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Therapeutic effect of Topical Sirolimus on Facial Angiofibromas in Patients of Tuberous Sclerosis Complex

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ABSTRACT

Introduction: Tuberous sclerosis complex (TSC) is a rare autosomal dominant disorder. Facial angiofibromas are the most common cutaneous findings of TSC. Treatment modalities such as laser, surgery, and/or cryotherapy are employed. Topical therapy with Sirolimus, an mTOR inhibitor, showed beneficial effects. **Objective**: To study the effects of topical sirolimus (0.1%) on Facial Angiofibromas in patients of TSC. **Methodology :** Four patients with facial angiofibromas were included. They applied Sirolimus preparation twice daily, for 3 months. The Facial Angiofibroma Severity Index (FASI) was recorded pre-intervention, at 3 months and after 6 months. **Results:** All the patients showed a reduction in the FASI score at the end of three months of therapy. In three patients, on discontinuing therapy, there was no change in the FASI score at the end of six months, i.e., FASI 3 and FASI 6 were the same. **Conclusion:** Topical sirolimus is an effective treatment for facial angiofibroma in patients with TSC.

KEYWORDS: Facial Angiofibroma, Topical Sirolimus, Tuberous Sclerosis Complex

INTRODUCTION

Tuberous Sclerosis Complex (TSC) is a genodermatosis with multisystem hamartomas. [1] It is a rare autosomal dominant disorder due to genetic mutation in either the TSC1 gene on chromosome 9 or the TSC2 gene on chromosome 16, which codes for hamartin and tuberin respectively. This results in up-regulation of mTOR, leading to uncontrolled cellular growth, proliferation and protein synthesis. [2]The organs affected include kidneys, brain, skin, heart, and lungs. [3] The presentation can vary depending on the specific system involved. Facial angiofibromas are the most frequent cutaneous findings of TSC. They are small, symmetrical, pink to red papules, which coalesce to form plaques composed of blood vessels and fibrous tissue, seen in 75%-80% of patients. Apart from complications like bleeding and obstruction of nasal openings, they can cause a great psychosocial burden to the patients. [1] Various treatment modalities such as laser, surgery, cryotherapy and dermabrasion are employed, but they can cause scarring and do not prevent recurrences. [2, 4]Topical therapy with sirolimus (rapamycin), an mTOR inhibitor, has been reported to have beneficial effects in facial angiofibromas. [1, 2, 5] We wanted to study the therapeutic effect of topical sirolimus (0.1%) on facial angiofibromas in patients of Tuberous Sclerosis Complex. We enrolled patients with facial angiofibromas during

our study period of six months.

Ethical Approval: Taken from the Institutional Ethics Committee before the beginning of the study: Reference number: IEC/TOMCHHRC/52/2023-24

CASE SERIES

Case 1

A 28 year old female presented with multiple lesions over the face since 9 years of age, predominantly over bilateral cheeks. Examination revealed multiple skin coloured, few pinkish and hyperpigmented papules, discrete to confluent, distributed over a bilateral malar area and dorsum of the nose, few scattered papules were noted on the forehead. (FASI score-6)

In this index, the erythema, size and extent of the lesions were considered. The scoring is done as follows: Table 1

Erythema	Size	Extent
Skin colour - 0 Light red - 1 Red - 2 Dark red /purple - 3	Small < 5 mm - 1 Large > 5 mm - 2 Confluent - 3	< 50 % of cheek area - 2 50% of cheek area - 3

FASI score less than 5 — Mild, FASI score is 6 to 7 — Moderate, FASI score is more than or equal to 8 — Severe

Table 1: FASI Index

The diagnosis of Facial angiofibroma was confirmed. The histopathological examination confirmed the same.

The patient applied Topical Sirolimus 0.1% which was prepared in our pharmacy twice daily for 3 months. [6] Photographs were taken at the beginning and end of the study.

She showed a reduction in the FASI score by 33% at the end of three months (FASI3). The FASI score was assessed 3 months after stopping therapy also and it was the same as the score after 3 months of therapy (FASI 6). There was no increase or deterioration of the lesions.

There was itching and redness for the first 10 days after starting Topical Sirolimus therapy which was relieved by reducing the application to once daily at night for 3 weeks. After these 3 weeks the application was made twice daily. No side effects were observed subsequently.

Case 2:

A 34 year old female presented with multiple lesions on the face since 10 years of age, distributed over bilateral cheeks.

Examination showed multiple skin coloured, red to pinkish and hyper-pigmented papules, a few coalescing to form

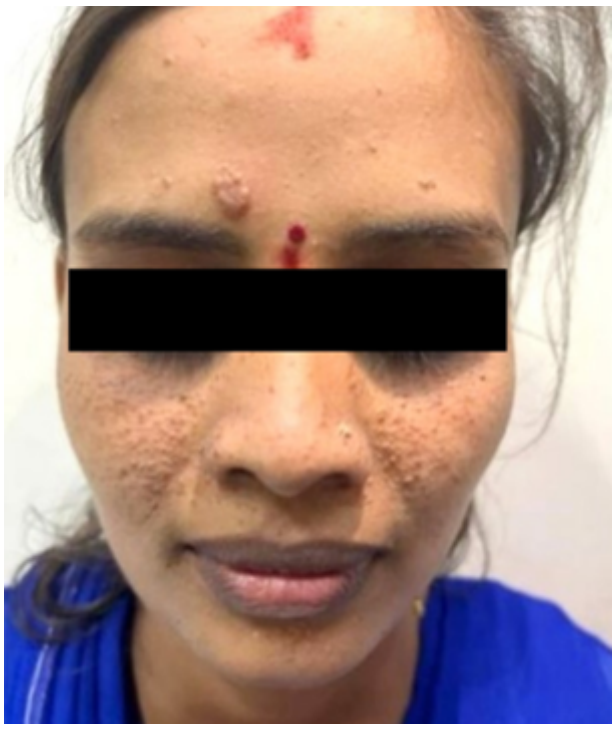

Figure 1: Pre-treatment

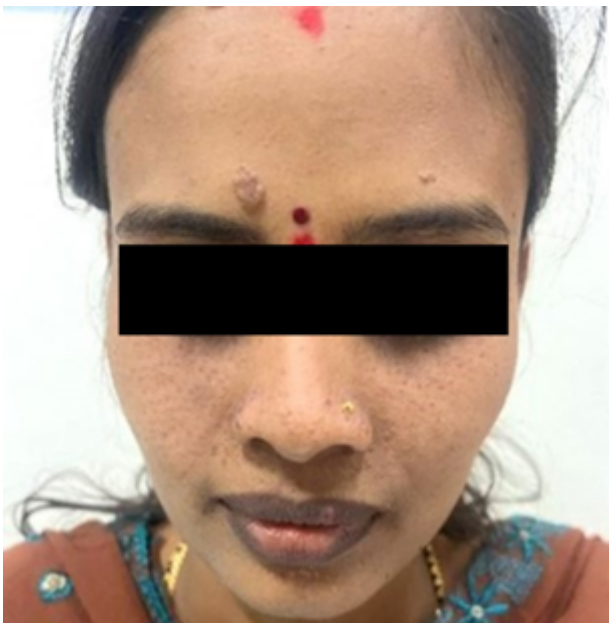

Figure 2: Post-treatment

plaque, distributed on bilateral malar area, and discrete papules on the forehead and dorsum of the nose. A diagnosis of Facial angiofibroma was made (FASI score — 8). The histopathological examination was done.

The patient applied Topical Sirolimus 0.1% twice daily for 3 months and the FASI score was assessed after 3 months and 3 months after stopping the therapy. There was a reduction in FASI score by 25% and this was the same at the end of 6 months .ie.3 months after stopping therapy.

Case 3:

A 36 year old female presented with multiple swellings on the face since 16 years of age, predominantly distributed over both cheeks. The lesions gradually increased in size. She was mentally challenged with delayed developmental milestones and was under treatment for epilepsy. The patient also had a history of previous hospitalisations for renal failure.

On examination, multiple reddish-pink, dome-shaped papules, discrete to confluent, distributed symmetrically over the nasolabial folds and cheeks, and confluent papules on the dorsum of the nose were also noted. (FASI score — 7).

Other cutaneous manifestations of TCS like pedunculated soft swellings, ash leaf macules and shagreen patches on the trunk were also observed. She had Facial Angiofibroma with TCS.

She applied the Topical Sirolimus 0.1% twice daily for 3 months. She had redness after application of Sirolimus but the application was reduced to once at night for 3 weeks and the redness reduced. Then the application was continued twice daily further for the remaining period of the study. The FASI score decreased by 28.57% at the end of three months. Later the patient passed away due to renal failure. So there is no FASI score at the end of 6 months.

Case 4:

A 25 year old female came with swelling and lesions on the face, since 11 years of age. Examination showed multiple skin-coloured and hyper-pigmented papules, discrete to confluent, distributed over the bilateral malar area and dorsum of the nose. She had facial angiofibroma (FASI score — 6).

Other cutaneous manifestations seen were multiple pedunculated swellings extending from bilateral nasolabial folds. Following application with Topical Sirolimus0.1% twice a day for three months there was a 33% reduction in FASI score.

Cases 1, and 3 were siblings. Their mother had died of renal failure due to TSC.

There was no relevant family history in cases 2 and 4.Table 2

Case	FASI 0 (pre interven-tion)	FASI 3 mths*	% reduction After 3 mths*	FASI 6 mths*
1	6	4	33.3	4
2	8	6	25.0	6
3	7	5	28.6	Died
4	6	4	33.3	4

Case 3 died of renal failure due to TCS complication.
*** The number indicate months of treatment.**

Table 2: Therapeutic effect of Topical sirolimus on Facial Angiofibromas

DISCUSSION

TSC has an incidence of 1 in 6000 to 10,000 individuals.[3] Sirolimus is an immunosuppressant. It inhibits mTOR activity and causes downregulation of cell growth. It also inhibits vascular endothelial growth factor (VEGF), and thereby, VEGF-induced endothelial proliferation and angiogenesis. Since systemic sirolimus is expensive and may cause carcinogenesis, hypersensitivity reactions, hypercholesterolemia, and hypertension; topical application was considered an alternative. [6]

Four of our patients (except the one lost to follow-up) showed considerable reduction in FASI score after 3 months of topical sirolimus, in conformation with earlier studies. [1, 5, 6] Our study reassessed the patients after a drug-free period of three months. There was no change in the FASI score of any of the patients at the end of this period, i.e., there was no recurrence seen until 3 months after discontinuing treatment. A study by Cinar et al. [1] reported relapse when the lesions were reassessed after a six-month drug-free period. High variability has been seen in the number of months to observe recurrence after discontinuation of treatment (1–3 months). [6] Previous studies have observed minimal side effects like erythema, and minor bleeding with topical sirolimus. [1, 5, 6] Localised itching and erythema were the side effects noted in our study. This seems to offer a huge advantage over other currently available treatment options.

CONCLUSION

Topical sirolimus seems to be an effective treatment modality for facial angiofibroma in patients with TSC. However, further studies are warranted to establish its efficacy in patients across all age groups, both as a singular agent in milder lesions and as part of combined treatment in more severe forms. Studies are also required to determine its role in prophylaxis and treatment of frequent relapses associated with the condition.

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