Reed syndrome presenting with leiomyosarcoma

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INTRODUCTION

Hereditary leiomyomatosis and renal cell cancer (HLRCC), also known as *familial leiomyomatosis cutis et uteri* or *Reed syndrome*, is a rare autosomal dominant disorder that manifests primarily as skin and uterine leiomyomas, usually at earlier ages than in the general population.[1] Renal cell carcinoma also develops in a subset of affected individuals. Cutaneous and subcutaneous leiomyomas are rare benign smooth-muscle tumors that can arise from the arrector pili muscle, dartos muscles in genital skin, or vascular smooth muscle.[2] Cutaneous leiomyosarcomas account for 2% to 3% of all soft tissue sarcomas and have been reported infrequently in patients with Reed syndrome.[3] We report the case of a 44-year-old white woman with Reed syndrome who presented with a primary cutaneous leiomyosarcoma in the right postauricular region, emphasizing the importance of cutaneous surveillance in patients affected by Reed syndrome.

Abbreviations used:

FH:	Fumarate hydratase
HLRCC:	Hereditary leiomyomatosis and renal cell cancer

CASE REPORT

A 44-year-old white woman was referred to our center for evaluation and treatment of multiple grouped red-brown papules (Fig 1). The lesions had been present for many years, were slowly increasing in number, and were asymptomatic until several months before presentation. The patient sought treatment when a papule behind her right ear began to grow and become tender. A biopsy of the lesion found histopathologic features of a well-differentiated dermal leiomyosarcoma including a well-circumscribed proliferation of spindle cells arranged in fascicles without necrosis and significant nuclear pleomorphism (Fig 2, *A* and *B*). There were 3 mitotic figures per high-power field. The spindle cells stained positively for smooth-muscle myosin. Further staining was not performed. A biopsy of a similar papule on the patient's distal left forearm had findings consistent with a leiomyoma.

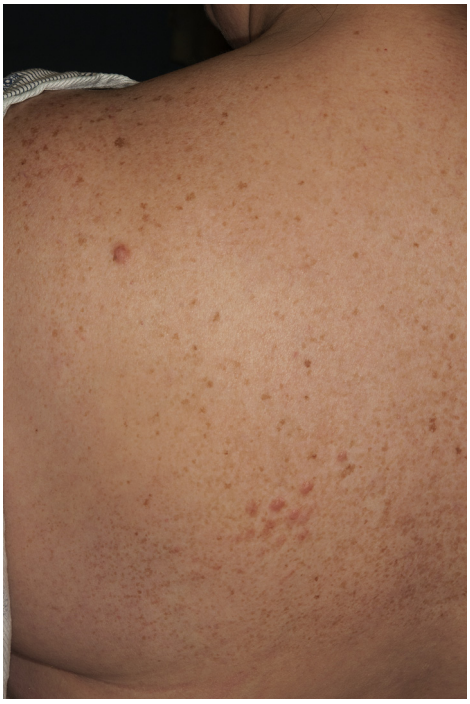

Fig 1. Cutaneous leiomyomas. Multiple indurated red-brown papules on the right side of the upper back.

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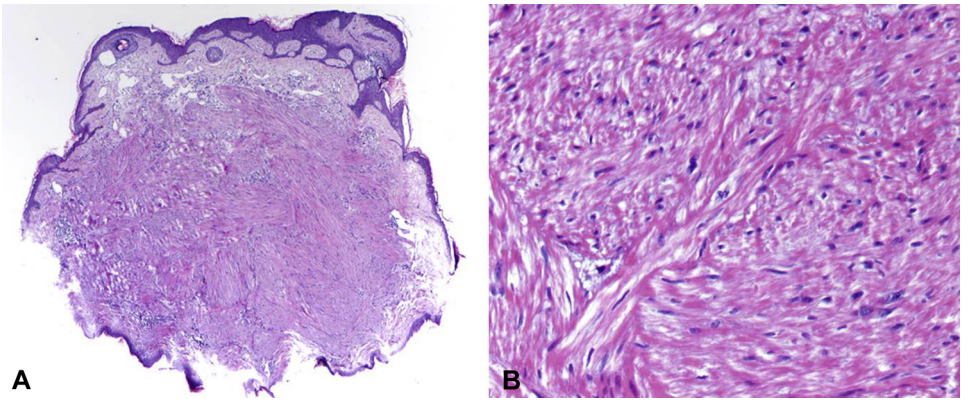

Fig 2. Histopathologic images of smooth-muscle tumors. **A**, Scanning magnification of a punch biopsy from the right posterior ear shows a proliferation of spindle cells forming an expansile nodule in the dermis without significant pleomorphism. **B**, Higher power examination finds smooth-muscle cells arranged in alternating fascicles and mitotic figures. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×40; **B**, ×400.)

At presentation to our clinic, she had 2 well-healed biopsy sites with no evidence of recurrence. A cluster of soft red-brown papules ranging 2 to 7 mm was present on the left side of her upper back with solitary papules on her lower extremities, consistent with leiomyomas. Because the deep edge of the leiomyosarcoma biopsy section was not clear, the patient underwent wide local excision of the right postauricular skin that found an ill-defined gray-white firm nodule of 0.4 × 0.4 × 0.4 cm. Biopsy results from a right postauricular lymph node were normal.

The patient's medical history is significant for hysterectomy for uterine fibroids at age 28. Her mother had similar skin lesions and underwent a hysterectomy in her 30s. The patient's daughter in her early 20s has multiple uterine fibroids requiring removal. Genetic testing of our patient found a fumarate hydratase (FH) gene mutation p.R233H (c.698G>A) consistent with findings in Reed syndrome. Renal ultrasound scan and computed tomography were negative for renal pathology. At 6 months follow-up, the patient's lesion numbers and sizes were stable, and there was no evidence of recurrence of the leiomyosarcoma.

DISCUSSION

Cutaneous leiomyosarcoma is a rare neoplasm of smooth-muscle origin that usually presents as a solitary firm nodule 0.2 to 3 cm in diameter. It is difficult if not impossible to clinically distinguish leiomyosarcomas from their benign counterpart, leiomyomas, making histopathologic examination crucial.[4] The nodules may resemble other solitary cutaneous nodules including neurofibroma, dermatofibroma, dermatofibrosarcomas, melanoma, and squamous cell carcinoma.[4,5] Clinical features that prompt a biopsy may be large or increasing diameter, ulceration, irregular shape, and pain. Histologically, well-differentiated cutaneous leiomyosarcomas show regularly arranged bundles of spindle cells with elongated nuclei and few mitotic figures. Poorly differentiated leiomyosarcomas have unorganized myofibrils, nuclear atypia, and many mitotic figures.[6] Immunohistochemical staining shows positivity for vimentin and smooth-muscle actin, desmin in 60% of cases, and negative staining for cytokeratin and S-100 protein.[5]

Most cutaneous leiomyosarcomas occur sporadically in the fourth decade of life and have been uncommonly associated with Reed syndrome, as in our patient.[3,7] Only one case of cutaneous leiomyosarcoma in Reed syndrome was reported in a study of 35 families.[8] Like our patient and her daughter, individuals with Reed syndrome almost always have uterine fibroids, typically starting in the third or fourth decades, approximately 10 years before they appear the general population.[9] The prevalence of early-onset fibroids in women with Reed syndrome is greater than 90%. Women with Reed syndrome are also at increased risk for uterine leiomyosarcomas.[8] Papillary renal cell carcinoma occurs in a subset of affected individuals (15%-25%), and tends to be type II, which is associated with more aggressive disease.[9,10] Genetic studies have localized the mutation responsible for Reed syndrome to the FH gene on chromosome 1q42.3-43.[8] Mutations in the FH gene correlate with tumor formation in families with HLRCC, although the role of FH in tumorigenesis is not entirely understood.[7] It is believed that FH functions as a tumor suppressor gene

whose loss of function in the cell with subsequent metabolic derangement caused by to defective Krebs cycle may play a role.[9]

The occurrence of multiple cutaneous leiomyomas should always raise concern for Reed syndrome, as cutaneous leiomyomas are uncommon skin neoplasms. Worldwide, Reed syndrome has been diagnosed in around 180 families.[9] Cutaneous leiomyomas in Reed syndrome classically present as a collection of pink, red, or dusky brown firm papules of varying size, most often on the extremities.[2] Although there are no established criteria for Reed syndrome, the patient's diagnosis is unequivocal, based on her consistent clinical presentation, family history, and the detection of an FH gene mutation by genetic testing. Cutaneous leiomyosarcomas often recur even after excision and rarely metastasize to distant sites, sometimes years after the initial excision. A retrospective analysis of 71 cases of cutaneous and subcutaneous leiomyosarcoma found that large tumor size, poor differentiation, and subcutaneous location correlated with greater likelihood of metastasis. Treatment with narrow (<1 cm) margins correlated with higher recurrence rate.[6] In addition to wide local excision, Mohs micrographic surgery may also be an effective treatment method for cutaneous leiomyosarcomas, as shown by a small retrospective case analysis.[5] Screening for patients with Reed syndrome includes an annual skin examination, abdominal magnetic resonance imaging, and gynecologic evaluation for women.[7]

REFERENCES

1. Reed WB, Walker R, Horowitz R. Cutaneous leiomyomas with uterine leiomyomata. *Acta Derm Venereol*. 1973;53:409-416.
2. Holst VA, Junkins-Hopkins JM, Elenitsas R. Cutaneous smooth muscle neoplasms: clinical features, histologic findings, and treatment options. *J Am Acad Dermatol*. 2002;46:477-494.
3. Badeloe S, Van Geest A, Van Marion AM, Frank J. Absence of fumarate hydratase mutation in a family with cutaneous leiomyosarcoma and renal cancer. *Int J Dermatol*. 2008;47:18-20.
4. Ciurea ME, Georgescu CV, Radu CC, Georgescu CC, Stoica LE. Cutaneous leiomyosarcoma – case report. *J Med Life*. 2014; 7(2):270-273.
5. Starling III J, Coldiron BM. Mohs micrographic surgery for the treatment of cutaneous leiomyosarcoma. *J Am Acad Dermatol*. 2011;64(6):1119-1122.
6. Winchester DS, Hocker TL, Brewer JD, et al. Leiomyosarcoma of the skin: clinical, histopathologic, and prognostic factors that influence outcomes. *J Am Acad Dermatol*. 2014;71(5):919-925.
7. Henley ND, Tokarz VA. Multiple cutaneous and uterine leiomyomatosis in a 36-year-old female, and discussion of hereditary leiomyomatosis and renal cell carcinoma. *Int J Derm*. 2012;51(10):1213-1216.
8. Toro JR, Nickerson ML, Wei MH, et al. Mutations in the fumarate hydratase gene causes hereditary leiomyomatosis and renal cancer in families in North America. *Am J Hum Genet*. 2003;73(1):95-106.
9. Lehtonen HJ. Hereditary leiomyomatosis and renal cell cancer: update on clinical and molecular characteristics. *Fam Cancer*. 2011;10(2):397-411.
10. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. *Fam Cancer*. 2014;13(4):637-644.