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Authors
Smith, S
Casady, M
Driscoll, MS

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Case presentation

Novel mutation in the fumarate hydratase gene in a patient with Reed syndrome

S Smith MD, M Casady BS, MS Driscoll MD PharmD.

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Department of Dermatology, University of Maryland School of Medicine, Baltimore, MD

Correspondence:

Megan Casady, B.S.
419 W. Redwood St. Suite 240
Baltimore, MD 21201
Phone: (240) 535-4343
Fax: (410) 328-0098
Email: megan.casady@som.umaryland.edu

Abstract

Reed syndrome is an autosomal dominant disorder characterized by cutaneous leiomyomas, uterine leiomyomas, and renal cell carcinoma caused by mutations in the fumarate hydratase gene. Dermatologic evaluation is often the first or only opportunity to discover the diagnosis of Reed syndrome in affected patients, which may prove to be life-saving. We present a 40-year-old woman with history of large uterine leiomyomas who presented with a two-year history of a pruritic papular eruption on the left neck refractory to topical corticosteroids. After histopathologic examination and genetic work-up, the patient was found to have a novel mutation in the fumarate hydratase gene and was subsequently diagnosed with Reed syndrome.

Keywords: Reed Syndrome, leiomyoma, fumarate hydratase, cancer prevention

Case synopsis

We report the case of a 40-year-old woman who presented to our clinic with a 2-year history of a pruritic papular eruption on her left neck. It was originally thought to be eczematous in nature, but did not respond to topical corticosteroid therapy. Targeted questioning revealed a personal history of large uterine leiomyomas and a family history of uterine leiomyomas in her mother, maternal aunt, and maternal grandmother. No other family

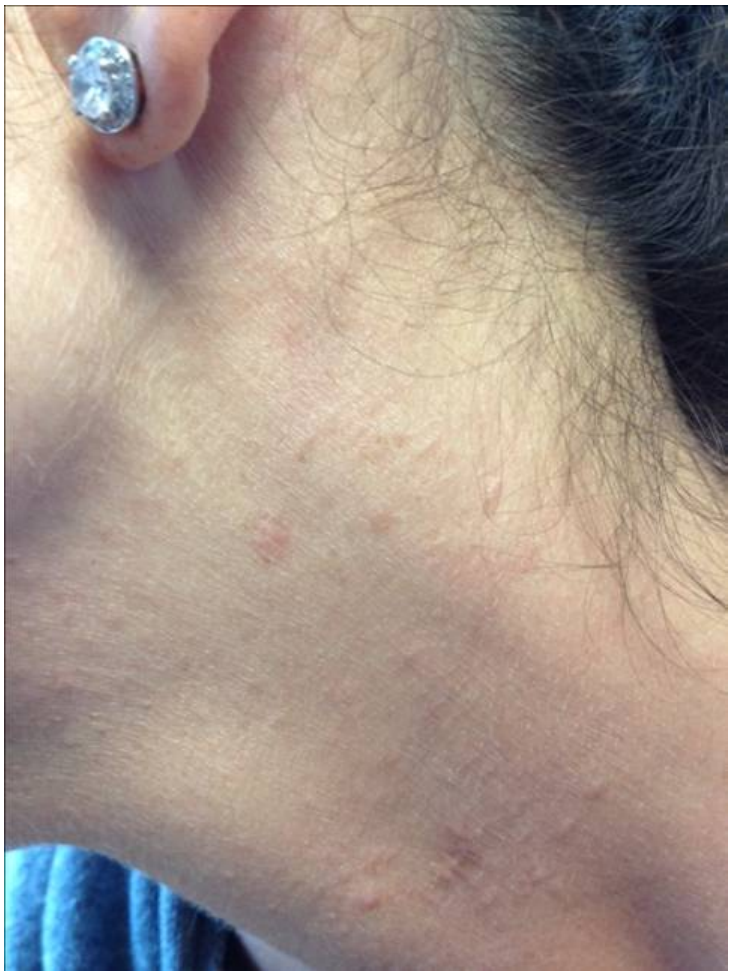

Figure 1. Multiple skin-colored to erythematous small papules on the left lateral neck.

members had similar skin lesions. There was a family history of renal cell cancer in both her maternal uncle and a second cousin. Physical examination revealed multiple flesh-colored to erythematous small papules on the left lateral neck (Figure 1). Histologic examination of a punch biopsy from a left neck lesion showed a poorly-circumscribed collection of interlacing bundles of smooth muscle fibers separated by collagen fibers (Figure 2). Staining for smooth muscle actin and desmin were both strongly positive (Figures 3 and 4). Our patient was referred for genetics counseling and further evaluation. Fumarate hydratase gene testing revealed a heterozygous frameshift mutation, L453Nfs, on exon 9 that has not previously been reported in the literature. The patient was diagnosed with Reed syndrome. She was referred to the departments of gynecology and urology for appropriate screening and continues to be followed by the dermatology service.

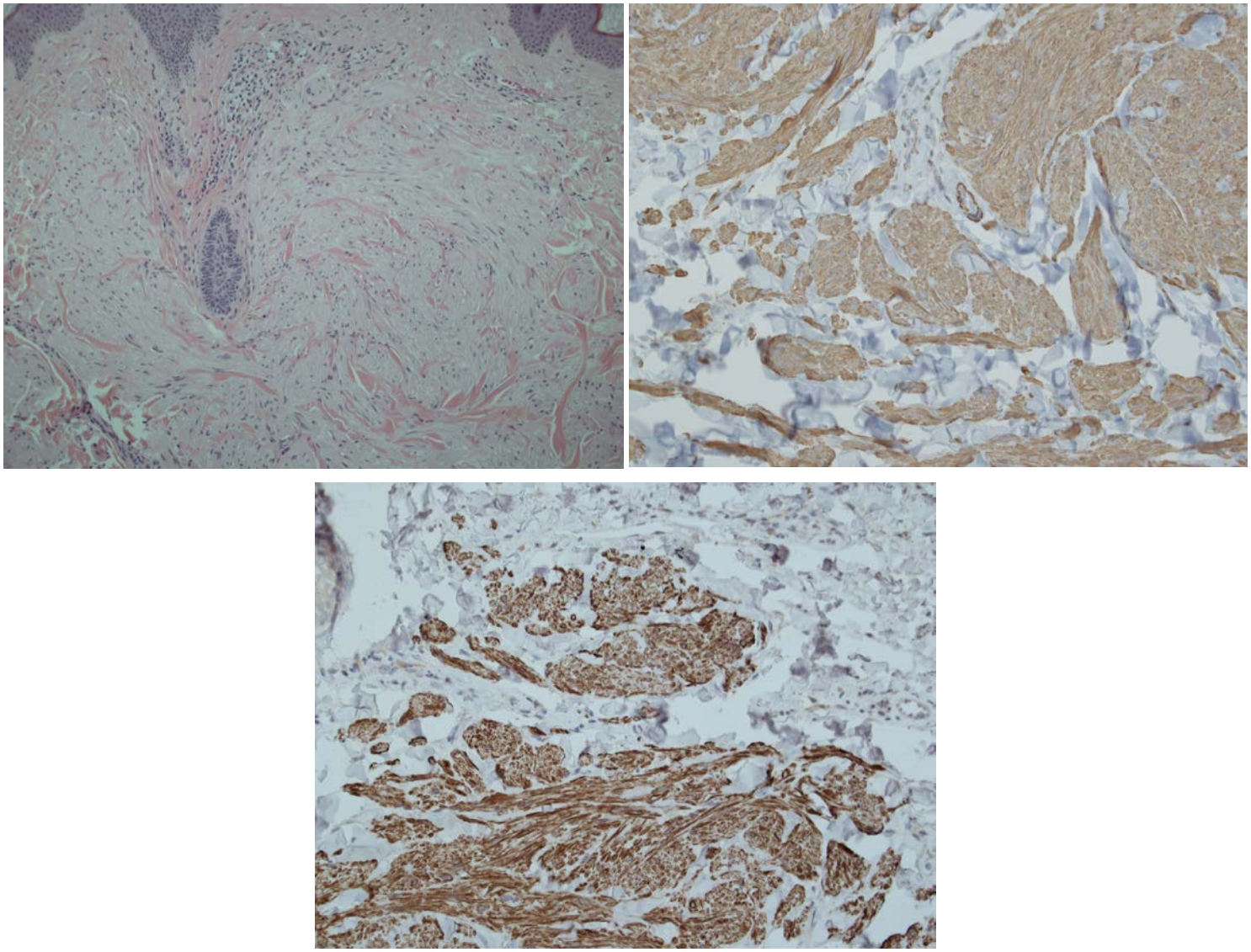

Figure 2. Histologic examination of a punch biopsy from the left neck showing a poorly circumscribed collection of interlacing bundles of smooth muscle fibers separated by collagen fibers. **Figure 3.** Immunostain of punch biopsy from the left neck with strongly positive stain for smooth muscle actin. **Figure 4.** Immunostain of punch biopsy from the left neck with strongly positive stain for desmin.

Discussion

The patient presented to our clinic with a history of persistent pruritic papules on her neck, a reported a history of uterine leiomyomas, and a family history of both uterine leiomyomas and renal cell carcinoma. This history along with her histopathologic findings are consistent with Reed Syndrome.

Reed syndrome, which is also called hereditary leiomyomatosis and renal cell carcinoma, is an autosomal dominantly inherited disorder that was first described in 1958. It is caused by mutations in the fumarate hydratase gene, and clinical features include the development of cutaneous leiomyomas in approximately 75% of individuals, uterine leiomyomas in greater than 90% of affected females, and an increased risk for the development of renal cell carcinoma, particularly the type 2 papillary subtype, which carries

a poor prognosis once metastatic. Other observed tumors in patients with Reed syndrome include breast carcinoma, prostate carcinoma, bladder carcinoma, Leydig cell tumor of the testis, cerebral cavernomas, ovarian and kidney cysts, and adrenal gland adenomas [1,2].

In over 200 cases reported, there have been only 73 different heterozygous mutations discovered in the fumarate hydratase gene. In all samples taken from cutaneous leiomyomas of these patients, the activity of fumarate hydratase was reduced [1]. The patient described in our report presented with a never before reported mutation in the fumarate hydratase gene, a heterozygous frameshift mutation, L453Nfs, on exon 9 (c.1357_1358del).

These mutations in fumarate hydratase, which is a member of the Krebs cycle, lead to abnormally high levels of fumarate that is typically only seen in hypoxic conditions. Subsequent overexpression of fumarate's downstream proteins leads to increased vascularity, autocrine stimulation, uncontrolled growth and enhanced survival of cells, which directly contributes to tumor development [3,4].

Dermatologically, patients develop multiple cutaneous leiomyomas, or smooth muscle hamartomas, which present as flesh-colored to light brown papules or nodules on the trunk and extremities. They may become painful with pressure or cold, and often increase in size and number with age. A segmental distribution suggesting mosaicism is often observed, but single, grouped/clustered, or disemminated lesions may also be found [5].

On histologic examination, cutaneous leimyomas appear as poorly-circumscribed dermal collections of interlacing bundles of smooth muscle fibers interspersed within collagen. The smooth muscle cells have an eosinophilic cytoplasm with a cigar shaped nucleus, and demonstrate positive staining for anti-desmin and anti-smooth muscle actin [6]. A very small number of affected patients may develop leiomyosarcoma, which display mitotic figures and atypical cells on histology.

Diagnostic criteria for Reed syndrome requires 1) multiple cutaneous leiomyomas with at least one confirmed histologically, 2) a single leiomyoma with a positive family history, or 3) a proven fumarate hydratase mutation plus either a cutaneous leiomyoma or renal cell carcinoma. Diagnosis can be confirmed with fumarate hydratase gene testing, which is indicated for any patients with multiple cutaneous leiomyomas [7].

Once diagnosed, Reed syndrome patients should undergo baseline and yearly dermatologic exam, gynecologic evaluation, and renal CT scan or MRI. A thorough family history may identify family members who could benefit from genetic testing [7].

Symptomatic cutaneous lesions can be treated with surgical excision, cryoablation or laser therapy. Other therapies, including calcuim channel blockers, nitroglycerin, and botox injections have been tried with varying success [8-10].

Dermatologic evaluation is often the first or only opportunity to diagnose Reed syndrome in affected patients. Diagnosis may be life-saving, particularly in patients with associated renal cell carcinoma that has not yet become metastatic. Our patient was found to have a novel mutation in the fumarate hydratase gene, and is now undergoing the appropriate cancer screening intervention.

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