

Allergic contact dermatitis caused by topical sirolimus used as an adjuvant for laser treatment of port wine stains

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Sirolimus (rapamycin) is a specific inhibitor of mammalian target of rapamycin, and, because of its antiangiogenic properties, its use as an adjuvant for the laser treatment of port wine stains (PWSs) has recently been suggested (1). We report a case of allergic contact dermatitis caused by sirolimus (Rapamune® 0.1% oral solution) that was used as an adjuvant topical treatment during laser treatment of a PWS.

Case Report

A 32-year-old healthy woman participated in our clinical trial in which a PWS on her left flank was treated

with laser therapy, and this was directly followed by topical application of sirolimus on three separate areas of 1 cm² (small areas were chosen in order to allow comparison of different experimental treatment combinations in one PWS, before treating the whole PWS with the 'best' treatment). Sirolimus was applied topically under occlusion on the treated PWS, and left *in situ* for 7 days. This treatment was repeated five times, with 2-week intervals. After the second and third treatments, the patient developed mild dermatitis (erythema) at the sirolimus application sites, which forced her to remove the occlusive bandage after 5 days. The skin irritation cleared spontaneously within 2 weeks. The treatment was repeated two more times according to the study protocol, but, because of increased itching and dermatitis, the occlusive bandages had to be removed after 2 days on both occasions. After the last treatment, the patient developed an itching rash on her entire upper body, in addition to the erythematous skin reaction at the application site, which slowly resolved within 2 weeks after daily applications of desoximetasone cream.

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Table 1. Patch test results

Allergens	D2	D3
Rapamune® 'as is'	++	+++
Rapamune® 1:3 olive oil	+	++
Rapamune® 1:3 aq.	+	+
p-Phenylenediamine	++	++
Caine mix III	++	+
Quaternium-15	–	+
Formaldehyde	++	++
Methyldibromo glutaronitrile	+	+
Carba mix	–	+
1,2-Benzisothiazolin-3-one	–	+

To evaluate the possibility of allergic contact dermatitis, patch tests were performed with the European baseline and additional series supplemented with topical Rapamune® (1 mg sirolimus/ml) 'as is', 1:3 in olive oil, and 1:3 aq. Patch tests were conducted with van der Bend Chambers® on the patient's back, and read on day (D) 2 and D3, according to ICDRG criteria (2). Readings showed extreme positive reactions to Rapamune®, and some positive reactions to common allergens, which were deemed to be of no relevance to this case. The positive results are summarized in Table 1.

Sirolimus is a macrolide immunosuppressant, and, to evaluate the possibility of cross-reactivity with, and subsequent allergy to, macrolide antibiotics (3),

further patch tests were performed 5 months later with azithromycin, clarithromycin, and erythromycin. To evaluate the possibility of an allergy not to sirolimus itself but to constituents of the solution, propylene glycol (5% pet.) and polysorbate (5% pet.) were also tested. The other ingredients of Rapamune® solution (i.e. phosphatidylcholine, monodiglycerides, ethanol, soya fatty acids, and ascorbyl palmitate) were not available for patch testing, but were considered to be unlikely allergens. All additional patch tests, again read on D2 and D3, showed no reactions.

We did not perform patch tests with Rapamune® in control patients; however, in our clinical trial, 16 other PWS patients had been treated with topical Rapamune® under occlusion (in van der Bend Chambers®, to match the 1 cm² treatment areas exactly); 5 of these developed irritant skin reactions, but no allergic reactions.

Discussion

We conclude that our patient most likely experienced an allergic reaction to topically applied sirolimus. Although there are some reports of skin irritation caused by topical sirolimus (4, 5), to our knowledge this is the first report of a true allergic contact dermatitis. As there is increasing interest in the use of topical sirolimus in the treatment of PWS, and also of angiofibromas (5), attention should be drawn to the risk of allergic contact dermatitis.

References

- 1 Marques L, Nunez-Cordoba J M, Aguado L et al. Topical rapamycin combined with pulsed dye laser in the treatment of capillary vascular malformations in Sturge–Weber syndrome: phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial. *J Am Acad Dermatol* 2015; **72**: 151–158 e1.
- 2 Johansen J D, Aalto-Korte K, Agner T et al. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact Dermatitis* 2015; **73**: 195–221.
- 3 Riley L, Mudd L, Baize T, Herzig R. Cross-sensitivity reaction between tacrolimus and macrolide antibiotics. *Bone Marrow Transplant* 2000; **25**: 907–908.
- 4 Ormerod A D, Shah S A, Copeland P et al. Treatment of psoriasis with topical sirolimus: preclinical development and a randomized, double-blind trial. *Br J Dermatol* 2005; **152**: 758–764.
- 5 Mutizwa M M, Berk D R, Anadkat M J. Treatment of facial angiofibromas with topical application of oral rapamycin solution (1mg/mL(-1)) in two patients with tuberous sclerosis. *Br J Dermatol* 2011; **165**: 922–923.