Journal of Clinical & Experimental Dermatology Research

Bachour et al., J Clin Exp Dermatol Res 2019, 10:2
DOI: 10.4172/2155-9554.1000489

Case Report Open Access

A Case Report of Hereditary Leiomyomatosis to Increase Awareness of the Correlation between Cutaneous Lesions and RCC

Julien Bachour[1,2], **Madona Sakkal**[1,2], **Zarouhie Bedoyan**[2,3] **and Alfred Ammoury**[1,2*]

[1]*Department of Dermatology, St George Hospital University Medical Center, Beirut, Lebanon*

[2]*Department of Dermatology, University of Balamand, Beirut, Lebanon*

[3]*Department of Pathology, St George Hospital University Medical Center, Beirut, Lebanon*

[*]**Corresponding author:** Alfred Ammoury, M.D., Associate Professor, Faculty of Medicine and Medical Sciences, Department of Dermatology, St George Hospital University Medical Center, PO Box 166378, Beirut 1100 2807, Lebanon, Tel: +961 70635954; E-mail: docalf@yahoo.com

Received date: January 27, 2019; **Accepted date:** March 04, 2019; **Published date:** March 11, 2019

Abstract

Cutaneous leiomyomas are rare, benign smooth muscle tumors of the skin, with autosomal dominant but incomplete penetrance. hereditary leiomyomatosis syndrome consists of the triad of uterine leiomyomas, cutaneous leiomyomas and renal cell cancer. Here, we present a case of previously healthy man with no past medical nor family medical history who seeked medical advice for asymptomatic skin lesions of 2 month durations. Upon examination, patient was found to have leiomyomas with renal cell cancer. Therefore, it is of a great importance to recognize these skin lesions for early detection of devastating associated tumors.

Keywords: Hereditary leiomyomatosis; Leiomyoma; Reed syndrome

Introduction

Cutaneous leiomyomas are a rare, benign smooth muscle tumors of the skin, subcategorized based on the origin of the smooth muscle within the tumor. They are classified as follows: piloleiomyomas, which originate from the erector pili; genital leiomyomas, which originate from the dartos muscle of the skin in the genital area; and angioleiomyomas, which originate from the smooth muscle of the vasculature. Most pilar leiomyomas occur singly, but can occur as multiple lesions. Reed's syndrome, also known as multiple cutaneous and uterine leiomyomatosis (MCUL: OMIM 150800) and hereditary leiomyomatosis and renal cell cancer (HLRCC: OMIM 605839), is a condition inherited as an autosomal dominant trait with incomplete penetrance, consisting of multiple pilar leiomyomas, uterine leiomyomas and, rarely, leiomyosarcomas, in the multiple cutaneous and uterine leiomyomatosis (MCUL) syndrome and in association with renal cell carcinoma in the hereditary leiomyomatosis renal cell cancer (HLRCC) syndrome. The diagnosis is made by the presence of multiple cutaneous leiomyomas with at least one histologically confirmed leiomyoma or by a single leiomyoma in the presence of a positive family history of HLRCC [1,2]. Here, we present a healthy man who presented for esthetic consultation for multiple asymptomatic lesions. Upon further investigation, he was diagnosed with leiomyomas and renal cell cancer. Therefore, it is of a great importance to recognize these skin lesions for early detection of devastating associated tumors.

Case Report

26-year-old male patient, previously healthy, presented to our clinic for asymptomatic upper and lower limbs lesions of two months' duration. The patient reported being bothered esthetically from the abundance and the appearance of the lesions especially that they were affecting his work socially and professionally.

On physical examination, he had more than 100 firm, papulonodules fixed to the skin, ranging in size from 4-8 millimeters to 1 cm, reddish-brown in color, affecting only his upper and lower limbs (Figures 1 and 2). No other sites were affected and he had no mucosal lesions. There was no increase in erythema or edema when rubbed.

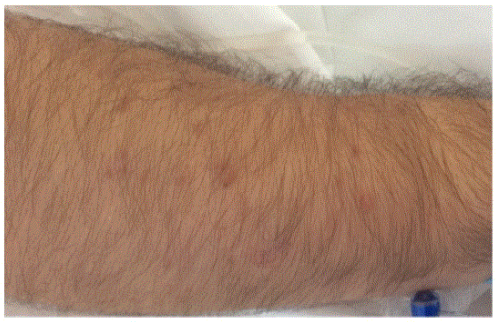

Figure 1: Papulonodules 4-8 millimeters to 1 cm reddish-brown lesions, affecting over upper limbs.

His past medical history was negative for skin cancers and his past surgical history was negative. There was no family history of skin problems and the generalized physical examination was normal. Our differential diagnosis included leiomyoma, dermatofibroma and schwannoma.

Histopathological examination from an excisional biopsy revealed a dermal nodule made up of multiple intersecting fascicles of fusiform shaped cells with ample eosinophilic cytoplasm. Multiple Cigar shaped nuclei with perinuclear vacuoles and interlacing bundles of smooth-muscle fibers were also seen (Figures 3a-3c). All the features were suggestive of cutaneous piloleiomyomas.

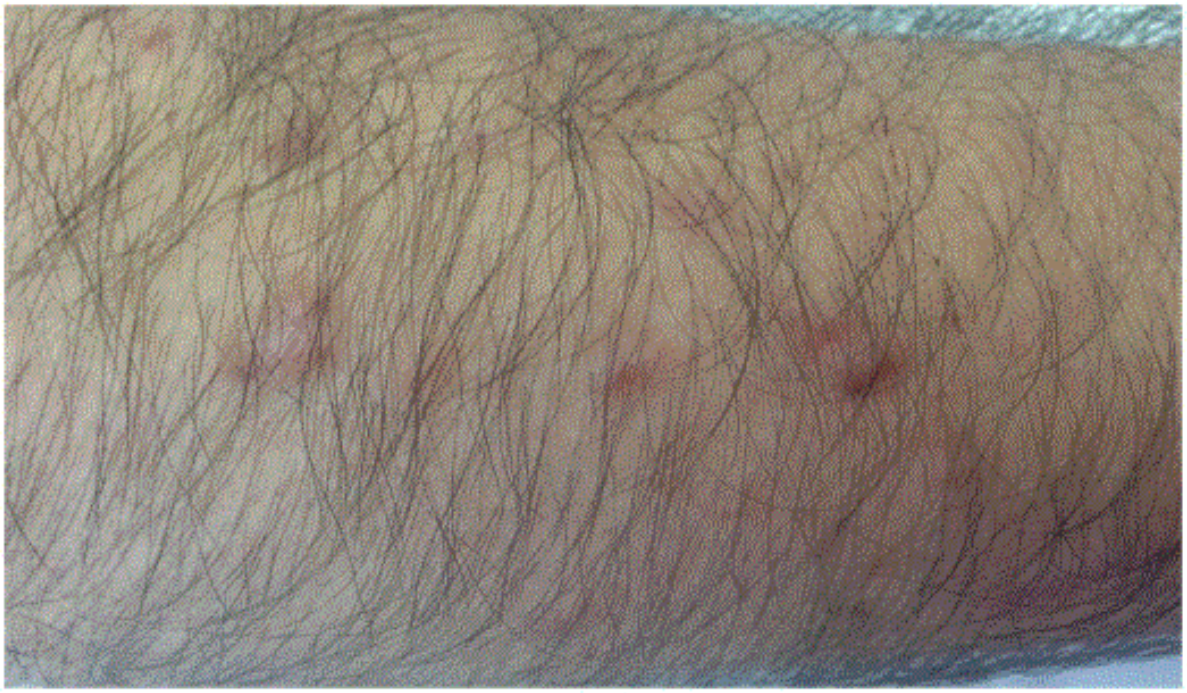

Figure 2: Papulonodules 4-8 millimeters to 1 cm reddish-brown lesions, affecting over lower limbs.

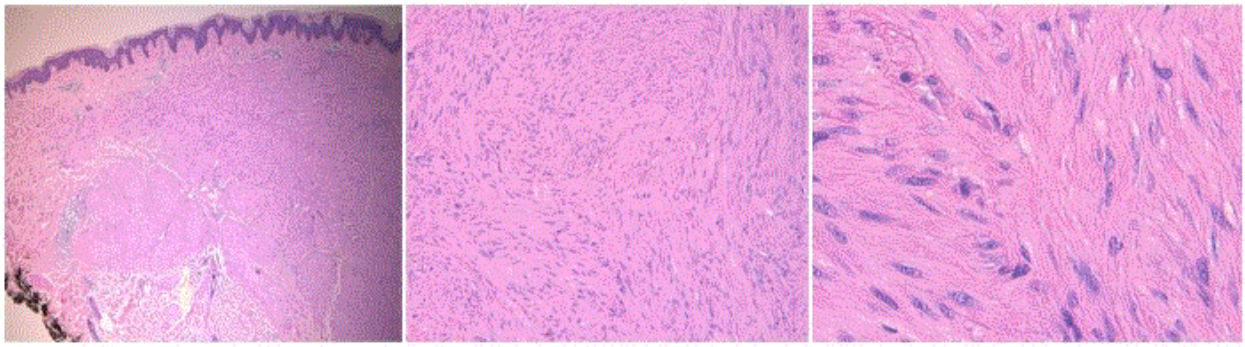

Figure 3: (a) (H&E, x4) multiple intersecting fascicles of fusiform shaped cells with ample eosinophilic cytoplasm, (b) (H&E, x10) multiple intersecting fascicles of fusiform shaped cells with ample eosinophilic cytoplasm, (c) (H&E, x40) Multiple Cigar shaped nuclei with perinuclear vacuoles and interlacing bundles of smooth-muscle fibers.

And by knowing that cutaneous piloleiomyomas can be associated with some syndromes, a blood workup was ordered for evaluation of complete blood count (CBC) and biochemistry (BUN, creatinine and electrolytes) as well as urine analysis and urine cytology. All the laboratory workup came up as normal. Also, an ultrasound of the kidneys was done which showed two complicated cysts in the left kidney, one in the upper pole with the cysts showing echogenic content and calcifications and one in the lower pole (Figure 4). Therefore, a CT scan was done to assess the complicated cysts in the left kidney and it showed two large malignant multi-cystic masses in the left kidney with thick septations, calcifications and soft tissue components (Bosniak IV). The right kidney showed also an exophytic heterogeneous solid lesion of its anterior lip (Figure 5). All these findings were highly suggestive of renal carcinoma.

Patient was scheduled for total left nephrectomy and the pathology showed Clear cell carcinoma of the kidney with no evidence of capsular invasion.

Then, a right partial nephrectomy was done after complete recovery of the first surgery and the biopsy also showed Clear cell carcinoma; which led us to the diagnosis of Hereditary Leiomyomatosis Renal Cell Cancer (HLRCC) or what is known as REED syndrome. Two months after recovery, the patient came for follow-up with a quasi-

disappearance of the lesions with only post inflammatory hyperpigmentation remaining.

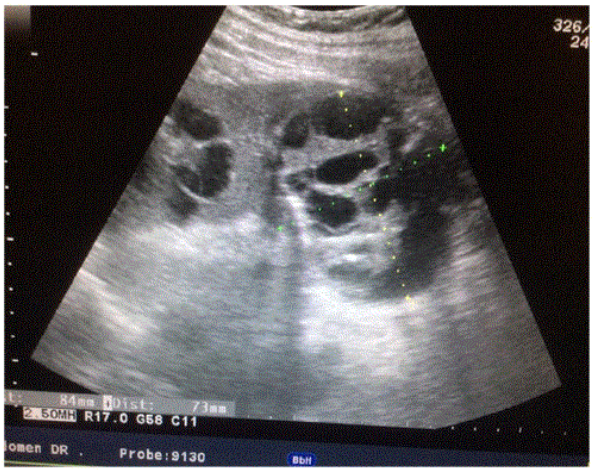

Figure 4: Two complicated cysts in the left kidney.

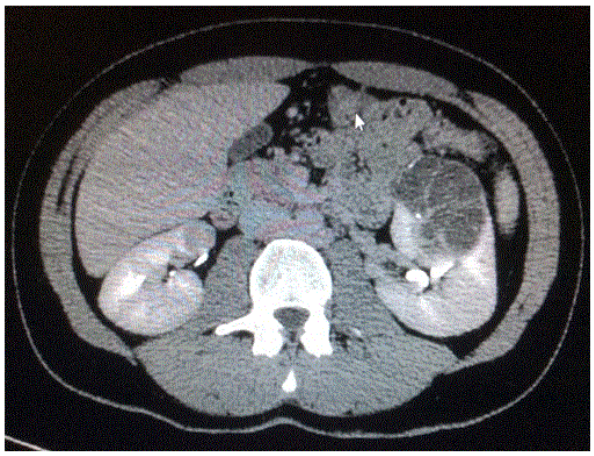

Figure 5: Exophytic heterogeneous solid lesion of its anterior lip in right kidney.

Discussion

In 1854, Virchow was the first one to describe cutaneous leiomyomas as a rare, benign smooth muscle tumor of the skin [1]. This is the same scientist that his work led to the discovery of virchow's node and virchow triad. Cutaneous leiomyomas originating from the arrector pili muscles became known as piloleiomyomas [3]. These lesions are sensitive to touch and cold temperatures and, in rare cases, may be painful.

A century after Virchow's first explanation, it was suggested that those leiomyomas can be present in families [4].

However, acquired cutaneous leiomyomas are the most commonly seen in literature [5]. Transmission of this disease is autosomal dominant with incomplete penetrance [6], appearing mostly in early adulthood. It is a disease of both genders, where affected women can develop uterine leiomyomas, a syndrome called "multiple cutaneous and uterine leiomyomatosis" also known as familial leiomyomatosis cutis et uteri or REED syndrome. Affected males can develop renal cell cancer and this has been named hereditary leiomyomatosis and renal cell cancer [5]. The age-of-onset of cutaneous leiomyoma ranged from 10 to 47 years of age, with a mean age of 25 years [2]. Genetic testing revealed that a loss of function mutation in the gene encoding fumarate hydratase (FH) on chromosome 1q42.3–43 was responsible of this syndrome [7]. FH is an essential enzyme for the conversion of fumarate to malate in the Krebs cycle. Fumarate accumulates due to loss of FH activity and the loss of FH function, impairs the Krebs cycle. Thereby, high fumarate levels inhibit HPH (hypoxia inducible factors prolyl hydroxylase) enzyme, therefore, leading to upregulation of HIF (hypoxia inducible factors) with concomitant increase of hypoxia response genes like vascular endothelial growth factors (VEGF) and glucose transporter-1 (GLUT-1), which will lead to more angiogenesis with a resultant higher risk of malignancy [8].

The differential diagnosis of cutaneous leiomyomas can be broad with non-specific appearance of classically painful solitary lesions. This includes the list of painful papulonodules tumours such as eccrine spiradenoma, neuroma, dermatofibroma, angiolipoma, neurilemmoma, endometrioma, glomus tumor and granular cell tumor. However, multiple cutaneous leiomyomas, specifically piloleiomyomas, tend to have a distinct clinical appearance.

Histopathological findings include, tumors typically centered within the reticular dermis, with focal extension into the subcutaneous fat in some cases with constant interlacing bundles or irregular collections of elongated cells with brightly eosinophilic cytoplasm and blunt-ended or cigar shaped nuclei. Mitotic figures are only very rarely seen. Tumor cells are usually uniformly positive for SMA, calponin, desmin and h-caldesmon. Histopathological differential diagnosis includes dermatofibroma and neurofibroma. Discrepancy from dermatofibroma is provided by the leiomyoma's uniform cell content and configuration in addition to desmin and SMA positivity. Cellular neurofibroma is S-100 protein positive and lacks the eosinophilic cytoplasm, myofibrils and blunt-ended nuclei of leiomyoma. Differentiation from cutaneous leiomyosarcoma is based on the presence of mitoses and the usually greater nuclear pleomorphism in the latter tumor. However, the clinical history, particularly in cases with multiple lesions, often makes the diagnosis straightforward.

Although renal cell carcinoma is a part of the triad, it will not develop in all individuals with this syndrome. Only 10-16% of individuals with cutaneous leiomyomas had a renal tumor at the time of imaging [9]. Most are unilateral, solitary & of an aggressive type, however our patient had a more aggressive disease with bilateral and multifocal kidney involvement.

Conclusion

Treatments for the isolated cutaneous leiomyomas are largely dictated by the patient's degree of skin discomfort. Options include surgical excision, cryoablation, CO_2 laser ablation and medications such as calcium channel blockers or alpha blockers. In addition, botulinum toxin has also been shown to decrease the intensity & frequency of the pain caused by the leiomyomas.

As for the hereditary leiomyomas, studies have shown that early hysterectomy or nephrectomy may be the treatment of choice because of their aggressive nature, as we have seen in our patient.

References

1. Stewart L, Glenn G, Toro JR (2006) Cutaneous leiomyomas: A clinical marker of risk for hereditary leiomyomatosis and renal cell cancer. Dermatol Nurs 18: 335-341.
2. Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, et al. (2003) Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet 73: 95-106.
3. Fisher WC, Helwig EB (1963) Leiomyomas of the skin. Arch Dermatol 88: 510-520.
4. Kloepfer HW, Krafchuk J, Derbes V, Burks J (1958) Hereditary multiple leiomyoma of the skin. Am J Hum Genet 10: 48-52.
5. Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, et al. (2012) Fitzpatrick's Dermatology in General Medicine. McGraw Hill, USA.
6. Fernandez-Pugnaire MA, Delgado-Florencio V (1995) Familial multiple cutaneous leiomyomas. Dermatology 191: 295-298.
7. Alam NA, Olpin S, Leigh IM (2005) Fumarate hydratase mutations and predisposition to cutaneous leiomyomas, uterine leiomyomas and renal cancer. Br J Dermatol 153: 11-17.
8. Sudarshan S, Linehan WM, Neckers L (2007) HIF and fumarate hydratase in renal cancer. Br J Cancer 96: 403-407.
9. Pithukpakorn M, Toro JR (1993) Hereditary Leiomyomatosis and Renal Cell Cancer. In: Pagon RA (Eds.) Gene Reviews. University of Washington, Seattle, USA.