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The VASCERN-VASCA working group diagnostic and management pathways for lymphatic malformations

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ABSTRACT

Lymphatic malformations (LMs) are developmental defects of lymphatic vessels. LMs are histologically benign lesions, however, due to localization, size, and unexpected swelling, they may cause serious complications that threaten vital functions such as compression of the airways. A large swelling of the face or neck may also be disfiguring and thus constitute a psychological strain for patients and their families. LMs are also highly immunologically reactive, and are prone to recurrent infections and inflammation causing pain as well as chronic oozing wounds.

The European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN) is dedicated to gathering the best expertise in Europe. There are only few available guidelines on management and follow up of LMs, which commonly focus on very specific situations, such as head and neck LM (Zhou et al., 2011). It is still unclear, what constitutes an indication for treatment of LMs and how to follow up the patients. The Vascular Anomalies Working Group (VASCA-WG) of VASCERN decided to develop a diagnostic and management pathway for the management of LMs with a Nominal Group Technique (NGT), a well-established, structured, multistep, facilitated group meeting technique used to generate consensus statements. The pathway was drawn following 2 face-to-face meetings and multiple web meetings to facilitate discussion, and by mail to avoid the influence of most authoritative members.

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The VASCA-WG has produced this opinion statement reflecting strategies developed by experts and patient representatives on how to approach patients with lymphatic malformations in a practical manner; we present an algorithmic view of the results of our work.

1. Introduction

Lymphatic malformations (LM) are rare congenital anomalies of the lymphatic system (Figs. 1–3). They may be macrocystic, microcystic or mixed and can occur anywhere in the body although most frequently in the head and neck region. LMs may be part of other vascular anomalies associated with overgrowth syndromes such as CLOVES and Klippel-Trenaunay syndrome. LM can be associated with serious morbidity such as swelling, obstruction of vital structures, deformity, pain, infection, and lymphatic leakage. Because of the rare character and serious morbidity, the care of patients with LM requires specific knowledge. In general, these patients should be managed in multidisciplinary centers of expertise. There are only few available guidelines on management and follow up of LMs, which commonly focus on very specific situations, such as head and neck LM (Zhou et al., 2011).

At the European level, selected centers of expertise are united in European Reference Networks (ERNs), all with the aim of bundling knowledge on rare diseases and taking better care of patients through collaboration. VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases, is dedicated to gathering the best European expertise to help patients with rare vascular diseases (an estimated 1.3 million concerned). There are five separate working groups to focus on arterial diseases (affecting main arteries from aorta to small arteries), hereditary hemorrhagic telangiectasia, primary and pediatric lymphoedema, and vascular malformations. VASCERN currently consists of 31 highly specialized multidisciplinary Healthcare Providers (HCPs) from 11 EU Member States and of multiple European Patient Organizations, and is coordinated in Paris, France.

2. Patients and methods

The Vascular Anomalies Working Group (VASCA-WG) is composed by a multidisciplinary panel of experts (dermatologists, geneticists, interventional radiologists, pediatricians, pediatric surgeons, plastic surgeons, vascular surgeons, pediatric hematologists and oncologists) and patient representatives. They represent national HCPs endorsed by their governments as board members of the European Reference Network for Rare Multisystemic Vascular Diseases.

Based on the principle that decisions from a group of experts are better than from single experts, the VASCA-WG decided to draw the patient pathway for lymphatic malformations (LM) with a nominal group technique (NGT), a well-established, structured, multistep, facilitated, group meeting technique used to generate consensus documents.

The pathway has been drawn within 2 face-to-face meetings in May and November 2019 to facilitate discussion and by WEBEX meetings during 2020 and by mail to avoid group dynamics. Two facilitators have been identified: one to purpose initial discussion points and draw the pathway and another to chair the discussion. A pediatric surgeon was chosen within the group of experts as first facilitator due to his particular experience on the management of LMs. Further decision-points were proposed by the group and best choices have been discussed within the panel of experts. Conflicting points were further discussed until a conclusion was agreed by the European multidisciplinary team. The chair of the group promoted inputs from all members, summarized the opinions and the reasons for the choices, identifying common ground. No limits of time have been set to reach consensus. After the first meeting the document has been circulated by mail in the WG to collect further peer comments. A final face-to face meeting was organized in order to definitely validate the pathway.

2.1. What are lymphatic malformations?

LMs are defined as developmental defects caused by defective lymphangiogenesis (Zadvinskis et al., 1992). The incidence of these

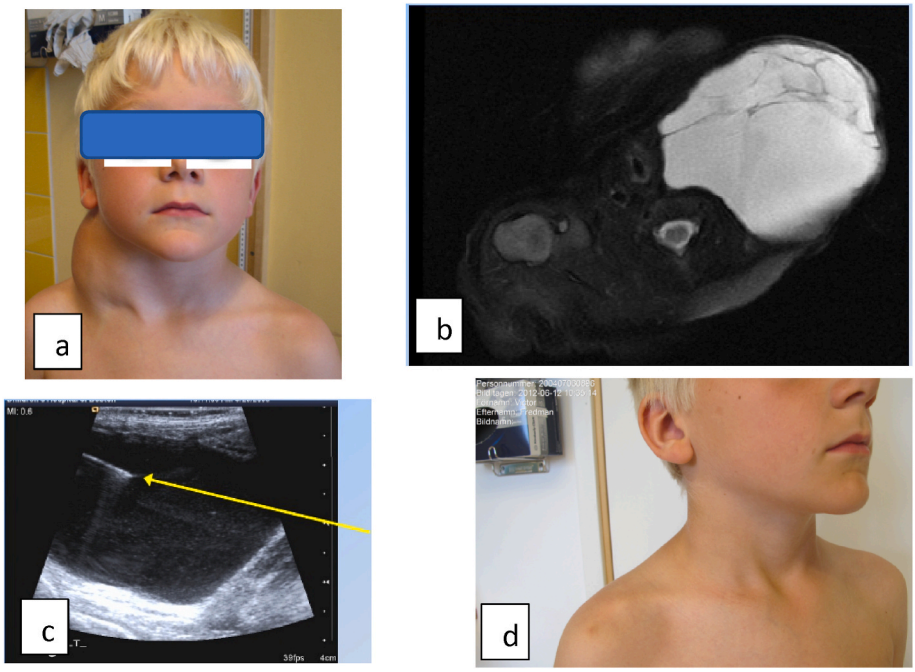

Fig. 1. Macrocystic LM: **a** clinical feature, **b** T2-weighted MRI image of large fluid filled cysts, **c** Ultrasound guided puncture of cysts with injection of OK-432, **d** Clinical outcome after one sclerotherapy session.

malformations is 1:6000 to 1:16.000 live births (McGill TJI FJJ Mulliken, 1998). There are no sexual or ethnic predilections. When evident at birth, LMs tend to be soft, fluctuating, non-tender masses. Ninety-five percent of LMs are diagnosed before 2 years of age. However, occasionally the LM may not be clinically evident until adulthood (Zadvinskis et al., 1992; McGill TJI FJJ Mulliken, 1998). LMs may occur in all parts of the body, any area of the skin, mucous membrane and also involving internal organs (Figs. 1–3). Seventy-five percent of the lesions occur in the head and neck region (Churchill et al., 2011; Orvidas and Kasperbauer, 2000). Superficial, palpable LMs expand into deeper cavities in 6% of the cases (Ghaffarpour et al., 2015).

The common LMs (a term currently used in the classification of vascular anomalies according to ISSVA, International Society for the Study of Vascular Anomalies) fit into three morphologic (Wassef et al., 2015; Arango Duque and Descoteaux, 2014; Smith et al., 2009) subtypes depending on the size of the cysts: macrocystic, microcystic and mixed lesions (a mixture with both macro- and microcystic components) (Figs. 1–3). The macrocystic type is made up of a single or multiple fluid-filled cysts, which are all larger than 2 cm in diameter; the microcystic type is made up of cysts smaller than 2 cm in diameter (Perkins et al., 2008). Most LMs have both macrocystic and microcystic portions (Perkins et al., 2008).

Macrocystic LMs generally form soft, large, translucent masses. When present in the subcutaneous tissue the overlying skin may have a bluish hue.

Microcystic LMs may appear as multiple small, raised vesicles, sometimes visible on the skin and containing clear or bloody fluid with occasionally recurrent leakage.

LMs may clinically present in a variety of forms, from cystic lymphatic lesions, i.e., slowly expanding lumps that may infiltrate the surrounding tissue, to complex lymphatic anomalies with chyle leakage, osseous lesions, and generalized lymphatic lesions (Florez-Vargas et al., 2008). LMs are histologically benign structures, however depending on localization, size and potential swelling they may cause serious complications such as airway compromise, pain and functional impairment, e.g., of vision or motility. A large swelling in the face or neck may also be a psychological burden to the patients and their families affecting quality of life.

LMs are highly immune-reactive and are prone to recurrent infections. When LMs become inflamed, they swell, and the skin in the involved area becomes red and warm. Recurrent infections or inflammations cause pain and disfigurement of the affected area. Large infected LMs may also present with septic shock.

In many patients genetic analysis of the malformed tissue has revealed an activating mutation in the *PIK3CA* gene (Luks et al., 2015; Brouillard et al., 2021; Mäkinen T). This is a somatic, non-inherited mutation engaging the lymphatic endothelial cells lining the malformation. *PIK3CA* is known to play an important role in regulating cell growth by signaling through the PI3K/mTOR pathway (McGill TJI FJJ Mulliken, 1998; Luks et al., 2015). Somatic mutations of the *PIK3CA* gene have been found to be an etiological factor in the development of LM and associated overgrowth syndromes.

Histologically, LMs are composed of thin-walled vascular channels lined by a single layer of flattened endothelium. Several specific markers are available for lymphatic tissue, such as D2-40, LYVE-1, PROX-1, desmoplakin and VEGF-C receptor VEGFR-3 (Luks et al., 2015), and they can be stained for and detected on tissue samples of suspected LM to rule out differential diagnoses (Vikkula et al., 1996; Perkins et al., 2008). The lumens and walls of the lymphatic cysts are filled with immunologically active proteins and cells such as interleukines, cytokines, macrophages and lymphocytes (Arango Duque and Descoteaux, 2014).

LMs are highly reactive to infections or inflammations. Blood can also fill the channels indicating spontaneous or traumatic intralesional bleeding. It may also indicate the presence venous components within the malformed tissue.

LMs do not grow by endothelial proliferation, however, they usually enlarge proportionally with the child. The pooled lymph within the malformation expands the affected tissue and causes the clinical symptoms of LMs. Trauma, infections and bleeding may cause them to swell rapidly. LMs can potentially obstruct or compress the larynx and the

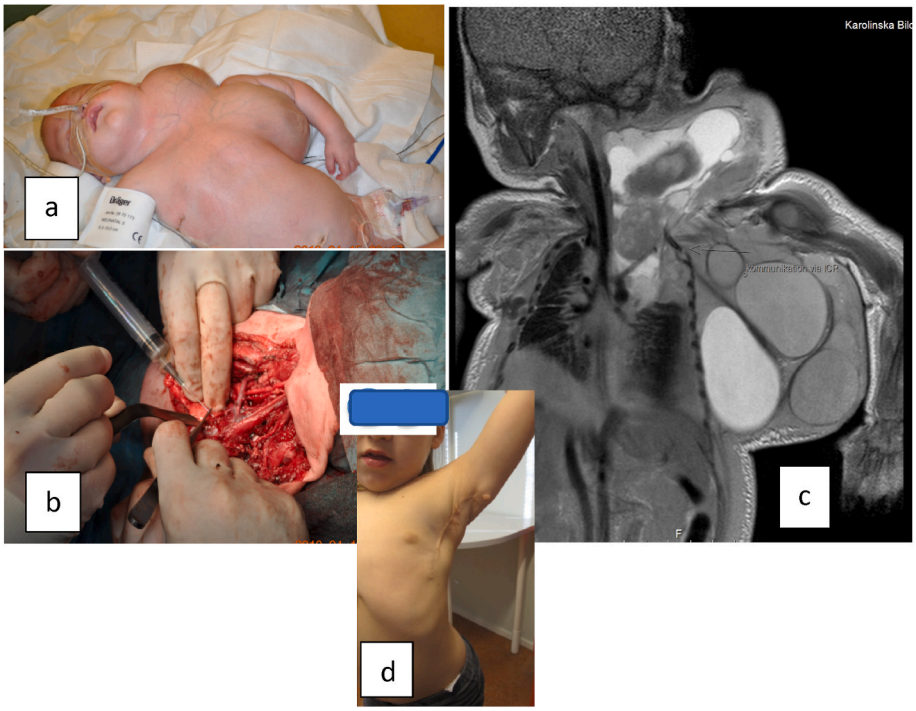

Fig. 2. Mixed LM with mediastinal expansion: **a** clinical feature at EXIT assisted delivery, **b** surgical debulking around the vital structures in the mediastinum and intraoperative sclerotherapy, **c** MRI T2 weighted image showing mixed LM with cysts expanding into the mediastinum compressing the heart and the left main bronchus **d** clinical outcome after staged surgeries and adjuvant sclerotherapies.

trachea requiring an EXIT (EX-Utero-Intrapartum Treatment) procedure at birth to secure the airways during the delivery.

Some anatomical regions, such as the mediastinum, are of additional concern (Gonzalez Marin et al., 2018). The mediastinum is a limited cavity with vital structures, such as the airways, the large vessels and the heart that may be compressed resulting in a life-threatening complication as a LM expands. LMs affecting the gastrointestinal tract or pelvis can cause constipation, bladder obstruction, recurrent bowel infection or protein loss (Lee et al., 2003; Leite et al., 2013). Large LMs in combination with venous malformations may be associated with a Localized Intravascular Coagulopathy (LIC) with elevated D-dimer and mild to moderate thrombocytopenia. The coagulopathy may progress to Disseminated Intravascular Coagulation (DIC) after trauma or surgery. Kasabach-Merritt phenomenon (KMP, severe thrombocytopenia) can be associated with Kaposiform lymphangiomatosis, KLA.

3. Results

The diagnosis of lymphatic malformations can often be made before birth using ultrasound. After birth, a diagnosis of an LM is based on a physical examination along with a detailed patient history. Doppler ultrasound (DU) is the imaging modality of choice to start the investigation of vascular anomalies (Fig. 4). With DU the flow characteristics of the lesion is measured and the tissue is visualized. Many times DU will give required information about the lesion and may already be diagnostic. Magnetic Resonance Imaging (MRI) is however the gold standard modality of investigation for vascular anomalies in general to determine the extent and type of the lesion (Perkins et al., 2010a, 2010b). MRI is always done prior to treatment decisions such as sclerotherapy or surgery.

Fine needle aspiration or biopsy is occasionally mandated to rule out differential diagnoses such as teratomas, other malignancies, pseudocysts from parenchymal organs, including thoraco-abdominal organs as well as ranulas from the salivary glands or remnants from brachial clefts. The discovery of LM molecular genetics has led to the possibility of targeted therapies (Padia et al., 2019). Genetic analyses can help to differentiate various forms of lymphatic anomalies.

3.1. Treatments

There is no clear-cut treatment algorithm for the management of LMs due, in part to heterogenic presentation among patients. The essential strategy of the treatment of LMs is directed toward the specific symptoms that are present in each individual (Fig. 5). Symptomatic treatment may be medical, such as antibiotics as well as analgesics, and anti-inflammatory medication or interventional/surgical. A curative treatment is not always possible and should not be sought aggressively as it may result in excessive and potentially dangerous treatments. The evaluations of patients are occasionally complex and require a multidisciplinary approach involving the insight and experience of pediatricians, pediatric surgeons, plastic surgeons, otorhinolaryngologists, dermatologists, geneticists, radiologists, and interventional radiologists among various other health care personnel. The specific treatment and interventions vary depending on multiple factors such as type of LM (macrocystic, microcystic, mixed) (Fig. 6), size and anatomical localization, as well as the presence of pain, recurrent infections, oozing, or associated anomalies. Generally, macrocystic LMs can be treated more effectively with better outcome, no matter the choice of treatment. Microcystic and mixed LMs are more difficult to treat, often requiring staged and repeated treatments, both interventional as well as surgical. Regardless of treatment modality there is always a risk of recurrence. Thus, in many cases LM treatment is symptomatic and requires life-long therapy. Rarely LMs may shrink and disappear spontaneously. This may be the case after infection in the malformation that has a similar effect on the cystic malformations as sclerotherapy (see Fig. 7).

A multidisciplinary team should always tailor the treatment of LMs for each patient individually and the potential risks for each treatment option must be considered. Appropriate follow-up should be

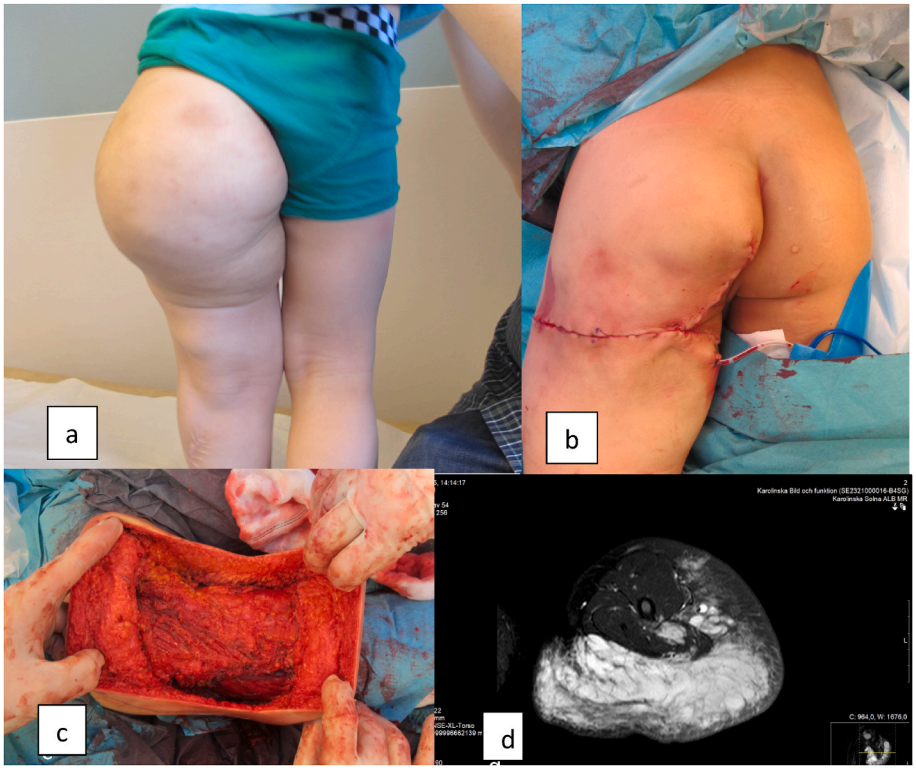

Fig. 3. Microcystic LM: **a** Clinical feature in the gluteal region, **b** After surgical debulking, **c** Intraoperative view after resection of microcytic LM, **d** MRI T2 weighted image showing microcystic LM.

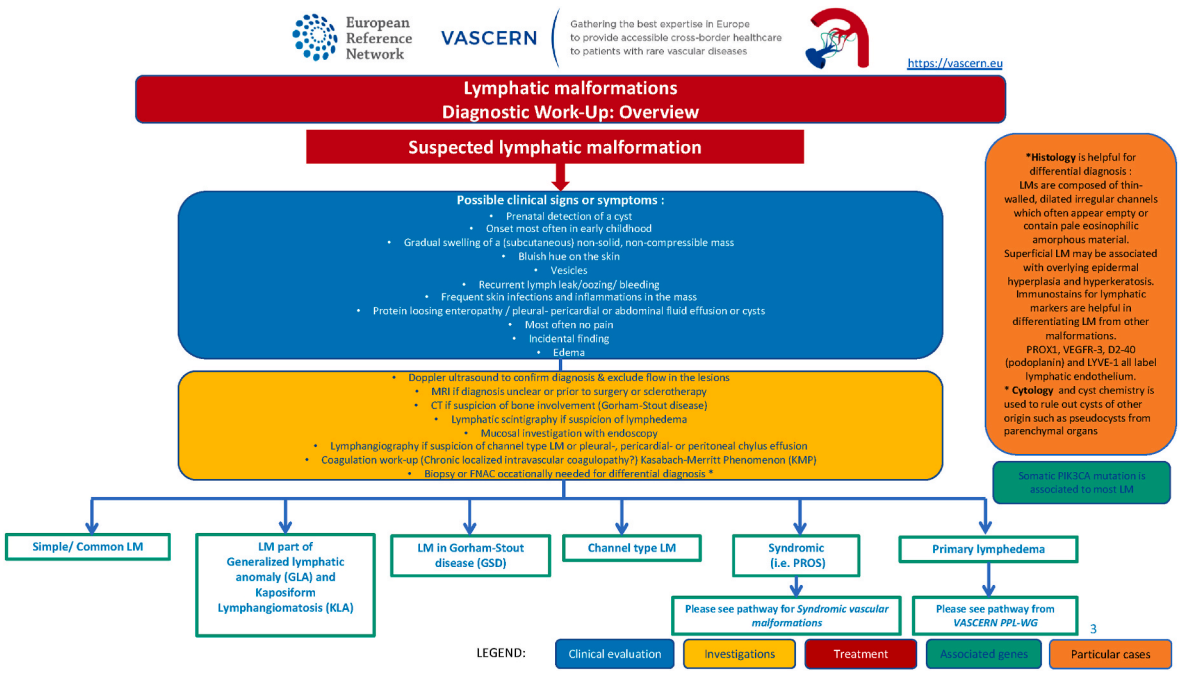

Fig. 4. Diagnostic Work-up for the management of lymphatic malformations.

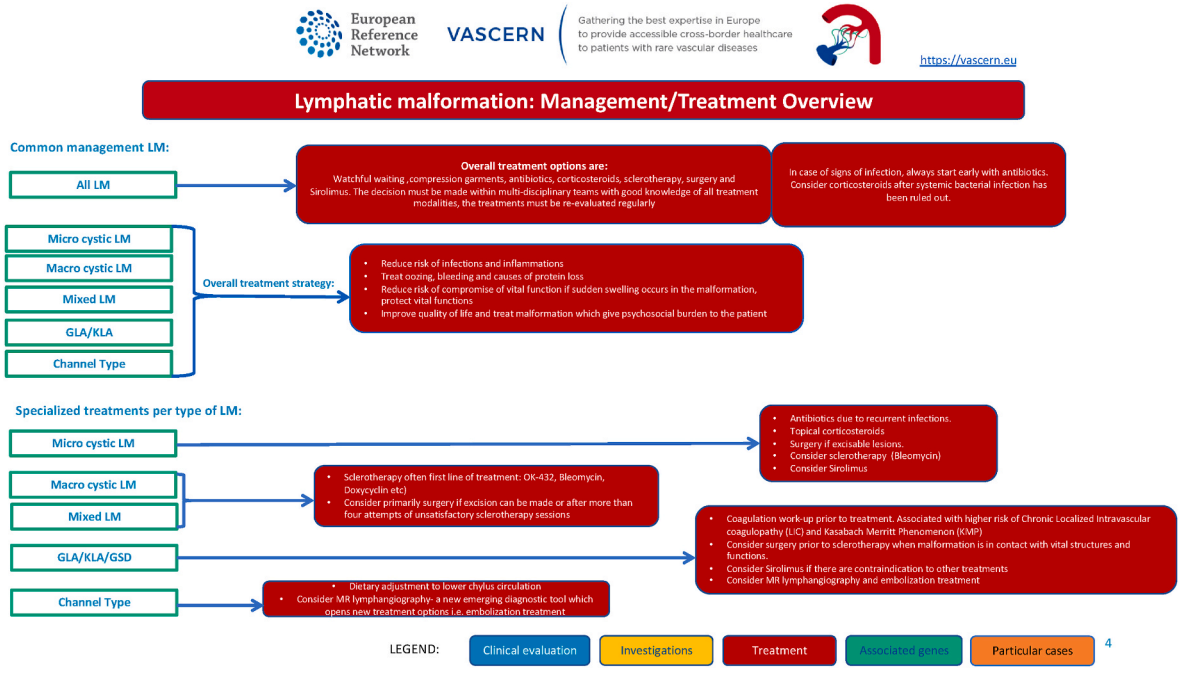

Fig. 5. General management of lymphatic malformations, an overview. Embolization treatment is mentioned as a management possibility when the clinical evaluation suggests KLA, GLA, chylus reflux and/or lymphatic obstruction in cases of channel type LM. In highly specialized institutions, lymphangiography and catheter guided embolizations may be performed.

recommended to all patients (Florez-Vargas et al., 2008; Acevedo et al., 2008).

The main therapeutic options are watchful waiting, surgery, and sclerotherapy.

In the last couple of years, drug therapy e.g. with sirolimus, specifically aimed at inhibiting the activated pathway due to the causative *PIK3CA* mutation has been reported with success (Luks et al., 2015; Adams et al., 2016; Rossler et al., 2017). Other treatments that are sometimes considered include compression garments, percutaneous drainage, laser therapy, or radiofrequency ablation. These different treatment options may be used in various combinations. All treatment modalities aim for the same effect as to remove the spaces where lymph could be pooled in the malformed tissue.

Watchful waiting is an excellent approach after the LM diagnosis is fully established, differential diagnoses are ruled out and the patient and the caretaker have received adequate information. Often watchful waiting is used in small LMs with few or limited symptoms or LMs in situations where the medical problem is not fully evaluated, and time

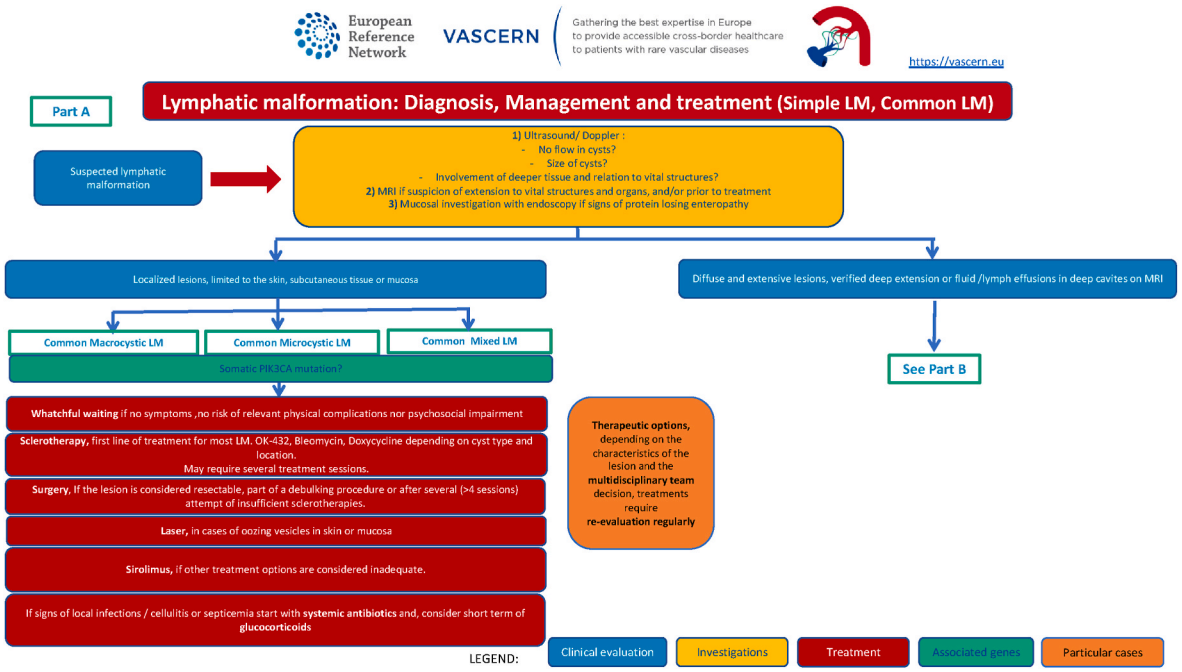

Fig. 6. Management of localized common lymphatic malformations; microcystic-, macrocystic- and mixed LM.

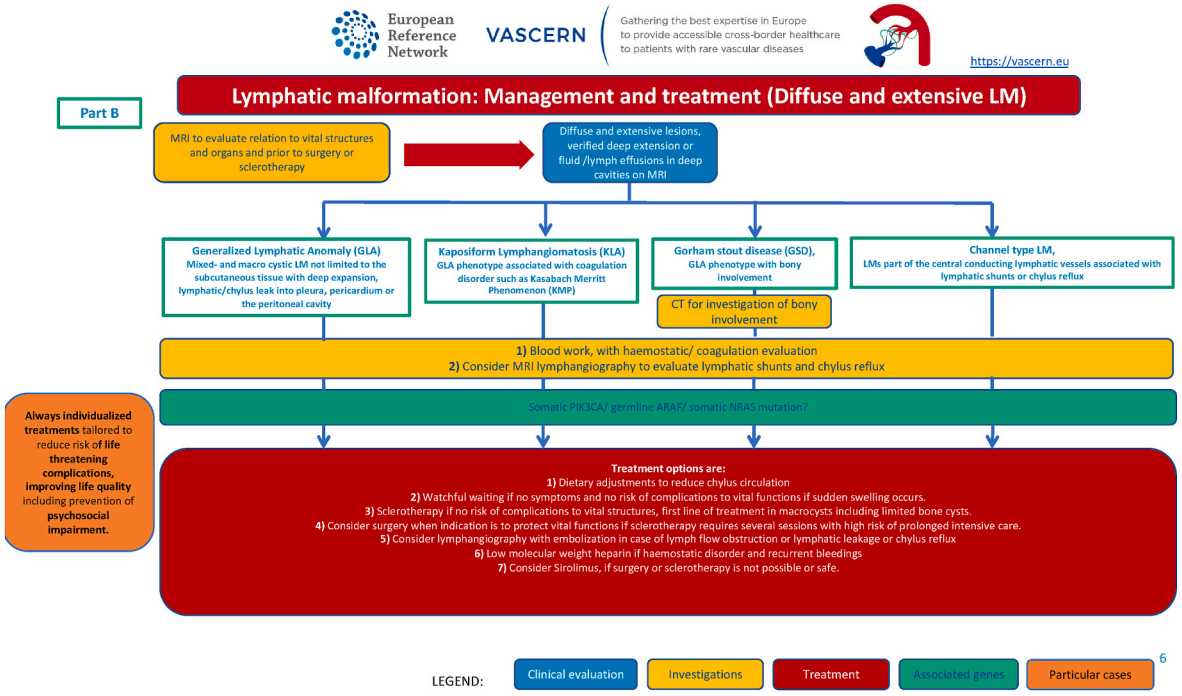

Fig. 7. Management of diffuse and extensive LM; GLA, KLA, GSD and Channel type. Embolization treatment is mentioned as a management possibility when the clinical evaluation suggests KLA, GLA, chylus reflux and/or lymphatic obstruction in cases of channel type LM. In highly specialized institutions, lymphangiography and catheter guided embolizations may be performed.

will add essential information prior to the decisions for medical or surgical interventions.

Compression garments are used when the LM presents as part of a syndrome with lymphedema and venous malformation. The malformation, often localized at the limb, is wrapped into compression dressings and the pooled lymph is gradually squeezed out from the malformed tissue. Unfortunately, this usually does not work in macro- or microcystic LMs.

Percutaneous drainage is a limited procedure, which means that the fluid in the LM is drained through a catheter or an incision. Drainage is often used in emergency situations in order to empty cysts that expand and compress vital structures or functions. The treatment must be combined with sclerotherapy or surgery in order to prevent re-accumulation of lymph in the cyst.

Surgery is one of the main treatment options for LMs (McGill TJI FJJ Mulliken, 1998; Orvidas and Kasperbauer, 2000). However, lesions sometimes present to the surgeon as challenging conditions. Although LMs are histologically benign, especially microcystic LMs frequently

infiltrate adjacent structures, such as, vessels and nerves.

This makes total resection difficult and potentially hazardous. Surgeons may be confronted with serious complications, such as bleeding, wound infection, wound healing problems, nerve damage, and recurrence (McGill TJI FJJ Mulliken, 1998; Orvidas and Kasperbauer, 2000). Large LMs often require staged excisions (Churchill et al., 2011; Poldervaart et al., 2009; Balakrishnan et al., 2014; Bajaj et al., 2011).

A multidisciplinary approach involving surgeons and interventional radiologists is often needed for complex LMs. The aim of surgery is to remove the lesion, improve function of an affected area and prevent disfiguring complications. Surgery is especially suitable if the LM is localized to one area of the body and if full excision may be performed without sacrifice of vital structures (Fig. 3). Surgery also has advantages as part of a staged treatment strategy where sclerotherapy and surgery are combined to maximize debulking of the malformed tissue. With this strategy large areas may be reduced (Fig. 2).

Lymphatic Malformation-Venous Anastomosis (LMVA) is a less invasive alternative with promising results. The LMVA procedure aims to provide an outflow venous conduct from the LM in order to reduce congested lymph within the malformation (Furuse et al., 2020).

Sclerotherapy is a procedure in which an irritant solution is injected directly into the LM. This solution causes scarring within the LM, which eventually leads to shrinking or collapse of the malformation (Fig. 1). Percutaneous sclerotherapy has replaced surgery in most cases of macrocystic malformations in the past 30 years (Acevedo et al., 2008; Poldervaart et al., 2009; Bajaj et al., 2011; Furuse et al., 2020; Burrows et al., 2008; Claesson and Kuylenstierna, 2002; Mitsukawa and Satoh, 2012).

Macrocystic LMs of moderate size can be easily treated with sclerotherapy. Sclerotherapy may require multiple sessions to be effective, especially in extensive malformations.

Many agents have been used for this purpose; among others OK-432 (picibanil), doxycycline, dextrose, bleomycin, ethanol, and interferon (Mitsukawa and Satoh, 2012).

A systematic review of the literature on nonsurgical treatment of lymphatic malformations has been carried out (Acevedo et al., 2008). The literature strongly suggests that the majority of patients who undergo sclerotherapy as first-line therapy for head and neck LMs will achieve a good to excellent clinical response. Serious complications and the need to progress to surgical salvage were infrequent. Given the heterogeneity of the treatment protocols used and variable results obtained between studies, there appears to be no clear consensus as to when sclerotherapy is indicated, what agents offer the most benefit, and how these agents should be administered for optimal results (Acevedo et al., 2008).

Furthermore, the use of sclerosing agents sometimes causes scarring due to the penetration of adjacent tissues, to the extent that subsequent surgery is difficult or impossible. Disadvantages are the need for repeated injections, skin and soft tissue necrosis, blistering, and to some extent unpredictable swelling with the risk of causing obstruction of vital structures after discharge from the hospital.

Although sclerotherapy for LMs is minimally invasive and often safe, complications may occur ranging from mild systematic symptoms such as fever and fatigue to local swelling causing compression to vital functions requiring prolonged intensive care.

Mediastinal LMs are of special concern and are prone to severe complications after sclerotherapy. Patients show variable response to sclerotherapy and occasionally the treatment is followed by significant swelling that can compromise vital functions such as compromise of the airways (Ghaffarpour et al., 2015). Lesions in the mediastinum represent a special challenge in this sense due to the narrow compartment with vital structures.

Laser therapy and **radiofrequency ablation** are techniques by which energy is deployed in the tissue in order to destroy affected lymphatic vessel tissue and induce shrinkage. These techniques are best suited for superficial skin or mucosal LMs (Grimmer et al., 2006).

Medical therapy has recently gained additional attention. Sirolimus can be used to treat both diffuse as well as localized LMs and is administrated orally. Sirolimus has been used in cancer treatment as well as for prevention of organ rejection after solid organ transplantations for a long time. The use of sirolimus for LMs has just recently been recognized and promising reports have been published (Adams et al., 2016; Triana et al., 2017; Rossler et al., 2017; Jennifer Hammer; Boscolo et al., 2015; Holm et al., 2021). Sirolimus acts as an mTOR inhibitor and targets the activated PI3K/mTOR pathway in the LM (Luks et al., 2015; Adams et al., 2016; Rossler et al., 2017). Additional research is required to fully develop treatment protocols with understanding of treatment duration as well as long-term outcome and side effects. In cases of failure of treatment with Sirolimus, new drug treatment options such as the PIK3CA-inhibitor Alpelisib are being studied and show favorable results (López Gutiérrez et al., 2019; Delestre et al., 2021).

4. Discussion

In the absence of clinical trials and meta-analyses in the field of rare conditions, expert opinion remains the best tool to improve the quality of treatment. Indeed, in rare diseases level V evidence is still a necessary means to answer to a clinical question, whereas the level of evidence assignment does not consider the value of the processes performed to reach an expert opinion.

The quality of the statements by an expert panel depends on the members' skills. The group expertise in the field of vascular anomalies is guaranteed by the selection of national reference centers endorsed by their governments and selected by the European Community's ERN network on the basis of well-defined criteria.

The NGT has been defined by Ven and Delbecq as "a structured meeting which seeks to provide an orderly procedure for obtaining qualitative information from target groups who are most closely associated with a problem area" (Ven and Delbecq, 1974). The structured process allows the participants to decide which topics require further discussion avoiding domination of the debate by more authoritative or dominant members. Moreover, equal participation for all group members in conflicting concepts is guaranteed by the facilitator. A limitation of the process is the absence of anonymity, guaranteed in the Delphi method, and therefore the inability to avoid completely that authority and personality of some experts may drive the process.

In conclusion, the VASCA-WG proposes an expert opinion on a diagnostic and management pathway of LMs as a useful tool to improve the care and management of these patients.

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CRediT authorship contribution statement

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Data availability

No data was used for the research described in the article.

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