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Review

Tubulocystic renal cell carcinoma, a rare tumor entity: Review of literature and report of a case

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Abstract

Tubulocystic renal carcinoma is a recently described neoplasm of low grade malignancy which was not included in the last WHO 2004 classification. The tumor is extremely rare with less than one hundred cases reported to date. In this article, the literature about that rare renal neoplasm is reviewed and an additional case is reported.

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Introduction

Tubulocystic renal carcinoma (TCRC) is a recently described neoplasm which was not included in the last WHO 2004 classification [1]. It consists of a mixture of tubules and micro/macro cysts with low-grade nuclear features and appears to derive from proximal convoluted tubule and distal nephron. The mean age is 54 years and

85% of patients are male [2]. Prognosis is usually excellent with only rare distant metastases or death from disease. The tumor is extremely rare with less than one hundred cases reported to date [3]. Herein, we review the literature about that rare renal neoplasm followed by report of an additional case.

Literature review

Kidney cancer is among the ten most common causes of cancer-related death in adults [4]. Over 64,700 new cases and over 13,500 deaths are expected to occur in the US in 2012 [5]. Renal cell carcinoma (RCC) constitutes more than 80% of all primary renal neoplasms, and clear cell RCC (ccRCC) accounts for most of these cases (80%). Updates to the histopathological diagnosis of kidney neoplasms were last reflected in the latest World Health Organization (WHO) classification of genitourinary and kidney neoplasms introduced in 2004 [1]. Ongoing research since then has led, however, to the description of new tumor entities. One of these is the extremely rare tubulocystic renal carcinoma of which less than one hundred cases have been reported to date [3]. TCRC was not

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included in the WHO 2004 classification. However, the very recent 2010 AJCC/UICC TNM, 7th edition, cancer protocol for RCC now recognizes this tumor as a distinct entity [6].

Clinically, TCRCs occur predominantly in men with a wide age range and a mean of 54 years [2]. They are less aggressive than other renal carcinomas. Most present when small (pT1); and only rarely progress, recur, or metastasize [3,7–9]. In the vast majority of reports, TCRC has been an incidental finding on autopsy, nephrectomy for a separate disease process, or imaging [6]. Other clinical presentations included abdominal distention, pain, hematuria or a renal mass [3,10,11].

TCRC was originally thought to be a subtype of collecting duct carcinoma (CDC) that was first described by Masson who named it “Bellinian epithelioma” or “carcinoma of the collecting ducts” as he believed it originated from collecting ducts of Bellini [12]. Collecting duct carcinoma is an uncommon variant of RCC that has been proven to be highly aggressive and associated with poor prognosis [13]. Beginning in the mid-90s, there were reports of a potentially low-grade variant of CDC that had a distinctively benign course. MacLennan et al. in 1997 hypothesized that this tumor represented the low grade of the spectrum of collecting duct carcinoma, as it shares similar characteristics with the latter tumor [14]. In 2004, Amin et al. named the tumor “tubulocystic carcinoma” in a series of 29 cases [15]. A recent study by Osunkoya et al. has shown that TCRC is distinct from CDC at the molecular level [16].

Histologically, TCRC is a well-circumscribed neoplasm consisting of cysts and tubules lined by mildly atypical cells with abundant eosinophilic cytoplasm, prominent nucleoli and a variable hobnail appearance. Grossly, these tumors frequently display a cystic component which renders a radiological classification of Bosniak III or IV [3]. The Bosniak classification system for CT evaluation of renal cysts, introduced in 1986, has been used to help evaluate the malignant risk of cystic renal masses and decide their clinical management [17]. Category I lesions are benign simple cysts with hairline-thin walls. These cysts contain no septa, calcifications, or solid components and do not show enhancement after intravenous contrast material administration. Category II masses are benign cystic lesions that may contain hairline-thin septa. Fine calcification in the walls or septa of such lesions, or a short segment of slightly thickened calcification, may be present. Minimal perceived (not measurable) enhancement of a hairline-thin smooth septum or wall is sometimes present. Lesions with uniformly high attenuation (high-attenuation cysts) that are less than 3 cm in diameter and do not enhance are included in this category. Category IIF (the “F” indicates need for follow-up imaging) lesions are more complex cysts that cannot be neatly classified as category II or III lesions. These cysts may contain an increased number of hairline-thin septa or have minimal but smooth thickening of the wall or septa. The wall and/or septa may contain calcifications, which may be thick and nodular, without obvious enhancement. Like category II cysts, these lesions may demonstrate minimal perceived enhancement of a hairline-thin smooth septum or wall; however, there are no enhancing soft-tissue components. Nonenhancing high-attenuation lesions (high-attenuation cysts) that are completely intrarenal and are 3 cm or larger are also included in this category. Category III lesions are indeterminate masses, and it usually cannot be determined at imaging whether they are benign or malignant. They have thickened irregular walls or septa, in which enhancement can be demonstrated. Category IV lesions are malignant cystic masses. They may have

findings similar to those seen in Category III masses but also have enhancing soft-tissue components adjacent to, but independent of, the wall or septum.

The relationship of TCRC to collecting duct (Bellini duct) carcinoma remains controversial. As mentioned previously, TCRC was considered in the past, to be a tumor of collecting duct origin and was sometimes confused with collecting duct carcinoma, an aggressive infiltrative solid tumor with poor prognosis. Therefore, an “evolving concept” of collecting duct carcinomas was proposed, and low-grade collecting duct carcinoma at the beginning of the spectrum corresponded to the current TCRC [14]. However, immunohistochemical and ultrastructural studies demonstrated the poor relationship between TCRC and collecting duct tumors [18]. These tumors show expression of proteins of proximal convoluted tubules (CD10 and P504S), distal tubules (CK19) and intercalated collecting duct cells (parvalbumin). They also show vimentin, p53 and alpha methylacyl CoA racemase (AMACR) over-expression in contrast to CDC [16]. Ultrastructurally, they display abundant microvilli with brush border organization as proximal convoluted tubule cells, but with short microvilli and cytoplasmic interdigitation, similar to intercalated cells of the collecting duct [18]. Those observations led to the conclusion that TCRC shows aberrant renal tubular differentiation rather than originating from collecting ducts.

Yang et al. demonstrated a unique molecular signature of tubulocystic carcinoma in comparison to other renal tumors and normal renal tissue using gene expression microarray analysis. Clustering analysis of that data revealed tubulocystic carcinoma to be closely related to papillary RCC; both types 1 and 2 dimensional clustering placed tubulocystic carcinoma between low and high grade papillary RCC. Comparative genomic microarray analysis was performed and demonstrated gains of chromosome 17p and 17q (trisomy 17), similar to papillary RCC. Gains of chromosome 7p and 7q (trisomy 7), also characteristic of papillary RCC, were not identified in the one case of tubulocystic carcinoma studied [8].

There are sporadic reports about the coexistence of TCRC with other renal tumors of different subtypes. Yang et al. reported 5 cases of TCRC associated with either papillary RCC or papillary adenomas [8]. Gonul et al. reported a case of synchronous clear cell RCC, micropapillary urothelial carcinoma and TCRC in a 57-year-old male with hematuria [19]. Brennan et al. presented a case of a 72-year-old male with end stage renal disease who developed a TCRC, a type 2 papillary RCC, a clear cell papillary and cystic RCC as well as renal oncocytosis, hybrid tumors and chromophobe RCC [20]. More recently, Deshmukh et al. reported a synchronous TCRC and papillary RCC in a young female with metastatic papillary RCC in para-aortic lymph nodes [21]. Thus, although TCRC has been reported in association with multiple other renal cell tumor subtypes, it appears that there is a slight predominance for synchronous TCRC and papillary tumors. An interesting question raised by the coexistence of TCRC with other renal tumors is whether there are common predisposing factors for these histologically different tumors.

The differential diagnosis of TCRC includes collecting duct carcinoma and other cystic renal tumors, mainly, cystic nephroma, low grade multilocular cystic renal cell carcinoma and mixed epithelial and stromal tumor of the kidney. Moreover, some chromophobe carcinomas and some oncocytomas may be entirely cystic. Non-neoplastic renal cysts and tumors commonly associated with renal cystic diseases have also to be considered.

Table 1 Clinical and radiological findings in present case as compared to 10 recently reported cases.

Author	Number of cases	Age (years)	Sex	Clinical presentation	Stage at diagnosis	CT
Present study (2012)	1	38	Male	Recurrent flank pain, renal mass	II	Bosniak III
Moses et al. (2010) [6]	1	68	Male	Incidental	I	Bosniak I
Horra et al. (2011) [3]	5	29–70 (mean 54)	Male	Renal mass	I (3 cases) IV (2 cases)	Bosniak III (2 cases) Bosniak IV (1 case) Solid (1 case)
Bhullar et al. (2011) [10]	1	33	Male	Back pain, renal mass	IV	Bosniak IV
Deshmukh et al. (2011) [21]	1	18	Female	Hematuria, renal mass	II	Bosniak IV
Quiroga-Garza (2012) [11]	1	67	Male	Incidental	I	Solid

Collecting duct carcinoma can be ruled out by its solid rather than cystic nature as well as its high grade nuclear features [13]. Immunohistochemical findings may also help in the differential diagnosis [16,18].

Cystic nephroma occurs in children under the age of 2 years old and women 40–69 years old. The architecture is cystic and contains no tubules and the cysts are lined by flattened cells with indistinct nucleoli. Of interest, cystic nephroma shows a striking female predominance (8:1), whereas TCRC occurs more often in men [7].

Low-grade multilocular cystic renal cell carcinoma was described in the WHO 2004 classification as a new entity, accounting for approximately 4% of cc RCCs [1]. It affects middle aged women with a male to female ratio of 1.2:2.1. Up to 90% of cases are discovered incidentally on radiologic investigation for other causes [22]. The tumor is a variant of clear cell carcinoma displaying large cysts lined by clear cells, separated by fibrous septa containing nests of clear cells [23].

The mixed epithelial and stromal tumor is a multicystic or biphasic tumor with solid and cystic areas. In the adult population, it shows a marked female preponderance like cystic nephroma to which it may be closely related [22]. Steroid hormones have been suggested to play a role in the genesis and evolution of this tumor; women with these tumors often have a history of long-term estrogen replacement, whereas many men with the tumor have had long-term sex steroid exposure. Estrogen receptors and progesterone receptors are frequently expressed in the mesenchymal component and the stroma may be of ovarian type [24].



Figure 1 Tubulocystic carcinoma. CT urography showing well defined, multiloculated cystic mass in the left kidney with thick enhancing septations and small mural nodules in keeping with category III Bosniak classification.

In cystic chromophobe carcinomas and oncocytomas, the cysts are lined by chromophobe cells or oncocytic cells, respectively. In the latter, oncocytic cells are usually cuboidal with round central nuclei and are classically CD10 and CK7 negative by immunochemistry [7].

Report of a case

A 38 years old Sudanese male presented with recurrent episodes of left flank pain of 8-month duration. No other relevant symptoms were present. On clinical examination, a firm right renal swelling



Figure 2 Tubulocystic carcinoma, gross. Note multilocular cystic appearance of excised tumor (left) and in tumor bed in center of kidney (right).

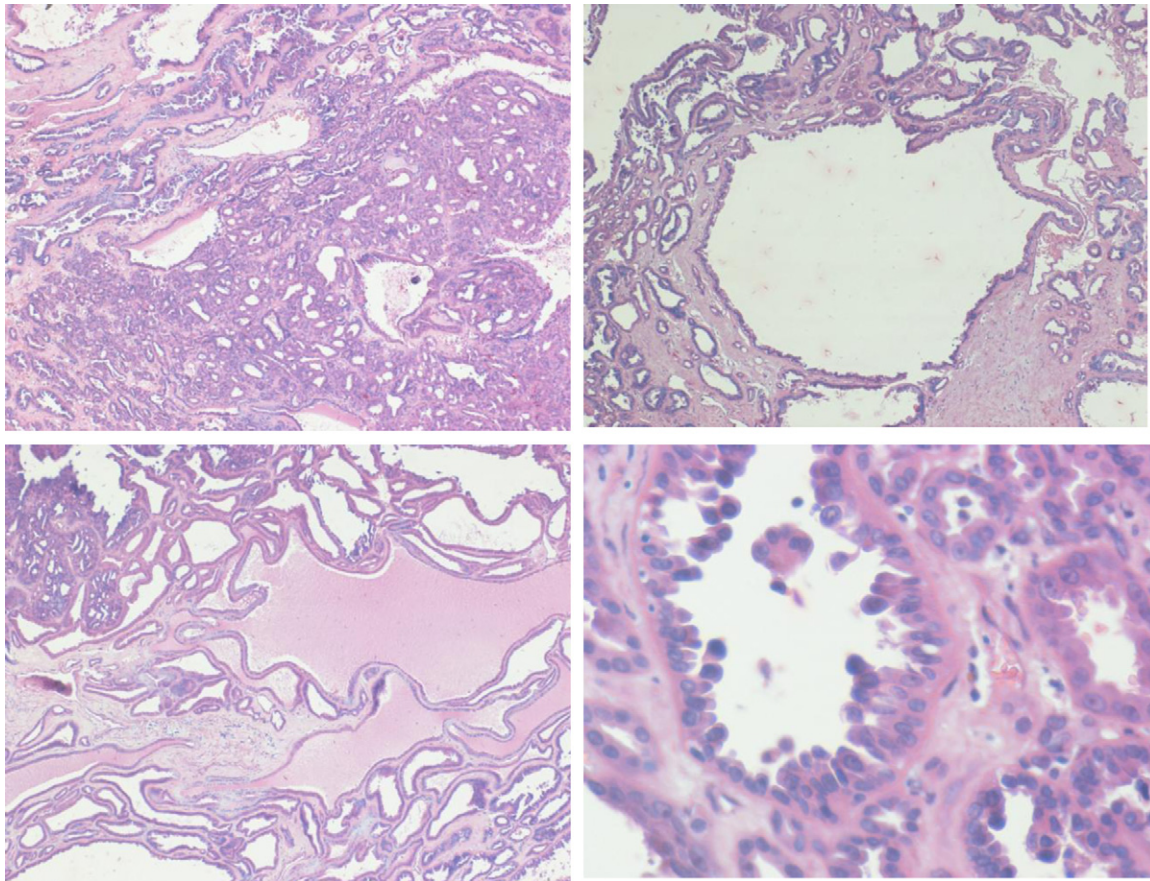


Figure 3 Tubulocystic carcinoma. H&E stained sections showing tubules and cysts (100 \times), and “hobnail cells”, some showing prominent nucleoli (400 \times , lower right).

was palpable. Past history was irrelevant. Family history was positive for renal cancer in the patient’s uncle. Laboratory investigations showed normal hematologic, renal and hepatic data.

CT urography revealed a 15 cm \times 13 cm well defined, multiloculated cystic mass in the left kidney with thick enhancing septations and small mural nodules in keeping with category III Bosniak classification, compressing and displacing the calyces with mild pelvicalyceal system dilatation (Fig. 1).

There were no metastases at the time of surgery.

The clinical and radiological findings in our case as compared to 10 recently reported cases are depicted in Table 1.

A left radical nephrectomy was performed and sent for pathologic study.

The specimen received in the laboratory consisted of a renal mass, an opened left kidney and few separate small grayish tissue fragments. The renal mass appeared grossly as an already opened large multilocular cystic mass, 15 cm \times 8 cm \times 3 cm (Fig. 2). The walls of the cyst were firm, gray with nodular and hemorrhagic areas. The kidney measured 10 cm \times 7 cm \times 3 cm and showed the tumor bed at its center. The small separate tissue fragments were firm, nodular and measured 6 cm \times 6 cm in aggregate.

Microscopic examination of 4 μ m thick, H&E-stained sections from the renal mass, the tumor bed in the kidney and the separate tissue fragments revealed a neoplasm composed of irregular tubules and variably sized cysts lined by cuboidal cells with abundant eosinophilic cytoplasm, exhibiting variable, mostly mild nuclear pleomorphism with focally prominent nucleoli (Fig. 3). Mitosis was only occasionally encountered. A fibrotic stroma and a “hobnail appearance” of neoplastic cells were focally observed. There was also focal tumoral necrosis, hemorrhage and mononuclear inflammatory cell infiltration. The tumor did not invade the renal capsule, peri-renal fat, renal sinus or adjacent renal parenchyma. There was no evidence of vascular invasion and no involvement of the renal vein, artery or renal pelvis or calyces. The ureteric resection margin was clear. Immunohistochemically, the neoplastic cells showed reactivity for CK18, CK19, EMA, CD10, high molecular weight cytokeratin 34betaE12, and vimentin but no reactivity for CK7 (Fig. 4). Immunoreactivity for CD10; CK19; and EMA, CK 18 and vimentin is in keeping with proximal convoluted tubular, distal tubular and collecting duct differentiation, respectively. The final diagnosis was “Tubulocystic carcinoma, nuclear grade 2, pathologic stage T2b, TNM stage T2 N0 M0 (Group stage II)”. It was based on rather typical CT, gross, microscopic and immunohistochemical features of the tumor.

The patient is free of disease 6 months after the surgery.

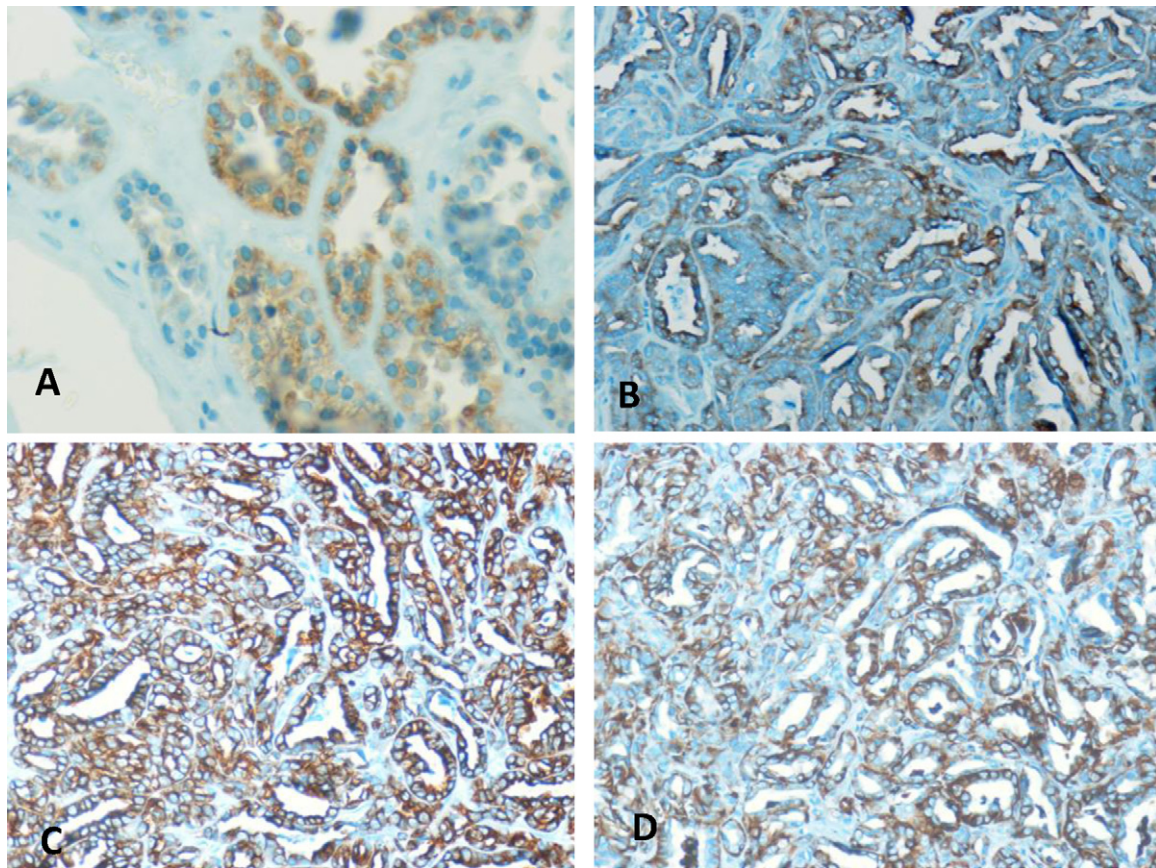


Figure 4 Tubulocystic carcinoma, immunohistochemistry. Note cytoplasmic immunoreactivity of cancer cells for: (A) CD10 (400 \times), (B) CK19 (200 \times), (C) CK18 (200 \times) and (D) Vimentin (200 \times).

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