

Case Presentation

Multiple labial melanotic macules occurring after topical application of calcineurin inhibitors

Vivian Y. Shi MD, Jayne S. Joo MD, Victoria R. Sharon MD DTMH

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University of California, Davis, Department of Dermatology

Correspondence:

Victoria R. Sharon, MD, DTMH
3301 C Street Suite 1400, Sacramento, California 95816, USA
Email: victoria.sharon@ucdmc.ucdavis.edu
Fax: 1-916-442-5702

Abstract

Topical calcineurin inhibitors are widely used to treat inflammatory dermatoses for their steroid-sparing advantage. Herein, we report a patient with chronic lip dermatitis who developed multiple labial melanotic macules after application of tacrolimus 0.1% ointment and pimecrolimus 1% cream. Prior and current reports raise concerns for potential development of pigmented lesions associated with topical calcineurin inhibitor use. These reports highlight the need for careful risk-benefit assessment when prescribing topical calcineurin inhibitors for inflammatory dermatoses, especially when used on sun-exposed sites.

Introduction

Since their FDA approval in 2006, topical calcineurin inhibitors (FK506) such as tacrolimus and pimecrolimus are nonsteroidal immunomodulatory agents now widely available for treating inflammatory dermatoses. This class of drug exerts its therapeutic effect by inhibiting calcineurin in T cells, thereby preventing pro-inflammatory cytokine production and subsequent T cell activation [1]. The efficacy of topical calcineurin inhibitors is well-established and there have not been significant adverse effects reported to date. However, the long-term safety of these steroid-sparing agents is unknown. Topical tacrolimus is commonly used to help with repigmentation in vitiligo [2-5]. The mechanism of how calcineurin inhibitors encourage pigmentation is not well understood. Some evidence has suggested the role of tacrolimus in inducing melanocyte growth, proliferation, and migration [6,7]. In contrast, other studies suggest that FK506 promotes cell migration and tyrosinase activation, but hinders melanocyte growth [7]. Cyclosporine, a systemic immunosuppressant that also inhibits the calcineurin-pathway, is known to induce a variety of cutaneous neoplasms including melanoma and non-melanoma skin cancers [8, 9].

Few reports have documented the development of lentiginos in association with topical tacrolimus use for the treatment of atopic dermatitis [10, 11]. Herein, we report a case of multiple labial melanotic macules developing after the use of both topical tacrolimus and pimecrolimus for the treatment of chronic lip dermatitis.

Case synopsis

A 40-year-old Asian female (skin type III) with a 10-year history of dry, chapped lips presented with multiple coffee-colored macules on her lips. Three years prior to presentation, her lip dermatitis was treated with two weeks of twice daily topical tacrolimus, but she subsequently switched to 6 months of twice daily topical pimecrolimus owing to a burning sensation upon application with tacrolimus. Within 2 months of using tacrolimus and pimecrolimus, over a period of several days she developed >10 light-brown uniformly pigmented macules on the upper and lower vermilion lips of varying sizes (1-5mm) (Figure 1A). The

macules continued to darken and increase in number for several months following drug cessation (Figure 1B). Complete blood count and chemistry panel at the time of presentation was significant only for mild chronic microcytic anemia. Thyroid stimulating hormone and zinc levels were normal.



Discussion

To our knowledge, this is the first reported case of labial melanotic macules associated with the use of both topical tacrolimus and pimecrolimus. This is an unusual case because of the sudden onset of multiple lesions confined to the vermilion lips, increasing in number for a period of time after discontinuing the medications. Additional reports have documented occurrence of melanocytic lesions subsequent to topical tacrolimus [10, 11] (Table 1), all in patients of light skin tone. One may postulate that the melanocytic stimulation is most prominent in this group. Treatment duration prior to macule onset ranged from 3 months to 3.5 years.

Regardless of whether topical tacrolimus was continued or stopped, the melanotic macules persisted in all reported cases within follow-up periods ranging between 3 to 18 months. The cases are listed in Table 1. For patient 1, topical tacrolimus was continued for another 6 months and no further changes in the lentiginos were noted. The lentiginos on his knees and ankles were persistent at follow up 18 months later (12 months after drug discontinuation). Patient 2 had lentiginos on the neck, trunk, and extremities. Biopsy confirmed a simple lentigo on her lower back. Her lentiginos persisted and were unchanged in number and appearance at 1 year after discontinuing topical tacrolimus. The lentiginos of patient 3 were on the upper and lower extremities. All lesions persisted at 6 months after stopping topical tacrolimus. Her eczema was poorly controlled on potent topical steroids. For patient 4, tacrolimus was continued under close follow-up. The lower lip lesion persisted and was unchanged over a 3-month period. Patient 5 decided to stop tacrolimus after developing two lower lip melanotic macules. The lesions persisted over a 6-month period after discontinuation.

We hypothesize that topical calcineurin inhibitors are a relevant trigger in the onset of labial melanotic macules in our patient. The predominance of melanotic macules on the lower lip suggests that sun exposure may also play a role. Topical tacrolimus has been shown to promote melanocyte growth and migration, leading to repigmentation in the treatment of vitiligo [7]. However, it may occasionally produce unwanted melanotic lesions in non-depigmented skin that does not improve with drug cessation. It is possible that topical calcineurin inhibitors and ultraviolet light exposure act synergistically to modulate melanogenesis, leading to pigmentation.

Conclusion

The current and prior reports raise concern for the association of topical calcineurin inhibitors and melanocyte growth. Careful long-term surveillance will be required to assess the prevalence of this phenomenon, evolution of the pigmented lesions, and potential for malignant transformation.

Table 1. Reports associating the occurrence of melanotic lesions subsequent to of topical calcineurin inhibitors

NR, not reported. †, drug continued after onset. *, drug stopped after onset.

| | Authors | Age (yrs), Sex, Race | Skin type | Treatment Before Onset | Treatment Location | Macule(s) Location | Length of Follow-up After Onset | Drug use after Onset |
|-----------|--------------------------------|-------------------------|--------------|---|---|---|--|-------------------------|
| Patient 1 | Hickey et al. [10] | 4, Male, Afro-Caribbean | I | Twice daily for 6 months | Knees, ankles, and other | Knees, ankles | 18 mo. † | Continued |
| Patient 2 | Hickey et al. [10] | 7, Female, NR | I | Twice daily for 5 months | Not reported | Neckline, wrists, ankles, upper thighs, lower back (>100) | 12 mo.* | Stopped |
| Patient 3 | Hickey et al. [10] | 11, Female, NR | II | > 3.5 years | Wrists, hands, upper thighs, knees, ankles, etc | Same as treatment site (multiple) | 6 mo.* | Stopped |
| Patient 4 | Zattra et al. [11] | 16, Male, Caucasian | NR | Once-twice daily for 9 months | Perioral, periocular | Lower lip (one) | 3 mo. † | Continued |
| Patient 5 | Zattra et al. [11] | 25, Female, Caucasian | NR | Once daily for 3 months | Lips | Lower lip (two) | 6 mo.* | Stopped |
| Patient 6 | Shi et al. (current report) | 40, Female, Asian | III | 2 weeks of twice daily topical tacrolimus, followed by 6 months of twice daily topical pimecrolimus | Lips | Upper and lower lips (multiple) | Lost to follow up | Stopped |

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