SKIN

IN-DEPTH REVIEW

A Review of Therapeutic Options for Linear Porokeratosis

Kritin K. Verma, MBA[1], Mojahed M. K. Shalabi, MD,[2] Aubrey C. Hartmann, MD[3], & Daniel P. Friedmann, MD[4]

[1] Texas Tech University Health Sciences Center School of Medicine, Lubbock, Texas
[2] Baylor Scott & White Medical Center, Department of Dermatology, Temple, Texas
[3] U.S. Dermatology Partners, Cedar Park, Texas
[4] Westlake Dermatology Clinical Research Center, Westlake Dermatology & Cosmetic Surgery, Austin, Texas

ABSTRACT

Linear porokeratosis (LP) is a rare and uncommon variant of porokeratosis presenting as linear annular papules or plaques along Blaschko's lines. It may arise spontaneously, although evidence of genetic predisposition exists via point mutations in the mevalonate pathway of cholesterol biosynthesis. Malignant transformation is the most serious complication of this chronic, progressive dyskeratosis. We review the currently available treatment options for LP, including topical, systemic, laser, photodynamic, and surgical therapies.

INTRODUCTION

Porokeratosis is a chronic, progressive cutaneous disorder of clonal keratinization that demonstrates sharply demarcated, hyperkeratotic, annular lesions with central atrophy and a characteristic raised keratotic edge corresponding histologically to a parakeratotic column within the stratum corneum, known as a coronoid lamella.[1] Among the different clinical variations of porokeratosis, Linear Porokeratosis (LP) is possibly the least prevalent, but it has major clinical consequences due to its propensity for malignant transformation and influence on patients' quality of life.[1,2]

LP demonstrates heterogeneous clinical features of mosaicism with unilateral blaschkoid segmental linear plaques on the trunk and extremities appearing congenitally or arising in infancy or childhood.[1,3] A combination of heterozygous germline and second-hit postzygotic somatic (*in utero*) loss-of-function mutations in mevalonate pathway genes (*PMKV*, *MVK*, *MVD*) have been implicated.[4] Familial (autosomal dominant) inheritance or *de novo* mutations are possible.[5] LP due to *PMKV* and *MVK* mutations may be more verrucous and inflammatory, while *MVD* mutations may lead to thinner but less inflammatory clinical lesions.[6] Loss of heterozygosity (allelic loss) at the root of LP may be the initial step in a multistep mutational process of carcinogenesis, posing a significant risk of malignant transformation to squamous cell (SCC) and basal cell carcinoma (BCC) in up to 11% of patients, particularly in LP and large or long-standing lesions in other clinical variants.[6-8] Overexpression of p53 within lesional epidermis, common to all forms of porokeratosis, also plays a role.[9] Early diagnosis and treatment of LP may reduce the risk of malignant degeneration.[8]

The purpose of this paper is to discuss the current treatment options for LP, which include topical, cryotherapy, photodynamic, laser, surgical, and systemic therapy.[1] These treatments are critical in controlling LP, lowering the risk of malignant transformation, and enhancing patients' quality of life.[1,2,6] Despite the disease's rarity, researching and enhancing these therapy choices is critical given the disease's potential morbidity and mortality, as well as the enormous impact it can have on patients' lives.[1,10]

MANAGEMENT OPTIONS

Although no randomized-controlled clinical trials have been performed for LP, several treatment options have been reported.[8]

Topical Therapies

Topical corticosteroids (e.g., clobetasol propionate) can reduce epidermal inflammation and normalize epidermal proliferation and may be valuable in the more inflammatory variant of LP.[11] Avoidance of long-term uninterrupted use of high-potency corticosteroids decreases the secondary risk of cutaneous atrophy and striae.[12]

Nonsteroidal topical immunosuppressive agents, such as tacrolimus (a calcineurin inhibitor) and imiquimod (a toll-like receptor agonist) can modulate the local cutaneous immune response, reducing inflammation and normalizing the epidermis.[13,14] A topical combination of betamethasone dipropionate ointment qdaily and tacrolimus 0.1% ointment BID led to rapid clinical improvement in lesion appearance and associated pain, pruritus, and paresthesias.[13] Use of topical imiquimod 5% cream qdaily (5 days per week) for 4 months led to complete lesion resolution, maintained at 1 year.[14] Imiquimod use with LP has been associated with irritation, burning, and pruritus, as well as focal hypopigmentation and ulceration.[8,14] Topical retinoids can regulate keratinocyte differentiation, decrease hyperproliferation, and modulate immune responses within the epidermis.[15] Treatment of generalized LP with tretinoin 0.05% (qdaily transitioned to qother day) produced lesion disappearance maintained at 1 year.[16] Topical tretinoin 0.05% gel qdaily was also reported to produce lesion resolution without relapse at 3 months.[17] Local irritation, dryness, and photosensitivity may nevertheless limit the use of these vitamin A derivatives over extended periods.[15]

Topical 5-fluorouracil (5-FU) is a cytostatic pyrimidine analog that inhibits DNA synthesis within hyperproliferative keratinocytes.[16,18] A case report of topical 5-FU 5% cream BID demonstrated lesion resolution maintained at 3 months.[16] However, 5-FU therapy may be commonly associated with cutaneous reactions such as tenderness, irritation, and erosion.[18]

Like retinoids, topical vitamin D_3 analogs can modulate epidermal keratinocyte differentiation, proliferation, and inflammation and are commonly used for psoriasis patients. Literature showed that applying topical vitamin D_3 ointment qdaily for 3 months resulted in minor lesional improvement.[19] While diclofenac 3% gel can produce symptomatic improvement of pruritus, other clinical benefits are minimal and inconsistent.[8] Topical salicylic acid 5% ointment has also been reported to show some benefit.[20]

The pathogenesis of LP is predicated on abnormalities of lipid biosynthesis, with loss-of-function mutations in mevalonate pathway genes leading to a deficiency in pathway end products (e.g., cholesterol) and accumulation of toxic early pathway metabolites (e.g.,

mevalonate).[21] A topical combination of statins and cholesterol may thereby block mevalonate generation and replenish deficient epidermal lipids, respectively.[21] Multiple case reports of LP patients treated with topical lovastatin 2%/cholesterol 2% have demonstrated lesion improvement (decreased erythema, thickness, and scaling) without adverse events.[21-24] A case series of LP treated with topical simvastatin/cholesterol had variable results, with some patients experiencing only mild improvement or lesion recurrence.[25]

Cryotherapy

Targeted lesion destruction with liquid nitrogen has been recommended.[20] A single patient treated with cryotherapy every 6-12 months over a 6-year period remained lesion-free at 2 years, albeit with hypopigmentation, atrophic scarring, and cicatricial alopecia.[26]

Photodynamic Therapy

Photodynamic therapy (PDT) combines an exogenous photosensitizing agent (e.g., 5-aminolevulinic acid [ALA] or methyl aminolevulinate [MAL]) with an activating light source, producing reactive oxygen species that selectively destroy aberrant porokeratotic keratinocytes.[27] Treatment of LP with PDT has been reported to produce promising results. A case report of 3 sessions of MAL-PDT produced very satisfactory results, while another case report of 2 sessions of MAL-PDT showed no recurrence at 11 months posttreatment.[28,29] Pain, tenderness, erythema, crusting, and most importantly, incomplete lesion clearance, have all been associated with PDT for LP.[30]

Laser Therapies

Multiple different lasers have been reported to improve or clear LP. Pulse dye lasers (PDL) can selectively target oxyhemoglobin within dilated superficial dermal blood vessels, leading to thermal injury and vessel eradication.[31] A case report of PDL for LP demonstrated complete clearance after 6 sessions.[32] Treatment typically produces erythema, edema, pain, and purpura, with a very low risk of scarring.[33] A report of ALA-PDT activated with PDL showed near-complete resolution 8 months after a single treatment.[34]

A case report of fractional carbon dioxide (CO_2) ablative laser therapy showed clearance in plantar lesions of LP with no evidence of recurrence 6 months posttreatment.[35] Periprocedural pain, posttreatment discomfort, erythema, and postinflammatory dyspigmentation may be associated with the procedure, although they were not seen in this case report.

Surgical Procedures

Dermabrasion with a diamond fraise motorized tip has been shown to produce lesion clearance without recurrence or scarring at 8 months, with only spotty dyspigmentation remaining.[36] Surgical management of LP with excision and Mohs micrographic surgery is typically only utilized when malignant transformation (SCC or BCC) has occurred within LP lesions.[37] Intralesional electrochemotherapy, combining intravenous bleomycin and intralesional electrode impulses, led to complete eradication of multiple SCCs and near-complete clearance of LP lesions, without recurrence at 1 year.[38]

Systemic Therapies

Systemic retinoid therapy (e.g., acitretin) may be considered in severe or generalized forms of LP.[15] A patient with a generalized form of LP refractory to ablative laser and numerous

topical therapies was started on acitretin (30 mg qdaily) in which they demonstrated clinical improvement after 1 month and complete resolution of cornoid lamella by 7 months.[39] Additionally, another case report showed that the clinical improvement produced by 1 mg/kg/day of acitretin for 7 weeks was further improved despite decreasing the dose to 0.5 mg/kg/day for an additional 5 weeks.[40] Careful monitoring is necessary to avoid potential side effects that include mucocutaneous dryness, hyperlipidemia, liver toxicity, and teratogenicity.[39]

CONCLUSION

Therapeutic options for LP are still being elucidated due to its rarity, propensity for malignant development, and lack of established therapeutic guidelines or algorithms. There are several treatment options available, ranging from pathogenesis-directed therapy with a combination of statins and cholesterol, which may be an effective first-line option, to symptom-directed medicines that target the disease's inflammatory, proliferative, or malignant aspects. Topical corticosteroids, tacrolimus, or imiquimod, as well as PDL, are anti-inflammatory medications. Topical retinoids, topical vitamin D3 analogs, topical 5-FU, oral retinoids, and PDT, on the other hand, provide both anti-inflammatory and anti-proliferative actions, regulating epidermal hyperkeratinization. Ablative therapies such as CO2 laser, cryotherapy, or dermabrasion can be used for very thick or treatment-refractory lesions.

Despite these possibilities, it is crucial to highlight that current LP care is mostly based on case reports and a few case series, with no randomized-controlled trials. This reveals a huge gap in our understanding and ability to manage this condition successfully. As a result, additional clinical research is critical for creating more successful, innovative therapeutic techniques. This is critical not just for preventing the premalignant disorder's malignant development but also for improving patient outcomes and quality of life. A critical need in the field is the pursuit of evidence-based therapy alternatives for LP, and future research should strive to address this.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:
Kritin K. Verma, MBA
3601 4th St, Lubbock, TX 79430
Phone: 858-539-9676
E-mail: kritin.k.verma@ttuhsc.edu

References:

1. Malhotra SK, Puri KJ, Goyal T, Chahal KS. Linear porokeratosis. Dermatol Online J. 2007;13(4):15.
2. Yang J, Du YQ, Fang XY, Li B, Xi ZQ, Feng WL. Linear porokeratosis of the foot with dermoscopic manifestations: A case report. World J Clin Cases. 2022;10(31):11585-11589. doi:10.12998/wjcc.v10.i31.11585
3. Nayak MK, Dhanta A, Hazarika N, Kumar A. Linear systematized porokeratosis - a rare case and dermoscopic clues to diagnosis. Indian Dermatol Online J. 2020;12(3):465-466. doi:10.4103/idoj.IDOJ_419_20
4. Atzmony L, Khan HM, Lim YH, Paller AS, Levinsohn JL, Holland KE, Mirza FN, Yin E, Ko CJ, Leventhal JS, Choate KA. Second-Hit, Postzygotic PMVK and MVD Mutations in Linear Porokeratosis. JAMA Dermatol. 2019 May 1;155(5):548-555. doi: 10.1001/jamadermatol.2019.0016
5. Zhang Z, Li C, Wu F, et al. Genomic variations of the mevalonate pathway in porokeratosis. Elife. 2015;4:e06322. doi:10.7554/eLife.06322
6. Saleva-Stateva M, Hess M, Technau-Hafsi K, et al. Molecular characterization and natural history of linear porokeratosis: A case series. J Am Acad Dermatol. 2021;85(6):1603-1606. doi: 10.1016/j.jaad.2020.11.061

7. Happle R. Cancer proneness of linear porokeratosis may be explained by allelic loss. Dermatology. 1997;195(1):20-5. doi: 10.1159/000245678.
8. Weidner T, Illing T, Miguel D, Elsner P. Treatment of porokeratosis: a systematic review. *Am J Clin Dermatol*. 2017;18(4):435-449. doi:10.1007/s40257-017-0271-3
9. Sasaki S, Urano Y, Nakagawa K, et al. Linear porokeratosis with multiple squamous cell carcinomas: study of p53 expression in porokeratosis and squamous cell carcinoma. Br J Dermatol. 1996;134(6):1151-1153. doi: 10.1111/j.1365-2133.1996.tb07965.x
10. Williams GM, Fillman EP. Porokeratosis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; September 28, 2022.
11. Balasubramanian S, Mangalampalli VR, Vasudevan B. Linear porokeratosis: an uncommon presentation of a common condition. Indian J Dermatol. 2017;62(6):632-634.
12. Pels R, Sterry W, Lademann J. Clobetasol propionate--where, when, why?. Drugs Today (Barc). 2008;44(7):547-557. doi:10.1358/dot.2008.44.7.1122221
13. Parks AC, Conner KJ, Armstrong CA. Long-term clearance of linear porokeratosis with tacrolimus, 0.1%, ointment. JAMA Dermatol. 2014;150(2):194-196. doi:10.1001/jamadermatol.2013.8526
14. Ahn SJ, Lee HJ, Chang SE, et al. Case of linear porokeratosis: successful treatment with topical 5% imiquimod cream. J Dermatol. 2007;34(2):146–7. doi:10.1111/j.1346-8138.2006.00236.x
15. Zasada M, Budzisz E. Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments. Postepy Dermatol Alergol. 2019;36(4):392-397. doi:10.5114/ada.2019.87443
16. Grover C, Goel A, Nanda S, et al. A case of extensive linear porokeratosis with evaluation of topical tretinoin versus 5-fluorouracil as treatment modalities. J Dermatol. 2005;32(12):1000-1004. doi:10.1111/j.1346-8138.2005.tb00890.x
17. Dervis E, Demirkesen C. Generalized linear porokeratosis. Int J Dermatol. 2006;45(9):1077–9. doi:10.1111/j.1365-4632.2004.02490.x
18. Balato N, Di Nardo G, Boccia L, Nappa P. [Linear Mibelli's porokeratosis. Treatment with topical 5-fluorouracil]. G Ital Dermatol Venereol. 1986;121(2):147-148.
19. Kohara Y, Takeo T, Oshima Y, et al. Linear porokeratosis with nail dystrophy. Eur J Dermatol. 2011;21(4):625–6. doi:10.1684/ejd.2011.1393
20. Yang J, Du YQ, Fang XY, et al. Linear porokeratosis of the foot with dermoscopic manifestations: a case report. World J Clin Cases. 2022;10(31):11585-11589. doi:10.12998/wjcc.v10.i31.11585
21. Atzmony L, Lim YH, Hamilton C, et al. Topical cholesterol/lovastatin for the treatment of porokeratosis: a pathogenesis-directed therapy. J Am Acad Dermatol. 2020;82(1):123-131. doi: 10.1016/j.jaad.2019.08.043
22. Buhle AC, Fagan KK, Johnson NM, Grider DJ. Treating linear porokeratosis with topical lovastatin/cholesterol cream. Dermatol Online J. 2022 Oct 15;28(5). doi: 10.5070/D328559247
23. Diep D, Janitz T, Kannan KS, Crane A, Aluri B, Wright K, Baker W. Bilateral linear porokeratosis treated with topical cholesterol 2%/lovastatin 2. Cureus. 2022 Jul 31;14(7):e27540. doi: 10.7759/cureus.27540
24. Blue E, Abbott J, Bowen A, Cipriano SD. Linear porokeratosis with bone abnormalities treated with compounded topical 2% cholesterol/2% lovastatin ointment. Pediatr Dermatol. 2021;38(1):242-245. doi: 10.1111/pde.14447
25. Saleva-Stateva M, Weibel L, Theiler M, Balabanova M, Boente MC, Has C. Lack of effect of topical statins in linear porokeratosis. J Eur Acad Dermatol Venereol. 2021;35(1):e26-e28. doi: 10.1111/jdv.16768
26. Bhushan M, Craven NM, Beck MH, Chalmers RJ. Linear porokeratosis of mibelli: successful treatment with cryotherapy. Br J Dermatol. 1999;141(2):389. doi: 10.1046/j.1365-2133.1999.03023.x
27. Calzavara-Pinton PG, Rossi MT, Aronson E, Sala R; Italian Group For Photodynamic Therapy. A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinate (MAL-PDT) in 20 Italian dermatology departments. Part 1: inflammatory and aesthetic indications. Photochem Photobiol Sci. 2013;12(1):148-57. doi: 10.1039/c2pp25124h
28. Curkova AK, Hegyi J, Kozub P, et al. A case of linear porokeratosis treated with photodynamic therapy with confocal microscopy surveillance. Dermatol Ther. 2014;27(3):144-147. doi:10.1111/dth.12097

29. García-Navarro X, Garcés JR, Baselga E, Alomar A. Linear porokeratosis: excellent response to photodynamic therapy. Arch Dermatol. 2009;145(5):526-527. doi:10.1001/archdermatol.2009.45
30. Garrido-Colmenero C, Ruiz-Villaverde R, Martínez-García E, Aneiros-Fernández J, Tercedor-Sánchez J. Photoletter to the editor: Response of linear porokeratosis to photodynamic therapy in an 11-year-old girl. J Dermatol Case Rep. 2015;9(4):118-119. doi:10.3315/jdcr.2015.1220
31. Bernstein EF. The pulsed-dye laser for treatment of cutaneous conditions. G Ital Dermatol Venereol. 2009;144(5):557-572.
32. Alster TS, Nanni CA. Successful treatment of porokeratosis with 585 nm pulsed dye laser irradiation. Cutis. 1999;63(5):265-266.
33. Husain Z, Alster TS. The role of lasers and intense pulsed light technology in dermatology. Clin Cosmet Investig Dermatol. 2016;9:29-40. doi:10.2147/CCID.S69106
34. Casale F, Tchanque-Fossuo CN, Durkin JR. Successful clearance of linear porokeratosis with aminolevulinic acid and pulsed dye laser. Dermatol Surg. 2021;47(9):1300-1301. doi: 10.1097/DSS.0000000000002996
35. Barnett JH. Linear porokeratosis: treatment with the carbon dioxide laser. J Am Acad Dermatol. 1986;14(5 Pt 2):902-904. doi:10.1016/s0190-9622(86)70108-4
36. Cohen PR, Held JL, Katz BE. Linear porokeratosis: successful treatment with diamond fraise dermabrasion. J Am Acad Dermatol. 1990;23(5 Pt 2):975-7. doi: 10.1016/0190-9622(90)70317-b
37. Abbott-Frey AM, Coromilas AJ, Niedt GW, Lewin JM. Recurrent squamous cell carcinoma arising within a linear porokeratosis. J Drugs Dermatol. 2020;19(2):205-206. doi:10.36849/JDD.2020.4640
38. Sommerlad M, Lock A, Moir G, McGregor J, Bull R, Cerio R, Harwood C. Linear porokeratosis with multiple squamous cell carcinomas successfully treated by electrochemotherapy. Br J Dermatol. 2016;175(6):1342-1345. doi: 10.1111/bjd.14669
39. Hong JB, Hsiao CH, Chu CY. Systematized linear porokeratosis: a rare variant of diffuse porokeratosis with good response to systemic acitretin. J Am Acad Dermatol. 2009;60(4):713-5. doi: 10.1016/j.jaad.2008.10.011
40. Pehamberger H, Konrad K. Treatment with an oral aromatic retinoid in linear porokeratosis. Dermatologica. 1980;160(4):270-4. doi: 10.1159/000250503