Case Report
Olgu Sunumu

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A case of lymphangioma circumscriptum successfully treated with topical sirolimus

Topikal sirolimus ile başarılı bir şekilde tedavi edilen bir lenfanjioma sirkumskriptum olgusu

Malik Güngör, Aslı Bilgiç

Akdeniz University Faculty of Medicine, Department of Dermatology and Venereology, Antalya, Türkiye
*Equal contributors

Abstract

Children who have lymphatic malformations frequently experience functional limitations and aesthetic abnormalities that have a significant impact on their quality of life and may pose a threat to their lives. Conventional treatments such as surgery or sclerotherapy are rarely curative, demonstrating the great need for new treatment modalities. Recently, oral or topical administration of sirolimus has successfully treated lymphatic malformations. We report the 6-month treatment outcome of a 7-year-old boy with lesions consistent with lymphangioma circumscriptum on the left side of the neck since birth who was successfully treated with topical sirolimus.
Keywords: Vascular malformation, topical therapy, sirolimus

Öz

Lenfatik malformasyonlu çocuklar genellikle yaşam kalitesini önemli ölçüde etkileyen ve hayatı tehdit edebilen fonksiyonel bozukluklardan ve estetik deformitelerden muzdariptir. Cerrahi ve/veya skleroterapi gibi geleneksel tedavilerin nadiren iyileştirici olması, yeni tedavi yöntemlerine duyulan büyük ihtiyacı ortaya koymaktadır. Son yıllarda, oral veya topikal sirolimus lenfatik malformasyonlarda başarıyla kullanılmaktadır. Bu yazıda, doğumundan beri boynun sol tarafında lenfanjioma sirkumskriptum ile uyumlu lezyonları olan ve topikal sirolimus ile başarılı bir şekilde tedavi edilen 7 yaşındaki bir erkek çocuğun 6 aylık tedavi sonucu sunulmaktadır.
Anahtar Kelimeler: Vasküler malformasyon, topikal tedavi, sirolimus

Introduction

Lymphangioma circumscriptum (LS) or microcystic lymphatic malformations (MLM) are hamartomatous formations with a maximum diameter of <1 cm and usually with a deeper malformation that occurs due to the proliferation of lymphatic vessels[1]. MLM may occur congenitally, usually in the first two years of life or secondary to acquired lymphatic system changes[2]. They typically occur in the head and neck area[1]. The general treatment approach is determined by the clinical symptoms, lesion size, anatomical localization and complications[2]. Treatment options include surgical excision, carbon dioxide laser, cryotherapy, electrocoagulation, and injection of sclerosing agents, but lesions almost always reappear after these treatments. A few case reports suggest topical sirolimus may be an effective treatment for lymphatic malformations[3-7].

Here, we report a 7-year-old boy with lesions consistent with LS on the left lateral aspect of the neck since birth who was treated with topical sirolimus successfully.

Case Report

A 7-year-old boy presented to our clinic with slow-growing lesions on the left side of the neck that started at birth. During the physical examination, we observed clusters of

Address for Correspondence/Yazışma Adresi: Aslı Bilgiç MD, Akdeniz University Faculty of Medicine, Department of Dermatology and Venereology, Antalya, Türkiye
Phone: +90 242 249 67 07 **E-mail:** aslibilgictemel@gmail.com **Received/Geliş Tarihi:** 24.03.2023 **Accepted/Kabul Tarihi:** 30.11.2023
ORCID: orcid.org/0000-0001-7910-7908

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pink-purple papules spread out on the left side of the neck (Figure 1). Biopsy was suggested with a preliminary diagnosis of LS; however, it was denied by his parents. Magnetic resonance imaging (MRI) of the neck showed millimetric lymph nodes in the neck region with no extension to the neck muscles.

The patient was diagnosed with LS with typical clinical and MRI features. He underwent one session of potassium titanyl phosphate laser in our clinic, however, he could not tolerate this treatment. Considering the limited involvement area and the patient's age, topical sirolimus was our next therapeutic choice. With the Ministry of Health's approval for off-label use, the pharmacy prepared the topical sirolimus, utilizing 1 mg/mL oral sirolimus solution (Rapamune®, Pfizer) and an adequate quantity of standard hydrophilic ointment containing methylparaben. Although the lesions improved rapidly with twice daily application, irritation was observed at the treatment site in the first month of therapy. Therefore, the application frequency was decreased to once a day, and topical methylprednisolone and moisturizer were applied to alleviate symptoms and continued with sirolimus treatment. After six months of treatment with topical sirolimus, the lesions almost completely resolved (Figure 2). At the end of this period, the patient discontinued the medication. However, after two months of observation without treatment, the lesions reappeared and the patient was restarted on topical sirolimus again on a once daily regimen. After the second course of treatment, a quick shrinkage of the lesions was observed. The patient continued the treatment with topical sirolimus for approximately one more month and discontinued the treatment when there was no change in the lesions. The patient has been followed up without treatment for about one year, and the lesions are smaller compared to the beginning of treatment. Informed consent was obtained from the parents.

Discussion

Sirolimus is a mammalian target of the rapamycin inhibitor (mTORI), which has found wide therapeutic use since its discovery. However, many studies have been published in the last two decades regarding the use of sirolimus in other areas, focusing on its anti-proliferative, anti-angiogenic and immunosuppressive properties. Sirolimus has a wide range of uses in dermatology. It is used in genodermatoses (Muir-Torre Syndrome, tuberous sclerosis complex, epidermolysis bullosa simplex), infections (warts), inflammatory/autoimmune diseases (dermatomyositis, psoriasis), neoplasms (melanoma, non-melanoma skin cancer) and vascular diseases (lymphatic malformation, Kaposi's sarcoma)[8].

Our case shows topical sirolimus could be a promising therapeutic choice in LS, a rare, challenging disorder due to the lack of definitive treatment[3]. Despite the availability of molecular data showing the effect of sirolimus on various intracellular signaling pathways, the mechanism of action of sirolimus in MLM is not fully understood[4]. Hori et al.[9] explained the efficacy of sirolimus in lymphatic anomalies by the possible dual inhibition of mTOR and vascular endothelial growth factor pathway.

Growing evidence indicates that sirolimus is viable for treating different vascular malformations[10]. Çalışkan et al.[3] demonstrated near-total disappearance of the lesions by the third month of topical sirolimus therapy in an 8-year-old girl with a MLM on the left trunk. Strychowsky et al.[5] reported that macrocystic LM may respond better than mixed or microcystic LM, and treatment could be more successful in younger patients. Leducq et al.[6] demonstrated that 0.1% topical sirolimus treatment applied for 12 weeks was more effective than placebo cream (control) in reducing oozing, bleeding, impairments, and pain in a multicentre, randomized, double-blind phase 2 study involving 55 patients with cutaneous MLM aged six years and older. Wataya-Kaneda et al.[11] demonstrated in a randomized clinical trial that topical sirolimus is an effective and safe treatment for facial angiofibromas in patients with tuberous sclerosis. Wiegand et al.[4] reviewed 28 case series and reports along with two prospective trials on systemic and topical sirolimus treatment of lymphatic malformations, and reported that sirolimus might be an effective treatment in children with large complicated LM of the head and neck. They evaluated 105 children

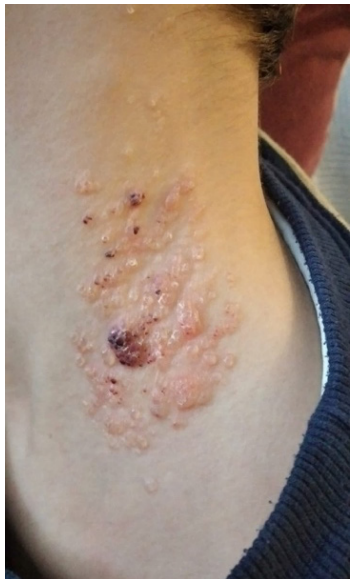

Figure 1. Clusters of pink-purple, occasionally skin-colored papules located in the left lateral part of the neck

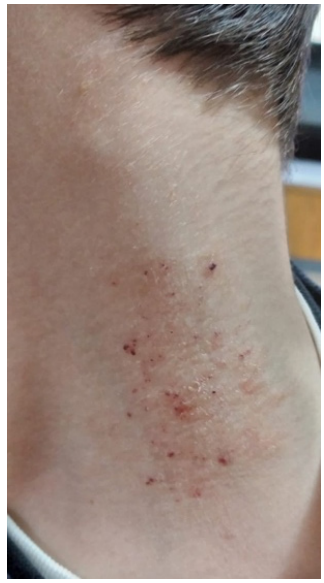

Figure 2. Almost complete resolution of lesions six months after topical sirolimus application

and found that 91.4% of them responded to sirolimus (95 patients with partial and one neonate with complete response), 49-90% had a reduction of LM and an improvement of pain. The target blood level was ≤20 ng/mL, and treatment duration varied between 6 months to 4 years. The most common systemic adverse effects were reported as hyperlipidemia, neutropenia, and infections[4].

Unfortunately, there is currently no commercially available topical sirolimus and therefore formulations with different concentrations of the oral form need to be prepared[10]. The optimal topical sirolimus concentration for facial angiofibromas has been reported to be 2%[9]. For treating LS, 1% or 0.8% topical sirolimus in petrolatum has been recommended[7,11]. Although the results with topical sirolimus are promising, the treatment is not without disadvantages. The main side effects of topical sirolimus have been reported as irritation and a burning sensation, as seen in our case. For these mild side effects, low-potency topical steroids and moisturizers have been suggested[10]. Since MLMs contain deep structures, the query arises as to whether or not topical sirolimus is likewise powerful on deeper lesions[3]. Topical sirolimus has limited ability to penetrate deeply into the skin, so it is unlikely to be effective for treating lesions that are located deeper[3]. Furthermore, the reappearance of lesions following the cessation of the medication indicates that prolonged usage is essential for managing the disease effectively[4]. In our case, recurrence was also observed as expected after the patient stopped the therapy; however, remission was again achieved after re-administration.

Our case endorses the effective utilization of topical sirolimus in managing LS. Nonetheless, prolonged and consistent therapy appears essential for symptom remission.

Ethics

Informed Consent: Informed consent was obtained from the parents.

Authorship Contributions

Surgical and Medical Practices: M.G., A.B., Concept: M.G., A.B., Design: M.G., A.B., Data Collection or Processing: M.G., A.B., Analysis or Interpretation: M.G., A.B., Literature Search: M.G., A.B., Writing: M.G., A.B.

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