CASE REPORT

Treatment of porokeratosis of Mibelli with combined use of topical fluorouracil and calcipotriene

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Key words: calcipotriene; fluorouracil; Mibelli; porokeratosis.

INTRODUCTION

Porokeratoses are precancerous keratinocyte proliferations with distinct hyperkeratotic rims called cornoid lamellae. The most common porokeratosis is disseminated superficial actinic porokeratosis, characterized by multiple thin papules on the lower extremities. The second most common porokeratosis is porokeratosis of Mibelli (PM), which typically begins as one to a few small brown papules on the extremities that enlarge into plaques.

Porokeratoses are prevalent in immunocompromised individuals, with reported incidences as high as 10% in transplant patients.1 Keratinocyte carcinomas show aggressive behavior in solid organ transplant recipients, leading to increased morbidity and mortality.1 Therefore, successful treatment of porokeratoses in this at-risk patient population may lead to better outcomes.

Unfortunately, all forms of porokeratosis have been notoriously difficult to treat. Previously reported treatments include cryotherapy, topical agents (5-fluorouracil [5-FU], imiquimod, retinoids, calcipotriene, and cholesterol/lovastatin2), acitretin, photodynamic therapy,3 laser, and surgery. Surgery may not always be feasible depending on the size and location of the lesion, as well as the risk of scarring, while the risk of long-term systemic medications may not be warranted for treating a few lesions. To date, a consistently effective long-term topical treatment for porokeratoses remains to be identified.

The combination of 5-FU/calcipotriene has been shown to have a synergistic effect in activating CD4+ T cell-mediated immunity against actinic keratoses and squamous cell carcinomas, resulting in a sustained effect.4,5 We hypothesized that a similarly effective immune response may be seen in treating PM. Here we present a transplant patient who experienced complete clearance of his PM after application of topical 5-FU/calcipotriene.

CASE DESCRIPTION

A 46-year-old man with a history of cardiac and renal transplant on tacrolimus, mycophenolate mofetil, and prednisone presented with an asymptomatic lesion on his left thigh. Skin examination showed a 1 cm thin pink plaque with telangiectasias and scale. Skin biopsy revealed a cornoid lamella consistent with PM (Fig 1, A). No treatments were performed at that time, given recurrence of a prior PM treated with cryotherapy. Two years later, the lesion had enlarged to 1.4 cm with hemorrhagic crusting. Given these changes, repeat skin biopsy was performed, which was again consistent with PM (Fig 1, B). No treatments were performed at that time. Two years later, the patient reported persistent bleeding and frequent catching of the lesion on his clothing. Skin examination showed a 1.5-cm oval pink plaque with a peripheral rim of scale and hemorrhagic crust on his left medial thigh (Fig 2, A). The patient was instructed to mix 5-FU 5% cream

Abbreviations used:

FU: fluorouracil
PM: porokeratosis of Mibelli

JAAD Case Reports 2021;9:54-6.

2352-5126

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https://doi.org/10.1016/j.jdcr.2021.01.012
in a 1:1 weight ratio with 0.005% calcipotriene cream and to apply a thin layer to the affected area twice daily for 5 days. This treatment was well-tolerated and followed by complete clearance of the PM, which has been sustained for 28 months (Fig 2, B).

DISCUSSION

Given the higher risk of poor outcome if malignant transformation of PM occurs in post-transplant patients, consistently effective therapies with sustained response are needed. In this case, we saw an effect of topical 5-FU/calcipotriene in PM, with 5 days of this regimen inducing complete and sustained clearance of PM. Of note, we have observed similar, partial clearance of a much larger PM with this regimen in another cardiac/renal transplant patient whose PM was refractory to cryotherapy, 5-FU alone, and tretinoin. The 5-FU/calcipotriene combination has previously been shown in mouse models to stimulate expression of thymic stromal lymphopoietin and synergistically activate CD4+ T cell-mediated immunity against actinic keratoses, thereby reducing the incidence of squamous cell carcinoma in treated areas.4,5 Topical 5-FU/calcipotriene has also been reported as an effective treatment option for refractory extramammary Paget disease, presumably through a similar synergistic activation of T cell anti-tumor immunity.6

Importantly, by generating T cell-mediated immunity against actinic keratoses, topical 5-FU/calcipotriene is thought to potentially establish an anti-tumor immune memory via skin-resident T cells, thereby affording long-term skin cancer suppression.5 Indeed, Rosenberg et al found that 5-FU/calcipotriene prevented squamous cell carcinoma development on the face and scalp within 3 years after treatment.3 While this case demonstrates the efficacy of topical 5-FU/calcipotriene in stimulating a localized immune response to successfully treat PM in an immunocompromised patient, it would be helpful to determine whether this combination similarly reduces skin cancer development in this high-risk population.

Imiquimod, a Toll-like receptor agonist that stimulates innate immune response, has also been shown to be effective in the treatment of PM.7 Topical 5% imiquimod applied 3–5 days per week for 5–6 weeks with occlusion led to clearance of PM.8 Topical imiquimod and 5-FU in combination have also successfully led to complete clearance of porokeratoses in immunosuppressed and post-transplant patients.9,10 It has been proposed that the presence of human papillomavirus within these lesions contributes to successful activation of the immune response.9 While topical imiquimod has been shown to be effective in PM, 5-FU/calcipotriene combined has a much shorter treatment course which may result in increased patient compliance. In addition, because 5-FU/calcipotriene is a T cell-directed immunotherapy, repeat treatment cycles in immunosuppressed patients may further boost the efficacy.

In summary, we describe a cardiac and renal transplant patient on immunosuppression with biopsy-proven PM recalcitrant to cryotherapy who achieved sustained complete clearance after immunotherapy with topical 5-FU/calcipotriene. Given the lack of consistently effective topical therapies with sustained response, immunotherapy with topical 5-FU/calcipotriene should be further studied and considered by dermatologists as a therapeutic option in the treatment of PM. While this isolated case is promising, further studies with larger patient cohorts and longer follow-up, as well as immunologic analysis of the response, will help confirm the clinical benefit of this topical regimen and help elucidate the mechanism of action. In addition, as our observation was made in an immunocompromised patient,
additional studies should examine the efficacy as well as distinguish the immunologic mechanisms involved in immunocompetent patients.

Proofreading assistance was provided by Shadmehr Demehri, MD, PhD, Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts.

Conflicts of interest
None disclosed.

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