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Low-grade Oncocytic Fumarate Hydratase-deficient Renal Cell Carcinoma in a Patient with Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome: A Case Report

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Short Report

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Abstract

Introduction:

Fumarate hydratase (FH)-deficient renal cell carcinoma (RCC) is generally an aggressive, high-grade tumor with a poor prognosis. We report a case of low-grade oncocytic FH-deficient RCC with a favorable course and discuss it in the context of the genotype-phenotype relationship in FH-deficient RCC.

Case presentation:

A woman in her 70s was found to have bilateral multifocal renal tumors on PET-CT performed during the work-up of a left cervical mass. She underwent robot-assisted partial nephrectomy of the left kidney. Histopathology showed a low-grade oncocytic renal tumor (pT1aNXMX, WHO/ISUP grade 2) without sarcomatoid change or necrosis, and immunohistochemistry demonstrated loss of FH expression with 2SC positivity, establishing the diagnosis of low-grade oncocytic FH-deficient RCC. Germline genetic testing identified a heterozygous *FH* missense variant, c.584T > C (p.Met195Thr), confirming hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. The pedigree showed maternal-line uterine leiomyomatosis consistent with autosomal dominant transmission. The postoperative course was uneventful, with no recurrence or metastasis. The cervical mass proved to be a benign thyroid nodule unrelated to the renal tumor.

Conclusion

FH-deficient RCC can present as a low-grade, organ-confined tumor with a favorable course. The identical germline *FH* variant (p.Met195Thr) has elsewhere caused an aggressive tumor, underscoring that the germline genotype does not by itself determine prognosis. Management according to FH-deficient RCC and genetic counseling of relatives remain essential.

Introduction

Fumarate hydratase (FH)-deficient renal cell carcinoma (RCC) is a rare, molecularly defined histological type recognized as a distinct entity in the 2022 World Health Organization classification [1]. It arises from biallelic inactivation of FH, encoding a Krebs-cycle enzyme and recognized as a tumor-suppressor gene located on chromosome 1q43 [2]. Immunohistochemically, the tumor is characterized by loss of FH expression with positivity for S-(2-succino)-cysteine (2SC) [4]. Some cases occur in the setting of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, an autosomal dominant syndrome caused by pathogenic germline *FH* variants that predisposes to cutaneous and uterine leiomyomas and to an aggressive form of RCC [2, 3].

Pathogenic *FH* variants are heterogeneous [5]. They include loss-of-function (LOF) variants (nonsense, frameshift, canonical splice-site variants, and large deletions) and missense variants. Whereas LOF variants generally abolish enzymatic activity completely, many missense variants retain partial residual activity. The relationship between the type of pathogenic *FH* variant and the behavior of FH-deficient RCC, however, remains conflicting and unresolved: no consistent genotype-phenotype or genotype-prognosis correlation has been established, several studies have found no clear correlation, and reports of individual cases are contradictory, with both indolent and aggressive tumors described across variant classes [6, 7, 8].

Although FH-deficient RCC is typically high-grade and aggressive, a low-grade oncocytic variant with an apparently more indolent course has been recognized [9, 10]. Here we report such a case, harboring a germline *FH* missense variant, c.584T > C (p.Met195Thr), with a favorable course, and discuss it in the context of the genotype-phenotype relationship in FH-deficient RCC.

Case Presentation

A woman in her 70s noticed swelling in the left side of her neck in September of year X − 1. In October of year X − 1, PET-CT performed to evaluate the cervical mass incidentally revealed multiple bilateral renal tumors with abnormal uptake, and she was referred to our department for further evaluation and treatment. Fine-needle aspiration cytology of the cervical mass showed benign findings (Papanicolaou class II), and imaging showed no features suggestive of cervical lymph node metastasis; the mass was therefore regarded as a benign thyroid nodule (thyroid adenoma). Her past medical history included appendicitis at age 19 and uterine leiomyoma at age 25, for which she underwent myomectomy and, subsequently, total hysterectomy. Her medications were olmesartan and amlodipine for hypertension, montelukast for asthma and allergic rhinitis, and pirenoxine for cataract. She had no skin lesions suggestive of cutaneous leiomyoma. Her family history was notable for uterine leiomyomas in a maternal-line distribution spanning four generations: her maternal grandmother (leiomyoma at age 50), her mother (age 40), the patient herself (age 25), her sister (age 63, who also developed a cecal carcinoma at age 65), and her niece (age 40), with hypertension frequent among affected relatives; her father had prostate cancer at age 60. The pedigree was consistent with autosomal dominant transmission (Fig. 1).

Contrast-enhanced computed tomography and magnetic resonance imaging demonstrated multiple solid renal tumors bilaterally. The left kidney contained multifocal lesions, including two tumors measuring approximately 15 mm and 7 mm, and a small tumor was also present in the contralateral right kidney. There was no evidence of lymphadenopathy or distant metastasis.

In February of year X, the patient underwent robot-assisted partial nephrectomy of the left kidney. The total operative time was 1 h 59 min, the console time was 1 h 39 min, and the warm ischemia time was 26 min, with minimal blood loss. Two tumors weighing approximately 3 g in total were resected, and the postoperative course was uneventful.

On gross and microscopic examination, the tumors measured 15 × 14 × 11 mm and 7 × 7 × 6 mm and were accompanied by a satellite lesion (enzyme-altered foci). The tumor cells had abundant eosinophilic cytoplasm and showed low-grade oncocytic morphology. The WHO/ISUP grade was 2, with no sarcomatoid or rhabdoid change and no necrosis, and the tumor was confined to the kidney (Fig. 2A, B). The pathological stage was pT1a NX MX, Ly0, V0.

Immunohistochemistry

Marker	Result
FH	Loss of expression
2SC (S-(2-succino)-cysteine)	Positive
AE1/AE3	Positive
CK7	Positive
AMACR	Positive
CA9	Negative
c-kit (CD117)	Negative

Immunohistochemistry showed loss of FH expression with 2SC positivity (Fig. 2C, D) in the tumor cells, indicating fumarate accumulation due to reduced FH activity. Cytokeratin (CK) (AE1/AE3), CK7, and AMACR were positive and SDHB was weakly positive (data not shown), whereas carbonic anhydrase 9 (CA9) and c-kit were negative, supporting the diagnosis of FH-deficient RCC and distinguishing it from other oncocytic renal tumors such as oncocytoma and chromophobe RCC positive for c-kit, and succinate dehydrogenase (SDH)-deficient RCC, in which SDHB expression is lost. Because this recently recognized subtype cannot be established only on morphology, the diagnosis of low-grade oncocytic FH-deficient RCC (with a satellite lesion of enzyme-altered foci) was made by integrating the histological exclusion of other eosinophilic renal tumors and the loss of FH expression with 2SC positivity.

Because of the bilateral multifocal tumors and the FH-deficient phenotype, HLRCC was strongly suspected. After genetic counseling, germline *FH* testing was performed on peripheral blood and identified a heterozygous missense variant, c.584T > C (p.Met195Thr) (*FH*, NM_000143.4). This variant corresponds to rs863223965, is classified as pathogenic/likely pathogenic in ClinVar, has an allele frequency of 0.000013 in the Japanese ToMMo (jMorp) database [11], and is absent from gnomAD. The diagnosis of HLRCC was thereby confirmed.

The clinical course is summarized in Table 1. The patient has remained free of recurrence or metastasis. The small contralateral lesion is being managed with imaging surveillance under a nephron-sparing strategy, and genetic counseling has been extended to her relatives.

Table 1
Timeline of the clinical course.

Time point	Events
September, year X − 1	The patient noticed swelling in the left side of the neck.
October, year X − 1	PET-CT performed to evaluate the cervical mass incidentally revealed multiple bilateral renal tumors with abnormal uptake; the patient was referred to our department. Fine-needle aspiration cytology of the cervical mass showed benign findings (Papanicolaou class II), and the mass was regarded as a benign thyroid nodule.
Year X − 1 to year X (preoperative)	Contrast-enhanced CT and MRI demonstrated multifocal solid tumors in the left kidney (15 mm and 7 mm) and a small tumor in the right kidney, without lymphadenopathy or distant metastasis.
February, year X	Robot-assisted partial nephrectomy of the left kidney (operative time 1 h 59 min; warm ischemia time 26 min). The postoperative course was uneventful.
After surgery	Histopathology and immunohistochemistry established low-grade oncocytic FH-deficient renal cell carcinoma (pT1a NX MX, WHO/ISUP grade 2; loss of FH expression with 2SC positivity).
After genetic counseling	Germline testing identified a heterozygous FH variant, c.584T > C (p.Met195Thr), confirming HLRCC syndrome.
Follow-up to date	No recurrence or metastasis. Imaging surveillance of the contralateral lesion under a nephron-sparing strategy; genetic counseling extended to relatives.

Discussion

One notable feature of the present case is that the low-grade, indolent phenotype was in line with what might be expected for a missense variant.

However, this concordance should be interpreted with caution, because the germline variant type does not by itself determine tumor grade or behavior. The phenotype is shaped largely by the somatic second hit, which can abolish FH activity regardless of whether the germline variant is missense or truncating, and by additional modifiers; accordingly, genotype-phenotype correlations in HLRCC are weak [3, 6]. Low-grade FH-deficient RCC is a recognized, generally indolent variant [9, 10] reported with both missense and inactivating variants [7, 8, 12, 13], and the identical variant in our patient (p.Met195Thr) has elsewhere caused an aggressive type 2 papillary RCC in a 42-year-old woman [14], in contrast to the low-grade, indolent tumor here. The favorable course therefore likely reflects the low-grade oncocytic histology rather than the germline variant alone. Notably, the cervical mass that led to the incidental detection of the renal tumors was a benign thyroid nodule rather than metastatic disease, supporting the organ-confined and indolent nature of the present tumor. The somatic second hit was not molecularly characterized in this case; FH loss with 2SC positivity confirms functional biallelic inactivation, but its mechanism (loss of heterozygosity, somatic mutation, or methylation) was not determined.

Regardless of grade, this tumor should be managed as FH-deficient RCC. Given the bilateral multifocal disease and the confirmed germline *FH* variant, a nephron-sparing approach with lifelong imaging surveillance of both kidneys was adopted, and genetic counseling with cascade testing of relatives is essential [3]. Because HLRCC-associated RCC can arise at a young age and may show genetic anticipation, renal imaging surveillance of at-risk relatives from an early age is warranted [14]; this is particularly relevant here given the extensive maternal-line leiomyomatosis in the pedigree.

Conclusion

We reported a rare, low-grade oncocytic FH-deficient RCC with a favorable course. The same germline *FH* variant (p.Met195Thr) has elsewhere caused an aggressive tumor, underscoring that the germline genotype does not by itself determine prognosis. Regardless of grade, such tumors should be managed as FH-deficient RCC, with genetic counseling and surveillance of at-risk relatives.

Declarations

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Conflicts of interest/Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This case report was conducted in accordance with the Declaration of Helsinki. In accordance with the policy of Jyoban Hospital of Tokiwa Foundation, ethics committee approval is not required for a case report of a single patient.

Consent to participate

Written informed consent to participate was obtained from the patient.

Written consent for publication

Written informed consent for publication of the clinical details and the accompanying images was obtained from the patient. A copy of the signed consent form is available for review by the Editor-in-Chief of this journal on request.

Availability of data and material

All data generated or analysed during this study are included in this published article. Additional data supporting the findings of this case report are available from the corresponding author on reasonable request, within the limits of patient confidentiality.

Code availability

Not applicable.

Authors' contributions

Haruhisa Ozawa and Akihiko Ozaki wrote the first draft of the manuscript. Haruhisa Ozawa, Yujin Kaneko, Kensuke Sakamoto, Ayane Tachiki, Genki Takei, Yukiko Kouchi, Naoto Yoshida and Hiroaki Shimmura were responsible for the urological management and surgical treatment of the patient and collected the clinical data. Kenji Gonda and Akihiko Ozaki were involved in genetic counselling and interpretation of the germline testing. Shinichi Hirooka and Yoji Nagashima performed the histopathological and immunohistochemical evaluation and established the pathological diagnosis. All authors critically revised the manuscript, and all authors read and approved the final version.

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Figures

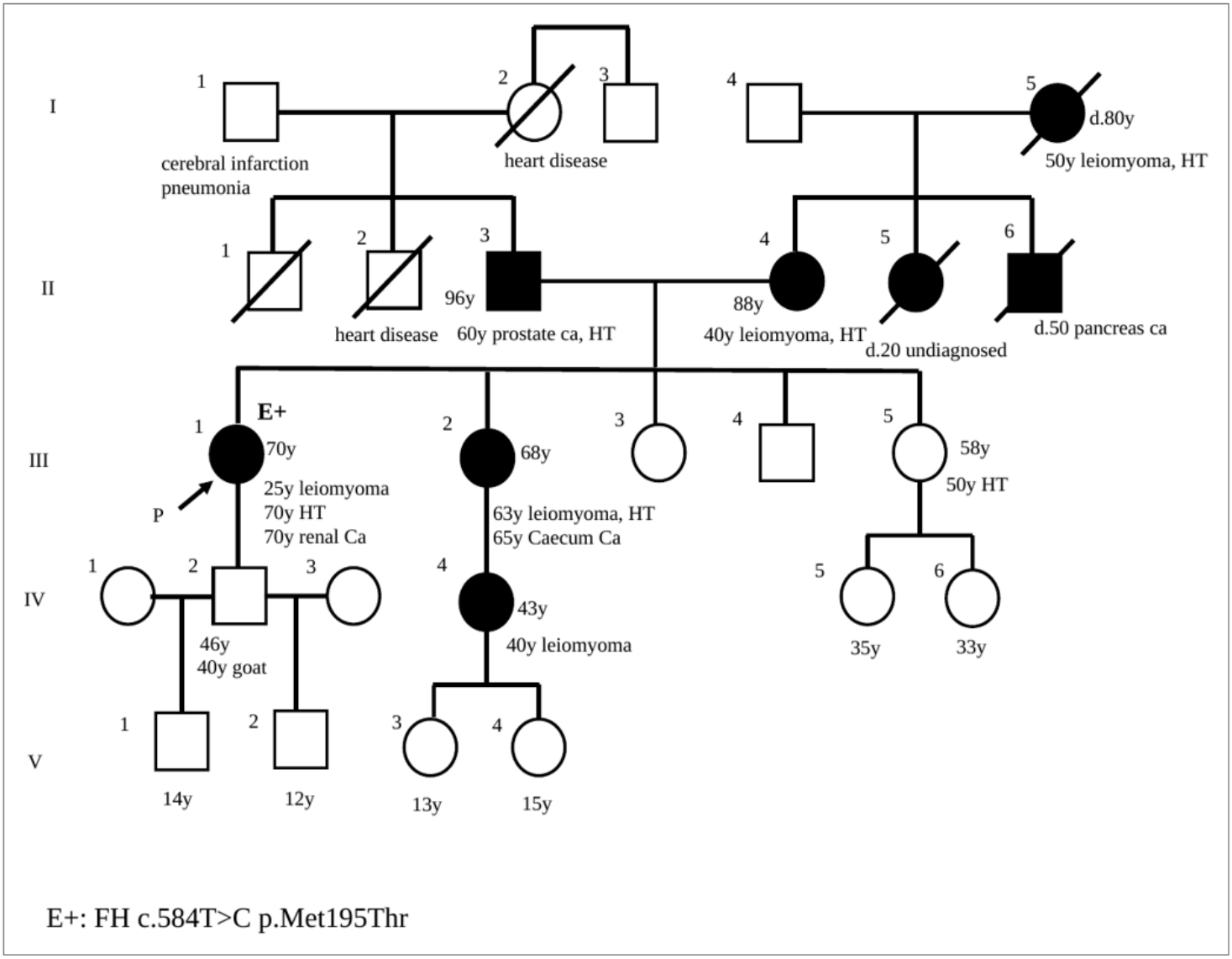


Figure 1

Family pedigree. The proband (arrow) is a heterozygous carrier of the germline *FH* variant c.584T>C (p.Met195Thr) (E+). Uterine leiomyomas (several of early onset) and hypertension are distributed along the maternal line across four generations, consistent with autosomal dominant transmission. Filled symbols denote affected individuals; a diagonal line denotes a deceased individual.

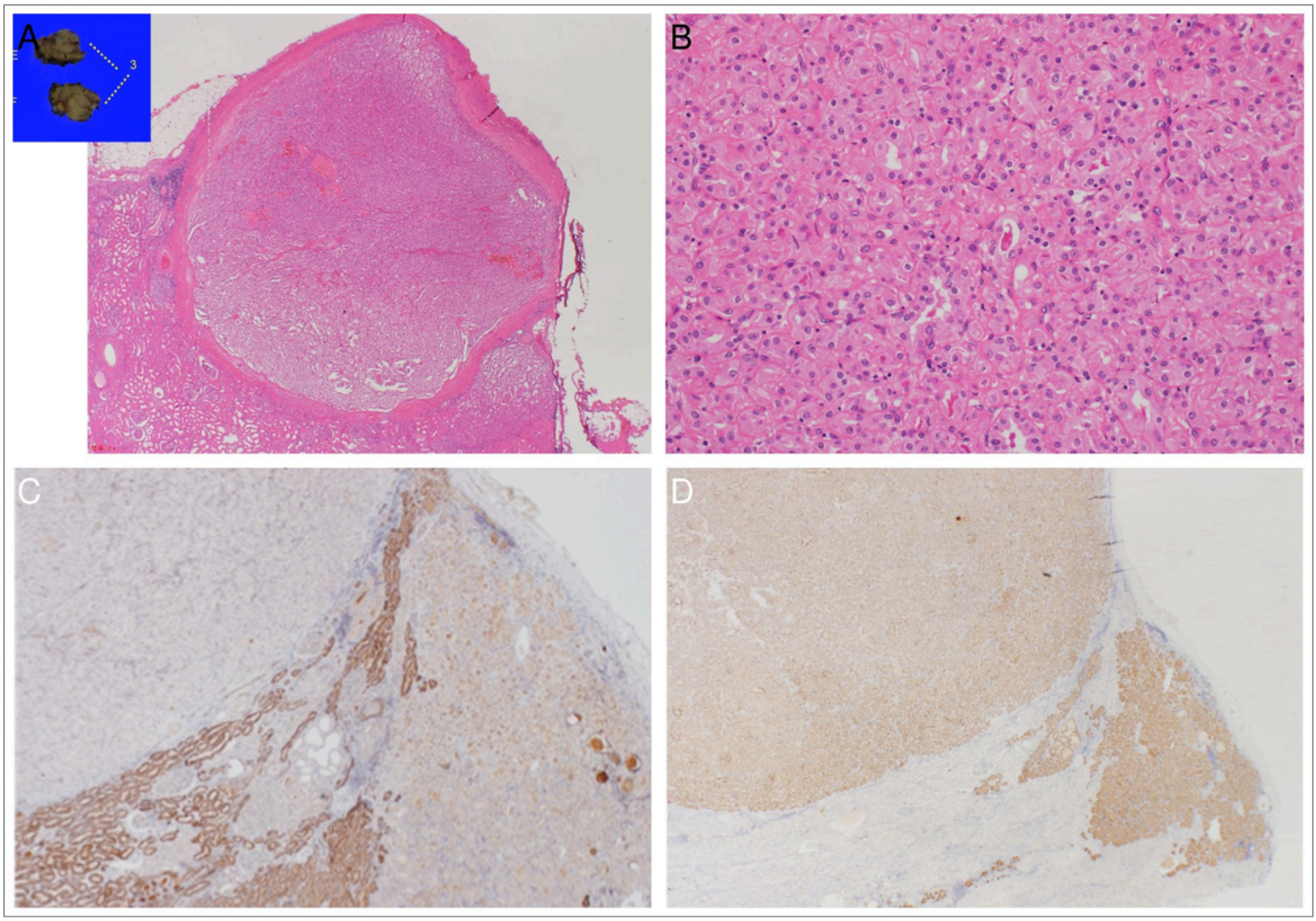


Figure 2

Pathological findings. (A) Low-power hematoxylin and eosin (H&E) staining shows a well-circumscribed tumor with a fibrous capsule (inset: gross specimen). (B) High-power H&E shows tumor cells with abundant eosinophilic cytoplasm and low-grade oncocytic morphology. (C) FH immunohistochemistry shows loss of expression in the tumor with retained staining in entrapped non-neoplastic tubules (internal control). (D) 2SC immunohistochemistry shows diffuse cytoplasmic positivity in the tumor.