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.
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.

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 have been 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/collection 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].

**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
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**


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

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