USEFULNESS OF DERMOSCOPY FOR DETECTING SKIN LEIOMYOMAS IN PATIENT WITH UTERINE FIBROIDS AND CEREBRAL CAVERNOMAS

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Abstract

Background: Hereditary syndromes frequently need cooperation of different specialties to increase the diagnostic competence. Multiple cutaneous and uterine leiomyomatosis syndrome is a rare autosomal dominant disorder due to mutations of fumarate hydratase gene, demonstrated in 80 to 100 percent of affected individuals, which can be linked to an increased risk of renal cancer in both sexes. The skin involvement is described to evidence the diagnostic role of the cutaneous counterpart in identifying this rare syndrome.

Case presentation: A 37-year-old woman suffering from several uterine fibroids presented multiple, painful, papulo-nodules on her left subscapular side, both forearms and legs. Patient was submitted to surgery of six lesions: five were leiomyomas and one dermatofibroma. Genetic sequencing did not evidence known fumarate hydratase gene mutations. Dermoscopy, showing a brown delicate pigmented network, included leiomyomas among the non-melanocytic benign skin tumours featuring a dermatofibroma-like pattern. Abdominal computerized-tomography scan did not reveal renal cancer, but brain magnetic resonance imaging showed one asymptomatic cerebral cavernoma. The patient received benefit from surgical removal of five larger cutaneous lesions and from gabapentin, which improved the painful symptom.

Conclusions: This observation evidences the usefulness of dermoscopy for the diagnosis of cutaneous leiomyomas disclosing multiple cutaneous and uterine leiomyomatosis syndrome. Dermoscopy should be performed for non-melanocytic multiple lesions mimicking leiomyomas in a large number of patients, to establish a strict classification, being able to identify false negative cases or evaluating them as dermatofibromas. In this case the dermatologist recognize patients and related for risk of renal cancer and cerebral cavernomas.
Keywords: cutaneous leiomyoma; dermoscopic pattern; dermatofibroma; differential diagnosis.

Background

Multiple cutaneous and uterine leiomyomatosis (MCUL), previously known as Reed's syndrome, is an autosomal dominant disease with incomplete penetrance characterized by the onset of uterine leiomyomas or fibroids and, in both sexes, skin leiomyomas [1,2]. The coexistence of cutaneous and uterine leiomyomas may cluster papillary type2 renal-cell carcinoma or renal collecting duct cancer, codifying a recent variant appointed as hereditary leiomyomatosis and renal cell cancer (HLRCC) [3]. Even though different gene mutations, missense, nonsense or whole gene deletions have been described in MCUL syndrome, a definite association among site or type of mutation and risk for papillary renal-cell carcinoma has not been yet found [4]. Cutaneous leiomyomas, accounting for 75% of all extra-uterine leiomyomas, are uncommon benign smooth muscle tumours derived either from the erector pili muscle of the pilosebaceous unit (piloleiomyomas), or from the cutaneous vascular smooth muscle fibers (angioleiomyomas) or from the dartos muscle (genital leiomyomas) [5]. Piloleiomyomas are the most common forms featuring as firm, skin-colored or pink-brown soft dermal papules or nodules, ranging up to 2.0 cm in diameter, distributed in single, clustered, segmental or disseminated pattern. Linear or segmental leiomyomas may present a dermatomal-like distribution [6]. Common locations include trunk, extensor surface of the extremities and face, more often in adulthood then in childhood. The neoplasms can be asymptomatic or quite debilitating, if painful, mainly in response to pressure or cold temperature [7]. Clinical differential diagnoses include several skin lesions, such as dermatofibroma, eccrine spiradenoma, neurofibroma, angiolipoma, neurilemmoma, glomus tumour, keloid, hamartomas and blue rubber bleb nevus syndrome, when painful, or dermal nevus, trichoepithelioma, lipoma, cylindroma or poroma, among asymptomatic tumours [8]. The skin involvement of a case of MCUL syndrome is reported to support the diagnostic role of the cutaneous counterpart in identifying this rare syndrome. We present and discuss a case of multiple cutaneous lesions and usefulness of
dermoscopy for better understanding skin leiomyomas in the wide spectrum of non-melanocitic lesions.

**Case presentation**

A 37-year-old woman complained of 18-year history of progressive onset of multiple, firm, smooth, soft, pink-to-brown papules and nodules on her left sub scapular region and both forearms, ranging from 1 to 2 cm in diameters. Some lesions were arranged in dermatomal-like clustered nodules and plaques on her left upper back (Fig. 1). The lesions could become symptomatic after mechanical injury, pressure, cold thermal stimuli or emotional stress. Moreover, we observed brownish nodular lesions on her leg similar to a dermatofibroma, displaying the most common pattern (Fig 4). Past medical history included early menarche, dismenorrheas, menometrorrhagia, anaemia and uterine fibromatosis with myomectomy in 2000. Her family history neither revealed similar skin lesions in kindred nor history for uterine diseases, hysterectomies or renal cancers. A total of 50 cutaneous lesions were counted in our patient, already in 2003 the patient had removed a large cutaneous leiomyoma. Five larger nodules were surgically removed in order to solve the pain and the distress caused by their size. The histology confirmed the diagnosis of cutaneous piloleiomyomas. A dermal proliferation of irregular interlacing bundles of benign smooth muscle cells with minimal atypia and scarce proliferative activity (Fig. 2a) was the main findings. Antibodies against α-smooth muscle actin (Fig. 2b), desmin and myosin positively stained the neoplastic growth. Moreover, the histological examination of the leg lesion confirmed the presence of dermatofibroma.

Genetic analysis has been performed using RNA extracted from a leiomyoma biopsy. Complete coding region sequencing of all 10 exons of *Fumarate Hydratase* gene (Gb #NM_000143) has been evaluated using direct sequencing of RT-PCR amplified FH transcript. The sequence did not reveal nucleotide changes in coding region, according for the presence of amino acid substitutions. This not excludes the possibility of the presence of complex genomic mutations, located inside introns, which could give rise to abnormal transcripts. The level of enzymatic FH analysis should be
investigated to further characterise the patients for FH activity depletion. Complete routine blood testing and urinalysis did not evidence anomalies. Abdominal computerized-tomography (CT) scan displayed uterine fibroids and normal appearing kidneys. Brain magnetic resonance imaging (MRI) showed one asymptomatic cerebral cavernoma (data not shown).

Dermoscopy was performed by using Dermlite ® with non–contact polarized light on each cutaneous leiomyoma. A delicate dermatofibroma-like pigment network, due to thin lines of pinkish-light brown colour and regular meshes, was evidenced in all lesions (Fig. 3). The network was regularly distributed and gradually fading into the surrounding skin. No vascular structures were observed. In some lesions a white cloud-like area without scar features were observed. As expected, reflectance confocal microscopy did not evidence any remarkable findings because of the deep dermal location of the proliferation. Considering the number of the tumours and the extension of the affected area, capsaicin <1% cream was firstly proposed to reduce the symptoms, twice a day, but without benefit after 3 months. Leiomyoma-related discomfort significantly improved with gabapentin, started from 75 mg/die and rose up to 225 mg/die for 1 month, with marked reduction of the pain.

Conclusions

Hereditary syndromes frequently need cooperation of different specialties, and MCUL/HLRCC disorder is a relevant example of this occurrence. The skin is often part of hereditary syndromes and the chance to increase the diagnostic competence is always requiring. Alongside the clinical and histological approach, we investigated if, in vivo, non-invasive, methods of investigations, dermoscopy or RCM, could increased the diagnostic skill. Cutaneous leiomyomas are dermal proliferations of benign smooth muscle fibres and, as consequence, the diagnostic role of superficial investigations is regarded as possibly uncertain. A new, interesting finding came from dermoscopy, which allowed to include leiomyomas among the non-melanocytic benign skin tumours featuring a dermatofibroma-like appearance. In all leiomyomas a delicate pigment network with thin lines of
pinkish-light brown colour and regular meshes, regularly distributed and gradually fading into the surrounding skin was evidenced. No vascular structures were observed (Fig. 3). In some lesions a white area without scar features were observed, as recently described by Paschoal [9].

The pigmented network pattern seems reasonably related to a reactive epidermal basal hyperpigmentation, as observed in the lesions histologically confirmed, due to the underneath neoplastic growth of dermatofibroma and leiomyoma. RCM, as expected, did not give consistent results because of the deep dermal location of the proliferation.

Surprisingly our patient presented also a dermatofibroma, characterized by white scar like patch surrounded by a delicate pigment network (Fig 4), giving us the opportunity to better distinguish their dermoscopic findings and to establish specific criteria for differential diagnosis [10]. When pigmented network pattern of clinically non-melanocytic lesions is observed, should be considered in the dermoscopic differential diagnosis seborrheic keratosis, solar lentigo, dermatofibroma, and supernumerary accessory nipple [11].

Although screening guidelines for MCUL/HLRCC syndrome is not yet defined, Smit listed practical criteria to ensure appropriate diagnostic approach [12]. Suspicion of MCUL should always motivate a histological diagnosis of at least one cutaneous lesion. DNA analysis to test FH mutations should be recommended for all patients with familiar or severe cutaneous or uterine leiomyomatosis to eventually detect an occult renal malignancy, with genetic counselling in positive cases. Furthermore, since some mutation could escape by the standard sequencing analysis, an accurate enzymatic test should be developed to test FH activity in patient cells. An accurate follow-up should include annual cutaneous and gynaecologist examinations for the risk of leiomyosarcoma, together with annual renal ultrasound investigations. Furthermore, since cerebral angiomatosis has been also described in MCUL patients, dermatologists and gynaecologists should consider the relative risk of cerebral haemorrhages by brain MRI [13]. If in female, coincident uterine fibroids with often multiple and segmental cutaneous leiomyomas suggest the diagnosis of MCUL syndrome, in male, the most common solitary appearance of the cutaneous lesions and the
obvious absence of the gynaecological counterpart, make the diagnostic suspicion difficult, amplifying the risk of a late diagnosis of a possible renal involvement. Besides surgery for large or painful lesions, nifedipine, phenoxybenzamine, nitroglycerine, doxazosin, gabapentin, topical lidocaine or capsaicin, carbon dioxide laser ablation or botulinum toxin injections, have been variously tested to improve the symptoms [14-16]. After inconsistent result with topical capsaicin, in our patient, a substantial pain relief was obtained within few weeks without side effects with gabapentin. This neuromodulator modulates the influx of calcium with secondary reduction in excitatory neurotransmitter release. Our observation highlights the role of dermoscopy for diagnosis of cutaneous leiomyomas disclosing this hereditary syndrome for the risk of renal cancer and cerebral cavernomas. Dermoscopy should be performed for non-melanocytic multiple lesions mimicking leiomyomas in a large number of patients, to establish a strict classification, being able to identify false negative cases or evaluating them as dermatofibromas.

Consent
Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare, that they have no competing interests.
References


Figure Legend

Fig. 1: Pink-to-brown papules and nodules on her left sub scapular region and both forearms. Fig. 2. Morphological and immunohistochemical myocytic aspect of a skin leiomyoma. (a) Hematoxilyn-Eosin stained section reveals a poorly circumscribed lesion from interlacing bundles of benign smooth muscle cells; (b) immunohistochemistry confirms the positivity for α-smooth muscle actin of leiomyoma cells. Original magnification, x200; B, Diaminobenzidine as chromogen. Fig. 3:
delicate dermatofibroma-like pigment network with thin lines of pinkish-light brown colour and regular meshes in all lesions. Fig. 4: central white scar like patch with delicate pigment network in dermatofibroma of the leg.