Title

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Journal

The American journal of the medical sciences, 360(6)

ISSN

0002-9629

Authors

Choi, Grace
Kimonis, Virginia
Hall, Katherine
et al.

Publication Date

2020-12-01

DOI

10.1016/j.amjms.2020.05.048

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC): Report of a Family Pedigree

Grace Choi, MD[1], Virginia Kimonis, MD[2], Katherine Hall, BS[2] and Wei Ling Lau, MD[1]

[1] Division of Nephrology, Department of Medicine, University of California (GC, WLL), Irvine, CA; [2] Division of Genetics and Metabolism, Department of Medicine, University of California (VK, KH), Irvine, CA

ABSTRACT

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a rare familial cancer syndrome with a germline mutation in the fumarate hydratase gene. Affected individuals are predisposed to development of cutaneous leiomyomas, uterine leiomyomas, and papillary renal cell carcinoma. We present a case of a mother and son pair affected with HLRCC, discuss clinical management, and examine potential syndromic manifestations in extended family members. Annual imaging surveillance for kidney cancer is recommended since 20-30% of individuals develop aggressive papillary type II renal cell carcinoma that can be difficult to treat once it has metastasized.

Key Indexing Terms: HLRCC; Hereditary leiomyomatosis and renal cell cancer; Reed's syndrome. **[Am J Med Sci 2020;360(6):724–727.]**

CASE PRESENTATION

A 31-year-old man was referred to our nephrology clinic due to high risk for renal cell carcinoma (RCC) associated with his skin condition. The patient first noted painless skin papules on his back and face at the age of 18 years. This led to an excisional biopsy with the diagnosis of leiomyomatosis. Since this diagnosis, he continued biannual skin surveillance with his dermatologist and had two further excisions. The lesions had grown increasingly widespread and painful over the years, described as sharp, stabbing sensation exacerbated by extreme temperature changes (Figure 1). He had tried various forms of pain management including low-dose opioid analgesics, acetaminophen, and heat pads with little to no relief. At the nephrology clinic the patient was started on low-dose nifedipine with marked improvement in pain control without orthostatic side effects; pain episodes decreased from 5 to 7 episodes a day to approximately once per week. When they did occur, pain intensity decreased from 10/10 to about 6/10 with nifedipine therapy.

He reported multiple family members with cutaneous leiomyomatosis, uterine fibroids, and ovarian cysts, including his mother (see pedigree in Figure 2). In view of his clinical and family histories, he was referred to a geneticist for counseling and testing. He underwent molecular testing, which confirmed a nonsense fumarate hydratase (FH) gene mutation FH c.301C > T (p.Arg101*) confirming hereditary leiomyomatosis and renal cell cancer (HLRCC). Abdominal imaging revealed a simple renal cyst, without characteristics concerning for malignancy. The patient continues to undergo surveillance for RCC annually via magnetic resonance imaging (MRI) with gadolinium.

The patient's mother initially experienced menorrhagia and dysmenorrhea in her late 20s and was diagnosed with uterine leiomyoma. She had an abdominal hysterectomy with unilateral oophorectomy when she was 35 years old. In her 40s and 50s, she underwent imaging workup for back pain and was found to have ovarian, hepatic, and pancreatic cysts. She had been under routine surveillance for her liver and pancreatic cysts, and she underwent oophorectomy of the remaining ovary at the age of 57. She did not have any abnormal skin findings on her annual appointments with dermatology.

When her son was diagnosed with HLRCC, she was referred to our genetics clinic and subsequent molecular testing confirmed presence of the same pathogenic variant in the FH gene c.301C > T (p. Arg101*). Review of prior and current imaging revealed simple renal cysts. She continues annual monitoring with abdominal MRI with gadolinium to monitor her cysts and for RCC screening.

DISCUSSION

Individuals with HLRCC are predisposed to development of cutaneous leiomyomas, uterine leiomyomas, and papillary RCC.[1-4] HLRCC is caused by a germline heterozygous mutation of the FH gene on chromosome

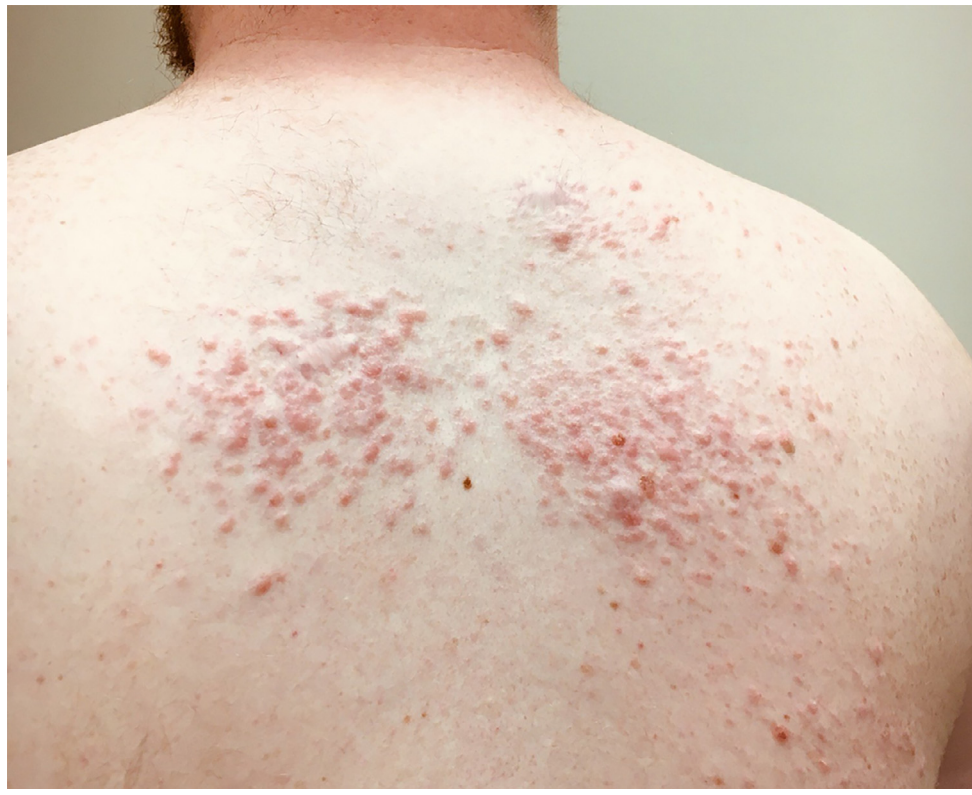

FIGURE 1. Cutaneous leiomyomas on the upper back in a patient with hereditary leiomyomatosis and renal cell cancer (HLRCC, Reed's syndrome). Cutaneous leiomyomas are often the first manifestation of HLRCC and are most commonly derived from arrector pili muscles of the hair follicle (piloleiomyomas). They can range from painless solitary lesions to (as in this case report) painful, erythematous papules, and nodules.

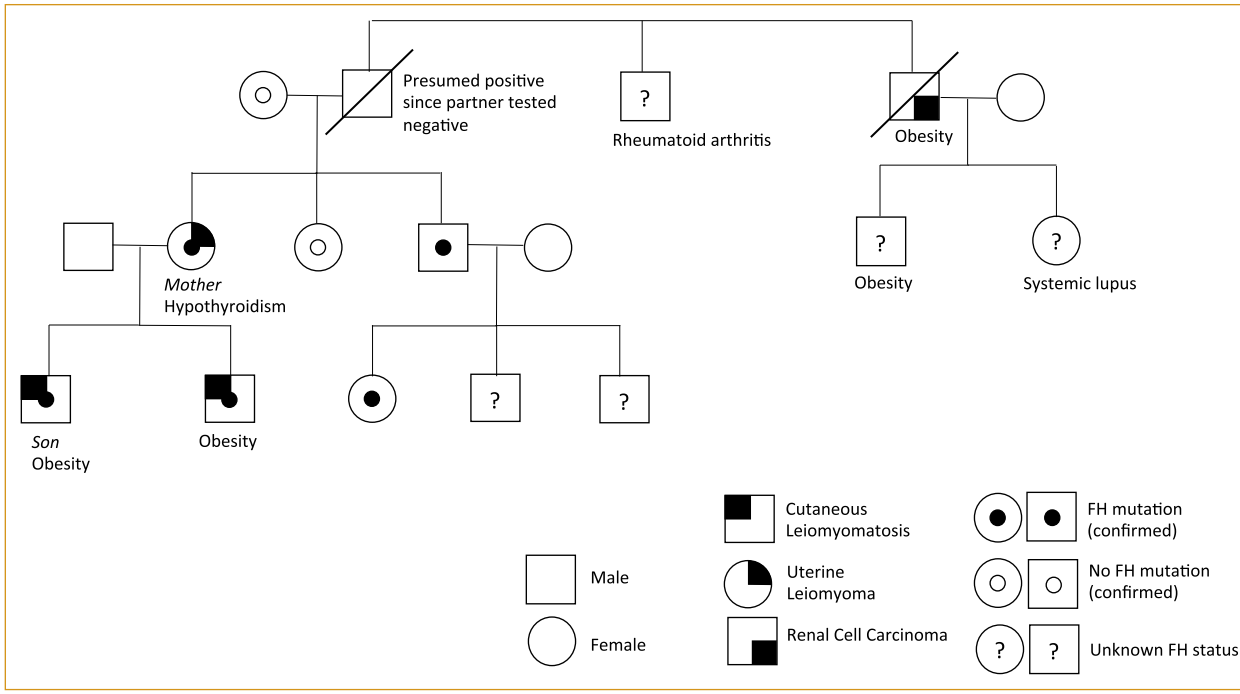

FIGURE 2. Family pedigree of mother-son case report with hereditary leiomyomatosis and renal cell cancer (HLRCC, Reed's syndrome) with confirmed mutation in fumarate hydratase gene FH c.301C > T (p.Arg101*). Co-morbid conditions outside of the expected HLRCC syndrome are also noted.

1q42.2-43. HLRCC is rare, with less than 200 affected kindreds reported worldwide.[5] Also known as Reed's syndrome, numerous missense mutations, nonsense mutations, in-frame deletions, truncations, and large deletions have been identified. The loss-of-function mutation in the FH gene leads to a severe reduction in the FH enzyme that catalyzes the hydration of fumarate to malate in the Krebs cycle.[6] The resultant build-up of fumarate leads to suppression of the homologous recombination DNA repair pathway and thereby interferes with the repair of DNA double-strand breaks and maintenance of genomic integrity.[7] The FH gene mutation found in proband and his mother, FH c.301C > T (p.Arg101*) has been reported in literature as a nonsense variant of HLRCC. By creating a premature stop codon (CGA > TGA), protein truncation or nonsense-mediated mRNA decay leads to loss of normal protein function.[4]

Exhibiting an autosomal dominant pattern of inheritance, an inactivating mutation in the remaining normal FH gene over an individual's lifetime leads to the variable phenotype observed with this genetic deficiency. Clinical features can range from minor skin involvement to highly metastatic kidney cancer. Sporadic cutaneous leiomyomas are very common among individuals with HLRCC, which are small, firm, pink, or salmon-colored papules and nodules that can range from few and asymptomatic to numerous and extremely painful. Cutaneous leiomyomas range in diameter from 0.2 to 2.0 cm[8,9] and are most commonly derived from arrector pili muscles of the hair follicle (piloleiomyomas); they rarely arise from vascular smooth muscle cells (angioleiomyomas).[2] A third subtype are genital leiomyomas which are rare and often painless, arising from the tunica dartos in the skin of genitals and mammary muscles of the nipple.[2] Cutaneous lesions can be associated with significant pain that leads to moderate to severe impairment in quality of life in up to 22% of HLRCC patients.[8] Transformation into cutaneous leiomyosarcoma is rare.[2] On histology, cutaneous leiomyomas demonstrate poorly circumscribed nodules of interlacing bundles of smooth muscle cells and varying amounts of collagen bundles, primarily in the dermis with occasional extension into subcutaneous tissue.[2]

Uterine leiomyomas are present in 70-80% of women with HLRCC, and typically become symptomatic at 20-35 years of age.[6,7,10,11] Approximately 20-30% of individuals with FH mutation develop papillary type II RCC that tends to be solitary and aggressive in nature, with approximately 70% mortality within 5 years of diagnosis. The prevalence of benign kidney cysts is higher in HLRCC patients younger than 40 years old compared to the age-matched general population (36% in HLRCC patients vs. 4.6-8.2% in general population). Observational studies report that the presence of benign cysts does not increase the risk of RCC in HLRCC individuals. Increased predisposition to uterine leiomyosarcomas and other malignant tumors at a younger age have been reported.[2,12,13]

Germline FH mutations have been detected in the majority of HLRCC families. However, in families with characteristic features (for example, cutaneous or uterine leiomyomas, or a relative with metastatic renal cancer at an early age), but without a demonstrated germline FH mutation, immunohistochemical evaluation of tumors (leiomyomas or kidney masses) may be helpful to support a HLRCC diagnosis. Cells lacking functional FH accumulate fumarate which reacts with cysteine residues in proteins to generate 2-succinocysteine (2SC), a stable post-translational modification termed succination.[14,15] Thus, positive 2SC immunostaining can be a useful tool in diagnosing patients suspected of having HLRCC where the pathological features are variable.

Both of the patients are under the care of a multidisciplinary team consisting of Nephrology, Genetics, and Dermatology. Once their familial FH gene mutation was identified, the patients voluntarily disclosed this information to extended family members to encourage genetic testing and appropriate cancer surveillance (pedigree shown in Figure 2). Current recommendations for affected women include regular gynecologic consultation for assessment and management of uterine leiomyomas. Our female patient had already undergone a full hysterectomy. Her niece, who recently tested positive for the FH mutation, will start routine gynecologic screening and follow-up. While the male patient and his brother are both obese and have the FH mutation, there was no consistent association with obesity in a paternal uncle who tested positive for the FH mutation.

There is no universal consensus on the frequency and modality of imaging surveillance for RCC in HLRCC individuals. Abdominal MRI or CT may be superior modalities over ultrasound as the most common RCC variant in HLRCC is type II papillary RCC which can be isoechoic and may be missed on ultrasound.[4] Annual screening is recommended based on expert opinion, given the aggressive, metastatic nature of type II papillary RCC, and increased mean survival with early detection.[16-19] After discussion with Radiology, we have recommended annual screening using abdominal MRI with gadolinium for both patients, to minimize radiation exposure while ensuring early tumor detection.

HLRCC-associated metastatic kidney cancer can be difficult to treat, and there is no standardized treatment protocol. A case report described good response with bevacizumab and erlotinib in a patient with liver metastases who failed treatments with temsirolimus (mTOR inhibitor) and axitinib (vascular endothelial growth factor receptors tyrosine kinase inhibitor).[20] A phase II study of bevacizumab and erlotinib in HLRCC patients with metastatic papillary RCC is anticipated to complete enrolment in 2022 (ClinicalTrials.gov Identifier: NCT01130519). Other phase II trials recently completed recruitment and outcomes data is pending; one trial evaluated the DNA methyl transferase inhibitor guadecitabine (ClinicalTrials.gov Identifier: NCT03165721) and the other trial utilized a vandetanib/metformin combination (ClinicalTrials.gov

Identifier: NCT02495103). A list of HLRCC-related clinical trials that are investigating novel therapies for cutaneous lesions and kidney cancers is available through the HLRCC Family Alliance website at http://hlrccinfo.org/clinical-trials/.

We noted a marked benefit from the use of nifedipine for symptomatic pain relief for the young male patient. Nifedipine is a dihydropyridine calcium channel blocker most commonly prescribed for blood pressure control and coronary anginal pain. Understanding the pathogenesis of cutaneous pain has led to a case-by-case trial of different medical therapies. With multiple stressors or extreme temperature variations, the postganglionic nerve fibers release norepinephrine, causing an influx of calcium ions into the arrector pili muscles. This results in abnormal excitation and smooth muscle contraction, which may be responsible for the pain phenomena. Other medications that dampen this nerve activity include nitroglycerin, phenoxybenzamine, doxazosin, gabapentin, and hyoscine.[16]

CONCLUSIONS

HLRCC is a rare syndrome characterized by cutaneous leiomyomas which can cause severe pain, and increased risk of uterine leiomyoma/leiomyosarcoma and aggressive RCC. Pain management and annual screening with abdominal imaging is warranted. Genetic testing of relatives of affected individuals is helpful to determine whether cancer surveillance is needed. Patients and family members can find useful information, including a description of ongoing clinical trials, on the HLRCC Family Alliance website (http://hlrccinfo.org/).

AUTHORS CONTRIBUTIONS

G.C., V.K., K.H., W.L.L. collected the data. G.C. and W.L.L. wrote the paper.

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Submitted December 28, 2019; accepted May 29, 2020.

Conflicts of Interest: The authors declare no conflict of interest.

Funding: There was no support/funding for this work.

Patient consent: The two patients described in our case report reviewed the manuscript and provided informed consent to proceed with peer review for publication.

Correspondence: Wei Ling Lau, MD, Division of Nephrology & Hypertension, University of California, Irvine, 101 The City Drive South, City Tower, Suite 400, Orange, CA 92868. (E-mail: wllau@uci.edu).