

Multiple Cutaneous Leiomyomas with Uterus Myomatosis (MCUL) – Two Case Reports and One New Mutation of FH Gene

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Abstract

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BACKGROUND: Reed syndrome or multiple cutaneous leiomyomas with uterine leiomyomas are part of the spectrum of heterozygous hereditary disorders with cutaneous, genital and renal manifestations.

CASE REPORTS: We report two female cases of multiple cutaneous leiomyomas with uterine leiomyomas (MCUL) without renal disease, in particular without cysts or papillary renal carcinoma, aged 52 and 55 years, respectively. The diagnosis of pilar leiomyomas was confirmed by histology and immunostaining for smooth muscle actin and desmin. Both females had a hysterectomy in the past because of uterus myomatosis. In one patient, a new mutation of the FH gene was detected, i.e. a heterozygote c1300_1301del (p.Cys434Argfs17) mutation in the exon 9 of the FH gene.

CONCLUSION: Since MCUL shares features with the genetic cancer syndrome hereditary leiomyomatosis and renal cell carcinoma (HLRCC), these patients need a regular follow-up to prevent the late diagnosis of renal cancer.

Introduction

The fumarate dehydrogenase (FH) gene is located on chromosome 1. In normal cells, FH is localised in both mitochondria and cytosol and catalyses fumarate to malate [1].

Fumarate is a covalent oncometabolite whose accumulation is characteristic for the genetic cancer syndrome hereditary leiomyomatosis and renal cell carcinoma (HLRCC). HLRCC is characterized by germline mutation of the fumarate hydratase (FH) gene, which leads to a shift to aerobic glycolysis in the affected cells (Warburg effect) [2]. The disease is autosomal dominant inherited. In homozygotes, FH deficiency is lethal in early childhood [3].

In the medical literature, only about 300 cases

of HLRCC are described with > 150 different mutations [4]. We report on two female patients with the milder type of the disease known as Reed syndrome or multiple cutaneous leiomyomas with uterine leiomyomas (MCUL; MIM 150800) and one new mutation.

Case Reports

Case One

A 52-year-old Caucasian woman presented with multiple flat painful tumours concentrated on her left shoulder (Figure 1).

Her medical history was positive for a uterus

myomatosis that was surgically removed by hysterectomy. She was otherwise healthy.



Figure 1: Multiple pilar leiomyomas on the left shoulder (case #1)

In her family, her mother had renal cancer at the age of 58 years, her son has multiple cutaneous leiomyomas (Fig. 2).

On examination, we observed multiple flat, livid nodules that were painful on pressure. Their size varied between 1 and 2 cm. The lesions were concentrated above her left shoulder blade, but single lesions were spread all over the body except palmoplantar skin and head and neck.

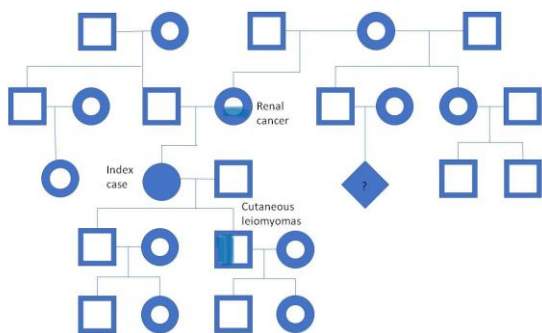


Figure 2: Family tree of the Case #1

We performed an excision of the most painful lesions. Histopathology disclosed dermal spindle cell tumours without cellular atypias or mitotic activity.

The lesions were well demarcated. Tumour cells were positive for smooth muscle actin and desmin (Figure 3) but Ki67 negative. The diagnosis of pilar leiomyomas was confirmed.

We performed molecular biology analysis of the fumarate hydrogenase (*FH*) gene. Extracted DNA was enriched by Nextera Rapid Capture on Illumina NextSequ 500 followed by Sanger sequencing, multiplex ligation-dependent probe analysis (MPLA) to detect possible duplications or deletions of exons, and biometric analysis by MutationSurveyor version 3.10,

GeneMarker V2 4.0 and Alamut Visual version 2.6.1 (MVZ Mitteldeutscher Praxisverbund Humangenetik GmbH, Dresden).

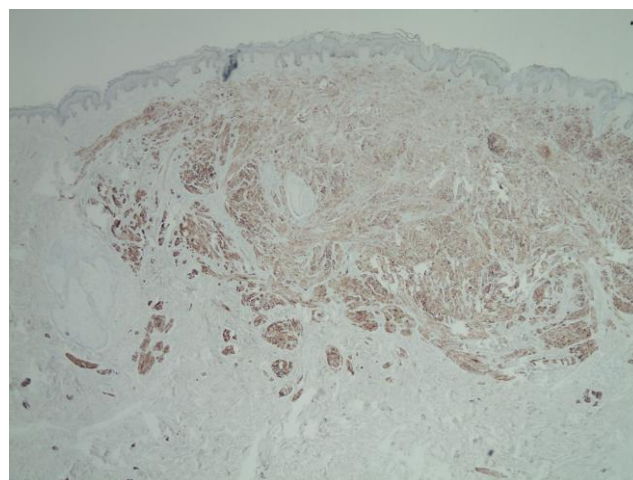


Figure 3: Desmin immunostaining of pilar leiomyoma (case #1, x 2)

A heterozygote c1300_1301del (p.Cys434Argfs17) mutation in the exon 9 of the *FH* gene could be detected, leading to a loss of function for the reading frame. This mutation has not been described before.

Routine laboratory investigations remained unremarkable. Tumour markers ICA 125 and ICEA were detected by chemiluminescence assays (Roche Diagnostics) and were within the normal range.

She was screened by diagnostic ultrasound, abdominal magnetic resonance imaging, and X-ray of the chest. There was no hint for renal cancer or any other renal disorder.

The diagnosis of MCUL (MIM 150800) was confirmed.

Case Two

A 55-year-old Caucasian woman presented with segmental painful tiny brownish nodules and plaques of the left supra- and infraclavicular region (Figure 4). She had a hysterectomy due to a uterus five years ago but no other disorders. Her family history was unremarkable.

A skin biopsy was taken, which disclosed circumscribed dermal tumours composed of interlacing and whorled bundles of smooth muscle cells expressing actin. The tumours appeared yellow-orange in van Giessen stain. The diagnosis of pilar leiomyomas was confirmed.

Screening for renal cancer by diagnostic ultrasound and contrast-enhanced computerised tomography (CT) was negative. No molecular analysis was available. Nevertheless, the diagnosis of MCUL (MIN 150800) was confirmed. This case had been reported earlier elsewhere [5]. Until now, no renal

cancer was detected in this patient.

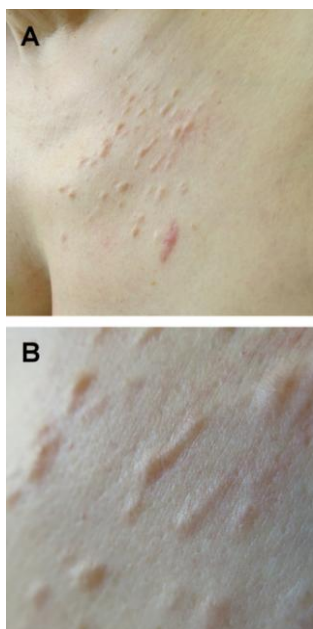


Figure 4: Pilar leiomyomas around the left clavicle (case # 2): a) Overview, b) detail (From Wollina U, Schönlebe J. Reed's syndrome: segmental piloleiomyomas type 1 and uterus myomatosis. *J Dermatol Case Rep.* 2014; 8(3):67-69) [5]

Discussion

We reported two cases of MCUL, a rare heterozygote FH deficiency, without renal cancer. In the case of heterozygote FH deficiency, fumarate suppresses the homologous recombination DNA repair pathway which is necessary for the repair of DNA double-strand breaks and genomic integrity by succination of proteins. the increases intracellular ferritin concentrations which drives tumour cell proliferation [6].

Hallmark of the disease is hereditary leiomyomatosis seen in > 75% of the affected patients. However, only 46% of affected individuals show cutaneous leiomyomas, benign smooth muscle tumours of the skin of the tumour. These tumours are sensitive to touch and cold and can be painful [7], [8]. Cutaneous pilar leiomyomas are benign tumours with an incidence of 0.04% in pathology files. Other cutaneous leiomyomas are angioleiomyoma and dartoic myoma, but the pilar type if the predominant one responsible for 88.5% of all cases [9]. A rare subtype of pilar leiomyoma is represented by symplastic pilar leiomyoma with focal cellular pleomorphism [10]. This particular subtype has been reported to be potentially developing in leiomyosarcoma in rare cases [11].

Women with HLRCC are prone to develop multiple leiomyomas of the uterus as well, which leads to uterus myomatosis. Hysterectomy is performed in

about 50% in patients younger than 35 years. The disease can cause dysmenorrhea, menorrhagias, and menstrual irregularities [12], [13].

Both of our patients had a hysterectomy due to uterine leiomyomas. Both presented with multiple cutaneous pilar leiomyomas. The lesions were segmental in case # 2 and segmental concentrated with single lesions on other body parts in case # 1. Painful lesions were removed by surgery.

The most dangerous feature of HLRCC, however, is the early onset of papillary kidney cancer in the affected families. This tumour has two subtypes. Type 1 is an indolent growing tumour associated with germline mutations of *MET*. It is found in hereditary papillary kidney cancer. Type 2, in contrast, is an aggressive tumour with early metastatic spread. This type is associated with HLRCC. It occurs in about 25% of patients with an average onset at 46 years. It may be without specific symptoms but can cause lumbar back pain or hematuria. Renal cysts are also more common in HLRCC than in the general population [14].

In case # 1, the mother of our index patient had an unspecified renal cancer but no leiomyomatosis. This could be an incidental coincidence. In case 2, there was no family history of other members affected by either MCUL or HLRCC. Nevertheless, these patients need a regular live-long follow-up for early detection of renal cell cancer.

In conclusion, MCUL may be considered a *forme fruste* of HLRCC or a more benign subtype. More investigations are needed.

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