The impact of the new WHO Classification of renal cell carcinoma on the diagnosis of hereditary leiomyomatosis and renal cell carcinoma

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Abstract

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome is caused by heterozygous germline variants in the *fumarate hydratase* (*FH*) gene [1,2]. Inheritance follows an autosomal dominant pattern. Loss of *FH* confers a predisposition for various benign and malignant neoplasms, including cutaneous leiomyomas, uterine fibroids and *FH*-deficient renal cell carcinoma [3]. While benign, cutaneous and uterine manifestations have a relevant impact on quality of life and risk for complications [4]. The vast majority of FH-deficient RCC exhibit an aggressive behavior with invasive growth and potential for early metastatic spread [5]. Additionally, pathogenic germline *FH* variants have been associated with other neoplasms, such as adrenal gland [10] and Leydig cell tumors[28, 29].
The aggressive behavior of FH-deficient RCC challenges nephron-sparing resection strategies, as a wide margin is recommended. Even after early nephrectomy for surgical removal of FH-deficient renal cell carcinomas, there is a relevant risk for distant metastasis as well as the remaining predisposition for *de novo* primary renal tumors in the other kidney. Active screening is central to HLRCC care since no preventative HLRCC-specific treatment

exists. VEGF/EGFR directed treatment regimes, such as Erlotinib/Bevacizumab demonstrate efficacy against HLRCC-associated RCC [6]. This emphasizes the importance of establishing the correct diagnosis in HLRCC early on to guide therapeutic decisions.
Morphologic criteria as well as specific immunohistochemical (IHC) staining and molecular genetics allow the identification of FH-deficient RCC. Changes made in the recent 2022 WHO classification impact the diagnosis of HLRCC in multiple ways. This commentary aims to point out this impact and to raise awareness among pathologists as well as clinicians involved in the care of patients with HLRCC.

Keywords: fumarate hydratase (FH), hereditary, hereditary leiomyomatosis and renal cell cancer (HLRCC), immunohistochemistry, pathology, renal cell carcinoma

HLRCC: an interdisciplinary challenge with disease-specific implications for the management of kidney involvement

HLRCC is an autosomal dominant disorder characterized by the formation of cutaneous leiomyomas, uterine fibroids and a predisposition to the formation of mostly aggressive FH-deficient RCC. Approximately, 10% - 30 % of carriers develop RCC in their lifetime [3, 9, 10]. RCC prevalence varies between affected families. However, a genotype-phenotype correlation for the development of RCC or other organ manifestations has not been established. Besides, patients with HLRCC have been described to be more likely to develop multiple kidney cysts than the general population potentially leading to a phenotype resembling other renal tumor syndromes associated with polycystic kidneys (e.g. Von-Hippel-Lindau [VHL] syndrome or Birt-Hogg-Dubé [BHD] syndrome). Additionally, pathogenic germline *FH* variants have been associated with other neoplasms, such as pheochromocytomas, adrenal gland [10] and Leydig cell tumors [28,29].
Mechanistically, carcinogenesis occurs typically upon somatic biallelic *FH* inactivation, which leads to metabolic reprogramming with activation of AMPK and HIF signaling [11] and accumulation of oncometabolites [12]. Importantly, FH-deficient RCC shows highly aggressive characteristics including early formation of metastases. In patients with HLRCC, kidney cancer develops earlier than sporadic RCC with a mean age at diagnosis of 44 years [13] and cases occurring even in young children [14]. This aspect, as well as the continued risk for tumor formation after treatment and the potential predisposition of other family members emphasize the importance of a timely and precise diagnosis of HLRCC among patients with RCC. The common management strategy to employ active surveillance for small tumors in other hereditary RCC syndromes (e.g., in VHL [15] or BHD [16,17] syndrome) is not appropriate in HLRCC cases that require prompt tumor removal upon detection [5]. In addition, early treatment might allow nephron-sparing surgery mitigating the impact of kidney function loss.
Clinical clues pointing towards a hereditary cause of RCC include positive family history, early onset (<=46 years), bilateral/multifocal tumors [7]. Specific histologic and immunohistochemical features, along with extrarenal manifestations such as skin leiomyomas or uterine fibroids in young women, are critical in guiding the histopathological workup and referral to geneticists or clinical specialists.

The recent update of the WHO classification introduced important changes with high relevance for HLRCC diagnostics and awareness of these adaptations among all disciplines involved is pivotal to provide optimal patient care.

Modern WHO classification of kidney tumors and the place of HLRCC

The 5th edition of the WHO Classification of Urinary and Male Genital Tumors (2022) [18] summarizes several tumor entities as “molecularly defined renal cell carcinomas”. This category is very heterogeneous both morphologically and regarding epidemiological and clinical features. However, this approach underscores the recent success of genitourinary pathology in identifying and systematizing multiple renal cell carcinoma (RCC) subtypes driven by a specific molecular-genetic alteration. Besides newly included FH-deficient RCC, other new molecularly defined renal cell carcinomas include TFE3/TFEB-rearranged/altered RCCs and succinate dehydrogenase (SDH)-deficient RCC, among others.

Subclassification of type 1 and 2 papillary renal cell carcinomas is no longer recommended. Clear cell papillary carcinomas have been redesignated as tumors instead of carcinomas given their indolent clinical behavior. Moreover, several provisional new papillary tumor entities are proposed to as subject to more extensive research such as papillary renal neoplasm with reversed polarity (PRNRP) with frequent RAS mutations [19], biphasic hyalinising psammomatous RCC (BHP RCC) with frequent NF2 mutations [20], biphasic squamoid/alveolar RCC [21], or thyroid-like follicular RCC (TLF RCC) [22]. These subtypes might have been diagnosed as classical papillary RCC earlier but might confer specific molecular driver alterations and crystallize as recognized tumor entities in further editions. FH-deficient carcinomas occur in context of HLRCC syndrome but can be also sporadic. While the updated approach to HLRCC diagnosis in histopathology is timely it is now important that all disciplines involved are aware of these changes. Previously, despite its shortcomings, the term type 2 papillary RCC was one of the key triggers for clinicians to consider HLRCC making awareness of this change an important asset.

Histopathological diagnosis of FH-deficient carcinomas

From a histomorphology point of view, FH-deficient carcinomas were first described as papillary tumors. Although they frequently show papillary morphology [Fig. 1 A-B, H-I] it is now recognized that these tumors can show numerous histomorphological patterns which makes their diagnosis challenging. FH-deficient carcinomas typically demonstrate multiple admixed morphological patterns, such as solid [Fig. 1 G], tubulocystic [Fig. 1 C-D, F], and some other, even including low-grade oncocytic morphology. This often leads to their classification as unclassified RCC. In general, FH-deficient carcinomas are rare and therefore might be underdiagnosed if awareness levels of pathologists are low or as a result of a lack of experience in kidney tumor pathology. Presence of eosinophilic macronucleoli is common but a very nonspecific feature of FH-deficient RCC.

Two immunohistochemical markers can be utilized as a combination to establish the diagnosis of FH-deficient RCC: fumarate hydratase (FH) and 2SC. Negative immunohistochemical staining for FH is highly specific for diagnosis [Fig. 1 K]. However, this marker might not be sensitive enough to exclude FH-deficient RCC [23], considering that there are many different *FH* variants and some pathogenic variants maintain normal

expression despite loss of heterozygosity [30]. 2SC positivity [Fig. 1 L] is highly sensitive in detecting FH deficiency but has lower specificity [24]. 2SC generation is believed to be a direct result of the post-translational modification of cysteine residues due to aberrant levels of fumarate [25]. The application of both FH and 2SC markers is crucial for differentiating FH-deficient tumors from other papillary tumors. Arguably, in cases with either loss of FH staining or marked induction of 2SC, this finding will often be sufficient to initiate genetic testing. However, the combination of FH and 2SC staining increases diagnostic confidence, particularly in ambiguous cases with mild 2SC positivity or uncertain results towards FH positivity and will allow the community to learn how closely the findings in these two markers correlate.

2SC staining can be considered a reflex immunohistochemical (IHC) test, especially in high-grade non-clear cell tumors, papillary tumors with mixed morphological patterns, tubulocystic tumors, eosinophilic tumors, and in cases with inactivating FH mutations or deletions identified through next-generation sequencing (NGS).

Importance of referral to expert centers for evaluation and genetic testing in case of FH-deficiency

Advances in understanding the mechanisms underlying hereditary tumor predisposition further emphasize timely and accurate diagnosis of these conditions. Meanwhile, diagnostic pathology of kidney tumors besides the classical histological subtypes can be very challenging. This underlines the critical role of the interface between specialties, starting at detailed collection of medical and family history, as well as assessment of possible HLRCC associated extrarenal manifestations at RCC diagnosis. It is of importance that unclear or complex cases from the morphological point of view as well as cases where proper classification will require additional stainings not established in all pathology institutes are being consulted by departments with sufficient expertise. Diagnosis of FH-deficient RCC should trigger the offer of genetic counseling and genetic testing to identify cases with causative pathogenic germline variants in *FH* (as alternative to biallelic somatic inactivation). The majority of *FH* variants characterized as pathogenic or likely pathogenic are missense variants, which are more likely to retain positive FH immunohistochemical (IHC) staining compared to the less frequent truncating variants or large deletions. Besides, as more clinical information becomes available, it is anticipated that many variants of uncertain significance will be reclassified with greater accuracy [26]. A confirmation of the diagnosis through genetic testing has substantial consequences for the patient with RCC and other family members affected. Extrarenal findings underscore the importance of close interdisciplinary collaboration, including urologists, nephrologists, radiologists, dermatologists, gynecologists, geneticists and pathologists, with important implications of early referral for genetic workup, both upon renal and extrarenal findings pointing towards HLRCC such as cutaneous leiomyomas. This close interaction is also crucial to coordinate optimal genetic counseling, renal surveillance, surgical and systemic RCC treatment, specific treatment for uterine and skin manifestations and to provide psychosocial resources and support for patients with HLRCC.

Conclusion

The 5th edition of the WHO Classification of Urinary and Male Genital Tumors provides a timely and very reasonable update to the approach towards diagnosis of hereditary forms of kidney cancer by considering molecular pathogenesis. For HLRCC, this includes both the abolition of the previous distinction of type 1 and 2 papillary RCC and the introduction of new immunohistochemical markers into clinical routine. Considering the need of close interdisciplinary interaction to allow for early diagnosis and optimal care in HLRCC it is important that all disciplines involved are aware of this update.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

None declared.

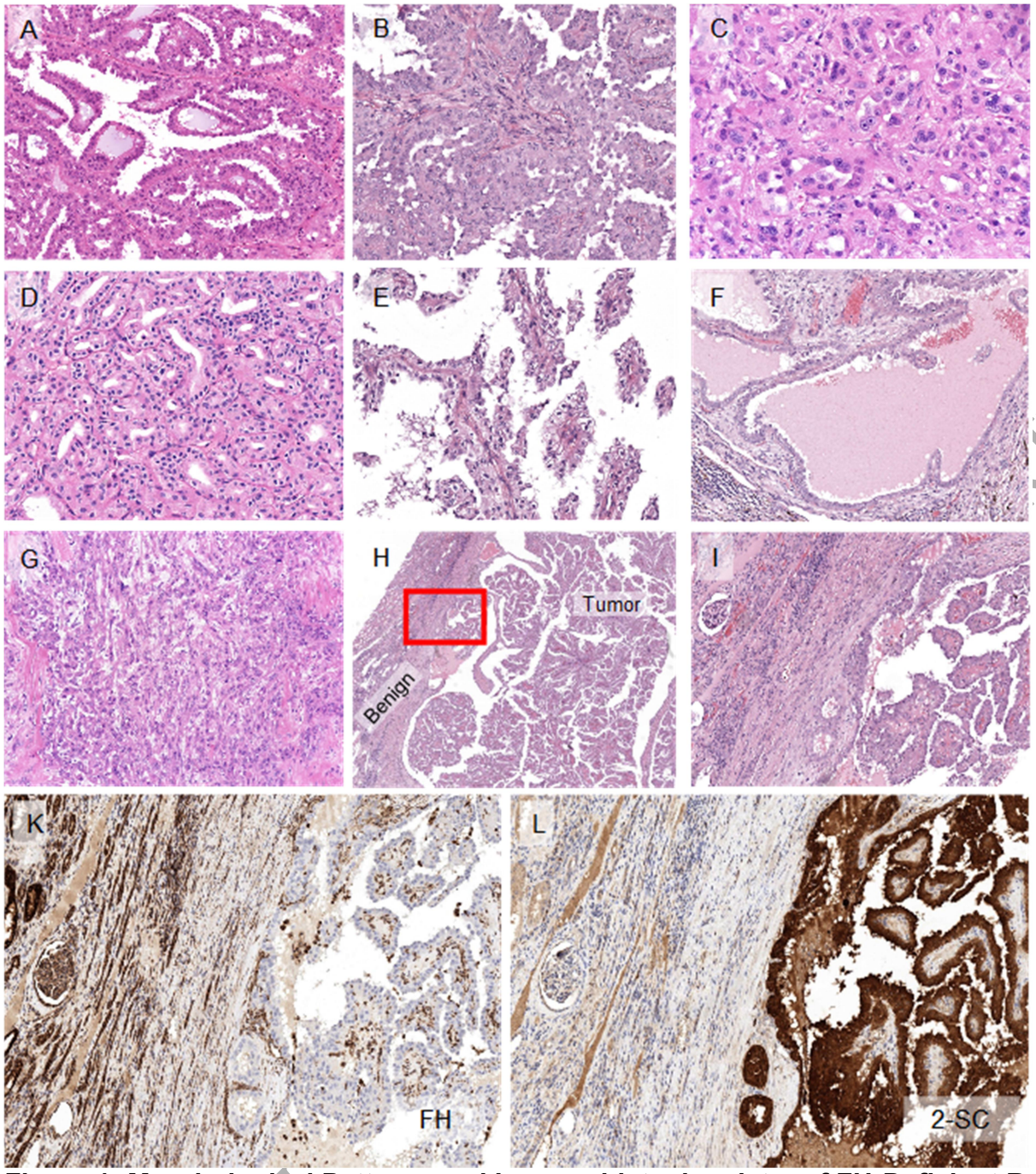

Figure 1: Morphological Patterns and Immunohistochemistry of FH-Deficient Renal Cell Carcinoma

A. Papillary pattern with a single epithelial layer.

B. Papillary pattern with pseudostratification.

C. High-grade tubular pattern.

D. Low-grade clear cell tubular pattern.

E. Low-grade papillary clear-cell pattern.

F. Cystic pattern.

G. Solid/sieve-like pattern.

H. FH-deficient renal cell carcinoma showing benign tissue (left side) and tumor tissue with papillary architecture (right side). The red region corresponds to I (higher magnification).

I. Higher magnification of region H, displaying benign tissue (left side) and tumor tissue with papillary architecture (right side).

K. Fumarate hydratase (FH) staining: retained expression in benign kidney tissue, immune cells, and stromal cells (left side), with complete loss of FH expression in tumor cells (right side). Note positive staining in stromal cells within the papillary cores.

L. 2SC staining showing the opposite pattern of FH: significant positivity in tumor cells (right side), absent in benign kidney tissue, stromal, and inflammatory cells (left side).

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