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CASE REPORT CRSLS

Leiomyoma with Bizarre Nuclei and Hereditary Leiomyomatosis and Renal Cell Carcinoma

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ABSTRACT

Introduction: Leiomyoma with bizarre nuclei (LBN) is a leiomyoma variant that can be associated with fumarate hydratase (FH) deficiency. Germline pathogenic variants in the *FH* gene are linked to hereditary leiomyomatosis and renal cell carcinoma (HLRCC), which presents with cutaneous leiomyomata, aggressive renal cell carcinomas (RCCs), and symptomatic uterine leiomyomas.

Case Description: A 22-year-old nulligravida female presented with multiple uterine fibroids, heavy menstrual bleeding and pelvic pain, lasting over two years. The patient subsequently underwent laparoscopic myomectomy. Histological analysis of the leiomyomas indicated the presence of bizarre nuclei. Immunohistochemical studies confirmed FH deficiency, characterized by loss of FH expression and overexpression of S-(2-succino)-cysteine (2SC). Genetic testing revealed a likely pathogenic variant (c. 1176_1181delTGCTGT) in the *FH* gene.

Discussion: Due to potentially devastating consequence and the occult nature of RCCs, the discovery of LBN should be followed with further investigation for HLRCC.

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INTRODUCTION

Uterine leiomyoma, or fibroid, is the most prevalent benign tumor in women. The estimated cumulative incidence is reported to be as high as 70% in white women and approaches 80% in black women during the premenopausal years.[1] Leiomyoma with bizarre nuclei (LBN) is one of the leiomyoma variants, having replaced the term "atypical leiomyoma" in the World Health Organization (WHO) classification after 2014.[2] According to Bell's criteria, LBN is characterized by moderate-to-severe nuclear atypia, fewer than 10 mitoses per 10 high power fields (HPFs) and absence of coagulative necrosis.[3] Interestingly, molecular studies indicate that aberrant expression of fumarate hydratase (FH) is more commonly found in LBN than in other types of leiomyomas or leiomyosarcoma. FH-deficient leiomyomas (FH-LMs) are now categorized as an independent histological subtype with distinct morphological features.[4] FH is a crucial enzyme in the tricarboxylic acid cycle, facilitating the conversion of fumarate to malate in the mitochondrial matrix.[5–7] Pathogenic variants in the *FH* gene are linked to the rare autosomal dominant hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome.[8] HLRCC commonly presents with cutaneous leiomyomata and symptomatic uterine leiomyomas at an early age and is associated with aggressive renal cell carcinomas (RCCs), that typically develop a decade later.[6,9–12] Renal tumors associated with HLRCC can be particularly aggressive, putting patients with pathogenic variants in *FH* at high risk for advanced or metastatic disease, even in the presence of small primary tumors.[13] Given the implications, systematic screening and subsequent genetic testing for HLRCC are essential.

Herein we report a case of LBN in a 22-year-old patient. Further investigation revealed FH deficiency in the fibroid specimen, and genetic testing identified a likely pathogenic variant in *FH*, indicating an HLRCC genotype in this patient.

CASE PRESENTATION

A 22-year-old nulligravida female presented with uterine fibroids, heavy menstrual bleeding and pelvic pain lasting over two years. She also reported dysmenorrhea, dyspareunia, bladder pain with straining, and pain with bowel movements. In the past, she had tried a subdermal implant and oral contraceptive pills with no relief of symptoms. Her medical and surgical history were unremarkable, and there was no significant family history of cancer. On physical examination, the uterus was found to be approximately 15-week size, positioned low in the pelvis, and fixed, with severe tenderness noted during bimanual examination. Pelvic magnetic resonance imaging (MRI) revealed an anterior pedunculated fibroid measuring 4.2 × 2.8 × 8.4 cm and a posterior partially subserosal fibroid measuring 3.2 × 2.1 × 1.0 cm (**Figure 1**).

The patient underwent laparoscopic myomectomy and treatment for endometriosis with the incidental finding of stage II endometriosis. She recovered well postsurgery. Histological examination confirmed the presence of leiomyomata uteri with focal bizarre nuclei with symplastic changes (**Figure 2**), as well as endometriosis. Immunohistochemical (IHC) staining showed a loss of expression of FH in the tumor cells, and overexpression of S-(2-succino)-cysteine (2SC) (**Figure 2**).

The patient was subsequently referred for genetic counseling due to the possibility of HLRCC. Genetic testing confirmed a likely pathogenic variant in *FH* (c. 1176_1181delTGCTGT), indicating that the patient carries the genotype associated with HLRCC.

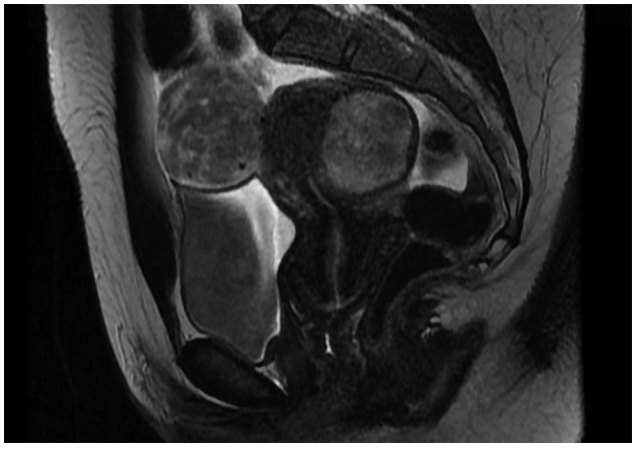

Figure 1. T2 weighted MRI image showing the fibroids exhibiting lace-like heterogeneous hyperintensity compared to the muscle.

DISCUSSION

HLRCC syndrome, also known as Reed syndrome, is an autosomal dominant disease and manifests as cutaneous leiomyomata, aggressive RCCs, and symptomatic uterine leiomyomas at a young age.[8,14] Patients with HLRCC tend to be diagnosed with uterine leiomyomas at a significantly younger age compared to the general population. Joseph et al found that 2.6% (5 out of 194) of leiomyomas in patients younger than 40 years of age carry *FH* gene aberrations.[15] Siegler et al reported 22 FH-LM cases diagnosed via immunohistochemistry for FH, revealing a median age of 36.[11] At least 18 (81.8%) of these patients had multiple leiomyomas (ranging from 2 to 14 cm), with the largest measuring 11.8 cm. In our case, there was no known family history of cutaneous leiomyomas or RCC, but the patient's mother has a history of uterine fibroids at a young age. Therefore, cascade testing for her mother was initiated.

The most common renal neoplasm associated with HLRCC is type 2 papillary RCC, known to be an aggressive and treatment resistant.[16] The incidence of this carcinoma in HLRCC patients is reported to be 6.5 times higher than in the general population.[17,18] HLRCC renal tumors are typically solitary and unilateral, with a mean age of onset around 40 years, and the lifetime risk of developing RCC is estimated at approximately 15%.[6,9–12] Early detection of HLRCC is crucial, as it allows for timely surveillance and testing of other family members.

Pathogenic or likely pathogenic (P/LP) *FH* variants are detected in 85% (89 out of 105) of patients with HLRCC.[19] The *FH* gene is located on the long arm of chromosome 1 at position 43 (1q42.3-q43).[5–7] The mitochondrial isoform of FH catalyzes the reversible hydration of fumarate to L-malate as part of the Krebs cycle, while the cytosolic isoform of FH is thought to be involved in fumarate metabolism produced by various cytosolic reactions.[20] Sporadic or germline mutations in FH lead to diminished enzyme activity and an accumulation of fumarate, which disrupts mitochondrial respiratory chain function. Most sporadic FH-LM are caused by somatic biallelic inactivation of FH.[21] Although the mechanism of tumorigenesis in FH-deficient cells remains incompletely understood, it is believed that *FH* is a tumor suppressor gene. Consequently, inactivation of both *FH* alleles results in reduced or complete loss of FH enzymatic activity, leading to fumarate accumulation.[22] Several proposed mechanisms suggest that elevated fumarate levels may act as an oncoprotein, for example, as seen with hypoxia-inducible factor (HIF) accumulation. It may lead to

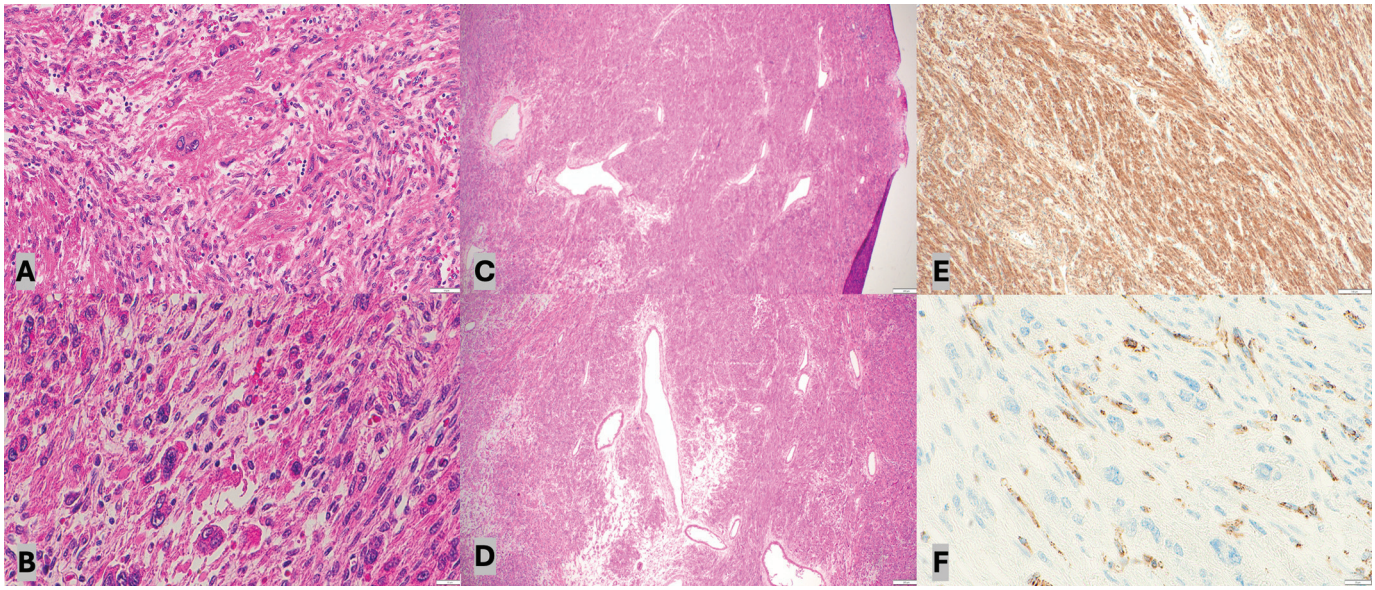

Figure 2. (**A**) Scattered bizarre cells with nuclear inclusions (20x), (**B**) multinucleated giant cells (40x), (**C**) staghorn vessels (4x), (**D**) stromal edema with vessels with (4x), (**E**) diffuse positive staining for S-(2-succino)-cysteine (2SC) (10x), (**F**) negative FH staining (40x).

proliferation and resistance to apoptosis, providing increased vasculature and glucose transport for these glucose-dependent FH-deficient tumors in phenomenon called "pseudohypoxia."[22–25] FH has also been identified as a suppressor of homologous recombination DNA repair, thereby compromising genomic integrity.[12] Another hypothesis regarding FH's role as a tumor suppressor includes the concept of hypermutability due to oxidative damage.[6] Additionally, accumulated fumarate may enhance the expression of the nuclear factor (erythroid-2) like-2 transcription factor, influencing processes such as angiogenesis, epithelial-to-mesenchymal transition, and cancer progression.[26] Increased fumarate levels lead to modifications of cysteine residues in numerous proteins, resulting in increased protein succination and the production of S-(2-succino)-cysteine (2SC). The IHC analysis of FH and 2SC has been described as highly specific for the identification of loss of FH activity.[27,28]

Among leiomyomas, FH (FH-LM)-deficient variants represent a rare subset, accounting for 0.4–1.6% of all cases.[29] The fifth edition of the WHO classification of female genital tumors in 2020 now recognizes FH-LM as a distinct histological subtype with unique morphological characteristics.[4] A comprehensive study of 1,583 uterine smooth muscle tumors identified FH deficiency in 86 cases (5.43%).[21,29] The frequency of FH deficiency was highest in LBN (37.3%), while it was low in usual-type leiomyomas (1–2%). Notably, none of the leiomyosarcomas assessed showed FH deficiency.[29] About one-third of FH-LM cases exhibit detectable *FH* gene mutations,[21] and while sporadic FH-LM is generally benign, true malignant transformation is exceedingly rare.[30]

It is recommended that individuals suspected or confirmed to have HLRCC, those with heterozygous P/LP variants in the *FH* gene regardless of clinical symptoms, and at-risk family members who have not undergone genetic testing, engage in regular surveillance. Currently, there are no universal guidelines for HLRCC surveillance, highlighting the need for ongoing research in this area. Regular screening for RCC and long-term follow-up imaging is a crucial component of managing HLRCC. Most providers recommend MRI scans with 1- to 3-mm slices through the kidneys every 6 to 12 months beginning at age 8 years to evaluate for renal tumors.[31,32] Regular dermatological exams are recommended, though there is no consensus on their frequency. For patients with an intact uterus, annual gynecologic exams, and periodic imaging (MRI or ultrasound) are advised to monitor uterine leiomyomas beginning at age 20 years old or earlier if symptomatic.[7,8,33,34] While recent studies have indicated that certain P/LP variants in *FH* may be associated with an increased risk for pheochromocytomas and paragangliomas, their surveillance is not included in HLRCC guidelines.[35]

The patient was advised to continue regular gynecologic surveillance to monitor for the recurrence of uterine fibroids. In addition, she has been referred to dermatology and urology for surveillance of cutaneous leiomyomas and RCC.

This case underscores the importance of considering HLRCC in young women with LBN and the necessity for genetic counseling and surveillance. This case report presents a single patient, and as such, the findings may not apply to all patients. Additionally, while this case highlights the potential association between LBN and FH deficiency, the lack of long-term follow-up further limits our ability to assess the long-term outcomes of this patient, particularly in regard to the development of RCC, a key concern for patients with HLRCC. Future studies involving larger cohorts and multicenter registries would provide more robust data, facilitating a deeper understanding of the clinical course of FH-LMs, the genetic landscape of HLRCC, and the best strategies for monitoring at-risk individuals.

CONCLUSION

LBN in a young patient can be a sentinel presentation of HLRCC. The known histomorphology of FH deficient leiomyomas should prompt further screening for HLRCC. Gynecologic surgeons should be aware of this association and initiate hereditary risk assessment when indicated.

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