Lymphatic malformations of the head and neck: literature review and case study

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INTRODUCTION

Vascular anomalies are soft tissue lesions, which result from congenital vascular defects and present in approximately 10% of neonates.[1]

Historically defined in 1982,[2] the International Society Study of Vascular Anomalies (ISSVA) (1997) is now regarded as the main reference for the classification of congenital vascular anomalies. These lesions are divided into either vascular tumours or malformations, based on their clinical, histological, molecular, biochemical and radiological differences.[3]

Vascular malformations are uncommon, developmental defects. They are usually composed of localised enlarged ectatic vessels and classified according to the type of vessel involved;[1] arteriovenous (AVM), capillaryvenous (CVM), venous (VM), lymphatic (LM) and combined. Vascular malformations are further divided into slow flowing (CVMs, VMs, LMs) and fast flowing (AVMs),[4] based on the velocity of the fluid flow through the vasculature.[1] They are usually present from birth, affect males and females equally and grow commensurably with the patient. They demonstrate variable rates of regression dependent on their vessel/lesion type and often recur following treatment.[1] Familial inheritance has been questioned in two cases of venous malformation, both positive for a mutation resulting in the increased activity of tyrosine kinase receptor tunica internal endothelial cell kinase-2 (Tie-2) and resultantly implicated in abnormal vascular growth.[5]

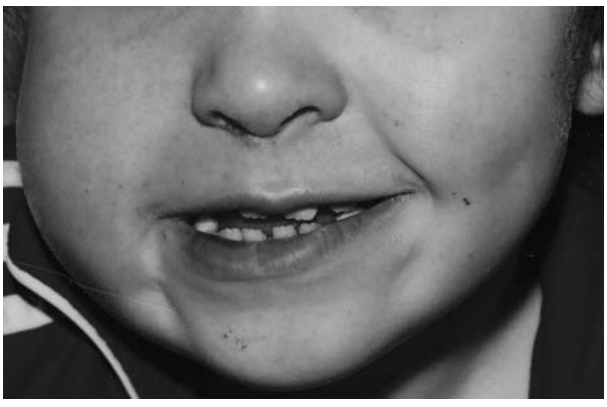


Figure 1 Swelling of the right buccal region

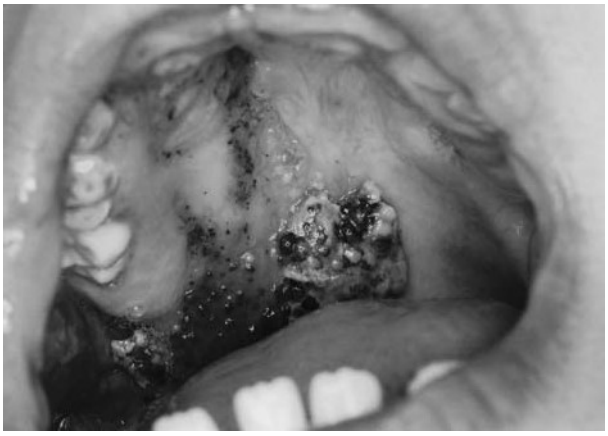


Figure 2 Lesion present on the palate, exhibiting crops of vesicles appearing to contain blood extending over the hard and soft palate

Vascular malformations are molecularly distinct from vascular tumours as their cells undergo a normal cell cycle.[2] In contrast, vascular tumours such as hemangiomas are richly composed of proliferating, hyperplastic endothelial cells. Hemangiomas most commonly occur as solitary lesions in the head and neck. They affect 10-12% of one-year-old children,[6] and are the most common type of tumour affecting the parotid gland and orbit. After initial proliferation in the first 12 months of life, they often stabilise and start to involute at variable rates.[1]

CASE STUDY

An eight-year-old girl presented with a raised temperature (38.4°C) and swelling of the right cheek (see figure 1) which

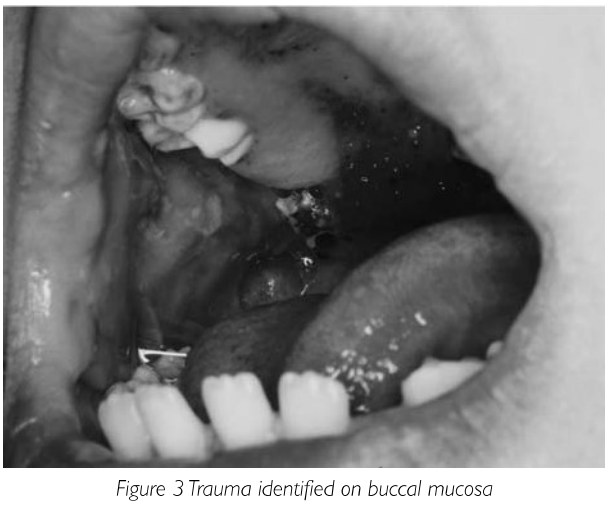


Figure 3 Trauma identified on buccal mucosa

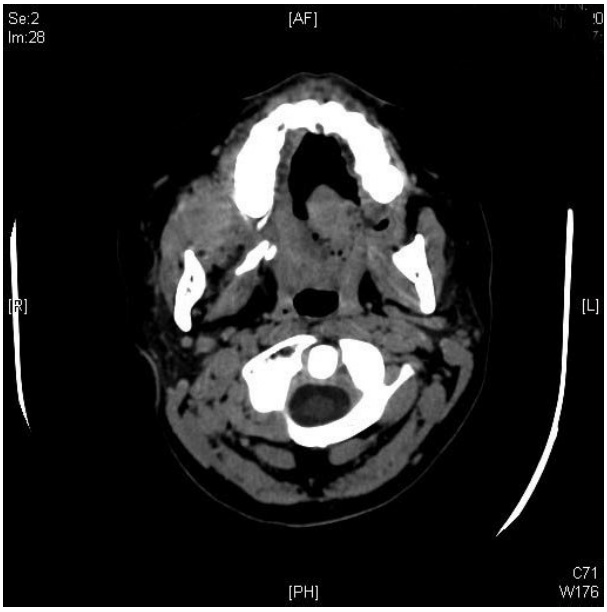


Figure 4 CT scan post collimation axial image

had been present for a couple of hours and was gradually worsening. Symptoms associated with inflammation (redness, temperature, swelling, and pain) were all localised to this area.

Her parents had noticed bleeding over a two-day period from a lesion on the palate reported to be present from birth (see figure 2).

No other symptoms were identified. The patient's mother reported a history of five past episodes of cellulitis, the last occurring six months ago, and that the patient was highly susceptible to bleeding gums, although oral hygiene appeared to be reasonable.

The patient's medical history exposed a variety of conditions: septo-optic dysplasia; pan-hypo pituitarism; diabetes insipidus; precocious puberty; and medication-controlled idiopathic epilepsy. Developmental history exposed left-sided weakness, fine motor problems, and a past history of delayed development. Medications included replacement of thyroxine, desmopressin, hydrocortisone, and growth hormone. There was no known family history of any conditions.

The right cheek felt extensively thickened, expanded inwards, and subjected to trauma through cheek biting (see figure 3).

A 2.5cm (approximately) red lesion was detected on the soft palate. An initial diagnosis based on clinical presentation was cellulitis/low grade infection of the right cheek, and a vascular anomaly extending from the right cheek, palate, and maxilla towards the medial aspect superior to the right eye. The patient was in mixed dentition stage with an anterior open bite, a few deciduous teeth appeared to be carious; however, she did not appear to have any associated infections/ symptoms.

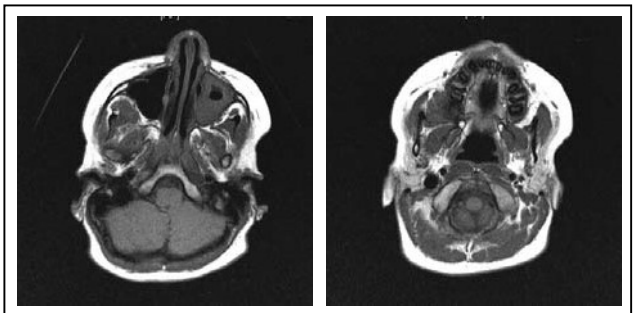
Shortly after admission, blood test results revealed high white cell counts (15.1 x 10^9/L), high neutrophil (9.0 x 10^9/L), basophil (0.18 x 10^9/L), monocyte (1.5 x 10^9/L) levels and a high C-reactive protein count (225.6 mg/L) which indicated an inflammatory process; however, lymphocytes (4.3 x 10^9/L) were normal and therefore did not support the possible sequestration/leucopenia theory.

The patient responded well to intravenous antibiotics and non-steroidal anti-inflammatory drugs. On discharge, antibiotics (flucoxacillin, metronidazole and penicillin) were administered and steroids increased for a week to attempt to reduce the inflammatory response.

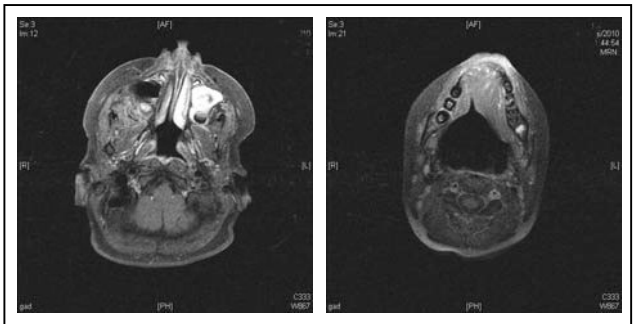
The computerised tomography (CT) images exhibited density enhancing tissue around the right tonsil extending laterally through the pterygoid region into the infra temporal fossa. These tissues were also identified in the right medial extra orbital tissues. Lobulated enhancing tissue also appeared to extend along the lateral aspect of the right nasal space and within the right antrum (see figure 4).

These features indicated the diagnosis of extensive microcystic lymphatic malformation. Macrocystic components were not identified, therefore a magnetic resonance image (MRI) was required to exclude this differential, in order to determine treatment options. The MRI (see figures 5, 6, 7, 8) was performed with contrast.

Fat-saturated images exposed an approximately 2cm lesion, with well-demarcated margins lying on the right side deep to the mandible extending slightly anterior to the masseter muscles. T2 sequences showed that the lesion extended into several other tissue planes. Superiorly, it extended close to the mid-right maxillary antrum level. The lack of large cysts and significant contrast enhancement were further indicative of a microcystic lymphatic malformation. Retrospectively from the MRI results, the lesion could be described as stage II (unilateral suprahyoid).



Figures 5, 6, MRI scans



Figures 7, 8 MRI scans

Treatment is currently being planned: the review below gives the non-specialist reader an overview of the condition, its differential diagnosis and the treatment strategies available.

LITERATURE REVIEW

This literature review will focus on lymphatic malformations to compliment the case study. A summary of current knowledge of lymphatic development and structure will help define current theories of the pathogenesis of LMs, complications and current and potential treatment options.

Lymphangiogensis: the development of the lymphatic system

A functional lymphatic system is essential for health. It regulates tissue fluid homeostasis, absorption of dietary lipids, and facilitates the immune system.

Embryology

The lymphatic system has a dual origin – from cardinal endothelia of veins and mesenchymal lymphoblasts.

Lymphatic vessel development begins embryonic weeks 6-7, after the cardiovascular system is established. In 1901, Florence Sabin theorised the centrifugal theory of lymphatic development, proposing primary lymph sacs bud from the cardinal endothelia of veins.[7] These endothelial cells express propero-related homeobox 1 (Prox-1), which commit cells to a lymphatic lineage. Prox-1 gene knockout studies in mice exhibit a collapse in lymphatic development as a result of incomplete migration of the endothelial cells. Another growth factor involved in this process includes LYVE-1, lymphatic vessel hyaluronon receptor 1, which is thought to play a role in committing cardinal endothelial cells to act as lymphatic precursors.[8] The endothelia sprout, migrate and remodel[3] to form functional peripheral lymphatic capillaries.[9] Other important vascular endothelial growth factors (VEGF), such as factor C (VEGF-C) and Tie-2, are thought to have a significant role during this remodelling stage.[3]

These deeper lymphatic vessels recruit smooth muscle cells and develop valves during the remodelling phase and develop into collecting vessels.[10] Podoplanin; a transmembrane glycoprotein is expressed on these vessels.[8] Co-expressed with growth factor VEGFR-3, podoplanin is found in cardinal veins and in lymphatic endothelial cells expressing Prox-1.[10,11] The presence and detection of lymphatic precursors, such as Prox-1, aid the identification of lymphatic tissues. As discussed earlier, Prox-1 is specific for lymphatic vessels and has a role in the up-regulation and expression of receptor VEGFR-3 on endothelial cells with a lymphatic fate. It is also thought to be involved in the dissociation of the lymphatic vessels from the venous vasculature.

Recent research on the deeper lymphatic system compliments Sabin's theory; however, superficial vessels are now thought to develop via a different pathway from mesenchymal lymphoblasts,[12] independent of the veins.[6]

Structure of the lymphatic system

The lymphatic system comprises of lymphatic capillaries which merge into vessels which transport the lymph to nodes, collect filtered lymph and return it to the venous system. These capillaries are 30-80µm in diameter and consist of a single layer of endothelial cells associated with very little basement membrane, few pericytes or valves. These features and lack of tight junctions make these capillaries very permeable. Anchoring filaments attach the capillary vessels to surrounding connective tissues. They become taut during periods of high interstitial pressure,[8] leading to expansion/opening of the capillary lumen, therefore decreasing intralumenal pressure and encouraging fluid uptake.[10] These filaments are composed of emilin-1 and fibrillin. It has been proposed that they adhere to lymphatic endothelial cells via integrin molecules.[10] Their potential role in the pathogenesis of LMs will be discussed later.

Blind-ended lymphatic capillaries merge to form the vast network of lymphatic vessels, which house valves preventing the back flow of lymph. These collecting vessels are composed of a layer of endothelial cells which are additionally surrounded by an incomplete layer of smooth muscle cells.[9] Contraction of the muscle cells and surrounding skeletal muscle in conjunction with arterial pulsation aids the propulsion of lymph fluid.[10] These channels do not permit the passage of fluid/cells from the interstitium. Lymphatic vessels are absent from the bone marrow and central nervous system.

Together, these capillaries and vessels network the unidirectional flow of the extravasated peripheral tissue fluid. This fluid contains electrolytes, water, macromolecules, lymphocytes (lymph). It is transported to lymphatic nodes to localise any antigen, and finally returned to the venous system in the form of filtered lymph. Lymph fluid from the head is returned to the right subclavian vein via the right lymphatic trunk.[10]

Lymphatic malformations

Considered benign, slow-flowing vascular malformations,[3] lymphatic malformations (LMs) can be described as focal, multifocal, diffuse, macrocystic, microcystic, or combined.[1]

The majority of children who are born with or develop an LM have normal chromosomes and no family history of vascular malformations.[8] There are no confirmed hereditary cases of LM. A 2003 study deduced that if there is a genetic cause it may occur in cases of lethal germline mutations, or as a result somatic mutations; however, there is an increased incidence in certain genetic conditions.[6] A 2008 study described how fetal karyotyping has shown a possible genetic association of LMs with chromosomal abnormalities,[12] such as Trisomies 13, 18, 21.[9] Turners syndrome (gonadal dysgenesis) was found to be most common in association with macrocystic lymphatic vessel hypoplasia. Klippel-Trenaunay and Proteus syndromes may also be associated with LMs. Characteristic features of Klippel-Trenaunay syndrome include cutaneous vascular stain in association with the malformation. Proteus syndrome signs include asymmetrical hypertrophy, exostoses, macrodactyly, epidermal nevi and lymphatic malformations.[12]

Approximately 50% of congenital LMs are diagnosed at birth; by the age of two years, 90% are identified and diagnosed.[13] The diagnosis of LMs is rare in adults; however, it should be considered as a possible diagnosis when presented with neck masses.[14] The majority of all LMs are found in the head and neck region; however, different studies report varying incidences – 75% in one study,[3] 60% in another,[13] with the tongue being most commonly affected. However, a 2008 study confirms these lesions can occur in any location.[12] They can be implicated in short- and longterm disfigurement,[8] and there is no predilection for any race/sex.[13]

Vascular anomalies	
Vascular malformations	*Vascular tumours*
Slow-flowing malformations: – capillary malformations (CM) – venous malformations (VM) – lymphatic malformations (LM) microcystic macrocystic combined Fast-flowing malformations: – arterial malformation (AM) – arteriovenous malformation (AVM) – arteriovenous fistula (AVF) Complex/combined malformations: – lymphatiovenous (LVM) – capillary venous (CVM) – capillary lymphaticovenous (CLVM) – capillary arteriovenous (C-AVM) – lymphatic arteriovenous (L-AVM)	Infantile hemangiomas Congenital hemangiomas (CH) Rapidly involuting (RICH) Non-involuting (NICH) Hemangioendotheliomas: – kaposiform – spindle cell – lymphangioendotheliomatosis – epitheloid Tufted angiomas Dermatologic-acquired tumours: – pyogenic granuloma – targetoid hemangioma – glomeruloid hemangioma – microvenular hemangioma

Table 1 Reproduced from the ISSVA classification of vascular anomalies: this is not an extensive list[16]

Lymphatic malformations can be divided into three groups:
- lymphedema – hypoplasia of lymphatic trunks and nodes
- problematic chyle circulation
- cystic malformations:
  - deep
  - superficial

These cystic lymphatic malformations are further classified based on radiographic examination into macrocystic (previously termed cystic hygromas/cavernous lymphangiomas) or microcystic (previously called lymphangiomas, lymphangima circumscriptum, lymphagioma simplex, verrucous hemangiomas, and angiokeratoma circumscriptum).

Both of these subgroups can present together as a combined lesion or in association with capillary, venous and arteriovenous structures forming a combined vascular malformation.[15] (See table 1.)

The severity of symptoms related to LMs tends to relate to the size of the malformation and structural/functional affect on the adjacent tissues.[3]

Microcystic, macrocystic and combined lesions

Microcystic LMs consist of cysts smaller than 2cm in diameter; in contrast, macrocystic lesions are greater than 2cm in diameter. Microcystic LMs can develop within the cutaneous or subcutaneous lymphatic system in any site in the skin and often occur in the suprahyoid region, or the anterior two thirds or lingual dorsum tongue. Other oral sites include the lips, buccal mucosa, soft/hard palate, sublingual region, retromolar region and tonsils.

LMs are congenital malformations that may not be manifest until an episode of infection, and their appearance is contingent on their location and depth. Features may include the presence of thickened dry skin appearances similar to a series of viral warts. Localised swelling or bruising may also occur.

Macrocystic lesions are most commonly located in the neck. Their differences in clinical behaviour and predilection for different regions has resulted in researchers questioning if microcystic lesions occurring in the aerodigestive tract are truly different entities to macrocystic lesions that occur in the neck.[8]

Combined macro/microcystic lesions present as fluctuant cysts with overlying bruised, vesicular or verrucous skin. They often are associated with a capillary malformation which presents as an overlying red/purple stain. Occasionally other deeper vascular malformations are also involved in these lesions.

There is no histological difference between the two types of lesion.

Histology

A 2009 study[8] found that the majority of patients with microcystic lesions were subject to recurrent episodes of infections, lymphocytopenia, and classed with higher stages of disease, stage 3 or 4,[17] whereas the majority with macrocystic lesions were classed as stage 1 (see table 2). The histological morphology of the single layer endothelial cells in both types of lesion was similar. The endothelial lining of channels appeared normal; however, it was reported that these cystic, dilated channels contained amorphous proteinaceous lymph fluid, blood cells and were associated with adipocytes and lymphoid aggregates. Larger lymphatic vessels of LMs have been described as thin-walled, heterogeneous in size and irregularly shaped.[3] These vessels are partially surrounded by disorganised smooth muscle cells and elastin fibers, their stroma demonstrates increased fibrosis; these features are thought to lead to the collapse of the vessels.[8] This stroma is complexed with adipocytes, fibroblasts, foci of leukocytes, adiopocytes.

Pathogenesis

The cause/aetiology of LMs is unknown; however, various studies have attempted to produce insightful jigsaw pieces of the pathogenesis. A 2010 study theorised that the inappropriate expression of lymphatic specific markers may be involved; VEGF-C, Ang 2, FOXC, LYVE1, Prox-1 and Podoplanin may increase the density and complexity of the lymphatic system.[3] Past studies showing an increased expression of the lymphatic markers, except receptor VEGFR-3, suggest possible autocrine involvement in the development of LMs. *In vitro* analysis of LM endothelium exhibited no functional differences in comparison to normal lymphatic endothelium.[3] Increased expression of VEGF-C and receptor VEGFR-3 have been identified in LM tissue – both factors have a role in proliferation of lymphatic cells.[1]

A 2009 study discussed how the disorganised smooth muscle surrounding the larger lymphatic vessels may promote differentiation of endothelial cells into a venous blood endothelial cell which no longer express podoplanin.[8] In this study, the authors identified the lack of consistent immunohistochemical staining of Prox-1 and LYVE-1 in the LMs and hypothesised that this indicates de-differentiation of lymphatic endothelial cells into blood endothelial cells.[8] They commented on how Prox-1 expression was deemed essential to maintain a lymphatic endothelium phenotype. Studies analysing the phenotypes of mice deficient in one of the following endothelial markers LYVE-1, Prox-1, podoplanin and VEGFR-3 demonstrated extravasation of lymph fluid into the interstitium, opposed to the sequence seen in LMs where the fluid is retained and vessels are subsequently dilated. They hypothesised that the pathogenesis of LMs is based upon problematic fluid exchange due to abnormalities in the extracellular matrix or stroma indicated by strong smooth muscle actin staining and not the endothelium and that LM vasculature is prematurely advanced towards the collecting vessel phenotype or remodelling stage. Two studies propose LMs are the result of dysregulation/errors of remodelling.[3,9] The authors of the previously mentioned 2009 study conclude that the main differences between microcystic/macrocystic lesions are not identified histochemically or histologically; however, at clinical level may be a result of their anatomical microenvironment and these lesions are distinguishable radiographically.

Another 2010 study investigated the role of Emilin 1 in anchoring filaments.[10] Emilin1 deficient mice have exhibited hyperplastic, disorganised lymphatic vessels, a reduced number of anchoring filaments and dysfunctional junctions in conjunction with impaired lymphatic drainage.[10] As discussed earlier, podaplanin has a role in the separation of lymphatic vessels from blood vessels during the remodelling phase of lymphatic development. Podoplanin gene-targeted mice resulted in dilated, dysfunctional lymphatic vessels.[10]

Matrix metalloproteinases (MMPs) are metal-dependent enzymes which degrade the extracellular matrix enabling the development of new blood vessels. These enzymes have been implicated in the pathogenesis of cancer and metastasis. Basic fibroblast growth factor bFGF and VEGF increased serum levels have also been identified in cancer patients. A 2005 study described how urinary high molecular weight MMPs and bFGF were found to be significantly increased in patients with LMs compared to control patients.[18] The authors of this study found the levels of these proteins corresponded with the extent and progression of malformation. They theorise that these results may indicate the use of angiogenesis inhibitors as a therapeutic measure to target the MMPs or bFGF preventing progression of an expanding vascular malformation and how these enzymes could be assayed to monitor the enlargement of a malformation following surgical resection.[18]

The increased levels of interferon B immunohistochemical staining in recurrent LMs, as described in 2008,[19] further exemplifies the magnitude of potential contributors to the persistence/recurrence of LMs.

Complications associated with lymphatic malformations

Common complications include leakage of lymph, recurrent localised bleeding, cellulitis/systemic sepsis, swelling, and bruising. Extensive osteolysis has also been identified in relation to LMs. Recurrent localised bleeding and infection enlarge LMs and can result in localised tissue hypertrophy.[20] Recurrent infection, along with localised bleeding is a common complication that can result in enlargement of the lesion, as in this case, and depending on the location this may even compromise the airway. In the event of infection resulting in potential respiratory compromise, patients are often administered broad-spectrum antibiotics and a short course of systemic corticosteroids. Corticosteroids reduce the associated inflammation and swelling. As well as airway complications due to sudden enlargement with infection, the slow growth may also cause problems due to pressure effects. Malformations are implicated in visual disturbance, soft tissue and skeletal overgrowth, macroglossia, asymmetry mandible prognathism, malocclusion (anterior open bites, lateral cross bites), problems with speech, masticatory/feeding difficulties, oral hygiene problems, and disfigurement present as symptoms. Periorbital LMs often present with swelling, proptosis, blepharoptosis, extraocular muscle dysfunction.[21] These numerous symptoms need to be addressed and factored-in during treatment planning due to their affect on quality of life. Malformations affecting the tongue increase the risk of haemorrhage and excess salivation.[13]

Lymphocytopenia, a decrease in the number of white blood cells in the blood, can be the result of decreased production, poor transport/sequestration or cell destruction. Lymphocytopenia has been associated with advanced LM stage/structure. The possible result of medical intervention,[20] chronic inflammation, viral illness,[22] or sequestration[12] of T lymphocytes in the malformation resulting in peripheral T cell lymphocytopenia, has been described.[23] The authors of a 2006 study failed to support this 'reservoir' theory in their study of lymphocytopenia in children with LMs.[20] They recognised the particular association between lymphocytopenia and large bilateral microcystic LM with recurrent infections. They recommend the referral of these patients to clinical immunologists.

Examination, investigations and diagnosis

Early identification and treatment has a better prognosis.[13] Symptoms often reflect the size and location of the lesion; the

most critical being airway obstruction, as seen in suprahyoid lesions.[24] However, the variety of clinical manifestations of microcystic lymphatic malformations can make clinical diagnosis difficult.[15] They often feel fluid-filled and are non-compressible, which aids differentiation from VMs. Small fluid-filled vesicles may be present on mucosal or skin surfaces – they may be blood filled and may weep.[1] It may be possible to estimate the extent of the lesion clinically. Diffuse lesions or those in close proximity to the airways pose an obstructive risk. Skeletal overgrowth, occlusal abnormalities and any impact on adjacent structures and functions should be noted.[1]

Lymphedema and LMs are now commonly diagnosed before birth by routine prenatal ultrasound examination.[12] Those diagnosed in childhood are usually highlighted when enlarged due to increased lymphatic flow and, as discussed, often involved in infection, eg respiratory infections or otis media.[1] Small, superficial LMs may be diagnosed clinically. Biopsy of lesions can result in haemorrhage, therefore, radiographic analysis is often preferred. As discussed earlier, histological examination does not differentiate between the different types of LMs ,unlike radiography.[13]

To diagnose, stage and plan the intervention of more extensive LMs, CT and MRI T2 imaging are employed for the diagnosis and determination of the anatomical site in relation to other structures, the presence of any complicating factors such as associated AVMs or proximity to neurovascular structures and extension of the lesion. CT is beneficial for the delineation of skeletal overgrowth which can be secondary to the LM.[25] MRI T2 imaging of LMs present with high signal intensity. T1-weighted image intensity is comparable or less than that of muscle.[13] These imaging modalities enable the classification of macrocystic (>2cm diameter) microcystic lesions (<2cm diameter cysts present), or combined (both macrocysts and microcysts present) based upon their cyst size and aid identification of LMs that may regress without intervention.[26]

Staging

The staging system described in 1995 relates the location of the lesion to the prognosis (see table 2).[17]

Increased incidences of recurrence/complications have been documented in suprahyoid regions, this is thought to be attributable to the influence of surrounding structures.[17] Microcystic LM locations and relationship to vital structures can often make them more difficult to treat. Microcystic lesions are often staged higher than macrocystic lesion and have correspondingly greater complications.[8]

Treatment planning

Prior to any treatment, prenatal diagnosis (where appropriate), staging based on clinical/radiological examination of the location and extent of the lesion, chromosomal analysis, and consideration of the aims of treatment collectively form the foundation of treatment planning.

The timing of treatment is often dependent on the presenting symptoms, eg life-threatening events may support surgical intervention, ie needle aspiration, to re-establish the airway. LMs free of any associated symptoms may be observed for a 18-24 month period, some LMs may indeed regress to a degree that makes definitive treatment unnecessary. The aims of treatment may include complete excision to ablate symptoms, size reduction, restore function and aesthetics.

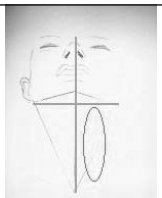
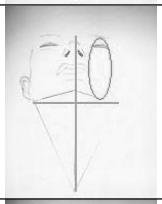
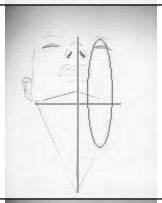
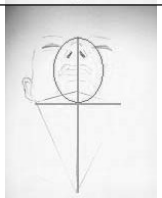
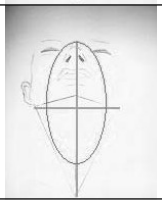
Stage	Lymphatic malformation location		Complication rate (%)
I	Unilateral infrahyoid		17
II	Unilateral suprahyoid		41
III	Unilateral infrahyoid and suprahyoid		67
IV	Bilateral suprahyoid		80
V	Bilateral infrahyoid and suprahyoid		100

Table 2 The staging of head and neck LMs based on location in reference to sagittal/midline and horizontal axis in relation to hyoid bone and the associated complication rates [24]

Spontaneous resolution of LMs are rare; however, they have been reported. A 2010 study discussed how resolution is most likely associated with small macrocystic LMs in the posterior triangle of the neck.[1] The formation of lymphatic-venous shunts is a possible explanation for this phenomenon.

Treatment

Treatment options can include aspiration, surgical excision, sclerotherapy, radiofrequency ablation, CO_2 laser treatment.[27]

Surgical treatment

Traditionally, conservative management of LMs reflected that of tumours (staged debulking of the malformation whilst attempting to preserve the function of vital structures) and is still indicated for extensive suprahyoid lesions involving the tongue, larynx, pharynx and orbit.

Complete surgical excisions of localised infrahyoid, suprahyoid and bilateral macrocystic lesions have been reported. Full excision of subcutaneous microcystic lesions may also be achieved. In these cases total excision should be considered in the first operation: via functional neck dissection/ parotidectomy, with the aim to preserve nerves and vessels; however, treatment may have to be staged.

Tissues surrounding infiltrative microcystic LMs tend to scar and may distort the normal anatomy. Total excision may result in subsequent swelling resulting in oropharyngeal obstruction requiring tracheostomy and gastrostomy tube placement.

Stage IV or V LMs of the tongue or floor of the mouth are common. Surgical intervention of these lesions often results in post-operative edema, therefore the management of the airway in anticipation of complications must be planned. Treatment is staged and the order of treatment may vary dependent upon the balance of benefits *vs* complication/risk; for instance, two equally possible, however, different, surgical paths both accommodating risk management – early tongue/floor of mouth treatment to enlarge the upper respiratory/oesophageal region then eventual neck LM resection, alternatively initial removal of the LM in the floor of mouth and neck and then reduction of the tongue in the event of macroglossia CO_2 laser treatment may be indicated in cases where microcystic malformations are localised to the dermis.

Surgical intervention such as orthognathic surgery is implemented to treat secondary related deformities such as skeletal overgrowth.[1]

Nerve damage is a potential complication of surgical intervention. Macrocystic LM involvement with the parotid gland indicates total parotidectomy with seventh cranial nerve dissection.

Sclerotherapy

Sclerotherapy involves the elimination of abnormal vessels via carefully targeted intravascular injection of sclerosing agents.[24] This method is highly technique sensitive and risks extravasation of agent into the surrounding tissues.

It is indicated in patients where surgical treatment is deemed unsuitable due to the lesion expanse or presence of multiple loculations. However, it is not suitable in regions were swelling could have longterm implications, ie the orbit. Various sclerosants (picinabil, bleomycin, doxycycline, ethanol, hypertonic saline, acetic acid) have been used in LM treatment; however, there is no consensus of the preferred agent in relation to LM type, as their mechanism of action is poorly understood at this stage.

Multistage ethanol treatment has been used for LM treatment. A 2003 study described double-needle sclerotherapy technique, where a combination of ethanol and contrast medium is injected into the site through one needle and drained by a second needle located in the distal aspect of the LM – whilst flow is controlled/visualised fluoroscopically.[28]

Picinabil (OK-432) is a lymphophilised combination of benzylpenicillin and group A *Streptococcus pyogenes*. After directed injection, it has been proposed that OK-432 remains within the LM and stimulates lymphatic channels destruction through the employment of immune cells and mediators; macrophages, cytotoxic T lymphoctes, interleukins, natural killer cells, predominantly neutrophils. Increased expression of tumour necrosis factor and interleukin 6 has also been noted. This is particularly useful for macrocystic lesions.

Bleomycin is an inhibitor of DNA synthesis and was initially used as an anti-tumour drug. It has an inflammatory effect on endothelial cells. Administered either in an oil form or as aqueous hydrochloride, it is mainly used for macrocystic treatment and has shown positive results in 88% of cases.[26] The incidence of side effects are presumed lower with bleomycin use compared to other sclerosants, therefore it is preferred in cases involving the orbit or in those at risk of respiratory obstruction.

Doxycyclin is a broad spectrum antibiotic and MMP inhibitor. It stimulates inflammatory response and fibrosis. It is deemed safe and effective when used repeatedly for macrocystic LM treatment or in combination with surgery in microcystic LMs; however, it has been reported to cause neural damage.

In comparison to macrocystic lesions, larger microcystic LMs are more difficult to treat and eradicate.[20] They are less amenable to aspiration, sclerotherapy and surgery.[1] Sclerotherapy of these microcystic lesions can be ineffective as the agents fail to diffuse lumen to lumen,[13] and total excision is often unachievable due to their extensive presence around muscle, vessels and nerves. Following excision they have a greater tendency to persist.

Oral care is important in patients with oral LMs. Poor periodontal health and dental care are implicated in the floor of mouth/tongue LMs swelling, which has significant risk associated. Orthodontic appliances used in the treatment of associate malocclusions and in conjunction with orthognathic surgery often trigger inflammation of the LM, therefore regular routine dental care is essential.[26]

Prognosis

Surgical removal of head and neck LM's carries a risk of nerve damage (VII, IX, X, XII and the sympathetic nerve); however, this depends on the location and extent of the lesion. A 1995 study of 17 patients with unilateral suprahyoid disease included lesions affecting mouth, tongue, parotid, buccal, submandibular, orbital and postauricular lesions.[17] The authors identified a 41% complication rate post-surgical treatment; 18% cranial nerve palsy incidence isolated to the seventh cranial nerve; buccal and zygomatic branch injury of a single patient post-excision of a buccal lesion; and two patients with marginal mandibular palsies which resolved after two months. There was a 29% incidence of persistent disease in this particular group of patients.

Staging parallels prognosis, eg stage 1 lesions are likely to have a better prognosis/treatment outcome than patients with stage 2 lesions, and so on, with stage 5 lesions having the worst prognosis in comparison.

CONCLUSION

The review and case study have highlighted the magnitude of vascular anomalies. They address the main characteristics that differentiate malformations and enable classification. Features of the case (ie occlusal abnormalities, recurrent infections/bleeding, and presentation of external bruising) support the discussed characteristics of LMs in the literature. The normal lymphocyte count, however, did not mirror the leucopenia theory in this case. Determination of the specific causes and actual pathogenesis of LMs will undoubtedly aid identification, help to define effective treatment toward complete resolution. Today, however, the current, various theories only provide interesting insight into the possible genetic, molecular and physiological causes. Initial diagnosis is based upon the presentation and symptoms.

One of the most important clinical points identified in the literature is that any lesions close to the airway must be carefully examined to enable airway planning prior to treatment and to avoid complications. A final point – it is important to identify the need, benefits and risks of treatment during treatment planning as intervention is a fine balance of improving quality of life/function and increasing morbidity due to the associated complications.

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