

# Oral Sildenafil for Macrocystic Lymphangioma in a Filipino Child: A Case Report



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## ABSTRACT

Lymphangioma is a rare developmental anomaly of the lymphatic system, commonly arising at birth, in infancy, or early childhood. Treatment is rarely curative. We report a case of macrocystic lymphangioma treated with sildenafil in a 16-year-old Filipino child diagnosed clinically, radiologically and histologically. The patient presented with grouped papulovesicles on the left lower extremity, associated with limb length discrepancy, unilateral leg pain and difficulty in ambulation. Given the recurrent course of this condition, even with surgical management, the use of a non-invasive approach such as sildenafil as a potential treatment option for lymphangioma is an important emerging area of study.

## INTRODUCTION

Lymphangioma is a rare developmental anomaly of the lymphatic system characterized by thin-walled cysts, representing lymphatic vessels which failed to connect to the normal lymphatic circulation. Based on size, lesions greater than 1 cm in size are called

macrocystic as in cystic hygromas and cavernous lymphangioma, whereas microcystic lymphangioma or lymphangioma circumscriptum are those measuring less than 1 cm.[1]

Although these lesions are benign in nature, life-threatening complications depending on the anatomic location, as well as both long- and short-term disfigurement are a concern.[2] However, management is a challenge as available treatment options are rarely curative, with frequent recurrences. The use of sildenafil for treatment of lymphangioma is an emerging research interest. As of date, there are only a few available studies on its use for lymphangioma, majority of which are for orbital and head and neck lesions.[3,4] To our knowledge, none of these is available locally.

This case describes macrocystic lymphangioma in a 16-year-old Filipino male presenting with multiple discrete to coalescing erythematous to violaceous papules and plaques, with grouped clear to hemorrhagic fluid-filled vesicles on the left lower extremity. Our patient was diagnosed clinically, confirmed radiologically and by histopathology.

## CASE REPORT

A 16-year-old Filipino male presented with vesicles, papules and plaques since he was four months of age. The lesion started as a solitary asymptomatic erythematous 0.1 x 0.1 cm papule on the medial aspect of the left leg, which gradually increased in number, coalescing into erythematous to violaceous plaques, with development of clear to hemorrhagic

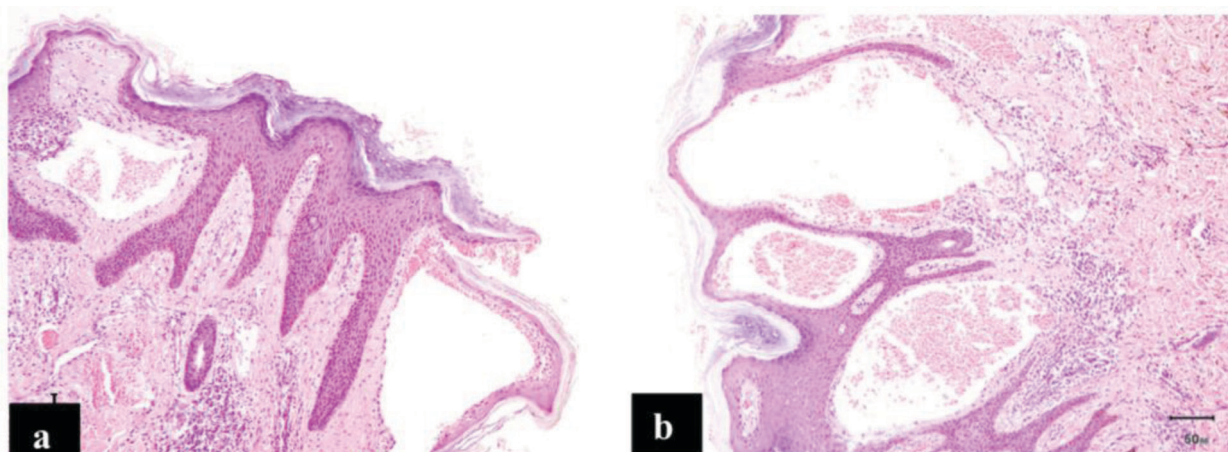
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**Figure 1:** Histopathologic findings of lymphangioma, showing a) hyperplastic epidermis, b) widely dilated spaces filled with clear fluid, lined by a single layer of endothelial cells, with predominance of lymphocytic infiltrate.

fluid-filled vesicles, which would then crust and resolve with hyperpigmentation.

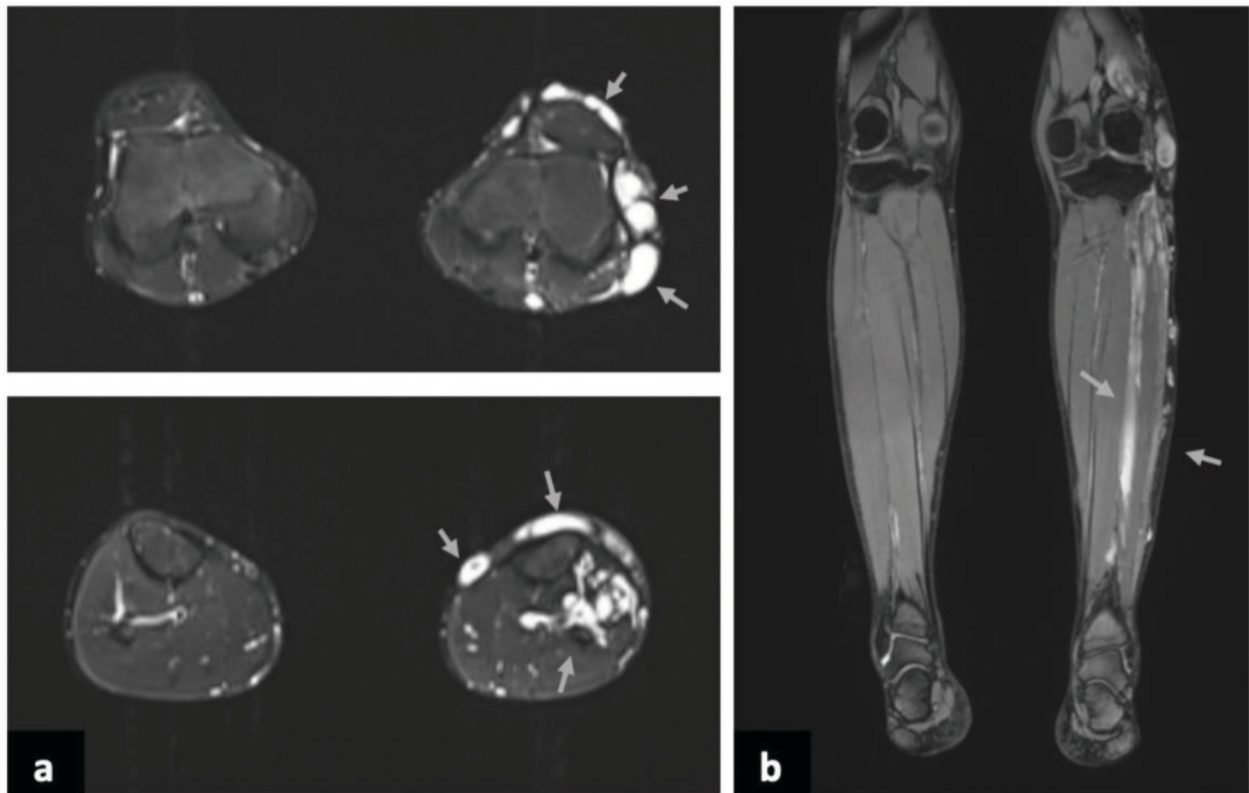
At around nine years prior to consult, the patient developed unilateral left leg pain graded 8/10, associated with difficulty in ambulation. Swelling of lymphatic vessels was also noted on the anterior leg with occasional tenderness graded 5/10. Skin punch biopsy was performed which revealed findings consistent with lymphangioma circumscriptum (Figure 1). The patient was advised laser therapy. However, having explained the possibility of recurrence, the parents refused and opted for observation.

Over the years, new lesions would appear extending to the left patellar region, anterior and posterior thighs, some resolving spontaneously whereas others persisting indefinitely. Increase in dilated vessels was also noted, including those on the posterior leg. Leg pain was still present, especially with prolonged walking or physical activity. At this point, work-up with complete blood count, chest x-ray and peripheral venous duplex scan of the lower extremities were done, all with normal findings. Plain magnetic resonance imaging (MRI) showed dilated and tortuous subcutaneous vessels on the left lower extremity (Figure 2). Dermoscopy was no longer done due to the already conclusive histologic findings and known superiority of MRI as a diagnostic modality for such cases.

On skin examination, multiple discrete to coalescing erythematous to violaceous papules and plaques, with grouped clear to hemorrhagic fluid-filled vesicles on the left anterior and posterior thigh and leg, measuring 0.3 x 0.2 cm to 8.0 x 6.0 cm were noted (Figure 3). Lesions were slightly tender.

No inguinal lymphadenopathies palpated. Length of left and right lower extremities were 89 cm and 87.5 cm, respectively, measured from the anterior superior iliac spine to the heel of both feet. Circumference was measured at the area of largest diameter around 20 cm above the medial malleolus and was noted to be 29 cm and 28 cm for the left and right leg, respectively.

Given the enlargement of previously noted lesions and associated MRI findings, a diagnosis of macrocystic lymphangioma was made. For patients presenting with a chronic history of vesicles, papules and plaques with unilateral lower limb affectation, other diagnoses considered were incontinentia pigmenti, inflammatory linear verrucous epidermal nevus (ILVEN), angiokeratoma and hemangioma. Incontinentia pigmenti presents with an initial vesicular phase from birth to approximately four months of age followed by a verrucous phase, a macular hyperpigmented phase and a linear hypopigmentation phase following the lines of Blaschko. Furthermore, patients usually have associated neurologic, ophthalmologic and dental sequelae, in addition to skeletal anomalies. ILVEN presents unilaterally as pruritic erythematous, hyperkeratotic, warty, sometimes psoriasiform or lichenoid patches in a linear arrangement. Angiokeratoma results from the proliferation of capillaries in the dermal papillae. These are asymptomatic, well-circumscribed, dark-red, hyperkeratotic papules and plaques, which may have a linear or zosteriform pattern. Hemangiomas present at birth or during the first few weeks or months of life. They may begin as pale macules with telangiectasias which become progressively more



**Figure 2:** Magnetic resonance imaging showing a) axial and b) coronal T2-weighted images of the lower extremities with signal intense areas on left lower extremity (arrows) representing dilated fluid-filled vessels.

erythematous and elevated, reaching its maximum size at around 6 to 8 months. Most infantile hemangiomas resolve by the age of 10, however, some do not completely regress leaving a faint erythema or discoloration on affected skin.

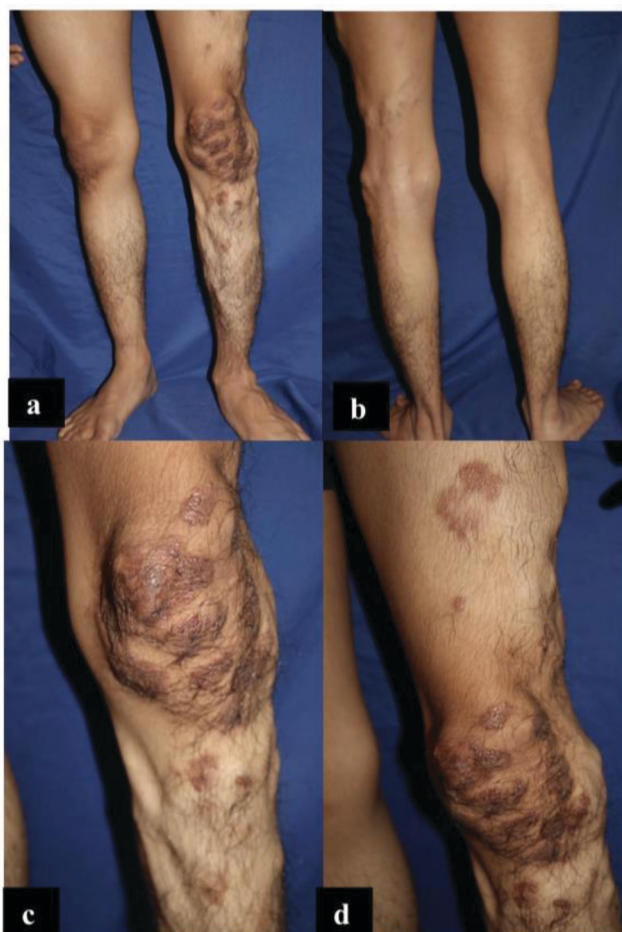
The patient was then started on sildenafil at 1 mg/kg/day equivalent to 25 mg per tablet twice a day for a duration of 20 weeks.[4] Vital signs were stable during the course of treatment. Daily blood pressures were taken, all within 90-110/70-80 mmHg. There were no subjective reports of headache, dizziness, flushing, or visual changes. The patient reported transient erection for a few days after initiation of treatment, which resolved spontaneously. Apart from sildenafil, no other medications or supportive measures were prescribed.

On follow-up after two weeks, symptomatic improvement was noted with decrease in pain from 5/10 to 2/10, with greater ease in ambulation and performance of physical activities. There were no new lesions noted. Measurement of limb length and leg circumference remained the same. After four weeks, circumference of the left leg decreased by 1.5 cm from 29 to 27.5 cm. After nine weeks of treatment, leg circumference further decreased

to 26 cm, a reduction of 10% from baseline. For many years since initial presentation of lesions and leg pain, the patient had preferential use of the right leg leading to dominant leg hypertrophy. This explains the greater circumference of the right or normal leg after improvement of vascular flow in the left or affected leg. Previously noted papules and plaques appeared flatter, less erythematous and more hyperpigmented with more areas of normal skin. Equal measurement of the length of both lower extremities was noted, making the discrepancy 0. Complete resolution of pain was also reported with associated increase in ambulatory capacity. The patient went on to complete the prescription for 20 weeks, and was ideal for repeat MRI. However, due to the pandemic during this time, repeat MRI was not done. Still, the patient reported complete resolution of pain and progressive improvement of lesions.

## DISCUSSION

Lymphangiomas are localized malformations of the lymphatics, most commonly presenting at birth or in infancy and early childhood. Most studies show no sexual predilection, whereas others report



**Figure 3:** Multiple erythematous to violaceous papules and plaques, with grouped clear to hemorrhagic fluid-filled vesicles on the left anterior and posterior thighs, knee and leg. There are also dilated vessels on both anterior and posterior aspects of the left leg (a, b).

a male predominance.[5] They account for 4% of all vascular malformations and 26% of all benign vascular tumors.[6]

Various attempts at classifying cutaneous lymphangiomas were done, but still with no standard clear definition and universal application. This is partly due to the nature of the disease representing a clinicopathologic continuum. Based on size, current classification subdivides them into microcystic and macrocystic forms. Mixed macrocystic and microcystic lesions may also occur.

Microcystic lymphatic malformations (LMs) are most commonly seen on the proximal parts of the limbs and in the limb girdle region. They present as scattered or grouped translucent vesicles and papulovesicles in an area of skin, which may become hemorrhagic, crusted, or develop black dots within them. Lesions may enlarge and spread with time, increasing especially during the inflammatory phase following an infectious episode or trauma. There may also be

other abnormalities of lymphatic drainage resulting in lymphedema and enlargement of the limb, sometimes, with involvement of the underlying muscle.

Macrocytic lymphatic malformations or deep lymphangiomas most commonly occur in the head and neck region as ill-defined soft subcutaneous masses. Lesions expand over time as the anomalous lymphatic channels become dilated. They may remain asymptomatic or develop localized pain and hardening with intracystic bleeding.[7]

In spite of differences in clinical behavior, recent studies have shown that they have indistinguishable histological features and immunohistochemical staining for markers of lymphatic endothelium.[2] Histopathologically, lymphatic vessels are lined with thin, attenuated endothelial cells with occasional gaps between the cells. Both microcystic and macrocystic lesions are composed of heterogeneous tissue consisting of amorphous proteinaceous material, lymphocytes, or occasional red blood cells. Thus, the initial diagnosis of lymphangioma circumscriptum in our patient based on physical examination and histopathology alone.

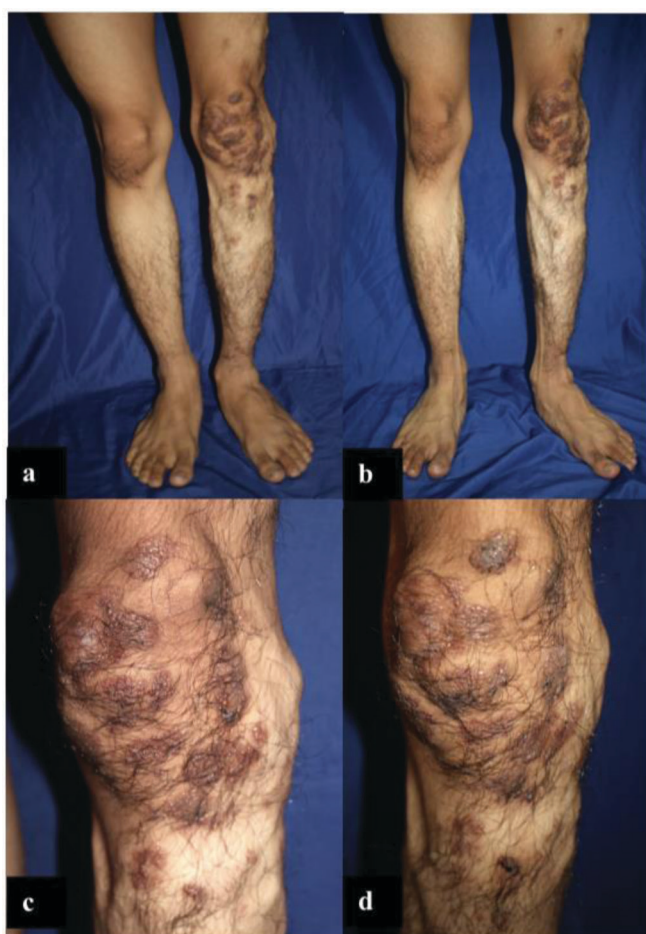
It is important to note that lymphangiomas are always more extensive than predicted during clinical examination. The superficial vessels typically communicate through deep vessels with large closed lymphatic cisterns in the subcutaneous or deeper tissues; hence, the tendency of the lesions to recur after superficial excision. Imaging studies confirm the diagnosis and delineate the extent of involvement of lesions. MRI is the best method for determining full extent of the lesion as was demonstrated in this case report.[8] This allowed the diagnosis of macrocystic lymphangioma to be established.

Again, treatment is rarely curative. The primary goal is to remove or destroy the diseased lymphatics and subcutaneous components, which may serve as nidus for recurrence. Microcystic lesions cannot generally be cured during childhood, with frequent recurrences seen even in cases of complete excision.[6] Macrocytic LMs are more amenable to percutaneous sclerotherapy, although patients would often still need repeated sclerotherapy treatments during their lifetime.

Sildenafil is a selective 5-phosphodiesterase inhibitor, and is a promising treatment option for lymphangiomas. Although the exact mechanism remains largely unclear, it is thought that inhibition of phosphodiesterase-5 decreases contractility of

**Table 1:** Leg length, circumference and pain scale during treatment with sildenafil

	Leg	Length (cm)	Circumference (cm)	Pain
<b>Initial consult</b>	Right	87.5	28	
	Left	89	29	5/10
<b>2 weeks</b>	Right	87.5	28	
	Left	89	29	2/10
<b>4 weeks</b>	Right	87.5	28	
	Left	89	27.5	2/10
<b>9 weeks</b>	Right	87.5	28	
	Left	87.5	26	0/10



**Figure 4:** Papules and plaques on the left anterior and posterior thighs, knee and legs on initial consult (a,c) and after 9 weeks of treatment (b,d) with sildenafil. Lesions appear flatter and more hyperpigmented. Note also the evenness of stance after treatment.

vascular smooth muscle, resulting in vasodilation. Relaxation of lymphatic vasculature may allow lymphatic spaces to open, thereby decreasing LM volume. Oral sildenafil administered for 20 weeks was shown to effectively reduce LM volume and symptoms in both macrocystic- and microcystic-predominant lesions.[4] In a study by Danial, et.al., LMs softened and became easily compressible in six out of seven subjects after completion of treatment. There was also decrease in LM volume as measured on MRI.[4] All subjects tolerated the medication well. The optimal duration of treatment and dosage regimen needs to be examined further. However, initial observations showed benefit from sildenafil within 8-12 weeks.[4] For this case report, limb length discrepancy and circumference were noted to significantly improved in as early as nine weeks. Symptomatic pain resolution was also noted, which may be due to softening in the LM.

This case showed that sildenafil is an effective and well-tolerated approach in LM treatment. Available literature further concludes that for patients who do not require urgent surgical intervention as seen with this case, it seems reasonable to attempt treatment with sildenafil before moving on to more aggressive treatments.[3] Still, given the limited amount of data available, larger clinical trials are needed to clarify optimal length of treatment, rate of recurrence after discontinuation, use as monotherapy and long-term adverse effects.

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