Check for updates

Australasian Journal of Dermatology

BRIEF REPORT

Topical Diltiazem in the Management of Cutaneous Leiomyoma–Associated Pain: Evaluation With a Cold-Provocation Test

Samet Öner[1] | Ceylan Avcı[1] | Arzu Avcı[2]

[1]Department of Dermatology, Dokuz Eylül University Medical Faculty, İzmir, Türkiye | [2]Department of Pathology, İzmir Tınaztepe University Medical Faculty, İzmir, Türkiye

Correspondence: Samet Öner (dr.sametoner@gmail.com)

Received: 19 December 2025 | **Revised:** 19 January 2026 | **Accepted:** 27 January 2026

Keywords: administration, topical | calcium channel blockers | diltiazem | *fumarate hydratase* | hereditary leiomyomatosis and renal cell cancer | leiomyoma | pain management

ABSTRACT

Cutaneous leiomyomas can cause severe pain that may be spontaneous or stimulus-evoked, and is commonly exacerbated by cold exposure, mechanical pressure/touch, or stress. We report a patient with genetically confirmed hereditary leiomyomatosis and renal cell cancer (HLRCC) in whom topical diltiazem 2% was associated with reduced pain, assessed using a controlled cold-provocation test and validated pain scores. This brief report suggests that topical diltiazem may be a useful symptomatic option and supports further evaluation.

1 | Introduction

Cutaneous leiomyomas are rare benign smooth muscle tumours classified according to their site of origin, including piloleiomyomas arising from arrector pili muscles, angioleiomyomas from vascular smooth muscle, and genital leiomyomas from periareolar or genital musculature. These lesions often cause recurrent, cold- or pressure-induced pain, which may also occur spontaneously or be triggered by minor stimuli such as touch or emotional stress, and can substantially impair quality of life. The pathogenesis of pain is multifactorial, involving Ca^{2+}-dependent contraction of smooth muscle, α-adrenergic activation, and mechanical nerve compression within dense dermal fascicles [1–3].

Management of cutaneous leiomyoma encompasses a broad range of therapeutic modalities, including systemic pharmacologic agents (oral calcium-channel blockers, α-adrenergic blockers, gabapentinoids, nitrates, and analgesics), topical agents (lidocaine, nitroglycerin, capsaicin, and hyoscine hydrobromide), and procedural or interventional approaches such as CO_2 laser ablation, cryotherapy, electrocautery, surgical excision, and intralesional injections. Despite these diverse approaches, pain control remains inconsistent and often temporary [1–4].

Recently, topical calcium-channel blockers have been proposed as a physiologically targeted approach for painful cutaneous leiomyomas, although published evidence remains limited, with topical nifedipine reported as a potentially effective option [5]. Here, we report pain improvement with topical diltiazem 2% cream for this indication, evaluated using a controlled cold-provocation test.

2 | Case Report

2.1 | Clinical Presentation & Histopathology

A 61-year-old man had a 38-year history of multiple cutaneous leiomyomas in a segmental (zosteriform/blaschkoid) distribution over the left anterolateral abdomen, approximating T8–T10, manifesting as numerous smooth, firm, pink dermal papules and nodules that coalesced into plaque-like clusters

© 2026 Australasian College of Dermatologists.



FIGURE 1 | Clinical features: Clinical presentation showing multiple smooth, firm, pink dermal papules and nodules coalescing into plaque-like clusters in a segmental (zosteriform/blaschkoid) distribution on the left anterolateral abdomen, approximating T8–T10.

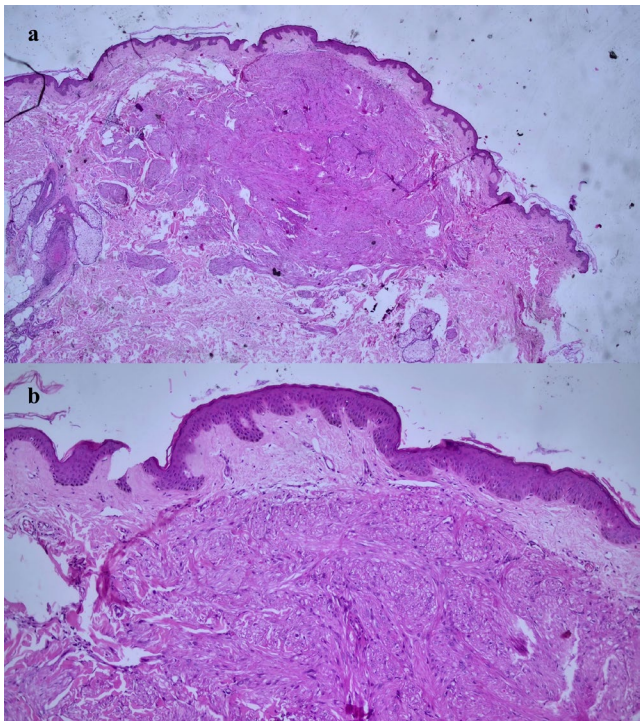


FIGURE 2 | Histopathological features: (a) Low-power histopathologic view showing myoid fascicular spindle cell arrangement forming a nodular structure (H&E stain, ×4). (b) High-power view demonstrating leiomyoma bundles located in the papillary dermis, composed of intersecting smooth muscle cells with characteristic oval, blunt-ended nuclei and eosinophilic cytoplasm, without atypia or mitosis (H&E stain, ×20).

(Figure 1). Histopathologic examination on haematoxylin and eosin (H&E)–stained sections revealed intersecting dermal fascicles of spindle-shaped smooth-muscle cells with oval, blunt-ended nuclei (Figure 2). Immunohistochemical staining showed diffuse smooth-muscle actin positivity, while S-100 and CD34 were negative, confirming the diagnosis of dermal leiomyoma.

2.2 | Genetic Evaluation

Given the multiplicity and segmental distribution of lesions, referral for genetic counselling and germline *fumarate hydratase* (FH) analysis was initiated together with baseline renal imaging. Molecular testing identified a heterozygous pathogenic splice-site variant in FH: c.1391-2A>G (rs863224008), confirming a diagnosis of hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. This specific mutation has been previously shown to significantly reduce *fumarate hydratase* enzymatic activity, establishing its pathogenicity [6].

2.3 | Prior Treatment and Baseline Assessment

The patient had undergone prior single-session CO_2 laser ablation without meaningful or durable benefit. At presentation, pain intensity and functional impact were quantified using the Visual Analogue Scale (VAS) and the Brief Pain Inventory–Short Form (BPI-SF) [7]. Baseline scores were VAS 9/10, BPI Pain Severity Score 7.25, and BPI Pain Interference Score 4.42.

2.4 | Therapeutic Intervention

Given the extent of lesional involvement and patient preference, surgical management was not pursued. A step-up calcium-channel blockade regimen was commenced with oral amlodipine 5 mg once daily. At 4 weeks, reassessment showed VAS 5/10, Pain Severity 5.0, and Pain Interference 3.14, consistent with partial improvement. Because the patient was initially normotensive (home BP ≈ 127/70 mmHg) and reported dizziness on amlodipine 5 mg, up-titration was not pursued. Instead, topical diltiazem 2% applied twice daily was added as an adjunct.

2.5 | Pain Assessment & Cold-Provocation Testing

Before initiating topical therapy, a controlled cold-provocation test was performed to document the cold-evoked pain response and provide a reproducible baseline. After 10–15 min of acclimatisation at room temperature, an ice cube wrapped in gauze was applied to the most tender plaque on the left upper abdomen with a constant contact surface until the VAS curve reached a stable plateau, which was observed for 1 min; in the absence of further increase, the ice was removed. Pre-topical therapy, the VAS began to rise at ~0.8 min (50 s), reached its peak at ~4.0 min, and plateaued until 5.0 min, and the ice was removed at 5.0 min; pain returned to baseline ~4 min after ice removal. After introducing topical diltiazem 2% to the entire affected field, the VAS began to rise later (~2.0 min), reached its peak at ~4.5 min and plateaued until 5.5 min, and the ice was removed at 5.5 min; baseline was re-attained ~3 min after ice removal. Peak intensity decreased from approximately VAS 9.5 pre-treatment to VAS 6.0 post-treatment, representing a reduction of about 3.5 VAS units. Topical diltiazem 2% delayed pain onset, prolonged time-to-peak, lowered

14409960, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ajd.70060 by Samet ÖNER - Dokuz Eylul University , Wiley Online Library on [12/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

peak intensity and accelerated recovery in cold-triggered pain (Figure 3).

2.6 | Outcomes and Tolerability

Patient-reported outcomes at presentation were VAS 9/10, BPI-SF Pain Severity 7.25, and BPI-SF Pain Interference 4.42; after 4 weeks of oral amlodipine 5 mg daily, VAS 5/10, BPI-SF Pain Severity 5.0, and BPI-SF Pain Interference 3.14; and 4 weeks after adding topical diltiazem 2%, VAS 2/10, BPI-SF Pain Severity 2.5, and BPI-SF Pain Interference 2.0.

The patient reported that the addition of the topical agent significantly reduced the frequency of spontaneous painful paroxysms and improved his sleep and daily functioning. No local irritation or systemic adverse effects were noted.

At 3-month telephonic follow-up, the patient reported continued adherence to the combined regimen with sustained maintenance of pain relief and functional improvement, and no late-onset adverse events.

3 | Discussion

Pain in cutaneous leiomyoma is thought to arise from convergent mechanisms that include Ca^{2+}-dependent smooth-muscle hypercontractility, α-adrenergic vasoconstriction with micro-ischemia, and mechanical compression of dermal nerve fibres within densely packed smooth-muscle fascicles. These pathways explain classic triggers—cold, pressure, and emotional stress—and provide a mechanistic rationale for calcium-channel blockade as a therapeutic strategy [1–3].

Topical calcium-channel blockade represents an emerging modality in cutaneous leiomyoma management. Published evidence remains limited, with topical nifedipine reported as a potentially effective option in painful cutaneous leiomyoma. In our case, topical diltiazem 2% was associated with improvement in pain in cutaneous leiomyoma, assessed using a controlled cold-provocation test. Notably, topical diltiazem has demonstrated analgesic benefit in anal fissure, a condition in which pain is likewise driven by Ca^{2+}-dependent smooth-muscle hypertonia. In a network meta-analysis of medical therapies for anal fissure, diltiazem ranked as the most effective agent for pain relief, supporting the biological rationale for topical diltiazem in cutaneous leiomyoma [8].

A practical advantage of topical calcium-channel blockers is the safety profile in normotensive patients, in whom escalation of oral agents may be constrained by systemic adverse effects such as dizziness, hypotension and headache. In our patient, oral amlodipine up-titration was intentionally avoided for this reason, and adjunctive topical diltiazem provided additional benefit without local irritation or systemic effects [9].

Our cold-provocation protocol—time-controlled ice application with VAS recorded at regular intervals until a stable plateau and

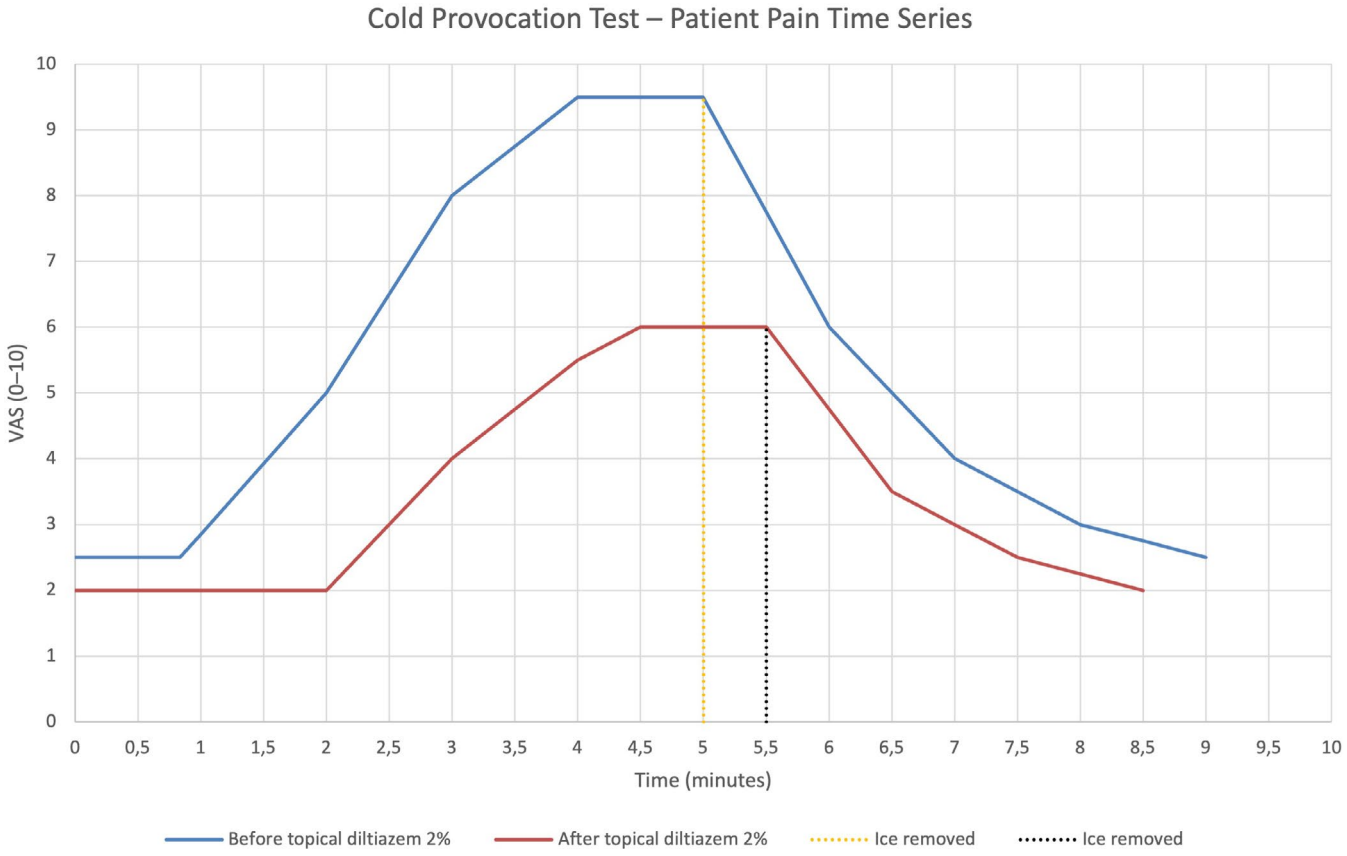


FIGURE 3 | Cold-provocation pain curves before and after topical diltiazem 2%: Ice was applied to a fixed area until a 1-min plateau, then removed (yellow/black lines). VAS (0–10) recorded every 30 s shows later onset, lower peak, and faster recovery after diltiazem (red) vs. before (blue).

14409960, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ajd.70060 by Samet ÖNER - Dokuz Eylul University , Wiley Online Library on [12/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

timed recovery—addresses a common gap in cutaneous leiomyoma studies: the lack of standardised assessments for trigger-evoked pain. We encourage future reports to include simple, repeatable stimulus–response curves with onset, peak, and recovery metrics to improve comparability across cases [1, 3].

Limitations of this report include the single-patient design, reliance on semi-quantitative VAS, and absence of blinding or sham control. Concomitant oral amlodipine constitutes a potential confounder; however, the incremental improvements after adding topical diltiazem—together with the shift in the stimulus–response curve—suggest an additional, localised effect. Follow-up duration remains modest; longer observation is needed to determine the sustainability of benefit.

4 | Conclusion

This brief report supports topical diltiazem 2% as a non-invasive, well-tolerated adjunct for painful, segmental cutaneous leiomyoma, providing objective improvements in cold-evoked hyperalgesia and daily-life pain metrics, and offering a mechanistically coherent alternative when systemic escalation is limited. Prospective, multicenter observational studies incorporating standardised provocation and recovery measures could help clarify patient selection, optimal formulations, and durability of response.

Acknowledgements

The authors thank the patient for granting permission to publish this case and the associated clinical images.

Funding

The authors have nothing to report.

Disclosure

AI Declaration: No artificial intelligence tools were used in the conception, analysis, or writing of this manuscript.

Ethics Statement

Ethics committee approval was not required for this single-patient case report, in accordance with institutional policy.

Consent

Written informed consent was obtained from the patient for publication of this report and accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. C. B. Archer, S. Whittaker, and M. W. Greaves, "Pharmacological Modulation of Cold-Induced Pain in Cutaneous Leiomyomata," *British Journal of Dermatology* 118, no. 2 (1988): 255–260, https://doi.org/10.1111/j.1365-2133.1988.tb01783.x.

2. V. A. Holst, J. M. Junkins-Hopkins, and R. Elenitsas, "Cutaneous Smooth Muscle Neoplasms: Clinical Features, Histologic Findings, and Treatment Options," *Journal of the American Academy of Dermatology* 46, no. 4 (2002): 477–490, https://doi.org/10.1067/mjd.2002.121358.

3. C. B. Archer and M. W. Greaves, "Assessment of Treatment for Painful Cutaneous Leiomyomas," *Journal of the American Academy of Dermatology* 17, no. 1 (1987): 141–142, https://doi.org/10.1016/s0190-9622(87)80546-7.

4. T. Hsu, L. A. Cornelius, I. S. Rosman, and K. M. Nemer, "Treatment of Cutaneous Leiomyomas With 5% Lidocaine Patches in a Patient With Hereditary Leiomyomatosis and Renal Cell Cancer (Reed Syndrome)," *JAAD Case Reports* 3, no. 5 (2017): 407–409, https://doi.org/10.1016/j.jdcr.2017.06.007.

5. R. Imhof, N. Bohrer, M. Youssef, and N. A. Mohandesi, "Topical Nifedipine for the Treatment of Painful Cutaneous Leiomyomas in Hereditary Leiomyomatosis and Renal Cell Cancer," *Journal of the American Academy of Dermatology* 93, no. 3 (2025): AB331, https://doi.org/10.1016/j.jaad.2025.05.1303.

6. M. Muller, S. Ferlicot, M. Guillaud-Bataille, et al., "Reassessing the Clinical Spectrum Associated With Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome in French FH Mutation Carriers," *Clinical Genetics* 92, no. 6 (2017): 606–615, https://doi.org/10.1111/cge.13014.

7. H. B. Naik, S. M. Steinberg, L. A. Middelton, et al., "Efficacy of Intralesional Botulinum Toxin A for Treatment of Painful Cutaneous Leiomyomas: A Randomized Clinical Trial," *JAMA Dermatology* 151, no. 10 (2015): 1096–1102, https://doi.org/10.1001/jamadermatol.2015.1793.

8. C. Wang, J. Ni, Y. Xiong, J. Chen, B. Li, and L. Xu, "The Efficacy of Diltiazem, Glyceryl Trinitrate, Nifedipine, Minoxidil, and Lidocaine for the Medical Management of Anal Fissure: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials," *International Journal of Surgery* 111, no. 4 (2025): 3020–3029, https://doi.org/10.1097/JS9.0000000000002263.

9. S. Aggarwal, D. De, A. J. Kanwar, U. N. Saikia, G. Khullar, and R. Mahajan, "Disseminated Cutaneous Leiomyomatosis Treated With Oral Amlodipine," *Indian Journal of Dermatology, Venereology and Leprology* 79, no. 1 (2013): 136, https://doi.org/10.4103/0378-6323.104694.

14409960, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ajd.70060 by Samet ÖNER - Dokuz Eylul University , Wiley Online Library on [12/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License