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Urology Case Reports 30 (2020) 101141

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: http://www.elsevier.com/locate/eucr

Oncology

Hereditary leiomyomatosis and renal cell cancer (HLRCC): A case report

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ARTICLE INFO

Keywords:
Uterine leiomyoma
Papillary renal cell cancer
Fumarate hydratase
Hereditary leiomyomatosis and renal cell cancer (HLRCC)

ABSTRACT

Hereditary leiomyomatosis and renal cell cancer is a rare, inherited disease caused by mutations in the fumarate hydratase gene. It is characterized by cutaneous leiomyomas, uterine leiomyomas, and/or renal cell cancer. We present the case of a 42-year-old woman with a heterozygous missense mutation (p.M195T) in the fumarate hydratase gene. Although the patient did not have cutaneous leiomyoma and she had no family history of hereditary leiomyomatosis and renal cell cancer, the presence of early onset symptomatic uterine leiomyoma and type 2 papillary renal cell cancer confirmed the diagnosis of hereditary leiomyomatosis and renal cell cancer.

Introduction

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an inherited autosomal dominant cancer syndrome caused by heterozygous germline mutations in the fumarate hydratase gene (*FH*). It is characterized by cutaneous leiomyoma, uterine leiomyoma, and/or renal cell cancer. Cutaneous leiomyomas are the most common clinical feature, arising in over 80% of HLRCC patients.

A sizable number of patients (20–35%) who have early onset HLRCC (30–50 years of age) develop renal cell cancer (RCC).[1] Unfortunately, the RCCs are primarily papillary type 2, with a propensity for early metastases. Here, we present the case in which a patient with a missense germline mutation in the *FH* gene had a uterine myoma and was later diagnosed with HLRCC and papillary type 2 RCC.

Case presentation

A 42-year-old woman, whose past medical history was significant for uterine myoma resulting in severe anemia (hemoglobin 3.6 g/dL) that required myomectomy at age 32, presented with abdominal pain. She had no significant family history. On examination, blood chemical analysis revealed a hemoglobin level of 8.1 g/dL. Contrast enhanced computed tomography showed a left cystic renal cell tumor 4 cm in diameter containing a solid component and a large multiple uterine myoma (Fig. 1). ^{18}F-Fluorodeoxyglucose–positron emission tomography revealed uptake of ^{18}F-fluorodeoxyglucose in the left cystic renal tumor (maximum standardized uptake value of 4.58) and uterine myoma (maximum standardized uptake value of 17.13; Fig. 1). There was no evidence of metastasis.

Because she had severe anemia and the image of uterine sarcoma could not be denied, a simple total hysterectomy was performed in June 20XX. One month later, an open radical left nephrectomy was performed. Pathological examination of the uterine myoma confirmed a leiomyoma (Fig. 2). The left cystic renal tumor was determined to be pathological papillary RCC type 2 (pT1aN0M0; Fig. 3). Immunohistochemistry results were partially positive for cytokeratin 7, and positive for cluster of differentiation 10 and alpha–methylacyl–coenzyme A racemase. Because of the presence of symptomatic uterine leiomyomas and type 2 papillary RCC, HLRCC was suspected. She underwent genetic testing, which revealed a heterozygous missense mutation (p.M195T) in *FH*. This mutation has been reported in one other family in North America.

Discussion

HLRCC is an autosomal-dominant inherited renal cancer syndrome. It is caused by a heterozygous mutation in *FH*, a gene that encodes for an enzyme in the Krebs cycle that catalyzes the conversion of fumarate to

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https://doi.org/10.1016/j.eucr.2020.101141
Received 20 January 2020; Accepted 18 February 2020
Available online 26 February 2020

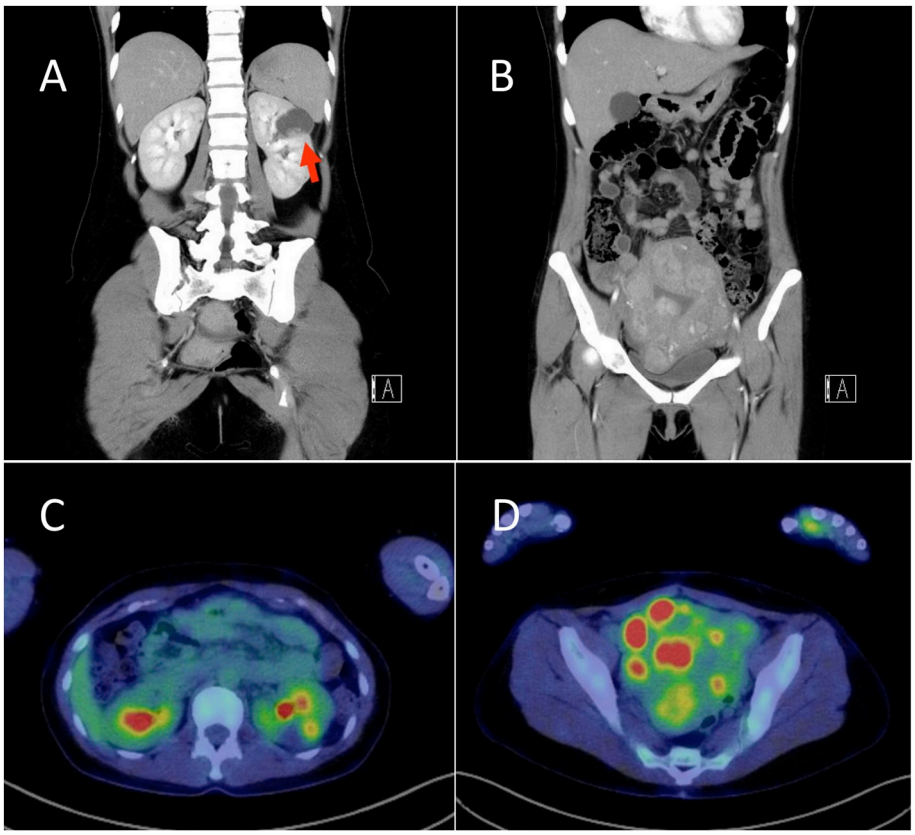

Fig. 1. Contrast enhanced computed tomography (CECT) revealed a left cystic renal cell tumor 4 cm in diameter containing a solid component (A) and a large multiple uterine myoma (B). 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed FDG uptake in a left cystic renal tumor (maximum standardized uptake value [SUVmax] = 4.58) (C) and uterine myoma (SUVmax = 17.13) (D). There was no evidence of metastasis.

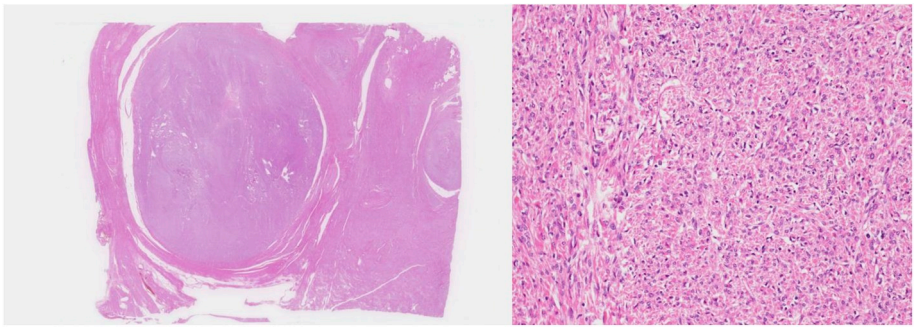

Fig. 2. Pathological examination of the uterine myoma revealed a leiomyoma.

malate.

HLRCC is typically diagnosed by the detection of cutaneous leiomyomas or the presence of both cutaneous and uterine leiomyomas. Uterine leiomyomas in HLRCC patents are severely symptomatic and have an early age of onset.[2] In total, 70% of women with uterine leiomyomas are younger than 30 years old at the time of diagnosis.[3] Cutaneous leiomyomas occur in over 80% of HLRCC patients. However, a father and son with HLRCC who developed papillary type 2 RCC in the absence of cutaneous leiomyomas were reported in Japan.[1] Similarly, no cutaneous leiomyomas were found in our patient, who had the same missense mutation as that identified in a North American HLRCC family.[2,4]

For clarity, Smit et al.[3] advocated the following criteria for the clinical diagnosis of HLRCC: major criterion, defined as histopathologically confirmed multiple cutaneous piloleiomyomas; and minor criteria, defined as 1) surgical treatment for severely symptomatic uterine leiomyomas before age 40, 2) type 2 papillary RCC before age 40, and 3) a first-degree family member who meets one of the above-mentioned criteria. The diagnosis is likely when a proband meets the major criterion, and HLRCC may be suspected when a proband meets at least two minor criteria.

Approximately 7% of HLRCC patients are diagnosed with RCC before age 20, with the youngest diagnosed at 11 years old. Given the potential effect of anticipation and considering that the primary life-limiting feature of this syndrome is RCC, renal ultrasound surveillance would be prudent for patients over the age of 10 who have HLRCC or suspected HLRCC.[5]

Although our patient had no family history of HLRCC, it is important to consider the possibility that the children of patients such as ours may have the same mutation as that of their parent, and to evaluate them for the presence of RCC.

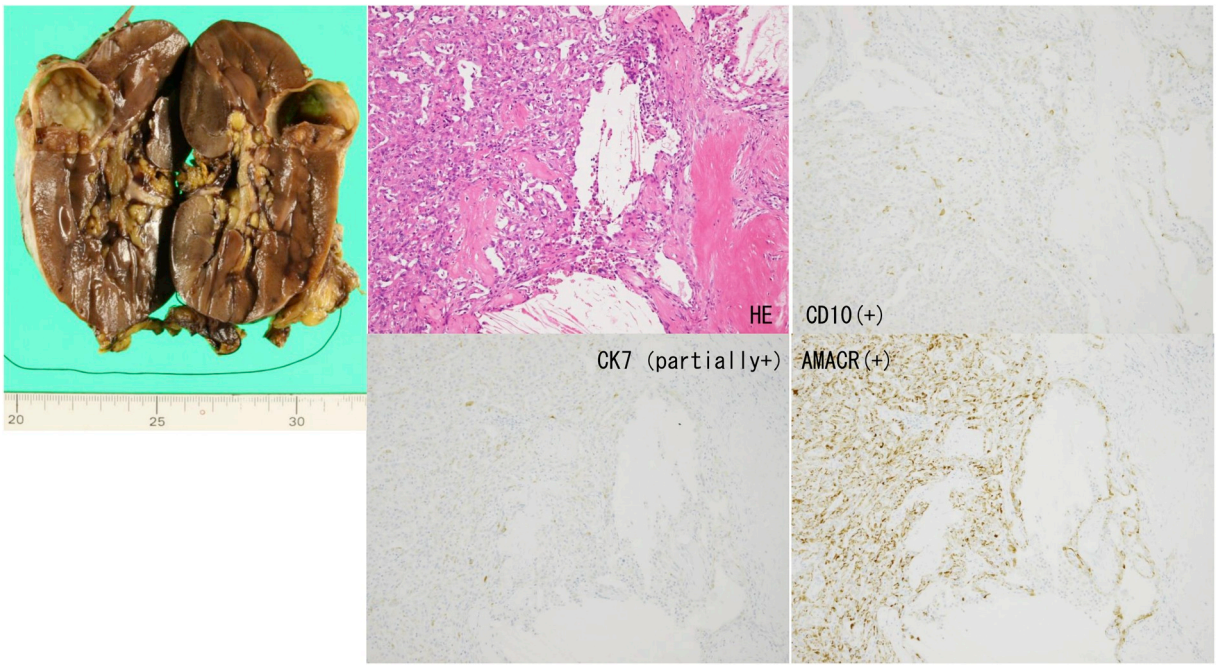

Fig. 3. The left cystic renal tumor was determined to be pathological papillary renal cell carcinoma type 2 (pT1aN0M0). Immunohistochemistry results were partially positive for cytokeratin 7 (CK7), and positive for cluster of differentiation (CD)10 and alpha–methylacyl–coenzyme A racemase (AMACR).

Conclusion

Our report indicates that cutaneous leiomyoma and/or the early onset of uterine myoma may provide an opportunity for the early detection of a life-threatening papillary RCC and can lead to early monitoring of a proband's progeny.

Consent

Verbal informed consent was obtained from the patient for the publication of this report.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of competing interest

None.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

Abbreviations

HLRCC	hereditary leiomyomatosis and renal cell cancer
FH	fumarate hydratase

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