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Review Article

Primary Thyroid-Like Follicular Carcinoma of Kidney: Review and Update

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Abstract

Thyroid-like follicular carcinoma of the kidney (TLFCK) is an exceedingly uncommon tumor which has been reported sporadically on very rare occasions that afflict individuals whose ages had tended to range between 10 years and 83 years. There are no specific manifesting symptoms for this neoplasm and TLFCK had most often been diagnosed incidentally during assessment of individuals for other conditions. Confirmation of the diagnosis of TLFCK is based upon histopathology examination and immunohistochemistry staining features of the tumor and exclusion of a primary thyroid follicular carcinoma metastasizing to the kidney with radiology imaging evidence of absence of follicular carcinoma of the thyroid gland. It also needs to be appreciated that immunohistochemistry staining features for thyroid-like follicular carcinoma of the kidney are different from the features of primary follicular carcinoma of thyroid gland. TLFCK does tend to afflict one kidney only generally. On rare occasions the kidney could be afflicted by metastasis from primary follicular carcinoma of thyroid gland but in such scenarios, there tends to be evidence of multiple metastases afflicting many other organs as disseminated tumor. TLFCK tends to portend generally a low-rate of malignancy; however, few cases had been reported associated with metastasis. Even though TLFCK is regarded to most often be a tumor that is associated with a low-rate of malignancy with no development of local recurrence or distant metastasis, because few cases of TLFCT had been ensued by the subsequent development of metastasis after a long-time, it would be recommended that all patients who had undergone treatment for a diagnosed TLFCK should be followed-up regularly over a period of a long-time. Patients who had been diagnosed as having primary TLFCK have tended to be treated by means of surgery in the form of partial nephrectomy or radical nephrectomy which could entail the undertaking of open surgery, laparoscopic surgery or robotic surgery. Other procedures including pre=operative biopsy of the tumor for pathology examination confirmation of the diagnosis followed by undertaking of less-invasive procedures including: cryotherapy of the tumor, radiofrequency ablation of the tumor, irreversible electroporation of the tumor, and selective renal artery angiography and super-selective embolization of the branch of renal artery supplying the tumor in the kidney, to the knowledge of the author has so far not been reported as treatment procedures for cases of primary TLFCK.

Key words: thyroid-like follicular carcinoma of the kidney; primary; metastatic; histopathology; immunohistochemistry; partial nephrectomy; radical nephrectomy

Introduction

Thyroid-like follicular carcinoma of the kidney (TLFCK) is stated to be a very rare clinical disease. [1] TLFCK is stated to be classified as a sub-type of renal cell carcinoma and it is stated to be typified by being morphologically similar to well-differentiated follicular thyroid carcinoma but does exhibit negative immunohistochemistry staining for thyroid marker expressions [1] [2] [3]. It has been documented that the clinical biological behaviour of this tumour is not certain due to the rarity of the cases so far reported in the English-language literature [1] [4] [5]. In 2004, many cases of a unique renal epithelial tumour were reported. Microscopically, these cases had shown histopathology examination features that simulated follicular lesions in a well-differentiated thyroid gland [1] [6], but this tumour had not been included in the World Health Organization (WHO) classification of kidney tumours until 2016 [7] Considering that TLFCK had

only been included in the WHO classification of renal tumours, recently in 2016, it would be envisaged that majority of clinicians all over the world including some Urologists, pathologists as well as some oncologists may not have encountered a case of TLFCT before and hence they may not be conversant with the manifestations, diagnostic features, treatment options and management outcomes of TLFCT. The ensuing review and updating article on TLFCT, is divided into two parts: (A) Overview which has discussed miscellaneous general aspects related to TLFCT and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to TLFCT.

Aim

Method

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: Primary Thyroid-Like Follicular Carcinoma of Kidney; Primary Renal Thyroid-Like Follicular Carcinoma; Primary Thyroid-Like Follicular Cancer of Kidney; Primary Renal Thyroid-Like Follicular Cancer. Forty-one (41) references were identified which were used to write the article which has been divided into two parts: (A) Overview which has discussed miscellaneous general aspects related to TLFCT and (B) Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to TLFCT.

Results

[A] Overview

Definition / general statements [8]

- It has been iterated that primary thyroid-like follicular carcinoma kidney is a very uncommon kidney neoplasm which morphologically simulates well-differentiated thyroid follicular neoplasms [8]
- It has been documented that primary thyroid-like follicular carcinoma of kidney is regarded as an emerging / provisional clinical tumour entity [8] [9] [10] [11]

Essential features

The essential features of primary thyroid-like follicular carcinoma of kidney had been summated as follows: [8]

- Primary thyroid-like follicular carcinoma of kidney is very rare with about 40 cases reported in the global literature. [8]
- Primary thyroid-like follicular carcinoma of kidney, simulates well-differentiated thyroid follicular tumours [8]
- Primary thyroid-like follicular carcinoma of kidney is an encapsulated mass with thyroid-like follicles including macroand micro-follicles, that contain inspissated, eosinophilic colloid-like material [8]
- Primary thyroid-like follicular carcinoma of kidney tumour cells upon immunohistochemistry staining studies exhibit negative staining for TTF1 and thyroglobulin [8]
- Most cases of primary thyroid-like follicular carcinoma of kidney have low malignant potential. [8]

Terminology

• With regard to terminology of the tumour, it has been iterated that primary thyroid-like follicular carcinoma of kidney is also referred to as thyroid-like follicular renal cell carcinoma. [8]

Epidemiology

The epidemiology of primary thyroid-like follicular carcinoma of kidney has been summated as follows: [8]

- There is a predominance of primary thyroid-like follicular carcinoma of kidney in women with a female to male ratio of 2:1 [8]
- It has been iterated that the age range of individuals who had been diagnosed as having Primary thyroid-like follicular carcinoma of kidney has ranged between 10 years and 83 years, with age mean age of between 41 years and 44.5 years [3] [8] [12]
- It has been iterated that the median age of individuals who have been diagnosed as being afflicted with Primary thyroid-like follicular carcinoma of kidney at the time their initial diagnosis is about 35 years. [10]

It has been documented that 10% of patients who had been reported to be afflicted by primary thyroid-like follicular carcinoma of kidney had concurrent or historical hematopoietic neoplasia [3]

Sites

It has been pointed out that the area of the kidney which tends to be afflicted by primary thyroid-like follicular carcinoma of kidney is the renal cortex. [8]

Clinical features [8]

• It has been iterated that primary thyroid-like follicular carcinoma of kidney has tended to be asymptomatic and they had been diagnosed incidentally based upon radiology imaging in the assessment of a different condition and found incidentally in most cases; however, primary thyroid-like follicular carcinoma of kidney but may be symptomatic, manifesting with haematuria, flank pain, abdominal pain, in up to 33% of patients [3]

Diagnosis

- It has been pointed out that the diagnosis of primary thyroid-like follicular carcinoma of kidney is made primarily based upon the microscopy histopathology Haematoxylin and Eosin features of the kidney tumour. [8]
- It has been iterated that diagnosis of primary thyroid-like follicular carcinoma of kidney is essentially a diagnosis of exclusion; and that adequate sampling of the tumour should be undertaken and immunohistochemistry staining studies of the kidney tumour could be considered, if clinically indicated, in order to exclude morphology simulants of primary thyroid-like follicular carcinoma of kidney. [8]

Radiology description

The radiology imaging features of primary thyroid-like follicular carcinoma of kidney had been summated as follows: [8]

- Radiology imaging of primary thyroid-like follicular carcinoma of kidney typically demonstrates typically solid, low attenuation mass without measurable postcontrast enhancement, metastatic disease or renal involvement. [8]
- Radiology imaging of the kidney tumour in primary thyroid-like follicular carcinoma of kidney may demonstrate tumour that contains calcifications and features of possible necrosis. [8]
- Radiology imaging in cases of primary thyroid-like follicular carcinoma of kidney would tend to demonstrate corresponding lack of thyroid mass suggestive of primary thyroid-like follicular renal cell carcinoma over metastatic thyroid carcinoma. [13] [14] [15]

Prognostic factors

The ensuing summations had been made about the prognostic factors of primary thyroid-like follicular carcinoma of kidney: [8]

- It has been iterated that majority of cases of primary thyroid-like follicular carcinoma of kidney do appear to be associated with low malignant potential. [6]
- It had also been iterated those aggressive cases of primary thyroid-like follicular carcinoma of kidney had been described with about 10% metastases association development and 13% of cases invading the perinephric tissues. [3] [15] [16]
- It has furthermore, been iterated those rare cases of primary thyroid-like follicular carcinoma of kidney had been reported associated with spread to lymph nodes and distant metastasis, including to skull, meninges and lung but all patients survived after surgical resection. [3] [10]

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Treatment

The treatment of primary thyroid-like follicular carcinoma of kidney had been summated to include the ensuing: [8]

- The undertaking of Partial nephrectomy,
- or the undertaking of radical nephrectomy

Gross description

The Macroscopy examination features of primary thyroid-like follicular carcinoma of kidney had been summated to include the ensuing: [8]

- Gross examination of a primary thyroid-like follicular carcinoma of kidney does tend to demonstrate a solitary mass, that measures between 1 cm and 16.5 cm and the mean measured size has been 4.7 cm. [11]
- Gross examination of a primary thyroid-like follicular carcinoma of kidney tends to demonstrate a well-circumscribed tumour with solid to cystic cut surface; and the examination may also demonstrate areas of haemorrhage and necrosis but this tends to be non-typical [3] [12]
- Gross pathology examination of primary thyroid-like follicular carcinomas of kidney tend to demonstrate tumour that is tan to brown in colour; some tumours had been described as having yellow or grey colour [3]

Microscopic (histologic) description

The Microscopy examination features of primary thyroid-like follicular carcinoma of kidney had been summated to include the ensuing: [8]

- Microscopy examination of primary thyroid-like carcinomas of the kidney had tended to demonstrate follicular-like architecture with variably sized follicles, with micro and macro-follicles, that contain inspissated, eosinophilic colloid-like material
- Microscopy examination features of primary thyroid-like follicular carcinomas of kidney tend to demonstrate follicles which had been lined by a single layer of cuboidal or low columnar epithelium with moderate amphophilic to eosinophilic cytoplasm, round nuclei, mostly inconspicuous to occasionally prominent nucleoli
- Majority of the tumours upon microscopy pathology examination do demonstrate pure follicular architecture, with some variations including branching, resulting in focal papillary-like pattern. [11]
- Microscopy examination features of primary thyroid-like follicular carcinomas of kidney may demonstrate papillary areas which may appear to be broken interfollicular septa rather than true papillae. [3]
- Microscopy examination of the tumour may also demonstrate tumours that may be cystically dilated. [17]
- Microscopy examination of the tumour may demonstrate focal tightly packed follicles without secretions, imparting a somewhat solid appearance
- Microscopy examination of few cases of the tumour may demonstrate nuclear grooves or ground glass nuclear appearance. [3]
- Microscopy pathology examination some of the tumours may demonstrate lymphocytic infiltrate which may be present intratumorally or around periphery and macrophages may be present in background. [18]
- Calcifications may be visualized upon microscopy examination of some of the tumours. [3]
- Necrosis and lympho-vascular invasion tend to be absent upon microscopy examination of most of the tumours

Sarcomatoid differentiation had been reported based upon microscopy pathology examination of some of the tumours. [7] [19] [20]

Cytology description

Cytology examination features of primary thyroid-like follicular carcinoma of kidney had been summated to include the ensuing: [8]

- Cytology examination of specimens in cases of primary thyroidlike follicular carcinoma of kidney may demonstrate hypercellular tumour which is arranged in sheets. [21]
- Cytology examination of specimens in cases of primary thyroidlike follicular carcinoma of kidney may demonstrate presence of acellular eosinophilic material which is associated with the neoplastic epithelial cells in the background of the smear
- Cytology examination of specimens in cases of primary thyroidlike follicular carcinoma of kidney may demonstrate individual tumour cells which may be oval, round and plasmacytoid with mild nuclear pleomorphism, finely stippled nuclear chromatin and inconspicuous nucleoli with a moderate amount of eosinophilic cytoplasm and rare nuclear grooves. [18] [21]

Immunohistochemistry staining studies:

It has been iterated that immunohistochemistry staining studies in cases of primary thyroid follicular-like carcinoma of the kidney does demonstrate the following features: [8]

Positive stains

The tumour cells tend to exhibit positive staining for: [8]

- CAM 5.2
- CK7
- PAX2,
- PAX8
- Vimentin [3] [4]
- Cyclin D1 [12]

Negative stains

The tumour cells tend to exhibit negative staining for: [8]

- Thyroglobulin
- TTF1
- The tumour may exhibit negative staining but focal staining to variable reactivity had been reported for Renal cell carcinoma (RCC) in 14% of cases, AMACR in 17% of case, CD10 in 23% of cases, and CK20 in 40% of cases. [11]
- The tumour had been reported to be typically negative for CD56, and WT1 [22]
- It has been iterated that other reports had documented carcinoembryonic antigen, CK7, CD15, CK19, CK 34 beta E12 and epithelial antigen are typically negative [23]

Molecular / cytogenetics description

The molecular and cytogenetics features of primary thyroid follicular -like carcinoma of the kidney had been summated as follows: [8]

- In 3 out of 3 tumours which had been tested in one study, an in frame fusion of exon 8 of EWSR1 and intraexonic of PATZ1, both on chromosome 22, were identified by RNA sequencing and confirmed with reverse transcription PCR; per authors, other approaches instead of FISH may be preferable to detect the EWSR1::PATZ1 fusion [12] [20]
- It has been iterated that Gene expression profile is primary thyroid follicular-like carcinoma of kidney is distinct from clear cell and chromophobe renal cell carcinoma

- Amin et al. had reported overexpression in cell cycle regulatory genes and mixed lineage leukaemia (MLL) / tri-thorax homolog in 3 tumours; nevertheless, comparative genetic hybridization had failed to demonstrate cytogenetic alterations in one study [6]
- Another study had demonstrated chromosomal gains of 7q36, 8q24, 12, 16, 17p11-q11, 17q24, 19q, 20q13, 21q22.3 and Xp and losses of 1p36, 3 and 9q21-33 detected by comparative genomic hybridization. [23]

Differential diagnoses

Some of the differential diagnoses of primary thyroid follicular-like carcinoma of kidney had been summated as follows: [8]

- Follicular architecture is not unique to thyroid-like follicular renal cell carcinoma (RCC) and this might be visualised in other renal cell carcinoma (RCC) subtypes, including: papillary RCC, clear cell RCC, FH deficient RCC, tubulocystic RCC, SDH deficient RCC, microcystic chromophobe RCC, atrophic kidney-like tumour / lesion (provisional entity) as well as mixed epithelial and stromal tumour. [9] [11]
- Papillary RCC.:
 - It has been pointed out that microscopy examination of papillary RCC would demonstrate ordinary papillary renal cell carcinoma areas
- Atrophic kidney-like tumour / lesion (provisional entity):
 - It has been iterated that in atrophic kidney-like tumour microscopy examination of the tumour does demonstrate the lesion to be atrophic and associated with flattened epithelium with occasional hob-nailing within follicles, more pronounced microcalcifications, entrapped benign atrophic renal tubular structures and morphologic similarity to glomerulocystic change
 - This tumour would demonstrate exhibition of tumour immunohistochemistry staining positively for WT1 / PAX8 and negative staining for CK7, as well as negative IHC profile. [9] [12]
- Metastatic thyroid carcinoma.[24] [25]
 - It has been pointed out that metastatic thyroid carcinoma metastasis within the kidney is very rare to have; in such a scenario it would usually be an obvious thyroid primary with widely disseminated metastases
 - It has been iterated that metastatic thyroid cancer to the kidney would the tumour specimen exhibiting positive immunohistochemistry staining for Thyroglobulin + or TTF1+
 - It has been pointed out that majority of follicular and follicular variant of papillary thyroid carcinomas do have RAS or BRAF mutations, respectively. [12]
 - It has been iterated that thyroid carcinomas could have a Hürthle (oncocytic) phenotype, which could be a potential pitfall for eosinophilic / oncocytic renal neoplasms; these more commonly metastasis to the lung and bone. [26] [27]
- Metastatic follicular carcinoma arising within struma ovarii in women:
 - It has been pointed out that if this tumour metastasizes, usually it goes to bone [28] [29]
 [30]
- Chronic pyelonephritis and end stage kidney disease:
 - ✤ It has been iterated that these may be considered due to presence of colloid-like

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hyaline casts in atrophic, microcytic tubules resembling thyroid (thyroidisation)

- It has also been pointed out that these lesions could be differentiated by clinical history, lack of mass formation and histologic differences (inflammation, demonstration of normal constituents, such as glomeruli and tubules, with chronic injury pattern resulting in fibrosis, atrophy, etc.)
- Well-differentiated neuroendocrine tumour (carcinoid tumour):
 - These tumours are stated to be rare
 - It has been iterated that the patterns in these tumours are insular, and the tumours contain cords, nests or ribbons but not follicular tissue.
 - It has been pointed out that pathology examination of these tumours demonstrates neuroendocrine histology
 - It has been pointed out that in neuroendocrine tumours, the tumour cells exhibit positive staining for neuroendocrine markers synaptophysin and chromogranin.
- Urothelial carcinoma with cystitis cystica pattern:
 - ✤ It has been iterated that these tumours arise from the renal pelvis and not the cortex of the kidney.
 - It has been pointed out that these tumour cells exhibit positive immunohistochemistry staining for GATA3. [12]
 - Oncocytoma of the kidney:
 - It has been pointed out that in oncocytoma, pathology examination of the kidney lesion does demonstrate areas of classical oncocytoma with nests of oncocytic cells embedded within loose myxoid stroma

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Primary Thyroid-Like Follicular Carcinoma of Kidney

Dong et al. [15] stated the ensuing:

- Thyroid-like follicular carcinoma of the kidney (TLFCK) is an extremely rare subtype of renal cell carcinoma with close simulation to the well-differentiated thyroid follicular neoplasms.
- TLFCK had not been included in the 2004 World Health Organization (WHO) classification due to the limited data available.
- By 2016, only 27 cases had been reported in the global literature.

Dong et al. [15] reported a unique case of TLFCK which had manifested as a striking skull and meningeal metastasis 5 years pursuant to the initial diagnosis. Dong et al. [15] stated that their reported case was the first case of TLFCK with such a novel metastasis pattern. Dong et al. [15] reported a 68year-old woman, who was found to have a right kidney lesion utilizing computed tomography (CT) scan during her regular clinical follow-up assessment visit for urinary bladder cancer, but at that time she did not exhibit any obvious clinical symptoms. The CT scan had demonstrated a 4.4cm diameter, slightly lobulated soft tissue mass within the right lower kidney, the pathological findings of which had shown a TLFCK. Five years subsequently, the patient had progressed to develop skull and meningeal metastasis. Both the kidney tumour and the metastasis lesion were noted to be composed almost entirely of follicles with a dense, colloid-like material that simulated thyroid follicular carcinoma. Nevertheless, no lesion was found within her thyroid gland. The neoplastic epithelial cells had exhibited

strong immunohistochemistry staining for cytokeratin 7 (and vimentin but negative immunohistochemistry staining for thyroid transcription factor-1 and thyroglobulin. Furthermore, Dong et al. [15] iterated that their reported case was the first reported case of TLFCK to consist of widespread metastases to the skull and meninges and which had provided evidence that this rare variant of renal cell carcinoma has uncertain malignant potential and could be more clinically aggressive than had been previously believed.

Dawane et al. [31] iterated the ensuing:

- Thyroid-like follicular carcinoma of the kidney has continued to confound the practicing pathologist with its close simulation of follicular variant of thyroid carcinoma, as well as other benign and malignant entities.
- Their goal was to expand the knowledge of this rare renal cell carcinoma subtype, which morphologically mimics follicular carcinoma of the thyroid but which does lack the immunohistochemistry expression of characteristic thyroid immunohistochemical markers such as TTF-1 and thyroglobulin.

Dawane et al. [31] evaluated the gross, histological, immunohistochemical, and fluorescence in situ hybridization (FISH) studies of a new case and they had undertaken a comprehensive review of the literature. Dawane et al. [31] summarized the results as follows:

- The lesion was noted to be spongy and well-circumscribed.
- Microscopy examination of the tumour demonstrated that the tumour contained variably sized follicular structures, that were filled with abundant, deeply eosinophilic, colloid-like material. At the periphery, the tumour had displayed areas that simulated metanephric adenoma and early stages of nephrogenesis.
- The tumour cells upon immunohistochemistry staining studies had exhibited strong immunohistochemistry expression for:CK7, PAX-8, PAX-2, vimentin, EMA, and CK19.
- The tumour cells upon immunohistochemistry staining studies exhibited negative staining for other tumour markers including: CD10, RCC, HBME-1, thyroglobulin, and TTF-1, were not immunoreactive.
- The kidney tumour was found to be negative for trisomy of both 7 and 17 and to have shown borderline monosomies (losses) of both chromosomes in FISH studies.

Dawane et al. [31] made the ensuing conclusions:

- Five years of preoperative observation and lack of recurrence bring further insight into the slow progressive nature of this tumour and does support a low malignant potential associated with the neoplasm.
- Proper identification is important in order to secure adequate treatment and follow-up of patients who have this type of tumour.

Jung et al. [23] reported an unusual kidney tumour, which to their knowledge had not been classified under a known subtype of renal cell carcinoma (RCC) and which characteristically had shown similar histology examination features to thyroid follicular carcinoma. Jung et al. [23] reported a 32-yearold asymptomatic woman who was found to have a kidney mass during her annual clinical examination. She did not have any lesions within her thyroid gland found during her clinical and ultrasound scan examinations, and she did not have any abnormal thyroid function test results. No abnormalities were found within her mediastinum and her ovaries. The resected kidney upon gross examination was demonstrated to have a well-defined nodular tumour that measured 11.8 cm x 8.0 cm x 8.0 cm. The mass was protruding into the pelvic cavity with areas of yellowish geographic necrosis. Histopathology examination of the tumour demonstrated that the tumour had shown follicular architectures with inspissated colloid-like material within their lumina. No conventional (clear cell) RCC or any other known subtypes of RCC component was found during pathology examination of the tumour.

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Immunohistochemistry staining studies of the tumour had demonstrated that the tumour cells had exhibited intensive staining for cytokeratin (CK) cocktail AE1/AE3 and CD10 and the tumour cells were not reactive to thyroid transcription factor-1 and thyroglobulin. The staining of the tumour for CK35betaH11 and vimentin had demonstrated focal cytoplasmic immunohistochemistry staining reaction. The tumour cells had exhibited complete negative staining for CK7, CK19, CK20, CK34betaE12, carcinoembryonic antigen, epithelial membrane antigen, and CD15. Chromosomal gains of 7q36, 8q24, 12, 16, 17p11-q11, 17q24, 19q, 20q13, 21q22.3, and Xp and losses of 1p36, 3, and 9q21-33 were identified by comparative genomic hybridization. Jung et al. [23] stated that these findings were dissimilar to previously classified kidney neoplasm. Jung et al. [23] only a report which included three cases of primary thyroid-like renal tumour had been described in the abstract form. Nevertheless, there was no fully documented case on this unusual form of RCC, which morphologically simulates that of thyroid follicular carcinoma.

Li et al. [32] in 2015 stated that thyroid-like follicular carcinoma of the kidney (TLFCK) is a provisional new entity of renal cell carcinoma (RCC). Li et al. [32] reported and compared one TLFCK case and one PRCC case with thyroid-like feature. Li et al. [32] stated the ensuing:

- The former entirely consisted of thyroid-like follicular architecture and the tumour cells were diffusely positive for PAX-8, but negative for CK7, AMACR, and CD10.
- By contrast, both papillary architecture which was demonstrated in 60% of cases and thyroid-like follicular architecture which was found in 40% of cases were identified in the latter.
- The tumour cells in both histology components had exhibited diffusely positive immunohistochemistry staining for PAX-8, CK7, AMACR, but negative staining for CD10.
- FISH analysis had demonstrated no aberration in TLFCK case but trisomy of chromosome 17 in PRCC case.
- They had intimated that recognition of TLFCK is important to distinguish it from other conditions that exhibit thyroid-like features.
- Additionally, a diagnosis of TLFCK should be cautiously undertaken when papillary component is present within the tumour.

Zhang et al. [33] stated that thyroid follicular carcinoma-like renal tumour (TFCLRT) is an uncommon primary renal epithelial tumour that was first reported in 2006. Zhang et al. [33] reported a case diagnosed of TFCLRT by their team to observe the pathology feature and to analyse comparatively the clinical and pathology examination features with all cases documented in reviewed literatures. Zhang et al. [33] reported a 54-year-old female patient who had manifested with urinary frequency and with the symptom of right flank pain with a history of more than half a year of hypertension and who had undergone uterine fibroid resection 12 years earlier. She underwent Bmode ultrasound scan examination and renal magnetic resonance which demonstrated a right renal sinus nodule. Histopathology examination of biopsy specimens of the kidney lesion demonstrated features of thyroid follicle-like structures of different sizes, which contained a colloid-like substance, while the periodic acid-Schiff (PAS) and diastase-resistant PAS staining had confirmed that it was mucus protein. Immunohistochemical staining studies of the specimen showed that the tumour cells had expressed the transcription factor PAX-8 but had not expressed the thyroid-specific antibodies TG and TTF-1. With regard to interventions, the patient underwent a tumour enucleation of right kidney. No other treatment was undertaken after her surgery. With regard to the outcome, no metastases to lymph nodes and other organs were found, and 9-months of follow-up had not demonstrated any tumour progression. Zhang et al. [33] made the ensuing iterations:

• Clinicians should differentially diagnose the renal metastasis of thyroid follicular carcinoma or papillary carcinoma.

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- Some related literatures had reported that the tumour cells had significant hetero-morphism, several of which had metastasized to lymph nodes or distal organs.
- Its biological behaviour does need to be studied intensively by further expanding the number of cases.

Rao et al. [19] stated the following:

- Thyroid-like follicular carcinoma of the kidney (TLFCK) is a rare subtype of renal cell carcinoma, which closely mimics follicular tumours of the thyroid and has a distinctive indolent clinical behaviour.
- Until 202, a single case of TLFCK with extensive sarcomatoid differentiation had been documented with aggressive clinical course.

Rao et al. [19] reported an unusual case of sarcomatoid TLFCK with a lowgrade spindle cell component in a 34-year-old male patient, that was associated with an indolent course following radical nephrectomy and regional node dissection.

Amin et al. [6] stated the following:

- Thyroidisation of kidney that is reminiscent of thyroid follicles with accumulation of inspissated colloid-like material in renal tubules is a hallmark of chronic pyelonephritis.
- They had identified 6 tumours within the kidney, which is distinct from currently known subtypes of renal cell carcinoma, with a striking histology which closely simulated well-differentiated thyroid follicular neoplasms and which had raised the possibility of metastatic follicular thyroid carcinoma.
- Three occurred in males and 3 in females whose ages had ranged between 29 years and 83 years and size of the tumours had ranged from 1.9 cm to 4 cm.
- All tumours were noted to be encapsulated and had exclusively demonstrated follicular architecture comprising of microfollicles and macrofollicles that contained inspissated colloid-like material.
- A minor component of small tightly packed follicles devoid of secretions was also identified.
- The follicles had been lined by cells that contained moderate amphophilic to eosinophilic cytoplasm with round nuclei and occasional prominent nucleoli.
- The tumours were non-immunoreactive with thyroglobulin and thyroid transcription factor 1 and for markers contemporarily utilised for renal differentiation.
- The tumours had a gene expression profile that was distinct from clear cell and chromophobe renal cell carcinoma.
- Comparative genetic hybridization had failed to demonstrate cytogenetic alterations.
- Mean follow-up of 47.3 months with a follow-up which had ranged between 7 months and 84 months had revealed that 5 patients had no evidence of disease and 1 had developed a metastasis to the renal hilar lymph nodes in which the follicular architecture with colloid was retained.
- Thyroid-like follicular renal cell carcinoma does represent a unique histology subtype of renal cell carcinoma of low malignant potential and its primary importance is for the

clinician to differentiate it from metastatic carcinoma from the thyroid gland.

Chen et al. [34] studied the clinicopathology features of thyroid-like follicular renal cell carcinoma. Chen et al. [34] collected clinical data in 5 cases of thyroid-like follicular renal cell carcinoma. Chen et al. [34] carried out HE staining and immunohistochemistry in surgically-removed specimen to analyse the clinical and pathological features with review of the literatures. Chen et al. [34] summarized the results as follows:

The ages of the patients had ranged between 20 to 55 years, with one male and four females; the tumour had afflicted the left kidney in three cases and the right kidney in two cases. One case had a history of thyroid papillary carcinoma 3 years earlier, and the patient had left flank pain, and visible haematuria for 2 weeks. The remaining four patients had no consciousness of clinical symptoms and signs, without history of thyroid gland surgery; the physical examination demonstrated a mass in the kidney and normal thyroid glands. Three patients had undergone radical nephrectomy, and the other two patients underwent partial nephrectomy of the tumour. The tumours had measured 2 cm to 4 cm in size. The tumours showed a solitary nodular mass that was well circumscribed with taupe and grev appearance on cut surface. Microscopically, most of the tumour cells were noted to be arranged in thyroid follicular pattern in different sizes, with papillary configuration in a small portion, in four cases; the follicular structure was intermixed with the papillary each half in one case. A large amount of thyroid colloid was noted to be deposited within follicle-like structure or papillary axis, that were lined by simple columnar cells or cubic cells, with obvious atypia, ground-glass nuclei, nuclear groove and rare mitosis. Immunohistochemical staining of the tumour had demonstrated that tumour cells had exhibited positive staining for PAX8, and negative staining for thyroid transcription factor 1 (TTF1) and thyroglobulin (Tg). One of five patients had manifested with lymph node metastases (4/4) of renal hilum the same time during the diagnosis. Five cases were followed up for between 5 months to 84 months after the operation, and no tumour progression was identified.

Chen et al. [34] made the ensuing conclusions:

- Thyroid-like follicular renal cell carcinoma is a primary renal epithelial malignant tumour.
- The diagnosis mainly depends upon its typifying histological appearance, namely similar to the histology morphology of well-differentiated thyroid follicular carcinoma and papillary carcinoma, and the metastasis from the thyroid papillary or follicular carcinoma should be excluded.
- Upon the premise of clinical history, immunohistochemical markers TTF1 and Tg have certain value in the differential diagnosis.

Alomar et al. [1] reported the case of a 75-year-old man who had a history of hypertension over the preceding 10 years and who had manifested with difficulty with micturition for two months. He underwent trans-urethral resection of prostate (TURP) and pathology examination of the prostatic chips revealed features of adenocarcinoma of prostate gland. About two weeks pursuant to undergoing the TURP procedure, the patient developed flank pain with visible haematuria and no other associated symptoms. He did not have any family history of abnormalities or tumours. He had only been taking medication to treat his hypertension. His general examination and abdominal examination were normal and he was noted to have voided well. The results of his laboratory blood tests were within normal ranges. He had ultrasound scan of his abdomen which demonstrated presence of a mass within his right kidney that measured about 6 cm \times 6 cm with no other

pathological findings in the abdomen or left kidney. He had Computed tomography (CT) of his abdomen, which revealed presence of a heterogeneous mass within his right kidney that measured $6 \text{ cm} \times 6 \text{ cm} \times 5 \text{ cm}$. No changes were noted in his spine or lungs (see figure 1 A-B).

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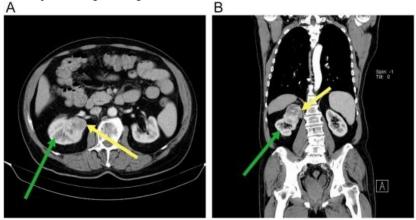


Figure 1. A: CT/cross axial view of the Abdominal showing a mass in the right kidney measuring $6 \times 6 \times 5$ cm, heterogeneous (green arrow shows kidney, yellow arrow shows tumour area). B: CT/cross coronal view, showing the tumour in the upper pole of the right kidney without extension of the renal blood elements (green arrow shows kidney, yellow arrow shows tumour area). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.). Reproduced from: [1] Under Creative Commons Attribution License which allows reproduction of figures and contents of the article provided the original source is cited.

Based upon the previous findings, it was decided that surgery was indicated. The surgery was undertaken at the tertiary teaching hospital of the authors. The surgical procedure was undertaken via a right-sided flank incision at the posterior part of the peritoneum, where the right kidney was exposed and isolated from the encompassing area. The kidney was found to be completely sutured by mass formation, and the vessels of the kidney were connected and radically removed without any complications. Macroscopy examination demonstrated that the tumour was well-defined with a brown focus and haemorrhagic cystic formations (see figure 2 A-B).

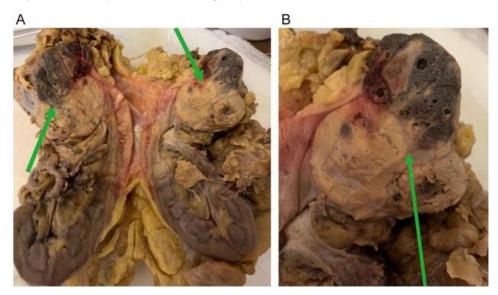


Figure 2 A - B: Macroscopic view of the tumour (green arrow shows tumour area). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) Reproduced from: [1] Under Creative Commons Attribution License which allows reproduction of figures and contents of the article provided the original source is cited.

Histopathology examination of the kidney tumour revealed that the tumour contained follicles of different sizes, which appeared to be follicular formations with colloid-like substances inside (see figure 3 A-B). Immunohistochemistry staining studies demonstrated that the tumour cells

had exhibited Negative staining for: prostate specific antigen (PSA), (see figure 4-A) and TTF1 (see figure 4-B), while the tumour cells had exhibited positive staining for vimentin (see figure 4 -C) and CK7 (see figure 4D).

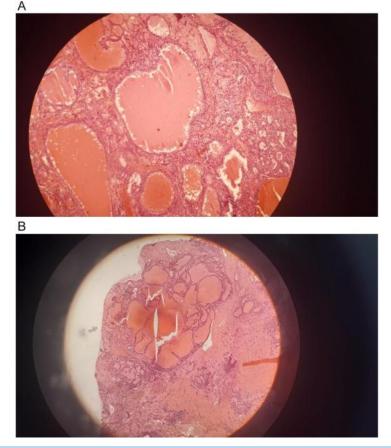


Figure 3. A-B: The follicles appear filled with a fluid like colloid in the area of tumour formation on H&E stain. Reproduced from: [1] Under Creative Commons Attribution License which allows reproduction of figures and contents of the article provided the original source is cited.

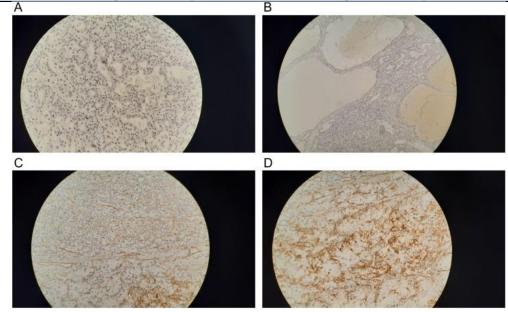


Figure 4. A: Immunohistochemical stain negative for PSA. B: Immunohistochemical stain negative for TTF1. C: Immunohistochemical stain positive for vimentine. D: Immunohistochemical stain positive for CK7. Reproduced from: [1] Under Creative Commons Attribution License which allows reproduction of figures and contents of the article provided the original source is cited.

Alomar et al. [1] made the ensuing educative discussion summations:

• It has been iterated that in order to comprehend the reality of this tumour formation, it is pivotal to know that kidney and renal

pelvis cancer in adults constitute about 4% of all cancers that afflict adults [36]

- The commonest documented type of kidney tumour is renal cell carcinoma (RCC), which alone constitutes about 85 % of all cases of kidney and renal pelvis cancer [5].
- Other types, of kidney and upper urinary tract tumours including transitional cell carcinoma and Wilms' tumour in children, are less common.
- RCC could be classified into many sub-types of kidney tumours including: (a) clear cell renal cell carcinoma, (b) papillary renal cell carcinoma, and (c) other less common types of tumours.
- Clear cell renal cell carcinoma is the commonest sub-type of kidney tumour which does constitute about 60 % of all cases of renal cell carcinoma.
- Thyroid-like follicular RCC is one of the very rare sub-types of RCC which was first described in 2006 [23].
- Women are stated to be more likely to be affected by this tumour in comparison with men, and its is more common in young and middle-aged people, with an average age at the time of initial diagnosis of the tumour documented to be about 43 years [5] [6] [7] [23] [33] [36]
- It has been documented that TLFCKs usually tend to be diagnosed incidentally and they tend to be typically small and confined to the kidney, with the initial diagnosis of rare cases of large kidney tumours. [16]
- It has been iterated that these tumours might be diagnosed in association with the manifestation of some urinary symptoms including: flank pain and visible haematuria, like had been the manifestation in their reported case.
- There had also been a case of reported hypertension that was associated with this tumour. Which had regressed significantly pursuant to the undertaking of tumour surgery. [33]
- Radiology imaging investigations such as ultrasound (US) scan, computed tomography (CT) scan, or magnetic resonance imaging (MRI) scan could be utilized for the identification of the tumour; nevertheless, these radiology imaging options are not reliable as diagnostic imaging tools for TPFCKs because they cannot differentiate TLFCKs from other differential diagnoses.
- CT scan does appear to be the best radiology imaging method for the identification as well as for the description of the radiology imaging features of this tumour.
- Majority of reported cases of TLFCKs had been documented to be unilateral tumours as well as often located within the right kidney.
- It has been documented that these tumours had tended to be located within the middle pole of the kidney and within the peripheral region [33], while in their reported case, it was located within the upper pole of the right kidney.
- Some of the documented differential diagnoses include: metastatic thyroid carcinoma, eosinophilic renal cell tumours, clear cell renal cell carcinoma (RCC), or papillary metastatic thyroid carcinoma arising in the stroma of the ovaries, and carcinoid tumours of the kidney, in addition to thyroidisation. [37]
- The TLFCK and thyroidisation could be differentiated by their pathology examination characteristics.
- TLFCK is a well-defined mass that is found within one kidney, and TLFCK is often diagnosed incidentally, and TLFCK has a thick capsule.
- Many authors had iterated that thyroidisation is often an emanation of end-stage renal disease or pyelonephritis, and it is diffuse as well as bilateral. [5] [6] [7] [16] [23] [33] [35] [36] [37] [38]
- It had been documented that based upon the features of these tumours upon microscopy pathology examination, these tumours tend to be visualised as small to medium-sized follicles that contain an eosinophilic, amorphous, colloid-like substance. These tumours might also be associated with calcifications, psammomas, cholesterol crystals, or haemorrhagic necrosis, as well as some of

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the tumours might demonstrate infiltration of large numbers of lymphocytes. [5] [6] [7] [16] [23] [35] [36]

- It had furthermore been iterated that immunohistochemistry staining studies had demonstrated that the tumour cells of this neoplasm consistently do exhibit positive immunohistochemistry staining for PAX 8, but negative staining for the thyroid-specific markers TG and TTF1. The majority of cases of this tumour had demonstrated that the tumour cells had exhibited positive staining for: CK7, EMA, Vimentin, and CK19. It has been documented that the diagnosis of this tumour is based primarily upon the utilisation of immunohistochemistry staining for PAX8, TG, and TTF1 based upon morphology analysis. [33]
- Surgical treatment is regarded as the main method of treatment for this tumour, either by the undertaking of radical or partial excision.
- It has been pointed out that with regard to tumours that are associated with distant metastases or invasive growth, radical excision is undertaken as treatment, while tumours that measure less than 6 mm in diameter, with a complete capsule and without metastases tend to be treated with partial resection of the tumour or lumpectomy. [33]
- It has been iterated that based upon available data, these tumours portend a low degree of malignancy, a low-recurrence rate, and a low rate of metastasis. [33]
- With regard to their reported case, the right kidney was radically removed, and the patient was followed-up for about one year without finding metastases of the tumour and the patient still had elevated blood pressure
- This tumour is mainly diagnosed based upon the clinical history, histopathology examination features of the kidney tumour as well as the immunohistochemistry staining features of the tumour.

Alomar et al. [1] made the ensuing concluding iterations:

[A] This tumour is mainly diagnosed based upon the clinical history, histopathology examination features of the kidney tumour as well as the immunohistochemistry staining features of the tumour

[B] This tumour has tended to be associated with low rate of malignancy and development of metastases.

[C] Surgical excision is regarded essential in the treatment of this neoplasm.

[D] Surgical removal of the tumour or radical nephrectomy could be undertaken depending upon the case.

Muscara et al. [2] stated that thyroid-like follicular carcinoma of the kidney (TLFCK) is an uncommon but emerging renal tumour which morphologically simulates follicular carcinoma of the thyroid but which lacks immunohistochemistry expression of thyroid tumour markers such as TTF-1 and thyroglobulin. Muscara et al. [2] reported a case of an incidentally discovered TLFCK in a 27-year-old man. Histology examination of the tumour revealed an encapsulated proliferation of variably sized thyroid follicle-like epithelial-lined spaces which had been filled with colloid-like eosinophilic secretions. Immunohistochemistry staining studies of the tumour confirmed lack of expression of the thyroid markers TTF-1 and thyroglobulin with expression of PAX8 and CD10, which confirmed that the tumour was of renal origin, which had correlated with the clinical and radiographic absence of thyroid pathology.

Lin et al. [39] stated that there had only been a few reports of thyroid-like follicular carcinoma of the kidney (TLFCK) up to 2014. Lin et al. [39] reported two patients with TLFCK as follows:

• Patient 1 was a 65-year-old man who had manifested with repeated visible hematuria and right back pain. No tumors were located in the patient's thyroid or lungs. His clinical examination demonstrated percussion tenderness over his right renal region. He had contrast-enhanced computed tomography (CT) scan which demonstrated a right renal pelvic carcinoma, for which the

patient underwent a radical right nephrectomy. Patient 2 was a 59-year-old man who had a mass within his right kidney, that was identified during a health examination and who had reported no obvious clinical symptoms. The patient was clinically diagnosed as having right renal carcinoma, which was confirmed by an enhanced CT scan. The patient underwent a radical right nephrectomy. The clinical features, radiology imaging results, pathology, immune phenotypes, treatment and prognosis were analyzed. The associated literature was also reviewed. The cut surface of each tumor had demonstrated grav-white material with a central solid area, including scattered grav-brown necrotic and gray hemorrhagic areas and small cystic cavities. Microscopically, the arrangement of the tumor cells had simulated thyroid follicles with red-stained colloid-like material in the lumen. No renal hilar lymph node involvement was identified. The tumor tissue of patient 1 had upon immunohistochemistry staining studies exhibited positive staining for: vimentin, epithelial membrane antigen (EMA), cytokeratin (CK), CK7, and neuron specific enolase; and negative staining for: CK34BE12, synapsin (Syn), CK20, cluster of differentiation 56 (CD56), CD10, Wilm's tumor-1 (WT-1), CD34, CD57, P53, CD99, thyroid transcription factor-1 (TTF-1), CD15 and thyroglobulin (TG); with a Ki-67 labeling index (LI) of 30%. The tumor tissue of patient 2 had upon immunohistochemistry staining studies exhibited positive staining for: vimentin, EMA, CK7 and CK20; and negative staining for: CD56, CD10, WT-1, CD34, CD57, P53, CD117, TTF-1, CD15, CD99, TG, chromogranin A and Syn; with a Ki-67 LI of 20%.

Lin et al. [39] made ensuing concluding iterations:

- TLFCK is a rare kidney tumor with low malignancy but medium invasiveness.
- It morphologically simulates thyroid follicular carcinoma but does not express TTF-1 or TG.
- Radical nephrectomy could achieve good patient outcomes.

de Jesus et al., [40] stated that the very rare thyroid-like carcinoma of the kidney (TLCK) is microscopically similar to thyroid follicular cell carcinoma (TFCC) and that differential diagnosis with secondary thyroid tumours depends upon non-reactivity to immunohistochemical (IHC) tumour markers for TFCC (thyroglobulin - TG and TTF1). de Jesus et al. [40] reported the fourth paediatric case in the global literature and extensively reviewed the subject. de Jesus et al. [40] made the ensuing iterations:

- Only 29 cases were published in the literature by July 2019.
- Majority of TFCC cases were asymptomatic and they were incidentally detected.
- Majority of the tumours are hyperechoic and hyperdense with low grade heterogenous enhancement on computed tomography (CT) scan and magnetic resonance imaging (MRI) scan.
- Most of the patients were treated by means of radical nephrectomy, but partial nephrectomy was undertaken in some cases, apparently with the same results.
- Metastases development tends to be uncommon and apparently do not change the prognosis of patients, but follow-ups of the patients are limited.
- Up to the moment, TLCK manifests as a low-grade malignancy that may be treated exclusively with surgery and frequently with partial kidney renal preservation.
- A preoperative percutaneous biopsy is a common procedure to investigate atypical tumours in childhood and adult tumours.
- To recognize the possibility of TLCK is fundamental in order to avoid unnecessary thyroidectomies in those patients, supposing a primary thyroid tumour.

Dhillon et al. [16] stated the following:

- Thyroid-like follicular carcinoma of the kidney is an extremely uncommon variant of renal cell carcinoma.
- Most previously reported cases had manifested as incidental small tumours that were confined to the kidney.

Dhillon et al. [16] reported a unique case in which the patient had presented with flank pain and visible haematuria. Radiology imaging studies had shown a large tumour within the right kidney and metastases to the lungs and retroperitoneal lymph nodes. Both the renal tumour and the sampled lung metastasis were found upon pathology examination to be composed almost entirely of follicles with dense, colloid-like material mimicking thyroid follicular carcinoma. Nevertheless, no lesion was found in the thyroid gland; and the patient's thyroid function test results were normal. The tumour cells upon immunohistochemistry staining studies were found to be immunoreactive for PAX2 and PAX8 but lacked reactivity for thyroglobulin and thyroid transcription factor-1. Dhillon et al. [16] stated that to their knowledge, their reported case was the first case of thyroid-like follicular carcinoma of the kidney to be initially associated with marked symptoms and widespread metastases, providing evidence that this rare variant of renal cell carcinoma could be clinically aggressive.

Ni et al. [41] stated that thyroid-like follicular renal cell carcinoma is a rare subtype of renal cell carcinoma which had only been recently recognized, as most of the cases had involved a solid tumour within one kidney. Ni et al. [41] reported a rare case of bilateral renal cell carcinoma wherein the tumour within the left kidney was diagnosed as clear cell carcinoma, while the tumour within right kidney as thyroid-like follicular renal cell carcinoma. Ni et al. [41] iterated that the difference between this case and the ones that had been described in previous reports is that thyroid-like follicular renal cell carcinoma had shown cystic changes upon radiology imaging. Ni et al. [41] also stated that this suggests that when renal cystic lesions are encountered, clinicians should consider the possibility of such rare tumours.

Jenkins et al. [7] stated the following:

- Thyroid-like follicular carcinoma of the kidney (TLFCK) is an extremely rare primary renal malignancy that typically portends an indolent course and good prognosis.
- Histologically, this tumour simulates follicular carcinoma of the thyroid gland; nevertheless, typical thyroid markers are negative.
- By 2019, there were fewer than 40 cases reported in the literature, and thus, the prognosis and course of disease is not well understood.
- Sarcomatoid differentiation had never been reported in a case of TLFCK.

Jenkins et al. [7] reported a case of a 48-year-old lady who had an aggressive TLFCK with extensive sarcomatoid differentiation and metastatic disease at manifestation. Jenkins et al. [7] undertook targeted next-generation sequencing of both the thyroid-like component and the poorly differentiated sarcomatoid component utilising their solid tumour panel to evaluate for any disease-associated mutations and to better understand the molecular profile of these tumours.

Conclusions and Recommendations

- Primary thyroid follicular-like carcinoma of the kidney (PTLFCK) is a very rare tumour which has been sporadically reported in the global literature.
- Most cases of reported PTLFCK had been diagnosed incidentally by the finding of a lesion during radiology image assessment for other conditions by means of ultrasound scan, computed tomography scan or magnetic resonance imaging scan because majority of cases of PTLFCK tend to be asymptomatic
- On rare occasions, PTLFCK may manifest with visible haematuria or loin pain.

- Diagnosis of PTLFCT is confirmed based upon histopathology and immunohistochemistry examination features of the tumour. Even though microscopy pathology examination features of PTLFCK simulate that of follicular carcinoma of thyroid gland, the immunohistochemistry staining features of these aforementioned two types of tumours are different.
- Most cases of PTLFCT are diagnosed as localized tumours that afflict one kidney and following their treatment by partial nephrectomy or radical nephrectomy, the development of local recurrence or distant metastases subsequently had not been common.
- Nevertheless, few cases of PTLFCK may be ensued by the development of metastases subsequently a long time after the initial diagnosis
- Even though PTLFCK generally tends to be associated with a non-aggressive biological behaviour, because few cases of development of metastasis a long time after diagnosis and treatment of the primary tumour, it would be important that clinicians who treat patients for PTLFCK, should follow-up their patients for a long-time over regular periods in order to identify any recurrent or metastatic tumour early to enable the undertaking of early subsequent treatment with curative intent
- In order not to misdiagnose PTLFCK, a high index of suspicion is required to be exercised by all pathologists, radiologists, and urologists.
- Some of the documented differential diagnoses of PTLFCT include: metastatic thyroid carcinoma, eosinophilic renal cell tumours, clear cell renal cell carcinoma (RCC), or papillary metastatic thyroid carcinoma with the primary tumour arising in the stroma of the ovaries, and carcinoid tumours of the kidney, in addition to thyroidisation.

Conflict of Interest - nil

Acknowledgements

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