Portuguese Journal of Dermatology and Venereology

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CASE REPORT

Sirolimus in the treatment of cystic lymphangioma in a pediatric patient

Sirolimus no tratamento de um linfangioma quístico num doente pediátrico

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Abstract

Cystic lymphangioma (CL) is a rare benign tumor, which occurs typically during childhood, with craniofacial, cervical or axillary being the most common locations. Lymphangiomas management can be challenging due to their permeative growth throughout tissue layers. Sirolimus is an immunosuppressive and antitumor agent that can inhibit abnormal vascular proliferation by blocking the mTOR/PI3K pathway. It is typically well-tolerated, with nausea, cytopenias, and metabolic imbalances as the most significant adverse effects. We present the case of a pediatric patient in which sirolimus was used to treat a macrocytic lymphangioma, highlighting its effectiveness and safety.

Keywords: Lymphangioma. Sirolimus. Pediatrics.

Resumo

Os Linfangiomas Quísticos são tumores benignos raros, que ocorrem tipicamente na infância e se localizam mais frequentemente nas regiões craniofacial, cervical ou axilar. Dada a sua natureza infiltrativa em todas as camadas de tecido, o tratamento dos linfangiomas torna-se desafiante. O Sirolimus é um agente imunossupressor e antitumoral que inibe a proliferação vascular anormal ao bloquear a via de sinalização mTOR/PI3K. Geralmente é bem tolerado, tendo como efeitos adversos mais significativos náusea, citopenias e desequilíbrios metabólicos. Descrevemos o caso de uma criança em que foi usado sirolimus no tratamento de um linfangioma macroquístico, demonstranto a sua eficácia e segurança.

Palavras-chave: Linfangioma. Sirolimus. Pediatria.

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Received: 19-12-2021
Accepted: 10-06-2022
DOI: 10.24875/PJDV.M22000035

Available online: 24-10-2022
Port J Dermatol and Venereol. 2022;80(3):227-230
www.portuguesejournalofdermatology.com

Introduction

Cystic lymphangioma (CL) is a rare benign tumor resulting from a failure in the development of the lymphatic system, which occurs more typically during childhood[1]. They consist of dilated lymphatic channels forming multiple cysts of variable size (macro- or microcystic lymphangioma), with craniofacial, cervical, or axillary being the most common locations[1,2]. Surgical excision has been historically considered the treatment of choice, but today less invasive therapeutic options are preferred[2].

Sirolimus is an antitumor agent that belongs to the mammalian target of rapamycin (mTOR) inhibitors group, it blocks the mTOR/PI3K pathway and reduces the production of vascular endothelial growth factor (VEGF) and responsiveness of its receptors, thus inhibiting abnormal vascular proliferation. Sirolimus and other mTOR inhibitors are predicted to be effective agents in disorders in which the mTOR growth control pathway is affected[2,3].

We present the case of a 3-year-old boy treated with oral sirolimus for a cervical CL.

Case description

A 3-year-old, previously healthy boy was referred to the pediatric outpatient clinic due to a right cervical mass, first noticed at the age of 17 months.

Physical examination was remarkable for a voluminous cervical mass on the right side, with approximately 6 cm (Fig. 1) with no other significant findings.

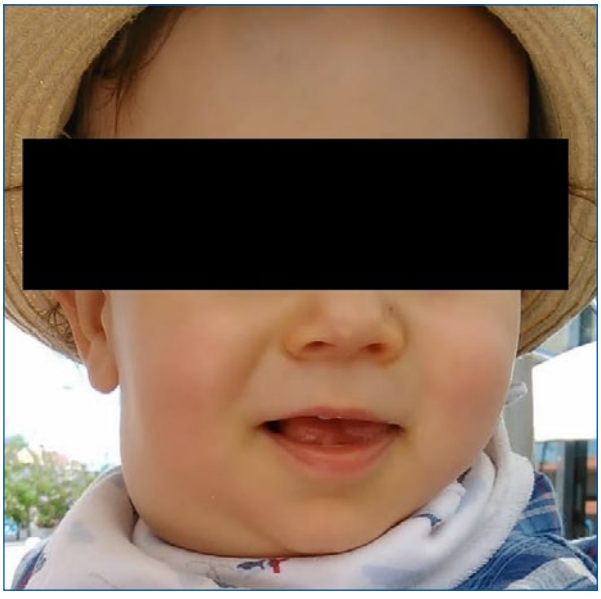

Figure 1. A voluminous cervical mass at the age of 3 years, before treatment.

The ultrasound of the mass revealed a cystic multiloculated image, with anechogenic content measuring 77.7 x 65 x 29 mm and permeating through the cervical structures, below the parotid, posteriorly to the submandibular gland and around the jugulo-carotid space. Magnetic resonance imaging (MRI) confirmed the existence of a right cervical mass consistent with a CL with 6.7 x 6 x 5.2 cm (Fig. 2).

Treatment with sirolimus was started at 1 mg/m^2/dose twice daily. Regular monitoring was carried out with no adverse effects reported.

After 1 year and 3 months of treatment, an important reduction of the mass was achieved (Figs. 3A and B). An MRI showed a significant reduction of the right cervical CL (40 x 28 x 40 mm (Figs. 4A and B).

The patient maintains treatment with sirolimus after 2 years and 3 months with no side effects, and clinically he has no visible mass (Figs. 3C and D).

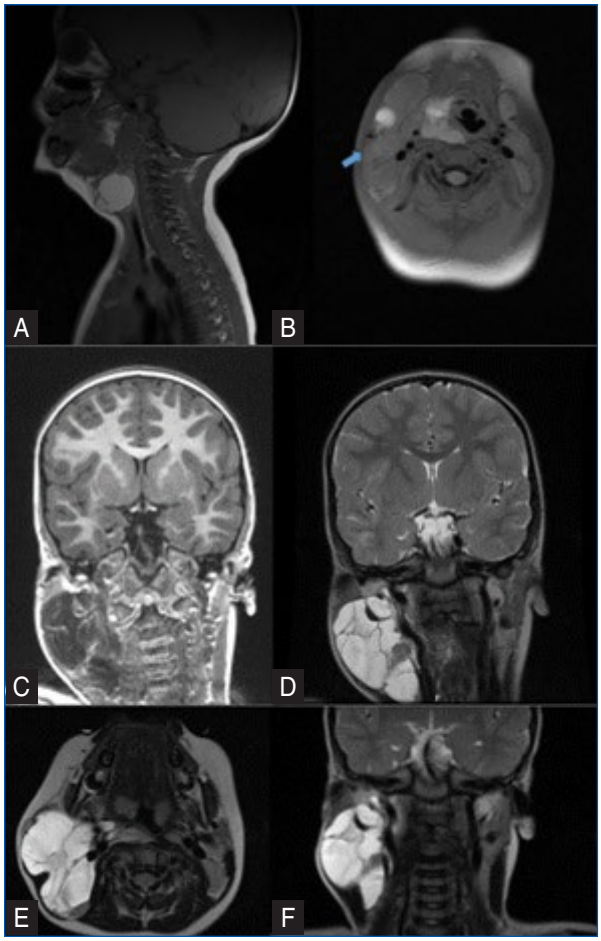

Figure 2. A and B-top: MRI images of the lymphangioma at the date of diagnosis. **Bottom-C, D, E, and F:** immediately before treatment with sirolimus was started.

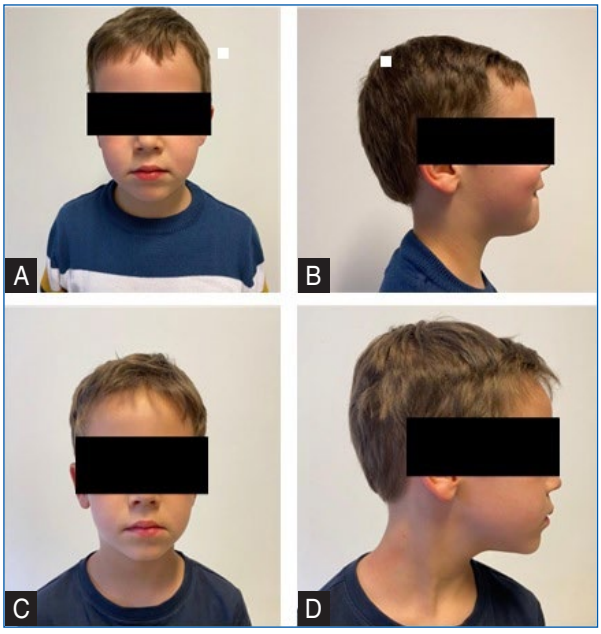

Figure 3. **A and B:** picture of the patients after 1 year. **C and D:** 2 years of treatment with sirolimus, both with no visible mass.

Discussion

It has been suggested that both the occurrence and development of CLs are caused by somatic activating mutations in PIK3CA. This mutation leads to an abnormal activation of the phosphatidylinositol-3′-kinase (PI3K)/AKT signaling pathway, which is critical in controlling cell growth and proliferation during development and has been implied in multiple syndromes with tissue overgrowth. Activation of mTOR signaling increases the expression of VEGF, therefore contributing to increased angiogenesis and lymphangiogenesis[3].

Lymphangiomas management can be challenging due to their permeative growth throughout tissue layers. To date, there is no uniform guideline for the treatment of CL, which currently intends to control related symptoms, maintain functionality, and preserve aesthetic integrity[4].

Sirolimus, also known as rapamycin, is a serine/threonine kinase that regulates the signaling pathway PI3K/AKT/mTOR. It is typically well tolerated[3,4], with the most significant adverse effects being nausea, cytopenia (thrombocytopenia and anemia), and metabolic imbalances (hyperglycemia, hypercholesterolemia, elevated alkaline phosphatase, elevated serum creatinine, and hypophosphatemia)[2], especially in the beginning of the treatment.

There have been reports of the successful use of sirolimus in children with vascular malformations[1-4]. The possibility of oral administration with a comfortable scheme (two administrations daily) makes it easy for parents to administer and stimulates compliance to treatment.

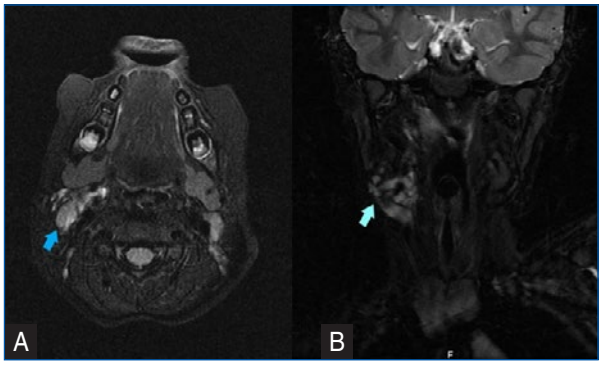

Figure 4. **A and B:** MRI images of the lymphangioma that was significantly reduced after treatment with sirolimus (blue arrow).

The optimal timing of treatment is yet to be determined, as there are no sufficient studies to state when to stop oral sirolimus in CLs.

In the case we described, there was good compliance to therapy and tolerance with no significant side effects reported during follow-up, adding evidence of the effectiveness and safety of oral sirolimus in the treatment of CLs.

What does this study add?

The data on the use of sirolimus in the treatment of vascular malformations are still scarce. With this case report we aim to demonstrate the role of sirolimus in the treatment of a macrocystic lymphangioma in a pediatric patient, highlighting its effectiveness and safety.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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