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Cutaneous Leiomyomas Unmasked; A Rare Genetic Syndrome, Reed's Syndrome: A Case of Multiple Cutaneous Leiomyomatosis with Uterine Fibroids, Genetically Confirmed by Fumarate Hydratase Mutation Testing

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Abstract

Cutaneous leiomyomas are benign smooth muscle neoplasms that, in isolation, are easily dismissed as incidental skin findings, yet their presence can be the first visible clue to a life threatening hereditary cancer syndrome. When multiple painful cutaneous leiomyomas coexist with uterine leiomyomas, the possibility of hereditary leiomyomatosis and renal cell cancer, also known as Reed's syndrome, must be considered, given its association with an aggressive, early-onset form of renal cell carcinoma. We report the case of a 41-year-old Omani woman with an eleven-year history of painful, discrete, skin-colored to pinkish papules and nodules over the right upper chest and left pelvic region, exacerbated by touch and cold exposure. Gynecological evaluation revealed a bulky uterus distorted by multiple intramural and subserosal fibroids and bilateral ovarian cysts, one suggestive of a mucinous cystadenoma. The patient had a strong family history of uterine fibroids, with her mother and sister both affected and her mother having undergone hysterectomy. This constellation of findings raised strong suspicion for Reed's syndrome. A skin biopsy confirmed cutaneous leiomyoma, and subsequent genetic testing identified a heterozygous pathogenic germline variant in the fumarate hydratase gene, confirming the diagnosis. The patient was counselled regarding autosomal dominant inheritance, the 50% risk of transmission to offspring, and the value of cascade testing for at-risk relatives, and she was referred for renal surveillance. This case highlights the pivotal role dermatologists play as first responders in recognizing this rare syndrome and reinforces the need for prompt interdisciplinary evaluation among dermatology, gynecology, genetics, and nephrology to prevent a potentially fatal outcome.

Keywords: Cutaneous Leiomyoma, Reed's Syndrome, Uterine Fibroids, Ovarian Cysts, Fumarate Hydratase, Renal Cell Carcinoma

Introduction

Cutaneous leiomyomas are rare benign tumors arising from the smooth muscle of the arrector pili. They may present as solitary or multiple lesions, often painful and triggered by cold or tactile stimuli. Multiple cutaneous leiomyomas may occur as part of Reed's syndrome, an autosomal dominant disorder characterized by the coexistence of cutaneous and uterine leiomyomas [1]. The syndrome results from heterozygous mutations in the fumarate hydratase gene, and affected individuals carry a predisposition to an aggressive, early-onset form of renal cell carcinoma [2]. As dermatologists often see these patients first, recognizing the cutaneous manifestations is essential for timely diagnosis and life-saving renal surveillance.

Case Report

A 41-year-old Omani woman presented to the dermatology clinic with an eleven-year history of painful, discrete, skin-colored to pinkish papules and nodules distributed over the right upper chest and scattered across the left pelvic region. The pain was exacerbated by touch and exposure to cold.

She reported two first-trimester miscarriages, attributed to uterine fibroids, and had been diagnosed with multiple fibroids for which she was receiving injectable therapy under gynecological supervision. Family history was significant for uterine fibroids in her mother, who had undergone hysterectomy for reasons that were not documented, and in a sister, whose daughter was

similarly affected with multiple uterine fibroids. There was no family history of renal disease.

On dermatological examination, multiple firm, tender, erythematous to skin-colored papules and nodules were noted over the right upper chest and left pelvic area. Pelvic ultrasonography revealed a bulky uterus distorted by multiple intramural and subserosal fibroids, the largest measuring 4.8 × 4.6 cm. The left ovary contained a multiloculated cyst (6.7 × 4.8 cm) suggestive of a mucinous cystadenoma, and the right ovary contained a smaller cyst (4.3 × 2.6 cm). Abdominal ultrasonography showed fatty liver without ascites. Laboratory investigations showed microcytosis with low hemoglobin; liver and renal function tests were within normal limits.

The clinical impression was multiple cutaneous leiomyomas, multiple uterine fibroids, and bilateral ovarian cysts, raising suspicion for Reed's syndrome.

A chest lesion punch biopsy showed an intradermal smooth muscle neoplasm with scattered nuclear atypia but no mitoses or necrosis, confirming cutaneous leiomyoma; subcutaneous tissue was not sampled to assess for deeper extension.

The patient was reassured and prescribed analgesics and hematinics for anemia. Cryotherapy was performed for symptomatic lesions, with further sessions planned. Gynecology follow-up was arranged for fibroid and cyst management, and she was referred for genetic counseling and renal MRI to screen for renal cell carcinoma.

On subsequent genetic evaluation, targeted testing of the fumarate hydratase gene identified a heterozygous pathogenic germline variant, FH c.425A>G (p.Gln142Arg; NM_000143.4, exon 4 of 10), confirming the molecular diagnosis of Reed's syndrome. She was counselled on autosomal dominant inheritance, the 50% transmission risk to offspring, and the value of cascade testing for at-risk relatives, including children over eight years [3], to guide surveillance; renal cell carcinoma risk is increased but not certain. She was referred for renal surveillance.

Written informed consent was obtained from the patient for publication of this case report and any accompanying clinical images.

Discussion

Cutaneous leiomyomas are uncommon tumors that typically present in the second to fourth decades of life, most often over the trunk and extremities, with a segmental or grouped distribution and characteristic cold- or touch-induced pain that helps distinguish them from other painful cutaneous tumors, including angiolipoma, eccrine spiradenoma, neuroma, and glomus tumor [4]. Multiple painful leiomyomas are particularly suggestive of Reed's syndrome, especially when accompanied by uterine fibroids.

Diagnostic criteria for hereditary leiomyomatosis and renal cell cancer classify the diagnosis as either multiple cutaneous leiomyomas with at least one histologically confirmed lesion, or fewer cutaneous lesions combined with minor criteria such as uterine leiomyomas requiring surgery before age 40, early-onset type II papillary renal cell carcinoma, or an affected first degree relative [5]. Our patient's histologically confirmed multiple cutaneous leiomyomas, together with symptomatic fibroids managed medically before age 40 and a first-degree family history of fibroids, satisfied this framework outright; the subsequent identification of a pathogenic fumarate hydratase variant provided molecular confirmation of the diagnosis.

The genetic basis lies in heterozygous mutations of the fumarate hydratase gene on chromosome 1q43, which disrupt the tricarboxylic acid cycle and drive tumorigenesis [2]. Renal carcinomas associated with this syndrome tend to be early-onset, highly aggressive, and often metastatic at presentation, which is why baseline renal imaging, preferably magnetic resonance imaging or computed tomography over ultrasound for sensitivity, and periodic surveillance are strongly recommended in all suspected or confirmed cases [6, 7] (Fig 1). Dermatologists should alert other clinicians once multiple cutaneous leiomyomas are identified, even before genetic confirmation.

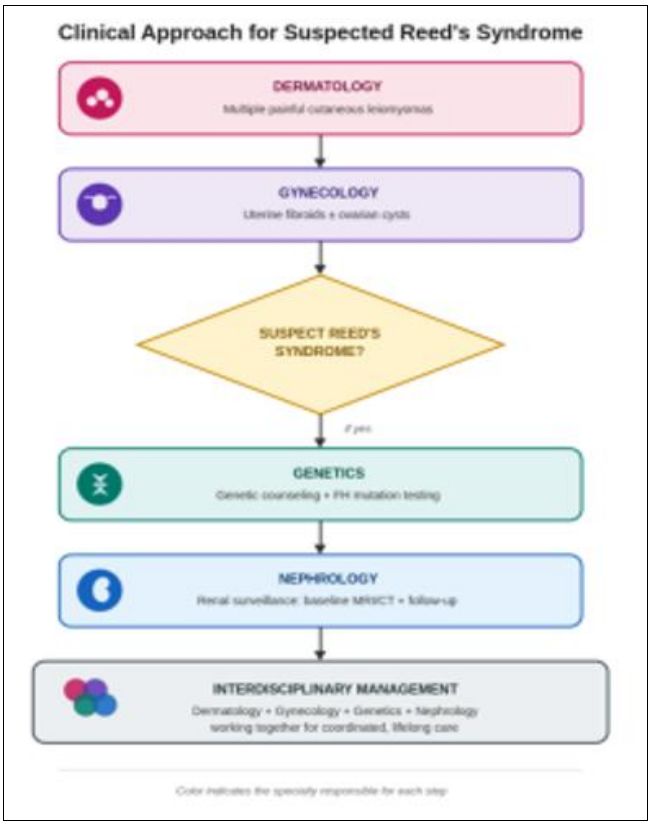

Fig 1: Flow diagram showing the recommended clinical approach for patients with suspected Reed's syndrome. Dermatology findings (multiple painful cutaneous leiomyomas) should prompt gynecological evaluation for uterine fibroids and ovarian cysts. If present, Reed's syndrome is suspected and genetic counseling with fumarate hydratase mutation testing is recommended. Renal surveillance with baseline magnetic resonance imaging or computed tomography and periodic follow-up is mandatory due to the high risk of aggressive renal cell carcinoma. Optimal management requires interdisciplinary collaboration among dermatology, gynecology, nephrology, and genetics

Treatment of the cutaneous lesions is symptomatic rather than curative, as no therapy reliably prevents new lesion formation. Options include oral agents that reduce smooth muscle contractility, such as calcium channel blockers or gabapentin for pain control [8], and destructive or excisional approaches, including cryotherapy, laser ablation, or surgical excision, for solitary bothersome lesions. None of these approaches alter the systemic cancer risk, underscoring that renal surveillance remains the priority once the diagnosis is confirmed.

Cascade testing offered to this family, including affected relatives across two generations, may reveal further carriers who benefit from surveillance.

This report is limited by biopsy of only a single lesion; the mild nuclear atypia noted, though unaccompanied by mitoses or necrosis, warrants clinical follow-up to exclude an atypical or malignant smooth muscle neoplasm [9]. Baseline renal imaging was reassuring but does not exclude future renal cell carcinoma, underscoring the need for the longitudinal surveillance already planned.

Conclusion

This case highlights the critical role dermatologists play in recognizing multiple cutaneous leiomyomas as a potential marker of Reed's syndrome. A single targeted question about menstrual or fibroid history can be the difference between a benign dermatologic diagnosis and identifying a hereditary cancer syndrome years before it becomes life-threatening. Molecular confirmation of a pathogenic fumarate hydratase variant in our patient enabled focused genetic counseling, cascade testing of at-risk relatives, and mandatory renal carcinoma surveillance, the most life-threatening aspect of the syndrome. Interdisciplinary collaboration between dermatology, gynecology, nephrology, and genetics is essential for optimal patient care.

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