TREATMENT OF ANGIOKERATOMAS OF FORDYCE WITH TOPICAL RAPAMYCIN 0.25% CREAM

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INTRODUCTION

Angiokeratomas are benign vascular neoplasms clinically described as well-defined hyperkeratotic, red-to-black papules or plaques, and histologically appear as dilated blood vessels in the papillary dermis that form lacunae with associated acanthosis and rete ridge elongation. Multiple variants of angiokeratomas exist, including angiokeratoma of Fordyce (located on the genitalia, including the scrotum), angiokeratoma corporis diffusum (associated with Fabry disease), angiokeratoma of Mibelli (located on acral sites), solitary or multiple angiokeratomas (often located on lower extremities), and angiokeratoma circumscriptum (congenital and occurs on the trunk and extremities). While angiokeratomas are typically asymptomatic, they can bleed, cause pruritus or pain, and impact psychological health, ultimately driving a patient to seek care. A wide variety of therapeutic options have previously been described including surgical excision, electrodessication, cautery, cryotherapy, and laser.1 Here, we describe a patient who demonstrated a positive response to topical rapamycin (sirolimus), an unconventional method of treatment.

CASE REPORT

A 61-year-old man presented for the appearance of numerous lesions on the scrotum, which were increasing in number, enlarging, and tender. A shave biopsy confirmed the diagnosis of angiokeratoma. Treatment with 595-nm pulsed dye laser (PDL) was initiated with second and third treatments performed at 4 and 6 months. A mild decrease in the size of lesions was noted after each PDL session; however, the lesions ultimately persisted, and the patient was unable to tolerate the PDL sessions secondary to pain. Lesions remained large and symptomatic (Fig 1, A), and the patient expressed preference for topical treatment. Thus, he was started on off-label topical rapamycin (1 mg tablets compounded into a 0.25% cream) twice daily to the affected areas, which he obtained from a local compounding pharmacy covered by Medicaid insurance. Apart from an initial transient mild burning irritation at the treatment site lasting for approximately 10 minutes post-application, the medication was well-tolerated, and this transient burning sensation no longer occurred with continued use.

At the 3-month follow-up, the patient reported resolution of pain and tenderness as well as a subjective “50% improvement” in the size and appearance of the angiokeratomas (Fig 1, B). Blood rapamycin levels were undetectable.

At the 7-month follow-up, the patient was very pleased and reported sustained resolution of pain and tenderness as well as continued improvement of the physical lesions with a subjective report of “100% improvement” in his angiokeratomas. Objective examination revealed at least moderate improvement in the appearance of the angiokeratomas, particularly in number and density of lesions (Fig 1, C). Due to his continued response, the patient chose to continue treatment with twice-daily application of topical rapamycin cream.

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DISCUSSION

Treatment of angiokeratomas can be challenging, especially in the case of larger and more extensive lesions in sensitive locations such as the scrotum. Rapamycin has recently emerged as a treatment for vascular tumors and malformations. Its mechanism of action is by inhibition of mTOR, a serine/threonine kinase in the phosphoinositide-3-kinase/Akt pathway, which acts by enhancing expression of vascular endothelial growth factor to drive angiogenesis. Inhibition by rapamycin stops vascular endothelial growth factor production and cellular proliferation, thus driving its efficacy in vascular tumors.2,3

Rapamycin is currently approved by the US Food and Drug Administration for use in renal transplant patients to prevent allograft rejection and for use in lymphangiomatosis patients.4 Topical rapamycin has most commonly been used off-label for facial angiofibromas in patients with tuberous sclerosis complex. It has also reportedly been used for other vascular conditions, including Kaposi sarcoma, port wine stains, and a solitary angiokeratoma of the buttock.5,6 To the best of our knowledge, this is the first report describing topical rapamycin for use in treating angiokeratomas of Fordyce.

Topical rapamycin is typically well-tolerated, with mild to moderate irritation at the application site reported as the most common side effect.5 A recent randomized controlled trial involving 179 patients with tuberous sclerosis complex-related facial angiofibromas was conducted to evaluate the efficacy and safety of topical rapamycin for use in facial angiofibromas. Topical rapamycin was reported to be well-tolerated as application site pain, pruritus, erythema, and irritation was seen in 10% or less of patients, and no serious adverse events occurred.7 To combat potential application site irritation, previous case studies have used topical rapamycin 1% ointment with a petroleum-based vehicle, which effectively prevented local irritation.8

With regard to concern for immunosuppression, most patients do not have detectable blood concentrations as rapamycin has a high molecular weight, which may limit cutaneous absorption. Those who do have detectable levels in the blood typically have concentrations below that associated with immunosuppression. It is important to note, however, that absorption levels may be altered by concurrent physical treatments, such as PDL, or with widespread application.7 Being aware of the fact that systemic absorption is possible, particularly with the thin skin of the scrotum, our patient had blood concentrations measured at his follow-up visit, which did not reveal detectable drug levels.

For our patient, given the undetectable blood rapamycin level and satisfaction with cost of therapy and minimal side effect profile, we anticipate that he will be able to continue this medication long-term for further improvement of his angiokeratomas of Fordyce, although future studies are required to evaluate the true efficacy and safety, including the consequences of long-term use. Topical rapamycin may be a promising alternative treatment for patients...
with angiokeratomas of Fordyce who are unable to tolerate other therapeutic options.

Conflicts of interest

Dr. DeKlotz is an inventor on a patent application filed by Georgetown University related to the technology described in this publication. Authors Bell and Guo have no conflicts of interest to declare.

REFERENCES

1. Nguyen J, Chapman LW, Korta DZ, Zachary CB. Laser treatment of cutaneous angiokeratomas: a systematic review. Dermatol Ther. 2017;30.
2. Le Sage S, David M, Dubois J, et al. Efficacy and absorption of topical sirolimus for the treatment of vascular anomalies in children: a case series. Pediatr Dermatol. 2018;35:472-477.
3. Ricci KW. Advances in the medical management of vascular anomalies. Semin Intervent Radiol. 2017;34:239-249.
4. Musalem HM, Alshaikh AA, Tuleimat LM, Alajlan S. Outcome with topical sirolimus for port wine stain malformations after unsatisfactory results with pulse dye laser treatment alone. Ann Saudi Med. 2018;38:376-380.
5. Leducq S, Giraudieu B, Tavernier E, Maruani A. Topical use of mammalian target of rapamycin inhibitors in dermatology: a systematic review with meta-analysis. J Am Acad Dermatol. 2019;80:735-742.
6. Camacho I, Scott J, DeKlotz C. Topical sirolimus for treatment of a solitary angiokeratoma. Dermatol Ther. 2020:e13907.
7. Koenig MK, Bell CS, Hebert AA, et al. Efficacy and safety of topical rapamycin in patients with facial angiofibromas secondary to tuberous sclerosis complex: the TREATMENT randomized clinical trial. JAMA Dermatol. 2018;154:773-780.
8. Haemel AK, O’Brian AL, Teng JM. Topical rapamycin: a novel approach to facial angiofibromas in tuberous sclerosis. Arch Dermatol. 2010;146:715-718.