# Reed's Syndrome - A Rare Case of Multiple Cutaneous and Uterine Leiomyomatosis With Renal Cyst

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Sir,

Reed's syndrome is characterized by coexistence of benign smooth muscle growths of skin and uterus, first described by Reed *et al*. in 1973.[1] Cutaneous leiomyomas are benign smooth muscle tumour, classified into three types namely piloleiomyomas, genital leiomyomas, and angioleiomyomas that originate from the arrector pilli muscles, dartos muscle, and smooth muscle vasculatures, respectively.[1] Herediatary leiomyomatosis and renal cell carcinoma (HLRCC) is a variant of Reed's syndrome associated with renal cell carcinoma.[2] Reed's syndrome is an autosomal dominant disorder caused due to heterozygous mutation in the fumarate hydratase gene located on chromosome 1q42.3-q43.[2] However, sporadic cases of Reed's syndrome have been reported only rarely in India.[3,4]

We report a case of a 53-year-old female presented with 3 years history of multiple painful skin-coloured elevated lesions over the right shoulder and arm. On clinical examination, multiple superficial, dusky pink to brown-colored papules and nodules were present in a dermatomal pattern over the right scapular area, right shoulder, and lateral aspect of the right arm [Figure 1]. The lesions were associated with severe bouts of pain every 10–15 minutes which radiated toward the forearm and hand. The pain was aggravated by touch, pressure, and exposure to cold. The patient also suffered from irregular menstrual periods for the past 4 years. No history of similar illness was present among family members.

Histopathology of cutaneous nodules revealed uniform interlacing fascicles of dermal spindle-shaped cells with bright eosinophilic cytoplasm [Figure 2a], blunt-ended or "cigar-shaped" nuclei without nuclear atypia, mitotic figures, and pleomorphism [Figure 2b]. Therefore, the patient was screened for Reed syndrome. Ultrasonography of abdomen and pelvis revealed multiple cervical and subserosal uterine fibroids [Figure 2c]. Computed tomography scan of abdomen revealed a single, discrete simple renal cyst of size approximately 4cm × 4cm over the left kidney [Figure 2d]. Genetic studies of the patient and family screening could not be done due to resource constraints.

Based on above findings, a diagnosis of Reed's syndrome with renal cyst was made. The patient was started on oral nifedipine and gabapentin for pain after which there was a dramatic improvement in pain control. She was referred to gynaecology, plastic surgery, and urology departments for further surgical procedures of uterine and cutaneous leiomyomas and renal cyst.

Cutaneous leiomyomas are the principal dermatological manifestations of Reed's syndrome.[5] Piloleiomyomas are the most common type of cutaneous leiomyomas which appear as skin coloured to pink-brown, asymptomatic to tender papules or nodules of size approximately 0.2cm–2cm.[5] Almost 90% of the cutaneous lesions are painful with cold, pressure, and stress being the triggering factors for pain.[6] Suggested pathogenesis of pain may be due to local stimulation of peripheral cutaneous nerve or by ischemia caused by contraction of local smooth muscles.[6] They may appear as solitary or multiple lesions usually located over extremities, trunk, neck, and face.[7] They may be present in a linear manner or dermatomal distribution or even disseminated in nature.[7] In the present case, multiple lesions were located over the right shoulder and right scapular area in a dermatomal pattern associated

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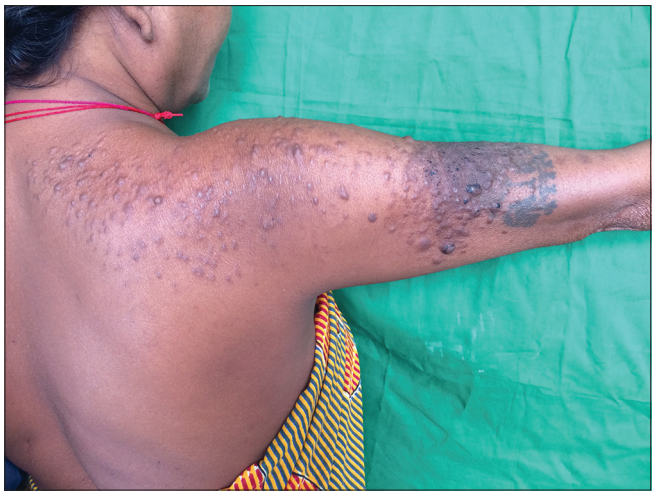

**Figure 1: Dusky pink to brown-colored papules and nodules present in a dermatomal pattern over the right scapular area, right shoulder, and lateral aspect of right arm**

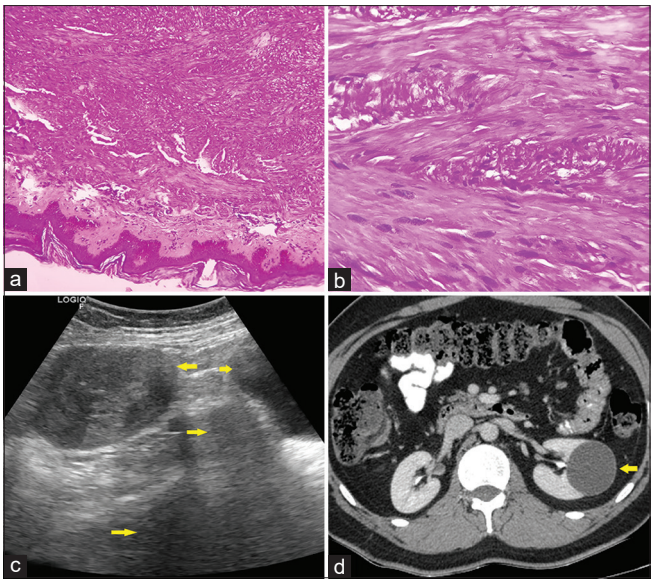


**Figure 2: (a) Histopathology showing uniform interlacing fascicles of dermal spindle-shaped cells with brightly eosinophilic cytoplasm (H and E, 10×). (b) Blunt-ended or "cigar-shaped" nuclei without nuclear atypia, mitotic figures, and pleomorphism (H and E, 40×). (c) Ultrasonography showing multiple subserosal uterine fibroids (yellow arrows). (d) Computed tomography scan of abdomen revealed a single, discrete, simple renal cyst of size approximately 4cm × 4cm over the left kidney (yellow arrow)**

with pain which was being aggravated by cold and pressure. The clinical differential diagnosis of leiomyomas are other painful cutaneous tumours like angiolipoma, neuroma, eccrinespiradenoma, glomus tumour, blue rubber bleb nevus which should be ruled out by skin biopsy.[7] Treatment of cutaneous leiomyomas include surgical excision, cryosurgery, carbon dioxide laser ablation with medical management of pain using nifedipine, phenoxybenzamine , nitroglycerine, doxazocin, gabapentin, and topical analgesic orbotulinum toxin type A injection.[1] In the present case, skin lesions were associated with intense pain which was managed with a combination of oral nifedipine and gabapentin, after which there was complete subsidence of pain.

Affected females develop uterine leiomyomas which appears earlier, usually larger in size and more numerous than general population.[7] Uterine leiomyomas may present with complaints of dysmenorrhea, menorrhagia, infertility, abdominal pain, urinary frequency or a palpable abdominal mass.[7] In the present case, patient was complaining of irregular menstrual cycles since last 4 years with ultrasonography of abdomen and pelvis showing multiple fibroids.

In HLRCC, aggressive papillary type 2 renal cell carcinoma is most commonly seen with most patients being asymptomatic or complaining of hematuria or lumbar pain.[8] Renal tumors are seen in a median age of 44 years and seen in 15% cases.[8] In HLRCC patients, incidence of benign renal cysts is higher in comparison to general population.[6] Mutation of fumarate hydratase gene causes activation of the hypoxia pathway through overexpression of hypoxia-induced factors (HIF), that is, HIF 1α and HIF 2α. HIF overexpression causes upregulation of HIF targets like GLUT1 and VEGF, which results in the formation of benign renal cysts as well as renal cell carcinoma via increased angiogenesis and cell proliferation.[9] In a retrospective study conducted on 13 cases of Reed's syndrome by Collgros *et al*., nine cases were screened for renal lesions which showed benign renal lesions in four cases but none of the cases were found to be having renal cell carcinoma.[10] Salvador *et al*. reported a case of Reed's syndrome associated with benign polycystic kidney disease without any malignancy.[11] Gupta *et al*. reported a case of Reed syndrome associated with simple renal cyst.[6] Aimeida *et al*. reported a case of Reed's syndrome showing multiple renal cysts with the largest being 17mm in diameter and located in the middle third of left kidney.[8] Mandal *et al*. also found a cystic renal lesion in one family member in their case report.[7] These findings are similar to the present case in which a simple renal cyst of size approximately around 4cm × 4cm was found without any calcification or suspicious malignant findings.

To conclude, Reed's syndrome is rare and usually has an unrecognised association and is a diagnostic challenge for dermatologists.

Multiple leiomyomas in a female patient warrants screening for presence of uterine leiomyomas and any occult renal malignancy. Screening of the first-degree relatives and genetic counselling is needed for early detection of aggressive renal cell carcinoma.

Benign renal lesions in Reed's syndrome could be a coincidental finding or may subsequently undergo malignant transformation (simple cyst to complex or dysplastic cyst to malignant cyst) because of similar pseudohypoxia-driven pathogenesis in both the entities as seen by Pollard PJ *et al*.[9] Hence, these group of patients should be kept under

active surveillance with regular radiological assessment to address malignant transformation at the earliest, so that early intervention can be possible for better outcome.

## *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.

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