Case Report

Fumarate Hydratase-deficient Uterine Leiomyoma in a 25-Year-Old Woman

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Fumarate hydratase (FH) is an essential enzyme in the citric acid (Krebs) cycle. Genetic mutations in the FH gene can contribute to tumor development. FH-deficient uterine leiomyoma is a rare subtype of uterine leiomyoma, accounting for approximately 0.4–1.6% of all uterine leiomyomas. It can occur in both syndromic and sporadic settings. Germline mutations in FH are associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, which presents with cutaneous and uterine leiomyomas and an aggressive form of renal cell carcinoma (RCC). Identifying FH-deficient uterine leiomyomas may facilitate early detection of patients at risk for RCC. Here, we present a case of a 25-year-old woman, gravida 0, had pelvic pain, dyspareunia, and heavy menstrual bleeding, significantly affecting her daily activities. Pelvic MRI revealed a 3.5 cm intramural fibroid in the posterior uterine wall. The patient opted for myomectomy. The surgical specimen consists of multiple tan, nodular, rubbery tissue fragments, including one large 4 cm nodule and several smaller nodules (0.4–1.3 cm). Sectioning shows whorled cut surface without hemorrhage or necrosis. Microscopically, the tumor exhibited spindle and epithelioid cell proliferation, alveolar edema, and staghorn/hemangiopericytoma-like vessels. Tumor cells also displayed ovoid nuclei with eosinophilic nucleoli and bizarre nuclei. Rhabdoid /eosinophilic cytoplasmic inclusions are present. Immunohistochemical analysis showed positivity for smooth muscle actin and desmin, confirming smooth muscle differentiation. The tumor was negative for FH and positive for S-(2-succino) cysteine (2SC). The diagnosis of FH-deficient leiomyoma was rendered based on these histological findings and confirmed by loss of FH expression on immunostaining. The negative FH and positive 2SC indicate biallelic FH inactivation. Genetic counseling was recommended to rule out germline FH mutations and HLRCC syndrome. Through this case report, we want to raise awareness that an early-onset large leiomyoma with bizarre nuclei needs to consider the possibility of FH-deficient uterine leiomyomas to facilitate early detection of patients at risk for RCC. *[N A J Med Sci. 2025;18(1):028-031. DOI: 10.7156/najms.2025.1801028]*

Key Words: *fumarate hydratase-deficient, leiomyoma, hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome*

INTRODUCTION

Uterine leiomyomas, or fibroids, are the most common benign tumors affecting women of reproductive age.[1] It is estimated that 70% of White women and over 80% of Black women develop fibroids by age 50.[2] While most leiomyomas are asymptomatic, approximately 25% of affected individuals experience symptoms such as abnormal uterine bleeding, pelvic pain, and compression of surrounding structures, significantly impacting their quality of life. Uterine leiomyomas typically occur sporadically, and most do not exhibit chromosomal abnormalities. However, somatic or germline genetic mutations have been identified in approximately 40% of uterine leiomyomas.[3] FH-deficient uterine leiomyomas represent a special subset of these tumors.

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Fumarate hydratase (FH) is an essential enzyme in the citric acid (Krebs) cycle, playing a crucial role in cellular energy production by converting fumarate into malate. Genetic mutations in the FH gene, whether inherited or resulting from somatic biallelic inactivation, can contribute to tumor development. Furthermore, biallelic pathogenic germline variants in FH are associated with fumaric aciduria, a metabolic condition characterized by neonatal or infantile encephalopathy, poor growth, muscle weakness, low muscle tone, lethargy, and seizures.[6]

A rare autosomal dominant hereditary tumor syndrome, HLRCC syndrome, is associated with heterozygous germline mutations in the FH gene. Patients with HLRCC syndrome present with cutaneous and uterine leiomyomas and are at high risk for aggressive renal cell carcinoma, which has a poor prognosis due to its metastatic potential. Uterine leiomyomas

in patients with HLRCC syndrome typically appear earlier, are larger, and are more numerous than sporadic leiomyomas, often preceding the development of RCC. This temporal relationship provides an opportunity for early diagnosis and intervention in patients with HLRCC syndrome.[4]

FH-deficient leiomyomas can arise from either germline or somatic mutations in the FH gene and account for approximately 0.4–1.6% of all uterine leiomyomas. The onset of FH-deficient uterine leiomyomas occurs about 10 years earlier than conventional leiomyomas. These tumors exhibit distinct histological features, including alveolar edema, staghorn or hemangiopericytoma-like vessels, hypercellularity, and prominent eosinophilic nucleoli. Both germline and sporadic mutations result in loss of FH staining in tumor cells on IHC. Here, we present a case of a young woman with an FH-deficient leiomyoma.

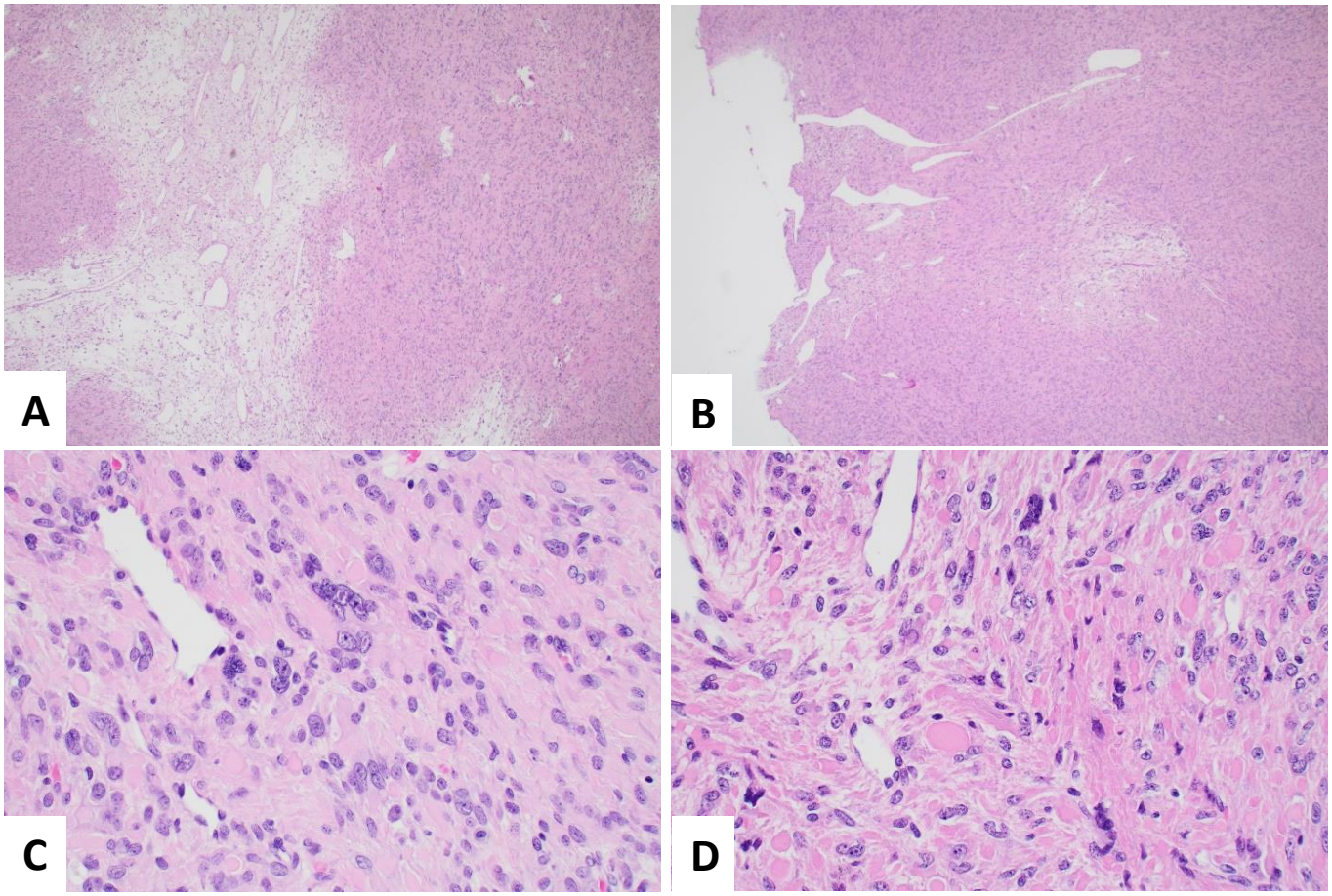

Figure 1. Histological features of the tumor. **A.** Hypercellular proliferation of spindle and epithelioid tumor cell with alveolar edema. **B**. Presence of staghorn vessels. **C**. The tumor cells show ovoid nuclei, prominent eosinophilic inclusion and rhabdoid cytoplasmic inclusion. **D**. Presence of bizarre nuclei.

CASE PRESENTATION

Clinical History

The patient is a 25-year-old, gravida 0, with a medical history of anxiety, who presented with pelvic pain, dyspareunia, and heavy menstrual bleeding. Since menarche, she had experienced heavy and painful menstrual cycles, which were managed with birth control pills from 2015 to March 2024, resulting in symptomatic improvement. However, upon discontinuing birth control, her cycles became excessively heavy, prolonged (8-9 days), and accompanied by severe cramping pain, significantly affecting her daily activities. Due to worsening symptoms, she sought emergency care, where she was diagnosed with uterine fibroids. Additionally, she reported dyspareunia and severe cramping pain lasting 1-2 days post-intercourse. Pelvic MRI revealed a 3.5 cm intramural fibroid in the posterior uterine wall, and ultrasound detected a 4.5 cm fibroid. After discussing management options, the patient opted for definitive surgical intervention rather than uterine artery embolization. She subsequently underwent myomectomy.

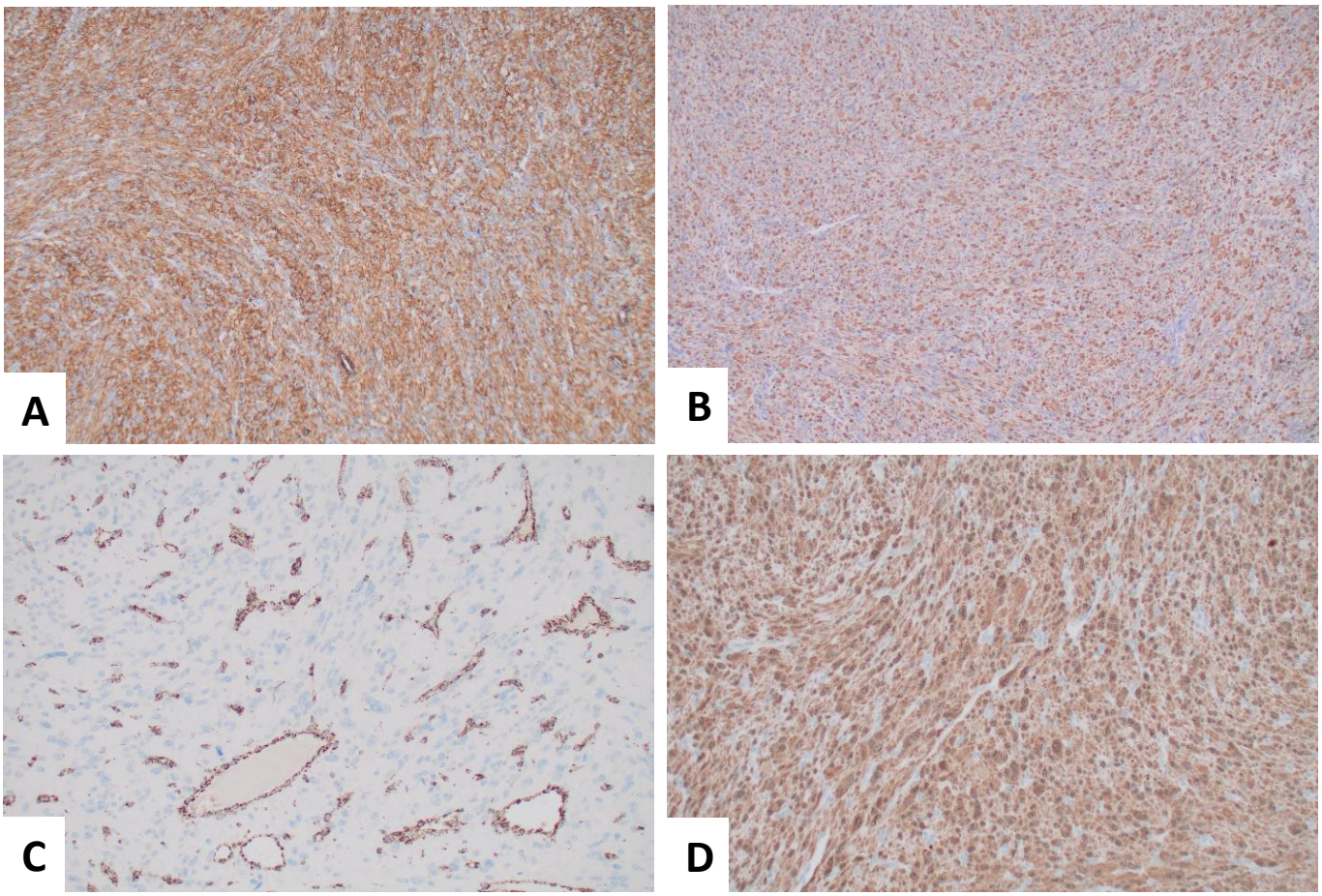

Figure 2. Immunohistochemical features of the tumor. The tumor cells are strongly and diffusely positive for SMA (**A**) and desmin (**B**). Tumor cells show loss of expression of FH (**C**) and positive for S-(2-succino) cysteine (2SC) (**D**).

Pathological Findings

Gross examination of the surgical specimen revealed a total weight of 186 grams, consisting of multiple tan, nodular, rubbery tissue fragments, including one large 4 cm nodule and several smaller nodules (0.4–1.3 cm). Sectioning shows tan, rubbery, whorled cut surface. No hemorrhage or necrosis is seen grossly. Microscopically, the tumor exhibited spindle and epithelioid cell proliferation, alveolar edema **(Figure 1A)**, and staghorn/hemangiopericytoma-like vessels **(Figure 1B)**. Tumor cells displayed ovoid nuclei with eosinophilic nucleoli and bizarre nuclei **(Figures 1C** and **1D)**. Rhabdoid /eosinophilic cytoplasmic inclusions are present. Immunohistochemical analysis showed positivity for smooth muscle actin (SMA) **(Figure 2A)** and desmin **(Figure 2B)**, confirming smooth muscle differentiation. The tumor was negative for FH **(Figure 2C)** and positive for S-(2-succino) cysteine (2SC) **(Figure 2D)**, indicating biallelic FH inactivation. A diagnosis of FH-deficient leiomyoma is rendered based on these histological findings. Genetic counseling was recommended to rule out germline FH mutations and HLRCC syndrome.

DISCUSSION

FH-deficient leiomyoma is an uncommon subtype of uterine smooth muscle tumors with characteristic histological findings and can be identified through IHC studies. FH mutations can be germline or somatic. Germline mutations are associated with HLRCC syndrome, in which affected patients typically develop multiple uterine leiomyomas requiring surgical treatment at or before 30 years of age (mean age 30 years), significantly earlier than the onset of RCC (mean age 44 years).[7] The earlier occurrence of leiomyomas compared to aggressive RCC provides an opportunity for early identification of patients with HLRCC syndrome, facilitating timely screening and intervention for them and their family members.

FH-deficient leiomyoma is a benign smooth muscle tumor that typically does not undergo malignant transformation or metastasis. However, due to its cytological atypia, the differential diagnosis includes leiomyosarcoma and STUMP. Leiomyosarcoma is a rare malignant smooth muscle tumor and the most common gynecologic sarcoma, often presenting as a

rapidly growing mass in postmenopausal women. Its defining histologic features include tumor cell necrosis, significant cytological atypia, and increased mitotic activity. FH-deficient leiomyomas typically lack tumor cell necrosis and show minimal mitotic activity. In a study by Harrison et al.[5] none of the FH-deficient leiomyomas exhibited malignant behavior, and all leiomyosarcomas retained FH staining. Reyes et al. also found that 29 leiomyosarcomas showed no staining for 2SC.[8] Existing studies suggest that FH mutations do not play a significant role in the development of uterine leiomyosarcoma. However, FH-deficient leiomyomas may mimic leiomyosarcoma due to hypercellularity and nuclear atypia. Loss of FH staining can be a reassuring finding of FH-deficient leiomyoma in mildly atypical uterine smooth muscle tumors.

STUMP typically presents at a younger age (mean 43 years), approximately 10 years earlier than leiomyosarcoma. Microscopically, STUMP exhibits at least one of the three diagnostic criteria for leiomyosarcoma (coagulative tumor cell necrosis, cytological atypia, or increased mitotic activity). STUMP usually lacks FH mutations.

At least 1% of all uterine leiomyomas show negative FH staining,[5] and most of these cases are associated with somatic FH mutations, exhibiting similar morphology to those with germline FH mutations. Genetic screening for all FH-deficient leiomyomas is not practical unless patients have a personal or family history of cutaneous leiomyomas, RCC, or symptomatic leiomyomas at a young age. However, identifying FH-deficient cases is crucial for recognizing potential syndromic disease.

CONFLICT OF INTEREST DISCLOSURE
The authors have no conflict of interest to disclose.

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