Treatment of Porokeratosis of Mibelli With Combined Use of Photodynamic Therapy and Fluorouracil Cream

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A 45-year-old white man with a medical history that was remarkable for human immunodeficiency virus and AIDS complicated by Kaposi sarcoma presented with a 14-year history of a recurring scaly, pruritic lesion on the dorsal aspect of his left shin. The lesion was refractory to treatment with topical corticosteroids, tazarotene, salicylic acid, and various emollient and keratolytic creams. Recently, the lesion had become increasingly large, pruritic, painful, and cosmetically displeasing. Skin examination of the left dorsal shin area showed a thick, hyperkeratotic plaque with a distinct, raised annular border (Figure 1). A skin biopsy specimen revealed a broad-based parakeratotic column of cells traversing the stratum corneum (cornoid lamella), an underlying epidermis devoid of a granular layer, and dissolution of basal cells with shouldering acantholysis. A sparse, nonspecific, lymphocytic infiltrate was seen in the upper dermis (Figure 2). The clinical and histopathologic features supported a diagnosis of porokeratosis of Mibelli (PM). The patient was treated with a 4-week trial of imiquimod cream followed by an 8-week trial of fluorouracil cream, without success.

Many treatments have been suggested for porokeratosis, and the results have often been disappointing. The approach to treatment is individualized and based on many factors, such as lesion size and location, risk of malignant transformation, and functional and aesthetic considerations. Sun protection, aggressive use of emollients, and observation for signs of malignant degeneration may be all that is needed in many cases. However, if the lesions are widespread or displeasing, curative therapy is warranted.

It has been suggested that a lesion of porokeratosis results from a local or systemic change in immune function that in turn allows the development of atypical clones of keratinocytes. Useful medical modalities should therefore work by inhibiting cell growth and proliferation as well as regulating and modulating keratinocyte differ-
Porokeratosis is a disorder of abnormal keratinization with many clinical variations. It is characterized by the appearance of 1 or more atrophic patches surrounded by a clinically and histologically unique ridgelike border termed the cornoid lamella. The cornoid lamella is formed by a rapid hyperproliferation of atypical keratinocytes that expands peripherally to form a raised boundary between abnormal and normal cells. Lesions are most commonly found on the extremities, and in the setting of immunosuppression, they are large and rapidly expanding. Most often, the skin lesions of porokeratosis are asymptomatic; however, ulcerative, verrucous, giant, and malignant lesions have been identified. Risk factors for all forms of porokeratosis include immunosuppression, genetic inheritance, and UV radiation. Microscopic examination of a skin biopsy specimen from an area of suspicion is essential for diagnosis.

The final common pathway in all forms of porokeratosis is a clonal hyperproliferation of atypical keratinocytes resulting in the cornoid lamella. Porokeratosis of Mibelli is perhaps the most distinctive variant both clinically and histopathologically. Histologically, the invaginations of the epidermis are wider and deeper, and there is prominent adjacent papillomatosis when compared with the other variants. Aside from this, all variants (and related disorders that harbor cornoid lamellae) seem to represent a uniform reaction pattern of cornoid lamella, diminution of the granular layer, dilated superficial plexus capillaries, and a nonspecific superficial chronic infiltrate.

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Photodynamic therapy is a relatively new treatment modality that is currently used for the treatment of various skin cancers, actinic keratosis, and acne. It uses topically applied aminolevulinic acid or methyl aminolevulinate that penetrates damaged or active epidermal cells and is converted to a potent photosensitizing protoporphyrin IX. Studies have shown that 3 mechanisms contribute to the efficacy of PDT: (1) direct cell destruction through the activation of protoporphyrin IX and the subsequent formation of reactive cytotoxic oxygen species; (2) microvascular damage that causes hypoxia and tissue necrosis; and (3) up-regulation of tumor necrosis factor α, interleukin 1, and interleukin 6, which aid in the elimination of tumor tissue. The penetration of light into tissue varies and is inversely proportional to the increasing wavelength. The largest absorption peak of the reactive intermediates is at 410 nm (blue light), with smaller absorption peaks at 505, 540, 580, and 630 nm (red light). Blu-U takes advantage of the largest absorption peak at 417 nm but is limited to a depth of penetration of 1.5 to 2 mm into the epidermis. Red light (>600 nm) requires higher energy levels to achieve the same effect because of the lower protoporphyrin IX light absorption at longer wavelengths, but it has the advantage of a deeper dermal penetration depth of 8 to 10 mm.

Currently, 3 case reports have reported the use of methyl aminolevulinate PDT with red light for the treatment of disseminated superficial actinic porokeratosis, with varying results, and, to our knowledge, no reports have cited the use of aminolevulinic acid PDT with blue light or in combination with any current traditional therapies for PM. In light of this and the known efficacy of PDT in treating actinic keratosis, a disorder similarly characterized by actinically mediated atypical cell proliferation, it is possible that the distinctive histologic features of PM make therapy with both PDT and fluorouracil a potentially useful treatment option when they are used in combination for recalcitrant cases. Photodynamic therapy and fluorouracil work by 2 indepen-
dent mechanisms of action: (1) PDT selectively targets highly active, atypical cells and causes destruction by the creation of toxic intermediates; and (2) fluorouracil works by inhibiting a major enzyme that is responsible in the rate-limiting step of DNA synthesis, thus selectively inhibiting the rapid division of cells. We hypothesize that PDT was the primary modality responsible for the clearance of the PM lesion given that the patient’s condition had not previously responded to fluorouracil monotherapy. We cannot exclude an additive or synergistic effect of fluorouracil to PDT. Nonetheless, PDT with or without combination therapy for PM appears to be safe, effective, and an excellent alternative solution for this therapeutically challenging condition.

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REFERENCES