ORIGINAL ARTICLE: GENETICS

Novel fumarate hydratase mutation in a family with atypical uterine leiomyomas and hereditary leiomyomatosis and renal cell cancer

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Objective: To describe a novel mutation in the fumarate hydratase (FH) gene in a family with atypical uterine leiomyomas.
Design: Case report and review of the literature.
Setting: Academic community hospital.
Patient(s): Three sisters who presented as nulligravidas aged 27–30 years with large atypical uterine leiomyomas.
Intervention(s): Abdominal myomectomy, robotic myomectomy, hysterectomy, gene sequencing.
Main Outcome Measure(s): Identification of a family with hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome and a novel mutation in the FH gene.
Result(s): Two of the three sisters tested positive for a novel FH mutation p.Leu99Glufsx6. The eldest sister was clinically diagnosed with HLRCC. The patients' father also carries the same mutation in the FH gene. The patients and their father are now undergoing yearly screening for renal cancer.
Conclusion(s): Patients with HLRCC are at risk for developing renal cancer as well as losing their fertility via early hysterectomy. Physicians must be aware of this condition and refer at-risk individuals for genetic testing. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Hereditary leiomyomatosis and renal cell cancer, fumarate hydratase, atypical leiomyoma, myomectomy

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Uterine leiomyomas are found in 25%–70% of reproductive-age women, depending on the method used for detection; most (>95%) present after the age of 30 years (1, 2). Approximately 40% of uterine leiomyomas carry specific chromosomal rearrangements, including trisomy 12 or deletions and rearrangements of portions of 7q, 12q15, 6p21, or 10q22 (3). There is a slight familial predisposition for the development of uterine leiomyomas, with a ~2.5-fold risk if a first-degree relative is affected. There is, however, only one known genetic syndrome that leads to the development of uterine fibroids. Heterozygous germline mutations in the fumarate hydratase (FH) gene cause a syndrome known as hereditary leiomyomatosis and renal cell cancer (HLRCC) that puts affected individuals at risk for uterine leiomyomas, cutaneous piloleiomyomas, and type II papillary renal cell cancer.

The pathology of a typical leiomyoma shows smooth muscle cells with bland nuclei and no increase in mitotic activity or necrosis. In contrast, malignant leiomyosarcomas have two of the following three characteristics: cytologic atypia, increased mitotic activity, and coagulative tumor cell necrosis (CTCN). Atypical leiomyomas lie in the spectrum between benign leiomyomas and malignant leiomyosarcomas. They have cytologic atypia, no CTCN, and fewer than ten mitoses per ten high-power fields (4). Leiomyomas

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that develop in patients with HLRCC often have increased cellularity, cytologic atypia, and a characteristic perinuclear halo (5).

MATERIALS AND METHODS

Three sisters each presented to a gynecologist at the ages of 27–30 years as nulligravidas with large uterine myomas. They all underwent myomectomies, and pathology was consistent with atypical myomas in each case. Owing to the familial clustering of atypical leiomyomas, they were recuited in December 2014 for more detailed investigation of possible underlying genetic disorders. The sisters were questioned regarding their family and personal history of symptoms of hereditary leiomyomatosis and renal cell cancer. Genetic testing was performed in concordance with genetic counseling. Patient III-4 had sequencing performed of her entire FH gene (Genedx). Genomic DNA was obtained via cheek swab and polymerase chain reaction amplified for exons 1–10 of the FH gene and the flanking splice sites. Bidirectional DNA sequencing was performed, compared with the published gene sequence, and confirmed with the use of repeat sequence analysis. Patients III-3 and II-2 had sequencing only of the segment of DNA that contained the p.Leu99Glufsx6 mutation (exon 3). The Leiden Open Variation Database version FH110817 was accessed to retrieve all known mutations in the FH gene (6). The variant found in these patients was not identified in the SNP database. The Institutional Review Board reviewed this work, and it was considered exempt. Consent was obtained from each patient before publication.

RESULTS

Case 1

The proband (patient III-1; Fig. 1) presented as a 27-year-old nulligravida with a 6-year history of dysmenorrhea and menorrhagia. She had no significant medical history and no abdominal surgeries. At presentation her hemoglobin was 6.4 and she had an 18-week-size uterus on vaginal examination. The remainder of her physical examination was unremarkable. A pelvic ultrasound showed an enlarged myomatous uterus with multiple fibroids including a posterior fibroid measuring ~8 × 7 cm. She was placed on continuous oral contraceptive pills and iron therapy with resulting improvement in her anemia, but she continued to experience dysmenorrhea.

After failing conservative management, she underwent an exploratory laparotomy and myomectomy for removal of 34 fibroids, two of which were 10 cm in size (Fig. 2). The pathology of her fibroids showed multifocal moderate to severe cytologic atypia, but no increased mitotic activity or necrosis, which was consistent with an atypical leiomyoma.

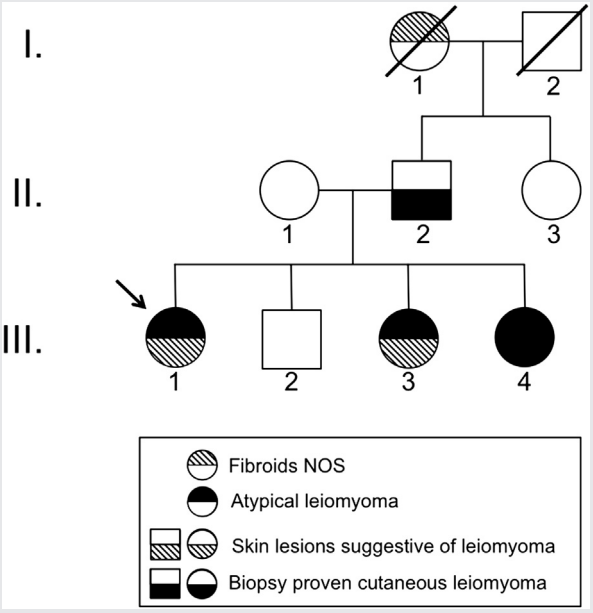
She had initial improvement in her symptoms, but she returned 3 years later with symptoms of uterine enlargement and again was found to have an 18-week-size uterus on examination. Magnetic resonance imaging (MRI) was obtained that showed a 14 × 11 cm uterus with several large fibroids up to 7 cm in size. She was taken for a second exploratory laparotomy and myomectomy in an attempt to preserve her fertility. This time, 58 fibroids were removed, the largest a conglomeration of approximately six fibroids that was 15 cm in largest diameter. An attempt was made to remove all visible fibroids, but they invaded the uterine muscle so extensively that at the end, there were many <1-cm fibroids that could not be removed. The patient's pathology showed more diffuse cytologic atypia, but there was no mitotic activity or necrosis and she was again given the diagnosis of atypical leiomyomas.

The patient was followed carefully with the use of serial ultrasounds, and another 3 years later, as a 33-year-old nulligravida, she showed evidence of recurrent uterine fibroids. On vaginal examination she had a 14–16-week-size uterus. Her ultrasound revealed a 12.9-cm uterus with four measurable fibroids 4–6 cm in largest dimension. At this point the patient desired definitive management and underwent a total abdominal hysterectomy. At the time of surgery, multiple adhesions were noted, but her surgery and postoperative course were uncomplicated. Her pathology again showed atypical leiomyomas. The largest fibroid in the hysterectomy specimen was 6 cm in diameter. The patient has been followed for 5 years after the hysterectomy and has shown no signs of extrauterine disease.

Case 2

The proband's middle sister (patient III-3; Fig. 1) presented at age 30 years with symptomatic uterine enlargement and dyspareunia. She was a nulligravida with no significant past medical or surgical history. Pelvic examination showed a 14-week-size uterus, and ultrasound identified

FIGURE 1



Pedigree of the family with novel fumarate hydratase mutation Leu99Glufsx6, showing hereditary leiomyomatosis and renal cell cancer (HLRCC)–associated conditions. NOS = not otherwise specified.

Wheeler. A novel FH mutation causing HLRCC. Fertil Steril 2015.