

Review

Exploring Lymphangioma: A Synthesis of the Literature and Clinical Perspectives

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Abstract: Lymphatic malformations (LMs) are benign, congenital vascular anomalies caused by abnormal lymphangiogenesis during embryology, often presenting as fluid-filled cystic lesions. Though LMs can affect any part of the body except the brain, they primarily manifest in the head and neck or axilla regions of children. With a prevalence of approximately 1 in 4000 births, LMs are commonly diagnosed by age two, with symptoms varying based on lesion location and size. This paper reviews the classification of LMs and discusses the de Serres staging system, which aids in assessing prognosis based on lesion site. Mutations in the (PIK3CA) gene are implicated in most cases, and LMs are also associated with syndromic conditions like Turner and Noonan syndromes. They are diagnosed by ultrasound (USS) or magnetic resonance imaging (MRI), while a histologic analysis can confirm lymphatic origin. Treatment options range from conservative approaches, such as observation, to sclerotherapy, pharmacotherapy, and surgery. Sclerotherapy, particularly with agents like OK-432, bleomycin, and doxycycline, has shown significant efficacy in reducing LM size and symptoms with minimal side effects. Pharmacological therapies, such as sirolimus, that target the mTOR pathway are also increasingly being used, with a good effect on the burden of disease. While surgical excision remains a choice for symptomatic or large lesions, minimally invasive approaches are often preferred due to lower morbidity. Emerging techniques include gravity-dependent sclerotherapy, electrosclerotherapy, alpelisib, everolimus, and Wnt/ β -catenin pathway stimulators (e.g., tankyrase inhibitors, porcupine inhibitors). Computational atomistic molecular dynamics (MD) and density functional tight binding (DFTB) techniques may offer an experimental approach to future therapeutic targets. This paper highlights a multidisciplinary approach to LM management, emphasising individualised treatment based on lesion characteristics and patient needs.

Keywords: lymphatic malformation; sclerotherapy; sirolimus; PIK3CA



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1. Background

Lymphatic malformations (LMs) are benign, congenital anomalies of the lymphatic system, resulting in the abnormal development of lymphatic vessels during embryonic growth as fluid-filled channels or spaces [1]. Although they can affect any part of the body, with the exception of the brain, 70% of these uncommon slow-flow vascular malformations are found in the head and neck of children, while 20% of lymphangiomas are found in the axilla [2]. A small proportion, around 5%, are found in the mesentery, retroperitoneum, abdominal organs, lungs, and mediastinum. These are often incidentally identified later in childhood or adulthood [3]. The estimated prevalence is 1:4000 births, making up

approximately 6% of all soft tissue lesions in children [4]. It was further reported that 90% of LMs are seen before the age of two years old, and around 60% are seen during birth. Most patients are young children, with equal effects on both genders [5].

They can be classified morphologically into several types based on their size and appearance:

- Macrocystic LMs typically appear as solitary lesions of varying sizes, comprising multiple large, fluid-filled cysts, and are most commonly found in the neck area [6].
- Microcystic LMs are smaller fluid-filled cysts and locally diffuse infiltrative lesions [6]. They can occur anywhere on the skin or mucous membranes, with a higher prevalence inside the mouth, in the throat, and on the tongue [7].
- Mixed LMs present with both macrocystic and microcystic characteristics.
- Lymphangiomatosis, also referred to as generalised lymphatic anomaly (GLA) or diffuse LM, involves diffuse and multicentric proliferative lesions that affect multiple organs [6].

2. Staging

A staging system, named de Serres classification of lymphatic malformations, was proposed in a paper by de Serres et al. in 1995 to predict the prognosis and outcome of surgical intervention based on the anatomic location of the lesion [8], shown in Table 1.

Table 1. de Serres classification of lymphatic malformations [9].

Stage	Location of Lesion
I	Unilateral infrahyoid
II	Unilateral suprahyoid
III	Unilateral Infra and suprahyoid
IV	Bilateral infrahyoid
V	Bilateral Infra and suprahyoid

3. Aetiology

The exact aetiology of lymphatic malformations is not yet unambiguously defined, with many pathways at play still an active area of research. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway and the mammalian target of rapamycin (mTOR) signalling pathway are found to be directly implicated in the formation of lymphatic malformations via impaired lymphangiogenesis [10]. An oncogenic mutation in the PIK3CA gene, which encodes the p110 α catalytic subunit of PI3K, leads to the hyperactivation of the PI3K/AKT pathway via enhanced AKT phosphorylation and influences upstream mTOR signalling, resulting in IL-2-induced lymphocyte proliferation and impaired lymphatic vessel maturation [11]. PIK3CA mutations were identified in approximately 80% of lymphatic malformation tissue samples, as described by Makinen et al. [6]. Mutations in this somatic activating gene are also present in head and neck squamous cell cancer, gastric cancer, gallbladder cancer, and melanoma [11].

Phosphatase and tensin homolog (PTEN) is a tumour suppressor and a key negative regulator of the PI3K/AKT/mTOR pathway described, in which mutations or a loss of function in the gene can also lead to the hyperactivation of the pathway. PTEN-deficient LECs exhibit increased sensitivity to vascular endothelial growth factor-C (VEGF-C), a potent lymphangiogenic factor, amplifying the pathological lymphatic proliferation seen in LMs. PTEN mutations are linked to syndromes like PTEN hamartoma tumour syndrome

(PHTS), which can include vascular malformations and lymphatic abnormalities as part of its spectrum [11].

The Wnt/ β -catenin pathway also regulates angiogenesis and lymphangiogenesis by controlling lymphatic endothelial cell (LEC) proliferation, migration, and differentiation; while β -catenin promotes the survival and stability of LECs, ensuring proper lymphatic vessel function and integrity in the way of lymphatic valve formation and maintenance. In 2016, Cha et al. reported that fluid-induced oscillatory shear stress (derived from disturbances in blood flow in arterial regions) is a key component of Wnt/ β -catenin activation [12]. The dysregulation of this pathway contributes to abnormal lymphatic growth/remodelling, increased fibrosis and chronic inflammation, all of which exacerbate LM pathology. Additionally, it may interact with PI3K/AKT pathways, amplifying pathological effects of aberrant signalling [12].

Moreover, lymphatic abnormalities may develop in utero as a component of a syndrome, such as Turner, Noonan, Patau, Edwards, or Down syndrome. Typically, the lymphatic abnormalities found during pregnancy regress and disappear after delivery.

Meanwhile, trauma, surgery, or conditions (e.g., chronic lymphoedema) that impair or destroy the lymphatic drainage system may result in acquired lymphatic abnormalities [13]. Certain events such as infection, puberty, trauma, or bleeding into a lymphatic malformation are also described in the literature to cause rapid growth of LMs [1].

4. Signs and Symptoms

The location and size of the malformation ultimately determine the specific symptoms and their severity. Most LMs typically appear as painless masses that grow in proportion to the child, leading to different levels of cosmetic deformity. As a result, they are often diagnosed within the first few years of life or even before birth [3]. Generally, a patient is likely to become symptomatic due to the mass effect exerted on local structures. For example, head and neck LMs may cause dysphagia, airway compromise, feeding intolerance, a limited ROM of the neck, and superior vena cava syndrome, while abdominal/retroperitoneal LMs may cause intestinal obstruction, volvulus, ischemia, portal hypertension, urinary obstruction, abdominal pain, or distension [5]. In addition, patients may present with non-specific symptoms of acute localised swelling, warmth/fevers, and tenderness/pain secondary to intra-lesional infection or haemorrhage, which is present in 35% of cases [5].

5. Diagnosis

Imaging may not be required for the diagnosis of simple LMs, which can be made based just on their clinical presentation. The first imaging modality of choice, ultrasound (USS) with Doppler, is frequently adequate for the identification of superficial lesions. According to Zhou et al., 50–75% of cases may be diagnosed by ultrasonography at birth, and 80–90% of the remaining cases may be diagnosed before the child is 2 years old [14]. If a lesion is extensive, atypical, or located deeply, further imaging, usually MRI, may be necessary to assess its extent. Although computed tomography (CT) is less frequently used to diagnose LMs, it can be useful in evaluating bone involvement or in locating intraabdominal malformations [15]. Furthermore, it may be essential to conduct histologic correlation to obtain a definitive diagnosis, in certain instances, an immunohistochemical analysis is particularly useful for confirming that the lesions originate from lymphatic endothelium, utilising markers like CD31, CD34, vascular endothelial growth factor receptor 3 (VEGF-R3), and notably D2-40, which selectively labels lymphatic endothelial cells [16].

6. Management

Typically, management begins with a multidisciplinary approach comprising expert opinions from, but not limited to, paediatricians, paediatric surgeons, paediatric dermatologists, and diagnostic and interventional radiologists. Characteristics, including size, location, and symptoms of the malformation, will determine the optimal treatment choice from either observation (watch and wait), conservative management (e.g., manual lymphatic drainage or compression therapy), systemic immunotherapy (e.g., topical medication), surgery, aspiration, sclerotherapy, or a combination of the above [17]. Small, asymptomatic LMs may not require immediate treatment and can be monitored by observation. Sclerotherapy is currently the most common choice of treatment, replacing surgery in recent years, while newer therapies such as sirolimus and laser therapies have proven certain effectiveness.

6.1. Sclerotherapy

Sclerotherapy is the injection of a sclerosing agent into the cystic malformation to lead to shrinkage by inducing an inflammatory immune response. In a paper by Renton and Smith, it was reported that when used to treat macrocystic LMs, sclerotherapy provides better results with less morbidity than surgery, while it is unlikely to cause a significant reduction in microcystic LMs [18]. Based on a review of the literature, sclerotherapy is consistently a simple and efficient method for treating LMs of the, but not limited to, eyelid, tongue, neck, breast, anterior chest wall, sub-sternum, and parotid gland. These treatments are typically administered under intraoperative ultrasound guidance [19]. General anaesthesia (GA) has been used in children for sclerotherapy of complex lesions or lesions involving the airway. However, most of the superficial and simple venous malformations can be performed under sedation [20]. The risks associated with general anaesthesia are higher within younger paediatric populations; therefore, the decision to proceed with sclerotherapy depends on if the benefits would outweigh the risks in each individual case. Generally, sclerotherapy is best delayed to at least 6 months of age to a year as long as the patient remains asymptomatic. This is mainly to reduce anaesthetic risk, but also to reduce systemic toxicity risk with the sclerosant used. As the number of treatments increases, the recurrence rate decreases. Recent studies have found that various sclerosants are both clinically and radiologically effective while maintaining a high degree of patient safety.

OK-432, as known as Picibanil, is a Japanese formulation, made from fragments of *Streptococcus pyogenes*, with anti-neoplastic activity. A study by Peters et al. in 2006 found that all patients with macrocystic malformations had complete resolution or good response to OK432, although ineffective on microcystic lesions [21]. Another study published in 2012 studied the effects of OK-432 on 15 children with head and neck macrocystic LMs. It was reported that eight patients (53.33%) underwent a complete resolution of LM, and five patients (33.33%) were found with a marked (>50%) reduction of LMs after OK-432 treatment. Some common side effects include fever, local inflammation, and transitory increase of blood platelets' concentration [22].

Bleomycin is an antibiotic used as a chemotherapy agent for its ability to destroy rapidly producing cells. It is also a widely used sclerosing agent for its effectiveness on lymphatic malformations. A retrospective review in 2022 reported an overall improvement in 82% of LMs using bleomycin [23], also known for its high success rates on large, diffuse microcystic LMs and low complication rates [24].

Doxycycline is a broad-spectrum antibiotic that is very effective for the treatment of macrocystic and mixed head and neck lymphatic malformations in children. A systematic review by Cheng highlighted that the overall success with doxycycline sclerotherapy treatment in children with lymphatic malformations of the head and neck was 84.2%. Doxy-

cycline has advantages over other sclerosing agents, including that it is widely available, is inexpensive, and has minimal side effects [25]. Additionally, a Chinese study published in 2024 reported a 93.2% mean reduction in retroperitoneal macrocystic and mixed LMs using doxycycline [26].

Polidocanol is an alcohol-containing liquid surfactant that possesses endothelial cytolytic activities. It is commonly used in the treatment of varicose veins and venous malformations. A retrospective observational study by De Corso et al. concluded that polidocanol sclerotherapy appears to be an effective and safe treatment for macrocystic venous and lymphatic head and neck malformations, reporting a 79.5% mean volume reduction in LMs [27].

Sodium tetradecyl sulfate (STS, as known as Fibro vein 1%) is also an alcohol containing substance. According to a paper in the Journal of Current Ophthalmology, when using STS 1%, 63.6% of cases showed partial resolution to less than half of primary size, and 36.3% showed complete resolution of LMs of the eyelids, conjunctiva, and anterior orbit [28].

6.2. Surgery

Complete or partial resection of the malformation is often necessary for larger or symptomatic LMs due to the acute reduction in bulk, but in many other cases, the risks of surgery (e.g., anaesthetic risk, iatrogenic/post-operative complications) do not outweigh the benefits. A retrospective study conducted in 2023 included 46 patients that received surgical management of their LMs between 2002 and 2022. This study found that 80% of the cohort underwent surgical intervention between 2002 and 2012, and the indication for surgery in every case was ineffective sclerotherapy and/or pharmacological intervention. It was recorded that 36.9% were macrocystic LMs, and 17.4% were microcystic, with the majority 45.6% being mixed [29].

Complications include nerve palsies (e.g., facial nerve palsy, diaphragmatic paralysis, impaired tongue mobility, scapular winging); cosmetic deformities (e.g., unilateral breast hypoplasia); and damage to local structures (e.g., bowel perforation), infection, and bleeding [30]. Recurrence rates range from 40% for incomplete excision to 17% to 25% for macroscopically complete excision. Nearly all recurrences were within 14 months of the initial resection, with 54% recurring within three months. There is a greater recurrence rate for larger lesions [30].

6.3. Laser Therapy

Laser therapy is particularly useful for superficial, cutaneous microcystic LMs. Some different laser modalities include radiofrequency energy, optical diode laser energy, or a carbon dioxide (CO₂) laser. A CO₂ laser is commonly utilised; however, it removes the entire layer of skin and may lead to scarring. Additionally, recurrences are quite common [19].

6.4. Sirolimus

Recent medical advancements have introduced the use of immunotherapeutics, like sirolimus (Rapamycin), to target the underlying molecular pathways of lymphangiogenesis. Sirolimus is a powerful immunosuppressive drug with antiproliferative properties that works by inhibiting the regulatory kinase mTOR [31], resulting in a reduction of the size and therefore symptoms of lymphatic anomalies.

A study in 2022 found sirolimus to be a very effective treatment for children with large, complicated head and neck LMs. It reported more than 91% of 105 children responded to treatment and described oral ulcers as the most common side effect. Other typical side effects include hyperlipidaemia, neutropenia, and infections [32].

A systematic review by Saibene et al. extrapolated that 89 out of 97 cases resulted in a satisfactory clinical response to treatment. The clinical response rate was 23 out of 24 cases for macrocystic lesions, 14 out of 17 for microcystic lesions, and 21 out of 25 for mixed lesions. In approximately half of the studies reviewed, sirolimus was only administered after other more commonly used treatments, like sclerotherapy, had failed or symptoms had recurred [33]. In addition, upper respiratory tract infections were a commonly reported side effect, along with oral ulcers. However, there are currently no data on the ideal duration of treatment for LMs.

7. Innovative/Emerging Therapies

Percutaneous sclerotherapy has proven effective for treating macrocystic lymphatic lesions, but it is not as effective for microcystic lesions due to their smaller size. The gravity-dependent technique is an innovative enhancement of traditional percutaneous sclerotherapy, allowing for the sclerosing agent to penetrate the tiny microchannels present in microcystic lesions that would normally be challenging to treat [34].

A potentially promising procedure is bleomycin electrosclerotherapy (BEST), also known as reversible electroporation. This technique involves applying an electric field to the malformation, which temporarily increases the permeability of the cell membrane and permits greater amounts of bleomycin to penetrate the cells [19].

A study published in 2022 titled “Alpelisib for the treatment of PIK3CA-related head and neck lymphatic malformations” investigated the therapeutic potential of alpelisib, a PI3K α inhibitor, in managing lymphatic malformations associated with the PIK3CA-related overgrowth spectrum (PROS). It was conducted as an open-label, single-arm study aiming to determine the impact of the drug on reducing the size of malformations, alleviating symptoms, and improving the quality of life in affected individuals. The study’s open-label design ensured that all participants (individuals diagnosed with genetically confirmed and clinically significant PIK3CA-related head and neck lymphatic malformations) received the experimental treatment, but it also meant that no control group was included for direct comparison, a notable limitation of the study. Instead, outcomes were evaluated against the patients’ baseline data. They reported reduced malformation size and local overgrowth, improved symptoms, and fewer invasive procedures required in PIK3CA-associated head and neck lymphatic malformations (HNLMs) or facial infiltrating lipomatosis (FIL). In terms of safety, alpelisib was generally well-tolerated by participants. Reported adverse effects included hyperglycemia and gastrointestinal symptoms, which are consistent with the known side-effect profile of PI3K α inhibitors [35].

An mTOR inhibitor comparable to rapamycin includes everolimus. It is a derivative of rapamycin that exhibits significantly improved pharmacokinetic properties, including enhanced absorption, higher oral bioavailability, faster achievement of steady-state levels after initiation, and quicker elimination following discontinuation. [36]. Clinical trials and case studies have demonstrated that it can reduce the size of lymphatic malformations, particularly in patients with extensive or refractory disease. For example, a study by Trenor et al. in 2018 reported significant reductions in lesion size and improvement in symptoms in children treated with everolimus [37]. The long-term efficacy and safety of everolimus in LMs require further investigation, particularly in preventing recurrence after discontinuation.

Modulating Wnt signalling to restore proper beta-catenin activity may represent a therapeutic approach for specific types of LMs. Agents targeting the stimulation of the Wnt/ β -catenin pathway (e.g., tankyrase inhibitors, porcupine inhibitors) are currently being explored. Tankyrase inhibitors, such as XAV939, have been effective in reducing pathological cell proliferation in models of vascular anomalies, indicating their potential

for LMs [38]. Of the porcupine inhibitors undergoing clinical trials, Wnt974 (LGK974) is particularly noteworthy for its demonstrated efficacy in various tumour models of head and neck squamous cell carcinoma and metastatic colorectal carcinoma with Wnt pathway mutations; demonstrating efficiency, tolerability, and target engagement [39]. While specific studies in LMs are limited, the underlying mechanisms are highly relevant.

8. Experimental Approaches to Disease

Using computational atomistic molecular dynamics (MD) and density functional tight binding (DFTB) techniques provide powerful tools to understand molecular interactions at the atomic level, particularly in complex biological systems like those related to LMs. Atomistic MD simulations allow for the modelling of molecular systems, which when applied can be used to study conformational flexibility and stability, observe responses following a controlled change to the system, and observe a dynamic process over time. This can assist with deciphering the structural impact of mutations, modelling interactions between mutated proteins and their substrates or inhibitors, and proposing therapeutic strategies by simulating the efficacy of potential treatments [40]. In the context of lymphangiogenesis, MD can simulate the behaviour of endothelial cell membranes under conditions that promote or inhibit LM formation and can elucidate how proteins involved in lymphangiogenesis interact with ligands or inhibitors. This method highlights therapeutic targeting by identifying potential drug-binding sites and predicting how small molecules might stabilise or destabilise pathological protein conformations.

DFTB is a quantum mechanical method for electronic structure calculations that is derived from density functional theory (DFT), which is the choice tool for atomic-scale simulations, but with reduced computational costs when sufficient parameters exist. One of the main objectives in developing DFTB was to enable the modelling of significantly larger systems than those feasible with DFT, while preserving a detailed electronic-scale representation of the studied systems [41]. In the context of LMs, DFTB can be used to understand the electronic structure and function/dysfunction of key biomolecules involved in LM, such as signalling proteins. It can also be used to investigate biochemical reactions (e.g., phosphorylation, redox reactions) that drive lymphatic development. Additionally, it can be used to examine how metal ions (e.g., zinc, calcium) influence protein activity or structural stability in lymphatic endothelial cells.

Combining MD and DFTB allows for multi-scale simulations where the quantum-level accuracy of DFTB can focus on atomic-level reactive or electronic processes, while MD captures the broader dynamics of the system via observing biomolecular processes in action. For example, modelling the binding of a therapeutic molecule to a receptor implicated in lymphangiogenesis, where DFTB is used to study the binding site's electronic properties and MD explores the overall binding process, can give researchers much greater insight to current and future therapeutic strategies, although these methods require specialised manpower and computational resources. Despite the complexity and costs, exploring this field in relation to lymphatic malformations and other complex processes would prove extremely beneficial in paving the most effective management plans.

9. Conclusions

Lymphatic malformations most commonly present as a painless lump in the head and neck region before the age of 2. There is a high likelihood of a somatic PIK3CA mutation, as simple or syndromic LMs are observed as part of the PIK3CA-related overgrowth spectrum (PROS) and have high morbidity rates. If not diagnosed antenatally, ultrasound or MRI can effectively be used for diagnosing. Sclerotherapy is very effective for treating LMs and is associated with a low side effect or recurrence risk. With the recent pharmaceutical and

technological advances, surgical excision is moving away from being the gold standard of treatment and is likely only performed if primary therapy (sclerotherapy and/or pharmacotherapy) fails. The effectiveness and safety of sirolimus are still uncertain because of the absence of high-quality studies. The integration of emerging therapies, such as sirolimus, alpelisib, or everolimus into the management plan by paediatric dermatologists could help overcome the shortcomings of sclerotherapy and bridge any necessary gaps for earlier and more effective treatment, for example, in cases where parent preference is to avoid sclerotherapy, when there is a need to delay treatment until after a certain age, when there is reduced effectiveness on smaller or microcystic malformations, or when the risks outweigh the benefits. Additionally, these drugs' systemic effects complement local interventions, e.g., sclerotherapy, by targeting underlying molecular abnormalities. This should be a target for future research, as it could shift the current primary management of sclerotherapy alone. By combining MD and DFTB, researchers can achieve a deeper understanding of the molecular basis of lymphatic malformations, offering insights into potential therapeutic interventions and guiding the experiment. A multidisciplinary approach is ideal in the management of LMs due to the high variability of patient presentation and the need for an individualised approach.

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