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Experience in the Treatment of Lymphatic Vascular Malformations with Sirolimus, A Prospective Cohort Study in a Tertiary Hospital

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ABSTRACT

Introduction: Lymphatic vascular malformations (LVM), previously known as lymphangiomas, are rare congenital malformations, generally diagnosed in the first months of life. Although they are benign, they produce significant morbidity and sometimes mortality from compression. They have a poor response to existing treatments, so Sirolimus began to be used. The objective of this work is to describe the response of LVM patients treated with Sirolimus in a 3rd level hospital in Mexico.

Methodology: A prospective cohort-type study was carried out. Patients from birth to 5 years -old with LVM were included. Patients with immunosuppressive diseases or who received other prior treatment were excluded. Those who completed less than 6 months of treatment due to loss of follow-up were eliminated. Of the total of 32 patients: 62.5% were male and 37.5% female. LVMs were located in the neck 46.8%, head: 21.8%, thorax: 25%, abdomen: 3.1% and extremities: 3.13%. They were macrocystic 59.3%, mixed: 31.2% and microcystic 9.3%. Average age of diagnosis: 1.3 years -old, and size: 101 cc. All received treatment for at least 6 months and up to 1 year. Favorable responses were observed in 12 (63%) patients with macrocystic LVM, 3 (30%) mixed and 1 (33%) microcystic. There were no significant differences between the type of LVM, nor its anatomical location. 31% of the LVM had minor adverse events. The Sirolimus response was similar to a previous study with OK-432.

We find 50% of the lesions presented a decrease greater than 90%, and 84.4% of all lesions presented a decrease in size. Sirolimus is a tolerable treatment

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List of Abbreviations
HIMFG: Hospital Infantil de México Federico Gómez
ISSVA: International Society for the Study of Vascular Anomalies
LVM: Lymphatic Vascular Malformations
MRI: Magnetic Resonance Image
CT: Computed Tomography
US: Ultrasound
HIV: Human Immunodeficiency Virus

Introduction

Lymphatic malformations or lymphangiomas are congenital malformations of the lymphatic system and are composed of lymphatic channels and cystic spaces of variable size. The head and neck region are the most frequently affected site, but it can occur throughout the body. Although histologically benign, these lesions can spread to surrounding organs and sometimes cause life-threatening complications [1, 2].

The International Society for the Study of Vascular Anomalies (ISSVA) classifies lymphatic malformations as microcystic, macrocystic, and mixed [3, 4]. Lesions are usually classified as macrocystic (cysts greater than 1 cm), microcystic (when the cysts are smaller than 1 cm), or mixed (when it consists of macrocystic and microcystic cysts) [5]. This classification has clinical implications because microcystic lymphangiomas appear to be less sensitive to clinical treatments, such as sclerotherapy [1].

Diagnosis is straightforward in most cases. The tumors are characterized by the presence of being a soft, rubbery, compressible, septate and poorly defined mass. Imaging studies such as ultrasound, CT or Magnetic Resonance can help the

diagnosis, or they can be used to define the relationship of the lesion with the neighboring structures and help during the surgical act [2].

These lymphatic malformations usually not resolve spontaneously, which is why expectant treatment is not recommended [1]. The classic treatment of first choice for cystic type LVMs is excisional surgery. Drawbacks of such invasive procedures include insufficient cosmetic outcomes and vascular or nerve involvement as associated complications. Thus, in some cases leading to a partial excision and increase in relapses in up to 50% of cases [5, 6].

This has propelled the study of the use of products as sclerosing therapy agents, among them Sodium Morruate, Dextrose, Tetracycline, Doxycycline, Bleomycin, the alcoholic solution of Zein (Ethibloc®) and OK-432. Outside of OK-432 (Picibanil), the remaining agents have been found to cause perilesional fibrosis and thus complicate eventual surgical excision if required [2]. There are also agents such as Sirolimus, a drug used as an immunosuppressant, which is still being studied for the treatment of lymphatic malformations [7].

Sirolimus is currently a new drug for the treatment of lymphangiomas, which seems to have a promising response in vascular malformations that are very difficult to control.

However, there is currently little published bibliography and most of the existing ones are retrospective or with a few patients. Above all, in the population of our country. Therefore, the objective of this work is to describe the response and complications of patients with lymphatic vascular malformations treated with Sirolimus in our population, in a 3rd level pediatric Hospital that receives patients from various parts of the country.

Methodology

This is a prospective, longitudinal, observational and descriptive cohort study design. It started from June 2018 to January 2020 in Mexico City, completed in a 3rd level pediatric hospital that cares for patients mainly from the middle and lower social class.

We included all patients from birth and younger than 5 years -old with a diagnosis of LVM receiving treatment with Sirolimus.

We excluded patients with an active infection, immunosuppression (HIV, chronic steroid use), and patients who received prior treatments for the LVM.

Proposed elimination criteria: patients who completed less than 6 months of treatment with Sirolimus did not continue treatment in our hospital and could not follow up or patients who were diagnosed with another type of vascular malformation other than LVM, during our follow-up.

The final sample consisted of 32 patients with inclusion criteria and without exclusion or elimination criteria (Figure 1).

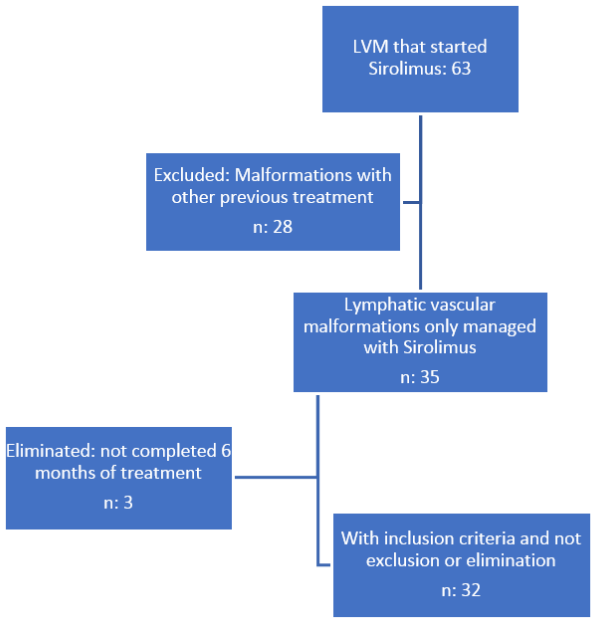

Figure 1: Patient Distribution Scheme

The variables studied were: a) Demographic variables, b) Anatomical location: head, neck, thorax, abdomen, extremities c) LVM size (qualitative type): 1. Macro: cysts greater than 1 cm, 2. Mixed: Composed of cysts where macrocystic and microcystic and 3. Micro: Composed of cysts smaller than 1 cm. The imaging studies were performed in our hospital by US. d) Response (qualitative): a) FAVORABLE: Greater than 90% decrease in LVM by US compared to the previous injury. b) PARTIAL: Decrease between 50-89%, c) UNFAVORABLE: Decrease of less than 50% and d) FAIL: Increase in volume of the LVM with US treatment compared to the previous injury. e) Adverse effects of treatment (qualitative): Adverse effects that occurred during treatment with Sirolimus.

The demographic statistics of lymphatic malformations are described, as well as the clinical characteristics of the patients before and after treatment and they are reported in pie charts and contingency tables, obtaining measures of central tendency that will include mean, median, mode, frequencies and percentages, later correlations are made frequencies and percentages. Correlations are made of the type of lymphatic malformations, anatomical location and response to treatment. Using the SPSS system, considering the value of $P < 0.05$ statistically significant.

Results

Of the total of 32 patients analyzed: 20 (62.5%) patients were male and 12 (37.5%) patients were female.

It was found that the LVM were anatomically found in the neck in 15 patients (46.88%), followed by thorax: 8 patients (25%), head: 7 patients (21.88%), abdomen: 1 patient (3.13%) and extremities: 1 patient (3.13%). (Figure 2).

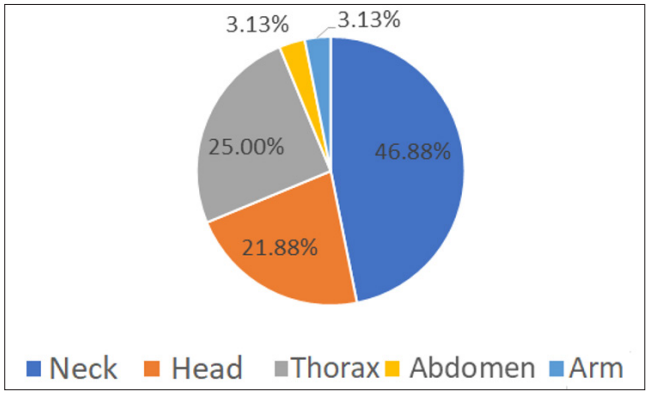

Figure 2: Anatomical distribution of MVL

The most common type of LVM was macrocystic with 19 patients (59.3%), followed by mixed with 10 patients (31.2%) and less common microcystic with 3 patients (9.3%). (Figure 3). The average age of diagnosis was 1.3 years (1 month – 4 years), and the average initial size of the LVM in volume: 101 cc (12.5 cc – 400 cc). All lymphangiomas received treatment for at least 6 months of management and a maximum of 1 year of treatment.

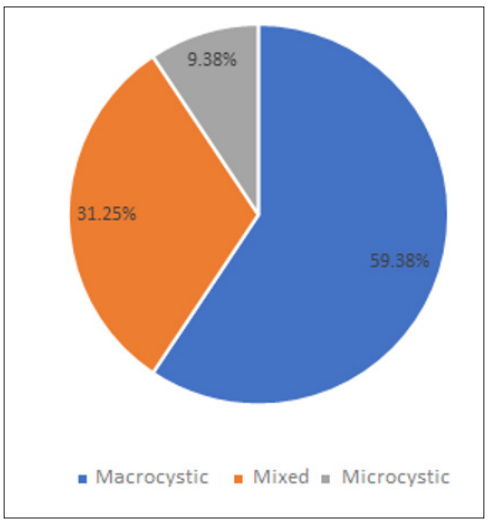

Figure 3: LVM type Distribution

In some patients, extended studies were required for full assessment of the LVM. The extended studies included MRI or CT imaging, which help to see if the LVM involves a cavity, such as the neck, chest and abdomen. We used extensive imaging in 4 patients (12.5%). The remaining 28 patients (87.5%) only required US to study the LVM in question.

Of the 32 patients with LVM studied favorable responses were observed in 12 patients with macrocystic 3 patients with mixed and 1 patient with microcystic LVM. There were no statistical differences in response rates in regards to the type of LVM or the anatomic location. Most of the LVM had a decrease in size.

Of the patients who received Sirolimus, 31% experienced side effects. A total of 15 side effects are reported among 10 patients. The side effects were presented as follows: 56.25% presented LVM infection, 25% presented some respiratory tract infection, 6.25% presented gastrointestinal infections, 6.25% presented hemorrhage and 6.25% presented metabolic laboratory abnormalities.

Discussion

In our study we were able to observe that in relation to gender, LVMs presented with a higher frequency in males, similarly to other studies, without finding a significant difference with most studies [1,2,6,8].

LVMs can appear anywhere in the body. Regarding the location in our investigation, the vast majority were located in the head and neck region, followed by the thorax. This agrees with the reports by Okazaki and Gallego who mention the head and neck as the main location, as well as other large studies [1, 2, 4, 8].

Most of the reported studies use the macrocystic, mixed and microcystic classification according to the size of the cyst it presents. Macrocystic type malformations were found more frequently, followed by mixed and finally microcystic, results very similar to other investigations where the macrocystic forms are reported as the most common [1, 2, 4, 6, 8].

In the results obtained in our research we could observe that the average age at which the type of injury was diagnosed was 1.3 years. This is highly variable across studies [1, 2, 4, 8]. This is because, although it has already been described that 60% of these malformations can be observed on physical examination at birth, the majority of these pathologies are discovered until later. This is depending on the size of the lesion; the average initial size of the LVM in volume in our study was: 101 cc. This size is highly variable in all studies. Time of diagnosis also depends on the anatomical site involved, the expertise of hospital or health service where the patient was born and the training of the personnel where follow ups were are performed [1, 5, 6, 8].

The imaging studies that we used for diagnosis were mostly US. This is because it is very precise in its methodology for diagnostic support and its classification according to the size of the cyst, which is why it is the study that we use the most. They were performed and interpreted by a single pediatric radiologist with extensive experience in lymphangiomas, in order to reduce operator-dependent bias. However, the use of MRI and CT can also was used for extension studies, especially in LVM of the neck, chest and abdomen. We use them in 12.5% of patients. These studies can also be used for diagnosis; however, they have the disadvantage of being more expensive, and in the case of MRI, sedation is required, and of CT, which also sometimes requires sedation, the patient is exposed to radiation [9, 10, 11].

Of the patients who received Sirolimus, 31% had a side effect, A total of 15 side effects were reported among 10 patients. Side effects are difficult to measure and compare. In our study, 3 patients presented altered Complete blood count and 2 presented metabolic tests with alterations. In addition, because it is an immunosuppressive treatment, we include all infections that occurred during the treatment time with Sirolimus. It is likely that some infections were not directly caused by treatment. Our complications differ from those reported in most bibliographic references, since most of them only report alterations measured by laboratory tests such as bone marrow and metabolic toxicity [12, 13, 14, 15].

In our study of the 32 patients with LVM studied, favorable responses were observed in 12 (63%) patients with macrocystic LVM, 3 (30%) patients with mixed and 1 (33%) patient with microcystic. There were no statistical differences in response rates in regards to the type of LVM or the anatomic location. However, there was a favorable clinical response. It is worth emphasizing

that although only 50% of the lesions were successfully cured, the vast majority of the LVM (84.4%) had a decrease in size.

In the literature, different classifications are used to assess the response to treatment, so the way of defining success and an adequate response varies. However, we decided to use the response classification according to a study previously carried out in the our institutions with OK-432, this in order to be able to compare the results between both studies. This study define success as a, reduction of more than 90% of the MVL, and this because both the family member and the patient feel satisfied with this result according to the study of Dr. Javier Leal, Dr. Eduardo Bracho and Dr. Roberto Dávila. Their study was similar to ours, a prospective, longitudinal, observational and analytical cohort. All patients diagnosed with MVL between the years 2014-2016 were included. They excluded patients with previous treatment or not applied by US [16].

There was a total of 27 patients in the study with OK-432, with a success rate of 59.2%, comparable with our study with Sirolimus of 50% [16]. (Table 1)

Table 1: Comparison of OK-432 vs Sirolimus result

Response	Percentage of patients treated with OK-432	Percentage of patients treated with Sirolimus
Decrease more than 90%	59.2%	50%
Decrease between 89% - 50%	22.2 %	9.4%
Decrease more than del 50%	11.1%	25%
Failure: no decrease.	7.4%	15.6%

We only measure the decrease in size objectively with imaging studies, however, some patients, regardless of the percentage of decrease in size, present improvement due to the decrease in symptoms, for example: those of the tongue have less discomfort to eat, a patient with lymphangioma in the eye with improvement of visual disturbances.

Within the limitations of the study, the researchers consider that the size of the sample would have to be increased to be able to find in some aspects of response and localization results with a statistically significant p value. Another limitation is that the ideal study for the follow-up of LVM to see the response for research purposes is MRI, however it is an expensive study, not always available and that also requires sedation, so the treatment controls were decided to perform with less invasive studies such as the US.

Conclusions

The use of Sirolimus is an alternative for the management of LVMs. Since the success or favorable response in the treatment of LVM is 50% and 84.4% of the patients to whom it was applied presented a decrease in size. It is also a tolerable treatment for the management of LVM.

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