

A Painful Flesh-Colored Papule on the Shoulder

Gabriela E. Beraja, DO, MS; Kaila A. Buckley, MD; Dawn L. Sammons, DO



A 65-year-old woman with a history of metabolic syndrome presented to the family medicine clinic for evaluation of a papule on the right shoulder that had started small and increased in size over the past 3 years. Physical examination revealed a 1.0×0.8×0.1-cm, smooth, flesh-colored to light brown papule on the right shoulder that was notably tender to palpation. The patient reported that her paternal uncle had multiple skin lesions of similar morphology dispersed on the bilateral upper extremities. A shave biopsy of the lesion was performed.

WHAT'S YOUR DIAGNOSIS?

- a. angioliipoma
- b. blue rubber bleb nevus
- c. dermatofibroma
- d. leiomyoma
- e. neurofibroma

PLEASE TURN TO **PAGE E15** FOR THE DIAGNOSIS

Dr. Beraja is from the Department of Family Medicine, OhioHealth Doctors Hospital, Columbus. Dr. Buckley is from CORPath, LLC, and RMH Pathology Associates, Columbus. Dr. Sammons is from Department of Dermatology, OhioHealth Riverside Methodist Hospital, Columbus. The authors have no relevant financial disclosures to report.

Correspondence: Gabriela E. Beraja, DO, MS, 2030 Stringtown Rd, Ste 300, Grove City, OH 43123 (gaby@beraja.co).

Cutis. 2025 March;115(3):E14-E16. doi:10.12788/cutis.1184

THE DIAGNOSIS:

Leiomyoma

Histopathology revealed a dermal mesenchymal tumor composed of fascicles of bland spindle cells with tapered nuclei, perinuclear vacuoles, eosinophilic cytoplasm, and low cellularity (Figure 1). Immunohistochemical studies of the cells stained strongly positive for smooth muscle actin and desmin, consistent with a smooth muscle neoplasm (Figure 2). Fumarate hydratase (FH) staining revealed loss of expression in tumor cells, consistent with FH deficiency (Figure 3). A diagnosis of cutaneous leiomyoma was made, and although the clinical and histologic findings suggested hereditary leiomyomatosis and renal cell cancer (HLRCC), genetic testing was negative for an *FH* gene mutation. This negative result indicated that HLRCC was unlikely despite the initial concerns based on the findings.

Leiomyomas are benign neoplasms that are challenging to diagnose based on the clinical picture alone. Leiomyomas most commonly are found in the genitourinary and gastrointestinal systems, with cutaneous manifestation being the second most common presentation.¹ These benign smooth muscle tumors manifest as tender, firm, flesh-colored, pink or reddish-brown nodules that are subcategorized based on the derivation of the smooth muscle within the tumor.² Angioleiomyomas, the most common type, arise from the tunica media of blood vessels, whereas piloleiomyomas and genital leiomyomas arise from the arrector pili musculature of the hair follicle and the smooth muscle found in the scrotum, labia, or nipple.² Rare cases of cutaneous leiomyosarcomas and angioleiomyosarcomas have been reported in the literature.^{3,4} Solitary leiomyomas tend to develop on the lower extremities, whereas multiple lesions frequently manifest on the extensor surfaces of extremities and the

trunk. Lesions often are painful, either spontaneously or in association with applied pressure, emotional stress, or exposure to cold temperatures.²

Although leiomyomas themselves are benign, patients with multiple cutaneous leiomyomas may have an underlying genetic mutation that increases their risk of developing HLRCC, an autosomal-dominant syndrome.⁵ Referral should be considered for individuals with a personal history of or a first-degree relative with cutaneous leiomyomas or renal cell carcinoma (RCC) with histology typical of hereditary leiomyomatosis and RCC, as recommended by the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors.⁶ In this case, the decision to refer the patient for genetic testing was based on her family history, specifically her paternal uncle having multiple similar lesions, which, while not a first-degree relative, still raised concerns about potential hereditary risks and warranted further evaluation. A germline mutation in

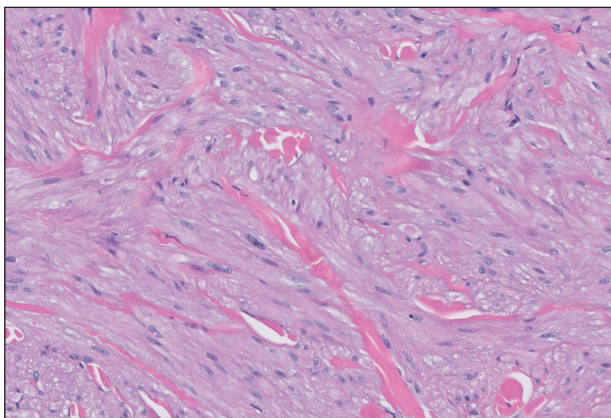


FIGURE 1. Histopathology revealed conspicuous neutrophils and eosinophils in the upper to mid dermis demonstrating perivascular accentuation (H&E, original magnification $\times 40$).

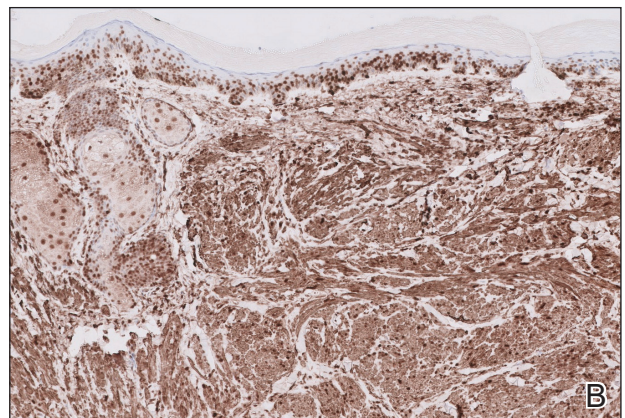
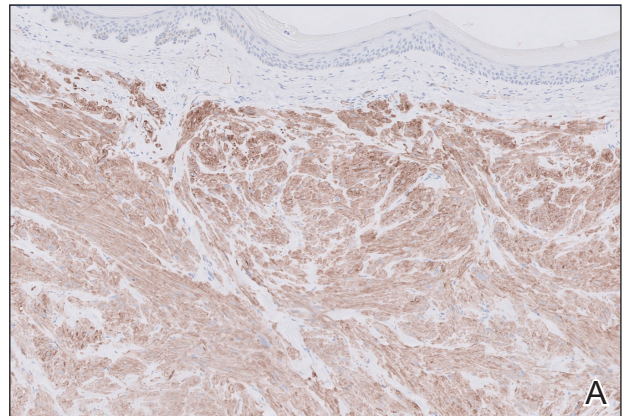


FIGURE 2. A and B, Immunohistochemistry revealed cells that stained strongly positive for smooth muscle actin and desmin (original magnification $\times 10$ and $\times 10$).

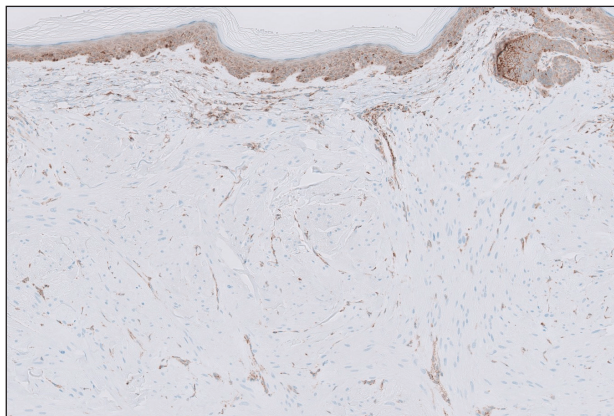


FIGURE 3. Nuclear expression of fumarate hydratase was lost in tumor cells, consistent with fumarate hydratase deficiency (original magnification $\times 10$).

the *FH* gene, which encodes an enzyme that converts fumarate to malate in the Krebs cycle and plays a role in tumor suppression, is the cause of HLRCC.^{2,7} When part of this genetic condition, cutaneous leiomyomas tend to occur around 25 years of age (range, 10–50 years).² A diagnosis of HLRCC should be strongly considered if a patient displays multiple cutaneous leiomyomas with at least 1 histologically confirmed lesion or at least 2 of the following: solitary cutaneous leiomyoma with family history of HLRCC, onset of severely symptomatic uterine fibroids before age 40 years, type II papillary or collecting duct renal cell cancer before age 40 years, or a first-degree family member who meets 1 of these criteria.^{5,8}

Diagnosis of cutaneous leiomyoma may be accomplished by microscopic examination of a tissue sample; however, further diagnostic workup is warranted due to the strong correlation with HLRCC.² A definitive diagnosis of HLRCC is confirmed with a germline mutation in the *FH* gene, and genetic screening should be offered to patients before renal cancer surveillance to avoid unwarranted investigations.⁸ Timely clinical diagnosis enables early genetic testing and enhanced outcomes for patients with confirmed HLRCC who may need a multidisciplinary approach of dermatologists, gynecologists, and urologic oncologists.^{5,8}

Cutaneous leiomyomas can be excised, and this typically is the gold standard of care for small and localized lesions, although the use of cryosurgery and carbon dioxide lasers has been reported as well.^{2,9,10} For more widespread lesions or for patients who are not appropriate candidates

for surgery, pharmacologic therapies (α -blockers, calcium channel blockers, nitroglycerin), intralesional corticosteroids, and/or botulinum toxin injections can be utilized.^{2,11}

The acronym BLEND AN EGG encompasses the clinical differential diagnosis for painful skin tumors: blue rubber bleb nevus, leiomyoma, eccrine spiradenoma, neuroma, dermatofibroma, angioliipoma, neurilemmoma, endometrioma, glomangioma, and granular cell tumor. Blue rubber bleb nevi are deep blue in color, and angioliipomas sit under the skin and present as subcutaneous swellings. Dermatofibromas and neurofibromas also are included in the differential.¹² Dermatofibromas are firm solitary lesions that have a pathognomonic pinch sign. Neurofibromas are soft and rubbery, have a buttonhole sign, and stain positively for S-100 protein and SOX-10 but negatively for actin and desmin.¹²

REFERENCES

1. Malhotra P, Walia H, Singh A, et al. Leiomyoma cutis: a clinicopathological series of 37 cases. *Indian J Dermatol*. 2010;55:337–341.
2. Bernett CN, Mammino JJ. Cutaneous leiomyomas. In: StatPearls. StatPearls Publishing; 2023.
3. Chayed Z, Kristensen LK, Ousager LB, et al. Hereditary leiomyomatosis and renal cell carcinoma: a case series and literature review. *Orphanet J Rare Dis*. 2021;16:34. doi:10.1186/s13023-020-01653-9
4. Perkins J, Scarbrough C, Sammons D, et al. Reed syndrome: an atypical presentation of a rare disease. *Dermatol Online J*. 2014;21:13030/qt5k35r5pn.
5. Schmidt LS, Linehan WM. Hereditary leiomyomatosis and renal cell carcinoma. *Int J Nephrol Renovasc Dis*. 2014;7:253–260. doi:10.2147/IJNRD.S42097
6. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2015;17:70–87. doi:10.1038/gim.2014.147
7. Alam NA, Barclay E, Rowan AJ, et al. Clinical features of multiple cutaneous and uterine leiomyomatosis: an underdiagnosed tumor syndrome. *Arch Dermatol*. 2005;141:199–206. doi:10.1001/archderm.141.2.199
8. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. *Fam Cancer*. 2014;13:637–644. doi:10.1007/s10689-014-9735-2
9. Uyar B, Acar EM, Subaşıoğlu A. Treatment of three hereditary leiomyomatosis patients with cryotherapy. *Dermatol Ther*. 2020;33:e13226. doi:10.1111/dth.13226
10. Christenson LJ, Smith K, Arpey CJ. Treatment of multiple cutaneous leiomyomas with CO₂ laser ablation. *Dermatol Surg*. 2000;26:319–322. doi:10.1046/j.1524-4725.2000.99250.x
11. Onder M, Adışen E. A new indication of botulinum toxin: leiomyoma-related pain. *J Am Acad Dermatol*. 2009;60:325–328. doi:10.1016/j.jaad.2008.05.044
12. Clarey DD, Lauer SR, Adams JL. Painful papules on the arms. *Cutis*. 2020;106:232–249. doi:10.12788/cutis.0109