

## Topical Tacrolimus-Induced Hyperpigmentation: A Rare Adverse Drug Reaction Worth Reporting

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### ABSTRACT

**Background:** Hyperpigmentation is a common dermatological condition characterized by darkening of the skin due to increased melanin synthesis or altered melanin distribution. Drug-induced pigmentation (DIP) accounts for approximately 20% of acquired hyperpigmentation cases, with over 50 implicated drugs, including chemotherapeutic agents, antibiotics and immunosuppressants. Tacrolimus, a calcineurin inhibitor used in atopic dermatitis, is rarely associated with hyperpigmentation.

**Case presentation:** A 22-year-old female presented with perioral eczema unresponsive to topical corticosteroids. She was prescribed tacrolimus 0.1% ointment for one month. After two weeks, she developed gradual darkening of her lips, with no associated itching, burning or edema. There was hyperpigmentation at the angles of the mouth without ulceration or scaling. She had no history of smoking, sun exposure or other drug use. Tacrolimus was discontinued and sunscreen with mild moisturizer was advised, leading to partial resolution of pigmentation within two months. Causality assessment using the Naranjo scale yielded a score of 6, indicating a probable relationship between tacrolimus and the adverse reaction.

**Discussion:** Hyperpigmentation due to topical tacrolimus is rare. The proposed mechanisms include increased melanin production secondary to mast cell activation or melanocyte stimulation. Photo-protection and early drug withdrawal are essential to prevent cosmetic complications.

**Conclusion:** This case highlights hyperpigmentation as an uncommon but noteworthy adverse drug reaction to topical tacrolimus. Clinicians should recognize and report such rare events to strengthen pharmacovigilance and enhance understanding of tacrolimus-related cutaneous adverse effects.

**Keywords:** Tacrolimus, Atopic dermatitis, Skin hyperpigmentation, Adverse drug reaction

## 1. Introduction

Hyperpigmentation of the skin is a common dermatological condition in which the color of the skin generally becomes darker. A common dermatological disorder known as hyperpigmentation causes the skin to become darker overall. Numerous internal and external variables, such as hormone fluctuations, inflammation, trauma, acne, eczema, certain medications, UV exposure, etc., can cause these colour changes in the skin. The biological mechanisms involving the synthesis of melanin, the skin pigment, by melanocytes in the different layers of skin control skin pigmentation and coloration. Skin hyperpigmentation diseases are thus caused by changes in melanocyte production or melanin dispersion<sup>1</sup>. Among the many causes the most common cause of skin hyperpigmentation is genetics, exposure to sun and drug induced<sup>2</sup>.

An estimated 20% of all cases of acquired hyperpigmentation are thought to be caused by drug-induced pigmentation (DIP). Antibiotics, antimalarials, antiretrovirals, antipsychotics, prostaglandin analogues, heavy metals and chemotherapeutic drugs are among the more than 50 substances that have been linked. The colour, location, onset and duration of pigmentation differ amongst offending chemicals and they can impact the skin, mucosal surfaces, nails and hair. Amongst these drugs, chemotherapeutic agents are a very likely cause of DIP<sup>3</sup>. In this case, the patient used Tacrolimus for atopic dermatitis which led to skin hyperpigmentation. Usually, the first choice of treatment for this condition is corticosteroids, however, Tacrolimus ointment is an alternative treatment<sup>4</sup>.

Tacrolimus being a calcineurin inhibitor it blocks the activation of T cells and production of inflammatory cytokines<sup>5</sup>. Both oral and topical formulation are available. The topical formulation is used in eczema and other inflammatory dermatological conditions and also an immunosuppressive agent for prophylaxis of organ rejection. Systemic usage of tacrolimus has adverse effects of nephrotoxicity, neurotoxicity, diabetes and other metabolic imbalances. Dermatological adverse reactions like hyperpigmentation on usage of topical tacrolimus are acne vulgaris, alopecia and rash but these are rarely seen<sup>6</sup>. According to the Vigibase database, skin hyperpigmentation was seen in 33 cases out of more than 96,000 reported ADR's (Adverse Drug Reaction)<sup>7</sup>. This makes it a very rare adverse event and hence is worth reporting.

## 2. Case Report

This case was collected as a part of the Pharmacovigilance elective under the Department of Pharmacology, Christian Medical College, Ludhiana, which is an ADR Monitoring Centre. A 22-year-old female patient presented to the Dermatology OPD with history of eczema on the lips and perioral region and was initially treated with topical steroids for 1 week. Since the issue didn't subside with topical steroids, she was prescribed with tacrolimus ointment 0.1 percent for 1 month HS. After 2 weeks of application of the ointment, she noticed gradual darkening of her lips. With progressive pigmentation, she was worried about the cosmetic effect. The patient was a non-smoker without a history of hyper exposure to the sun, drug exposure or other etiological conditions for lip hyperpigmentation. There were no systemic symptoms of itching, burning, edema. There was hyperpigmentation at the angle of mouth without any scaling or ulceration. Tacrolimus was stopped and sunscreen and mild

moisturizer were advised. The pigmentation decreased to a certain degree within 2 months. This is shown in (Figure 1).



a) 1 week after patient started with Tacrolimus b) 2 months after stopping the treatment with Tacrolimus.

**Figure 1:** Shows skin hyperpigmentation after starting and stopping tacrolimus.

The Naranjo score was 6[probable] and hence, causality assessment showed a probable correlation with the current adverse effect.

The standardized, structured Naranjo Probability Scale, which is used to assess the likelihood that a specific medicine is the cause of an adverse event, consists of ten components. Each question is assigned a score based on the response- "Yes," "No," or "Do not know"-with corresponding point values of -1, 0, +1 or +2, depending on the direction and intensity of the evidence. Based on the cumulative score, the likelihood of an ADR is categorized as questionable (score  $\leq 0$ ), plausible (score 5–8), possible (score 1–4) or definite (score  $\geq 9$ ). The overall score, which indicates the extent of causality, ranges from -4 to +13<sup>8</sup>.

## 3. Discussion

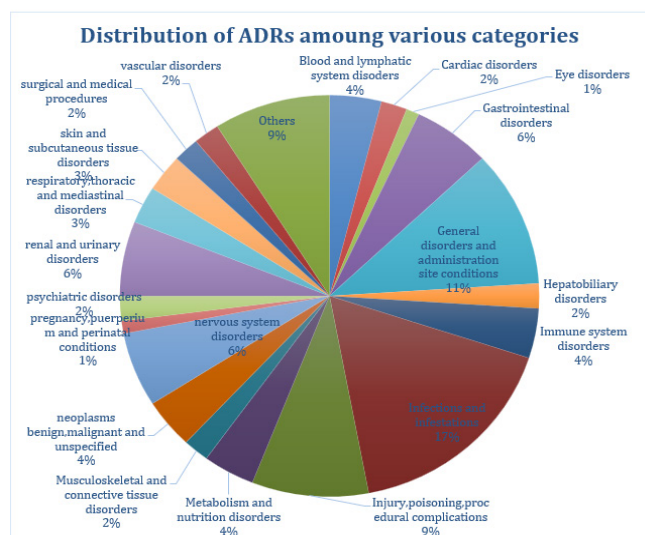
World Health Organization defines ADR as "a response to a medication that is noxious and unintended and occurs at doses normally used in man<sup>9</sup>." Patients' quality of life may be significantly impacted by ADRs, which can also put more strain on the healthcare system. ADRs are one of the leading causes of morbidity and mortality on a global scale and they continue to pose a serious health concern if not identified and tackled diligently<sup>10</sup>. Tacrolimus, a calcineurin inhibitor, is an immunosuppressive drug used in organ rejection prophylaxis after organ transplantation and for autoimmune conditions like atopic dermatitis and is of the rare causes of DIP<sup>3,5</sup>.

Identification of drug causing DIP requires a comprehensive physical examination and medication history are required. The most common mechanism of DIP is accumulation of melanin which is either by a direct trigger of the medication or nonspecific inflammation caused by the drug. A key factor in preventing DIP aggravation is photo-protection, which includes wearing photo-protective clothes, applying a broad-spectrum sunscreen and finding shade. DIP clearance has been achieved using a number of lasers, including the picosecond alexandrite, Q-switched ruby, Q-switched alexandrite and Q-switched Nd:YAG lasers<sup>3</sup>.

Hyperpigmentation is an unusual ADR of tacrolimus, with isolated reports. The mechanism of this effect is unclear, but theories include enhanced melanin production secondary to tacrolimus induced mast cell activation, melanocyte stimulation or phototoxicity. In systemic tacrolimus, hyperpigmentation in transplant patients manifests as an effect on the face and the nails. In topical tacrolimus, events are far less frequent<sup>11</sup>.

The following pie chart shows the distribution of ADRs related to tacrolimus affecting different body systems<sup>7</sup>. This is

shown in (Figure 2). The “others” category involves categories with less than 1% reported cases.



**Figure 2:** Distribution of Adverse Drug Reactions of Tacrolimus.

In this case, patient developed hyperpigmentation following the use of topical tacrolimus. Since the pigmentation in the patient resolved after tacrolimus withdrawal, there is a probable definite causal relationship between the drug and the ADR. Hence, this case is worth reporting.

#### 4. Conclusion

This particular case illustrates hyperpigmentation; an uncommon but significant ADR linked to topical tacrolimus treatment. Clinicians should be on the lookout for rare dermatological adverse effects like DIP, even though tacrolimus is frequently used to treat inflammatory skin disorders like atopic dermatitis. To avoid long-term cosmetic issues, early detection, timely removal of the offending substance and patient counselling are crucial. Since this ADR is uncommon, recording and disclosing such cases helps to improve pharmacovigilance and gain a better knowledge of the side effects associated with tacrolimus.

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