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CLINICAL CASE

CLOVES syndrome: Treatment with oral Rapamycin. Report of two cases

Síndrome de CLOVES: Tratamiento con Rapamicina oral. Reporte de dos casos

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Abstract

CLOVES syndrome is characterized by lipomatous overgrowth associated with vascular malformations, representing a diagnostic and a therapeutic challenge. Rapamycin, an mTOR inhibitor, has proved to be a good therapeutic option in some vascular anomalies. In this article, we report two cases of CLOVES syndrome with good response to oral rapamycin treatment. **Objective:** To report the outcome of two patients with CLOVES syndrome treated with oral rapamycin. **Clinical Cases:** Case 1: A three-year-old female preschooler with CLOVES syndrome and history of repeated hospitalizations due to severe infections resulting from macrocystic lymphatic malformations and due to thrombotic episodes. The patient evolved with poor quality of life, multiple hospitalizations, surgical risk and progression of the lesions, therefore, oral rapamycin was indicated. After six months of treatment, clinical and radiological reduction in the size of the lipomatous and lymphatic masses, cutaneous lymphorrhea absence and a significant improvement of her quality of life were observed, without requiring new hospitalizations. Case 2: a ten-year-old female schooler with CLOVES syndrome, who developed scoliosis and deterioration of her motor skills, becoming wheelchair-dependent. Oral rapamycin was indicated, showing improvement in her physical capacity, independence and autonomy, and absence of lymphorrhea after four months of treatment. **Conclusion:** We propose oral rapamycin for the treatment of patients with CLOVES syndrome who present with complications and deterioration in the quality of life as a result of the disease.

Keywords:
CLOVES;
rapamycin;
sirolimus;
vascular malformations

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Introduction

CLOVES syndrome (CS), according to the ISSVA (International Society for the Study of Vascular Anomalies) classification, is an overgrowth syndrome clinically characterized by congenital lipomatous overgrowth mainly in the trunk, vascular malformations (macro and microcystic lymphatic malformations, 'geographic'-type capillary malformation (CM), phlebectasia and/or arteriovenous malformations), epidermal nevus, and skeletal malformations such as scoliosis and spinal alterations. The acronym CLOVES stands for 'Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Skeletal/Scoliosis/Spinal abnormalities'[1,2]. It is caused by an activating PIK3CA somatic mutation which is part of the PI3K-Akt-mTOR intracellular signaling pathway (mTOR: mammalian Target of Rapamycin)[2,3,4].

The umbrella term PROS (PIK3CA-related overgrowth spectrum), encompasses clinical entities that have in common somatic activating mutations in the phosphatidylinositol-3-kinase (PI3K) pathway. These include CS, fibroadipose overgrowth (FAO), hemihyperplasia with multiple lipomatosis (HHML), Klippel-Trenaunay Syndrome, CLAPO Syndrome (lower lip Capillary malformation + face and neck Lymphatic malformation + Asymmetry and Partial/generalized Overgrowth), Megalencephaly-Capillary Malformation (MCAP), and Macrodactyly (table 1)[5,6].

Many of the overgrowth syndromes share clinical manifestations, sometimes making differential diagnosis difficult. This occurs with CLOVES Syndrome and Proteus Syndrome, the latter due to somatic mutation of AKT1. Both syndromes occur sporadically and present scoliosis and linear epidermal nevi[7]. The main difference is that patients with Proteus Syndrome are born with few manifestations and develop overgrowth and asymmetry in the postnatal stage, whereas patients with CS are born with large lipomatous masses, which is a striking feature since the neonatal period. Table 2 shows the main differences between both pathologies[1,7].

Complex and combined vascular malformations are difficult to treat. They are often diffuse and cannot be resolved by sclerotherapy, embolization, or surgery alone. The ideal therapy for this diverse group of patients should selectively target the involved cellular pathways.

mTOR is a Serine/Threonine Kinase pik3 dependent that promotes angiogenesis. In murine models, it was demonstrated that activation of the PI3K/AKT/mTOR pathway produces vascular malformations. An mTOR inhibitor would have antiangiogenic and anti-lymphangiogenic properties, playing a role in the treatment of this type of vascular anomaly (VA)[8,9,10].

Table 1. Clinical entities that are part of the PROS (PIK3CA-related overgrowth spectrum)[5,6]

Syndrome	Clinical characteristics
CLOVES	Lipomatous overgrowth, present at birth, predominantly of the trunk, vascular malformations (macro and microcystic lymphatic malformations LM, capillary malformations of geographical type CM, venectasia and arteriovenous malformation AVM), epidermal nevus and skeletal malformations such as scoliosis and spinal alterations
Fibroadipose overgrowth (FAO)	Segmental and progressive overgrowth of subcutaneous and visceral fibroadipose tissue, sometimes associated with skeletal and muscular overgrowth. Congenital or early childhood onset
Hemihyperplasia-Multiple Lipomatosis (HHML)	Asymmetry and overgrowth of multiple subcutaneous lipomas. Hemihyperplasia may be static or mildly progressive. Congenital or early childhood onset
Megalencephaly-capillary malformation syndrome (MCAP)	It affects the central nervous system; overgrowth with body asymmetries (hemihyperplasia), generalized reticulated CM and distal limb malformations (polydactyly and syndactyly). Congenital or early childhood onset
Macrodactyly	Also known as lipomatous macrodystrophy. It is characterized by fibroadipose and bone overgrowth in the zone innervated by a given nerve which displays an increase in its diameter and length. They may also include muscular hemihyperplasia. Congenital or early childhood onset
Klippel – Trenaunay	Syndrome characterized by CM and VM associated with LM and excessive limb growth
CLAPO	Syndrome characterized by CM of lower lip associated with LM of head and neck; and partial or generalized asymmetric overgrowth

CM: capillary malformation; VM: venous malformation; LM: lymphatic malformation; AVF: arteriovenous fistula; AVM: arteriovenous malformation.

Table 2. Differences between clinical characteristics of CLOVES and Proteus syndromes[1]

CLOVES	Proteus
Lipomatous masses	Connective tissue nevus
Mixed and complex vascular malformations, mainly in the trunk	Mixed vascular malformations, rarely in the trunk
Congenital lipomatous overgrowth, of globular aspect, not progressive, that grows proportionally with the patient, and in general, it is symmetrical in the lower limbs	Increase in volume is not found from birth, but rather is a progressive growth, disproportionate and asymmetrical, affecting any tissue, including bone tissue
Infrequent ocular involvement	Frequent ocular involvement (ptosis, cataracts, lateral nystagmus)
Thick, wrinkled soles of feet	Soles of feet and other areas with brain-like folds (the brain nevus of connective tissue is pathognomonic of this condition)
Non-evolutionary clinical manifestations	Clinical evolutionary aggravation

Rapamycin (Sirolimus), the only mTOR pathway inhibitor approved by the FDA, has been used with a favorable effect in both vascular tumors and malformations, especially in those with a predominant lymphatic phenotype[10]. Oral rapamycin is approved by the FDA for use in kidney transplantation in patients over 13 years of age. Multiple studies consider mTOR inhibitors for a wide range of indications, including advanced cancers, organ transplantation, tuberous sclerosis complex, and VAs[11].

In VAs, rapamycin has shown efficacy vascular tumors, such as kaposiform hemangioendothelioma[12], and in complex, generalized and multifocal vascular malformations, particularly the low-flow ones (predominantly lymphatic and/or venous)[13,14].

Currently, the use of oral rapamycin in patients with CS is based on the evidence regarding the effects on the quality of life, with better response in predominantly venous and lymphatic malformations (LM). A recent study describes the use of PIK3CA specific inhibitor (BYL719), initially tested in a murine model, and then prescribed in patients with PROS (including patients with CS) with favorable clinical response in all cases, confirming the usefulness of the PI3K/AKT/mTOR pathway inhibitor treatment in patients with CS[15].

Oral rapamycin is indicated in VAs for prolonged periods, generally undefined. Doses should be adjusted to maintain plasma levels around 8 - 12 ng/ml, or lower depending on the therapeutic response. Its safety profile is adequate, reporting adverse effects such as hyperlipidemia, mucositis, hypertension, and elevated transaminases[8]. In order to reach the target dose, patients aged between three months and two years begin their treatment with 0.7 to 1.6 mg/m^2 based on body surface area twice daily and those older than 2 years with 1.8 mg/m^2 based on body surface area twice daily, and then adjust the dosage according to plasma levels[11]. The minimum dose necessary to achieve an optimal balance between therapeutic efficacy and the lowest probability of adverse effects should be administered[11].

Objective

To report the experience of treat two patients with CS with oral rapamycin.

Clinical Cases

Case 1

Three years-old female patient with history of CS, characterized by macro and microcystic LM, lipomatous overgrowth in the trunk, buttocks, thighs, and thoracic, abdominal and pelvic cavities; 'geographic'-type CM in the trunk, superficial phlebectasia, and severe bilateral hip dysplasia (figure 1). In addition, she presented coagulation disorder compatible with Localized Intravascular Coagulopathy (LIC)[16], and had recurrent hospitalizations due to macrocystic LM infections of difficult manage, requiring drainage and sclerotherapy, and also the patient presented intravascular coagulopathy episodes (D-dimer levels higher than 25,000 ng/mL). Due to the poor quality of life, the severity of its infectious conditions, surgical bleeding risk, and the progression of the lesions, treatment with oral rapamycin was initiated, according to the protocol for Complicated VA in Childhood created by the interdisciplinary VA group of Cincinnati Children's Hospital Medical Center[11]. Oral rapamycin was indicated at 0.6 mg every 12 hours, equivalent to 0.8 mg/m^2/dose, adjusting the dose to reach plasma levels of 7-10 ng/dL. After six months of treatment, the size of the lipomatous and lymphatic masses was clinically and radiologically reduced, with no cutaneous lymphorrhea and a

significant improvement in her quality of life, without requiring new hospitalizations. The patient presented moderate hypertriglyceridemia only during the first month of treatment. After four years of treatment, the positive therapeutic effects are maintained, without complications derived from the drug.

Case 2

Ten years-old female patient with CS. From birth, she presented extensive lipomatous masses in the trunk, buttocks and thighs, low-flow vascular malformations ('geographic'-type CM, macro and microcystic lymphatic malformations, and phlebectasia), and extensive epidermal nevus in the cervical region (figure 2). The patient progressively developed scoliosis and mild cognitive delay. Her motor skills deteriorated, making her wheelchair-dependent. Due to the permanent microcystic LM exudation, she required new dressings several times a day. Due to the progressive deterioration of her physical capacity and intense lymphorrhea, oral rapamycin was indicated at 1.3 mg every 12 hours, equivalent to 0.8 mg/m^2/dose. According to plasma levels, the dose was readjusted, achieving stable levels between 8 and 10 ng/dL three weeks after starting treatment. After 4 months of therapy, there was an important improvement in her physical capacity and self-reliance, and she was able to move around without a wheelchair. The patient never presented microcystic LM exudation again. Her cognitive development showed no variation in this period. The patient has undergone 14 months of treatment with a successful response and without any complications.

Figure 1. Case 1: Posterior view of the patient in which a lipomatous overgrowth of the trunk, pelvis and thighs is observed, associated with erythemato-violaceous macules of defined edges consistent with geographical CM in the lateral aspects of the trunk and hips and, altered posture secondary to bilateral hip dysplasia and scoliosis.

Figure 2. Case 2: Latero-anterior view of a patient in which a lipomatous overgrowth of trunk predominance is observed, associated to a large eritemato-violaceous macule of defined borders consistent with CM. This last one presents on its surface multiple vesicles of hemorrhagic content (like frog eggs) that are microcystic LM with hemorrhage (the use of diaper in the picture is due to lymphorrhea from these lesions).

Discussion

Extensive and complex VA have limited therapeutic options and cause significant morbidity and mortality in patients with this condition. Its expansion and/or growth can cause clinical problems such as disfigurement, chronic pain, recurrent infections, coagulopathy (thrombotic and hemorrhagic), organ dysfunction, and death[10].

Oral rapamycin has shown to improve clinical signs related to vascular malformations. Reduced pain, improved quality of life, and daily functioning have been described as well as a decreased number of hospitalizations, and infections[9,10]. The clinical response of the patients described in this report replicates what is described in the literature, achieving a special response in LM with a decrease in lymphorrhea, associated skin infections, and a decrease in the lipomatous masses in the trunk, which, in a variable proportion, are composed of LM and adipose tissue. Coagulation parameters were also normalized with the treatment.

In 2016, Adams et al published the first prospective trial of patients with complicated VA treated with oral rapamycin, concluding that this drug was a safe and effective treatment in most cases[10]. Subsequently, Triana et al published a retrospective analysis of 41 patients with VA treated with oral rapamycin with favorable response rates (improvement in radiological images and decrease in symptoms) averaging 80.4%[17].

Currently, the treatment duration is not well determined, and it is presumed that regular and prolonged administration would be necessary[9,10]. In previous studies, patients with VA that have presented a successful response to rapamycin, present recurrence of symptoms on discontinuing the treatment, therefore the drug must be reintroduced[10,17].

This drug has an immunosuppressive effect, which is why it is used in solid organ transplantation, thus patients should receive prophylaxis against Pneumocystis *jirovecii* (formerly P. *carinii*) and vaccines against pneumococcus and influenza[9,10]. The follow-up of VA patients includes plasma drug levels, renal function study, lipid profile, complete blood count[9, 10], D-dimer and fibrinogen levels.

The D-dimer is a marker of LIC, almost exclusively for vascular malformations. This condition is due to the chronic consumption of coagulation factors secondary to the turbulent flow within these malformations. The higher the D-dimer levels, the greater the extent of this malformation and the risk of complications such as venous thrombosis, pulmonary thromboembolism, and hemorrhage[16].

Central nervous system anomalies have not been associated with CLOVES/PROS syndromes. There is only one report in the literature which suggests that the defects of neuronal migration, hemimegalencephaly, and partial aplasia or agenesis of the corpus callosum, with the consequent cognitive and convulsive manifestations, could be a feature of CS[18]. Under this suggestion, the question of whether or not the cognitive delay in the second case would be associated with CS is not yet answered, and more studies.

Our patients received oral rapamycin according to the protocol for Complicated VA of Childhood. Plasma levels of/at 8-10 ng/dL showed good clinical response, better physical mobility, less pain, decreased number of hospitalizations, and disappearance of lymphorrhea. The patients showed good tolerance to treatment, presenting only transient hypertriglyceridemia in the first case.

Conclusion

Vascular malformations represent a broad and heterogeneous spectrum of lesions, which often appear as a diagnostic and therapeutic challenge. Unlike childhood hemangiomas, these malformations do not present spontaneous regression but, on the contrary, they get worse and more complicated, requiring a timely treatment that allows improving the quality of life of these patients.

We presented two patients with CS treated with oral rapamycin, with good clinical response and little systemic toxicity. Currently, the first patient has been on treatment for four years and the second one for 14 months, maintaining the positive effects without presenting complications derived from this drug.

We propose the use of oral rapamycin for the treatment of patients with CS who present complications and deterioration of the quality of life due to their disease.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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