Porokeratosis is a disorder of abnormal keratinization with multiple clinical variants. It is often difficult to achieve complete resolution of porokeratosis even with a variety of therapies that have been reported to have some efficacy.

Report of a Case

A woman in her 40s with no significant medical history was referred for evaluation of a painful dermatitis on her left arm. Approximately 1 year earlier, a painful, pruritic, erythematous papule had developed on her left arm, which subsequently spread into a linear array of papules extending from her left wrist up her arm to her neck, associated with pruritus, paresthesias, and pain. 3- to 10-mm erythematous papules with overlying scales were arranged in a linear pattern extending up the ventral part of her arm, across her shoulder to the left side of her neck and chest (Figure 1). Several lesions exhibited an outer hyperkeratotic rim. She had similarly shaped areas of hyperpigmentation without overlying epidermal change on her left arm and on the left side of her chest and neck.

A skin biopsy sample revealed a vertical column of parakeratosis within the stratum corneum, an absent granular layer underly- ing the column, and a focal lymphohistiocytic infiltrate underlying the epidermal change. The clinical and histopathologic features confirmed a diagnosis of linear porokeratosis. The patient had been treated with betamethasone dipropionate, 0.05%, ointment for several months with minimal improvement; oral acitretin treatment was subsequently started at 25 mg/d. After 3 months of acitretin treatment, she had no improvement of the lesions on her arm but had adverse effects, including scaling of her palms and soles and dryness of her lips and face.

We continued daily treatment with betamethasone dipropionate, 0.05%, ointment and added tacrolimus, 0.1%, ointment, administered twice daily, to the patient’s treatment regimen. Oral acitretin treatment was discontinued because it had caused adverse effects with no skin improvement. With the combination of betamethasone and tacrolimus, the skin lesions improved rapidly and dramatically. At the 2-month follow-up examination, the patient had hyperpigmented macules and patches in a linear pattern up the ventral side of her left arm and across the shoulder to her neck on the left side, consistent with postinflammatory hyperpigmentation. The inflammation had completely cleared. In addition to improved skin lesions, the patient reported complete resolution of associated pain, pruritus, and paresthesia.

The patient was followed up at 3- to 6-month intervals for 2½ years, during which her skin showed continued improvement. Tacrolimus treatment was tapered down to once-daily administration to areas of postinflammatory hyperpigmentation and any new lesions, with betamethasone used only on new lesions. At 2½-year follow-up, the daily tacrolimus treatment was discontinued. At examination, the patient’s skin was essentially back to baseline, with only a few very faint reticulated pale-brown macules (Figure 2), thus demonstrating the long-term efficacy of treatment with topical betamethasone and tacrolimus.

Discussion

Porokeratosis is a disorder of abnormal keratinization characterized by at least 5 known clinical variants: porokeratosis of Mibelli, disseminated superficial actinic porokeratosis, linear porokeratosis, punctate porokeratosis, and porokeratosis palmaris et plantaris disseminata. The varying clinical presentations of porokeratosis are unified by the classic histologic finding of the cornoid lamella, which is thought to correlate with the hyperkeratotic ridge found clinically and is the result of hyperproliferation of keratinocytes. Although its exact pathogenesis remains unknown, porokeratosis may be triggered by immunosuppression, exposure to UV radiation, or genetic predisposition.

Linear porokeratosis was first described as a distinct clinical entity in the 1970s.1 Lesions typically arise in infancy or childhood and consist of annular papules and plaques with a hyperkeratotic border, similar to classic porokeratosis. The lesions characteristically follow the lines of Blaschko and are most commonly found on the extremities. Linear porokeratosis is particularly difficult to treat because of its widespread distribution, but it is particularly important to treat because of its risk of malignant degeneration. Although the rate of malignant transformation for porokeratosis overall is 7.5%, the rate for linear porokeratosis is 19%.2 Therefore, treatment approaches that effectively clear these lesions may decrease the risk of local malignant degeneration.

Although many treatment options have been reported to improve porokeratosis, achieving complete resolution of lesions is notoriously difficult. Because of the varied clinical presentations of porokeratosis, treatment options must be tailored based on the size and location of the lesions and the amount of distress experienced by the patient. Many patients may be treated conservatively with sun protection, emollients, and observation for malignant degeneration.

A variety of reported treatments have demonstrated some degree of success, including topical retinoids, fluorouracil cream, 5% imiquimod cream, and topical vitamin D analogues. Treatment with oral retinoids has also proved beneficial, yet disease often recurs after discontinuation of therapy.3 Destructive options more appropriate for local variants include excision, cryotherapy with liquid nitrogen, dermabrasion, and chemical peels. In addition, a variety of laser therapies and photodynamic therapy have shown variable efficacy. These destructive, surgical, and laser therapies are not suitable for widespread disease, however, because they cause scarring and pain. Because recurrence is common with the treatment options currently available for disseminated disease, alternative therapies are necessary, and because several of the conventional treat-
ments for porokeratosis had been tried without success in our patient, we tried using a novel therapy.

To our knowledge, there are no previous reported cases of successful treatment of any clinical variant of porokeratosis with a calcineurin inhibitor, such as tacrolimus. One report described minimal efficacy of topical pimecrolimus in a 25-year-old woman with facial porokeratosis. Calcineurin inhibition results in downregulation of T-cell activity and disturbance of cytokine transcription. Currently, topical calcineurin inhibitors are used to treat atopic dermatitis by interrupting proinflammatory cytokines of the early immune response and potentially acting on other cells important to the pathophysiologic mechanism of this condition, such as dendritic cells, mast cells, keratinocytes, basophils, and eosinophils.

Treatment of porokeratosis with calcineurin inhibitors seems contradictory because of the potent immunosuppressive action on T cells, but a newly proposed pathophysiologic mechanism might explain the effectiveness of tacrolimus in porokeratosis. Low concentrations of a calcineurin inhibitor, pimecrolimus, enhanced expression of activation markers of the innate immune system in human keratinocytes. Specifically, pimecrolimus enhances expression of cathelicidin, CD14, and human β-defensin 2 and 3 in response to toll-like receptor 2/6 ligands. Keratinocytes rely on toll-like receptors to detect breaches in the skin barrier and activate the innate immune response. Further results suggest that pimecrolimus can amplify innate immune responses in keratinocytes. Therefore, we
hypothesize that tacrolimus similarly amplifies the innate immune response in keratinocytes, prevents the proliferation of abnormal keratinocytes, and thus improves the lesions of porokeratosis. This may also explain why imiquimod leads to improvement of porokeratosis by inducing inflammation through activation of toll-like receptors. Because systemic immunosuppression potentially increases the risk of porokeratosis, this highlights the distinct regulation of innate and adaptive immunity.

This is the first report, to our knowledge, of linear porokeratosis successfully treated with topical tacrolimus. The report is unique because of both the linear appearance of our patient’s disease and its rapid and dramatic response to tacrolimus. We hypothesize that topical tacrolimus was the treatment primarily responsible for the resolution of her porokeratosis, given that her lesions had not previously responded to betamethasone or acitretin monotherapy. However, acitretin was still present in her body, and its role in association with betamethasone and tacrolimus cannot be determined.

In conclusion, tacrolimus may be an effective and safe alternative to conventional treatments for porokeratosis. However, controlled studies with more patients and long-term follow-up are needed to evaluate its true effectiveness.

REFERENCES