case report

# Outcome with topical sirolimus for port wine stain malformations after unsatisfactory results with pulse dye laser treatment alone

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We used a topical formulation of sirolimus for treating port wine stain (PWS). Although pulsed dye laser (PDL) is the current treatment of choice for PWS, fast neovascularization after treatment is a major drawback. With PDL therapy there has been insufficient improvement and frustrating side effects. The objective was to study the efficacy and safety of combining topical sirolimus with PDL as dual therapy in managing PWS. We report five PWS cases that were treated with PDL initially, followed by 0.5-1% topical sirolimus. With dual therapy there was significant improvement over a shorter duration. More published studies of topical sirolimus are needed to clarify the role of dual therapy in managing PWS associated with capillary malformations. We encourage further prospective and comparative studies with a larger sample size.

**SIMILAR CASES PUBLISHED:** 1

Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, is an antifungal metabolite produced by *Streptomyces hygroscopicus*. Originally named rapamycin, it was initially used as an antifungal and is now used as an anticancer agent because of its immunosuppressive and antiproliferative properties.[1] In recent years, sirolimus was found to be efficacious in managing a range of conditions, such as pulmonary lymphangiomyomatosis, giant cell astrocytoma and complex tuberous sclerosis (renal angiomyolipoma). Sirolimus is used to coat drug-eluting stents in cardiac angioplasty.[1] It is manufactured in two pharmaceutical forms: Rapamune oral solution (60 mg per 60 mL) and Rapamune tabletsavailable in 1 mg and 2 mg strength. The oral solution should be kept at a temperature of 2-8°.[1] Topical sirolimus was approved by the FDA in 1999 as an immunosuppressant in renal transplant patients. In 2015, it was ap- proved for use in lymphangiomatosis.[2] Pharmacists in KFSHRC were asked to manufacture ready-to-administer pharmaceutical formulas of sirolimus, which were formulated as 1% and 0.5% creams which could be absorbed through the superficial epidermis, deep dermis, and subcutaneous tissues.

Port wine stain (PWS) is a progressive cutaneous vascular lesion that presents at birth. It affects the postcapillary venules, and is present in every 3 to 4 infants for each 1000 live births.[1] PWS lesions are a serious concern for most patients, since malformations can occur on visible areas of the body like the head and neck region.[3] As a result, PWS malformation is accompanied by psychological distress, which increases the demand for treatment.[3] PWS starts as erythematous macules and lesions which prog-

ress to dark-red or purple plaques in which nodules may gradually arise.[4]

Pulsed dye laser (PDL) is the mainstay of therapy for PWS. The emitted yellow beam is taken up by hemoglobin in the PWS vasculature. Afterwards, the light beam converts to heat causing thermal injury and thrombosis. The initial phase of PDL results in mild purpura, that disappears completely in 7 to 14 days. Although PDL has been considered a mainstay therapy for PWS over the last 10 years, the results are inadequate in some resistant cases.

In KFSHRC, PDL treatment of PWS is a course of five sessions over 5 years. Only superficial lesions have shown high rates of response to the laser. On the other hand, hypertrophic and extensive lesions rarely respond. There is little documentation on the efficacy of topical sirolimus formula in PWS management, in part because topical formulas of sirolimus are rarely formulated, and thus there is little information on managing the hypertrophic and extensive lesions of PWS with sirolimus. We present a case series of five patients who presented with PWS and were treated with topical sirolimus due to unsatisfactory PDL treatment.

Since revascularization is a major disadvantage of PDL treatment, inhibition of revascularization is necessary for better outcomes.[5] Various investigators have verified that topical sirolimus causes regression of facial angiofibroma,[6] leading to better outcomes.[1] Sirolimus inhibits mTOR, an enzyme that regulates cell growth and metabolism, and as a result can inhibit the revascularization post-PDL treatment as a synergistic effect. The purpose of this study was to prove the efficacy and safety of combining topical sirolimus with PDL in managing reformation and recanalization of PWS blood vessels after PDL therapy.

## METHODS

We retrieved the documentation for five patients with PWS referred to KFSHRC from 2014-2017. These cases were treated initially with PDL (585 nm, fluence 7-12 joules, spot size 6 mm, pulse width 0.5 ms) starting from 2012, followed by the addition of 0.5% -1% topical sirolimus in 2014 (1 gram per application) as dual therapy. Written informed consent was obtained from the patients and patient's parents for publication of this case series and any accompanying images.

## CASES

### *Case 1*

A 17-month-old female with PWS over the right side of her face had undergone 22 sessions of PDL, the last was in January 2017. She had subjective clearance of 70% laterally and 40% centrally until her 23rd session in August 2016, when she was started on topical sirolimus 1% cream daily. Clearance was noticed by the patient's parents after only 4 months from starting sirolimus. On her 26th PDL session, a significant subjective clearance of 90% laterally and 45% centrally occurred after only 4 dual therapy sessions (**Table 1**).

### *Case 2*

A 2-year-old male with PWS of the left upper limb and adjacent area of the chest. After receiving his 8th PDL session, there was a subjective clearance of 60% centrally and 40% laterally. In May 2016, topical sirolimus 0.5% cream daily was added as part of the dual therapy. On his 10th PDL session during October 2016, a subjective clearance of 80% centrally and 50% laterally was noticed after two dual therapy sessions (**Table 1**).

### *Case 3*

A 9-year-old female with PWS and overlying angiokeratoma on her left lower limb was refractive to PDL therapy so the laser was changed from PDL to energy multiplex, which showed a minimal clearance of 5% after 14 sessions. In December 2015, she received her 15th session of Cynergy Multiplex in addition to topical sirolimus 1% cream daily. The last or 16th session of Cynergy Multiplex was done in November 2016 and subjective clearance after the initiation of dual therapy was 15% (**Table 1**).

### *Case 4*

A 34-year-old female had a large PWS over the left upper limb and chest. She received nine sessions of PDL with only mild subjective clearance of 10%, which she had also noticed. In view of the suboptimal response to laser, 1% topical sirolimus was added to laser therapy on August 2016 to be started on the 10th PDL session. She had her 11th PDL session in January 2017. A moderate clearance of 30% was noted after initiation of dual therapy (**Table 1**).

### *Case 5*

An 11-year-old Saudi male with PWS over the left side of his face received 17 sessions of PDL therapy with no remarkable clearance despite adequate tissue reaction. (**Figure 1 and 2**). As a result, in January 2016 topical sirolimus of 1% was started as a part of dual therapy. On the 20th PDL session, his parents reported subjective clearance of 20%. On the 21st session the parents were pleased with the final results compared with the initial presentation (**Figure 3 and 4**) (**Table 1**).

**Table 1.** Subjective clearance before and after the addition of topical sirolimus (TS).

| | | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|---|
| **Age at time of presentation** | | 17 months | 2 years | 9 years | 34 years | 11 years |
| **Gender** | | F | M | F | F | M |
| **Length of follow up** | | 4 years | 2 years | 4 years | 2 years | 5 years |
| **Lesion** | | PWS on right side of face | PWS of left UL and adjacent area of the chest. | PWS and angiokeratoma on left LL was refractive to PDL. | Large PWS over the left UL and chest. | PWS over the left side of the face. |
| **Before TS** | No. of PDL sessions | 22 | 8 | 14 | 9 | 17 |
| | PDL Subjective | Lateral: 70%<br>Central: 40% | Lateral: 40%<br>Central: 60% | 5% | 10% | 0% |
| **After TS** | No. of PDL sessions | 26 | 10 | 16 | 11 | 21 |
| | PDL+TS Subjective clearance | Lateral: 20%<br>Central: 5% | Lateral: 10%<br>Central: 20% | 10% | 20% | 20% |
| **Overall subjective clearance of PDL + TS** | | Lateral: 90%<br>Central: 45% | Lateral: 50%<br>Central: 80% | 15% | 30% | 20% |

PWS: port wine stain, PDL: pulse dye laser, TS: topical sirolimus, M: male, F: female, LL: lower limb, UL: upper limb.

## DISCUSSION

mTOR (serine/threonine kinase) regulates cell metabolism and growth through multiple external mitogenic stimuli. These stimuli trigger mTOR to activate the translational cascade and enhance cell growth.[7] The mTOR-mediated path also stimulates the oncogenic processes by regulating gene expression.[8] PWS is a slow-flow vascular malformation that extends over large areas of the newborn's skin at birth.[9] They are faint macules during childhood and darken gradually to red-purple.[10] PWS shows an abnormal plexus beneath a normal epidermis histopathologically.[11] Although PWS can resolve spontaneously with growth and skin tightening in minor cases, the main consequence is lifelong psychological distress even though they do not alter long-term life expectancy.[12] In general, complete clearance of PWS lesson needs medical treatment.[13]

No therapy for PWS was successful until the 1970s when the argon laser began to be used in the management of PWS.[14] In the early 1990s, PDL therapy became available and became the standard of PWS treatment.[14] Photothermolysis is the core mechanism of PDL therapy with a wavelength of 577 to 595 nanometre and 0.45 to 1.5 millisecond pulse durations.[15] Although PDL results in a reduction in PWS in size and color, with minor side effects in some cases,[16] the extent of lesion blanching noticed after PDL treatment is inconsistent and random despite improvements in PDL technology and a prolonged management protocol.[17] PWS relapses early after laser therapy due to the quick neovascularization of the blood vessels. In a study by Lanigan and Katugampola, 62 cases out of 300 discontinued therapy since PDL treatment did not lighten the PWS.[16]

Since the dermatology department in KFSHRC began using dual therapy with PDL and topical sirolimus 1% and 0.5% in treating PW, the highest clearance values were 30% to 50%, subjectively. Clearance was amplified sooner with dual therapy. In addition, the target improvement of 90% was almost reached in some with better cosmetic results and less frustration from side effects (**Table 1**). Cases 3 and 5 were refractive to PDL therapy, with only 0-5% clearance following multiple sessions of PDL. After combining topical sirolimus with PDL as dual therapy there was a significant improvement. The overall response reached a clearance sooner with fewer sessions (Case 5 had no response after 17 sessions of PDL over 3 years). After dual therapy the overall response reached 20% in 1-2 years and the lesion borders became hazy and the color became less intense (**Figure 4**).

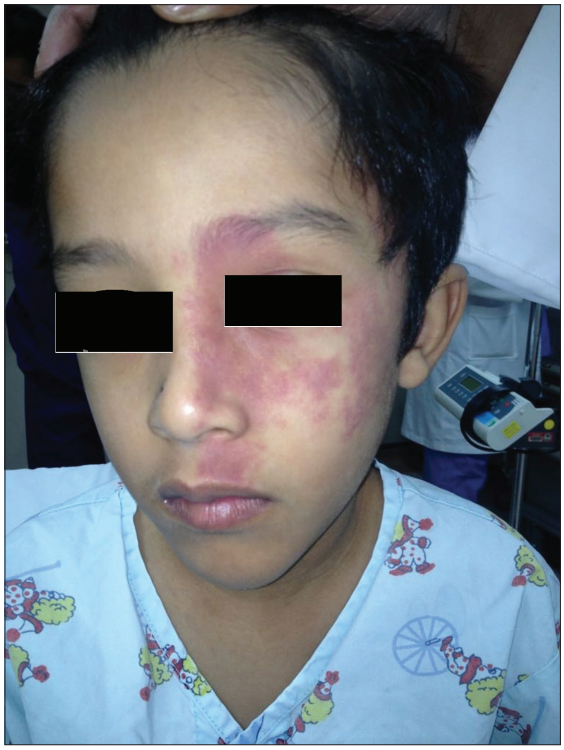

**Figure 1.** Case 5 with PWS on the left side of his face before treatment.

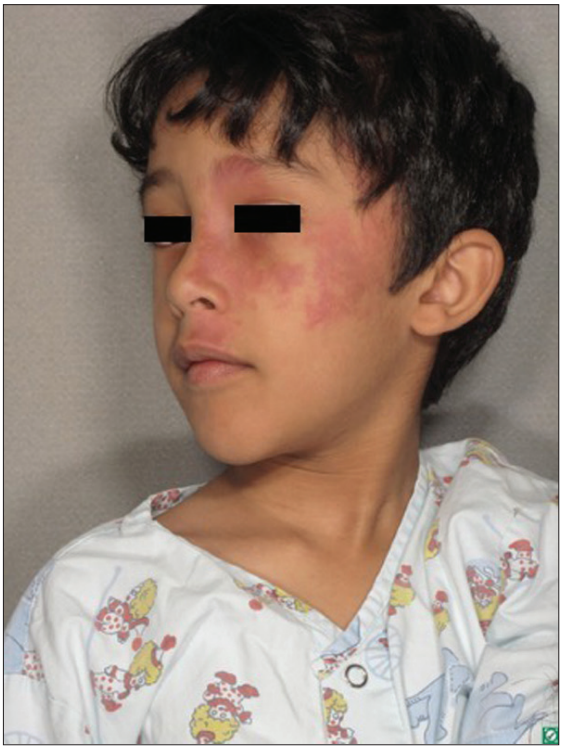

**Figure 2.** PWS on the left side of his face after 17 PDL sessions with no response. Lesion borders are well demarcated with high color intensity.

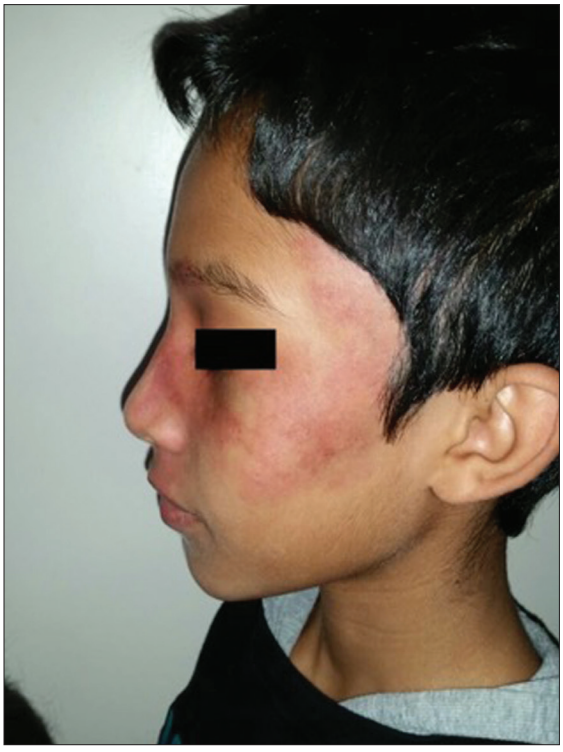

**Figure 3.** Case 5 after three sessions of dual therapy. Lesion borders are hazy and the color intensity is less compared to Figure 2. This picture was taken directly after the PDL session.

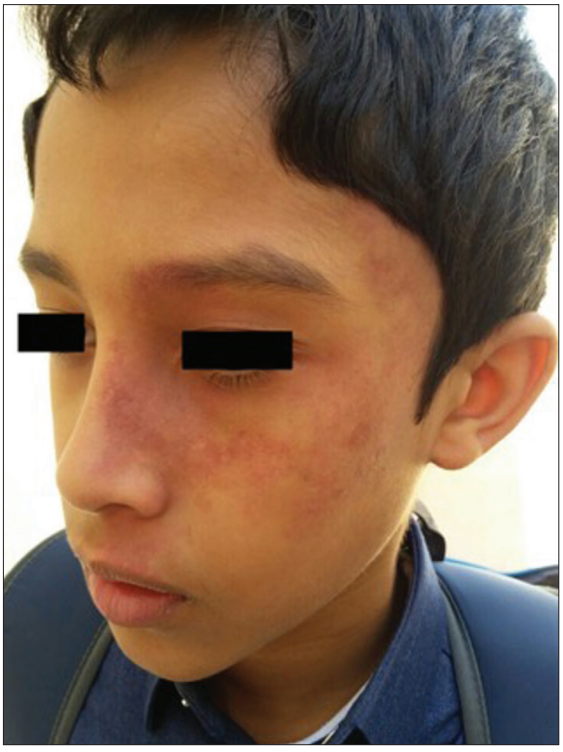

**Figure 4.** Case 5 after three sessions of dual therapy. Lesion borders still hazy, and the color intensity is reduced in comparison with Figure 3. This picture was taken 3 weeks after his last PDL session.

This case series highlights the significance of topical sirolimus, which showed an effective response in resistant cases. Our report supports Nelson and Jia who reported enhanced PWS blanching with combined PDL and rapamycin administration.[17] Dual therapy can guarantee a better quality of life, with psychological and cosmetic effects[14] for the patient and few treatment side effects especially for those who require scarification due to chronic PWS.

A limitation of this report is that there are no pictures of the initial presentation because the PDL sessions were started elsewhere. In summary, combined therapy with PDL and topical sirolimus is more effective when compared with PDL therapy alone in treating capillary malformations. We propose the implementation of dual therapy in managing PWS and other capillary malformations. Future clinical trials with a control group should be conducted to study the safety and efficacy of topical as well as the systemic formulas of sirolimus along with PDL in managing PWS resistant cases. Clear guidelines and management criteria for PWS are needed.

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