**Volume 21 Number 3**
**March 2015**

**Case report**

# Reed syndrome: an atypical presentation of a rare disease.

**Jessie C. Perkins OMS IV[1], Chase Scarbrough DO[2], Dawn Sammons DO[1], Cynthia Magro MD[3]**

**Dermatology Online Journal 21 (3): 6**

**[1]Ohio University Heritage College of Osteopathic Medicine, Athens, Ohio, Oakview Dermatology, Athens, Ohio, [2]O'Bleness Health Systems, Athens, Ohio, [3]Department of Pathology & Laboratory Medicine Division of Dermatopathology, Weill Cornell Medical College of Cornell University, New York, New York.**

**Correspondence:**

Jessie Perkins, OMS IV
Ohio University Heritage College of Osteopathic Medicine
Athens, OH
Jc327009@ohio.edu
(513) 292-1798

## Abstract

Reed syndrome, also known as Multiple Uterine and Cutaneous Leiomyomas (MCUL), is an autosomal dominant defect in the fumurate hydrase gene, leading to a predisposition of leiomyomas of the skin and uterus. Patients with Reed syndrome may present with cutaneous leiomyomas, uterine leiomyomas and/or leiomyosarcomas. A 37-year-old woman presented to the dermatology clinic with several subcutaneous nodules. Punch biopsy was performed and the diagnosis of angioleiomyosarcoma with supervening degenerative changes was made. Medical history was positive for uterine leiomyomas. These concomitant findings led to the diagnosis of Reed syndrome. At the present time, genetic counseling is a suggested screening parameter for patients with multiple cutaneous leiomyomas. The superficial nature of these lesions and the low staging made surgical excision the preferred and actual treatment method. Adjunct radiation and chemotherapy have not been shown to provide clear benefit of survival. Owing to an association with renal cell carcinoma, a referral for nephrology consultation is also recommended.

## Introduction

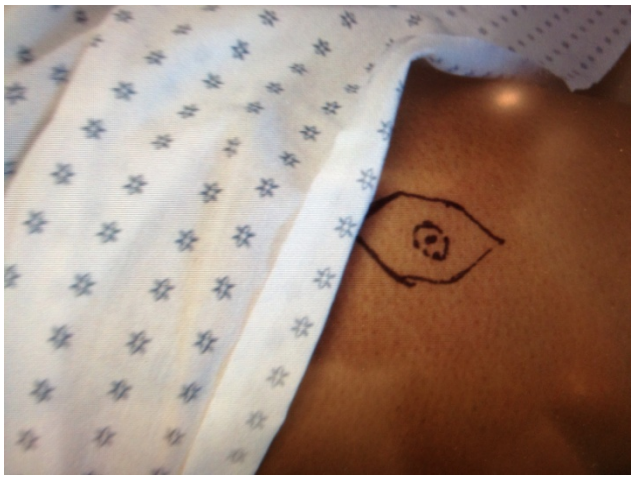
Reed syndrome, also known as Multiple Uterine and Cutaneous Leiomyomas (MCUL), is produced by an autosomal dominant defect in the fumurate hydrase gene, leading to a predisposition of leiomyomas of the skin and uterus [1, 2]. Patients with Reed syndrome may present with cutaneous leiomyomas, uterine leiomyomas, and/or leiomyosarcomas [2].

## Case synopsis

A 37-year-old woman presented to the dermatology clinic with several subcutaneous nodules. The nodules were growing in size and number, causing increasing pain and irritation with sitting. Past medical history was positive for uterine fibroid removal. Family history was positive for lung, breast, and brain cancer on the maternal side.

On examination, no cutaneous manifestations were present (Figure 1). Palpation revealed 4 distinct, firm subcutaneous nodules, semi-fixed to surrounding tissues. The nodules ranged from 0.5 to 4.5cm in size and were located in the right buttock region, left and right thighs, and left upper arm. A 4 millimeter punch biopsy was taken from the left thigh. Initial pathology report described a nodular proliferation of spindle shaped cells that appeared to have blood vessels at the epicenter. Microscopic analysis showed a very irregular growth pattern with enhanced cellularity and moderate atypia. Mitoses were scattered at 1 per square millimeter.

Individual cell necrosis was also noted. Owing to the atypical/borderline features of this lesion, the specimen was sent to a bone and soft tissue pathologist, who confirmed the diagnosis of angioleiomyomasarcoma. Excision with appropriate margins was recommended by both pathologists.



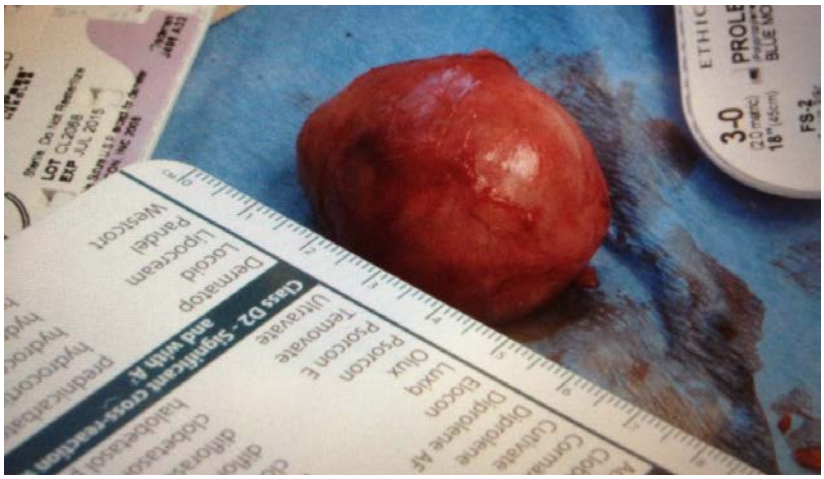


**Figure 1.** Clinical Figure of nodule revealed no cutaneous findings. Here it is marked in preparation for surgical excision. **Figure 2.** Specimen excised from left buttock region measuring 4.5 cm by 4.5 cm.

The lesion in the left buttock region measuring 4.5 cm by 4.5 cm was removed by blunt dissection and sent for pathology analysis (Figure 2). Microscopic examination of the tumor (Figure 3) showed a very extensive multinodular spindle cell tumor associated with large areas of degeneration, inflammation, and vascular ectasia. The dominant morphology was characterized by a highly cellular fascicular growth of atypical mitotically active cells, with a potentially aggressive course. There were several dilated, thrombosed blood vessels noted. Within the thrombosed lumens were atypical spindle cells that could represent reactive fibroblasts, although tumor embolization is possible. Atypical mitoses (up to five per high power field) and individual cell necrosis were present. The tumor cells were desmin and calponin positive, indicating cells of smooth muscle origin. These findings led to the diagnosis of angioleiomyosarcoma with supervening degenerative changes. The three remaining nodules were also excised with appropriate margins. These nodules were also found to be angioleiomyosarcomas with the exception of the tumor in the left upper arm. This lesion was examined and determined to be a well-differentiated leiomyosarcoma. All nodules were treated with surgical excision until margins were clear.

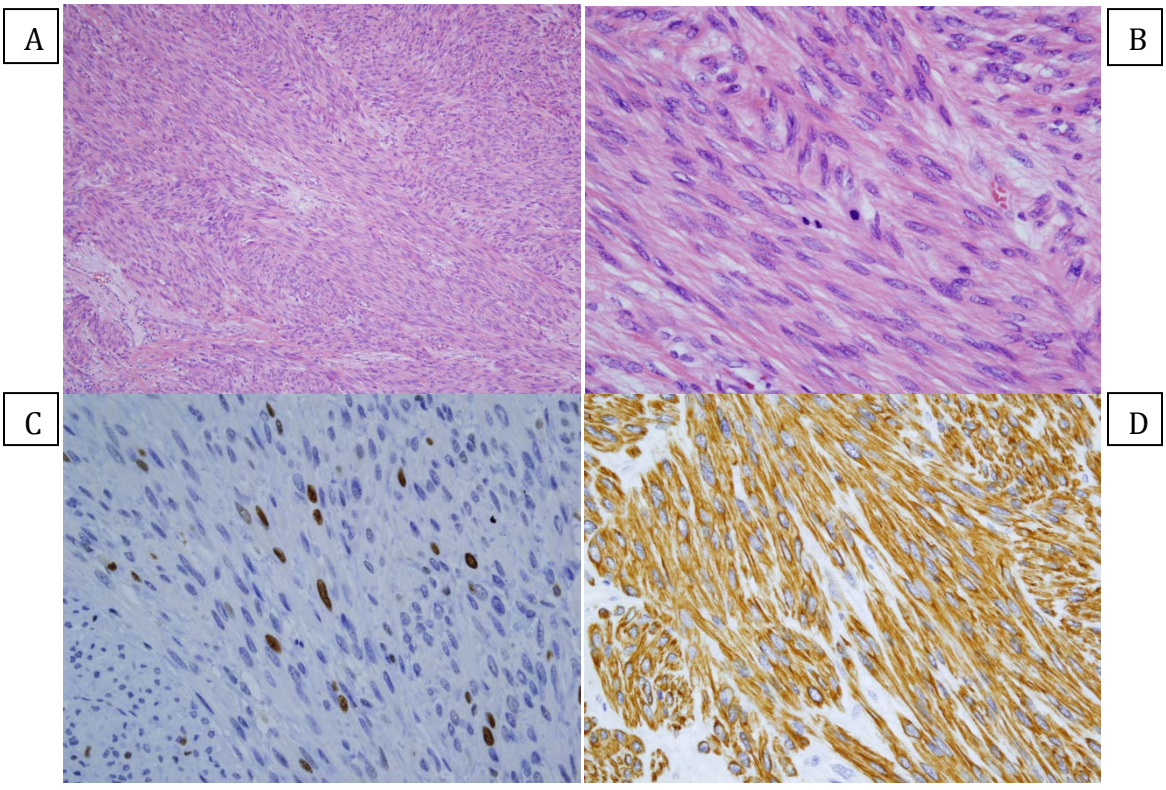



**Figure 3: A)** Specimen is remarkable for an expansile multinodular tumor composed of intersecting fascicles of atypical spindle cells. **B)** Higher power magnification demonstrates a somewhat monomorphic cell populace exhibiting distinctive blunt ended nuclear contours typical of its smooth muscle ontogeny. The cells exhibit a coarse irregular chromatin and mitoses are conspicuous. **C)** The tumor demonstrates an

intermediate proliferation index as demonstrated by nuclear staining for Ki67 amidst 15% of the neoplastic cell population. **D)** The categorization of this neoplasm as one of smooth muscle origin is revealed by the extensive staining for calponin, smooth muscle actin and desmin. Illustrated is desmin.

The patient was also seen by a local gynecologist for a chief complaint of menorrhagia. On physical exam, the patient was found to have a palpable endometrial mass. A hysteroscopy with myomectomy was performed and a sample of the mass was sent for histological evaluation. The mass was found to be an angioleiomyoma. A subsequent CT scan of the abdomen was performed and no abnormalities were identified within the renal parenchyma.

# Discussion

Multiple angioleiomysarcomas of the skin and subcutaneous tissue have been studied little, if at all. Literature review yielded few results. Of the cases that have been identified, only one was located in skin and subcutaneous tissue. Other locations included the mediastinum, lesser omentum, pelvis, lungs, kidney, and ureters [3-7].

Cutaneous soft tissue sarcomas (CSTS) were diagnosed at a rate of 24.4 per 1,000,000 person-years from 1992-2004 [30]. Of these cutaneous lesions, 2.2% were leiomyosarcomas and 1.6% angiosarcomas. Angioleiomyosarcomas were not identified as an independent category. CSTS not otherwise specified had a rate of 0.1% [30]. Incidence of CSTS was highest among African Americans; our patient is also African American [23].

In a study analyzing cutaneous soft tissue sarcomas from 1992-2004, leiomyosarcoma had a predilection for the head and neck (32.6% of cases), followed by lower extremity (24.4%), upper extremity (21.1%), and trunk (20.0%). Angiosarcoma also had a predilection for the head and neck (59.3% of cases), followed by trunk (25.4%), lower extremity (8.5%), and upper extremity (4.8%) [23]. A study looking at soft tissue sarcoma in black Africans found a peak incidence in ages 30-69, with highest frequency between 30-39 [24]. This study also found a male predominance with 55% of cases being male and 45% female [24]. However, superficial leiomyosarcomas were found to occur more often in females (64%) [23, 25, 26]. They were most commonly found on hair bearing surfaces of upper and lower extremities [22, 23, 26, 27].

Mutiple Uterine and Cutaneous Leiomyomas (MUCL) or Reed syndrome is a condition characterized by multiple leiomyomas of the uterus and/or skin. The finding of uterine leiomyomas and subcutaneous leiomyosarcoma in this patient makes the diagnosis of Reed syndrome highly likely. The cutaneous leiomyomas of Reed syndrome can arise from three sites: 1) the arrector pili muscles leading to pilar leiomyomas, 2) the genital skin and areola leading to dartoicleiomyomas, or 3) from vascular smooth muscles leading to angioleiomyomas [8]. There are currently no documented cases of angioleiomyosarcoma in relation to Reed syndrome, making this a rare and atypical presentation of the disease. About 75% of people with this condition are found to have a mutation in the fumarate hydrase (FH) gene [9].

MCUL or Reed syndrome generally presents with several firm papules and nodules, flesh to pink in color when arising from pilar or dartoic tissue or as a single nodule when arising from vascular smooth muscle [10, 2, 11]. These lesions are commonly distributed over the trunk but have been found on the temple, upper extremity, and face [2, 10, 11]. Patients with MCUL were found to have an average of 25 tumors at presentation [12]. The papules or nodules can be up to 2cm in size and are frequently associated with pain [13]. A sub-set of patients with MCUL also have renal cell carcinoma and should be evaluated appropriately. Uterine leiomyomatosis represents the other finding in MUCL, but is not always present. One study found that out of 67 women with the genetic defect in the fumarate hydrase gene, 69% had both skin and uterine leiomyomas, 15% had only skin leiomyomas, and 7% had leiomyomas of the uterus alone [12].

For confirmation of MUCL, one cutaneous lesion should be analyzed histologically. Histologic examination of a leiomyoma will show bundles of smooth muscle fibers with eosinophilic cytoplasm. The nuclei are elongated with blunt ends often described as eel or cigar-shaped [14]. Markers for smooth muscle, such as desmin and actin, will be positive [15]. Genetic testing may show a defect in the FH gene. At the present time, genetic counseling is a suggested screening parameter for patients with multiple cutaneous leiomyomas. The superficial nature of these lesions and the low staging made surgical excision the preferred and actual treatment method. Adjunct radiation and chemotherapy have not been shown to provide clear benefit of survival [16, 17, 18]. However, in leiomyosarcomas larger than 5 cm, radiation may reduce local recurrence [19]. The National Institutes of Health recommends screening for renal cell carcinoma in all patients with leiomyomatosis [20, 21]. The majority of leiomyomas will not spontaneously regress and will require removal if causing pain or cosmetic concern [22]. A referral to the gynecology and nephrology departments is also recommended for monitoring and treatment of uterine leiomyomas and renal cell carcincoma, respectively [20, 21].

# Conclusion

Multiple subcutaneous angioleiomyosarcomatous nodules are a rare finding. Found in conjunction with uterine leimyomatosis, a diagnosis of Reed syndrome should be applied. Surgical excision with appropriate margins is the preferred treatment method. When suspected, screening for renal cell carcinoma is recommended, as well as referral to specialists in nephrology and gynecology for further monitoring.

# References


1. Alam NA, Olpin S, Leigh IM. Fumarate hydratase mutations and predisposition to cutaneous leiomyomas, uterine leiomyomas and renal cancer. British Journal of Dermatology. 2005. 153:11–17. [PMID: 16029320]
2. Emer J, Solomon S, Mercer S. Reed's Syndrome. A case of Multiple Cutaneous and Uterine Leiomyomas. Journal of Clinical Aesthetic Dermatology. 2011 December. 4(12): 37-42. [PMID: 22191007]
3. Decoster T, Van der Stinghelen Y, Vanderprutte S, Cools P. Primary angioleiomyosarcoma of the lesser omentum. ActaChir Belg. 2001 Mar-Apr;101(2):78-80. [PMID: 11396057]
4. Firsova PP, Maklakov NI, Medvedev VN, Mikhaĭlenko GG. Metachronous combination of angioleiomyosarcoma and lung cancer. VoprOnkol. 1979;25(4):73-5. [PMID: 433225]
5. Kalamkarian AA, Vasil'ev VV, Danielian EE, Rukavishnikova VM. Angioleiomyosarcoma of the skin and subcutaneous tissue. VestnDermatolVenerol. 1983 May. (5):31-5. [PMID: 6683913]
6. PavlakisJ, Pratsica K, Becopoulos T. Angioleiomyosarcoma of the kidney and ureter. ActaUrol Belg. 1965 October. 33(4):520-4. [PMID: 5859498]
7. Schlittenbauer M, Müller KM. Angioleiomyosarcoma of the lung-primary tumor or metastasis? Pneumologie. 1996 February. 50(2):215-8. [PMID: 8868596]
8. Fischer WC, Helwig EB. Leiomyomas of the skin. Archives of Dermatology. 1963;88:510–20. [PMID: 14060062]
9. Alam NA, Rowan AJ, Wortham NC, et al. Genetic and functional analyses of FH mutations in multiple cutaneous and uterine leiomyomatosis, hereditary leiomyomatosis and renal cancer, and fumaratehydratase deficiency. Human Molecular Genetics. 2003;12:1241–1252. [PMID: 12761039]
10. Cassety CT. Familial leiomyomatosis cutis et uteri. Dermatology Online Journal. 10(3):5. [PMID: 15748575]
11. Srivastava KP, Bajaj AK. Reed's Syndrome. Indian Journal of Dermatology. 2012 Mar-Apr. 57(2): 156–157. [PMID: 22615521]
12. Alam NA, Barclay E, Rowan AJ, Tyrer JP, et al. Clinical features of multiple cutaneous and uterine leiomyomatosis: an underdiagnosed tumor syndrome. Archives of Dermatology. 2005 February. 141(2):199-206. [PMID: 15724016]
13. GarcíaMuret MP, Pujol RM, Alomar A, et al. Familial leiomyomatosis cutis et uteri (Reed's syndrome). Archives of Dermatologic Research. 1988. 280:S29–S32. [PMID: 3408259]
14. Kilpatrick SE, Mentzel T, Fletcher CD. Leiomyoma of deep soft tissue. Clinicopathologic analysis of a series. American Journal of Surgical Pathology. 1994. 18:576–582. [PMID: 8179073]
15. Miettinen M, Lehto VP, Virtanen I. Antibodies to intermediate filament proteins. The differential diagnosis of cutaneous tumors. Archives of Dermatology. 1985. 121:736–741. [PMID: 2408582]
16. Guron G, Neugut AI. Soft tissue sarcomas: is adjuvant chemotherapy indicated? N Y State Journal of Medicine. 1993. 93:156-8. [PMID: 8455843]
17. Hwang ES, Gerald W, Wollner N, Meyers P, La Quaglia MP. Leiomyosarcoma in childhood and adolescence. Annals of Surgical Oncology. 1997. 4:223-7. [PMID: 9142383]
18. Lange J. Leiomyosarcoma. In: Miller SJ, Maloney ME, editors. Cutaneous oncology: pathophysiology, diagnosis, and management. Malden (MA): Blackwell Science; 1998. p. 893-6.
19. Suit HD, Mankin HJ, Wood WC, Proppe KH. Pre-operative, intraoperative, and post-operative radiation in the treatment o f primary soft tissue sarcoma. Cancer 1985. 55:2659-67. [PMID: 3995476]
20. Pithukpakorn M, Toro JR. Hereditary Leiomyomatosis and Renal Cell Cancer. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews. Seattle, Washington: University of Washington; 1993–2006 Jul 31. [Updated 2010 Nov 02] [PMID: 20301430]
21. Rongioletti F, Fausti V, Ferrando B, et al. A novel missense mutation in fumaratehydratase in an Italian patient with a diffuse variant of cutaneous leiomyomatosis (Reed's syndrome.) Dermatology. 2010. 221:378–380. [PMID: 21051878]
22. Enzinger FM, Weiss SW. Soft tissue tumors. St Louis: Mosby-Year Book; 1995.
23. Stout AP, Hill WT. Leiomyosarcoma of the superficial soft tissues. Cancer. 1958. 111:844-54. [PMID: 13561254]
24. Adigun I, Rahman G, Buhari M, Ogundipe K, Omotayo J. Soft-Tissue Sarcoma in Black Africans: Pattern, Distribution and Management Dilemma. Journal of the National Medical Association. 2007, January. 99(1): 88-93. [PMID: 17304972]
25. Dahl I, Angervall L. Cutaneous and subcutaneous leiomyosarcoma—a clinicopathological study of 47 patients. PathologiaEuropaea 1974. 9:307. [PMID: 4457785]
26. Fields JP,Helwig EB. Leiomyosarcoma of the skin and subcutaneous tissue. Cancer. 1981. 47:156-69. [PMID: 7459804]
27. Nunnery EW, Lipper S, Reddick R, Kahn LB. Leiomyosarcoma arising in a chronic venous stasis ulcer. Human Pathology. 1981. 12:951-3. [PMID: 7298054]


Figures and description provided by Cynthia Magro, M.D. Weill Cornell Medical College of Cornell University. New York, New York.