Hereditary leiomyomatosis and renal cell carcinoma syndrome-associated renal cell carcinoma: Morphological appraisal with a comprehensive review of differential diagnoses

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ABSTRACT

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant syndrome wherein affected individuals are at risk for the development of cutaneous leiomyomas, early-onset multiple uterine leiomyomas, and an aggressive subtype of renal cell cancer. HLRCC is caused by germline mutations in the fumarate hydratase (FH) gene, which inactivates the enzyme and alters the function of the tricarboxylic acid/Krebs cycle. This article reviews the hitherto described morphologic features of HLRCC-associated renal cell carcinoma (RCC) and outlines the differential diagnosis and ancillary use of immunohistochemistry and molecular diagnostics for these tumors. The morphologic spectrum of HLRCC-associated RCC is wide and histologic features, including tumor cells with prominent nucleoli, perinucleolar halos, and multiple architectural patterns within the same tumor, which are suggestive of this diagnosis. FH immunohistochemistry in conjunction with genetic counseling and germline FH testing are the important parameters for detection of this entity. These kidney tumors warrant prompt treatment as even smaller sized lesions can demonstrate aggressive behavior and systemic oncologic treatment in metastatic disease should, if possible, be part of a clinical trial. Screening procedures in HLRCC families should preferably be evaluated in large cohorts.

KEYWORDS: Collecting duct carcinoma, fumarate hydratase, Hereditary leiomyomatosis and renal cell carcinoma, papillary type 2 renal cancer, targeted therapy

INTRODUCTION

Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) or Reed’s syndrome[1-3] is a hereditary cancer syndrome characterized by a predisposition to cutaneous and uterine leiomyomas and renal cell carcinoma (RCC) in a subset of cases developing as a result of a germline mutation in the fumarate hydratase (FH) gene. HLRCC is an autosomal dominant syndrome clinically characterized by three main features: (a) multiple cutaneous piloleiomyomas, presenting as firm tan-red skin papules or nodules, frequently in a segmental distribution; (b) multiple early-onset uterine leiomyomas treated with myomectomies or hysterectomy; and (c) renal cell cancer with a propensity to metastasize early or demonstrating aggressive behavior.

Clinical parameters required for a diagnosis of HLRCC include (1) multiple cutaneous piloleiomyomas confirmed with histopathologic examination or (2) at least two of the following manifestations: surgical treatment for symptomatic uterine leiomyomas before the age of 40 years, type 2 papillary RCC before the age of 40 years, or a first-degree family member meeting one of these criteria.[4] Collecting duct renal carcinoma before the age of 40 years has also been suggested as an additional histological subtype indicative of the syndrome.[5]

In 2002, Tomlinson et al.[6] identified heterozygous germline mutations in the FH gene which encodes the tricarboxylic acid (TCA)/Krebs cycle enzyme catalyzing...
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I n d I a n  J o u r n a l  o f  P a t h o l o g y  a n d  M I c r I o b I o l o g y  ¦  V o l u M e  6 3  ¦  S p e c I a l  I S s u e  1  ¦  f e b r u a r y  2 0 2 0

Germline FH mutations have been identified in the vast majority (75%–100%) of families with clinical features suggestive of HLRCC. Germline mutational testing for FH is mandated for confirmation of HLRCC in a proband or familial case. Germline mutational testing for FH is mandated for confirmation of HLRCC in a proband or familial case. The lifetime risk for renal carcinoma in HLRCC is approximately 15%, and the type of FH mutation does not appear to be a statistically significant factor in risk assessment. A significant proportion of low-stage tumors may behave aggressively and metastasize with published reports of several patients dying of disease within 5 years of diagnosis. In addition, there is no evidence that renal cancer risk is significantly higher in families with prior occurrence of renal carcinoma. Merino et al. documented in their study of 40 renal tumors resected from a cohort of 38 HLRCC patients with established FH germline mutations that the kidney tumors were predominantly solitary and unilateral. Grubb et al. published in their cohort of 19 cases of HLRCC-associated RCC that cases with small-sized tumors were observed to have a favorable prognosis with disease-free survival after partial or radical nephrectomy in those with localized disease. However, they also noted that the rate of distant metastasis in HLRCC was higher than observed for other hereditary renal cancer syndromes such as Birt–Hogg–Dubé syndrome. A high mortality rate of 74% due to metastatic disease was observed in the series reported by Gardie et al. reflecting the aggressive nature of this subtype of renal cancer as well as detection of these cases at a later stage.

Approximately 20%–35% of patients with germline FH mutations develop RCC. Annual surveillance in patients with known HLRCC should begin at the age of 10 years, and excision of even small renal tumors is recommended owing to the aggressive nature of these tumors.

Extrarenal manifestations of HLRCC often present clinically in patients younger than those with HLRCC-associated RCC, including cutaneous and uterine leiomyomata. The presence of multiple cutaneous leiomyomata warrants the performance of FH germline mutational testing and requires follow-up as a result of a distinct possibility of malignant transformation of these tumors. HLRCC patients tend to undergo myomectomies or hysterectomies for symptomatic leiomyomata approximately 10 years (in their third decade) earlier than the regular female population. Uterine leiomyomata in HLRCC patients demonstrate variable penetrance and exhibit nuclear features similar to those seen in HLRCC-associated RCC well as increased cellularity, nuclear pleomorphism, and the presence of eosinophilic globular cytoplasmic inclusions. Uterine leiomyosarcoma can also develop in HLRCC patients at a younger age. Figure 1 showcases examples of cutaneous and uterine benign as well as malignant leiomyomata with corroborative immunohistochemical staining seen in patients with HLRCC.

Several types of involvement of adrenal glands have been reported in this group, including adrenal cortical hyperplasia, pheochromocytoma, and rarely even adrenal cortical carcinoma. Testicular Leydig cell tumors have been reported to occur in patients with FH mutations, and this finding requires further studies to establish a definitive association.

MORPHOLOGICAL FEATURES OF HLRCC-ASSOCIATED RENAL CELL CARCINOMA

Initial descriptions of HLRCC-associated RCC documented tumors resembling papillary RCC or collecting duct carcinoma (CDC) demonstrating foci of a papillary growth pattern, abundant cytoplasm, and notably enlarged nuclei with inclusion-like features.

Figure 1: (a) Cutaneous leiomyoma in HLRCC resembles a regular piloleiomyoma forming a dermal nodule (×20); (b) Atypical intradermal smooth muscle neoplasm demonstrating mitotic activity (note inset, 200x) without significant nuclear pleomorphism in an HLRCC case (×100); (c) Loss of fumarate hydratase expression by immunohistochemistry in a cutaneous leiomyoma (immunoperoxidase, ×200); (d) Uterine leiomyosarcoma in HLRCC with a glistening myxoid gross appearance in a hysterectomy specimen; (e) Uterine leiomyosarcoma with necrosis and significant nuclear pleomorphism in a patient with HLRCC (×100); (f) High-power view of uterine leiomyosarcoma depicted in Figure 1e with elevated mitotic activity (arrows) but lacking the well-described features of prominent macronucleoli and perinuclear haloes; (hematoxylin and eosin staining, except C)
Eosinophilic nucleoli. Other growth patterns identified included tubulopapillary areas and variably admixed sarcomatoid foci. A characteristic morphologic feature posed as being characteristically representative of these tumors was the notably enlarged nuclei with a prominent inclusion-like nucleolus and a surrounding perinucleolar halo even identified in tumor foci with sarcomatoid and rhabdoid differentiation. In our experience, this feature is not always identified in all cases but is certainly helpful when present. Other series of HLRCC-associated RCC patients with germline FH mutations have identified papillary architecture with hyalinized or edematous fibrovascular cores in up to one-third of cases. Areas of micropapillary growth pattern were seen in several cases in this cohort. All tumors exhibited variably admixed architectural patterns, including tubulopapillary, solid, and cystic in addition to intracystic papillary or tubulopapillary foci. A significant number of these tumors also demonstrated overlapping features with CDC with infiltrative growth with a desmoplastic stromal response and interspersed inflammation.

A sizable cohort of RCC cases with tubulocystic and associated dedifferentiated CDC-like areas (“tubulocystic carcinoma with poorly differentiated foci,”) have been demonstrated to exhibit somatic FH loss, with a smaller subset of these same tumors representing HLRCC-associated RCC. Another rare morphologic pattern included in the spectrum of HLRCC-associated RCC is the recently reported low-grade oncocytic variant resembling succinate dehydrogenase (SDH)-deficient RCC. Rarely, HLRCC-associated RCCs may be entirely cystic. Muller et al. recently reported a series reviewing 24 renal tumors in 23 FH mutation carriers and comparing them to 12 type 2 papillary RCCs from FH wild-type patients. They observed that RCCs in FH mutation carriers demonstrated complex morphology with multiple patterns, including papillary, tubulopapillary, and tubulocystic, as well as sarcomatoid and rhabdoid differentiation. These variegated growth patterns were not identified in noncarriers, and the authors suggest that the multiplicity of different growth patterns is a more specific feature a diagnosis of HLRCC-associated RCC than the presence of prominent nuclei with perinucleolar halos. The uninvolved renal parenchyma in patients with HLRCC may contain cysts lined by epithelial cells with eosinophilic to clear cytoplasm and similar nuclear features. Figure 2 highlights various morphologic patterns seen as part of the spectrum of HLRCC-associated RCC along with select FH immunohistochemical staining examples.

**IMMUNOHISTOCHEMICAL AND MOLECULAR FEATURES**

Two immunohistochemical markers are of significant importance in establishing the diagnosis of HLRCC-associated RCC-FH and S-(2-succino)-cysteine (2SC). Loss of FH expression within tumor cells occurs as a consequence of inactivating mutations in the FH gene, whereas cytoplasmic and granular (mitochondrial) expression is considered a positive result. Appropriate positive internal control can be assessed in blood vessels, inflammatory cells, or other

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**Figure 2:** Gross findings and different morphologic patterns of hereditary leiomyomatosis and RCC syndrome (HLRCC)-associated renal cell carcinoma. (a) Gross appearance of HLRCC-associated renal cell carcinoma demonstrating a widely infiltrative multinodular tan-white tumor with prominent invasion of renal sinus fat. (b) HLRCC-associated renal cell carcinoma case with a papillary growth pattern (×200). Note the tumor cells with prominent enlarged nuclei; (c) A different growth pattern with tubular differentiation from the same case in image A with similar nuclear features and scattered perinuclear haloes (×200); (d) Prominent glandular differentiation in HLRCC-associated renal cell carcinoma (×200). The tumor cells exhibit uniformly prominent macronucleoli with high-grade cytologic features. The infiltrative malignant tubules impart an appearance resembling collecting duct carcinoma; (e) Intracystic papillary growth pattern in an HLRCC-associated renal cell carcinoma with oncocyctic features mimicking type 2 papillary renal cell carcinoma (×200). Characteristic nuclear features are present; (f) Sarcomatoid differentiation in noted in this high-grade/poorly differentiated carcinoma (×100); (g) Metastatic HLRCC-associated renal cell carcinoma with a tubulocystic pattern amid bony trabeculae in a vertebral body biopsy. The tumor is composed of bland tubules lined by a single layer of cuboidal cells (×100); (h) A corresponding biopsy image of the renal mass from the same case as image G demonstrating the presence of poorly differentiated foci with an infiltrating adenocarcinoma-like growth pattern accompanied by a desmoplastic stromal response (×100); (i) Absent fumarate hydratase immunohistochemical staining in the metastatic focus of carcinoma with a tubulocytic pattern depicted in image G (immunoperoxidase, ×200); (j) Loss of fumarate hydratase staining in the poorly differentiated foci of HLRCC-associated renal cell carcinoma with a tubulocystic component (images g, i). Staining is retained in the internal control vasculature and further corroborates the absence of staining in the tumor cells (immunoperoxidase, ×200) (hematoxylin and eosin staining, except i and j).
nonneoplastic cells.\textsuperscript{[37,42]} Increased levels of fumarate in tumor cells lead to aberrant succination of cellular proteins, which is detected with the 2SC antibody, currently employed in research settings, and not for commercial testing purposes. Interpretation is based on strong cytoplasmic and nuclear expression of 2SC in tumor cells with absent staining in the uninvolved kidney parenchyma.\textsuperscript{[37,42]} Loss of FH immunostaining with overexpression of 2SC in a kidney tumor with histologic features suggestive of HLRCC-associated RCC is adequate evidence to warrant additional clinical workup and germline mutational testing in a case without a prior proven diagnosis of HLRCC.

It is noteworthy to state that the type of FH mutation itself may define whether FH loss can be detected by immunohistochemical testing. A small subset of patients with HLRCC-associated RCC may demonstrate equivocal results or retained FH expression in tumor cells, which is further corroborated in the published literature by the fact that cases with FH missense mutations have altered protein–antibody interactions resulting in equivocal or retained FH expression.\textsuperscript{[26,43]} Immunohistochemical evaluation of FH and 2SC on cutaneous or uterine leiomyoma is very useful in segregating cases that require clinical follow-up and additional germline mutation testing for HLRCC.\textsuperscript{[26,43-45]} Although screening uterine leiomyomatata in a younger age group may be considered as another screening strategy to identify HLRCC cases, one major caveat is that both sporadic and syndromic uterine leiomyomatata can be FH deficient.\textsuperscript{[40]}

HLRCC syndrome has germline-inactivating mutations in the FH gene (1q42.3–q43).\textsuperscript{[5,6,11]} The loss of FH function results in increased levels of intracellular fumarate, leading to several proteomic and epigenetic alterations affecting protein stability including hypoxia-induced factor 1 (HIF1) and succinylation of several proteins, including KEAP1, a component of the cullin 3 E3 ubiquitin ligase leading to dysregulation of nuclear factor erythroid 2-related factor 2 (NRF2). Antioxidant response genes, such as AKR1B10, that are overexpressed in HLRCC are regulated by NRF2.\textsuperscript{[47-52]} Several alpha-ketoglutarate-dependent dioxygenases such as the TET family of 5-methylcytosine hydroxylases and histone demethylases are inhibited competitively causing decreased histone and DNA demethylation. A DNA hypermethylation phenotype of HLRCC results from TET inhibition. The Cancer Genome Atlas RCC cases with hypermethylation also list a subset of tumors with loss of FH expression.\textsuperscript{[53,54]} Until novel diagnostic or predictive biomarkers are identified through further studies exploring the various molecular pathogenetic mechanisms causing the development of HLRCC-associated RCC, germline FH mutational testing remains the mainstay for establishing an HLRCC diagnosis.

**Differential Diagnosis of HLRCC-Associated Renal Cell Carcinoma**

**Papillary renal cell carcinoma, type 2**

A significant number of renal tumors previously categorized as type 2 papillary RCC are now recognized as fumarate-deficient RCC or HLRCC-associated RCC using contemporary diagnostic criteria and ancillary immunohistochemical staining. The overall prognosis for this category of tumors is better than HLRCC-associated RCC; thus, proper classification is mandated and metastatic disease is not commonly present at the time of diagnosis in papillary RCC.\textsuperscript{[55-57]} Type 2 papillary RCC is characterized by pseudostratified epithelium with abundant eosinophilic cytoplasm lining tumoral papillae and high-grade nuclear features. It is well-recognized that a significant proportion (>50%) of type 2 papillary RCCs may contain tumor cells with prominent nucleoli with perinucleolar halos akin to HLRCC-associated RCC.\textsuperscript{[40]} Papillary RCCs are often well-circumscribed and encapsulated tumors without an extensively infiltrative growth pattern. Microscopic examination shows a predominantly papillary growth pattern with variable glomerations and solid and tubular components.\textsuperscript{[58]}

The morphologic features of HLRCC-associated RCC and type 2 papillary RCC overlap vastly. However, an admixture of several architectural patterns within the same tumor is more frequently identified in HLRCC-associated RCC along with a prominent infiltrative growth pattern and lack of tumor circumscription.\textsuperscript{[40]} Immunohistochemical staining is helpful in this distinction with papillary RCC often demonstrating diffuse positivity for cytokeratin 7 and racemase (AMACR), whereas HLRCC-associated RCC cases show negative or focal, patchy staining for these markers. Sporadic cases of papillary RCC demonstrate trisomy of chromosomes 7 and 17, with loss of chromosome Y on cytogenetic analysis. Both sporadic and hereditary papillary renal carcinoma syndrome-associated cases are also documented to demonstrate activating MET oncogene mutations on molecular analysis.\textsuperscript{[59]}

Most importantly, HLRCC-associated RCC demonstrates a loss of FH expression by IHC in the majority of cases in contrast to papillary RCC with retained FH expression.

**Collecting duct carcinoma**

Apart from type 2 papillary RCC, CDC represents one of the most significant and challenging differential diagnoses for HLRCC-associated RCC due to similarities in clinical presentation, prognostic outcome, and major overlap in histologic features as well as immunohistochemical profiles. It comprises <1% of renal malignancies with over 250 reported cases in the literature, the first case being reported in 1986.\textsuperscript{[60,61]} This renal carcinoma affects all ages, with a mean age of 55 years, and occurs more commonly in male patients, with a male-to-female ratio of 2:1. Approximately 50% of patients with CDC have metastatic disease at the time of presentation, and the overall prognosis is poor with high disease-related mortality within 2 years of diagnosis.\textsuperscript{[60,62]} CDC is centered in the renal medulla when smaller and larger tumors show a multifocal invasion of kidney parenchyma. This malignancy shows multiple architectural patterns with an infiltrative growth pattern in the same tumor and even multinodularity similar to HLRCC-associated RCC. Several growth patterns described in CDC include tubular, solid, acinar, papillary, cribriform, and signet ring. Dysplasia is often seen in the tubules of the kidney parenchyma adjacent to
these tumors. A diagnosis of CDC is based on tumors meeting
the following criteria – medullary involvement, presence of
unequivocal glandular or tubular growth pattern, desmoplastic
stromal response, high-grade cytologic features, an infiltrative
growth pattern, and the exclusion of other subtypes of RCC or
urothelial carcinoma on morphologic and immunohistochemical
findings.[1]

Renal CDCs show immunohistochemical positivity for PAX8
with varying degrees of expression of high-molecular-weight
cytokeratin, cytokeratin 7, and carcinoembryonic antigen and are
generally negative for markers of urothelial differentiation.[60-66]
A recently published study by Pal et al. reported that almost
one-third of CDCs demonstrate genomic alterations in NF2,
paving the way for mechanistic target of rapamycin (mTOR)
inhibitors to be used for treatment of at least a subset of CDC cases.

HLRCC-associated RCCs have been previously reported
as CDCs in the literature due to notably overlapping
morphologic and immunohistochemical features; currently,
FH immunohistochemical studies and germline testing, if
required, are of great assistance in classifying these tumors
more accurately. Although a tubulopapillary growth pattern
is common in both HLRCC-associated RCC and CDC, intracytic
papillary and tubulocystic growth is more often seen in
HLRCC-associated RCC.[64] Cytoarchitectural features are high
grade, with notable pleomorphism and significantly increased
mitotic activity in both tumors. Tumors with prominent
macronucleoli and perinuclear halos can also be seen in CDC.
Again, FH expression is lost in most HLRCC-associated RCCs
whereas the immunoprofile for CDC cases shows a variable
expression of cytokeratins and other markers routinely
employed as part of the workup for RCC cases.[63-64] It is possible
that a small subset of CDCs might demonstrate the loss of
FH protein expression owing to a somatic FH gene mutation.
Thus, evaluation of clinical features and germline FH testing
is crucial in cases with CDC-like tumors and FH protein loss
on immunohistochemical staining in order to categorize them
correctly as HLRCC-associated RCC.

Clear cell renal cell carcinoma, high-grade
High-grade clear cell RCC can demonstrate tumor cells with
eosinophilic cytoplasm and pseudopapillary or rarely focal
papillary architecture resulting in a differential diagnosis of
HLRCC-associated RCC and other high-grade renal tumor
subtypes, particularly in core needle biopsy specimens. If the
architectural pattern shows a predominant papillary morphology
in the absence of the typical racemase vascular network seen
in clear cell RCC, other diagnoses such as papillary RCC and
HLRCC-associated RCC should be considered.

Clear cell RCC is notably positive for pancytokeratin and carbonic
anhydrase IX (CAIX, diffuse membranous) and negative for CD117
with negative or mild, patchy staining for cytokeratin 7.[70-73]
Diffuse membranous CAIX positivity is generally not seen in
HLRCC-associated RCC. Cytokeratin 7 is negative or shows
scattered patchy positivity in HLRCC-associated RCC. Most clear
cell RCCs show band 3p copy number losses at the molecular
level. Von Hippel–Lindau syndrome confers predisposition to the
development of clear cell RCC.[80] High-grade clear cell RCC and
HLRCC-associated RCC are both aggressive neoplasms that can
show a papillary or pseudopapillary growth pattern. Clear cell
RCC often shows diffuse membranous positivity for CAIX and
does not exhibit loss of FH expression, whereas HLRCC-associated
RCC shows loss of FH expression and lacks diffuse positivity for
CAIX expression.

Microphthalmia family translocation renal cell
 carcinomas
Microphthalmia (MiT) family translocation RCCs are a
heterogeneous category of renal tumors, all of which express
MiT transcription factors, usually due to chromosomal
translocations and rarely from gene amplifications. There
are two major subtypes in this family of tumors – Xp11
translocation RCCs (TFE3-translocation RCCs) and t (6;11)
RCCs (TFEB-rearranged RCCs) in addition to other related
neoplasms (i.e., TFEB amplification RCC and melanotic Xp11
translocation renal cancers/Xp11 translocation PEComas.

TFE3-translocation RCC and TFEB-amplified RCC are usually
high-grade tumors with papillary morphology amid different
types of admixed architectural patterns. TFE3-translocation
RCC typically exhibits areas of papillary architecture and cells
with voluminous clear to eosinophilic cytoplasm and scattered
psammomatous calcifications. TFE3-translocation RCC also
exhibits morphologic features that overlap with several other RCC
subtypes, including HLRCC-associated RCC.[72-75] TFEB-amplified
RCC is a more recently recognized entity in the MiT translocation
RCC family with most reported cases showing predominant
papillary architecture with high-grade nuclear features and
an oncocytic phenotype. TF3-translocation RCC and
TFEB-amplified RCC are the more aggressive RCC subtypes in
this family of tumors.[77-80]

A diagnosis of MiT translocation-associated RCC should be
included in the differential for renal tumors that demonstrate
absent or reduced of cytokeratins or epithelial markers by
immunohistochemistry, but it must also be borne in mind that
these tumors can actually also demonstrate focal or diffuse
cytokeratin expression. Immunohistochemical stains for
evaluating TFE3 and TFEB protein expression are available but
are technically difficult to set up in the laboratory. However,
fluorescence in situ hybridization (FISH) is reliable and serves
as the mainstay for correct diagnosis and classification of these
tumors.[72-76]

Both MiT family translocation RCCs and HLRCC-associated RCC
show overlapping clinical and morphologic features, including
papillary architecture with high-grade tumor cells containing
prominent nucleoli. Features that are useful in diagnosing
TFE3-translocation RCC include the presence of areas with
eosinophilic and clear cytoplasm and psammoma bodies, as well
as identification of TFE3 rearrangement by FISH. TFEB-amplified RCC exhibits high-grade oncocyotic features with papillary growth pattern and demonstrates TFEB amplification by FISH testing. On the other hand, HLRCC-associated RCC, unlike MiT-translocation or amplified RCCs, demonstrates loss of FH expression by IHC and does not show MiT factor amplifications or translocations on FISH testing. When MiT family translocation RCCs and HLRCC-associated RCCs are in the differential diagnosis for high-grade tumors with prominent nucleoli and papillary architecture, immunohistochemical and molecular assessment is a key in establishing the diagnosis.

Tubulocystic carcinoma with poorly differentiated foci
Smith et al. published a series of 29 tubulocystic carcinomas with poorly differentiated foci of infiltrative adenocarcinoma resembling CDC and focal papillary growth pattern. They demonstrated that RCCs with this particular morphological appearance also exhibit loss of FH. Per se, tubulocystic RCC is a well-circumscribed tumor, classically composed of variably dilated or cystic small-to-intermediate-sized tubules lined by a single layer of flat, cuboidal, columnar, or hobnail epithelium with uniform, large nuclei and prominent nucleoli without solid or papillary tumor foci.

RCCs with a tubulocystic growth pattern and associated poorly differentiated foci with high-grade poorly differentiated carcinoma or CDC-like areas raise a strong differential diagnosis of HLRCC-associated RCC. Purely tubulocystic RCC, a low-grade tumor, demonstrates positivity for cytokeratin 7 and racemase (AMACR) with retained FH expression, whereas tubulocystic RCC with poorly differentiated foci, a surrogate pattern for HLRCC-associated RCC, shows loss of FH expression in most cases.

Succinate dehydrogenase-deficient renal cell carcinoma
SDH-deficient RCC is considered in the differential diagnosis for the low-grade oncocyotic variant of HLRCC-associated RCC in rare cases due to overlapping morphologic features. Both FH and SDH are involved in metabolic pathways of the mitochondrial TCA cycle that is based on oxidative phosphorylation leading to energy production. Mutations in both FH and SDH can result in dysregulation of metabolic pathways leading to tumorigenesis stemming from metabolic dysfunction. SDH-deficient RCC is characteristically an oncocyotic neoplasm with predominantly solid or nested architecture containing dilated entrapped tubules. The defining feature is the loss of SDHB protein expression by immunohistochemistry or mutational analysis resulting from mitochondrial instability due to mutations of members of the SDHA-D complex. The tumor cells are of low grade and are uniform with round nuclei containing fine-stippled chromatin and inconspicuous nucleoli (“neuroendocrine features”) and flocculent or vacuolated eosinophilic cytoplasm with pink hyaline inclusions. Intratumoral mast cells are frequently present along benign entrapped renal tubules at the periphery of the tumor with variable cystic dilatation. The tumor cells express PAX8 with variable positivity for cytokeratins (AE1/AE3 and CAM 5.2) and epithelial membrane antigen (EMA), and these are usually negative for cytokeratin 7 and c-kit (CD117).

A recent study identified a small cohort of 4 RCCs with oncocyotic morphology with retained strong and diffuse SDHB expression but loss of FH expression and overexpression of 2SC by immunohistochemistry. Thus, a subset of HLRCC-associated RCCs may also exhibit a low-grade morphological pattern and require exclusion of HLRCC with appropriate testing. The tumors in this small case series were associated with a better prognosis. HLRCC-associated RCCs reported in the published literature demonstrate intact SDHB expression and absent FH expression, in contrast to the loss of SDHB staining and retained FH expression in SDH-deficient RCC.

Renal cell carcinoma, unclassified
RCC, unclassified, is a diagnostic category for the designation of RCCs that have histologic features that cannot be categorized under any of the well-characterized RCC subtypes. Morphologic patterns in this category include tumors that show a composite mixture of recognized types, novel or unrecognized cell types, tumors with mucin production, and renal carcinomas with entirely sarcomatoid morphology, lacking recognizable epithelial elements. Low- or high-grade unclassifiable oncocyotic neoplasms were also included in this category. In a molecular study of 62 unclassified RCCs by Chen et al., approximately 75% of cases were categorized into several subsets of abnormalities of variable prognostic significance that might be useful for either diagnostic or therapeutic implications.

One small cohort of cases with poor prognosis comprised four FH-deficient RCCs with unclassified histology wherein three patients were determined to have germline FH mutations and the fourth demonstrated a somatic FH mutation. Further studies with a greater number of cases are required to analyze the clinical behavior of RCC with somatic FH mutations as compared to HLRCC-associated RCC.

The entities described above in the differential diagnosis section for HLRCC-associated RCC are summarized in Table 1, and Figure 3 provides image-based examples of the aforementioned diagnoses that lead to a diagnostic dilemma with HLRCC-associated RCC.

TREATMENT OF HLRCC-ASSOCIATED RENAL CELL CARCINOMA
Surgical treatment of renal cancer in HLRCC
Nephron sparing therapy is a routinely performed surgical procedure in present times as compared to nephrectomy in previous years and is especially crucial for patients with...
Table 1: Differential diagnoses for hereditary leiomyomatosis and renal cell carcinoma syndrome-associated renal cell carcinoma

| Tumor                          | Histologic features                                                                 | Immunohistochemistry and ancillary testing                                                                 |
|-------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| HLRCC-associated RCC          | Wide spectrum, different architectural patterns within the same tumor; tumor cells with prominent inclusion-like macronuclei and perinuclear halos | Loss of FH expression; overexpression of 2SC, PAX8 positive and negative or patchy staining for CK7 and AMACR expression germline FH mutation(s) |
| Papillary RCC, type 2         | Papillary architecture with pseudostratified tumor cells, high-grade cytologic features, abundant eosinophilic cytoplasm | Positive for PAX8, pancytokeratin, CK7, EMA, and AMACR; intact FH; chromosome 7/17 FISH |
| Collecting duct carcinoma     | Infiltrative growth pattern; medullary involvement; high-grade cytoarchitectural features; predominant tubular or glandular morphology, desmoplastic stromal response; exclude urothelial and other nonrenal carcinomas | PAX8 positive, variable positivity for cytokeratins AMACR and renal lineage markers; intact FH |
| Clear cell RCC                | Nested pattern; cells with clear cytoplasm and delicate vascular network; high-grade areas with eosinophilic cytoplasm; sarcomatoid and rhabdoid differentiation; pseudopapillary architecture | Positive for PAX8, pancytokeratin, EMA, and CAIX (diffuse strong membranous expression); negative or patchy CK7; intact FH |
| Tubulocystic carcinoma        | Small-to intermediate-sized, variably cystic, tubules lined by a single layer of flat, hobnail, cuboidal, or columnar epithelium and prominent nuclei | Positive for PAX8, CK7, and AMACR; intact FH |
| Tubulocystic carcinoma with poorly differentiated foci | Two components - tubulocystic carcinoma and collecting duct carcinoma-like features or infiltrative adenocarcinoma | Positive for PAX8, CK7, and AMACR; loss of FH in significant number of cases (representing HLRCC-associated RCC in subset), FH mutation(s) present in HLRCC-related cases |
| MiTF translocation family RCC (TFE3-translocation RCC and TFEB-amplified RCC) | Papillary, nested, and mixed growth patterns with high-grade cytologic features; abundant eosinophilic cytoplasm; variable psammomatous calcification | PAX8 positive, variable (usually absent or decreased) pancytokeratin expression; melanocytic markers expressed in TFEB tumors; intact FH; TFE3 and TFEB FISH |
| SDH-deficient RCC             | Nested and solid patterns, low-grade cells with uniform nuclei, fine-stippled chromatin, and folliculent/vacuolated eosinophilic cytoplasm with scattered inclusions; dilated entrapped tubules | Positive for PAX8 and Ksp-cadherin; negative or weak focal positivity for pancytokeratin; negative for CD117, RCC-Ma, p63, CAIX, vimentin, and neuroendocrine markers; loss of SDH subunit B expression; intact FH |

RCC: Renal cell cancer; HLRCC: Hereditary leiomyomatosis and renal cell carcinoma; MiTF: Microphthalmia transcription factor; SDH: Succinate dehydrogenase; FISH: Fluorescence in situ hybridization; CAIX: Carbonic anhydrase IX

Hereditary RCCs that are associated with a predisposition to bilateral and multifocal tumors. Synchronous or metachronous renal cancers require several episodes of treatment, and preservation of renal function is, therefore, an essential consideration in these patients. Therefore, surgical intervention is recommended in these cases when the diameter of the largest tumor exceeds 3 cm. However, HLRCC provides an exception to this “3 cm” rule since metastases can occur even in cases of small primary HLRCC-associated RCCs. Therefore, an active surveillance approach is not recommended for renal tumors in HLRCC patients.

Management of a suspected renal cancer most often consists of partial nephrectomy if the tumor is relatively small or a radical nephrectomy. Surgical excision with wide margins and consideration of retroperitoneal lymphadenectomy are recommended. Radiofrequency ablation and cryotherapy for renal cancer are not recommended for HLRCC cases making recognition of these tumors on core needle biopsies a daunting yet important process.

Systemic treatment of metastatic renal cancer in HLRCC

Advancements in understanding the molecular pathogenesis of renal cancer have resulted in the development of novel forms of targeted therapy aimed at molecular pathogenetic pathways. As previously outlined, aberrant metabolism in renal cell cancer has been identified as an essential factor in kidney tumorigenesis, and newer forms of targeted therapy are aimed at dysfunctional metabolic pathways, especially abnormalities at the TCA cycle and glycolysis. Yamasaki et al. reported a case of a 24-year-old woman with HLRCC-associated RCC, initially treated with a mTOR inhibitor. The disease progressed, and 2-deoxy-D-glucose, an inhibitor of glycolysis, was used for treatment as these tumors are dependent on glycolysis for ATP production but was unsuccessful.

Currently, no standard therapy has been developed for patients with metastatic HLRCC-associated RCCs. Tyrosine kinase inhibitors or mTOR inhibitors are being employed in the treatment of these tumors. Current Phase II clinical trials include vandetanib (kinase inhibitor with activity against vascular endothelial growth factor receptor, epidermal growth factor receptor [EGFR], and RET tyrosine kinase) in combination with metformin (http://clinicaltrials.gov NCT02495103), guadecitabine (SGI-110, DNA methyltransferase inhibitor) (http://clinicaltrials.gov NCT03165721), and bevacizumab (VEGF inhibitor) and erlotinib (tyrosine kinase inhibitor with activity against EGFR) (http://clinicaltrials.gov NCT01130519). The basis for this treatment approach is the presumed role of decreasing FH activity leading to HIF stabilization and activation of HIF targets.

**Summary and Conclusion**

HLRCC-associated RCC frequently demonstrates aggressive clinical behavior, with associated metastatic spread and disease mortality. It is very important to recognize this cohort of patients since they...
and their families should undergo a thorough clinical workup with genetic counseling and ancillary testing as deemed necessary. The morphologic spectrum of HLRCC-associated RCCs is wide and bears a significant degree of overlap with several other commonly encountered and rare RCCs. Histologic features such as diffuse distribution of tumor cells with prominent nucleoli and perinucleolar halos as well as growth patterns such as tubulocystic carcinoma with poorly differentiated foci are helpful pointers in order to recognize HLRCC-associated RCC cases. FH immunohistochemistry is crucial for detection of this tumor category. In our practice, we render a diagnosis of FH-deficient RCC as being most apt for renal tumors with loss of FH protein expression upon immunohistochemistry until corroborated further with germline FH testing.

Clinicoradiological correlation and input from the clinical team regarding clinical features and family history is very significant in these cases with familial implications due to HLRCC syndrome. Loss of FH protein expression in renal tumors upon immunohistochemistry is adequate evidence to undertake germline mutational testing coupled with a detailed clinical workup to detect these HLRCC cases and provide optimal therapeutic options dependent on the diagnosis. A minor cohort of cases with HLRCC-associated RCC may demonstrate preserved or decreased FH protein expression, yet the complete genetic testing and clinical examination is recommended if the index of suspicion meets the required threshold for HLRCC-associated RCC.

The diagnosis of HLRCC aptly highlights the challenges associated with recognition of rare diseases exhibiting wide phenotypic variation ranging from minor cutaneous involvement to widely metastatic RCC resulting in mortality. Molecular profiling of renal cancers is also becoming increasingly prevalent in practice resulting in enhanced risk stratification and optimized approach to treatment of these kidney masses. With these factors in mind, surgical pathologists, therefore, play a vital role in the recognition of tumors in this category prompting clinical triaging and genetic counseling with appropriate testing.

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There are no conflicts of interest.

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