



Treatment of Microcystic Lymphatic Malformation with Oral Sildenafil Suspension in Paediatric Age Group

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Lymphatic malformations (LM) are an uncommon group of benign vascular anomalies with equal frequency in both sexes and incidence of 1 in 6000 to 16,000 live births [1]. LM have predilection for head and neck region due to abundance of lymphatic glands [2]. Half of the LM cases are apparent at birth while almost 90% become symptomatic within two years [3]. Complications depend upon extent, severity, and type of LM, anatomic location and internal organs involvement. Traditionally, LM is divided into macrocystic, microcystic and mixed types. Conventional treatments for macrocystic variant include sclerotherapy, debulking procedures and surgical excision, but none of these is effective against microcystic group [4].

Swetman in 2012 reported incidental improvement in LM of a child who was taking Sildenafil for pulmonary hypertension [5]. Sildenafil is a selective inhibitor of phosphodiesterase-5 enzyme. In last decade, many studies with convincing results were published around the globe regarding role of Sildenafil in LM [6-8] but such data from Pakistan is entirely lacking.

This was a retrospective, descriptive study conducted at the Vascular Anomalies Centre (VAC), Indus Hospital and Health Network (IHHN), Karachi, Pakistan. Pure microcystic LM cases or

mixed cases with remaining microcystic component after initial treatment were reviewed. The study included patients of either gender, age one to <12 years, who attended the VAC clinics between October 2019 to December 2021. Children with syndromic malformations and multisystem complications were excluded. Institutional ethical review committee approval was received (Study IRB Number: IHHN_IRB_2022_03_006).

Complete blood count, renal and liver function tests, urine analysis, chest x-ray, ultrasounds and magnetic resonance imaging (MRI) of affected regions, pretreatment audiometric and ophthalmic examinations were performed in all cases while blood glucose, ECG and echocardiography were done in selected cases before starting Sildenafil. Laboratory investigations were repeated after a 24-week interval. Ultrasound was repeated after 24 and 48 weeks of treatment. Photographs were taken at baseline and then every 4 weeks to monitor response to the drug.

Sildenafil suspension was formulated by the IHHN Pharmacy with a strength of 2 mg/ml. It was given as per European Medicines Agency (EMA) guidelines i.e., if weight is >20 kg then 60 mg/day in 3 divided doses and if weight is 8 to 20 kg, then 30 mg/day in 3 divided doses [9].

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Initially an oral test dose of Sildenafil was given in IHNN day-care setting; vitals and oxygen saturation were monitored after every 30 minutes during initial 2 hours; and then discharged to continue treatment at home. Clinical evaluation was planned at every 4 weeks of treatment as per recommendation [10]. The VAC helpline number was provided for any assistance or queries.

In this study, 8 children met the selection criteria of which 6 were female and 2 were male. Mean age at initial presentation to our service was 7.5 years. A visible swelling was noted at birth in all but one case where the LM manifested for the first time during the 9th year of life. None of the children had a family history of vascular anomalies. Affected body regions, type of LM at initial diagnosis, associated complications and history of past treatments are detailed in Table 1. Prior treated cases were off treatment for at least 6 months before Sildenafil was considered.

Case No	Gender	Body region/s affected	Age of presentation at VAC (years)	Associated complications	Type of LM at initial diagnosis	History of past treatments
1	Female	Face and neck	5	Eating and respiratory difficulties	Mixed	IST (B+D)
2	Female	Face and neck	4	Eating and respiratory difficulties	Mixed	IST (B+D)
3	Female	Left thigh	8	None	Microcystic	None
4	Female	Right midarm	9	None	Mixed	IST (B)
5	Female	Left arm, axilla, chest wall	10	Limb movements	Mixed	Excision
6	Male	Right groin, scrotum, penile shaft	10	None	Microcystic	Excision
7	Female	Left side of chest	10	None	Mixed	Aspiration
8	Male	Left abdominal wall up to thigh	4	None	Mixed	IST (B)

Table 1: Clinical and demographic details of microcystic LM cases.

IST (B) = Intralesional sclerotherapy with Bleomycin, IST (B+D) = Intralesional sclerotherapy with Bleomycin and Doxycycline, LM = Lymphatic malformation, VAC = Vascular Anomalies Centre.

Sildenafil was started and monitored as per above-mentioned protocols. The dose was increased in 3 cases due to increase in their body weight during the course of therapy (Table 2). No ocular, auditory, erectile dysfunction, cardiac or neurological side effects were seen. Laboratory values remained within limits during therapy. A positive response was observed as early as one month after commencement of Sildenafil (Table 2). Considerable reduction in size of swelling was appreciated (Figures 1 and 2) but duration of drug therapy and response time was variable. Ultrasounds and MRI scans documented reduction of size and disappearance

of microcysts. Both patients with face and neck involvement had repeated herpetic gingivostomatitis during Sildenafil therapy. Two patients relapsed within 12 weeks of cessation of drug therapy; sildenafil was therefore re-started.

The limitations of this study include its retrospective design, the limited number of cases, single center study with no local precedents for comparison, and the absence of histopathological and molecular services at our institution.

Case No	Gender	Age of starting Sildenafil (years)	Body weight before starting Sildenafil (kg)	Dose of Sildenafil given (mg/day)	Duration (months)	Response started after (months)	Relapse
1	Female	9	17	30 then 60	25	2	Yes
2	Female	8	18	30 then 60	27	1	No
3	Female	9	22	60	22	2	No
4	Female	10	35	60	11	1	Yes
5	Female	12	37	60	18	3	No
6	Male	11	39	60	8	3	No
7	Female	11	18	30 then 60	8	2	No
8	Male	4	16	30	14	3	No

Table 2: Therapeutic outcomes after oral Sildenafil suspension.



Figure 1: Pre and post treatment images of case no 2.

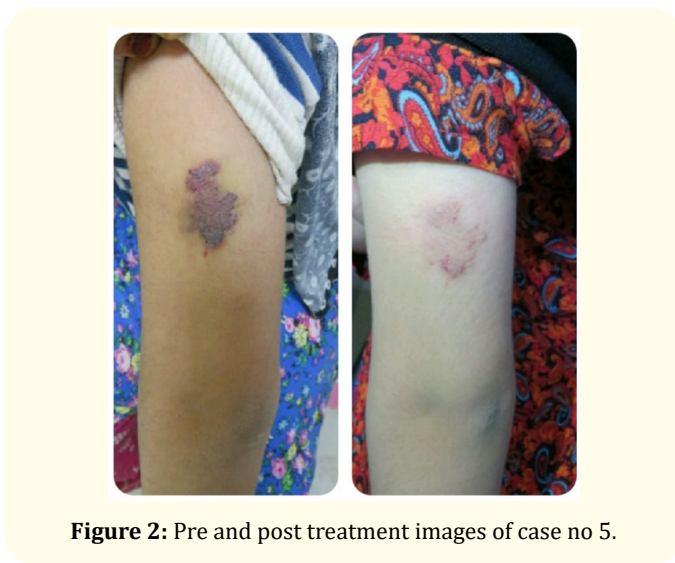


Figure 2: Pre and post treatment images of case no 5.

However, despite these limitations, the authors report a consistent response with no side effects, thus adding to the available literature on the use of Sildenafil as a useful addition to the management options for microcystic LM. Recurrence may occur requiring prolonged treatment.

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