Diagnostic Pathology

CASE REPORT

Open Access

A rare case of FH-deficient renal cell carcinoma with signet ring cells features

Yin Lu[1,2], Chunfang Hu[1,3], Jiedong Jia[1,4], Ye Liu[1,2], Yanlin Wen[1,2], Huijuan Zhang[1,2], Xiaoliang Wang[1,2], Haitao Li[1,4], Guihua Shen[1,2] and Wenting Huang[1,2*]

Abstract

Fumarate hydratase-deficient renal cell carcinoma (FH-deficient RCC) is a clinically aggressive tumor with high rates of progression and mortality. A wide range of morphological variations has been observed in FH-deficient RCC, initially described as type 2 papillary RCC or unclassified RCC. Here, we report a case of FH-deficient RCC with rare signet ring cells features. The patient was diagnosed with FH-deficient renal cell carcinoma and suspected to have hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. After 4 months, pulmonary metastasis occurred in the patient. We herein describe the first case of FH-deficient renal tumor with signet ring cells features, which expands the morphological spectrum of this tumor. More importantly, this variant can be a diagnostic pitfall, we emphasize that pathologists should consider not only the diagnosis of metastatic signet ring cell carcinoma and ALK rearrangement renal cell carcinoma but also FH-deficient renal cell carcinoma.

Keywords Fumarate hydratase, Renal cell carcinoma, Signet ring cells, Metastasis, Hereditary leiomyomatosis and renal cell cancer syndrome

Introduction

FH-deficient RCC was first included as a separate entity in the 2016 WHO classification of renal cell tumors [1]. Germline mutations in tumor are associated with hereditary leiomyomatosis and renal cell cancer (HLRCC). *FH* is located on chromosome 1q42.3-43 and encodes fumarate hydratase. The latter catalyzes the conversion of fumarate to malate in the tricarboxylic acid cycle. Elevated levels of fumarate lead to the accumulation of HIF1a protein, resulting in the dysregulation of cellular metabolism and promotion of tumorigenesis [2]. FH-deficient RCC, previously categorized as type 2 papillary RCC or unclassified RCC, is reported to occur in approximately 15–30% of patients with HLRCC [3]. Elevated levels of fumarate lead to the succination of proteins and the production of S-(2-succino)-cysteine (2SC), which can serve as a marker for detecting tumors in FH-deficient RCC. Herein, we report a rare case of FH-deficient RCC with signet ring cells features.

Case presentation

A 60-year-old woman with a history of uterine leiomyoma, underwent hysterectomy 20 years previously. The patient had no relevant family history. Abdominal magnetic resonance imaging (MRI) revealed a 35×33×32 mm mass in the right kidney (Fig. 1a), suggesting the possibility of oncocytoma or chromophobe

*Correspondence:
Wenting Huang
huangwt@cicams.ac.cn
[1]Shenzhen Hospital, National Cancer Center, National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China
[2]Departments of Pathology, Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences, Shenzhen, China
[3]Departments of Pathology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China
[4]Departments of urology, Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences, Shenzhen, China

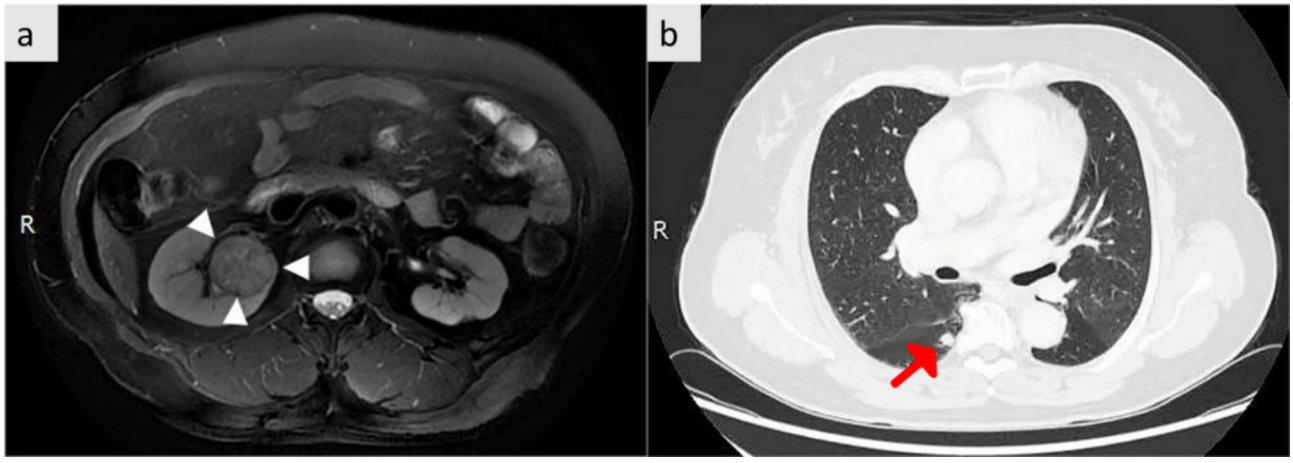

Fig. 1 Abdominal magnetic resonance imaging (MRI) revealed a right renal tumor measuring 35×33×32 mm (the white head of arrow) (**a**). Enhanced computed tomography (CT) showed an 8 mm diameter nodule in the right pulmonary (the red head of arrow) (**b**)

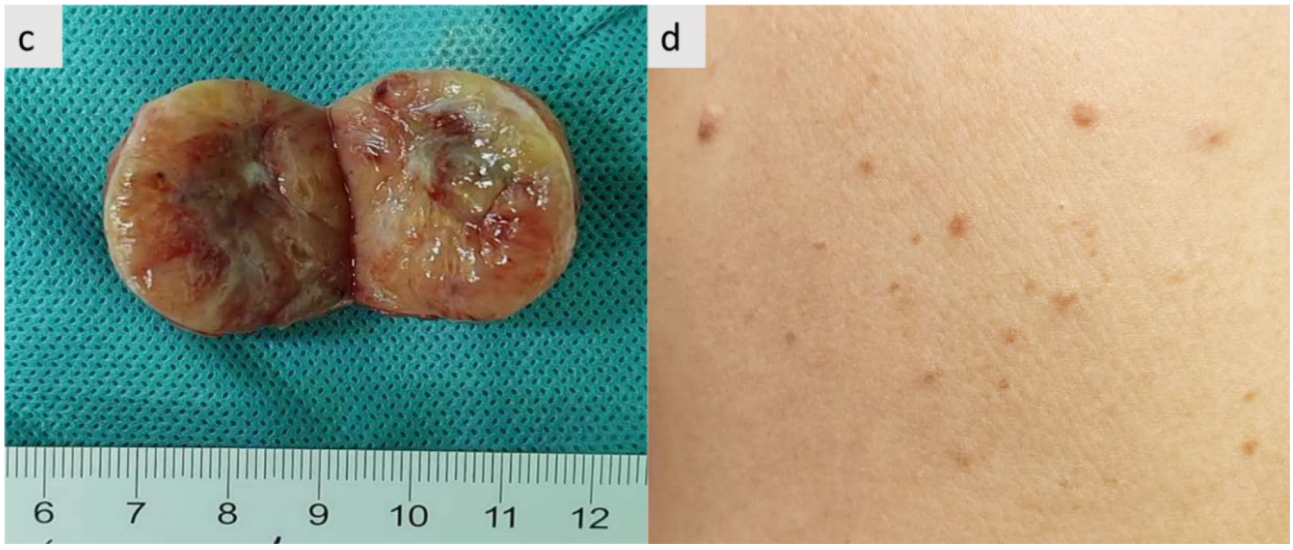

Fig. 2 Gross specimen examination revealed a predominantly solid and encapsulated mass (**c**). Multiple papules or nodules were observed on the skin of the trunk, suspected to be cutaneous leiomyomas (**d**)

renal cell carcinoma. Recently, nodules or papules have been observed on the patient's trunk skin (Fig. 2d), suggesting the potential presence of cutaneous leiomyomas. However, this remains to be confirmed by pathology. The patient underwent partial nephrectomy. Histological examination of the gross specimen revealed an encapsulated mass measuring 41×35×33 mm (Fig. 2c). Microscopically, a variety of growth patterns were observed in the tumor, including papillary, tubulocystic, cystic, and cribriform patterns (Fig. 3e-g). The tumor cells displayed eosinophilic cytoplasm and a high nuclear grade (WHO/ISUP 3), characterized by viral inclusion-like macronucleoli and perinucleolar halos (Fig. 3j). Additionally, some areas demonstrated intracytoplasmic mucin resembling signet ring cells (Fig. 3h-i). Foamy macrophages and hemosiderin were also observed. Immunohistochemically, the tumor cells were positive for CK8/18, Pax-8, Pax-2, P504s, SDHB, and 2-succinylcysteine (2SC) protein (Fig. 4l) but negative for CK7, CD10, CD117, CAIX, FH (Fig. 4k), ALK, and TFE3 protein. Intracytoplasmic mucin was detected by MUC1 (Fig. 4m) and Alcian blue staining (Fig. 4n). The proliferation rate of Ki-67 was approximately 20%.

Finally, the patient was diagnosed with FH-deficient renal cell carcinoma. Owing to the presence of uterine leiomyomas and suspected cutaneous leiomyomas, we strongly considered it to be associated with hereditary leiomyomatosis and renal cell cancer syndrome.

The postoperative course of the patient was uneventful, and neither adjuvant radiotherapy nor chemotherapy was performed. After a period of four months, a nodule measuring 8×7 mm was observed in the right pulmonary

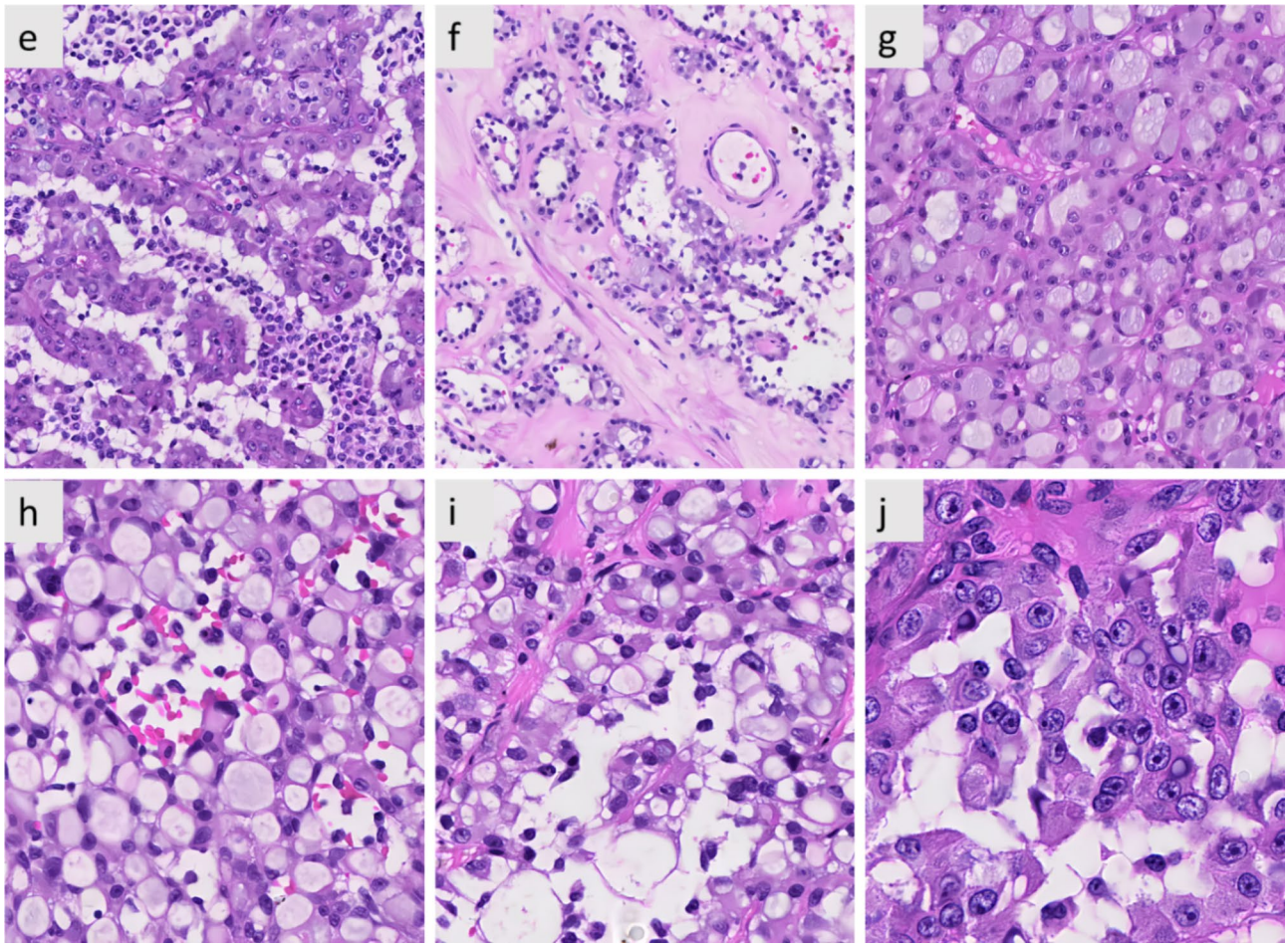

Fig. 3 Various growth patterns of FH-deficient RCC. There were papillary (**e**), tubulocystic/cystic (**f**) and cribriform (**g**) patterns observed in the tumor. Prominent intracytoplasmic mucin or non-mucous vacuole was observed in the section of the tumor, resembling signet ring cells (**h-i**). These tumor cells displayed a high nuclear grade (WHO/ISUP 3), with eosinophilic cytoplasm, viral inclusion-like macronucleoli and perinucleolar halos (**j**)

area (Fig. 1b), indicating the presence of pulmonary metastasis.

Discussion

The term "FH-deficient RCC" is increasingly used to describe RCC with FH protein loss by IHC, especially in cases where the genetic status is unknown [4] or there is no evidence of an *FH* germline mutation [5] at pathological diagnosis. Tumors with *FH* germline mutations are associated with HLRCC. FH-deficient RCC occurs in approximately 15–30% of patients with HLRCC, with a risk 6.5-fold higher than that in the general population [6]. Therefore, it is important to recognize of this entity. FH-deficient RCC often show a morphologically overlapping spectrum with type 2 papillary renal cell carcinoma. Several studies [5, 7–9] have described a rare, low-grade form of FH-deficient RCC, characterized by abundant eosinophilic cytoplasm with variable flocculence and vacuolization. These tumors morphologically resemble low-grade oncocytic renal tumors, such as oncocytoma, succinate dehydrogenase (SDH)-deficient RCC, or other oncocytic tumors. In this study, we report a case of FH-deficient renal cell carcinoma with rare signet ring cells morphology and intracytoplasmic mucin. The differential diagnosis we initially considered are metastatic signet ring cell carcinoma and ALK rearrangement renal cell carcinoma. Interestingly, it has been reported that the presence of signet ring cells morphology was observed in renal cell carcinoma with a novel *STRN::ALK* fusion [10]. Signet ring cells features are commonly observed in poorly differentiated adenocarcinomas of the stomach, breast and colorectum. Tumor with predominant signet ring cells features (>50%) can be categorized as signet ring cells carcinoma, which represents a subset of tumors with an aggressive biological behavior that is prone to a peritoneal spreading pattern [11] and has a poor prognosis [12–15]. It is crucial for pathologists to identify and report the presence of signet ring cells features from a clinical perspective.

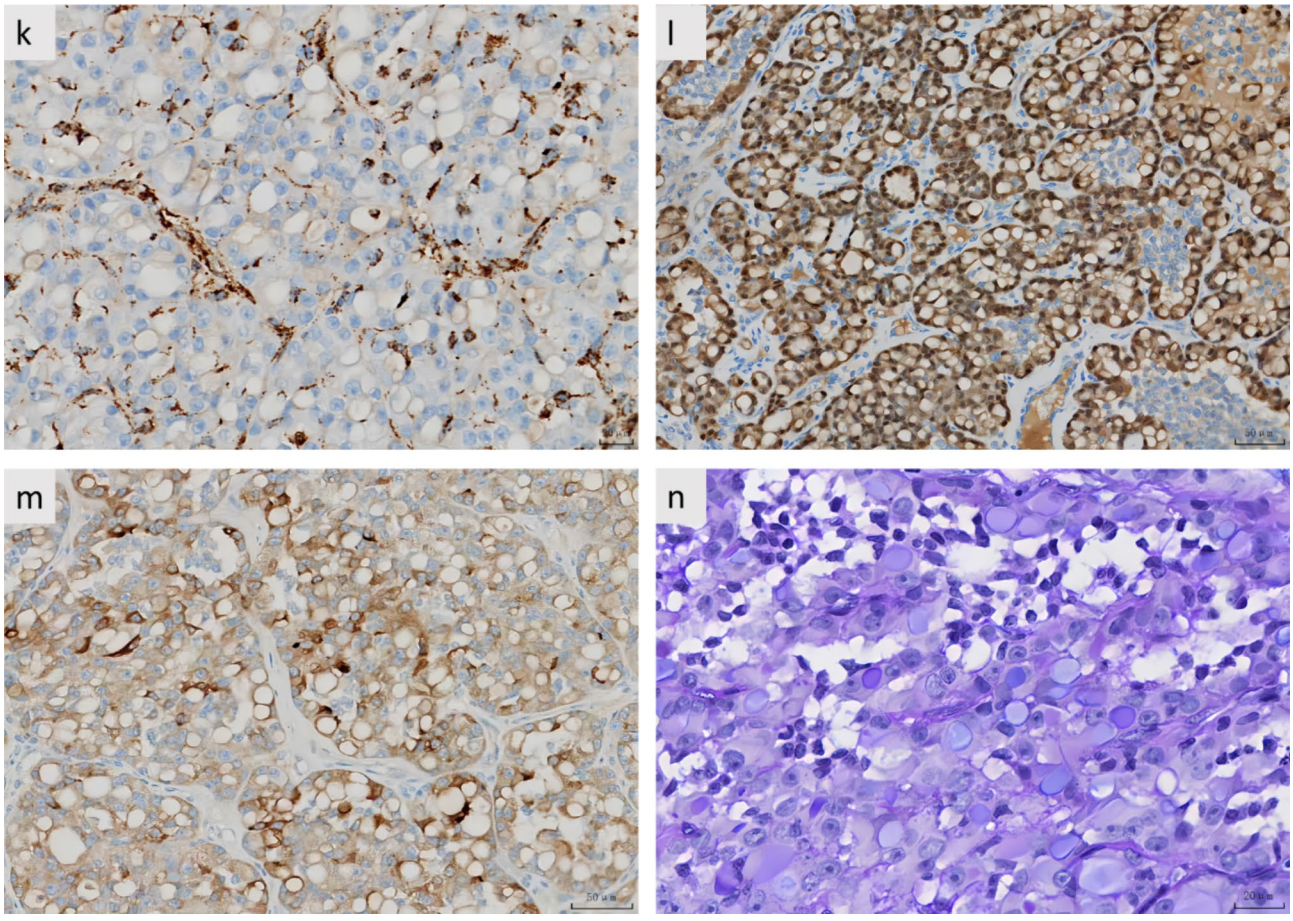

Fig. 4 Immunohistochemical staining showed diffuse loss of FH staining in tumor cells, with stromal cells and blood vessel endothelial cells serving as internal positive controls (**k**). The tumor cells showed diffuse expression of 2SC staining (**l**). Intracytoplasmic mucin was demonstrated by MUC1 (**m**) and Alcian blue staining (**n**)

FH and 2-SC IHC are highly sensitive and reliable adjunct tools for the detection of FH-deficient RCC. However, FH is not 100% sensitive for detecting FH-deficient RCC [8, 16–18]. Up to 20-25% of FH-deficient RCC may still show FH expression, which can be a diagnostic pitfall, especially without access to 2SC immunohistochemistry. There are similar reports on missense mutations in the *FH* gene that may retain FH expression [6, 19, 20]. Additionally, it is uncommon to observe heterogeneous FH expression in some genomically proven FH-deficient RCC [6]. Therefore, it is crucial to recognize and confirm *FH* mutation analysis. Member B10 of the aldo-keto reductase family 1 (AKR1B10), is a potential biomarker for FH-deficient uterine leiomyomas [21], with 100% sensitivity and 99% specificity. A recent new study [22] indicated that AKR1B10 is a significant diagnostic biomarker with 100% sensitivity and 91.4% specificity for FH-deficient RCC. Therefore, the combination of FH, AKR1B10, and 2SC is expected to improve the detection rate of FH-deficient RCC.

Notably, there is a high incidence of early and extensive distant metastases in FH-deficient RCC, although the primary tumor is small, which is the primary factor contributing to mortality. The most recent common ancestor (MRCA)-dominated punctuated evolutionary pattern [23] was primarily proposed in FH-deficient RCC, suggesting that metastatic competence is acquired in primary MRCA and leads to rapid progression. Similar findings were also observed by TRACERx renal team [24]. In our case, the patient developed rapid lung metastasis. We attribute this to two potential factors. First, occult micro-metastases may be present at the time of initial diagnosis or even earlier. Second, signet ring cells features may indicate poor prognosis, leading to rapid metastasis and potentially fatal consequences. However, we currently lack adequate evidence to establish that the presence of signet ring cell features is indicative of a poor prognosis in this highly aggressive malignant tumor, which requires more clinical cases and related clinical experiments. Although it was not possible to alter the inherent invasiveness of the FH gene mutation, according

to the MRCA-dominated punctuated evolutionary pattern, primary tumors may act as a reservoir of metastasis and early intervention can lead to a positive clinical therapeutic outcome. To eliminate tumors to the maximum extent possible, radical nephrectomy may be the preferred local treatment for individuals without metastasis. Several prospective clinical trials have recommended cytoreductive nephrectomy (CN) for metastatic ccRCC patients [23, 25, 26]. Therefore, some scholars have proposed that patients with metastatic FH-deficient RCC could also benefit from CN [23].

In recent years, there has been growing focus on exploring the potential therapeutic value of FH-deficient renal cell carcinoma. *CDKN2A* promoter hypermethylation is commonly observed in FH-deficient RCC, suggesting the potential of CDK4/6 inhibitors in this type of RCC. The study conducted by Liang et al. [23] reported an unfavorable response to PD-1/PD-L1-based therapy and a poor prognosis in patients with *NF2* mutations. Several studies have revealed that bevacizumab plus erlotinib (Bev/Erlo) therapy shows promising results for advanced HLRCC-associated RCC [27, 28]. A prospective study showed that VEGF treatment presented an ORR of 22.2% and a disease control rate (DCR) of 30% in FH-deficient RCC, while combined therapy with VEGF and checkpoint inhibitors in the tumor had an ORR of 40% and a DCR of 100% [29]. A clinical trial of patients with advanced FH-deficient RCC showed that ICI/TKI combination therapy was associated with more favorable OS and PFS on first-line therapy than Bev/Erlo combination therapy [30]. In a prospective clinical trial, a 49-year-old man with HLRCC-associated RCC showed a complete response to combination immunotherapy with nivolumab and ipilimumab [31]. Although some clinical trials have shown encouraging results, owing to limited clinical data, there is currently no consensus on the treatment of FH-deficient RCC.

Conclusion

We are the first to describe signet ring cells features in FH-deficient RCC, which expands the morphological spectrum of FH-deficient tumors. Early identification and clinical intervention are crucial for patients. Subsequent genetic counseling and screening for *FH* variants are advised for patients and their family members.

Acknowledgements
The author would like to thank their colleagues and reviewers for their clinical data and critical advice.

Author contributions
YL wrote the manuscript; CFH, JDJ, and YL collected the patient's clinical data and radiologic findings; XLW, YLW, and HTL analyzed the figures; WTH and HJZ revised the manuscript; GHS performed immunohistochemical studies; all authors revised and endorsed the manuscript.

Funding
Supported by Shenzhen High-level Hospital Construction Fund and Shenzhen Clinical Research Center for Cancer (No. [2021] 287).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics statement
Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Conflict of interest
All authors have no conflicts of interest to declare in relation to this article.

Competing interests
The authors declare no competing interests.

Received: 11 September 2024 / Accepted: 28 November 2024
Published online: 18 December 2024

References

1. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of Tumours of the urinary system and male genital organs-Part A: renal, Penile, and testicular tumours. Eur Urol. 2016;70(1):93–105.
2. Patel VM, Handler MZ, Schwartz RA, Lambert WC. Hereditary leiomyomatosis and renal cell cancer syndrome: an update and review. J Am Acad Dermatol. 2017;77(1):149–58.
3. Menko FH, Maher ER, Schmidt LS, Middelton LA, Aittomaki K, Tomlinson I, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer. 2014;13(4):637–44.
4. Trpkov K, Hes O. New and emerging renal entities: a perspective post-WHO 2016 classification. Histopathology. 2019;74(1):31–59.
5. Pan X, Zhang M, Yao J, Zeng H, Nie L, Gong J, et al. Fumaratehydratase-deficient renal cell carcinoma: a clinicopathological and molecular study of 13 cases. J Clin Pathol. 2019;72(11):748–54.
6. Anderson WJ, Tsai HK, Sholl LM, Hirsch MS. A clinicopathological and molecular analysis of Fumarate Hydratase (FH)-deficient renal cell carcinomas with heterogeneous loss of FH expression. Int J Surg Pathol. 2022;30(6):606–15.
7. Lau HD, Chan E, Fan AC, Kunder CA, Williamson SR, Zhou M, et al. A clinicopathologic and molecular analysis of Fumarate Hydratase-deficient renal cell carcinoma in 32 patients. Am J Surg Pathol. 2020;44(1):98–110.
8. Smith SC, Sirohi D, Ohe C, McHugh JB, Hornick JL, Kalariya J, et al. A distinctive, low-grade oncocytic fumarate hydratase-deficient renal cell carcinoma, morphologically reminiscent of succinate dehydrogenase-deficient renal cell carcinoma. Histopathology. 2017;71(1):42–52.
9. Li Y, Reuter VE, Matoso A, Netto GJ, Epstein JI, Argani P. Re-evaluation of 33 'unclassified' eosinophilic renal cell carcinomas in young patients. Histopathology. 2018;72(4):588–600.
10. Kusano H, Togashi Y, Akiba J, Moriya F, Baba K, Matsuzaki N, et al. Two cases of renal cell carcinoma harboring a Novel STRN-ALK Fusion Gene. Am J Surg Pathol. 2016;40(6):761–9.
11. Solomon D, DeNicola N, Feingold D, Liu PH, Aycart S, Golas BJ, et al. Signet ring cell features with peritoneal carcinomatosis in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are associated with poor overall survival. J Surg Oncol. 2019;119(6):758–65.
12. Remo A, Fassan M, Vanoli A, Bonetti LR, Barresi V, Tatangelo F et al. Morphology and Molecular Features of Rare Colorectal Carcinoma Histotypes. Cancers (Basel). 2019;11(7).
13. Sheng H, Wei X, Mao M, He J, Luo T, Lu S, et al. Adenocarcinoma with mixed subtypes is a rare but aggressive histologic subtype in colorectal cancer. BMC Cancer. 2019;19(1):1071.
14. Legue LM, van Erning FN, Creemers GJ, de Hingh I, Lemmens V, Huysentruyt CJ. The prognostic relevance of histologic subtype in appendiceal adenocarcinoma. Eur J Surg Oncol. 2020;46(3):433–8.

15. Tuncel D, Basturk O, Bradley KT, Kim GE, Xue Y, Reid MD, et al. Poorly cohesive (Signet Ring Cell) Carcinoma of the Ampulla of Vater. Int J Surg Pathol. 2020;28(3):236–44.
16. Chen YB, Brannon AR, Toubaji A, Dudas ME, Won HH, Al-Ahmadie HA, et al. Hereditary leiomyomatosis and renal cell carcinoma syndrome-associated renal cancer: recognition of the syndrome by pathologic features and the utility of detecting aberrant succination by immunohistochemistry. Am J Surg Pathol. 2014;38(5):627–37.
17. Muller M, Guillaud-Bataille M, Salleron J, Genestie C, Deveaux S, Slama A, et al. Pattern multiplicity and fumarate hydratase (FH)/S-(2-succino)-cysteine (2SC) staining but not eosinophilic nucleoli with perinucleolar halos differentiate hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinomas from kidney tumors without FH gene alteration. Mod Pathol. 2018;31(6):974–83.
18. Trpkov K, Hes O, Agaimy A, Bonert M, Martinek P, Magi-Galluzzi C, et al. Fumarate Hydratase-deficient renal cell carcinoma is strongly correlated with Fumarate Hydratase Mutation and Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome. Am J Surg Pathol. 2016;40(7):865–75.
19. Skala SL, Dhanasekaran SM, Mehra R. Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HLRCC): a contemporary review and practical discussion of the Differential diagnosis for HLRCC-Associated Renal Cell Carcinoma. Arch Pathol Lab Med. 2018;142(10):1202–15.
20. Kuroda N, Tsutsui M, Iguchi M, Nobuoka E, Uehara T, Sonobe Y, et al. Fumarate hydratase-deficient renal cell carcinoma: a clinicopathological study of seven cases including hereditary and sporadic forms. Ann Diagn Pathol. 2020;49:151599.
21. Ahvenainen T, Kaukomaa J, Kampjarvi K, Uimari O, Ahtikoski A, Makinen N, et al. Comparison of 2SC, AKR1B10, and FH Antibodies as potential biomarkers for FH-deficient Uterine Leiomyomas. Am J Surg Pathol. 2022;46(4):537–46.
22. Zheng L, Zhang X, Pan X, Huang Z, Zhang M, Xian J, et al. AKR1B10 is a new sensitive and specific marker for Fumarate Hydratase-Deficient Renal Cell Carcinoma. Mod Pathol. 2023;36(11):100303.
23. Liang J, Sun G, Pan X, Zhang M, Shen P, Zhu S, et al. Genomic and transcriptomic features between primary and paired metastatic fumarate hydratase-deficient renal cell carcinoma. Genome Med. 2023;15(1):31.
24. Turajlic S, Xu H, Litchfield K, Rowan A, Chambers T, Lopez JI, et al. Tracking Cancer Evolution reveals constrained routes to metastases: TRACERx Renal. Cell. 2018;173(3):581–94. e12.
25. Mejean A, Ravaud A, Thezenas S, Colas S, Beauval JB, Bensalah K, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med. 2018;379(5):417–27.
26. Bex A, Mulders P, Jewett M, Wagstaff J, van Thienen JV, Blank CU, et al. Comparison of Immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving Sunitinib: the SURTIME Randomized Clinical Trial. JAMA Oncol. 2019;5(2):164–70.
27. Choi Y, Keam B, Kim M, Yoon S, Kim D, Choi JG, et al. Bevacizumab Plus Erlotinib Combination Therapy for Advanced Hereditary Leiomyomatosis and Renal Cell Carcinoma-Associated Renal Cell Carcinoma: a Multicenter Retrospective analysis in Korean patients. Cancer Res Treat. 2019;51(4):1549–56.
28. Park I, Shim YS, Go H, Hong BS, Lee JL. Long-term response of metastatic hereditary leiomyomatosis and renal cell carcinoma syndrome associated renal cell carcinoma to bevacizumab plus erlotinib after temsirolimus and axitinib treatment failures. BMC Urol. 2019;19(1):51.
29. Bai J, Li X, Wen Y, Lu Q, Chen R, Liu R, et al. The clinicopathologic and molecular features, and treatment outcome of fumarate hydratase-deficient renal cell carcinoma: a retrospective comparison with type 2 papillary renal cell carcinoma. Aging. 2024;16(4):3631–46.
30. Xu Y, Kong W, Cao M, Wang J, Wang Z, Zheng L, et al. Genomic profiling and response to Immune Checkpoint inhibition plus tyrosine kinase inhibition in FH-Deficient Renal Cell Carcinoma. Eur Urol. 2023;83(2):163–72.
31. Iribe Y, Furuya M, Shibata Y, Yasui M, Funahashi M, Ota J, et al. Complete response of hereditary leiomyomatosis and renal cell cancer (HLRCC)-associated renal cell carcinoma to nivolumab and ipilimumab combination immunotherapy by: a case report. Fam Cancer. 2021;20(1):75–80.

Publisher's note