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Result of using Sirolimus in a child with lymphangioma of the thigh. Case report

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ABSTRACT

Lymphangioma is a benign tumor, often representing a congenital anomaly of the lymphatic system, most commonly manifesting as soft, nodular reddish or bluish lesions on the skin and mucous membranes. While typically asymptomatic and merely a cosmetic concern, larger forms may cause complications. The pathology arises from disrupted embryogenesis, where isolated lymphatic cavities fail to connect with the main vascular network, leading to their dilation, fibrosis of surrounding tissues, and secondary skin changes. Conservative treatments are largely ineffective, making surgical excision or minimally invasive procedures the mainstay of management, depending on the lesion's size and location.

The case we describe is a 15-year-old female patient with an extensive lymphangioma of the right thigh, who had been observed at the Pediatric University since childhood. Despite years of treatment (staged excisions, sclerotherapy), recurrent papillomatous growths and lymphorrhea persisted. MRI revealed multiple cystic cavities up to 1 cm in the subcutaneous tissue.

Histologically confirmed lymphangioma with chronic inflammation and weak expression of vascular endothelial growth factor (VEGF). Despite minimal VEGF expression, sirolimus demonstrated clinical efficacy. The patient responded favorably to this treatment, whereas surgical approaches had proven less effective. Significant local improvement was documented, including reduction of lymphatic vesicles and soft tissue swelling in the thigh.

Keywords: vascular malformations, lymphangioma, children, endothelial expression

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Результат применения препарата Сиролимус у ребенка с лимфангиомой бедра (клинический случай)

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АННОТАЦИЯ

Лимфангиома — доброкачественная опухоль, часто представляющая собой врожденную аномалию лимфатической системы, наиболее часто проявляющаяся в виде мягких бугристых образований красноватого или синюшного цвета на коже и слизистых оболочках. Хотя чаще она протекает бессимптомно и является лишь косметическим дефектом, крупные формы могут вызывать осложнения. Патология развивается из-за нарушения эмбриогенеза, когда изолированные лимфатические полости не соединяются с основной сетью сосудов, что приводит к их расширению, фиброзу окружающих тканей и вторичным изменениям кожи. Консервативные методы лечения малоэффективны, поэтому основным подходом остается хирургическое удаление или малоинвазивные процедуры в зависимости от размера и локализации образования.

В описанном нами случае представлена 15-летняя пациентка с обширной лимфангиомой правого бедра, которая наблюдалась в Педиатрическом университете с детства. Несмотря на многолетнее лечение (этапные иссечения, склеротерапия), сохранялись рецидивирующие папилломатозные разрастания и лимфорея. Магнитно-резонансная томография выявила множественные кистозные полости до 1 см в подкожной клетчатке. Гистологически подтверждена лимфангиома с хроническим воспалением и слабой экспрессией фактора роста эндотелия сосудов (VEGF).

Несмотря на слабовыраженную экспрессию VEGF, была отмечена положительная динамика при назначении препарата Сиролимус. Ребенок получал лечение с положительным клиническим эффектом на фоне остальных методов терапии, в то время как хирургические подходы были менее эффективны. Зафиксировано значительное улучшение местного статуса, включая уменьшение лимфатических пузырьков и окружности мягких тканей бедра.

Ключевые слова: сосудистые мальформации, лимфангиома, дети, экспрессия эндотелия

Как цитировать
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Lymphangioma is a benign tumor, typically originating from a congenital anomaly of the lymphatic system. Lesions can develop in any area of the body, presenting as soft-tissue masses with a lobulated surface of reddish-brown or bluish discoloration. The malformation is often asymptomatic and primarily a cosmetic concern; however, upon significant growth, it can lead to serious complications. Lymphangioma is a relatively rare condition. According to various sources, it accounts for 1.3–10.6% of all vascular tumors (up to 25% in the pediatric population), with an estimated incidence of 1 in 20,000 to 250,000 admissions to surgical departments. Lymphangiomas are most commonly identified in neonates and infants (90% of cases), less frequently within the first 2–3 years of life, but may also be diagnosed prenatally or much later in adulthood [1, 2]. Epidemiological data are inconsistent: some studies report a predominance of superficial lymphangiomas in females, while others indicate a threefold higher incidence among males. Most lesions are considered congenital vascular malformations rather than true neoplasms. They typically develop during fetal life, at the end of the first or beginning of the second trimester of gestation [3, 6]. Although the exact etiology of lymphangiomas remains incompletely understood, several factors have been implicated in their pathogenesis.

- *Embryonic development anomalies* are considered pivotal, with lesions being linked to malformations of the embryonic lymphatic system (dysontogenesis). The role of vascular endothelial growth factor C (VEGF-C) and its receptor (VEGFR-3) in driving lymphatic endothelial cell proliferation has been highlighted.
- *Genomic and genetic mutations* also contribute; it is recognized that over half of vascular anomaly cases are associated with fetal chromosomal aberrations. Lymphangiomas are frequently observed in syndromes such as Turner, Down, trisomy 13, and trisomy 18. An autosomal dominant inheritance pattern is characteristic of Noonan syndrome.
- *Intrauterine intoxications* represent another potential mechanism, where impaired lymphatic development may be mediated by toxic exposure. Cases have been reported in children born to mothers exposed to lead or its compounds during pregnancy.

Secondary tumors may arise from impaired lymphatic drainage — manifesting as superficial anomalies in the setting of lymphangitis, lymphogranuloma, or panniculitis — or in association with intestinal malrotation and volvulus (intra-abdominal forms). Furthermore, vascular malformations can develop following mechanical trauma, particularly in the context of Gorham-Stout disease.

Pathogenesis. The mechanisms of lymphangioma development remain incompletely understood. Most authors consider the primary pathological process to be the fusion of lymphatic cisterns in the deep subcutaneous space. These structures are segregated from the normal vascular network but communicate with superficial capillaries via vertically oriented, dilated channels. It is theorized that the cisterns originate from a primitive lymphatic sac that fails to integrate into the developing lymphatic system during embryogenesis. Hypertrophied smooth muscle fibers within the walls of these sequestered spaces exhibit rhythmic contractions, which increase intraluminal pressure and lead to dilation of the ascending channels toward the skin. Fibrotic changes develop around the abnormal lymphatic vessels in both the superficial and deep dermis, while the overlying epidermis demonstrates acanthosis, papillomatosis, and hyperkeratosis. Certain lymphangioma subtypes are characterized by significant infiltrative growth, albeit without true tissue destruction.

Classification. Based on anatomical location, lymphangiomas are categorized as superficial (involving the skin and subcutaneous tissue) and deep. Superficial lesions may affect virtually any site, with the head, neck, and axillary regions being most frequently involved. Deep lesions are located within internal organs — such as the liver, spleen, and kidneys — or body cavities, including the abdominal, retroperitoneal, and mediastinal spaces. In clinical angiology, a widely used pathomorphological classification distinguishes several types.

- Capillary (simple) lymphangiomas result from the proliferation of lymphatic capillaries in the skin and subcutaneous tissue; these tumor-like foci are typically small, thin-walled, and localized.
- Cavernous lymphangiomas are characterized by the dilation of larger lymphatic channels, forming cavities and clefts filled with lymph. They exhibit a honeycombed architecture due to numerous connective tissue septa and resemble spongy tissue on cross-section.
- Cystic lymphangiomas (hygromas) present as fluid-filled cavities of variable size that are isolated from the normal lymphatic network. Their content may be serous, chylous, or hemorrhagic, and they can occur as solitary or multiple, sometimes interconnected, cysts.

Additionally, mixed variants such as lymphangiofibroma and lymphohemangioma are recognized. Regarding etiology, malformations are classified as primary (congenital) or secondary (acquired). Based on extent, forms are distinguished as localized or diffuse. Furthermore, depending on their impact on surrounding tissues, lymphangiomas may follow an asymptomatic course or lead to significant dysfunction and structural distortion.

The clinical presentation depends on several factors: lesion location, histological architecture, tumor extent, the anatomical-topographic characteristics of the involved site, and the efficacy of any previous therapy. Angiomatous foci can arise in any region containing lymphoid tissue. The face (lips, tongue, parotid-masseteric area) and trunk are commonly involved [9]. However, the

pathological process may also extend to lymph nodes, visceral organs, and bone. Tumor progression is generally slow, parallels the child's somatic growth, and remains asymptomatic in the majority of cases.

Capillary lymphangioma initially presents as a small area of gradually indurating skin. The lesion features poorly defined margins and a lobulated surface studded with small (2–4 mm in diameter), elastic, pinkish-red nodules. The affected skin area tends to expand over time. Typically, the anomaly causes no discomfort other than its cosmetic appearance. Occasionally, lymph may weep from the nodular lesions, which can also bleed following minor trauma. As the tumor enlarges and becomes more diffuse, it exerts pressure on underlying tissues, a process that in children may lead to secondary bone deformities.

Cystic or cystic-cavernous lymphangiomas of the face and neck typically present as a circumscribed swelling, ranging from 3 to 30 cm in diameter, that may project externally or toward the oral cavity. The overlying skin may appear normal or have a cyanotic hue; it is often stretched and can be either freely mobile or fixed to the underlying tumor mass. The lesion surface is smooth or lobulated, its consistency is soft, and it is non-tender to palpation. Fluctuation is a characteristic finding.

A hallmark of *extensive lymphangiomas* involving the oral cavity, neck, mediastinum, or trunk is the occurrence of intermittent inflammatory episodes. These episodes are associated with systemic symptoms such as fever and malaise, along with local signs — including erythema, swelling, and marked tenderness in the affected region. The inflammatory process typically persists for 1–2 weeks before gradually subsiding, often resulting in increased induration of the tumor.

Diagnosis. Superficial lymphangioma can often be clinically suspected based on its characteristic presentation and the finding of lymph leakage upon needle aspiration. In diagnostically challenging cases, including those with deep-seated anomalies, the vascular surgeon relies on data obtained from instrumental imaging techniques [6, 9].

- *Tumor Ultrasonography.* Ultrasound examination (US) of superficial lymphangiomas typically reveals increased soft tissue volume with heightened echogenicity, containing multiple hypoechoic to anechoic, round or oval areas that coalesce into a single conglomerate. Sonography provides information not only on the tumor's internal architecture and precise location but also on the status of adjacent anatomical structures.
- *Magnetic Resonance Imaging (MRI).* Magnetic resonance imaging of soft tissues enables accurate assessment of the lesion's extent and detailed morphological characterization of the vascular malformation. The results of this study are crucial for formulating an appropriate management strategy and avoiding unnecessary surgical procedures.
- *Lymphography.* This technique enables evaluation of the lymphatic vessels, determination of the lesion's dimensions, and assessment of its anatomical relationship to adjacent structures. The procedure involves direct intralesional injection of a water-soluble contrast agent, followed by acquisition of a series of targeted radiographs in two planes.

Dermoscopy is a useful adjunct in diagnosing superficial, circumscribed lymphangioma, as it visualizes fluid-filled nodules and a distinct lacunar pattern. In cases with hemorrhagic content, differentiation from hemangioma requires histological examination supplemented by immunohistochemical staining (for Factor VIII-related antigen and laminin).

Differential Diagnosis. Lymphatic lesions must be distinguished from other tumors, including teratomas, lipomas, and cervical cysts. Certain vascular malformations should be differentiated from conditions such as primary congenital lymphedema, meningomyelocele, and localized scleroderma (morphea). For intra-abdominal presentations, acute surgical conditions must be excluded.

Treatment of Lymphangioma. No conservative therapeutic strategy has demonstrated proven efficacy against lymphatic malformations. Achieving a reduction in tumor volume or complete eradication requires invasive approaches [4, 6, 8]. The selection of a treatment modality is guided by several factors: the lesion's location, size, depth of involvement, extent, and the presence of any complications. The following options are considered available.

- *Sclerotherapy.* This involves the intralesional injection of sclerosing agents—such as bleomycin, OK-432 (picibanil), or ethanolamine oleate (Ethoxysclerol) — which induces fibrosis and leads to a reduction in the size of the vascular anomaly. Sclerotherapy offers a favorable cosmetic outcome and is therefore often the preferred first-line option for cervicofacial lesions. It can be employed as a neoadjuvant procedure prior to surgery or when complete surgical resection is not feasible.
- *Surgical Excision.* For the definitive removal of a tumor focus, conventional surgical excision remains the most definitive approach. Complete (radical) excision is regarded as the treatment of choice for large cavernous lesions and in situations requiring urgent intervention. However, the resection of deep-seated malformations is associated with a significant risk of local recurrence [5, 7].
- *Minimally Invasive Therapies.* Superficial lymphangiomas can be managed with modalities such as carbon dioxide (CO_2) laser ablation, cryotherapy, or electrocoagulation. These techniques are less traumatic than conventional surgery, promote faster wound healing, and can shorten the overall recovery period. In selected cases, a single treatment session may yield a satisfactory clinical response.

Postoperative Management. During the postoperative period, follow-up imaging is performed to evaluate treatment outcomes and assess the risk of recurrence. Pharmacological management typically includes non-steroidal anti-inflammatory drugs (NSAIDs) and, when indicated, antibacterial agents. For lesions located on the lower limbs, adjunctive compression therapy is routinely recommended.

Case Presentation.A 15-year-old female has been under long-term management for an extensive lymphangioma of the right thigh at the Department of Microsurgery, Saint Petersburg State Pediatric Medical University, since early childhood. At the time of the current presentation, she reported multiple coalescing papillomatous lesions on the anterolateral aspect of the right thigh and persistent lymphatic fluid leakage from areas of postoperative scarring and papillomas. According to her medical history, between the ages of 5 and 14, she received follow-up care and treatment at the university hospital, which involved staged surgical excisions of the thigh lymphangioma and multiple sclerotherapy sessions. Despite these interventions, the condition demonstrated a recurrent pattern.

Ultrasonography and magnetic resonance imaging (MRI) findings revealed multiple variably sized cystic cavities within the subcutaneous adipose tissue along the outer semicircle of the thigh, set against a backdrop of postoperative scar tissue. These cavities were seen to coalesce and contained isolated, non-flowing cystic spaces measuring up to 1 cm in diameter.

A decision was made to perform a biopsy for immunohistochemical analysis using antibodies against VEGF. The macroscopic findings were as follows: 1. Received was a skin flap, measuring 2.5×1.3 cm, of greyish-pink color with a finely nodular surface. Attached to the skin was a lobulated, yellowish segment of adipose tissue measuring 2.5×1.8×1.1 cm. On sectioning, multiple small cavities up to 0.2 cm in diameter were observed, filled with clear serous fluid. 2. Received was a whitish, hair-bearing skin flap measuring 1.7×1.0 cm. A few rounded, thin-walled cavities measuring 0.2 to 0.5 cm in diameter protruded from its surface. Attached was a lobulated, yellowish portion of adipose tissue measuring 1.0×0.7×0.4 cm. Microscopic description: both specimens (1 and 2) consisted of skin fragments with adjacent adipose tissue, exhibiting an identical morphological pattern. This pattern was characterized by numerous irregularly shaped, empty cavities of varying size, alongside cavities filled with eosinophilic material and lined by a single layer of flattened endothelial cells. These vascular structures were located predominantly in the subepithelial layer. Additional cavities were identified within deeper layers, extending into the subcutaneous fat. A prominent, large-focal lymphocytic infiltrate surrounded the cavities, with formation of multiple lymphoid follicles containing pale germinal centers. Immunohistochemistry revealed weak VEGF expression within the lymphatic endothelial lining, with no evidence of endothelial cell proliferation. Conclusion: Lymphangioma with chronic inflammation.

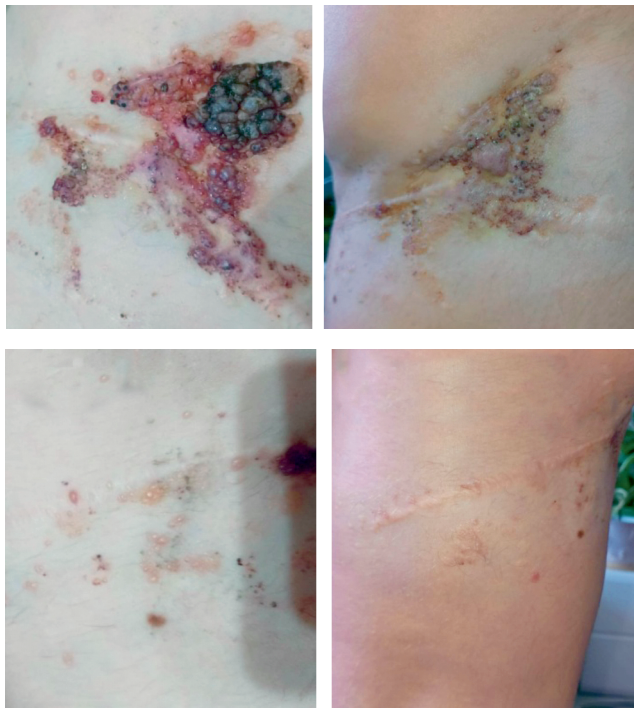

Fig. 1. Skin appearance of a patient diagnosed with lymphangioma of the right thigh before and after starting treatment with Sirolimus (3 months difference)

Рис. 1. Внешний вид кожи пациента с диагнозом «лимфангиома правого бедра» до и после начала применения препарата Сиролимус (разница в 3 месяца)

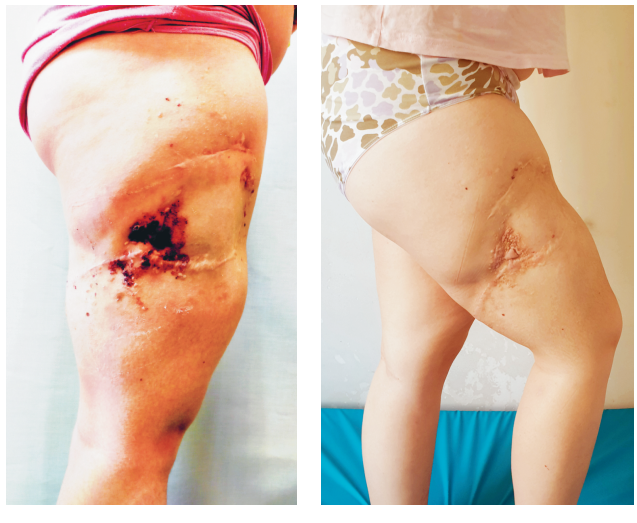

Fig. 2. Changes in the right lower limb against the background of the therapy (3 months difference)

Рис. 2. Изменения правой нижней конечности на фоне проведенной терапии (разница в 3 месяца)

Due to the infeasibility of radical surgical resection, the decision was made to initiate treatment with sirolimus.

Targeted immunosuppressive therapy with sirolimus (rapamycin) represents a contemporary therapeutic strategy for such complex cases. Sirolimus functions as an mTOR pathway inhibitor. The mTOR protein is a serine/threonine kinase regulated by phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt). The PI3K/AKT/mTOR signaling cascade serves as a master regulator of multiple cellular processes, encompassing cellular catabolism and anabolism, cell motility, angiogenesis, and cell growth. By inhibiting mTOR, sirolimus blocks downstream protein synthesis, thereby suppressing cell proliferation and angiogenesis.

The patient was administered oral sirolimus twice daily. Dosage titration, both at treatment initiation and during subsequent maintenance, was performed with the goal of sustaining trough blood concentrations within the target range of 8–15 ng/mL. A positive clinical response was evident within the initial months of therapy, characterized by a reduction in malformation volume, alleviation of pain, resolution of bleeding episodes, regression of cutaneous papillomatous lesions, and a decrease in thigh circumference of up to 8.0 cm (Figs. 1, 2).

In this clinical case, treatment with the mTOR inhibitor sirolimus demonstrated clinical efficacy in a pediatric patient with lymphangioma of the thigh. This positive outcome was observed despite the weak VEGF expression or immunohistochemical evidence of endothelial cell proliferation within the lymphatic vessels. Clinical improvement was evidenced by regression of lymphatic vesicles, reduction of edema, and resolution of inflammatory changes. These findings suggest a potential therapeutic role for sirolimus in select forms of lymphangioma, particularly in cases refractory to surgical management, although it is not considered a first-line therapy for this condition.

ADDITIONAL INFORMATION

Competing interests. The authors declare that they have no competing interests.

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Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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