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Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome in a young patient presenting with a large uterus: A case report and review of the literature

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ABSTRACT

Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome is a rare genetic disorder caused by a germline mutation in the fumarate hydratase (FH) gene. It is clinically characterized by cutaneous leiomyomas, uterine leiomyomas and renal cell cancer. A 31-year-old woman presented with severe abdominopelvic pain associated with severe menorrhagia which required a visit to the emergency department. Computed tomography (CT) showed a severe enlargement of the uterus with newly diagnosed fibroids. Magnetic resonance imaging (MRI) confirmed the finding of an enlarged uterus with mild left and moderate right hydronephrosis and hydroureter. The patient tried to manage the pain with oral over-the-counter medications and heat pads without significant relief. She was recommended to proceed with total abdominal hysterectomy and bilateral salpingectomy. She tolerated the procedure well and had an uneventful postoperative recovery. Pathology showed morphologic features, including the staghorn vessels, alveolar edema, eosinophilic cytoplasmic inclusions and prominent nucleoli which are characteristics for FH-deficient leiomyomas. Genetic testing was positive for a pathogenic variant in the FH gene associated with HLRCC. This case highlights the importance of proceeding with genetic testing in patients with personal and family history of leiomyomas and unusual pathology findings. Early identification of the syndrome can lead to appropriate screening for renal cell carcinoma.

1. Introduction

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an inherited autosomal-dominant condition with a variable or *de novo* penetrance [1,2]. HLRCC is caused by a heterozygous germline mutation in the fumarate hydratase (FH) gene, which is involved in the tricarboxylic acid (TCA) cycle or Krebs cycle which transforms fumarate to malate [1–7]. The most serious manifestation of genetic condition is renal cell carcinoma (RCC).

It is estimated that around 300 families are affected with HLRCC worldwide [3,8]. However, the presence of an FH germline mutation does not always lead to a tumor. According to the two-hit hypothesis, an additional somatic mutation of the wild type of an allele is necessary for the development of a tumor due to a reduction or inactivation of the FH enzyme [3]. This results in an accumulation of fumarate, which promotes the development of an FH-deficient tumor.

The common manifestation includes multiple cutaneous and uterine leiomyomas with or without renal cysts or tumors in women aged around 25 years [6]. In HRLCC, renal cells tend to display a type 2 renal papillary carcinoma. Cells in uterine leiomyoma show diffuse nuclear atypia, in contrast to focal or scattered foci of severe nuclear atypia in atypical leiomyomas. The tumor cells can have a single or multinucleated nuclei which are epithelioid with very prominent nucleoli surrounded by a perinuclear halo.

We present the case of a young patient with uterine leiomyomata and severe menorrhagia, without cutaneous lesions, and discuss the adequate management of HLRCC after a hysterectomy.

2. Case Presentation

A 31-year-old woman was referred from urgent care for an enlarged uterus, abdominopelvic pain and severe menorrhagia. She stated that the pain started a couple months prior to her visit as intermittent with a severity of 5 on 10-point scale. She mentioned having severe and diffuse

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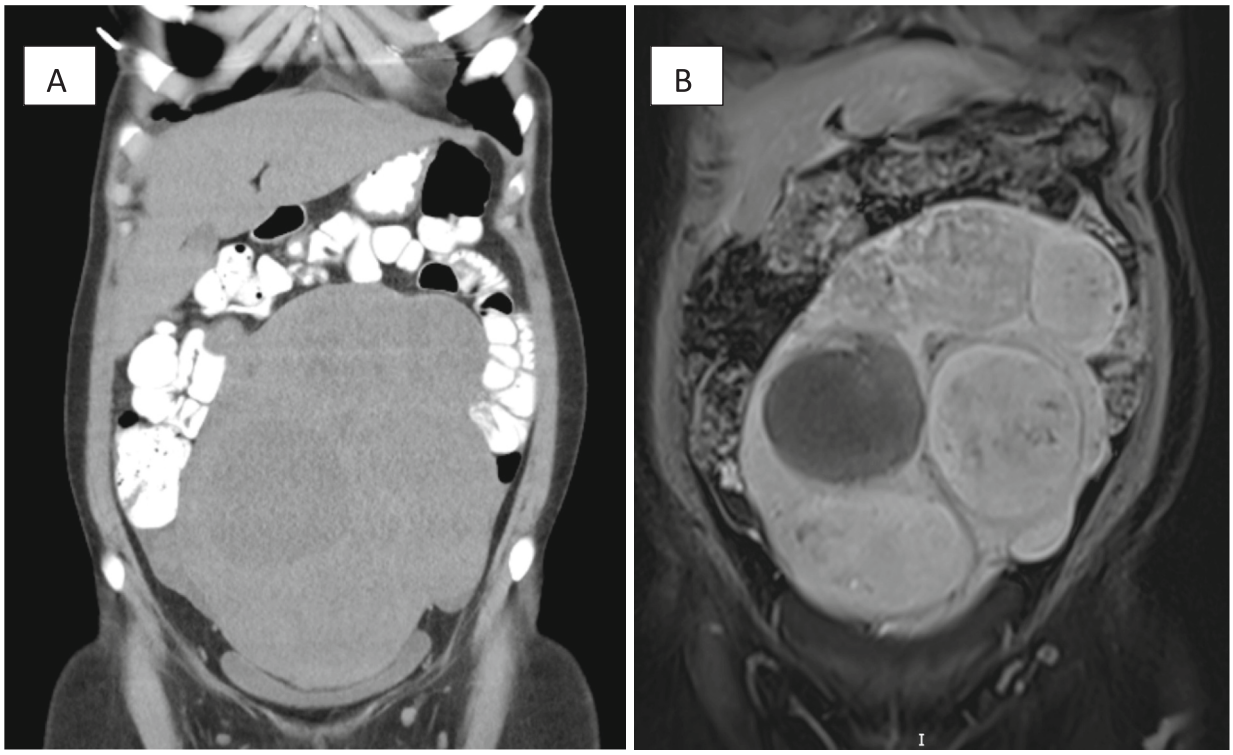

Fig. 1. Imaging showing enlargement of uterus with multiple fibroids.
A: CT of pelvis and abdomen showed a 22 × 13 × 17 cm severe enlargement of the uterus extending 5 cm above the umbilicus, with multiple large uterine fibroids.
B: MRI confirmed the findings of an enlarged uterus with multiple fibroids.

pressure in her pelvic area and her lower back. She also reported abdominal distension and firmness since the onset with bloating during her periods. The patient tried to manage the pain with non-steroidal anti-inflammatory drugs (NSAIDs) and heat pads, but she remained very uncomfortable, especially when sitting. She has a regular monthly period cycle that lasts 7 days. Her first 2–3 days were very heavy in

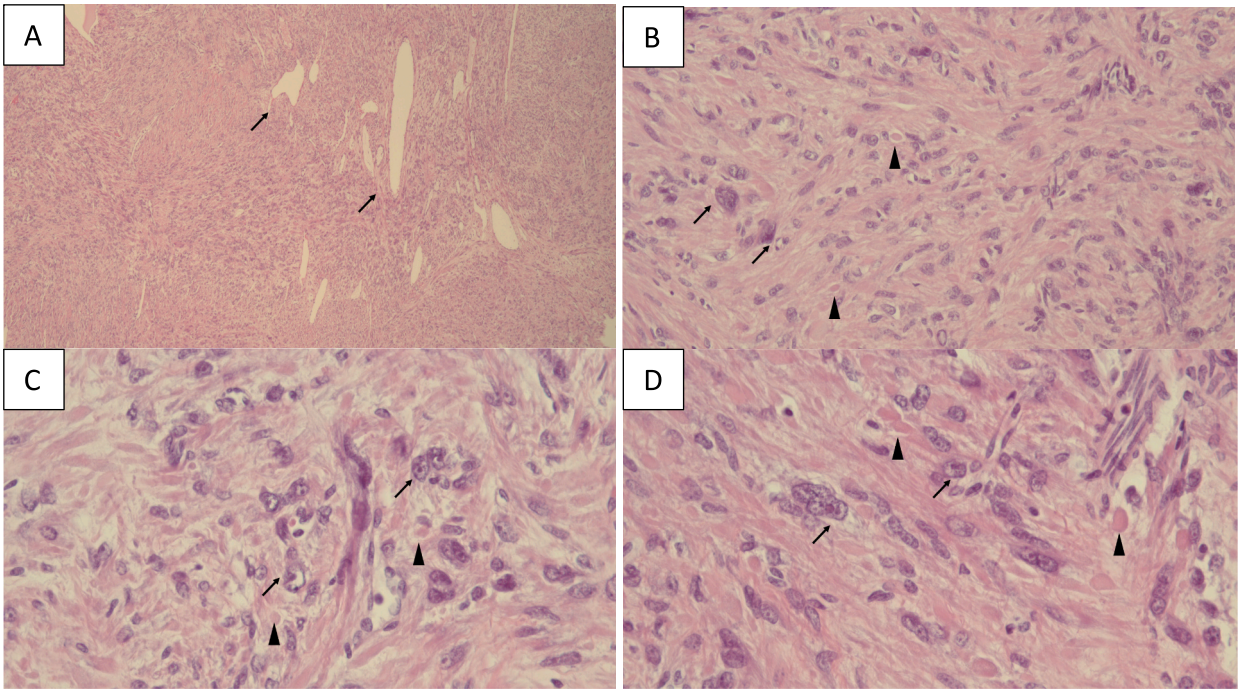

Fig. 2. Histopathology of uterine fibroids.
A: Low magnification shows staghorn blood vessels (arrows) and areas of patchy edema.
B: High magnification shows epithelioid nuclei (arrows) and cytoplasmic eosinophilic granules (arrowheads).
C, D: High magnification shows macronucleoli (arrows) with perinucleoli clearing and cytoplasmic eosinophilic granules (arrowheads).

Table 1
5 cases reports related to hereditary leiomyomatosis and renal cell cancer.

Year and authors	Case	Timing of hysterectomy or myomectomy	HLRCC markers	HLRCC confirmation methods
2022, Catarina T & al. [3]	41-year-old female with hematuria and right lumbar pain	Hysterectomy at 38-years-old due to large symptomatic myoma	1. Piloleiomyomas 2. Renal tumors on right kidney	Genetics of *FH* locus after nephrectomy and cutaneous lesions
2020, Yonamine T & al. [11]	42-year-old female with abdominal pain	Myomectomy at 32-years-old due to pain and anemia	1. Renal cyst-tumor 2. Multiple uterine myomas	Genetics of *FH* locus after open nephrectomy confirming type 2 papillary RCC and total hysterectomy
2020, Popa L. & al. [1]	62-year-old female with multiple cutaneous coloured and nodular lesions	Multiple myomectomies before 30-years-old and total hysterectomy (not specified)	1. Cutaneous leiomyomas 2. Renal cyst	Histopathology from skin biopsy with personal and family history
2018, Natalia F & al. [4]	27-year-old female with hematuria, right flank pain, menorrhagia and dysmenorrhea	Open myomectomy performed few months after nephrectomy	1. Solid mass in right kidney 2. Multiple uterine leiomyomas 3. Cutaneous leiomyomas	1. Genetics not conclusive for FH mutation 2. Dermatologic examination (not specified)
2016, Tulandi T & Foulkes WD [12]	30-year-old female with swelling and pain in her abdomen with painful-coloured cutaneous nodules	Myomectomy at the time of chief complaint	1. Cutaneous leiomyomas 2. Uterine leiomyomas 3. Right renal cyst	1. Genetics of *FH* gene 2. Histopathology from skin biopsy and uterine myomectomy

which she changed her tampon every 1–2 h. She stated having painful cramping with her periods which she typically also managed with NSAIDs.

Her mother had had a hysterectomy due to fibroids and her father had leukemia. Her maternal grandmother had breast cancer in her 50s.

Computed tomography (CT) pelvis and abdomen showed a 22x13x17 cm severe enlargement of the uterus extending 5 cm above the umbilicus, with multiple large uterine fibroids. The image also showed mild right hydronephrosis and upper right hydroureter due to extrinsic compression from the uterus. The other organs were unremarkable (Fig. 1A).

Two weeks later, magnetic resonance imaging (MRI) confirmed the findings of an enlarged uterus with multiple fibroids. Her uterus measured around 22.5 cm in length by 17.6 cm in width by 12.8 cm in anteroposterior diameter. The largest fibroid measured 11.4 cm in diameter with incomplete enhancement (Fig. 1B).

After discussion, the patient stated not being interested in fertility preservation. She agreed to proceed with total abdominal hysterectomy, bilateral salpingectomy with preservation of her both ovaries due to her age.

A total abdominal hysterectomy and bilateral salpingectomy was performed. Her uterus weighed 2498 g with dimensions of 22 × 18 × 14 cm. Both fallopian tubes were grossly normal. No lymphadenopathy in the pelvic and para-aortic area was identified. The upper abdomen, including surface of the liver, diaphragm, stomach, gutters and intestine, revealed no gross extrauterine disease.

Gross examination of the specimen showed multiple nodules ranging in size from 0.8 to 10 cm. The cut surface had a variegated appearance with some degenerative changes without necrosis. On microscopic examination, at low power, staghorn blood vessels and areas of patchy edema and degenerative changes, including infarct-type necrosis, were present (Fig. 2A). On higher magnification, the cells contained abundant eosinophilic cytoplasm and many cells showed prominent intracytoplasmic eosinophilic inclusions. The nuclei were atypical, ovoid and many showed prominent nucleoli surrounded by perinucleolar halos. In some areas, the tumor showed more severe cytologic atypia in the form of enlarged and multilobated nuclei with smudgy chromatin, similar to those seen in a leiomyoma with bizarre nuclei (LBN). Mitotic activity was 3–5/10 HPFs (Fig. 2B, C, D). These morphologic features were suggestive of FH-deficient leiomyomas. The tumor cells showed loss of staining for FH and positive staining for to 2-succinocysteine (2SC), supporting the presence of FH deficiency. Genetic testing was positive for a pathogenic variant, specifically FH c.698G > T (p.Arg233Leu).

The patient was discharged 3 days postoperatively with an uneventful period. A kidney ultrasound scan after this period was also unremarkable and she was followed up by a urologist.

3. Discussion

The prevalence of HLRCC is extremely low, with only around 300 families affected worldwide. However, data suggest that many cases may not be diagnosed [2]. To our knowledge, this is the first case to present without cutaneous lesions or kidney abnormalities as seen with other HLRCC cases. Our young patient presented with uterine leiomyoma and severe menorrhagia causing her excruciating pain.

In HLRCC, most patients present with cutaneous leiomyoma, with 76–100% between 20 and 40 years old [6]. Approximately 70% of women with HLRCC develop uterine leiomyomas at a median age of 30 years and 68% of them will undergo a myomectomy or hysterectomy before 40 years [9,10]. RCC occurs in about 10–16% of patients with this condition and requires close surveillance from a young age [5].

A total of 5 cases with HLRCC were found in the literature and these are summarized in Table 1, which gives the patients' chief complaint, timing of hysterectomy or myomectomy, the clinical manifestation of HLRCC and the methods to confirm HLRCC. The first four patients (cases 1–4) underwent either hysterectomy or myomectomy and HLRCC was confirmed later by genetic testing [1,3,4,11]. These patients came back months or years later with other clinical manifestations of HLRCC and further workup helped confirmed the condition by histopathology and genetics. Only one patient (case 5) had genetic testing before surgery since she presented with all the telltale signs of HLRCC and had a family history of the condition [12]. In most reports, the authors suggested using cutaneous leiomyomas as the primary indicator of HLRCC [1,3,4,12]. However, no case used uterine myomas as the only indicator in a young woman with suspected HLRCC after hysterectomy or myomectomy.

Many cases of HLRCC remain undiagnosed since most researchers do not use uterine leiomyomas after a hysterectomy or myomectomy as a sufficient indicator in this condition followed by genetic testing. On the other hand, uterine leiomyosarcoma (ULMS) is a rare and aggressive type of smooth muscle tumor. The association of ULMS and HLRCC has been described in a previous study in young women [13]. We suggest future studies to evaluate ULMS in young women with suspected HLRCC.

4. Conclusion

This case concerns a young woman with symptomatic uterine

leiomyomas without any cutaneous or kidney abnormality, and a family history of uterine fibroids (in the patient's mother). Genetic testing confirmed HLRCC associated with FH deficiency. This case highlights the importance of performing genetic testing in young women with symptomatic uterine leiomyomas with suggestive histologic features who undergo hysterectomy, even without cutaneous or kidney abnormality. Characteristic histopathologic features include staghorn-shaped blood vessels and alveolar-pattern edema in low power and tumor macronucleoli surrounded by halo and cytoplasmic eosinophilic globules in high power. Providers should closely monitor their kidneys to help prevent the development or to facilitate the early detection of RCC.

Contributors

Nora Shero participated in the conception of the case report, acquired and interpreted the data, Esther Yoon was involved in patient care, contributed to data interpretation and revised the article critically for important intellectual content.

Joel Cardenas-Goicoechea was involved in patient care, contributed to data interpretation and revised the article critically for important intellectual content.

All authors approved the final submitted manuscript.

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Patient consent

Obtained.

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This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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