Clear cell papillary renal cell carcinoma, renal angiomyoadenomatous tumor and renal cell carcinoma with leiomyomatous stroma-relationship of three types of renal tumors: A review

Ondrej Hes, Eva Maria Compérat, Nathalie Rioux-Leclerc

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Abstract

Renal angiomyoadenomatous tumor has been described in 2000, followed by description of clear cell papillary renal cell carcinoma in 2006. Discussion about possible relationship of both tumors were published since their description. As the main differencial diagnostic feature was considered presence/absence of fibroleiomyomatous stroma favoring diagnosis of RAT in stroma-rich tumors. However it was shown, that stroma is reactive, non-neoplastic by its nature and that all other histologic, immunohistochemical, and molecular-genetic features of both entities are identical. In upcomming WHO classification of renal tumors (2016) both lesions are considered as single entity (CCPRCC). Vaste majority of the published cases followed benign/indolent clinical course. Also vaste majority of the tumors has normal status of *VHL* gene (methylation, LOH 3p, mutations), however CCPRCC was referred in patients with VHL syndrome, Another issue covered by this review is possible relationship of CCPRCC and „renal cell carcinoma with leiomyomatous stroma“ (RCCLS). RCCLS shows clear cell cytology, abundand leiomyomatous stroma. Some of RCCLS are positive for CK 7, some negative. Similar situation exists for relation of RCCLS and *VHL* gene abnormalities. It is so far unclear, whether any relation between CCPRCC and RCCLS exists. From all published studies seems that these tumors are less likely each other related.

Key words : kidney ; renal angiomyoadenomatous tumor ; clear cell papillary renal cell carcinoma ; *VHL* gene ; renal cell carcinoma with leiomyomatous stroma ; relationship

Introduction

Renal angiomyoadenomatous tumor (RAT) has been described by Michal et al in 2000 in form of case report, and later in 2009 as series of 5 cases. Since initial description, several reports describing this distinct renal tumor have been published (1-4) (Fig 1). Morphologically, RATs are composed of tubules, small compact nests and abortive papillae lined by neoplastic columnar epithelial cells with optically clear cytoplasm, frequently with an apical „blister“ quality and low-grade (Fig 2), basally located nuclei, a well-developed peritubular capillary network and slightly open, variably angulated tubules which have been likened to the „shark smile“ (Fig 3) and variable presence of a leiomyomatous/myofibroblastic stroma (Fig 4). Immunohistochemically, the neoplastic epithelial cells of RAT express carbonic anhydrase-9 (CANH 9) (cup-shape pattern), CK7, PAX8 while expression of vimentin, CD10 and racemase (AMACR) is variable.

Clear cell papillary renal cell carcinoma (CCPRCC) has been introduced in 2006 by Tickoo et al in end-stage kidney disease. Majority of the cases reported since initial description have been

recognized in non-atrophic kidney (5-8). Numerous studies were addressed to further characterization of this relatively common, previously under-recognized renal tumor.

According ISUP Vancouver Classification 2012 CCPRCC is well circumscribed and well encapsulated. The cut surface is whitish to tan. Tumors are composed of clear cells of low nuclear grade, variable papillary, tubular/acinar, and cystic architecture, and a characteristic linear arrangement of nuclei away from the basal aspect of cells (Fig 5). Immunohistochemical profile is nearly identical with RAT, ie tumors are positive for CK7 (Fig 6), CANH 9, high-molecular weight cytokeratin positivity and CD10 and AMACR negativity (9). Coexpression of CK 7, which is by definition diffuse and strong, and CANH 9 is usually consider as immunohistochemical landmark of CCPRCC. Expression of CANH 9 is mostly diffuse with characteristic cup-like shape pattern (7). Such pattern correspond with shape of neoplastic cells. Typically they are cylindrical with elongated blister-shape snouts in luminal aspect of neoplastic glands. Apical portion of such cells is negative for CANH 9, thus “cup-shape” of the membranous positivity is obvious.

Relationship of clear cell papillary RCC and RAT

RAT and CCRCC share almost equal morphology and immunophenotype. Both types are characterized by the presence of

fibroleiomyomatous stroma and CK 7 positivity, they also bear similar molecular genetic attributes (lack of *VHL* gene abnormalities) (10, 11). Presumably, the difference between them inheres in stromal component, in the sense that RAT exhibit a voluminous stromal component and CCPRCC, in contrast, usually features a much less prominent smooth muscle stroma.

There is no strict line between CCPRCC and RAT. Minimum volume/amount of stroma has never been defined. Thus it is very subjective issue without exact criteria for differential diagnostic process.

However, the presence of the abundant fibroleiomyomatous stroma has been becoming as an important mark of distinction between RAT and CCPRCC and hence these two entities are regarded as related tumors and viewed as two ends of spectrum of one nosologic entity in ISUP 2012 (9).

Two multicentric studies have been published recently (7, 8). As conclusion of both papers is obvious, that RAT and CCPRCC are 2 morphologic ends of one etiologic entity. Similar view will be expressed in upcoming WHO classification 2016.

CCPRCC/RAT differential diagnosis

Majority of the cases are easily recognizable tumors with characteristic morphology. There are several issues which should be addressed:

Clear cell renal cell carcinoma with RAT-like areas.

Morphologic changes resembling CCPRCC can be seen within "typical" CCRCC. Such changes can produce tubopapillary architecture, "shark smiles", even blister like proliferation within lumens of cystic or tubular changes. In typical CCRCC such areas are mostly CK 7 negative.

However, CCRCC are considered as CK 7 negative tumor, but it is possible to find cases with strong CK 7 positivity. Expression of CK 7 in CRCC (albeit not strong and diffuse) has been documented by Gatalica et al as early as 1995. (12) The authors described immunoreactivity for CK7 in 24% of classic CRCC. Thus according our opinion, CK 7 immunoreactivity is one of the key diagnostic feature for CCPRCC, but should be interpreted with caution.

Mimickers of CCPRCC/RAT has been described in literature (13) (14). In all cases in series of Petersson et all resembled CCPRCC/RAT by morphology and also by some aspects of immunohistochemical profile (Fig 7). Majority of the cases demonstrated some degree of abnormalities on morphologic, immunohistochemical or molecular genetic level. Coexpression of strong immunoreactivity for CK7 and AMACR in tumors with overlapping features of both CCRCC and both CCPRCC have been documented, altogether with abnormalities

of *VHL gene* and numerical chromosomal aberrations (15). It was also clearly shown that „aberrant“ expression of cytokeratin 7 and AMACR in CRCC should not lead the diagnostician astray from a diagnosis of CRCC. (15)

Another group of tumors which should be taken into the consideration in differential diagnosis is MiT family (translocation) renal cell carcinomas group, mostly tumors associated with Xp11.2 translocation. These tumors are morphologically variable, mostly are arranged in papillary pattern and are composed of large, weakly eosinophilic or clear cells. There is no general morphologic feature specific for Xp11.2 RCCs. However tumors usually display tubulopapillary or papillary pattern, are composed of clear cell elements with psammoma bodies, eosinophilic hyaline nodules and occur mostly in younger patients. All tumors express TFE3 protein, albeit immunohistochemical detection is very problematic and a number of false positive/negative cases can be expected (16) (9). Thus more reliable is a *TFE3* break-apart FISH assay, which works on paraffin-embedded tissue (9, 17) (18). Cathepsin K was referred as reliable diagnostic tool for translocation RCC (19). Translocation RCC is further negative or only weakly and focally positive for keratins (including CK 7) and EMA, negative for racemase (AMACR) and CANH-9. Translocation RCC is positive with the antibody to vimentin and strongly positive with CD10. RAT/CCPRCC is low-grade tumor without psammoma bodies and hyaline nodules. For RAT/CCPRCC characteristic “shark-smiles” are not present in

translocation RCC, a swell as smooth muscle stroma. RAT/CCPRCC is diffusely positive for CK 7 and CANH-9, negative for TFE3 and cathepsin K.

VHL gene and CCPRCC/RAT

Mostly it is accepted, that CCPRCC/RAT has no changes in *VHL gene* (methylation, mutation) and has not LOH3p. However, recently CCPRCC has been referred in patient with VHL syndrome(20). Another studies describing CCPRCC showed abnormalities in *VHL gene* in 3 out of 37 cases of RAT/CCPRCC (8), and in about one third of the patients(21).

Based on detailed search in literature, analysis of our own cases seems that cases with doubtful morphology and/or unusual immunohistochemical profile bearing any *VHL gene* abnormalities should be not be classified as CCPRCC/RAT. In tumors, where the morphology is typical and immunohistochemical features are compatibile with the diagnostic of CCPRCC/RAT caution is needed, when any *VHL gene* (including LOH 3p and hypermethylation) abnormality is found. The reason is obvious. CCPRCC is a renal tumor with minimal aggressive potential. We are aware of case report presented in ECP in 2015, where the authors showed aggressive metastazing. RAT/CCPRCC (22). Detailed study dealing with prognosis of RAT/CCPRCC has been published recently. Authors

made exhaustive search in the English-written literature and found 268 reported cases and carefully examined their own series of 32 cases. Metastatic activity was approved only in 2 patients, in 1 patient suspect metastatic structures were found using imaging methods. The vast majority of RAT/CCPRCC documented in literature followed benign course (23). As we have minimal evidence of biologic behavior of RAT/CCPRCC mimickers, caution is needed when pathologists face such tumor. Both low-grade CCRCC, and PRCC can behave aggressively and patient should be carefully followed.

Renal cell carcinomas with a prominent smooth muscle stroma

Renal cell carcinomas with a prominent smooth muscle stroma (RCCSMS) are rare neoplasms. First case has been described by Canzonieri et al. in 1993 and subsequently documented by Kuhn et al in 2006 and others (24-27). Histologically RCCSMSs are composed of an intimate intermixture of two distinct components: epithelial and stromal. The epithelial component is represented by clear epithelial cells with mild nuclear atypia (mostly nuvleolar ISUP/Fuhrman grade 2) arranged in adenomatous structures with predominantly nested or tubular pattern associated with focal papillary and solid areas (Fig 8).

Exact diagnostic criteria are not established. Morphology and immunohistochemical features (namely CK 7 positivity among others) are variable in previous studies.

Tuberous sclerosis complex and RAT/CCPRCC

Guo et all described recently series of RCC occurring in patients with tuberous sclerosis complex (TS). 30% of RCC described in this study had features similar to tumors previously described as "renal angiomyoadenomatous tumor" or "RCC with smooth muscle stroma"; 59% showed features similar to chromophobe RCC; and 11% showed a granular eosinophilic-macrocystic morphology (so-called solid and cystic RCC) (28).

Besides above cited paper, RATs described in the literature were present in the background of end-stage-kidney or in sporadic settings. Also cases described under the term CCPRCC were not part of TS complex.

CCPRCC/RAT and RCC with leiomyomatous stroma

It was pointed out by Martignoni et al, that RCCSMS is tumor distinct from clear cell RCC and that these tumors could be related to RAT/CCPRCC (29). Our results indicate, at least on the morphologic and immunohistochemical level, that there are some differences

between RCCSMS and RAT/CCPRCC. Further studies with a larger cohort of patients should be performed to confirm any possible link between RCCSMS and CCPRCC/RAT.

Leiomyomatous stroma is mostly reactive, non-neoplastic tissue, possibly derived from vascular structures as it is indicated by immunohistochemical profile. Leiomyomatous stroma is not restricted to renal tumors like RAT or RCCSMS. It was shown in otherwise typical clear cell RCC or in papillary RCC (30). We believe that leiomyomatous/fibroleiomyomatous stroma is just reactive condition, which not preclude any particular diagnosis. Hence tumors with clear cell morphology and voluminous stromal component should be tested for *VHL gene* abnormalities. It is possible to speculate about relationship between CCPRCC/RAT and RCCSMS only in tumors, which are *VHL gene* mutation, hypermethylation (and LOH3p) negative and CK 7 positive (Fig 9).

We have analyzed 8 cases of RCCSMS with *VHL gene* abnormalities and without such changes using next generation sequencing. We were not able to find any *VHL gene* abnormality using NGS (Fig 10). Also compared our results with NGS study conducted by Lawrie et al. Authors analyzed 17 CCPRCC/RAT and they found that EMT in CCPRCC tumor cells is incomplete or blocked, consistent with the indolent clinical course typical of this malignancy (31). We were not able to disclose any similar genetic changes in both groups (cases with *VHL gene* abnormalities and cases without abnormalities) of RCCSMS (Ondrej Hes, unpublished data).

TCEB-1 mutated RCC and RCCSMS

Peculiar renal tumors composed of clear cells and distinct leiomyomatous stroma have been documented recently. Pathologically, all *TCEB1*-mutated tumors shared characteristic features including thick fibromuscular bands transecting the tumor, pure clear cell cytology frequently with cells showing voluminous cytoplasm, and clear cell renal cell carcinoma-like acinar areas associated with infolding tubular and focally papillary architecture. Such tumors harbored *TCEB-1 gene* mutations, lacked LOH 3p. According authors, the presence of voluminous cytoplasm, absence of luminal polarization of tumor nuclei, and lack of extensive cup-like distribution of carbonic anhydrase-IX expression distinguish it from clear cell papillary carcinoma. (32)

From the photodocumentation and description is obvious that TCEB-1 tumors are morphologically similar to RCCSMS. As the authors mentioned, morphology and immunohistochemical profile of *TCEB1*-mutated tumors is different from RAT/CCPRCC. From morphological

point of view it would be extremely difficult to distinguish *TCEB1*-mutated tumor from RCCSMS and seems that molecular genetic analysis of *TCEB-1* gene would be in such tumors beneficial part of analytical algorythm.

As we have mentioned earlier, we have performed NGS analysis of RCCSMS. We have not be able to show any *TCEB-1* abnormalities in both groups (Hes, unpublished results).

As a summary it is possible to conclude, that RAT and CCPRCC are two morphologic ends of one nosologic entity. Vaste majority of the published cases followed benign/indolent clinical course. Tumors displaying similar morphologic attributes, ie mostly clear cell low-grade population and abundand leiomyomatous stroma are designated as renal cell carcinomas with leiomyomatous stroma. It is so far unclear, whether any relation between CCPRCC and RCCLS exists.

Disclosure of Conflict of Interest

All authors declare no conflict of interest.

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Legends to figures

Fig 1: Typical clear cell papillary renal cell carcinoma (RAT). Tumor is encapsulated by thick whitish tissue with prominent septae crossing neoplastic mass.

Fig 2: Clear cell papillary renal cell carcinoma (RAT) is composed of tubules, small compact nests and abortive papillae lined by neoplastic columnar epithelial cells with optically clear cytoplasm, with an apical „blister“ quality and low-grade, basally located nuclei.

Fig 3: Angulated tubules which have been likened to the „shark smile“ seen scattered in neoplastic mass

Fig 4: Capsule and leiomyomatous stroma is clearly visible in histotopogram of clear cell papillary renal cell carcinoma (RAT).

Fig 5: Linear arrangement of nuclei away from the basal aspect of cells is characteristic feature for clear cell papillary renal cell carcinoma (RAT).

Fig 6: Clear cell papillary renal cell carcinoma (RAT) is diffusely positive for CK 7.

Fig 7: Clear cell papillary renal cell carcinoma mimicker. This tumor was diagnosed as clear cell renal cell carcinoma (morphology supported by abnormalities in *VHL* gene and negative reaction with CK 7). A, Gross section demonstrated fibroleiomaomatous capsule and prominent leiomyomatous component. B, Tumor is composed of low-grade clear cells arranged in tubulopapillary pattern. Basally oriented nuclei are clearly visible. C, CK 7 is strongly, but focally positive.

Fig 8: Renal cell carcinomas with a prominent smooth muscle stroma. Histologically tumors are composed of an intimate intermixture of two distinct components: clear cell epithelial and leiomyomatous. This tumor was negative for all *VHL gene* abnormalities and positive for CK 7.

Fig 9: Another example of tumor, of which morphology is compatible with diagnosis of renal cell carcinomas with a prominent smooth muscle stroma. However, this particular case was positive for CK 7 and *VHL gene* mutation was detected.

Fig 10: Another case, which has morphologic features of renal cell carcinomas with a prominent smooth muscle stroma. Tumor was negative for CK 7 and we were not able to find any *VHL gene* abnormalities.

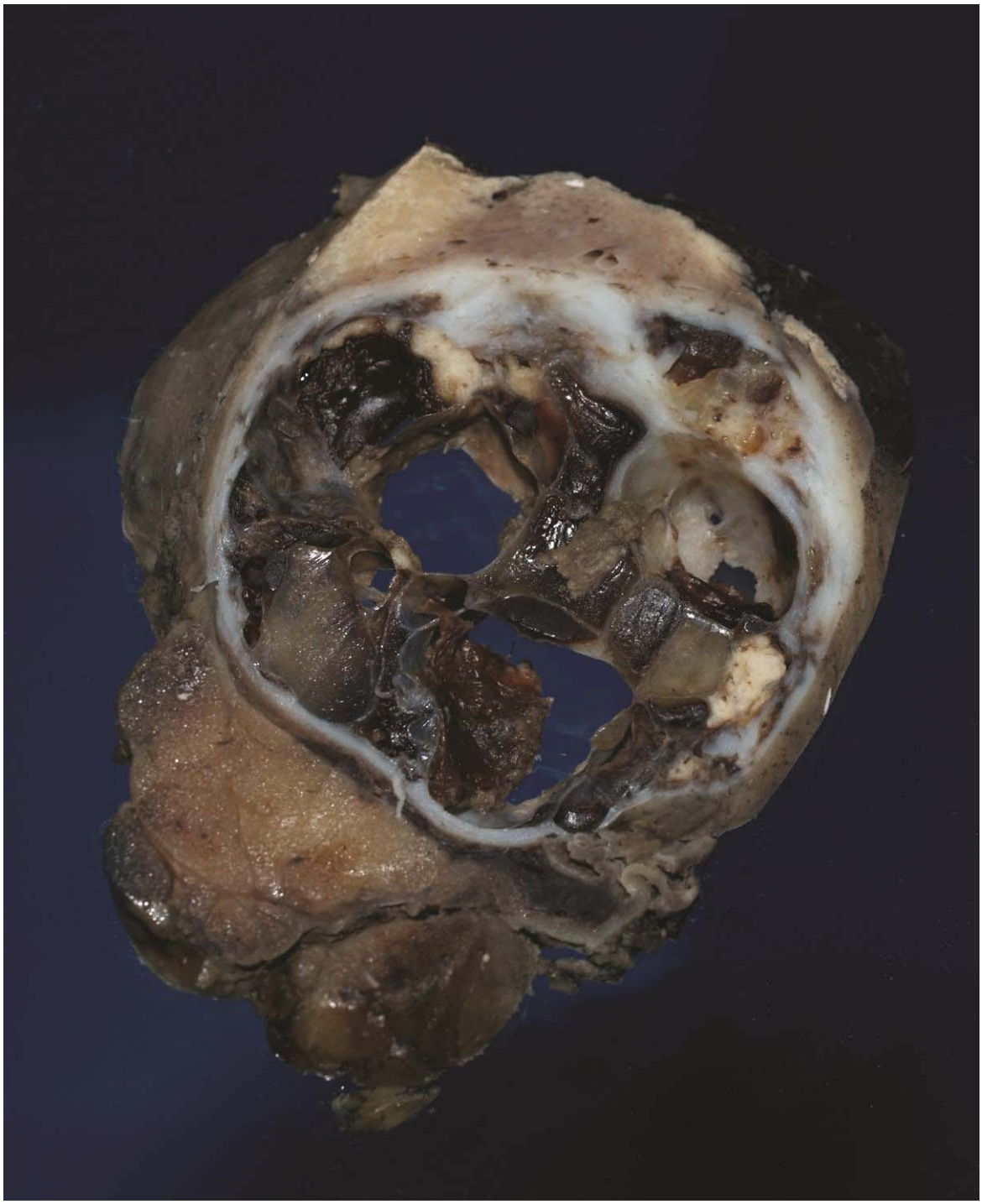


Figure 1

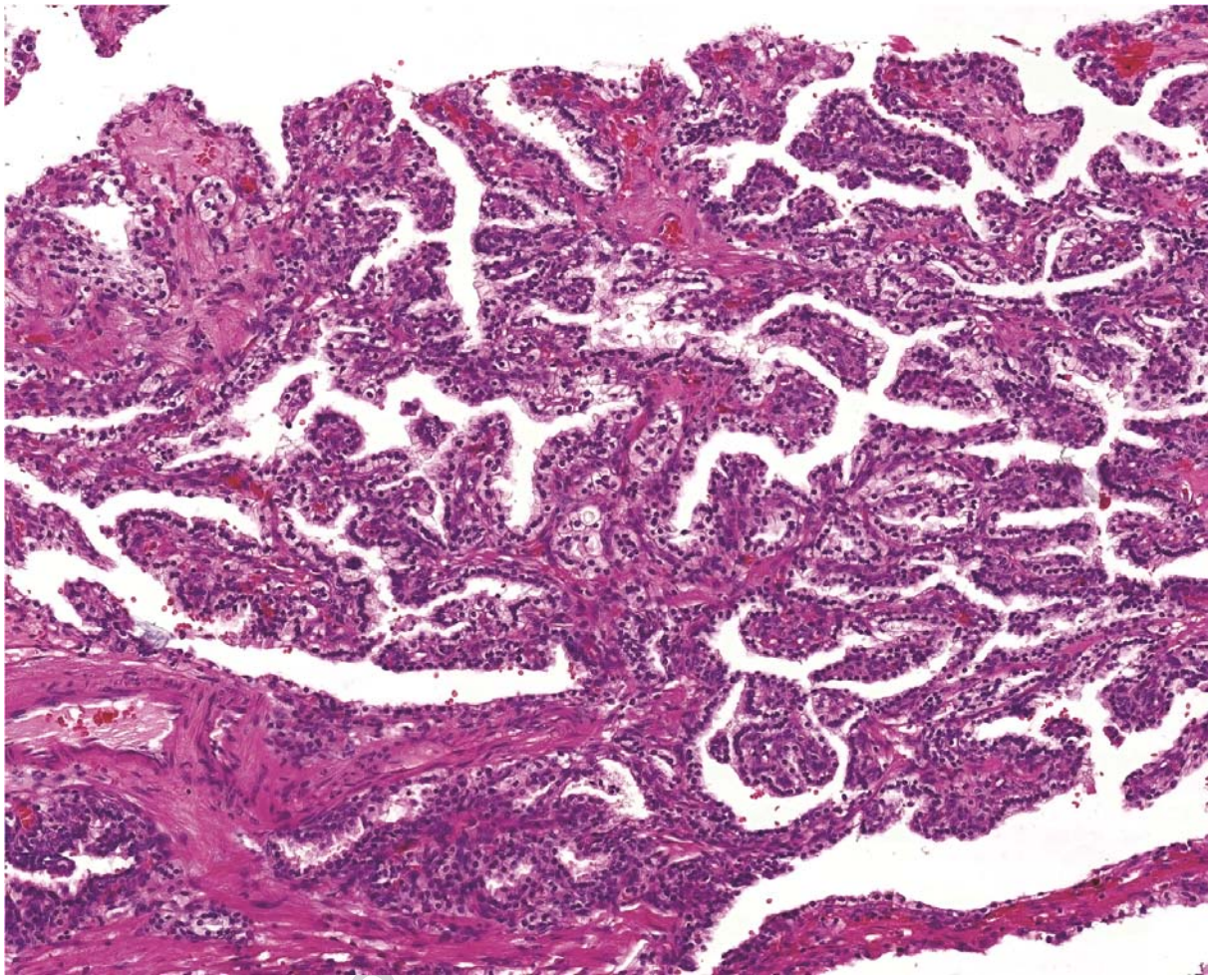
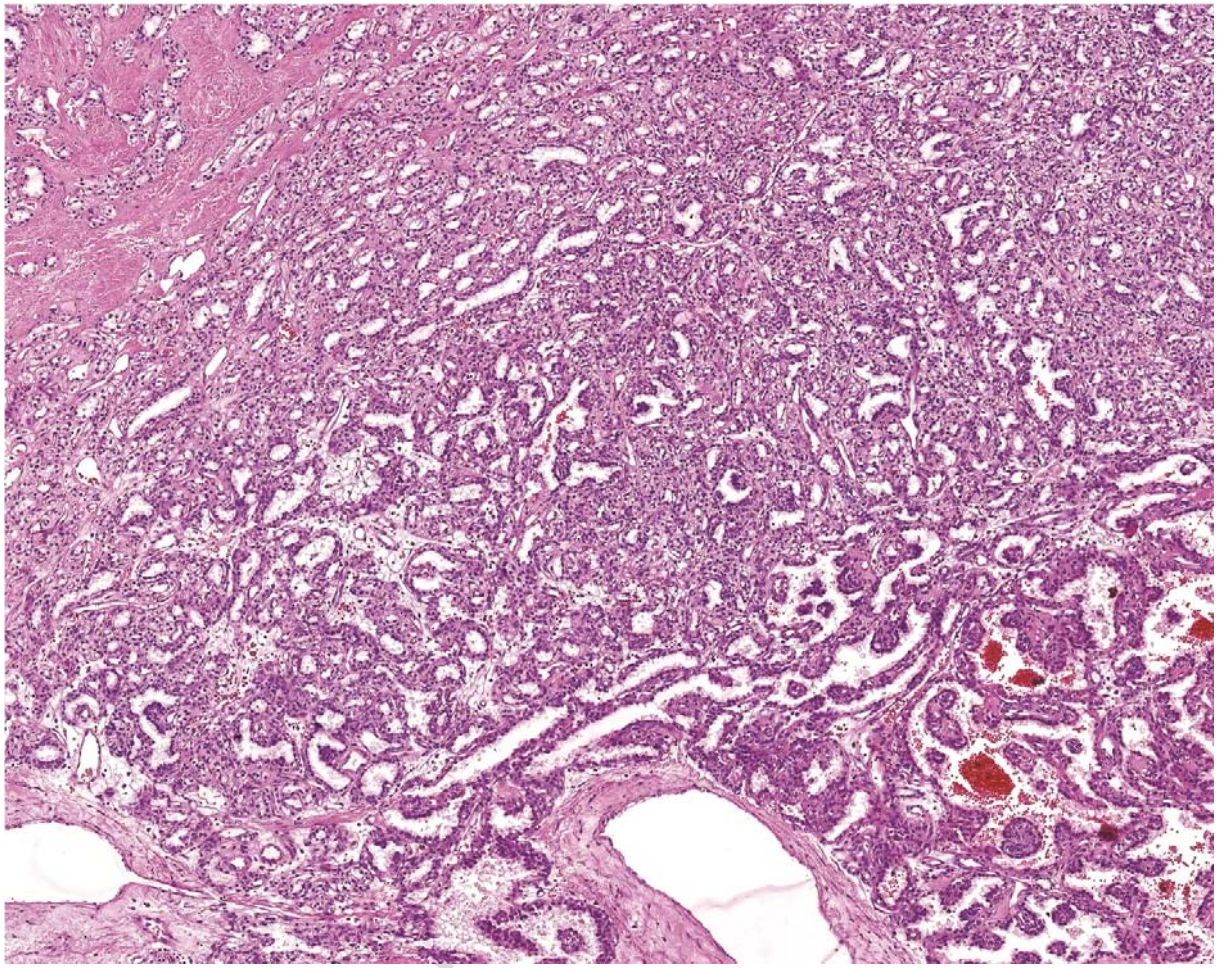


Figure 2



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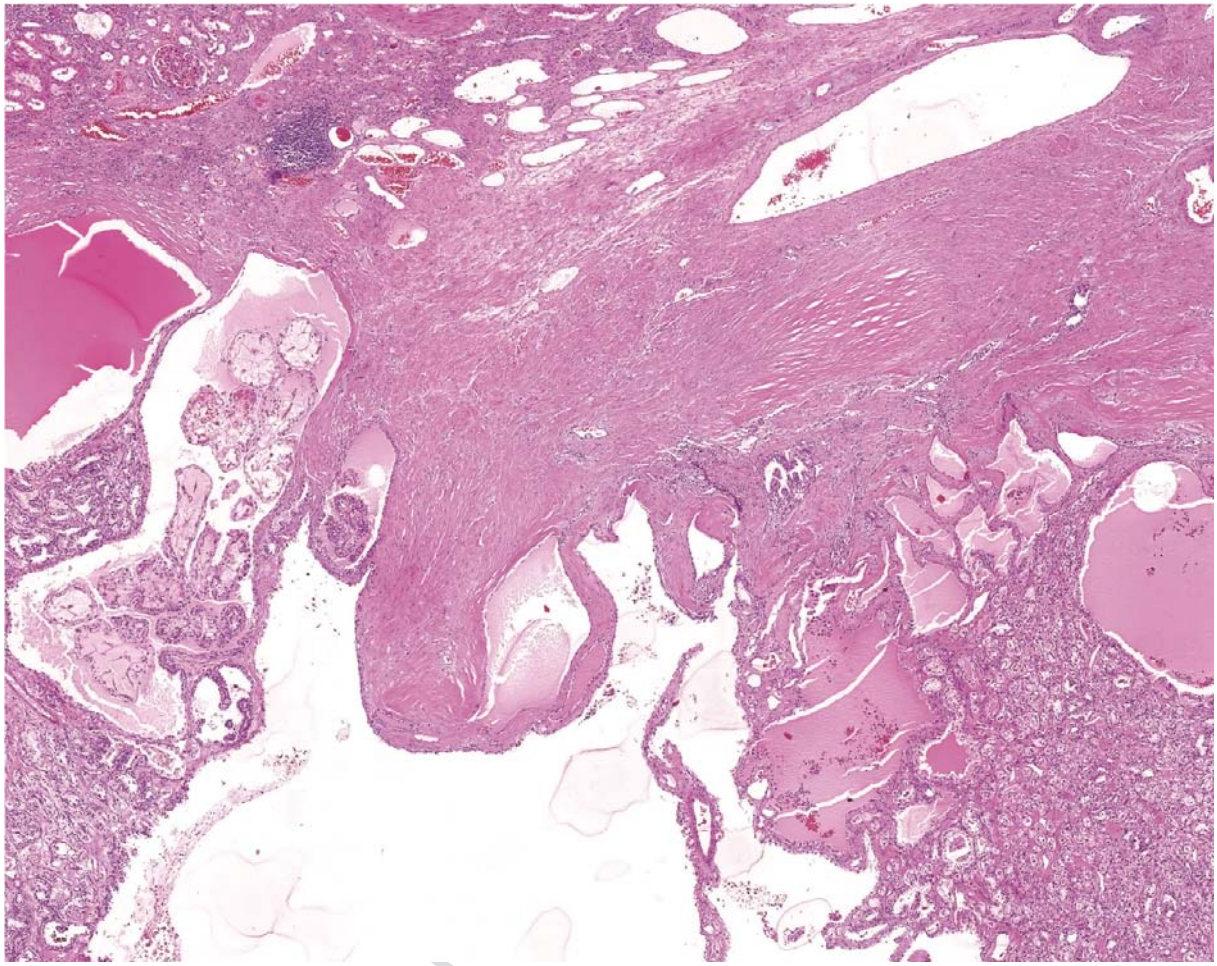

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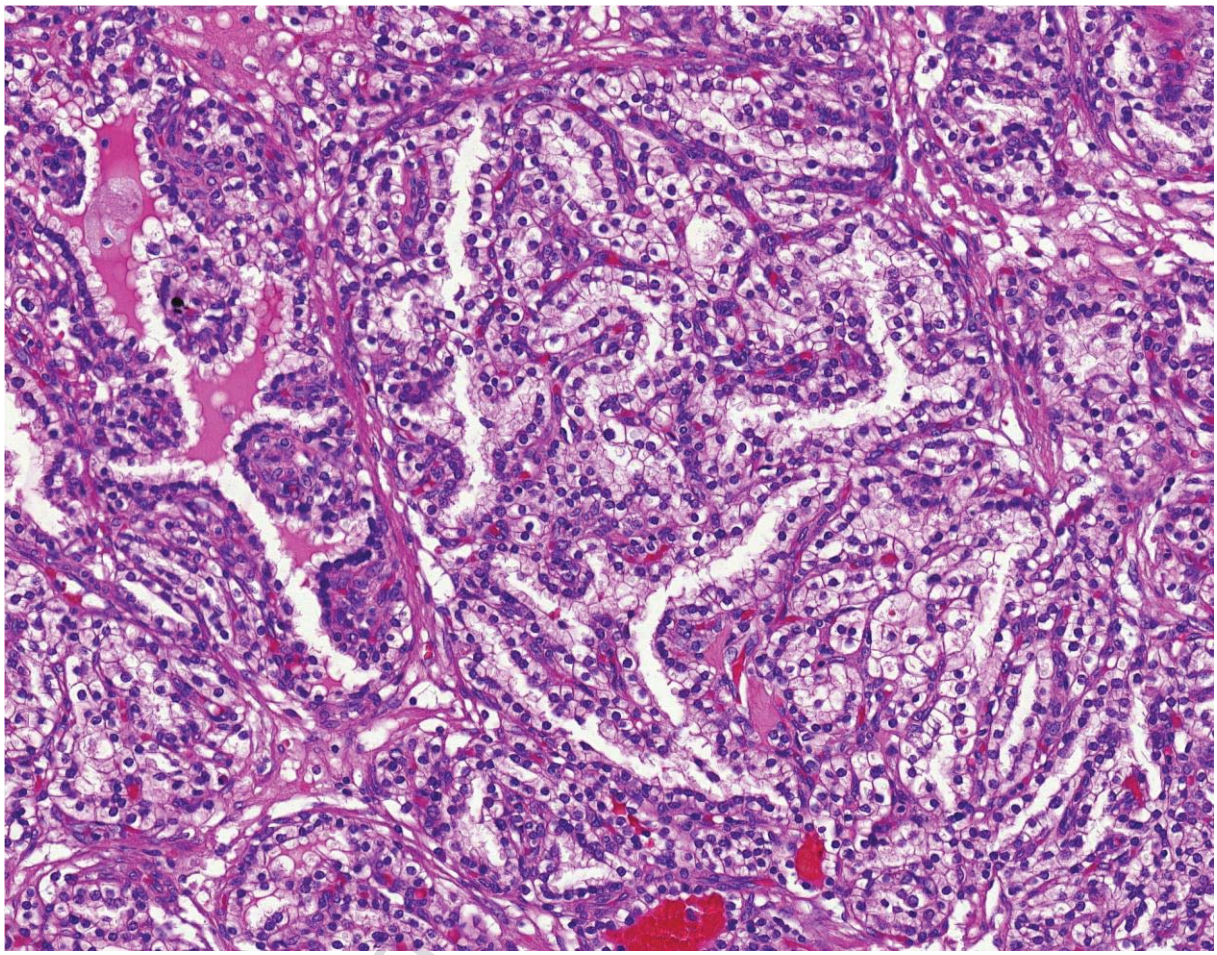

Figure 5

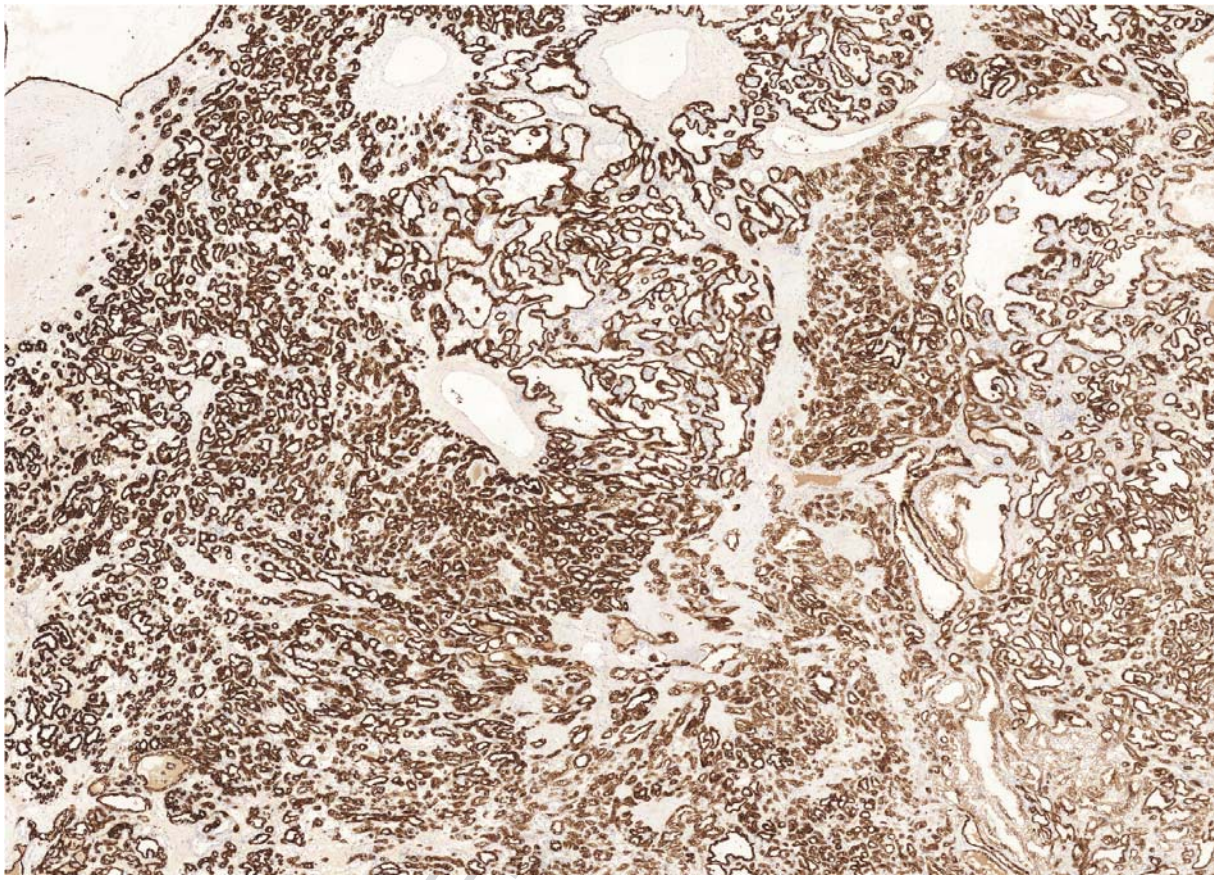

Figure 6

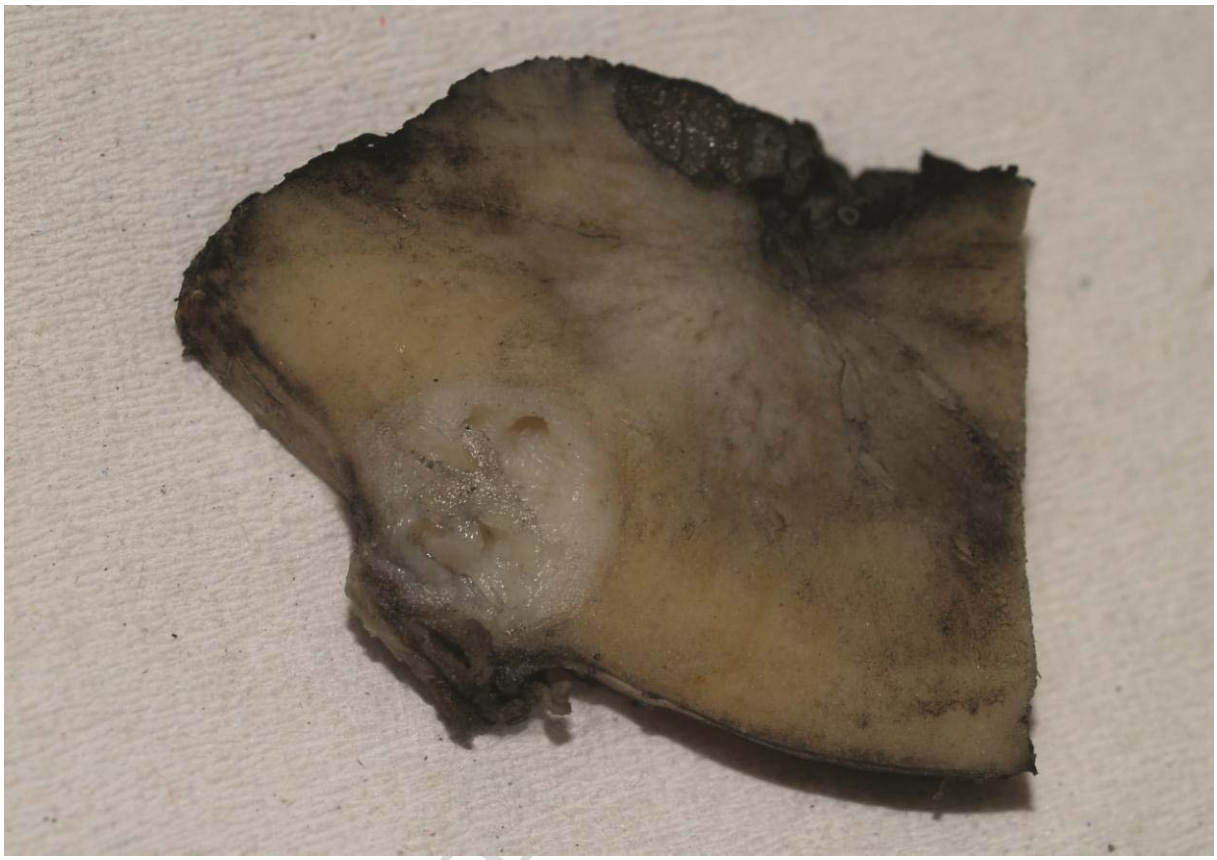

Figure 7A

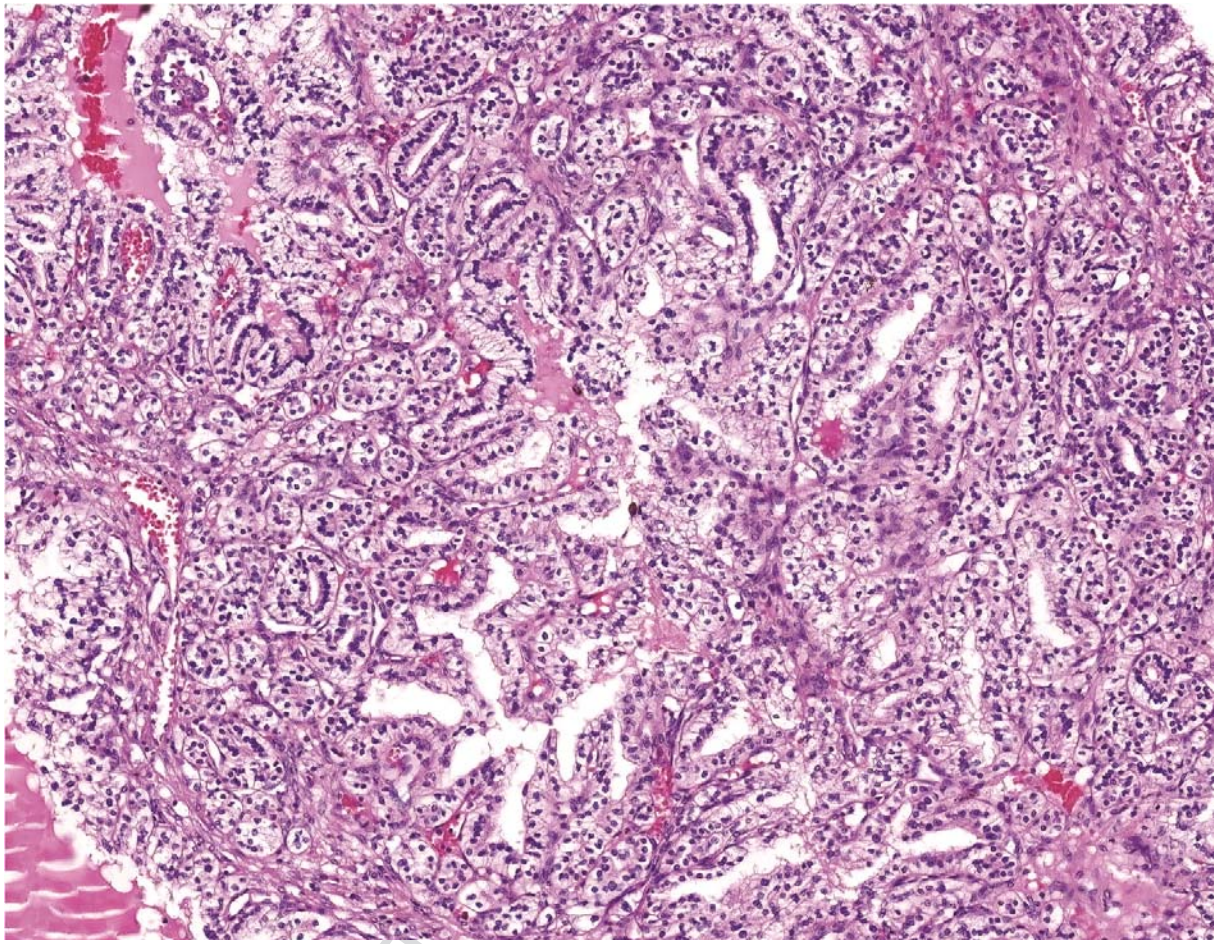

Figure 7B

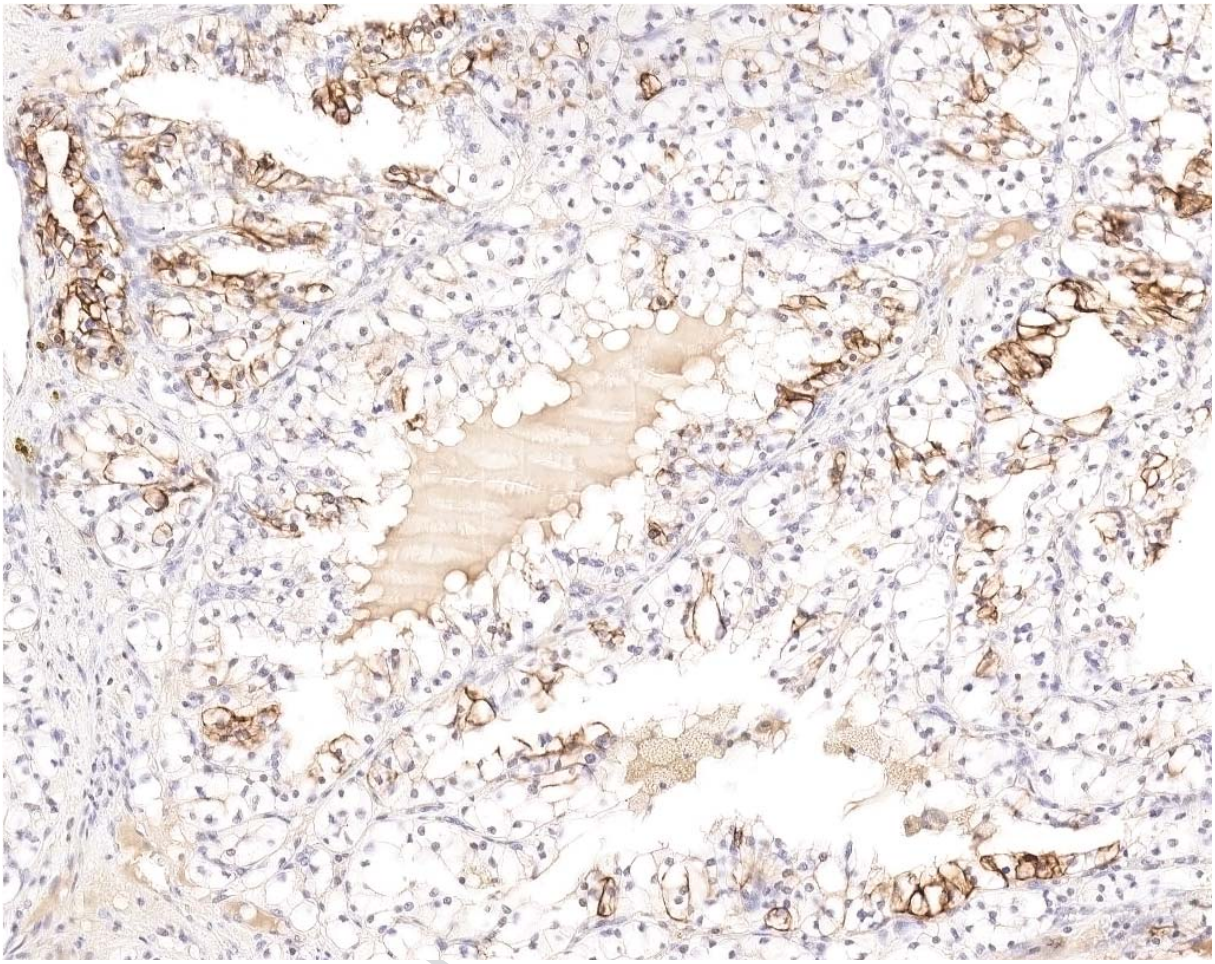

Figure 7C

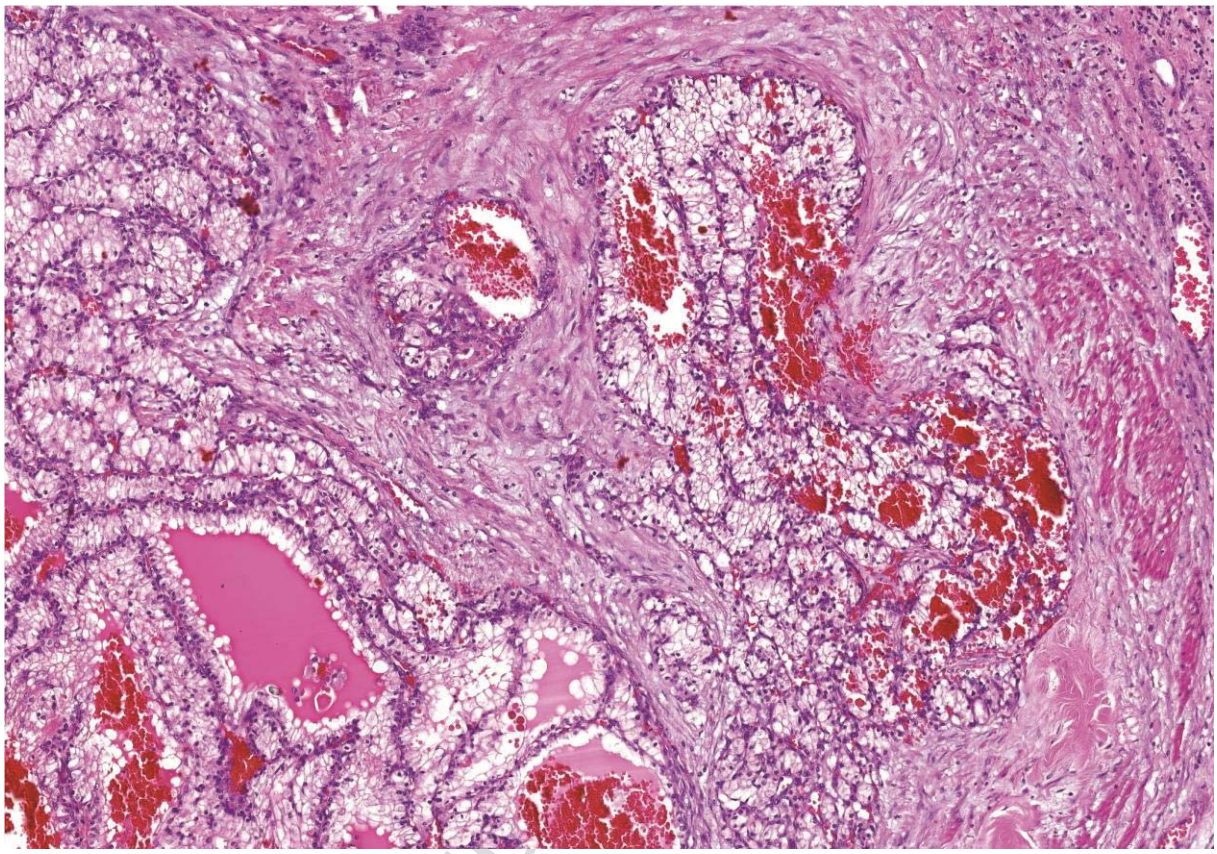

Figure 8

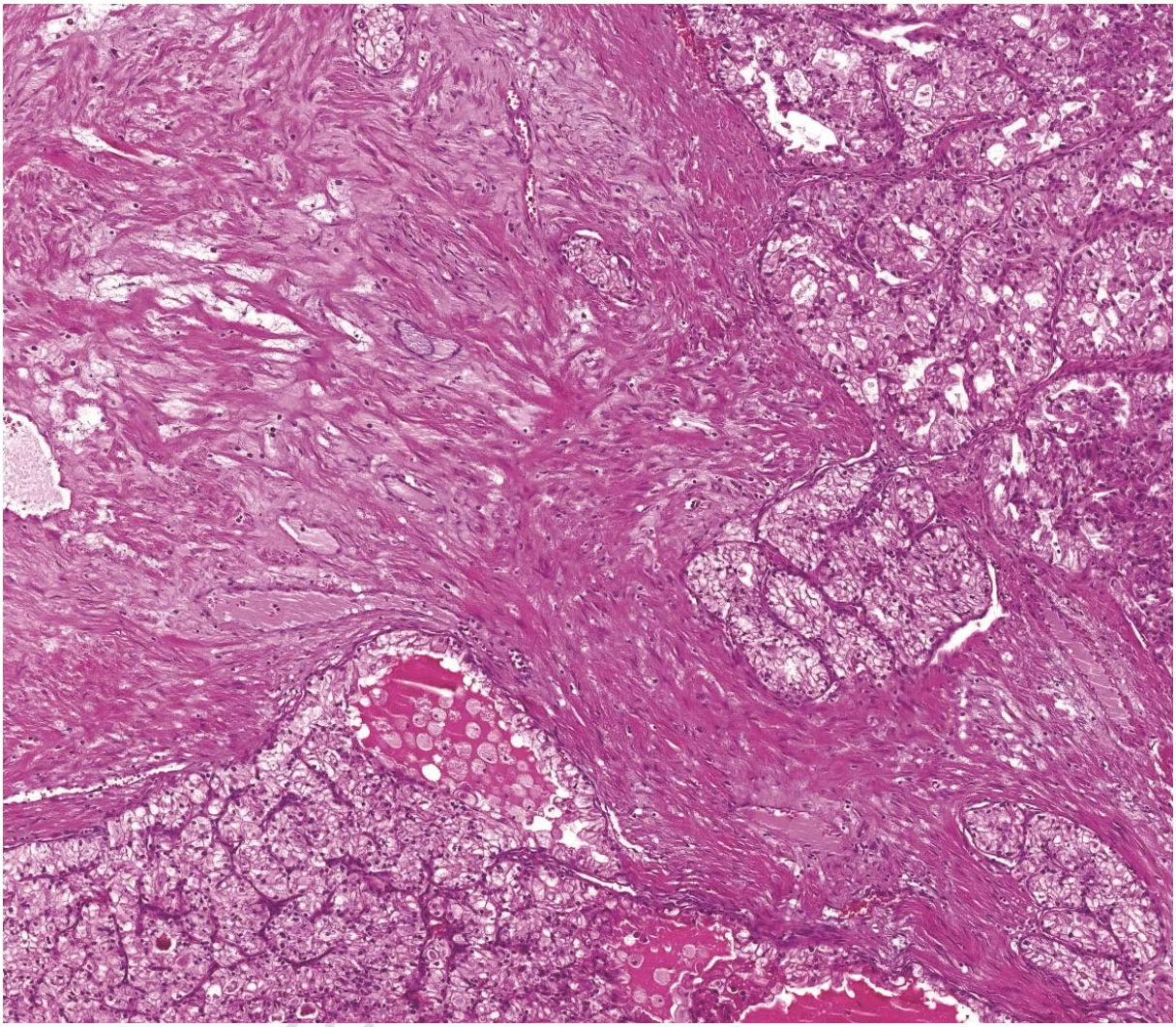

Figure 9

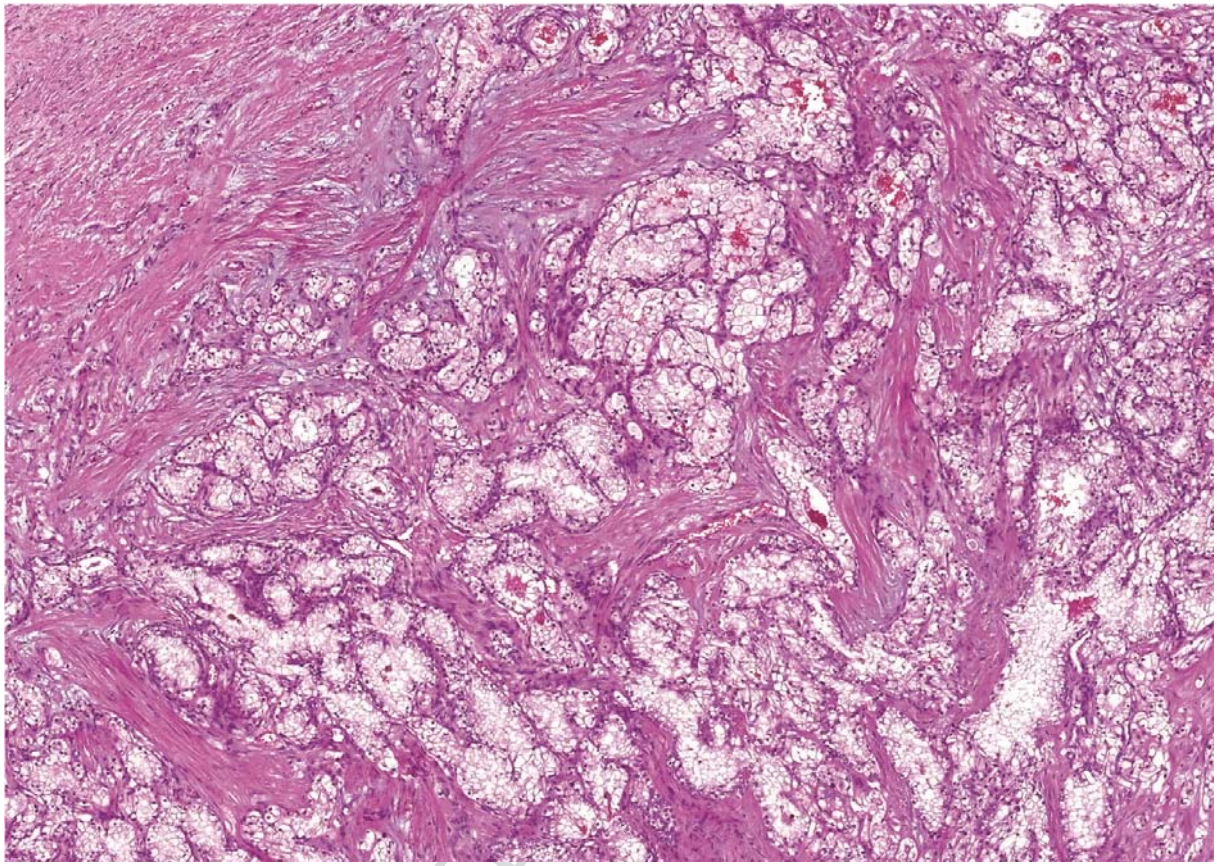

Figure 10

“ Clear cell papillary renal cell carcinoma, renal angiomyoadenomatous tumor and renal cell carcinoma with leiomyomatous stroma-relationship of three types of renal tumors. A review.”-highlights

1, Paper describes author´s opinion about three different neoplastic entities occuring in the kidney.

2, Relation of renal angiomyoadenomatous tumor and clear cell papillary renal cell carcinoma will be discussed in upcoming WHO 2016 classification. Authors expressed their opinion in context of new WHO classification.

3, Relation of *VHL* gene mutations and abnormalities and above mentioned renal tumors is discussed in detail.

4, Morphologic and molecular genetic characteristics of renal cell carcinoma with leiomyomatous stroma are described as well as relation between renal angiomyoadenomatous tumor/ clear cell papillary renal cell carcinoma and renal cell carcinoma with leiomyomatous stroma.