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Case Report
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Tacrolimus Induced Photodistributed Lichenoid Eruption

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Abstract

The topical calcineurin inhibitors have an effect on various cells of the cutaneous immune system, specifically on T-cells, by inhibiting the phosphatase calcineurin and preventing the transcription of proinflammatory cytokines. Tacrolimus ointment (Protopic®) is a topical calcineurin inhibitor used to control the symptoms of moderate to severe Atopic Dermatitis (AD). The most common adverse effect following the application of topical calcineurin inhibitors is mild to moderate symptoms of irritation such as burning, erythema and pruritus and usually fades after a few days. To our knowledge, no case of photo-distributed lichenoid eruption associated with tacrolimus has been formally reported up to date. Therefore we report here a patient who developed photo-distributed hyperpigmentation after topical application of tacrolimus ointment 0.1% for her allergic contact dermatitis.

Keywords: Tacrolimus; Photoallergic lichenoid eruptions

Introduction

It is known that topically used tacrolimus enters the systemic circulation minimally and does not accumulate in the tissues in the case of repeated use. Therefore, side effects associated with systemic use of tacrolimus such as nephrotoxicity, hypertension and neurotoxicity are not usually seen in topical use [1].

Reported side effects associated with topical tacrolimus are limited to burning sensation and itching. These most common, subjective complaints are seen to decline a short time after the treatment. Tacrolimus can lead to an increase in local cutaneous infections with bacterial, fungal, viral and parasitic causes. However, it is known that cutaneous infections are already elevated in atopic dermatitis patients in particular [2,3]. Previous studies did not describe a significant side effect for topical tacrolimus with the exception of burning sensation, irritation and pruritus [1,2,4].

We describe a case of a 71-year-old patient, who developed photo-distributed hyperpigmentation during treatment with topical tacrolimus ointment 0.1% that was not previously described.

Case Presentation

A 71-year-old (Fitzpatrick skin phototype IV) female with a past medical history allergic contact dermatitis presented with a 2-months history of progressive darkening of his face (Figure 1), feet, neck and dorsum of hands (Figure 2A and 2B). The patient did not give either a history of significant sun exposure, photosensitivity and inflammatory skin diseases, or systemic illness before the onset of the lesions. Approximately 2-months prior to the presentation, the patient had begun therapy with tacrolimus ointment 0.1% (twice daily). The patient did not use any topical or systematic treatment except for tacrolimus ointment. According to her medical history, the hyperpigmentation started approximately 1 week after she began tacrolimus ointment 0.1% topical therapy. Hyperpigmentation started on the face and spread to the dorsal areas of the hands and feet. The patient did not have any complaints except for mild itching and burning sensation.

Dermatological examination demonstrated dark brown hyperpigmented patches over the face, dorsum of the hands and feet (Figure 1 and 2) sparing the submental region and retroauricular areas bilaterally. A thorough physical examination revealed no other abnormalities. The results of the laboratory studies, including complete blood count, liver function tests, and a comprehensive chemistry panel were within normal range. Antinuclear antibodies were negative. Photodistributed hyperpigmentation due to tacrolimus ointment was suspected. After her consent was taken, the patient was photographed and her skin biopsy was conducted.

Histopathologic examination of the skin biopsy material showed focal parakeratosis on the surface, apoptotic bodies and markedly increased pigmentation in the epidermis, as well as band-

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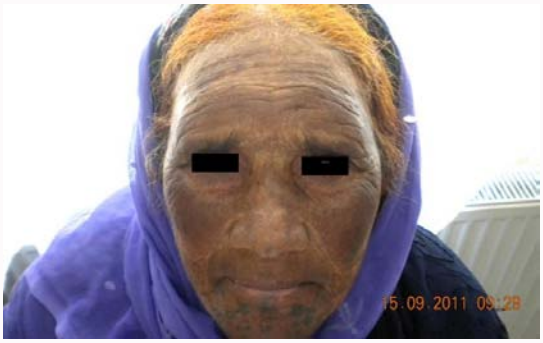
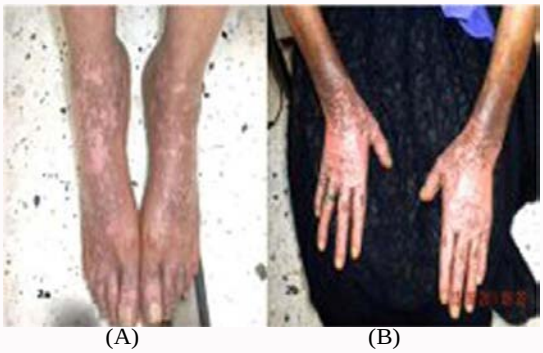


Figure 1: Diffuse hyperpigmented patches on the face of the patient.



(A) (B)

Figure 2: A) Hyperpigmented patches accompanying the previous post-inflammatory hypopigmentation areas on the feet of the patient. B) Hyperpigmented patches on the hands and forearms of the patient accompanying previous post-inflammatory hypopigmentation areas.

like infiltration formed from mononuclear inflammatory cells in the papillary dermis. Papillary dermis was also found to contain a high number of melanophages. Basal layer of the epidermis was observed to have marked vacuolar degeneration together with lymphocytic exocytosis (Figure 3). Although the clinical and histological features were similar to those of lichen planus pigmentosus, compact hyperkeratosis and wedge-shaped hypergranulosis which are typical histological features of lichen planus were absent.

Management of the hyperpigmentation was consisted of discontinuation of tacrolimus ointment 0.1% therapy, photoprotection, and twice-daily applications of a 4% hydroquinone cream. Use of 4% hydroquinone cream caused partial resolution across time and the patient is still being treated.

Discussion

Tacrolimus (FK506) is a macrolide immunomodulator which was isolated in 1984 from the fungus Streptomyces Tsukubaensis, which was found near Tsukuba Mountain in Ibaraki, Japan [5]. Since then, topical calcineurin inhibitors have been used off-label in many resistant cutaneous lesions in other diseases such as psoriasis, systemic lupus erythematosus, chronic actinic dermatitis, Behçet's disease, lichen planus, steroid-induced rosacea, vitiligo, hand eczema, asteatotic eczema, autoimmune bullous dermatosis, seborrheic dermatitis, allergic contact dermatitis, and graft-versus-host disease [5]. The commercially available forms are Protopic® 0.03% and 0.1% ointment (tacrolimus) [5,6].

Tacrolimus appear to be safe for use in chronic inflammatory skin diseases [7]. Side effects are usually mild, and include irritation,

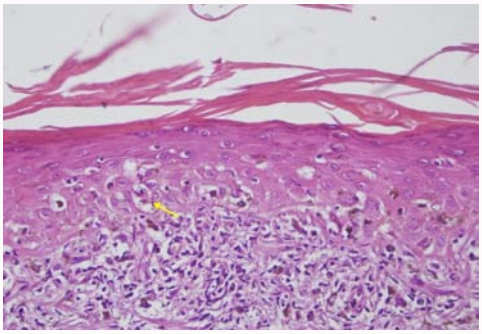


Figure 3: Focal parakeratosis on the epidermal surface, apoptotic bodies (shown with arrows) in the epidermis, marked vacuolar degeneration in basal layer cells, marked hyperpigmentation and a multitude of melanophages and band-like mononucleer inflammatory infiltration in the papillary epidermis (H&E × 400).

pruritus, burning sensation, or increased erythema. These adverse reactions are usually transient and subside with continuation of treatment. Low penetration of the inflamed skin reduces the risks of any systemic side effects. Tacrolimus can be used safely over sensitive areas like the face, mucous membranes, and genitalia where the skin is thin [8], or during infancy and early childhood. There have been no reports of any statistically significant incidence of local infections (bacterial, viral, or fungal) during their use although there may be a slightly increased risk for local Varicella zoster virus [8], Herpes simplex virus, eczema herpeticum, impetigo, and molluscum contagiosum [9]. There have also been reports of some other side effects such as skin erythema, flu-like symptoms, headache and skin infection, acne, dysesthesia [10], focal hypertrichosis [11], local bullous eruptions and stinging [12], and transient hyperpigmentation associated with combination of excimer laser therapy [13].

Remitz et al. [14] applied tacrolimus ointment daily to 316 adults with atopic dermatitis for a period ranging between 6 months and 1 year. Their objective was to evaluate the safety and efficacy of the tacrolimus ointment. They found local irritation, burning sensation, itching and erythema only at the preliminary stage of the treatment. They concluded that one-year use of tacrolimus ointment was safe in atopic dermatitis patients. Similarly, other studies reported temporary burning sensation and itching that developed at the site of application and showed a tendency to decrease in repeated applications in association with the tacrolimus ointment [15,16].

Although generally safe, Langeland et al. [17] first report was that of a squamous cell cancer of the penis after use of tacrolimus in 2005. Since then, more than 19 cases of cancer were reported in association with tacrolimus use. Half of them involved lymphomas and the rest were skin tumors at the site of application (squamous cell carcinoma, sarcoma, and melanoma) [18].

Zattra et al. [19] report two patients with AD who developed labial melanotic macules after topical application of tacrolimus ointment 0.1%. It was emphasized that tacrolimus ointment was effective and safe, but the patients should be followed carefully for long periods of time against development of melanotic macules. To date, no direct effects on melanocytes have been clearly demonstrated but repigmentation in vitiligo has been reported [20]. The literature includes reports of cases that developed multiple lentigines in the areas where tacrolimus ointment was applied and such reports stress that the patients who use tacrolimus ointment should be carefully followed against melanocytic neoplasia [21]. Although there are cases

that developed photo-distributed hyperpigmentation months after systemic tacrolimus use in the literature, there is no case that had photo-distributed hyperpigmentation caused by lichenoid eruption after the use of topical tacrolimus, like our case.

One point that needs to be addressed in this respect is whether tacrolimus caused this side effect topically or by entering the systemic circulation. We know that topically applied tacrolimus enters systemic circulation minimally and does not accumulate in the tissues in repeated use. Besides, the fact that our patient applied the medicine to limited areas like the hands, face and feet and that hyperpigmentation developed only at the sites where the ointment was applied suggest a topical, rather than a systemic side effect.

In conclusion, we want to attract the dermatologist's attention to the possibility that, just like systemic use, topical use of tacrolimus can cause hyperpigmented lichenoid eruptions on sun-exposed areas. We recommend that these patients have to limit sun exposure, wear sun-protective clothes, and use broad-spectrum sunscreens from the beginning of tacrolimus ointment therapy.

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