Hereditary Leiomyomatosis: Report of 3 Sisters

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Received Date: 25 February, 2024; Accepted Date: 28 February, 2024; Published Date: 02 March, 2024

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ABSTRACT

Background: Cutaneous leiomyomas are rare, benign and painful smooth muscle tumors. Reed syndrome (RS) is an autosomal dominant disorder characterized by multiple cutaneous and uterine leiomyomas, with possible association with renal neoplasia.

Objective: To report the case of three sisters affected by this rare genodermatosis and review the diagnosis and management of the disease.

Case report: Three sisters aged 42, 43, and 45 years presented with complaints of isochromatic, hardened, and painful nodules on the chest and upper limbs. Café-au-lait spots on the trunk. All underwent hysterectomy for uterine fibroids. The biopsy of the nodules revealed piloleiomyoma.

Discussion: RS is an underdiagnosed disease. Early diagnosis may delay gynecological complications and renal neoplasia. Regular dermatological evaluation is recommended to investigate transformation into leiomyosarcoma, along with annual screening for renal cell carcinoma.

Keywords: Leiomyoma; Renal cell carcinoma; Skin neoplasms.

INTRODUCTION

Cutaneous leiomyomas are rare tumors originating from smooth muscle, subdivided according to their origin: Angioleiomyoma - originating from the middle layer of blood vessels; Dartoid or genital leiomyoma - arising from smooth muscle of the scrotum, vaginal lips or nipples; Piloleiomyoma - arising from the arrector pili muscle. The last two subtypes’ subtypes are often painful, causing discomfort upon touch and exposure to cold. Due to its rarity, the prevalence is still unknown, but it is more common in adults, with no distinction between sexes[1].
Piloleiomyomas may arise sporadically or be related to a genetic syndrome. It is estimated that 89% of patients with multiple leiomyomas have a heterozygous mutation in the Fumarate Hydratase (FH) gene, an enzyme involved in the Krebs cycle. Of these, 85% also have the Reed Syndrome (RS), characterized by cutaneous and uterine leiomyomatosis. In these cases, symptoms manifest early, around the age of 25, and often lead to hysterectomy in 50% of patients before the age of 35\[^2\]. Among those affected by the mutation, 15% develop an aggressive variant of renal cell carcinoma, with 50% being diagnosed late with distant metastases. This association, primarily reported in 2001, led to the syndrome being termed Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)\[^1,3\].

The aim of this study is to report cases of three sisters affected by this rare genodermatosis and to review the literature regarding the diagnosis and management of affected patients given the potential severity and underdiagnosis of the condition.

**CASE REPORT**

**Case 1**

A 42-year-old woman presented to the dermatology outpatient clinic complaining of progressively appearing lesions on her trunk for the past 10 years, which were painful to the touch of clothing and contact with cold water. She had normochromic, hardened and painful nodules on the upper chest and upper limbs, as well as café-au-lait spots. She underwent hysterectomy for uterine myomatosis at the age of 35 (Figure 1). Biopsy revealed Piloleiomyoma (Figure 2).

![Figure 1: Patient 1. Brownish nodules and papules on the right upper limb](image)
Case 2

A 43-year-old woman sought medical attention due to the appearance of disseminated nodules over the past 8 years, which were painful to the touch and contact with cold water. On examination, there were hyperchromic and normochromic papules and nodules on the upper limbs, face, neck, abdomen, and back. She underwent hysterectomy for uterine fibroids at the age of 30 (Figure 3). Biopsy findings were consistent with piloleiomyoma. She received counseling regarding disease progression and opted for clinical follow-up without surgical treatment.
Case 3

A 45-year-old woman accompanied her sister to a dermatology appointment and reported experiencing the same symptoms. She noticed the appearance of disseminated and painful papules 4 years ago. She underwent excision of one of the lesions, located on the breast, confirming piloleiomyoma. She had hyperchromic and normochromic papules and nodules on the trunk, breasts, and upper limbs (Figures 4 and 5). She underwent hysterectomy at the age of 35 for uterine fibroids.

Figure 4: Patient 3. Brownish papules on the neck

Figure 5: Brownish nodules and papules on the back, affecting all three sisters reported in the case

They reported that the mother and son of patient 3 exhibited similar symptoms. Initial imaging studies did not reveal evidence of renal involvement. Patients in Cases 1 and 3 underwent excision of the most painful lesions and were treated with Gabapentin, showing symptomatic relief.

DISCUSSION

Typically, piloleiomyomas manifest as well-defined erythematous-brown nodules that are painful, mainly on extensor surfaces, trunk, face, and neck, as well as genitals and nipples. The origin of the pain is not clear, whether it arises from smooth muscle contraction or compression of nerves at the periphery of the lesion[2]. Histologically, it presents as a tumor composed of intertwined smooth muscle fibers, located in the dermis amidst collagen fibers, adjacent to the erector pili muscle, with dermoscopic patterns varying among patients and lesions, lacking specific standards, and sometimes resembling dermatofibromas[2,4].

Multiple cutaneous leiomyomas, associated with uterine fibroids, represent Reed Syndrome (RS), a rare autosomal dominant genodermatosis with incomplete penetrance, also described as leiomyomatosis cutis et uteri or as part of Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC), following the discovery of its
association with renal cell carcinomas. Molecular analysis showing enzyme FH activity of less than 60% is indicative of RS, with mutation detection being the only definitive criterion. However, due to limited accessibility, this test was not conducted for these patients. It is described that the presence of 1 major criterion or 2 minor criteria strongly suggests the diagnosis. Major criteria consist of multiple cutaneous leiomyomas with histological confirmation of at least one; family history plus one minor criterion. Minor criteria include severely symptomatic uterine leiomyomas before 40 years; histologically confirmed isolated cutaneous leiomyoma; onset of papillary type 2 renal cell carcinoma before 40 years of age\textsuperscript{2,3,5}. Our patients meet the clinical criteria for Hereditary Leiomyomatosis.

The management is complex, with no known cure. Lesions can be removed by excision, electrocauterization, CO\textsubscript{2} laser, or cryotherapy. The choice is based on the extent, experience of the professional and characteristics of the patient's skin. Some report satisfaction with the use of makeup and symptomatic treatments, including nifedipine (10mg 3-4 times a day), nitroglycerin (0.8-1.6mg on demand), and doxazosin (1mg per day). Secondary options in monotherapy or combination include gabapentin, pregabalin, duloxetine, and topical anesthetics. Lesions may recur in at least half of the patients between 6 weeks and 15 years\textsuperscript{2,3,6}. Patients 1 and 3 showed a good response to gabapentin use and requested excision of the most aesthetically displeasing lesions.

Recent studies reveal that the number of patients with RS is underdiagnosed, potentially resulting in more delayed diagnoses of renal neoplasia and gynecological complications\textsuperscript{3,5,6}. Annual or biennial dermatological evaluations are recommended to investigate transformations into leiomyosarcoma. Annual gynecological assessment is suggested, with hysterectomy often required early, as observed in the three sisters\textsuperscript{6}. Early diagnosis appears to be the key to enabling effective treatment of renal cell carcinoma, with annual screening recommended, although there are currently no studies demonstrating its impact on life expectancy\textsuperscript{6}.

In conclusion, when benign skin tumors are suspected, piloleiomyoma should be considered among the differential diagnoses, as it can mimic other lesions such as lipoma, neurofibroma, dermatofibroma and acrochordon. Given the rarity of this condition, its diagnosis warrants thorough investigation, particularly for associated gynecological and renal conditions. Therefore, clinicians should remain vigilant and include piloleiomyoma in their differential diagnosis to ensure timely and appropriate management for affected individuals.

Conflict of Interest Statement and Funding Statement

The authors have no conflicts of interest to declare. There were no external funding sources.

REFERENCES


