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CASE REPORT

Use of Topical Rapamycin as Maintenance Treatment after a Single Session of Fractionated CO_2 Laser Ablation: A Method to Enhance Percutaneous Drug Delivery

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Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder with an incidence of approximately 1 in 5,000 to 10,000 live births. TSC has various clinical manifestations such as multiple hamartomas in systemic organs, including the skin. Angiofibromas are the most common skin lesions in patients with TSC. Although benign, angiofibromas develop in childhood and puberty, and can be psychosocially disfiguring for patients. Skin lesions in TSC, specifically angiofibromas, have no significant risk of malignant transformation after puberty; thus, they require no treatment if not prominent. However, the presentation of TSC is important owing to its impact on patient cosmesis. Surgical treatment and laser therapy are the mainstream treatments for angiofibromas. Although the evidence is limited, topical mammalian target of rapamycin inhibitors such as sirolimus (rapamycin) are effective in facial angiofibroma treatment. We describe an adult patient with an angiofibroma who had an excellent response to treatment with topical rapamycin after a single session of carbon dioxide (CO_2) laser ablation. The patient showed no sign of relapse or recurring lesions for a year. CO_2 laser ablation may serve as a new paradigm of treatment for angiofibromas in TSC. Since the selection of laser devices can be limited for some institutions, we suggest a rather basic but highly effective approach for angiofibroma treatment that can be generally applied with the classic CO_2 device. **(Ann Dermatol 31(5) 555～558, 2019)**

-Keywords-
Angiofibroma, CO_2 laser, Sirolimus, Tuberous sclerosis complex

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder characterized by pleomorphic features of systemic organs. The skin is the most commonly affected organ system with up to 90% involvement[1]. Facial angiofibroma is the main feature of this disease, affecting approximately 75% of patients. Angiofibromas appear in early childhood (ages 2～5 years) as red papules and increase in number and size throughout puberty[2,3].

To date, various treatment modalities for angiofibromas have been proposed, including surgical excision, curettage, dermabrasion, electrocautery, and laser ablation[4-7]. Despite the use of rigorous approaches to completely remove the lesions, the outcomes have been suboptimal with a high recurrence rate[8,9]. In addition to improved understanding of the genetic and molecular pathogenesis of the disease, prominent vascular proliferation due to an increased vascular endothelial growth factor (VEGF) level and mammalian target of rapamycin (mTOR) overactivation were noted in angiofibromas. Rapamycin binds to mTOR with high specificity and represses the VEGF output by inhibiting the

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hypoxia-inducible factor and endothelial cell proliferation[10,11]. Additionally, it suppresses T-cell activity and antibody production, resulting in decreased keratinocyte proliferation and inflammation[12].

The use of topical rapamycin has been proposed and shown successful outcomes for both preventing and reducing angiofibroma lesions[12]. The current general consensus among the considered studies suggests that topical rapamycin is an efficient therapy for facial angiofibromas, providing improvement in 94% of cases[8]. Unlike pediatric patients who can benefit from preventive measures with the early application of topical rapamycin, adult patients with an already fully developed disease that includes nodular lesions report poor outcomes with monotherapy[13].

We describe the case of an adult patient who showed an excellent clinical response after a single session of carbon dioxide (CO_2) laser ablation and continued use of 0.2% topical rapamycin for maintenance.

CASE REPORT

A 20-year-old Korean male previously diagnosed as having TSC was referred to the dermatology department for the treatment of extensive angiofibromas on his face. His DNA test revealed mutations in *TSC2*. He presented with scattered and grouped lesions of facial angiofibromas of various sizes and thicknesses. Additionally, periungual fibroma and hypomelanotic macules were noted. Regarding the systemic features of the disease, multiple hamartomas of the heart and kidney were noted.

One year before visiting Scar Laser and Plastic Surgery center, the patient underwent ablative laser treatment for cheek lesions. However, most of the lesions recurred within a few months during the late pubertal period, and wound healing was delayed for large nodules.

He underwent extensive CO_2 laser ablations for all facial lesions. We used a starting fluence between 100 and 150 mJ of continuous CO_2 pulses (eCO$_2$^{TM}; Lutronic, Goyang, Korea), and multiple passes were performed until the lesions were flattened. To improve the absorption of topical rapamycin and wound healing, a fractional CO_2 laser was additionally applied on the whole face. The treated areas were cooled with ice packs for 10∼15 minutes, and topical rapamycin was directly applied. Thereafter, a foam dressing was applied for protection and maintained for 1 day. To minimize the risk of post-inflammatory hyperpigmentation (PIH), sunscreen with broad-spectrum ultraviolet (UV) A and UVB protection was prescribed.

The patient returned to the clinic on the following day without any complication. He was encouraged to use top-

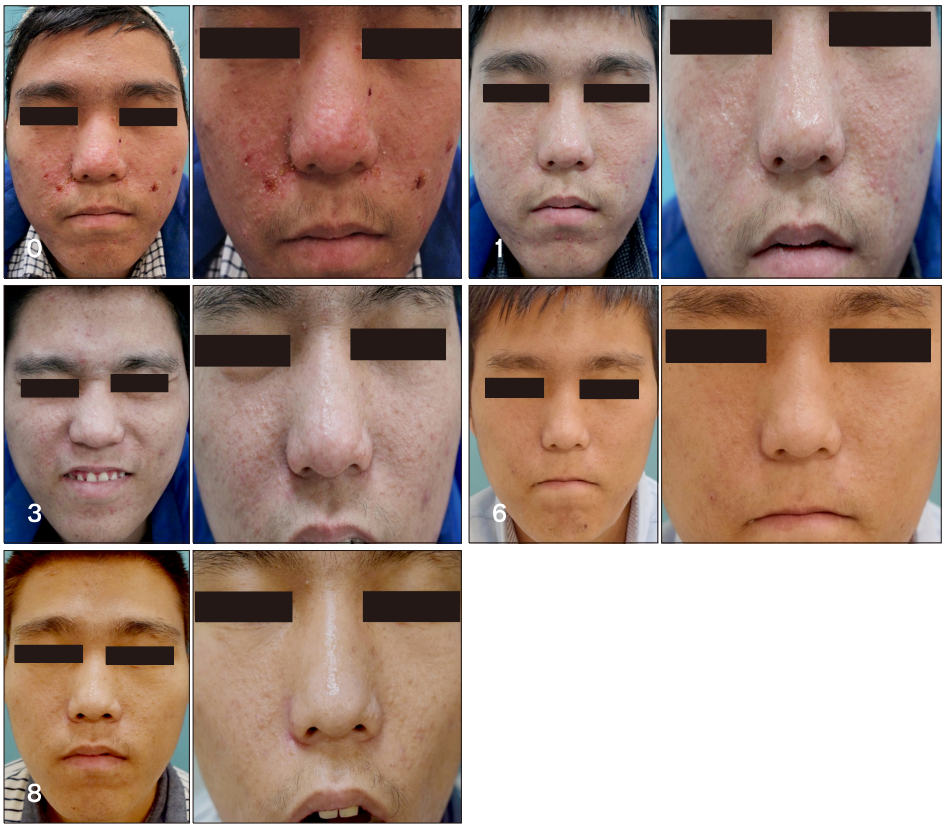

Fig. 1. Improvement of facial angiofibroma lesions in a 20-year-old patient with tuberous sclerosis complex during rapamycin therapy after a single session of CO_2 laser ablation. Left panels, labeled 0: before the administration of laser ablation. Pronounced improvement was observed at 1, 3, 6, and 8 months after the start of systemic rapamycin therapy after a single session of CO_2 laser ablation.

Table 1. Facial Angiofibroma Severity Index (FASI) scores after treatment

Parameter	FASI score				
	Pretreatment	1 month	3 months	6 months	8 months
Erythema	2	1	1	0	0
Size	3	2	1	1	1
Extension	3	3	3	2	2

ical rapamycin once a day afterward. He regularly visited the clinic every 2～3 months, and no sign of recurrence or irritation was noted at 1 year after laser ablation (Fig. 1). We received the patient's consent form about publishing all photographic materials. Additionally, there were no signs of hypertrophic scarring or delayed wound healing during the follow-up period (Table 1).

DISCUSSION

The advent of topical rapamycin has dramatically changed the paradigm of angiofibroma treatment. However, topical rapamycin monotherapy is insufficient for fully developed lesions in adults. Various types of lasers have been popular options, and many studies have reported successful results with CO_2, copper vapor, argon, pulsed dye, potassium-titanyl-phosphate, and Nd:YAG lasers[6,14-16]. For flattened lesions, lasers targeting the vascular structure or melanin pigments may generate sufficient energy to destroy individual lesions with photothermolysis. However, full-thickness ablation of abnormal keratinization and underlying fibrosis is indispensable for bulky lesions. The CO_2 laser is one of the most widely used lasers in dermatology[17]. CO_2 lasers with a 10,600-nm wavelength target the water component of tissues. As a single CO_2 laser can be modulated to cause tissue reactions of incision, excision, vaporization, and coagulation, it can successfully have a debulking effect even for extensive lesions.

Unlike previous reports showing that the CO_2 laser caused hypertrophic scarring in a considerable percentage of patients[6], we did not experience scarring or delayed wound healing in our patient. This outcome can be partially due to the fractionated application of the CO_2 laser after ablation of single lesions. The ablative fractional CO_2 laser can compensate for the lack of specific photothermolysis in CO_2 laser monotherapy. By thoroughly producing microthermal zones on the CO_2-ablated surface, columns of thermal damage cause collagen remodeling and promote wound healing[18].

PIH can occur at any age and in any skin type, and it has no sex preference. However, this type of hypermelanosis is more common in patients with Fitzpatrick skin types IV～VI. Previous research showed that the degrees of erythema and pigmentation correlated linearly after UVB irradiation[18]. Additionally, crusts after laser treatment protect the wound and help prevent the development of PIH after laser treatment. To minimize the risk of PIH, it is necessary to avoid early removal of the crusts and to apply sunscreen with broad-spectrum UVA and UVB protection.

We also postulate that topically applied rapamycin could have contributed to normal wound healing after full-thickness ablation. mTOR is a regulator of cell growth and survival, and acts as a mediator of inflammatory and fibrotic processes. In recent *in vitro* reports, the mTOR signaling pathway was shown to cause proliferation of abnormal fibroblasts, causing pathologic scars[19,20]. Therefore, topical rapamycin can induce a synergistic effect of angiogenesis inhibition for the recurrence of angiofibroma lesions and abnormal scarring repression after CO_2 laser ablation. Notably, even with a 0.2% preparation, topical rapamycin did not cause immediate irritation when directly applied on the laser-ablated surface.

Angiofibromas in TSC significantly affect patients' quality of life by causing psychosocial comorbidities. It can be especially burdensome for late adolescent and young adult patients who have already developed extensive lesions throughout puberty. Despite the use of expensive approaches, there is no sustained efficacy in the long term and the risks of complications such as scarring remain. TSC is a predominantly inherited genetic condition that occurs in all races and ethnic groups. We concede with current reports describing the successful outcomes of various laser devices. However, the selection of laser devices can be limited for some institutions. Therefore, we suggest a rather basic but highly effective approach for angiofibroma treatment that can be generally applied with the classic CO_2 device.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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