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Delayed Onset of Alcohol-Induced Flushing Following Chronic Topical Tacrolimus Application

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INTRODUCTION

A 48-year-old white woman presented with a twelve-month history of intermittent pruritic pink facial papules and two months of alcohol-induced circumscribed centrofacial flushing. She reported applying tacrolimus 0.03% ointment nightly to the pruritic pink papules for the preceding six months. Topical tacrolimus initially reduced her redness and pruritus; however, after a few months of therapy, the papules became resistant to treatment. She then developed a transient, strikingly well-demarcated centrofacial bright pink patch involving the perinasal region superiorly with inferior extension to the mental chin, within two minutes of alcohol consumption. Concurrent cutaneous irritation was noted during these episodes, without pruritus, oropharyngeal swelling, or periorbital edema. Within thirty minutes, even with continued imbibition, her facial flushing spontaneously resolved without sequelae. Alcohol-induced circumscribed flushing consistently recurred with imbibition initiation, regardless of the type or quantity of alcohol consumed. She denied any history of prior similar episodes.

Her past medical history was significant for childhood atopic dermatitis. She denied recent medication changes and reported a stable daily regimen of gentle fragrance-free cosmetic products. Systemic medications included ethinyl estradiol/norethindrone oral contraceptive and lisinopril. Physical examination revealed subtle diffuse telangiectases and erythematous pink patches on the malar cheeks, forehead, and chin. Thin pink papules were scattered around the lateral nares with extension to the medial malar cheeks.

The diagnosis of erythematotelangiectatic rosacea with a mild inflammatory component was rendered. Metronidazole 1% cream was initiated, and tacrolimus ointment was discontinued. Four days after tacrolimus cessation, the patient reported alcohol consumption with no subsequent circumscribed flushing. Due to reported cutaneous irritation with topical metronidazole application, she was transitioned to oral doxycycline 100 mg daily and over-the-counter azelaic acid 10% cream. One month after tacrolimus cessation, the patient reported no recurrence of alcohol associated circumscribed perioral flushing.

Topical tacrolimus may interact with alcohol producing a cutaneous reaction that mimics alcohol allergy in patients with and without atopic comorbidities.[1] In an open-label trial, alcohol intolerance occurred in nearly 4% of patients using tacrolimus 0.03% ointment and in nearly 7% of patients using the 0.1% formula to manage atopic dermatitis.[2] The pathogenesis of this reaction is largely unknown. Proposed mechanisms theorize that aldehyde dehydrogenase inhibition localized to the topical tacrolimus application site may result in elevated acetaldehyde levels and subsequent vasodilation.[3] In murine studies, topical tacrolimus induces a capsaicin-like reaction in the skin, leading to the release of neuropeptides, such as substance P.[4] Ingestion of ethanol may further increase neuropeptide release, potentiating capsaicin's effects. Alcohol-induced cutaneous flushing in the setting of topical tacrolimus demonstrates chronological variability. Time to initial manifestation ranges from less than one week to three months after topical tacrolimus application, and resolution has been reported within two to four weeks after tacrolimus cessation.[1,3,5,6] In contrast, our patient tolerated topical tacrolimus therapy and ethanol consumption for four months before ethanol-induced facial flushing developed; resolution occurred within four days of cessation.

Rosacea is a common condition that peaks in incidence during the third and fourth decades of life. Various topical and oral medications may effectively treat papules and pustules, yet other symptoms of rosacea, including erythema and flushing are often more resistant to standard therapies. Topical tacrolimus should be used with caution in patients with rosacea. In an open-label trial of 24 patients with erythematotelangiectatic or papulopustular rosacea, 12 weeks of tacrolimus topical monotherapy significantly improved erythema; however, the authors suggested that skin irritation, pruritus, and flushing occurred more frequently in patients with rosacea.[7] In a small case series, topical tacrolimus successfully treated perioral dermatitis and steroid-induced rosacea in three patients.[8] In another report, topical tacrolimus initially improved papular rosacea in three patients, followed by an abrupt pustular rosaceiform flare within two to three weeks.[9]

Alcohol intolerance associated with topical tacrolimus appears to be self-limited following tacrolimus cessation. However, flushing induced by topical tacrolimus may pose an unnecessary additional burden for patients with rosacea, who are already predisposed to vasoactive instability.[9] Providers

should inform patients who consume ethanol of this potential reaction before starting tacrolimus therapy. Future studies are needed to determine whether this adverse effect occurs more frequently in patients with rosacea.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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