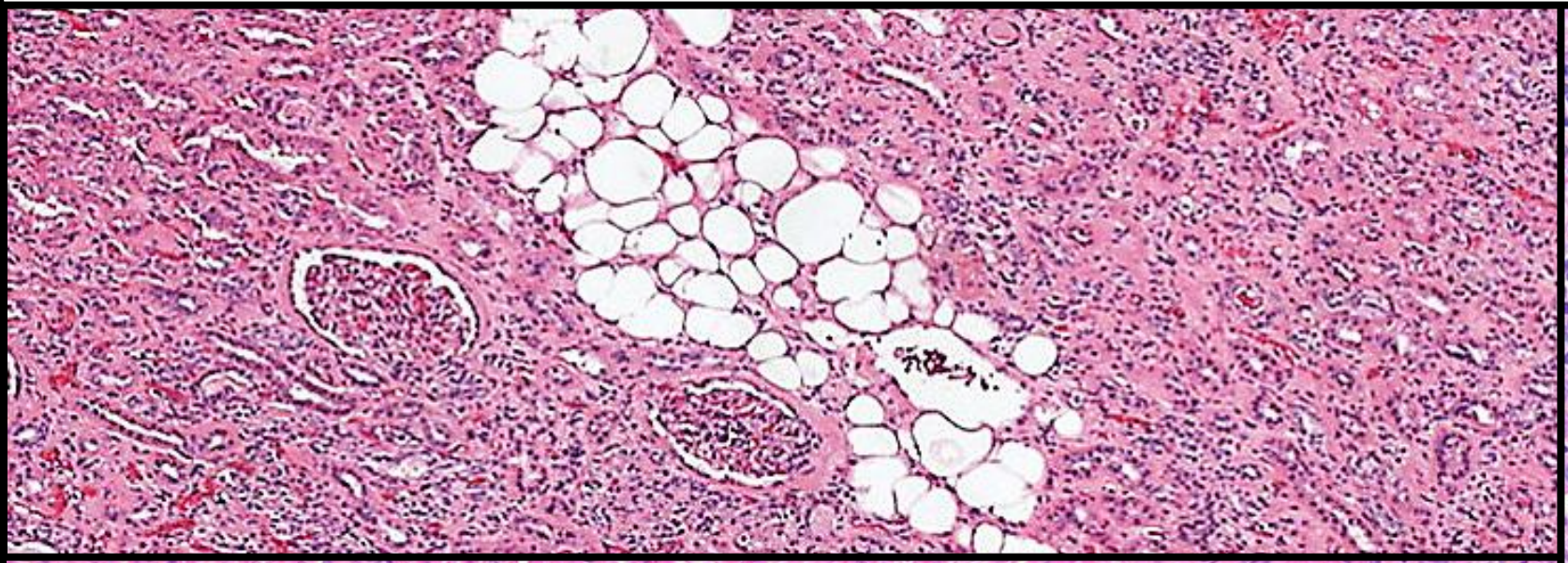


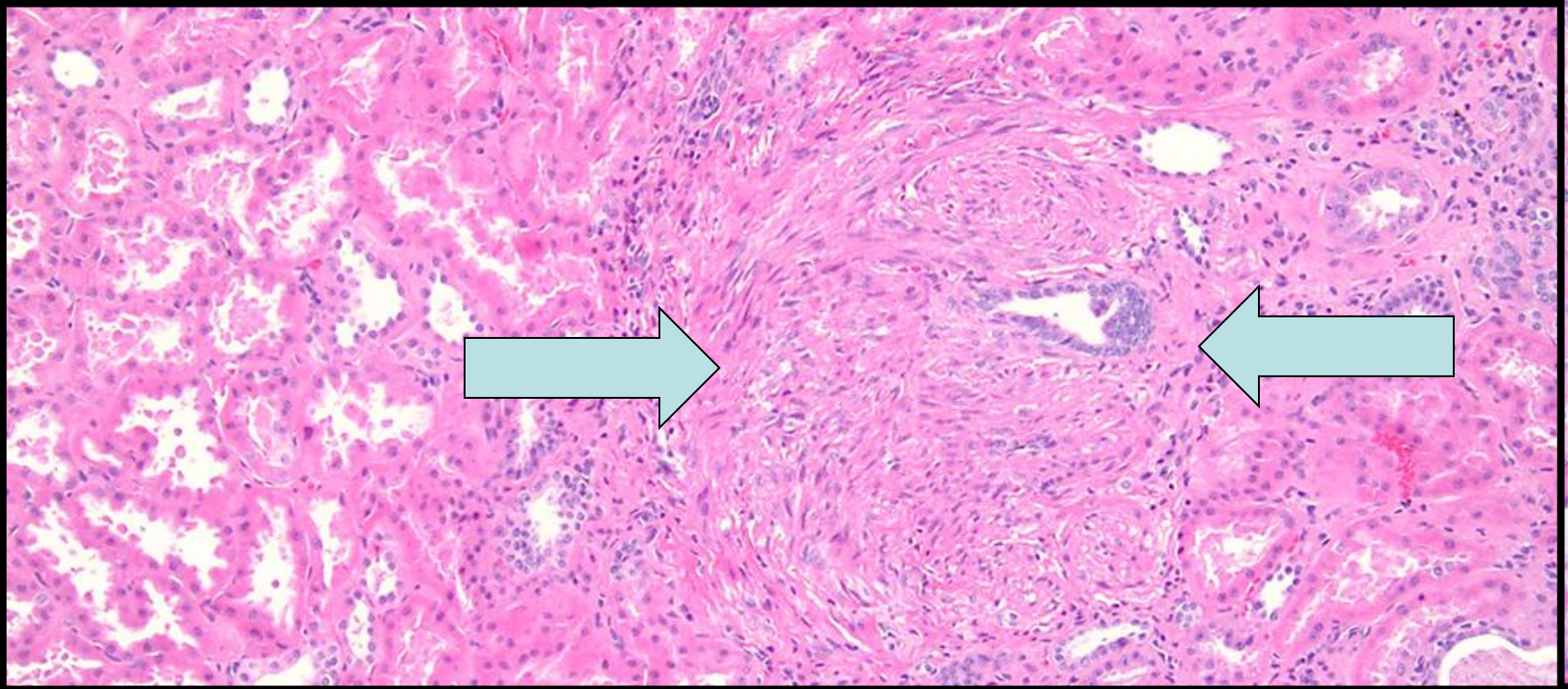


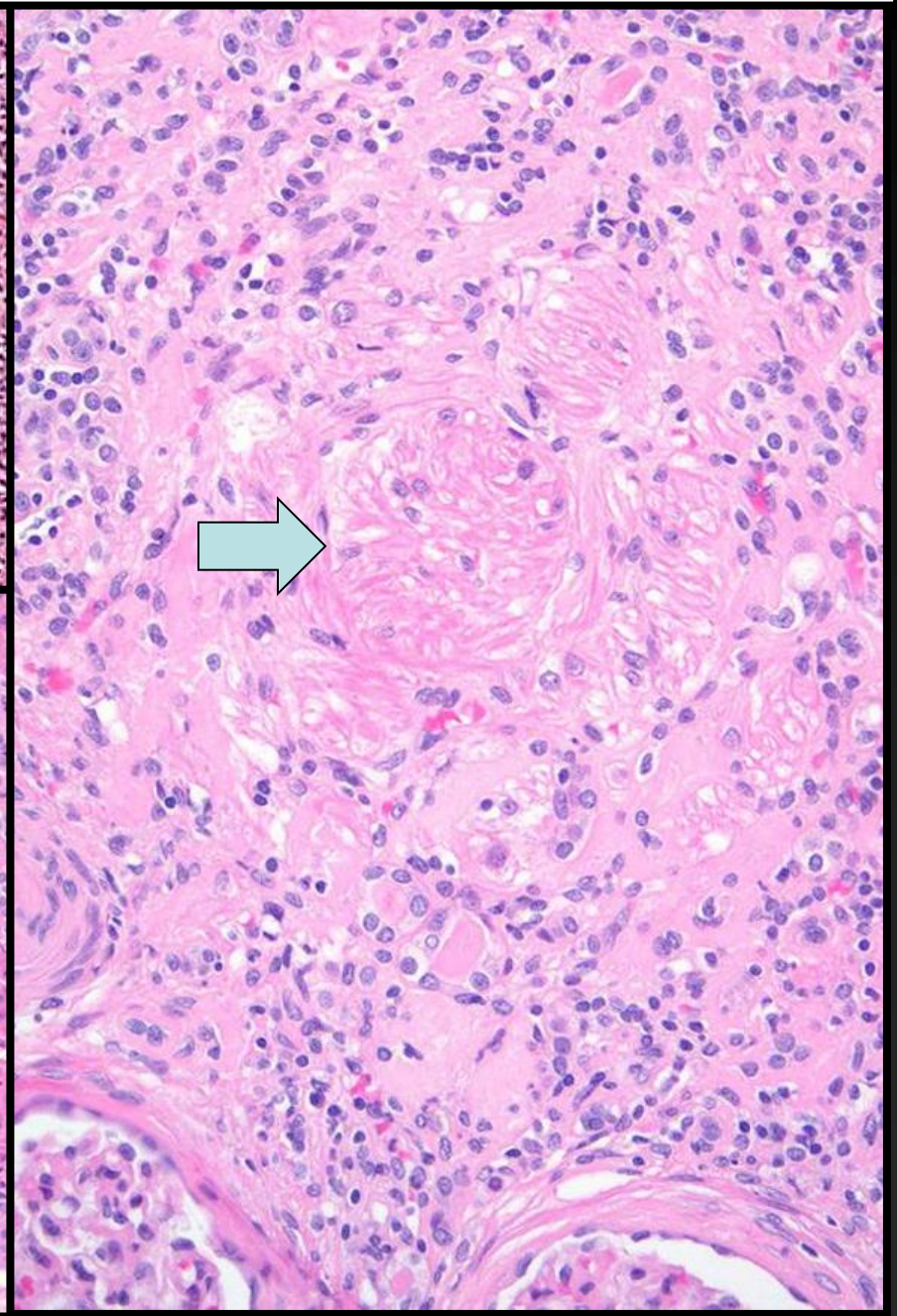




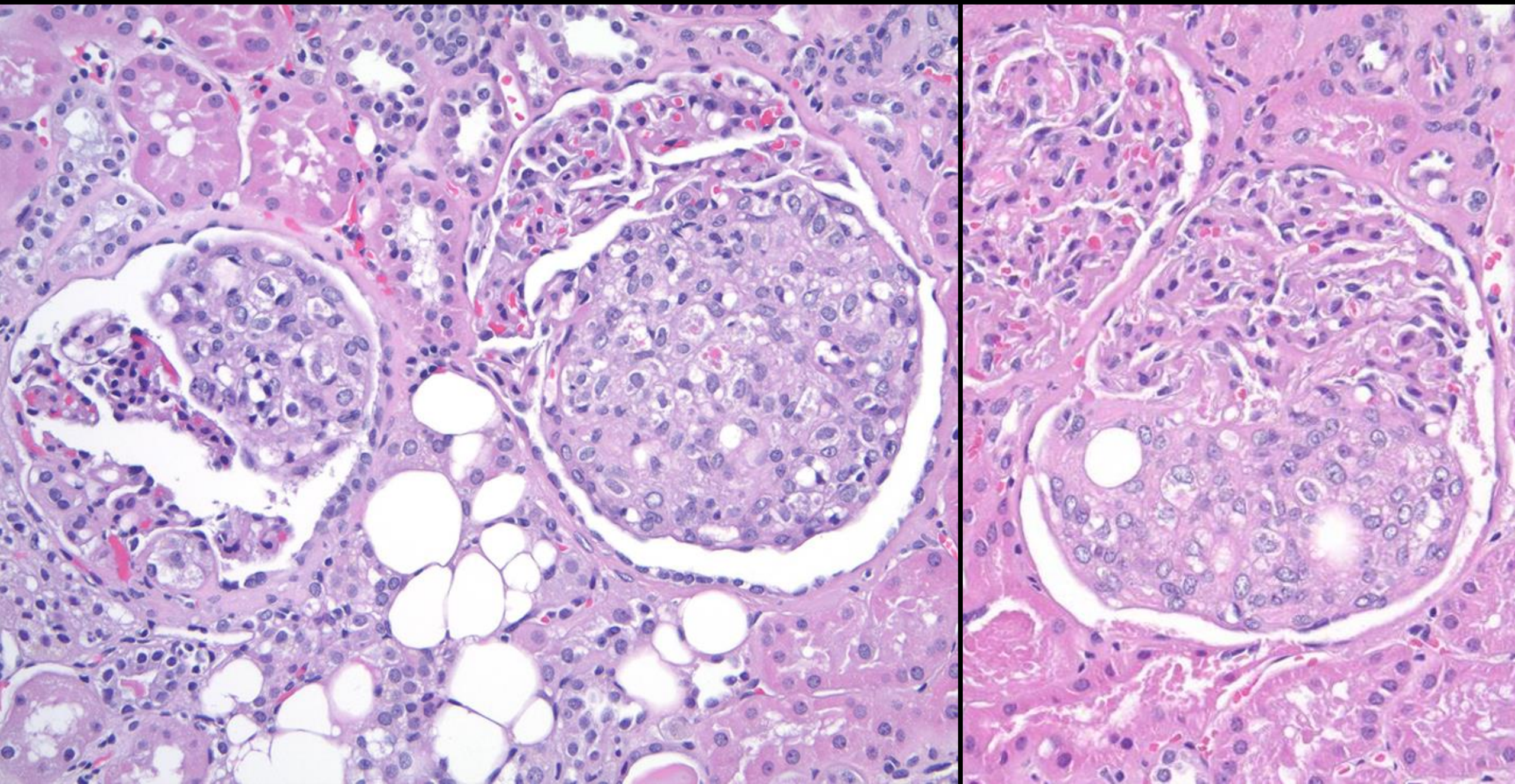
Tuberous Sclerosis: AML “Tumorlet”



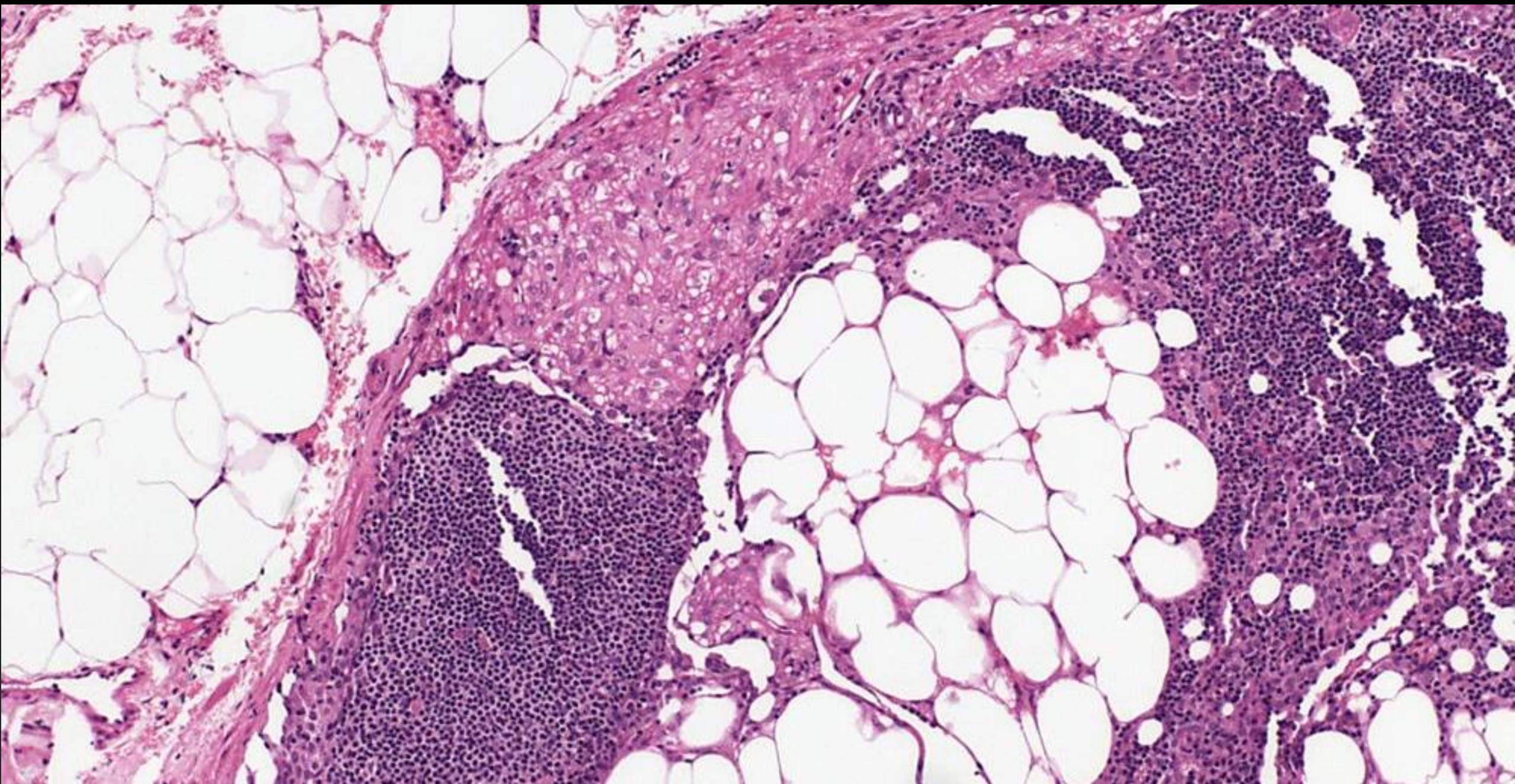




Tuberous Sclerosis: AML in Bowman's Space



Tuberous Sclerosis: AML in adjacent lymph nodes



Tuberous Sclerosis Complex: AML with Epithelial Cysts

ORIGINAL ARTICLE

Angiomyolipoma With Epithelial Cysts (AMLEC)

A Distinct Cystic Variant of Angiomyolipoma

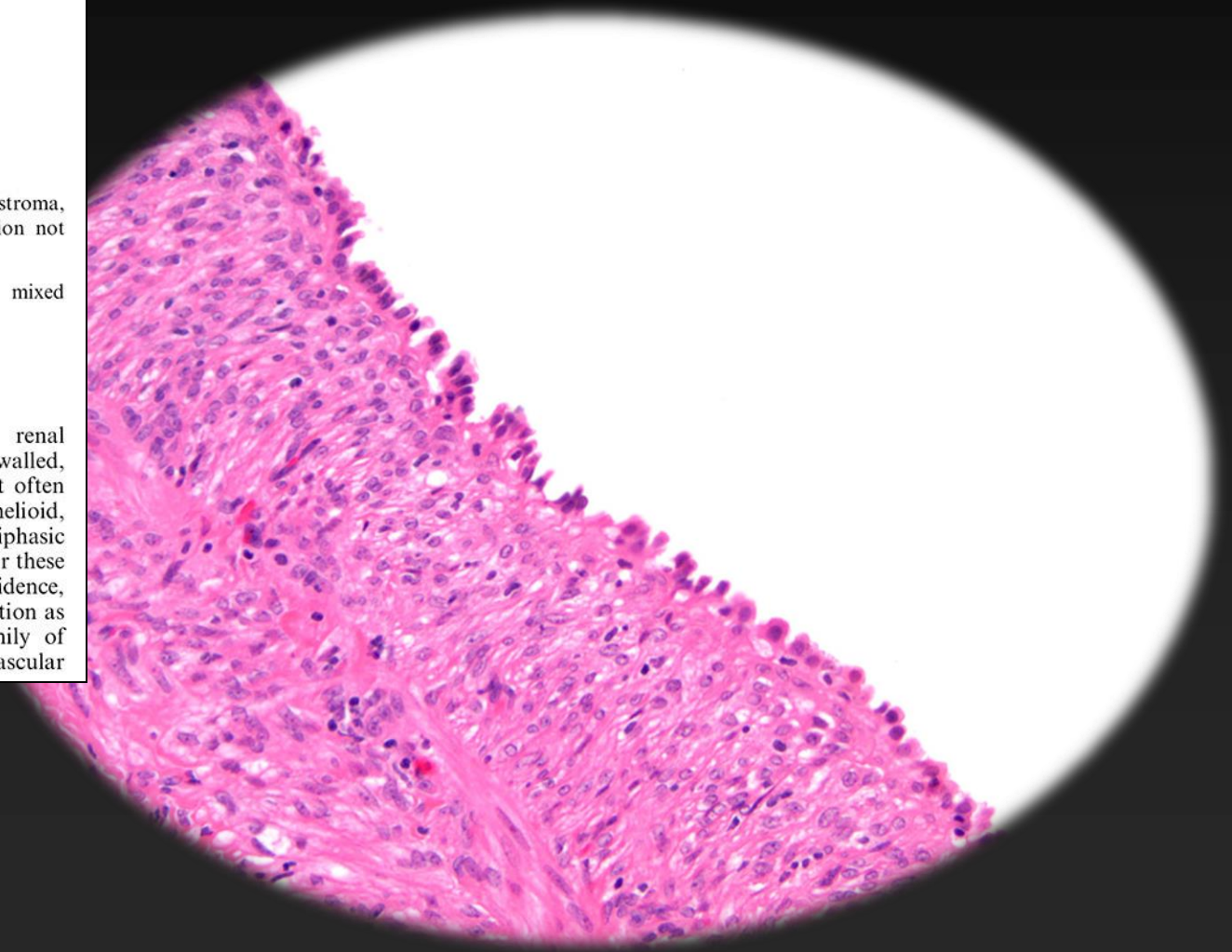
Samson W. Fine, MD, Victor E. Reuter, MD,§ Jonathan I. Epstein, MD,*† ‡ and Pedram Argani, MD*‡*

Abstract: Renal angiomyolipoma (AML) is typically a solid lesion, composed of varying amounts of adipose, vascular, and muscular tissue, lacking an epithelial component. Although it is known that entrapped renal tubules may be observed in AML, presentation as a cystic mass has not been previously reported. We report the clinicopathologic and immunohistochemical features of four cystic renal AML. The lesions were found in 2 male and 2 female patients, ranging in age from 37 to 76 years, none with a history of hormonal therapy. One of the four patients had known tuberous sclerosis, and this patient and 1 other presented with bilateral cystic renal lesions. Grossly, the lesions measured between 1.3 and 4.5 cm in greatest dimension. Histologically, the lesions were each composed of three components: 1) epithelial cysts lined by cuboidal to hobnail cells; 2) a compact subepithelial "cambium-like" layer of cellular, müllerian-like AML stroma with prominent admixed chronic inflammation; and 3) muscle-predominant AML with associated dysmorphic blood vessels exterior to the cellular subepithelial stroma. Immunohistochemically, the stromal features suggesting differentiation toward endometrial stroma, may represent epithelial-induced müllerian differentiation not previously reported in AML.

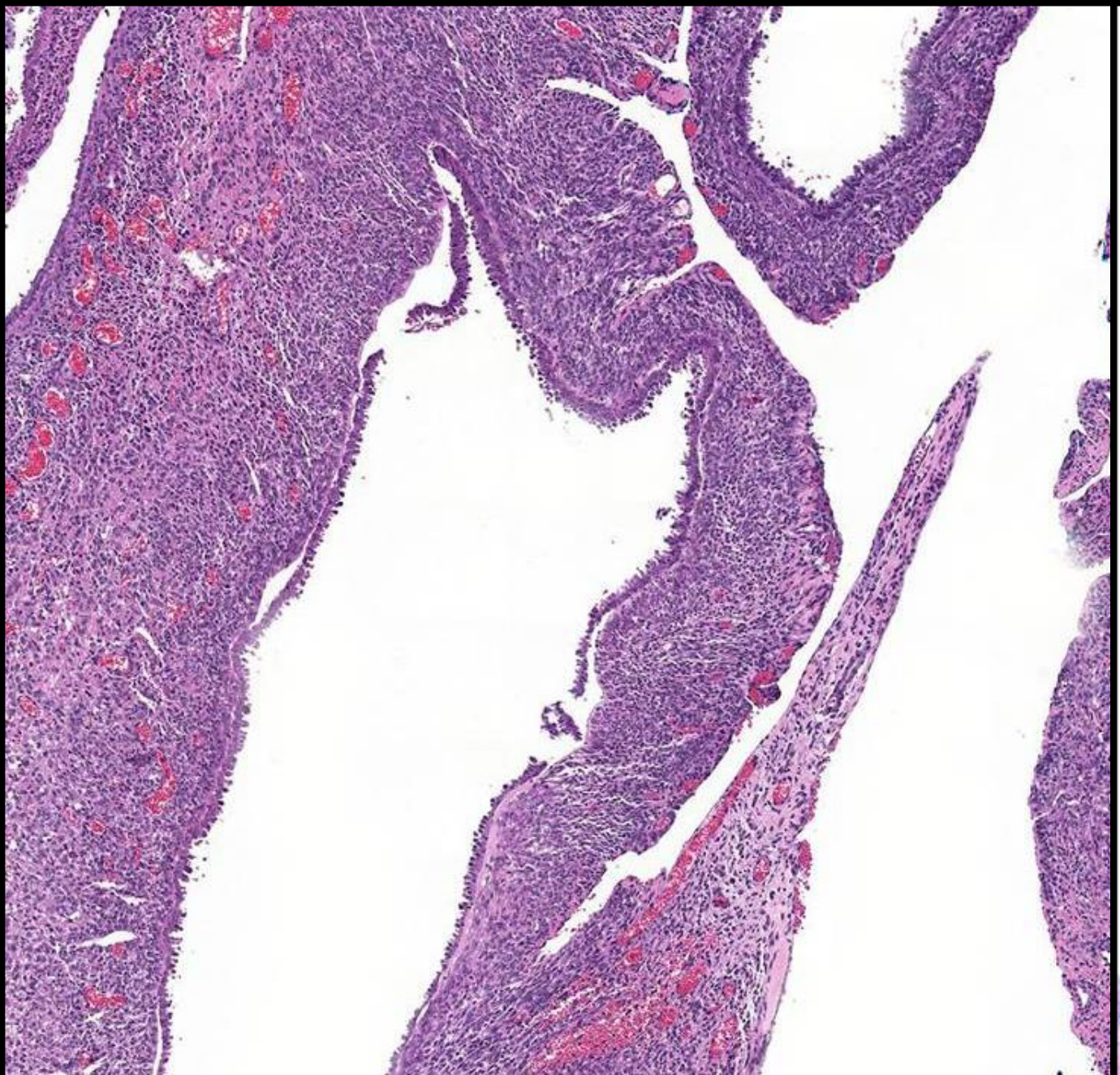
Key Words: kidney, angiomyolipoma, epithelial cysts, mixed epithelial-stromal tumor

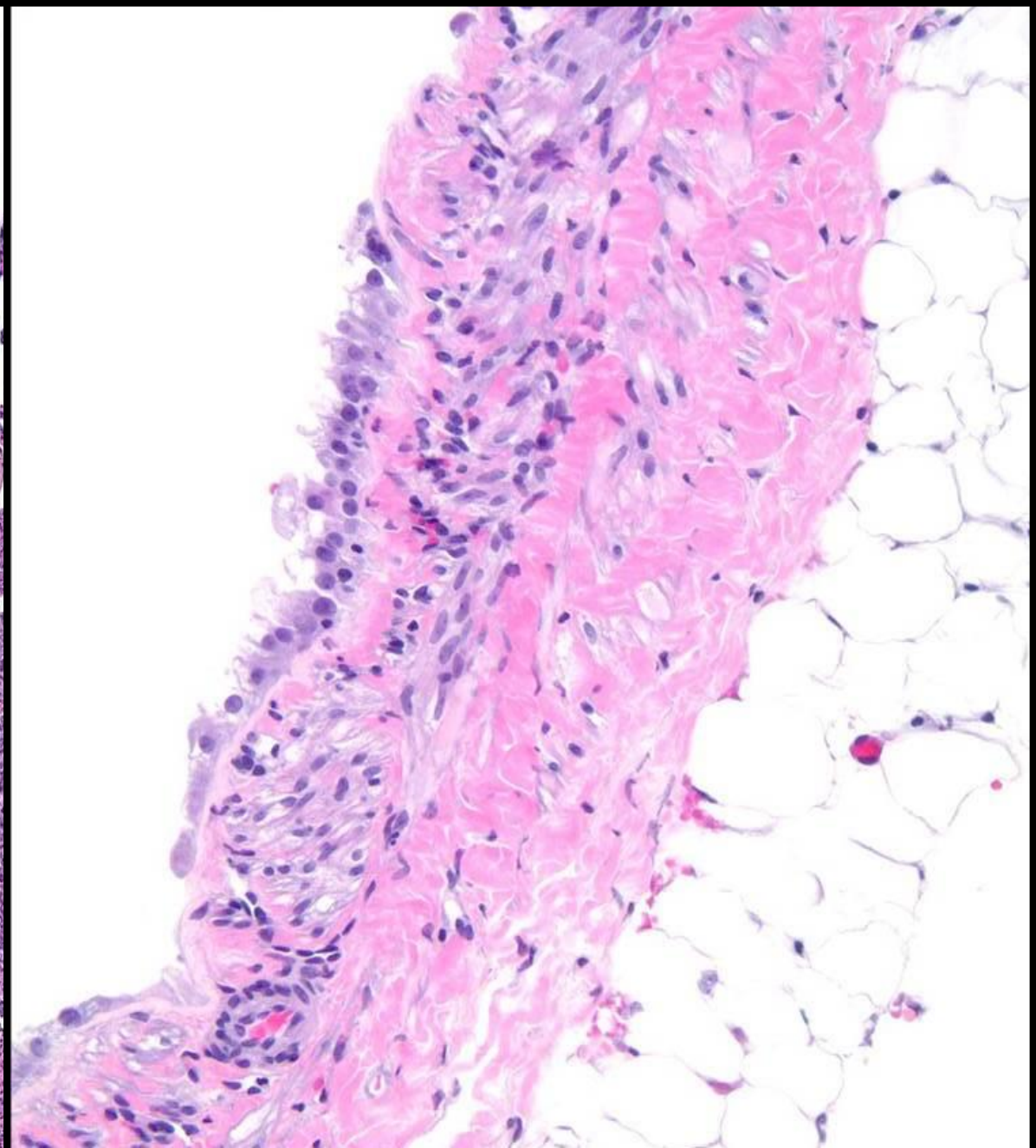
(*Am J Surg Pathol* 2006;30:593–599)

Angiomyolipomas (AMLs) are well-described renal lesions characterized by the presence of thick-walled, dysplastic blood vessels, smooth muscle cells that often have clear cytoplasm and may be spindled or epithelioid, and fat resembling mature adipocytes.[18] The triphasic nature of AML has led many in the past to consider these lesions as hamartomatous; however, current evidence, based on clonality studies, supports their classification as neoplastic.[13] AMLs are part of a growing family of lesions thought to originate from the perivascular



Tuberous Sclerosis Complex: AML with Epithelial Cysts

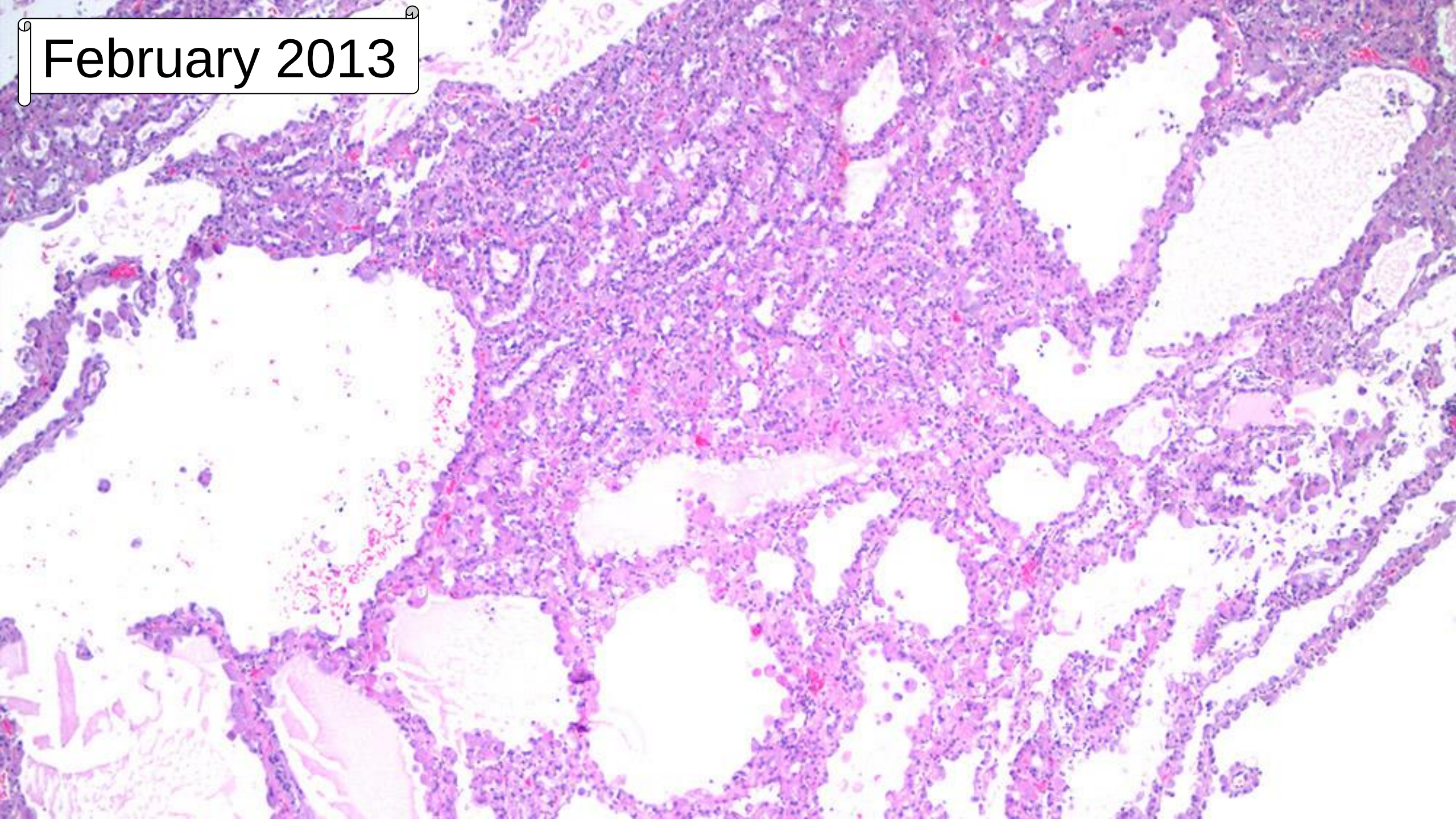




What we didn’t know…

What is the spectrum of renal epithelial neoplasia in tuberous sclerosis complex (TSC)?

Literature has too many contradictions…


February 2013

Distinctive Morphology of Renal Cell Carcinomas in Tuberous Sclerosis

International Journal of Surgical Pathology
18(5) 409–418

DOI: 10.1177/1066896909333510
http://ijsp.sagepub.com
SAGE

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Abstract

Tuberous sclerosis complex results from mutations in 1 of 2 interacting gene produc
syndrome is characterized by hamartomas and neoplastic lesions, including angiomyolip
organs. Renal cell carcinoma (RCC) in tuberous sclerosis remains relatively poorly ch
studies were confounded by the inclusion of epithelioid angiomyolipomas. The authors pr
sclerosis and bilateral renal lesions, including multiple minute angiomyolipomas, cortical
unclassified type. The carcinomas shared distinctive morphological features, including shee
cystic architecture and abundant granular eosinophilic cytoplasm. By definition, the carcino
negative for HMB-45 and Melan-A. Detailed immunohistochemical analysis revealed het
cysts and carcinomas. The histopathological features of these carcinomas illustrate char
that are probably related to genetic alterations of tuberous sclerosis.

Keywords

renal cell carcinoma, tuberous sclerosis complex, angiomyolipoma

Introduction

by the variable classification criteria and scheme used

Case Report: Unusual eosinophilic and cystic RCC in TSC

Tuberous Sclerosis
and
Renal Epithelial Neoplasia

American Journal of Pathology, Vol. 149, No. 4, October 1996

Tuberous Sclerosis-Associated Renal Cell Carcinoma

Clinical, Pathological, and Genetic Features

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David J. Kwiatkowski,‡ and
Elizabeth Petri Henske‡

HMB-45

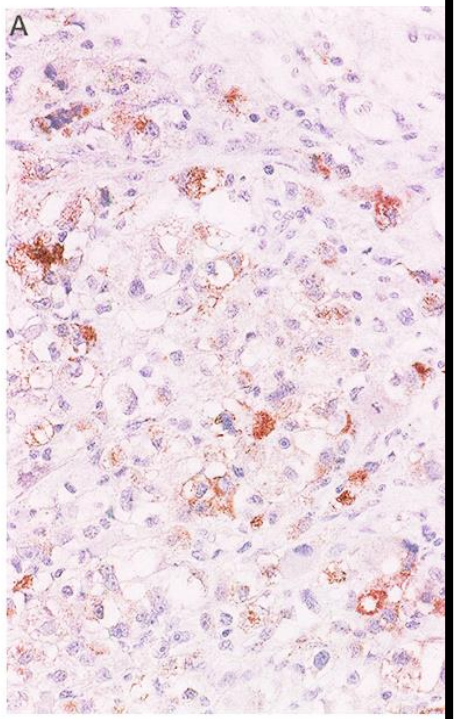

Figure 4. *RCC (patient 120) by melanoma-associated antigen.* A: *Cl... Anti-HMB-45, magnification, ×200.*

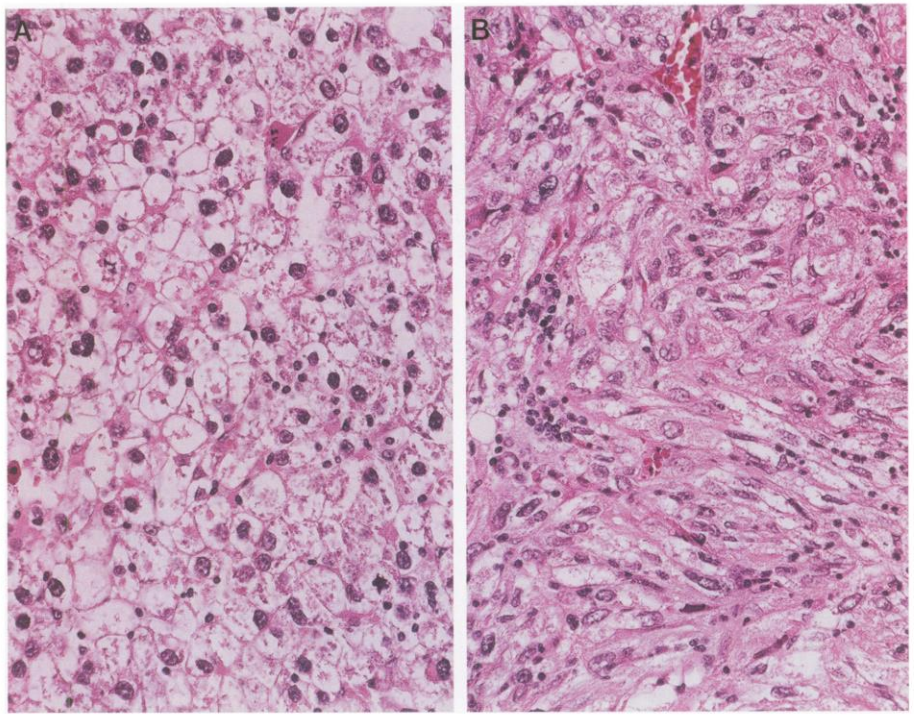

Figure 3. *RCC (patient 120) by conventional histology.* A: *Clear cell region. H&E, magnification, ×200.* B: *Anaplastic region. H&E, magnification, ×200.*

TSC Associated RCC: Historical Literature

- Oncocytoma
- Chromophobe RCC
- Clear cell RCC
- Papillary RCC
- Unclassified RCC

Tuberous Sclerosis–associated Renal Cell Carcinoma

A Clinicopathologic Study of 57 Separate Carcinomas in 18 Patients

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Abstract: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with characteristic tumors involving multiple organ systems. Whereas renal angiomyolipoma (AML) is common in TSC, renal cell carcinoma (RCC) is rarely reported. Fifty-seven RCCs from 13 female and 5 male TSC patients were reviewed. Age at surgery ranged from 7 to 65 years (mean: 42 y). Nine patients (50%) had multiple synchronous and/or metachronous RCCs (range of 2 to 20 RCCs) and 5 had bilateral RCCs (28%). Seventeen patients (94%) had histologically confirmed concurrent renal AMLs, including 15 with multiple AMLs (88%) and 9 (50%) with AMLs with epithelial cysts. None of the 15 patients with available clinical follow-up information had evidence of distant metastatic disease from 6 to 198 months after their initial surgery (mean: 52 mo). The 57 RCCs exhibited 3 major distinct morphologies: (1) 17 RCCs (30%) had features similar to tumors previously described as "renal angiomyoadenomatous tumor" or "RCC with smooth muscle stroma"; (2) 34 RCCs (59%) showed features similar to chromophobe RCC; and (3) 6 RCCs (11%) showed a granular eosinophilic-macrocystic morphology. Distinct histologic changes were also commonly present in the background kidney parenchyma and included cysts or renal tubules lined by epithelial cells with prominent eosinophilic cytoplasm, nucleomegaly, and nucleoli. Immunohistochemically, all RCCs tested showed strong nuclear reactivity for PAX8 and HMB45 negativity. Compared with sporadic RCCs, TSC-associated RCCs have unique clinicopathologic features including female predominance, younger age at diagnosis, multiplicity, association with AMLs, 3 recurring histologic patterns, and an indolent clinical course. Awareness of the morphologic and clinicopathologic spectrum of RCC in this setting will allow surgical pathologists to better recognize clinically unsuspected TSC patients.

Key Words: tuberous sclerosis, renal cell carcinoma, angiomyolipoma, renal angiomyoadenomatous tumor, CA9, CK7, CD117, HMB45, PAX8

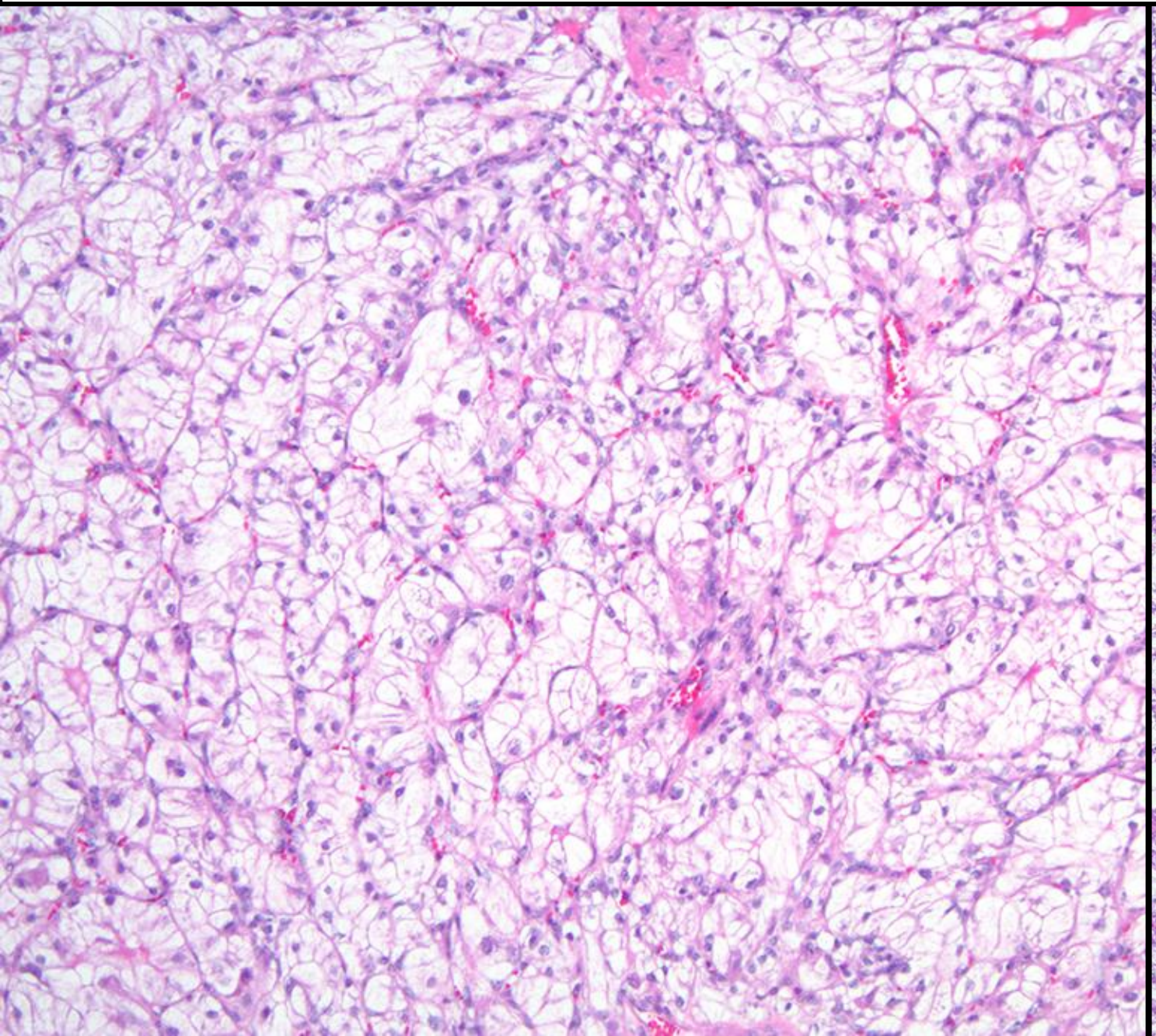
(*Am J Surg Pathol* 2014;00:000–000)

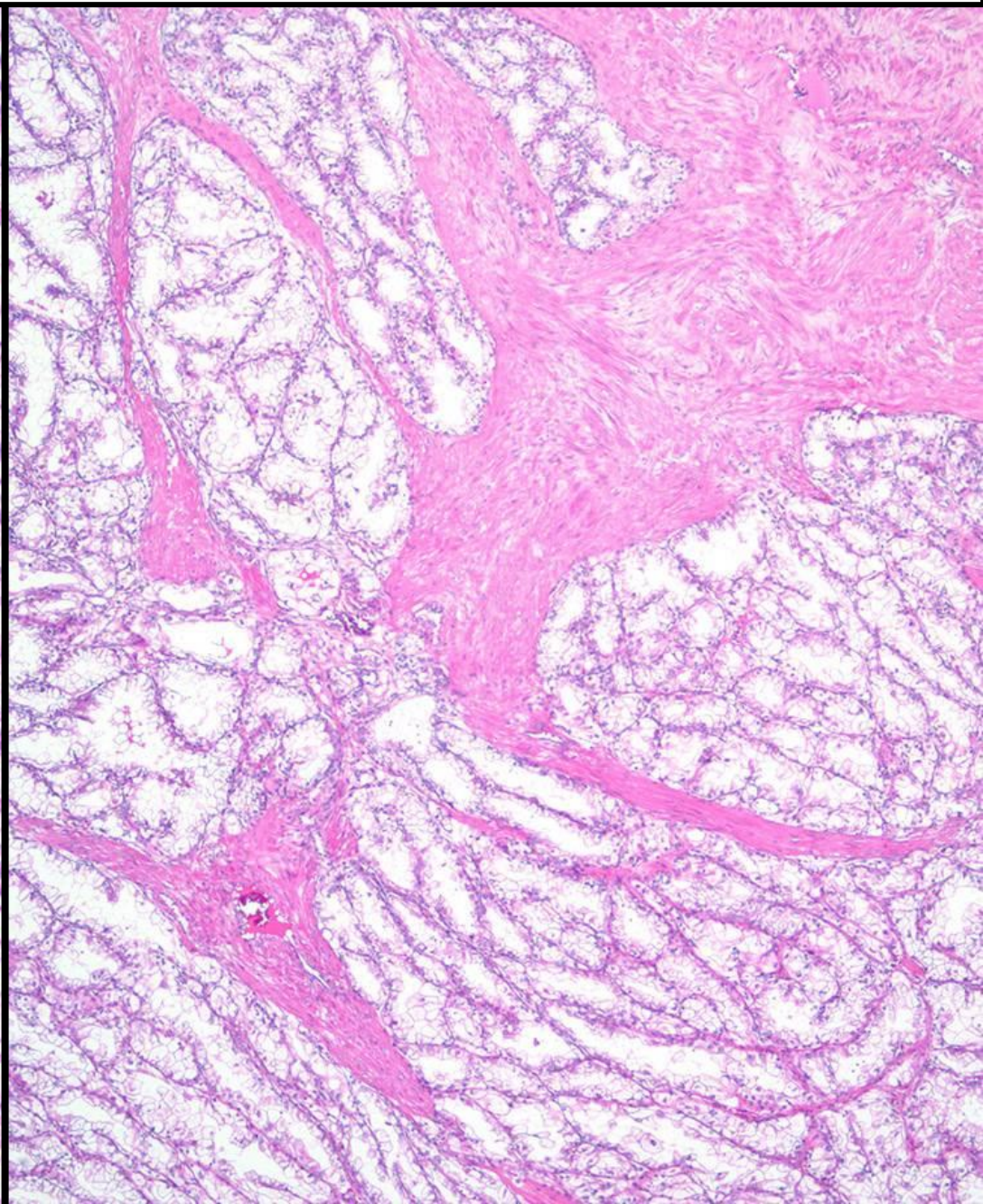
From the *Cleveland Clinic, Robert J. Tomsich Pathology & Laboratory Medicine Institute; ***Glickman Urological and Kidney In-

TSC RCC: Histologic Patterns

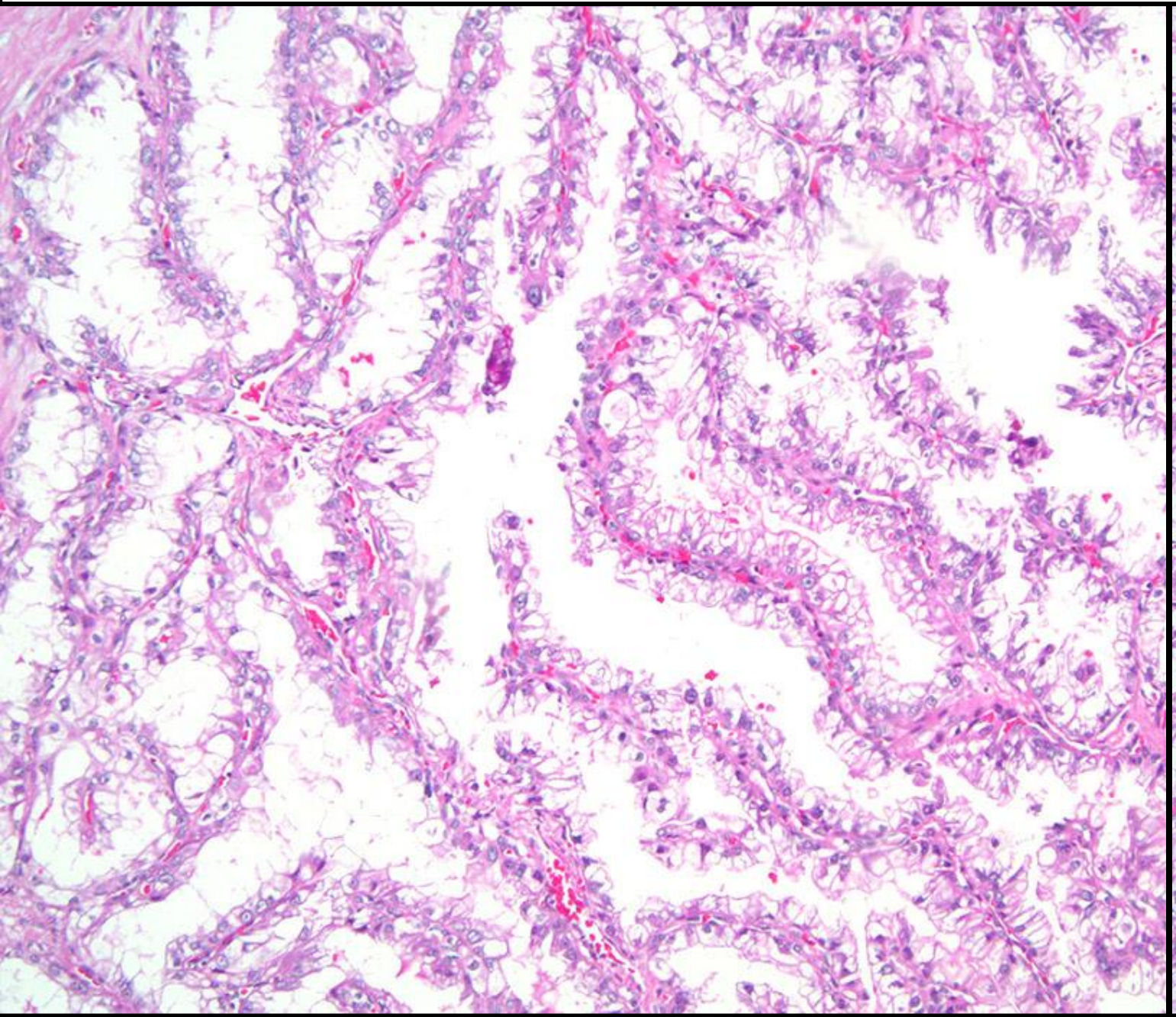
- RCC with fibromyomatous stroma
  - Exists in literature in sporadic setting
  - Poorly defined and controversial
- RCC, eosinophilic and macrocystic pattern
  - Single case report?
  - No sporadic counterpart
- Oncocytic spectrum (chromophobe-like)
  - Sporadic and hereditary tumors in literature
  - Heterogeneous?

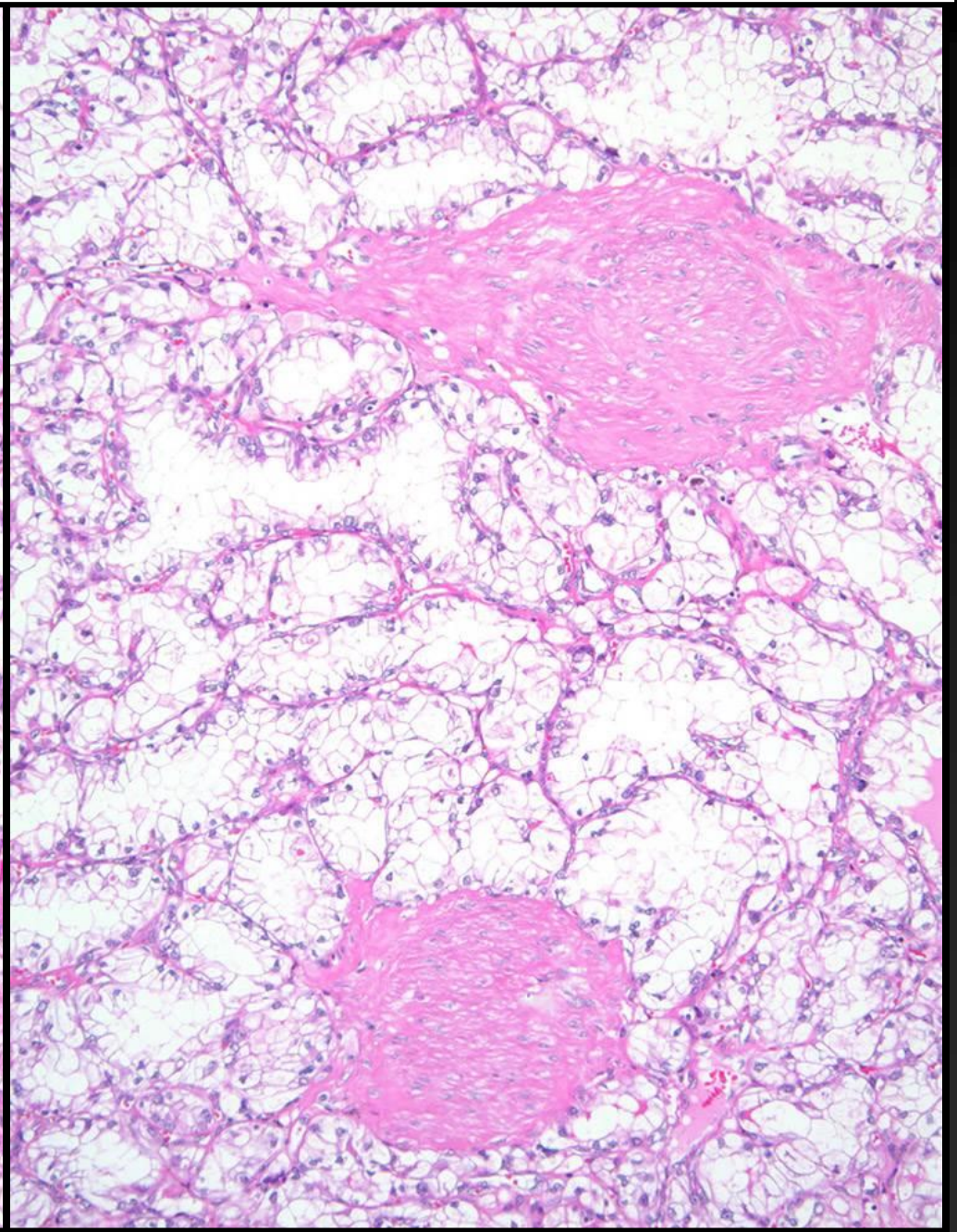
TSC Associated RCC: Fibromyomatous



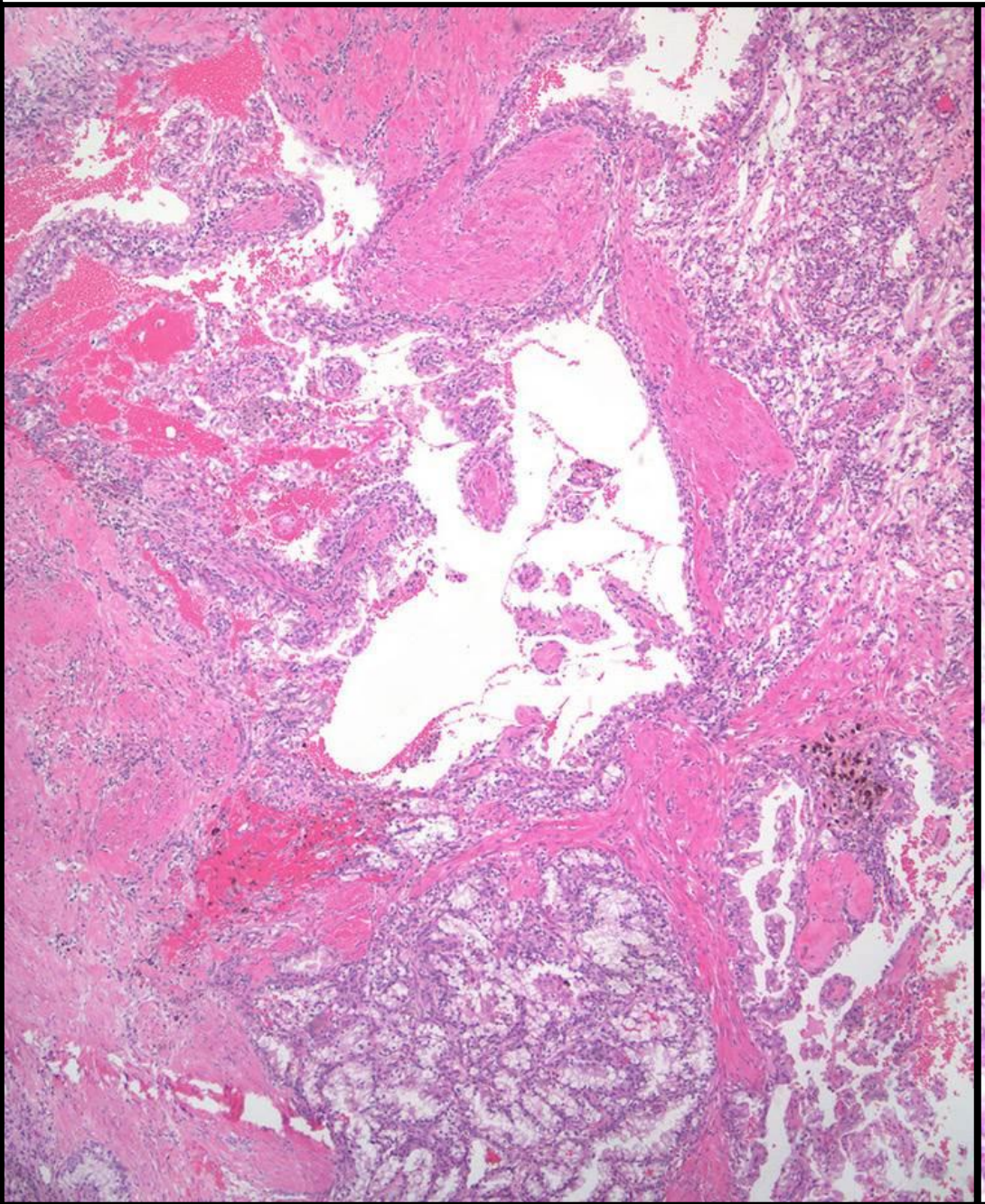


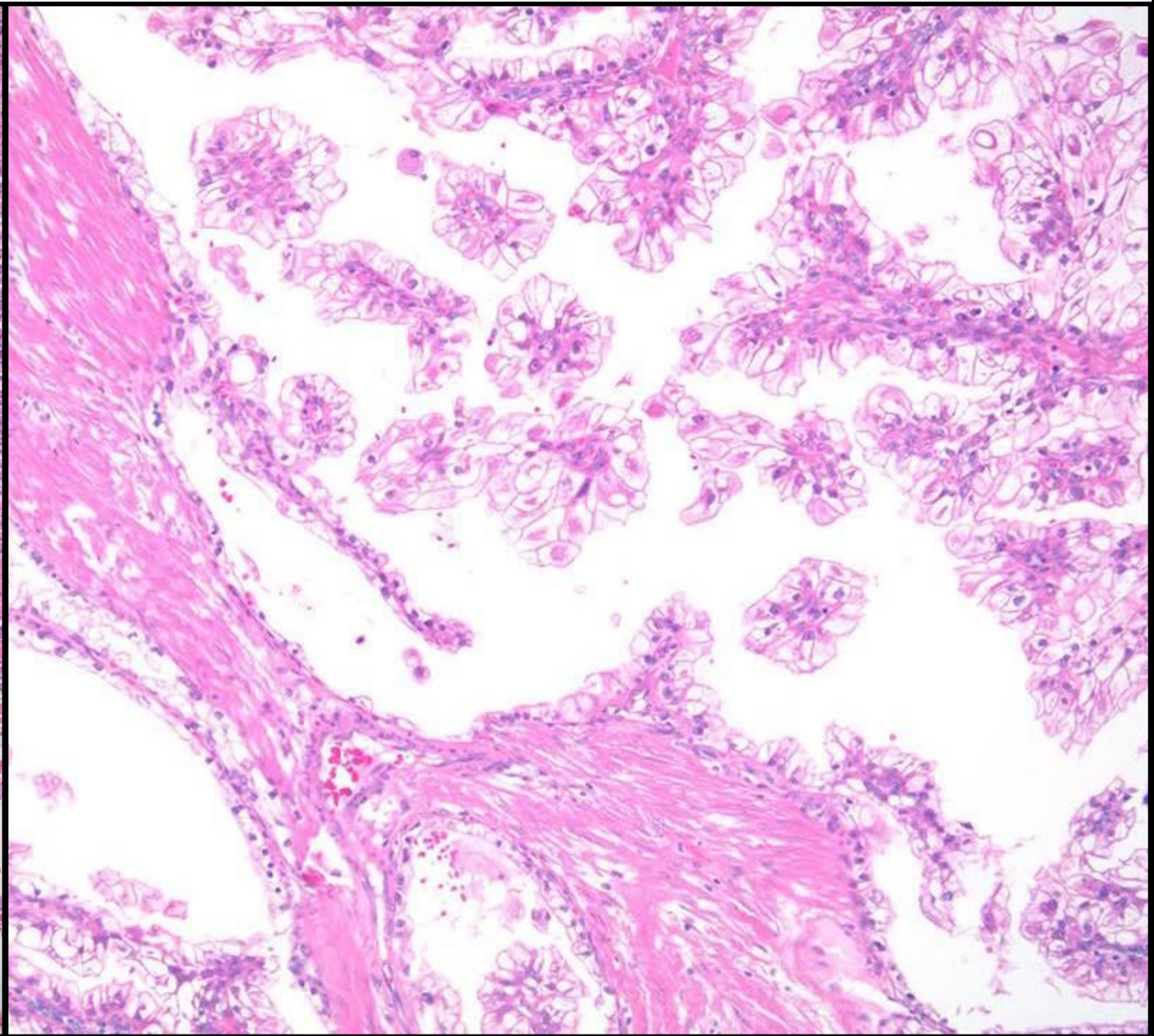
TSC Associated RCC: Fibromyomatous





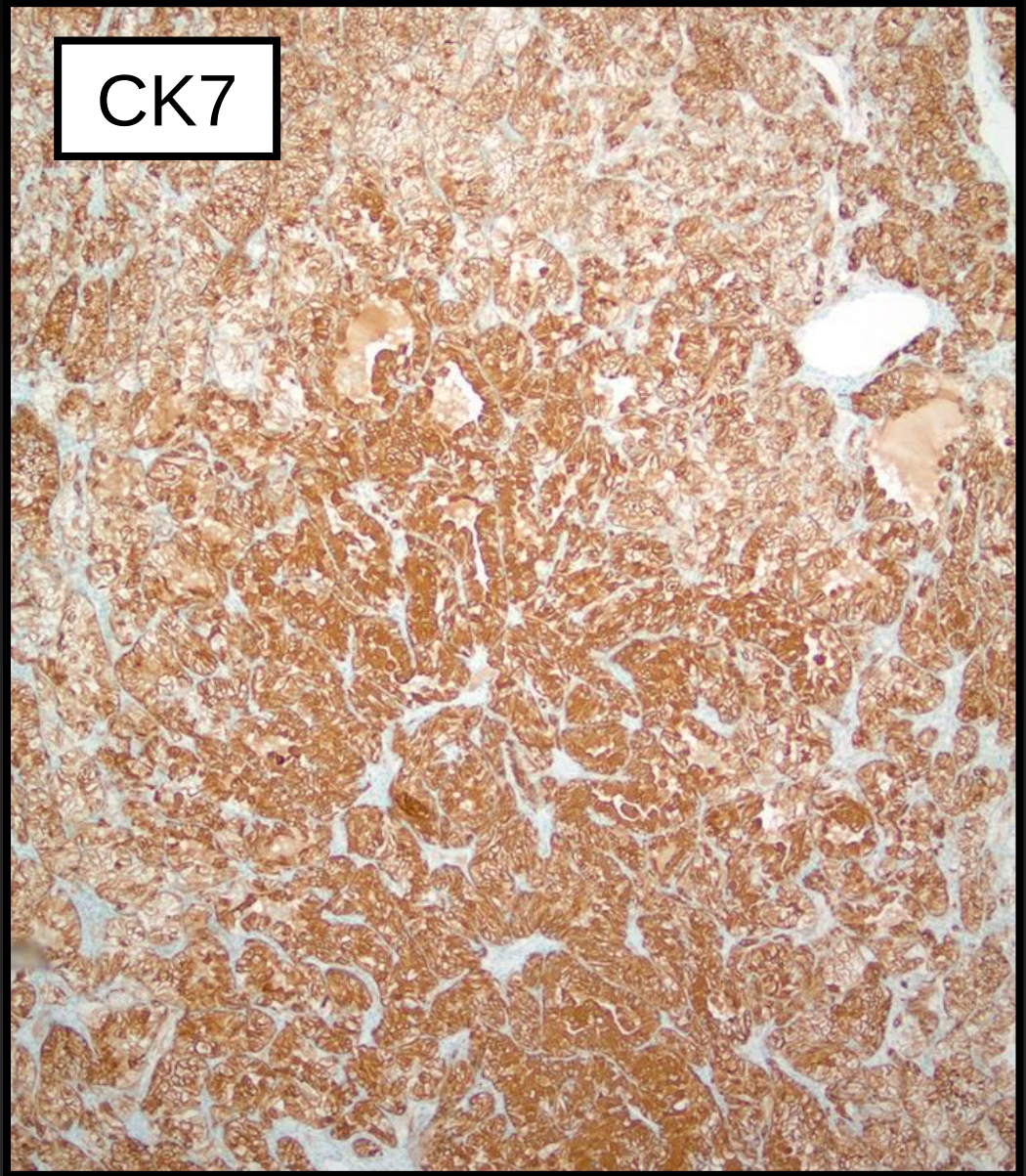
TSC Associated RCC: Fibromyomatous



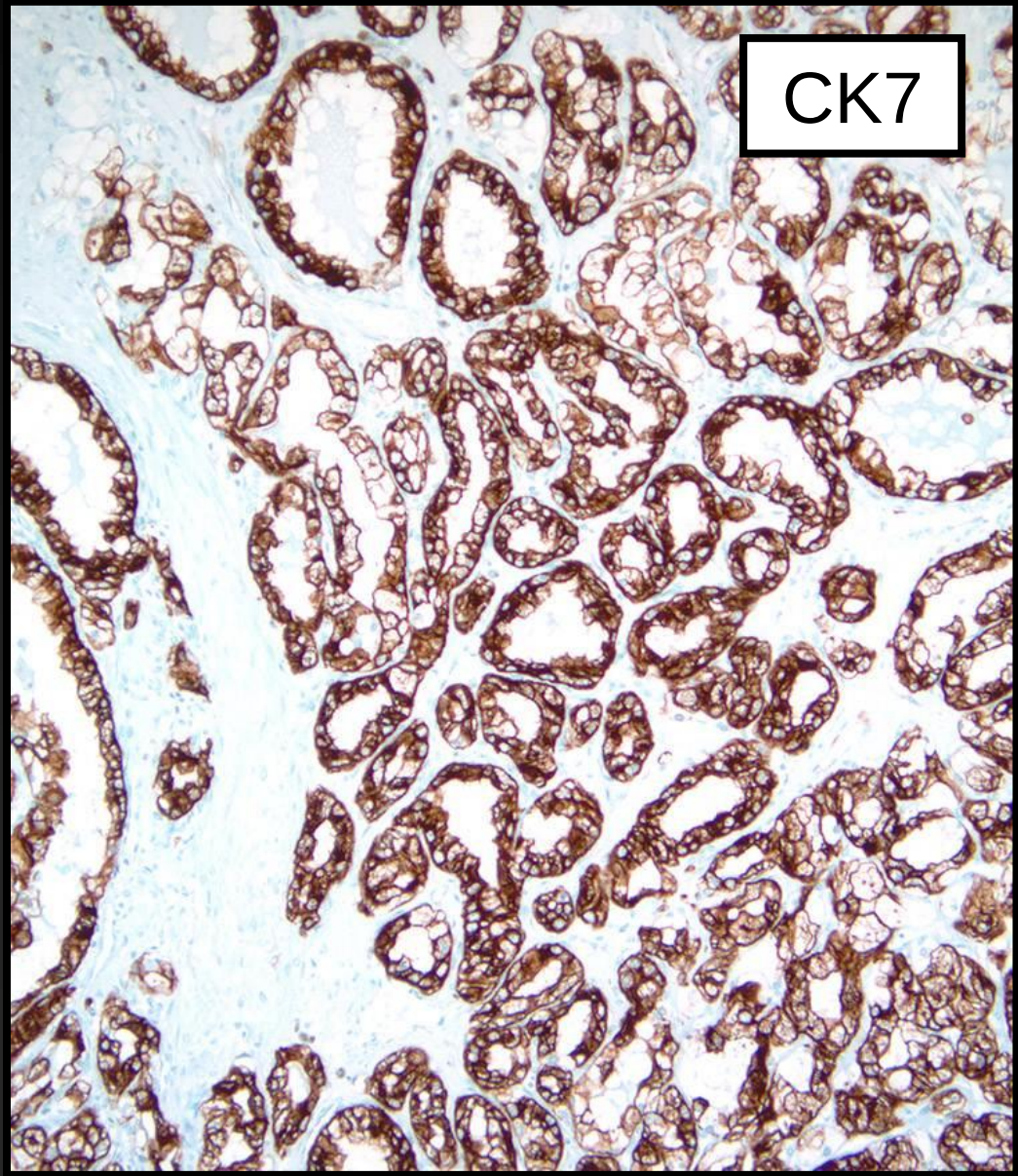


TSC Associated RCC: Leiomyomatous

Solid



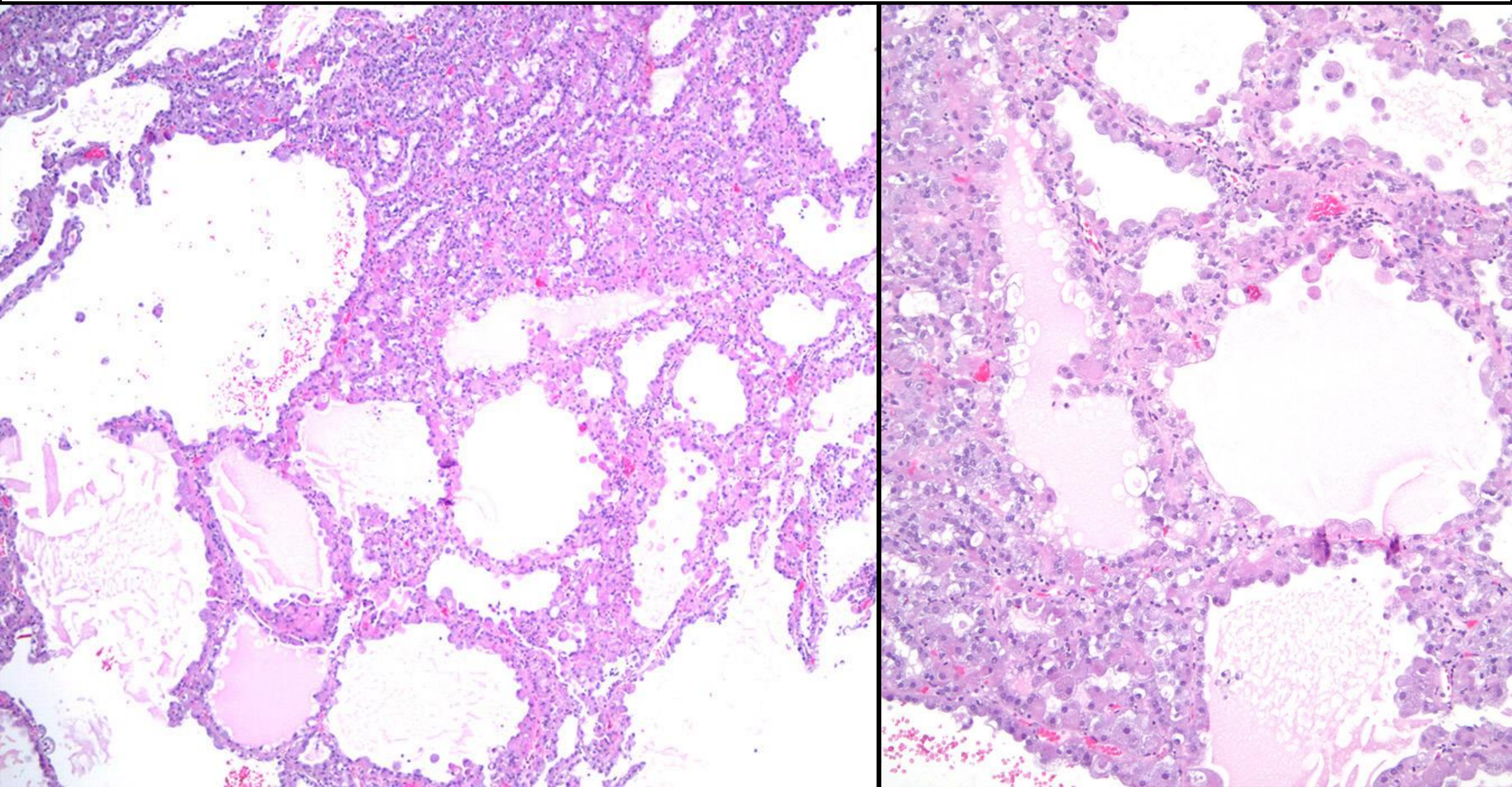
Tubular and Papillary



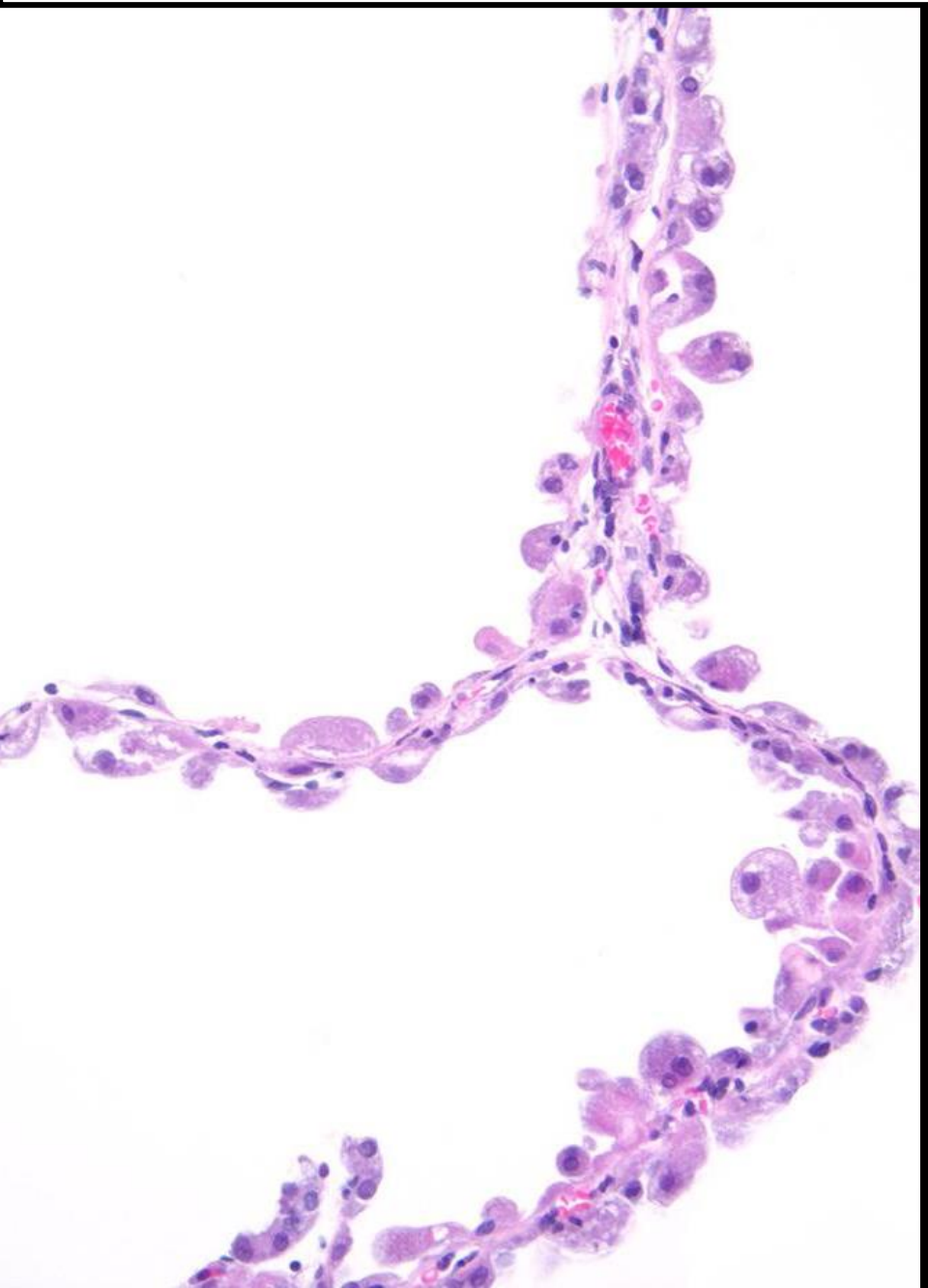
TSC Associated RCC: Historical Literature and Fibromyomatous Pattern?

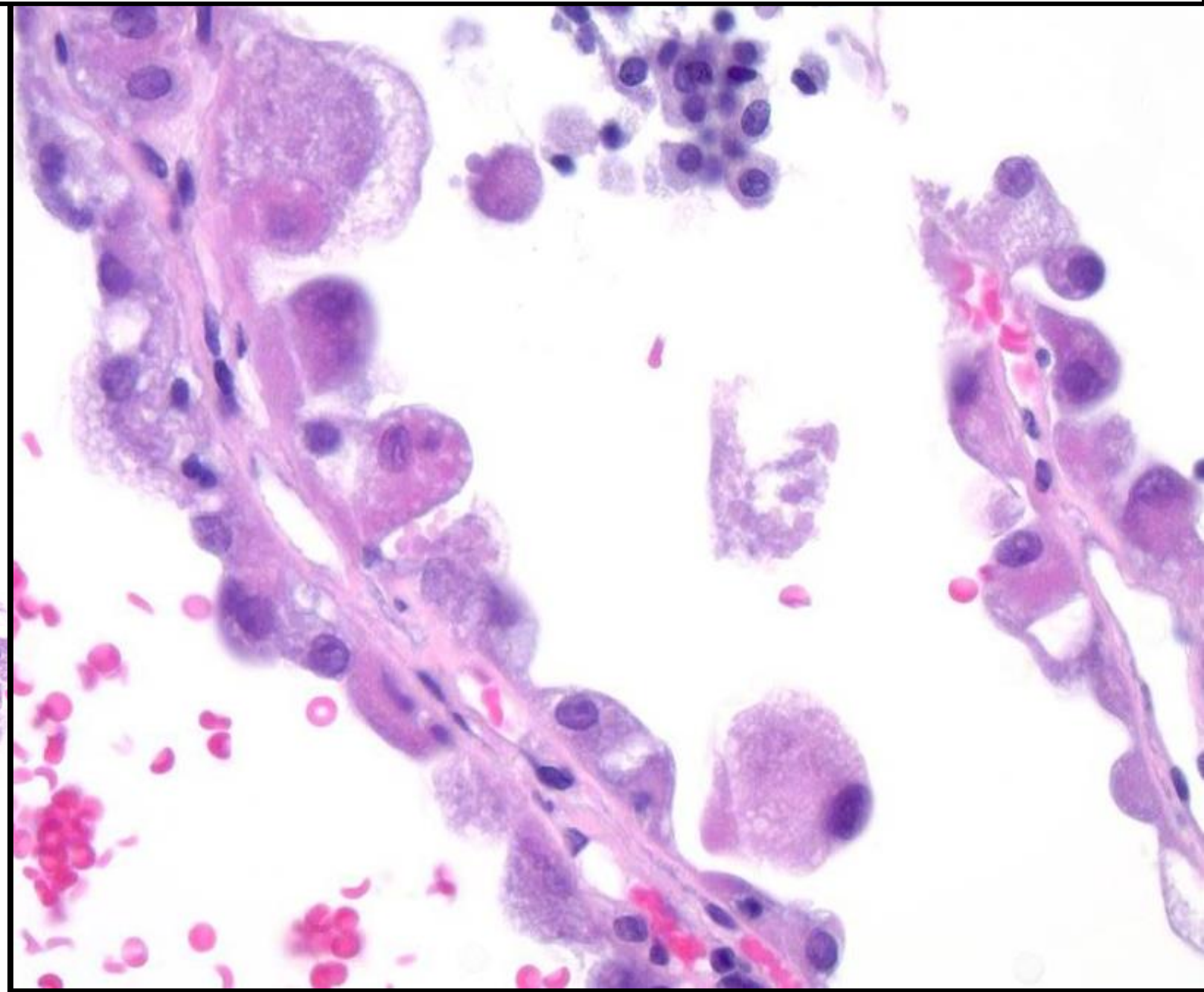
- Reports of….
  - –Clear cell RCC
    - VHL alteration?
  - –Papillary RCC
    - MET alteration?

TSC Associated RCC: Eosinophilic, Solid, Cystic (ESC)

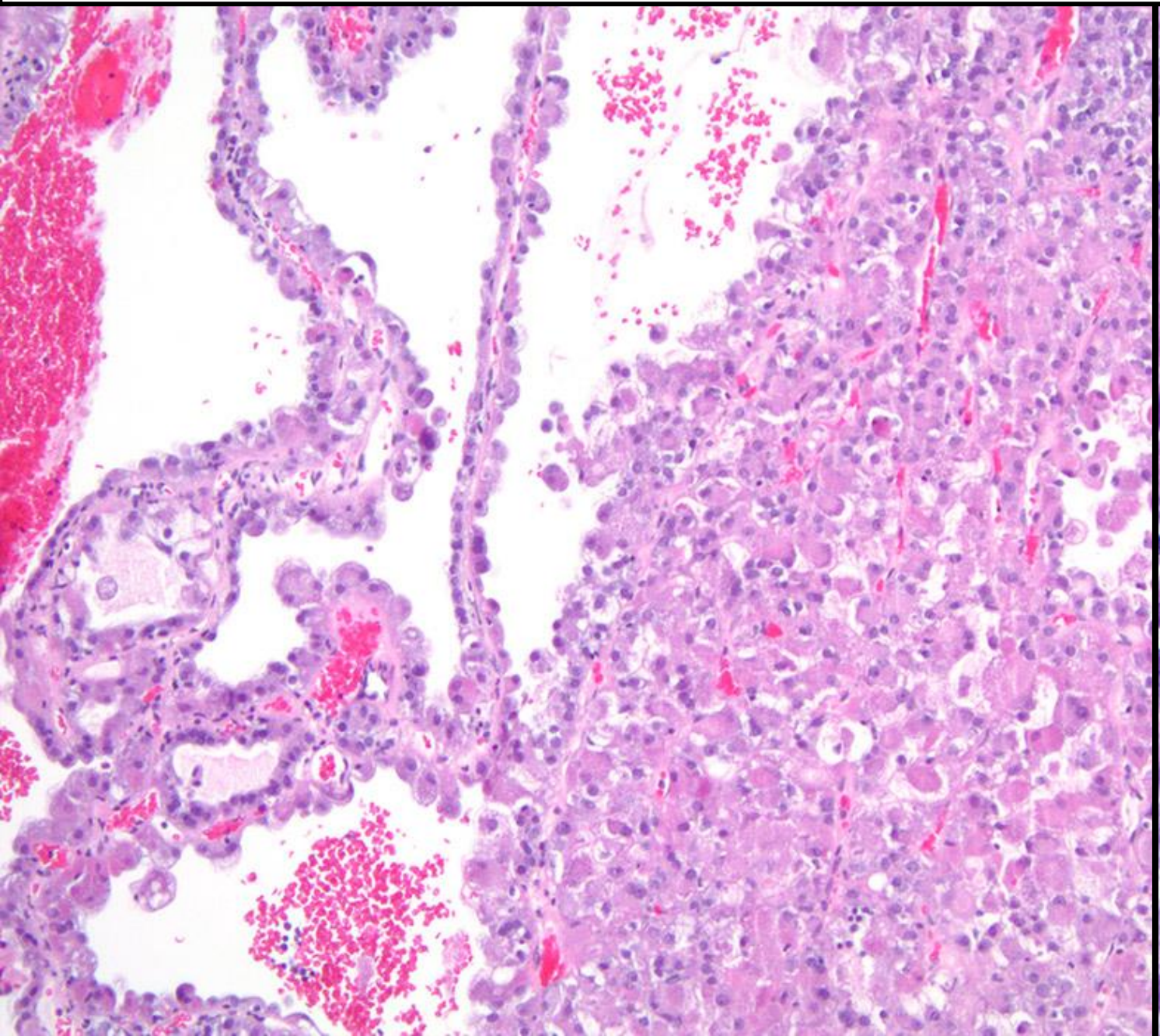


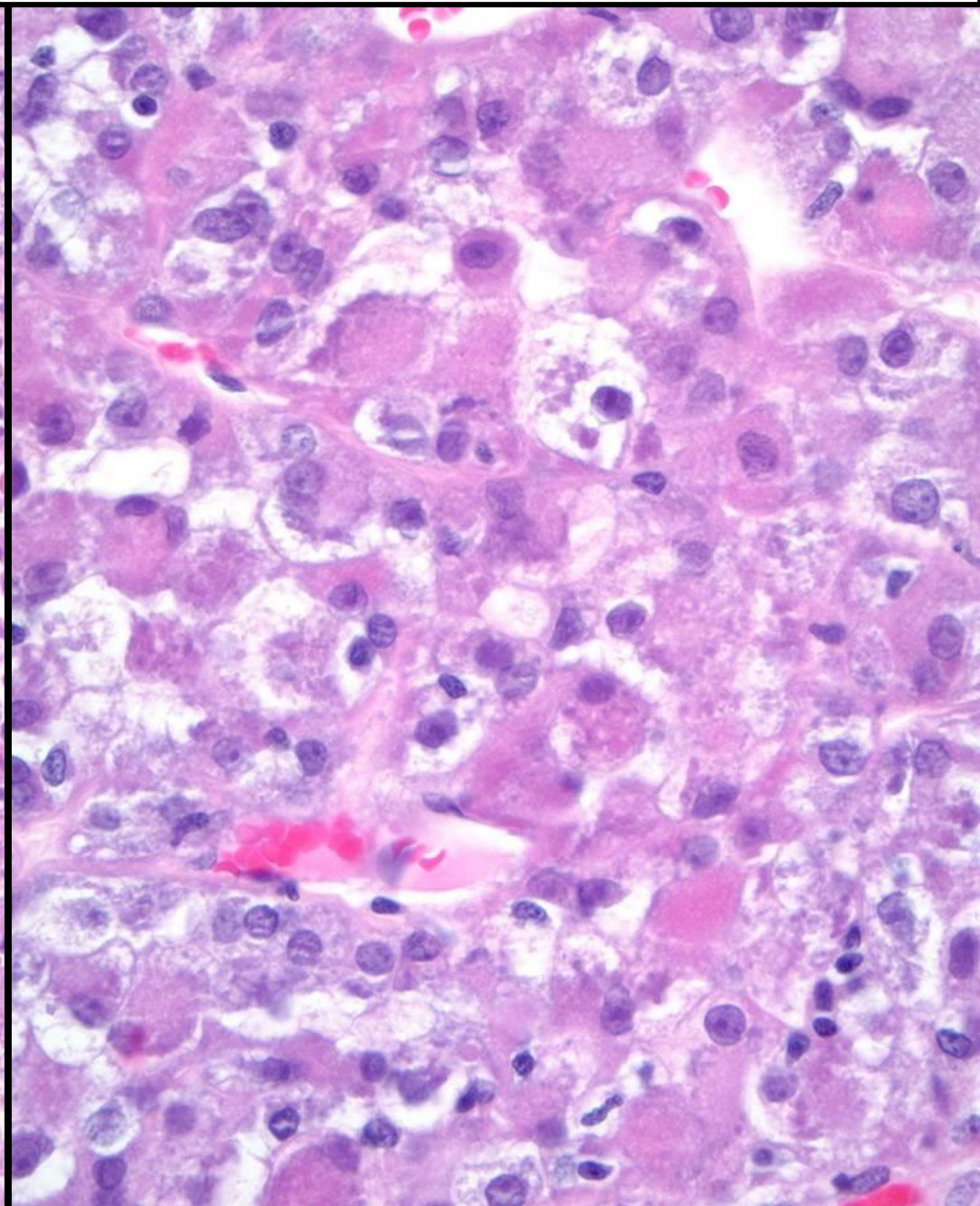
TSC Associated RCC: Eosinophilic, Solid, Cystic (ESC)



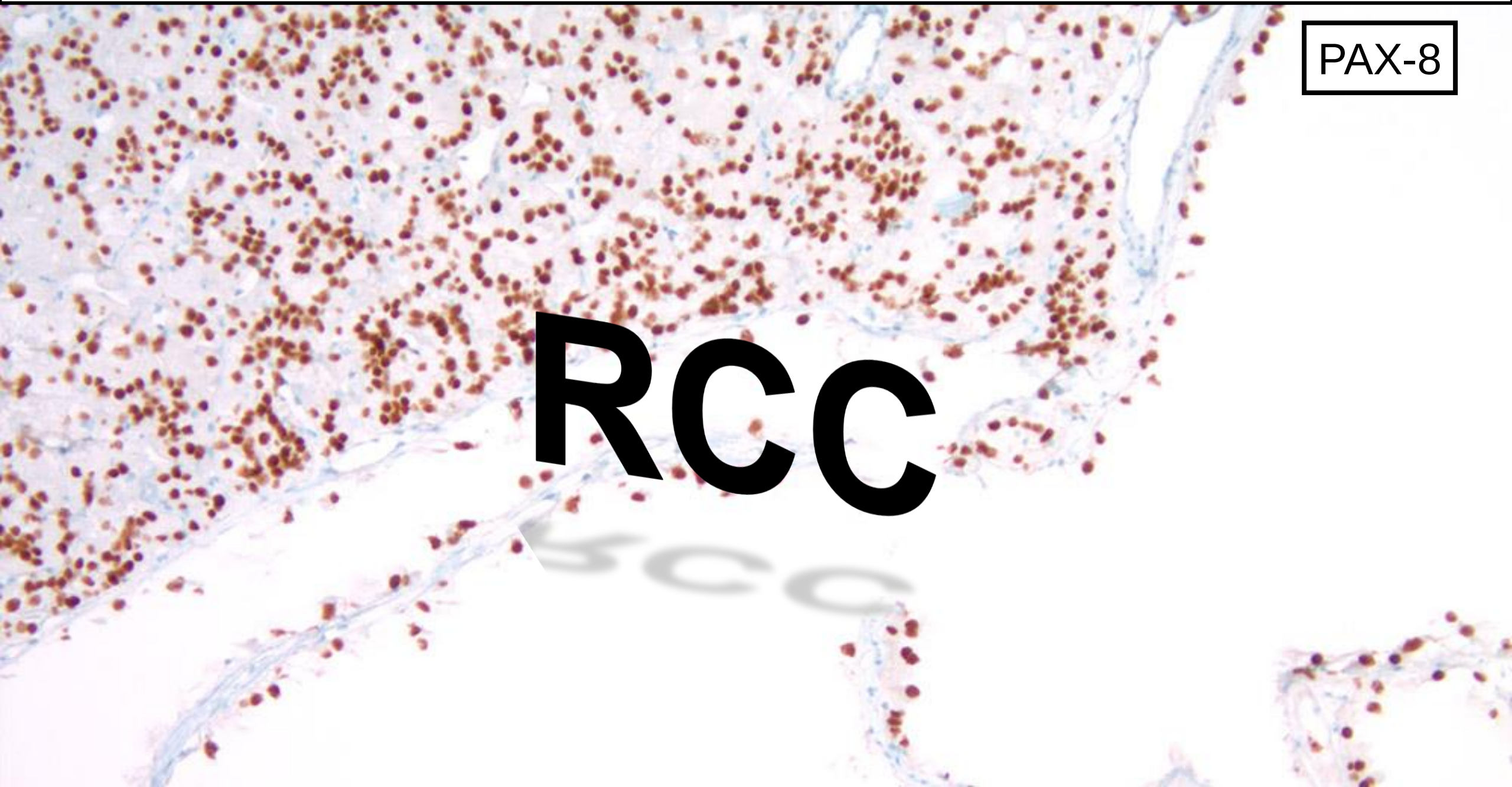


TSC Associated RCC: Eosinophilic, Solid, Cystic (ESC)





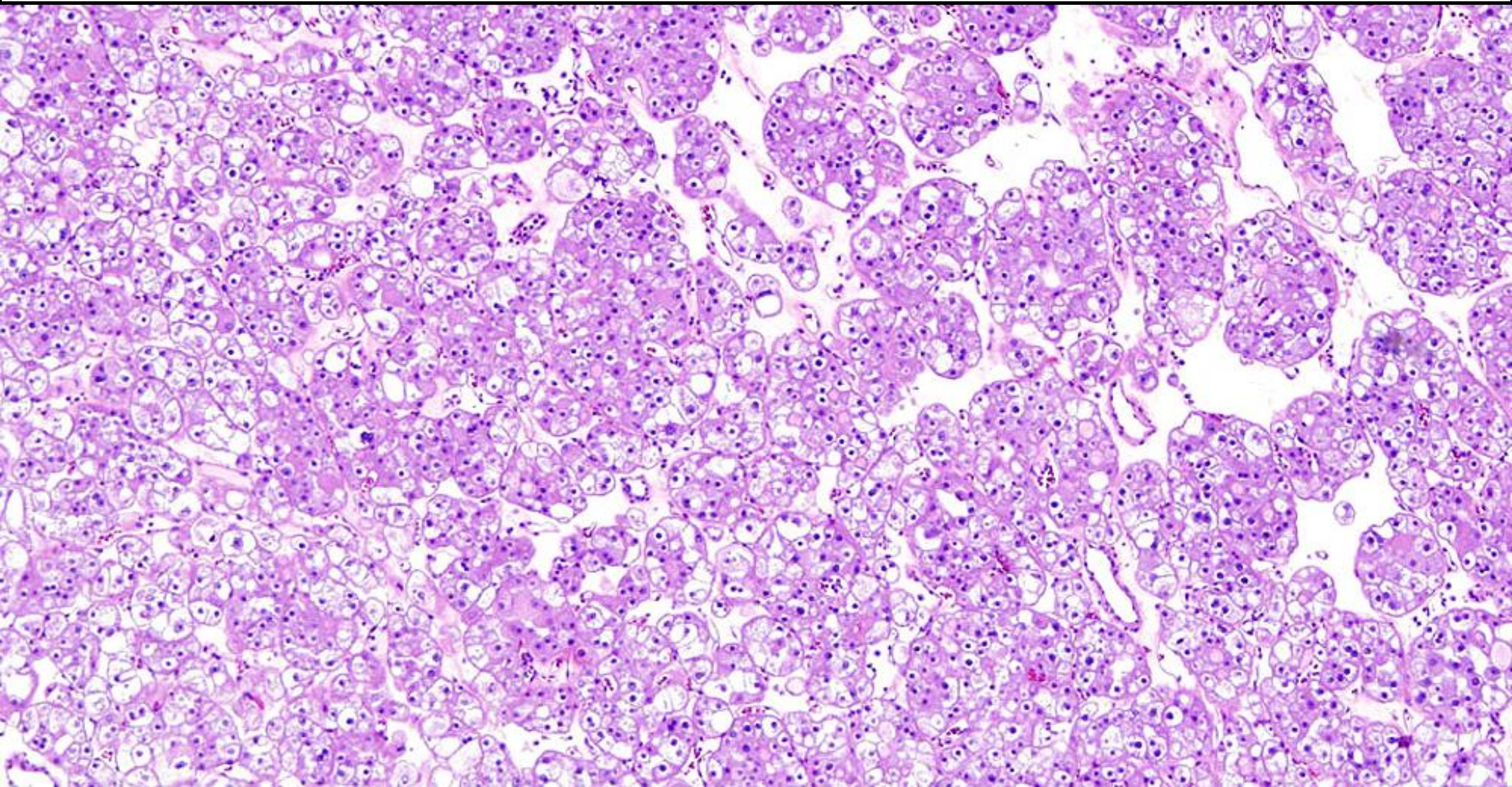
TSC Associated RCC: Eosinophilic, Solid, Cystic (ESC)



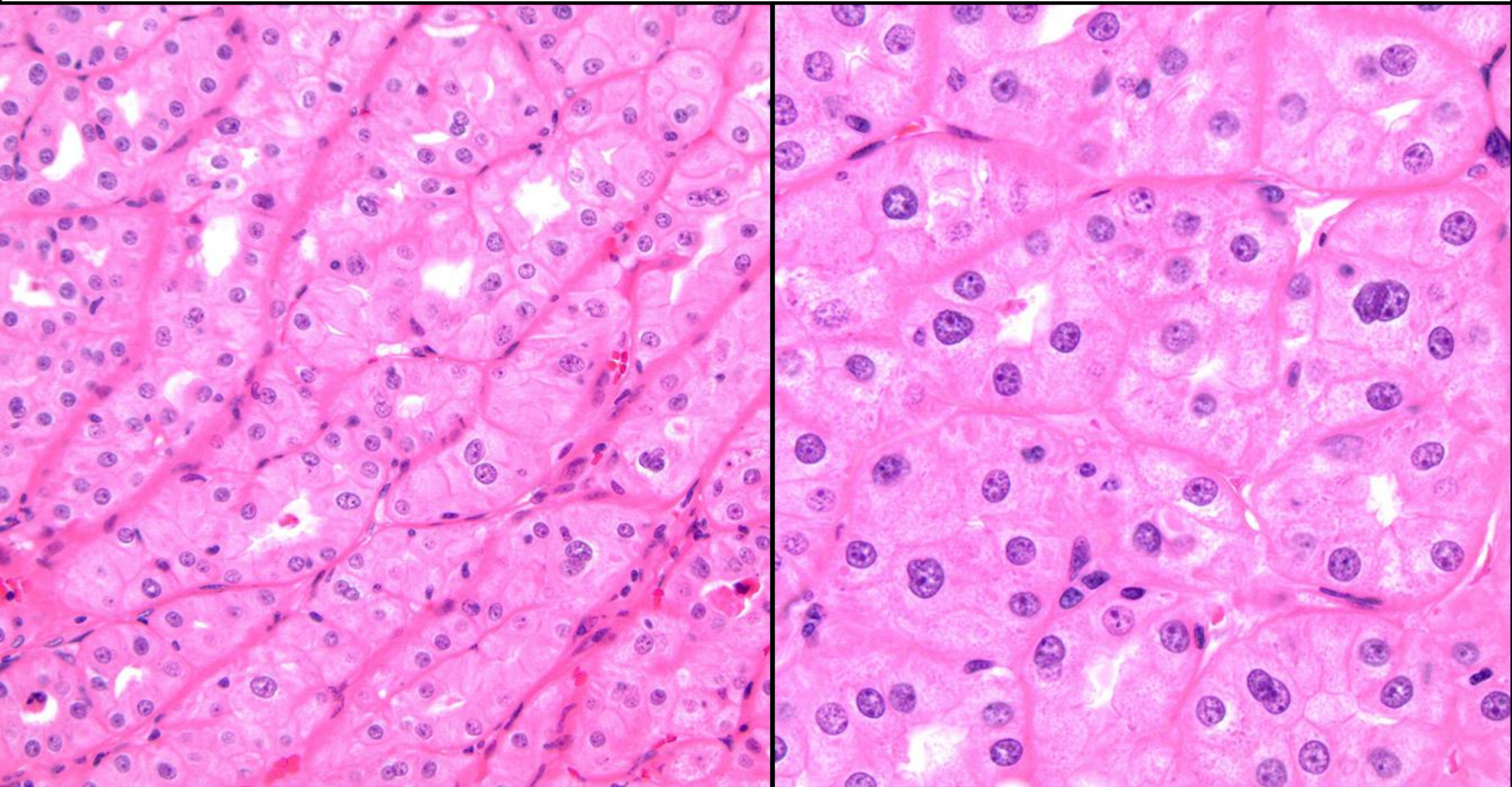
TSC Associated RCC: Historical Literature of “ESC” pattern

- Angiomyolipoma
  - Pre-test probability
- Unclassified RCC
- Chromophobe RCC?

TSC Associated RCC: Chromophobe-like/Hybrid-like



TSC Associated RCC: Chromophobe-like/Hybrid-like



TSC Associated RCC:
Historical Literature of Chromophobe-like Pattern

- Oncocytoma
- Chromophobe RCC
- Hybrid Oncocytic Tumor
- “Unclassified” RCC

Renal Cell Carcinoma in Tuberous Sclerosis Complex

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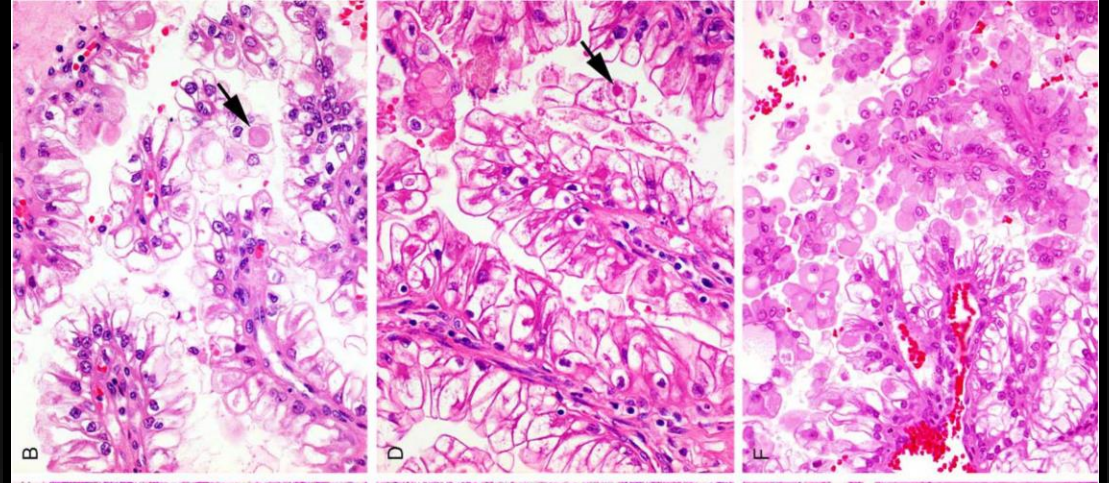
Abstract: Renal cell carcinoma (RCC) occurs in 2% to 4% of patients with tuberous sclerosis complex (TSC). Previous reports have noted a variety of histologic appearances in these cancers, but the full spectrum of morphologic and molecular features has not been fully elucidated. We encountered 46 renal epithelial neoplasms from 19 TSC patients and analyzed their clinical, pathologic, and molecular features, enabling separation of these 46 tumors into 3 groups. The largest subset of tumors (n = 24) had a distinct morphologic, immunologic, and molecular profile, including prominent papillary architecture and uniformly deficient succinate dehydrogenase subunit B (SDHB) expression prompting the novel term "TSC-associated papillary RCC (PRCC)." The second group (n = 15) were morphologically similar to a hybrid oncocytic/chromophobe tumor (HOCT), whereas the last 7 renal epithelial neoplasms of group 3 re-

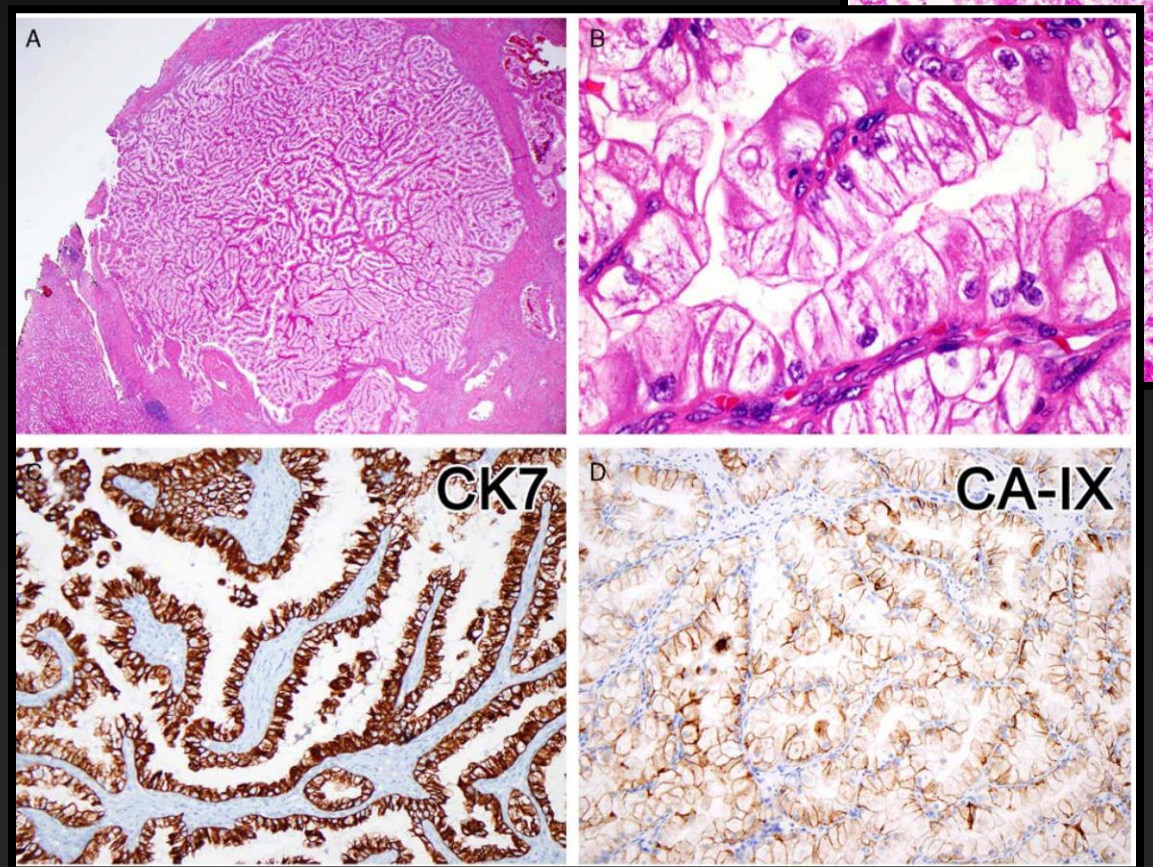
TSC-associated PRCCs showed strong, diffuse labeling for carbonic anhydrase IX (100%), CK7 (94%), vimentin (88%), and CD10 (83%) and were uniformly negative for SDHB, TFE3, and AMACR. Gains of chromosomes 7 and 17 were found in 2 tumors, whereas chromosome 3p deletion and TFE3 translocations were not detected. In this study, we reported a sizable cohort of renal tumors seen in TSC and were able to identify them as different morphotypes, which may help to expand the morphologic spectrum of TSC-associated RCC.

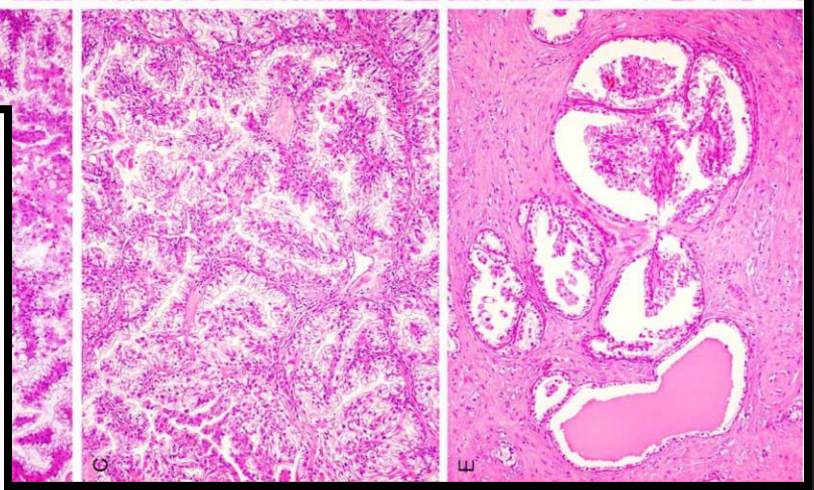
Key Words: renal cell carcinoma, tuberous sclerosis complex, succinate dehydrogenase, hybrid oncocytic/chromophobe tumor, immunohistochemistry, molecular genetics

(*Am J Surg Pathol* 2014;38:895–909)

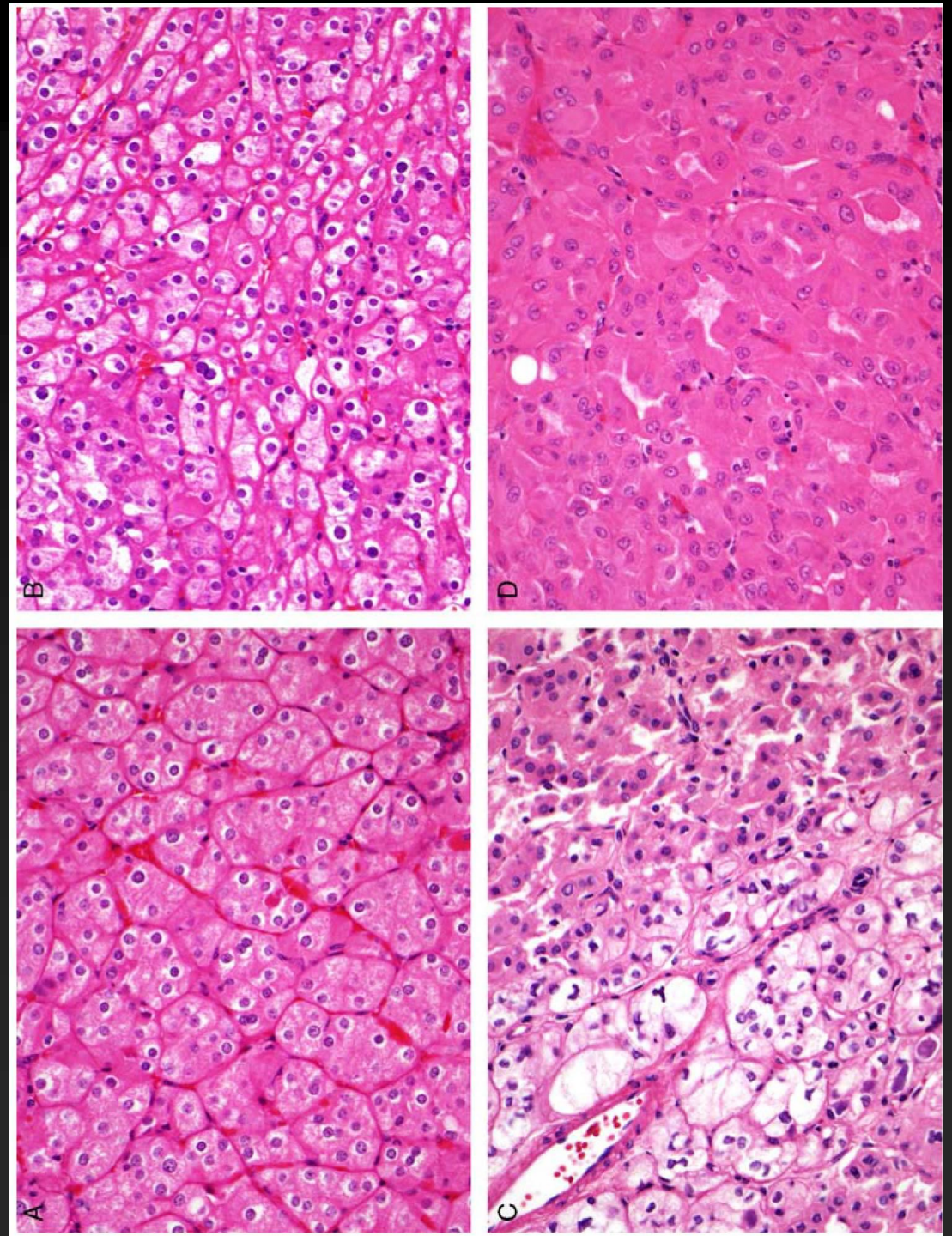
“Papillary RCC”





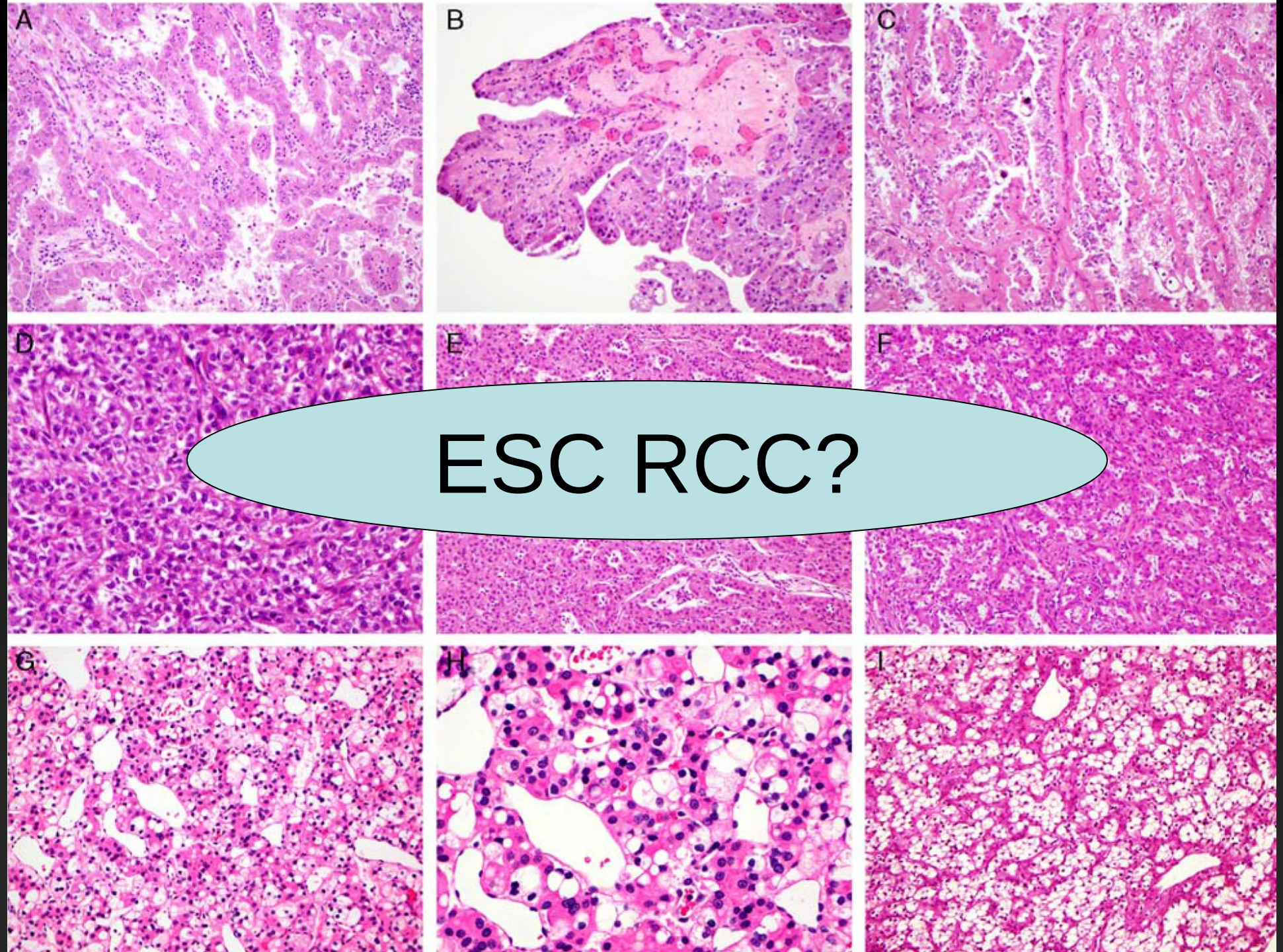


“RCC with fibromyomatous stroma”



“Hybrid Oncocytic Renal Tumor”

“Chromophobe-like”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ESC RCC?

The Journal of Pathology: Clinical Research
J Pathol Clin Res July 2018; **4**: 167–174
Published online 13 June 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/cjp2.104

ORIGINAL ARTICLE

Atypical tuberous sclerosis complex presenting as familial renal cell carcinoma with leiomyomatous stroma

Ismaël Bah[1], Somayyeh Fahiminiya[2,3], Louis R Bégin[4], Nancy Hamel[2], Maria D D'Agostino[5,6], Simon Tanguay[7] and William D Foulkes[2,5,8,9]*

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[2] *Cancer Research Program, Research Institute of the McGill University Health Centre, Montreal, QC, Canada*
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[4] *Division of Anatomic Pathology, Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada*
[5] *Department of Human Genetics, McGill University, Montreal, QC, Canada*
[6] *Department of Medical Genetics, McGill University Health Center, Montreal, QC, Canada*
[7] *Division of Urology, McGill University Health Center, Montreal, QC, Canada*
[8] *Department of Medical Genetics, Lady Davis Institute, Segal Cancer Centre, Jewish General Hospital, Montreal, QC, Canada*
[9] *Program in Cancer Genetics, Department of Oncology and Human Genetics, McGill University, Montreal, QC, Canada*

Correspondence to: William D Foulkes, Department of Medical Genetics, Lady Davis Institute, Segal Cancer Centre, Jewish General Hospital, 3755 Cote St. Catherine Road, Montreal, QC, Canada H3T 1E2. E-mail: william.foulkes@mcgill.ca

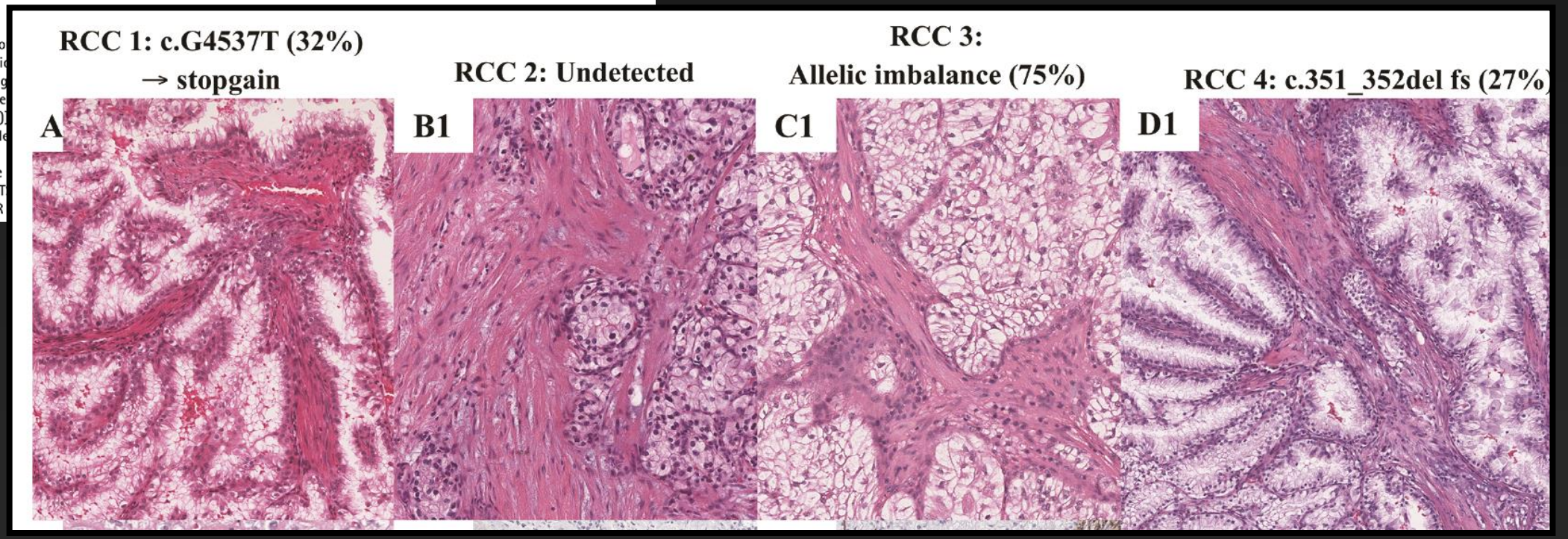
Abstract

We report an atypical tubero
carcinomas (RCCs) with (angi
ple angiomyolipomas, hypopig
and three relatives, germline
[c.2714 G>A, (p.Arg905Gln)]
milder TSC phenotype. Whole
mother demonstrated either
imbalance at the *TSC2* gene
specific *TSC2* second hits in T
to abnormalities of the mTOR

Table 1. Tumour-specific *TSC2* alterations in various RCCs as per WES

RCC tumour	RCC histotype	*TSC2* alteration on WES
Mother's RCC	RCCLS	c.T1670A: p.L557X (29% AF) stopgain
RCC #1	RCCLS	c.G4537T: p.E1513X (32% AF) stopgain
RCC #2	RCCLS	Undetected
RCC #3	RCCLS	Allelic imbalance (75% AF)
RCC #4	RCCLS	c.351_352del:p.G117 fs (27% AF) frameshift deletion
RCC #5	Chromophobe-like	Allelic imbalance (72% AF)

AF, Allelic frequency.



The current state of renal neoplasia in TSC…

- Multiple, bilateral AMLs
  - Typical types
  - AMLEC
  - Other PEComa patterns
    - Epithelioid
    - Sclerosing
- RCC is rare
  - Consistent morphology (3 patterns)
    - “Contradictory” papers limits acceptance

The next step…

Are there sporadic counterparts to these three RCC patterns and what can they teach us?

Unknown

RCC with abundant eosinophilic granular cytoplasm and solid and cystic architecture

ESC RCC

Known

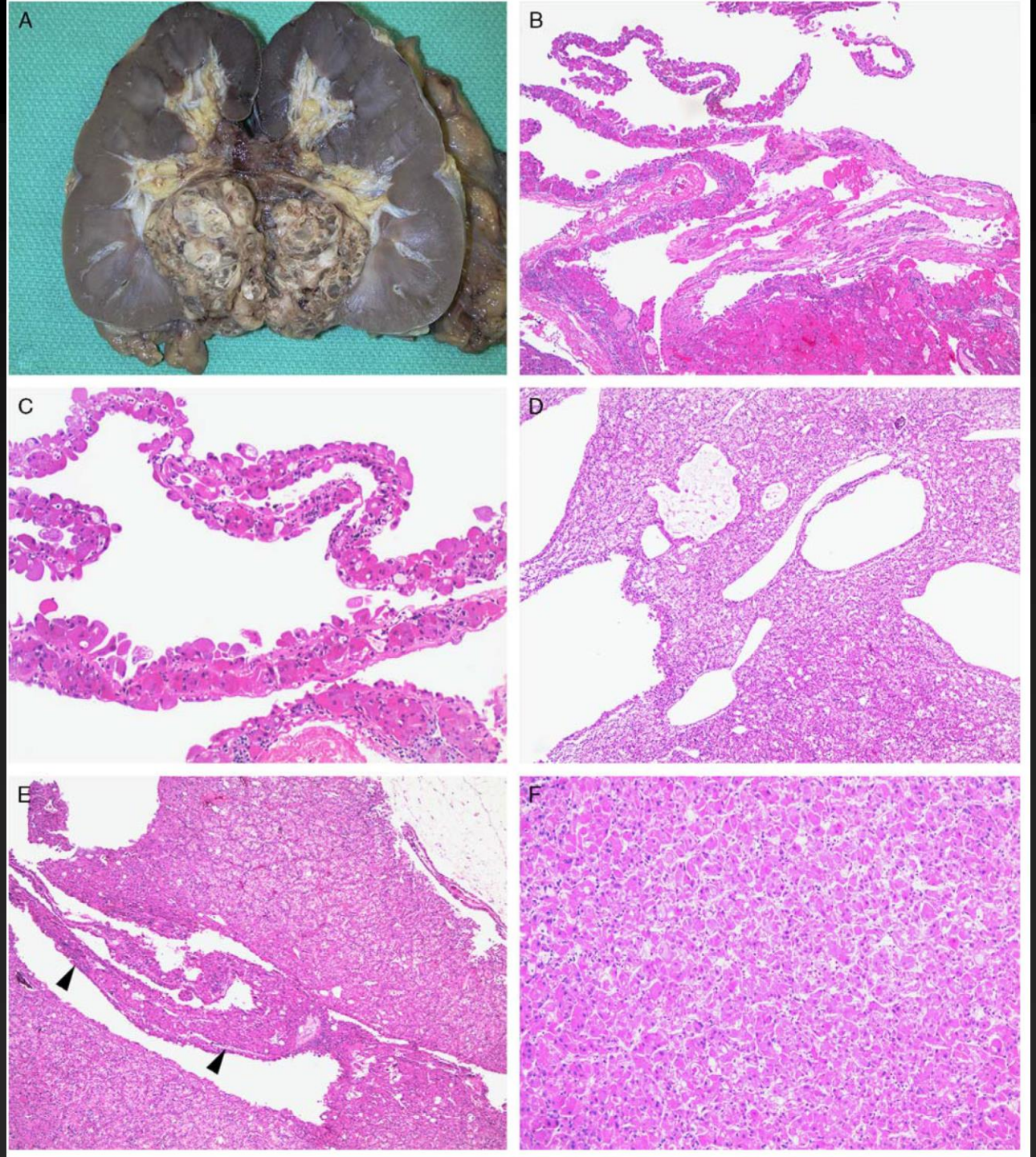
RCC with "fibromyomatous stroma"

Chromophobe RCC/ Hybrid Oncocytic Tumor

Sporadic ESC RCC

“Eosinophilic and Macrocystic” Pattern of RCC

- No known sporadic counterpart in 2013
- During TSC series by Juan Guo, Kiril Trpkov was on sabbatical reviewing our “unclassified” RCCs in CLE
- We shared our “ESC” tumors in TSC, and he searched for possible sporadic examples from our “unclassified” RCCs



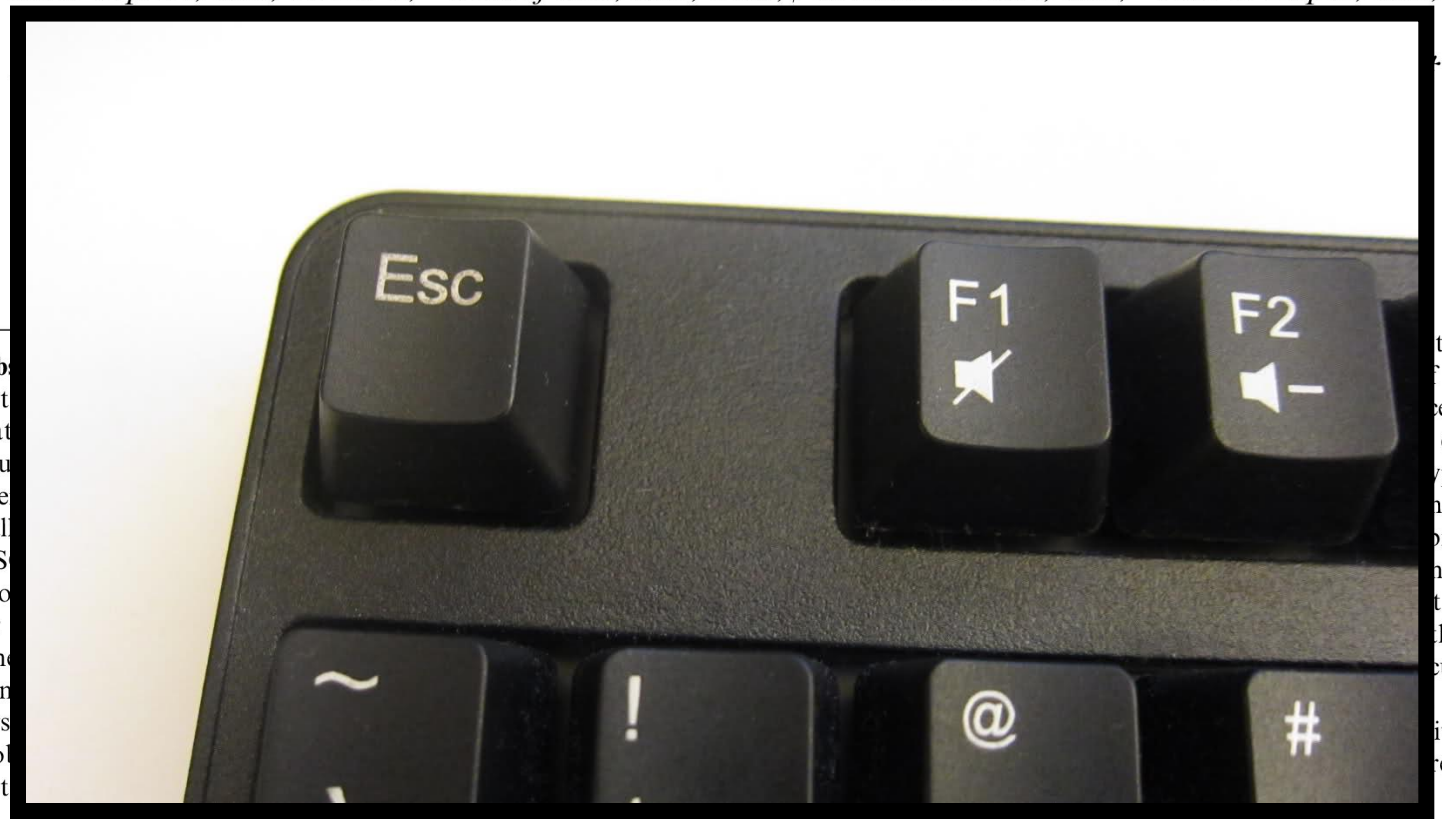
Identified cases identical to TSC associated tumors, but no signs of TSC

No AMLs

Eosinophilic, Solid, and Cystic Renal Cell Carcinoma

Clinicopathologic Study of 16 Unique, Sporadic Neoplasms Occurring in Women

Kiril Trpkov, MD, FRCPC, Ondrej Hes, MD, PhD,† Michael Bonert, MD,* Jose I. Lopez, MD,*



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From the *Calgary Laboratory Services and University of Calgary, Calgary, AB, Canada; †Department of Pathology, Charles University, Pilsen, Czech Republic; ‡Cruces University Hospital, Bio-Cruces Institute, University of the Basque Country (UPV/EHU), Barakaldo, Bizkaia, Spain; §Nephropath, Little Rock, AR; ‡‡Medical College Wisconsin, Milwaukee, WI; §§El Camino Hos-

Key Words: eosinophilic tumor, renal cell carcinoma, tuberous sclerosis, CK20, unclassified oncocytic tumor, unclassified renal cell carcinoma

(*Am J Surg Pathol* 2016;40:60–71)

Histopathology

Histopathology 2018, **72**, 588–600. DOI: 10.1111/his.13395

Re-evaluation of 33 'unclassified' eosinophilic renal cell carcinomas in young patients

Yunjie Li,[1] Victor E Reuter,[2] Andres Matoso,[1] George J Netto,[1,3] Jonathan I Epstein[1] & Pedram Argani[1]

[1]*Johns Hopkins University School of Medicine, Pathology, Baltimore, MD,* [2]*Memorial Sloan Kettering Cancer Center, Pathology, New York, NY, and* [3]*University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA*

10 ESC RCC cases in archives

Date of submission
Accepted for public
Published online *Article Accepted* 12 September 2017

Ages 14-35

Li Y, Reuter V
(2018) *Histopath*

Re-evaluation of 33 'unclassified' eosinophilic renal cell carcinomas in young patients

Aims: We sought to determine if some unclassified renal cell carcinomas (RCCs) in children and young

the characteristic macronucleoli typical of FH-deficient RCC. Eight RCC (24%) (median age 20.5 years)

ORIGINAL ARTICLE

Are Sporadic Eosinophilic Solid and Cystic Renal Cell Carcinomas Characterized by Somatic Tuberous Sclerosis Gene Mutations?

Megan Parilla, MD, Sabah Kadri, PhD, Sushant A. Patil, PhD, Lauren Ritterhouse, MD, Jeremy Segal, MD, PhD, Kammi J. Henriksen, MD, and Tatjana Antic, MD

EUROPEAN UROLOGY 74 (2018) 483–486

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Kidney Cancer

Editorial by Pedram Argani on pp. 487–488 of this issue

Somatic Bi-allelic Loss of *TSC* Genes in Eosinophilic Solid and Cystic Renal Cell Carcinoma

Rohit Mehra [a,b,c,†], Pankaj Vats [a,c,d,†], Xuhong Cao [c,e], Fengyun Su [a,c], Nicole D. Lee [c], Robert Lonigro [a,c], Kumpati Premkumar [c,e], Kiril Trpkov [f], Jesse K. McKenney [g], Saravana M. Dhanasekaran [a,c,‡], Arul M. Chinnaiyan [a,b,c,e,‡,]*

ORIGINAL ARTICLE

Eosinophilic Solid and Cystic (ESC) Renal Cell Carcinomas Harbor *TSC* Mutations

Molecular Analysis Supports an Expanding Clinicopathologic Spectrum

Doreen N. Palsgrove, MD, Yunjie Li, MD,* Christine A. Pratilas, MD,* Ming-Tseh Lin, MD, PhD,* Aparna Pallavajjalla, MS,* Christopher Gocke, MD,* Angelo M. De Marzo, MD, PhD,* Andres Matoso, MD,* George J. Netto, MD,*† Jonathan I. Epstein, MD,* and Pedram Argani, MD**


DETOUR

An accidental finding…

“Unrelated”, we were also studying the possible role of SDHB in the rare and often questioned entity of “oncocytoid RCC post-neuroblastoma”

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Paraganglioma, Neuroblastoma, and a *SDHB* Mutation: Resolution of a 30-Year-Old Mystery

R. Neil Schimke,[1] Debra L. Collins,[1]* and Catherine A. Stolle[2]

[1]Department of Medicine, Kansas University School of Medicine, Kansas City, Kansas

[2]Molecular Genetics Laboratory, Department of Pathology and Laboratory Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Received 27 April 2009; Accepted 12 January 2010

Familial paraganglioma/pheoch
genetically heterogen
subunits of the hetero
enzyme succinate dehydrogenase (SDH)
sible for the majority of cases. In addition to PGL/PCC an array of non-paraganglial tumors have been described in affected individuals. We present a 30-year follow-up on the family of a deceased patient who synchronously developed malignant neu-

SDHB deficient RCC?

tole CA. 2010.
Paraganglioma, neuroblastoma, and a *SDHB* mutation: Resolution of a 30-year-old mystery.
Am J Med Genet Part A 152A:1531–1535.

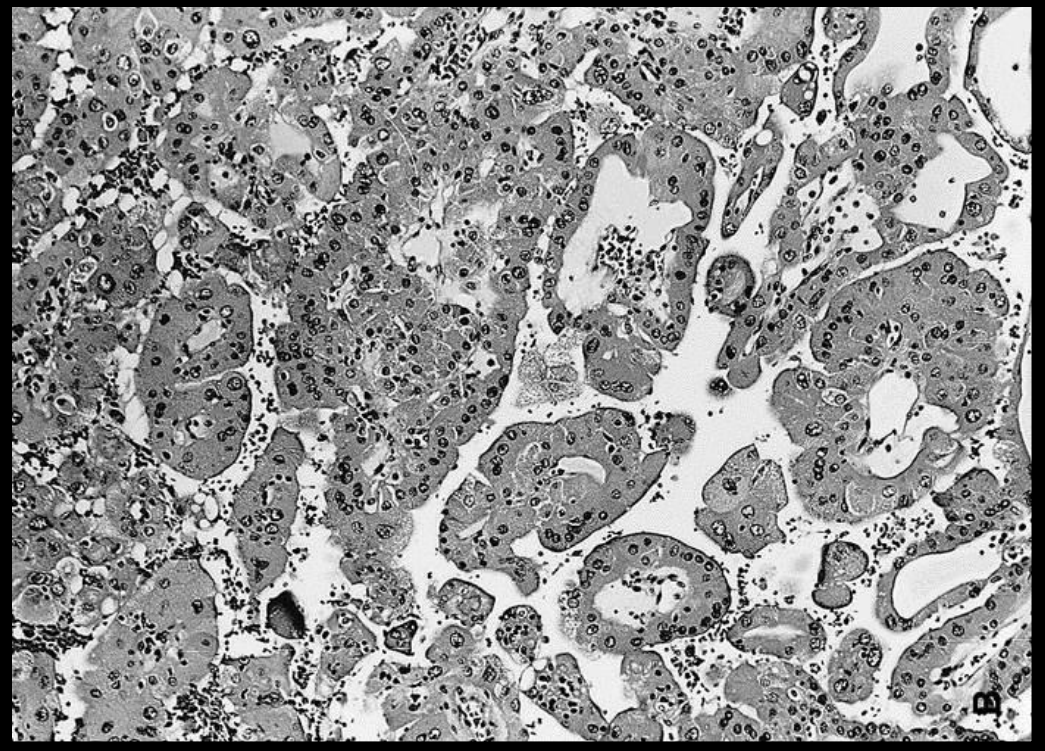
The American Journal of Surgical Pathology *23(7): 772–780, 1999*

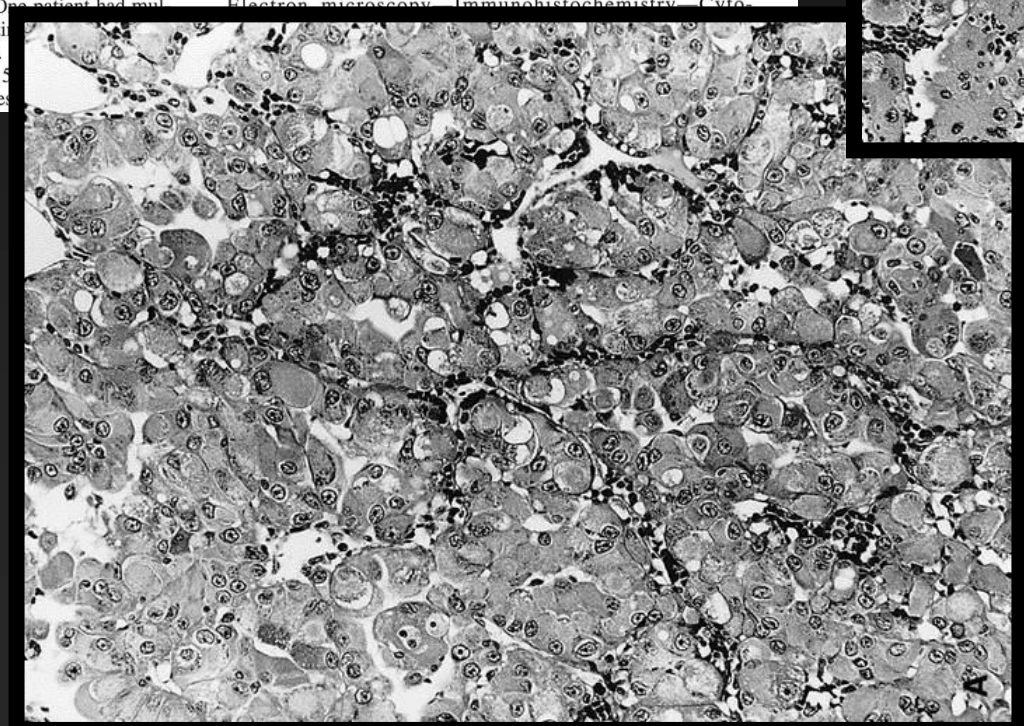
Oncocytoid Renal Cell Carcinoma After Neuroblastoma: A Report of Four Cases of a Distinct Clinicopathologic Entity

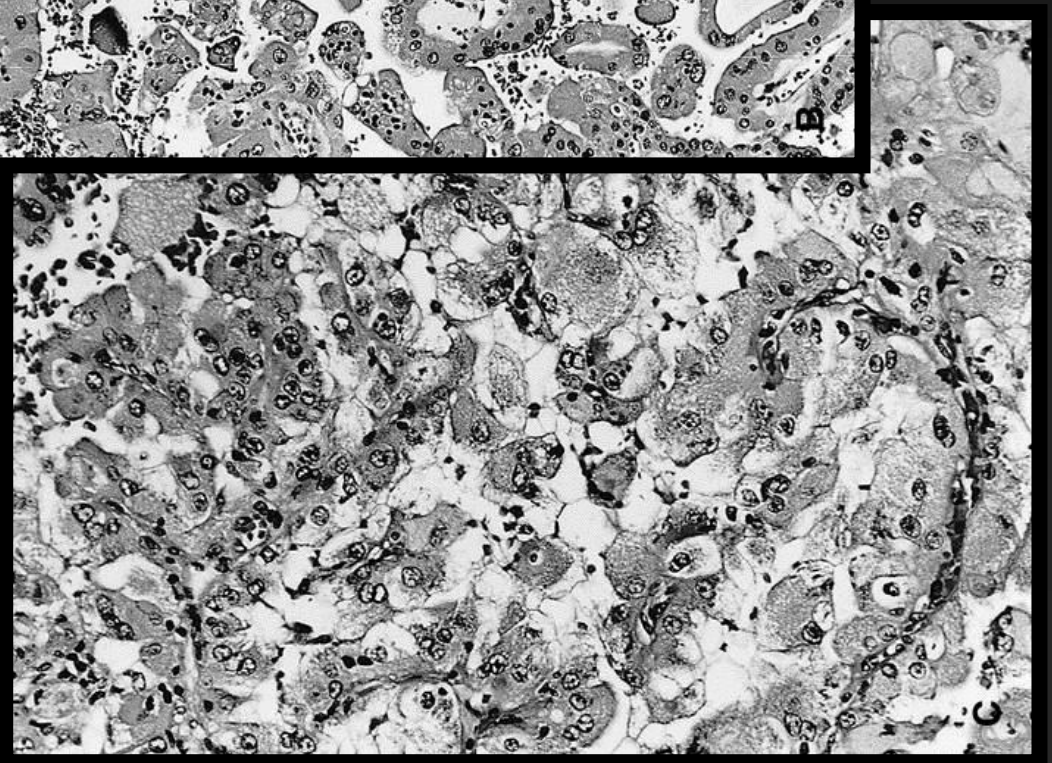
L. Jeffrey Medeiros, M.D., Gabriele Palmedo, Ph.D., Hannah R. Krigman, M.D., Gyula Kovacs, M.D., and J. Bruce Beckwith, M.D.

Four children who developed oncocytoid renal cell carcinoma (RCC) after neuroblastoma are reported. One patient had mul-
tiple, bilateral RCCs. The mean age at ti-
RCC was 8.8 years (range, 5–13 years).
between neuroblastoma and RCC was 7.1
11.5 years). The histologic findings of thes-

Key Words: Renal cell carcinoma—Neuroblastoma—
Electron microscopy—Immunohistochemistry—Cyto-







Renal Cell Carcinoma Occurring in Patients With Prior Neuroblastoma

A Heterogenous Group of Neoplasms

Sara M. Falzarano, MD, Jesse K. McKenney, MD,* Rodolfo Montironi, MD,† John N. Eble, MD,‡ Adeboye O. Osunkoya, MD,§ Juan Guo, MD,‖ Shengmei Zhou, MD,¶ Hong Xiao, PhD,# Saravana M. Dhanasekaran, PhD,# Sudhanshu Shukla, PhD,# Rohit Mehra, MD,# and Cristina Magi-Galluzzi, MD, PhD**

Abstract: Renal cell carcinoma (RCC) associated with neuroblastoma (NB) was included as a distinct entity in the 2004 World Health Organization classification of kidney tumors. A spectrum of RCC subtypes has been reported in NB survivors. We herein describe a series of 8 RCCs diagnosed in 7 patients with a history of NB. Microscopic evalu histochemical staining for PAX8, cathepsin dehydrogenase subunit B (SDHB), and fluore bridization (FISH) for *TFE3* and *TFEB* were distinct morphologic subtypes were identifie needed to clarify whether they may represent a distinct entity with unique molecular abnormalities or may belong to other emerging RCC subtypes.

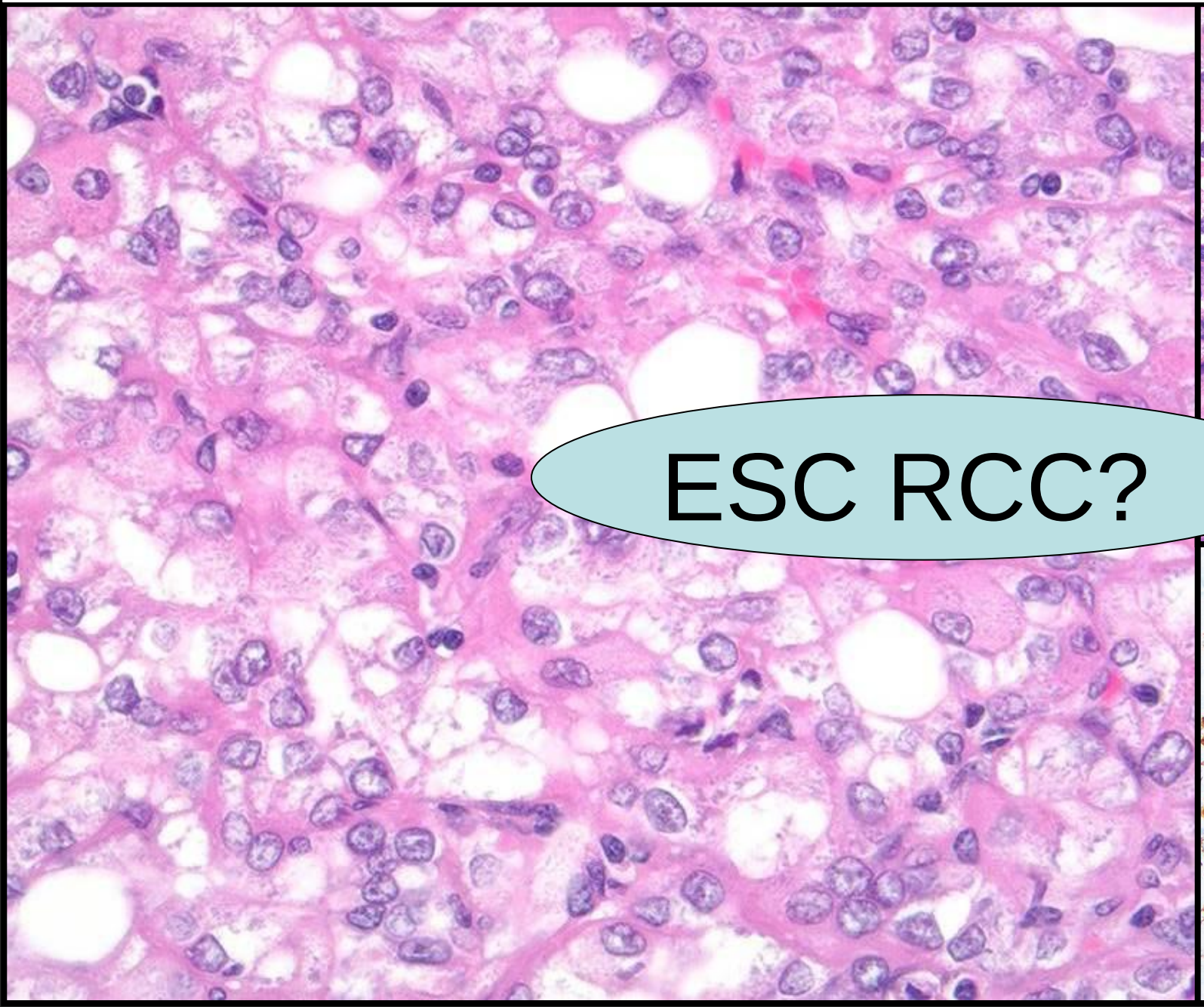
Key Words: renal cell carcinoma, neuroblastoma, oncocytoid features, microphthalmia transcription factor family trans-

TABLE 3. Immunohistochemistry and FISH Findings in RCC post NB

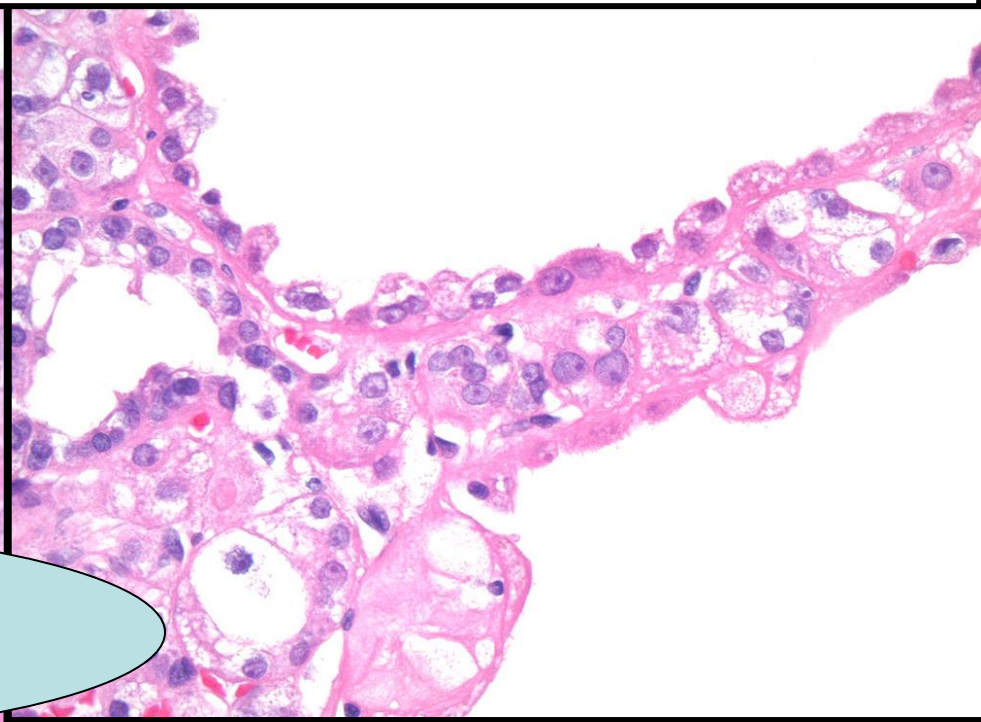
Case #	Morphologic Subtype	Cathepsin K	PAX8	SDHB	CK20	EMA	TFE3 FISH	TFEB FISH
1.1	Oncocytoid	–	+	wt	Focal +	N/A	–	Indet
1.2	Oncocytoid	–	+	wt	+	N/A	–	–
2	Oncocytoid	–	+	wt	Focal +	N/A	–	–
3	MiTF-RCC	–	+	wt	N/A	–	+	IH
4	MiTF-RCC	Focal +	+	wt	N/A	–	–	Indet
5	MiTF-RCC	+	+	wt	N/A	N/A	–	+
6	HOCT	–	+	wt	N/A	N/A	IH	IH
7	PRCC	–	+	wt	N/A	N/A	–	–

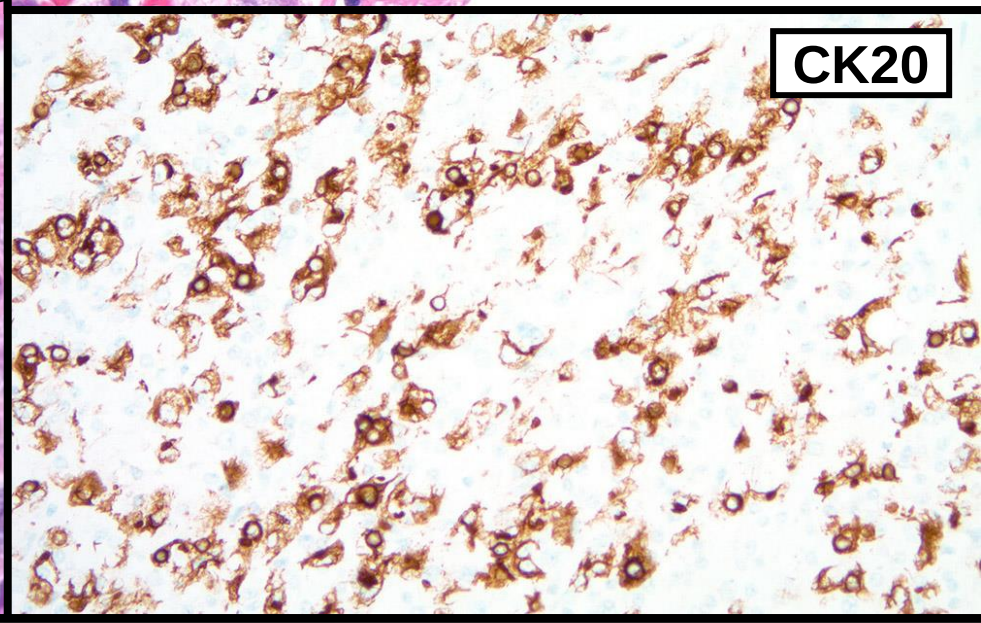
IH indicates insufficient hybridization; Indet, indeterminate FISH status; N/A, not available (not performed); PRCC, papillary RCC; wt, wild type.

Oncocytoid RCC Post-Neuroblastoma



ESC RCC?





Eosinophilic Solid and Cystic (ESC) Renal Cell Carcinomas Harbor *TSC* Mutations

Molecular Analysis Supports an Expanding Clinicopathologic Spectrum

Doreen N. Palsgrove, MD, Yunjie Li, MD,* Christine A. Pratilas, MD,* Ming-Tseh Lin, MD, PhD,* Aparna Pallavajjalla, MS,* Christopher Gocke, MD,* Angelo M. De Marzo, MD, PhD,* Andres Matoso, MD,* George J. Netto, MD,*† Jonathan I. Epstein, MD,* and Pedram Argani, MD**

RCC post NB with “ESC-like” features also had TSC mutation!!

RCC post-Neuroblastoma

- Heterogeneous group of tumors
  1. MiTF Family Translocation Carcinomas (TFE3)
     - Known to occur after chemotherapy
  2. Common “incidental” types of RCC
     - Papillary RCC, etc…
  3. ESC RCC (previously “oncocytoid”)

RCC post-Neuroblastoma

- Current data…


END
DETOUR

Eosinophilic, Solid, Cystic (ESC) RCC

- Distinct “entity”
- Most common in a sporadic setting
- Marked female predominance
- Somatic *TSC1* or *TSC2* mutations in most
- Appears indolent, despite nuclear pleomorphism
  - Rare cases with high stage disease
  - Metastases are reported

Sporadic RCC with Fibromyomatous Stroma

Benign Renal Angiomyoadenomatous Tumor: A Previously Unreported Renal Tumor

Michal Michal, MD, Ondrej Hes, MD, and Frantisek Havlicek, MD

We describe a unique benign tumor of the kidney in a 93-year-old man. Microscopi-
cal … ent
an … the
epi … ts.
These clear sprouts had a blister-like quality and grew on the secretory cells lining the tubules. No atypias, mitoses, or pleomorphism were present in the tumor. The muscular component consisted of poorly cellular, HMB-45–negative, leiomyomatous bundles, which greatly differed from that of angiomyolipoma. It encircled the whole tumor and intimately intermingled with the epithelial component. These leiomyomatous bands formed focally abortive vessels, which had incomplete and irregular walls and lacked an elastic layer. Even more interesting was a peculiar vascularization of the tumor. All epithelial tubular structures of the tumor revealed an intimate association with small capillaries. A fine labyrinth of the

Heterogeneous mixture…

Ann Diagn Pathol 2000;4(5):311-5.

Renal Cell Carcinoma Associated With Prominent Angioleiomyoma-like Proliferation

Report of 5 Cases and Review of the Literature

Elisabetta Kuhn, MD, Jazmín De Anda, MD,† Samanta Manoni, MD,‡ George Netto, MD,§ and Juan Rosai, MD*‖*

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www.elsevier.com/locate/humpath

Case study

Clear cell renal cell carcinoma with smooth muscle stroma

Beverley A. Shannon [a], Ronald J. Cohen [b,*], Amanda Segal [c], Elizabeth G. Baker [d], Ashleigh R. Murch [d]

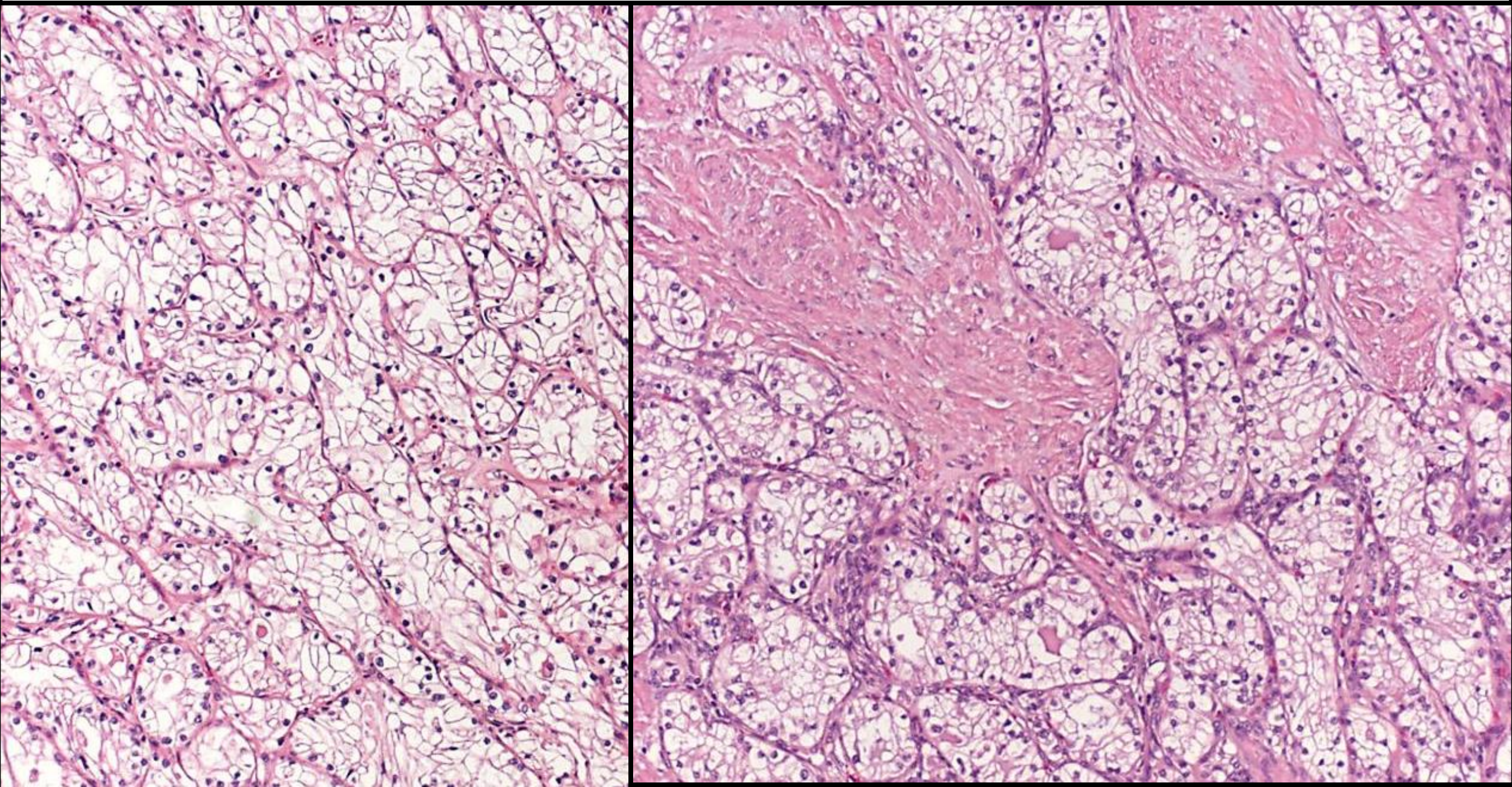
Renal angiomyoadenomatous tumor: morphologic, immunohistochemical, and molecular genetic study of a distinct entity

M. Michal · O. Hes · J. Nemcova · R. Sima · N. Kuroda · S. Bulimbasic · M. Franco · N. Sakaida · D. Danis · D. V. Kazakov · C. Ohe · M. Hora

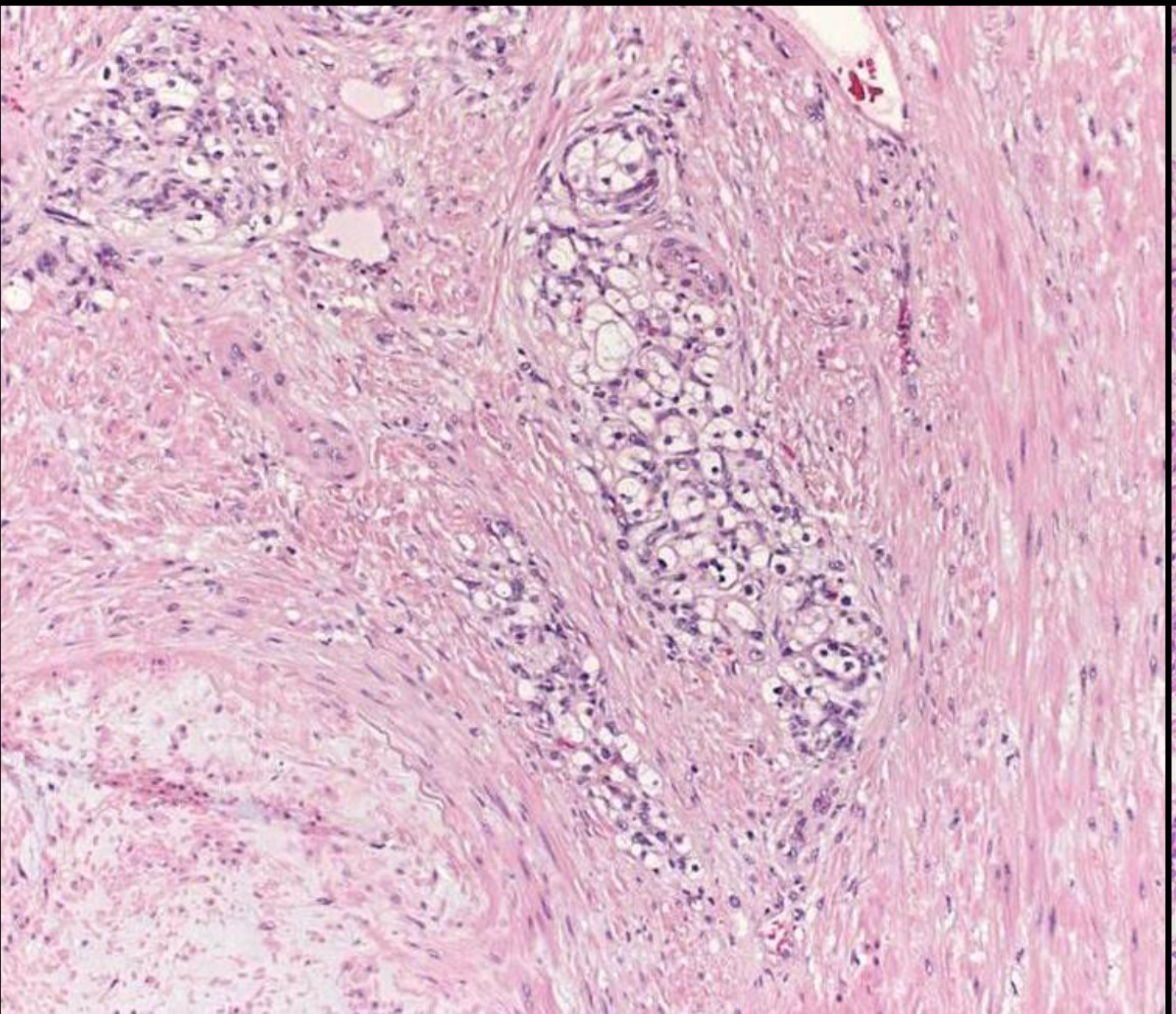
RCC with smooth muscle/RAT

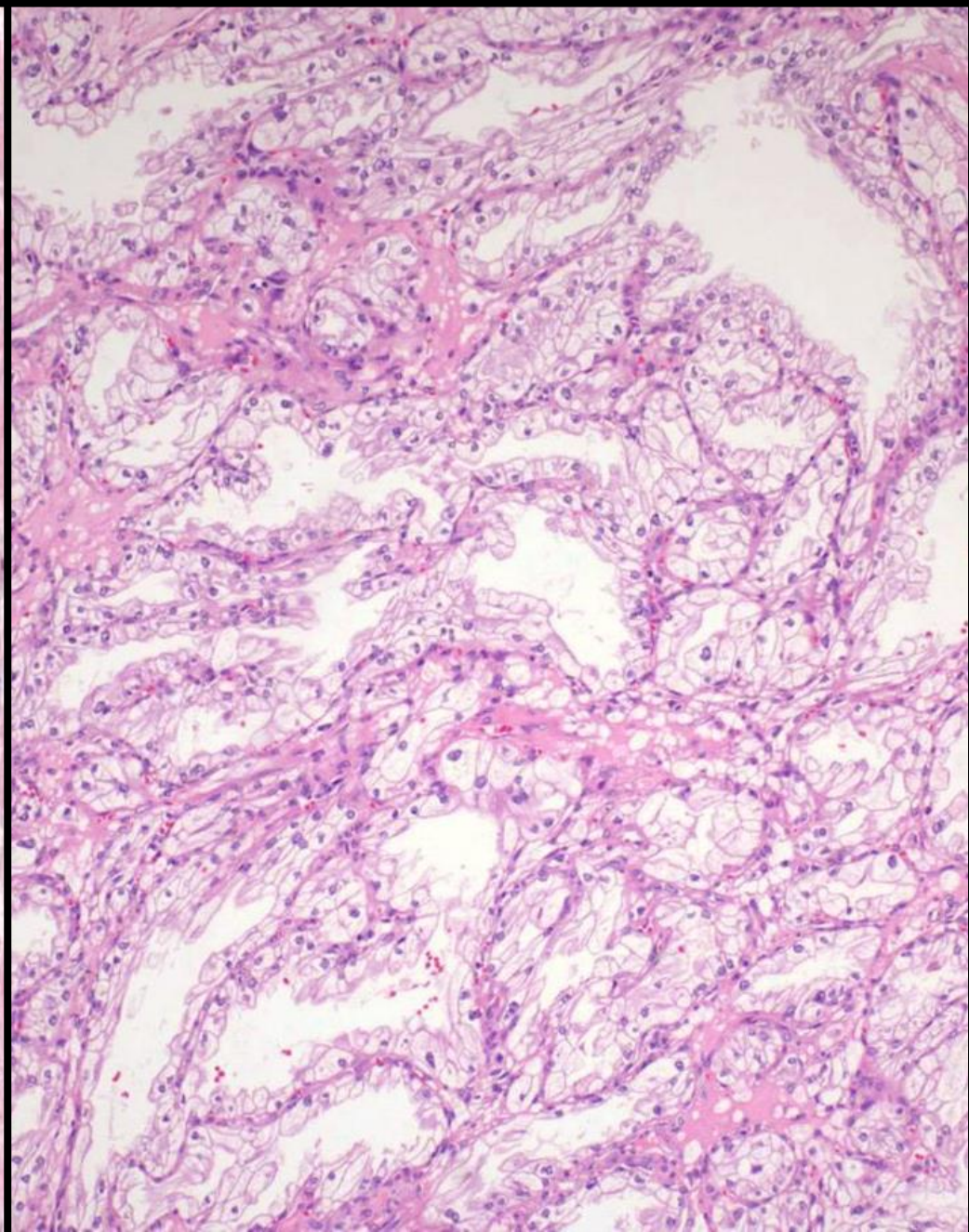
- Clear cell RCC
- Clear cell-papillary RCC
- RCC with (angio)leiomyomatous stroma

RCC with Leiomyomatous Stroma

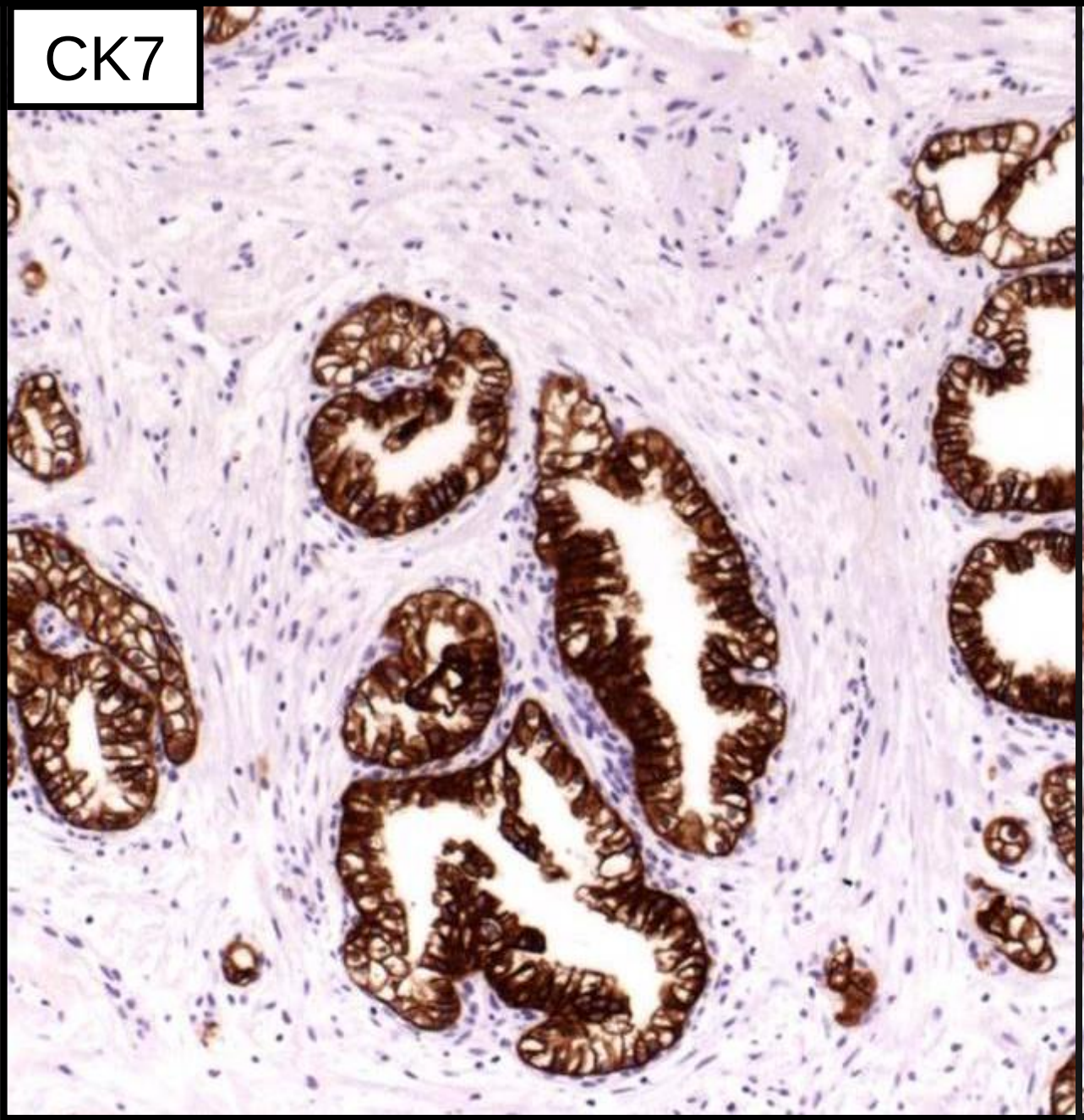


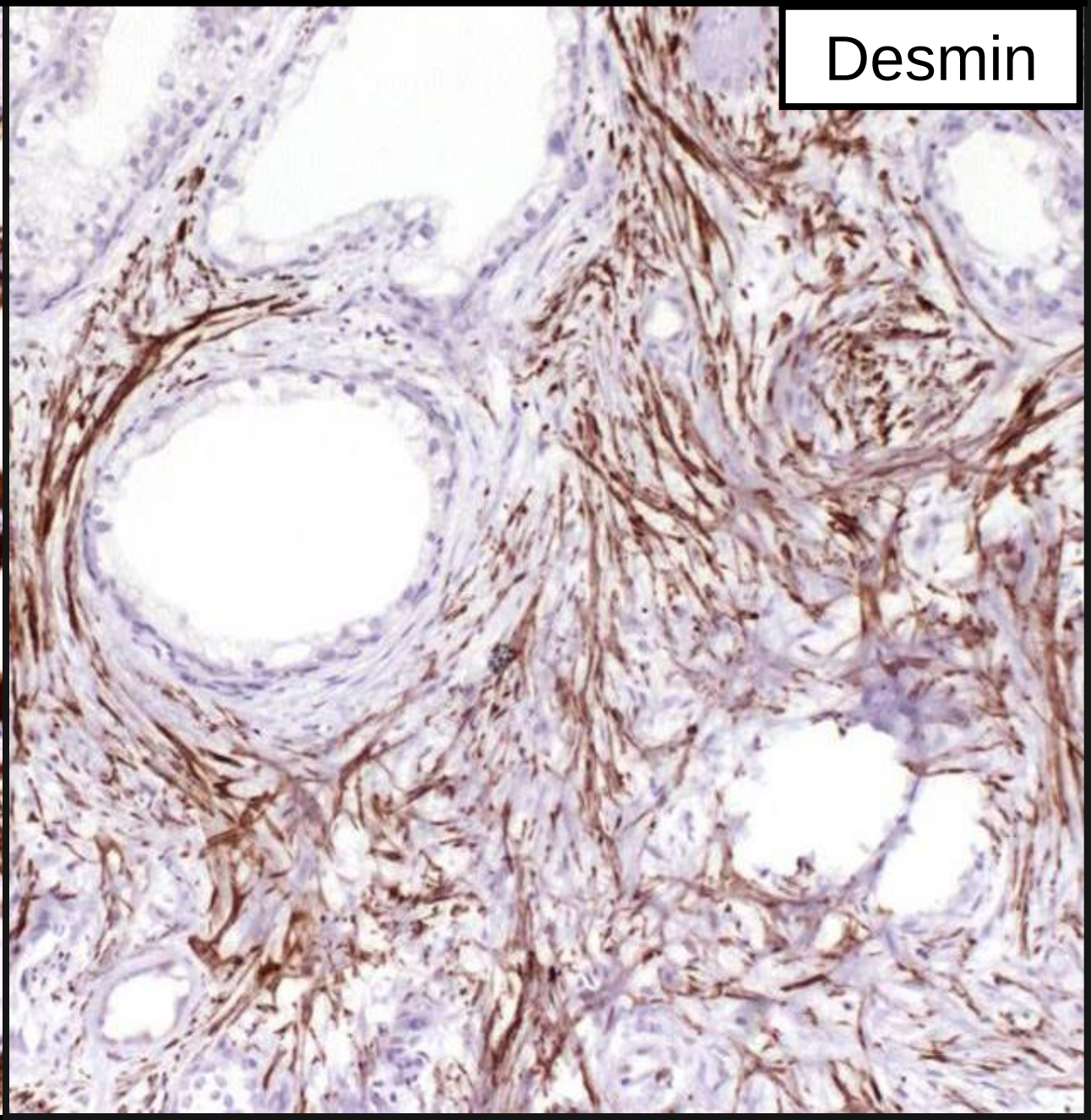
RCC with Leiomyomatous Stroma





RCC with Leiomyomatous Stroma





Integrated molecular analysis of clear-cell renal cell carcinoma

Yusuke Sato[1,2,11], Tetsuichi Yoshizato[1,11], Yuichi Shiraishi[3,11], Shigekatsu Maekawa[1,2,11], Yusuke Okuno[1,11], Takumi Kamura[4], Teppei Shimamura[3], Aiko Sato-Otsubo[1], Genta Nagae[5], Hiromichi Suzuki[1], Yasunobu Nagata[1], Kenichi Yoshida[1], Ayana Kon[1], Yutaka Suzuki[6], Kenichi Chiba[3], Hiroko Tanaka[7], Atsushi Niida[3], Akihiro Fujimoto[8], Tatsuhiko Tsunoda[8], Teppei Morikawa[9], Daichi Maeda[9], Haruki Kume[2], Sumio Sugano[6], Masashi Fukayama[9], Hiroyuki Aburatani[5], Masashi Sanada[1,10], Satoru Miyano[3,7], Yukio Homma[2] & Seishi Ogawa[1,10]

Nature Genetics 2013;45:860

Small subset of “clear cell RCC” had mutations in *TCEB1*

Table 1 Significantly mutated genes in whole-exome analysis of 106 ccRCCs

Gene	Missense mutations	Nonsense, indel or splicing mutations	Total mutations	Samples	Passenger probability (*P* value)	*q* value
VHL	19	23	42	42	1.32×10^{-102}	1.03×10^{-99}
PBRM1	4	24	28	28	2.63×10^{-36}	1.02×10^{-33}
BAP1	3	5	8	8	1.82×10^{-9}	4.71×10^{-7}
TCEB1	5	0	5	5	7.07×10^{-9}	1.37×10^{-6}
SETD2	5	7	12	12	2.06×10^{-8}	3.20×10^{-6}
FPGT	4	1	5	3	1.13×10^{-7}	1.46×10^{-5}
MUDENG	6	1	7	2	3.38×10^{-7}	3.75×10^{-5}
KEAP1	3	2	5	5	5.95×10^{-5}	5.78×10^{-3}
TET2	7	1	8	6	5.59×10^{-5}	4.83×10^{-3}
MUC4	6	0	6	6	1.02×10^{-4}	7.91×10^{-3}
MLLT10	3	0	3	3	2.30×10^{-4}	1.62×10^{-2}
MSGN1	3	0	3	2	2.85×10^{-4}	1.85×10^{-2}
KRT32	3	1	4	4	2.21×10^{-4}	1.32×10^{-2}
M6PR	1	2	3	3	2.77×10^{-4}	1.54×10^{-2}
RPL14	3	0	3	2	3.90×10^{-4}	2.02×10^{-2}
GRB7	4	0	4	4	4.20×10^{-4}	2.04×10^{-2}
TP53	1	2	3	3	3.85×10^{-4}	1.76×10^{-2}
CSMD3	8	1	9	8	7.08×10^{-4}	3.06×10^{-2}
DNHD1	3	1	4	3	6.44×10^{-4}	2.64×10^{-2}
PIK3CA	5	0	5	5	6.90×10^{-4}	2.68×10^{-2}
NLRP12	3	0	3	3	8.93×10^{-4}	3.31×10^{-2}
VMO1	2	0	2	2	9.89×10^{-4}	3.49×10^{-2}
OR4C13	2	1	3	3	1.10×10^{-3}	3.72×10^{-2}
KCNMA1	4	1	5	5	1.24×10^{-3}	4.00×10^{-2}
LMAN2L	1	2	3	2	1.69×10^{-3}	5.24×10^{-2}
MTOR	7	0	7	6	1.44×10^{-3}	4.31×10^{-2}
ZNF536	5	0	5	5	1.63×10^{-3}	4.70×10^{-2}
YIPF3	2	1	3	2	1.57×10^{-3}	4.36×10^{-2}

MODERN PATHOLOGY (2015), 1–9

TCEB1-mutated renal cell carcinoma: a distinct genomic and morphological subtype

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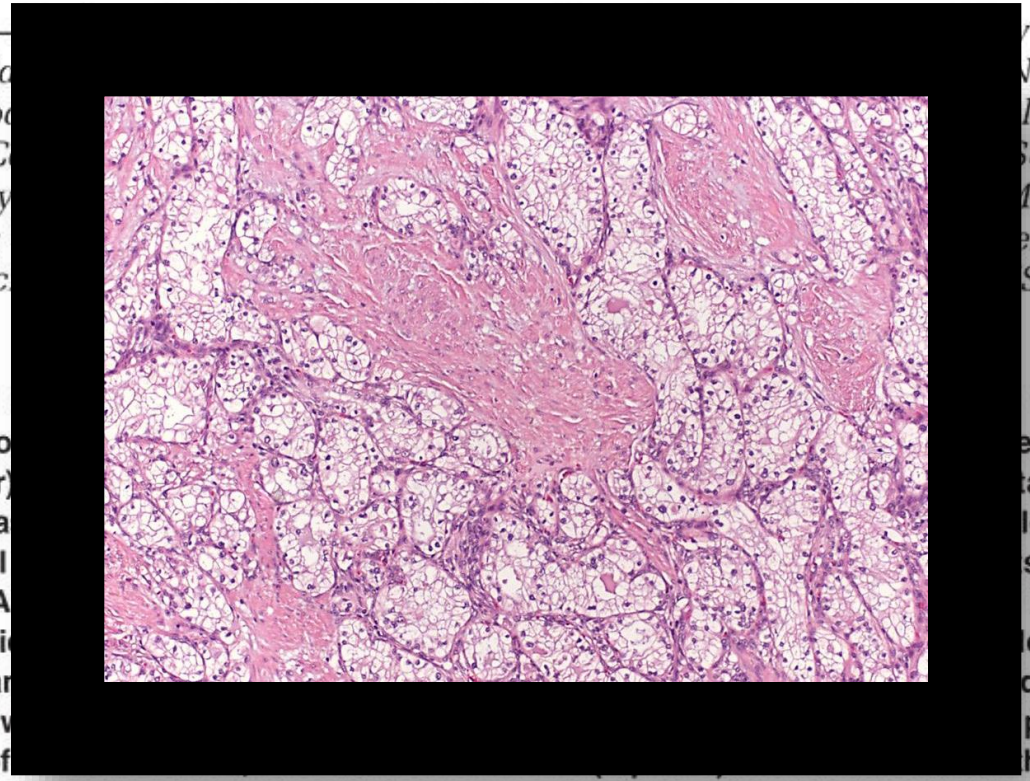
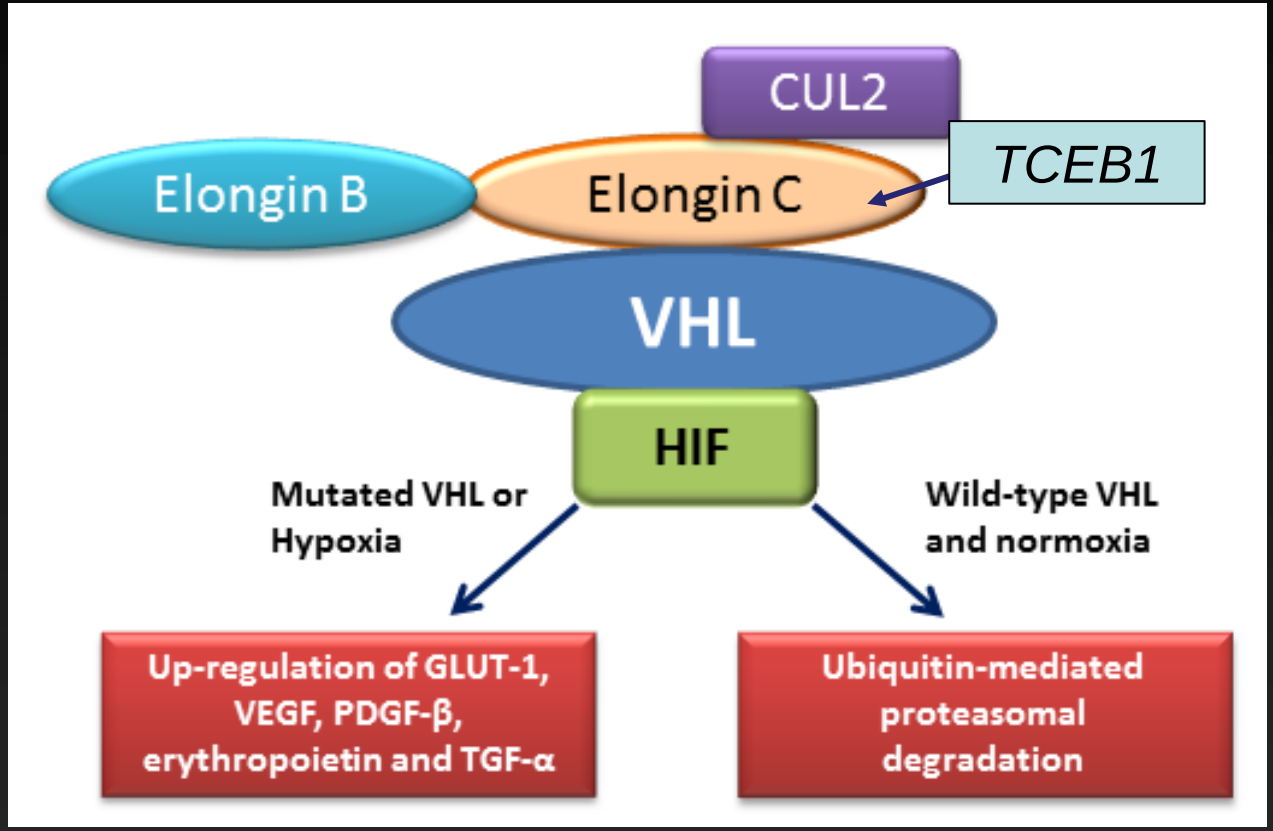


Integrated sequencing cell carcinomas characterized by hotspo ex to ubiquitinate hypoxia-inducible factor) tations along with an expanded cohort to a lear cell renal cell carcinoma and clear cell spot mutations in *TCEB1* Y79C/S/F/N or A the tumors were assessed by two experi les, copy number alterations, mutations, ar d-type tumors. All *TCEB1*-mutated tumors v profiles including loss of heterozygosity of he clear cell renal



ELOC: The gene formally known as *TCEB1*

Virchows Arch (2016) 469:81–91
DOI 10.1007/s00428-016-1952-7

ORIGINAL ARTICLE

Unclassified renal cell carcinoma with tubulopapillary architecture, clear cell phenotype, and chromosome 8 monosomy: a new kid on the block

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Received: 12 February 2016 / Revised: 5 April 2016 / Accepted: 27 April 2016 / Published online: 12 May 2016

Abstract Accurate subtyping of renal cell carcinomas (RCCs) has become clinically important for therapy and prognostication. RCC subtypes are defined by distinct morphologic and immunohistochemical profiles, and in some instances recurrent cytogenetic and molecular properties. However, some tumors exhibit overlapping morphologic and immunophenotypic features, frequent enough to pose diagnostic dilemmas. This report concerns six histologically unusual RCCs that showed tubulopapillary architecture, clear cell phenotype, and non-diagnostic immunohistochemical

pathogenic variants were de
genes *VHL*, *PBRM1*, *SETD2*,
of molecular investigations su
histologically and immunohist
help to define additional subty
opment of targeted therapy fo

Keywords Renal cell carcino
assay · Next-generation sequencing · Chromosome 8 monosomy

ORIGINAL ARTICLE

Genetic Underpinnings of Renal Cell Carcinoma With Leiomyomatous Stroma

Megan Parilla, MD, Mir Alikhan, MD, Mustafa Al-Kawaaz, MD, Sushant Patil, PhD, Sabah Kadri, PhD, Lauren L. Ritterhouse, MD, PhD, Jeremy Segal, MD, PhD, Carrie Fitzpatrick, PhD, and Tatjana Antic, MD

Abstract: Renal cell carcinoma (RCC) with leiomyomatous stroma is a provisional category of RCC in the 2016 World Health Organization Classification of Tumors of the Urinary System. Microscopic examination of hematoxylin and eosin–stained sections reveals this entity to be well-circumscribed with tubulopapillary growth of cells with clear cytoplasm in a background of leiomyomatous stroma. Herein we describe the genetic features of 15 University of Chicago Medical Center archived cases with hematoxylin and eosin histology matching the provisional diagnosis. Immunohistochemical (IHC) stains revealed 1/15 of these tumors to be clear cell renal cell carcinoma (ccRCC) and 6/15 to be clear cell papillary renal cell carcinoma (ccpRCC), demonstrating the morphologic overlap with these discrete known entities. Interestingly 3/6 of the ccpRCCs had chromosome 18 gain suggesting there may be novel specific genetic changes in ccpRCC with leiomyomatous stroma. Of the remaining 8 tumors with IHC staining patterns that do not fit either ccRCC or ccpRCC only 3 of these had mutations in

emerging entity histologically is composed of "branching tubules and papillary tufts" with clear cytoplasm embedded in a prominent smooth muscle stroma.[1] The microscopic features of this tumor have significant histologic overlap with clear cell renal cell carcinoma (ccRCC) and clear cell papillary renal cell carcinoma (ccpRCC).

Clinically, patients with RCC-LS typically do well as the tumor appears to be indolent. It is found predominantly in adult males and may or may not be associated with tuberous sclerosis complex (TSC).[1] Recently mutations in *TCEB1* with concurrent loss of chromosome 8 (monosomy 8) have been associated with in the sporadic form of RCC-LS (RCC-LS in patients without TSC).[2,3] More studies are needed to both assess the role of *TCEB1* mutations in the pathogenesis of this disease and to determine the clinical course of this emerging entity.[1]

The overlap in morphology between RCC-LS, ccRCC, and ccpRCC, as seen on hematoxylin and eosin (H&E)-

"Renal Cell Carcinoma With Leiomyomatous Stroma" Harbor Somatic Mutations of *TSC1*, *TSC2*, *MTOR*, and/or *ELOC* (*TCEB1*): Clinicopathologic and Molecular Characterization of 18 Sporadic Tumors Supports a Distinct Entity

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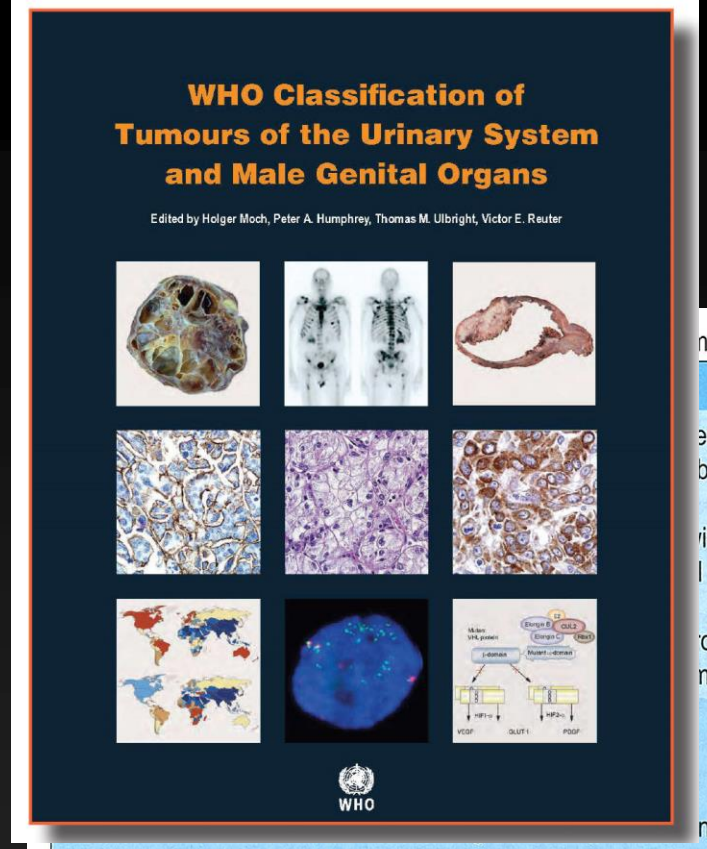
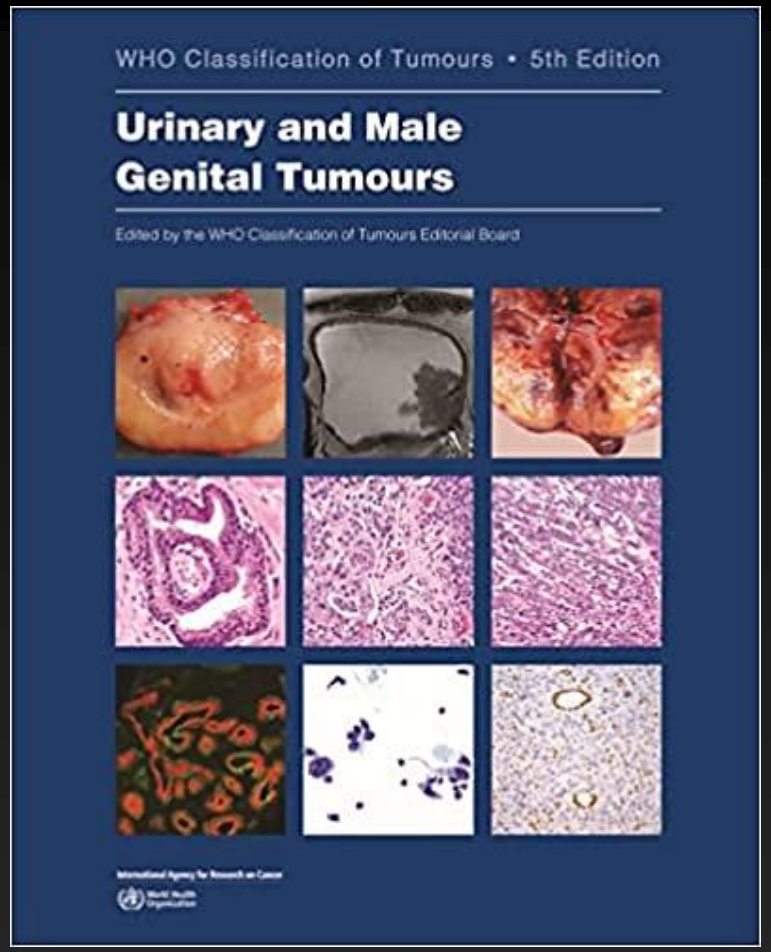
Abstract: Renal cell carcinoma with (angio) leiomyomatous stroma (RCCLMS) is included as a provisional entity in the 2016 World Health Organization (WHO) classification of renal epithelial neoplasia; however, debate remains whether it represents a distinct entity or a heterogeneous group of renal cell carcinomas (RCCs) with overeosinophilic cytoplasm (100%), separated by focal to prominent smooth muscle stroma. Additional frequently identified features included: biphasic pattern of collapsed acini surrounding tubules with voluminous cytoplasm (50%), focal papillary architecture (39%), peritumoral lymphoid aggregates (39%), and hemosiderin-laden macro-



nas

		Morphological	Molecular	Outcome
		enal cell blastoma		
		ith some MiT l cell	• No molecular marker	• Limited follow-up
		oup with or notherapy		
		• Tan-brown gross appearance • Resembles thyroid parenchyma, with follicles and colloid • No distinctive immunohistochemistry, but thyroid transcription factor 1 and thyroglobulin are negative	• Limited studies and no distinctive molecular marker	• Most are indolent • There are rare examples of lymph node and lung metastasis
ALK rearrangement–associated renal cell carcinoma	• Rare (< 10 cases reported) • 3 distinct cases with ALK-vinculin fusion in children with sickle cell trait	For paediatric cases: • Medullary location • Large polygonal/spindle cells • Eosinophilic cytoplasm with intracytoplasmic lumina	• *VCL-ALK* gene fusion	• Limited follow-up
Renal cell carcinoma with (angio)leiomyomatous stroma	• Adults • Male predominance • Historically categorized as a clear cell or clear cell papillary renal cell carcinoma • Has also been called renal angiomyoadenomatous tumour • Occurs sporadically or is associated with tuberous sclerosis	• Branching tubules / papillary tufts • Clear cells • Prominent vascular and smooth muscle stroma • Positive for CK7, 34βE12, and CD10; negative for racemase	• No 3p deletion • No trisomy 7 or 17 • *TCEB1* gene mutation recently described	• Indolent, but limited follow-up



ELOC (formerly *TCEB1*)-mutated renal cell carcinoma

Argani
Martign
McKenn
Tickoo S

Definition
ELOC-mutated renal cell carcinomas (RCCs) are RCCs that harbour mutations in the *ELOC* (*TCEB1*) gene at 8q21.11.

ICD-O coding
8311/3 *ELOC* (formerly *TCEB1*)-mutated renal cell carcinoma

ICD-11 coding
2C90.0 Renal cell carcinoma of kidney, except renal pelvis

Related terminology
None

Subtype(s)
None

Localization
These tumours arise in the kidney cortex.

Clinical features
These neoplasms appear as renal masses, often as incidental findings detected in imaging studies for other conditions such as haematuria {2824,1261,870,2451,1787}.

Epidemiology
Approximately 20 cases have been reported. The majority (> 90%) have occurred in male patients with a median age of 60 years {1261,1787,2451}.

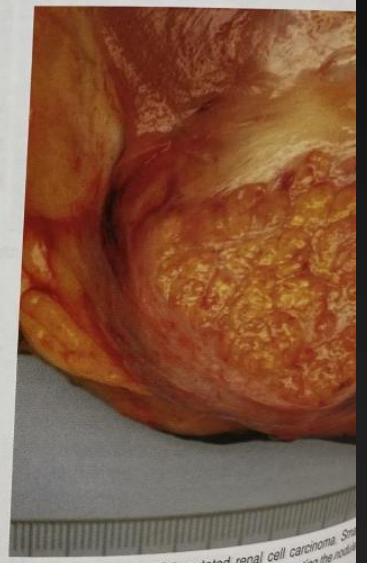


Fig. 2.50 ELOC (*TCEB1*)-mutated renal cell carcinoma. Sm
renal tumour with fibrous-appearing bands separating the nodul

is that of branching infolding tubules and well-
The neoplastic cells have voluminous clear cy
prominent cell borders. The neoplastic cells a
immunoreactive for CK7 (with labelling ranging

RCC with Fibromyomatous Stroma

- Distinct “entity”
  - Voluminous clear cytoplasm and elongated tubules
  - CK7 immunoreactivity
  - Indolent… not aggressive like clear cell RCC
  - Must exclude other entities with smooth muscle
    - Clear cell RCC
    - Clear cell papillary RCC
- Somatic mutations
  - *TSC1, TSC2, MTOR, or TCEB1*

Sporadic “Low-Risk” Oncocytic Neoplasia

Chromophobe RCC

- Obviously, a well-described RCC subtype
- Are the TSC-associated tumors related?

Cancer Cell
Article

CellPress

The Somatic Genomic Landscape of Chromophobe Renal Cell Carcinoma

Caleb F. Davis,[1,34] Christopher J. Ricketts,[2,34] Min Wang,[1,34] Lixing Yang,[3,34] Andrew D. Cherniack,[4] Hui Shen,[5] Christian Buhay,[1] Hyojin Kang,[32] Sang Cheol Kim,[6] Catherine C. Fahey,[7] Kathryn E. Hacker,[7] Gyan Bhanot,[8,9] Dmitry A. Gordenin,[10] Andy Chu,[11] Preethi H. Gunaratne,[1,12] Michael Biehl,[13] Sahil Seth,[14] Benny A. Kaipparettu,[15,16] Christopher A. Bristow,[14] Lawrence A. Donehower,[1] Eric M. Wallen,[17] Angela B. Smith,[17] Satish K. Tickoo,[18] Pheroze Tamboli,[19] Victor Reuter,[18] Laura S. Schmidt,[2,20] James J. Hsieh,[21,22] Toni K. Choueiri,[23,24] A. Ari Hakimi,[25] The Cancer Genome Atlas Research Network, Lynda Chin,[4,14] Matthew Meyerson,[4,23] Raju Kucherlapati,[26,27] Woong-Yang Park,[6,28] A. Gordon Robertson,[11] Peter W. Laird,[5] Elizabeth P. Henske,[4,23,24] David J. Kwiatkowski,[4,23,24] Peter J. Park,[3,26] Margaret Morgan,[1] Brian Shuch,[33] Donna Muzny,[1] David A. Wheeler,[1] W. Marston Linehan,[2] Richard A. Gibbs,[1] W. Kimryn Rathmell,[17,29,30,35,*] and Chad J. Creighton[1,15,31,35,*]

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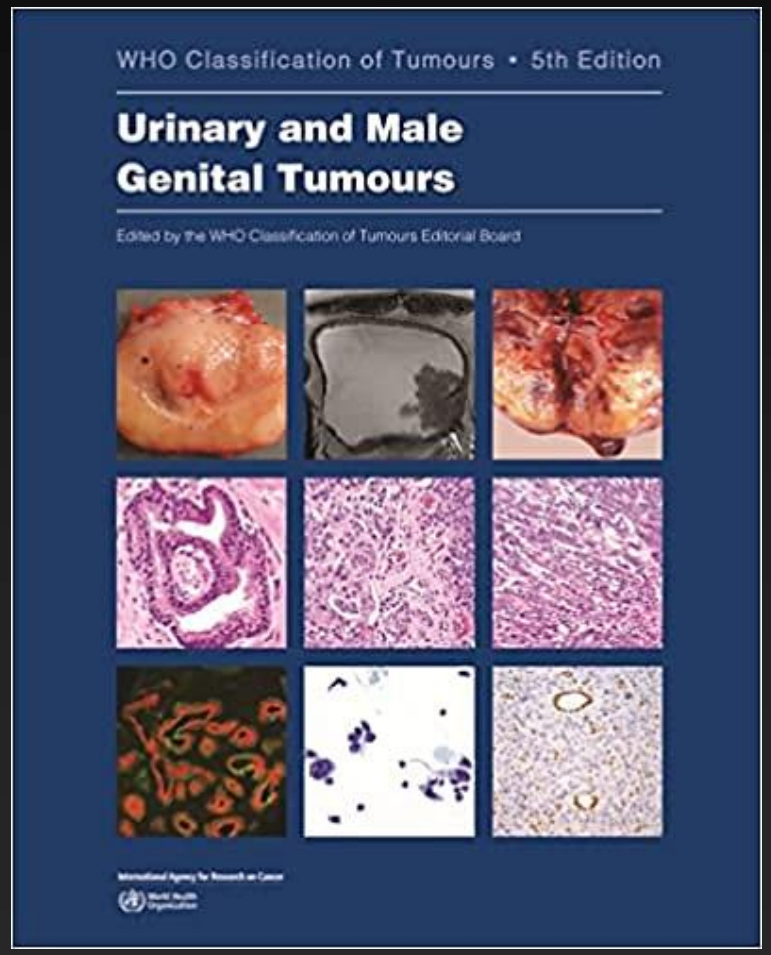
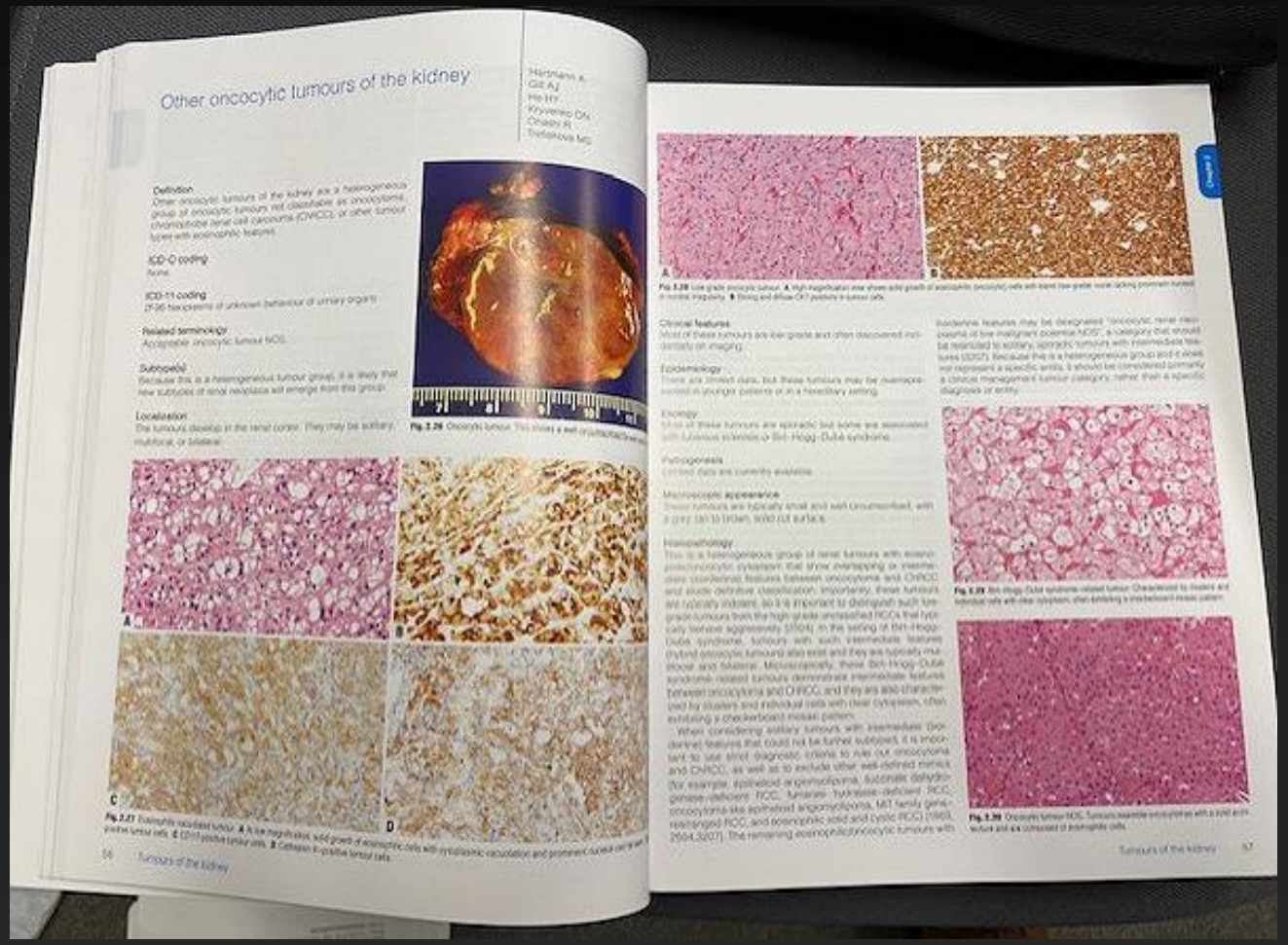
of p53 transcriptional targets (Figures S1A–S1C). *PTEN* was the next most frequently mutated, with 9% (6 of 66) nonsilent mutations detected. No other genes were found to be mutated at a frequency higher than 5%, though mutations involving cancer-relevant genes were found at lower frequencies (Figure 1B). Mutations were seen in *MTOR* (2 cases), *NRAS* (1 activating mutation), and *TSC1* or *TSC2* (4 cases), and two homozygous deletions were seen in *PTEN*, indicating that genomic targeting of the mTOR pathway occurred overall in 15 (23%) of 66 ChRCCs (Figure 1B). Biological significance could be ascribed to infrequently mutated genes, in terms of associated pathways, including the p53 and PTEN pathways (Table S2). The genetic diseases BHD and tuberous sclerosis complex both predispose to the development of ChRCC, and associated

Other oncocytic tumors of the kidney





ORIGINAL ARTICLE

Somatic Mutations of *TSC2* or *MTOR* Characterize a Morphologically Distinct Subset of Sporadic Renal Cell Carcinoma With Eosinophilic and Vacuolated Cytoplasm

Ying-Bei Chen, MD, PhD, Leili Mirsadraei, MD, Gowtham Jayakumaran, MS, Hikmat A. Al-Ahmadie, MD, Samson W. Fine, MD, Anuradha Gopalan, MD, S. Joseph Sirintrapun, MD, Satish K. Tickoo, MD, and Victor E. Reuter, MD

Abstract: The differential diagnosis of renal cell neoplasms with solid or nested architecture and eosinophilic cytoplasm has become increasingly complex. Despite recent advances in classifying a number of entities exhibiting this morphology, some tumors remain in the unclassified category. Here we describe a morphologically distinct group of sporadic renal cell carcinoma (RCC) with predominantly nested architecture, eosinophilic and

tumors tested) or activating mutations of *MTOR* (2/5) as the primary molecular alterations, consistent with hyperactive mTOR complex 1 signaling which was further demonstrated by phospho-S6 and phospho-4E-BP1 immunostaining. Copy number analysis revealed a loss of chromos
MTOR mutation. These tumors rep
sporadic RCC characterized by alt

EVT

Eosinophilic Vacuolated Tumor

Virchows Archiv (2018) 473:725–738
https://doi.org/10.1007/s00428-018-2456-4

ORIGINAL ARTICLE

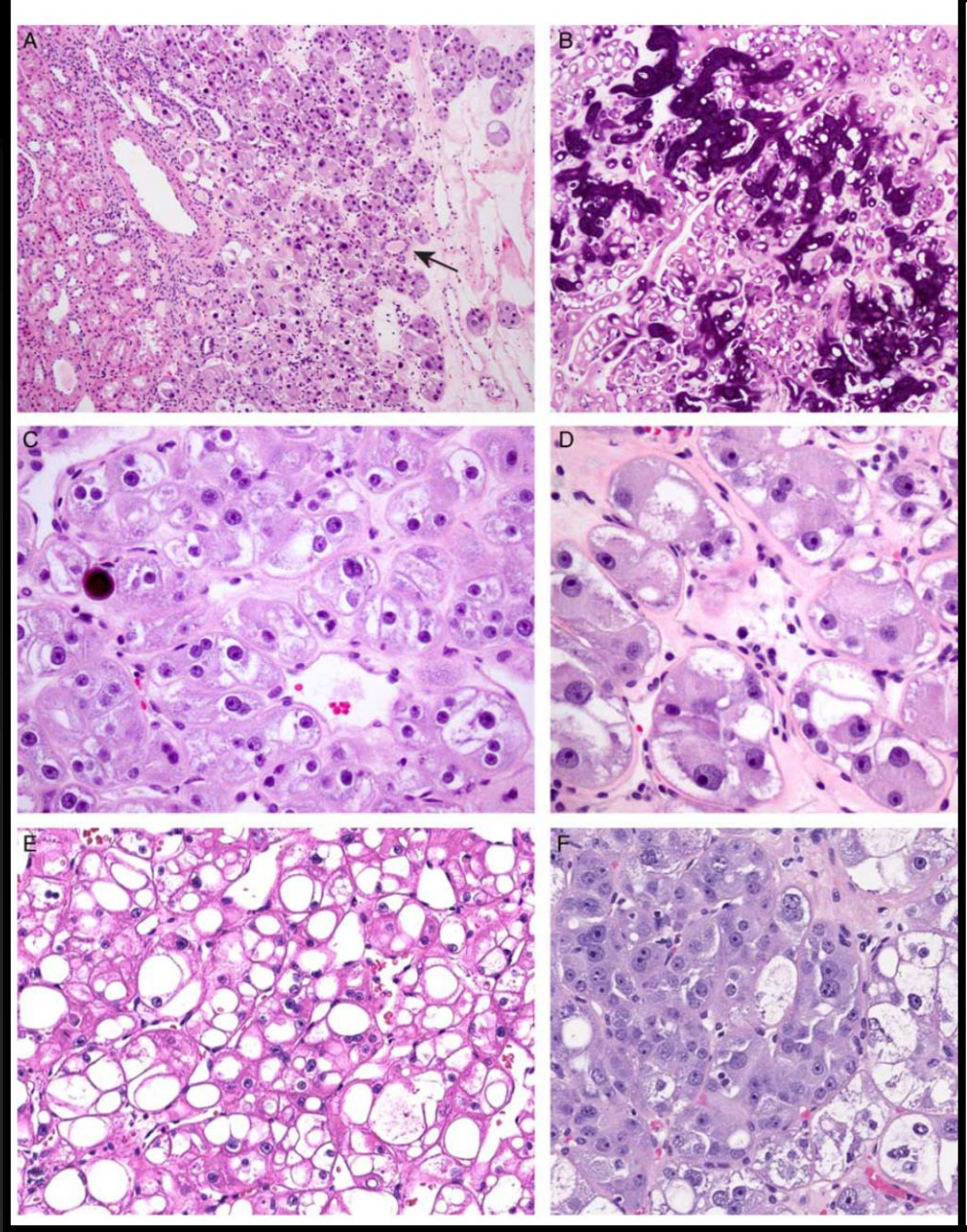
CrossMark

"High-grade oncocytic renal tumor": morphologic, immunohistochemical, and molecular genetic study of 14 cases

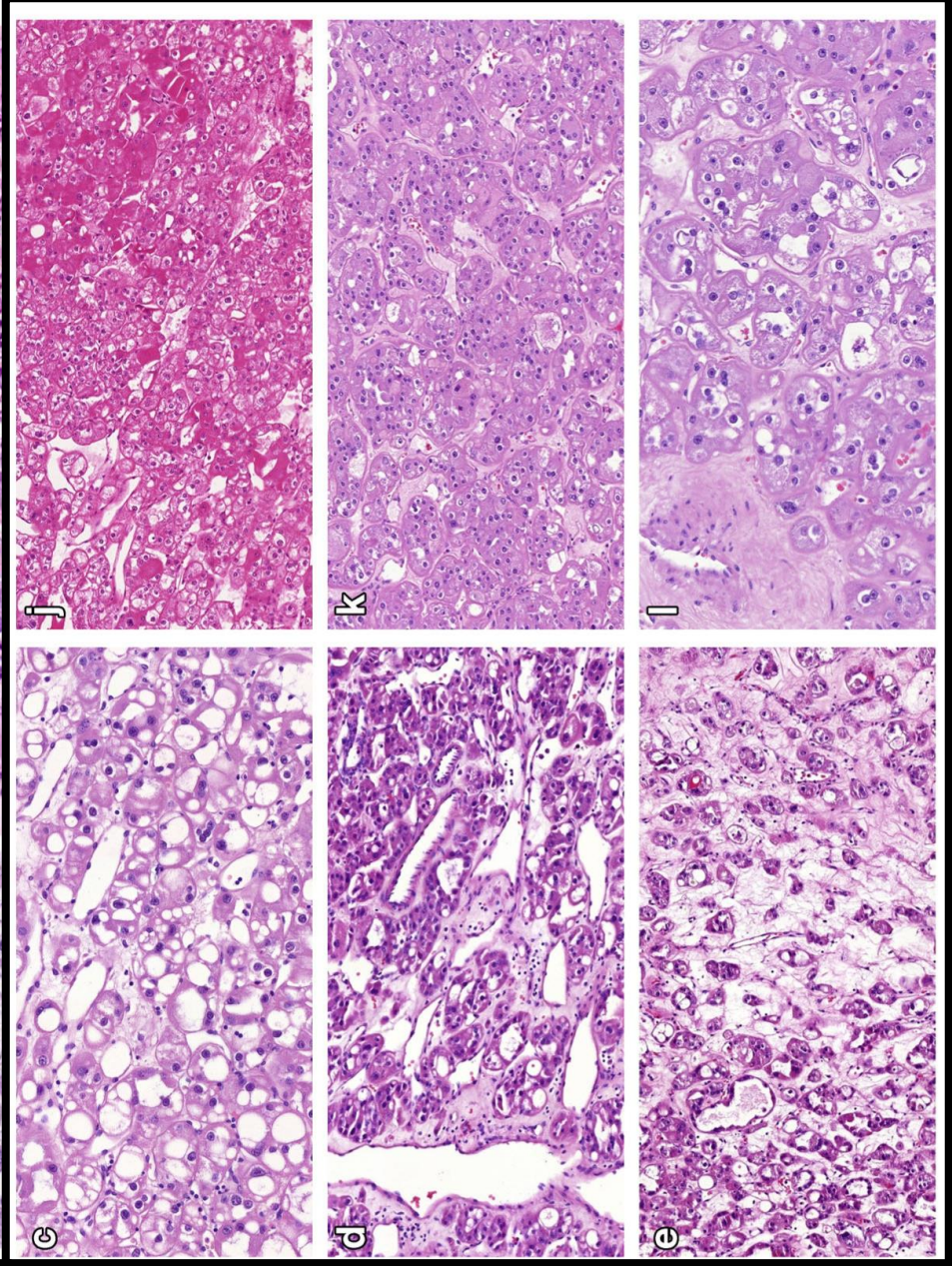
Huiying He[1] · Kiril Trpkov[2] · Petr Martinek[3] · Ozlem Tanas Isikci[4] · Cristina Maggi-Galuzzi[5] · Reza Alaghehbandan[6] · Anthony J Gill[7,8,9] · Maria Tretiakova[10] · Jose Ignacio Lopez[11] · Sean R. Williamson[12] · Delia Perez Montiel[13] · Maris Sperga[14] · Eva Comperat[15] · Fadi Brimo[16] · Ali Yilmaz[2] · Kristyna Pivovarcikova[3] · Kveta Michalova[3] · David Slouka[17] · Kristyna Prochazkova[18] · Milan Hora[18] · Michael Bonert[19] · Michal Michal[3] · Ondrej Hes[3]

Received: 11 May 2018 / Revised: 29 August 2018 / Accepted: 10 September 2018 / Published online: 19 September 2018

Abstract
The spectrum of the renal oncocytic tumors has been expanded in recent years to include several novel and emerging entities. We

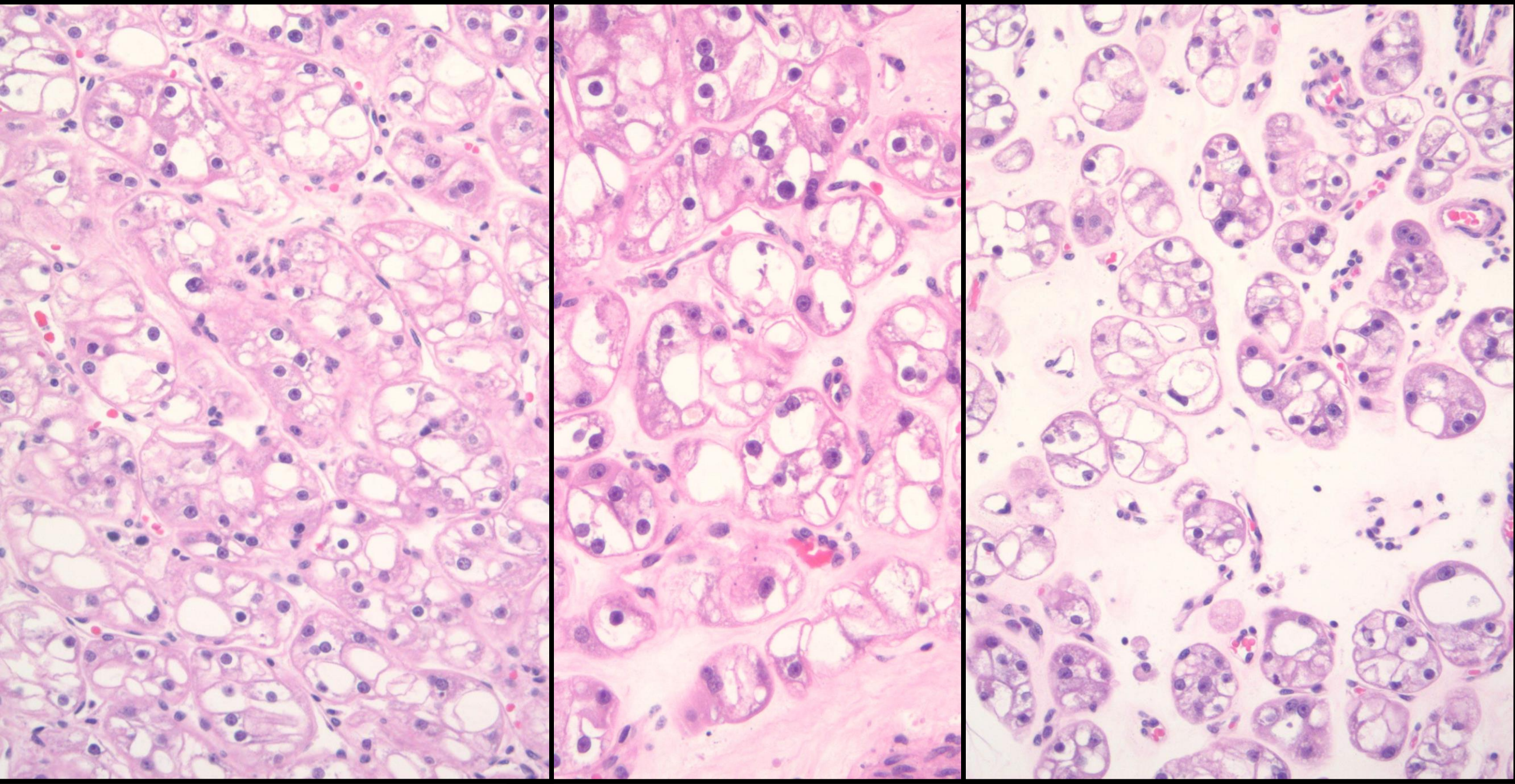


Chien et al. *Am J Surg Pathol* 2018
(MSKCC cohort)



He et al. Virchow Archiv 2018
(International cohort)

Eosinophilic Vacuolated Tumor



Histopathology

Histopathology 2019, **75**, 174–184. DOI: 10.1111/his.13865

LOT

Low-grade oncocytic tumour of kidney (CD117-negative, cytokeratin 7-positive): a distinct entity?

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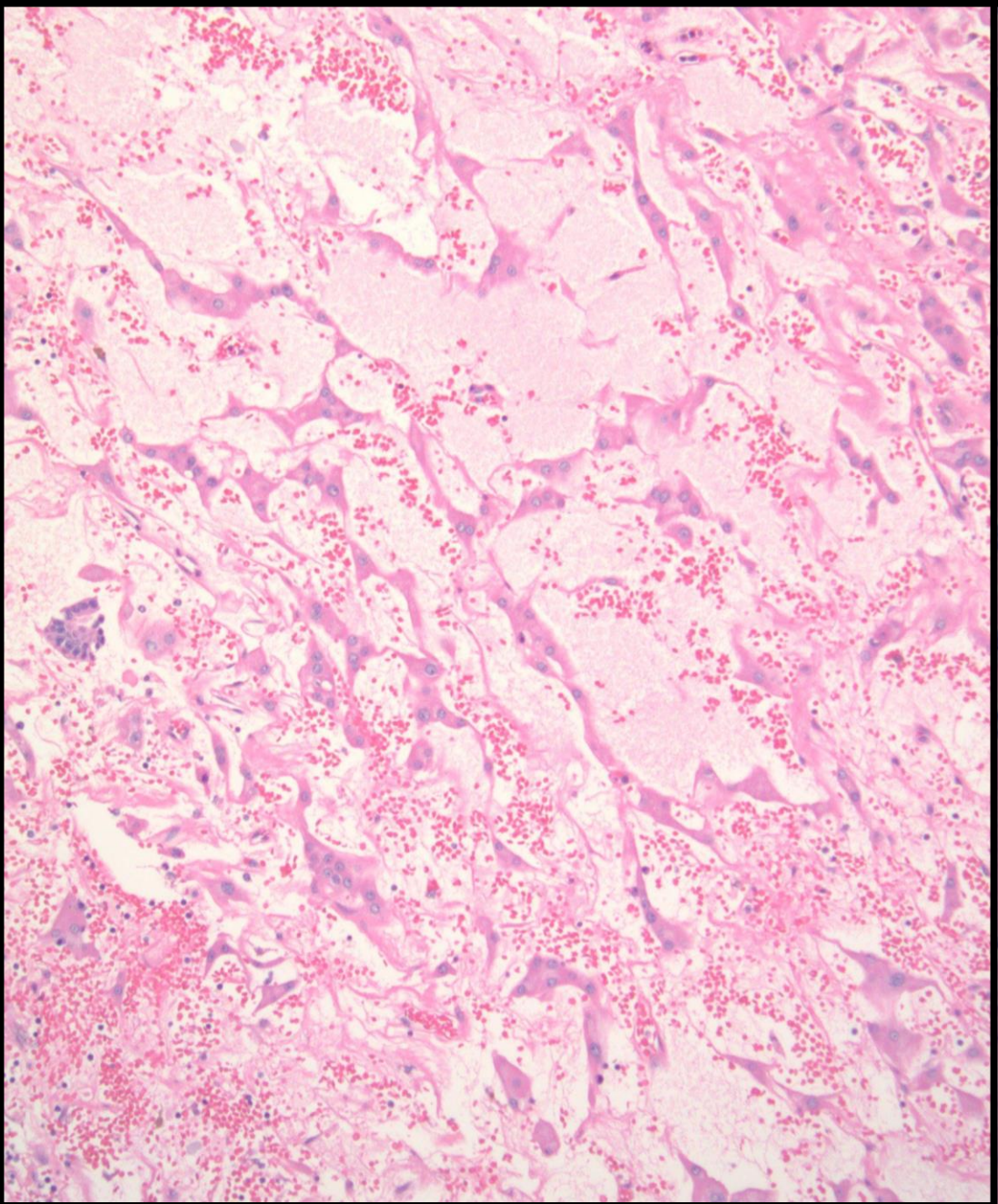
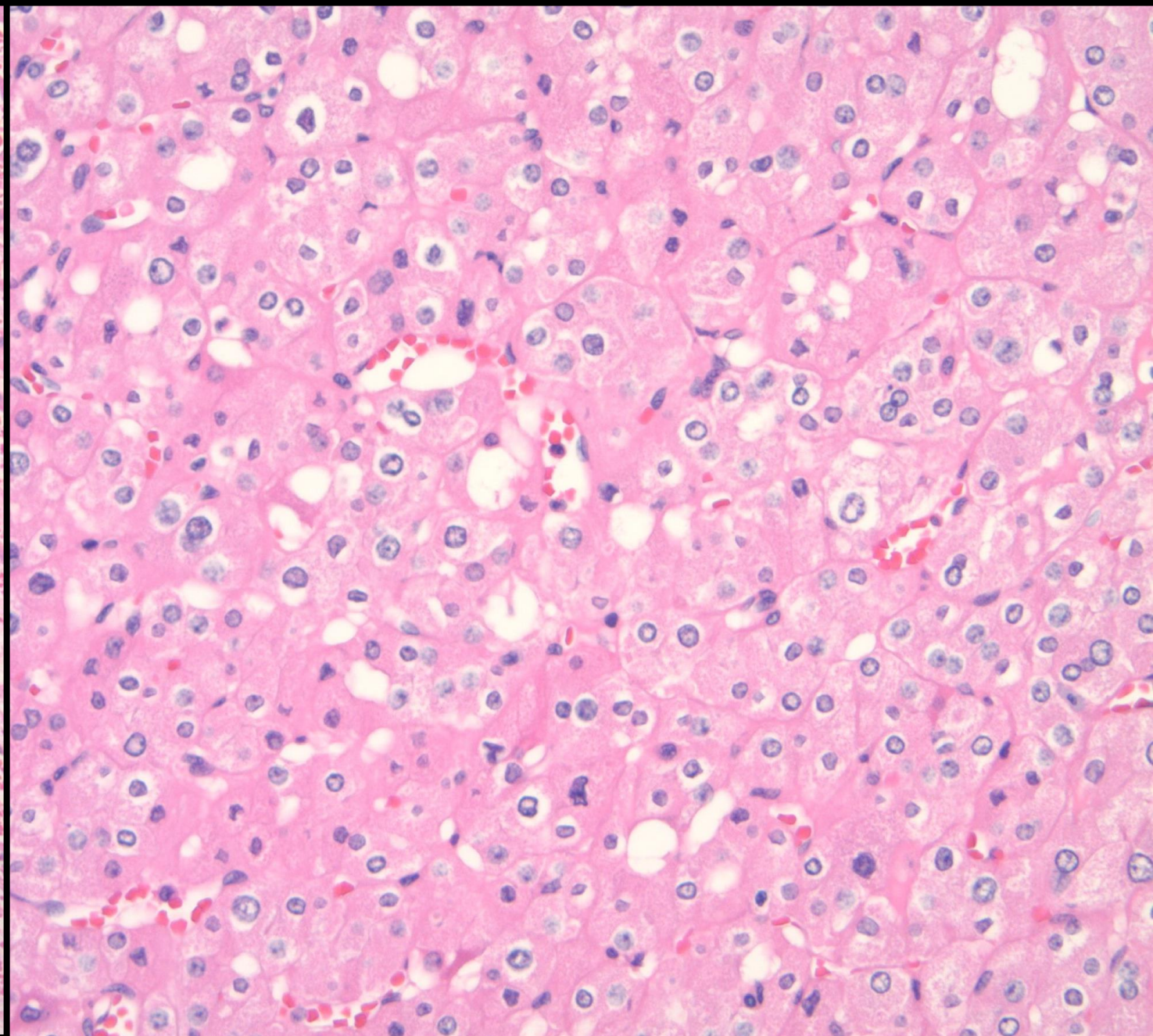
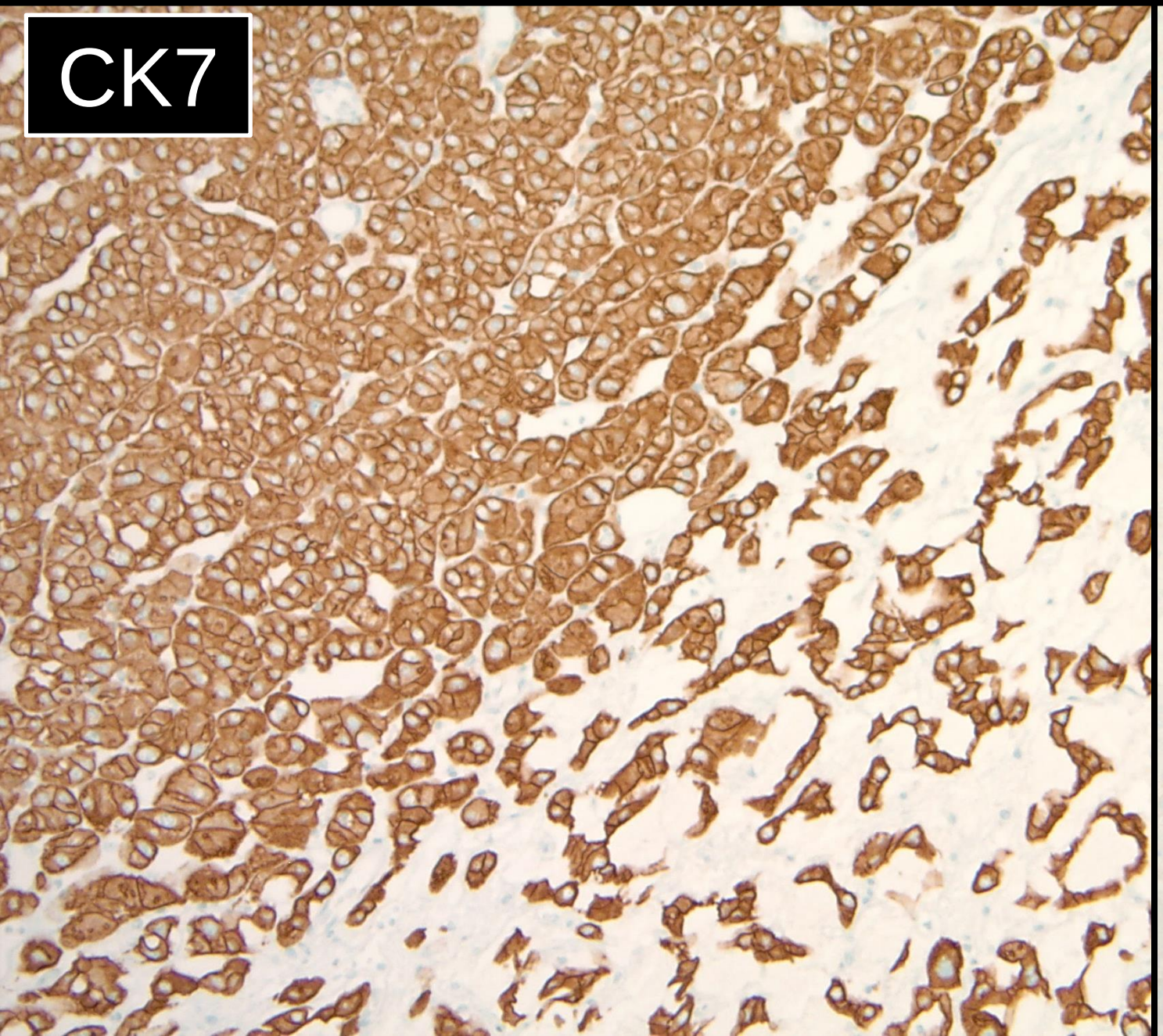
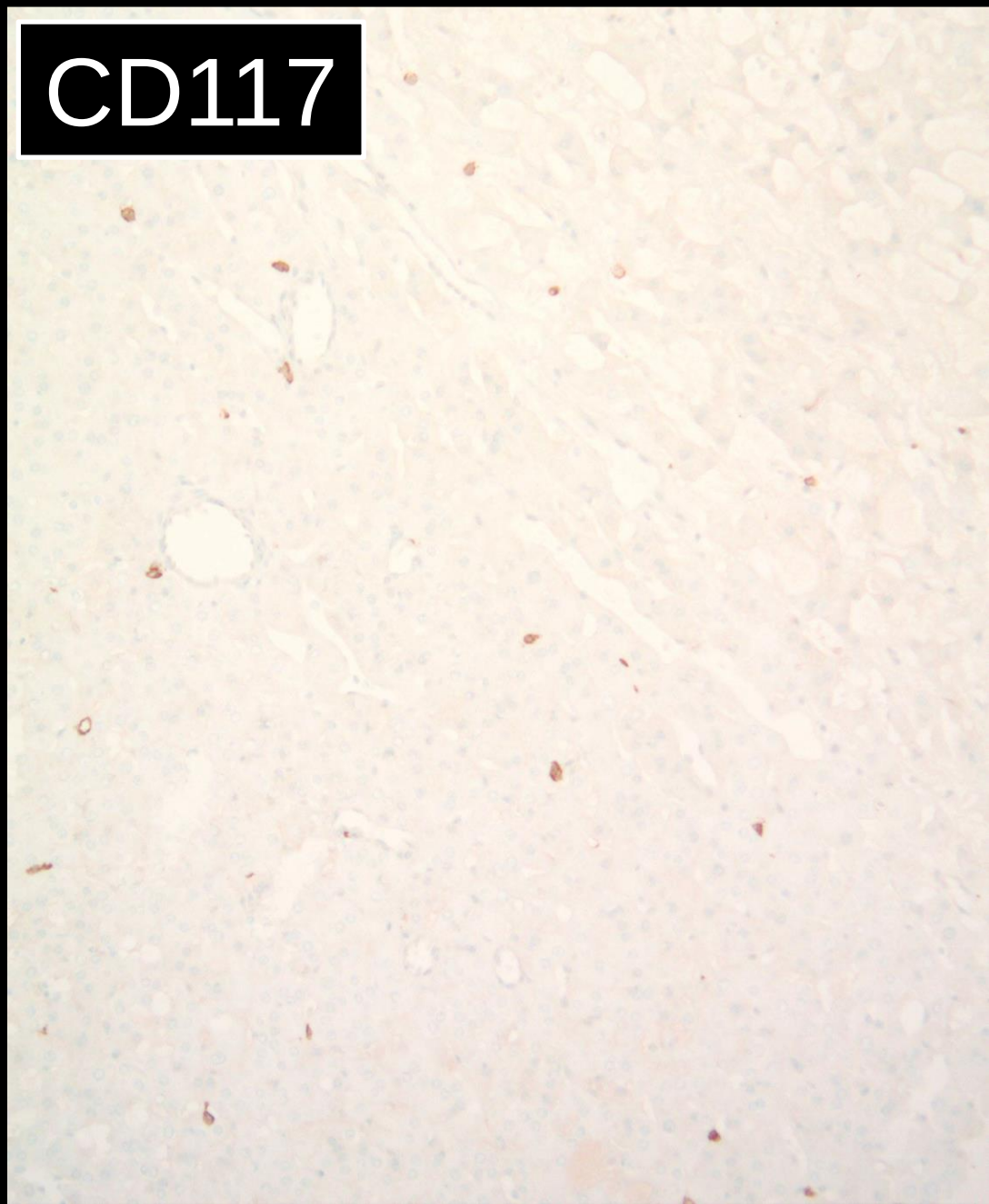
Low-grade Oncocytic Tumor/Eosinophilic Chromophobe RCC





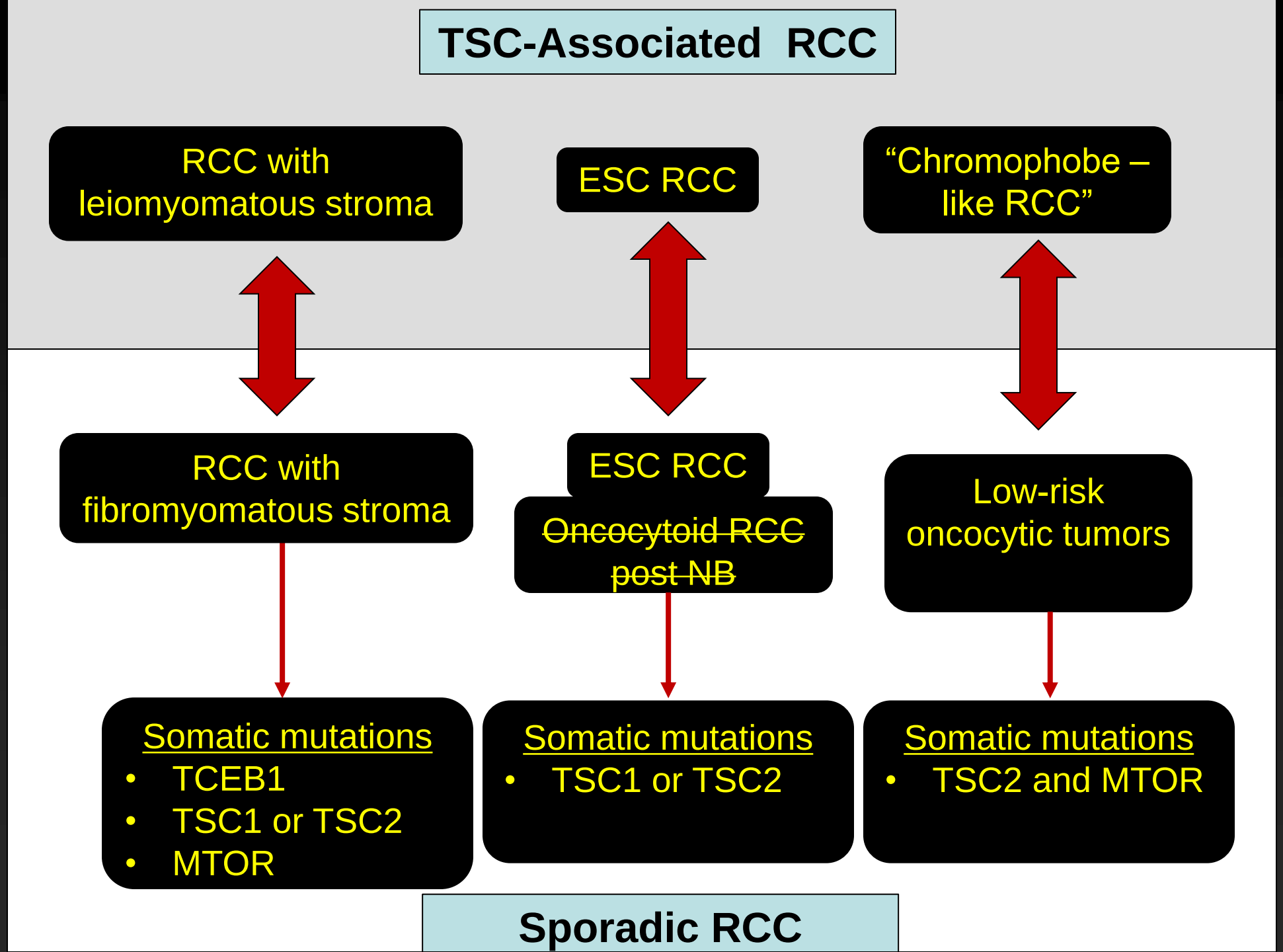
Low-grade Oncocytic Tumor/Eosinophilic Chromophobe RCC





“Non-ESC Oncocytic Tumors Resembling Chromophobe RCC” with *TSC/MTOR* Mutation

- Early in evolution of their description
- Subtle histologic difference from typical ChRCC
  - Reproducible?
  - Need diagnostic adjunct?
  - Behavior?
- Do we need to split these tumors?
  - Probably not….


TSC-Associated RCC
RCC with leiomyomatous stroma
ESC RCC
"Chromophobe – like RCC"
RCC with fibromyomatous stroma
ESC RCC
~~Oncocytoid RCC post NB~~
Low-risk oncocytic tumors
Somatic mutations
• TCEB1
• TSC1 or TSC2
• MTOR
Somatic mutations
• TSC1 or TSC2
Somatic mutations
• TSC2 and MTOR
Sporadic RCC

Summary

- TSC is an autosomal dominant disorder, but…
  - Highly variable penetrance
  - 70% are new sporadic mutations (i.e., no family history)
- Renal pathology
  - AMLs
  - RCCs
  - Cysts

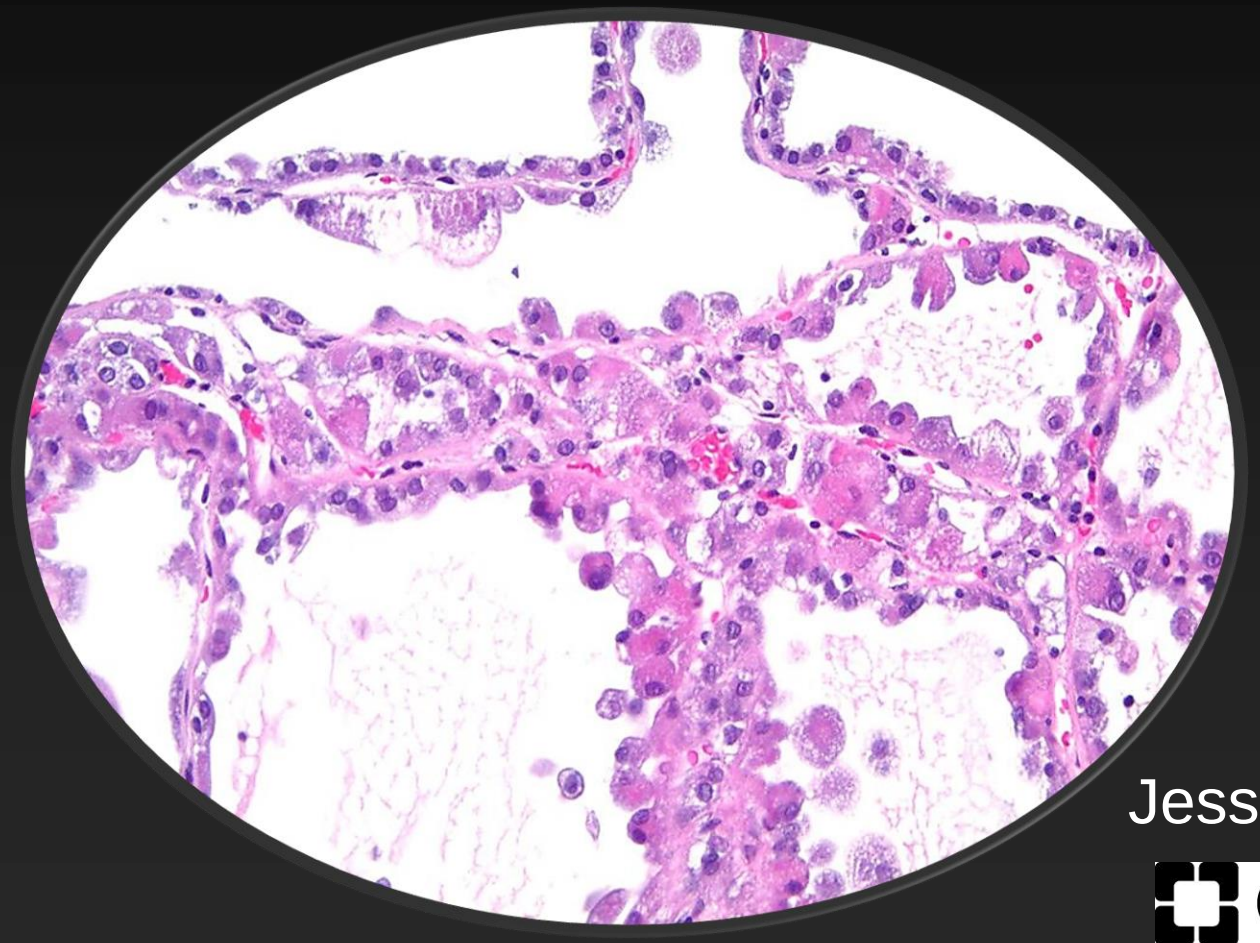
Summary

- TSC-associated RCC has three histologic patterns, which have sporadic counterparts with somatic mutations
  - **ESC RCC**
    - ***TSC1* or *TSC2***
  - **RCC with fibromyomatous stroma**
    - ***TCEB1, TSC1, TSC2, or MTOR***
  - **“Low-risk oncocytic renal neoplasia family”**
    - ***TSC2* or *MTOR***

Morphology Driven Molecular Discovery

The Story of Tuberous Sclerosis Associated Renal Neoplasia and ESC RCC

IAP Brisbane 2023



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Robert J. Tomsich Pathology & Laboratory Medicine Institute