肾细胞癌伴平滑肌瘤样间质具有TSC1、TSC2、MTOR和/或ELOC（TCEB1）的体细胞突变：18例散发性肿瘤的临床病理和分子特征分析支持其为一个独立肿瘤

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背景-2016WHO肾癌分类

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1
Papillary renal cell carcinoma	8255/1
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3
MiT Family translocation carcinomas	8311/3
Succinate dehydrogenase (SDH)-deficient renal carcinoma	8312/3
Mucinous tubular and spindle cell carcinoma	8480/3
Tubulocystic renal cell carcinoma	8316/3
Acquired cystic disease associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0

背景--Emerging/provisional renal cell carcinomas

肾细胞癌伴平滑肌瘤样间质： Renal Cell Carcinoma With Leiomyomatous Stroma，RCCLMS

Table 1.02 Features of emerging/provisional renal cell carcinomas

	Clinical	Morphological	Molecular	Outcome
Oncocytic renal cell carcinoma occurring after neuroblastoma	• Increased incidence of renal cell carcinoma among neuroblastoma survivors • Heterogeneous group, with some MiT family translocation renal cell carcinomas • One distinct oncocytic group with or without exposure to chemotherapy	• Solid, cystic, and papillary • Oncocytic cells with vacuoles and calcification • No distinctive immunohistochemistry	• No molecular marker	• Limited follow-up
Thyroid-like follicular renal cell carcinoma	• Broad age range • Slight female predominance	• 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	• *ALK-VCL* 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

背景-RCCLMS

- 第一个病例报告是在1993年由Canzonieri等人描述，该患者有血管平滑肌脂肪瘤，但没有结节性硬化综合征（TSC）病史。
- 从以往病例上看，RCCLMS由两种不同的成份混合而成：
  - ✓ (1) 一种是上皮成分，特征是上皮细胞具有低级别的核，胞浆清晰，形成巢状或管状结构（在某些情况下与局灶性乳头状和实性区域混合）
  - ✓ (2) 另一种是有突出的平滑肌和纤维间质成分

目的

- RCCLMS已被列为最新WHO肾上皮肿瘤的分类中，然而，该类型肿瘤病例少，对于它是一个不同的肿瘤分类还是一个形态重叠的RCCs仍存在争议。其与结节性硬化综合征（TSC）中发生的类似肿瘤的关系尚未完全阐明。
- 作者推测：除了ELOC（TCEB1）突变外，这些散发性肿瘤中的一些病例还可能存在TSC1/TSC2基因突变和/或MTOR通路基因的机制性靶点改变。

材料与方法

入选标准：

形态学特征包括：突出的结节状结构、富含透明细胞质的肿瘤细胞，呈分枝状的细长管状排列、局灶可见乳头状结构和血管平滑肌间质

免疫组化为CK7弥漫强阳性表达

与分子结果无关

最终选用18个RCCLMS作为研究对象。

材料与方法

病理分析：对每个肿瘤的上皮和间质特征进行评估

- **上皮特征**包括肿瘤细胞排列结构（巢、小管、乳头成分）、核特征（与基底膜相关的特殊极化）和细胞质特征（颜色、体积）。
- **间质特征**包括肿瘤周围是否存在厚的纤维平滑肌组织，平滑肌间质的数量（局灶性定义为肿瘤体积的<10%，中度为10%至50%，突出＞50%）；
- **脉管系统**（纤细，复杂的分支血管形态，以及其与间质相互作用特征（肿瘤周围存在炎症和含铁血黄素色素沉着的巨噬细胞）。

材料与方法

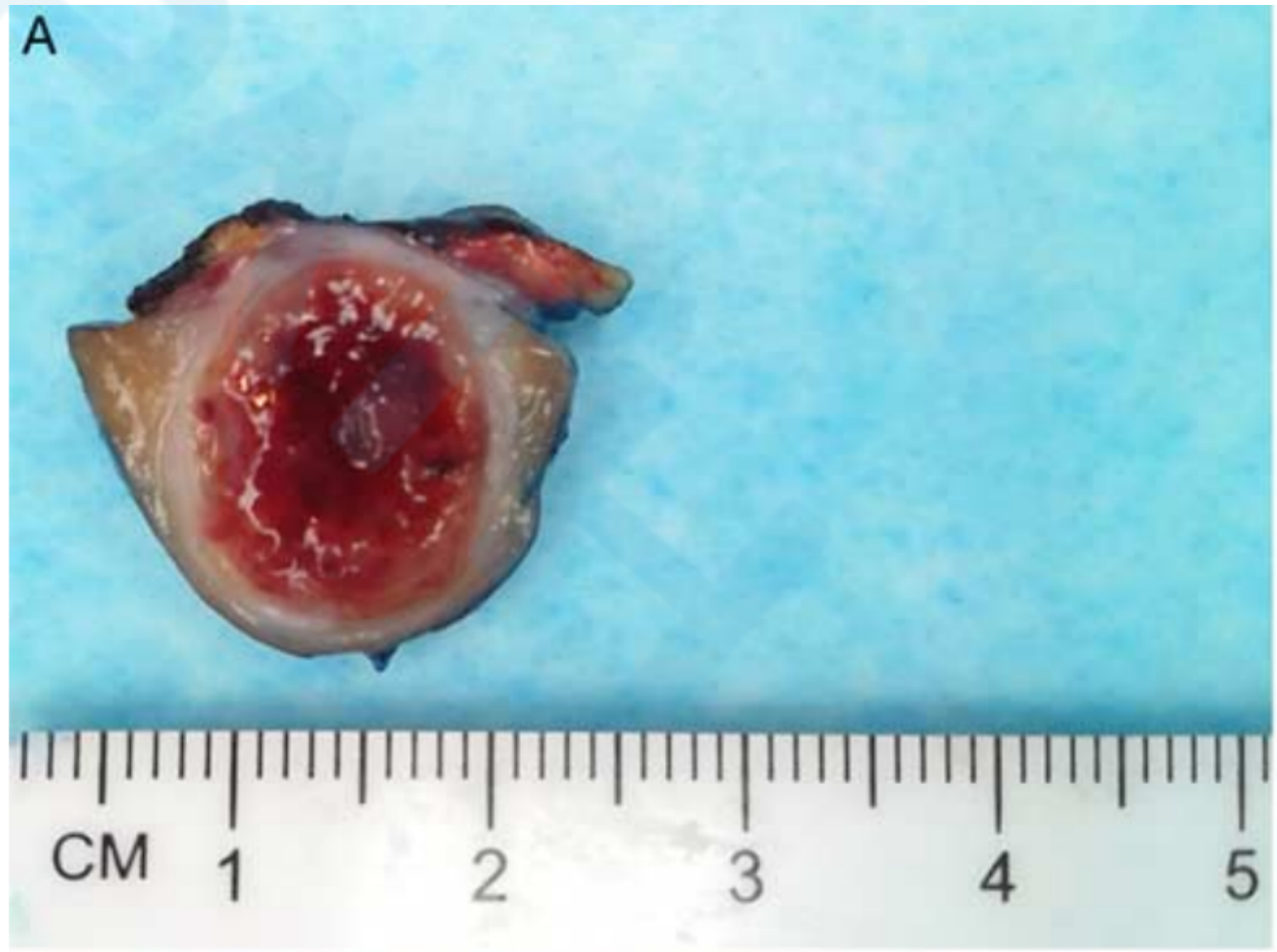
- 免疫组化染色：使用聚合物检测试剂盒，Ventana自动免疫染色仪进行IHC分析。一抗有CA9、CK7、CAM5.2、Des、CD10、α甲基酰基辅酶A消旋酶
- 分子分析：通过一种基于杂交捕获的二代测序（NGS）分析。

结果1：临床特征

- RCCLMS患者的平均年龄为52岁（33～69岁），男女比例为1:2。
- 患者表现为孤立性肾脏肿块，临床上出现血尿或影像学检查发现肿块或其他症状。
- 患者无肾癌既往史或家族史
- 所有患者在相同或对侧肾脏中也没有其他病变

结果2：病理特征

大体上，所有肿瘤都是孤立的，主要呈棕褐色/红色，界限分明，呈实性，似有一个纤维结缔组织包膜，肿瘤平均大小2.3cm（范围1.1～4.5cm）。



结果2：病理特征

- 镜下特征包括肿瘤细胞呈结节状分布，结节内瘤细胞呈细长且常有分支的小管状结构，核位于基底部，细胞质透明至轻度嗜酸性，由不等量的反应性平滑肌组织分隔。
- 围绕小管的腺泡塌陷（双相型）
- 可出现局灶性乳头状结构（39%），
- 瘤周淋巴细胞聚集（39%），含铁血黄素的巨噬细胞（33%）。

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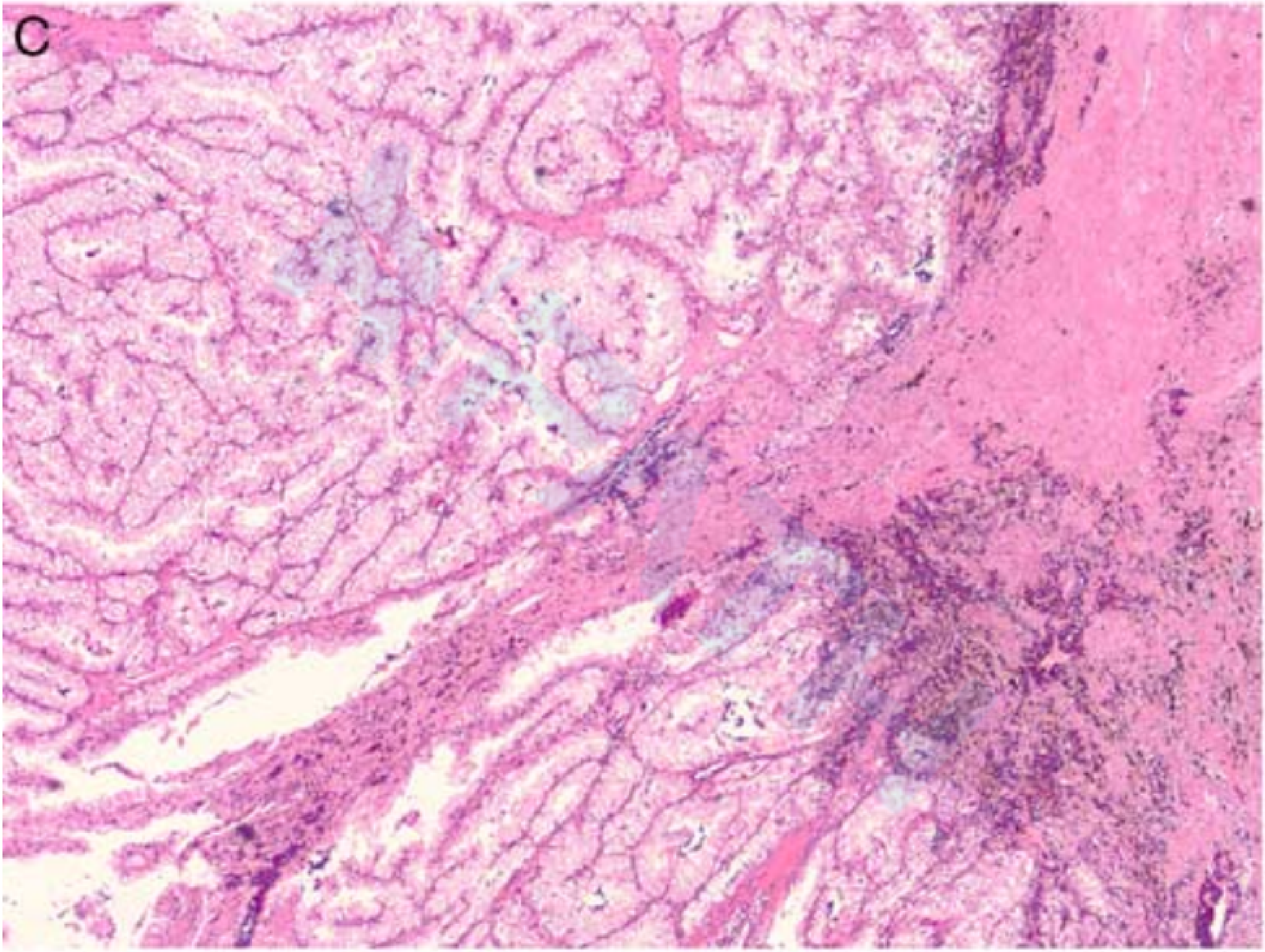
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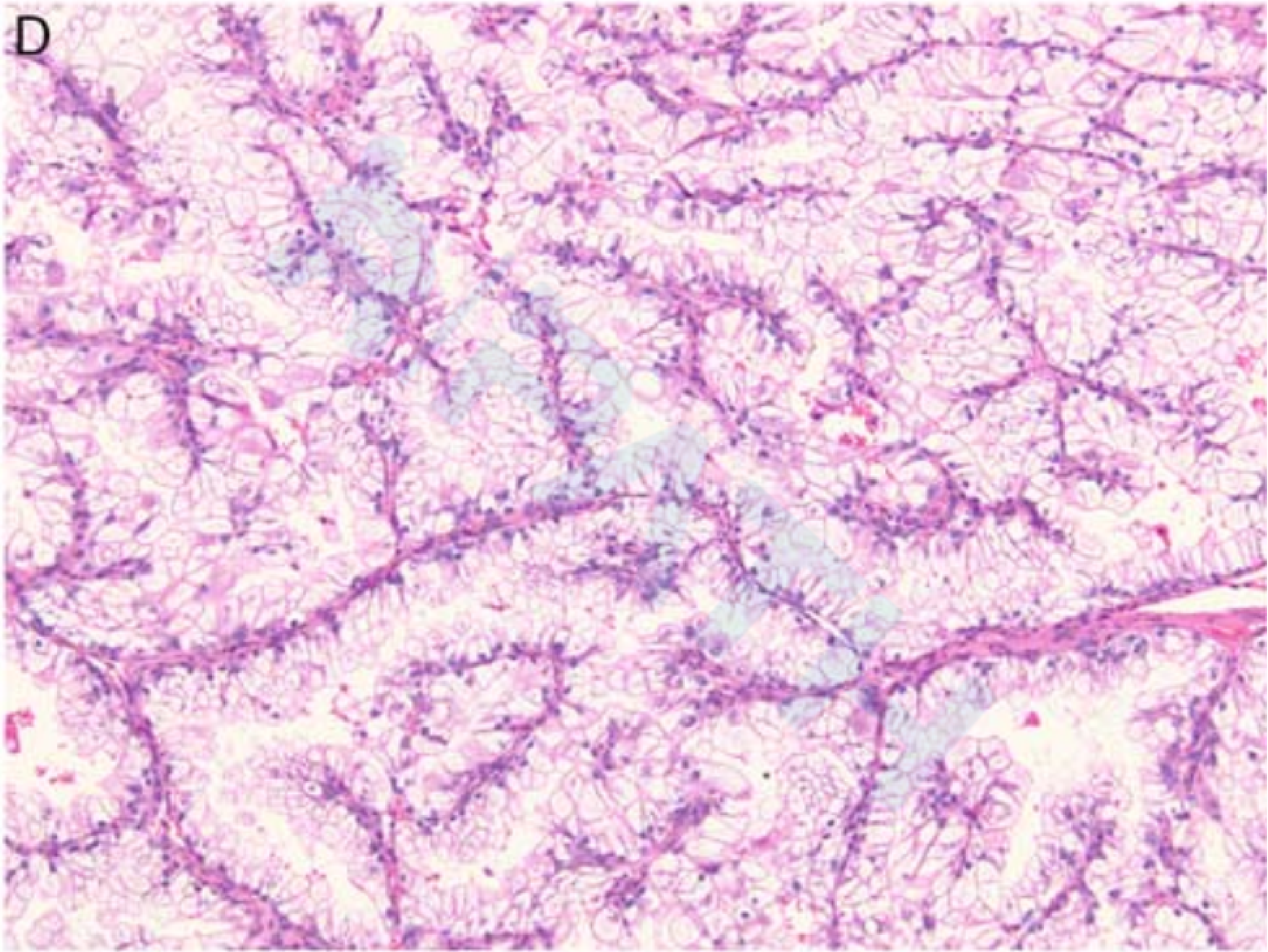
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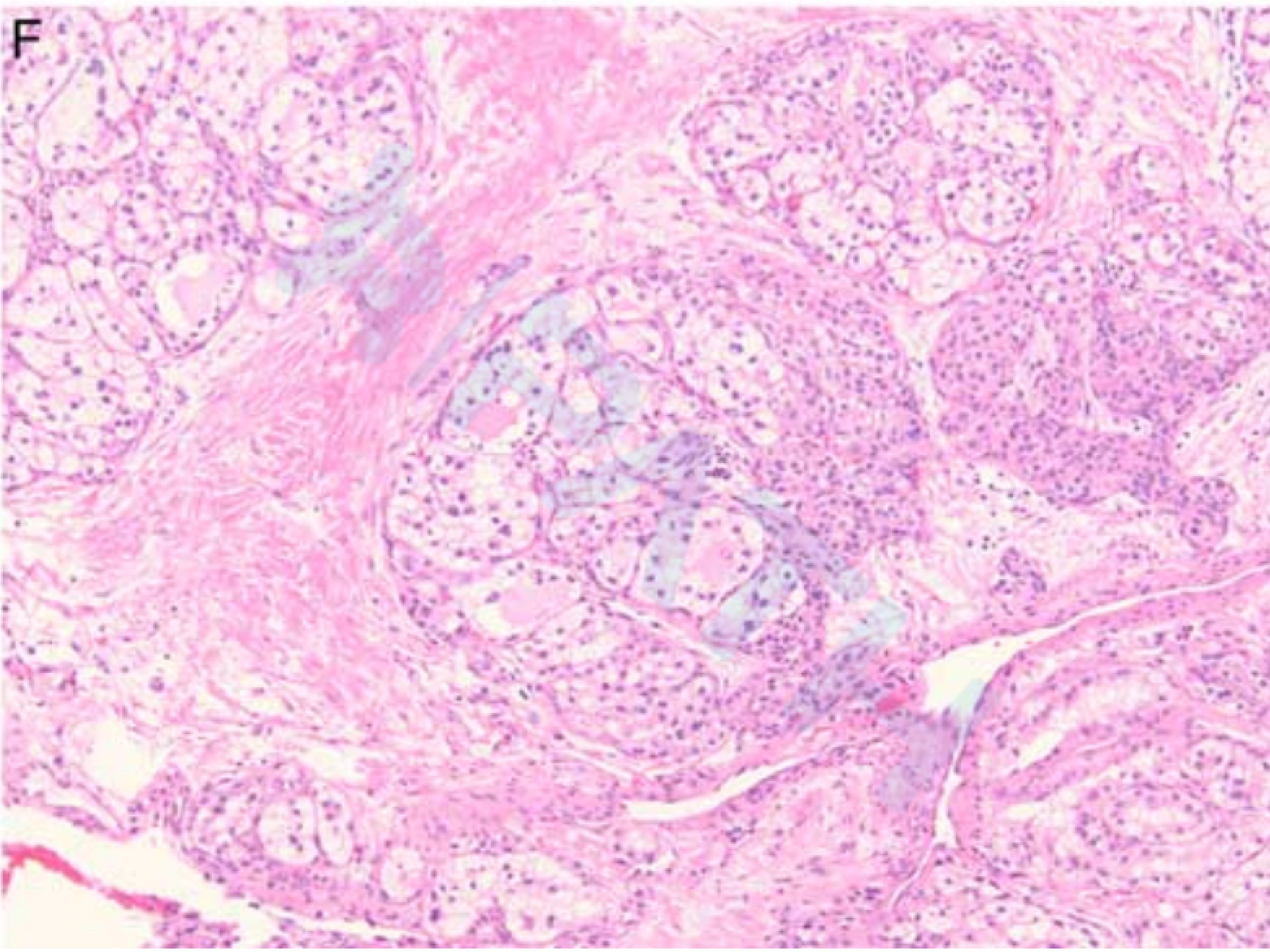
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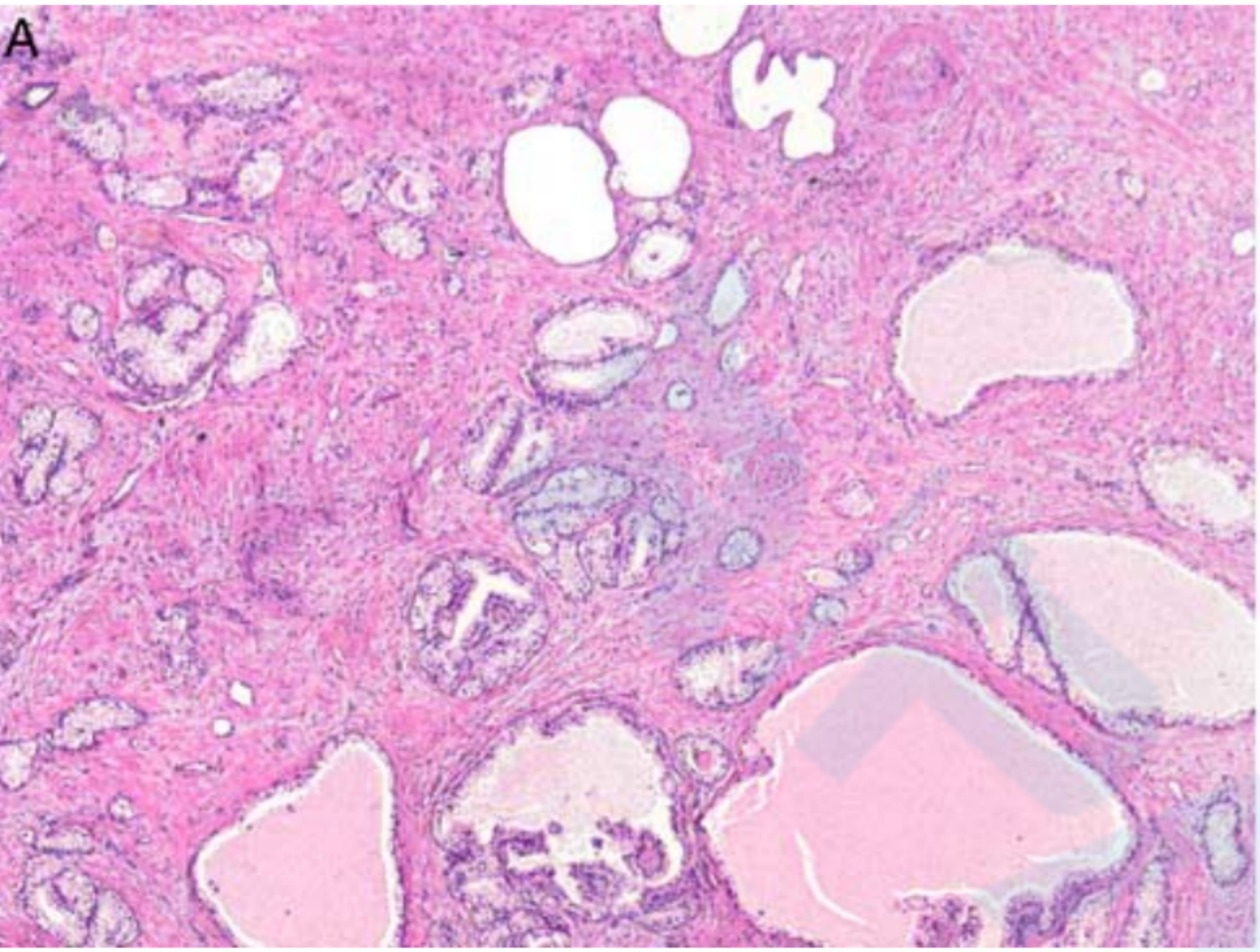
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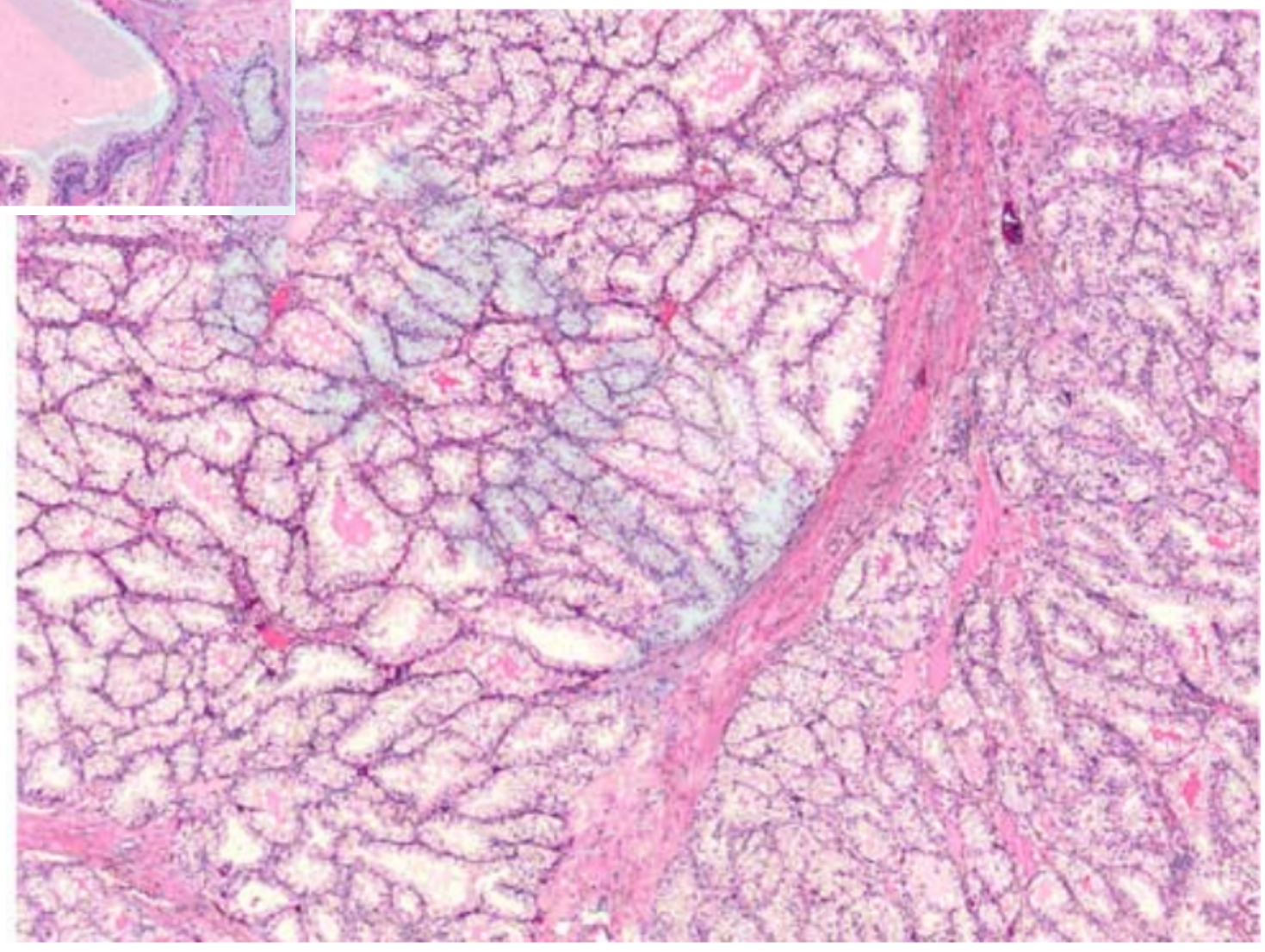

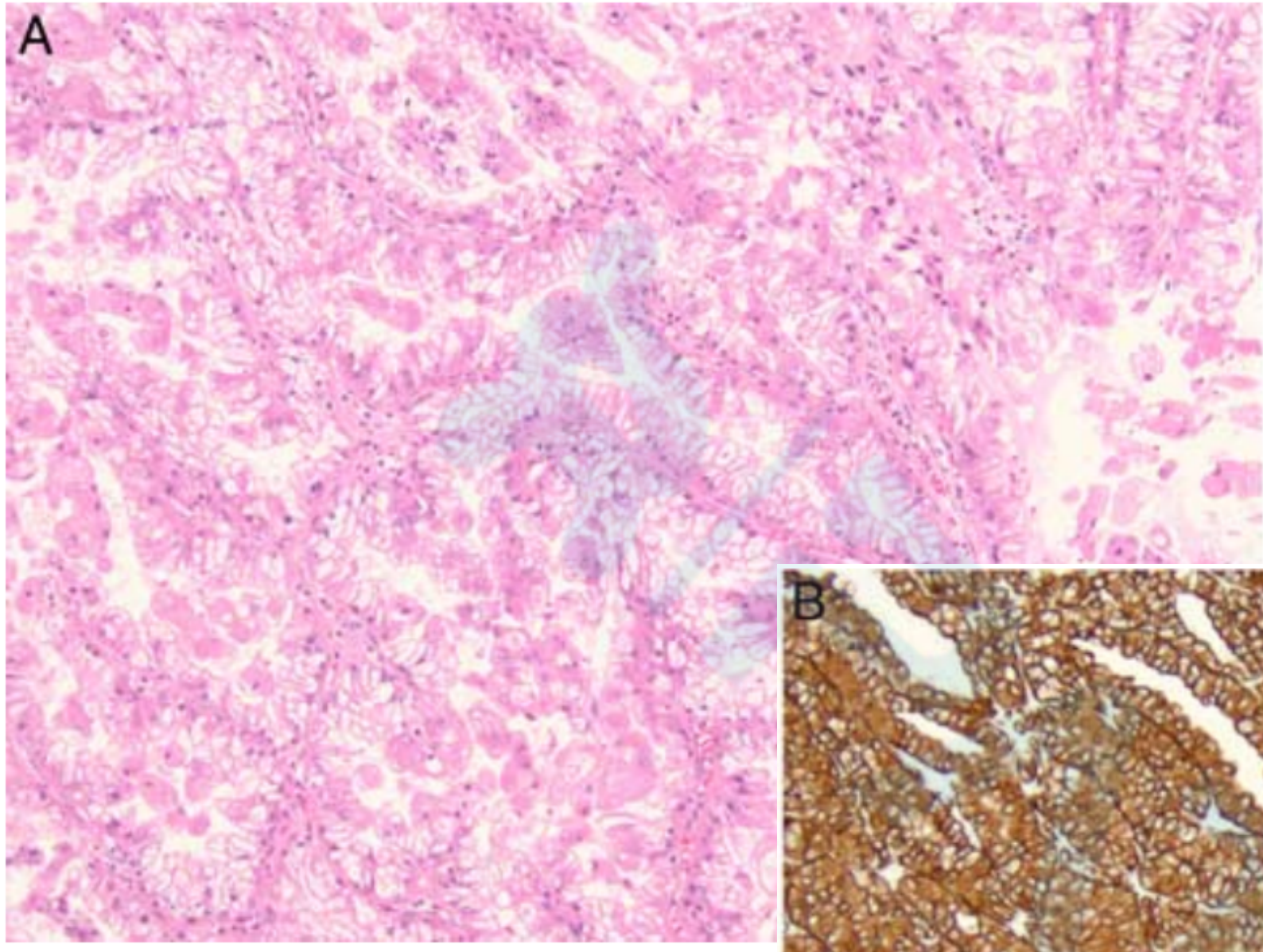
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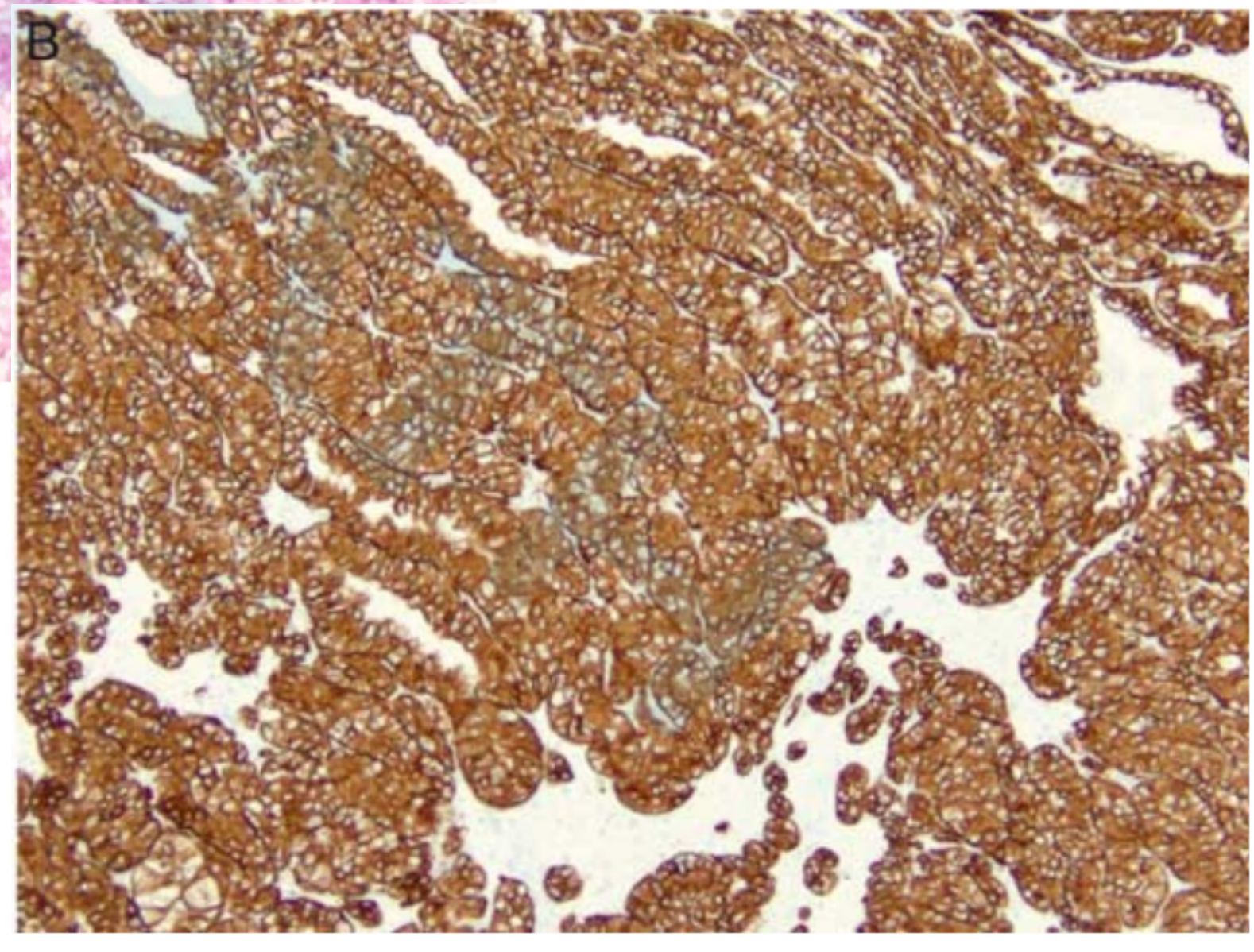
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临床病理资料

TABLE 1. The Clinicopathologic and Follow-up Information of 18 RCCLMS Cases

Case No.	Age (y)	Sex	Clinical Presentation	Surgery	Size (cm)	ISUP/WHO Grade	Stage	Status	Follow-up (mo)
1	NA	NA	NA	NA	NA	2	NA	LIF	NA
2	NA	NA	NA	NA	NA	2	NA	LIF	NA
3	NA	NA	NA	NA	NA	2	NA	LIF	NA
4	55	Female	Incidental	PN	2.3	2	NA	LIF	NA
5	68	Female	Incidental	RN	NA	3	T1a	NED	58
6	56	Female	Incidental	PN	2	3	T1b	NED	25
7	43	Male	Incidental	PN	1.5	2	T1a	NED	39
8	33	Female	Incidental	PN	1.4	2	T1a	NED	1
9	69	Female	Incidental	PN	2	2	T1a	NED	17
10	49	Male	Incidental	PN	1.3	2	T1a	NED	8
11	54	Female	Incidental	PN	1.5	2	T1a	NED	9
12	63	Male	Incidental	PN	3.5	2	T1a	NED	NA
13	41	Female	Incidental	Bx	NA	2	NA	ND	NA
14	68	Male	Incidental	PN	2.9	2	T1a	ND	31
15	36	Female	Incidental	PN	3	2	T1a	NED	12
16	45	Male	NA	PN	1.1	2	T1a	LIF	NA
17	37	Female	NA	RN	4.5	3	NA	LIF	NA
18	62	Female	Incidental	Bx	2.4	3	NA	NED	36

Bx indicates biopsy; LIF, lost in follow-up; NA, not available; ND, new diagnosis; NED, no evidence of disease; PN, partial nephrectomy; RN, radical nephrectomy.

52 1:2 2.3cm 2 级 pT1 25

结果3：镜下形态及免疫组化特征

TABLE 2. Important Microscopical and IHC Features of 18 RCCLMS Cases

	Microscopical Features							IHC Features				
Case No.	Elongated Tubules Lined by Voluminous Clear to Eosinophilic Cytoplasm	Branching of Tubules	Thick Fibromuscular Tissue at the Periphery of the Tumor	Amount of Smooth Muscle Dissecting Tumor Nodules	Focally Prominent Papillary Architecture	Foci of Collapsed Acini	Peritumoral Lymphoid Aggregates	Diffuse CK7	CAM5.2	CA9	CD10	Desmin
1	+ve	+ve	−ve	Prominent	−ve	−ve	−ve	+ve	NA	NA	NA	NA
2	+ve	+ve	+ve	Moderate	−ve	+ve	+ve	+ve	NA	NA	NA	NA
3	+ve	+ve	+ve	Focal	−ve	−ve	−ve	+ve	NA	NA	NA	NA
4	+ve	+ve	+ve	Prominent	−ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
5	+ve	+ve	+ve	Focal	+ve	−ve	+ve	+ve	+ve	+ve-Cup	+ve	+ve
6	+ve	+ve	+ve	Prominent	+ve	+ve	−ve	+ve	+ve	+ve	+ve	+ve
7	+ve	+ve	+ve	Prominent	−ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
8	+ve	+ve	+ve	Focal	−ve	+ve	−ve	+ve	+ve	+ve	+ve	+ve
9	+ve	+ve	+ve	Moderate	−ve	+ve	+ve	+ve	+ve	+ve	NA	+ve
10	+ve	+ve	+ve	Moderate	−ve	+ve	−ve	+ve	+ve	+ve	NA	+ve
11	+ve	+ve	+ve	Focal	−ve	−ve	+ve	+ve	+ve	+ve	NA	+ve
12	+ve	+ve	+ve	Moderate	−ve	−ve	−ve	+ve	NA	NA	+ve	NA
13	+ve	+ve	−ve	Focal	−ve	−ve	−ve	+ve	+ve	NA	NA	NA
14	+ve	−ve	+ve	Focal	−ve	−ve	−ve	+ve	NA	NA	+ve	+ve
15	+ve	+ve	+ve	Moderate	+ve	−ve	−ve	+ve	NA	+ve-Cup	+ve	NA
16	+ve	+ve	+ve	Moderate	+ve	−ve	−ve	+ve	NA	+ve-Cup	+ve	NA
17	+ve	+ve	+ve	Focal	+ve	−ve	−ve	+ve	+ve	+ve-Cup	+ve	NA
18	+ve	−ve	+ve	Moderate	+ve	−ve	−ve	+ve	+ve	NA	+ve	NA

Cup indicates positive in a “cup-shaped” membranous staining pattern; NA, not available.

结果4：分子特征

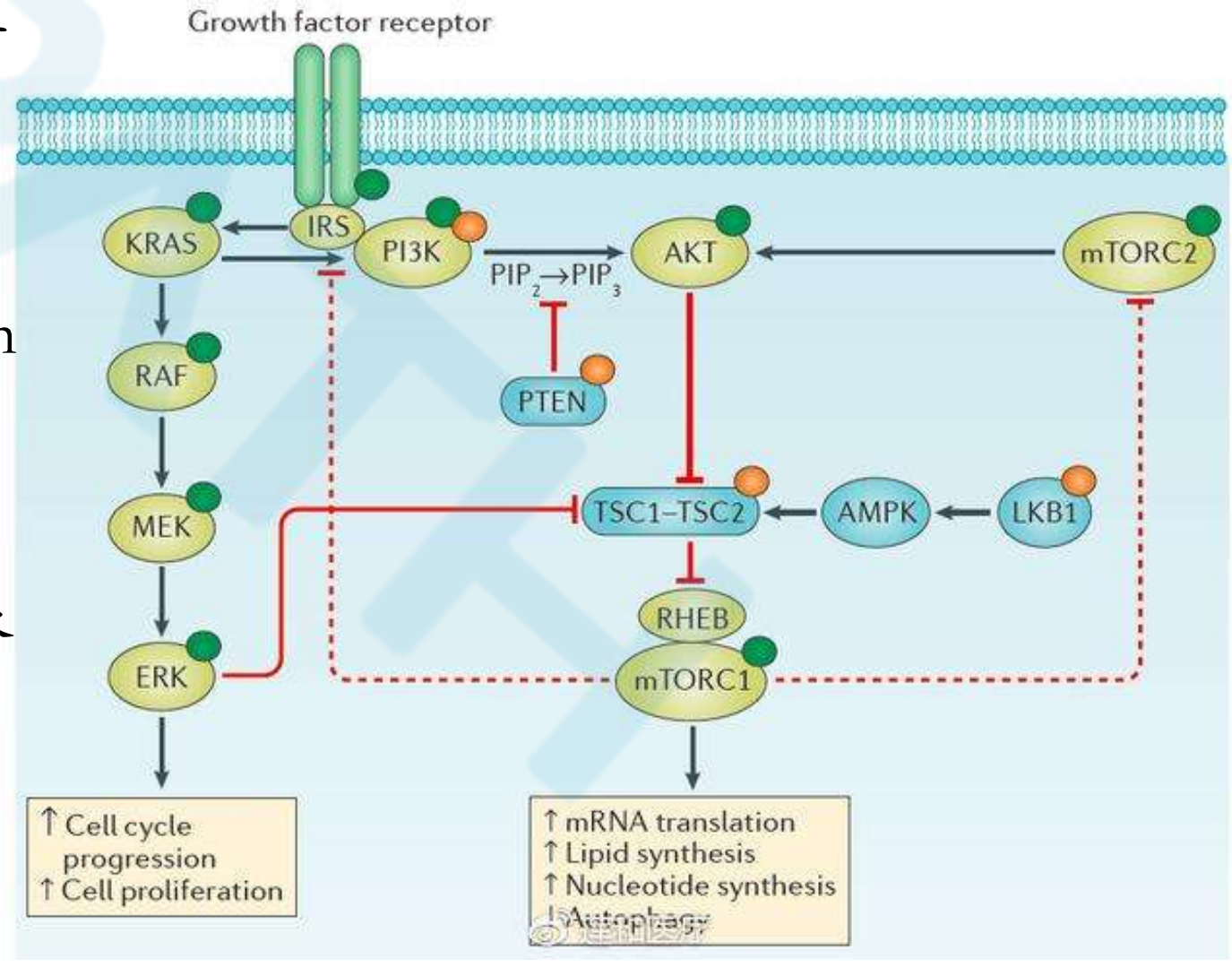
TABLE 3. Summary of Molecular Alterations of 14 RCCLMS Cases

Molecular Test Case No.	Monosomy 8	Gene Mutations
1	Not identified	*TSC2* Pro670Leu
5	Not identified	TCS2 Glu393Ter *TSC2* Arg1713His
6	Not identified	*MTOR* Leu2427Gln
14	Not identified	*MTOR* lle2500Phe
15	Not identified	*TSC1* Gln842Ter
17	Not identified	*TSC1* Leu388Pro
21	Not identified	*MTOR* Tyr1450Asp
22	Present	*ELOC* (*TCEB1*) Tyr79Cys
23	Not identified	*MTOR* Tyr1950_Trp1456del
26	Not identified	*MTOR* Ser2215Tyr
27	Not identified	*TSC2* Thr783Ser
31	Not identified	*TSC1* Glu663Ter *TSC1* Thr360Asn *TSC2* Ala460Thr
33	Present	*TSC1* Glu846fs *ELOC* (*TCEB1*) Pro97del
34	Not identified	*MTOR* Asn382Ser

在RCCLMS中发现了TSC1，TSC2，MTOR和/或ELOC（TCEB1）基因突变
部分病例出现8号染色体的单倍体

讨论1：TSC1及TSC2信号通路

- 肿瘤抑制物TSC1和TSC2基因是mTOR complex 1信号通路的负调控因子。它们分别编码蛋白质hamartin和tuberin，它们相互作用并形成一个异二聚体，抑制MTORC1的激活，MTORC1是营养丰富的生长因子诱导的信号传导的主要调节因子。
- TSC1和TSC2蛋白产物还负责通过RHEB/MTORC1/4E-BP1通路灭活H1F1α。
- ELOC基因编码蛋白质elongin C，一种与VHL形成复合物的蛋白质。elongin C的丢失导致VHL复合物不能降解为H1F1α。未降解的H1F1α最终激活了许多导致肿瘤发生的基因的转录。



讨论2: TSC、TCEB1相关的肾细胞癌

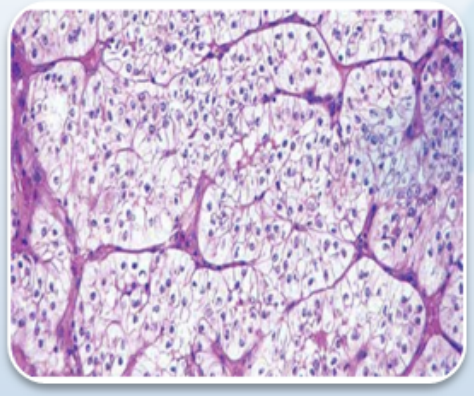
TSC相关肾细胞癌

- Guo等报道了TSC患者出现了3种不同的RCC形态学特征，其中30%具有类似于先前称为“RAT”或“具有平滑肌基质的RCC”的肿瘤的特征。
- 这些肿瘤的形态学特征是明显的结节状结构，肿瘤细胞具有丰富的透明细胞质，呈分枝状、细长的管状排列，并伴有平滑肌基质。部分病例可见局灶性乳头状结构，CK7呈弥漫性阳性。

TCEB1突变肾细胞癌

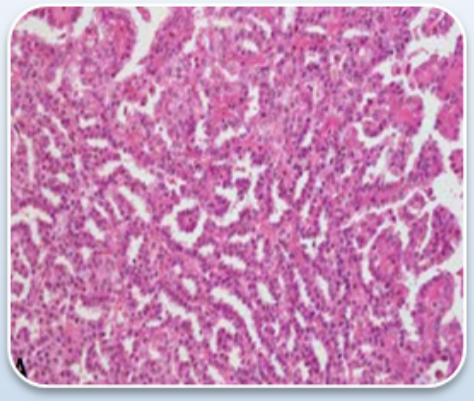
- Hakimi等人描述了一组散发的类似肿瘤，其特征是TCEB1（现在称为ELOC）中的热点突变，同时丢失了8号染色体（8号单体性）。
- 所有TCEB1突变的肿瘤具有共同特征，包括厚纤维平滑肌穿插在肿瘤细胞间将其分割成结节状；具有大量细胞质透明的细胞以及与CCRCC样腺泡相关的区域具有折叠的管状和局灶性乳头状结构。

讨论3:鉴别诊断



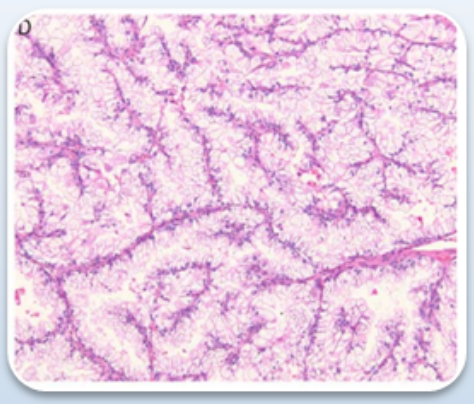
CCRCC

- 紧密排列的透明的细胞巢内衬“分支状”血管
- CK7不表达
- VHL基因突变



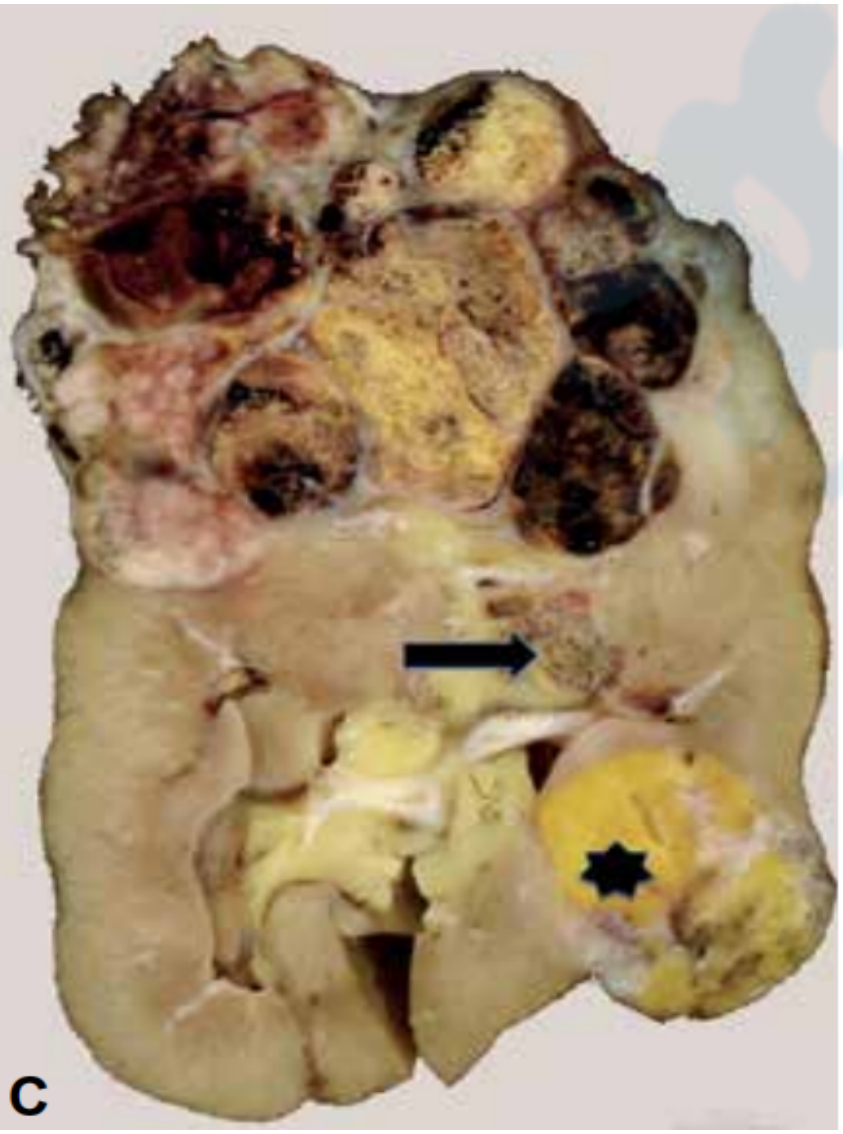
CCPRCC

- 紧密排列的管状-乳头状结构，胞浆内空泡位于顶端，胞质不透亮，细胞核离开基底部
- CK7弥漫强阳性
- 7、17号染色体的多倍体，Y染色体的缺失



RCCLMS

- 结节状、细长分支的乳头状小管结构、透亮至轻度嗜酸的胞浆，被反应性的平滑肌组织分隔。
- CK7弥漫强阳，
- TSC1/TSC2, mTOR, 和/或TCEB1突变，无VHL基因突变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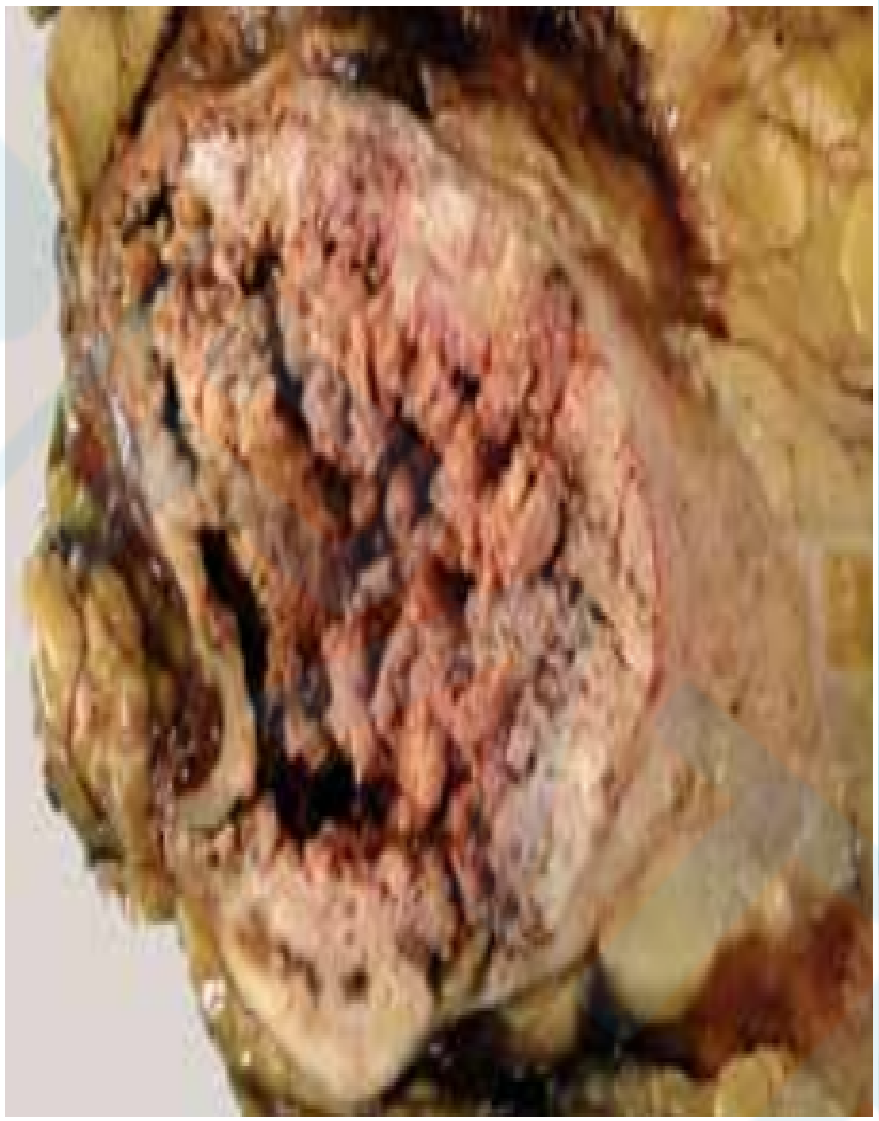

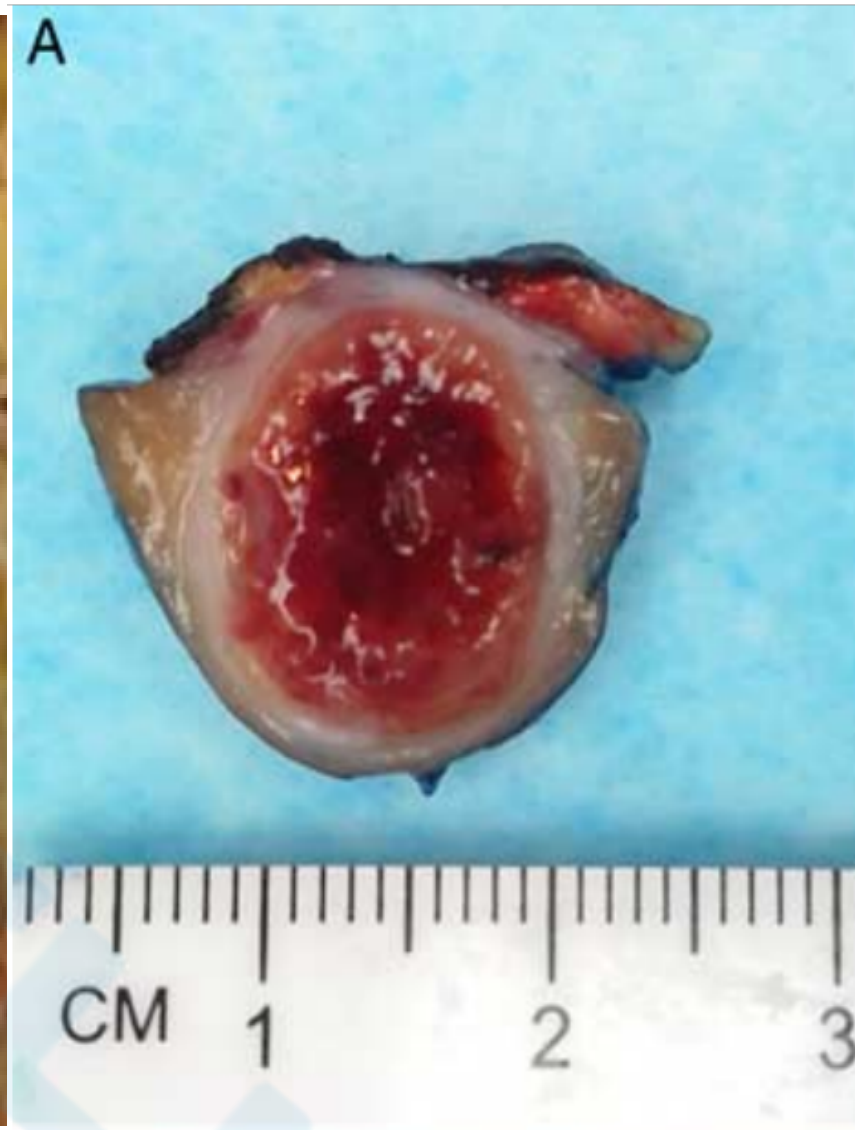
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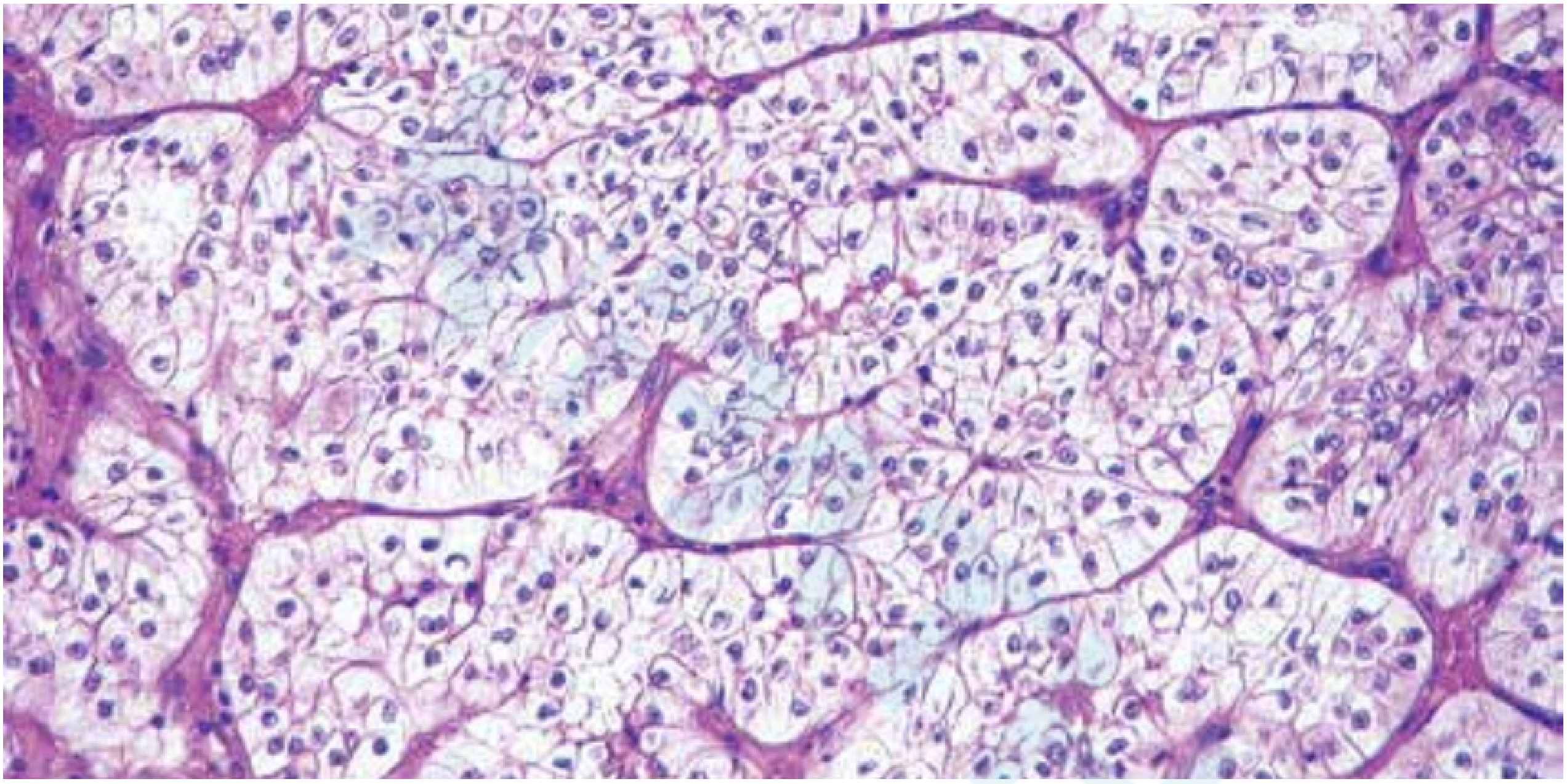

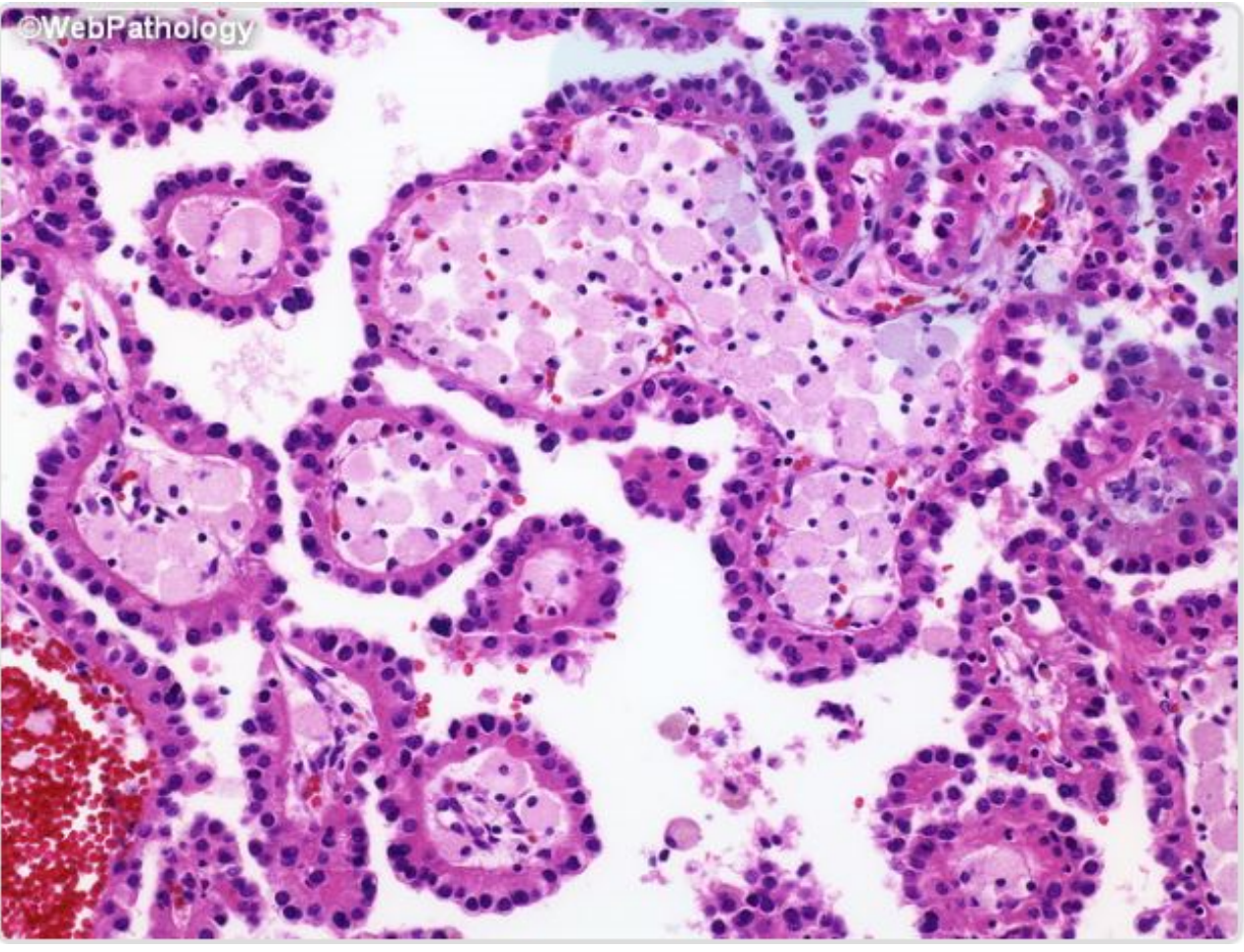
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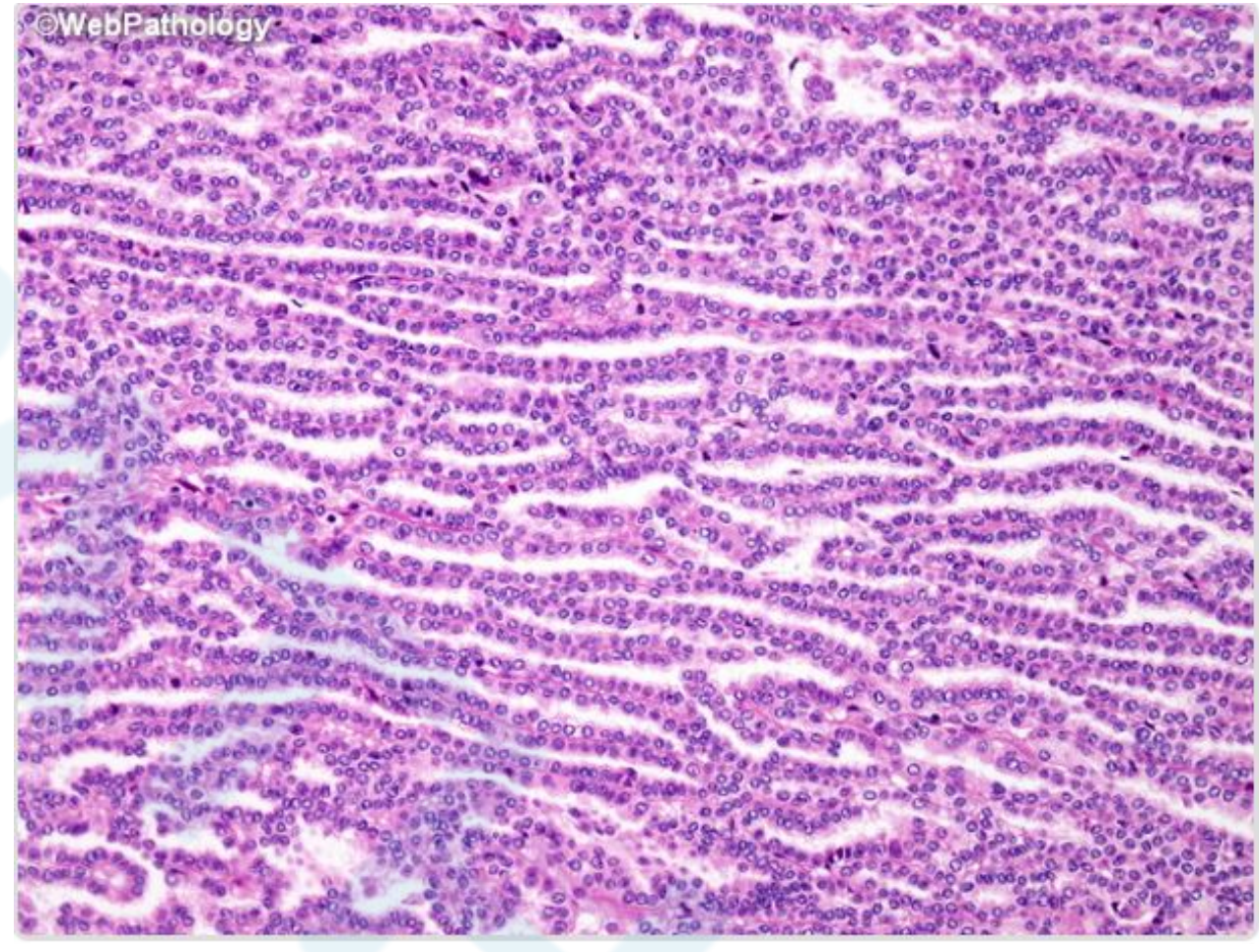
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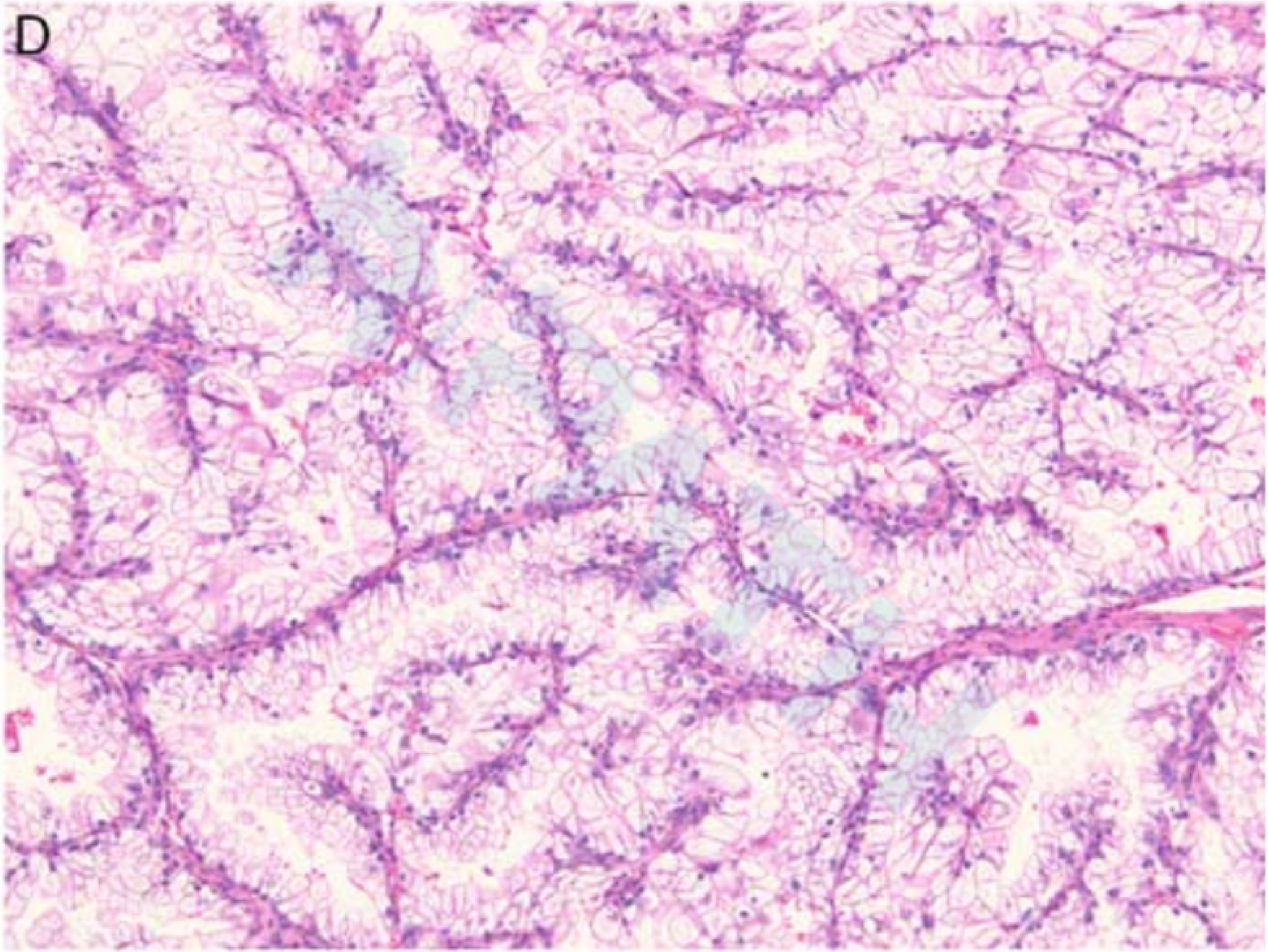

总结

- RCCLMS是RCC的一种新亚型，具有独特的形态学，免疫组化和分子特征
- RCCLMS具有TSC1，TSC2，MTOR和/或ELOC（TCEB1）的突变，并且缺乏VHL基因突变或其他与RCC常见组织学亚型相关的特征性拷贝数改变
- RCCLMS与TSC相关肾癌的相同亚型属于同一个肾肿瘤家族。

致谢：感谢范林妮老师的悉心指导

感谢西京医院病理科同仁的关怀

THANK YOU