


Tubulocystic renal cell carcinoma: Two-case report and literature review

International Journal of
Immunopathology and Pharmacology
Volume 35: 1–6
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DOI: 10.1177/20587384211002966
journals.sagepub.com/home/iji


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Abstract

Tubulocystic renal cell carcinoma is a rare neoplasm of kidney with low metastatic tendency. There has only been a relatively small collection of literature dedicated to this subtype. Here we present two cases diagnosed in our center with detailed clinical information. Along with literature review, we aim to paint a comprehensive profile of TC-RCC. Hematuria and asthenia could be the chief complaints although most patients are asymptomatic. This lesion has a signature multilocular cystic form on radiology and enhancement of septa should reveal malignancy. Histologically, the cysts are lined by a single layer of flattened, cuboidal/columnar, and hobnail epithelium with enlarged nuclei and intermediate to large nucleoli. PAX8 and AMACR are most commonly positive while CD10 or CK7 could be focally stained in some cases. Overall, the diagnosis of TC-RCC should be based on comprehensive clinical and molecular results because early determination of the lesion could prelude a timely intervention and favorable prognosis.

Keywords

case report, literature review, tubulocystic renal cell carcinoma, TC-RCC

Date received: 1 February 2021; accepted: 22 February 2021

Introduction

Kidney cancer was reported to have caused approximately 114,000 deaths worldwide, with an incidence rate at 6.0% in the year of 2018.¹ Although stage-based clinical practice guidelines were redacted to ensure a satisfactory prognosis for kidney cancer patients,² accumulating evidence has suggested that determination of exact pathological cell type of the tumor could help make a more accurate therapeutic plan and thus a better outcome.³

Among all subtypes of kidney cancer, there exists one that ignited heated debates. Tubulocystic renal cell carcinoma (TC-RCC) was first considered a variant of collecting duct carcinoma because of its similarly multi-cystic growth pattern of the latter type.⁴ It was not until 2016 that TC-RCC was classified as an independent RCC subtype by WHO.⁵ However, the final rectification of name has not helped advance our knowledge of this pathological

subtype due to its low occurrence. Less than 100 cases have been documented in literature and most cases were detected at an early stage. Patients could enjoy a rather positive prognosis and survive for a long period of time after surgery without evidence of tumor recurrence or metastasis.

Here we report two cases administered in our center and review related literature to provide a synthetic description of TC-RCC.

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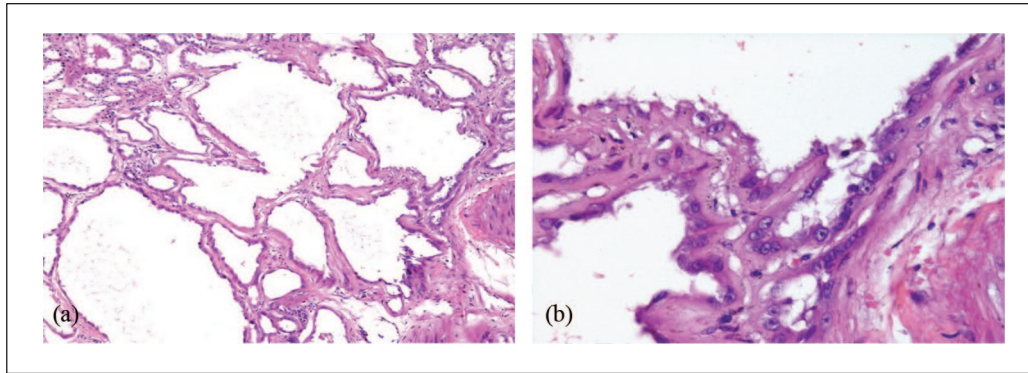


Figure 1. Our pathological examination confirmed typical structure of TC-RCC in both cases. It is composed of tubules or cystic structures lined by a single layer of epithelial neoplastic cells with eosinophilic cytoplasm. The nuclei are diffusely enlarged with grade 3 nucleoli according to International Society of Urological Pathology (ISUP) grading protocol. (a) Case 1, $\times 100$ magnification. (b) Case 2, $\times 400$ magnification.)

Methods

Two cases of TC-RCC were identified from our clinical database from 2012 to 2019. For both cases, all hematoxylin and eosin (HE)-stained slides were available for inspection and one representative paraffin block was available for further analysis. Immunohistochemical studies were already performed at the time of diagnosis. Laboratory-developed antibody against fumarate hydratase (FH) and following commercially available antibodies were used: cytokeratin 7 (CK7), PAX8, CD10, and P504S. Appropriate positive and negative controls were run concurrently for all the markers tested. Macroscopic information was retrieved from the reference pathologic reports and follow-up information was obtained by clinical interviews.

Case presentation

Case 1

A 66-year-old female was admitted for a multilocular cystic renal mass with heterogeneous enhancement on echography. The patient did another computed tomography (CT) exam. Manuscript results reported a 7.3 cm \times 6.5 cm mass in her left kidney with no significant signs of lymph nodes or cancer embolus in left renal vein. The patient had no history of notice and did not claim any discomfort at the time of admission. Following blood and urine tests found no abnormalities. Left laparoscopic radical nephrectomy was then performed and the patient was discharged after a week of recovery in hospital. The patient did a follow-up CT 3 months later and the exam was featureless.

The pathological exam reported a final measurement of the tumor: 8.5 cm \times 5.0 cm \times 5.0 cm, limited to the kidney, presenting a multilocular cystic macroscopic view with bloody fluid inside. Pathological examination found the lesion's combined structure of tubules and cystic components with enlarged nuclei and nucleoli (Figure 1). Immuno-staining revealed that the tumor was positive with PAX8, AMACR (alpha-methylacyl CoA racemase), CK7, and FH. A partial response to antibodies against CD10 was also observed (Figure 2). The patient was then followed up for 21 months and presented no signs of local or distal metastasis.

Case 2

A 50-year-old male presented to our center because of the finding of a septal renal cyst during a CT check-up of left renal cyst diagnosed 6 years previously. Radiological findings included several septa in the cyst and an enhancement of these septa. 3D image reconstruction further visualized the lesion. The patient claimed no physical discomfort and no other chronic disease. Laparoscopic partial nephrectomy of the tumor was conducted, and the patient was discharged after full recovery. Three-month follow-up results were not significant, and the final pathological examination reported a honeycomb-form pale tumor presenting the typical microscopic tubulocystic view (Figure 1). The tumor was responsive to antibodies against CD10, PAX8, FH, and AMACR while the staining of CK7 was negative (Figure 2). Our final follow-up time at 17th month from the surgery did not find any local or distant site of concern.

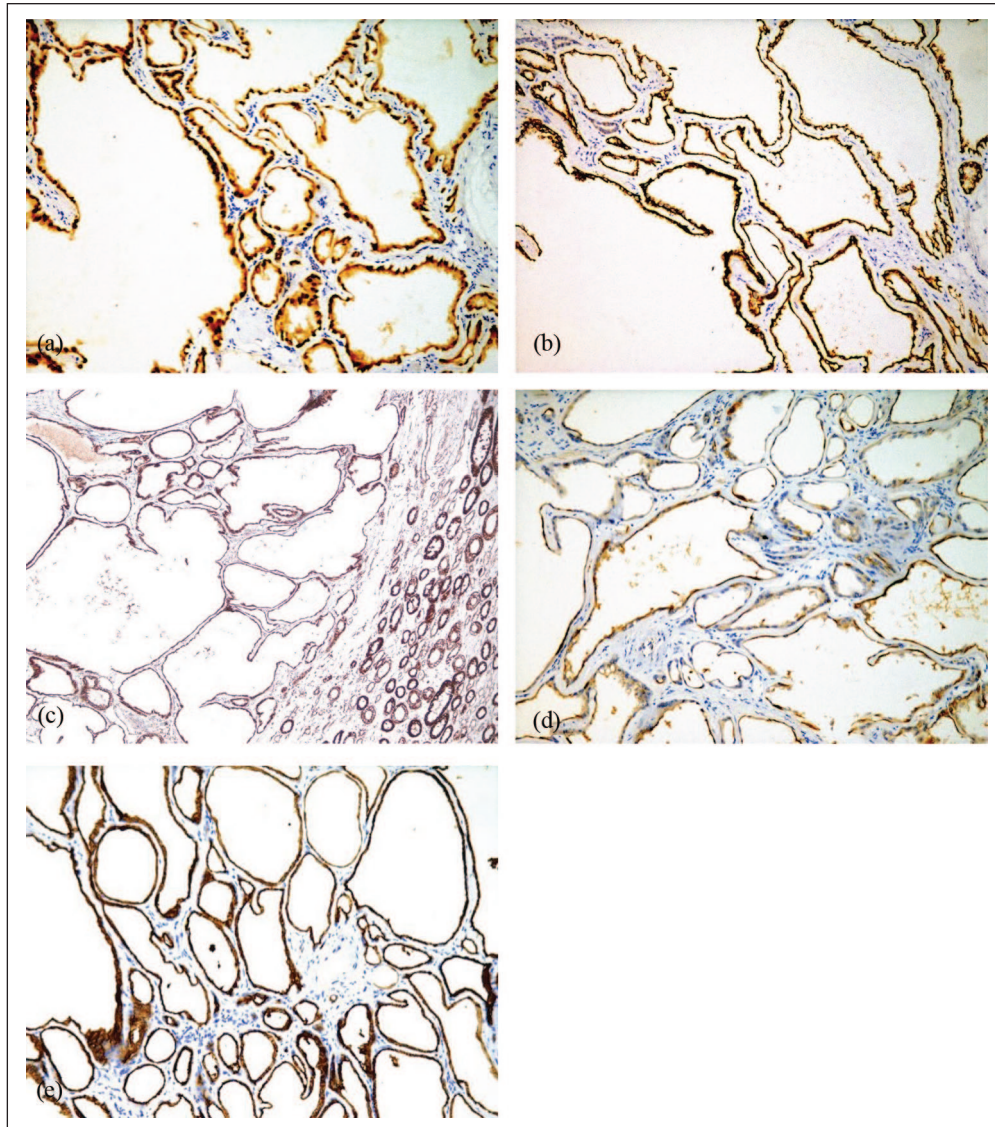


Figure 2. Both samples showed similar diffused staining features of PAX8, AMACR, and FH labeling. Other staining with CD10 and CK7 was only observed locally in selected tumor sample. ($\times 100$ magnification. (a) PAX8 I. (b) P504S. (c) FH. (d) CK7 for case 1. (e) CD10 for case 2.)

Discussion

Known for its signature histological manifestation, TC-RCC has stood a decade of trial for its very existence and differentiation from other lesions of the kidney. Due to the low occurrence of this pathological subtype and lack of a comprehensive profiling, we seek to present TC-RCC in a most extensive way by literature review combined with our own clinical experience. Thus, we browsed main database for related literature based on the term of (“Carcinoma, Renal Cell” and “Tubulocystic”) since the year of 2016. Integrated information of presentive aspects was summarized in Table 1.

Hereafter, we will present characteristics of TC-RCC in four parts.

Generalities

As shown in Table 1, TC-RCC occurs to middle-aged adults with a male predominance and no laterality preference. Most cases were detected incidentally and therefore treated at an early stage. Patients usually claimed few clinical symptoms because of its indolent behaviors. Due to a relatively early clinical staging at the time of diagnosis, surgical intervention as indicated in guidelines could ensure a satisfactory prognosis and long-term

Table 1. Clinical characteristics of TC-RCC cases.

Author(s)	Number of cases	Gender (M/F)	Medium age	Side (R/L)	Tumor size (cm)				Associated P-RCC	Metastasis
					≤4	>4but≤7	>4but≤10	>10		
Cornelis et al. ⁶	17	15/2	56.1	8/9	15	1	0	1	4	0
Korabecna et al. ⁷	2	2/0	68	NA	1	0	1	0	0	0
Maeda et al. ⁸	1	1/0	46	0/1	0	0	1	0	1	0
Skenderi et al. ⁹	15	10/5	59.8	NA	6	5	4	0	0	1
Tran et al. ¹⁰	12	7/5	58.5	NA	10	2	0	0	0	0
Derquin et al. ¹¹	1	1/0	78	0/1	0	0	0	1	0	0
Raspollini et al. ¹²	1	1/0	47	NA	1	0	0	0	0	1
Renshaw and Gould ¹³	2	2/0	50	1/1	1	0	1	0	0	1
Lawrie et al. ¹⁴	13	13/0	61.8	NA	5 (2 cases NA)	3	3	0	2	0
Alfaseh et al. ¹⁵	1	0/1	22	1/0	0	0	0	1	0	0
Martinez et al. ¹⁶	1	1/0	36	NA	1	0	0	0	0	0
McFadden et al. ¹⁷	1	1/0	59	1/0	1	0	0	0	0	0
Salvatori et al. ¹⁸	1	1/0	70	0/1	NA				0	1
Total	68	55/13	56.6	11/13					7	4

M= male; F= female; R= right; L= left; P-RCC= papillary RCC.

survival although few cases were claimed to have developed metastatic sites.⁴ It was also noted that approximately 10% of reported cases were found to co-exist with papillary renal cell carcinoma (P-RCC). This association echoes with earlier observations while its nature and underlying mechanism require further inquisition.^{6,14}

Radiological features

As indicated by the name, TC-RCC is characterized by multilocular cystic lesions on radiological imaging. These lesions could be graded as II–IV according to the widely applied Bosniak classification, which refers to numerous small cysts or a tubular structure with a clear serous fluid inside and multiple thin septa.¹⁹ According to consensus of radiologists, MRI is apparently superior to CT despite the common and preferential employment of the latter, for detection of non-fluid content (solids or septa) or subtle contrast-enhancement of septa could efficiently upgrade cystic category and help introduce a timely intervention or further inspection⁶. Though current techniques suffice in detecting malignant lesions, differentiation between TC-RCC and other cystic renal tumors solely by the means of imaging remains challenging. Doctors should consider multilocular cystic RCC, adult cystic nephroma, and mixed epithelial and stromal tumor (MEST) while making the distinctive diagnosis facing similar lesions.¹⁹

Histopathological findings

The typical tubulocystic microscopical morphology could be the first clue for diagnosis of TC-RCC. It should be noted that the tubules and cystic spaces are commonly lined by a single layer of cuboidal-to-flat epithelial cells. The nuclei are enlarged and irregular, with intermediate to large nucleoli (WHO/ISUP grade 3).²⁰ Papillary structures, solid areas, necrosis, and mitotic activity are not present in the “pure” form.¹⁰ Immunohistochemically, TC-RCC is responsive to antibodies against PAX8 and even more strongly with AMACR labeling while the tumors are generally non-responsive to antibodies against CK20 or p63. This suggests an indolent nature of the tumors, corresponding to the established good prognosis of the cancer. Other bio-markers such as CK7 or cytokeratin CD10 were also reported to be focally positive in some of the tumors, as presented in our cases respectively.²¹ FH is another marker worthy of special notice because its low expression or even deprivation has been found in relatively younger patients and could indicate a worse outcome for the patients, which call for further mutational tests.^{21,22}

Genetic analyses

Genomic profiling was the most powerful argument for the entity of TC-RCC as an independent RCC subtype.²³ The signature mutational findings about “pure” TC-RCC are the combined losses at

chromosome 9 and Y with gains at chromosome 17.²¹ This discovery confirmed that the molecular features of TC-RCC are distinct from any other known RCC subtypes. Further studies have been conducted at genetic level and found the most mutated genes in TC-RCC being ABL1 and PDGFRA,¹⁴ which are rarely mutated in other RCC subtypes such as clear cell renal cell carcinoma (CC-RCC), P-RCC, or chromophobe renal cell carcinoma (Ch-RCC). Normally, genetic analyses should not be the preferred diagnostic tool yet could play a decisive role in cases of doubt or differential diagnosis.

Conclusion

In summary, TC-RCC is an independent RCC subtype with a characteristic biochemical profile. Despite its low incidence rate, patients could benefit from surgical removal due to its indolent nature and low potential for metastasis. Therefore, physicians are advised to perform an accurate recognition and differentiation from other multi-cystic RCCs based on combined radiological and pathological findings.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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