Lymphatic malformations: A proposed management algorithm

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1. Introduction

Lymphatic malformations (LMs) are rare benign tumours that result from localized congenital malformations of the lymphatic system. These lesions are diagnosed during infancy in the overwhelming majority of cases and most often present as an asymptomatic mass in the cervicofacial region [1]. The management of LMs remains a challenge. Surgical excision has traditionally been the first line of treatment however due to the close proximity of vital structures this often leads to incomplete excision and recurrence, or damage to vital structures e.g. cranial nerves [2]. More recently the use of OK-432 has gained popularity especially in the management of macrocystic lesions [3]. The authors reviewed the records of all cases treated for LMs at our institution during a 10-year period. Whilst the majority of cases were managed surgically, promising results were obtained with observation alone as well as with OK-432 injection. Based on experience gained in the management of these lesions as well as current literature on the subject the authors of this paper have formulated a proposed management algorithm for LMs.
suffering from extensive disease encompassing both the supra and infrathyroid areas. In 2 of these cases there was significant mediastinal extension of the tumour. Only 1 case of exclusively infrathyroid LM was treated at our institution during the 10-year period. The most commonly affected area was the submandibular region affecting 5 cases (36%). Six cases had combined macro- and microcystic disease and 2 cases suffered from predominantly microcystic disease.

The predominant reason for referral to our service was an asymptomatic mass (50%); the remaining patients presented with either airway compromise (36%) or dysphagia (14%). In all cases the diagnosis of LM was confirmed with radiologic investigations. Magnetic resonance imaging (MRI) was the most commonly used modality and was employed in 71% of cases. Other investigations included computed tomography (CT) and ultrasound (US) scanning.

Treatment modalities employed consisted of observation, OK-432 injection, surgery or a combination of these (Table 1). All cases of microcystic disease of the oral cavity were managed with surface potassium–titanyl-phosphate (KTP) laser therapy in order to control symptoms. Of the seven patients treated with surgical excision, four had been operated on at other hospitals prior to referral to our institution. Major complications of treatment included a single case of facial nerve palsy and another of hypoglossal nerve palsy. Both of these cases had undergone previous surgery and the above complications occurred during revision surgery for recurrent disease. Minor complications included seroma and haematoma formation in 2 separate cases.

Two cases (14%) were lost to long term follow up and were therefore not included in the final outcome measurement. Outcome was defined as excellent in cases with complete resolution of the lesion and no residual cosmetic or functional impairment. In cases with minimal residual or recurrent disease, of little concern, the outcome was classified as good. A patient with recurrent or persistent disease staying stagnant or showing some degree of improvement was rated as fair. Finally patients with severe progressive disease showing minimal or no response to treatment were classified as having poor outcome. Favourable outcomes were obtained in 10 cases (83%). Of these five were classified in the “excellent” and the remainder in the “good” outcome groups. Persistent or recurrent disease was encountered in 4 cases. The most common site of recurrent disease was the tongue (50%).

4. Discussion

LMs once referred to as either cystic hygroma or lymphangioma depending on cyst size is now more commonly divided into macrocystic, microcystic or combined disease [4]. The reported incidence of these tumours in the literature is quite variable, ranging between 4 per 10,000 births in one study [5] and 1 per 16,000 births in another [6]. The overwhelming majority of LMs occur in the cervical region with an increased incidence on the left side. There is no difference in distribution between the sexes with both equally affected. The age at diagnosis is reportedly 75% at birth with 90% of the remaining cases diagnosed by the age of two [7]. Two cases in our series (14%) were diagnosed during the antenatal period. Five cases (36%) were diagnosed at birth and 86% of cases were diagnosed within the first 3 years of life. To date numerous theories have been proposed regarding the embryological aetiology of these lymphatic malformations. These include the centrifugal and centripetal theories, the former proposed by Sabin and the latter by McClure and Huntington, as well as the combined theory proposed by van der Jagt and Kutsuna [3,7]. Regardless of the proposed theory the final result is failure of either the peripheral lymphatics to flow to into the jugular sacs or failure of the jugular sacs to reunite with the venous system [7]. It is also widely accepted that LMs can be acquired secondary to surgery, trauma, infections, neoplasms and chronic inflammation [3,7]. The histopathological classification of LMs as proposed by Kennedy in 1989 includes four distinct groups [7]. It is widely accepted however that all these lesions form part of the same disease process [8].

The majority of cases (43%) in our series presented with an asymptomatic mass in the cervicofacial region. The remainder either presented due to airway concerns (36%) or dysphagia (21%). These findings are consistent with previously reported presenting symptoms and signs [9]. In the group that presented with airway compromise, three patients required tracheotomies two of which were emergent. Infective episodes as well as haemorrhage into these cysts are quite common, often leading to rapid enlargement of the cyst with potential airway compromise [10]. This can occasionally, as illustrated in our case series, require an emergency tracheostomy. Current guidelines on the management of these episodes advocate the use of parenteral Gram positive coverage for up to 3 weeks followed by a prolonged course of oral antibiotics [10]. In our case series 64% of patients developed at least one such episode whilst others suffered from recurrent infections, all of which were successfully managed medically. A recent report by Sires et al. [11] showed promising results with use of systemic corticosteroids in the treatment of these episodes in ophthalmic LMs.

In an effort to predict the prognosis of LMs several staging systems have been proposed. Orvidas and Kasperbauer [12] used the variables of functional impairment, cosmesis, number of locations and age at diagnosis in order to formulate a staging system. They demonstrated an increase in persistence as well as complication rate with increasing stage. However the most commonly used staging system was developed by de Serres et al. and published in 1995 [13]. It is based on the anatomical location of the LM and consists of five stages (Table 2). In their paper they described a clear correlation between the stage of the disease and the prognosis as well as associated complication rate. Group 1 patients had a complication rate of 17% compared to 67% in group 3 and 100% in group 5. Clearly demonstrating a progressive increase in complication rate associated with higher staging. In a retrospective study of 22 cases Hamoir et al. [14] applied the proposed staging system and reported findings consistent with those of de Serres et al. In our case series 7% were classified in group 1, 64% in group 2 and 29% in group 3. There were no patients in group 4 or 5. Our results reflect the findings of de Serres as well as Hamoir et al. with a more favourable outcome
and a range of different imaging modalities (Fig. 5). Clinically these disease. Other imaging options include US and CT scanning. Each of these modalities describes as soft; doughy masses which US is very useful in evaluating superficial lesions[15] and in the evaluation of deeper structures in the neck and mediastinum[15]. Sonographically these lesions are multilocular however in the evaluation of deeper structures in the neck and mediastinum[15]. Sonographically these lesions are multilocular cystic masses with septa of variable thickness[16]. MRI is regarded as the modality of choice in order to evaluate the involvement of neighbouring structures and to effectively plan any surgical intervention [3,8]. Some of the benefits of MRI include superior multiplanar capabilities, no ionizing radiation and lack of bony artefact [15]. The typical appearance of LMs on MRI scanning includes low signal intensity on T1-weighted images, high signal intensity and multiple cysts with well demarcated margins on T2-weighted images[15,17]. Massive osteolysis, skeletal distortion and hypertrophy have been reported secondary to cervicofacial LMs [9]. If this is suspected CT scanning is the investigation of choice due to its excellent delineation of bony structures.

The diagnosis of LMs usually depends on physical examination and range of different imaging modalities (Fig. 5). Clinically these lesions have been described as soft; doughy masses which transilluminate [8]. In our case series nearly all the patients had a MRI scan performed in order to delineate the extent of the disease. Other imaging options include US and CT scanning. Each of these modalities has distinct advantages as well as disadvantages. US is very useful in evaluating superficial lesions [15] and in the guidance of OK-432 injection therapy (see below). It is limited however in the evaluation of deeper structures in the neck and mediastinum [15]. Sonographically these lesions are multilocular cystic masses with septa of variable thickness [16]. MRI is regarded as the modality of choice in order to evaluate the involvement of neighbouring structures and to effectively plan any surgical intervention [3,8]. Some of the benefits of MRI include superior multiplanar capabilities, no ionizing radiation and lack of bony artefact [15]. The typical appearance of LMs on MRI scanning includes low signal intensity on T1-weighted images, high signal intensity and multiple cysts with well demarcated margins on T2-weighted images[15,17]. Massive osteolysis, skeletal distortion and hypertrophy have been reported secondary to cervicofacial LMs [9]. If this is suspected CT scanning is the investigation of choice due to its excellent delineation of bony structures.

The use of routine ultrasound evaluation of the fetus during the antenatal period has become commonplace throughout the world. This has led to an increased proportion of LMs being diagnosed during the antenatal period. A high incidence of associated chromosomal abnormalities has been noted in prenatally diagnosed LMs and therefore amniocentesis is advised in cases presenting with polyhydramnios, fetal hydrops and fetal LMs [10]. Once the suspicion of an obstructing neck mass is raised on US further imaging is essential in order to evaluate the extent of airway obstruction. In their report of 31 cases Bouchard et al. employed ultrafast MRI imaging with Half-Fournier single shot turbo spin echo sequence [18]. If this confirms airway compromise an ex utero intrapartum treatment procedure (EXIT) should be planned.

The senior author of this report has a special interest in paediatric airway management and has been involved in EXIT procedures in the past. Other members of the multidisciplinary team include anaesthetists, obstetricians, neonatologists and paediatric surgeons. The procedure is performed under general anaesthetic. A hysteroctomy is performed and the fetal head and shoulders are delivered. In certain instances decompression of the cystic mass can be performed under ultrasound guidance prior to hysterotomy. Placental separation is prevented and adequate uteroplacental blood flow is maintained by ensuring uterine relaxation, normal mean arterial pressure and by maximizing uterine volume. Once the head and shoulders are delivered the fetus is monitored throughout the procedure with pulse oximetry and echocardiography. The airway is then secured. This is achieved via endotracheal intubation following direct laryngoscopy or rigid bronchoscopy. If this fails reverse endotracheal intubation is the next described option. This is achieved by isolating the trachea and performing a tracheostomy where after a fine feeding tube is passed back through the trachea and into the oral cavity. An endotracheal tube can then be advanced over the feeding tube into the trachea allowing closure of the tracheostomy. If this is not a feasible option a formal tracheostomy is performed. Once the airway is secured manual ventilation is started and surfactant administered. Finally the cord is clamped only after the insertion of an umbilical arterial line and upon achieving good oxygen saturation [18].

The treatment of LMs still poses a formidable challenge to those confronted with managing this rare entity. Observation, aspiration, surgery and sclerotherapy are just some of the treatment modalities described. Some authors view spontaneous regression of LMs as unlikely and rare [5,14]. The weight of evidence does however support spontaneous regression of LMs [7–10,19], some describing rates of up to 15% [3]. Because of these findings some physicians opt to manage asymptomatic lesions conservatively for up to 24 months [8,10]. Extreme vigilance is required in managing these lesions conservatively as sudden expansion of these lesions can occur as described above. In a recent study Perkins et al. [19] identified certain radiologic characteristics that indicate a high likelihood of spontaneous regression. These features included LMs with predominantly macrocystic tissue, less than five intracystic septations and limited extent. These are however lesions that would typically respond well to other forms of management as well.

Simple aspiration of LMs whilst once a recognised treatment option and still favoured by some [9], is now rarely used due to rapid recurrence, infection and haemorrhage [3]. However needle decompression may be beneficial in instances where there is rapid expansion of the lesion with concomitant airway compromise [3,10]. Sclerotherapy on the other hand has long been proposed as an alternative to surgery in an effort to avoid its hazardous complications. Some of the substances used in practice included bleomycin, ethibloc, tetracycline, dextrose and sodium morrhuate

<table>
<thead>
<tr>
<th>Case</th>
<th>A.A.D.</th>
<th>Site</th>
<th>Side</th>
<th>Sex</th>
<th>Presenting complaint</th>
<th>Type</th>
<th>Intervention</th>
<th>Size (cm)</th>
<th>Complications</th>
<th>Outcome</th>
<th>Recurrent/persistent</th>
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<tbody>
<tr>
<td>1</td>
<td>8 months</td>
<td>SM, T/M</td>
<td>R</td>
<td>M</td>
<td>Swallowing</td>
<td>Mic</td>
<td>KTP</td>
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<td>G</td>
<td>P</td>
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<td>F, AT, T/M</td>
<td>R</td>
<td>F</td>
<td>Airway</td>
<td>Comb</td>
<td>S, KTP</td>
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<td>F</td>
<td>L</td>
<td>M</td>
<td>Swallowing</td>
<td>Comb</td>
<td>O</td>
<td>–</td>
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<td>E</td>
<td>–</td>
</tr>
<tr>
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<td>6 weeks</td>
<td>SM</td>
<td>R</td>
<td>F</td>
<td>Airway</td>
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<td>E</td>
<td>–</td>
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<td>SM</td>
<td>L</td>
<td>M</td>
<td>Swallowing</td>
<td>Comb</td>
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<td>–</td>
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<td>E</td>
<td>–</td>
</tr>
<tr>
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<td>AT, M</td>
<td>L</td>
<td>M</td>
<td>Cosmetic</td>
<td>Mac</td>
<td>S</td>
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<td>Nil</td>
<td>G</td>
<td>P</td>
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<td>7 years</td>
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<td>G</td>
<td>P</td>
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<tr>
<td>9</td>
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<td>SM</td>
<td>L</td>
<td>F</td>
<td>Airway</td>
<td>Comb</td>
<td>O</td>
<td>–</td>
<td>Nil</td>
<td>G</td>
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</tr>
<tr>
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<td>M</td>
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<td>O</td>
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<td>P</td>
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<td>Airway</td>
<td>Mac</td>
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<td>–</td>
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<td>F</td>
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<td>LF</td>
<td>–</td>
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</table>

A.A.D. = age at diagnosis, SM = submandibular, T/M = tongue/mucosa, F = face, AT = anterior triangle, P = parotid, M = mediastinal extension, PT = posterior triangle, Comb = combined disease, Mac = macrocystic, Mic = microcystic, O = observation, KTP = KTP laser, S = surgery, G = good, P = poor, F = fair, LF = lost to follow up.
Microcystic disease of the oral cavity is notoriously difficult to treat with a large percentage of cases showing persistent or recurrent disease. Traditionally these lesions have been managed surgically with conservative resection in order to avoid the morbidity associated with complete excision; this however leads to high recurrence rates and the need for repeated procedures [28]. In our case series 21% of cases suffered from microcystic disease of the oral cavity. All of these cases were principally treated with surface KTP laser therapy to control symptoms. The use of laser therapy in the management of these lesions has been previously documented [29]. Laser treatment offers the following advantages over surgery: less postoperative oedema, less tissue trauma and less blood loss [3]. Favourable results were obtained with this modality; however recurrent disease was encountered in 66% of cases treated for LMs of the oral cavity. Another described treatment option for microcystic disease of the oral cavity is radiofrequency ablation therapy [28,23,30,31] which has recently shown promising results.

Traditionally surgical excision (Figs. 3 and 4) of LMs has been the mainstay of treatment [12,32]. The complete surgical excision of these lesions offers excellent results. However due to the close proximity of vital structures this can be very challenging and leads to partial resection in approximately 60% of cases [9]. Recurrence rates of partially or incompletely resected lesions are reported to be as high as 50–100% of cases [3]. Surgery is associated with significant morbidity and some of the recognised complications include muscle weakness, seroma formation, infection e.g. mediastinitis, chylothorax, Frey and Horner’s syndrome, injury to the cervical oesophagus and cranial nerve damage [3,7,9]. Cranial nerve injury can occur in up to a third of LMs treated surgically with the facial nerve most frequently involved [4].

Half of the patients in our case series were treated surgically with only one patient in this group lost to long term follow up. Some of these had undergone surgery prior to being referred to our institution. In the majority (66%) of these cases a favourable outcome was achieved. Two patients developed cranial nerve palsies, one facial and the other hypoglossal nerve. The first patient had been operated previously at another institution and the hypoglossal nerve palsy was present at the time of referral to our institution. Both of these patients had extensive cervicofacial disease encompassing both the infra and suprahypophyseal regions (stage 3) and in both cases the nerve damage occurred during revision surgery.

Based on experience in managing these tumours as well as current literature the authors of this report have developed a figure 1. Management of antenatally diagnosed LM.
management algorithm for paediatric cervicofacial LMs. The aim of this algorithm is to provide definitive management in the majority of cases prior to school going age. As already mentioned above, surgery was the principal management option in the past, however its complication and recurrence rate are unacceptably high in what is essentially a benign condition. The spontaneous regression of LMs whilst once described as unlikely has since been well documented and therefore in asymptomatic lesions the authors of this report would advocate expectant management initially. Should this fail OK-432 injection therapy offers an excellent alternative to surgery due to its high success rate, especially in macrocystic disease, as well as the lack of perilesional fibrosis which does not compromise future surgery if required. Sclerotherapy of microcystic disease with high dose doxycycline is a promising development and is something that might be considered as an adjunct to OK-432 in future. Finally should sclerotherapy fail the degree of cosmetic and functional impairment should be thoroughly assessed and weighed against the potential risks of surgery. It is however of utmost importance that each case be assessed on an individual basis in order to achieve the best possible outcome and in certain instances this might necessitate deviation from the guidelines above.

5. Conclusion

LMs are essentially benign tumours and the management of these should reflect this. Even though surgery might have been the principal management option in the past, its complication rate is unacceptably high in the management of a benign condition. This combined with the prospect of new innovative management
options that have been proven to be effective, have led the authors of this report to formulate a proposed algorithm (Figs. 1 and 2) for the management of LMs.

References