

What Is Your Diagnosis?



A 40-year-old woman presented with multiple nodules on her right forearm and mid back of 10 years' duration. The nodules were occasionally painful to touch or temperature changes. They were stable in size and she had not developed any new lesions in several years. Her medical history revealed a hysterectomy due to uterine fibroids. Her family history included 2 brothers with similar skin findings; her mother also underwent a hysterectomy due to uterine fibroids.

On physical examination there were multiple flesh-colored papules clustered in groups on the right forearm, mid back, and right anterior shoulder. The lesions ranged in size from 3 to 10 mm in diameter. There was no lymphadenopathy and the liver and spleen were normal to palpation. A punch biopsy was performed of the most tender lesion on the left mid back.

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The Diagnosis: Multiple Cutaneous and Uterine Leiomyomatosis (Reed Syndrome)

The patient was diagnosed with Reed syndrome. A biopsy specimen from the mid back (Figure 1) revealed a dermal nodule composed of intersecting fascicles of smooth muscle bundles (Figures 2 and 3). Nuclei were uniform, elongated, and blunt ended. There was no notable cytologic atypia, mitotic activity, or necrosis.

Multiple cutaneous and uterine leiomyomatosis (MCUL) is an autosomal-dominant condition characterized by cutaneous and uterine leiomyomas (fibroids) and rarely renal cell carcinoma.¹ Other names for this condition are familial leiomyomatosis, Reed syndrome, familial leiomyomatosis cutis et uteri, and hereditary leiomyomatosis and renal cell cancer.^{2,3} The condition is uncommon and affects both men and women.

The cutaneous leiomyomas of MCUL most frequently involve the trunk and extensor surfaces of the extremities. Skin findings consist of firm, smooth, flesh-colored or brownish red dermal papules or nodules.¹ The lesions range in size from 0.2 to 2.0 cm in diameter. They can present in grouped, linear, or dermatomal patterns, and are few to hundreds in number. The lesions can be asymptomatic but pain often can be elicited by pressure, temperature changes, or stress. In women, uterine fibroids can cause pelvic pain, abnormal uterine bleeding, and infertility.^{1,2}

Multiple cutaneous and uterine leiomyomatosis as well as hereditary leiomyomatosis and renal cell cancer are due to germline mutations in fumarate hydratase, a mitochondrial enzyme of the Krebs cycle.^{3,4} The fumarate hydratase gene, *FH*, is a tumor suppressor gene that has been mapped to chromosome 1 (1q42.3-43). Although genetic testing is available, the diagnosis of MCUL is based on clinical and histopathologic findings.^{3,5}

The histopathology of cutaneous leiomyomas consists of interlacing bundles of smooth muscle cells in the dermis. The smooth muscle cells demonstrate a typical pattern of eosinophilic cytoplasm with elongated, blunt-ended nuclei.^{1,2}

Most patients with MCUL have a benign clinical course.¹ Cutaneous leiomyomas do not resolve but often enlarge, with new lesions developing over many years. Uterine leiomyomas can necessitate a hysterectomy due to the associated symptoms. Families with MCUL are at an overall 2% to 6% risk for renal cancer, either renal collecting duct carcinoma or more commonly type II papillary renal cell cancer.^{3,6}



Figure 1. Multiple leiomyomas presenting as smooth dome-shaped papules on the back.

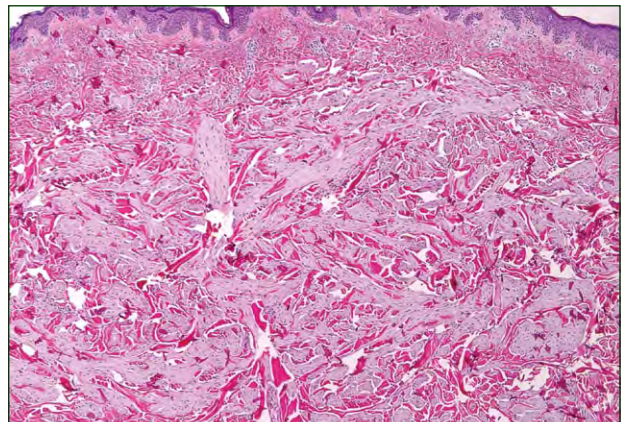


Figure 2. Scanning magnification showed intersecting fascicles of smooth muscle bundles in the dermis (H&E, original magnification ×100).

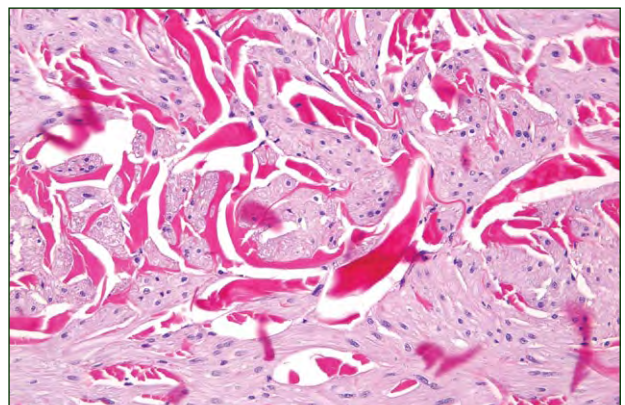


Figure 3. Smooth muscle bundles demonstrating elongated, cigar-shaped nuclei and abundant cytoplasm (H&E, original magnification ×400).

Screening Guidelines for Multiple Cutaneous and Uterine Leiomyomatosis (MCUL)

Condition	Screening Method	Screening Population
Cutaneous leiomyoma	Skin examination	Carriers of the <i>FH</i> gene mutation, individuals with affected relatives
Uterine leiomyoma	Pelvic ultrasound	Women with cutaneous leiomyomas, women with gynecologic concerns (ie, pain, menorrhagia, infertility), women with affected relatives, carriers of the <i>FH</i> gene mutation
RCC	Abdomen and pelvic CT or MRI	Carriers of the <i>FH</i> gene mutation, individuals affected with MCUL and/or individuals with a family history of HLRCC or RCC ^a
<i>FH</i> gene mutation	Genetic testing	Individuals with MCUL and their relatives

Abbreviations: *FH*, fumarate hydratase; RCC, renal cell cancer; CT, computed tomography; MRI, magnetic resonance imaging; HLRCC, hereditary leiomyomatosis and renal cell cancer.

^aScreening for RCC in the appropriate individuals at frequent repeated intervals can help identify RCC at an early and potentially curative stage; however, screening remains optional given the low overall risk (2%–6%) of RCC and the radiation associated with repeated CT scanning.⁶

Treatment is based on symptoms and cosmesis.⁵ Lesions may be surgically excised but can recur. Calcium channel blockers, α -adrenergic blocking agents, nitroglycerin, gabapentin, and topical analgesics can help with pain control.^{1,5} Patients and their relatives should undergo the appropriate screenings (Table).^{3,5,6} For individuals undergoing DNA analysis, genetic counseling also should be offered.³

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