

BCOR Overexpression in Renal Malignant

Solitary Fibrous Tumors

A Close Mimic of Clear Cell Sarcoma of Kidney

Pedram Argani, MD,* Yu-Chien Kao, MD,† Lei Zhang, MD,‡ Yun-Shao Sung, MS,‡ Rita Alaggio, MD, §

David Swanson, BSc, // Andres Matoso, MD,* Brendan C. Dickson, MD, // and Cristina R. Antonescu, MD‡

汇 报 人：谭凤梅

指 导 老 师：郭双平

2019. 7. 3

1

背 景

2

目 的

3

材料和方法

4

结 果

5

讨 论

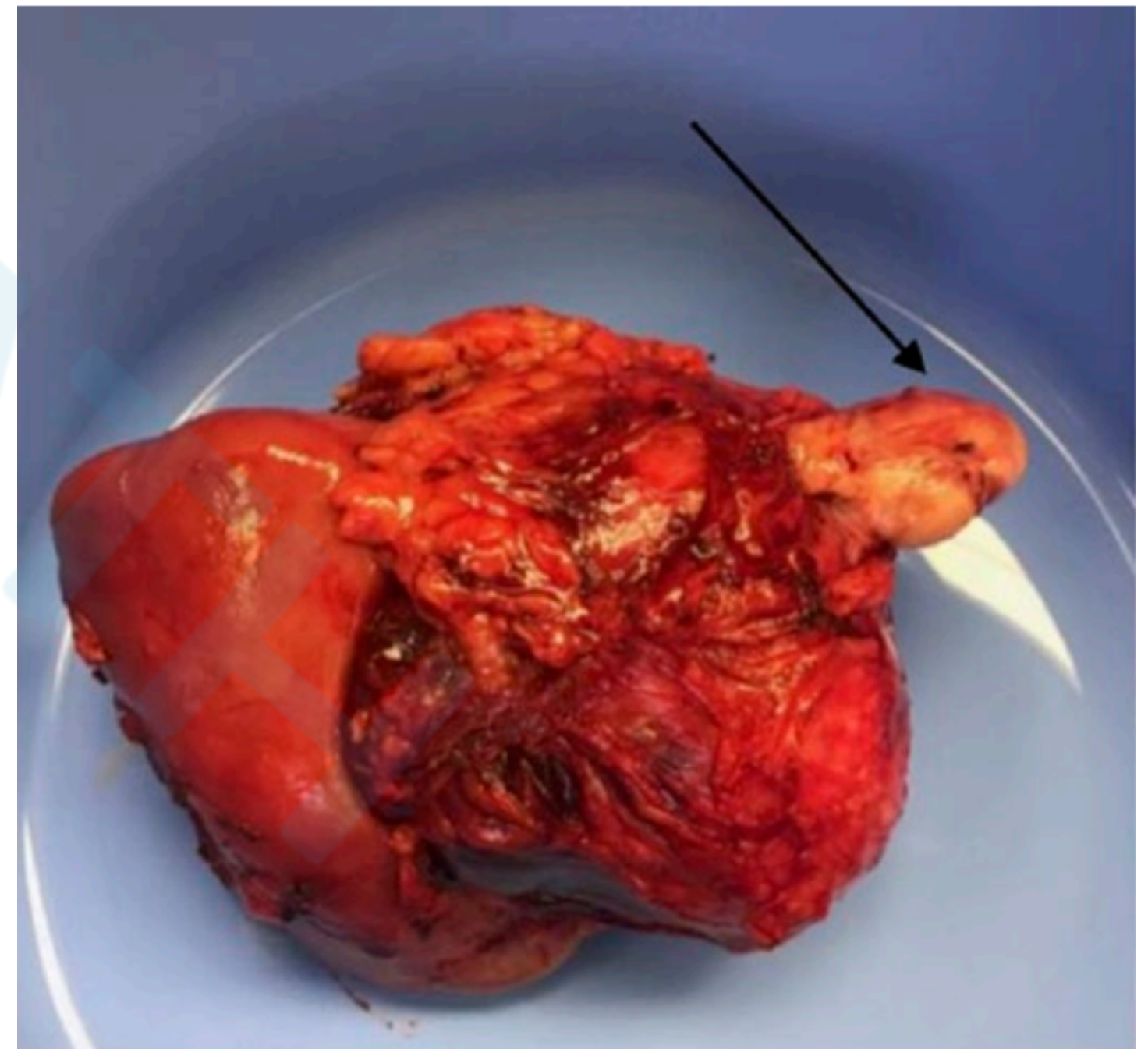
恶性孤立性纤维性肿瘤 (malignant solitary fibrous tumors, MSFT)

定义：是一种好发于胸膜的纤维母细胞性肿瘤，瘤细胞具有CD34+树突状间质细胞分化

【ICD-O编码】 8815/3

临床表现：年龄19-85岁，高峰40-60岁，女性略多见，好发于胸膜，侵袭性生长

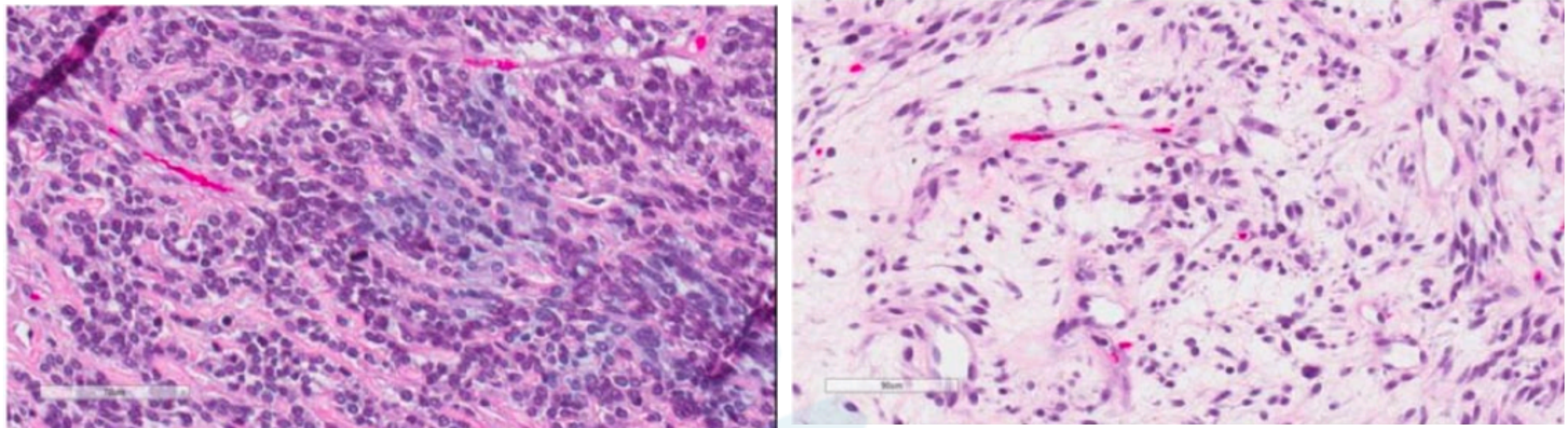
大体：肿块呈圆形或卵圆形，常>10cm，切面鱼肉状，可伴有出血、囊性变及坏死



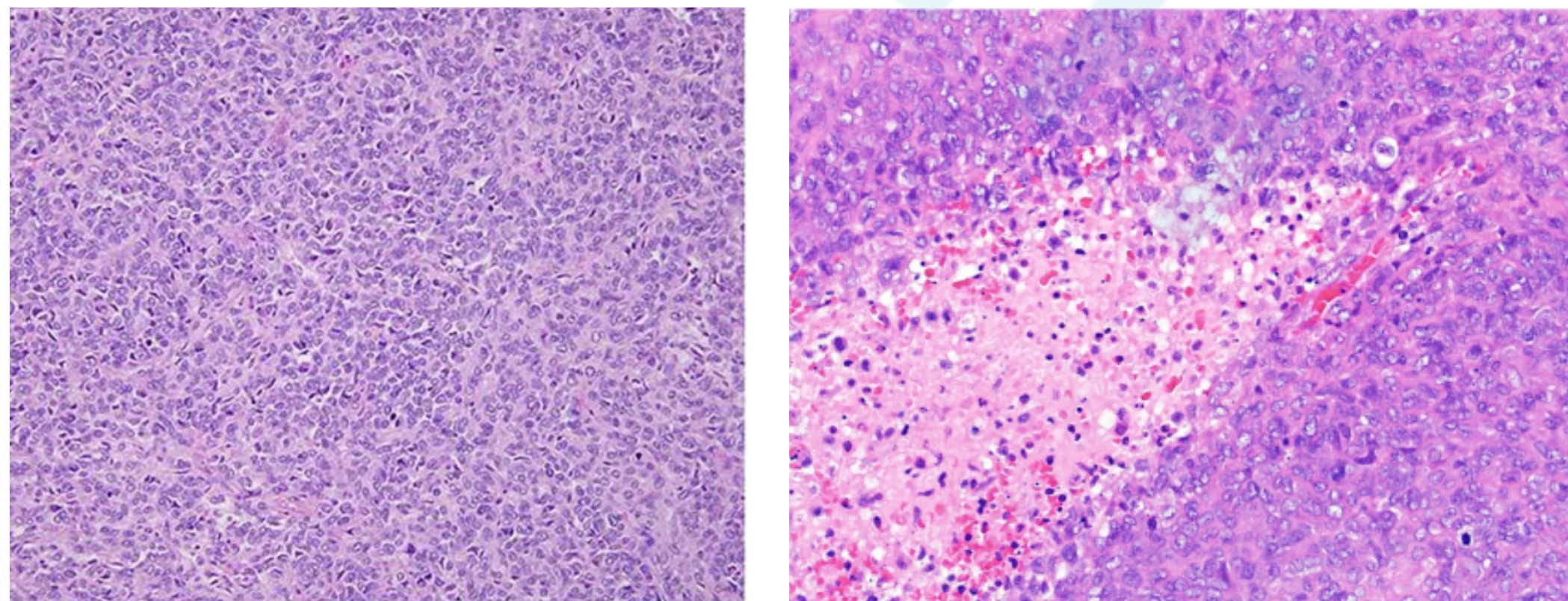
Hertz, A. M., Childers, C. K. M. I. (2018). *Malignant Solitary Fibrous Tumor of the Renal Vein Presenting as a Giant Renal Artery Aneurysm: A Case Report and Review of Literature. International Journal of Surgical Pathology*

MSFT镜下表现:

- 1) 典型SFT病理特征: ①瘤细胞呈梭形或卵圆形; ②细胞密集区与稀疏区相间;
③“无结构样”生长模式; ④“鹿角样”玻变血管; ⑤瘢痕疙瘩样胶原



- 2) MSFT病理诊断标准: ①细胞丰富密集; ②细胞异型性明显; ③核分裂象
 ≥ 4 个/10HPF; ④肿瘤体积大; ⑤浸润性边缘; ⑥坏死



MSFT

免疫组化： bcl-2 、 CD99和STAT6阳性， 灶性或弱阳性表达actin和desmin， CD34在MSFT中可失表达

基因： 最常见的是NAB2外显子4与STAT6外显子2/3基因融合， NAB2外显子6/7与STAT6外显子16/17基因融合（少见）

预后： 具有明显的侵袭性， 局部复发和转移率高

肾透明细胞肉瘤（clear cell sarcoma of the kidney, CCSK）

定义：起源于原始间胚叶细胞，无上皮分化能力，因镜下肿瘤细胞胞质和胞核均为透明空泡样而得名

流行病学：十分罕见，占儿童肾脏恶性肿瘤的3%左右。该病以前归为肾母细胞瘤的一种预后不良的亚型，1970年由 Kidd 首先报道该肿瘤与肾母细胞瘤有差别而成为独立类型。常发生骨转移 (40%~60%)，故又有学者称之为儿童骨转移性肿瘤

【ICD-O编码】 8964/3

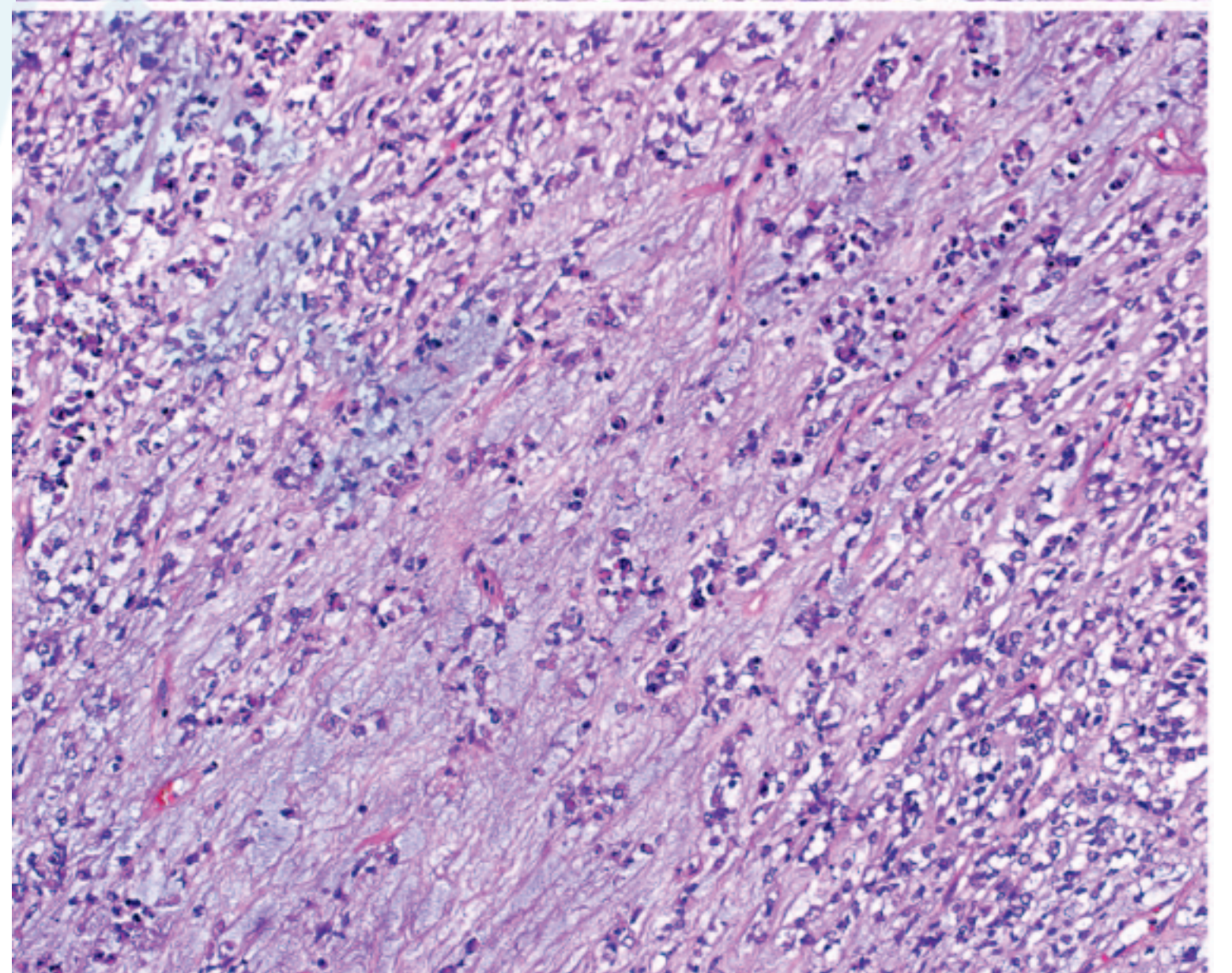
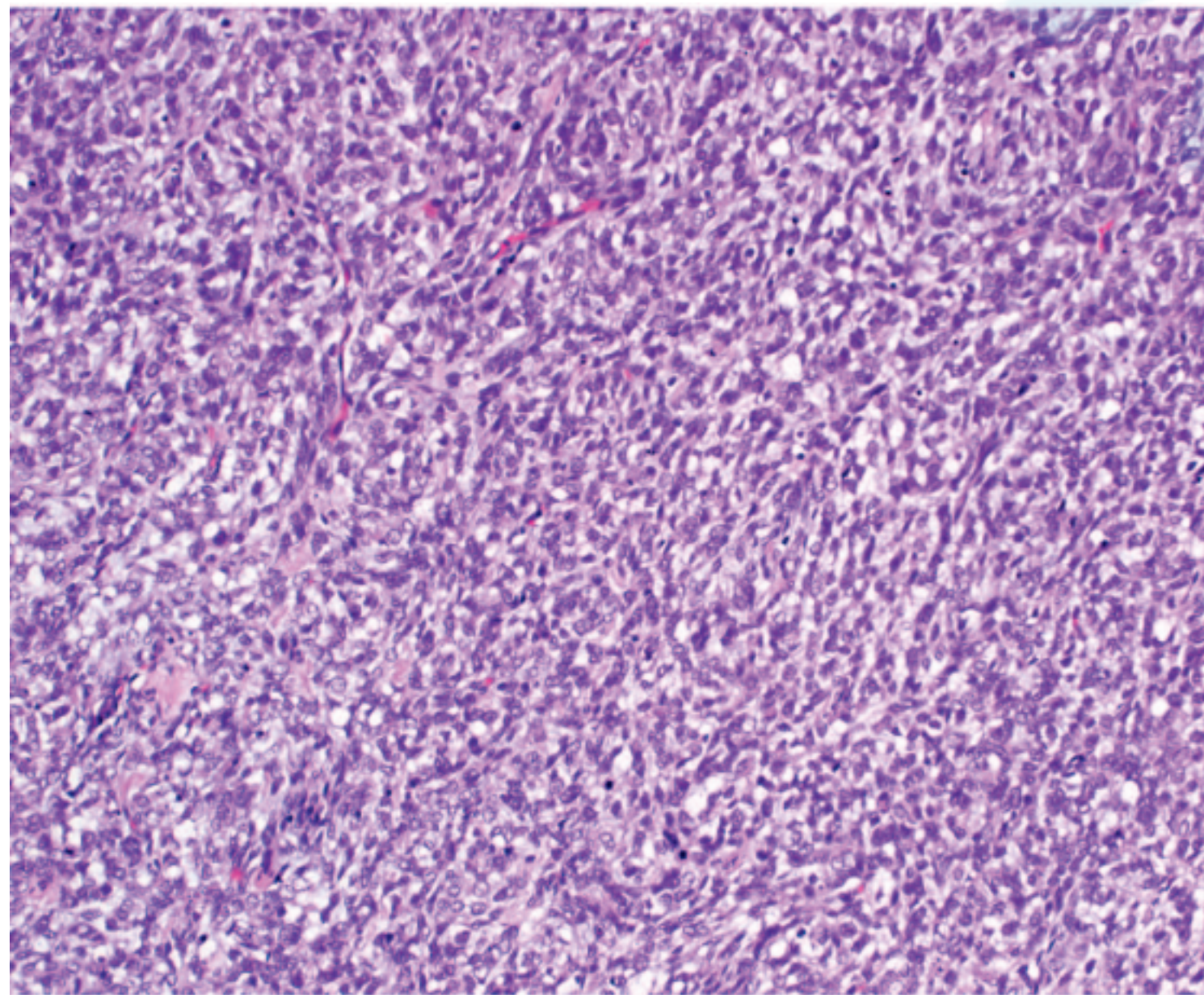
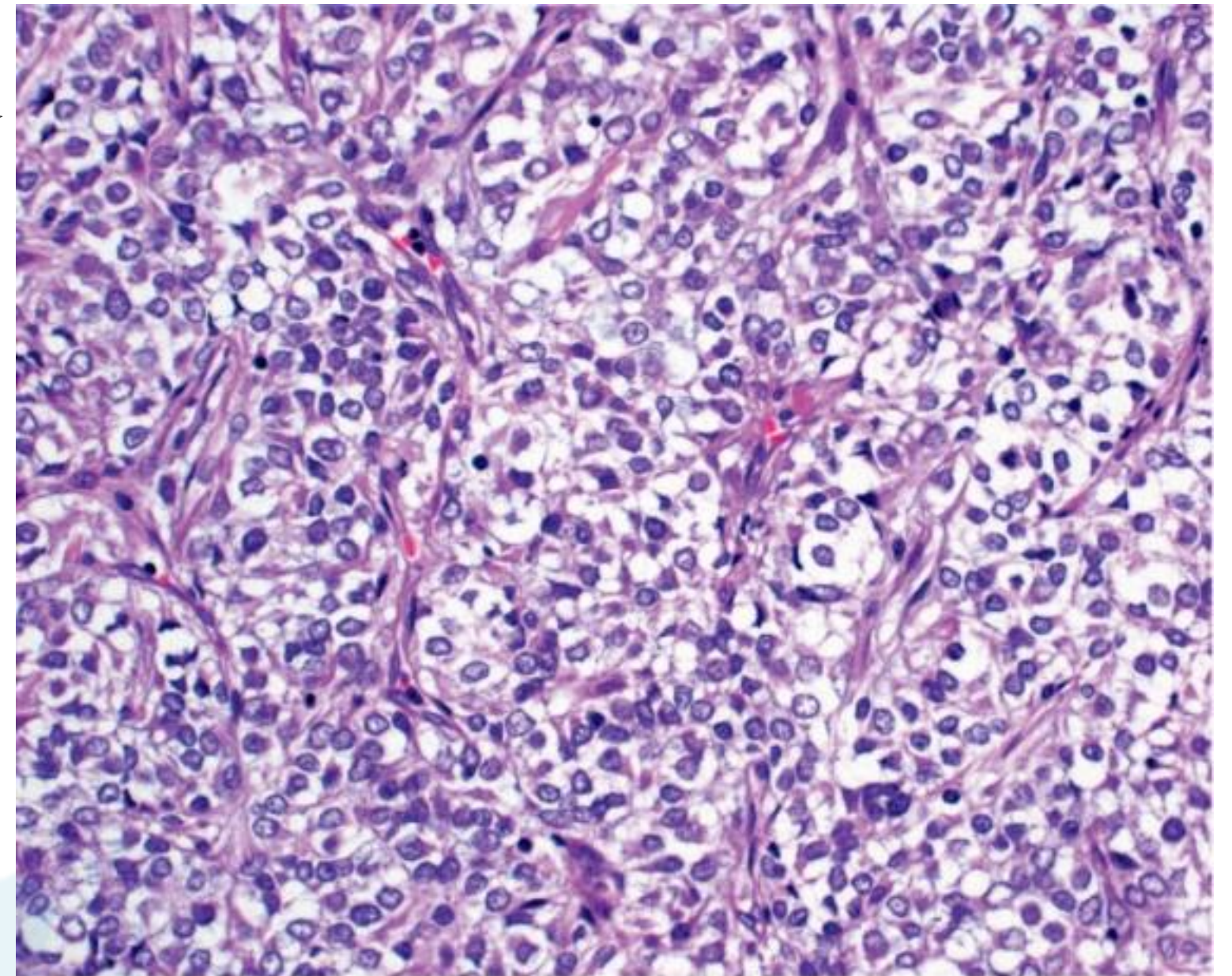
大体：体积通常较大，平均11.3cm，好发于肾髓质，常为单个肿块。

包膜不明显，切面呈浅棕色，肉色



Aw, S. J., & Chang, K. T. E. (2019). *Clear Cell Sarcoma of the Kidney*. *Archives of Pathology & Laboratory*

CCSK镜下表现：瘤细胞大小较一致，界限不清，核圆形或卵圆形，细胞质透明，染色质细，染色浅，核仁不明显，核分裂象少见。纤维血管将瘤细胞分隔成巢状或条索状，条索状排列的瘤细胞可呈上皮样或梭形，黏液样改变



CCSK

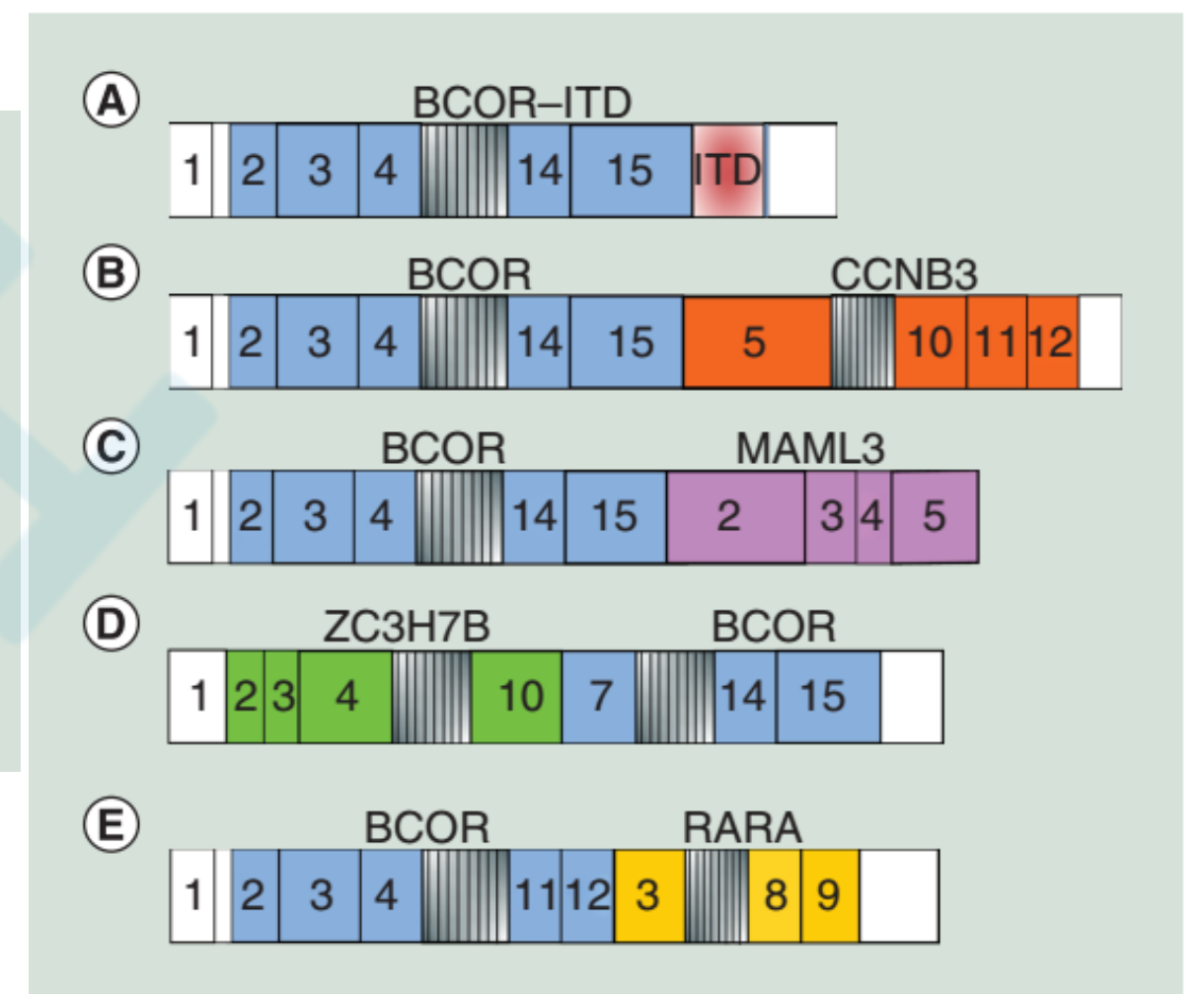
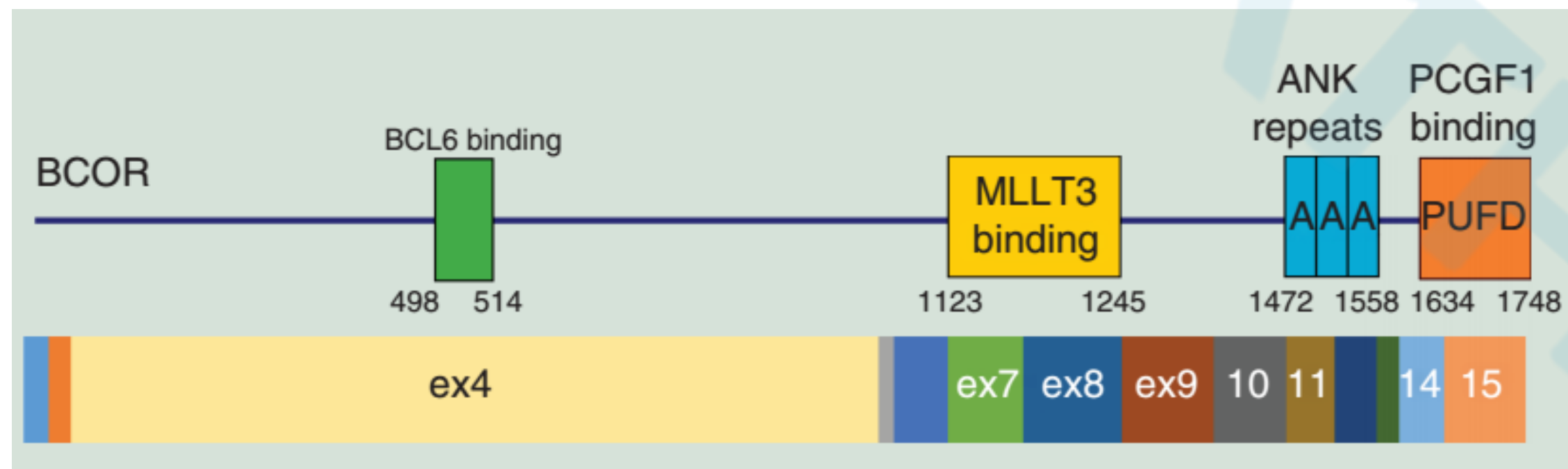
免疫组化：B 细胞淋巴瘤因子 6 共抑制因子(BCL6 co-repressor, BCOR) 是CCSK的敏感和高度特异性免疫标记物

基因学： 包括BCOR基因内部串联重复(> 90%)、
YWHAE-NUTM2B基因融合、BCOR-CCNB3（8-14岁）基因融合

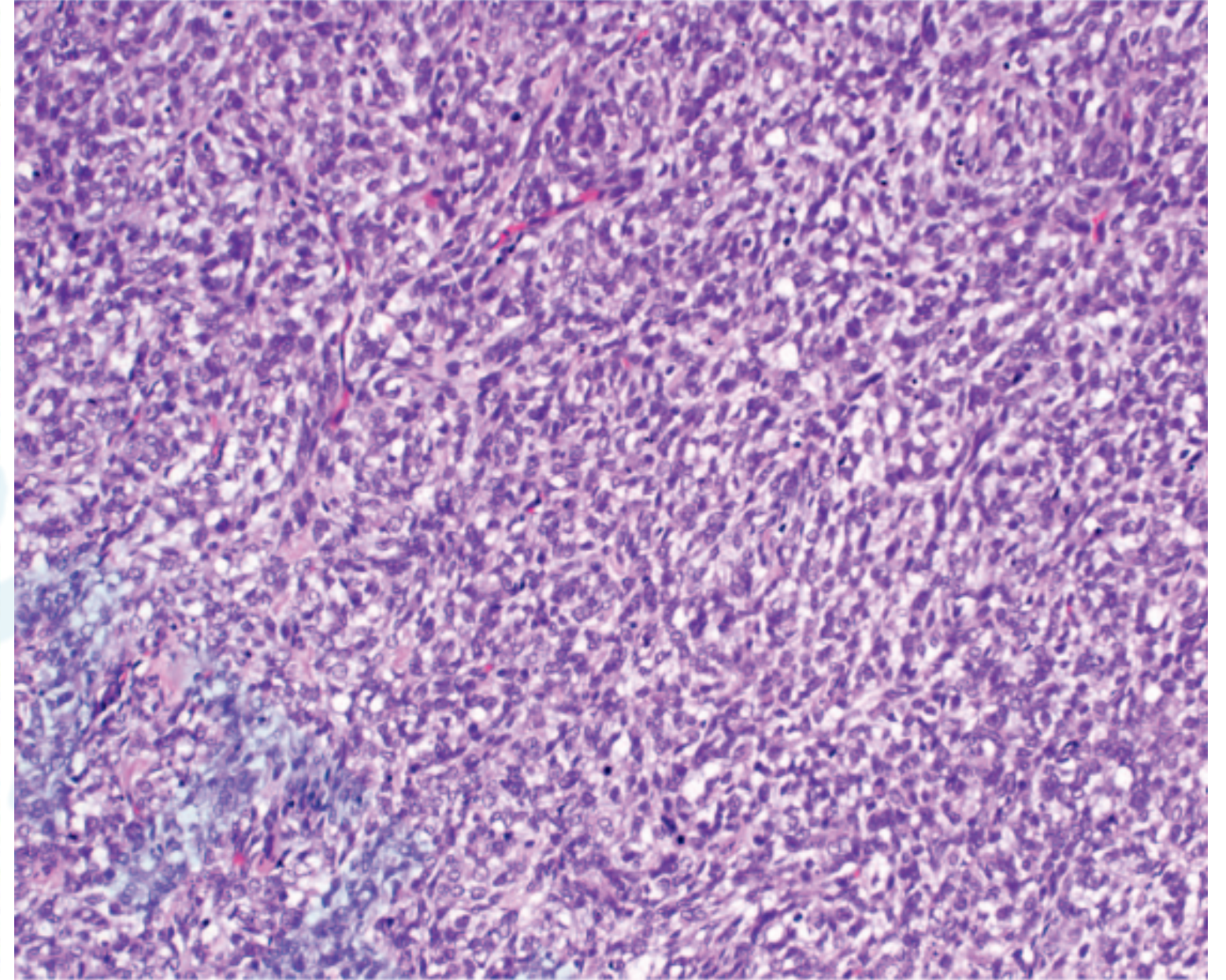
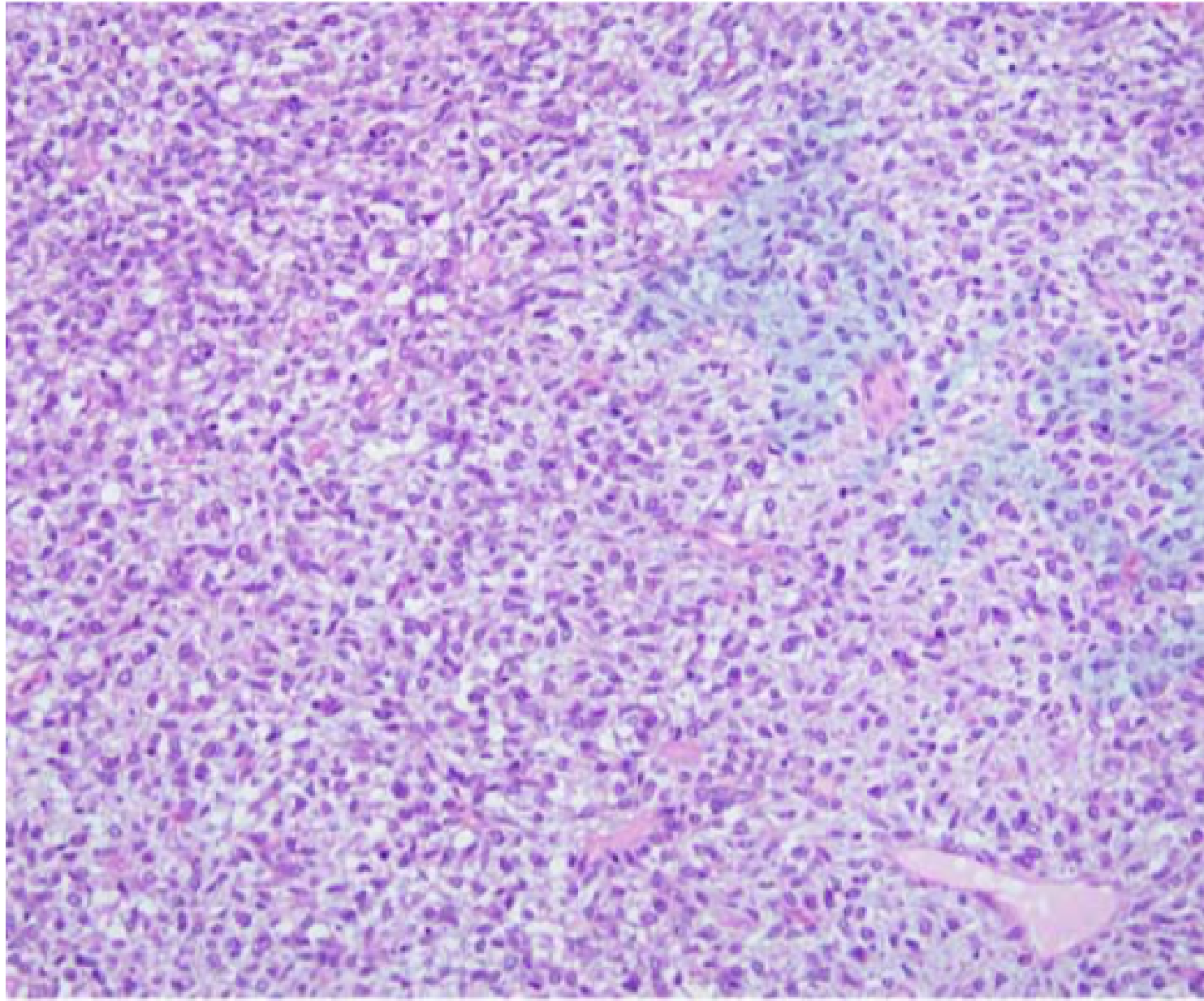
预后：①临床分期，②有没有使用放线菌素D等化疗药物，
③肿瘤内是否出现坏死，④年龄是否大于4岁

BCOR

- 1) BCOR是一种编码表观遗传调节因子的基因，位于X染色体Xp11.4
- 2) BCOR基因的蛋白产物为BCL6的一个新的结合伴侣，为一种含有POZ/锌指结构域的转录抑制蛋白，增强BCL6介导的抑制作用的DNA连接时起辅助转录抑制的作用，尤其是通过BCOR与I类和II类组蛋白乙酰化酶的关联



目的



材料和方法

- 1) 病例选择：5例（最初诊断为肾/肾周未分化肉瘤）
机构审查委员会已批准
- 2) 免疫组化：BCOR, SATB6, CD34, HMB45,
TLE1, Desmin, S100
- 3) 靶向RNA测序
- 4) 良性和恶性肾外SFT的平均H指数
- 5) 肾外SFT的BCOR免疫组化评分（H指数）：核阳性细胞所占肿瘤细胞百分比乘以阳性程度（0=无、1=弱、2=中等、3=强），范围0~300%，>50%认为BCOR是阳性

结果

TABLE 1. Malignant Renal/Perirenal Solitary Fibrous Tumor

Case	Age (y)/Sex	Location	Tumor Size (cm)	IHC Positive	IHC Negative
1	30/F	Kidney	10	BCOR, STAT6, CD99 (focal), CD34 (focal)	S100, Desmin, HMB45, Melan A, PAX8
2	40/M	Kidney	18.5	BCOR, CD99 (focal)	CD34, Desmin, HMB45, PAX8, S100
3	62/F	Kidney	26	BCOR, STAT6, CD34 (focal)	Desmin, Actin, S100, CD117, HMB45
4	48/M	Kidney	10	BCOR, STAT6, CD99	CD34, ERG, HMB45, Melan A, S100, Desmin, Cytokeratin, PAX8
5	46/F	Perirenal	NA	BCOR, STAT6, CD99 (focal)	CD34, CD31, HMB45, Melan A, S100, Desmin, Cytokeratin

F indicates female; IHC, immunohistochemistry; M, male; NA, not available.

- 1) 所有病例BCOR（弥漫强+）
- 2) 4例STAT6（核+），病例2未显示
- 3) 所有病例S100，Desmin，HMB45（-）
- 4) 2例CD34（局灶+），3例阴性
- 5) 4例CD99（+）

RNA测序

5例均表现出NAB2-STAT6基因融合：4例发生NAB2外显子6-STAT6外显子16融合，另一例（病例3）发生NAB2外显子7-STAT6外显子17融合。

病例1

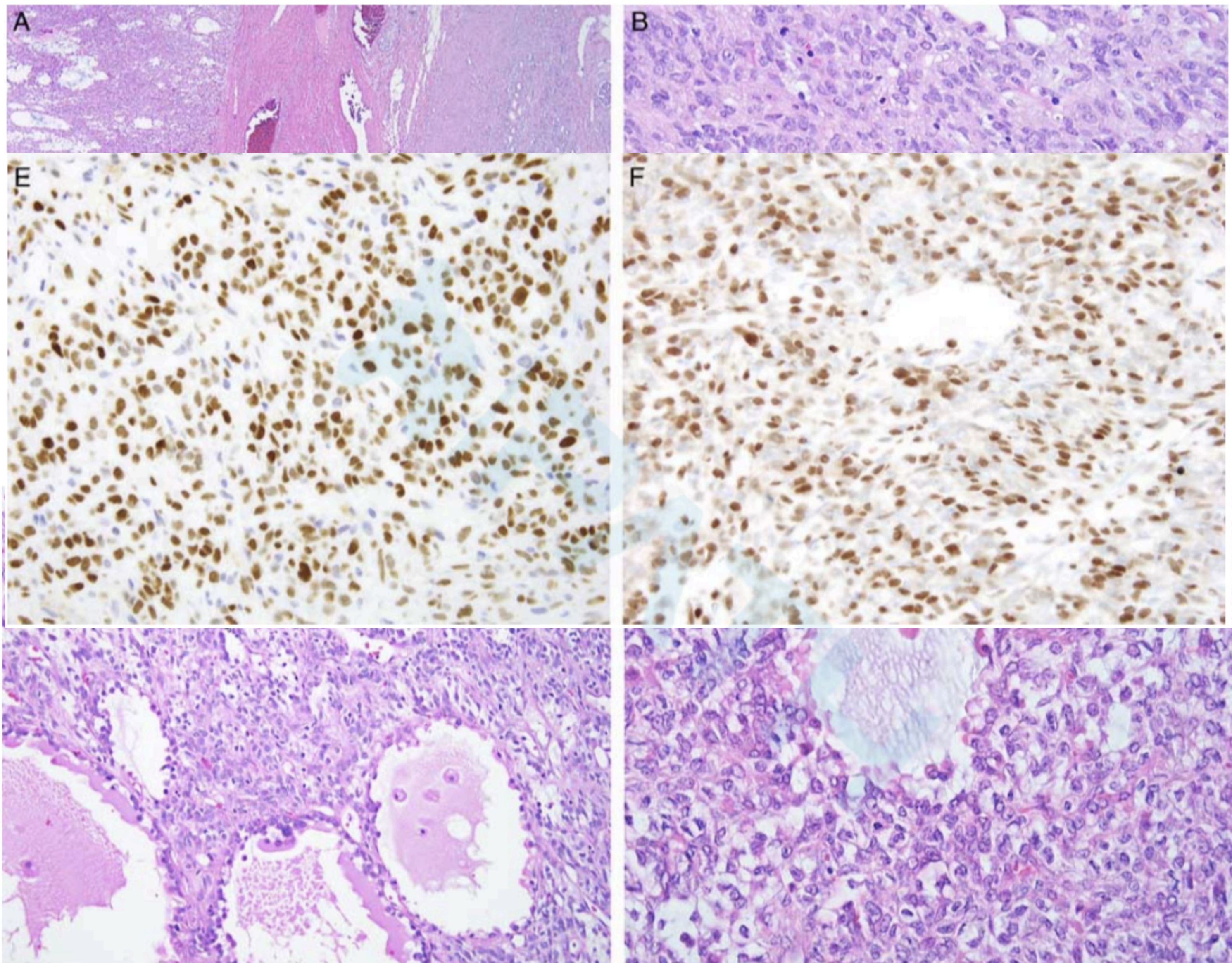


FIGURE 1. Malignant SFT of the kidney (case 1). This is a cellular neoplasm (left) separated from the kidney (right) by a fibrous pseudocapsule (A). The neoplasm is composed of monomorphic round to epithelioid cells with scant pink cytoplasm (B). Multiple areas demonstrate small mucoid cysts, similar to those seen in CCSK (C, D). The neoplasm demonstrated diffuse nuclear labeling for BCOR (E), but also showed diffuse nuclear labeling for STAT6 (F), supporting the molecular finding of a NAB2-STAT6 gene fusion.

病例2

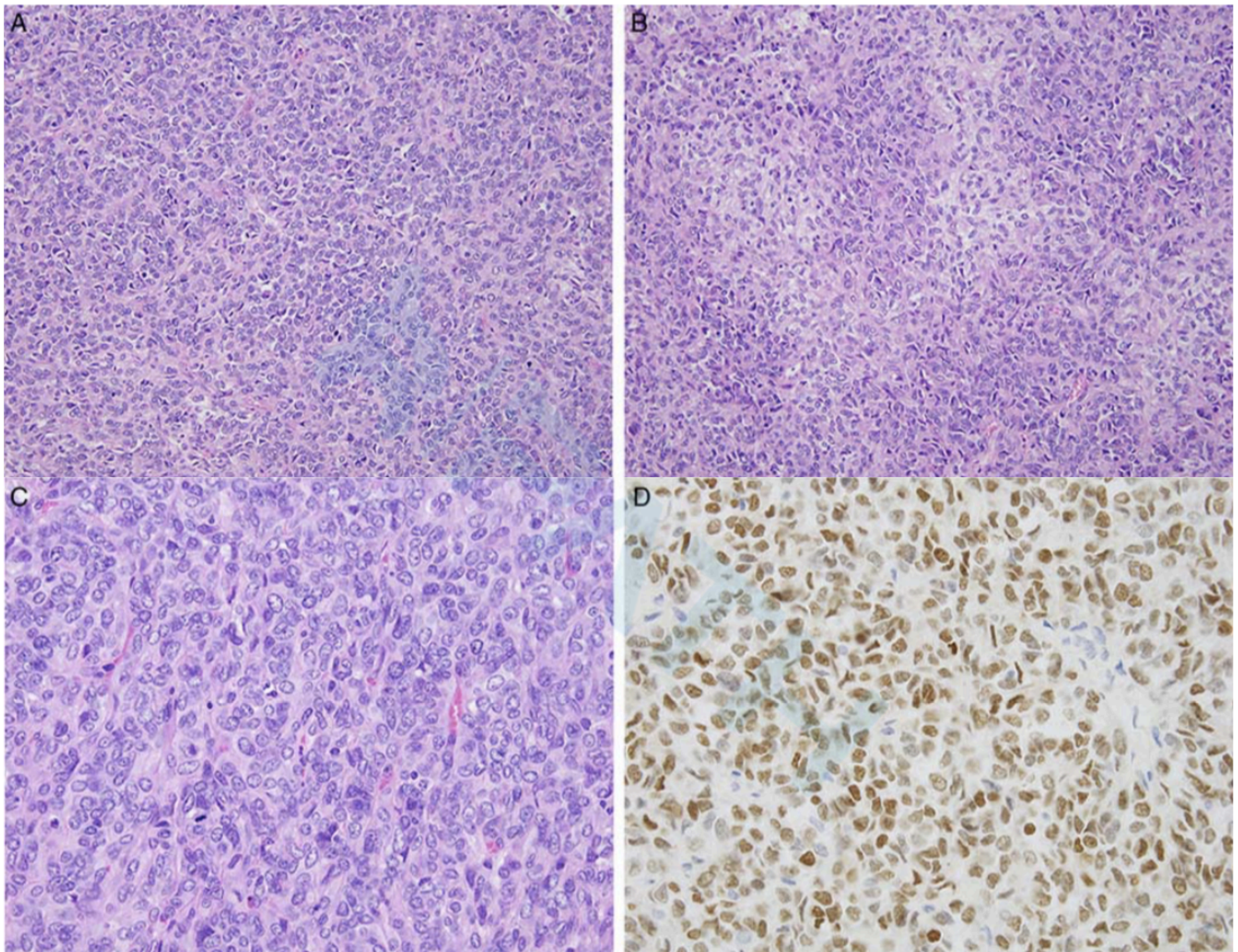


FIGURE 2. Malignant SFT of the kidney (case 2). This is a highly cellular renal neoplasm with a primitive small blue round phenotype (A–C). There are vague nodular variations in cellularity (B). The neoplasm demonstrated diffuse strong nuclear labeling for BCOR (D) suggesting a diagnosis of cellular CCSK. The neoplasm demonstrated a NAB2-STAT6 gene fusion, supporting the diagnosis of SFT.

病例3

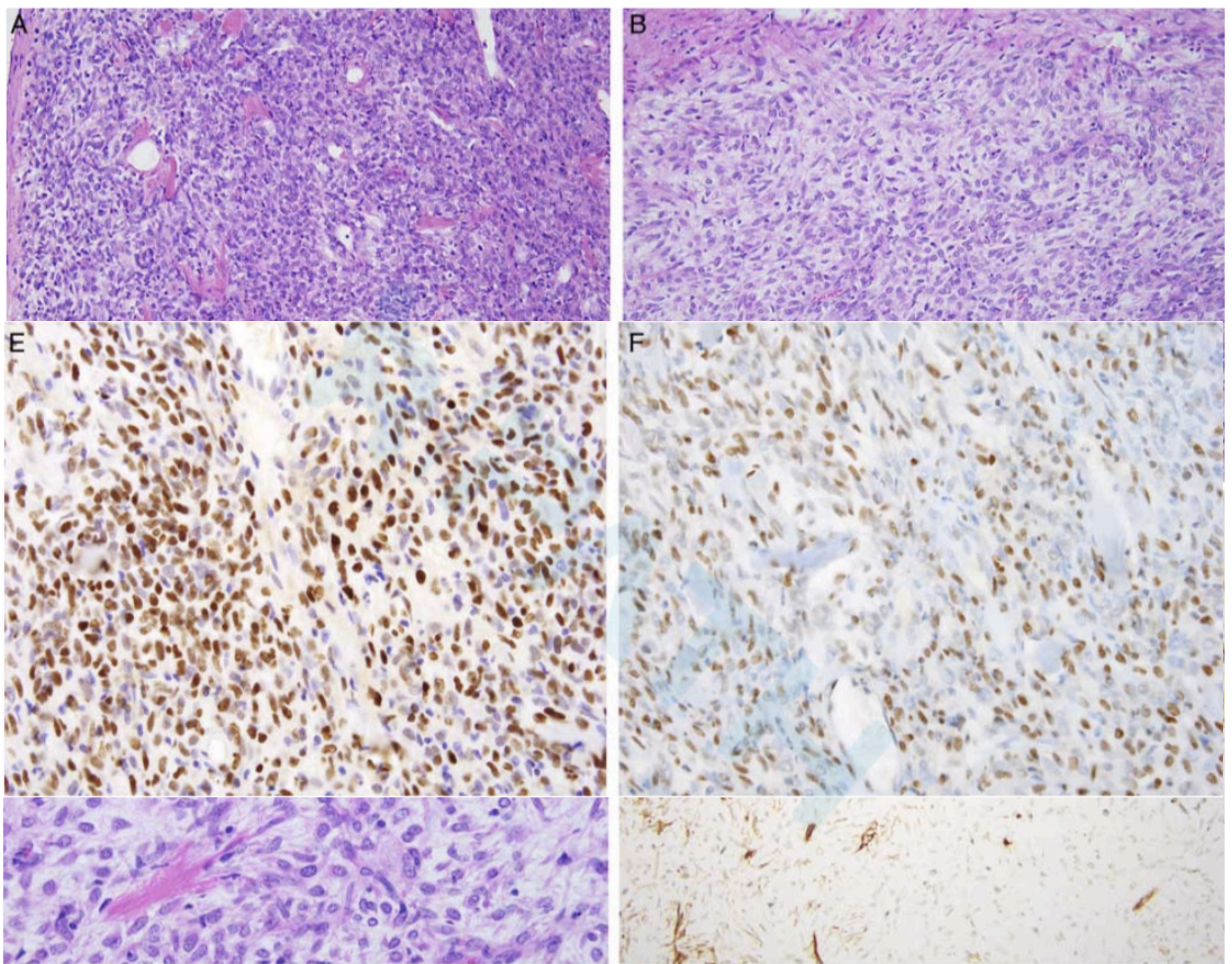


FIGURE 3. Malignant SFT of the kidney (case 3). This is a cellular neoplasm composed of bland ovoid to epithelioid cells with thin strands of ropy collagen (A). High power examination reveals a uniform branching capillary vasculature supporting nests and cords of neoplastic cells with indistinct cytoplasm and fine chromatin, suggestive of CCSK (B, C). The neoplasm is negative for CD34 (D), and demonstrates strong diffuse nuclear labeling for BCOR (E). The neoplasm demonstrates strong diffuse nuclear labeling for STAT6 (F), supporting the molecular finding of a NAB2-STAT6 abnormality.

病例4

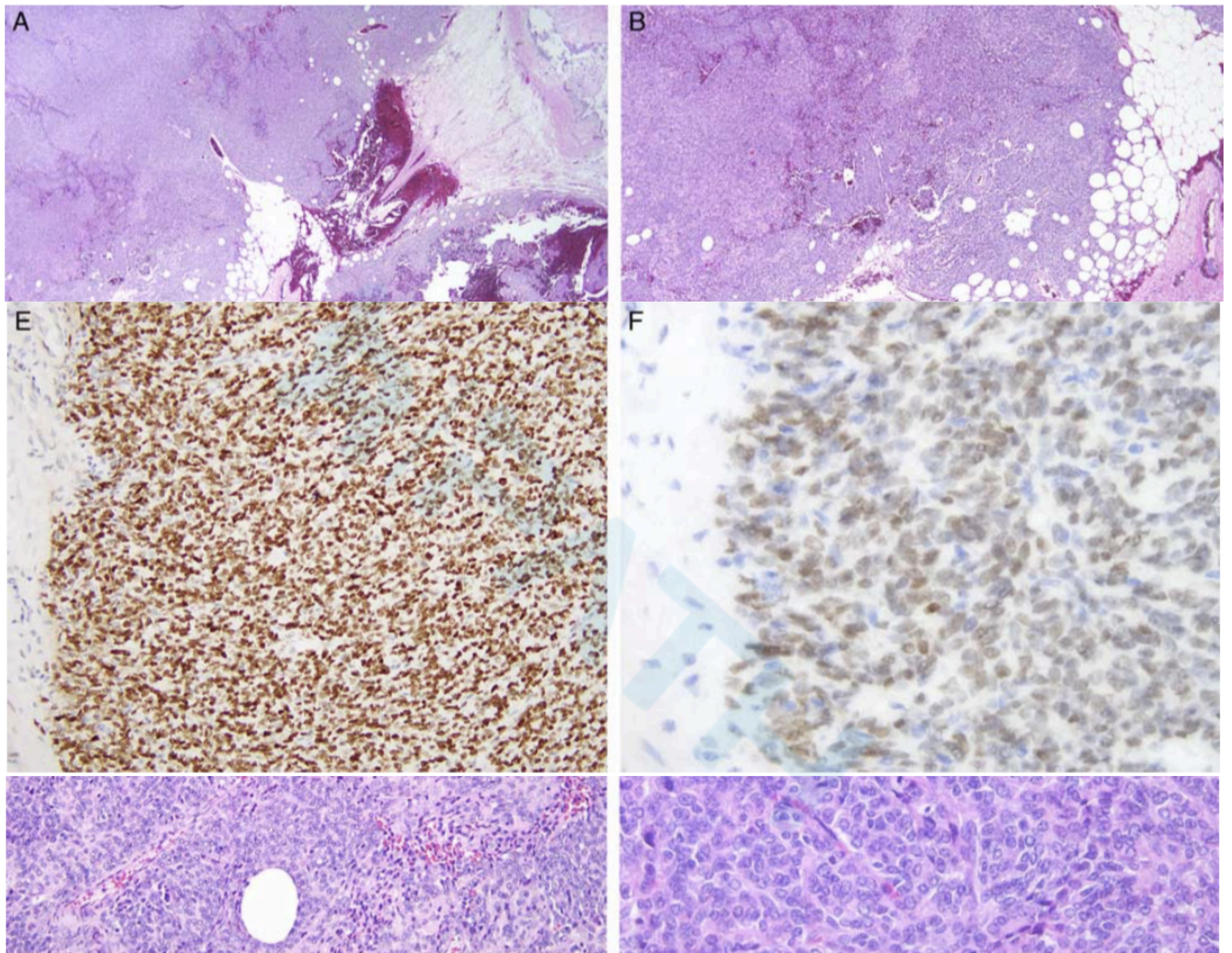


FIGURE 4. Malignant SFT of the kidney (case 4). This an undifferentiated sarcoma centered in the renal pelvis. Note the renal medullary tissue present at the lower left and the renal pelvic urothelium at the upper right (A). The neoplasm permeates the renal sinus fat in a diffuse manner (B). The neoplasm consists of undifferentiated small round blue cells, with focal clustering (C) but a predominant diffuse sheet-like growth pattern (D). The neoplasm demonstrates strong diffuse nuclear immunoreactivity for BCOR (E) and weaker but tumor cell-specific nuclear labeling for STAT6 (F).

病例5

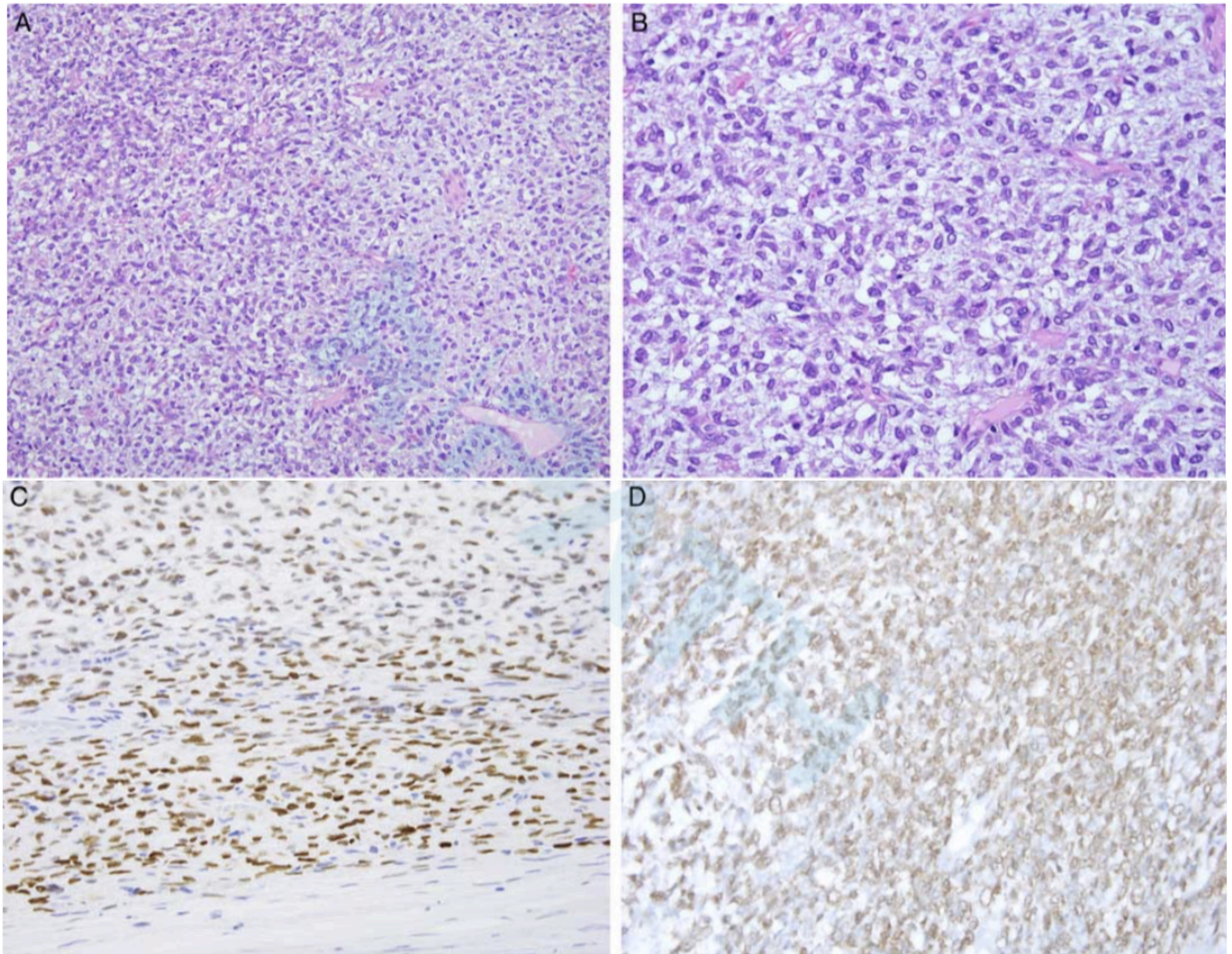


FIGURE 5. Malignant perirenal SFT (case 5). This is a cellular neoplasm demonstrating monotonous cells with indistinct cytoplasm and fine open chromatin, along with regular capillary branching vasculature, highly suggestive of CCSK (A, B). The neoplasm demonstrates strong nuclear labeling for BCOR (C), also suggesting CCSK. The neoplasm demonstrates strong diffuse nuclear labeling for STAT6 (D), supporting the RNA-Seq findings.

BCOR和STAT6 mRNA表达

1) 肾和肾外MSFT BCOR和STAT6 mRNA表达明显高于其他类型肉瘤

2) 使用Affymetrix U133A平台进行表达谱分析，发现23例SFT BCOR和STAT6 mRNA表达高于其他34种软组织肿瘤(7种常见组织学亚型)

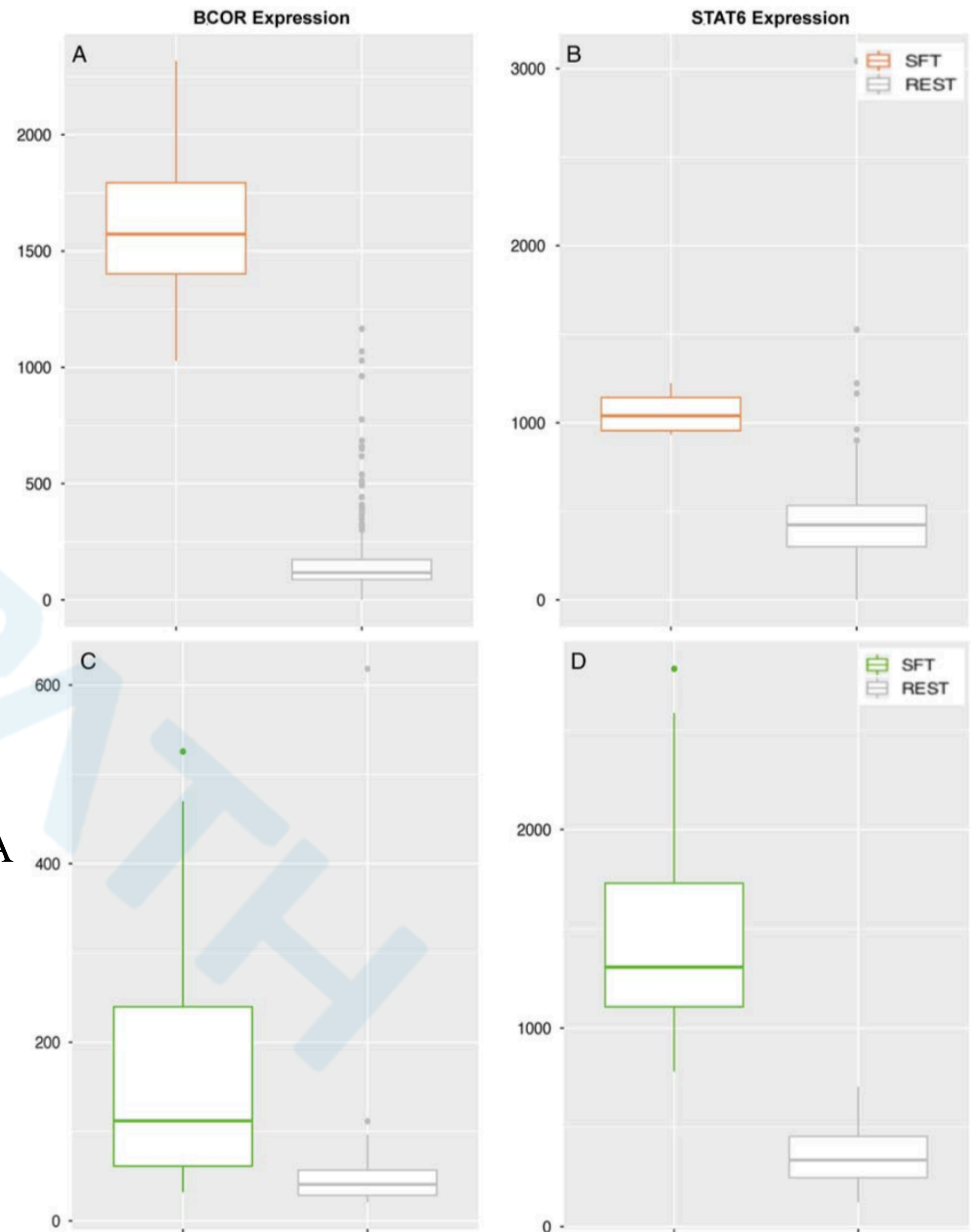


FIGURE 6. BCOR and STAT6 expression in SFT. A and B, Targeted RNA-Seq showing marked upregulation of BCOR (A) and STAT6 (B) in 4 SFT study cases (orange) versus other sarcoma types (gray box-plot). C and D, Expression profiling using the Affymetrix U133A platform showing upregulated BCOR (C) and STAT6 (D) in 23 SFT (various sites and risk of malignancy) (green box-plot) compared with a set of 34 soft tissue sarcomas spanning 7 common histotypes (gray box-plot).

讨论

CCSK与MSFT形态学特点

- 1) **MSFT**: ①细胞丰富密集, ②细胞异型性明显, ③核分裂象 ≥ 4 个/10HPF, ④肿瘤体积大, ⑤浸润性边缘, ⑥坏死
- 2) **CCSK**: 瘤细胞大小较一致, 界限不清, 核圆形或卵圆形, 细胞质透明, 染色质细腻, 染色浅, 核仁不明显, 核分裂像少见
- 3) 本文报道的5例肾和肾周MSFT与CCSK的形态学相似: 所有病例均显示肿瘤细胞圆形或上皮样, 大小一致, 染色质细腻, 由规则分支的毛细血管分割

CCSK与MSFT免疫组化特点

免疫组化	CCSK	MSFT
BCOR	弥漫阳	弥漫阳
CD34	阴性	局灶阳或阴性
STAT6	阴性	阳/阴

CCSK与MSFT基因特点

1) **MSFT**: 最常见的是NAB2外显子 4与STAT6外显子2/3基因融合, 本文5例MSFT均显示NAB2外显子6/7与STAT6外显子16/17发生了基因融合 (少见), 导致BCOR mRNA高表达, 从而导致BCOR蛋白高表达

2) **CCSK**:① BCOR基因内部串联重复 (> 90%), ② BCOR-CCNB3基因融合 (8-14岁), ③ YWHAE-NUTM2B基因融合; 这3种基因改变相互排斥, 但均可导致BCOR mRNA高表达, 从而导致BCOR蛋白高表达

结论

CCSK 与MSFT的形态学和免疫组化相似，但CCSK 需要采用特定的有效化疗方案治疗，所以当诊断CCSK 的时候，需与MSFT进行鉴别，目前基因检测是比较有效的鉴别方法。

谢谢聆听！

THANK YOU VERY MUCH!

