Review of tubulocystic carcinoma of the kidney with focus on clinical and pathobiological aspects

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Tubulocystic carcinoma of the kidney (TCK) is a recently established entity in renal neoplastic pathology. This review aims to give an overview of the clinical and pathobiological aspects of TCK. Grossly, the TCKs are well-demarcated multicystic lesions giving a "wrapped bubble" or "spongy" appearance. Microscopically, the tumors are composed of multiple, variably sized cysts separated by thin fibrous septa lacking ovarian stroma or desmoplastic reaction. The cysts are lined by tumor cells with eosinophilic cytoplasm and nuclear atypia of variable, but not infrequently of high grade corresponding to Fuhrman grade 3. A frequent association with papillary tumors has been reported. Recent molecular genetic studies of TCK have revealed distinct features separating this subset of renal cell carcinomas (RCCs) from other types of renal tumors including collecting duct carcinoma of Bellini and renal medullary carcinoma as well as pointing towards a close kinship with papillary RCC. Tubulocystic carcinoma of the kidney generally pursues an indolent clinical course. However, several cases with aggressive clinical behavior have been reported. We strongly feel that there is enough clinicopathological evidence to corroborate TCK as a separate entity and that it should be incorporated into the next WHO classification of renal tumors as a separate neoplastic category.

Key words: tubulocystic carcinoma, kidney, new entity.

Introduction

Tubulocystic carcinoma of the kidney (TCK) is a recently established entity in renal neoplastic pathology, but not yet listed in the World Health Organization (WHO) classification of renal cell carcinoma (RCC). Masson *et al.* originally perceived these tumors as being derived from the ducts of Bellini and designated them as "Bellinian epithelioma" [1]. Subsequently, in 1997, MacLennan *et al.* reported 13 cases which they labeled as "low-grade collecting duct carcinoma of the kidney" [2]. In 2004 (at the United States and Canadian Association of Pathology (USCAP) meeting), Amin

et al. reported on 29 tumors and established the term TCK [3]. Subsequently, the 13 low-grade collecting duct carcinomas in the original series by MacLennan in 1997 were subdivided into 8 TCKs and 5 mucinous tubular and spindle cell carcinomas (MTSCCs) [4]. The latter entity has already been listed in the WHO classification largely due to the well-documented and distinct molecular genetic characteristics [5]. Recent studies have clearly established that TCK is morphologically and cytogenetically different from other renal tumors [6-9]. This review aims to introduce TCK with a focus on clinical and pathobiological aspects.

Fig. 1. Macroscopic findings. The cut surface shows a spongy or "wrapped bubble" appearance

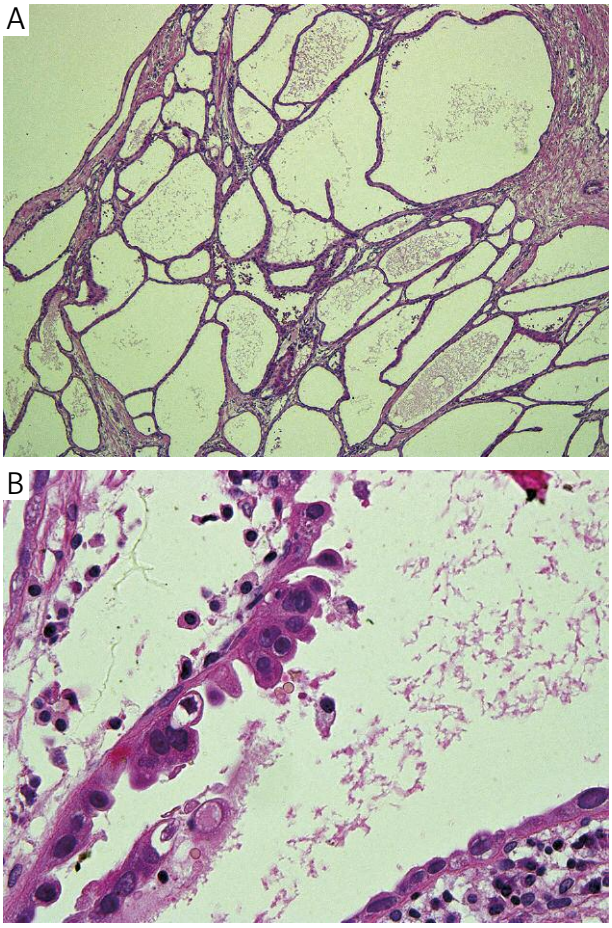

Fig. 2. Microscopic findings: A) Low magnification. The tumor consists of multicystic lesions lined by epithelial neoplastic cells with eosinophilic cytoplasm. B) High magnification. Hobnail pattern is seen and the nuclei of tumorous cells are enlarged

Clinical characteristics

Tubulocystic carcinomas of the kidney occur most commonly in the fifth and sixth decades of life and there is a strong male predominance [3, 6, 10-12]. Most TCKs are discovered incidentally and are typically small in size (almost 40% are smaller than 2 cm) [3, 13, 14]. However, some patients are symptomatic and may present with abdominal pain, abdominal distention and hematuria [15]. Radiologically, TCK may demonstrate Bosniak type II, type III or even type IV. Hence, this disease may pose a serious challenge in differential diagnosis and clinical management [6, 11, 15]. The radiological features of TCK overlap with other benign or malignant lesions including cystic nephroma (CN), mixed epithelial and stromal tumor (MEST), renal oncocytoma (RO) with tubulocystic pattern, multilocular cystic RCC and renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions (Xp11.2 RCC). 18-fluorodeoxyglucose (FDG) positron emission tomography/CT is useful in the detection of metastatic lesions [11]. Tubulocystic carcinomas of the kidney may occur in patients with end-stage kidney disease [16].

Pathological findings

Macroscopic findings

Grossly, the epicenter of TCK is located in the renal cortex, but the tumors may involve the renal medulla [3, 6]. The tumors are well circumscribed but unencapsulated, with a white or gray color [3, 11, 15]. The cut surface demonstrates various-sized cysts giving the tumor a spongy, wrapped bubble-like, or Swiss cheese-like appearance (Fig. 1) [6, 13, 14].

Microscopic findings

Histologically, the tumor consists of variably sized cysts which are lined by a single layer of atrophic flat, hobnail, cuboidal, cylindrical to columnar neoplastic cells with eosinophilic cytoplasm (Fig. 2A) [7, 17]. The nuclei are round and nucleoli are usually prominent (Fig. 2B). The nuclear grade generally corresponds to Fuhrman grade 3, but grade 2 or even grade 1 may be seen [4, 6, 7, 10]. Nuclear chromatin is evenly dispersed [7]. A solid sheet pattern is absent [6]. Rarely, minor areas with clear cell change or papillary con-

figuration have been reported [7, 15]. Necrosis, hemorrhage and mitotic figures are rare [4, 7, 17]. The fibrous septa separating the cystic spaces are generally thin and do not show features of ovarian-type stroma or desmoplastic reaction [6, 17]. Few cases with multiple lesions are on record [9]. Tubulocystic carcinomas of the kidney have been associated with papillary renal tumors including both adenoma and RCC [6, 9, 18]. Based on the cytological features, papillary RCC can be subdivided into type 1 and type 2 [9, 16]. Tubulocystic carcinomas of the kidney associated with other types of RCCs and micropapillary urothelial carcinoma have been described [16, 19, 29]. A single case of TCK with sarcomatoid change has been reported [21].

Immunohistochemical findings

Neoplastic cells show the immunohistochemical characteristics/protein expression of both proximal tubules (CD10, P504S, carbonic anhydrase IX) (Fig. 3A), and distal tubules/collecting ducts (cytokeratin 7, cytokeratin 19, keratin 903, and parvalbumin) (Fig. 3B) [10, 13, 17, 22-24]. The staining pattern of cytokeratin 7 may be weak and focal [10, 15].

Ultrastructural findings

An electron microscopic study demonstrated features of both proximal convoluted tubules – abundant microvilli with brush border – and of the intercalated cells of the collecting ducts – shorter microvilli and cytoplasmic interdigitation [7, 13-15, 22]. The cytoplasm of tumorous cells may contain abundant mitochondria [19].

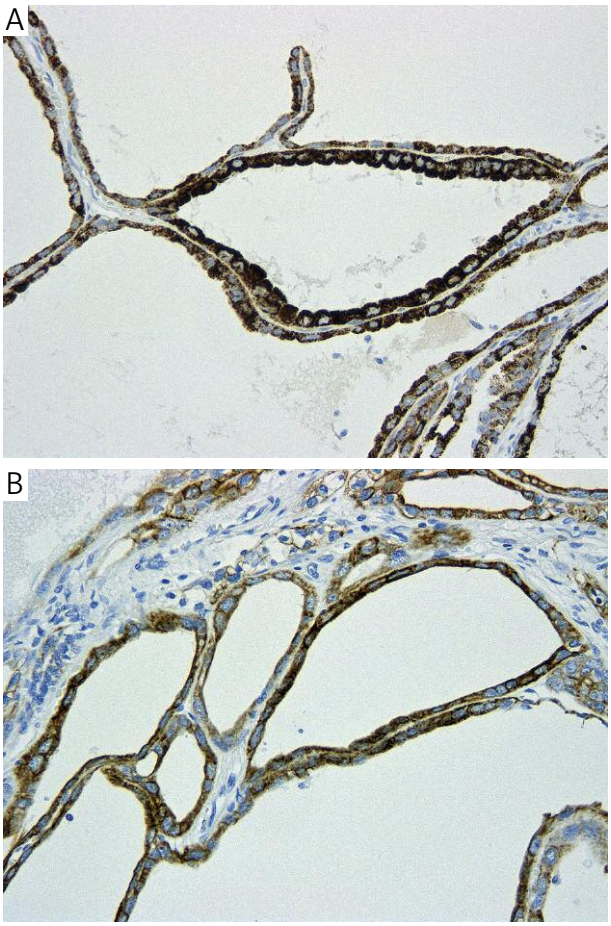

Fig. 3. Immunohistochemical findings: A) The tumor exhibits positivity for AMACR (detected by P504S antibody). B) Cytokeratin 19 is expressed in the cytoplasm of neoplastic cells

Molecular genetic findings

Compared with collecting duct carcinoma, using quantitative reverse transcription polymerase chain reaction analysis, TCK was characterized by relative overexpression of *vimentin*, *p53* and *AMACR* [8]. According to gene expression microarray analysis, the molecular signature of TCK is different from collecting duct carcinoma and renal medullary carcinoma, but similar to papillary RCC [6]. In contrast, the gene expression profiling of TCK reported by Amin *et al.* did not overlap with that of papillary RCC and showed overexpression of genes related to amino acid metabolism and cell cycle, and underexpression of biopolymer metabolism genes [7]. The discrepancies between these two studies may be explained by the difference in materials examined (formalin-fixed tissue versus frozen tissue) and array platforms used (cDNA array versus oligonucleotide array) [9]. One tumor showed a distinct profile with gain of chromosomes 8 and 17 and loss of chromosome 9 [20]. With fluorescence *in situ* hybridization, gain of chromosomes 7 and 17 and loss of chromosome Y are frequently observed (Fig. 4A, B). These results suggest that TCK is related to papillary RCC [6, 9]. Significantly elevated mRNA level of TP53 was found, whereas the mRNA levels of FLT1 and C-FOS were reduced in TCK samples [25].

Differential diagnosis

Pathologists should distinguish TCK from CN, MEST, RO with tubulocystic pattern, thyroid-like follicular carcinoma of the kidney, multilocular cystic RCC, Xp11.2 RCC, collecting duct carcinoma and renal medullary carcinoma [15]. Cystic nephroma has a low nuclear grade and cellular stroma. MEST generally occurs in middle-aged women and contains ovarian-type stroma with or without smooth muscle differentiation [4, 26]. Renal oncocytoma with tubulocystic pattern is composed of cells with deeply eosinophilic and granular cytoplasm and low nuclear grade. Additionally, an organoid pattern and edematous stroma may be seen [27]. In thyroid-like follicular carcinoma of the kidney, glandular lumens contain eosinophilic, colloid-like materials [28]. Multilocular cystic RCC is lined by neoplastic cells with clear cytoplasm and low nuclear grade corresponding to Fuhrman grade 1 [29]. Xp11.2 RCC

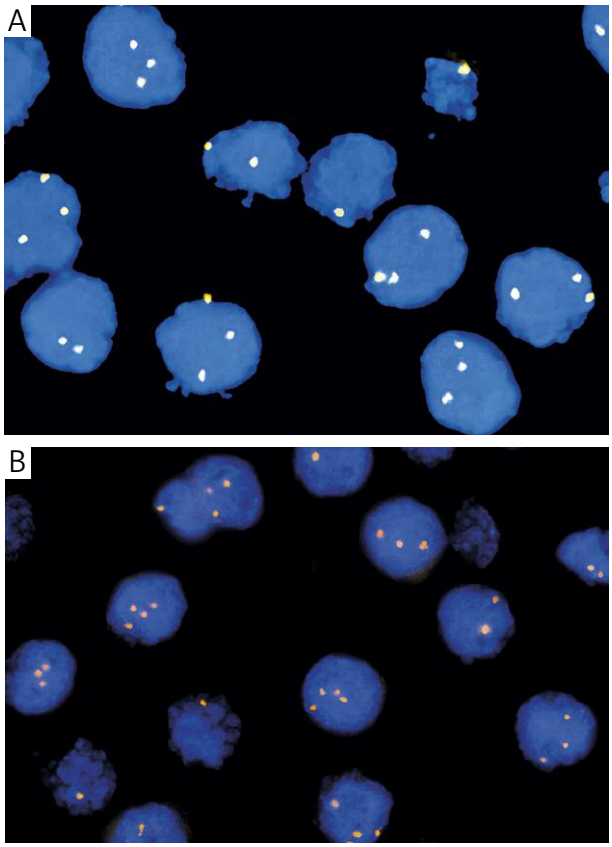

Fig. 4. Fluorescence *in situ* hybridization findings: A) Trisomy of chromosome 7 is seen. B) Polysomy of chromosome 17 is noted

with tubulocystic pattern may be rarely observed. This tumor often occurs in young adults and has mixed clear and eosinophilic cells frequently with abundant cytoplasm. Immunohistochemistry for TFE3 (strong nuclear staining) and cathepsin K is helpful in the differential diagnosis [30]. Collecting duct carcinoma and renal medullary carcinoma occur in the renal medulla, and demonstrate a poorly differentiated adenocarcinoma, inflammatory infiltration, frequent perirenal fat invasion, lymphovascular invasion, intraluminal mucin and high nuclear grade [31].

Therapy

Radical nephrectomy is generally recommended, but partial nephrectomy may be performed for small tumors located in the superficial renal cortex. There is limited information on the potential beneficial effects of molecular target therapy to date. Sunitinib, a tyrosine kinase inhibitor, may exhibit a partial response or temporary effect for this tumor [11, 32]. Tubulocystic carcinoma of the kidney with sarcomatoid change has responded poorly to sorafenib [21]. The antiangiogenic targeted therapeutic protocols such as VHL/HIF, RTK/MAPK and PI3K/Akt/mTOR seem to have no rationale of general recommendation [25].

Prognosis

The biological behavior of TCK is generally indolent and the stage is typically low at presentation [10, 13, 14, 33]. To date, local recurrence has developed in one patient and metastases to liver, bone, pleura, peritoneum, and lymph nodes have developed in five patients [7, 11, 21]. Three patients have died from metastatic disease [3, 11, 21]. The risk for metastasis is less than 10% [3].

Future perspectives

Although a close relationship to papillary RCC has been suggested [6, 9, 18], based on morphological as well as genetic data, we consider TCK to be a separate and distinct neoplastic entity and that as such it should be incorporated into the next WHO classification of renal tumors [10].

The authors declare no conflict of interest.

References

1. Masson P. Tumeurs Humaines 1955. In: Kobernick S (trans). Human tumors, histology, diagnosis and technique. Chapter 5. 2nd ed. Wayne State University Press, Detroit 1970.
2. MacLennan GT, Farrow GM, 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. Amin MB, MacLennan GT, Paraf F, et al. Tubulocystic carcinoma of the kidney: clinicopathologic analysis of 29 cases of a distinctive rare subtype of renal carcinoma. Mod Pathol 2004; 17: 137A.
4. MacLennan GT, Bostwick DG. Tubulocystic carcinoma, mucinous tubular and spindle cell carcinoma, and other recently described rare renal tumors. Clin Lab Med 2005; 25: 393-416.
5. Rakozy C, Schmahl GE, Bogner S, Störkel S. Low-grade tubular-mucinous renal neoplasms: morphologic, immunohistochemical and genetic features. Mod Pathol 2002; 15: 1162-1171.
6. Yang XJ, Zhou M, Hes O, et al. Tubulocystic carcinoma of the kidney: clinicopathologic and molecular characterization. Am J Surg Pathol 2008; 32: 177-187.
7. Amin MB, MacLennan GT, Gupta R, et al. 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.
8. Osunkoya AO, Young AN, Wang W, et al. Comparison of gene expression profiles in tubulocystic carcinoma and collecting duct carcinoma of the kidney. Am J Surg Pathol 2009; 33: 1103-1106.
9. Zhou M, Yang XJ, Lopez JI, et al. Renal tubulocystic carcinoma is closely related to papillary renal cell carcinoma: implications for pathological classification. Am J Surg Pathol 2009; 33: 1840-1849.
10. Azoulay S, Vieillefond A, Paraf F, et al. Tubulocystic carcinoma of the kidney: a new entity among renal tumors. Virchows Arch 2007; 451: 905-909.
11. Hora M, Urge T, Eret V, et al. Tubulocystic renal carcinoma: a clinical perspectives. World J Urol 2011; 29: 349-354.
12. Bai X, Wu CL. Renal cell carcinoma and mimics: pathologic primer for radiologists. AJR Am J Roentgenol 2012; 198: 1289-1292.

13. Okoń K. Pathology of renal tumors in adults. Molecular biology, histopathological diagnosis and prognosis. Pol J Pathol 2008; 59: 129-176.
14. MacLennan GT, Cheng L. Tubulocystic carcinoma of the kidney. J Urol 2011; 185: 2348-2349.
15. Srigley JR, Delahunt B. Uncommon and recently described renal carcinoma. Mod Pathol 2009; 22: S2-S23.
16. Brennan C, Srigley JR, Whelan C, et al. Type 2 and clear cell papillary renal cell carcinoma, and tubulocystic carcinoma. A unifying concept. Anticancer Res 2010; 30: 641-644.
17. Moch H. Cystic renal tumors: new entities and novel concepts. Adv Anat Pathol 2010; 17: 209-214.
18. Deshmukh M, Shet T, Bakshi G, Desai S. Tubulocystic carcinoma of kidney associated with papillary renal cell carcinoma. Indian J Pathol Microbiol 2011; 54: 127-130.
19. Gönül II, Cakr A, Sözen S, et al. A case of tubulocystic carcinoma simultaneously occurring with clear cell type renal cell carcinoma and micropapillary urothelial carcinoma of bladder. South Med J 2009; 102: 754-757.
20. Quiroga-Garza G, Pina-Oviedo S, Cuevas-Ocampo K, et al. Synchronous clear cell renal cell carcinoma and tubulocystic carcinoma: genetic evidence of independent ontogenesis and implications of chromosomal imbalances in tumor progression. Diagn Pathol 2012; 7: 21.
21. Bhullar JS, Thamboo T, Esuvaranathan K. Unique case of tubulocystic carcinoma of the kidney with sarcomatoid features: a new entity. Urology 2011; 78: 1071-1072.
22. Radhakrishnan A, MacLennan GT, Hennigar RA, et al. Ultrastructural and immunohistochemical (IHC) appraisal of tubulocystic carcinoma (TCCa) of the kidney: histogenetic and diagnostic implications. Mod Pathol 2005; 18: 160A.
23. Skinnider BF, Folpe AL, Hennigar RA, et al. Distribution of cytokeratins and vimentin in adult renal neoplasms and normal renal tissue: potential utility of a cytokeratin antibody panel in the differential diagnosis of renal tumors. Am J Surg Pathol 2005; 29: 747-754.
24. Gupta R, Balzer B, Picken M, et al. Diagnostic implications of transcription factor PAX2 protein and transmembrane enzyme complex carbonic anhydrase IX immunoreactivity in adult renal epithelial neoplasms. Am J Surg Pathol 2009; 33: 241-247.
25. Steiner P, Hora M, Stehlik J, et al. Tubulocystic renal cell carcinoma: Is there a rational reason for target therapy using angiogenic inhibition? Analysis of seven cases. Virchows Arch 2013; 462: 183-192.
26. Michal M, Hes O, Bisceglia M, et al. Mixed epithelial and stromal tumors of the kidney. A report of 22 cases. Virchows Arch 2004; 445: 359-367.
27. Amin MB, Crotty TB, Tickoo SK, Farrow GM. Renal oncocytoma: a reappraisal of morphologic features with clinicopathologic findings in 80 cases. Am J Surg Pathol 1997; 21: 1-12.
28. Amin MB, Gupta R, Ondrej H, et al. Primary thyroid-like follicular carcinoma of the kidney: report of 6 cases of a histologically distinctive adult renal epithelial neoplasm. Am J Surg Pathol 2009; 33: 393-400.
29. Kuroda N, Ohe C, Mikami S, et al. Multilocular cystic renal cell carcinoma with focus on clinical and pathobiological aspects. Histol Histopathol 2012; 27: 969-974.
30. Kuroda N, Mikami S, Pan CC, et al. Review of renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions with focus on pathobiological aspect. Histol Histopathol 2012; 27: 133-140.
31. Gupta R, Billis A, Shah RB, et al. Carcinoma of the collecting ducts of Bellini and renal medullary carcinoma: clinicopathologic analysis of 52 cases of rare aggressive subtypes of renal cell carcinoma with a focus on their interrelationship. Am J Surg Pathol 2012; 36: 1265-1278.
32. Mego M, Sycova-Mila Z, Rejlekova K, et al. Sunitinib in the treatment of tubulocystic carcinoma of the kidney. A case report. Ann Oncol 2008; 19: 1655-1661.
33. Moses KA, Decaro JJ, Osunkoya AO, Issa MM. Tubulocystic carcinoma of the kidney: A case report of natural history and long-term follow-up. ScientificWorldJournal 2010; 10: 586-589.

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