Eosinophilic Renal Cell Tumors With a *TSC* and *MTOR* Gene Mutations Are Morphologically and Immunohistochemically Heterogenous

Clinicopathologic and Molecular Study

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汇报人：徐 红

Eosinophilic renal neoplasms

- Eosinophilic renal neoplasms have a wide spectrum of histologic presentations

- the differential diagnosis includes：
- renal oncocytoma (RO)
- eosinophilic variant of chromophobe renal cell carcinoma (CHRCC)
- type 2 papillary renal cell carcinoma (pRCC)
- clear cell RCC with predominant eosinophilic cytoplasm
- eosinophilic solid and cystic (ESC) RCC
- MiT (TFE3 or TFEB) translocation RCC
- fumarate hydratase (FH)-deficient RCC
- succinate dehydrogenase (SDH)-deficient RCC
- RCC, unclassified
- epithelioid angiomyolipoma (EAML)

嗜酸细胞腺瘤 (Oncocytoma)

- Oncocytoma is a benign epithelial tumour with solid, solid–nested, or (rarely) cystic architecture, composed predominantly of large eosinophilic cells packed with mitochondria
- **ICD-O code** 8290/0

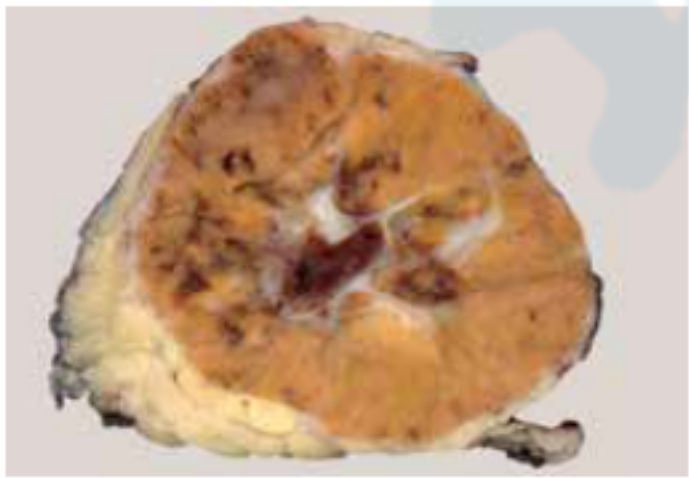


Fig. 1.44 Large, well demarcated renal oncocytoma with a central scar. The cut surface is yellowish/tan, slightly lobulated, with small haemorrhages.

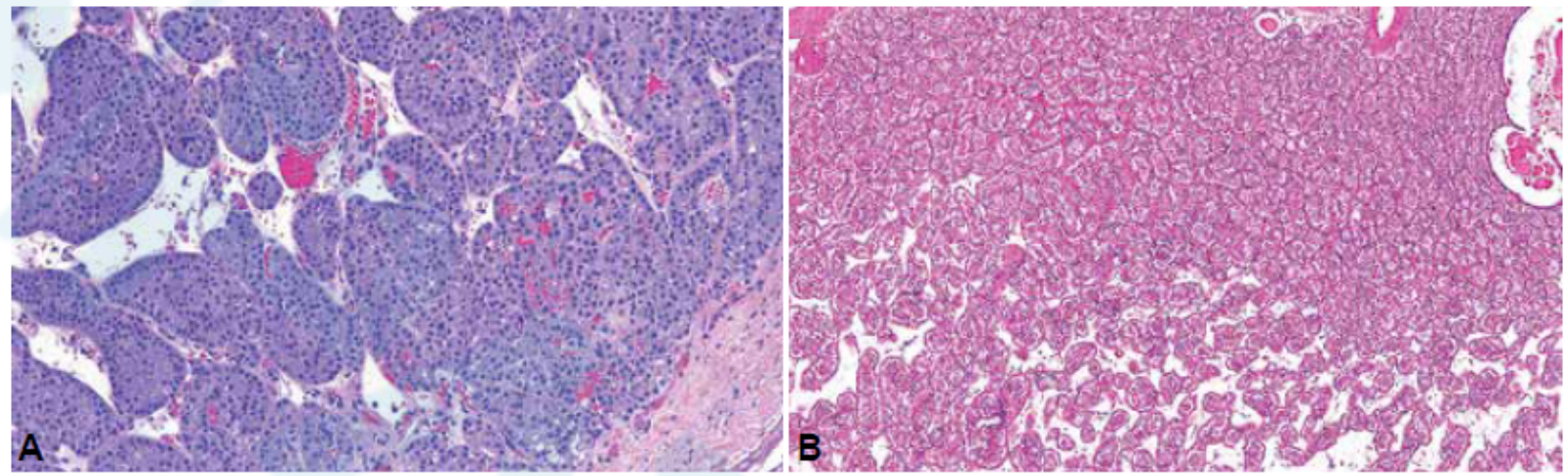


Fig. 1.45 **A** Oncocytoma. **B** Oncocytoma is an epithelial tumour with typically solid or solid-nested architecture composed of predominantly large eosinophilic cells.

- Their cytoplasm is densely granular; the nuclei are usually round and regular, with small but visible nucleoli. Binucleated cells are often present

- IHC Staining: **positive** (KIT, E-cadherin, S100A, pancytokeratin, and low–molecular weight cytokeratins); **negative** (CK7, Vimentin)

2016 World Health organization (WHO) renal tumor classification

嫌色细胞肾细胞癌 (Chromophobe renal cell carcinoma, ChRCC)

- Chromophobe renal cell carcinoma (ChRCC) is characterized by cells with prominent cell membranes, wrinkled nuclei with perinuclear halos, and pale to eosinophilic cytoplasm
- **ICD-O code** 8317/3

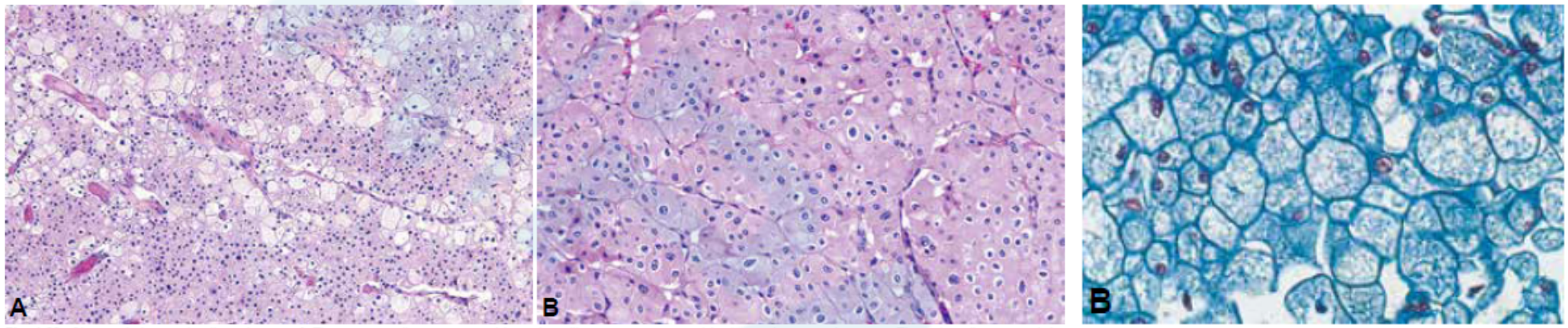


Fig. 1.22 Chromophobe renal cell carcinoma. **A** The tumour cells are arranged in a sheet-like pattern, separated by incomplete vascular septa. The pale cells surround the eosinophilic cells peripherally. **B** The tumour is composed of eosinophilic granular cells with irregular nuclei and perinuclear halos. B Hale colloidal iron positivity.

- The classic ChRCC shows predominance of larger pale cells with reticular cytoplasm and prominent cell membranes (plant cell–like)
- The eosinophilic variant of ChRCC shows predominance of smaller cells with fine oxyphilic granularity
- The nuclei often have a distinctive irregular wrinkled (so-called raisinoid) appearance, with coarse chromatin, common binucleation, and perinuclear halos (koilocytic atypia)

- Hale colloidal iron staining often shows diffuse cytoplasmic staining
- IHC Staining: **positive** (KIT, CK7); **negative** (Vimentin)

2016 World Health organization (WHO) renal tumor classification

杂合性嗜酸细胞/嫌色细胞肾肿瘤
(hybrid oncocytic/chromophobe tumour)

- a small subset of tumours have overlapping histology between oncocytoma and ChRCC (hybrid oncocytic/chromophobe tumour)
- These are commonly seen in Birt–Hogg–Dubé syndrome and renal oncocytosis; may also occur sporadically

Syndrome	Chromosome(s)	Gene	Protein	Tumour type	Extrarenal manifestations	
					In the dermis	In other organs
Birt–Hogg–Dubé syndrome	17p11	*BHD*	Folliculin	Multiple chromophobe renal cell carcinoma, hybrid chromophobe oncocytoma, papillary renal cell carcinoma	Facial fibrofolliculoma	Pulmonary cysts; spontaneous pneumothorax

2016 World Health organization (WHO) renal tumor classification

乳头状肾细胞癌 (Papillary renal cell carcinoma)

- Papillary renal cell carcinoma (PRCC) is a malignant tumour derived from renal tubular epithelium
- It has papillary or tubulopapillary architecture and is often well circumscribed
- **ICD-O code** 8255/1

- Two types of PRCC have been described based on the cells lining the papillae and tubules
- **Type 2 PRCC** is composed of large cells with eosinophilic cytoplasm, pseudostratified nuclei, and prominent nucleoli

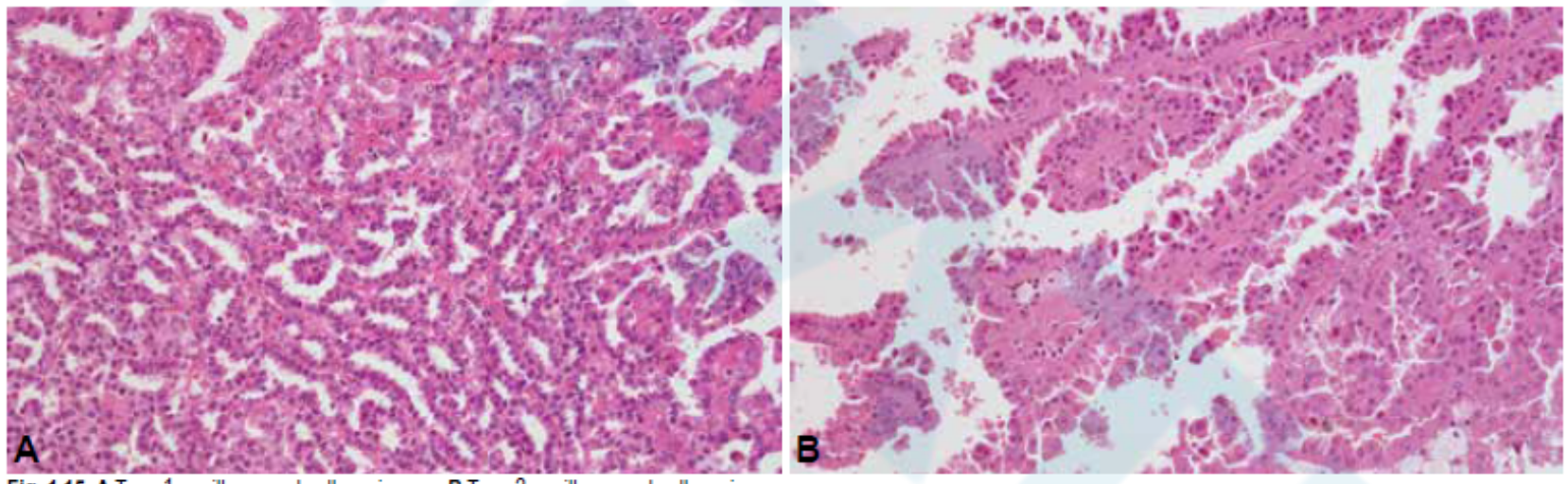


Fig. 1.15 A Type 1 papillary renal cell carcinoma. B Type 2 papillary renal cell carcinoma.

- **oncocytic PRCCs**:
- PRCCs with voluminous, finely granular, evenly distributed eosinophilic cytoplasm and oncocytoma-like nuclei (usually with low nucleolar grade) have been called oncocytic PRCCs

- IHC Staining: **positive** (AE1/AE3, AMACR, RCC antigen, CD10, vimentin; CK7 expression is more common in type 1 PRCCs than in the type 2 tumours)

2016 World Health organization (WHO) renal tumor classification

未分类肾细胞癌 (Unclassified renal cell carcinoma)

- Unclassified renal cell carcinoma (RCC) is not a distinct type of RCC but a diagnostic category for tumours that do not readily fit into any of the recognized subtypes of RCC
- Histologically, it could be low or high grade
- **ICD-O code** 8312/3

- Tumours with pure sarcomatoid morphology and no recognizable epithelial component
- **low or high grade unclassified oncocytic neoplasms**

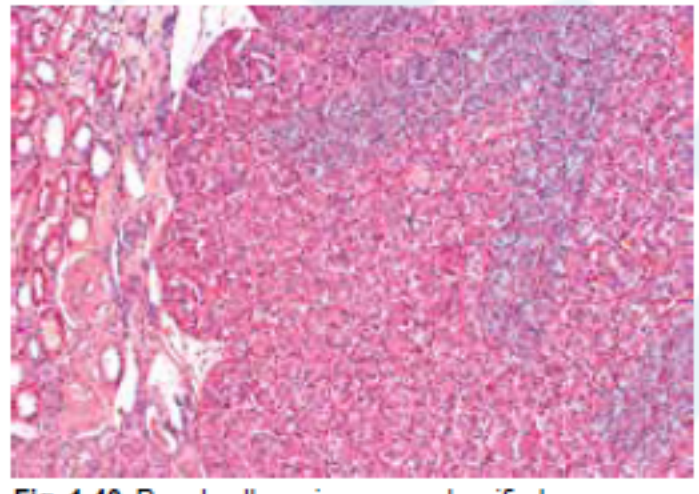


Fig. 1.40 Renal cell carcinoma, unclassified.

- Immunohistochemistry is useful to support renal histogenesis; markers include PAX8, PAX2, RCC marker, and CD10

2016 World Health organization (WHO) renal tumor classification

结节性硬化症相关性肾细胞癌
Tuberous Sclerosis Complex (TSC)-associated RCCs

- Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder resulting from inherited or sporadic germline mutations of 1 of 2 genes, TSC1 or TSC2 (encoding hamartin and tuberin, respectively)

Syndrome	Chromosome(s)	Gene	Protein	Tumour type	Extrarenal manifestations	
					In the dermis	In other organs
Tuberous sclerosis	9q34 16p13	*TSC1* *TSC2*	Hamartin Tuberin	Multiple, bilateral angiomyolipomas; lymphangioleiomyomatosis; rare renal cell carcinomas	Angiofibroma, subungual fibroma	Cardiac rhabdomyoma; adenomatous small intestine polyps; pulmonary and renal cysts; cortical tuber; subependymal giant cell astrocytomas

- The 57 RCCs from 13 female and 5 male TSC patients exhibited 3 major distinct morphologies:
- (1) 17 RCCs (30%) had features similar to tumors previously described as “renal angiomyoadenomatous tumor/RAT” or “RCC with smooth muscle stroma”;
- (2) 34 RCCs (59%) showed features similar to chromophobe RCC
- (3) 6 RCCs (11%) showed a granular eosinophilic-macrocystic morphology

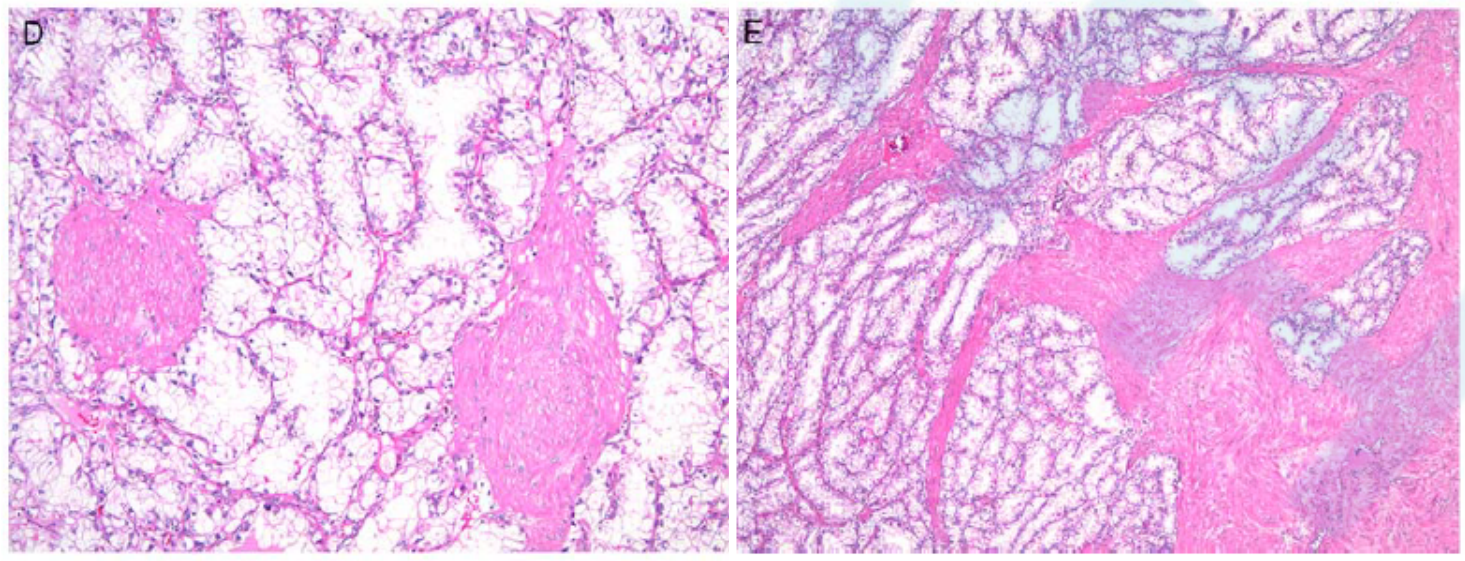


FIGURE 1. RCC resembling RAT/RCC with smooth muscle stroma.

Tuberous sclerosis-associated renal cell carcinoma: a clinicopathologic study of 57 separate carcinomas in 18 patients. Am J Surg Pathol. 2014;38:1457–1467.

Tuberous Sclerosis Complex (TSC)-associated RCCs

- **eosinophilic renal neoplasms in TSC patients**： 2 types of tumors described as having CHRCC-like or eosinophilic-macrocystic morphology

- **CHRCC-like morphology**:
  solid, nested, and tubular architecture;
  the neoplastic cells exhibiting eosinophilic and granular cytoplasm;
  vimentin(-), CK7 and AMACR(+)
- **eosinophilic-macrocystic morphology**:
  solid and cystic architecture;
  voluminous granular eosinophilic cytoplasm, prominent nucleoli, and an occasional hobnail appearance;
  vimentin and AMACR(+), CK7(-)

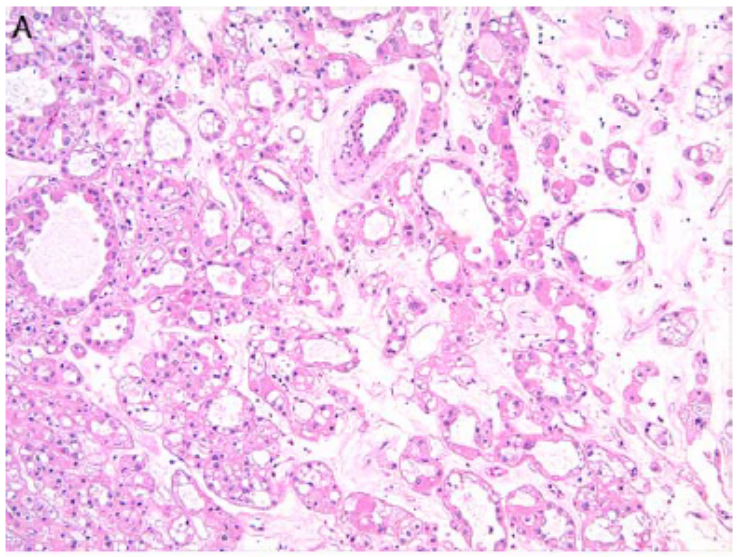


FIGURE 2. RCC resembling chromophobe type.

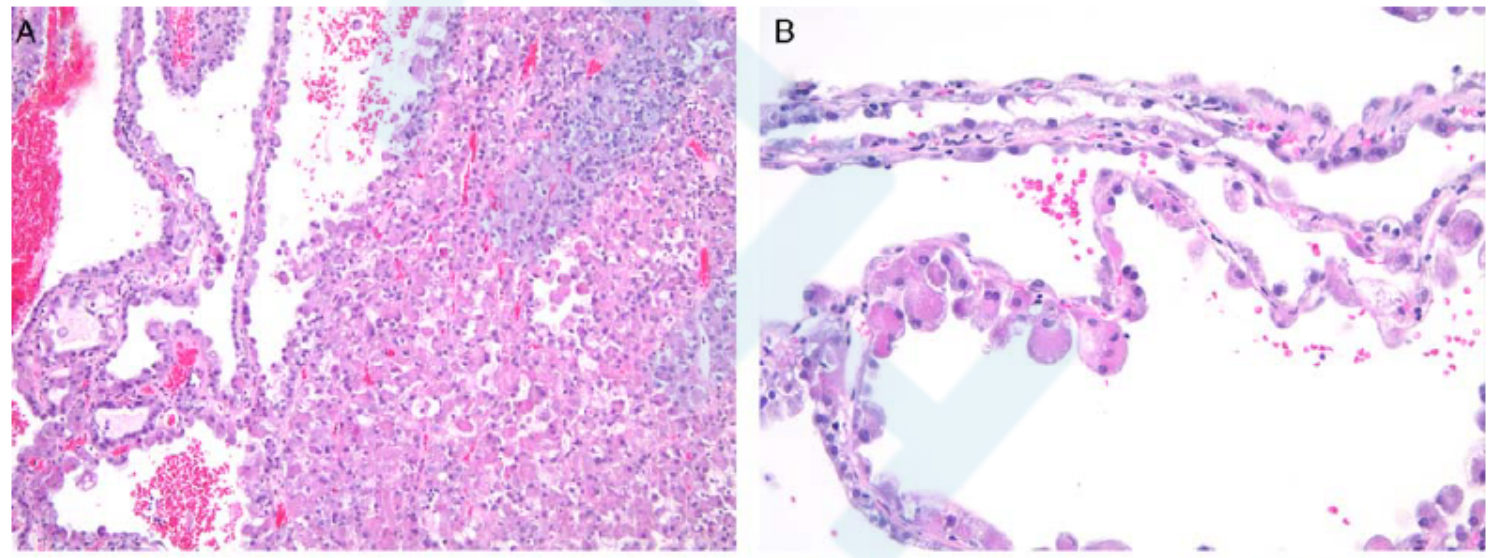


FIGURE 3. RCC with a granular eosinophilic and macrocystic pattern.

Tuberous sclerosis-associated renal cell carcinoma: a clinicopathologic study of 57 separate carcinomas in 18 patients. Am J Surg Pathol. 2014;38:1457–1467.

嗜酸性实性和囊性肾细胞癌
(Eosinophilic Solid and Cystic Renal Cell Carcinoma, ESC RCC)

- ESC RCC has been recently described as a unique and indolent renal neoplasm, found in female patients **with and without tuberous sclerosis complex (TSC)**

- typical microscopic features with **solid areas admixed with variably sized macrocysts and microcyst**s
- **eosinophilic cytoplasm** with granular cytoplasmic stippling and round-to-oval nuclei
- **a predominant CK20+/CK7- immunophenotype**, PAX-8 expression, patchy AMACR staining, but no CD117 reactivity

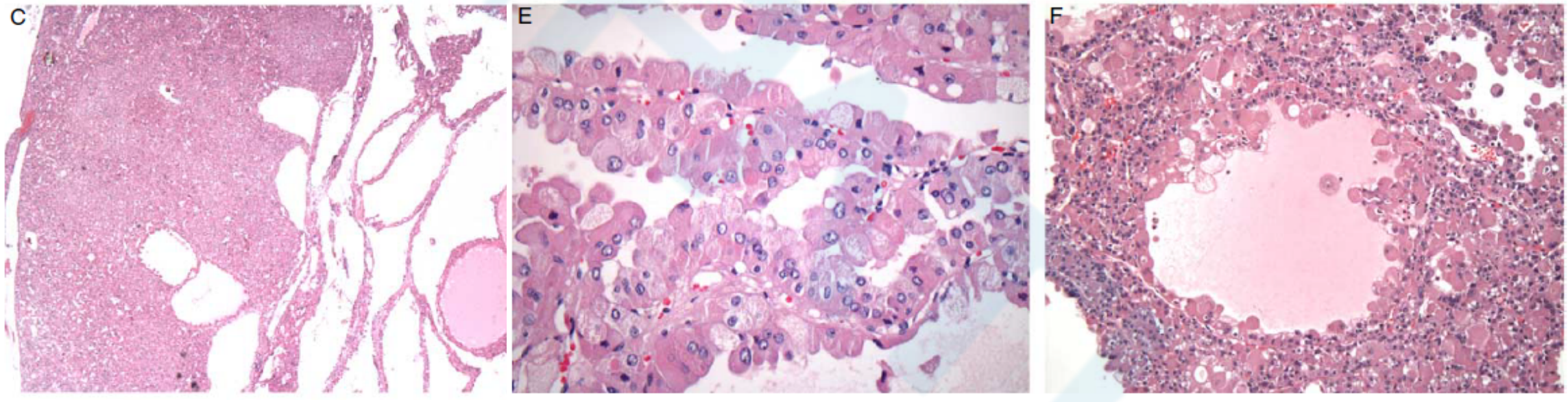


FIGURE 1. Typical features of eosinophilic solid and cystic renal cell carcinoma (ESC RCC).

- ESC RCC is **not** currently included in the 2013 ISUP Vancouver Classification of renal tumors and in the updated 2016 WHO renal tumor classification

Eosinophilic solid and cystic renal cell carcinoma (ESC RCC): further morphologic and molecular characterization of ESC RCC as a distinct entity. Am J Surg Pathol. 2017;41:1299–1308.

- Eosinophilic renal neoplasms have a wide spectrum of histologic presentations

- several studies have demonstrated a subtype of renal cell carcinomas (RCCs) associated with the tuberous sclerosis complex (TSC)/mammalian target of rapamycin pathway

- We set out to expand on these studies and further identify **unusual eosinophilic renal neoplasms** and define them by morphologic, IHC, and molecular studies

METHODS

➢ Study Population

- We retrospectively reviewed the Department of Pathology database (the University of Chicago) from 2005 to 2018 and identified renal oncocytic tumors with unusual morphology

➢ Pathologic Analysis

3 different architecture patterns; IHC stains were utilized to further characterize these cases

- **Group 1 tumors**: solid;
  morphologically similar to CHRCC but exhibit an IHC profile similar to ROs
- **Group 2 tumors**: solid;
  morphologic and IHC features similar to CHRCC, eosinophilic variant;
  a minority of the tumors in this category exhibit focal nuclear atypia and perinuclear halos
- **Group 3 tumors**: solid, cystic and papillary;
  architecturally variable but consistently exhibit an IHC profile consistent with ESC RCC

➢ IHC Staining

- carbonic anhydrase IX (CA IX), CK7, CK20, Vimentin, CD117, racemase (P504S), SDHB

➢ Next-generation Sequencing

- a representative formalin-fixed, paraffin-embedded block
- a hybrid-capture panel targeting 1213 cancer-associated genes

RESULTS

TABLE 1. Patient Demographics

Cases	Age (y)	Sex	Laterality	Focality	Size (cm)	Stage	Architecture	Original Diagnosis
Group 1								
I	56	Male	Right	Unifocal	1.2	T1a, NX	Solid	Unclassified RCC
II	57	Female	Right	Unifocal	1.4	T1a, NX	Solid	CHRCC
III	14	Male	Left	Unifocal	13.0	T2b, NX	Solid	Unclassified RCC
Group 2								
I	43	Female	Right	Unifocal	3.7	Not assigned	Solid	RO
IIA	40	Male	Right	Unifocal	23.3	T2b, NX	Solid	CHRCC
IIB	40	Male	Left	Multifocal	21.0	T2b, NX	Solid	CHRCC, eosinophilic variant
III	64	Male	Right	Unifocal	1.5	T1a, NX	Solid	CHRCC, eosinophilic variant
IV	57	Female	Left	Unifocal	3.8	T1a, NX	Solid	CHRCC
V	76	Female	Right	Unifocal	4.0	T1a, NX	Solid	CHRCC, eosinophilic variant
VI	66	Female	Left	Multifocal	4.1	(m)T1b, NX	Solid	Unclassified RCC
VII	66	Male	Right	Unifocal	2.5	T1a, NX	Solid	CHRCC, eosinophilic variant
Group 3								
I	52	Female	Right	Unifocal	5.5	T1b, NX	Solid and cystic	Unclassified RCC
II	33	Female	Left	Unifocal	1.7	T1a, NX	Solid and cystic	Unclassified RCC
III	47	Female	Right	Unifocal	3.0	T1a, NX	Solid and cystic	Unclassified RCC
IV	65	Female	Left	Unifocal	11.5	T3a, NX	Solid and cystic	Unclassified RCC
VA	48	Female	Right	Unifocal	6.0	T3b, N2	Solid and papillary	Type 2 pRCC
VB	49	Female	Left	Multifocal	2.5	T1a, N2	Solid and papillary	Unclassified RCC
VI	67	Female	Right	Unifocal	2.9	Not assigned	Solid and papillary	RO

- **renal oncocytic tumors with unusual morphology: 18 cases**
- **group 2, case II; group 3, case V**: a second renal mass in the contralateral kidney after resection of the first renal mass
- **Male: 5; Female: 11**
- **Age:** 14 to 76 years (mean: 52.7 y)
- **group 3, case III:** tuberous sclerosis; **group 3, case VI:** multiple endocrine neoplasia, type 1
- **tumor size:** 1.2 to 23.3 cm (mean: 6.08 cm)
- AJCC pathologic T categories: pT1a (n=9), pT1b (n=2), pT2b (n=3), pT3a (n=1), and pT3b (n=1)
- group 3, case V: >1 regional lymph node metastases
- 3 different architecture patterns: solid, solid and cystic, and solid and papillary
- All cases were originally diagnosed as RO, CHRCC, type 2 PRCC, or unclassified RCC

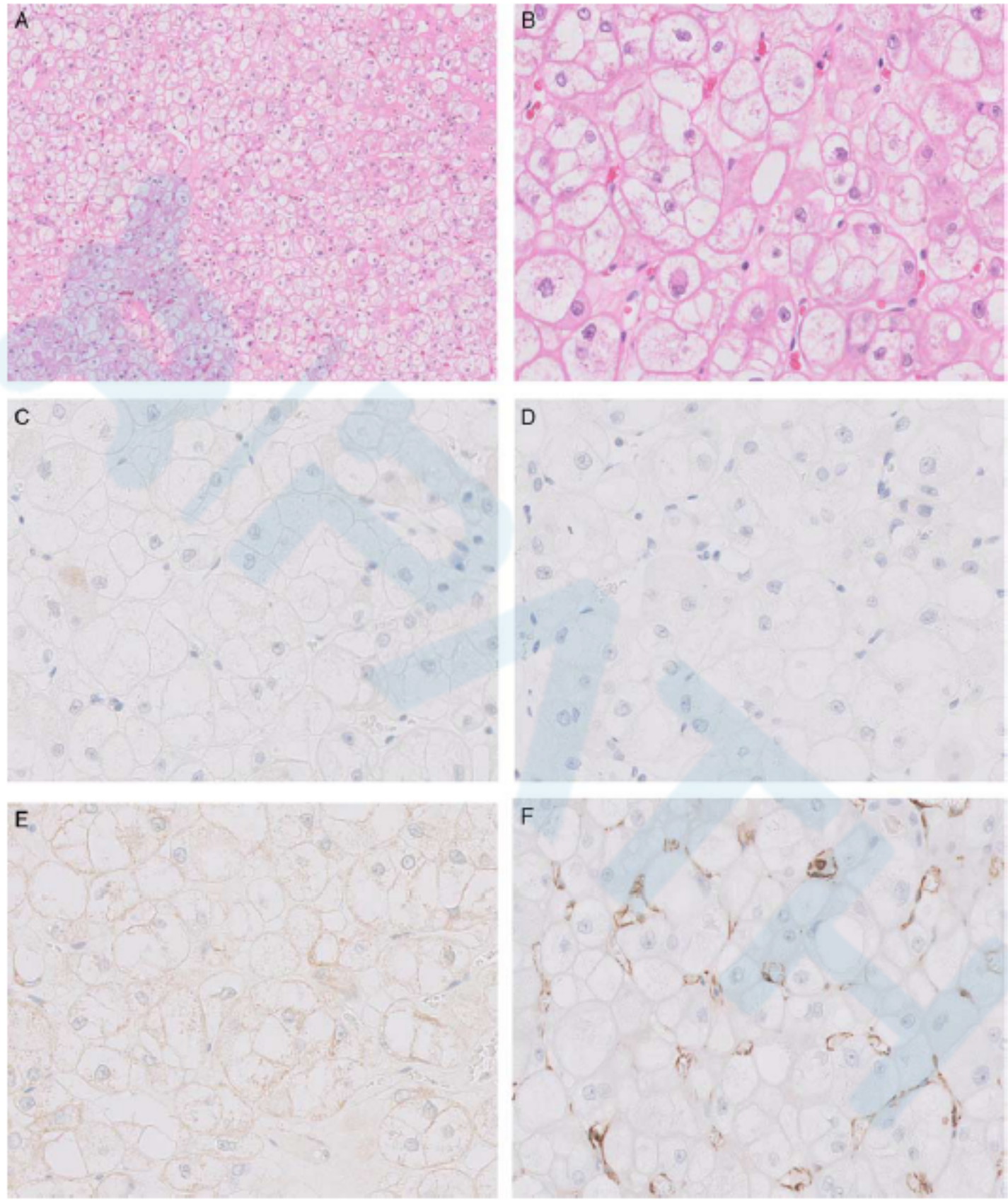


FIGURE 1. The tumor cells in group 1 had abundant flocculent cytoplasm that was granular and eosinophilic. They formed small nests and had sharply delineated cytoplasmic membranes (A). The nuclei were round with occasional conspicuous nucleoli (B). IHC staining demonstrated that the tumor cells were focally weakly positive for CK7 (C), negative for CK20 (D), focally weakly positive for P504S (E), and negative for vimentin (F).

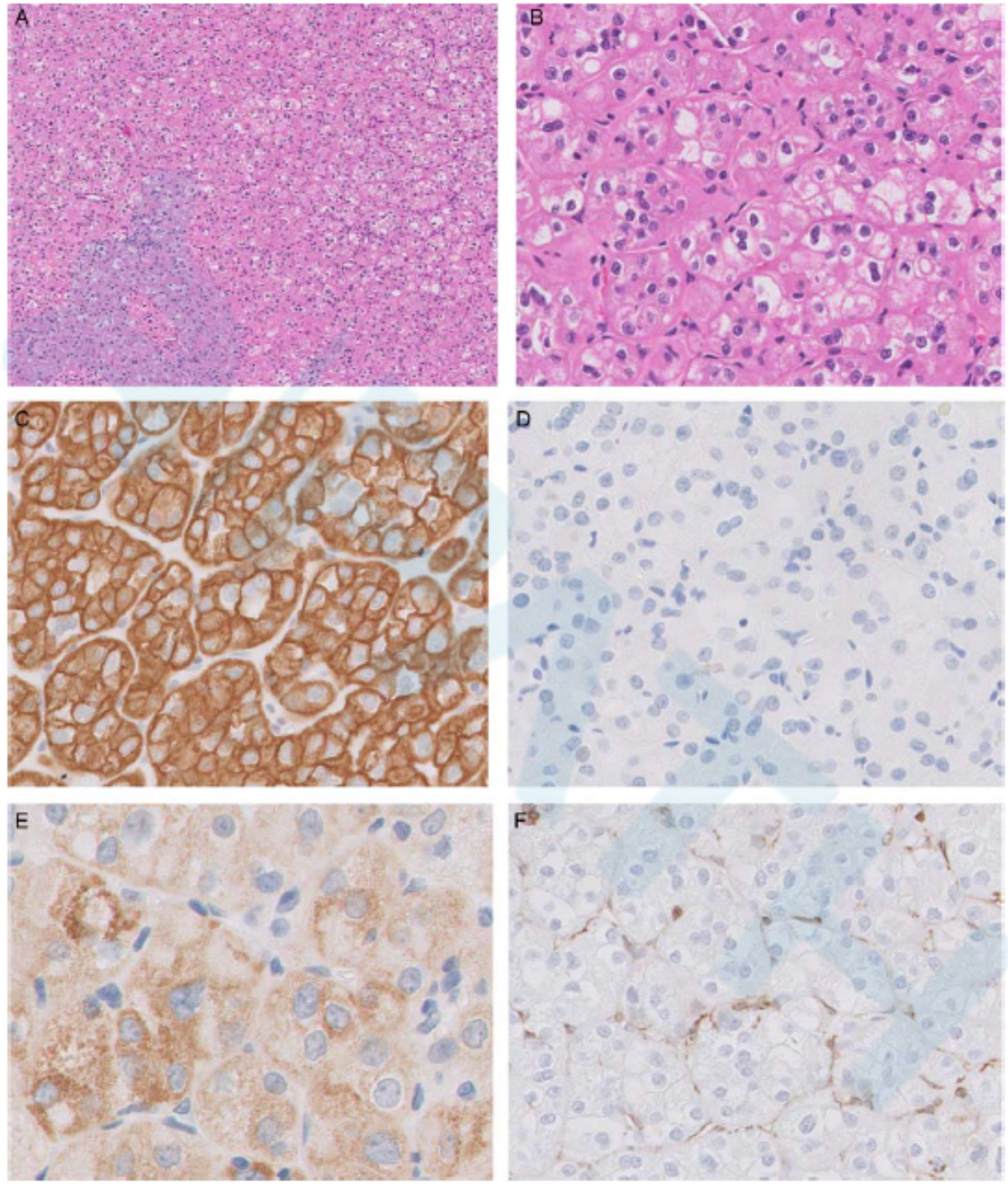


FIGURE 2. The tumor cells of group 2 exhibited more abundant eosinophilic cytoplasm (A). Some nuclei were round with open chromatin and inconspicuous nucleoli and others showed irregular nuclear membranes and perinuclear halos (B). IHC staining demonstrated that the tumor cells were diffusely strongly positive for CK7 (C), negative for CK20 (D), diffusely moderately positive for P504S (E), and negative for vimentin (F).

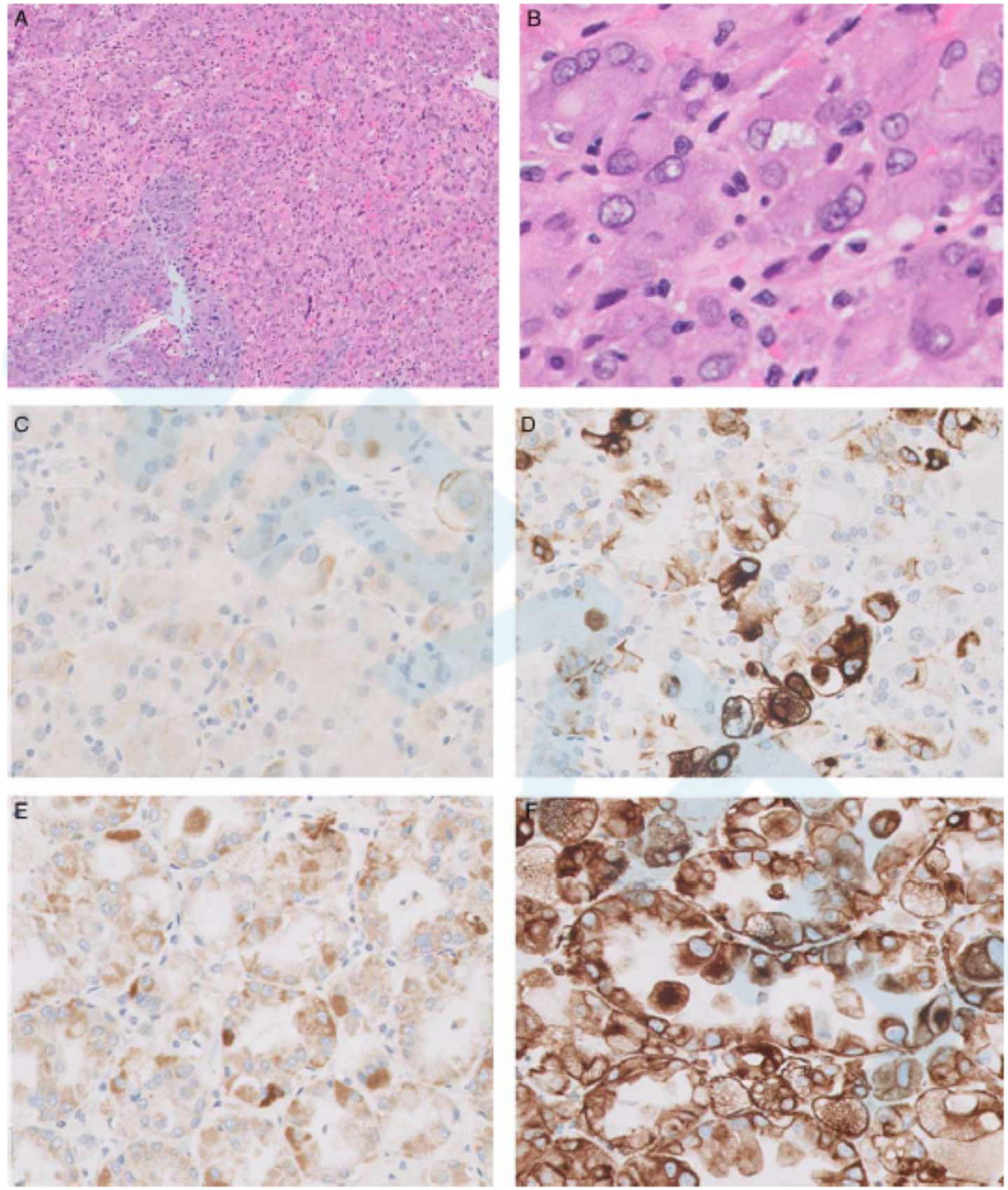


FIGURE 4. The tumors in group 3 that were solid and cystic had denser eosinophilic cytoplasm with occasional vacuolated cells (A). The nuclei were overlapping and were more pleomorphic with variably conspicuous nucleoli (B). IHC staining demonstrated that the tumor cells were negative for CK7 (C), and focally moderately to strongly positive for CK20 (D), diffusely moderately positive for P504S (E), and diffusely strongly positive for vimentin (F).

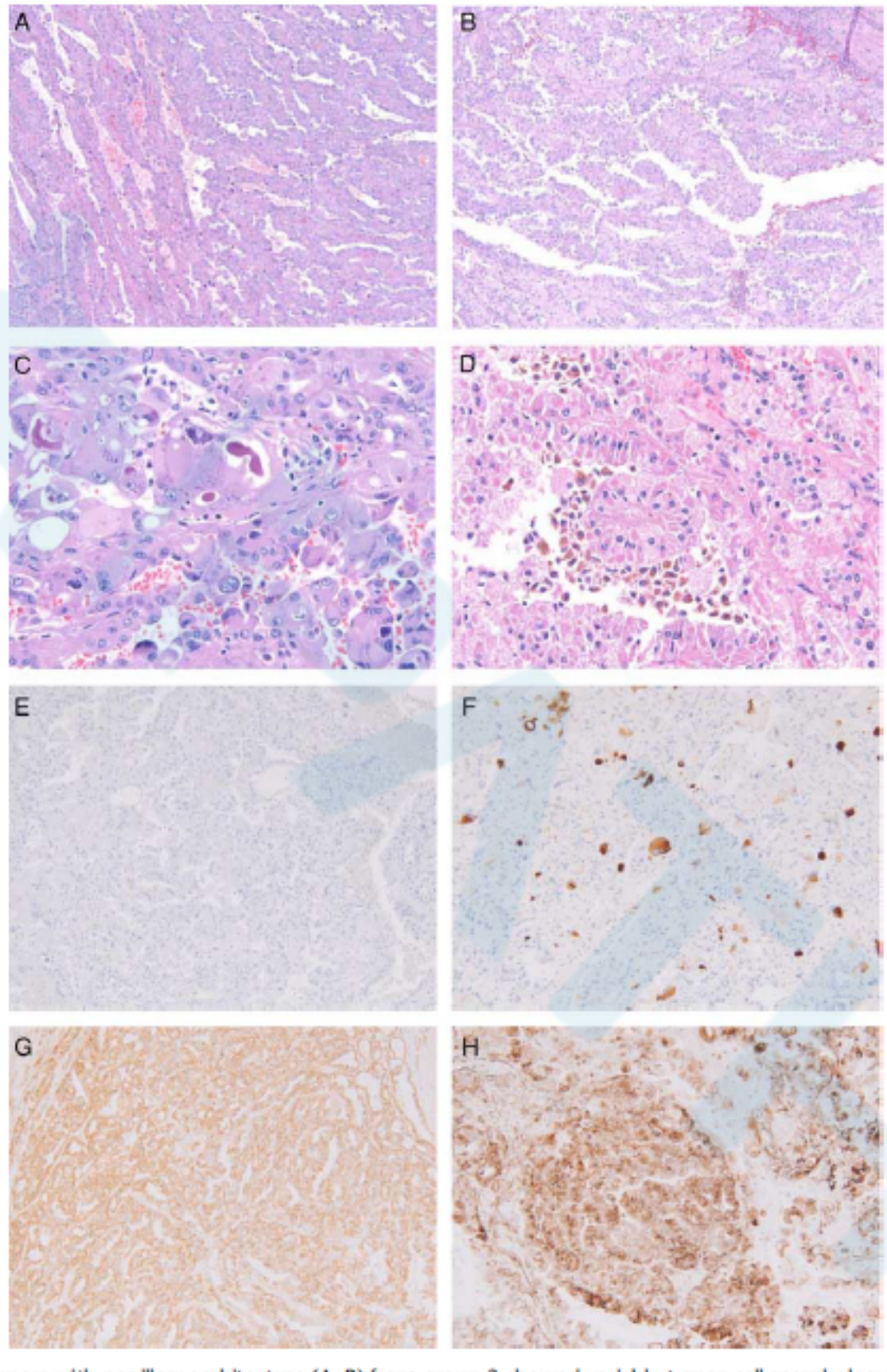


FIGURE 5. The tumors with papillary architecture (A, B) from group 3 showed variable tumor cell morphology. The cells in some areas had abundant dense eosinophilic cytoplasm with magenta globules and basophilic granules and large nuclei with prominent nucleoli (C). Other tumor cells had cytoplasm with fine eosinophilic granules and bland nuclei with inconspicuous nucleoli (D). IHC staining demonstrated that the tumor cells were negative for CK7 (E), focally strongly positive for CK20 (F), and diffusely moderately positive for P504S (G) and vimentin (H).

TABLE 2. Histologic Features

Histologic Features	Group 1	Group 2	Group 3
Architecture pattern	Solid	Solid	Solid, cystic, and papillary
Cytoplasmic features	Flocculent, sparsely granular and eosinophilic, prominent cell membranes	Abundant eosinophilic cytoplasm	Dense abundant eosinophilic cytoplasm with occasional basophilic and magenta color granules
Nuclear features	Round nuclei and occasional conspicuous, large nucleoli	Occasional binucleated cells, predominantly round nuclei with open chromatin and inconspicuous nucleoli, rare nuclei with irregular nuclear membranes and perinuclear halos	Overlapping nuclei exhibiting greater pleomorphism and variable size nucleoli

- The tumors in **groups 1 and 2** were almost entirely without mitotic activity and no necrosis was identified
- For **group 3** mitotic activity was present primarily in the papillary cases (group 3, cases V and VI) ; necrosis was not identified in any of the cases

TABLE 3. IHC Results

Cases	CK7	CK20	P504S	Vimentin	CD117	CAIX	SDHB
Group 1							
I	1	0	2	0	3	ND	ND
II	2	0	1	0	3	ND	ND
III	2	0	2	0	3	0	ND
Group 2							
I	3	0	3	0	0	ND	3
IIA	3	1	3	0	0	0	3
IIB	3	0	3	0	0	0	ND
III	3	1	3	0	3	0	3
IV	3	0	3	0	2	0	ND
V	3	0	3	0	1	0	ND
VI	2	0	3	0	1	ND	3
VII	3	0	3	0	0	ND	ND
Group 3							
I	0	3	2	3	0	0	ND
II	0	3	2	3	0	0	3
III	0	3	3	2	ND	0	ND
IV	0	3	2	3	0	0	3
VA	0	2	3	3	0	0	ND
VB	0	2	2	3	0	0	ND
VI	1	3	ND	3	2	0	ND

ND indicates not done.

- **IHC staining:**

0%—negative, 1% to 5%—1, 5% to 50%—2, and >50%—3

- **group 1**: absent staining of CK20 and vimentin, focal weak staining for CK7 and P504S
- **group 2**: diffuse strong staining for CK7, absent to focal staining of CK20, diffuse moderate staining for P504S, and negative staining for vimentin
- **group 3**: negative staining for CK7, except for 1 case, along with moderate to strong staining of CK20, P504S, and vimentin
- Most of the cases in groups 1 and 2 had weak to strong staining of **CD117**, which was absent in group 3 except for 1 case
- All of the cases that were tested were negative for **CAIX** and diffusely strongly positive for **SDHB**

TABLE 4. NGS Results

Cases	Gene	Coding Effect	Nucleotide Change	Amino Acid Alteration	Copy Number Variation
Group 1					
I	*TSC2*	Splicing	NM_000548.4:c.5160+3G> C		11p barely deleted
II	*TSC2*	Missense	NM_000548.4:c.5228G> A	p.Arg1743Gln	5q amplification
III	*TSC2*	Complex rearrangement and deletion	NM_000548.4		
Group 2					
I	*TSC1*	Nonsense	NM_000368.4:c.2101C> T	p.Gln701*	1p deleted, 1q barely amplified
IIA	*TSC1*	Nonsense	NM_000368.4:c.2590G> T	p.Glu864*	2q, 11p, and 12q amplification
IIB	*TSC1*	Nonsense	NM_000368.4:c.2590G> T	p.Glu864*	19p and 19q barely deleted
	TSC1	Frameshift	NM_000368.4:c.1453_1454del	p.Glu485Thrfs*3	
III	*TSC2*	Splicing	NM_000548.4:c.-1-1874C> T		4q, 7p, 7q, 8p, 18q barely amplified
IV	*TSC1*	Frameshift	NM_000368.4:c.1851_1852del	p.His617Glnfs*8	1p deleted, 6q, 9q, 19p barely deleted
V	*TSC2*	Missense	NM_000548.4:c.5227C> T	p.Arg1743Trp	
VI	*MTOR*	Missense	NM_004958.3:c.7280T> A	p.Leu2427Gln	
VII	*MTOR*	Missense	NM_004958.3:c.5930C> G	p.Thr1977Arg	19p and 19q barely deleted
Group 3					
I	*TSC2*	Frameshift	NM_000548.4:c.276_279dup	p.Pro94Alafs*33	19p deleted
	TSC2	Frameshift	NM_000548.4:c.938_939del	p.Arg313Lysfs*24	
II	*TSC2*	Splicing	NM.000548.4:c.975+1G> T	p.Hisl746_Arg1751del	
	TSC2	In-frame deletion	NM.000548.4:c.5238_5255del		
III			Known TSC mutation		
IV	*TSC2*	Splicing	NM.000548.4:c.2356-1G >C	p.Glu546*	
	TSC2	Nonsense	NM.000548.4:c.1636G> T		
VA			Technical failure		
VB	*TSC1*	Frameshift	NM_000368.4: c.2599_2600insCG	p.Gln867Profs*12	16p barely amplified; 6p and 6q barely deleted
VI	*TSC1*	Missense	NM_000368.4:c.2195A> G	p.His732Arg	6p, 6q, 14p, and 18p barely amplified

- **Group 1**: all 3 cases had mutations in *TSC2*
- **Group 2**: pathogenic variants were identified in 3 genes (*TSC1, TSC2, MTOR*)
- **Group 3**:

  case III was not sequenced, with a known tuberous sclerosis syndrome

  case VA, technical failures prevented sequencing

  the other cases: genetic alterations and pathogenic variants were identified in *TSC1* and *TSC2*

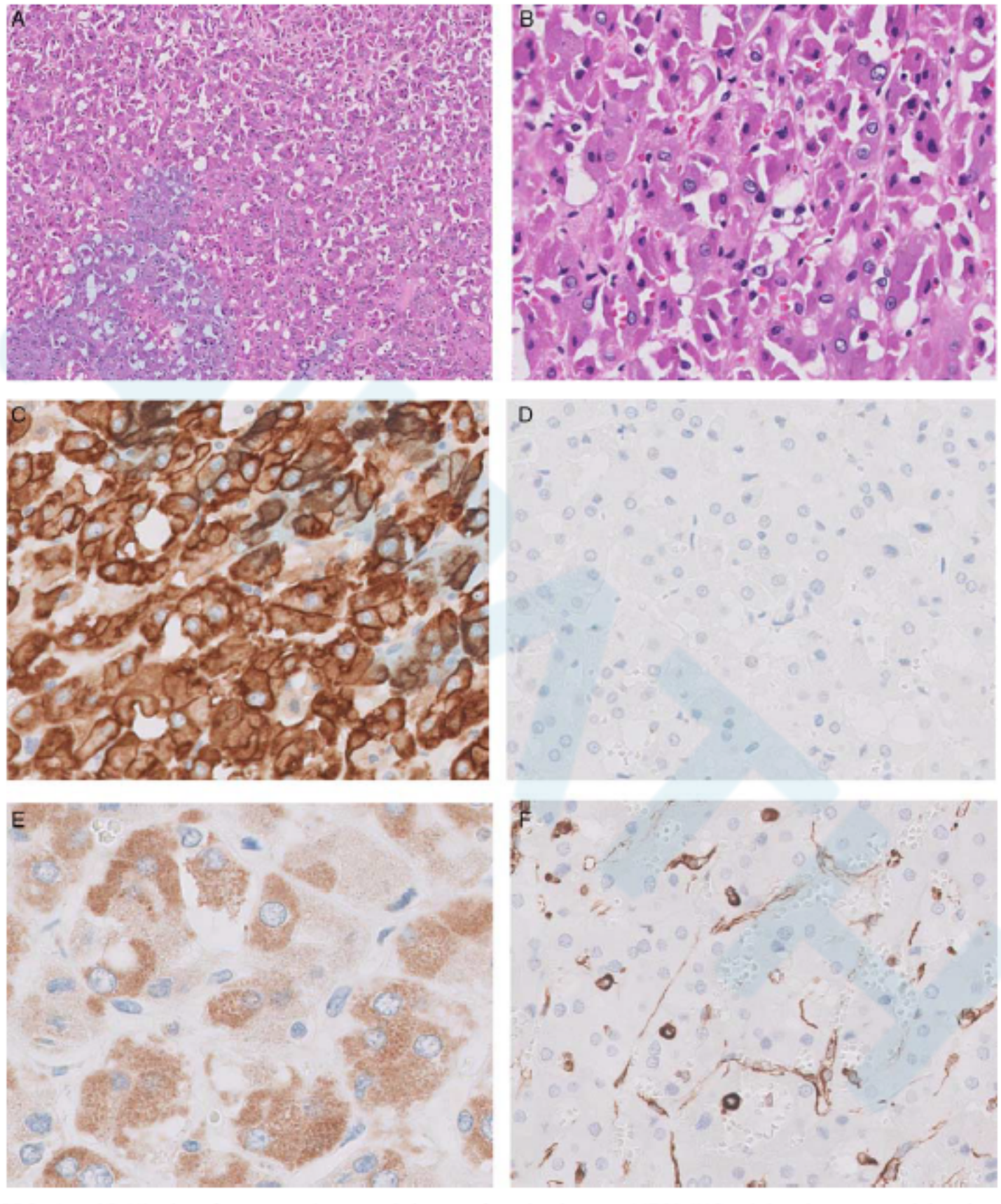


FIGURE 3. A and B, Histology from a case in group 2 that was found to have an *MTOR*. IHC staining demonstrated that the tumor cells were diffusely strongly positive for CK7 (C), negative for CK20 (D), diffusely moderately positive for P504S (E), and negative for vimentin (F).

TABLE 5. Follow-up Data

Cases	Months Postsurgery	Alive/Deceased
Group 1		
I	65	Alive
II	42	Alive
III	12	Alive
Group 2		
I	Lost to follow-up	
IIA	Lost to follow-up	
IIB	Lost to follow-up	
III	12	Alive
IV	54	Deceased*
V	90	Alive
VI	6	Alive
VII	156	Alive
Group 3		
I	154	Alive
II	36	Alive
III	108	Alive
IV	6	Deceased†
VA	Lost to follow-up	
VB	Lost to follow-up	
VI	83	Alive

*Unknown cause of death.
†Secondary to primary myelofibrosis.

- **Male: 5; Female: 11**
- lost to follow-up：3
- deceased：2

- alive at the time of analysis：11
- follow-ups：6 months to 156 months (mean: 63.4mo)

DISCUSSION

	Group 1	Group 2	Oncocytoma	CHRCC, eosinophilic variant
Architecture pattern	solid architecture	solid architecture	solid and tubular growth	solid lesion
Cytoplasmic features	morphology similar to CHRCC	morphology similar to either RO or CHRCC, eosinophilic variant	granular eosinophilic cytoplasm, round nuclei with **absent** perinuclear halos, and small nucleoli	bland oncocytic cells with or without perinuclear halos
IHC pattern	CK7(weak focal+) P504S(weak focal+) Vimentin(-) CK20(-)	CK7(diffuse+) P504S(diffuse+) Vimentin(-) CK20(-/weak+)	CK7(-) P504S(-) Vimentin(-) CD117(diffuse+) E-cadherin(diffuse+)	CK7(+) P504S(-) Vimentin(-) CD117(+)

Group 1 tumors are morphologically similar to CHRCC but exhibit an IHC profile similar to Ros.
Although the cases from **group 2** were immunohistochemically consistent with CHRCC, the molecular findings were inconsistent.

classic CHRCC: numerous chromosomal losses (chromosomes 1, 2, 6, 10, 13, 17, and 21)

Group 3	solid, cystic and papillary architecture； CK7(-), CK20、P504S、Vimentin (moderate to strong+)
Type 2 pRCC	large cells with eosinophilic cytoplasm, pseudostratified nuclei, and prominent nucleoli CK7(variably), P504S(+), Vimentin(+)
Epithelioid angiomyolipoma (EAML)	angiomyolipoma is a benign mesenchymal tumor that can occur sporadically or in association with TSC EAML is a rare variant of angiomyolipoma that consists of at least 80% epithelioid cells epithelioid cells with abundant eosinophilic and granular cytoplasm and oval nuclei with enlarged vesicular nuclei (which can overlap with ESC RCC) IHC： positive for melanocytic markers including HMB-45, Mart-1/Melan-A, tyrosinase, and MiTF

Other differential entities:

Succinate dehydrogenase (SDH) deficient renal carcinoma

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC/FH-deficient RCC

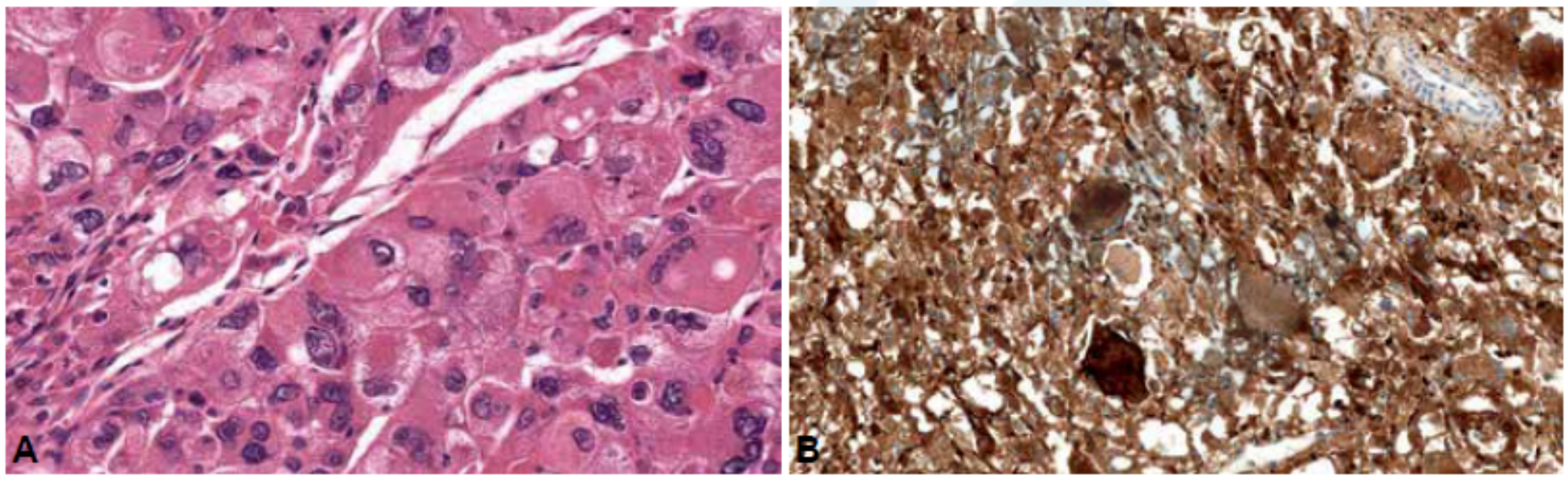
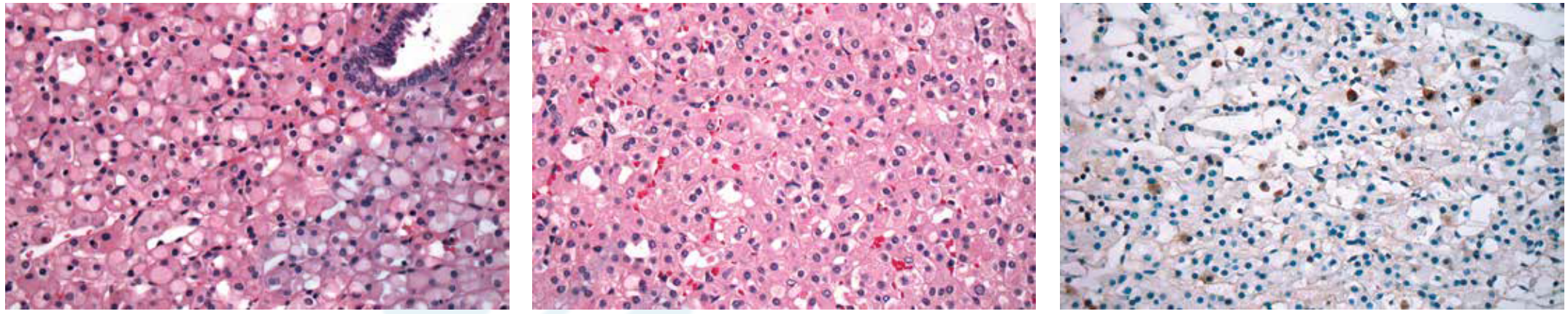


Fig. 1.80 Epithelioid angiomyolipoma. **A** This tumour shows a pattern of carcinoma-like growth; the tumour is composed of large polygonal cells with dense, deeply eosinophilic cytoplasm and atypical nuclei. **B** Strong immunoexpression of cathepsin k.

- **Succinate dehydrogenase (SDH) deficient renal carcinoma 琥珀酸脱氢酶缺陷型肾癌**



The tumour is well circumscribed but may entrap benign tubules; cytoplasmic vacuoles containing eosinophilic fluid are a distinctive feature but may be sparse. The cytoplasm of these tumours commonly has a flocculent quality.
The tumour shows complete loss of immunohistochemical staining for SDHB, whereas scattered mast and inflammatory cells show preserved staining and act as an internal positive control.

- **Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC/FH-deficient RCC**

遗传性平滑肌瘤病和肾细胞癌综合征相关性肾细胞癌/延胡索酸水合酶缺陷型肾癌

germline *FH* mutations
papillary growth pattern; The nuclei contain inclusion-like nucleoli with perinucleolar clearing

IHC：
loss of fumarate hydratase (FH);
overexpression of modified cysteine – S(2succino)cysteine

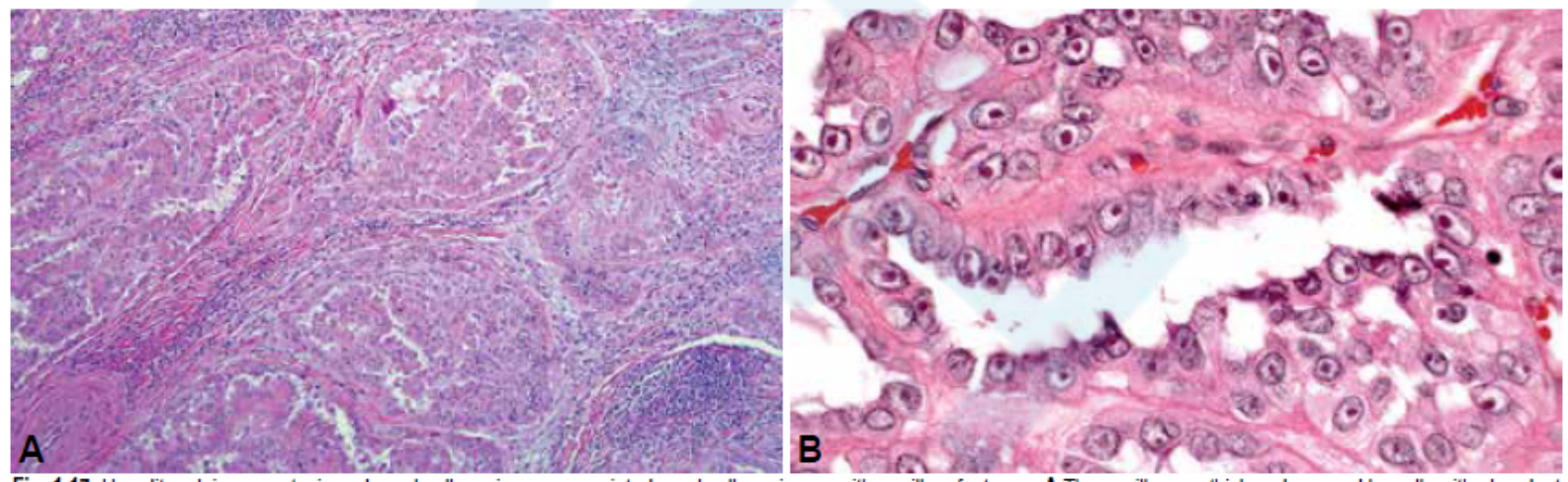


Fig. 1.17 Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma with papillary features. **A** The papillae are thick and covered by cells with abundant eosinophilic cytoplasm. **B** Higher magnification shows cells with large nuclei, prominent eosinophilic nucleoli, and a clear perinucleolar halo, characteristic of this tumour.

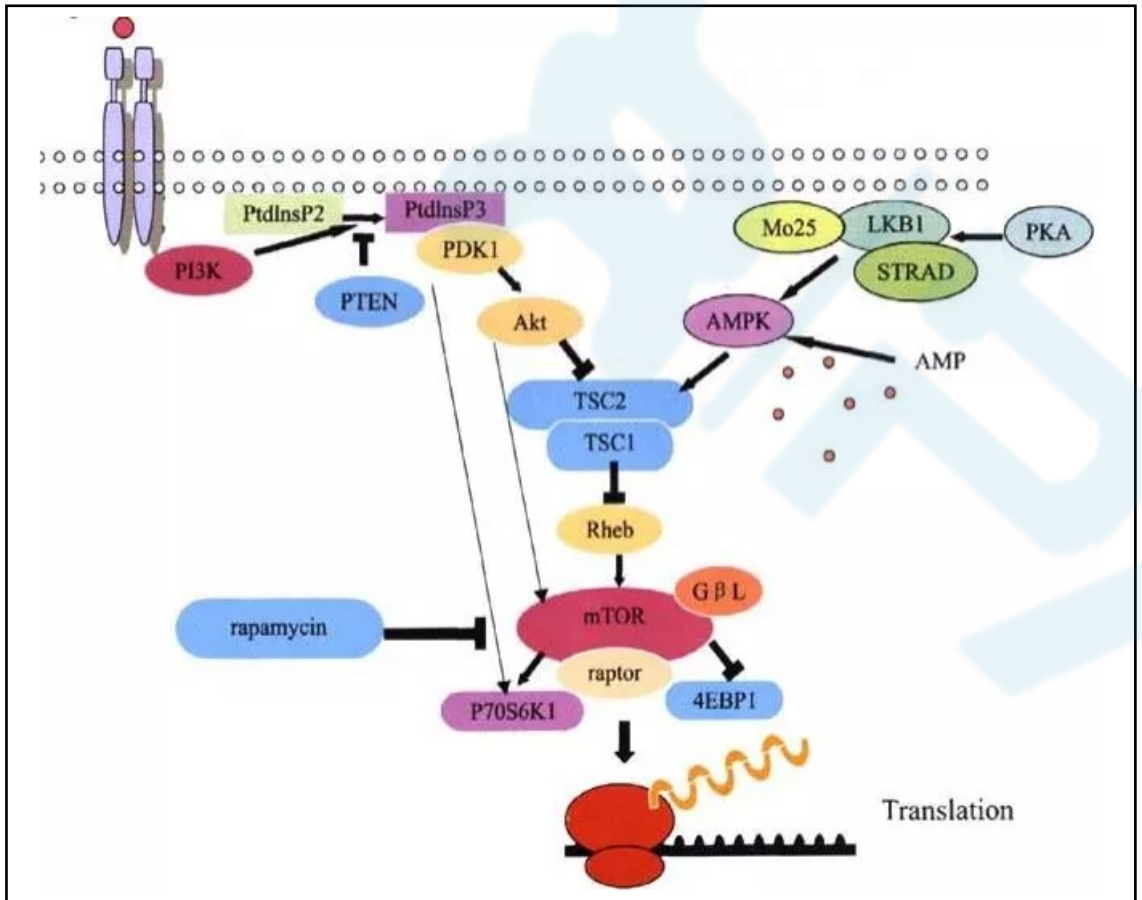
(2SC，一种改组的半胱氨酸，是因FH失活致延胡索酸异常富集而形成的产物)

Molecular analysis

- Of note, our NGS studies did not identify any **driver RCC-associated mutations** (VHL, PBRM1, BAP1, SETD2, MET, PTEN, TP53, FLCN, FH, SDH, TFE3, TFEB, and ALK)
- In addition, there was no loss of 3p which is seen in CCRCC or multiple chromosomal losses which is seen in CHRCC
- Molecular analysis demonstrated that the lesions in our study had mutations in either **TSC1, TSC2, or MTOR**

- molecular-targeted therapy
- a few case reports have demonstrated clinical benefit in using mTOR inhibitors to treat TSC-associated RCCs, including complete response in a case of sporadic, metastatic ESC RCC

经典信号通路：PI3K-AKT-mTOR



正常情况下，结节性脑硬化复合物-1(TSC-1)和TSC-2形成二聚体复合物，是小GTP酶Rheb的抑制剂，而Rheb是mTOR活化所必需的刺激蛋白，因此TSC-1 / TSC-2在正常情况下抑制mTOR的功能。当Akt活化后，它可磷酸化TSC-2的Ser939和Thr1462，抑制了TSC-1 / TSC-2复合物的形成，从而解除了对Rheb的抑制作用，使得mTOR信号通路被激活。

哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)是一种丝 / 苏氨酸蛋白激酶，其广泛存在于哺乳动物中，且进化十分保守，在调节细胞生长、增殖、调控细胞周期等多个方面起到重要作用

*MTOR*基因突变发生于多种肿瘤，包括：肾透明细胞癌、多形性胶质母细胞瘤、急性淋巴细胞白血病、肺腺癌、结直肠癌、子宫内膜样癌、前列腺癌、甲状腺乳头状癌

mTOR抑制剂（雷帕霉素）可与体内的FKBPI2结合形成FKBP-雷帕霉素复合物，再与mTOR的FRB区相结合，而抑制mTOR激酶的活性

Conclusion

- Our results support TSC/MTOR-associated neoplasms as a distinct group that exhibits heterogenous morphology, IHC staining, and possibly clinical behavior
- 3 groups：different architecture patterns; vimentin, CK7 and CK20 IHC staining
- NGS studies further demonstrated that these lesions were positive for mutations in TSC1, TSC2, or MTOR

- Previous eosinophilic renal tumors with unusual morphologies should be reevaluated with additional IHC stains and molecular studies to determine if they belong in this subgroup given the clinical implications

Thanks for your attention!

4.肾脏血管平滑肌腺瘤样肿瘤（renal angiomyoadenomatous tumor，RAT）

RAT是由上皮性小管和成熟的血管平滑肌瘤样间质构成的一种具有独特组织形态学特征的肾肿瘤，由Michal等[12]于2000年首次报道。此后，类似的病变在文献报道中曾被冠以各种名称，如“肾细胞癌伴有显著的血管平滑肌样增生”、“肾细胞癌伴有血管平滑肌瘤样间质”、“肾细胞癌伴有区域类似于RAT”以及“透明细胞乳头状肾细胞癌伴有血管平滑肌瘤样间质”。因此，关于RAT是否是一种疾病实体及其与透明细胞肾细胞癌和透明细胞（管状）乳头状肾细胞癌之间的关系一直争议不断。新近，两个独立小组的大宗病例研究结论表明，RAT与透明细胞（管状）乳头状肾细胞癌在临床表现、组织形态学、免疫表型以及分子遗传学特征上存在明显的相似和重叠，支持两者为同一肿瘤的不同形态学亚型[13,14]。RAT好发于中老年男性，中位年龄约60岁，临床上肿瘤多为偶然发现，少数表现为腹痛或血尿，偶尔发生于终末期肾疾病（ESRD）。大体上，RAT直径较小，从1.0～3.5 cm不等，切面实性为主，可见不同程度的囊性变，常见厚的纤维性假包膜。RAT的镜下表现取决于上皮与间质的比例，后者的比例有时可达95%。肿瘤周边一般为厚的致密的平滑肌束，平滑肌细胞分化成熟，具有明显的嗜酸性胞质，常见厚薄不等的血管性间质。肿瘤的中央为上皮成分，具有透明或弱嗜酸性胞质，排列成致密的腺泡/小管或大小不等的囊肿包被于致密的血管平滑肌瘤样间质之中，囊肿内可见突向囊腔的分支乳头状结构（图4）。上皮细胞的核级别低，一般为Fuhrman 1级或2级，偶尔可见细胞核远离小管的基底部朝向腔面分布，形成类似于分泌期子宫内膜的核下空泡。免疫表型特征，上皮细胞弥漫表达PAX8、CK7、碳酸酐酶Ⅳ（CAⅣ）、波形蛋白以及高相对分子质量角蛋白（34βE12），局灶或弱表达CD10，不表达肾细胞癌抗原（RCCm）和α–甲酰基辅酶A消旋酶（AMACR）；血管平滑肌样间质弥漫表达SMA和结蛋白，不表达HMB45、Melan A以及ER和PR。分子遗传学研究表明RAT无透明细胞肾细胞癌常见的第3号染色体短臂缺失和乳头状肾细胞癌常见的第7号和第17号染色体的三体性以及Y染色体的丢失。RAT在生物学行为上是一种惰性肿瘤，目前所报道的病例在随访中均未见肿瘤复发或转移的证据[13,14]。

- **ALK rearrangement–associated renal cell carcinoma**

	Clinical	Morphological	Molecular	Outcome
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	• *ALK-VCL* gene fusion	• Limited follow-up