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CASE REPORT

Topical sirolimus for the treatment of angiofibromas in a child with tuberous sclerosis complex: first reported case in the Philippines

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ABSTRACT

INTRODUCTION Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder causing a mutation in the tumor suppressor genes, *TSC1* or *TSC2*. Loss of function of these genes leads to dysfunction of hamartin and tuberin, resulting in hamartoma formation. It usually manifests with cutaneous manifestations at childhood. However, it also affects other organ systems. Based on the Philippine Dermatological Society Health Information System census, there have been 104 cases of TSC from 2011-2018. Currently, limited data is available regarding the treatment options in the local setting.

CASE REPORT The case involves a 4 year-old boy, with a two year history of flesh-colored to dusky red firm papules on the centrofacial areas and neck. Lesions have been increasing in number since first appearance. He had a normal birth history. Family history was insignificant. However, delay in expressive speech development was noted. Physical examination revealed multiple well-defined angiofibromas on centrofacial areas and neck; fibrous cephalic plaque on the left temporal area, and several ash-leaf spots on the trunk. Periungual and subungual fibromas, confetti macules, shagreen patch and dental pits were absent. Based on the clinical manifestations, he was diagnosed with TSC. Histopathology of a papule on the chin was consistent with angiofibroma.

Parents were concerned with the appearance of the lesions and preferred conservative management. Hence, topical sirolimus 0.2% ointment was applied once daily on the angiofibromas for 4 months. Monthly follow-up showed marked improvement, manifested by the decrease in number and by flattening of the lesions.

CONCLUSION To the best of our knowledge, this is the first case report of successful treatment of topical sirolimus for TSC in the Philippines.

KEYWORDS tuberous sclerosis complex, topical, treatment success, conservative management, hematoma

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Conflict of interest
None

Source of funding
None

Cite as
Esguerra AM, Lao-Ang JFS. Topical sirolimus for the treatment of angiofibromas in a child with tuberous sclerosis complex: first reported case in the Philippines. J Phil Dermatol Soc. 2022;31(1):42-45.

INTRODUCTION

Tuberous sclerosis complex (TSC) is a rare genodermatosis with autosomal dominant inheritance. It involves dysfunction of hamartin and tuberin secondary to mutation of the *TSC1* and *TSC2* gene respectively. Most patients are diagnosed before or at 15 months of age, but adults can also be affected.[1] Dermatologic manifestations are the usual initial clinical signs. The lesions in TSC are most often managed through procedures. However, there are emerging topical management options as well.

CASE REPORT

The patient is a 4 year-old Filipino male, with a 2 year history of firm dusky red to skin-colored papules on centrofacial areas. Lesions gradually increased in size and in number, eventually appearing on the neck. Other significant skin manifestations include ash leaf spots characterized as oval-shaped hypopigmented patches, which were apparent at birth on the lower back and buttocks. He also had a fibrous cephalic plaque, soft and flesh-colored, measuring 0.8 x 0.8 cm on the left temporal area. Periungal and subungual fibromas, confetti macules, shagreen patch and dental pits were not evident. He had one episode of benign febrile seizure when he was 11 months old, but there was no recurrence. No family members manifested the same lesions.

Based on the 2012 International TSC Guidelines[1] patient had definite TSC given that he fulfilled 2 major clinical criteria (presence of angiofibromas or fibrous cephalic plaque and presence of hypopigmented macules). The skin punch biopsy of the papule on the chin was consistent with angiofibromas as well, further supporting the diagnosis.

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Due to an increase in facial angiofibromas, he underwent electrocautery on some facial lesions. However, parents reported scar formation and recurrence of lesions.

At the initial visit to the pediatric dermatologist, he was referred to pediatric neurology, neurodevelopmental service and ophthalmology for baseline assessment. Ophthalmologic work-up revealed normal visual acuity and absence of retinal hamartoma. As for neurodevelopmental service, he had normal cognitive development but was noted to have expressive speech delay.

Since parents were concerned with disfigurement, they opted for conservative management of the angiofibromas. He underwent 4-month therapy of topical sirolimus 0.2% ointment applied once daily on the lesions. Slight stinging was noted after application. Otherwise, there were no other adverse reactions. Monthly follow-up showed satisfactory results in terms of flattening and of decrease in number.

DISCUSSION

TSC is an autosomal dominant genodermatosis with hamartomatous tumors in multiple organ systems. It affects 1 per 6000 to 1000 live births with no gender predilection. Based on the Philippine Dermatological Society Health Information System census, there have been 104 cases of TSC from 2011-2018.[2]

Eighty percent of cases exhibit de novo mutation involving *TSC2* gene encoding tuberin protein while 20% exhibit familial mutation involving *TSC1* gene encoding hamartin protein. The normal function of the hamartin - tuberin complex is to inhibit mTOR signaling cascade, that regulates cell proliferation. In patients with TSC, mutations lead to a loss of this inhibition, resulting in upregulation in the mTOR pathway. This increases cell proliferation, including vascular endothelial growth factors (VEGF). Ultimately, hamartoma formation is the end result.[4] For the case, the patient has de novo mutation since no one in the family has the same clinical presentation.

A detailed skin examination is warranted. Lesions usually start with hypopigmented macules at birth followed by appearance of facial angiofibromas and shagreen patch at toddler age, then periungual fibromas at adolescence. This is consistent with the sequence of appearance of the patient's lesions.

Based on the recent international TSC consensus,[1] TSC can be diagnosed clinically. A definite diagnosis is fulfilled if the patient has either a positive genetic mutation or 2 major clinical features or 1 major and 2 or more minor features. For the case, the patient has definite TSC since he has 2 major clinical criteria (presence of angiofibromas or fibrous cephalic plaque and presence of hypopigmented macules). Skin punch biopsy, though not required, can be done to further justify TSC. In this case, histopathologic finding on the chin's papule was consistent with angiofibroma (Figure 1).

Since the patient has definite TSC, a multidisciplinary management is essential since other organ systems can be affected.[6]

In 79%-90%, the earliest neurologic manifestation is seizure. It presents as infantile spasms with a peak age of 3-7 months. In the case, the patient had one episode of febrile sei-

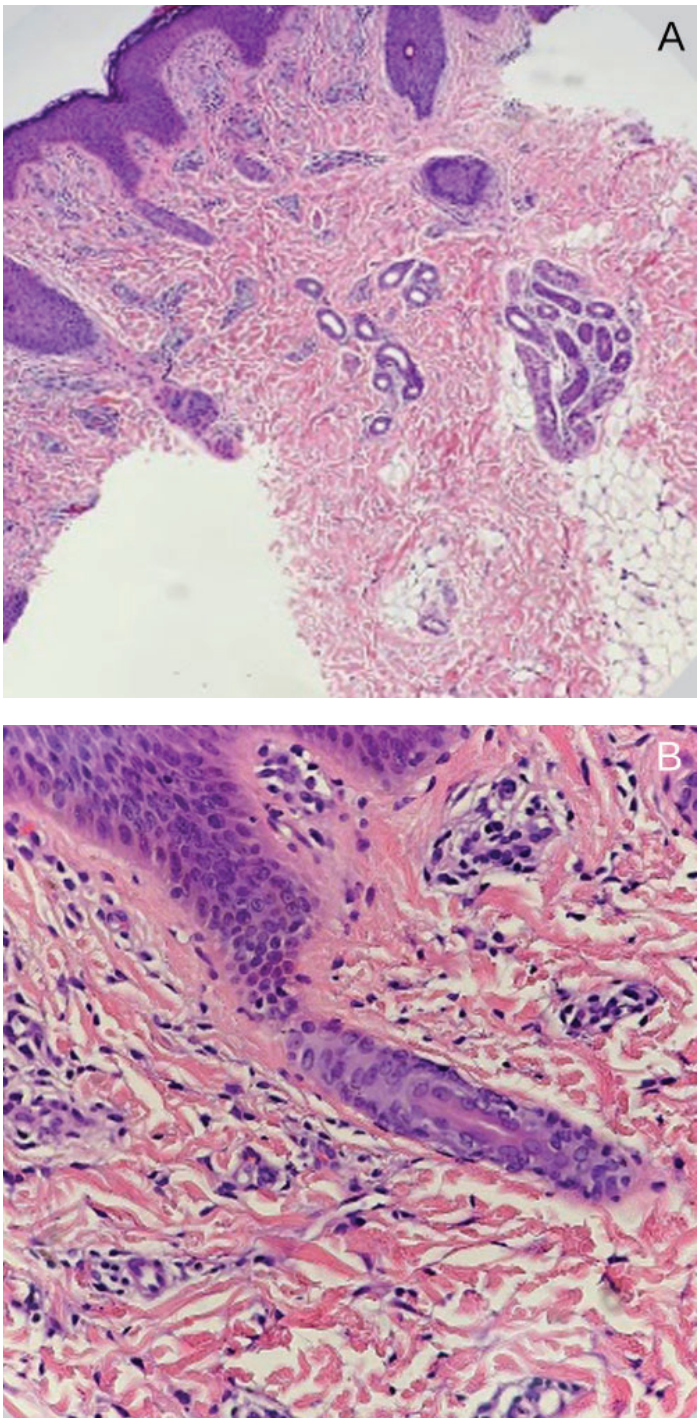

Figure 1. Skin punch biopsy (H&E x40) **A.** Epidermis focal parakeratosis overlying basket weave stratum corneum, scant spongiosis **B.** Concentric perivascular and periadnexal fibrosis with stellate fibroblasts.

Table 1. Monitoring of tuberous sclerosis[1]

Organ System	Diagnostic
Skin, and eye	Detailed physical exam
Brain	Brain MRI ± contrasts, EEG
Heart	ECG ; 2D echo
Kidneys	Kidney function with GFR, Renal ultrasound
Lungs	Pulmonary function test (adults with dyspnea)

zure at 11 months, with no recurrence after. It was assessed as a benign febrile seizure. Upon current consultation, he was referred to neurology and neurodevelopment services. Clinically, he has a normal nervous system. Monitoring is recommended by doing baseline electroencephalogram or magnetic resonance imaging to check for cortical tubers.[5]

As for the renal system, the most common findings are renal cysts in 45% and angiomyolipomas in 80%. These lesions are benign but are the usual cause of TSC-related mortality due to renal hemorrhage and renal failure. These can be evaluated by ultrasonography of the renal system. As for the cardiac system, the usual lesion is cardiac rhabdomyoma in at least 50% of newborns. However, this is detected on prenatal ultrasound. As for the case, he had a normal prenatal and birth history. Given the multiorgan system involvement in TSC, close monitoring is essential. The international TSC consensus has published the recommended surveillance and monitoring guideline as listed in Table 1.[1]

In this case, the major concern was the cosmetic impact of the angiofibromas. Various treatment options are available but there is still no gold standard at the moment. Based on available literature, physical treatment, laser therapy and topical therapy have been reported.[6]

Electrocoagulation is most commonly done. Other physical therapy includes cryotherapy and radiofrequency ablation. However, the abovementioned physical treatment can lead to post-inflammatory hyperpigmentation, scar formation and recurrence. Also, multiple sessions may be required to achieve favorable results. In the case, the patient had a previous electrocoagulation session that led to scar formation and recurrence.

With the advent of laser, it was used for its ablative function in managing angiofibromas. Use of carbon dioxide, and pulsed dye laser leads to excellent results.[7,8] However, scarring and hyperpigmentation are also the major drawbacks.

Hence, topical therapy offers novel management to facial angiofibromas. The most recent development is the use of topical sirolimus (also known as rapamycin) which is an mTOR inhibitor.[9] It is a macrolide, originally intended to be used as an antifungal. Its mechanism in angiofibromas is to regulate the abnormal increase in mTOR signaling. Also, it inhibits angiogenesis by decreasing vascular endothelial growth factors. There have been numerous reports on the successful use of sirolimus for angiofibromas in TS. History began in 2008 when oral sirolimus was given to prevent kidney rejection in a patient with TS, who also exhibited improvement of his angiofibromas. This was followed by formulation of the first topical sirolimus in 2010 showing the same results.[9] Based on review of literature, topical sirolimus has better response rate in younger patients. Remarkable results were evident by the significant decrease in lesion number and in erythema.

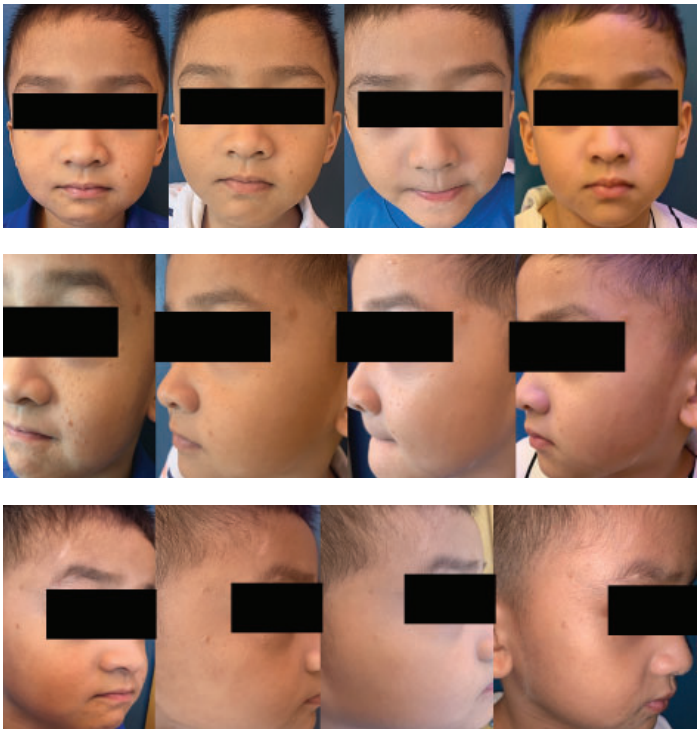

Figure 2. From left to right. Response of patient's angiofibromas after application of topical sirolimus: baseline; at 4 weeks; at 12 weeks and at 16 weeks.

Since there has been no standardized concentration for topical sirolimus, a randomized controlled trial was done in Japan to determine the most effective concentration. The study compared three different sirolimus concentrations (0.05%, 0.1% and 0.2% gel). The result from the trial revealed that the 0.2% sirolimus was the most optimal concentration.[10] The reported side effect was just local irritation on the application site. Among all reported cases, sirolimus had below level of detection in the blood. Hence, it had minimal systemic absorption.[10]

For the case, the patient's parents agreed to use topical sirolimus 0.2% ointment, which was applied once a day over facial angiofibromas. It was compounded by a local pharmacist using crushed sirolimus tablets incorporated in dimethicone-based ointment. After 16 weeks of therapy, significant improvement

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was noted. Decrease in the size of the angiofibroma and of the cephalic plaque on the left temporal area was noted. However, scar from the previous electrocurettage did not respond to sirolimus (Figure 2). Patient had occasional stinging on the application site. No other side effects were noted. Hence, from this case, topical sirolimus has proven to be an effective treatment in improving facial angiofibromas of TSC.

Recurrence rate upon discontinuation is high and can reach 100%,[10] thus many patients are maintained in this medication. The longest reported use was at 3 years, with good response and no side effects.

CONCLUSION

TSC is a progressive disease. Disease severity varies among individuals. For the case, the patient has limited cutaneous disease hence the prognosis is favorable. Also, the use of topical sirolimus serves as a treatment option for patients seeking conservative management. There has been no long-term known complication from its use. This serves to be the first case report in the Philippines to successfully manage facial angiofibromas in TSC with topical sirolimus in the best knowledge of the authors. Despite clinical improvement of the facial angiofibromas, the patient is monitored in a multisystem approach regularly.

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