

Induction of Rosaceiform Dermatitis During Treatment of Facial Inflammatory Dermatoses With Tacrolimus Ointment

Christophe Antille, MD; Jean-Hilaire Saurat, MD; Jann Lübke, MD

Background: Tacrolimus ointment is increasingly used for anti-inflammatory treatment of sensitive areas such as the face, and recent observations indicate that the treatment is effective in steroid-aggravated rosacea and perioral dermatitis. We report on rosaceiform dermatitis as a complication of treatment with tacrolimus ointment.

Observations: Six adult patients with inflammatory facial dermatoses were treated with tacrolimus ointment because of the ineffectiveness of standard treatments. Within 2 to 3 weeks of initially effective and well-tolerated treatment, 3 patients with a history of rosacea and 1 with a history of acne experienced sudden worsening with pustular rosaceiform lesions. Biopsy revealed an abundance of *Demodex* mites in 2 of these pa-

tients. In 1 patient with eyelid eczema, rosaceiform periocular dermatitis gradually appeared after 3 weeks of treatment. In 1 patient with atopic dermatitis, telangiectatic and papular rosacea insidiously appeared after 5 months of treatment.

Conclusions: Our observations suggest that the spectrum of rosaceiform dermatitis as a complication of treatment with tacrolimus ointment is heterogeneous. A variety of factors, such as vasoactive properties of tacrolimus, proliferation of *Demodex* due to local immunosuppression, and the occlusive properties of the ointment, may be involved in the observed phenomena. Future studies are needed to identify individual risk factors.

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TACROLIMUS IS AN IMMUNOSUPPRESSIVE macrolide that acts by blocking the calcineurin-dependent signal transduction pathway inside T cells, which results in the inhibition of cytokine gene transcription and thereby of T-cell activation.¹ Numerous clinical trials have demonstrated the effectiveness and safety of topical tacrolimus in the treatment of moderate to severe atopic dermatitis.² Tacrolimus ointment does not induce skin atrophy even after long-term treatment.³ Therefore, it is increasingly used for the treatment of inflammatory dermatoses in sensitive areas such as the face and mucosal areas.^{4,5} Recent reports suggest that the treatment is also effective in inflammatory pustular dermatoses such as erosive pustular dermatosis,⁶ eosinophilic folliculitis,⁴ pyoderma gangrenosum.⁷ A recent article documents successful management of steroid-induced rosacea and perioral dermatitis with tacrolimus ointment.⁸ Taken together, these observations indicate that tacrolimus ointment may be a useful treatment alternative in inflammatory dermatoses with a component of amicrobial folliculitis or

pustulosis, such as rosacea and steroid-aggravated facial dermatoses. We describe 6 patients with chronic facial inflammatory dermatoses in whom treatment with the commercial form of 0.1% or 0.03% tacrolimus ointment (Protopic; Fujisawa Healthcare Inc, Grand Island, NY) resulted in aggravation or exacerbation of rosaceiform dermatitis.

REPORT OF CASES

CASE 1

A 56-year-old woman with a 20-year history of rosacea and atopic rhinoconjunctivitis presented with inflammatory papular lesions on the nose, cheeks, and periorbital area. She had been using topical 0.05% retinaldehyde for the last 14 weeks, and systemic therapy with metronidazole had been stopped 10 weeks earlier. Given the strong inflammatory component of the lesions, a treatment with 0.1% tacrolimus ointment once daily was prescribed. After 14 days of efficient and well-tolerated therapy, the patient experienced a sudden aggravation with erythema, papules, and pustules on the

From the Department of Dermatology, University Hospital, Geneva, Switzerland. The authors have no relevant financial interest in this article.



Figure 1. A, A 49-year-old man with rosacea before onset of treatment with 0.1% tacrolimus ointment. B, After efficient initial treatment, a sudden aggravation with marked pustulation developed at the end of the third week of treatment. Biopsy specimen and pustular smears revealed pustular rosacea with an abundance of *Demodex* mites.

treated areas. Treatment with topical tacrolimus was replaced with systemic doxycycline therapy, upon which the symptoms rapidly resolved.

CASE 2

A 49-year-old man who had had rosacea for 12 years presented with telangiectatic and papular rosacea on the cheeks and forehead (**Figure 1 A**). His condition had progressively deteriorated in spite of intermittent systemic treatments with ciprofloxacin. Six months previously, the patient had stopped all treatment except antihypertensive and antiuricemic therapies. An alternating treatment with clindamycin solution and 0.03% tacrolimus ointment once daily was initially effective and well tolerated. Three weeks later, however, he experienced an acute flare with intense erythema and extensive pustulation (**Figure 1B**). A pustular smear revealed an abundance of *Demodex* mites, which were also seen in a biopsy specimen that confirmed the diagnosis of rosacea. Tacrolimus treatment was discontinued, and the flare resolved rapidly with systemic ciprofloxacin therapy. Ciprofloxacin therapy was stopped 1 month later, and there was no relapse during a 11-month follow-up.

CASE 3

A 27-year-old man presented with a mixed facial dermatitis, with features of seborrheic dermatitis as well as telangiectatic and papular rosacea. The first symptoms had appeared 5 years previously, and for the last 2 years the condition had been treated intermittently with clindamycin solution and 0.05% retinaldehyde emulsion; no systemic treatments were prescribed. Treatment with 0.1% tacrolimus ointment once daily resulted in rapid improvement, but after 10 days of well-tolerated treatment there was a sudden flare with intense erythema and numerous pustular lesions. Tacrolimus ointment was stopped and the patient received adjuvant treatment with emollient wet wraps. A biopsy showed spongiosis, intraepidermal pustules, a perifollicular lymphohistiocytic infiltrate, and follicular *Demodex*, all suggestive of rosacea. Subsequent reintroduction of 0.1% tacrolimus ointment, together with topical metronidazole and 10 mg/d of systemic isotreti-

noin, was well tolerated. The patient did not experience any new flare during 4 months of follow-up.

CASE 4

A 36-year-old woman with a history of acne during adolescence presented with a mixed facial dermatitis consisting of seborrheic dermatitis in the nasolabial folds and rosaceiform lesions with small papules, pustules, and telangiectasias on her cheeks. She had been successfully treated with systemic doxycycline, but experienced a relapse after cessation of treatment. A topical, once-daily regimen of 0.05% retinaldehyde and 0.1% tacrolimus ointment was introduced, as well as intermittent use of ketoconazole shampoo. After 2 weeks of effective and well-tolerated treatment, she experienced a flare on her cheeks with papulopustular lesions. Surface biopsy with a cyanoacrylate strip revealed the presence of *Demodex*. Tacrolimus ointment was discontinued, and the lesions slowly resolved.

CASE 5

A 35-year-old woman presented with a bilateral pruritic erythematosquamous dermatitis of the eyelids. She had a history of childhood atopic dermatitis. There was no history of rosacea, but 6 months before she had been diagnosed with mild acné excoriée located on the chin. Epicutaneous patch testing revealed sensitization to colophonium. A diagnosis of allergic contact dermatitis was made, and cosmetics were discontinued. Because treatment with 2% hydrocortisone cream was ineffective, she was treated with 0.1% tacrolimus ointment once daily. After 3 weeks of treatment, she noted a gradual aggravation of the treated area that was now characterized by small papules and micropustules resembling periorcular dermatitis. Follicular smears did not reveal the presence of *Demodex*. Tacrolimus ointment was discontinued, and the patient responded well to treatment with 50 mg of doxycycline once daily.

CASE 6

A 49-year-old woman with childhood-onset atopic dermatitis of the head and neck, but no history of acne or rosa-

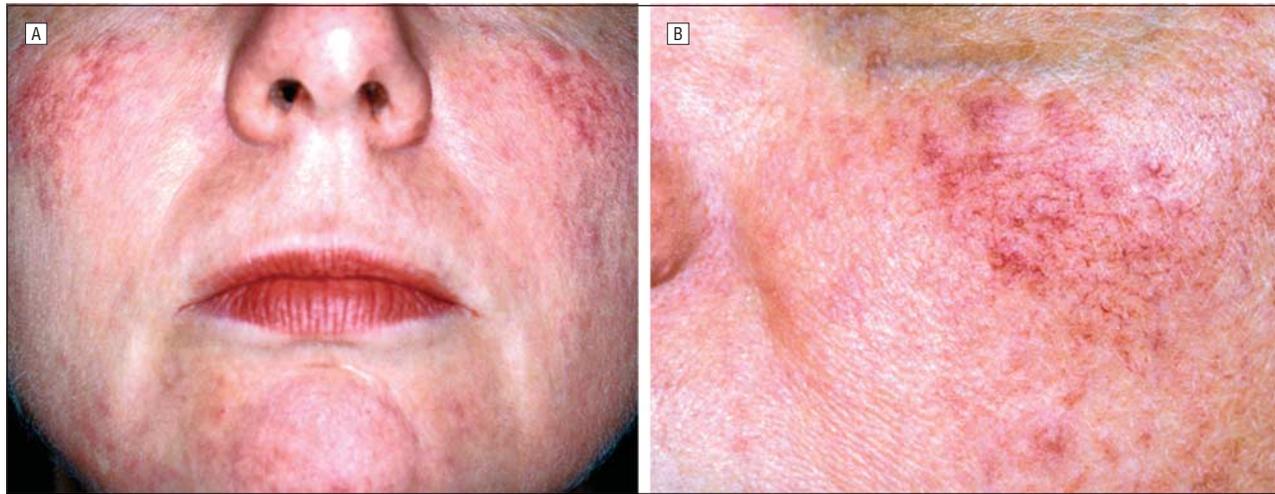


Figure 2. A 49-year-old woman with atopic dermatitis was treated with 0.03% tacrolimus ointment. Telangiectatic and papular lesions on the chin (A) and cheeks (B) insidiously developed after 5 months of treatment.

cea, presented with telangiectasias and erythematous papules on her cheeks that had developed after 5 months of treatment with 0.03% tacrolimus ointment. The treatment had been effective, but the patient reported having experienced a mild burning sensation after each application that persisted even after several weeks of treatment. Tacrolimus therapy was discontinued, but resumed 5 months later because a relapse of her atopic dermatitis. After 5 weeks of treatment with 0.1% tacrolimus ointment once daily, rosaceiform lesions reappeared on the face (**Figure 2**) but not on other treated areas such as the neck and shoulders. Tacrolimus treatment was discontinued and the lesions resolved with systemic doxycycline therapy. Two subsequent attempts to reintroduce tacrolimus ointment had to be abandoned because of the reappearance of rosaceiform dermatitis after 2 to 3 weeks of treatment. Tacrolimus treatment was then definitively discontinued. The patient is now treated with topical tar derivatives and mild corticosteroid emulsions, and there have been no more relapses of rosaceiform dermatitis during 12 months of follow-up.

COMMENT

In all patients, the rationale for treatment with topical tacrolimus originated in the predominantly inflammatory nature of the lesions, combined with the ineffectiveness of, or patient intolerance to, the topical standard therapies. While the 6 patients share a common phenomenon, ie, the appearance of rosaceiform lesions during treatment with tacrolimus ointment, there are important differences in their histories—for example, with respect to their history or lack of history of rosacea, or the interval between the onset of their exposure to tacrolimus and the appearance of the complication (**Table**).

Four patients (cases 1-4) share a similar reaction pattern, with rapid initial improvement followed by a sudden flare within 2 to 3 weeks of exposure to tacrolimus ointment. However, 3 of them (cases 1-3) had a history of rosacea of at least 5 years whereas patient 4 had a history of acne. While it cannot be formally excluded that the observed flares simply reflected a relapse in patients with a history of rosaceiform dermatitis, the homoge-

neous reaction pattern in all 4 patients strongly suggests a shared external factor, ie, tacrolimus ointment. As there was an interval of at least 10 weeks between discontinuation of systemic therapy and introduction of tacrolimus ointment, withdrawal rebound is equally unlikely to have contributed to the flares.

In contrast, 2 patients (cases 5 and 6) developed *de novo* rosaceiform lesions during therapy with topical tacrolimus. Both were treated for facial eczema and had no history of rosacea. The onset of rosaceiform complication was insidious and less dramatic in these patients, especially in patient 6 who developed telangiectatic and papular rosacea after 5 months of treatment of her facial atopic dermatitis (**Figure 2**). In this patient, a causal relationship is likely as repeated relapses of rosacea occurred whenever tacrolimus treatment was reintroduced.

This pattern of insidious reactions brings to mind a recent report by Bernard et al,⁹ where the authors describe a rosacealike granulomatous dermatitis that developed after 9 months of treatment of atopic dermatitis with topical tacrolimus. However, their case bears several unique features. For example, the rosaceiform complication in their patient, who had a history of mild rosacea, occurred as a pruritic rash that extended to other treated areas beyond the facial region, while in our patient 6, the reaction was confined to the cheeks and chin in spite of extensive treatment of the head, neck, and shoulders. The granulomatous character of the lesions in the case reported by Bernard and colleagues was confirmed by biopsy, but they do not describe a telangiectatic component, which was so prominent in our patient (**Figure 2**). Both our patient 6 and their patient responded well to systemic therapy with doxycycline, but while their patient tolerated subsequent therapy with tacrolimus ointment, our patient experienced a relapse at each attempt to reintroduce the treatment, which finally had to be abandoned.

Taken together, the available information suggests that the clinical spectrum of rosaceiform dermatitis as a complication of treatment with tacrolimus ointment is heterogeneous. This may reflect the variety of the factors involved and point to the importance of the underlying skin

Clinical Features of 6 Patients Who Developed Rosaceiform Dermatitis During Therapy With Tacrolimus Ointment

Case No.	Diagnosis	History	Modes of Testing and Findings*	Once-Daily Treatment With Tacrolimus Ointment, Concentration	Treatment Interval Before Complication	Aspect
1	Papular rosacea	Rosacea, atopic rhinoconjunctivitis	...	0.1%	2 wk	Flare, pustular rosaceiform dermatitis
2	Papular rosacea (Figure 1A)	Rosacea	Histologic evaluation: rosacea with <i>Demodex</i> ; pustular smear: <i>Demodex</i>	0.03%	3 wk	Flare, pustular rosaceiform dermatitis (Figure 1B)
3	Mixed facial dermatitis: seborrheic dermatitis, rosacea	Rosacea, seborrheic dermatitis	Histologic evaluation: rosacea with <i>Demodex</i>	0.1%	10 d	Flare, pustular rosaceiform dermatitis
4	Mixed facial dermatitis: seborrheic dermatitis, rosacea	Acne	Cynoacrylate strip: <i>Demodex</i>	0.1%	2 wk	Flare, pustular rosaceiform dermatitis
5	Allergic contact dermatitis of the eyelids	Acné excoriée	Epicutaneous patch test: colophonium sensitization	0.1%	3 wk	Insidious periocular rosaceiform dermatitis
6	Atopic dermatitis of the head and neck	Atopic dermatitis	...	0.03%	5 mo	Insidious telangiectatic and papular rosacea (Figure 2)

*Ellipses indicate that no test was performed.

condition of the patients. On the one hand, the immunosuppressive properties of tacrolimus might facilitate overgrowth of follicular *Demodex* in susceptible patients, as suggested by the predominance of the pustular component in the flares (Figure 1B) and the abundance of *Demodex* in 2 patients who underwent biopsy. Rosacealike demodicosis has been reported in local¹⁰ and systemic immunosuppression,¹¹ which suggests that *Demodex* proliferation is facilitated by local or systemic immunosuppressive factors. We recently observed a case where a flare of rosaceiform dermatitis during treatment of facial atopic dermatitis with 1% pimecrolimus cream was associated with the appearance of *Demodex*,¹² and the good response of patients to oral doxycycline is another indication of the pathogenic role of *Demodex*. On the other hand, tacrolimus ointment has vasoactive properties, and facial flushing is a significant adverse reaction to the treatment.¹³ As local vasomotor instability is a feature of rosacea, tacrolimus ointment may in the long term constitute an additional risk factor in sensitive patients. This may explain the insidious development of rosacea during long-term treatment, as was seen in our patient 6 and in the report of Bernard et al.⁹ Moreover, the occlusive properties of the tacrolimus ointment base may play an aggravating role, especially in patients with seborrhea.

In conclusion, the present observations suggest that the indication of tacrolimus ointment as a treatment alternative for inflammatory facial dermatoses is not clear-cut. While an increased alertness for subtle signs of increased vascular reactivity and alcohol intolerance, and a specific search for *Demodex* mites in patients with a follicular or papulopustular lesional component, is a recommended approach, future studies are needed to increase our understanding of the risk factors for the development of rosaceiform dermatitis during treatment with topical calcineurin inhibitors.

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Corresponding author and reprints: Jann Lütbe, MD, Department of Dermatology, Geneva University Hospital, rue Micheli-du-Crest 24, CH-1211 Genève, Switzerland (e-mail: jann.lutbe@hcuge.ch).

REFERENCES

- Shaw KT, Ho AM, Raghavan A, et al. Immunosuppressive drugs prevent a rapid dephosphorylation of transcription factor NFAT1 in stimulated immune cells. *Proc Natl Acad Sci U S A*. 1995;92:11205-11209.
- Lütbe J, Saurat JH. A monograph on topical tacrolimus (Protopic®). *Ann Dermatol Venereol*. 2003;130:290-302.
- Reitamo S, Wollenberg A, Schopf E, et al, for the European Tacrolimus Ointment Study Group. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. *Arch Dermatol*. 2000;136:999-1006.
- Dale S, Shaw J. Clinical picture: eosinophilic pustular folliculitis [letter]. *Lancet*. 2000;356:1235.
- Rozycki TW, Rogers RS III, Pittelkow MR, et al. Topical tacrolimus in the treatment of symptomatic oral lichen planus: a series of 13 patients. *J Am Acad Dermatol*. 2002;46:27-34.
- Brouard MC, Prins C, Chavaz P, Saurat JH, Borradori L. Erosive pustular dermatosis of the leg: report of three cases. *Br J Dermatol*. 2002;147:765-769.
- Richter-Hintz D, Schuppe HC, Homey B, Lehmann P, Ruzicka T. Topical tacrolimus (FK 506) is effective in the treatment of pyoderma gangrenosum. *J Am Acad Dermatol*. 2000;42:304-305.
- Goldman D. Tacrolimus ointment for the treatment of steroid-induced rosacea: a preliminary report. *J Am Acad Dermatol*. 2001;44:995-998.
- Bernard LA, Cunningham BB, Al-Suwaidan S, Friedlander SF, Eichenfield LF. A rosacea-like granulomatous eruption in a patient using tacrolimus ointment for atopic dermatitis. *Arch Dermatol*. 2003;139:229-231.
- Nunzi E, Rebora A, Cornelis JJ, Cormane RH. UV-induced pyrimidine dimers and rosacea [brief communication]. *Br J Dermatol*. 1981;104:711.
- Morras PG, Santos SP, Imedio IL, Echeverria ML, Hermosa JM. Rosacea-like demodicidosis in an immunocompromised child. *Pediatr Dermatol*. 2003;20:28-30.
- Lütbe J, Stucky L, Saurat JH. Rosaceiform dermatitis with follicular DEMODEX after treatment of facial atopic dermatitis with 1% pimecrolimus cream. *Dermatology*. 2003;207:205-207.
- Milingou M, Antille C, Saurat JH, Lütbe J. Alcohol intolerance in adult patients with atopic dermatitis treated with 0.1% tacrolimus ointment [abstract]. *J Europ Acad Dermatol Venereol*. 2003;17 (suppl 3):462.