Annals of Case Reports
Lortholary A, et al. Ann Case Rep: 10: 102168
www.doi.org/10.29011/2574-7754.102168
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Case Report

About 2 Cases of Familial Leiomyomatosis with FH Mutation

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Citation: Lortholary A, Castanie H, Auffret M, Vildy S, De Paillerets BB (2025) About 2 Cases of Familial Leiomyomatosis with FH Mutation. Ann Case Report. 10: 2168. DOI:10.29011/2574-7754.102168

Received: 21 January 2025, **Accepted:** 24 January 2025, **Published:** 27 January 2025

Abstract

2 cases of familial leimyomatosis are described: one with caracteristic skin lesions and the other with endometrial lesion. Both have a FH mutation. The major risk in these families is renal carcinoma.

Keywords: Familial Leîomyomatosis; FH Gene Mutation; Kidney Cancer.

Introduction

Familial leiomyomatosis is a rare autosomal dominant hereditary syndrome that can cause skin and/or uterine leiomyomas in heterozygotes, as well as a rare form of kidney cancer (in 20% of cases): type II papillary carcinoma, an aggressive form with a poor prognosis [1].

Other tumors described include paragangliomas, pheochromocytomas, adrenal adenomas and, very rarely, uterine leiomyosarcomas [2].

The prevalence of this syndrome has been estimated at 1 per 200,000.

Onset of symptoms averages 25 years (10 - 47 years).

Uterine leiomyomas are very common in women, appearing on average around the age of 30 (18 - 52).

Kidney tumors appear at an average age of 44.

This syndrome is characterized by a constitutional mutation in the fumarate hydratase (FH) gene, located at 1q42.3. Mutations are most often inherited and transmissible, affecting several generations. Rare cases of de novo mutations have been described [3].

In homozygous children (a mutation in the FH gene has been inherited from both parents, usually as a result of consanguinity) or composite heterozygotes (each parent has inherited a different mutation), severe encephalopathy with a very poor prognosis can occur. The parents of these children have variable cutaneous and/or uterine leiomyoma phenotypes.

The FH gene encodes a mitochondrial enzyme of the Krebs cycle, fumarate hydratase, which catalyzes the reversible hydration of fumarate to malate. Loss of function of this enzyme leads to an accumulation of fumarate, disrupting energy production. The result is an increase in metabolic signals promoting angiogenesis, cell proliferation and growth, and epithelial-mesenchymal transition, all of which may contribute to the development of poor-prognosis renal cancers [4].

FH gene mutations are identified by sequencing DNA extracted from the blood of symptomatic patients. These analyses are usually prescribed by an oncogeneticist. Additional tests, such as enzyme activity assays, can help to confirm the hereditary nature of the disease. Pathologists perform FH protein immunostaining with varying degrees of accuracy. Specialists detect so-called "FH-deficient" leiomyomas, of which only 2.7% to 13.9% are linked to the hereditary syndrome, the majority resulting from somatic loss of function of Fumarate hydratase [5].

In 2011, 32 different FH gene mutations were identified in patients with renal cell carcinoma in France [1]. Papillary renal cancer may be the only manifestation of this syndrome.

Observations

We report two families with a mutation in the FH gene:

Case 1: (family tree 1):

A 52-year-old female patient came to my oncogenetic consultation at the request of her dermatologist for multiple cutaneous leiomyomas: multiple lesions grouped in popular, firm, buff-coloured or erythematous clusters, tender to palpation on the arms, thighs, buttocks and abdomen (Figures1 and 2).

Abdominopelvic ultrasound on March 1, 2024 showed no lesions in the kidney and a 23 mm right corporal sub serous uterine fibroid.

Her 77-year-old mother had uterine fibroids and several skin lesions identical to those of the patient.

Her maternal grandmother, who died aged 95, also had basal cell carcinoma on the forehead, uterine fibroids and a brain tumour.

Her father, aged 76, had a leiomyomatous hyperplasia of the prostate diagnosed at age 70.

Case 2: (family tree 2):

The patient, aged 31, underwent total hysterectomy and bilateral salpingectomy on November 17, 2023 for a multi-myomatous uterus and fibroid, presenting with atypical hypersignal on MRI.

Histology revealed 5 lesions ranging in size from 0.6 to 7.5 cm, corresponding to fumarate hydratase-deficient leiomyomas. Immunohistochemistry: absence of fumarate hydratase staining (positive internal control).

Mutation testing revealed a class 5 variant of the FH gene: c.908_909insTCTTTAG, p. (Leu303Phefs*3).

The patient had no skin lesions and renal ultrasound was normal.

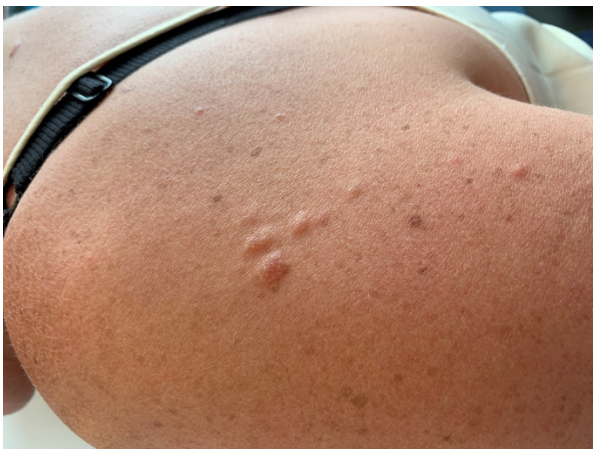

Figure 1: case N° 1 (A1).

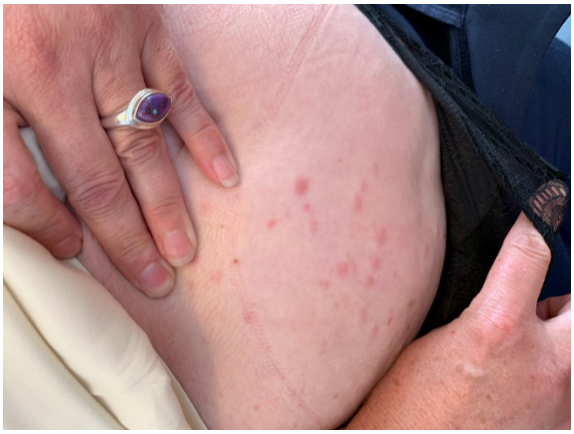

Figure 2: case N° 1 (A2).

Conclusion

This rare disease, of autosomal dominant transmission, should be known mainly because of the risk of kidney cancer, which has been estimated at 21% over a lifetime. This cancer, which has a poor prognostic could be detected early by renal imaging and therefore operated on before metastases occur [6].

A case of metastatic kidney cancer has recently been reported, with a good response to immunotherapy [7].

As in these two cases, the disease can be diagnosed after the discovery of skin or uterine lesions.

Once the mutation has been identified, predictive tests can be proposed for relatives, and early screening with dermatological examination, endometrial ultrasound and annual abdominal ultrasound can be envisaged, starting at the age of 10 [8].

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