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

► To cite this version:

Ondrej Hes, Eva Maria Compérat, Nathalie Rioux-Leclerc. 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. *Annals of Diagnostic Pathology*, 2016, 21, pp.59-64. 10.1016/j.anndiagpath.2015.11.003 . hal-01263114

HAL Id: hal-01263114

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-01263114>

Submitted on 28 Jan 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

1, Department of Pathology, Charles University in Prague, Faculty of Medicine in Plzeň, Czech Republic

2, Department of Pathology, Hôpital La Pitié Salpêtrière, Faculty of Medicine UPMC Paris VI, France

3, Department of Pathology, CHU Pontchaillou, Université de Rennes 1, Rennes, France

The authors declare that they have no conflict of interest.

The study was supported by the Charles University Research Fund (project number P36) and by the project CZ.1.05/2.1.00/03.0076 from European Regional Development Fund

Address for correspondence:

Ondrej Hes, MD, PhD

Department of Pathology, Charles University, Medical Faculty and
Charles University Hospital Plzen, Alej Svobody 80, 304 60 Pilsen,
Czech Republic.

E-mail: hes@medima.cz

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.

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 differential 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 upcoming 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

ACCEPTED MANUSCRIPT

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 (CAH 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 al 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, as well 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 compatible 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 nucleolar 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 al 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-macrocytic 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 algorithm.

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.

1. Michal M, Hes O, Havlicek F. Benign renal angiomyoadenomatous tumor: a previously unreported renal tumor. *Annals of diagnostic pathology*. 2000 Oct;4(5):311-5. PubMed PMID: 11073338.
2. Michal M, Hes O, Nemcova J, Sima R, Kuroda N, Bulimbasic S, et al. Renal angiomyoadenomatous tumor: morphologic, immunohistochemical, and molecular genetic study of a distinct entity. *Virchows Archiv : an international journal of pathology*. 2009 Jan;454(1):89-99. PubMed PMID: 19020896.
3. Kuroda N, Michal M, Hes O, Taguchi T, Tominaga A, Mizobuchi K, et al. Renal angiomyoadenomatous tumor: fluorescence in situ hybridization. *Pathology international*. 2009 Sep;59(9):689-91. PubMed PMID: 19712141.
4. Singh C, Kendi AT, Manivel JC, Pambuccian SE. Renal angiomyoadenomatous tumor. *Annals of diagnostic pathology*. 2012 Dec;16(6):470-6. PubMed PMID: 22534244.
5. Tickoo SK, dePeralta-Venturina MN, Harik LR, Worcester HD, Salama ME, Young AN, et al. Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. *The American journal of surgical pathology*. 2006 Feb;30(2):141-53. PubMed PMID: 16434887.
6. Williamson SR, Eble JN, Cheng L, Grignon DJ. Clear cell papillary renal cell carcinoma: differential diagnosis and extended immunohistochemical profile. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc*. 2012 Dec 14. PubMed PMID: 23238627.
7. Aron M, Chang E, Herrera L, Hes O, Hirsch MS, Comperat E, et al. Clear cell-papillary renal cell carcinoma of the kidney not associated with end-stage renal disease: clinicopathologic correlation with expanded immunophenotypic and molecular characterization of a large cohort with emphasis on relationship with renal angiomyoadenomatous tumor. *The American journal of surgical pathology*. 2015 Jul;39(7):873-88. PubMed PMID: 25970682.
8. Deml KF, Schildhaus HU, Comperat E, von Teichman A, Storz M, Schraml P, et al. Clear cell papillary renal cell carcinoma and renal angiomyoadenomatous tumor: two variants of a morphologic, immunohistochemical, and genetic distinct entity of renal cell carcinoma. *The American journal of surgical pathology*. 2015 Jul;39(7):889-901. PubMed PMID: 25970683. Pubmed Central PMCID: 4465996.
9. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *The American journal of surgical pathology*. 2013 Oct;37(10):1469-89. PubMed PMID: 24025519.
10. Verine J. Renal angiomyoadenomatous tumor: morphologic, immunohistochemical, and molecular genetic study of a distinct entity. *Virchows Archiv : an international journal of pathology*. 2009 Apr;454(4):479-80. PubMed PMID: 19205727.

11. Petersson F, Yan B, Huang J, Thamboo TP, Bing TK, Consigliere DT. Low-grade renal carcinoma with histologic features overlapping with renal angiomyoadenomatous tumor and featuring polysomy 7 and 17 and a mutation in the von Hippel-Lindau gene: report of a hybrid tumor and a few comments on renal angiomyoadenomatous tumor and papillary renal tumors with clear cells. *Annals of diagnostic pathology*. 2011 Jun;15(3):213-6. PubMed PMID: 21396864.
12. Gatalica Z, Miettinen, M. Consistent expression of cytokeratin 7 in papillary renal-cell carcinoma. *J Urol Pathol* 1995;3:205-11.
13. Kuroda N, Hosokawa T, Michal M, Hes O, Sima R, Ohe C, et al. Clear cell renal cell carcinoma with focal renal angiomyoadenomatous tumor-like area. *Annals of diagnostic pathology*. 2011 Jun;15(3):202-6. PubMed PMID: 20952290.
14. Williamson SR, Gupta NS, Eble JN, Rogers CG, Michalowski S, Zhang S, et al. Clear Cell Renal Cell Carcinoma With Borderline Features of Clear Cell Papillary Renal Cell Carcinoma: Combined Morphologic, Immunohistochemical, and Cytogenetic Analysis. *The American journal of surgical pathology*. 2015 Nov;39(11):1502-10. PubMed PMID: 26457355.
15. Petersson F, Grossmann P, Hora M, Sperga M, Montiel DP, Martinek P, et al. Renal cell carcinoma with areas mimicking renal angiomyoadenomatous tumor/clear cell papillary renal cell carcinoma. *Human pathology*. 2013 Jul;44(7):1412-20. PubMed PMID: 23434146.
16. Macher-Goeppinger S, Roth W, Wagener N, Hohenfellner M, Penzel R, Haferkamp A, et al. Molecular heterogeneity of TFE3 activation in renal cell carcinomas. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 2012 Feb;25(2):308-15. PubMed PMID: 22037260.
17. Gaillot-Durand L, Chevallier M, Colombel M, Couturier J, Pierron G, Scoazec JY, et al. Diagnosis of Xp11 translocation renal cell carcinomas in adult patients under 50 years: interest and pitfalls of automated immunohistochemical detection of TFE3 protein. *Pathology, research and practice*. 2013 Feb 15;209(2):83-9. PubMed PMID: 23246378.
18. Hayes M, Peckova K, Martinek P, Hora M, Kalusova K, Straka L, et al. Molecular-genetic analysis is essential for accurate classification of renal carcinoma resembling Xp11.2 translocation carcinoma. *Virchows Archiv : an international journal of pathology*. 2015 Mar;466(3):313-22. PubMed PMID: 25544614.
19. Martignoni G, Bonetti F, Chilosi M, Brunelli M, Segala D, Amin MB, et al. Cathepsin K expression in the spectrum of perivascular epithelioid cell (PEC) lesions of the kidney. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 2012 Jan;25(1):100-11. PubMed PMID: 21874011.
20. Williamson SR, Cheng L. Do clear cell papillary renal cell carcinomas occur in patients with von Hippel-Lindau disease? *Human pathology*. 2015 Feb;46(2):340-1. PubMed PMID: 25476124.
21. Xu W, Deng, F.-M., Melamed, J., Zhou, M. Incidence and genetic characteristics of clear cell tubopapillary renal cell carcinoma. *Modern Pathol.* 2014;27(Suppl 2):270A.
22. Micsik T, Kuthi, L., Iványi, B., Sápi, Z. Case study of a metastatic clear cell tubulopapillary renal cell cancer. *Virchows Archiv*. 2015;467(Suppl 1):S242.
23. Diolombi ML, Cheng L, Argani P, Epstein JI. Do Clear Cell Papillary Renal Cell Carcinomas Have Malignant Potential? *The American journal of surgical pathology*. 2015 Sep 29. PubMed PMID: 26426379.
24. Canzonieri V, Volpe R, Gloghini A, Carbone A, Merlo A. Mixed renal tumor with carcinomatous and fibroleiomyomatous components, associated with angiomyolipoma in the same kidney. *Pathology, research and practice*. 1993 Sep;189(8):951-6; discussion 7-9. PubMed PMID: 8302716.
25. Kuhn E, De Anda J, Manoni S, Netto G, Rosai J. Renal cell carcinoma associated with prominent angioleiomyoma-like proliferation: Report of 5 cases and review of the literature. *The American journal of surgical pathology*. 2006 Nov;30(11):1372-81. PubMed PMID: 17063076.
26. Shannon BA, Cohen RJ, Segal A, Baker EG, Murch AR. Clear cell renal cell carcinoma with smooth muscle stroma. *Human pathology*. 2009 Mar;40(3):425-9. PubMed PMID: 18789480.

27. Iczkowski KA, Shanks JH, Burdge AH, Cheng L. Renal cell carcinoma with clear cells, smooth muscle stroma, and negative for 3p deletion: a variant of renal angiomyoadenomatous tumour? A case report. *Histopathology*. 2013 Feb;62(3):522-4. PubMed PMID: 23339367.
28. Guo J, Tretiakova MS, Troxell ML, Osunkoya AO, Fadare O, Sangoi AR, et al. Tuberous sclerosis-associated renal cell carcinoma: a clinicopathologic study of 57 separate carcinomas in 18 patients. *The American journal of surgical pathology*. 2014 Nov;38(11):1457-67. PubMed PMID: 25093518.
29. Martignoni G, Brunelli M, Segala D, Gobbo S, Borze I, Atanesyan L, et al. Renal cell carcinoma with smooth muscle stroma lacks chromosome 3p and VHL alterations. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 2014 May;27(5):765-74. PubMed PMID: 24201123.
30. Petersson F, Branzovsky J, Martinek P, Korabecna M, Kruslin B, Hora M, et al. The leiomyomatous stroma in renal cell carcinomas is polyclonal and not part of the neoplastic process. *Virchows Archiv : an international journal of pathology*. 2014 Jul;465(1):89-96. PubMed PMID: 24838683.
31. Lawrie CH, Larrea E, Larrinaga G, Goicoechea I, Arestin M, Fernandez-Mercado M, et al. Targeted next-generation sequencing and non-coding RNA expression analysis of clear cell papillary renal cell carcinoma suggests distinct pathological mechanisms from other renal tumour subtypes. *The Journal of pathology*. 2014 Jan;232(1):32-42. PubMed PMID: 24155122.
32. Hakimi AA, Tickoo SK, Jacobsen A, Sarungbam J, Sfakianos JP, Sato Y, et al. TCEB1-mutated renal cell carcinoma: a distinct genomic and morphological subtype. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 2015 Jun;28(6):845-53. PubMed PMID: 25676555. Pubmed Central PMCID: 4449825.

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

Figure 3

Figure 4

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 occurring 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.