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Case Report

FH–Deficient Uterine Leiomyomas: Pathological Insights into a Rare Tumor

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Abstract

Background: Uterine leiomyomas represent a widespread health challenge for women in the general population. Fumarate hydratase–deficient uterine leiomyomas (FH–def ULs) are a rare form of uterine smooth muscle tumors, accounting for 0.5–2% of cases. These tumors are distinguished by their unique histological features and the inactivation of the fumarate hydratase (FH) gene. While most FH–deficient ULs arise sporadically due to somatic mutations in FH, a smaller subset occurs as part of the hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, which is caused by inherited germline mutations in FH.

Case presentation: A 29–year–old unmarried woman visited a gynecological clinic with symptoms of gradual abdominal distention and epigastric pain for nearly 10 months.

MRI showed a uterine mass likely fibroid 16.7 x 19.5 x 32 cm with the possibility of sarcomatous changes and bulky ovaries. The patient underwent total transabdominal hysterectomy and right salphingo–oophorectomy with left salpingectomy. The pathological features were consistent with fumarate hydratase (FH) deficient leiomyoma. Immunohistochemistry results demonstrated FH deficiency. Genetic testing revealed a somatic pathogenic *FH* variant (Heterozygous, c.956_957insTGA, p.Asp319dup)

Discussion and Conclusion: The present case was reported to emphasize that the importance of atypical presentation of these cases largely depends on the pathologist's ability to recognize unique histopathologic features and the challenges of differential diagnosis. Once these characteristics are identified, they should prompt a referral to a gynecologist to consider conducting germline genetic testing. The management of FH–d uterine fibroids necessitates a multidisciplinary approach, including proper genetic screening and regular surveillance.

Keywords: Fumarate hydratase–deficient leiomyoma, Hereditary leiomyomatosis and renal cell carcinoma, Genetic screening, uterine smooth muscle tumor

Background

Uterine leiomyoma, the most common tumor of the female reproductive system, affects up to 70% of women. [1] These benign smooth muscle tumors exhibit diverse morphological patterns and are classified into several subtypes. [2] The genetic alterations linked to uterine leiomyomas are heterogeneous, including mutations in the *MED12* gene, overexpression of *HMGA2*, and inactivation of the *FH* (fumarate hydratase) gene. Fumarate hydratase–deficient uterine leiomyomas (FH–dUL) are rare, accounting for 0.5–2% of all uterine smooth muscle tumors. [1] These tumors typically occur at a younger age and may present sporadically or as part of a syndromic condition, such as Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome—a rare autosomal dominant disorder.[2] HLRCC is associated with cutaneous leiomyomas, aggressive renal cell carcinomas (RCCs), and early–onset symptomatic uterine leiomyomas. [3] Both syndromic and sporadic FH–dUL share distinct morphological and immunohistochemical features. The *FH* gene encodes fumarate hydratase, an essential enzyme in the tricarboxylic acid (TCA) cycle. Pathogenic mutations in *FH* disrupt its function, leading to significant metabolic and signaling alterations that promote oncogenesis, thereby linking germline *FH* mutations with an increased risk of specific neoplasms. [4,5] However, FH–deficient UL is poorly documented and may be under–recognized or under–reported. This case report elucidates the clinical

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presentation, imaging findings, histopathological features, and diagnostic challenges in reporting of FH–dUL.

Case presentation

A 29–year–old unmarried female presented with gradual abdominal distention accompanied by dull aching epigastric pain. She reported no additional symptoms, prior treatment, or history of drug use, including oral contraceptives. There was no family history of malignancy or tuberculosis. Her menstrual and obstetric history were unremarkable. Clinical examination identified a pelvic mass. Laboratory investigations revealed moderate microcytic hypochromic anemia (hemoglobin: 9.9 g/dL), with normal biochemical parameters. The tumor marker CA–125 was elevated at 263.7, while CA 19–9 and CEA levels were within normal limits. Other investigations, including coagulation profile, routine hormone studies, and autoimmune and viral panels, were unremarkable. A pelvic ultrasound demonstrated a large, well–defined, lobulated pelvic–abdominal mass with cystic components originating from the uterus, measuring 30.0 × 15.0 cm and extending to the xiphisternum. Further imaging with contrast–enhanced CT and MRI of the abdomen revealed a midline pelvic–abdominal mass originating from the uterus, measuring 16.7 × 19.5 × 32.0 cm (Fig 1). The mass had mixed solid and cystic components, displaced the small and large bowel laterally, and abutted the dome of the urinary bladder. Radiological findings suggested a uterine mass, likely a fibroid, with possible sarcomatous changes. A provisional clinical diagnosis of a uterine mass, possibly leiomyosarcoma, was made. The patient underwent a total abdominal hysterectomy with right salpingo–oophorectomy and left salpingectomy.



FIG 1. CT scan showing pelvic–abdominal mass originating from the uterus, measuring 16.7 × 19.5 × 32 cm.

The specimen included a large, solid, fleshy, tan–white mass measuring 25.0 × 13.0 × 10.0 cm, and involving the outer myometrium at the uterine fundus. Its cut surface appeared tan–grey–white with areas of hemorrhage, extensive necrosis, and cavitation (Fig 2). Histopathology revealed diffuse sheets of tumor cells interspersed with areas of alveolar edema, staghorn vasculature, and thick–walled blood vessels. The tumor consisted of spindle to epithelioid cells with ovoid nuclei, symplastic atypia, multinucleated cells, bizarre nuclei, prominent eosinophilic nucleoli with perinucleolar halos, and eosinophilic/rhabdoid cytoplasmic inclusions. Mitotic activity was ~2/mm². Coagulative necrosis was absent, but ischemic necrosis and thrombosed vessels were noted. (Fig 3)

Immunohistochemistry showed tumor cells positive for estrogen receptor (ER), progesterone receptor (PR), smooth muscle actin (SMA), caldesmon, and desmin, but negative for FH, CD10, S100, cyclin D1, and CD117. p16 exhibited patchy positivity, p53 displayed a wild–type expression pattern, and the Ki–67 proliferation index was low. (Fig 4)

Based on the histopathological and immunohistochemical findings, the patient was diagnosed with uterine leiomyoma with FH deficiency. She was referred for genetic counseling and further testing, which identified a somatic pathogenic FH variant (heterozygous, c.956_957insTGA, p.Asp319dup). On follow–up, she remained well and symptom–free.



FIG 2. Gross appearance of a large solid mass involving myometrium of uterus. The cut surface is tan–grey–white with irregular areas of hemorrhage, necrosis, and cavitation, indicative of degenerative changes

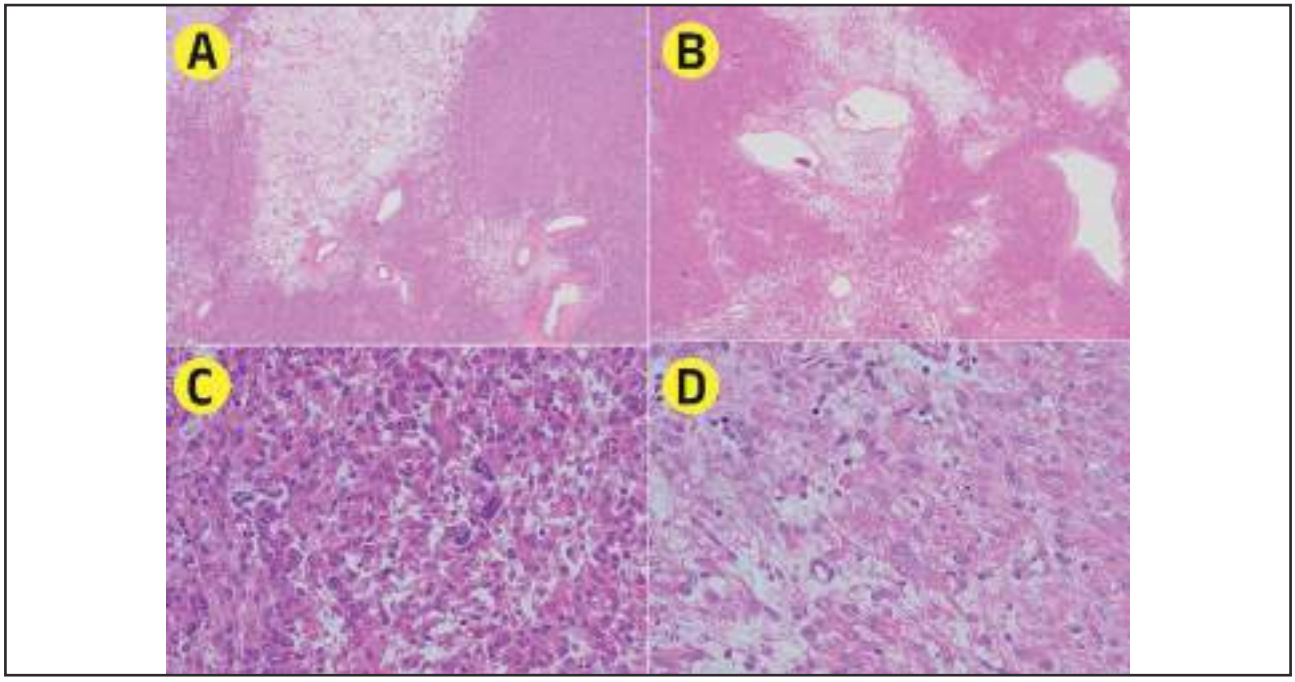


FIG 3. Morphological characteristics of uterine leiomyoma with fumarate hydratase deficiency.

A) 'Alveolar–type' stromal oedema (HE, 10x).

B) Hemangiopericytoma–like or "staghorn" vasculature (HE, 40x).

C) Spindle to epithelioid cells with ovoid nuclei, multinucleated cells, bizarre nuclei, prominent eosinophilic nucleoli with perinucleolar halos. (HE, 40x).

D) Eosinophilic /rhabdoid cytoplasmic inclusions (HE, 40x).

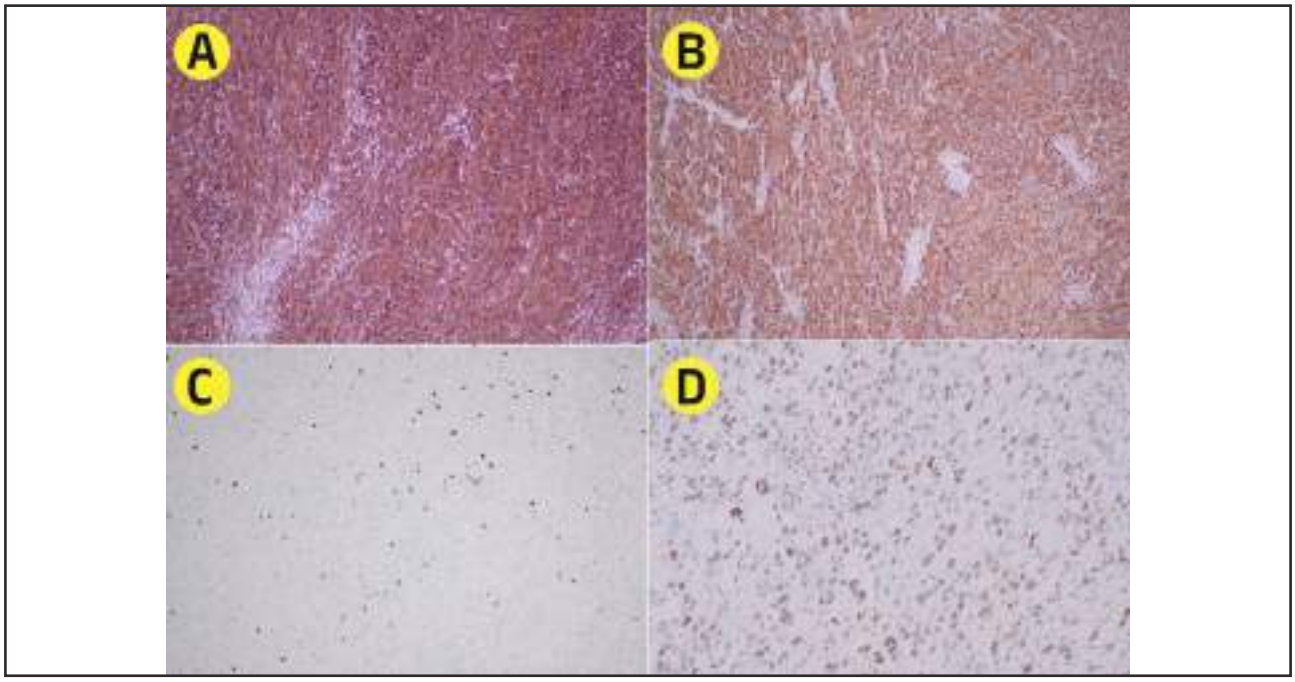


Fig 4. Results of immunohistochemistry of uterine leiomyoma with fumarate hydratase (FH) deficiency. A) Positive staining for smooth muscle actin (Immunostain, 10x).

B) Positive staining for Desmin (Immunostain, 10x).

C) Ki–67 proliferation index is low. (Immunostain, 10x).

D) Positive staining for estrogen receptor. (Immunostain, 10x)

Discussion

Leiomyomas can develop in any body area where they arise from the smooth muscle of visceral organs or the musculature of vascular walls, such as the uterus, digestive tract, skin, and soft tissues. FH–d ULs make up to 2% of all uterine leiomyomas, and considering the high prevalence of uterine fibroids in the general population, these tumors are likely encountered often, though they may be underreported. [1] Given the presented case, it is crucial to address the role of the FH gene. The FH gene, found on chromosome 1 (1q42.3–q43), encodes fumarate hydratase, an enzyme responsible for converting fumarate to L–malate in the tricarboxylic acid (TCA) cycle. [4] Mutations in the FH gene reduce enzyme activity, leading to fumarate accumulation. Increased fumarate levels cause protein succination and activate antioxidant response elements, which contribute to tumorigenesis. Moreover, FH deficiency creates a pseudo–hypoxic condition by stabilizing hypoxia–inducible factor (HIF) 1α, further promoting tumor progression through mechanisms like angiogenesis and epithelial–mesenchymal transition. [2] FH deficiency is associated with several neoplasms, including FH–deficient renal cell carcinomas (RCCs), leiomyomas, cutaneous leiomyomata, and, rarely, malignant paragangliomas and pheochromocytomas. FH–deficient RCCs are almost exclusively seen in patients with hereditary leiomyomatosis and renal cell cancer (HLRCC), typically presenting with early onset and aggressive progression. It is important to understand that not all FH–deficient fibroids are identical. While sporadic FH–deficient fibroids are more common, accounting for approximately 1% of all unselected uterine leiomyomas and up to 25% of atypical or symplastic leiomyomas, syndromic, FH–deficient fibroids are rare and are usually associated with hereditary leiomyomatosis.[3]

A recent study done in the year 2022 identified 52 out of 161 uterine smooth muscle tumors as fumarate hydratase (FH) deficient, with the majority classified as symplastic leiomyomas or STUMPs. These tumors are commonly observed in younger women and are characterized by multiple large masses, often requiring early surgical intervention. [7] In the present case, the patient was a 29–year–old unmarried woman with an unremarkable menstrual and obstetric history. The patient's aunt had a history of breast cancer; however, while studies have documented a family history of FH–associated tumors, such as uterine leiomyomata or cutaneous leiomyomas, no association with pancreatic or breast cancers has been reported in the literature to date. [2]

The distinctive histomorphological features of FH deficiency–driven neoplasms of the uterus and kidney underscore the crucial role of pathologists in their initial recognition and in identifying patients at increased risk for hereditary tumor syndromes. FH–deficient uterine leiomyomas exhibit specific morphological characteristics, including hemangiopericytomatous or staghorn vasculature, stromal edema, eosinophilic cytoplasmic globules resembling lung alveolar parenchyma ("alveolar" edema), prominent eosinophilic nucleoli with perinucleolar clearing, hypercellularity, nuclear atypia, and cytoplasmic hyaline globules, as reported in the literature.[2,9] These leiomyomas are more likely than other types to present with symplastic nuclear atypia, which may be misinterpreted as leiomyosarcoma. While none of these features alone offer perfect diagnostic accuracy, their pronounced presence in a tumor, particularly in a young patient, should prompt further evaluation for FH deficiency.[6] In our case, the tumor exhibited diffuse sheets of spindle to epithelioid cells with ovoid nuclei, symplastic atypia, multinucleated and bizarre nuclei, eosinophilic nucleoli with perinucleolar halos, and eosinophilic/rhabdoid cytoplasmic inclusions, along with alveolar edema, staghorn vasculature, thick–walled blood vessels, and mitotic activity.

Differentiating FH–deficient leiomyomas from STUMP, leiomyosarcoma, or other malignant spindle cell tumors is crucial, as these conditions require distinct therapeutic approaches and have different prognostic implications. [2,6] Misinterpretation of the cytological atypia and hypercellularity in FH–deficient leiomyomas can lead to diagnostic errors.

STUMPs exhibit morphological features that surpass those of leiomyomas but do not meet the criteria for leiomyosarcoma.[1] These rare tumors typically display only one characteristic of leiomyosarcoma, such as increased mitosis, atypia, or coagulative tumor cell necrosis.[6] A diagnosis of conventional uterine leiomyosarcoma requires the presence of at least two criteria: marked cytological atypia, tumor cell necrosis, or mitosis ≥4/mm².[2] In our case, coagulative necrosis was absent, but ischemic necrosis and thrombosed vessels were observed, with mitotic activity of ~2/mm².

This emphasizes the necessity of thoroughly assessing the type of necrosis alongside other histopathological findings and the patient's clinical history to prevent diagnostic error.

Immunohistochemistry can be an essential supplementary tool in making the diagnosis. In most cases, there is a loss of staining for FH, as observed in our case. However, some reports indicate that weak expression may also occur, possibly due to a pathogenic missense mutation. [2,8]

Pathologists must be familiar with the morphological patterns of FH–deficient uterine leiomyomatosis to initiate FH testing and identify potential genetic conditions. While uterine leiomyomatosis with FH deficiency may occur independently of HLRCC syndrome, identifying germline FH variants allows at–risk relatives to undergo testing. Therefore, molecular genetic testing remains the gold standard for confirming HLRCC. [9] In our case, genetic testing identified a pathogenic FH variant (heterozygous, c.956_957insTGA, p.Asp319dup).

Conclusion

FH–deficient uterine leiomyomas are not directly associated with an increased risk of malignancy, but their identification is crucial, as identifying germline FH variants allows at–risk relatives to undergo testing. Recognizing the characteristic phenotype and confirming FH deficiency through IHC or molecular testing is essential. This case report highlights the importance of a thorough patient evaluation. Based on clinical, surgical, and diagnostic findings, the most likely diagnosis is FH–deficient leiomyoma not associated with HLRCC syndrome. However, a small possibility of other diagnoses, such as HLRCC syndrome, remains, as the relevant mutations may not yet be identified. Ultimately, based on the available medical history and findings, healthcare professionals have determined the most suitable treatment approach.

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References

1. Yin X, Wei X, Shamsi R, Ali F, Kindi F, Zhang X, Liang J, Pan X, Masqari M, Zheng L, Zhou Q, Agaimy A, Chen N. Benign metastasizing fumarate hydratase (FH)–deficient uterine leiomyomas: clinicopathological and molecular study with first documentation of multi–organ metastases. Virchows Arch. 2024;485:1–9. doi:10.1007/s00428–024–03806–8.
2. Kamboj M, Chadha P, Sharma A, Singh R, Gupta N, Verma R, Malhotra V, Mehta A. FH deficient uterine leiomyomas—a case series. Heliyon. 2024;10:e24449. doi:10.1016/j.heliyon.2024.e24449.
3. Alkhrait S, Abdefatah Ali M, Kertowidjojo E, Al–Qasem F, Ahmed S, Menon S, Al–Hussaini M. Investigating fumarate hydratase–deficient uterine fibroids: A case series. J Clin Med. 2023;12:5436. doi:10.3390/jcm12175436.
4. Zyla R, Hodgson A. Gene of the month: FH. J Clin Pathol. 2021;74:jclinpath–2021. doi:10.1136/jclinpath–2021–207830.
5. Bu□inskien□ D, Grinci□t□ D, Šilk□nas M, Uleckien□ S, Drungilas D, Baušys R, Daukša A, Juozaityt□ E. Case report: Uterine leiomyoma with fumarate hydratase deficiency. Front Med. 2024;11:1391978. doi:10.3389/fmed.2024.1391978.
6. Harrison W, Castellano J, Maclean F, Baranov E, Li N, Mowat D, Gilks B, Stewart C. Fumarate hydratase–deficient uterine leiomyomas occur in both the syndromic and sporadic settings. Am J Surg Pathol. 2015;40:1234–1241. doi:10.1097/PAS.0000000000000573.
7. Li H, Yang W, Tu X, Liu J, Zhang Q, Wang Y, Chen Z, Zhao X, Xu Y, Deng W, Zhou J. Clinicopathological and molecular characteristics of fumarate hydratase–deficient uterine smooth muscle tumors: a single–center study of 52 cases. Hum Pathol. 2022;126:136–145. doi:10.1016/j.humpath.2022.05.011.
8. Popp B, Erber R, Kraus C, Wenzel F, Strohner R, Rübenthaler J, Thiel CT, Jauch A, Koster J, Wittler L, Horn D. Targeted sequencing of FH–deficient uterine leiomyomas reveals biallelic inactivating somatic fumarase variants and allows characterization of missense variants. Mod Pathol. 2020;33:1863–1873. doi:10.1038/s41379–020–0596–y.
9. Huang Y, Zhou Y, Chen X, Lin X, Zhang L, Wang H, Yang J. Uterine leiomyoma with fumarate hydratase deficiency. Medicine. 2021;100:e28142. doi:10.1097/md.0000000000028142.