Venyo A K G. (September 2014) Tubulocystic carcinoma of the kidney: A review of the literature. *Jour of Med Sc & Tech*; 3(3); Page No: 145 – 161.

RA Publications
Journal of Medical Science & Technology

Original Article Open Access

Tubulocystic carcinoma of the kidney: A Review of the Literature

Anthony Kodzo-Grey Venyo*
*North Manchester General Hospital, Department of Urology, Manchester, United Kingdom.

Abstract
Tubulocystic carcinoma of kidney TCOK is a rare primary carcinoma of the kidney which has been added to the pathology register recently. TCOK was formerly called low-grade collecting duct carcinoma. Further molecular analysis had revealed that tubulocystic carcinoma is a distinct entity which is separate from the more aggressive collecting duct carcinoma. TCOK, occurs predominantly in the male; has not yet been classified in the WHO classification of malignancies of the kidney; is characterized by spongy appearance on macroscopic examination; is on microscopic examination characterized by cysts and tubules which are often lined by "hob-nail-like"cells separated by thin fibrotic stroma; on immunohistochemistry stain positively with the following markers (a) Mucin; (b) Keratins (AE1-3, (c) Cam 5.2 [CK8/18], (d) CK19 (e) Vimentin (f) EMA, (g) PAX2; also exhibits variable staining with (a) 34betaE12; and (b) CK7; has characteristic features which include: (a) Distinct molecular signature from other carcinomas; (b) Often gain of chromosome 7 and 17; loss of Y; suggesting a relationship to papillary renal cell carcinoma; (c) on electron microscopy they exhibit short microvilli with brush border organization; (d) abundant microvilli which form a brush border resembling that of proximal convoluted tubule; some cells may resemble the intercalated cells of the collecting ducts. TCOK is a low-grade malignancy but some cases have developed local recurrences or metastases to lymph nodes, liver, or bone. The macroscopic and histological characteristics of TCOK are distinct. Academic and world reknown pathologists should meet and discuss TCOK in order to arrive at a concensus opinion to include the disease entity in the WHO classification of kidney tumours as a distinct entity.

Key Words: Tubulocystic carcinoma; collecting duct carcinoma; macrocysts; microcysts; Tubules; low-grade; malignancy; microvilli; immunohistochemistry; electron microscopy:

*Corresponding Author: Dr Anthony Kodzo-Grey Venyo. MB ChB FRCS(Ed) FRCSI FGCS Urol LLM, North Manchester General Hospital, Department of Urology, Manchester, United Kingdom, Email: akodzogrey@yahoo.co.uk

Received: March 27, 2014, Accepted: June 25, 2014. Published: September 20, 2014.

Introduction
Collecting duct carcinoma is an uncommon variant of renal cell carcinoma which had been shown to be highly aggressive and associated with inferior prognosis. Over approximately the last fifteen to twenty years reports of a potential low-grade variant of collecting duct carcinoma which had a distinctively benign course have been published. Tubulocystic carcinoma of the kidney was previously termed low-grade collecting duct carcinoma. However, subsequent studies on the tumour had indicated that the so called low-grade collecting duct carcinoma is a separate entity which has been called tubulocystic carcinoma of the kidney. In the ensuing document literature on tubulocystic carcinoma of the kidney is discussed including the recommendation for the tumour to be included in the World Health Organization classification as a separate distinct entity amongs carcinomas of the kidney.

Materials and Methods
Various internet search engines including: google, google scholar, PuBMed, Educus and up to date were used to search for case /case series and review data on tubulocystic carcinoma of the kidney which formed a pivot for the review of the literature. 31 references were identified which were used to

document the presentation, investigation including the histological, morphological and immunohistochemical characteristics of the tumour.

Literature Review

Definition: Tubulocystic renal cell carcinoma refers to a mixture of tubules, micro-cysts and macrocysts which have low-grade nuclear features. [1] Other authors have defined them as cytologically high grade renal neoplasms which are composed of densely packed cysts and tubules [2] Tubulocystic renal cell carcinomas appear to be derived from the proximal convoluted tubules and the distal nephron. Tubulocystic carcinoma of the kidney has also been called by other names which include: Bellini duct carcinoma, low-grade collecting duct carcinoma. A number of tumours were added to the World Health Organization classification (WHO) in 2004; however, tubulocystic renal cell carcinoma is not one of them. This type of tumour is therefore yet to be added to the WHO classification. It is uncertain whether tubulocystic carcinoma is a distinct entity or a variant of collecting duct carcinoma. They exhibit features of proximal convoluted tubule and distal nephron.

Epidemiology

It has been stated that tubulocystic renal cell carcinoma which is a rare tumour is more commonly found in men (85% in male) and the mean age at its diagnosis is 54 years. [2] [3] Others stated that the mean age was about 60 years and the age range was between 30 years and 90years with a male to female ratio of 7:1 and 2 cases out of 31 were reported with metastates [2] [3] Tubulocystic renal carcinoma is a rare neoplasms of adults with a mean age of age of 54 years and age range between 34 and 74 years and a male preponderance. [3] [4] Tubulocystic carcinoma of the kidney may be solitary or multiple. Often the patients also have separate papillary nodules.

Clinical Presentation

The presenting symptoms of tubulocystic carcinoma of the kidney include: haematuria, abdominal distention, and abdominal pain (as elucidated in case reports and case series in the narration of reported cases).

Macroscopic appearance

Tubulocystic renal cell carcinomas tend to be variable in size and may measure up to 17 cm. The tumours tend to be greyish-white in appearance, well circumscribed and cystic ("bubble wrap" appearance), with a medullary location. Their other features include: Quite often there is compression of the tumour by fibrous tissue and there is minimal haemorrhage, necrosis or invasion of adjacent renal parenchyma. [1] The tumours are circumscribed. There are multi-locular cysts filled with clear fluid and this gives a spongy or the "bubble wrap" appearance.

Occurrence and Outcome

Tubulocystic renal cell carcinoma is quite often incidentally found and they tend to be of low stage. The prognosis is usually excellent with recurrences but only rare distant metastases or death from disease (as elucidated in the narration of reported cases)

Microscopic features

Microscopic examination tubulocystic renal carcinomas reveal (a) a mixture of closely packed tubules, microcysts and macrocysts of varying sizes which exhibit low-grade nuclear features [5]; (b) the cysts and tubules tend to be lined by a single layer of cuboidal or columnar cells which have abundant eosinophilic cytoplasm, uniform nuclei with distinct nucleoli which often demonstrate hobnail appearance; (c) the overall picture is that of low-grade nuclear characteristics; (d) the cysts tend to be closely spaced with intervening fibrous tissue that are variable; (e) 40% of tubulocystic renal cell carcinomas co-exist with papillary renal carcinoma; (f) evidence of minimal mitotic activity, no atypia, and no dysplasia [1] Occasionally large cysts up to 1cm may be seen.

The cells tend to have enlarged irregular nuclei with fine chromatin and prominent nucleoli corresponding with Fuhrman grade 3. [2] There may also be patchy clear cell change. There is no necrosis. Solid sheets and papillae are lacking.

Immunohistochemical staining characteristics

Tubulocystic renal cell carcinomas on immunohistochemistry stain positively with the following markers (a) Mucin, (b) Keratins (AE1-3, (c) Cam 5.2 [CK8/18], (d) CK19 [6] (e) Vimentin (f) EMA, (g) PAX2. [1] They also exhibit variable staining with (a) 34betaE12, and (b) CK7 [1]

Other stated immunohistochemical staining features of tubolocystic carcinoma of the kidney include [2] (a) Low molecular weight keratin positive; (b) CK7 weak, focal positive staining; (c) AMACR/acemase/P504S > 75%; (d) CD10 variable staining; (e) PAX2 40%; (f) PAX8 positive; High molecular weight keratin 18%. The percentage

immunohistochemical staining characteristics of the tumour are as follows: AMACR 8/8 [4], 77% [4]; CK7 7/8 [4] 62% [4]; CK8 100% [4], CK18 100% [4], CK19 100% [4], Pavalbumin 100% {yang], CD10 85%, [4] Kidney specific cadherin 71% , [4] Pax2 42%, [4] Carbonic anhydrase IX 36%, [4] 34be!2 15% [4] Staining characteristics of some of the reported cases has been illustrated in table 1.

Molecular description

The ensuing molecular characteristic features have been described in tubulocystic renal cell carcinomas: (a) Distinct molecular signature from other carcinomas; (b) Often gain of chromosome 7 and 17, loss of Y, suggesting a relationship to papillary RCC [7], [4]

Electron microscopic features

Tubulocystic renal cell carcinomas on electron microscopy exhibit short microvilli with brush border organization. There are abundant microvilli which form a brush border resembling that of proximal convoluted tubule. Some cells may resemble the intercalated cells of the collecting ducts.

Prognosis

This is a low-grade malignancy but some cases have developed local recurrences or metastases to lymph nodes, liver, or bone. [3]

Grading and staging

Grading: Tubulocystic carcinoma of the kidney is by definition cytologically high grade but its clinical correlation is not clear [2]

It has been stated that the most commonly grading scheme which has been cited is the Fuhrman grading which entails the simultaneous assessment of three features including nuclei size; shape; and nucleoli [2]. Some authors [2] suggested that some problems exist with regard to the Fuhrman grading system in that the Fuhrman grading system requires the simultaneous assessment of three features (a) nuclear size, (b) shape, (c) nucleoli. However, the nuclear size may be subject to fixation variables and nuclear size may be difficult to measure. They also stated that no provision had been made for cases with discrepant grade features and that poor interobserver agreement does exist with regard to the use of the Furhman grading system. [2] The Stanford group of pathologists and other pathologists are of the opinion that a simplified version of grading based primarily upon nuclear prominence would be a more practical approach to the grading of the tumours. They stated that a mumber of authors [8] [9] [10] [11] [12] [13] had shown this approach has a predictive value for clear cell and papillary carcinoma; the grade was based upon the worst high powered field; the grading does not apply to chromophobe carcinoma or oncocytomas; the grading system is provisionally applied to various other types and variants of renal cell carcinoma but it has not been validated. Furthermore it has been stated that complete Furhman grading has not been validated on other types of tumours. [2] The Stanford group of pathologists have adopted a simplified Fuhrman grading for tubulocystic carcinomas of the kidney which has divided the tumorus into 4 grades as follows: (a) Grade 1 which comprises of tumours with small, round, dark-lymphocyte-like nuclei with without visible nucleoli; (b) Grade 2 which is composed of tumours with inconspicuous nucleoli that are visible at 200 – 400 magnification (the nuclei are usually small and uniform with open, finely granular chromatin; (c) Grade 3 which comprises of tumours with prominent nucleoli that are easily visible at 100 magnification (the nuclei tend to be mildly to moderately pleomorphic; (d) Grade 4 which includes tumours that have markedly pleomorphic, bizzare nuclei, giant cells, and multiple nucleoli.

Staging: The TNM staging that is used for renal cell carcinomas is used for tubulocystic carcinoma of the kidney. [2]

Diagnostic Criteria

The diagnostic criteria of tubulocystic carcinoma of the kidney have been summarized as follows: [2]

- Closely packed variably sized tubules and cysts
- 0.05-2 mm diameter
- Separated by bland fibrous stroma
- No desmoplasia or ovarian stromal features
- Lined by cuboidal to flattened and hobnail cells
- Abundant eosinophilic or amphophilic cytoplasm
- Cells resemble those of oncocytoma but show uniform prominent nucleoli
- Focal clear cell or papillary features are seen in rare cases
- No foamy macrophages or psammoma bodies

ISSN: 1694-1217 JMST. An open access journal

- High grade nuclear features
- Large hyperchromatic nuclei
- Prominent round nucleoli
- Mitotic figures and necrosis rare
- Sharply circumscribed and spongy gross appearance

Differential diagnosis: Some of the differential diagnoses of tubulocystic renal cell carcinoma include: (a) Multi-locular cystic renal cell carcinoma which exhibits aggregates of clear cells with atypia within the septae dividing cystic spaces; (b) multi-locular renal cyst/ cystic nephroma which tend to occur in children under 2 years old and in women who are aged between 40 to 69 years. The architecture of multi-locular renal cyst/cystic nephroma is predominantly cystic, not tubulocystic; multilocular cysts are lined by flattened or attenuated epithelium with indistinct nucleoli; occasionally hobnail morphology; hyalinized, fibrotic or ovarian-like stroma; (c) Mucinous tubular and spindle cell neoplasm which occurs predominantly in females. They exhibit. typically long tubular profiles or cordlike growth pattern of uniform, low cuboidal cells with eosinophilic, focally vacuolated cytoplasm and spindling; stroma is myxoid and bubbly with abundant extracellular mucin

Other stated differential diagnoses include [2]: collecting duct carcinoma; Multilocular cystic renal cell carcinoma; mixed epithelial and stromal tumour; Oncocytoma; Cystic nephroma [2]

The characteristic features which help in differentiating the differential diagnoses from tubulocystic carcinoma of the kidney have been summarized as follows: [2]

1. Tubulocystic carcinoma of the kidney in comparison with Collecting duct carcinoma [2]

(a) Tubulocystic Carcinoma of the kidney lacks invasion and desmoplastic stroma; it has prominently dilated cystic spaces; it lacks necrosis and mitotic figures; there are infrequent metastases.
(b) Collecting Duct Carcinoma exhibits prominent invasion and desmoplastic stroma; the tumour is composed predominantly of tubules; frequent necrosis and mitotic figures are seen in this tumour; frequent metastases are found at initial presentation of this tumour

2. Tubulocystic Carcinoma of the kidney in comparison with Multi-locular Cystic Renal Cell Carcinoma [2]

(a) Tubulocystic Carcinoma of the kidney characteristically has lining cells which have abundant eosinophilic cytoplasm and these tumours have no nest of clear cells but they have high-grade nuclear features.
(b) Multi-locular Cystic Renal cell carcinomas have clear cells lining the cysts; they also have nests of clear cells in the stroma; they have low-grade nuclear characteristics.

3. Tubulocystic carcinoma of the kidney in Comparison with Mixed Epithelial and Stromal Neoplasm [2]

(a) Tubulocystic Carcinoma of the kidney is overwhelmingly cystic; they also have fibrotic stroma as well as large irregular nuclei.
(b) Mixed Epithelial and stromal Neoplasms are commonly found to contain cysts but the stroma is the prominent feature; the stroma is cellular; their nuclei are bland.

4. Tubulocystic carcinoma of the kidney in comparison with Renal Oncocytoma with Cystic Features [2]

(a) Tubulocystic Carcinoma of the kidney is overwhelmingly cystic; it has fibrotic stroma; it has large irregular nuclei; it has consistent prominent nucleoli; Racemase and CD10 are positive in these tumours.
(b) Renal Oncocytoma with Cystic Features usually consist of solid nests with focal cystic dilatation; they have loose hypocellular stroma; they have large round nuclei; Racemase and CD10 are usually negative in these tumours.

5. Tubulocystic Carcinoma of the kidney in comparison with Cystic Nephroma [2]

(a) Tubulocystic Carcinoma of the kidney has a male to female incidence ratio of 7:1; it has high grade nuclear features; it lacks ovarian type stroma.
(b) Cystic Nephroma involves nearly all female; it has low-grade nuclear features; it has ovarian type stroma.

Outcome

The prognosis of tubulocystic renal cell carcinoma is usually excellent with recurrences but only rare distant metastases or death from disease [1]

Narrations from reported cases

Amin et al. [3] reported a detailed study of 31 cases to further characterize tubulocystic carcinoma of the kidney (TCRCC) which is a rare sub-type of renal cell carcinoma. They reported that the tumour occurred in adults (mean age, 54 years) with a strong male predominance (Male to female ration; 7:1). They also reported that grossly, the tumours ranged in size from 0.7 to 17 cm, and exhibited a spongy or "bubble wrap" appearance reflecting the microscopic presence of variably sized cystically dilated tubules lined by a single layer of epithelium. The lining varied with a cuboidal, flat, and "hobnail-cell appearance" and the neoplastic cells had abundant eosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Amin et al. [3] also reported that:

- The cysts were closely spaced with an intervening variably fibrotic stroma.
- Immunohistochemical studies and ultrastructural examination revealed features of proximal convoluted tubules (Pax 2 immunoreactivity and short microvilli with brush border organization) and distal nephron (kidney-specific cadherin immunoreactivity and cytoplasmic interdigitation).
- Gene expression profiling revealed that tubulocystic carcinoma displayed a unique molecular signature. Twenty-four tumours were stage pT1, 4 stage pT2, and 3 stage pT3. Disease progression (median follow-up of 56 months) occurred in 3 patients; 1 with local recurrence, and 2 with distant metastasis to bone and liver.

Amin et al. [3] concluded that in light of the distinctive clinicopathologic features and a low but definite metastatic potential, this unique sub-type of renal cell carcinoma deserves formal recognition in the contemporary classification of renal neoplasms.

Yang et al. [4] stated that:

- The nature of tubulocystic carcinoma, a rare renal tumour composed of tubular and cystic structures, is poorly understood.
- It had been suggested that tubulocystic carcinoma of the kidney may represent a low-grade collecting duct carcinoma of the kidney despite the lack of sufficient molecular and pathologic evidence.

Yang et al. [4] examined the clinical and pathologic features of 13 cases of tubulocystic carcinoma of the kidney (TCRCC). They used gene expression microarray analysis, and defined the molecular signature of tubulocystic renal cell carcinoma by comparing it with other renal tumours in their previously established molecular profile database. They found that histologically, all 13 tumours were composed of closely packed tubules and cysts of varying sizes separated by fibrovascular septa. The epithelial lining cells of the tubules and cysts in this tumour were found to be characterized by abundant eosinophilic cytoplasm with prominent nucleoli often showing a hobnail appearance. Clinically, one of the 13 cases showed metastasis to the pelvic lymph nodes. Five of the 13 cases co-existed with papillary renal cell carcinoma (RCC) (n=3) or papillary adenoma (n=2). In addition, the molecular profile of tubulocystic carcinoma was similar but not identical to those of papillary RCC by clustering analysis. Through comparative genomic microarray analysis, tubulocystic carcinoma showed gains of chromosome 17, but not chromosome 7, whereas most papillary RCCs showed chromosomal gains in both 7 and 17 (trisomies). Yang et al. [4] recommended that based upon its unique pathologic features and molecular signature as well as its biologic behaviour to develop metastasis either by itself or in association with papillary RCC, tubulocystic carcinoma of the kidney should be recognized as a distinct subtype of RCC and be distinguished from other malignant and benign cystic lesions of the kidney.

Yang et al. [4] stated that there is only scant information in the literature including a few meeting abstracts and a couple of full articles describing this unusual tumour. Yang et al. [4] also stated that the finding of tubulocystic carcinoma of the kidney was first reported by Farrow et al, in an abstract which was presented at the Annual Meeting of United States and Canada Academy of Pathology. The authors described this distinct entity as typically well-circumscribed with well-differentiated tubules and cysts lined by tumour cells with eosinophilic cytoplasm. Firstly, it was believed that the properties of this tumour were more consistent with origin from the collecting ducts. Nevertheless, in the later reported cases, the tumour seemed to be a low-grade malignancy that differs significantly from that of the classic aggressive and highly infiltrative collecting duct carcinoma. Therefore, at that time the term of

‘‘low-grade collecting duct carcinoma’’ was proposed for this neoplasm.

Zhou et al. [7] stated that tubulocystic carcinoma of the kidney (TC-RCC) is a rare renal tumour which has unique gross and microscopic features different from other types of renal cell carcinoma (RCC). They also stated that several recent studies had recommended that tubulocystic carcinoma of the kidney should be classified as a distinct renal cell carcinoma sub-type. In their study, they provided pathologic and cytogenetic evidence which support that tubulocystic carcinoma of the kidney is closely related to papillary renal cell carcinoma. The study included 20 cases of renal tumours that partially or exclusively comprised a tubulocystic renal carcinoma component. Zhou et al., [7] stated that the pathologic examination documented the macroscopic and microscopic characteristics of tubulocystic renal carcinoma, including multicentricity and the presence of concomitant papillary renal cell carcinoma and papillary adenoma.

Zhou et al. [7] subjected formalin-fixed, paraffin-embedded sections from 12 TC-RCC and 20 papillary renal cell carcinomas to a multicolor fluorescence in situ hybridization assay containing probes for chromosomes 7, 17, and Y. Zhou et al. [7] examined one hundred nuclei in order to enumerate the copy numbers of chromosomes in each tumour and its corresponding normal kidney tissue. A tumour which has a percentage of cells harbouring a chromosomal change Zmean+3 SD of normal tissue was considered to harbour that chromosomal change, and a tumour with a percentage of cells with null Y chromosome count (loss of Y chromosome) Zmean+3SD of normal tissue was considered to harbor Y chromosome loss. Four of the 20 tubulocystic renal carcinomas were multicentric. Ten had associated papillary renal cell carcinoma or papillary adenoma within the same kidney as the tubulocystic renal cell carcinoma. In 4 cases, the tubulocystic and papillary components were admixed together within the same lesion. The tumour cells lining both the tubulocystic and papillary components had similar cytologic features. Ten of 12 tubulocystic renal cell carcinomas had a chromosome 7 gain, 8 of 12 cases had a chromosome 17 gain, and 8 of 9 cases had a loss of Y chromosome. Six of 9 cases with all 3 chromosomes studied had a gain of chromosomes 7 and 17 and a loss of Y chromosome. They concluded that:

- Their study showed that tubulocystic renal cell carcinomas and papillary renal cell carcinomas are closely related entities.
- With its distinctive gross and microscopic features, tubulocystic renal cell carcinoma may be considered a unique ‘‘morphologic entity.’’ However, before it has been accepted as a distinct renal cell carcinoma subtype, further studies were needed to document a characteristic molecular signature associated with this tumour.

Azoulay et al [14] reported a series of 11 cases of tubulocystic carcinoma of the kidney, 6 of which were examined by immunohistochemistry using a panel of five antibodies (CK7, CK34βE12, CK19, CD10 and P504S). All the patients were men. Each had renal tumour stage of pT1N0M0, with a diameter of 1.7 to 7 cm (mean, 3.3 cm). None of the patients presented with recurrence or metastases. Grossly, the tumors were microcystic masses with a bubble-wrap appearance. Histological features of the tumours included cysts and small tubules, separated by delicate septa and lined by flat to columnar or hobnail cells. The cyst and tubule epithelium showed immunohistochemical characteristics of both proximal and distal tubules. Azoulay et al [14] stated that:

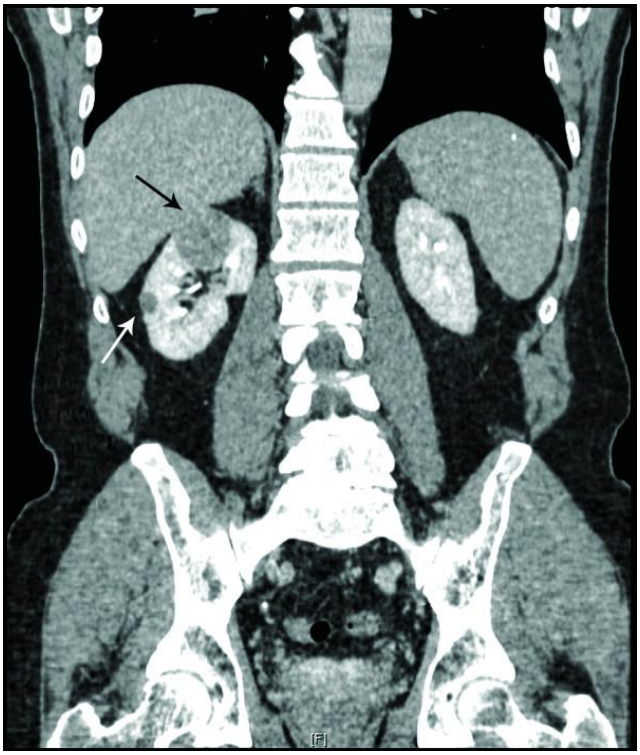
- Tubulocystic carcinoma is a distinctive kidney tumour, with noteworthy macroscopic and microscopic characteristics, which can be distinguished from other cystic kidney tumours, including cystic nephroma, multilocular cystic renal cell carcinoma and some solid tumours with extensive cystic changes.
- More cases are needed to ascertain its prognosis.

They recommended that tubulocystic carcinoma should be considered as a new subtype of renal cell carcinoma in the next revision of the WHO classification.

Khallaf et al, [15] stated that tubulocystic carcinoma of the kidney is extremely rare with less than one hundred cases reported at the time of their publication. Khallaf et al. [15] reported a 38 years-old Sudanese male who presented with recurrent episodes of left flank pain of 8-month duration. He

did not have any other relevant symptoms. He did not have any relevant past

Figure 1: Computed tomography (CT) scan showed the presence of two incidental well-circumscribed masses with similar density in the right kidney. The larger lesion was solid and enhancing and measured 3.5 cm; it was located in the upper pole and approached but did not extend into the renal sinus (black arrow). The smaller lesion measured 1.2 cm and was located along the mid lateral aspect of the kidney (white arrow). The contralateral kidney was normal. This figure was taken from Quiroga-Garza G, Pina-Oviedo S, Cuevas-Ocampo K, Goldfarb R, Schwartz M R, Ayala A G, Monza F A. Synchronous clear cell renal cell carcinoma and tubulocystic carcinoma: genetic evidence of independent ontogenesis and implications of chromosomal imbalances in tumor progression. Diagnostic Pathology 2012: 7:21 doi:10.1186/1746-1596-7-21 Acknowledgement to the editorial board and publishers of Diagnostic Pathology who have a policy of not requiring copy right permission to reproduce tables or figures from their journal but who require the source of tables and figures to be clearly stated.



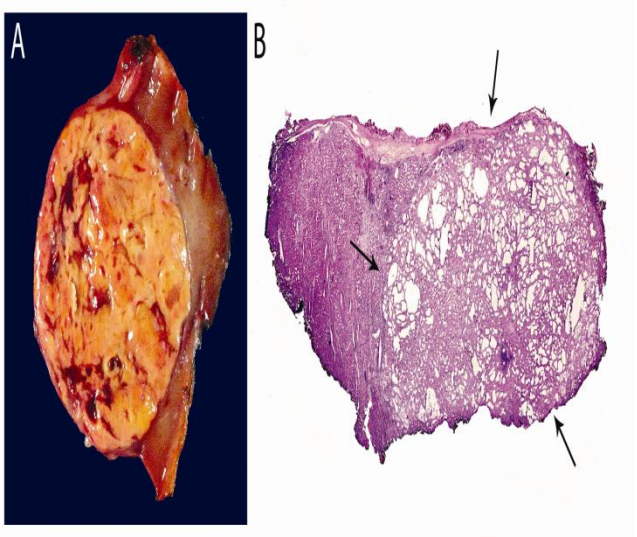


Figure 2: Gross image and full-montage of clear cell renal cell carcinoma (ccRCC) and tubulocystic renal carcinoma (TCRC), respectively [A] The larger mass was well encapsulated, tan-yellow to red and grossly suggestive of ccRCC. This lesion was not associated with the smaller nodule. [B] Full montage of the smaller lesion. The 'spongy' nodule encountered in the gross description (arrows) was composed of cystic only-dilated irregular tubules of different sizes, separated by fibrovascular septae (Haematoxylin and Eosin stain). This figure was taken from Quiroga-Garza G, Pina-Oviedo S, Cuevas-Ocampo K, Goldfarb R, Schwartz M R, Ayala A G, Monza F A. Synchronous clear cell renal cell carcinoma and tubulocystic carcinoma: genetic evidence of independent ontogenesis and implications of chromosomal imbalances in tumor progression. Diagnostic Pathology 2012: 7:21 doi:10.1186/1746-1596-7-21 Acknowledgement to the editorial board and publishers of Diagnostic Pathology who have a policy of not requiring copy right permission to reproduce tables or figures from their journal but who require the source of tables and figures to be clearly stated.

medical history. He had positive family history for renal cancer in the patient's uncle. His laboratory investigations showed normal hematologic, renal and hepatic data. He had a computed tomography urography which revealed a 15 cm × 13 cm well defined, multiloculated cystic mass in the left kidney with thick contrast-enhancing septations and small mural nodules in keeping with category III Bosniak classification, compressing and displacing the calyces with mild pelvi-calyceal system dilatation. There were no metastases at the time of surgery. A left radical nephrectomy was performed and the specimen was sent for histopathological 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 × 8 cm × 3 cm.The walls of the cyst were firm, gray with nodular and hemorragic areas. The kidney measured 10 cm × 7 cm × 3 cm and showed the tumour bed at its center. The small separate tissue fragments were firm and nodular and measured 6 cm × 6 cm in aggregate. Microscopic examination of 4 m thick, Haematoxylin and Eosin stained sections from the renal mass, the tumour 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. Mitosis was only occasionally encountered. A fibrotic stroma and a "hobnail appearance" of neoplastic cells were focally observed. There was also focal tumoural necrosis, haemorrhage and mononuclear-inflammatory-cell infiltration. The tumour 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 there was no reactivity for CK7. Immunoreactivity for CD10; CK19; and EMA, CK 18 and vimentin was in keeping with proximal convoluted tubular, distal tubular and collecting duct differentiation, respectively. The final diagnosis was "TubulocysticCarcinoma", 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 tumour. The patient was free of disease 6 months after the surgery.

Hora et al. [16] stated that at the time of publication of their paper in 2011, the clinicopathological features on less than hundred cases of tubulocystic carcinoma of the kidney had been characterized exclusively in the pathological literature. Hora et al [16] reported five additional cases emphasizing clinical aspects on these rare renal neoplasms. They stated that all the five patients were men, mean age 56 years (range 29-70). The features of the tumours on computed tomography (CT) scan were in two cases Bosniak III, one IV and two were solid tumours. In four patients, nephrectomy was performed, and one patient underwent resection. At the time of surgery, two patients had metastases. In one case, both primary tumour and metastases were active on FDG positron emission tomography (PET)/CT. Both patients with metastatic disease were treated with sunitinib with partial response. One patient died 26 months postoperatively and the other patient was alive, 5 months after surgery. Three patients with localized tumours were without evidence of disease 31, 28 and 7 months after surgery. In one case, the resected tumour was histologically combined with a papillary renal cell carcinoma (PRCC).

Hora et al [16] concluded that:

- Tubulocystic carcinoma of the kidney (TCRC) occurs predominantly in men with a wide age range.
- Tubulocystic carcinoma of the kidney frequently displays a cystic component which may render a radiological classification of Bosniak III or IV.
- FDG PET/CT is helpful in the detection of metastases. TCRC has definitive malignant potential.
- Their findings support a possible relationship to papillary renal cell carcinoma (PRCC).
- The tyrosine kinase inhibitor sunitinib may be used as a therapeutical agent with partial response and temporary effect.

Bhullar et al. [17] reported a 33-year-old man who presented with back pain. His investigations revealed multiple metastases and a large, solid, cystic left renal tumour. He underwent decompression of the spine followed by left radical nephrectomy. The final histopathological diagnosis was tubulocystic carcinoma of the kidney with sarcomatoid features. He presented after 2 months with intestinal obstruction, and underwent an exploratory laparotomy which revealed multiple peritoneal metastases with ascites.

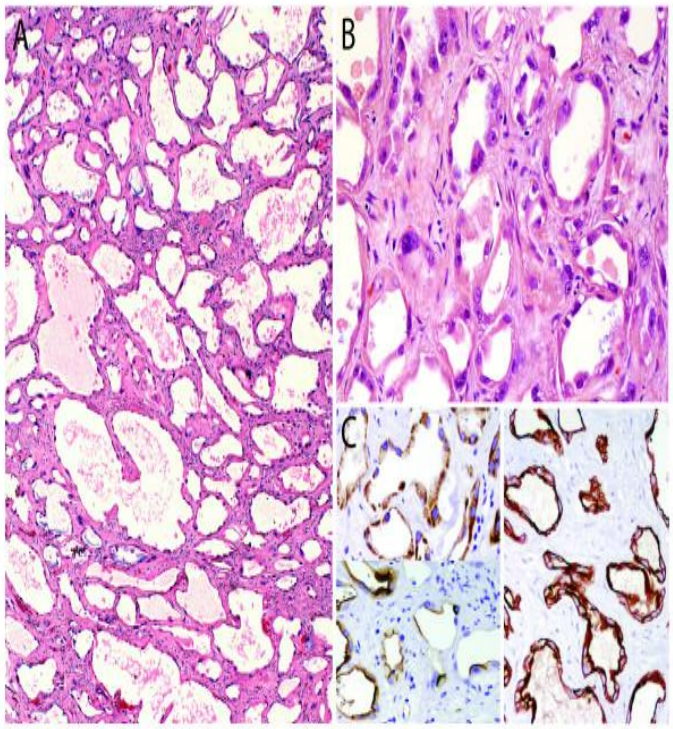
Moses et al [18] reported a 68-year-old man who had an incidentally discovered 1.6 cm lower pole renal lesion and nearby Bosniak 1 renal cyst which was identified by computed tomography scan. He had a significant medical history for squamous cell carcinoma of the larynx which was treated with external beam radiation therapy and chemotherapy 6 years prior to his presentation, colonic polyps, coronary artery disease, peripheral vascular disease, hypertention, and hepatitis B and C. Mag-3 renogram

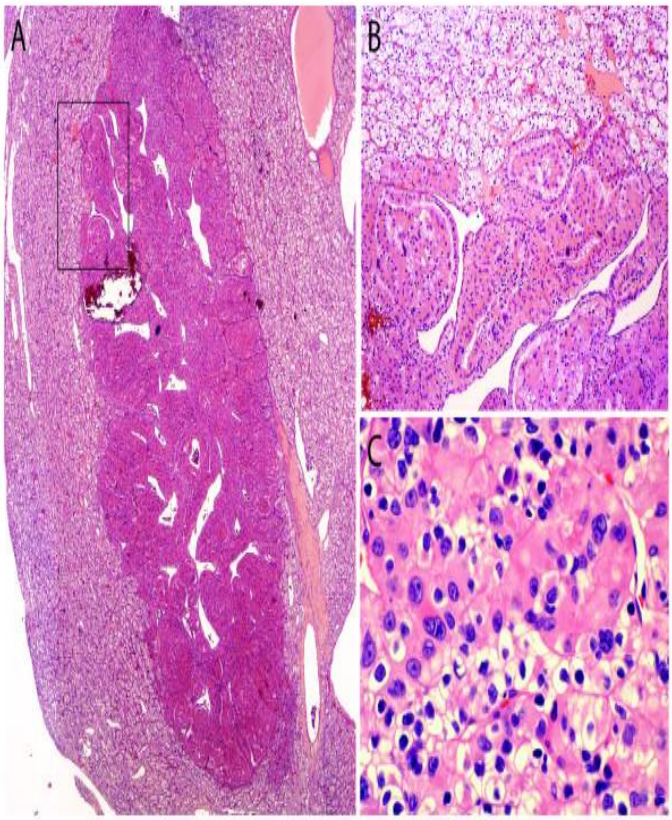
demonstrated 35% function on the right and 65% function on the left. His baseline serum creatinine

Figure 3: Tubulocystic carcinoma component [A] Higher magnification of the image shown on figure 2B (Haematoxylin and Eosin staining, 4 x magnification). [B] The cystically-dilated tubules were lined by flat to polygonal clear cells (some with a hobnail profile) with enlarged nucleus, prominent nucleolus, and occasional abundant eosinophilic cytoplasm. The fibrous septae contained scattered fibroblast-like spindle cells interspersed within a collagenous stroma (Haematoxylin and Eosin, 20 x Magnification).[C] Tubular cells were positive for AMACR (left, top) and CD10 (left, bottom) and CK 19 (right) confirming their proximal and distal convoluted tubule cell origin, respectively (all images, 20 x Magnification). Estrogen receptor was negative in both epithelial and stromal elements (not shown)This figure was taken from Quiroga-Garza G, Pina-Oviedo S, Cuevas-Ocampo K, Goldfarb R, Schwartz M R, Ayala A G, Monza F A. Synchronous clear cell renal cell carcinoma and tubulocystic carcinoma: genetic evidence of independent ontogenesis and implications of chromosomal imbalances in tumor progression. Diagnostic Pathology 2012: 7:21 doi:10.1186/1746-1596-7-21 Acknowledgement to the editorial board and publishers of Diagnostic Pathology who have a policy of not requiring copy right permission to reproduce tables or figures from their journal but who require the source of tables and figures to be clearly stated.

Figure 4: Clear cell renal cell carcinoma (RCC) component [A] The largest lesion described in the gross description was composed of cells with abundant clear cytoplasm and well-demarcated cellular borders. Marked oncocytic changes with a nodular configuration were present in some areas (Haematoxylin and Eosin staining, 2 X Magnification) [B] The rectangle in A at higher magnification shows the transition between the clear (top) and oncocytic cells (bottom). Nuclear features in the clear cell areas were consistent with Furhman nuclear grade 2 whereas the oncocytic nodule's cells showed increased pleomorphism and slightly enlarged nuclei (Haematoxylin and Eosin staining 10 x Magnification). [C} A separate area of the tumour showed clusters of tumour cells with marked nuclear pleomorphism; irregular nuclear contours, and prominent nucleoli consistent with Furhman nuclear grade 3 (Haematoxylin and Eosin staining x 40 Magnification).This figure was taken from Quiroga-Garza G, Pina-Oviedo S, Cuevas-Ocampo K, Goldfarb R, Schwartz M R, Ayala A G, Monza F A. Synchronous clear cell renal cell carcinoma and tubulocystic carcinoma: genetic evidence of independent ontogenesis and implications of chromosomal imbalances in tumor progression. Diagnostic Pathology 2012: 7:21 doi:10.1186/1746-1596-7-21 Acknowledgement to the editorial board and publishers of Diagnostic Pathology who have a policy of not requiring copy right permission to reproduce tables or figures from their journal but who require the source of tables and figures to be clearly stated.

was 0.8mg/dl. The initial managent of his renal lesion was by means of conservative management, which included serial imaging with renal ultrasound scan and yearly computed tomography scans, which were





consistent with a slow-growing renal tumour. His most recent imaging preceding surgical excision

showed the mass measured 1.9 cm, showing minimal interval growth of 3 mm in 5 years. The patient eventually underwent exploratory laparotomy and right hemicolectomy for recurrent colonic polyps 5 years later, at which time he had simultaneous right partial nephrectomy. Macroscopic examination of the renal tumour revealed a 1.7 cm x 1.5 cm x 1.3 cm cystic mass and 4.5-cm simple cyst. Initial analysis of the cystic mass was described as low-grade CDC; nevertheless subsequent analysis of the molecular and morphologic features of the tumour, were consistent witth tubulocystic carcinoma of the kidney. The tumour was Fuhrman nuclear grade 2, with positive stains associated with proximal collecting tubule (CD10, P504S/AMACAR) and distal nephron/collecting ducts (high molecular weight CK 34βE12). Additionally, CK7 and EMA were also positive. Mucicarmine staining was negative. The surgical margin was negative. Thirty months post-operatively, the patient remained free, with normal postoperative renal imaging and preservation of his baseline renal function. His final colonic pathology was tubular adenoma.

It has been stated that collecting duct carcinoma (CDC) is an uncommon variant of renal cell carcinoma (RCC) which has been proven to be highly aggressive and to be associated with poor prognosis [19]. From the mid-90s, there have been reports of a potential low-grade variant of collecting duct carcinoma which had a distinctively benign course [5]. Tubulocystic carcinoma of the kidney was originally termed low-grade collecting duct carcinoma, however, subsequent studies had described this tumour as a separate entity known as tubuloystic carcinoma (TC) [3] [14] [18] [20] and stated that:

- Of the 55 initial cases described, there were reports of a generally benign behaviour of the disease, nevertheless, there are some reports of patients with metastatic disease requiring further treatment [3] [4] [21]
- The vast majority of reports of tubulocystic carcinomas have been incidental findings on autopsy, or of patients who had radical or partial nephrectomy for the concern of malignancy.
- Tubulocystic carcinoma was not formally recognized under contemporary classification systems of renal neoplasia, including the World Health Organization2004 classification of tumours. Nevertheless, the very recent 2010 AJCC/UICC TNM, 7th edition, cancer protocol for renal cell carcinoma (RCC) now recognizes this tumour as a distinct entity.

MacLennan et al. [5] reported on 13 cases of renal tumours which were believed to be of collecting duct origin which had low malignant potential. MacLennan et al. [5] in their report stated that the patients had a mean age of 61 years and the tumours had a mean diameter of 6 cm. macroscopically, the tumours were well circumscribed with evidence of mnimal necrosis and low nuclear grade. MacLennan et al [20] later on observed that the 13 cases were infact actually two distinct groups of tumours as follows:

- One group which they termed mucinous tubular and spindle cell carcinoma exhibited complex anastomotic tubular structures which had abundant mucin.
- The second, tubulocystic carcinoma of the kidney, exhibited immunoreactivity to UEA-1 or 34βE12, and no production of mucin or little production of mucin.

Moses et al. [18] stated that the characteristics of tubulocystic carcinoma that are distinct from collecting duct carcinoma include well-circumscribed tumours with low-grade appearance. Azoulay et al [14] as well as Amin et al [3] stated that the tubules and cystic structures within a fibrous stroma are characteristically lined by a single layer of low cuboidal epithelial cells and eosinophilic cytoplasm, with areas of hobnail appearance and that further histopathological analysis had revealed that the majority of tubulocystic carcinomas are pT1, and with a small sub-set being pT2 or T3 (up to 10-15% each). Azoulay et al. [14] stated that tubulocystic carcinoma shares immunohistochemical staining characteristics of both proximal (CD10 and P504S staining characteristics) and distal (CK19 staining characteristics) tubules. Majority of tubulocystic carcinomas are classified as Fuhrman grade 3, nevertheless, it has been stated that the clinical course of the tumours does not appear to correlate with nuclear grade as it does with conventional clear cell or papillary renal cell carcinoma. Metastatic disease from tubulocystic carcinoma of the kidney in four patients and one local recurrence was reported by Azoulay et al [14] as well as Amin et al [3] but on the whole it would appear that the overall the disease tends to generally assume a benign course. Osunkoya et al [22] illustrated that tubulocystic carcinoma of the kidney (TCRCC) is distinct from collecting duct

carcinoma at molecular level even though tubulocystic carcinoma was at first thought to be a sub-type of collecting duct carcinoma, Furthermore, Zhou et al [7] showed that tubulocystic carcinoma has a molecular profile that is similar to but distinct from papillary renal cell carcinoma. Moses et al [18] stated that tubulocystic carcinoma was characterized by vimentin, p53, and α-methylacyl CoA racemase overexpression in comparison with collecting duct carcinoma.

Zhang et al [23] investigated the clinicopathological features and differential diagnosis of tubulocystic carcinoma of the kidney. Zhang et al [23] analysed the clinical features, histological and immunohistochemical findings in 3 cases of tubulocystic carcinoma of the kidney. They reported that:

- The three patients were males with a mean age of 59 years and their ages ranged from 44 years to 71 years
- All the three patients were asymptomatic and their tumours were found on routine examination.
- The size of the tumours ranged from 1.5 cm to 5.0 cm in greatest dimension.
- The tumours exhibited a spongy cut surface and they were grossly well-circumscribed without capsules.
- Microscopic examination of all the three tumours revealed that they were composed of tubules and cysts of various sizes which were separated by fibrous septa. The epithelial lining cells were noted to be flat, cuboidal and columnar, with often a hobnail-like appearance which was characterized by abundant eosinophilic cytoplasm with prominent nucleoli. Two of the cases showed focal clear cytoplasm. One of the three cases was found to coexist with a papillary renal cell carcinoma.
- Immunohistochemical staining revealed that all the three tumours showed positive staining for pan-CK, vimentin, CK 19, CD10, P504S, and focal positivity for 34βE12. Two cases showed focal positivity for CK7.

. Zhang et al. [23] concluded that:

- Tubulocystic carcinoma of the kidney is a rare neoplasm which occurs predominantly in males.
- The tumour is characterized by gross spongy appearance and microscopic cysts and tubules which are often lined by thin fibrotic stroma.
- The differential diagnosis mainly includes lesions of the kidney that have a multicystic growth pattern.

Steiner [24] stated that patients with renal cell carcinoma (RCC) are regarded as potential candidates for antiangiogenic targeted therapy. Steiner et al. [24] also stated that tubulocystic renal cell carcinoma (TCRC) is a recently described entity which may behave aggressively, and the rationale for angiogenic therapy in this group of renal tumours is yet to be determined. Steiner et al. [24] subjected seven tubulocystic carcinomas of the kidney and five non-tumour tissue samples from seven patients to relative expression analysis of mRNA levels of 16 genes involved in three angiogenic pathways: (1) VHL/HIF, (2) RTK/mitogen-activated protein kinase (MAPK), and (3) PI3K/Akt/mTCR. Two of them, pathways (2) and (3), are often targeted by antiangiogenic agents. Steiner et al [24] determined the mutation and methylation status of the VHL gene. Steiner et al [24] finally determined the levels of vascular endothelial growth factor A (VEGFA), HIF-1α, HIF-2α proteins, and phosphorylated mTOR protein. Steiner et al [24] stated that the comparison of tumour and control samples revealed no changes of mRNA levels of the ensuing genes: VHL, HIF-1α, HIF-2α, PTEN, Akt2, Akt3, mTOR, VEGFA, KDR, HRas, C-Jun, EGFR, and FGF2. Steiner et al [24] reported that they found significantly elevated mRNA level of TP53, while the mRNA levels of FLT1 and C-FOS were reduced in tumour samples. They did not find any mutations or methylation in the VHL gene. Furthermore, they did not find changes in levels of studied proteins VEGFA, HIF-1α, HIF-2α, and increased phosphorylation of mTOR protein. Steiner et al. [24] concluded that the three studied angiogenic pathways (VHL/HIF, RTK/MAPK, and PI3K/Akt/mTOR) seemed not to be up regulated in tubulocystic renal cell carcinoma samples, so there appeared to be no rationale for a general recommendation of antiangiogenic targeted therapeutic protocols for patients with these tumours. Quiroga-Garza et al [25] reported a 67-year-old healthy man who presented with acute chest pain of sudden onset. He did not have any significant past medical history. He had a family history of renal cell carcinoma (his mother). His general examination and examination of his chest were unremarkable. As part of work-up in the investigation of his symptom, he

had a computed tomography scan which revealed two incidental masses in his right kidney (see figure 1). A 3.5 cm solid, enhancing mass which was located in the anterior aspect of the upper pole of the right kidney, and a 1.2 cm mass which was located along the mid lateral pole of the kidney. The patient denied having had flank pain, haematuria, or weight loss. He underwent further work-up for metastatic disease which was negative. The initial plan was for him to undergo partial nephrectomy; however, during the operation it was not possible for a partial nephrectomy to be performed therefore total nephrectomy was performed. He did not receive any adjuvant therapy. Twenty-four months pursuant to the operation, the patient remained free of disease. At the operation, a wedge biopsy including the smaller lesion was initially submitted for frozen section and was interpreted as tubulocystic carcinoma vs. cystic nephroma, followed by a partial nephrectomy of a larger lesion which was interpreted as a clear cell renal cell carcinoma. The smaller nodule (2 x 1.7 x 1 cm) was a tan-gray small sphere with a spongy cut surface that was adjacent to a 0.3 cm haemorrhagic cyst. The larger tumour was a relatively well encapsulated tan-yellow to red mass (4.1 x 3.4 x 2.5 cm) macroscopically compatible with clear cell renal cell carcinoma (ccRCC) which showed no association with the previous lesion (see figure 2A). A radical nephrectomy was ultimately performed.

Microscopic examination revealed that the smaller lesion comprised of multiple cystic tubules of various sizes which were separated by fibrovascular septae (see figure 2B, arrows). The tubules were lined by flat to polygonal and epitheliod cells which displayed a promonent hobnail pattern. There was evidence of nuclear enlargement, prominent nucleoli, and eosinophilic cytoplasm (see figure 3A-B), but there was no evidence of mitotic figures. Some of the tubules occasionally contained intra-luminal clumps of eosinophilic material. Immunohistochemical staining of the tumour revealed that the tubular cells were positively stained for alpha-methylacyl-CoA racemace (AMACR), CD10 and cytokeratin 19 (CK 19), which are markers that are commonly positive in tubulocystic renal carcinoma tumours (tubulocystic carcinomas of the kidney) (see figures 3C [4] [14] while the stromal cells were negative for oestrogen receptor. To the contrary, the larger tumour primarily compried of nests of cells which had abundant clear cytoplasm with well-demarcated cellular borders and hyperchromatic nuclei with nucleoli that were inconspicuous (Fuhrman nuclear grade 2) separated by a well-formed capillary network. In some areas, the tumour exhibited well-demarcated nodules with oncocytic change together with mild nuclear pleomorphism and slightly enlarged nucleoli (see figures 4A –B). Furthermore, a focal area of the tumour contained cells that had marked pleomorphism, irregular contours, and prominent nucleoli (Fuhrman nuclear grade 3) (see figure 4C). Sarcomatoid features were not seen. A final diagnosis of synchronous tubulocystic renal cell carcinoma and clear cell renal cell carcinoma, Fuhrman grade 3, stage T1b, was made. The tumour was also studied by means of virtual karyotyping. DNA was extracted from microdissected tumour tissue from the clear cell and oncocytic areas with Fuhrman grade 2, the region of clear cell renal cell carcinoma (ccRCC) with Fuhrman grade 3, from the tubulocystic renal carcinoma ((TCRCC), and from uninvolved kidney tissue. Virtual karyotyping was done using Affymetrix 250 K Nsp (single nucleotide polymorphism) arrays as previously described by Kim et al. [26]. The results for SNP oligonucleotide microarray karyotype analysis for each region of the tumours and normal kidney are illustrated in figure 5. All the analysed areas of the clear cell renal cell carcinoma (ccRCC) exhibited loss of chromosome 3p and gains in chromosome 5 and 7. Additionally, the area of oncocytic change exhibited a gain of 2p and a loss of 10q. The area of tumour with Fuhrman nuclear grade 3 showed a profile that was consistent with polyploidy (likely trisomic) with the ensuing additional imbalances: +2, +5, -6, +7, +10, +12, +15, +16, +17, +18, +19, +20, +21. The tubulocystic renal carcinoma (TCRC) exhibited a profile which was distinct from that of clear cell renal cell carcinoma (ccRCC), with gains of chromosomes 8 and 17 and loss of uniparental disomy in regions of chromosomes 2 and 6 [UPD2 (q21.3-q22.1), UPD6 (q23.2-q23,3)] was found in tumoural and non-neoplastic kidney from the patient (asterisks, see figure 5) which indicated a germline abnormality.

Deshmukh et al. [27] reported an 18-year-old girl with tubulocystic carcinoma (TCRCC) of kidney which was associated with primary renal cell carcinoma (PRCC) with metastases to the para-aortic nodes. She presented with haematuria and a right renal mass and enlarged regional lymph nodes for which she underwent radical nephrectomy with retroperitoneal lymph node dissection. Macroscopic examination of the specimen revealed a solid cystic lesion which involved the lower pole and middle pole of the kidney and this measured 12 cm x 9 cm x 9 cm

along with an additional cystic lesion within the upper pole of the kidney. Microscopic examination of the specimen revealed that the main tumour exhibited the typical histology of a tubulocystic carcinoma with multiple cysts filled with secretions which were lined by variably flattened epithelium with hobnailing of

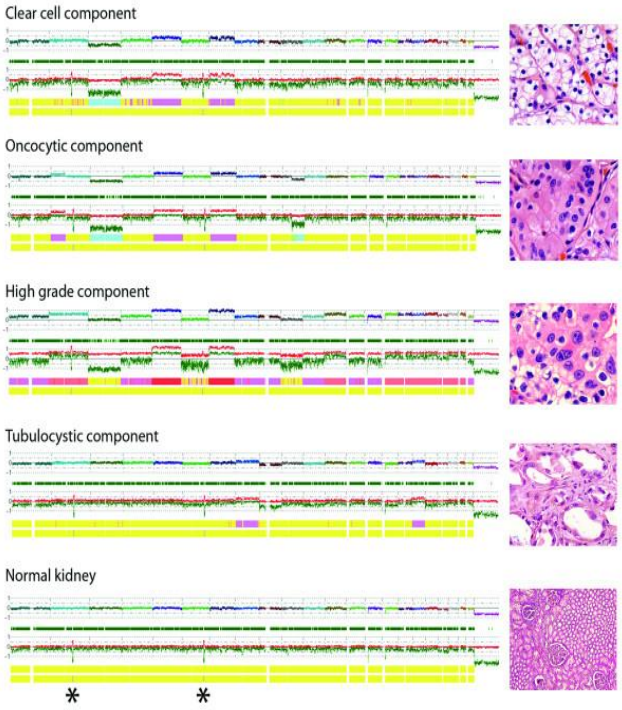


Figure 5: Denomic profile of tumour components. The uppermost plot for each sample represents the estimated copy number as a log 2 ratio averaged over 30 SNB; middle bar represents a color-coded Hidden Markov Model (HMM) for copy (yellow = copy number 2, pink = copy number 3, aqua = copy number 1), and bottom bar is a color-coded HMM for LOH (yellow = no LOH, blue = LOH). Genomic analysis revealed loss of chromosome 5 and 7 in all clear cell renal carcinoma (ccRCC) components, a gain of 2p and loss of 10q in the oncocytic component, and a profile consistent with polyploidy (likely trisomic) with additional gains and losses in the high-grade component. The tubulocystic component showed a profile distinct from that of clear cell renal carcinoma (ccRCC). Germline uniparental disony (UPD) of chromosomes 3 and 6 [UDP2 (cq21.3-q22.1), (q23.2-q23.3)] (asterisks) was found in all (tumour and normal) specimens from the patients. This figure was taken from Quiroga-Garza G, Pina-Oviedo S, Cuevas-Ocampo K, Goldfarb R, Schwartz M R, Ayala A G, Monza F A. Synchronous clear cell renal cell carcinoma and tubulocystic carcinoma: genetic evidence of independent ontogenesis and implications of chromosomal imbalances in tumor progression. Diagnostic Pathology 2012: 7:21 doi:10.1186/1746-1596-7-21 Acknowledgement to the editorial board and publishers of Diagnostic Pathology who have a policy of not requiring copy right permission to reproduce tables or figures from their journal but who require the source of tables and figures to be clearly stated.

cells. The mass in the upper pole was a high-grade primary renal cell carcinoma (PRCC) and the nodal metastases had morphology which was similar to this component. Deshmukh et al. [27] concluded that:

- At least for a small but definite sub-set of tubulocystic carcinomas of the kidney (TCRCC) is associated with primary renal cell carcinoma (PRCC).
- Cases associated with primary renal cell carcinoma (PRCC) do seem to have a higher propensity for nodal metastasis as in their reported case.

Al-Hussain et al. [28] reported 3 cases of tubulocystic carcinoma of the kidney with poorly differentiated areas. Two of the lesions which measured 9.5 cm x 3.8 cm were described as partly solid and cystic. One case was grossly a 14.0 cm-cyst, which had a granular lining. Microscopic examination revealed that all the 3 cases had classic areas of circumscribed tubulocystic renal cell carcinoma which occupied 30%, 80% and 90% of the tumour, 2 cases had small components of papillary renal cell carcinoma, and 1 case had a central large cystic component. Al-Hussain et al. [28] stated that:

- In 2 cases, prolifrations of small tubules infiltrated away from the main mass with typical features of collecting duct carcinoma.
- In the third case, a focus of poorly differentiated carcinoma was found adjacent to the tubulocystic renal cell carcinoma.
- In 2 cases the tumour invaded the perirenal tissue.
- The third case was organ confined with vascular invasion.
- One patient died 9 months post-operatively with metastases to the abdominal wall and femur.
- The second case developed a recurrence in the renal bed 3 years post-operatively.
- The third patient was lost to follow-up.
- Fluorescence in situ hybridization studies results revealed some features which overlapped with papillary renal cell carcinoma in both the tubulocystic and collecting duct-like components with 1 exception which showed identical cytogenetic findings the 2 components.
- Morphologically, in 2 cases, the collecting duct-like areas were also indistinguishable from

collecting duct carcinoma which was suggestive of a relationship between the two entities.

- Al-Hussain et al. [28] further stated that their case series was the first series and only the second report of tubulocystic renal cell carcinoma with poorly differentiated components and that their case series documented the increased risk of aggressive behaviour above that of the usual tubulocystic renal cell carcinoma.

Conclusions

- Tubulocystic carcinoma of the kidney is a rare neoplasm which occurs predominantly in males but it has also been reported in the female sex.
- Tubulocystic carcinoma of the kidney has not yet been classified in the World Health Organization classification of malignancies of the kidney.
- Tubulocystic carcinoma of the kidney is characterized by spongy appearance on macroscopic examination and microscopic examination reveals cysts and tubules which are often lined by "hob-nail-like"cells which are separated by thin fibrotic stroma.
- The differential diagnosis of tubulocystic carcinoma of the kidney includes other lesions of the kidney which have a multicystic growth pattern.
- The macroscopic and histological characteristics of tubulocystic carcinoma of the kidney are distinct and in view of this it would be strongly recommended that academic and world renown pathologists should meet and discuss tubulocystic carcinoma in order to arrive at a concensus opinion to include the disease entity in the WHO classification of kidney tumours as a distinct entity.

References

1. Williamson S. Kidney tumor – adult malignancies Adult renal cell carcinoma Tubulocystic carcinoma PathologyOutlines.com 2012 June 30; can be found at http://www.pathologyoutlines.com/kidneytumor malignanttub
2. Higgins J P. Rouse R V. Tubulocystic Carcinoma of the Kidney. Urology 1997 Nov; 50(5): 679 - 684 obtained from Surgical Pathology Criteria at: http://surgpathcriteria.stanford.edu/ original posting January 24, 2011
3. Amin MB, MacLennan GT, Gupta R, Grignon D, Paraf F, Vieillefond A, 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
4. Yang X J, Zhou M, Hes O, Shen S, Li R, Lopez J, Shah R B, Yang Y, Chuang S T, Lin F, Tretiakova M M, Kort E J, Teh B T. Tubulocystic carcinoma of the kidney: clinicopathologic and molecular characterization. Am J Surg Pathol 2008 Feb; 32(2): 177 – 187,
5. 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 Nov; 50: 679- 684
6. Skinnider BF, Folpe AL, Hennigar RA, Lim SD, Cohen C, Tamboli P, 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 Jun; 29(6): 747 – 754
7. Zhou M, Yang X J, Lopez J I, Shah R B, Hes O, Shen S S, Li R R, Yang Y, Lin F, Elson P, Sercia L, Magi-Galluzzi C, Tubbs R. Renal tubulocystic carcinoma is closely related to papillary renal cell carcinoma: Implications for pathologic classification. Am J Surg Pathol 2009 Dec; 33(12): 1840 – 1849
8. Lohse C M, Blute M L, Zincke H, Weaver A L, Cheville J C. Comparison of standardized and nonstandardized nuclear grade of renal carcinoma to predict outcome among 2,042 patients. Am J Clin Pathol; 2002 Dec; 118(6): 877 - 886
9. Sika-Paotonou D, Bethwaite P B, McCredie M R, William Jordan T, DelaHunt B,. Nuclear grade but not Fuhrman grade is applicable to papillary renal cell carcinoma. Am J Surg Pathol. 2006 Sep; 30(9): 1091 – 1096
10. DelaHunt B. Advances and Controversies in Grading and Staging of Renal Cell Carcinoma. Mod Pathol 2009 Jun 22; Suppl 2: S24 - S536
11. DelaHunt B, MacKenney J K, Lohse C M, Leibovich M D, Thompson H, Boorjcain S A, Cheville J C. A Novel Grading System for Clear Cell Renal Cell Carcinoma Incorpirating Tumor Necrosis. Am J Surg Pathol 2013; 37: 311 – 322
12. DelaHunt B, Sika-Paotonu D, Bethwaite P B, William Jordan T, Magi-Galluzi C, Zhou M, Samaratunga H, Srigley J R. Grading of clear cell renal cell carcinoma should be based on

nucleolar prominence. Am J Surg Pathol. 2011 Aug; 35(8): 1134 - 1139
13. DelaHunt B, Bethwaite P B, Nacey J N. Outcome prediction for renal cell carcinoma: evaluation of prognostic factors for tumours divided according to histologic sub-type. Pathology. 2007 Oct; 39(5): 459 -465
14. Azoulay S, Vieillefond A, Paraf F, Pasquier D, Cussenot O, Callard P, et al. Tubulocystic carcinoma of the kidney: A new entity among renal tumors. Virchows Arch 2007 Nov; 451(5): 905 - 909.
15. Khallaf I, El-Badawy N, Shawarby M A. Tubulocystic renal carcinoma, a rare tumor entity: Review of literature and report of a case. African Journal of urology. 2013; 19: 1 – 6
16. Hora M, Urge T, Eret V, Stránsk´y P, Kle˘cka J, Kreuzberg B, Ferda J, Hyrst L, Breza J, Holeckova P, Mego M, Michal M, Petersson F, Hes O. Tubulocystic renal carcinoma: a clinical perspective. World Journal of Urology 2011 Jun; 29(3): 349 – 354.
17. Singh Bhullar J, Thamboo T, Esuvaranathan K. Unique case of tubulocystic carcinoma of the kidney with sarcomatoid features: a new entity. Urology 2011 Nov; 78(5): 1071 – 1072
18. Moses K A, DeCaro J J, Osunkoya A O, Issa M M. Tubulocystic Carcinoma of the Kidney: A Case Report of Natural History and Long-Term Follow-up. The Scientific World Journal 2010; 10: 586 -589
19. Cromie W J, Davis C J, De Ture F A. Atypical carcinoma of kidney: possibly originating from collecting duct epithelium. Urology 1979; 13: 315 -317] [1 in moses].
20. MacLennan G T, Bostwick D G. Tubulocystic carcinoma, mucinous tubular and spindle cell carcinoma, and other recently described rare tumors. Clin Lab. Med. 2005; 25: 393 – 416
21. Mego M, Sycova-Mila Z, Rejlekova K, Rychly B, Obertova J, Rajee J, Hes O, Mardiak J. Sunitinib in the treatment of tubulocystic carcinoma of the kidney. A case report. Ann. Oncol. 2008; 19: 1655 – 1656
22. Osunkoya A O, Young A N, Wang W, Netto G J, Epstein J I. Comparison of gene expression profiles in tubulocystic carcinoma of collecting duct carcinoma of the kidney. Am J. Surg Pathol. 2009; 33: 1103 – 1106
23. Zhang S H, Shi S F, Huang S F, Zhang Y N, Zheng Y Y, Chen G Y. Clinical and pathologic features of tubulocystic carcinoma of kidney. 2012 Aug; 41(8): 543 – 546
24. Steiner P, Hora M, Stenlik J, Martinek P, Vanecek T, Petersson F, Michal M, Korabecha M, Travnicek I, Hes O. Tubulocystic renal cell carcinoma: Is there a rational reason for targeted therapy using angiogenic inhibition? Analysis of seven cases Virchows Arch. 2013 Feb; 462(2): 183 – 192
25. Quiroga-Garza G, Pina-Oviedo S, Cuevas-Ocampo K, Goldfarb R, Schwartz M R, Ayala A G, Monzon F A. Synchronous clear cell renal cell carcinoma and tubulocystic carcinoma: genetic evidence of independent ontogenesis and implications of chromosomal in tumour progression. Diagn Pathol 2012 Feb 27; doi: 10.1186/1746-1596-721
26. Kim H J, Shen S S, Ayala A G, Ro J Y, Truong L D, lvarez K, Bridge J A, Gatalica Z, Hagenkord J M, Gonzalez-Berjon J M, +Monzon F A. Virtual-karyotyping with SNP microarrays in morphologically challenging renal cell neoplasms: a practical and useful diagnostic modality. Am J Surg Pathol 2009; 33: 1276 – 1286
27. Deshmukh M, Shet T, Bakshi G, Desai S. Tubulocystic carcinoma of kidney associated with primary renal cell carcinoma. Indian J Pathol Microbiol 2011; 54: 127 130.
28. Al-Hussain T O, Cheng L, Zhang S, Epstein J I. Tubulocystic carcinoma of the kidney with poorly differentiated foci: a series of 3 cases with fluorescence in situ hybridization. Human Pathology. 2013 February 18. Can be found at: http://dx.doi.org/10.1016/j.humpath.2012.11.015
29. Brennan C, Srigley J, Whelan C, Cooper J, DelaHunt B. Type 2 and Clear Cell Papillary Renal Cell Carcinoma, and Tubulocystic Carcinoma: A unifying Concept. Anticancer Research 2010; 30: 641 - 642
30. Yin Ming, Falls Randall. Eosinophilic Variant of Chromophobe Renal Cell Carcinoma with Tubulocystic Features: A Case Report. BJUI Nov6:www.bjui.org/ContentFullterm.aspx?id=85 3 DOI: 10.1002/BJUIw-2012
31. Muniz G, Corominas A, Perez A, Cerda N, Gonzalez M, Caamano V, Andres L, Lopez J I. Tubulocystic renal cell carcinoma: Clinicopathologic study of two cases. Uropathology Poster Session of 25th European Congress of Pathology 31 August – 4 September 2013 No. PS-22-Poster Session-Session title: Uropathology. 058, Lisbon.: URL: www.europepmc.org/abstract/MED/23427871

Table 1: Immunohistochemistry of tubulocystic carcinomas of kidney found by some authors

Type of marker	Authors Yang et al. [4]	Brennan et al. [29] 1 patient 72 year old man	Moses et al. [18] 1 patient 68 year old man	Yin and Randall [30]	Muniz et al [31]	Quiroga-Garza et al. [25]	Singh Bhullar et al. [17]	Azoulay et al. []
	Numbers studied / Percentage positive	**1 case 72 year old man**	**1 case 68 year old man**	**1 case 63 year-old female**	**2 cases 55 yearl old female and 72 year old man**	**1 case 67 year old man**	**33 year old man died after 14 months)**	**3 cases**
AMACR	8/8 [4]; 77% [4]	Diffuse positive staining +++	Positive	Not done	Positive staining in both	Positive staining	Strongly positive	Not done
CK7	7/8 [4] 62%	Diffuse positive staining ++	Positive	Diffuse positive staining	Positive staining in both	Not done	Not done	2 cases positive ; 1 case negative
CK8	100% [4]	Not done	Not done	Not done	Not done	Not done	Not done	Not done
CK18	100% [4]	Not done	Not done	Not done	Not done	Not done	Not done	Not done
CK19	100% [4]	Not done	Not done	Not done	Not done	Positive staining	Not done	All 3 cases positive
Parvalbumin	100% [4]	Not done	Not done	Not done	Not done	Not done	Not done	Not done
CD10	85%	Diffuse positive staining ++	Positive	Negative	Positive staining in both	Positive staining	Not done	3 cases all positive
Kidney-specific cadherin	71%]4]	Not done	Not done	Not done	Not done	Not done	Not done	Not done
Pax2	42% [4]	Not done	Not done	Not done	Not done	Not done	Not done	Not done
Carbonic anhydrase IX	36% [4]	Not done	Not done	Not done	Not done	Not done	Not done	Not done
34βE12	15% [4]	Negative	Positive	Not done	Not done	Not done	Not done	All focally positive
CK20	Not done	Negative	Not done	Not done	Not done	Not done	Not done	Not done
P504S	Not done	Not done	Positivr	Not done	Not done	Not done	Not done	All 3 cases positive
EMA	Not done	Not done	Positive	Not done	Not done	Not done	Not done	Not done

Pancytokeratin (AE1/3)	Not done	Not done	Not done	Diffuse positive staining	Not done	Not done	Not done	All 3 cases positive
Ber-EP4	Not done	Not done	Not done	Diffuse positive staining	Not done	Not done	Not done	Not done
CD117	Not done	Not done	Not done	Diffuse positive staining	Not done	Not done	Not done	Not done
Vimentin	Not done	Not done	Not done	Negative	Not done	Not done	Not done	All 3 cases positive
e-cadherin	Not done	Not done	Not done	Not done	Diffuse positive staining	Not done	Not done	Not done