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Reed's Syndrome

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Abstract

Go to:

Multiple cutaneous and uterine leiomyomatosis (MCUL), also known as Reed's syndrome, is a rare genodermatosis, with an autosomal dominant pattern of inheritance. It results from a germline heterozygous mutation of fumarate hydratase gene, that is classified as a tumor suppressor gene. Hereditary leiomyomatosis and renal cell cancer is characterized by the association of MCUL with renal cell carcinoma. We report a case of a 57-year-old woman, with multiple cutaneous leiomyomas as the presenting sign of Reed's syndrome.

Keywords: *Fumarate hydratase*, *leiomyomatosis*, *renal cell cancer*

What was known?

Reed's syndrome is a rare genodermatosis characterized by multiple cutaneous leiomyomas and uterine leiomyomas in women. When presenting with renal cell carcinoma, it is labeled as hereditary leiomyomatosis and renal cell cancer.

Introduction

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Reed's syndrome is a genodermatosis reported in approximately 200 families worldwide.[1] In both, multiple cutaneous and uterine leiomyomatosis (MCUL), and hereditary leiomyomatosis and renal cell cancer (HLRCC), successive generations develop leiomyomas through an autosomal dominant pattern of inheritance.[2] They result from a germline heterozygous mutation of fumarate hydratase (FH) gene on chromosome 1q42.3–q43. FH gene encodes the fumarate enzyme, which converts fumarate to malate in the Krebs cycle.[3]

Case Report

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A 57-year-old woman presented with a 10-year history of multiple skin lesions, intermittently painful, especially with cold and pressure. Physical examination revealed multiple erythematous-to-brownish papules and nodules, with a smooth surface, grouped in the upper back [Figure 1]. The patient's past medical history was significant for a hysterectomy, due to uterine leiomyomas, 11 years ago. Concerning family history, she had a sister with both skin and uterine leiomyomas. A biopsy of a papule from her back was taken, and the histological examination revealed a leiomyoma [Figure 2]. Immunohistochemistry showed positivity for smooth muscle actin [Figure 3].

Clinical and histological findings combined with surgical and family history suggested Reed's syndrome, and a genetic test was conducted. The result was a heterozygous deletion of FH exon, confirming the diagnosis of Reed's syndrome.

Given this, the patient underwent tomographic examination, which showed multiple renal cysts, the largest with 17 mm diameter, located on the middle third of the left kidney. No evidence of renal carcinoma was found. The patient was medicated with oral nifedipine and topical capsaicin, resulting in symptomatic improvement.

Patient's sister and daughter were also referred to genetic testing and counseling.

Discussion

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MCUL is a rare syndrome, with characteristic clinical expressions. Cutaneous leiomyomas are often the first manifestation of the disease, presenting at a median age of 25 years, but the majority appear at the age of 40.[4] They appear as skin-colored or pink-brown papules or nodules, often associated with pain and paresthesias.[5] These lesions are usually located in the trunk, extremities, and occasionally in the face and tend to increase in number and dimension with aging. A pseudo Darier sign may occur, which is a transient piloerection or elevation of the lesion induced by rubbing.[6] Although it is rare, leiomyomas can degenerate into leiomyosarcomas.[7] Treatment of leiomyomas depends on the number, extension, and symptomatology. For single and small lesions, surgical excision is an option, but camouflaging the area and avoiding exposure to cold may be sufficient. For extensive and more symptomatic cases, treatment with calcium-channel blockers such as nifedipine, alpha-adrenergic-blocking agents, or gabapentin can be tried. Destructive therapies such as cryotherapy, electrodessication, and carbon dioxide laser ablation may also be employed.[8]

Uterine leiomyomas are present in almost all women at a median age of 30 year and can cause dysmenorrhea, menstrual irregularities, and menorraghias. Concerns about fertility emphasize the importance of an early diagnosis, allowing a proper counseling to female patients.[9]

In HLRCC, renal tumors are usually aggressive, occurring in 15% of the cases, at a median age of 44 year. Papillary type 2 renal cell carcinoma is the most frequent subtype. The patient can be asymptomatic or can complain about lumbar pain and hematuria. Annual renal imaging should be recommended, and the modalities of choice are magnetic resonance imaging and/or computerized tomography.[8]

It is noteworthy that the incidence of benign renal cysts is high in HLRCC patients (36%), compared to the general population (4.6%–8.2%).[10]

Conclusion

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When a patient presents with cutaneous leiomyomas, it is important to perform a complete history, including family and surgical antecedents, and physical examination. If Reed's syndrome is suspected, female patients should be referred to gynecologist. As uterine leiomyomas can reduce fertility, this strategy allows for early family planning. Genetic testing and counseling should also be offered, including family members. All the patients should be screened for renal cell carcinoma every 12 months to anticipate the detection and treatment of renal cell carcinoma.[8]

This case highlights the importance of skin lesions as a diagnostic clue for systemic diseases. It is essential to recall the correlation between these cutaneous lesions and renal cell carcinoma, to identify individuals with HLRCC early. A prompt diagnosis enables the genetic counseling of the patient and his relatives, through a multidisciplinary approach, allowing the early detection of the underlying malignancies - renal cell carcinoma and leiomyosarcoma.

Considering previous reports, Reed's syndrome also seems to be associated with benign renal cysts. Further research is needed to determine whether this association is coincidental or not and if it be, it may be a predisposing factor to renal cell carcinoma.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will

not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest There are no conflicts of interest.

What is new?

Patients with Reed1s syndrome may be predisposed to develop renal cysts.

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Figures and Tables

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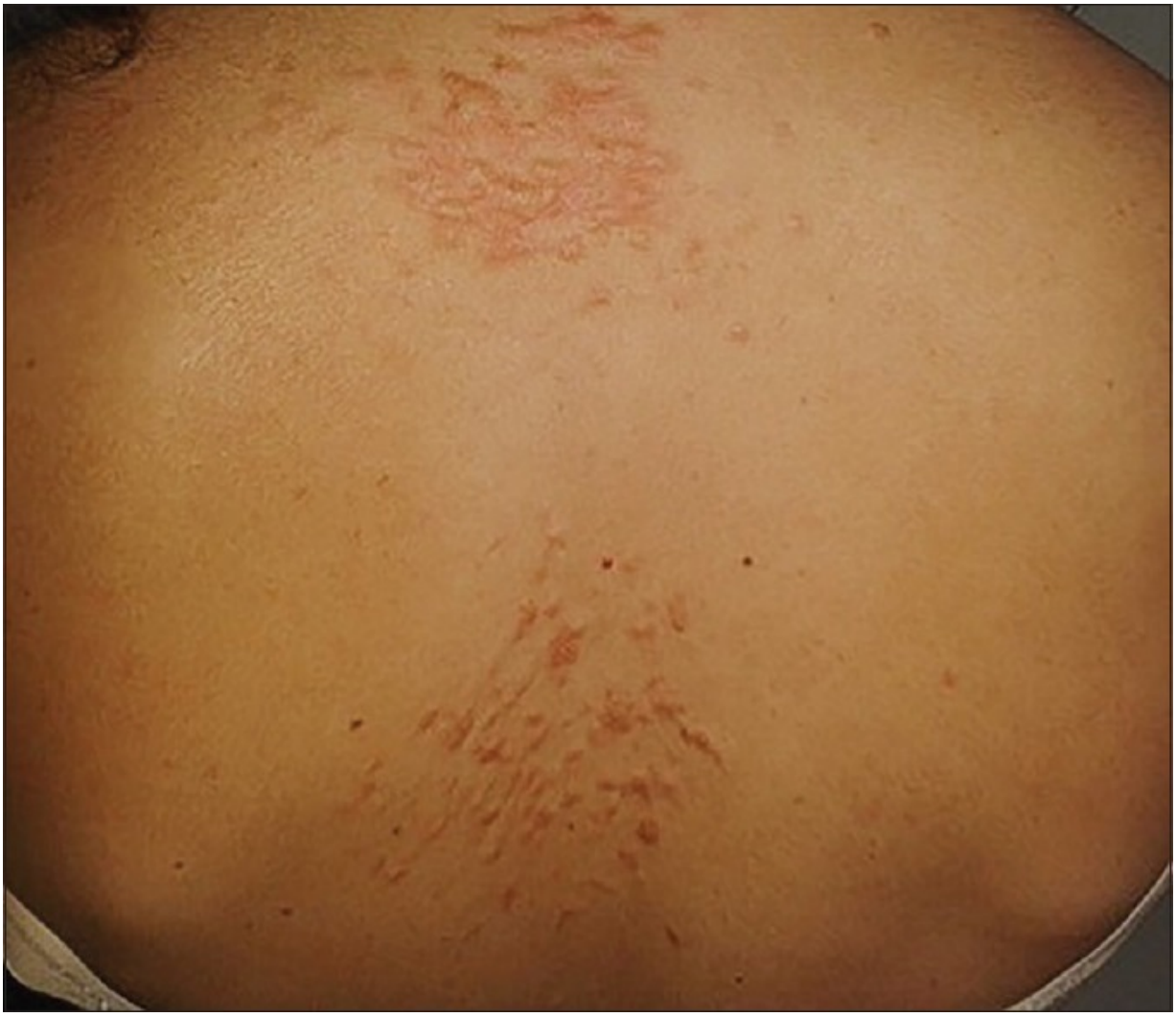
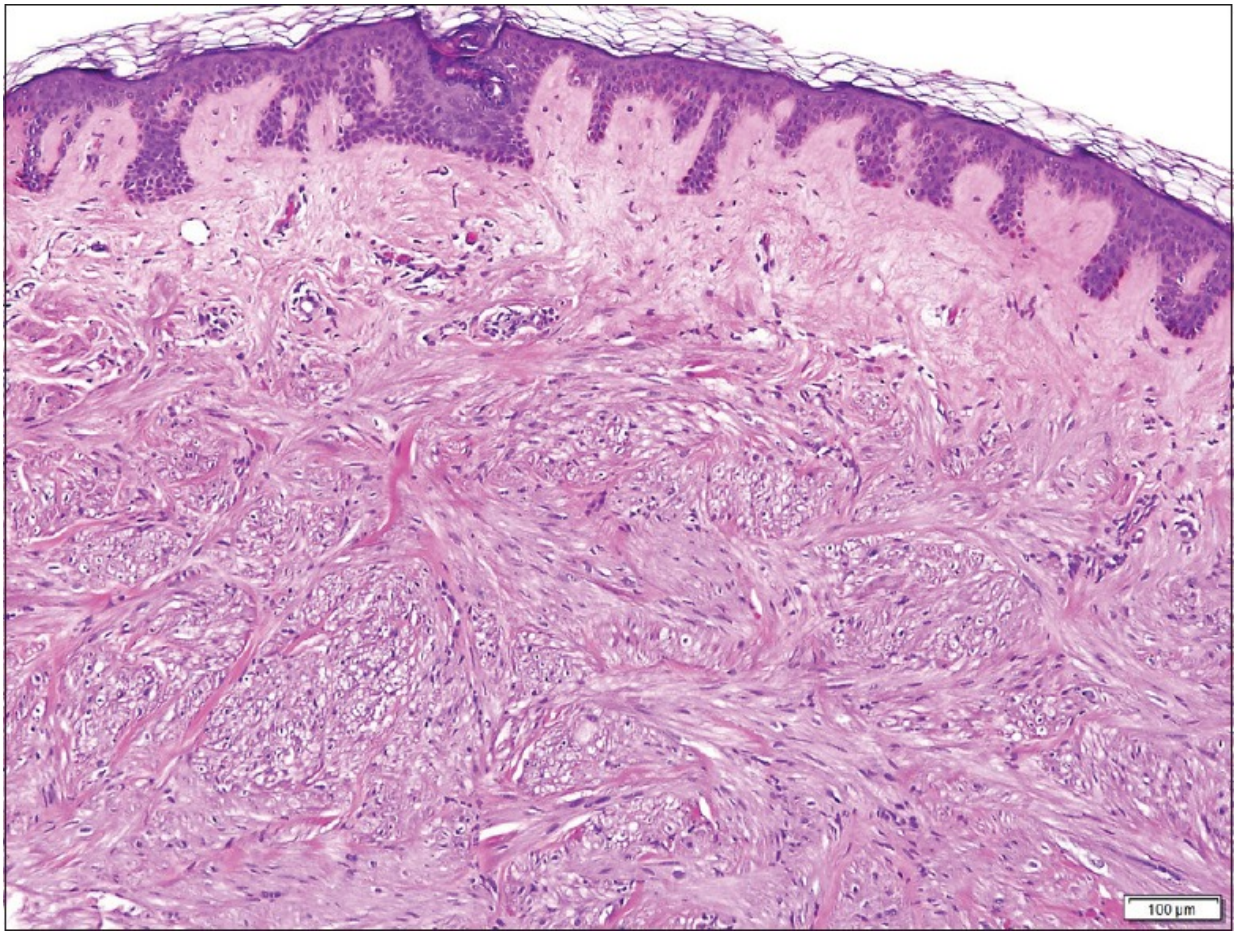
Figure 1



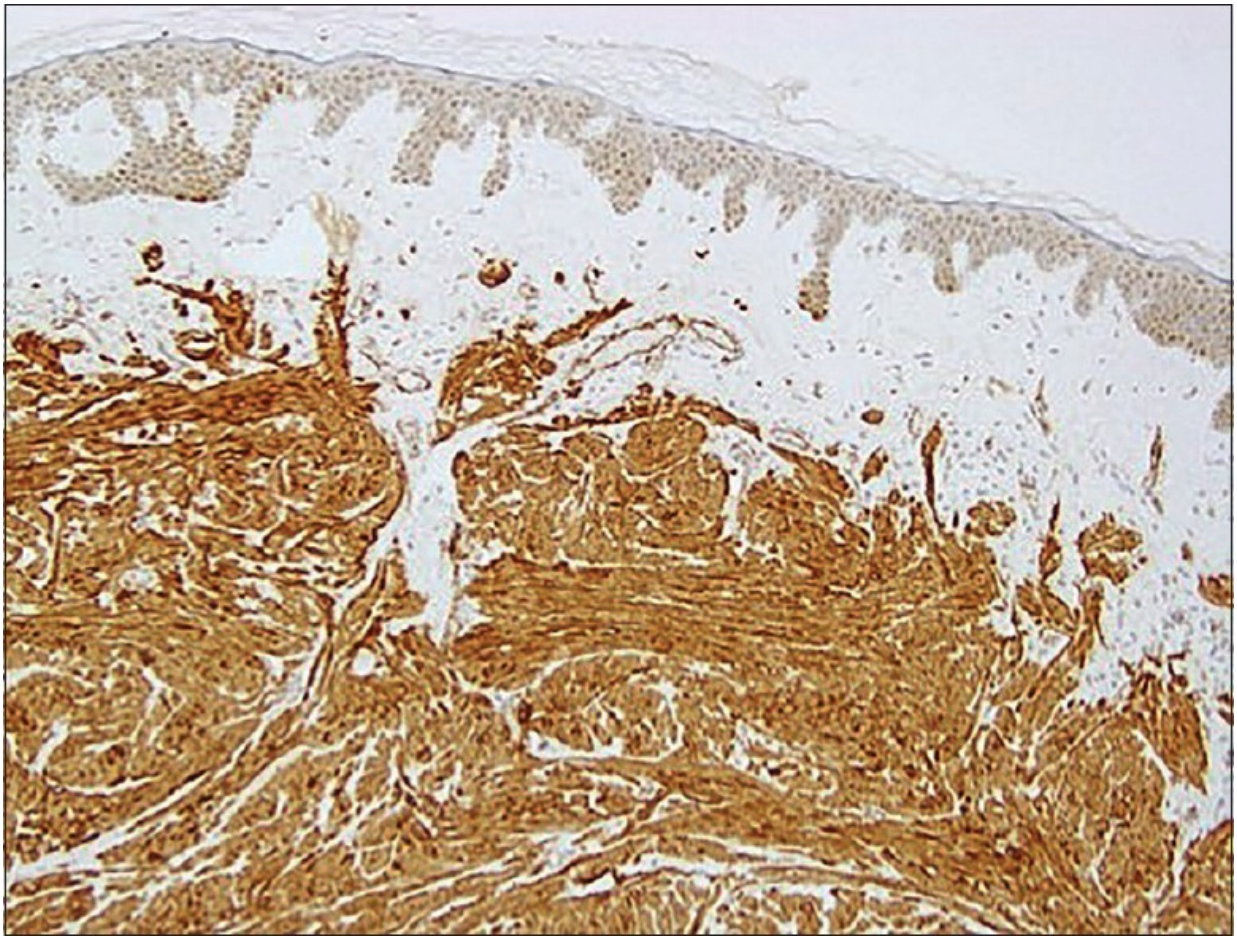
Cutaneous leiomyomas grouped in the upper back

Figure 2



Cutaneous leiomyoma (H and E, ×100)

Figure 3



Cytoplasmic expression of smooth muscle actin (Immunohistochemistry, ×100)