Case Report

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Tubulocystic Renal Cell Carcinoma: A Rare Cystic Renal Neoplasm with Relatively Indolent Clinical Course

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Tubulocystic renal cell carcinoma (TC-RCC) is a rare RCC subtype. Although it is categorized as a malignant tumor in current World Health Organization (WHO) tumor classification, TC-RCC presents clinically as a slowly progressing tumor, which is unusual compared to that of most other malignant renal neoplasms. Detailed pathogenic mechanisms of this tumor as well as genetic relationship between TC-RCC and the other RCC subtypes (especially papillary RCC) are not clearly understood. Here, we share a case of a 51-year-old Taiwanese male who came to our outpatient department with abnormal renal function and a complaint of hematuria. Imaging revealed a lesion at the upper pole of the left kidney. The patient subsequently underwent partial nephrectomy. Pathological examination revealed classical features of TC-RCC. No evidence of metastasis or recurrence was found during post-surgery clinical follow-up.

Key words: tubulocystic renal cell carcinoma, molecular study, indolent

Introduction

Tubulocystic renal cell carcinoma (TC-RCC) is a rare RCC subtype. TC-RCC was not officially recognized as a separate pathological diagnosis in the World Health Organization (WHO) classification of tumors of the urinary system and male genital organs until 2016.[1] TC-RCC accounts for < 1% of all malignant renal epithelial neoplasms, and displays male predominance and a wide age distribution (with most patients in their 50s or 60s). More than 50 cases have been reported worldwide in the literature. However, actual cases of TC-RCC may be fewer, as many of the reported cases may not be true TC-RCC according to the current research results and molecular evidence. Clinically, the most common location of this tumor is the left side of the kidney. Patients are often asymptomatic, and more than half of the tumors are discovered incidentally. Possible symptoms include hematuria, abdominal distention, and abdominal pain. One reported described a post-renal transplant patient with TC-RCC of the native kidney whose medical conditions included hypertension, type II diabetes mellitus, and end stage renal disease.[2] TC-RCC classically exhibits unique macroscopic and microscopic features, which are the primary basis for diagnosis. Surgery is the mainstream treatment. The

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prognosis tends to be favorable in most cases, with a metastatic rate of approximately 5% – 6%.[3,4] Herein, we report a case of a middle-aged male patient with TC-RCC and discuss the clinical, radiological, and pathological characteristics, as well as the latest findings related to molecular studies of this unique tumor.

Case Report

A 51-year-old man with no history of systemic disease visited our urologic outpatient department because of abnormal renal function and hematuria found during a regular health check-up. Renal ultrasonography revealed a left renal mass lesion. A subsequent abdominal computed tomography revealed a 3 cm, lobulated, hypo-attenuated mass at the posterior side of the upper pole of left kidney, with slow and gradual contrast enhancement (Fig. 1, arrow). A differential diagnosis from the attending radiologist indicated a renal tumor or a complicated cyst. After discussion with the patient, a partial nephrectomy was performed. Gross examination of the submitted specimen revealed a relatively well-defined, light-tan colored, multicystic and spongy mass measuring 3 cm × 2 cm × 1 cm (Fig. 2). Microscopically, the tumor was composed of mixed dilated tubules and cysts of varying sizes, lined with a single layer of flattened cuboid or hobnail epithelium. The nuclei were enlarged and displayed irregular contours, accompanied by occasional prominent nucleoli. The cytoplasm is usually abundant and eosinophilic. In our patient, the tubules/cysts were divided by fibrous septa of varying thicknesses (Fig. 3). Necrosis and efficient mitotic activity were absent. These neoplastic lining cells showed diffuse immunoreactivity for paired box gene 8 (PAX-8) as well as proximal tubule marker alpha methylacyl CoA racemase (AMACR) and distal tubule/collecting duct markers (high molecular weight cytokeratin [HMWCK] and cytokeratin 7 [CK7]). Nuclear expression of integrase interactor 1 (INI1) was also preserved. No definite evidence of lymph node or distant metastasis was found; Therefore, the final cancer staging was designated as pT1aN0M0.

After the surgery, the clinical condition of the patient was stable. He was discharged, and regular follow-ups at our urologic outpatient department revealed the lack of definite evidence of metastatic or recurrent disease.

Discussion

TC-RCC is a rare subtype of malignant

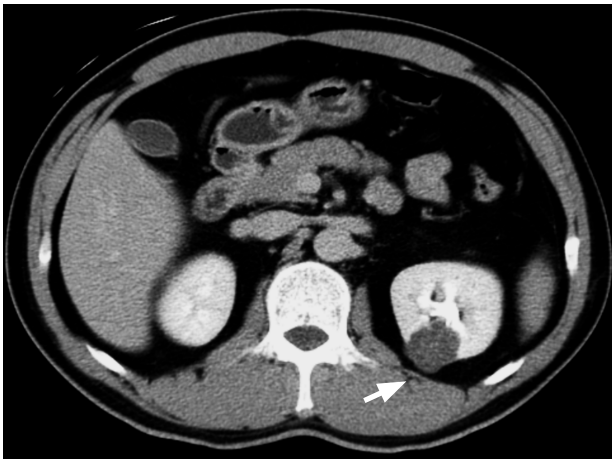

Fig. 1 Abdominal computed tomography scan shows a lobulated, hypoattenuating mass lesion at the upper pole of left kidney (arrow).

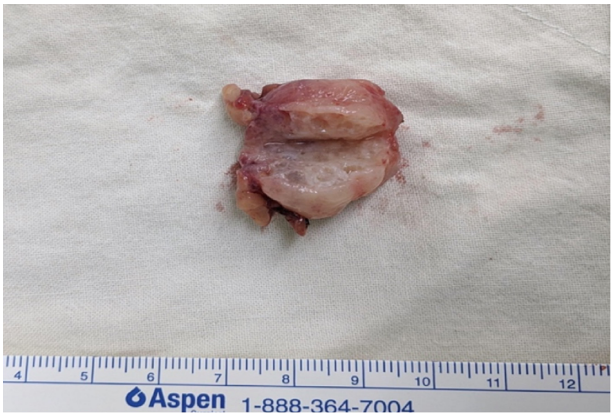

Fig. 2 The gross photography of the partial nephrectomy specimen. One relatively well-circumscribed light tan tumor with spongy and multicystic appearance is found.

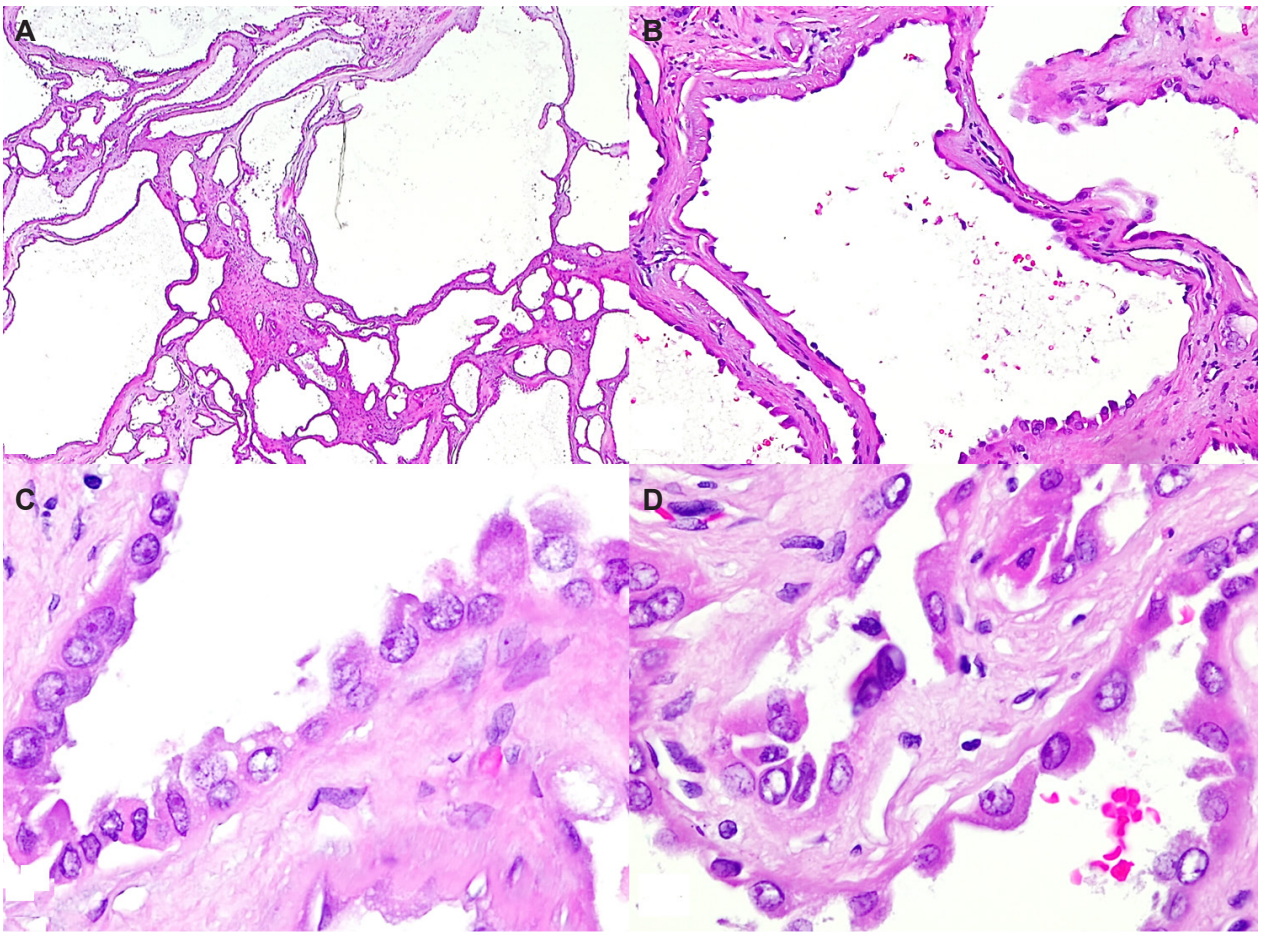

Fig. 3 The histopathological features of this tumor, which is characteristic for tubulocystic renal cell carcinoma (A) The tumor composes of admixture of variable-sized dilated tubules and cysts (20x magnification, H&E stain). (B) The tubules and cysts are lined by a single layer of flattened, cuboid, or hobnail neoplastic epithelial cells (200x magnification, H&E stain). (C) The neoplastic cells bear enlarged, irregular nuclei with prominent nucleoli and eosinophilic cytoplasm (400x magnification, H&E stain). (D) Hobnail epithelial lining is also seen (400x magnification, H&E stain).

renal cell neoplasm with a relatively slow progressing clinical course. Initially, because of its' similar histomorphological features, this carcinoma was thought to arise from the distal collecting duct.[5] Collecting duct carcinoma, another rare subtype of renal cell neoplasm, shows aggressive behavior, in contrast to classical TC-RCC. Subsequent studies described the co-occurrence of a papillary RCC-like component and a poorly differentiated component within the same tumor of TC-RCC. Other studies further revealed a gain of chromosomes 7 and 17, but loss of the Y chromosome in TC-RCC. A close relationship between TC-RCC and papillary RCC was suggested, due to their overlapping features related to both immunohistological and molecular profiles.[1,4]

Charles et al., a 2018 study utilized quantitative real-time polymerase chain reaction (qRT-PCR) to determine noncoding ribonucleic acid (RNA)/microRNA(miRNA) expression as well as targeted next-generation sequencing.[6] The authors found novel molecular evidence of differences between TC-RCC and papillary RCC. Specifically, two non-synonymous mutations in the ABL1 and platelet-derived growth factor receptor alpha genes were detected in more than 60% of the TC-RCC cases in the study, and synonymous and non-synonymous mutations in the epidermal growth factor receptor gene were present in approximately 31% of the patients. The mutations were found

in < 5% of the cases of clear cell RCC, papillary RCC, and chromophobe RCC in The Cancer Genome Atlas database. Furthermore, similar to papillary RCC, downregulation of miRNAs such as miR-155 and miR-34a has also been found in TC-RCC.[6] Another study published in 2019 described the loss of chromosome 9 and gain of chromosome 17, rather than a gain of chromosome 7 or loss of chromosome Y, as well as mutations in the chromatin-modifying genes lysine methyltransferase 2C and lysine-specific demethylase 5C in nine "pure" TC-RCC cases.[3] These findings further support the idea that pure TC-RCCs may be essentially different from tumors that are combined with papillary RCC-like or poorly differentiated components. More studies that apply new molecular analytical tools and instruments are needed to help clinicians make an appropriate diagnosis and identify the actual relationship between TC-RCC and other renal neoplasms at the genetic level.

Most TC-RCC cases are detected incidentally and the clinical presentation is non-specific. TC-RCC characteristically presents as a cystic-dominant tumor with high echogenicity and posterior acoustic enhancement on ultrasonography. Using abdominal computerized tomography, a small, hypovascular, and multilocular cystic lesion exhibiting slow progress may be diagnosed as TC-RCC. Although it is impossible to differentiate TC-RCC from other cystic lesions showing similar imaging findings that solely rely on radiological studies,[7] a more conserved surgical approach can be considered under certain clinical conditions. Gross characteristics of TC-RCC usually include a bubble wrap-like or spongy cut surface. Histopathologically, such tumors typically comprise tubules or cysts of variable sizes that are divided by fibrous septa. The cells that line such neoplasms are composed of a single layer of flattened, cuboid, or hobnail epithelial cells with enlarged and irregular nuclei, accompanied by occasional prominent nucleoli (WHO/International Society of Urologic Pathologists grade 3) and eosinophilic cytoplasm. In our case study, the neoplastic cells showed positive immunoreactivity for CK7, AMACR, HMWCK, and PAX-8, but were negative for 2SC, CD117 (c-kit), and p63 staining. Some studies have reported that a loss of SMARCB1 (INI1) expression is not observed in TC-RCC.[1,3]

Some carcinomas may mimic TC-RCC. Examples include renal lesions with predominantly multicystic growth patterns, such as collecting duct carcinoma, oncocytoma with cystic structure, adult cystic nephroma, multilocular cystic renal neoplasm of low malignant potential, hereditary leiomyomatosis, and RCC syndrome-associated renal carcinoma. These mimicking carcinomas can confound the diagnosis of TC-RCC. No specific immunohistochemical markers have been discovered for TC-RCC. Diagnostic molecular testing studies designed to identify markers are ongoing. According to the current version of the WHO classification of tumors of the urinary system and male genital organs, and recommendations of the International Society of Urologic Pathologists,[1,3] the presence of characteristic histological features is a mandatory criterion for the diagnosis of TC-RCC. With the characteristic gross and microscopic features, our case is consistent with the diagnosis of TC-RCC.[3,8] The relatively slow clinical course of our patient also supports this diagnosis.

The first-line treatment for TC-RCC is surgery, either partial or radical nephrectomy, depending on the condition and staging of patients. Although adjuvant therapy with temsirolimus and sunitinib has been reported,[9] the benefit of adjuvant therapy for resectable tumors is still doubtful, due to the potential side effects of these adjuvant regimens and the relatively indolent behavior of pure TC-RCC. Further research to elucidate detailed molecular mechanisms and more specific diagnos-

tic methods are needed to study this unique neoplasm.

Conclusions

Overlapping grossly evident, histomorphological, and immunohistological features of TC-RCC with benign lesions (such as adult cystic nephroma and oncocytoma) or aggressive neoplasms (such as collecting cell carcinoma, hereditary leiomyomatosis, and RCC syndrome-associated renal carcinoma) can complicate the diagnosis of TC-RCC. Careful correlation with clinical, radiological, and histopathological findings is crucial to make an appropriate diagnosis of TC-RCC, because of the very different treatment strategies used for such patients and their prognosis.

Author Contributions

Study Design, Yi-Ru Chen and Chia-Chi Chen; Data Collection and Interpretation, Yi-Ru Chen and Hua-Pin Wang; Manuscript Preparation, Yi-Ru Chen, Hua-Pin Wang, Chia-Chi Chen, and Chao-Tien Hsu; Literature Search, Yi-Ru Chen; Conducted the review and Edited the paper, Chia-Chi Chen, and Chao-Tien Hsu. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of E-Da Hospital (EMRP-110-003, 2021/03/29).

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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