Review

Exploring Lymphangioma: A Synthesis of Literature and Clinical Perspectives

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Exploring Lymphangioma: A Synthesis of 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 or MRI, while 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 good effect on 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 and electrosclerotherapy. This paper highlights a multidisciplinary approach to LM management, emphasizing individualized treatment based on lesion characteristics and patient needs.

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1. Background

Lymphatic malformations (LMs) are benign, congenital anomalies of the lymphatic system, resulting in 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 & 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, throat, and on the tongue [7].

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- Mixed LMs present with both macrocystic and microcystic characteristics.
- Lymphangiomatosis, also referred to as generalized 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].

Table 1. de Serres classification of lymphatic malformations.

Stage	Location of lesion
I	Unilateral infrahyoid
II	Unilateral suprahyoid
III	Unilateral Infra & suprahyoid
IV	Bilateral infrahyoid
V	Bilateral Infra & suprahyoid

3. Aetiology

The exact aetiology of lymphatic malformations is not yet unambiguously defined but is attributed to impaired lymphangiogenesis. The mammalian target of rapamycin (mTOR) signalling pathway plays a crucial role in regulating cell proliferation and is directly implicated in the formation of these lymphatic malformations. An oncogenic mutation in the PIK3CA gene influences upstream mTOR signalling, which activates the mTOR pathway and contributes to the development of LMs [9]. Approximately 80% of LM cases are caused by mutations in the somatic activating PIK3CA gene, as described by Makinen et al. [6].

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 [10]. Certain events such as infection, puberty, trauma or bleeding into a lymphatic malformation are described in the literature to cause rapid growth of LMs [1].

4. Signs & 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 [11]. Generally, a patient is likely to become symptomatic due to the mass effect exerted on local structures. For example, head & neck LMs may cause dysphagia, airway compromise, feeding intolerance, 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 Gross et al., 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 [12]. If a lesion is extensive, atypical, or located deeply,

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further imaging, usually magnetic resonance imaging (MRI), may be necessary to assess its extent. Although CT is less frequently used to diagnose LMs, it can be useful in evaluating bone involvement or in locating intraabdominal malformations [13]. Furthermore, it may be essential to conduct histologic correlation to obtain a definitive diagnosis, in certain instances Immunohistochemical analysis is particularly useful for confirming that the lesions originate from lymphatic endothelium, utilizing markers like CD31, CD34, vascular endothelial growth factor receptor 3, and notably D2-40, which selectively labels lymphatic endothelial cells [14].

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 (eg. manual lymphatic drainage or compression therapy), systemic immunotherapy (e.g., topical medication), surgery, aspiration, sclerotherapy, or a combination of the above [15]. Small, asymptomatic LMs may not require immediate treatment and can be monitored by observation.

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 & 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 [16]. 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 [17]. 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 [18]. 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.

6.2. OK-432

OK-432, aka 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 [19]. Another study published in 2012 studied the effects of OK-432 on 15 children with head & neck macrocystic LMs. It was reported that eight patients (53.33%) underwent 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 [20].

6.3. Bleomycin

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

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bleomycin [21], also known for its high success rates on large, diffuse microcystic LMs and low complication rates [22].

6.4. Doxycycline

Doxycycline is a broad-spectrum antibiotic that is very effective for 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%. Doxycycline has advantages over other sclerosing agents including that it is widely available, inexpensive and has minimal side effects [**23**]. Additionally, a Chinese study published in 2024 reported a 93.2% mean reduction in retroperitoneal macrocystic and mixed LMs using doxycycline [24].

6.5. Polidocanol

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 [25].

6.6. Sodium Tetradecyl Sulfate

Sodium tetradecyl sulfate (STS aka Fibrovein 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 [26].

6.7. 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 (eg. 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 [27].

Complications include nerve palsies (eg. facial nerve palsy, diaphragmatic paralysis, impaired tongue mobility, scapular winging), cosmetic deformities (eg. unilateral breast hypoplasia), and damage to local structures (eg. bowel perforation), infection and bleeding [28]. 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 [28].

6.8. Laser Therapy

Laser therapy is particularly useful for superficial, cutaneous microcystic LMs. Some different laser modalities include radiofrequency energy, optical diode laser energy or carbon dioxide laser. A CO2 laser is commonly utilized; however, it removes the entire layer of skin and may lead to scarring. Additionally, recurrences are quite common [17].

6.9. Sirolimus

Recent medical advancements have introduced the use of immunotherapeutics, like Sirolimus (Rapamycin) to target the underlying molecular pathways of lymphangiogenesis. As previously

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discussed, expression of the mTOR signalling pathway plays a key role in the pathogenesis of LMs. Sirolimus is a powerful immunosuppressive drug with antiproliferative properties that works by inhibiting the regulatory kinase mTOR, thereby blocking IL-2-induced lymphocyte proliferation and causing cell cycle arrest [29]. This results 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 [30].

A systematic review by Saibene et al. extrapolated that 89 out of 97 cases resulted in satisfactory clinical response to treatment. The clinical response rate was 23 out 24 cases for macrocystic lesions, 14 out 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 [31]. In addition, upper respiratory tract infections were a commonly reported side effect, along with oral ulcers. Although, there is 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 the sclerosing agent to penetrate the tiny microchannels present in microcystic lesions that would normally be challenging to treat [32].

As observed in this study, bleomycin is the sclerosant of choice to target microcycts, but in 16% of cases, there was no effect produced. 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 [17].

A study published in 2022 reviewing the use of the PI3K inhibitor alpelisib monotherapy, previously shown to be effective in PIK3CA-related overgrowth spectrum (PROS), 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) [33].

8. Conclusion

Lymphatic malformations most commonly present as a painless lump in the head & 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 done 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. 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.

Conflicts of Interest: The authors declare no conflicts of interest.

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