Lymphatic Malformations

70

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Contents

70.1 Introduction

The term "lymphatic malformation" refers to a group of benign vascular anomalies which result from embryologic abnormalities in the development of the lymphatic system. Lymphatic malformations occur in about 1:1700 live births, with an incidence that has remained relatively stable. Lymphatic malformations are generally divided into three major groups: Cystic (by far the most common), lymphangiectasia, and lymphedema. This chapter will focus on the clinical diagnosis and treatment of cystic lymphatic malformations.

70.2 Nomenclature and Classification

Historically there has been significant confusion regarding the nomenclature of vascular malformations in general and lymphatic malformations in particular. In 1996, the Society for the Study of Vascular Anomalies adopted a classification system aimed at minimising such confusion (Table 70.1). "Cystic hygroma" and "lymphangiomas" are commonly used to describe lymphatic malformations. These terms should be abandoned and the term lymphatic malformation should be used instead. Morphologically, cystic lymphatic malformations can be classified as microcystic, macrocystic or combined.

70.3 Pathology and Embryology

The lymphatic system develops from five primitive sacs: two in the neck, one in the retroperitoneum and two sacs posterior to the sciatic veins. Later on it was

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Table 70.1 Classification of Vascular Malformations including: Lymphatic malformations

Vascular tumors	Slow-flow VM	Fast-flow VM	Combined VM
Hemangioma	Capillary Malformations	Arteriovenous Fistula (AVF)	Klippel-Trenaunay syndrome (CLVM)
Kaposiform Hemangioendothelioma (KHE)	Venous Malformation	Arteriovenous malformation (AVM)	Parkers-Weber syndrome (CAVM)
Tufted Angioma	Lymphatic Malformation		

suggested that lymphatic malformations actually result from failure of the lymphatic spaces to join the venous system. Whether the cause of lymphatic malformation is related to sequestration of lymphatic sac, failure of fusion with the venous system or obstruction of lymph drainage remains unknown.

Lymphatic malformations consist of cystic cavities filled with clear or straw coloured fluid, which is usually eosinophilic and protein rich. Occasionally haemorrhage into the cyst can be seen. These lesions usually have an infiltrative pattern of growth, a factor that may complicate planning for operative treatment.

Due to the close development of the lymphatic system with that of the venous system, the cysts are usually lined with a single layer of endothelial cells. The relationship between the developing lymphatic system and the cardiovascular system have led to a number of theories to explain the pathogenesis of lymphatic malformations, including abnormalities in the development of extracellular matrix and neural crest migration. The wall of a lymphatic malformation usually also contains abnormal muscle cells of both the smooth and striated variety. Histologically these malformations can be composed of one or more of the following architectural patterns: capillary, cavernous and cystic. Whether growth of these lesions is due to neo-tissue formation or thrombosis with ongoing re-organization within the malformation remains a subject of debate. It is important to note that the microcystic, macrocystic or combined micro and macrocystic classification is based on morphology. The exact aetiology remains unclear.

70.4 Epidemiology and Prenatal Diagnosis

Lymphatic malformations are often diagnosed prenatally. The natural history ranges from progression to hydrops, to complete resolution, a possibility that has been well documented.

Prenatally diagnosed lymphatic malformation may be a marker of aneuploidy (>50%), syndromicity and other congenital structural anomalies. This subgroup is usually diagnosed early in pregnancy, is predominantly nuchal, and is associated with diffuse lymphatic abnormalities (Fig. 70.1). Isolated lymphatic malformations presenting early in pregnancy often resolve spontaneously. This is in sharp contrast to isolated lymphatic malformation diagnosed late in pregnancy, which are similar to those presenting to pediatric surgeons postnatally. This "late" group is rarely associated with aneuploidy (<1%), affects a variety of sites, and almost never resolves.

The incidence of lymphatic malformation is variable. In a population-based study from Wessex region the incidence was estimated at 1 in 1,750 live births. It is important to note that the incidence in spontaneous abortions is much higher, estimated at 1 in 200. The rate of aneuploidy seen in association with prenatal diagnosis of lymphatic malformation is estimated at 50–60%. Of the multiple syndromes associated with

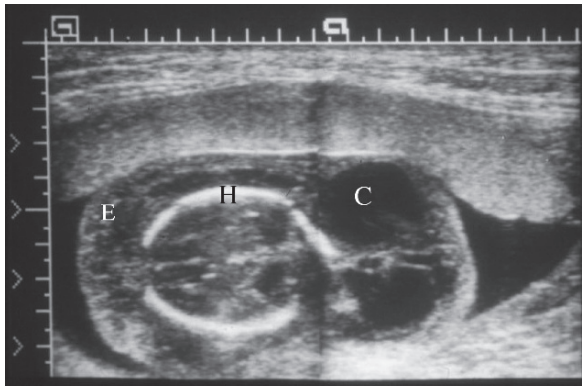

Fig. 70.1 Prenatal ultrasound of a fetus with Turner syndrome and a large posterior cervical cystic hygroma. Note the diffuse subcutaneous edema (E), which is indicative of hydrops fetalis. H = fetal head, C = cystic hygroma

Table 70.2 Syndromes commonly associated with prenatally diagnosed LM

Non-aneuploidies	Aneuploidies
Noonan's	Turner
Multiple pterygium	Down
Achondrogenesis type-1	Edward
Short-rib-polydactyly syndrome	Patau
Fryn's	
Robert's	
Fetal alcohol	

the prenatal diagnosis of lymphatic malformation, Turner's syndrome and Noonan's syndrome are probably the most common (Table 70.2).

In a key study, Howarth et al. reported population based estimates of prevalence and natural history of lymphatic malformation in the United Kingdom. The database included more than 175,000 live births over a 3-year period, of which 99 patients with lymphatic malformation were identified, (yielding a prevalence of 1 in 1,775 live births). Karyotyping was performed in 88% of pregnancies, of which 61% were abnormal. Moreover, structural abnormalities were seen in 21 patients. Cardiac anomalies were the most prevalent, especially A-V canal defects. This could not be explained only by aneuploidy, since almost 40% of these defects were seen in euploid fetuses. Other structural anomalies seen included: exomphalos, renal, skeletal and central nervous system anomalies. Of the 99 pregnancies identified with an associated lymphatic malformation, 19 suffered spontaneous fetal demise, and 64 underwent pregnancy termination. The other 16 went on to live birth. Of these, only 6 were completely normal postnatally. One required surgery for the lymphatic malformation but was otherwise normal, four died, and the remaining patients had significant chromosomal anomalies and neurological impairment. This "hidden mortality" of lymphatic malformation has been well documented by others.

Because of the high risk of associated syndromes, parental counseling should take place in a specialized center, where complete fetal investigation, including karyotype analysis and detailed ultrasound examination, can be undertaken.

Prenatal diagnosis of a large cervical mass should raise suspicion for potential airway obstruction that may impact planning for delivery. The treating team should include a surgeon, and should be prepared to perform life-saving procedures such as ex-utero intrapartum treatment (EXIT), endoscopy and a surgical airway (Fig. 70.2).

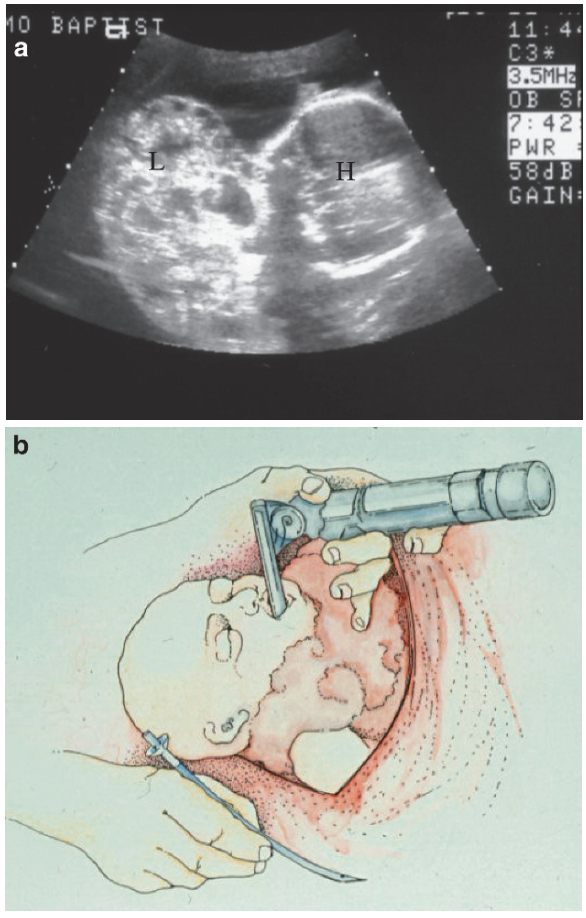

Fig. 70.2 (a) Prenatal sonogram showing a large pretracheal lymphatic malformation. H = fetal head, T = lymphatic malformation. (b) The EXIT procedure, in which intubation is accomplished prior to delivery while still on placental support

70.5 Clinical Features

Most lymphatic malformations are diagnosed postnatally. More than half are evident at birth and more than 80% are diagnosed by the age of 5 years; rarely lymphatic malformations may present later in the first 2 decades of life. These lesions vary widely in size. The most common anatomic location is the head and neck (Figs. 70.3 and 70.4); Table 70.3). Other areas commonly affected are: axilla, mediastinum, groin and retroperitoneum (Fig. 70.5). The predilection to these sites is thought to be related to the rich lymphatics in these areas.

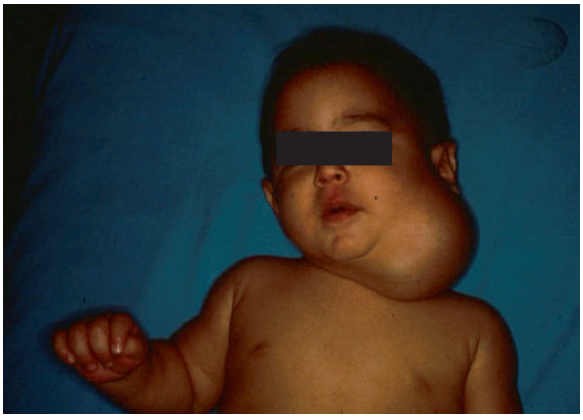

Fig. 70.3 Five month old child with moderate-sized lymphatic malformation, which was relatively asymptomatic

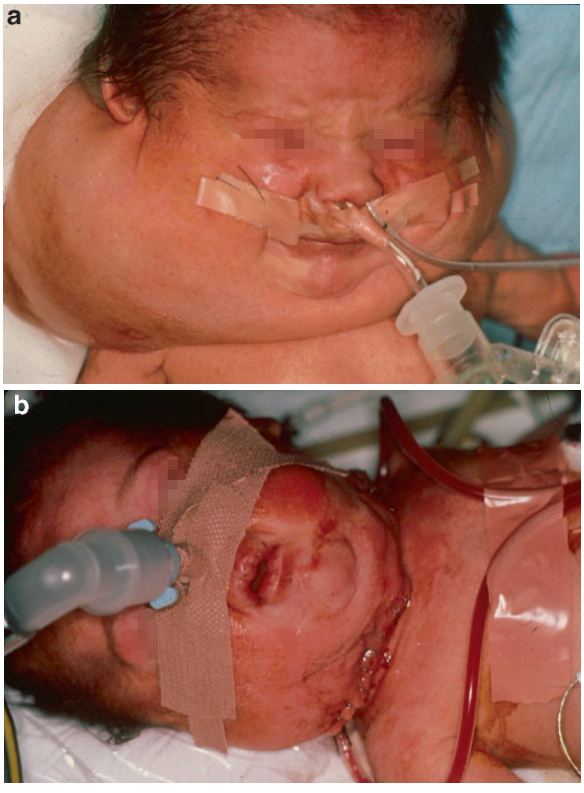

Fig. 70.4 Newborn with large cystic hygroma and airway obstruction. (a) Preoperatively, (b) Postoperatively

Table 70.3 Lymphatic malformations of the head and neck at The Hospital for Sick Children (1988–2000)

Sites of Involvement (130 Patients)	
Site	Number of cases
Neck[a]	97
Posterior	40
Anterior	38
Submandibular	37
Face and Oropharynx[b]	46
Tongue	14
Floor of mouth	14
Cheek	17
Parotid	14
Larynx	5
Mediastinum and chest wall	14

[a] Neck Only–69, Entire Neck (all three sites)–17
[b] Face and Oropharynx Only–19

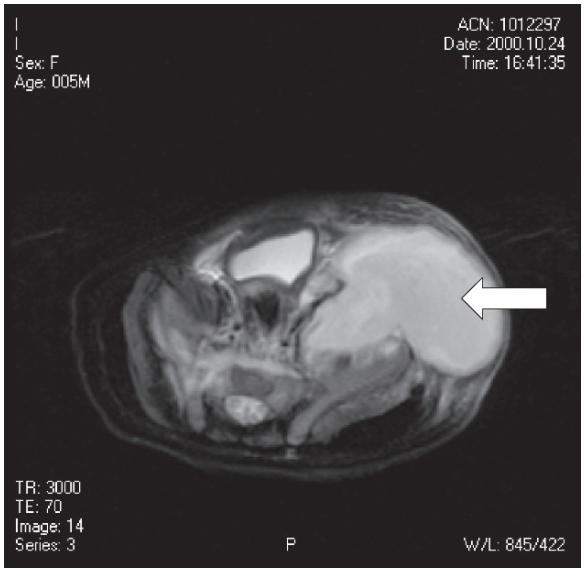

Fig. 70.5 MRI image of a retroperitoneal cystic hygroma presenting as an asymptomatic abdominal mass in a newborn (arrow)

Microcystic lymphatic malformations usually present as clear small vesicles infiltrating underlying tissues and are commonly found above the level of the mylohyoid muscle. Macrocystic lesions on the other hand are usually large, compressible masses under normal or bluish skin and are commonly below the level of the mylohyoid in the anterior or posterior triangles of the neck. Lymphatic malformations of the extremities are relatively uncommon but can be quite disfiguring.

Symptoms caused by lymphatic malformations are related to anatomical site, size and the presence or absence of complications such as bleeding or infection. However, most lymphatic malformations are asymptomatic and their effect on cosmesis is related to their site and size. Complications of lymphatic

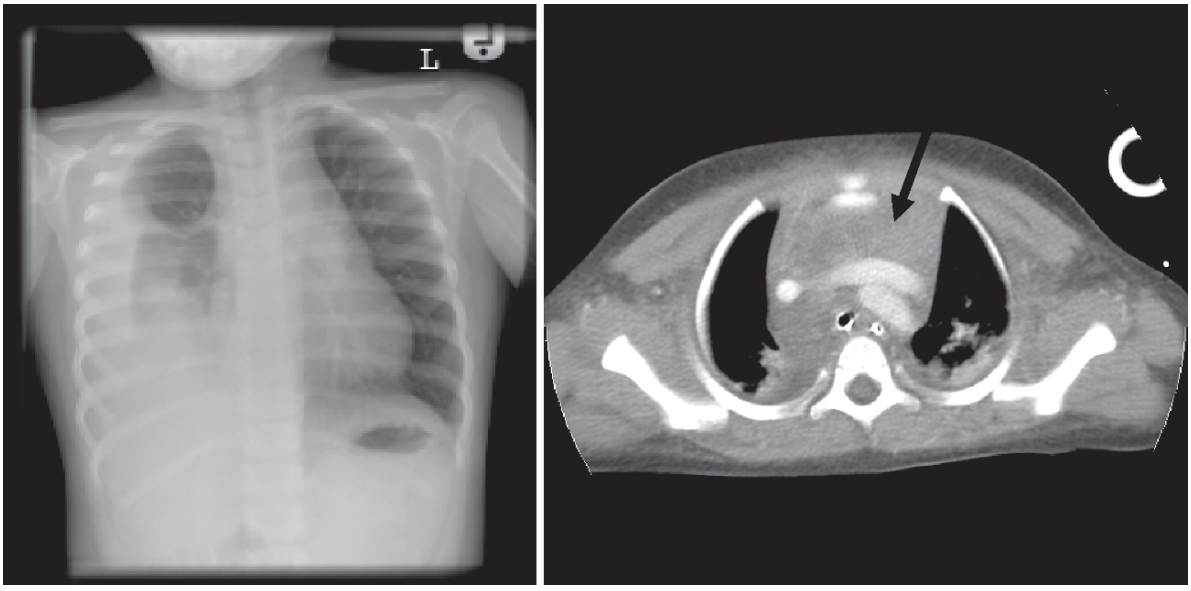

Fig. 70.6 Chest X-ray and CT from a child with persistent chylothorax due to a mediastinal lymphatic malformation (arrow)

malformations include *infections* which may be caused by bacteria contaminating cutaneous vesicles related to the malformation, or which travel to the malformation from distant sites through lymphatic channels. Such infections must be treated expeditiously and aggressively, since they can progress to life-threatening sepsis.

Hemorrhage into the cyst is also a well-described complication and may be spontaneous or related to minor trauma. Both infection and/or trauma may account for sudden rapid increase in the size of the malformation and may be the first presenting symptom. Less commonly, large malformations may cause airway obstruction. Such complex lesions require prompt treatment by an expert multi-disciplinary team. Rarely, *chylothorax*, *chylopericardium*, or *chylous ascites* may complicate lymphatic malformations (Fig. 70.6).

70.6 Investigations

No laboratory tests are necessary to diagnose a lymphatic malformation. If oncological diagnoses such as teratoma or lymphoma are being considered, measuring tumor markers specific to the tumor in question would be appropriate.

Ultrasound is usually the first imaging study to be performed. In some cases, no further testing is necessary, since ultrasound often provides adequate information regarding the consistency and location of the mass. However, it is often necessary to further delineate surrounding anatomy and relationships of the lesion to nearby vital structures, and for these cases *computerized tomography (CT)* and *magnetic resonance imaging (MRI)* are superior to ultrasound. Of these two imaging studies, most authors believe that MRI provides superior information, particularly with respect to the relationship of the lymphatic malformation to nearby neurovascular structures (Fig. 70.7).

70.7 Treatment

70.7.1 Non-operative Treatment

70.7.1.1 Expectant Treatment

The risk of complications associated with sclerotherapy and surgery must always be weighed against the risk of infection and bleeding, and the cosmetic implications of the lymphatic malformation. There is no risk for malignant transformation of these lesions. For

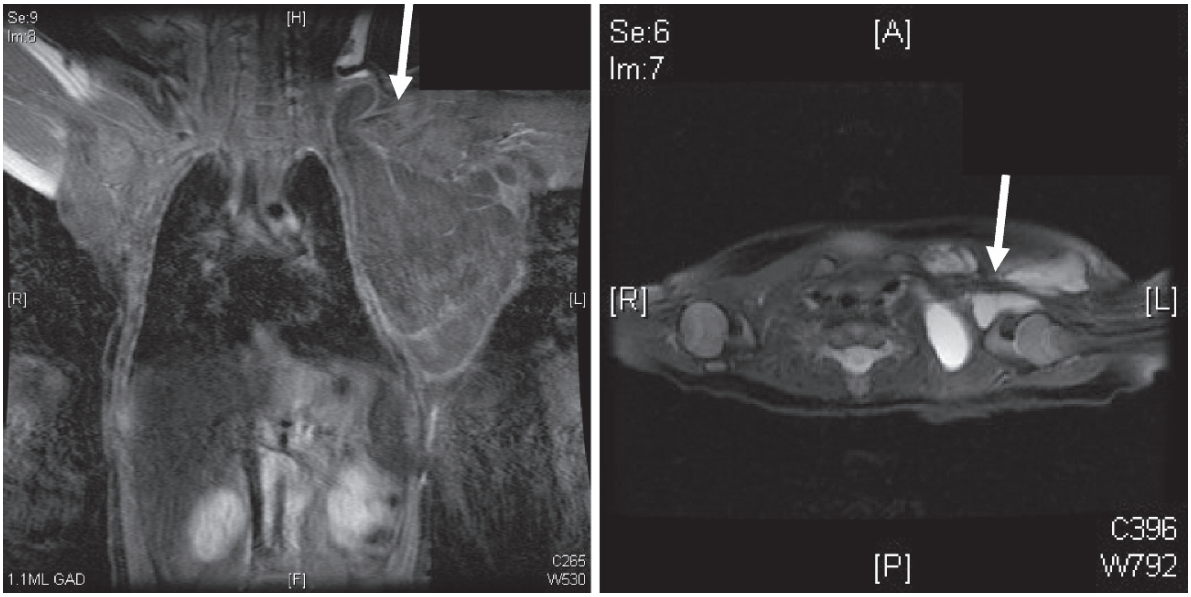

Fig. 70.7 Child with a large lymphatic malformation of the chest wall, extending into the axilla. The MRI demonstrates clearly the relationship of the lesion with the axillary neurovascular structures (arrows)

some asymptomatic lesions, or for lymphatic malformations that are located in a sensitive anatomic location that creates significant risk, some authorities would recommend expectant treatment.

70.7.1.2 Sclerotherapy

The increasing interest in sclerotherapy in recent years is a response to the relatively high complication rate reported after surgical resection, including recurrence, injury to vital structures, and large scars. The risk for neurovascular injury is higher in remedial surgery; hence, use of sclerosing agents has been recommended both as primary and adjuvant therapy. Multiple agents have been used with varying degrees of success, including: OK 432, Bleomycin, Ethibloc, dextrose solutions and fibrin glue. Injecting sclerosing agents is best performed under ultrasound guidance. The cyst is usually emptied prior to injecting the sclerosant.

OK432

OK432 is a compound derived by incubating a lyophilized group A streptococcus pyogens in benzyl penicillin. This agent was initially developed in Japan, and is still not approved for use in the United States. Advocates of this sclerosing agent note the relatively safe profile of the drug, particularly in contrast to bleomycin which may be associated with pulmonary fibrosis. Likewise, ethanol and sotradecol may produce life-threatening complications if injected in the blood stream. It remains unclear how OK432 produces its sclerosing effect. Although the agent produces an intense inflammatory reaction, no necrosis is seen on pathologic examination. This suggests that OK 432 causes cytokine-induced permeability of the endothelial lining of the malformation. The proposed increase in plasmin induced by OK 432 might allow for diffusion of OK 432 throughout the lesion, explaining its surprising effectiveness on microcytic lesions.

There are some well known complications of OK 432.

Anaphylaxis can be life threatening and is a result of the penicillin component in OK 432.

Swelling compressing vital structures: Swelling can result in significant airway compromise and it is advised that patients with lesions in the head and neck be admitted to hospital for observation post injection. Significant swelling is observed in up to 50% of patients. *Fever* is almost a universal finding in patients

injected with OK 432. Fever is usually more than 38 degrees and persists on average for a day or two. There have been reports of fever lasting up to 10 days post injection.

No long-term studies are available yet to examine recurrence after treatment with OK 432. However in a recent report from Italy, recurrence was seen in a third of patients treated with this agent. Re-treatment with OK 432 is reasonable.

The use of OK 432 for the treatment of lymphatic malformations was first reported by Ogita et al. in 1987 with a subsequent report from the same group in 1994. However, very few studies have reported similar results outside Japan in part due to the relative difficulty of obtaining the material elsewhere. In a recent review from Sweden, Claesson et al. reported their experience with OK 432 in 32 patients, 28 of whom were children. In this series the authors excluded patients with an allergy to penicillin and those with significant medical problems. The mean age at the time of treatment with OK 432 was 3 years and 9 months (2 months to 11 years). In this cohort the injection treatment was used as primary treatment in 93% of patients (26 children). The authors rated the results of their treatment visually based on the response of the lesion to injection treatment. Results were said to be excellent when no residual disease was seen, fair when a > 50% reduction was observed and poor if such reduction was less than 50%. Fifteen patients had large cysts that were not previously treated; an excellent response was recorded after a mean of 2.6 injections (range 1–7). Another four children had microcystic disease and an excellent result was seen in two. A third developed a recurrence after 6 months, the results however were still considered fair. In the group of patients who had combined malformations (n = 8), all received OK 432 primarily. 87.5% (7 patients) had excellent results; the eighth patient had a large malformation for which he received a tracheostomy at birth. The neck part of the malformation responded well to OK 432, but due to the persistence of the mediastinal part of the malformation operative treatment was performed with excellent results. The authors note that there was no increased difficulty observed secondary to the use of the sclerosing agent. Claesson et al. concluded that the OK 432 is an excellent alternative to surgery in the treatment of lymphatic malformations.

A more recent case series on the use of OK 432 from New Zealand in 2004 reported 7 children under the age of 5 years who were treated with OK 432. In this series the surgeons used ultrasound guidance to aspirate the malformations and inject a maximum of 0.1 mg per session. Two lesions were in the neck, four in the axilla and one in the floor of the mouth extending to the anterior neck. Of note the injection therapy was performed as day surgery. The authors report "excellent" results in macrocystic lesion and "disappointing" results in their microcystic counterparts.

The most recent review is a case series by Luzzatto et al. In this study the authors report two separate cohorts. The first cohort comprised 29 children with lymphatic malformations who underwent treatment with OK 432 over a period of 4 years from 1999 to 2003. The second cohort described long term follow up of a previously reported series of 15 patients who underwent the same treatment in an earlier time period. In the recent group of 29 patients 12 had complete resolution with OK 432 treatment. Eight patients had more than 50% reduction and seven had no change in their lesions. The remaining two patients were lost to follow up. When the lesions were stratified by type the authors noted that about a half of the patients had no response in the microcystic and combined groups. As for long term results, the authors also reported an overall 30% recurrence rate in the cohort that was treated in earlier years. Two important lessons are learned from this report: the authors noticed ongoing regression beyond 6 weeks, and have become less aggressive in terms of repeat injections so long as the lesion continues to involute on ongoing clinical and ultrasound follow up. The second lesson is that persisting with injections beyond two sessions was worthwhile in early "non-responders", once the lesion did not respond to the third injection then further persistence was not indicated.

Bleomycin

The advantages of bleomycin are low cost and ready availability. Bleomycin as a chemotherapeutic agent works by DNA inhibition. It is postulated however, that it produces the sclerosing effect by inducing non-specific inflammation of the endothelial cells. The most feared complication of Bleomycin is the

development of pulmonary fibrosis. The association of pulmonary complications and bleomycin are well documented in the oncology population. Even when the drug is not injected directly in the blood stream—as seen when using it for pleurodesis—there is significant systemic absorption. Currently in most North American centers the use of this agent has been abandoned.

In a recent review from India seven patients with lymphatic malformations were treated with Bleomycin with technique described above. All the lesions were confined to the neck. All malformations were macrocystic. All patients showed an initial response, with three patients having complete resolution of their lesions. The rest of the patients had a greater than 50% initial response, but subsequent recurrence in three patients necessitated surgical excision. Sanlalip reported similar results.

Ethiblock (Alcohol Solution of Zein)

Ethiblock is a mixture consisting of ethanol, contrast agents, and amino acids, which has been used as a sclerosing agent for vascular malformations as well as other applications

Ethiblock is both biodegradable and thrombogenic. The mechanism by which it produces its sclerosing effect is not completely understood.

Ethiblock has been used in Europe since the early 1990s. The agent has yet to be approved by the FDA in the US. In a recent review from Montreal, 63 patients underwent treatment with this agent for 67 lymphatic malformations. Most lesions (67%) were in the head and neck region. Median follow up time in this report was 3.5 years. Purely microcystic lesions were excluded.

The majority of the patients underwent sclerosing therapy as primary treatment. Only six patients had had previous resection. The average treatment sessions per patient were 1.5 session /patient (range 1–6). The results were classified in a similar fashion to the aforementioned studies. Cosmetic results were generally encouraging. 49% of patients in the predominantly macrocystic lesions had excellent results. This is in sharp contrast to lesions which were mainly micro-cystic where only 23% had excellent results.

Analogous to most other sclerosing agents, patients experienced post injection pyrexia that lasted on average 1–2 days. Interestingly five patients required surgery post injection: two for scar revision, two for persistent drainage and one for a salivary fistula. Contrary to most surgeons' expectations, the authors claimed that the surgical resection was not more difficult due to scar formation from the previous sclerotherapy.

A common complication of Ethiblock injection is extravasation from the lesion post-injection. In the Montreal study, 80% of the patients experienced this problem. Although a cause for parental concern, the authors consider such extravasation a "good" sign, indicating the sclerosing effect of the agent is underway.

70.7.2 Surgical Management

Most lymphatic malformations remain readily amenable to surgical resection. With recent advances in surgical technique, anesthesia and critical care, post-operative mortality has significantly decreased.

When attempting surgical resection of a lymphatic malformation certain surgical principals must be remembered and adhered to. *First*, these malformations are benign lesions and hence, radical resection sacrificing vital structures is contraindicated. In all cases, slow careful dissection must be used, and all neurovascular structures must be identified (Fig. 70.8). *Second*, wide exposure with meticulous haemostatic dissection should be always carried out. Such dissection can be aided by the use of microbipolar techniques. *Thirdly*, intra-operative identification and individual ligation of lymphatic channels feeding into the lesion should be performed wherever possible. This is thought to decrease the likelihood of clinically significant post-operative lymphatic leak. *Finally*, closed suction drains should be left at the operative site to prevent accumulation of lymphatic fluid which could compress underlying structures.

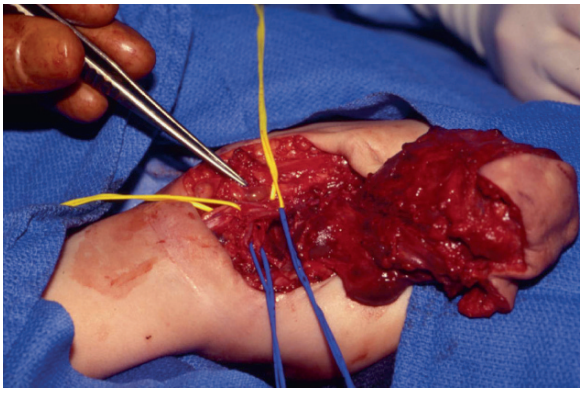

Fig. 70.8 Exposure of an axillary lymphatic malformation. Neurovascular structures must be identified and preserved, even if it means leaving some of the lesion behind.

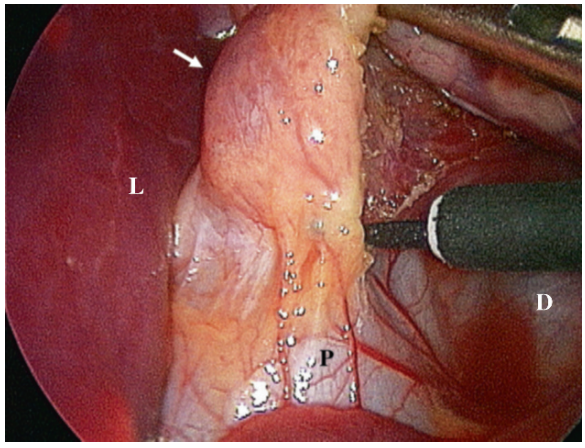

Fig. 70.10 Thoracoscopic resection of a mediastinal lymphatic malformation (arrow). P = pericardium, D = diaphragm, L = collapsed lung

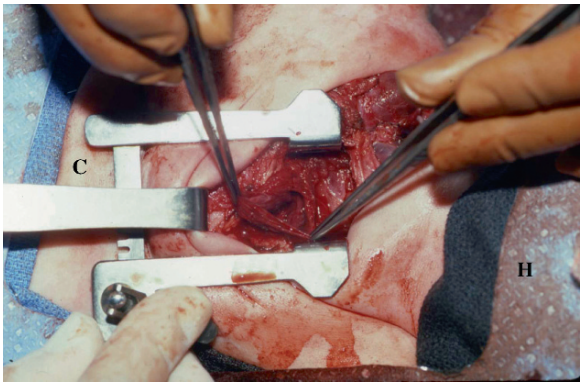

Fig. 70.9 Use of a "hockey stick" incision for a large cervicomediastinal lymphatic malformation. C = chest, H = head

The surgical approach should be individualized according to the anatomical position of the malformation. In the neck most surgeons would approach such lesions with a transverse incision. Lesions extending into the mediastinum could be approached by extending the neck incision into a median sternotomy (a "hockey stick" incision) as described by Grosfeld et al. (Fig. 70.9). Lesions in the chest and abdomen can be approached using laparoscopic or thoracoscopic techniques, as long as the aforementioned principals are adhered to (Fig. 70.10).

70.7.3 Surgical Resection Versus Sclerotherapy

Very few studies have compared surgical versus sclerosing treatment for lymphatic malformations. In a recent review from Japan, Okazaki et al. compared 78 patients who underwent surgical resection for lymphatic malformations with a group of 50 patients who were treated with OK 432 over a 26-year period. Similar to other reports, the most common location was head and neck (53.9%). The authors noted a significant increase in the utilization of primary OK 432 over the study period. Surgical treatment was effective for eradication of the malformation in 88.5% of patients compared to 64% in the OK 432 group. This difference was statistically significant. Eighteen patients failed initial OK 432 treatment and subsequently underwent surgical resection with good results. As observed in other series, the authors noted that surgical resection was not difficult after OK 432 injection. Although surgical treatment was more effective, it was associated with a higher rate of complications. In particular, 27% of surgical patients suffered lymphatic leaks, a complication that was not seen in the OK 432 group. The authors concluded that because OK 432 treatment was not as effective as reported in the literature, surgical treatment, especially in an area where there is little risk of damage to vital structures, is probably the initial treatment of choice.

70.8 Complications

70.8.1 Treatment of Recurrence

Little has been written about the indications and techniques for treatment of recurrent lymphatic malformations, or the morbidity associated with it. In the aforementioned study, 52.9% of patients had recurrent disease. Factors predisposing to recurrence include microcystic disease and/or incomplete initial resection. Location of the malformation—particularly lesions in the floor of the mouth and tongue—influences the rate of recurrence. The choice of treatment for recurrent lymphatic malformation should be individualized, based on the degree of symptomatology, the risk of injury to vital structures, and the cosmetic implications of further surgery.

70.8.2 Other Complications

Complications of sclerosing agents have been discussed previously. In the modern era, the mortality associated with surgical resection of a lymphatic malformation should approach zero. In a large series of 263 procedures performed for lymphatic malformations, 31.3% of the cohort experienced a complication over the 10-year period of the study. Local complications, mainly seromas and hematomas, occurred in 50% of patients. Neurological complications were seen in 17% of patients. These results are similar to our own experience, outlined in (Table 70.4).

Table 70.4 Perioperative complications–120 cases

Complication	Number
Infection	6
Bleeding[a]	5
Cranial neuropathy	12
Marginal mandibular branch VII [b]	10
Cranial nerve XI	1
Cranial nerve XII	1
Horner's syndrome	1
Seroma	4
Salivary fistula	1
Wound dehiscence	3
Tongue edema	3

[a]Requiring blood transfusion
[b]Paresis resolved completely

70.9 Conclusion

Lymphatic malformations are rare, challenging lesions that require significant expertise. A multidisciplinary approach is optimal for providing excellent care and maximizing the chances for a favorable outcome. With the current increasing interest in non-operative treatment, a standardized well-organized comparative study is needed to help define the role of these agents as primary treatments for lymphatic malformations.

Further Reading

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