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Case Report

The use of Sirolimus for an unresectable and refractory venous malformation: A case series ☆,☆☆

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ABSTRACT

Vascular malformations (VM) may become symptomatic and extensive, leading to deranged coagulation and bleeding. Sirolimus®, an antiangiogenic agent, has recently emerged as treatment for VM. We report its short-term outcomes for VMs of the extremities. Case 1: A 47-year-old female reported left forearm pain. MRI confirmed a VM. Lesion shrinkage and pain relief were not achieved despite sclerotherapy. After 5 months on Sirolimus®, improved pain, decreased forearm circumference and decreased lesion size on MRI were observed. Case 2: 62-year-old male reported left knee pain. MRI and biopsy confirmed a VM. After 3 months on Sirolimus®, improved pain, decreased leg circumference, and decreased lesion size on MRI were observed. Our series demonstrates that Sirolimus® is efficacious in downsizing VMs with resultant symptom relief in the short-term. Other series has likewise shown effectivity in extensive and refractory lesions, with benefits outweighing side effects.

Introduction

Vascular anomalies (VA) are categorized into malformations or tumors. Vascular malformations are developmental anomalies of vessels characterized by structural issues and errors of morphogenesis [1–3]. They are divided into arterial, capillary, venous, arteriovenous, lymphatic, or combined [1–3]. This is differentiated by vascular tumors by proliferative endothelial cells and aberrant vessel architecture [1].

Many venous malformations (VM) may become aggressive and infiltrative and produce pain and deformities which warrant interventions and multidisciplinary management [1,2]. Treatment should be guided by type of anomaly, size, and how extensive the lesion is [2].

Sirolimus®, also known as rapamycin, is an allosteric inhibitor of mammalian target of rapamycin (mTOR) initially used as an immunosuppressant to prevent organ rejection [3]. Understanding signal transduction defects has led to the recent emergence of Sirolimus® in 2010 as a medication for VM

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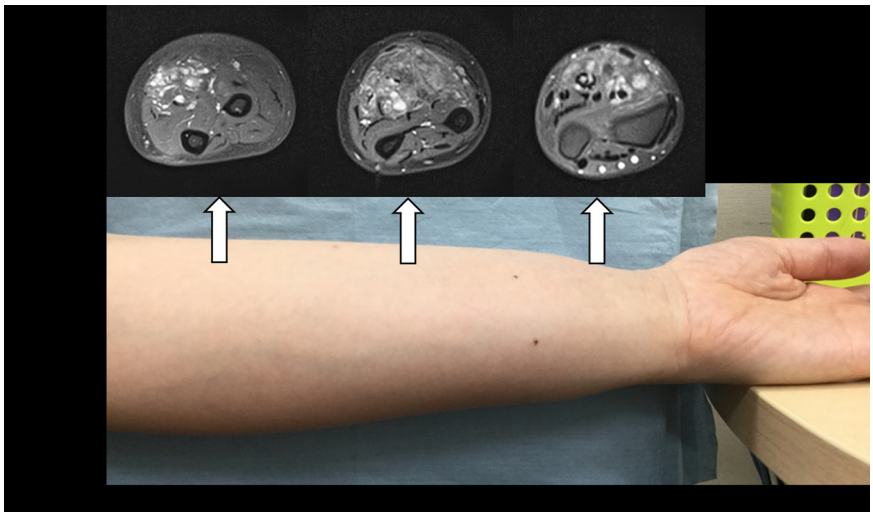

Fig. 1 – Case 1. The left forearm; proximal, middle and distal portion. MRI imaging in axial cuts showing an extensive T2 hyperintense lesion (venous malformation) occupying the whole flexor compartment.

[4]. Current studies are investigating its efficacy and safety especially in cases refractory to standard treatments. We aim to report the short-term outcomes of Sirolimus® in patients with unresectable and refractory VMs of the extremities.

Case report (summarized Table 1)

This is a case series of 2 patients with VM deemed unresectable or refractory, and not indicated for surgery, sclerotherapy, or ablation. Following disclosure of the mechanism of action, benefits, side effects, and complications, Sirolimus® was administered once patients' consents were granted. Institutional review board approval was obtained prior to conducting this study.

Sirolimus® was initiated with a dose of 2 mg/day. A medication diary was provided for daily documentation of vital signs and side effects. Periodic serum levels were tested, and medication dosage was adjusted to maintain trough concentration of 5-15 ng/mL.

Regular follow-up for monitoring and repeat magnetic resonance imaging (MRI) for surveillance of lesions were instructed. Decrease in the size of the lesions, improvement in signs and symptoms, and/or improvement in the function of patients were considered a positive response to treatment.

Case 1

A 47-year-old, right-handed female nurse complained of intermittent swelling and pain of her left forearm since childhood, with no relief despite intake of analgesics. Physical examination revealed a soft, tender, ill-defined mass across the volar aspect of her left forearm. Grip was weak due to pain. Radiographs revealed phleboliths while MRI showed T2 hyperintense signals within the muscles of the flexor compartment (Fig. 1). A vascular malformation was suspected. During this time, the patient opted to observe the lesion instead.

After 3 years, repeat MRI showed increase in the size of the lesion, associated with increasing severity of pain. Doppler sonography revealed a low-flow venous malformation with no arterial component. Sclerotherapy with 3% polidocanol was performed, however symptoms ensued. A repeat MRI after 1 year confirmed no volume change in the lesion.

Patient was hence started on Sirolimus®, with resultant improvement of visual analog scale (VAS) of pain from 8 to 3 at 3 months follow-up. Similarly, forearm circumference decreased from 28 to 23.5 cm. There were no reported side effects. An MRI 3 months (Fig. 2) after starting Sirolimus® showed significant decrease in lesion size. She is currently 5 months on regimen, able to resume her work, and do activities of daily living (ADLs) with minimal episodes of pain (Table 1).

Case 2

A 62-year-old male reported swelling of his left knee since adolescence with repetitive hemarthrosis occurring once a year despite no traumatic incidents. Recent increase in the swelling and pain prompted consult. On MRI (Fig. 3), a T2 hyperintense and T1 isointense mass originating from the Hoffa's fat pad and extending to the tibialis anterior muscle was visualized. Open biopsy confirmed a venous malformation.

Due to the repetitive hemarthrosis and extent of the lesion, use of Sirolimus® was advised. Six weeks after starting Sirolimus®, a pruritic rash developed on his trunk. Because this was deemed mild, a dermatologist instructed continuation of Sirolimus® and application of topical steroids. The rash subsequently resolved 3 days.

He is currently 4 months on regimen and denies symptoms. At 3 months follow-up, leg circumference decreased from 36.5 to 33.2 cm. Repeat MRI (Fig. 3) revealed significant

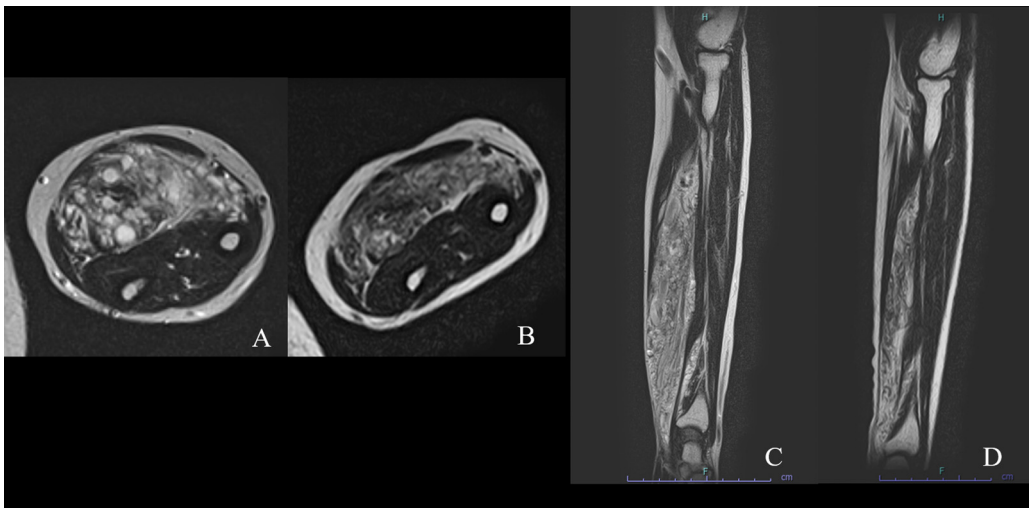

Fig. 2 – MRI imaging prior (A, C) and 3 months (B, D) after Sirolimus therapy. (A, B) Axial cut; (C, D) Sagittal cuts, showing significant decrease in the are of the lesion.

Table 1 – Patients details.

Case	Location	Symptom	Previous treatment	Sirolimus dose	Serum level (ng/dL) 2w 4w	VAS 0 1m 3m	COL (cm) 0 1m 3m	Max tumor area (MRI, mm^2) 0 3m	Adverse effects	F/U
1	Flexor muscles in the forearm	Pain Motor weakness	Sclero-therapy	2 mg/d	13.3 14.7	8 5 3	28 24 23 (−18%)	1299 931 (−29%)	None	5 m
2	Anterior compartment in the leg	Pain	None	2 mg/d	13.5 16.4	5 4 3	37 35 33 (−11%)	837 704 (−16%)	pruritic rash on the trunk	4 m

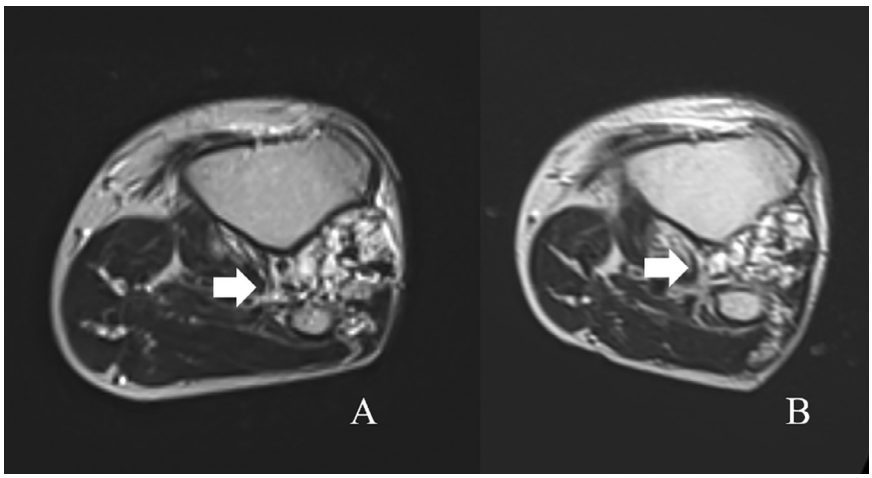

Fig. 3 – Case 2. MRI imaging prior (A) and 3 months (B) after Sirolimus therapy. Axial cuts in T2 sequence showing an extensive hyperintense lesion (venous malformation) extending to the anterior compartment of the leg. The area of the lesion was decreasd after Sirolimus therapy.

Table 2 – Current evidence on Sirolimus®.

Authors	Case	Indication	Target level (ng/dL)	F/U (mo)	Results	Adverse effect
Boscolo, et al. [7]	4	Sporadic VM	10-15	12	Symptoms improved No change to mild decrease in size	Fatigue, headache, rash, joint pain, mucositis
Salloum, et al. [11]	4	Blue rubber bleb nevus syndrome	10-13	21	Symptoms improved Decrease in size	Neutropenia, mucositis
Hammer, et al. [3]	5	Sporadic VM	10-15	12	Symptoms improved in 80% VM reduction in 20%	Headache, rash, mucositis fatigue, diarrhea
Our patients	2	Refractory, unresectable VM of extremities	10-15	4, 5	Symptoms improved and VM reduction in both cases	Rash

decrease in lesion size. He is currently able to continue his work as a tourist guide and do ADLs without limitations.

Discussion

Diagnostic modality of choice of VMs depends on the lesion location, age of the patient, and expertise [3,5–7]. Doppler sonography is useful for determining compressibility and determining high- (or arterial) and low- (or venous/lymphatic) lesions [4,6]. For VMs, imaging may demonstrate phleboliths, which are due to the stagnant flow of blood in veins. MRIs demonstrate marked T2 hyperintensity and T1 hypo- to isointensity with occasional visualized ectatic veins, as compared to flow voids seen in arterial lesions. Further, contrast enhancement patterns range from homogenous to heterogenous [3,5–8]. These descriptions are consistent with the findings in our series and supports the diagnosis of VM.

Greater than 90% of VM occur sporadically, with most phenotypes arising from endothelial dysgenesis via the tyrosine kinase receptor (TIE2) - phosphatidylinositol-3-kinase (PI3K) - AKT - mTOR pathway. Mutations affect cell proliferation, migration, and survival resulting to enlarged, convoluted venous channels. Majority are usually unifocal, such as that in our patients, while hereditary forms are commonly multifocal, associated with other anomalies, and are best confirmed with genetic testing [3,4,7].

VMs may thrombose and produce pain, deformation, and skin changes because of slow blood flow [1–4]. For symptomatic lesions, surgical resection, sclerotherapy, and ablation may be utilized. It is important to emphasize that the goal of management is to decrease pain and risk of future complications, and to improve function [4].

Surgery is suitable for smaller and well-defined masses and should not lead to functional or aesthetic outcomes worse than the disease [2]. However, some VMs are diffusely invested into tissue, making vascular walls thin, delicate, and friable [2]. Additionally, local intravascular coagulation (LIC) can result to elevation of D-dimer and reduction in fibrinogen, potentially leading to disseminated intravascular coagulation (DIC) and propensity for bleeding [2,3,7]. Preoperative sclerotherapy may decrease surgical complications, but larger resections may nevertheless lead to risky surgeries with poor outcomes, and recurrence is also observed despite curative removal [2,9].

Sclerotherapy is effective for low-flow lesions as sclerosants like polidocanol are not rapidly washed out of the lesion [8]. It is not established as an alternative to surgery, however due to its minimally invasive nature, it has been regarded as a gold standard procedure with or without surgery [3,4,7,8]. According to a recent meta-analysis, the efficacy rate of polidocanol was 86% [9]. However, extensive VM in the distal extremities such as in the forearm may be prone to compartment syndrome and DIC following sclerotherapy [4]. Ablation delivers endothelial thermal injury and eventual vein fibrosis [4]. A systemic review reported complete resolution in 63.6% of cases, and an overall improvement rate of 94.5% [10]. Conversely, complications of this procedure are common and include myositis, bruising, swelling, and rarely, frostbite and persistent dysesthesia [4,10].

Pharmacotherapy with the use of Sirolimus® is reserved for extensive lesions where surgical intervention is not ideal, and where other treatment modalities have failed [1,4]. The PI3K/AKT/mTor pathway is responsible for various cellular process including expression of vascular endothelial growth factor, a key regulator of angiogenesis [1,3,11]. Sirolimus®, the only mTOR inhibitor currently approved by the U.S. Food and Drug Administration, binds FK506-binding protein and thus have antitumoral and antiangiogenic properties [1,11].

Boscolo et al. [7] reported 4 patients with severe symptoms of sporadic VM treated with Sirolimus®. Results showed cessation of bleeding, decreased pain, and improved quality of life. Objectively, D-dimer levels were reduced but MRI showed no or mild decrease in the volume of lesions after 12 months of treatment. Side effects such as fatigue, headache, rash, arthralgia, mucositis, possible development of basal cell carcinoma was reported, hence careful follow-up is emphasized [7] (Table 2). Salloum et al. reported the treatment in 4 patients diagnosed with blue rubber bleb nevus syndrome with Sirolimus®. Results illustrate significant improvement of all cases, described as decrease in the size and pain of the lesions. Side effects noted include neutropenia and mucositis, but with no infections [11]. In Hammer et al. report, 5 patients with refractory VMs were started on Sirolimus®. After a year, partial response (80%) was observed in all patients described

as improvement of symptoms, decrease in D-dimer levels, but volume reduction was obtained only in 20% in imaging. Adverse reactions include headache, rash, mucositis, fatigue, and diarrhea. Despite the heterogeneity of vascular malformations, a common pathophysiologic basis underscores the efficacy of Sirolimus® for these varied lesions [3].

Conclusion

Recent literature has shown the short-term efficacy of Sirolimus® in a small number of patients with extensive and refractory VMs, with benefits outweighing side effects. Our cases further demonstrate that the goals of controlling lesion growth and symptoms are achievable with the use of Sirolimus®. Larger prospective studies with longer follow-up are desired to determine the overall safety and effectiveness of Sirolimus® in these cases.

Ethical statement

The patient was informed that data from the case would be submitted for publication and gave his consent.

Authors contribution

DC-Manuscript drafting. KM-Manuscript review, supervision. YT, HS, MU-Data correction, editing figures.

Patient consent

The patient was informed that data from the case would be submitted for publication and gave his consent.

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