

# The Utility of Immunohistochemistry in Diagnosing Tubulocystic Renal Cell Carcinoma with Papillary Morphology

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## ABSTRACT

Tubulocystic renal cell carcinoma (TC-RCC) is a recently recognized, rare but distinct malignant entity. Pathologists have endeavored to completely define its histomorphologic, immunohistochemical and molecular features. Recounted is a case where the diagnosis of TC-RCC was confounded by presence of papillary morphology. Immunohistochemical expression of alpha-methyl acyl-CoA-racemase and vimentin with corresponding negativity for CK7 and CD10, following distinctive gross and microscopic findings, confirmed a diagnosis of TC-RCC. This report demonstrates the strategic value of performing immunohistochemistry studies to establish a diagnosis of TC-RCC especially when unusual histologic features are encountered. Immunohistochemistry continues to be the most practical approach to diagnosis as molecular testing methods, such as next generation sequencing, remain unfeasible in the local setting. Cautious prognostication is required as accounts of recurrence and metastasis continue to emerge.

*Key words:* renal cell carcinoma, histology, immunohistochemistry, diagnosis, surgical pathology

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## INTRODUCTION

Tubulocystic renal cell carcinoma (TC-RCC) of the kidney is a rare entity with only about a hundred cases reported in literature.<sup>1</sup> Though recognized to have distinct macroscopic, microscopic and immunohistochemical features in the 2016 World Health Organization Classification of Tumors,<sup>2</sup> recent studies have challenged the presence of papillary architecture as an acceptable morphologic variation of the disease. Immunohistochemistry studies have emerged as a reliable, affordable and readily available means of confirming a diagnosis of TC-RCC when tumor morphology deviates from its classic histologic description and are further augmented by molecular and cytogenetic testing. This report aims to demonstrate the diagnostic utility of immunohistochemistry studies in the case of a young adult male with tubulocystic renal cell carcinoma exhibiting classic and papillary morphology with later occurrence of pulmonary and skeletal metastases.

## CASE PRESENTATION

A previously healthy 27-year-old male presented with a one-year history of intermittent and progressive right flank pain. Sudden onset hematuria prompted consult and subsequent work-up. Urinalysis revealed red, turbid urine with significant elevations in leukocyte, erythrocyte and bacterial counts with presence of ghost cells. Serum creatinine (1.0 mg/dL) and estimated glomerular filtration rate (102.69 mL/min/1.73 m<sup>2</sup>) were within normal limits. Triple phase computed tomography (CT) scan of the whole abdomen identified a globularly enlarged right kidney (11.7 x 7.2 x 7.2 cm) with a heterogeneously enhancing, endophytic, mid- to inferior pole mass measuring 5.3 x 5.3 x 6.5 cm with involvement of the infundibulo-calyceal system. The radiographic impression was transitional cell carcinoma (Figure 1).



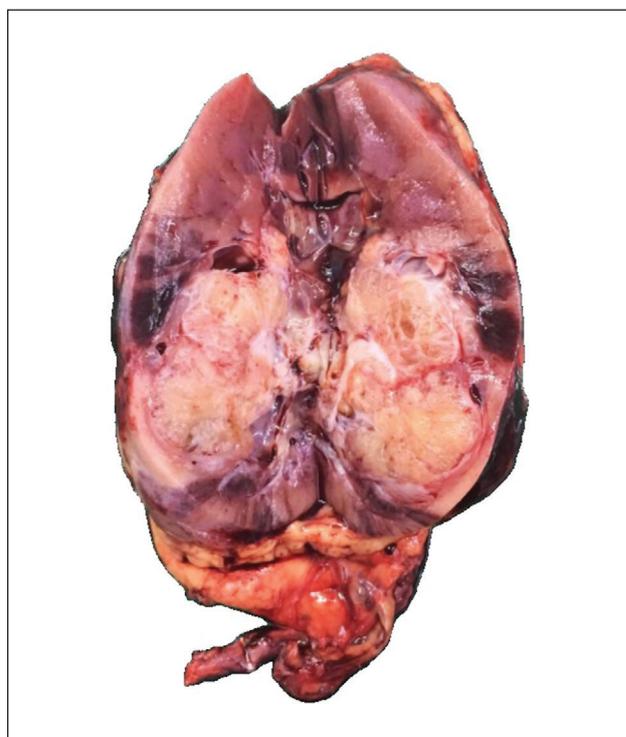


**Figure 1.** Triple-phase CT scan (A) plain, (B) arterial phase, (C) venous phase showing a heterogeneously enhancing, endophytic renal mass involving the infundibulo-calyceal system.

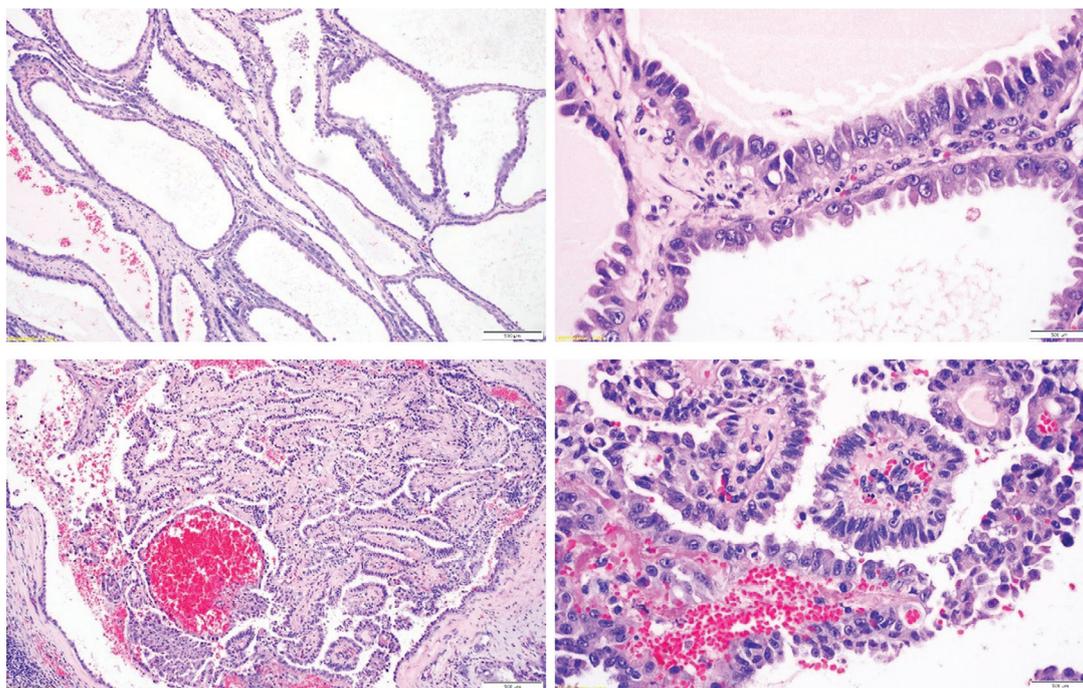
Longitudinal anti-hilar sectioning of the nephrectomy specimen revealed a 6 x 6 x 5 cm, firm, well-circumscribed, multicystic, cream-white to tan-yellow, mid- to inferior pole mass, bearing resemblance to a sponge. Cyst linings appeared smooth with sizes ranging from less than 1 mm to approximately 9 mm in diameter. Serous, straw-colored fluid cyst contents were expressed on sectioning. Gross evidence of previous intralesional hemorrhage was not observed. No solid areas were noted and no stones were retrieved. Renal sinus involvement was grossly observed but tumor was limited to the kidney without involvement of the pelvicalyceal system, Gerota’s fascia, renal vein nor ureter (Figure 2).

Microscopic sections disclosed a tumor composed of varisized cystic structures lined by a single layer of cuboidal cells with hobnailed appearance. Some cysts displayed a proliferation of this lining epithelium forming papillary configurations. Neoplastic cells were characterized by enlarged, moderately pleomorphic, vesicular nuclei with prominent to inclusion-like eosinophilic nucleoli and abundant amounts of cytoplasm with occasional vacuolization and clearing (WHO/ISUP histologic grade 3) (Figure 3). Lymphovascular space invasion was not identified. Minimal necrosis was noted. A pathologic stage classification of pT3a was assigned.

Immunohistochemistry studies revealed diffuse expression of vimentin and alpha-methyl acyl-CoA racemase



**Figure 2.** Bivalved nephrectomy specimen revealing a mid-to inferior pole mass with sponge-like or “bubble wrap” appearance. No solid areas are identified.



**Figure 3.** Microscopic tumor sections exhibiting tubulocystic and papillary morphology lined by hobnail cells with World Health Organization/International Society of Urologic Pathology (WHO/ISUP) grade 3 nuclei (H&E, 100x and 400x).

(AMACR). CD10 was negative in neoplastic cells with uninvolved glomeruli and scattered inflammatory cells serving as the internal control. Cytokeratin 7 (CK7) was likewise negative in tumor cells but was expressed in entrapped benign renal tubules. Papillary formations did not express CK7 (Figure 4). A final immunomorphologic diagnosis of tubulocystic renal cell carcinoma was rendered.

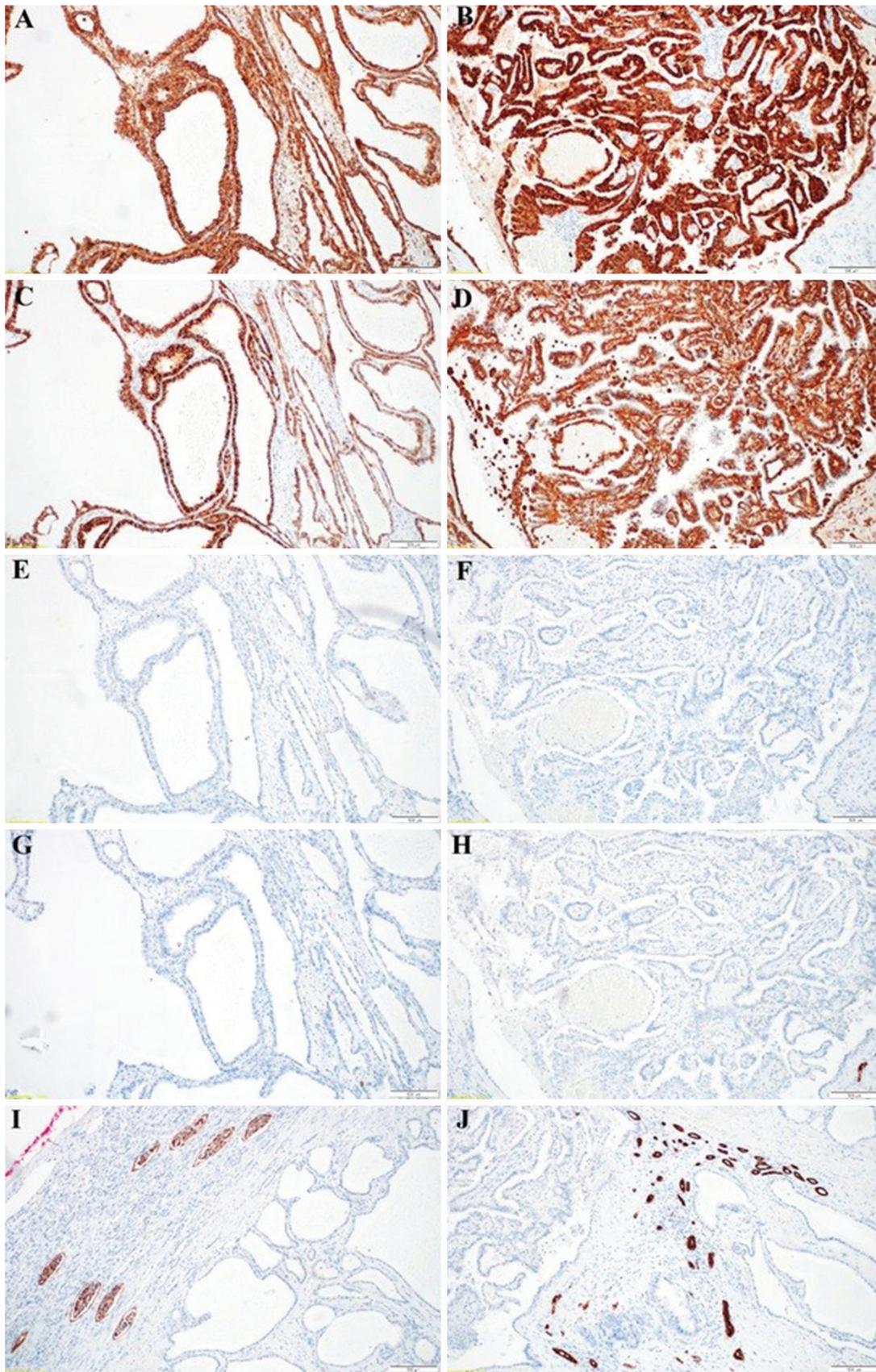
Fifteen months post-operatively, multiple pulmonary nodules and a lytic lesion in the manubrium were visualized on chest CT. Five months following detection of the pulmonary nodules, the patient suffered from a pathologic fracture of the right femoral neck. Bone scintigraphy displayed increased tracer uptake in the clavicles, pelvis, vertebrae and right femur signifying high probability of osseous metastases. Biopsy of the most accessible pulmonary nodule revealed metastatic TC-RCC with morphology and immunohistochemical expression being consistent with the previously diagnosed renal mass. In addition, Napsin-A was performed to assess for a primary lung adenocarcinoma which was subsequently ruled out by its lack of expression in tumor cells (Figure 5). A multidisciplinary approach to management was initiated.

## DISCUSSION

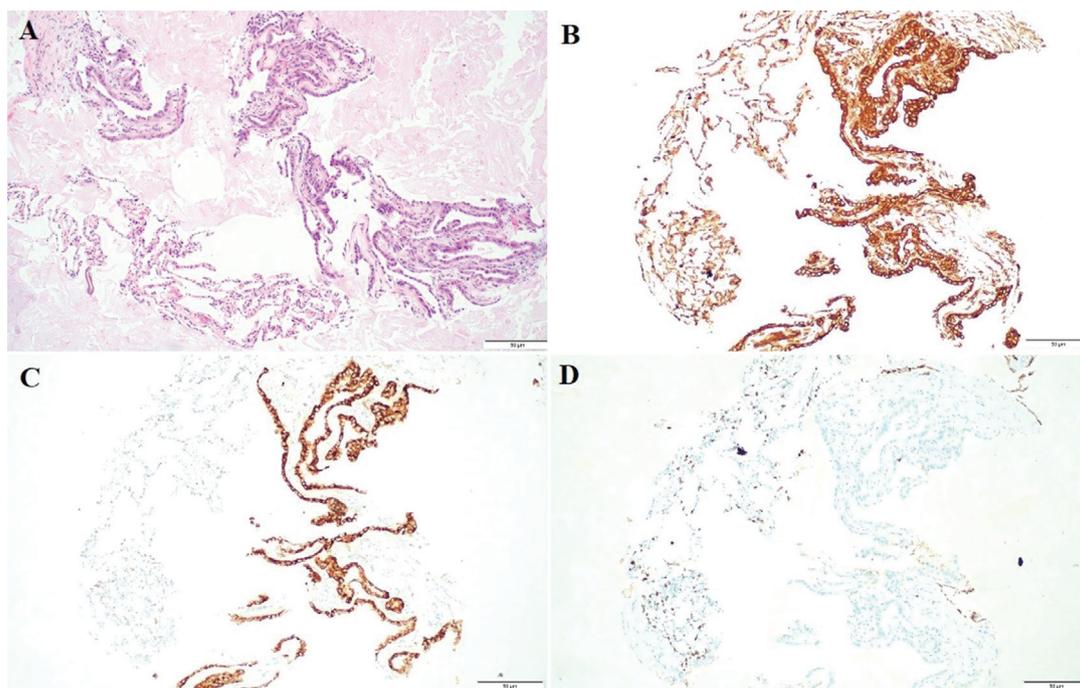
Tubulocystic renal cell carcinoma is a rare malignant yet indolent entity, constituting less than 1% of all renal cell carcinomas with only about a hundred cases reported in literature to date. It exhibits a strong male predilection and wide age distribution. Abdominal pain and hematuria are presenting symptoms, but the vast majority of tumors are discovered incidentally. Grossly, there is involvement of the renal cortex or corticomedullary junction by a solitary, well-circumscribed mass composed of multiple

small to intermediate-sized cysts creating a spongy or “bubble-wrap” cut surface. Microscopically, the tumor is composed of varisized tubules lined by a single layer of flattened, cuboidal to columnar, hobnail epithelium exhibiting WHO/ISUP grade 3 nucleoli and abundant eosinophilic, oncocyoma-like cytoplasm.<sup>2</sup> The diagnosis is largely based on the presence of classic histological features however, immunohistochemical markers may aid in diagnosis. TC-RCC is consistently positive for AMACR, vimentin, parvalbumin and cytokeratins 8, 18 and 19. Variable positivity for CD10, CK7 (focal weak expression), carbonic anhydrase IX, PAX2 and cytokeratin 34BE12 have been reported.<sup>1,3-5</sup>

There have been accounts of TC-RCC occurring in association with other neoplasms, most commonly papillary renal cell carcinoma (PRCC).<sup>3</sup> It is observed that TC-RCC may bear pathologic similarities with PRCC but gene expression profiling data indicates that TC-RCC has a unique molecular signature.<sup>4</sup> Driven by the contradictory results of cytogenetic approaches in several studies that supported or refuted the presence of aberrations in chromosomes 7 and 17 in TC-RCC, Lawrie et al., conducted the largest molecular study on TC-RCC employing miRNA expression analysis and targeted next generation sequencing and discovered a high prevalence of ABL1 and PDGFRA gene mutations only rarely expressed in other renal cell carcinoma types including PRCC.<sup>6</sup> In addition, losses in chromosome 9 and the Y chromosome detected via next generation sequencing and fluorescence in situ hybridization have been reported.<sup>7</sup> FISH analysis using chromosome enumeration on the patient’s specimen revealed gains in both chromosome 7 and 17 – expected findings given the close molecular relationship of TC-RCC and PRCC.



**Figure 4.** Immunohistochemistry. **(A and B)** Vimentin, positive diffuse strong cytoplasmic expression. **(C and D)** Alpha-methyl acyl-CoA racemase (AMACR), positive diffuse strong cytoplasmic granular expression. **(E and F)** CD10, negative expression in tubulocystic and papillary areas. **(G and H)** Cytokeratin 7 (CK7), negative expression in tubulocystic and papillary areas. **(I)** CD10 internal control, non-neoplastic glomeruli. **(J)** CK7 internal control, non-neoplastic renal tubules entrapped between papillary and tubulocystic areas.



**Figure 5.** Pulmonary metastasis, cell block and immunohistochemistry. **(A)** Metastatic tubulocystic renal cell carcinoma (TC-RCC) (right) with non-neoplastic pulmonary alveoli (left) (H&E, 100x). **(B)** Vimentin, positive diffuse strong cytoplasmic expression in metastatic neoplastic cells and pulmonary alveoli. **(C)** AMACR, positive diffuse strong cytoplasmic granular expression in metastatic neoplastic cells; negative expression in pulmonary alveoli. **(D)** Napsin-A, negative expression in neoplastic cells with patchy cytoplasmic expression in scattered pneumocytes serving as internal control.

As TC-RCC is a diagnosis primarily based on histology, pathologists have sought to refine the morphologic criteria applicable to this disease. Although papillary components are deemed acceptable in current tumor classification texts,<sup>2</sup> a study of nine TC-RCC cases by Sarungbam et al., recommended that TC-RCC be diagnosed using strict morphologic criteria and only when presenting in “pure” form, that is, without variable architectural patterns such as papillary or poorly differentiated foci.<sup>7</sup> The considerable presence of papillary morphology became a diagnostic dilemma for the case at hand. Pending more extensive molecular analysis, the highly characteristic spongy gross appearance with distinct lack of solid areas, cytologic features such as diffuse cellular hobnailing with presence of high-grade nuclei, and immunohistochemical expression of AMACR and vimentin with absence of reactivity for CK7 and CD10, all favored a profile of TC-RCC over the main differential of PRCC.

Other considered differentials with tubulocystic patterns and hobnailed cells are easily distinguished from TC-RCC by clinical, macroscopic and histopathologic criteria. Multilocular cystic renal neoplasm of low malignant potential shows cysts lined by neoplastic cells with abundant clear cytoplasm and WHO/ISUP grade 1 to 2 nuclei. Fumarate hydratase deficient RCC distinctly occurs with cutaneous and uterine leiomyomas in 85% of cases. Identification of perinuclear halos and AMACR negativity aids in diagnosis of this tumor. Collecting duct carcinoma grossly appears solid and necrotic and is associated with a desmoplastic stromal reaction and high-grade behavior<sup>2</sup> (Table 1).

Although majority of TC-RCCs behave indolently, there still exist reports of tumor recurrence and distant metastasis.<sup>8-10</sup> Given the evolving body of knowledge on TC-RCC, an integrative approach to management becomes imperative to providing optimal care.

## CONCLUSION

Tubulocystic renal cell carcinoma presents with unique histopathologic features and specific genetic aberrations. Immunohistochemistry serves as a valuable tool in establishing a diagnosis of TC-RCC amidst morphologic mimics. As the biologic behavior of TC-RCC remains to be established, due caution must be exercised in its prognostication. Further studies are necessary to better define the diagnostic criteria for this new subtype of renal tubular epithelial malignancies and to provide greater insight into its clinical outcomes.

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## ETHICAL CONSIDERATION

Patient consent was obtained before submission of the manuscript.

**Table 1. Differential diagnosis for tubulocystic renal cell carcinoma<sup>2-5</sup>**

Differential diagnosis	Morphologic findings	Immunohistochemical expression	Molecular features
Tubulocystic RCC	varisized tubules lined by a single layer of flattened, cuboidal to columnar, hobnail epithelium exhibiting WHO/ISUP grade 3 nucleoli and abundant eosinophilic cytoplasm	Positive Expression: PAX8 AMACR RCC marker Vimentin Parvalbumin CK8, CK18 and CK19 Variable Expression: CD10 CK7 CA IX PAX2 Cytokeratin 34βE12 Negative Expression: p63	ABL1 and PDGFRA gene mutations <sup>6</sup>  Aberrations in chromosomes 7 and 17 and loss in chromosome 9 and Y chromosome have been reported <sup>7</sup>
Papillary RCC	papillary/ tubulopapillary structures with delicate fibrovascular cores often containing foamy macrophages and psammoma bodies, lined by a single or pseudostratified layer of neoplastic cells with high WHO/ISUP nuclear grade and abundant eosinophilic cytoplasm; necrosis and hemorrhage	Positive Expression: PAX8 PAX2 AMACR RCC marker Vimentin CD10 CK7 Cytokeratin AE1/AE3 CAM 5.2 EMA Negative Expression: Cytokeratin 34βE12 p63	Gains (trisomy / tetrasomy) in chromosome 7 and 17 and loss of Y chromosome are classic findings among other various reported mutations
Multilocular Cystic Renal Neoplasm of Low Malignant Potential	cyst walls are lined by a single layer of tumor cells with abundant clear cytoplasm and WHO/ISUP grade 1 nuclei; fibrous septa also contain clusters of tumor cells	Positive Expression: PAX8 CA IX	Chromosome 3p deletion and VHL gene mutations
Fumarate Hydratase-deficient RCC	papillary structures lined by large cells with large nuclei, inclusion-like eosinophilic nucleoli and abundant eosinophilic cytoplasm; solid, tubular and tubulocystic variants have been noted	Positive Expression: S-(2-succino)cysteine Negative Expression: FH	Germline mutations in fumarate hydratase gene at 1q42.3-q43
Collecting Duct Carcinoma	morphologic criteria include medullary involvement, predominant tubular (tubulopapillary or tubulocystic) morphology, stromal desmoplasia, high-grade cytology, infiltrative growth pattern and absence of other RCC types or urothelial carcinoma	Positive Expression: PAX8 CK7 CK19 Cytokeratin 34βE12 Vimentin Variable Expression: AMACR Negative Expression: SMARCB1 CD10 RCC marker	Various chromosomal losses  HER2/neu amplification and SMARCB1 mutations have been reported

AMACR, alpha-methyl acyl-CoA racemase; CA IX, carbonic anhydrase IX; CK, cytokeratin; EMA, epithelial membrane antigen; FH, fumarate hydratase; PAX2, paired box 2 transcription factor; PAX8, paired box 8 transcription factor; PDGFRA, platelet-derived growth factor receptor alpha; RCC, renal cell carcinoma; SMARCB1, switching defective/sucrose nonfermenting (SWI/SNF) related, matrix associated, actin dependent regulators of chromatin; VHL, Von Hippel-Lindau gene; WHO/ISUP, World Health Organization / International Society of Urologic Pathology

**STATEMENT OF AUTHORSHIP**

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**AUTHOR DISCLOSURE**

Both authors declared no conflict of interest.

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