

Review Article

Renal cell carcinoma with leiomyomatous stroma: a review of an emerging entity distinct from clear cell conventional renal cell carcinoma

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Abstract: Clear cell renal cell carcinomas accounts for 65 to 75% of all malignant renal tumors. The International Society of Urological Pathology 2012 Vancouver Classification of renal neoplasia and the World Health Organization 2016 Classification of renal tumors have included renal cell carcinoma with leiomyomatous stroma in a category of emerging/provisional entities of renal cell carcinoma. Macroscopically, renal cell carcinomas with leiomyomatous stroma are well circumscribed tumors with a cut surface of gray-white fibrotic tissues. Microscopically, the tumors are composed of nodules and anastomosing tubules of renal cells with clear cytoplasm. The carcinoma cells are embedded in a cellular stroma composed of intertwining bundles of smooth muscle. Immunohistochemically, the neoplastic cells are typically positive for CK7 and CD10 immunomarkers. Biomarkers including CAIX, pankeratin, vimentin, and HIF1-alpha stain positively in many renal cell carcinomas with leiomyomatous stroma. Molecular genetic studies of this variant of tumor reveal no *VHL* mutation, trisomy 7 or trisomy 17. However, a *TCEB1* mutation has been demonstrated in a subset of tumors and rare cases are reported from patients with a family history of tuberous sclerosis. The biological behavior of this variant of tumor is indolent and the prognosis is favorable.

Keywords: Renal cell carcinoma, leiomyomatous stroma, smooth muscle stroma

Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of cancer cases in adults and rarely occurs in children [1]. Renal neoplasms occur more often in North America and northern Europe and are uncommonly found in Asia and South America [1, 2]. RCCs affect males more than females in a ratio of approximately 2 to 1 [1, 2]. Clinically, many patients remain asymptomatic and most RCCs are diagnosed in patients who undergoing radiologic imaging studies for unrelated medical conditions. The classical triad of hematuria, tumor mass, and flank pain occurs in less than one third of the patients. RCCs are thought to arise from renal tubular cells and the majority of RCCs are clear cell RCC accounting for 65% to 75% of all malignant renal tumors [3, 4]. A subset of RCC with clear cells and leiomyomatous stroma (RCCLS) has been described by Kuhn *et al.* in

2006 and Shannon *et al.* in 2009 [5, 6]. The International Society of Urological Pathology (ISUP) 2012 Vancouver Classification of renal neoplasia and the World Health Organization (WHO) 2016 Classification of renal tumors include RCCLS in a category of emerging/provisional entities of RCC [3, 4]. In 64 cases of RCCLS, 56 tumors had unique morphological features, immunohistochemical data, and molecular genetic findings [5, 8-17]. RCCs lacking chromosome 3p deletion or *VHL* hypermethylation or mutation are considered distinctive variants of RCC [5, 7].

Clinical features

Patients with RCCLS range in age from 31 to 79 years old. There is no gender predominance. The majority of tumors measure from 0.6 to 5.0 cm. The right kidney is affected as common as the left. Most RCCLSs are confined to the kid-

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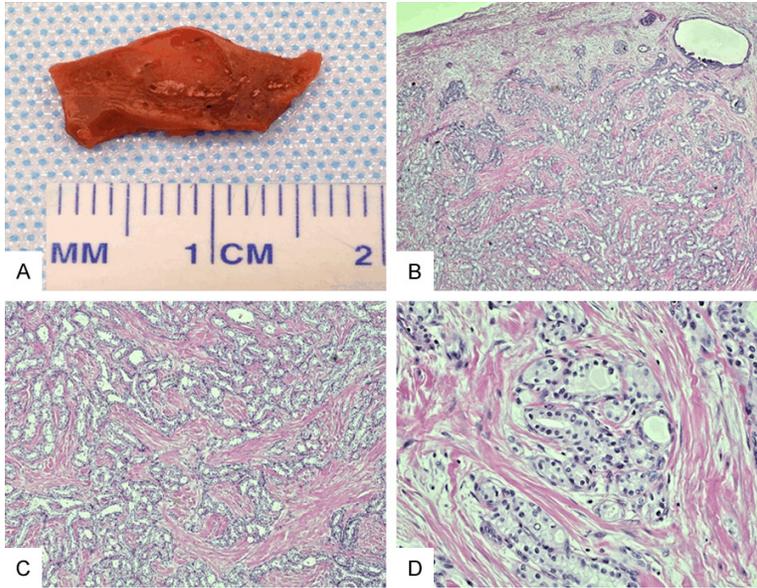


Figure 1. Morphological features of R CCLS. A. Grossly, the tumor is well circumscribed and has a cut surface of solid gray-white and fibrotic, which mimicked that of a leiomyoma or fibroma. B and C. The tumor is composed of small nodules and anastomosing tubules of renal epithelial cells (hematoxylin and eosin, 100 \times and 200 \times). D. Tumor nodules are encircled by a capillary network embedded in a cellular stroma composed of intertwining bundles of benign smooth muscles (hematoxylin and eosin, 400 \times).

neys and most patients have stage pT1a tumors [5, 8-17]. There was a single case report of familial RCCLS associated with an atypical tuberous sclerosis complex [17]. No other clinical syndromic association was found. The prognosis of the patients was generally good. Of the 42 patients reported in the literature, 41 were alive and 18 patients showing no tumor recurrence over 2 months to 11 years. One patient did not survive because of metastatic breast cancer and another patient had either tumor metastasis to the pancreas or a primary pancreatic neoplasm [5, 16].

Pathologic features

Macroscopically, RCCLS demonstrated a well-circumscribed non-encapsulated tumor with diameters ranged from 0.8 to 5.0 cm. The cut surface was homogeneously solid white and fibrotic (**Figure 1A**). Multiple grayish white trabeculae arranged in a crisscross pattern were observed on the surface of the tumor that seemed to be easily detachable from the peripheral uninvolved parenchymal tissue. There were no yellow-tan or hemorrhagic areas as typically seen in clear cell conventional RCC. No tumor necrosis was noted. The gross

appearance of this tumor mimicked that of a leiomyoma or fibroma (**Figure 1A**).

Microscopically, RCCLS showed a well circumscribed tumor composed of small nests and nodules of renal epithelial cells encircled by a capillary network embedded in a cellular stroma composed of intertwining bundles of spindle cells of benign smooth muscles (**Figure 1B** and **1C**). The renal epithelial cells had clear cytoplasm (**Figure 1D**). Cellular nuclei were usually grade 2 by WHO/ISUP histologic grading system for clear cell RCC and papillary RCC (**Figure 1D**). No hyaline globules were present in the cytoplasm of tumor cells (**Figure 1D**). Fascicles of crisscrossed smooth muscles were most prominent at the tumor edges (**Figure 1B-D**). There was no

sinusoidal pattern with branching vessels seen in RCCLS. In addition, no tumor necrosis or mitotic figures in the epithelial and spindle cell components of the tumor was described.

Immunohistochemically, the neoplastic epithelial cells of RCCLS were positive for CK7 and CD10 (**Figure 2A** and **2B**). Other immunomarkers, CAIX, pankeratin, vimentin, and HIF1-alpha stained positively, as reported in the majority of RCCLSs published in the literature (**Table 1**). The smooth muscle cells were highlighted by smooth muscle actin and muscle specific-actin (**Figure 2C**). HMB-45, MART-1, MiTF, and RCC immunomarkers were negative. The morphology and immunohistochemical studies were consistent with RCCLS.

Molecular genetic studies included VHL status, copy number and morphological changes of chromosomes 7 and 17 were thoroughly investigated in RCCs [8, 9, 11-13]. Since VHL aberrations and trisomy 7 and trisomy 17 defined clear cell conventional RCC and papillary RCC, respectively, only those clear cell renal neoplasms with absence of the above molecular findings were considered a distinct entity of RCCLS (**Table 1**). While there was no consen-

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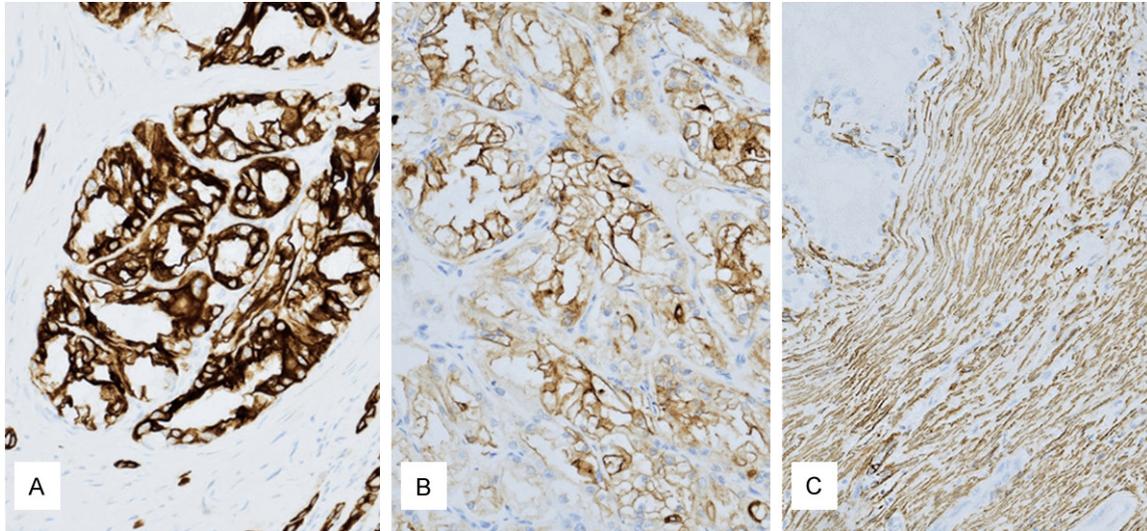


Figure 2. Immunohistochemical features of RCCLS. A. Neoplastic renal epithelial cells show positive membranous and cytoplasmic staining of CK7 immunohistochemical marker (immunoperoxidase stain, 200 \times). B. CD10 immunomarker shows positive membranous staining in the renal epithelial cells. (immunoperoxidase stain, 200 \times). C. Smooth muscle actin immunomarker highlights the intertwining bundles of benign smooth muscles (immunoperoxidase stain, 200 \times).

sus of any definitive gene mutation, *TCEB1* mutation was reported in 14 of 18 RCCLS [12, 16]. Sporadic *TSC1* and *TSC2* mutation were found in 4 of 7 RCCLS [16]. Another study demonstrated that *TSC1* mutation and *TSC2* alterations included gene mutations and allelic imbalance was discovered in 5 RCCLS from 2 patients with a family history of tuberous sclerosis [16]. Other genes of which mutations were found included *TPR*, *PIK3C2b*, *CSF1R*, *PDGFR*, *FANCA*, *EPHB1*, *ROS1*, *SAMD9*, *MET*, *CCNE1*, *BCR*, *MN1*, *KDM6A* [13].

Discussion

Renal neoplasms with clear cells and smooth muscle differentiation are observed in various types of renal cell carcinoma (RCC) including clear cell conventional RCC, papillary RCC, clear cell papillary RCC, and translocation-associated RCC [6, 18-20]. Smooth muscle component is also present in renal angiomyoadenomatous tumor (RAT) [18]. Many of these renal tumors could be distinguished by the morphology and arrangement of clear cells and the quantity of intratumoral and intracapsular smooth muscles [3, 4].

RCCLS and clear cell papillary RCC/RAT

Clear cell papillary RCC and RAT demonstrate very similar morphologic and immunohisto-

chemical features [19]. The renal epithelial cells in both entities are positive for CK7 and their leiomyomatous stroma can be highlighted by smooth muscle actin and muscle specific-actin. Although the quantity of smooth muscle component was not defined for RAT, RAT usually contains voluminous smooth muscle stroma more than that in clear cell papillary RCC. Since the leiomyomatous component present in RCCs is found to be polyclonal in nature, both clear cell papillary RCC and RAT are considered as two related tumors represented two ends of the spectrum of a unique entity [10, 19]. Although the tumors composed of clear renal cells, low-grade and basally located nuclei typically are seen in clear cell papillary RCC, these features are not present in RCCLS. In addition, the amount of the leiomyomatous component noted in RCCLS is voluminous when compare to that of clear cell papillary RCC. The malignant epithelial cellular features of RCCLS can easily distinguish this tumor from RAT.

RCCLS and clear cell conventional RCC

Macroscopically, the cut surface of RCCLS shows solid white tissue with a “leiomyoma-like” appearance in contrast to variegated brown to golden yellow areas with hemorrhage or necrosis typically seen in clear cell RCC. Histopathologically, the majority of clear cell

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Table 1. Summary of immunohistochemical and molecular features of RCCLS

Number of cases	Immunohistochemical stains	Molecular findings	References
5	CK7+ (1/1), AE1/AE3+ (3/5) EMA+ (3/3), HHF35+ (3/3), Vimentin+ (4/4), RCC+ (1/2), CAM5.2+ (3/5), HMB-45- melanA-, mart-1-	NA	Kuhn et al. [5]
3	CK7+ (3/3), AE1/AE3+ (3/3) 34BE12+ (3/3), CAIX+ (2/3) CD10+ (1/3), GLUT1+ (3/3) S100+ (2/3), AMACR-, vimentin-	3p deletion (0/3) VHL mutation (0/3) VHL methylation (0/3) VHL copy number changes (0/3)	Martinoni et al. [8]
5	CK7+ (3/5), CD10+ (5/5), CAIX+ (5/5), vimentin+ (5/5)	Absence of VHL mutation hypermethylation, LOH3p (5/5) CEP7, CEP17 disomy (5/5) No TCEB mutation (4/5)	Pecova et al. [9]
11	CAIX+, CK7+, CD10+ 34BE12, PAX8+, AMACR+	No 3p deletion by FISH CEP7, CEP17 disomy	Williamson et al. [11]
11	CAIX+ (8/8) HIF-1alpha+ (8/8) CK7+ (8/8) CD10+ (7/8)	TCEB1 mutation (11/11) no VHL mutation, no 3p LOH no PBRM mutation (0/11) Chr 5 trisomy (1/11), no chr9p loss Chr7 gain (4/11), 5q amp (0/11) Chr5 trisomy (1/11), no chr14 loss	Hakimi et al. [12]
6	NA	Absence of VHL mutation, hypermethylation, LOH3p (6/6) CEP7, CEP17 disomy No TCEB mutation (2/2) Gene mutation: TPR, PIK3C2b, CSF1R, PDGFR, FANCA (1/2) EPHB1, ROS1, SAMD9, MET, CCNE1, BCR, MN1, KDM6A (1/2)	Petersson et al. [13]
1	CK7+, pankeratin+, SMA, desmin+ (in stroma)	NA	Kiremit et al. [14]
2	MNF117+, PAX8+, CK7+ 34BE12-, CD10-, WT1-, HMB-45-	NA	Massaeli et al. [15]
15	CK7+ (7/7), CD10+ (7/7) CAIX+ (7/7)	TCEB1 mutation (3/7) TSC1 (2/7), TSC2 (2/7)	Parilla et al. [16]
2	CK7+ (1/1), CD10+ (1/1) CAIX+ (1/1), vimentin+ (1/1)	TSC2 alteration	Bah et al. [17]

Abbreviations: NA: not available; LOH: loss of heterozygosity; chr: chromosome; amp: amplification.

RCCs are composed of widely trabecular and small nests of clear cells with interconnecting capillary or prominent sinusoidal vasculature (acinar and alveolar pattern) [3, 4]. Other areas of tumor showed dilated acinar structures with microcyst and macrocyst formation. Neither alveolar nor acinar pattern of clear cell RCC is seen in RCCLS. The intracytoplasmic hyaline globules and acidophilic inclusions described in clear cell RCC are not identified in the clear cells of RCCLS [3, 4]. In addition, the proliferating leiomyomatous stroma admixed thoroughly with carcinoma cells in this case argued against the possibilities of focal smooth muscle differentiation in clear cell RCCs. Moreover, the posi-

tive results of VHL mutation, hypermethylation, and loss of heterozygosity (LOH) 3p and negative findings of the above genetic changes could be used to distinguish clear cell RCC from RCCLS [8, 11].

RCCLS and papillary RCC

Many papillary RCCs have a cut surface of variegated red-brown to golden-yellow fragile tissue with somewhat "granular" appearance. Occasionally, a fibrous capsule is seen. Intratumoral hemorrhage and necrosis are noted in two thirds of cases. Microscopically papillary RCCs shows eosinophilic and clear cells cover-

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ing the surface of branching fibrovascular cores (papillary pattern), which is not seen in RCCLS [3, 4, 18]. Although papillary may have fibromuscular stroma, the amount of smooth muscle is much less than that of RCCLS [18].

RCCLS and MiT family translocation RCC

MiT family translocation RCCs consists of Xp11 and t(6;11) translocation RCCs. Either Xp11 or t(6;11) RCC is composed of voluminous renal cells with optically clear cytoplasm [20]. Distinctive papillary structure is typically seen in Xp11 [20]. A biphasic pattern with large epitheloid cells and clusters of smaller cells associated with basement membrane material are characteristics for t(6;11) RCCs [20, 21]. These morphological features and the specific loci of chromosomal translocations are not present in the newly proposed entity of RCCLS [20, 21].

Loss of chromosome 3p or *VHL* hypermethylation leading to inactivation of *VHL* or *FHIT* gene has been proposed in the pathogenesis of clear cell conventional RCC. The activation of hypoxia-inducible factor (*HIF*) and overexpression of its down-stream regulatory genes, including *VEGF*, plays a major role in the survival and growth of the tumors. Absence of *VHL* mutation, *VHL* hypermethylation, or LOH 3p have been consistently reported in several series of studies [8, 9, 11-13]. *TCEB1* mutation has been found a subset of RCCLS and an alternative route of cell signaling is suggested in the tumorigenesis of RCCLS [12]. *TCEB1* encodes an elongin C protein which interacts with elongin B and regulates elongin A in stabilizing the transcription activities of transcription factor B complex. The transcription factor B complex can bind to VHL suppressor protein and inhibit HIF1- α that suppresses cell survival and growth eventually. In RCCLS, it has been proposed that *TCEB1* mutation leads to the production of dysfunctional elongin C protein and subsequently deregulates transcription activities of transcription factor B complex. As a result, the binding and suppression action of VHL protein is disrupted and leads to activation of HIF1- α protein and promotion of the survival and growth of RCCLS.

Conclusion

Clear cell RCCs with leiomyomatous stroma is a rare and distinct entity of RCC. Documented cases and other tumors with similar morpholo-

gy that may have been interpreted as different entities have been reported in the literature. The biological behavior of this type of tumor is indolent and the prognosis is favorable. Clinical follow-up of many patients did not reveal tumor recurrence. Further studies using a laser-captured microdissection technique and fluorescent in-situ hybridization and next generation gene sequencing performed on frozen fresh tissues or formalin-fixed paraffin embedded tumor tissues are necessary to explore the molecular abnormalities of this peculiar entity of clear cell RCC.

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Disclosure of conflict of interest

None.

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