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# Multiple Painful Papules on the Arm: A Clue to Reed Syndrome

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## Abstract

We report a case of multiple painful cutaneous piloleiomyomas that prompted evaluation for hereditary leiomyomatosis and renal cell carcinoma (HLRCC). A 26-year-old man presented with multiple painful erythematous-to-brown papules on the left upper arm that were exacerbated by cold exposure and emotional stress. Histopathologic examination demonstrated piloleiomyoma, prompting evaluation for HLRCC despite the absence of a personal or family history of similar lesions. The patient was counseled regarding the association between multiple cutaneous leiomyomas and HLRCC, and referred for genetic evaluation and appropriate renal surveillance. This case highlights the importance of recognizing multiple painful cutaneous leiomyomas as a potential cutaneous marker of an underlying hereditary cancer syndrome. Early recognition can facilitate timely genetic counseling, appropriate renal surveillance, and multidisciplinary management.

**Categories:** Genetics, Oncology, Dermatology
**Keywords:** fumarate hydratase (fh) gene mutation, hereditary leiomyomatosis and renal cell carcinoma (hlrcc), piloleiomyoma, reed syndrome, uterine fibroids

## Introduction

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC), also known as Reed syndrome, is a rare autosomal dominant cancer predisposition syndrome caused by germline mutations in the fumarate hydratase (FH) gene [1]. The FH gene, located on chromosome 1q42, encodes a mitochondrial enzyme in the Krebs cycle that catalyzes the conversion of fumarate to malate [1]. Loss of FH function results in intracellular accumulation of fumarate, which inhibits prolyl hydroxylase domain (PHD) enzymes and leads to stabilization of hypoxia-inducible factor-1α (HIF-1α) even under normal oxygen conditions, creating a pseudohypoxic state that promotes angiogenesis, metabolic reprogramming, and tumorigenesis [1]. Cutaneous piloleiomyomas, benign smooth muscle tumors arising from the arrector pili muscles of hair follicles, are the most common and often earliest manifestation of HLRCC [1,2].

Clinically, HLRCC is characterized by a triad of cutaneous leiomyomas (piloleiomyomas), uterine leiomyomas (fibroids), and an increased risk of renal cell carcinoma (RCC). Cutaneous piloleiomyomas are benign smooth muscle neoplasms arising from the arrector pili muscle [2]. They typically present as flesh-colored to reddish-brown papules or nodules measuring 2-22 mm on the trunk, extremities, or face, with a median age of onset of approximately 25 years (range, nine to 45 years) [2]. Up to 90% of lesions are painful, with pain characteristically triggered by cold exposure, pressure, or emotional stress [2]. In women, early-onset symptomatic uterine leiomyomas are another hallmark feature and may present with menorrhagia, pelvic pain, infertility, or recurrent miscarriage [2]. Furthermore, RCC develops in approximately 15-21% of patients over their lifetime, with a mean age of diagnosis around 36 years (youngest reported at age 7) [3].

Because cutaneous piloleiomyomas are often the earliest manifestation of HLRCC, dermatologists play a critical role in recognizing the syndrome and facilitating timely genetic counseling and renal surveillance. We present a case of a young man with multiple painful cutaneous piloleiomyomas whose diagnosis prompted evaluation for HLRCC, highlighting the importance of recognizing characteristic cutaneous findings as an opportunity for early identification of this hereditary cancer predisposition syndrome.

## Case Presentation

A 26-year-old man presented to the dermatology clinic with multiple reddish-brown papules on the proximal anterior aspect of the left arm (Figure *1*). He first noticed the lesions at age 19 and was initially diagnosed with keratosis pilaris, for which he was treated with topical salicylic acid lotion without improvement. Due to persistent symptoms, a punch biopsy was performed, and demonstrated an atypical smooth muscle neoplasm in which leiomyosarcoma could not be excluded. He was subsequently referred for complete surgical excision to obtain a deeper specimen for definitive histopathologic evaluation (Figure *2*).

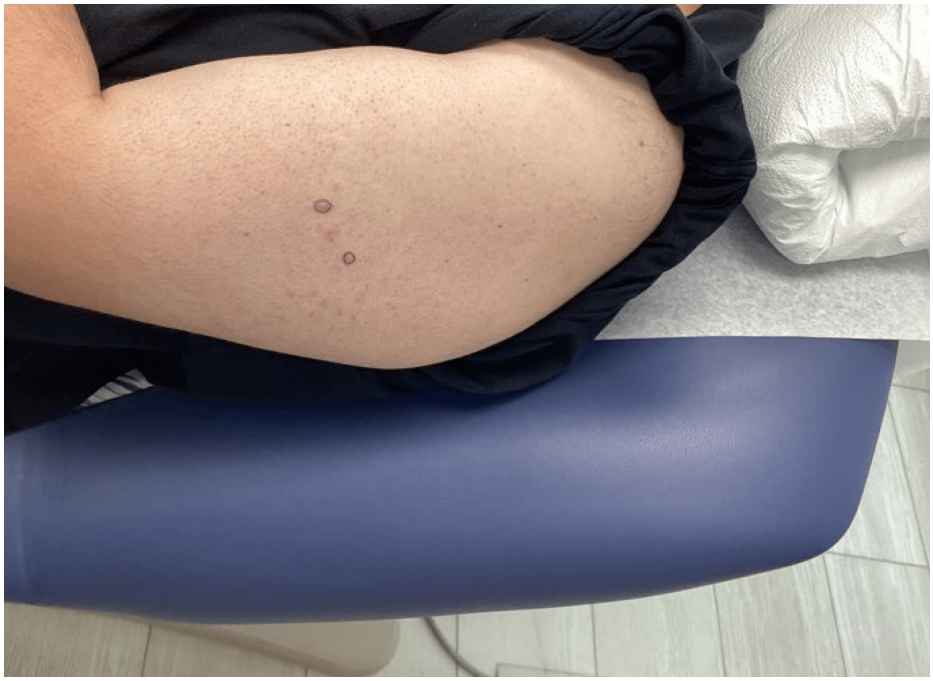


**FIGURE 1: Redish-brown firm papules on the left proximal arm.**



**FIGURE 2: Clustered piloleiomyomas prepared for fusiform excision.**

Physical examination revealed clustered erythematous-to-brown, firm papules on the extensor aspect of the left upper arm that were tender to palpation (Figure *1*). The patient reported that the lesions became increasingly painful with cold exposure and emotional stress. He denied recent illness, new medications, supplements, topical exposures, or a personal or family history of similar lesions.

Histopathologic examination of the excised lesion demonstrated a well-circumscribed dermal smooth muscle proliferation composed of intersecting fascicles, confirming the diagnosis of piloleiomyoma (Figures *3*-*4*). Given the presence of multiple painful piloleiomyomas, the patient was subsequently counseled regarding the possibility of Reed syndrome and the importance of renal surveillance. A renal ultrasound was recommended as part of the initial evaluation.

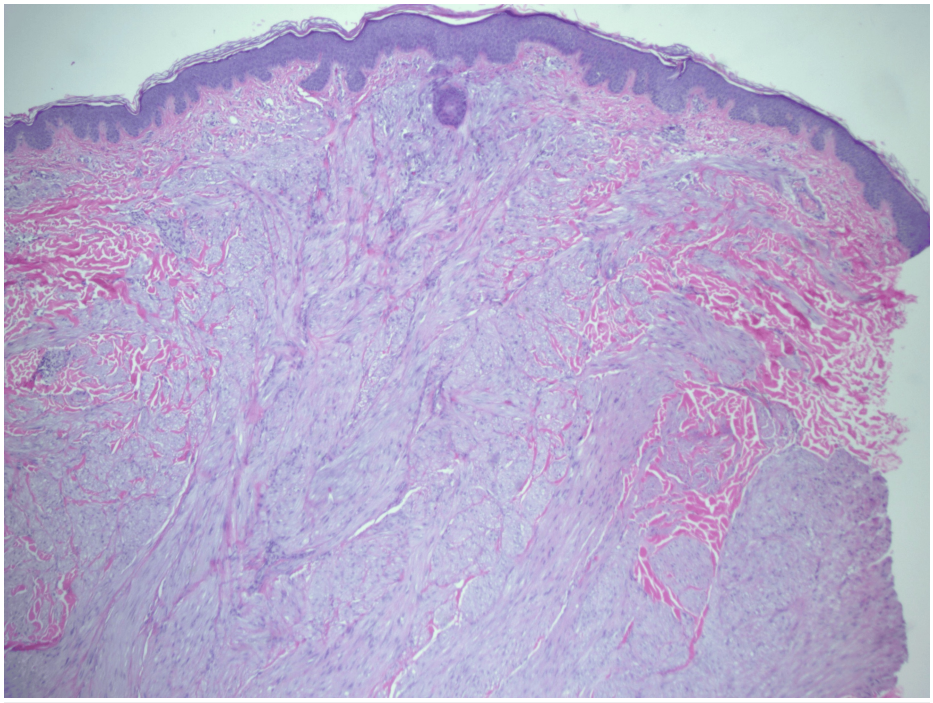


**FIGURE 3: Low-power hematoxylin and eosin (H&E) demonstrated a well-circumscribed dermal proliferation of intersecting fascicles of smooth muscle.**

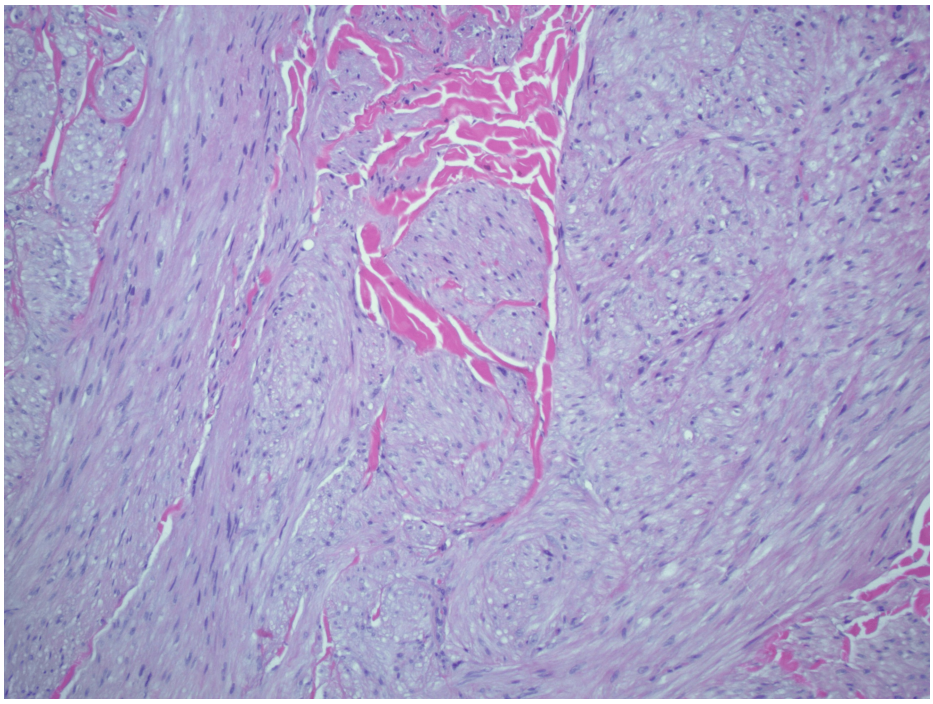


**FIGURE 4: High-power hematoxylin and eosin (H&E) showed abundant eosinophilic cytoplasm and elongated, blunt-ended ("cigar-shaped") nuclei.**

At follow-up, the patient reported complete resolution of pain and tenderness at the excision site. Histopathologic evaluation confirmed a benign piloleiomyoma without evidence of malignancy (Figures *3*-*4*). Renal function testing was within normal limits, and renal ultrasound demonstrated no evidence of

renal masses. Although these findings are reassuring, a normal renal ultrasound does not exclude HLRCC, and continued surveillance with consideration of genetic evaluation and appropriate renal imaging was recommended.

## Discussion

The absence of renal malignancy in our patient may be explained by several factors. First, HLRCC demonstrates incomplete penetrance. Analyses of the 1000 Genomes Project (1000GP) and ExAC, two large public genetic databases used to estimate the frequency of genetic variants in the general population, estimated the lifetime penetrance of FH-associated RCC to be only 1.7%-5.8%, indicating that many FH mutation carriers never develop renal cancer [4]. Second, tumor development follows the Knudson two-hit model. Individuals with HLRCC inherit one pathogenic FH allele, but tumor formation requires a second somatic mutation or loss of the remaining normal FH allele. Because this second event does not occur in all carriers, many never develop renal malignancy [5]. Finally, HLRCC exhibits variable expressivity, with penetrance differing substantially by organ system. Cutaneous leiomyomas occur in approximately 76% of carriers, and uterine leiomyomas develop in nearly 100% of affected women (mean onset 25-30 years), whereas renal cancer remains the least penetrant manifestation of the syndrome [6].

Historically, HLRCC-associated renal tumors were classified as type 2 papillary RCC; However, the 2022 WHO classification recognizes them as a distinct entity, FH-deficient RCC, because they have unique genetic features, variable histologic patterns, and a more aggressive clinical course than conventional papillary RCC [7]. Therefore, the National Comprehensive Cancer Network recommends annual renal surveillance with abdominal MRI (preferred) or contrast CT beginning at age eight to 10 years for all individuals with confirmed FH mutations, regardless of whether renal cancer or only cutaneous leiomyomas are present [8].

A broad differential diagnosis should be considered when evaluating a painful cutaneous tumor. The mnemonic "LEND AN EGG" encompasses several classic painful skin neoplasms, including leiomyoma, eccrine spiradenoma, neuroma, dermatofibroma, angiolipoma, neurilemmoma (schwannoma), endometrioma, glomus tumor, and granular cell tumor [9]. Recognition of these entities is important, as some may be associated with inherited cancer predisposition syndromes. For example, Brooke-Spiegler syndrome (CYLD cutaneous syndrome) is characterized by multiple spiradenomas, cylindromas, and trichoepitheliomas, with spiradenomas typically presenting as painful, slow-growing pink, blue, or flesh-colored nodules [10]. Patients may also develop parotid basal cell adenomas [10]. Similarly, Birt-Hogg-Dubé syndrome is an autosomal dominant disorder characterized by fibrofolliculomas, trichodiscomas, and acrochordons, and is associated with an increased risk of renal tumors, pulmonary cysts, and spontaneous pneumothorax [11]. Distinguishing these syndromes from HLRCC is essential, as each has unique systemic manifestations, surveillance recommendations, and genetic implications.

Management depends on lesion burden and symptom severity. Surgical excision is preferred for solitary lesions, while destructive therapies such as $CO_2$ laser, cryotherapy, and electrodessication may be used for multiple lesions or for patients who have a contraindication to surgery or medication [1]. Medical management for pain includes vasodilators such as nifedipine and doxazosin, neuropathic agents such as gabapentin, and, more recently, botulinum toxin A, which may reduce pain by inhibiting cholinergic signaling and decreasing release of pain-mediating neuropeptides, including substance P and calcitonin gene-related peptide (CGRP) [1].

### Limitation

A limitation of this report is that it describes the clinical presentation and management of a single patient, limiting the ability to systematically evaluate pain severity, treatment response, and long-term outcomes. Future prospective studies could employ standardized frameworks, such as the baseline-edit-rescue (BER) framework, to systematically assess baseline pain severity, evaluate treatment response, and monitor long-term outcomes in patients with painful cutaneous leiomyomas [11].

## Conclusions

This case describes a 26-year-old man with multiple painful cutaneous piloleiomyomas whose diagnosis prompted evaluation for Reed syndrome despite the absence of a personal or family history of the syndrome. Although our patient had no evidence of renal malignancy on initial evaluation, the diagnosis prompted appropriate counseling and renal surveillance, emphasizing the critical role of dermatologists in the early identification and management of this hereditary cancer predisposition syndrome. Because cutaneous leiomyomas can develop years before renal manifestations become clinically apparent, recognition of these characteristic lesions should prompt consideration of HLRCC even in the absence of a personal or family history of renal malignancy. While genetic confirmation was not available at the time of this report, the characteristic clinical and histopathologic findings were sufficient to prompt appropriate surveillance, and genetic counseling was recommended. Increased awareness of HLRCC among clinicians may facilitate earlier diagnosis, appropriate genetic counseling, and implementation of surveillance strategies aimed at reducing the morbidity and mortality associated with this hereditary cancer predisposition syndrome.

# Additional Information

## Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Simona Kogan, Tara Howard, Daniel Lutwak, Stanley Skopit, Adam Greenberg, Eric Levy

**Acquisition, analysis, or interpretation of data:** Simona Kogan, Mindy Kresch-Vatch, Tara Howard, Daniel Lutwak, Moises Lutwak, Stanley Skopit, Adam Greenberg, Eric Levy

**Drafting of the manuscript:** Simona Kogan, Mindy Kresch-Vatch, Tara Howard, Daniel Lutwak, Moises Lutwak, Stanley Skopit, Adam Greenberg, Eric Levy

**Critical review of the manuscript for important intellectual content:** Simona Kogan, Mindy Kresch-Vatch, Tara Howard, Daniel Lutwak, Moises Lutwak, Stanley Skopit, Adam Greenberg, Eric Levy

## Disclosures

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