Case Report

Topical Sirolimus in Facial Angiofibroma

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Abstract

We represent a case of 11-year-old child with multiple facial angiofibromas who showed moderate improvement after application of 0.1 and 1% sirolimus. We evaluated the results clinically and dermoscopically.

Keywords: Facial angiofibroma, sirolimus, tuberous sclerosis complex

Introduction

Tuberous sclerosis complex (TSC) is a genodermatoses characterized by hamartomas in multiple organs such as the skin, brain, eyes, kidney, and heart. Among all, skin is the most commonly involved organ, the manifestations of which mainly comprise angiofibromas, shagreen patch, white ovoid or ash-leaf macules, and periungual fibromas.[1] Facial angiofibromas are pathognomonic cutaneous findings which occur in 70%–80% cases of TSC. They pose a great psychological and cosmetic distress as they are refractory to treatment. There are multiple therapeutic options described for treating angiofibromas.[2] Here, we are sharing a case of an 11-year-old child showing improvement in color, size, and number of facial angiofibromas after topical application of sirolimus.

Case Report

An 11-year-old male child born to nonconsanguineous marriage presented to us with the complaint of multiple asymptomatic skin to brown-colored small, round, elevated skin lesions on the face for 2 years.

Except the facial lesions, child did not have any other cutaneous manifestations. He did not reveal any history of seizures, decreased vision, changes in weight, and bowel habits or early puberty. Similar complaint and history were not elicited from other family members.

On examination, we found multiple (30), discrete, small, round, firm, well-defined dome-shaped, reddish-brown telangiectatic papules present on cheeks, nose, and forehead. Few papules coalesced to form plaque.

Routine investigations such as complete blood count, renal and liver function tests, and viral markers were carried out before and after 3 months of starting topical sirolimus. Extracutaneous involvement was excluded by carrying out appropriate investigations such as computed tomography scan brain, Chest X-ray, and fundus examination. Histopathology of facial lesions confirmed the case as angiofibroma by the presence of concentric arrangement of collagen bundles around multiple hair follicles and dilated blood vessels.

Topical sirolimus was prepared in pharmacology department of the institute after crushing the 1 mg tablets of sirolimus and mixing it with white petrolatum jelly in sterilized airtight metal containers to prepare a concentration of 0.1 and 1%. Prior written informed consent was obtained from the guardian.

The patient was advised twice daily application and explained regarding the side effects of topical sirolimus.

We evaluated the patient by digital photographs, dermoscopy, and FASI (facial angiofibroma severity index).[2] About 0.1% topical rapamycin was given for 1 month for a trial purpose which was increased to 1% topical sirolimus for the next 3 months.

Pre and postanalysis at monthly intervals are mentioned in Table 1, Figures 1 and 2. We observed gradual decrease
in the size of angiofibromas on the face as the duration of treatment increased. Color of the lesion also changed from reddish-brown to light-brown. Fortunately, patient did not experience any side effects such as redness, burning, or irritation.

Patient presented to us late after 4th month of application so there was a little increase in the size of lesions.

**Table 1: Facial angiofibroma severity index**

|                | Pretreatment | 1 month (0.1%) | 2nd month (1%) | 3rd month (1%) | 4th month (1%) |
|----------------|--------------|----------------|----------------|----------------|----------------|
| Erythema       | 3            | 2              | 2              | 1              | 2              |
| Size           | 1            | 1              | 1              | 1              | 1              |
| Extension      | 2            | 2              | 2              | 2              | 2              |
| Score          | 6            | 5              | 5              | 4              | 5              |
| Severity       | Moderate     | Mild           | Mild           | Mild           | Mild           |

**Discussion**

TCS is an autosomal dominant neurocutaneous syndrome caused by mutation in two genes: TCS 1 and TCS 2. The disease was first recognized in the 19th century by Rayer and Bournville. The disease manifests by overstimulation of mammalian target of rapamycin (mTOR) complex 1 through dysfunction of two regulatory proteins—hamartin and tuberin. This results in uncontrolled cell growth and proliferation giving rise to hamartomas in multiple organs such as the skin, brain, eyes, kidney, and heart.

Cutaneous manifestations of TCS include facial angiofibromas (previously named “adenoma sebaceum”), forehead fibrous plaques, shagreen patch, hypomelanotic or confetti-like macules and periungual fibromas (Koenen’s tumors).

Facial angiofibromas are the most common cutaneous finding of TSC which are included as major diagnostic criteria in the...
Rapamycin (sirolimus) is a macrocyclic lactone isolated from soil bacterium "Streptomyces hygroscopicus." It is an antimalignant drug which was previously used in transplant recipients and as a drug-eluting stent. However, recently, its antineoplastic and antiangiogenic action has been reported in benign tumors of TCS such as facial angiofibroma, renal angiomyolipoma, and subependymal astrocytoma. Angiofibromas of TCS shows overactivation of mTOR and overexpression of vascular endothelial growth factor both of which promote angiogenesis. Rapamycin inhibits mTOR activity, the transition from G1 to S phase, T lymphocyte formation, keratinocyte proliferation, and neutrophilic inflammatory activity.[5,6] The role of rapamycin was discovered in TCS after Hofbauer et al. observed a decrease in the size of facial angiofibromas and renal angiomyolipoma following use of systemic sirolimus in a renal transplant patient. However studies have found that oral rapamycin carries risk for carcinoma, hypersensitivity, hypercholesterolemia, and hypertension.[5,7] Growing tumors in early stage of life have more proliferative component thus sirolimus would be more effective in early childhood.[2,3] This explains the reason for the drastic improvement in angiofibromas in our pediatric patient.

Wataya-Kaneda et al. have reported the effect of different topical concentrations of sirolimus in angiofibromas for varying duration.[8] To watch for any adverse effects, we started with 0.1% topical rapamycin for the 1st month and later increased the concentration to 1% resulting in marked improvement which is similar to the observation in Indian study.[1]

We observed that after 1 month of applying 0.1% topical rapamycin, FASI score reduced from 6 to 5. At the end of 3 months, lesions decreased to the size of a pinhead and faded in color to light brown. FASI reduced to a score of 4 at the end of the 3rd month which later increased to 5 at the end of 4th month as the patient presented late for follow-up. This suggests that the effect of topical sirolimus transient and needs long-term maintenance for effective results. Similar finding was mentioned by Cinar et al.[3] Dermoscopically, we observed decrease in size and fading of color of yellowish globules observed in lesions on the cheeks (Table 1 and Figures 1, 2).

Few studies have reported dryness, mild burning, and erythema with topical application of sirolimus. However, fortunately, our patient tolerated the medication very well without any side effects or adverse events.