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CASE REPORT

Fumarate Hydratase–Deficient Leiomyoma with Double Mutation Sites in the FH *Gene*: A Rare Case Report and Literature Review

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Background: Fumarate Hydratase (FH)-deficient uterine leiomyomas are a rare type of uterine fibroid associated with somatic or germline mutations in the FH gene. Herein, we report a case of FH-deficient uterine leiomyoma with a double-site mutation of *FH* in a 41-year-old woman.

Case Presentation: The woman was found to have an intrauterine mass during a routine physical examination two years prior. She had no previous medical history or family history of genetic diseases. Ultrasound examination revealed a slightly hypoechoic mass on the posterior wall of the uterus, approximately 4 cm × 4.1 cm in size, suggesting the possibility of a uterine fibroid. The patient opted for regular annual follow-ups and received no specific treatment. However, during the subsequent two years of follow-up, the mass was found to increase in size annually. The patient then came to our hospital and underwent laparoscopic myomectomy. Postoperative pathology indicated that the tumor was negative for FH but positive for 2-succinocysteine (2SC), suggesting a potential diagnosis of FH-deficient leiomyoma. Sanger sequencing analysis demonstrated that the leiomyoma harbored the c.724C>T (p.L242F) mutation in exon 5 and the c.1292C>T (p.T431I) mutation in exon 9 of the FH gene, further confirming the diagnosis of FH-deficient leiomyoma.

Conclusion: We report a rare case of FH-deficient uterine leiomyoma with double mutation sites in the FH gene. Pathological examination and genetic testing are crucial for a definitive diagnosis.

Keywords: fumarate hydratase–deficient leiomyoma, double-site mutation, fumarate hydratase, 2-succinocysteine

Introduction

Uterine leiomyoma is a common benign tumor that mainly originates from the proliferation of uterine smooth muscle cells in the female reproductive system and occurs in the fifth decade of life. Fumarate hydratase (FH)-deficient uterine leiomyoma is a special pathological type of uterine leiomyoma, accounting for only 0.4–1.6% of all types of uterine leiomyoma. The onset age of FH-deficient uterine leiomyoma is about 10 years earlier than that of cases without FH deficiency.[1] This tumor is characterized by a distinct morphology and loss of FH protein expression or *FH* inactivation. The different types of *FH* mutations can be further divided into germline and somatic mutations. Germline mutations are associated with a rare autosomal dominant syndrome, known as hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. Affected individuals are prone to developing skin leiomyomas, early-onset uterine leiomyomas, and kidney cancer.[2] Somatic mutation diseases are sporadic, and the accompanying symptoms include increased menstrual flow, prolonged menstrual periods, lower abdominal masses, increased vaginal discharge, and pressure-related symptoms such as abdominal pain and bloating.[3] Herein, we present a case of a patient with FH-deficient leiomyoma who presented with no specific clinical symptoms and was found to have a somatic mutation in the *FH* gene.

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Case Presentation

A 41-year-old female patient who complained of progressive enlargement of uterine fibroids for over three years was admitted to our hospital. The patient had a history of cesarean section as a gravida 3, para 1. She denied any other significant medical or family history and had a normal menstrual cycle. The uterine fibroid was found incidentally three years prior during a physical examination. Ultrasonography revealed heterogeneous echoes in the myometrium, with a slightly hypoechoic area of approximately 4.0×4.1 cm^2 in the posterior wall (Figure 1A). Since there was no specific discomfort, the patient did not receive any specific treatment and chose to have annual follow-ups. However, during the subsequent 2-year follow-up, the mass increased from 5.0×4.3 cm^2 (Figure 1B) to 6.6×4.7 cm^2 (Figure 1C). Abdominal computed tomography revealed no significant space-occupying lesions in the kidneys, ruling out HLRCC (Figure 1D). The patient then underwent laparoscopic myomectomy. Hematoxylin and eosin staining showed that the tumor nuclei were enlarged and irregular, and eosinophilic nucleoli with surrounding empty halos were observed (Figure 2A). Immunohistochemical analysis demonstrated positive staining for desmin, smooth muscle actin, and 2-succinocysteine (Figure 2B–D) but negative staining for FH (Figure 2E), with a low Ki67 index (Figure 2F, around 10%). Retrieve the formalin-fixed, paraffin-embedded (FFPE) tumor tissue sample from the pathology department for Sanger sequencing analysis. The result indicated that the tumor harbored mutations in NM_000143.4:c.724C>T (p.L242F) and NM_000143.4:c.1292C>T (p.T431I), specifically point mutations in exons 5 and 9 of the FH gene (Figure 2G and H). The final diagnosis was FH-deficient leiomyoma with somatic mutations in FH. The patient recovered well after surgery and is currently undergoing regular follow-up visits at our hospital. This case was approved for publication by the Ethics and Scientific Committee of Hubei University of Medicine under approval number 2022PR-H002.

Discussion

FH-deficient uterine leiomyoma is an uncommon subtype of uterine smooth muscle tumors, and few studies on this subtype have been reported. Most cases of FH-deficient uterine leiomyoma are sporadic and associated with somatic *FH* inactivation, including whole-gene deletions, frameshift mutations, and point mutations.[4] We report the first case of sporadic FH-deficient uterine leiomyoma with double-site point mutations in the *FH* gene.

The FH gene, located on chromosome 1(q42.3–43), catalyzes reversible hydration and dehydration reactions between fumarate and malate salts in the mitochondria, playing a crucial role in the tricarboxylic acid cycle.[5] Currently, the etiology and pathogenesis of FH-deficient leiomyoma are not completely understood. The metabolic derangement caused by FH deficiency may be related to the occurrence of this disease. First, inactivation or reduced production of FH leading to disruption of the tricarboxylic acid cycle can promote anaerobic glycolysis within cells, causing pseudohypoxia, which is closely related to tumor development. Second, the accumulation of fumarate caused by FH deficiency can inhibit the hydroxylation reaction of hypoxia-inducible factors, leading to elevated levels of hypoxia-inducible factors and their downstream transcription factors. Through pathways involving vascular endothelial growth factor and glucose transporter 1, this promotes tissue cell proliferation and angiogenesis and facilitates tumor development.[6,7] Finally, the accumulation of high levels of fumarate and succinate inhibits lysine demethylase, suppresses homologous recombination repair during

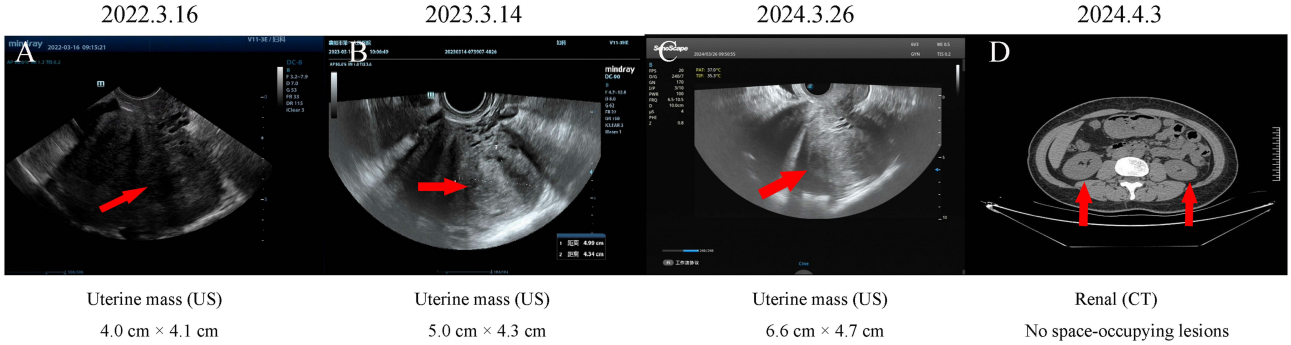

Figure 1 The timelines and follow-up imaging. **(A–C)** The ultrasound reveals a slightly hypoechoic mass in the posterior wall muscle layer, and the mass has been increasing in size annually. (**D**) Computed tomography indicates no significant space-occupying lesions in both kidneys.

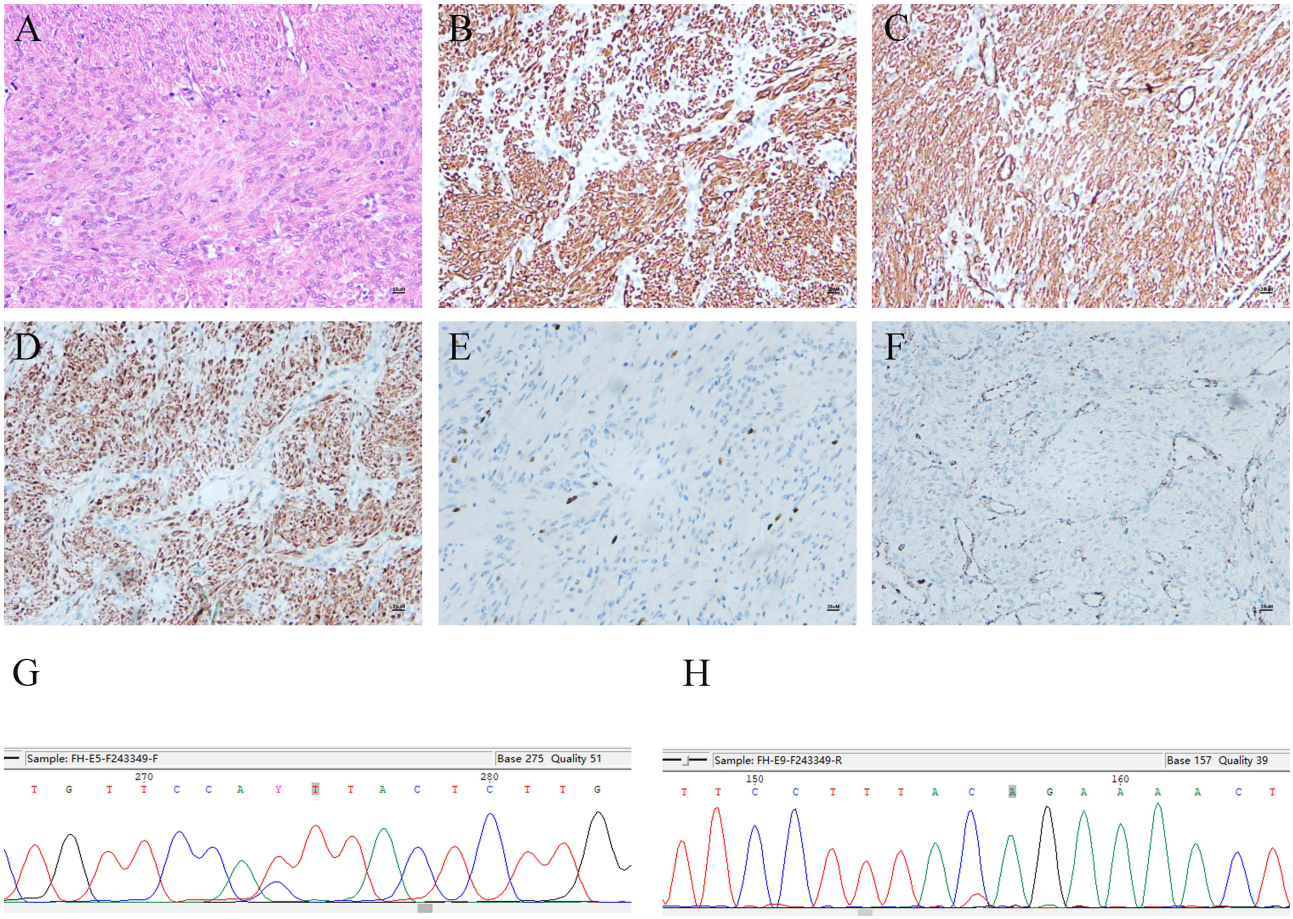

Figure 2 The pathology and genetic testing findings. **(A)** Hematoxylin and eosin staining reveals that the tumor nuclei were enlarged and irregular, and eosinophilic nucleoli with surrounding empty halos were observed at a magnification of 100x. **(B–F)** Immunohistochemical analysis shows positive staining for Desmin (**B**), SMA (**C**), and 2SC (**D**), but negative staining for FH (**E**), with a Ki67 positivity around 10% (**F**) at a magnification of 100x. (**G** and **H)** Sanger sequencing analysis reveals that the leiomyoma harbors the c.724C>T (p.L242F) mutation in exon 5 and the c.1292C>T (p.T431I) mutation in exon 9 of the FH gene.

DNA double-strand breaks, and hinders DNA damage repair processes, thus impairing the integrity of the genome and promoting tumor formation.[8]

The diagnosis of FH-deficient uterine leiomyomas mainly relies on morphology and histopathology. Microscopically, the typical pathological features include bizarre cells, prominent nucleoli, perinuclear halos, eosinophilic globules within or outside the cytoplasm, antler-like blood vessels, and focal alveolar edema.[9] The typical immunohistochemistry manifestations are FH-negative and 2-succinocysteine-positive.[10] However, FH mutations do not always indicate a loss of FH expression. Some tumors with FH missense mutations can produce stable but inactive FH protein, leading to positive FH immunohistochemical staining.[11] Depending solely on FH immunohistochemistry may lead to missed diagnoses; therefore, genetic testing remains the gold standard for diagnosing FH-deficient uterine leiomyomas.

Uterine leiomyomas bearing FH deficiency from somatic mutations are primarily sporadic and generally do not undergo malignant transformation or metastasis. Some scholars contend that the suspicion of HLRCC syndrome in leiomyomas solely due to FH-deficient uterine leiomyomas may be somewhat overcautious,[12] a stance that is reasonable. Nevertheless, patients with a family history should remain vigilant. More attention should be paid to FH-deficient leiomyomas with extrauterine symptoms. Although cutaneous leiomyomas are sensitive and specific clinical manifestations of HLRCC syndrome, lung metastasis of FH-deficient leiomyomas with germ line mutations has also been reported.[13] HLRCC syndrome is closely associated with FH germline mutations, with kidney cancer being the most serious disease and the main cause of death in patients.[14,15] The clinical manifestations of FH-deficient uterine leiomyomas without HLRCC syndrome do not differ significantly from those of typical uterine fibroids. When associated

with HLRCC syndrome, the clinical manifestations of uterine fibroids include a higher number of fibroids, larger size, and an earlier onset age.[16] In addition, skin lesions are the most sensitive and specific clinical manifestations of HLRCC syndrome, primarily presenting as multiple cutaneous or piloleiomyomas with associated stinging pain.[15]

Since patients with FH-deficient uterine leiomyomas tend to develop the condition at an early age and the majority need to preserve their fertility, the initial surgery is typically a myomectomy. However, the recurrence rate after surgery is high because these leiomyomas have a rich blood supply, and most patients require a second surgery or even multiple surgeries. Postoperative administration of gonadotropin-releasing hormone analogs can help prevent recurrence.[17] In severe cases, a hysterectomy may be recommended when symptoms are severe or for those without fertility needs to reduce the harm caused by multiple surgeries.[18,19]

FH-deficient uterine leiomyomas are significant indicators for screening HLRCC patients. Identifying HLRCC-related leiomyomas and screening for renal cell carcinoma in these patients for early intervention are crucial for improving patient prognosis.[14] It is recommended that family members at risk, aged 8 years and above, undergo predictive germline mutation testing.[20] For carriers of the *FH* gene germline mutation, annual renal examinations are advised. Upon the detection of renal cell carcinoma lesions, extensive surgical resection should be performed as early as possible because HLRCC-related renal cell carcinoma has a high early metastasis rate and a poor prognosis.[21,22] For metastatic renal carcinoma, a combination of immunotherapy and targeted therapy, including pembrolizumab, nivolumab, axitinib, and bevacizumab, can be employed.[23] Additionally, treatments targeting the glycolytic pathway with 2-deoxy-D-glucose and immunotherapies have also shown some therapeutic effects.[24,25]

In conclusion, we reported a rare case of FH-deficient uterine leiomyoma harboring somatic double mutation sites in the *FH* gene. We also reviewed the pathogenesis, diagnosis, and treatment strategies of this disease. This case not only enriches the database of FH-deficient smooth muscle tumors but also provides clinical experience for the diagnosis and treatment of this type of disease.

Ethics Approval

This study was approved by the Ethics and Scientific Committee of Hubei University of Medicine with approval number 2022PR-H002. Written informed consent was obtained from the individual for the publication of any potentially identifiable images included in this article.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors listed above have no conflicts of interest to declare.

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