Case Report

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Tuberous Sclerosis Complex Associated Renal Cell Carcinoma with Leiomyomatous Stroma

Pathology Section

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ABSTRACT

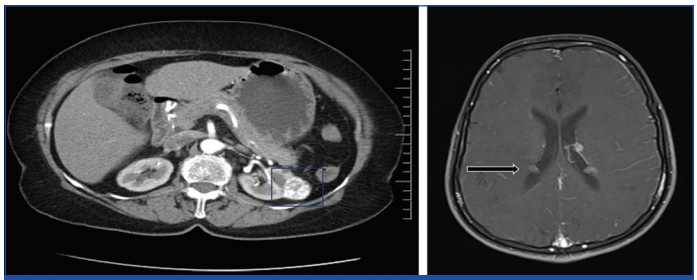
This case report is about an unusual subtype of renal cell carcinoma with distinct morphological pattern in a 24-year-old female patient with tuberous sclerosis complex. She presented with pain in the left flank and an Magnetic Resonance Imaging (MRI) upper abdomen showed a solid cystic lesion in the interpolar region of left kidney, measuring 2.8×2.8×2.8 cm. She underwent partial nephrectomy which revealed a solid cystic tumour. Microscopically, the tumour was composed of long branching tubules lined by cells with voluminous clear/vacuolated cytoplasm. A prominent fibromyomatous stroma was seen focally, separating the tumour into nodular aggregates. Tumour cells were positive for Cytokeratin 7 (CK7) on immunohistochemical study. These features were consistent with renal cell carcinoma with leiomyomatous stroma. Genetic study showed a heterozygous non sense variation in Tuberous Sclerosis 1 (TSC1), gene, diagnostic of tuberous sclerosis. This report exemplifies the pivotal role pathologists play in the initial identification of certain hereditary cancer syndrome. The distinct morphology and immunohistochemical profile of the tumour is described.

Keywords: Abdomen, Cytokeratin 7, Kidney, Nephrectomy

CASE REPORT

A 24-year-old female patient presented with left flank pain and microscopic haematuria for the past five months. She gave a history of seizures from the age of 10 years and multiple recurring skin lesions on the face. Patient denied a history of similar illness in other family members.

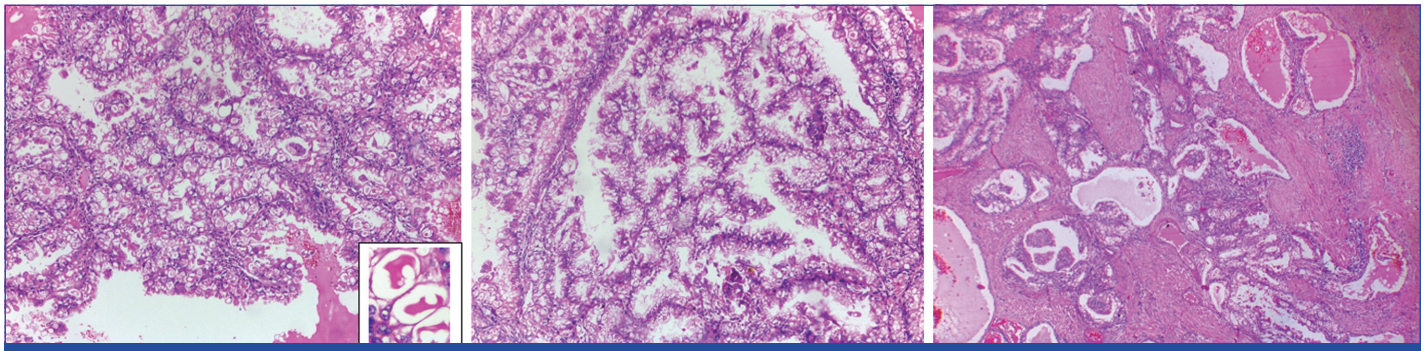
Computed Tomography (CT) scan of upper abdomen showed a solid cystic lesion in the interpolar region of left kidney, measuring 2.8×2.8×2.8 cm [Table/Fig-1]. MRI scan of the brain showed tiny enhancing subependymal nodules and radial bands in the juxtacortical white matter region [Table/Fig-2], which were consistent with precursor lesions of subependymal giant cell astrocytoma. She underwent partial nephrectomy which revealed a solid cystic tumour, measuring 3×3×3 cm. The patient had visited after nephrectomy for a second opinion from the oncologist who then requested the Pathology Department to review the histopathology slides.



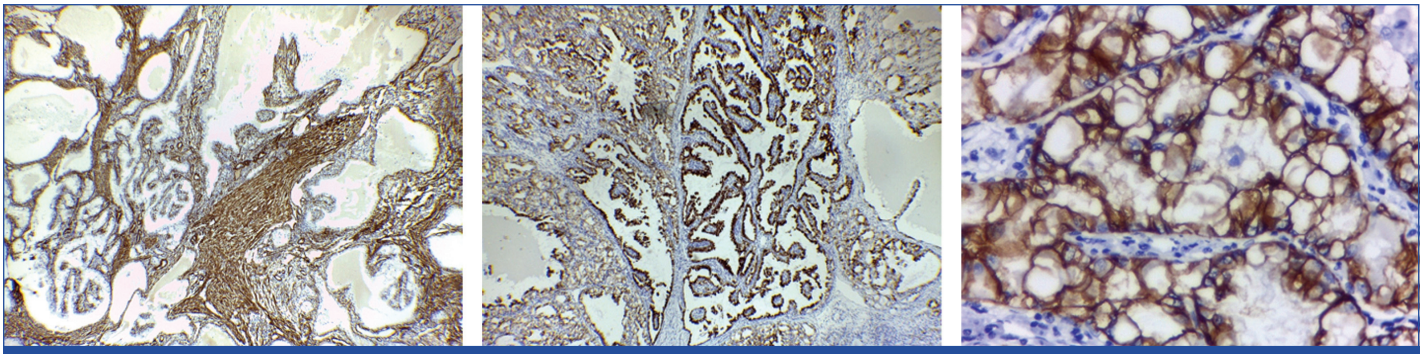
[Table/Fig-1]: Computed tomography scan abdomen showing a tumour located in the left kidney. **[Table/Fig-2]:** MRI brain showing subependymal nodules in the juxtacortical white matter. (Images from left to right)

Microscopically, the tumour was composed of long branching tubules lined by cells with voluminous clear/vacuolated cytoplasm [Table/Fig-3]. Several intracytoplasmic globules were observed. Focal papillary pattern with slender fibrovascular cores [Table/Fig-4] and in places, tightly packed tubules lined by low grade clear cells resembling clear cell papillary renal cell tumour but without the characteristic abluminal arrangement of nuclei were noted. A prominent fibromyomatous stroma was seen focally, separating the tumour into nodular aggregates [Table/Fig-5,6]. Immunohistochemical study showed diffuse Cytokeratin 7 (CK7) [Table/Fig-7] and Carbonic Anhydrase IX (CAIX) staining, the latter with a complete circumferential membranous pattern [Table/Fig-8]. Cluster Differentiation 10 (CD10) was focally positive. Alpha-methylacyl-CoA racemase (AMACR) and Cytokeratin 20 (CK20) were negative. Based on these findings, a provisional diagnosis of renal cell carcinoma with tubulopapillary pattern and fibromyomatous stroma was offered with an advice for further detailed work up. The tumour was confined within the kidney, TNM stage pT1a.

Considering the young age of the patient, unusual morphology of the tumour and brain lesions on MRI study, genetic study was done which confirmed a heterozygous non sense variation in TSC1 gene involving exon 5 with autosomal dominant inheritance pattern that



[Table/Fig-3]: Elongated branching tubules lined by cells with voluminous clear cytoplasm with several intracytoplasmic globules (inset) (H&E, 40X).
[Table/Fig-4]: Focal papillary pattern with thin fibrovascular cores (H&E, 40X).
[Table/Fig-5]: Nodular aggregates of tumour cells separated by leiomyomatous stroma (H&E, 20X). (Images from left to right)



[Table/Fig-6]: Immunohistochemical stain for smooth muscle actin (PathnSitu) highlighting smooth muscle stroma separating tumour nodules (Bond Polymer refine detection method using Leica BOND MAX fully automated IHC machine, 20X). **[Table/Fig-7]:** Immunohistochemical staining with CK7 (PathnSitu) showing diffuse positive staining (Bond Polymer refine detection method using Leica BOND MAX fully automated IHC machine, 20X). **[Table/Fig-8]:** Immunohistochemical staining with CAIX (Quartett) showing complete circumferential membranous staining pattern (Bond Polymer refine detection method using Leica BOND MAX fully automated IHC machine, 40X). (Images from left to right)

results in a stop codon and premature truncation of the protein at codon 79. A final diagnosis of tuberous sclerosis complex associated renal cell carcinoma with leiomyomatous stroma was rendered.

DISCUSSION

The 2016 World Health Organisation (WHO) classification of renal epithelial neoplasia includes several emerging/provisional entities, one of which is Renal Cell Carcinoma with Leiomyomatous Stroma (RCCLMS), described as a distinct subtype occurring either sporadically or associated with Tuberous Sclerosis (TSC) [1]. It is characterised by branching tubules and papillae lined by cells with voluminous clear cytoplasm and focal to prominent smooth muscle and fibrous stromal component [2]. It closely resembles Renal Angiomyoadenomatous Tumour (RAT), another tumour having prominent leiomyomatous stroma which is now considered as a morphological variation of clear cell papillary renal cell tumour due to considerable overlap between the two [2].

The association of RCCLMS with TSC originated from the observations in two large studies by Guo J et al., and Yang P et al., [3,4]. Guo J et al., reported a series of Renal Cell Carcinomas (RCCs) occurring in TSC patients, of which 30% had features similar to tumours previously described as "RAT" and therefore termed "RAT" like. In a separate series of TSC-associated RCC, Yang P et al., used the term "TSC-associated RCC with prominent papillary structure" to describe morphologically identical tumours composed of large clear cells with fine eosinophilic thread-like strands in the cytoplasm and diffuse immunoreactivity for CK7, CD10 and CAIX [4]. Subsequently, Hakimi AA et al., described tumours with similar morphology occurring in patients without TSC and associated with hotspot mutations in TCEB1 (ELOC) [5]. All tumours lacked the 3p loss characteristic of clear cell RCC. Recently, Shah RB et al., reported the clinicopathologic, immunohistochemical, and molecular characteristics of 18 sporadic RCCs with similar morphology, harbouring recurrent mutations of TSC1/TSC2, MTOR, and/or ELOC and without Von Hippel-Lindau (VHL) gene mutations or other copy number alterations associated with other subtypes of RCC [2]. Based on these findings, they hypothesised that RCCLMS is a novel subtype of RCC that occurs in sporadic setting which is identical to both the subsets of RCCs described in patients with TSC (described as "RAT-like" and "TSC-associated papillary"), and the recently described sporadic RCCs with ELOC mutation but distinct from clear cell RCC and clear cell papillary renal cell tumour. Parilla M et al., also recently reported three similar sporadic cases associated with genetic alterations in either TSC1 or TSC2 [6].

The index case showed identical morphology as described in these reported cases, composed of nodular aggregates of long branching tubules lined by cells with voluminous clear/vacuolated cytoplasm and focal prominent fibromyomatous stroma. Tumour cells were diffusely positive for CK7 and CAIX. Patient had other features of tuberous sclerosis complex and showed genetic alterations in TSC1 gene.

The RCCLMS should be differentiated from other RCCs showing leiomyomatous stroma, mainly clear cell RCC, papillary RCC, clear cell papillary renal cell tumour and translocation RCC. The characteristic morphology allows distinction from other RCC subtypes in most cases. It is also characterised by complete membranous CAIX staining pattern and diffuse CK7 expression, the latter being unusual in clear cell RCC.

Most reported RCCLMS were associated with an indolent behaviour except one case with a single lymph node metastasis [2]. Therefore, additional studies are needed to fully characterise the biological behaviour of this group of tumours. No recurrence/metastases has developed in the index case over the short follow-up period of one year.

Renal cell carcinoma associated with alterations in TSC genes encompasses a broad histological spectrum and has been described under different terminologies. One such tumour Eosinophilic Solid and Cystic (ESC) RCC has now been accepted as a separate entity in the 2022 WHO classification of renal epithelial neoplasia [7]. It is characterised by solid and cystic architecture, polygonal neoplastic cells with voluminous eosinophilic cytoplasm, basophilic cytoplasmic stippling, and frequent patchy immunoreactivity for cytokeratin 20 [8-11]. Other tumours associated with TSC gene alterations such as Eosinophilic Vacuolated Tumour (EVT) and low grade oncocytic tumour (LOT) are considered as emerging entities under the category of "other oncocytic/chromophobe RCC" [12-14]. ELOC mutated RCC which has a similar morphology to RCCLMS is also included in the 2022 WHO classification as a prototype of a molecularly based RCC subtype [7].

CONCLUSION(S)

Here, a distinct subtype of RCC with specific morphology that occurs in the setting of TSC is described. Despite distinct molecular features, a careful morphologic analysis, along with the diffuse CK7 positivity, is sufficient for an accurate diagnosis in vast majority of the cases. Pathologists should be aware of the expanding spectrum of RCC subtypes and their association with several hereditary renal neoplasia since it helps to guide the clinicians for performing specific molecular testing that has potential role in the development of targeted therapies.

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