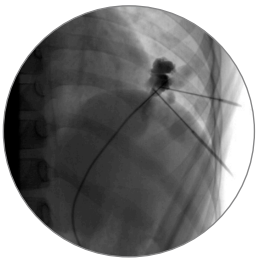

Experience In the Management of Macrocystic Lymphatic Malformations with Alcohol and Microcystic Malformations with Bleomycin

Experiencia en el manejo de malformaciones linfáticas macroquísticas con alcohol y microquísticas con bleomicina

Key words (MeSH)
Lymphatic diseases
Sclerotherapy
Magnetic resonance imaging

Palabras clave (DeCS)
Enfermedades linfáticas
Escleroterapia
Imagen por resonancia magnética

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DOI: https://doi.org/10.53903/01212095.124

Summary

Lymphatic malformations are rare slow and low flow abnormalities that occur in 1 of 6,000 to 1 in 16,000 live newborns. Cystic malformations are classified according to their size as macrocystic, microcystic, or mixed. This classification has an impact on treatment and prognosis. Macrocystic lymphatic malformations have a better response to treatment, while microcystic malformations are difficult to treat and frequently recur. The objective of this study is to describe the results obtained in patients with macro and microcystic lymphatic malformations who underwent sclerotherapy using alcohol and Bleomycin, respectively. A descriptive study of patients with lymphatic malformations treated in the Radiology Service of the National Institute of Pediatrics was carried out during the period from 2014 to 2016. Thirty-eight patients were included, 24 with macrocystic, 10 microcystic and 4 mixed lesions. 68% were treated with alcohol and 32% of the patients were treated with Bleomycin. The treatment showed excellent resolution in 5 patients, 25 patients had a lesion size reduction between 50 and 90%, 13% had a poor response, and only 7% had growth despite sclerosing treatment. From the above we conclude that percutaneous treatment is safe, reduces the size of the lesions and there are few reported complications. It could be used as initial treatment before considering surgery.

Resumen

Las malformaciones linfáticas son anomalías raras de flujo lento y bajo que se presentan en 1 de 6.000 a 1 en 16.000 recién nacidos vivos. Las malformaciones quísticas se clasifican según su tamaño en macroquísticas, microquísticas o mixtas. Esta clasificación tiene impacto sobre el tratamiento y el pronóstico. Las malformaciones linfáticas macroquísticas tienen mejor respuesta al tratamiento, mientras que las microquísticas son difíciles de tratar y con frecuencia recidivan. El objetivo de este trabajo es describir los resultados obtenidos en pacientes con malformaciones linfáticas macro y microquísticas intervenidos con escleroterapia utilizando alcohol y bleomicina, respectivamente. Se realizó un estudio descriptivo de pacientes con malformaciones linfáticas tratadas en el Servicio de Radiología. Se incluyeron 38 pacientes, de los cuales 24 tenían lesiones macroquísticas, 10, microquísticas y 4, mixtas. El 68 % fueron tratados con alcohol y el 32 % con bleomicina. El tratamiento mostró una resolución excelente en 5 pacientes, 25 tuvieron reducción del tamaño de la lesión entre 50 y 90 %, 13 % mostró una respuesta pobre, y solo en un 7 % hubo crecimiento, a pesar del tratamiento esclerosante. De lo anterior se concluye que el tratamiento percutáneo es seguro, reduce el tamaño de las lesiones y hay pocas complicaciones informadas. Se podría utilizar como tratamiento inicial, antes de considerar una cirugía.

1. Introduction

Lymphatic malformations (LM) are rare anomalies with slow and low flow. They occur in 1 in 6,000 to 16,000 live newborns and manifest clinically as skin-colored, soft, reluctant, subcutaneous neoformations with no visible venous tracts. They can be located anywhere, although they predominate in the head and neck. They are usually asymptomatic; however, when

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they affect the upper airways they may obstruct breathing. They appear from birth, but may manifest and become visible at a later age when associated with upper airway infections, in the case of those located in the neck, or trauma, when they are in other locations.

LM are classified as macrocystic, microcystic or mixed (1, 2). This classification determines the treatment and prognosis. Macrocystic malformations have better response to treatment, mainly treated with sclerosis, with percutaneous application of absolute alcohol. Microcystic lesions are difficult to treat, may recur and intralesional application of bleomycin has proven to be useful in their management (3-5).

Percutaneous treatment with sclerosing substances has shown better results than surgical procedures in this type of lesions, since surgical resection causes greater recurrence (5, 6).

Therefore, it is important to know the experience on this type of lesions and their outcome with percutaneous treatment.

2. Study Design

A retrospective study was conducted for the period from January 1, 2014 to June 30, 2016.

The target population were pediatric patients with clinical and imaging diagnosis of macrocystic, microcystic or mixed lymphatic malformation (LM), seen in the Radiology Department by percutaneous procedure and application of alcohol or bleomycin.

Patients registered in the statistical book of percutaneous procedures performed in the Radiology Department were included. Eighty-six patients with lymphatic malformations were selected from the interventional radiologist's report. 41 patients were excluded when ultrasound or resonance imaging diagnosed venous malformations or if the patients had previous surgical treatment. Data were obtained from 45 patients who met the inclusion criteria, which were subjected to comparison with the database of the Dermatology Service; as a result, 7 patients were excluded for having clinical features of venous malformations or scarring at the site of the malformation. Finally, the sample consisted of 38 patients.

The inclusion criteria were: patients with cystic lymphatic malformations of any size, of both sexes, under 18 years of age, with imaging studies from the Instituto Nacional de Pediatría (INP), with sclerotherapy in the Radiology Service, with alcohol or bleomycin, and registered in the Service's database.

The exclusion criteria were: patients who had undergone surgery, patients treated with sclerosants other than alcohol or bleomycin, patients whose sclerosing treatment put their lives at risk due to the location of the malformation, and those whose treatment put the functionality of the organ at risk.

The studies had to include ultrasound, nuclear magnetic resonance or both. Ultrasound images were used to calculate the volume of the lesion before and after the procedure; subsequently, the percentage reduction of the lesion was determined to evaluate its response. Ultrasonographic control was performed between 60 and 120 days after the procedure.

Macrocystic lesions were treated with percutaneous application of alcohol and microcystic lesions with bleomycin. Mixed lesions were treated with both agents.

The procedures were performed by two pediatric interventional radiologists with experience in this type of treatment. Ultrasound guidance and later fluoroscopic guidance were used to locate the lesions; to demonstrate the absence of communication between the cystic spaces and the vascular structures, intralesional contrast medium was initially instilled to determine the approximate volume, and 10% of what was indicated by the contrast medium or of the aspirated volume was placed without exceeding the maximum dose of the sclerosant. The procedure was always performed under general anesthesia. For the puncture 25 G needles were used with microset or 22 G helmets. One month after the procedure a control with ultrasound (US) was performed and a new dose was applied, if the lesion still measured more than 1 cm. No routine prophylactic antibiotic was administered. Management was ambulatory, with discharge 6 hours after the procedure.

In microcystic lesions the contents were not aspirated. Due to the difficulty in cannulating a microcystic lesion, the drug was only administered in one or two regions according to its extension, based on the volume of the lesion measured by ultrasound. A volume corresponding to 10% of the lesion was administered.

Data were recorded in an Excel and Google Drive database and analyzed in the statistical program STATA.

Response to treatment was measured based on the decrease in lesion size. It was considered excellent when there was resolution between 91 % and 100 %; good, when resolution was between 50 % and 90 %; poor, when less than 50 % and bad, when there was no change or lesion increased.

3. Analysis and measurement of variables

This study describes the variables of frequency of sex, age, type of lesion, location and percentage of lesion reduction according to the type of LM and the drug used, with a statistical analysis based on absolute and relative frequencies.

4. Results

4.1. Sex

The distribution of the lymphatic malformations was similar in both sexes: 54 % of the macrocystic malformations were in males, 46 % in females. Of the 10 microcystic lymphatic malformations, 60% were in females. Mixed lymphatic malformations were the same for both sexes.

4.2. Age at which treatment was applied

Although lymphatic malformations are present from birth, in many cases the age at which they manifest clinically is variable. In this study, 53% were treated before the age of one year and 77% before the age of 5 years (Table 1).

Table 1. Age at treatment

Age (years)	Number	%
<1	20	53
1-4	9	24
5-9	6	16
= o > 0,10	3	7
Total	38	100

4.3. Anatomical location of the lymphatic malformations

The frequency distribution in Table 2 shows that 56% (21 cases) of the lymphatic malformations are located in the face and neck: 9 (24%) in the face, 12 (32%) in the neck, 10 (26%) in the thorax, 3 (8%) in the abdomen and 4 (10%) in the extremities.

Table 2. Anatomical localization of the lymphatic malformations

Location	Number	%
Face	9	24
Neck	12	32
Chest	10	26
Abdomen	3	8
Extremities	4	10
Total	38	100

4.4. Type of lymphatic malformation

Macrocystic malformations are the most frequent, followed by microcystic and mixed malformations. In some cases, macrocystic malformations after sclerosing treatment may behave as mixed. In this study, 24 (63%) were macrocystic, 10 (26%) were microcystic and 4 (11%) were mixed.

Magnetic resonance imaging (MRI) was used in some cases as an initial complement to evaluate the extent of the lesion and to support therapeutic planning. US was performed in 74% of the cases and MRI in 26%. Ultrasound provided more information on the dimensions of the lesion and its extension, given that most of them are irregular, and was used in diagnosis, therapeutic guidance and post-treatment control (Figures 1, 2 and 3). Of the 10 MRI studies, 4 cases corresponded to macrocystic, 3 to microcystic and 3 to mixed malformations.

4.5. Treatment

Percutaneous treatment with bleomycin and/or alcohol was used in all cases. Alcohol was used in patients with macrocystic lymphatic malformations, or when they were mixed and their main component was large cysts. The dose administered was up to a maximum of 1 cm3 per kilogram of weight; in patients weighing less than 10 kg, in whom the dose should be very low, 1 to 2 cm3 were administered, due to the risk of necrosis, because of a smaller body surface area.

Bleomycin was used in microcystic lesions or when the main component was fibrous (Figure 4). Its 15 U (Units) presentation was diluted in 8 cm3 of normal saline (NS) and 6 cm3 of water-soluble contrast medium, to obtain 1 U/cm3. A maximum of 1 cm3/kg per session was administered without exceeding 15 U per session. The procedure was performed under general anesthesia and no routine chest X-ray was taken, which was foreseen if the patient manifested any respiratory symptoms, which did not occur in our patients.

Most of the mixed malformations were treated with alcohol initially, to manage the macrocystic component, and with bleomycin later, to manage the microcystic component. In 26 cases (68%), the sclerosing treatment used was alcohol, and in 12 cases (32%), bleomycin.

The response to treatment was good in 25 patients (66%), excellent in 5 (13%), poor in 5 (13%) and bad in 3 (7%).

The patients who had the best response to treatment had a macrocystic lymphatic malformation located in the neck, and of these 2 were completely cured.

The 5 cases that had a response of less than 50 % were located 3 of them in the thorax and 2 in the face. Four received sclerotherapy with absolute alcohol and one with bleomycin. Three received surgical treatment after sclerotherapy, because they did not achieve the expected results.

Of the cases that worsened, one had a microcystic malformation in the right axillary region and despite sclerotherapy its volume increased (Figure 5). The second was a microcystic lymphatic malformation on the tongue and the third located in the superciliary arch, also microcystic. All three received initial treatment with bleomycin and due to the increase in size were subjected to surgical treatment.

5. Discussion

The classification of vascular anomalies proposed by Mulliken and Glowacki in 1982 is based on histopathological features, separated into two major groups. This system was adopted by the International Society for the Study of Anomalies (ISSVA), which divides them into vasoproliferative neoplasms and vascular malformations (6-9). Terms such as lymphangioma, hemolymphangioma, and cystic hygroma were eliminated and replaced by lymphatic malformations.

The classification of lymphatic malformations is divided into common (cystic), syndromic and primary lymphedema. The former, in turn, are subdivided according to the size of the cysts -macrocystic, if the cysts are larger than 2 cm, microcystic if they are smaller than 2 cm, or mixed if they are of various sizes (9-11)-. These cysts may be filled with proteinaceous material and eosinophils. Other less common types are generalized lymphatic anomaly, Gorham-Stout disease, canalicular lymphatic malformation and primary lymphedema (6, 11-14).

Lymphatic malformations are mainly located in the face and neck, followed by the extremities, trunk, internal organs, bones and muscle. It has been documented that between 48% and 75% of lymphatic malformations are found in the head and neck, of which the majority are macrocystic (15).

There is an increased incidence if they are associated with Turner syndrome (9, 14, 16-19).

Approximately 25% of lymphatic malformations occur in the axilla. They rarely affect the intestinal wall or the lung, causing severe hypoproteinemia, volume loss, ascites and pleural fluid (9, 14, 16, 20).

Lymphatic malformation may not be evident at birth and may be observed later in childhood or adolescence associated with trauma or infection, usually of the upper airways; they are present at birth in 65% of cases and around 2 years of age in 80 to 90%. There is no predilection for sex or ethnicity. The most frequent symptoms are well delimited increase in volume, with an unaltered skin, smooth surface, which causes deformity of the region. Lesions in the neck may cause vascular or airway compression, dysphagia or symptoms of nerve compression (21, 22). Characteristically, this type of lesions grow with the child; when the lymphatic malformation is associated with soft tissue hypertrophy -as in Klipell-Trenaunay syndrome-, dilatation of superficial cutaneous lymphatics characterized by small translucent or purplish millimetric vesicles caused by increased pressure of deeper lymphatics can be observed in the skin. Giant lesions may present with water loss, hypoproteinemia or both. If the lesion is associated with infection, it presents with rapid growth and/or internal bleeding.

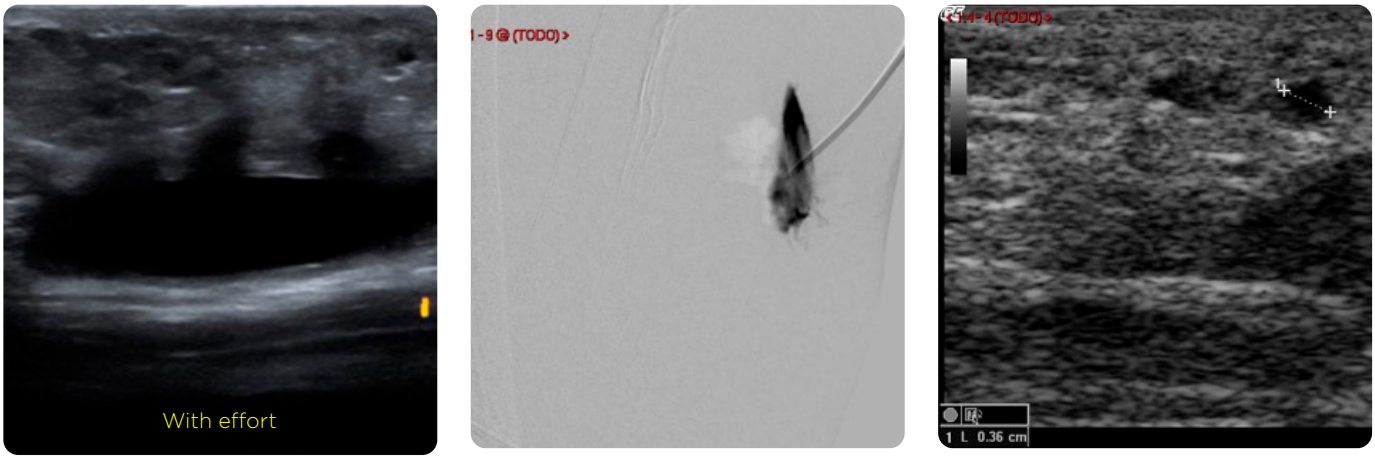


Figure 1. a) Macrocystic lymphatic malformation in the right thigh: high frequency ultrasound, an anechoic lesion with well-defined walls, soft consistency, which increases in size with Valsalva maneuvers. b) Injection with alcohol and contrast medium of the macrocystic malformation for sclerotherapy, under fluoroscopic vision. c) Significant decrease of the macrocystic lymphatic malformation, a small residual cyst was found.

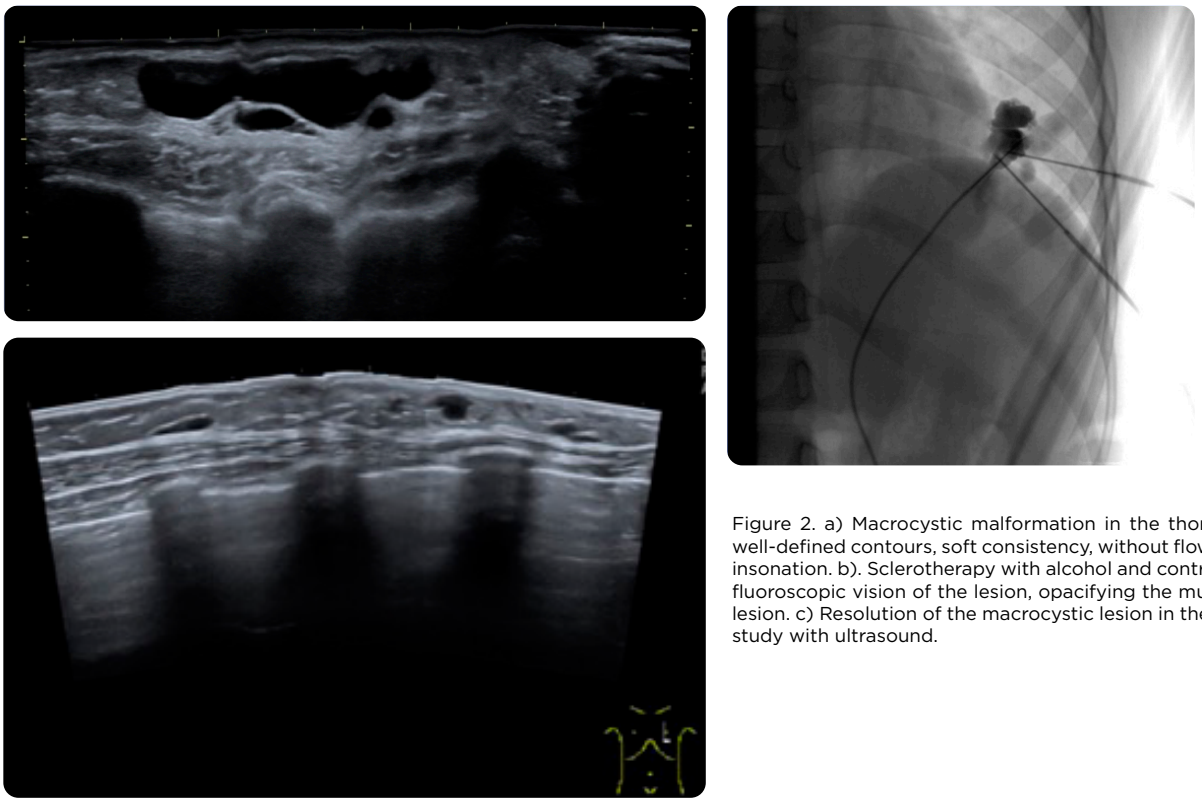
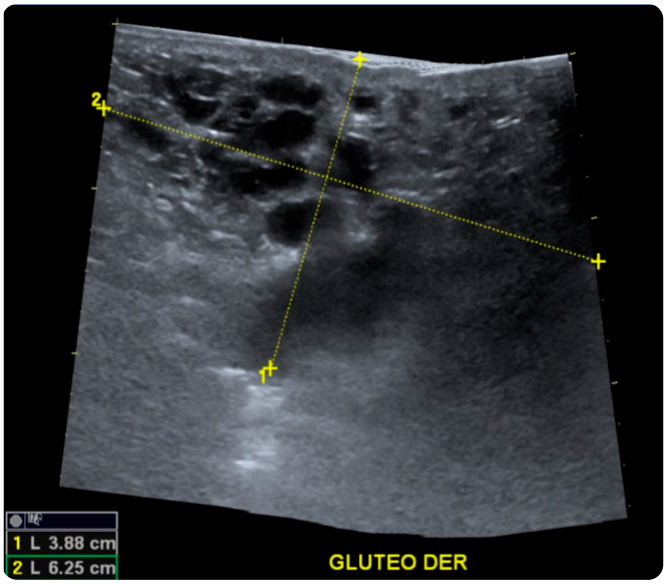
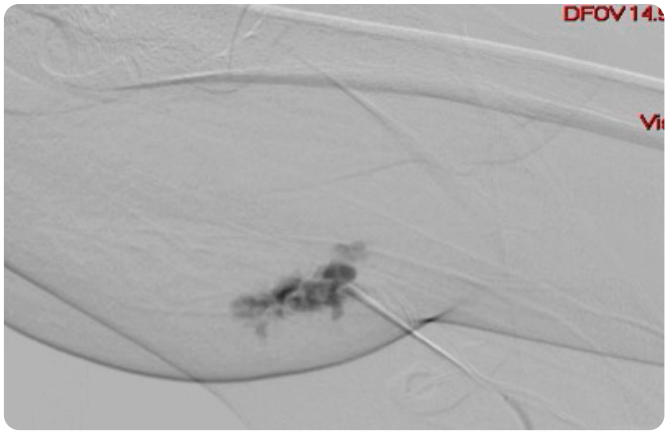


Figure 2. a) Macrocystic malformation in the thorax, oval image of well-defined contours, soft consistency, without flow on color Doppler insonation. b). Sclerotherapy with alcohol and contrast medium under fluoroscopic vision of the lesion, opacifying the multilobulated cystic lesion. c) Resolution of the macrocystic lesion in the thorax, in control study with ultrasound.





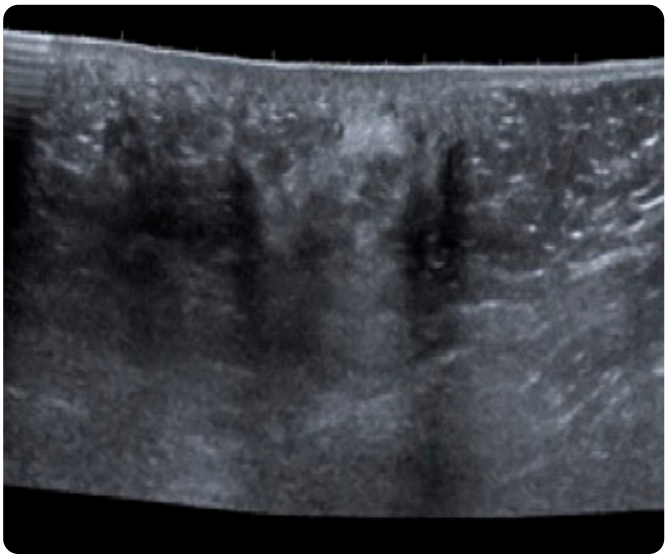
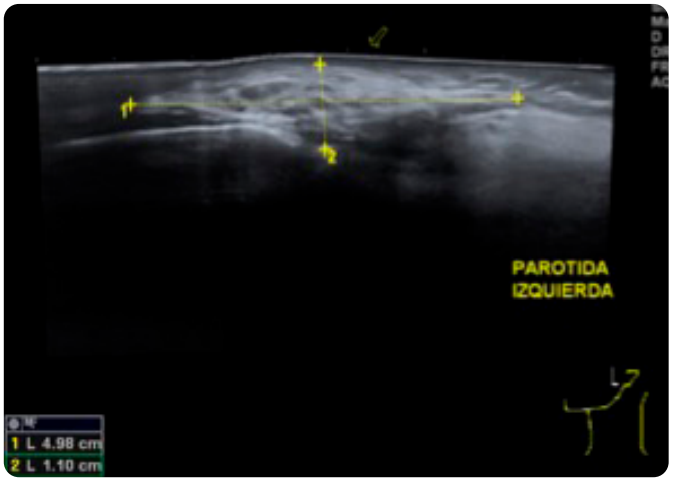


Figure 3. a) Mixed lymphatic malformation located in the right buttock. Linear ultrasound identifies an image with multiple cysts of variable size, with fine septa and a fibrous component. b) Sclerotherapy with alcohol of the lesion located in the buttock under fluoroscopic vision. c) Noticeable improvement of the lesion, with disappearance of the cystic lesions.



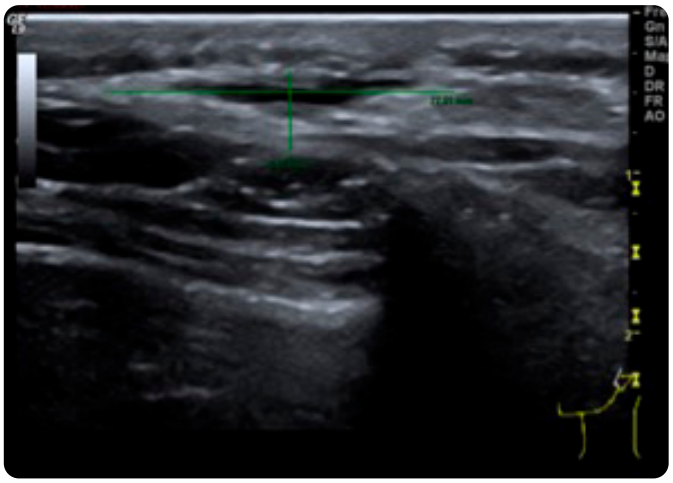


Figure 4. a). Microcystic lymphatic malformation in the face, ultrasound with high resolution transducer: echogenic lesion, with well-defined borders in left parotid, with small cysts without flow on color Doppler examination, of soft consistency. b) Subsequent sclerotherapy with bleomycin: reduction in the size of microcysts, with a residual anechoic area.

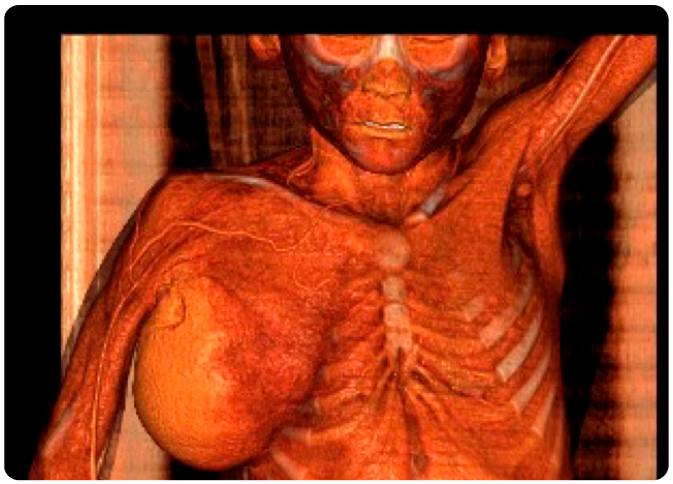


Figure 5. 3D reconstruction: microcystic lymphatic malformation, no improvement with sclerotherapy with bleomycin, three sessions and growth of the lesion despite the intervention.

When ultrasound is performed and the lesion is compressed with the transducer, a soft, partially depressible and reluctant lesion is observed, with internal septa and no flow in its interior; in contrast to arterial malformations, which have high flow and venous malformations, which have low flow. The macrocystic malformation can be single, with production of posterior acoustic reinforcement, or have mobile echoes in its interior in relation to detritus or hemorrhage. The septa are thin, non-vascularized, there may be scant peripheral vascularity, except if infected, in which case there is hypervascularity. Unlike the venous malformation that can have great changes with respiration, changes of position and can be totally compressed, the lymphatic malformation does not have this characteristic and is only partially compressed.

In microcystic lymphatic malformations, small cysts with numerous septa are observed. Because they are so small, microcysts are sometimes difficult to identify, but they produce posterior acoustic enhancement.

Computed tomography (CT) and MRI better delineate the extent and show their relationship to other anatomical structures more clearly than US. CT shows homogeneous multicystic lesions with low attenuation close to the density of the fluid; it also helps to visualize whether there is bony extension and is useful for surgical planning. When the lesion becomes infected, there is evidence of thickening of the walls of the cystic image with increased inner density or reinforcement of the lesion (15, 23, 24).

In MRI, depending on the hematic or proteinaceous content, the image is homogeneous or heterogeneous with different degrees of intensity in T1 according to its component. In T2-weighted images they are markedly hyperintense, commonly with a liquid level within the cyst, mainly in macrocystic lymphatic malformations, and with a solid component in microcystic ones. After the administration of contrast medium there is no enhancement, or it is minimal and localized in a ring or peripheral, or distributed in the septa (25-27).

The management of lymphatic malformations is aimed at maintaining regional functionality, reducing symptoms and preserving esthetic integrity. Management should be performed by an interdisciplinary group of specialists including a dermatologist, a pediatric surgeon, a surgical oncologist, a plastic surgeon and an interventional radiologist. Specialists may also be integrated according to the topography of the malformation; thus, if it is located in the orbit, it should be assessed by an ophthalmologist; in a limb with limb deformity, by an orthopedist, etc.

In general, the patient comes for symptomatic lesions that cause pain, bleeding, functional damage and/or deformity. Surgical management has not proven to be beneficial and is only reserved for small lesions. This is because surgery can cause fibrosis and, consequently, increased pressure that generates dilatation in other lymphatics. Patients at risk of upper airway compression should be treated in different stages and may sometimes require tracheostomy prior to sclerotherapy if it is not possible to ensure airway patency with endotracheal intubation.

The application of the sclerosant should be performed under general anesthesia, with image-guided guidance which can be ultrasound, fluoroscopy or both; the lesion is punctured with a 23 to 25 G needle and a certain amount of the content is aspirated so that an empty space is formed in which the same amount of the sclerosing agent is injected. As a secondary effect, inflammation of the lymphatic walls is produced, which will later fuse. It is common to observe soft tissue edema that lasts approximately 7 days. Undesirable side effects or complications are superficial skin necrosis, as well as neuropathy when a nerve pathway is damaged. The best results are observed in macrocystic lymphatic malformations, since it is easier to extract the content of a large chamber than of several very small ones.

Lymphatic malformations are present from birth in most cases, but may become obvious later. In the literature it is described that 80 % to 90 % become evident before 2 years of age. It does not have prevalence by sex, which was evidenced in this work (28, 29); neither is a significant difference seen between the type of lymphatic malformation and sex. Although a study performed in China with 65 patients showed a ratio of 1.7 to 1 (male to female), in the present study the ratio was 1:1 (30); on the contrary, in a study performed at the University of Oslo it was predominant in the female sex: 37 males and 48 females (31).

Most of the lesions are macrocystic, in different studies a frequency between 49 and 52 % is documented; in this study 63 % were also macrocystic, 26 % were microcystic and 11 % were mixed.

In different articles there is talk of a presentation in the head and neck between 48 and 75%, 56% of the patients studied here had this location (32-34). Most of them are submandibular or diffusely located in the neck, with extension to the mediastinum. Malformations in the neck have a good response to treatment. In this study all patients showed a favorable response and three of them had a total cure, of these, two were macrocystic lymphatic malformations and one was mixed.

US and MRI were used for diagnosis. Ultrasound has the advantage that it is not necessary to sedate the patient and it was performed prior to the procedure, but with the limitation that in deep lesions or those larger than 10 cm, it was difficult to obtain the visual field to cover the whole image. MRI, on the other hand, provides an adequate definition of the lesion, as well as its extension, which facilitated surgical treatment; likewise, post-treatment control was much more objective, since it was possible to observe the lesion in extension and its reduction. However, the disadvantages of MRI are that its high cost of use increases the value of the study for the patient, it is not widely available and requires general sedation in patients under 5 years of age. The different studies do not go into much detail about the imaging modality or post-surgical controls (35-37).

In the work performed by Yang et al. with 65 patients in whom they applied bleomycin in macrocystic, microcystic and mixed lymphatic malformations, they also used ultrasound guidance to locate the puncture site and repeated the procedure every 2 to 3 weeks, regardless of the size of the lesion. In the patients studied here, a new procedure was performed at 6 weeks, only if the cavity was larger than 1 cm; 32 patients received more than one sclerotherapy session; 5 patients improved with one sclerotherapy session, and 1 of those who received 6 sessions worsened, despite management.

The lesions that had the worst response were located in the thorax and it is noteworthy that when they started their sclerotherapy treatment they were larger than 10 cm; on the other hand, small lesions had a good response in the thorax. It would be important to determine if in future studies this type of behavior is reproducible and if another type of initial management can be provided to these patients, since sclerosing treatment would not be useful for them.

Among the symptoms associated with lymphatic vascular malformations, we described facial paralysis, xerophthalmia, palpebral ptosis, pelvic limb dysmetry -apparently the pelvic limb affected by the malformation was larger-. The time at which the lesion appeared was not specified, so it could not be determined whether it was secondary to sclerotherapy or to the growth of the malformation prior to treatment. Seromas were the only complication described associated with the procedure in the present study.

On many occasions, and in the experience of the interdisciplinary group, lesions recurred or appeared on the contralateral side where they had previously received sclerosing treatment; in the study this characteristic was not evident, because follow-up was only done for two years, but in an extension of the study it could be determined if in at least ten years this characteristic could be documented, as well as the type of lymphatic malformation and the characteristics in terms of size, location and age at the beginning of treatment, to provide better care to the patients.

6. Conclusions

Lymphatic malformations are complex entities with physical sequelae and distortion of the anatomy, which can alter the psychological development and affect the function of the compromised organ, so early and multidisciplinary treatment is necessary to provide the patient with the least sequelae for their pathology. Percutaneous treatment is effective and reduces lesions in size, it is safe and with few complications described, so it should be considered as an initial approach before surgery.

Acknowledgments

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Received for evaluation: May 3, 2020
Accepted for publication: January 10, 2021