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CASE REPORT

A Case of Recurrent Multiple Uterine Fibroids Associated with Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC): Insights into Fumarate Hydratase (FH) Deficiency

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Abstract: Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is a rare genetic disorder caused by mutations in fumarate hydratase (FH) gene. The main manifestations include cutaneous leiomyoma, uterine leiomyoma, and type 2 papillary renal cell carcinoma (PRCC2). This case report is about a 37-year-old patient with multiple uterine leiomyomas. The patient had recurred within a short period after both previous myomectomies. A renal tumor was accidentally detected during a routine examination before the third myomectomy and was confirmed to be advanced RCC associated with HLRCC. The patient was treated with immunization and targeted therapy (Sunitinib and Tislelizumab injection) and subsequently received a robotic radical nephrectomy. Patients with similar conditions might initially present gynecology for uterine fibroids, easily ignored due to their rarity, missing the time window for diagnosing and treating RCC. This case underscores the need for early genetic screening in patients with recurrent uterine leiomyomas suggestive of FH deficiency.

Keywords: hereditary leiomyomatosis and renal cell carcinoma, HLRCC, fumarate hydratase, FH deficiency, renal cell carcinoma, RCC

Introduction

Uterine leiomyomas are the most common benign tumors in women. Fumarate hydratase (FH) deficiency leiomyomas is a clinical subgroup with an incidence rate of only 1% to 2%.[1] It is associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome.[1] HLRCC is an autosomal dominant cancer syndrome linked to heterozygous mutations in the FH gene.[2] HLRCC is characterized by the presence of cutaneous leiomyomas, uterine leiomyomas and renal cell carcinomas (RCC). HLRCC-associated RCC is quite rare but is highly invasive and often detected at an advanced stage and had a poor prognosis.[3] Current clinical research focuses on the diagnosis and treatment of RCC from urology perspective. In gynecology, HLRCC patients usually visit for uterine fibroids, and due to rarity, their diagnosis and treatment easily stop at the level of uterine fibroids. Currently, there is a lack of standardized screening protocols for FH-deficient uterine fibroids in gynecological clinical practice. As a result, this rare group is very susceptible to missing early RCC diagnosis time window. This case report presents a patient with multiple uterine leiomyomas, underwent three myomectomies for recurrence in a short period and was ultimately diagnosed with advanced HLRCC-related RCC. If screening awareness for HLRCC syndrome is enhanced in the gynecology stage, the potential risk of RCC can be identified and managed earlier. This will help to improve the prognosis and quality of life of such patients.

Case Presentation

A 37-year-old woman with heavy menstruation and blood clots (7–8/30 days) was found to have uterine leiomyoma by vaginal ultrasound during pregnancy in 2010. In the same year, the initial myomectomy was performed during cesarean

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section. Subsequent regular ultrasound examinations still indicated the presence of uterine fibroids. In 2018 (eight years later), due to frequent urination, multiple uterine fibroids were detected by vaginal ultrasound. And the second myomectomy was performed. Four months later, uterine fibroids on size of 2.6 × 2.1 cm were observed again on re-examination. Then, the fibroids were gradually enlarged along annual re-examination. This patient has no significant menstrual change or other symptoms. Therefore, no special treatment was performed.

In 2024 (six years later), the patient presented frequent urination accompanied by lumbar discomfort. As shown in Figure 1A, a gynecological B-ultrasound examination revealed that the uterus was enlarged to 10.5 × 10.4 × 9.3 cm and low echoes of varying sizes were seen. The larger fibroids measured as 4.7 × 4.2 × 3.9 cm, 5.2 × 5.1 × 4.4 cm, and 4.4 × 4.6 × 2.9 cm (posterior wall), 2.9 × 3.2 × 2.5 cm (anterior wall), respectively. The physical examination showed anemic appearance, uterine enlargement on the size of 3 months pregnancy, limbs and trunk no obvious papules or nodules. The patient had no significant family history. Hemoglobin 7.6 g/dL suggested moderate anemia. Routine urine test and renal function were not abnormal. In Figure 1B, epigastric color ultrasound indicated a 5 cm mass lesion in the upper part of the left kidney. The lesion had an unclear boundary, uneven internal echoes, and visible blood flow signals. Due to reproductive needs, a single-hole laparoscopic myomectomy (the third myomectomy) was performed on May 23, 2024. As shown in Figure 1C, extensive adhesion between the intestine and the uterus was observed during the operation. After dissecting the adhesions, in Figure 1D, the enlarged uterus was seen with an extremely irregular shape and with more than a dozen protuberances resembling fibroids. The surgery was very difficult, with an intraoperative blood loss of about 1000 mL. Histopathological examination of postoperative myoma specimens showed local cell density (Figure 2). Further immunohistochemical analysis showed: FH (-), 2SC (+). This is consistent with FH-deficient leiomyoma.

Subsequently, the patient was treated at the urology department in another hospital for left renal space occupation. Kidney MRI examination showed the enlarged left kidney, with a mixed isointense/long T1 and isointense/short T2 signal in the upper pole, with unclear boundaries as shown in Figure 3A and B. The lesion size was approximately 5.8 × 4.0 × 4.0 cm. Multiple irregularly enlarged lymph nodes were observed around the left kidney and along the abdominal aorta, some of which were in a fused state. The left adrenal gland was deformed, with a spotted isointense T1 and slightly short T2 signal. The perirenal fascia of the left kidney was thickened, while no abnormal signal shadows were observed in the right kidney. The hospital performed left kidney biopsy for the patient. As shown in Figure 3C and D, postoperative findings confirmed RCC.

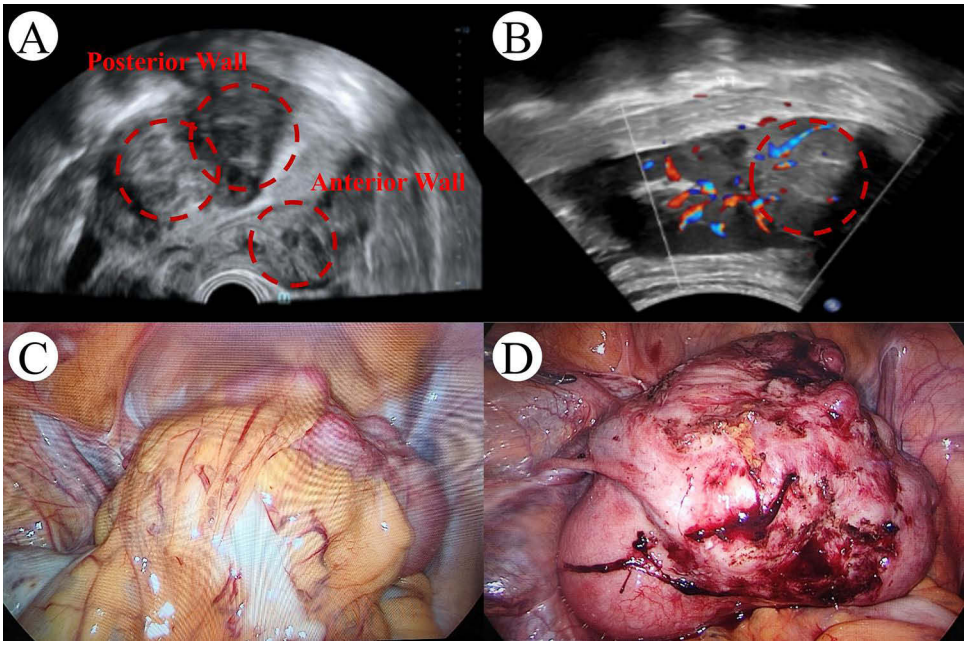

Figure 1 (**A**) transvaginal ultrasound images of uterus. The red circle indicates the visualization of some of the fibroids. (**B**) renal ultrasound. (**C**) intraoperative snapshot showing extensive adhesions between the intestine and the uterus. (**D**) intraoperative snapshot showing the enlarged uterus with an extremely irregular shape and with more than a dozen protuberances resembling fibroids.

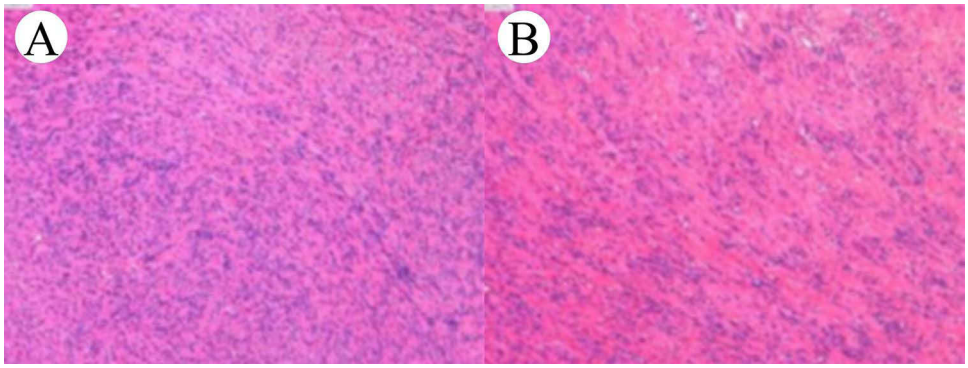

Figure 2 Both (**A**) and (**B**) are pathologic images of leiomyomas.

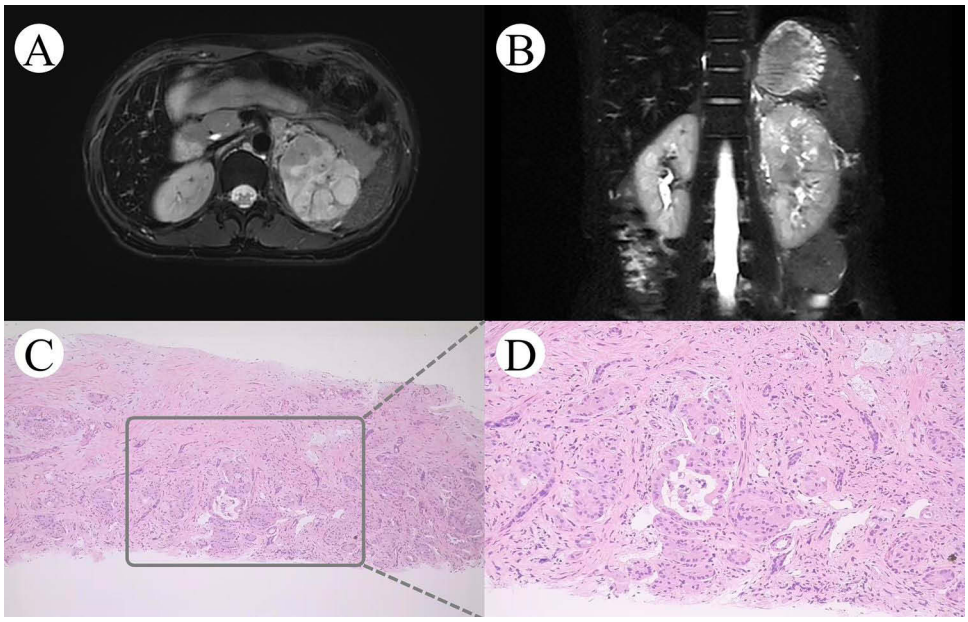

Figure 3 (**A**) renal MRI transverse plane. (**B**) renal MRI coronal plane. (**C**) and (**D**) pathologic images of left kidney biopsy.

The tumor tissue and blood samples of patients were individually detected using "Hejian 876" platform. The results showed that the patient had a germline heterozygous mutation in the FH gene, consisting of a frameshift mutation on exon 10 (c.1448dupA; p.E484fs) and another frameshift mutation on exon 7 (c.966delT; p.E323fs), with a mutation abundance of 11.34%. Meanwhile, on chromosome 16 encoding the NTHL1 gene, there were heterozygous mutations with a mutation abundance of 46.28% (C.22g > C; p.G8R). However, the significance of this mutation is unknown. No pathogenic variations were detected in the patient's MMR genes, HRR genes, and genes associated with immunotherapy. The tumor mutation burden (TMB) was 2.00 mutations/mb, and the microsatellite instability was of the stable type (MSS). Based on the genetic test results, the patient was diagnosed with HLRCC syndrome. For renal cell carcinoma, immunization and targeted therapy (Sunitinib 5 mg twice/day and Tislelizumab Injection 200 mg intravenous drip) was performed, and robotic radical nephrectomy for kidney cancer on October 14, 2024.

Discussion

FH is a highly conserved homotetrameric cytoplasmic and mitochondrial enzyme that plays an important role in the tricarboxylic acid (TCA) cycle.[4] The FH gene is expressed in most tissues, except muscle, adipose tissue, bone marrow, ovaries and vagina.[4] For gynecology, its main expression is in uterine. Its mutations can lead to hereditary and sporadic

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cancers.[4] HLRCC syndrome is a rare syndrome due to heterozygous pathogenic mutation in the FH gene. The incidence of HLRCC is about 1/200,000[5] and it is listed in Orphanet's catalog of rare diseases.[6] HLRCC follows an autosomal dominant inheritance pattern with incomplete penetrance.[2] The onset age of HLRCC is usually between puberty and adulthood, and the epistasis increases with age.[2] It is characterized by the development of multiple tumor types, including cutaneous leiomyoma, uterine leiomyoma, and type 2 papillary renal cell carcinoma (PRCC2). Uterine leiomyoma and cutaneous leiomyoma have been reported to occur in up to 70% of affected individuals, whereas the risk of RCC is less clear but generally estimated to be 15–20%.[5]

Sporadic cutaneous leiomyoma are very common in HLRCC patients and present as small, firm, purplish or reddish-brown papules and nodules that can be single and asymptomatic or multiple with paroxysmal pain.[7] Single lesions can be removed surgically. For multiple unresectable ones with severe pain, calcium channel blockers can be used to relieve the pain. In the present case, the patient was examined systemically, and no abnormal nodules or papules were found.

FH-deficient uterine leiomyoma, as a subgroup of uterine fibroids, shows early onset, large number, large size and severe clinical symptoms. The average onset age is 28–32 years old.[8] It has a high recurrence rate after myomectomy. The tumors grow rapidly. Most patients need to have a second or even more surgeries 3–4 years after the initial surgery.[9] Those with severe symptoms need to undergo hysterectomy. The present patient was a 37-year-old woman of reproductive age with anemia due to heavy menstrual flow. Multiple uterine fibroids were first detected, and myomectomy was performed in 2010 (23 years old). And the patient underwent the second and third surgeries in the 8th and 14th years after the initial surgery. The pelvic adhesions were severe during the third surgery. Patients with FH-deficient uterine fibroids are generally younger, and most of them have the need to preserve their reproductive functions. Myomectomy is the most common choice for initial surgery, with post-operative supplements of gonadotropin-releasing hormone analogue (GnRH-a) to prevent recurrences. If without reproductive needs, surgical removal of the uterus is recommended to minimize the recurrence risk.

HLRCC-related RCC is much rarer and aggressive. It is primarily PRCC2 and usually associated with advanced metastasis, poor prognosis and high mortality.[10,11] A cohort study revealed 15.6% of patients with FH deficiency develop HLRCC-associated RCC.[12] These renal tumors tend to be early-onset, isolated, unilateral, and aggressive, which can lead to death within five years of diagnosis.[12] In this case, renal tumors were accidentally detected on preoperative examination before the third surgery. The patient was diagnosed at an earlier age than the 44-years-old average age.[12] And it was already advanced. As the current understanding about this cancer is limited, there is no standard treatment or consensus for advanced HLRCC-related RCC. Targeted therapies and immunotherapies are more commonly applied. The patient underwent immunization and targeted therapy for 3 months after the initial diagnosis and subsequently received a robotic radical nephrectomy for kidney cancer.

HLRCC-associated RCC is usually detected at an advanced stage, and even small primary tumors carry a considerable risk of metastasis.[13] Therefore, early diagnosis and recognition are important for HLRCC patients. HLRCC-associated uterine leiomyomas usually appear in the second to third decade of life, whereas RCC usually occurs in the fourth decade.[3] HLRCC-associated uterine leiomyomas are the main gynecologic-related etiology for which this group of patients is hospitalized. This provides an opportunity for early recognition of RCC, but it is easy to ignore clinically. There is no defined biomarker that can be used to differentiate FH-deficient uterine fibroids from other types of uterine fibroids. FH-deficient tumors may exhibit specific morphological features: antler-like blood vessels, alveolar-type edema, dispersed oddball nuclei, ovoid nuclei, eosinophilic cytoplasmic inclusions, eosinophilic nuclei protruding from the nucleus surrounded by a perinuclear halo, and so on.[3] Immunohistochemistry using FH and S-(2-succino)-cysteine (2SC) antibodies can be performed in patients with typical morphological features. FH staining may lead to false-positive results because it also detects stable but nonfunctional protein products.[1,8] Therefore, genetic counseling and testing are still recommended for patients with highly suspicious clinical features, even if FH staining is not abnormal. However, the reality is that due to the high financial burden associated with genetic testing, it cannot currently serve as a routine screening method. This is a major reason why such patients are not diagnosed in a timely manner. In the present case, there were no abnormal findings in the postoperative pathology of the two previous surgeries, and the postoperative pathology specimen from the third surgery did not reveal the typical morphologic features of HLRCC. However, the patient had recurrent multiple uterine fibroids in a short period of time, so we highly suspected to FH-deficient uterine

leiomyomas. Further examinations were performed, the results of which revealed FH (-) and 2SC (+). Eventually, genetic testing confirmed HLRCC-associated uterine leiomyomas. If diagnosing HLRCC and recognizing RCC at an earlier stage, the patient may receive a better prognosis and quality of life.

Conclusion

In summary, FH gene mutations may lead to the development of HLRCC syndrome, and FH-deficient uterine leiomyomas with a high prevalence may serve as a gynecologic outpost for RCC detection. Therefore, we recommend that people with abnormal immunohistochemistry tests, especially those with younger onset, multiple leiomyomas, and short-term recurrence, should undergo genetic testing as early as possible. It will help for definitive diagnosis to formulate monitoring plans and provide genetic counseling as well as to assess RCC risk.

Abbreviations

HLRCC, hereditary leiomyomatosis and renal cell carcinoma; FH, fumarate hydratase; PRCC2, type 2 papillary renal cell carcinoma; RCC, renal cell carcinoma; 2SC, S-(2-succino)-cysteine; MRI, Magnetic Resonance Imaging; MMR, Mismatch Repair; HRR, homologous recombination repair; NTHL1, Nth Like DNA Glycosylase 1; TMB, tumor mutation burden; MSS, microsatellite stable; TCA, tricarboxylic acid; GnRH-a, gonadotropin-releasing hormone analogue.

Data Sharing Statement

The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

Written informed consent was obtained from the patient for publication of the health information in anonymised form. Institutional review board approval to publish was not required, given the patient provided written consent.

Consent for Publication

The patient provided consent for publication of the case report and images.

Acknowledgments

This case report is based on the disease of the present patient. The authors would like to express their heartfelt thanks and best wishes to this patient. The authors sincerely hope that more patients with HLRCC will be screened early, which requires a physician-patient concerted effort.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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