A Review of Therapeutic Options for Linear Porokeratosis

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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.¹²

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.¹³ 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

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The purpose of this paper is to discuss the current treatment options for LP, which include topical, cryotherapy, photodynamic, laser, surgical, and systemic therapy. These treatments are critical in controlling LP, lowering the risk of malignant transformation, and enhancing patients’ quality of life. 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.

**MANAGEMENT OPTIONS**

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

**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. Avoidance of long-term uninterrupted use of high-potency corticosteroids decreases the secondary risk of cutaneous atrophy and striae.

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. 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. Use of topical imiquimod 5% cream qdaily (5 days per week) for 4 months led to complete lesion resolution, maintained at 1 year. Imiquimod use with LP has been associated with irritation, burning, and pruritus, as well as focal hypopigmentation and ulceration. Topical retinoids can regulate keratinocyte differentiation, decrease hyperproliferation, and modulate immune responses within the epidermis. Treatment of generalized LP with tretinoin 0.05% (qdaily transitioned to qother day) produced lesion disappearance maintained at 1 year. Topical tretinoin 0.05% gel qdaily was also reported to produce lesion resolution without relapse at 3 months. Local irritation, dryness, and photosensitivity may nevertheless limit the use of these vitamin A derivatives over extended periods.

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

Like retinoids, topical vitamin D3 analogs can modulate epidermal keratinocyte differentiation, proliferation, and inflammation and are commonly used for psoriasis patients. Literature showed that applying topical vitamin D3 ointment qdaily for 3 months resulted in minor lesional improvement. While diclofenac 3% gel can produce symptomatic improvement of pruritus, other clinical benefits are minimal and inconsistent. Topical salicylic acid 5% ointment has also been reported to show some benefit.

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.,...
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 (CO2) 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 Intraleisonal electrochemotherapy, combining intravenous bleomycin and intraleisonal 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.\(^\text{39}\) 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.\(^\text{40}\) Careful monitoring is necessary to avoid potential side effects that include mucocutaneous dryness, hyperlipidemia, liver toxicity, and teratogenicity.\(^\text{39}\)

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.

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