Alcohol Intolerance With Facial Flushing Due to Topical Pimecrolimus Treatment

C. de la Torre
Servicio de Dermatología, Complejo Hospitalario de Pontevedra, Pontevedra, Spain

To the Editor:

Episodic or transient erythema (flushing) is a condition that consists of episodes of sudden reddening of skin on the face, neck, and upper part of the chest or abdomen, that can be accompanied by a sensation of heat or burning as the result of circulatory changes within the skin prompted by a wide variety of triggers.[1] Alcohol is a potent mediator of flushing, mainly through its metabolite acetaldehyde, and this effect can also occasionally be triggered by various drugs, including topical immunomodulators.[2,3]

We recently observed a case triggered by pimecrolimus—a phenomenon that has been recognized previously,[2] but for which we were unable to find cases described in the literature. The patient was a 54-year-old woman with no relevant history, who had suffered from facial seborrheic dermatitis and sensitive skin. She had been prescribed topical pimecrolimus that had been applied regularly morning and night. Two weeks after treatment began, over the Christmas period, she experienced episodes of more than 30 minutes of intense and marked facial flushing following the ingestion of alcohol. The flushing was not associated with any general symptoms, nor was it accompanied by sweating. The patient had never experienced these symptoms before, she was taking no other treatment, and she had not changed her behavior in any other way, and hence, she established the possible link with the pimecrolimus cream and reported this to her doctors. Although the patient had stopped applying the pimecrolimus a week previously, a challenge test completed with her consent proved positive within 10 minutes (Figure) although the patient said the flushing had been more intense when she had been using the cream. In the follow-up 3 months after suspending the medication, the patient showed no further symptoms.

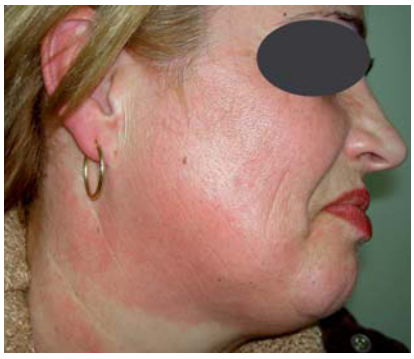

Figure 1. Flushing affecting the face and neck 10 minutes after a challenge test with ingestion of alcohol.

Flushing can be the exaggeration of a physiological process or a sign of an underlying condition.[1] The erythema is due to increased blood flow that can be due to the direct action of vasodilator substances or changes in the neurologic control of vascularization. Alcohol (ethanol) is rapidly absorbed by the gastrointestinal tract after ingestion. More than 90% is oxidized in the liver into acetaldehyde by alcohol dehydrogenase and then into acetate by aldehyde dehydrogenase. In some individuals of Asian origin intense flushing has been observed even with low doses of alcohol and associated high plasma levels of acetaldehyde. This unusual reaction has been linked to a deficit of an aldehyde dehydrogenase isoenzyme and can be detected through patch testing with ethanol. It has been explained as an increase in plasma levels of acetaldehyde and is possibly triggered by the release of prostaglandins. The ingestion of alcohol with some medicines, fungi, and chemical agents can cause the inhibition of aldehyde dehydrogenase and the accumulation of acetaldehyde, unleashing a clinical condition known as *aldehyde syndrome*, *disulfiram syndrome*, or *Antabuse syndrome* accompanied by a marked cutaneous reaction with flushing.[1,3]

Local intolerance to topical tacrolimus is common and is observed in 50% of patients.[4] It is generally transient and is different to the uncommon reaction of alcohol intolerance with flushing also described with this medication.[5] This phenomenon has been described in 6% of patients,[6] and a controlled safety study showed this to occur in 7% and 35% of patients treated with 0.1% and 0.03% tacrolimus ointment, respectively.[4] This type of alcohol intolerance has been described in patients treated for atopic dermatitis and in those treated for rosacea, and it has even been described in cases where children have ingested minimal quantities of alcohol in medications containing ethanol.[7-9]

The mechanism is unknown, although the release of neuropeptides with possible vasodilatory effects in a similar manner to those produced by capsaicin has been implicated.[7] Cyclosporin has similar mechanisms of action and secondary effects, including flushing that has been related to increased levels of prostaglandins and arachidonic acid.[10] Changes in the modulation of aldehyde concentration or dehydrogenase activity have not been reported.[7]

This type of reaction to topical calcineurin inhibitors has been reported with both tacrolimus and pimecrolimus,[2] not surprisingly given their molecular

similarity, which also explains the recently described possibility of cross-reactivity between the 2 substances.[11] It is also possible that the lower absorption of pimecrolimus is responsible for the lower incidence of this secondary effect, as seen with low-concentration tacrolimus.[4]

References

1. Izikson L, English JC 3rd, Zirwas MJ. The flushing patient: differential diagnosis, workup, and treatment. J Am Acad Dermatol. 2006;55:193-208.
2. Lubbe J, Milingou M. Images in clinical medicine. Tacrolimus ointment, alcohol, and facial flushing. N Engl J Med. 2004;351:2740.
3. Sticherling M, Brasch J. Alcohol: intolerance syndromes, urticarial and anaphylactoid reactions. Clin Dermatol. 1999;17:417-22.
4. Soter NA, Fleischer AB Jr., Webster GF, Monroe E, Lawrence I. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety. J Am Acad Dermatol. 2001;44: S39-46.
5. Alaiti S, Kang S, Fiedler VC, Ellis CN, Spurlin DV, Fader D, et al. Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. J Am Acad Dermatol. 1998;38:69-76.
6. Reitamo S, Wollenberg A, Schöpf E, Perrot JL, Marks R, Ruzicka T, et al. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. Arch Dermatol. 2000;136:999-1006.
7. Milingou M, Antille C, Sorg O, Saurat JH, Lubbe J. Alcohol intolerance and facial flushing in patients treated with topical tacrolimus. Arch Dermatol. 2004;140:1542-4.
8. Knight AK, Boxer M, Chandler MJ. Alcohol-induced rash caused by topical tacrolimus. Ann Allergy Asthma Immunol. 2005;95:291-2.
9. Calza AM, Lubbe J. Tacrolimus ointment-associated alcohol intolerance in infants receiving ethanol-containing medication. Br J Dermatol. 2005;152: 569.
10. Ramsay HM, Harden PN. Cyclosporin-induced flushing in a renal transplant recipient resolving after substitution with tacrolimus. Br J Dermatol. 2000;142:832-3.
11. Shaw DW, Maibach HI, Eichenfield LF. Allergic contact dermatitis from pimecrolimus in a patient with tacrolimus allergy. J Am Acad Dermatol. 2007;56:342-5.

Congenital Self-Limiting Tufted Angioma

D. Barco,[a] E. Baselga,[a] A. Ribé,[b] and A. Alomar[a]

[a]Servicio de Dermatología and [b]Servicio de Anatomía Patológica, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

To the Editor:

We report the case of a 1-month-old boy who had had a 5-cm violaceous plaque on the right arm since birth. The plaque was not hot, pulsatile, or painful and had a peau d'orange surface covered with downy hair (Figure1). The biopsy showed a normal epidermis with dermal vascular proliferation in the form of lobules. The lobules were arranged in a birdshot pattern and were composed of endothelial cells with no signs of atypia or mitosis and with occasional half-moon-shaped peripheral vascular spaces (Figure 2). Immunostaining was negative for glucose transporter-1 (GLUT1). The histologic and immunohistochemical characteristics of the lesion suggested a diagnosis of congenital tufted angioma. The tumor became gradually flatter and had partially disappeared by the time the baby was 1 year old (Figure 3).

Tufted angioma (TA) is a rare benign vascular tumor. Most TAs are acquired and appear during the first year of life or in young people as violaceous macules, plaques, or nodules high on the torso, on the neck, or on the arms.[1,2] They may present hyperhidrosis, be painful to the touch, or covered with

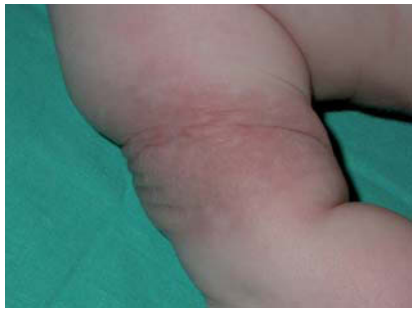

Figure 1. Clinical appearance of the lesion at birth.

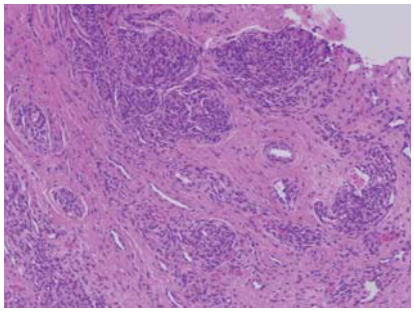

Figure 2. Histologic appearance of the lesion (hematoxylin–eosin, ×100).