# Unilateral Segmental Type 2 Hereditary Leiomyomatosis and Renal Cell Cancer

**Chaninart Jittanit MD, Sirinda Jamjanya MD.**
*Institute of Dermatology, Department of Medical Services, Ministry of Public Health, Bangkok, Thailand.*

**ABSTRACT**:
Our case report describes a patient who exhibited clinical unilateral segmental involvement of painful, firm papules and nodules on the right side of the face, upper chest, back, and forearm. Leiomyomatosis was preferred and confirmed by skin biopsy based on clinical presentation and uterine leiomyoma history. Our patient meets the criteria diagnosis of hereditary leiomyomatosis and renal cell carcinoma (HLRCC), known as Reed syndrome, with multiple cutaneous leiomyomas confirmed by biopsy and early-onset symptomatic uterine fibroids. Imaging revealed benign renal cysts, a finding with increased incidence in HLRCC patients. Genetic testing revealed a heterozygous *FH*:c.574C>T variant in exon 5, establishing the diagnosis of HLRCC. Due to the risk of renal malignancies in HLRCC patients, ongoing surveillance and early genetic screening are essential to improve patient outcomes and prevent serious complications.

**Key words**: Hereditary leiomyomatosis and renal cell carcinoma, Reed syndrome, Uterine leiomyoma, cutaneous leiomyoma, FH mutation, unilateral segmental type 2

**Case presentation**

A woman, 54 years old, came with multiple painful red-brown nodules on her face, upper chest, back, and right arm, persisting for 15 years prior to her medical visit. She reported pain aggravated by cold weather and denied any pharmaceutical use prior to consulting the doctor. The patient had an underlying condition of dyslipidemia and was only taking oral atorvastatin. She had undergone a total abdominal hysterectomy 25 years prior to this visit due to severe dysmenorrhea with menorrhagia and a tissue diagnosis of uterine leiomyoma. She did not have any food or medication allergies. No family members had experienced similar conditions. A dermatological examination revealed unilateral segmental multiple painful, well-defined, smooth-surfaced nodules with a firm consistency and faint erythematous to hyperpigmented papules on the right side of her face, right upper chest, right back, and right forearm (Figure 1). The differential diagnosis for unilateral segmental painful skin nodules included lesions originating from fibrous, neural, and muscle tissues. In our case, the absence of skin dimple signs and firm brownish skin nodules excluded dermatofibroma, a fibrous tissue entity. Additionally, there were no soft, skin-colored nodules with the buttonhole sign, axillary freckling, café-au-lait macules, Lisch nodules, or skeletal abnormalities, ruling out neurofibromatosis type 1, a neural tissue-related disorder. Given the uterine leiomyoma history and the presence of painful, firm, skin-colored to erythematous nodules, a provisional diagnosis of multiple cutaneous leiomyomatosis, a muscle tissue-related condition, was proposed, pending confirmation through histopathological examination.

Correspondence Author: Sirinda Jamjanya MD., Email: pum_sirin@yahoo.com

Received: 27 December 2023 Revised: 15 November 2024 Accepted: 13 January 2025

A skin biopsy from the back revealed a non-encapsulated, dermal-located neoplasm. At higher magnification, interlacing smooth muscle fiber bundles with elongated nuclei and eosinophilic cytoplasm were observed, but there was no mitotic activity or atypia. The overall histologic findings correlated with leiomyoma (Figure 2). Genetic analysis identified *FH*:c.574C>T (heterozygote), p.Pro192Ser (NM_000143.4), as the dominant heterozygous (missense) mutation (Figure 3). As a result, a diagnosis of unilateral segmental type 2 hereditary leiomyomatosis and renal cell cancer (HLRCC; Reed syndrome) was established.

This patient received genetic counseling and disease information as part of her treatment. She was referred for renal investigations, specifically a whole abdominal computed tomography, for renal cell carcinoma surveillance. Fortunately, the examination revealed large, thin-walled renal cysts in both kidneys without evidence of malignancy. However, continued surveillance for potential renal malignancy is warranted. The painful nodules affecting the patient's quality of life were surgically excised, while the asymptomatic lesions remain under close observation, with vigilance for possible malignant transformation into leiomyosarcoma.

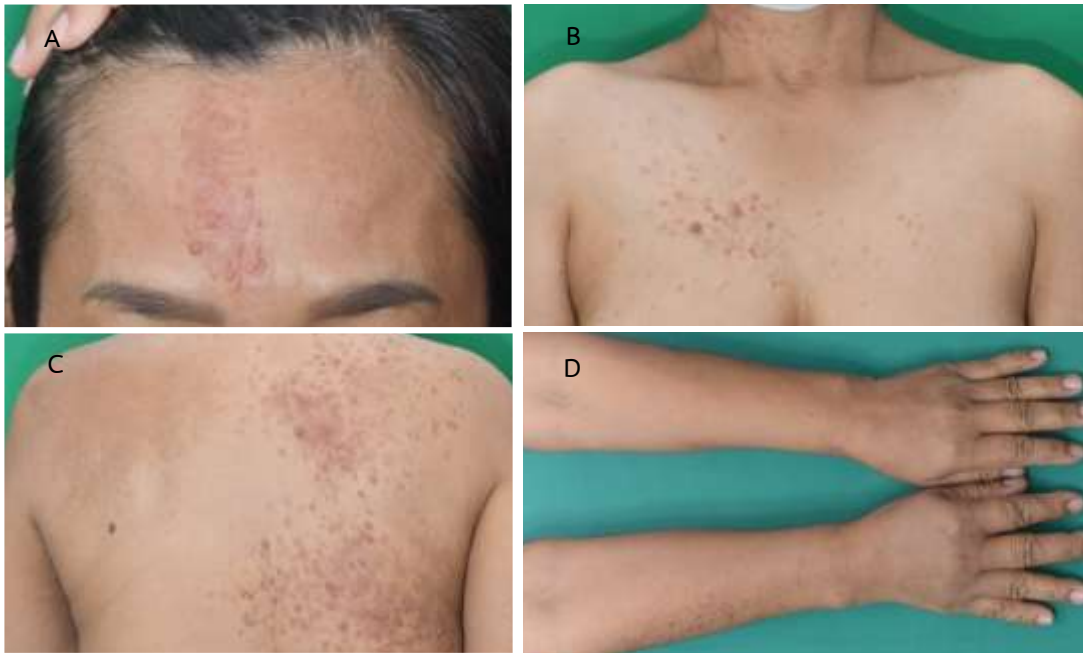


**Figure 1** Unilateral segmental multiple painful, well-defined, smooth-surfaced nodules with a firm consistency and mild erythematous to hyperpigmented papules on the right side of her face (A), right upper chest (B), right back (C), and right forearm (D)

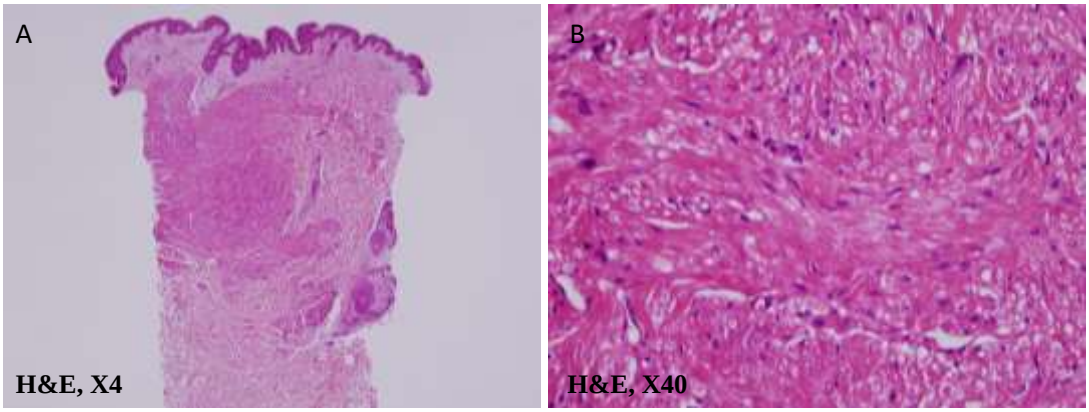


**Figure 2** A skin biopsy specimen from the right back demonstrated a non-encapsulated, dermal-located neoplasm. (A). Interlacing smooth muscle fiber bundles with elongated nuclei and eosinophilic cytoplasm, but there is no mitotic activity or atypia. (B). (H&E; original magnification: A. X4, B. X40)

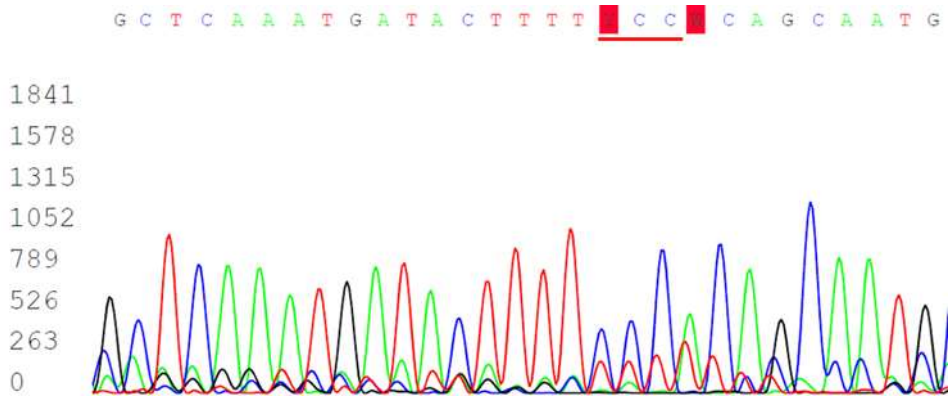


**Figure 3** Genetic analysis identified *FH*:c.574C>T (heterozygote), p.Pro192Ser (NM_000143.4) as the dominant heterozygous (missense) mutation.

**Discussion**

Our patient exhibits clinical unilateral segmental involvement on the right side of the face, upper chest, back, and forearm, presenting with faint erythematous to hyperpigmented, painful firm papules and nodules. Considering the cellular origin, the differential diagnosis for painful cutaneous nodules includes leiomyoma, dermatofibroma, neurofibroma, spiradenoma, and angiolipoma[1]. However, the differential diagnosis for the unilateral type 2 segmental pattern includes multiple leiomyomas, multiple dermatofibromas, neurofibromatosis type 1, multiple syringomas, and multiple trichoepitheliomas[2]. Due to the morphology of painful, firm, smooth-surfaced erythematous papules and nodules, as well as their distribution in the unilateral segmental type 2 presentation on the face, trunk, and extremities, the clinical diagnosis leans toward leiomyomatosis.

A skin biopsy can be used to diagnose three forms of cutaneous leiomyomas: piloleiomyomas, angioleiomyomas, and genital leiomyomas. Histopathology demonstrates cutaneous smooth muscle fiber bundle growth,

with positive immunohistochemistry for anti-desmin and anti-smooth muscle actin[3-5] . Reed syndrome should be considered in cases of multiple cutaneous leiomyomas with a history of uterine leiomyomas. Multiple cutaneous leiomyomas can be found in 76% of Reed's patients and manifest as solitary or clustered lesions ranging from 0.2 to 2.0 centimeters, with a mean age of initiation of 25 years[3]. Variable patterns, such as zosteriform or segmental, linear, bilateral, symmetrical, or disseminated, can be identified[3-5]. Two types of mosaic manifestations are described for autosomal dominant disorders. Type 1 mosaicism has only segmental skin lesions; compared to type 2, it has a pattern of segmental lesions combined with disseminated lesions. In our case, we diagnosed unilateral segmental type 2 HLRCC as the coexistence of multiple unilateral segmental cutaneous leiomyomas and uterine leiomyoma[3,5].

Reed *et al*. described multiple cutaneous and uterine leiomyomatosis (MCUL), in 1973. The gene encoding fumarate hydratase (FH), associated with Reed syndrome in 76% to 93% of cases, is located on chromosome 1q42.3-q43. About 58% of these mutations are missense, 27% are frameshift, 9% are nonsense, and 7% involve complete gene deletions[6]. Individuals with a mutated *FH* gene require a second genetic alteration that inactivates the remaining normal *FH* gene to develop tumors[3]. A mutation in the gene encoding FH, the enzyme that convert fumarate to malate, causes fumarate accumulation and leads to a malfunction in hypoxia-inducible factor (HIF) hydroxylase. When HIF levels rise, transforming growth factor-alpha, vascular endothelial growth factor, glucose transporter-1, and platelet-derived growth factor are upregulated. As a consequence, cellular proliferation and angiogenesis are increased, defining the mechanism underlying Reed syndrome[7,8].

Menstrual irregularities, heavy bleeding, and pain are common symptoms of uterine leiomyoma. Approximately 50% of women in their 30s and 40s undergo hysterectomy or myomectomy to manage this condition, as observed in this patient[3,8].

Multiple studies have linked MCUL to solitary unilateral type 2 papillary renal cell carcinoma, now recognized as HLRCC. Renal malignancy associated with HLRCC has become aggressive and has the potential to metastasize, resulting in a 70% mortality rate within 5 years, particularly in individuals ranging in age from 10 to 90 on average[3]. Symptoms such as hematuria, lower back pain, and the presence of a palpable mass should be examined for suspected renal cell carcinoma[3]. In addition to renal cell carcinoma, benign renal cysts are also more common in HLRCC patients than individuals without the condition (36% vs. 4.6–8.2%)[3]. In this case, the patient did not exhibit any renal symptoms, and renal imaging revealed only benign cysts, with no signs of malignancy.

The criteria diagnosis for hereditary leiomyomatosis and renal cell carcinoma (HLRCC), as outlined by Smit et al., require a germline *FH* mutation for definitive diagnosis. Clinically, HLRCC is strongly suspected in patients with biopsy-confirmed multiple cutaneous leiomyomas (major criterion) or in those meeting at least two minor criteria: a solitary cutaneous leiomyoma with a family history of HLRCC, early-onset type 2 papillary renal tumors, or multiple uterine fibroids before age 40[3,8,9]. Although our patient's initial diagnosis was made without genetic results, the presence of one major criterion, biopsy-confirmed multiple cutaneous leiomyoma, and one minor criterion, symptomatic uterine fibroids, strongly suggested HLRCC. However, genetic testing revealed a positive germline *FH* mutation result, confirming our patient's definitive diagnosis. According to genetic analysis (Figure 3), our patient carries the heterozygous *FH*:c.574C>T variant in exon 5. This missense mutation replaces proline with

serine at position 192 of the dominant heterozygous variant. We are certain that the variant mutation in our patient is pathogenic based on the Association for Clinical Genomic Science and American College of Medical Genetics and Genomics criteria, supported by the following pathogenicity evidence: PM1 and PP2 functional data, PM2 population data, PM5 effect on protein, PP3 in-silico predictions, and PP5 reputable source data[9,10].

A literature review identified eight case reports of type 2 segmental cutaneous leiomyomatosis published in the English language[11-14]. Most cases had a family history of cutaneous leiomyomatosis[11,12,14]. However, in one case, a 13-year-old was confirmed to have renal cell carcinoma. Notably, this patient had no family history of similar skin lesions or renal cancer but did have a family history of symptomatic leiomyoma[12, 13]. Genetic testing, when performed, consistently revealed mutations in the *FH* gene across all tested cases. In our case, there is no family history of uterine leiomyoma, cutaneous leiomyomatosis, or renal cell carcinoma, but the criteria for a diagnosis of HLRCC are still met.

The primary objectives of managing multiple cutaneous leiomyomas include lesion reduction, pain relief, and aesthetic improvement. Cryotherapy, electrodessication, CO2 laser treatment, or surgery are the main modalities available for treating painful leiomyoma lesions. Additionally, medications including oral nitroglycerin, phenoxybenzamine, nifedipine, and doxazosin effectively reduce smooth muscle contractions. Pharmaceutical agents like gabapentin and pregabalin can be considered therapeutic options to modulate nerve activity. Narcotics, lidocaine, capsaicin, and intralesional corticosteroids have also demonstrated effectiveness[3,4]. In our patient, we performed an excision to eradicate unpleasant cutaneous lesions.

The recommended surveillance plan involves evaluating cutaneous leiomyoma for malignant leiomyosarcoma every 1-2 years. Annual gynecologic examinations for uterine leiomyoma should be performed. Starting at the age of 10, individuals should undergo annual screening with magnetic resonance imaging to ensure early detection of renal cancer. Those with affected first-degree relatives should consider *FH* gene testing between the ages of 8 and 10[3,8,10]. Our patient had benign renal cysts, and we counseled her about the risk of renal cell carcinoma before referring her to a nephrologist. We were unable to examine the patient's family members, but the patient reported that none of the family members have similar conditions.

In conclusion, for patients presenting with cutaneous and uterine leiomyomas, raising suspicion for HLRCC, annual follow-up examinations are recommended to screen for renal malignancy. Additionally, genetic testing and counseling should be provided to both the patient and their family members.

### *References*

1. Cohen PR, Erickson CP, Calame A. Painful tumors of the skin: "CALM HOG FLED PEN AND GETS BACK". Clin Cosmet Investig Dermatol 2019;12:123-32.
2. Happle R. Dohi Memorial Lecture. New aspects of cutaneous mosaicism. J Dermatol. 2002;29:681-92.
3. Patel VM, Handler MZ, Schwartz RA, Lambert WC. Hereditary leiomyomatosis and renal cell cancer syndrome: An update and review. J Am Acad Dermatol 2017;77:149-58.
4. Holst VA, Junkins-Hopkins JM, Elenitsas R. Cutaneous smooth muscle neoplasms: clinical features, histologic findings, and treatment options. J Am Acad Dermatol 2002;46:477-90.
5. Albuquerque MM, Rocha CF, Costa IS, Maia Rda R, Branco FJ, Gonçalves Hde S. Piloleiomyoma with segmental distribution--Case report. An Bras Dermatol 2015;90:178-80.
6. Alam NA, Olpin S, Leigh IM. Fumarate hydratase mutations and predisposition to

cutaneous leiomyomas, uterine leiomyomas and renal cancer. Br J Dermatol 2005;153:11-7.
7. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. Fam Cancer 2014;13:637-44.
8. Schmidt LS, Linehan WM. Hereditary leiomyomatosis and renal cell carcinoma. Int J Nephrol Renovasc Dis 2014;7:253-60.
9. Smit DL, Mensenkamp AR, Badeloe S, et al. Hereditary leiomyomatosis and renal cell cancer in families referred for fumarate hydratase germline mutation analysis. Clin Genet 2011;79:49-59.
10. Forde C, Lim DHK, Alwan Y, et al. Hereditary Leiomyomatosis and Renal Cell Cancer: Clinical, Molecular, and Screening Features in a Cohort of 185 Affected Individuals. Eur Urol Oncol 2020;3:764-72.
11. König A, Happle R. Two cases of type 2 segmental manifestation in a family with cutaneous leiomyomatosis. Eur J Dermatol 2000;10:590-2.
12. Ritzmann S, Hanneken S, Neumann NJ, Ruzicka T, Kruse R. Type 2 segmental manifestation of cutaneous leiomyomatosis in four unrelated women with additional uterine leiomyomas (Reed's Syndrome). Dermatology 2006;212:84-7.
13. Çaliskan E, Bodur S, Ulubay M, et al. Hereditary leiomyomatosis and renal cell carcinoma syndrome: a case report and implications of early onset. An Bras Dermatol 2017;92:88-91.
14. Parmentier L, Tomlinson I, Happle R, Borradori L. Evidence for a new fumarate hydratase gene mutation in a unilateral type 2 segmental leiomyomatosis. Dermatology 2010;221:149-53.