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CASE REPORT

Oral sirolimus in the treatment of adult eruptive cherry angiomas

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ABSTRACT

INTRODUCTION Cherry angiomas are a common type of acquired vascular proliferation of the skin which manifest as single or multiple bright red spots that usually appear on the trunk and arms. They are generally asymptomatic; patients may opt to remove the lesions for cosmetic reasons and prevention of bleeding. Conventionally, most cherry angiomas are treated with curettage, laser, and electrosurgery. Herein, we report a case of multiple cherry angiomas managed alternatively with oral sirolimus.

CASE REPORT A 47-year-old Filipino female presented with a 10-month history of gradually enlarging multiple bright-red papules and pedunculated nodules with a propensity to spontaneously bleed on gentle manipulation involving the scalp and forehead. Clinicopathological correlation suggests a diagnosis of eruptive cherry angiomas. The patient was started on oral sirolimus, a mammalian target of rapamycin (mTOR) inhibitor.

CONCLUSION We present a case of a patient with eruptive cherry angiomas who experienced significant decrease in size and bleeding with treatment of oral sirolimus with minimal adverse effects. For patients with eruptive cherry angiomas, especially with contraindicated comorbidities, first-line therapeutic option treatments with oral sirolimus can be beneficial.

KEYWORDS sirolimus, eruptive hemangiomas, cherry angiomas, vascular malformation

INTRODUCTION

Cherry hemangiomas, also known as adult hemangiomas, senile angiomas or Campbell de Morgan spots, are the most common type of acquired vascular proliferation of the skin. These tend to increase in number and size with age.[1,2] They usually occur in the third or fourth decade of life and present as small red macules that may appear on both sun-exposed and unexposed skin.[2] Lesions present as multiple, bright red, dome-shaped papules measuring 1 to 5 mm in size on the trunk or upper limbs and rarely on hands, feet, and face.[1] They are usually asymptomatic, but may bleed with trauma.[3] Eruptive cherry angiomas are described as the development of multiple cherry angiomas.[4] The etiology is not well-known, however, lesions may be associated with aging, pregnancy, climate, and exposure to chemicals.[3] Other predisposing risk factors for the development of cherry angiomas include skin tumors and chronic immunosuppression that suggest imbalance of skin immune competence.[5]

Cherry angiomas are diagnosed clinically based on characteristic appearance and aided by dermoscopy with the characteristic features of red background, clustered red lacunae, and white surfaces.[6] Histopathologic findings show thinned epidermis and many newly developed, polypoid, neovascularized capillaries that have thin narrow lumens along with prominent endothelial cells. The majority of patients have excellent prognosis since most lesions are asymptomatic.[1] Some might have complications such as pain, bleeding, and recurring infections affecting quality of life.[7] Removal of lesions are most often due to cosmetic reasons or for prevention of complications. Treatment modalities are mostly interventional and surgical including cryosurgery, electrosurgery, curettage, or pulsed dye laser.[1] Ideal therapy for patients with vascular malformation would be targeting the cellular pathways involved in the vascular growth and proliferation. Si-

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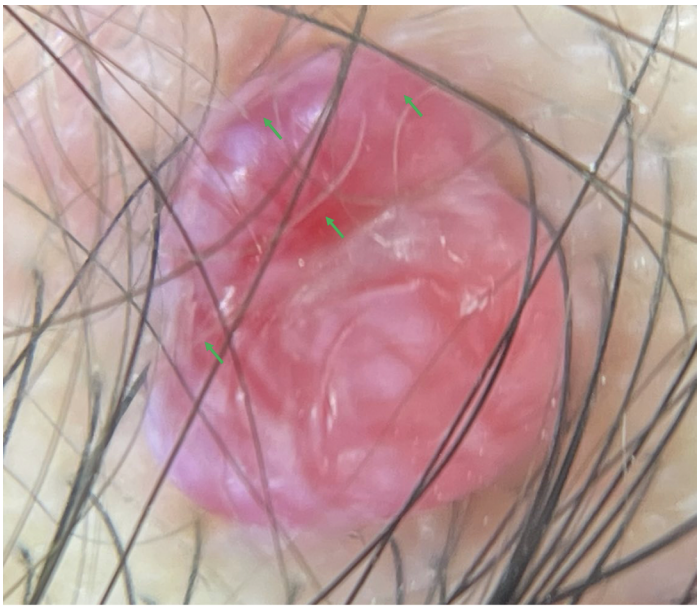

Figure 1. Dermoscopy on initial consult showed clustered red lacunae (green arrows) and white surfaces on a red background.

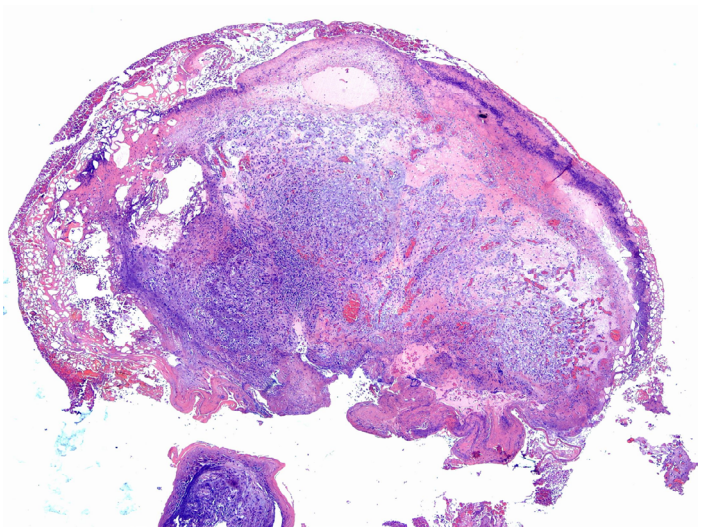

Figure 2. The dermis showed numerous capillaries lined by endothelial cells and dilated medium sized vessels (H&E, scanning view).

rolimus, a mammalian target of rapamycin (mTOR) inhibitor, targets the regulation of angiogenesis and lymphangiogenesis leading to inhibition of tissue overgrowth.[8] Studies reported sirolimus to be safe and effective in the treatment of complicated vascular anomalies.[8,9]

CASE SUMMARY

A 47-year-old Filipino female presented with a 10-month history of a solitary, soft, erythematous papule on the right temporal scalp region after sustaining trauma. The lesion was associated with pruritus, pain, and bleeding with manipulation. It developed into a solitary well-defined, ovoid, smooth, erythematous pedunculated nodule measuring approximately 3x3mm. No interventions were done during this time. Two (2) months prior to consultation, lesions eventually increased in size and number evolving to multiple, well-defined, ovoid, smooth, erythematous nodules measuring approximately 0.5x1mm to 2x2mm now involving the right temporal region. The patient did not complain of any other systemic manifestations such as fever, weight loss, or lymphadenopathy. Patient is hypertensive and maintained on metoprolol. There were no similar lesions described in the family. On physical exam, there were multiple well-defined, ovoid, smooth, erythematous pedunculated aggregated nodules measuring approximately 3x3mm on the scalp and 8x10mm, in its largest diameter on the right temporal region. Dermoscopic examination showed clustered red lacunae and white surfaces on a red background (Figure 1).

A 4-mm skin punch biopsy was obtained from the temporal region of the scalp and two (2) tissue samples from the right temple. Hematoxylin and eosin-stained (H&E) sections revealed extravasated red blood cells, numerous capillaries, and thrombosed blood vessels on the scalp. Hyperkeratosis of the stratum corneum and the dermis showed numerous capillaries lined by endothelial cells and dilated medium sized vessels on the right temporal region (Figure 2). These findings were consistent with a hemangioma.

Initial laboratory evaluation included complete blood count, lipid profile, liver enzymes, blood urea nitrogen, creatinine, lactate dehydrogenase, peripheral blood smear, chest x-ray, whole abdomen ultrasound, and HIV antibody screening test. Results revealed slightly elevated liver enzymes, creatinine, and cholesterol, while the sonographic report showed cholelithiasis. Patient was prescribed phospholipids capsule and atorvastatin.

The patient was initially started with oral sirolimus 1 mg/day for four (4) weeks. After three weeks of sirolimus 1 mg/day, there were increasing oral ulcers with a slight improvement in lesion size. Thus, dose was decreased to 0.5 mg/day. Patient was also given a mixture of sucralfate (4g), aluminum hydroxide and magnesium hydroxide sus-

pension (60 ml), diphenhydramine HCl 12.5 mg/5ml syrup (30 ml), in addition to topical application of benzocaine 20%, menthol 0.1% and zinc chloride 0.15% (Orajel). This regimen provided improvement in the size and number of oral ulcers. At the start of fourth week of treatment, there was a significant decrease in size of the lesions on the forehead and no new lesions were noted. Lower dose of 0.5 mg/day was continued for 14 weeks which showed further decrease in size of the lesions (Figure 3A-D) and no recurrence of oral ulcers. Repeat laboratory workup was done which revealed normal complete blood count, blood urea nitrogen, and creatinine. Cholesterol and liver enzyme levels had decreased from baseline.

DISCUSSION

Mammalian target of rapamycin (mTOR), a serine/threonine kinase, integrates the signals from phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT). PI3K/AKT/mTOR pathway is involved in cellular processes involving cellular catabolism and anabolism, cell motility, angiogenesis, and cell growth. The mTOR signaling pathway activates angiogenesis and lymphangiogenesis through increasing the expression of the vascular endothelial growth factor (VEGF). Tissue overgrowths leading to vascular anomalies develop when there are errors in the activation of the PI3K/AKT/mTOR pathway.[7,8]

Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor. It has anti-proliferative, antiangiogenic, and immunosuppressive properties. The inhibition results in reduced protein synthesis, induction of apoptosis, cell migration inhibition and decreased expression of vascular endothelial growth factor (VEGF).[10] By controlling ribosome biogenesis and protein synthesis, sirolimus combines signals from PI3K/AKT pathway to coordinate cell growth and proliferation.[8] Sirolimus is considered one of the alternative options for complicated vascular anomalies including tufted angioma, kaposiform hemangioendotheliomas, and arteriovenous malformations.[7,8] Systematic reviews on the efficacy and safety of topical and oral sirolimus demonstrated significant improvement in the treatment of vascular tumors related with venous malformations, lymphatic malformations, inflammatory/autoimmune disorders, and neoplasm.[10] Patients treated with sirolimus were observed to have reduction of symptoms and reduction of tumor size.[8,9,10]

The most common dosing for systemic treatment of sirolimus are initiated at 0.8 mg/m^2 body surface twice daily for children and 1 mg twice daily for adults.[10] A study used similar dosing regimens where efficacy of sirolimus were evaluated after 1 year of treatment. Reduction in the size of the lesions; reduction of pain, bleeding or oozing; or cessation of infections were observed within three (3)

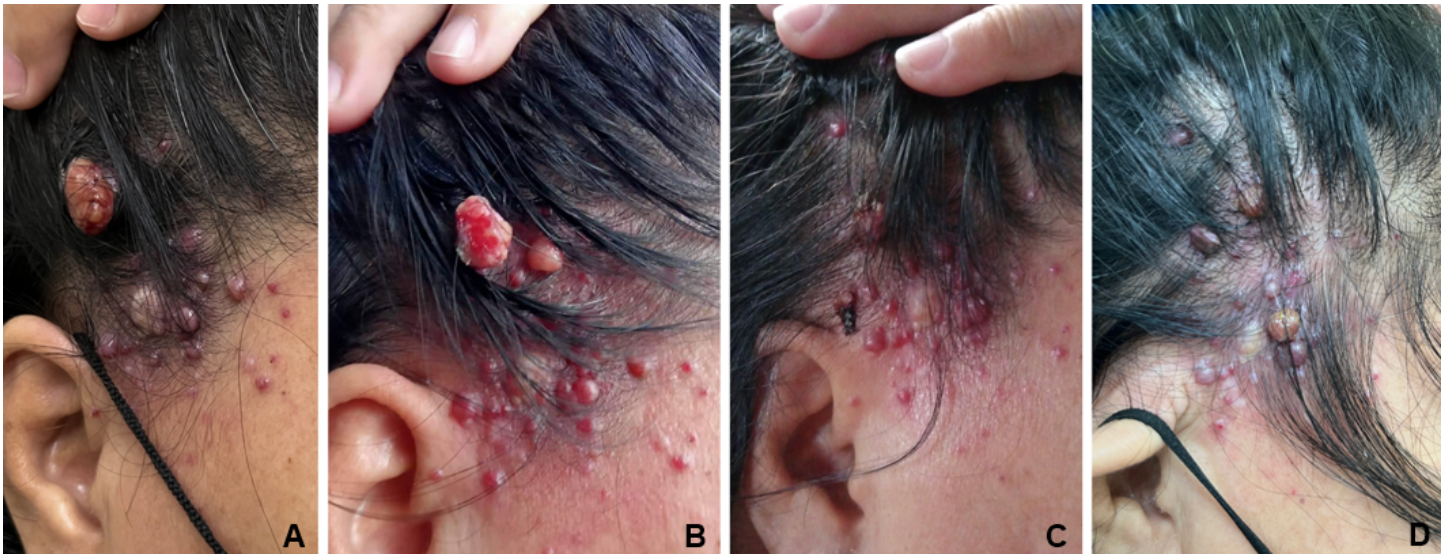

Figure 3. Baseline and follow-up photos while on oral sirolimus treatment. A. Initial consult B. Four weeks after initiation of treatment C. Eight weeks of treatment D. Fourteen weeks of treatment.

months from the start of treatment.[9] After stopping sirolimus, some patients had recurrence of symptoms, and when treatment was resumed improvements were noted again.[8,9]

Adverse effects reported with oral sirolimus include mucositis, lipid abnormalities, cytopenias, nausea and vomiting.[10] In this case, reduced dose of 0.5 mg/day was given since the patient had oral ulcers on the second week of treatment. Oral ulcers, which eventually resolved, were the only adverse event seen in the patient.

For complicated vascular tumors, studies have shown a wide range of treatment duration from 2 to 60 months.[7,8] The patient completed 14 weeks of treatment with significant decrease in size of the lesions with minimal adverse effects.

CONCLUSION

Eruptive hemangiomas are the most common type of acquired vascular proliferation of the skin. As the patient ages, lesions tend to increase in number and size. Oral sirolimus was the treatment option for this case due to the increasing size and number of lesions. On the fourth week of treatment, there was a significant decrease in size and number of lesions. Oral sirolimus offers promising results to capillary hemangiomas not only in the pediatric group but may also be given to adult patients who have capillary hemangiomas. For complicated vascular anomalies, it is recommended to continue sirolimus treatment for 12 to 24 weeks with monthly follow-up to evaluate the progress and monitor for possible adverse effects.

This report adds to the growing use of sirolimus in dermatological conditions. Further studies are still warranted, and more patients are needed to test the safety and efficacy of sirolimus. In the best knowledge of the authors, this is the first case report in the Philippines to successfully manage an adult patient with eruptive hemangiomas using oral sirolimus.

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