

Original Article

Tubulocystic renal cell carcinoma of the kidney: a clinical, pathological, immunohistochemical, and fluorescence *in situ* hybridization study

Pei-Pei Zhang¹, Xiao-Qun Yang², Lin Yu¹, Yong Wu¹, Chao-Fu Wang²

¹Department of Pathology, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; ²Department of Pathology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin 2nd Rd, Shanghai 200025, China

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Abstract: Tubulocystic renal cell carcinoma (TCRCC) is a relatively recently recognized renal neoplasm that exhibits distinct macroscopic and microscopic characteristics. Herein, we report a comprehensive study of pure TCRCC in 9 patients in which we evaluated the clinical, pathological, immunohistochemical and molecular characteristics of this disease. The patients' ages ranged from 21 to 46 years (mean 33 years), and the ratio of men to women was 5:4. The tumor sizes ranged from 2.0 to 5.0 cm (mean 3.5), and the tumors exhibited a spongy appearance reminiscent of bubble wrap. Tissue samples from all of the patients exhibited a microscopic appearance characterized by cystic dilated tubules of various sizes lined by a single layered epithelium. The cells of the epithelial lining varied with respect to cuboidal, flat or squamous morphology. All cases were classified as International Society of Urological Pathology (ISUP) grade 3 and renal tumor stage pT1a. During a median follow-up period of 41 months, no patients presented with recurrent or metastatic disease. Immunohistochemistry revealed that all of the patient samples expressed AMACR, vimentin and PAX-8. The samples exhibited variable weak staining for CK7, CK8, CK19, 34bE12, CD10, CAIX, and SMA and negative immunoreactivity for TFE3 and CD34. Fluorescence *in situ* hybridization analysis revealed that 3p deletion and trisomy 7 and 17 were absent. In our study, pure TCRCCs appear to have a favorable prognosis. In addition, this study also provides the most convincing molecular evidence that TCRCC is a distinct disease and has poor relationship with papillary renal cell carcinoma.

Keywords: Kidney, tubulocystic carcinoma, cystic renal tumors, immunohistochemistry, fluorescence in situ hybridization

Introduction

Tubulocystic renal cell carcinoma (TCRCC) is a rare renal tumor characterized by unique morphological features. TCRCC was recently recognized to be a distinct subtype of renal tumor at the 2013 consensus conference of the International Society of Urological Pathology (ISUP), and it was subsequently incorporated into the organization's Vancouver Classification [1]. The distinct morphological features of TCRCC were first described by Dr. George Farrow in an abstract presented at an annual meeting of the United States and Canada Academy of Pathology [2]. In 1997, MacLennan and colleagues reported 8 cases and referred to the TCRCC as low-grade collecting duct carcinoma [3]. In 2004, Amin et al. presented a series of 31

cases at the USCAP meeting and renamed the lesions tubulocystic renal cell carcinomas [4]. Several recent studies reported considerable similarity between TCRCC and papillary renal cell carcinoma with respect to immunohistochemistry staining and molecular features [4-7]. Previous studies have also demonstrated that TCRCC carries a low but definitive risk of metastasis, and 2 documented cases of metastases in 1 case of recurrent disease has been reported [6, 8-10]. However, pure tubulocystic renal cell carcinomas are indolent. These tumors associated with a favorable prognosis and are not prone to local recurrence and metastases [11]. At the gross level, these tumors exhibit definitive borders and are unencapsulated with a spongy surface that was likened to bubble wrap. Histologically, the neoplasms exhibited

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tubules varying in size and cysts separated by fibrous septa. The cysts and tubules were lined by a single layer of cuboidal cells with eosinophilic cytoplasm.

We studied and evaluated 9 cases of pure tubulocystic renal cell carcinoma and characterized distinctive clinicopathological, immunohistochemical and molecular characteristics of TCRCC. In addition, our findings strengthen the notion that TCRCC is a distinct low-grade renal cell carcinoma with an extremely favorable prognosis and minimal association with papillary renal cell carcinoma (PRCC).

Materials and methods

We searched Fudan University Shanghai Cancer Center files for cases of tubulocystic renal cell carcinoma (TCRCC) between 2000 and 2015 using the terms “tubules” and “cystic” in the search parameters. Tissues obtained from patients with an unclassified type renal cell carcinoma (RCC) that were diagnosed before the formal designation of TCRCC as a unique subtype were stained with hematoxylin and eosin (H&E) and evaluated using immunohistochemistry (IHC) staining. The cases identified with these embedded search terms were centrally reviewed by the first and senior authors of the study for established morphological and molecular characteristics of TCRCC. Nine cases of TCRCC were identified. Seven cases were reported to the senior author, and 2 were identified internally. The cases did not present with multiple tumors or other types of renal carcinoma. Follow-up information for all of the cases was available. Clinical and pathological data were obtained from patient medical records. All patients lacked the stigmata of von Hippel Lindau disease (VHL) disease. The following characteristics were recorded: age, sex, number of TCRCC and location (unilateral vs. bilateral), absence of other RCC and precursor lesions, kidney disease, previous procedures, margin status, gross morphology of the tumor, tumor size, pathology, and clinical updates after the documented follow-up. Pathology stage was assigned for each tumor based on the intraoperative and pathology findings according to the TNM (tumor, node, and metastasis) system.

Immunohistochemistry

Immunohistochemistry experiments using antibodies against α -methylacyl-CoA-racemase

(AMACR/P504S, 13H4; Dako Corp.), carbonic anhydrase IX (CA-IX; rhCA9; Dako Corp.), CD10 (56C6; Dako Corp.), cytokeratin (CK) 34betaE12 (34betaE12; Dako Corp.), CK7 (OV-TL12/30; Dako Corp.), smooth muscle actin (1A4; Dako Corp.), TFE3 (MRQ-37; Cell Marque), CD34 (QB-End; Dako Corp.), CK19 (BA17; Dako Corp.), CK8 (35BH11; Dako Corp.), vimentin (V9; Dako Corp.) and PAX-8 (polyclonal; Chicago, Corp.) were conducted in a Dako automated instrument. Positive and negative controls were used for each procedure. The extent of immunostaining was visually estimated and patterns of immunostaining were classified as membranous, cytoplasmic, apical, granular, cytoplasmic, or cup-shaped.

Fluorescence *in situ* hybridization

Fluorescence *in situ* hybridization (FISH) analysis was performed as previously described [12-14]. Briefly, 3- μ m thick sections were obtained from formalin-fixed paraffin-embedded tissue blocks containing neoplastic tissue. A hematoxylin and eosin (H&E)-stained section from each block was examined to select areas of neoplastic tissue for FISH analysis. To deparaffinize the slides, they were washed twice with xylene for 15 minutes each wash, washed twice with 100% ethanol for 10 minutes each wash, and air-dried in a fume hood. The slides were then treated with 0.1 M citric acid (pH 6.0) (Zymed, South San Francisco, CA) at 95°C for 10 minutes, rinsed in distilled water for 3 minutes, and washed with 2 \times standard saline citrate for 5 minutes. The tissues were digested with 0.4 ml of pepsin (5 mg/ml in 0.1 N HCl/0.9 NaCl) (Sigma, St Louis, MO) at 37°C for 40 minutes. The slides were rinsed with distilled water for 3 minutes, washed with 2 \times standard saline citrate for 5 minutes, air-dried and incubated with probes directed against chromosome 3p25 and the probes used to detect the chromosome 7 and 17 copy number. The definition of chromosomal trisomy of chromosomes 7 and 17 was based on the Gaussian model and normalized to the non-neoplastic controls. The cutoff values for each probe were defined as the mean \pm 3 standard deviations (SDs) of the control values. The 3p25 deletion was evaluated according to methods described in previous studies of chromosome 1p and 19q deletions in oligodendrogliomas [15, 16]. The cut off value for the 3p deletion was defined as a

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Table 1. Clinical and pathologic features

Case No	Age	Sex/Side	Size (cm)	Stage	Surgery	Mo	Metastasis	Status
1	45	F/Right	5.0	T1aNOM0	Total Nephrectomy	66	A	NED
2	46	M/Right	2.0	T1aNOM0	Partial Nephrectomy	20	A	NED
3	32	M/Left	2.7	T1aNOM0	Partial Nephrectomy	38	A	NED
4	31	F/Right	3.4	T1aNOM0	Partial Nephrectomy	39	A	NED
5	21	F/Left	4.1	T1aNOM0	Total Nephrectomy	41	A	NED
6	42	M/Left	3.8	T1aNOM0	Partial Nephrectomy	29	A	NED
7	33	M/Right	4.2	T1aNOM0	Total Nephrectomy	80	A	NED
8	32	F/Right	3.2	T1aNOM0	Partial Nephrectomy	73	A	NED
9	43	M/Left	3.1	T1aNOM0	Total Nephrectomy	68	A	NED

A = metastasis absent; NED = no evidence of disease.

3p25/CEP3 ratio of ≤ 0.7 , as previously described.

Aneuploidy was scored by counting the number of fluorescent signals in 100 randomly selected, non-overlapping tumor cell nuclei. Two observers read the slide independently. Monosomy and polysomy for the evaluated chromosomes were defined as the presence of 1 signal per cell in $>45\%$ of cells and 3 or more signals in $>10\%$ of cells (mean + 3 SDs) in normal non-neoplastic control tissues.

Results

Clinical findings

The patient clinicopathological data are summarized in **Table 1**. The patient age ranged from 21 to 46 years with a mean of 33 years. The tumors were incidentally detected in 6 cases, and the remaining cases presented with abdominal distension, pain or hematuria. All patients presented with sporadic TCRC and exhibited no signs of BHD syndrome. The tumors localized to the left kidney in 4 cases and to the right kidney in 5 cases. All cases were multilocular. Three tumors were located in the upper pole, 2 in the mid-upper pole, 2 were located centrally, and 2 were located in the lower pole. Four of the patients had received total nephrectomies, and five received partial nephrectomies. In the mean follow-up time of 41 months (range 20-80 months), no patients presented with recurrent or metastatic disease.

Tumor pathology

At the gross level, TCRC of the kidney was well circumscribed and often involved the cortex

and/or the medulla of the kidney. All cases were stage pT1a. The tumors measured in size from 2.0 to 5.0 cm with a mean size of 3.5 cm. Most tumors appeared cystic and lacked signs of hemorrhage or necrosis. The largest tumor was almost completely cystic. The cut surface appeared spongy and exhibited an appearance similar to bubble wrap in 2 cases. Microscopically, the tumors were composed of a circumscribed proliferation zone of small to intermediate sized tubules admixed with cystically dilated tubules evenly dispersed in stroma that was frequently fibrotic (**Figure 1A**). The tubules and cysts were lined by a single layer of flat or cuboidal epithelial cells with modest to abundant levels of eosinophilic cytoplasm. No papilla or solid sheets of clear cells were observed in the tubules or cysts. In addition, tumors lacked the ovarian type of stroma and desmoplasia (**Figure 1B, 1C**). The nuclei were round with poorly defined nuclear membranes, irregularly dispersed chromatin and prominent nucleoli. The cells lining the tumor exhibited prominent nucleoli with a morphology resembling Fuhrman nuclear grade 3 (**Figure 1D**). Signs of lymphovascular involvement and mitotic activity were minimal to absent.

Immunohistochemistry

The neoplastic cells of all 9 cases exhibited strong and uniform staining (75% of cells) of AMACR (**Figure 2A**), PAX-8 (**Figure 2B**) and vimentin (**Figure 2C**). CK7 staining was observed in 7 of 9 cases (**Figure 2D**) and localized to foci (5 cases) or appeared as a weak diffuse staining pattern (2/9). Some tumor cells exhibited weak CK8, CK19, CD10, 34bE12, CAIX and SMA staining. TFE3 and CD34 staining was not observed in any of the tumors evaluated.

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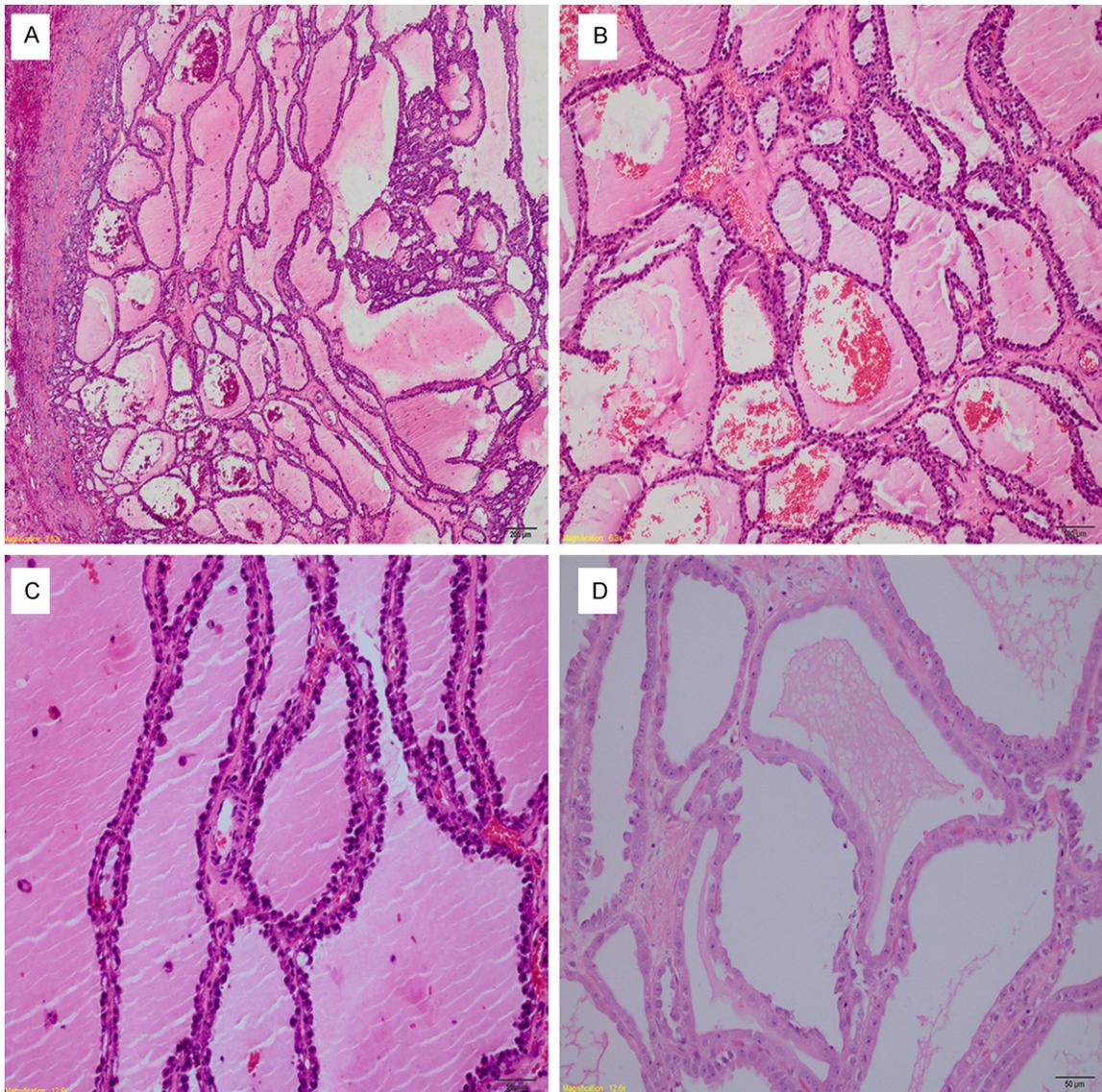


Figure 1. Histological features of tubulocystic renal cell carcinoma. A. The tumor is composed of well-differentiated tubules and cysts, and the stroma is frequently fibrotic; B, C. The tubules and cysts were lined by a single layer of flat, hobnail, cuboidal to columnar epithelial cells, which demonstrated abundant eosinophilic cytoplasm; D. The nuclei were round with irregular nuclear membranes and prominent nucleoli, and all cases show ISUP nuclear grade 3.

Fish

FISH was performed in the 2 cases identified internally. Neither case exhibited chromosome 3p deletion or trisomy of chromosomes 7 and 17.

Discussion

TCRCC is a recently recognized subtype of renal neoplasms composed of an admixed population of cystic and tubules components lined by a single layer of cuboidal to flat eosinophilic epithelial cells embedded in a fibrotic stroma.

These tumors have previously been referred to by various names, including Bellinien epithelioma, low-grade collecting duct carcinoma and recently TCRCC. The tumor was first described by Farrow et al. in an abstract presented at the Annual Meeting of United States and Canada Academy of Pathology [3]. Initially, the characteristics of TCRCC were considered to be consistent with tumors originating from the collecting ducts [2, 17] and were classified as low-grade collecting duct carcinomas. At the USCAP meeting in 2004, Amin et al. reported a series of 31 cases and labeled them tubulocys-

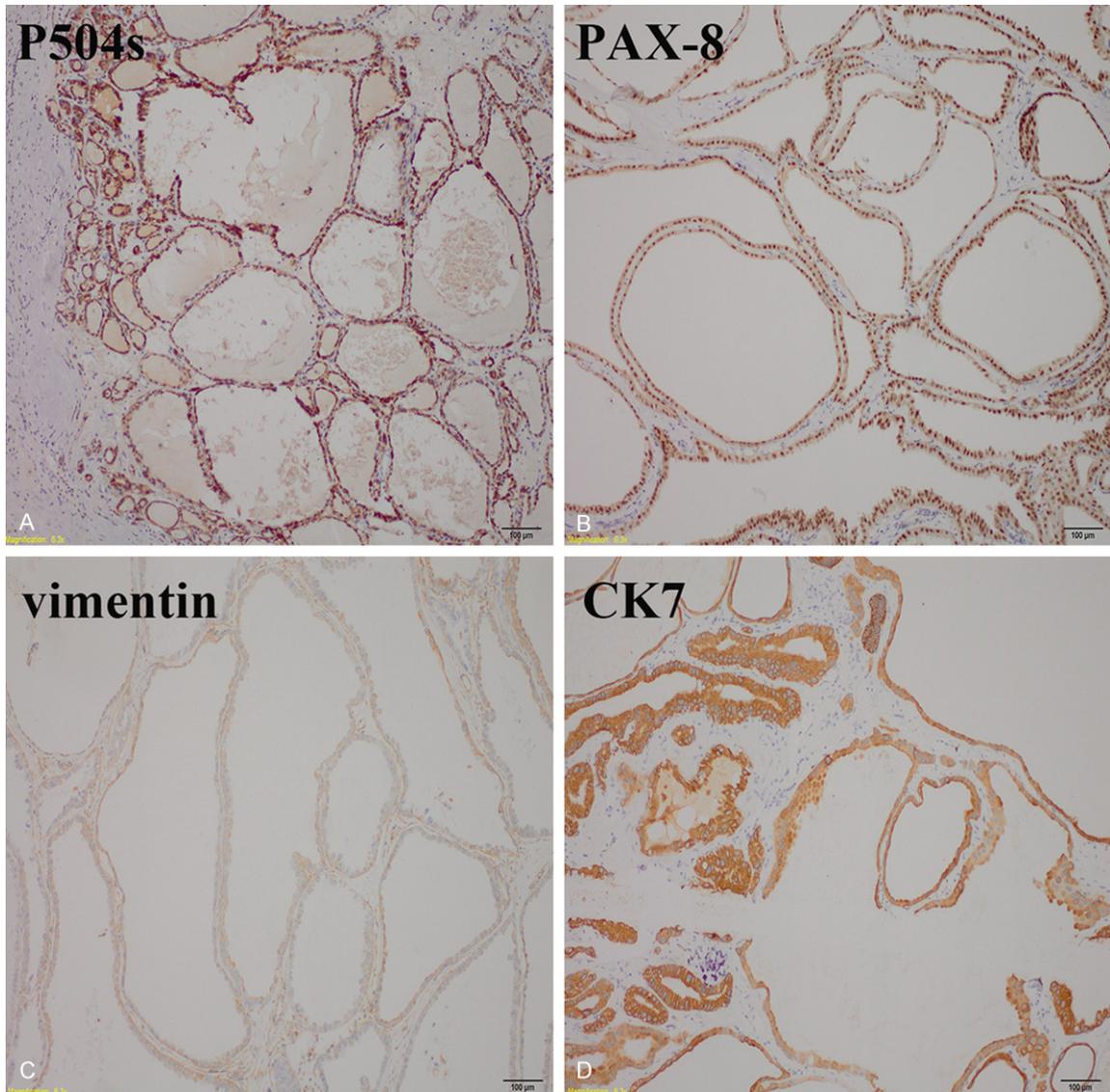


Figure 2. Immunohistochemical stains of tubulocystic renal cell carcinoma. A, B, D. The tumor is diffuse and strong positive for AMACR, PAX-8 and CK7. C. The tumor is moderate positive for vimentin.

tic renal cell carcinoma [4]. To date, some researchers consider TCRCC to be closely related to papillary renal cell carcinoma [5-7, 17]. However, some previous studies revealed that TCRCC often coexisted with papillary renal cell carcinoma or papillary adenoma in the same lesions. Of the 13 TCRCC cases reported by Yang et al. [6], 3 coexisted with papillary renal cell carcinoma and 2 with papillary adenoma. Among 20 cases of TCRCC reported by Zhou et al. [7], 10 cases presented with papillary renal cell carcinoma in the same kidney. In this study, we reported 9 cases of pure TCRCC. Consistent with a previous study published by Tran et al.

[11], immunohistochemistry and molecular analyses demonstrated that TCRCC is distinct from papillary renal cell carcinoma. In addition, TCRCC exhibits an extremely favorable prognosis and no risk of disease recurrence after surgery. According to published reports and consistent with the present study, TCRCC most commonly presents as an incidental kidney mass. Other symptoms associated with TCRCC include abdominal distension, pain and hematuria. At the gross level, the tumors were well circumscribed and exhibited a spongy appearance reminiscent of bubble wrap and exhibited no signs of necrosis. Tumor sizes ranged from

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2.0 to 5.0 (mean 3.5) cm, and all cases were classified as stage pT1a. The reported patient age ranges from 33 to 94 years with a strong male preponderance. These findings are consistent with previous reports describing TCRCC. Clinical follow-up data were available for all the patients evaluated. All patients were alive and exhibited no evidence of disease during the median follow-up period of 41 months (range, 20 to 80 months). However, the tumors exhibited a low but definitive risk of local recurrence and metastasis given that metastases were documented in 2 patients. All cases exhibited uniform immunostaining for AMACR, PAX-8 and vimentin, and variable weak staining for CK7, CK8, CK19, 34bE12, CD10, CAIX and SMA. TFE3 and CD34 immunostaining was not observed in any of the TCRCC samples evaluated. These immunohistochemistry results are consistent with observations from previous studies. However, the cases evaluated in this study are not consistent with the classic immunoprofile of PRCC, and none of the patients in this study presented with PRCC. These findings strengthen the hypothesis that TCRCC is a distinct subtype of renal cell carcinoma that distinctly differs from PRCC. Two cases were analyzed using FISH assays; however, neither case exhibited chromosome 3p deletion or chromosome 7 or 17 trisomy. Amin et al. [4] previously described 31 cases of TCRCC and demonstrated that the molecular signature of TCRCC is distinct from PRCC. In addition, Tran et al. revealed that these tumors were negative for trisomy 7 and 17, supporting the hypothesis that TCRCC is a neoplasm that distinctly differs from papillary renal cell carcinoma. Moreover, the FISH analysis conducted in this study demonstrated that TCRCC is a distinct entity that distinctly differs from papillary renal cell carcinoma, similar to previous reports.

The differential diagnosis of TCRCC mainly involves other cystic lesions of the kidney, including cystic nephroma (CN), low-grade multilocular cystic renal cell carcinoma, mixed epithelial and stromal tumors (MEST) and cystic renal oncocytoma (CRO). CN occurs in adult patients with a female to male ratio of approximately 8:1 and primarily affects women at reproductive ages to early menopausal stages. In contrast, TCRCC occurs more frequently in men [18, 19]. At the gross level, CN is encapsulated, well demarcated, and presents as a diffuse cystic tumor with no clearly defined bor-

ders. In contrast, TCRCC is an unencapsulated tumor. As previously mentioned, the World Health Organization (WHO) classification defines CN as a tumor composed of cysts and cyst septa, which may be cellular or reminiscent of ovarian stroma [20]. Low-grade multilocular cystic renal cell carcinoma is a tumor composed of numerous cysts, the septa of which contain small groups of clear cells indistinguishable from low-grade clear cell carcinoma cells. The morphology of the epithelium varies and can feature flattened, cuboidal or squamous cells, and occasionally, clear cells. In contrast, small groups of clear cells in the septa were absent in TCRCC [21]. MEST presents almost exclusively in females that are middle-aged, perimenopausal or older [18, 22]. At the macroscopic level, MEST appears as an admixture of cysts and solid areas. The WHO criteria defines MEST as a tumor composed of large cysts, microcysts and tubules lined by a columnar, cuboidal, or flattened epithelium that occasionally resembles Mullerian ducts and stroma composed of some spindle cells [19, 23]. The gross appearance of cystic renal oncocytoma, a mostly solid tumor with scattered cysts, is distinct from the cystic, bubble wrap-like appearance of TCRCC [24]. At the microscopic level, focal solid nests or tumor cell islands were rarely observed in TCRCC, suggesting that this feature might be a distinguishing characteristic that can be used to help differentiate TCRCC from other tumors. In CRO, the stroma is loose, whereas the stromal component of TCRCC is typically fibrotic and more compact [25, 26].

In summary, TCRCC is a relatively rare neoplasm of the kidney distinct from other renal neoplasms. Although the overall prognosis of TCRCC is favorable, disease recurrence and metastasis can occur. However, pure TCRCC in the absence of other neoplasms is associated with a favorable prognosis and is regarded as an indolent tumor. Additional studies documenting the characteristic molecular features associated with TCRCC are required to further strengthen the recognition of TCRCC as a distinct renal tumor subtype.

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Disclosure of conflict of interest

None.

Address correspondence to: Chao-Fu Wang, Department of pathology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin 2nd Rd, Shanghai, 200025, China. Tel: +86-137642-74180; E-mail: wang_chaofu@163.com

References

[1] Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, Hes O, Moch H, Montironi R, Tickoo SK, Zhou M and Argani P. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *Am J Surg Pathol* 2013; 37: 1469-1489.

[2] MacLennan GT, Farrow GM and Bostwick DG. Low-grade collecting duct carcinoma of the kidney: report of 13 cases of low-grade mucinous tubulocystic renal carcinoma of possible collecting duct origin. *Urology* 1997; 50: 679-684.

[3] MacLennan GT, Farrow GM and Bostwick DG. Low-grade collecting duct carcinoma of the kidney: report of 13 cases of low-grade mucinous tubulocystic renal carcinoma of possible collecting duct origin. *Urology* 1997; 50: 679-684.

[4] Amin MB, MacLennan GT, Gupta R, Grignon D, Paraf F, Vieillefond A, Paner GP, Stovsky M, Young AN, Srigley JR and Cheville JC. Tubulocystic carcinoma of the kidney: clinicopathologic analysis of 31 cases of a distinctive rare subtype of renal cell carcinoma. *Am J Surg Pathol* 2009; 33: 384-392.

[5] Azoulay S, Vieillefond A, Paraf F, Pasquier D, Cussenot O, Callard P and Sibony M. Tubulocystic carcinoma of the kidney: a new entity among renal tumors. *Virchows Arch* 2007; 451: 905-909.

[6] Yang XJ, Zhou M, Hes O, Shen S, Li R, Lopez J, Shah RB, Yang Y, Chuang ST, Lin F, Tretiakova MM, Kort EJ and Teh BT. Tubulocystic carcinoma of the kidney: clinicopathologic and molecular characterization. *Am J Surg Pathol* 2008; 32: 177-187.

[7] Zhou M, Yang XJ, Lopez JI, Shah RB, Hes O, Shen SS, Li R, Yang Y, Lin F, Elson P, Sercia L, Magi-Galluzzi C and Tubbs R. Renal tubulocystic carcinoma is closely related to papillary renal cell carcinoma: implications for pathologic classification. *Am J Surg Pathol* 2009; 33: 1840-1849.

[8] Al-Hussain TO, Cheng L, Zhang S and Epstein JI. Tubulocystic carcinoma of the kidney with poorly differentiated foci: a series of 3 cases with fluorescence in situ hybridization analysis. *Hum Pathol* 2013; 44: 1406-1411.

[9] Steiner P, Hora M, Stehlik J, Martinek P, Vanecek T, Petersson F, Michal M, Korabecna M, Travnicek I and Hes O. Tubulocystic renal cell carcinoma: is there a rational reason for targeted therapy using angiogenic inhibition? Analysis of seven cases. *Virchows Arch* 2013; 462: 183-192.

[10] Iakovleva G, Iakovlev V, Ordon M, Srigley J and Yousef GM. Tubulocystic carcinoma of kidney: a challenging diagnostic entity mimicking multicystic kidney and presenting with bone metastasis. *Histopathology* 2015; 66: 892-894.

[11] Tran T, Jones CL, Williamson SR, Eble JN, Grignon DJ, Zhang S, Wang M, Baldrige LA, Wang L, Montironi R, Scarpelli M, Tan PH, Simper NB, Comperat E and Cheng L. Tubulocystic renal cell carcinoma is an entity that is immunohistochemically and genetically distinct from papillary renal cell carcinoma. *Histopathology* 2016; 68: 850-7.

[12] Tetzlaff MT, Wang WL, Milless TL, Curry JL, Torres-Cabala CA, McLemore MS, Ivan D, Bassett RL and Prieto VG. Ambiguous melanocytic tumors in a tertiary referral center: the contribution of fluorescence in situ hybridization (FISH) to conventional histopathologic and immunophenotypic analyses. *Am J Surg Pathol* 2013; 37: 1783-1796.

[13] North JP, Garrido MC, Kolaitis NA, LeBoit PE, McCalmont TH and Bastian BC. Fluorescence in situ hybridization as an ancillary tool in the diagnosis of ambiguous melanocytic neoplasms: a review of 804 cases. *Am J Surg Pathol* 2014; 38: 824-831.

[14] Ishibashi K, Ito Y, Masaki A, Fujii K, Beppu S, Sakakibara T, Takino H, Takase H, Ijichi K, Shimozato K and Inagaki H. Warthin-like Mucoepidermoid Carcinoma: A Combined Study of Fluorescence In Situ Hybridization and Whole-slide Imaging. *Am J Surg Pathol* 2015; 39: 1479-1487.

[15] Idbaih A, Kouwenhoven M, Jeuken J, Carpentier C, Gorlia T, Kros JM, French P, Teepen JL, Delattre O, Delattre JY, van den Bent M and Hoang-Xuan K. Chromosome 1p loss evaluation in anaplastic oligodendrogliomas. *Neuropathology* 2008; 28: 440-443.

[16] Horbinski C, Nikiforova MN, Hobbs J, Bortoluzzi S, Cieply K, Dacic S and Hamilton RL. The importance of 10q status in an outcomes-based comparison between 1p/19q fluorescence in situ hybridization and polymerase chain reaction-based microsatellite loss of heterozygosity analysis of oligodendrogliomas. *J Neuropathol Exp Neurol* 2012; 71: 73-82.

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- [17] MacLennan GT and Bostwick DG. Tubulocystic carcinoma, mucinous tubular and spindle cell carcinoma, and other recently described rare renal tumors. *Clin Lab Med* 2005; 25: 393-416.
- [18] Turbiner J, Amin MB, Humphrey PA, Srigley JR, De Leval L, Radhakrishnan A and Oliva E. Cystic nephroma and mixed epithelial and stromal tumor of kidney: a detailed clinicopathologic analysis of 34 cases and proposal for renal epithelial and stromal tumor (REST) as a unifying term. *Am J Surg Pathol* 2007; 31: 489-500.
- [19] Zhou M, Kort E, Hoekstra P, Westphal M, Magi-Galluzzi C, Sercia L, Lane B, Rini B, Bukowski R and Teh BT. Adult cystic nephroma and mixed epithelial and stromal tumor of the kidney are the same disease entity: molecular and histologic evidence. *Am J Surg Pathol* 2009; 33: 72-80.
- [20] Michal M, Hes O, Kuroda N, Kazakov DV, Petersson F, Hora M and Daum O. What is a cystic nephroma? *Am J Surg Pathol* 2010; 34: 126-127; author reply 127.
- [21] Williamson SR, Halat S, Eble JN, Grignon DJ, Lopez-Beltran A, Montironi R, Tan PH, Wang M, Zhang S, MacLennan GT, Baldrige LA and Cheng L. Multilocular cystic renal cell carcinoma: similarities and differences in immunoprofile compared with clear cell renal cell carcinoma. *Am J Surg Pathol* 2012; 36: 1425-1433.
- [22] Adsay NV, Eble JN, Srigley JR, Jones EC and Grignon DJ. Mixed epithelial and stromal tumor of the kidney. *Am J Surg Pathol* 2000; 24: 958-970.
- [23] Kum JB, Grignon DJ, Wang M, Zhou M, Montironi R, Shen SS, Zhang S, Lopez-Beltran A, Eble JN and Cheng L. Mixed epithelial and stromal tumors of the kidney: evidence for a single cell of origin with capacity for epithelial and stromal differentiation. *Am J Surg Pathol* 2011; 35: 1114-1122.
- [24] Schmidt PR, Bock D, Gasser G and Redtenbacher S. [Multicystic renal oncocytoma]. *Urologe A* 1991; 30: 253-255.
- [25] Leroy X, Aubert S, Lemaitre L, Haffner J, Biserte J and Gosselin B. Multilocular cystic renal oncocytoma. *J Clin Pathol* 2006; 59: 223-224.
- [26] Skenderi F, Ulamec M, Vranic S, Bilalovic N, Peckova K, Rotterova P, Kokoskova B, Trpkov K, Vesela P, Hora M, Kalusova K, Sperga M, Perez Montiel D, Alvarado Cabrero I, Bulimbasic S, Branzovsky J, Michal M and Hes O. Cystic Renal Oncocytoma and Tubulocystic Renal Cell Carcinoma: Morphologic and Immunohistochemical Comparative Study. *Appl Immunohistochem Mol Morphol* 2016; 24: 112-119.