

Histologic Aspect of Renal Cell Carcinomas

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ABSTRACT

International guidelines for the classification of renal tumors in adults are provided from the ISUP (International Society of Urologic Pathology). The most recent recommendations were established in 2012, and the 2016 WHO classification incorporated these guidelines but also clinical, pathological, and molecular characteristics of the renal cell carcinomas (**RCC**). In this review, we focus on the macroscopic, histologic immunohistochemical and cytogenetic criteria that lead to the diagnosis of RCC. The main histologic subtypes of RCC include clear cell RCC (**ccRCC**), papillary RCC (**P-RCC**), chromophobe RCC (**Ch-RCC**), MiT family translocation RCC, collecting duct carcinoma, and medullary renal cell carcinoma. We also describe the other and rare entities of RCC recognized in the 2016 WHO classification: hereditary leiomyomatosis associated RCC, succinate dehydrogenase deficient RCC, mucinous tubular and spindle cell carcinoma, tubulocystic RCC, acquired cystic disease associated RCC, mixed epithelial and stromal tumor of the kidney, clear cell papillary RCC, and epithelioid angiomyolipoma (**AML**).

Keywords: Renal cell carcinoma; diagnosis; histology; WHO classification²

Abbreviations: **Ch-RCC:** Chromophobe renal cell carcinoma; **ccRCC:** Clear cell renal cell carcinoma; **ISUP:** International Society of Urologic Pathology; **P-RCC:** Papillary renal cell carcinoma; **RCC:** Renal cell carcinoma; **WHO:** World health organization

INTRODUCTION

The last WHO histologic classification of renal tumors was published in 2014. In the past decade, the ISUP members organized several consensus conferences to redefine renal tumor entities with a 2012 ISUP Vancouver classification published in 2013. The new WHO classification was just published in 2016 and included the ISUP recommendations [1,2,3]. In this review, we focus and describe the new entities and changes proposed by the 2016 WHO classification for renal cell carcinomas (**RCC**) in adults.

MATERIALS AND METHODS

A systematic review of the literature search was performed for relevant publications from the database Pubmed/MedLine, and focused on the following keywords: Carcinomas, Kidney, Renal Cell carcinomas, Classification, ISUP, WHO. We also use the diagnostic criteria for RCC published in the 2016 WHO classification of the urinary system and male genital organs.

RESULTS

The main histologic subtypes of RCC include clear cell RCC (**ccRCC**), papillary RCC (**P-RCC**), chromophobe RCC (**Ch-RCC**), MiT family translocation RCC, collecting duct carcinoma, and medullary renal cell carcinoma. All these subtypes represent almost 80% - 90% of RCC. Even if more than 20 subtypes of renal tumors have been defined, 5% of RCC remain unclassified RCC.

Among the different prognostic markers published in the literature, only 5 were approved by the ISUP members to be reported in routine practice:

- The histologic subtype: medullary RCC and collecting duct carcinoma are considered to have the worse prognosis of RCC with a highly aggressive behavior and a high risk of dissemination and metastases. Chromophobe RCC has a favorable prognosis compared to ccRCC and papillary RCC with a 5-year survival of 80% -100% [1].
- The ISUP nucleolar grading system: the ISUP system includes 4 nucleolar grades: grade1 (nucleoli are not present at x400 magnification), grade 2 (nucleoli visible at x400 magnification), grade 3 (nucleoli visible and prominent at x100 magnification), and grade 4 (nuclear and nucleolar pleomorphism with tumor giant cells). A sarcomatoid and/or a rhabdoid component are considered as a grade 4. The ISUP grading system is applied only for clear cell RCC and papillary RCC [4].
- Sarcomatoid and/or rhabdoid differentiation is associated with a less favorable behavior and should be reported in the pathologic report.

- The presence of tumor necrosis and vessel invasion
- The pTNM 2010 tumor staging [Table 1] [5].

Table 1: pTNM 2010 classification of renal carcinomas.

T : Primary Tumour

Tx: primary tumour cannot be assessed

T0 : no evidence of primary tumour

T1: Tumour ≤ 7 cm in greatest dimension limited to the kidney

- T1a : Tumour ≤ 4 cm

- T1b : Tumour > 4 cm

T2 Tumour > 7 cm in greatest dimension limited to the kidney

- T2a : > 7 cm but ≤ 10 cm

- T2b : > 10 cm

T3 Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia

- T3a :Tumour grossly extends into the renal vein or its segmental (muscle containing) branches, or tumour invades perirenal and/or renal sinus fat but not beyond the Gerota fascia

- T3b :Tumour grossly extends into the vena cava below the diaphragm

- T3c :Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava

T4 Tumour invades beyond the Gerota fascia, including contiguous extension into the ipsilateral adrenal gland

N : Regional lymph nodes

Nx :Regional lymph nodes can not be assessed

N0 :No regional lymph node metastasis

N1 : Regional lymph nodes metastasis

M :Distant metastasis

M0 :No distant metastasis

M1 :Distant metastasis

The main histologic subtypes of adult renal epithelial neoplasm are clear cell RCC (ccRCC), papillary RCC (P-RCC), Chromophobe RCC (Ch-RCC), MiT family translocation RCC, Collecting duct carcinoma, and Medullary RCC. We review the macroscopic, histologic and immunohistochemical features of these tumours.

Clear Cell RCC (ccRCC)

CcRCC are usually solitary and cortical carcinoma with a variable size. Macroscopically, the tumour is golden yellow with frequent haemorrhage, and possible necrosis [Figure 1]. Histologically, the architecture can be alveolar, acinar or cystic. In low grade tumor, the tumor cells have a clear cytoplasm filled with lipids that becomes eosinophilic in higher nucleolar grade 3 or 4. These tumours are characterized by a well-developed vascular network [Figure 2]. Immunohistochemically, as all RCC, tumor cells are positive for PAX8 and can be also positive for CAIX and focally positive for CK7 [6]. In young adults under the age of 30 years, an autosomal dominant Von Hippel Lindau disease has to be ruled out.



Figure 1: Macroscopic aspect of clear cell renal cell carcinoma.

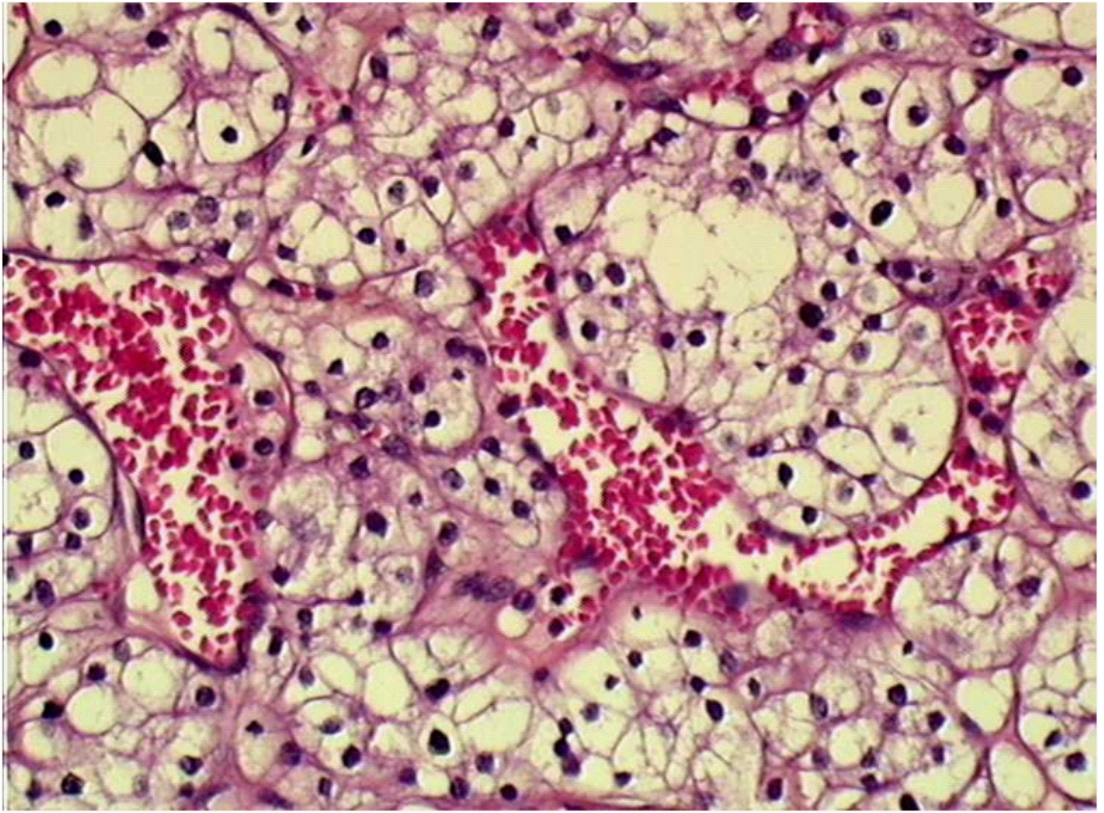


Figure 2: Histologic aspect of clear cell renal cell carcinoma.

Papillary RCC (P-RCC)

P-RCC is a heterogeneous disease including 2 types of renal cancers with indolent to aggressive behavior. Type 1 P-RCC has a better prognosis than P-RCC of type 2. Macroscopically, P-RCC has a friable consistency with a colour varying from grey to yellow; tan or dark [Figure 3]. Type 1P-RCC has small cubical cells with scanty pale cytoplasm arranged in a single layer, and is defined by multiple chromosomal gains including at least gain of chromosomes 7 and 17 [Figure 4]. Tumor cells in type 2 P-RCC are cylindrical, and have eosinophilic cytoplasm with atypical nuclei and nucleoli and nuclear pseudo stratification [Figure 5]. Type 2 P-RCC has a high degree of aneuploidy with multiple chromosomal losses especially loss of chromosome 9p [7].

P-RCC is characterized by a strong cytokeratin 7 and P504S immunoexpression [8].

Concerning papillary adenoma, in the 2016 WHO classification of renal tumours, the diagnosis is based on a tumour with a papillary architecture with a diameter < 15 mm [WHO 2016].



Figure 3: Macroscopic aspect of papillary renal cell carcinoma.

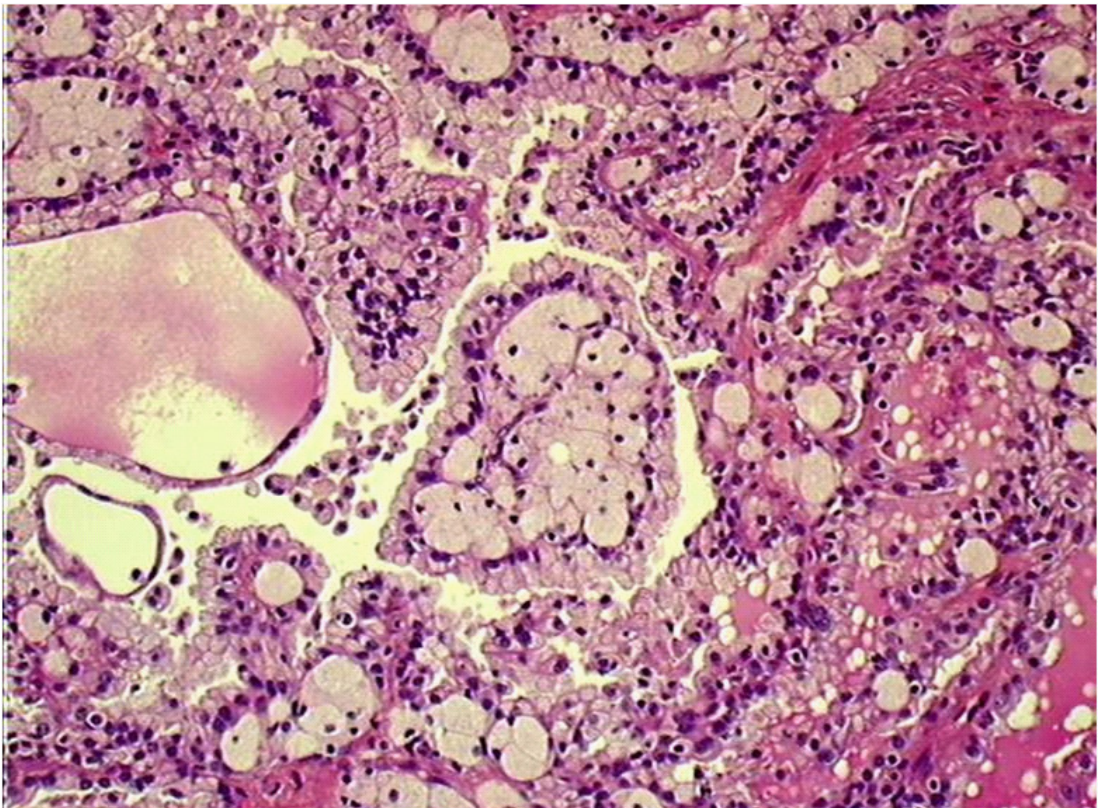


Figure 4: Histologic aspect of type 1 papillary renal cell carcinoma.

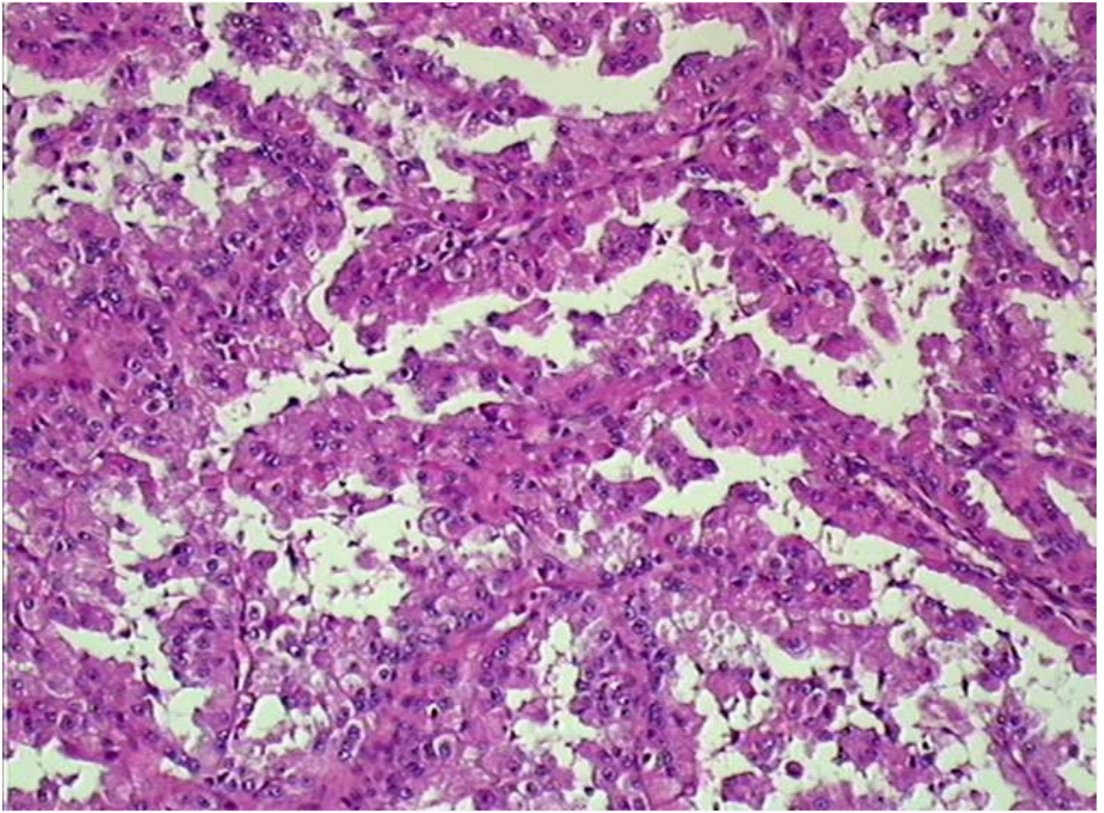


Figure 5: Histologic aspect of type 2 papillary renal cell carcinoma.

Chromophobe RCC (Ch-RCC)

The majority of Ch-RCC is sporadic but some cases are hereditary and associated with Birt-Hogg-Dubé autosomal dominant disorder. The tumors are well circumscribed and vary from light tan to brown in colour [Figure 6]. Tumor architecture consists usually of tubular or solid-sheet pattern. The classic form of oncocytic Ch-RCC presents large and pale cytoplasm with prominent cell membranes [Figure 7]. In the oncocytic Ch-RCC, the cytoplasm shows an oncocytic appearance with a deeply eosinophilic aspect. The tumor cells have a wrinkled or raisinoid aspect with perinuclear halo [Figure 8]. Immunohistochemically, Ch-RCC present a diffuse and membranous positivity for CK7 but the staining can be negative in 30% of cases [Figure 9]. The prognosis is usually favorable except if necrosis, vascular invasion or sarcomatoid/rhabdoid component are present [9]. Cytogenetically, it is associated with allelic loss of chromosomes, especially 1, 2, 7, 10, 13, and 17. Hybrid renal cell tumors contain areas of chromophobe RCC and renal oncocytoma, and have a very favorable clinical behavior with no dissemination or metastases [10].

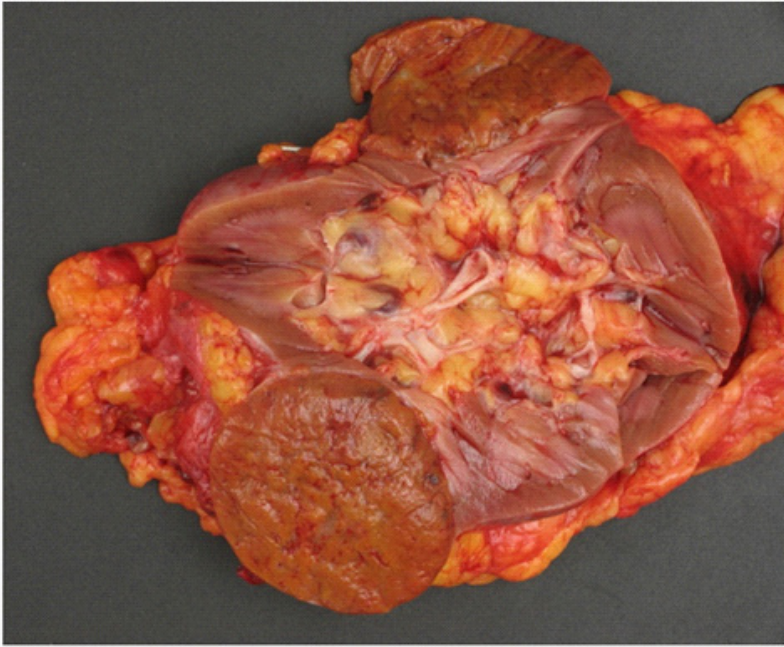


Figure 6: Macroscopic aspect of chromophobe cell renal cell carcinoma.

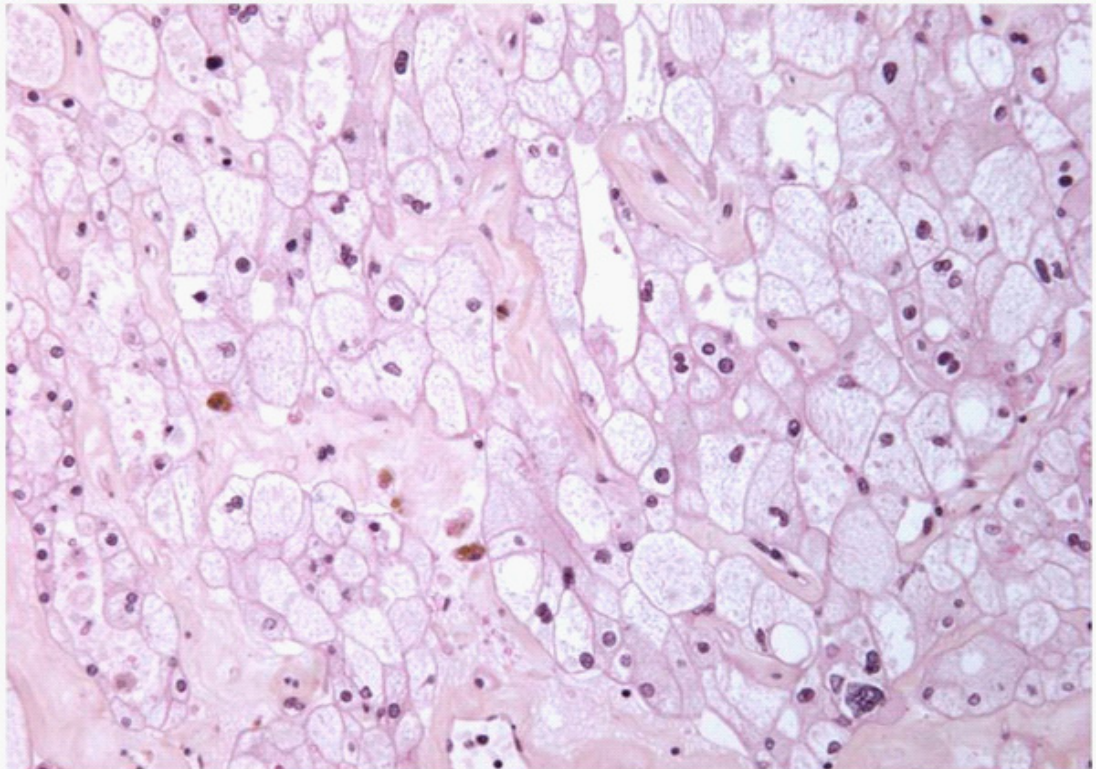


Figure 7: Histologic aspect of classic chromophobe cell renal cell carcinoma.

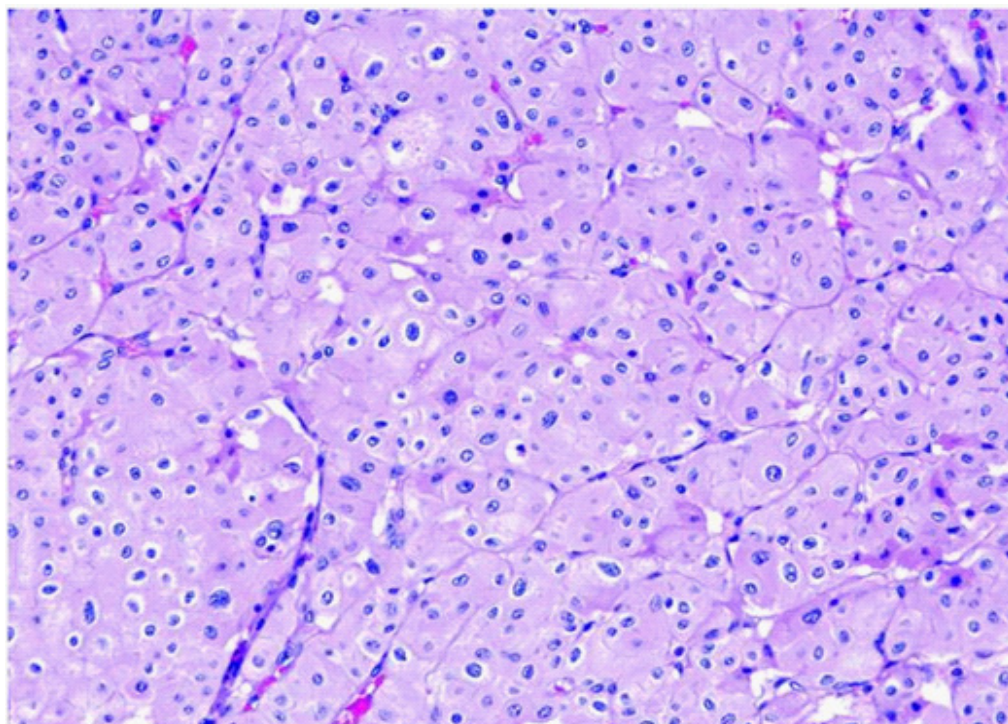


Figure 8: Histologic aspect of chromophobe cell renal cell carcinoma, oncocyctic variant.

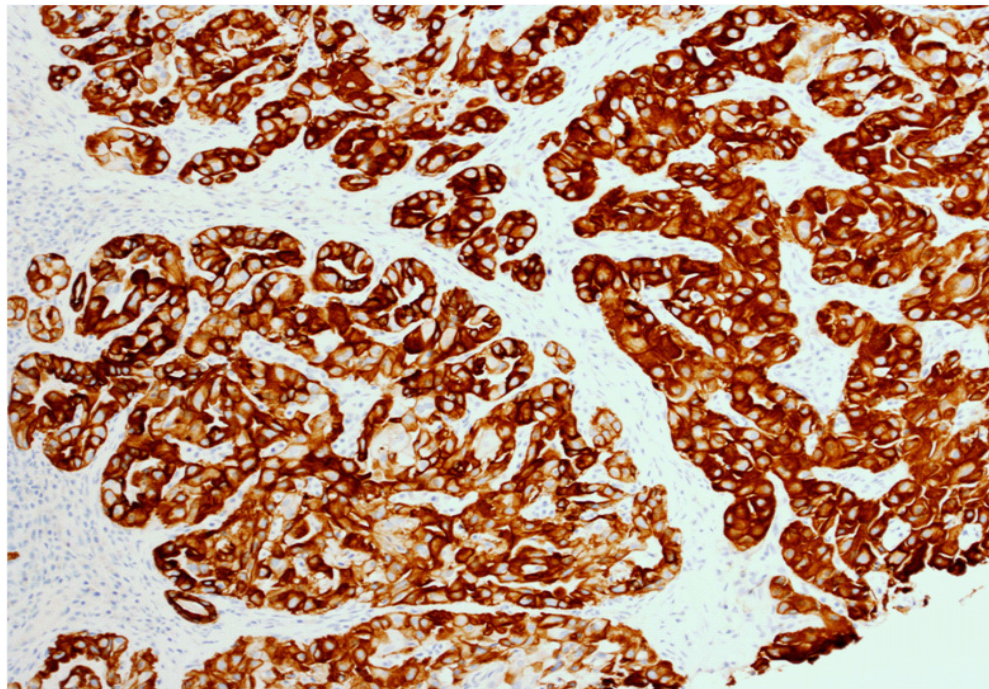


Figure 9: Membranous and strong CK7 immunostaining in a chromophobe renal cell carcinoma.

MiT Family Translocation RCC

TFE3 and TFEB translocation carcinomas are characterized by translocations involving members of the microphthalmia transcription factor subfamily, and are considered under the designation of MiT family translocation RCC. The tumors usually occur in the second and third decade of life with a mean age at diagnosis of 21 years. There is a predominant variable architecture with papillary, solid, alveolar, acinar and tubular pattern. The cells have clear or eosinophilic cytoplasm. Diagnosis is based on cytogenetics and immunohistochemistry. There is a strong nuclear immunostaining for TFE3/TFEB proteins [Figure 10]. The two main Xp11 translocation RCCs present either a t(X;1) (p11.2;q21) translocation which fuses the PRCC and TFE3 genes, or a t (X;17)(p11.2;q25) translocation which fuses the ASPSCR1 and TFE3 genes. The t (6;11) translocation fuses TFEB with MALAT1. Almost 10% of the patients develop metastatic disease [6,11].

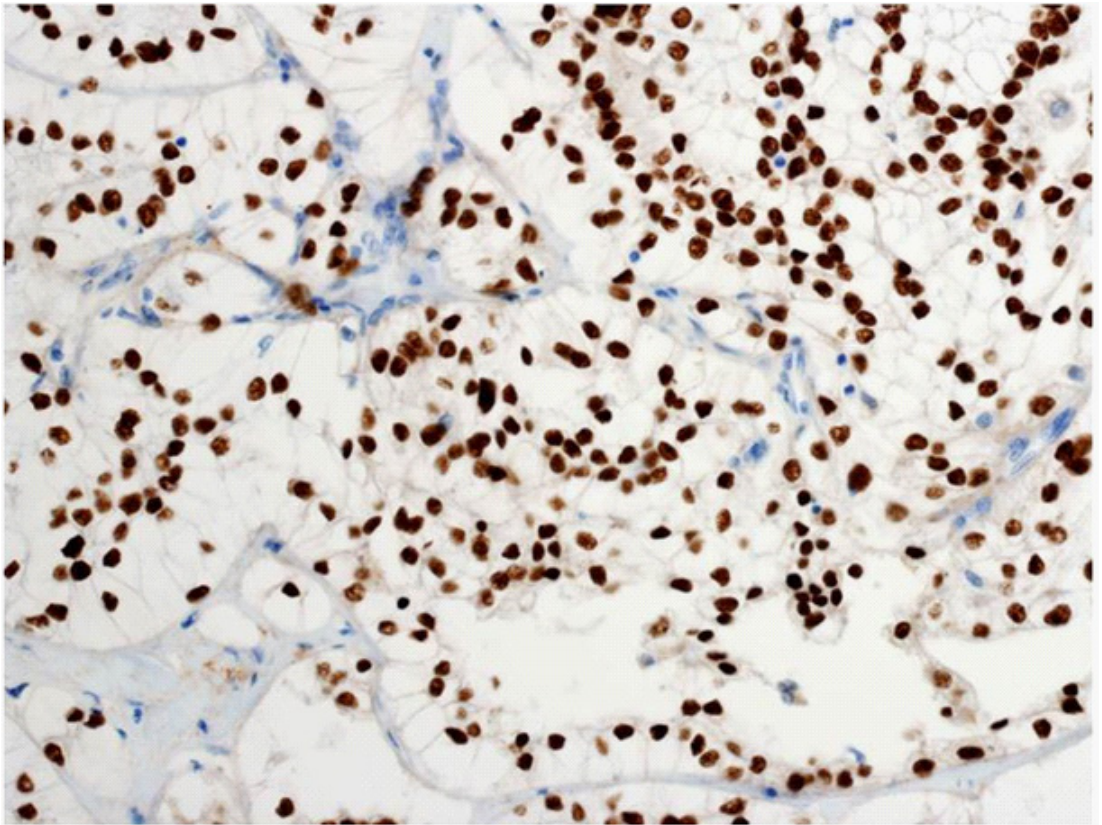


Figure 10: Strong nuclear immunoreactivity with the TFE3 antibody in a TFE3 translocation RCC.

Collecting Duct Carcinoma

The 2012 ISUP Vancouver criteria that are established in the 2016 WHO classification for the diagnosis of collecting duct carcinoma (Bellini carcinoma) are histologic: the tumor must involve the medullary part of the kidney; there is an infiltrative growth pattern between the glomeruli ; the tumor has a predominant tubular architecture ; there is a desmoplastic stromal reaction ; cytologically the atypia are of high grade ; there is no argument for another subtype of RCC or for transitional cell carcinoma [Figure 11]. There is a high prevalence of metastases, and two thirds of patients die within 2 years of diagnosis [6].

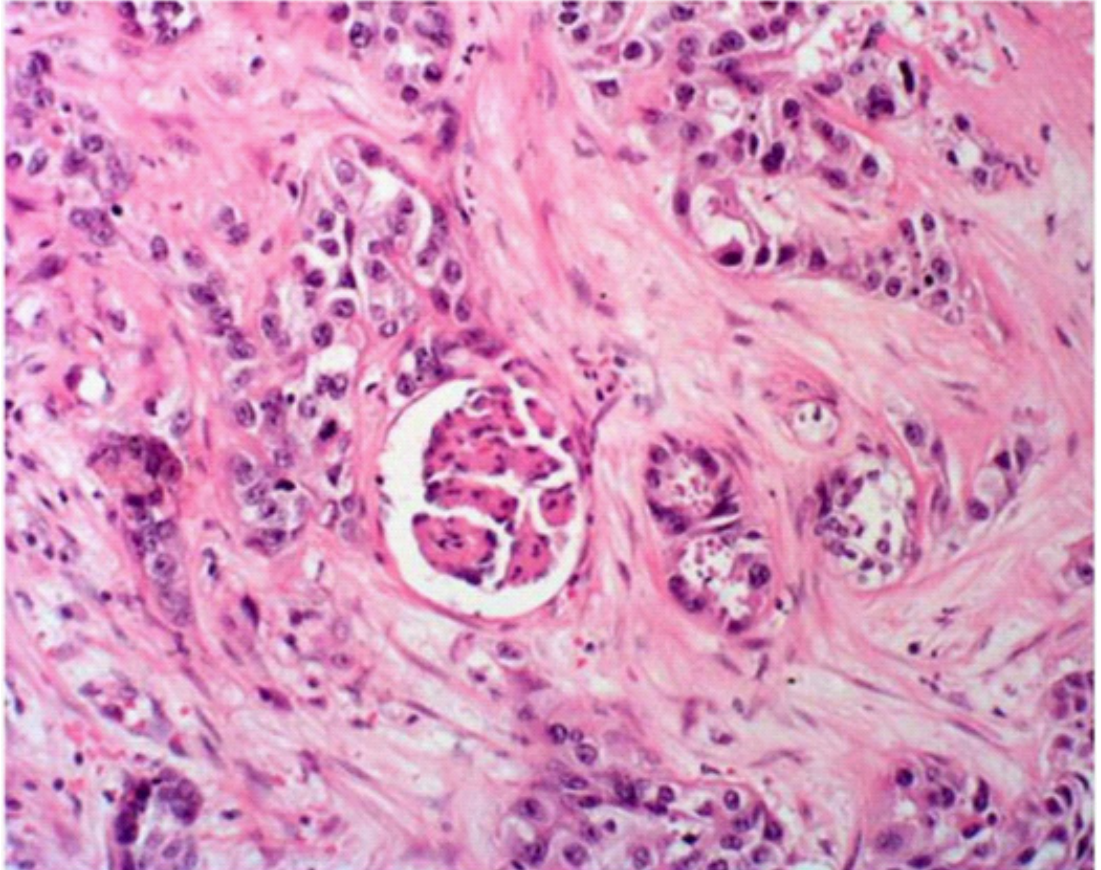


Figure 11: Histologic aspect of collecting duct carcinoma.

Medullary Renal Cell Carcinoma

This tumor occurs in young adults with sickle traits of other hemoglobinopathies. The medullary RCC is located in the renal medulla and is histologically similar to collecting duct carcinoma. It is also a highly aggressive tumor [6].

Other and rare entities of RCC are recognized now in the 2016 WHO classification.

Hereditary Leiomyomatosis associated RCC

This rare histologic entity is a part of the hereditary leiomyomatosis RCC autosomal dominant disease which present a germline mutation in the fumarate hydratase gene. Patients present cutaneous and uterine leiomyomas, and in 30% of cases, develop a RCC. RCC have a papillary architecture with prominent nucleolus, abundant eosinophilic cytoplasm and a nuclear pseudostratification. These tumors have an aggressive outcome with a poor prognosis compared to papillary RCC or ccRCC [12].

Succinate Dehydrogenase deficient RCC

These renal tumors are associated with pheochromocytoma, paraganglioma, and type 2 gastrointestinal stromal tumors in a syndrome consisting of germline succinate dehydrogenase B mutation. Renal tumors are characterized by cytoplasmic vacuoles and pale eosinophilic cytoplasmic inclusions among eosinophilic non atypical tumor cells [Figure 12]. Very few cases have been reported in the literature and follow up is limited [12].

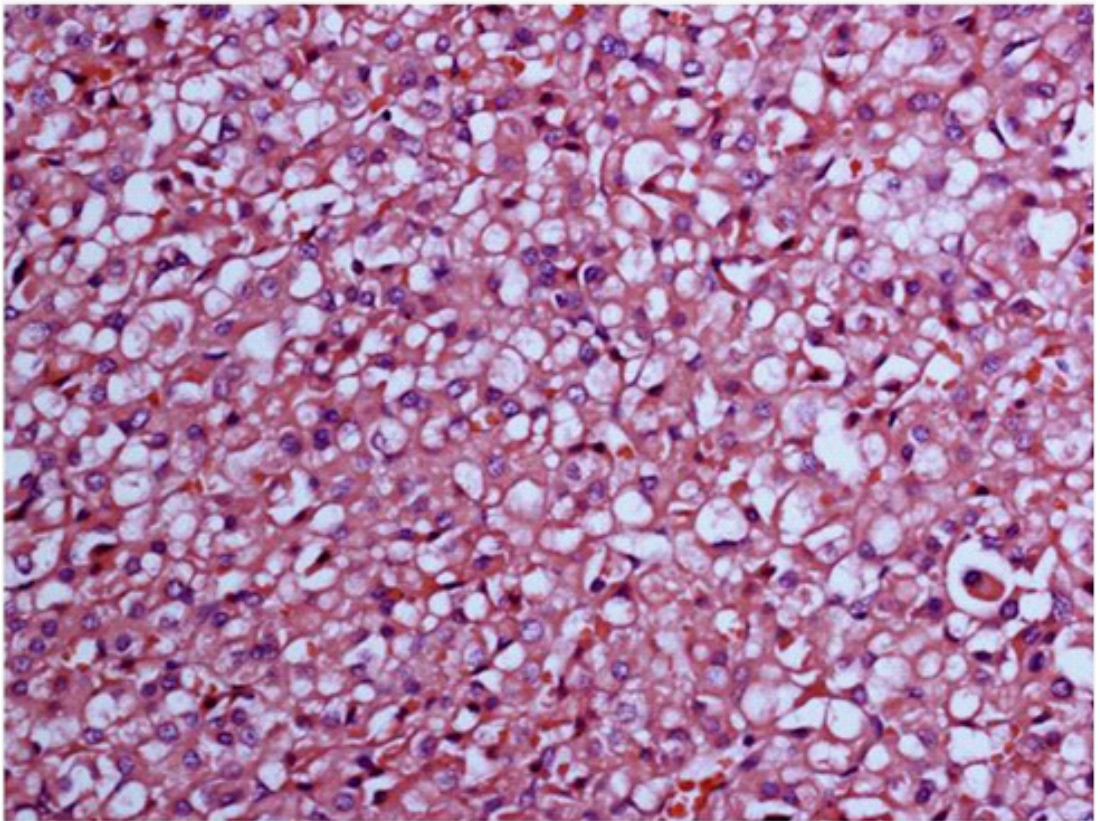


Figure 12: Histologic aspect of succinate dehydrogenase deficient RCC

Mucinous Tubular and Spindle Cell Carcinoma

This low grade carcinoma is composed of tightly packed and elongated tubules separated by mucinous stroma with usually not a typical spindle cell component [Figure 13]. There is a high female predominance. Less than 5 cases have developed metastases with sarcomatoid component in the spindle cell component. Cytogenetically, tumors present multiple chromosomal losses [6].

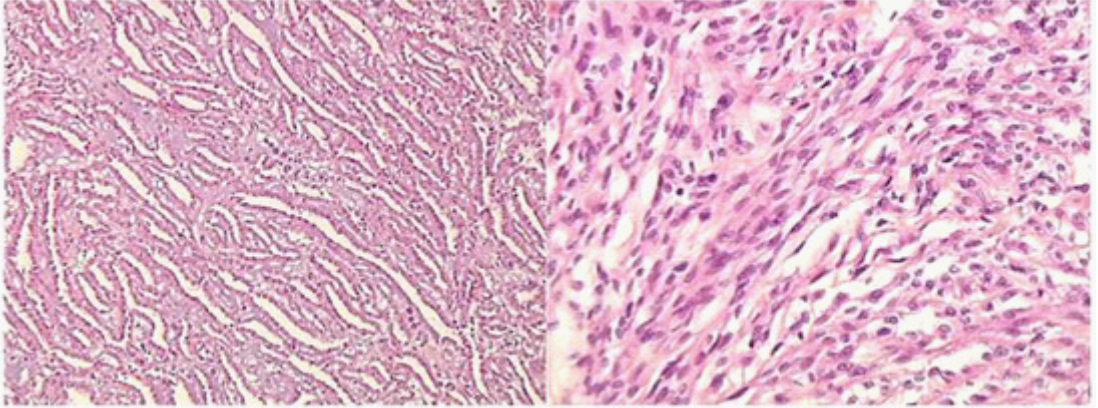


Figure 13: Histologic aspect of mucinous tubular and spindle cell carcinoma with tubular and spindle cell component. Note the mucinous stroma between the tubes.

Tubulocystic RCC

Most of the tumors present as a Bosniak 3 or 4 multilocular cyst, and are composed of small to intermediate-sized cysts with a spongy cut surface. The tumor cells have eosinophilic oncocytic-like cytoplasm with prominent nucleoli [Figure 14]. As P-RCC they show gains of chromosomes 7 and 17, and loss of the Y chromosome. These tumors have indolent behavior [12].

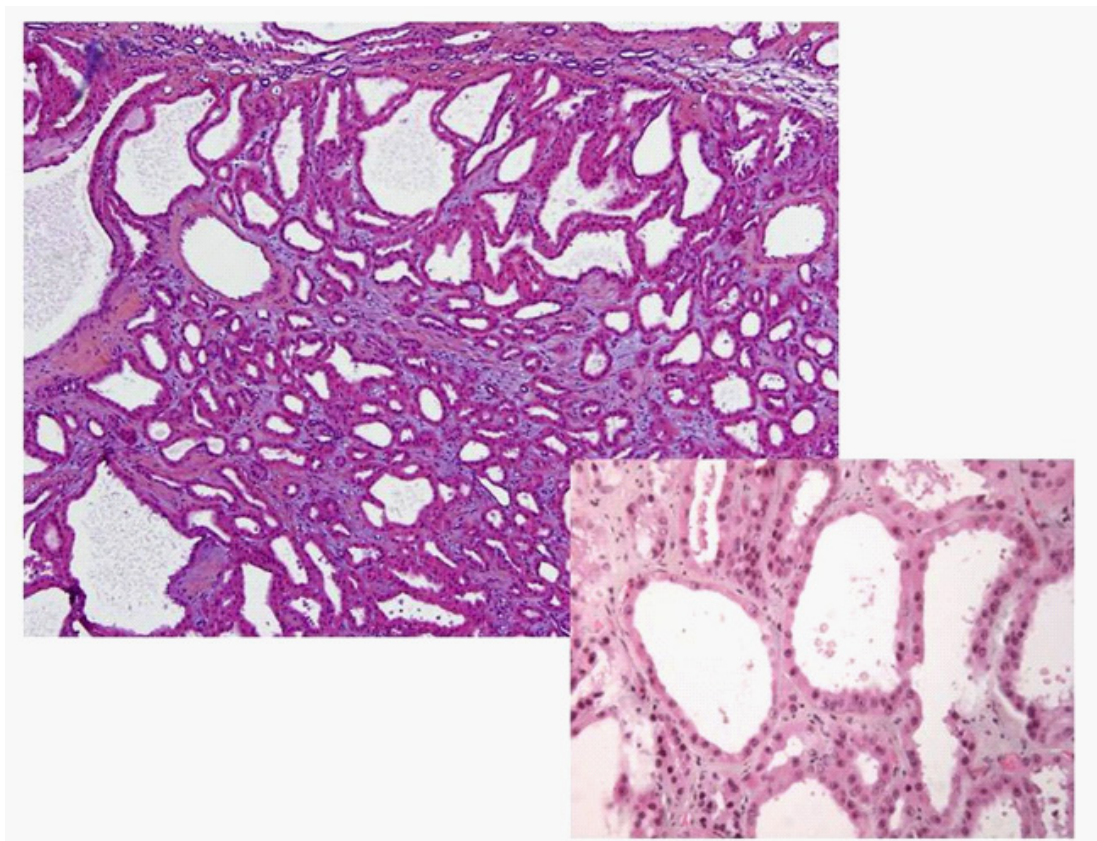


Figure 14: Histologic aspect of tubulocystic RCC

Acquired Cystic Disease Associated RCC

These tumors occur in patients with long term haemodialysis with end-stage renal disease. The tumor architecture is complex with acinar, cribriform, papillary, tubular and/or cystic growth pattern. The tumor cells show usually eosinophilic cytoplasm with prominent nucleoli [Figure 15]. Frequent calcium oxalate crystals are observed in renal tumor as well as in non tumoral kidney. The tumor cells are positive for AMACR but negative for CK7, and present gains of the 3, 16 and Y chromosomes that distinguish this tumor from papillary RCC [6].

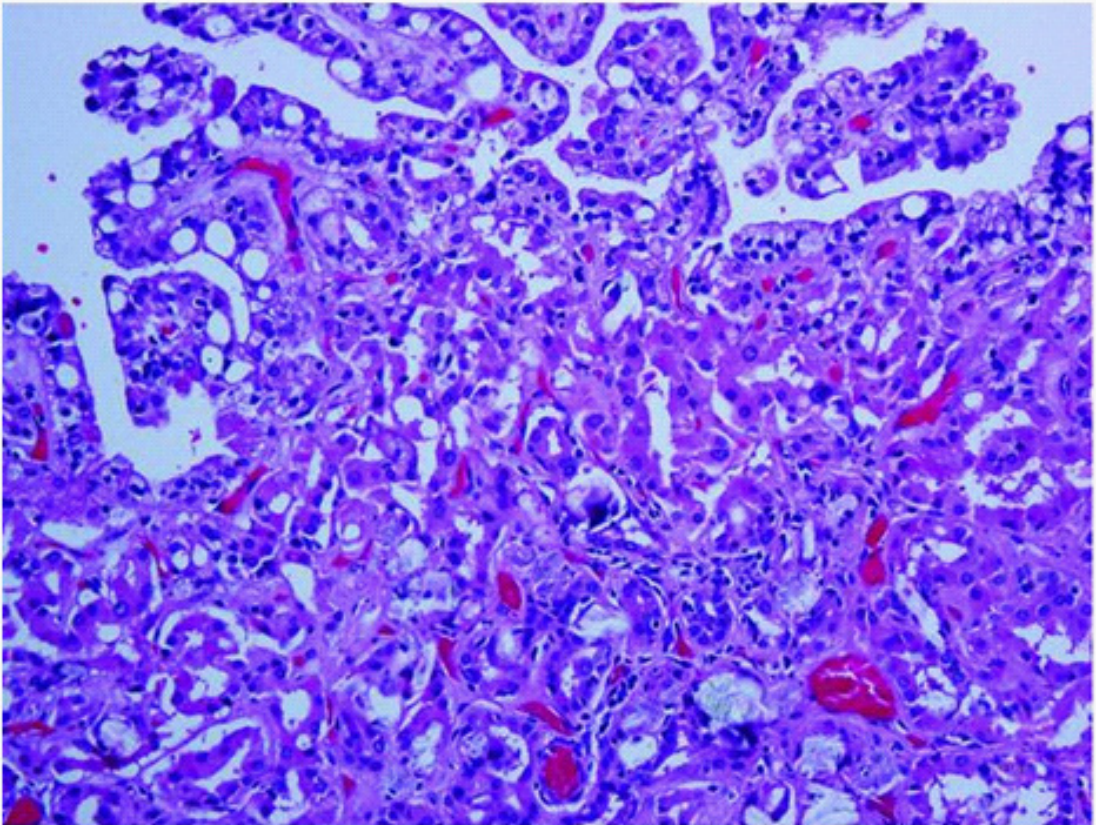


Figure 15: Histologic aspect of acquired cystic disease associated RCC. Note the presence focally of small calcium oxalate crystals.

Mixed Epithelial and Stromal Tumor of the Kidney (MEST)

As the cystic nephroma, mixed epithelial and stromal tumor of the kidney are benign tumors with stromal and epithelial component. MEST occur in perimenopausal women with a female to male ratio of 7:1. Macroscopically, the tumor presents both solid and cystic areas. The cysts lined by flat to hobnail eosinophilic cells, are separated by ovarian-like stroma and show immunoreactivity for estrogen and progesterone receptors [Figure 16]. A few cases of malignant transformation have been reported with sarcomatoid features in the stromal component. Except the cases with sarcomatoid transformation, MEST have benign outcome [13].

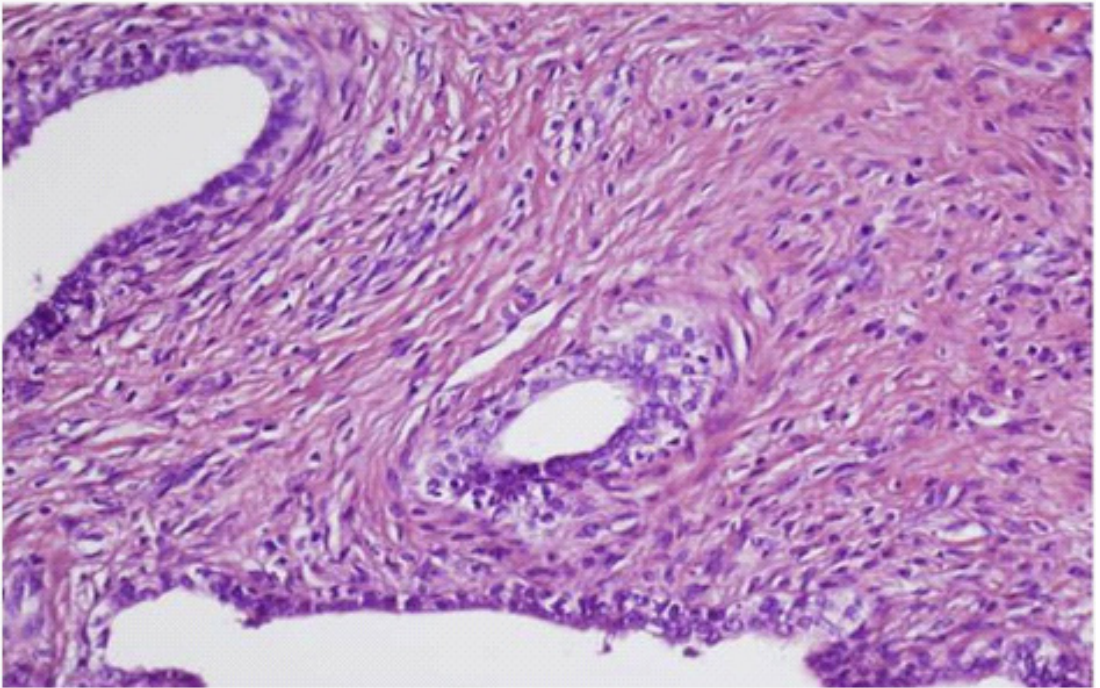


Figure 16: Histologic aspect of mixed epithelial and stromal tumor of the kidney (MEST).

Clear Cell Papillary RCC

This tumor usually occurs in end-stage kidney disease but some cases have been reported sporadically. Clear cell papillary RCC have a predominant papillary architecture, and are composed of non atypical clear cells with inconspicuous nucleoli, and a typical apical linear arrangement of nuclei [Figure 17]. The genetic profile of these tumors is distinct from those of cc-RCC and P-RCC. No progression or metastases has been reported [14].

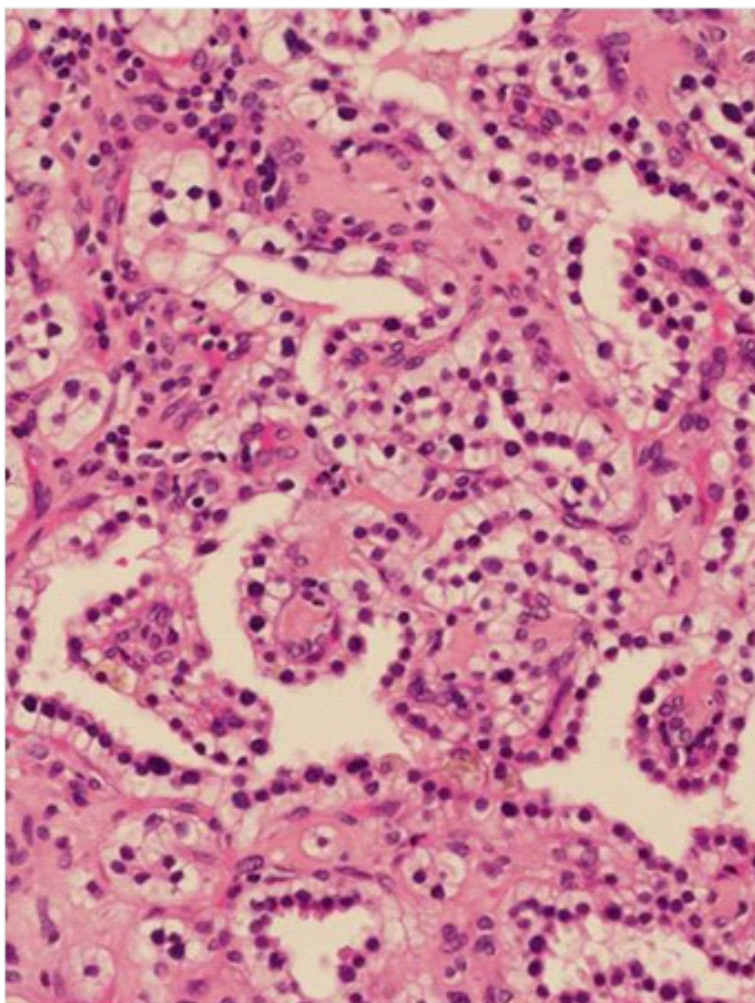


Figure 17: Histologic aspect of clear cell papillary RCC.

Epithelioid Angiomyolipoma (AML)

This entity represents 5% of all AMLs, and can be sporadic or associated with tuberous sclerosis complex (TS). Two patterns can be present: a carcinoma-like pattern, and an epithelioid component [Figure 18]. Tumor cells express melanocytic markers. These tumors have a risk of metastases and are classified into low, intermediate, and high risk of progression based on the association with TS, the presence of multiple AMLs, necrosis, extrarenal extension and/or renal vein invasion, carcinoma-like pattern, and tumor size > 7 cm [3,6].

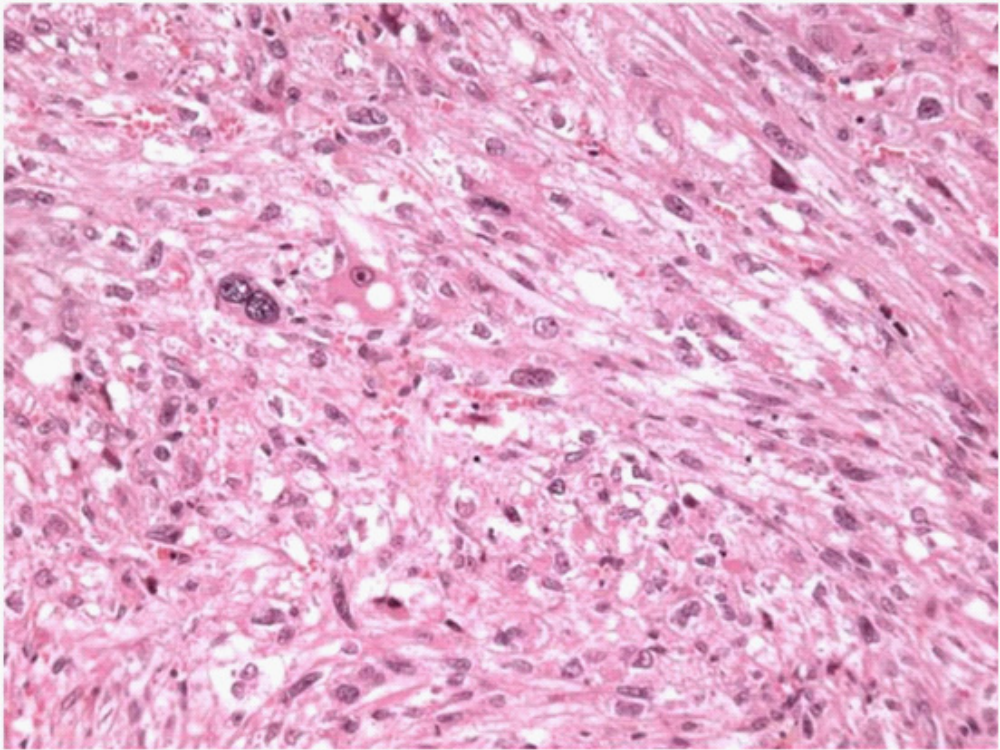


Figure 18: Histologic aspect of epithelioid angiosarcoma.

CONCLUSION

In the new 2016 histologic classification of renal tumors in adults the terminology used for the different subtypes of RCC has referred in the majority of the cases to histologic features of tumor cells. Rare histologic subtypes are characterized by molecular alterations.

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