Case Report

Clear-cell variant renal cell carcinoma with leiomyomatous stroma: World Health Organization new entity

Gagan Kumar Rangari, Neeraj Dhameja, Manjula Lader, Mary June Nongphud, Sameer Trivedi

Departments of Pathology and Urology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Abstract

Renal cell carcinoma (RCC) represents about 3% of all newly diagnosed cancers in the United States and accounts for 85% of renal cancers in adults. These are approximately 65,000 new cases per year and 13,000 deaths from the disease. RCC with leiomyomatous stroma is an emerging entity. The risk factor and etiology of RCC were obesity, smoking, hypertension, acquired cystic kidney disease, and occupational exposure like trichloroethylene. Most of the RCC are sporadic, 2%–4% have a familial cause. In this study, 62 years' male patient comes with flank pain, flank mass on the right side, and hematuria, on imaging shows solid and homogeneous to heterogeneous with cystic area and hemorrhage. Histopathological features show the nest of tumor cells with clear cytoplasm arranged in an alveolar and acinar pattern having conspicuous nucleoli surrounded by abundant vascular and smooth muscle stroma. On the basis of histological and immunohistochemistry studies, findings were suggestive of clear-cell RCC Grade 2 with leiomyomatous stroma.

Keywords: Clear cell carcinoma, immunohistochemistry, leiomyomatous stroma, renal cell carcinoma, VHL gene

Address for correspondence: Dr. Gagan Kumar Rangari, Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Semicircle Road Number 4, Varanasi - 221 005, Uttar Pradesh, India.
E-mail: gagan13690@gmail.com

Submitted: 06-Jan-2021 **Accepted:** 03-Feb-2021 **Published:** 22-Dec-2021

INTRODUCTION

Renal cell carcinoma (RCC) is generally a tumor of an adult, the average age at diagnosis is 55–60 years. The male-to-female ratio was 2:1. Cigarette smoking, obesity, and hypertension are the most common risk factors for sporadic RCC worldwide. RCC usually presents with hematuria, flank pain, and abdominal mass. Clear-cell RCC (CCRCC) is the commo subtype of RCC, 65%–70% of all renal cancers. CCRCC morphologically heterogeneous group of malignant neoplasms composed of cells with clear or eosinophilic cytoplasm. These neoplasms have typical vessel formation and a characteristic molecular background.Clear cell renal cell carcinoma with leiomyomatous stroma is a rare histopathological entity and the World Health Organization (WHO) has kept it as a provisional entity. These tumors occur sporadically and have been associated with tuberous sclerosis. The tumor does not show loss of VHL or 3p deletion or trisomy 7 or 17. Recent cases associated with transcription elongation factor B, polypeptide 1 (TCEB1) gene mutation with RCC morphology.[1,2]

Access this article online	
Quick Response Code:	Website: www.ijcpc.org
	DOI: 10.4103/ijcpc.ijcpc_1_21

How to cite this article: Rangari GK, Dhameja N, Lader M, Nongphud MJ, Trivedi S. Clear-cell variant renal cell carcinoma with leiomyomatous stroma: World Health Organization new entity. Int J Clinicopathol Correl 2021;5:74-7.

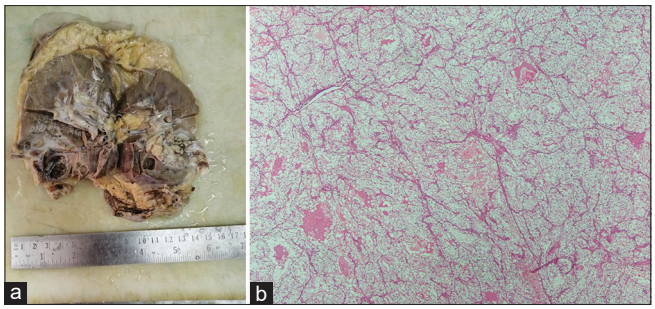

Figure 1: (a) Gross section of the kidney with 5 cm tumor, one was typical clear-cell renal cell carcinoma with abundant leiomyomatous stroma. (b) Tumor is composed of clear cells arranged in acinar pattern

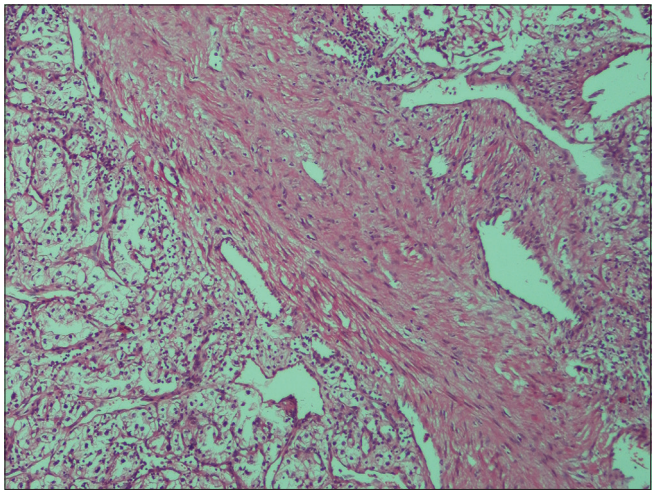

Figure 3: Clear-cell renal cell carcinoma with leiomyomatous stroma

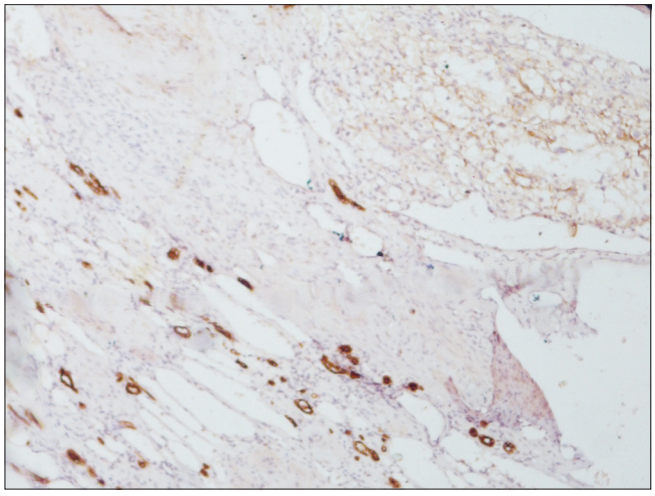

Figure 5: Cytokeratin 7 is strongly but focally positive

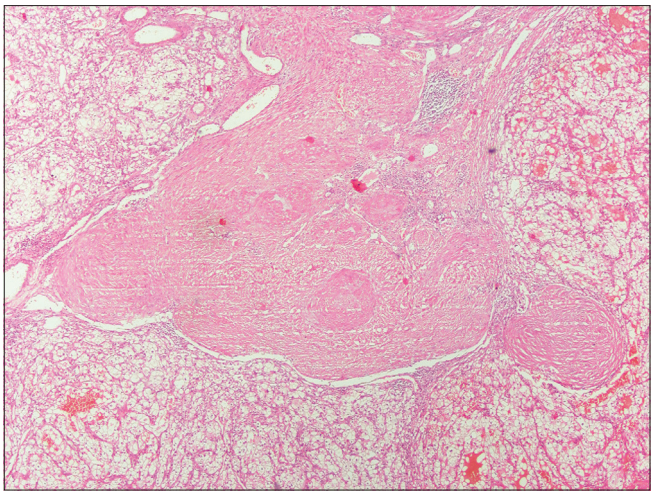

Figure 2: Clear-cell renal cell carcinoma with abundant leiomyomatous stroma

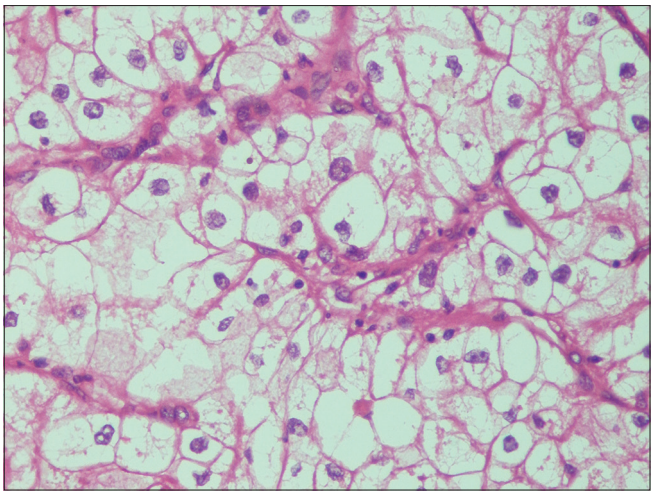

Figure 4: Clear-cells with conspicuous nucleoli at ×40 ISUP Grade-2

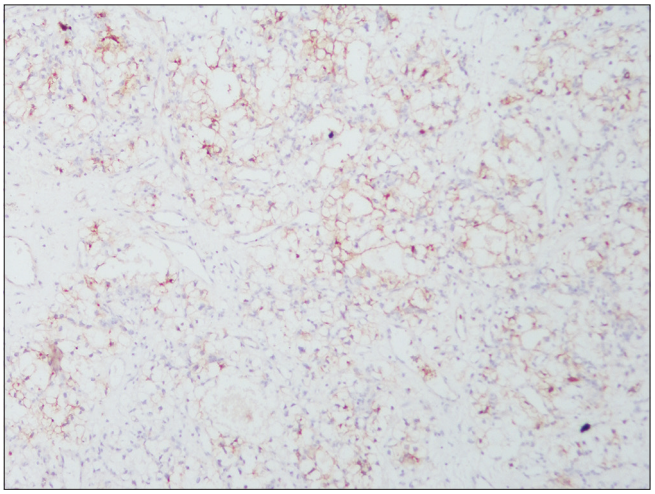

Figure 6: Cluster of differentiation 10 membranous positivity

CASE REPORT

A 62-year-male patient presented with unilateral (right side) flank mass, hematuria, and flank pain. The patient underwent a radical nephrectomy and the specimen was sent to our department. The specimen was submitted as a right radical nephrectomy specimen with an attached adrenal gland. Total specimen measuring 14 cm × 8 cm × 4 cm attached ureter measuring 7 cm in length and adrenal

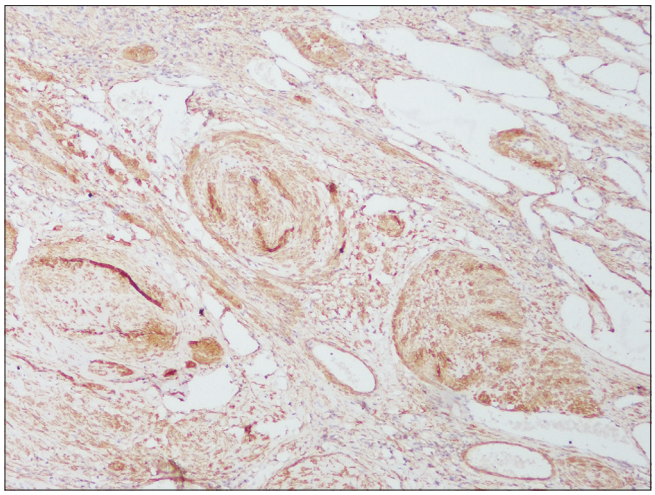

Figure 7: Smooth muscle actin membranous and cytolasmic positivity

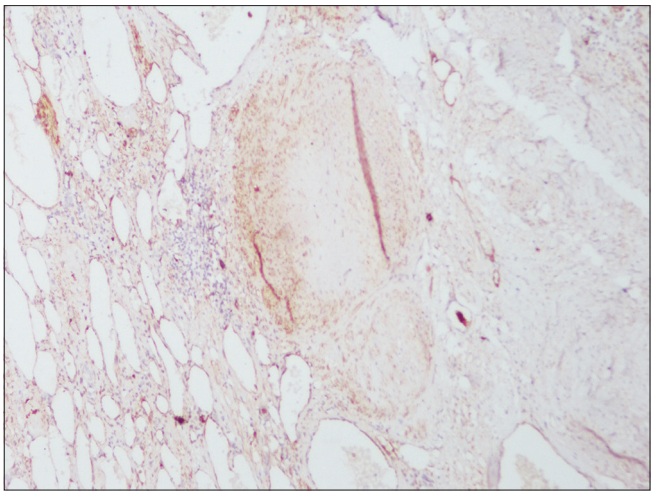

Figure 8: WT1 is negative

gland measuring 4 cm × 2 cm × 1 cm. On serial section, a well-circumscribed growth was identified at the upper pole measuring 5 cm × 3.5 cm × 3 cm [Figure 1a]. Cut section of growth shows variegated appearance with solid fibrotic areas and fatty areas. The rest of parenchyma is normal. Grossly, the tumor was reaching up to the capsule. Adrenal was identified and appeared uninvolved and unremarkable.

Histopathological findings showed the presence of a tumor comprising the nest of clear cells with an alveolar and acinar pattern [Figure 1b]. The tumor cells showed abundant clear cytoplasm with conspicuous nucleoli [Figure 2]. Areas of hyalinization and leiomyomatous stroma were also identified [Figure 3], and ISUP/WHO nucleoli grading-2 [Figure 4]. On immunohistochemistry (IHC), tumor cells are positive for cytokeratin (CK) 7 [Figure 5], Pan-CK, cluster of differentiation (CD) 10 [Figure 6], and smooth muscle actin (SMA) [Figure 7] and negative for WT-1 [Figure 8]. Leiomyomatous stroma comprised fascicles of spindle cells without significant pleomorphism or mitosis however no infiltration into the renal capsule seen. No atypia, mitosis, and necrosis were identified.

RESULTS

Based on the histological and IHC findings, features suggested CCRCC with leiomyomatous stroma. IHC for CK7, CD10, SMA, DESMIN, Pan-CK, and WT-1 was done which shows positive for CK7, CD10, SMA, DESMIN, and Pan-CK and negative for WT-1.

DISCUSSION

RCC clear-cell variant with leiomyomatous stroma is a recently recognized provisional entity in the WHO 2016 (WHO Classification of Tumor of Urinary System and Male Genital Organs 4th edition) defined as clear cells with prominent vascular and smooth muscle stroma. Prominent smooth muscle in the stroma, so-called leiomyomatous stroma, is an unusual finding in RCC. RCCLS historically was categorized as abundant CCRCC.[1,2] Renal tumors with leiomyomatous and/or fibroleiomyomatous component are unusual type of RCC composed of clear cells, which are intermingled with voluminous mostly leiomyomatous stroma. These tumors have been descriptively referred to as "RCC with smooth muscle stroma," "mixed renal tumor with carcinomatous and fibroleiomyomatous components," "RCC associated with prominent angioleiomyoma-like proliferation," or "CCRCC with smooth muscle stroma." These tumors constitute a heterogeneous group. Some of these cases obviously represented CCRCC, which produced smooth muscle stroma, and another part are, according to our opinion, distinct renal neoplasms, which probably differ from CCRCC by their molecular genetic features and perhaps prognosis. Presence of a prominent smooth muscle stroma may be encountered not only in "RCC with smooth muscle stroma," CCRCC, and renal angiomyoadenomatous tumour (RAT)/clear cell papillary renal cell carcinoma (CCPRCC) but also in papillary RCC. Moreover, this stroma is not part of the monoclonal, neoplastic proliferation but represents a reactive, polyclonal proliferation that is possibly derived from the smooth muscle cells of large caliber veins. Another authors postulated that angioleiomyoma-like change is an epiphenomenon caused by overproduction of growth factors by epithelial neoplastic cells with inactivation of VHL gene. Such a pathway could be an explanation for the production of the leiomyomatous stroma in CCRCC. It seems that there could be different pathways for stroma production in tumors such as papillary RCC, RAT/CCPRCC, and RCC with smooth muscle stroma.[3,4] Gournay *et al*. observed RCCLS sharing the same morphology: They showed nested, papillary, or trabecular architecture, an

epithelial component with clear and eosinophilic granular cytoplasm, and a stromal component with thick bunds of smooth muscle cells.[4] In Hes *et al*. study, histological findings showed clear cell type of RCC surrounded by abundant smooth muscle stroma, whereas in our study, histological findings were that of conventional RCC. RCCLS historically was categorized as a CCRCC. RAT, as a term has become obsolete by the newest edition.[5] RCC with prominent smooth muscle is an evolving area that currently encompasses RCCLS, a subset with mutation of TCEB1, a subset of CD10+ RCC with angioleiomyoma-like stroma, and some tumors in tuberous sclerosis patients have had overlap features. However, IHC findings were similar in both the studies. In comparison to other studies, our study showed similar findings to that of Yeh *et al*., which show CD7, CD10, Pan-CK and SMA positivity. Based on the above histological findings, a provisional diagnosis of clear-cell variant RCCLS was made.[6] They expressed CK7, CK20, CAIX, and CD10, and their cytogenetic profile showed no alteration.[6] It is a rare entity and has been kept as a provisional entity in the WHO 2016 (WHO Classification of Tumor of Urinary system and Male Genital Organs 4th edition). Renal cell carcinoma cases with leiomyomatous stroma having indolent in nature and good fair prognosis, Clinical and radiological correlation with follow up. Studies related to RCC with leiomyomatous stroma have shown the involvement of TCEB1 gene and VHL gene mutation..[7]

CONCLUSION

It is possible to conclude that clear-cell RCCLS are morphologic ends of nosologic entity. Tumors displaying similar morphologic attributes, that is, mostly clear cell low-grade population and abundant leiomyomatous stroma are designated as clear-cell RCCLS.

Our study highlights the following conclusions:

1. We reported clear-cell RCCLS, most published cases followed a benign/indolent clinical course with good prognosis
2. Clear-cell RCCLS is a new WHO provisional entity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgment

The authors sincerely acknowledge all the teaching and the technical staff of the Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India, for their guidance and support to conduct this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Moch H, Humphrey PA, Ulbright TM, Reuter VE. Clear cell renal cell carcinoma. In: WHO Classification of Tumors of the Urinary System and Male Genital Organs. Moch H, Humphrey PA, editors. 4th ed. Lyon: IARC press; 2016. p. 18-21.
2. Jesse K. Mckenney. Kidney tumors and tumor like conditions. In: Rosai and Ackerman Surgical Pathology. Goldblum JR, Lamps LW, editors. 11th ed. Philadelphia: Elsevier; 2018. p. 1025-39.
3. Peckova K, Grossmann P, Bulimbasic S, Sperga M, Perez Montiel D, Daum O, *et al*. Renal cell carcinoma with leiomyomatous stroma--further immunohistochemical and molecular genetic characteristics of unusual entity. Ann Diagn Pathol 2014;18:291-6.
4. Gournay M, Dugay F, Belaud-Rotureau MA, Peyronnet B, Mathieu R, Verhoest G, *et al*. Renal cell carcinoma with leiomyomatous stroma in tuberous sclerosis complex: A distinct entity. Virchows Arch, 2020. doi: 10.1007/s00428-020-02910-9.
5. Hes O, Compérat EM, Rioux-Leclercq N. Clear cell papillary renal cell carcinoma, renal angiomyoadenomatous tumor, and renal cell carcinoma with leiomyomatous stroma relationship of 3 types of renal tumors: A review. Ann Diagn Pathol 2016;21:59-64.
6. Yeh YA, Constantinescu M, Chaudoir C, Tanner A, Serkin F, Yu X, *et al*. Renal cell carcinoma with leiomyomatous stroma: A review of an emerging entity distinct from clear cell conventional renal cell carcinoma. Am J Clin Exp Urol 2019;7:321-6.
7. Massaeli M, Bogun Y, Watson G: Renal Cell Carcinoma with Leiomyomatous Stroma – A New Provisional Entity. Pathology 2019 Abstract Supplement. doi: 10.1016/j.pathol.2018.09.055..