

Severe Tacrolimus-Induced Granulomatous Rosacea Recalcitrant to Oral Tetracyclines

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ABSTRACT

Topical tacrolimus has been observed to induce granulomatous rosacea (GR) in prior case reports and series. In most cases, patients recover fully after withdrawing tacrolimus and initiating doxycycline or minocycline. Herein, we describe a case of severe GR, which required further therapy. Clinicians should be aware of this rare complication because of the frequent use of topical tacrolimus.

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INTRODUCTION

Tacrolimus ointment, a topical calcineurin inhibitor, is a common corticosteroid-sparing agent frequently used for atopic dermatitis.[1] Topical tacrolimus has also been used to treat seborrheic dermatitis, contact dermatitis, psoriasis, cutaneous lupus erythematosus, and rosacea, amongst other cutaneous conditions.[2] Given its proven efficacy and favorable side effect profile, tacrolimus ointment is often preferred over topical corticosteroids for maintenance therapy in thinner-skinned areas such as the face and intertriginous regions. The dermatologic side effects of topical tacrolimus include skin burning, pruritus, and erythema. Importantly, unlike topical corticosteroids, tacrolimus does not induce skin atrophy.[3] However, previous case reports have demonstrated an association between granulomatous rosacea (GR) and topical tacrolimus use.[4-7] Only 5 of these cases have been biopsy proven.[4-6] We describe an additional case of biopsy-proven, tacrolimus-induced GR, but with particular severity.

CASE REPORT

A 21-year-old woman with a long-standing history of atopic dermatitis presented with an acute onset of an exuberant erythematous facial eruption, worsening over a one-month period. She first developed small, red papules on her left cheek, which then spread over the next few days to involve her entire face along with a background of intense erythema. The rash was asymptomatic except for occasional burning and was not photosensitive. Given her long-standing history of atopic dermatitis, the patient had used tacrolimus 0.1% ointment on her face occasionally for several years, but had recently increased the frequency and quantity of application prior to the onset of this new eruption. She was evaluated by rheumatology for her new-onset facial eruption and was initiated on hydroxychloroquine 200 mg daily for a possible diagnosis of systemic lupus erythematosus based on the impressive facial erythema. The patient's symptoms persisted, however, and continued to worsen over a month-long period. She was then referred to dermatology for further evaluation.

On physical examination, the patient appeared well and in no apparent distress. Her face was notable for edematous pink papules and papulonodules, coalescing into plaques (Figure 1). Laboratory investigations included a negative antinuclear antibody (ANA), anti-Ro, anti-La, anti-dsDNA, anti-Smith, as well as normal complement levels, complete blood count, and comprehensive metabolic panel. Histologic assessment of punch biopsies from two papules demonstrated prominent perifollicular and interstitial granulomatous inflammation with suppurative folliculitis and perifolliculitis (Figure 2). No epidermal atrophy was noted, and no organisms were seen on gram stain or Periodic acid-Schiff-diastase (PAS-D) stain. As the patient had no prior history of rosacea and timing coincided with increased tacrolimus use, she was given a diagnosis of topical tacrolimus-induced severe GR. Topical tacrolimus was discontinued and doxycycline 100mg twice daily was initiated. Subsequently, due to the severity of this patient's presentation and minimal response to doxycycline, additional topical therapies were initiated including: metronidazole cream, sodium sulfacetamide 10% cleanser, tretinoin 0.025% cream, and three combination 20% Jessner (Rejuvenize®) and 0.3% retinoic acid peels. The most notable improvement was seen following the combination peels, and the patient's facial eruption continued to improve without scarring over the sixth months of treatment (Figure 3).

FIGURE 1. Granulomatous rosacea. Before therapy.

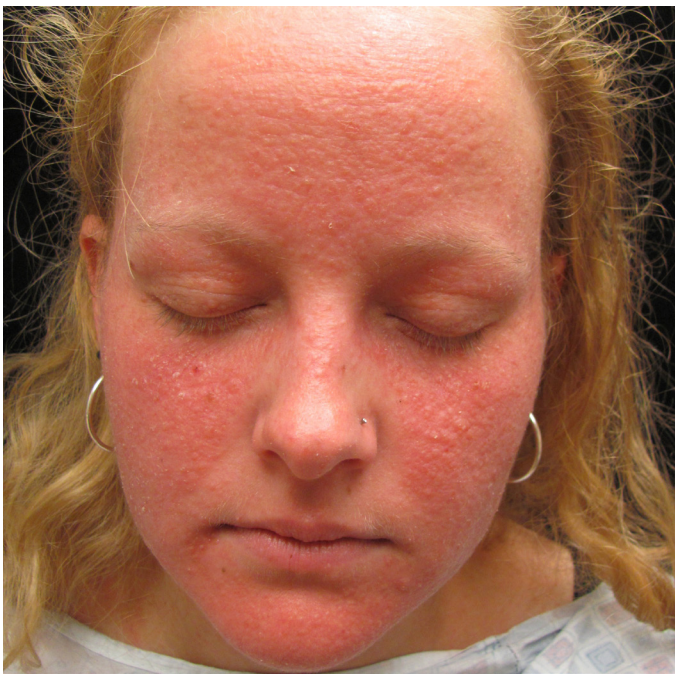
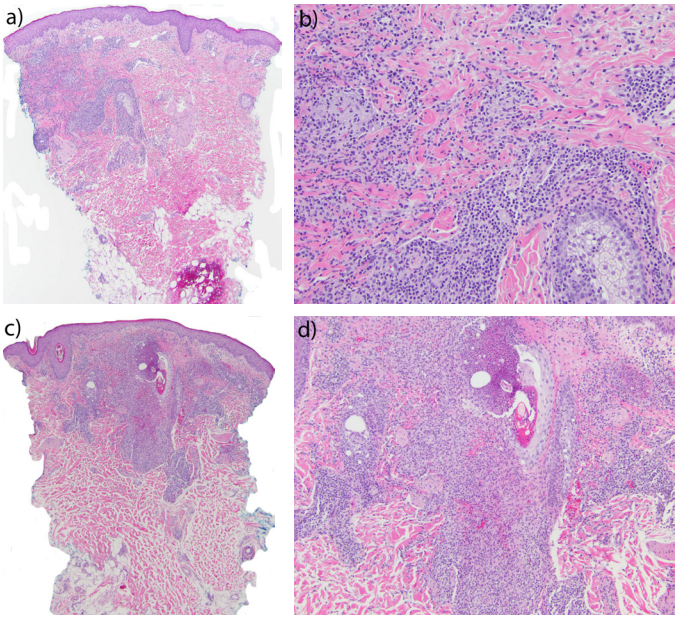


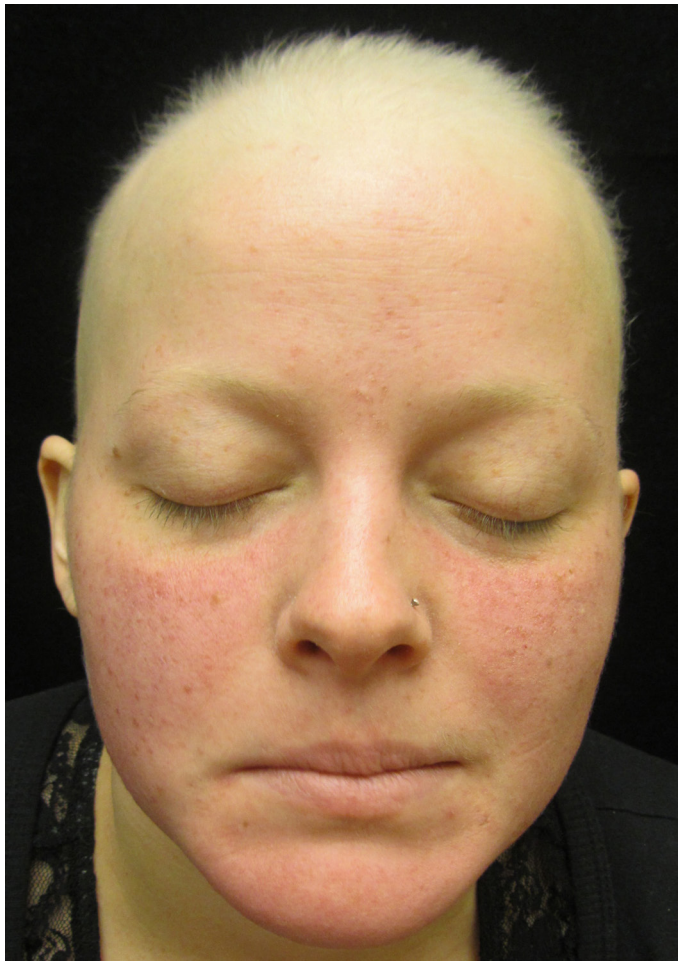
FIGURE 2. (a) A punch biopsy shows a dense perifollicular and superficial dermal inflammatory infiltrate. **(b)** The inflammatory infiltrate is composed of lymphocytes and histiocytes, and non-caseating granulomas are also present. **(c)** A punch biopsy from the other papule reveals a dense perifollicular inflammatory infiltrate, **(d)** with central suppuration.



DISCUSSION

Topical tacrolimus-induced GR presents acutely, with onset of symptoms within 3 days to 28 months after initiation of therapy (average time to onset is 5 months). Tacrolimus-induced GR may also develop after the dosage is escalated in patients who previously used topical tacrolimus without complications.[4] Our patient had used tacrolimus intermittently for several years and developed symptoms after increasing the frequency and quantity of application. In tacrolimus-induced GR, histology typically reveals a perifollicular lymphohistiocytic infiltrate with non-caseating granulomas. Unlike corticosteroid-induced rosacea-like eruptions, no epidermal atrophy is appreciated in this condition. When making the diagnosis of tacrolimus-induced GR, other granulomatous disorders and rosaceiform eruptions to be considered include sarcoidosis, lupus vulgaris, pyoderma faciale, and lupus miliaris disseminatus faciei.

FIGURE 3. Six months after starting treatment.



The exact pathogenesis of topical tacrolimus-induced GR remains unknown. Some case reports have suggested that the immunosuppressive properties of tacrolimus may facilitate overgrowth of *Demodex folliculorum*, which has been implicated in the pathogenesis of rosacea[8] and GR.[9] Other reports postulate that rosacea is an inflammatory disorder and that an exaggerated innate immune response (whereby

D. folliculorum is one precipitant) plays a central role in the pathogenesis.[10] Pimecrolimus cream, another topical calcineurin inhibitor, has also been reported to induce rosaceiform eruptions.[11-14] However the eruptions associated with pimecrolimus cream, which is mostly water-based, are less severe than those reported with tacrolimus ointment due to the occlusive properties of the latter.[11]

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To the best of our knowledge, severe GR induced by tacrolimus and recalcitrant to tetracyclines has not previously been reported. In prior case reports, patients improved within a few months after topical tacrolimus was withdrawn and oral doxycycline or minocycline was initiated. The severity of this patient's eruption may correspond to the duration of tacrolimus use, which spanned multiple years, given that topical tacrolimus can disrupt epidermal permeability and antimicrobial function by impairing skin-barrier recovery, as shown in recent studies.[15] These barrier-recovery deficiencies, acquired over long-term use of tacrolimus, may have predisposed our patient to a more severe eruption and protracted recovery. Accordingly, our patient required aggressive treatment with multiple topical therapies in conjunction to oral tetracyclines.

Topical tacrolimus is generally a well-tolerated medication that is used successfully for a variety of conditions. Although tacrolimus-induced granulomatous rosacea is rarely reported, recognition of the entity is important, and successful treatments strategies may include combining systemic and topical therapies with chemical peels.

DISCLOSURES

The authors have no conflicts of interest to declare.

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