Skin, Uterus, and Genes: When Painful Skin Lesions Tell a Familial Syndrome

Pele, Útero e Genes: Quando Lesões Cutâneas Dolorosas Revelam uma Síndrome Familiar

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Palavras-chave: Leiomioma/genética; Leiomiomatose/diagnóstico; Neoplasias da Pele/genética; Neoplasias Uterinas/genética; Síndromes Neoplásicas Hereditárias

Dear Editor,

Cutaneous leiomyomas are rare benign smooth muscle tumors that may occur sporadically or as part of a hereditary syndrome. The presence of multiple painful cutaneous leiomyomas, particularly piloleiomyomas – the subtype most frequently associated with hereditary disease – together with uterine fibroids should raise suspicion of hereditary leiomyomatosis and renal cell carcinoma (HLRCC), also known as fumarate hydratase (FH) tumor predisposition syndrome (formerly Reed syndrome), caused by heterozygous germline mutations in the *FH* gene.[1] Recognition of the cutaneous lesions is crucial, as they may represent the earliest clinical clue to a potentially life-threatening renal tumor.

We report the case of a 58-year-old woman (Fitzpatrick phototype III) presenting with multiple brown-violaceous papulonodules on the trunk and limbs, painful to touch and progressively increasing in size over five years. She had a history of symptomatic uterine fibroids diagnosed at the age of 40. Clinical examination revealed more than 20 firm papulonodules, measuring 0.5 to 1 cm in diameter, some tender on palpation (Fig.1). Dermoscopy showed a delicate, symmetric pigment network with a reddish hue, a non-specific pattern, which may also be observed in other entities such as dermatofibroma or piloleiomyoma. A punch biopsy revealed interlacing bundles of spindle-shaped cells with eosinophilic cytoplasm and blunt-ended nuclei in the dermis. Immunohistochemistry was positive for smooth muscle actin and muscle-specific actin, confirming cutaneous leiomyoma (Fig. 2).

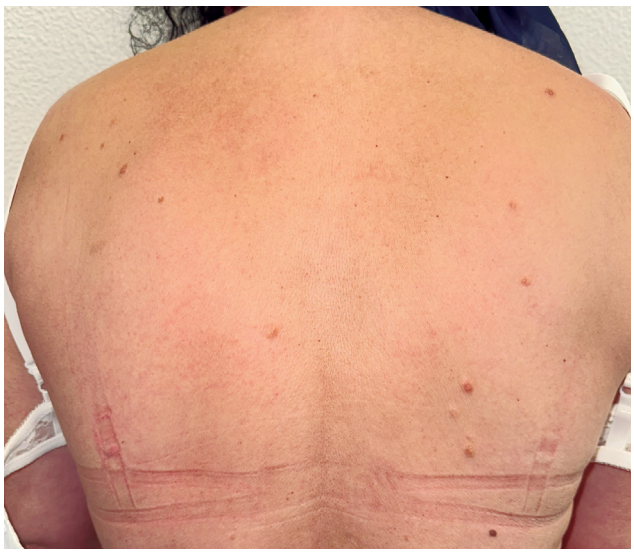

Figure 1 – Multiple brown-violaceous papulonodules, some tender to palpation

Given the combination of multiple cutaneous leiomyomas and a history of uterine fibroids, HLRCC/FH tumor predisposition syndrome was suspected. Genetic testing identified a heterozygous *FH* variant [NM_000143.4:c.1119C>G; p.(Asn373Lys)], not previously reported in the literature, but classified as likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria. This was based on the absence from population databases (PM2), supporting a deleterious effect (PP3), and a phenotype highly specific for FH-related disease (PP4). Imaging (thoracoabdominopelvic magnetic resonance imaging) and renal/pelvic ultrasound showed multiple uterine fibroids without renal abnormalities. Her 23-year-old daughter presented with two small papules on her left arm and carried the same FH mutation, with unremarkable renal imaging.

HLRCC/FH tumor predisposition syndrome is characterized by multiple cutaneous and uterine leiomyomas and an aggressive form of type 2 papillary renal cell carcinoma.[2-4] Diagnostic criteria rely on a combination of major criteria (multiple cutaneous leiomyomas with histological confirmation) and minor criteria, including early-onset uterine fibroids, characteristic renal tumors, and a confirmed pathogenic FH variant. Penetrance of the cutaneous and uterine features is high, while renal cancer develops in only a subset of mutation carriers, often at a young age and with high metastatic potential. Once an *FH* mutation is confirmed, contrast-enhanced renal magnetic resonance imaging (MRI) with thin slices (1 - 3 mm) should be performed at least annually, beginning in childhood or adolescence, as ultrasound alone is insufficient for surveillance.[4,5] Management of cutaneous leiomyomas is usually conservative; painful lesions may be treated by excision, cryotherapy, or medical therapies such as calcium channel blockers, alpha-blockers, neuroactive agents, or botulinum toxin, although evidence remains limited.[3]

This case underscores the diagnostic relevance of cutaneous leiomyomas as cutaneous markers of hereditary cancer syndromes, highlighting the pivotal role of dermatology in early recognition, genetic counselling, appropriate renal surveillance, and family screening.

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The authors declare that ChatGPT was used to improve the semantics in academic English. After using this tool, the work was reviewed and edited by the authors, who assume full responsibility for its content.

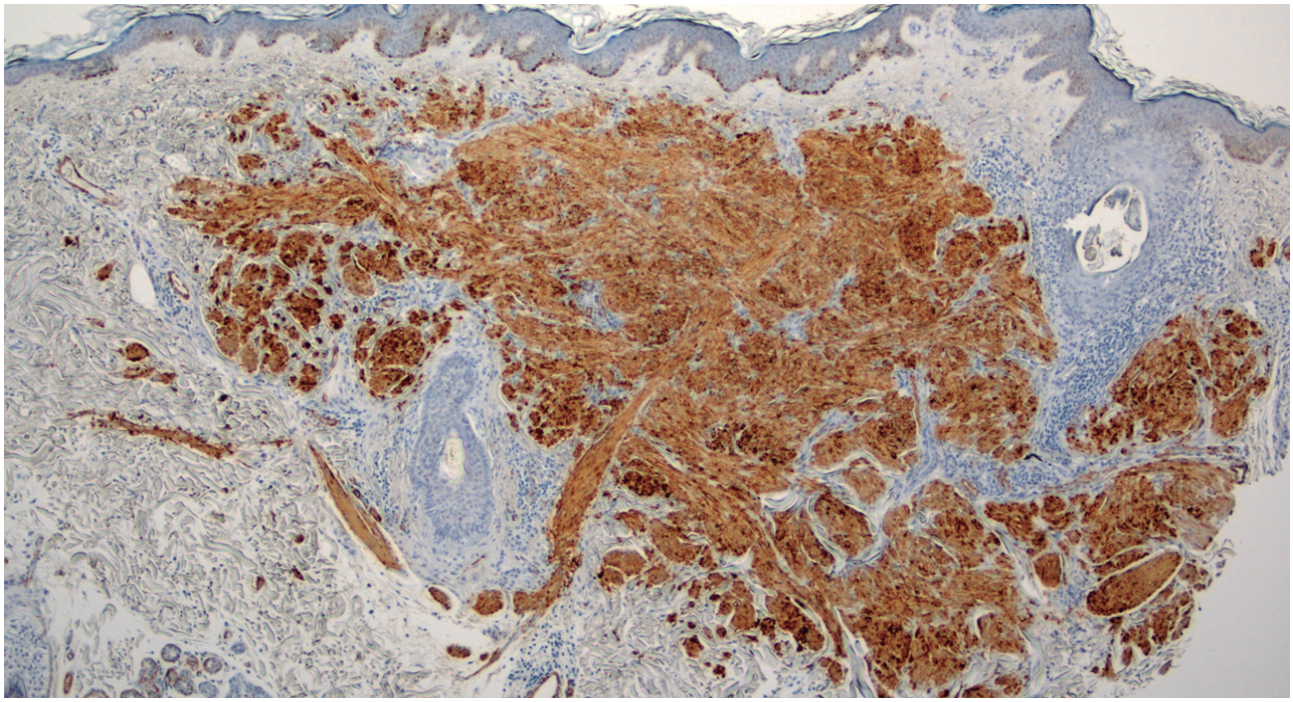

Figure 2 – Immunohistochemistry for α-smooth muscle actin (SMA) demonstrates diffuse strong cytoplasmic positivity, supporting smooth muscle differentiation

AUTHOR CONTRIBUTIONS

IS, IPA: Writing of the manuscript.
PV, PF: Critical review of the manuscript.
All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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