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Original Article

Fumarate Hydratase-Deficient Renal Cell Carcinoma—A Clinicopathological Study of a Series of 11 Cases

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Abstract

Introduction Fumarate hydratase (FH)-deficient renal cell carcinoma (RCC) is a rare, molecularly defined renal tumor with aggressive behavior. The diagnosis of these tumors is challenging because of varied morphology and limited access to molecular testing and immunohistochemistry (IHC) for FH and 2-succinocysteine. We aim to elucidate the histomorphology, clinical presentation, and follow-up of this tumor in this first series of cases of FH-deficient RCCs from India.

Objectives This article aims to understand and elucidate the clinical presentation, pathologic findings, treatment options, and outcomes of FH-deficient RCC.

Materials and Methods Diagnosed cases of FH-deficient RCC between January 2021 and January 2023 including clinical details were retrieved from the electronic medical record database. Histopathological and immunohistochemical slides were reviewed.

Results Out of 11 cases of FH-deficient RCC, 36% had been referred with a diagnosis of type 2 papillary RCC. One patient presented with metastatic disease. All had mixed histologic patterns with the predominant pattern being papillary and showed FH loss on IHC. The classically described inclusion like nucleoli was present only focally in most cases. A subset of tumors had low-grade solid-nested morphology and these patients presented at an earlier stage (T2a). Two patients on multikinase inhibitors are alive with disease at 14 months' follow-up.

Conclusion FH-deficient RCCs can have varied histologic patterns within the same tumor and show loss of FH expression by IHC. A subset has low grade morphology and tends to have a more indolent course. It is important to have a high index of suspicion for this diagnosis due to its varied histological appearance and aggressive behavior.

Keywords
- fumarate hydratase-deficient renal cell carcinoma
- fumarate hydratase
- RCC
- FH IHC
- HLRCC

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Introduction

The classification of renal tumors has evolved phenomenally and at an expeditious rate in less than a decade. The introduction of "molecularly defined renal tumors" in the 2022 World Health Organization (WHO) classification of urogenital tumors officially marks the commencement of the molecular era in renal cell carcinomas (RCCs). The fumarate hydratase (FH)-deficient RCCs belong to this subgroup. These tumors, which display diverse morphologies, were largely labeled as type 2 papillary RCC (PRCC), RCC unclassifiable, and collecting duct carcinoma. The diagnosis of these tumors is challenging partly because of their heterogeneous morphology and partly due to the limited accessibility to specific immunostains and molecular testing in resource-limited settings. Accurate identification of these tumors is vital due to their syndromic association with hereditary leiomyomatosis and RCC syndrome (HLRCC) and potential for aggressive behaviour.[1] Although considered to be rare, a study by Shuch et al have estimated a carrier frequency of germline FH alterations of 1 in 1,000 individuals.[2]

Treatment options for these patients are under active research and combination therapies with vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR) inhibitors have shown promising results in patients with metastatic FH-deficient RCC.[3,4] In low resource settings, where access to molecularly driven immunohistochemical (IHC) markers may not be universal, it is crucial to be able to suspect the diagnosis on a hematoxylin and eosin (H&E)-stained section so that the patient may be referred to a specialized center for a definitive diagnosis and management. The number of reported cases of FH-deficient RCCs from India is limited with only one case report published till date.[5]

Our objective is to add to the existing limited body of literature on treatment options and clinical outcomes in these patients and to assess their histomorphologic spectrum through this first series of cases of FH-deficient RCCs from India.

Materials and Methods

Study Setting

The recent WHO 2022 5th series has advocated classifying a category of renal cancers under the rubric of "molecularly defined RCC" of which the FH-deficient renal cancers form an important group. There has been no series from India reported till date and hence we embarked to study these RCCs diagnosed at our institute.

Sample Size

We retrospectively analyzed 11 cases of FH-deficient RCC and discuss their clinicopathological characteristics.

Study Design

This was a retrospective study designed to describe the clinical presentation, morphologic spectrum, and treatment options of FH-deficient RCC. Clinical, radiological, and treatment information, where available, was obtained from the electronic medical record. H&E-stained slides and IHC stains performed on paraffin-embedded tissue were available in all cases and were reviewed and tabulated.

Primary and Secondary Outcome

As this is a retrospective case series of a rare type of renal cancer (FH-deficient RCC), the first series from India, follow-up and outcome details are limited.

Inclusion and Exclusion Criteria

All cases diagnosed as FH-deficient RCC in our center over a period of 24 months (between January 2021 and January 2023) were included in the study. Loss of IHC staining for FH was taken as the diagnostic criteria for inclusion in the study.[1]

Statistical Analysis

Descriptive statistics for univariate analysis to measure central tendency including median and to measure dispersion in the form of ranges and percentages was performed using Microsoft Office Excel.

Ethics

This study was approved by the Tata Memorial Hospital Institutional Ethics Committee on May 16, 2023, project number 4165. Waiver of consent was granted since this was a retrospective study with less than minimal risk. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards.

Results

We identified 11 cases of FH-deficient RCC during the study period. Nine out of 11 patients were referral/consult cases and these patients had undergone radical nephrectomy elsewhere. In one patient, only a core biopsy of the renal mass, done for diagnosis, was available for review. The details of these cases are described below.

Clinical Presentation and Investigation

There were seven men and four women in this series with a median age at presentation of 35 years (age range = 12–60 years). There was no laterality predilection with left-sided tumors in 6 out of 11 patients (54.5%), while one patient presented with synchronous, bilateral renal tumors. Clinical and radiological details have been tabulated in ►**Table 1** (►**Fig. 1**).

Macroscopic and Microscopic Findings

Detailed gross findings were available in only two tumors; both were solid and cystic with a tan to hemorrhagic cut surface. The tumor size as measured grossly or on radiology ranged from 5.1 to 13 cm ($n = 7$). All tumors had mixed architectural patterns with the most common predominant pattern being papillary ($n = 6$). The other predominant patterns encountered were nested tubules ($n = 3$), tubulocystic ($n = 1$), and infiltrating tubules ($n = 1$). The most commonly

Table 1 Patient details and treatment and follow-up history

Patient	Age (y)/Sex	Laterality	Tumor size (cm)	Stage	Radiology	Metastasis	Therapy received	Follow-up time (mo)	Status
1	30/M	Left	13	T3aM1	Heterogeneously enhancing mass, interpole region of kidney	Adrenal, pleural, and pericardial cavities, duodenum	None	5	DOD
2	35/M	NA	NA	NA	NA	NA	NA	NA	NA
3	60/M	Left	NA	NA	NA	NA	NA	NA	NA
4	53/F	Left	NA	NA	NA	NA	NA	NA	NA
5	26/M	Right	NA	NA	NA	NA	NA	NA	NA
6	44/M	Right	6.2	NA	NA	Lung, bone, retroperitoneal lymph nodes	Pazopanib	14	AWD
7	44/M	Left	NA	NA	NA	NA	NA	NA	NA
8	35/M	Bilateral	Right - 6, Left - 5.1	NA	NA	Liver, adrenal, peritoneum	Sunitinib	16	AWD
9	43/F	Left	13	T2b	Heterogeneously enhancing mass, anterior aspect of kidney	No	NA	NA	NA
10	16/F	Left	13	T2b	NA	No	NA	NA	NA
11	12/F	Right	9.5	T2a	Heterogeneously enhancing mass with internal calcification, lower pole of kidney	No	None	4	NED

Abbreviations: AWD, alive with disease; DOD, died of disease; F, female; M, male; NA, not available; NED, no evidence of disease.
Note: American Joint Committee on Cancer (AJCC) 8th edition is used for staging.

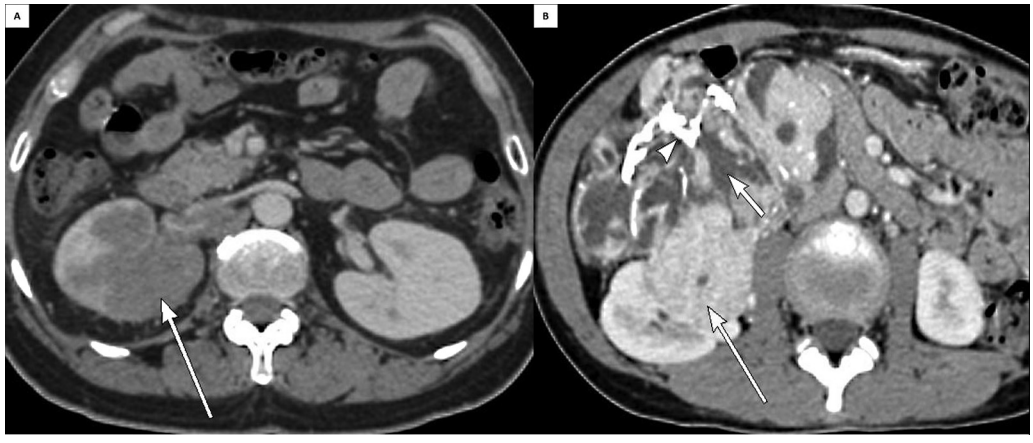

Fig. 1 (**A**) Axial contrast-enhanced computed tomography (CT)—Hypoenhancing endophytic mass in the right kidney (arrow). (**B**) Axial contrast-enhanced CT—Exophytic mass in the anterior interpolar region of the right kidney with enhancing solid (long arrow) and necrotic (short arrow) components and calcifications (arrowhead).

seen secondary pattern was tubulocystic ($n = 7$) followed by tubules ($n = 1$), papillary ($n = 1$), solid papillary ($n = 1$), and cribriform ($n = 1$). The papillae were broad with hierarchical branching, edematous, and sometimes hyalinized cores and were lined by columnar cells with abundant eosinophilic to focally clear or vacuolated cytoplasm. Some papillae appeared to be intracystic. The nuclei were vesicular with focally ($n = 7$) to diffusely present ($n = 2$) prominent eosinophilic "cytomegalovirus-like inclusion" nucleoli with perinuclear halo (►**Fig. 2**).

Three tumors had a predominant nested tubular pattern and were composed of eosinophilic cells with low-grade, minimally pleomorphic nuclei. One of these tumors had very focally prominent eosinophilic nucleoli, spireme-type

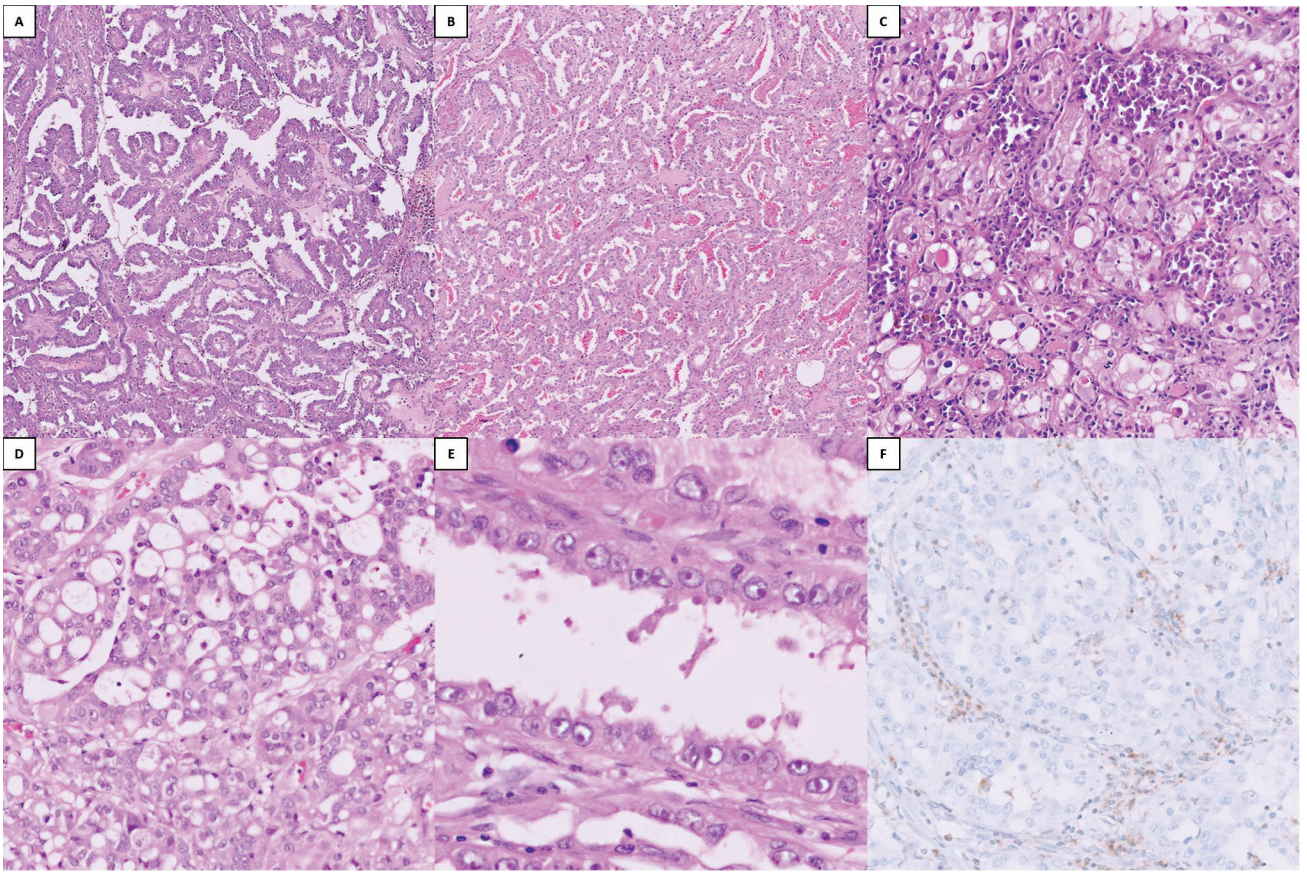

Fig. 2 Pattern heterogeneity in fumarate hydratase (FH)-deficient renal cell carcinoma (RCC). (**A**) Hierarchically branching papillae (hematoxylin and eosin [H&E], 10 ×). (**B**) Tubules (H&E, 5 ×). (**C**) Infiltrating tubules and nests (H&E, 20 ×). (**D**) Cribriform appearance (H&E, 20 ×). (**E**) Prominent eosinophilic nucleoli with perinuclear halo (H&E, 40 ×). (**F**) Negative staining for FH (inflammatory cells—positive internal control) (H&E, 20 ×).

chromatin, metaplastic bone, and tubules with mucin in the lumen. Psammoma bodies were noted consistently in these three tumors (►**Fig. 3**). The features in these three tumors were compatible with the "low-grade" morphology. Rhabdoid or sarcomatoid morphologies were not seen in any of the cases.

Immunohistochemical Findings

IHC with various antibodies was performed on all cases, the details of which have been summarized in ►**Table 2**. For FH IHC, clone used was BSB-151 from Bio SB. All the 11 cases showed uniform loss of FH staining.

Treatment and Follow-Up

Two patients are on treatment with multikinase inhibitors and are alive with disease at 12 months' follow-up. One patient is on observation and is disease-free at 4 months of follow-up. One patient who presented with adrenal metastasis was referred for palliation but progressed with systemic metastasis and died of disease within 5 months of initial diagnosis.

Discussion

FH is an enzyme coded for by the *FH* gene which is located on chromosome 1 (1q42.3-q43) that converts fumarate to L-malate in the tricarboxylic acid cycle.[6] Heterozygous germline mutations in the *FH* gene lead to the autosomal dominant inherited disorder, HLRCC syndrome, which has an estimated 15% lifetime risk of developing renal cancer in addition to multiple cutaneous and uterine leiomyomas.[7,8] However, somatic mutations in the *FH* gene can also lead to the development of RCC without other stigmata of HLRCC syndrome and hence it was renamed as FH-deficient RCC instead of HLRCC-related RCC in the WHO 2022 classification.[9]

FH deficiency leads to fumarate accumulation which has multiple downstream effects including stabilization of the hypoxia-inducible factor alpha (HIF-1α) complex that lead to tumorigenesis. Pathogenic levels of fumarate also causes succination of cysteine residues on proteins leading to formation of 2-succinocysteine (2SC) and abnormal protein function.[10,11] FH-deficient RCCs are typically solitary, unilateral tumors with age at presentation ranging from 36 to 46 years and no gender predilection, which is in keeping with the findings of this series.[12–15] The earliest stage at presentation was T2a with one patient presenting with metastases to adrenal and T3b primary disease. The aggressive nature of these tumors has been shown in previous studies with one study having 71% of patients presenting at least with T3a disease, 40 to 50% with regional lymph node metastasis, and around 20% with distant metastases (usually to adrenal and bone) at presentation. These

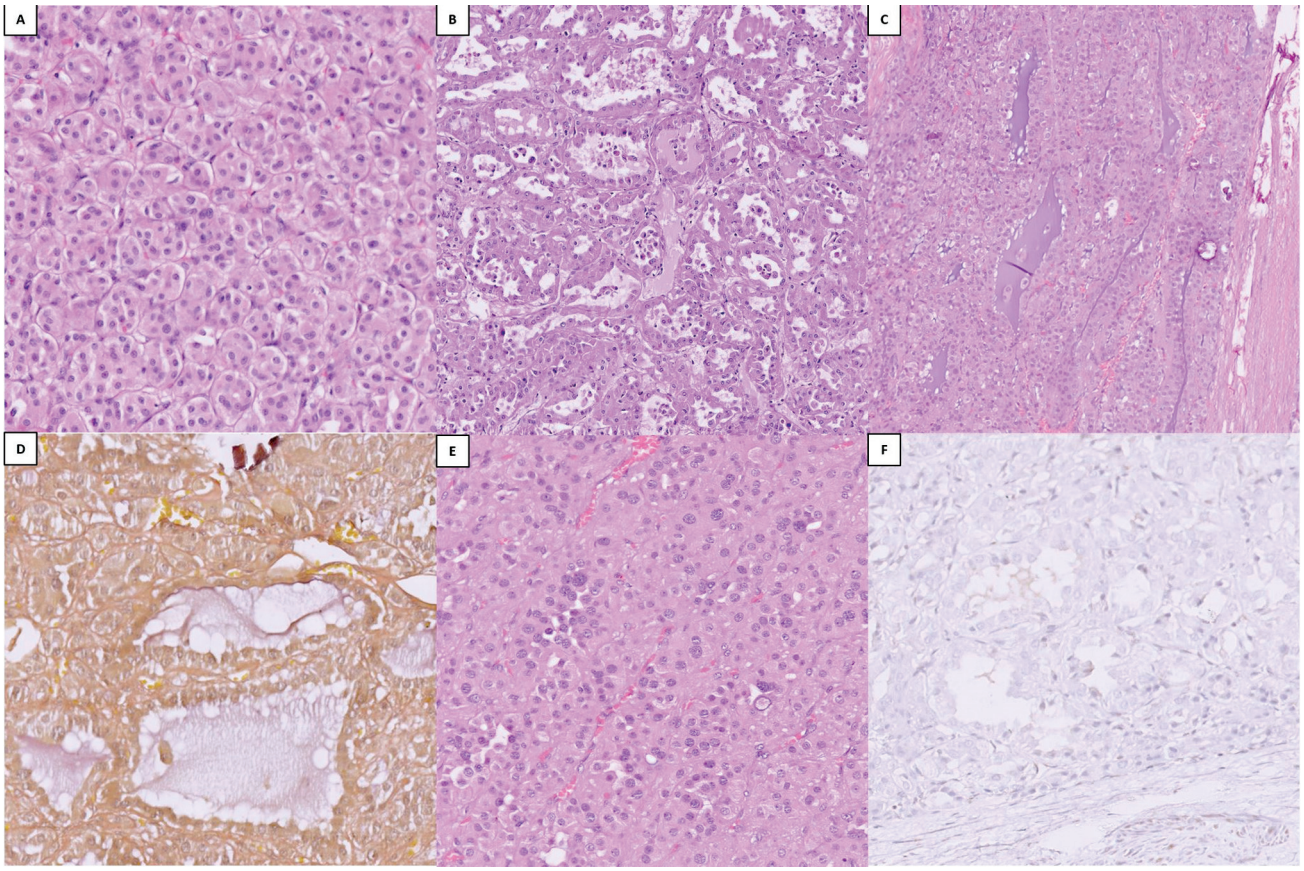

Fig. 3 Fumarate hydratase (FH)-deficient renal cell carcinoma (RCC) with low grade morphology. (**A**) Solid nests of eosinophilic cells with inconspicuous nucleoli (hematoxylin and eosin [H&E], 20 ×). (**B**) Tubulocystic (H&E, 10 ×). (**C**) Mucin secretion (H&E, 10 ×) with (**D**) mucicarmine positive intraluminal mucin (20 ×). (**E**) Spireme-type chromatin (H&E, 20 ×). (**F**) Negative staining for FH (smooth muscle in vessel wall—positive internal control) (H&E, 20 ×).

studies also reported 39 to 50% disease-related mortality within 3 years of diagnosis.[12–14,16]

FH-deficient RCCs have classically been described to have a type 2 PRCC-like morphology and four of our cases had been diagnosed on morphology as type 2 PRCC. However, heterogeneity is probably the first important clue toward a diagnosis of FH-deficient RCC, even if the tumor shows type 2 PRCC-like areas. All published series of cases have demonstrated heterogeneity within the same tumor which is also reflected in the present series. In literature, the most predominant pattern encountered was papillary followed by tubulopapillary, intracystic papillae, tubulocystic, cribriform/sieve like, sarcomatoid, and low-grade oncocytic.[12,14–21] An infiltrating collecting duct carcinoma-like morphology and tubulocystic carcinoma with poorly differentiated foci have also been described.[5,12,22,23] In our study, the most predominant pattern was also papillary followed by tubulocystic and cribriform with minor patterns including solid and nested and three cases with a collecting duct carcinoma-like morphology.

Merino et al in their seminal study of 40 FH-deficient RCCs described the presence of prominent, inclusion-like, cherry red nucleoli with perinuclear halos in all their cases which became the defining histological feature of this tumor. However, subsequent studies including the current cohort show that this feature is not uniformly present in all FH-deficient RCCs and if present, more often than not, is very focal.[15,18]

A subset of patients with FH deficiency has renal tumors with low grade oncocytic morphology similar to other low grade eosinophilic/oncocytic renal cell tumors. Although they appear to have low grade nuclei, Smith et al have reported two cases, one with occurrence of a synchronous high-grade RCC and another metachronous high-grade RCC occurring 4 years later, both with low grade oncocytic morphology.[22] Three of our cases had uniformly low grade oncocytic morphology with retained expression of succinate dehydrogenase B and focal areas of psammomatous calcification. This latter feature has been described by Li et al in FH-deficient RCCs with low grade morphology.[24] One of these low-grade morphology tumors also showed tubules containing mucin and osseus metaplasia, both of which have not previously been described in literature. All were T2 at presentation and one patient is disease-free at 4 months of follow-up; however, we did not have follow-up data for the other two patients. The use of the term “low grade” for this subset of FH-deficient RCC is a matter of debate and it may not hold good as more data emerges.[25]

Loss of FH ICH staining combined with positivity with 2SC IHC is used in the routine diagnosis of these tumors. Muller et al reported that loss of FH has a sensitivity of 87.5% and a specificity of 100% in the diagnosis of FH-deficient RCCs.[18] In the present series, all cases showed FH loss by IHC. Positive nuclear and cytoplasmic staining for 2SC is a more sensitive

Table 2 Immunohistochemical findings in FH-deficient RCC

IHC	Patients										
	1	2	3	4	5	6	7	8	9	10	11
FH	–	–	–	–	–	–	–	–	–	–	–
SDHB	ND	ND	ND	+	+	ND	+	ND	+	+	+
AMACR	+	F+	+	+	+	ND	ND	+	–	W+	+
CK7	–	–	–	–	F+	F+	–	–	–	–	–
CK20	–	ND	–	–	ND	–	ND	ND	–	–	ND
EMA	ND	ND	ND	ND	ND	ND	ND	ND	ND	F+	ND
AE1/AE3	ND	ND	+	ND	ND	+	ND	ND	ND	–	ND
PAX8	ND	ND	ND	ND	+	ND	+	+	ND	F+	ND
HMB45	–	ND	ND	–	ND	–	ND	ND	–	ND	–
Melan A	ND	ND	–	ND	ND	ND	ND	ND	–	–	–
ALK	–	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
TFE3	–	–	ND	ND	ND	ND	ND	ND	–	–	F+
CAIX	ND	ND	ND	ND	–	–	–	–	–	ND	–
KIT	ND	ND	ND	ND	ND	–	ND	ND	–	–	–
GATA-3	ND	F+	ND	ND	ND	ND	ND	ND	ND	ND	ND
Vimentin	ND	F+	ND	ND	ND	ND	ND	ND	ND	ND	ND
L1cam	ND	F+	ND	ND	ND	ND	ND	ND	ND	ND	ND

Abbreviations: F, focal; FH, fumarate hydratase; IHC, Immunohistochemistry; ND, not done; RCC, renal cell carcinoma; W, weak.
Note: +, positive; –, negative.

although less specific marker, with one study quoting a sensitivity and specificity of 91.7%. This paper also quotes an increase in sensitivity of 100% when FH and 2SC are used in concert.[18] 2SC staining was not done in the current series due to nonavailability at our center. It must be noted that 2SC is a sensitive marker but not specific and hence is of limited utility in confirming FH-deficient RCC on IHC without combining with FH IHC or molecular testing.[26]

These tumors morphologically form a part of the so-called "type 2 PRCC histology" (barring the FH-deficient tumors with low nuclear grade histology). Hence, the IHC panel to address type 2 PRCC histology includes CK7, AMACR, FH, INI-1, ALK, HMB45, Melan-A, Cathepsin K, TFE3, TFEB, and CK20.

For tumors that are localized to the kidney, the recommendation is wide margin surgical excision with retroperitoneal lymph node excision. For patients with confirmed HLRCC syndrome, annual screening with abdominal magnetic resonance imaging starting at age 8 to 10 years is recommended.[7] Systemic treatment options for metastatic FH-deficient RCCs are under active research and initial studies have focused on therapies targeting the classic clear cell RCC-associated HIF targets including inhibitors of VEGF, EGFR, and mTOR. A phase II clinical trial (AVATAR trial) with bevacizumab and erlotinib showed a median progression-free survival (PFS) of 21.1 months in patients with advanced disease.[3] However, Choi et al in a retrospective study of 10 patients treated with bevacizumab and erlotinib showed a median PFS of 13.3 months.[27] A study by Gleeson et al concluded that the longest median overall survival (OS) of 33 months was obtained with a combination therapy of mTOR and VEGF inhibitors (combination of bevacizumab or lenvatinib with everolimus) as opposed to monotherapy with these agents.[4] An European study by Carril-Ajuria et al demonstrated a median OS of 44 months on treatment with antiangiogenics like sunitinib and cabozantinib.[28] In the present series, two patients are on treatment with sunitinib and pazopanib and have shown a decrease in tumor burden at 14 and 16 months' follow-up, respectively.

Future studies can aim at longer follow-up periods to try to better understand the behavior of FH-deficient RCCs with low grade morphology and effectivity of different treatment modalities in tumors with conventional morphology.

Conclusion

This series of 11 cases highlights the aggressive nature, histological heterogeneity including "low grade nuclei" and younger median age at presentation of FH-deficient RCC. Ancillary IHC with FH is a sensitive test to diagnose these tumors although a combination with 2SC maybe better. The limitation of our series is lack of follow-up details due to the referral nature of the cases. Another limitation is the lack of molecular testing since FH IHC has less than 100% sensitivity as a molecular surrogate for FH mutation and does not provide information on germline versus somatic nature of mutations. Germline testing of all cases with FH loss and or 2SC loss would have allowed for genetic counseling to be initiated where necessary.

Awareness of this entity both in the urological and pathology community is of utmost importance as these are known to have an aggressive course, implying radical management and also may trigger genetic counseling with germline mutation testing and surveillance.

Patient Consent

Waiver of consent was obtained since this was a retrospective study with less than minimal risk and participants are de-identified or cannot be contacted.

Ethics clearance letter stating the same has been provided during manuscript submission and also the ethics project approval number is provided within the manuscript.

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None.

Conflict of Interest

None declared.

Acknowledgment

None.

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