Case Report

Bilateral fumarate hydratase deficient renal cell carcinoma in a patient with hereditary leiomyomatosis and renal cell cancer syndrome

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Abbreviations & Acronyms
CT = computed tomography
FH = fumarate hydratase
HLRCC = Hereditary leiomyomatosis and renal cell cancer
RCC = renal cell carcinoma

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How to cite this article: Ono A, Nakamura M, Takada T *et al*. Bilateral fumarate hydratase deficient renal cell carcinoma in a patient with hereditary leiomyomatosis and renal cell cancer syndrome. *IJU Case Rep*. 2024; 7: 144–147.

Received 20 September 2023; accepted 17 December 2023. Online publication 2 January 2024

Introduction: Patients with hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome have high risks of uterine and cutaneous leiomyomas and renal cell carcinoma (RCC), which are caused by germline mutation of the fumarate hydratase (FH) gene. RCC lesions are mostly high-grade tumors with a poor prognosis.
Case presentation: A 37-year-old man who had previously undergone treatment for a left RCC was referred to our hospital with a diagnosis of right RCC. Robot-assisted partial nephrectomy was performed, and the pathological diagnosis revealed fumarate hydratase (FH)-deficient RCC. The left RCC, which was originally diagnosed as mucinous tubular and spindle cell carcinoma, was reviewed and diagnosed as FH-deficient RCC. The patient's father and uncle both died of RCC, and the father's tumor was also immunohistochemically proven to be FH-deficient RCC.
Conclusion: HLRCC-related RCC should be considered in a differential diagnosis of young patients with a family history of RCC.

Key words: fumarate hydratase, hereditary leiomyomatosis and cancer, nephrectomy, renal cell, renal cell carcinoma.

Keynote message

HLRCC-related renal cell carcinoma (RCC) is pathologically characterized as FH-deficient RCC due to mutations in the FH gene. HLRCC-related RCC is mostly high-grade tumors, leading to poor prognoses and shows pathological ambiguity. For early therapeutic intervention, HLRCC-related RCC should be considered in a differential diagnosis of young patients with a family history of RCC and genetic counseling should also be offered.

Introduction

Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome is an autosomal dominant disorder featuring germline mutation of the fumarate hydratase (FH) gene.

Patients with HLRCC are at high risk of developing uterine and cutaneous leiomyomas and renal cell carcinoma (RCC). Due to mutations in the FH gene, HLRCC-related renal cell carcinoma (RCC) is pathologically characterized as FH-deficient RCC.

RCC is reported to occur in around 15% of patients with HLRCC.[1,2] Importantly, HLRCC-related RCCs are mostly high-grade tumors, leading to poor prognoses.[1,3] Pathologically, HLRCC-related RCC, i.e., FH-deficient RCC was recently listed as a separate entity in the WHO classification of renal tumors 2016.[4]

Reports on the occurrence of bilateral HLRCC-related RCC are rare. In this study, we report the first case of metachronous bilateral HLRCC-related RCC in Japan.

Case

A 37-year-old man was referred to our hospital with a 30-mm right renal tumor. The patient had been diagnosed with left RCC, and he underwent left radical nephrectomy at the previous hospital when he was 29 years old. The pathological diagnosis was mucinous tubular and spindle cell carcinoma and the pathological stage was pT1bN0M0. The patient did not receive neo-adjuvant or adjuvant chemotherapy. Genetic testing was not conducted at that time, although his father died of "collecting duct carcinoma" at the age of 55. He underwent follow-up by computed tomography (CT) after nephrectomy. There was no sign of recurrence until a 10-mm cystic lesion emerged in the right kidney 5 years after left nephrectomy. Magnetic resonance imaging revealed that the lesion was a hemorrhagic cyst without a clear solid component. Thereafter, the mass steadily increased over 2 years to a size of 30 mm, and it was classified as Bosniak IV at the time of referral.

The patient underwent a robotic-assisted right partial nephrectomy. Macroscopically, the tumor was predominantly cystic, with a whitish-walled nodule measuring 6 mm in size (Fig. 1). Microscopically, the nodule was composed of high-grade tumor cells exhibiting nuclear irregularities and eosinophilic cytoplasm, proliferating mainly in a papillotubular pattern and occasionally in a microcystic pattern. Viral inclusion-like macronucleoli were occasionally observed. The inner surface of the cyst was also covered with similar atypical cells. Immunohistochemical staining revealed positivity for alpha-methylacyl-CoA racemase and S-(2-succinyl) cysteine (2SC) and negativity for FH and CK7, leading to a diagnosis of FH-deficient RCC. The pathological stage was pT1aN0M0.

We reexamined the tissue specimens of his left renal tumor (originally diagnosed as mucinous tubular and spindle cell carcinoma) and his father's renal tumor (originally diagnosed as collecting duct carcinoma). The previously diagnosed left renal tumor exhibited proliferating patterns generally similar to the right renal tumor and was confined to the left kidney (pT1b). In contrast, his father's renal tumor predominantly displayed small tubular, cord-like, and solid patterns, and had invaded outside the kidney (pT3a). Immunohistochemical investigation of both tumors was consistent with FH-deficient RCC (Figs. 1, 2).

Genomic sequencing was performed with the consent of the patient, revealing a germline mutation in the *FH* gene (*FH* c.698G>A(R233H)). This mutation is previously reported as a relatively frequent mutation in families with HLRCC.[5] No other mutation was detected by ACTRisk™. According to an interview with his family, his uncle also died of renal cancer (Fig. 2). Because of the lack of tissue specimens, we did not perform further histological examination.

The patient, at the one-year mark since the surgery, shows no sign of recurrence.

Discussion

Heterozygous germline mutations in the *FH* gene, which encodes an enzyme involved in the tricarboxylic acid (Krebs) cycle, were first reported in 2002.[6] FH catalyzes the conversion of fumarate to malate. Thus, in patients with FH defects, elevated fumarate results in the accumulation of the HIF1α

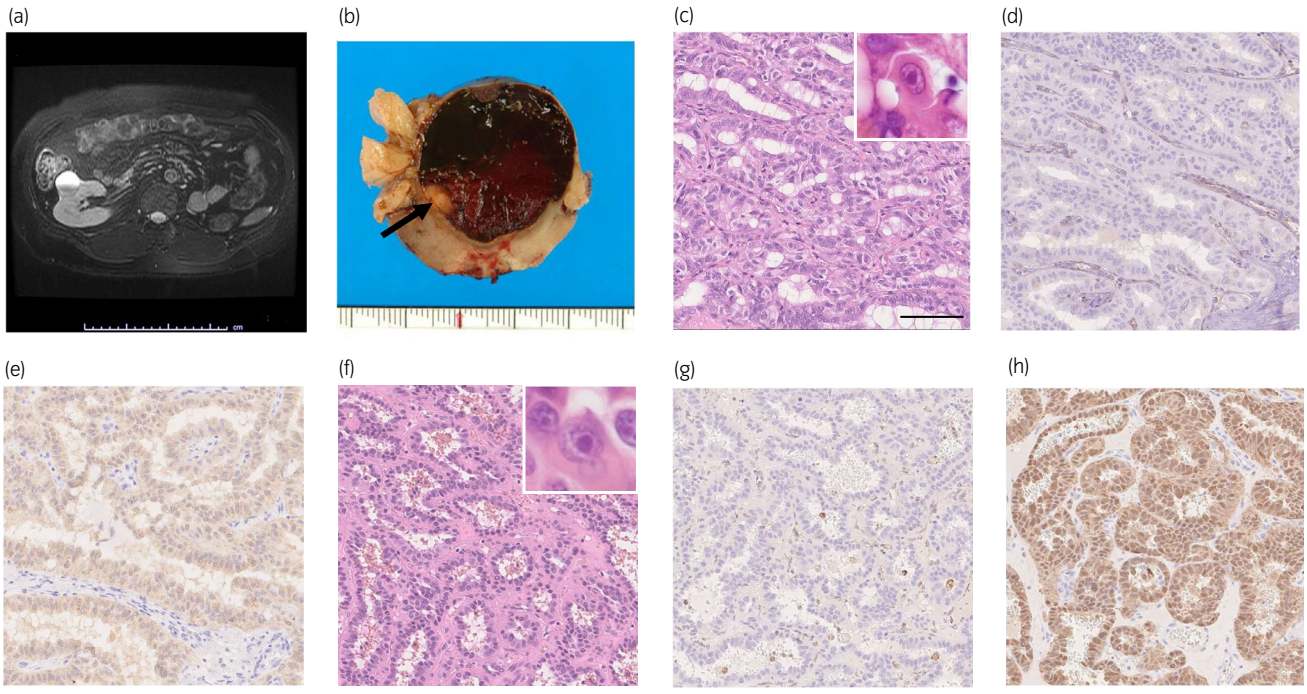

Fig. 1 MRI image and pathological findings of patient's kidneys. (a) T2-weighted magnetic resonance image of the right renal tumor. (b) Gross appearance of the tumor. A 6 mm-sized whitish nodule (arrow) is seen in a cystic lesion. (c) Hematoxylin–eosin staining of the right kidney's tumor reveals tumor cells with small tubular structures. Inset shows macronucleolus. Bar, 100 μm. (d) Immunohistochemistry for FH. Tumor cells of the right kidney are negative for FH, whereas capillaries intervening in the tumor are positive. (e) Immunohistochemistry for 2SC. Tumor cells of the right kidney are positive for 2SC. (f) Hematoxylin–eosin staining of the left renal tumor. Inset shows macronucleolus. (g) Negative FH staining of the left renal tumor. (h) Positive 2SC staining of the left renal tumor.

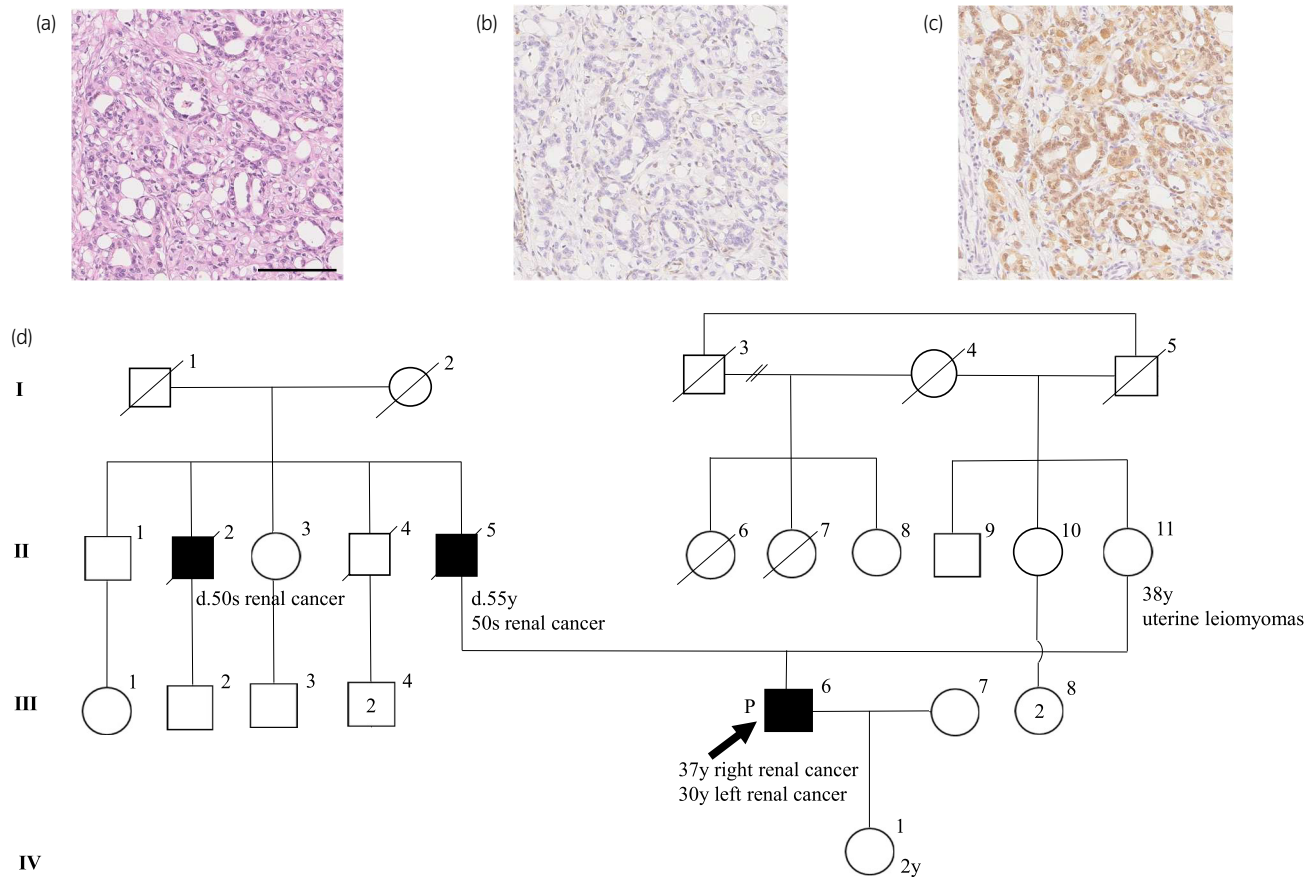

Fig. 2 Pathological findings of the renal tumor of the patient's father. (a) Hematoxylin–eosin staining of the father's renal tumor. Bar, 100 μm. (b) Negative FH staining of the father's renal tumor. (c) Positive 2SC staining of the father's renal tumor. (d) The patient's pedigree.

protein, leading to tumorigenesis.[7] HLRCC-related RCCs are mostly high-grade tumors with a poor prognosis. According to Muller et al., 82% of patients with HLRCC-related RCC had metastasis at diagnosis or rapidly developed metastases, and the median overall survival among such patients was 18 months.[3]

In cases of slow-glowing hereditary RCC including von Hippel–Lindau disease, hereditary papillary RCC, and Birt–Hogg–Dubé syndrome, tumor resection is recommended when the tumor size exceeds 3 cm. For patients with HLRCC-related RCC, lymph node metastases or visceral metastases have been reported at an early stage.[8] Thus, immediate partial nephrectomy or radical nephrectomy is advised even when the tumor is smaller than 3 cm. Focal therapy including radiofrequency ablation or cryotherapy is not a choice of treatment.[2]

Combination therapy with bevacizumab and erlotinib is recommended as the first-line systemic therapy for patients with metastasis.[2] Because programmed death-ligand 1 is highly expressed in HLRCC-related RCC and CD8-positive lymphatic cells accumulate around tumors,[9] immune checkpoint inhibitors are effective in some cases.[10,11] To date, no effective treatment has been established for neo-adjuvant or adjuvant chemotherapy.

In our case, the patient was previously diagnosed with left mucinous tubular and spindle cell carcinoma at his first nephrectomy. In fact, HLRCC-related RCC pathologically resembles other RCC subtypes such as type-2 papillary RCC, collecting duct carcinoma, medullary carcinoma, and mucinous tubular and spindle cell carcinoma. Therefore, it is often difficult to differentiate HLRCC-related RCC from these tumors. Negativity for FH staining is crucial in differential diagnosis, although FH is not always negative in HLRCC-related RCCs. Positive staining for 2SC is also helpful in the diagnosis of HLRCC-related RCCs.[12]

With pathological ambiguity, genetic diagnosis is mandatory considering the possibility of HLRCC syndrome, especially in younger patients with family histories of renal cancer. Genetic counseling should also be offered to the patient and his/her family.

Conclusion

We have reported a patient with bilateral HLRCC-related RCC who underwent partial nephrectomy of his remaining kidney after prior contralateral nephrectomy. FH-deficient RCC or HLRCC-related RCC should be considered in the differential diagnosis of young patients with RCC.

Acknowledgments

We would like to thank Drs. Yusuke Sato, Katsutoshi Oda, and Hyangri Chang at the University of Tokyo hospital for

genetic counseling and diagnosis, and Drs. Yasushi Inoue, Hiroki Inatsu, Ryo Amakawa, and Tadashi Yoshimatsu at NTT Medical Center Tokyo for informative discussions and the critical review of our manuscript.

Author contributions

Akihiro Ono: Writing – original draft. Masaki Nakamura: Conceptualization; data curation; supervision; writing – original draft; writing – review and editing. Takuya Takada: Writing – review and editing. Sakiko Miura: Resources; writing – review and editing. Ibuki Tsuru: Writing – review and editing. Taro Izumi: Writing – review and editing. Masashi Kusakabe: Writing – review and editing. Sachiko Mitarai: Writing – review and editing. Yoji Nagashima: Resources; writing – review and editing. Haruki Kume: Supervision; writing – review and editing. Teppei Morikawa: Supervision; writing – review and editing. Yoshiyuki Shiga: Supervision.

Conflict of interest

None of the contributing authors has any conflicts of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Informed consent

Written informed consent for publication was obtained from the patient.

Approval of the research protocol

Not applicable.

Registry of the study

Not applicable.

Financial support

None.

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