A few pink papules in an adult woman: Incidental finding leads to diagnosis of hereditary leiomyomatosis and renal cell cancer

Kelly Z. Young, BA,[a] Tom D. Raisanen, MD,[a] Tobias Else, MD, PhD,[b] Paul W. Harms, MD, PhD,[a,c] and Kelly B. Cha, MD, PhD[a]
Ann Arbor, Michigan

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INTRODUCTION

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is an autosomal dominant condition caused by highly penetrant pathogenic variants in the fumarate hydratase (*FH*) gene.[1] Fumarate hydratase is an enzyme responsible for the conversion of fumarate to malate in the Krebs cycle and is thought to be a tumor suppressor gene.[1] Classically, HLRCC has a predisposition to the development of cutaneous leiomyomas, uterine leiomyomas (fibroids), and renal cell carcinoma (RCC).[1] However, clinical presentation and disease phenotypes vary widely. We present a case in which the incidental observation of a few pink papules led to the diagnosis of HLRCC.

Abbreviations used:

FH:	fumarate hydratase
HLRCC:	hereditary leiomyomatosis and renal cell carcinoma
MRI:	magnetic resonance imaging
RCC:	renal cell carcinoma

CASE

A 44-year-old woman presented to seek dermatologic care, and 3 pink papules were incidentally noted on her right forearm. These had developed over the preceding year. Upon questioning, she acknowledged that they were slightly tender, particularly in cold temperatures. A similar lesion in this location had been biopsied in the remote past with a benign but unrecalled result. She had a few additional similar-appearing papules on her back and extremities. Her medical history was remarkable for uterine fibroids necessitating hysterectomy. Her mother and sister also had similar skin papules and histories of uterine fibroids necessitating hysterectomy. There was no personal or family history of renal cell cancer.

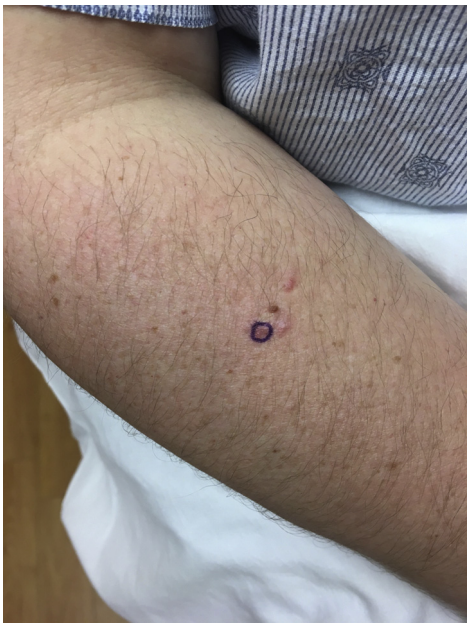

Fig 1. Clinical presentation. A cluster of a few pink papules was noted on the dorsal right forearm within close proximity to a small scar and an incidental brown macule. The papule selected for biopsy is marked in purple.

From the Departments of Dermatology[a]; Internal Medicine, Division of Metabolism, Endocrinology and Diabetes[b]; and Pathology,[c] Michigan Medicine.
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Correspondence to: Kelly B. Cha, MD, PhD, 1910 Taubman Center, 1500 East Medical Center Dr, Ann Arbor, MI 48109-5314. E-mail: kellycha@med.umich.edu.

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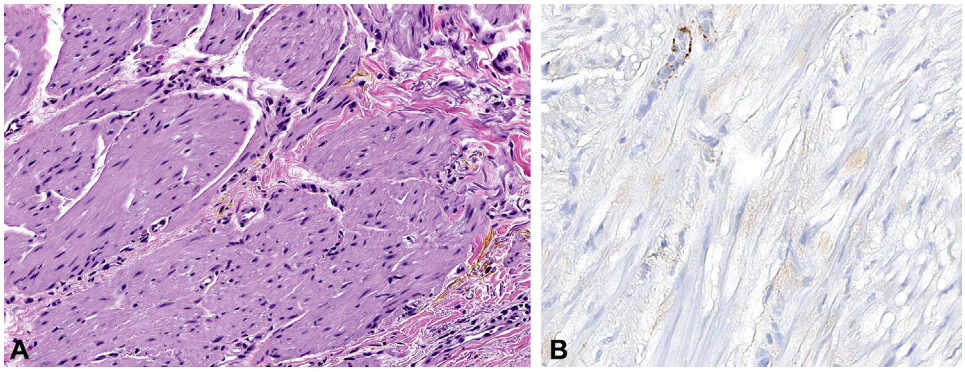

Fig 2. **A**, Histopathologic analysis found intersecting fascicles of smooth muscle bundles with centrally located nuclei and elongated blunt ends. **B**, With fumarate hydratase staining, a vessel at top left reveals granular brown chromogen. Staining is absent within the smooth muscle bundles. (**A**, Hematoxylin-eosin stain; **B**, Fumarate hydratase stain. Original magnifications **A** and **B**, ×200.)

Physical examination of the right dorsal forearm found a cluster of 3 smooth pink papules approximately 4 mm each, a healed scar from the previous biopsy, and an incidental brown macule (Fig 1). Some similar subtle papules were noted on her upper back and legs. Punch biopsy of a typical forearm papule was performed.

Histopathologic examination found intersecting fascicles of smooth muscle bundles with centrally located nuclei and elongated blunt ends, consistent with piloleiomyoma (Fig 2, *A*). Fumarate hydratase stain found loss of expression in tumor cells (Fig 2, *B*). The presence of cutaneous piloleiomyomas in the setting of uterine fibroids and a supportive family history, even in the absence of a family history of RCC, was suggestive of HLRCC. Subsequent genetic analysis of the *FH* gene found a rare variant, c.1041delT, p.Gly348Valfs*9. This variant results in early protein truncation, leads to the loss of conserved amino acids of the protein, and is not present in large population databases (ExAC), thus was classified as a pathogenic variant. This finding confirms the diagnosis of HLRCC. Family cascade testing and screening for RCC with annual magnetic resonance imaging (MRI) scans were recommended. Initial MRI of the patient's abdomen was unremarkable, although a few subcentimeter renal cysts were noted.

DISCUSSION

The first manifestation of HLRCC in many patients is solitary or multiple cutaneous leiomyomas, most often on the trunk or extremities, typically developing by early adulthood and ultimately affecting most patients.[2-4] The diagnosis may be suspected clinically, but biopsy is typically required for confirmation. Immunohistochemistry for loss of FH may be used to screen apparently sporadic cutaneous leiomyomas and assist in identifying patients at risk for HLRCC, as absence of FH corresponds well with the presence of *FH* pathogenic variants.[5] Germline genetic testing, however, remains the mainstay for molecular confirmation of the diagnosis and should be recommended for all patients with multiple cutaneous leiomyomas. Painful cutaneous leiomyomas can be excised, managed with medications such as nifedipine and gabapentin, or treated with destructive approaches such as carbon dioxide laser ablation.[6] Annual skin examinations allow monitoring for changes suspicious for leiomyosarcomas, which have rarely been reported.[6,7]

Most affected women develop early-onset, symptomatic uterine leiomyomas (fibroids) at a mean age of 30.[3,4] These are more prevalent and severe than fibroids in the general population, and treatment to alleviate associated pain and irregular menses, including myomectomy and hysterectomy, can lead to secondary infertility. The absolute risk increase for malignant transformation is unknown. Rarely, uterine leiomyosarcoma has been associated with HLRCC.[8]

Patients with HLRCC have an approximately 15% risk of RCC development, including type 2 papillary, tubule-papillary, or collecting duct cancer, by a mean age of 44.[2,3,4] Some patients have RCC diagnosed in adolescence or early adulthood.[3,9] Genotype-phenotype correlations are not well understood, and there are often shared pathogenic *FH* variants in families with and without renal cancer.[2] This finding suggests that there could be additional genetic modifiers or environmental factors involved in renal cancer development in HLRCC. Annual MRI of the kidneys beginning in adolescence or early adulthood is recommended to monitor for renal cell carcinoma, and early surgical intervention is

recommended because of the aggressive nature of these neoplasms.[10,11]

Because HLRCC is inherited in an autosomal dominant fashion, and there is potential for development of early-onset renal cell cancer, individuals at risk for HLRCC should consider predictive genetic testing for pathogenic *FH* variants. Genetic counseling should be offered to all patients and at-risk relatives, including the circumstance in which testing in childhood is under consideration.[12]

The presence of multiple cutaneous leiomyomas is rare, may be only incidentally noted, and should always lead to consideration of HLRCC. Dermatologists are uniquely positioned to suspect the diagnosis and facilitate genetic evaluation. HLRCC requires multidisciplinary management, often overseen by cancer geneticists. Appropriate management includes annual dermatologic examination to monitor for changes concerning for cutaneous leiomyosarcoma, annual gynecologic examination for symptom management of fibroids and monitoring for uterine leiomyosarcoma, and annual MRI of the kidneys to monitor for renal cell carcinoma.

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