Treatment of Porokeratosis of Mibelli With Ingenol Mebutate
A Possible New Therapeutic Option

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Report of a Case
A woman in her 50s presented with an 8-year history of an annular plaque in the left perioral area. Physical examination showed a thick hyperkeratotic annular plaque with elevated edges and an atrophic center (Figure 1). Histopathologic examination of the lesion revealed a cornoid lamella, an underlying epidermis devoid of a granular layer, and a lymphocytic infiltration in the upper dermis. The clinical and histopathologic features were consistent with a diagnosis of porokeratosis of Mibelli.

The patient had received diverse consecutive treatments since 2008, including photodynamic therapy with aminolevulinic acid, electrocoagulation, an 8-week course of fluorouracil cream, topical treatment with the 2-compound formulation betamethasone (50 μg/g) and calcipotriol (0.5 mg/g), carbon dioxide laser, and 2 courses of imiquimod, 5%, for 6 weeks. None of the treatments had been successful. Significant hypopigmentation, possibly triggered by the strong inflammatory response, was observed in the lesion after treatment with fluorouracil cream. This hypopigmentation remained unchanged at last follow-up. The patient was also treated with pulsed-dye laser in 2012 and with diclofenac sodium, 3%, gel applied twice daily for 3 months in 2013. Neither of these treatments achieved partial or total remission of the lesion.

Therapeutic Challenge
Multiple treatments have been described for porokeratosis of Mibelli, but the results have frequently been disappointing. Treatment should be individualized, with consideration of cosmetic and functional impact and patient preferences. The possibility of malignant transformation must also be taken into account.

Multiple topical treatments, including corticosteroids, retinoids, fluorouracil, diclofenac, imiquimod, calcipotriol, keratolytics, and emollients have been used, with variable results. 1,2 In a recent report, cantharidin, 0.7%, was used successfully in 2 patients. 3 In another recent publication, topical tacrolimus was reported to have been used for linear porokeratosis. 4 Other, more aggressive, treatments have also been used, including surgical excision, fractional photothermolysis, dermabrasion, cryotherapy, and oral retinoids. 1,5,6

Because treatment can cause scarring and pain, asymptomatic lesions are often managed conservatively with sun protection, emollients, and monitoring for signs of malignant degeneration. Our patient was a woman who had a single lesion without indication of malignant transformation on the face, where cosmetic results were very important. The treatment therefore had to be nonscarring and safe.

Solution
The patient was treated with 2 courses of ingenol mebutate, 0.015%, topical gel applied once daily for 3 consecutive days. The courses were separated by a month. The lesion showed slight inflammation for a week after both treatment courses.

Three weeks after completion of the second course, the lesion had partially cleared, and the clinical and cosmetic results were highly satisfactory (Figure 2). The lesion exhibited central atrophy and hypopigmentation identical to that present before treatment.
porokeratosis, possibly due in part to the typical central atrophy of porokeratosis of Mibelli and to the multiple previous treatments. The hypopigmentation was most striking after treatment with fluorouracil cream. Treatment with ingenol mebutate resolved the hyperkeratotic annular plaque but had no noticeable effect on the atrophy or hypopigmentation.

At the 4-month follow-up visit, there were no signs of recurrence. The patient was very satisfied, and she was completely free of pain throughout the treatment course.

Discussion
Porokeratosis is a primary disorder of epidermal keratinization, characterized by annular plaques with an atrophic center and hyperkeratotic edges. The disorder encompasses a group of diseases with diverse phenotypic expressions of the same genetic defect that is mainly inherited in an autosomal dominant form. Although the pathogenesis remains unclear, porokeratosis is thought to result from clonal proliferation of genetically abnormal epidermal keratinocytes that form the cornoid lamella seen on histologic analysis. Other histologic features are loss of the granular layer at the base of the cornoid lamella, dilated superficial plexus capillaries, and a non-specific superficial chronic infiltrate.

Our patient had classic porokeratosis of Mibelli. Porokeratosis lesions can affect any part of the skin but are more common on the trunk and extremities. They are generally asymptomatic. Skin biopsy and histologic examination are essential for diagnosis. Poro-

keratosis has oncogenic potential, with malignant transformation occurring in approximately 7% of patients. Squamous cell carcinoma is the most commonly associated tumor. Treatment should therefore preferably target the inhibition and differentiation of keratinocytes, with minimal disfiguration, discomfort, and recurrence.

Ingenol mebutate, also known as ingenol 3-angelate, is an extract from the sap of the noninvasive weed Euphorbia peplus. It is formulated as a propyl alcohol–based gel for topical use and is approved for the treatment of actinic keratosis. The gel is available in 2 concentrations: 0.015% for treatment of the face and scalp and 0.05% for treatment of other parts of the body. The recommended treatment is once-daily application for 3 consecutive days. The direct effect of the drug, along with local production of inflammatory cytokines, is initial lesion ablation characterized by rapid disruption of the plasma membrane and subsequent mitochondrial swelling followed by cell death via primary necrosis. The second phase is marked by an acute inflammatory response due to neutrophil infiltration. Additionally, ingenol mebutate is a protein kinase C pathway activator and promotes caspase apoptosis, p53 stability, and phosphorylation of signaling molecules.

Treatments that target keratinocyte inhibition and differentiation (eg, ingenol mebutate) could be successful in porokeratosis of Mibelli, where there is a clonal proliferation of genetically abnormal epidermal keratinocytes. Although further studies are required to prove its effectiveness, ingenol mebutate appears to be a promising treatment for single lesions of porokeratosis of Mibelli.

REFERENCES