

Management of Refractory Pain From Hereditary Cutaneous Leiomyomas With Nifedipine and Gabapentin

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PRACTICE POINTS

- Cutaneous leiomyomas (piloleiomyomas) are benign smooth muscle tumors derived from the arrector pili muscle.
- Patients presenting with multiple cutaneous leiomyomas should be evaluated for hereditary leiomyomatosis and renal cell carcinoma syndrome, an autosomal-dominant disorder, which also predisposes to the development of symptomatic uterine fibroids and uterine leiomyosarcoma.
- Cutaneous leiomyomas may be a source of considerable pain, which may respond to treatment with nifedipine in combination with gabapentin.

To the Editor:

Leiomyomas are benign smooth muscle tumors. There are 3 types of cutaneous leiomyomas: (1) piloleiomyomas, arising from the arrector pili muscles; (2) angioleiomyomas, arising from the muscles surrounding dermal blood vessels; and (3) leiomyomas of the external genitalia, arising from the dartoic, vulvar, or mammary smooth muscles.¹ There is no gender predilection for cutaneous leiomyomas, and lesions present on average at approximately 40 to 45 years of age.²

Piloleiomyomas are the most common type of cutaneous leiomyomas and typically present as red-brown papules and nodules on the trunk, arms, and legs.³

Piloleiomyomas often are associated with spontaneous or induced pain (eg, with cold exposure). The pain associated with piloleiomyomas can be severely debilitating to patients and may have a considerable impact on their quality of life.

A 40-year-old woman presented to our clinic with numerous widespread, painful, red-brown papules and nodules on the head, neck, chest, abdomen, back, arms, and legs of 6 years' duration that were increasing in number (Figure 1). She had a history of uterine leiomyomas and type 2 renal papillary carcinoma following a left nephrectomy at 38 years of age. The patient's mother had a history of similar skin lesions as well as uterine cancer. Multiple excisional biopsies were performed, all of which showed piloleiomyomas on histopathology (Figure 2). The pain associated with the patient's extensive cutaneous leiomyomas considerably impaired her quality of life. Although she experienced pain in all affected areas of the body, the pain was the worst in the upper arms. She reported having requested a nerve ablation procedure from an outside pain management clinic, which was denied for unknown reasons.

Two years prior to the current presentation, the patient had been treated by a pain management specialist with gabapentin 300 mg twice daily as needed for pain associated with leiomyomas. The patient followed this regimen approximately 3 times weekly for the preceding 1 to 2 years with reduction in her pain symptoms; however, the painful episodes became more frequent and

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FIGURE 1. Numerous painful red-brown papules and nodules on the neck, chest, and left arm.

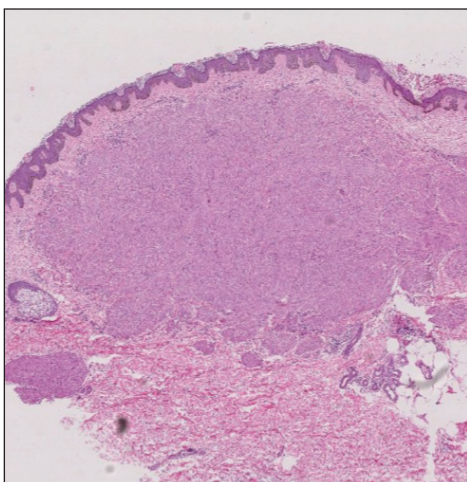


FIGURE 2. Piloleiomyoma in the reticular dermis forming a nodule with fascicles of myocytes between collagen bundles at the periphery (H&E, original magnification $\times 100$).

severe over time. The patient reported being unable to further increase the gabapentin dosing frequency because it made her too drowsy and impacted her ability to work a job that required heavy lifting. Thus, the patient requested additional therapy and was subsequently treated at our clinic with numerous excisional biopsies of the most painful lesions during the 2 years prior to her current presentation.

When the patient re-presented to our clinic, she requested additional lesion excisions given that she had experienced some pain relief from this treatment modality in the past; however, these prior excisions only resulted in local pain relief limited to the site of the excision. Because of the extent of the lesions and the patient's inability to tolerate pain from the lidocaine injections, we did not feel multiple excisions were a practical treatment option. The patient subsequently was offered a trial of cryotherapy for symptom relief based on a reported case in which this modality was successfully used.⁴ After discussing the risks and benefits associated with this treatment, cryotherapy was attempted on a few of the leiomyomas on the patient's right shoulder; however, she experienced severe pain during cryotherapy treatment, and the procedure had to be aborted.

We then increased the patient's gabapentin regimen to 300 mg in the morning and 600 mg in the evening, as tolerated. The patient reported that she was better able to tolerate the sedating side effects of the increased dose of gabapentin because she had stopped working due to her severe pain episodes. We also added oral nifedipine 10 mg 3 times daily, as needed. Within 30 minutes of starting this treatment regimen, the pain associated with the lesions remarkably improved (10/10 severity before starting treatment vs 3/10 after starting treatment). Her pain levels remained stable (3/10 severity) during 3 weeks of treatment with this combination regimen, but unfortunately she developed headaches and malaise, which she associated with the nifedipine at the 3 times daily dose.

The patient was able to better tolerate the nifedipine after reducing the dose to once daily on an as-needed basis. On average, the patient took nifedipine once every 3 days; however, she reported that she had to periodically increase the frequency of the nifedipine to once daily for up to 2 weeks at a time for periods of more frequent pain flares. The patient reported a consistent pattern of the breakthrough symptoms rapidly improving with each dose of nifedipine, though she did feel that taking consistent gabapentin enhanced baseline symptom control. The patient also noticed on a few occasions when she did not have access to her nifedipine that her pain would flare to 10/10 severity and would decrease to 4/10 severity 30 minutes after restarting nifedipine at 10 mg once daily. She experienced breakthrough pain due to exacerbating factors including her menstrual cycle; exposure to the sun and cold temperatures or water; excessive physical activity; and mild trauma. Due to exacerbations from sun exposure, the patient often wore long-sleeved shirts,

which helped reduce the severity of the pain episodes while she was outdoors.

The exact mechanism for the pain associated with cutaneous leiomyomas is unknown but is thought to be due to infringement of the lesion on the surrounding cutaneous nerves. In addition, norepinephrine activates alpha receptors on the smooth muscle to contract through an influx of ions such as calcium. When smooth muscle contracts, the compression of nerves likely is worsened.

There are a limited number of case reports in the literature that have demonstrated successful treatment of the pain associated with cutaneous leiomyomas. Previously reported treatment modalities have included phenoxybenzamine, an alpha-blocking agent that may reduce pain through its antiadrenergic effects²; nitroglycerin, a venous and arterial dilator that may reduce pain by decreasing muscle oxygen requirements²; gabapentin, an antiepileptic and analgesic medication with structural similarity to the gamma-aminobutyric acid neurotransmitter for which the exact mechanism of action is unknown³; botulinum toxin, a neuromuscular blocker that prevents the release of presynaptic acetylcholine and may decrease neuropathic pain by reducing hyperactive nerves^{5,6}; hyoscine butylbromide and topical hyoscine hydrobromide, both antispasmodics that may reduce pain through their anticholinergic effects, which relax smooth muscle^{7,8}; and the CO₂ laser, a treatment that has been utilized for its resurfacing, excisional, and ablative properties.^{9,10}

Calcium channel blockers such as amlodipine, verapamil, and nifedipine also have been used to treat the pain associated with piloleiomyomas.¹¹ Calcium ion channel antagonists inhibit the influx of calcium ions across the cell membrane; therefore, nifedipine and other calcium channel blockers may prevent the smooth muscle contraction that is hypothesized to cause pain in patients with cutaneous leiomyomas.¹²

Mean plasma concentration of nifedipine has been shown to reach maximum values of 160 +/- 49 µg/L after 30 to 60 minutes following oral administration of 10 mg of nifedipine.¹³ After 8 hours, the mean concentration drops to 3.4 +/- 1.2 µg/L. The clinical response in our patient appeared consistent with the reported pharmacokinetics of the drug, as she was able to consistently obtain considerable reduction in her pain symptoms within 30 minutes of starting nifedipine, coinciding with the period of time it takes for the nifedipine to reach maximum plasma concentrations.¹³

Interestingly, our patient had worsening pain episodes associated with sun exposure, which typically is not reported as one of the usual triggers for cutaneous leiomyomas. We are not aware of any described mechanisms that would explain this phenomenon.

Importantly, any patient presenting with multiple cutaneous and uterine (if female) leiomyomas should be screened for hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC), an autosomal-dominant disorder linked to a mutation in the fumarate hydratase

tumor suppressor gene. Clinically, HLRCC patients typically present with multiple cutaneous leiomyomas, uterine leiomyomas, and renal cell cancer (most often type 2 papillary renal cell carcinoma).¹⁴ Hereditary leiomyomatosis and renal cell carcinoma syndrome (also known as multiple cutaneous and uterine leiomyomatosis syndrome) previously was thought to be a separate disease entity from Reed syndrome; however, after the same mutation in the fumarate hydratase tumor suppressor gene was found to be responsible for both Reed syndrome and HLRCC, they are now thought to be the same disease process.¹⁵

Diagnosis of HLRCC is likely when the patient meets the major criterion of multiple cutaneous piloleiomyomas confirmed histopathologically. Clinical diagnosis of HLRCC is suspected if 2 or more of the following minor criteria are present: type 2 papillary renal cell carcinoma before 40 years of age; onset of severely symptomatic (requiring surgery) uterine fibroids before 40 years of age in females; and first-degree family member who meets 1 or more of these criteria.¹⁵ At the time of presentation, the patient met clinical criteria for HLRCC, including multiple cutaneous leiomyomas (major criterion) and type 2 papillary renal cell carcinoma before 40 years of age (minor criterion). The patient also had a history of uterine leiomyomas, but these lesions did not fulfill the criterion of being severely symptomatic requiring surgery. Furthermore, the patient's mother had similar cutaneous leiomyomas and a history of uterine cancer, which fulfilled additional minor criterion, consistent with an autosomal-dominant inheritance pattern (with variable penetrance) seen in HLRCC. An important issue for counseling and monitoring patients is that premenopausal women with HLRCC are at an increased risk of developing uterine leiomyosarcoma.¹⁵ Our patient followed up with an oncologist for tumor surveillance and subsequently underwent genetic testing, which revealed a mutation in the fumarate hydratase gene.

Treatment of painful cutaneous leiomyomas, particularly in patients with HLRCC, remains a therapeutic challenge. Although surgical and/or destructive treatments can provide pain relief for patients who have a limited number of lesions, these options are impracticable when a patient has numerous widespread leiomyomas; therefore, systemic therapies may be more beneficial. Clinicians should be aware of nifedipine, which may be used in combination with gabapentin as a viable treatment option in the management of acute and breakthrough pain associated with cutaneous leiomyomas.

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