Hereditary leiomyomatosis and renal cell cancer syndrome: An update and review

Viral M. Patel, MD,[a] Marc Z. Handler, MD,[a] Robert A. Schwartz, MD, MPH, DSc (Hon),[a,b,c,d] and W. Clark Lambert, MD, PhD[a,b]
Newark, New Jersey

Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome is a rare genetic disorder that predisposes individuals to multiple cutaneous leiomyomas, renal cell carcinomas, and in women, uterine leiomyomas. Also known as Reed syndrome, it is caused by a germline heterozygous mutation of the fumarate hydratase tumor suppressor gene. HLRCC is associated with significant morbidity because of pain from cutaneous and uterine leiomyomas, the cutaneous pain often of unique character. Although genetic testing is currently considered the criterion standard to diagnose HLRCC, newer immunohistochemistry markers may provide rapid and cost effective alternatives to genetic testing. Because of the potentially aggressive nature of renal cell carcinomas that develop as early as in childhood, close annual cancer surveillance is desirable in individuals with HLRCC. In this review, we offer an update and an approach to the diagnosis, management, and renal cancer surveillance in HLRCC. (J Am Acad Dermatol 2017;77:149-58.)

Key words: cancer surveillance; cutaneous leiomyomas; piloleiomyomas; Reed syndrome; renal cancer; uterine leiomyomas.

Reed syndrome, also known as syndromic multiple cutaneous and uterine leiomyomatosis (MCUL), multiple leiomyomatosis, or leiomyomatosis cutis et uteri (Online Mendelian Inheritance in Man 150800), is a rare genodermatosis that was first described by Blum and Jean in 1954.[1] Subsequently in 1973, Reed et al[2] delineated members of 2 families whose successive generations developed cutaneous or uterine leiomyomas, establishing an autosomal dominant pattern of inheritance. This condition has recently been termed hereditary leiomyomatosis and renal cell cancer (HLRCC) because of the increased risk of renal carcinoma.

Abbreviations used:

2SC:	S-(2-succinyl) cysteine
CLM:	cutaneous leiomyoma
FH:	fumarase hydratase
HIF:	hypoxia-inducible factor
HLRCC:	hereditary leiomyomatosis and renal cell cancer syndrome
MCUL:	multiple cutaneous and uterine leiomyomatosis
RCC:	renal cell carcinoma
ULM:	uterine leiomyoma

EPIDEMIOLOGY

The prevalence of HLRCC is unknown. This disorder has been reported in approximately 200 families worldwide, but it may be underdiagnosed.[3,4] No sex predilection has been noted.[5] Although HLRCC has been documented in patients of various ethnic backgrounds, its incidence appears to be greater among those of Eastern European descent.[6,7] Cutaneous leiomyomas (CLMs) develop by the mean age of 25 years (range, 9-47 years), with most patients developing them by 40 years of age.[5,7,8] Uterine leiomyomas (ULMs) are diagnosed by the mean age of 30 years (range, 18-53 years), while renal tumors are diagnosed by the mean age of

From Dermatology,[a] Pathology,[b] and Pediatrics,[c] Rutgers New Jersey Medical School, and the Rutgers University School of Public Affairs and Administration.[d]
Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication January 11, 2017.
Reprints not available from the authors.

Correspondence to: Robert A. Schwartz, MD, MPH, DSc (Hon), Dermatology, Rutgers—New Jersey Medical School, 185 S Orange Ave, Medical Science Bldg H-576, Newark, NJ 07103-2757. E-mail: roschwar@cal.berkeley.edu.
Published online March 15, 2017.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2017.01.023

44 years (range, 10-90 years).[5,8,9] The overall penetrance of HLRCC in affected families approaches 90% to 100%.[10]

ETIOLOGY

HLRCC syndrome is caused by an autosomal dominantly inherited germline heterozygous mutation of the fumarate hydratase (FH) gene on chromosome 1q42.3-43. Individuals who inherit a mutated FH gene (heterozygotes) require an inactivating mutation in the remaining normal FH gene to develop the tumor phenotype (Knudson's 2-hit hypothesis). Based upon this observation, FH gene was classified as a tumor suppressor gene.[11] FH gene mutations have been identified in 76% to 93% of families with clinical features consistent with HLRCC.[7,11,12] Those without identifiable mutations may have a novel FH gene mutation, causing reduced fumarase enzyme activity.[12,13] If the fumarase enzyme activity is normal and the genetic aberration in the patient is not found in either parent, they may represent sporadic or mosaic cases. No genotype–phenotype correlation has been identified.[14]

CAPSULE SUMMARY

- Hereditary leiomyomatosis and renal cell cancer syndrome is an autosomal dominant disorder characterized by cutaneous leiomyomas often linked with shooting pain induced by cold, renal cell carcinomas, and, in women, uterine leiomyomas.
- Screening recommendations for renal cell carcinomas vary, but should begin at 10 years of age with annual magnetic resonance imaging scans.
- An approach to diagnosis and management is offered to guide clinicians evaluating patients with hereditary leiomyomatosis and renal cell cancer.

PATHOGENESIS

FH gene encodes the fumarase enzyme (also known as FH), which catalyzes the hydration of fumarate to malate in the Krebs cycle. The mechanism of tumorigenesis in fumarase-deficient cells is poorly understood. Recent studies suggest that under normal circumstances, hypoxia-inducible factor (HIF) is hydroxylated by HIF prolyl-hydroxylase, which causes ubiquitin-mediated destruction of HIF. In the absence of fumarase, fumarate accumulates, which inhibits HIF prolyl hydroxylase, resulting in elevated HIF levels within the cytoplasm.[3] In addition, impaired oxidative phosphorylation results in oxidative stress, activation of the hypoxia pathway, and a shift toward anaerobic metabolism. The resulting pseudohypoxic environment further stabilizes HIF and alters the activities of several proteins and transcription factors, such as GLUT1, NRF2, and AMPK.[3,15] The net result is an increased transcription of genes integral for tumor vascularity (eg, vascular endothelial growth factor), increased cellular proliferation, and resistance to apoptosis.[3,15-18]

Recent studies have shown that the accumulated fumarate reacts spontaneously with cysteine sulfhydryl groups in a process termed succination. It forms S-(2-succinyl) cysteine (2SC), which may be potentially used as an immunohistochemistry marker for impaired fumarase activity, and therefore mutations in the FH gene.[19,20] In addition, there is preliminary evidence to suggest that succination may cause dysregulation of cellular metabolism and contribute to oncogenesis.[21]

CLINICAL MANIFESTATIONS

HLRCC presents as CLMs, ULMs, or renal tumors.

Cutaneous leiomyomas

CLMs are often the first manifestation and the most sensitive and specific clinical marker of HLRCC.[8,22,23] CLMs occur as smooth-surfaced, skin-colored or erythematous hyperpigmented, solitary or multiple papules or nodules, ranging from 0.2 to 2.0 cm in diameter, and average 26 (range, 1-150) in number (Figs 1 and 2).[10,24] CLMs frequently involve the extensor surfaces, trunk, face, and neck.[24] CLMs are divided into 3 categories, any of which may be seen: 1) piloleiomyomas—these are the most common and often the most painful, arising from arrector pili muscles of the hair follicle; 2) genital leiomyomas—rare and often painless, these emerge from the tunica dartos in the skin of genitals and mammary muscles of the nipple; and 3) angioleiomyomas—rare and often painful, these originate from vascular smooth muscles.[25-28] Various patterns and distributions have been described, such as segmental or zosteriform (Fig 2), bilateral, symmetrical, linear, or disseminated.[29-31] Pseudo–Darier sign, a transient piloerection or elevation of the nodule induced by rubbing, may be present.[32,33] CLMs are painful in ≤90% of patients, with 22% of patients experiencing moderate to severe impairment in their quality of life.[10] Pain is most commonly sharp and shooting, but burning, pinching, or aching pain may also occur.[10,29] Pain may occur spontaneously, or may be induced by cold, stress, touch, trauma, pressure, or emotions.[10,25,34] CLM transformation into cutaneous leiomyosarcoma is rare, and