Reed Syndrome: A Varied Presentation

Reed's syndrome (RS) is an autosomal dominant genetic disorder characterized by cutaneous and uterine leiomyomas. We report three cases of Reed syndrome with varied morphologies or presentations.

A 38 year old female presented with multiple, painful papules and nodules since childhood. The lesions were associated with pain on cold exposure. She also reported a similar complaint in her sibling. She had history of hysterectomy four years back for uterine fibroid,which was large in size and caused heavy and irregularity of her menstrual-cycle. On examination, multiple discrete and clustered erythematous tender papules and nodules with a smooth and shiny surface were present on the left side of upper chest, arm, and extensor aspect of forearm [Figure 1]. The pseudo-Darier sign was positive on storking the lesion. Complete hemogram and biochemical tests were within normal range. Skin biopsy revealed a circumscribed tumor in dermis,comprising of inter secting fascicles of spindle-shaped cells having moderate amount of eosinophilic cytoplasm, plump,blunt-ended,and oval-shaped nuclei with vesicular chromatin and inconspicuous nuclei [Figures 2a, b and 3]. On immunohistochemistry, the cells were positive for smooth muscle actin.

Another, 72-year-old female, presented with multiple papules and nodules over her right breast for 2 year duration. Initially,the lesions were associated with occasional pruritus for which she had been using topical steroid for 5 to 6 months, without any relief. She underwent hysterectomy 35 years ago for uterine fibroid. As the patient had lost the records of it,the size and number of the fibroid could not be commented. There was absence of such complaints in her family. There were multiple skin-colored discrete papules and nodules present over the upper medial side of the right breast [Figure 4a]. The pseudo-Darier sign could be elicited on the lesion. All biochemical examinations and ultrasound of abdomen and pelvis were within normal limit. Skin biopsy showed circumscribed lesions in dermis comprised of spindle cells arranged in whorls and fascicles. Spindle cells were found with abundant eosinophilic cytoplasm and blunt-ended vesicular nuclei.

The third patient was a 48-year-old female who presented with multiple painless nodules over the left side of upper back and shoulder for 3 years. She had a history of hysterectomy 18 years back for uterine fibroid. Detailed records of her hysterectomy were not available. None of the family members had such complaints. There were multiple, discrete, hyperpigmented, and non tender nodules and plaques present over the left side of upper back and shoulder [Figure 4b]. The psedo-Darier sign was negative. All routine biochemical tests and ultrasound of abdomen and pelvis were normal. Skin biopsy showed mild hyperkeratosis,dermal tumor comprising of interlacing bundles of smooth muscle with intervening collagen.

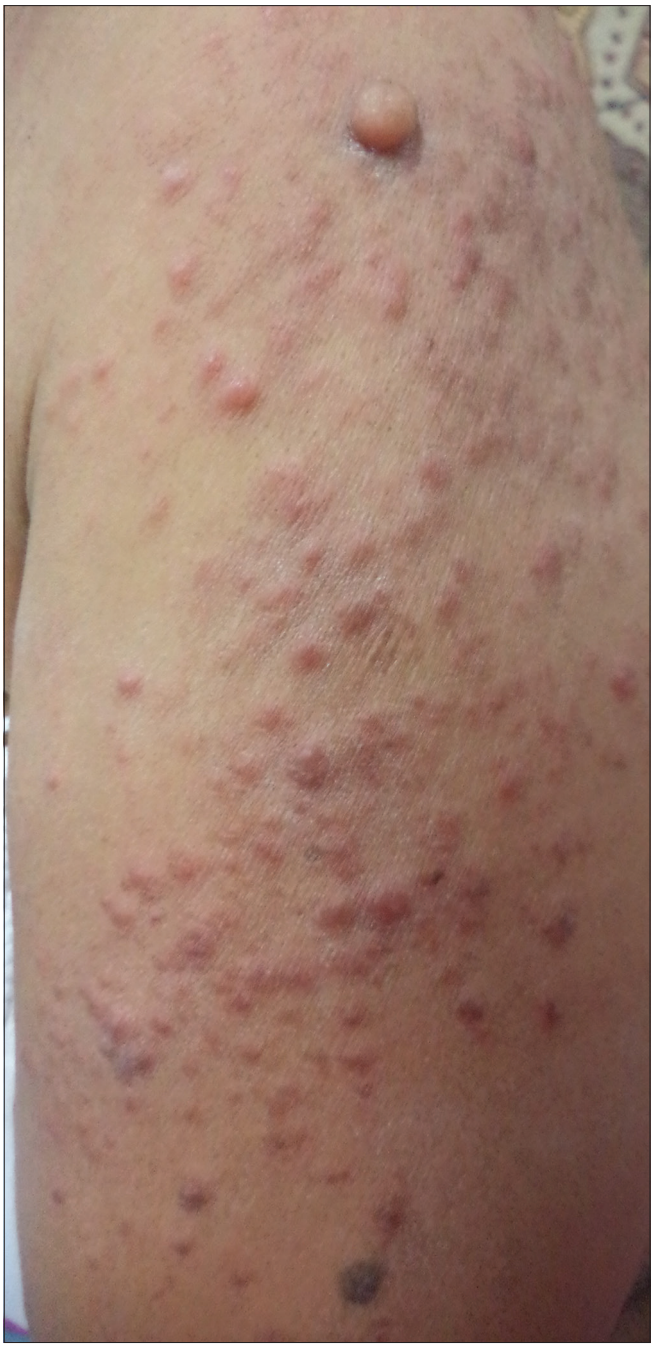

Figure 1: Multiple, discrete,and coalescing erythematous papules nodular lesions

In all three cases, histopathological reports were suggestive of piloleiomyoma and all had undergone hysterectomy for uterine leiomyoma. Although details about the fibroid was available only with the the first case,we have kept

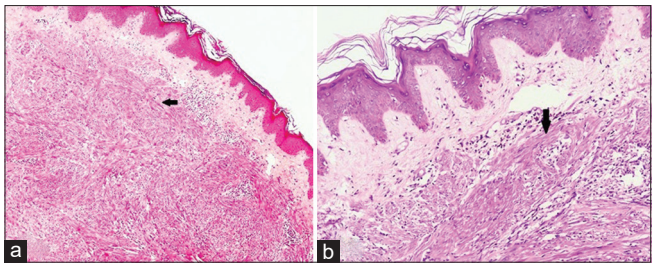

Figure 2: (a) A circumscribed lesion in the dermis comprised of interlacing fascicles of spindle cells. (H and E, x40). (b) The circumscribed dermal proliferation of spindle cells. (H and E, x100)

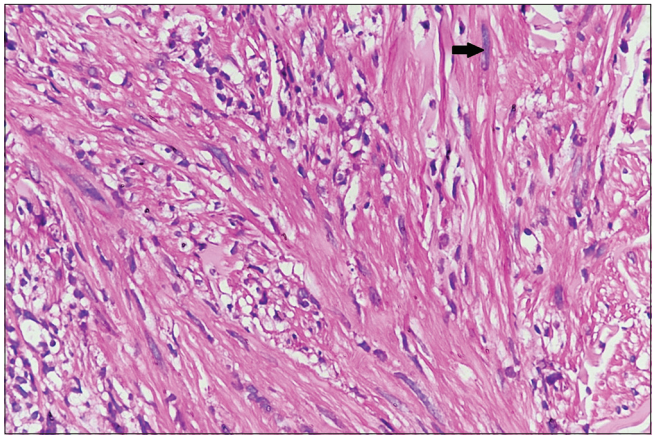

Figure 3: Interlacing fascicles of spindle cells showing fibrillar eosinophilic cytoplasm and blunt-ended cigar-shaped nuclei. (H and E, x400)

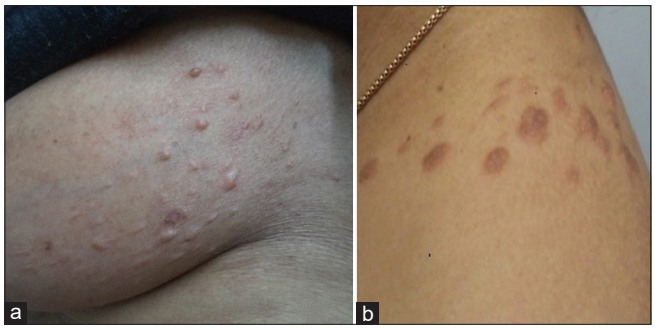

Figure 4: (a) Multiple papules and nodular lesions over the right breast. (b) Multiple,discrete,hyperpigmented,and non tender nodules and plaques present over the left side of the upper back and shoulder

a diagnosis of RS. Due to the non availability of genetic analysis at our institution and economical constraints,it could not be done. The family members of the patients were counselled about the genetic transmission of the disease.

Because of multiple lesions, surgery was not feasible;all were put on pregabalin treatment with symptomatic relief in the second patient. The first patient was lost to follow-up and the second and third patients were in follow-up.

Piloleiomyomas are benign smooth muscle tumors arising from the erector pilorum muscles in the skin and affects males and females in their third decade of life. Their association with uterine fibroids, is referred to as RS or familial leiomyomatosis cutiset uteri.

RS was initially described in 1954 in a 45-year-old woman[1] and have been determined to have mutations in the fumarate hydratase gene,a Krebs cycle enzyme that acts as a tumor suppressor.[2] RS is a genodermatosis reported in approximately 200 families world wide.[3] Fumarate hydratase is the enzyme responsible for converting fumarate to malate in the tricyclic carboxylic acid cycle. Fumarate hydratase acts as a tumor suppressor gene by regulating the hypoxia inducible factors (HIFs), which in increased quantities appear to be strongly associated with renal malignancies. HIF1 and 2 alpha participateas transcription factors for multiple genes, including the proto oncogenes vascular endothelial growth factor (VEGF), glucose transporter-1 (GLUT-1), platelet-derived growth factor (PDGF), and transforming growth factor alpha (TGF alpha). Under hypoxic conditions, HIF hydroxylase is unable to hydroxylate HIF. This results in elevated levels of HIF which activate the expression of its down stream genes. Patients with RS are thought to be in a pseudohypoxic state in which a build up of 2-oxoglutarate can competitively inhibit HIF hydroxylase for poorly understood reasons, thus ultimately decreasing the proteasomal degradation of HIF and leading to up regulation of its downstream protooncogenes, there by promoting tumorigenesis.[4] Affected females frequently develop uterine leiomyomas (fibroids) that are larger and more numerous and emerge earlier than those in the general population. Depending on the age of the studied individuals,79–100% of women with FH mutation have uterine leiomyomas that occur typically at the age of 20–35 years compared with around 40 years in sporadic cases.[5] The principal dermatologic manifestation of RS is the presence of cutaneous leiomyomas. Clinically,they occur as small, smooth-surfaced, skin-colored or pinkish-brown,solitary and/or multiple papules or nodules that range from 0.2 to2.0 cm india meter.[6] Cutaneous leiomyomas are divided into three categories: piloleiomyomas arising from the arrector pili muscle of the hair follicle,genital leiomyomas emerging from the tunica dartos of the scrotum and the mammary muscles of the nipples,and angioleiomyomas originating from smooth vascular muscles[7] and the lung (pulmonary lymphangio leiomyomatosis).[8] The extremities are the most frequently involved sites, particularly the extensor surfaces,followed by the trunk,face,and neck.[6] They can be asymptomatic or the lesions are often sensitive to touch,cold,emotional stress,or spontaneous pain. The pathogenesis of pain associated with these lesions is not clearly understood.It could be attributed to the local pressure exerted by the tumor on cutaneous nerves. Other hypothesis includes infiltration of mast cells or contraction of the arrector pili muscle.[6,7] A sub-sets of patients with multiple cutaneous and uterine leiomyomatosis (MCUL) also have renal cell carcinoma (RCC) and should be evaluated appropriately.RCC, the most aggressive manifestation of the disease, occurs in about 10%–16% of patients and is frequently classified as Type II papillary RCC. Since it can present at a young age and is usually more aggressive than the sporadic form,close cancer surveillance

is recommended in carriers of hereditary leiomyomatosis and renal cell cancer syndrome(HLRCC).[9] All the patients should be screened for RCC every 12 months to anticipate the detection and treatment of RCC preferably by contrast-enhanced MRI. Treatment of cutaneous leiomyoma depends upon the number of lesions and discomfort produced by it. To reduce the pain,pharmacological agents including calcium channel blockers (e.g., nifedipine), gabapentin, pregabalin, hydrobromide,nitroglycerin, phenoxybenzamine, and alpha-adrenergic receptor blockers have been tried. In addition, therapies such as cryotherapy, carbon dioxide laser ablation,iontophoresis,botulinum toxin injections,and intralesional steroid injections have been used with varying success.[10]

Because cutaneous leiomyomas are rare in the general population,their presence should elicit suspicion of underlying hereditary leiomyomatosis and renal cell cancer syndrome with further investigation warranted.When suspected, screening for RCC counseling of patients and at-risk relatives can be instituted.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Seema Rani, Singdha Saxena, Sweta Singh, Purnima Malhotra[1]

Department of Dermatology, ABVIMS DR RMLH, [1]Department of Pathology, Dr. RMLH ABVIMS, New Delhi, India

Address for correspondence:
Dr. Seema Rani,
Department of Dermatology, ABVIMS Dr. RMLH,
New Delhi - 110 001, India.
E-mail: drseemashekhar@gmail.com

References

1. Blum P, Jean L. Besnier's eruptive leiomyoma. Bull Soc Fr Dermatol Syphiligr 1954;61:349-50.
2. Emer JJ, SolomonS, Mercer SE. Reed's syndrome: A case of multiple cutaneous and uterine leiomyomas. J Clin Aesthet Dermatol 2011;12:37-42.
3. Arenas Valencia C, Rodriguez Lopez ML, Cardona Barreto AY, Garavito Rodriguez E, Arteaga Diaz CE. Hereditary leiomyomatosis and renal cell cancer syndrome: Identification and clinical characterization of a novel mutation in the FH gene in a Colombian family. Fam Cancer 2017;16:117-22.
4. Laufer CB, Green LB, Whittemore DE. A case of reed syndrome with a novel mutation in the fumarate hydratase gene. Case Rep Med 2013;2013:926896.
5. Tolvanen J, Uimari O, Ryynänen M, Aaltonen LA, Vahteristo P. Strong family history of uterine leiomyomatosis warrants fumarate hydratase mutation screening. Hum Reprod 2012;27:1865-69.
6. Garman ME, Blumberg MA, Ernst R, Raimer SS. Familial leiomyomatosis: A review and discussion of pathogenesis. Dermatology 2003;207:210-13.
7. Spencer JM, Amonette RA. Tumors with muscle differentiation. Dermatol Surg 1996;22:761-8.
8. Kogan EA, Mikhaĭlov OI, Sekamova SM, Kornev BM, Osipova IN, Osipenko VI, *et al*. Combination of pulmonary lymphangio leiomyomatosis with skin leiomyomatosis and uterine leiomyoma. Arkh Patol 2001;63:39-44.
9. Gironi LC, Pasini B, Farinelli P, Zottarelli F, Ferrando B, Valente G, *et al*. Hereditary leiomyomatosis and renal cell cancer: Do you know this syndrome? J Pathol Microbiol 2016;1:1001.
10. Yaldiz M, Metin M, Erdem MT, Dikicier BS, Kahyaoglu Z. Two sisters with Reed's syndrome: Treatment with pregabalin. Dermatol Online J 2015;21:13030/qt4wx2s2xm.

Access this article online	
Website: www.idoj.in	Quick Response Code
DOI: 10.4103/idoj.IDOJ_501_20	

How to cite this article: Rani S, Saxena S, Singh S, Malhotra P. Reed syndrome: A varied presentation. Indian Dermatol Online J 2021;12:628-30.

Received: 04-Jul-2020. **Revised:** 18-Sep-2020.
Accepted: 20-Oct-2020. **Published:** 14-Jul-2021.