# Tubulocystic Renal Cell Carcinoma: A Great Imitator

**Indraneel Banerjee, MS, MCh, Sher Singh Yadav, MS, MCh, Vinay Tomar, MS, MCh, Suresh Yadav, MS, MCh, Shyam Talreja, MS, MCh**
Department of Urology, Sawai Man Singh Medical College and Hospital, Jaipur, India

Tubulocystic renal cell carcinoma (TCRC) is a rare renal tumor. Patients are usually asymptomatic; it is usually detected incidentally, during imaging studies for Bosniak type III and type IV renal cysts. These tumors rarely metastasize. The role of targeted therapy in such rare tumors is still controversial. We report a case of TCRC initially presented as a Bosniak type II renal cyst and was discovered ultimately to be a metastatic disease. This type of presentation might broaden our understanding of this rare disease.

[Rev Urol. *2016;18(2):118-121 doi: 10.3909/riu0692*]



**KEY WORDS**

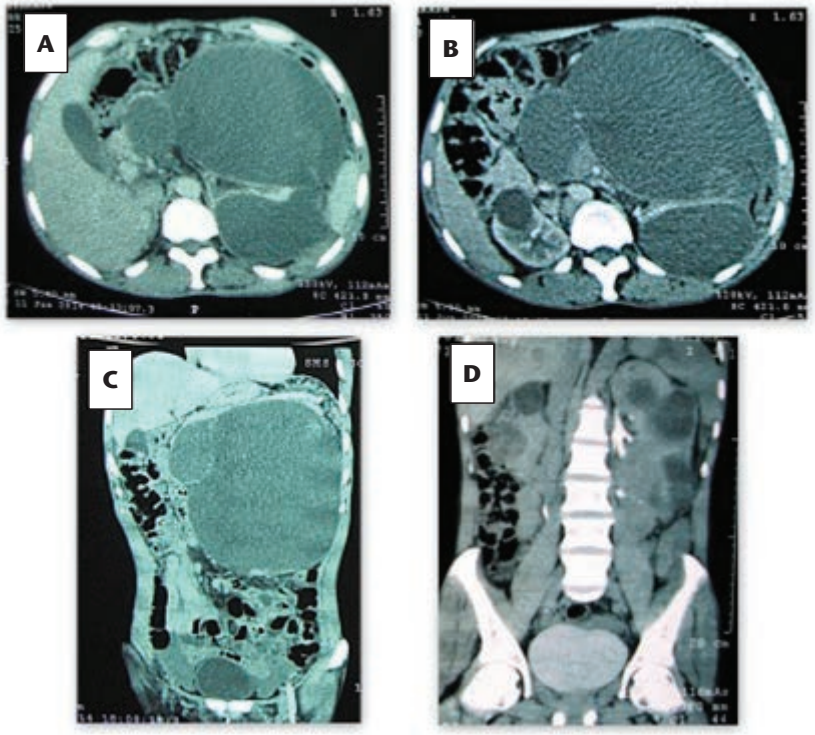
Tubulocystic renal cell carcinoma • Bosniak type II cyst • Targeted therapy

A 45-year-old previously healthy man presented to our clinic with left lumbar back pain and abdominal distension for the past 6 months. There was no history of fever, weight loss, night sweats, fatigue, hematuria, or graveluria. Past medical, surgical, and family history were noncontributory. On physical examination, his vital signs were within normal limits. A left-sided large (~ 15 × 15 cm) nontender abdominal mass was palpable, extending from the left lumbar region to the left hypochondrium. His initial laboratory results showed normal hematologic, renal, and hepatic data. A contrast-enhanced computed tomography (CECT) scan of the abdomen and pelvis revealed bilateral, multiple renal cortical cysts, the largest of which was 63 × 35 mm, in the middle of the right kidney, and a 131 × 154 mm cyst in the lower pole of the left kidney (Bosniak type II; Figure 1).

## Management and Outcome

The patient had persistent left flank pain, even after taking adequate analgesics, and underwent laparoscopic left renal cyst deroofing and cyst wall biopsy. The postoperative period was uneventful. Renal cyst fluid cytology revealed no malignant cells. Histopathologic examination revealed tubules, lined by cuboidal to polygonal and hobnail cells, with eosinophilic to clear cytoplasm and prominent nucleoli. Immunohistochemistry

**Figure 1.** Preoperative contrast-enhanced computed tomography of the abdomen and pelvis showing bilateral multiple renal cortical cysts (Bosniak type II).

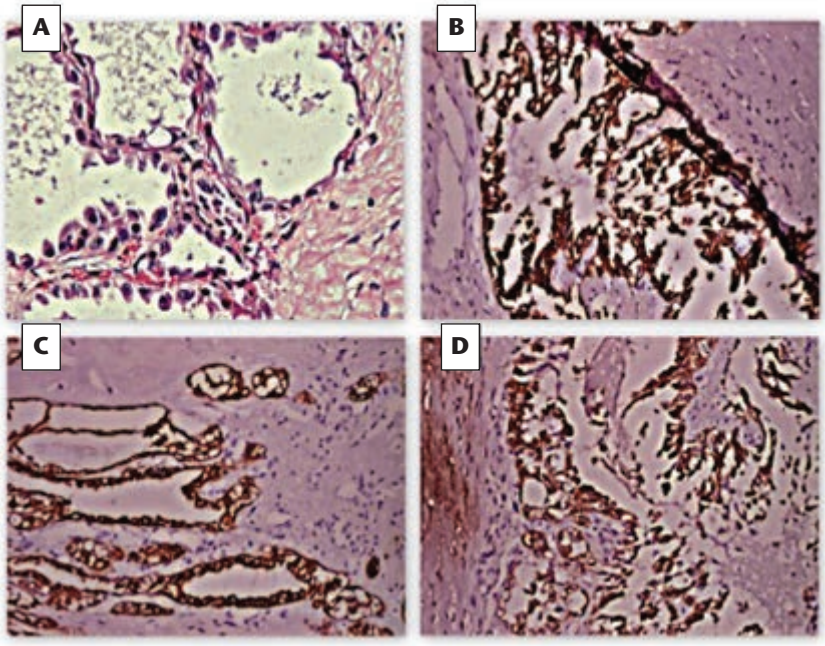



results were strongly positive for cytokeratin (CK) 7, CK19, and α-methylacyl-CoA racemase (AMACR), and negative for CD10 (Figure 2). Based on these findings, a final diagnosis of tubulocystic renal cell carcinoma (TCRC) was made. The patient was advised to have a left radical nephrectomy, but he declined any further treatment.

He came back to the emergency department after 1.5 months, with respiratory distress and huge abdominal distension suggestive of ascites. Therapeutic ascitic fluid tapping was performed and sent for analysis. Ascitic fluid was exudative in nature, fluid creatinine level was 0.9 mg/dL, and cytologic analysis revealed few round cells exhibiting prominent nucleolus, suggestive of malignancy. His basic hematologic, renal, and liver function test results were normal. CECT scan of the abdomen and thorax showed moderate to gross ascites, multiple nodular enhancing peritoneal lesions suggestive of peritoneal metastasis, evidence of omental metastasis, a large cystic lesion of 146 × 108 × 146 mm anterolateral to the left kidney, a large cortical cyst 132 × 110 × 130 mm at the upper pole of the right kidney, and heterogeneously enhancing nodular mass of 56 × 59 × 63 mm arising from the midpole of the right kidney. There was no evidence of lung or liver metastasis (Figure 3); a diagnosis of metastatic TCRC was made.

As per the hospital tumor board decision, sunitinib, 50 mg, was initiated. The patient subsequently developed hand-foot syndrome. The dose was reduced to 37.5 mg but the symptoms persisted and sunitinib was discontinued. Everolimus, 10 mg, was then started; the patient responded well, with a decrease in ascites, the peritoneal metastasis shrank, and renal deposits remained stable. At 8-month follow-up, at the time of this writing, the patient is fully ambulatory and doing well on everolimus with few complications.

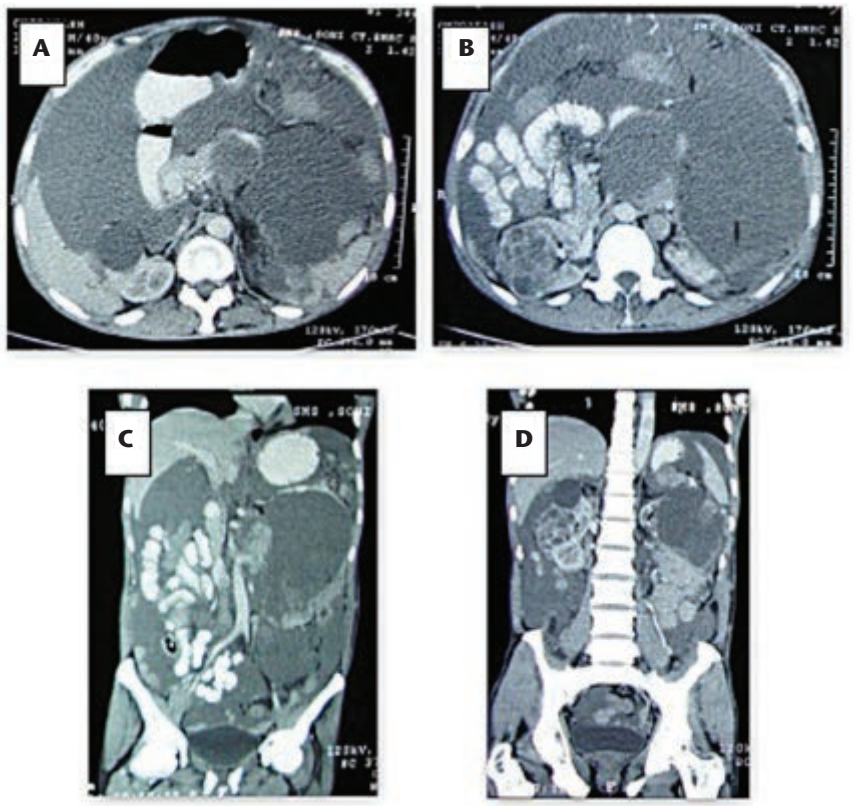
**Figure 2. (A)** Hematoxylin-eosin staining of tubulocystic renal cell carcinoma showing cystically dilated tubular cells lined by cuboidal and hobnail cells. **(B-D)** Strongly positive immunohistochemistry findings of cytokeratin (CK) 19, CK7 and α-methylacyl-CoA racemase.




## Discussion

TCRC is a recently established, rare renal cancer. It was not included in the World Health Organization 2004 classification of genitourinary tumors. However, in 2010, the American Joint Committee on Cancer recognized it as a distinct entity.[1] It was included in the

**Figure 3.** Postoperative contrast-enhanced computed tomography of the abdomen and pelvis showing gross ascites, a cystic lesion anterolateral to the left kidney, a right renal cortical cyst, peritoneal deposits, and a heterogeneously enhancing nodular mass at the midpole of the right kidney.




Vancouver classification of renal cancer in 2012.[2] In 1956, Masson thought it to be a subtype of collecting duct carcinoma (CDC) and called it "carcinoma of the collecting duct."[3] Amin and colleagues named the tumor "tubulocystic carcinoma" in a series of 31 cases published in 2004.[4] A recent study by Osunkoya and associates[5] has shown, at the molecular level, that it is distinct from CDC.

Clinically, TCRC occurs mostly in the fifth or sixth decade of life, with a strong male preponderance (male:female ratio, 7:1).[4] It is less aggressive than other renal carcinoma; patients are usually asymptomatic. Patients may also present with abdominal pain, distension and hematuria.[6] Most often the lesions are small (pT1), but occasionally pT2 and pT3 lesions have also been reported. The majority of tumors have an indolent course, and rarely progress, recur, or metastasize. Only a few cases of tumor metastasizing to the lymph node, liver, bone, and pleura have been reported,[7] and a single case with sarcomatoid features and multiple peritoneal metastasis has been reported.[8]

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Grossly, these tumors are well circumscribed and unencapsulated; they frequently display a cystic component (Bosniak type III, Bosniak type IV). The cut surface is spongy white or gray, often described as "bubble wrap." Microscopically, TCRC is composed of tightly packed tubules and cysts, lined by cuboidal and columnar cells containing abundant eosinophilic cytoplasm with large nuclei and prominent nucleoli. Hobnail cells are commonly found.[4] Electron microscopy reveals abundant microvilli, with a brush border appearance in most cells, resembling proximal convoluted cells (PCT).[5]

In the past, TCRC was considered to be a low-grade CDC, but immunohistochemistry showed a poor association between the two. They show expression of proteins of PCT (CD10 and p50S), distal tubules (CK19), and intercalated collecting duct cells (parvalbumin). In contrast to CDC, these tumors also show vimentin, p53, and AMACR overexpression, and are always negative for high molecular-weight cytokeratin (34bE12).[5] Yang and colleagues,[9] by using gene expression microarray analysis, demonstrated a unique molecular signature of TCRC, as compared with other renal tumors and normal renal tissue. The data revealed that TCRC is closely related to papillary renal cell carcinoma (RCC); both type 1 and type 2 dimensional clustering analysis placed it between low- and high-grade papillary RCC. Yang and colleagues[9] also reported that TCRC shows gain in chromosome 17 (trisomy 17), but not chromosome 7. Trisomy 7 and 17 are the most common karyotypic changes in papillary RCC. Thus, although multiple other renal cell tumor subtypes have been reported to be associated with TCRC, there is a slight preponderance of synchronous TCRC and papillary tumor.

The differential diagnosis includes CDC, multilocular cystic RCC, cystic nephroma, mixed epithelial and stromal tumor, and cystic oncocytoma. CDC is solid rather than cystic, and it has high-grade nuclear features.

Immunohistochemistry aids in the differential diagnosis.[10]

Multilocular cystic RCC is a variant of clear cell carcinoma; it primarily affects middle-aged women (male:female ratio, 1.2:2.1), accounting for approximately 4% of clear cell RCC; 90% of cases are incidentally diagnosed on radiologic investigation for other reasons, and characterized by variable-sized cystic spaces lined by flattened to cuboidal clear cells of low Fuhrman nuclear grade.[11]

Cystic nephroma in adults has a striking female preponderance (female:male ratio, 8:1), characterized by larger cysts and contains no tubules. The cysts are lined by flattened cells with indistinct nuclei.[12] Mixed epithelial and stromal tumor in adults has a female preponderance and frequently express estrogen and progesterone receptor in the mesenchyme. The stroma may be of ovarian type. Long-term estrogen replacement in women and sex steroid exposure in men have been suggested to play a role in tumor genesis.[13] In cystic oncocytoma the cysts are lined by cuboidal oncocytic cells with round central nuclei and they are negative for CK10 and CK7.[12]

Radical nephrectomy is the recommended treatment; for small tumors, partial nephrectomy is an option. There is no established targeted therapy in metastatic TCRC, but a few case reports suggested a partial response to sunitinib (a tyrosine kinase inhibitor) and everolimus (a mammalian target of rapamycin [mTOR] inhibitor).[14,15]

## Conclusions

TCRC is a distinct group of RCC whose clinical and pathologic aspects are still not well studied. A combination of histology, electron microscopy, and immunohistochemistry is essential for proper diagnosis. TCRC presenting as a Bosniak type II cyst is still unreported. It should be considered in the differential diagnosis of Bosniak type II cysts. To date, no guidelines exist for the optimal management of the condition. For a better understanding of this rare condition, examination of additional cases is required. ■

*Long-term estrogen replacement in women and sex steroid exposure in men have been suggested to play a role in tumor genesis.*

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## MAIN POINTS

- Tubulocystic renal cell carcinoma (TCRC) is a rare renal cancer. A recent study showed, at the molecular level, that it is distinct from collecting duct carcinoma (CDC).
- TCRC was previously considered a low-grade CDC, but immunohistochemistry did not show a strong association between the two. In contrast to CDC, these tumors also show vimentin, p53, and α-methylacyl-CoA racemase overexpression.
- The differential diagnosis includes CDC, multilocular cystic renal cell carcinoma, cystic nephroma, mixed epithelial and stromal tumor, and cystic oncocytoma.
- Radical nephrectomy is the recommended treatment; for small tumors, partial nephrectomy is an option. There is no established targeted therapy in metastatic TCRC, but a few case reports suggested a partial response to sunitinib and everolimus.