Inhibition of Angiofibromas in a Tuberous Sclerosis Patient Using Topical Timolol 0.5% Gel

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Angiofibromas are the most recognized cutaneous manifestations of tuberous sclerosis complex. Angiofibromas can be associated with disfigurement, bleeding, pruritus, and erythema and may lead to significant psychosocial consequences for affected patients. Histopathologically, angiofibromas consist of a mixture of vascular and interstitial cells. Traditional treatment options include cryotherapy, electrocoagulation, radiofrequency ablation, dermabrasion, laser treatment, and topical agents such as podophyllotoxin. However, complications such as pain, postinflammatory hyperpigmentation, scarring, and the frequent recurrence rate reduce the utility of these treatment options. The introduction of topical rapamycin marked a turning point for treatment of facial angiofibromas; however, the lack of a standardized formulation, limited insurance coverage, and significant financial cost restrict universal access for patients and their caregivers. Both oral and topical β-blockers have proven extremely effective treatments for superficial vascular tumors such as hemangiomas and pyogenic granulomas. Topical β-blockers may potentially be useful for treatment of angiofibromas considering these lesions also contain a vascular component. Here we present an exploratory case report of a patient with tuberous sclerosis complex who had significant clinical improvement of her facial angiofibromas utilizing a “split-face” comparison protocol of topical timolol 0.5% gel after full-field treatment with ablative fractional laser resurfacing and pulsed-dye laser.

Tuberous sclerosis complex (TSC) is a neurocutaneous disorder characterized by benign hamartomatous growths in multiple organs including the brain, heart, kidneys, eyes, lungs, and skin\textsuperscript{1}. It is caused by an autosomal dominant mutation in either the TSC1 (hamartin) or TSC2 (tuberin) gene, and affects ~1 in 6000 live births with variable expressivity\textsuperscript{1}. The major dermatologic features of TSC including ash-leaf spots, shagreen patches, and angiofibromas appear in ~81% to 96% of cases\textsuperscript{2,3}. Angiofibromas in patients with TSC typically arise during childhood and early adulthood presenting as reddish-brown papules on malar aspects of the face, which may be confused with acne\textsuperscript{2,4}. Histopathologically, angiofibromas are composed of a mixture of vascular and interstitial cells expressing angiogenic factors including vascular endothelial growth factor (VEGF)\textsuperscript{4}. Angiofibromas may be associated with disfigurement, bleeding, pruritus, and erythema leading to psychosocial consequences for affected patients. Therefore, treatments aimed at reducing fibrous growth and erythema are often employed. Cryotherapy, electrocoagulation, radiofrequency ablation, dermabrasion, laser treatment such as ablative fractional laser resurfacing (AFR) and pulsed-dye laser...
(PDL), and topical podophyllotoxin have all demonstrated some success in the treatment of facial angiofibromas. However, complications such as pain, postinflammatory hyperpigmentation, and scarring have reduced the utility of these treatment options. Most notably, recurrences after these procedures have been reported in up to 80% of cases necessitating frequent, serial treatments. The medication rapamycin (sirolimus) has received recent attention for its role in helping to regulate the formation of angiofibromas; it too has disadvantages, however, including limited availability and potentially prohibitive financial cost. Consequently, the “ideal” treatment of angiofibromas remains elusive.

Recently, the potential mechanisms of action for β-blockers in the treatment of infantile hemangiomas were postulated. Herein we present a patient with TSC whose multiple facial angiofibromas were treated by using a protocol combining full field AFR with pulsed-dye laser. Two weeks before her laser surgery and then restarting on postoperative day 5, topical timolol 0.5% gel was applied twice a day to the patient’s right cheek only; this administration protocol is similar to that used for the topical treatment of superficial infantile hemangiomas. At her 4-month postoperative follow-up, demonstrating sustained and markedly reduced recurrence of angiofibromas on the treated side of her face suggesting the topical β-blocker had some inhibitory effect on angiofibroma genesis.

**CASE REPORT**

A 26-year-old woman with a history of TSC followed by pediatric dermatology presented for symptomatic management of multiple refractory facial angiofibromas (Fig 1A) on the nose and bilateral cheeks. The facial angiofibromas had been present for ~2 decades. The patient’s father reported cyclical “flushing” and increased number of lesions associated with her menses. The patient had previously been treated with PDL (595 nm) 2 years before presentation, and her angiofibromas recurred within 2 to 3 months of her treatment. The family denied using any other oral or topical therapies in the last 15 years. Physical examination revealed hundreds of near-confluent, 1- to 2-mm, pinkish-red, fibrous papules with an erythematous base on the patient’s nose and bilateral cheeks, consistent with the diagnosis of angiofibromas. Therapeutic options were discussed with the patient and family who opted for laser treatment with full field AFR and pulsed-dye laser. The patient was started on oral acyclovir 1 day before her laser surgery for prophylaxis against herpes virus infection. The patient and father also agreed as a novel intervention to apply topical timolol 0.5% gel twice a day to the patient’s right cheek only, starting 2 weeks before her scheduled laser surgery and then restarting on postoperative day 5.

After obtaining informed consent, the patient was placed under general anesthesia due to the extent and location of her angiofibromas. Her bilateral medial cheeks and nose were first treated with a 595-nm pulsed-dye laser (Vbeam; Candela Corporation, Wayland, MA) with a 10-mm spot size, fluence of 9 J/cm², and 1.5 milliseconds pulse width, and the clinical end point of moderate...
purpura was achieved. Next, her lesions were treated using a macro-
fractionated 10 600-nm CO₂ laser (Active Fx; Ultrapulse Encore;
Lumenis, Ltd, Yokneam, Israel) at the following settings: 125 mJ/3.5 W/0.1
second repeat delay/size 5/density 5-6, which result in nonfractionated,
full-field ablative resurfacing in the desired areas. Using sterile water, the
treatment area was moistened and a sterile cotton tip applicator was
rubbed vigorously over the surface, removing the lesions down to the
superficial papillary dermis. No papules were observed after the
ablation. As is typical with CO₂ laser ablation, bleeding in the area was
negligible.

Immediately after treatment, a petrolatum-based ointment was
applied (Aquaphor ointment, Beiersdorf, Inc, Wilton, CT). The
patient was discharged from the hospital with instructions to clean the
surgical areas for 5 days with vinegar soaks and to continue oral acyclovir
for a total of 7 days. Her father began applying the topical timolol 0.5% gel
twice a day on the right cheek starting 5 days postoperatively. No
postoperative complications were reported, and the patient was able to
resume essentially normal activities 2 days later.

At her follow-up appointment 4 months later, the patient was noted to
have markedly reduced erythema and reduced number and size of
angiofibromas on the timolol-treated right cheek as compared with her
untreated nose and left cheek (Fig 1B), which served as internal
controls.

**DISCUSSION**

Treatment intervention for facial angiofibromas is often undertaken
because of the significant effect on patients’ quality of life. Several
treatments have been developed to try to reduce the growth and
erythema associated with these lesions. Procedural options for
angiofibromas include radiofrequency ablation, cryotherapy,
electrocoagulation, dermabrasion, and laser treatment such as AFR and
PDL.⁵ Reported complications such as lesion recurrence, pain,
postinflammatory hyperpigmentation, and scarring, as well as the potential risks of general anesthesia, reduce the universal
utility of these procedural options.⁵

Several topical agents have also been used in the treatment of
angiofibromas including tranilast, podophyllotoxin, and rapamycin.⁵
Topical rapamycin, in particular, has become a focus of TSC-related
research. Rapamycin is a mechanistic target of rapamycin (mTOR) inhibitor
that is commonly used as an immnosuppressant in transplant recipients. However, because mTOR
dysregulation can cause uncontrolled cell growth and proliferation,
rapamycin also demonstrates antiproliferative and antineoplastic
effects.¹⁰ The antiproliferative and antineoplastic actions of rapamycin
make it a useful agent for the treatment of hamartomas associated
with TSC. Several studies have demonstrated the efficacy of oral
rapamycin for treatment of giant cell astrocytomas and angiomylipomas
associated with TSC.¹¹,¹² In 2008, Haemel et al¹³ demonstrated a
significant reduction in number of facial angiofibromas and associated
erthema after 3 months of treatment with topical rapamycin without the
systemic toxicity associated with oral administration. Later studies
confirmed the profound effect of topical rapamycin on angiofibroma
size and erythema and reported a reduction in recurrence rates.⁵,¹⁴–¹⁶

Side effects associated with topical rapamycin were minimal with local
irritation being the most commonly reported symptom.⁵

Several factors confound the use of topical rapamycin for patients with
TSC with facial angiofibromas. First, topical rapamycin demonstrates
decreased efficacy when angiofibromas exceed 4 mm in size. Park et al¹⁷ found that ablative laser pretreatment before topical
rapamycin application was successful in treating these larger lesions.
Second, early studies on the use of this topical agent did not use
a standardized formulation or dosage, which may have influenced response
to treatment and interpretation of data. In 2011, DeKlotz et al¹⁸
proposed a standardized formulation of 1% rapamycin ointment, though
this methodology has yet to be universally adopted. Finally,
recurrence of angiofibromas with cessation of topical rapamycin is the
expected result. Maintaining topical rapamycin therapy, however, may be
difficult because of limited insurance coverage and because of potential
“out-of-pocket” financial expenses associated with formulating the
topical medicament, which can still range from several hundred to
several thousand dollars (Andrew C. Krakowski, Costco Wholesale
Corporation Pharmacy, November 19, 2014, personal communication).

β-blockers, or β-adrenergic receptor blockers, have traditionally been used
for treatment of cardiac disease by decreasing heart rate and
contractility. In 2008, Leaute-Labreze et al¹⁹ published a landmark study
demonstrating significant and sustained improvement in infantile
hemangioma size and erythema after the use of oral propranolol,
a nonselective β-blocker. Since its introduction to the dermatologic
therapeutic armamentarium, numerous studies have revealed that
even topical formulations of β-blockers, such as timolol 0.5% suspenison or gel, are extremely
effective treatments for superficial vascular tumors such as
hemangiomas and pyogenic granulomas.²⁰–²⁶ The mechanism of
action of β-blockers for treatment of vascular tumors is likely
 multifactorial, arising from
a combination of vasoconstriction, inhibition of angiogenic factors such as VEGF, matrix metalloproteinase-2, matrix metalloproteinase-9, and interleukin-6, and induction of apoptosis.7–9

In this limited case report, the patient had significant, sustained improvement of her facial angiofibromas after laser treatment and twice a day topical timolol 0.5% gel application without reported complications. Importantly, her untreated nose and left cheek served as internal controls. Because angiofibromas are known to contain a highly vascular component expressing angiogenic factors such as VEGF, it is likely the patient’s right cheek improved due to the antiangiogenic and proapoptotic effects of the topically administered β-blocker.

Further studies are necessary to elucidate the exact mechanism of action of β-blockers in angiofibroma genesis and to explore what role, if any, this class of medication might play in treating angiofibromas and other clinical manifestations of tuberous sclerosis. It is likely that any ideal treatment will use a multifactorial mechanism of action. Consequently, β-blockers could prove a useful adjuvant to rapamycin and more traditional directly destructive procedures. Additionally, because of their histologic similarities to facial angiofibromas, clinical investigations may be warranted to explore the use of β-blockers as a novel treatment of subungual fibromas (Koenen’s tumors), pearly penile papules, and fibrous papules of the nose.

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