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Fumarate Hydratase-Deficient Uterine Leiomyoma with Bizarre Nuclei in a 32-Year-Old Woman: "Diagnostic and Genetic Implications"

Divyesh V. Shukla*, Shilpi D. Shukla, Shivani Shukla, Vinayak Dave

Isha Multispecialty Hospital, Sarabhai Campus, Vadodara, India
Email: *divyeshshukla@yahoo.com

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Abstract

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) syndrome is a rare autosomal dominant genetic disorder, also known as Reed syndrome, and is caused by germline mutations in the fumarate hydratase (FH) gene. It is characterized by a triad of features "cutaneous leiomyomas, uterine leiomyomas and renal cell cancer". These patients present at a young age with complaints of menorrhagia and abdominal pain. (1) With full FH deficiency, there is severe neurological impairment, ventriculomegaly, cortical dysplasia, or cysts. Survival beyond childhood is not possible. We present a case report of a 32-year-old female with countless fibroids who underwent total laparoscopic hysterectomy (TLH) with bilateral salpingectomy for complaints of menorrhagia, lower abdominal heaviness, and pain. The histopathological (HP) report was leiomyoma with bizarre nucleus (LM BN). On IHC, the final report was FH-deficient leiomyoma. This case is an addition to the few case reports of FH-deficient leiomyoma reported in the literature. This case is unique as, from 23 years of age onwards, she had undergone two laparoscopic myomectomies, two lower segment caesarean section (LSCS), and a final TLH at 32 years of age. The HP report was normal in the first myomectomy specimen, but in the second and third specimens of surgery, LM BN histopathology was reported with the immunohistochemistry (IHC) result of the FH-deficient type.

Keywords

Case Report, Leiomyoma, Fibroid, LM BN, FH-Deficient, Variant of Unknown Clinical Significance (VUS), Somatic and Genetic Mutation

1. Introduction

With HLRCC syndrome, 80% to 100% of females have benign uterine leiomyoma, and at a very young age, they undergo either myomectomy or hysterectomy [1]. About 0.4% of leiomyoma are FH-deficient. With LM BN, about 60% are expected to be FH-deficient [2] [3]. Here, predictive morphology and histology are superior to blind IHC screening to detect them [3]. In young patients with early onset multiple fibroids, one should have an insight into the possibility of FH-deficiency [1]. Many such women with multiple fibroids may not have cutaneous lesions; these are related to incomplete penetrance of the cutaneous phenotype or there is an age-related expression. Meanwhile, patients with cutaneous leiomyomas eventually will develop uterine leiomyomas [4]. The FH gene encodes the fumarate hydratase enzyme, also called fumarase. This enzyme functions in the Krebs cycle, converting fumarate to malate. It is critical for aerobic energy metabolism in mitochondria. The FH-deficient state acts by fumarate accumulation, epigenetic dysregulation, pseudohypoxia pathway activation, free radical formation, and by succination of proteins, all of which promote proliferation, neovascularization, and oncologic signalling, promoting tumor growth [5]-[7]. Mutation in the fumarate hydratase (FH) gene is located on the long arm of chromosome 1 at position 43. 1q42. 3-q43 [8].

2. Case Report

The clinical course of the patient has been summarized in tabular form for clarity, divided into three phases covering the years 2016 to 2025 (**Tables 1-3**).

Table 1. Timeline of clinical events from September 2016 to August 2018.

Month/Year	Event	Details/Findings
September 2016	First presented with complaints	A 23-year-old nulliparous patient with a married life of 2 years, a known case of hypertension on treatment, presented with menorrhagia and dysmenorrhoea for the past 2 months. Her general examination was normal. On abdominal examination the uterus was just palpable in the midline above the symphysis pubis. Per speculum and per vaginal examinations revealed an enlarged, firm, mobile uterus of approximately the size of a 12 - 14-week pregnancy.
	TVS USG	Transvaginal ultrasonography (TVS USG) revealed a single 12 cm posterior wall fibroid of FIGO type 2 - 5. The uterine cavity was pushed anteriorly, and the anterior myometrium was also significantly compressed. The cervix and ovaries were normal. Color Doppler examination of the fibroid showed circumferential benign blood flow with a normal resistance index. (**Figure 1**)
	1st Laparoscopic myomectomy	As she was desirous of preserving fertility after counseling, laparoscopic myomectomy with open power morcellation was performed under general anesthesia. (**Figure 2**, **Figure 3**)
	HP report	The HP report was suggestive of a typical leiomyoma. The description was, as follows: sections revealed whorled and interlacing bundles of smooth muscle fibres interspersed with connective tissue. The nuclei were spindle shaped and ovoid. No significant nuclear atypia, mitosis or necrosis was evident. (**Figure 4**)

Continued

	Follow up period	A follow-up TVS USG performed 8 weeks post-surgery showed a uterus with multiple small fibroids throughout the myometrium, measuring 5 mm - 10 mm in size. It was difficult to identify normal myometrium between small hypoechoic areas of leiomyoma. She was prescribed ulipristal acetate 5 mg., once daily for two 3-month cycles, as she wanted to delay fertility.
August 2018	LSCS, full term delivery	She conceived 14 months after the 1st laparoscopic myomectomy procedure via intrauterine insemination (IUI). Delivery was at full term by LSCS. (Aug. 2018) She delivered a baby weighing 2.6 kg. Her postoperative follow-up was uneventful.

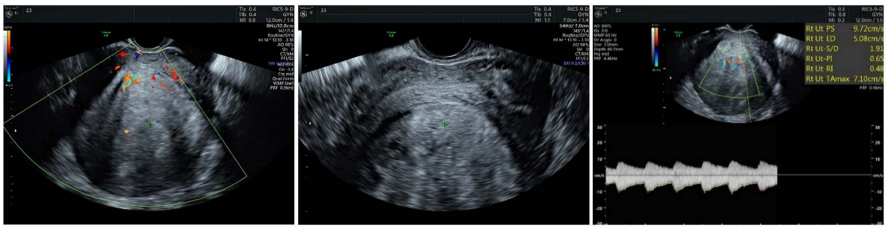

Figure 1. TVS USG, at the time of presentation, large posterior wall fibroid, FIGO type 2 - 5, Color Doppler indicates benign flow.

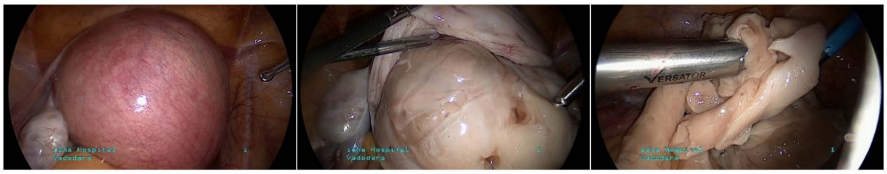

Figure 2. 1st Laparoscopic myomectomy, removal of single soft fibroid, eneucleation, open power morcellation.

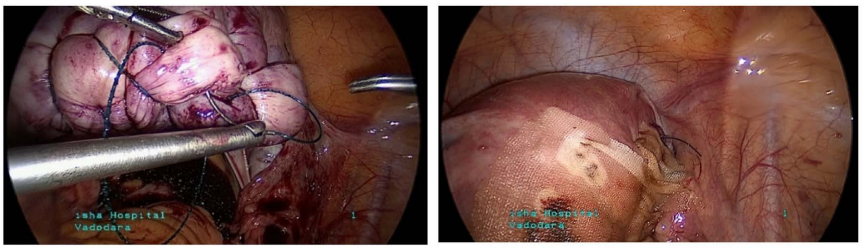

Figure 3. 1st Laparoscopic myomectomy, suturing, interseed barrier covering suture site.

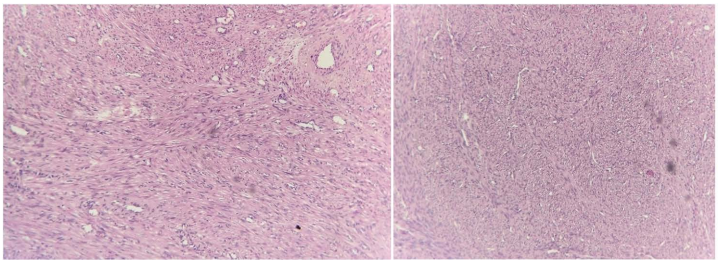

Figure 4. HP, the tumor shows spindle cells arranged in intersecting fascicles with indistinct borders, eosinophilic fibrillary cytoplasm, and cigar-shaped nuclei. (100× H & E) (1st Myomectomy)

Table 2. Timeline of clinical events from September 2018 to October 2023.

Year/Month	Event	Details/Findings
September 2018 to June 2022	Follow up	She was advised to undergo six-monthly TVS USG during the period from 2018 to 2022 to assess the growth of the leiomyomas.
July 2022	Presented with complaints	By July 2022, the uterus had increased to the size of an 18 - 20-week pregnant uterus. During this period, she had increasing symptoms of menorrhagia, lower abdominal pain, and discomfort.
	TVS USG	This time the TVS USG report showed multiple, countless fibroids, with large fibroids measuring 6, 5, and 4 cm. in size, demonstrating benign flow on Color Doppler. (**Figure 5**)
	2nd Laparoscopic myomectomy	She was counseled once again for laparoscopic myomectomy, as she still wanted to preserve her fertility. Laparoscopic myomectomy was performed again. Preoperatively, it was decided to remove leiomyomas greater than 3 cm. A total of six fibroids were removed. In-bag morcellation was performed to retrieve leiomyomas. (9.8.2022) (**Figure 6**, **Figure 7**)
	HP report/IHC report	The HP report was suggestive of LM BN. (**Figure 8**, **Figure 9**) IHC was suggestive of FH-deficient leiomyoma. (**Figure 10**)
	Postoperative period	Her postoperative period was uneventful.
October 2022	TVS USG	Follow-up TVS USG performed in Oct 2022 reported that the uterine myometrium had multiple fibroids of size 6-20 mm all around, with minimal uterine muscle in between. She was kept under follow up every 6 months.
October 2023	LSCS, preterm IUGR delivery	She conceived spontaneously fourteen months after the sedond laparoscopic myomectomy. This time, a preterm LSCS was performed at 35 weeks. She delivered a growth-restricted baby weighing 2 kg. (22.10.23)

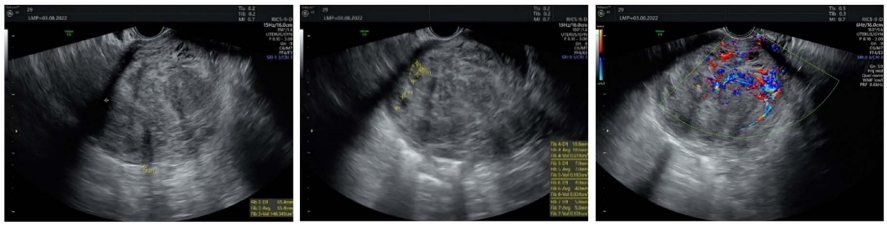

Figure 5. 2nd TVS USG before myomectomy, multiple leiomyomas, small, large, endometrial cavity distorted, with benign blood flow on Color Doppler.

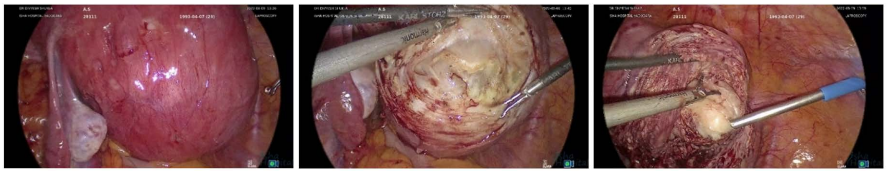

Figure 6. 2nd Laparoscopic myomectomy, enlarged irregular uterus, multiple fibroid eneucleation.

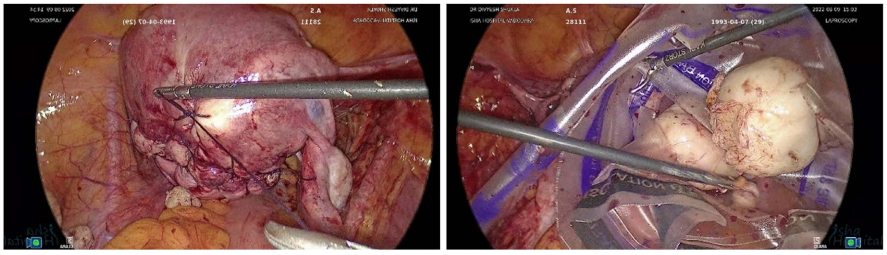

Figure 7. 2nd Laparoscopic myomectomy, suturing of the uterine myometrium, in-bag morcellation.

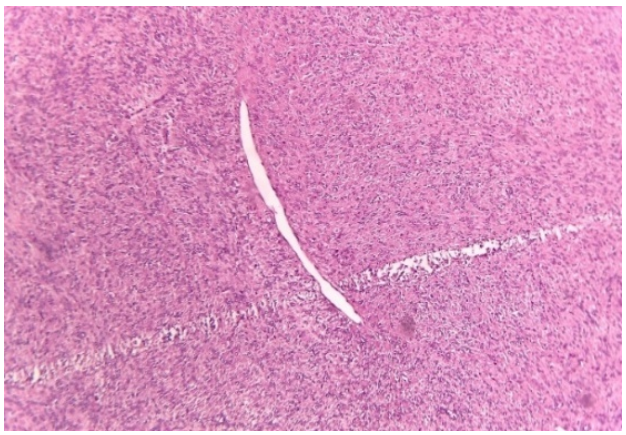

Figure 8. HP, prominent Stag-horn blood vessels are noted. (40× H&E) (2nd Myomectomy)

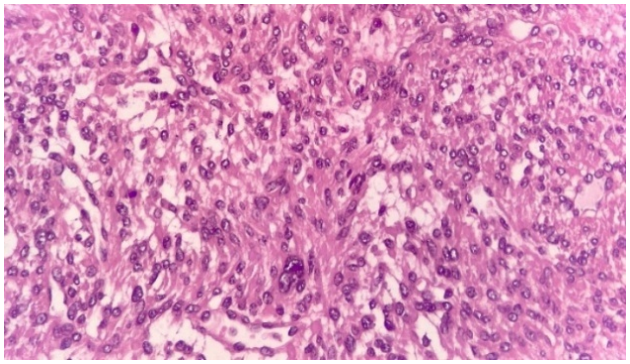

Figure 9. HP, the tumor shows scattered bizarre nuclei exhibiting marked nuclear atypia and prominent nucleoli surrounded by peri nucleolar haloes. (400× H & E) (2nd Myomectomy)

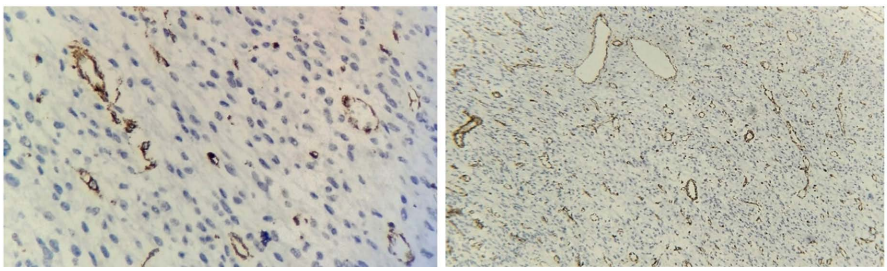

Figure 10. IHC for fumarate FH shows loss of expression in tumor cells along with retained expression in endothelial cells (internal control). (400× DAB) (2nd Myomectomy)

Table 3. Timeline of clinical events from 2023 October to May 2025.

Month/Year	Event	Details/Findings
October 2024	Follow up with TVS USG	On routine examination one year after the last LSCS in October 2024, TVS USG was suggestive of multiple fibroids all around the myometrium of varying size, the largest measuring 23 mm. Color Doppler indicated benign blood flow.
May 2025	Presented with complaints. TVS USG performed	At follow-up 7 months later, in May 2025, the patient presented again with complaints of heaviness in the lower abdomen, dysmenorrhoea, and menorrhagia. Clinical examination suggested a uterus equivalent to 14 weeks of pregnancy, with multiple fibroids of varying size measuring 9 mm to 5 cm. Color Doppler again indicated benign flow. (**Figure 11**)
May 2025	TLH with bilateral salpingectomy	With the similar complaints developing again she came prepared with her decision for hysterectomy. TLH with bilateral salpingectomy, adhesinolysis and bilateral ovariopexy was performed in May 2025, at the age of 32 yrs. The complete specimen was removed via the vaginal route without morcellation. (**Figure 12**, **Figure 13**)
	HP report/IHC report	The HP report was suggestive of LM BN. (**Figure 14**). An IHC study was requested, which was suggestive of an FH-deficient leiomyoma. (**Figure 15**) Ultrasound of the kidney, ureter, and bladder (KUB) performed on 24-05-2025 was normal. Her postoperative period was uneventful. She is currently under close follow-up.

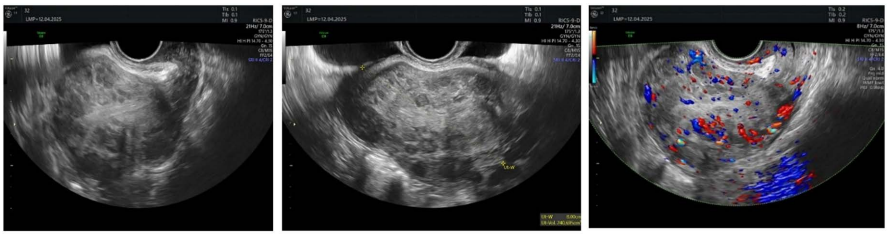

Figure 11. 3rd TVS USG, before TLH, multiple small and large fibroids with benign blood flow on Color Doppler.

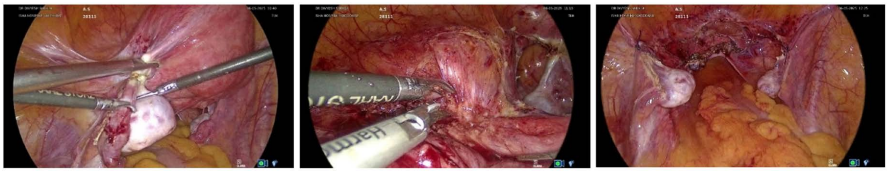

Figure 12. TLH, bladder dissection, vaginal vault closure.

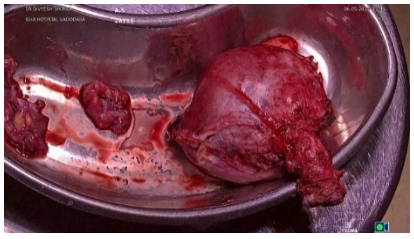

Figure 13. TLH, specimen of uterus and fallopian tubes.

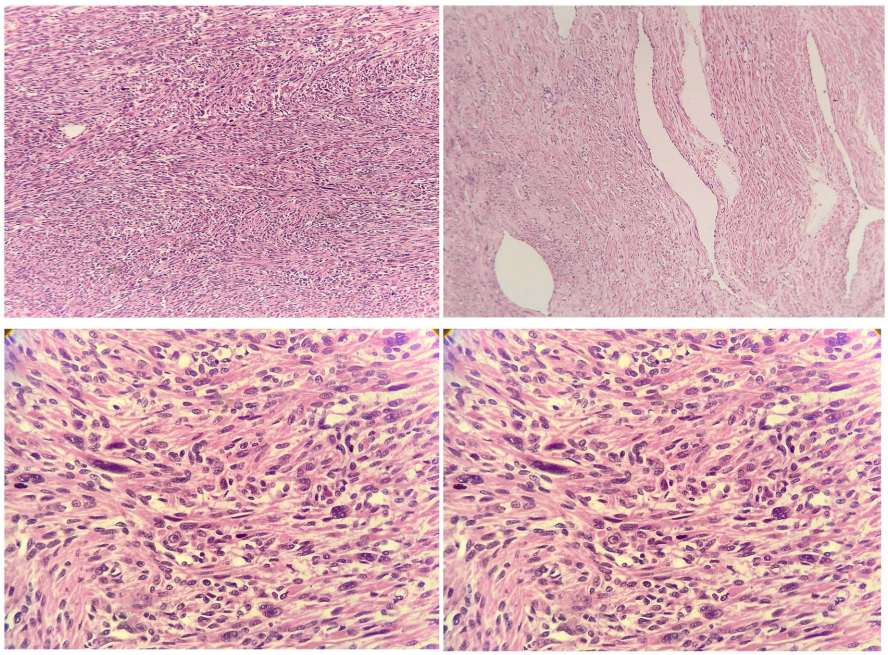

Figure 14. HP, morphology features of FH-deficient leiomyomas. A. Spindle cells arranged in intersecting fascicles with indistinct borders, eosinophilic fibrillary cytoplasm, and cigar-shaped nuclei, 100x H&E. B. Prominent staghorn vessels are typically seen, 40× H & E. C & D. Scattered bizarre nuclei exhibiting marked nuclear atypia and prominent nucleoli surrounded by peri nucleolar haloes, 400× H & E. (TLH)

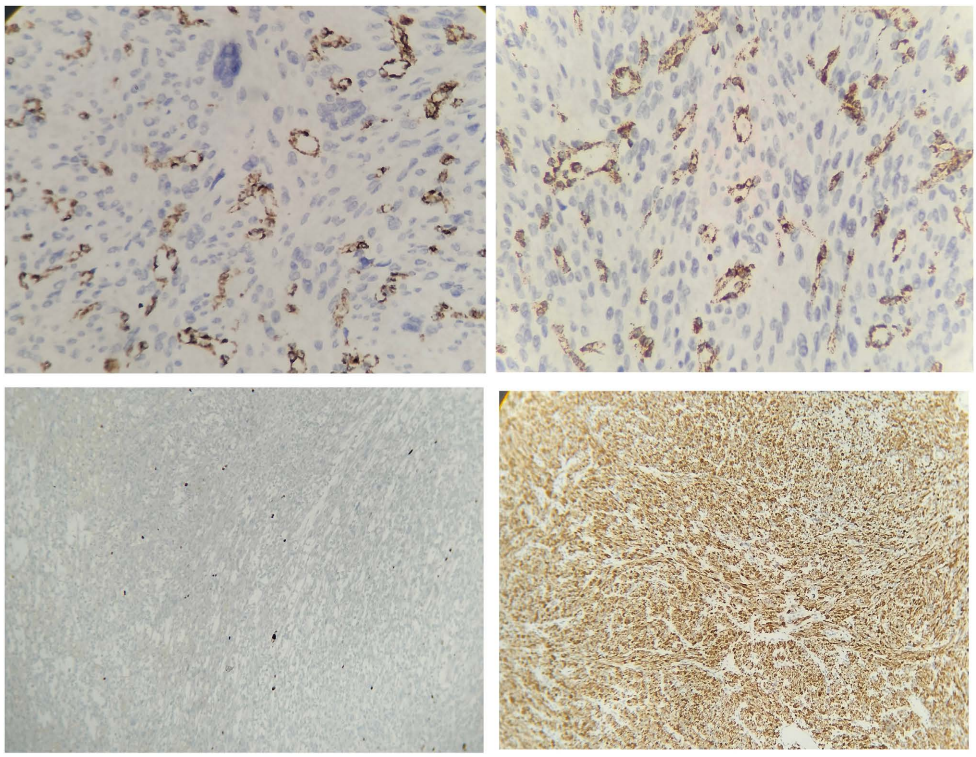

Figure 15. IHC for FH shows loss of expression in tumor cells along with retained expression in endothelial cells (internal control). (400× DAB). D The tumor cells are diffusely positive for Desmin (40× DAB). (TLH)

3. Discussion

The major molecularly distinct subtypes of uterine leiomyoma include MED12 mutations (70%), HMGA2 upregulation (10% - 15%), and inactivation of FH (1.2% - 1.5%) [9]. Each has different genetic drivers, behaviours, and potential clinical implications. Sporadic FH-deficient fibroids, 80% - 90% of which occur due to somatic mutations, are more common, and are non-inherited, resulting from biallelic inactivation of the FH gene. In contrast, 10% - 20% have germline FH mutations and occur as part of a hereditary syndrome inherited in an autosomal dominant manner.

The loss of FH enzymatic activity is most commonly demonstrated by negative IHC staining for FH and positive IHC staining for 2-succinocysteine (2SC), due to its accumulation [10].

Table 4. Comparative HP findings.

Feature	LM BN [11]	MED12-mutant [12]	HMGA2-overexpression [13]	FH-deficient [14]
Cellularity	Moderate to high	Variable	High	Variable; often high
Nuclei	Bizarre, pleomorphic, hyperchromatic; multinucleated	Uniform, cigar-shaped	Small, round to oval; regular	Enlarged, round to oval; prominent pleomorphism
Nucleoli	Eosinophilic, often prominent	Inconspicuous	Inconspicuous	Very prominent, eosinophilic; perinucleolar halos are often present
Cytoplasm	Eosinophilic; may show inclusions	Eosinophilic, fibrillary	Pale or vacuolated	May have globular eosinophilic inclusions
Mitoses	<5 per 10 HPF; no atypical mitoses	Low	Low	0 - 7/10 HPF; may have atypical mitoses [15]
Necrosis	Absent	Absent	Absent	Usually absent (but may show degeneration)
Vascular Pattern	Generally unremarkable vessels	Scattered, thin-walled	Prominent vasculature (thin/thick walls)	Staghorn (hemangiopericytoma-like) vessels
Growth Pattern	Fascicular, may be non-fascicular	Whorled fascicles	Cellular fascicles, trabeculae, or cords	Diffuse or nested, sometimes vague fascicles
IHC (FH/2SC staining)	FH retained; 2SC negative	FH retained	FH retained	FH lost, 2SC positive
Associated Molecular Defect	Not specific; may rarely be FH-negative	MED12 exon 2 mutation	12q14-15 rearrangement, HMGA2 upregulation	FH gene biallelic inactivation
Age/Clinical Notes	Typically perimenopausal; benign behavior	Commonest subtype	Often solitary and large; younger patients	Sporadic or syndromic (HLRCC); younger age if syndromic

Based on the HP of leiomyoma, one can have a high suspicion of the LM BN subtype or other mutations seen in leiomyoma. The comparative HP findings commonly observed are outlined below (Table 4).

The first myomectomy specimen from this patient, performed in 2016 at the age of 23, had HP findings reported as follows; sections revealed whorled and interlacing bundles of smooth muscle fibres interspersed with connective tissue. The nuclei were spindle shaped and ovoid, with no significant nuclear atypia, mitotic activity, or necrosis. These are typical HP features of benign leiomyoma.

The second myomectomy, performed in 2022, had HP findings reported as follows: sections revealed whorled and interlacing bundles of smooth muscle fibres interspersed with connective tissue. The nuclei were spindle-shaped and ovoid. There were a few areas showing cells with bizarre, hyperchromatic, multinucleated nuclei. The mitotic count was 2 - 3 per 10 high-power fields (HPF). No necrosis was seen. The blood vessels were of the staghorn-type. The impression was leiomyoma with bizarre nuclei or FH-deficient leiomyoma. The description of the vessels favoured FH-deficient leiomyoma [14]. An IHC study was requested. On IHC, the spindle cells were positive for vimentin, desmin, smooth muscle actin (SMA), and hcaldesmon, with focal positivity for p16 protein, and a wild-type staining pattern for p53 protein. The MIB-1 labelling index (Ki-67) was 1% - 2%. In addition, IHC for FH showed loss of expression in tumour cells, with retained expression in endothelial cells (internal control). These findings were in favour of FH-deficient leiomyoma.

2SC testing is not commercially available in India. 2SC testing is only required when classic FH-deficient morphology is present, but FH IHC results are equivocal, as it can uncover functional loss missed by FH IHC. Such study was not perused in this case. In presence of FH-deficiency, IHC is more specific (approximately 100%), while 2SC is a more sensitive marker.

The third specimen of TLH, performed in 2025, on HP, showed the endometrium with a proliferative pattern. The intramural tumor showed interlacing bundles and whorls of spindle cells having uniform, elongated, vesicular nuclei, moderate pale, indistinct cytoplasm, and hyalinized fibroconnective tissue. In addition, staghorn-type vessels were noted. There were scattered bizarre nuclei, exhibiting marked atypia and prominent nucleoli surrounded by a perinuclear halo. No significant mitosis or necrosis was seen. The mitotic count was 0 - 1 per 10 HPF. With the same impression of LM BN or FH-deficient leiomyoma, IHC was performed. On IHC, the tumor cells were diffusely positive for Desmin. The Mib-1 labelling index was 3% - 4%. IHC for FH shows loss of expression in tumor cells along with retained expression in endothelial cells (Internal control). The immunoprofile favored FH-deficient Leiomyoma.

Gene	Variant Nomenclature	Location	Tier	Diagnostic
FH (NM_000143.4) VAF: 14.29%	p.G397R c.1189G>A p.Gly397Arg	Exon 8	1B	Yes

This time, the mutation study was performed from FFPE (Formalin-Fixed Paraffin-Embedded); the results were as follows.

The FH G397R mutation is likely oncogenic. Such somatic FH mutations may occur in sporadic uterine leiomyomas with loss of FH enzymatic activity, leading to characteristic morphological and IHC features. Isolated somatic FH variants are not indicative of an inherited cancer risk but may contribute to tumorigenesis in the affected tissue, and they are not a part of HLRCC [6]. With such somatic mutations, one case each of soft tissue sarcoma, uterine leiomyosarcoma, and cutaneous leiomyoma has been reported [16] [17].

Based on this, we ordered the patient's blood for a mutation study. The summary of genetic test findings is given below (**Table 5**).

Table 5. Summary of genetic findings.

Field	Value
Gene	FH (Fumarate Hydratase), NM_000143.4
Exon	Exon 7
Nucleotide Change	c.1004T > C
Protein Change	p. Leu335Pro
Variant Depth	64 out of 146 reads
Zygosity	Heterozygous
Classification	Variant of Uncertain Significance (VUS)
OMIM Phenotype	Leiomyomatosis and Renal Cell Cancer (HLRCC)
Inheritance	Autosomal Dominant

The variant c.1004T > C leads to an amino acid substitution from Leucine to Proline at codon 335 (p. Leu335Pro). This residue is within a conserved region of the FH enzyme, which is essential in the Krebs cycle. The mutation is heterozygous consistent with autosomal dominant inheritance, seen in FH-associated syndromes like HLRCC. This variant is currently labelled as a Variant of Uncertain Significance (VUS). This means that the clinical significance of this variant is not known, and it could be either pathogenic or benign. Further investigations, including functional studies, family segregation analysis or evidence from large variant databases (ClinVar, gnomAD, etc.), are required to clarify pathogenicity [18]. This type of variant is called a missense mutant. This means it is a type of mutation where single gene nucleotide changes lead to the insertion of a different amino acid in the protein sequence. Many FH missense changes fall into this category. Further molecular and clinical analysis was not performed for this for this variant.

The tumor shows biallelic inactivation of FH, with a germline FH missense variant (p. Leu335Pro) and a somatic missense variant (p. Gly397Arg), along with complete loss of FH protein expression by IHC. This molecular and IHC profile is consistent with an FH-deficient tumor and supports the possibility of HLRCC syndrome. Genetic counseling and clinical surveillance are recommended. The

germline variant (p. Leu335Pro) is now clinically suspicious for pathogenicity even if still labelled a VUS in databases.

The HP report of the first myomectomy specimen was normal. It is important to know that the biallelic inactivation of FH likely occurred later, resulting in the transition from normal leiomyomas to FH-deficient tumors in the same patient. This evolution is characteristic of hereditary cancer syndromes like HLRCC, where timing and location of the somatic "second hit" determine when and where the disease manifests.

FH-deficient tumors follow the Knudson two-hit model of tumor suppressor gene inactivation [19]. In the germline FH mutation, the first hit, occurs in all cells, while the somatic second hit (e.g., point mutation, deletion, epigenetic silencing) occurs in specific tissues later, triggering tumorigenesis.

In this patient there was no suspicion of STUMP as the HP did not have differentiating features suggestive of STUMP according to the WHO 2020 criteria. Below is the algorithm to differentiate LM BN, STUMP, and leiomyosarcoma (LMS) [20].

WHO 2020 criteria to differentiate between LM BN, STUMP, and Leiomyosarcoma.

Uterine Smooth Muscle Tumor (leiomyoma)			
No significant atypia, low mitoses, no necrosis	At least one atypical feature: (atypia, high mitoses > 10 per 10 HPF, or tumor cell necrosis)		
	Classic Leiomyoma (or Variant)		
Evaluate all three: nuclear atypia, mitotic count, and necrosis			
Only nuclear atypia	Only increased	Only tumor cell	≥2 features especially
Mitosis 0 - 7/10HPF	Mitoses ≥5/10 HPF	Necrosis	Necrosis + Mitoses > 10/10 HPF

FH mutations are generally present only in the LM BN type of leiomyoma histology. Additional HP features such as increased mitosis or tumor necrosis must be excluded when diagnosing LM BN [10] [11]. This patient has Type 1 LM-BN on HP, were the cells have round or oval nuclei with distinct smooth nuclear membranes and prominent nucleoli with open chromatin. The HP of Type II LM BN is characterized by cells with elongated or spindled nuclei, irregular nuclear membranes, pinpoint or absent nucleoli, and dark smudgy chromatin [2].

In this patient, the tumor harbors a somatic FH mutation, which is not inherited and does not follow an autosomal dominant inheritance pattern. The genetic mutation coexisting in this patient is classified as a VUS. Further testing is only

warranted only if there is a family history of uterine fibroids before the age of 30, type 2 papillary renal cancer, or cutaneous leiomyomas. Although rare, two cases of benign metastatic FH-deficient leiomyoma have been reported in the literature, hence close clinical monitoring of such cases may be necessary [21]. In view of this, the patient is referred for genetic counselling and considered for HLRCC surveillance protocols, including renal imaging preferably by MRI, dermatologic evaluation, and family cascade testing [22].

4. Conclusions

This case describes a uterine leiomyoma in a 32-year-old woman, who has been followed up since the age of 23 for a uterus with multiple leiomyomas, and who had undergone a total of five surgeries. HP of the last two specimens—from the second laparoscopic myomectomy and the final TLH—reported leiomyomas with features suggestive of LN BN with specific characteristics of FH-deficient leiomyoma. The IHC demonstrated complete loss of FH protein expression, and molecular analysis from the tissue blocks confirmed a somatic FH G397R (c.1189G > A) mutation. This somatic mutation is likely to be oncogenic and to contribute to tumorigenesis in the affected tissue, but it is not inherited and is therefore not associated with HLRCC.

Interestingly, the patient was found to harbor both somatic and germline mutations. The identified germline mutation p. Leu335Pro (c. 1004T > C), is a missense mutation currently classified as a VUS. Clinical and genetic surveillance is ongoing in accordance with established protocols of HLRCC. This includes annual dermatological and contrast enhanced abdominal MRI.

The family history is suggestive of paternal inheritance of the mutant allele through an autosomal dominant pattern, as the patient's paternal aunt had a history of uterine fibroids requiring hysterectomy.

To date, only a limited number of case reports and many case series of FH-deficient leiomyoma have been documented. Further assessment of FH mutation status within the patient's first-degree relatives and the other family members is underway.

Ethical Approval and Consent for Publication

Institutional ethical approval and the patient's consent have been obtained for the publication of clinical data and images.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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