

Bilateral Segmental Leiomyomas: A Case Report and Review of the Literature

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GOAL

To understand cutaneous leiomyomas to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the clinical presentations of cutaneous leiomyomas.
2. Identify patients with multiple cutaneous and uterine leiomyomatosis (MCUL) and hereditary leiomyomatosis and renal cell cancer (HLRCC).
3. Recognize the genetic defects in MCUL and HLRCC.

CME Test on page 47.

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Cutaneous leiomyomas are benign tumors of smooth muscles. We report a rare case of bilateral

segmental leiomyomas in an 81-year-old man. We also provide a concise review of the literature on leiomyomas, their associations, and genetic defects of multiple cutaneous and uterine leiomyomatosis (MCUL) and hereditary leiomyomatosis and renal cell cancer (HLRCC) syndromes.

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Cutaneous leiomyomas are benign tumors of smooth muscle bundles. Of the 5 subtypes of cutaneous leiomyomas, multiple piloleiomyomas (pilar leiomyomas) are the most common.¹ Originating from arrector pili muscles of hair follicles, they usually present as small, red-brown, firm papules

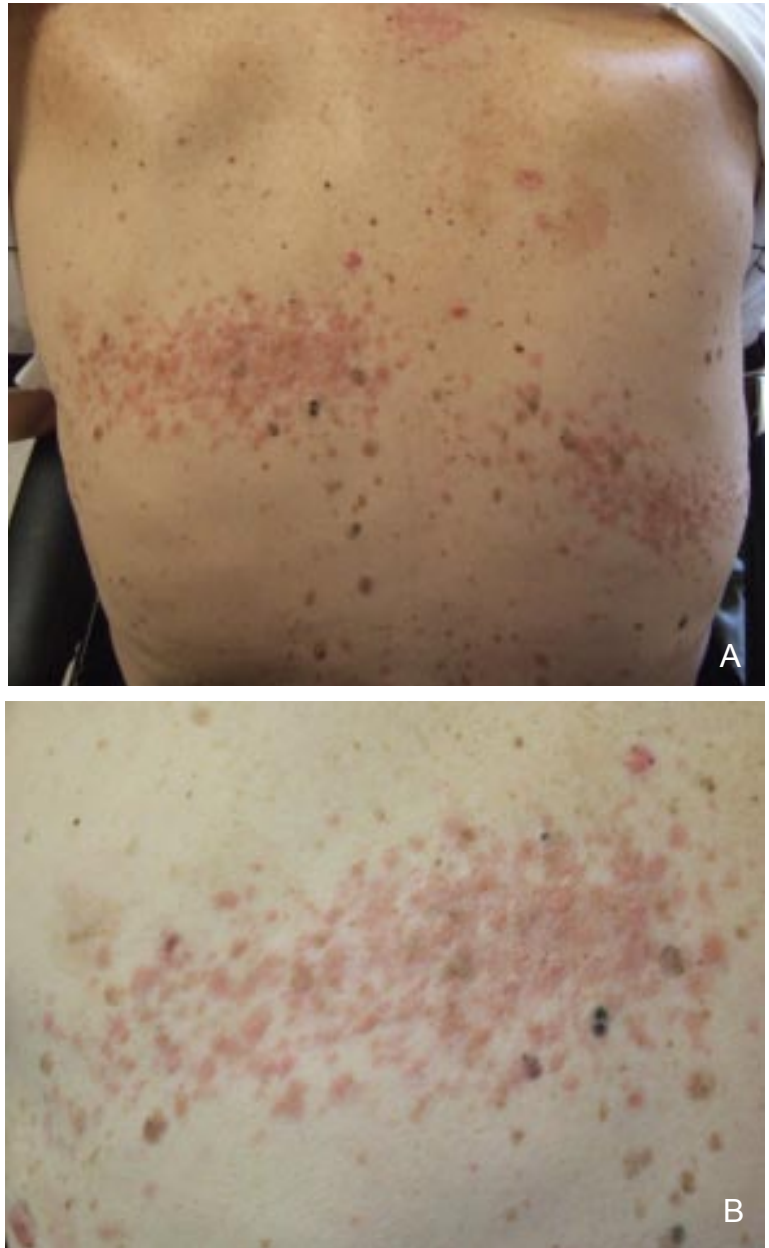


Figure 1. More than 100 red-brown papules in a segmental distribution in multiple dermatomes on the back (A and B).

on the extremities or trunk of young adults. Solitary piloleiomyomas occur more commonly in women as larger nodules, measuring up to 2 cm. Occasionally, lesions can be symmetrical, Blaschkoid, diffuse (disseminated), or segmental (zosteriform).² Multiple eruptive lesions have been described in patients with chronic lymphocytic leukemia, erythrocytosis, and human immunodeficiency virus infection. Patients may have a history of spontaneous burning, pinching, or stabbing pain. In addition, pain may be triggered by pressure, cold temperature, trauma, or emotional stress.³ Although the pathophysiology of pain is still unknown, it may be caused by pressure of the nerve fibers within the tumors upon contraction of the smooth muscles.⁴ Pain tends to occur

more frequently in diffuse and segmental forms of leiomyomas.⁵

Multiple cutaneous leiomyomas may occur in conjunction with uterine leiomyomas, also known as multiple cutaneous and uterine leiomyomatosis (MCUL), familial leiomyomatosis cutis et uteri, Reed syndrome, or multiple leiomyomatosis.⁶ An autosomal dominant mode of transmission with incomplete penetrance occurs with MCUL. In this syndrome, multiple piloleiomyomas usually occur in both sexes. However, affected women also have severely symptomatic uterine leiomyomas or fibroids that usually require early hysterectomy for symptom control. Some patients with MCUL also were found to have uncommon and aggressive forms of renal cell

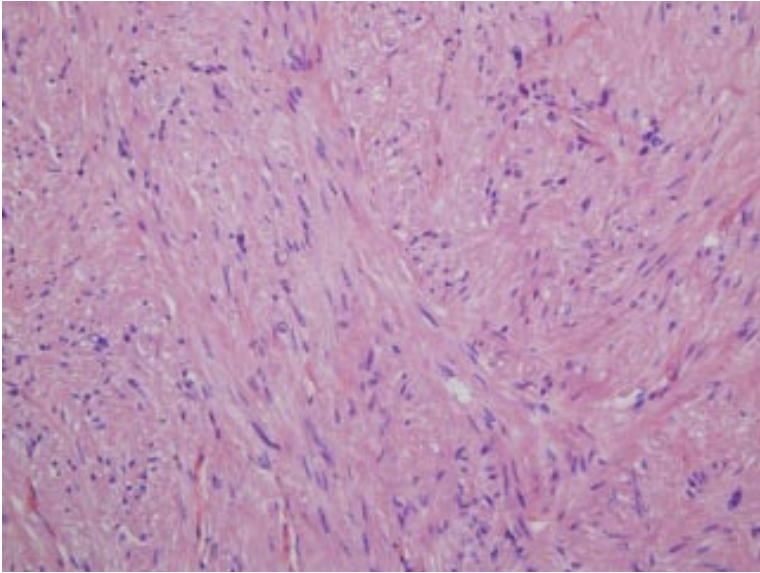


Figure 2. Smooth muscle bundles with vacuolization and cigar-shaped nuclei (H&E, original magnification $\times 400$).

carcinoma, especially papillary renal cell carcinoma type 2 or renal collecting duct carcinoma, which also is known as hereditary leiomyomatosis and renal cell cancer (HLRCC).⁷

Case Report

An 81-year-old man presented with a 50-year history of multiple red-brown papules and nodules on both sides of his back. He denied any pruritus, tenderness, or burning sensation. His medical history included type 2 diabetes mellitus, cardiomyopathy, peripheral neuropathy, peripheral vascular disease, and benign prostatic hypertrophy. A thorough family history was unremarkable for any neoplasm including kidney cancer or uterine fibroids. On examination, there were multiple red-brown flattopped papules and nodules coalescing into plaques in a segmental distribution on both sides of his back (Figure 1). These papules were not tender on palpation. Upon stroking, there was no accentuation or piloerection.

Histopathologic findings showed a poorly circumscribed spindle cell proliferation with blunt-ended cigar-shaped nuclei and abundant pink cytoplasm in the deep papillary and reticular dermis. Perinuclear vacuolization was present in the cross-section of the smooth muscle bundles (Figure 2). There was no cytologic atypia or mitotic activity. Immunohistochemistry stains were positive for vimentin, smooth muscle actin, and desmin. The diagnosis of bilateral segmental leiomyomas (piloleiomyomas) was confirmed. Further history did not reveal any cancer or neoplasm. Radiographic and genetic studies were offered, but the patient and his family declined.

Comment

There are 5 subtypes of cutaneous leiomyomas: multiple piloleiomyomas, solitary piloleiomyomas,

solitary genital leiomyomas, solitary angioleiomyomas, and leiomyomas with mesenchymal elements.¹ Solitary genital leiomyomas usually are asymptomatic. They originate from the superficial smooth muscles of the scrotum, labia majora, and nipples. Solitary angioleiomyomas present with painful solitary nodules deep in the mid-dermis or subcutaneous tissues and are derived from vascular smooth muscles. They most commonly present on the lower extremities in women aged 30 to 60 years. Rarely, mature adipocytes are found within the nodules as seen in angiolipoleiomyomas. Although they most likely represent metaplastic change, the presence of adipocytes is now accepted to be a hamartomatous process.⁸ Cutaneous angiolipoleiomyomas are more common in men and, contrary to renal angioleiomyomas, have no association with tuberous sclerosis.¹

Histologically, piloleiomyomas and genital leiomyomas are composed of poorly demarcated, well-differentiated, interlacing bundles of smooth muscle fibers. The centrally located nuclei are long and thin with blunt ends in a cigar or eel shape (Figure 2). Angioleiomyomas are more sharply circumscribed. Round, slitlike, or stellate lumina also may be seen. Differential diagnosis may include other spindle cell proliferative tumors such as neurofibroma, dermatofibroma, schwannoma, and leiomyosarcoma. Nuclear pleomorphism and atypical mitoses are abundant in leiomyosarcomas. Immunohistochemistry also may help to confirm the diagnosis of leiomyomas and differentiate them from other similar entities.

Genetic defects in MCUL and HLRCC were colocalized to band 1q42.3-43.⁹ Heterozygous germ line mutations in the fumarate hydratase gene, *FH*, that resulted in either decreased or absent *FH* enzymatic activity were subsequently identified in

42 patients affected with leiomyomatosis.¹⁰ The *FH* gene comprises 22 kilobases with 10 exons¹¹ and encodes both the cytosolic and mitochondrial isoforms. Fumarate hydratase functions within the Krebs cycle by converting fumarate to L-malate. While the pathway by which tumorigenesis occurs in MCUL and HLRCC is still unknown, it is postulated that mutations in the *FH* gene exert a tumor suppressive effect by altering Krebs cycle activity.¹² To date, there have been approximately 70 different mutations of the *FH* gene reported. Although the incidence of *FH* gene mutations in patients with uterine leiomyomas and papillary renal cell carcinoma type 2 remains unknown, 90% (80/89) of patients with cutaneous leiomyomas have *FH* gene mutations, determined by either DNA analysis or decreased enzymatic activity.¹³

Apoptotic and antiapoptotic factors also may play a role in the pathogenesis of leiomyomas. Wortham et al¹⁴ reported increased expressions of antiapoptotic BCL2 and the proliferation factor proliferating cell nuclear antigen in uterine leiomyomas from both sporadic patients and patients with HLRCC. Furthermore, an increase in antiapoptotic BCLX with a simultaneous decrease in proapoptotic Bak (BCL2 antagonist/killer) protein also has been reported.¹⁴

It is controversial if patients presenting with multiple cutaneous or uterine leiomyomas should be screened for MCUL and HLRCC.¹³ However, a thorough personal and family history of cutaneous leiomyomas, fibroids, and renal cell carcinoma should be performed. If needed, a computed tomographic scan with contrast or magnetic resonance imaging should be performed. Both modalities are sensitive to detect smaller lesions and some types of papillary renal cell carcinoma that may be isoechoic and undetectable on ultrasound.¹⁵

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