

Hereditary leiomyomatosis and renal cell cancer syndrome

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Abstract

Introduction: Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) is a rare autosomal dominantly inherited cancer predisposing syndrome giving rise to cutaneous and uterine leiomyomatosis, leiomyosarcoma and renal cell cancer. Patients with this syndrome harbours germline pathogenic variants in the fumarate hydratase (*FH*) gene.

Case presentation: A 28-year-old Sri Lankan female, a product of a consanguineous marriage with strong family history of young onset fibroids presented with progressive dysmenorrhea, menorrhagia and irregular menstrual cycles for 2 years duration. There was recent onset lower abdominal colicky pain lasting for 3-5 min occurring during the post coital and intermenstrual period over 2 months. Examination did not reveal abnormal skin lesions or abdominal masses.

Ultrasound examination revealed enlarged uterus with 2 large fibroids in the posterior wall and fundus of the uterus. She underwent laparoscopic myomectomy without perioperative complications. Histology revealed a leiomyoma with morphological features supporting the variant "fumarate hydratase deficient leiomyoma".

Whole exome sequencing of the patient revealed her to be harbouring a pathogenic variant c.878T>G| p.Val293Gly in the *FH* gene for which she was heterozygous confirming that she had inherited the cancer predisposing syndrome of hereditary leiomyomatosis and renal cell cancer (HLRCC).

Postoperatively her symptoms resolved, and she was able to sustain an uncomplicated pregnancy one year after. Currently she is closely followed up for future development of tumors including renal cell cancer both clinically and via imaging.

Conclusion: HLRCC is a rare autosomal dominantly inherited cancer syndrome predisposing to skin, uterine and renal tumors warranting surveillance at a younger age.

Key words: fibroids, hereditary leiomyomatosis and renal cell cancer, *FH* gene, autosomal dominant, inherited cancer syndrome

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Case presentation

A 28-year-old previously healthy Sri Lankan female presented with progressive severe pain and heavy bleeding during menstruation for 2 years. Pain and heavy menstrual bleeding were affecting her quality of life significantly. Her menstrual cycles were irregular (ranging in between 30 days – 51 days) during this time. She also complained of recent onset colicky pain in the lower abdomen lasting for 3-5min which occurred during the post coital and intermenstrual period over 2 months. There was no intermenstrual bleeding, vaginal discharge, abdominal distension, or fever.

She was a product of a consanguineous marriage where her parents were first cousins. Her family history revealed her mother, a paternal aunt and two first cousins (daughters of a paternal uncle) were affected with fibroids in their twenties. Among the two cousins mentioned above, one had undergone hysterectomy around 25 years of age and the other

one had passed away around the same age during myomectomy due to massive hemorrhage. Her mother and the affected aunt also had hysterectomies as treatment for fibroids around 30 years of age.

Examination of the patient did not reveal abnormal skin lesions or abdominal masses. However, ultrasound imaging of abdomen and pelvis revealed that her uterus to be enlarged (15.6×11.1×11.9cm). There were two fibroids. One in the posterior uterine wall (8.8×7.9cm) and the other in the fundus (5×3.6cm). Endometrial thickness was 7mm. There were no adnexal and renal masses or any other abnormalities detected.

She underwent a laparoscopic myomectomy, however, at the time of operation the myomas appeared suspicious and the specimens were retrieved via a laparotomy instead of morcellation. She had an uncomplicated postoperative period and recovered well. Images captured during the surgery are illustrated in Figure 1.

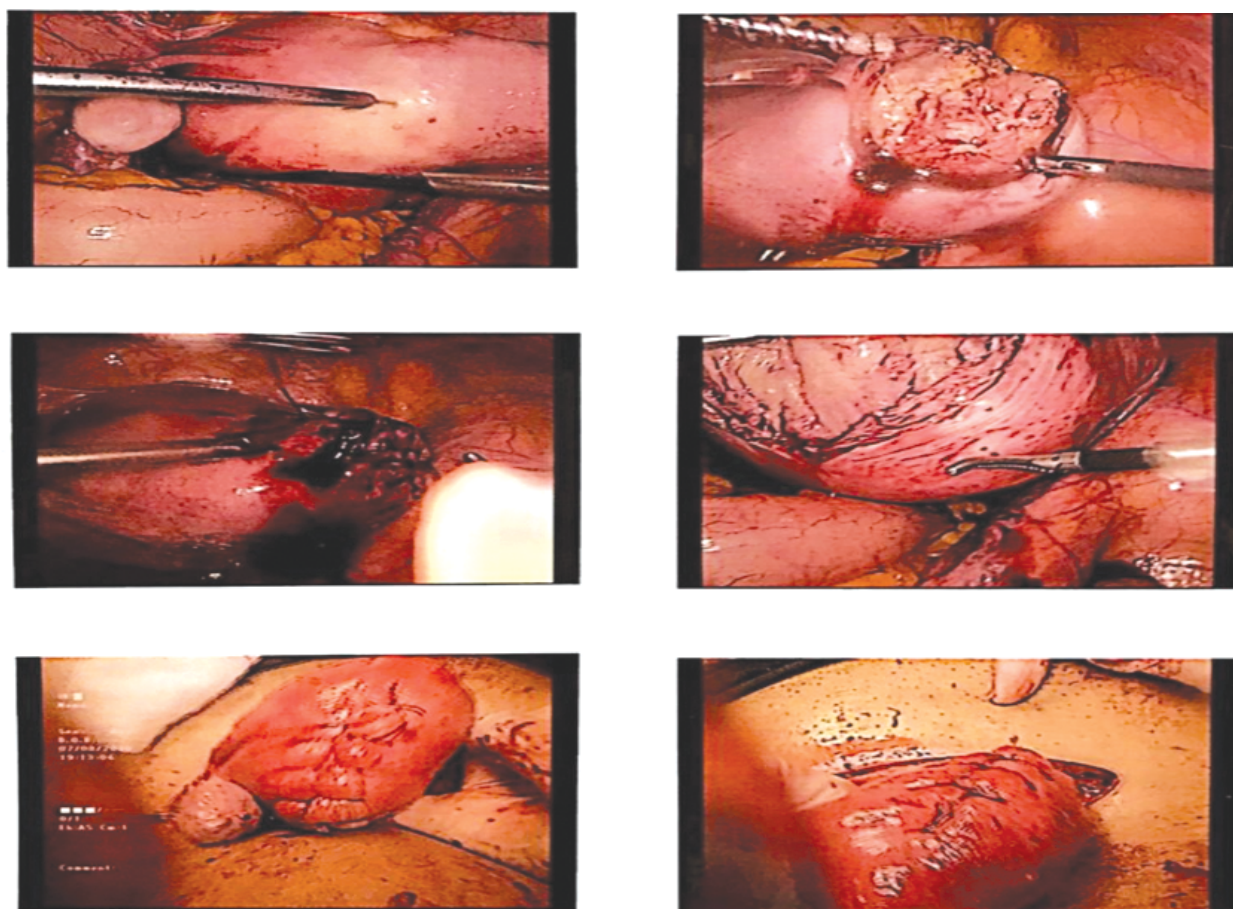


Figure 1. Laparoscopic myomectomy images.

Histology revealed a leiomyoma with morphological features supporting the variant “Fumarate hydratase deficient leiomyoma” (FHD leiomyoma). These features included increased cellularity, presence of staghorn type blood vessels, focal neurilemmoma like pattern and focal stromal oedema (alveolar like pattern). There were cells with prominent nucleoli with peripheral halo and eosinophilic cytoplasmic globules. There was no evidence of symplastic nuclear atypia, linear arrangement of cell nuclei, hyaline/coagulative necrosis or increased mitotic activity as shown in Figure 2.

Whole exome sequencing of the patient revealed her to harbour a pathogenic variant c.878T>G|p: Val293Gly in the *FH* gene for which she was heterozygous confirming the diagnosis of inherited cancer syndrome; hereditary leiomyomatosis and renal cell cancer (OMIM 150800).

Following surgery her symptoms resolved, and she was able to conceive after 1 year and delivered a healthy term neonate by a cesarean section. Her recent

ultrasound scan of kidneys revealed a para pelvic cystic lesion measuring 14×10mm in the left kidney with eccentric calcification without internal vascularity. Conservative management was suggested by the urology team.

Currently, she is under close observation and follow-up due to the future risk of development of skin, uterine and renal tumors, clinically and with imaging.

Discussion

Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) is a rare autosomal dominant condition characterized by cutaneous and uterine leiomyomatosis and renal cell cancer^{1,2}. It's pathogenesis stems from germline variants of the fumarate hydratase (*FH*) gene on chromosome 1q42-44, in the heterozygous state³.

Its prevalence is unknown and had been reported in approximately 200 families throughout the world^{4,5}. There is no sex predilection⁶. It may be underdiagnosed

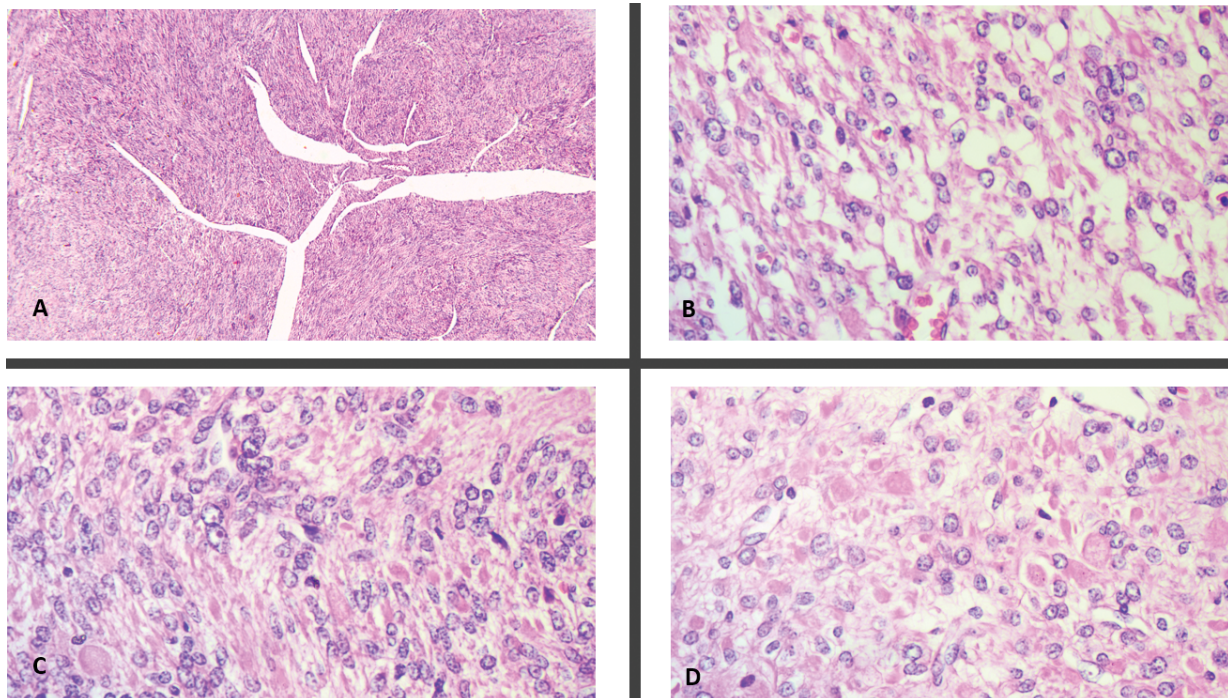


Figure 2. A. Stag horn shaped blood vessels and focal nuclear atypia. 4×.bmp.

B. Cells in loose alveolar arrangement 400×.bmp.

C. Focal nuclear atypia, nuclei with eosinophilic nucleoli and perinuclear halos 40×.bmp.

D. Rhabdoid inclusions 40×.bmp.

in certain communities however, a higher incidence is being reported in individuals with Eastern European descent^{7,8}. The treatment of choice is radical nephrectomy with close monitoring as it can metastasize rapidly.

As *FH* acts as a tumor suppressor gene, HLRCC patients with germline *FH* gene variants acquire somatic mutations in the wild type *FH* allele through a second hit leading to reduced fumarate hydratase activity in the tumor tissues⁹⁻¹¹. This inhibits conversion of fumarate to malate leading to fumarate accumulation which induces tumors through several proposed mechanisms^{12,13}. The most common clinical manifestation of HLRCC is cutaneous leiomyomata seen in 76%-100% of patients with a mean age of onset at 30 years (range: 10-77 years)¹⁴. They are multiple, firm, flesh-colored nodules distributed along the trunk and extremities sometimes in a segmental distribution associated with pain and paresthesia and has a risk of converting to leiomyosarcomas¹⁵. Histologically, they appear as proliferating bundles of smooth muscle fibers with central blunt-edged nuclei¹⁶.

Females with HLRCC develop uterine fibroids at a younger age than the normal population and these are larger and more numerous as well, like in the illustrated case¹⁵. Mean age of identification of fibroids is 30 years (range: 18 to 53 years)¹⁵. Histology is the key in identifying this entity characterized by alveolar pattern edema, staghorn-shaped blood vessels under low magnification, and smooth muscle cells with a macro-nucleolus surrounded by a halo and eosinophilic globules seen under high magnification¹⁷. Uterine leiomyosarcomas are being reported in some case series^{15,18}.

Renal cancers that develop in this cancer syndrome are mostly unilateral and solitary with a mean age of onset at 30 years of age¹⁴. Histology associated with HLRCC syndrome consists of a spectrum including type 2 papillary, undefined papillary, unclassified, tubulocystic, and collecting-duct carcinoma¹⁹. *FH* germline variants were reported in patients with Pheochromocytoma and paragangliomas in some case studies^{14,20,21}. Currently there's no phenotype genotype correlation identified in this entity¹⁹.

In the appropriate context genetic confirmation should be offered to these patients and family screening with genetic tests are warranted at 8-10 years of age especially with regards to surveillance for renal cell cancer²².

Conclusion

Hereditary leiomyomatosis and renal cell cancer syndrome is an underdiagnosed autosomal dominant cancer syndrome predisposing to multiple tumors involving skin, uterus and kidneys. Genetic screening is recommended for early detection and disease surveillance.

Ethical approval

The study was conducted following ethical approval (EC-16-179) from the Ethics Review Committee, Faculty of Medicine, University of Colombo. Written informed consent was obtained from the patient.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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