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REVIEW ARTICLE

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Orbital vascular malformation: Successful outcome in two patients treated with rapamycin

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Abstract

Combined vascular malformations are complex vascular anomalies that have high morbidity and therefore, therapeutic strategies are hard to establish. In this report, we aim to present two pediatric cases of ocular combined vascular malformations successfully treated with rapamycin.

KEYWORDS
orbital, pediatric, Proptosis, rapamycin, vascular malformation

1 | CLINICAL CASE

The first case is a 5-year-old female, otherwise healthy, born with an erythematous-violaceous macule in the left ocular conjunctiva, initially diagnosed as a hemangioma. The lesion remained stable over time, growing proportional to the patient's growth. At the age of 2 years old, her mother noticed a slight increase in volume, which evolved into acute exophthalmos. Physical exam revealed a significant proptosis on the left eye with slight eyelid erythema and red-eye in the peripheral conjunctiva (Figure 1). An ophthalmologic evaluation was requested, and no visual alterations were reported. Magnetic resonance image (MRI) and magnetic resonance angiographies (MRA) were performed, and both were compatible with a combined veno-lymphatic malformation involving the intra and extraconal spaces and infraorbital region of the left orbit. Based on the location and the size of the lesion, treatment with rapamycin was initiated at a dose of 0.8 mg/m^2 every 12 h. Dramatic improvement was observed with no side effects reported (Figure 2). Subsequent doses remained adjusted according to plasma levels of rapamycin, with a targeted range of 10–15 ng/ml. The patient maintained her excellent response, with a progressive decrease in the size of the lesion. After 4 years, the patient is still being treated with rapamycin. The follow-up until today has been favorable, without recurrence of the lesion and no visual alterations. No adverse effects have been reported to date.

The second case is a full-term female newborn, with a history of mucopurulent conjunctival secretion of the left eye that was noticed when she was 2 days old. She was evaluated by an ophthalmologist

FIGURE 1 First patient, with a left orbital veno-lymphatic malformation, before initiation of treatment.

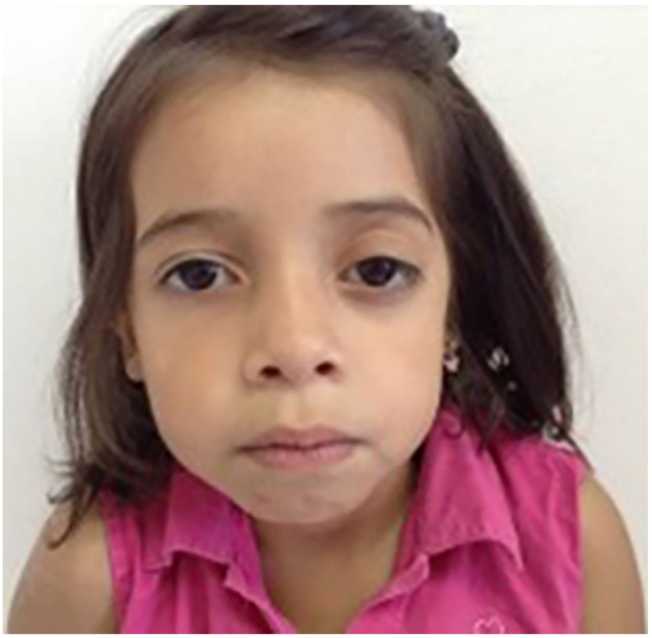

FIGURE 2 First patient after 3 months of treatment with rapamycin.

FIGURE 3 Second patient, with a left orbital veno-lymphatic malformation, before initiation of treatment.

and treated with topical antibiotics for 7 days, without response. At the age of one-month-old, she developed ecchymosis and abrupt exophthalmos (Figure 3). An MRI was performed which confirmed the diagnosis of combined vascular malformation with venous, arterial, and lymphatic components (Figure 4). At the age of 7 weeks old, oral rapamycin was initiated at a dose of 0.8 mg/m^2 every 12 h, observing a significant reduction of the tumor size after 15 days of treatment. Subsequent dosage was adjusted according to plasma levels of rapamycin, with a target range of 10–15 mg/ml. After 11 months of treatment, she presented a successful clinical response, with serum levels between 8 and 10 ng/mL, and a dose of 0.5 mg/m^2 every 12 h (Figure 5). The patient is 5 years old now, she is still being treated with rapamycin, with serum levels between 9 and 14 ng/ml. Treatment was discontinued for 11 months after an embolization cycle, but it had to be restarted because of a recurrence. The only reported adverse effect to date has been some self-resolving oral ulcers. Her current physical exam reveals a slight proptosis of the left eyeball and eyelid. The patient is being followed up by an ophthalmologist, and no visual alterations have been diagnosed.

2 | REVIEWS OF CLINICAL CASES

Vascular anomalies are a heterogeneous group of disorders characterized by abnormal growth and/or development of lymphatic and/or blood vessels. Diagnostic and therapeutic progress for these disorders has been greatly facilitated by the classification in vascular tumors and vascular malformations, which differ as much in their biological origin as in their physio-pathological features.[1–4]

Vascular malformations are inborn errors of vascular morphogenesis and consist of networks of abnormal blood and/or lymphatic vessels with endothelial cell proliferation.[4]

The International Society for the Study of Vascular Anomalies (ISSVA) categorizes vascular malformations into four groups: (1) simple—containing only one type of vessel or an arteriovenous malformation; (2) combined—defined as two or more vascular malformations found in one lesion; (3) major named vessels involved; and (4) associated with other anomalies.[5]

In terms of pathophysiology, extensive insight into the genetic and molecular basis is being accumulated. It is now established that most vascular malformations are caused by somatic or mosaic mutations that activate at least one of the two major intracellular signaling pathways: the RAS/MAPK/ERK or the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway.[4]

The PI3K/AKT/mTOR pathway is implicated in many cellular processes, such as cell-cycle regulation, proliferation, protein synthesis, and cell survival. TIE2 is a tyrosine kinase receptor that is specifically expressed on endothelial cells and within dysregulation of this pathway, results in secondary endothelial cell proliferation.[4]

Common unifocal venous malformation is due to a single somatic mutation of the TEK or PIK3CA gene[6] and lymphatic malformation is caused by somatic activating mutations in PIK3CA gene.[7,8]

Literature is scarce regarding the exact prevalence of vascular malformations in the general population, and they have no gender predilection. The most common vascular malformations are the capillary and venous types, even though they have a suggested 0.5% incidence in the general population.[1]

Combined vascular malformations are extremely rare in the orbit and differential diagnoses may include vascular tumors (such as

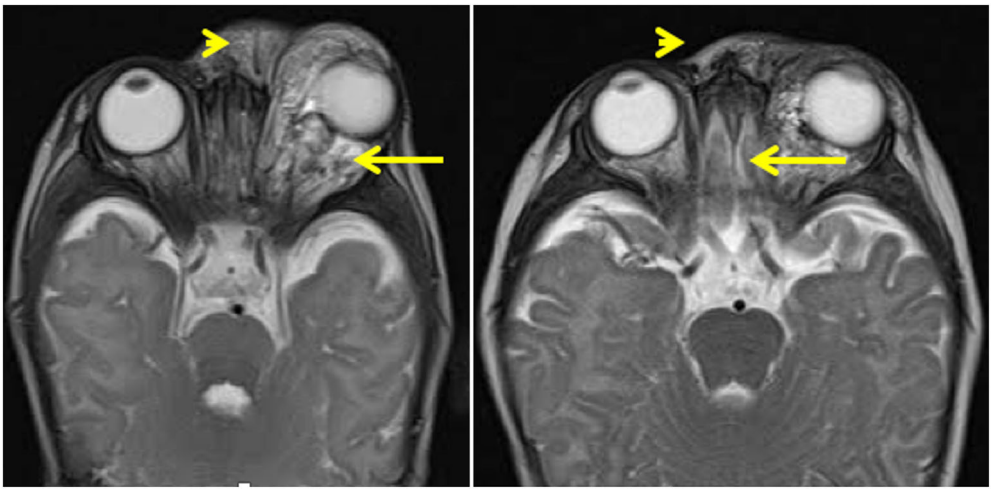

FIGURE 4 Magnetic resonance image of patient number two, before initiation of treatment and after 3 months of treatment.

FIGURE 5 Second patient, after 1 month of treatment with rapamycin.

retroocular infantile hemangioma), soft tissue tumors (such as ocular sarcoma, or neuroblastoma metastasis), and infectious processes such as orbital cellulitis.

A timely diagnosis and treatment are necessary due to their high morbidity and spectrum of treatments depending on the subtype. Treatment depends on the nature of the vascular malformation. Slow flow and combined vascular malformations include sclerotherapy, embolization, or surgical excision depending on each case, however, in many cases, only partial response and prompt recurrence are observed.[1,2]

The discovery of the pathogenic involvement of the RASMAPK-ERK pathway and the PI3K-AKT-mTOR pathway in vascular malformations has paved the way for targeted.

Drug treatment of these lesions.[4]

In the last decade, the use of rapamycin has been included in the treatment options, with good outcomes.

To our knowledge, only 11 cases of orbital vascular malformations treated with rapamycin have been reported.[9,10]

Rapamycin corresponds to a macrolide found years ago, produced by a bacteria that is originally from Easter island (hence its name, Rapamune), scientifically named Streptomyces hygroscopicus, isolated for the first time in 1965.[11] Traditionally it has been used to prevent transplant rejection (mainly kidney transplantation) as well as in pulmonary lymphangioleiomyomatosis.[12] It was initially prescribed as an antifungal.[11,12] Later, its immunosuppressive properties were discovered, by inhibiting the activation of T and B cells, decreasing the production of interleukin 2 (IL-2).[12] Namely, the course of action of rapamycin is by opposing the survival advantage that results from the activation of the mTOR signal,[2,13] turning it into a targeted and highly effective immunosuppressive and antiproliferative biological therapy with the cellular target.

In a study from Adams et al.,[14] 61 patients with combined vascular malformations were analyzed, to determine the efficacy and safety of rapamycin treatment in 12 courses of 28 days each. The initial oral dose was 0.8 mg/m^2 twice a day, with a guided pharmacokinetic target, expecting blood levels of the drug of 10 to 15 ng/ml. Of all the patients, 57 met the inclusion criteria to be evaluated, and 47 of them presented a partial response to therapy. None of them presented a complete remission of the lesion. The adverse effects observed were bone marrow toxicity in 27%, gastrointestinal toxicity in 3%, and metabolic or laboratory toxicity of 3%.

Mostly, rapamycin is well tolerated when adjusted to plasma levels, but patients may present side effects such as aphthous ulcers, peripheral edema, hypercholesterolemia, abdominal pain, headache, nausea, diarrhea or constipation, impaired renal function, hypertension, fever, urinary tract infection, anemia, arthralgia, and thrombocytopenia.[15]

A review from Geeurickx et al.,[2] which included a total of 324 cases with any type of vascular malformation treated with

rapamycin, highlights that at least one side effect was reported in 171 patients (53%). The two most frequently observed side effects were mucositis and bone marrow suppression.

Both patients had a significant response to treatment. One of the patients did not present any adverse effects, while the other one reported self-resolving oral ulcers.

We were able to avoid amblyopia, improve functionality and restore facial aesthetics. We performed strict monitoring of blood levels to titrate the dose, allowing a low rate of adverse effects. Our patients did not develop gastric intolerance or impact on bone marrow or renal function, which represent some of the most worrying adverse effects.

We underline, however, that this drug should be used with great caution due to its wide variability between patients in terms of bioavailability (up to eight times of variation in intestinal absorption between one patient and another, hence the importance of having thorough monitoring of the serum levels of the drug). Most adverse effects appear when plasmatic levels are not well monitored, and they may be potentially severe and of vital risk to the patient.

We propose that when the drug is suspended, the lesion interrupts its inhibitory cycle, so it can present a new growth and reincrease in volume, which means that it must be maintained for long periods. Further studies are needed for long-term follow-up and durability of response with this new-targeted cell therapy.

In an anatomical zone where there is no space for the vascular malformation to keep growing, it is crucial to rapidly reduce the lesion volume to avoid sequelae. In both patients, this purpose was achieved with the use of rapamycin.

In addition to rapamycin, inhibitors of other proteins along the PI3K/AKT/mTOR pathways are emerging as targeted therapeutic options for different types of vascular malformations. Thus far, inhibitors of AKT1and PIK3CA (Miransertib and Alpelisib respectively) have promising clinical results,[16,17] but further studies are needed to draw representative results.

AUTHOR CONTRIBUTIONS

Francisca Reculé and Rosario Agüero: literature review, manuscript writing. Ximena Chaparro, Cecilia Fischer: patient care. Trinidad Hasbún: patient care, literature review, manuscript writing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

The subjects in the study have consented to the use of their data and photographs.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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