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CASE REPORT

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Novel molecular aberrations and pathologic findings in a tubulocystic variant of renal cell carcinoma

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Abstract

Tubulocystic renal cell carcinoma (TRCC) is an indolent type of renal cell carcinoma with a good prognosis based on the limited number of published cases. Herein, we describe the unusual clinical, pathologic and molecular findings in a case of TRCC. Our patient with TRCC had two local recurrences and a brain metastasis following radical nephrectomy. Unusual histologic findings included focal solid growth pattern and cytologic atypia. A genome-wide molecular inversion probe assay identified copy number (CN) loss in three chromosome regions and one region with copy-neutral loss of heterozygosity (copy-neutral LOH). Copy number variations (CNVs) were observed (chromosomes 4p16.1 and 17q21.31-q21.32) in both the tumor and the normal tissue, and most likely represents benign variations. The loss of entire chromosomes 9, 18 and 15 and copy-neutral LOH involving 6p22.1 was observed only in the tumor. The presence of these clinical, pathologic and molecular findings could be related to an increased risk for tumor recurrence and poor prognosis. The novel molecular findings described in TRCC might represent new targets for novel therapies.

Keywords: Molecular aberrations, pathologic findings, tubulocystic renal cell carcinoma

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Tubulocystic renal cell carcinoma (TRCC) is a recently described subtype of renal cell carcinoma (RCC) not formally recognized in the World Health Organization (WHO) 2004 classification. Recent studies suggest that TRCC is characterized by unique gross, microscopic, molecular and prognostic features mandating classification as a distinct RCC subtype. TRCC was described in the third series of the Armed Forces Institute of Pathology (AFIP) fascicle as "renal cell carcinoma, collecting duct type," followed by reclassification of some of these tumors as "low-grade collecting duct carcinoma." [\[1\]](#) The current name was received in an abstract presented at the 2004 United States and Canadian Academy of Pathology (USCAP) meeting by Amin *et al.* [\[2\]](#) Two recent series containing 13 and 11 cases each have described the clinical and pathologic features. [\[3\]](#),[\[4\]](#) From a clinical perspective, it was initially described to carry a favorable prognosis with only a few cases of established metastasis. [\[5\]](#) A more comprehensive study published in 2009 [\[6\]](#) further emphasized the histologic and ultrastructural features, differential diagnostic considerations and gene expression profile of this unique entity. Herein, we present a case of tubulocystic RCC with unusual histologic and clinical features, along with certain genetic abnormalities not previously reported in the English language literature.

Materials and Methods

Multiple sections of the recurrent tumor resected from the right renal fossa were processed for routine histopathologic examination.

Immunohistochemical Analysis

Immunohistochemical stains for AMACR (racemase), CK7, EMA, 34 β E12, CD10 and vimentin were performed.

Molecular inversion probe (MIP) assay

A cancer panel of 330,000 single nucleotide polymorphisms (SNPs) was chosen for CN and allelic imbalance analysis (OncoScan™ FFPE Express, Affymetrix, Santa Clara, CA, USA). Each probe in the assay was 40-60 nucleotides in length and flanked the targeted SNP position. Probes were chosen from intragenic sequences of >1000 genes that have been reported to be involved in cancer development. The remaining probes in the assay were chosen to fill in the gaps across the genome. Each gene was represented on average by three to six probes. SNP locations for each probe refer to human genome build 35 (NCBI 35). The TRCC tumor sample and the paired normal renal tissue from the same patient were run on the MIP 330K assay as previously described in the literature. [\[7\]](#),[\[8\]](#),[\[9\]](#)

MIP assay data analysis

The MIP assay data analysis and CN determination have been described previously. [\[8\]](#),[\[9\]](#),[\[10\]](#) The data were analyzed with Nexus Copy Number 5.1 software (BioDiscovery, El Segundo, CA, USA). A pre-filter was applied by deleting any CN intervals reported in the normal samples that had overlap with intervals reported in the TRCC sample set. The remaining intervals were further restricted after segmentation using the following criteria: >1 SNP and CN cut-off of >0.8 deviation from baseline (loss = smoothed value <1.5 and gain = smoothed value >2.5).

Fluorescent in situ Hybridization (FISH) analysis

Interphase FISH was performed on paraffin-embedded normal and tumor tissues to verify the microarray findings using the CDKN2A (chromosome 9p21)-Spectrum Orange/CEP 9 (Centromere 9) - SpectrumGreen and CEP 18 (D18Z1) (Chromosome 18 centromere) - SpectrumAqua probes (Abbott Molecular Abbott Park, IL, USA).

Results

The nephrectomy specimen (15.5 cm x 12.0 cm x 6.0 cm) contained a predominantly hemorrhagic tumor mass 4.5 cm in maximum diameter. The neoplasm extended through the renal capsule into the perinephric fat. The excision specimen of the patient's local recurrence consisted of five fibro-fatty tissue fragments weighing in aggregate 53.0 g and two "solid" yellowish-white and hemorrhagic nodules, each measuring 1.0 cm in diameter. The local recurrence specimen did not show a cystic component macroscopically. Each of the surgically resected lesions showed identical histologic features characterized by cystically dilated tubules lined by a single layer of cuboidal to columnar epithelial cells [\[Figure 1\]](#) and [\[Figure 2\]](#). Focally, the cell cytoplasm was eosinophilic and granular. The resections from the patient's local recurrences showed a distinct hobnailed lining epithelium with irregular nuclear membranes and prominent nucleoli [\[Figure 3\]](#). Focal to patchy distinct solid areas composed of large cells with cytologic features similar to those of the adjacent lining epithelial cells were also identified [\[Figure 4\]](#). The solid component amounted to 10-15% of the total tumor volume in the recurrence specimen. In contrast, sections from the initial nephrectomy specimen lacked solid areas and had cysts lined by a low cuboidal-type epithelium with minimal hobnailing. The nuclei had regular nuclear membranes. The background stroma was predominantly fibrotic and hyalinized. A clear cell component, resembling clear cell renal cell carcinoma (cRCC), was not identified in the initial or subsequent tumor specimens. No ovarian-type stroma, desmoplasia or areas reminiscent of papillary RCC were seen. The patient's initial tumor was staged as pT3 tumor. Five lymph nodes were sampled at the time of nephrectomy; all were negative for metastasis (pN0). Immunohistochemical stains showed that the recurrent tumor cells were immunoreactive for AMACR (racemase) [\[Figure 5\]](#), vimentin and EMA. The tumor cells were negative for CK7, 34 β E12, CD10, C-kit and RCC antigen.

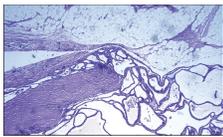


Figure 1: Tumor from the primary resection (nephrectomy) showing cystic spaces lined by low cuboidal epithelium, containing a moderate amount of cytoplasm with conspicuous nucleoli and regular nuclear membranes with perinephretic fat involvement (H/E [hematoxylin/ eosin], $\times 40$)

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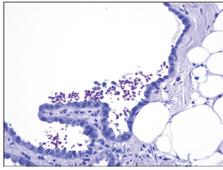


Figure 2: Higher magnification depicting the cuboidal epithelium lining the cystic spaces (H/E [hematoxylin/eosin], $\times 20$)

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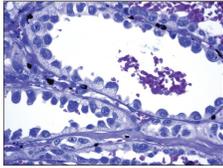


Figure 3: Tubulocystic areas in the excision specimen from the local recurrence showing lining epithelial cells with hobnailing, abundant eosinophilic cytoplasm, irregular nuclear membranes and prominent nucleoli (H/E [hematoxylin/eosin], $\times 40$)

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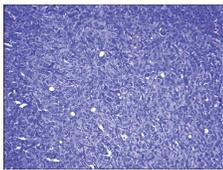


Figure 4: Excision specimen from a local recurrence showing distinct solid areas with similar cytological features as the adjacent lining epithelial cells. The cells contained in the solid areas did not show cytoplasmic clearing but had abundant eosinophilic cytoplasm and cytological atypia in the form of irregular nuclear membranes, open chromatin and prominent nucleoli (H/E [hematoxylin/eosin], $\times 40$)

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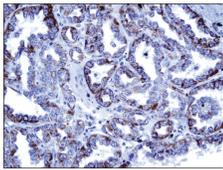


Figure 5: Lining epithelial cells of the recurrent tumor showing strong diffuse immunoreactivity for AMACR (racemase) antibody ($\times 40$, clone 13H4, 1:50; Zeta Corp)

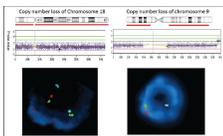
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Molecular MIP results and FISH confirmation

When the TRCC tissue was compared with the paired normal renal tissue on the MIP microarray, we observed two regions of CN aberration of chromosome 4p16.1 and chromosome 17q21.31-q21.32 in both the tumor and the normal tissue, most likely representing benign CNVs. However, the loss of entire chromosomes 9 (arr9p24q34(0-43,091,472) $\times 1$), 15 (arr15p11q26(0-102,531,392) $\times 1$) and 18 (arr18p11.3q23(0-16,451,257) $\times 1$) were observed only in the tumor tissue. In addition, copy-neutral loss of heterozygosity (LOH) of chromosome 6p22.1 (arr6p22.1(26,007,707-28,433,295) 2.43ZMb region) was also observed only in the tumor tissue.

Initial presentations of a pT3 tumor, with recurrences, and solid growth patterns were unexpected for a usually benign TRCC. The loss of chromosomes 15, 18 and copy-neutral LOH for the chromosome 6p22.1 region has not been previously reported in TRCC. To confirm the CN loss, FISH probes for chromosome 9p21 CDKN2A gene (fluorescent in Orange), CEP9 in centromere 9 (fluorescent in Green) and the chromosome 18 centromere CEP18 (D18Z1, fluorescent in Aqua) were used on both TRCC and normal tissue from the same patient. FISH analysis demonstrated two Orange, two Green and two Aqua signals in the normal tissue, while only a single Orange, a single Green and a single Aqua signal was detected in TRCC [Figure 6].

Figure 6: The loss of chromosomes 9 and 18 were observed in only tumor tissue; see Figure 2A and B using molecular inversion probe array. The probe value = 2 is copy number neutral, probe value < 1.5 is loss and that > 2.5 is gain. Figure 2A shows the loss of chromosome 18 and 2B shows the loss of chromosome 9. Figure 2C and D are fluorescent in situ hybridization (FISH) analyses for chromosomes 9 and 18 using the LSI probe for the CDKN2A locus at 9p21 in spectrum Orange and centromeric probes CEP 9 in spectrum Green and CEP 18 (D18Z1) in spectrum Aqua. Figure 2C is FISH from the normal tissue; two Orange, two Green and two Aqua signals detected, indicating disomy for chromosomes 9 and 18. Figure 2D is FISH for tumor tissue, which has only one Orange, one Aqua and one Green signal, indicating a loss of chromosomes 9 and 18



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Discussion

A 45-year-old woman presented with a right renal cortical mass for which she underwent radical nephrectomy. The surgical resection and subsequent pathologic evaluation were performed at an outside institute. The resection specimen

showed a predominantly hemorrhagic 4.5 cm diameter cortical mass extending through the renal capsule into the perinephric fat. The original referral diagnosis on the nephrectomy specimen was a conventional cRCC. The referral pathologist requested a second opinion, which resulted in a diagnosis of collecting duct carcinoma. Six years later, a magnetic resonance imaging scan was performed for neurological symptoms, which revealed a small focal lesion in the parietal lobe suspicious for metastatic RCC. The patient received chemotherapy and, 1 year later, the brain lesion showed near-total regression. A concurrent abdominal computed tomography scan performed at this time showed a mass in the right renal fossa, suspicious for local recurrence. This lesion was resected at our institute. Pathological evaluation of the recurrent neoplasm revealed histologic features suggestive of a TRCC. Because this diagnosis differed from the previous diagnoses, the outside slides from the patient's previous resection were retrieved and reviewed by three surgical pathologists in our department (TL, LL, EJ). All three pathologists agreed that the initial resection had morphologic features similar to those of the newly diagnosed TRCC in the right renal fossa. Recently, the patient developed a second recurrence of TRCC in the same renal fossa, along with metastatic involvement of the paraspinal tissue, peritoneal sidewall and right adrenal gland.

TRCC has been previously described in different case series. [\[3\]](#),[\[4\]](#),[\[6\]](#),[\[11\]](#),[\[12\]](#) In these studies, the mean size ranged from 3.3 to 4.5 cm, [\[3\]](#),[\[4\]](#),[\[6\]](#) and the reported mean age at presentation was 62.9 years. [\[4\]](#) All authors described a strong male preponderance, a low but definitive risk of metastatic spread and local recurrence, with pT1 being the most common stage at presentation. In contrast to the above observations, our patient was a 45-year-old female who initially presented with a stage pT3 tumor and subsequently developed probable brain metastasis (stage pT4). The tumor size (4.5 cm diameter) was within the range described by the other authors. Although a single case with lymph node metastasis has been described, [\[4\]](#) all five lymph nodes examined in our case at the time of initial resection were negative for metastatic disease. Only one case of TRCC with sarcomatoid features has been reported by Bhullar *et al.* [\[13\]](#) The most recent three case series were published by Al-Hussain *et al.*, [\[12\]](#) wherein two cases had small components of papillary RCC and one case had a focus of poorly differentiated carcinoma.

Grossly, TRCC has been described as a well-circumscribed spongy multicystic tumor composed of variably sized cysts with no intervening solid areas and appearing reminiscent of "Swiss cheese." [\[4\]](#),[\[6\]](#),[\[11\]](#) In our case, these classical gross features were reported in the primary tumor resection; however, in the subsequent excisions of the recurrent lesions, a cystic component was not identified grossly. The nephrectomy specimen showed a unifocal tumor; however, multicentricity has been observed in up to 20% of the cases in one study. [\[11\]](#) The tumor in the nephrectomy specimen showed varying sized cysts lined by low cuboidal cells with moderate amounts of eosinophilic cytoplasm, regular nuclear membranes and occasional conspicuous nucleoli. The histologic appearances of the recurrent lesions were different from the primary renal tumor, in that the cyst lining the epithelium in the recurrent samples showed abundant eosinophilic granular cytoplasm with hobnailed appearance, nuclei demonstrating irregular nuclear membranes and prominent nucleoli. Although these features are considered to be within the normal histologic spectrum of TRCC, we identified another finding that was also recently described by Al-Hussain *et al.* [\[12\]](#) in one of their cases where they identified a small focus of poorly differentiated carcinoma. The recurrent lesions were marked by distinct solid tumor foci representing up to 10-15% of the total tumor volume. All TRCC cases in the peer-reviewed literature were Fuhrman nuclear grade 3, although Amin *et al.* [\[6\]](#) have proposed that the Fuhrman nuclear grading does not carry any prognostic significance for the entity of TRCC. Two prior reports have provided pathologic and cytogenetic evidence to suggest that TRCC and papillary RCC are closely related entities. [\[4\]](#),[\[11\]](#) They have identified papillary renal neoplasms admixed with or in close proximity to TRCC in up to 50% of the 20 cases studied. A papillary lesion was not identified in any of the primary or recurrent specimens in our patient. Lack of papillary features was also the observation in the largest case series published by Amin *et al.* [\[6\]](#) Immunohistochemical staining showed immunoreactivity of the tumor cells with ACAMR (racemase), vimentin and EMA. The tumor cells did not stain for CD10, C-kit, RCC antigen, CK7 or 34βE12. In the largest case series so far, variable staining of the lining epithelial cells has been reported with CK8, CK18, CK19, parvalbumin, CD10, AMACR, CK7, Pax2, carbonic anhydrase and 34βE12. [\[6\]](#) TRCC cases stained with immunohistochemical markers in another study demonstrated positive staining for CD10, AMACR, 34βE12 and CK19. [\[11\]](#) Because of the distinctive and characteristic morphologic features of this entity, the value of immunohistochemical stains appears limited.

In two of 31 TRCC cases that metastasized in the series published by Amin *et al.*, [\[6\]](#) focal cytoplasmic clearing was a distinguishing histologic finding. Neither cytoplasmic clearing nor solid areas of clear cells were observed in our case. However, our case was marked by other distinctive and unusual clinical and histologic features. The neoplasm in our case occurred in a relatively young adult female with an initial presentation as a stage pT3 tumor. Over a period of 7 years, the patient experienced two local recurrences and a distant metastasis. There was a distinct histological difference between the lining epithelial cells in the primary resection specimen as compared with the excision specimens of the local recurrences. The distinct solid areas and cysts lined by large hobnailed cells with abundant eosinophilic cytoplasm, irregular nuclear membranes and prominent nucleoli were not a feature of the primary resection specimen. We suggest that the findings in our case might be related to the propensity of this tumor to behave aggressively, possibly leading to poorer prognosis. Another possibility explaining the aggressive behavior of the present neoplasm could be that the original tubulocystic variant of RCC biologically transformed to a conventional cRCC. Such RCCs have an established clinical behavior, characterized by local recurrence and spread to other organ systems. Given the rarity of TRCC and the limited number of case reports in the literature, it is hard to prove or disprove this hypothesis.

The frequent genetic abnormalities reported in cRCC include partial loss of the short arm of chromosome 3 due to deletions or unbalanced translocations as well as inactivation of the *VHL* gene at 3p25.3 due to mutation or DNA methylation around the promoter region. The regions frequently deleted include 3p12-14, 3p21 and 3p25. [\[14\]](#) Other aberrations frequently found in cRCC are (partial) trisomy for chromosomes 5, 12 and 20; loss of chromosomes 8, 9, 13 and 14; and structural abnormalities of the long arm of chromosomes 6 and 10. [\[15\]](#) A recent study showed the LOH at

chromosomes 14q21-23, 14q31-q32.2, 14q32-32.2 and 14q24.2-qter regions, which are preferentially detected in high-grade and high-stage cRCC. [\[16\],\[17\]](#)

Because TRCC is rare, we analyzed CN aberrations as well as allelic imbalance by the MIP 330K assay (OncoScan™ FFPE Express, Affymetrix). This novel microarray platform contains 330,000 SNP probes across the genome with dense coverage in over 1000 genes reported to be involved in cancer development. Two regions of CN of chromosome 4p16.1 and chromosome 17q21.31-q21.32 were observed in both tumor and normal tissues. We do not consider these regions to play a role in the pathogenesis of cancer development as they were present in the normal tissue and most likely represent CNVs in the population. The loss of chromosomes 9, 15 and 18 was only observed in the tumor tissue. Monosomy of chromosome 9, partial loss of 9q or LOH in 9p21 and 9p13 are seen in up to 30% of cRCC. The cRCC cases with aberration in chromosome 9 are at a high risk for recurrence and poorer prognosis, which suggests that tumor suppressor genes may exist in this region. [\[17\],\[18\]](#) Four candidate genes in chromosome 9, namely *CDKN2B*, *GAS1*, *DBC1* and *AUH*, are considered to play important roles in tumorigenesis and dismal clinical outcome. [\[19\]](#) The loss of chromosome 18 has been reported in a sole case of cRCC, while loss of chromosome 15 has not been seen in cRCC. There are 10 genes in the chromosome 6p22.1 (arr6p22.1(26,007,707-28,433,2950)] region. The copy neutral-LOH involving the chromosome 6p22.1 region is a novel finding and has not been previously reported to the best of our knowledge. A table documenting the differences in cytogenetic abnormalities between cRCC and TRCC is presented [\[Table 1\]](#).

Cytogenetic abnormalities reported in conventional clear cell RCC (cRCC)	Cytogenetic findings in our case of tubulocystic RCC (TRCC)
Complete or partial loss of chromosome 9 or 9q, or LOH at 9p21 and 9p13 in up to 30% of the cases	Loss of entire chromosomes 9, 15 and 18
Loss of chromosome 15 never reported before	
Loss of chromosome 18 reported in one case	
LOH at chromosomes 14q21-23, 14q31-q32.2	Copy neutral LOH involving chromosome 6p22.1
3q deletion (3p11-16, 3p21 and 3p25 deletions most common)	
Trisomy 5, 12, 20	
Loss of chromosomes 8, 13q and 14q	
*Not lost of heterozygosity	

Table 1: Cytogenetic abnormalities reported in conventional clear cell RCC versus those that identified in tubulocystic RCC

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In summary, TRCC is a distinctive entity with novel genetic findings. In our case, we identified the loss of chromosomes 9, 15 and 18 and copy neutral LOH in the region of 6p22.1. These CN aberrations have not been previously reported in TRCC. In addition, we describe the unusual clinical and pathologic features of this uncommon and probably underrecognized subtype of RCC. Further analysis of additional cases by a combination of FISH and MIP arrays will help us better understand the molecular pathogenesis of TRCC tumor development and to better define the biologic behavior of this entity. Also, microarray analysis may be able to help predict poor outcome or more clinically aggressive TRCCs based on genomic instability. Ultimately, this may lead to the discovery of candidate loci for targeted therapeutics in TRCC or the other subtypes of renal tumors.

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Figures

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